Oxidations in Organic Chemistry

Miloš Hudlický
Virginia Polytechnic Institute and State University

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To my dear wife Alena

FOREWORD

ACS MONOGRAPH SERIES was started by arrangement with the interallied Conference of Pure and Applied Chemistry, which met in London and Brussels in July 1919, when the American Chemical Society undertook the production and publication of Scientific and Technological Monographs on chemical subjects. At the same time it was agreed that the National Research Council, in cooperation with the American Chemical Society and the American Physical Society, should undertake the production and publication of Critical Tables of Chemical and Physical Constants. The American Chemical Society and the National Research Council mutually agreed to care for these two fields of chemical progress.

The Council of the American Chemical Society, acting through its Committee on National Policy, appointed editors and associates to select authors of competent authority in their respective fields and to consider critically the manuscripts submitted. The first Monograph appeared in 1921. Since 1944 the Scientific and Technological Monographs have been combined in the Series.

These Monographs are intended to serve two principal purposes: first, to make available to chemists a thorough treatment of a selected area in a form usable by persons working in more or less unrelated fields so that they may correlate their own work with a larger area of physical science; and second, to stimulate further research in the specific field treated. To implement this purpose, the authors of Monographs give extended references to the literature.

Publisher's Acknowledgment

The American Chemical Society thanks Robert J. Alaimo of Norwich Eaton Pharmaceuticals, Inc., and chairman of the Division of Chemical Health and Safety of the American Chemical Society for thoroughly evaluating the safety aspects of this book, for writing the safety advisory that precedes the preparative procedures, and for advising us in the presentation of safety information.

ABOUT THE AUTHOR

MILOŠ HUDLICKÝ, a native of Czechoslovakia, obtained his Ph.D. from the Technical University in Prague, Czechoslovakia. After having spent the year 1948 at the Ohio State University as a UNESCO postdoctoral fellow, he taught as an assistant professor and, later, as an associate professor at the Technical University in Prague until 1958. He then worked as a research associate in the Research Institute of Pharmacy and Biochemistry in Prague. After the Russian occupation of Czechoslovakia in 1968, he moved to the United States, where he was offered a professorship at Virginia Polytechnic Institute and State University.

His field of interest is organofluorine chemistry. He has written 65 research papers, 17 review papers, 28 patents, and 12 books (5 in English). His chefs-d'oeuvre are *Chemistry of Organic Fluorine Compounds* and *Reductions in Organic Chemistry*, published in 1976 and 1984, respectively.

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PREFACE

FOUR YEARS after my book *Reductions in Organic Chemistry* was published by Ellis Horwood in Chichester, England, I submitted its pendant, *Oxidations in Organic Chemistry*. The present monograph is intended to become an aid to a bench chemist. That means that its scope is experimental rather than theoretical, and emphasis is laid on the preparative aspects and synthetic usefulness of individual reactions rather than on the historical developments and mechanisms. This is the only way to compress a critical survey of countless oxidations into a book of reasonable size. The criteria for inclusion of oxidation reactions were simplicity of the reactions, clarity of their descriptions, availability of the oxidants, and yields of the products. The last aspect is somewhat problematic, because analogous compounds may give widely varied results.

To compare the results of oxidations by various oxidants, fairly simple types of compounds are shown to illustrate reaction conditions. After all, these compounds were selected by the researchers who tried to advertise their new methods. More sophisticated examples were avoided, especially because of lack of space.

The systematic literature coverage, initiated by screening *Organic Syntheses,* Theilheimer's *Synthetic Methods,* Harrison and Harrison's *Compendium of Synthetic Methods, Methods in Organic Synthesis, Synthetic Pathways,* and my own files, includes original papers in some 50 major chemical journals through the end of 1986 (with a few more recent additions). Quotations of patents and cyclopedias were avoided, because these sources are generally not very readily available in chemical libraries.

Acknowledgments

It is my pleasure to express my gratitude to my wife, Alena, without whose efficient support, loving care, and understanding this book would not have been written. I gladly acknowledge the help of my son, Tomáš Hudlický, for his critical comments after reading the manuscript. I also appreciate very much the secretarial help of Angela Miller, Wanda Ritter, and Vera Good for typing the text and handling the ChemDraw software; the permission of the Department of Chemistry of Virginia Polytechnic Institute and State University to use the word-processing facilities; and the permission of A. Bader, Aldrich Chemical Company, Inc., to quote physical constants of many reagents from the Aldrich 1988–1989 catalog.

Finally, I would like to give credit to my reviewers, M. S. Newman and J. F. Wolfe, for helping me improve the quality of my book, and to the ACS Books Department editors, Paula M. Bérard, Robin Giroux, and especially A. Maureen Rouhi, for the meticulous, yet humane, editorial work.

MILOŠ HUDLICKÝ
Virginia Polytechnic Institute
and State University
Blacksburg, VA 24061–0699
July 19, 1989

DISCLAIMER

THIS BOOK CONTAINS information and materials involving chemicals and chemical reactions, and included within some of the chapters are certain procedures for preparing oxidation agents and performing oxidation reactions. These materials and procedures have been compiled carefully, and introductory safety statements precede the preparative procedures section of this book. There are also indications of the preparations and reactants that should be noted as particularly hazardous. The running notice at the bottom of each page alerts each reader to the fact that oxidations are strong reactions. The safety information is included within this book by the American Chemical Society as a precaution to the readers.

The materials, safety information, and procedures contained in this book are believed to be reliable. This information and these procedures should serve only as a starting point for laboratory practices, and they do not purport to specify minimal legal standards or to represent the policy of the American Chemical Society. No warranty, guarantee, or representation is made by the American Chemical Society as to the accuracy or specificity of the information contained herein, and the American Chemical Society assumes no responsibility in connection therewith. The added safety information is intended to provide basic guidelines for safe practices. Therefore, it cannot be assumed that all necessary warnings and precautionary measures are contained in this document and that other or additional information and measures may not be required. Users of this book and the procedures contained herein should consult the primary literature and other sources of safe laboratory practices for more exhaustive information.

THE SYSTEM OF THE BOOK
(HOW TO USE THIS BOOK)

IN ADDITION to the subject index with entries of several aspects, such as oxidation with . . . , oxidation of . . . , or . . . by oxidation of, the desired oxidation can be located in the following ways.

The first part of the book surveys oxidizing agents and their scopes and limitations in the oxidation of different functional groups. The arrangement is indicated in the table of contents: first, oxygen and ozone; then, hydrogen peroxide and its inorganic and organic derivatives; then, oxidants according to the sequence in the periodic table; and, finally, organic oxidants, chiral agents, and microorganisms.

The second larger part of the book lists oxidations of individual functional groups and types of compounds. The system is remotely reminiscent of Beilstein's *Handbuch der Organischen Chemie* (with certain modifications), and the oxidations of organic compounds are discussed according to the following order: alkanes and cycloalkanes; alkenes and cycloalkenes; aromatic (including heterocyclic aromatic) compounds; halogen derivatives; alcohols; ethers; aldehydes and ketones and their derivatives; carboxylic acids and their derivatives; nitrogen compounds; phosphorus and arsenic compounds; sulfur compounds; selenides; iodo compounds; and compounds of boron, silicon, tin, magnesium, and mercury.

If two or more functional groups are present, the oxidation of either group is described in the place where the functional group higher up in the system is discussed. For example,the oxidation of hydroxy aldehydes to oxo aldehydes or hydroxy acids is dealt with in the section on aldehydes (not alcohols). Sometimes, especially if one functional group is far enough from and unaffected by the other, such oxidation may be described in the place where the lower functional group is reviewed. For example, the epoxidation of oleic acid is discussed under "Alkenes" rather than "Carboxylic Acids." The discussion of the oxidation affecting a particular functional group precedes that of the oxidation in a more distant part of the molecule. Thus the oxidation of propene to its epoxide is described prior to the oxidation of propene to allyl hydroperoxide or acrolein.

The relative importance of individual oxidants is shown in different fonts: the most common oxidants are printed in **boldface** type, and the less frequently used ones are set in *italic* type. Normal type is used for agents with which there is not yet enough laboratory experience. No distinction is made between yields of products as found by gas–liquid chromatography, by derivatization, or by isolation.

Frequent cross-references should help locate the searched-for reaction. Despite all these provisions, there will certainly be reactions that cannot be found in this book, simply because this monograph contains only a few parts per million of all oxidations described in the chemical literature.

Chapter 1
Oxidation Agents

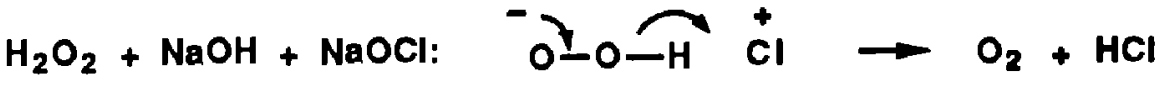
AIR, OXYGEN, OZONE, AND ELECTROLYSIS

Air, the cheapest oxidant, is used only rarely without irradiation and without catalysts. Examples of oxidations by air alone are the conversion of aldehydes into carboxylic acids (autoxidation) and the oxidation of acyloins to α-diketones. Usually, exposure to light, irradiation with ultraviolet light, or catalysts are needed. Under such circumstances, dehydrogenative coupling in benzylic positions takes place at very mild conditions [*1*]. In the presence of catalysts, terminal acetylenes are coupled to give diacetylenes [*2*], and anthracene is oxidized to anthraquinone [*3*]. Alcohols are converted into aldehydes or ketones with limited amounts of air [*4, 5, 6, 7*]. Air oxidizes esters to keto esters [*8*], thiols to disulfides [*9*], and sulfoxides to sulfones [*10*]. In the presence of mercuric bromide and under irradiation, methylene groups in allylic and benzylic positions are oxidized to carbonyls [*11*].

Oxygen, O_2, exists in two states. Stable **ground-state oxygen (triplet oxygen)** has two odd electrons with parallel spins. It behaves like a diradical and is paramagnetic: $\uparrow \bullet O:O \bullet \uparrow$. In **excited-state oxygen (singlet oxygen),** the two odd electrons possess antiparallel spins: $\uparrow \bullet O:O \bullet \downarrow$. Such a molecule is unstable, with a half-life of 10^{-6} s, and is diamagnetic. Each form reacts differently with organic molecules.

Singlet oxygen [*12*] is formed by irradiation of gaseous oxygen with ultraviolet light in the presence of sensitizers that absorb the light of the particular wavelength: benzophenone, methylene blue, rose bengal, chlorophyll, and others. It reacts with organic compounds in the same way as singlet oxygen generated chemically by several reactions, such as the treatment of hydrogen peroxide in alkaline medium with sodium hypochlorite [*13, 14, 15*], calcium hypochlorite [*14*], bromine [*16*], or organic peroxy acids [*16*]. Singlet oxygen can be also obtained by the decomposition of aromatic endoperoxides, such as 9,10-diphenylanthracene endoperoxide [*17*] or rubrene peroxide [*18*], and by the decomposition of triphenyl phosphite ozonide [*19, 20*] (equations 1–4).

[13] 1



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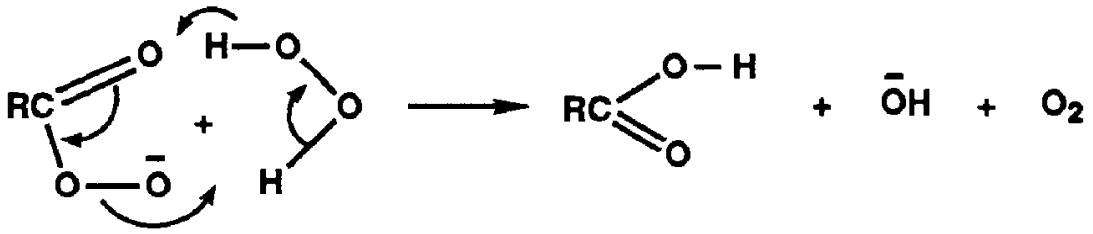

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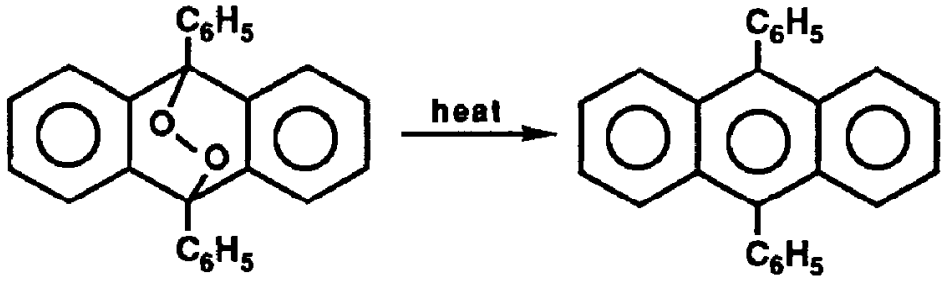

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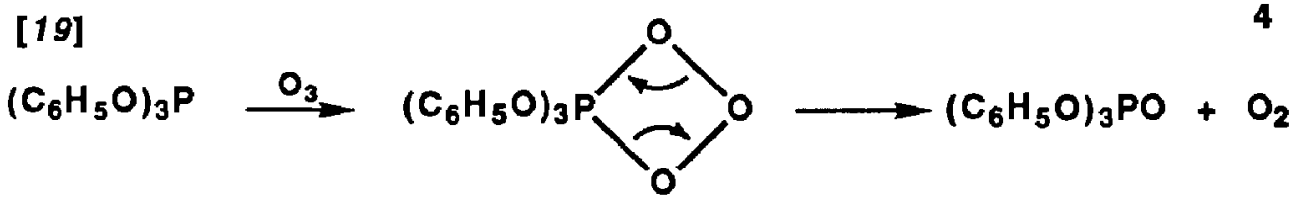

A reaction peculiar to singlet oxygen is the formation of hydroperoxides in the α positions with respect to double bonds [*14, 15, 19, 21, 22, 23, 24, 25, 26*] or aromatic rings [*23, 27, 28, 29, 30*] (equation 5).

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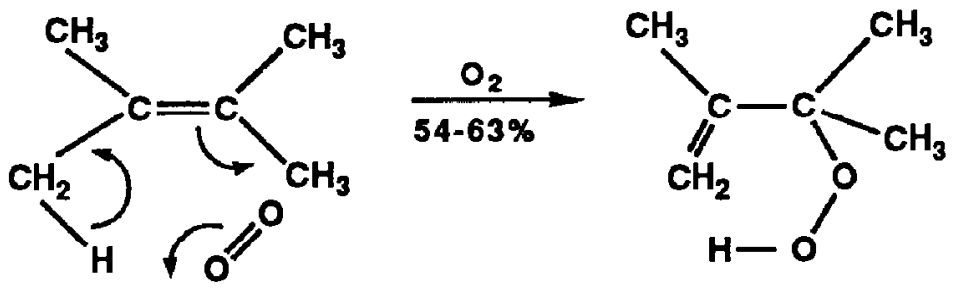
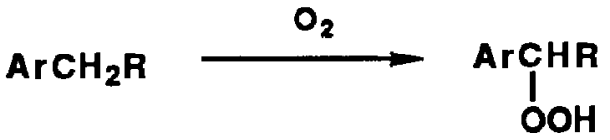
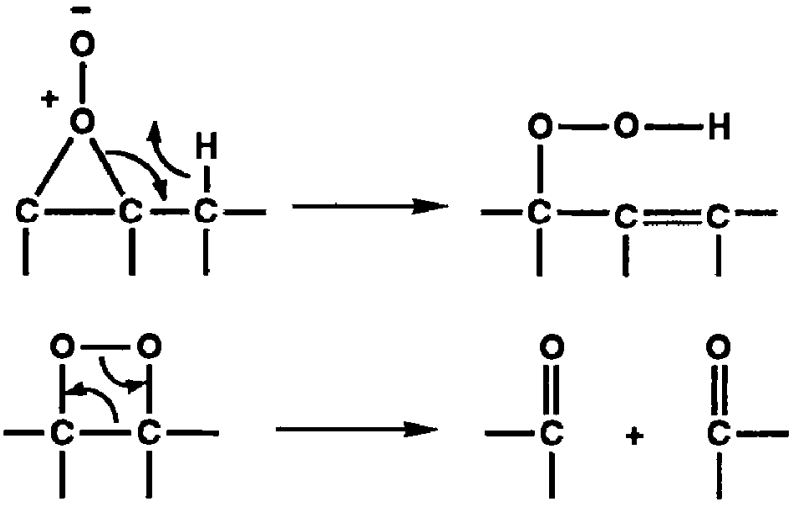




Instead of the fully accepted concerted mechanism via an ***ene reaction***, a mechanism with perepoxides and dioxetanes as intermediates for hydroperoxides and carbonyl products, respectively, was proposed [*21*] (equation 6).

Another type of oxidation typical of singlet oxygen is the formation of oxides or ***endooxides*** from conjugated dienes by 1,4-addition (Diels–Alder reaction) [*13, 15, 17, 19, 24, 31, 32, 33, 34, 35*] (equation 7).

[21]



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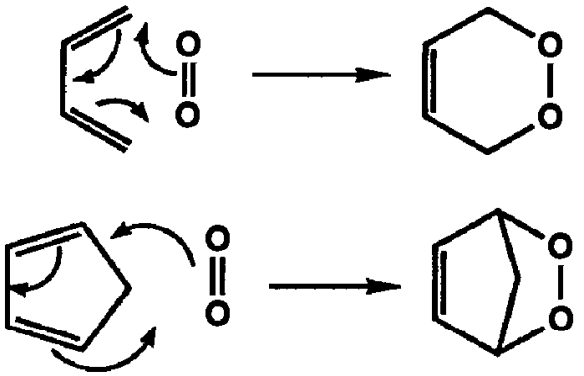

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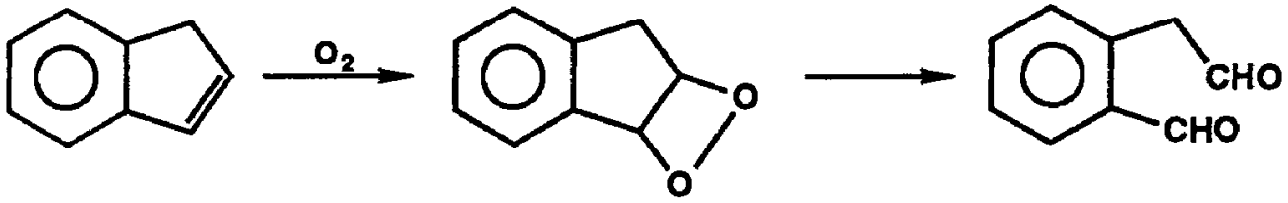
A less frequent reaction is the formation of ***dioxetanes*** from compounds containing double bonds [*20, 36, 37, 38, 39, 40, 41, 42*]. Such compounds are not stable and disintegrate to dicarbonyl compounds (equation 8).

[39]



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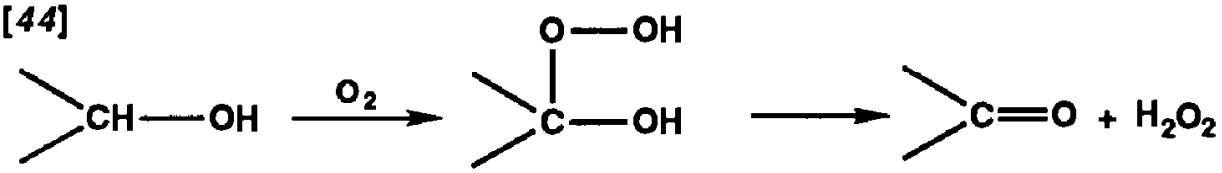
Other oxidations with singlet oxygen are conversions of alkenes into epoxides [*43*], of secondary alcohols into ketones via alcohol hydroperoxides [*44, 45*] (equation 9) and the oxidative degradation of tertiary amines to secondary amines [*46*] (equation 10).

[44]



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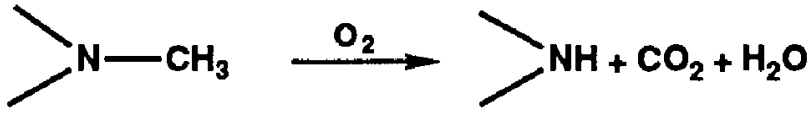

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Ground-state oxygen alone rarely oxidizes organic compounds. A classical example is the autoxidation of benzaldehyde to benzoic acid, a usually undesirable reaction that takes place even in the absence of light. Other examples of autoxidation without illumination are oxidations at the α positions with respect to aromatic rings or at tertiary carbons [*47, 48, 49, 50*] and the formation of alkyl hydroperoxides from alkyl dichloroboranes [*51*]. Some oxidations take place when a compound is treated with oxygen in the presence of bases [*9, 52, 53*].

Because oxidations with oxygen are free-radical reactions, free radicals should be good initiators. Indeed, in the presence of hydrogen bromide at high enough temperatures, lower molecular weight alkanes are oxidized to alcohols, ketones, or acids [*54*]. Much more practical are oxidations catalyzed by transition metals, such as platinum [*5, 6, 55, 56*], or, more often, metal oxides and salts, especially salts soluble in organic solvents (acetates, acetylacetonates, etc.). The favored catalysts are vanadium pentoxide [*3*] and chlorides or acetates of copper [*2, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66*], iron [*67*], cobalt [*68, 69*], palladium [*60, 70*], rhodium [*10*], iridium [*10*], and platinum [*5, 6, 56, 57*].

Oxidations by oxygen and catalysts are used for the conversion of alkanes into alcohols, ketones, or acids [*54*]; for the epoxidation of alkenes [*43*]; for the formation of alkenyl hydroperoxides [*22*]; for the conversion of terminal alkenes into methyl ketones [*60, 65*]; for the coupling of terminal acetylenes [*2, 59, 66*]; for the oxidation of aromatic compounds to quinones [*3*] or carboxylic acids [*68*]; for the dehydrogenation of alcohols to aldehydes [*4, 55, 56*] or ketones [*56, 57, 62, 70*]; for the conversion of alcohols [*56, 69*], aldehydes [*5, 6, 63*], and ketones [*52, 67*] into carboxylic acids; and for the oxidation of primary amines to nitriles [*64*], of thiols to disulfides [*9*] or sulfonic acids [*53*], of sulfoxides to sulfones [*10*], and of alkyl dichloroboranes to alkyl hydroperoxides [*51*].

Ozone, O_3 (O=O–O:), a blue gas or a dark blue liquid (bp –106, –116, or –125 °C, depending on the source of data), is used in a mixture with oxygen. Such mixtures are commercially available but are usually prepared in the laboratories. For microscale ozonization that is suitable for handling 0.01–0.1 mL of solutions, a microozonizer is assembled by using an electrical vacuum tester as a source of high-voltage electricity [*71*].

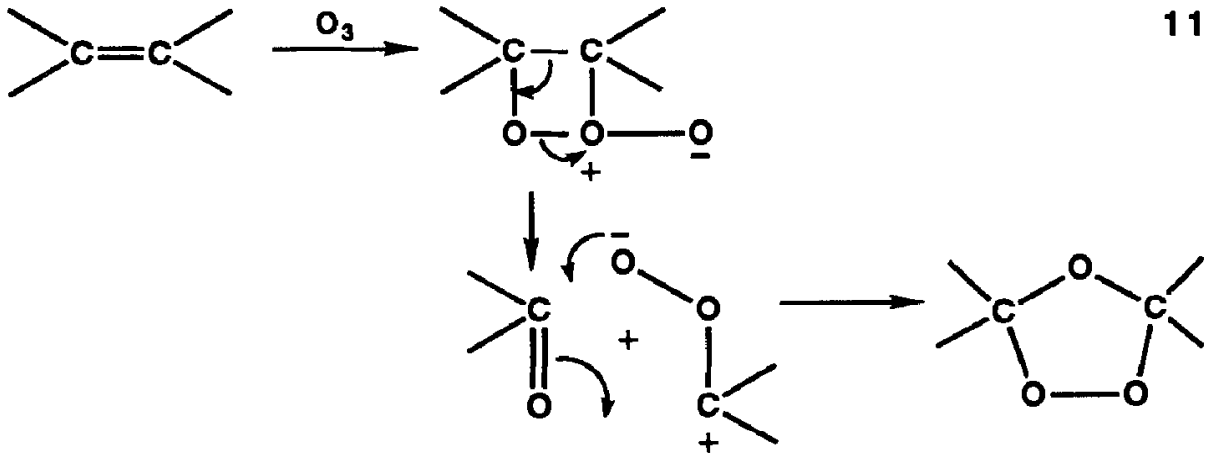
To prepare larger amounts of ozone, oxygen is passed through a silent electrical discharge with a potential drop of 11,000–15,000 V in an especially designed apparatus [*72, 73*]. Although the conversion of oxygen into ozone was reported to be as high as 6–8%, the commonly reached concentration of ozone in oxygen is 2–3%. Some compounds tend to decompose ozone, for example, dilute sodium hydroxide and phosphorus pentoxide [*74*].

Ozonizations are carried out by passing ozone-containing oxygen through solutions of organic compounds in solvents that do not react with

ozone and are liquid at low temperatures. Cooling with dry-ice–acetone baths (−78 °C) is frequently needed to prevent the decomposition of ozonides, some of which are unstable at room temperature. The most common solvents are pentane, cyclohexane, dichloromethane, chloroform, methanol, acetic acid, and ethyl acetate.

To avoid an excess of ozone, the gas is metered by using conventional flow meters. Otherwise, the introduction of ozone is maintained until ozone appears in the exit gas. The presence of ozone is easily recognized by the starch–iodine reaction. The exit gas is passed through an aqueous solution containing 5% of alkaline iodide, 5% of sulfuric acid, and a few drops of a starch solution. Iodine, which is liberated by ozone, forms a dark blue color with starch [*71*]. Another sign of the end of ozonization is the light-blue tinge of the ozonized solution.

By far the most common reaction of ozone is that with alkenes, which first add ozone to form unstable molozonides. The molozonides break down into two separate species, which recombine to form true ozonides [*75, 76*] (equation 11).



11

Ozonides are rarely isolated [*75, 76, 77, 78, 79*]. These substances tend to decompose, sometimes violently, on heating and must, therefore, be handled with ***utmost safety precautions*** (safety goggles or face shield, protective shield, and work in the hood). In most instances, ozonides are worked up in the same solutions in which they have been prepared. Depending on the desired final products, ozonide cleavage is done by reductive or oxidative methods. Reductions of ozonides to ***aldehydes*** are performed by catalytic hydrogenation over palladium on carbon or other supports [*80, 81, 82, 83*], platinum oxide [*84*], or Raney nickel [*85*] and often by reduction with zinc in acetic acid [*72, 81, 86, 87*]. Other reducing agents are triphenylphosphine [*88*], trimethyl phosphite [*89*], dimethyl sulfide (DMS) [*90, 91, 92*], and sodium iodide [*93*]. Lithium aluminum hydride [*94, 95*] and sodium borohydride [*95, 96*] convert ***ozonides into alcohols.***

The oxidative cleavage of ***ozonides to carboxylic acids*** is achieved with hydrogen peroxide in sodium hydroxide solution [*97*], in formic acid

[*98, 99, 100*], or in acetic acid [*81, 101, 102, 103*] and, less often, with silver oxide and nitric acid [*77*].

If only one molecule of a carboxylic acid is expected from the ozonolysis, boiling the ozonide with acetic acid is sufficient, because the ozonide contains one atom of oxygen necessary for such oxidation.

In addition to the ozonolysis of alkenes and a few aromatic compounds [*93, 104*], ozone oxidizes other groups. Thus saturated hydrocarbons containing tertiary hydrogen atoms are converted into tertiary alcohols [*105, 106*], and some alkenes are transformed into epoxides [*107*] or α,β-unsaturated ketones [*108*]. Benzene rings are oxidized to carboxylic groups [*109*]; ethers [*110*] and aldehyde acetals [*111*] to esters; aldehydes to peroxy acids [*112*]; sulfides to sulfoxides and sulfones [*113*]; phosphines and phosphites to phosphine oxides and phosphates, respectively [*113*]; and organomercury compounds to ketones or carboxylic acids [*114*].

Electrolytic oxidation takes place at the anode of an electrolytic cell, which may or may not contain a diaphragm to separate cathodic and anodic spaces. The anode must be made of a metal that resists oxidation, such as lead [*115*], nickel [*116*], or, most frequently, platinum. The anode is usually in the shape of a cylinder made of a wire gauze [*117, 118*]. The possible electrolytes are dilute sulfuric acid [*117*] or sodium methoxide prepared in situ from methanol and sodium [*118*]. The direct-current voltage is 3–100 V, the current density is 10–20 A/dm^2, and the electrolysis temperature is 20–80 °C.

Electrooxidation is rarely encountered. Examples are the epoxidation of alkenes [*119*]; the conversion of alkenes into ketones [*120*]; the oxidation of aromatic rings and side chains to carboxylic acids [*117*]; the oxidation of primary alcohols to carboxylic acids [*116*], of secondary alcohols to ketones [*121*], and of vicinal diols to carboxylic acids [*122*]; the hydroxylation or dehydrogenative coupling of phenols [*115*]; and, especially, the Kolbe synthesis of hydrocarbons. The Kolbe reaction cannot be performed in any other way and gives moderate to high yields of products resulting from the one-electron oxidation of carboxylate anions, decarboxylation, and subsequent coupling of the remaining free radicals [*118, 123*] (*see* equation 469).

HYDROGEN PEROXIDE AND ITS DERIVATIVES

Hydrogen peroxide, H_2O_2, is commercially available in aqueous solutions of 30 or 90% concentration. The 30% hydrogen peroxide is a colorless liquid (*d* 1.110) and is stabilized against decomposition, which occurs in the presence of traces of iron, copper, aluminum, platinum, and other transition metals.

Under reduced pressure, water can be distilled off from 30% hydrogen peroxide by using a column, and a solution of up to 90% hydrogen peroxide can thus be obtained. All the all-glass apparatus for such a distillation must be scrupulously clean and free of organic materials and transition metals and their compounds. The 90% hydrogen peroxide is a clear colorless liquid (mp −11 °C, bp 140 °C dec, d^{18} 1.393, n_D^{20} 1.3998 [*124*]).

Although 90% hydrogen peroxide is stable at 30 °C (the decomposition rate is 1%/year), it decomposes slowly at higher temperatures and rapidly with boiling at 140 °C. All ***safety precautions*** should be taken when working with highly concentrated hydrogen peroxide.

Practically anhydrous hydrogen peroxide as a solution in *tert*-butyl or *tert*-amyl alcohol is prepared by azeotropic removal of water by distillation of a mixture of 35% hydrogen peroxide in the alcohol at 50 °C and 50 mm of Hg until no more water distills. A solution containing 12% of hydrogen peroxide in *tert*-amyl alcohol is thus obtained [*125*].

A solution of anhydrous hydrogen peroxide in ether (~2.5 M) is obtained by repeated extraction of 30% aqueous hydrogen peroxide with ether and drying of the ether extracts over anhydrous magnesium sulfate. The hydrogen peroxide content is determined by iodometric titration [*126*].

Molecular complexes can be prepared from some tertiary amines and 90 or 30% solutions of hydrogen peroxide. 1,4-Diazabicyclooctane (Dabco) forms an adduct with two molecules of hydrogen peroxide. The adduct consists of hygroscopic crystals melting at 112 °C (dec), is stable for a limited time at room temperature, and can be used as a source of hydrogen peroxide in oxidations [*127*].

Whereas 90% hydrogen peroxide is difficult to obtain commercially, 30% hydrogen peroxide is commonly available under the trade names of Perhydrol or Superoxol. The 30% hydrogen peroxide does not mix with nonpolar organic compounds. To increase its solubility, ethanol, *tert*-butyl alcohol, trifluoroethanol [*128*], tetrahydrofuran, acetonitrile, formic acid, and, especially, acetic acid are used. When formic or acetic acid is used, the reacting species is the corresponding peroxy acid. Under such conditions, the products of oxidation by hydrogen peroxide resemble those obtained with peroxy acids. Different products may result from oxidation by hydrogen peroxide in alkaline medium, such as in pyridine, ammonia, and, most often, sodium or potassium hydroxide.

Transition metal catalysts not only increase the reaction rate but may also affect the outcome of the oxidation, especially the stereochemistry of the products. Whereas hydrogen peroxide alone in acetonitrile oxidizes alkenes to epoxides [*129*], osmic acid catalyzes *syn* hydroxylation [*130*], and tungstic acid catalyzes *anti* hydroxylation [*131*]. The most frequently used catalysts are titanium trichloride [*132*], vanadium pentoxide [*133, 134*], sodium vanadate [*135*], selenium dioxide [*125*], chromium trioxide [*134*], ammonium molybdate [*136*], tungsten trioxide [*131*], tungstic acid [*137*],

sodium tungstate [*135, 138*], ferric chloride [*87*], palladium or palladium acetate [*139,140*], and osmium tetroxide (osmic acid) [*130, 141*].

The domain of oxidations with hydrogen peroxide includes the epoxidation [*129, 133, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151*] and hydroxylation [*130, 131, 134, 137, 152*] of double bonds and the oxidation of primary amines to nitroso compounds [*153*], of secondary amines to hydroxylamines [*154*], of tertiary amines to amine oxides [*155, 156, 157, 158, 159, 160, 161, 162*], of sulfides to sulfoxides or sulfones [*132, 135, 163, 164, 165, 166*], of selenides to selenoxides [*167, 168, 169*], of aldehydes to acids [*125, 170*], of aromatic aldehydes to phenols [*171, 172, 173*], and of carboxylic acids to peroxy acids [*174, 175, 176*]. Hydrogen peroxide also oxidizes organic compounds to hydroperoxides or peroxides [*177, 178, 179, 180, 181, 182*], alkylboranes to alcohols [*183, 184, 185*], thiols to disulfides [*186*], and disulfides to sulfonic acids [*187*]. It is also used for the ***Baeyer–Villiger reaction*** [*128*], oxidation to quinones [*139*], and oxidative degradations [*87, 134, 188, 189*].

Sodium peroxide, Na_2O_2, a pale-yellow solid (mp 460 °C), is used very rarely. Some examples are the conversion of aldoximes into carboxylic acids [*190*] and the oxidation of ketones to esters (lactones) [*128, 191*].

Potassium superoxide, KO_2, when in a phase-transfer system with Aliquat 336 (methyltrioctylammonium chloride), oxidizes ketones containing α-hydrogens to acids at room temperature [*192*].

Sodium perborate, $NaBO_3 \cdot 4H_2O$ (mp 60 °C dec), is used for oxidations of primary aromatic amines to azo compounds [*193*] or nitro compounds [*194*] and of sulfides to sulfoxides and sulfones [*194*]. This reagent does not affect alcohols and only slightly affects alkenes [*194*].

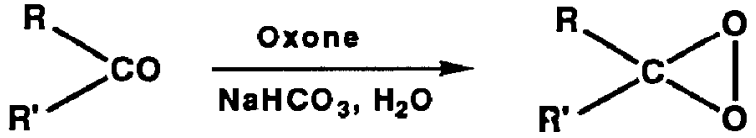
Sodium persulfate ($Na_2S_2O_8$), potassium persulfate ($K_2S_2O_8$), and ammonium persulfate [$(NH_4)_2S_2O_8$], when applied in the presence of sulfuric acid, act as H_2SO_5 or $KHSO_5$ [*195*]. Alkaline persulfates are also used for the reoxidation of high-valency metal salts such as K_2RuO_4 [*196*]. A reaction peculiar to persulfates is the ***Elbs persulfate oxidation*** of phenols to *p*- or *o*-dihydroxy aromatic compounds [*197*]. Aliphatic primary amines are dehydrogenated to imines [*198*], and aromatic primary amines are oxidized to nitroso compounds [*199*].

Persulfuric acid (sulfomonoperacid, peroxymonosulfuric acid, or Caro acid), H_2SO_5, is prepared in situ either from hydrogen peroxide [*200*], potassium persulfate ($K_2S_2O_8$), or ammonium persulfate [$(NH_4)_2S_2O_8$] [*200*]. The reagent converts aldehydes into esters (in the presence of alcohols) [*200*]; ketones into lactones or esters [*201*]; primary aromatic amines into azoxy [*202*], nitroso [*195, 202*], or nitro [*195,203*] compounds; and iodo compounds into iodoxy compounds [*204*]. Explosions have occurred after the addition of concentrated peroxymonosulfuric acid to some secondary and tertiary alcohols [*see* reference 1157]. The use of persulfuric acid is very limited, because organic peroxy acids are now preferred.

Potassium persulfate, $KHSO_5$, when used in the mixture $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ **(Oxone,** a registered trade mark of E. I. du Pont de Nemours and Company), is a very versatile although not too common oxidant [*205*]. Good yields are obtained in the oxidation of alcohols to ketones and esters [*205*], of amines to nitroso compounds [*205*], of mercaptans to sulfonic acids [*205*], of sulfides to sulfoxides [*206*] and sulfones [*205, 207, 208*], of phosphines to phosphine oxides [*205*], and of iodo compounds to iodoxy compounds [*205*]. Selective oxidations of sulfides to sulfones in the presence of double bonds and carbonyl groups can also be carried out [*207*]. Because the reagent is practically insoluble in organic solvents, a phase-transfer technique using tetrabutylammonium bromide is advantageous [*208, 209*].

Dioxiranes, prepared from acetone and other aliphatic ketones by treatment with Oxone, can accomplish oxidations that are usually not achieved by Oxone itself [*210, 211*]. Dioxiranes can be isolated by vacuum codistillation with the respective ketones [*210*], or else, they may be formed in situ and applied in the same reaction vessel [*210, 211*]. Examples of the applications of dioxiranes are epoxidations [*210*] and the oxidation of primary amines to nitro compounds [*211*], of tertiary amines to amine oxides [*210*], and of sulfides to sulfoxides [*210*] (equation 12).

[*210*]



12

tert*-Butyl hydroperoxide, $(CH_3)_3COOH$,** bp 33–34 °C at 17 mm of Hg [*212*], is prepared from *tert*-butyl hydrogen sulfate and 27% hydrogen peroxide [*212*] and is commercially available as a 70 or 90% solution containing water and *tert*-butyl alcohol. Anhydrous *tert*-butyl hydroperoxide is obtained from the 70% aqueous solution by azeotropic distillation with toluene [*213*]. Anhydrous, as well as highly concentrated, *tert*-butyl hydroperoxide must be ***handled with utmost care, because it may decompose violently in the presence of strong acids and some transition metals, especially manganese, iron, and cobalt [*213, 214*].

The bulk of oxidations with *tert*-butyl hydroperoxide consists of epoxidations of alkenes in the presence of transition metals [*147, 215, 216, 217, 218*]. In this way, α,β-unsaturated aldehydes [*219*] and ketones [*220*] are selectively oxidized to epoxides without the involvement of the carbonyl function. Other applications of *tert*-butyl hydroperoxide such as the oxidation of lactams to imides [*225*], of tertiary amines to amine oxides [*226, 227*], of phosphites to phosphates [*228*], and of sulfides to sulfoxides [*224*] are rare. In the presence of a chiral compound, enantioselective epoxidations of alcohols are successfully accomplished with moderate to high enantiomeric excesses [*221, 222, 223*].

Sharpless reagent is the most popular of the chiral oxidants. It is a mixture of tetraisopropoxytitanium, diethyl (*R,R*)- or (*S,S*)-tartrate, water, and *tert*-butyl hydroperoxide in the molar ratio 1:2:1:1 [*224*].

Benzoyl peroxide (dibenzoyl peroxide), $(C_6H_5COO)_2$ (mp 104–106 °C dec), and ***p*-nitrobenzoyl peroxide $(p\text{-}O_2NC_6H_4COO)_2$** (mp 156 °C dec), which is synthesized from *p*-nitrobenzoyl chloride and sodium peroxide [*229*], are rarely used as oxidants, and if so, they do not offer appreciable advantages over other organic oxidation agents. The *anti* addition of benzoyl groups to double bonds and the benzoxylation of aromatic rings are achieved in the presence of iodine [*230*], and alcohols are oxidized to carbonyl compounds in the presence of nickel dibromide [*231*].

Diisopropyl peroxydicarbonate, $[(CH_3)_2CHOCOO]_2$, is a rather exotic reagent with limited availability and use. The treatment of toluene with diisopropyl peroxydicarbonate yields a mixture of all three tolyl isopropyl carbonates [*232*].

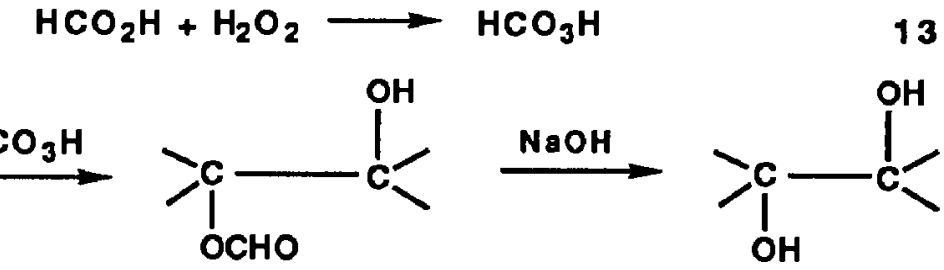
***tert*-Butyl peroxyacetate, $(CH_3)_3COOCOCH_3$** [*233*], and, better still, ***tert*-butyl peroxybenzoate, $(CH_3)_3COOCOC_6H_5$** (bp 75–76 °C at 0.2 mm of Hg) [*233, 234*], in the presence of cuprous salts, are used for the acetoxylation and benzoxylation of alkenes in the α positions with respect to the double bonds. Treatment of a Grignard compound with *tert*-butyl peroxybenzoate gives a *tert*-butyl ether, which decomposes to a hydroxy compound on heating [*235*].

Bis(trimethylsilyl) peroxide, $(CH_3)_3SiOOSi(CH_3)_3$, is prepared from trimethylsilyl chloride, 1,4-diaza[2,2,2]bicyclooctane, and Dabco's complex with 2 mol of hydrogen peroxide [*127*]. It is used alone [*228*] or in the presence of catalysts such as pyridinium dichromate [*236*]; trimethylsilyl trifluoromethanesulfonate, $CF_3SO_3Si(CH_3)_3$ [*228, 237*]; or tris(triphenylphosphine)ruthenium dichloride, $[(C_6H_5)_3P]_3RuCl_2$ [*236*]. This reagent oxidizes primary alcohols to aldehydes (in preference to the oxidation of secondary alcohols to ketones [*236*]), ketones to esters or lactones (***Baeyer–Villiger reaction***) [*238*], and nucleoside phosphites to phosphates [*228*]. All these oxidations require anhydrous conditions.

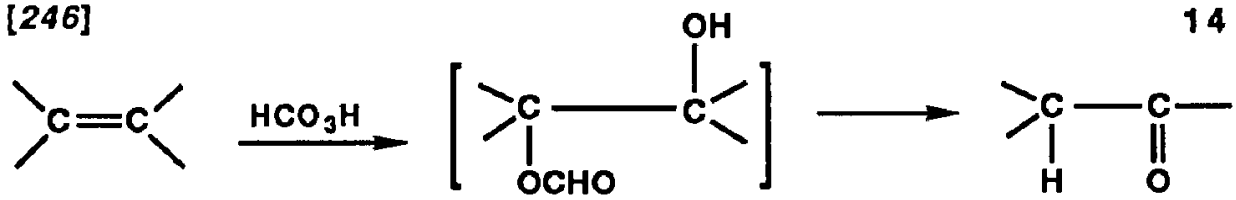
ORGANIC PEROXY ACIDS

Peroxyformic acid (performic acid), HCO_3H, is always prepared in situ from 25–30% hydrogen peroxide and 88 or 98–100% formic acid. At 26.5 °C, the conversion of formic acid into peroxyformic acid requires approximately 1 h (as proven by analysis of peroxyformic acid and hydrogen peroxide contents [*239*]). The preparation of peroxyformic acid is carried out in the presence of the compounds to be oxidized, most often alkenes and double-bond-containing carboxylic acids. After an induction period of

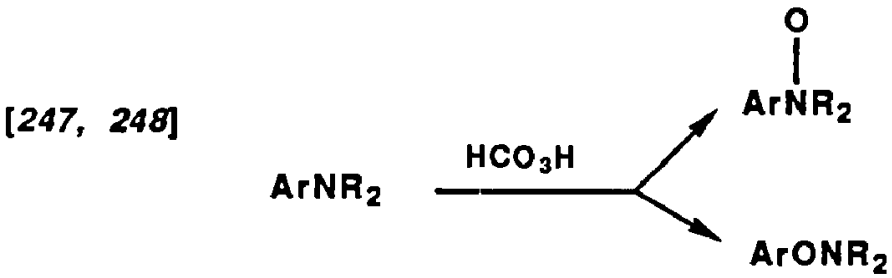
about 5 min, the reaction becomes very exothermic (and may even become explosive) and requires cooling, which is best accomplished with ice and water. The temperature is maintained at 40 °C, and after a few hours, the reaction of peroxyformic acid is finished. In the case of alkenes or other unsaturated compounds, the reaction products are formyl esters of diols. These products are not isolated but are heated with sodium or potassium hydroxide to give vicinal diols with *anti* stereochemistry [*101, 240, 241, 242, 243, 244*] (equation 13).



Sometimes the formyl ester of the diol is directly converted into a ketone [*245, 246*] (equation 14).



A much rarer application of performic acid is the transformation of 2- or 4-dialkylaminoperhalopyridines into either amine oxides or *N,N*-dialkylhydroxylamines [*247, 248*] (equation 15).



Peroxyacetic acid (peracetic acid), CH_3CO_3H, can be formed in situ from 30 or 90% hydrogen peroxide, usually in the presence of catalytic amounts of sulfuric or perchloric acid and sometimes also in the presence of acetic anhydride. The reaction of hydrogen peroxide with acetic acid to form peroxyacetic acid is reversible. The presence of substrate to be oxidized drives the oxidation to completion at moderate temperatures (25–70 °C). External cooling is frequently necessary, because the reaction is strongly exothermic.

Peroxyacetic acid is commercially available as 40–45% solutions in acetic acid. Such a reagent is prepared by adding 1 mol of 90% hydrogen peroxide to a cooled mixture of 1.5 mol of glacial acetic acid and 1% of

sulfuric acid (based on the total weight). After 4 h, the reaction mixture contains 45% of peroxyacetic acid and 6% of hydrogen peroxide [*249*].

Reactions with such peroxyacetic acid solutions are carried out without solvents or in solutions in acetic acid, dichloromethane [*250, 251, 252*], chloroform [*148, 253, 254*], ethyl acetate [*225, 255*], or the dimethyl ether of ethylene glycol (dimethyl cellosolve) [*256*].

The most important applications of peroxyacetic acid are the epoxidation [*250, 251, 252, 254, 257, 258*] and *anti* hydroxylation of double bonds [*241, 252*]; the ***Dakin reaction*** of aldehydes [*259*]; the ***Baeyer–Villiger reaction*** of ketones [*148, 254, 258, 260, 261, 262*]; the oxidation of primary amines to nitroso [*153*] or nitrocompounds [*253*], of tertiary amines to amine oxides [*158, 263*], of sulfides to sulfoxides and sulfones [*264, 265*], and of iodo compounds to iodoso or iodoxy compounds [*266, 267*]; the degradation of alkynes [*268*] and diketones [*269, 270, 271*] to carboxylic acids; and the oxidative opening of aromatic rings to aromatic dicarboxylic acids [*256, 272, 271, 272, 273, 274*]. Occasionally, peroxyacetic acid is used for the dehydrogenation [*275*] and oxidation of aromatic compounds to quinones [*249*], of alcohols to ketones [*276*], of aldehyde acetals to carboxylic acids [*277*], and of lactams to imides [*225,255*]. The last two reactions are carried out in the presence of manganese salts. The oxidation of alcohols to ketones is catalyzed by chromium trioxide, and the role of peroxyacetic acid is to reoxidize the trivalent chromium [*276*].

Peroxytrifluoroacetic acid (trifluoroperacetic acid), CF_3CO_3H, is prepared from 90% hydrogen peroxide, trifluoroacetic acid, and, usually, trifluoroacetic anhydride. Trifluoroacetic acid is a very strong acid so that no catalyst is needed for its conversion into peroxytrifluoroacetic acid. A peroxy acid of lower concentration can also be obtained by using 30% hydrogen peroxide [*278, 279*]. Pure peroxytrifluoroacetic acid results from the addition of the calculated amount of trifluoroacetic anhydride to 90% hydrogen peroxide without solvent [*280*] or in dichloromethane [*281*]. Cooling of the reaction mixture is necessary. The amounts of peroxy acid and unreacted hydrogen peroxide are determined by iodometric and cerimetric titrations, respectively [*239*].

Peroxytrifluoroacetic acid is usually applied as its solution in trifluoroacetic acid. Other solvents are 1,2-dichloroethane [*280, 282*] and, especially, dichloromethane. To neutralize trifluoroacetic acid, sodium carbonate [*253, 283*] or disodium hydrogen phosphate [*284*] is used.

The scope of peroxytrifluoroacetic acid oxidations resembles that of peroxyacetic acid and other peracids, although sometimes the outcome may be different [*285*]. The advantage of peroxytrifluoroacetic acid is that it reacts faster than the other peroxy acids: peroxyacetic acid, peroxybenzoic acid, *m*-chloroperoxybenzoic acid [*286*], and peroxyformic acid [*285*].

Peroxytrifluoroacetic acid is used for the epoxidation [*283, 287*] and *anti* hydroxylation [*285, 288*] of alkenes; the ***Baeyer–Villiger oxidation*** of

ketones [*280, 282, 284, 289*]; and especially the oxidation of primary amines [*253, 278, 281, 285, 290*] and nitroso compounds [*278, 291*] to nitro compounds, of tertiary amines to amine oxides [*158, 248*], and of sulfides to sulfoxides and sulfones [*279*]. In the presence of cobalt salts, benzene is converted into phenyl trifluoroacetate [*292*].

Peroxybenzoic acid (perbenzoic acid), $C_6H_5CO_3H$ (mp 41–43 °C), is commercially available. It is prepared from dibenzoyl peroxide according to equation 16 [*293*] and is obtained as a solution in chloroform. The peroxyacid content of the solution can be determined iodometrically [*293*].

[*293*] 16

$$(C_6H_5COO)_2 \xrightarrow{CH_3ONa} C_6H_5CO_2CH_3 + C_6H_5CO_3Na \xrightarrow{H_2SO_4} C_6H_5CO_3H$$

Solid peroxybenzoic acid is obtained by evaporation of the chloroform under reduced pressure. Better procedures for the preparation of peroxybenzoic acid are the reaction of benzoyl chloride with sodium peroxide [*294*] and the treatment of benzoic acid with 70% hydrogen peroxide in the presence of methanesulfonic acid [*176*]. Peroxybenzoic acid can also be prepared in situ from benzaldehyde and oxygen [*295*] or ozone [*112*].

Oxidations with peroxybenzoic acid are carried out in solutions in dichloromethane, chloroform, benzene, ether, or ethyl acetate at or below room temperature and include epoxidation of double bonds [*295, 296, 297, 298, 299, 300, 301*], oxidation of benzaldehydes to carboxylic acids or phenols [*302*], the ***Baeyer–Villiger reaction*** of ketones [*303, 304, 305, 306, 307*], and oxidation of sulfides to sulfoxides [*308, 309*]. Peroxybenzoic acid is also used for the *anti* hydroxylation of double bonds [*310*], the oxidation of pyrrolidines to pyrrolidones [*311*] and of pyrroles to succinimides [*311*], and the preparation of azoxy compounds from azo compounds [*312*].

***m*-Chloroperoxybenzoic acid (*m*-chloroperbenzoic acid), *m*-$ClC_6H_4CO_3H$,** is commercially available in 80–85% purity (mp 92–94 °C dec). It is prepared from *m*-chlorobenzoyl chloride and sodium peroxide [*294*] or sodium hydrogen peroxide [*313*].

Oxidations with *m*-chloroperoxybenzoic acid are carried out in solutions in hexane, dichloromethane, chloroform, methanol, or tetrahydrofuran at temperatures ranging from –78 to 40 °C. The applications of *m*-chloroperoxybenzoic acid are epoxidation [*287, 314, 315, 316*]; the ***Baeyer–Villiger reaction*** [*286, 315, 317, 318*]; and the oxidation of primary amines to nitro compounds [*319*], of tertiary amines to amine oxides [*320*], of sulfides to sulfoxides [*321, 322, 323, 324*], and of selenides to selenones [*325*]. Secondary alcohols are oxidized to ketones in the presence of hydrogen chloride [*326*], and acetals are oxidized to esters with boron trifluoride etherate as a catalyst [*327*]. The addition of potassium fluoride to reaction mixtures facilitates product isolation, because both *m*-chlorobenzoic acid and the unreacted *m*-chloroperoxybenzoic acid are precipitated

as solids from the solutions in dichloromethane [*315*]. The results of oxidations by *m*-chloroperoxybenzoic acid resemble those of other peroxyacids, although some differences are found in the regiochemistry [*286*] and the stereochemistry of the products [*287*].

***p*-Nitroperoxybenzoic acid, *p*-$O_2NC_6H_4CO_3H$** (mp 155–156 °C), is prepared from *p*-nitrobenzaldehyde and ozone [*112*] or from *p*-nitrobenzoyl chloride and sodium peroxide [*229*]. In addition to its use for the stereoselective epoxidations of allylic alcohols [*328*], *p*-nitroperoxybenzoic acid is also used for the highly regio- and stereoselective hydroxylation of hydrocarbons at tertiary carbons [*329*].

Peroxyphthalic acid, *o*-$C_6H_4(CO_2H)CO_3H$, is obtained from phthalic anhydride and hydrogen peroxide [*330*] or sodium hydrogen peroxide [*331*] and is applied usually in ethereal solutions to epoxidations [*330, 332*], the ***Baeyer–Villiger reaction*** [*333, 334*], and oxidations of sulfides to sulfoxides [*163, 335*] and sulfones [*336, 337*]. The oxidation of sulfides to sulfones takes precedence over epoxidation, as evidenced by the fact that unsaturated ketone thioacetals are oxidized to unsaturated disulfones [*337*].

Peroxymaleic acid, *cis*-$HO_2CCH=CHCO_3H$, is prepared from 90% hydrogen peroxide and maleic anhydride [*338*], and **peroxydichloromaleic acid, *cis*-$HO_2CCCl=CClCO_3H$,** from 90% hydrogen peroxide and dichloromaleic anhydride [*339*]. Both oxidizing agents are used in solutions in dichloromethane. Peroxymaleic acid oxidizes alkenes to epoxides [*338*], ketones to esters [*338*], primary aromatic amines to nitro compounds [*338*], and sulfoxides to sulfones [*338*]. Peroxydichloromaleic acid oxidizes 3-chloropyridazine to its 1-oxide [*339*].

Peroxypropionic acid ($C_2H_5CO_3H$) [*340*], **peroxylauric acid ($C_{11}H_{23}CO_3H$)** [*174*], and other aliphatic peroxy acids [*341*] are used rarely, and the results do not differ appreciably from those obtained from more common peracids. The same is true of **peroxypentafluorobenzoic acid, $C_6F_5CO_3H$,** which is obtained from pentafluorobenzaldehyde and ozone and is used for epoxidations; the Baeyer–Villiger reaction; and the preparation of amine oxides, sulfoxides, and sulfones [*342*].

Benzeneperoxyseleninic acid, $C_6H_5Se(O)OOH$, is prepared in situ from benzeneseleninic acid and 30% hydrogen peroxide in tetrahydrofuran or methylene chloride. This reagent oxidizes cyclic ketones to lactones, sometimes with better results than those with other oxidants [*343*].

DERIVATIVES OF GROUP 1 ELEMENTS

Elemental copper is used as a dehydrogenation catalyst for the conversion of alcohols into aldehydes or ketones [*344*]. Its efficiency is en-

hanced when it is applied on large-surface-area supports and in the presence of silver [*345*].

Copper bronze (finely ground copper, which may lose its activity on aging) is a hydrogenation–dehydrogenation catalyst in the ***Guerbet reaction***, in which a primary aliphatic alcohol, in the presence of sodium and copper, is dehydrogenated to the corresponding aldehyde. The aldehyde undergoes aldol condensation and subsequent dehydration, and the resulting α,β-unsaturated aldehyde is reduced by the hydrogen formed to a saturated alcohol [*346*]. The reaction requires temperatures around 300 °C and autoclaves that will stand the autogenous pressure (50–60 atm). A classical example is the preparation of 2-ethylhexanol from butanol [*346*].

Cuprous chloride, CuCl (mp 430 °C), when complexed with amines such as pyridine or phenanthroline, catalyzes the oxidation of alcohols to aldehydes and ketones by air [*347*]. In the presence of palladium dichloride, $PdCl_2$, in aqueous dimethylformamide, terminal alkenes are converted by oxygen into methyl ketones [*348*].

Copper oxide, CuO, is an oxidant for the conversion of alcohols into aldehydes or ketones [*349*] and for the transformation of hydrazo compounds into azo compounds [*350*].

Copper sulfate, $CuSO_4 \cdot 5H_2O$, is used for the oxidative coupling of terminal acetylenes [*58*]; for the conversion of α-hydroxy ketones (acyloins) into α-diketones [*351, 352*]; and, in cooperation with potassium peroxydisulfate, for the selective oxidation of methyl groups on benzene rings to aldehyde groups [*353*].

Copper chromite, $CuCr_2O_4$, and mixtures of cupric oxide with chromium sesquioxide and special additives (the ***Adkins*** catalyst), dehydrogenate primary alcohols to aldehydes [*354, 355*] and secondary alcohols to ketones [*354, 355, 356*].

Copper acetate, $Cu(OCOCH_3)_2$ or **$Cu(OCOCH_3)_2 \cdot H_2O$,** resembles copper sulfate in its oxidizing properties and is used for the oxidative coupling of terminal acetylenes [*58, 357*] and for the conversion of acyloins into α-diketones [*358, 359*]. Its presence favorably affects the acetoxylation of toluenes to benzyl acetates by sodium persulfate [*360*].

Copper carbonate, basic, $CuCO_3 \cdot Cu(OH)_2$, causes the hydroxylation of benzoic acids exclusively in the *ortho* position to produce salicylic acids [*361*].

Silver, Ag, (as well as **silver oxide, Ag_2O,** and **silver nitrate, $AgNO_3$**), is used as a catalyst in the oxidation of aromatic aldehydes to carboxylic acids in the presence of alkalies (***Cannizzaro reaction***) [*362, 363, 364*].

Silver oxide (argentous oxide), Ag_2O, is a brown-black powder. It is available commercially or can be prepared by treatment of a solution of silver nitrate with a solution of potassium hydroxide. The resulting precipitate is decanted and washed with distilled water until no nitrate ions

are detectable in the supernatant liquid. Ultimately, the precipitate, hydrated silver oxide, is filtered with suction; washed with water, alcohol, and ether; and dried in the air. If the oxidations are carried out in an aqueous solution, silver oxide (hydroxide) is prepared in situ from silver nitrate and sodium or potassium hydroxide.

The domain of oxidations with silver oxide includes the conversion of aldehydes into acids [*63, 206, 362, 365, 366, 367*] and of hydroxy aromatic compounds into quinones [*171, 368, 369*]. Less frequently, silver oxide is used for the oxidation of aldehyde and ketone hydrazones to diazo compounds [*370, 371*], of hydrazo compounds to azo compounds [*372*], and of hydroxylamines to nitroso compounds [*373*] or nitroxyls [*374*] and for the dehydrogenation of CH–NH bonds to –C=N– [*375*]. Similar results with **silver carbonate** are obtained in oxidations of alcohols to ketones [*376*] or acids [*377*] and of hydroxylamines to nitroso compounds [*378*].

Argentic oxide, AgO, which is prepared by the electrolysis of silver nitrate in nitric acid [*379*], converts aromatic methyl homologues into aldehydes [*380*], primary alcohols into aldehydes [*380*] or acids [*381*], aldehydes into acids [*382*], primary amines into aldehydes and nitriles [*381*], and phosphines into phosphine oxides [*381*].

DERIVATIVES OF GROUP 2 ELEMENTS

Mercuric bromide, $HgBr_2$ (mp 236 °C), oxidizes methylene groups that are adjacent to double bonds or aromatic rings to carbonyls [*11*].

Mercuric oxide, HgO (yellow modification or the less reactive red modification), resembles silver oxide in its oxidizing properties. This reagent transforms phenols and hydroquinones into quinones [*383, 384*] and is used especially for the conversion of hydrazones into diazo compounds [*385, 386, 387, 388, 389, 390, 391, 392*]. Dihydrazones of α-diketones furnish acetylenes [*393, 394, 395, 396*]. *N*-Aminopiperidines are dehydrogenated to tetrazenes [*397*] or converted into hydrocarbons [*398*].

Mercuric acetate, $Hg(OCOCH_3)_2$ (mp 179–182 °C), is used for dehydrogenations, resulting in the introduction of double bonds into the α positions with respect to conjugated systems [*399, 400*], and for the dehydrogenation of amines to imines [*401, 402*]. The reagent can also demethylate tertiary amines to secondary amines [*403*] and introduce acetoxyl groups into the α positions with respect to double bonds [*404*].

Mercurous trifluoroacetate, $HgOCOCF_3$, converts ketone monohydrazones into acetylenes [*405*].

Mercuric trifluoroacetate, $Hg(OCOCF_3)_2$, parallels the actions of mercuric oxide. It oxidizes hydroquinones to quinones [*383*] and hydrazones to diazo compounds [*406*].

DERIVATIVES OF GROUP 3 ELEMENTS

Aluminum chloride (anhydrous), $AlCl_3$, is used successfully for the dehydrogenative cyclization of aromatic polynuclear compounds [*407, 408*].

Thallium trinitrate, $Tl(NO_3)_3 \cdot 3H_2O$ (mp 102–105 °C), oxidizes phenols and dihydroxy aromatic compounds to quinones [*409*]; acetylenes to α-hydroxy ketones, α-diketones, or carboxylic acids [*413*]; and methyl ketones to α-keto acids [*414*].

Thallium monoacetate, $TlOCOCH_3$ (hygroscopic), behaves similarly to silver acetate or silver benzoate. In the presence of iodine, it accomplishes stereoselective hydroxylations of alkenes [*410*].

Thallium triacetate, $Tl(OCOCH_3)_3 \cdot 1.5H_2O$ (mp 182 °C), like the monoacetate, is used for the stereoselective acetoxylation of alkenes [*411*] and for oxidations of alkenes to epoxides [*412*].

All thallium compounds are highly toxic and must be handled with utmost care.

DERIVATIVES OF GROUP 4 ELEMENTS

Ammonium cerium nitrate (ceric ammonium nitrate), $(NH_4)_2Ce(NO_3)_6$, a newcomer to the arena of oxidants, is useful for the acetoxylation of aromatic side chains in benzylic positions [*415, 416*] and for the oxidation of methylene or methyl groups that are adjacent to aromatic rings to carbonyl groups [*238, 415, 417*]. The reagent also oxidizes alcohols to aldehydes [*418, 419, 420, 421*] and phenols to quinones [*422, 423*], cleaves vicinal diols to ketones and α-hydroxy ketones to acids [*424, 425*], and converts diaryl sulfides into sulfoxides [*426*]. A specialty of ammonium cerium nitrate is the oxidative recovery of carbonyl compounds from their oximes and semicarbazones [*422, 427*] and of carboxylic acids from their hydrazides [*428*] under mild conditions.

Ammonium cerium sulfate (ceric ammonium sulfate), $(NH_4)_2Ce(SO_4)_4 \cdot 2(NH_4)_2SO_4 \cdot 2H_2O$, converts aromatic polynuclear hydrocarbons into quinones [*429*].

Lead dioxide (lead superoxide), PbO_2, and red lead, Pb_3O_4, are used only to a limited extent. PbO_2 is used mainly for the oxidation of phenols to quinones [*368, 430, 431*] and of aromatic methyl groups to carboxyls [*432*]. Red lead, Pb_3O_4, in acetic acid oxidizes α-hydroxy acids to carbonyl compounds [*143, 433*] and cleaves vicinal diols to carbonyl compounds [*433*]. In this respect, red lead acts as lead tetraacetate in situ [*434*]. Lead oxide, Pb_3O_4, is also used in the preparation of lead tetraacetate and tetrakis(trifluoroacetate) [*435*].

Lead tetraacetate, $Pb(OCOCH_3)_4$, a white hygroscopic crystalline compound, is easily hydrolyzed with water to lead dioxide. Therefore, oxidations have to be carried out in strictly anhydrous solvents such as benzene, dioxane, and glacial acetic acid, usually at room temperature or at slightly elevated temperatures. In reactions of lead tetraacetate, acetoxyl radicals are the reactive species. The addition of acetoxy radicals across double bonds produces vicinal diacetates [*436*], and their attack at the benzylic positions and at the α positions with respect to carbonyl groups produces benzylic acetates [*434, 437*] and α-acetoxy ketones [*438, 439*], respectively. Lead tetraacetate also causes one-electron oxidations resulting in the formation of quinones from phenols [*369, 440*] and from aromatic amino compounds with *p*-amino groups [*441*]. Primary alcohols are dehydrogenated to aldehydes [*442*], and primary amines are converted into nitriles [*443, 444*]. Ketone hydrazones are transformed into diazo compounds [*445*]. A very important application of lead tetraacetate is the cleavage of the carbon chains in vicinal diols in nonaqueous media [*446, 447, 448*].

Lead tetrakis(trifluoroacetate), $Pb(OCOCF_3)_4$, which is prepared from red lead oxide (Pb_3O_4), trifluoroacetic acid, and trifluoroacetic anhydride [*435*], has very limited applications. It converts alkylbenzenes into benzylic trifluoroacetates [*435*] and benzene and its derivatives into phenyl trifluoroacetates [*435, 449*].

DERIVATIVES OF GROUP 5 ELEMENTS

Nitrous anhydride (nitrogen sesquioxide), N_2O_3, is obtained by the reduction of nitric acid by heating with starch or arsenic oxide, As_2O_3 [*450*]. This reagent is used for the oxidation of a methylene group flanked by two carbonyl or carboxyl groups to a carbonyl group [*450*].

Nitrous acid, HNO_2, is stable only at low temperatures. It is prepared in situ from sodium or potassium nitrite and dilute sulfuric or hydrochloric acid. This reagent is used for the oxidation of *p*-aminophenols to quinones [*451*].

Alkyl nitrites, RONO, such as ethyl nitrite, C_2H_5ONO; butyl nitrite, C_4H_9ONO; and amyl (pentyl) nitrite, $C_5H_{11}ONO$, are commercially available. These reagents are obtained from alkaline nitrites, alcohols, and sulfuric acid and act like nitrous anhydride. Methylene groups that are sufficiently activated by two adjacent aromatic rings or two carbonyl or carboxyl groups are converted into carbonyl groups via nitroso and isonitroso compounds (oximes) [*452*].

Dinitrogen tetroxide, N_2O_4, a light-brown gas or liquid (bp 21.5–22.5 °C), is commercially available and is prepared from nitrososulfuric acid and potassium nitrate [*453*] or, more simply, by the thermal decomposition

of lead nitrate [*454*]. Dinitrogen tetroxide is utilized for the oxidation of perfluoroalkyl iodides to perfluorocarboxylic acids [*455*] and of benzylic alcohols to ketones [*456*]. A mixture of predominantly dinitrogen tetroxide and nitrous anhydride, N_2O_3, produced by heating fuming nitric acid, concentrated sulfuric acid, and arsenous oxide, is applied to a clean-cut transformation of hydroquinones into quinones [*457*].

Nitric acid, HNO_3, is available as concentrated (68%) nitric acid (*d* 1.41, azeotropic mixture with water, bp 120.5 °C), fuming (100%) nitric acid (*d* 1.52), and, rarely, red fuming nitric acid, containing nitrogen oxides. For many oxidations, dilute nitric acid (approximately 35%) obtained by dilution with water in a 1:1 ratio is employed. Most of the oxidations are carried out at atmospheric pressure in glass equipment or in porcelain dishes. If higher temperatures are needed, either sealed glass tubes or stainless steel or glass-lined autoclaves must be used.

Nitric acid is a very strong but not very selective oxidant. The advantages of its use are simple and usually clean-cut isolation of the products. The obnoxious fumes generated during the oxidations are a disadvantage. The main applications of nitric acid are the dehydrogenation (aromatization) of dihydropyridines [*458*]; the degradation of aromatic rings to carboxylic acids [*459*]; the oxidation of aromatic side chains to carboxyls [*460, 461, 462, 463, 464*]; the oxidation of alcohols [*465, 466, 467, 468, 469*], aldehydes [*467,470*], ketones [*471*], and esters [*472*] to carboxylic acids; and the oxidation of aromatic amines to quinones [*473*], thiols to sulfonic acids [*474*], and iodo compounds to iodoso compounds [*475*]. In combination with silver oxide, nitric acid is used for the oxidative cleavage of ozonides to carboxylic acids [*77*].

Ammonium nitrate, NH_4NO_3, oxidizes acyloins to α-diketones in the presence of catalytic amounts of cupric acetate [*476*].

Lead nitrate, $Pb(NO_3)_2$ (mp 470 °C dec), converts benzylic halides into the corresponding carbonyl compounds [*477*].

Vanadium pentoxide, V_2O_5 (mp 690 °C), is one of the strongest catalysts used for dehydrogenations [*478*] and oxidations with air or oxygen [*3, 479*], especially in the gas phase and at very high temperatures. It also catalyzes the hydroxylation of alkenes with aqueous hydrogen peroxide [*134*].

Vanadyl acetylacetonate, $VO(acac)_2$, catalyzes stereoselective epoxidations of unsaturated alcohols [*216, 328*].

Arsenic pentoxide, As_2O_5, functions as an oxidant in the ***Skraup synthesis*** of quinolines [*480*].

Bismuth sesquioxide, Bi_2O_3, in the presence of acetic acid, oxidizes acyloins to α-diketones in high yields [*481*].

Sodium bismuthate, $NaBiO_3$, cleaves vicinal diols to dicarbonyl compounds [*482, 483*] but offers no advantage over the more common oxidants of vicinal diols, such as lead tetraacetate and periodic acid.

Potassium nitrosodisulfonate (Fremy salt), $\cdot ON(SO_3K)_2$, is a free radical capable of converting phenols [*487, 488, 489*] and aromatic amines [*490*] into quinones.

DERIVATIVES OF GROUP 6 ELEMENTS

Potassium hydroxide, KOH, is applied to the conversion of fatty alcohols into salts of fatty acids (having the same number of carbon atoms) [*484*] and to the hydroxylation of aromatic compounds of low electron density, such as nitrobenzene [*485*] and pyridine [*486*].

Sulfur, S_x, is a dehydrogenating agent that converts compounds containing six-membered rings into their aromatic analogues. In the reaction, sulfur is reduced to hydrogen sulfide [*491, 492*]. Such dehydrogenations occur at lower temperatures compared with those by selenium [*493*] or noble metals [*494, 495, 496, 497*].

The most useful application of sulfur is the ***Willgerodt reaction***—the conversion of ketones into acids having the same number of carbon atoms [*498*]. The conversion is accomplished by heating ketones with sulfur and ammonium sulfide [*499, 500, 501, 502*] at 160–210 °C under pressure. The ***Kindler modification*** avoids operation under pressure by using sulfur and high-boiling secondary amines such as morpholine, instead of ammonium sulfide [*503, 504*]. Such a reaction carried out at reflux gives the thiomorpholides, which are subsequently hydrolyzed to acids.

A peculiar oxido-reductive reaction takes place when *p*-aminotoluene is heated with sodium polysulfide; the product is *p*-aminobenzaldehyde [*505*].

Sulfuric acid, H_2SO_4, rarely acts as an oxidant. It can be used for the dehydrogenative coupling of aromatic rings [*395*]. Equally rare is the oxidation of a sulfide to a sulfoxide with **sulfuryl chloride, SO_2Cl_2** [*506*].

Selenium, Se (its red modification), has been successfully employed for dehydrogenations of six-membered rings to aromatic systems. Compared with sulfur, selenium requires higher temperatures. Consequently, side reactions such as rearrangements occur [*493*].

Selenium dioxide, SeO_2 (mp 315 °C, sublimes), and **selenious acid, H_2SeO_3,** which is obtained by the evaporation of an aqueous solution of SeO_2 [*507, 508*], are very selective oxidants. They are capable of mild dehydrogenation to form double bonds [*375*] and can oxidize alkenes and acetylenes to vicinal dicarbonyl compounds [*509, 510*] and allylic ethers to aldehydes [*511*]. The most important applications are conversions of alkenes into allylic alcohols [*512*]; of benzylic, methyl, or methylene groups into carbonyl groups [*513, 514, 515*]; and of carbonyl compounds into α-

dicarbonyl compounds [*507, 508, 516, 517, 518, 519, 520*]. Other oxidations, such as the conversion of sulfides into sulfoxides, are exceptions [*521*].

Selenium dioxide oxidations may be accomplished by heating with neat substrates [*519*], but more often, they are carried out in solvents such as water, *tert*-butyl alcohol, ethanol, dioxane, acetic acid, and acetic anhydride. The solvent used often affects the outcome of the reaction. The use of acetic acid or acetic anhydride favors oxidation to acetates (and thence to alcohols), whereas in water or dioxane, carbonyl compounds are usually formed. An unpleasant feature of oxidations with selenium dioxide is the formation of red colloidal selenium, which cannot always be separated by distillation but can be removed by treatment of the product with potassium cyanide [*522*], mercury [*523*], or deactivated Raney nickel [*524*].

Benzeneseleninic anhydride, $C_6H_5Se(O)O(O)SeC_6H_5$, which is prepared in situ from diphenyldiselenide and *tert*-butyl hydroperoxide, is used for the oxidation of alcohols to aldehydes or ketones [*525*]. This reagent is a suitable dehydrogenating agent for the introduction of double bonds α to carbonyl groups [*526*] and the regeneration of ketones from their oximes, semicarbazones, and phenylhydrazones [*527*].

Molybdenum hexafluoride, MoF_6 (mp 17 °C, bp 35 °C) [*528*], and **molybdenum oxychloride, $MoOCl_3$,** which is prepared by the partial hydrolysis of molybdenum pentachloride [*528*], are suitable for the recovery of ketones from their dimethylhydrazones and tosylhydrazones under very mild conditions [*528*].

Molybdenum hexacarbonyl, $Mo(CO)_6$ [*328*], and **molybdenum acetylacetonate, $MoO_2(acac)_2$** [*530*], catalyze the stereoselective epoxidation of allylic alcohols with *tert*-butyl hydroperoxide.

Oxodiperoxymolybdenum–pyridine–hexamethylphosphoric triamide, $MoO_5 \cdot C_5H_5N \cdot HMPA$ (MoOPH), which is prepared from molybdenum trioxide, MoO_3 [*531,532*], hydroxylates the enolates of ketones and esters in the α position with respect to the carbonyl groups [*531, 532, 533*] and, in the presence of mercuric acetate, converts acetylenes into α-dicarbonyl compounds [*534*].

Tungsten hexafluoride, WF_6 (mp 2.5 °C, bp 17 °C) [*529*], resembles MoF_6 and $MoOCl_3$ in its oxidative properties. However, less exotic reagents such as ozone, ammonium cerium sulfate, or zinc dichromate may be used for a similar purpose.

Chromium trioxide [chromium(VI) oxide, chromic acid, or chromic anhydride], CrO_3 (dark red crystals, mp 195 °C), is one of the most powerful and universal oxidants. It is applied in solutions in acetic acid, dilute sulfuric acid, a mixture of acetic acid and dilute sulfuric acid, dilute sulfuric acid and acetone (**Jones reagent**), acetic anhydride and acetic acid (**Fieser reagent**) [*535*], water, water and ether [*536, 537, 538*], dichloromethane [*539*],

benzene [*540*], pyridine [*541*], dimethylformamide (DMF) [*542*], and hexamethylphosphoric triamide (HMPA) [*543*]. It provides 1.5 equivalents of oxygen per mole.

Oxidations with chromic oxide encompass hydroxylation of methylene [*544*] and methine [*544, 545, 546*] groups; conversion of methyl groups into formyl groups [*539, 547, 548, 549*] or carboxylic groups [*550, 551*] and of methylene groups into carbonyls [*275, 552, 553, 554, 555*]; oxidation of aromatic hydrocarbons [*556, 557, 558*] and phenols [*559*] to quinones, of primary halides to aldehydes [*540*], and of secondary halides to ketones [*560, 561*]; epoxidation of alkenes [*562, 563, 564*]; and oxidation of alkenes to ketones [*565, 566*] and to carboxylic acids [*567, 568, 569*].

The main applications of oxidation with chromium trioxide are transformations of primary alcohols into aldehydes [*184, 537, 538, 543, 570, 571, 572, 573*] or, rarely, into carboxylic acids [*184, 574*], and of secondary alcohols into ketones [*406, 536, 542, 543, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584*]. **Jones reagent** is especially successful for such oxidations. It is prepared by diluting with water a solution of 267 g of chromium trioxide in a mixture of 230 mL of concentrated sulfuric acid and 400 mL of water to 1 L to form an 8 N CrO_3 solution [*565, 572, 579, 581, 585, 586*]. Other oxidations with chromic oxide include the cleavage of carbon–carbon bonds to give carbonyl compounds or carboxylic acids [*482, 566, 567, 569, 580, 587, 588*], the conversion of sulfides into sulfoxides [*541*] and sulfones [*589*], and the transformation of alkyl silyl ethers into ketones or carboxylic acids [*590*].

Chromium trioxide–pyridine complex or dipyridine chromium(VI) oxide (Collins reagent), $CrO_3 \cdot 2C_5H_5N$, is commercially available. It forms red crystals and is prepared by adding chromic oxide to an excess of anhydrous pyridine cooled below 20 °C. Efficient stirring is essential to prevent local overheating, which might result in flashes and in flaming. (This overheating would occur if pyridine were added to chromic oxide [*591, 592, 593, 594*]). The complex is practically insoluble in carbon tetrachloride, benzene, and ether [*591*] and sparingly soluble in chloroform (4.5 g/100 mL), pyridine (6.1 g/100 mL), and *cis*-1,2-dichloroethylene (7.1 g/100 mL). The best solvent is dichloromethane (12.5 g/100 mL) [*595*]. A solution of dipyridine chromium(VI) oxide in dichloromethane is conveniently prepared by adding 1 mol of chromic oxide to a solution of 2 mol of pyridine in dichloromethane [*596*]. The complex may also be formed on the surface of silica gel by adding pyridine to silica gel impregnated with chromic oxide [*597*].

Oxidations with dipyridine chromium(VI) oxide are carried out (usually at room temperature) in solutions in dichloromethane. Primary alcohols, including allylic and benzylic alcohols, are oxidized to aldehydes [*594, 595, 596, 597, 598, 599, 600*] and secondary alcohols to ketones [*592, 595,*

597, 599]. Methylene groups next to double [593] or triple [601] bonds are converted into carbonyl groups to yield α,β-unsaturated ketones.

Chromium trioxide–3,5-dimethylpyrazole complex, $CrO_3 \cdot C_5H_8N_2$, is prepared in situ by adding 1 mol of 3,5-dimethylpyrazole to a suspension of 1 mol of chromium trioxide in dichloromethane at room temperature. The scope and limitations of this oxidant are similar to those of the chromium trioxide–pyridine complex: the oxidation of primary alcohols to aldehydes and of secondary alcohols to ketones at room temperature [602].

Pyridinium chlorochromate (PCC), $C_5H_5N \cdot HCl \cdot CrO_3$, mp 205 °C (dec), which is commercially available, is prepared by adding chromium trioxide to a solution of pyridine in hydrochloric acid [603]. The preparation is easier than that of the chromium trioxide–pyridine complex.

Oxidations by pyridinium chlorochromate resemble those by dipyridine chromium(VI) oxide, both in scope and the mild conditions required. At room temperature, primary alcohols give aldehydes [604, 605], secondary alcohols afford ketones [605], allylic and benzylic methylene groups are oxidized to carbonyl groups [606, 607], enol ethers are converted into esters [608] or lactones [609], trimethylsilyl ethers of diphenols are transformed into quinones [610], and alkylboranes are converted into aldehydes [611].

4-Dimethylaminopyridinium chlorochromate, $4\text{-}(CH_3)_2NC_5H_4NH \cdot CrO_3Cl$, is a yellow-orange solid prepared by the addition of 1 mol of 4-dimethylaminopyridine to a solution of 1 mol of chromium trioxide in dilute hydrochloric acid. The reagent is light sensitive [530]. For the oxidation of allylic and benzylic alcohols to aldehydes in dichloromethane at room temperatures, 4–6 mol of 4-dimethylaminopyridinium chlorochromate is used. Saturated alcohols are not oxidized [530].

Poly(vinylpyridinium) chlorochromate (PVPCC) is obtained as a bright-orange solid by adding chromium trioxide and concentrated hydrochloric acid to an aqueous suspension of cross-linked poly(vinylpyridine) (PVP) resin (50–100 mesh). Oxidations of primary and secondary alcohols to carbonyl compounds are carried out on heating with a slight excess of the resin at 75–80 °C. The reaction is best carried out in cyclohexane [612].

Potassium chromate, K_2CrO_4, is used very rarely. It converts hydrazomethane into azomethane [613]. In the presence of hexamethylphosphoramide and crown ether, it transforms allylic and benzylic bromides into α,β-unsaturated aldehydes [614], and in the presence of dilute sulfuric acid, it oxidizes chlorohydroquinone to chloro-*p*-benzoquinone [615].

Silver chromate, Ag_2CrO_4, a reddish-brown precipitate prepared by adding an aqueous solution of silver nitrate to an aqueous solution of potassium chromate, is used with iodine for the preparation of α-iodoketones from alkenes [616].

Tetrabutylammonium chromate, $(C_4H_9)_4NHCrO_4$, is obtained as a

yellow-orange precipitate when aqueous solutions of chromium trioxide and tetrabutylammonium chloride are mixed. After having been dried, the reagent is used in organic solvents such as dichloromethane [*617*] and chloroform [*618*] for the oxidation of alcohols to carbonyl compounds. The reagent can be prepared and used in situ in a mixture of water and chloroform [*618*].

Tetrabutylammonium chlorochromate, $(C_4H_9)_4NCrO_3Cl$, is formed by adding a solution of chromium trioxide in concentrated hydrochloric acid to a solution of tetrabutylammonium hydrogen sulfate in 5 N hydrochloric acid at 0 °C. The dry compound is used in chloroform for the oxidation of alcohols to carbonyl compounds and the oxidative coupling of thiols to disulfides [*619*].

Sodium dichromate, $Na_2Cr_2O_7$, is applied not only in solutions in sulfuric acid but also in solutions in perchloric acid [*620, 621*], acetic acid [*622, 623, 624, 625, 626, 627, 628*], benzene, and dimethyl sulfoxide [*629*]. In the presence of tetrabutylammonium bisulfate, dichloromethane, used as a water-insoluble solvent, extracts the product from the aqueous phase (phase transfer) [*630*].

Sodium dichromate hydroxylates tertiary carbons [*620*] and oxidizes methylene groups to carbonyls [*622, 623, 625, 626, 631*]; methyl and methylene groups, especially as side chains in aromatic compounds, to carboxylic groups [*624, 632, 633, 634, 635*]; and benzene rings to quinones [*630, 636, 637*] or carboxylic acids [*638*]. The reagent is often used for the conversion of primary alcohols into aldehydes [*629, 630, 639*] or, less frequently, into carboxylic acids or their esters [*640*]; of secondary alcohols into ketones [*621, 629, 630, 641, 642, 643, 644*]; of phenylhydroxylamine into nitrosobenzene [*645*]; and of alkylboranes into carbonyl compounds [*646*].

Potassium dichromate, $K_2Cr_2O_7$, is applied under similar conditions as its sodium analogue to oxidize benzene rings to quinones [*647, 648, 649, 650*], methylene groups adjacent to aromatic rings to carbonyls [*514*], primary alcohols to aldehydes [*651, 652, 653*], secondary alcohols to ketones [*644, 652, 654, 655*], and aldehydes to acids [*656*]. Phenylhydroxylamine is transformed into nitrosobenzene [*657*], and an aromatic nitroso compound, into a nitro compound [*658*].

Sodium dichromate and potassium dichromate possess almost identical oxidative properties. Both reagents furnish an equivalent of three oxygen atoms, as the oxidation state of chromium changes from hexavalent to trivalent, through tetravalent and pentavalent chromium as intermediates. The molecular weights of both reagents are almost identical, because sodium dichromate crystallizes with two molecules of water of crystallization. In the presence of dilute sulfuric acid, the most common solvent, chromic acid, H_2CrO_4, is liberated. Standard 10% solutions of CrO_3 are known as a **Kiliani mixture** or a **Beckmann mixture**. The Kiliani mixture is obtained by dissolving 60 g of $Na_2Cr_2O_7 \cdot 2H_2O$ in dilute sulfuric acid, prepared by

adding 80 g of concentrated sulfuric acid to 270 mL of water (not the other way around). The Beckmann mixture is prepared by dissolving 60 g of $K_2Cr_2O_7$ in dilute sulfuric acid (80 g of concentrated sulfuric acid and 270 mL of water).

Silver dichromate–pyridine complex (tetrapyridine silver dichromate), $Ag_2Cr_2O_7 \cdot 4C_5H_5N$, an orange-yellow solid prepared by adding a warm solution of potassium dichromate to a solution of silver nitrate in water and pyridine, oxidizes allylic and benzylic alcohols to aldehydes and acyloins to α-diketones [*659*].

Zinc dichromate trihydrate, $ZnCr_2O_7 \cdot 3H_2O$, is obtained as an orange-red solid by adding zinc carbonate to a cold solution of chromium trioxide in dilute sulfuric acid [*660*]. The applications are oxidations of acetylenes to α-diketones, of aromatic hydrocarbons to quinones, of alcohols to aldehydes, and of ethers to esters and the oxidative regeneration of carbonyl compounds from their oximes [*660*].

Pyridinium dichromate, $(C_5H_5NH)_2Cr_2O_7$, a stable bright-orange solid (mp 144–146 °C), is prepared by adding pyridine to a cooled solution of chromium trioxide in water at a temperature lower than 30 °C and by diluting the mixture with acetone [*603*]. The reagent is applied at room temperature in solutions in dichloromethane or dimethylformamide (DMF). In dichloromethane solutions, primary alcohols are oxidized to aldehydes and secondary alcohols to ketones [*603*]. In DMF solutions, allylic alcohols are oxidized to α,β-unsaturated aldehydes or ketones. Nonconjugated aldehydes are converted into carboxylic acids, when an excess of the reagent is used. Acid- and base-sensitive functional groups are not endangered [*603*].

α,β-Unsaturated aldehydes and trimethylsilyl cyanide give trimethylsilyl cyanohydrins, which are transformed by pyridinium dichromate into α-keto nitriles and ultimately give unsaturated γ-lactones [*661*]. In the presence of trimethylsilyl peroxide, primary alcohols are oxidized in preference to secondary alcohols in a ratio of 20:1 [*236*].

***Utmost care must be taken in preparing and handling pyridinium dichromate, because explosions have occurred even in aqueous media* [662].**

3-Carboxypyridinium dichromate and 4-carboxypyridinium dichromate, $(HO_2CC_6H_4NH)_2Cr_2O_7$, are prepared by adding nicotinic and isonicotinic acid, respectively, to aqueous solutions of chromium trioxide at 0–5 °C followed by acetone [*663*]. The orange-yellow solids (mp 215–217 and 250–253 °C, respectively) are applied in dichloromethane or in dichloromethane–pyridine solutions at room temperature to oxidize alcohols to carbonyl compounds, thiols to disulfides, and aromatic rings to quinones [*663*].

Quinolinium chlorochromate, $C_9H_7N \cdot HCl \cdot CrO_3$, is obtained as a yellowish-brown solid by addition of quinoline to a stirred mixture of chromic

acid and concentrated hydrochloric acid in water. When applied in dichloromethane, this reagent oxidizes primary alcohols in preference to secondary alcohols [*664*].

All the pyridine- and pyridine-analogue-containing hexavalent chromium compounds excel by giving good to very high yields under very mild conditions, usually at temperatures not higher than room temperature. In addition, these compounds are sometimes selective oxidants. The disadvantage is the necessity of often using a large excess of the reagent.

Chromyl chloride, $Cr_2O_2Cl_2$, a dark-red liquid (mp –96.5 °C, bp 117 °C, *d* 1.911), is prepared from chromium trioxide or sodium dichromate, hydrochloric acid, and sulfuric acid [*665*]. The reagent is used in solutions in carbon disulfide, dichloromethane, acetone, *tert*-butyl alcohol, and pyridine. Oxidations with chromyl chloride are often complicated by side reactions and do not always give satisfactory yields. The mechanism of the oxidation with chromyl chloride, the ***Etard*** reaction, is probably of free-radical nature [*666*]. Complexes of chromyl chloride with the compounds to be oxidized have been isolated [*666, 667, 668*].

The reaction of chromyl chloride with alkenes gives epoxides, chlorohydrins, chloroketones, and ketones [*668, 667, 668, 669, 670*] or aldehydes (in the presence of zinc) [*671, 672*]. Benzene homologues are oxidized to aldehydes [*667, 668*] or ketones [*666, 668, 673*]. Primary alcohols are converted into aldehydes [*674, 675*], and trimethylsilyl ethers of enols are transformed into α-hydroxy ketones [*676*].

***tert*-Butyl chromate, $(tert\text{-}C_4H_9O)_2CrO_4$,** results from the addition of chromium trioxide to ice-cooled *tert*-butyl alcohol and is used in benzene or petroleum ether solutions [*677*]. This reagent oxidizes primary alcohols to aldehydes at low temperatures [*678*]; but its applications are rare.

Acetyl chromate, $(CH_3CO)_2CrO_4$; trichloroacetyl chromate, $(CCl_3CO)_2CrO_4$; trifluoroacetyl chromate, $(CF_3CO)_2CrO_4$; and benzoyl chromate, $(C_6H_5CO)_2CrO_4$, are prepared from chromium trioxide and the respective anhydrides [*679, 680*]. Trifluoroacetyl chromate reacts with many solvents and with silicone stopcock grease.

Acyl chromates are used for epoxidation [*679*] and for the conversion of alkenes into aldehydes [*680*].

DERIVATIVES OF GROUP 7 ELEMENTS

Chlorine, Cl_2, a greenish-yellow gas (mp –101 °C, bp –34.1 °C) delivered in steel containers under a pressure of 6 atm at 21 °C, is extremely corrosive and toxic. The use of good hoods is imperative for any work involving chlorine. Applications of chlorine gas for oxidation purposes are rare; rather, its compounds such as sodium, potassium, and calcium hy-

pochlorites; *tert*-butyl hypochlorite; sodium chlorite; and sodium, potassium, silver, and barium chlorates are used. Chlorine is soluble in dichloromethane, chloroform, and carbon tetrachloride and is frequently applied in water, in which it is only sparingly soluble.

Oxidations by chlorine are limited to only few types of compounds. In organic solvents and pyridine [*681*] or hexamethylphosphoramide (HMPA) [*682*] as cosolvents, primary alcohols are oxidized to aldehydes and secondary alcohols to ketones [*681, 682*]. Secondary alcohols are oxidized in preference to primary alcohols [*681*]. Many oxidations with chlorine are carried out in aqueous media and involve sulfur-containing compounds. Mercaptans [*683*], alkyl thiolcarboxylates [*683*], thiocyanates [*684*], isothioureas [*684*], disulfides [*685*], and sulfinic acids [*686*] are transformed into sulfonyl chlorides. The chlorination of dimethyl disulfide in acetic anhydride yields methanesulfinyl chloride [*687*].

Sodium hypochlorite, NaOCl, is stable only as a very dilute aqueous solution (5.25%) and is commercially available under the name Clorox or bleach. This reagent can be prepared in situ by introducing chlorine into an aqueous solution of sodium hydroxide [*688*]. In the presence of tetrabutylammonium hydrogen sulfate, it is transformed into tetrabutylammonium hypochlorite, which is soluble in organic solvents [*689, 690*].

Sodium hypochlorite is used for the epoxidation of double bonds [*689, 691*]; for the oxidation of primary alcohols to aldehydes [*692*], of secondary alcohols to ketones [*693*], and of primary amines to carbonyl compounds [*692*]; for the conversion of benzylic halides into acids or ketones [*690*]; for the oxidation of aromatic rings to quinones [*694*] and of sulfides to sulfones [*695*]; and, especially, for the degradation of methyl ketones to carboxylic acids with one less carbon atom [*688, 696, 697, 698, 699*] and of α-amino acids to aldehydes with one less carbon [*700*]. Sodium hypochlorite is also used for the reoxidation of low-valence ruthenium compounds to ruthenium tetroxide in oxidations by ruthenium trichloride [*701*].

Potassium hypochlorite, KOCl, acts like sodium hypochlorite. This reagent is prepared in situ from potassium hydroxide and chlorine and oxidizes primary alcohols to aldehydes [*702*] and methyl ketones to carboxylic acids [*703*].

Calcium hypochlorite, $Ca(OCl)_2$, is a solid compound and is used for the epoxidation of double bonds [*704*] and the oxidation of alcohols to carbonyl compounds [*705*].

***tert*-Butyl hypochlorite, *tert*-C_4H_9OCl,** is obtained when chlorine is passed through a solution of *tert*-butyl alcohol in aqueous sodium hydroxide. The reagent is a liquid (bp 77–78 °C at 760 mm of Hg, d_{20}^{20} 0.910, n_D^{20} 1.403 [*706*]) and effects the dehydrogenation of amines to imines [*707*] and of alcohols to carbonyl compounds [*708, 709*] and the oxidation of sulfides to sulfoxides [*710*] and of selenides to selenoxides [*711*].

Sodium chlorite, $NaClO_2$, which is commercially available, oxidizes

aldehydes to carboxylic acids at room temperature [*69, 712*]. The byproducts, hypochlorous acid and chlorine dioxide, must be removed during the oxidation to prevent side reactions, especially when unsaturated aldehydes are involved. As scavenger of the byproducts, hydrogen peroxide [*712*], sulfuric acid [*69, 712*], dimethyl sulfoxide [*712*], or resorcinol [*69*] is used. Another application of sodium chlorite is the oxidation of aldehyde–bisulfite compounds to carboxylic acids in the presence of dimethyl sulfoxide and acetic anhydride [*713*]. Oxidations of aldehydes to acids with sodium chlorite are very selective and much cheaper than those with silver oxide.

Sodium chlorate, $NaClO_3$; potassium chlorate, $KClO_3$; silver chlorate, $AgClO_3$; and barium chlorate, $Ba(ClO_3)_2$, oxidize organic compounds only in the presence of catalysts, usually osmium tetroxide [*310, 714, 715, 716, 718*] or vanadium pentoxide [*716, 718*]. Because such oxidations do not occur without catalysts, it is likely that the real oxidants are osmium tetroxide and vanadium pentoxide, respectively, and that the function of the chlorates is reoxidation.

Such oxidants cause the *syn* hydroxylation of double bonds [*310, 714, 715, 716*] and convert triple bonds into vicinal carbonyls [*717*]. Other applications, such as the conversion of furfural into fumaric acid [*716, 718*] or the oxidation of hydroquinone to quinone [*719*], are rare.

Organochlorine compounds with chlorine bonded to nitrogen give different oxidation products, depending on the nature of the organic molecule.

***N*-Chlorosuccinimide, $C_4H_4ClNO_2$** (mp 144-146 °C), either alone [*709*] or in the presence of dimethyl sulfide [*720, 721*], dehydrogenates alcohols to carbonyl compounds.

Trichloroisocyanuric acid, $C_3Cl_3N_3O_3$ (mp 249–251 °C), converts ethers into esters [*722*], and **sodium *N*-chloro-*p*-toluenesulfonamide (Chloramine-T), p-$CH_3C_6H_4SO_2NClNa{\cdot}3H_2O$** (mp 167–170 °C), in the presence of osmium tetroxide, transforms alkenes into vicinal hydroxy sulfonamido compounds [*723*].

Bromine, Br_2, a dark brown liquid (mp –7.3 °C, bp 59.5 °C, *d* 3.1), forms crystalline molecular complexes with **dioxane, $C_4H_8O_2{\cdot}Br_2$** (mp 60–61 °C) [*724*]; **pyridine, $C_5H_5N{\cdot}Br_2$** (mp 62–63 °C) [*725*]; and **1,4-diazabicyclo[2,2,2]octane (Dabco), $C_6H_{12}N_2{\cdot}2Br_2$ (Dabco·2Br$_2$)** (mp 155–160 °C dec), that are very stable to light and moist air [*726, 727*]. Bromine can also be generated in situ from sodium bromate and sodium bromide in acidic solutions [*728*]. It is applied in aqueous media [*729, 730*] or organic solvents, such as dichloromethane [*682*], carbon tetrachloride [*731, 732*], ethanol [*733*], acetonitrile [*726*], or hexamethylphosphoric triamide (HMPA) [*682*].

Bromine dehydrogenates alcohols to carbonyl compounds [*682, 726, 729, 734*] (secondary alcohols in preference to primary alcohols [*682*]) and hydrazo compounds to azo compounds [*733*] and oxidizes sulfides to sulf-

oxides [*727, 728*] and disulfides to sulfonic acids [*730*]. Benzyl alkyl ethers are degraded to benzaldehyde [*731*].

Sodium hypobromite, NaOBr, is prepared in situ from bromine and aqueous sodium hydroxide under cooling. Its almost exclusive application is the degradation of methyl ketones to acids with one less carbon [*635, 735, 736, 737*]. Such degradation is achieved not only with methyl ketones but also with other alkyl ketones [*103, 160*]. Other oxidations, such as the conversion of hydroxylamines into nitroso compounds, are rare [*738*].

Sodium bromite, $NaBrO_2 \cdot H_2O$, a crystalline compound, oxidizes secondary alcohols to ketones [*739*] and sulfides to sulfoxides [*739*]. Primary alcohols are transformed into esters [*739*].

Sodium bromate, $NaBrO_3$, a white crystalline compound, converts acyloins into α-diketones under forcing conditions [*740*]. More often, this reagent is used as a reoxidant of ammonium cerium nitrate [*421*], cerium sulfate [*741*], or ruthenium trichloride [*741*] in oxidations of alcohols to aldehydes [*421*] or carboxylic acids [*741*].

Potassium bromate, $KBrO_3$, and hydrobromic acid are used in the in situ generation of bromine for the oxidation of primary alcohols to esters [*742*].

Organobromine compounds most frequently used for dehydrogenations and oxidations are *N*-bromoacetamide, **$CH_3CONHBr$** (mp 108–109 °C), and *N*-bromosuccinimide, **$C_4H_4BrNO_2$** (mp 180–183 °C), both of which are commercially available.

***N*-Bromoacetamide** is successfully applied to the oxidation of secondary alcohols in preference to allylic primary alcohols [*743*].

***N*-Bromosuccinimide** is used in the dehydrogenation of hydrazo compounds to azo compounds [*744*] and in the oxidative degradation of α-hydroxy acids to aldehydes or ketones [*745*]. This reagent also oxidizes alkyl trimethylsilyl ethers to esters or ketones [*744*].

In aqueous solutions, *N*-bromosuccinimide converts alkenes into bromohydrins or, ultimately, into epoxides (after the treatment of bromohydrins with alkali [*746*] or when the oxidation is done in alkaline media).

***N*-Bromobenzophenoneimine, $(C_6H_5)_2C{=}NBr$** (mp 38.5 °C) [*747*], which is prepared from benzophenoneimine, bromine, and alkalies, is used for the conversion of alcohols into carbonyl compounds [*748*].

Iodine, I_2 (dark-violet crystals, mp 113.5 °C), sublimes, and its vapor is violet. It is suitable for the oxidation of thiols and thiol-group-containing compounds to the corresponding disulfides [*749*].

Sodium hypoiodite, NaOI, which is used for the iodoform reaction [*750*], is prepared in situ from iodine and sodium hydroxide.

Iodine and silver oxide oxidize alkenes to epoxides [*751*], whereas **iodine and silver chromate** convert alkenes into α-iodoketones [*610*].

Potassium hypoiodite, KOI, which is prepared in situ from iodine and potassium hydroxide, oxidizes methyl ketones (and compounds that are

oxidizable to methyl ketones) to carboxylic acids. The byproduct of the reaction, iodoform, is a heavy yellow crystalline compound possessing a unique smell and is easily identifiable by its melting point (120-123 °C). Because of this conspicuous byproduct, the reaction has long been used for the identification of methyl ketones [*750*]. With the advent of NMR spectroscopy, in which the $COCH_3$ group gives a characteristic singlet at 2.1 ppm, the importance of the iodoform reaction (***Lieben test***) has decreased considerably. Not only methyl ketones but also some cyclic ketones are oxidized to carboxylic acids by potassium hypoiodite [*752*].

Sodium iodate, $NaIO_3$, is used rarely; its applications are limited to the oxidation of aromatic polyhydroxy compounds to quinones [*753, 754*].

Periodic acid (metaperiodic acid), HIO_4, and its dihydrate (paraperiodic acid, H_5IO_6, mp 122 °C) are commercially available. Both reagents are applied usually in aqueous or aqueous–alcoholic solutions and only rarely in anhydrous tetrahydrofuran [*755*], aqueous dioxane [*756*], acetone [*567*], or acetic acid [*757, 758*].

The oxidative cleavage of carbon–carbon bonds in vicinal diols [*756, 759*] is a reaction widely used in saccharide chemistry. Besides its application in this reaction, periodic acid achieves the oxidative coupling [*757*] or oxidation to quinones [*758*] of polynuclear aromatic hydrocarbons, the oxidation of methyl groups in aromatic compounds to carbonyl groups [*760*], the conversion of epoxides into dicarbonyl compounds [*761*], and the oxidative cleavage of trimethylsilyl ethers of acyloins to carboxylic acids [*755*].

Sodium periodate (sodium metaperiodate), $NaIO_4$ (mp 300 °C dec), which is commercially available, is applied mainly in aqueous or aqueous–alcoholic solutions. Like the free periodic acid, sodium periodate cleaves vicinal diols to carbonyl compounds [*762*]. This reaction is especially useful in connection with potassium permanganate [*763, 764*] or osmium tetroxide [*765*]. Such mixed oxidants oxidize alkenes to carbonyl compounds or carboxylic acids, evidently by way of vicinal diols as intermediates. Sulfides are transformed by sodium periodate into sulfoxides [*322, 323, 766, 767, 768, 769, 770, 771, 772*], and selenides are converted into selenoxides [*773*]. Sodium periodate is also a reoxidant of lower valency ruthenium in oxidations with ruthenium tetroxide [*567, 774*].

Potassium periodate, KIO_4, when used in dilute sulfuric acid, acts like periodic acid in degrading α-hydroxy acids to aldehydes [*775*].

Tetrabutylammonium periodate, $(C_4H_9)_4NIO_4$ (mp 175 °C dec), which is usually prepared in situ from tetrabutylammonium hydrogen sulfate and sodium periodate [*776*], is useful in two-phase systems, because it dissolves in chloroform and other organic solvents. Its scope and limitations resemble those of periodic acid and alkaline periodates: the oxidation of carboxylic acids [*777*] and α-hydroxy acids [*776, 778*] to aldehydes with one less car-

bon, the oxidation of sulfides to sulfoxides [*776,778*], and the oxidation of benzyl-type bromides to aldehydes [*778*].

Acetyl hypoiodite (iodine acetate), CH_3COOI, is prepared by treatment of silver acetate in acetic acid with iodine at room temperature [*779, 780*]. The reagent cleaves vicinal diols to dicarbonyl compounds [*779*] and degrades tertiary alcohols to ketones [*780*]. Acetyl hypoiodite is also an intermediate in the reaction of alkenes with the so-called **"Simonini complex,"** an addition product of **iodine** with 2 mol of **silver acetate** [*781, 782, 783*].

Benzoyl hypoiodite, C_6H_5COOI, a similar complex with similar applications, is formed from **iodine** and 2 mol of **silver benzoate** [*783, 784*]. Silver *p*-chloro- and 3,5-dinitrobenzoates react analogously [*783*] (equation 17).

[*783*]

$$2\ C_6H_5CO_2Ag + I_2 \longrightarrow C_6H_5CO_2Ag.C_6H_5CO_2I + AgI \qquad 17$$

Both complexes are used in the hydroxylation of double bonds via diacetates or dibenzoates of vicinal diols. The reaction is stereospecific. In anhydrous medium (the ***Prévost reaction*** [*783*]), the reaction takes place in the *anti* mode. In the presence of water (the ***Woodward modification*** [*783*]), the reaction results in a *syn* addition. The mechanisms of both reactions are shown in the section Hydroxylation of Alkenes and Cycloalkenes in Chapter 3 (*see* equation 78).

Iodine triacetate, $I(OCOCH_3)_3$, which is prepared from iodine trichloride and silver acetate in acetic acid at room temperature, cleaves vicinal diols to dialdehydes [*779*].

Iodine tris(trifluoroacetate), $I(OCOCF_3)_3$, forms epoxides from certain alkenes [*785*].

Several oxidants are derivatives of iodoaromatic compounds containing trivalent and pentavalent iodine.

Iodobenzene dichloride, $C_6H_5ICl_2$, oxidizes selenides to selenoxides [*773*].

Iodosobenzene, C_6H_5IO (mp 210 °C, explodes), which is prepared by way of iodobenzene diacetate [*266*], is used for the conversion of acetylenes into α-dicarbonyl compounds [*786, 787*], of alcohols into aldehydes or ketones [*788*], and of aldehydes into acids [*788*]. This oxidant is also applied to the preparation of carbonyl compounds from vicinal diols [*789*], the syntheses of α-hydroxy ketones [*790*], and the oxidation of sulfides to sulfoxides [*791*]. Similar reactions can be accomplished by ***p*-iodosotoluene** or ***o*-iodosobenzoic acid** [*792*].

Iodobenzene diacetate, $C_6H_5I(OCOCH_3)_2$ (mp 163–165 °C) (Aldrich's product), is obtained by treatment of iodobenzene with peroxyacetic acid [*266*] or with 30% hydrogen peroxide and acetic anhydride at 40 °C

[*793*]. The reagent hydroxylates double bonds via diacetates [*789*], hydroxylates esters in the α position with respect to the carboxylic group [*794*], cleaves vicinal diols to carbonyl compounds [*789*], and oxidizes sulfides to sulfoxides [*795*].

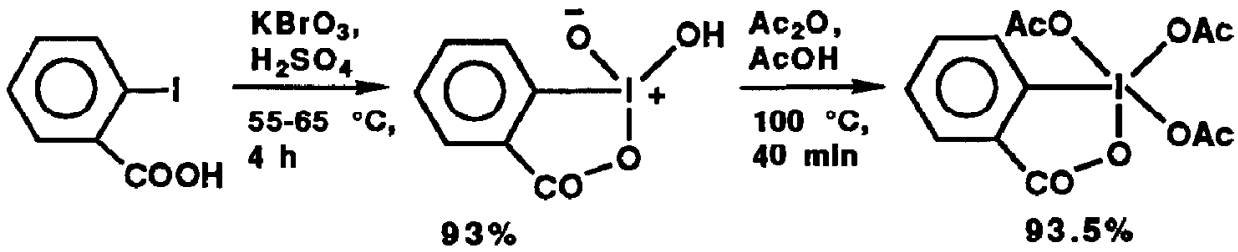
Pentafluoroiodobenzene bis(trifluoroacetate), $C_6F_5I(OCOCF_3)_2$ (mp 119–120 °C), a product of the treatment of iodopentafluorobenzene with trifluoroacetic anhydride and fuming nitric acid [*796*], converts acetylenes into carboxylic acids [*797*].

Iodoxybenzene, $C_6H_5IO_2$ (mp 230 °C, explodes), is prepared by the oxidation of iodobenzene with peroxyacetic acid [*267*]. This reagent cleaves vicinal diols to aldehydes [*798*] and, in the presence of α-dipyridyl diselenide, converts alkenes into α-carbonyl alkenes (α,β-unsaturated ketones) [*799*].

***m*-Iodoxybenzoic acid, *m*-$O_2IC_6H_4CO_2H$,** in connection with phenylseleninic anhydride, is used for the dehydrogenation of ketones to α,β-unsaturated ketones [*526*].

Dess–Martin "periodinane" (mp 138–140 °C), which is derived from *o*-iodobenzoic acid, accomplishes the oxidation of primary and secondary alcohols under very mild conditions and in high yields [*800, 801*] (equation 18).

[*801*] **18**



Manganic sulfate, $Mn_2(SO_4)_3$, is obtained by the oxidation of manganese sulfate (tetrahydrate) in 6 M sulfuric acid by aqueous potassium permanganate at 0–25 °C. This oxidant oxidizes aromatic hydrocarbons to quinones [*802*].

Manganic acetate (manganese triacetate), $Mn(OCOCH_3)_3$, is prepared by refluxing a solution of manganese acetate tetrahydrate in acetic acid with potassium permanganate [*803*]. This oxidant hydroxylates benzylic methylene groups [*416*] and forms lactones from terminal alkenes [*803, 804*] (*see* equation 88).

Manganese dioxide, MnO_2, is a commercially available, dark-brown powder prepared by the simultaneous addition of a 42.5% aqueous solution of manganese sulfate tetrahydrate and a 40% solution of sodium hydroxide to a hot stirred 14% aqueous solution of potassium permanganate. The brown precipitate is collected and washed with water until the washings are colorless, dried at 100–120 °C, and ground to a fine powder before use

[*805*]. Its activity can be modified by changing the particle size, by using different drying temperatures (220–280 °C), and by aftertreatment with 15% nitric acid and drying at 220–250 °C [*806*]. A different procedure involves the addition of a slight excess of a concentrated aqueous solution of potassium permanganate to a stirred solution of manganese sulfate at 90 °C; filtration of the precipitate; washing of the solid with hot water, methanol, and ether; and drying at 120–130 °C to constant weight [*807*]. Many more modifications are described in the literature [*808*]. The removal of water from the hydrated manganese dioxide can also be achieved by azeotropic distillation with benzene [*809*].

The differences in the activities and the results of oxidations with manganese dioxide are due to differences in methods of preparation [*808, 810*] and solvents used [*808*]. The most frequently used solvents are petroleum ether [*541, 805, 806, 808*], hexane [*382, 806, 811*], cyclohexane [*812*], benzene [*808, 813, 814, 815, 816*], dichloromethane [*817, 818*], chloroform [*807, 808, 811, 813, 816*], carbon tetrachloride [*805,808*], ether [*806, 808, 811, 813, 819, 820*], acetone [*821, 822*], acetic acid [*823*], and water [*813*].

Manganese dioxide is a reagent of choice for the oxidation of allylic [*382, 805, 806, 807, 808, 809, 810, 815, 819, 821, 824*] and benzylic [*382, 806, 808, 809, 811, 815, 816*] alcohols to aldehydes or ketones. Saturated alcohols do not always give good yields [*807, 808, 813, 815*]. The oxidation of aldehydes to acids is exceptional [*813*].

In addition, manganese dioxide oxidizes benzylic methyl or methylene to carbonyl [*814*] and cleaves the carbon bonds of vicinal diols [*817, 822*]. It converts amines into imines [*811, 825*]; tertiary amines into secondary amines [*812*], formamides [*826, 827, 828*], or ketones; aromatic primary amines [*813, 825*] and hydrazo compounds [*825*] into azo compounds; hydroxylamines into nitroso [*816*] or nitro compounds [*823*]; hydrazones into diazo compounds [*820*]; phosphines into phosphine oxides [*813*]; thiols into disulfides [*816*]; and sulfides into sulfoxides [*541*].

Potassium manganate, K_2MnO_4, purple crystals similar to potassium permanganate [*829*], forms a dark-green aqueous solution [*830*]. It is prepared from potassium permanganate and potassium hydroxide at 100 °C [*830*] or 120–140 °C [*829*]. Its use is limited to the *syn* hydroxylation of double bonds [*829*] and the hydroxylation of tertiary carbons in branched carboxylic acids [*830, 831*]. It offers no advantages over potassium permanganate.

Barium manganate, $BaMnO_4$, is commercially available. The dark-blue crystals are obtained from aqueous solutions of barium chloride and potassium permanganate [*832, 833*]. It oxidizes alcohols, especially benzylic alcohols, to carbonyl compounds [*832, 833*]; hydroquinone to quinone [*833*]; benzylamines to benzaldehydes [*833*]; aromatic amines to azo compounds [*833*]; and phosphines to phosphine oxides [*833*].

Sodium permanganate monohydrate, $NaMnO_4 \cdot H_2O$, which is commercially available, is used for the oxidation of alkenes to carboxylic acids [*834*] and of alcohols to carbonyl compounds [*835*], the conversion of sulfinic acids into sulfonic acids [*836*], and the selective oxidation of sulfoxides to sulfones (sulfides are not oxidized with sodium permanganate in dioxane solutions) [*837*].

Potassium permanganate, $KMnO_4$, dark-purple crystals with a metallic luster (*d* 2.7, solubility: 6.6% in cold water and 22% in boiling water), is soluble in acetone without reacting with the solvent [*838*]. It is applied most frequently in aqueous solutions but can be used in the presence of organic solvents such as petroleum ether [*839*], benzene [*840, 841, 842, 843, 844, 845, 846, 847*], dichloromethane [*848, 849*], *tert*-butyl alcohol [*850, 851, 852, 853*], acetone [*296, 838, 853, 854, 855, 856, 857, 858, 859*], acetic acid [*843, 857*], acetic anhydride [*860, 861*], and pyridine [*855, 862*]. The solubilization of potassium permanganate in organic solvents can be achieved by crown ethers [*841*] or by phase-transfer agents, such as quaternary ammonium salts that form quaternary permanganates soluble in solvents immiscible with water [*843, 845, 848*] (purple benzene [*841*]). Oxidations in organic solvents can also be carried out with potassium permanganate adsorbed on molecular sieves [*847, 863*], bentonite [*849*], montmorillonite [*863*], or copper sulfate pentahydrate [*844, 849*].

Potassium permanganate furnishes three oxidation equivalents per mole (three oxygens per 2 mol). Its reduction to manganese dioxide liberates potassium hydroxide. Therefore, most oxidations with potassium permanganate take place in strongly alkaline medium. Some oxidations occur at or require lower pH, which can be attained by using buffers such as carbon dioxide [*858, 864*], sodium bicarbonate [*856*], potassium carbonate [*852*], aluminum oxide [*865*], disodium hydrogen phosphate [*839*], magnesium nitrate [*866*], magnesium sulfate [*853, 856, 859, 867*], zinc sulfate [*850, 851*], calcium sulfate (better than zinc sulfate) [*851*], or sulfuric acid [*846, 868*].

The results of some oxidations with potassium permanganate differ depending on the pH of the reaction. For example, stearolic acid gives 9,10-diketostearic acid at pH 7–7.5 (achieved with carbon dioxide) and azelaic acid on treatment at pH 12 [*864*]. In some reactions, potassium permanganate is used as a catalyst for oxidation with other oxidants, such as sodium periodate. Thus alkenes are cleaved to carbonyl compounds or acids via vicinal diols obtained by hydroxylation with potassium permanganate, followed by cleavage by sodium periodate [*763, 852*].

The intensity of oxidations by potassium permanganate can be regulated further by concentration of the oxidant in water or water–organic solvent systems and by temperature variations (from –5 °C to refluxing temperature). Usually, a slight excess of the reagent over the stoichiometric amount required for the oxidation is used. Frequently, potassium permanganate or its solution is added to the organic substrate until the oxidant

ceases to react. The excess of potassium permanganate is difficult to notice, because the reaction mixture is dark owing to the presence of the dark-brown manganese dioxide. If a drop of the dark mixture is placed on a filter paper, an excess of potassium permanganate is revealed by a purple ring surrounding the brown spot of manganese dioxide. An excess of potassium permanganate is easily destroyed by adding methanol or ethanol to the mixture until the test for the presence of potassium permanganate is negative.

The workup of reaction mixtures after oxidations with potassium permanganate starts with the removal of the manganese dioxide, either by centrifugation or by filtration. The microcrystalline manganese dioxide easily clogs the pores of filters, and the filtrations are slow. In addition, colloidal solutions of manganese dioxide are sometimes formed. Both these drawbacks can be handled by filtering the reaction mixture with suction over a layer of activated charcoal. Because of the large surface area of manganese dioxide, some products are obstinately retained in this by-product. Intensive washing of the dioxide is necessary to remove the adsorbed products.

All these difficulties can be avoided when the manganese dioxide is reduced to manganese sulfate, which is water soluble and almost colorless. Such reductions are easily accomplished by passing a stream of sulfur dioxide through the reaction mixture until the complete disappearance of the manganese dioxide [*838, 868, 869*].

The spectrum of applications of potassium permanganate is very broad. This reagent is used for dehydrogenative coupling [*870*], hydroxylates tertiary carbons to form hydroxy compounds [*830, 831*], hydroxylates double bonds to form vicinal diols [*101, 296, 858, 871*], oxidizes alkenes to α-diketones [*860, 861*], cleaves double bonds to form carbonyl compounds [*840, 842, 852*] or carboxylic acids [*763, 841, 843, 845, 852, 869, 872, 873, 874*], and converts acetylenes into dicarbonyl compounds [*848, 856, 864*] or carboxylic acids [*843, 864*]. Aromatic rings are degraded to carboxylic acids [*875, 876*], and side chains in aromatic compounds are oxidized to ketones [*866, 877*] or carboxylic acids [*503, 878, 879, 880, 881, 882, 883*]. Primary alcohols [*884*] and aldehydes [*749, 868, 885*] are converted into carboxylic acids, secondary alcohols into ketones [*749, 839, 844, 863, 865, 886, 887*], ketones into keto acids [*888, 889, 890*] or acids [*889, 891*], ethers into esters [*855*], and amines into amides [*854, 855*] or imines [*851*]. Aromatic amines are oxidized to nitro compounds [*738, 859, 892*], aliphatic nitro compounds to ketones [*862, 867*], sulfides to sulfones [*846*], selenides to selenones [*325*], and iodo compounds to iodoso compounds [*893*].

Cupric permanganate, $Cu(MnO_4)_2 \cdot 8H_2O$, is commercially available and oxidizes primary alcohols and aldehydes to acids, secondary alcohols to ketones, and sulfides to sulfones in very high yields [*894*].

Bis(2,2′-bipyridyl)copper(II) permanganate (BBCP) (mp 105–110 °C)

is prepared as a crystalline product on cooling the dark-purple solution obtained by adding an aqueous solution of potassium permanganate to an aqueous solution of 2 mol of bis(2,2′-bipyridyl)copper(II) chloride [*895*]. The compound is used in dry dichloromethane and is more selective than potassium permanganate. It oxidizes allylic and benzylic alcohols to aldehydes [*895*], acyloins to α-diketones [*895*], primary aromatic amines to azo compounds [*895*], and thiols to disulfides [*896*]. Similar results are obtained with purple crystalline **bis(2,2′-bipyridyl)silver permanganate** [*897*].

Magnesium permanganate, $Mg(MnO_4)_2$, and **zinc permanganate, $Zn(MnO_{24})_2$,** are much more reactive than potassium permanganate and may cause ignition when added to alcohols, tetrahydrofuran, acetone, and acetic acid. They are used safely when supported on silica gel in dichloromethane or chloroform at room or refluxing temperature [*898*]. Their specialties are the conversion of acetylenes into α-diketones, of cyclic ethers into lactones, and of amines into amides [*898*].

Tetrabutylammonium permanganate, $(C_4H_9)_4NMnO_4$ (mp 120–121 °C dec), is prepared by adding a slight excess of a concentrated aqueous solution of tetrabutylammonium bromide to a stirred aqueous solution of potassium permanganate. The purple precipitate is filtered, washed with water, and dried in vacuo [*899*]. The reagent is applied in solutions in dichloromethane, chloroform, acetone, or pyridine at room temperature and oxidizes alkenes to diols, dialdehydes [*900*], or acids [*899*] and aromatic aldehydes to acids [*899*]. Tetrabutylammonium permanganate is to be ***handled with caution,*** because ignition of the crystalline material during weighing has been reported [*901*].

Benzyltriethylammonium permanganate, $C_6H_5CH_2N(C_2H_5)_3MnO_4$ (violet crystals, mp 127-129 °C dec), is obtained by the dropwise addition of an aqueous solution of benzyltriethylammonium chloride to an aqueous solution of potassium permanganate. The crystals are filtered and dried at 40 °C at 0.2 mm of Hg [*902*]. The reagent is used in dichloromethane or acetic acid for the hydroxylation of some tertiary carbons and the conversion of methylene in hydrocarbons and ethers into carbonyl [*902*], of aldehydes into carboxylic acids [*903*], and of amines into amides [*904*]. Like tetrabutylammonium permanganate, benzyltriethylammonium permanganate should be ***handled with due precaution.***

Triphenylmethylphosphonium permanganate, $(C_6H_5)_3PCH_3MnO_4$, a violet solid, is obtained by adding an aqueous solution of potassium permanganate to an aqueous solution of triphenylmethylphosphonium bromide. The crystals are filtered and dried in vacuo over phosphorus pentoxide. The compound can be stored for several weeks in the dark but may decompose explosively at 70 °C. An ***explosion*** may also occur when organic compounds are added to the solid oxidant. Oxidations of alkenes to vicinal diols are carried out by adding solutions of alkenes in dichlo-

romethane to a solution prepared by adding, portionwise, triphenylmethylphosphonium permanganate to dichloromethane at –70 °C [*905*].

DERIVATIVES OF GROUP 8 ELEMENTS

Ferric chloride, $FeCl_3$ or $FeCl_3 \cdot 6H_2O$, is a fairly selective reagent capable mainly of various dehydrogenations: of alcohols to aldehydes or ketones [*906*], of hydroquinones to quinones [*907*], of diamino [*908*] and amino hydroxy aromatic compounds [*909*] to quinones, and of α-amino ketones to α-diketones [*910*]. The reagent is also used for the dehydrogenative coupling of ketones in the α positions with respect to carbonyl groups [*911*] and the coupling of naphthols [*912*] or of aromatic *o*-diamines [*913*] and of thiols to disulfides [*907*].

Ferric sulfate, $Fe_2(SO_4)_3$, either as such [*914*] or prepared in situ from **ferric oxide and sulfuric acid** [*915*], is used for similar intra- and intermolecular dehydrogenations.

Potassium ferrate, K_2FeO_4, which is prepared from ferric nitrate and alkaline hypochlorites [*916*], is a selective oxidant for the conversion of primary alcohols into aldehydes (not acids), of secondary alcohols into ketones, and of primary amines into aldehydes [*917, 918*].

Potassium ferricyanide [potassium hexacyanoferrate(III)], $K_3Fe(CN)_6$, in the presence of a base, dehydrogenates hydroaromatic compounds to aromatic compounds [*919*] and can cause dehydrogenative cyclizations [*920*]. The reagent is used for the conversion of acid hydrazides into aldehydes [*921*], of sterically hindered phenols into phenoxy radicals [*922, 923*], and of primary amines into nitriles [*924*]. Tertiary amines are demethylated to secondary amines [*925, 926*].

Raney nickel, Ni(R), effects the dehydrogenation of secondary alcohols to ketones in excellent yields at moderate temperatures in the presence [*927*] or absence [*927, 928*] of hydrogen acceptors.

Nickel peroxide, an undefined black oxide of nickel, is prepared from nickel sulfate hexahydrate by oxidation in alkaline medium with an ozone–oxygen mixture [*929*] or with sodium hypochlorite [*930, 931, 932, 933*]. Its main applications are the oxidation of aromatic side chains to carboxyls [*933*], of allylic and benzylic alcohols to aldehydes in organic solvents [*929, 932*] or to acids in aqueous alkaline solutions [*929, 930, 932*], and of aldehydes to acids [*934*]; the conversion of aldehyde or ketone hydrazones into diazo compounds [*935*]; the dehydrogenative coupling of ketones in the α positions with respect to carbonyl groups [*931*]; and the dehydrogenation of primary amines to nitriles or azo compounds [*936*].

Ruthenium tetroxide, RuO_4, a reddish-orange substance (mp 25.5 °C,

bp 108 °C dec) that is 60 times more soluble in carbon tetrachloride than in water [*937*], is prepared usually in situ from black ruthenium dioxide, **RuO_2 or $RuO_2 \cdot XH_2O$,** or ruthenium trichloride, **$RuCl_3$ or $RuCl_3 \cdot 3H_2O$** (mp 500 °C dec), by oxidation with sodium hypochlorite [*701, 938, 939*], sodium bromate [*940*], periodic acid [*939*], sodium periodate [*774*], or peroxyacetic acid [*939*]. This reagent actually acts as a catalyst, because it is reoxidized after the reaction with organic compounds by one of the previously mentioned oxidants. All work with ruthenium tetroxide should be done in hoods, because the reaction mixtures generate an obnoxious smell reminiscent of ozone. A thorough study of oxidation by ruthenium tetroxide generated in situ from ruthenium dioxide or ruthenium trichloride hydrates shows especially the importance of using hydrates containing no less than 20% of water. Ruthenium dioxide hydrate with less than 10% of water did not work [*see 1207*].

The applications of ruthenium tetroxide range from the common types of oxidations, such as those of alkenes, alcohols, and aldehydes to carboxylic acids [*701, 774, 939, 940*]; of secondary alcohols to ketones [*701, 940, 941*]; of aldehydes to acids (in poor yields) [*940*]; of aromatic hydrocarbons to quinones [*942, 943*] or acids [*701, 774, 941*]; and of sulfides to sulfoxides and sulfones [*942*], to specific ones like the oxidation of acetylenes to vicinal dicarbonyl compounds [*938*], of ethers to esters [*940*], of cyclic imines to lactams [*944*], and of lactams to imides [*940*].

Sodium ruthenate, Na_2RuO_4, is prepared in situ from ruthenium tetroxide (in solution in carbon tetrachloride) and 1 M sodium hydroxide by shaking for 2 h at room temperature. The reagent remains in the aqueous layer, which acquires bright-orange color [*937*]. It oxidizes primary alcohols to carboxylic acids and secondary alcohols to ketones and is comparable with but stronger than potassium ferrate [*937*].

Potassium ruthenate, K_2RuO_4, is prepared in situ from ruthenium trichloride and aqueous persulfate. The reagent catalyzes persulfate oxidations of primary alcohols to acids, secondary to ketones, and primary amines to nitriles or acids at room temperature in high yields [*196*].

Palladium, Pd, and **platinum, Pt,** usually on activated carbon or asbestos, are catalysts for the dehydrogenation of hydroaromatic and some heterocyclic compounds to aromatic compounds. The reaction takes place at high temperatures (300–350 °C), and consequently, side reactions such as rearrangements often take place [*495, 496, 497, 945, 946, 947, 948*]. The catalytic dehydrogenations played a very important role in the elucidation of terpene and alkaloid structures. Because spectroscopic methods, especially NMR spectroscopy, can help to determine structures much more reliably, catalytic dehydrogenation over palladium and platinum are rare nowadays.

Osmium tetroxide (osmic acid), OsO_4 (white crystals, mp 39.5–41 °C, bp 130 °C), is used rarely in stoichiometric amounts, because it is expensive

and very toxic. It is applied in solutions in ether [*949*], dioxane [*482*], or pyridine [*950*] and reacts with alkenes to form five-membered cyclic esters of vicinal diols, which, on hydrolysis, afford vicinal diols. The result is the *syn* addition of two hydroxylic groups across a double bond [*482, 949, 950*]. In the presence of chiral amines such as quinuclidine, enantioselective addition with an enantiomeric excess of 26–82% of one enantiomer has been accomplished [*951*]. Most of the *syn* hydroxylations with osmium tetroxide are carried out with only catalytic amounts in the presence of oxidants that regenerate osmium tetroxide, such as hydrogen peroxide [*130*], sodium chlorate [*715,716*], potassium chlorate [*715*], silver chlorate, barium chlorate [*310*], and amine oxides [*952*]. In the presence of sodium perchlorate [*953*], sodium periodate [*765*], and an excess of hydrogen peroxide [*141*], alkenes are oxidized to carbonyl compounds after cleavage of the carbon–carbon bond of the vicinal diols formed primarily. Osmium tetroxide oxidizes sulfoxides (but not sulfides) to sulfones [*837*].

ORGANIC OXIDANTS

Carbon tetrachloride, CCl_4, in the presence of potassium hydroxide at 25–80 °C, transforms primary alcohols into carboxylic acids, methyl ketones into acids with the same number of carbons or with one less carbon in the chain, and aryl methyl sulfones into arenesulfonic acids [*954*].

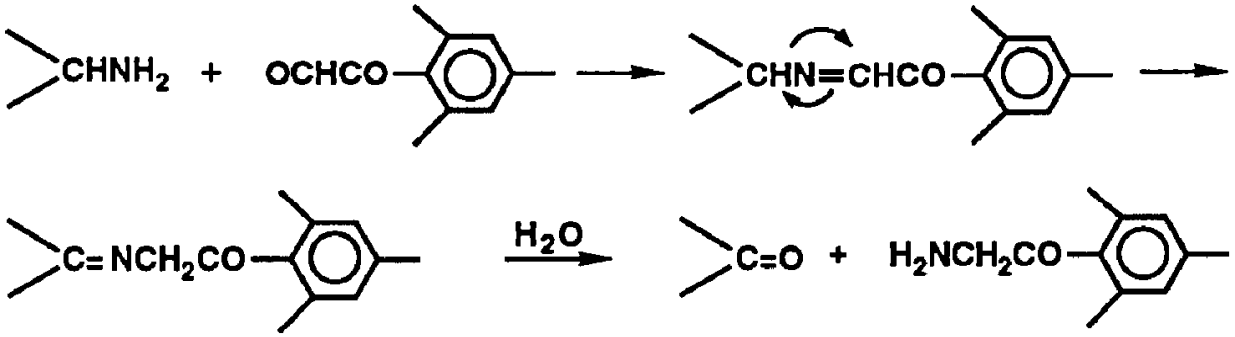
Hexamine (hexamethylenetetramine or methenamine), $C_6H_{12}N_4$ (white crystals, mp 280 °C, sublimes), reacts with reactive (allylic or benzylic) halides to form salts, which, on steam distillation or refluxing with water, yield aldehydes [*955, 956*] (***Sommelet reaction***). Aromatic aldehydes can be obtained from benzyl chlorides on treatment with formaldehyde and hydrochloric acid and subsequent refluxing with hexamethylenetetramine [*957*].

Chloral (trichloroacetaldehyde), CCl_3CHO, oxidizes secondary alcohols to ketones in the presence of very active aluminum oxide (Woelm). This reaction seems to be superior to the ***Oppenauer oxidation,*** because it takes place at room temperature or at only slightly elevated temperatures [*958, 959, 960*].

Acetone, cyclohexanone, benzophenone, cinnamaldehyde, and other carbonyl compounds are hydrogen acceptors in the ***Oppenauer oxidation*** of alcohols to carbonyl compounds. The reaction is catalyzed by Raney nickel [*961*], aluminum alkoxides [*962*], tris(isopropoxide), or tris(*tert*-butoxide) as bases soluble in organic solvents [*963, 964*]. These dehydrogenations of alcohols to aldehydes and ketones require refluxing or distillations and have given way to dimethyl sulfoxide oxidations, which take place at room temperature.

Mesitylglyoxal, 3-nitromesitylglyoxal, 3,5-dinitromesitylglyoxal, and **3,5-di-*tert*-butyl-*o*-benzoquinone** are used for the conversion of primary amines with the amino groups on secondary carbons into ketones via ***Schiff bases*** at 0–23 °C in high yields (transamination) [*965*] (equation 19).

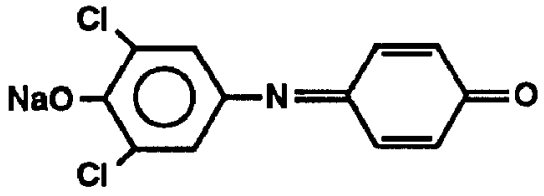
[*965*] 19

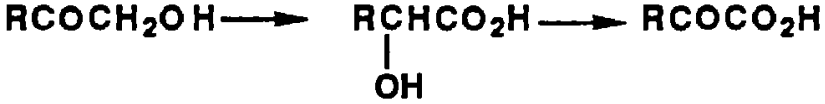


Chloranil (tetrachloro-*p*-benzoquinone), 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), and other high-potential quinones are good hydrogen acceptors in dehydrogenations forming double bonds adjacent to conjugated double bonds [*966*] or aromatic rings [*967, 968*], in aromatizations of six-membered alicyclic compounds [*969, 970*], in dehydrogenative coupling [*971, 972*], in oxidations of allylic alcohols to α,β-unsaturated carbonyl compounds [*973, 974, 975*], and in oxidations of phenols to quinones [*971*]. Some of these dehydrogenations take place at room temperature, whereas some reactions require refluxing in ether, benzene, xylene, methanol, or dioxane.

The sodium salt of 2,6-dichlorophenolindophenol, *N*-(3,5-dichloro-4-hydroxyphenyl)-*p*-benzoquinone imine **(Tillman reagent),** is used especially in steroid chemistry for the conversion of α-hydroxy ketones into α-hydroxy acids and α-keto acids [*976*] (equation 20).

[*976*] 20





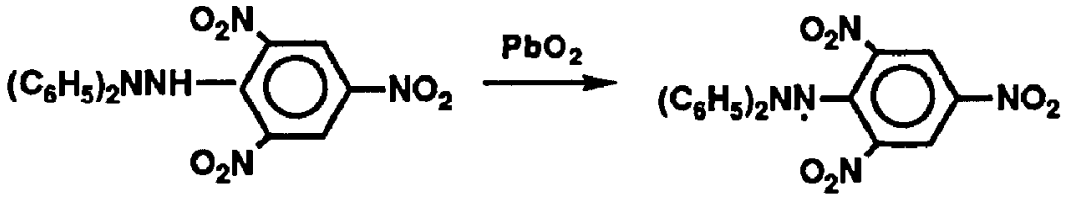
Diethyl azodicarboxylate, $C_2H_5O_2CN{=}NCO_2C_2H_5$ (bp 106 °C at 13 mm of Hg), is a strong hydrogen acceptor in dehydrogenations and oxidations. It is converted into diethyl hydrazodicarboxylate and reacts usually at room temperature, although some of its reactions require refluxing in benzene. The reagent converts alcohols into aldehydes or ketones, thiols into disulfides, aromatic amines and hydrazo compounds into azo compounds [*977*], hydroxylamines into nitroso compounds [*978*], and

sulfides into sulfoxides [*979*]. Diethyl azodicarboxylate is very useful for the demethylation of tertiary amines to secondary amines [*980*].

Triphenylmethyl tetrafluoroborate, $(C_6H_5)_3C^+BF_4^-$, oxidizes secondary alcohols in preference to primary alcohols [*981*].

Diphenylpicrylhydrazyl, which is prepared from *N,N*-diphenyl-*N'*-(2,4,6-trinitrophenyl)hydrazine by oxidation with lead dioxide [*982*], is used for the dehydrogenation of 1,4-dihydronaphthalene to naphthalene and of hydrazobenzene to azobenzene [*983*]. Simpler and cheaper compounds are, however, available for such purposes (equation 21).

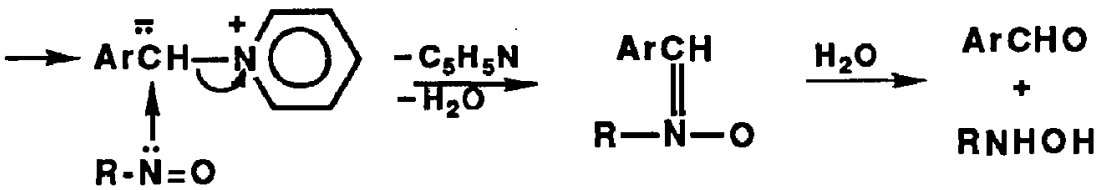
[*982*] 21



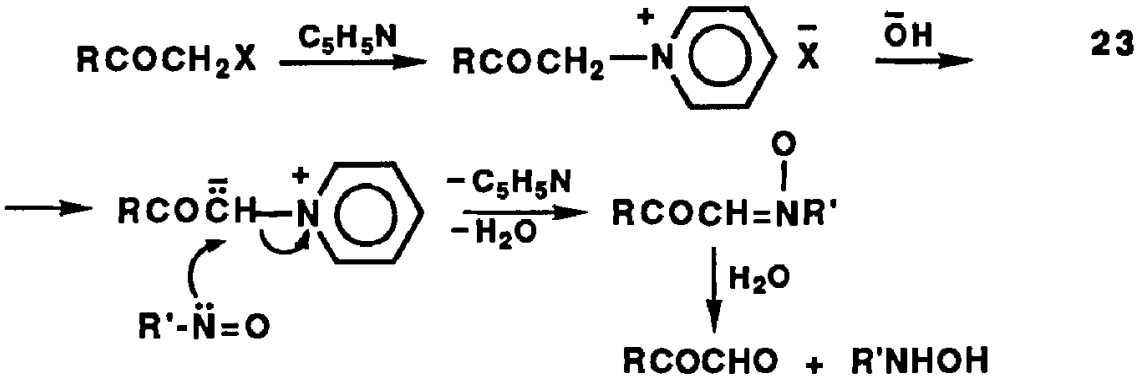
Nitrosobenzene, C_6H_5NO, which is obtained by the oxidation of phenylhydroxylamine, and ***p*-nitrosodimethylaniline, p-$(CH_3)_2NC_6H_4NO$,** which is easily prepared by the nitrosation of dimethylaniline, are fairly specific oxidizing agents for the preparation of aromatic aldehydes from benzyl halides or tosylates and of α-dicarbonyl compounds from from α-halo ketones [*984, 985*]. Also, a methylene group flanked by two carbonyls can be oxidized to a carbonyl group by nitrosodimethylaniline [*986*]. Pyridine is frequently used to form quaternary pyridinium salts from reactive halides prior to their oxidation to aromatic aldehydes, α-ketoaldehydes, or α-diketones [*984*] (equations 22 and 23).

[*984*] 22

X = Cl, Br, I, or TosO



[*984*] 23



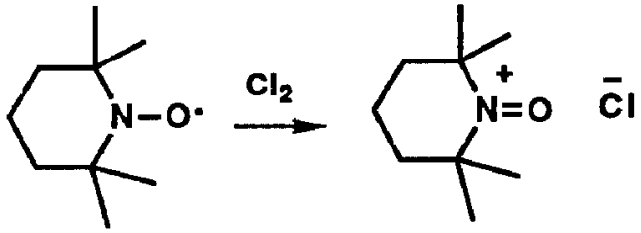
Nitro compounds in alkaline medium are used for rather specific oxidations. **2-Nitropropane** in the form of its sodium salt converts benzylic halides into aromatic aldehydes under fairly mild conditions [*987*]. **Nitrobenzene** transforms isoeugenol [*988*] and similar aromatic compounds with side chains that contain double bonds conjugated with the aromatic rings into aldehydes [*988, 989*]. In the ***Skraup synthesis,*** nitrobenzene dehydrogenates the dihydroquinoline intermediate to quinoline.

In the presence of alkalies and sulfur, *p*-nitrotoluene gives *p*-aminobenzaldehyde. The nitro group oxidizes the methyl group intramolecularly [*990*].

Trimethylamine oxide, $(CH_3)_3NO$, or its dihydrate, **$(CH_3)_3NO{\cdot}2H_2O$** (mp 97–100 °C), oxidizes boranes to alcohols [*991, 992*] and alkyl iodides to aldehydes [*993*] under gentle conditions. ***N*-Methylmorpholine oxide, $O(CH_2CH_2)_2NO$,** is used as a reoxidant in hydroxylations of alkenes with osmium tetroxide [*952*] and for the oxidation of nucleoside phosphites to nucleoside phosphates in an anhydrous medium [*228*]. **Pyridine oxide** hydroxylates aromatic rings to phenols [*994*].

1-Oxo-2,2,6,6-tetramethylpiperidinium chloride, an exotic reagent prepared from chlorine and 2,2,6,6-tetramethyl-1-piperidinyloxyl (a free-radical Tempo), converts diols into acyloins or lactones [*995*] (equation 24).

[*995*]

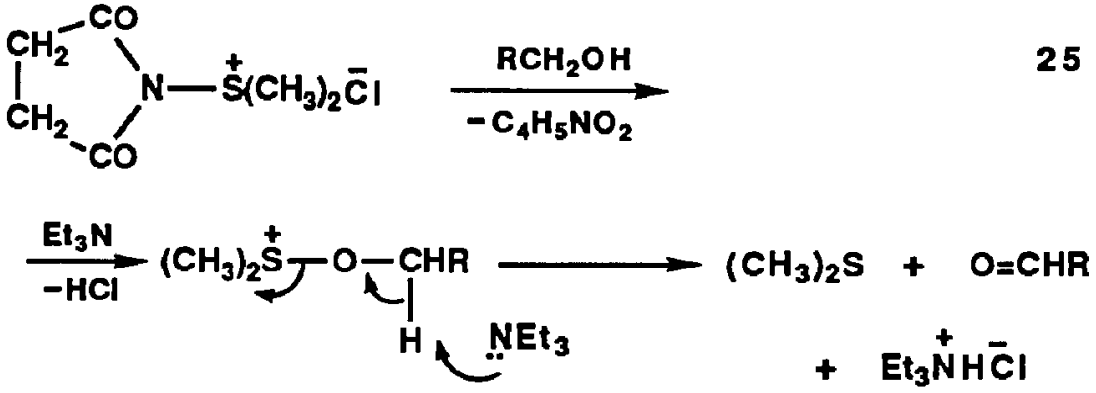


24

Triphenyl phosphite ozonide, $(C_6H_5O)_3PO_3$, which is obtained by ozonization of triphenyl phosphite in dichloromethane solution at –78 °C, decomposes to triphenyl phosphate and singlet oxygen [*178*]. As an oxidant, it converts the trimethylsilyl ethers of enols of α,β-unsaturated ketones into unsaturated hydroxy ketones [*996*].

Dimethyl sulfide and chlorine or, better still, **dimethyl sulfide and *N*-chlorosuccinimide,** form a system capable of the selective dehydrogenation of alcohols to aldehydes or ketones. The intermediates, such as $(CH_3)_2S^+Cl\ Cl^-$, react with bases according to the scheme in equation 25 [*720*].

[*720*]



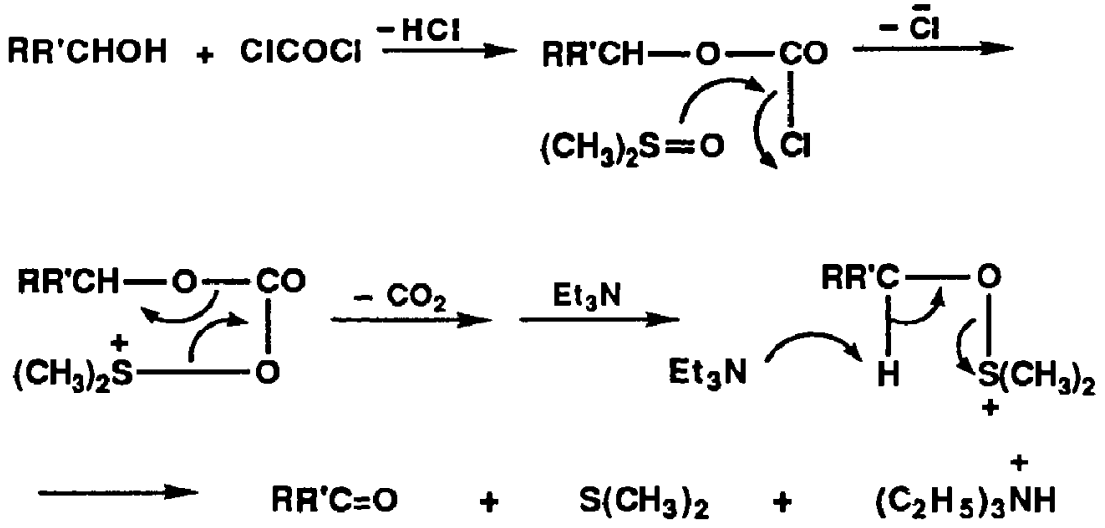
25

Dimethyl sulfoxide (DMSO), $(CH_3)_2SO$, is a versatile reagent for the oxidation of alcohols to carbonyl compounds under gentle conditions. In addition to the previously mentioned dehydrogenations, it is capable of other oxidations: acetylenes to α-diketones [*997*], alkyl halides to aldehydes [*998, 999*], tosyl esters to aldehydes [*1000*], methylene groups adjacent to carbonyl groups to carbonyls [*1001, 1002*], α-halocarbonyl compounds to α-dicarbonyl compounds [*1003, 1004, 1005*], aldehydes to acids [*1006*], and phosphine sulfides and selenides to phosphine oxides [*1007*].

The main domain of oxidation with dimethyl sulfoxide is the conversion of primary alcohols into aldehydes and of secondary alcohols into ketones. These reactions are accomplished under very mild conditions, sometimes at temperatures well below 0 °C. The reactions require the presence of acid catalysts such as acetic anhydride [*713, 1008, 1009*], trifluoroacetic acid [*1010*], trifluoroacetic anhydride [*1011, 1012, 1013*], trifluoromethanesulfonic acid [*1014*], phosphoric acid [*1015, 1016*], phosphorus pentoxide [*1006, 1017*], hydrobromic acid [*1001*], sulfur trioxide [*1018*], chlorine [*1019, 1020*], *N*-bromosuccinimide [*997*], carbonyl chloride (phosgene) [*1021*], and oxalyl chloride (the ***Swern oxidation***) [*1022, 1023, 1024*]. Dimethyl sulfoxide also converts sufficiently reactive halogen derivatives into aldehydes or ketones [*998, 999*] and epoxides to α-hydroxy ketones at −78 °C [*1014*].

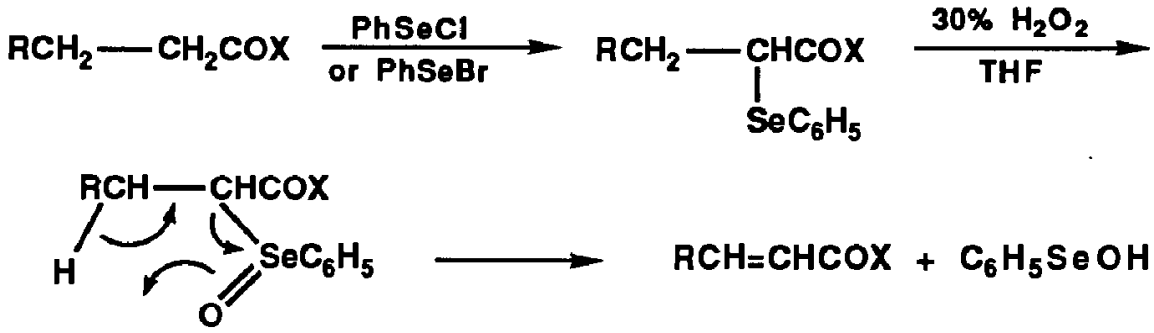
The mechanism of the reactions of DMSO with alcohols is shown in equation 26 and in a few more examples. Dicyclohexylcarbodiimide is sometimes used in addition to the acid catalysts (equation 26).

[*1021*] **26**



Phenylselenyl chloride, C_6H_5SeCl, and phenylselenyl bromide, C_6H_5SeBr, in connection with oxidizing agents such as hydrogen peroxide or sodium periodate, are used for the conversion of aldehydes, ketones, and esters into their α,β-unsaturated analogues. The key intermediate is alkyl phenyl selenoxide, which decomposes via a five-membered transition state [*167*] (equation 27).

[167] 27

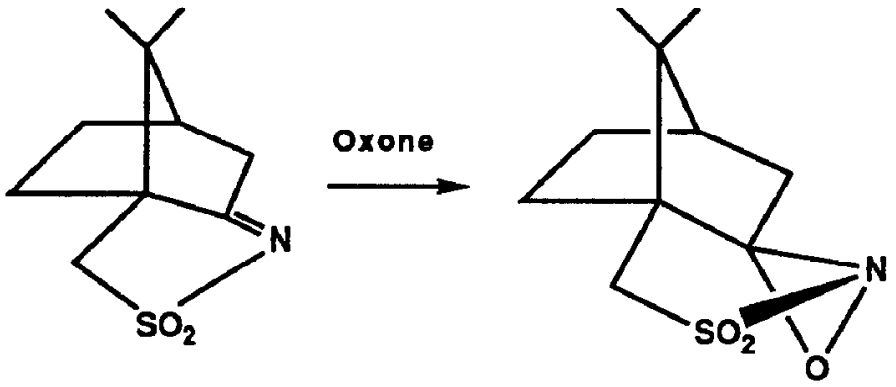


CHIRAL OXIDANTS

The ambition of synthetic organic chemists is not satisfied by inventing oxidations that are diastereospecific, that is, reactions that yield only, or predominantly, one of the two possible diastereomers, for example, either the *cis* or the *trans* product. The predominant formation of one enantiomer is desirable whenever it is possible. Such ***enantioselective oxidations*** take place when microorganisms or enzymes are involved. Only recently have such oxidations been accomplished by purely chemical means. Enantioselective oxidations require the presence of a chiral component and a metal catalyst that forms a complex with the chiral reagent. Some metallic compounds used are vanadyl acetylacetonate, $VO(acac)_2$ [*216*]; molybdenyl acetylacetonate, $MoO_2(acac)_2$ [*1025*]; and especially titanium tetraisopropoxide, $Ti[OCH(CH_3)_2]_4$. **Sharpless reagent,** which gives the best results, is a mixture of 1 mol of titanium isopropoxide, 1–2 mol of *tert*-butyl hydroperoxide as the oxidant, and 2 mol of (*R,R*)- or (*S,S*)-diethyl tartrate as the chiral component [*221, 222, 223, 224, 1025, 1026, 1027, 1028*]. The addition of 1 mol of water to this mixture is claimed to give better results in aqueous media [*224, 1029*]. *N*-Methyl- and *N*-ethylephedrine [*1030*], quinine and quinidine acetates [*951*], and *N*-phenylcamphoryl hydroxamic acid [*1031*] have also been used as chiral reagents.

(+)-(2*R*,8*aS*)- or (–)-(2*S*,8*aR*)-camphorylsulfonyloxaziridine, another chiral reagent, contains oxygen that reacts with the enolates of esters to form chiral α-hydroxy esters [*1032*] (equation 28).

[1032]



28

The main applications of chiral oxidations are the epoxidation of double bonds, especially in allylic alcohols [*221, 222, 223, 1026, 1027, 1028, 1030, 1031*], the hydroxylation of double bonds [*951, 1033*] and of the α position with respect to an ester group [*1032*], and the oxidation of nonsymmetrical sulfides to chiral sulfoxides [*224, 1025, 1029*]. Optical yields (enantiomeric excesses [ee]) are frequently over 95%.

BIOCHEMICAL (MICROBIAL) OXIDATIONS

The oxidations accomplished by microorganisms or enzymes excel in regiospecificity, stereospecificity, and enantioselectivity. Although the yields of such oxidations are sometimes fair and even low, optical purity (enantiomeric excess) is usually very high and frequently 100%. The spectrum of microbial and enzymatic oxidations is unbelievably broad; many different positions in steroidal rings can be hydroxylated by different microorganisms, and usually, only one diastereomer is formed. From achiral molecules, optically active compounds are generated.

Microbial oxidations occur under very mild conditions, usually around 37 °C, and in dilute solutions, for example, 1 g of a substance in 6 L of water. They are very slow and often take days. The isolation of products from the reaction media is done by extraction with proper solvents. Out of countless examples described in the literature, only a very narrow selection is presented in this chapter to show the versatility of microbial and enzymatic oxidations.

A single enzyme is sometimes capable of many various oxidations. In the presence of NADH (reduced nicotinamide adenine dinucleotide), **cyclohexanone oxygenase** from ***Acinetobacter*** NCIB9871 converts aldehydes into acids, formates of alcohols, and alcohols; ketones into esters (***Baeyer–Villiger reaction***); phenylboronic acids into phenols; sulfides into optically active sulfoxides; and selenides into selenoxides [*1034*]. **Horse liver alcohol dehydrogenase** oxidizes primary alcohols to acids (esters) [*1035*] and secondary alcohols to ketones [*1036*]. **Horseradish peroxidase** accomplishes the dehydrogenative coupling [*1037*] and oxidation of phenols to quinones [*1038*]. **Mushroom polyphenol oxidase** hydroxylates phenols and oxidizes them to quinones [*1039*].

The following is an alphabetical list of microorganisms capable of various oxidations: ***Acetobacter*** **spp.** [*1040, 1041*], ***Acinetobacter*** **spp.** [*1034, 1042, 1043*], ***Arthrobacter*** **spp.** [*1044*], ***Aspergillus*** **spp.** [*1045, 1046, 1047, 1048, 1049, 1050*], ***Bacillus megaterium*** [*1051*], ***Calonectria*** **spp.** [*575, 1052*], ***Cellulomonas*** **spp.** [*1053*], ***Cladiosporium*** **spp.** [*1054*], ***Corynebacterium*** **spp.** [*1055, 1056, 1057, 1058*], ***Cunninghamella*** **spp.** [*1059, 1060, 1061*], ***Curvularia*** **spp.** [*1062, 1063, 1064*], ***Cylindrocarbon*** **spp.** [*1065*], ***Fusarium*** **spp.** [*1066*], ***Gibberella*** **spp.** [*1067*], ***Heliostylum*** **spp.**

[*1059*], ***Helminthosporium*** **spp.** [*1054, 1068*], ***Hygroporus*** **spp.** [*1069*], ***Mortierella*** **spp.** [*1068*], ***Nocardia*** **spp.** [*1070, 1071*], ***Penicillium*** **spp.** [*1065, 1072*], ***Pseudomonas*** **spp.** [*92, 1073, 1074*], ***Rhizopus*** **spp.** [*1059, 1075, 1076, 1077, 1078, 1079*], ***Sporotrichum*** **spp.** [*1080, 1081, 1082, 1083, 1084*], ***Streptomyces*** **spp.** [*1050, 1085*], ***Torulopsis*** **spp.** [*1086, 1087*], and ***Saccharomyces*** **spp. (yeast)** [*1088*].

Among the various dehydrogenations and oxidations achieved by microorganisms are dehydrogenation to form double bonds [*1053, 1056, 1057, 1065, 1071*]; dehydrogenative coupling [*1037*]; oxidation of methyl groups to primary alcoholic groups [*1087*] or carboxylic groups [*1053, 1071, 1086, 1087*]; oxidation of $-CH_2X$, in which X is a halogen, to carboxylic groups [*1086*]; hydroxylation of methylene [*575, 1039, 1045, 1050, 1051, 1054, 1060, 1061, 1062, 1064, 1066, 1067, 1075, 1076, 1077, 1078, 1079, 1080, 1081, 1082, 1083, 1084*] and methine [*1059, 1062, 1083, 1089*] groups; oxidation of methylene groups to carbonyls [*1070, 1080, 1081*]; epoxidation of double bonds [*1055, 1063*]; hydroxylation of double bonds [*1073*]; conversion of alkenes into ketones [*1069*]; oxidation of primary alcohols to carboxylic acids [*1035, 1044*], of secondary alcohols to ketones [*1040, 1041, 1056, 1059, 1088*], of aldehydes to carboxylic acids, [*1034*], and of ketones to esters (Baeyer–Villiger reaction) [*1034, 1042, 1043, 1049, 1065, 1072*]; hydroxylation of aromatic rings [*1039*]; and oxidation of phenols to quinones [*1038, 1039*], of phenylboronic acids to phenols [*1034*], of primary amines to nitro compounds [*1085*], of sulfides to optically active sulfoxides [*1034, 1046, 1047, 1048, 1052, 1058*], of sulfoxides to sulfones [*1034, 1048*], and of selenides to selenoxides [*1034*].

Chapter 2
Dehydrogenations

DEHYDROGENATIONS, which involve the elimination of hydrogen from organic molecules, lead to compounds containing double bonds, multiple bonds, or aromatic rings. For practical reasons, only the formation of carbon–carbon double bonds, of carbon–nitrogen double bonds in cyclic amines, and of aromatic rings (both carbocyclic and heterocyclic) will be discussed in this chapter. The conversion of alcohols into aldehydes and ketones and of amines into imines and nitriles will be discussed in the chapter Oxidations (Chapter 3).

In addition to the reactions just mentioned, dehydrogenations also give rise to coupled products (intermolecular coupling) and to cyclic structures from open-chain compounds (intramolecular dehydrogenation). Examples are the formation of diphenyl from benzene (intermolecular coupling) and of toluene from heptane (intramolecular dehydrogenation). However, similar dehydrogenative doublings of compounds, such as the formation of hydrazo compounds from amines or of disulfides from thiols, will be treated in Oxidations (Chapter 3).

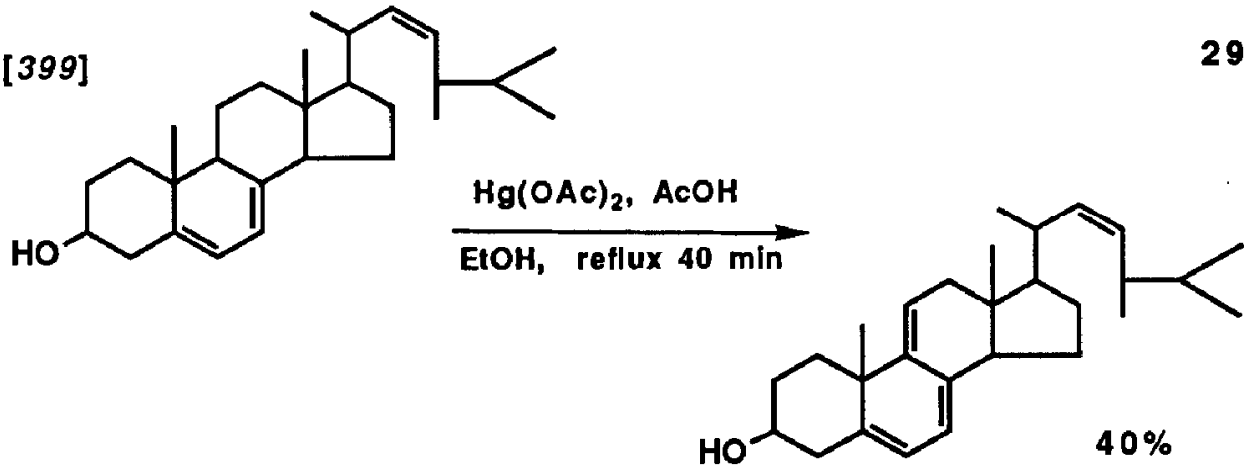
INTRODUCTION OF DOUBLE BONDS

Many dehydrogenations resulting in the ***formation of carbon–carbon double bonds*** are known in steroids and occur always in the α positions with respect to double bonds or carbonyl groups. Thus ergosterol or ergosterol acetate gives dehydroergosterol or its acetate in 40 or 37% yield, respectively, by refluxing in acetic acid with *mercuric acetate* [*399, 400*] (equation 29).

3β-Acetoxylanost-8-ene is converted into 3β-acetoxylanosta-7,9(11)-diene in 92% yield on treatment with acetic acid and 30% *hydrogen peroxide* for 45 h at 22 °C [*275*].

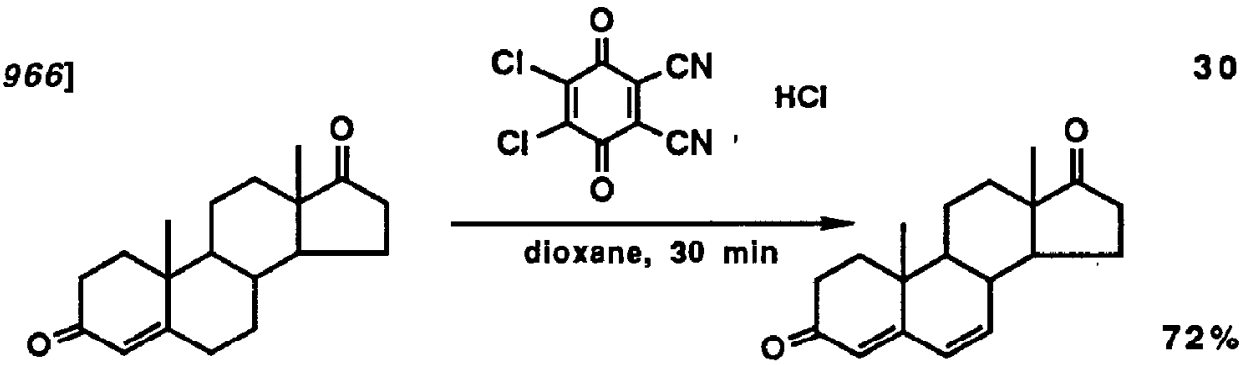
When testosterone acetate is refluxed with *2,3-dichloro-5,6-dicyano-p-benzoquinone* and *p*-toluenesulfonic acid in benzene for 5 h, a 60% yield of 6-dehydrotestosterone acetate is obtained [*966*]. The treatment of androst-4-ene-3,17-dione in dioxane with the same quinone and gaseous hydrogen chloride gives a 72% yield of androsta-4,6-diene-3,17-dione [*966*] (equation 30).

[399]



29

[966]

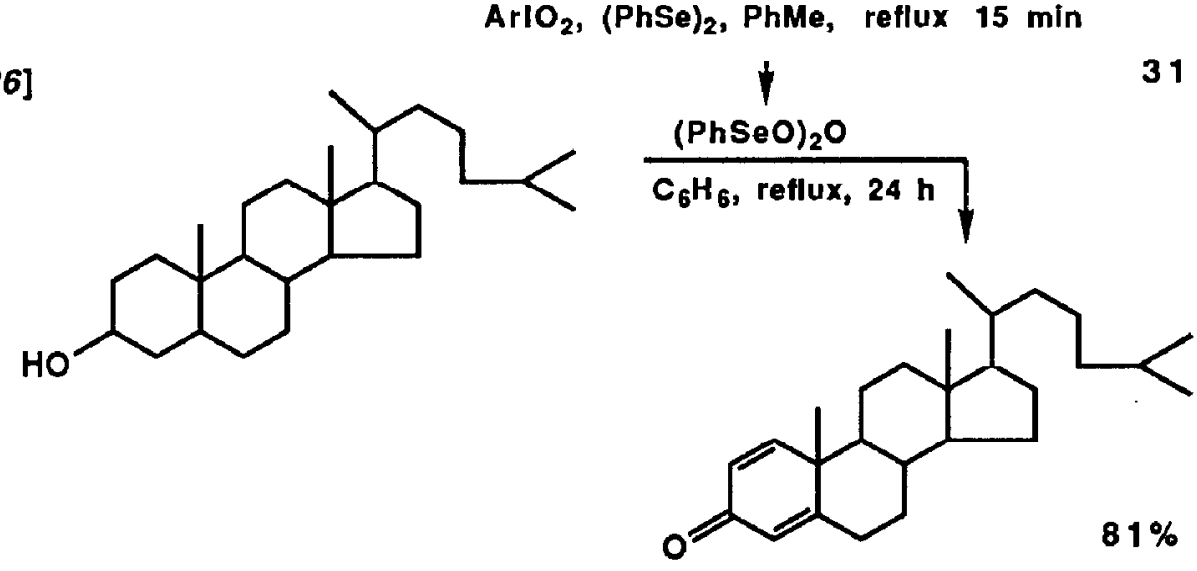


30

Both cholestan-3-one and cholestan-3-ol yield 1,4-cholestadien-3-one on treatment with iodoxybenzene or *m*-iodoxybenzoic acid and a catalytic amount of benzeneseleninic anhydride, which is generated in situ from diphenyldiselenide [*526*]. The treatment of cholestan-3-one with phenylselenyl chloride and hydrogen peroxide gives 1-cholesten-3-one [*167*] (equations 31 and 32).

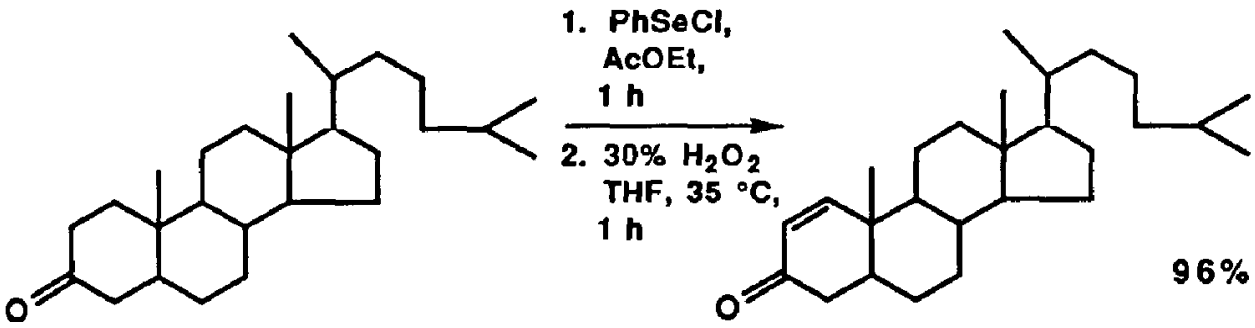
Similar dehydrogenations are often accomplished *biochemically*. On treatment with *Corynebacterium simplex*, 19-nortestosterone is transformed into estradiol [*1056*]. Many adrenocortical hormones are converted

[526]



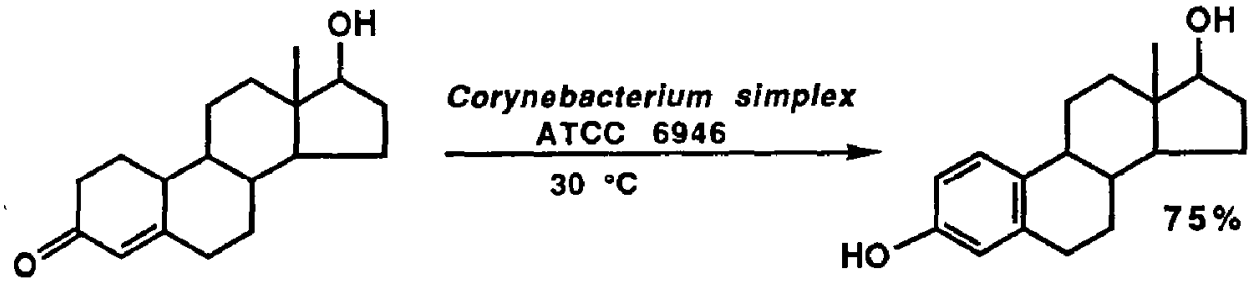
31

[167] 32



into their 1,2-dehydro analogues by the same microorganism [*1057*] (equation 33).

[1056] 33

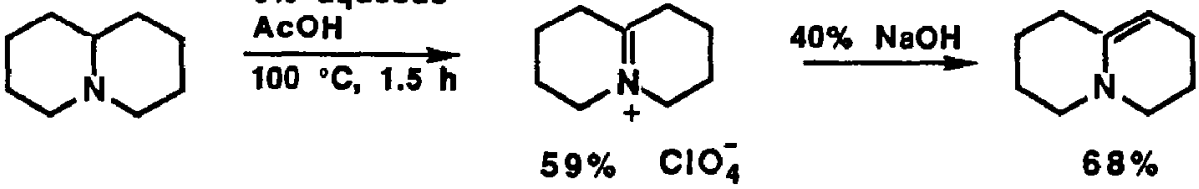


A classical example of the dehydrogenative formation of a carbon–carbon double bond conjugated with an aromatic ring is the dehydrogenation of ethylbenzene to styrene at 500–600 °C over a complex *catalyst* containing oxides of zinc and chromium [*1090*] or at 625 °C over vanadium pentoxide on alumina [*478*].

Several dehydrogenations forming double bonds conjugated with aromatic rings are achieved by heating with *quinones*. Acenaphthene gives a 75% yield of acenaphthylene when refluxed with chloranil for 16 h in xylene at 140 °C [*967*], and *p,p'*-dimethoxybibenzyl affords an 83–85% yield of *p,p'*-dimethoxystilbene when refluxed with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in dioxane at 105 °C [*968*].

Double bonds between carbon and nitrogen in secondary and tertiary cyclic amines are formed on treatment with *mercuric acetate* [*401, 402, 1091*], *silver oxide* [*375*], or tert-*butyl hypochlorite* [*707*]. *tert*-Butyl hypochlorite converts methyl pyrrolidine-2-carboxylate into methyl 1-pyrroline-2-carboxylate in 71% yield [*707*], and mercuric acetate transforms 2-*tert*-butylpiperidine into 2-*tert*-butyl-1-piperideine in 75% yield [*1091*]. Tertiary cyclic amines are dehydrogenated by mercuric acetate via quaternary salts [*401,402*]. 1-Methyl-2-ethylpiperidine yields ultimately 1-methyl-2-ethyl-2-piperideine [*402*] and quinolizidine $\Delta^{1(10)}$-dehydroquinolizidine [*401*] (equation 34).

[401]



34

59% ClO_4^- 68%

DEHYDROGENATIVE AROMATIZATIONS

Compounds containing six-membered rings are usually dehydrogenated all the way to carbocyclic and heterocyclic aromatic compounds. The driving force for such a deep dehydrogenation is the resonance energy liberated during the process: 36 kcal for benzene, 61 kcal for naphthalene, 84 kcal for anthracene, 92 kcal for phenanthrene, and 23 kcal for pyridine. Such "aromatizations" are easier if one or especially two double bonds are already present in a ring. The tendency for the aromatization is so strong that the formation of aromatic compounds occurs even when it requires the elimination of quaternary groups [*495*] and intramolecular rearrangements [*493*].

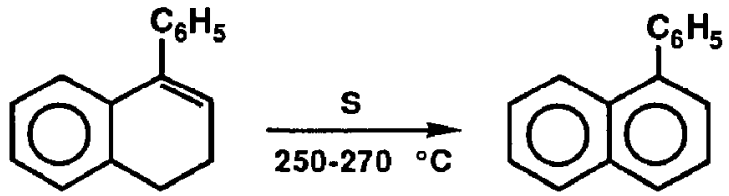
Dehydrogenative aromatizations are effected by heating hydroaromatic compounds with catalytic amounts of *platinum* [*496, 945, 946*] or, more often, *palladium* [*408, 494, 496, 497, 945, 946, 948, 1092*], usually supported on activated charcoal, asbestos, or other large-surface-area materials. Such ***catalytic dehydrogenations*** require temperatures of 250–350 °C and are carried out by refluxing the compounds with the metals or by passing their vapors over the metals. ***Chemical dehydrogenations*** are achieved by heating the compounds with elemental *sulfur* at 230–270 °C [*491, 492*] or red *selenium* at 280–350 °C [*493*].

During dehydrogenations, quaternary groups such as carboxyl or methyl are eliminated [*495*]. Other side chains are preserved [*495*], and if they are unsaturated, they may be hydrogenated [*1093*]. Alcohols are dehydrated, reduced, or rearranged [*1092*]. Ketones in six-membered rings are converted into phenols or hydrocarbons [*496, 947*], whereas those in side chains are left unchanged. However, if the ketone groups are adjacent to six-membered aromatic rings, they are hydrogenated [*494,1092*]. Cyclic structures other than six-membered rings are unchanged or rearranged [*497*].

The yields of dehydrogenations often leave much to be desired, but in many cases, the purpose of such reactions is not to prepare but, rather, to identify natural products such as terpenes or alkaloids by converting them into known aromatic compounds. With the advent of spectroscopic techniques, dehydrogenative aromatizations have lost much of their im-

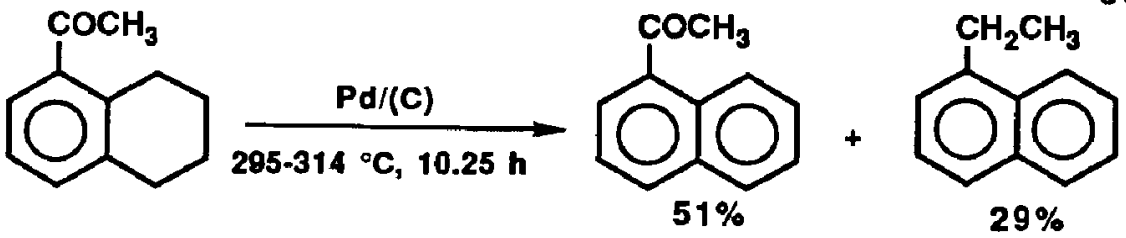
portance. Selected examples of both catalytic and chemical dehydrogenations are shown in equations 35–40 [*492*, *493*, *494*, *495*, *496*, *497*].

[*492*]

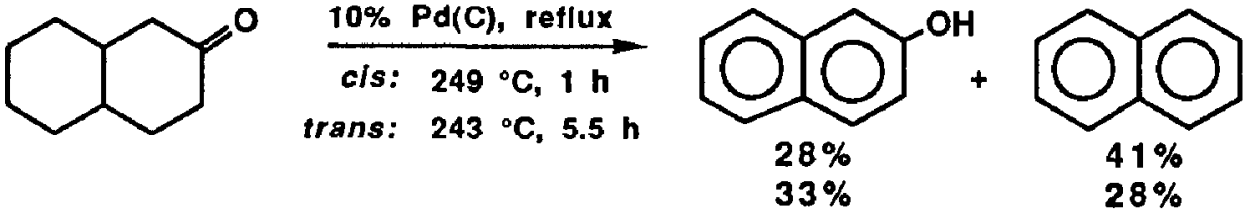


91-94% 35

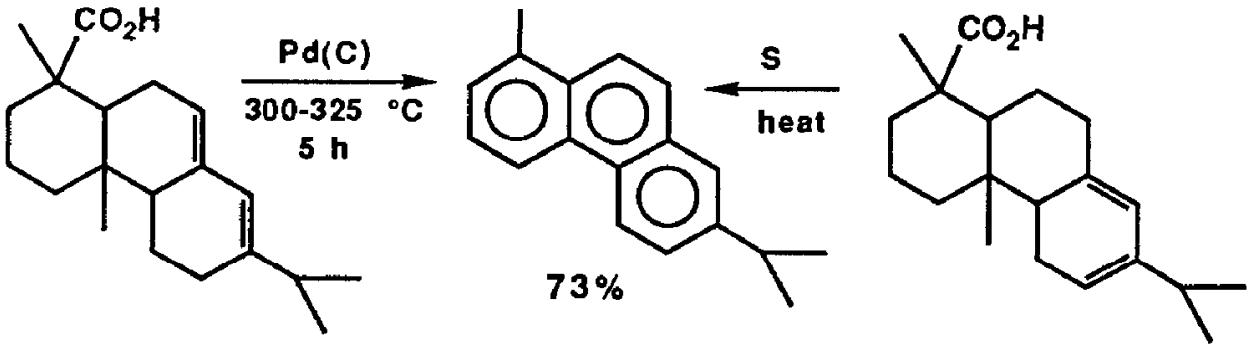
[*494*] 36



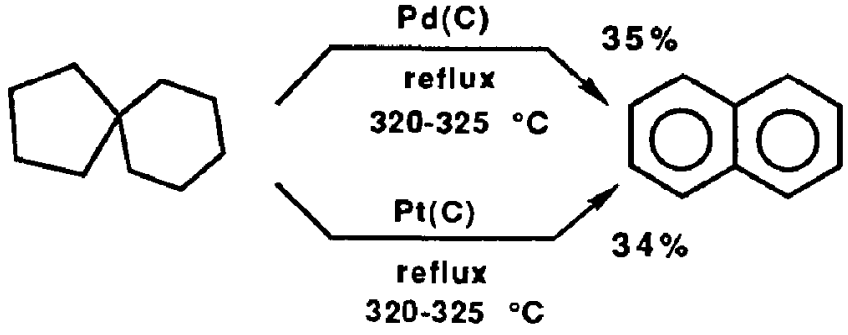
[*496*] 37



[*495*] 38

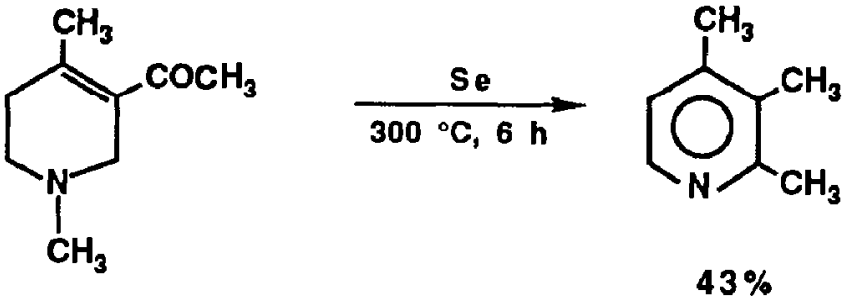


[*497*]



39

[493]



43%

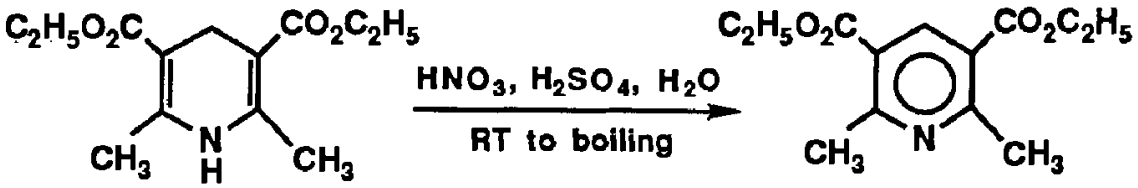
40

Some aromatizations are accomplished with agents other than those previously mentioned. Thus tetralin is converted quantitatively into naphthalene by refluxing with *2,3-dichloro-5,6-dicyano*-p-*benzoquinone* [*970*], and 1,2,3,4-tetrahydrocarbazoles are transformed into carbazoles in 50–95% yields by refluxing with *chloranil* in xylene [*969*]. Anhydrous *aluminum chloride* in refluxing carbon disulfide is used in the preparation of coronene [*408*].

Dehydrogenations are very easy in ***six-membered nitrogen-containing compounds*** that already contain one or two double bonds in the heterocyclic ring. Such dehydrogenations are carried out by *nitric acid* [*458*], *arsenic oxide* (As_2O_5) [*480*], *manganese dioxide* [*825*], *potassium ferricyanide* [*919*], *nitrobenzene*, and others (equations 41 and 42).

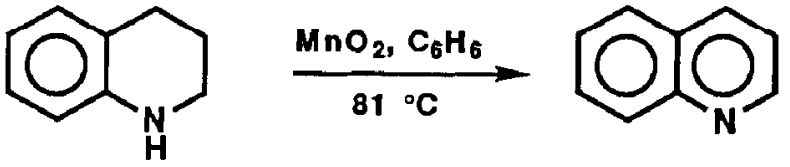
[458]

41



58-65%

[825]



79%

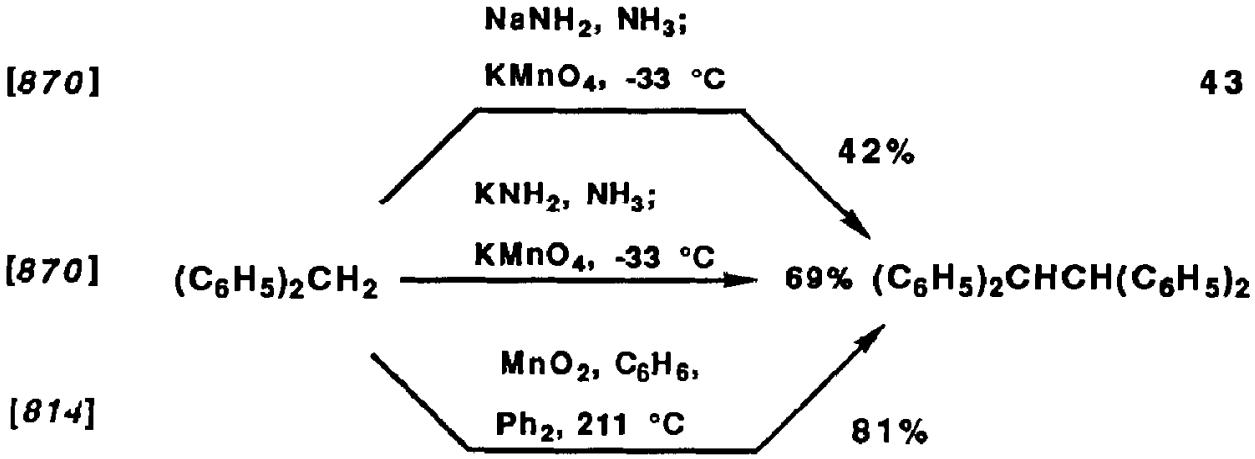
42

DEHYDROGENATIVE COUPLINGS

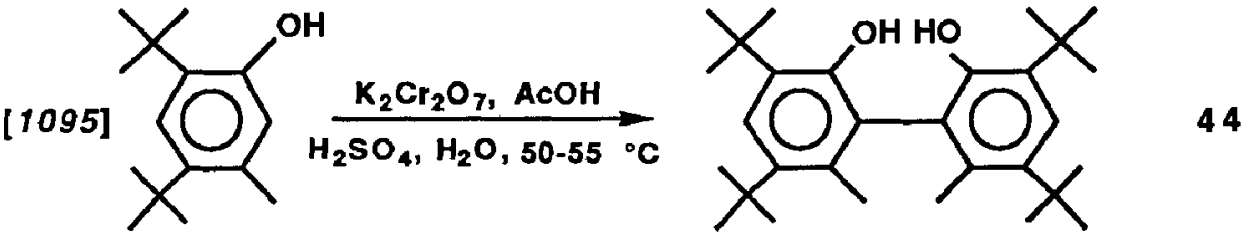
Some compounds are capable of coupling after the initial abstraction of a hydrogen atom from one carbon, usually by a free-radical process. Such abstraction of hydrogen occurs easily when the remaining free radical is stabilized by resonance.

Thus benzene is converted into biphenyl in 54% yield when its vapors are passed at 720 °C through an iron tube [*1094*], and pyrene furnishes

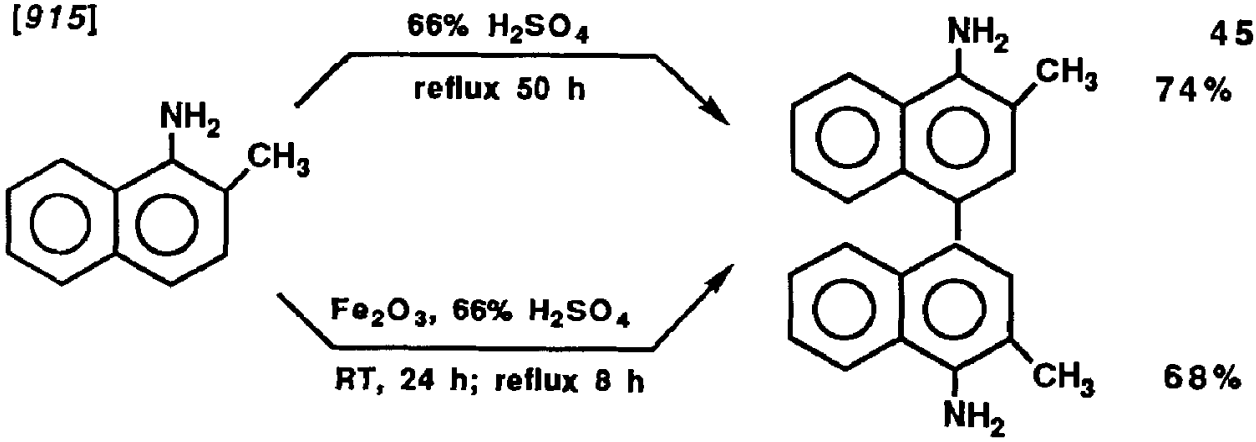
1,1'-bipyrene in 70–75% yield when heated with a solution of *periodic acid* in acetic acid at 48–51 °C [*757*]. Coupling takes place easily at benzylic positions. Diarylmethanes give tetraarylethanes on treatment with *oxygen* in alcoholic potassium hydroxide [*1*] and on oxidation with *manganese dioxide* [*814*] or *potassium permanganate* [*870*] (equation 43).



Coupling in *para* or *ortho* positions is easily accomplished with phenols [*912, 1037, 1095*] and aromatic amines [*915*]. β-Naphthol, on refluxing with anhydrous *ferric chloride* in ether, is converted in 60% yield into α,α'-bi-β-naphthol [*912*], and 2,4-bis(*tert*-butyl)-5-methylphenol, on heating with *chromic acid*, yields the corresponding "dimer" [*1095*] (equation 44).

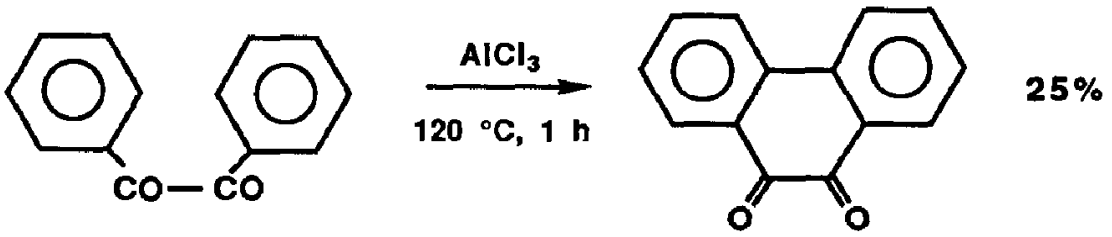


The refluxing of 1-amino-2-methylnaphthalene with *66% sulfuric acid* for 50 h or in the presence of *ferric oxide* for 8 h yields 4,4'-bis(1-amino-2-methyl)binaphthyl [*915*] (equation 45).



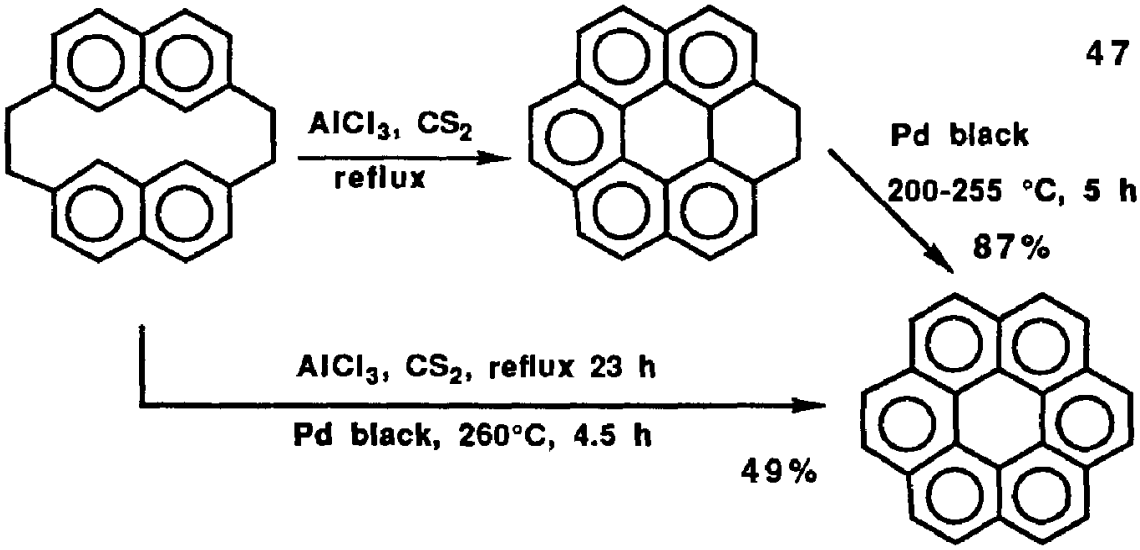
If such oxidative couplings occur within the same molecule, cyclizations, usually to six-membered rings, take place. Anhydrous *aluminum chloride* proves useful in such intramolecular dehydrogenations. At 120 °C, it cyclizes benzil to 9,10-phenanthrenequinone [*407*] and bridges benzene rings in the synthesis of coronene [*408*]. At the same time, partial aromatization takes place (equations 46 and 47).

[*407*] 46

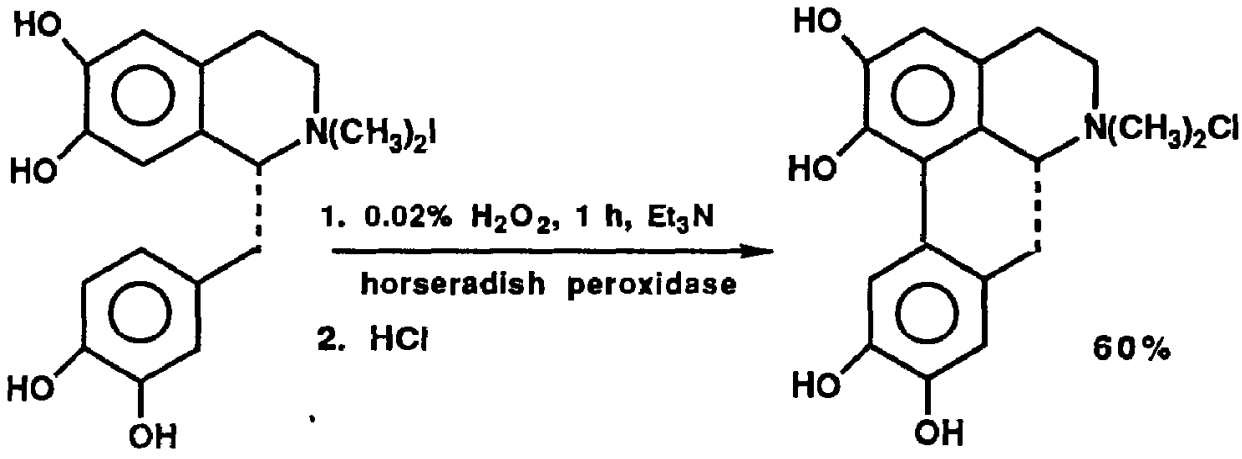


25%

[*408*] 47



[*1037*] 48



laudanosoline methiodide

apomorphine methochloride

A large-scale application of intramolecular coupling combined with concomitant aromatization is the industrial conversion of heptane into toluene in 72% yield on heating at 500 °C in the presence of chromium and aluminum oxides [*1096*].

Dehydrogenative cyclizations are also accomplished with *potassium ferricyanide* [*920*] and with *hydrogen peroxide* in the presence of horseradish peroxidase [*1037*] (equation 48).

Chapter 3
Oxidations

OXIDATIONS OF INDIVIDUAL FUNCTIONAL GROUPS are organized according to the following sequence: alkanes and cycloalkanes; alkenes and cycloalkenes; alkynes (acetylenes); aromatic compounds (including heterocyclic aromatic compounds); halogen compounds; alcohols; ethers; aldehydes, ketones, and their derivatives; carboxylic acids and their derivatives; nitrogen compounds; phosphorus and arsenic compounds; sulfur compounds; selenium compounds; iodo compounds; boron compounds; silicon and tin compounds; and organomagnesium and organomercury compounds. Within the individual sections, the oxidants are arranged more or less in the same order as in Chapter 1, Oxidation Agents. The most commonly used oxidants are printed in **boldface** type, and the less frequently used ones are printed in *italic* type. The rest of the oxidants are applied only on special occasions or sporadically or have been tested only on a limited number of cases. Other items of importance, such as important compound types or reactions and safety warnings, are emphasized by printing in ***boldface italic*** type.

If a functional group characteristic of the classes of compounds just mentioned is remote enough to be affected by another functional group present in the molecule, its oxidation may be discussed at the same place as would be the oxidation of the parent compound. For example, the epoxidation of oleic acid is described in the section on alkenes. However, the oxidation of mesityl oxide, where the double bond is conjugated with the carbonyl group, is discussed under ketones. Oxidations of difunctionalized compounds are described in the sections discussing the higher functional groups. Thus, oxidations of aldols to dicarbonyl compounds will be discussed in the section on aldehydes or ketones (not alcohols). Frequent cross-references should facilitate location of the desired oxidation.

ALKANES AND CYCLOALKANES

Oxidations of alkanes and cycloalkanes are rare and not easy. The rates of oxidation with chromic acid of methyl, methylene, and methine

groups differ by 2 orders of magnitude: CH_3:CH_2:CH 1:65:3500 (later, rates in the ratio 1:114:7000–18,000 were found) [*1097*]. These rates are comparable with those of hydrogen abstraction by bromine (1:82:1640) [*620*].

A similar increase in reactivities in the methyl–methylene–methine series is found in the free-radical oxidations of lower alkanes with oxygen in the presence of hydrogen bromide as an initiator of the reaction. Ethane gives a 64% yield of acetic acid at 220 °C, propane gives a 72% yield of acetone at 189 °C, and isobutane gives a 69.5% yield of *tert*-butyl hydroperoxide, a 10% yield of *tert*-butyl alcohol, and a 6% yield of di-*tert*-butyl peroxide at 163 °C [*54*].

Terminal ***methyl groups,*** as well as the halomethyl groups in aliphatic halides with 15–18 carbon atoms, are oxidized biochemically to ***carboxyls*** (equation 49) [*1086, 1087*].

49

[*1086*] [*1087*]

$$CH_3(CH_2)_{14}CH_2X \xrightarrow[25\ ^\circ C,\ 24\ h]{\textit{Torulopsis gropengiesseri}} HO_2C(CH_2)_{14}CO_2H^*$$

X	Yield (%)
F	9
Cl	33
Br	50
I	43

***The products were isolated as the methyl esters.**

Similar microbial oxidations of terminal methyl groups accompanied by degradation and dehydrogenations of the carbon chains take place in alkyl benzenes [*1053, 1071*].

Methylene groups are hydroxylated to give alcoholic groups. Such ***hydroxylations*** are rarely achieved chemically but occur frequently in *biochemical processes.* The vast majority of such hydroxylations takes place in steroidal ketones and will be discussed in the section on ketones.

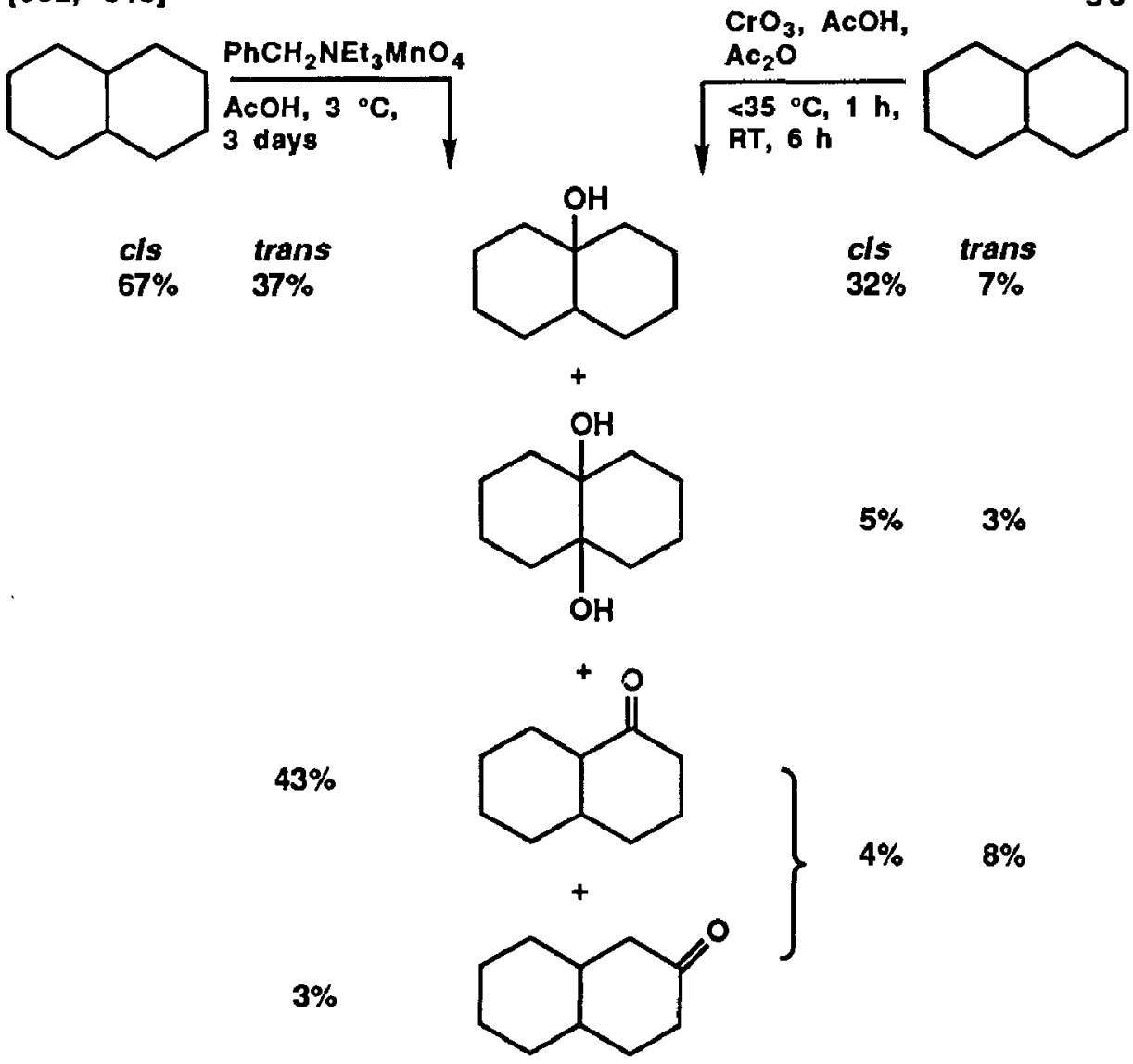
A methylene group is oxidized to a carbonyl group only if it is activated by neighboring aromatic rings, as in fluorene, or by carbonyl or carboxyl groups.

The relatively most frequent reaction is oxidation at the ***methine group*** giving tertiary alcohols as main products and secondary alcohols and ketones as minor products [*902*]. The hydroxylation occurs predominantly with retention of configuration [*329, 620*]. The oxidation of 3-ethylpentane with benzyltriethylammonium permanganate yields 24% of 3-ethyl-3-pentanol, 25% of 3-ethyl-2-pentanone, and 25% of 3-pentanone [*902*]. Under the same conditions, methylcyclohexane yields 72% of 1-methylcyclohexanol and 3% of 2-methylcyclohexanone [*902*].

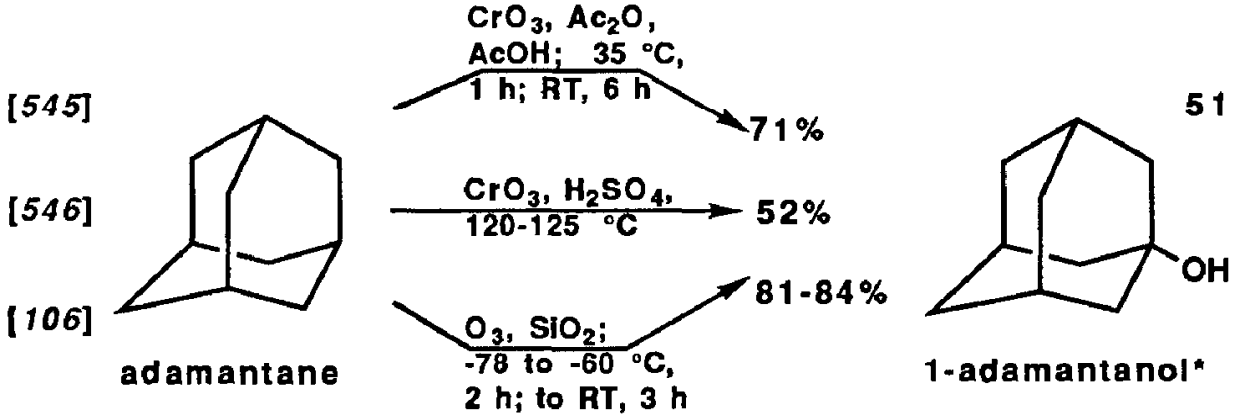
Decalins oxidized by *p*-nitroperoxybenzoic acid in refluxing chloro-

form give 9-decalols with 95–96% regiospecificity and 99–100% stereospecificity (the isolated yield of *cis*-decalol is 69%) [*329*]. The distribution of the products of oxidation of diastereomeric decalins with other oxidants is shown in equation 50 [*545, 902*].

[*902, 545*] **50**



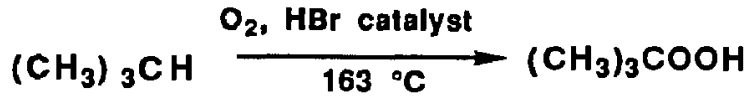
The oxidation of adamantane occurs almost exclusively at the tertiary carbon, C-1 (equation 51) [*106, 545, 546*].



*The byproduct (7%) was 2-adamantanone.

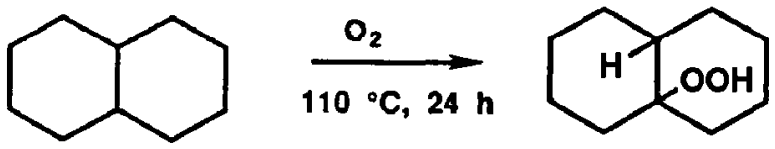
The oxidation of hydrocarbons containing tertiary hydrogens gives ***hydroperoxides*** [*54*], sometimes in very low conversions [*48*] (equations 52 and 53).

[*54*]



70% 52

[*48*]



trans 1.5% 53

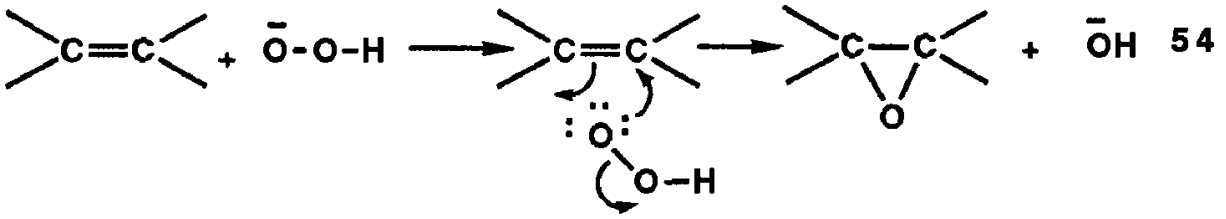
ALKENES AND CYCLOALKENES

The oxidation of alkenes and cycloalkenes may affect the double bonds, the rest of the molecule, or both. Also included in this section are aromatic hydrocarbons containing double bonds in their side chains. Compounds containing double bonds and other functional groups, such as hydroxyl, carbonyl, or carboxyl, will be discussed in the appropriate sections, such as unsaturated alcohols, aldehydes, ketones, acids, and esters.

Epoxidation

The simplest imaginable case of oxidation of a double bond is the industrial production of ethylene oxide from ethylene and oxygen in the presence of silver oxide on alumina at 270 °C [*1098*].

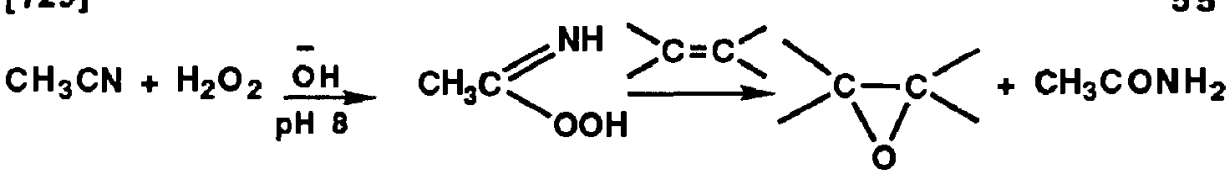
In the laboratory, epoxidations of alkenes are usually accomplished by hydrogen peroxide or its derivatives. **Hydrogen peroxide** is applied in an alkaline medium so that it reacts as an anion (equation 54) [*138, 142, 143, 146, 147, 148, 1099*].



54

In the presence of a nitrile, alkaline hydrogen peroxide forms peroxycarboximidic acid, which, in the presence of an alkene, gives an epoxide and a carboxamide (equation 55) [*129*].

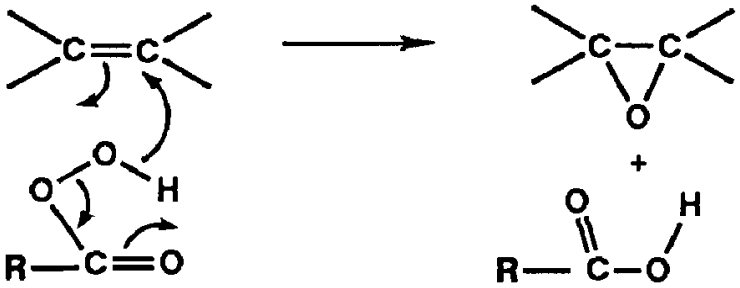
[*129*]



55

***tert*-Butyl hydroperoxide** epoxidizes double bonds either in alkaline solutions [*220*] or in the presence of transition metal compounds of titanium, vanadium, chromium, or molybdenum [*215, 216, 217, 221, 222, 223*]. In the presence of chiral reagents, such as titanium tetraisopropoxide and (*R,R*)- or (*S,S*)-diethyl tartrate, chiral epoxides are obtained (where applicable) [*223*].

The most popular derivatives of hydrogen peroxide used for epoxidation are organic **peroxy acids** (equation 56): peroxyacetic [*250, 251*], peroxytrifluoroacetic [*283, 287*], peroxybenzoic [*295, 296, 297, 300*], *m*-chloroperoxybenzoic [*315, 316*], *p*-nitroperoxybenzoic [*328*], peroxyphthalic [*330*], peroxymaleic [*338*], and peroxylauric [*174*].



56

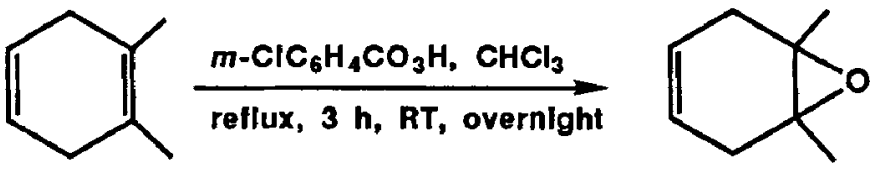
Other oxidants used for epoxidation are dimethyldioxirane [*210*], ozone [*107*], thallium triacetate [*412*], *chromic oxide* [*564*], chromyl compounds [*679*], *sodium hypochlorite* [*112, 689*], calcium hypochlorite [*704*], N-*bromosuccinimide* in water [*746*], iodine and silver oxide [*751*], iodine triacetate [*785*], electrolysis [*119*], and *microorganisms* [*1055, 1063*].

Epoxidation takes place preferentially or more rapidly at ***electron-rich*** (i.e., tetraalkylated) ***double bonds*** [*217*]. The reaction is ***stereospecific:*** *cis* alkenes give *cis* epoxides, and *trans* alkenes give *trans* oxides [*217*]. 1,2-Dimethylcyclopentene is oxidized with *peroxybenzoic acid* to 1,2-dimethylcyclopentene oxide in 85% yield [*296*], and *cis*-cyclooctene is transformed by hydrogen peroxide into *cis*-cyclooctene oxide in 60–61% yield [*1099*].

4-Vinylcyclohexene and *tert*-butyl hydroperoxide, in the presence of chromium acetylacetonate, yield exclusively 4-vinylcyclohexene oxide [*217*].

In 1,2-dimethylcyclohexa-1,4-diene, m-*chloroperoxybenzoic acid* epoxidizes only the electron-rich tetrasubstituted double bond to give a 68–78% yield of the 1,2-oxide (equation 57) [*316*].

[*316*]



57

68-78%

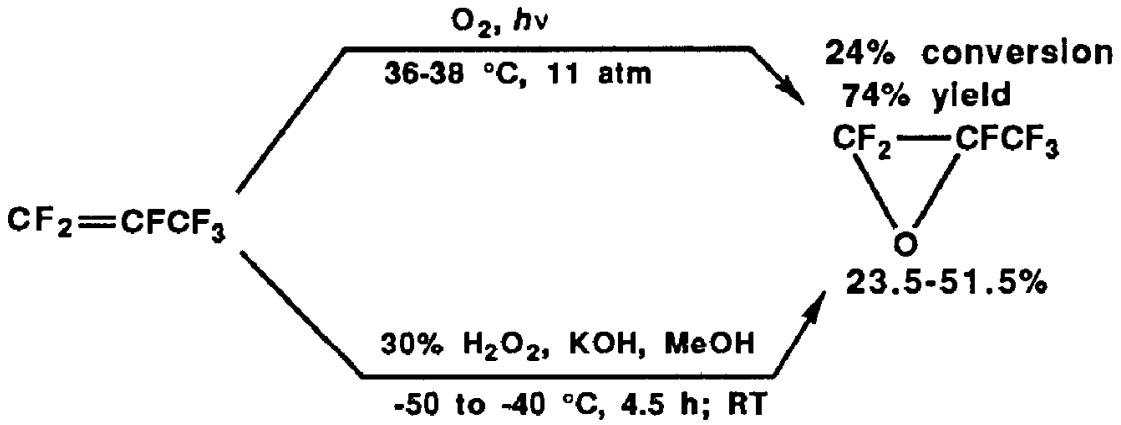
The oxidation of isobutylene with thallium triacetate gives 82% of isobutylene oxide [*412*]. The oxidation of 1-pentene with *peroxytrifluoroacetic acid* yields 81% of propyloxirane [*283*]. The electrooxidation of

2-octene in dimethylformamide gives 73% of 1-methyl-2-pentyloxirane [*119*], and the oxidation of 1-hexadecene with *Corynebacterium equii* furnishes a 41% yield of (*R*)-1-tetradecyloxirane of 100% optical purity [*1055*]. 2-Cholestene is converted by iodine tris(trifluoroacetate) at –18 °C into 2-cholestene oxide [*785*], and the treatment of 1-mesitylstyrene with ozone in pentane at –78 °C gives 1-mesitylstyrene oxide in 71% yield [*107*]. The reaction of 1,1-dimethyl-2,2-diphenylethylene with *chromic oxide* in acetic anhydride yields 76% of the corresponding epoxide (oxirane) [*564*].

In *cis,trans*-1,5-cyclodecadiene, only the *trans* double bond is epoxidized with *peroxyacetic acid* in 80% yield.

Halogenated alkenes are transformed into halogenated epoxides by oxygen or hydrogen peroxide (equation 58) [*1100*].

[*1100*] 58

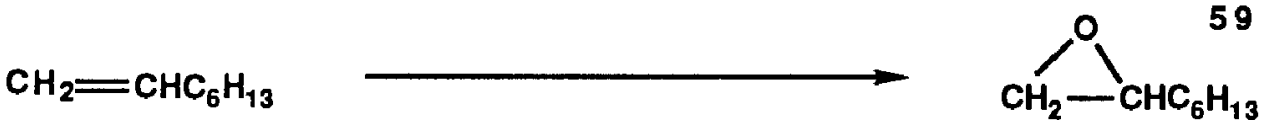


More examples of epoxidations of alkenes, cycloalkenes, and aromatic compounds having double bonds in their side chains are shown in equations 59–63 [*129, 210, 217, 251, 300, 315, 330, 338, 679, 689, 746, 751*].

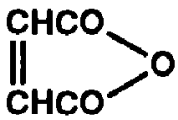
Epoxidations of unsaturated alcohols, aldehydes, ketones, and acids and their derivatives are discussed in the appropriate sections.

EXAMPLES OF EPOXIDATION

59



[*679*] $CrO_2(NO_3)_2$, DMF, CH_2Cl_2, CCl_4, -78 °C, 30 min 43%

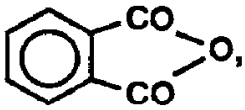
[*338*] 90% H_2O_2,  , CH_2Cl_2, 0 °C, 1.8 h 80%

[*217*] *t*-BuOOH; Cr, V, VO, or MoO_2 acetylacetonates; 25 °C 53%

60

[129] 50% H_2O_2, MeCN, MeOH, NaOH (pH 9.5-10), 60 °C, 3.5 h — 85%

[315] *m*-$ClC_6H_4CO_3H$, KF, CH_2Cl_2, RT, overnight — >95%

[330] 30% H_2O_2,  , Et_2O, RT; 0 °C — 64%

[679] $CrO_2(NO_3)_2$, C_5H_5N, CH_2Cl_2, CCl_4, -78 °C, 30 min — 75%

[746] NBS, H_2O, RT, 10 min; aqueous NaOH, 60 °C, 30 min — 81%

[751] I_2, Ag_2O, dioxane-H_2O (12:1), RT, 7 h — 80%

61

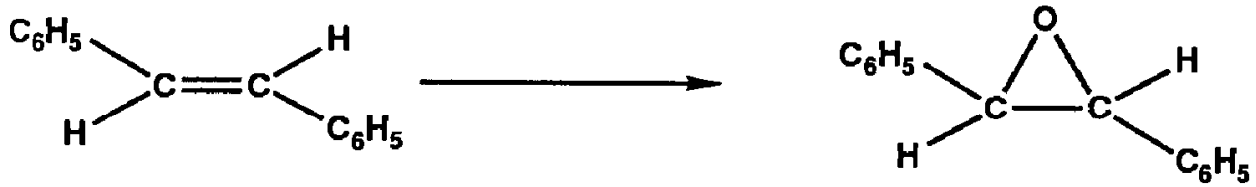
[129] 50% H_2O_2, MeCN, MeOH, NaOH (pH 7.5), 50 °C, 6 h — 74%

[300] BzO_2H, $CHCl_3$, 0 °C, 24 h — 69-75%

[746] NBS, H_2O, RT; 20% NaOH, 60 °C, 30 min — 85%

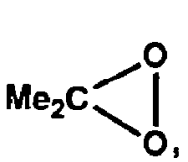
[679] $CrO_2(NO_3)_2$, DMF, CH_2Cl_2, -78 °C, 30 min — 83%

62



[251] 40% AcO_2H, AcONa, CH_2Cl_2, 20-35 °C, 15 h — 70-75%

[210] [$2KHSO_5.KHSO_4.K_2SO_4$ (Oxone) + Me_2CO]



Me_2CO, 22 °C, 2 h — 73%

[679] $CrO_2(NO_3)_2$, DMF, CH_2Cl_2, CCl_4, -78 °C, 30 min — 30% + C_6H_5CHO (9%)

63

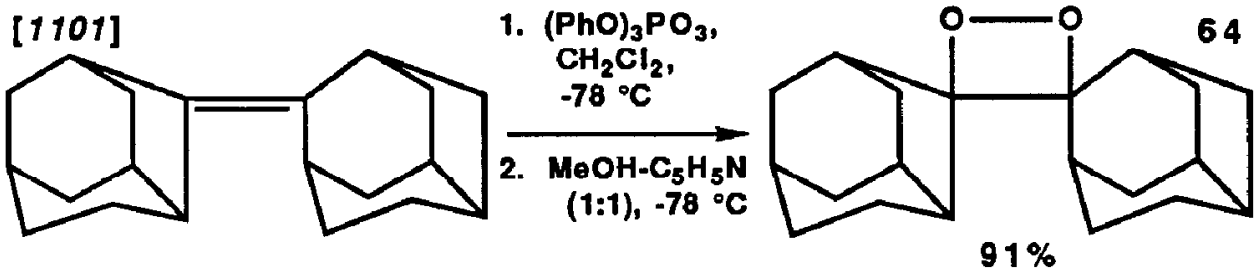
[689] NaOCl (pH 8-9), Bu_4NHSO_4, $CHCl_3$, RT, 15 min to 24 h — 90%

[210] Me_2CO, K_2SO_5, Bu_4NHSO_4 (pH 7.5-8.5), CH_2Cl_2, 0-10 °C, 5.5 h — 65%

Formation of Dioxetanes

The addition of one molecule of oxygen across a double bond results in the formation of dioxetanes, compounds containing two atoms of oxygen in a four-membered ring. Such compounds are formed especially from alkenes that do not possess allylic hydrogens. The addition is stereospecific, occurs in the *syn* mode [*36*], and takes place when **singlet oxygen,** generated chemically or photochemically, is applied. Many dioxetanes are isolated and even distilled at low temperatures. In other cases, they are assumed to be intermediates in the formation of dicarbonyl compounds.

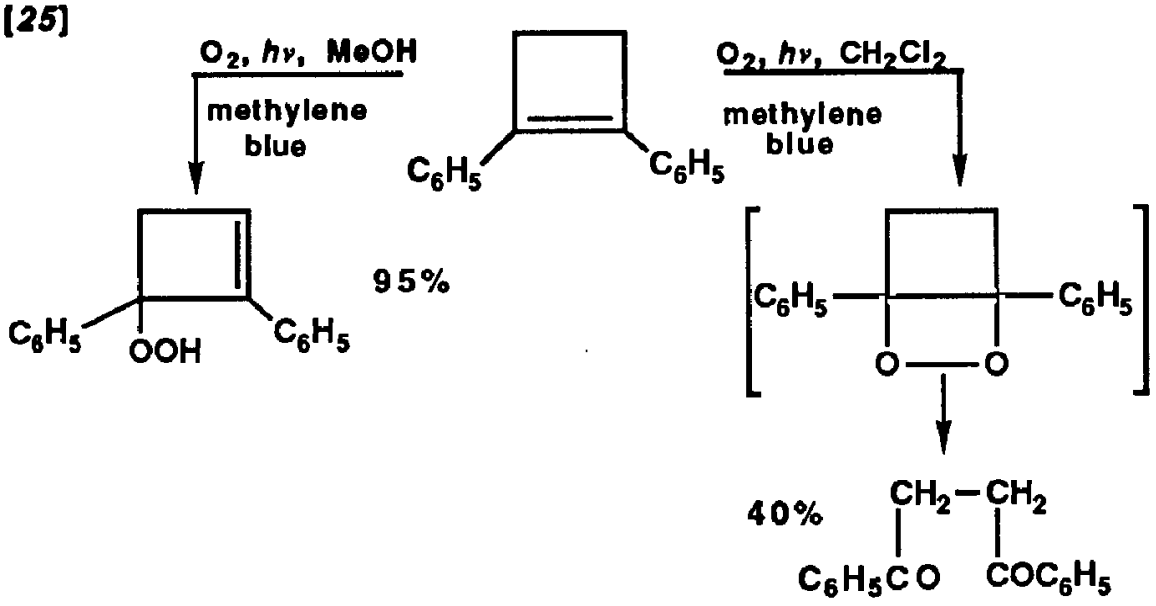
Biadamantylene dissolved in methylene chloride at –78 °C and treated with a solution of triphenyl phosphite ozonide in the same solvent and subsequently with a mixture of methanol and pyridine gives biadamantylene dioxetane in 91% yield (equation 64). The dioxetane decomposes at 150 °C [*1101*].



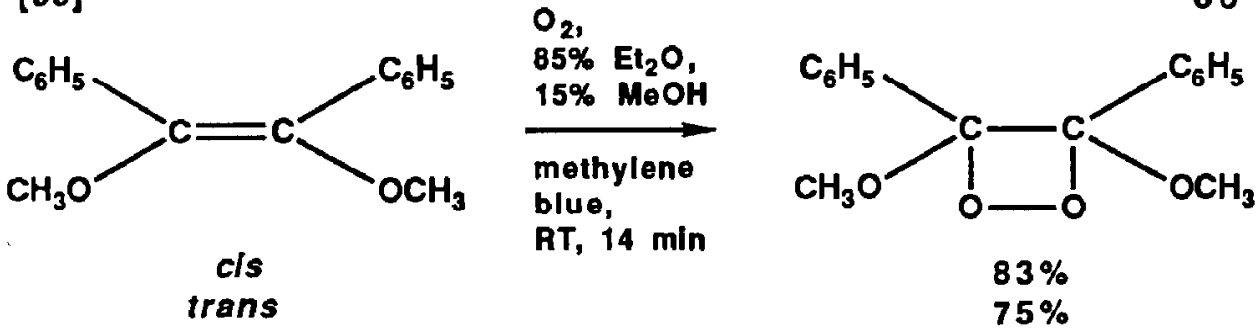
In the oxidation of indene [*39*] and of 1,2-diphenylcyclobutene [*25*] with singlet oxygen generated by irradiation of the solutions of the compounds in the presence of sensitizers, dioxetanes are the probable intermediates in the conversion of the unsaturated hydrocarbons into dialdehydes and diketones, respectively. Different products may be formed depending on the solvents used (equation 65) [*25*].

The stereospecific addition of singlet oxygen to *cis*- and *trans*-1,2-diethoxyethylene under irradiation with rose bengal as a sensitizer in fluorotrichloroethane at –78 °C gives *cis*- and *trans*-1,2-diethoxydioxetane [*40*]. Similarly, *cis*- and *trans*-α,α′-dimethoxystilbene give *cis*- and *trans*-1,2-dimethoxy-1,2-diphenyloxetane (equation 66) [*38*].

[25] 65

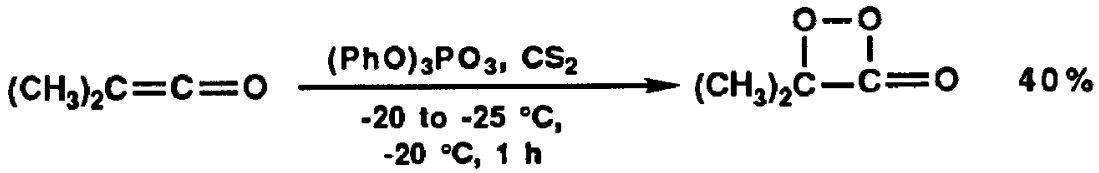


[38] 66



Tetramethoxyethylene in ether at –70 °C treated with oxygen under irradiation in the presence of zinc tetraphenylporphyrin furnishes a 94% yield of 1,1,2,2-tetramethoxydioxetane [*37*]. Chemically generated singlet oxygen converts substituted ketenes into α-peroxylactones (equation 67) [*20*].

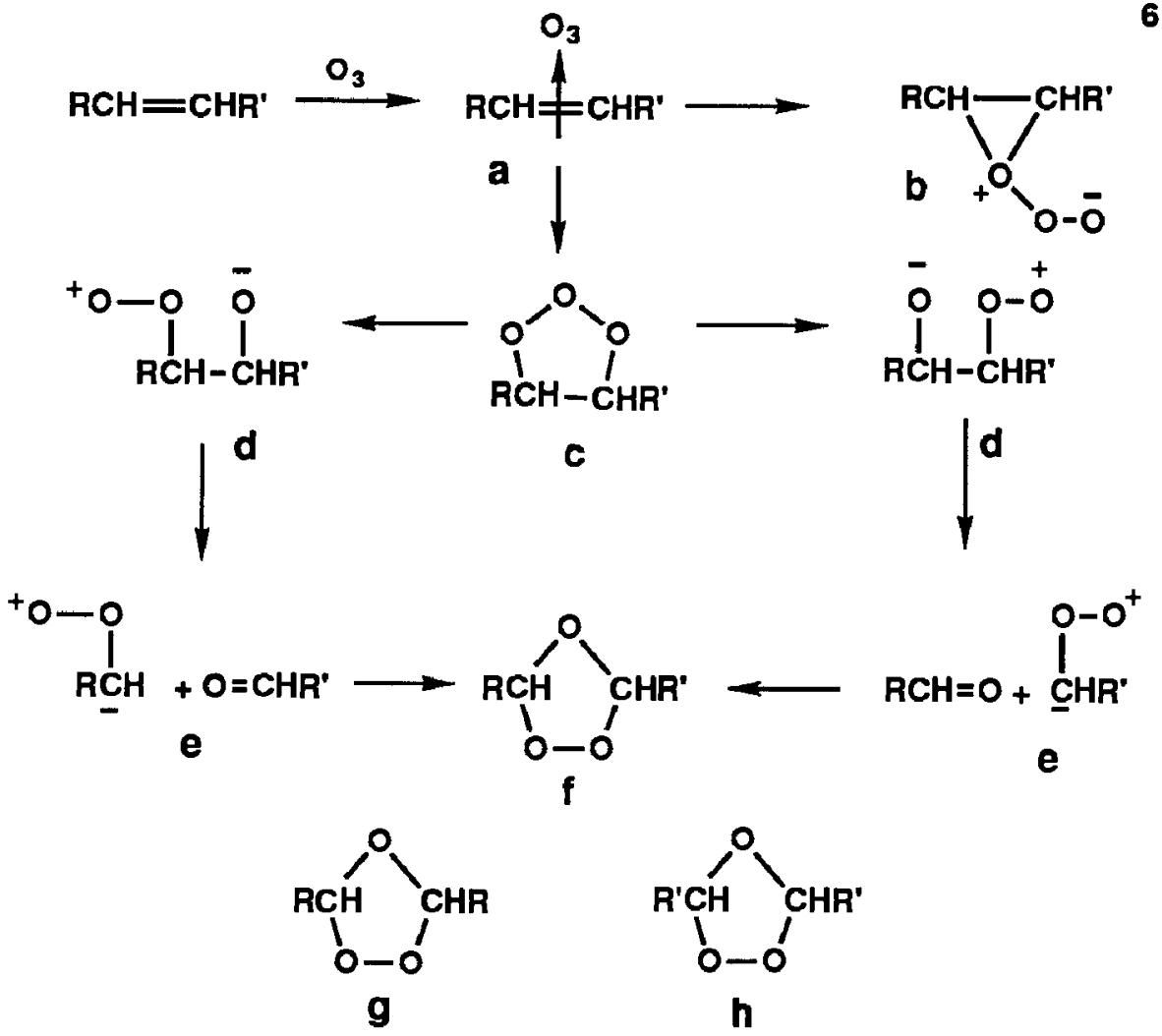
[20] 67



Formation of Ozonides

The mechanism of the reaction of **ozone** with double bonds (equation 68) is very complex and still subject to arguments. An alkene and ozone may first form a π complex (**a**), which forms a σ complex (**b**), a "molozonide" (**c**), or both. The molozonide may change to a dipolar ion (**d**), which breaks down with the fission of the carbon–carbon bond to a carbonyl compound and another dipolar ion (**e**). The two species recombine to give the ultimate product, ozonide (**f**) (1,3,4-trioxolane, also known as 1,3,4-trioxacyclopentane) [*76*]. The temporary presence of the carbonyl com-

68



pounds and the dipolar ion **e** explains formation of the "crossed" ozonides **g** and **h**.

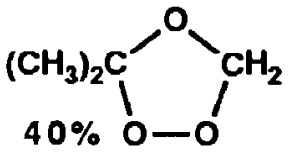
The reaction is even more complicated when *cis–trans* isomerism is involved. Whereas *trans*-2,2,5,5-tetramethyl-3-hexene gives *trans*-di-*tert*-butylethylene ozonide, the *cis* isomer gives a mixture of 70% of *cis* ozonide and 30% of *trans* ozonide [*79*]. The ratios of *cis* and *trans* isomers may vary over a wide range depending mainly on the bulkiness of the alkyl groups at the double bonds. Whereas both *cis*- and *trans*-2-butene yield *cis* and *trans* ozonides in the ratio 2:3, *cis*-ethyl-*tert*-butylethylene gives *cis* and *trans* ozonides in the ratio 2:1. With the *trans* alkene, the ratio is 3:7 [*76*].

In the majority of cases, the ozonide structure is unimportant, because the purpose of the ozonation of double bonds is to prove structures by cleaving the chain or ring to form alcohols, aldehydes, ketones, or acids after reductive or oxidative workup of the ozonides.

When ozonides are to be isolated, a stream of 2–6% ozone in oxygen is passed through a solution of an alkene or a cycloalkene in low-boiling solvents, such as methyl chloride, pentane, hexane, chloroform, or carbon tetrachloride, at low temperatures (−78 to 5 °C) until the solution acquires a blue tinge (the color of ozone). The solvent is then evaporated at reduced

pressure, and the ozonide is left as a solid, which is frequently polymeric, or a liquid, which can sometimes be distilled in vacuo. ***Safety precautions*** such as the use of face shields or protective shields and working in a hood ***are imperative*** [75].

Isobutylene gives a liquid ozonide, which is isolated in 40% yield by distillation at 43–43.5 °C at 143 mm of Hg (equation 69) [75].

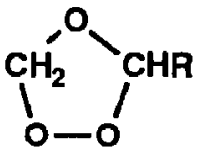
[75] $(CH_3)_2C{=}CH_2 \xrightarrow[\text{-75 °C; distillation}]{\text{6\% } O_3,\ MeCl}$  69

40%

bp 43-43.5 °C
at 143 mm of Hg

Similarly, 1-pentene ozonide distilling at 44–45 °C (at 32 mm of Hg) is obtained in 48% yield from 1-pentene [75]. *cis*- And *trans*-di-*tert*-butylethylene ozonides (bp 23 °C at 0.3 mm of Hg) are obtained by ozonization of *cis*- and *trans*-2,2,5,5-tetramethyl-3-hexene in pentane solutions at -75 °C in 82 and 58% yields, respectively [78, 79].

1-Dodecene and 1-tridecene give quantitative yields of the ozonides in pentane and chloroform solutions, respectively. Pentane is more suitable as a solvent than chloroform or carbon tetrachloride (equation 70) [77].

[77] $CH_2{=}CHR \xrightarrow{O_3}$  70

$R = C_{10}H_{21}$	C_5H_{12}, -10 °C	99%
$R = C_{11}H_{23}$	$CHCl_3$, -5 °C	99%

Ozonides are hardly ever isolated. Rather, conversions to products of **ozonolysis** are carried out in the same reaction vessels (*see* Oxidative Cleavage of Double Bonds, page 77).

Hydroxylation

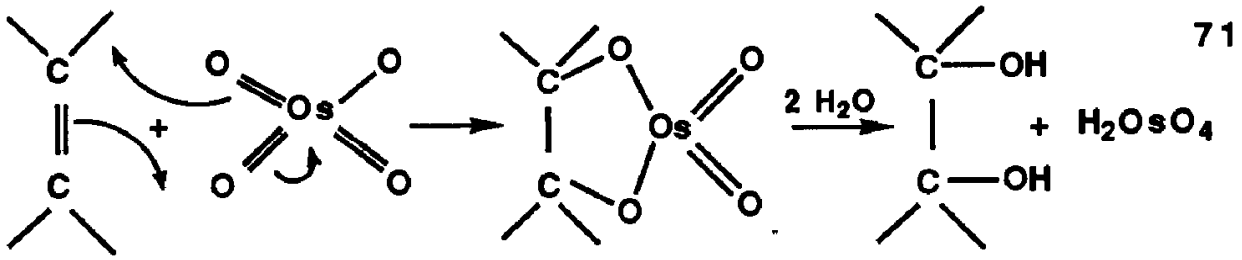
Hydroxylation, the addition of two hydroxyl groups across double bonds, converts ***alkenes and cycloalkenes into vicinal diols. Stereochemically***, the addition may occur in the *syn* or the *anti* mode. In open-chain alkenes (with the exception of terminal alkenes for which stereochemistry is irrelevant), *syn* hydroxylation transforms *cis* alkenes into *erythro* (or *meso*) diols and *trans* alkenes into *threo* (or DL) diols. *anti* Hydroxylation of *cis* alkenes gives *threo* (or DL) diols, whereas *anti* hydroxylation of *trans* alkenes yields *erythro* (or *meso*) diols. *syn* Hydroxylation of cycloalkenes gives *cis* diols, whereas *anti* hydroxylation furnishes *trans* diols (Table I).

syn Hydroxylation results from the hydrolysis of five-membered cyclic

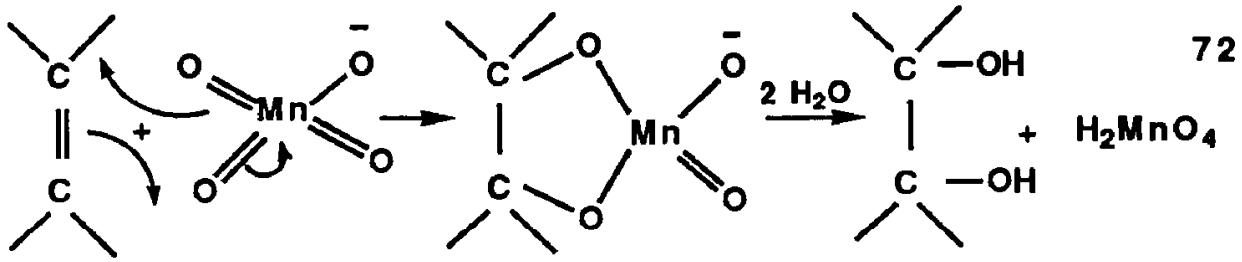
Table I. Stereochemistry of Hydroxylation of Alkenes and Cycloalkenes

Structure of Alkene	*Mode of Addition*	*Structure of Diol*
cis (symmetrical)	*syn*	*meso*
	anti	DL
trans (symmetrical)	*syn*	DL
	anti	*meso*
cis (nonsymmetrical)	*syn*	DL-*erythro*
	anti	DL-*threo*
trans (nonsymmetrical)	*syn*	DL-*threo*
	anti	DL-*erythro*
cyclic (3–7-membered ring)	*syn*	*cis*
	anti	*trans*

esters of osmic or permanganic acid obtained by treatment of alkenes with osmic acid (osmium tetroxide) or potassium permanganate (equations 71 and 72).



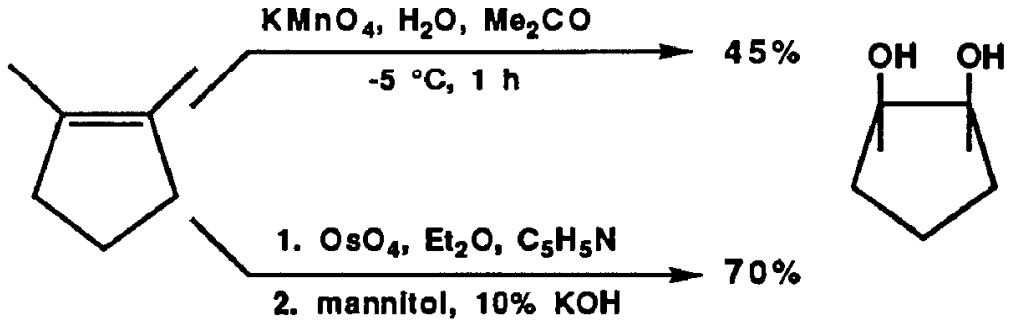
71



72

syn *Hydroxylations* (equation 73) are achieved by dilute aqueous solutions (1–2%) of **potassium permanganate** at low temperatures (0–5 °C). Yields are not too high because the isolation of the water-soluble diols from dilute aqueous solutions is very difficult [*296, 853*]. Therefore, the alternative hydroxylation with **osmium tetroxide (osmic acid)** is preferred [*949*]. Because this reagent is very toxic and very expensive, usually only

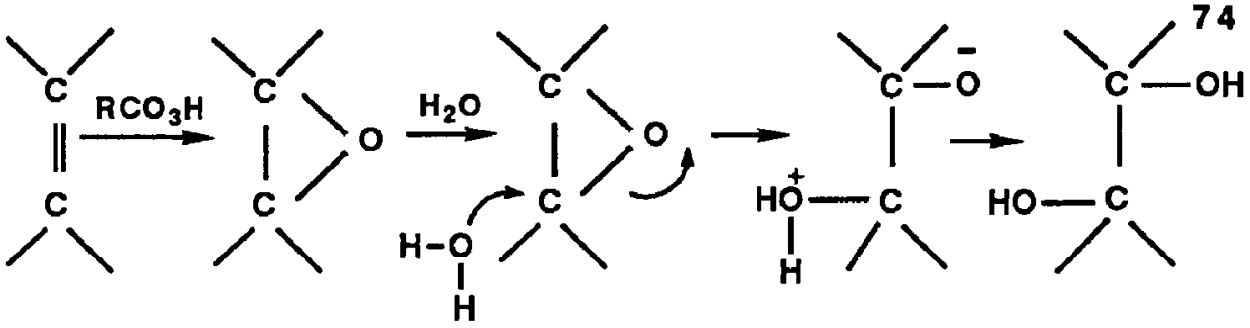
[*296*] 73



[*949*]

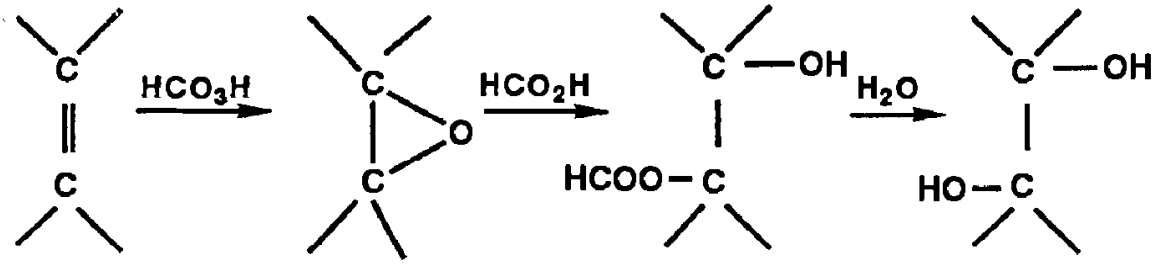
catalytic amounts are used in the presence of oxidizing agents such as *hydrogen peroxide* [*130, 152*], *sodium chlorate* [*714*], *potassium chlorate* [*715*], silver chlorate [*310*], barium chlorate [*310*], or amine oxides [*952*], which reoxidize hexavalent osmium to octavalent osmium.

anti *Hydroxylations* are achieved by reagents forming three-membered epoxides, which are hydrolytically cleaved by back-side nucleophilic attack (inversion) (equation 74).



74

With strong acids such as **formic acid** or **trifluoroacetic acid,** the opening of the epoxide gives the half-ester of the diol, which is easily hydrolyzed to the diol (equations 75–77) [*240, 288*].



75

[*240*]

76

$$CH_2{=}CHC_{12}H_{25} \xrightarrow[\text{40 °C, 24 h}]{\text{1. 25.6\% } H_2O_2\text{, 98-100\% } HCO_2H} \xrightarrow[\text{2. 3 N KOH/EtOH, reflux 1 h}]{} CH_2CHC_{12}H_{25}\ (HO,\ OH)$$

95% crude
69% pure

[*288*]

77

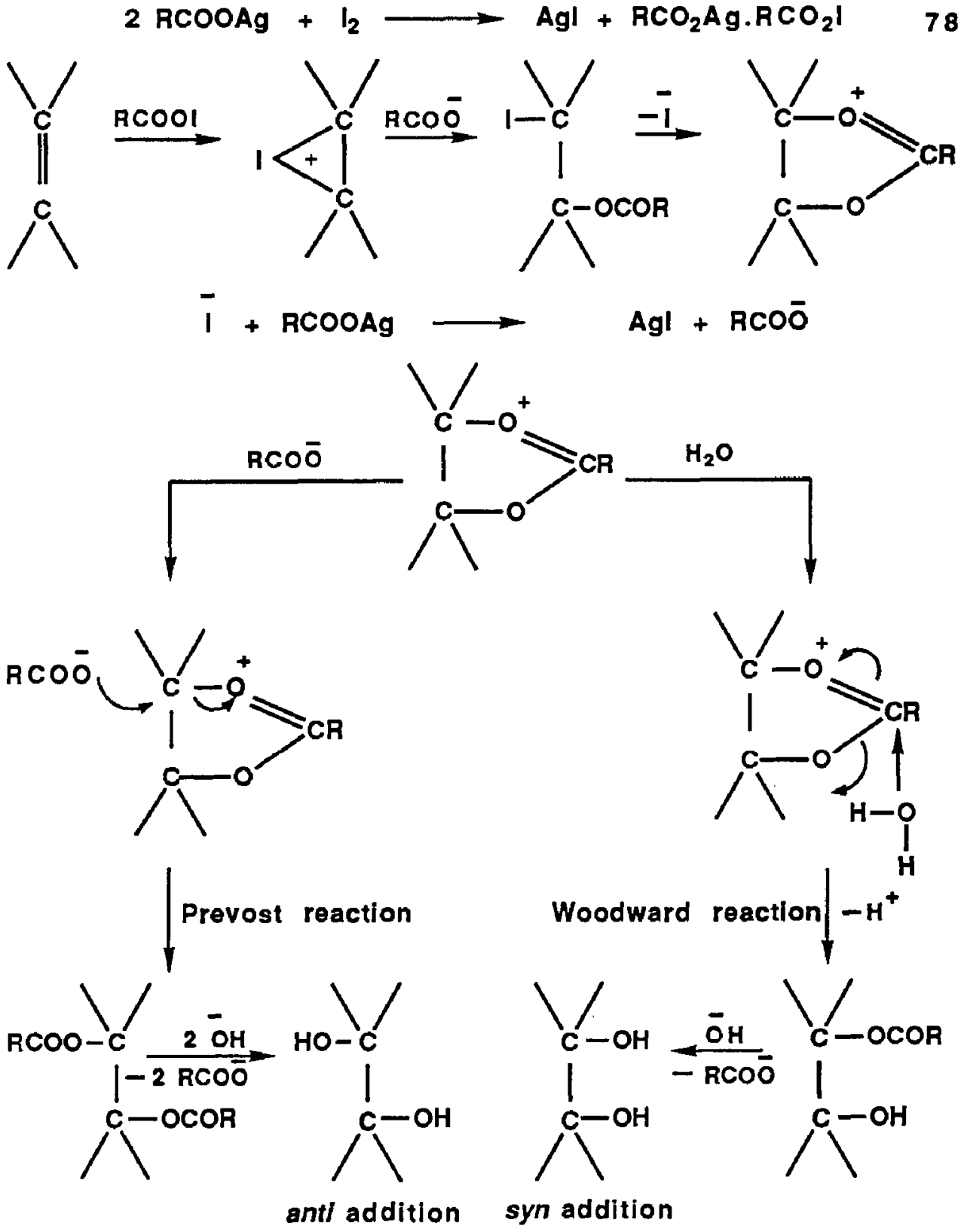
$$CH_3CH{=}CHC_2H_5 \xrightarrow[\text{2. 3\% HCl/MeOH, reflux 2 h}]{\text{1. 90\% } H_2O_2\text{, } (CF_3CO)_2O\text{, } CH_2Cl_2\text{, } CF_3CO_2H.Et_3N} CH_3CH(OH)-CHC_2H_5\ (OH)$$

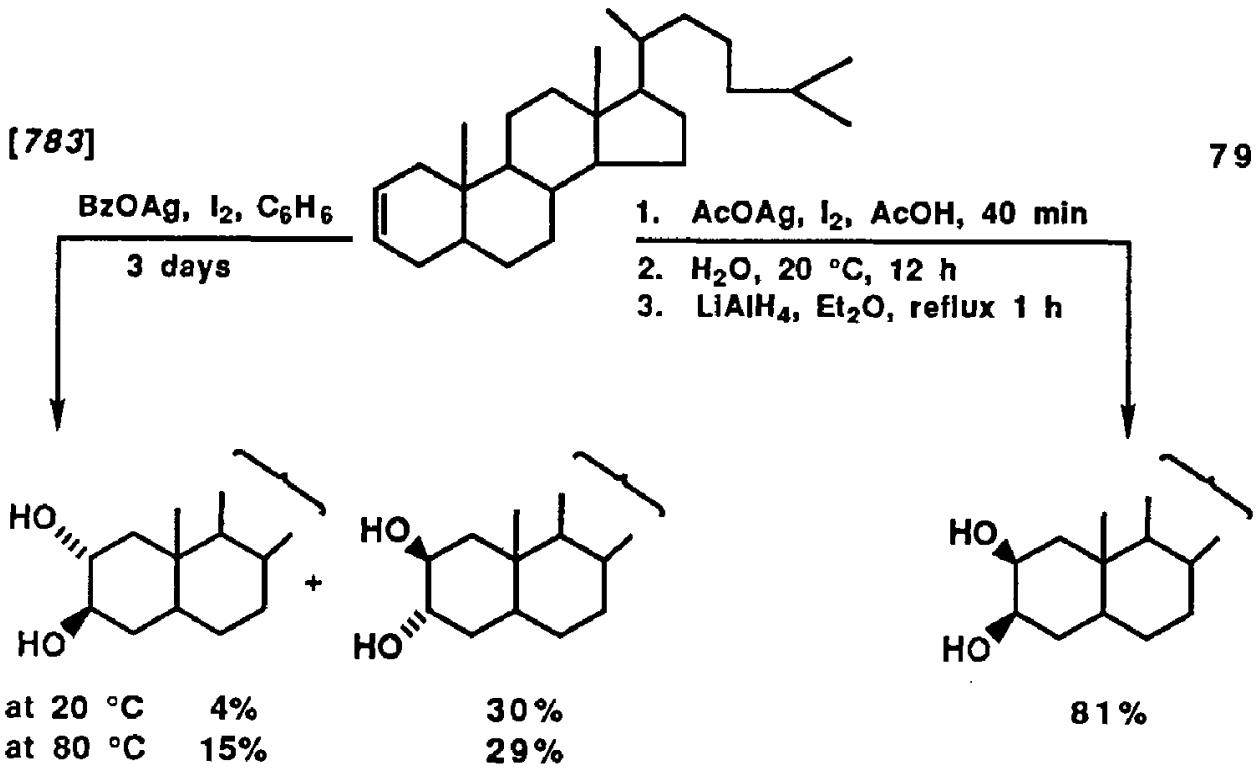
74%

Another kind of *anti* hydroxylation is the reaction of alkenes with **hydrogen peroxide** in the presence of vanadium pentoxide, molybdenum trioxide, selenium dioxide, and especially tungsten trioxide (tungstic acid) [*131, 144*]. Cyclohexene is thus converted into DL-*trans*-1,2-cyclohexanediol [*131*].

Stereospecific hydroxylations can also be accomplished via **silver acetates** [*781, 782*] or **silver benzoates** [*784*] and **iodine** followed by hydrolysis of the intermediate esters. Depending on the reaction conditions, either *syn* or *anti* hydroxylation (acyloxylation) can be accomplished (equations 78 and 79).

With dry reagents, *anti* addition takes place to form diesters, which yield diols on hydrolysis ***(Prévost reaction)***.





If, on the other hand, aqueous acetic acid is added to the reaction mixture containing the positively charged intermediate, the product is a monoester of the diol, which, on hydrolysis, gives a diol. Such a reaction mimics a *syn* addition ***(Woodward reaction)*** [*781, 783*].

Instead of silver salts, the somewhat cheaper but more toxic thallium(I) acetate may be used [*410*]. Examples of *syn* and *anti* hydroxylations of cycloalkenes are shown in equations 80–82 [*131, 242, 244, 410, 782, 900, 905, 952*].

Double bonds in the side chains of aromatic compounds undergo hydroxylation in the same way as those in simple alkenes [*784*]. With some compounds, such as stilbene, ***enantioselective hydroxylation*** can be accomplished with *chiral compounds,* which, by complexing osmium tetroxide, form enantiomeric products in high enantiomeric excesses (equation 83) [*951, 1033*].

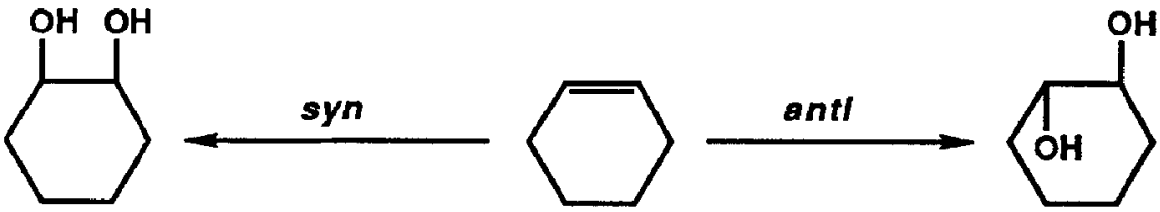
The presence in alkenes of chiral groups, such as phenyl sulfoxide [*1102*] or *N,S*-dimethyl-*S*-phenylsulfoximine [*1103*], affects the direction of the access of osmium tetroxide from just one (or predominantly one) face of the double bond. Thus predominantly one enantiomer of the *syn*-hydroxylation product is formed (equations 84 and 85).

Enantioselective hydroxylation of double bonds also occurs in *biochemical oxidation* by ***Pseudomonas putida*** [*1073*].

The same oxidizing agents and conditions used for the hydroxylation of alkenes and cycloalkenes are applied to unsaturated alcohols, ethers, aldehydes, ketones, and acids and their derivatives.

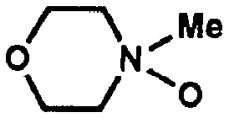
EXAMPLES OF *syn* AND *anti* HYDROXYLATIONS

80



syn hydroxylation

[*782*] 1. AcOAg, I_2, AcOH, RT, 4.5 h — 66%
2. AcOH, H_2O, reflux, 1 h

[*952*] OsO_4,  — 89-90%

Me_2CO, H_2O

[*410*] 1. AcOTl, I_2, AcOH, 80 °C, 0.5 h — 70-75%
2. H_2O, reflux 9 h
3. NaOH, EtOH, reflux 2 h

anti hydroxylation

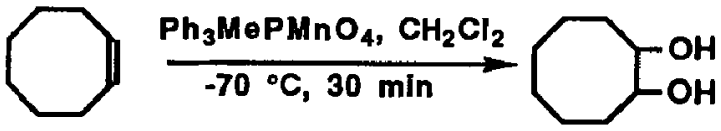
[*242*, *244*] 1. 30% H_2O_2, 88% HCO_2H, 40-45 °C — 73-75%
2. 35% NaOH, 45 °C

[*131*] 30% H_2O_2, AcOH, WO_3, 50 °C, 5-6.5 h — 74-77%

[*410*] 1. AcOTl, I_2, AcOH, reflux 9 h — 65-70%
2. NaOH, EtOH, reflux 3 h

[*905*]

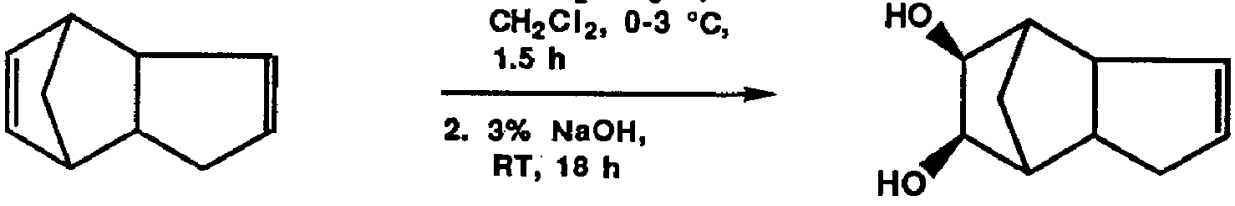
81



cis 80%

[*900*]

82

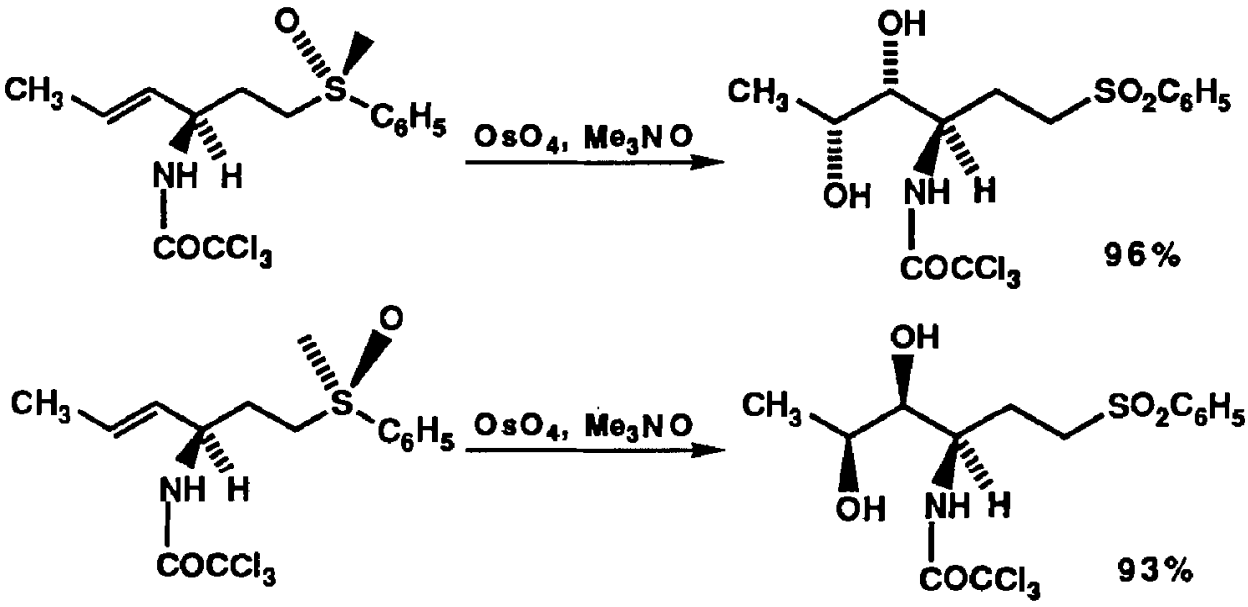


83%

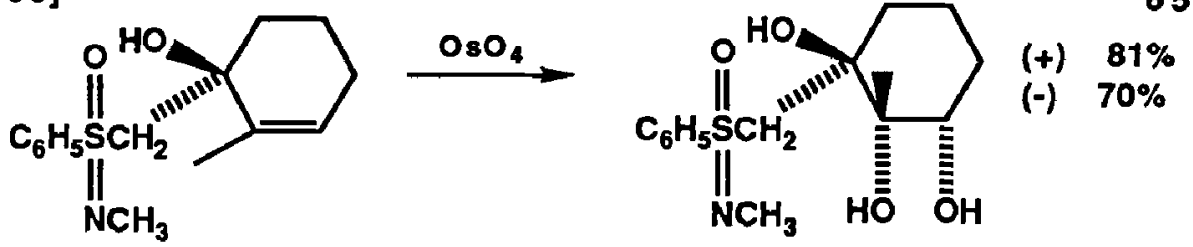
[951] 1. OsO_4, PhMe, RT, dihydroquinidine acetate 83
2. $LiAlH_4$ 85%, 82% ee

[1033] OsO_4, CH_2Cl_2, -100°, 6 h 71%, 90% ee
2-α-naphthyl-*trans*-4,5-bis(*N*-piperidylmethyl)-1,3-dioxolane

[1102] 84



[1103] 85

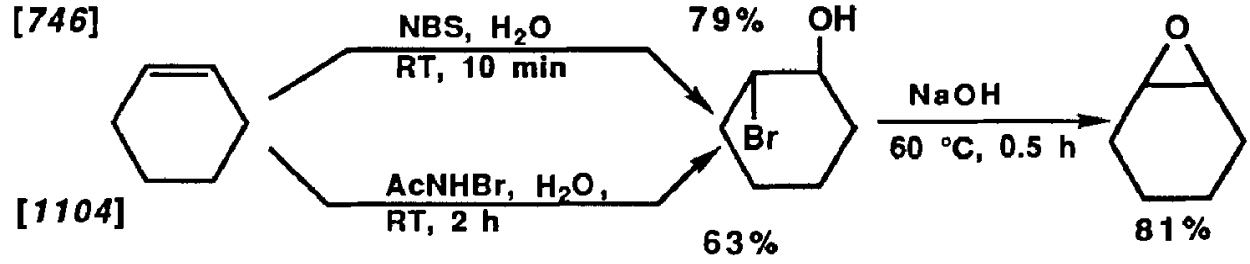


Conversion into Halohydrins, Amino Hydroxy Compounds, and Esters

The addition of halogens and hydroxyls across double bonds leads to ***halohydrins,*** which are useful intermediates, especially for the synthesis of epoxides. Such additions are achieved by treatment of alkenes with ***N*-bromoacetamide** [*1104*] or ***N*-bromosuccinimide** [*746*] in aqueous media and give products of *anti* addition. On heating with alkalies, bromohydrins

give epoxides in good yields. Thus, styrene affords an 82% yield of styrene bromohydrin (2-bromo-1-phenylethanol) and an 85% yield of styrene oxide [*746*]. Cyclohexene is converted into cyclohexene bromohydrin and cyclohexene oxide in good yields (equation 86) [*764, 1104*].

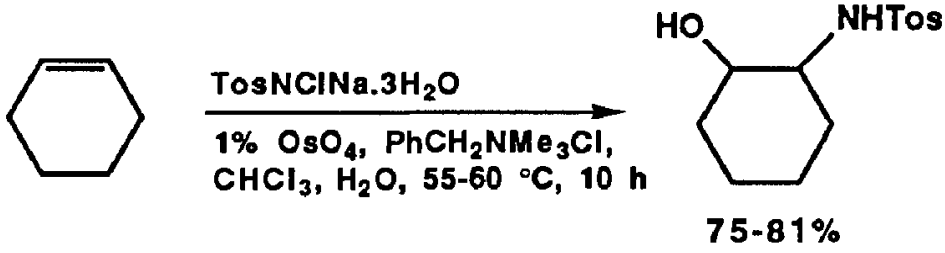
86



Vicinal ***amino hydroxy compounds*** are prepared by treatment of alkenes with ***N*-chloroamides** in the presence of osmium tetroxide (equation 87) [*723, 1105*].

[723]

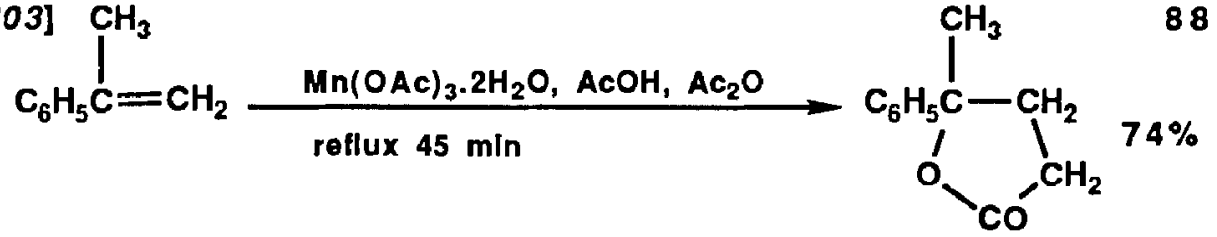
87



Heating alkenes and cycloalkenes with manganese triacetate yields lactones resulting from an oxidative addition of acetoxyls across the double bonds (equation 88) [*803*].

[803]

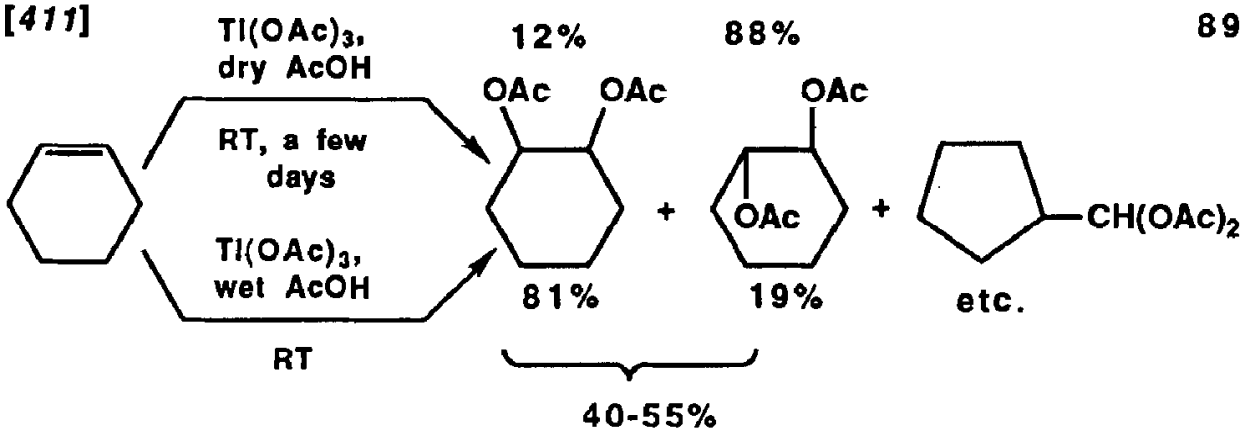
88



Acyl esters of vicinal diols are obtained by the reaction of alkenes with metal carboxylates [*436*]. **Lead tetraacetate** in acetic acid at 70 °C converts 1,2-dihydronaphthalene to *trans*-1,2-diacetoxy-1,2,3,4-tetrahydronaphthalene in 72% yield [*436*]. The reaction is not always stereospecific. Cyclohexene treated with thallium triacetate gives a mixture of diastereomers in varying ratios, depending on reaction conditions, and byproducts as a result of rearrangements (equation 89) [*411*].

Heating stilbene with benzoyl peroxide and iodine in carbon tetrachloride at 80 °C for 48 h gives an 83% yield of the dibenzoyl ester of hydrobenzoin (1,2-dibenzoxy-1,2-diphenylethane) [*230*]. Esters of vicinal diols are intermediates in the preparation of diols by the Prévost and the Woodward methods (equation 78).

[411]



89

Conversion into Ketones

Alkenes can be oxidized to ***ketones of the same chain length*** by using salts of copper, palladium, and mercury as catalysts and *air, electrolysis* [*120*], *hydrogen peroxide,* or *chromium compounds* as oxidants [*60, 65, 140, 565*] (equation 90).

EXAMPLES OF OXIDATION OF ALKENES TO KETONES

90

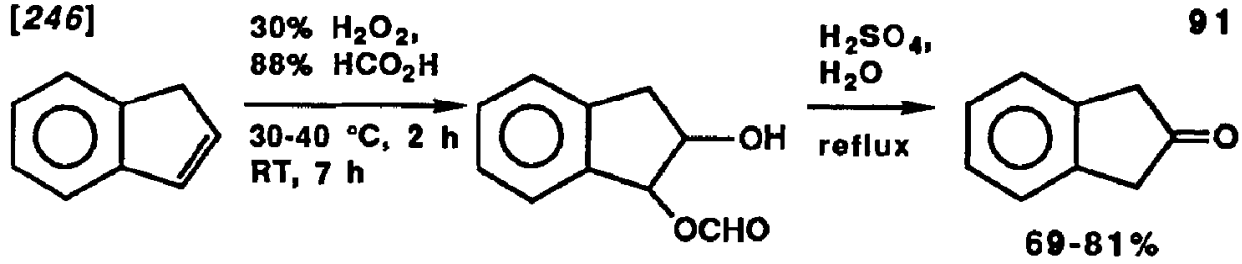
$CH_2=CHR$		⟶	CH_3COR
	R		
[*65*]	C_8H_{17}	O_2, $PdCl_2$, CuCl, H_2O, DMF, RT, 24 h	65-73%
[*60*]	$C_{10}H_{21}$	O_2, $PdCl_2$, $CuCl_2.2H_2O$, H_2O, DMF, 60-70 °C, 2.5-3.5 h	51-87%
[*140*]	C_6H_{13}	30% H_2O_2, $Pd(OAc)_2$, AcOH, 80 °C, 6 h	96%
[*140*]	$C_{10}H_{21}$	30% H_2O_2, $Pd(OAc)_2$, AcOH, 80 °C, 6 h	92%
[*565*]	C_6H_{13}	CrO_3, H_2SO_4, H_2O, $Hg(OCOEt)_2$ Me_2CO, 25 °C, 4 h	82%
[*120*]	C_8H_{17}	DDQ*, electrolysis, $Pd(OAc)_2$, Et_4NBF_4, Pt anode, 0.83 A/dm^2, RT	63%

*DDQ is 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

The oxidation of indene with peroxyformic acid gives a 69–81% yield of 2-indanone after hydrolysis of the intermediate, 1-formoxy-2-hydroxyindane (equation 91) [*246*].

The oxidation of 2,4,4-trimethylpentene with *chromyl chloride* followed by treatment with zinc affords a 70–78% yield of 2,4,4-trimethyl-

[246]



91

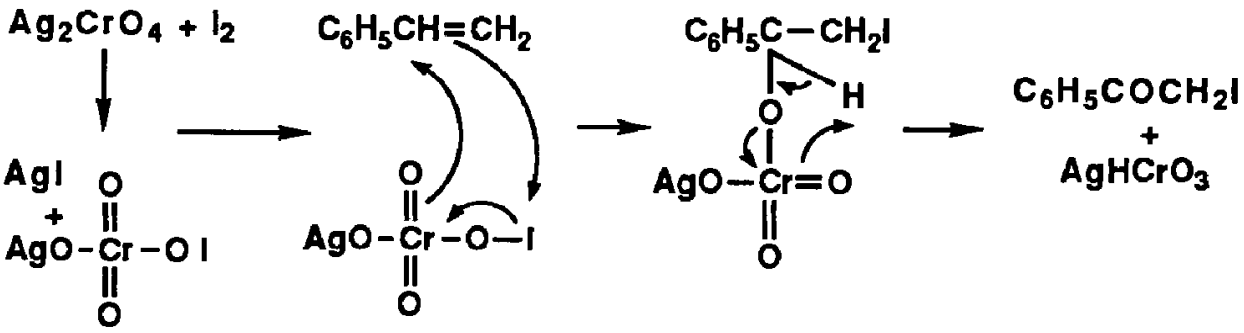
69-81%

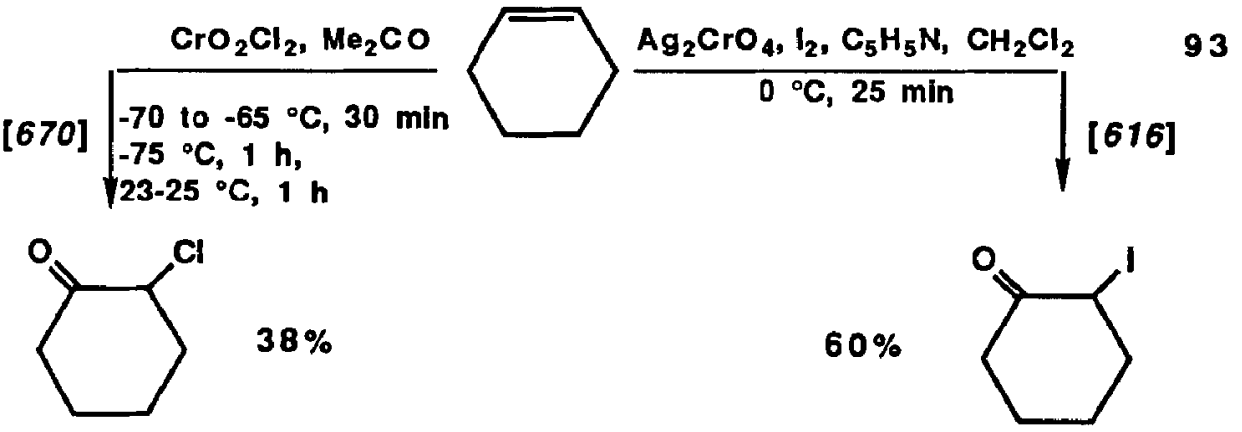
pentanal [*672*]. A similar reaction of *trans*-cyclododecene with chromyl chloride followed by treatment with zinc dust in acetic acid affords cyclododecanone in 75% isolated yield [*670*]. The intermediates in these reactions are ***α-chloro ketones,*** which are prepared in 38–79% yields by adding chromyl chloride to alkenes or cycloalkenes in acetone solutions at low temperatures (–70 or –5 °C) [*670*].

α-Iodo ketones result from the reaction of alkenes and cycloalkenes, especially the electron-rich ones, with *silver chromate and iodine* (equations 92 and 93) [*616*].

[616]

92





93

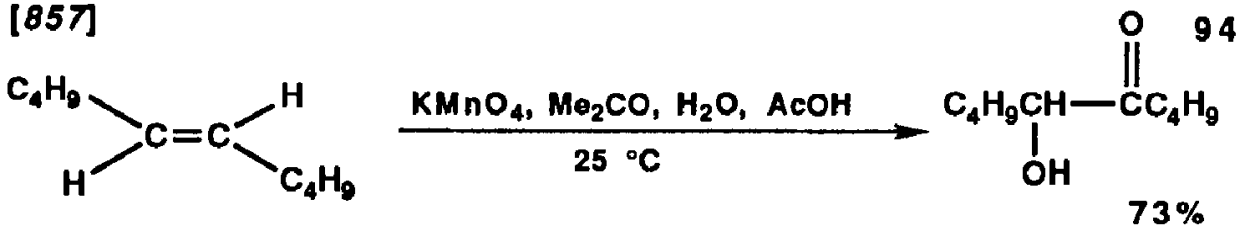
38%

60%

A solution of *potassium permanganate* in aqueous acetone buffered with acetic acid converts internal alkenes into ***α-hydroxy ketones*** (equation 94) [*857*].

Alkenes may also be transformed into ***vicinal dicarbonyl compounds.*** The treatment of alkenes with selenium dioxide, although possible, does not give satisfactory yields [*509*]. Better results are obtained when unsaturated compounds such as oleic acid are oxidized with ***potassium permanganate*** buffered with acetic anhydride [*861*].

[857]



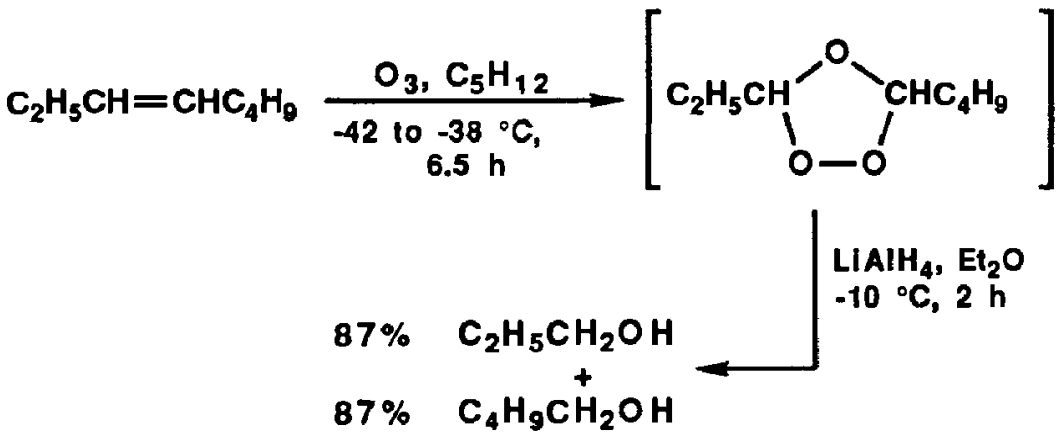
94

Oxidative Cleavage of Double Bonds

Double bonds are oxidatively cleaved to alcohols, aldehydes, ketones, or acids. The specific product formed depends on the structure of the alkene, that is, the presence or absence of hydrogen atoms at the carbons of the double bonds, and on the oxidants used.

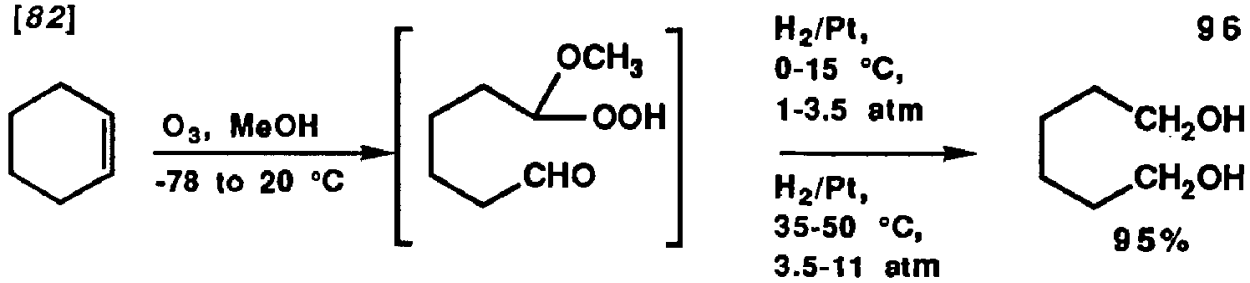
The oldest and still very common cleavage is the reaction of unsaturated compounds with ozone and the subsequent treatment of the ozonides formed (equations 95 and 96). Reduction by strong reducing agents such as complex hydrides gives ***alcohols*** [*94*]. Cycloalkenes yield ***diols*** [*82*].

[94]



95

[82]

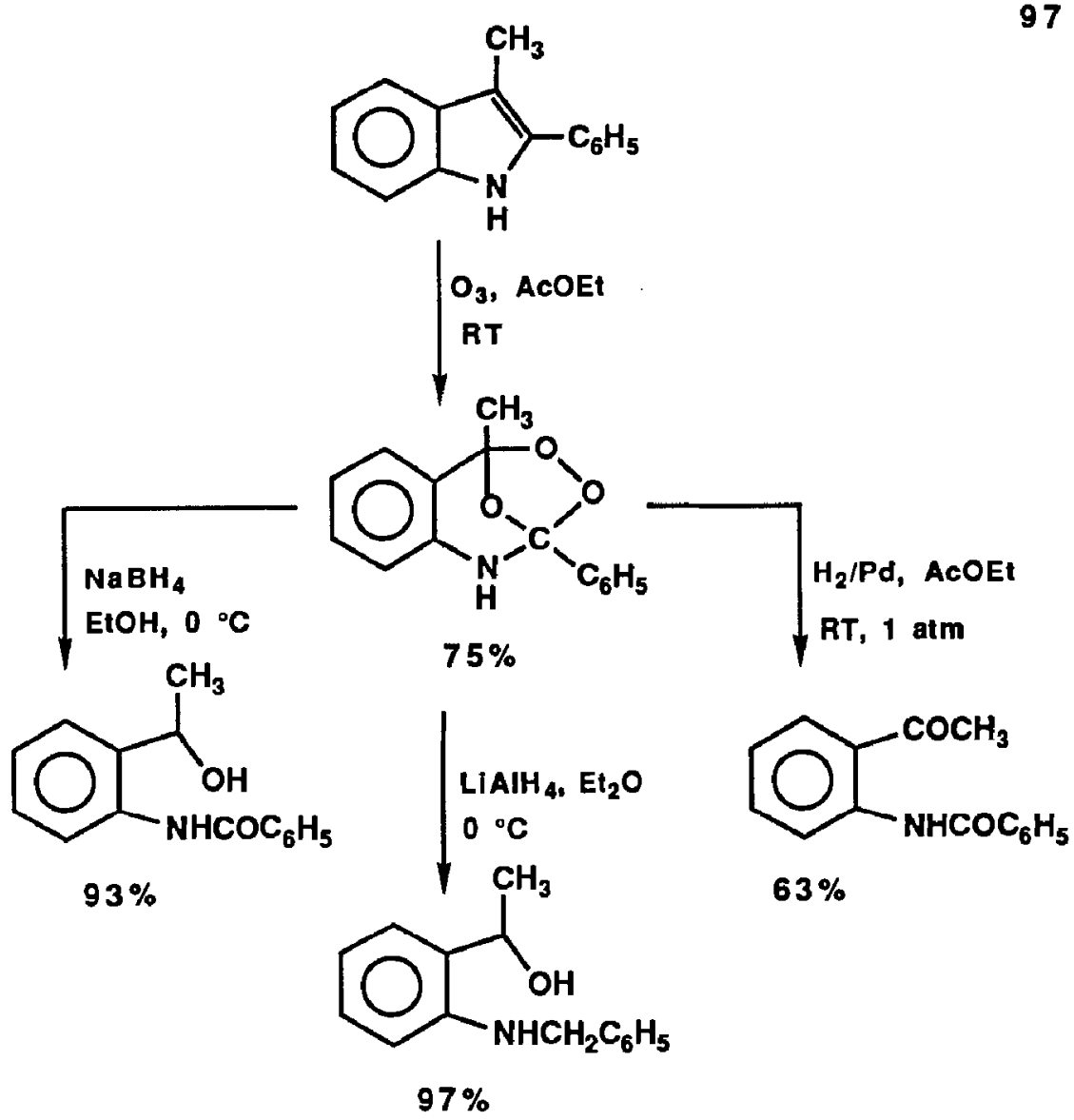


96

An example showing the different products formed by different reducing agents is the ozonolysis and reduction of 2-phenylskatole (3-methyl-2-phenylindole) (equation 97) [*95*].

A much more frequently used reaction is the cleavage of unsaturated compounds to ***aldehydes*** (equations 98 and 99). Alkenes and cycloalkenes that possess one or two hydrogens at the double bonds are oxidized by ozone to ozonides, which have to be reduced to prevent a subsequent oxidation to acids by the excess oxygen atom. Reductions are carried out, usually without isolation of the ozonides, by ***catalytic hydrogenation over palladium catalyst*** [*80, 81, 1106*] or Raney nickel [*85*] or by treatment with

[95] 97

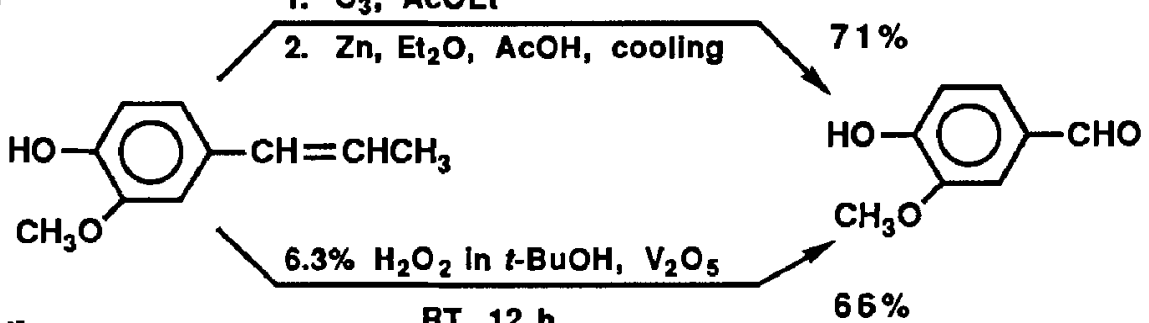


zinc and acetic acid [*81, 86, 87, 1107*], with **trimethyl phosphite** [*89*], or with **dimethyl sulfide** [*90, 91, 92, 1108*] (equations 100 and 101).

As alternatives to ozonolysis, other oxidations are used to prepare aldehydes from unsaturated compounds: treatment of alkenes with chromyl

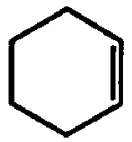
[91] $C_6H_{13}CH{=}CH_2$ —(1. O_3, MeOH, -30 to -60 °C; 2. Me_2S, -60 °C; -10 °C, 1 h; RT, 1 h)→ $C_6H_{13}CHO$, 75% 98

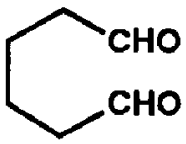
[86] 99



[134]

100





[*80, 1106*]	1. O_3, AcOEt, -50 to - 70 °C 2. $H_2/Pd(CaCO_3)$	70%
[*89*]	1. O_3, MeOH, -65 to -70 °C 2. $(MeO)_3P$, -20 °C	85%
[*1108*]	1. O_3, MeOH, CH_2Cl_2, -78 °C 2. TosOH, RT, 1.5 h 3. $NaHCO_3$, RT, 15 min 4. Me_2S, 12 h	68-70%
[*765*]	OsO_4, $NaIO_4$, Et_2O, H_2O 24-26 °C, 2 h	77%
[*680*]	$CrO_2(OCOCCl_3)_2$, CCl_4, Me_2CO, 1.25 h; $(CO_2H)_2$, 3 h	46%

[*81*] $CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2CH_3$ 101

$\xrightarrow[\text{-20 °C, 3.25 h}]{O_3,\ MeOH}$ $CH_3(CH_2)_7CHO + OCH(CH_2)_7CO_2CH_3$

$H_2/Pd(C)$, AcOMe, AcOH, 22 °C, 1.5 h	76%	83%
Zn, AcOH, MeOH, 30-35 °C	81%	94%

acetate, trichloroacetate, or benzoate followed by reduction with oxalic acid [*680*] or their oxidation with sodium periodate [*760*], with **osmium tetroxide and sodium metaperiodate** [*765*], with osmium tetroxide and anhydrous hydrogen peroxide in ether [*141*], with anhydrous hydrogen peroxide in *tert*-butyl alcohol in the presence of vanadium pentoxide [*134*], or with **potassium permanganate** under special conditions [*834, 840, 842, 853, 895, 900*] (equations 102–104).

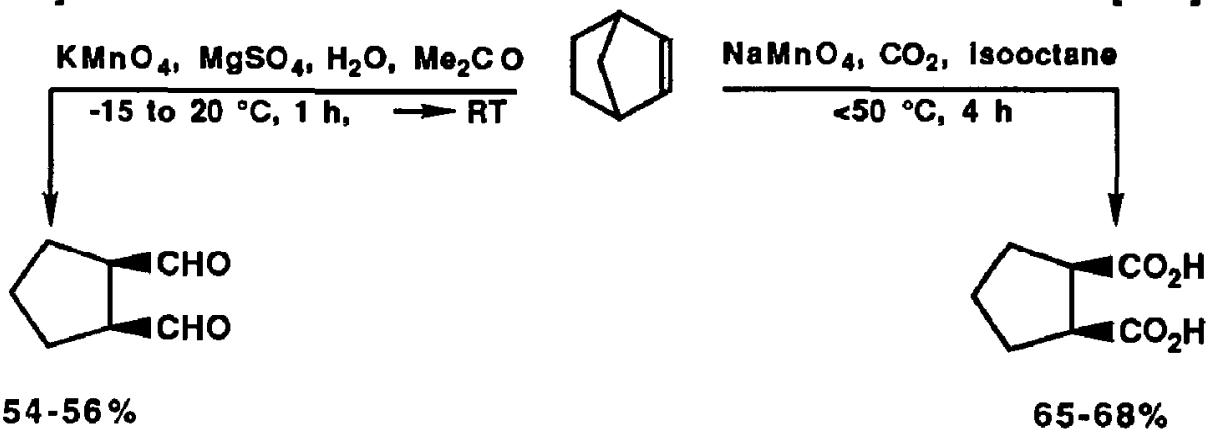
[*141*] 102

$C_6H_5CH{=}CHC_6H_5$ $\xrightarrow[Na_2SO_4,\ \text{spontaneous reflux, RT, overnight}]{4\ H_2O_2\ (20\%\ \text{in}\ Et_2O),\ OsO_4}$ C_6H_5CHO

79%

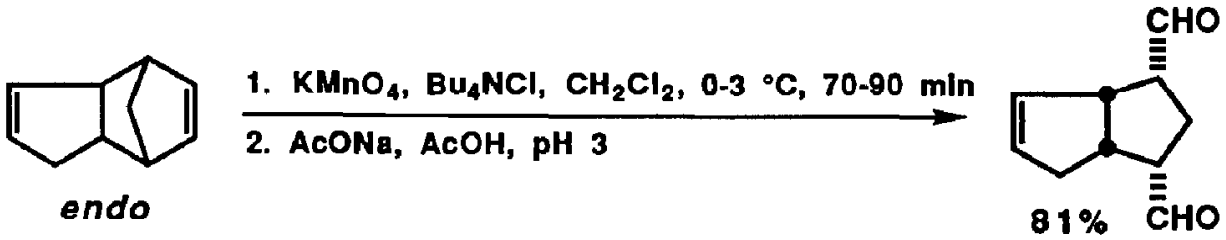
103

[853] [834]



54-56% 65-68%

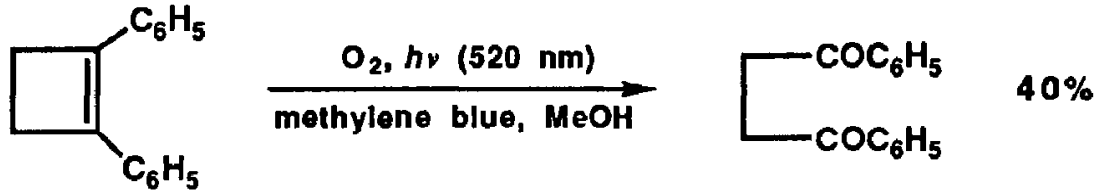
[900] 104



endo 81%

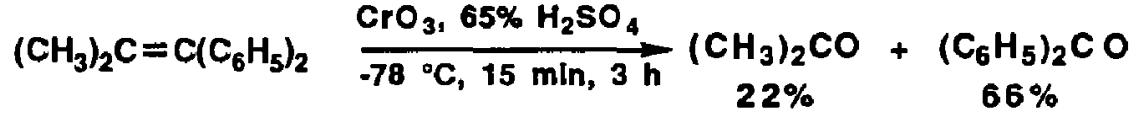
Unsaturated hydrocarbons with tetrasubstituted double bonds are cleaved to ***ketones*** by ***ozonolysis*** followed by reduction with zinc in acetic acid [*1107*], by *oxygen* sensitized with methylene blue under irradiation [*25, 1109*], by *chromium trioxide* and sulfuric acid at low temperature [*564*], or by sodium periodate [*760*] (equations 105–107).

[25] 105

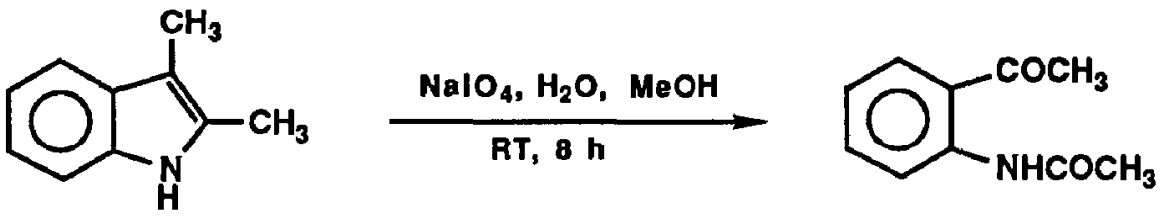


40%

[564] 106



[760] 107

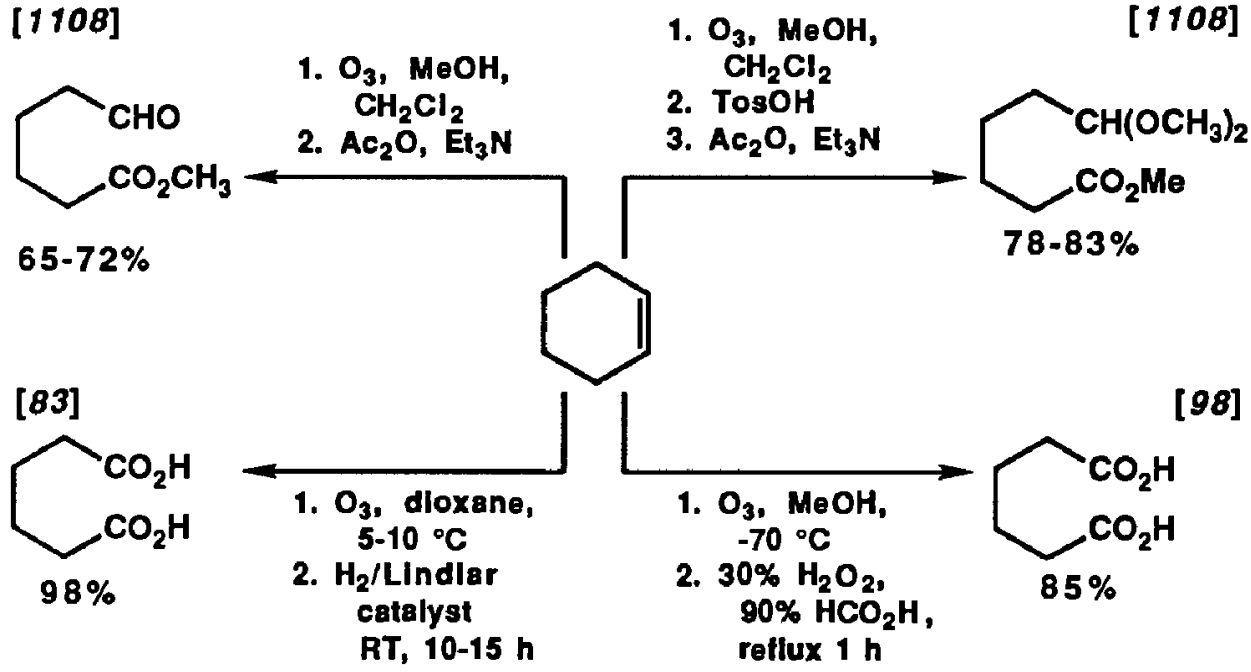


85%

The cleavage of double bonds in unsaturated alcohols (including saccharides) [*87*], phenols [*86, 989*], unsaturated ketones [*1110*], and unsaturated acids [*840, 842*] and esters [*81*] are discussed in the appropriate sections.

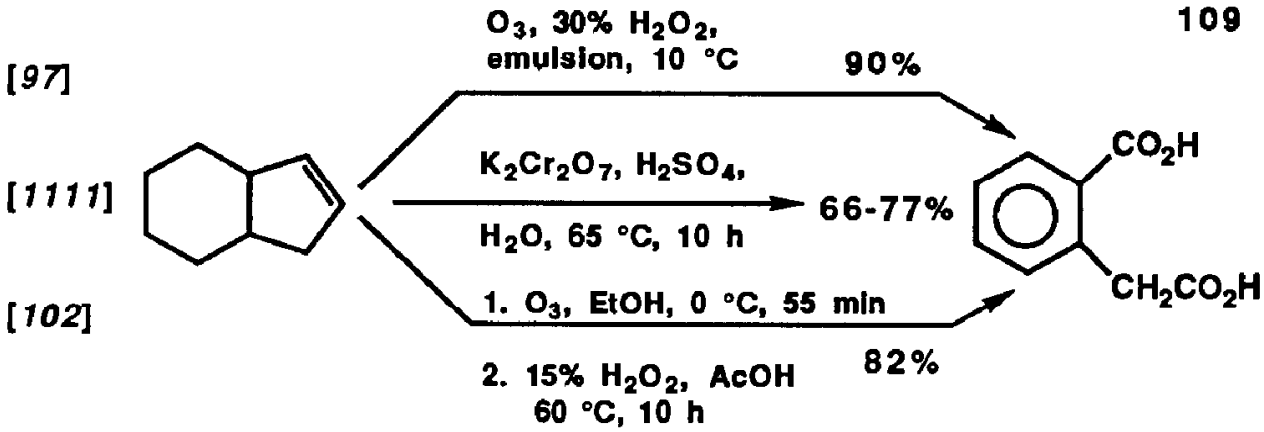
The oxidation of alkenes and cycloalkenes and their halogen derivatives with at least one hydrogen or halogen atom at the double bond leads to ***carboxylic acids. Ozonolysis*** usually requires the oxidative decomposition of the ozonide. The oxygen content of the ozonide is not sufficient for the formation of two molecules of acids or one dicarboxylic acid. The nonoxidative decomposition of cyclohexene ozonide gives an aldehyde–acid or its derivatives [*1108*]. It comes, therefore, as a surprise that carboxylic acids are claimed as products of the decomposition of ozonides by hydrogenation over the Lindlar catalyst [*83*] (equation 108).

108

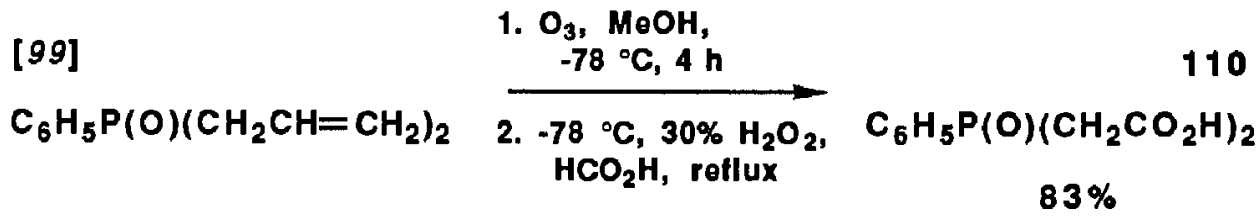


The oxidative decomposition of ozonides is further accomplished by their treatment with **hydrogen peroxide** [*97*] in the presence of formic acid [*98, 99*] or acetic acid [*102, 103*] or with silver oxide and nitric acid [*77*] (equations 109–112).

109

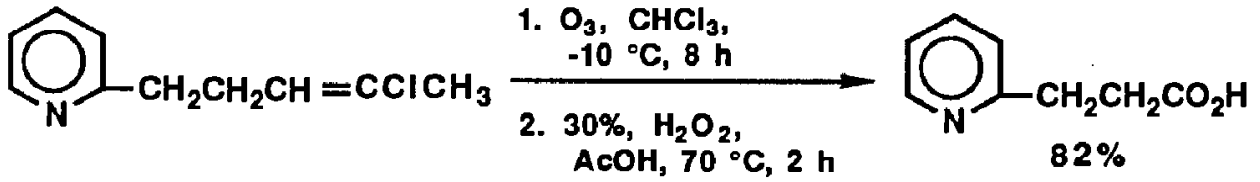


[99]



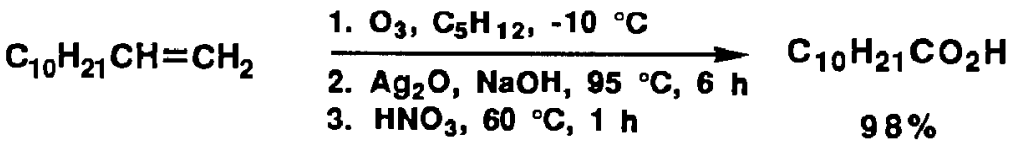
110

[103]



111

[77]

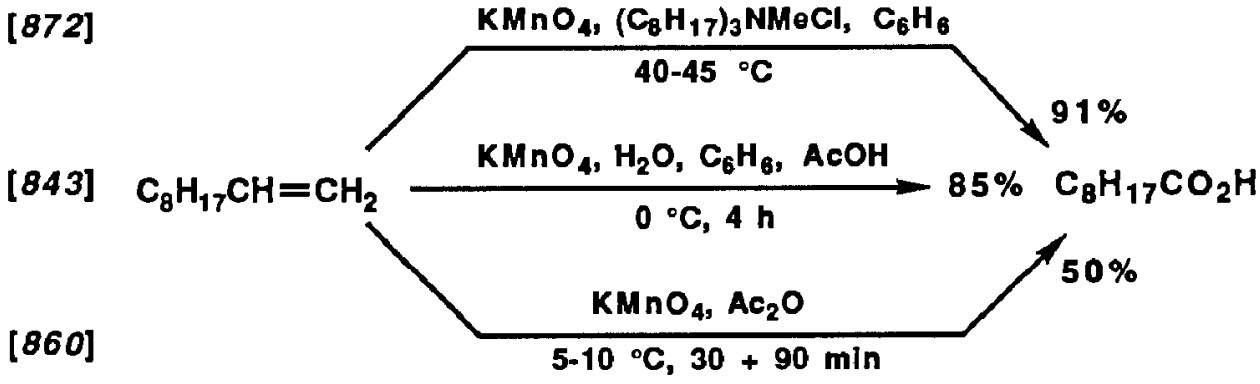


112

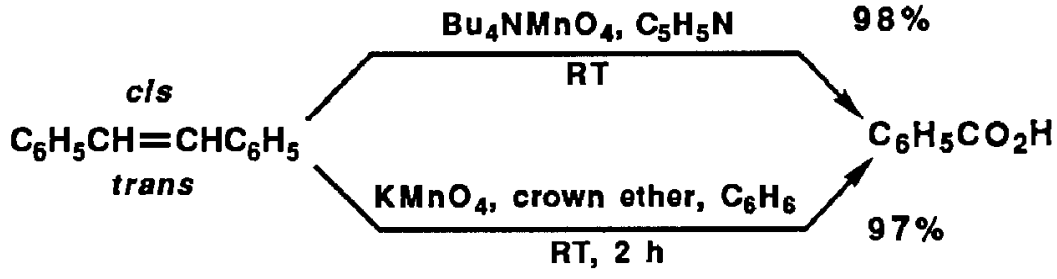
The most common and simplest cleavage of double bonds to carboxyls is achieved with **potassium permanganate** [*838, 841, 843, 852, 860, 869, 874*] or sodium permanganate [*834*] in aqueous solution (equation 113) or with tetraalkylammonium permanganate in organic solvents (equation 114) [*845, 872, 899*].

113

[872]



[899]

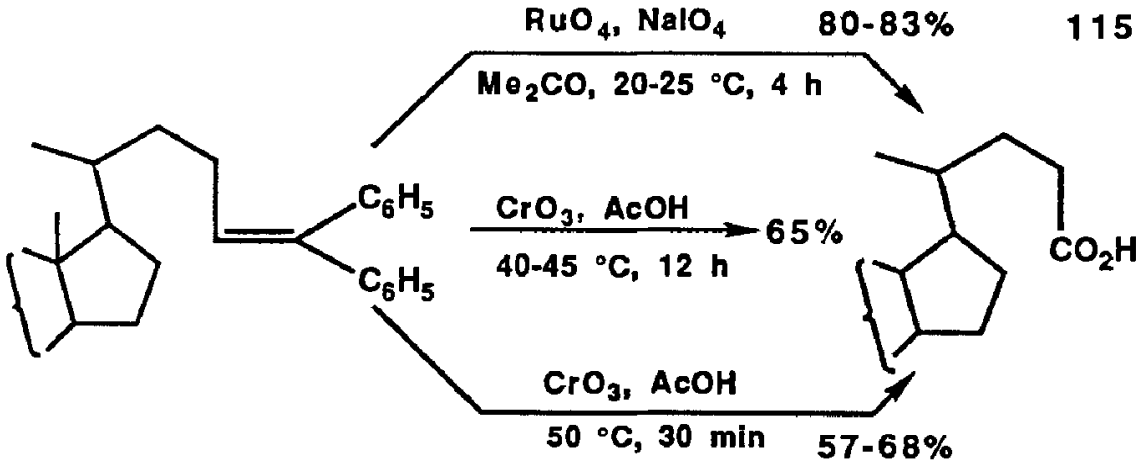


114

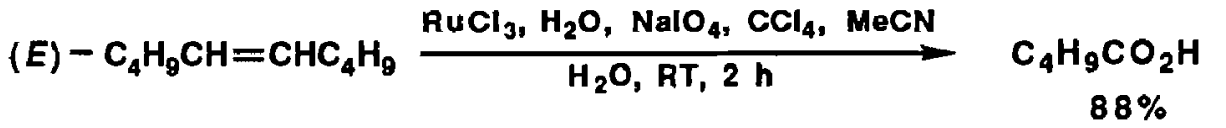
The oxidative cleavage of alkenes resulting in the formation of carboxylic acids is also accomplished with *chromium trioxide* in sulfuric acid or acetic acid [*567, 569*]; with *potassium dichromate* in sulfuric acid [*1111*]; and with **ruthenium tetroxide**, generated in situ from ruthenium trichloride

and sodium periodate [*774*] or from ruthenium dioxide and sodium periodate [*567, 774*], sodium hypochlorite [*939*], periodic acid [*939*], or peroxyacetic acid [*939*] (equations 115–117).

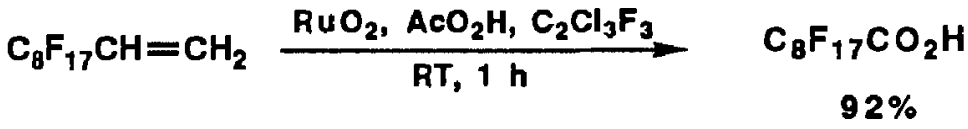
[*567*] 115



[*774*] 116

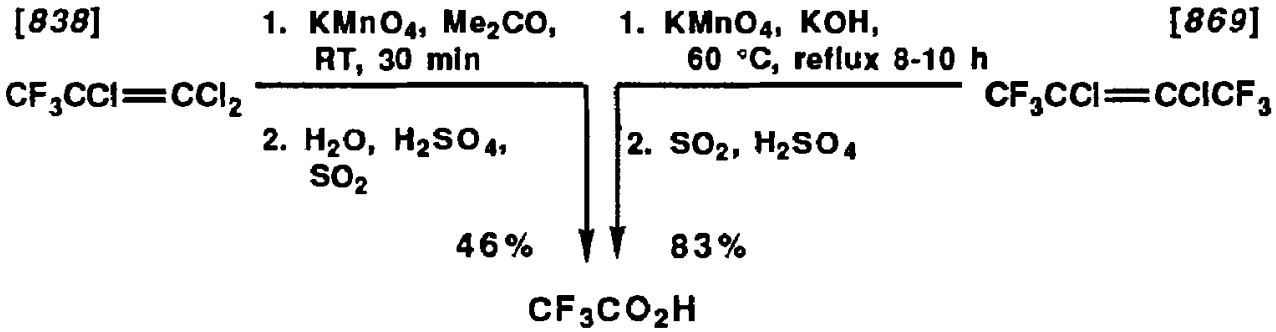


[*939*] 117

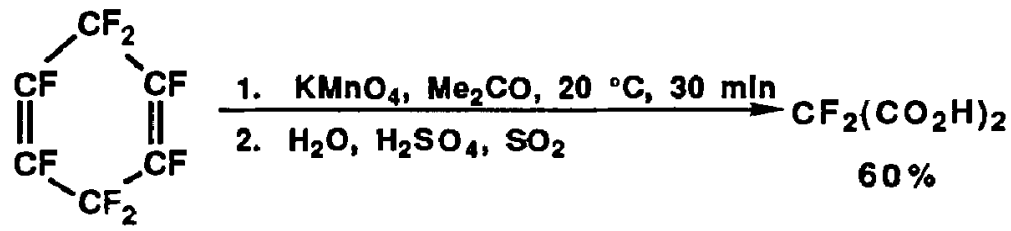


Alkenes and cycloalkenes with ***at least one halogen*** linked to the double bonds are oxidized in aqueous or acetone solutions with *potassium permanganate* to carboxylic acids via acyl chlorides. Such oxidations are frequently used to prepare highly fluorinated or perfluorinated carboxylic acids (equations 118–120) [*838, 869, 874*].

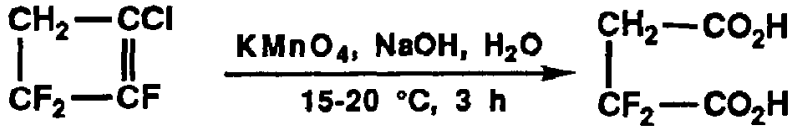
118



[*838*] 119



[874]



120

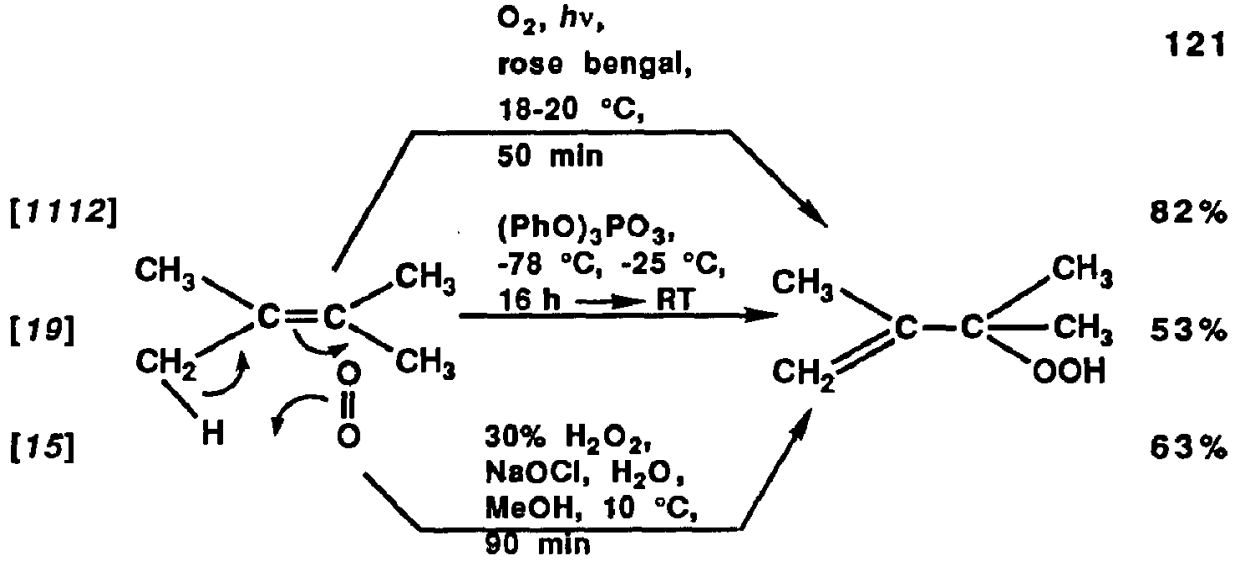
74-80%

Oxidations at Allylic Positions

Allylic positions may be oxidized to give unsaturated hydroperoxides, alcohols, esters, and carbonyl compounds.

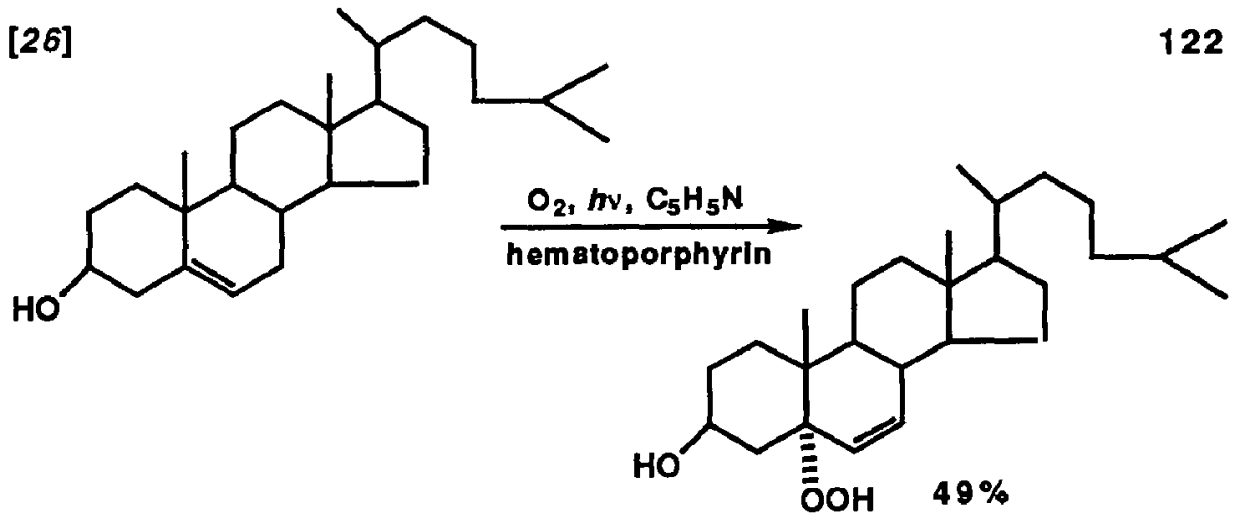
Singlet oxygen, generated usually by the irradiation of solutions of oxygen in the presence of sensitizers, is incorporated into alkenes and forms ***hydroperoxides*** via an ***"ene"*** mechanism (equations 121 and 122) [*15, 19, 26, 1112*].

121



[26]

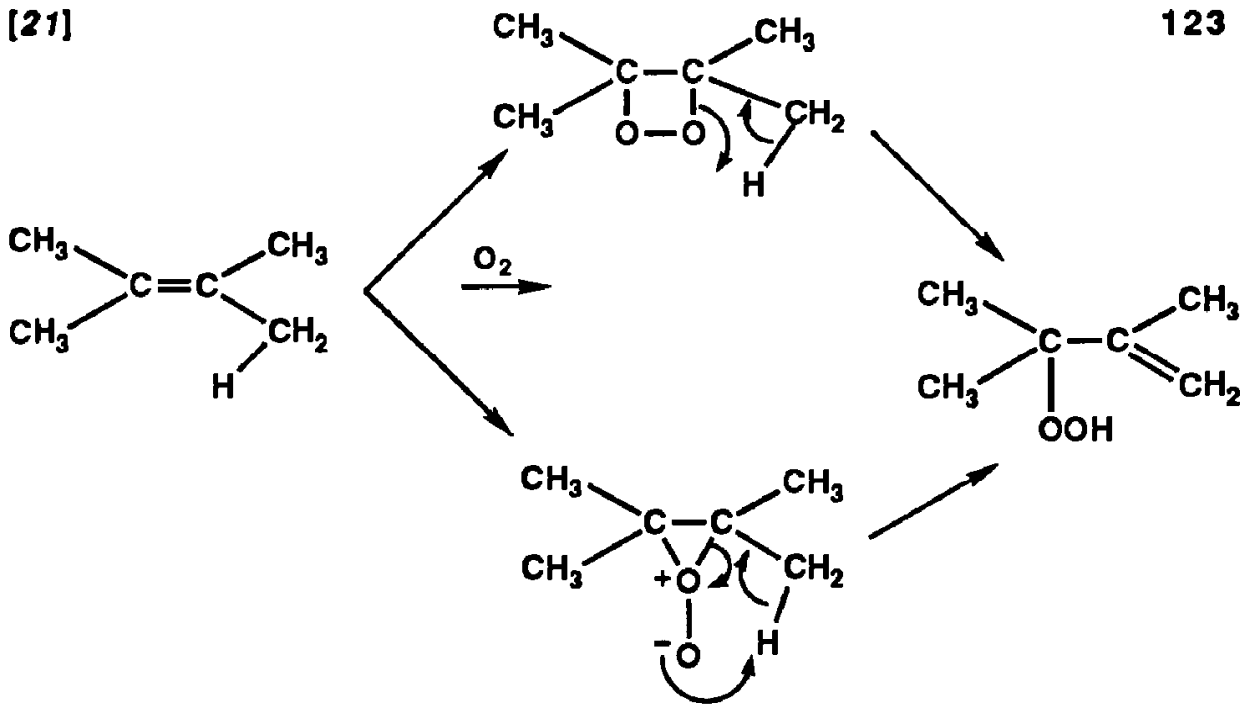
122



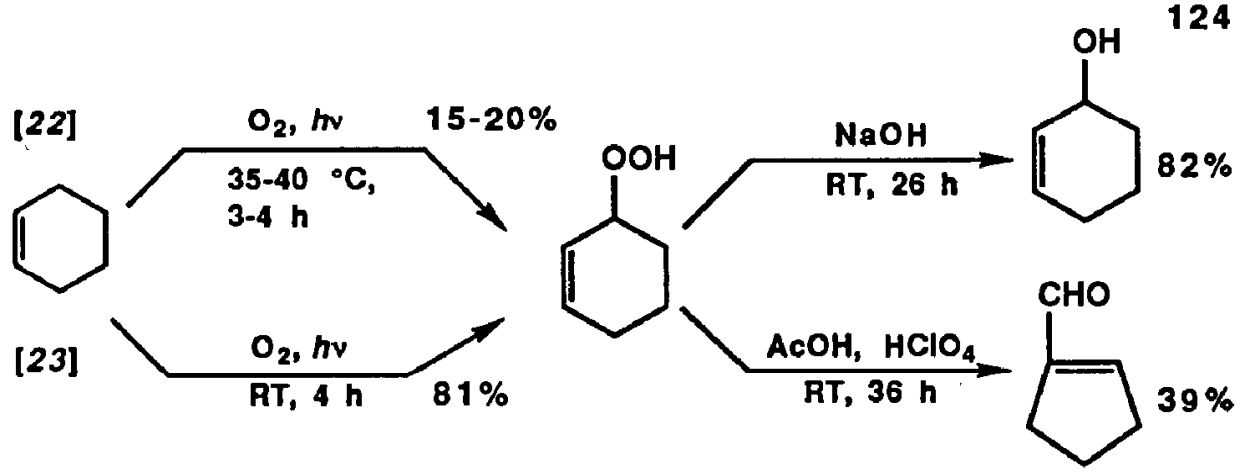
An alternative mechanism via ***dioxetanes*** or ***perepoxides*** has been suggested (equation 123) [*21*].

The hydroperoxides can be transformed further into alcohols or carbonyl compounds (equation 124) [*22, 23*].

[21] 123

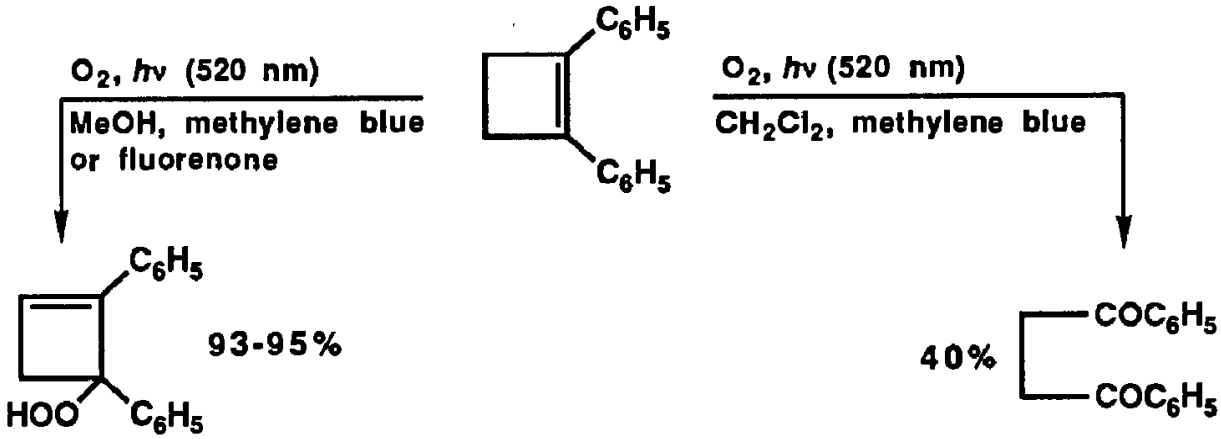


124



The outcome of the autoxidation can be affected by solvents (equation 125) [25].

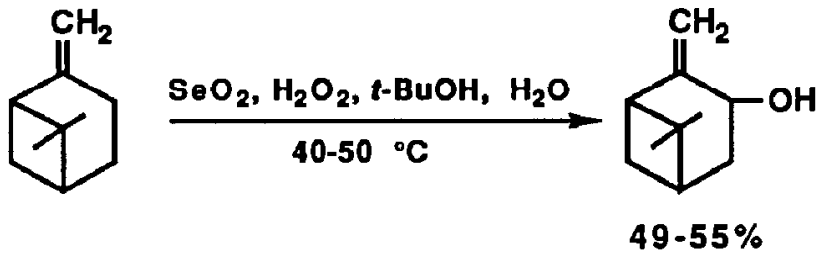
[25] 125



Allylic alcohols are obtained from allylic hydroperoxides by treatment with *alkalies* [22] or by reduction with *sulfites* [27]. They are also formed

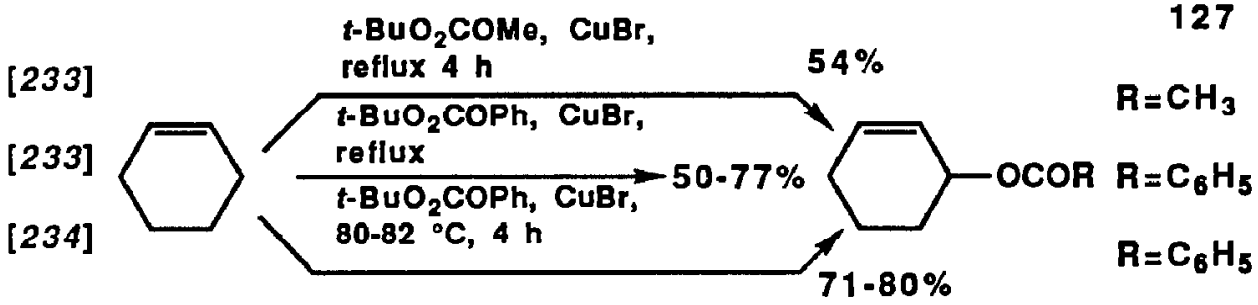
from alkenes with **selenium dioxide** in aqueous solvents (equation 126) [*512*].

[*512*]



49-55% 126

Allylic esters result from the reaction of alkenes with tert-*butyl peroxyacetate* [*233*], or the more reactive *peroxybenzoate* [*233, 234, 1113*], in the presence of cuprous bromide; with mercuric acetate [*404*]; or with lead tetraacetate [*1114*] (equation 127).



127

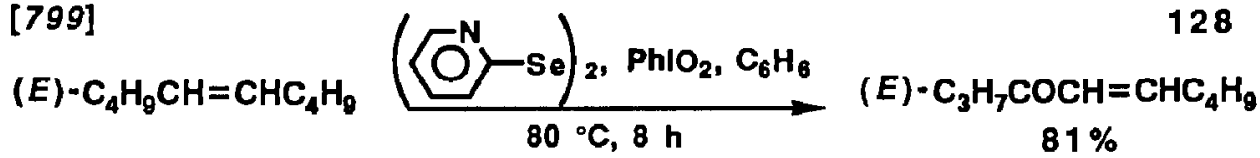
R=CH3

R=C6H5

R=C6H5

α,β-*Unsaturated ketones* are products of the oxidation of alkenes and cycloalkenes in allylic positions. *trans*-5-Decene is converted into *trans*-5-decen-4-one in 81% yield by pyridine-α-seleninic anhydride prepared in situ from pyridine-α-diselenide and iodoxybenzene (equation 128) [*799*].

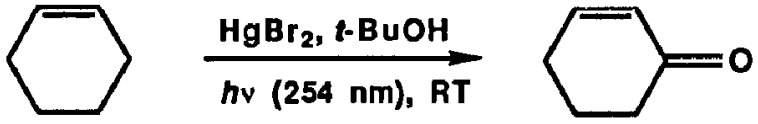
[*799*]



128

Cyclohexene, on irradiation in the presence of mercuric bromide, forms 2-cyclohexenone in 80% yield (equation 129) [*11*].

[*11*]

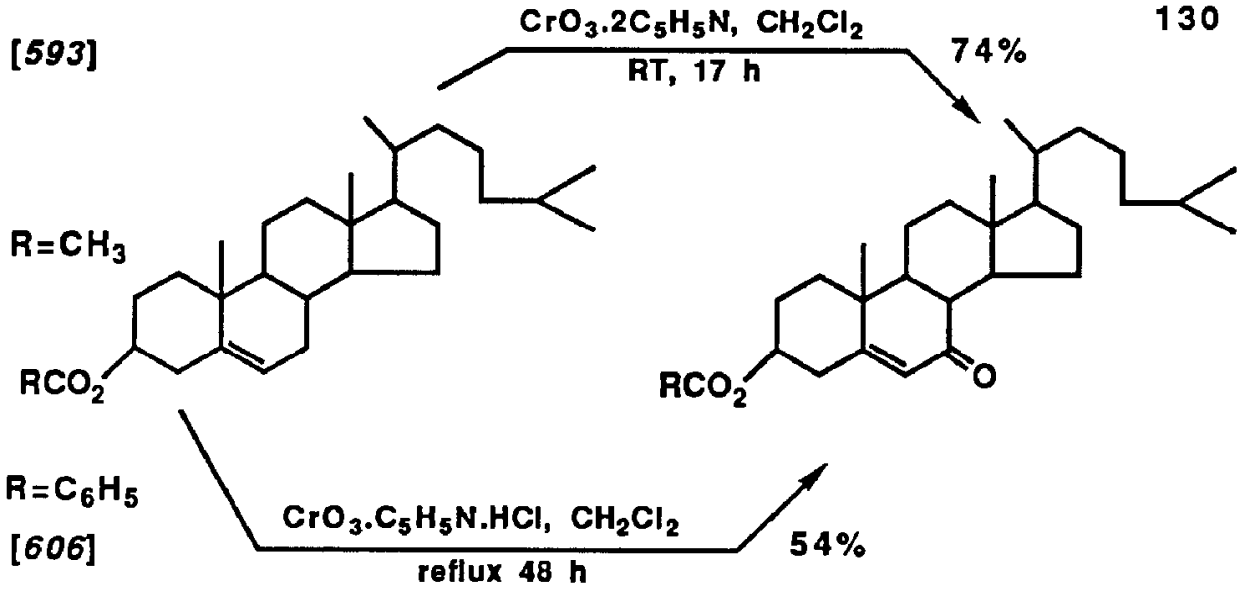


80% 129

Most allylic oxidations of methylene to carbonyl groups are carried out by **chromic oxide** [*552, 553*] or its *complexes with pyridine* [*593, 606*] and performed on steroidal esters [*552, 593, 606*] and ketones [*61, 552*] (equation 130).

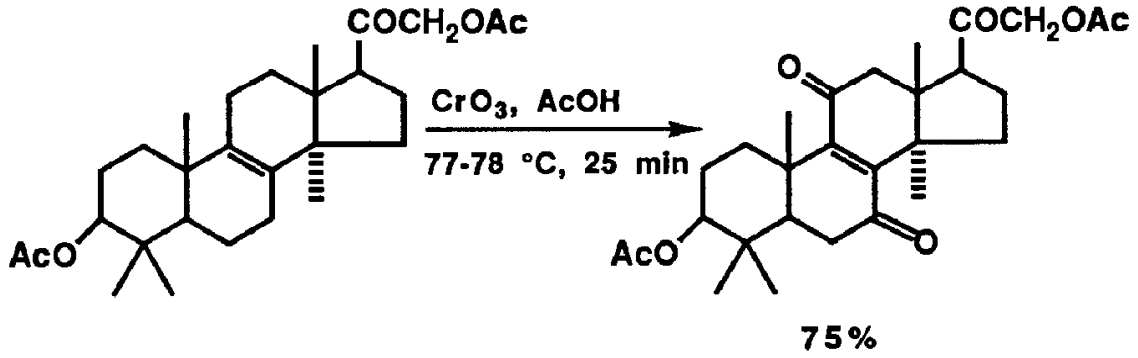
The treatment of 5-cholesten-3-one with oxygen in the presence of cupric nitrate or cupric acetate in pyridine and triethylamine in methanol furnishes 5-cholesten-3,6-dione in 75% yield [*61*]. 4,4,14α-Trimethyl-Δ^8-

[593] 130



pregnene-20-one 3,21-diacetate is oxidized to 3β,21-diacetoxy-4,4,14α-trimethyl-Δ^8-pregnene-7,11,20-trione in 75% yield (equation 131) [*552*].

[552] 131

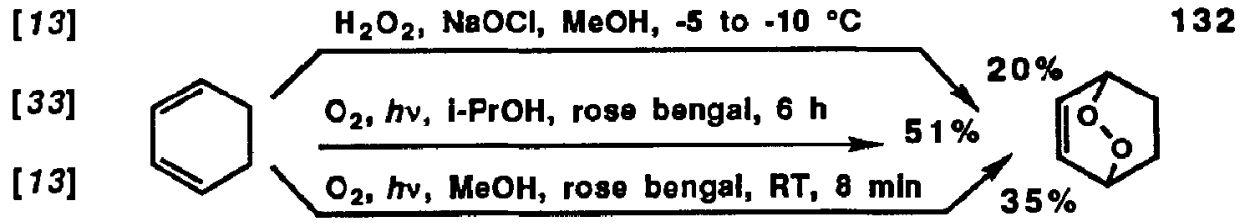


DIENES

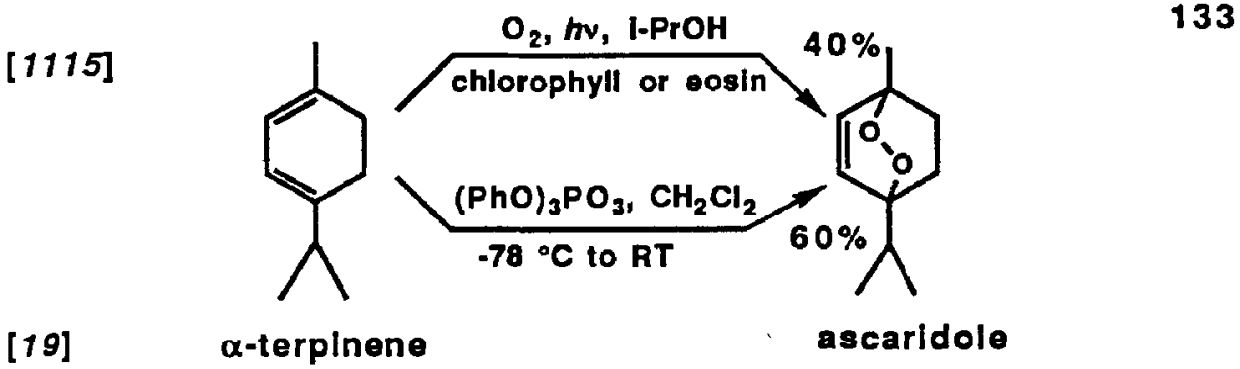
Conjugated dienes (and compounds that behave like conjugated dienes in the Diels–Alder reaction) react with **singlet oxygen** to form ***cyclic peroxides*** as if molecular oxygen acted as a dienophile. The yields of the peroxides, prepared by *photochemical oxidation* [*13, 33*] or by chemical oxidations with *hydrogen peroxide and sodium hypochlorite, alkaline hydrogen peroxide and bromine, alkaline salts of peroxy acids* [*14, 16*], or the *ozonide of triphenyl phosphite* [*19*], are comparable.

A 2% solution of isoprene in dichloromethane and methanol with *methylene blue or rose bengal* as *sensitizers* gives, on irradiation under oxygen with a 500-W iodine lamp, a 50% yield of 4-methyl-1,2-dioxa-4-cyclohexene [*32*]. Cyclic dienes are converted into bicyclic endoperoxides (equation 132). The naturally occurring ascaridole is thus synthesized from α-terpinene (equation 133) [*19, 1115*].

The unsaturated endoperoxides afford ***unsaturated* cis *diols*** on re-

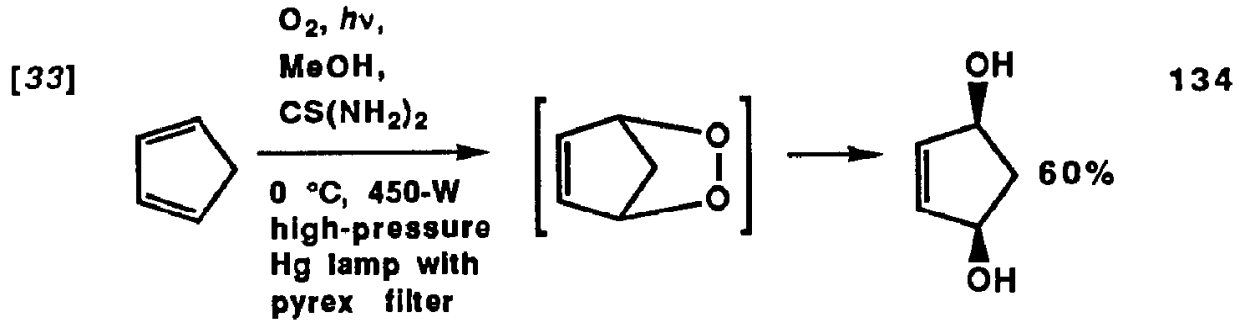


132



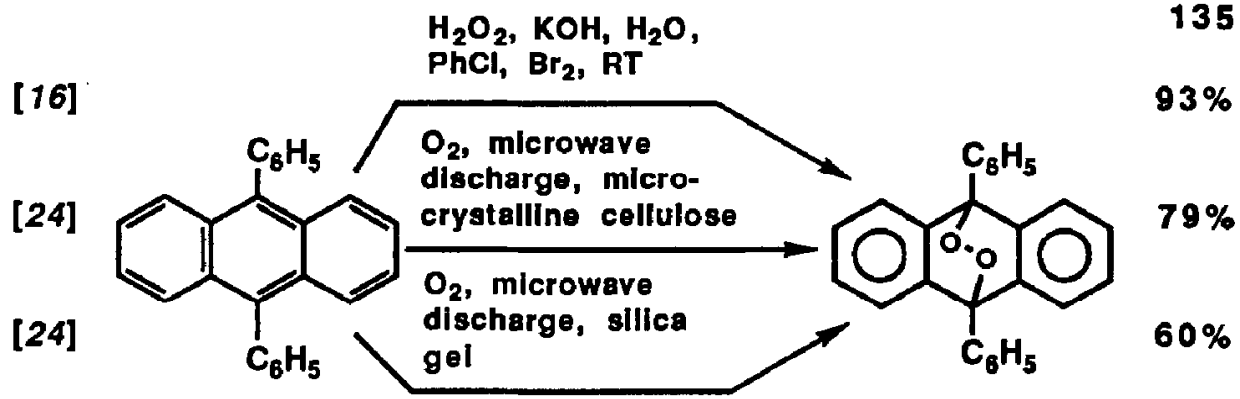
133

duction with thiourea [*33*]. Both the oxidation and the subsequent reduction may be carried out in one step (equation 134) [*33*].



134

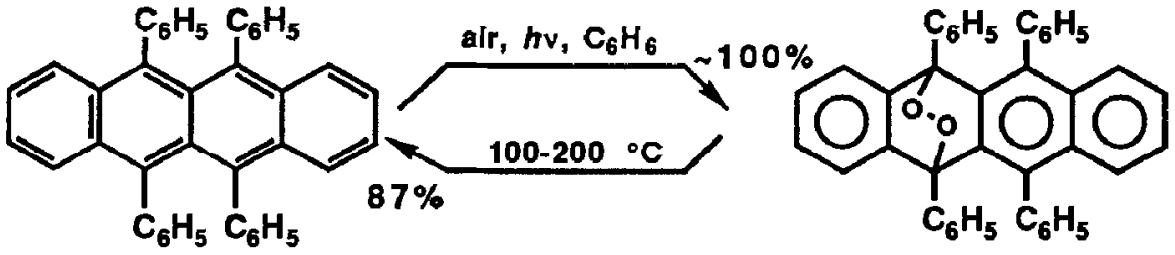
Just as anthracene and its homologues behave like conjugated dienes in the Diels–Alder reaction, they react with singlet oxygen to form 9,10-endoperoxides (equation 135) [*16, 24*].



135

Such endoperoxides generated from anthracene and its homologues release oxygen in singlet form when heated [*17, 18, 19, 1116*]. This reversible reaction is typical of rubrene (tetraphenylnaphthacene), a red compound that yields a colorless endoperoxide (equation 136) [*18, 19, 1116*].

[18] 136

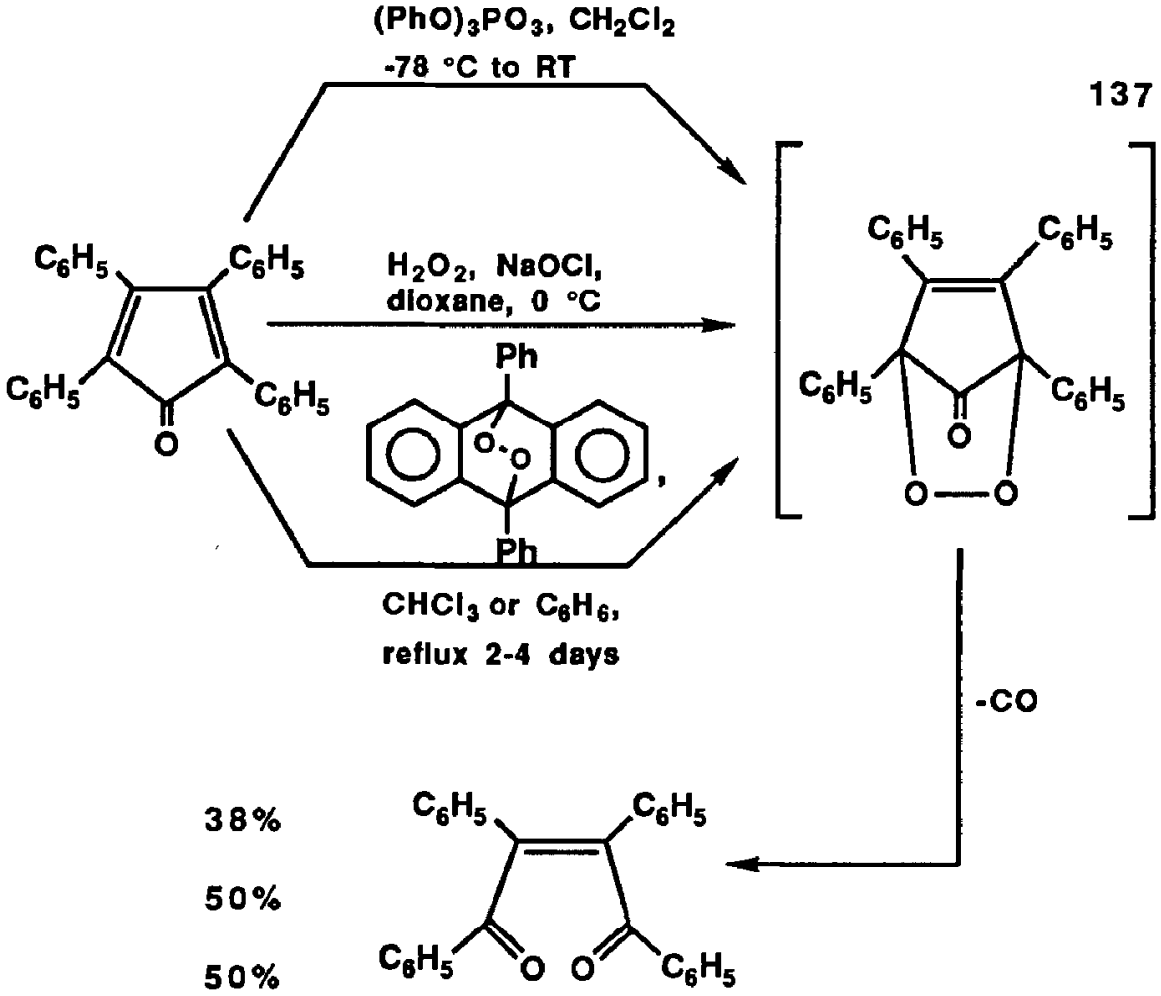


Not only hydrocarbon dienes but also conjugated diene–ketones, such as tetraphenylcyclopentadienone (tetracyclone), and heterocyclic dienes, such as furan derivatives, afford endoperoxides, which may undergo subsequent decompositions (equation 137) [*13, 17, 19*].

[19] 137

[13]

[17]

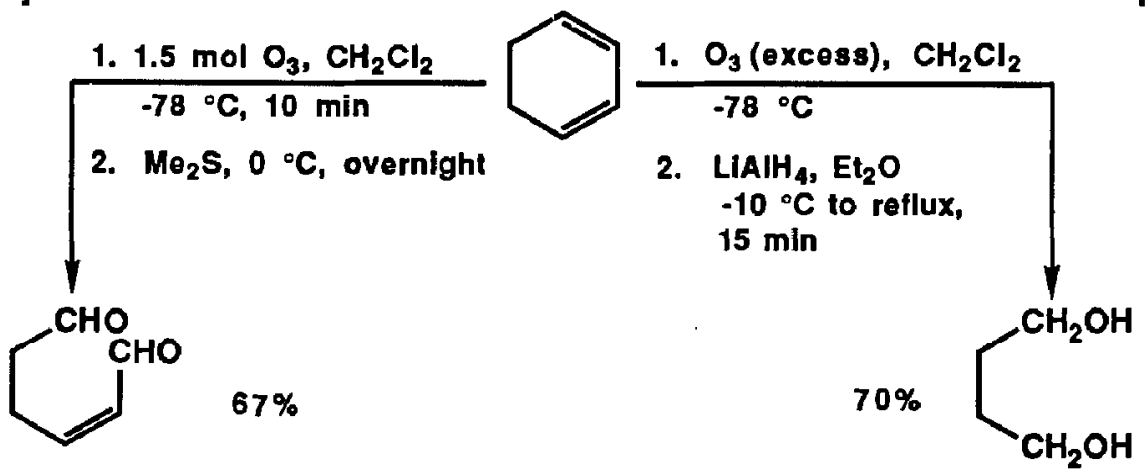


Dienes may be ***hydroxylated*** at one or at both double bonds, depending on the amount of oxidants used. Cyclopentadiene, on treatment with an excess of hydrogen peroxide and osmium tetroxide as a catalyst in *tert*-butyl alcohol, gives a mixture of 21% of 3,5-cyclopentenediol and 61% of 1,2,3,4-cyclopentanetetrol [*152*].

The cyclopentadiene dimer, when treated with potassium permanganate and triethylbenzylammonium chloride as a phase-transfer agent, furnishes an 83% yield of *exo,cis*-diol resulting from the hydroxylation of the double bond in the cyclohexene ring [*900*] (equation 82).

Dienes react with **ozone** at one or both double bonds to give ***carbonyl compounds.*** When 1,3-cyclohexadiene is dissolved in dichloromethane at –78 °C and treated with 1.5 mol of ozone in dichloromethane solution and the resulting ozonide is stirred overnight at 0 °C with dimethyl sulfide, 2-hexenedial is obtained in 67% yield. If, on the other hand, an excess of ozone is passed through a solution of 1,3-cyclohexadiene at –78 °C until a blue color appears, both double bonds are ozonolyzed, and a 70% yield of 1,4-butanediol is obtained by reducing the reaction mixture with lithium aluminum hydride (equation 138) [*92*]. More substituted double bonds react with ozone preferentially.

[*92*] 138

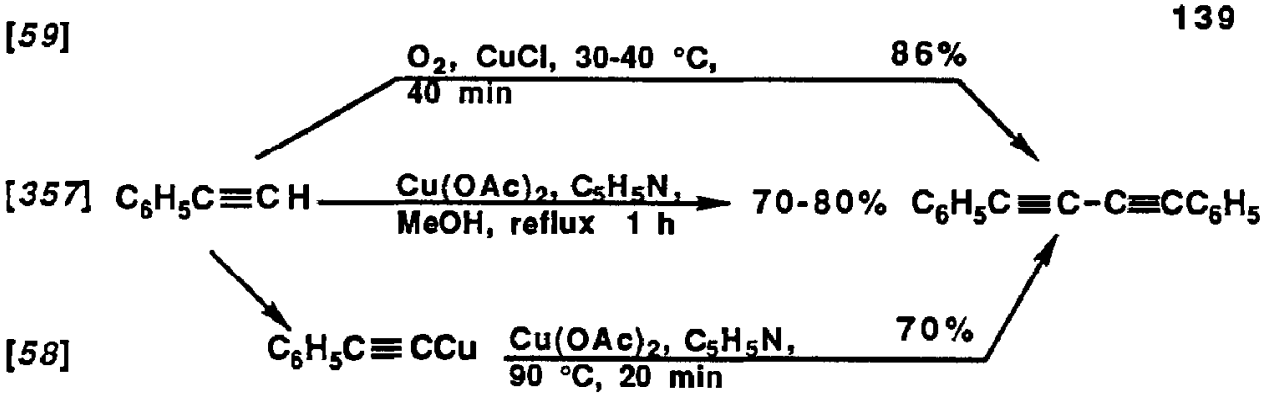


ALKYNES (ACETYLENES)

Terminal alkenes containing hydrogen linked to the triple bond undergo ***oxidative coupling to diacetylenes*** by *cupric salts* [*58, 357*] or by *oxygen* in the presence of *cuprous salts* [*59, 66*] (equation 139). Copper salts are solubilized by complexing with tertiary amines, most frequently pyridine [*59, 357*] and tetramethylethylenediamine [*66*]. The coupling can also be carried out with cuprous salts of acetylenes [*58*].

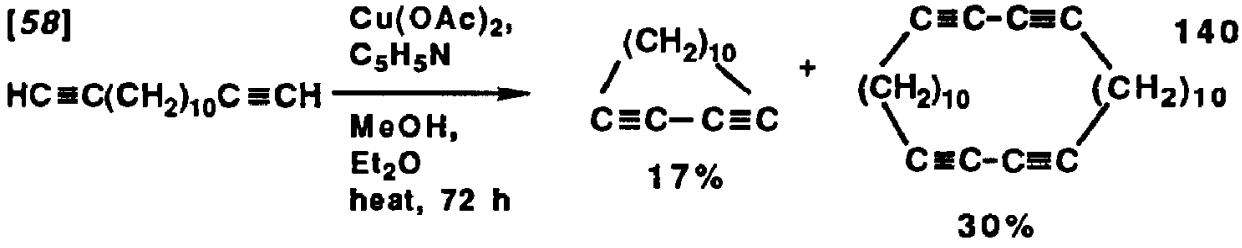
The oxidative coupling of long-chain terminal diacetylenes carried out in very dilute solutions gives macrocyclic diacetylenes and polyacetylenes

[*59*] 139



in low yields (equation 140) [*58*]. Oxidative coupling is frequently applied to acetylenic alcohols [*2*, *58*].

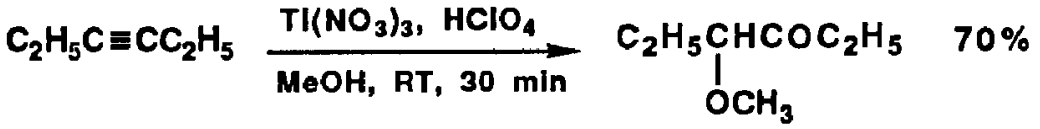
[*58*]



140

Dialkylalkynes are oxidized to ***acyloins*** or their alkyl ethers by thallium trinitrate in aqueous or aqueous–alcoholic solutions, respectively [*413*]. Only symmetrical alkynes give acceptable yields (70–90%) (equation 141).

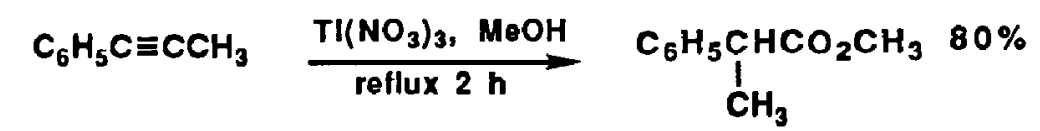
[*413*]



141

Alkylarylacetylenes undergo oxidative rearrangement to esters of alkylarylacetic acid (equation 142) under similar conditions [*413*].

[*413*]



142

Diarylacetylenes are converted in 55–90% yields into ***α-diketones*** by refluxing for 2–7 h with thallium trinitrate in glyme solutions containing perchloric acid [*413*]. Other oxidants capable of achieving the same oxidation are ozone [*84*], selenium dioxide [*509*], zinc dichromate [*660*], molybdenum peroxo complex with HMPA [*534*], **potassium permanganate in buffered solutions** [*848*, *856*, *864*, *1117*], zinc permanganate [*898*], osmium tetroxide with potassium chlorate [*717*], ruthenium tetroxide and sodium hypochlorite or periodate [*938*], dimethyl sulfoxide and *N*-bromosuccinimide [*997*], and iodosobenzene in the presence of a ruthenium catalyst [*787*] (equation 143).

A triple bond activates the adjoining methylene group for ***oxidation to a carbonyl group.*** Thus 5-decyne furnishes a 46% yield of 5-decyn-4-one on treatment with chromium–pyridine in dichloromethane for 24 h at room temperature [*601*].

Whereas internal acetylenes are oxidized to α-diketones, terminal acetylenes give ***carboxylic acids*** with one less carbon on treatment with thallium trinitrate [*413*], potassium permanganate [*843*], iodosobenzene with tris(triphenylphosphine)ruthenium dichloride as a catalyst [*787*], or a rather rare oxidant, pentafluoroiodobenzene bis(trifluoroacetate) [*797*] (equation 144).

EXAMPLES OF OXIDATION OF ACETYLENES 143

$C_6H_5C{\equiv}CC_6H_5 \longrightarrow C_6H_5COCOC_6H_5$

[*413*]	$Tl(NO_3)_3$, 70% $HClO_4$, glyme, reflux 3 h	85%
[*509*]	SeO_2, 280 °C	35%
[*660*]	$ZnCr_2O_7.3H_2O$, CCl_4, RT, 8 h	81%
[*534*]	$MoO(O_2)_2$, $Hg(OAc)_2$, HMPA MeOH/CH_2Cl_2 (1:9), 40 °C, 20 h	77%
[*856*]	$Zn(MnO_4)_2/SiO_2$, CH_2Cl_2, 40 °C, 45 min	67%
[*938*]	RuO_2, NaOCl or $NaIO_4$, CCl_4, RT, 1 h	83%
[*997*]	DMSO, NBS (2 mol), 22 °C, 24 h	98%
[*787*]	$PhIO/(Ph_3P)_3RuCl_2$, CH_2Cl_2, RT, 15 min	86%

$RC{\equiv}CH \longrightarrow RCO_2H$ 144

[*413*]	$Tl(NO_3)_3$, $HClO_4$, glyme, H_2O, RT, 1 h	R = C_6H_{13}	80%
[*843*]	$KMnO_4$, H_2O, C_5H_{12}, AcOH, Aliquat 336, cooling with ice, 5 h	R = C_8H_{17}	70%
[*787*]	$PhIO/(Ph_3P)_3RuCl_2$, CH_2Cl_2, RT, 5 min	R = C_6H_5	69%
[*797*]	$C_6F_5I(OCOCF_3)_2$, C_6H_6, H_2O, reflux overnight	R = C_6H_5	79%

Oxidations of acetylenic acids [*101, 268, 864*] and esters of acetylenic alcohols [*84, 1117*] to the corresponding α-dicarbonyl compounds and carboxylic acids are discussed in the section on carboxylic acids.

AROMATIC COMPOUNDS

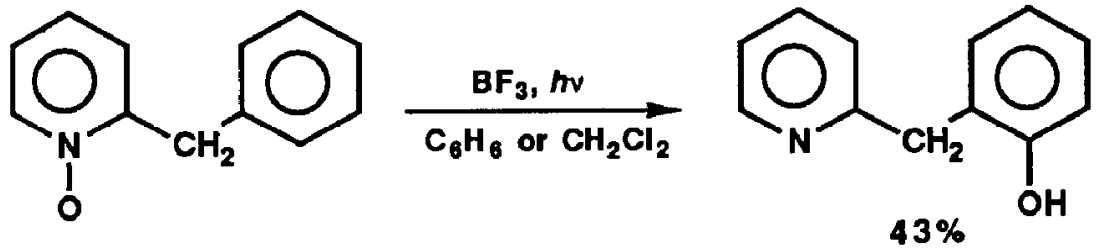
This section will encompass the reactions of carbocyclic and heterocyclic aromatic compounds in which oxidation affects the aromatic rings and the attached side chains.

Hydroxylation of Aromatic Rings

The hydroxylation of aromatic compounds takes place on heating with solid **potassium hydroxide** of compounds with low electron density in the ring and occurs in positions prone to nucleophilic attack. Nitrobenzene is converted into *o*-nitrophenol on heating with potassium hydroxide for 2 h at 60–70 °C (yield 45%) [*485*]. Quinoline gives carbostyril (2-hydroxyquinoline) on heating with potassium hydroxide for 3 h at 225 °C (yield 77%) [*486*]. A historically important reaction is the hydroxylation of both α- and β-anthraquinonesulfonic acid by alkali fusion to yield alizarin (1,2-dihydroxyanthraquinone).

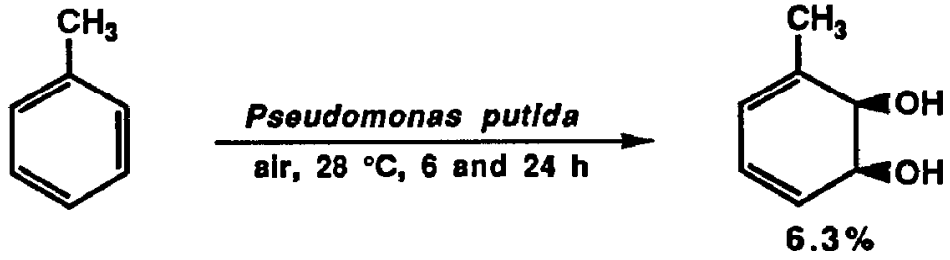
An interesting hydroxylation takes place, probably by an intramolecular transfer of oxygen, on irradiation of the 2-benzylpyridine *N*-oxide complex with boron trifluoride (equation 145) [*994*].

[*994*] 145



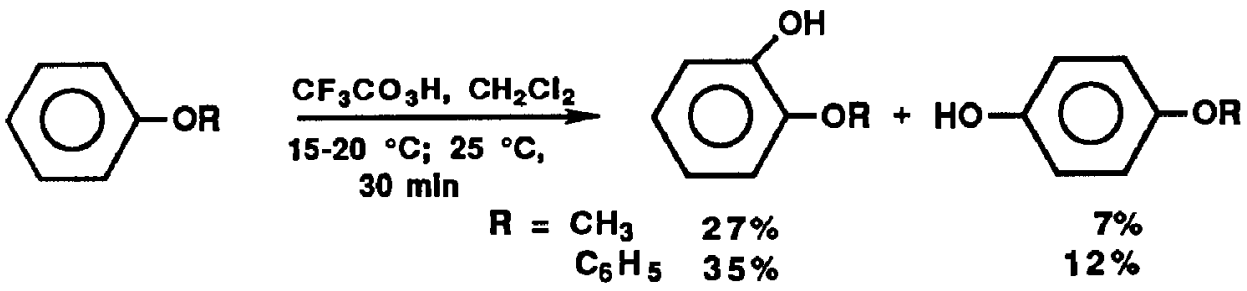
The benzene rings in toluene [*92*, *1074*], chlorobenzene [*92*], styrene [*92*], and phenylacetylene [*92*] undergo stereospecific *syn* hydroxylation in positions 2 and 3 with concomitant reduction to methyl-, chloro-, vinyl-, and acetylenyl-*cis*-2,3-dihydroxycyclohexa-4,6-dienes when treated with a culture of ***Pseudomonas putida*** (equation 146) [*92*, *1074*].

[*92*] 146



Hydroxylations of aromatic rings are also achieved via transient esters that are easily hydrolyzed in situ to the corresponding phenols. In this way, anisole and diphenyl ether are oxidized by peroxytrifluoroacetic acid to predominantly *ortho*-hydroxy compounds in low yields (equation 147) [*1118*].

[*1118*] 147

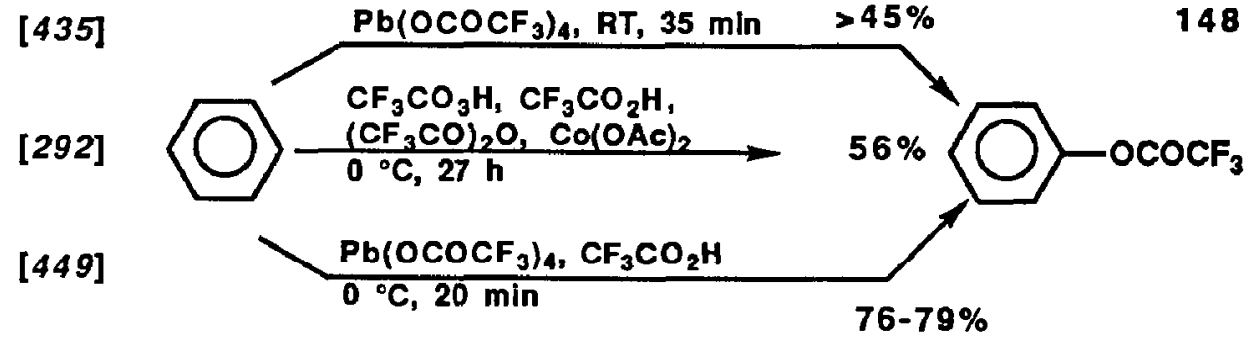


The oxidation of benzoic acid by divalent copper carried out by heating cupric benzoate to 210–260 °C in high-boiling liquids furnishes 73–100% of salicylic acid [*361*].

Esters of phenols are obtained by treatment of aromatic hydrocarbons with peroxy acids [*292*], organic peroxides [*1119*, *1120*], and lead tetraacetate or tetrakis(trifluoroacetate) [*435*, *449*]. Benzene treated with tri-

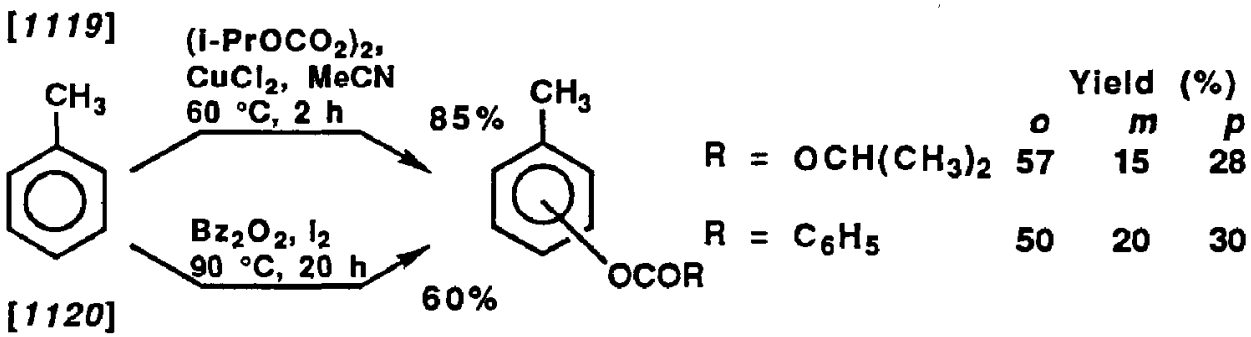
fluoroacetic acid, trifluoroacetic anhydride, and peroxytrifluoroacetic acid in the presence of cobaltous acetate gives a 56% yield of phenyl trifluoroacetate [*292*]. The same product is obtained on treatment of benzene with lead tetrakis(trifluoroacetate) [*435, 449*] (equation 148).

148



Heating benzene homologues with diisopropyl peroxydicarbonate and cupric chloride or with dibenzoyl peroxide and iodine gives isopropyloxycarbonyl or benzoyl esters of the corresponding phenols [*232, 1119, 1120*]. Unfortunately, all three isomers are usually obtained so that the synthetic uses are limited (equation 149).

149



	Yield (%)		
	o	*m*	*p*
R = $OCH(CH_3)_2$	57	15	28
R = C_6H_5	50	20	30

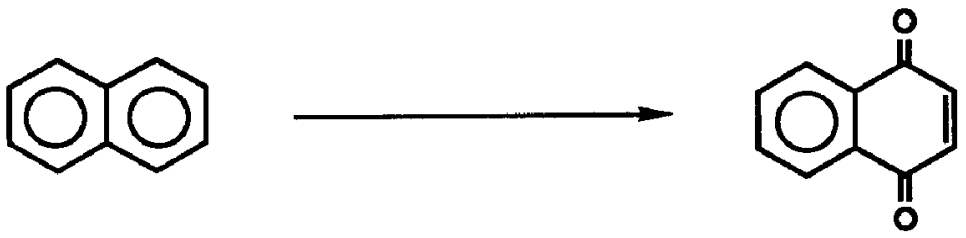
Like the acyloxylation with peroxides, the treatment of benzene homologues and derivatives with lead tetrakis(trifluoroacetate) gives mixtures of *ortho, meta,* and *para* isomers, with the *para* isomers predominating [*449*].

Oxidation of Aromatic Compounds to Quinones

The oxidation of benzene to *p*-benzoquinone is impractical, because benzoquinone is obtained from other compounds [*647*]. Condensed aromatic hydrocarbons are oxidized to quinones by many reagents [*429, 758, 802*], most frequently by the compounds of hexavalent chromium [*1121*] (equation 150).

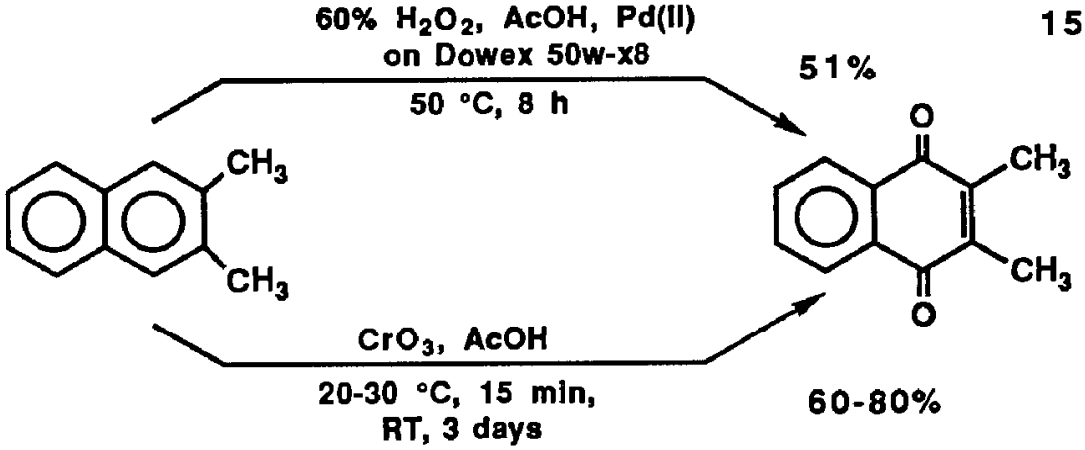
Alkylnaphthalenes are converted into alkyl-1,4-naphthoquinones with peroxyacetic acid [*139*] or chromic acid [*557*]. Under the conditions of these reactions (equation 151), the alkyl groups resist oxidation to carboxyl groups.

150



[*429*]	$Ce(SO_4)_2.2(NH_4)_2SO_4.2H_2O$, 4 N H_2SO_4, 25 °C, 6 h	90-95%
[*1121*]	CrO_3, AcOH, 0 °C, 2-3 h, RT, 3.5 days	32-35%
[*802*]	$Mn_2(SO_4)_3$ (from $MnSO_4.4H_2O$ + $KMnO_4$), MeCN, H_2O, 25 °C, 4 h	75%
[*758*]	HIO_4, AcOH, 110 °C, 5 min, 70 °C, 30 min	70-76%

151



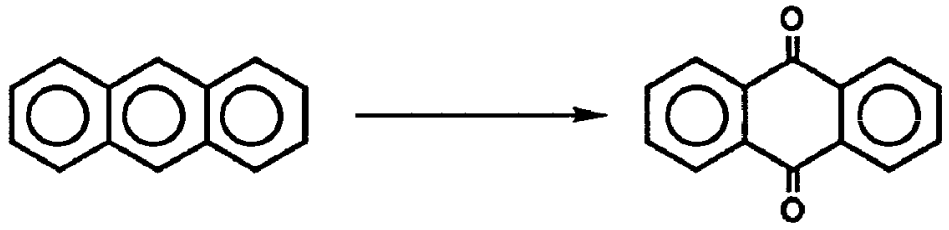
[*139*]

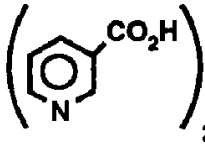
[*557*]

The oxidation of ***anthracene*** to anthraquinone takes place in positions 9 and 10 [*3, 249, 509, 630, 660, 663*] and has industrial application in the synthesis of lake and vat dyes (equation 152).

EXAMPLES OF FORMATION OF QUINONES

152

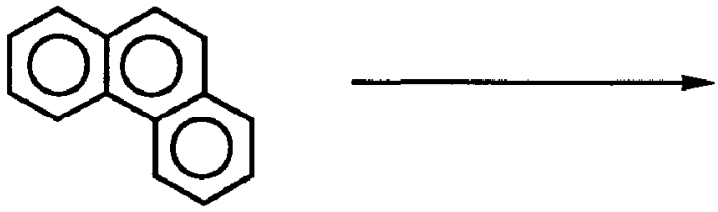


[*3*]	air, V_2O_5/pumice, 420-425 °C	81%
[*509*]	SeO_2, 165-170 °C	76%
[*249*]	40% AcO_2H, AcOH, 50 °C, 6 h	70%
[*630*]	$Na_2Cr_2O_7$, H_2SO_4, Bu_4NHSO_4, 70 °C, 2 min	82-92%
[*660*]	$ZnCr_2O_7.3H_2O$, CCl_4, RT, 3.5 h	80%
[*663*]	 Cr_2O_7, AcOH, reflux 75 h	67%

9,10-Anthraquinone is also formed from 9-methylanthracene on refluxing with sodium dichromate in acetic acid for 30 min (yields are 97% of crude product and 88% of pure product) [*1122*].

Phenanthrene is oxidized to 9,10-phenanthrenequinone [*429, 649, 650, 802*] and, to a smaller extent, to 1,4-phenanthrenequinone (yield 19%) [*802*] (equation 153).

The oxidation of ***chrysene*** (1,2-benzophenanthrene) by refluxing for 8–10 h with chromic oxide in acetic acid gives a 96–97% yield of 5,6-chrysenequinone [*556*].



153

[*429*]	$Ce(SO_4)_2.2(NH_4)_2.2H_2O$, 4 N H_2SO_4, 50 °C, 4 h	60%
[*650*]	CrO_3, H_2SO_4, H_2O, boil 20 min	44-48%
[*649*]	$K_2Cr_2O_7$, H_2SO_4, H_2O, 1 h	79%
[*802*]	$Mn_2(SO_4)_3$ (from $MnSO_4.4H_2O$ + $KMnO_4$), MeCN, H_2O, 25 °C, 4 h	32%

Oxidative Cleavage of the Benzene Ring

The breakdown of the benzene ring to aldehydes is extremely rare and has been achieved only by ozone. A historical and classical example is the disintegration of *o*-xylene to a mixture of glyoxal, methyl glyoxal, and diacetyl (butanedione) in the predicted ratios [*104*]. From the preparative point of view, the conversion of phenanthrene into *o,o'*-diformylbiphenyl (diphenaldehyde) [*1123*] or *o*-formylbiphenyl-*o'*-carboxylic (diphenaldehydic) acid [*1124*] is more important (equation 154).

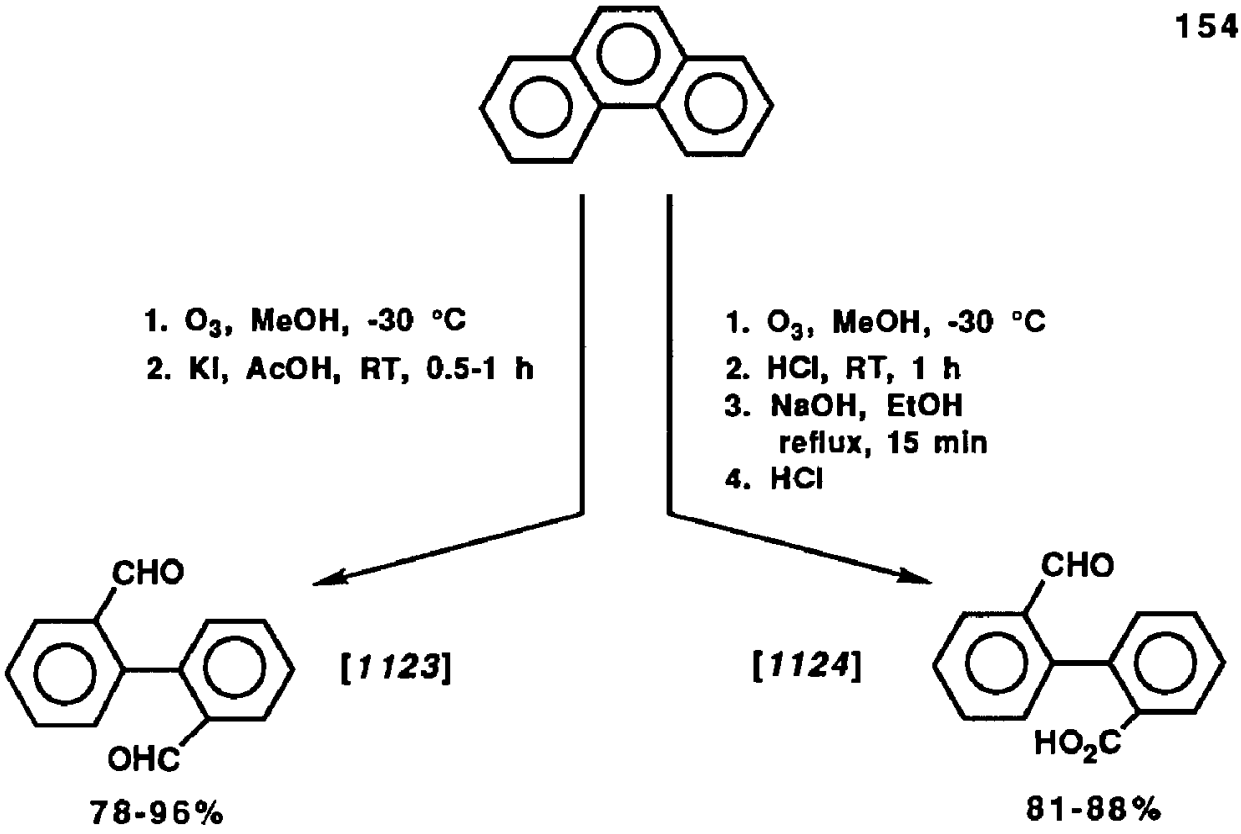
The conversion of the benzene ring in benzene homologues to carboxylic groups is encountered rarely and has hardly any preparative value. One example involves the treatment of α-truxillic acid with ozone and subsequent oxidation with hydrogen peroxide (equation 155) [*109*].

The reagent of choice for the oxidation of phenyl groups to carboxyls seems to be ruthenium tetroxide with sodium periodate [*231, 941*] or sodium hypochlorite [*701*] as reoxidants. Phenylcyclohexane is oxidized to cyclohexanecarboxylic acid (equation 156) [*774, 941*], and β-phenylpropionic acid is transformed mainly into succinic acid (equation 157) [*701*].

The degradation of benzene rings to carboxyls is facilitated by the presence of electron-donating groups. *m*-Trifluoromethylaniline is converted into trifluoroacetic acid in 90–95% yield on heating with **sodium dichromate** and dilute sulfuric acid for 30–40 min at 70–170 °C [*638*].

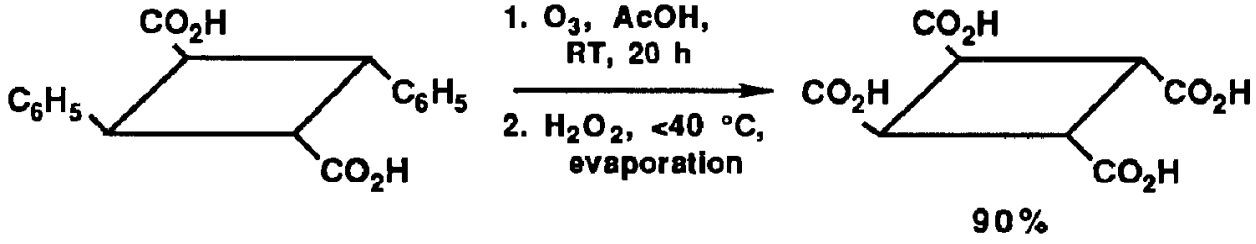
Condensed polynuclear hydrocarbons and aromatic heterocycles are converted into dicarboxylic acids. Naphthalene is oxidized to phthalic an-

154



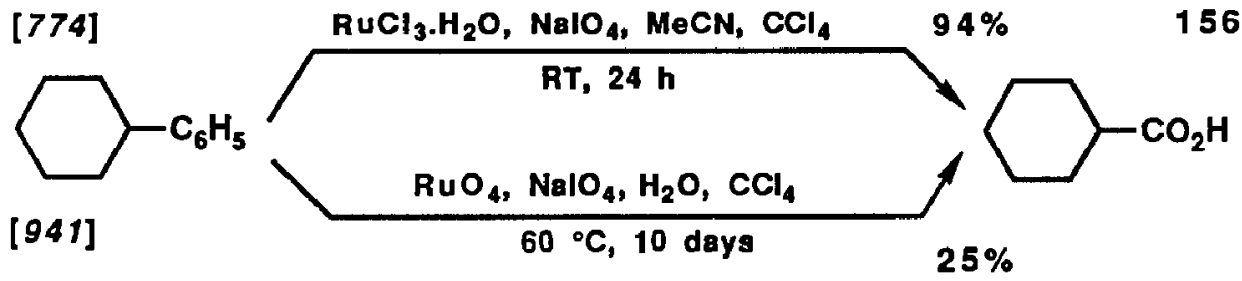
[109]

155



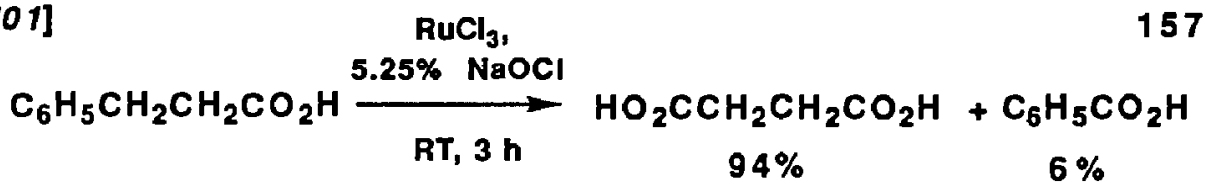
[774]

156



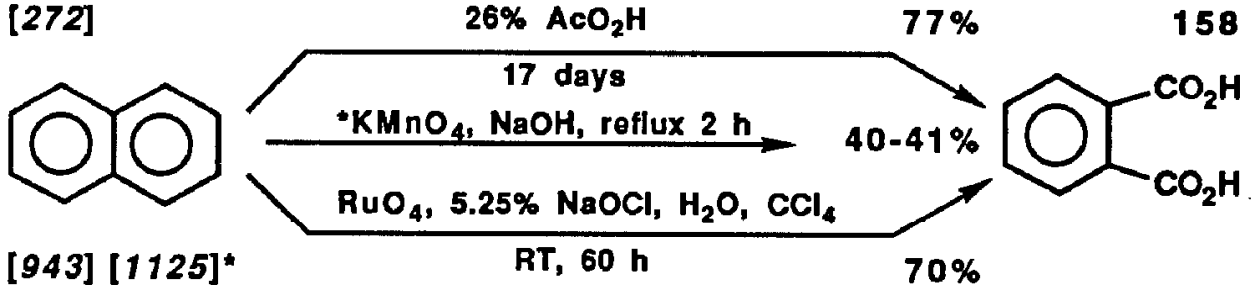
[701]

157

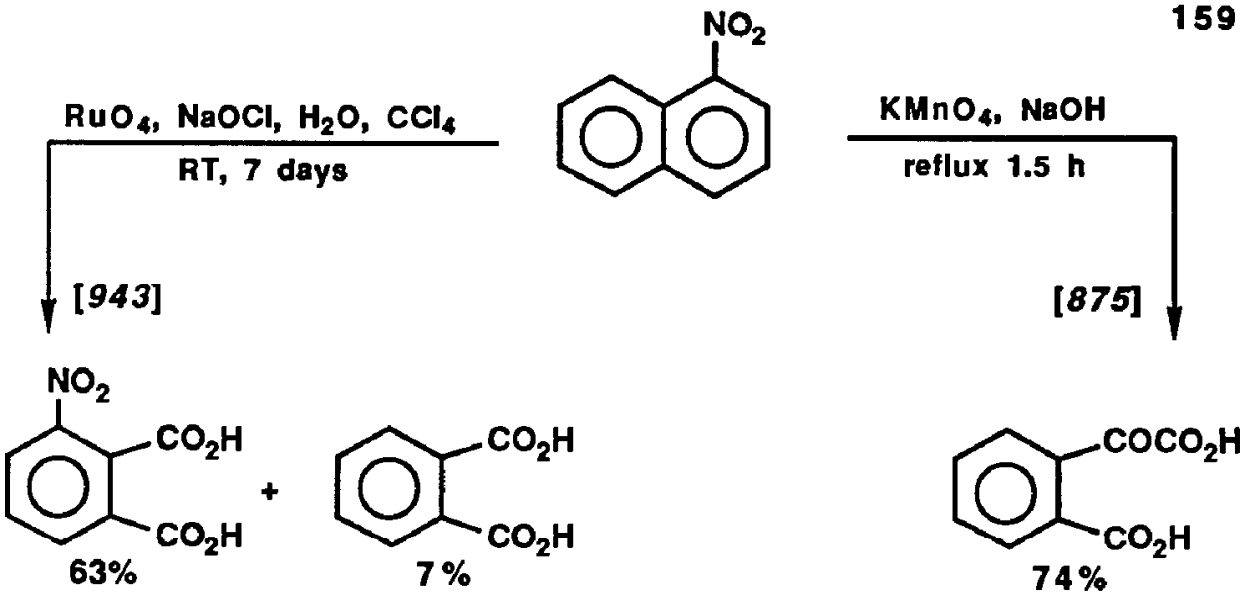


hydride by oxygen or air over vanadium pentoxide at high temperatures [*479*] and to phthalic acid by peroxyacetic acid [*272*], potassium permanganate [*1125*], or ruthenium tetroxide [*943*] (equation 158).

α-Nitronaphthalene is oxidized by ruthenium tetroxide to give 63% of 3-nitrophthalic acid and 7% of phthalic acid [*943*]. When oxidation is

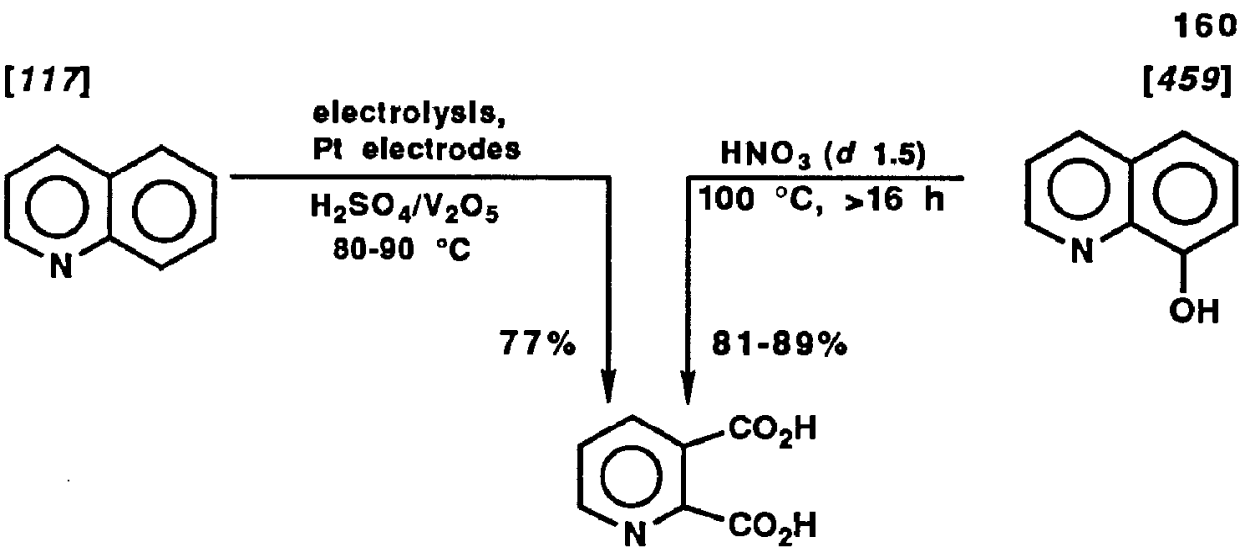


carried out by potassium permanganate, the nitro-group-containing ring yields phthalonic acid [*875*] (equation 159).



Phenanthrene is oxidized with 40% peroxyacetic acid in glyme at 100–110 °C to α,α′-diphenic acid in 65–70% yield [*256*]. Quinoxaline affords a 75–77% yield of pyridazine-2,3-dicarboxylic acid on refluxing for 1.5 h with potassium permanganate [*876*].

In heterocyclic aromatic compounds, the ring containing electron-withdrawing substituents is more resistant to oxidative degradation. Both quinoline and 8-hydroxyquinoline give quinolinic (pyridine-2,3-dicarboxylic) acid (equation 160) [*117, 459*].



Oxidation of Side Chains of Carbocyclic and Heterocyclic Aromatic Compounds

The alkyl groups attached to aromatic rings undergo several types of oxidation. The common denominator is an attack at the carbon adjacent to the ring—the benzylic carbon. This position of attack is understandable, because an intermediate resulting from such a reaction is stabilized by resonance with the ring and is formed more readily than at any other place of the chain. Only rarely does the oxidation affect more distant carbons of the chain.

FORMATION OF ARALKYL HYDROPEROXIDES

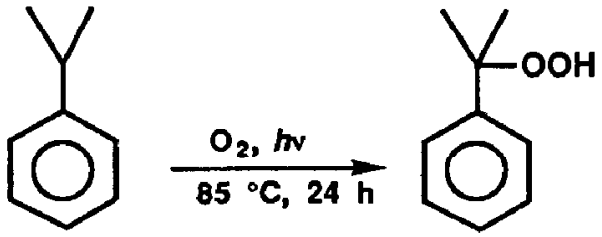
The treatment of compounds possessing primary, secondary, and especially tertiary benzylic hydrogens with oxygen, usually under irradiation, results in a free-radical chain reaction giving hydroperoxides as the final products (equation 161).

$$ArCH_3 \xrightarrow{h\nu} ArCH_2\cdot \xrightarrow{O_2} RCH_2\text{-}O\text{-}O\cdot \qquad 161$$

$$RCH_2\text{-}O\text{-}O\cdot + ArCH_3 \longrightarrow RCH_2\text{-}O\text{-}O\text{-}H + ArCH_2\cdot$$

Such reactions take place with *p*-xylene [*28*], ethylbenzene [*28*], and especially readily with isopropylbenzene (cumene) [*29*], where the intermediate free radical is stabilized not only by the aromatic ring but also by the two adjacent methyl groups. The oxidation of cumene to cumyl hydroperoxide (equation 162) followed by acid treatment is a basis for the large-scale production of phenol.

[*29*]



6% conversion

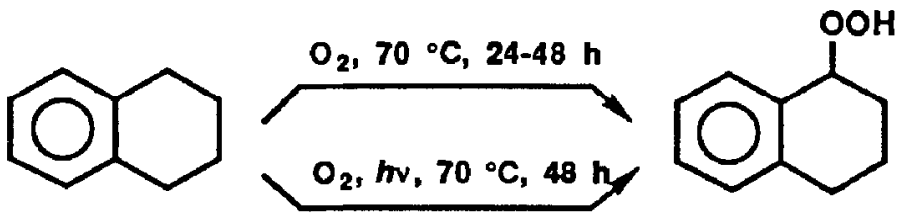
162

In compounds containing saturated rings attached to aromatic nuclei, for example, indane [*27*], tetralin [*23*, *50*], and octahydroanthracene [*47*], oxidations take place at carbons adjacent to the aromatic rings and usually give low conversions. Only a few reactions have preparative importance (equation 163).

163

[*50*] O_2, 70 °C, 24-48 h — 44-57%

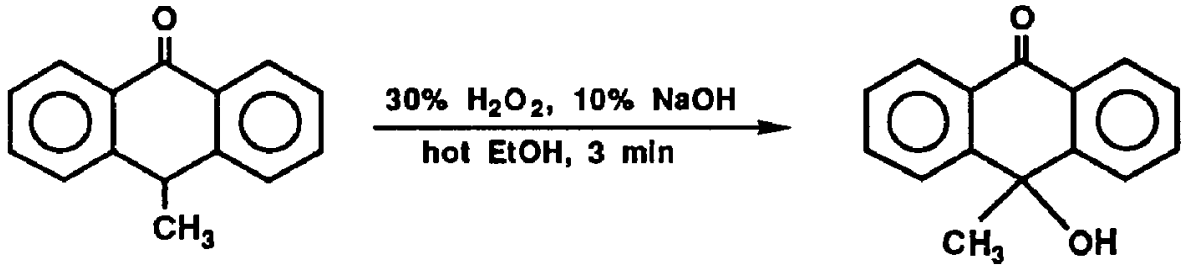
[*23*] O_2, $h\nu$, 70 °C, 48 h — 66%



OXIDATION TO BENZYLIC ALCOHOLS AND ESTERS

Hydroxylation at the benzylic position is encountered very rarely. An example is the oxidation of 10-methylanthrone to 10-hydroxy-10-methylanthrone in 67% yield on treatment with 30% hydrogen peroxide in 10% sodium hydroxide in hot ethanol for 3 min (equation 164) [*1126*].

[*1126*] 164

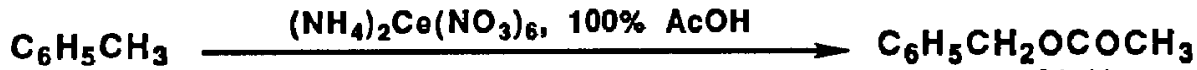


67%

More frequently, the benzylic hydrogen is replaced by an acyloxy group on refluxing with ceric ammonium nitrate in 100% acetic acid [*415*], with **lead tetraacetate** [*434, 437*], or with lead tetrakis(trifluoroacetate) [*435*].

Oxidation with ammonium cerium nitrate has to be done in 100% acetic acid (equation 165). In 50% acetic acid, carbonyl compounds are

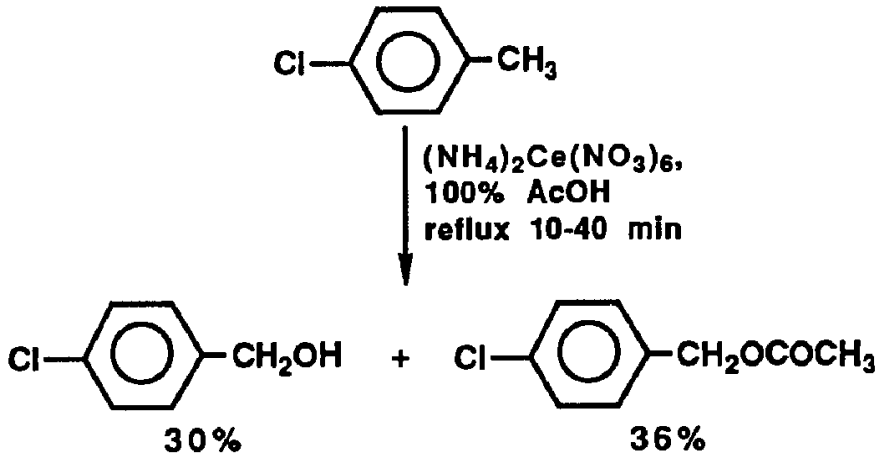
[*415*] 165



90 %

formed. In some cases, more than one product is generated. For example, in the oxidation of *p*-chlorotoluene, a mixture of *p*-chlorobenzyl alcohol and *p*-chlorobenzyl acetate is obtained (equation 166) [*415*].

[*415*] 166

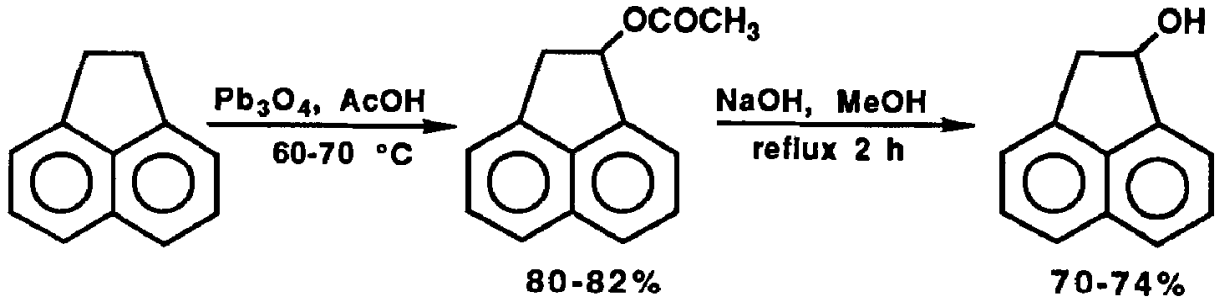


30% 36%

Heating toluene with lead tetraacetate at 80 °C for 54 h gives only 25% of benzyl acetate, but ethylbenzene and anisole give 63% of α-methylbenzyl acetate after 16 h and 60% of *p*-methoxybenzyl acetate after 3 h at 80 °C, respectively [*437*]. Under similar conditions, acenaphthene yields

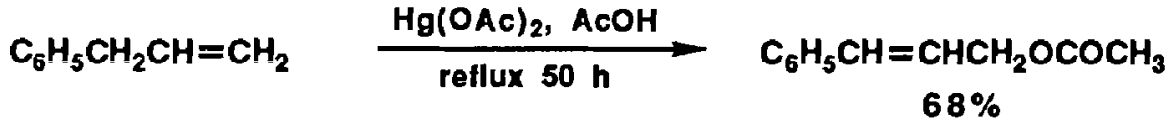
1-acetoxyacenaphthene (equation 167) [*434*]. Subsequent hydrolysis of the esters with sodium hydroxide yields the corresponding alcohols [*434, 435*].

[*434*] 167



In allylbenzene, an easy oxidation at the benzylic, and at the same time allylic, carbon would be expected. However, cinnamyl acetate is formed instead on treatment with mercuric acetate, evidently as a result of an S_N2' reaction at the double bond (equation 168) [*404*].

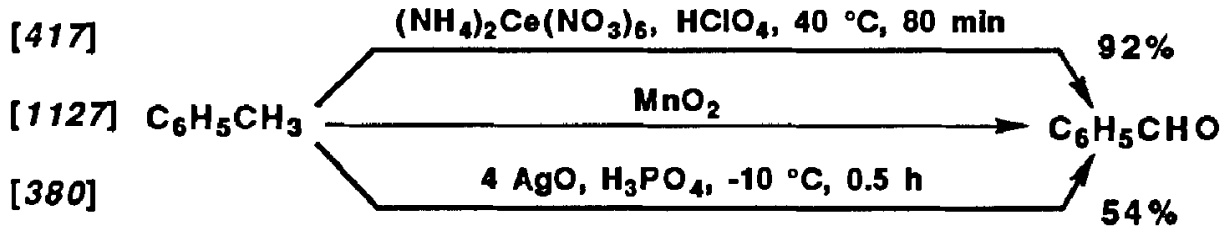
[*404*] 168



OXIDATION TO ALDEHYDES, KETONES, AND THEIR DERIVATIVES

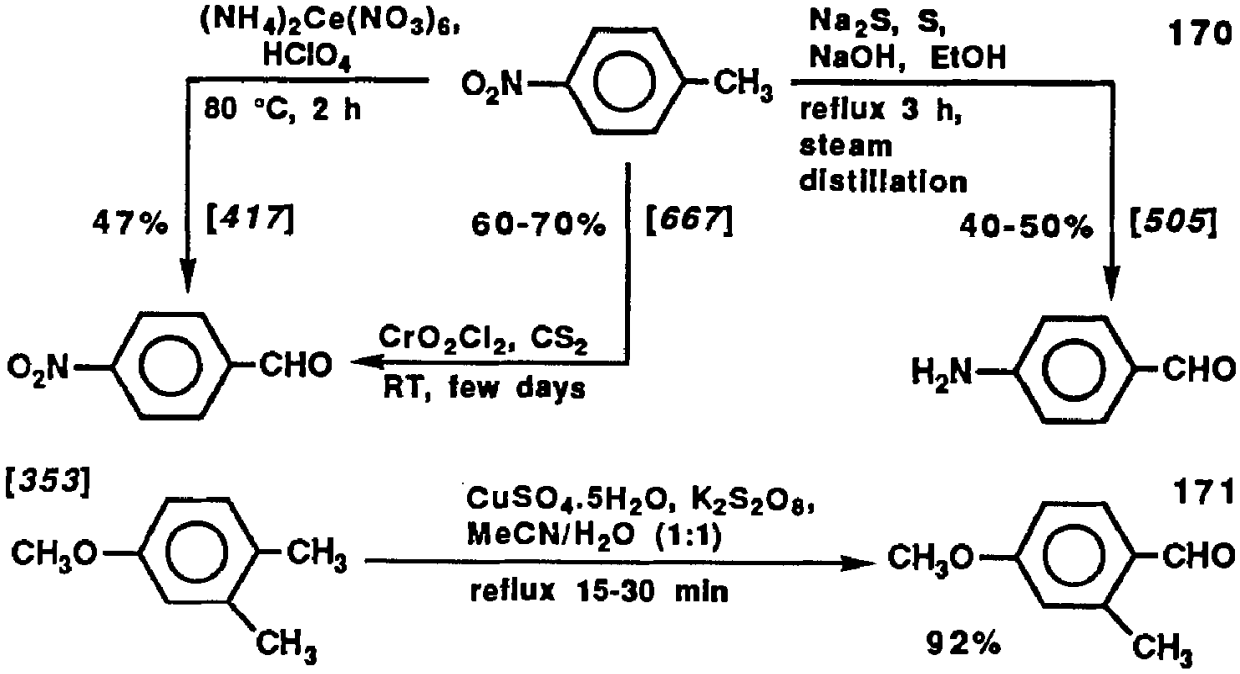
Methyl homologues of aromatic compounds are oxidized to ***aldehydes*** by silver(II) oxide (argentic oxide) [*380*], by ceric ammonium nitrate [*238, 417, 422*], by **selenium dioxide** [*513, 514, 515*], by chromyl chloride [*477, 667*], by periodic acid [*760*], and by **manganese dioxide** [*1127*] (equation 169).

169

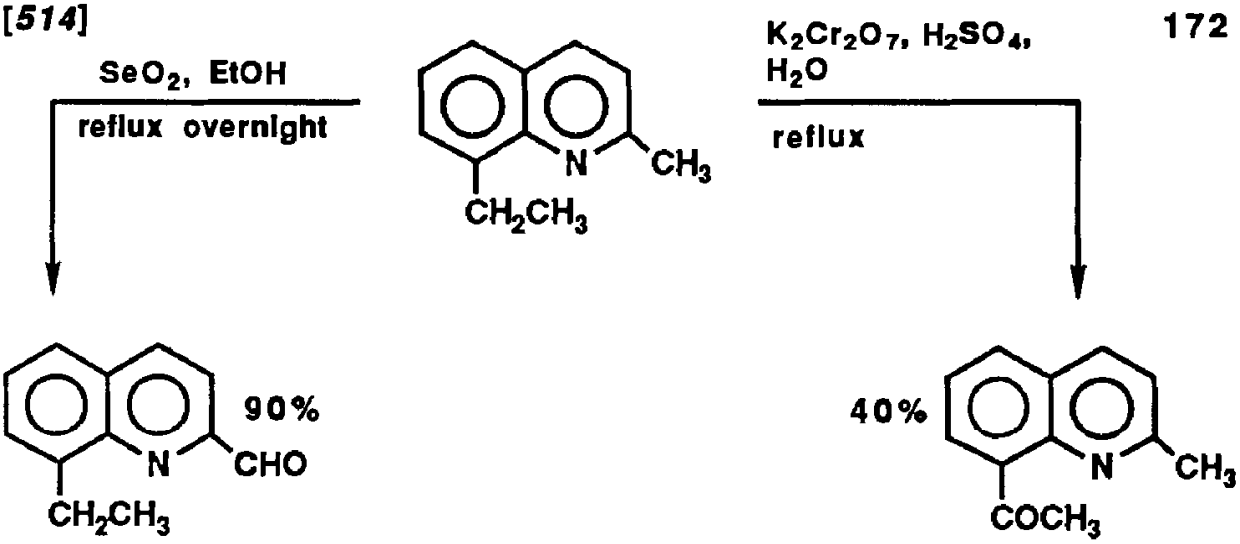


p-Nitrotoluene is oxidized by ceric ammonium nitrate [*417*] or by chromyl chloride [*667*] to *p*-nitrobenzaldehyde, whereas refluxing with aqueous alcoholic sodium polysulfide gives *p*-aminobenzaldehyde by an internal redox reaction [*505*] (equation 170).

The regiospecific oxidation of dimethylanisoles to methoxymethylbenzaldehydes is accomplished with copper sulfate and potassium peroxydisulfate, which oxidize selectively only the methyls in the *ortho* or *para* positions with respect to the methoxy group (equation 171) [*353*].

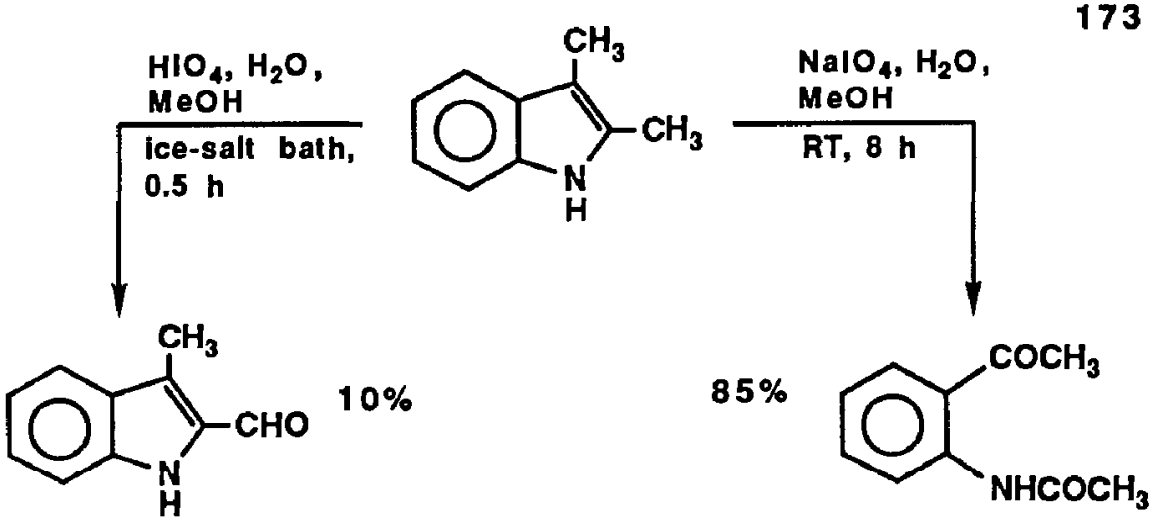


In aromatic heterocycles, the methyl groups in α positions with respect to nitrogen are oxidized especially easily. Thus quinaldine gives a 50% yield of quinoline-α-carboxaldehyde on refluxing for 1 h with selenium dioxide in aqueous dioxane [*513*], and 2,3,8-trimethylquinoline gives an 82% yield of 3,8-dimethylquinoline-2-carboxaldehyde on refluxing for 6 h with selenium dioxide in ethanol [*515*]. A similar selective oxidation is achieved when 8-ethyl-2-methylquinoline is treated with selenium dioxide or **potassium dichromate** [*514*]. Treatment with selenium dioxide gives 8-ethyl-2-formylquinoline, whereas treatment with potassium dichromate gives 8-acetyl-2-methylquinoline (equation 172) [*514*].



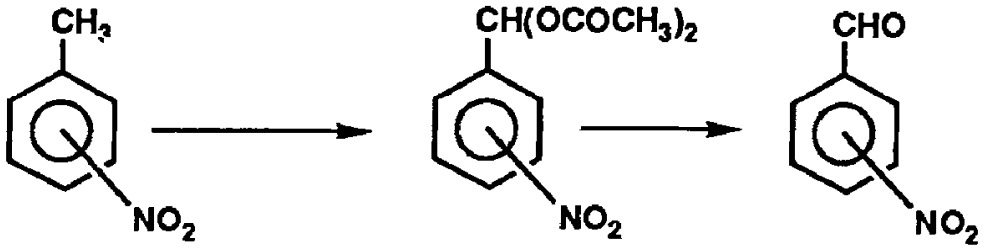
Selectivity is also noticed in oxidations of 2,3-dimethylindole. Whereas sodium periodate cleaves the double bond and gives an 85% yield of *o*-acetamidoacetophenone, periodic acid oxidizes the methyl group adjacent to the heterocyclic nitrogen to an aldehyde group in a low yield (equation 173) [*760*].

[760]



173

In the presence of acetic anhydride, acetic acid, and sulfuric acid, chromic acid (**chromium trioxide**) converts *o*-nitrotoluene and *p*-nitrotoluene into the corresponding ***nitrobenzaldehyde diacetates,*** from which the aldehydes are obtained on hydrolysis (equation 174) [*547, 548, 549*].



174

[*548, 549*]

ortho	CrO_3, Ac_2O, H_2SO_4 10 °C, 3 h	36-37%	HCl, EtOH reflux 45 min	74%

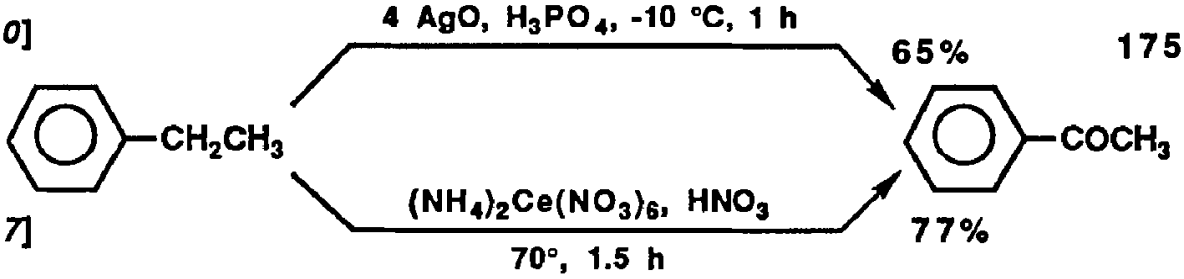
[*547*]

para	CrO_3, Ac_2O, AcOH, H_2SO_4, <10 °C	48-54%	H_2SO_4, EtOH reflux 30 min	89-94%

Methylene groups adjacent to aromatic rings are oxidized to ***keto groups*** by oxygen with chromium sesquioxide as a catalyst [*1128*] or by mercuric bromide [*11*], ceric ammonium nitrate [*380, 417, 422*], selenium dioxide [*509*], sodium dichromate [*622, 625*], pyridinium chlorochromate [*607*], manganese dioxide [*814*], potassium permanganate [*866, 877*], and alkyl nitrites [*452*].

Ethylbenzene is converted into acetophenone by argentic oxide [*380*], by ceric ammonium nitrate [*417*], and by other oxidants (equation 175).

[380]



[417]

175

The conversion of methylene to carbonyl is especially easy when the group is flanked by two aromatic rings. Thus, diphenylmethane yields benzophenone on treatment with ceric ammonium nitrate [*417*, *422*], selenium dioxide [*509*], and pyridinium chlorochromate [*607*]. Manganese dioxide at 125 °C converts diphenylmethane into benzophenone, whereas at 211 °C, tetraphenylethylene is formed in 81% yield [*814*] (equation 176).

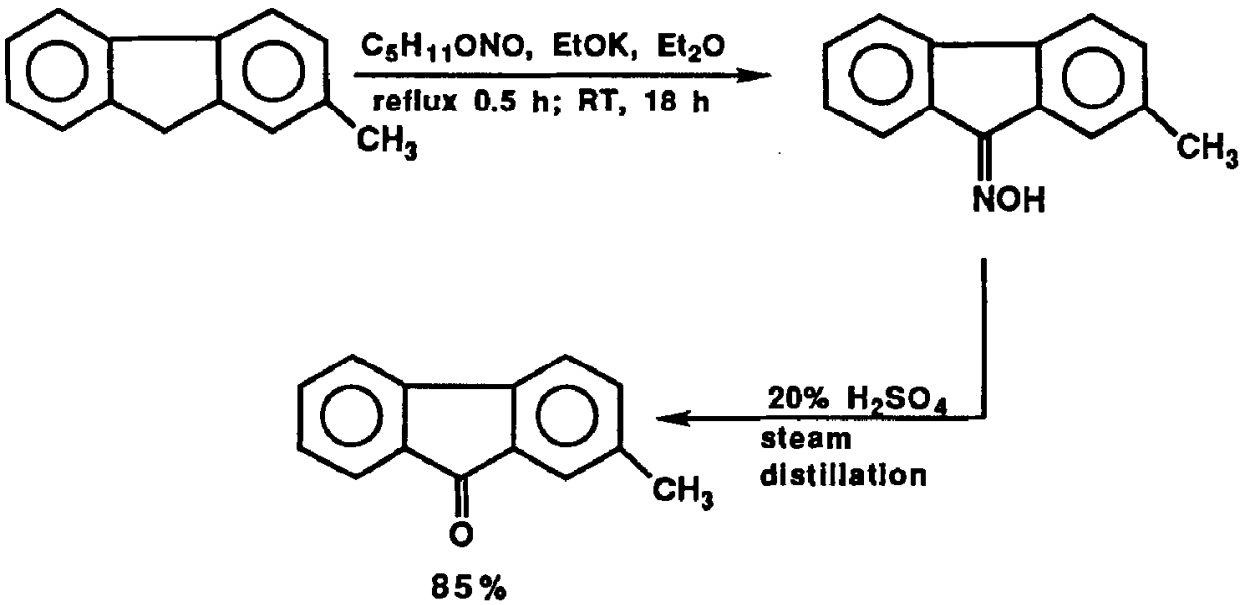
176

[*417*]	$(NH_4)_2Ce(NO_3)_6$, HNO_3, 90 °C, 75 min	76%
[*509*]	SeO_2, 200-210 °C, 30 min	87%
[*607*]	$C_5H_5N.HCl.CrO_3$, Celite*, C_6H_6, reflux 10 h	88%
[*814*]	MnO_2, 125 °C, 6 h	74%

*Celite is diatomaceous earth or infusorial earth.

Fluorene is oxidized to fluorenone in 65–70% yield by refluxing for 3 h with **sodium dichromate** in acetic acid [*622*], and 2-methylfluorene is converted into 2-methylfluorenone via its oxime on treatment with amyl nitrite (**pentyl nitrite**) [*452*]. The methylene group between two aromatic rings is oxidized in preference to the methyl group because nitrites react only with highly activated methylene groups (equation 177).

[*452*] 177

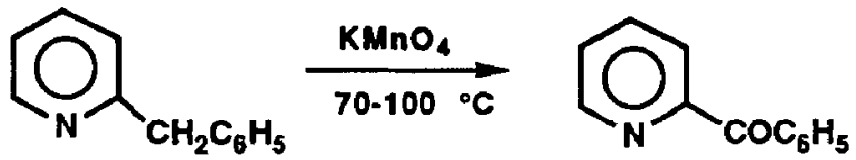


85%

2-Benzylpyridine forms 2-phenacylpyridine on heating with potassium permanganate (equation 178) [*877*].

Indane is oxidized to 1-indanone and tetralin is converted into 1-tetralone by mercuric bromide under irradiation [*11*] or by argentic oxide [*380*] (equation 179).

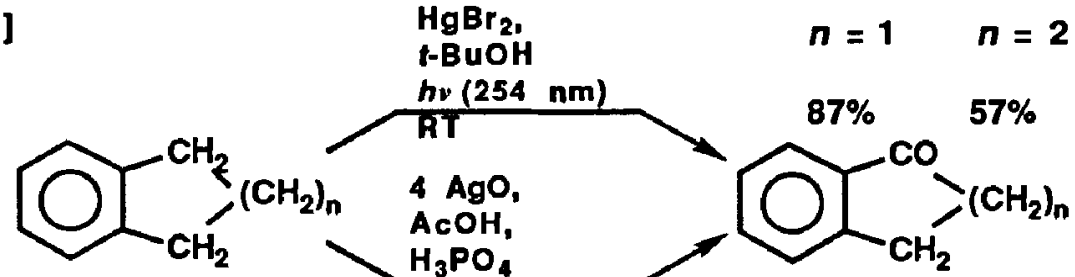
[877]



178

88-94%

[11]

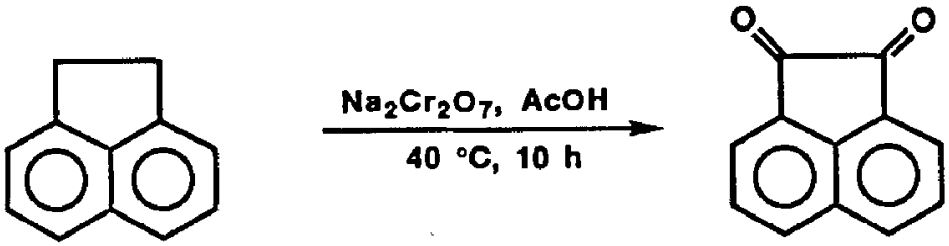


[380]

179

In acenaphthene, both methylene groups are oxidized by sodium dichromate to give acenaphthenequinone (equation 180) [*625*].

[625]



180

38-60%

Oxidations with chromyl chloride (Etard reaction) of aromatic compounds with longer chains are not always suitable because the reactions result in more than one product [*673*].

OXIDATION TO CARBOXYLIC ACIDS

Not only methyl groups but practically any other alkyl groups attached to aromatic rings are oxidized to carboxyls by sufficiently strong oxidants, such as **nitric acid** [*460, 461, 462, 463, 464, 891*], **chromic acid and its derivatives** [*550, 551, 624, 633, 634, 1129, 1130*], and **potassium permanganate** [*503, 841, 880, 881, 882, 883, 1131*]. Occasionally, such oxidations have been effected by other reagents, such as ozone [*68*], sulfomonoperacid (Oxone) [*205*], sodium hypochlorite [*696*], and nickel dioxide [*933*], or by electrooxidation [*117*] (equation 181).

Ethylbenzene and isopropylbenzene give 80 and 75%, respectively, of benzoic acid on oxidation with 15% nitric acid at higher temperatures [*462*]. The disadvantages of oxidations with nitric acid are the formation of nitrated byproducts (up to 12% of nitrobenzoic acid in the oxidation of ethylbenzene) and the necessity of working in glass-lined or stainless steel autoclaves [*462*].

EXAMPLES OF OXIDATION OF TOLUENES TO BENZOIC ACIDS

181

[*841*]	X = H	$KMnO_4$, crown ether, C_6H_6, 25 °C, 72 h	78%
[*205*]	X = H	$2KHSO_5.KHSO_4.K_2SO_4$, reflux 22 h	50%
[*462*]	X = H	15% HNO_3, 170-200 °C, 30-50 atm	85-90%
[*68*]	X = *o*-CH_3	O_3, $Co(OAc)_2$, AcOH, 115-120 °C, 1.5 h; O_2, 115-120 °C, 8.5 h	77%
[*463*]	X = *o*-CH_3	HNO_3 (dilute 1:2), 145-155 °C, reflux, 55 h	53-55%
[*461*]	X = *p*-F	20% HNO_3, 190-195 °C, 70 atm, 6 h	96%
[*460*]	X = *p*-CH_3 *o*-F	22% HNO_3, 200 °C, 52 atm, 15 min	79%
[*882*]	X = *o*-Cl	$KMnO_4$, H_2O, boil 3-4 h	76-78%
[*880*]	X = *o*-Br	$KMnO_4$, NaOH, H_2O, reflux	59% (76%)*
	m-Br		63% (81%)*
	p-Br		76% (83%)*
[*634*]	X = *p*-NO_2	$Na_2Cr_2O_7$, H_2SO_4, reflux 1 h	82-86%
[*551*]	X = 3,4-$(NO_2)_2$	CrO_3, H_2SO_4, 45-50 °C, 3-4 h	85-90%
[*1129*]	X = 2,4,6-$(NO_2)_3$	$Na_2Cr_2O_7$, H_2SO_4, 45-55 °C, 3-4 h	57-69%
[*881*]	X = HgCl	$KMnO_4$, NaOH, 95 °C, 15 min	61-74% X = OH

*The yields are based on the consumed bromotoluenes.

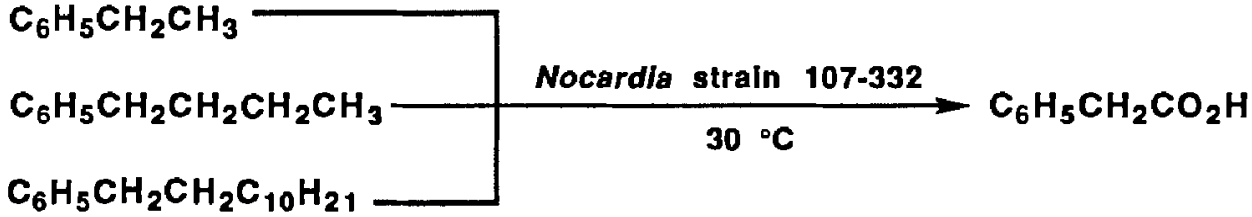
The partial oxidation of polyalkylated aromatic compounds is also observed. *o*-Xylene is oxidized to *o*-toluic acid by heating with ozone and oxygen at 115–120 °C in the presence of cobalt acetate in acetic acid (yield 77%) [*68*] or by refluxing with dilute nitric acid (1:2) (yield 53–55%) [*463*]. In *p*-cymene (*p*-isopropylbenzene), the isopropyl group is oxidized in preference to the methyl group to give a 51% yield of *p*-toluic acid on refluxing with dilute nitric acid (1:36) [*464*]. On the contrary, biochemical oxidation with *Nocardia* strain 107–332 converts *p*-cymene into *p*-isopropylbenzoic acid [*1071*].

In fairly rare cases, alkyl benzenes are converted into carboxylic acids without, or with only partial, degradation of the carbon chain. Propylben-

zene is converted into benzoic acid on heating in an autoclave with an aqueous solution of sodium dichromate at 270 °C, but at 200 °C, 54% of 3-phenylpropionic acid is obtained [*632*]. Ethyl-, isopropyl-, and butylbenzene give similar results albeit in not so clear-cut reactions: isopropylbenzene yields 70% of 2-phenylpropionic acid and less than 10% of benzoic acid at 200 °C and 76% of benzoic acid and 24% of 2-phenylpropionic acid at 275 °C [*632*].

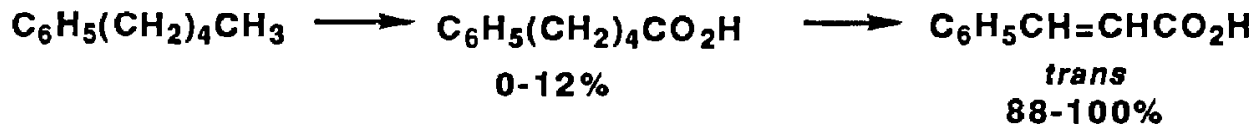
Biochemical oxidations of side chains proceed without degradation or with only limited degradation. Both ethylbenzene and butylbenzene, and even dodecylbenzene, give phenylacetic acid on incubation at 30 °C with *Nocardia* strain 107–332 (equation 182) [*1071*].

[*1071*] **182**



Amylbenzene (pentylbenzene) is first oxidized to 5-phenylvaleric acid and later transformed, by β-degradation and dehydrogenation, to *trans*-cinnamic acid in high yields by *Cellulomonas galba* (equation 183) [*1053*].

[*1053*] **183**

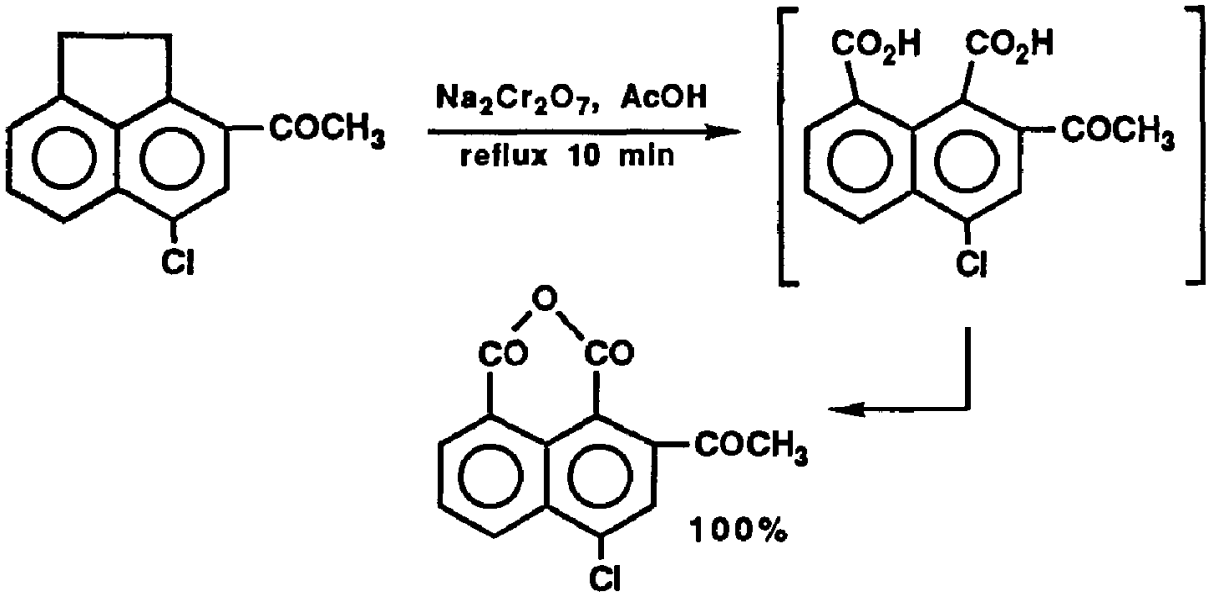


Homologues of *naphthalene* are oxidized to naphthalenecarboxylic acids on heating in an autoclave at 250 °C for 18 h with an aqueous solution of sodium dichromate. β-Methylnaphthalene affords β-naphthoic acid in 93% yield [*633*], and 2,3-dimethylnaphthalene, 2,3-naphthalenedicarboxylic acid in 87–93% yield [*1130*]. *Methylanthracenes* and *methylphenanthrenes* are similarly converted into the corresponding carboxylic acids in yields well over 90% [*633*].

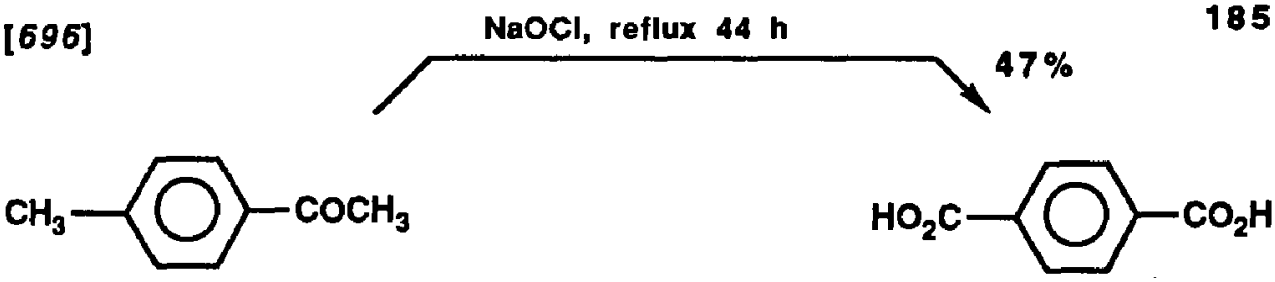
In a derivative of acenaphthene, the five-membered ring is cleaved to form a dicarboxylic acid that yields an anhydride (equation 184) [*624*].

Alkyl groups are oxidized to carboxyls also in aromatic compounds containing functional groups, which may or may not be affected by the oxidant. Thus *p*-methylbenzophenone is transformed, on refluxing with chromium trioxide in acetic and sulfuric acid, into benzophenone-*p*-carboxylic acid (yield 62–69%) [*550*], whereas in *p*-methylacetophenone, both the methyl and the acetyl groups are converted into carboxyls (equation 185) [*696, 891*].

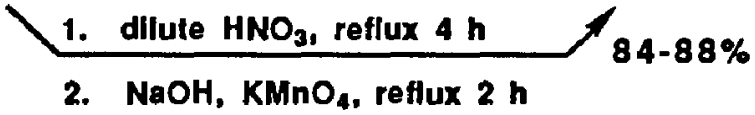
[624] 184



[696] 185

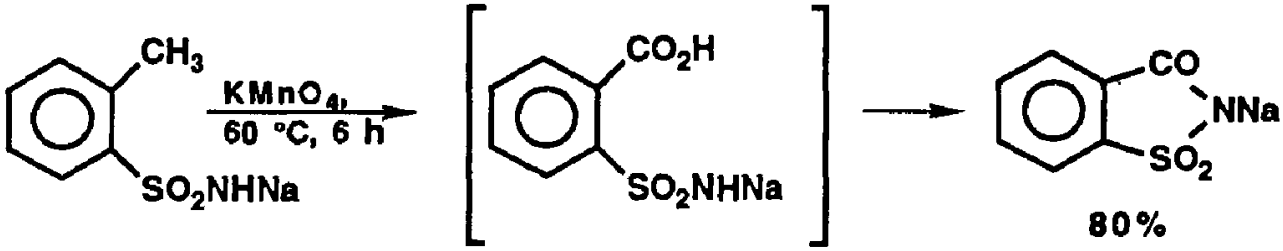


[891]



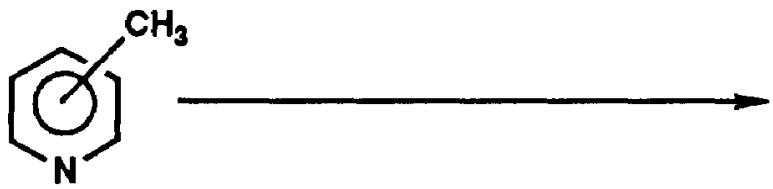
On treatment with potassium permanganate, the sodium salt of toluene-*o*-sulfonamide yields the corresponding carboxylic acid, which cyclizes to form saccharin (equation 186) [*1131*].

[1131] 186



Homologues of pyridine are converted into the corresponding pyridinecarboxylic acids by electrooxidation [*117*], by oxidation with dilute nitric acid [*462*], or by treatment with potassium permanganate [*503, 883*] (equation 187).

2-Methylquinoline-3-carboxylic acid is oxidized quantitatively by nickel dioxide in sodium hydroxide after 12 h at 25 °C to quinoline-2,3-dicarboxylic acid [*933*].



187

[*883*]	2-(α)-	$KMnO_4$, H_2O, 100 °C, 3-3.5 h	50-51%
[*117*]	3-(β)-	electrooxidation, Pb electrodes, H_2SO_4	60%
[*462*]	3-(β)-	15% HNO_3, 200 °C, 35-40 atm	50-60%
	4-(γ)-	10% HNO_3, H_3PO_4, 230 °C, 40 atm	93%
[*503*]	4-(γ)-	$KMnO_4$, H_2O, reflux	60-70% (50-60% pure)

HALOGEN DERIVATIVES AND TOSYLATES

In this section, only oxidations that result in the removal of halogen substituents will be discussed. Oxidations that do not affect halogens are discussed in sections describing oxidations of individual functional groups. The exception is the oxidative cleavage of haloalkenes, which leads to carboxylic acids and which is mentioned in the section Alkenes and Cycloalkenes.

Halogen compounds can be oxidized to aldehydes, ketones, or acids, depending on their structures and on the oxidants used.

Aliphatic ***primary halides***—chlorides, bromides, and especially iodides—are converted into ***aldehydes*** by treatment with dimethyl sulfoxide [*998, 999, 1000*] or trimethylamine oxide [*993*]. The reactivity of alkyl chlorides and bromides is increased by converting them in situ to alkyl iodides by the addition of sodium iodide into the reaction mixtures [*999*] (equation 188).

A modification of the oxidation of alkyl halides to aldehydes is the transformation of the halides into ***alkyl tosylates*** on treatment with silver tosylate in acetonitrile at 0–5 °C followed by heating of the crude tosylates with dimethyl sulfoxide and sodium bicarbonate (equation 189) [*1000*].

Secondary bromides such as 2-bromobutane and 2-bromooctane are oxidized by dimethyl sulfoxide in the presence of sodium iodide and sodium bicarbonate after 2 h at 115 °C to 2-butanone and 2-octanone in 65 and 56% yields, respectively (equation 190) [*999*].

Allylic halides are transformed into α,β-unsaturated aldehydes or ke-

EXAMPLES OF OXIDATION OF ALKYL HALIDES TO ALDEHYDES

188

$RCH_2X \longrightarrow RCHO$

[999]	R = C_3H_7, X = Br NaI, DMSO, $NaHCO_3$, 115 °C, 2 h	75%
[998]	R = C_5H_{11}, X = I DMSO, $NaHCO_3$, 150 °C, 3 min	86%
[999]	R = C_7H_{15}, X = Cl NaI, DMSO, $NaHCO_3$, 115 °C, 2 h	73%
[999]	R = C_7H_{15}, X = Br NaI, DMSO, $NaHCO_3$, 115 °C, 2 h	60%
[998]	R = C_7H_{15}, X = I DMSO, $NaHCO_3$, 148 °C, 4 min	74%
[993]	R = C_7H_{15}, X = I $(CH_3)_3NO$, $CHCl_3$, 40-50 °C, 1 h; reflux 20 min	41.5-43%

[1000]

189

$C_7H_{15}CH_2X \xrightarrow[0\text{-}5\ °C]{TosOAg,\ MeCN} C_7H_{15}CH_2OTos \xrightarrow[150\ °C,\ 3\ min]{DMSO,\ NaHCO_3} C_7H_{15}CHO$

X =	
Cl	71%
Br	74%
I	70%

[999]

190

$CH_3CHBrR \xrightarrow[115\ °C,\ 2\ h]{DMSO,\ NaI,\ NaHCO_3} CH_3COR$

R = C_2H_5	65%
R = C_6H_{13}	56%

tones by the ***Sommelet reaction*** on treatment with hexamine (hexamethylenetetramine) (equation 191) [*1132*].

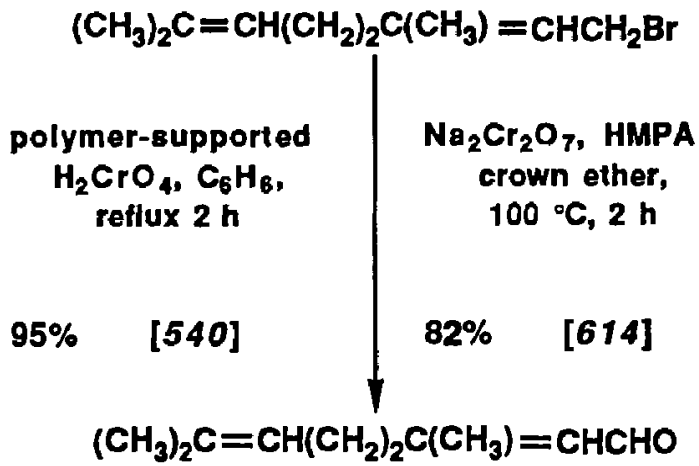
[1132]

191

$$RCH{=}CHCH_2X \xrightarrow{C_6H_{12}N_4} RCH{=}CHCH_2.C_6H_{12}N_4.X \xrightarrow{\text{steam distillation or reflux with water}} RCH{=}CHCHO$$

γ,γ-Dimethylallyl bromide and geranyl bromide are converted into the corresponding aldehydes in 75 and 82% yields, respectively, by heating at 100 °C with *sodium dichromate* in hexamethylphosphoramide in the presence of dicyclohexyl-18-crown-6 ether [*614*]. Similar results are achieved with polymer-supported chromic acid [*540*] (equation 192).

The oxidation of ***benzylic halides to aromatic aldehydes and ketones*** is very easy and is accomplished by many reagents. Very simple ways to prepare aromatic aldehydes from benzyl chlorides and bromides are treat-



ment with **dimethyl sulfoxide** [*999, 1003*], refluxing with copper or lead nitrate [*477*], treatment with the sodium salt of 2-nitropropane [*987*] or with tetrabutylammonium periodate [*778*], and the ***Sommelet reaction,*** which involves refluxing in water [*1132*] or in chloroform with hexamine (hexamethylenetetramine) and subsequent hydrolysis [*955, 956*] (equations 193–196).

193

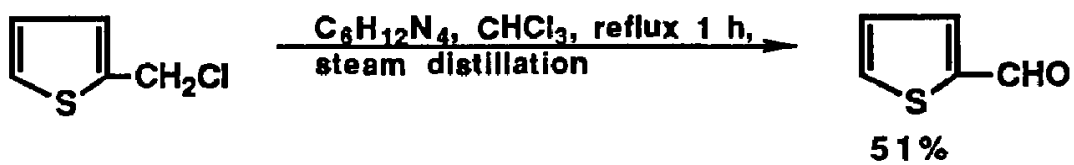
[*614*]	X = Cl	$K_2Cr_2O_7$, HMPA, dicyclohexano-18-crown-6 ether, 100 °C, 2 h	80%
[*540*]	X = Cl	H_2CrO_4 (polymer supported), C_6H_6, reflux 75 min	95%
[*987*]	X = Cl	Na, EtOH, Me_2CHNO_2, 80 °C, 3 h	73%
[*778*]	X = Br	Bu_4NIO_4, dioxane, reflux, 3 h	85%

194

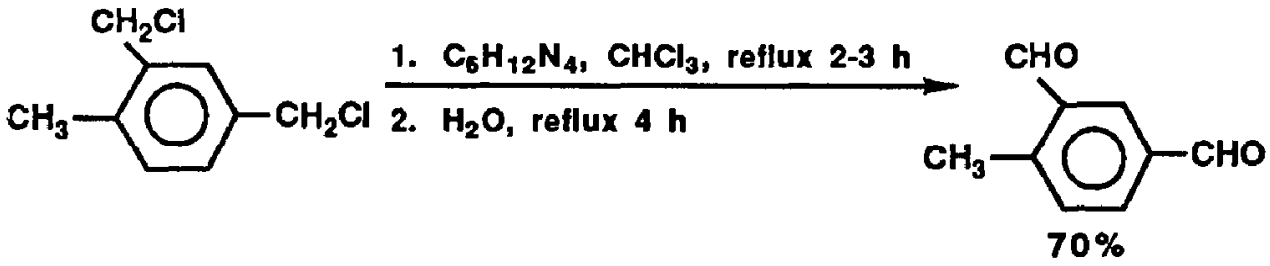
[*477*]	X = Br, Y = *o*-F	$Pb(NO_3)_2$, H_2O, reflux 5-6 h	61%
[*1003*]	X = Br, Y = *p*-NO_2	DMSO, MeCN, RT, 9 h	48%
[*999*]	X = Cl, Y = *p*-NO_2	DMSO, NaI, 120 °C, 4 h	62%

[*955*]

195

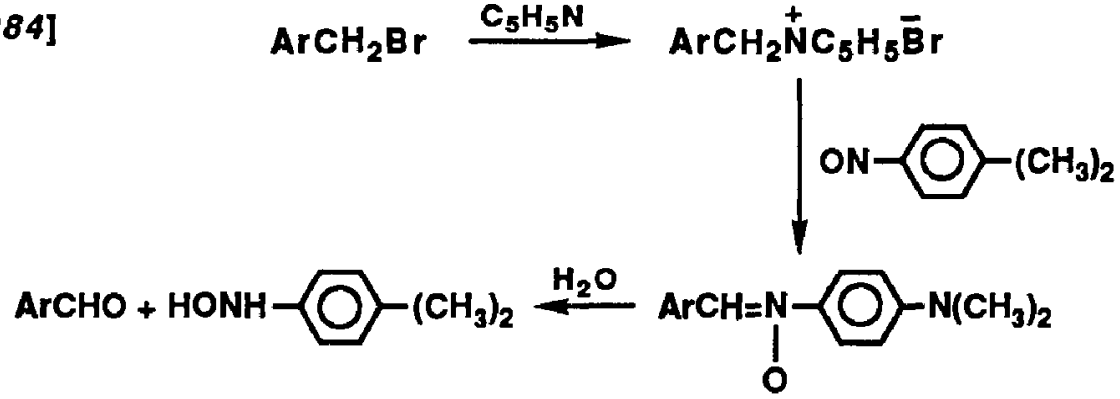


[956] 196



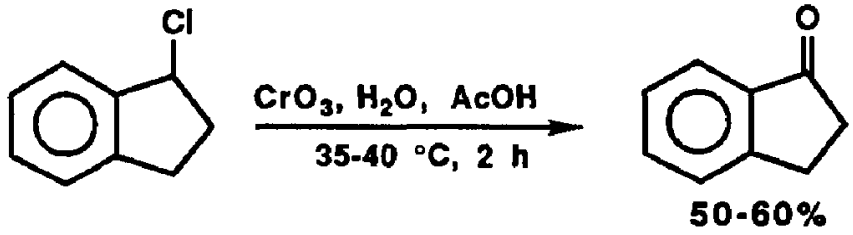
Benzylic halides are also converted into aldehydes on treatment with **nitroso compounds**, usually the easily prepared *p*-nitrosodimethylaniline, in the presence of pyridine with subsequent hydrolysis of the nitrones by hydrochloric acid or by hydrazine (equation 197) [*984*].

[984] 197

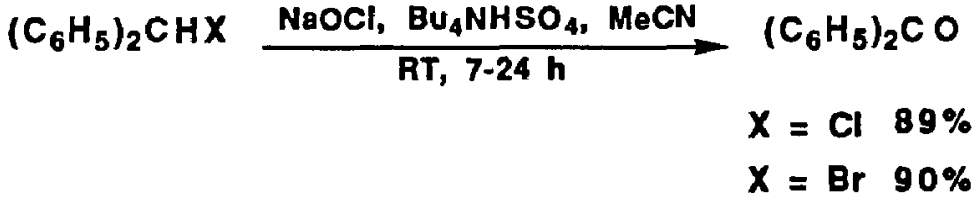


Secondary benzylic chlorides and bromides give ***aromatic ketones*** on oxidation with chromium trioxide [*560*] or with tetrabutylammonium hypochlorite [*690*] (equations 198 and 199).

[560] 198

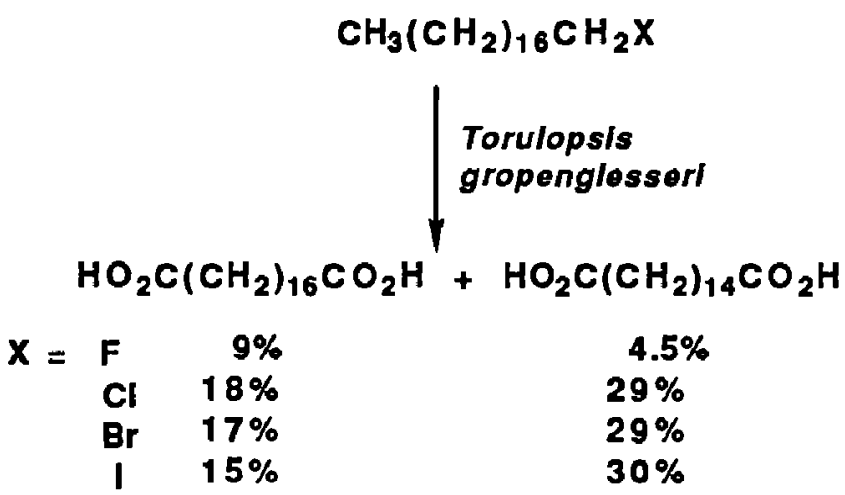


[690] 199



The oxidation of ***primary alkyl halides to carboxylic acids*** is accomplished on incubation of long-chain aliphatic fluorides, chlorides, bromides, and iodides with the yeast *Torulopsis gropengiesseri* [*1086, 1087*] (equation 200). The biooxidation starts at the terminal methyl groups and gives ω-halogenoalkanoic acids, which are ultimately converted to α,ω-dicarboxylic

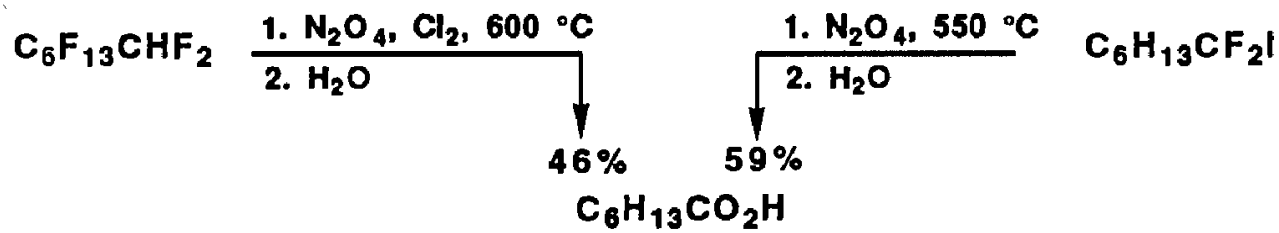
[1086]



acids. In addition, dicarboxylic acids with two less carbons are produced concomitantly.

High-temperature oxidations with **nitrogen dioxide** or nitrogen dioxide and chlorine followed by treatment with water convert perfluoroalkyl hydrides and perfluoroalkyl iodides into perfluorocarboxylic acids. Perfluoroalkyl bromides and especially perfluoroalkyl chlorides do not react appreciably (equation 201) [*455*].

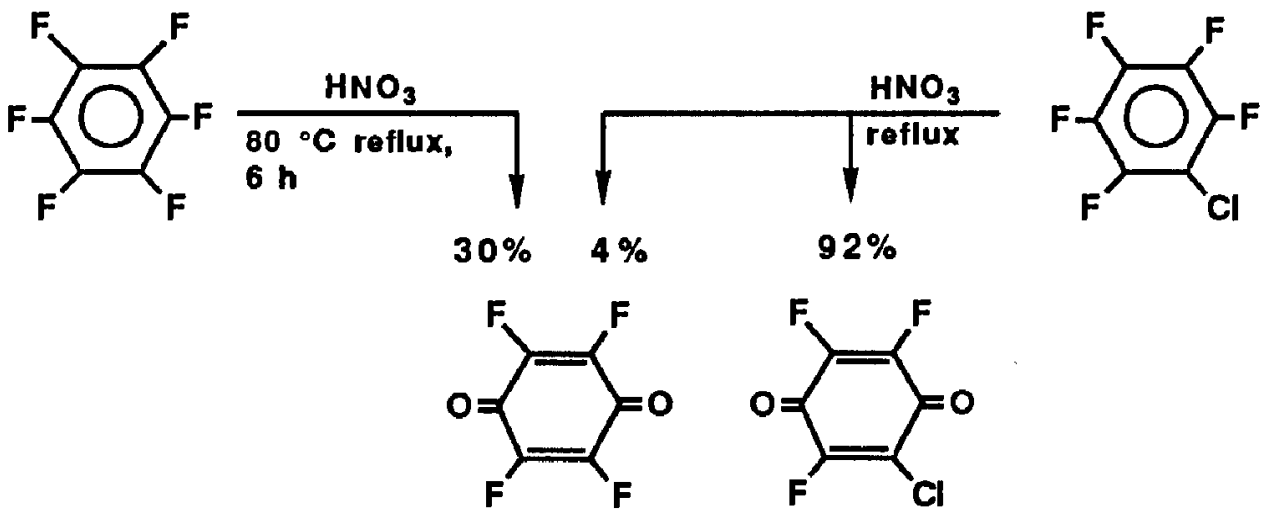
[*455*]



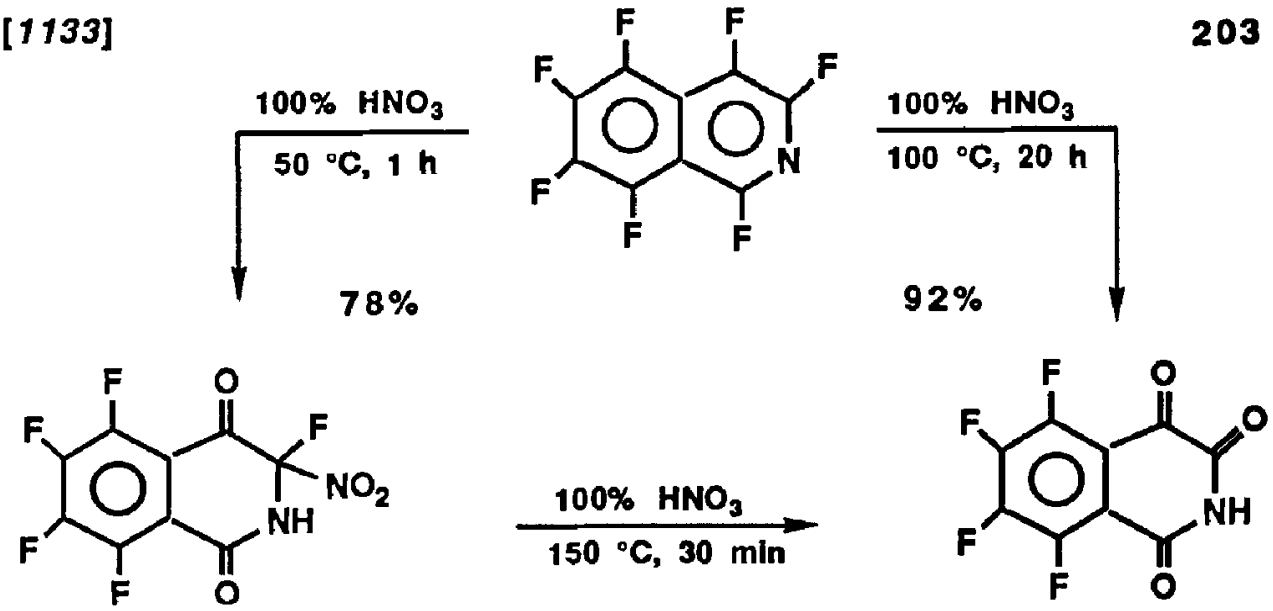
Oxidations of halogenated alkenes to carboxylic acids are discussed in a previous section, Oxidative Cleavage of Double Bonds (equations 118–120).

Perfluorinated aromatic compounds are oxidized to quinones (equations 202 and 203) [*1133, 1134*].

[*1134*]



[1133] 203



ALCOHOLS

Primary alcohols are oxidized to aldehydes or acids, and secondary alcohols are oxidized to ketones. Tertiary alcohols resist oxidation, unless they are dehydrated in acidic media to alkenes, which are subsequently oxidized. The conversion of alcohols into carbonyl compounds can be achieved by catalytic dehydrogenation or by chemical oxidation. Catalytic dehydrogenation is especially of advantage with primary alcohols, because it prevents overoxidation to carboxylic acids. Examples are tabulated in equations 223–227 and 265–268.

Dehydrogenation and Oxidation of Primary Alcohols to Aldehydes

Catalytic dehydrogenations of primary alcohols are achieved by passing vapors of the alcohols at 275–350 °C over a catalyst, usually supported on asbestos, silica gel, pumice, etc. Ethyl alcohol is converted into acetaldehyde in 88% yield at 93% conversion by passing it at 275 °C over a mixture of **oxides of copper, cobalt, and chromium** on asbestos [*1135*].

Over copper chromite on Celite (diatomaceous earth) at 300–350 °C, aliphatic alcohols with three to eight carbons are converted into aldehydes in 53–67% yields [*354*]. Catalytic dehydrogenations over **copper, silver, or both** [*7, 345*] are carried out in a current of an insufficient amount of air or oxygen at 300–380 °C and give aldehydes in yields ranging from 70 to 100%. An example of an industrial dehydrogenation is the conversion of methallyl alcohol into methacrolein [*4*] (equation 204).

Vapor-phase dehydrogenation of primary alcohols to aldehydes takes

[4] $CH_2{=}C(CH_3)CH_2OH \xrightarrow{Cu,\ 350\ °C,\ air} CH_2{=}C(CH_3)CHO$ **204**

conversion 71%
yield 95%

place at 250–300 °C over **cupric oxide** in a current of helium. Yields of 90–100% are obtained with saturated and unsaturated alcohols [*349*].

The vapor-phase dehydrogenations just mentioned are applicable only to the preparation of aldehydes that tolerate such high temperatures. A catalytic oxidation of alcohols carried out by passing a current of air or oxygen through solutions of alcohols in solvents such as heptane [*56*] or ethyl acetate [*55*] in the presence of **platinum** [*55, 56*], or, better still, **platinum dioxide** [*56*], or active cobalt oxide [*1136*] is applicable even to alcohols that cannot be vaporized and that contain double bonds (equation 205) [*56*].

[*56*] **205**

$$CH_3CH{=}C(CH_3)CH_2OH \xrightarrow[60\ °C,\ 2\ h]{O_2/PtO_2,\ C_7H_{16}} CH_3CH{=}C(CH_3)CHO$$

77%

Both aliphatic and aromatic alcohols, as well as unsaturated alcohols, are oxidized in the liquid phase with argentic oxide in nitric or acetic acid at temperatures from −10 through 60 °C [*380*].

Ceric ammonium nitrate in water or in 50% acetic acid oxidizes benzylic alcohols at 90 °C in very good yields [*420*]. Only catalytic amounts of the reagent and **sodium bromate** as a reoxidant are needed to convert benzyl alcohol into benzaldehyde in 90% yield on heating in acetonitrile at 80 °C [*421*]. A similar result is obtained on treatment of benzyl alcohol with **lead tetraacetate** in pyridine at room temperature for a few hours (yield 85%) [*442*].

A very simple and gentle oxidation of primary alcohols to aldehydes is their treatment in chloroform or carbon tetrachloride with a solution of *dinitrogen tetroxide,* obtained either commercially or by thermal decomposition of lead nitrate. The reaction is carried out at 0 °C through room temperature and gives high yields (91–98%) of benzaldehydes (equation 206) [*454*].

[*454*] **206**

$$p\text{-}ClC_6H_4CH_2OH \xrightarrow[0\ °C,\ 15\ min,\ RT\ overnight]{CHCl_3,\ N_2O_4} p\text{-}ClC_6H_4CHO$$

98%

The classical oxidants for the conversion of alcohols into aldehydes are compounds of **hexavalent chromium.** The stoichiometry of these oxi-

dations is shown in equation 207, and the mechanism is discussed in the section Oxidation of Secondary Alcohols to Ketones (equations 243–245).

207

$$3\ RCH_2OH + K_2Cr_2O_7 + 4\ H_2SO_4 \longrightarrow 3\ RCHO + Cr_2(SO_4)_3 + K_2SO_4 + 7\ H_2O$$

When **sodium or potassium dichromate** in the presence of dilute sulfuric acid is used, care must be taken to prevent overoxidation of the products to carboxylic acids. Lower boiling aldehydes can be removed by concomitant steam distillation and thus escape from further oxidation. The disadvantage of dichromate oxidations is the need for rather high reaction temperatures, often those of refluxing aqueous solutions [*639, 653*].

"Neutral" sodium dichromate even under these conditions does not cause much overoxidation. Benzyl alcohol is oxidized to benzaldehyde at pH 5.6 at a rate 18 times faster than that of the oxidation of benzaldehyde to benzoic acid [*639*].

A modern version of dichromate oxidation in aqueous media is a "phase-transfer" reaction carried out in a two-phase system. Alkaline dichromate is converted into tetraalkylammonium dichromate, which is soluble in organic solvents such as dichloromethane, chloroform, or benzene ("orange benzene"). The treatment of alcohols with a solution of potassium dichromate in acetic acid in the presence of Adogen 464 (Aldrich's trade name for methyltrialkyl [C_8–C_{10}] ammonium chloride) and benzene gives aldehydes at 55 °C [*651*]. Similar results are obtained with a chloroform solution of tetrabutylammonium chromate at 60 °C [*618*].

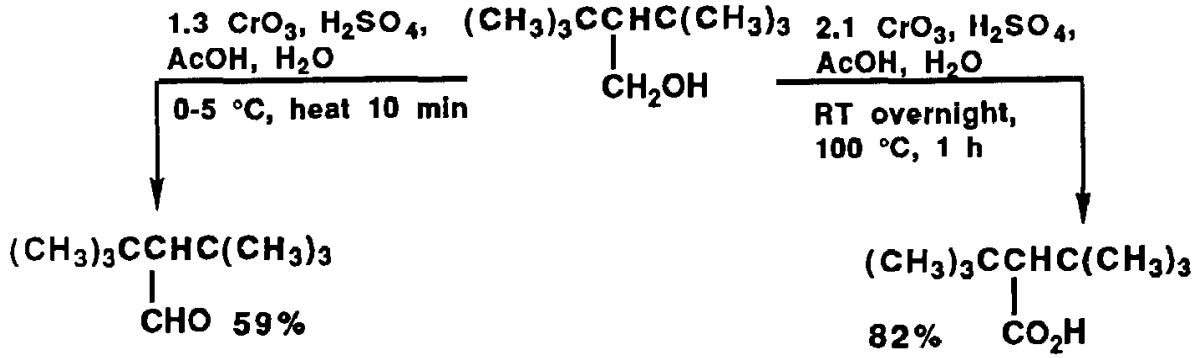
The best modifications of the phase-transfer reaction is oxidation with tetrabutylammonium dichromate prepared in situ from sodium dichromate and tetrabutylammonium bisulfate in 3 M sulfuric acid and methylene chloride. Under such conditions, oxidation takes place at room temperature and is finished within minutes [*630*]. The results of oxidations with **pyridinium dichromate, $(C_5H_5NH)_2Cr_2O_7$,** a stable bright-orange solid, mp 144–146 °C, prepared by precipitating with pyridine from a solution of chromium trioxide in a minimum amount of water, depend on the solvent used in the oxidations. In methylene chloride at 25 °C, decanol gives a 98% yield of decanal, and 2-octynol gives a 70% yield of 2-octynal. In dimethylformamide, the oxidation yields carboxylic acids [*603*]. Similar reagents, 3- and 4-carboxypyridinium dichromate prepared by the treatment of nicotinic and isonicotinic acid, respectively, with chromium trioxide in water, oxidize benzylic alcohols to aldehydes in dichloromethane–pyridine solutions at room temperature in 72–90% yields [*663*].

Oxidations with a complex of pyridine with silver dichromate in benzene do not offer any advantages, and refluxing is necessary [*659*].

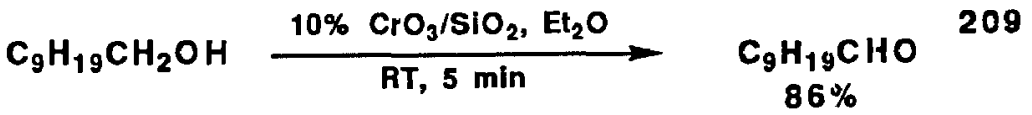
Instead of dichromates, **chromic acid** obtained by dissolving chromium trioxide in water and sulfuric acid and acetic acid is used [*184, 573*].

A solution of chromium trioxide in dilute sulfuric acid used in aqueous acetone is called **Jones reagent** [*572*]. Other solvents of chromium trioxide are ether [*538*] and hexamethylphosphoric triamide (HMPA) [*543*]. Oxidations are also carried out with *chromium trioxide adsorbed on Celite (diatomaceous earth)* [*538*], *silica gel* [*537*], *or an ion exchanger* such as Amberlyst A26 (a macroreticular quaternary ammonium salt anion exchanger) [*571, 617*]. Such oxidations often take place at room temperature and can be used not only for saturated alcohols but also for unsaturated and aromatic alcohols (equations 208 and 209).

[*184*] 208



[*537*] 209

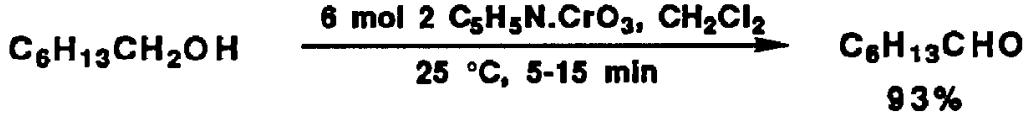


Collins reagent, a complex of **chromium trioxide with two molecules of pyridine,** is prepared by adding, in small portions, chromium trioxide to pyridine. The mixture is stirred and cooled in an ice bath. Reverse addition may cause ignition [*599*]. The reagent may also be prepared by adding chromium trioxide to a solution of pyridine in methylene chloride [*596*] or by adding pyridine to a suspension in petroleum ether of chromium trioxide adsorbed on silica gel [*597*]. The best solvent for oxidations with Collins reagent is dichloromethane, in which the solubility of the reagent is 12.5 g/100 mL [*595*]. The pyridine–chromium trioxide complex is very hygroscopic and is readily converted into insoluble dipyridinium dichromate, $(C_5H_5NH)_2Cr_2O_7$.

Collins reagent is not acidic and, consequently, is very suitable for oxidations of acid-sensitive substrates, especially because most of the oxidations are carried out at room temperature [*595, 596*]. The disadvantages are that up to a 1:6 ratio of the substrate to the reagent is sometimes to be used to obtain best yields [*594, 595, 596, 600*] and that saturated aliphatic alcohols often give low yields [*599*] (equation 210).

A similar complex obtained by adding one equivalent of *3,5-dimethylpyrazole* to a suspension of *chromium trioxide* in dichloromethane

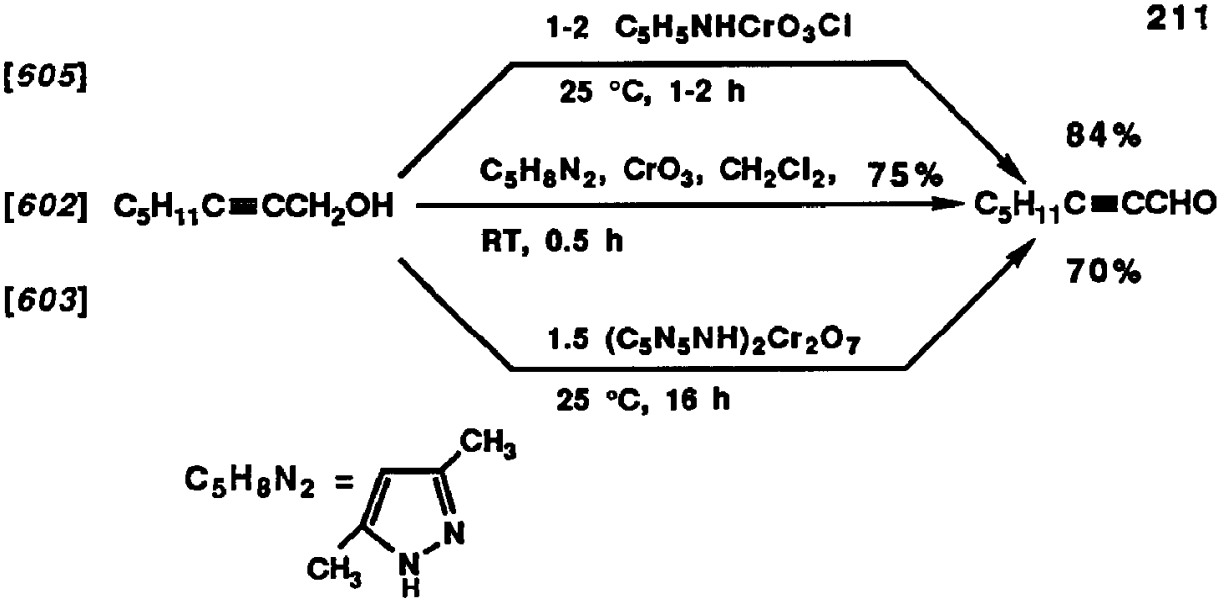
[595] 210



gives very high yields of allylic and benzylic aldehydes at room temperature after 30 min (the ratio of substrate to oxidant is 1:2.5) [*602*].

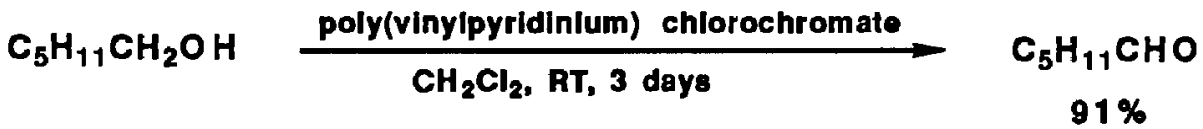
Another pyridine–chromium trioxide complex, **pyridinium chlorochromate, $C_5H_5NHCrO_3Cl$ (PCC),** is prepared by adding pyridine to a solution of chromium trioxide in 6 M hydrochloric acid [*605*]. This complex is superior to Collins reagent in that much a smaller excess is needed, with the ratio of the substrate to the oxidant being 1:1.5–2 (equation 211).

211



Because the reagent is slightly acidic, it cannot be used to oxidize acid-sensitive compounds [*605*]. For easier isolation of the products, the complex may be formed *in the presence of alumina.* After the reagent is stirred with the alcohol at room temperature for 2 h, the aldehyde is isolated by filtration and evaporation of the filtrate [*604*]. Another solid-support oxidant of pyridinium chlorochromate is prepared by treatment of cross-linked *poly(vinylpyridine) with chromium trioxide and hydrochloric acid* (equation 212) [*612*].

[612] 212



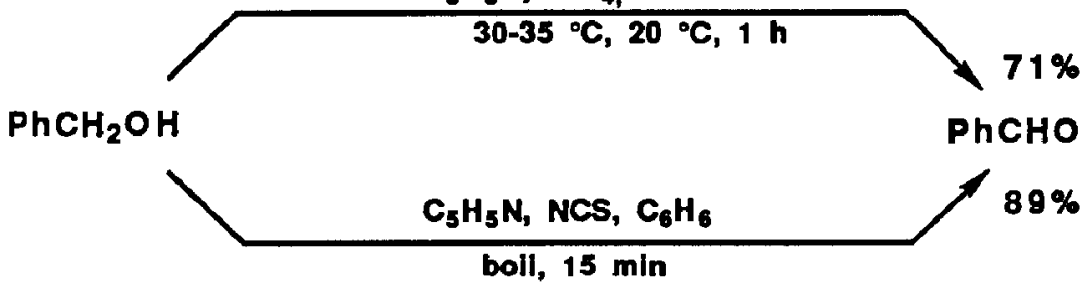
Instead of pyridine, 4-dimethylaminopyridine can be converted into a chlorochromate, and the complex can be used to oxidize benzylic alcohols to aldehydes [*530*]. Also, tetrabutylammonium chlorochromate gives good yields of unsaturated and aromatic aldehydes from the respective alcohols [*619*].

Other oxidants of hexavalent chromium are **chromyl chloride** and **di-*tert*-butyl chromate.** Chromyl chloride adsorbed on alumina–silica gel from its solution in dichloromethane oxidizes aliphatic and aromatic alcohols at room temperature within hours in 77–100% yields [*675*]. Di-*tert*-butyl chromate, prepared in situ from chromyl chloride in *tert*-butyl alcohol at −70 °C, gives comparable results under similar conditions [*674*]. Di-*tert*-butyl chromate, prepared from chromium trioxide and *tert*-butyl alcohol, oxidizes primary aliphatic and aromatic alcohols to the corresponding aldehydes even at low temperatures (1–2 °C) [*677, 678*].

Benzylic alcohols are successfully transformed into aldehydes by potassium hypochlorite containing 24 or 35% of available chlorine. In aqueous methanolic solution, a spontaneous exothermic reaction takes place and is finished at 36–40 °C overnight to yield 77% of benzaldehyde from benzyl alcohol [*702*].

Both tert-*butyl hypochlorite* and N-*chlorosuccinimide* dehydrogenate primary benzylic alcohols to the aldehydes (equation 213), whereas primary aliphatic alcohols are converted into esters of the corresponding acids [*709*]. Butyl alcohol dissolved in carbon tetrachloride and treated with *tert*-butyl hypochlorite in the presence of pyridine at 40–45 °C gives, after 2 h, a 66% yield of butyl butyrate [*709*].

[*709*] 213



A useful addition to the roster of oxidants converting primary alcohols into aldehydes is **manganese dioxide,** which can be prepared by several methods [*805, 806, 807, 808, 809, 810*]. It is used as a suspension in petroleum ether [*805, 808*], ether [*806, 808, 811*], hexane [*806, 811*], benzene [*808, 813*], chloroform [*808, 811, 813*], and carbon tetrachloride [*808, 813*]. The oxidations are carried out at room temperature and are especially suitable for allylic and benzylic alcohols, which are oxidized more readily than the saturated alcohols [*808, 810*]. Yields vary widely depending on the substrate, on the ratio of the substrate to oxidant (which in turn depends on the particle size of the oxide [*810*]), on the solvent, and on the reaction time [*808, 811*] (equation 214).

Manganates and permanganates are rarely used to convert alcohols into aldehydes because permanganate oxidizes aldehydes to acids. However, when adsorbed on molecular sieves, potassium permanganate in benzene at 70 °C oxidizes benzyl alcohol and cinnamyl alcohol to the aldehydes in 80 and 94% yields, respectively. Saturated aliphatic alcohols give very

[811]

$$C_6H_5CH_2OH \xrightarrow{MnO_2,\ RT} C_6H_5CHO \qquad 214$$

Reaction time (h)	Yield (%) Hexane	Chloroform	Ether
1	61	61	70
24	78	89	78

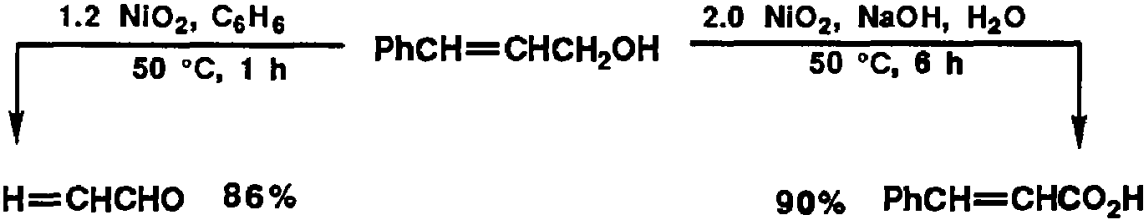
low yields of aldehydes [*863*]. Benzyl alcohol [*833*] and other aromatic alcohols [*832*] are also oxidized to aldehydes by barium manganate.

The rarely used potassium ferrate transforms benzylic and allylic alcohols to aldehydes at room temperature in good to high yields. Saturated alcohols give unsatisfactory results [*917, 918*].

The oxidation of benzyl alcohol and cinnamyl alcohol with high-valency nickel oxide results in the formation of aldehydes or acids depending on the reaction conditions [*929, 932*].

Nickel peroxide, obtained by oxidation of nickel sulfate hydrate with an alkaline 6% solution of sodium hypochlorite, oxidizes alcohols either to aldehydes, when benzene is used as a solvent, or to acids, when the reaction is done in aqueous alkaline solution (equation 215) [*932*]. Allenic alcohols are converted into the aldehydes in ether at 20 °C in good yields [*1137*].

[932] 215



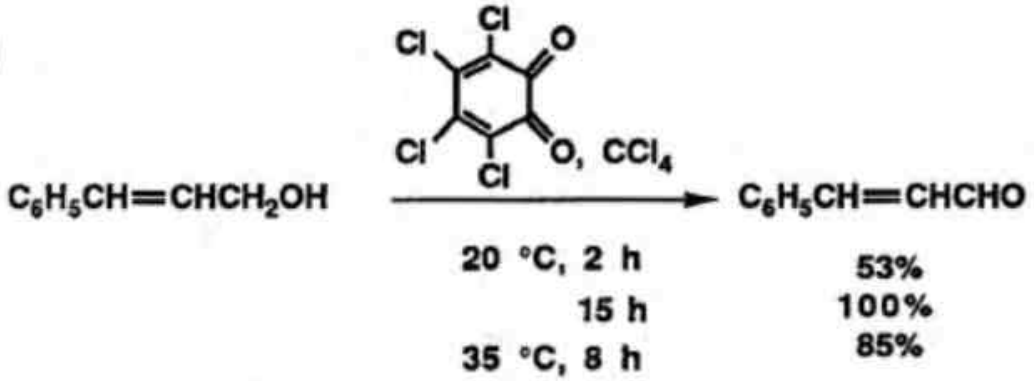
The oxidation of alcohols with ruthenium tetroxide prepared by oxidation of ruthenium trichloride hydrate with sodium bromate takes place at room temperature. However, aldehydes may undergo further oxidation to carboxylic acids [*940*].

Very selective oxidizing agents suitable for the conversion of primary alcohols into aldehydes are high-potential quinones such as **tetrachloro-*o*-benzoquinone, tetrachloro-*p*-benzoquinone**, and **2,3-dichloro-5,6-dicyano-*p*-benzoquinone** [*973*]. Such dehydrogenations are carried out in chloroform, carbon tetrachloride, or ethanol, usually under very mild conditions at room temperature or in refluxing ether, and give fair to good yields (equation 216) [*973*].

Dehydrogenations of saturated alcohols, as well as benzylic alcohols, to aldehydes are carried out by refluxing with a benzene solution of diethyl azodicarboxylate, but the yields are only fair [*977*].

Dimethyl sulfide and **chlorine** or ***N*-chlorosuccinimide (NCS)** oxidize primary alcohols to aldehydes in high yields under very mild conditions.

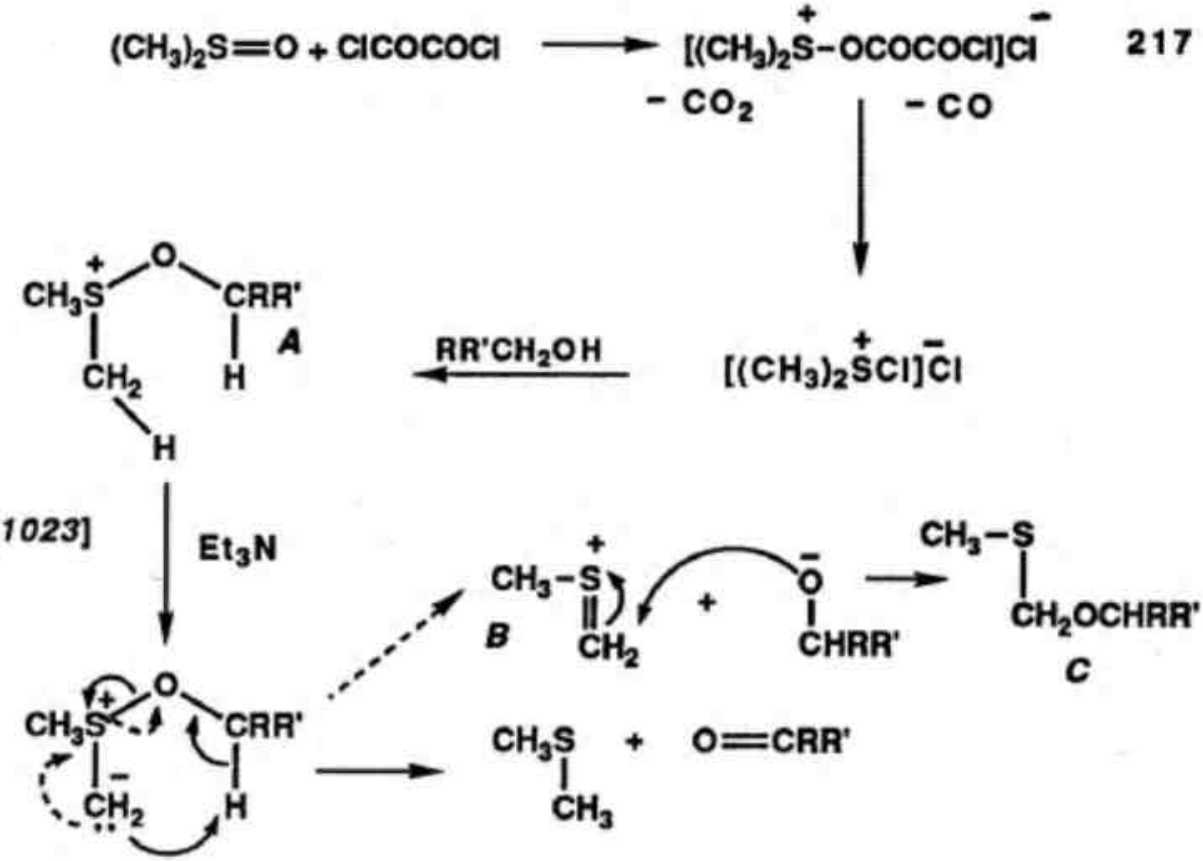
[973]



216

1-Octanol is converted into octanal in 96% yield on treatment with dimethyl sulfide and *N*-chlorosuccinimide in toluene at –25 °C [*1138*].

A similar oxidation by **dimethyl sulfoxide (DMSO)** has attracted much attention because of the gentle conditions under which it takes place and the high yields of the resulting carbonyl compounds, especially those obtained from sterically hindered alcohols. In addition to dimethyl sulfoxide, an "activator" of DMSO is needed for the formation of a complex with the alcohol, and a base is required for the abstraction of a proton from the complex to initiate its collapse to the aldehyde (or ketone). The course of the reactions is summarized in equation 217.



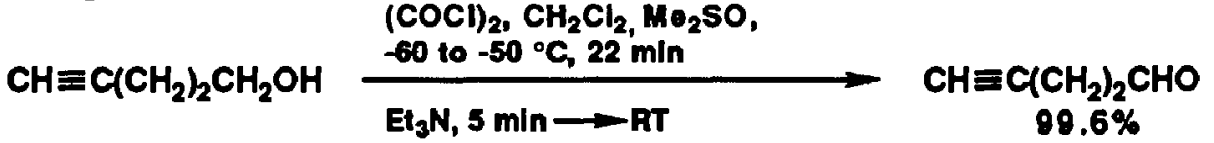
217

The roles of the various reagents are as follows [*1023*]: The activator converts dimethyl sulfoxide into a reactive sulfonium intermediate, which reacts with the alcohol and forms a complex ***A***. A base, usually triethylamine, abstracts a proton from one of the methyl groups linked to sulfur. An intramolecular shift of electrons causes the disintegration of the com-

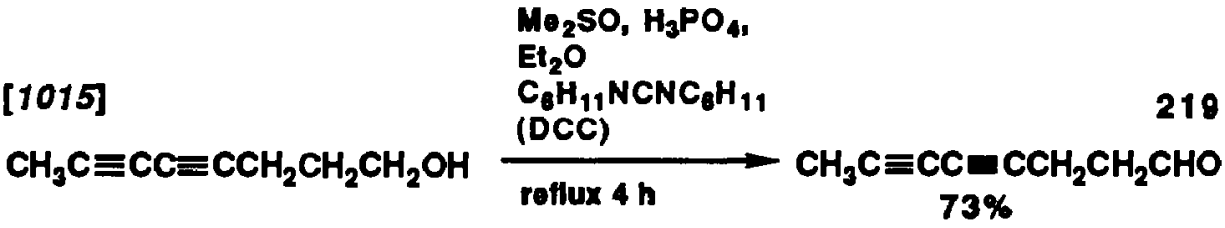
plex ***A*** into dimethyl sulfide and the carbonyl compound. A side reaction results from a competitive shift of electrons along the dotted arrows to form a sulfur ylide ***B***, which recombines with the alkoxide thus generated to form a methylthiomethyl alkyl ether ***C***. The side reaction forming an ether takes place at somewhat higher temperatures (above –60 °C) and is favored by some DMSO activators such as dicyclohexylcarbodiimide and trifluoroacetic anhydride. Formation of the methylthiomethyl alkyl ethers is suppressed and yields of the carbonyl compounds are increased by using bases bulkier than triethylamine, especially triisopropylamine [*1012, 1023*].

The best activator seems to be oxalyl chloride [*1022, 1023*], but chlorine [*1020*], phosgene [*1023*], thionyl chloride [*1023*], sulfur trioxide–pyridine [*1023*], phosphoric acid [*1016*], dicyclohexylcarbodiimide [*1010, 1015*], pyridinium trifluoroacetate [*1010*], trifluoroacetic anhydride [*1012, 1023, 1139*], and other acyl chlorides and anhydrides give very good yields [*1023*] (equations 218 and 219). The use of more than one equivalent of oxalyl chloride may lead to α-chloroketones [*1024*].

[*1022*] 218



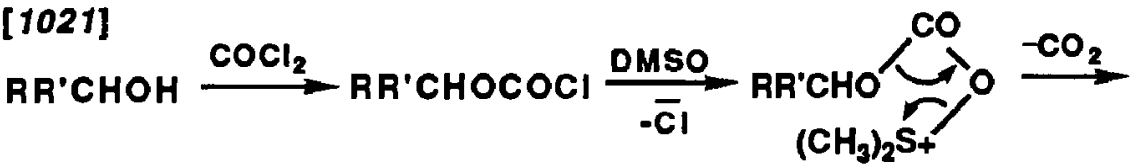
[*1015*] 219

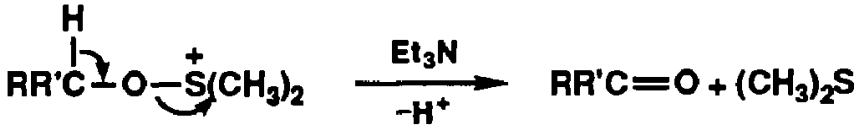


A modification of alcohol oxidation with dimethyl sulfoxide is the reaction of DMSO with alkyl chloroformates, which are formed from alcohols and phosgene (equations 220 and 221) [*1021*].

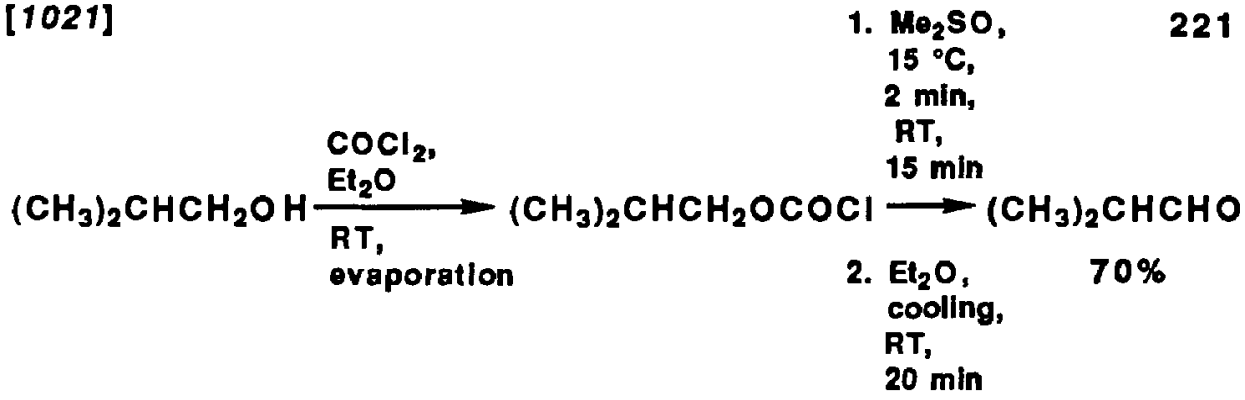
The oxidation of alcohols to aldehydes can also be accomplished by benzeneseleninic anhydride, $(C_6H_5SeO)_2O$, either as such [*525*] or prepared in situ from diphenyldiselenide, $(C_6H_5)_2Se_2$, and *tert*-butyl hydroperoxide [*1140*]. Benzylic alcohols are oxidized more rapidly than allylic

[*1021*] 220



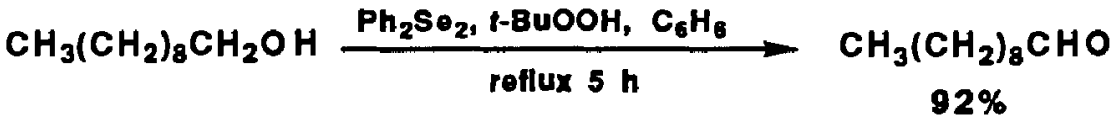


[*1021*] 221



and saturated alcohols [*525*]. The fairly selective reaction usually requires refluxing in benzene [*525, 1140*] (equation 222).

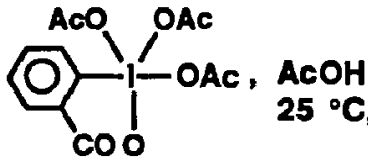
[*1140*] 222



Examples of oxidizing agents and conditions for the conversion of primary alcohols into aldehydes are displayed in equations 223–227.

EXAMPLES OF OXIDATION OF PRIMARY ALCOHOLS TO ALDEHYDES

223

[*55*]	O_2/Pt, AcOEt, RT, 20 h	21%
[*349*]	CuO, He, 250-300 °C	98%
[*630*]	$Na_2Cr_2O_7$, 3 M H_2SO_4, Bu_4NHSO_4, CH_2Cl_2, RT, 1 min	95%
[*571*]	CrO_3 on Amberlyst A26 in Cl cycle, dried at 50 °C for 5 h, C_6H_6, reflux, 9 h	89%
[*617*]	CrO_3, Bu_4NCl (catalyst) CH_2Cl_2, 90 min	60%
[*596*]	$CrO_3.2C_5H_5N$, CH_2Cl_2; RT, 15 min	90%
[*675*]	CrO_2Cl_2 in CH_2Cl_2 adsorbed at Al_2O_3-SiO_2, RT, 5 h	94%
[*1138*]	NCS.Me_2S, PhMe, -25 °C, 1.5 h; Et_3N, 5 min	96%
[*801*]	 AcOH, CH_2Cl_2, 25 °C, 1 h	93%

224

$CH_2{=}CHCH_2OH \longrightarrow CH_2{=}CHCHO$

[7]	air/Ag, 230-300 °C	70-75%
[380]	AgO, H_3PO_4, 20 °C, 7 min	70%
[442]	$Pb(OAc)_4$, C_5H_5N, RT, h	35%
[808]	MnO_2, petroleum ether, RT, 19 h	99%

225

$(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH_2OH \longrightarrow (CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCHO$

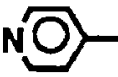
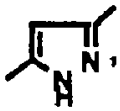
[597]	H_2CrO_4, C_5H_5N, SiO_2, AcOH, CH_2Cl_2, 30-35 °C, 4 h	92%
[599]	$CrO_3.2C_5H_5N$, C_5H_5N, cooling with ice, RT, 15-22 h	63%
[806]	MnO_2, C_6H_{14}, RT, 96 h	61-79%
[530]	Me_2N–  .HCl, CrO_3, CH_2Cl_2, RT, 15 h	88%
[674]	CrO_2Cl_2, C_5H_5N, *t*-BuOH, CH_2Cl_2, -78 to -70 °C, 15 min, RT, 2 h	87%
[572]	CrO_3, Me_2CO, 0 °C, ~20 min	91%
[543]	CrO_3, HMPA, RT, 12 h	85%
[1140]	$(PhSe)_2$, *t*-BuOOH, CCl_4, reflux 1 h	100%

226

$C_6H_5CH_2OH \longrightarrow C_6H_5CHO$

[345]	air/Cu, Ag on pumice, 300 °C	77%
[55]	O_2/Pt, AcOEt, RT, 24 h	72%
[56]	air or O_2, PtO_2, C_7H_{16}, 60 °C, 1 h	78%
[1136]	O_2/Co_2O_3, C_6H_6, 80 °C, 30 min	81%
[380]	AgO, HNO_3, -10 °C, 3 min	71%
[442]	$Pb(OAc)_4$, C_5H_5N, RT, a few hours	85%
[808]	MnO_2, CCl_4, RT, 4.3 h	69%
[349]	CuO, He, 250-300 °C	92%
[420]	$(NH_4)_2Ce(NO_3)_6$, 50% AcOH, 90 °C, 8 h	95%
[599]	$CrO_3.2C_5H_5N$, cooling with ice, RT, 15-22 h	63%

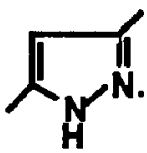
$C_6H_5CH_2OH \longrightarrow C_6H_5CHO$ 226

[597]	H_2CrO_4, C_5H_5N, SiO_2, AcOH, CH_2Cl_2, 30-35 °C, 4 h	82%
[674]	CrO_2Cl_2, C_5H_5N, *t*-BuOH, CH_2Cl_2, -78 to -70 °C, 15 min, RT, 2 h	85%
[678]	CrO_3, *t*-BuOH, cooling with ice, C_6H_6; 1-2 °C, 6 h	90%
[639]	$Na_2Cr_2O_7$, H_2O, 98 °C, 3 h	85%
[630]	$Na_2Cr_2O_7$, Bu_4NHSO_4, 3 M H_2SO_4, CH_2Cl_2, RT, 1 min	100%
[618]	CrO_3, Bu_4NCl, H_2O; CCl_4, 60 °C, 1 h	81%
[572]	CrO_3, Me_2CO, 0 °C, ~20 min	76%
[543]	2 CrO_3, HMPA, RT, 3 h	85%
[538]	1-2 CrO_3, Et_2O, CH_2Cl_2; SiO_2, 35 min	75%
[596]	$CrO_3.2C_5H_5N$, CH_2Cl_2, RT, 15 min	89%
[595]	6 $CrO_3.2C_5H_5N$, CH_2Cl_2, 25 °C, 5-15 min (Collins reagent)	95%
[603]	1.5 $CrO_3.2C_5H_5N$, CH_2Cl_2, 25 °C, 20-24 h	83%
[530]	3 CrO_3, HCl,  , CH_2Cl_2, RT, 3 h	64%
[602]	2.5  , CrO_3, CH_2Cl_2, RT, 45 min	83%
[675]	CrO_2Cl_2, CH_2Cl_2, Al_2O_3-SiO_2, RT, 5 h	94%
[863]	$KMnO_4$, molecular sieves 4Å, C_6H_6, 70 °C, 2 h	80%
[833]	$BaMnO_4$, C_6H_6, reflux 9 min	90%
[895]	bis(2,2'-bipyridyl)$Cu(MnO_4)_2$, CH_2Cl_2, RT, 15 min	95%
[692]	10% NaOCl, Bu_4NHSO_4, H_2O, 24 °C, 75 min	76%
[709]	*t*-BuOCl, C_5H_5N, CCl_4, 30-35 °C, 20 °C, 1 h	71%
[709]	NCS, C_5H_5N, C_6H_6, 100 °C, 15 min	89%
[917]	K_2FeO_4, H_2O, RT, 4 min	80%
[929]	NiO_2, C_6H_6, reflux 1 h	100%
[940]	RuO_4, CCl_4, 10-15°, RT, overnight	90%
[973]	*p*-$C_6Cl_4O_2$, Et_2O, reflux 3 h,	66%
[1138]	NCS.Me_2S, PhMe, -25 °C, 1.5 h; Et_3N, 5 min	90%
[1011]	Me_2SO (DMSO), $(CF_3CO)_2O$, CH_2Cl_2, -50 °C, 40 min; Et_3N, 10 min, RT, 40 min	80%
[1023]	Me_2SO (DMSO), $(COCl)_2$, CH_2Cl_2, -60 °C, 35 min; Et_3N, 5 min	98%
[236]	$(Me_3SiO)_2$/$(Ph_3P)_3RuCl_2$, CH_2Cl_2, 25 °C, 2 h	91%
[1140]	$(PhSe)_2$, *t*-BuOOH, CCl_4, reflux 2 h	100%
[977]	$EtO_2CN{=}NCO_2Et$, C_6H_6, reflux 4 h	61%

$C_6H_5CH_2OH \longrightarrow C_6H_5CHO$ 226

[663]	$(3\text{-}C_5H_4NCO_2H)_2Cr_2O_7$, C_5H_5N, CH_2Cl_2, RT, 25 min	85%
[619]	Bu_4NCrO_3Cl, $CHCl_3$, RT, 18 h	68%
	reflux 4 h	65%
[702]	KOCl, H_2O, MeOH, 46 °C, 36-40 °C overnight	77%

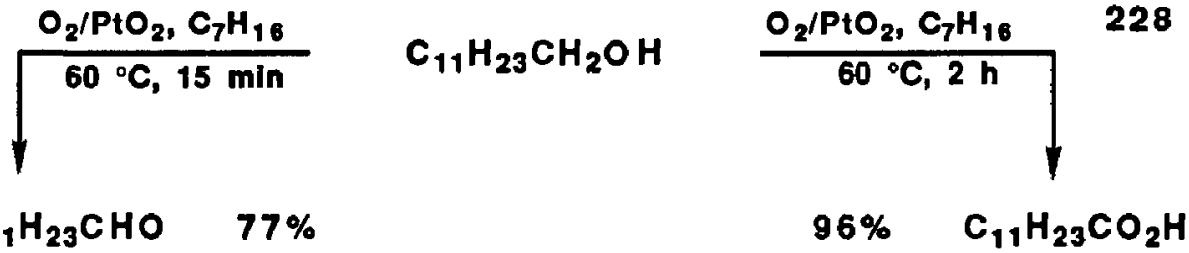
$PhCH{=}CHCH_2OH \longrightarrow PhCH{=}CHCHO$ 227

[7]	air/Ag, 300 °C	60-70%
[1136]	air, Co_2O_3, C_6H_6, 80 °C, 0.5 h	94%
[380]	AgO, AcOH, 20 °C ,C 3 h, 40 °C, 100 min	75%
[442]	$Pb(OAc)_4$, C_5H_5N, RT, h	91%
[805]	MnO_2, CCl_4, RT, 30 min	70%
[806]	MnO_2, Et_2O, RT, 188 h	77%
[599]	$CrO_3.2C_5H_5N$, cooling with ice, RT, 15-23 h	81%
[597]	H_2CrO_4, C_5H_5N, SiO_2, AcOH, CH_2Cl_2, 30-35 °C, 4 h	87%
[674]	CrO_2Cl_2, C_5H_5N, *t*-BuOH, CH_2Cl_2, -78 to -70 °C, 15 min, RT, 2 h	78%
[572]	CrO_3, Me_2CO, 0 °C, ~20 min	84%
[543]	CrO_3, HMPA, RT, 1 h	92%
[596]	$CrO_3.2C_5H_5N$, CH_2Cl_2; RT, 15 min	96%
[863]	$KMnO_4$, molecular sieves 4 A, C_6H_6, 70 °C, 2 h	94%
[833]	$BaMnO_4$, C_6H_6, reflux 45 min	100%
[895]	bis(2,2'-bipyridyl)Cu$(MnO_4)_2$, CH_2Cl_2, RT, 1 h	95%
[618]	2 Bu_4NHCrO_4, $CHCl_3$, 60 °C	91%
[604]	2 $CrO_3.HCl.C_5H_5N$, Al_2O_3, C_6H_{14}, RT, 2 h	84%
[917]	K_2FeO_4, H_2O, RT, 7 min	75%
[918]	K_2FeO_4, 10% KOH, *t*-BuOH, RT, 1 h	96%
[973]	*o*-$C_6Cl_4O_2$, CCl_4, RT, 15 h	99%
[1011]	Me_2SO (DMSO), $(CF_3CO)_2O$, CH_2Cl_2, -50 °C, 40 min; Et_3N, 10 min, RT, 40 min	81%
[1023]	Me_2SO (DMSO), $(COCl)_2$, CH_2Cl_2, -60 °C, 35 min; Et_3N, 5 min	97%
[1140]	$(PhSe)_2$, *t*-BuOOH, CCl_4, reflux 1 h	87%
[639]	$Na_2Cr_2O_7$, H_2O, 98 °C, 3 h	91%
[602]	 $N.CrO_3$, CH_2Cl_2, RT, 45 min	90%
[663]	$(3\text{-}C_5H_4NCO_2H)_2Cr_2O_7$, C_5H_5N, CH_2Cl_2, RT, 30 min	80%
[619]	Bu_4NCrO_3Cl, $CHCl_3$, RT, 52 h	84%
	reflux 3 h	82%
[932]	1.2 NiO_2, C_6H_6, 50 °C, 1 h	86%

Oxidation of Primary Alcohols to Carboxylic Acids

The conversion of primary alcohols into carboxylic acids is not a difficult task. Often, the same oxidant that has been used to oxidize alcohols to aldehydes is applicable to the oxidation to acids when used in appropriate amounts, in different solvents, at higher temperatures, or at longer reaction times. An example is the oxidation of primary alcohols with **air or oxygen** with platinum-on-charcoal or, better still, platinum dioxide as catalyst (equation 228) [*56*].

[*56*]



228

Electrolytic oxidation with nickel anodes and stainless steel cathodes and sodium hydroxide or potassium hydroxide as the electrolyte converts saturated, unsaturated, acetylenic, and aromatic alcohols into acids at 25–75 °C in yields ranging from 51 to 92% (equation 229) [*116*].

[*116*]

229

Potassium hydroxide can act as an oxidant at higher temperatures. Heating heptadecyl alcohol with 3 times its weight of powdered potassium hydroxide for 15 min at 240–250 °C results in a 76% yield of heptadecanoic acid [*484*]. Under much milder conditions, benzyl alcohol is converted into benzoic acid in a 75% yield on heating for 10–60 min at 25–80 °C with an excess of powdered potassium hydroxide in aqueous *tert*-butyl alcohol and carbon tetrachloride [*954*].

Vanillyl alcohol yields 93% of vanillic acid on heating with aqueous sodium hydroxide and silver oxide for a few minutes at 75 °C. The oxidation most probably involves a Cannizzaro-type reaction [*366*].

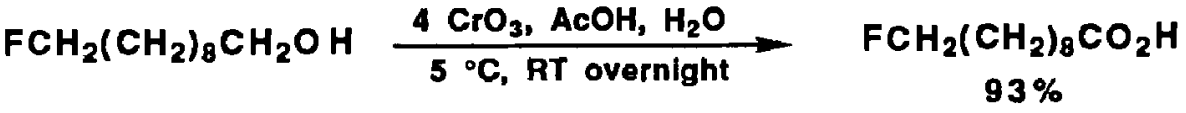
The oxidation of primary alcohols to acids has been accomplished with **nitric acid.** Concentrated nitric acid (*d* 1.42) at 25–30 °C oxidizes 3-chloropropanol to 3-chloropropanoic acid in 78–79% yield after several hours [*469*] and converts 6-bromohexanol into 6-bromohexanoic acid in 91% yield after heating for 45 min at 100 °C [*465*].

Oxidations with dilute nitric acid (*d* 1.15) are commonly used to transform sugars into dicarboxylic (glycaric) acids. Evaporation of a solution of

100 g of lactose in 1200 mL of dilute nitric acid (*d* 1.15) on a steam bath to a volume of 200 mL gives 40 g (64%) of mucic (galactaric) acid [*467*].

Chromic acid dissolved in water and sulfuric acid, acetic acid, or both can be used to oxidize primary alcohols to carboxylic acids, provided that enough oxidant and more energetic conditions than those for oxidation to aldehydes are applied [*184, 574*] (equations 208 and 230).

[*574*] **230**

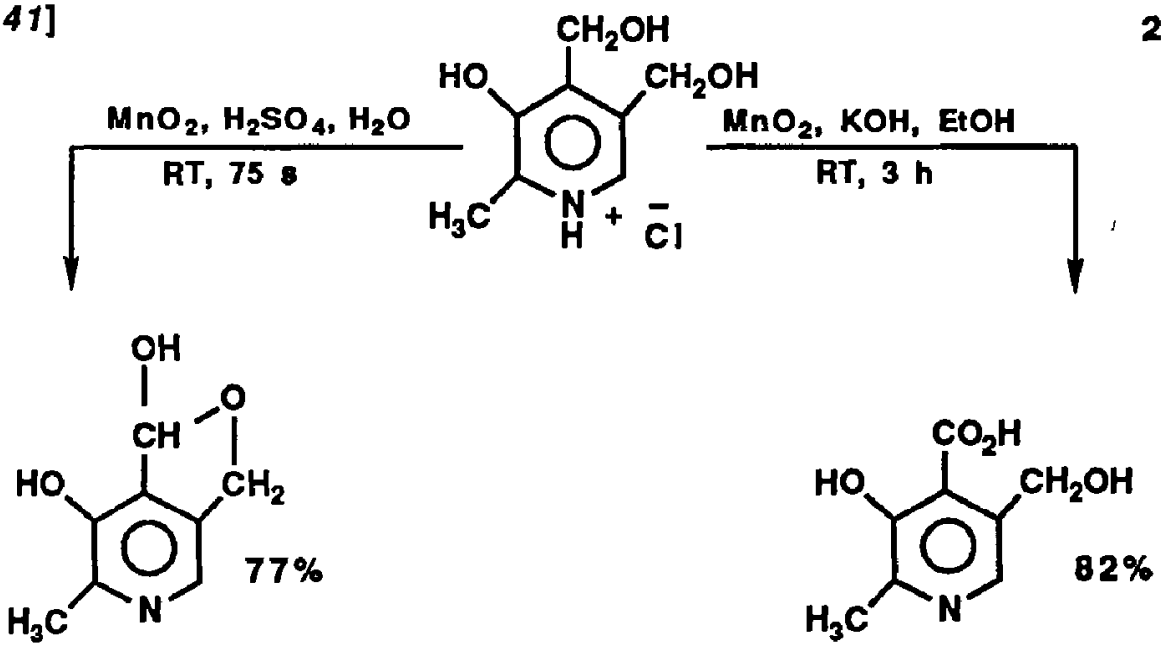


Not very many other chromium compounds are suitable for the preparation of carboxylic acids from alcohols. One such compound is zinc dichromate, which oxidizes benzyl alcohol to benzoic acid in 90% yield in dichloromethane solution at room temperature [*660*].

Pyridinium dichromate in dichloromethane solution converts primary alcohols into aldehydes. In dimethylformamide at 25 °C, carboxylic acids are formed. Cyclohexylmethanol thus gives cyclohexanecarboxylic acid in 84% yield [*603*]. Oxidations of aliphatic alcohols with tert-*butyl chromate* yield mixtures of acids with aldehydes and esters [*677*].

Manganese dioxide, an oxidant of primary alcohols to aldehydes, can also yield acids under proper conditions (equation 231) [*1141*].

[*1141*] **231**



Oxidations with **permanganates** are suitable for the preparation of carboxylic acids from saturated and benzylic alcohols. Unsaturated alcohols may suffer cleavage of double bonds. Conventional oxidations are carried out in aqueous media, usually in the presence of alkali hydroxides. Thus

2-benzoylaminobutanol is converted into α-benzoylaminobutyric acid in 67–72% yield by stirring in aqueous sodium hydroxide and potassium permanganate at autogenous temperature (40 °C) [*884*].

In nonaqueous media, the oxidation of alcohols to acids is accomplished in heterogeneous systems by refluxing primary alcohols with solid **sodium permanganate monohydrate** in hexane (equation 232). The reaction is applicable even to allylic alcohols [*835*].

[*835*]

$$CH_3(CH_2)_6CH_2OH \xrightarrow[69\ ^\circ C,\ 5\ h]{NaMnO_4.H_2O,\ C_6H_{14}} CH_3(CH_2)_6CO_2H \quad 67\% \qquad 232$$

Similar results are obtained when saturated and benzylic alcohols are stirred at room temperature or refluxed in dichloromethane with cupric permanganate octahydrate, $Cu(MnO_4)_2 \cdot 8H_2O$. The octahydrate reacts faster than the anhydrous salt. Decanol and benzyl alcohol give 91 and 84% yields of decanoic acid and benzoic acid, respectively, at room temperature after 24 h [*894*].

Homogeneous oxidations are accomplished with *tetrabutylammonium permanganate* prepared by treating an aqueous solution of potassium permanganate with tetrabutylammonium bromide and isolating the crystalline precipitate [*845, 899*]. Tetrabutylammonium permanganate is soluble in dichloromethane, chloroform, acetone, and pyridine and sparingly soluble in benzene ("purple benzene").

Other quaternary ammonium salts can be used to dissolve the permanganate [*845*]. The reaction can also be carried out in a two-phase system by preparing the quaternary ammonium permanganate in situ while using only a catalytic amount of the quaternary salt (equation 233) [*845*].

[*845*]

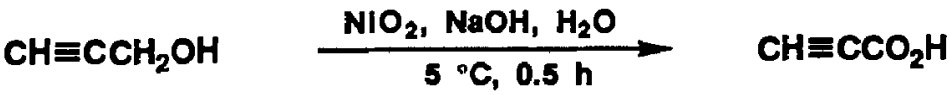
$$CH_3(CH_2)_6CH_2OH \xrightarrow[Bu_4NBr\ (catalyst),\ RT,\ 3\ h]{KMnO_4,\ H_2O,\ C_6H_6} CH_3(CH_2)_6CO_2H \quad 47\% \qquad 233$$

Another method of solubilizing potassium permanganate in organic solvents is the addition of catalytic amounts of crown ethers, for example, dicyclohexano-18-crown-6 ether, to a mixture of potassium permanganate and benzene rolled in a ball mill for 2 h. Heptanol affords a 70% yield of heptanoic acid, and benzyl alcohol gives a 100% yield of benzoic acid [*841*]. The ball-milling step and the rather high price of the crown ether make this method less attractive than the catalytic tetrabutylammonium permanganate process [*845*].

Nickel peroxide, prepared by adding an alkaline solution of 6% sodium hypochlorite to a solution of nickel sulfate hydrate at 20 °C, is used to oxidize alcohols to carbonyl compounds or carboxylic acids. The oxidation

to carbonyl compounds is carried out in benzene solutions, and the oxidation to carboxylic acids takes place in aqueous sodium hydroxide. Fair to high yields of saturated and unsaturated acids, as well as aromatic acids, are obtained at 5–50 °C (equations 215 and 234) [*932*].

[*932*]



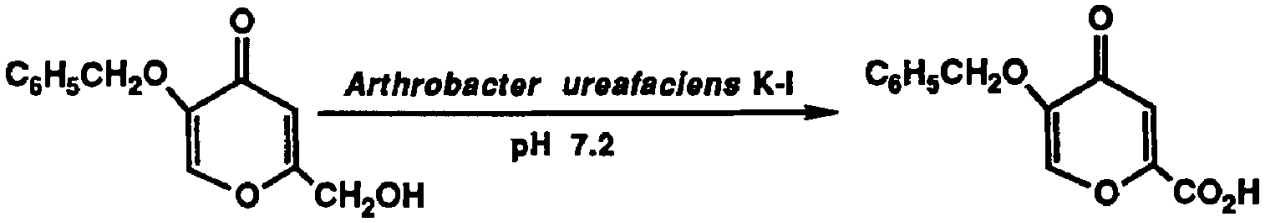
234

Sodium ruthenate [*937*] and *potassium ruthenate* [*196*] oxidize allylic and benzylic alcohols to carboxylic acids at room temperature. Cinnamyl alcohol is transformed into cinnamic acid with sodium ruthenate in 1 M sodium hydroxide at 10 °C after 1 h in 70% yield [*937*]. In oxidations with potassium ruthenate, only catalytic amounts can be used in the presence of a persulfate, which reoxidizes the reduced ruthenium salt [*196*].

An example of ***biooxidation*** is the conversion of the benzyl ether of kojic acid into the benzyl ether of comenic acid by *Arthrobacter ureafaciens* in a phosphate buffer at pH 7.2 in up to 97% yield (equation 235) [*1044*].

[*1044*]

235

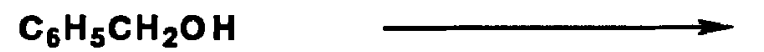


72-97%

Reaction conditions for the transformation of primary alcohols into carboxylic acids are exemplified by the conversion of benzyl alcohol into benzoic acid (equation 236).

236

OXIDATIONS OF PRIMARY ALCOHOLS TO CARBOXYLIC ACIDS



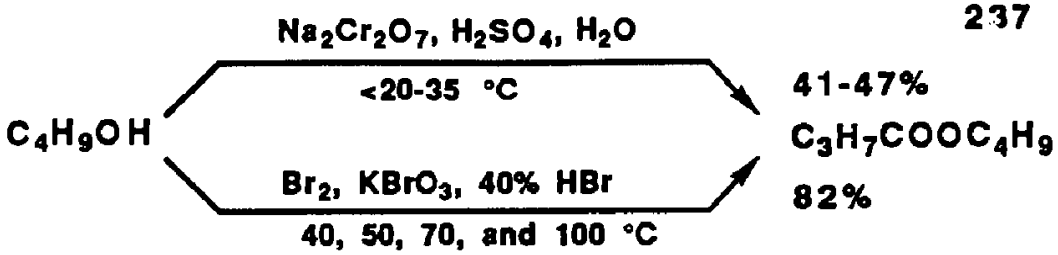
[*56*]	O_2/Pt(C), H_2O, reflux 10 h	97%
[*116*]	Ni anode, 1 M NaOH, 25 °C, 1.5 h	86%
[*954*]	KOH, H_2O, *t*-BuOH, CCl_4, 25-80 °C, 10-60 min	75%
[*660*]	$ZnCr_2O_7.3H_2O$, CH_2Cl_2, RT, 6 h	90%
[*835*]	$NaMnO_4.H_2O$, hexane, 69 °C, 6 h	81%
[*894*]	$Cu(MnO_4)_2.8H_2O$, CH_2Cl_2, RT, 24 h	84%
[*899*]	Bu_4NMnO_4, C_5H_5N, RT	98%
[*845*]	$KMnO_4$, H_2O, C_6H_6; Bu_4NBr (catalyst), RT, 3 h	92%
[*841*]	$KMnO_4$, dicyclohexano-18-crown-6 ether, RT, 2 h	100%
[*932*]	1.5 NiO_2, C_6H_6, 30 °C, 3 h	97%
[*937*]	Na_2RuO_4, NaOH, H_2O, 25 °C, 1 h	97%
[*196*]	K_2RuO_4, $K_2S_2O_8$, RT, 1.5 h	98%

Oxidation of Primary Alcohols to Esters

In acidic oxidations of primary alcohols, esterification of the alcohol by the acid produced by its oxidation sometimes takes place. Thus the oxidation of ethanol with potassium peroxymonosulfate (**Oxone**) in the presence of concentrated sulfuric acid at 70 °C gives a quantitative yield of ethyl acetate [*205*].

Butyl alcohol treated with **sodium dichromate and sulfuric acid** at 20–35 °C furnishes a 41–47% yield of butyl butyrate [*640*]. Butyl butyrate is also obtained in 82% yield by oxidation of butanol by bromine and potassium bromate in 40% hydrobromic acid [*742*] (equation 237).

[*640*] 237

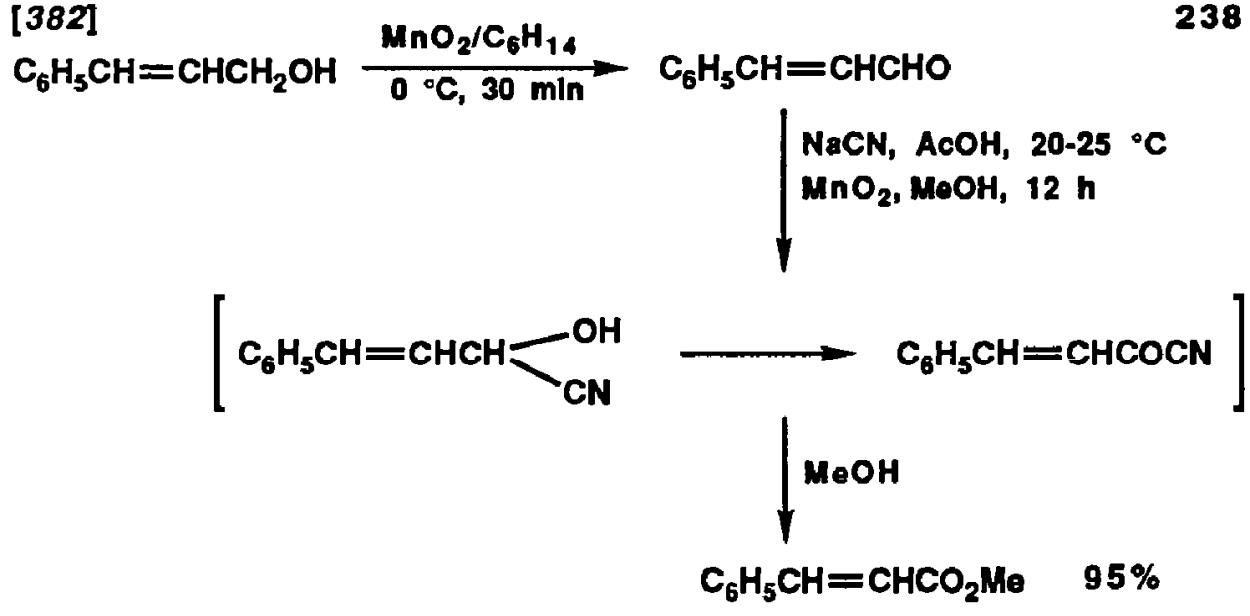


The oxidation of aliphatic alcohols in benzene or petroleum ether with *tert*-butyl chromate at 1–2 °C for 6 h leads to mixtures of aldehydes, acids, and their esters. Butanol gives 30% of butanal, 27% of butyric acid, and 36% of butyl butyrate [*677*]. Also, electrolysis of aliphatic alcohols on platinum or carbon electrodes in aqueous potassium iodide at room temperature results in 80–83% yields of the corresponding esters [*121*].

Ester formation is especially easy in oxidations of diols (with at least one primary hydroxyl group) that can cyclize to five- or six-membered lactones after partial oxidation [*355, 1035*] (*see* equations 292–295).

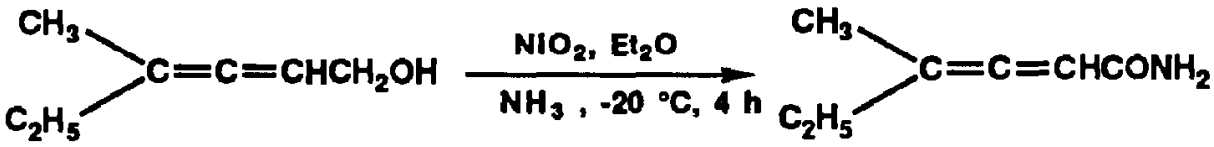
A different type of ester formation takes place when α,β-unsaturated alcohols are oxidized with **manganese dioxide** and subsequently treated with sodium cyanide, acetic acid, manganese dioxide, and methanol. The final result is shown by the sequence of reactions in equation 238 [*382*].

[*382*] 238



In the presence of ammonia, some primary alcohols are oxidized to amides with **nickel peroxide** (equation 239) [*1137*].

[*1137*] **239**



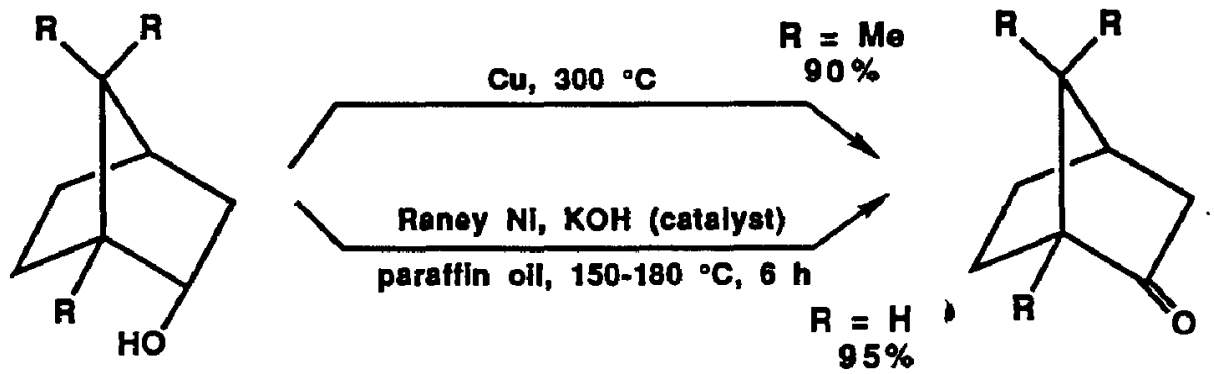
Oxidation of Secondary Alcohols to Ketones

All oxidants used for the oxidation of primary alcohols to aldehydes can be applied to secondary alcohols. Because the products, ketones, are much less sensitive to overoxidation than aldehydes, more intensive reaction conditions, such as an excess of the oxidant, higher temperatures, or longer reaction times, can be used. Examples of oxidations of secondary alcohols to ketones are shown in equations 265–268.

Catalytic dehydrogenation of volatile alcohols is carried out by passing their vapors over **copper** at 300 °C [*344*] or over copper chromite at 275–325 °C for 1.7–4 h, with yields ranging from 20 to 80% [*354*]. Dehydrogenation in the liquid phase is accomplished by refluxing the alcohol with **copper chromite** in xylene for 4 h [*356*] or by heating the alcohol in paraffin oil with **Raney nickel** and a catalytic amount of potassium hydroxide at 150–180 °C for 6 h. Thus *endo*-norborneol is transformed into norcamphor in 95% yield [*928*].

Secondary alcohols are converted into ketones in 70–98% isolated yields when refluxed with Raney nickel in benzene for 1–24 h with azeotropic removal of water [*927*]. The addition of 1-octene as a hydrogen acceptor does not affect the yields. Primary alcohols, under such reaction conditions, usually suffer decarbonylation and yield hydrocarbons with one less carbon [*927*] (equation 240).

[*344*] **240**



[*928*]

A similar dehydrogenation is accomplished in 90–100% yield by passing vapors of the alcohol in a current of air (less than the stoichiometric amount) over a copper or, better still, silver catalyst at 350–400 °C [*7*].

Photooxidation of alcohols to ketones in high yields is performed at room temperature with oxygen in the presence of at least 1 mol of a base (Na, NaH, NaOH, KOH, or *tert*-BuOK) under irradiation with rose bengal as a sensitizer [*45*].

Catalytic oxidation is effected by passing **oxygen** through solutions of alcohols in the presence of metal catalysts.

Alcohols in ethylene carbonate containing sodium acetate and palladium chloride are oxidized by oxygen at room temperature in 62–98% yields [*70*]. Oxygen passed at room temperature under irradiation through a solution of catalytic amounts of chloroplatinic acid and cuprous chloride in alcohols produces ketones in yields of up to 98% [*57*]. Other catalysts used for this purpose are platinum [*55*], platinum-on-charcoal [*56*], and, better still, platinum oxide [*56*]. Such oxidations are carried out usually at room temperature and give fair to high yields.

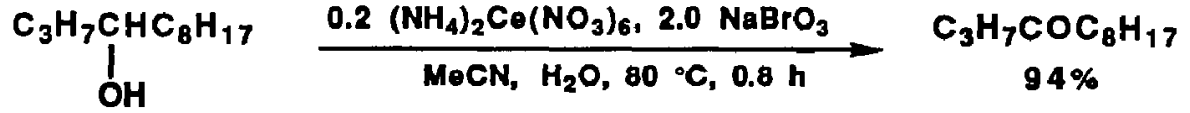
Electrolysis of secondary alcohols in a solution of potassium iodide in aqueous *tert*-butyl alcohol results in 57–98% yields of ketones at room temperature when 4–15 F/mol of electricity in cells with platinum or carbon electrodes is used [*121*].

Relatively rare reactions are chemical oxidations of secondary alcohols to ketones by derivatives of hydrogen peroxide: potassium peroxymonosulfate (Oxone) [*205*] and *m*-chloroperoxybenzoic acid [*276*]. These compounds do not offer any advantages over more-common oxidants.

Oxides of copper and **silver** are used to oxidize secondary alcohols in the vapor phase at 250–300 °C [*349*] or in the liquid phase at room temperature [*380*], respectively. A similar effect is achieved with lead tetraacetate in pyridine at room temperature. Benzhydrol is thus converted into benzophenone in 80% yield [*442*]. The oxidation of codeine with silver carbonate requires 1 h of refluxing in benzene to give a 75% yield of codeinone [*376*].

Ceric ammonium nitrate or **ceric sulfate** is used to oxidize saturated and unsaturated secondary alcohols to ketones. The ceric salts are used only in catalytic amounts with sodium bromate as a reoxidant (equation 241) [*741*].

[*741*] **241**



Dinitrogen tetroxide passed through an ice-cooled chloroform solution of secondary benzylic alcohols produces aromatic ketones in 88–98% yields [*456*].

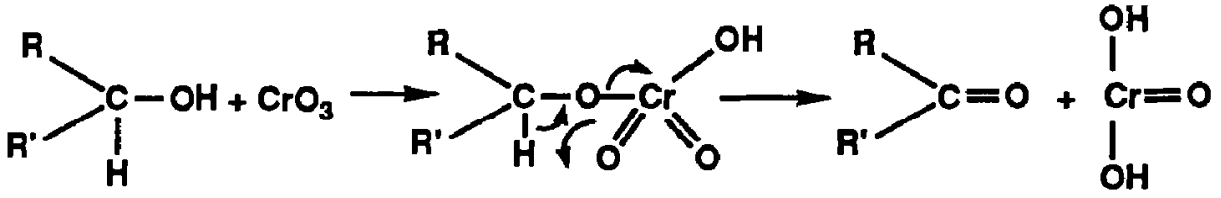
The oxidation of secondary alcohols to ketones by compounds of **hexavalent chromium** is not only the most common but also the best known reaction as far as the mechanism is concerned. The stoichiometry is the same as that of primary alcohols (equation 242).

242

$$3\ RR'CHOH + 2\ CrO_3 + 3\ H_2SO_4 \longrightarrow 3\ RR'CO + Cr_2(SO_4)_3 + 6\ H_2O$$

The initial step in the mechanism is the formation of an ester of the alcohol and chromic acid [*561, 577, 1142*]. The ester decomposes to the carbonyl compound and chromium(IV) acid (equation 243). The tetrava-

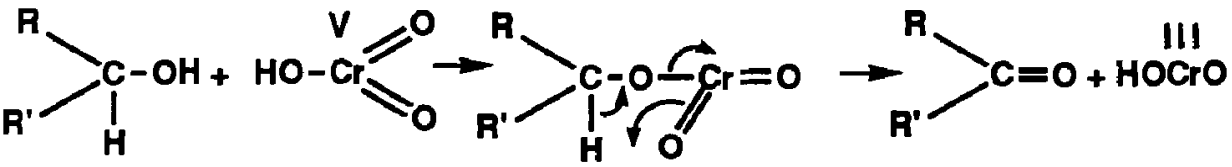
243



lent chromium(IV) acid reacts with chromic oxide to form chromium(V) acid (equation 244), and the chromium(V) acid oxidizes the alcohol via its ester (equation 245).

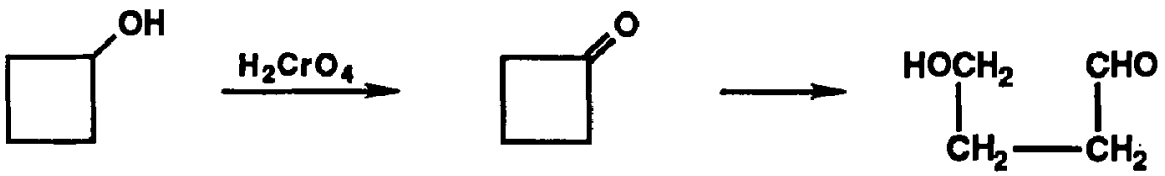
244

245



The presence of three oxidizing species, chromium(VI), chromium(V), and chromium(IV) acids, accounts for differences in the oxidation products of some alcohols. Thus in the reaction of cyclobutanol with chromic acid, not only cyclobutanone but also 4-hydroxybutanal is obtained, evidently by oxidation with chromium(V) or chromium(IV) acid via a free-radical pathway [*577, 621, 654, 655, 1143*] (equation 246).

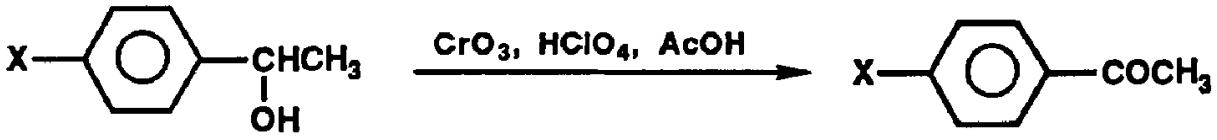
[*577*] 246



Reactions with chromium(IV) involve one-electron transfer via free radicals [*577*].

The rates of oxidation are affected by electronic and steric effects. In oxidations of *p*-substituted 1-phenylethanols, electron-releasing substituents increase the reaction rate, whereas electron-withdrawing substituents decrease the reaction rate (equation 247) [*1144*].

[1144] 247

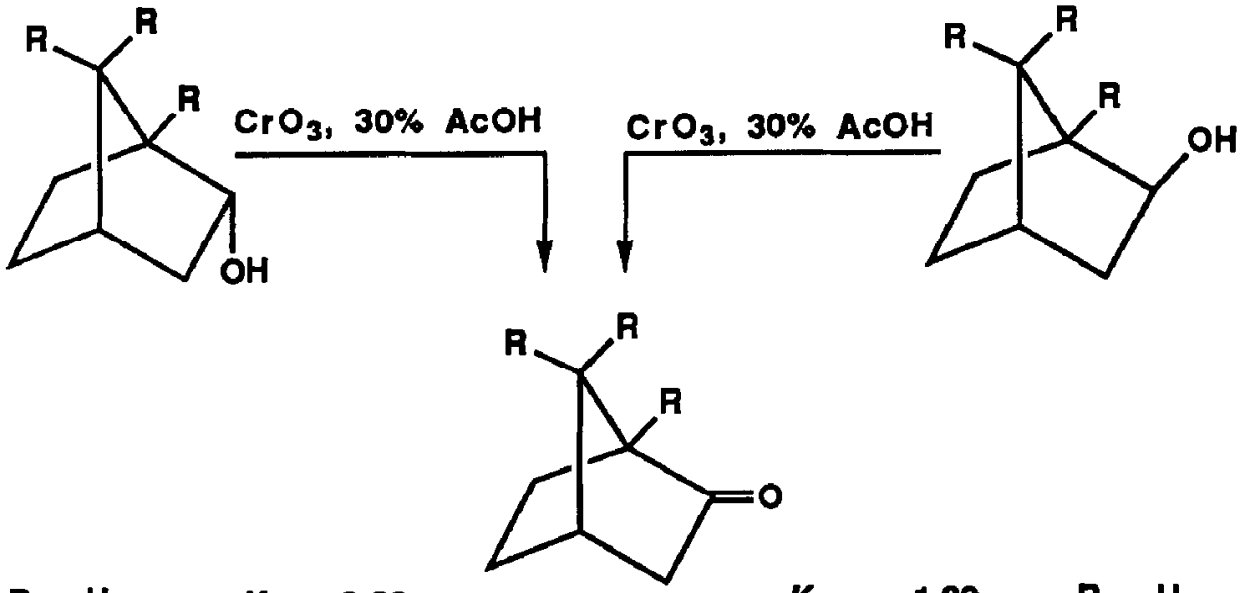


Relative reaction rates

X =	CH_3O	2.7
X =	H	1
X =	NO_2	0.2

Steric effects are evident in the oxidation of sterically hindered alcohols: *exo*-isoborneol is oxidized 2 times faster than *endo*-borneol, and *endo*-norborneol is oxidized 2.5 times faster than *exo*-norborneol (equation 248) [*1145*].

[1145] 248

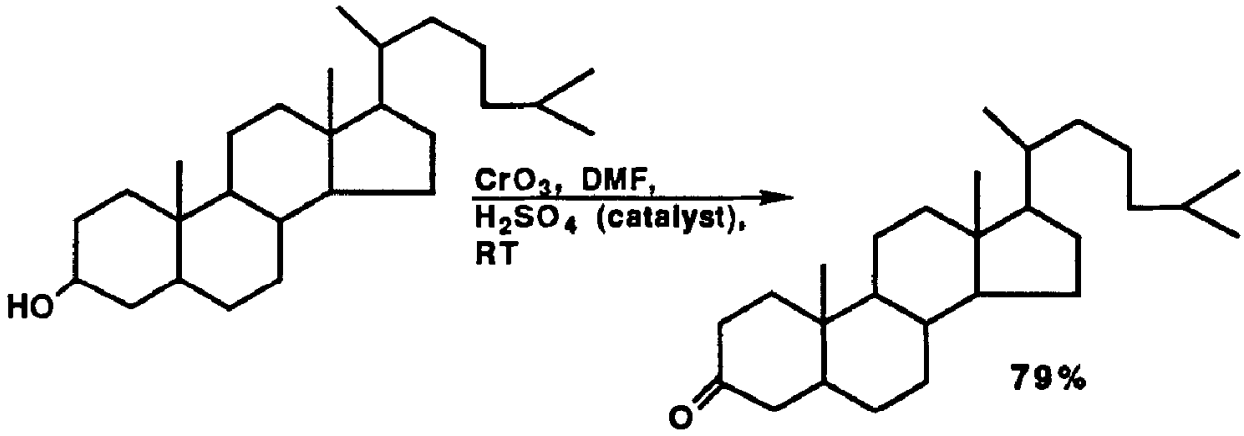


R = H	K_2 = 3.23	K_2 = 1.30	R = H
R = CH_3	K_2 = 8.46	K_2 = 16.6	R = CH_3

Oxidations with **chromium trioxide** (chromic oxide or chromic anhydride) and with **chromic acid** are carried out in different solvents, usually by adding solutions of chromic oxide or chromic acid to the solutions of the alcohols. When chromium trioxide dissolved in 80% acetic acid is added to a stirred solution of *cis*-2-phenylcyclohexanol in acetic acid at 50 °C and the mixture is allowed to stand at room temperature for 1 day, an 80% yield of 2-phenylcyclohexanone is obtained [*576*]. Other solvents used are dimethylformamide [*542*], hexamethylphosphoric triamide (HMPA) [*543*], acetone [*578, 581*], ether [*538*], dichloromethane [*538, 617*], and benzene [*571*] (equation 249).

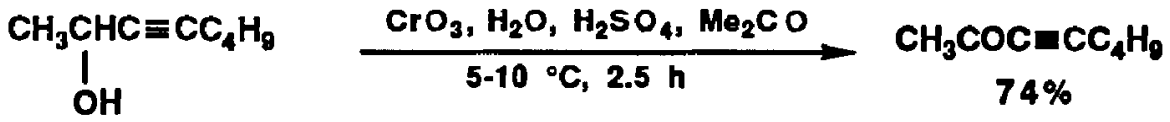
An especially favored oxidizing agent is **Jones reagent,** which is prepared by diluting to 100 mL with water a solution of 26.7 g of chromium

[542] 249



trioxide in 23 mL of sulfuric acid [*579*]. The resulting solution is added to a solution of the alcohol in acetone (equation 250) [*578*].

[578] 250



The addition of chromium trioxide to solutions of alcohols in ether and dichloromethane in the presence of Celite furnishes ketones in 71–93% yields after 35 min at room temperature [*538*]. Oxidation can also be performed by refluxing the alcohols in solvents such as chloroform, ether, hexane, or benzene with chromium trioxide on an anion exchanger, Amberlyst A26 [*571*]. Very good results are obtained when chromium trioxide is converted into **tetrabutylammonium chromate** by addition of catalytic amounts of tetrabutylammonium chloride in dichloromethane [*617*].

Chromic acid is also the reacting compound in oxidations with **sodium dichromate** or **potassium dichromate** in dilute sulfuric acid [*641, 642, 643, 644, 1146*], perchloric acid [*621, 655*], or acetic acid [*627, 628*]. Modifications lie in the use of excess chromic acid [*536*] and of additional solvents such as benzene [*627*], ether [*536, 641*], or dimethyl sulfoxide [*629*] and in the control of the reaction temperature at 50–55 °C [*644*], 30–68 °C [*642*], 25 °C [*536, 641*], or 0 °C [*536*]. Results of some of the different procedures are tabulated in Table II.

Table II. Oxidation of Menthol to Menthone at Various Conditions

Conditions	*Yield (%)*
H_2CrO_4, water, 50–55 °C	90
H_2CrO_4, 90% acetic acid, 25 °C	71
H_2CrO_4, acetone, 5–10 °C	86
H_2CrO_4, water, diethyl ether, 25–30 °C	97
H_2CrO_4 (20% excess), dilute sulfuric acid, 30–68 °C	94

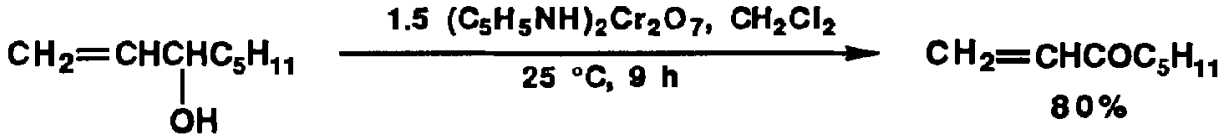
SOURCE: The data were taken from references 641, 642, and 644.

Oxidations with dichromates can be accomplished in nonaqueous media or in a two-phase system by using phase-transfer reagents. The addition of 1-phenylethanol to a slurry of potassium dichromate and Adogen 464 (methyltrialkylammonium chloride) in benzene heated at 55 °C for 15 h results in an 80% yield of acetophenone. However, 2-octanol gives only a 33% yield of the ketone after being heated at 55 °C for 24 h [*651*]. Other solvents suitable for the reaction are dichloromethane, chloroform, and carbon tetrachloride, but not hexane [*651*]. Better results are obtained when the alcohol is shaken for 1 min at room temperature with a mixture of a catalytic amount (10%) of tetrabutylammonium bisulfate and sodium dichromate in dichloromethane and aqueous 3 M sulfuric acid [*630*].

Hexavalent chromium compounds soluble in organic solvents are pyridinium chromate [*597*] and pyridinium dichromate [*603*]. **Pyridinium chromate** is prepared by adding 2 mol of pyridine to 1 mol of chromium trioxide adsorbed on silica gel.

Pyridinium dichromate, prepared from chromium trioxide in a minimum amount of water and pyridine, forms a bright-orange solid and is soluble in water, dimethylformamide, dimethyl sulfoxide, and dimethylacetamide; sparingly soluble in dichloromethane, chloroform, and acetone; and almost insoluble in hexane, toluene, ether, and ethyl acetate. Allylic secondary alcohols are oxidized more rapidly than their saturated analogues. Oxidations are carried out in dichloromethane solutions at 25 °C, and ketones are obtained in high yields (equation 251) [*603*].

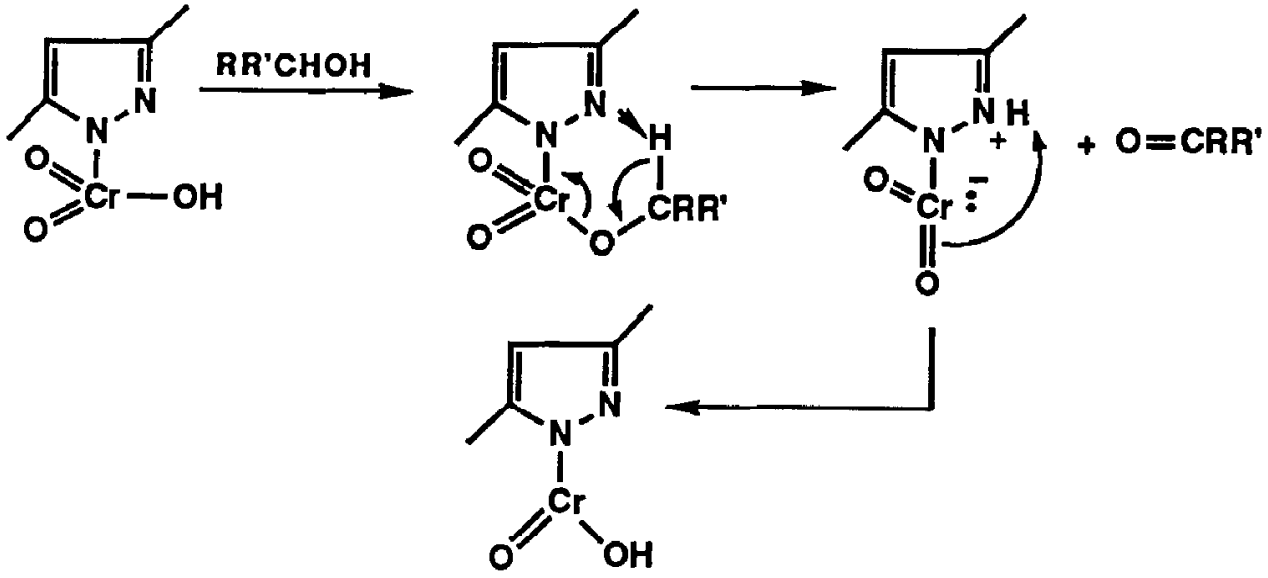
[*603*] **251**



A chromium(VI) oxidant that is applicable to oxidations of acid-sensitive substrates is the **complex of chromium trioxide with two molecules of pyridine (Collins reagent).** As described on pages 22 and 274, its preparation requires the portionwise addition of chromium trioxide to dry pyridine at 15–20 °C (addition of pyridine to chromium oxide could cause ignition) [*592, 595, 599*]. Up to 6 mol of the complex is used to oxidize alcohols in dichloromethane solutions at 25 °C, and the reaction is finished in 5–15 min [*595*]. Alternatively, the oxidation can be carried out in pyridine cooled with an ice bath and is finished at room temperature within 15–22 h [*592, 599*].

Instead of pyridine, **3,5-dimethylpyrazole** may be used for **complexing chromium trioxide.** It forms a 1:1 complex that can be generated in situ in dichloromethane at room temperature. The reaction is finished within 10 min. Addition of the alcohols and stirring of the mixture for 30 min at room temperature result in 78–100% yields of ketones (equation 252) [*602*].

[602] 252



The addition of pyridine to chromium trioxide in 6 M hydrochloric acid produces **pyridinium chlorochromate, $C_5H_5NHCrO_3Cl$ (PCC),** a yellow-orange solid stable in air. If used in a 1:1.5 ratio, it oxidizes secondary alcohols to ketones in solutions in dichloromethane at room temperature within 1–2 h in high yields [*605*].

The reagent can be also ***adsorbed on silica gel*** [*604*] or formed with ***cross-linked poly(vinylpyridine)*** resin [*612*]. The yields of carbonyl compounds with the reagent adsorbed on cross-linked resin depend on the relative amounts used, the solvent (dichloromethane, cyclopentane, tetrahydrofuran, benzene, cycloheptane, and, best of all, cyclohexane), the temperature, and the reaction time [*612*].

Tetrabutylammonium chlorochromate is prepared by adding a solution of chromium trioxide in concentrated hydrochloric acid to a solution of tetrabutylammonium hydrogen sulfate in 5 N hydrochloric acid. Refluxing 3–6 mol of the precipitated product with alcohols in chloroform affords good yields of ketones [*619*].

Halogens and their oxygen-containing compounds are useful and selective oxidants for secondary alcohols. The addition of a **chlorine** solution in carbon tetrachloride to a chloroform solution of 5α-cholestane-3β,19-diol below 30 °C gives a 77% yield of 5α-cholestan-19-ol-3-one after 15 min [*681*].

Similar selectivity is found with chlorine (or bromine) in the presence of hexamethylphosphoric triamide (HMPA). The addition of solutions of chlorine in chloroform to stirred solutions of the alcohols in a mixture of HMPA, dichloromethane, and an aqueous solution of sodium dihydrogen phosphate at 0–5 °C results in very good yields of ketones. Competitive experiments with equimolar mixtures of primary and secondary alcohols show a 95–97% predominance of ketones over aldehydes [*682*].

Hypochlorites are very good oxidizers of alcohols and are frequently selective enough to oxidize secondary alcohols in preference to primary alcohols (*see* equations 288–291). Solutions of *sodium hypochlorite* in acetic acid react exothermically with secondary alcohols within minutes [*693*]. *Calcium hypochlorite* in the presence of an ion exchanger (IRA 900) oxidizes secondary alcohols at room temperature in yields of 60–98% [*705*]. *Tetrabutylammonium hypochlorite,* prepared in situ from 10% aqueous sodium hypochlorite and a 5% dichloromethane solution of tetrabutylammonium bisulfate, oxidizes 9-fluorenol to fluorenone in 92% yield and benzhydrol to benzophenone in 82% yield at room temperature in 35 and 150 min, respectively [*692*]. Cyclohexanol is oxidized to cyclohexanone by tert-*butyl hypochlorite* in carbon tetrachloride in the presence of pyridine. The exothermic reaction must be carried out with due precautions [*709*].

Like chlorine, **bromine** is used to convert secondary alcohols into ketones. A convenient way is to apply the addition product of 2 mol of bromine with 1,4-diazabicyclo[2,2,2]octane (Dabco), a nonhygroscopic yellow solid, prepared by mixing carbon tetrachloride solutions of bromine and Dabco. The compound decomposes at 155–160 °C [*726*]. Oxidation with this addition product is carried out in acetonitrile solution at 50 °C and results in 50 and 71% yields of cyclopentanone and cyclohexanone, respectively, but very low yields of 2-pentanone [*726*].

Better results are obtained on treatment of alcohols with bromine in dichloromethane solution in the presence of hexamethylphosphoric triamide (HMPA) and aqueous sodium bicarbonate. This reagent is highly selective for the oxidation of secondary alcohols in preference to primary alcohols [*682*].

A very selective method of oxidizing secondary alcohols is brominolysis of tributyltin ethers prepared by the treatment of hydroxy compounds with bis(tributyl)tin oxide. The reaction is regio- and stereospecific and is an important means of oxidizing unprotected glycosides [*734*].

Thus, refluxing methyl β-D-glucoside; two equivalents of tributyltin oxide, $[(C_4H_9)_3Sn]_2O$; and molecular sieves (3 Å) in chloroform for 2–3 h followed by treatment with two equivalents of bromine at 0 °C furnishes methyl β-D-3-dehydro-3-ketoglucoside in more than 90% yield. Similarly, methyl β-D-xyloside gives the 3-oxo compound, whereas methyl α-D-glucoside, α-D-galactoside, α-D-xyloside, and β-L-arabinoside yield 70–80% of the corresponding 4-keto derivatives [*734*].

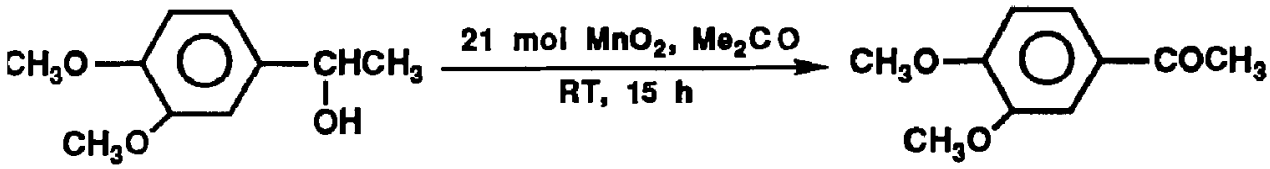
Sodium bromite oxidizes secondary alcohols in preference to primary alcohols. Menthol treated with sodium bromite in aqueous acetic acid at room temperature affords an 86% yield of menthone after 5.5 h [*739*].

Secondary alcohols are oxidized in preference to primary alcohols also by **sodium bromate** in the presence of catalytic amounts of ceric ammonium nitrate or ceric sulfate [*741*].

Reaction conditions for the oxidation of secondary alcohols by halogens and their compounds are shown in equations 265–268.

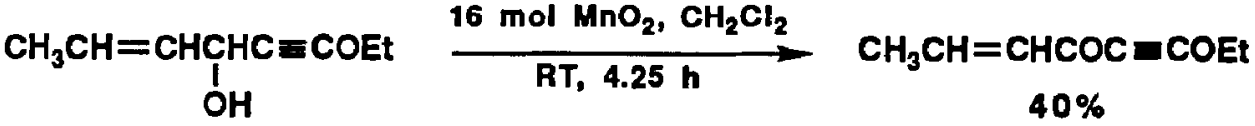
Like primary alcohols, secondary alcohols are oxidized by **manganese dioxide.** The reaction is of free-radical nature and results in the formation of ketones and manganous(II) oxide [*815*]. Manganese dioxide is used in a large molar excess (14.7:1 [*809*], 16:1 [*824*], or 21:1 [*822*]), but a molar ratio as low as 2.3:1 gives very good yields [*808*]. Oxidations in carbon tetrachloride and petroleum ether usually result in higher yields than those in chloroform or benzene [*808*]. Aryl carbinols react faster than allylic alcohols, and these, in turn, react faster than saturated alcohols [*815*]. The reaction is accelerated by removal of the reaction water by azeotropic distillation with benzene [*815*] (equation 253).

[*822*] **253**



Oxidations with manganese dioxide are well suited for the preparation of unsaturated and acetylenic ketones [*824*]. The yields depend on the method of preparation, dryness and particle size of the oxidant, and, to a smaller extent, on reaction temperatures and times [*808*] (equation 254).

[*824*] **254**



Barium manganate, prepared from potassium manganate and barium chloride [*833*] or by the reduction of potassium permanganate with potassium iodide in the presence of barium chloride and sodium hydroxide [*832*], is used for the quantitative oxidation of benzhydrol to benzophenone. The reaction mixture is refluxed in benzene for 0.5–2 h [*833*]. The result is comparable with and even better than that of oxidation with manganese dioxide [*180, 813*].

Sodium permanganate, which is used as its monohydrate in solid form in refluxing dichloromethane or hexane, oxidizes allylic alcohols more slowly and in lower yields than the saturated alcohols. 2-Cyclohexen-1-ol, after a 24-h reflux in hexane, furnishes a 47% yield of the ketone, whereas cyclohexanol gives a 100% yield after 1.5 h [*835*].

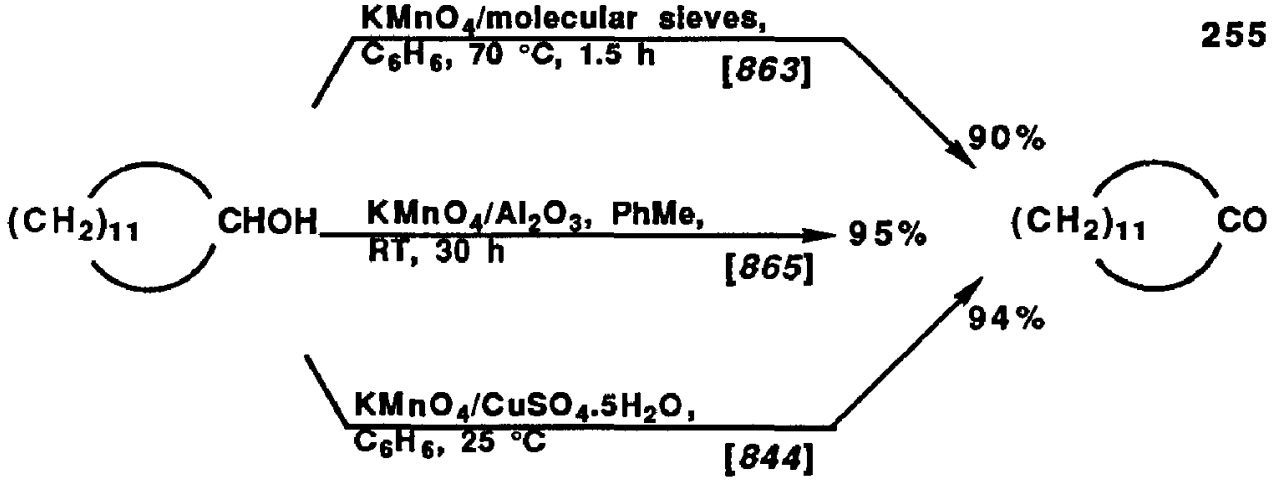
Aqueous **potassium permanganate** is hardly ever used to oxidize secondary alcohols to ketones, because further oxidation of ketones to carboxylic acids occurs even under mild conditions (15–30 °C) [*1147*]. On the other hand, oxidations of alcohols to ketones are successfully accomplished

in organic solvents with **solid or supported permanganates.** As a bonus, isolation of the products obtained by this method is much easier than that from oxidations in aqueous media; the products are isolated just by simple filtration.

Potassium permanganate adsorbed on ***molecular sieves*** is prepared by adding 20 g of Linde 13X molecular sieves (1/16-in. [0.16-cm] pellets) to 500 mL of 0.06 M potassium permanganate, evaporating the water under reduced pressure, and removing the unadsorbed potassium permanganate by screening through a 20-mesh gauze. In this way, up to 0.27 mmol of potassium permanganate is loaded in 1 g of the reagent [*863*]. Cyclododecanol (1.36 mmol) in 20 mL of benzene refluxed with 15 g of the reagent for 1.5 h gives a 90% yield of cyclododecanone [*863*].

An even better result is obtained with potassium permanganate in toluene in the presence of **neutral alumina.** After a mixture of 5 g of alumina, 7.9 g (0.05 mol) of potassium permanganate, and 0.01 mol of cyclododecanol in 50 mL of toluene has been stirred for 30 h at room temperature, a 95% yield of cyclododecanone is obtained [*865*].

The role of the supports in the reactions just described is not clear. Even less clear is the function of *copper sulfate pentahydrate,* in the presence of which oxidations with solid potassium permanganate result in excellent yields of ketones. Traces of water are essential. Primary alcohols, on the other hand, give poor yields of aldehydes and acids [*844*] (equation 255).



255

Similar results are obtained with *copper permanganate octahydrate,* $Cu(MnO_4)_2 \cdot 8H_2O$. Addition of this salt to a solution of 2-decanol in dichloromethane results in an exothermic reaction and boiling of the mixture for 5 min. After 10 additional minutes at room temperature, 2-decanone is isolated in 93% yield [*894*]. Allylic alcohols are oxidized in 84–85% yields to α,β-unsaturated ketones after boiling in dichloromethane for 24 h [*894*].

In contrast to the previous examples of oxidations with solid permanganates insoluble in organic solvents, potassium permanganate may be

dissolved in organic solvents after forming a ***complex with crown ethers.*** Equimolar amounts of dicyclohexano-18-crown-6 ether and potassium permanganate stirred in benzene at 25 °C give a purple solution (half-life 48 h at 25 °C), which can be used directly to oxidize secondary alcohols to ketones. Because large amounts of the expensive crown ether are necessary, this method can hardly compete with the ones previously described [*841*].

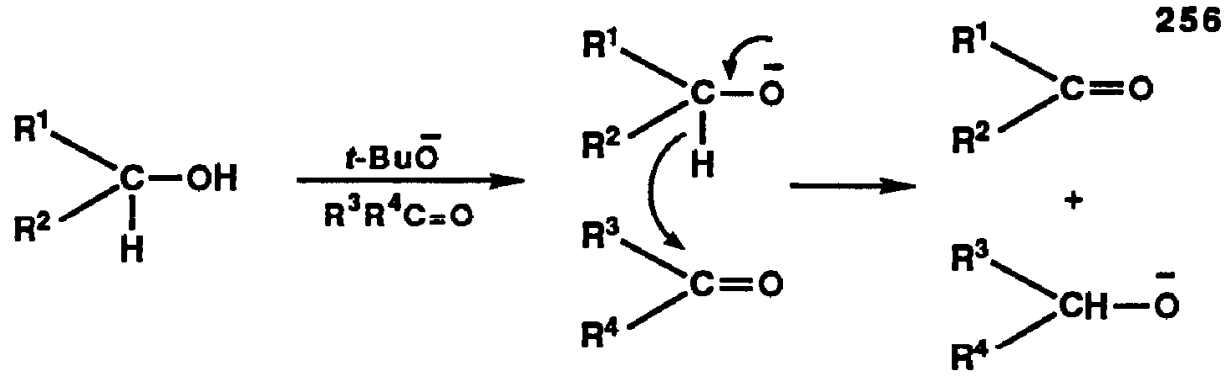
Another way of solubilizing potassium permanganate is its conversion into *tetrabutylammonium permanganate.* The crystalline purple compound, which is obtained as a precipitate after aqueous solutions of tetrabutylammonium bromide and potassium permanganate have been mixed, is sparingly soluble in benzene but easily soluble in dichloromethane, chloroform, acetone, and especially pyridine. The reagent oxidizes alcohols to carbonyl compounds in pyridine at room temperature [*899*]. The disadvantage of tetrabutylammonium permanganate is the possibility of a spontaneous ignition [*901*].

Potassium ferrate in aqueous solution at room temperature transforms 1-phenylethanol in 18 min into acetophenone in 90% yield. However, under similar conditions, cyclohexanol gives a very low yield of the ketone (20–30%). The reagent does not attack double bonds and does not oxidize aldehydes [*917*].

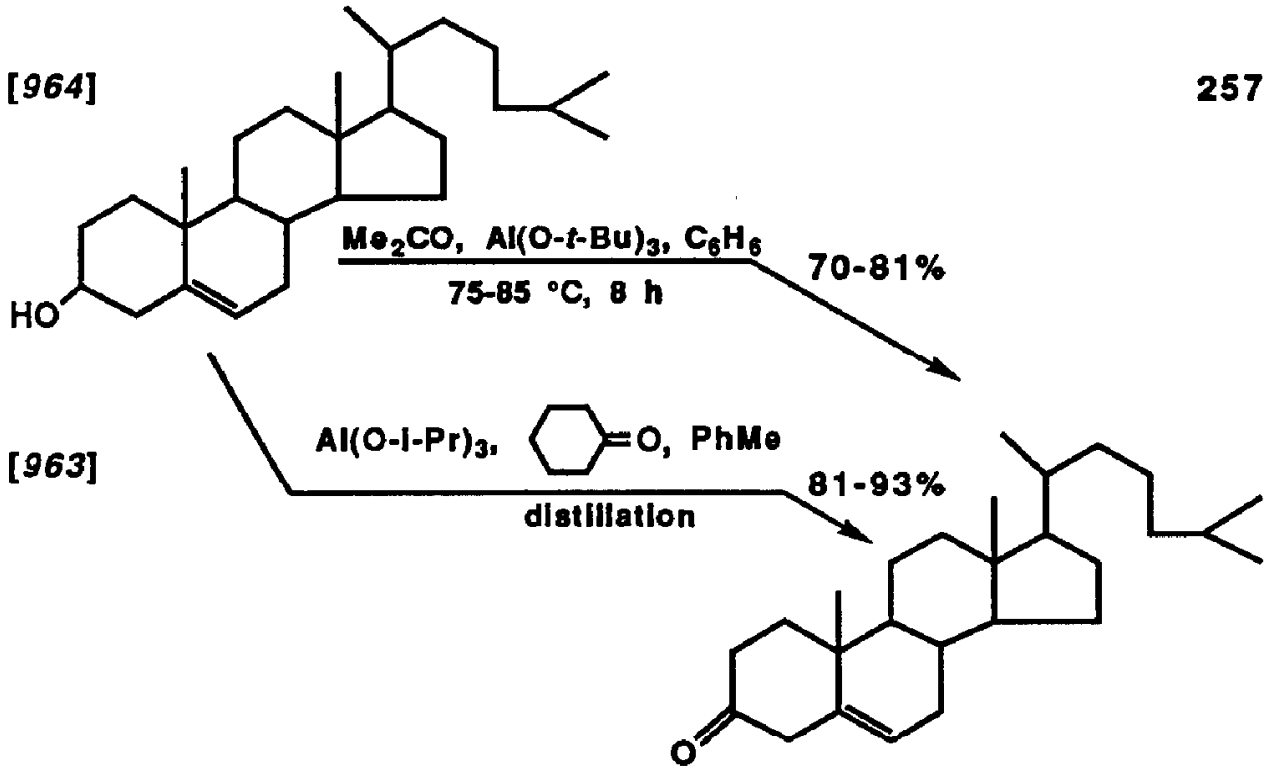
High yields of ketones result from the gentle oxidation of alcohols with compounds of ruthenium. **Ruthenium tetroxide** oxidizes cyclohexanol to cyclohexanone in carbon tetrachloride at room temperature in 93% yield [*940*]. Instead of the rather expensive ruthenium tetroxide, which is required in stoichiometric amounts, catalytic amounts of ruthenium trichloride may be used in the presence of sodium hypochlorite as a reoxidant with the same results [*701*]. **Sodium ruthenate** [*937*] and **potassium ruthenate** [*196*], which are prepared from ruthenium dioxide and sodium periodate in sodium hydroxide and from ruthenium trichloride and potassium persulfate, respectively, also effect oxidations to ketones at room temperature.

Carbonyl compounds act as hydrogen acceptors in the ***Oppenauer oxidation*** of alcohols to aldehydes or ketones. The reaction is based on hydride transfer from the alkoxide ion of the starting alcohol prepared in situ from anhydrous bases, aluminum isopropoxide, or, better still, *tert*-butoxide (equation 256).

The byproduct $R^3R^4CH{-}O^-$ is a strong base that perpetuates the reaction so that only catalytic amounts of aluminum *tert*-butoxide are needed to initiate the oxidation. The reaction is reversible and leads to an equilibrium, which must be systematically destroyed by removal of the byproduct to drive the reaction to completion. Carbonyl compounds used as hydrogen acceptors are acetone, cyclohexanone, benzaldehyde, cinna-



maldehyde, and benzophenone [*962, 1148*]. The product or byproduct is removed by distillation or azeotropic distillation. The Oppenauer oxidation is eminently suited for high-boiling alcohols such as hydroxy steroids (equation 257) [*963, 964*].

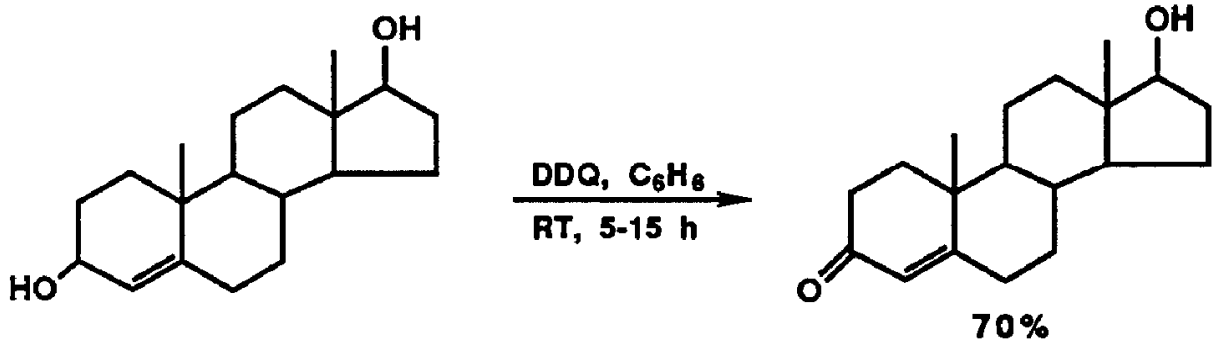


Chloral is used as the hydrogen acceptor in the quantitative oxidation of cyclobutanol to cyclobutanone. The reaction takes place on Woelm alumina at room temperature in carbon tetrachloride after 24 h [*958*]. Under similar conditions, primary alcohols are oxidized in preference to secondary alcohols [*959*].

Another catalyst for the dehydrogenation of alcohols by carbonyl compounds is **Raney nickel,** which is used to convert dihydrocholesterol into 3-cholestanone in 80% yield by refluxing for 24 h with cyclohexanone in toluene [*961*].

Allylic alcohols in steroids are oxidized by **2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),** either alone (equation 258) [*975*] or as a catalyst with periodic acid as a reoxidant [*974*]. Saturated alcohols and other func-

[975] 258



tional groups present in the molecules remain untouched. DDQ competes successfully with manganese dioxide, because it reacts at room temperature and the oxidation is finished within hours [*974, 975*].

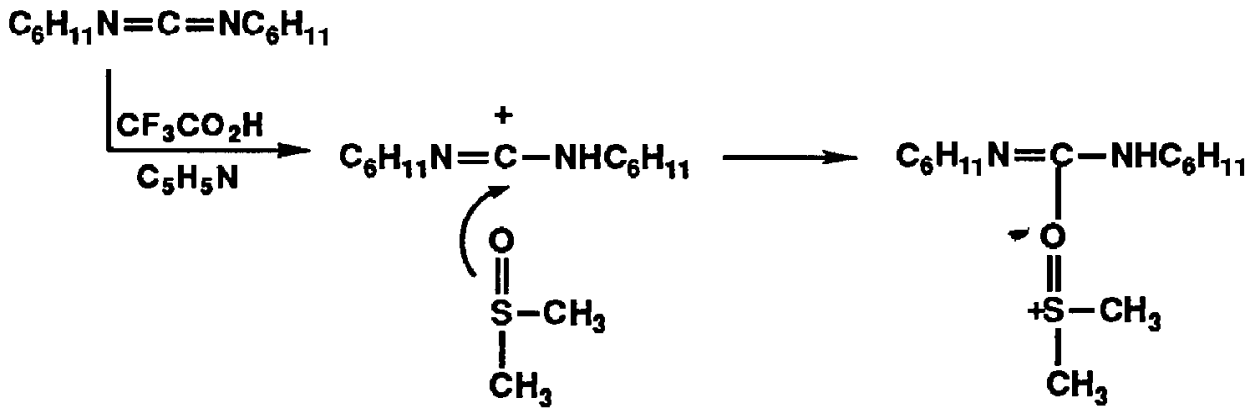
Both saturated and benzylic alcohols are dehydrogenated by refluxing with *diethyl azodicarboxylate* in benzene for 10 h. The azodicarboxylate is converted into hydrazodicarboxylate, while the alcohols give ketones in 51–87% yields [*977*].

Cyclohexanol is converted into cyclohexanone by heating for a few minutes on a steam bath with ***N*-chlorosuccinimide (NCS)** in pyridine and benzene [*709*].

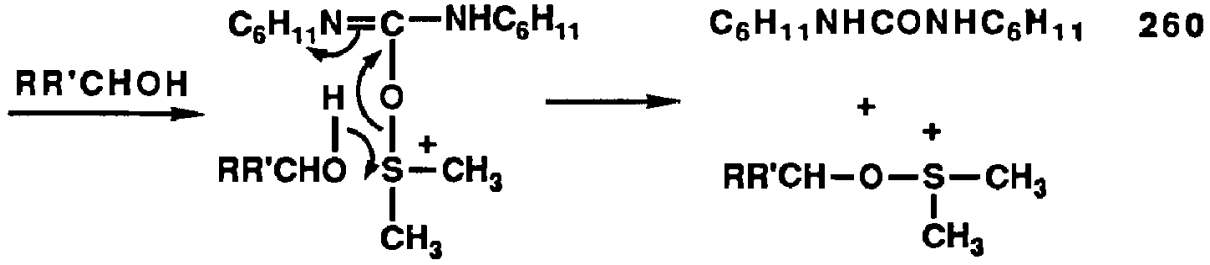
A mixture of N-*chlorosuccinimide and dimethyl sulfide* oxidizes alcohols to ketones under very mild conditions and in high yields. The treatment of 4-*tert*-butylcyclohexanol with this mixture in toluene at 0–25 °C, followed by the addition of triethylamine in toluene, results in a 90–93% yield of 4-*tert*-butylcyclohexanone [*721*].

Dimethyl sulfoxide (DMSO), which is successfully used to dehydrogenate primary alcohols to aldehydes, converts secondary alcohols into ketones in very high yields and under very gentle conditions. The mechanism is discussed in a previous section, Dehydrogenation and Oxidation of Primary Alcohols to Aldehydes (equation 217). The first oxidations were carried out in the presence of dicyclohexylcarbodiimide and an acid catalyst such as pyridinium trifluoroacetate [*1016*], which protonates the diimide and facilitates the attack by dimethyl sulfoxide (equation 259).

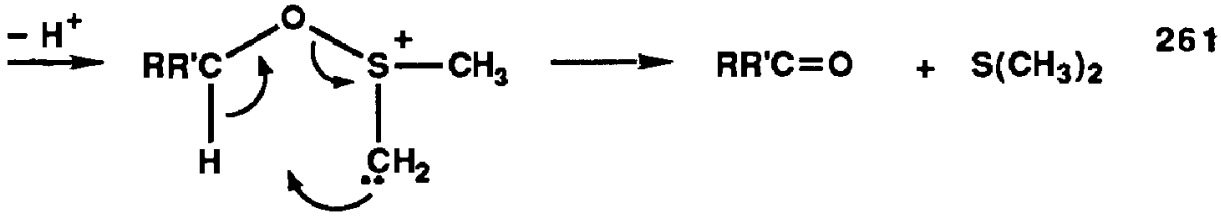
[1016] 259



The intermediate reacts with the alcohol as shown by the arrows in equation 260 and yields dicyclohexylurea and an alkoxysulfonium cation.

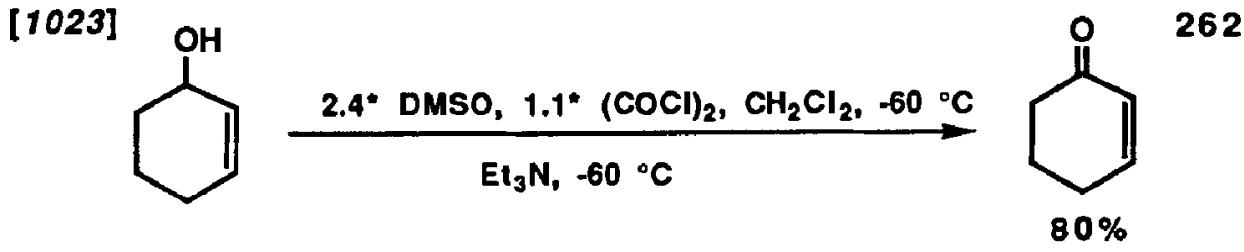


A base (the trifluoroacetate ion) abstracts a proton from one of the methyl groups of the oxysulfonium ion, and a bond shift through a five-membered transition state gives the ketone and dimethyl sulfide [*1016*] (equation 261).



In more recent works, the use of dicyclohexylcarbodiimide has been abandoned because the reaction works satisfactorily with acid catalysts alone, followed by bases such as triethylamine or diisopropylethylamine, which gives, sometimes, even better yields than triethylamine [*1012, 1023*]. Several activators are being used, and the best seems to be oxalyl chloride (the ***Swern oxidation***) [*1023, 1149*]. Other activators are mentioned in the section Oxidation of Primary Alcohols to Aldehydes. The advantages of oxidations with dimethyl sulfoxide lie in the mildness of the reagent and in the low temperatures, sometimes –45 °C [*1020*] or –60 °C [*1023*], at which the reactions are run.

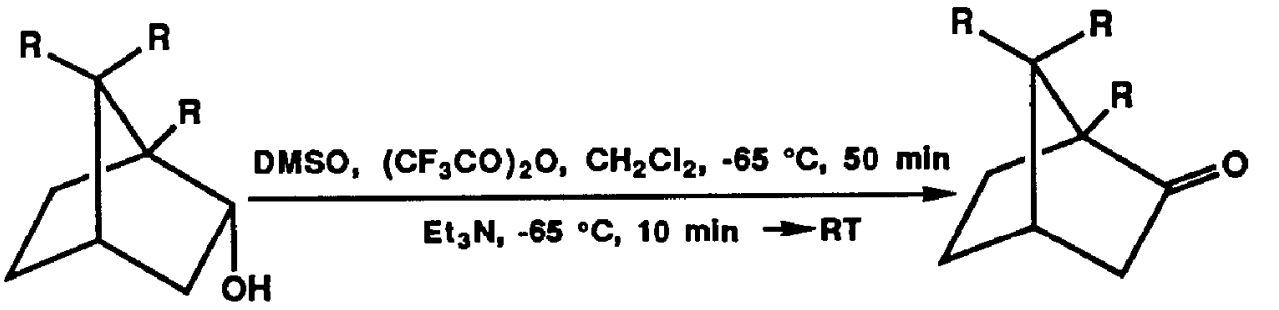
In a typical example, 10 mmol of an alcohol, 11 mmol of oxalyl chloride, and 24 mmol of DMSO in 40 mL of dichloromethane react at –60 °C. The mixture is then made alkaline with 50 mmol of triethylamine [*1023*] (equation 262). In other instances, the molar ratios of the alcohol to DMSO and to the activator (benzoic anhydride) were 1:47 and 1:17, respectively; with phosphorus pentoxide as the activator, the respective molar ratios were 1:47 and 1:1 [*1009*], and with pyridine–sulfur trioxide, they were 1:70 and 1:3 [*1018*]. Dichloromethane and toluene [*1012*] are the best solvents.



*Values are moles per mole of alcohol.

Dimethyl sulfoxide oxidizes primary allylic alcohols in preference to cyclic secondary alcohols [*1018*] and is suitable for oxidations of sterically hindered alcohols in high yields [*1009, 1139*] (equation 263).

[*1139*] **263**



R = H 96% (85%)*
R = CH_3 98% (81%)*

***Values in parentheses are isolated yields.**

The disadvantages of oxidations with dimethyl sulfoxide are the large excess of the oxidant needed and the obnoxious smell of the dimethyl sulfide formed. Therefore, oxidations with this reagent should be carried out in hoods.

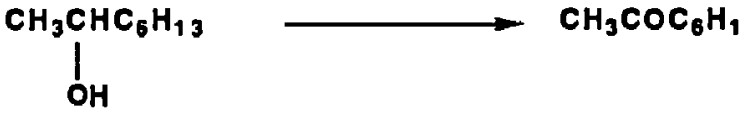
A very peculiar oxidation of secondary alcohols and primary–secondary diols to ketones in 53–84% yields is a reaction with *triphenylmethylfluoroborate,* which reacts according to equation 264 and which affects exclusively secondary alcohols [*981*].

[*981*] **264**

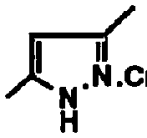
Several biochemical oxidations can be applied to the conversions of secondary alcohols into ketones. In a complex system containing **horse liver alcohol dehydrogenase,** (±)-*trans*-3-methylcyclohexanol and (±)-*cis*-2-methylcyclopentanol are dehydrogenated to (–)-(*S*)-3-methylcyclohexanone (yield 50%; ee 100%) and to (+)-(*S*)-2-methylcyclopentanone (yield 55%; ee 96%), respectively [*1036*].

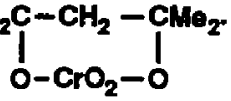
The oxidation of a secondary alcoholic group in the presence of primary alcoholic groups by ***Acetobacter suboxydans*** converts adonit into adonose [*1041*]. The treatment of androstenediol and dehydroandrosterone with **yeast** yields Δ^4-androstenedione [*1088*]. Steroidal hydroxy ketones are dehydrogenated to dicarbonyl compound with ***Corynebacterium simplex*** [*1056*] (*see* equations 446 and 447). Examples of oxidations of secondary alcohols to ketones are shown in equations 265–268.

EXAMPLES OF OXIDATION OF SECONDARY ALCOHOLS TO KETONES



265

[*815*]	MnO_2, C_6H_6, distillation	42-65%
[*835*]	$NaMnO_4.H_2O$, C_6H_{14}, 69 °C, 2.5 h	95%
[*863*]	$KMnO_4$/molecular sieves, C_6H_6, 70 °C, 7 h	92%
[*844*]	$KMnO_4/CuSO_4.5H_2O$, C_6H_6, 25 °C	94%
[*927*]	Raney Ni, C_6H_6, 125-135 °C, 4 h	93%
[*1023*]	DMSO, $(COCl)_2$, CH_2Cl_2, -60 °C, 35 min, Et_3N, -60 °C, 20 min	98%
[*981*]	2 Ph_3CBF_4, CH_2Cl_2, 25 °C, 10 h	84%
[*276*]	AcO_2H/catalyst*, AcOEt, CH_2Cl_2, 0 °C, 0.35 h	99%
[*70*]	$O_2/PdCl_2$, AcONa, $CO(OCH_2)_2$, RT, 36 h	76%
	133 h	86%
[*55*]	O_2, AcOEt, RT, 20 h	21%
[*56*]	O_2/PtO_2, C_7H_{16}, 20 °C, 96 h	80%
[*326*]	*m*-$ClC_6H_4CO_3H$, THF, HCl, RT, 1 h	75%
[*675*]	CrO_2Cl_2/SiO_2-Al_2O_3, CH_2Cl_2, 25 °C, 24 h	94%
[*682*]	Cl_2, $CHCl_3$, HMPA, CH_2Cl_2, H_2O, NaH_2PO_4, 0-5 °C, 2 min	95%
[*682*]	Br_2, CH_2Cl_2, HMPA, H_2O, $NaHCO_3$, 0-5 °C	95%
[*693*]	NaOCl, H_2O, AcOH, 15-25 °C	96%
[*121*]	electrolytic oxidation, KI, H_2O, *t*-BuOH, 6-10 F/mol	92-99%
[*543*]	CrO_3, HMPA, RT, 15 H	40%
[*538*]	CrO_3, CH_2Cl_2, Et_2O, Celite, 35 min	80%
[*571*]	CrO_3, Amberlyst A26, C_6H_6, reflux, 9 h	97%
[*599*]	3 (2 $C_5H_5N.CrO_3$), C_5H_5N, ice bath, 30 min, RT,15-22 h	18%
[*595*]	6 (2 $C_2H_5N.CrO_3$), CH_2Cl_2, 25 °C, 5-15 min	97%
[*602*]	 CrO_3, CH_2Cl_2, RT, 30 min	93%
[*612*]	12 mol of poly(vinylpyridine).HCl.CrO_3, CH_2Cl_2, RT, 4 days	76%
[*617*]	CrO_3, $Bu_4NO_3SCF_3$, CH_2Cl_2, RT, 1 h	80%

*The catalyst is 

266

[*45*]	O_2, *t*-BuOK, *hv*, rose bengal, 25-27 °C	97%
[*70*]	$O_2/PdCl_2$, AcONa, $CO(OCH_2)_2$, RT, 56 h	88%
[*56*]	O_2/PtO_2, C_7H_{16}, 20 °C, 1.5 h	92%
[*55*]	O_2/Pt, AcOEt, RT, 18 h	68%
[*55*]	air/Pt, AcOEt, RT, 24 h	74%
[*121*]	electrolytic oxidation, KI, H_2O, *t*-BuOH, 8 F/mol, RT	74%
[*326*]	*m*-$ClC_6H_4CO_3H$, THF, HCl, RT, 1 h	85%
[*380*]	2 AgO, H_3PO_4, 20 °C, 8 h	55%

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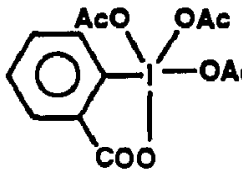
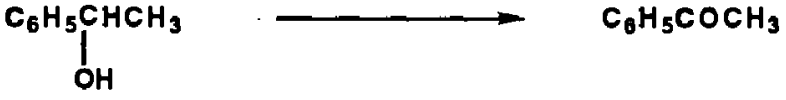
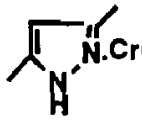
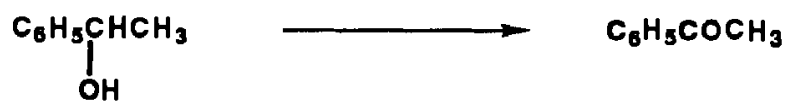
[349]	CuO, He, 250-300 °C	90%
[917]	K_2FeO_4, H_2O, RT, 1.5 h	20-30%
[682]	Cl_2, $CHCl_3$, HMPA, CH_2Cl_2, H_2O, NaH_2PO_4, 0-5 °C, 2 min	81%
[682]	Br_2, CH_2Cl_2, HMPA, H_2O, $NaHCO_3$, 0-5 °C, 5 min	87%
[693]	NaOCl, H_2O, AcOH, 15-25 °C, 2 h	96%
[705]	$Ca(OCl)_2$, IRA 900 (OCl), <40 °C, RT, 3 h	80%
[709]	*t*-BuOCl, C_5H_5N, CCl_4, -5 °C	90.5%
[726]	$2Br_2$.DABCO, MeCN, 50 °C, 3 h	71%
[739]	$NaBrO_2$, H_2O, AcOH, RT, 5.5 h	100%
[709]	NCS, C_5H_5N, C_6H_6, 100 °C, <5 min	50%
[940]	RuO_4, CCl_4 0-15 °C, RT, overnight	93%
[701]	$RuCl_3$, H_2O, NaOCl, 0 °C, 0.5 h	90-95%
[937]	RuO_2, $NaIO_4$, NaOH, 25 °C, 1 h	85%
[196]	$RuCl_3$, $K_2S_2O_8$, RT, 2 h	64%
[543]	CrO_3, HMPA, RT, 15 h	49%
[571]	CrO_3, Amberlyst A26, C_6H_{14}, 3 h	77%
[536]	$Na_2Cr_2O_7.2H_2O$ (equivalent amount), H_2SO_4, Et_2O, 25 °C	92%
[536]	$Na_2Cr_2O_7.2H_2O$ (100% excess), H_2SO_4, Et_2O, 0 °C	98%
[629]	$Na_2Cr_2O_7.2H_2O$, H_2SO_4, DMSO, 70 °C, >30 min	89%
[641]	$Na_2Cr_2O_7.2H_2O$, H_2SO_4, Et_2O, 25 °C, 2.25 h	92%
[617]	CrO_3, Bu_4NCl, CH_2Cl_2, RT, 2 h	70%
[630]	$Na_2Cr_2O_7$, Bu_4NHSO_4 (10%), 3 M H_2SO_4, RT, 1 min	88%
[597]	2 $(C_5H_5N)_2CrO_4$ on SiO_2, AcOH, 30-35 °C, 9 h	64%
[597]	2 $(C_5H_5N)_2CrO_4$ on SiO_2, AcOH, C_6H_6, reflux 3 h	76%
[599]	3 (2 $C_5H_5N.CrO_3$), C_5H_5N, cooling with ice, 30 min, RT, 15-22 h	45%
[595]	6 (2 $C_5H_5N.CrO_3$), CH_2Cl_2, 25 °C, 5-15 min	98%
[612]	poly(vinylpyridine).HCl.CrO_3, C_6H_{12}, 75 °C, 24 h	94%
[815]	MnO_2, C_6H_6, reflux	49%
[835]	$NaMnO_4.H_2O$, C_6H_{14}, 69 °C, 1.5 h	100%
[1023]	DMSO, $(COCl_2)_2$, CH_2Cl_2, -60 °C, 35 min; Et_3N, -60 °C, 5 min	94%
[981]	Ph_3CBF_4, CH_2Cl_2, 25 °C, 13.5 h	66%
[801]	 CH_2Cl_2, RT, 30 min, NaOH, 10 min	90%



267

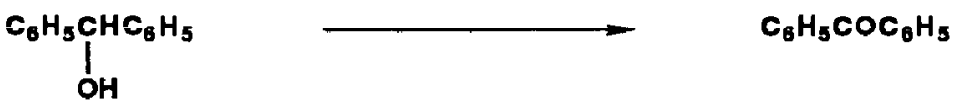
[456]	N_2O_4, $CHCl_3$, 0 °C, 1 h, RT, 6 h	98%
[602]	 CH_2Cl_2, RT, 30 min	100%



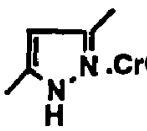
267

[619]	Bu_4NCrO_3Cl, $CHCl_3$, reflux 2 h	80%
[651]	$K_2Cr_2O_7$, Adogen 464*, 3 M H_2SO_4, C_6H_6, 55 °C, 15 h	80%
[675]	CrO_2Cl_2/SiO_2-Al_2O_3, CH_2Cl_2, 25 °C, 5 h	100%
[682]	Cl_2, $CHCl_3$, HMPA, CH_2Cl_2, H_2O, NaH_2PO_4, 0-5 °C, 15 min	98%
[682]	Br_2, CH_2Cl_2, HMPA, H_2O, $NaHCO_3$, 0-5 °C, 15 min	98%
[815]	MnO_2, C_6H_6, distillation	72%
[809]	MnO_2 (15 equivalents), C_6H_6, RT, 0.5 h	70%
[917]	K_2FeO_4, H_2O, RT, 18 min	90%
[959]	CCl_3CHO, Al_2O_3 (Woelm), CCl_4, 25 °C, 24 h	90%
[977]	$EtO_2CN{=}NCO_2Et$, C_6H_6, reflux, 10 h	87%

*Adogen 464 is methyltrialkyl (C_8-C_{10}) ammonium chloride.



268

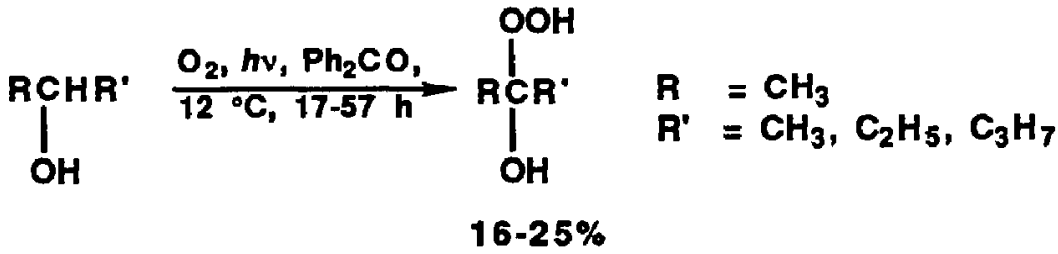
[45]	O_2, KOH, t-BuOH, $h\nu$, rose bengal, 25-26 °C	91%
[442]	$Pb(OAc)_4$, C_5H_5N, RT, a few hours	80%
[456]	N_2O_4, $CHCl_3$, 0 °C, 1 h, RT, 6 h	89%
[543]	CrO_3, HMPA, RT, 2 h	100%
[538]	CrO_3, CH_2Cl_2, Et_2O, Celite, RT, 35 min	93%
[571]	CrO_3, Amberlyst A26, C_6H_6, 1 h	77%
[599]	3 ($2C_5H_5N.CrO_3$), C_5H_5N, cooling with ice, 30 min, RT, 15-22 h	71%
[595]	6 ($2C_5H_5N.CrO_3$), CH_2Cl_2, 25 °C, 5-15 min	96%
[602]	 CrO_3, CH_2Cl_2, RT, 30 min	98%
[605]	$C_5H_5N.CrO_3Cl$, CH_2Cl_2, 25 °C, 1-2 h	100%
[619]	Bu_4NCrO_3Cl, $CHCl_3$, reflux 1 h	82%
[660]	$ZnCr_2O_7.3H_2O$, CH_2Cl_2, RT, 6 min	95%
[815]	MnO_2, C_6H_6, distillation	92%
[692]	NaOCl, H_2O, Bu_4NHSO_4, CH_2Cl_2, RT, 2.5 h	82%
[833]	2 $BaMnO_4$, C_6H_6, reflux, 0.5-2 h	100%
[863]	$KMnO_4$/molecular sieves, C_6H_6, 70 °C, 7 h	100%
[844]	$KMnO_4/CuSO_4.5H_2O$, C_6H_6, 70 °C, 4 h	100%
[841]	$KMnO_4$, dicyclohexyl-18-crown-6 ether, C_6H_6, 25 °C	100%
[899]	Bu_4MnO_4, C_5H_5N, RT	97%
[977]	$EtO_2CN{=}NCO_2Et$, C_6H_6 reflux, 10 h	71%
[1023]	DMSO $(COCl)_2$, CH_2Cl_2, -60 °C, 35 min; Et_3N, 20 min	98%
[525]	$(PhSeO)_2O$, THF, RT, 3 h	85%

Oxidation of Secondary Alcohols to α-Hydroxy Hydroperoxides

A unique reaction leading to unique compounds takes place when secondary alcohols are treated with oxygen in the presence of benzophenone as a sensitizer for photooxidation. The products, which are isolated by distillation at room temperature at 0.1–0.8 mm of Hg in 16–25% yields, show the presence of "active" oxygen and react with 2,4-dinitrophenylhydrazine to form 2,4-dinitrophenylhydrazones of the corresponding ketones.

The compounds must be handled with utmost care because they ***tend to explode*** (equation 269) [*44*].

[*44*]

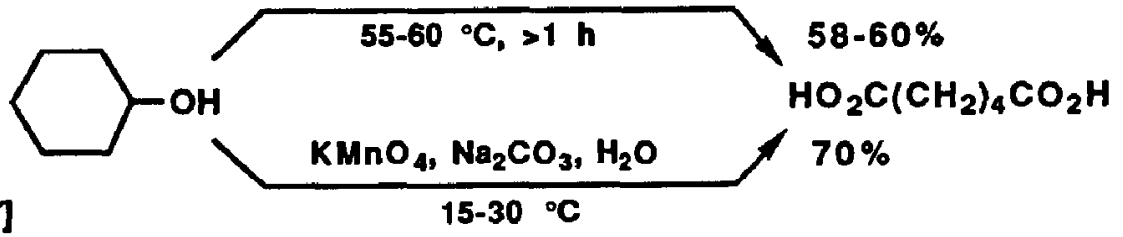


269

Oxidation of Secondary Alcohols to Carboxylic Acids

The treatment of secondary alcohols with powerful oxidants such as **nitric acid** [*466, 468*], **chromium trioxide** [*580*], or **potassium permanganate** [*1147*] results not only in oxidation to ketones but also in subsequent oxidation of the ketones to carboxylic acids. Thus cyclohexanol gives adipic acid [*468, 1147*], 4-isopropylcyclohexanol gives β-isopropyladipic acid [*466*], and 2-methylcyclohexanol gives 6-ketoenanthoic (δ-acetylvaleric or heptanon-6-oic) acid [*580*] (equations 270 and 271).

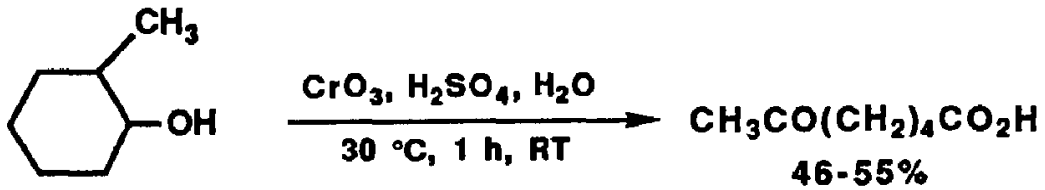
[*468*]



270

[*1147*]

[*580*]

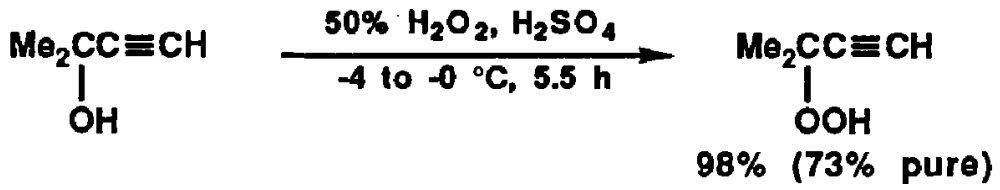


271

Oxidation of Tertiary Alcohols

Tertiary alcohols are resistant to oxidation. *tert*-Butyl alcohol is frequently used as a solvent in oxidations. However, some tertiary alcohols are converted into tertiary hydroperoxides on treatment with *hydrogen peroxide in sulfuric acid* [*177, 179*]. Dimethylphenylcarbinol added to a mixture of 87% hydrogen peroxide and sulfuric acid at a temperature below 0 °C gives a 94% yield of cumyl hydroperoxide after 3.5 h [*177*]. Similarly, acetylenic alcohols with the tertiary hydroxyl group adjacent to the triple bonds are converted into the corresponding hydroperoxides in high yields [*179*] (equation 272).

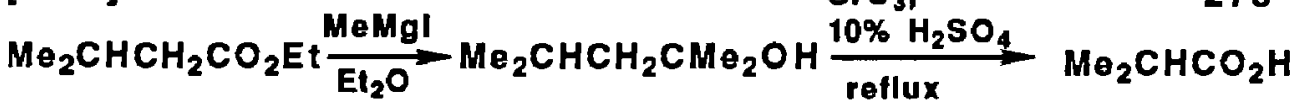
[179]



272

In acid media, for example, in **chromic acid in sulfuric acid,** tertiary alcohols that can suffer dehydration form alkenes, which are degraded to ketones and carboxylic acids (***Barbier–Loquin*** and ***Wieland degradation*** of carboxylic acids) [*1150*] (equation 273).

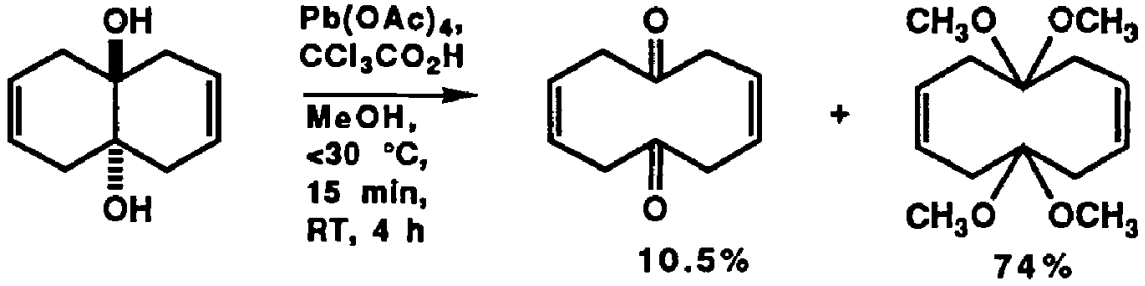
[1150]



273

Rather rare examples of the oxidation of tertiary alcohols are the degradation of 3-ethyl-3-pentanol to 3-pentanone and iodoethane in respective yields of 90 and 84% by acetyl hypoiodite in acetic acid and chlorobenzene under irradiation for 1 h at 20–25 °C [*780*] and the conversion of *trans*-9,10-dihydroxy-1,4,5,8,9,10-hexahydronaphthalene into 3,8-cyclodecadiene-1,6-dione and its tetramethylacetal by lead tetraacetate (equation 274) [*447*].

[447]



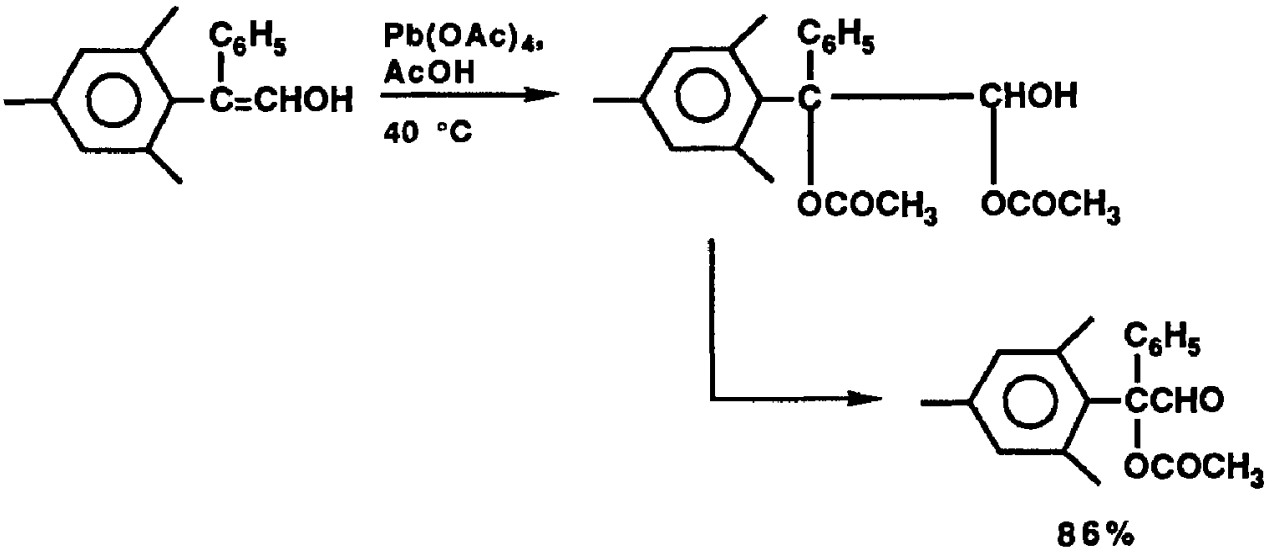
274

Oxidation of Unsaturated Alcohols at Multiple Bonds

The enol form of mesitylphenylacetaldehyde, a **vinylic alcohol,** when dissolved in acetic acid and treated with lead tetraacetate at 40 °C, gives 2-acetoxy-2-mesitylphenylacetaldehyde in 86% yield [*1151*]. The result can be interpreted as the addition of acetoxyls across the enol double bond followed by elimination of one molecule of acetic acid (equation 275).

The oxidation of the alcoholic groups of ***allylic alcohols*** and ***phenylallylic alcohols*** was thoroughly discussed in previous sections on the oxidation of primary and secondary alcohols. In this section, only such reactions in which the double bond is oxidized while the alcoholic group is preserved will be discussed.

[1151] 275

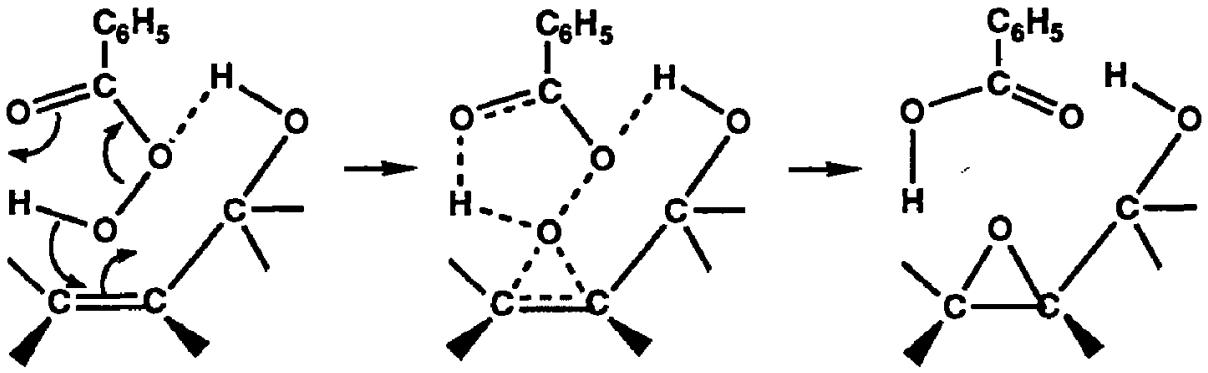


86%

The regio- and stereospecificity of ***epoxidation*** depend on the structure of the alcohols and on the oxidants. Most of the examples of epoxidation include allylic alcohols. In geraniol, where both allylic and a nonallylic double bonds are present, epoxidation occurs almost exclusively at the allylic double bond [*215*].

Stereoselectivity in cyclic allylic alcohols depends on the ring size and on the reagent used. 2-Cyclohexen-1-ol, on treatment with **peroxybenzoic acid,** gives a *cis* epoxide, probably because of the hydrogen bond of the hydroxyl hydrogen in the transition state. If the acetate of the alcohol is treated with peroxybenzoic acid, the *trans* epoxide predominates over the *cis* epoxide in a ratio of 4:1 (equation 276) [*298*].

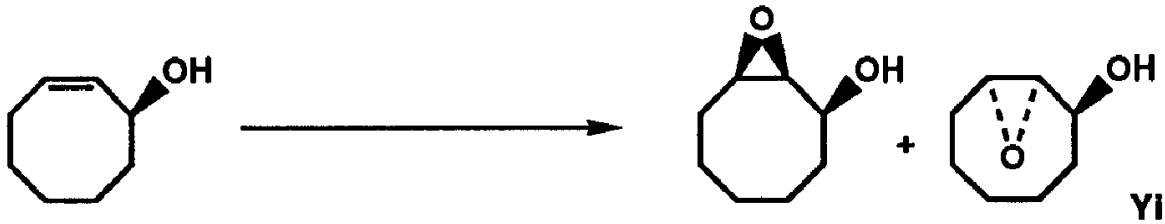
[298] 276



In *cis*-2-cycloocten-1-ol, oxidation with ***tert*-butyl hydroperoxide** catalyzed by vanadium acetylacetonate yields almost exclusively the *cis* epoxide, whereas ***m*-chloroperoxybenzoic acid** produces exclusively the *trans* epoxide. In *trans*-2-cycloocten-1-ol, both oxidants furnish predominantly the *cis* epoxide (equation 277) [*216*].

In the epoxidations of acyclic allylic alcohols by ***m*-chloroperoxyben-**

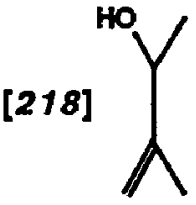
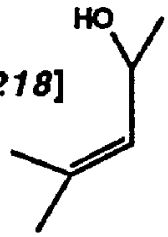
[216] 277



			Yield
***cis*-2-cycloocten-1-ol (above)**			
***t*-BuOOH/VO(acac)$_2$, C_6H_6, 40 °C, 24 h**	97%	3%	83%
***t*-BuOOH/MoO_2(acac)$_2$, C_6H_6, 80 °C, 5 h**	42%	58%	78%
***m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 0 °C, 24 h**	0.2%	99.8%	81%
***trans*-2-cycloocten-1-ol (not shown)**			
***t*-BuOOH/VO(acac)$_2$, C_6H_6, 40 °C, 24 h**	93%	7%	62%
***m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 0 °C, 24 h**	84%	16%	58%

zoic acid, *p*-nitroperoxybenzoic acid, and ***tert*-butyl hydroperoxide** with vanadyl acetylacetonate and molybdenum hexacarbonyl, fairly large differences occur in the ratios of the diastereomers formed. The main factor determining the ratios of stereoisomers seems to be the structure of the allylic alcohol (equations 278 and 279) [*218, 328*].

For the synthesis of natural products containing oxirane rings, it is desirable to prepare not only the correct diastereomers but also the proper enantiomers. To this effect, different chiral oxidants were tested: ***tert*-butyl hydroperoxide** and *chiral hydroxamic acids* as ligands to *vanadyl acetylacetonate* [*1031*] and especially ***tert*-butyl hydroperoxide, titanium tetra-**

		Oxidant			
					t-BuOOH +
Compound	**Epoxide**	***p*-$O_2NC_6H_4CO_3H$***	***m*-$ClC_6H_4CO_3H$**	**$VO(acac)_2$**	**$Mo(CO)_6$**
 [218]	***threo*** / ***erythro***	32/68	45/55	5/95	16/84
 [218]	***threo*** / ***erythro***	96/4	95/5	86/14	95/5

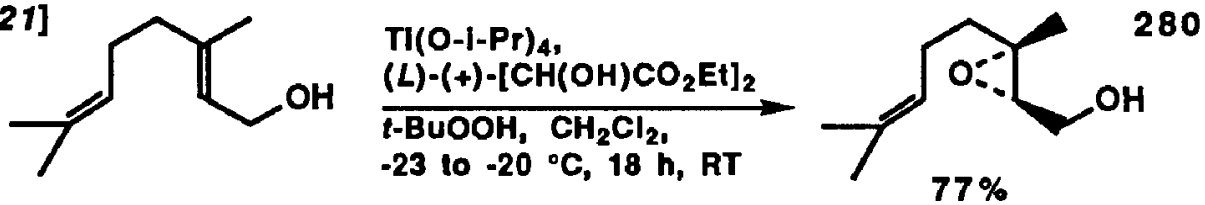
278

279

*Data on the oxidation with peroxy-*p*-nitrobenzoic acid are from reference 328.

isopropoxide, and **(+)** or **(–) dialkyl tartrate (Sharpless reagent)** [*221, 222, 1026, 1027*], with which 90–95% enantiomeric excesses at 70–82% yields are obtained (equation 280) [*221*].

[*221*]



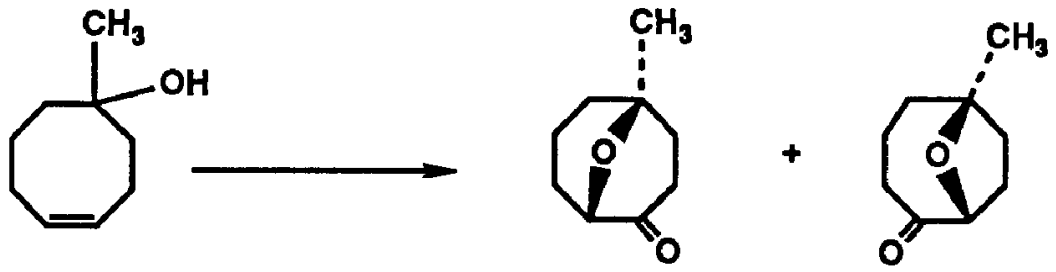
280

77%
95% ee

Not only allylic alcohols but also homoallylic alcohols can be epoxidized. A peculiar transannular oxidation takes place when 1-methyl-4-cycloocten-1-ol is treated with the **Fieser reagent, [CrO_3–$(CH_3CO)_2O$–CH_3COOH],** or with **pyridinium chlorochromate.** Two diastereomeric keto oxides are formed in different ratios (equation 281) [*535*].

[*535*]

281

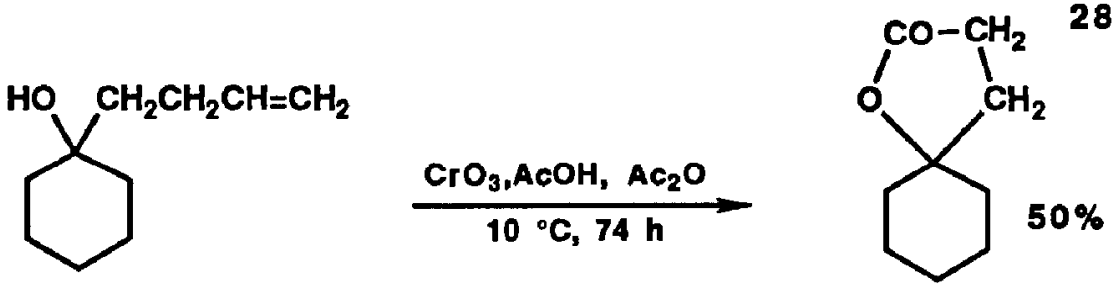


CrO_3, AcOH, Ac_2O, RT, 12 h	33%	:	67%
Na_2CrO_4, AcOH, 90 °C, 1 h	0	:	100% (yield 53%)
$C_5H_5NHCrO_3Cl$, CH_2Cl_2, reflux 40 h	0	:	100%

When 1-(buten-3-yl)cyclohexanol and 1-(penten-4-yl)cyclohexanol are treated with **chromium trioxide** in acetic acid and acetic anhydride, oxidation at the double bonds results in the formation of carboxylic acids, which cyclize to form γ- and δ-lactones, respectively [*568*]. The same reaction occurs with the cycloheptanol analogues in better yields (equation 282) [*568*].

[*568*]

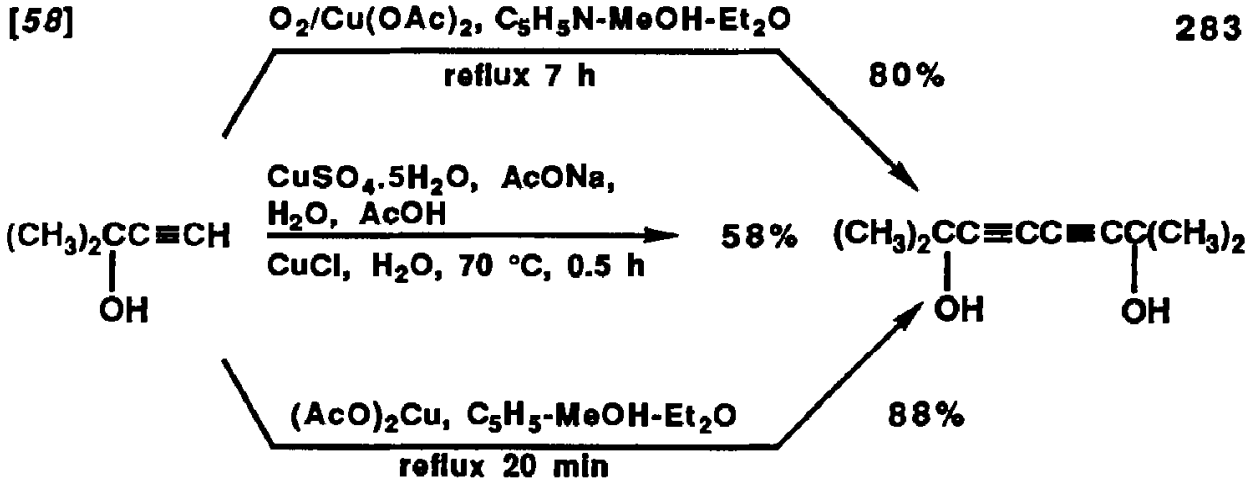
282



50%

Oxidation of the alcoholic group in acetylenic alcohols is discussed in previous sections (equations 218, 219, 250, 254, and 272). Oxidations affecting the rest of the molecule, that is, acetylenic hydrogen, are shown in equation 283. Such oxidations are carried out analogously to those of simple terminal acetylenes and lead to diacetylenic diols [*2*, *58*].

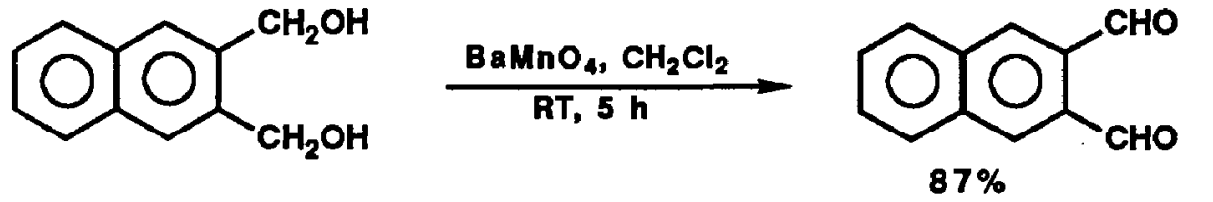
[*58*] 283



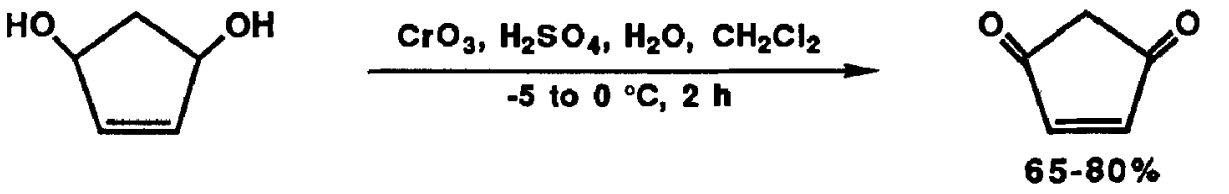
Oxidation of Diols

The oxidation of diols having alcoholic groups of the same nature, for example, both alcoholic groups are primary, secondary, allylic, or benzylic, is usually carried out at both groups to yield ***dialdehydes*** [*832*] or ***diketones*** [*582*]. Such reactions are achieved by chromium trioxide [*582*], barium manganate [*832*], dimethyl sulfoxide activated with acetic anhydride [*1013*], and others (equations 284 and 285).

[*832*] 284



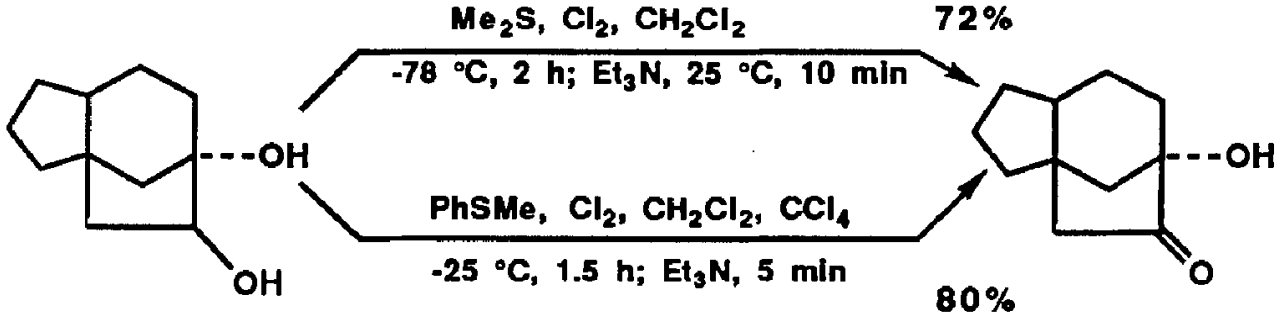
[*582*] 285



If the hydroxyl groups in a diol are tertiary and secondary, only the secondary alcoholic group is oxidized (equation 286) [*1019*].

Selective oxidations can be accomplished when the molecule contains hydroxyls of different nature. Many examples of selective oxidations have been carried out with steroids, where, in addition to the chemical nature

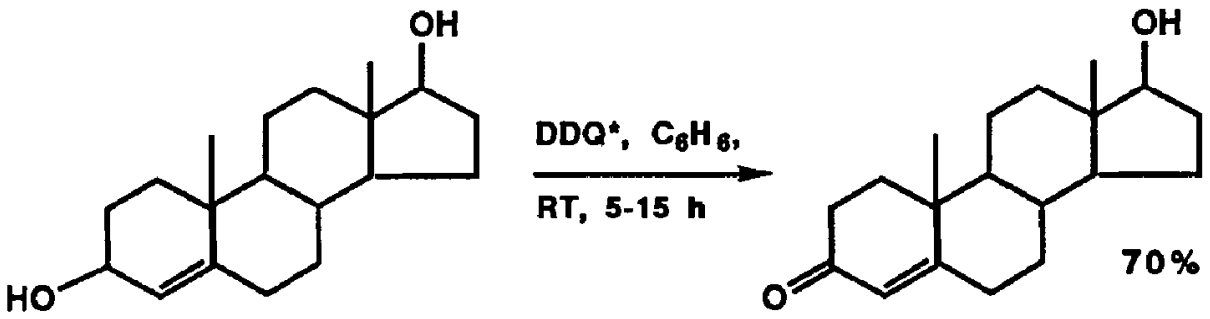
[1019] 286



of the alcoholic group, its accessibility and stereochemistry may play a significant role [*681, 743, 975, 1059*].

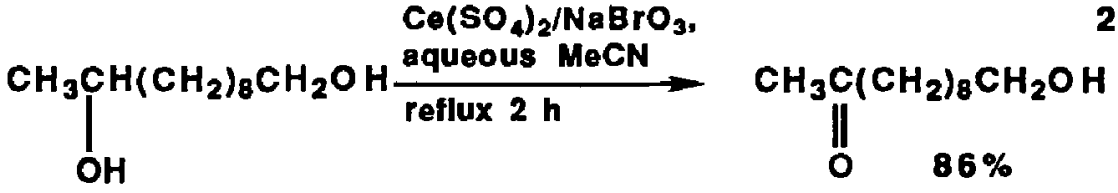
A general rule is that ***allylic alcohols*** are more readily oxidized than ***saturated secondary alcohols*** [*975*], and these, in turn, are ***more readily oxidized than saturated primary alcohols*** [*681, 741, 1041, 1152*]. Ceric sulfate [*741*], ceric ammonium nitrate [*741*], chlorine [*681*], sodium hypochlorite [*1152*], and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone [*975*] are successfully used for this purpose (equations 287–289).

[975] 287

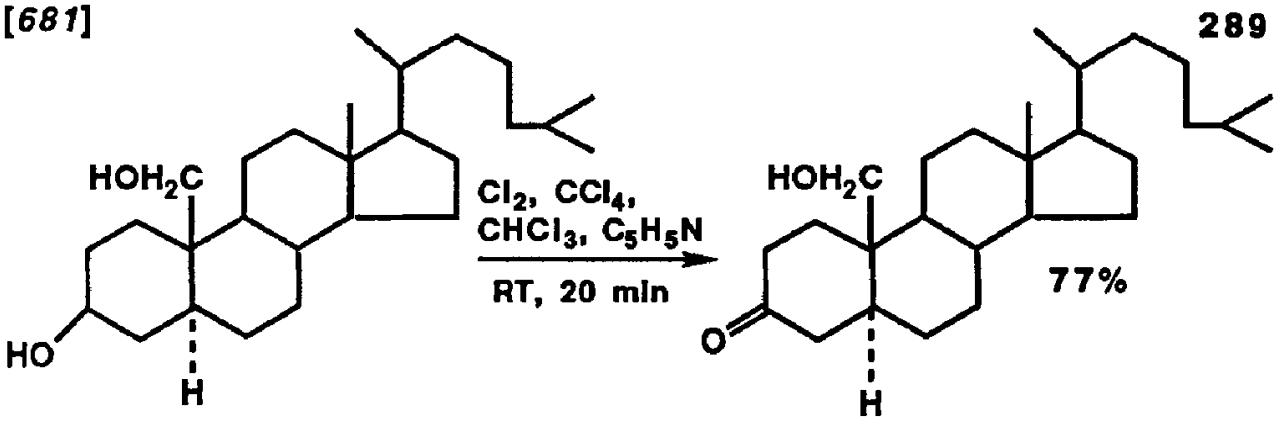


*DDQ is 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

[741] 288

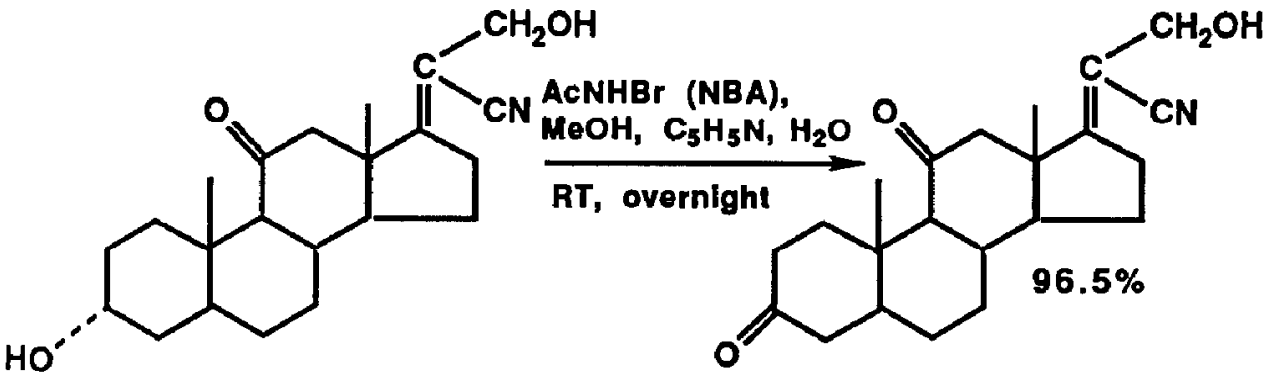


[681] 289



However, exceptions do occur, especially when the allylic grouping contains electron-withdrawing groups in the vicinity of the hydroxylic function (equation 290) [*743*].

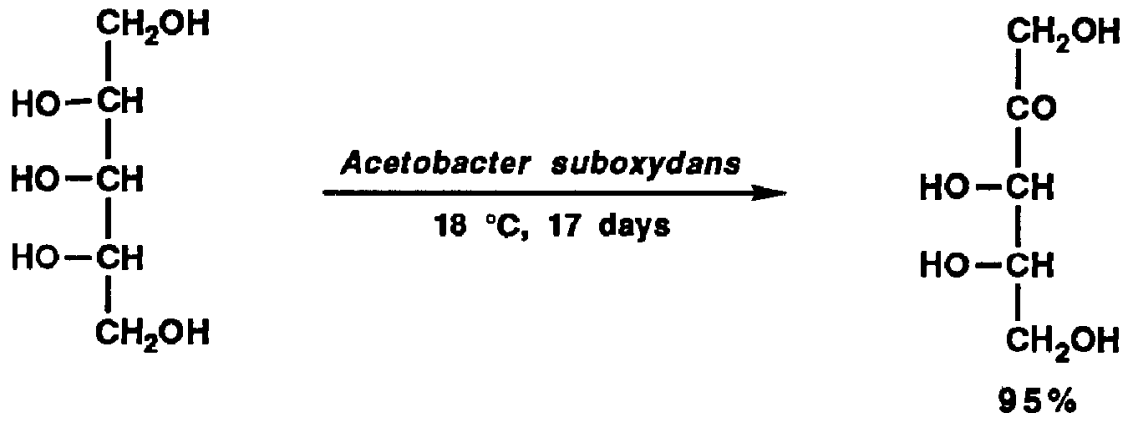
[*743*] **290**



Secondary steroidal alcohols react in preference to primary allylic alcohols in biochemical oxidations using ***Rhizopus arrhizus*** and ***Helicostylum piriforme*** or ***Cunninghamella blakesleeana***. However, the reaction is complicated by hydroxylations in positions 6 (with *Rhizopus arrhizus*) and 9 (with *Helicostylum piriforme* or *Cunninghamella blakesleeana*) [*1059*].

Another example of the preferential oxidation of secondary hydroxyls versus primary hydroxyls is the formation of L-adonose from L-adonit by bakers' yeast (***Acetobacter suboxydans***) (equation 291) [*1041*].

[*1041*] **291**



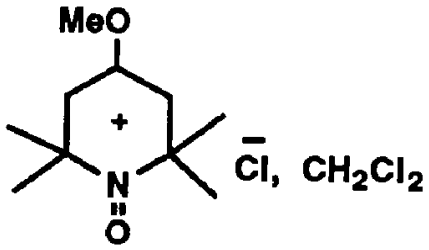
Oxidation of the ***primary alcoholic group to a carboxyl group*** in diols with primary and secondary hydroxyls is accomplished by **silver carbonate** [*377*]. Unfortunately, an extremely large excess of the reagent is needed. Similar results are obtained with a rather exotic oxidant, 4-methoxy-2,2,6,6-tetramethyl-1-oxopiperidinium chloride, which is prepared by treatment with chlorine of a stable radical, 4-methoxy-2,2,6,6-tetramethylpiperidin-1-oxyl. The compound oxidizes 1,4-butanediol to γ-butyrolactone in 100% yield (isolated yield 81%) and 1,5-pentanediol to δ-valerolactone in 61% yield (isolated yield 40%) [*995*] (equation 292).

292

[377] Ag_2CO_3, Celite, C_6H_6, reflux

n = 2, 24 equivalents of Ag_2CO_3, 6 h	90%
n = 3, 25 equivalents of Ag_2CO_3, 3 h	94%
n = 4, 23 equivalents of Ag_2CO_3, 2.5 h	96%

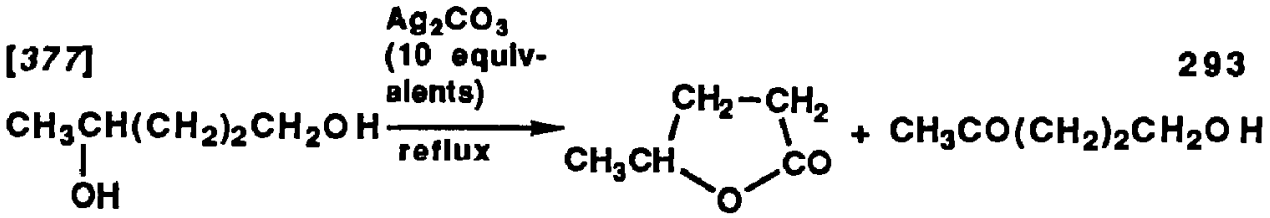
[995]



n = 2, 10 min	81%
n = 3, 30 min	40%

Diols with primary and tertiary hydroxyls also give lactones on treatment with silver carbonate, but diols with primary and secondary hydroxyls yield, besides lactones, hydroxy ketones, resulting from preferential oxidation at the secondary center (equation 293) [377].

[377]

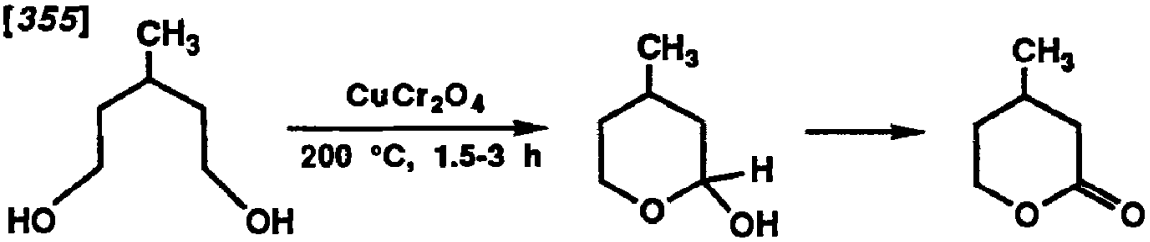


293

C_6H_6, 1 h	40.5%	49.5%
$CHCl_3$, 5 h	72%	8%

Because the conversion of primary diols into lactones is accomplished not only by oxidizing agents but also by ***catalytic dehydrogenation,*** it is likely that the reaction takes place stepwise via hemiacetal intermediates (equation 294) [355].

[355]

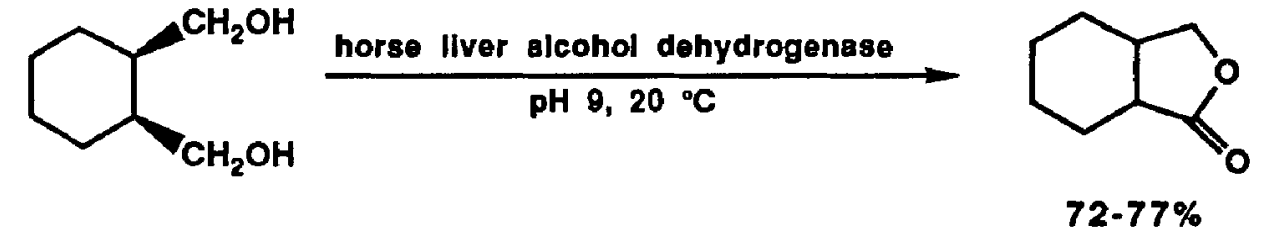


294

90-95%

A similar conversion of a bis-primary diol into a lactone is achieved by ***biochemical dehydrogenation*** (equation 295) [*1035*].

[*1035*] 295



72-77%

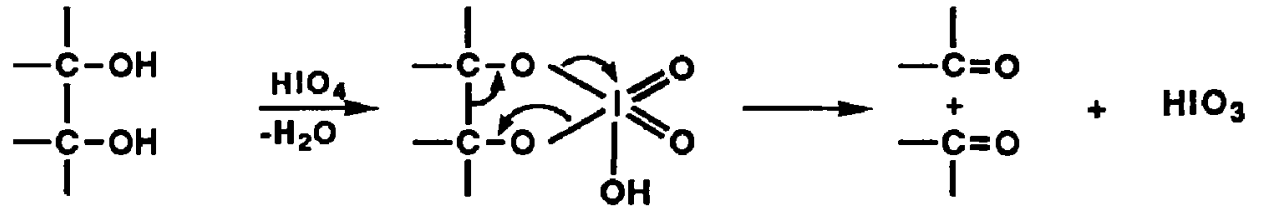
Cleavage of Vicinal Diols to Carbonyl Compounds

The carbon–carbon bond between two ***vicinal free hydroxyl groups*** can be cleaved to give ***two carbonyl compounds.*** This reaction is invaluable in the structure determination and transformation of sugars. In connection with hydroxylation of double bonds, it can be used as an alternative to the cleavage of double bonds by ozone [*953*] (*see* equation 305).

Two oxidants essentially dominate these oxidations: **lead tetraacetate** in organic solvents and **periodic acid** in aqueous media. On occasion, other oxidation reagents cause the cleavage of vicinal diols: **ceric ammonium nitrate** [*424*], *sodium bismuthate* [*482, 483*], *chromium trioxide* [*482, 588*], *potassium dichromate* with perchloric acid [*949*], *manganese dioxide* [*817*], and *trivalent* [*779, 789*] or *pentavalent* [*798*] *iodine compounds.*

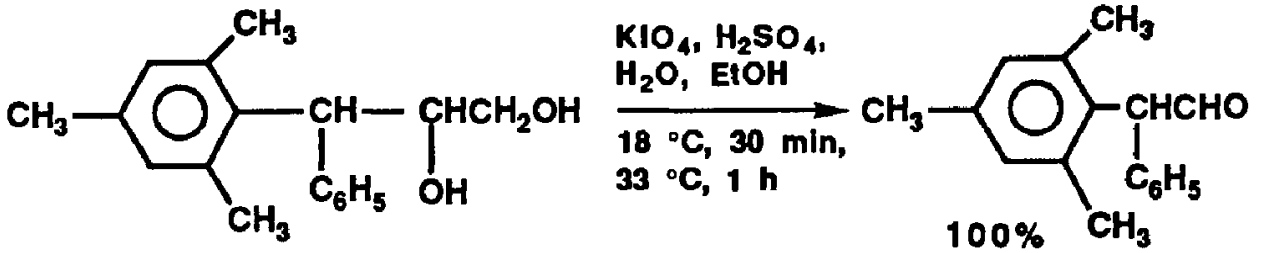
The mechanism of the cleavage of vicinal diols can be represented by the reaction of diols with **periodic acid, HIO_4 or H_5IO_6** (equation 296).

296



The cleavage of secondary straight-chain diols is a good source of aldehydes [*433, 448, 775, 789, 798*] (equations 297–299).

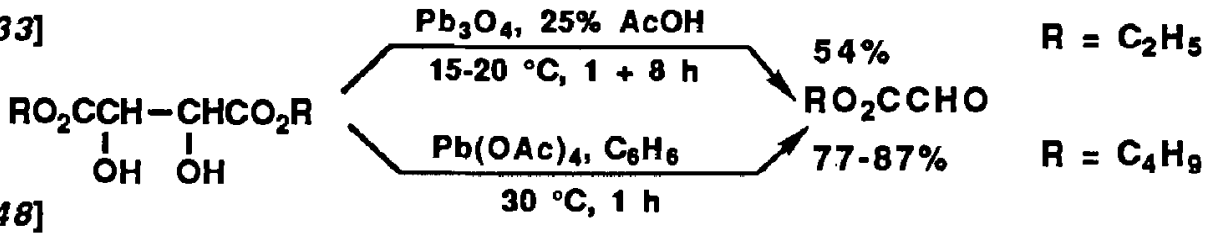
[*775*] 297



100%

298

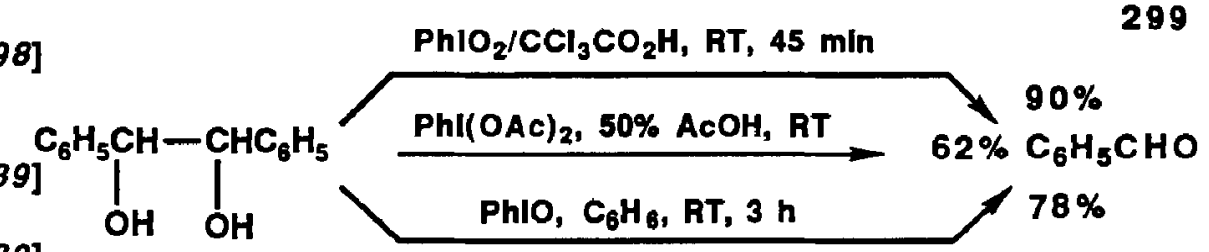
[433]



[448]

299

[798]



[789]

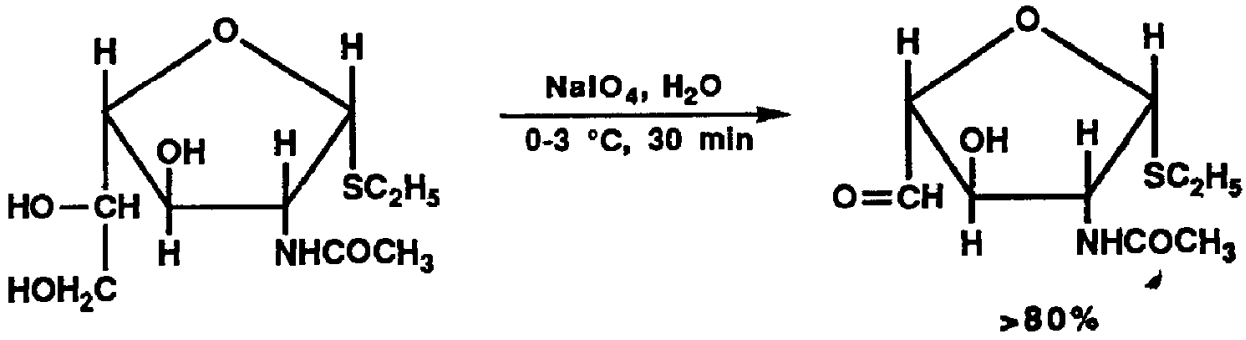
[789]

In saccharides, cleavage by **periodic acid** or **sodium periodate** occurs between any carbons possessing ***free*** hydroxylic groups. Thus glucosazone treated with periodic acid in aqueous ethanol at room temperature is degraded to the 1,2-bis(phenylhydrazone) of mesoxalaldehyde (propanonedial) in 85% yield [*759*].

With proper protection of certain hydroxyl groups, a desired degradation can take place. 3,4:5,6-Diisopropylidene-D-mannitol treated with sodium periodate in water at 0–5 °C for 30 min furnishes an 89% yield of 2,3:4,5-diisopropylidene-D-arabinose [*1153*]. Ethyl 2-acetamido-2-deoxy-1-thio-α-D-galactofuranoside yields 80% of a 4-formylthioacetalfuranoside on oxidation with an aqueous solution of metaperiodate at 0–3 °C (equation 300) [*762*].

[762]

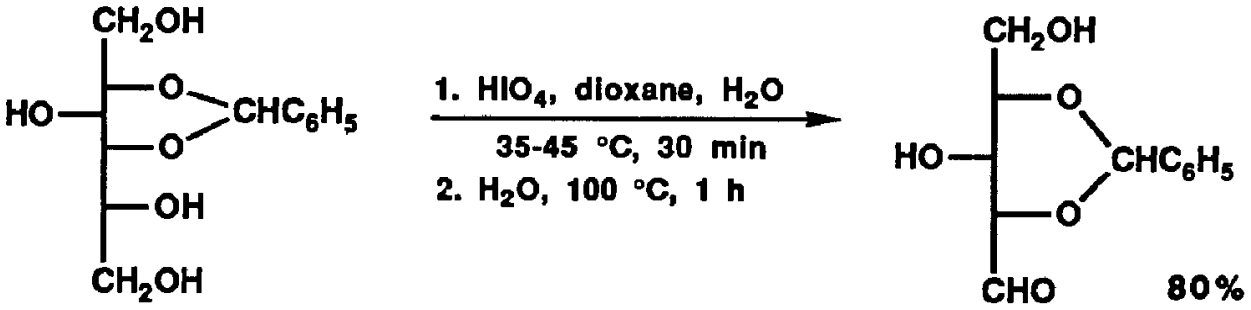
300



2,4-Benzal-D-sorbitol is degraded by periodic acid in aqueous dioxane at 35–45 °C to 2,4-benzal-L-xylose [*756*] (equation 301).

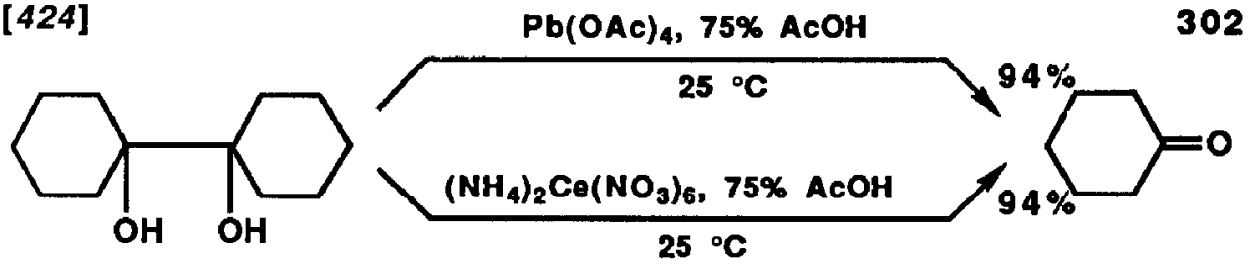
The rate of oxidation of diols with lead tetraacetate depends strongly on their configurations: *cis* diols react 200–3000 times faster than *trans* diols [*1154*], and the racemates of certain diols react about 15 times faster than the *meso* forms [*1154*]. The rates of oxidation of pinacols prepared from cyclopentanone, cyclohexanone, and cycloheptanone are in the ratio

[756] 301



1:314:62,000, evidently because of the increasing accessibility of the hydroxyls [*1154*]. Yields of oxidation with ceric ammonium nitrate are comparable with those of oxidation with lead tetraacetate (equation 302) [*424*].

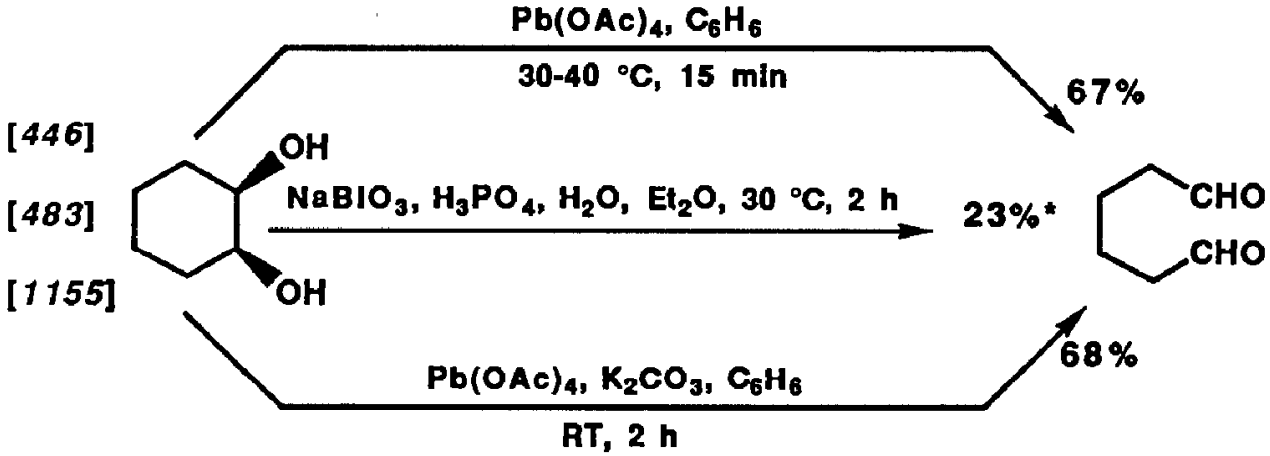
[424] 302



Cyclic vicinal diols are split to dialdehydes or diketones, depending on the atoms or groups bonded to the carbons carrying the hydroxyls. *cis*-1,2-Cyclohexanediol and **lead tetraacetate** yield adipic aldehyde [*446, 1155*].

The stereochemistry of the diols often affects the yields of carbonyl compounds. Thus, the oxidation of *cis*-1,2-cyclohexanediol with **sodium bismuthate** in aqueous phosphoric acid and ether at 30 °C gives only 23% of adipic aldehyde, whereas the *trans* isomer gives a 49% yield [*483*] (equation 303).

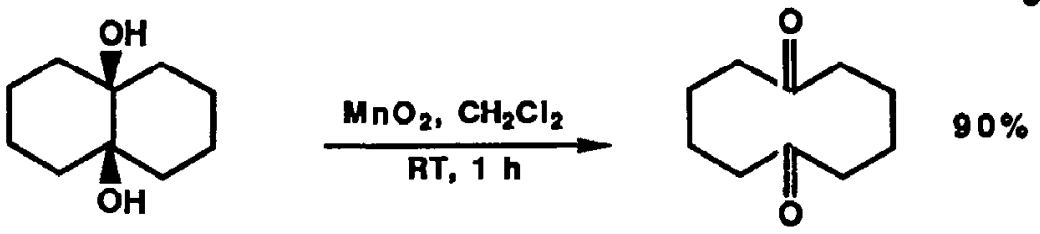
303



***The yield of adipic aldehyde from the *trans* isomer was 49%.**

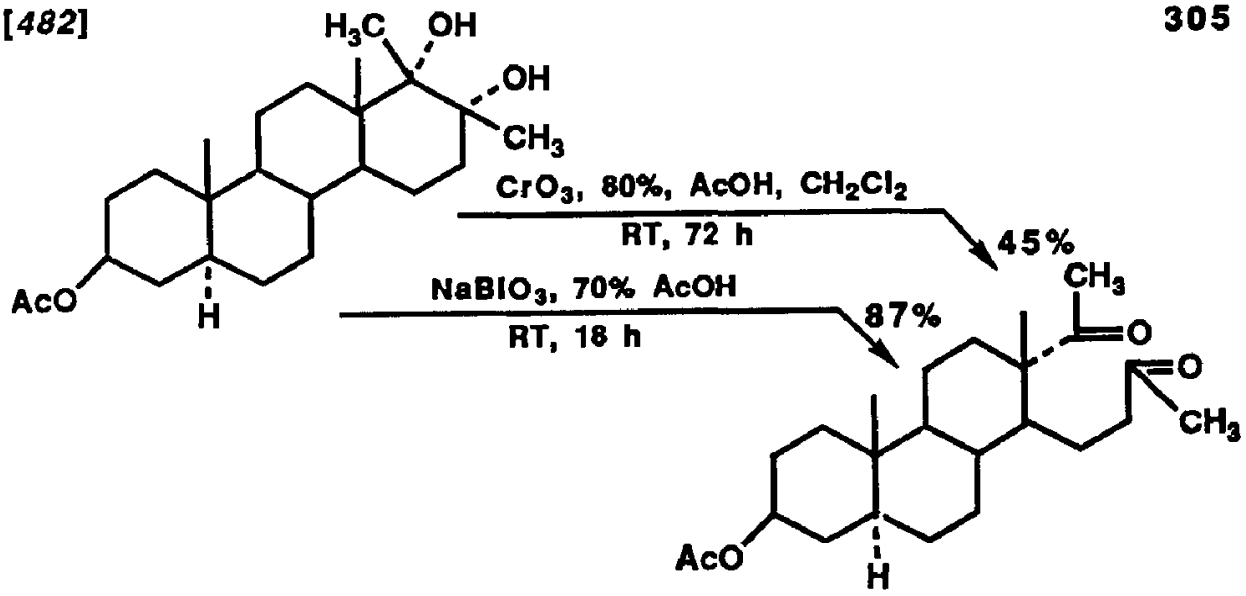
1,2-Dimethyl-1,2-cyclopentanediol, *potassium dichromate*, and aqueous perchloric acid yield, after 1.5–2 h at room temperature, up to 96% of 2,6-heptanedione [*949*]. *cis*-Decalin-9,10-diol produces cyclodecane-1,6-dione on treatment with *manganese dioxide* in 90% yield (equation 304) [*817*].

[817] 304



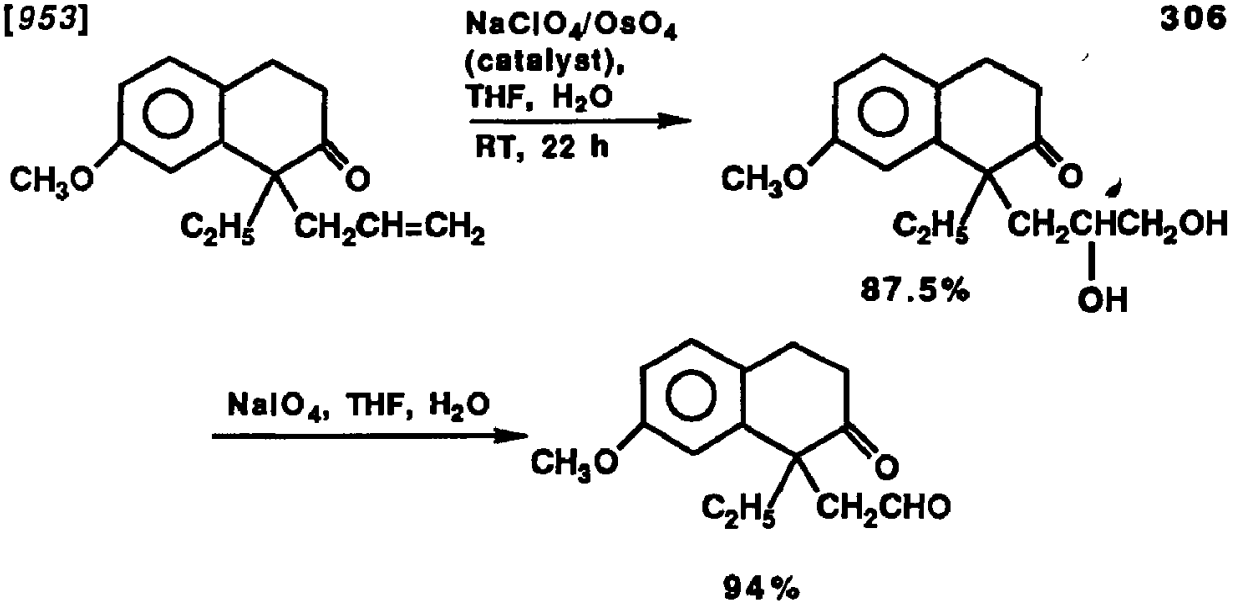
A mixture of *cis*- and *trans*-1,2-dimethylacenaphthene-1,2-diol dissolved in acetic acid is oxidized with *chromium trioxide* to 1,8-diacetylnaphthalene in 89% yield [*588*]. The treatment of 17β,17aβ-dimethyl-D-homoandrostane-3β,17α,17aα-triol 3β-acetate with *chromium trioxide* or with *sodium bismuthate* yields 3β-acetoxy-17,17a-dimethyl-17,17a-seco-homoandrostane-17,17a-dione (equation 305) [*482*].

[482] 305



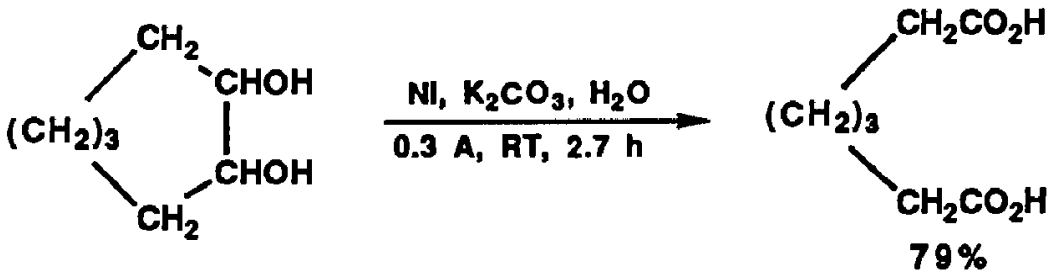
An example of a ***cleavage of a double bond*** by using a sequence of hydroxylation by **osmic acid** and the subsequent fission of the diol by **sodium periodate** is the conversion of 1-allyl-1-ethyl-7-methoxy-2-tetralone into 1-ethyl-1-formylmethyl-7-methoxy-2-tetralone (equation 306) [*953*].

[953] 306



Vicinal diols are also oxidized to ***carboxylic acids.*** 1,2-Dihydroxydecane in benzonitrile shaken with *oxygen* at atmospheric pressure at 100 °C in the presence of cobalt laurate as a catalyst furnishes, after 2 h, a 66% yield of pelargonic (nonanoic) acid [*69*]. Electrolysis at 20–30 °C in aqueous potassium carbonate with nickel electrodes in an undivided cell and a current of 0.3 A yields 74–84% of dicarboxylic acids from both *cis* and *trans* cyclic diols having six to eight carbons in the rings (equation 307) [*122*].

[*122*] **307**

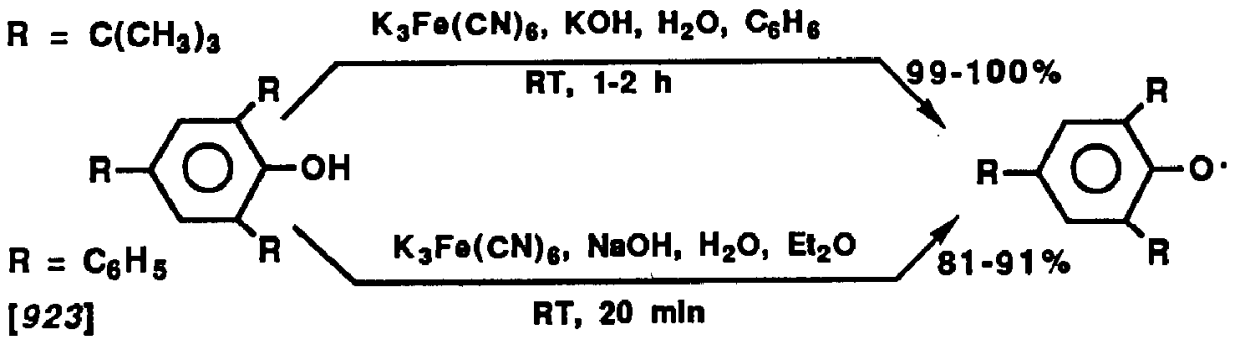


PHENOLS

Apart from ***dehydrogenative coupling*** in *para* and *ortho* positions [*1095*] (equation 44), phenols undergo ***oxidations to free radicals*** [*922, 923*], ***hydroxylation*** in the aromatic rings [*197, 1039*], and especially ***oxidation to quinones.*** Peroxy acids cleave the aromatic rings and give ***carboxylic acids*** [*249, 273, 274*]. Phenols containing side chains with double bonds conjugated with the aromatic rings are oxidized to phenol aldehydes [*86, 989*].

Potassium ferricyanide effects the one-electron oxidation of sterically hindered phenols to ***phenoxyl radicals*** (equation 308) [*922, 923*].

[*922*] **308**

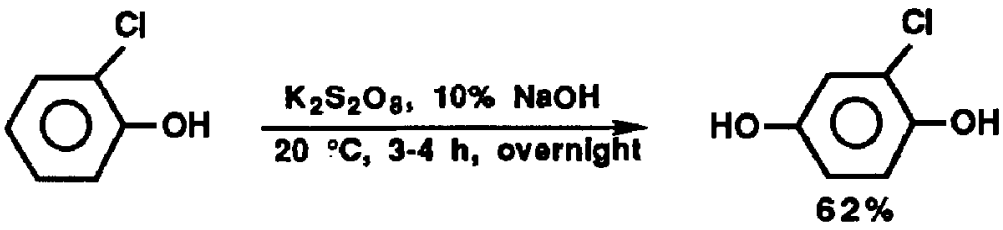


[*923*]

Hydroxylations in the aromatic rings take place in the *para* or *ortho* positions with respect to the hydroxylic group and are achieved by alkaline **persulfate *(Elbs hydroxylation)*** (equation 309) [*197*].

Another route to hydroxylated phenols is the application of mushroom **polyphenol oxidase** in chloroform. The primary products of oxidation,

[197]

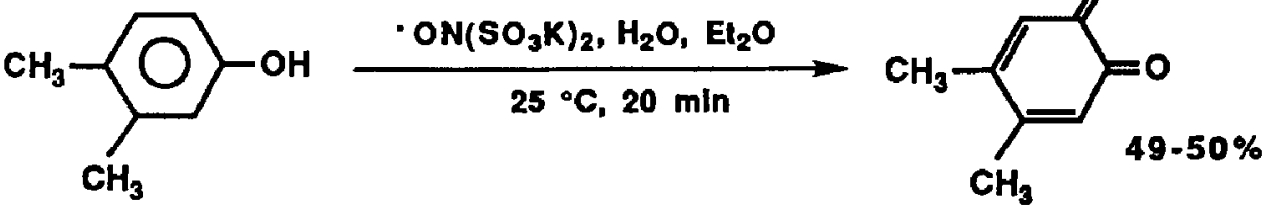


309

hydroxy phenols, are further oxidized to quinones, which can be easily reconverted into dihydroxy compounds by ascorbic acid [*1039*].

Conversion to ortho- and ***para-quinones*** is by far the most common oxidation of phenols. **Mercuric oxide** or **mercuric trifluoroacetate** [*383*], **lead dioxide** [*430*], **chromium trioxide** [*559*], **bromine** [*732*], **2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)** [*971*], **Fremy salt** [*487, 488, 489*], and **hydrogen peroxide** in the presence of **horseradish peroxidase** [*1038*] are the most widely used oxidants (equations 310 and 311).

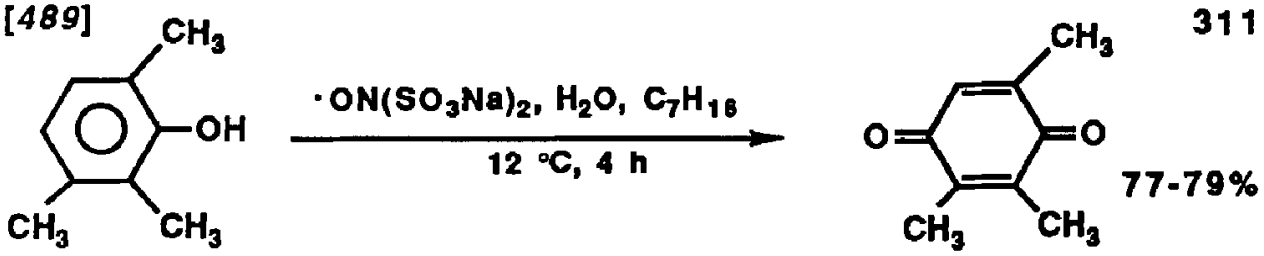
[488]



310

49-50%

[489]



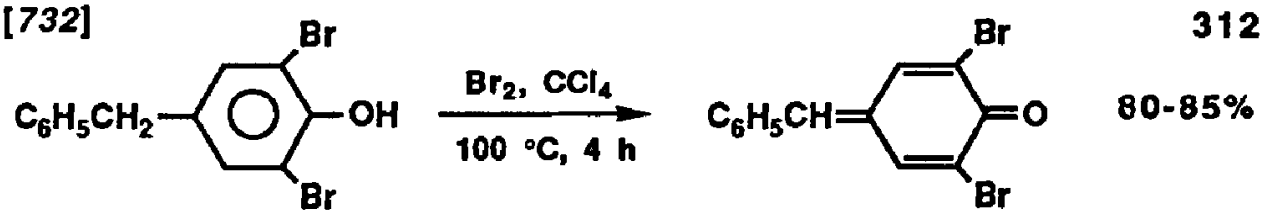
311

77-79%

Oxidations to *p*-benzoquinones occur even if the *para* position is occupied by a substituent [*383, 559, 732*] and even if an *ortho* position is free [*383*]. The substituent in the *para* position is either eliminated or modified.

2,4,6-Tribromo-*m*-cresol is oxidized by **chromium trioxide** in 70% acetic acid at 70–75 °C within 10 min to dibromo-*m*-toluquinone (3,5-dibromo-2-methyl-*p*-benzophenone) in 77% yield [*559*]. 2-Bromo-4-hydroxy-5-methoxybenzyl alcohol treated with Fremy salt at pH 6 at room temperature for 1 h gives an 84% yield of 2-bromo-5-methoxy-*p*-benzoquinone [*487*]. 4-Benzyl-2,6-dibromophenol, on oxidation with **bromine** in a sealed tube, yields 2,6-dibromophenylchinomethide [*732*] (equation 312). The oxidation of 2,5-di-*tert*-butyl-4-methoxyphenol with mercuric oxide or

[732]

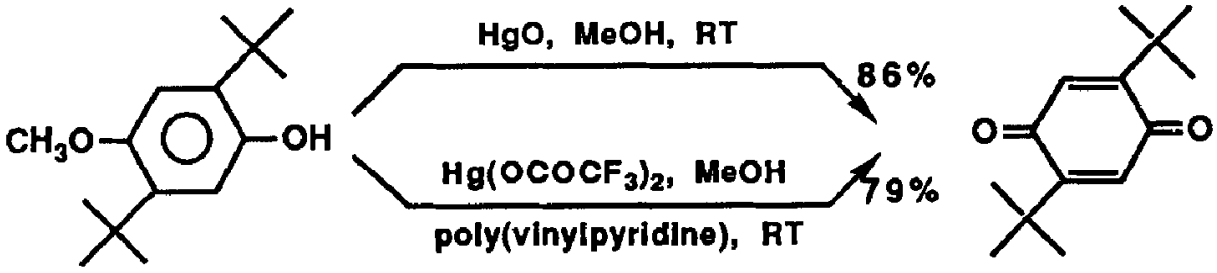


312

80-85%

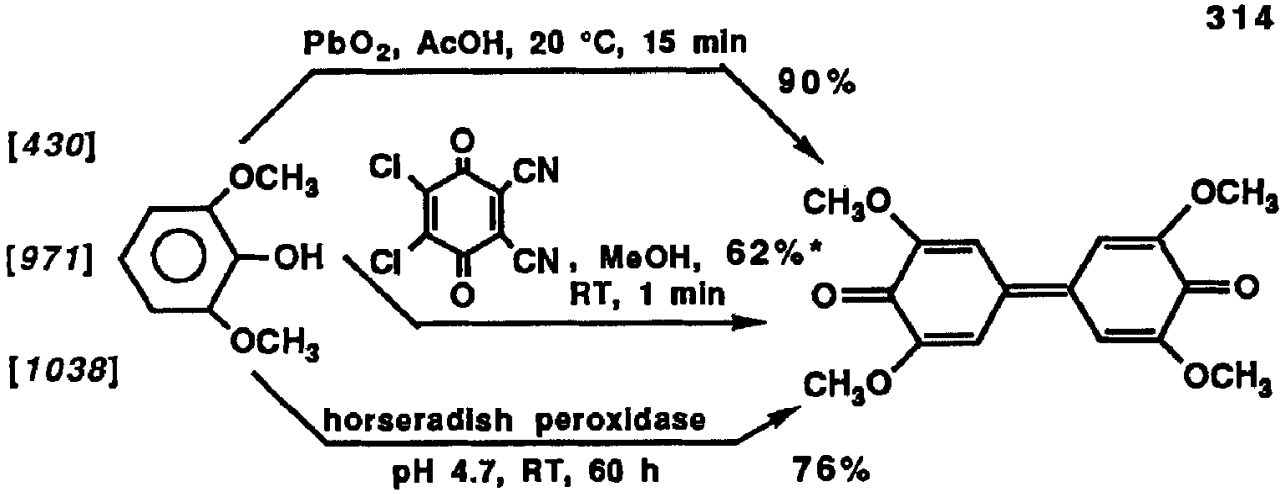
mercuric trifluoroacetate results in elimination of the methoxy group and formation of 2,5-di-*tert*-butyl-*p*-benzoquinone [*383*] (equation 313).

[*383*] 313



Sometimes the oxidation to quinones is accompanied by doubling of the molecule (equation 314) [*430, 971, 1038*].

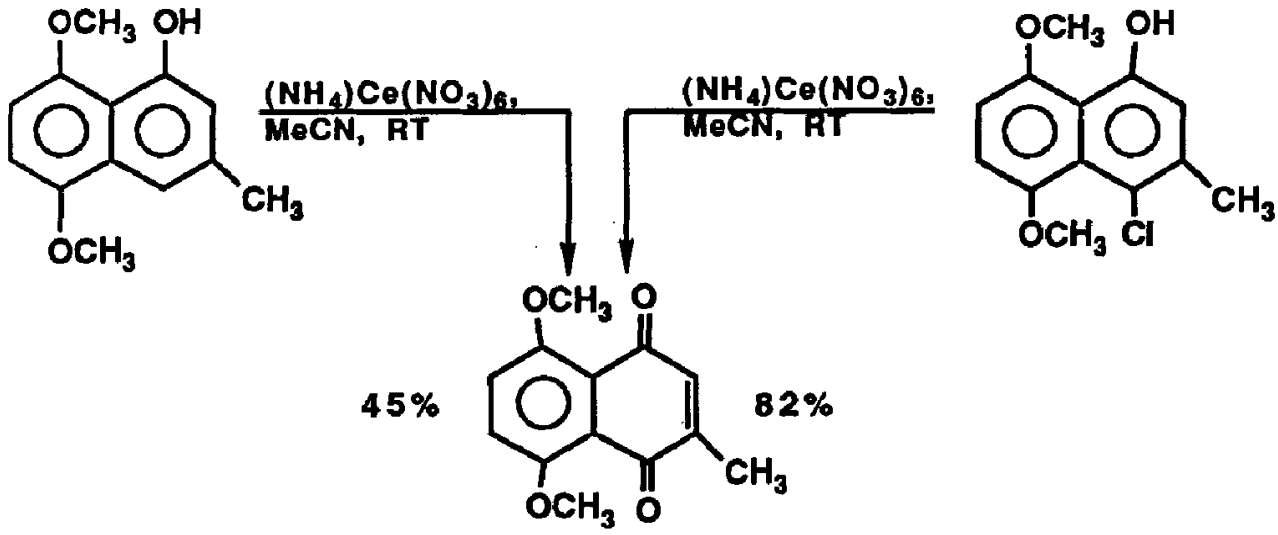
314



*In addition, a 13% yield of 2,6-dimethoxy-*p*-benzoquinone was obtained.

The oxidation of naphthols to 1,4-naphthoquinones is accomplished by ceric ammonium nitrate (equation 315) [*423*].

[*423*] 315



Oxidations to quinones are easier if two hydroxylic groups in *para* or *ortho* positions are present in the aromatic rings. A classical example is

the oxidation of hydroquinone and its substitution derivatives to *p*-benzoquinones by **mercuric oxide** [*384*], **ceric ammonium nitrate** [*422*], **lead dioxide** [*431*], *dinitrogen tetroxide* [*457*], *potassium chromate* [*615*], **sodium dichromate** [*636*], **sodium chlorate** [*719*], *barium manganate* [*833*], **ferric chloride** [*907*], **ferric sulfate** [*914*], and others (equation 316). These oxidations are usually very fast.

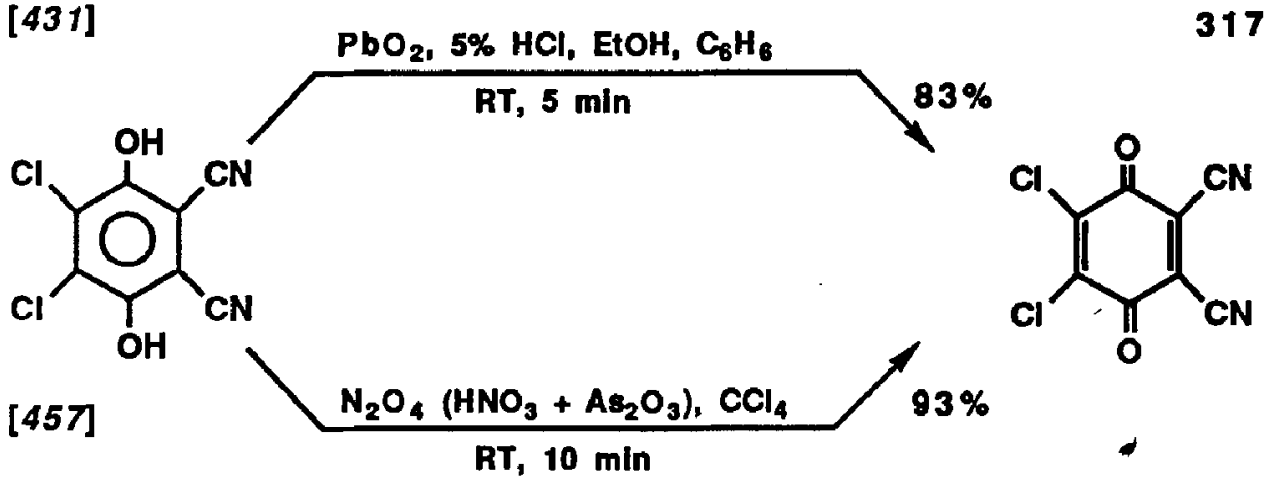
316

[*422*]	$(NH_4)_2Ce(NO_3)_6$, 75% aqueous MeCN, RT, 2 min	83%
[*636*]	$Na_2Cr_2O_7$, H_2SO_4, H_2O, 20-30 °C, 30-45 min	76-81%
[*719*]	$NaClO_3/V_2O_5$, H_2SO_4, H_2O, 40 °C, 4 h	92-96%
[*833*]	$BaMnO_4$, C_6H_6, reflux 20 min	75%

Oxides of silver [*171, 368*], **mercury** [*384*], **lead** [*431*], and nitrogen [*457*] react at room temperature. 2,5-Hydroquinone diacetic acid and mercuric oxide in ether, after several hours at room temperature, give *p*-benzoquinone-2,5-diacetic acid in 90% yield [*384*].

The dehydrogenating agent 2,3-dichloro-5,6-dicyano-*p*-benzoquinone **(DDQ)** is prepared from 2,3-dichloro-5,6-dicyanohydroquinone by oxidation with lead dioxide [*431*] or dinitrogen tetroxide [*457*] (equation 317).

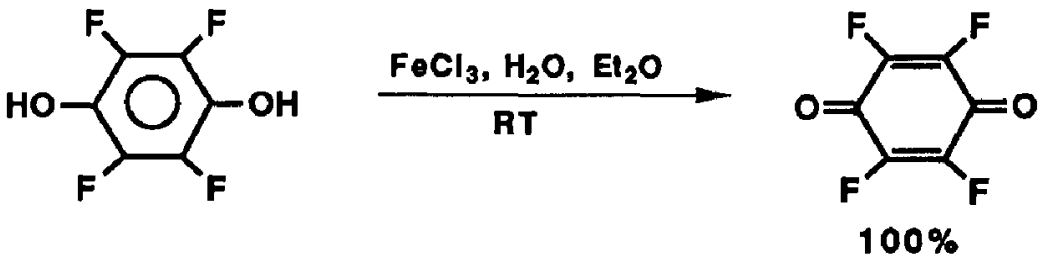
[*431*] 317



Oxidants especially suitable for the preparation of quinones are salts of trivalent iron. Bromo-*m*-xyloquinone (2-bromo-3,5-dimethyl-*p*-benzoquinone) is obtained in 84% yield by steam distillation of 2-bromo-3,5-dimethylhydroquinone with **ferric sulfate** and dilute hydrochloric acid [*914*]. The treatment of 2-mercaptohydroquinone with 2 N ferric chloride in ethanol at room temperature gives a quantitative yield of *p*-benzoquinone disulfide [*907*]. Just shaking halogenated hydroquinones with an

aqueous solution of **ferric chloride** and ether results in up to quantitative yields of the halogenated *p*-benzoquinones (equation 318) [*1156*].

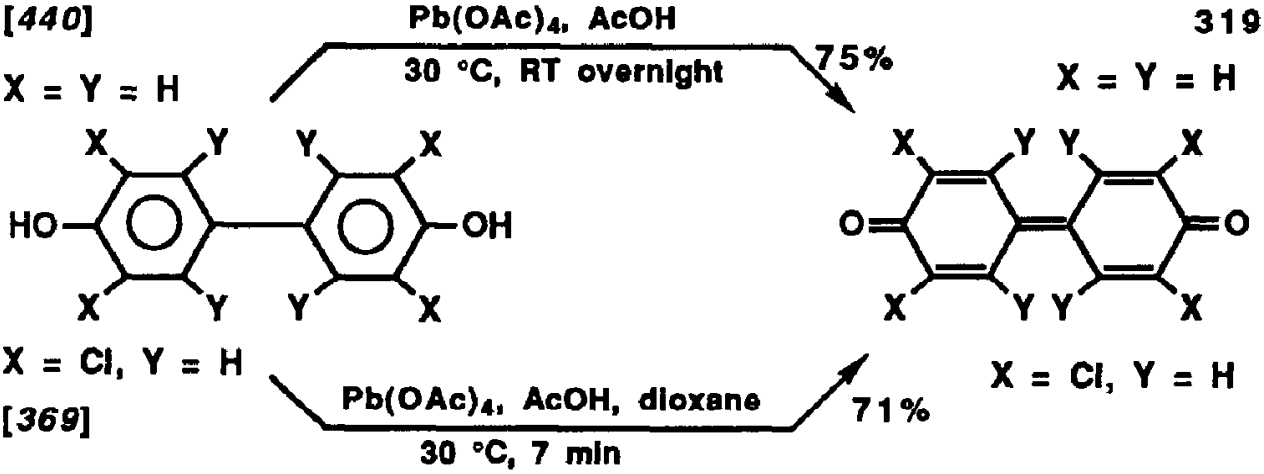
[*1156*]



318

p,p'-Dihydroxybiphenyls are converted with **lead tetraacetate** into diphenoquinones (equation 319) [*369, 440*]. *p,p'*-Dihydroxystilbene is oxidized to stilbene quinone with **silver oxide** [*369*].

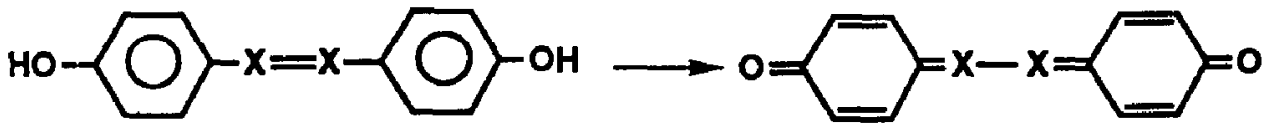
[*440*]



319

p,p'-Dihydroxyazobenzene (azophenol) is transformed into quinoneazine with **lead dioxide or silver oxide.** Anhydrous sodium sulfate is added to remove the water of reaction [*368*] (equation 320).

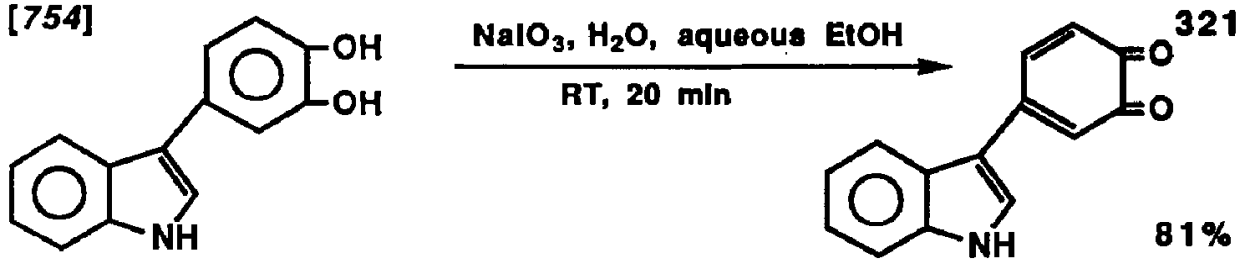
320



[*368*]	X = N:	Ag_2O, Na_2SO_4, Et_2O, RT, 1 h	90%
[*369*]	X = CH:	Ag_2O, Me_2CO, reflux 1 h	40-45%
[*368*]	X = N:	PbO_2, Na_2SO_4, Et_2O, RT	70%

Silver oxide and sodium sulfate are frequently used to oxidize 1,2-dihydroxy aromatic compounds to *ortho*-quinones. Phenanthrene furnishes, after being shaken for 15 s with the mixture in ether at room temperature, a 65% yield of 3,4-phenanthrenequinone [*171*]. Another oxidant used to prepare *ortho*-quinones is **sodium iodate** (equation 321) [*754*].

[754]



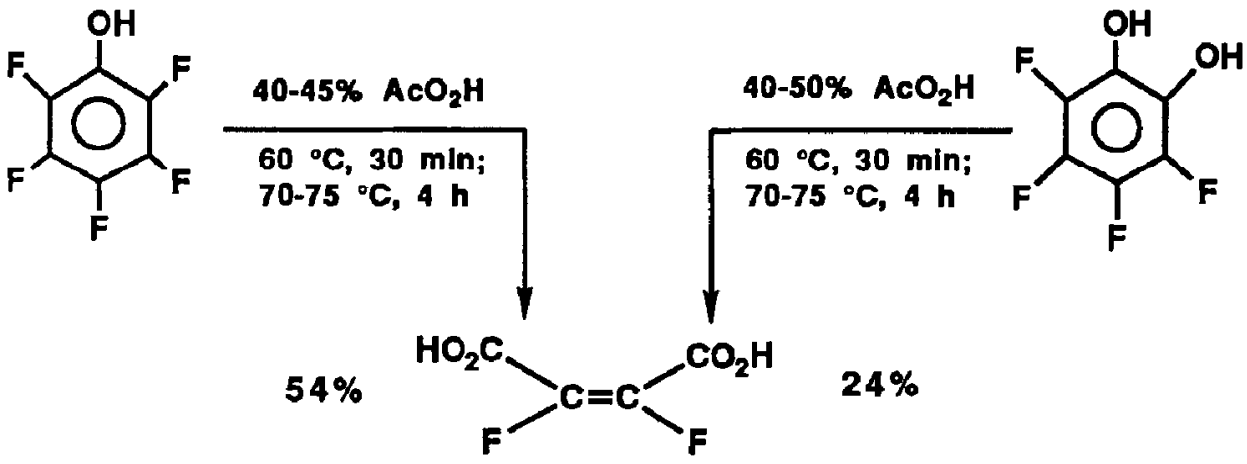
321

81%

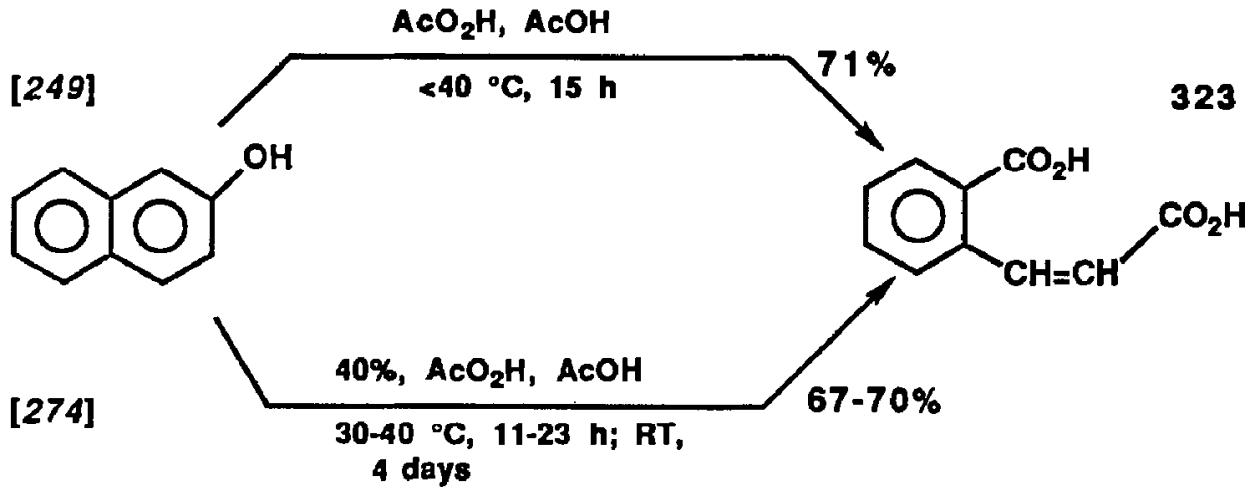
Organic peroxy acids oxidize phenols and *ortho*-dihydroxy aromatic compounds with the concomitant opening of the rings to dicarboxylic acids (equations 322 and 323) [*249, 273, 274*]. The reaction is very exothermic and requires external cooling.

[273]

322



[249]



323

[274]

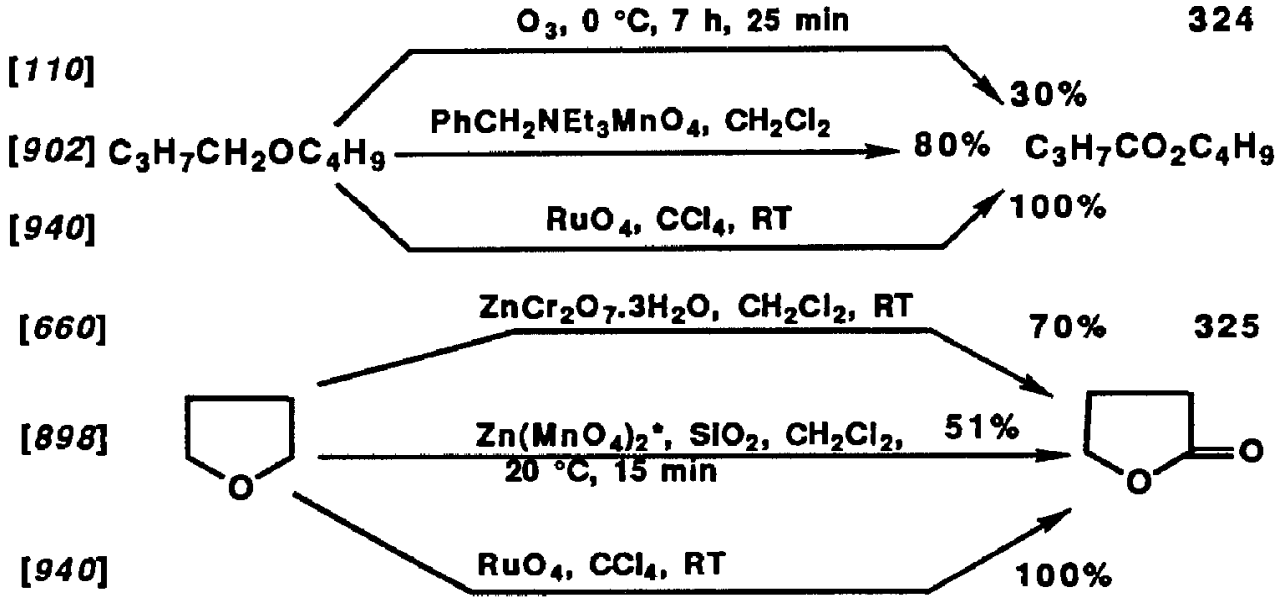
ETHERS

Ethers having α-hydrogens form ***hydroperoxides***, which are highly explosive in the dry state. Hydroperoxide formation is facilitated by light. Although no absorption of oxygen was noticed when tetrahydrofuran and dioxane were exposed to oxygen at 12 and 15 °C for 30 min under irradiation [*44*], it is strongly recommended to store diethyl ether, other dialkyl ethers,

tetrahydrofuran, and dioxane in metal containers or dark-glass bottles and away from direct light.

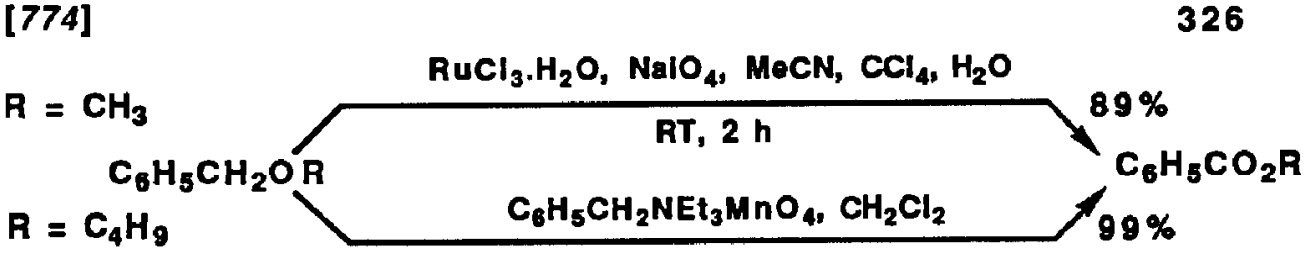
In the presence of benzophenone as a sensitizer and under irradiation with ultraviolet light, a 46% yield of tetrahydrofuran α-hydroperoxide is obtained when **oxygen** is bubbled through tetrahydrofuran at 12 °C for 28.5 h. Dioxane, methyl butyl ether, diisopropyl ether, dibutyl ether, and diisoamyl ether, under similar conditions, give α-hydroperoxides in yields of 10, 15, 12, 6, and 8%, respectively, based on the reacted ethers [*44*].

By far the most important oxidation of ethers is their ***conversion into esters and lactones.*** Only a few reagents are capable of such a transformation: **ozone** [*110*], **chromium trioxide** [*539, 586*], **zinc dichromate** [*660*], **potassium permanganate** [*855*], **zinc permanganate** [*898*], **benzyltriethylammonium permanganate** [*902*], and **ruthenium tetroxide** (which gives the best yields) [*774, 940*] (equations 324 and 325).



***Support on silica gel is essential for such work, because zinc permanganate is a potentially dangerous reagent [*898*].**

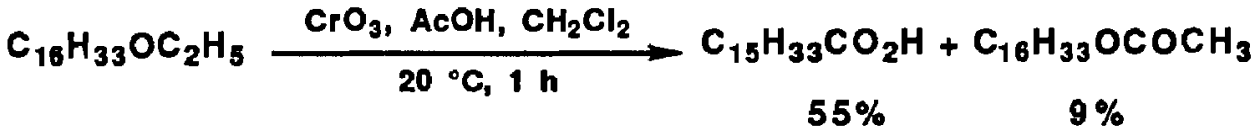
In nonsymmetrical ethers, the oxidation of various groups takes place preferentially in the following sequence: benzyl > phenylalkyl > primary alkyl > secondary alkyl > methyl [*902*] (equation 326).



The oxidation products of mixed ethers may differ when different oxidants are used. Whereas **ruthenium tetroxide** oxidizes benzyl methyl

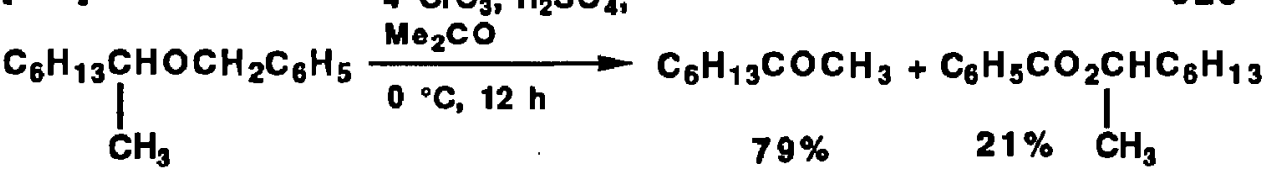
ether to methyl benzoate in 89% yield [*774*], **chromium trioxide** in acetic acid converts hexadecyl methyl ether into palmitic acid and hexadecyl formate and hexadecyl ethyl ether into palmitic acid and hexadecyl acetate (equation 327) [*539*].

[*539*] 327



In secondary benzyl ethers, cleavage to the ketone usually predominates over the formation of alkyl benzoates (equation 328) [*586*].

[*586*] 328

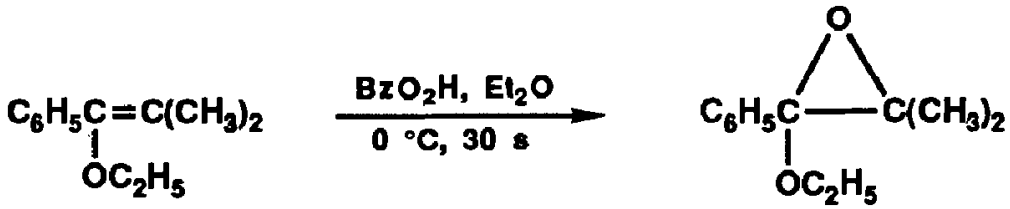


A similar cleavage of benzyl methyl ethers takes place when a solution of equimolar amounts of **bromine in carbon tetrachloride** is added dropwise to a refluxing solution of the ether in carbon tetrachloride under irradiation. Benzyl methyl ether gives a 77% yield of benzaldehyde, and benzhydryl methyl ether gives a 36% yield of benzophenone [*731*].

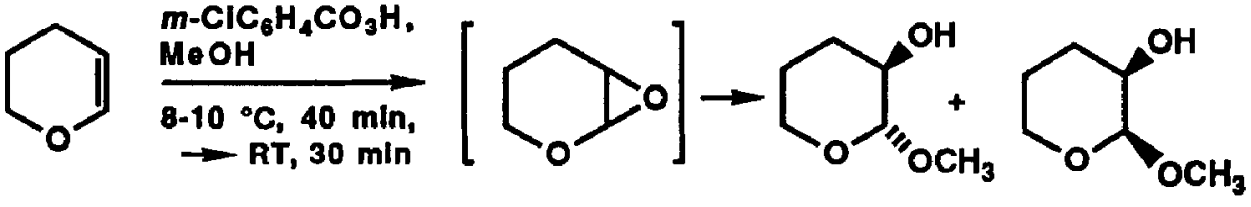
Oxidation of Unsaturated Ethers at Multiple Bonds

Vinyl ethers and ***peroxy acids*** give primarily ***epoxides***, which can be isolated [*297*] or which can react further with the reaction medium [*314*] (equations 329 and 330).

[*297*] 329

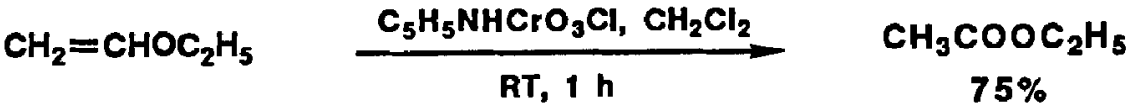


[*314*] 330

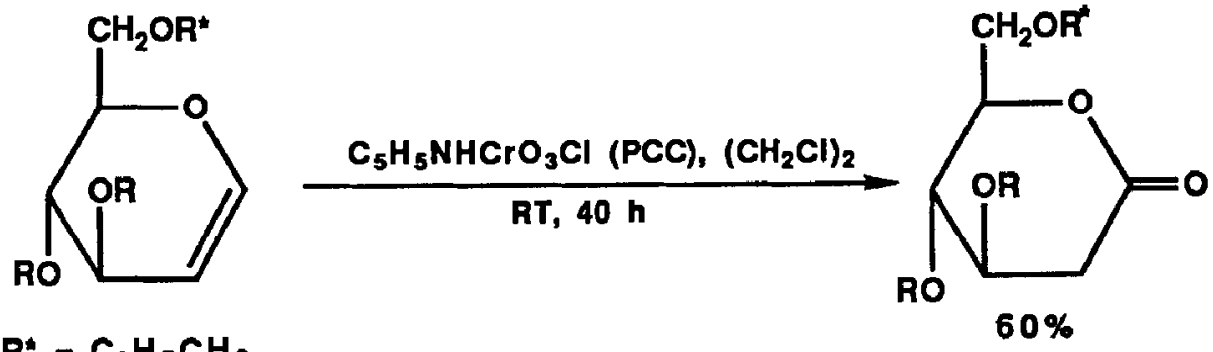


Stronger oxidants convert ***enol ethers*** into ***esters or lactones.*** Ethyl vinyl ether added to a suspension of **pyridinium chlorochromate (PCC)** in dichloromethane at room temperature furnishes ethyl acetate in 75% yield after 1 h (equation 331) [*608*]. Glucals produce lactones (equation 332) [*609*].

[*608*] 331



[*609*] 332

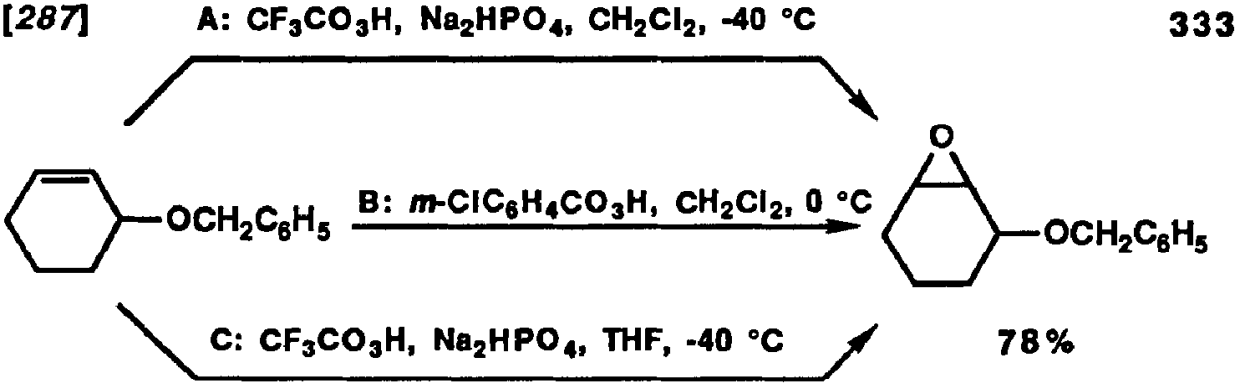


R* = $C_6H_5CH_2$

Even stronger oxidative agents such as dilute **nitric acid** transform 3,4-dihydro-2*H*-pyran at 100 °C into glutaric acid in 70–75% yields [*1158*].

Allylic ethers are ***epoxidized*** stereoselectively to predominantly *syn* products with **peroxytrifluoroacetic acid** in dichloromethane. In tetrahydrofuran, *anti* epoxidation prevails. Also, ***m*-chloroperoxybenzoic acid** in dichloromethane gives a higher proportion of *anti*-addition products (equation 333) [*287*].

[*287*] 333



	syn/*anti*
A	1.4:1
B	1:2.7
C	1:5

Selenium dioxide converts ***aryl and aralkyl allyl ethers*** into aldehydes and the corresponding alcohols. Allyl benzyl ether refluxed with selenium dioxide in acetic acid and dioxane for 1 h gives a 50% yield of benzyl

alcohol and acrolein. Cinnamyl methyl ether is converted into methanol and cinnamaldehyde in 66% yield (equation 334) [*511*].

[*511*]

$$C_6H_5CH{=}CHCH_2OCH_3 \xrightarrow[\text{reflux 1 h}]{SeO_2,\ AcOH,\ \text{dioxane}} CH_3OH + C_6H_5CH{=}CHCHO \quad 66\% \qquad (334)$$

Alkyl acetylenyl ethers treated with iodosobenzene in dichloromethane in the presence of 1% of tris(triphenylphosphine)ruthenium dichloride for 15 min at room temperature furnish keto esters in 59–70% yields (equation 335) [*786*].

[*786*]

$$C_6H_5C{\equiv}C\text{-}OC_2H_5 \xrightarrow[\text{RT, 15 min}]{PhIO/(Ph_3P)_3RuCl_2,\ CH_2Cl_2} C_6H_5COCO_2C_2H_5 \quad 70\% \qquad (335)$$

A special category of ethers are ***trimethylsilyl ethers.*** Trimethylsilyl ethers of primary alcohols, on treatment with Jones reagent, give acids [*590*]. On treatment with *N*-bromosuccinimide under irradiation, trimethylsilyl ethers yield esters [*744*]. Secondary alkyl trimethylsilyl ethers are converted into ketones by oxidation with both reagents [*590, 744, 981*]. Oxidation with Jones reagent is regiospecific: the 2-*tert*-butyldimethylsilyl 11-*tert*-butyldiphenylsilyl ether of 2,11-dodecanediol is oxidized only in the sterically less hindered position [*590*]. Trimethylsilyl ethers of tertiary alcohols are degraded by periodic acid to carboxylic acids with shorter chains [*755*] (equations 336–339).

Trimethylsilyl enol ethers treated with chromyl chloride in dichloromethane at −78 °C furnish α-hydroxy ketones in 62–82% yields [*676*]. The same products are obtained by oxidation with *m*-chloroperoxybenzoic acid

[*744*]

$$C_5H_{11}CH_2OSi(CH_3)_3 \xrightarrow[0\ ^\circ C,\ 5\ h]{NBS,\ CCl_4,\ h\nu} C_5H_{11}CO_2CH_2C_5H_{11} \quad 80\% \qquad (336)$$

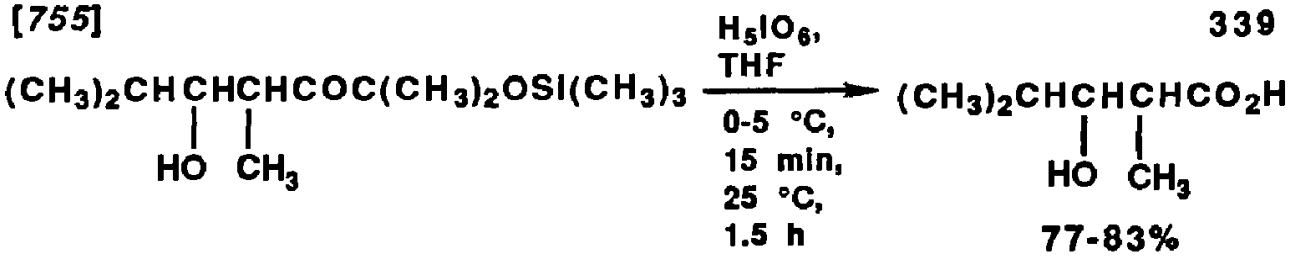
[*744*]

$$C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HOSi(CH_3)_3 \xrightarrow[\text{RT, 3.5 h}]{NBS,\ C_5H_5N,\ h\nu} C_6H_5COCH_3 \quad 76\% \qquad (337)$$

[*590*]

$$t\text{-}BuMe_2SiO\underset{\displaystyle CH_3}{\underset{|}{C}}H(CH_2)_8\underset{\displaystyle CH_3}{\underset{|}{C}}HOSiPh_2Bu\text{-}t \xrightarrow[\text{acetone, 0 °C, 1 h}]{\text{Jones reagent, KF}} CO(CH_2)_8\underset{\displaystyle CH_3}{\underset{|}{C}}HOSiPh_2Bu\text{-}t \quad 90\% \qquad (338)$$

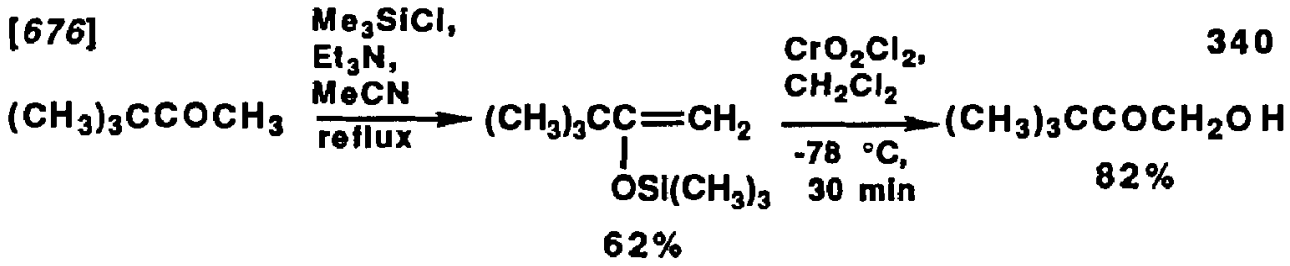
[755]



339

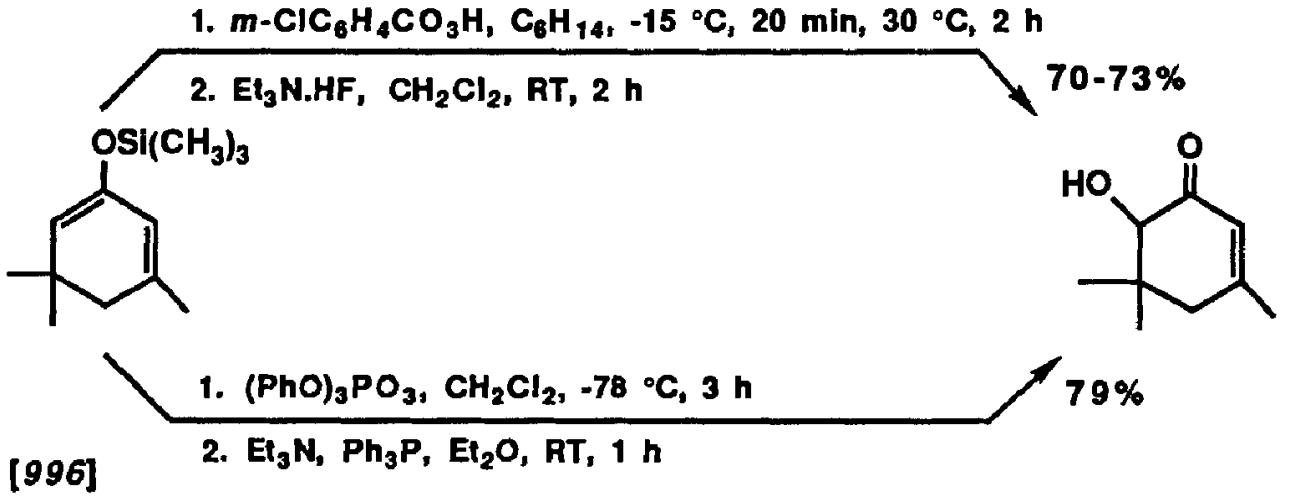
[1159] or with triphenyl phosphite ozonide followed by triphenylphosphine [996] (equations 340 and 341).

[676]



340

[1159]

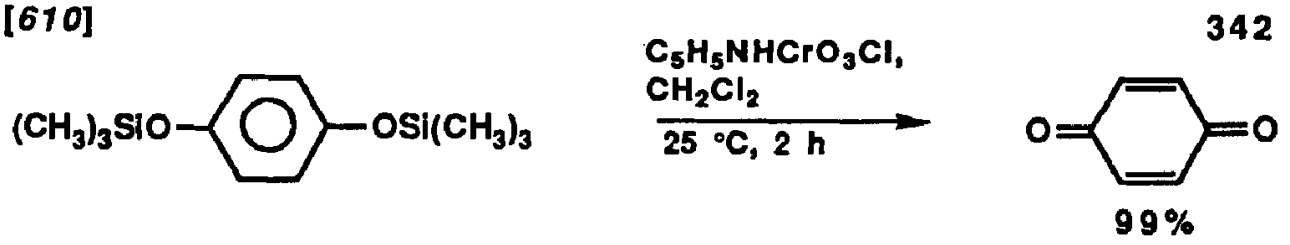


341

[996]

The bis(trimethylsilyl) ether of hydroquinone is oxidized by pyridinium chlorochromate to *p*-benzoquinone (equation 342) [610].

[610]

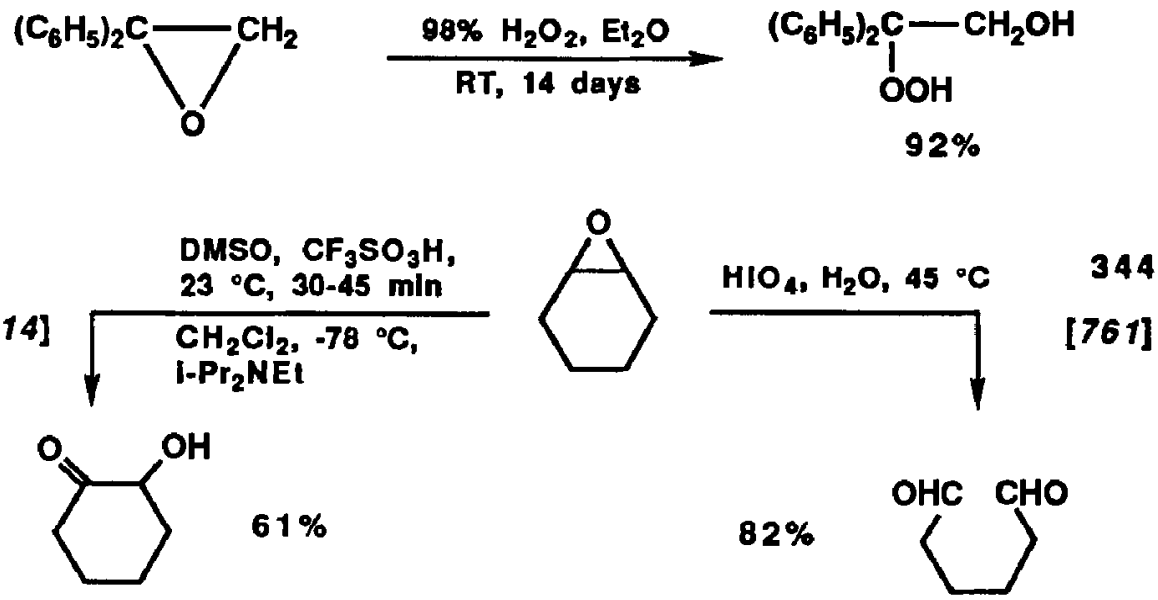


342

Oxidation of Epoxides (Oxiranes)

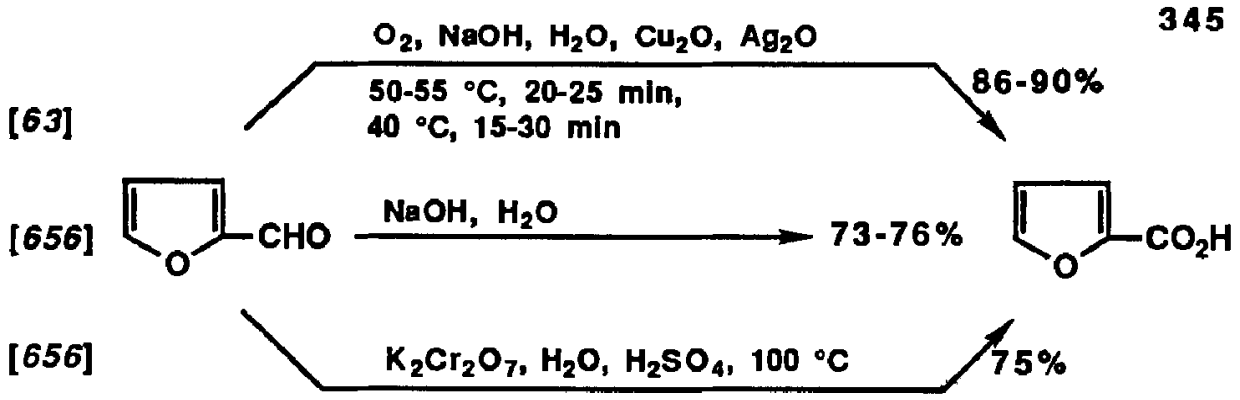
The oxidative cleavage of epoxides with **hydrogen peroxide** gives vicinal hydroxy hydroperoxides [178]. With **dimethyl sulfoxide** in the presence of trifluoromethanesulfonic acid and diisopropylethylamine, epoxides are converted into α-hydroxy ketones [1014], and with **periodic acid**, dicarbonyl compounds are formed [761] (equations 343 and 344).

[178]



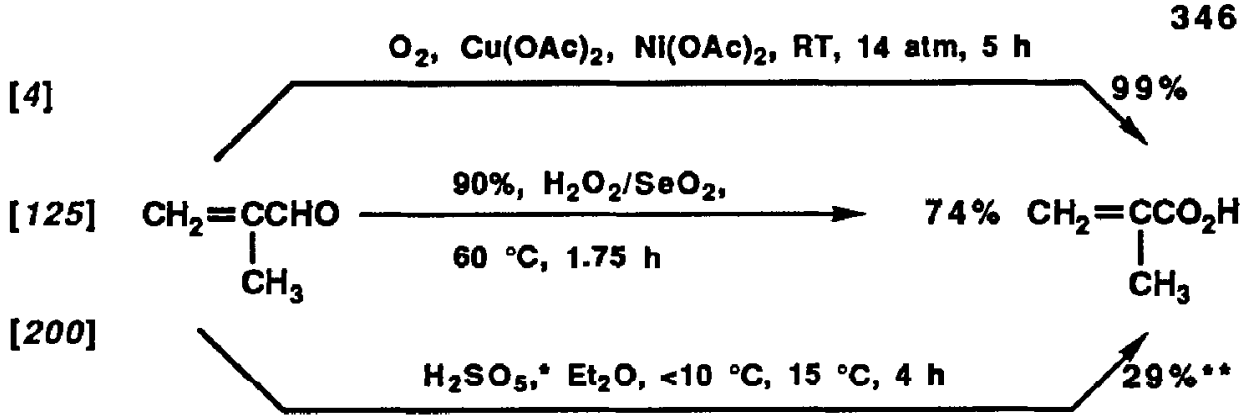
ALDEHYDES

Aldehydes are easily oxidized to carboxylic acids; the reaction sometimes occurs spontaneously on contact of the aldehyde with air. Benzaldehyde, for example, when left in an open bottle, is slowly converted into benzoic acid at room temperature. Such oxidation is accelerated if the aldehyde is exposed to **oxygen,** especially under irradiation with ultraviolet light. The same effect is achieved by using catalysts, such as salts or oxides of metals. Oxygen in the presence of copper acetate and nickel acetate converts methacrolein into methacrylic acid in 99% yield at 62% conversion at room temperature and a pressure of 14 atm [*4*]. Platinum catalyzes the oxidation of sugars to aldonic acids [*5, 6*] (*see* equation 366). Furfural, when treated with oxygen in aqueous alkaline solutions in the presence of cuprous oxide and silver oxide at 50–55 °C, is converted into furoic acid in high yields [*63*]. The same acid is obtained as a product of the Cannizzaro reaction [*656*] and by heating with potassium dichromate and sulfuric acid [*656*] (equation 345).



Aldehydes are transformed into carboxylic acids by **hydrogen peroxide** and its derivatives. In the presence of selenium dioxide as a catalyst, acrolein is oxidized to acrylic acid in 90% yield on treatment with a 12% solution of hydrogen peroxide in *tert*-amyl alcohol at 40 °C for 3 h [*125*]. Methacrolein is converted into methacrylic acid by 90% hydrogen peroxide in the presence of selenium dioxide at 60 °C [*125*] or by peroxysulfuric acid [*200*] (equation 346).

346

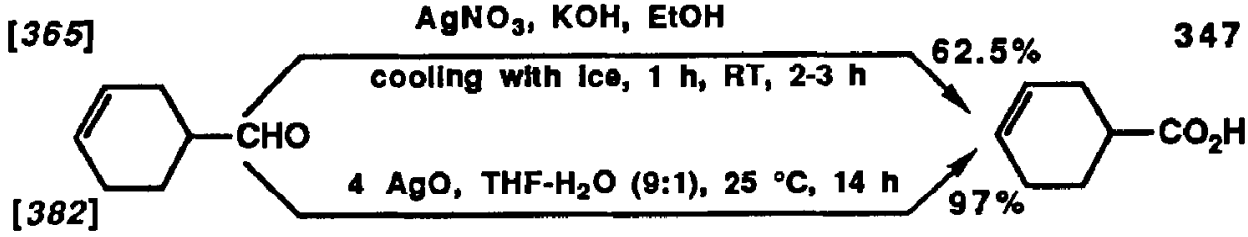


***H_2SO_5 is prepared either by adding ammonium persulfate to 85% sulfuric acid below 15 °C, or by adding 90% hydrogen peroxide to concentrated sulfuric acid below 15 °C, and keeping the mixture for 2 h at room temperature.**

****When methanol was used as the solvent, a 91-97% yield of methyl methacrylate was obtained [*602*].**

Potassium peroxymonosulfate ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) oxidizes benzaldehyde in chloroform and dilute sulfuric acid to benzoic acid at room temperature within 2 days in a 70% yield [*205*].

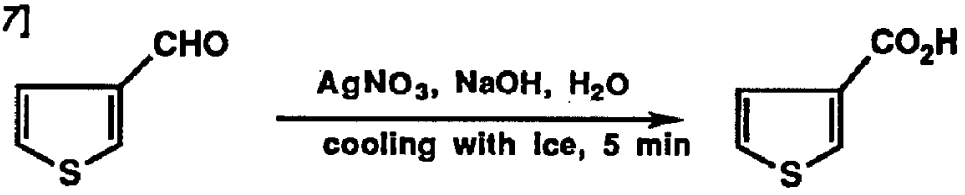
The reagent of choice for the conversion of aldehydes into carboxylic acids is **silver oxide,** which is often prepared in situ from silver nitrate in alkaline medium [*365*]. Enanthol heated with silver oxide affords enanthoic acid [*77*]. 3-Cyclohexene-1-carboxaldehyde (1,2,3,6-tetrahydrobenzaldehyde) gives a 62.5% yield of the carboxylic acid on treatment with silver nitrate and ethanolic potassium hydroxide at room temperature [*365*] (equation 347).



Other examples of oxidations using silver oxide in alkaline media are variations of the preceding reaction [*206, 362, 366, 367*] (equation 348).

Aldehydes are also oxidized to carboxylic acids in high yields by *argentic oxide* at room temperature in aqueous tetrahydrofuran. However,

[367]



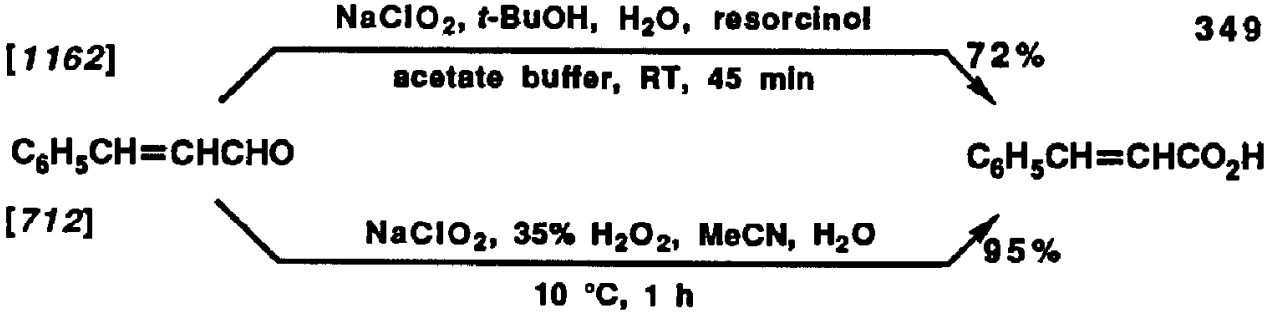
348

95-97%

this method has the disadvantage of requiring large excesses of the fairly expensive oxidant (4–10 equivalents) [*382*] (equation 347).

Some aldehydes are oxidized to acids by very strong oxidizing agents. β-Chloropropionaldehyde gives a 60–65% yield of β-chloropropionic acid on treatment with fuming **nitric acid** for 25 min at 30–35 °C [*470*]. Vanillin is converted into vanillic acid in 89–95% yield by heating for 5 min with a mixture of *sodium hydroxide and potassium hydroxide* at 180–195 °C [*1160*]. Furfural furnishes a 75% yield of furoic acid by heating for 30–45 min with **potassium dichromate** and aqueous sulfuric acid at 100 °C [*656*] (equation 345). Heating enanthal with sulfur and ammonium sulfide affords only a 46% yield of enanthoic acid [*1161*].

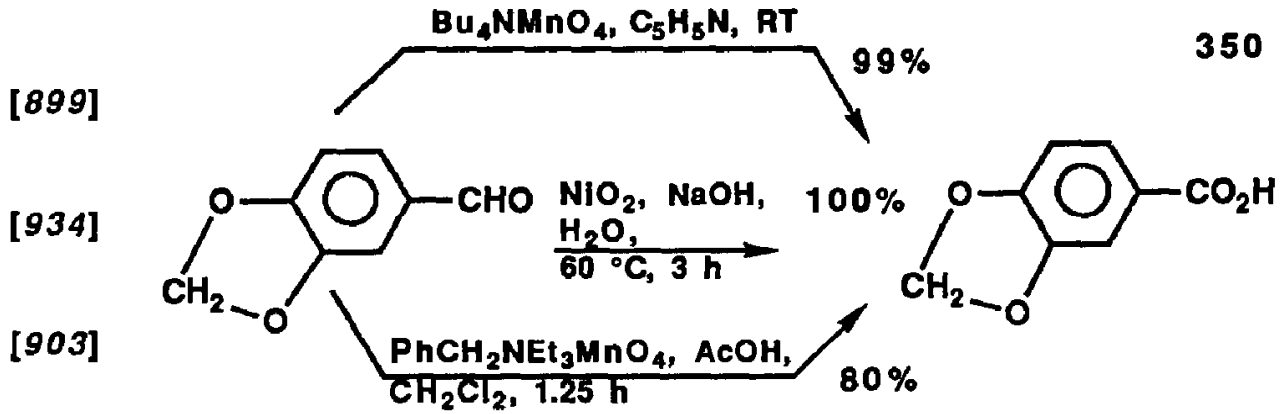
An oxidant very suitable for the conversion of aldehydes into acids is **sodium chlorite** [*712*]. Because the byproducts of the reaction, NaOCl and ClO_2, are themselves oxidants and could decrease yields, scavengers such as hydrogen peroxide [*712*], sulfamic acid [*1162*], or resorcinol [*1162*] are added to the solution of the substrate and sodium chlorite in water, aqueous acetonitrile, or *tert*-butyl alcohol. Under such conditions, unsaturated aldehydes can be oxidized to unsaturated acids without destruction of the double bond (equation 349).



349

The oxidation of aromatic aldehydes to carboxylic acids with **manganese dioxide** is somewhat surprising because manganese dioxide is used to oxidize toluenes to benzaldehydes. The transformation of benzaldehyde into benzoic acid is achieved in 75% yield by refluxing with manganese dioxide in petroleum ether for 24 h [*813*].

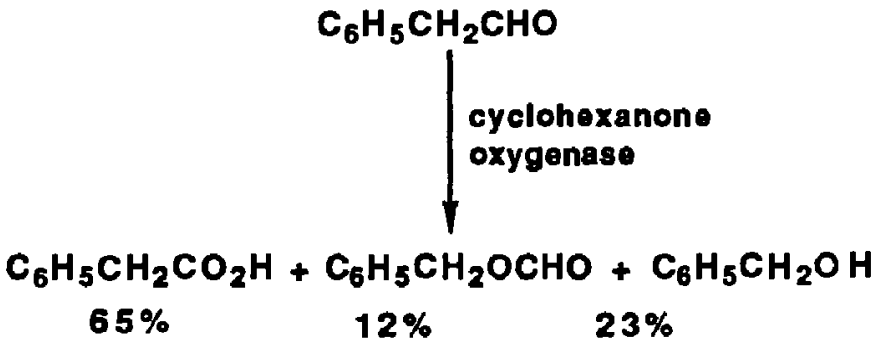
On the other hand, **potassium permanganate** is frequently used to prepare carboxylic acids from both aliphatic [*868*] and aromatic aldehydes [*885*]. High yields of carboxylic acids are also obtained by oxidation with **tetrabutylammonium permanganate** [*899*] or **benzyltriethylammonium permanganate** [*903*] (equation 350). Recently, doubts about the safety of work with quaternary ammonium permanganates have been raised [*901*].



The unusual oxidant **nickel peroxide** converts aromatic aldehydes into carboxylic acids at 30–60 °C after 1.5–3 h in 58–100% yields [*934*]. The oxidation of aldehydes to acids by pure ruthenium tetroxide results in very low yields [*940*]. On the contrary, **potassium ruthenate,** prepared in situ from ruthenium trichloride and potassium persulfate in water and used in catalytic amounts, leads to a 99% yield of *m*-nitrobenzoic acid at room temperature after 2 h. Another oxidant, iodosobenzene in the presence of tris(triphenylphosphine)ruthenium dichloride, converts benzaldehyde into benzoic acid in 96% yield at room temperature [*788*]. The same reaction with a 91% yield is accomplished by treatment of benzaldehyde with osmium tetroxide as a catalyst and cumene hydroperoxide as a reoxidant [*1163*].

The biochemical oxidation of phenylacetaldehyde with **cyclohexanone oxygenase** produces phenylacetic acid, in addition to smaller amounts of benzyl formate and benzyl alcohol (equation 351) [*1034*].

[*1034*]



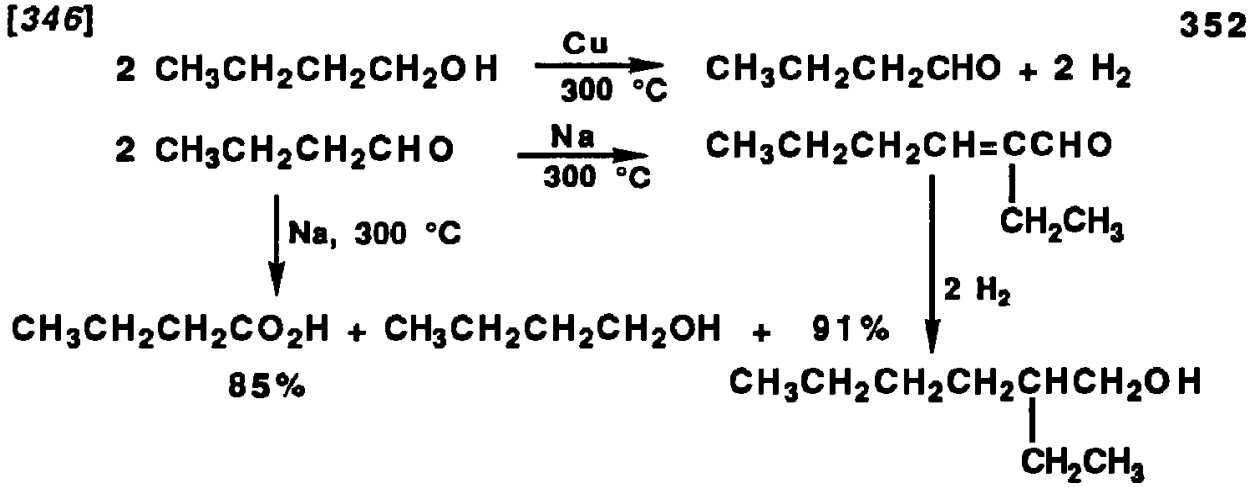
351

The oxidation of aldehyde groups in sugars is accomplished by ***Acetobacter suboxydans*** [*1040*] (*see* equation 368).

The conversion of aldehydes into carboxylic acids as a result of disproportionation occurs in the Cannizzaro and Guerbet reactions. The ***Cannizzaro reaction*** takes place when aromatic aldehydes are treated with alkali hydroxides and results in the formation of carboxylic acids and the corresponding alcohols. Yields of the acids can therefore be 50% at a maximum. The reaction is catalyzed by silver [*363*] and silver oxide [*362*], which is sometimes generated in situ from silver nitrate [*364*] (*see* equation 357).

The ***Guerbet reaction*** is a complex combination of oxidation of a primary alcohol to an aldehyde, aldol condensation followed by dehydration, hydrogenation of the α,β-unsaturated aldehyde to a saturated alcohol, and oxidation of the aldehyde to an acid. The reaction is catalyzed by sodium and copper bronze and is carried out by heating the mixture in an autoclave at 270–300 °C and 50–60 atm for 6–10 h (equation 352).

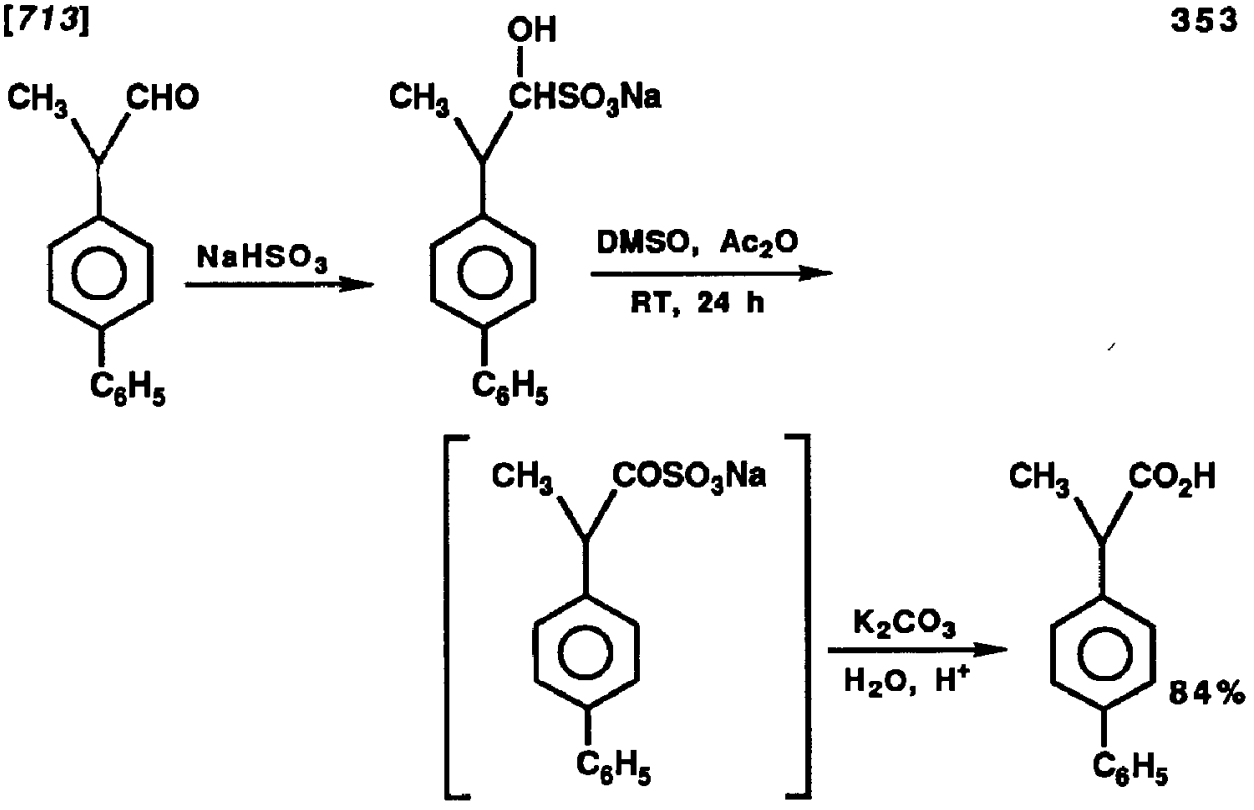
[*346*] 352



Because the purpose of the reaction is to prepare a branched saturated alcohol, the Guerbet reaction cannot be considered a method of oxidation [*346*].

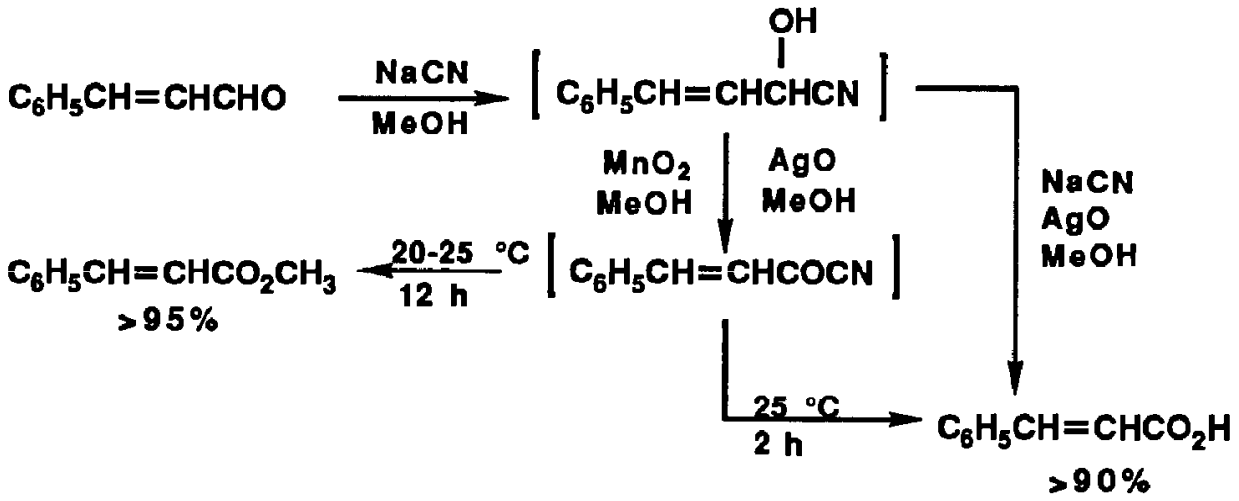
An elegant method for the gentle and selective oxidation of aldehydes to carboxylic acids is the oxidation of the ***aldehyde–bisulfite*** addition compound by **dimethyl sulfoxide.** Depending on the workup of the reaction mixture, the acid, its ester, or its amide can be prepared at room temperature (equation 353) [*713*].

[*713*] 353



A somewhat similar oxidation takes place when an aldehyde is treated with **sodium cyanide** and **manganese dioxide** or **argentic oxide** [*382*]. The reaction is assumed to proceed through a cyanohydrin, which is oxidized to an α-keto nitrile. The α-keto nitrile in turn is converted into an acid (by argentic oxide in methanol) or an ester (by manganese dioxide in methanol). The method is especially suited for α,β-unsaturated aldehydes [*382*] (equation 354).

[*382*] 354



Examples of other oxidations of aldehydes to carboxylic acids are given in equations 355–357.

EXAMPLES OF OXIDATION OF ALDEHYDES TO CARBOXYLIC ACID

$C_6H_{13}CHO \longrightarrow C_6H_{13}CO_2H$ 355

[*77*]	Ag_2O, 10% NaOH, 95 °C, 7 h; HNO_3, 70 °C, → RT, 1 h	97.5%
[*1161*]	$(NH_4)_2S$, S, C_5H_5N, 140 °C, 5 h	46%
[*868*]	$KMnO_4$, H_2SO_4, H_2O, 15-20 °C	76-78%
[*940*]	RuO_4, CCl_4, RT	30%

$C_6H_5CHO \longrightarrow C_6H_5CO_2H$ 356

[*1163*]	$PhCMe_2OOH$, OsO_4 catalyst, 0 °C, 1.5 h	91%
[*205*]	2 $KHSO_5.KHSO_4.K_2SO_4$, H_2SO_4, H_2O, $CHCl_3$, RT, 2 days	70%
[*1162*]	$NaClO_2$, *t*-BuOH, resorcinol, pH 4, RT, 18 h	88%
[*788*]	2 PhIO, $(Ph_3P)_3RuCl_2$, CH_2Cl_2, RT, 24 h	96%
[*813*]	MnO_2, petroleum ether, reflux 24 h	75%
[*903*]	$PhCH_2NEt_3MnO_4$, AcOH, RT, 1.25 h	84%
[*934*]	NiO_2, NaOH, H_2O, 30 °C, 1.5 h	94%
[*940*]	RuO_4, CCl_4, RT	33%

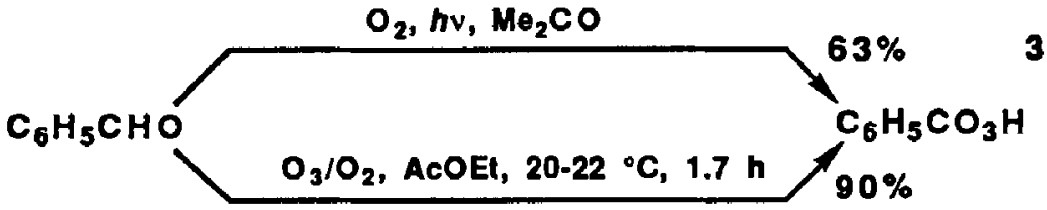
357

[366]	Ag_2O, NaOH, H_2O, reflux 2 h	50%
[206]	Ag_2O, NaOH, H_2O, 55-60 °C, 10 min	83-95%
[364]	$AgNO_3$, NaOH, H_2O, 55-85 °C	100%
[363]	NaOH/Ag, reflux 1 h	50%
[1160]	NaOH, KOH, 180-195 °C, 5 min	89-95%
[885]*	$KMnO_4$, 10% KOH, 70-80 °C, 40-45 min + 1 h	90-96%* (78-84% pure)
[1162]	$NaClO_2$, H_2NSO_3H, H_2O, RT, 1 h	84%

*The reference shows the reaction conditions for the oxidation of piperonal [3,4-(methylenedioxy)benzaldehyde].

Oxidation of aldehydes to peroxy acids is accomplished by passing **oxygen** under irradiation through a solution of benzaldehyde in acetone [*1164*] or by passing a current of ozone-containing oxygen through a solution of benzaldehyde in ethyl acetate at 20–22 °C for 1–2 h [*112*] (equation 358).

[1164]



[112]

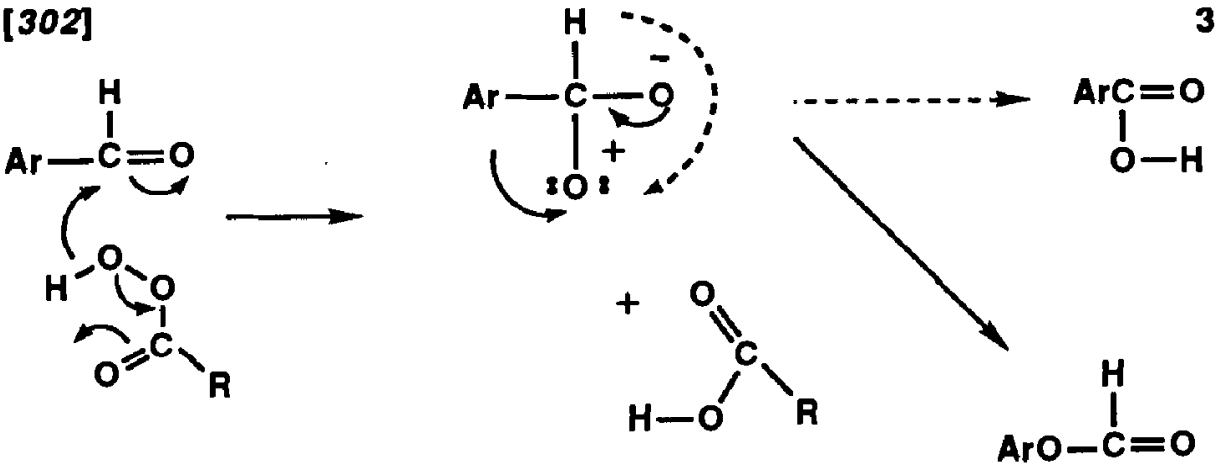
358

Aromatic aldehydes, especially those containing hydroxyl or alkoxy groups, undergo ***oxidation to aryl formates (Dakin reaction)*** on treatment with hydrogen peroxide or peroxy acids [*302*]. Because the formyl esters of phenols are easily hydrolyzed, the formates may not even be intercepted, and phenols are isolated as the oxidation products [*302*]. The reaction may be interpreted as a nucleophilic attack by the oxygen of the peroxy compound at the carbon of the carbonyl group, followed by migration of one of the substituents of the carbonyl group.

Hydride migration results in carboxylic acids (the usual reaction). Migration of the aryl group gives aryl formates but practically only when electron-releasing groups are present in the benzene ring in the *ortho* or *para* positions with respect to the aldehyde group (equation 359) [*302*].

Oxidations of aromatic aldehydes to formyl esters of phenols and to phenols are accomplished by **hydrogen peroxide** [*171, 172, 173*] or by **organic peroxy acids** such as **peroxyacetic acid** [*259*], **peroxybenzoic acid** [*302*], and ***m*-chloroperoxybenzoic acid** [*315, 318*] (equations 360–363).

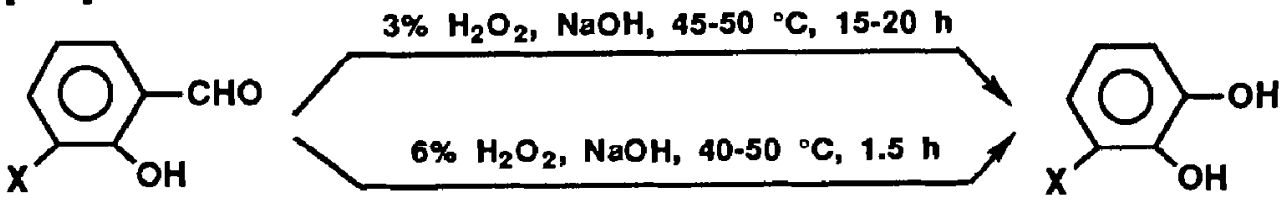
[302]



359

360

[172] X = H

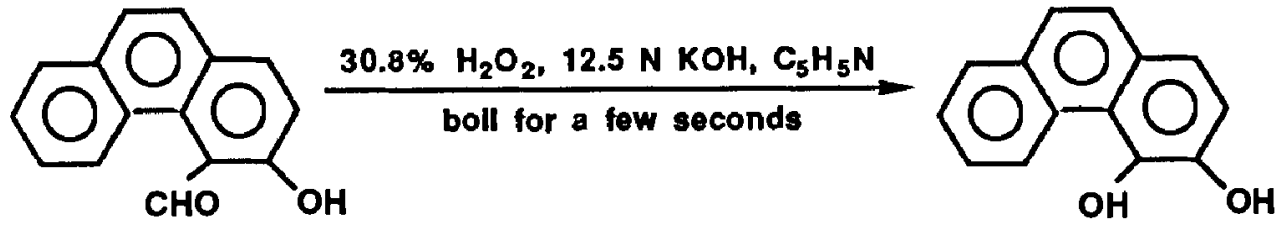


69-73%

68-80%

[173] X = MeO

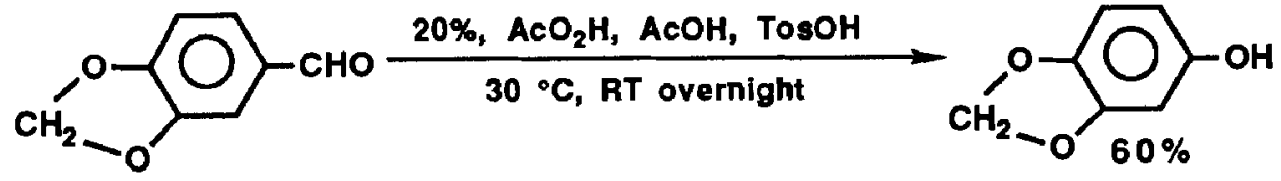
[171]



361

80%

[259]

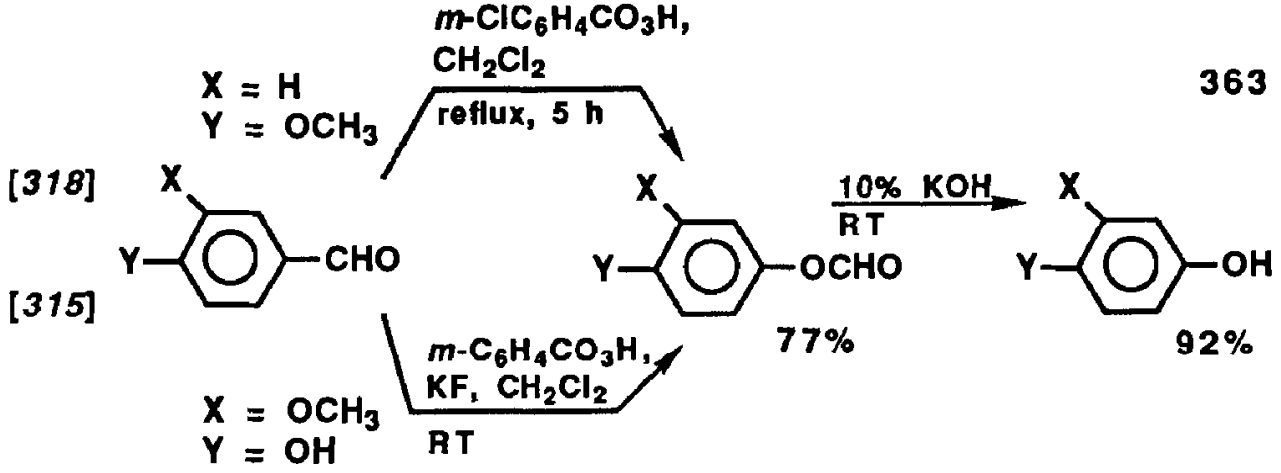


362

60%

[318]

[315]



363

77%

92%

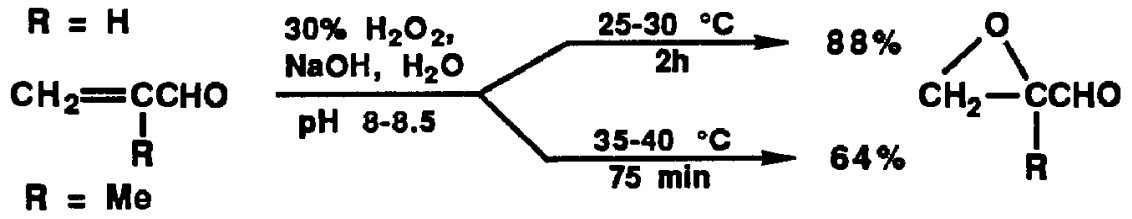
Oxidation of Aldehydes Having Other Functionalities

Oxidations of ***unsaturated aldehydes,*** as long as the oxidation affected only the aldehyde group, have been discussed with the oxidations of saturated and aromatic aldehydes. In this section, only such oxidations that affect the double bonds are described.

Because of the easy oxidizability of the aldehydes to carboxylic acids, any oxidation at the double bond is a delicate operation. Only a few oxidants are suitable to produce aldehyde epoxides, if used under controlled conditions.

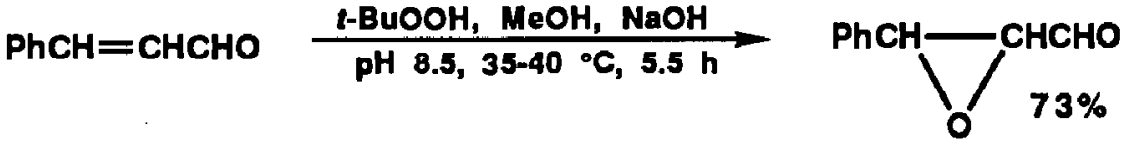
Whereas hydrogen peroxide in acids [*125*] and peroxysulfuric acid [*200*] convert methacrolein into methacrylic acid, **hydrogen peroxide** in an alkaline medium (best at pH 8–8.5) forms the epoxy aldehydes (equation 364) [*146*].

[*146*] 364



The procedure just mentioned fails with cinnamaldehyde. The epoxidation of cinnamaldehyde is accomplished by tert-*butyl hydroperoxide* in aqueous methanolic sodium hydroxide (equation 365) [*219*].

[*219*] 365

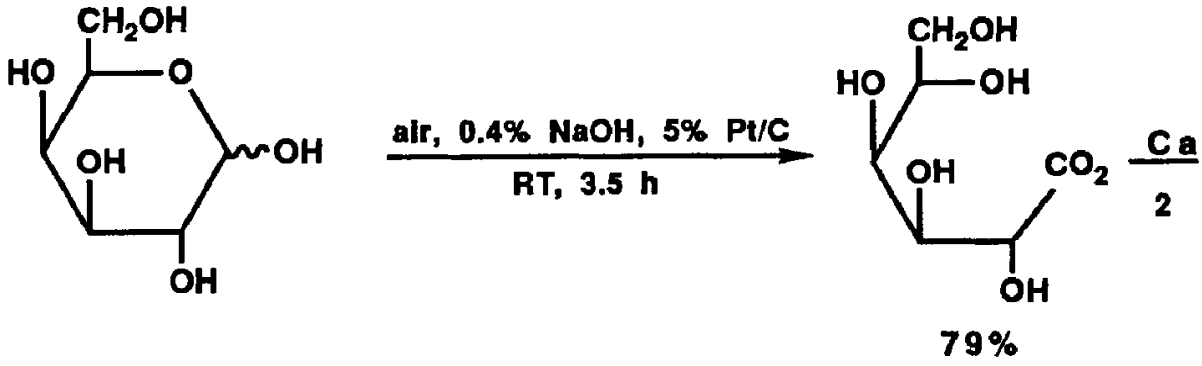


Oxidation of hydroxy aldehydes may affect only the aldehyde group or both the aldehyde and alcoholic groups. Both types are especially common in sugar chemistry; for example, aldoses may be converted into aldonic acids or aldaric acids.

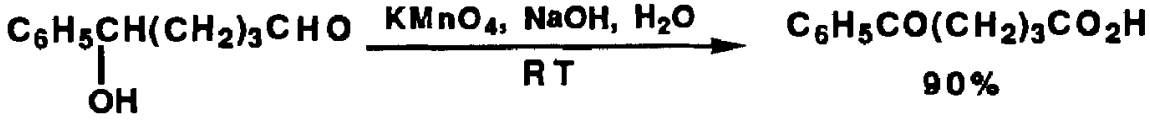
Arabinose, xylose, glucose, galactose, and mannose are transformed into the corresponding ***aldonic acids*** by air or oxygen passed through their solutions in dilute sodium hydroxide in the presence of 5% platinum on carbon as a catalyst [*5, 6*] (equation 366). The acids are usually isolated as calcium salts after calcium chloride has been added to the reaction mixture. The classical oxidant for this purpose is **bromine water** [*1165*] (*see* equation 368).

Both the aldehyde and the alcoholic groups are affected in δ-phenyl-δ-hydroxyvaleraldehyde, which is oxidized by **potassium permanganate** to γ-benzoylbutyric acid (equation 367) [*749*].

[5] 366



[749] 367

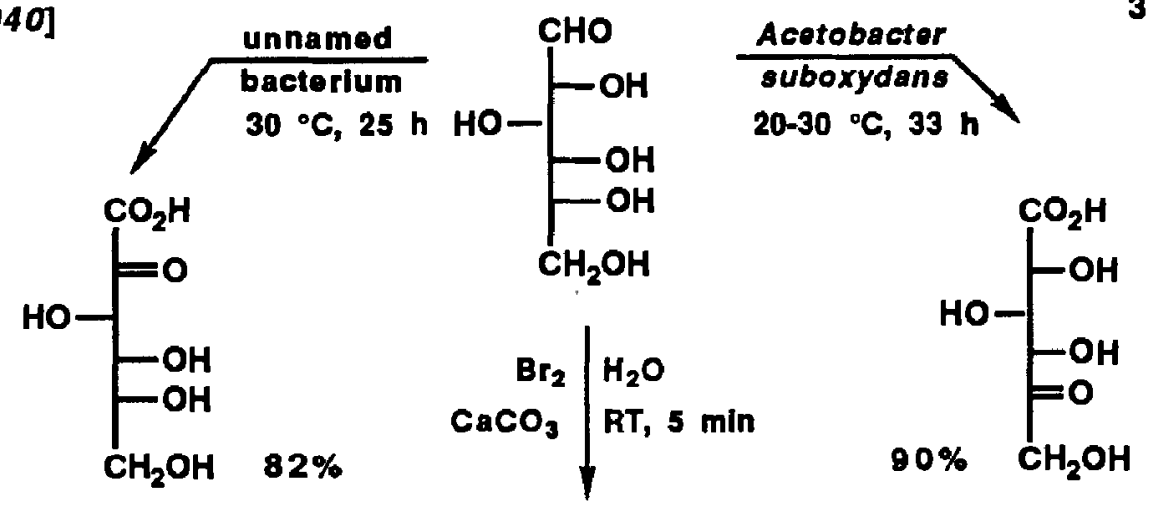


Biochemical oxidations of sugars are very common and versatile. Depending on the microorganism used, hydroxylic groups in various positions can be oxidized to keto groups, and the aldehyde group is converted into a carboxyl group.

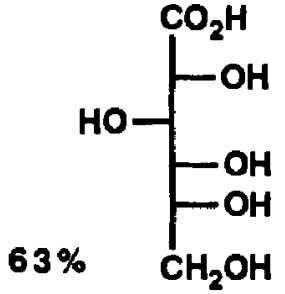
Glucose fermentation at 25–30 °C with ***Acetobacter suboxydans*** first gives gluconic acid and then oxidizes the alcoholic group on C-5 to give 5-ketogluconic acid in 90% yield. An unnamed bacterium converts glucose into 2-ketogluconic acid in 82% yield (equation 368) [*1040*].

The oxidation of both the aldehyde group and the terminal primary alcoholic group in sugars is traditionally carried out with **dilute nitric acid**

[1040] 368



[1165]

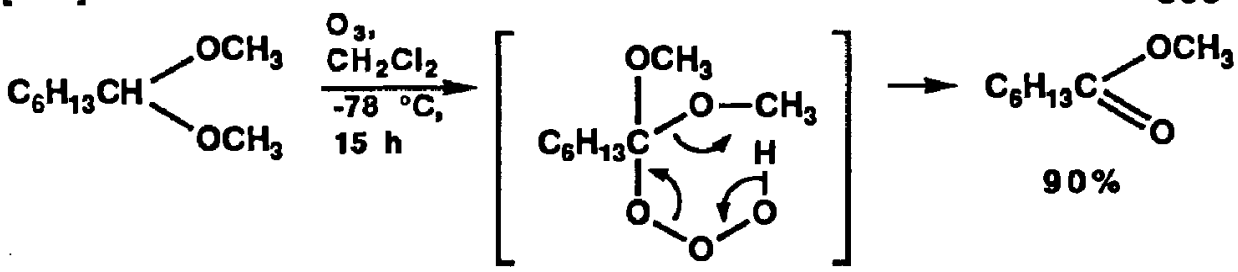


at 100 °C and leads to ***aldaric acids*** (dicarboxylic acids). Thus a solution of lactose (100 g) in 1200 mL of dilute nitric acid (25%; *d* 1.15) evaporated on a steam bath to a volume of 200 mL gives 40 g (67% yield) of mucic acid (*galacto*-tetrahydroxyadipic acid) [*467*].

Oxidation of Aldehyde Derivatives

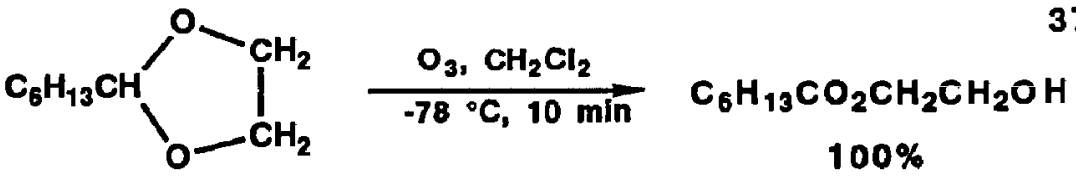
Acetals of aldehydes are converted into esters by the action of **ozone** [*111*] or **peroxy acids** [*277, 327*]. Butyraldehyde diethylacetal, when treated for 30 min with peroxyacetic acid and sulfuric acid as a catalyst, furnishes ethyl butyrate in a 69% yield after 11 h at 40 °C [*277*]. Enanthaldehyde (heptanal) dimethyl acetal reacts with ozone in dichloromethane at −78 °C for 15 h or at room temperature for 1.5 h to produce methyl heptanoate in 90% yield (equation 369) [*111*].

[*111*] 369

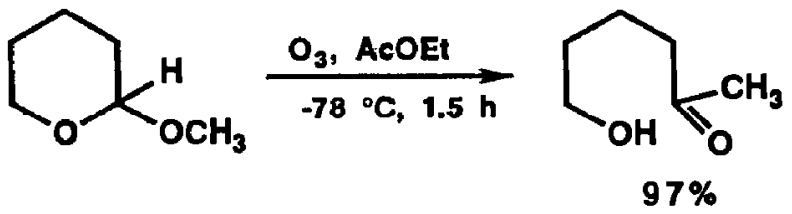


Cyclic acetals react faster; their reactions require less than 2 h at −78 °C [*111*]. Tetrahydropyranyl ethers are cleaved to hydroxy esters (equations 370 and 371) [*111*].

[*111*] 370



[*111*] 371

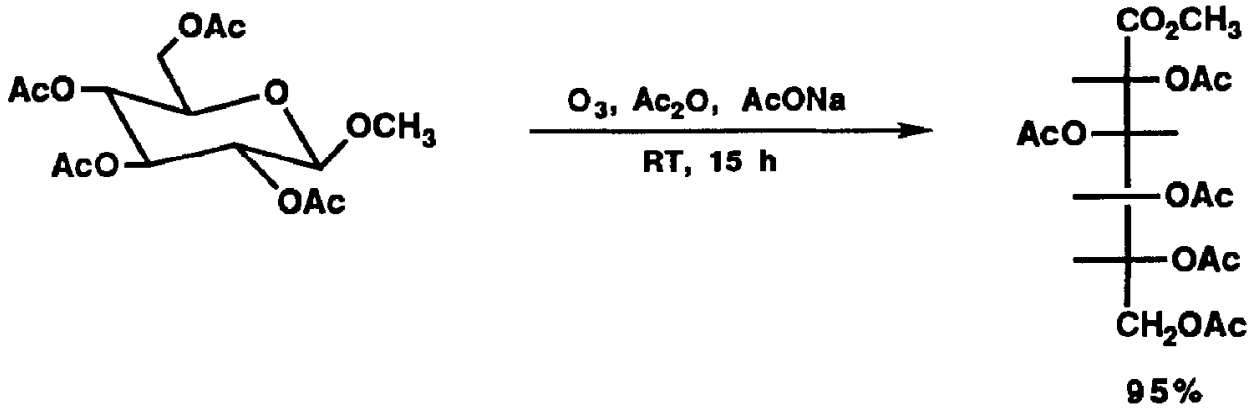


The oxidation of glycosides to esters by ozone is stereoselective. It affects only the β anomers; α anomers do not react [*111*]. Ozone can also be used to deprotect ethylidene and benzylidene glycosides, because it cleaves the acetal bonds (equation 372) [*111*].

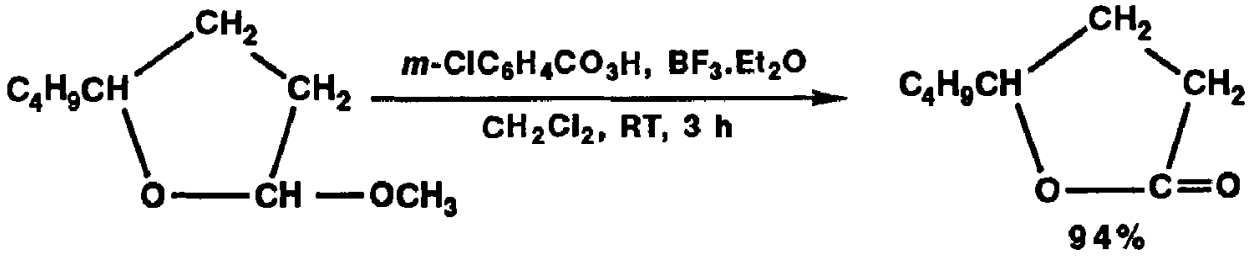
***m*-Chloroperoxybenzoic acid** converts γ-lactols into lactones. δ-Lactols give low yields (equation 373) [*327*].

Unsaturated aldehyde acetals may be transformed either into ***unsaturated esters*** or into ***epoxy acetals.*** **Peroxyacetic acid** in ethyl acetate epox-

[111] 372

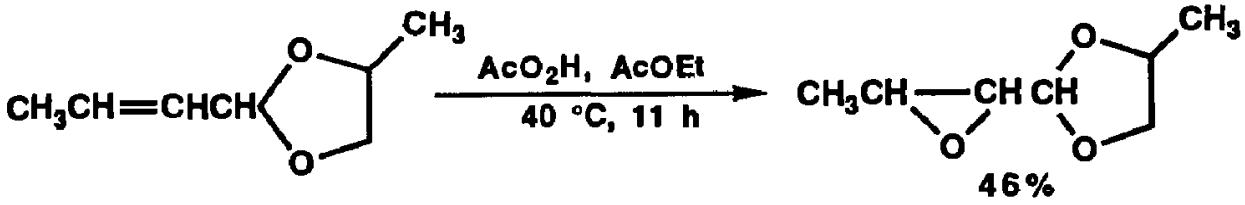


[327] 373

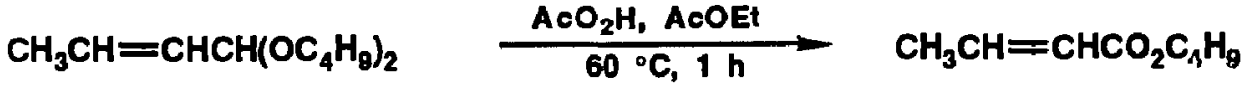


idizes 2-(1-propenyl)-4-methyl-1,3-dioxolane after 11 h in 46% yield [277]. On the other hand, crotonaldehyde dibutylacetal, with the same reagent and solvent at 60 °C, gives butyl crotonate in 73% yield (equations 374 and 375) [277].

[277] 374

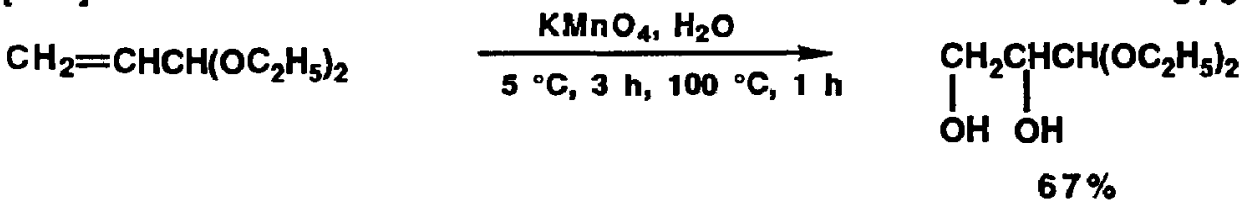


[277] 375



The treatment of ***acrolein diethyl acetal*** with **potassium permanganate** results in the ***hydroxylation*** of the double bond (equation 376) [871].

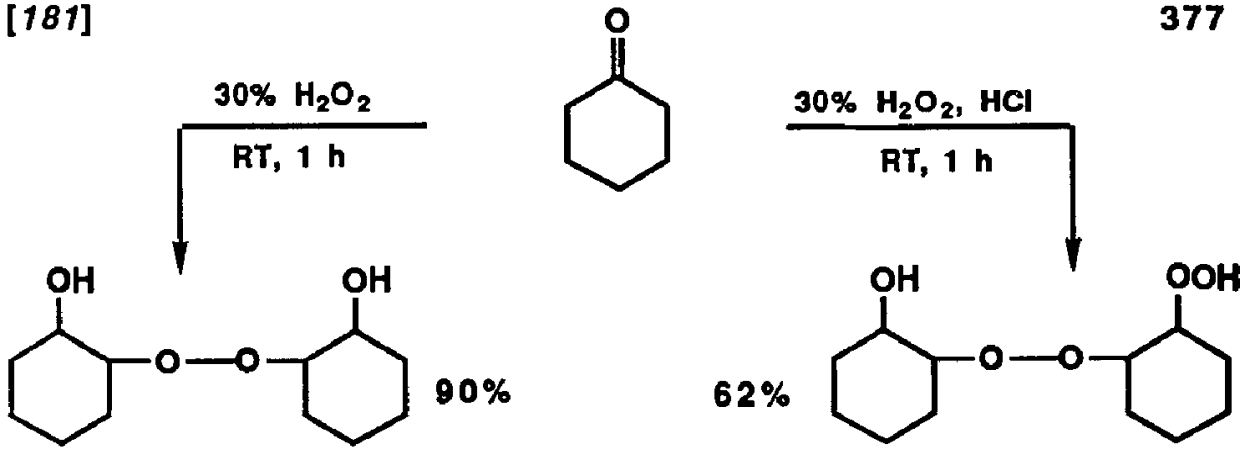
[871] 376



KETONES

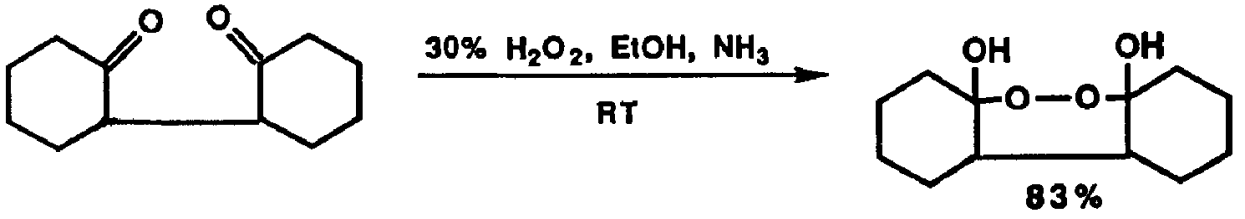
The results of the oxidation of ketones depend on the oxidants used. **Aqueous hydrogen peroxide,** in the absence of mineral acid, converts cyclohexanone into 1,1′-dihydroxydicyclohexyl ***peroxide,*** whereas with hydrochloric acid as a catalyst, 1-hydroxy-1′-hydroperoxydicyclohexyl peroxide is formed (equation 377) [*181*].

[*181*] 377



Dicycloalkyl-2,2′-diones prepared from cyclopentanone, cyclohexanone, 4-methylcyclohexanone, and cycloheptanone undergo peroxidation with hydrogen peroxide to yield homologues of 3,6-dihydroxy-1,2-dioxanes (equation 378) [*180*].

[*180*] 378

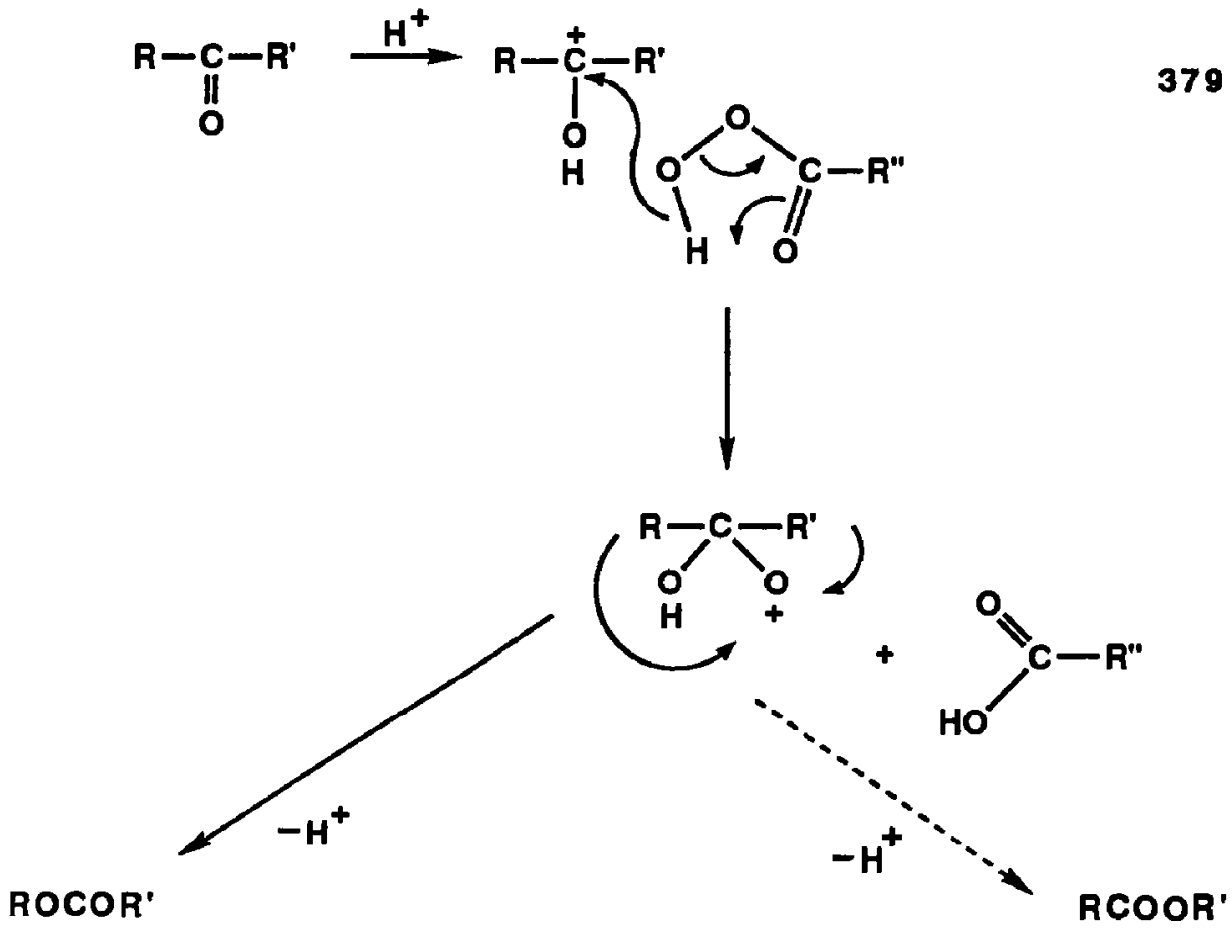


Oxidation of Ketones to Esters (Baeyer–Villiger Reaction)

The oxidation of ketones to esters is known as the ***Baeyer–Villiger reaction*** and is effected mainly by hydrogen peroxide and peroxy acids, especially the organic peroxy acids.

The mechanism is the same as that of the ***Dakin reaction*** of aromatic aldehydes (equation 359). The reaction is acid-catalyzed. The peroxy acid transfers oxygen onto the carbon of the carbonyl group and generates an unstable intermediate. A rearrangement of the groups bonded to the original carbonyl carbon results in the formation of ***esters*** or, with cyclic ketones, ***lactones*** [*262, 303*] (equation 379).

Because migration of the groups attached to the carbonyl carbon takes place with the bonding electron pair, the migratory aptitudes of the two

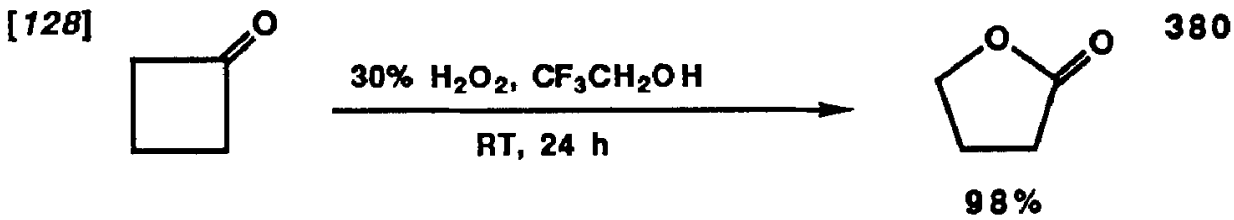


groups are determined by their relative nucleophilicities. Such group will migrate preferentially that has more nucleophilic character, that is, higher electron density owing to electrons or electron-releasing substituents.

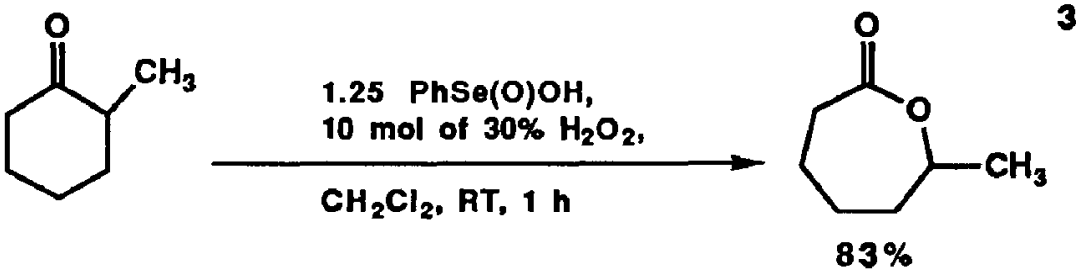
Although there are deviations and differences due to the type of ketones, the migratory aptitudes can be arranged in the following sequence [*282, 284*]: *tert*-butyl > cyclohexyl ~ secondary alkyl ~ benzyl ~ phenyl > primary alkyl > cyclopropyl >> methyl [*282, 284, 286, 304*]. In substituted benzophenones, the benzene ring with electron-releasing groups rearranges preferentially [*1166*]. The migration occurs intramolecularly. As a consequence, the rearrangement takes place with complete retention of configuration and chirality [*306, 1034*].

Hydrogen peroxide alone rarely converts ketones into esters [*148, 1167*]. It is used usually in the presence of an acid [*128*] or as a reoxidant [*343*] (equations 380 and 381).

Its derivative, bis(trimethylsilyl) peroxide, effects the ***Baeyer–Villiger reaction*** in aprotic solvents in the presence of trimethylsilyl trifluoromethanesulfonate [*237*] (*see* equation 388).



[343]

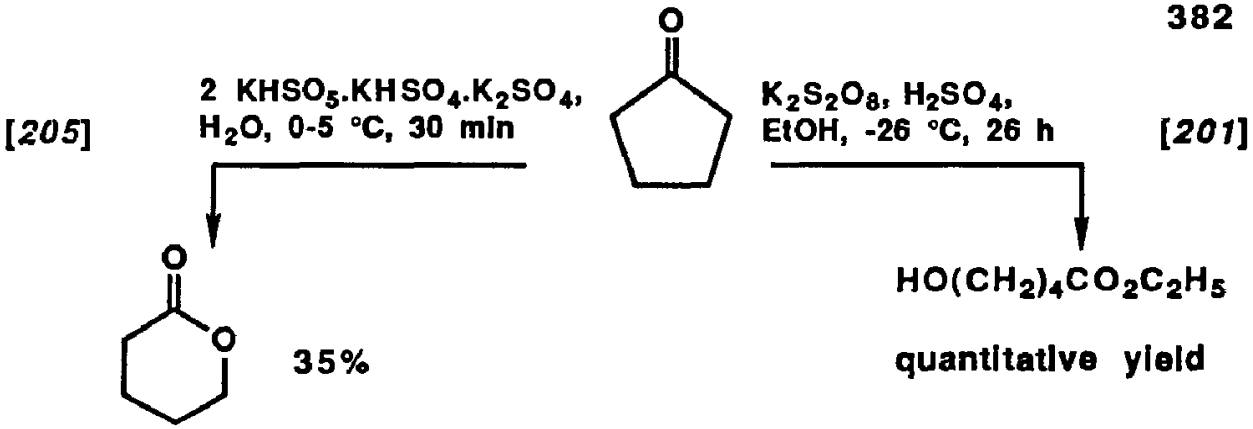


381

83%

Potassium peroxymonosulfate oxidizes benzophenone to phenyl benzoate (yield 77%), cyclopentanone to δ-valerolactone (yield 35%), and cyclohexanone to ϵ-caprolactone (yield 46%) [*205*]. In an excess of sulfuric acid and in the presence of alcohol, the δ-valerolactone is immediately transesterified to ethyl δ-hydroxyvalerate [*201*] (equation 382).

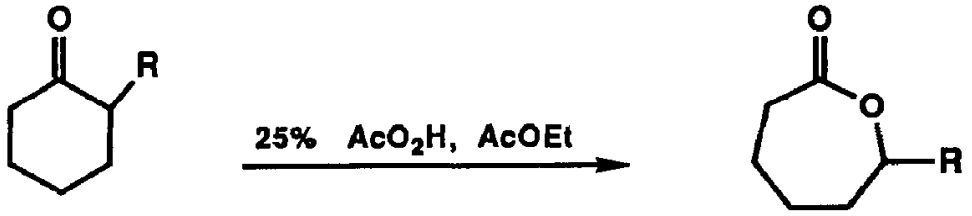
382



Peroxyacetic acid is used frequently to oxidize all kinds of ketones to esters [*261*] and lactones [*262*]. The usual concentration of commercial peroxyacetic acid is 40%, but acids of concentrations of 20–28% can also be used. The reactions are exothermic and are run at temperatures ranging from room temperature to 40 °C, sometimes in the presence of sulfuric acid [*261*]. In oxidations of aromatic ketones, the rings containing activating substituents, such as methyl and methoxy groups, migrate preferentially. In benzophenones containing a phenyl group and chlorophenyl, bromophenyl, and nitrophenyl groups, the phenyl group migrates preferentially [*261*]. Cyclopentanone and cyclohexanone are oxidized to δ-valerolactone and ϵ-caprolactone in 84 and 70–94% yields, respectively. Little polymerization of the lactone to polyesters was observed [*262*]. Cyclohexanones with alkyl groups in the α position with respect to the carbonyl give consistently ϵ-alkyl-ϵ-caprolactones, in agreement with the results obtained with other reagents [*262, 343*] (equation 383).

An important addition to the arsenal of oxidants for the Baeyer–Villiger reaction is **peroxytrifluoroacetic acid** [*282, 283, 284*]. Although this reagent is less easily accessible than peroxyacetic acid and aromatic peroxy acids, it is more reactive. The yields of esters obtained by oxidation of ketones with peroxytrifluoroacetic acid are high enough to justify the use of this oxidant for the quantitative determination of aldehydes and

[262]

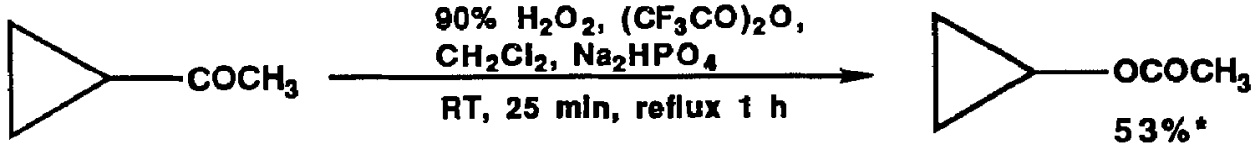


383

R	Time (h)	Temperature (°C)	Yield (%)
H	6.5	40	90
Me	8.5	40	92
i-Pr	9	50	84.5
s-Bu	13	50	92
cyclo-C_6H_{11}	10	50	82

ketones with an accuracy within 3–10% [*280*]. The disadvantage is the necessity of 90% hydrogen peroxide for the preparation of peroxytrifluoroacetic acid from trifluoroacetic anhydride [*283, 284*] (equation 384).

[284]

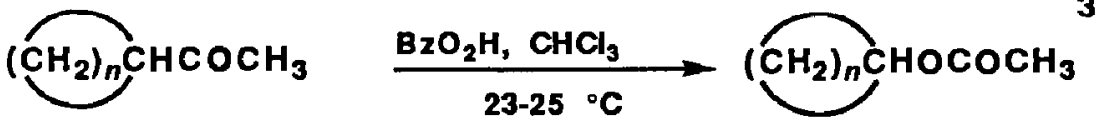


384

*The purity of the product is 96%, 4% being methyl cyclopropanecarboxylate.

Peroxybenzoic acid is used to oxidize cyclanones [*303*], as well as alkyl and phenyl cycloalkyl ketones [*304, 305*]. Yields of cycloalkyl acetates obtained on treatment of cycloalkyl methyl ketones with a 10–15% stoichiometric excess of peroxybenzoic acid in chloroform at room temperature range from 58 to 72% (equation 385) [*305*].

[305]



385

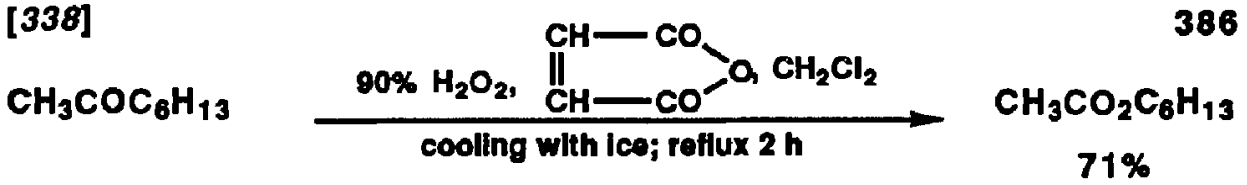
n	Time (h)	Yield (%)
3	45	58
4	73	61
5	77	72
6	49	69

Cyclohexyl phenyl ketone oxidized by peroxybenzoic acid in chloroform at 24–26 °C for 239 h furnishes an 85% yield of esters, of which 71% is cyclohexyl benzoate and 14% is phenyl cyclohexanecarboxylate. This result shows that the migratory aptitude of the cyclohexyl group is 5 times greater than that of the phenyl group [*304*].

***m*-Chloroperoxybenzoic acid** gives almost identical results as peroxytrifluoroacetic acid in the oxidation of alkyl cyclopropyl ketones [*286*]. On treatment of methyl cyclopropyl ketone with a dichloromethane solution of *m*-chloroperoxybenzoic acid at 25 °C for 35 days or with a dichloromethane solution of peroxytrifluoroacetic acid at room temperature for 25 min and at reflux for 1 h, the ratio of cyclopropyl acetate to methyl cyclopropanecarboxylate is 95:5 or 96:4, respectively. In contrast, the corresponding ratios of cyclopropyl alkanoate to alkyl cyclopropanecarboxylate are 1:99 and 6:94, respectively, for the two acid treatments of isopropyl cyclopropyl ketone and 3:97 for phenyl cyclopropyl ketone (the product ratios are the same with both acids) [*286*].

Peroxymaleic acid, prepared from 90% hydrogen peroxide and maleic anhydride in dichloromethane with cooling with ice, oxidizes ketones to esters or lactones in 40–83% yields on refluxing in dichloromethane for 2–12 h [*338*]. Because the peroxymaleic acid solution in dichloromethane decomposes to the extent of 5% in 6 h at room temperature and because the oxidation of ketones with this reagent requires refluxing in dichloromethane, peroxymaleic acid does not offer any advantages over the more readily accessible peroxy acids (equation 386).

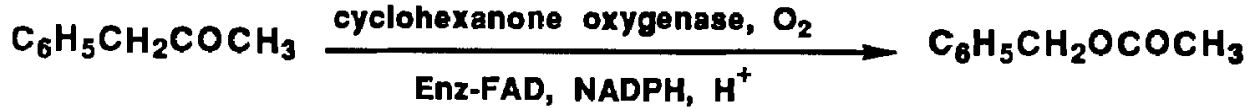
[*338*] 386



Another dicarboxylic peroxy acid, **peroxyphthalic acid,** is used for the Baeyer–Villiger reaction of β-diketones and α-keto esters [*334*]. Besides peroxy acids, *ceric ammonium nitrate* oxidizes 2-adamantanone to 2-oxahomoadamantanone in aqueous acetonitrile in 73% yield at 60 °C after 3 h [*422*]. Tetracyclone (2,3,4,5-tetraphenyl-2,4-cyclopentadien-1-one) is oxidized by ceric ammonium nitrate in aqueous acetonitrile to tetraphenyl-2-pyrone in 77% yield [*422*].

The Baeyer–Villiger reaction is also effected by ***biochemical oxidation*** using the enzyme **cyclohexanone oxygenase** from ***Acinetobacter*** strain NCIB 9871. Cyclohexanone is thus converted into ϵ-caprolactone [*1043*], and phenylacetone (1-phenyl-2-propanone) is transformed into benzyl acetate. The formation of benzyl acetate from phenylacetone involves the same migration as that in oxidation with peroxytrifluoroacetic acid (equation 387) [*1034*]. More examples of biochemical Baeyer–Villiger reactions occur in diketones and steroids (*see* equation 397).

[*1034*] 387

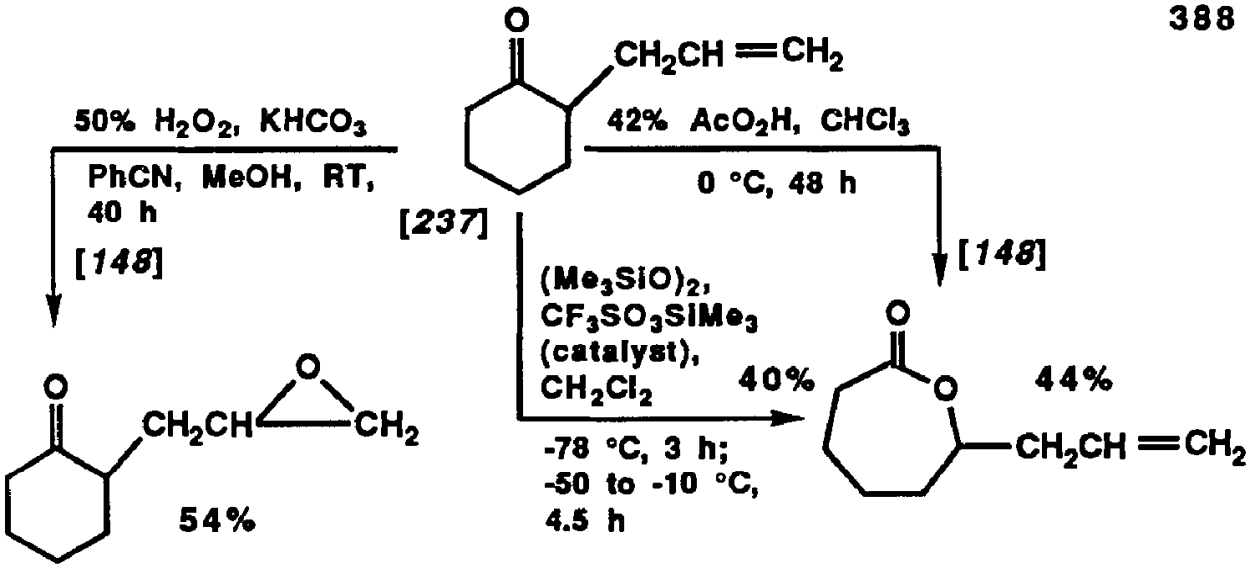


Baeyer–Villiger Oxidation of Functionalized Ketones

Because of the common mechanisms and the same specific oxidants, the ***Baeyer–Villiger oxidation*** of ketones possessing other functional groups will be mentioned in this section rather than in the places where it should be discussed according to the system of the book.

The results of oxidation of ***unsaturated ketones*** depend on the position of the double bond with respect to the carbonyl group and on the oxidant.

An example showing the behavior of a ketone containing a nonconjugated double bond is the oxidation of 2-allylcyclohexanone. Hydrogen peroxide in benzonitrile produces exclusively an epoxide [*148*], whereas peroxyacetic acid [*148*] or bis(trimethylsilyl) peroxide [*237*] yields the lactone of 6-hydroxy-8-nonenoic acid (equation 388).



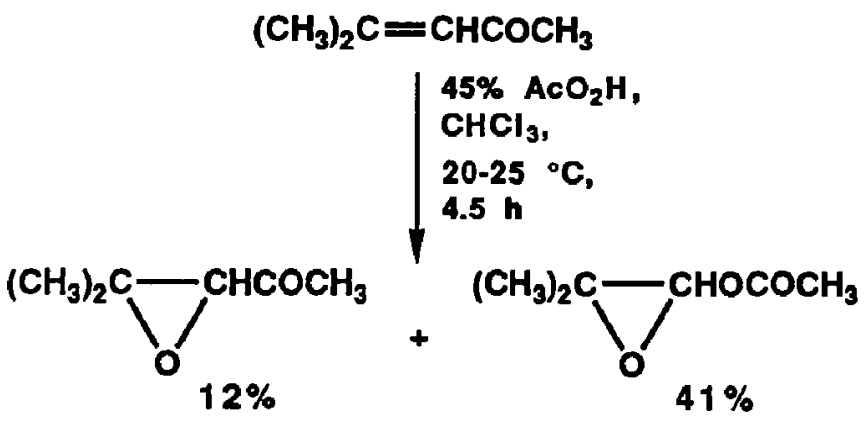
Most of the discussion of the Baeyer–Villiger reaction of unsaturated ketones is devoted to α,β-unsaturated ketones, such as mesityl oxide [*254*], benzalacetophenone [*307*], and, especially, benzalacetone [*258*]. The oxidation of ionones does not involve the Baeyer–Villiger reaction and is, therefore, discussed elsewhere (*see* equations 440 and 441).

The treatment of mesityl oxide with 45% peroxyacetic acid in chloroform at 20–25 °C for 4.5 h gives a 53% yield of a mixture containing 22% of 4-methyl-3,4-epoxypentan-2-one and 78% of 2-acetoxy-3,3-dimethyloxirane (the combined products of epoxidation and the Baeyer–Villiger reaction) (equation 389) [*254*].

The predominance of oxidation at the keto group over epoxidation in α,β-unsaturated compounds carrying phenyl groups in β positions with respect to carbonyls is mechanistically explained for benzalacetophenone [*258*] and proven by the oxidation of 3,4-diphenyl-3-buten-2-one [*307*] (equations 390 and 391).

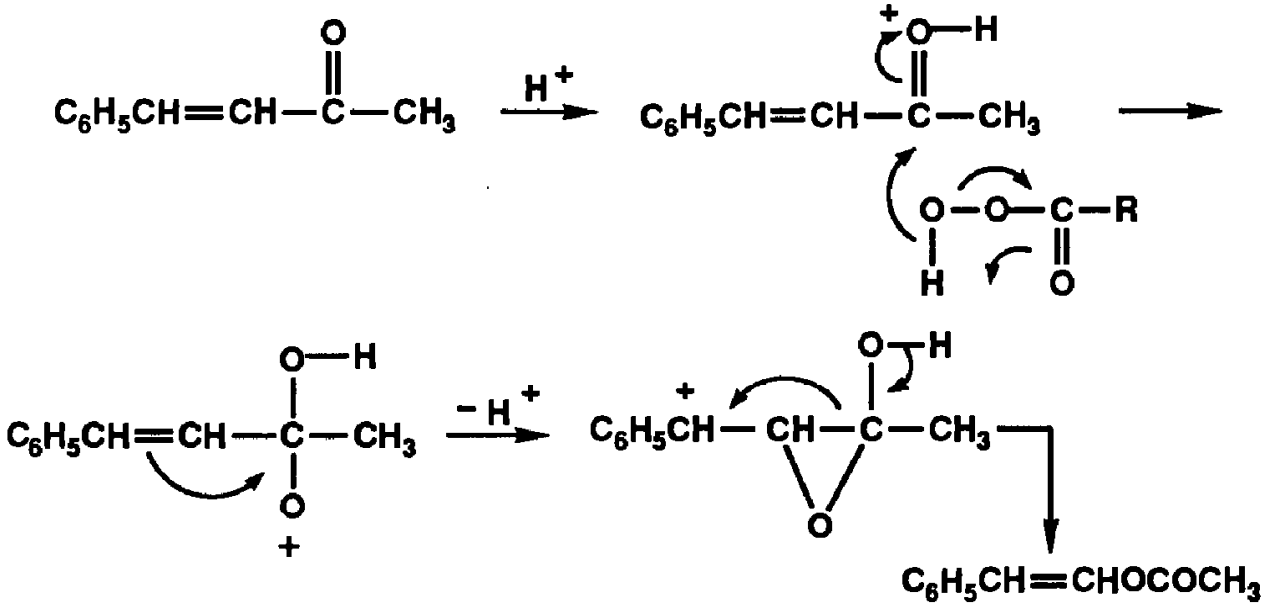
The same reaction that converts ketones into lactones transforms α-

[254]



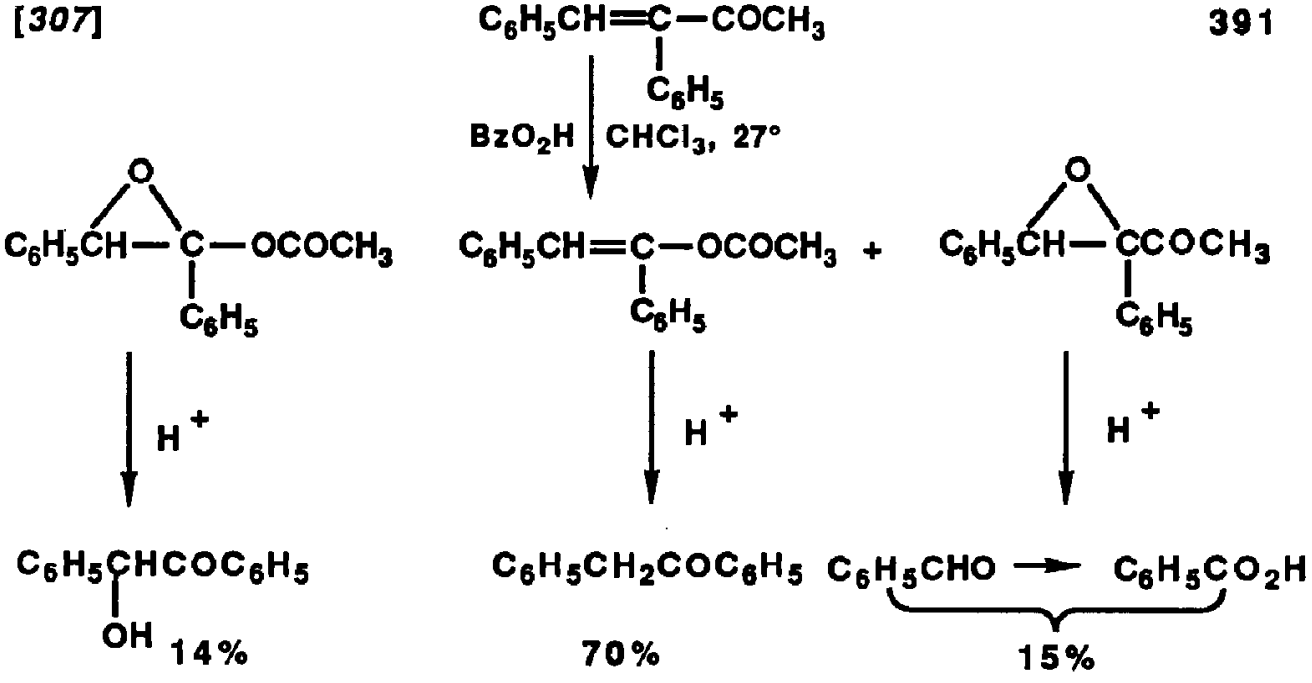
389

[258]



390

[307]

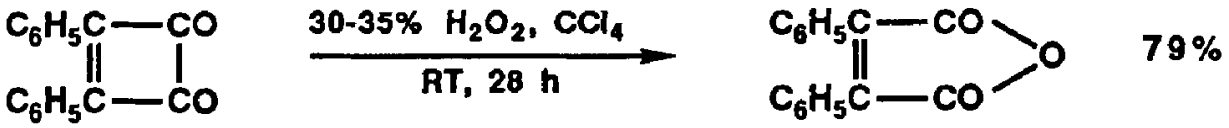


391

diketo compounds into acid anhydrides, which are sometimes isolable and sometimes hydrolyzed immediately to the corresponding acids.

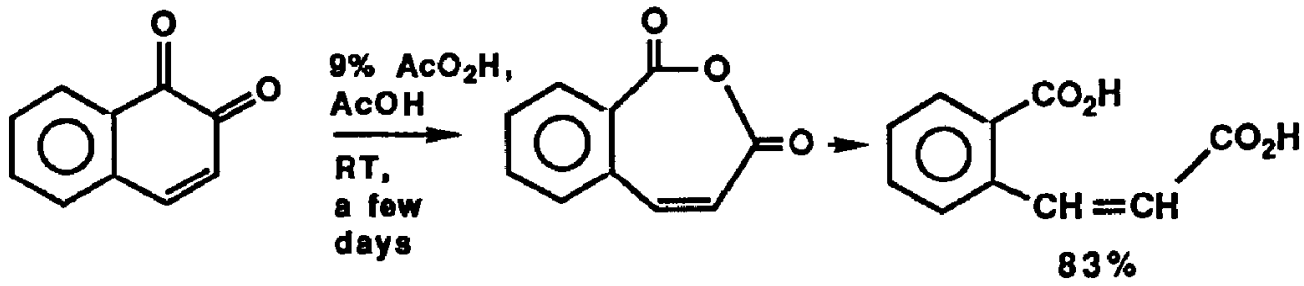
The treatment of diphenylcyclobutene-1,2-dione with hydrogen peroxide in carbon tetrachloride affords a 79% yield of diphenylmaleic anhydride (equation 392) [*1167*].

[*1167*] 392



β-Naphthoquinone reacts exothermically with 9% peroxyacetic acid in acetic acid and gives an 83% yield of the anhydride of *o*-carboxyallocinnamic acid [*271*] (equation 393). A similar oxidation of 9,10-diketostearic acid gives a 90% yield of pelargonic acid and a 95% yield of azelaic acid [*271*].

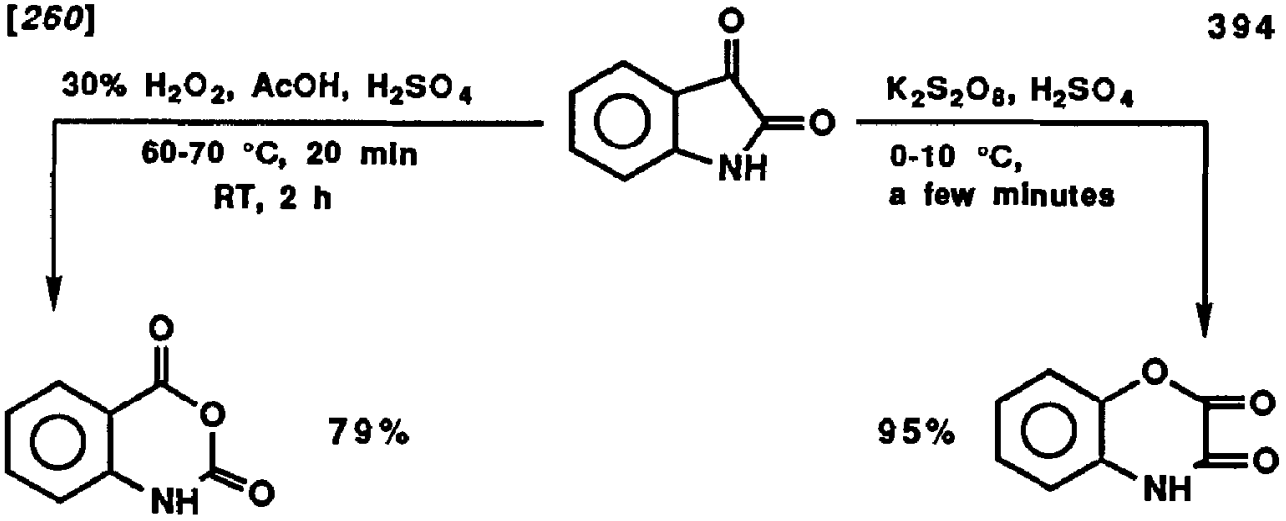
[*271*] 393



The oxidation of ethyl pyruvate and ethyl phenylglyoxylate with peroxyphthalic acid at 20–22 °C produces, after 48 and 90 h, mixed anhydrides of ethylcarbonic acid and acetic and benzoic acids, respectively [*334*].

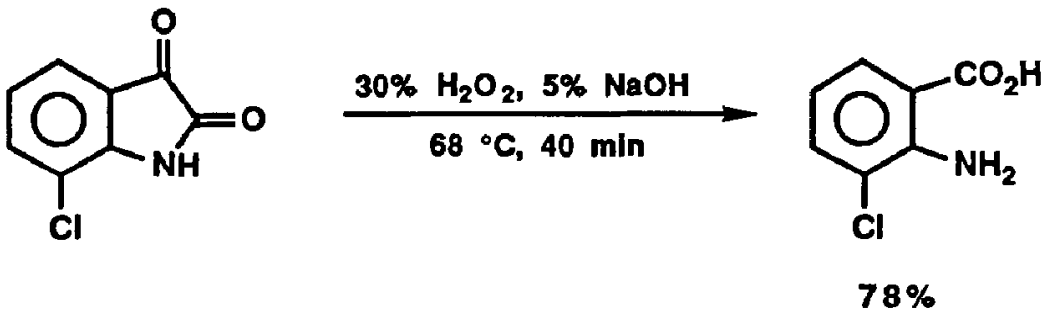
Isatin, which can be considered a cyclic α-keto amide, is oxidized by hydrogen peroxide exclusively to isatoic anhydride, whereas with potassium peroxydisulfate, 2,3-dioxo-1,4-benzoxazine is obtained (equation 394) [*260*].

[*260*] 394



Some isatoic acid anhydrides are readily hydrolyzed during oxidation so that the corresponding *N*-(2-hydroxyphenyl)oxamidic acids are isolated as products [*260*]. With 7-chloroisatin, treatment with 30% hydrogen peroxide in 5% aqueous sodium hydroxide for 40 min at 65 °C produces chloroanthranilic acid in 78% yield (equation 395) [*1168*].

[*1168*] 395

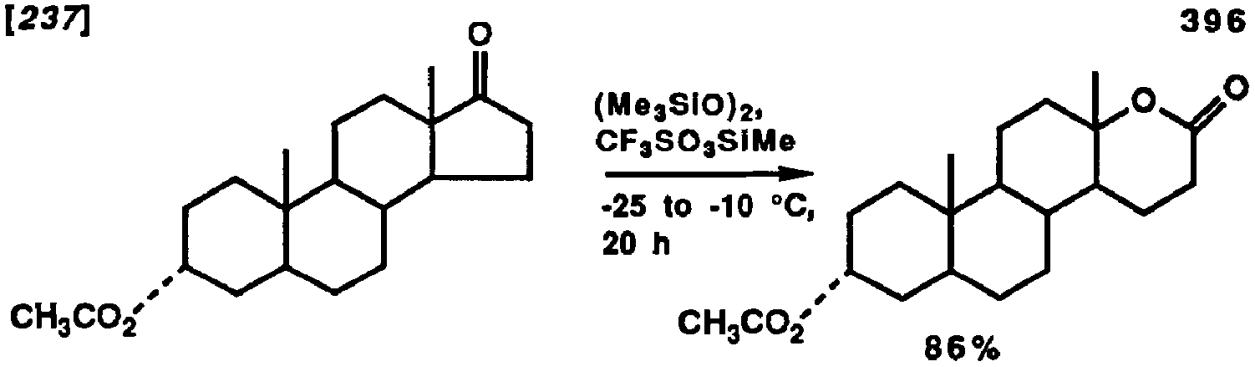


78%

The Baeyer–Villiger reaction of ***hydroxy ketones*** and ***unsaturated diketones*** is very common in steroids, where it occurs preferentially at the keto group on C-17 and leaves the carbonyls in position 3 intact.

Chemical oxidation is achieved with bis(trimethylsilyl) peroxide in the presence of trimethylsilyl trifluoroacetate (triflate). Androsterone acetate is converted into androstenolactone acetate in 86% yield (equation 396) [*237*].

[*237*] 396

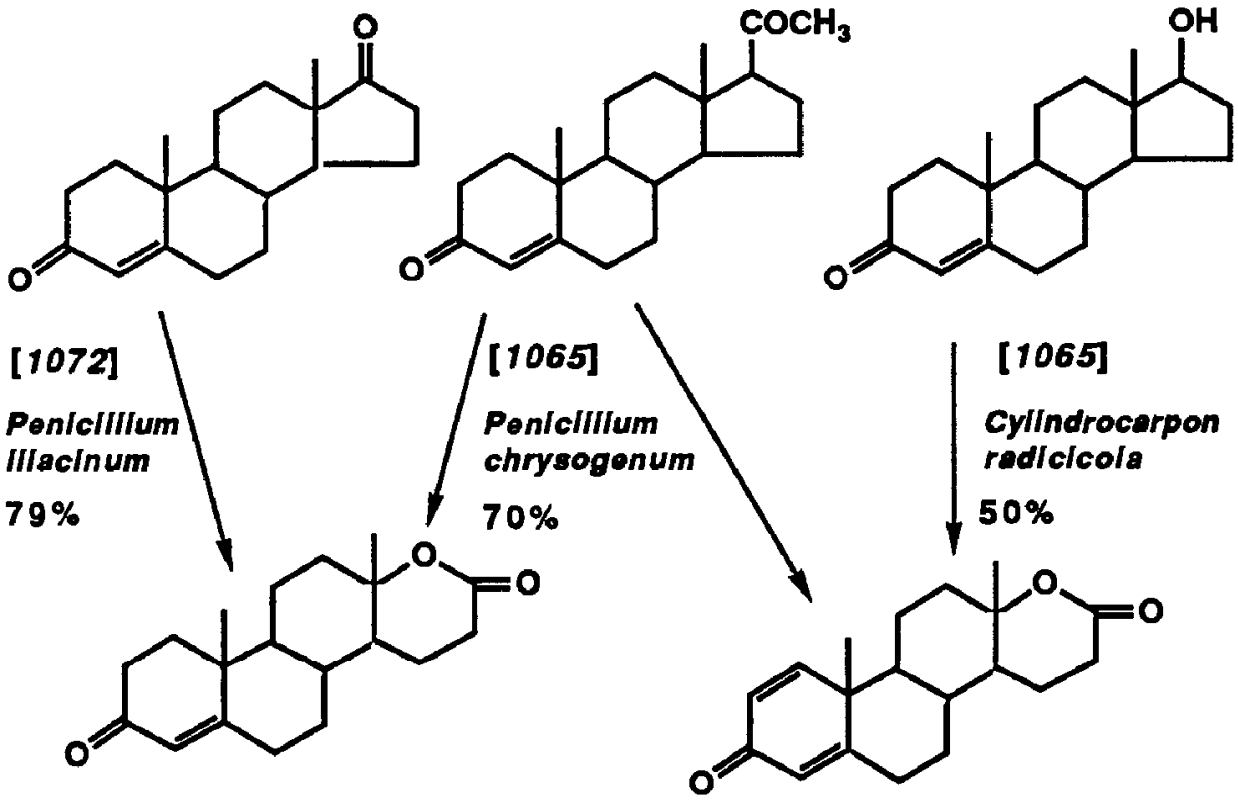


86%

Most of the ***Baeyer–Villiger oxidations*** of steroids are accomplished ***biochemically***. 19-Nortestosterone treated with ***Aspergillus tamarii*** furnishes a 70% yield of 19-nortestololactone [*1049*]. Progesterone and testosterone are converted into Δ^1-dehydrotestololactone by fermentation with ***Cylindrocarpon radicicola*** (in ref. 1065, *radicola*) [*1065*]. Testololactone is obtained from progesterone by oxidation with ***Penicillium chrysogenum*** [*1065*] and from 4-androstene-3,17-dione by treatment with ***Penicillium lilacinum*** [*1072*] (equation 397).

Other examples of the ***Baeyer–Villiger reaction*** are given in equations 398–399.

397



EXAMPLES OF THE BAEYER-VILLIGER REACTION

398

[*205*]	2 $KHSO_5.KHSO_4.K_2SO_4$; H_2O, 0-5 °C, 30 min	46%
[*262*]	20-28% AcO_2H, 40 °C, 6.25 h	85%
[*303*]	BzO_2H, $CHCl_3$, 22-25 °C, 6.5 h	71%
[*237*]	$(Me_3SiO)_2$, $CF_3SO_3SiMe_3$ (catalyst), CH_2Cl_2, -78 °C, 6 h; -40 °C, 1 h	76%
[*1043*]	Cyclohexanone oxygenase from *Acinetobacter* strain NCIB 9871	28%

399

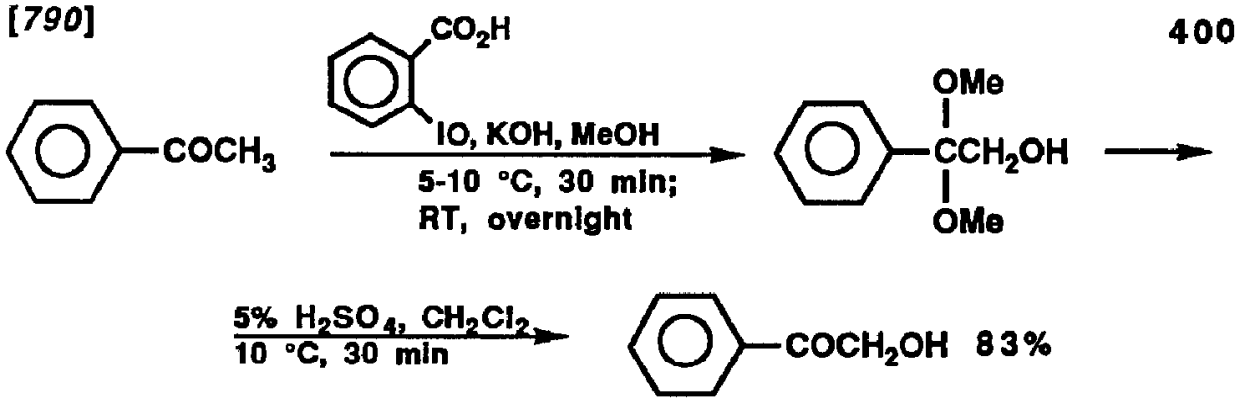
$C_6H_5COC_6H_5$ ⟶ $C_6H_5COOC_6H_5$

[*205*]	$2KHSO_5.KHSO_4.K_2SO_4$, H_2SO_4, AcOH, <35 °C, 30 min	77%
[*261*]	40% AcO_2H, AcOH, H_2SO_4, RT, 0.5 h	82%
[*284*]	90% H_2O_2, $(CF_3CO)_2O$, CH_2Cl_2, Na_2HPO_4, RT, 25 min reflux 1 h	88%
[*338*]	$HO_2CCH=CHCO_3H$, CH_2Cl_2, reflux, 2 h	70%

Hydroxylation of Ketones

Ketones having at least one hydrogen next to the carbonyl group can be hydroxylated to form α-hydroxy ketones (acyloins). Acetophenone is oxidized to α-hydroxyacetophenone by ***o*-iodosobenzoic acid.** In the presence of potassium hydroxide and methanol, dimethyl acetal is obtained, which on subsequent hydrolysis gives the hydroxy ketone in 83% yield (equation 400) [*790*].

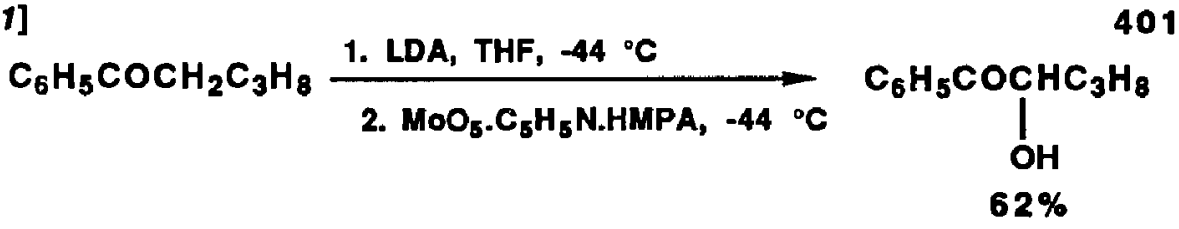
[*790*]



400

The conversion of ketones into α-hydroxy ketones can be achieved by the oxidation of enolates or enol ethers. A special reagent for enolates is the *oxodiperoxy molybdenum complex with pyridine and hexamethylphosphoramide.* The reaction is applied to aromatic aliphatic ketones and cyclic ketones and furnishes 34–81% yields of α-hydroxy ketones with up to 26% of α-diketones (equation 401) [*531*].

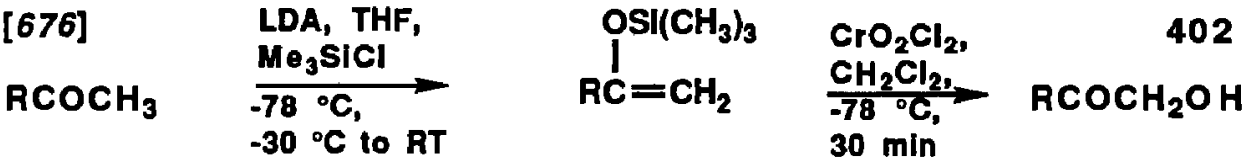
[*531*]



401

Trimethylsilyl enol ethers prepared in 60–91% yields from ketone enolates and trimethylsilyl chloride are converted into α-hydroxy ketones by **chromyl chloride** in 62–82% yields (equation 402) [*676*] (equation 340).

[*676*]



402

R		Yield (%)	
$C(CH_3)_3$		62	82
C_6H_5		85	62

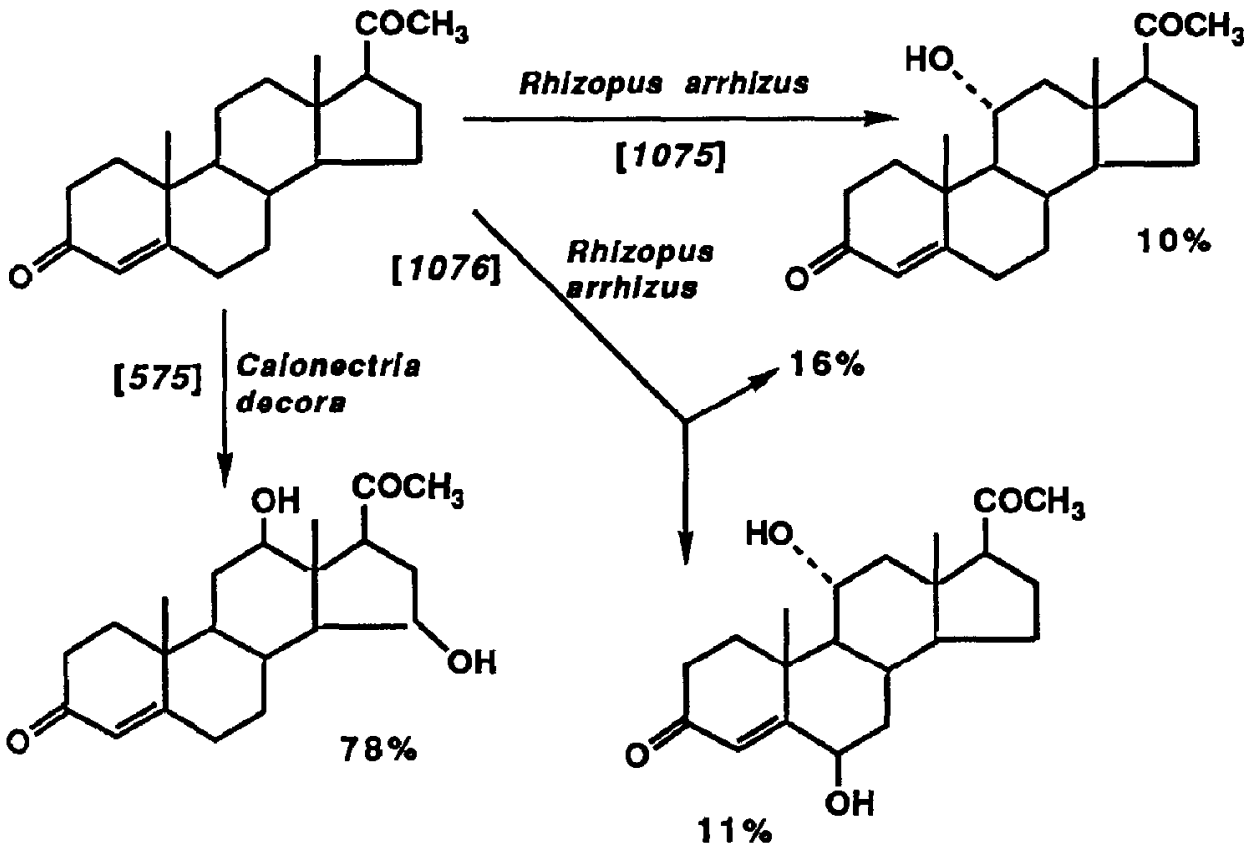
Hydroxylations of steroidal and unsaturated steroidal ketones in different positions are accomplished by **microorganisms,** a fact that shows how much ahead microorganisms are in synthetic chemistry as far as regio-

and stereoselectivity are concerned. The most favored position of hydroxylation is 11α [*1045, 1060, 1061, 1075, 1076, 1077, 1078, 1079*] followed by 11β [*1062, 1067*], 6β [*1062, 1066*], 7α [*1064*], 10β [*1062*], 12α [*1062*], 12β [*575*], 13β [*1062*], 14α [*1062*], 15α [*1064, 1066*], 15β [*575, 1051, 1064*], 17α [*1060*], and 17β [*1062*]. Hydroxylations are applied to progesterone [*575, 1075, 1076*], deoxycorticosterone [*1045, 1064*], pregnanedione [*1078*], androstenedione [*1066*], and their derivatives.

The biochemical hydroxylations are carried out under the conditions required for the cultivation of individual microorganisms. The common denominator in the cultivation of microorganisms is an aerated aqueous solution containing nutrient material, buffered to the required pH, and kept at a temperature of 26 to 28 °C for a few days or weeks. The products are isolated by extraction with dichloromethane, chloroform, ethyl acetate, and the like. The yields are usually low, and chromatography is often used in isolations.

The oxidation of progesterone with ***Rhizopus arrhizus*** yields 11α-hydroxyprogesterone [*1075*], together with 6β,11α-dihydroxyprogesterone [*1076*]. In contrast, ***Calonectria decora*** converts progesterone into 12β,15β-dihydroxyprogesterone [575] (equation 403).

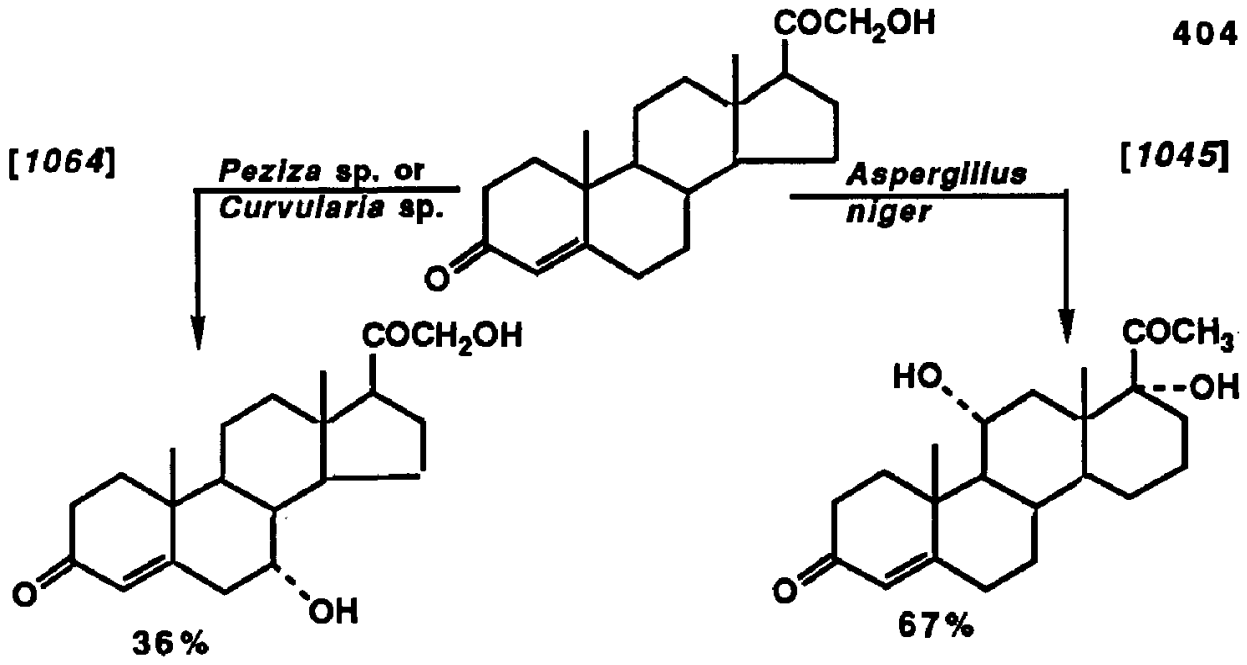
403

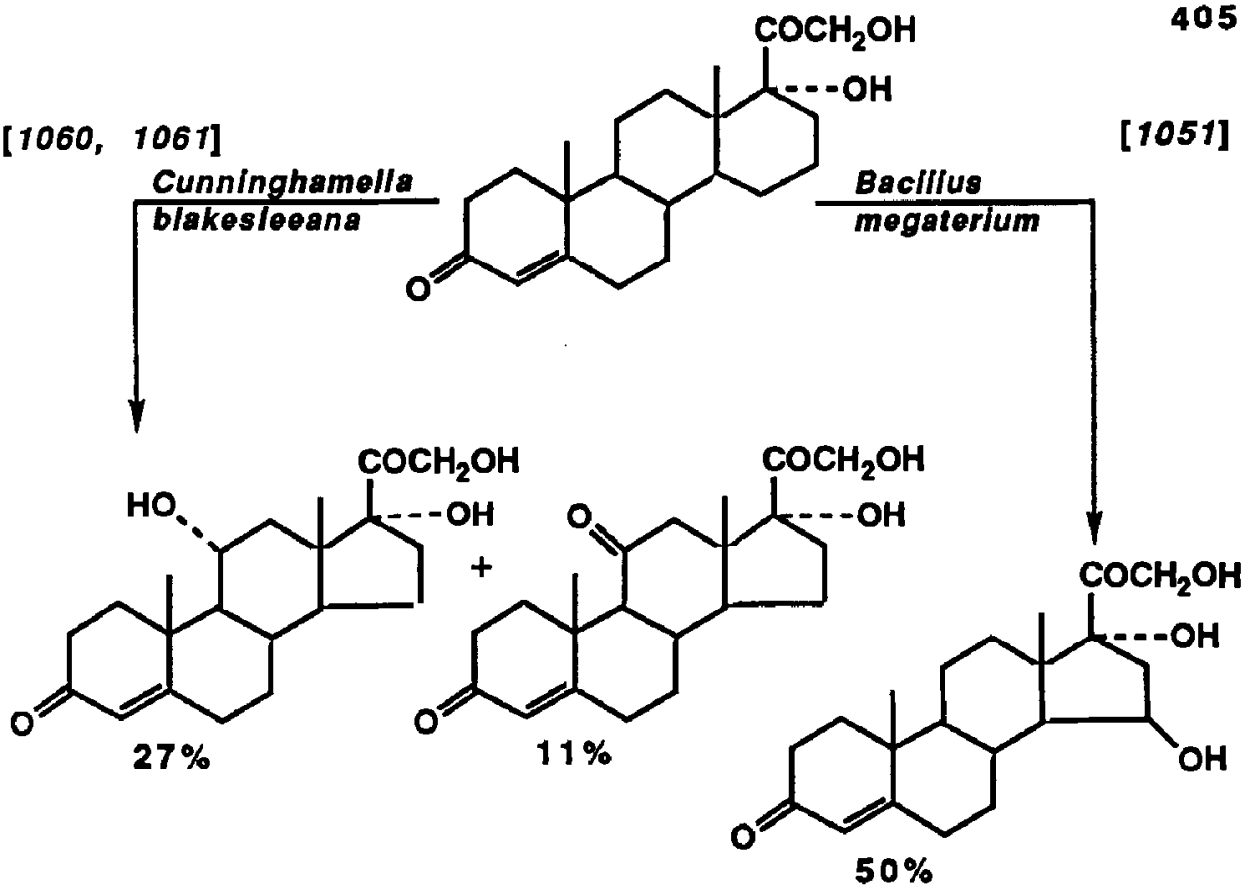


6-Dehydroprogesterone [*1077*] and 3,17-pregnanedione [*1078*] are hydroxylated in the 11α position by ***Rhizopus nigricans*** in 50–60 and 39% yields, respectively. The same microorganism gives a 73.5% yield of 11α-

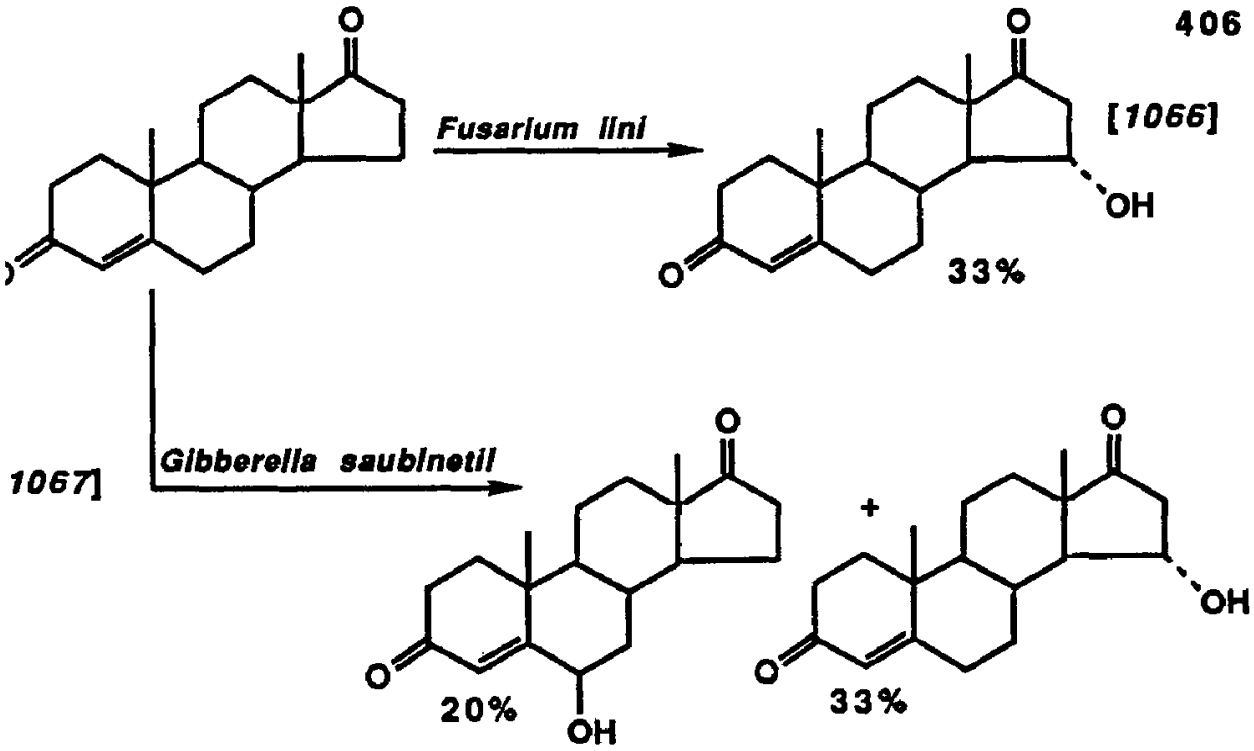
hydroxy-16α,17α-epoxyprogesterone from 16α,17α-epoxyprogesterone [*1079*].

Desoxycorticosterone (4-pregnen-21-ol-3,20-dione) is converted into Δ^4-pregnene-11α,17α-diol-3,20-dione by ***Aspergillus niger*** in 67% yield [*1045*] and to 7α-hydroxydesoxycorticosterone in 36% yield by ***Peziza* sp.** ETH,M.23 [*1064*]. 17α-Hydroxydesoxycorticosterone is hydroxylated in the 11α position by ***Cunninghamella blakesleeana*** H-334 [*1060, 1061*] and in the 15β position by ***Bacillus megaterium*** in 50% yield [*1051*] (equations 404 and 405).





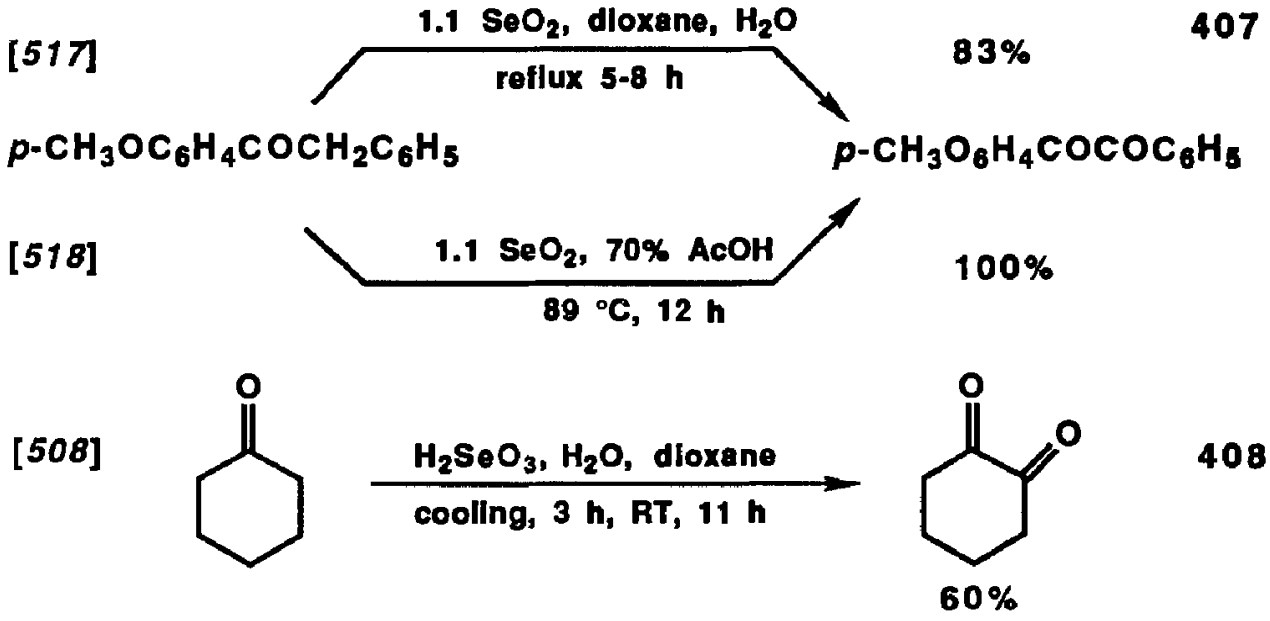
Δ^4-Androstene-3,17-dione gives a 24% yield of 15α-hydroxy-Δ^4-androstene-3,17-dione on treatment with ***Fusarium lini*** at 25–27 °C [*1066*] and a mixture of the same compound (yield 33%) together with 6β-hydroxy-Δ^4-androstene-3,17 dione (yield 20%) on incubation with ***Gibberella saubinetii*** (in ref. 1066, *saubinetti*) [*1066, 1067*] (equation 406).



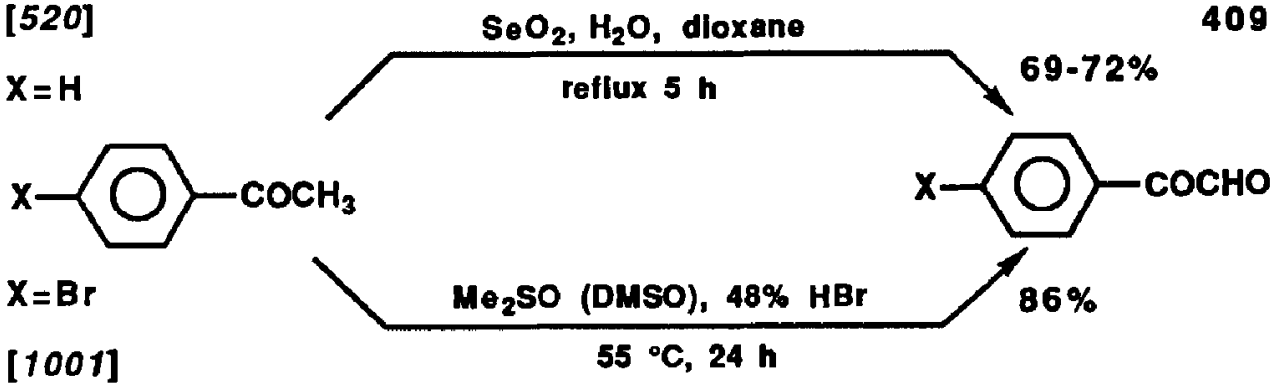
Esters of hydroxy ketones are prepared by acetoxylation with lead tetraacetate in benzene. Cyclohexanone furnishes a 75% yield of 2-acetoxycyclohexanone and a 3% yield of *cis*-2,6-diacetoxycyclohexanone after heating at 80 °C for 8 h [*438*]. Similarly, 3α-hydroxy-5β-pregnan-20-one yields 64% of 21-acetoxy-3α-hydroxy-5β-pregnan-20-one [*439*] after 4 h at room temperature.

Oxidation of Ketones to α-Dicarbonyl Compounds

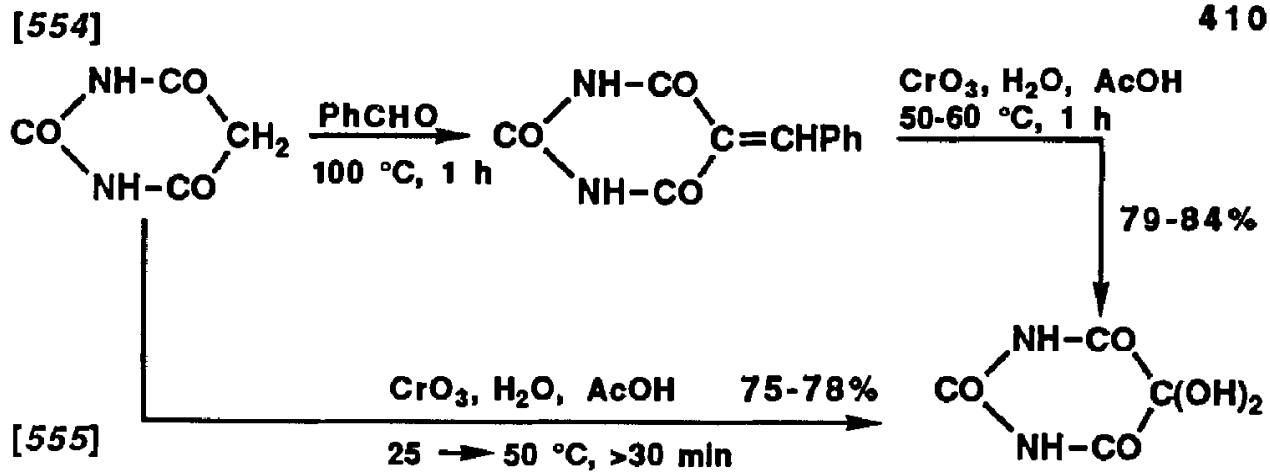
Methyl and methylene groups adjacent to carbonyl groups are easily oxidized to carbonyls to yield α-keto aldehydes or α-diketones. The reagent of choice is **selenium dioxide** or *selenious acid.* The reaction is catalyzed by acids and by acetate ion and proceeds through transition states involving enols of the carbonyl compounds [*518*]. The oxidation is carried out by refluxing the ketone with about 1.1 mol of selenium dioxide in water, dilute acetic acid, dioxane, or aqueous dioxane [*517*]. The byproduct, black selenium, is filtered off, but small amounts of red selenium sometimes remain in a colloidal form and cannot be removed even by distillation of the product. Shaking the product with mercury [*523*] or Raney nickel [*524*] takes care of the residual selenium. The α-dicarbonyl compounds are yellow oils that avidly react with water to form white crystalline hydrates (equations 407 and 408).



Refluxing 2-acetylmesitylene with selenium dioxide in aqueous dioxane for 5 h yields 82.5% of mesitylglyoxal as a yellow oil [*516*]. The reaction is applicable to acetophenones [*520, 678, 1001*]; to deoxybenzoin, its homologues, and their derivatives [*517, 518*]; and to cyclic ketones [*508*]. α-Dicarbonyl compounds are produced in good yields (equation 409).



The oxidation of methylene groups to carbonyls is especially easy if the methylenes are flanked by two carbonyl groups. The methylene group in barbituric acid is oxidized to the keto group by *chromium trioxide* either directly [*555*] or after reaction with benzaldehyde [*554*] (equation 410).



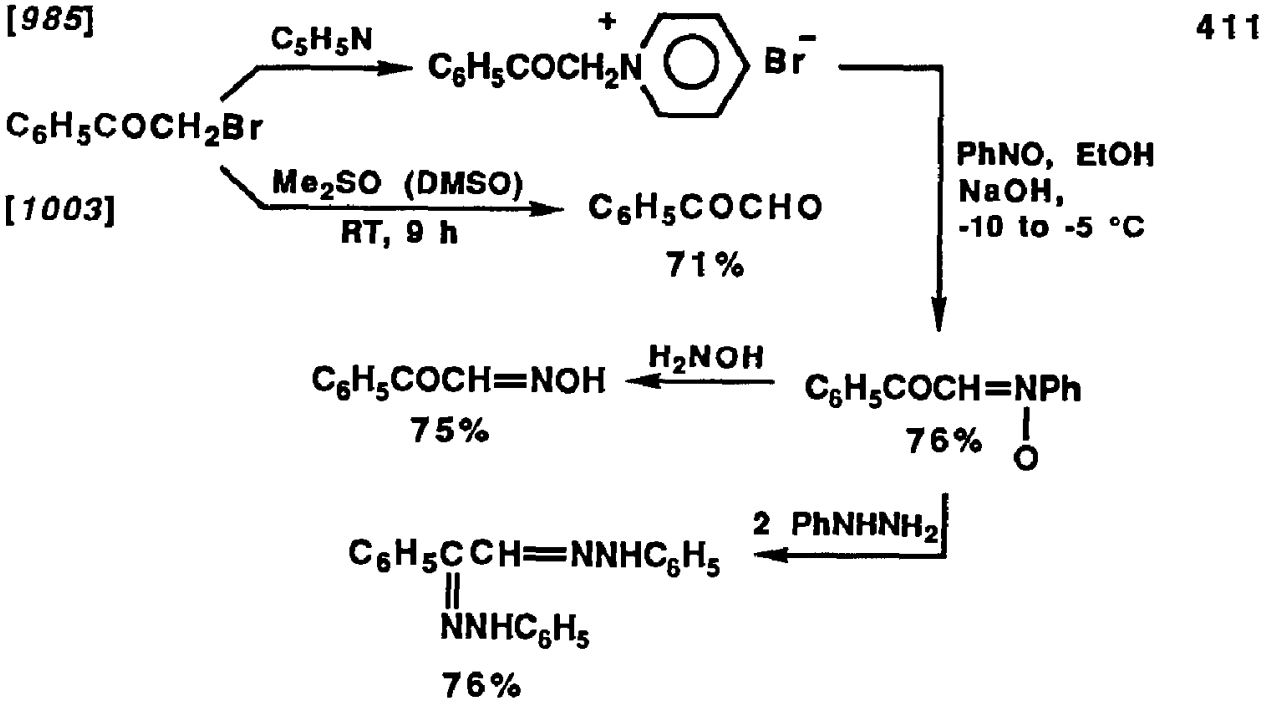
Oxidations of α-methyl and α-methylene groups are also effected by **dimethyl sulfoxide** in the presence of aqueous hydrobromic acid [*1001*] or hydrogen bromide [*1002*] (equation 409).

Heating 1,3-indanedione with dimethyl sulfoxide and anhydrous hydrogen bromide at 70–90 °C, removing the resulting dimethyl sulfide by distillation, and heating the residue for 1 h at 100 °C with 0.3 N hydrochloric acid furnish ninhydrin in 80–82% yield [*1002*].

Before the discovery of the applications of selenium dioxide and dimethyl sulfoxide, oxidations of methylene groups in β-diketones or β-keto esters were achieved with nitroso compounds. Thus acetylacetone boiled with ***p*-nitrosodimethylaniline** in alcoholic sodium hydroxide gives triketopentane in 55% yield [*986*].

The oxidants dimethyl sulfoxide and nitroso compounds react easily with ***α-bromo ketones*** and convert them into ***α-dicarbonyl compounds.*** The reaction with nitroso compounds is usually carried out in the presence of pyridine and proceeds through a nitrone stage. Phenacyl bromide (α-bromoacetophenone) is thus transformed first into phenacylpyridinium bromide and further, with **nitrosobenzene,** into α-ketoaldonitrone, which is subsequently treated with hydroxylamine to give phenylglyoxal monoxime or with phenylhydrazine to give phenylglyoxal osazone [*985*] (equation 411).

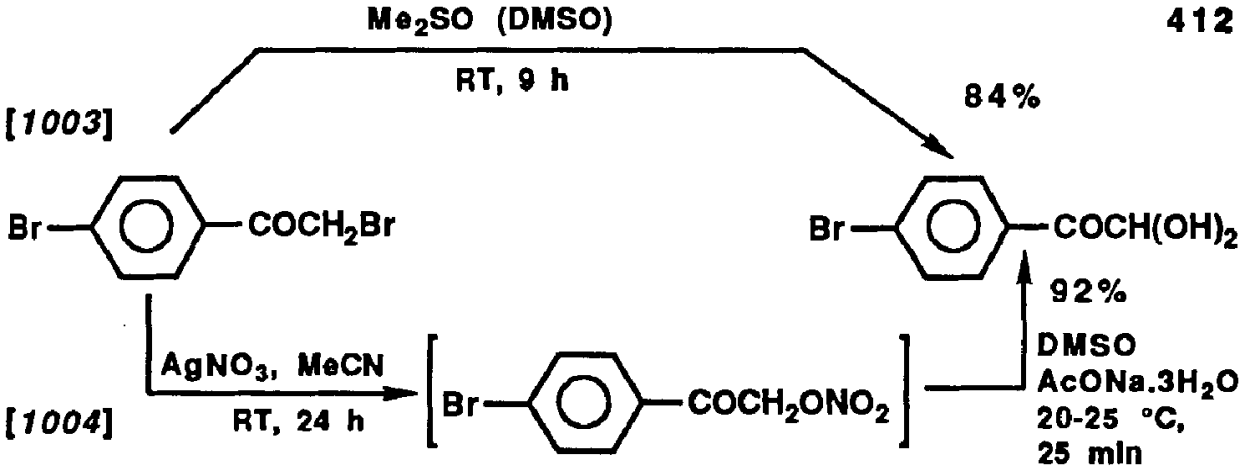
[*985*]



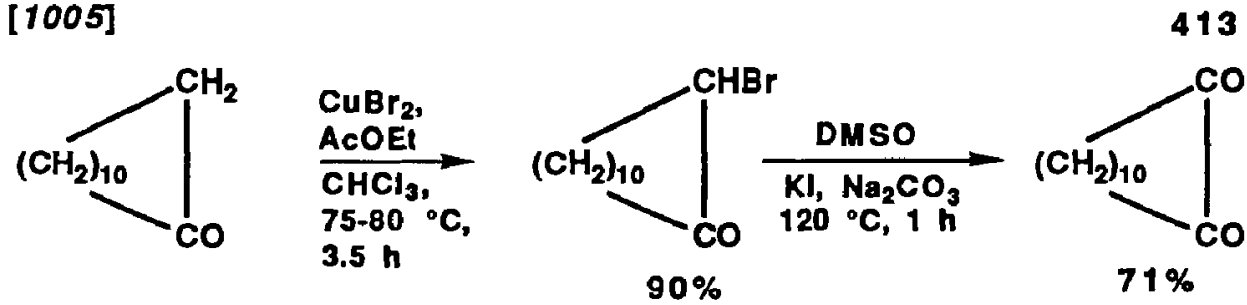
411

A direct and simpler conversion of ω-bromoacetophenone into phenylglyoxal is achieved by treatment with **dimethyl sulfoxide** at room temperature [*1003*]. The reaction of α-bromo ketones with dimethyl sulfoxide can be carried out in anhydrous medium [*1003*], as well as in the presence of water [*1001*]. The mechanism of the reaction in aqueous medium is more

complex, but the results are the same (α-dicarbonyl compounds or their hydrates). Finally, α-bromo ketones may be converted first by silver nitrate into nitrates of α-hydroxy ketones, which are oxidized to α-dicarbonyl compounds by dimethyl sulfoxide [*1004*]. This two-step oxidation is especially useful with sterically hindered α-bromo ketones [*1005*] (equation 412).



Another variation on the same theme is the oxidation of α-bromo ketones by dimethyl sulfoxide in the presence of potassium iodide and sodium carbonate. In situ conversion of the bromo ketone into iodo ketone evidently facilitates the reaction, because it is successful even with secondary α-bromo ketones, with which simple oxidation fails. Depending on the steric environment, the reaction may occur at room temperature, but it may require a temperature of 120 °C. Yields range from 71 to 95% (equation 413) [*1005*].



Oxidation of Ketones to Carboxylic Acids

Oxidations of ketones give carboxylic acids with the same or smaller number of carbon atoms.

THE WILLGERODT REACTION

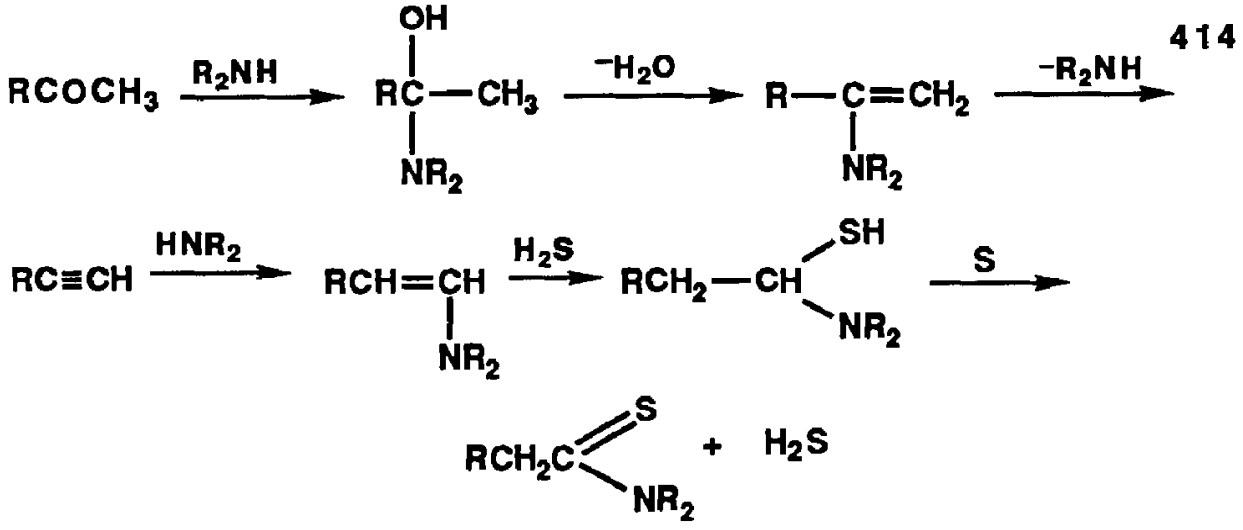
The ***Willgerodt reaction,*** which involves heating ketones with ammonium polysulfide, is the most important route to carboxylic acids without degradation of the carbon chain. It applies especially to methyl and alkyl

ketones of the aromatic series but has been carried out even with aliphatic ketones, although usually with much lower yields. The primary products are thioamides, which are hydrolyzed to amides and carboxylic acids [*501, 1169*]. In the original version of this reaction, a ketone was treated with a mixture of sulfur and ammonium sulfide prepared by saturating a concentrated aqueous solution of ammonia with hydrogen sulfide [*499, 501*]. The temperatures required for the reaction ranged from 160 to 220 °C, and the reaction had to be carried out in sealed tubes or autoclaves. The reaction products, mixtures of amides, thioamides, and sometimes acids, were hydrolyzed with dilute aqueous sodium or potassium hydroxide to give the desired carboxylic acids [*499*].

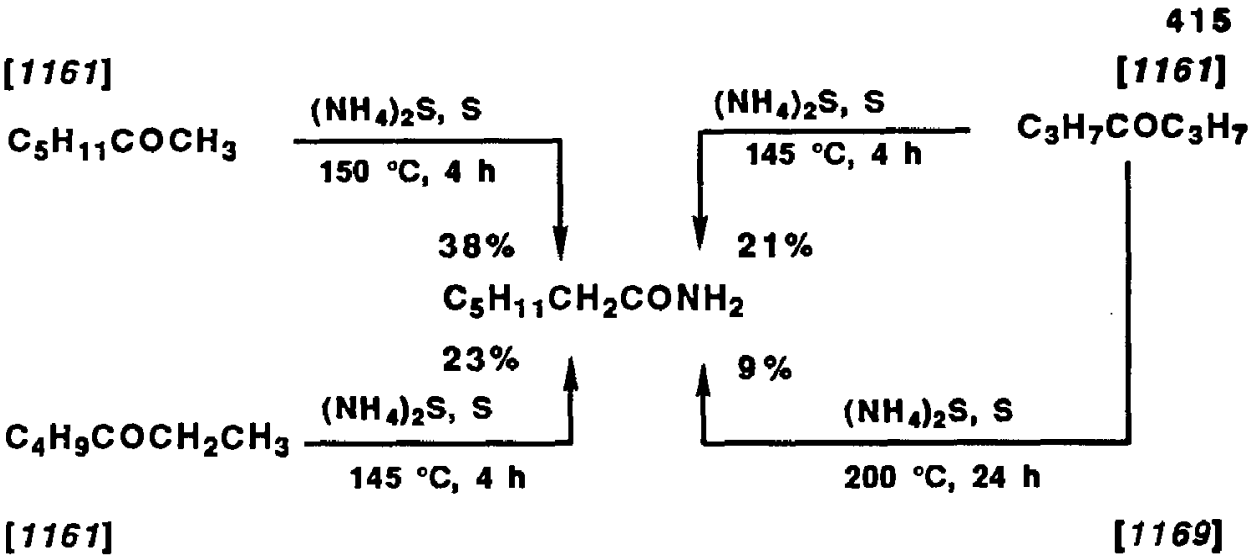
The ***Kindler modification*** dodges heating in closed vessels under pressure by using, instead of aqueous ammonium polysulfide, a mixture of sulfur and morpholine. After being refluxed for 6–12 h, the ketone is converted into the thiomorpholide of the carboxylic acid. Subsequent alkaline hydrolysis yields the carboxylic acid as the final product [*501, 503, 504, 1170*].

The uniqueness of the Willgerodt reaction lies in the ultimate formation of acids from ketones regardless of the position of the carbonyl group in the chain.

Despite numerous studies of the mechanism of the Willgerodt–Kindler reaction, the interpretation of the experimental results still leaves something to be desired. It has been demonstrated that the same amides or thiomorpholides that result from the Willgerodt–Kindler reaction of ketones are formed under the same conditions from terminal mercaptans [*1169*], terminal alkenes [*502, 1169*], and terminal alkynes [*502*]. However, the yields of the products from ketones are consistently higher than those obtained from the other starting materials. In addition, some discrepancies have been found in explaining changes in the carbon skeleton that occur sometimes, especially with branched ketones. Generally, the mechanism may be depicted as a series of addition and elimination reactions (equation 414).

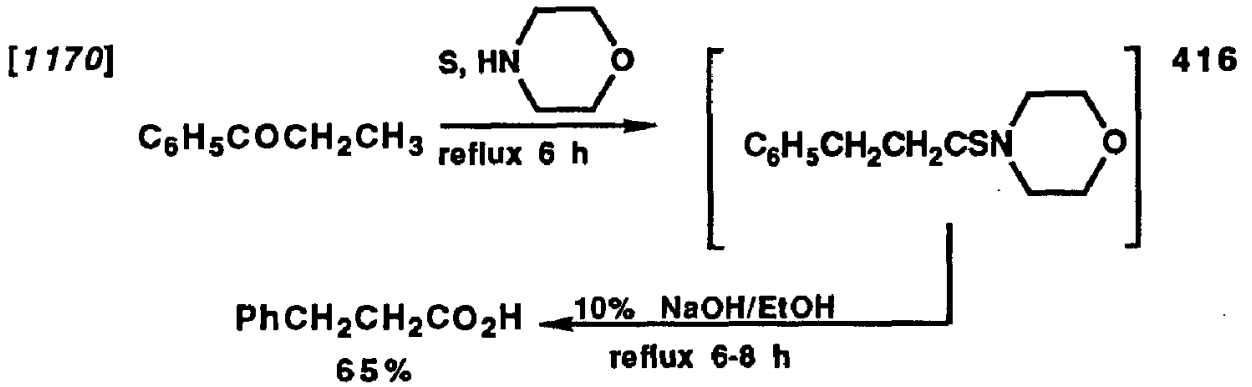


The Willgerodt reaction of isobutyl methyl ketone with ammonium polysulfide at 200 °C gives an 88% yield of isocapronamide after 4 h of heating [*1169*]. Yields of other aliphatic ketones are not nearly as high [*1161, 1169*] (equation 415).



The amides and thioamides obtained by the Willgerodt–Kindler reaction are, sometimes without isolation, converted into acids by refluxing with 15–20% sodium or potassium hydroxide or converted into esters by refluxing for 3 h with alcohols in the presence of gaseous hydrogen chloride [*501*].

The Willgerodt reaction is frequently used to convert alkyl aryl ketones, which are synthesized easily by the Friedel–Crafts reaction, into aryl alkanoic acids with or without isolation of the intermediate thiomorpholides [*499, 504, 1170*] (equation 416).

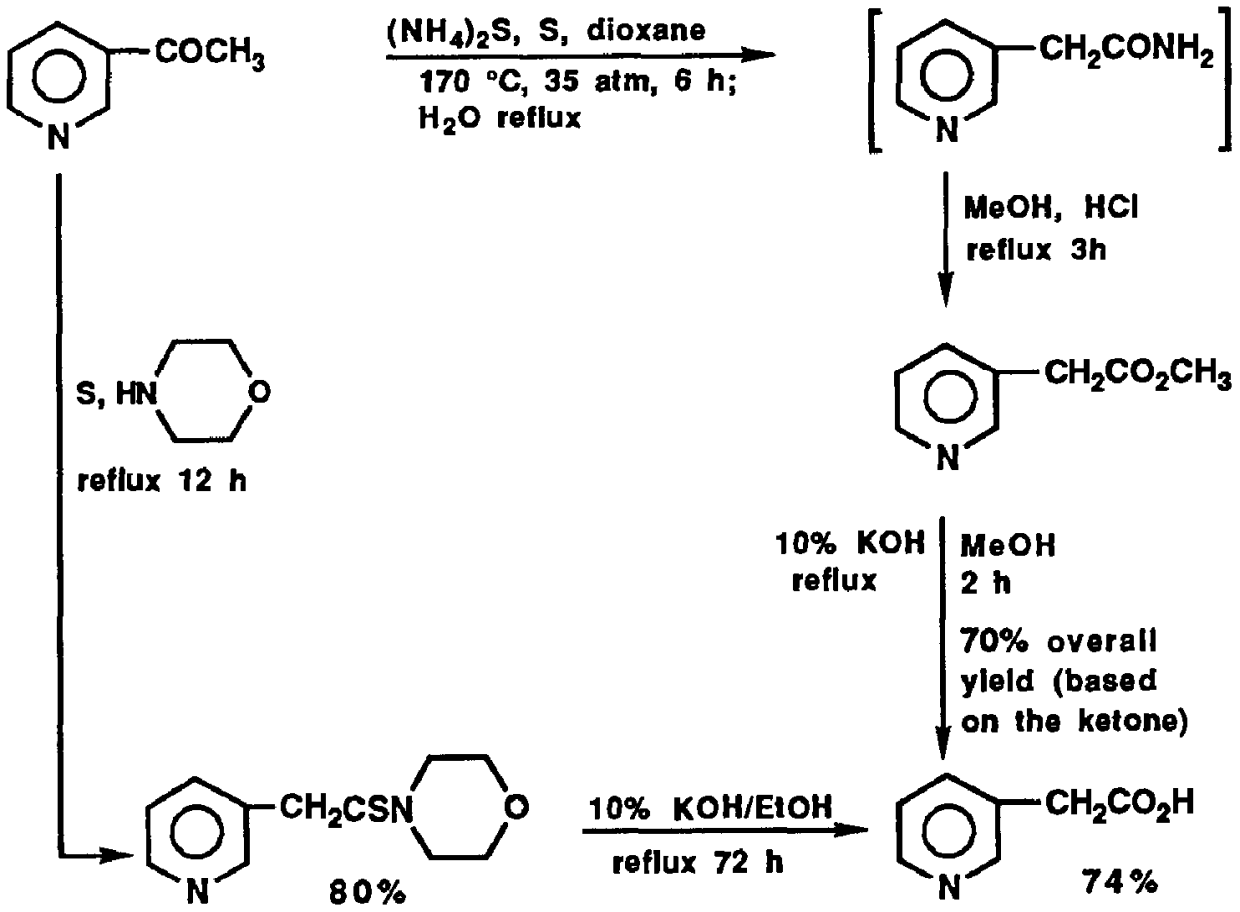


The reaction with sulfur and morpholine can be applied to the preparation of aromatic acids containing polynuclear residues. Methyl 2-naphthyl ketone refluxed for 16 h with a 50% excess of sulfur and morpholine furnishes a 90% yield of the thiomorpholide of 2-naphthylacetic acid, from which 2-naphthylacetic acid is obtained by refluxing for 5 h with aqueous sulfuric and acetic acid (yield 90%). 1-Acenaphthylacetic acid is prepared by heating 1-acetylacenaphthene with sulfur and ammonium sulfide at

160 °C in a sealed tube for 12 h and by hydrolyzing the product amide by refluxing for 4 h with 15% sodium hydroxide (yield 57%) [*499*].

Heterocyclic ketones, too, undergo the Willgerodt reaction with good yields. 3-Pyridylacetic acid (homonicotinic acid) is obtained in 70% yields from methyl 3-pyridyl ketone on heating with ammonium polysulfide [*501*]. 3-Pyridylacetic acid and 4-pyridylacetic acid are also prepared from methyl pyridyl ketones by refluxing for 12 h with sulfur and morpholine, followed by hydrolysis of the isolated thiomorpholide (yield 80%) by refluxing for 72 h with ethanolic potassium hydroxide (yield 74%) [*503*] (equation 417).

[*501*] **417**



[*503*]

OXIDATION OF METHYL KETONES

An interesting reaction, giving an acid with the same number of carbon atoms, takes place when some ketones (having α and α′ hydrogens) are stirred for 10–60 min at 25–80 °C with powdered potassium hydroxide, **carbon tetrachloride,** water, and *tert*-butyl alcohol [*954*] (equation 418). Ketones with α hydrogens but not α′ hydrogens give the same product as that obtained by oxidation with hypohalites [*954*].

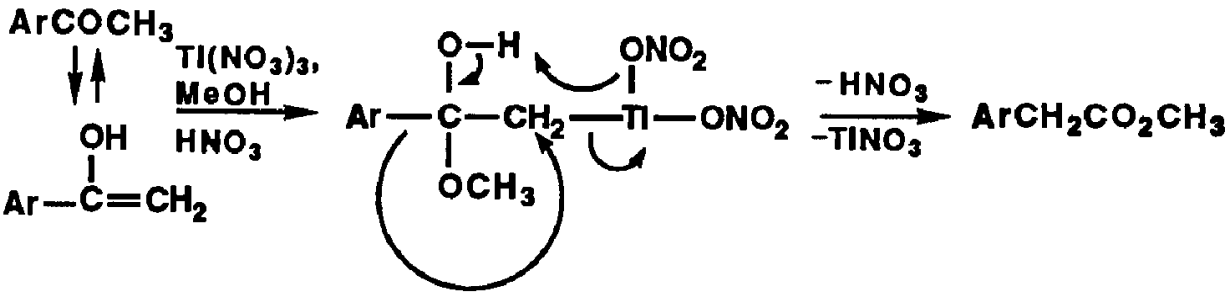
Another way of oxidizing aryl methyl ketones without degradation is by their reaction with **thallium trinitrate** in methanolic solution and in the

[954] 418

$$(C_6H_5)_2CHCOCH_3 \xrightarrow[25\text{-}80\ ^\circ C,\ 10\ min\ to\ 1\ h]{CCl_4,\ KOH,\ t\text{-}BuOH,\ H_2O} Ph_2CHCH_2CO_2H \quad 70\%$$

presence of perchloric acid. Acetophenone and its substituted derivatives are thus converted into methyl arylacetates in 61–94% yields by treatment with thallium triacetate at room temperature for 2–18 h (equation 419) [*414*].

[414] 419



The oxidation of ***methyl ketones to α-keto carboxylic acids*** is rare and is accomplished by treatment with a cold solution of *potassium permanganate*. However, the reaction is not general; acetophenone, *p*-methylacetophenone, and 3,4-dimethylacetophenone are oxidized all the way to the corresponding benzoic acids. On the other hand, 2,4-dimethylacetophenone, when shaken with approximately 1% aqueous potassium permanganate at room temperature, gives 66–72% yields of 2,4-dimethylphenylglyoxylic acid [*888, 889*].

The oxidation of ethyl *p*-xylyl ketone (2,5-dimethylpropiophenone) with cold dilute aqueous potassium permanganate furnishes 2,5-dimethylbenzoylacetic acid (a β-keto acid) in an unstated yield [*890*].

DEGRADATIVE OXIDATIONS OF METHYL KETONES TO ACIDS WITH ONE LESS CARBON ATOM

The conversion of methyl ketones into carboxylic acids having one carbon less is an old method and is popular for its simplicity and high yields. The oxidants are ***hypohalites in alkaline media.*** The reaction consists of two stages, which are carried out in one reaction vessel without the isolation of the intermediates. The methyl group is halogenated to a trichloro-, tribromo-, or, less often, triiodomethyl group, and the trihalomethyl ketone is subsequently hydrolyzed with alkalies to a haloform and a salt of the acid. Instead of hypohalites, halogens in alkaline media can be used [*688, 698, 737*]. Because of the strongly electronegative trihalomethyl group, the hydrolysis is facile and takes place at moderate temperatures.

The hypohalite oxidations are easy to carry out. The methyl ketones, pure or dissolved in dioxane, are added to cooled or warm solutions of hypohalites in water. The reverse order of addition has also been used [*736*]. An exothermic reaction ensues, and the haloform starts forming a heavy organic layer. The excess hypohalite is destroyed by sodium bisulfite, the heavy layer is separated, the residual haloform is removed by steam distillation, and the aqueous solution of the alkaline salt of the carboxylic acid is treated with sulfuric or hydrochloric acid (equation 420).

$$RCOCH_3 \xrightarrow{3\ NaOX} RCOCX_3 \xrightarrow{NaOH} RCO_2Na + CHX_3 \qquad 420$$

X = Cl, Br, or I

The reaction is applicable to saturated and unsaturated methyl ketones of the aliphatic and alicyclic series, to aryl methyl ketones, and to methyl ketones of heterocyclic aromatic compounds.

Pinacolone (*tert*-butyl methyl ketone) is transformed into pivalic acid (trimethylacetic acid) in 71–74% yield [*737*]. Mesityl oxide is converted into β,β-dimethylacrylic acid in 49–53% yield [*703*]. Isopropenyl methyl ketone gives methacrylic acid in 41% yield [*697*], and pregnenolone acetate furnishes 3-acetoxyetienic acid in 91–95% yield [*1171*] (equations 421–424).

Aryl methyl ketones give generally high yields of acids on treatment with hypohalites [*688, 696, 698, 736*]. The reaction of 1,3,5-triacetylbenzene and sodium hypochlorite results in a 94% yield of trimesic acid [*688*], and that of methyl β-naphthyl ketone and sodium hypochlorite gives an 87–88% yield of β-naphthoic acid [*698*]. 4-Acetyl-4′-methoxybiphenyl is converted

[*737*] 421

$(CH_3)_3CCOCH_3$ —(1. Br_2, NaOH, 0-10 °C, 15-20 min; 2. 0-10 °C, 1 h, RT, 3 h; 3. steam distillation; 4. H_2SO_4)→ $(CH_3)_3CCO_2H$ 71-74%

[*954*] $(CH_3)_3CCOCH_3$ —(KOH, CCl_4, *t*-BuOH, H_2O; 25-60 °C, 10-60 min)→ $(CH_3)_3CCO_2H$ 80%

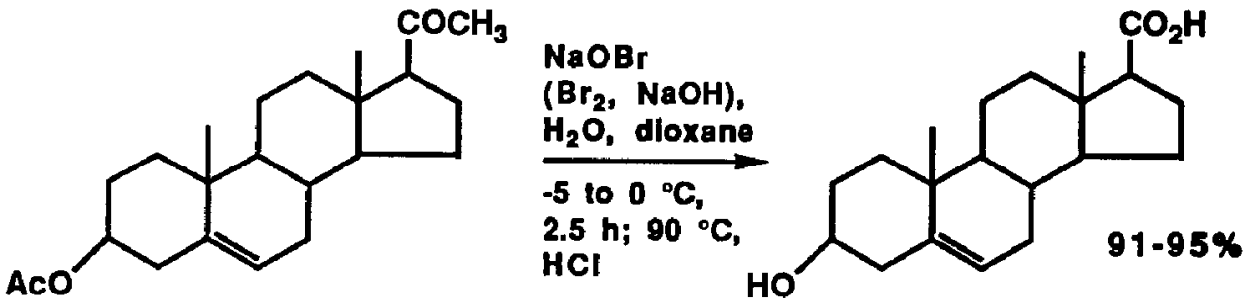
[*703*] 422

$(CH_3)_2C{=}CHCOCH_3$ —(KOCl, H_2O, dioxane; reflux 3-4 h; H_2SO_4)→ $(CH_3)_2C{=}CHCO_2H$ 49-53%

[*697*] 423

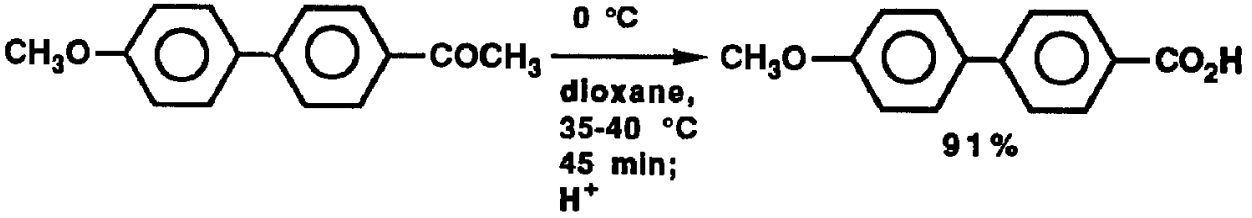
$CH_2{=}C(CH_3)COCH_3$ —(3 N NaOCl, 6 N NaOH; <20 °C, >1 h; H_2SO_4)→ $CH_2{=}C(CH_3)CO_2H$ 41%

[1171] 424



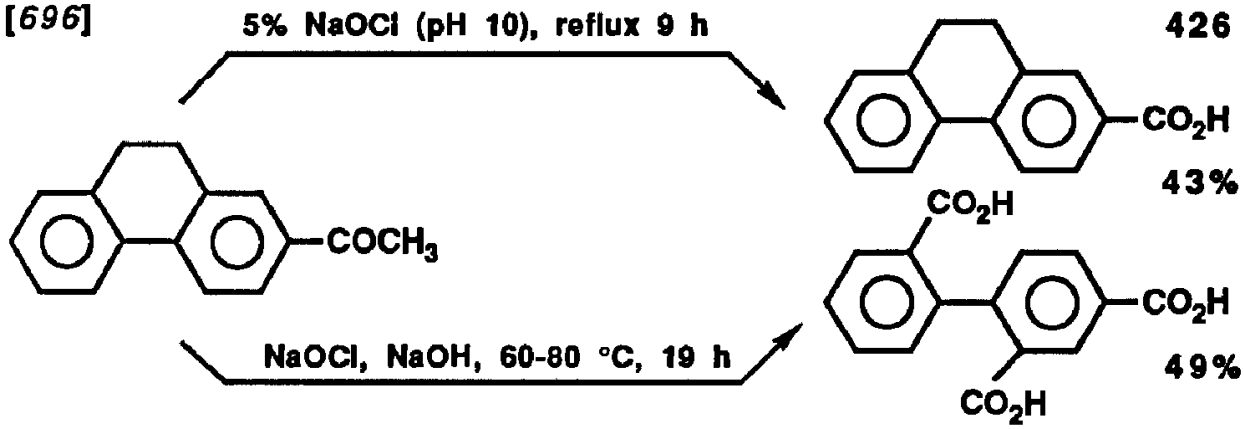
by sodium hypobromite into 4-(4′-methoxyphenyl)benzoic acid (equation 425) [*736*].

[736] 425



Side reactions are observed in some hypohalite oxidations. Thus 2-acetyl-9,10-dihydrophenanthrene furnishes, depending on the reaction conditions used, either the expected 9,10-dihydrophenanthrene-2-carboxylic acid, or biphenyl-2,2′,4-tricarboxylic acid (equation 426) [*696*].

[696] 426

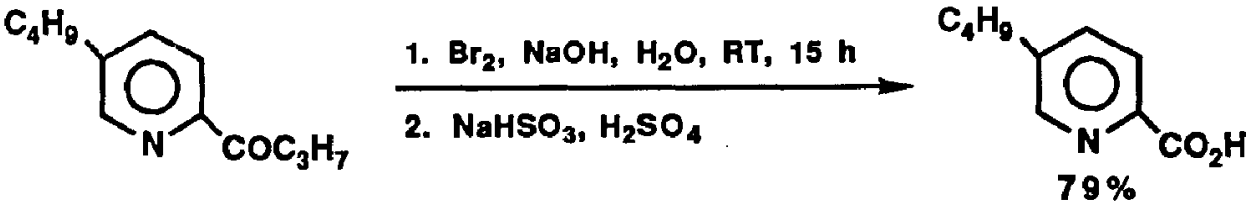


Refluxing *p*-ethylacetophenone with sodium hypochlorite results not only in the oxidation of the methyl ketone but also in the conversion of the ethyl group into carboxyl so that the product is terephthalic acid in 95% yield [*696*].

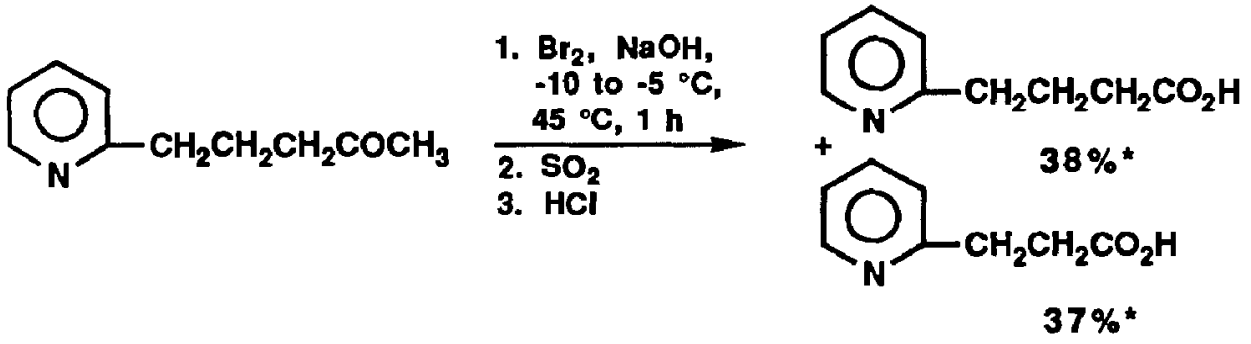
In a few instances, not only methyl ketones but other alkyl ketones are degraded to shorter carboxylic acids resulting from halogenation of the ***methylene*** group adjacent to the carbonyl and subsequent hydrolysis [*103, 160, 1172*]. The reaction between propiophenone and sodium hypobromite at 22–25 °C gives a 96% yield of benzoic acid [*303*]. Under similar conditions, 5-butyl-2-butyrylpyridine is converted into 5-butyl-α-picolinic acid in 79% yield [*160*]. Methyl 3-(α-pyridyl)propyl ketone yields not only the

expected 4-(α-pyridyl)butyric acid but also 3-(α-pyridyl)propionic acid [*103*] (equations 427 and 428).

[*160*] 427



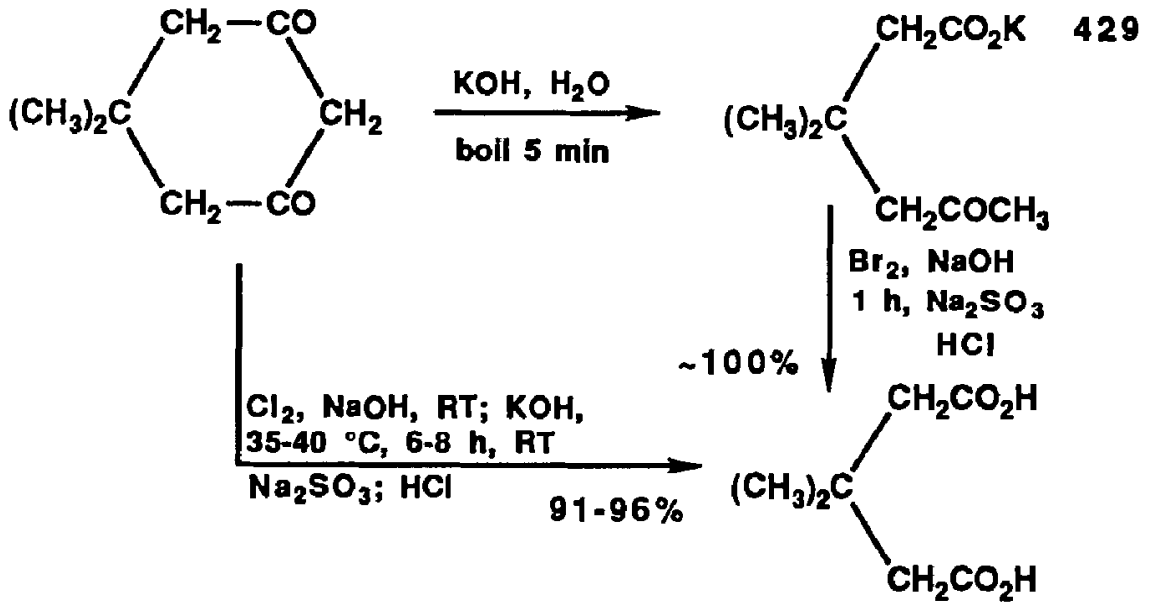
[*103*] 428



*The yield is based on the reacted ketone.

Dimethyldihydroresorcinol (dimedone) is converted into β,β-dimethylglutaric acid on treatment with sodium hypochlorite or sodium hypobromite. As a β-diketone, it suffers alkaline hydrolysis to 3,3-dimethyl-5-ketohexanoic acid, which undergoes regular hypohalite degradation of the methyl ketone end (equation 429) [*735*]. Both the hydrolytic opening of the ring and the hypohalite reaction are accomplished in one step [*699*].

[*735*]

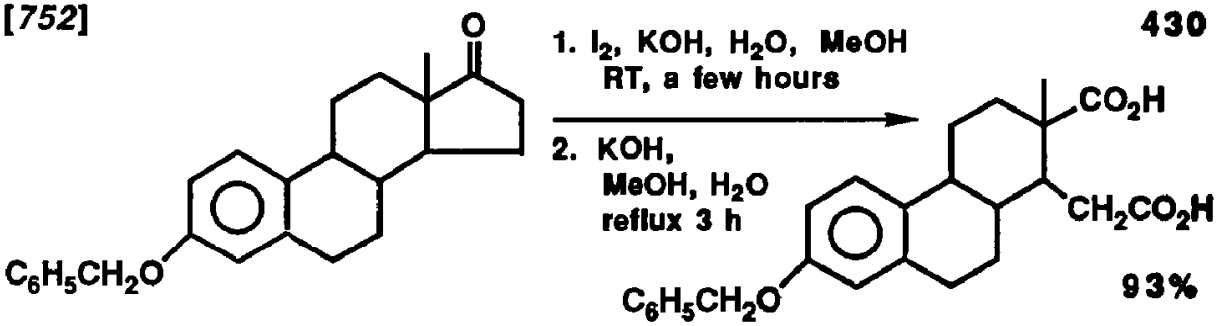


429

The vast majority of the preparative oxidations of methyl ketones are carried out with alkaline hypochlorites or hypobromites. The same effect can be achieved by alkaline hypoiodites, but examples are scarce. One example is the opening of the D ring of benzyl estrone to benzyl marrianolic

acid by treatment with potassium hypoiodite prepared in situ from iodine and potassium hydroxide (equation 430) [*752*].

[*752*]

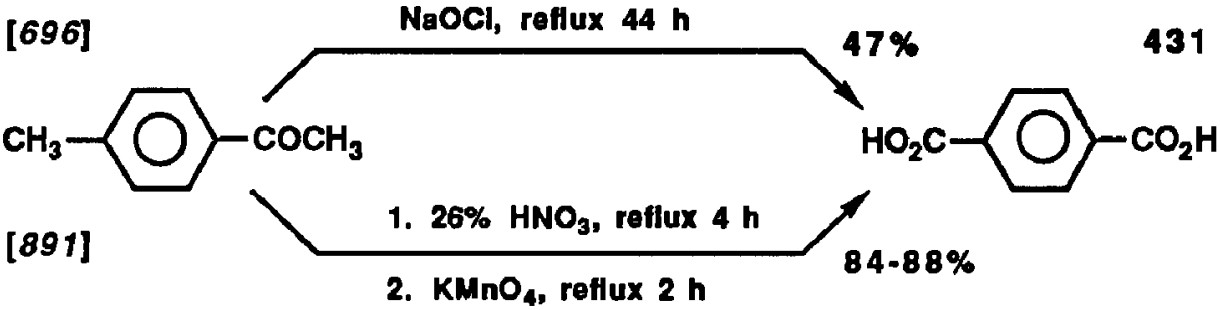


430

Hypoiodites are used for qualitative tests for methyl ketones ***(Lieben test)***. For this purpose, a compound to be tested is stirred with an aqueous solution of sodium hydroxide (80 mol/mol of methyl ketone). Iodine (4.5 mol of I_2) is added portionwise with stirring, and the mixture is set aside for 20 min at 25 °C before acidification. In the presence of a methyl keto group, a yellow heavy precipitate of iodoform settles at the bottom of the test tube. Iodoform can be identified easily not only by its characteristic smell but also by its melting point (120–123 °C) [*1173*]. This test applies not only to methyl ketones but to any compound that can be converted in the reaction medium into a species containing the $COCH_3$ group, for example, isopropyl or ethyl alcohol.

Hypohalites rarely affect alkyl groups bound to aromatic rings. However, *p*-methyl- and *p*-ethylacetophenone give terephthalic acid when refluxed with sodium hypochlorite [*696*]. The same product is obtained by the oxidation of *p*-methylacetophenone with *nitric acid* and *potassium permanganate* (equation 431) [*891*].

[*696*]

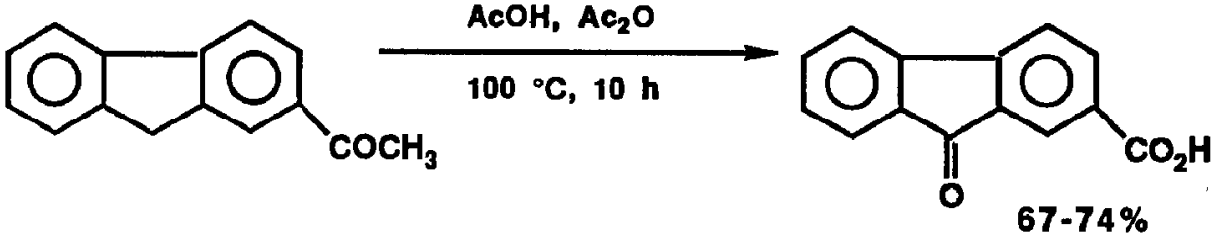


431

[*891*]

The oxidation of a methyl ketone to a carboxylic acid with one less carbon by oxidants other than hypohalites is exemplified by the oxidation of 2-acetylfluorene with **sodium dichromate.** In addition to the methyl keto group, the methylene group is also oxidized (equation 432) [*626*].

[*626*]

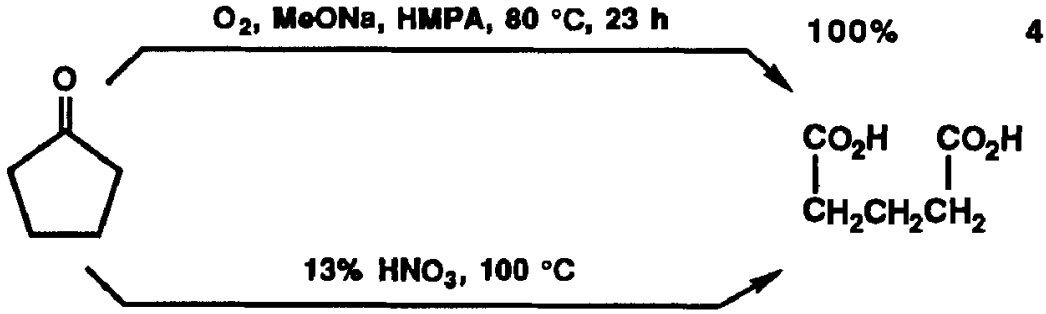


432

OXIDATIVE CLEAVAGE OF KETONES

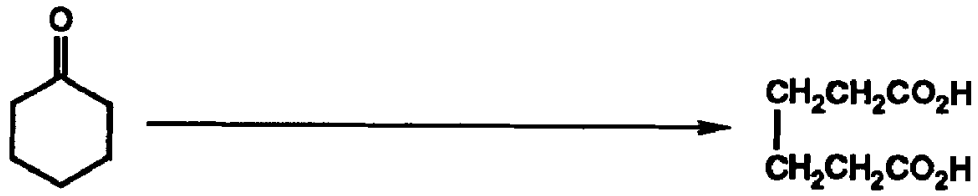
Strong oxidation agents such as **chromic acid** and **potassium permanganate** oxidize ketones with the simultaneous cleavage of the carbon skeleton next to the carbonyl group. With nonsymmetrical ketones, as many as four products may result. The practical applications of such oxidations are therefore limited to cases where, for structural reasons, the cleavage of the carbon skeleton takes place preferentially at only one side of the carbonyl or where identical products result from the cleavage on either side of the keto group, as occurs with symmetrical cyclic ketones.

The oxidation of cyclopentanone with oxygen [*52*] or with **nitric acid** [*471*] gives glutaric acid in 100 or 82% yields, respectively (equation 433).



The reaction with nitric acid is exothermic, and careful control of temperature is needed to prevent further oxidation and degradation of the product.

Analogously, cyclohexanone can be oxidized to adipic acid with several oxidants (equation 434) [*52, 192, 1174*]. As in the case of cyclopentanone, too energetic oxidation gives lower homologous acids, which have to be separated from the main product.

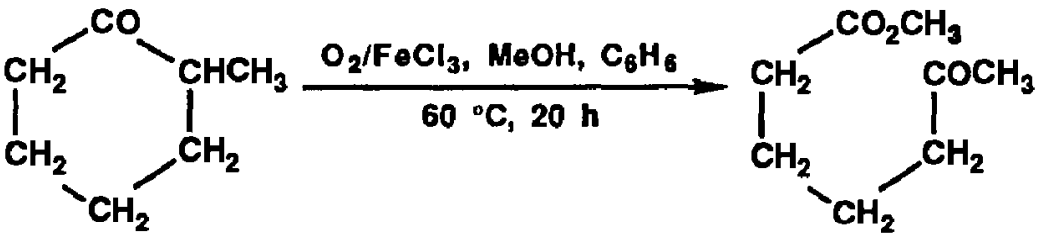


[*52*]	O_2, MeONa, HMPA, 23.5 °C, 20 h	100%
[*192*]	KO_2, C_6H_6, $(C_8H_{17})_3NMeCl$ (Aliquat 336), RT, 1-8 h	92%
[*1174*]	33% HNO_3, warm, gradual addition	~100%

2-Methylcyclohexanone is converted regiospecifically into 6-ketoheptanoic acid (or its esters in the presence of alcohols) by **oxygen** in the presence of ferric salts as catalysts (equation 435) [*67*].

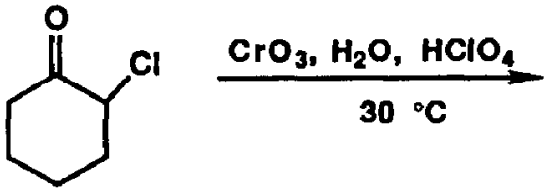
The oxidation of ketones with **chromic acid** proceeds through enol intermediates, as proven by kinetic measurements [*1175*]. 2-Chlorocyclohexanone is oxidized predominantly to adipic acid, with 2-chloroadipic acid, glutaric acid, and succinic acid as byproducts (equation 436) [*1175*].

[67]



93% 435

[1175]



$HO_2CCH_2CH_2CH_2CH_2CO_2H$ 77%
$HO_2CCH_2CH_2CH_2CHClCO_2H$ 14%
$HO_2CCH_2CH_2CH_2CO_2H$ 5%
$HO_2CCH_2CH_2CO_2H$ 4%

436

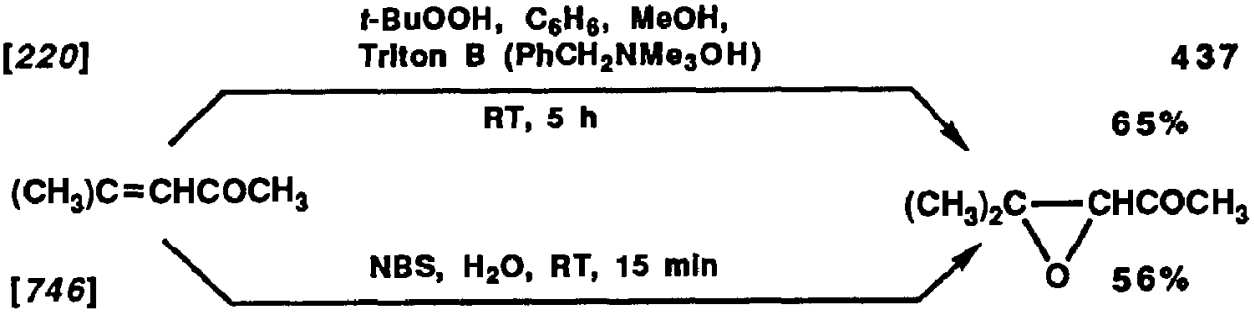
Oxidation of Unsaturated Ketones

Oxidations of unsaturated ketones affecting solely the carbonyl group were discussed in the section Baeyer–Villiger Reaction of Functionalized Ketones (equations 379–399). In this section, only such oxidations that add oxygen to the double bond will be described.

The most dependable reagent for the ***epoxidation*** of unsaturated ketones is **hydrogen peroxide**, especially in alkaline media [*142, 143, 149, 151*]. Because the Baeyer–Villiger reaction is acid-catalyzed, it does not take place during epoxidations with alkaline hydrogen peroxide or its neutral derivatives, such as *tert*-butyl hydroperoxide [*220*]. Most examples of epoxidation involve unsaturated ketones with conjugated double bonds.

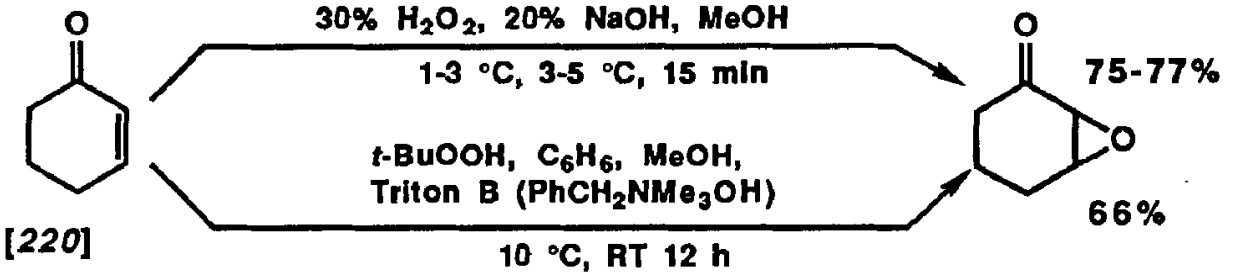
Peroxy acids may epoxidize unsaturated ketones [*299, 332*], but a concomitant Baeyer–Villiger reaction is possible [*254*] (equations 389 and 391). Other ways of forming epoxy ketones are reactions with salts of hypochloric acid [*691, 704*] and with *N*-bromosuccinimide [*746*]. Mesityl oxide is converted into its epoxide, as shown in equation 437 [*142, 220, 254, 746*].

[220] 437



2,3-Cyclohexen-1-one oxide is obtained from 2-cyclohexen-1-one on treatment with hydrogen peroxide [*151*] or *tert*-butyl hydroperoxide [*220*] (equation 438). 1,4-Naphthoquinone is oxidized with sodium [*691*] or cal-

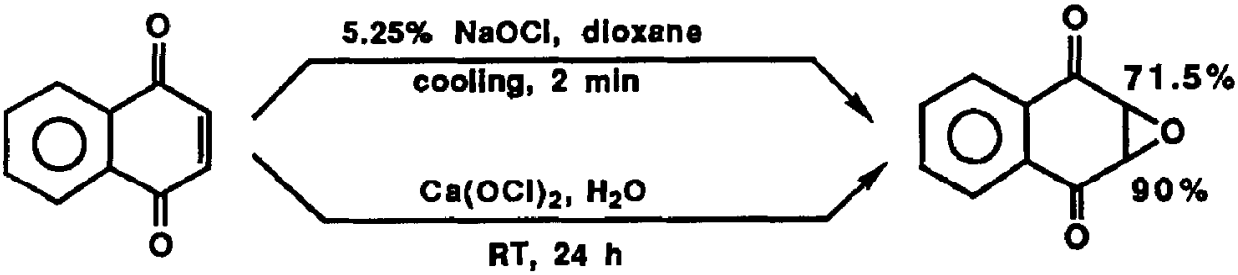
[151] 438



[220]

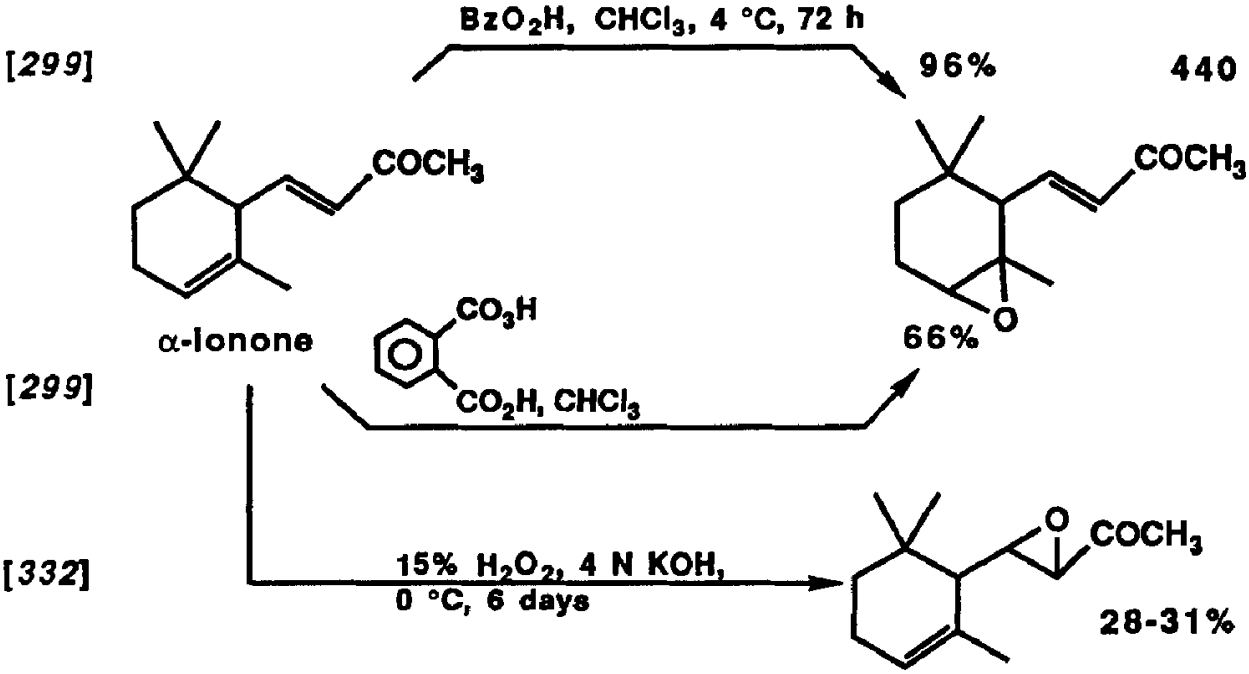
cium hypochlorite [*704*] to 2,3-epoxy-2,3-dihydro-1,4-naphthoquinone [*691*] (equation 439).

[691] 439



[704]

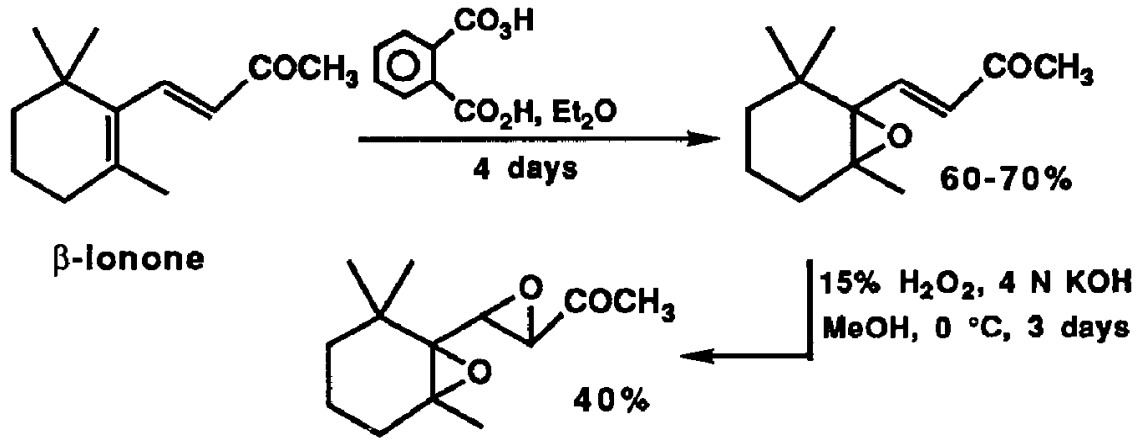
In α-ionone, peroxybenzoic acid and peroxyphthalic acid epoxidize solely the endocyclic double bond to give 3,4-epoxy-α-ionone in 96.5 and 66% yields, respectively [*299*]. Alkaline hydrogen peroxide, on the other hand, epoxidizes only the double bond conjugated with carbonyl to give a 28–31% yield of α-ionone-α′,β′-epoxide [*332*] (equation 440).



β-Ionone, when treated with peroxybenzoic acid [*299*] or with peroxyphthalic acid [*332*], is converted into the 2,3-epoxide in respective yields of 86 or 60–70% [*332*]. The 2,3-epoxide product is further epoxidized at

the double bond conjugated with the keto group to yield β-ionone-3,4,α′,β′-diepoxide in a 40% yield (equation 441) [*332*].

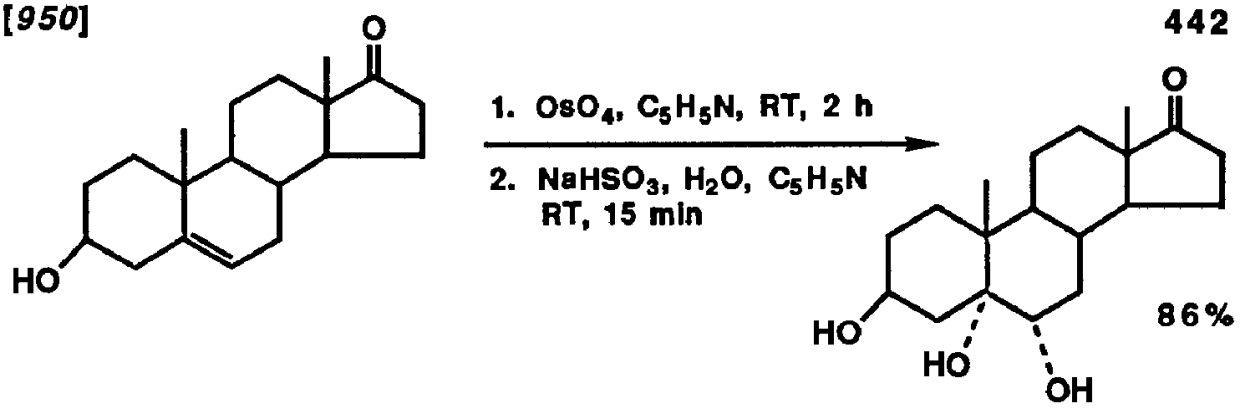
[*332*] 441



HYDROXYLATION OF UNSATURATED KETONES

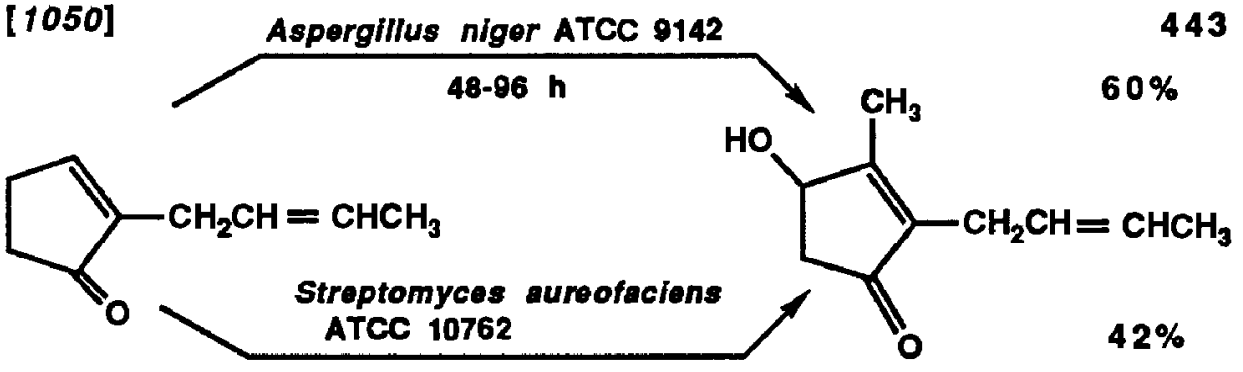
The addition of two hydroxylic groups to the double bonds of unsaturated ketones is carried out by the same methods used for hydroxylations of alkenes (equations 71–83). As an example, hydroxylation of the double bond in 3β-hydroxyandrost-5-en-17-one is accomplished by treatment with one equivalent of **osmium tetroxide** in pyridine and subsequent reductive cleavage of the osmate ester with sodium bisulfite in aqueous pyridine (equation 442) [*950*].

[*950*] 442



Hydroxylation in the γ position of an α,β-unsaturated ketone is exemplified by the biological transformation of cinerone into cinerolone by ***Aspergillus niger*** or ***Streptomyces aureofaciens*** (equation 443) [*1050*].

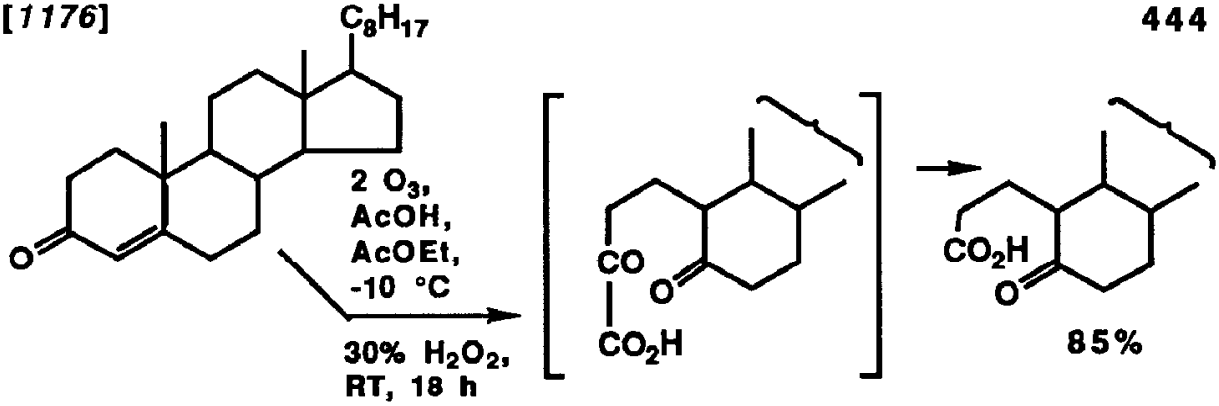
[*1050*] 443



CLEAVAGE OF UNSATURATED KETONES

The oxidative cleavage of unsaturated ketones takes place under the same conditions as that of alkenes or other unsaturated derivatives. The fate of the primary fission product depends on the position of the double bond with respect to the carbonyl group and on the subsequent reactions. ***Ozonization*** of Δ^4-cholestenone in acetic acid and ethyl acetate, followed by treatment with 30% hydrogen peroxide, gives a keto acid, evidently resulting from the decomposition of the primarily formed diketo acid (equation 444) [*1176*].

[*1176*] 444



Oxidation of Hydroxy Ketones to Diketones

Oxidations of hydroxy ketones to diketones occur frequently in steroidal alcohols. If the alcoholic group, usually secondary, is remote enough from the keto group, its oxidation takes place independently and is achieved by the same reagents that are used for the oxidation of alcohols. A solution of **chromium trioxide** in aqueous sulfuric acid oxidizes 5-pregnen-3β-ol-20-one in acetone solution at room temperature within 2–5 min to 5-pregnen-3,20-dione in 90% yield [*579*]. Similarly, 11β-hydroxytestosterone 17-acetate is transformed by chromium trioxide in 80% acetic acid at room temperature in 30 min into 11-ketotestosterone 17-acetate in 92% yield [*807*].

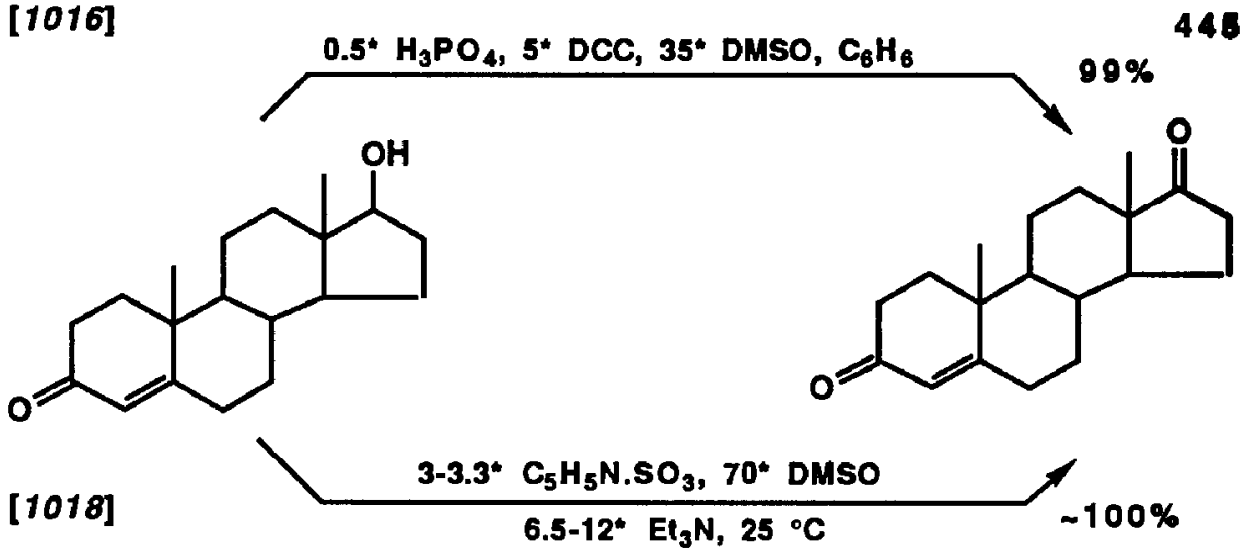
A reagent suitable for oxidations of steroidal hydroxy ketones to diketones is **dimethyl sulfoxide** in the presence of various activators. It converts testosterone into 4-androstene-3,17-dione in 95–100% yields (equation 445) [*1016, 1018*].

Oxidations of steroidal keto alcohols to diketones are frequently accomplished ***biochemically.*** In addition, isomerization of double bonds, dehydrogenations, and hydroxylations often take place.

Dehydroandrosterone [*1088*] and dehydroepiandrosterone [*1056*] are converted by **bacterium-infected yeast** and ***Corynebacterium simplex*** ATCC 6946 into 4-androstene-3,17-dione in 87 and 55% yields, respectively (equation 446) [*1056*].

Oxidations of 11β-hydroxysteroids to 11-ketosteroids are accompanied

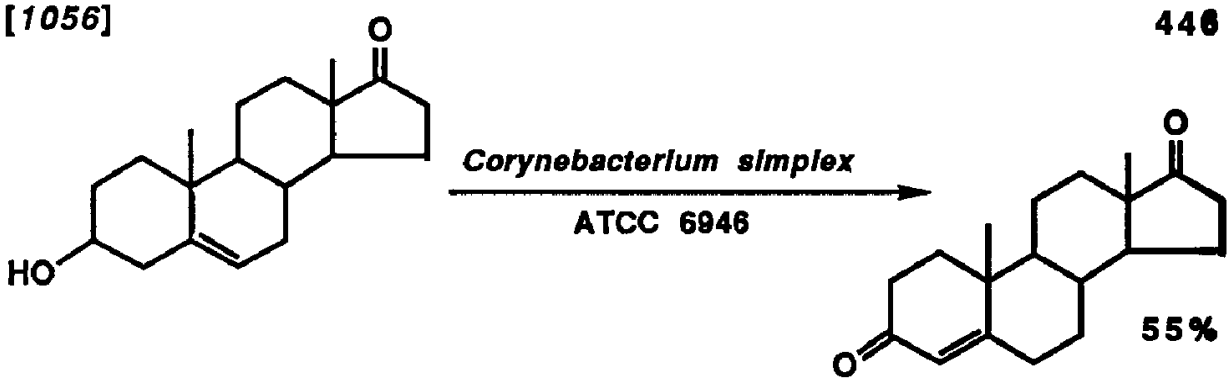
[*1016*] 445



[*1018*]

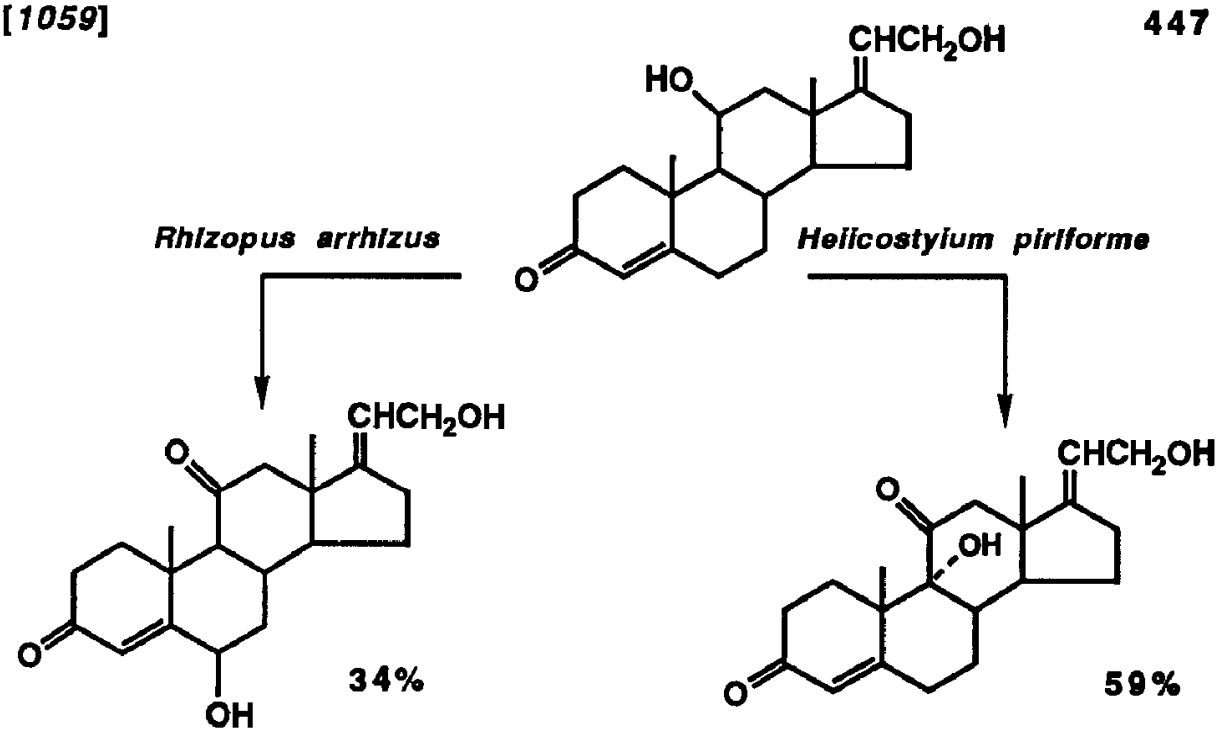
*Values are moles per mole of alcohol.

[*1056*] 446



by β-hydroxylation in position 6 with ***Rhizopus arrhizus*** or in position 9α with ***Helicostylum piriforme*** or ***Cunninghamella blakesleeana*** [*1059*]. Only the secondary alcoholic group is affected. The primary hydroxyl group remains intact (equation 447) [*1059*].

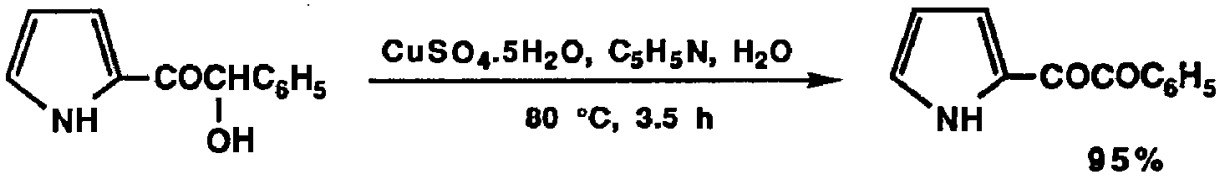
[*1059*] 447



When the hydroxylic group is in an α position with respect to the keto group, as in ***acyloins,*** oxidation to α-diketones is easily accomplished by many oxidants.

Air in the presence of cupric sulfate as a catalyst oxidizes benzoin to benzil in 86% yield [*62*]. **Cupric sulfate** in stoichiometric amounts converts furoin into furil in 63% yield in aqueous pyridine at 100 °C after 2 h [*351*]. α-Hydroxybenzyl 2-pyrryl ketone is oxidized by stoichiometric amounts of cupric sulfate to phenyl-2-pyrrylglyoxal in 95% yield in aqueous pyridine at 85 °C after 3.5 h (equation 448) [*352*].

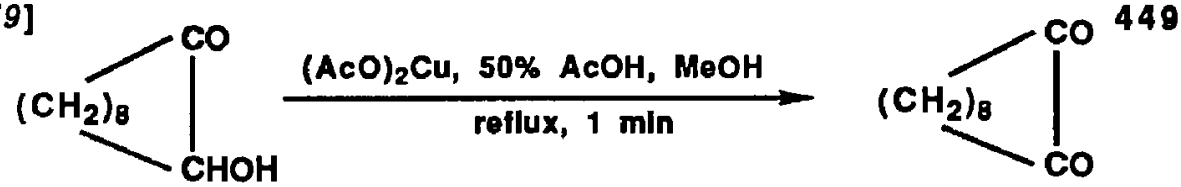
[*352*] 448



95%

Cupric acetate is also used for oxidations of acyloins. Diphenylacetoin is converted almost quantitatively into dibenzylglyoxal when refluxed with cupric acetate in 70% acetic acid for 7 min [*358*]. Sebacoin (2-hydroxycyclodecanone) gives sebacil in 88–89% (equation 449) yield [*359*].

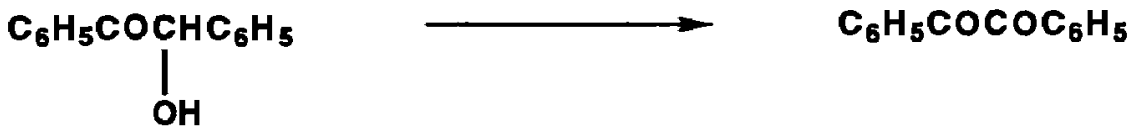
[*359*] 449



88-89%

A very suitable oxidant for the conversion of acyloins into α-diketones is **ammonium nitrate** in the presence of catalytic amounts of cupric acetate. This reagent converts benzoin into benzil in 90% yield [*476*]. The same result is obtained with bismuth sesquioxide [*481*] and **sodium bromate** [*740*] (equation 450). On the other hand, **ceric ammonium nitrate** does not give benzil but cleaves the bond between the alcoholic and the keto groups and cleaves benzoin into benzaldehyde and benzoic acid [*425*].

450



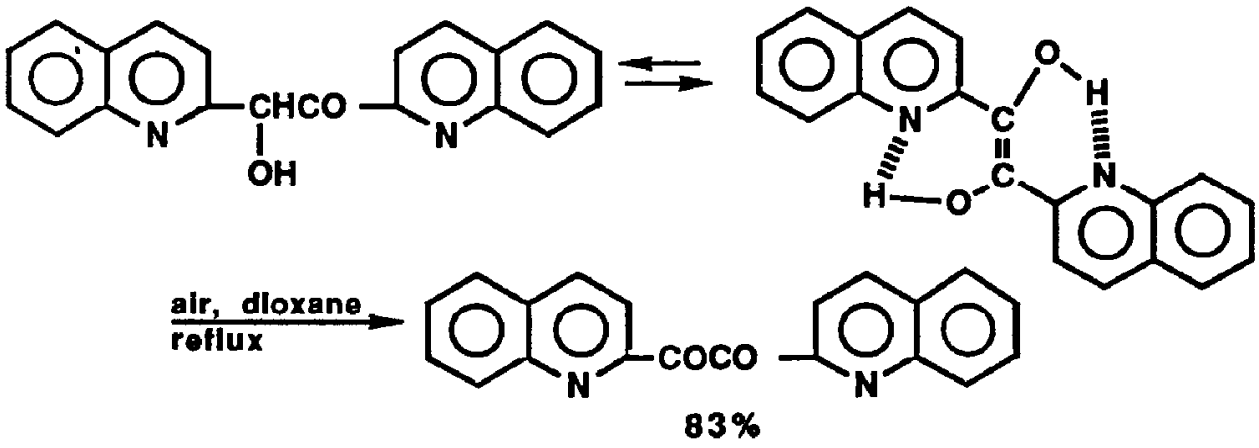
[*62*]	$O_2/CuSO_4$, C_5H_5N, H_2O, 100 °C, 2 h	86%
[*476*]	$NH_4NO_3/(AcO)_2Cu$, 80% AcOH, reflux 1.5 h	90%
[*481*]	Bi_2O_3, AcOH, $EtOCH_2CH_2OH$, 104 °C, 1 h	95%
[*740*]	$NaBrO_3$, NaOH, H_2O, 100 °C, 5-6 h	84-90%*

*The product is benzilic acid resulting from the rearrangement of benzil, formed as the primary product.

The conversion of pivaloin into pivalil (2,2,5,5-tetramethyl-3,4-hexanedione) is best accomplished with chromium trioxide in acetic acid and dilute sulfuric acid (yield 87%) [*406*].

Acyloins are tautomeric with 1,2-enediols, and in some cases, enediols predominate if they are stabilized by resonance and hydrogen bonds. Such is the case with quinaldoin, which is easily oxidized to quinaldil by passing air through its boiling solution in dioxane (equation 451) [*1177*].

[*1177*] **451**



Oxidation of Dicarbonyl Compounds to Carboxylic Acids

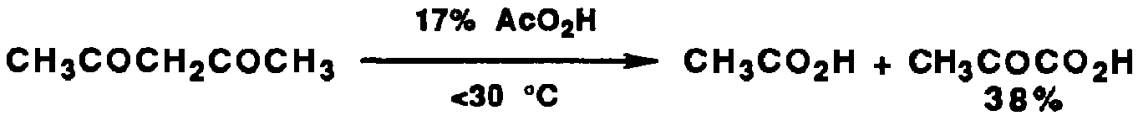
The conversion of α-dicarbonyl compounds into carboxylic acids is the monopoly of **hydrogen peroxide and peroxy acids.** The reaction is actually a ***Baeyer–Villiger oxidation*** producing acid anhydrides, which, in some cases, were isolated. Benzil, when refluxed for 15 min with 95% hydrogen peroxide and 70% perchloric acid, gives benzoic acid. Anisil, under the same conditions, is converted into anisic acid [*269*]. 9,10-Diketostearic acid, on treatment with 8.7% peroxyacetic acid at room temperature for 1 day, furnishes 90 and 95% yields, respectively, of pelargonic acid and azelaic acid [*271*].

Cyclic α-diketones and *o*-quinones give, under comparable conditions, dicarboxylic acids. β-Naphthoquinone is converted in 83% yield into *o*-carboxyallocinnamic acid by 9% peroxyacetic acid in an exothermic reaction [*271*] (equation 393).

The treatment of tetrafluoro-*o*-benzoquinone with 40% peroxyacetic acid at 70–75 °C for 4.75 h degrades the quinone to difluoromaleic acid in 55% yield. The same acid is obtained in 59% yield under similar conditions from fluoranil (tetrafluoro-*p*-benzoquinone) [*273*].

The oxidation of β-diketones and β-keto esters with peroxyacetic acid [*270*] and peroxyphthalic acid [*333*] leads to complex products that ultimately undergo hydrolysis. In the case of acetylacetone, the products are acetic acid and pyruvic acid [*270*] (equation 452).

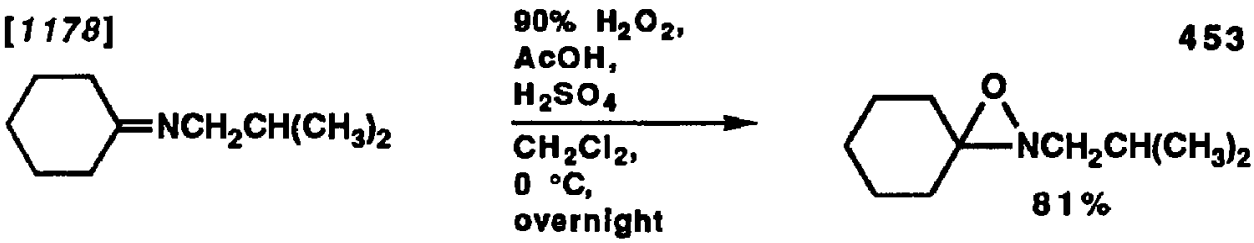
[270] 452



Oxidation of Ketone Derivatives

The treatment of ***ketimines*** (Schiff bases) with peroxyacetic acid gives ***oxaziridines*** (equation 453) [*1178*].

[1178] 453



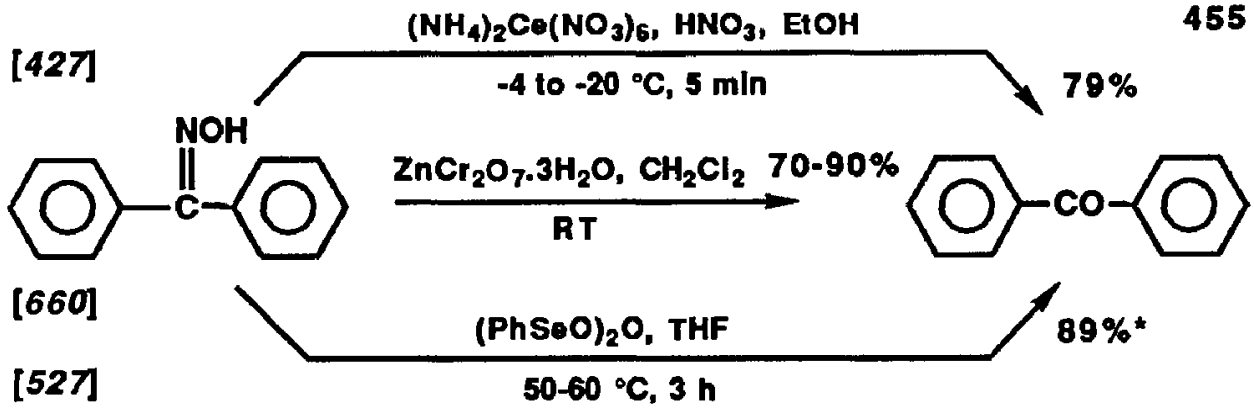
Oximes are either oxidized to ***nitro compounds*** [*823*] or converted into their respective ***parent ketones*** [*422, 427, 527, 660*]. Oxidation to the parent ketones applies also to ***semicarbazones*** [*427, 527*], dimethylhydrazones [*528, 529*], tosylhydrazones [*527, 528, 529*], ***phenylhydrazones*** [*527*], *p*-nitrophenylhydrazones [*527*], and 2,4-dinitrophenylhydrazones [*527*] (equations 454–456).

Because such exotic reagents as those shown in equations 455 and 456 are not readily available, cleavage by ozone may be preferred [*1179*].

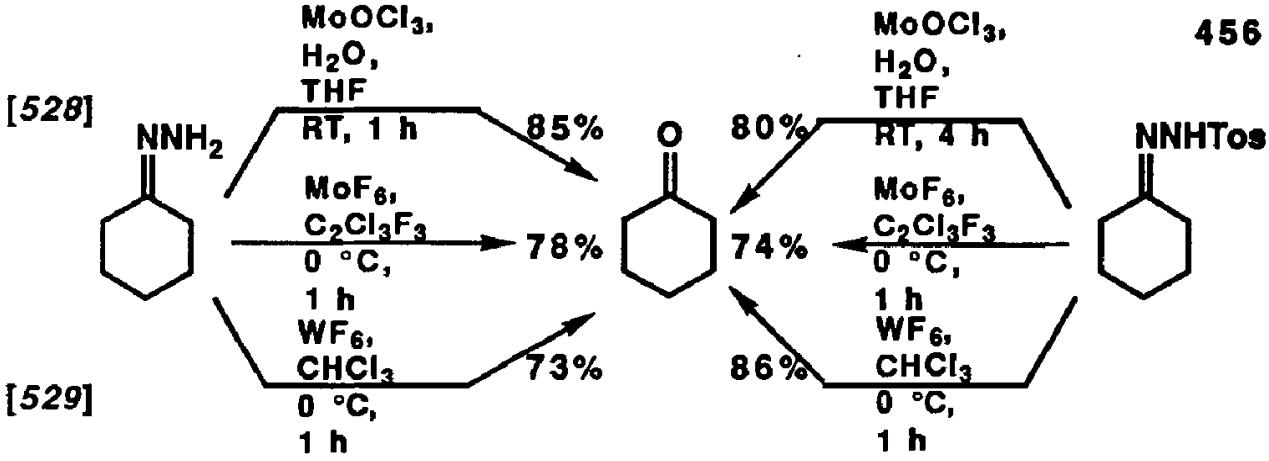
Ketone derivatives whose oxidations have wide applications in synthesis are ***hydrazones*** and ***vicinal dihydrazones***. Hydrazones are transformed into ***diazo compounds***, and vicinal dihydrazones are converted into ***acetylenes***. By far the most widely used oxidant is yellow **mercuric oxide**

[823] 454

455

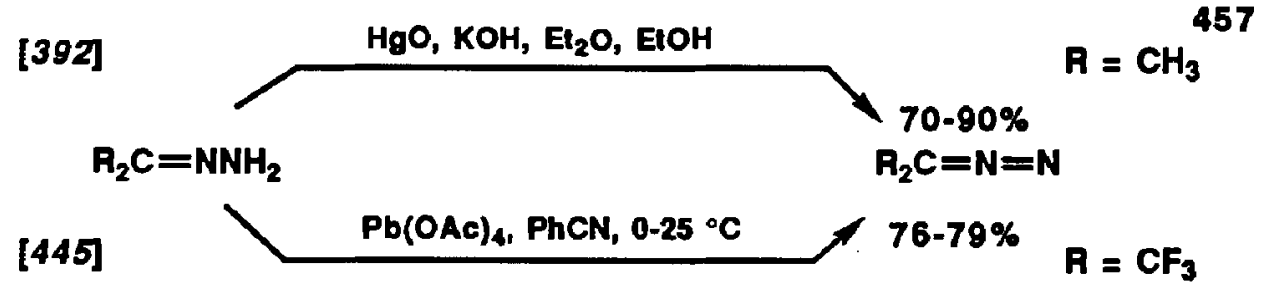


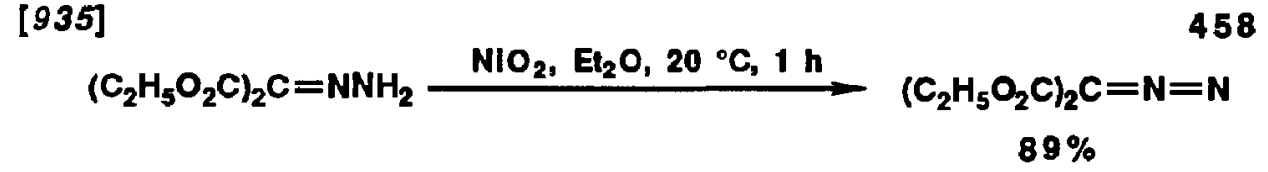
*The same yield was obtained from the semicarbazone after 2 h, and a 90% yield was obtained from the phenylhydrazone after 3 h [*527*].



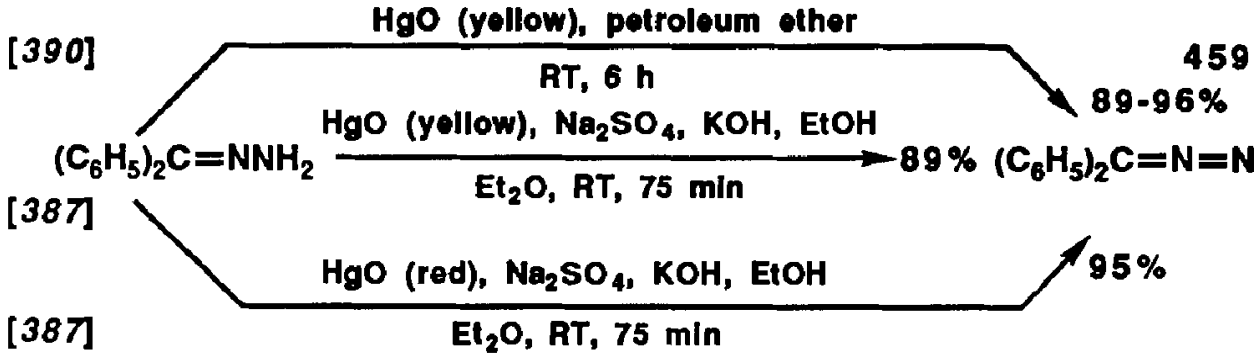
[*387, 388, 390, 391, 392*]. Red mercuric oxide is less reactive [*387*]. Less often, oxidations are carried out with silver oxide [*370*], mercurous trifluoroacetate [*405*], mercuric trifluoroacetate [*406*], lead tetraacetate [*445*], manganese dioxide [*370*], and nickel peroxide [*935*]. The most common solvents are pentane, petroleum ether, benzene, toluene, ether, and benzonitrile. Basic catalysts such as alcoholic potassium hydroxide are sometimes used. Anhydrous calcium oxide, sodium sulfate, and magnesium sulfate are frequently added to remove the water of reaction. The reaction temperatures range from room temperature to the reflux temperature of the solvents.

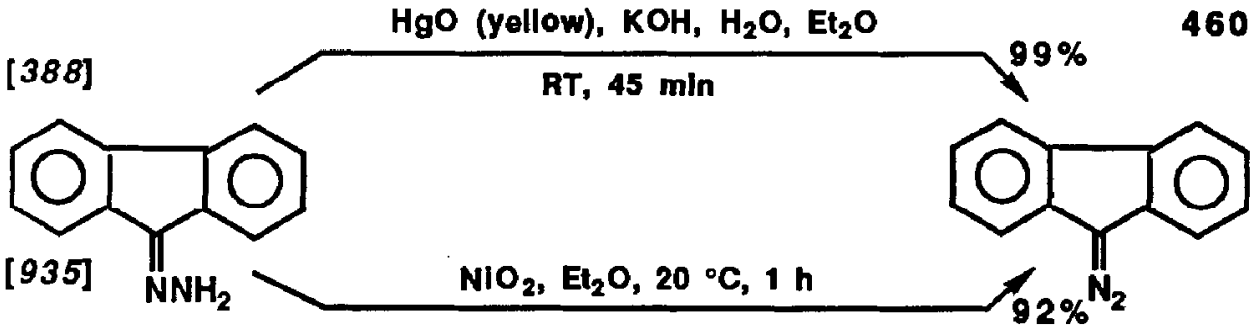
Examples of the oxidation of aliphatic hydrazones are the conversion of acetone hydrazone into 2-diazopropane [*386, 392*], of hexafluoroacetone hydrazone into 2-diazohexafluoropropane [*445*], of 4-octanone hydrazone into 4-diazooctane [*386*], and of the hydrazone of diethyl mesoxalate into diethyl diazomalonate [*935*] (equations 457 and 458).

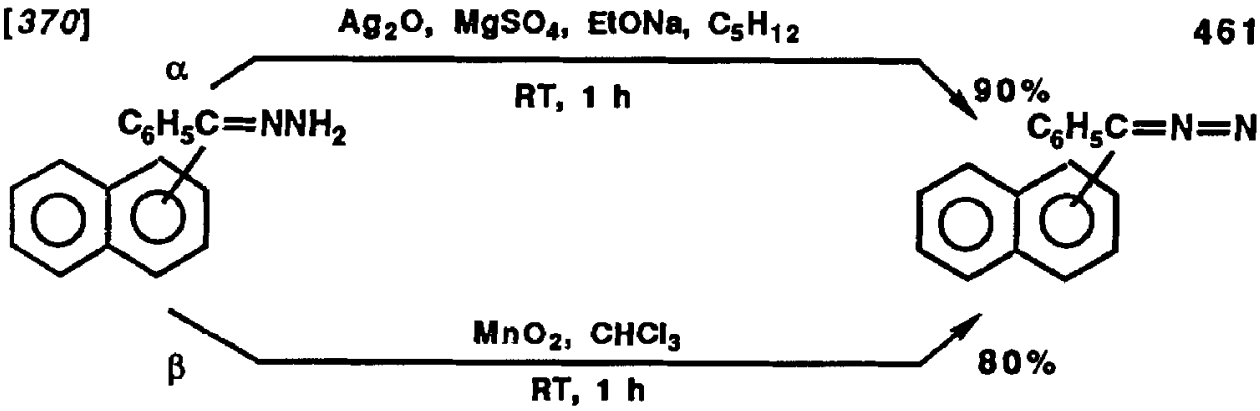




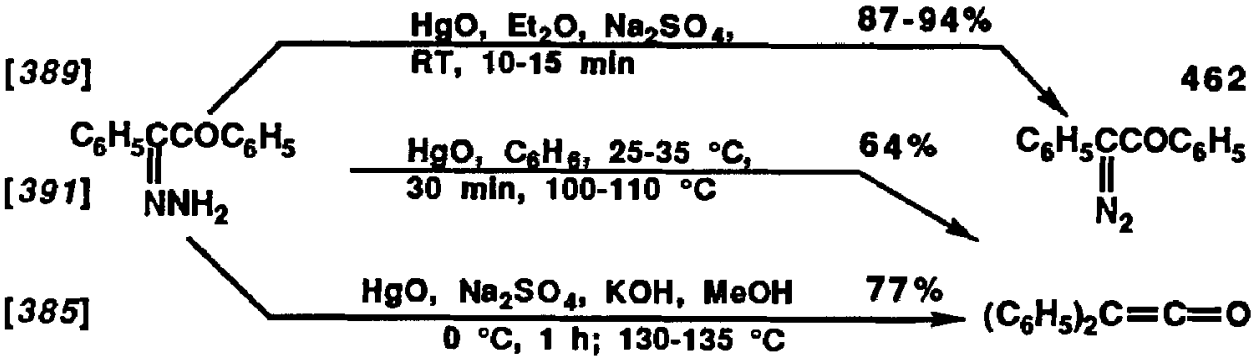
Of aromatic ketone hydrazones, benzophenone hydrazone is oxidized with yellow mercuric oxide [*387, 390*] or red mercuric oxide [*387*], fluorenone hydrazone is oxidized with mercuric oxide [*388*] or nickel peroxide [*935*], and di-α-thienyl ketone hydrazone and phenyl naphthyl ketone hydrazones are oxidized with silver oxide or manganese dioxide [*370*] (equations 459–461).







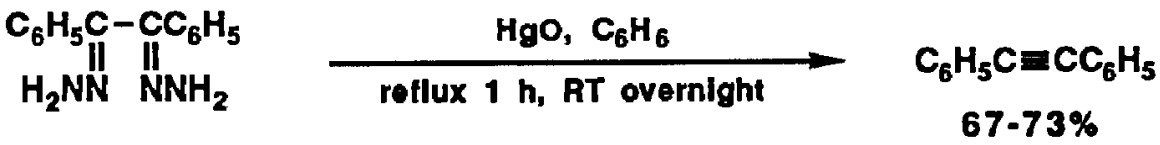
Monohydrazones of α-diketones are converted into α-diazoketones [*389, 391, 406*], which, at higher temperature, give ketenes [*385, 406*] (equation 462).



Dihydrazones of α-diketones, when treated with mercuric oxide at higher temperatures, yield ***acetylenes*** [*393, 394, 395, 396*]. Diphenylacetylene is obtained by refluxing benzil dihydrazone with mercuric oxide [*396*] in benzene or by refluxing benzil monohydrazone with mercurous trifluoroacetate in ether for 2 h (yield 43%) [*405*]. The oxidation of dihydrazones

of α-diketones is suitable for the synthesis of macrocyclic acetylenes [*393*, *394*] (equations 463 and 464).

[*396*] 463



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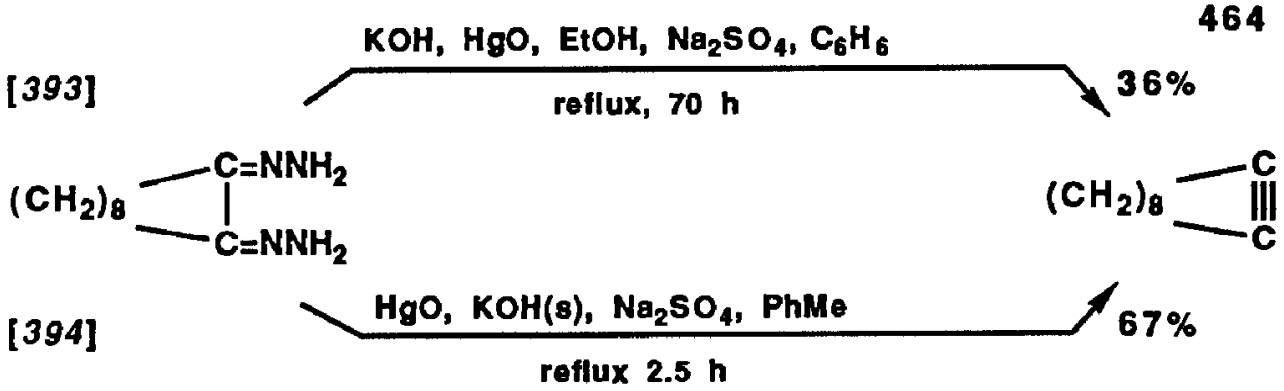


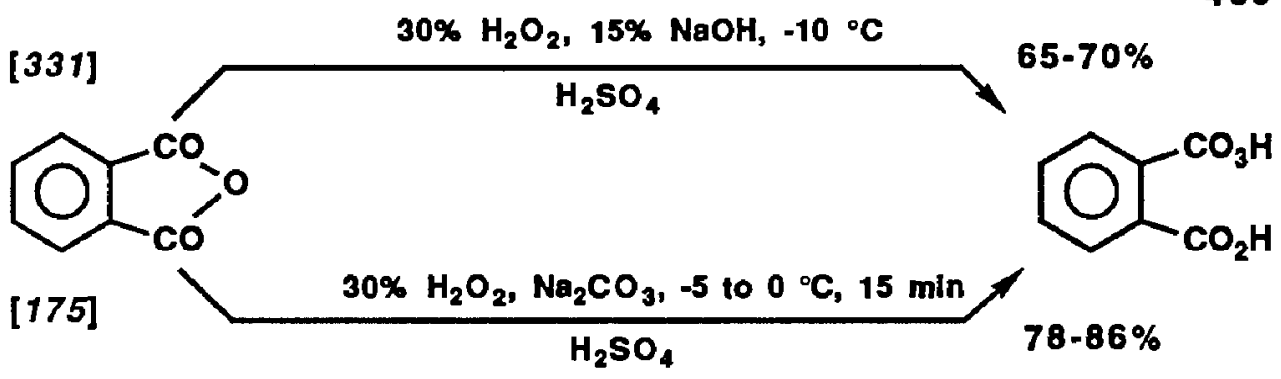
CARBOXYLIC ACIDS AND THEIR DERIVATIVES

Oxidation of Carboxylic Acids and Their Esters

The oxidation of ***carboxylic acids to peroxy acids*** is carried out by hydrogen peroxide. Lauric acid heated with 90% hydrogen peroxide in the presence of *p*-toluenesulfonic acid and a detergent for 2.25 h furnishes 95% of peroxylauric acid [*174*]. Benzoic acid is converted into peroxybenzoic acid in 85–90% yield on treatment with 70% hydrogen peroxide in the presence of methanesulfonic acid at 25–30 °C for 2.5 h [*176*].

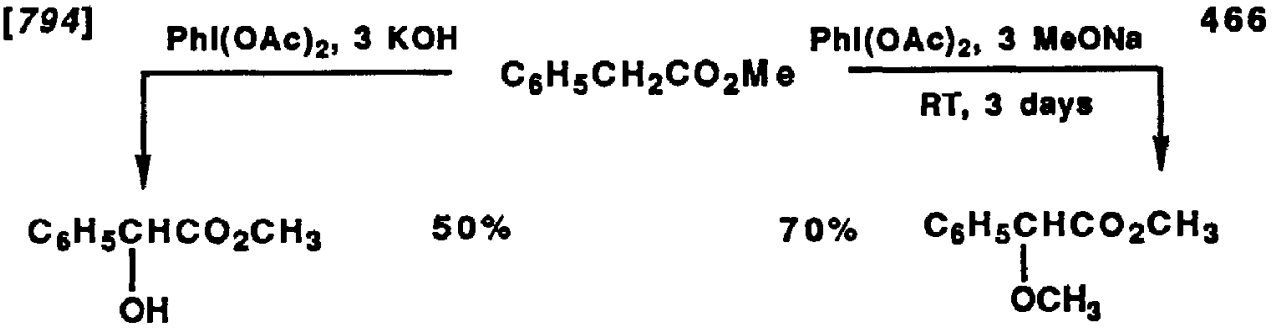
m-Chloroperoxybenzoic acid is obtained in an 80–85% yield by the reaction at 15–25 °C of *m*-chlorobenzoyl chloride with 30% hydrogen peroxide in a solution of sodium hydroxide in aqueous dioxane [*1180*]. Peroxyphthalic acid is similarly prepared from phthalic anhydride (equation 465) [*175*, *331*].

465

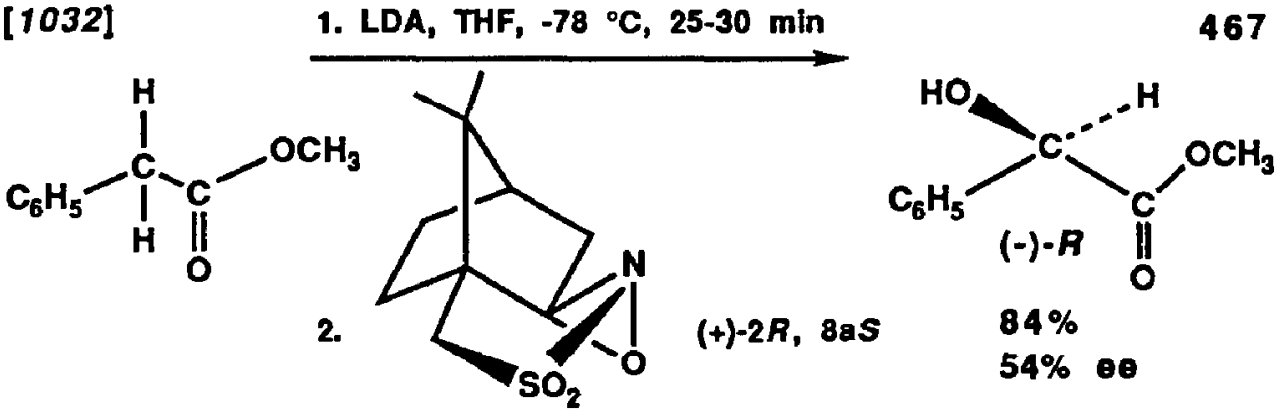


Esters of carboxylic acids undergo oxidative ***coupling in the α positions*** with respect to ester groups when treated in the enolate form with ferric chloride. Thus ethyl acetate stirred with lithium diisopropylamide in tetrahydrofuran at –78 °C for 10 min and subsequently with anhydrous ferric chloride in dimethylformamide yields 69% of diethyl succinate [*911*].

Under similar conditions but with different oxidants, ***esters*** are ***hydroxylated*** in the α positions with respect to the ester groups. Ethyl phenylacetate in tetrahydrofuran treated with lithium diisopropyl amide at –78 °C followed by oxidation with molybdenum oxide complex gives ethyl mandelate in 58% isolated yield [*531*]. Another way to obtain α-hydroxylated (or methoxylated) esters is by oxidation with iodobenzene diacetate in the presence of potassium hydroxide (or sodium methoxide) (equation 466) [*794*].



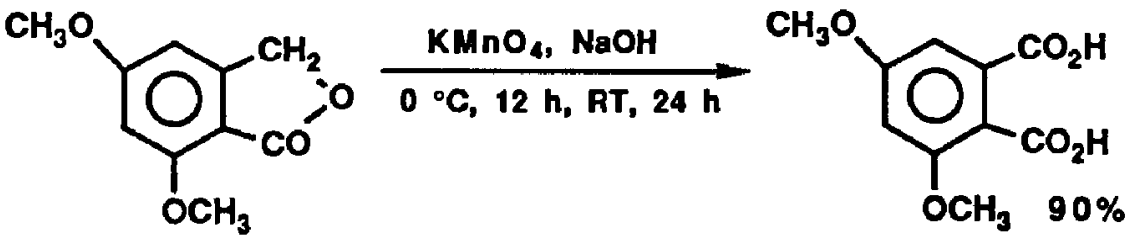
When chiral oxidants such as (+)-2*R*,8a*S* and (–)-2*S*,8a*R* camphorylsulfonyloxaziridines are used, the hydroxylation of enolates in the α positions with respect to the ester groups occurs enantioselectively, with enantiomeric excesses ranging from 12 to 85.5% and yields ranging from 35 to 88.5% (equation 467) [*1032*].



Methylene groups in the α positions with respect to carboxylic groups are changed to carbonyl groups; thus ***α-keto esters*** are formed. Methyl phenylacetate is oxidized with air in the presence of cobalt benzoate at 110–115 °C to methyl phenylglyoxylate in 86% yield [*8*]. Diethyl malonate is converted by nitrogen sesquioxide (N_2O_3) into diethyl mesoxalate in 74–76% yield [*450*].

Esters and ***lactones*** can be oxidized at the alcoholic parts to give carboxylic acids with the same number of carbon atoms. 2-Fluoroheptyl acetate is transformed in 78–84% yield into 2-fluoroheptanoic acid by heating for 25 h at 48 °C with **nitric acid** and acetic acid [*472*]. 3,5-Dimethoxyphthalide is converted into 3,5-dimethoxyphthalic acid in 90% yield by treatment with alkaline **potassium permanganate** at 0 °C for 12 h and at room temperature for 24 h (equation 468) [*879*].

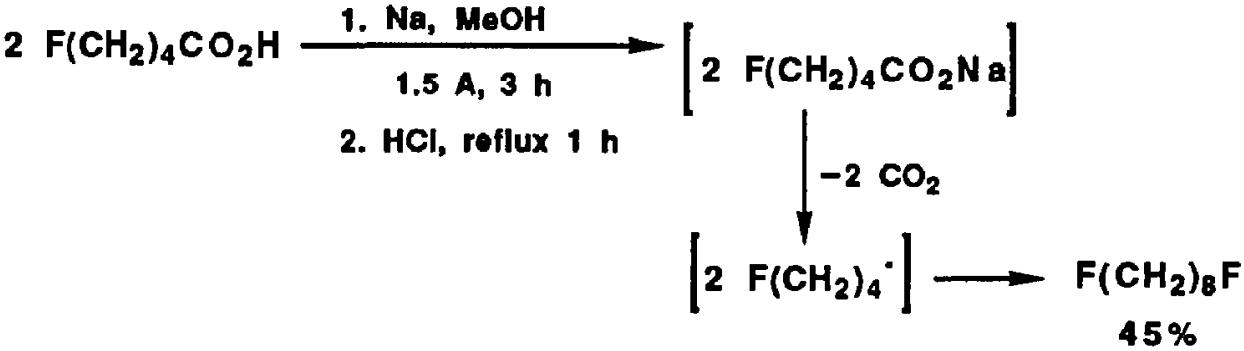
[*879*] 468



Degradative oxidation of acids to aldehydes with one less carbon is achieved by **tetrabutylammonium periodate.** Phenylacetic acids give benzaldehydes in 50–85% yields when refluxed with the reagent in dioxane [*777*].

Electrolytic decarboxylative coupling of sodium salts of carboxylic acids takes place during their electrolysis. Carbon dioxide is eliminated, and the free radicals thus generated couple to form ***hydrocarbons*** or their derivatives. The reaction is referred to as the ***Kolbe electrosynthesis*** and is exemplified by the synthesis of 1,8-difluorooctane from 5-fluorovaleric acid (equation 469) [*574*]. Yields of homologous halogenated acids range from 31% to 82% [*574*].

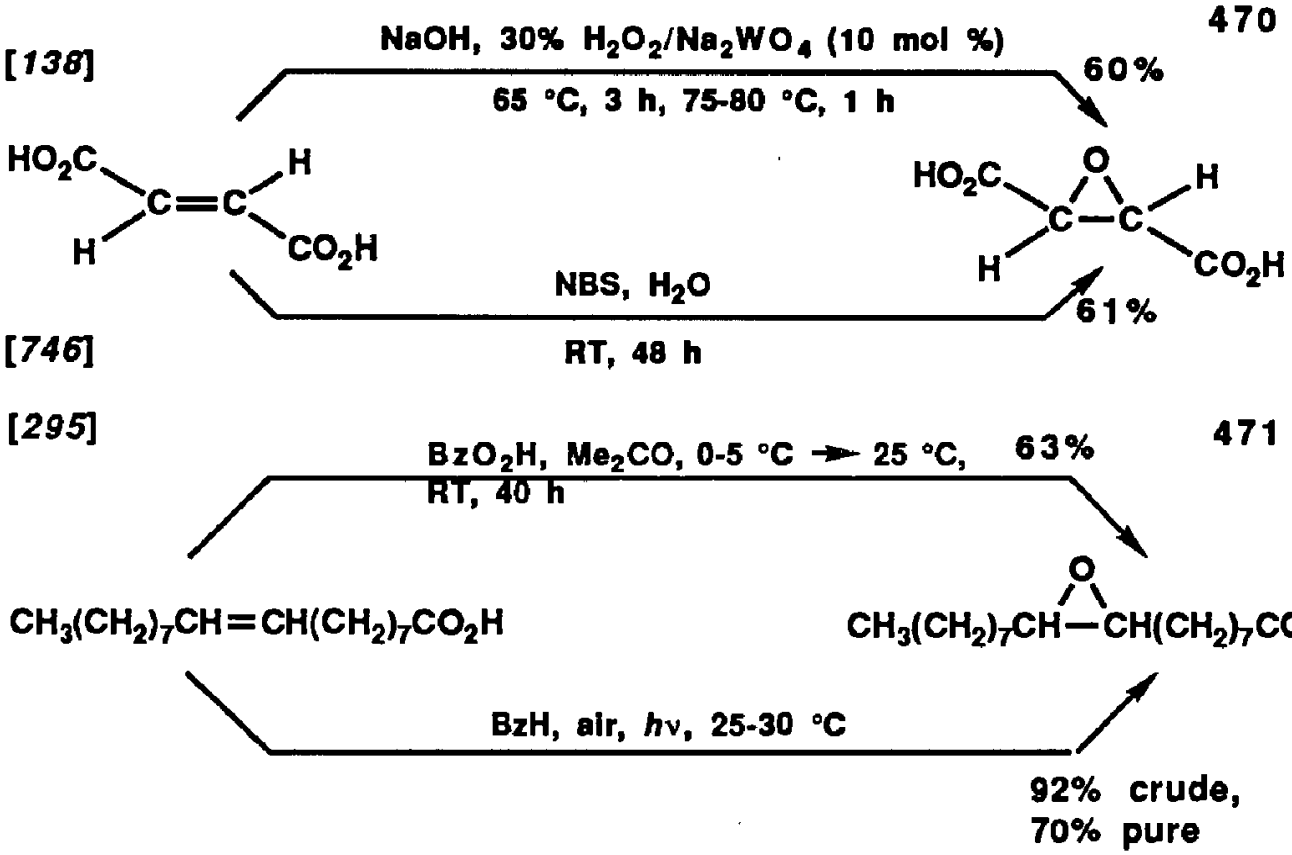
[*574*] 469



Destructive oxidation of any methyl-group-containing compound to acetic acid is accomplished by heating the compound with chromic acid and sulfuric acid at 165–170 °C for 30–60 min. The oxidation is known as the ***Kuhn–Roth determination of methyl groups*** [*1181*]. Its significance waned with the advent of nuclear magnetic resonance techniques.

Unsaturated acids undergo many oxidative reactions. ***Epoxidation*** of unsaturated acids is carried out with the same oxidants as those used with

simple alkenes and unsaturated carbonyl compounds: **hydrogen peroxide** [*138*], **peroxybenzoic acid** [*295*], and ***N*-bromosuccinimide** [*746*] (equations 470 and 471).

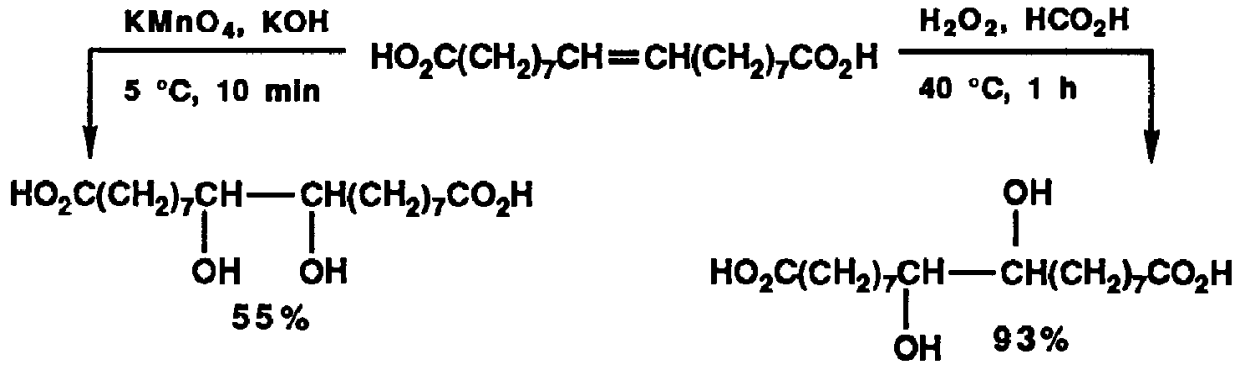


Similar oxidants are used for ***epoxidation of esters*** of unsaturated carboxylic acids. Methyl oleate is oxidized with peroxybenzoic acid [*295*] or peroxylauric acid [*174*] to methyl 9,10-epoxystearate acid in respective yields of 67 and 76%. Alkaline 50% hydrogen peroxide in methanolic solution transforms diethyl ethylidenemalonate at pH 8.5–9.0 and at 35–40 °C over a period of 1 h into ethyl 2-ethoxycarbonyl-2,3-epoxybutyrate in 82% yield [*145*]. A somewhat exotic oxidizing agent, *dimethyldioxirane,* converts ethyl *trans*-cinnamate into ethyl 2,3-epoxyhydrocinnamate in 63% isolated yield [*210*].

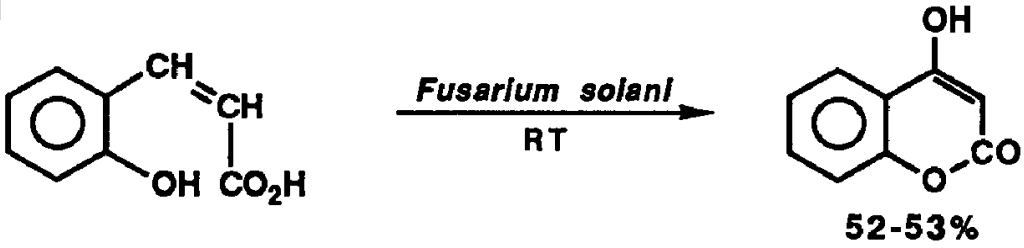
Hydroxylation at double bonds of unsaturated carboxylic acids is accomplished stereoselectively by the same reagents as those used to hydroxylate alkenes. *syn* Hydroxylation is carried out with potassium permanganate [*101*] or **osmium tetroxide** with hydrogen peroxide [*130*], sodium chlorate [*310, 715*], potassium chlorate [*715*], or silver chlorate [*310*] as reoxidant. *anti* Hydroxylation is achieved with peroxyacids, such as peroxybenzoic acid [*310*] or peroxyformic acid, prepared in situ from hydrogen peroxide and formic acid [*101*] (equation 472).

A rare ***substitution hydroxylation*** is effected by ***Fusarium solani,*** which converts *o*-hydroxy-*cis*-cinnamic acid into 4-hydroxycoumarin (equation 473) [*1089*].

[101] 472



[1089] 473



In the presence of acetic anhydride, **potassium permanganate** oxidizes oleic acid at –5 to 10 °C over a period of 2.5 h to ***9,10-diketostearic acid*** in 46% isolated yield [*861*].

The oxidation of unsaturated esters to ***unsaturated keto esters*** is accomplished with **chromium trioxide** in acetic acid and acetic anhydride. Methyl 2-nonenoate is thus converted in benzene solution at 0–20 °C into methyl 4-keto-2-nonenoate in 86% yield [*553*].

Degradative oxidation of unsaturated carboxylic acids leads either to ***aldehydes*** or to ***dicarboxylic acids.*** In the presence of sodium carbonate and benzene, *o*-nitrocinnamic acid is oxidized with **potassium permanganate** at 10 °C to *o*-nitrobenzaldehyde in 64% isolated yield [*842*].

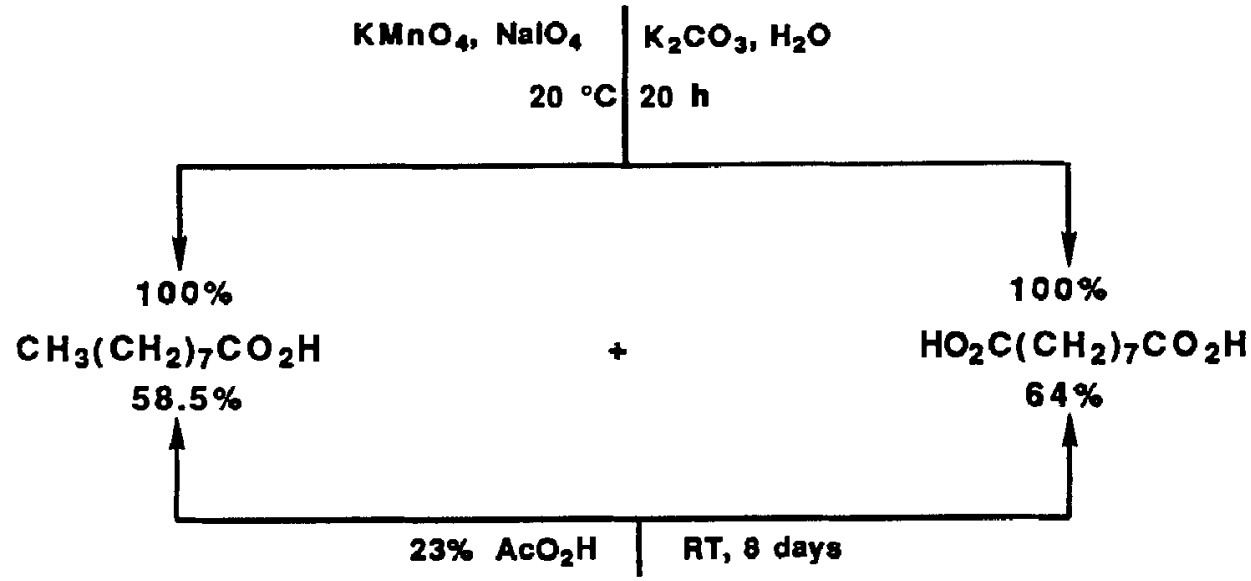
Undecylenic acid (10-undecenoic acid), when treated with **potassium permanganate and sodium periodate** in an aqueous solution of potassium carbonate at 20 °C for 20 h, gives sebacic acid (decanedioic acid) in 73% isolated yield [*763*]. A similar oxidation of oleic or elaidic acid yields a mixture of pelargonic acid and azelaic acid [*763*] (equation 474).

Acetylenic acids are oxidized to ***α-diketo carboxylic acids*** by **potassium permanganate** in aqueous solutions buffered to pH 7.0–7.5 by carbon dioxide (equation 475) [*864*].

Ozone, when combined with hydrogen peroxide [*101*] or **peroxyacetic acid** [*268*], cleaves the triple bond to yield ***carboxylic acids.*** Stearolic acid is converted into a mixture of pelargonic acid and azelaic acid [*268*] (equation 474). 9-Octadecynedioic acid, on treatment with ozone in acetic acid at room temperature followed by oxidation with hydrogen peroxide, gives azelaic acid in 81% yield [*101*].

The triple bond in ***esters of acetylenic alcohols*** behaves similarly. 2,5-Diacetoxy-2,5-dimethyl-3-hexyne is converted by a 2% aqueous solution

[763] $CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$ 474

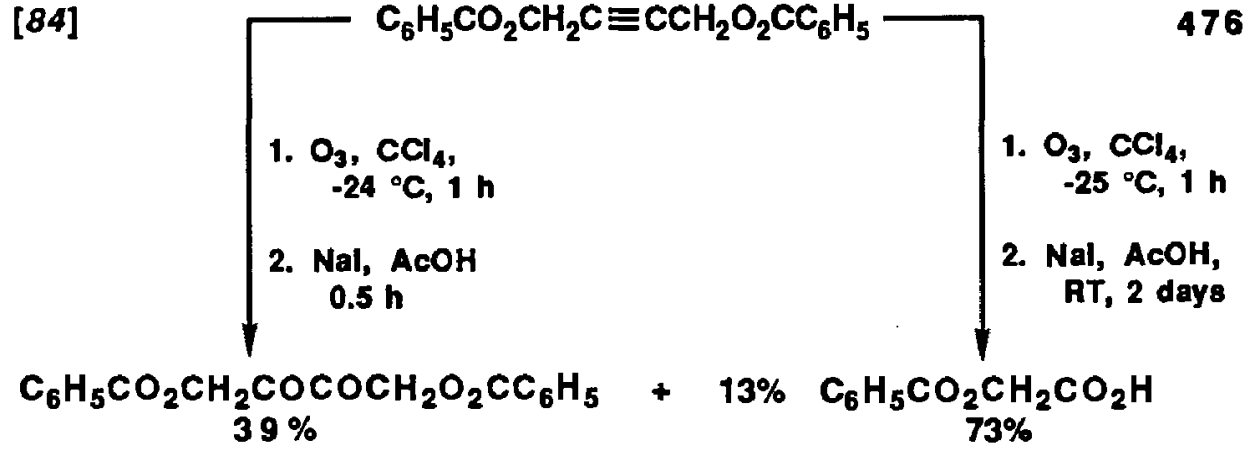


[268] $CH_3(CH_2)_7C{\equiv}C(CH_2)_7CO_2H$

[864] $CH_3(CH_2)_7C{\equiv}C(CH_2)_7CO_2H \xrightarrow[\text{pH 7.0-7.5, 25 °C}]{\text{KOH, KMnO}_4,\ CO_2} CH_3(CH_2)_7COCO(CH_2)_7CO_2H$ (92-96%) 475

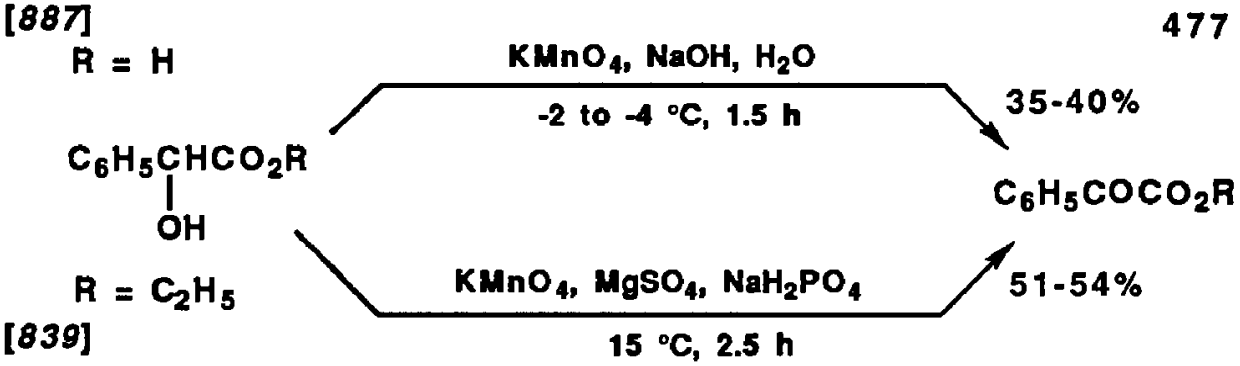
of **potassium permanganate,** while cooled with ice, into 2,5-diacetoxy-2,5-dimethyl-3,4-hexanedione in 67% yield [*1117*]. 1,4-Dibenzoxy-2-butyne yields, on **ozonization** at –25 °C and subsequent treatment with a solution of sodium iodide in acetic acid, 39% of 1,4-dibenzoxy-2,3-butanedione and 13% of benzoylglycolic acid. After 2 days at room temperature, the yield of the benzoylglycolic acid rises to 73% (equation 476) [*84*].

[84] $C_6H_5CO_2CH_2C{\equiv}CCH_2O_2CC_6H_5$ 476

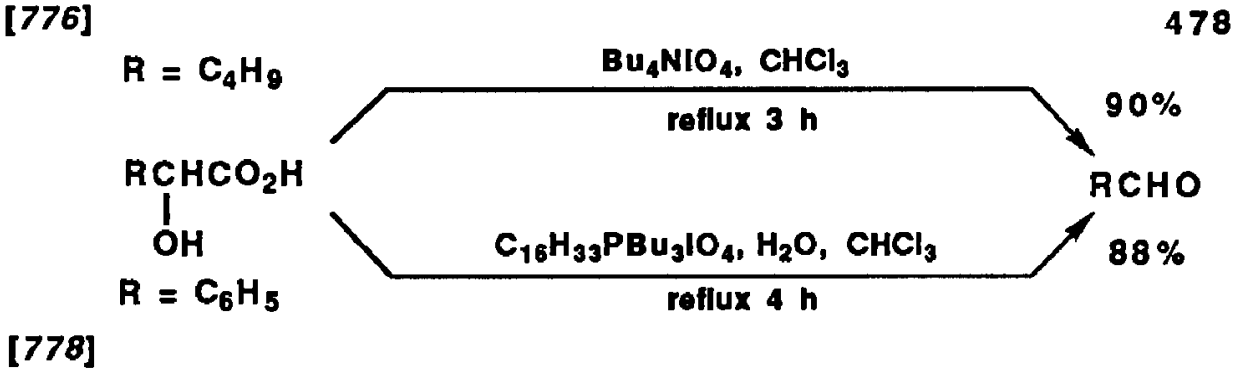


Hydroxy carboxylic acids and their esters are oxidized to ***keto acids and their esters,*** respectively. *o*-Nitromandelic acid is oxidized to *o*-nitrophenylglyoxylic acid with a dilute solution of **potassium permanganate** at room temperature in 54% yield [*886*]. The oxidation of ethyl 3-hydroxycyclobutanecarboxylate with **ruthenium tetroxide and sodium periodate** in

a mixture of water and carbon tetrachloride at room temperature overnight gives ethyl 3-cyclobutanonecarboxylate in 78% yield [*941*]. 4-Hydroxyundecanoic acid (in the form of its lactone) is oxidized with **bromine** in aqueous sodium hydroxide at pH 6–6.5 at 0 °C to give a 75–85% yield of 4-ketoundecenoic acid [*729*]. Mandelic acid [*887*] and ethyl mandelate [*839*] are oxidized with potassium permanganate to phenylglyoxylic acid and its ethyl ester, respectively (equation 477).



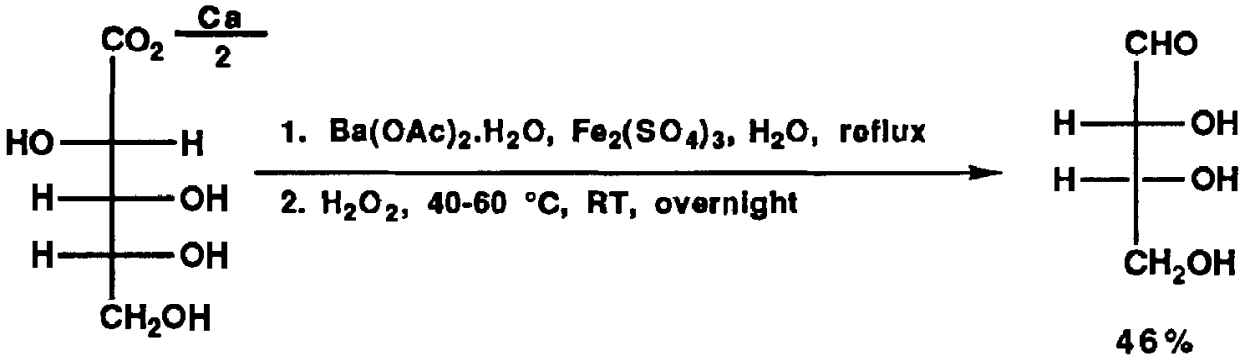
Degradative oxidation of α-hydroxy carboxylic acids furnishes ***aldehydes*** or ***ketones.*** Glycolic acid, lactic acid, and mandelic acid are converted into formaldehyde, acetaldehyde, and benzaldehyde, respectively, in 50% yields on refluxing with ***N*-bromosuccinimide** in water [*745*]. **Periodates,** with phase-transfer reagents, convert α-hydroxyhexanoic acid and mandelic acid into valeraldehyde and benzaldehyde in respective yields of 90 and 88% (equation 478) [*776, 778*].



The conversion of α-hydroxy acids into aldehydes with one less carbon has great importance in the chemistry of sugars. Oxidation with **bromine water** transforms aldoses into the corresponding aldonic acids, which, in the form of their calcium salts, are treated with aqueous **hydrogen peroxide** in the presence of ferrous or ferric sulfate ***(Fenton reagent)*** and are degraded to aldoses with one less carbon (***Ruff degradation***) (equation 479) [*87*].

If the hydroxylic group next to the carboxyl is tertiary, decarboxylative oxidation gives ketones. Benzilic acid is degraded to benzophenone in 85–90% yield on refluxing for 20 min with water and ***N*-bromosuccinimide** [*745*]. 2-(*p*-Methoxybenzyl)-*p*-methoxymandelic acid is converted into des-

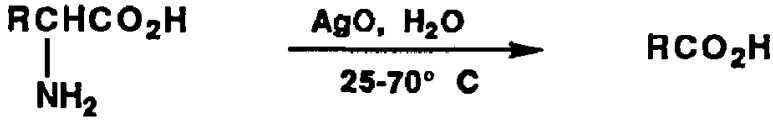
[87] 479



oxyanisoin (*p*-methoxybenzyl *p*-methoxyphenyl ketone) in 98% yield on heating with **red lead oxide** (Pb_3O_4) in acetic acid at 65–70 °C [*143*].

The oxidation of ***α-amino acids*** gives either ***aldehydes or acids*** with one less carbon. ***Aldehydes*** result from the treatment of the amino acids with a slightly alkaline solution of **sodium hypochlorite.** Valine, sodium hypochlorite, and 10 mol % of sodium hydroxide, on steam distillation, furnish isobutyraldehyde in 79% yield [*700*]. Oxidation to carboxylic acids is achieved on heating of the amino acid with 2.5% **hydrogen peroxide** to 70 °C. Glutamic acid is transformed into succinic acid in 47% yield [*188*]. A more general method seems to be oxidation with *argentic oxide* at 25–70 °C to give 49–100% yields of ***carboxylic acids*** (equation 480) [*381*].

[381] 480

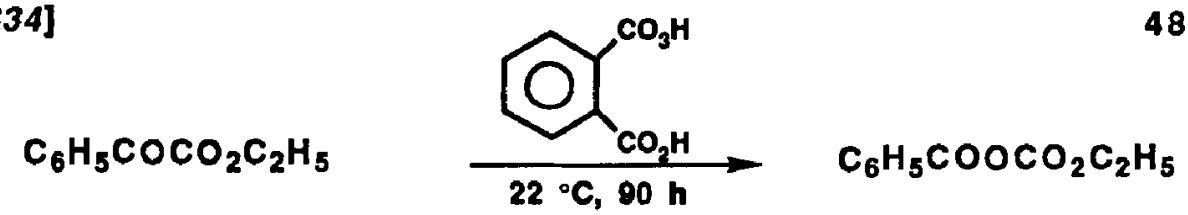


R = $(CH_3)_2CH$ 100%

R = $(CH_3)_2CHCH_2$ 61%

α-Keto acids are oxidized to carboxylic acids having one less carbon with hydrogen peroxide. For example, 3,4-dimethoxyphenylpyruvic acid is degraded to homoveratric acid with 30% **hydrogen peroxide** at room temperature [*189*]. ***α-Keto esters*** undergo the ***Baeyer–Villiger reaction*** on treatment with **peroxyphthalic acid** and give mixed anhydrides (equation 481) [*334*].

[334] 481

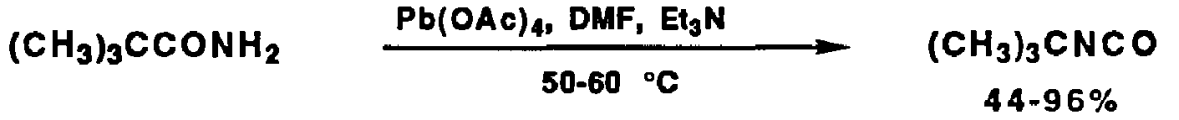


Oxidation of Amides, Hydrazides, and Nitriles

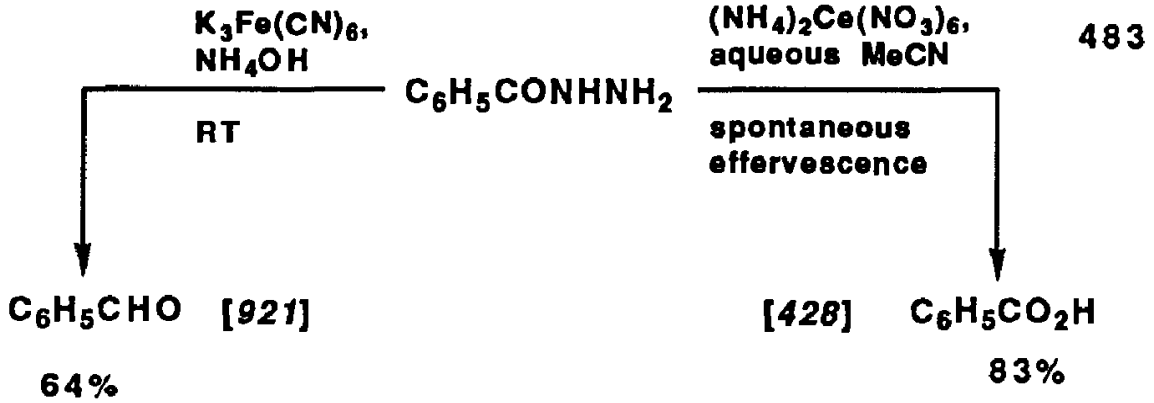
The oxidation of amides, when it takes place at carbon atoms not adjoining the nitrogen atom, is discussed in the section Oxidation of the Carbon Chain of Amines (*see* equations 516–518).

The oxidation of ***primary amides*** with **lead tetraacetate** gives ***isocyanates,*** when carried out in dimethylformamide; ***carbonates,*** when carried out in the presence of alcohols; and ***ureas,*** when carried out in the presence of amines (equation 482) [*1182*].

[*1182*] 482



Hydrazides are converted into ***aldehydes*** by **potassium ferricyanide** in the presence of aqueous ammonia in 23–64% yields [*921*]. On treatment with **ceric ammonium nitrate,** the corresponding ***carboxylic acids*** are formed in 65–90% yields [*428*] (equation 483).



483

Unsaturated nitriles are ***epoxidized*** with **hydrogen peroxide.** Tetracyanoethylene, after treatment with 30% hydrogen peroxide in acetonitrile at 10–12 °C, furnishes tetracyanoepoxyethane in 59–68% yield [*150*]. A similar treatment of acrylonitrile gives a 62% yield of glycidamide (epoxypropionamide) [*147*].

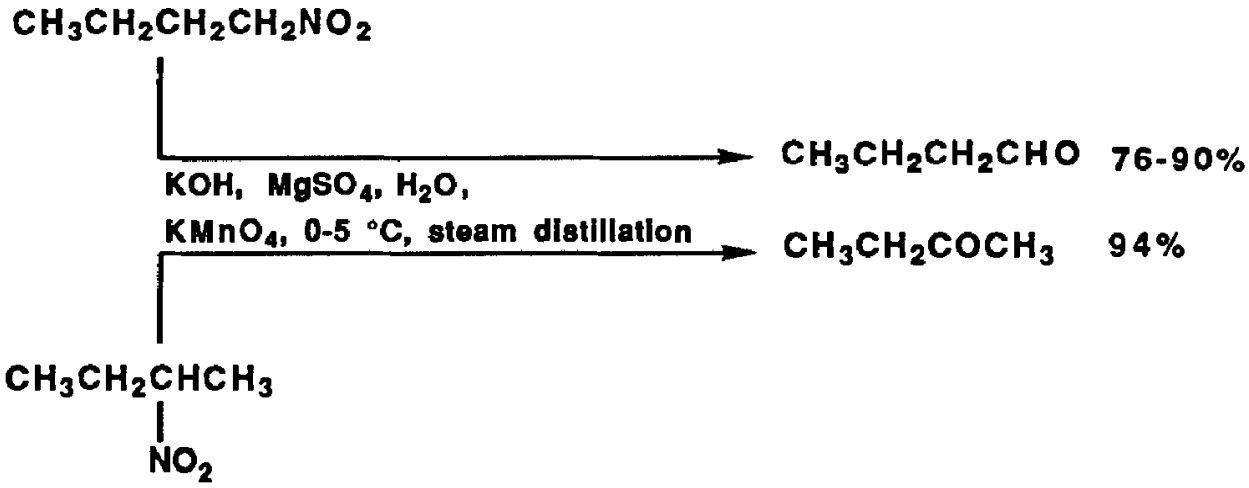
NITROGEN COMPOUNDS

Oxidations of nitrogen compounds include oxidation at nitrogen as well as oxidations at carbons carrying the nitrogen functional groups.

Oxidation of Nitro Compounds

Because the nitrogen in nitro compounds is at the highest oxidation state, nitro compounds can be oxidized only in the carbon chain to which the nitro group is attached. The oxidation of ***primary and secondary nitro compounds*** in the form of their nitronic acids in alkaline medium by **potassium permanganate** represents a variation of the ***Nef reaction*** and gives the same products: ***aldehydes*** from primary nitro compounds and ***ketones*** from secondary nitro compounds (equation 484) [*867*].

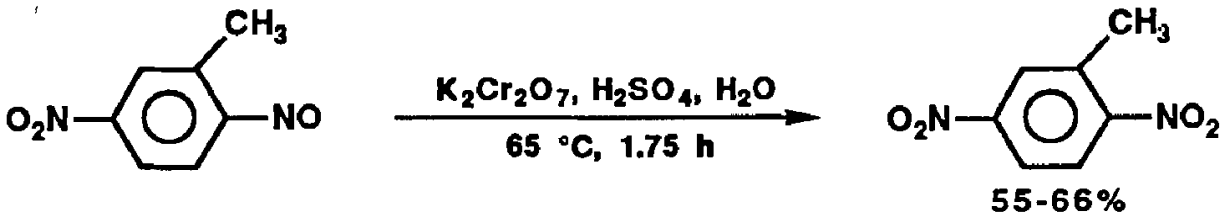
[867] 484



Oxidation of Nitroso Compounds

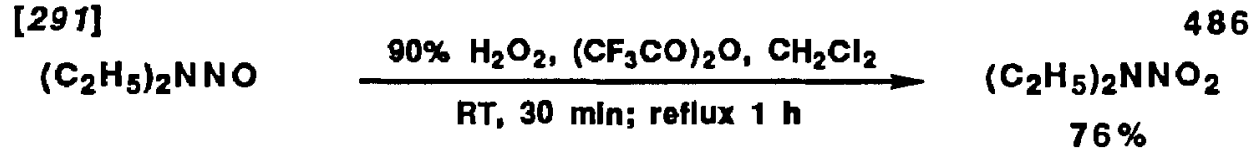
Nitroso compounds are oxidized to ***nitro compounds*** by **hydrogen peroxide** or its derivatives and also by **potassium dichromate** (equation 485) [*658*].

[658] 485



The oxidation of 3-nitroso-2,6-diaminopyridine with 30% hydrogen peroxide at 35 °C for 1.5 h furnishes 3-nitro-2,6-diaminopyridine in 96% yield [*278*]. Under these conditions, the primary amino groups are not affected. Nitrosoamines are oxidized with **peroxytrifluoroacetic acid** to nitroamines in 73–95% yields (equation 486) [*291*].

[291] 486



Oxidation of Hydroxylamines

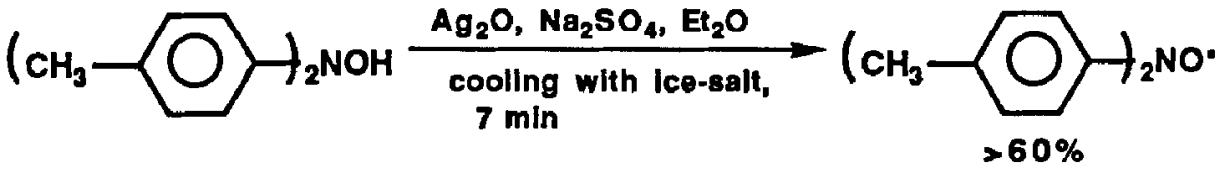
Because nitroso compounds cannot be prepared by the reduction of nitro compounds, the oxidation of ***hydroxylamines*** is often the best way for their preparation. Nitroso compounds are obtained by treatment of hydroxylamines with **silver oxide** [*373*], **silver carbonate** [*378*], **sodium dichromate** [*645*], **potassium dichromate** [*657*], manganese dioxide [*816*], and diethyl azodicarboxylate [*978*] (equation 487).

$C_6H_5NHOH \longrightarrow C_6H_5NO$ 487

[378]	Ag_2CO_3, CH_2Cl_2, RT, 2 min	85%
[645]	$Na_2Cr_2O_7$, H_2SO_4, H_2O, 0 °C, 3 min	49-53%
[657]	$K_2Cr_2O_7$, H_2SO_4, H_2O, 0 °C	90%
[816]	MnO_2, H_2O, 0 °C, 3 h	40%
[978]	$EtO_2CN{=}NCO_2Et$, Et_2O, 0 °C, a few hours	89%

N,N-disubstituted hydroxylamines are converted into free-radical ***nitroxyls*** by **silver oxide** in ether in the presence of anhydrous sodium sulfate (equation 488) [*374*].

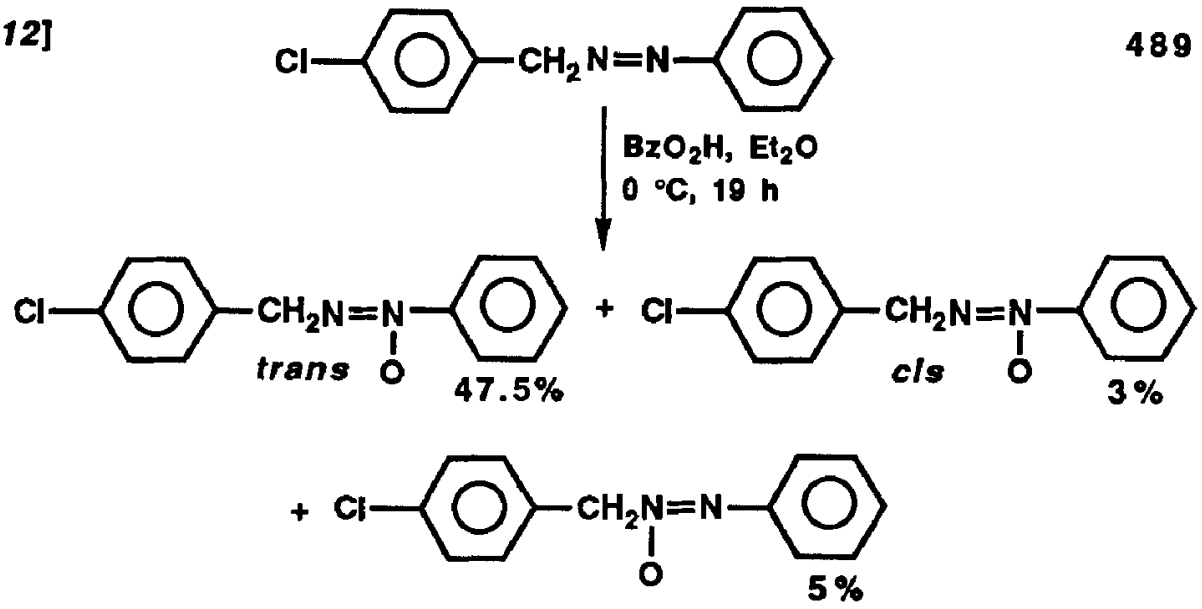
[374] 488



Oxidation of Azo Compounds and Azides

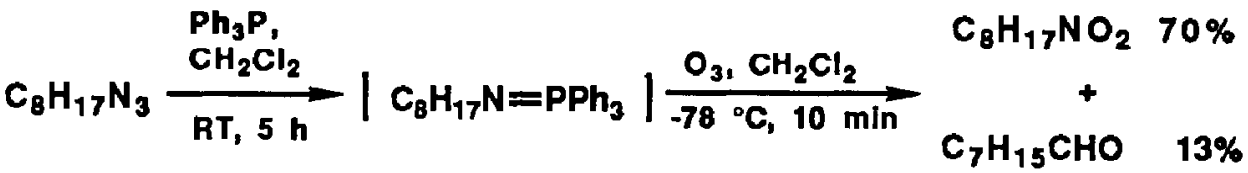
Azo compounds are oxidized with **peroxybenzoic acid** to mixtures of ***azoxy compounds*** (equation 489) [*312*].

[312] 489



Alkyl ***azides*** are converted into ***nitro compounds*** by the sequence of reactions shown in equation 490 [*1183*].

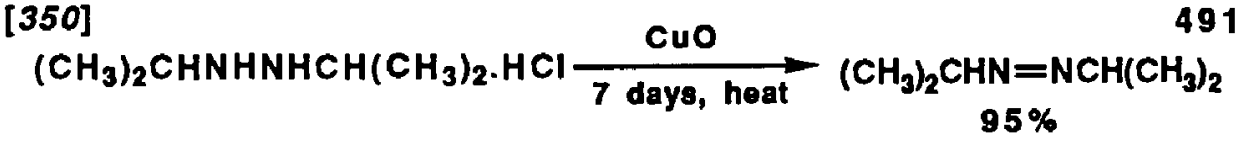
[1183] 490



Oxidation of Hydrazo Compounds

Hydrazo compounds are dehydrogenated to ***azo compounds*** by many oxidants. 2,2′-Bisazopropane is prepared by the oxidation of *sym*-diisopropylhydrazine with **cupric oxide** (equation 491) [*350*].

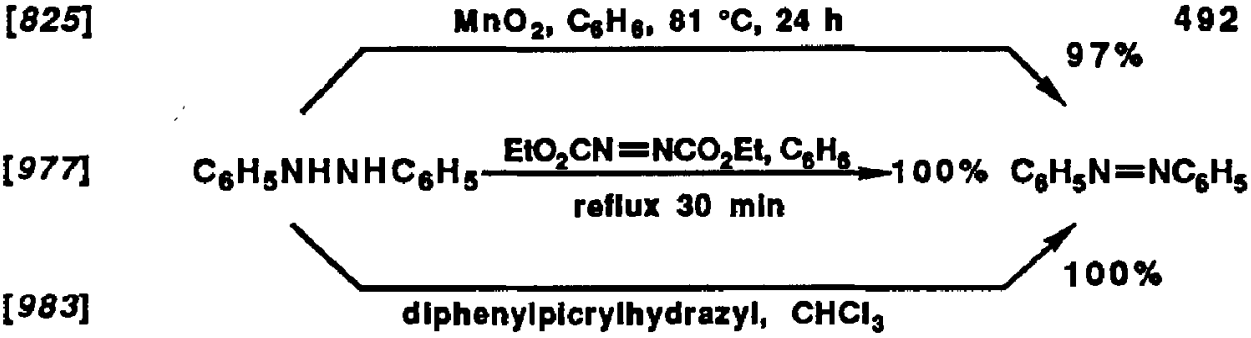
[*350*]



491

Hydrazobenzene is transformed into azobenzene by **air**, by **manganese dioxide** [*825*], by diethyl azodicarboxylate [*977*], and by diphenylpicrylhydrazyl [*983*] (equation 492).

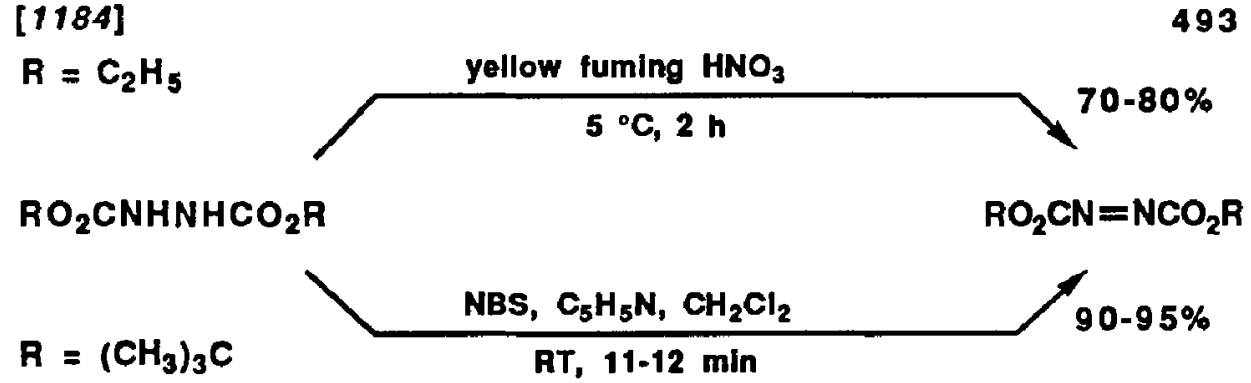
[*825*] [*977*] [*983*]



492

Diethyl and di-*tert*-butyl hydrazodicarboxylate are dehydrogenated to diethyl- and di-*tert*-butylazodicarboxylate, respectively, by **nitric acid** [*1184*] and by ***N*-bromosuccinimide** [*1185*] (equation 493).

[*1184*]

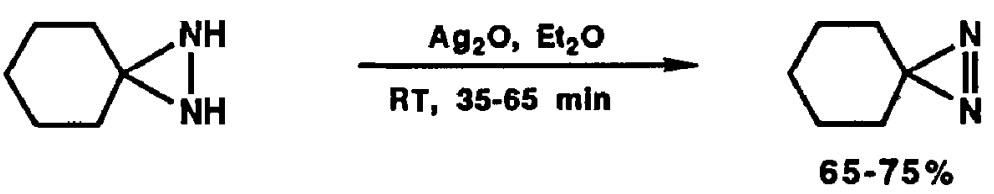


493

[*1185*]

The dehydrogenation of 1,1′-dicyanohydrazocyclohexane by **bromine** in ethanolic hydrochloric acid at 15 °C furnishes 1,1′-dicyanoazocyclohexane in 84–90% yield [*733*]. The treatment of 3,3-pentamethylenediaziridine with **silver oxide** gives the corresponding diazirine (equation 494) [*372*].

[*372*]



494

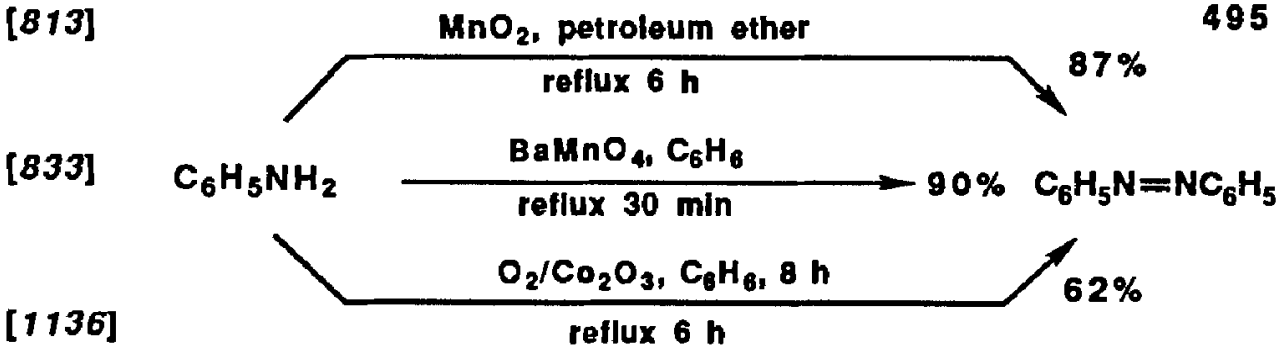
Oxidation of Primary Amines at Nitrogen

Primary amines are oxidized to azo, azoxy, nitroso, or nitro compounds, depending on the oxidants used. Most of the examples include aromatic amines, because aliphatic amines that have hydrogens on the carbons carrying the amino groups may undergo dehydrogenations to carbonyl compounds, imines, and nitriles (*see* equations 508–514).

CONVERSION OF PRIMARY AMINES INTO AZO COMPOUNDS

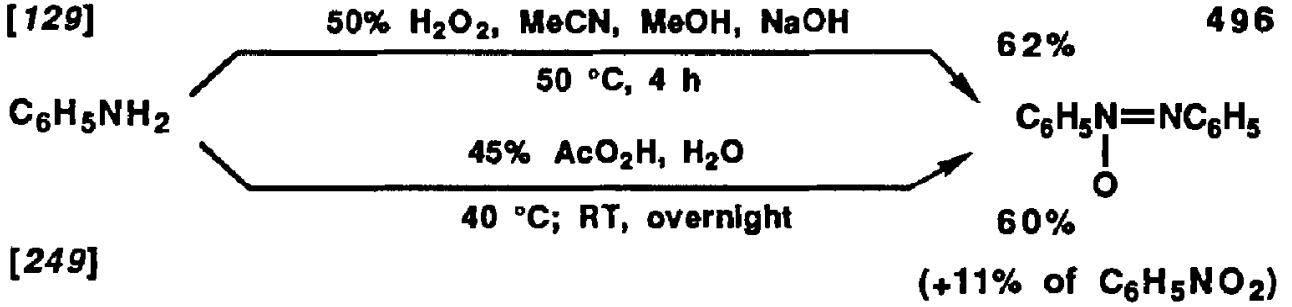
The dehydrogenation of ***primary amines into azo compounds*** is achieved by sodium perborate, which converts *N*-acetyl-*p*-phenylenediamine into *p,p'*-diacetamidoazobenzene in 58% yield on heating at 50–60 °C with boric acid and acetic acid for 6 h [*193*].

More common oxidation reagents are **oxygen** in the presence of cobalt peroxide [*1136*], **manganese dioxide** [*813*], barium manganate [*833*], silver permanganate [*897*], and nickel peroxide [*936*] (equation 495).



p-Chloroaniline is oxidized to *p,p'*-dichloroazobenzene on refluxing for 15 min with a silver permanganate–pyridine complex in benzene (yield 85%) [*897*]. *p*-Nitroaniline is converted into *p,p'*-dinitroazobenzene on refluxing with nickel peroxide in benzene for 6 h (yield 44%) [*936*].

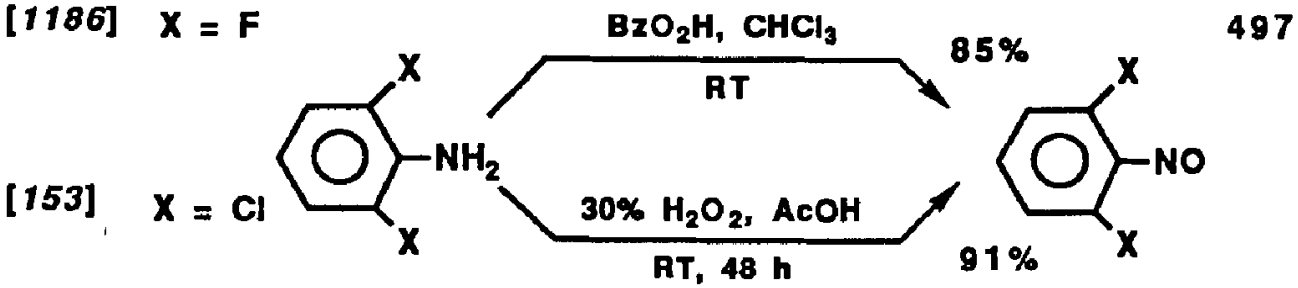
Hydrogen peroxide [*129, 249*] and **peroxy acids** [*1186*] oxidize primary aromatic amines to ***azoxy compounds.*** Peroxyacetic acid oxidizes 2,6-difluoroaniline to 2,2',6,6'-tetrafluoroazoxybenzene in 48% yield [*1186*]. The oxidation of aniline with hydrogen peroxide or with peroxyacetic acid yields azoxybenzene (equation 496) [*129, 249*]. Azoxy compounds are usually accompanied by nitroso and nitro compounds.



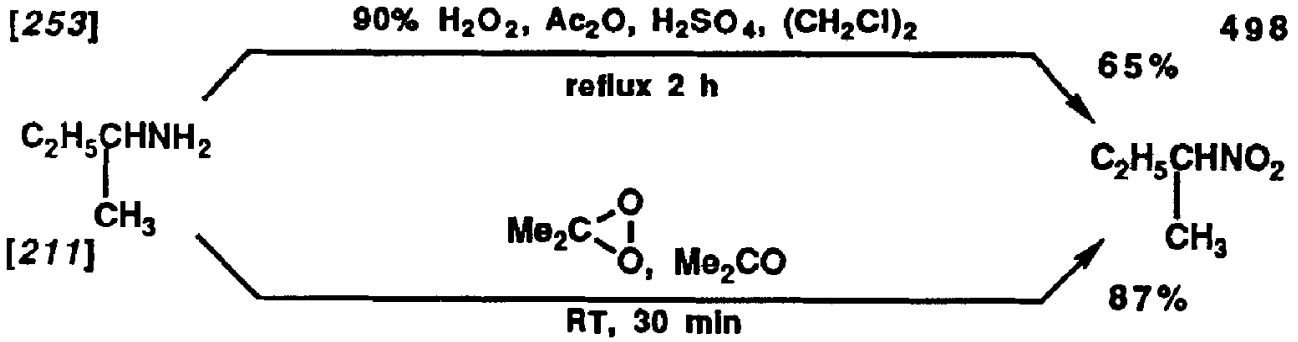
OXIDATION OF PRIMARY AMINES TO NITROSO AND NITRO COMPOUNDS

Oxidants suitable for the partial oxidation of amines to ***nitroso compounds*** are peroxy acids: **Caro acid,** which is prepared in situ from potassium persulfate and sulfuric acid [*195, 199*]; **potassium peroxysulfate (Oxone)** [*295*]; **peroxyacetic acid** [*153*], and **peroxybenzoic acid** [*1186*].

3-Nitro-*o*-toluidine [*195*] and 5-nitro-*o*-toluidine [*199*] in aqueous–alcoholic solutions, when treated with a mixture of potassium persulfate and concentrated sulfuric acid, give 3-nitro-2-nitrosotoluene and 5-nitro-2-nitrosotoluene in respective yields of 60 and 55–66%. Organic peroxy acids convert 2,6-dihaloanilines into 2,6-dihalonitrosobenzenes (equation 497) [*153, 1186*]. *p*-Phenylenediamine (1,4-diaminobenzene) is oxidized by Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in an aqueous suspension at room temperature to *p*-dinitrosobenzene in a quantitative yield [*205*].

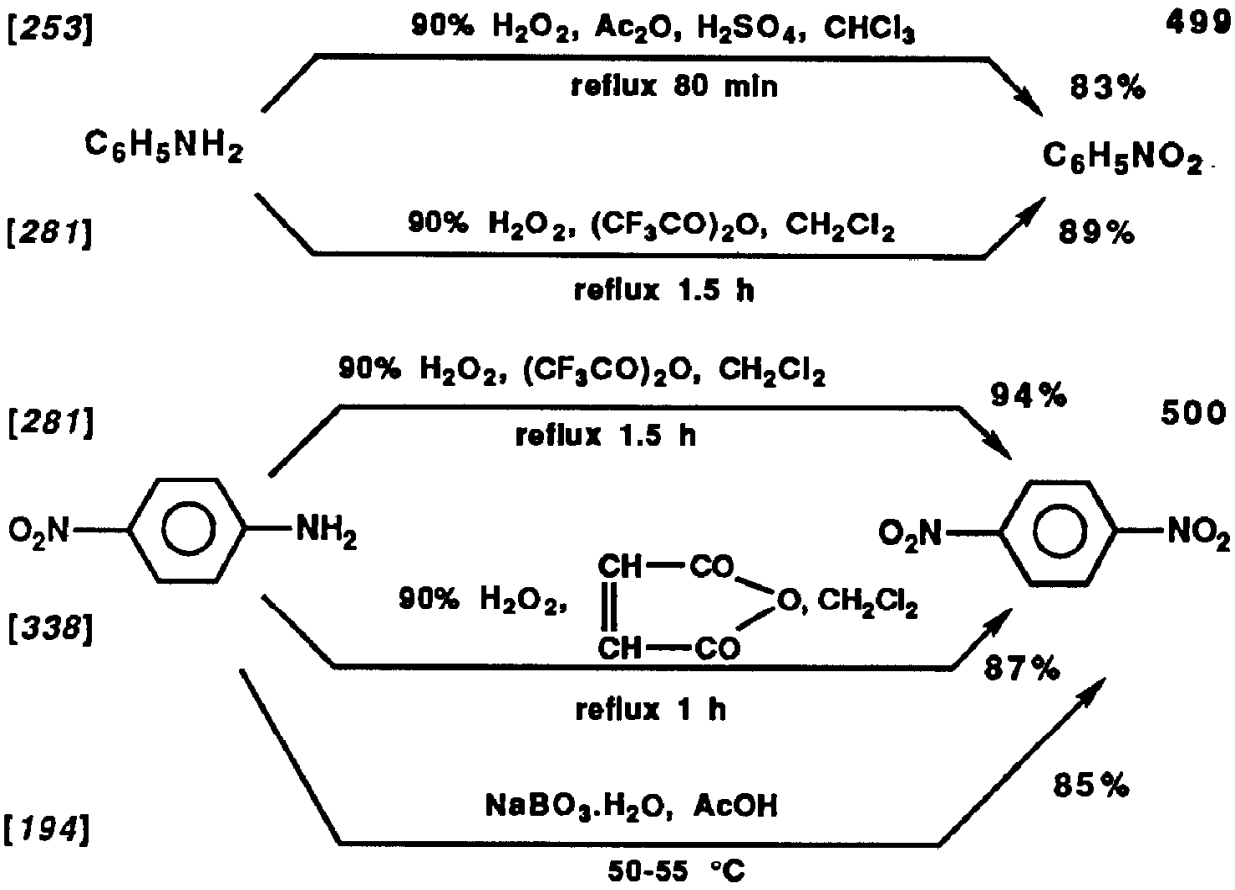


The oxidation of some ***aliphatic amines*** is a good route to ***aliphatic nitro compounds.*** *tert*-Butylamine is oxidized in 83% yield to 2-methyl-2-nitropropane by **potassium permanganate** in water at 45 °C for 8 h and at 55 °C for 8 h [*738, 892*]. Under similar conditions, 4-amino-2,2,4-trimethylpentane is converted into 4-nitro-2,2,4-trimethylpentane in 69–82% yields [*859*]. Refluxing 3α-acetoxy-20α-amino-5β-pregnane with a chloroform solution of ***m*-chloroperoxybenzoic acid** for 40 min furnishes 3α-acetoxy-20α-nitro-5β-pregnane in 66% yield [*319*]. 2-Aminobutane is converted into 2-nitrobutane by **peroxyacetic acid** [*253*] or **dimethyldioxirane** [*211*] (equation 498).



Primary aromatic amines are oxidized to ***nitro compounds*** by **peroxy acids:** perboric acid [*194*], peroxysulfuric acid [*203*], peroxyacetic acid [*253*],

peroxytrifluoroacetic acid [*281, 285, 290*], and peroxymaleic acid [*338*] (equations 499 and 500).



Whereas peroxyacetic acid oxidizes 2,6-dichloroaniline to 2,6-dichloronitrosobenzene [*153*], peroxytrifluoroacetic acid carries the oxidation to the nitro compound. Refluxing 2,6-dichloroaniline with peroxytrifluoroacetic acid, which is prepared in situ from 90% hydrogen peroxide and trifluoroacetic anhydride in dichloromethane, gives 2,6-dichloronitrobenzene in 89–92% crude yields and 59–73% pure yields [*290*]. 2-Amino-4-methylpyridine treated with 30% hydrogen peroxide in fuming sulfuric acid at 10–25 °C for 50 h yields 68% of 4-methyl-2-nitropyridine [*203*].

The ***biochemical oxidation*** of an amino group to a nitro group is exemplified by the treatment of *p*-aminobenzoic acid with ***Streptomyces thioluteus***. At pH 7 and 30 °C, 90% of the amino acid is converted into *p*-nitrobenzoic acid in 2 h [*1085*].

Oxidation of Secondary and Tertiary Amines at Nitrogen

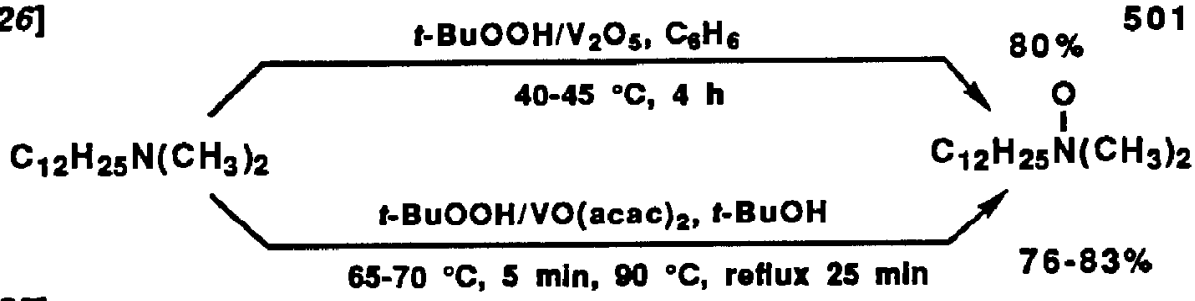
The oxidation of ***secondary amines*** with dilute (6%) hydrogen peroxide at room temperature furnishes ***dialkylhydroxylamines***. *N,N*-Diethylhydroxylamine is prepared with a yield not higher than 50%. With dipropylamine, the yield is not stated [*154*].

The oxidation of ***tertiary amines*** to ***amine oxides*** is carried out by peroxy compounds, most often **hydrogen peroxide** and **peroxyacetic acid.**

Other peroxides such as ***tert*-butyl hydroperoxide** [*226, 227*], performic acid [*247, 248*], peroxytrifluoroacetic acid [*158*], peroxydichloromaleic acid [*339*], and dimethyldioxirane [*210*] are used less frequently.

Trialkylamines such as tributylamine are oxidized either with aqueous–methanolic 30–35% hydrogen peroxide at 0 °C to room temperature over 26.5 h or with 40% peroxyacetic acid at 0 °C to room temperature for 4.5 h. The yields of tributylamine oxide are comparable: 98 and 95%, respectively [*156*]. Dimethyldodecylamine oxide is prepared by heating the tertiary amine with *tert*-butyl hydroperoxide in the presence of vanadium catalysts (equation 501) [*226, 227*].

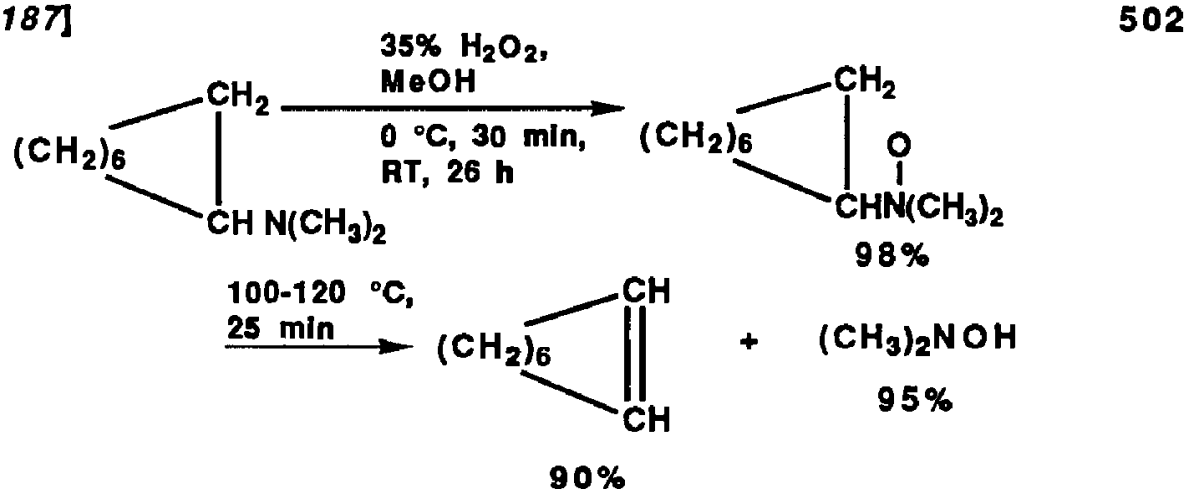
[*226*] 501



[*227*]

The purpose of preparing aliphatic amine oxides is usually their thermal decomposition to *cis* alkenes and *N,N*-dialkylhydroxylamines (Cope rearrangement) [*156, 161, 1187*]. Thus *N,N*-dimethylcyclohexylmethylamine is oxidized with 30% hydrogen peroxide in methanol to its oxide, whose decomposition at 90–100 °C at 10 mm of Hg and at 160 °C for 2 h furnishes 79–88% of methylenecyclohexane and 78–90% of *N,N*-dimethylhydroxylamine [*161*]. Another example is the preparation of *cis*-cyclooctene from dimethylcyclooctylamine (equation 502) [*1187*].

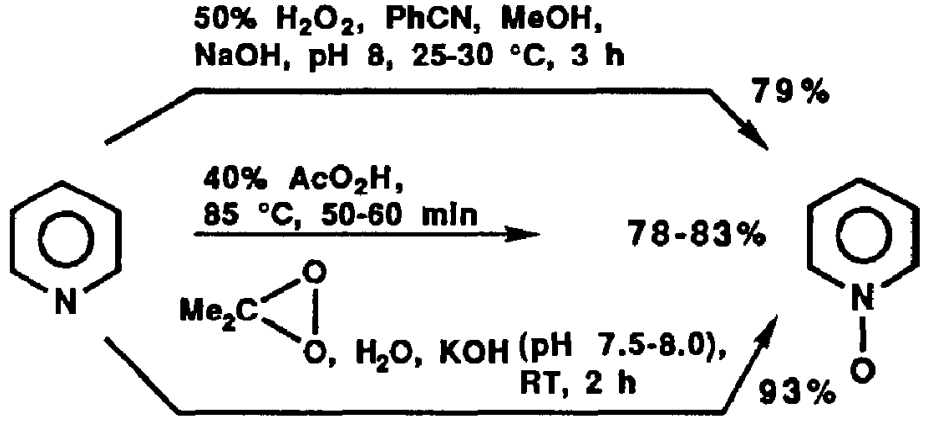
[*1187*] 502



An easy route to amine oxides is the oxidation of tertiary amines with ***m*-chloroperoxybenzoic acid** in chloroform solution at 0–5 °C for 3 h. Trimethylamine oxide, tribenzylamine oxide, and dimethylaniline oxide are obtained in 96, 96, and 94% yields, respectively [*320*].

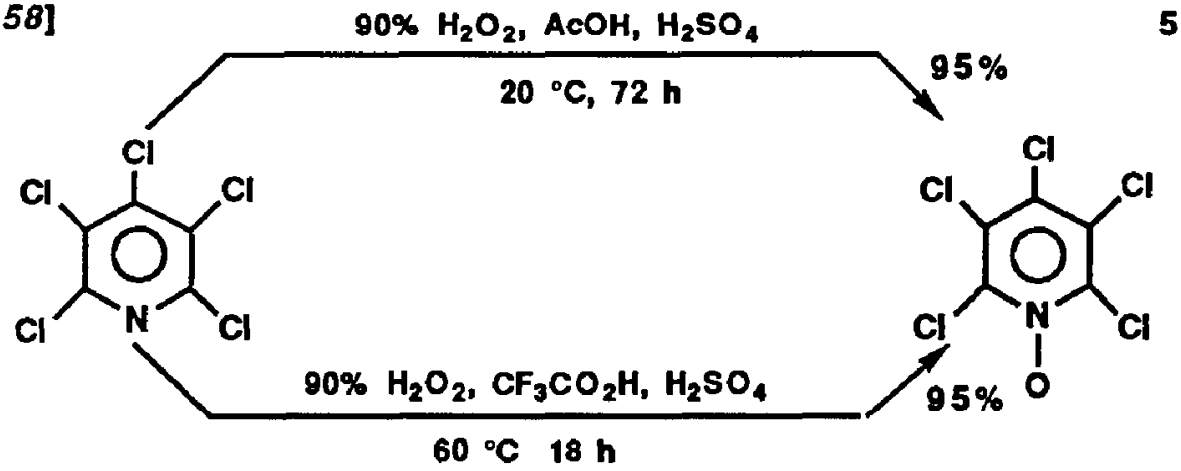
Pyridine is frequently oxidized to pyridine oxide (equation 503) [*129, 210, 263*]. Pyridine oxide is an oxidant capable of hydroxylating aromatic rings [*994*]. But more important, the presence of oxygen on the nitrogen of the pyridine ring reverses the direction of electrophilic substitutions in the pyridine ring. Whereas electrophilic attacks on pyridine occur in β positions, attacks on pyridine oxide occur in α and γ positions. After the introduction of the electrophiles, the pyridine oxide is converted into pyridine by mild reductions, such as treatment with salts of iron or titanium.

[*129*] 503



Like pyridine, pyridine homologues and derivatives are converted into amine oxides. α-Picoline oxide is prepared by oxidation with hydrogen peroxide in acetic acid in 83% yield [*1188*]. Under identical conditions, 2,5-dimethylpyridine oxide and nicotinamide oxide are obtained in 84% yield [*160*] and 73–82% yield [*162*], respectively. Pentachloropyridine is oxidized to its oxide by peroxyacetic or peroxytrifluoroacetic acid (equation 504) [*158*].

[*158*] 504

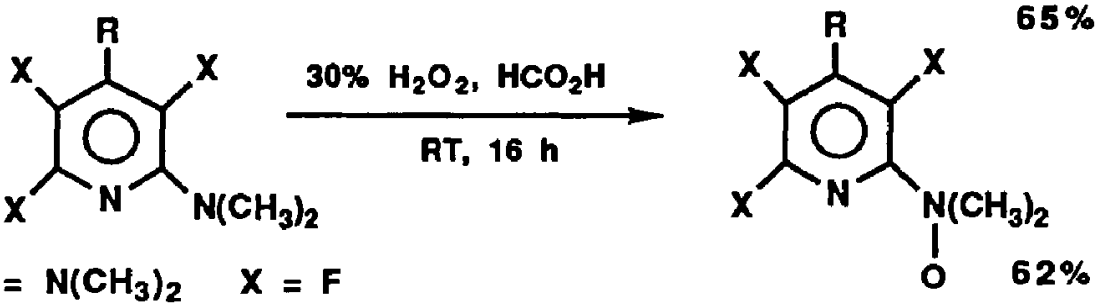


Interesting oxidations by peroxyformic acid take place with α- or γ-dimethylaminopolychloro- and polyfluoropyridines. Normal *N*-oxides are obtained only when a hydroxyl or a dimethylamino group is present in the γ position of the polyhalogenated pyridine ring (equation 505) [*247, 248*].

Without the presence of the electron-releasing hydroxyl or dimethylamino group, the primary products of oxidation, amine oxides, rearrange

[248] R = OH X = Cl

[247] R = $N(CH_3)_2$ X = F



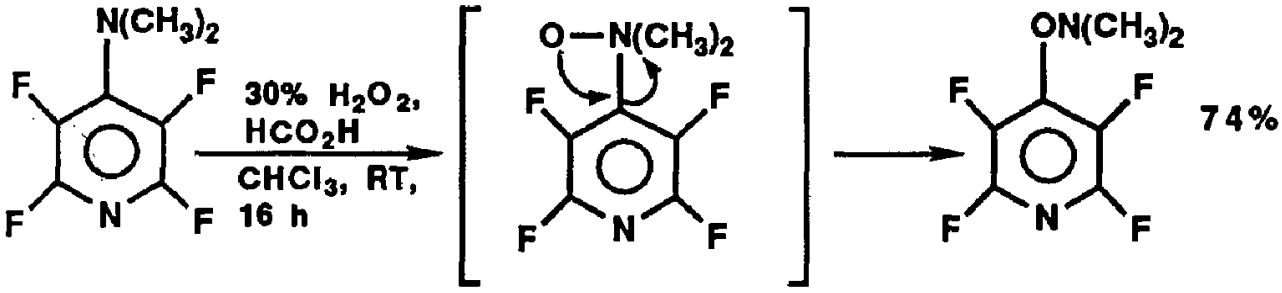
505

65%

62%

intramolecularly to *N,N*-dimethylhydroxylamines [*247, 248*] (equation 506).

[247]

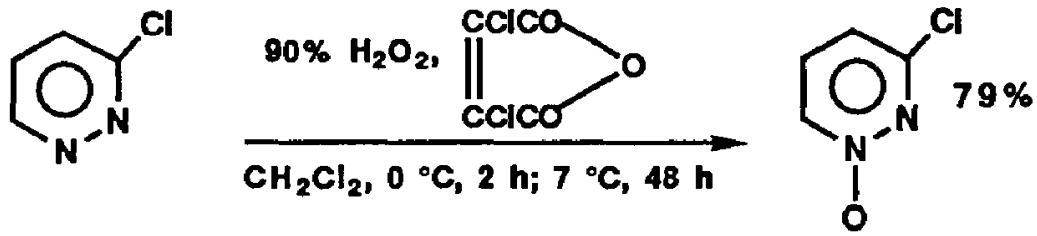


506

74%

Pyridazines are oxidized to mono-*N*-oxides by peroxydichloromaleic acid prepared in situ from 90% hydrogen peroxide and dichloromaleic anhydride (equation 507) [*339*].

[339]



507

79%

m-Phenanthroline and hydrogen peroxide in acetic acid give *m*-phenanthroline di-*N*-oxide in 71% yield after a 2-h reflux [*155*].

Dehydrogenation of Primary Amines to Imines and Aldehydes or Ketones

The elimination of hydrogen from nitrogen of the amino group and from the carbon of the adjacent methylene or methine group converts ***primary amines into imino*** compounds and, in the presence of water, ***into aldehydes or ketones.*** Imines are sometimes intercepted [*198, 833, 850, 917, 918, 957, 1189*] (equation 508).

In amines with the primary amino group bonded to a secondary carbon, dehydrogenation results in the formation of ***ketones*** [*850, 851, 692*] (equation 509).

508

$C_6H_5CH_2NH_2 \longrightarrow C_6H_5CHO$

[198]	$Na_2S_2O_8/AgNO_3$, NaOH, H_2O, 0 → 20 °C, 1-3 h	96%*
[850]	$KMnO_4$, $ZnSO_4$, *t*-BuOH, H_2O, 50-75 °C, steam distillation	61%
[833]	$BaMnO_4$, C_6H_6, reflux 1 h	95%
[918]	K_2FeO_4, 10% KOH, *t*-BuOH, RT, 30 min	44%
[917]	K_2FeO_4, H_2O, RT, 1 min	70%
[957]	40% CH_2O, HCl, reflux; $C_6H_{12}N_4$, H_2O, reflux 15 min; HCl, reflux 5 min	66%
[1189]	$NaNO_2$, CF_3CO_2H, Me_2SO (DMSO) (mole ratio 1:2:3), 100 °C, 20 h	82%

*$C_6H_5CH{=}NCH_2C_6H_5$, product of a reaction of benzaldimine and benzylamine, was isolated and hydrolyzed to benzaldehyde and benzylamine.

509

[850] $KMnO_4$, $CaSO_4$, H_2O, *t*-BuOH; 70 °C, distillation; 75%*

[692] $NaOCl$, Bu_4NHSO_4, AcOEt; RT, 2 h; 98%

[850] $KMnO_4$, $CaSO_4$, H_2O, *t*-BuOH; 55 → 75 °C, distillation; 56%

*The product was isolated as the 2,4-dinitrophenylhydrazone.

The oxidation of benzhydrylamine with **potassium permanganate** gives different products depending on the cation of the buffer used in the reaction (equation 510) [*851*].

510

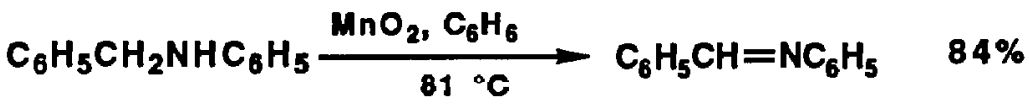
[851] $KMnO_4$, $ZnSO_4$, H_2O, Me_2O; RT, 45 min; $(C_6H_5)_2CHNH_2$; $KMnO_4$, $CaSO_4.2H_2O$, H_2O, *t*-BuOH, 70 °C, reflux 8 h

$(C_6H_5)_2C{=}NCH(C_6H_5)_2$ 74% 73% $(C_6H_5)_2C{=}N{-}N{=}C(C_6H_5)_2$

Dehydrogenation of Secondary Amines to Imines

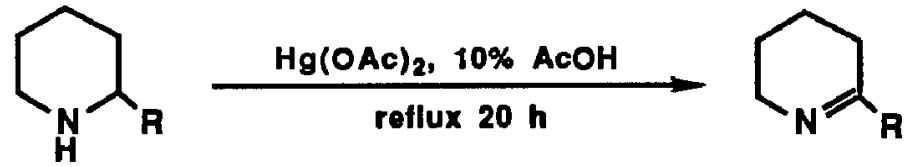
Secondary amines having hydrogens on the α carbon are dehydrogenated to imines by **mercuric acetate** or **manganese dioxide** [*825*, *1091*]. Piperidines give Δ^1-piperideines [*1091*] (equations 511 and 512).

[825]



511

[1091]



512

R	Temp. (°C)	Yield (%)
Me	64	31
Pr	86	42
Bu	86	32
t-Bu	~100	75

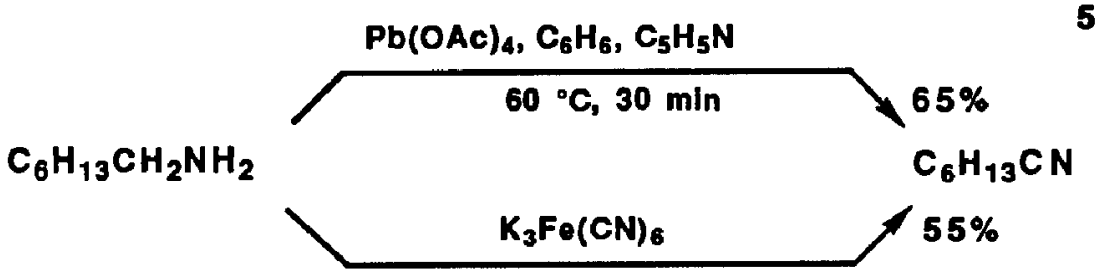
Dihydropyridine derivatives resulting from the Hantzsch synthesis are dehydrogenated to pyridines by heating with a dilute mixture of nitric acid and sulfuric acid (yields 58–65%) [*458*] (*see* equation 41).

Dehydrogenation of Primary Amines to Nitriles

More intensive dehydrogenation of primary amines having two hydrogen atoms on the adjacent carbons leads to nitriles. Such dehydrogenations are accomplished by argentic oxide [*381*], cobalt peroxide [*1136*], nickel peroxide [*936*], **lead tetraacetate** [*443, 444*], **sodium hypochlorite** [*692*], **potassium ferricyanide** [*924*], and potassium ruthenate [*196*] (equation 513).

[443]

513

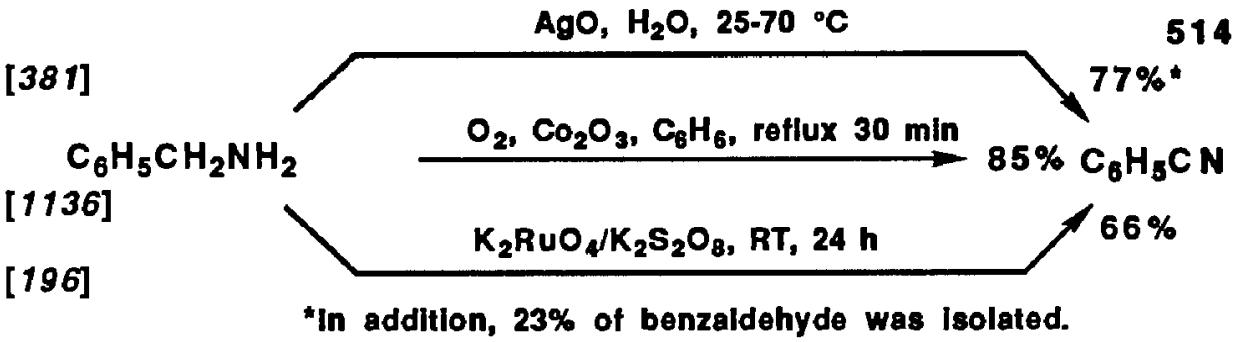


[924]

Hexylamine is converted into capronitrile in 73% yield on refluxing with nickel peroxide in benzene for 1.5 h [*936*]. Octylamine is dehydrogenated to octanenitrile in 60% yield by treatment with sodium hypochlorite and tetrabutylammonium hydrogen sulfate in ethyl acetate at room temperature for 35 min [*692*]. The preparation of benzonitrile is shown in equation 514 [*196, 381, 1136*].

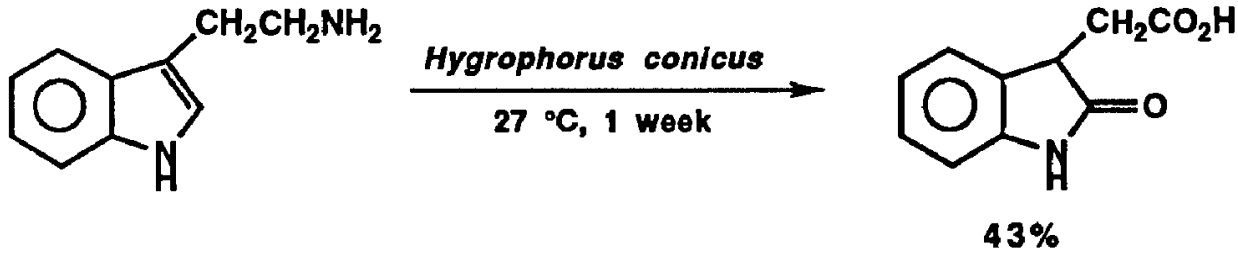
The oxidation of *o*-phenylenediamine with oxygen in the presence of cuprous chloride in pyridine at 25 °C furnishes muconononitrile (1,4-dicyano-1,3-butadiene) in 73–77% yield [*64*].

Biochemical oxidation with ***Hygrophorus conicus*** converts tryptamine into 2-indolone-3-acetic acid in 43% yield (equation 515) [*1069*].



[381] [1136] [196] 514

*In addition, 23% of benzaldehyde was isolated.

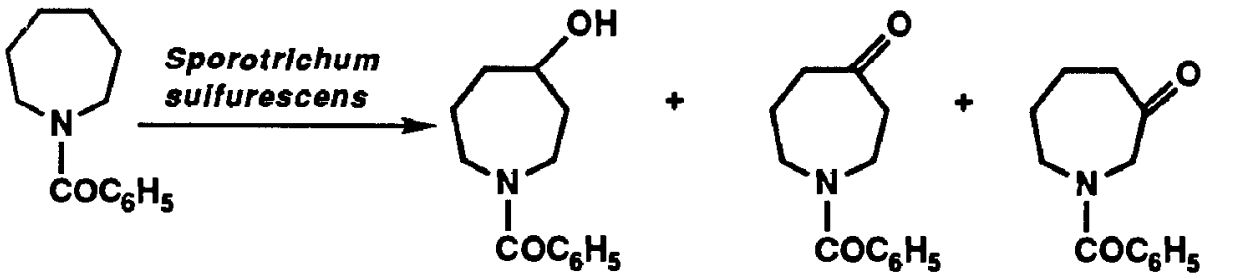


[1069] 515

Oxidation of the Carbon Chain of Amines

N-benzoylated cyclic amines and bicyclic amines undergo transannular ***hydroxylation*** when incubated with ***Sporotrichum sulfurescens.*** 1-Benzoylpiperidine is converted into 1-benzoyl-4-hydroxypiperidine in approximately 20% yield [*1081*]. *N*-Benzoylhexamethyleneimine gives 4-hydroxy-3-keto and 4-keto derivatives as a result of transannular hydroxylation and subsequent oxidation (equation 516).

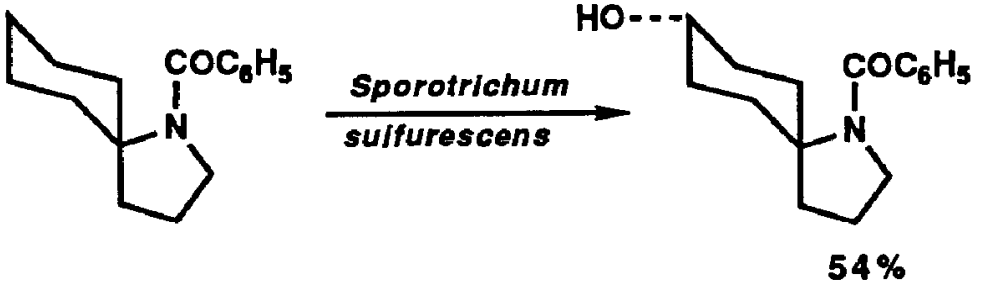
[1081] 516



Similar oxidations are achieved in bicyclic amides [*1082*], spirocyclic amides [*1084*], and acylated 1-adamantamines [*1083*]. *N*-Acetyladamantamine is hydroxylated on the tertiary as well as the secondary carbons to yield *N*-acetyl-1-adamantamine-4α-ol and *N*-acetyl-1-adamantamine-3-ol [*1083*]. The yields of all hydroxylated products are not very high (equations 517 and 518).

Tertiary amines containing a methyl group bound to carbon are oxidized to ***formamides.*** Dimethylaniline gives *N*-methylformanilide in 78% yield on treatment with **manganese dioxide** in chloroform for 18 h at room temperature [*826*]. Other reagents for this purpose are **potassium permanganate** in acetone and acetic acid at room temperature (yields 67–82%)

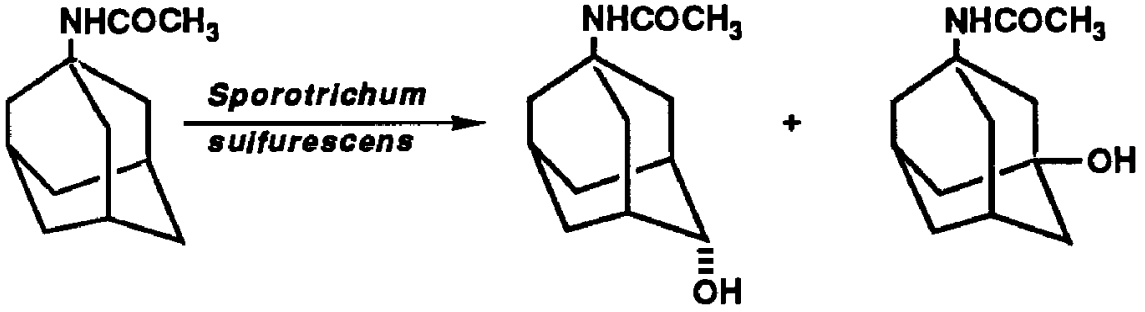
[1084]



517

54%

[1083]

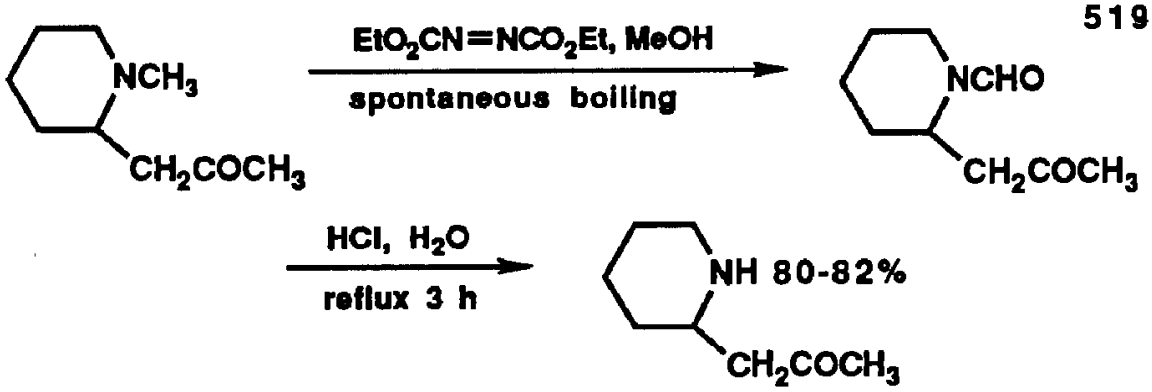


518

35% 7%

[854] and **diethyl azodicarboxylate** [980]. The formamide, on hydrolysis, is converted into a demethylated amine. Thus *N*-methylisopelletierine gives isopelletierine (equation 519) [980].

[980]

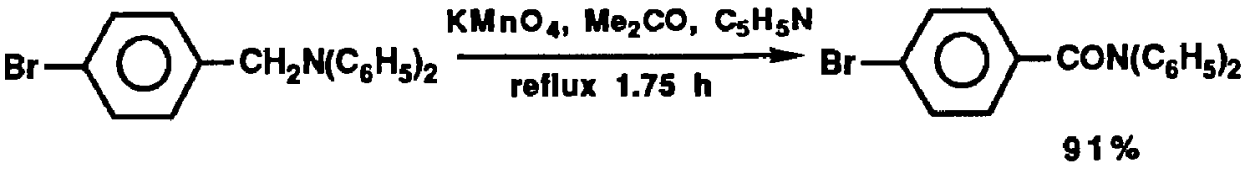


519

Such ***demethylation*** takes place often without interception of the formamide. Dicyclohexylmethylamine, on treatment with **potassium ferricyanide** in potassium hydroxide at room temperature overnight, is converted into dicyclohexylamine in 87% yield [926]. Other oxidants suitable for the demethylation of tertiary amines are mercuric acetate in 5% aqueous acetic acid at 100 °C [403], manganese dioxide in cyclohexane at 20 °C [812], and even oxygen, which, under irradiation at 20 °C in the presence of rose bengal in aqueous *tert*-butyl alcohol, converts codeine into norcodeine in 75% yield [46].

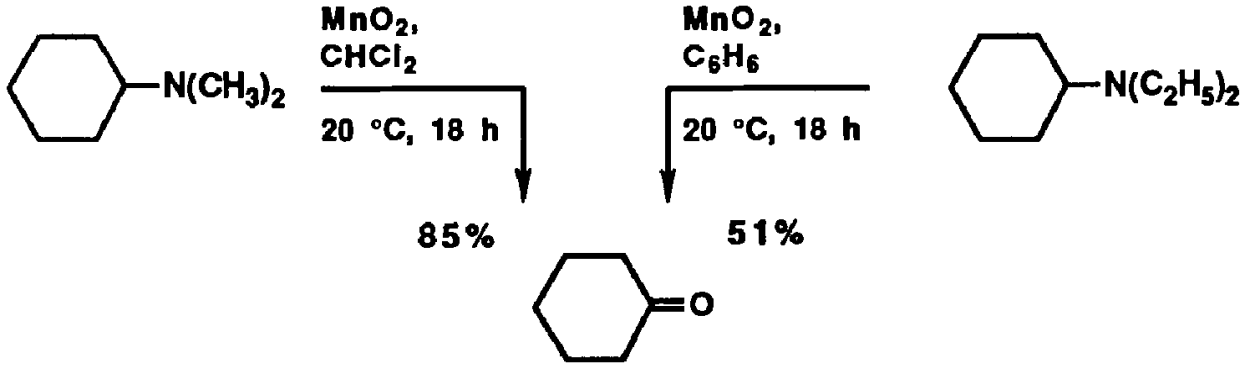
Tertiary amines with groups other than methyl are oxidized to ***amides***. *N,N*-Diethylaniline gives a 63% yield of *N*-ethylacetanilide on heating with benzyltriethylammonium permanganate in methylene chloride at 0–40 °C [904]. *p*-Bromobenzyldiphenylamine, on refluxing with potassium permanganate in acetone and pyridine, gives a 91% yield of diphenyl-*p*-bromobenzamide (equation 520) [855].

[855] 520



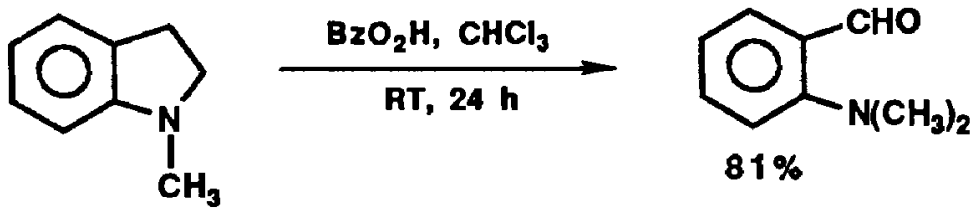
In some cases, tertiary amines are cleaved to carbonyl compounds (equation 521) [*818*].

[818] 521

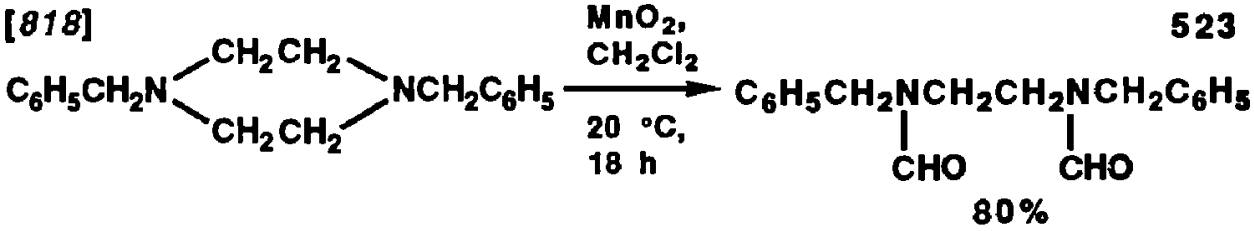


Peroxybenzoic acid converts *N*-methylindoline into *o*-dimethylaminobenzaldehyde (equation 522) [*311*], and manganese dioxide opens the ring in dibenzylpiperazine to give *N,N'*-dibenzyl-*N,N'*-diformylethylenediamine (equation 523) [*818*].

[311] 522



[818] 523

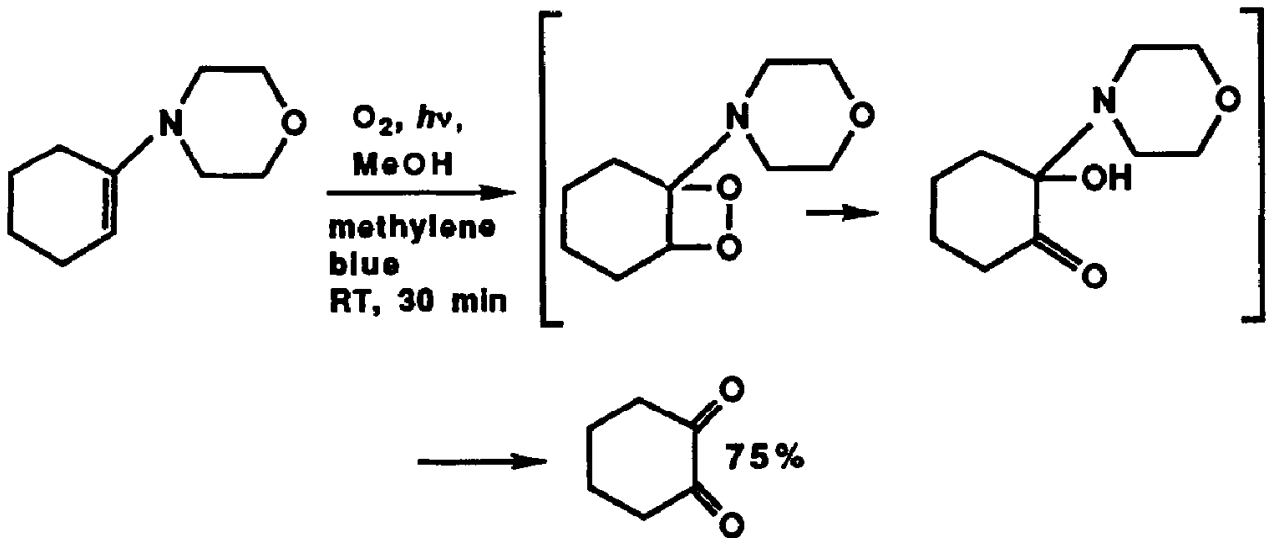


Tertiary ***enamines*** are oxidized to different compounds. *N*-Methylpyrrol gives 92% of *N*-methylsuccinimide by oxidation with peroxybenzoic acid in chloroform at room temperature [*311*]. *N*-Cyclohexenylmorpholine, with singlet oxygen, is oxidized to cyclohexanedione (equation 524) [*42*].

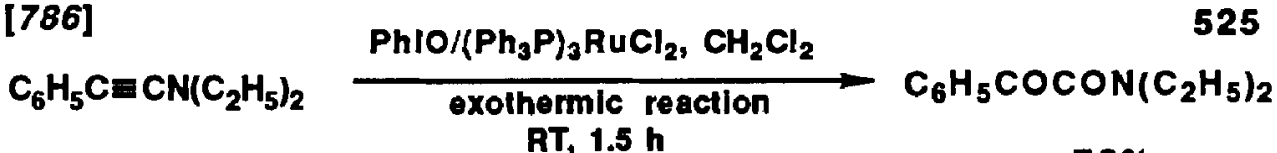
The oxidation of *N*-phenylacetylenyl-*N,N*-diethylamine yields the *N,N*-diethylamide of phenylglyoxylic acid (equation 525) [*786*].

Amides containing methylene groups linked to the nitrogen atoms are oxidized to ***imides*** by **ruthenium tetroxide,** which is usually generated in situ from ruthenium dioxide or ruthenium chloride and **sodium periodate**

[42] 524

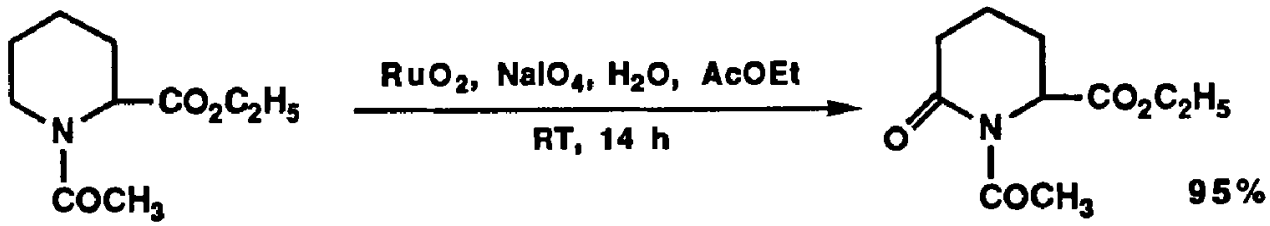


[786] 525



[940, 944]. *N*-Hexylenanthamide gives a 58% yield of *N*-caproylenanthamide [940] on treatment with ruthenium tetroxide in carbon tetrachloride at 10–15 °C. Ethyl *N*-acetyl-α-pipecolinate, when treated with ruthenium dioxide and sodium periodate in aqueous ethyl acetate at room temperature, gives a 95% yield of ethyl 1-acetyl-2-piperidone-6-carboxylate (equation 526) [944].

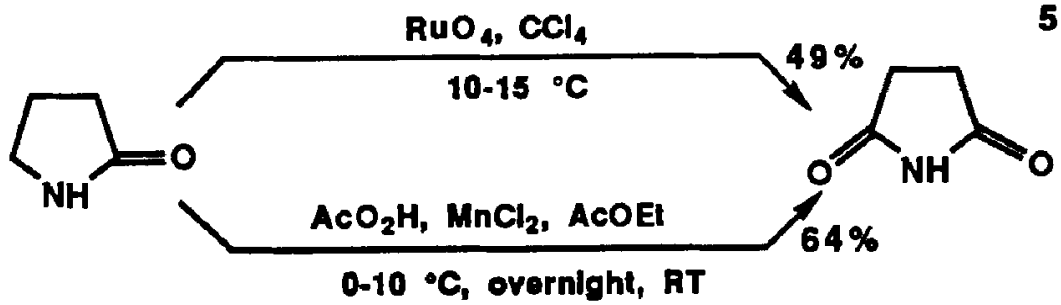
[944] 526



A similar oxidation converts ***lactams into imides.*** The reaction can be carried out with **ruthenium tetroxide** [940, 944] or with *tert*-butyl hydroperoxide or peroxyacetic acid in the presence of manganese dichloride or diacetylacetonate [225, 255] (equation 527).

[940] 527

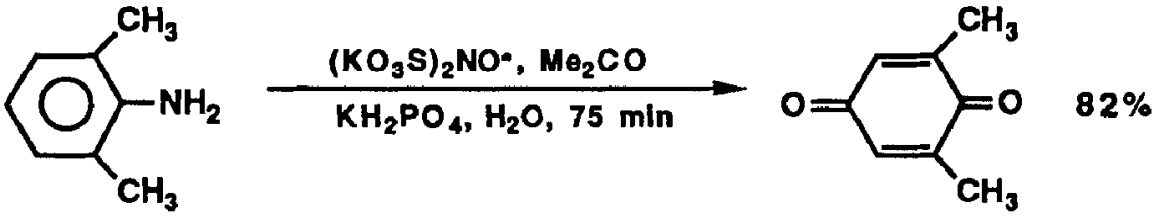
[225]



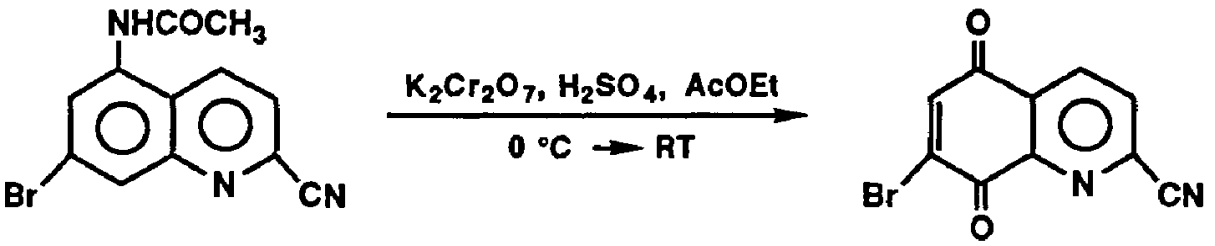
Oxidation of Aromatic Amines to Quinones

The presence of an amino group on an aromatic ring often results in oxidation of the ring to a ***quinone***. The classical and industrial method is the treatment of anilines with **potassium dichromate** and sulfuric acid. Thus, aniline at room temperature is converted into *p*-benzoquinone in 86% yield [*647*], and 2,5-dimethylaniline at 80 °C gives a 55% yield of *p*-xyloquinone [*648*]. A specific reagent for such oxidations is the *Fremy salt, potassium nitrosodisulfonate* (equation 528) [*490*]. The oxidation of the amino group takes place even if it is acylated (equation 529) [*1190*].

[*490*] **528**



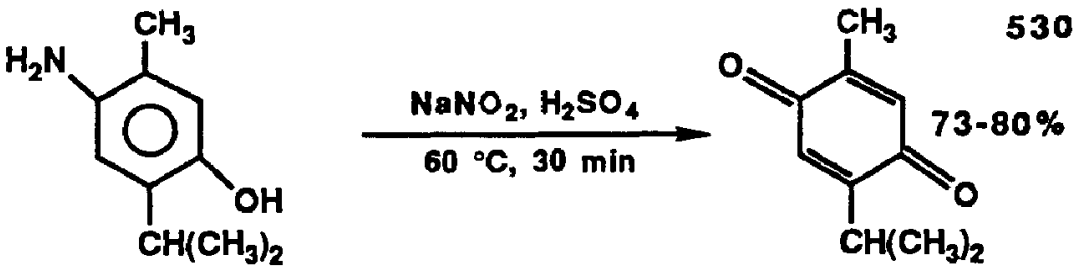
[*1190*] **529**



73%

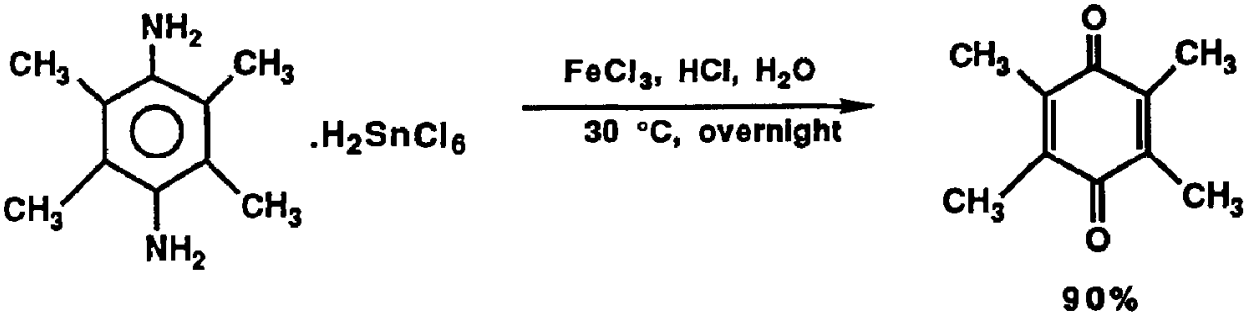
Such oxidations are especially easy, if electron-releasing groups such as hydroxyls or amino groups are located in *para* or *ortho* positions with respect to the amino groups. 3-Chloro-4-aminophenol stirred with **sodium dichromate** and sulfuric acid at a temperature below 35 °C gives a 58–63% yield of chloro-*p*-benzoquinone after the reaction mixture is allowed to stand at room temperature for 1 h [*637*]. Aminothymol is converted into thymoquinone on warming for 30 min with dilute sulfuric acid and sodium nitrite (equation 530) [*451*].

[*451*] **530**



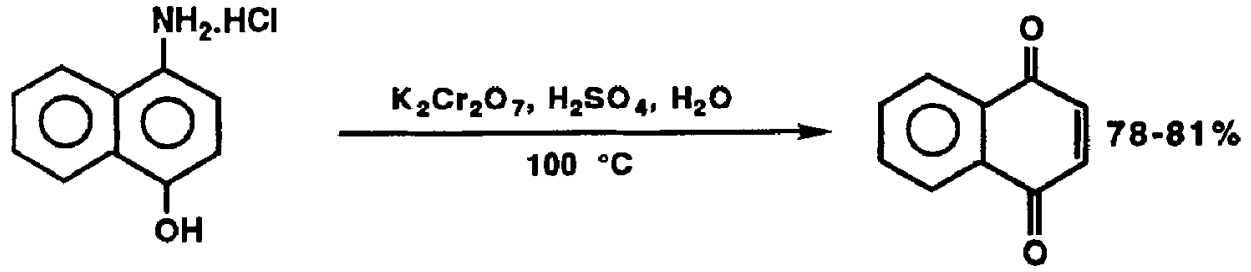
Diaminodurene in the form of its hexachlorostannate is oxidized to duroquinone with **ferric chloride** (equation 531) [*908*].

[908] 531

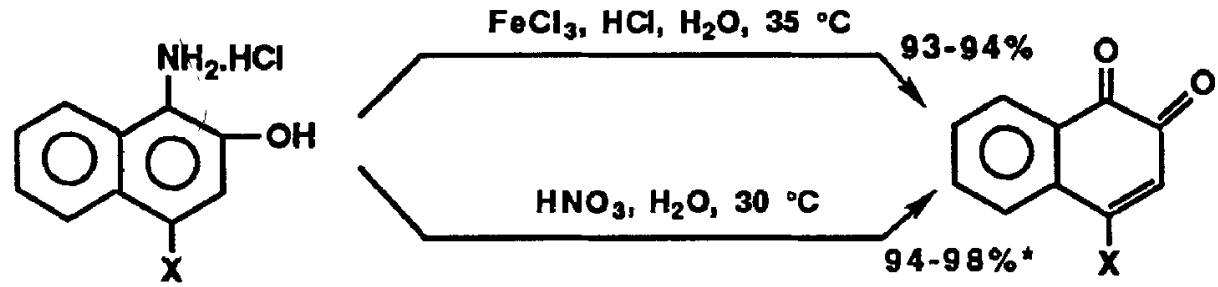


Aminonaphthols are converted into naphthoquinones [*1191*, *1192*, *1193*] by nitric acid [*1193*], by potassium dichromate [*1191*], or by ferric chloride [*1192*] (equations 532 and 533).

[1191] 532



[1192] X = H 533

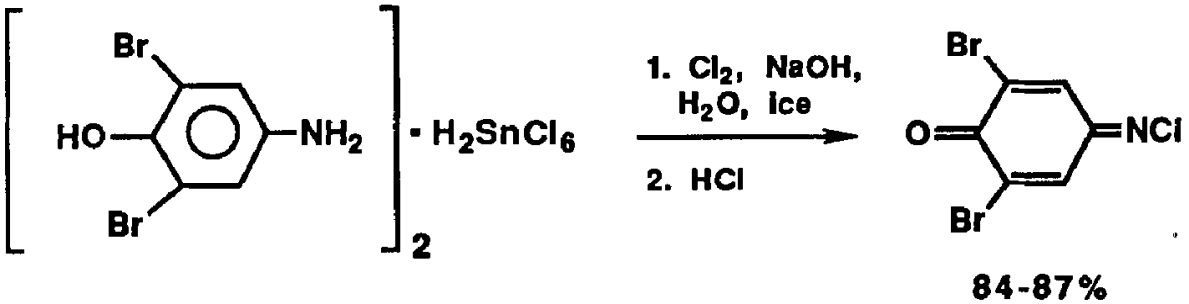


[1193] X = SO_3H

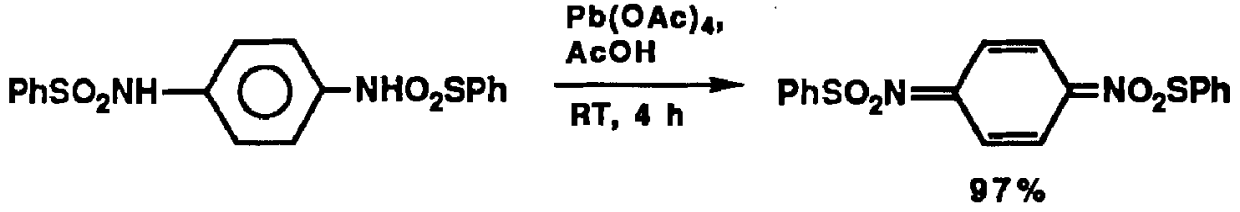
*The product was isolated as the NH_4^+ salt.

Several other examples of the oxidation of hydroxyamino and diamino aromatic compounds with silver oxide [*368*], lead dioxide [*368*], lead tetraacetate [*441*], and sodium hypochlorite [*694*] are documented in equations 534–536.

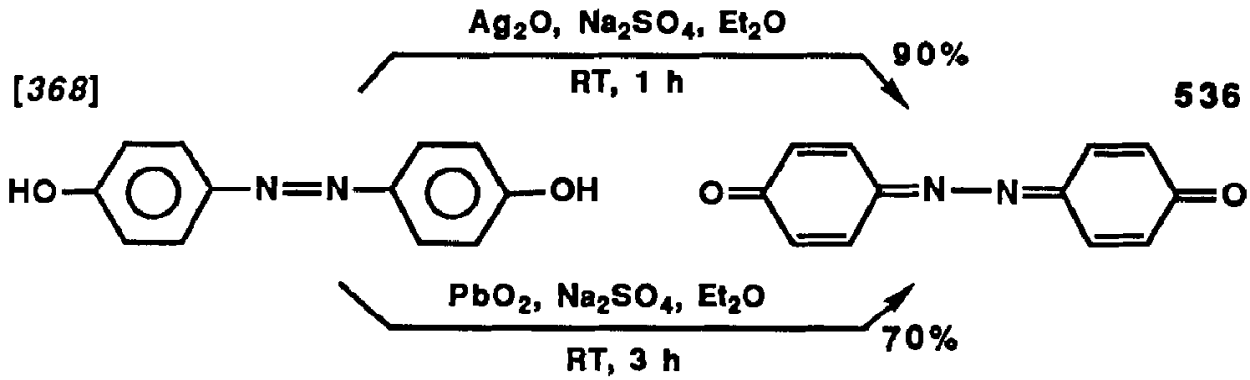
[694] 534



[441] 535



[368] 536



PHOSPHORUS AND ARSENIC COMPOUNDS

Like tertiary amines, ***tertiary phosphines*** are readily transformed into the corresponding oxides, ***phosphine oxides.*** Tributylphosphine in dichloromethane is oxidized with **ozone** adsorbed on silica gel at −70 °C to tributylphosphine oxide in 92% yield [*113*]. Other oxidants used to transform phosphines into phosphine oxides are **potassium peroxysulfate** [*205*], argentic oxide [*381*], **manganese dioxide** [*813*], and **barium manganate** [*833*] (equation 537).

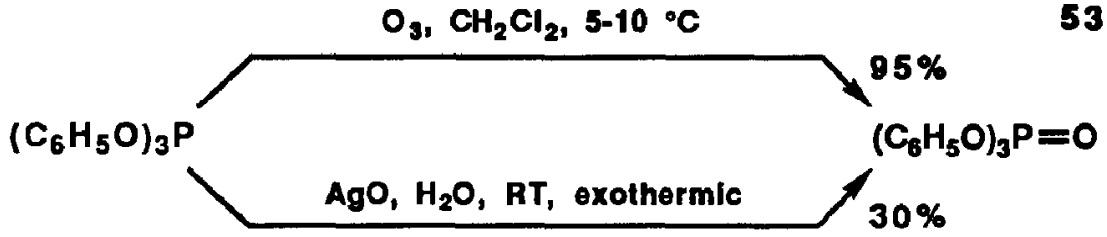
537

[*113*]	O_3, SiO_2, CH_2Cl_2, -65 °C	99%
[*205*]	$2KHSO_5.KHSO_4.K_2SO_4$, H_2O, EtOH, 70 °C, 4 h	100%
[*381*]	AgO, H_2O, RT, exothermic reaction	40%
[*813*]	MnO_2, petroleum ether, reflux 5 h	75%
[*833*]	$BaMnO_4$, C_6H_6, reflux 2 h	100%

A similar oxidation of trivalent phosphorus to pentavalent phosphorus occurs in trialkyl or triaryl phosphites. Triphenyl phosphite is converted by ozone in dichloromethane at 5–10 °C into triphenyl phosphate in 95% yield [*113*] and by argentic oxide in 30% yield [*381*] (equation 538).

The oxidation of ***phosphites to phosphates*** is very important in the chemistry of nucleoside phosphites, which must be handled under anhydrous conditions. For this purpose, **anhydrous hydrogen peroxide, bis(trimethylsilyl) peroxide, cumene hydroperoxide,** and ***N*-methylmor-**

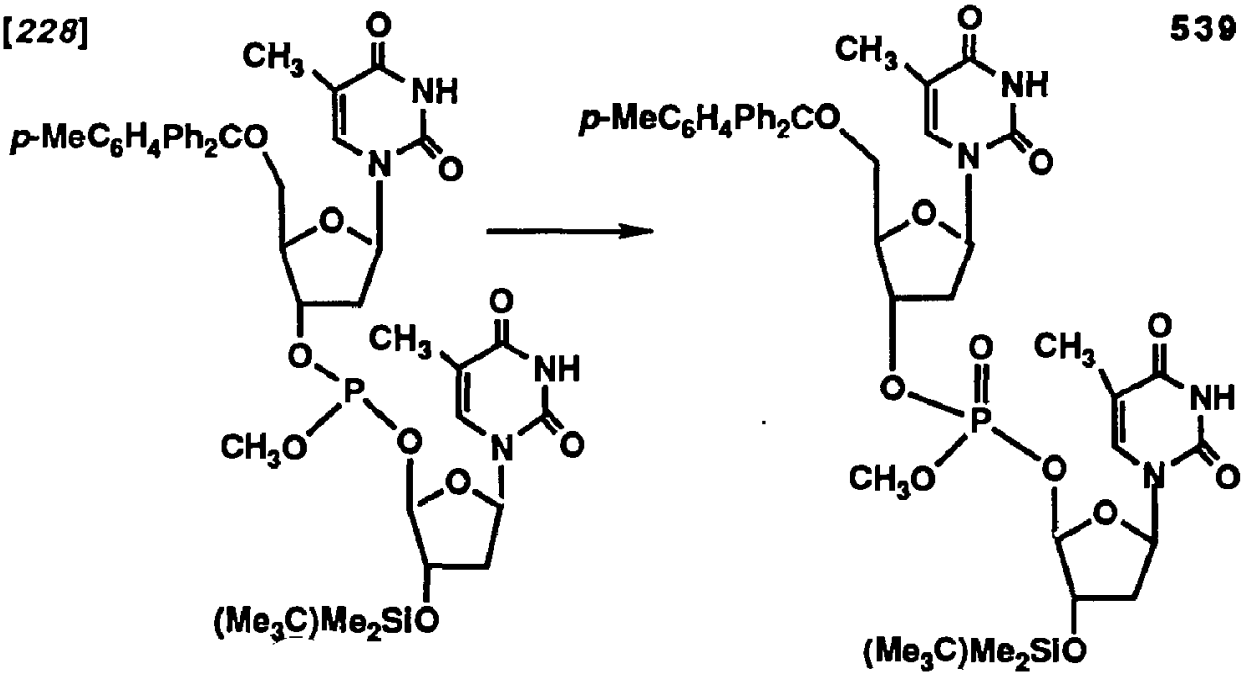
[113] 538



[381]

pholine *N*-oxide are used in solutions in dichloromethane and give 80–92% yields of the phosphates (equation 539) [228].

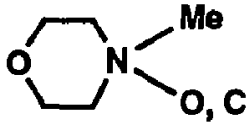
[228] 539



$(Me_3SiO)_2$, CH_2Cl_2, 20 °C, 3 h — 85%

$(Me_3SiO)_2$, $Me_3SiOSO_2CF_3$, Et_3N, CH_2Cl_2, -20 °C, 5 min — 87%

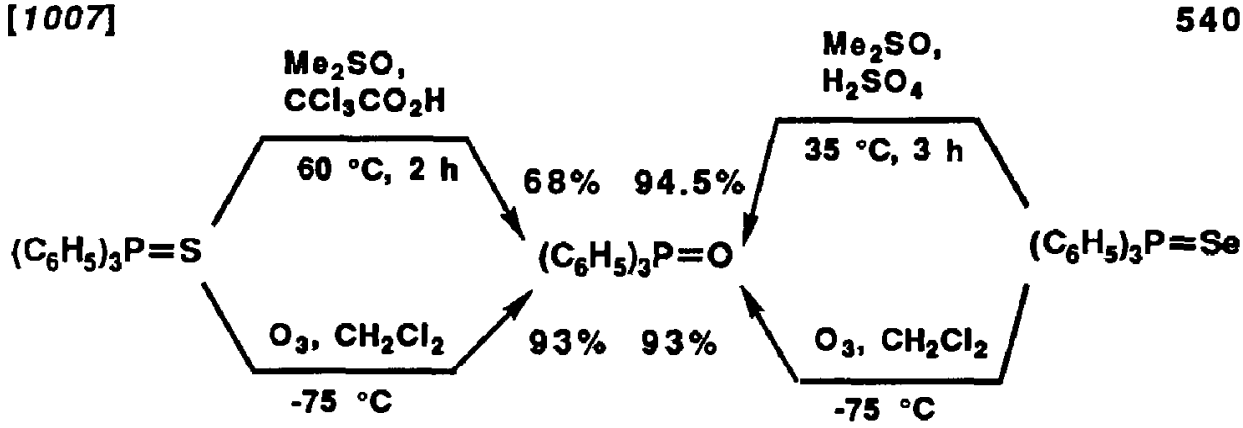
$PhCMe_2OOH$, CH_2Cl_2, 0 °C, 40 min — 92%



80%

Trialkyl and triarylphosphine oxides are also prepared by ***oxidation of trialkyl and triarylphosphine sulfides and selenides*** (equation 540) [1007, 1194].

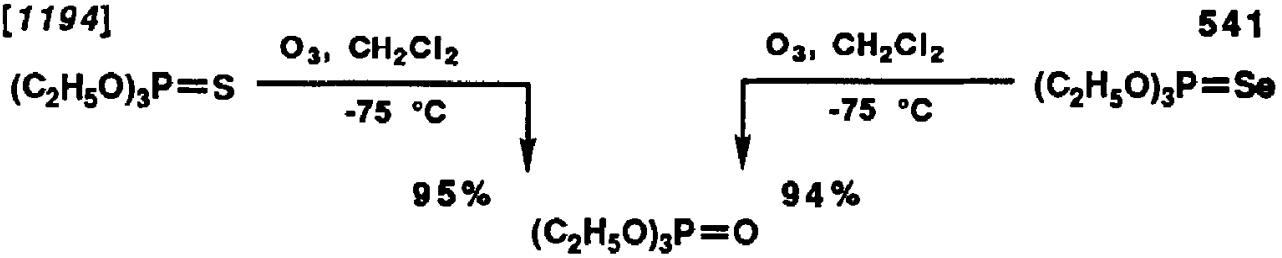
[1007] 540



[1194]

The same oxidation procedures apply to the conversion of ***trialkyl or triaryl thiophosphates*** and ***selenophosphates*** into ***phosphates*** [*1007, 1194*] (equation 541).

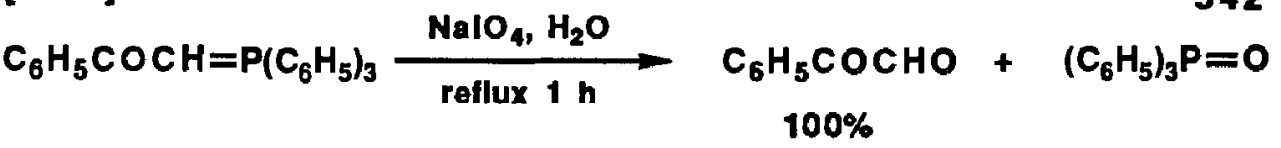
[*1194*]



541

Triphenylphosphine ylides are cleaved by sodium periodate to triphenylphosphine oxides and carbonyl compounds (equation 542) [*1195*].

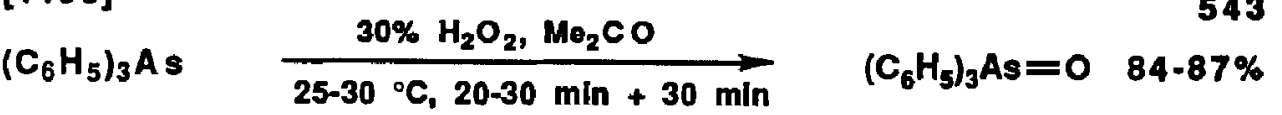
[*1195*]



542

Tertiary arsines are oxidized to ***arsine oxides*** by **hydrogen peroxide** (equation 543) [*1196*].

[*1196*]



543

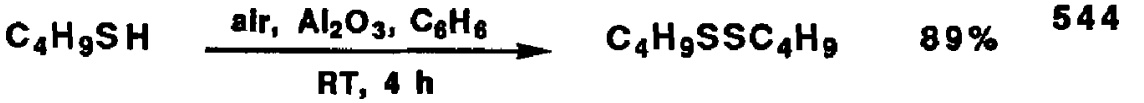
SULFUR COMPOUNDS

The oxidation of some sulfur-containing compounds, such as thioketones and thioamides (derivatives of ketones and acids, respectively), has been mentioned in earlier sections.

Oxidation of Thiols (Mercaptans)

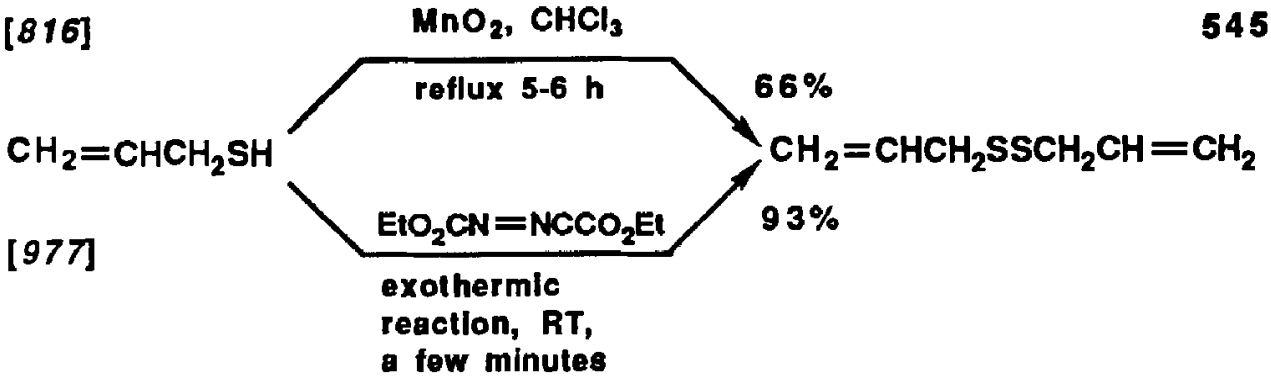
Gentle oxidation of mercaptans and thiols leads to coupled products—***disulfides***. The oxidants used for this purpose are **air** [*9*], **hydrogen peroxide** [*186*], **dichromates** [*663*], **chlorochromates** [*619*], **manganese dioxide** [*816*], copper permanganate [*896*], **ferric chloride** [*907*], and **diethyl azodicarboxylate** [*977*] (equations 544–546).

[*9*]



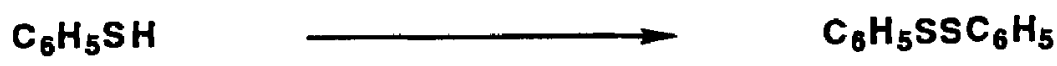
544

[816] 545

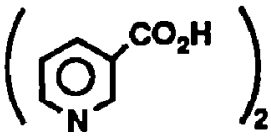


[977]

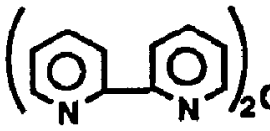
546



[9] air, Al_2O_3, C_6H_6, RT, 6 h 96%

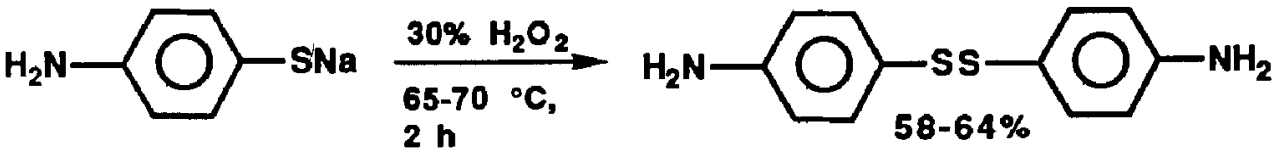
[663]  90%

[619] Bu_4NCrO_3Cl, $CHCl_3$, RT, 1 h 87%

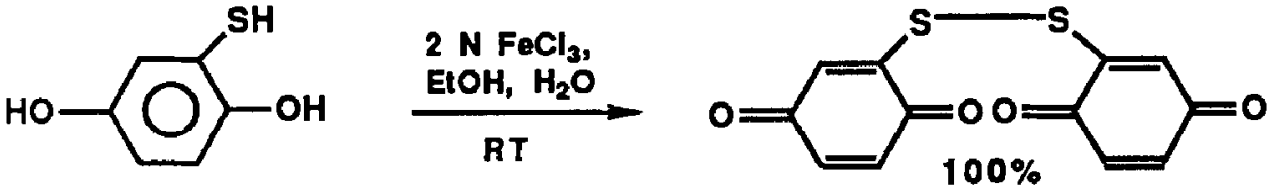
[896]  100%

In compounds containing oxidizable functional groups, these groups may be left intact [*163, 186*] or oxidized concurrently [*907*] (equations 547 and 548).

[186] 547



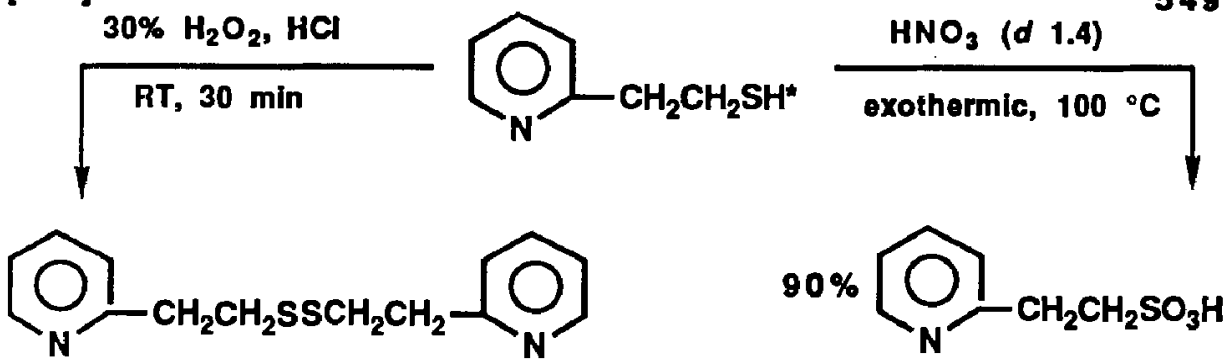
[907] 548



More energetic oxidation ***of thiols*** leads ***to sulfonic acids.*** Thiophenol dissolved in a solution of potassium hydroxide in dimethylformamide is oxidized by **oxygen** at 23.5 °C over a 22-h period to benzenesulfonic acid in 91% yield [*53*]. Lauryl mercaptan gives dodecanesulfonic acid in 100% isolated yield upon treatment with potassium peroxymonosulfate, $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, at room temperature for 30 min [*205*].

Whereas 2-(2-pyridyl)ethanethiol is oxidized with hydrogen peroxide to 2-(2-pyridyl)ethyl disulfide, its oxidation by nitric acid yields 2-(2-pyridyl)ethanesulfonic acid (equation 549) [*474*].

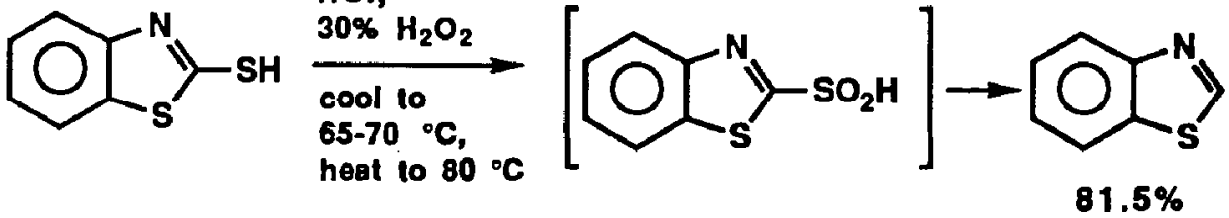
[*474*] 549



*The starting material was the hydrochloride of the compound.

In 2-mercaptobenzothiazole, energetic oxidation with hydrogen peroxide leads to the replacement of the mercapto group by hydrogen, probably via oxidation to sulfinic acid (equation 550) [*1197*].

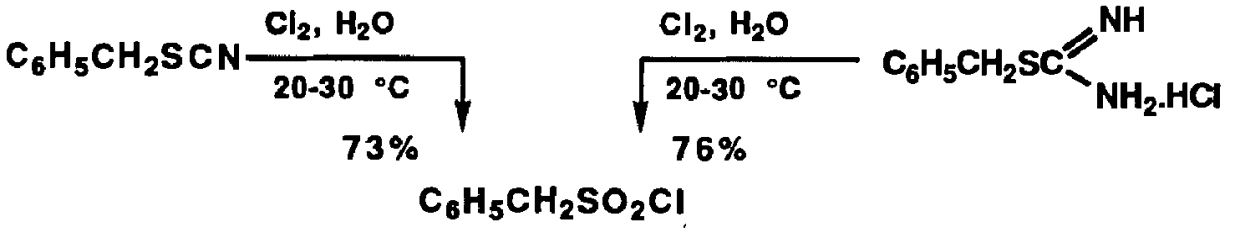
[*1197*] 550



The oxidation of ***mercaptans*** with **chlorine** in water gives ***sulfonyl chlorides.*** Ethyl mercaptan and pentyl mercaptan afford ethanesulfonyl chloride and pentanesulfonyl chloride in yields of 73 and 78% at 5 and 1–5 °C, respectively [*683*].

Sulfonyl chlorides result also from oxidations, with chlorine in aqueous media, of ***isothiocyanates and isothioureas*** (equation 551) [*684*].

[*684*] 551



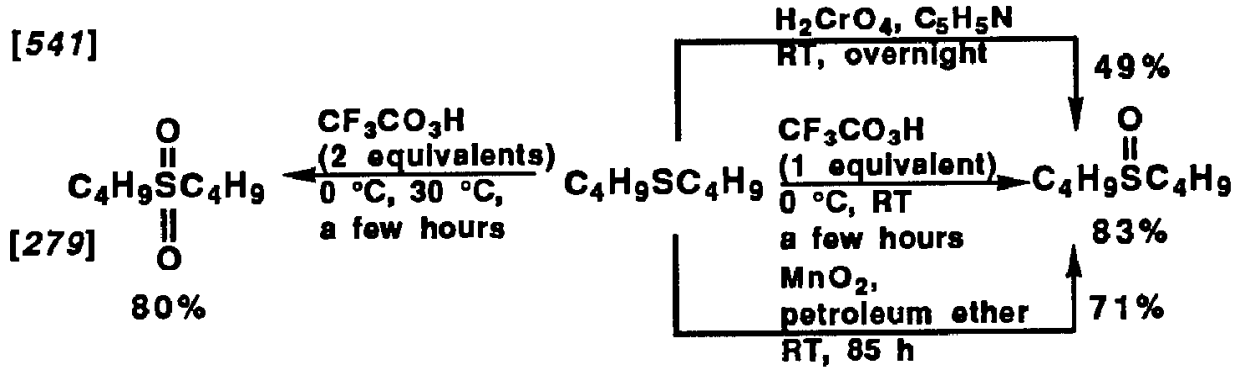
Oxidation of Sulfides

Dialkyl ***sulfides***, alkyl aryl sulfides, diaryl sulfides, and cyclic sulfides are oxidized to the corresponding ***sulfoxides*** or ***sulfones.*** Often, both products can be obtained on oxidation with the same oxidant, depending on

whether one or two equivalents of the reagent are used [*164, 279*]. Some of the oxidants, however, selectively oxidize sulfides to sulfoxides only [*541, 770*] or to sulfones only [*207, 209, 589*]. The rate constant of the oxidation of diphenyl sulfides to diphenyl sulfoxides by peroxyacetic acid is several hundred times greater than that of the oxidation of sulfoxides to sulfones [*265*]. Oxidations at sulfur take precedence over oxidation at other functional groups.

Dibutyl sulfide is converted into dibutyl sulfoxide with one equivalent of **peroxytrifluoroacetic acid** and into dibutyl sulfone with two equivalents of peroxytrifluoroacetic acid [*279*]. On the other hand, with **manganese dioxide,** dibutyl sulfide yields dibutyl sulfoxide exclusively [*541*], and with **chromic acid,** it yields dibutyl sulfoxide, even when an excess of the oxidant is used and even when the reaction is carried out at 100 °C [*541*] (equation 552).

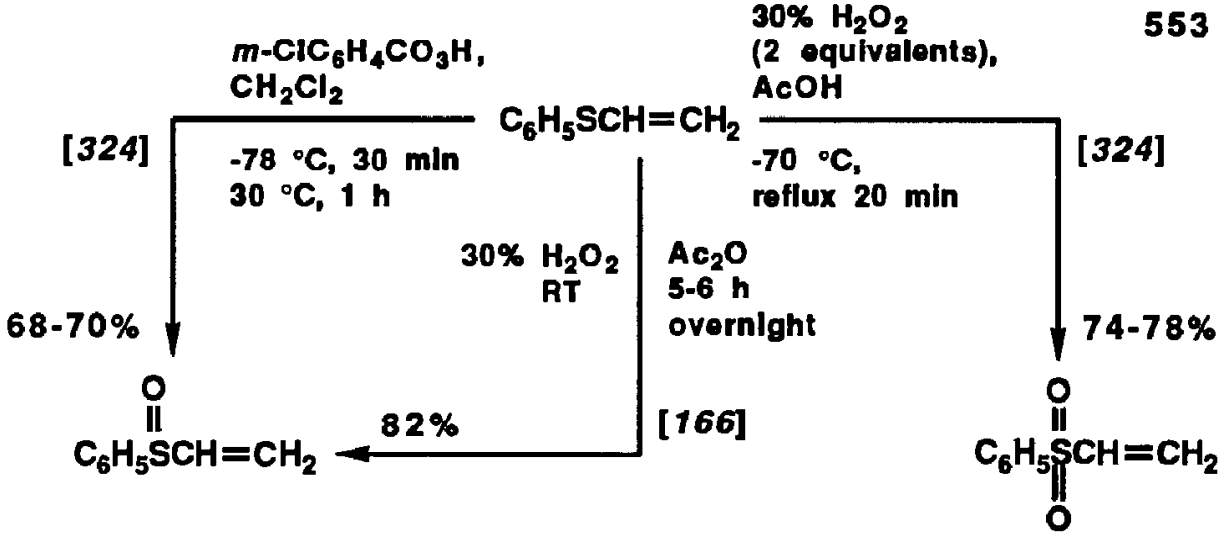
552



[*541*]

Organic peroxy acids, especially at low temperatures, oxidize sulfides to sulfoxides [*163, 324*], whereas tetrabutylammonium persulfate [*209*] at room temperature and hydrogen peroxide at higher temperatures yield sulfones [*163, 324*]. However, hydrogen peroxide in acetic anhydride at room temperature yields sulfoxides [*166*]. Under these conditions, double bonds resist epoxidation [*163, 166, 324*] (equation 553).

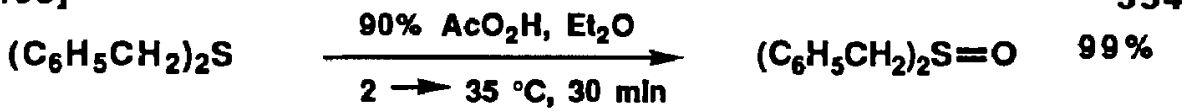
553



The oxidation reagents used most frequently for the conversion of sulfides into sulfoxides and sulfones are **hydrogen peroxide, peroxy acids,** and **periodates.** Periodates usually do not oxidize sulfoxides to sulfones [*770 771, 772, 776, 778*]. In addition, many other, even rather exotic, oxidants have been used especially for chemoselective oxidations of sulfides containing functional groups vulnerable to attack by peroxy compounds, such as double bonds and carbonyl groups.

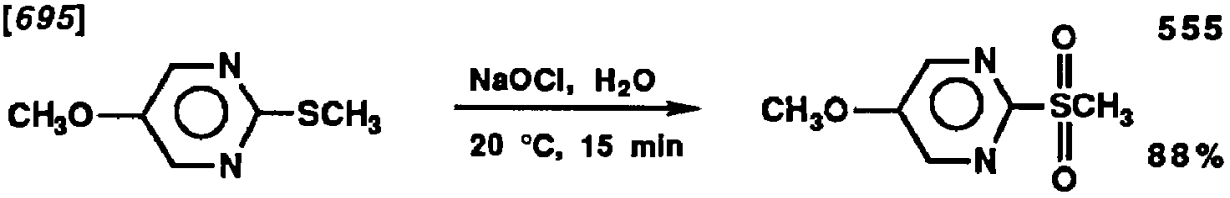
Many examples with references are quoted in equations 554–557 to show various reaction conditions.

[*1198*]

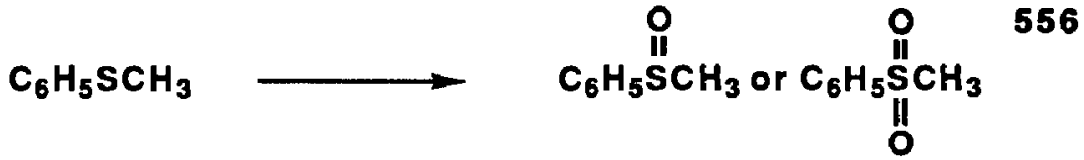


554

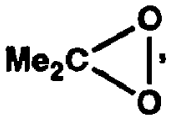
[*695*]



555



556

[*132*]	30% $H_2O_2/TiCl_3$, H_2O, MeOH, RT, 5 min	100%
[*207*]	$2KHSO_5.KHSO_4.K_2SO_4$ (Oxone) (3 equivalents), MeOH, H_2O, 0 °C, RT, 4 h	95%
[*209*]	$2KHSO_5.KHSO_4.K_2SO_4$ (Oxone), Bu_4NBr, CH_2Cl_2, RT	78%
[*224*]	*t*-BuOOH, $Ti(O\text{-}i\text{-}Pr)_4$, (*R,R*)-diethyl tartrate (1:1:2) (Sharpless reagent), CH_2Cl_2, -20 °C, 5 h	80% (ee 89%) (*R*)
[*710*]	*t*-BuOCl, MeOH, -78 °C, 15 min; $NaHCO_3$, RT, 2 h	90%
[*770*]	$NaIO_4$, H_2O, 0 °C, 3-12 h	99%
[*772*]	$NaIO_4$, H_2O, 0 °C, 15 h	91%
[*771*]	$NaIO_4/Al_2O_3$, EtOH, RT, 5 h	88%
[*210*]	 , Me_2CO, RT	65%

[*1058*] *Corynebacterium equli* IFO 3730, $C_{16}H_{34}$,30 °C, 3 days* 100% (ee 70%) (+)

*Exceptionally, the same microorganism converts decylphenyl sulfide to decyl phenyl sulfone in 88% yield with only 7% yield of the sulfoxide.

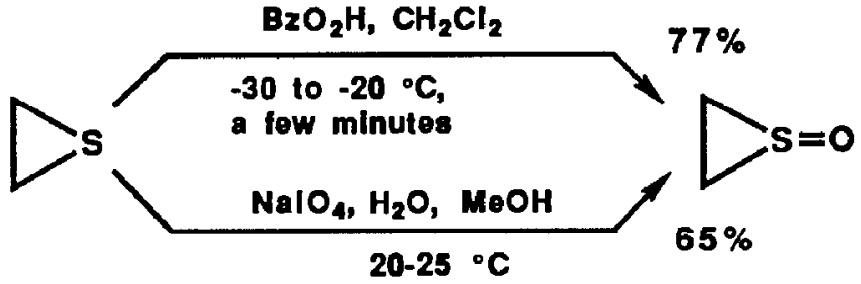
557

$C_6H_5SC_6H_5$ ⟶ $C_6H_5S(O)C_6H_5$ and/or $C_6H_5S(O)_2C_6H_5$

[*132*]	30% $H_2O_2/TiCl_3$, MeOH, H_2O, RT, 5 min	100%	
[*194*]	$NaBO_3$ (small excess), AcOH, 50-55 °C	71%	
[*194*]	$NaBO_3$ (large excess), AcOH, 50-55 °C		98%
[*208*]	$2KHSO_5.KHSO_4.K_2SO_4$ (2:1:1) (Oxone), Bu_4NBr, CH_2Cl_2, -10 °C ⟶ RT, 18 h	30%	+ 70%
[*205*]	$KHSO_5.KHSO_4.K_2SO_4$, H_2O, EtOH, H_2SO_4, AcOH RT, 5 h		97%
[*426*]	$(NH_4)_2Ce(NO_3)_6$ (4 mol), MeCN, H_2O, RT, 3 min	82%	
[*506*]	SO_2Cl_2, CH_2Cl_2, -30 to -40 °C, 9 min; EtOH	95%	
[*739*]	$NaBrO_2$, H_2O, RT, 30 min	78%	
[*770*]	$NaIO_4$, H_2O, 0 °C, 3-12 h	98%	
[*778*]	$NaIO_4$, $C_{16}H_{33}PBu_3Br$, $CHCl_3$, reflux 36 h	70%	
[*942*]	RuO_4, CCl_4, 0 °C, 14 h	32%	+ 42%

Sulfides containing sulfur in the ring are oxidized to ***cyclic sulfoxides.*** Ethylene sulfide, upon treatment with sodium periodate in aqueous methanol at 20–25 °C, is converted into ethylene sulfoxide in 65% yield [*768*]. With **peroxybenzoic acid** in dichloromethane, a 77% yield is obtained [*309*] (equation 558).

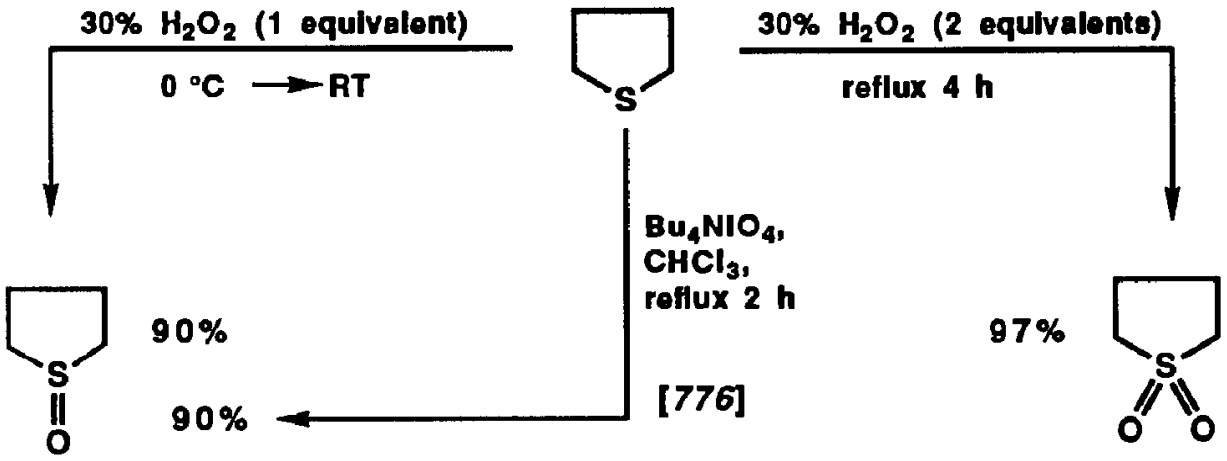
558



Tetrahydrothiophene (tetramethylene sulfide) gives tetramethylene sulfoxide in 90% yield on refluxing for 2 h with **tetrabutylammonium periodate** [*776*]. The oxidation of tetramethylene sulfide with one equivalent of **hydrogen peroxide** at room temperature affords tetramethylene sulfoxide; with two equivalents at refluxing temperature, tetramethylene sulfone is obtained (equation 559) [*164*].

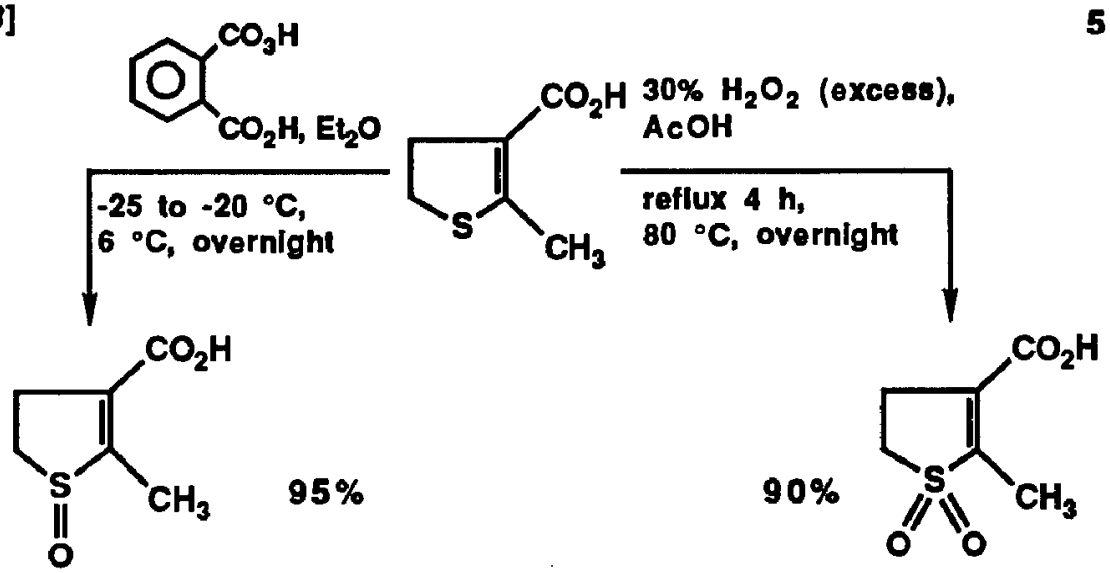
559

[164] [164]



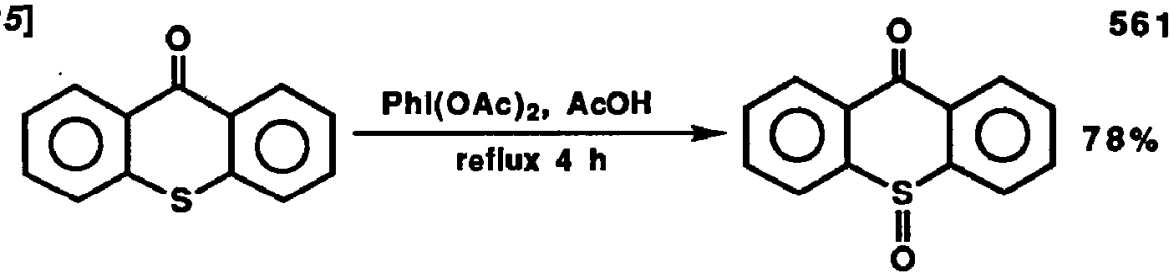
2-Methyl-4,5-dihydrothiophene-3-carboxylic acid yields the corresponding sulfoxide on treatment with **peroxyphthalic acid** and the sulfone on refluxing with hydrogen peroxide in acetic acid (equation 560) [*163*]. Neither oxidant affects the double bond under the conditions used.

[163] 560



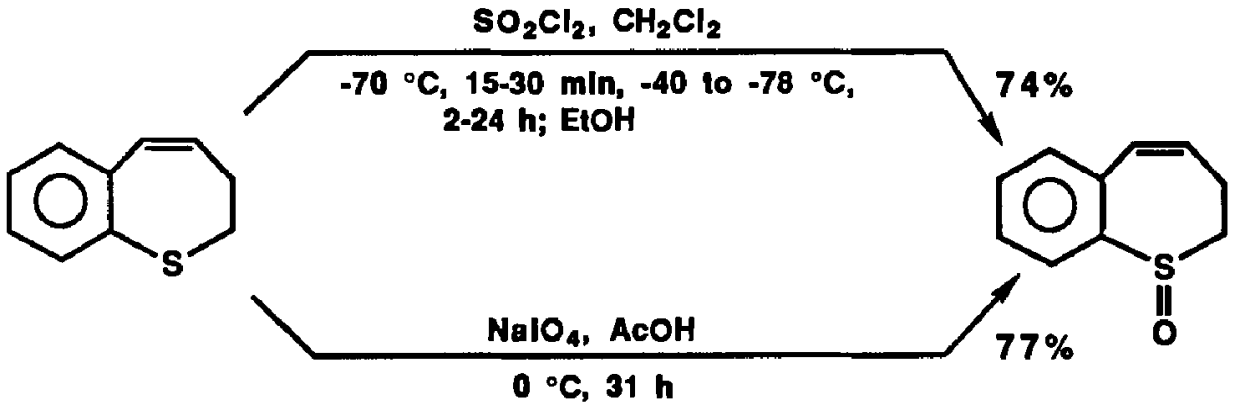
Thiaxanthone is oxidized to thiaxanthone oxide in 78% yield by refluxing for 4 h with iodobenzene diacetate in acetic acid (equation 561)

[795] 561



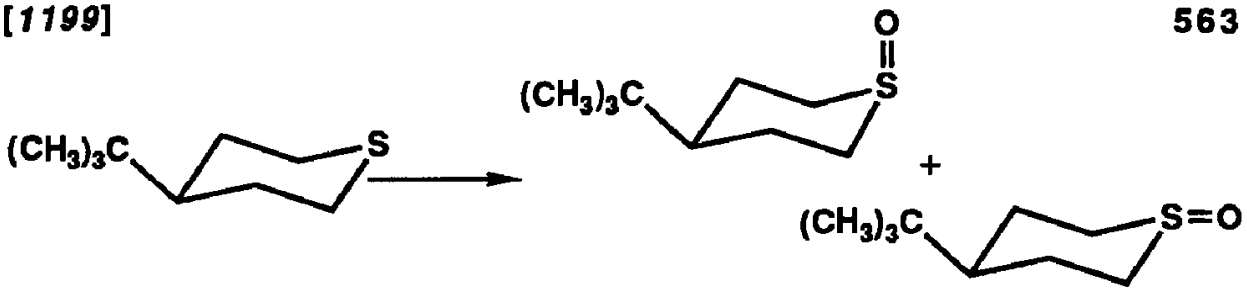
[*795*]. 2,3-Dihydro-1-benzothiepin is converted into 2,3-dihydro-1-benzothiepin 1-oxide with sulfuryl chloride in 79% yield or with sodium periodate in 77% yield (equation 562) [*506*].

[506] 562



Thiacyclohexane (thiane) is oxidized to thiane oxide by the enzyme *cyclohexanone oxygenase* [*1034*]. Thiacyclohexanes substituted at position 4 give two possible stereoisomers of the sulfoxides, *cis* and *trans*, in different ratios, depending on the oxidants used (equation 563) [*1199*].

[1199] 563

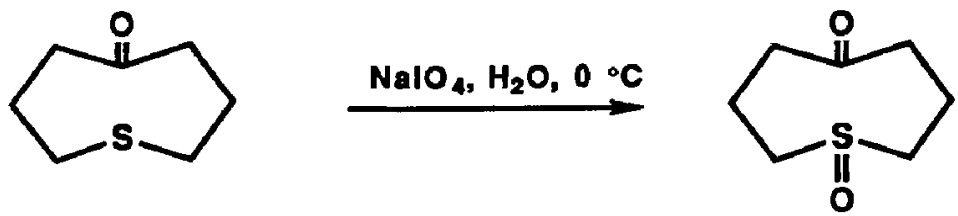


	cis	*trans*
30% H_2O_2, Me_2CO, 25 °C	37%	63%
30% H_2O_2, AcOH, 25 °C	35%	65%
t-BuOOH, C_6H_6, 50 °C	36%	64%
t-BuOOH, MeOH, 50 °C	27%	73%
m-$ClC_6H_4CO_3H$, CH_2Cl_2, 0 °C	36%	64%
N_2O_4, 0 °C	81%	19%
HNO_3, Ac_2O, 0 °C	67%	33%
H_2CrO_4, C_5H_5N, 25 °C	27%	73%
t-BuOCl, MeOH, -70 °C	100%	0%
$NaIO_4$, H_2O, 0 °C	75%	25%
PhIO, C_6H_6, 80 °C	46%	54%

1-Thiacyclooctan-5-one is converted into 1-thiacyclooctan-5-one 1-oxide by aqueous sodium periodate at 0 °C in 91% yield (equation 564) [*767*].

Optically active sulfoxides are obtained either by chemical enantioselective oxidation with the **Sharpless reagent** (page 44) or by ***biochemical processes.***

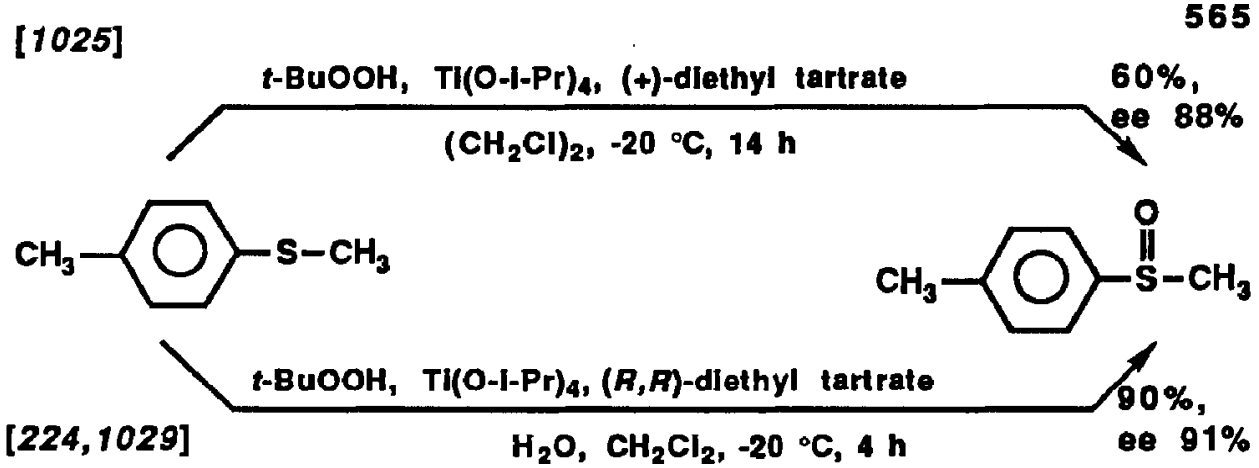
[767]



564
91%

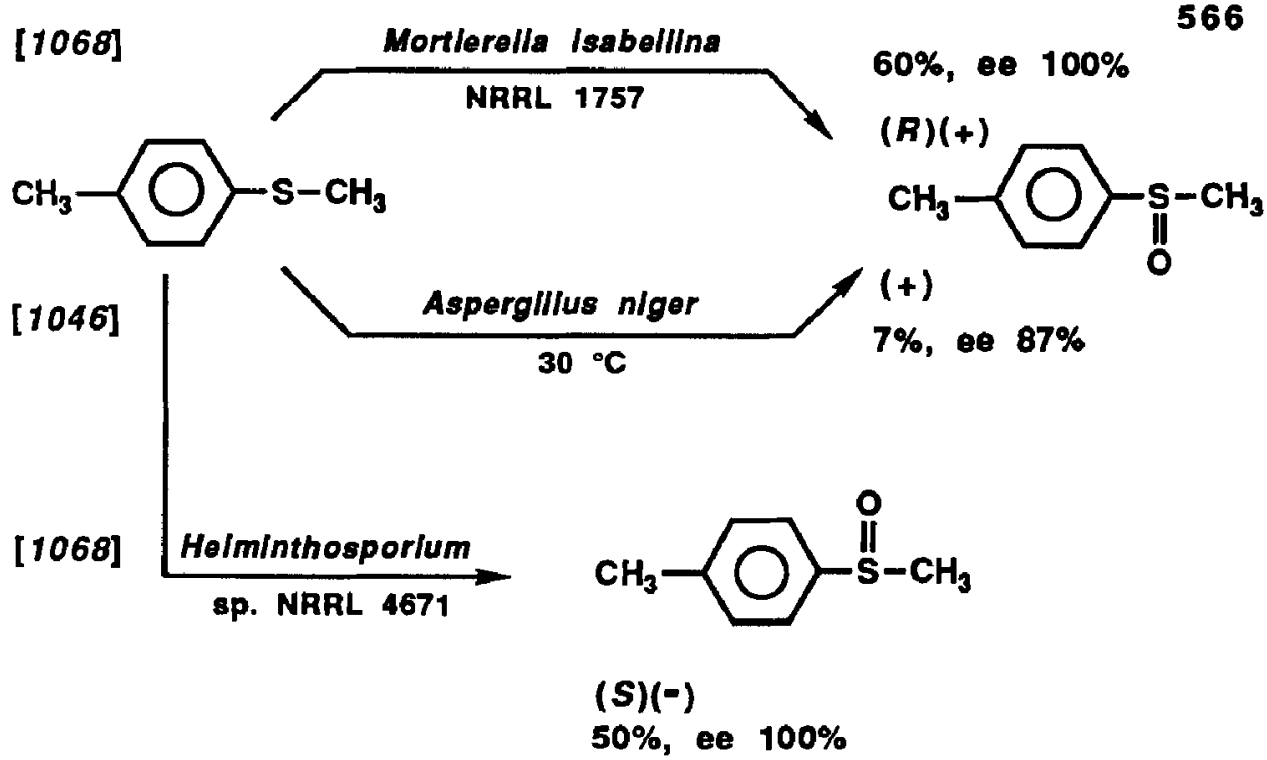
The original Sharpless reagent, a mixture of tetraisopropyl orthotitanate, (*R,R*)-diethyl tartrate, and *tert*-butyl hydroperoxide in the ratio 1:1:2 in dry dichloromethane or 1,2-dichloroethane [*1025*], is modified by adding 1 mol of water [*224, 1029*]. Such a reagent gives higher enantiomeric excesses. Of many sulfide oxidations that have been carried out, the conversion of methyl *p*-tolyl sulfide into the sulfoxide is shown in equation 565.

565



Different microorganisms oxidize sulfides to sulfoxides, usually in low yields but with high enantiomeric excesses [*1046, 1047, 1068*] (equation 566).

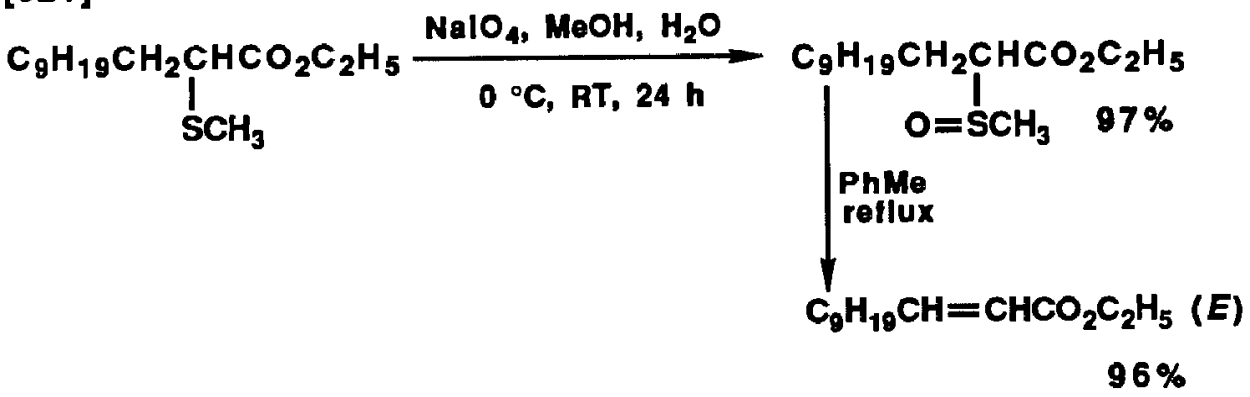
566



Steroidal sulfides are converted into optically active sulfoxides by ***Calonectria decora*** [*1052*] and by ***Rhizopus stolonifer*** [*1048*]. ***Aspergillus niger*** transforms benzyl phenyl sulfide into optically active benzyl phenyl sulfoxide in 23% yield and into benzyl phenyl sulfone in 9% yield [*1048*].

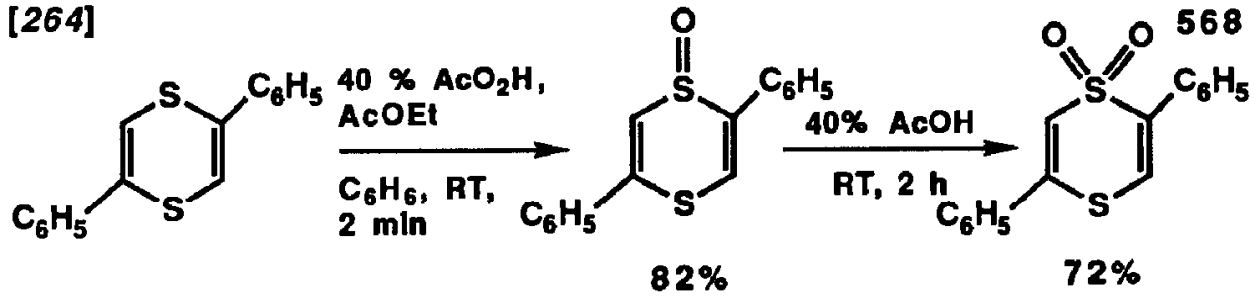
The thermal decomposition of sulfoxides whose sulfur atom is attached to the α carbons of ketones or esters leads to α,β-unsaturated ketones or esters, respectively, via a *cis* elimination. The reaction is reminiscent of alkene formation by Cope elimination of dialkylhydroxylamines from tertiary amine oxides (equation 567) [*321*].

[*321*] 567



The oxidation of sulfides having two remote sulfur atoms may affect only one sulfur atom; monosulfoxide and monosulfone are obtained by the oxidation of 2,5-diphenyl-1,4-dithiadiene (equation 568) [*264*].

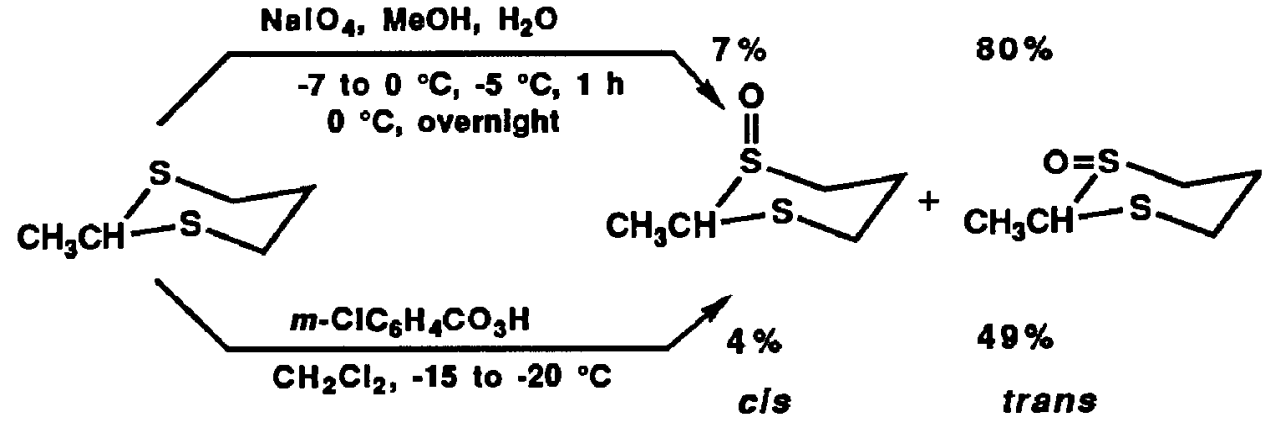
[*264*] 568



Oxidation of Thioacetals (Mercaptals and Mercaptoles)

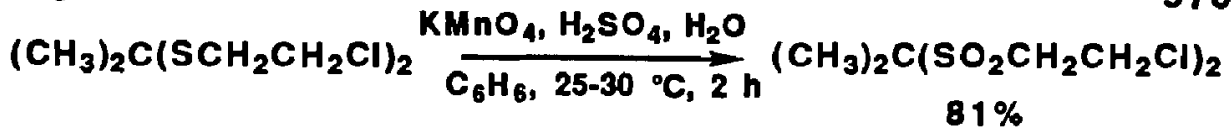
The cyclic mercaptal of acetaldehyde (2-methyl-1,3-dithiane) is oxidized by ***m*-chloroperoxybenzoic acid** or **sodium periodate** to a mixture of diastereomeric *cis* and *trans* monosulfoxides (equation 569) [*323*].

[*323*] 569



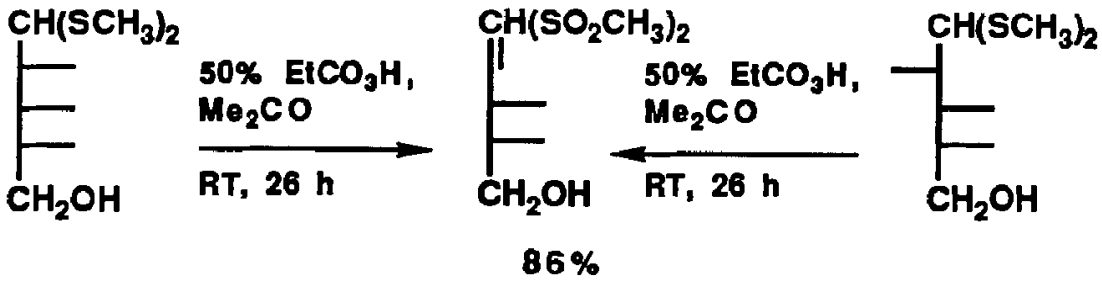
Acetone 2-chloroethylmercaptole is oxidized with **potassium permanganate** to the corresponding disulfone (sulfonal) (equation 570) [*846*].

[*846*] 570



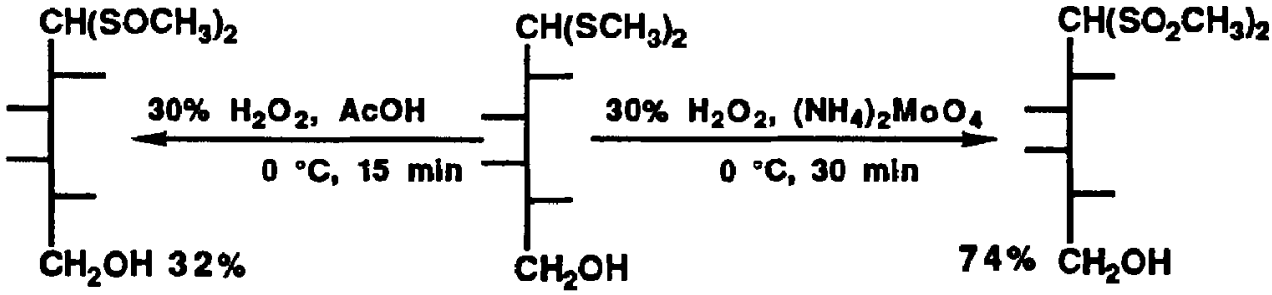
Mercaptals of pentoses and hexoses are converted into sulfonals (disulfones), which easily undergo dehydration. The dimethylmercaptal of D-ribose or D-arabinose gives, on oxidation with peroxypropionic acid, 1,1-bis(methylsulfonyl)-D-*erythro*-pentos-1-ene (equation 571) [*340*].

[*340*] 571



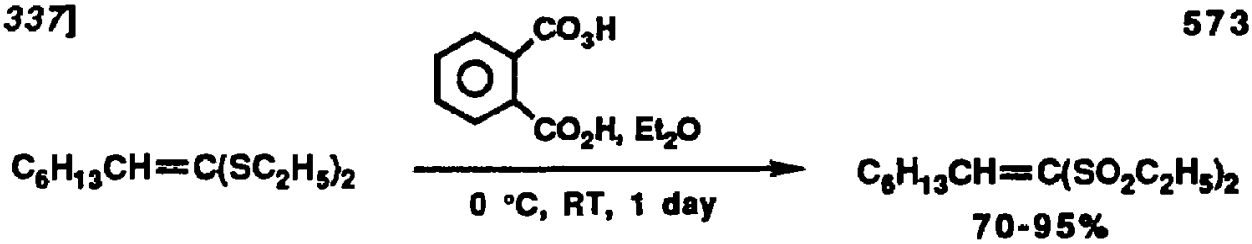
Under controlled conditions, ***thioacetals*** can be transformed into ***disulfoxides*** or ***disulfones*** (equation 572) [*136*].

[*136*] 572



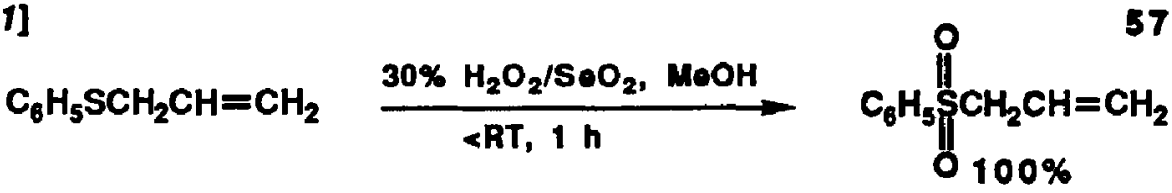
Hexylketene diethylmercaptole is oxidized with peroxyphthalic acid to 1,1-bis(ethanesulfonyl)-1-octene (equation 573) [*337*].

[*337*] 573

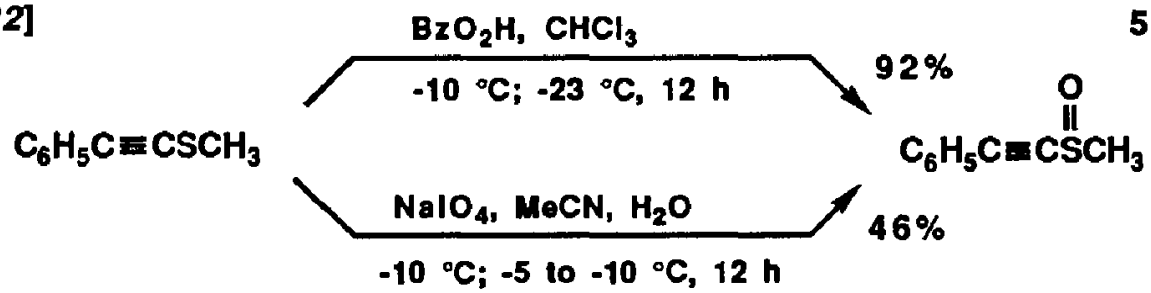


In most instances, double and triple bonds remain unaffected by the oxidation of sulfides to sulfoxides or sulfones, even when hydrogen peroxide and peroxy acids are used [*163, 264, 322, 324, 506, 521*]. Evidently, the affinity of sulfur to oxygen is higher than that of the carbon–carbon multiple bonds (equations 574 and 575).

[521] 574

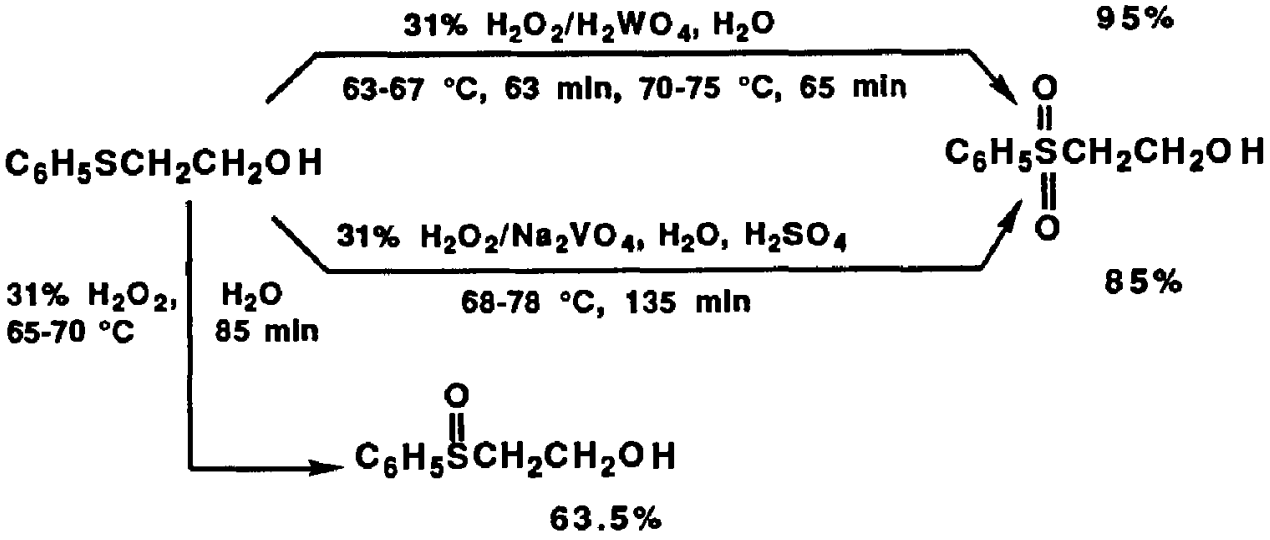


[322] 575



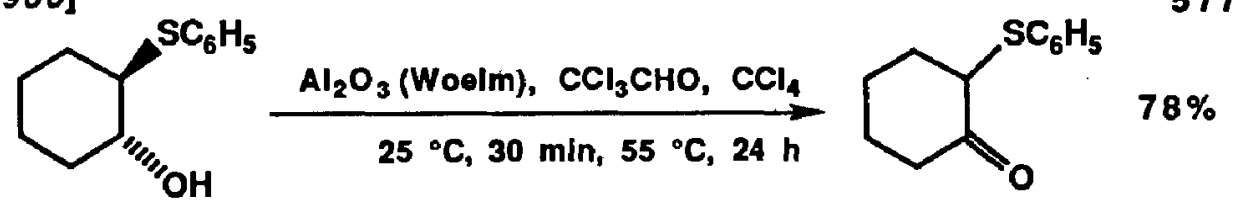
Other functional groups are also unaffected. 2-Phenylmercaptoethanol is oxidized at sulfur only. With hydrogen peroxide alone, it is converted into a sulfoxide. When catalysts such as tungstic acid or sodium orthovanadate are used, the product is the corresponding sulfone (equation 576) [*135*].

[135] 576



On the other hand, secondary β-hydroxy sulfides yield β-keto sulfides on treatment with chloral on alumina (equation 577) [*960*]. This result is understandable because dehydrogenation, and not true oxidation, is involved.

[960] 577

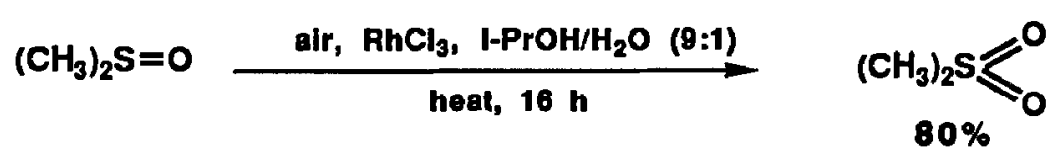


Primary amino groups remain untouched when methionine is oxidized to methionine *S*-oxide in 97.5% yield by diethyl azodicarboxylate in aqueous ethanol at room temperature [*979*].

Oxidation of Sulfoxides

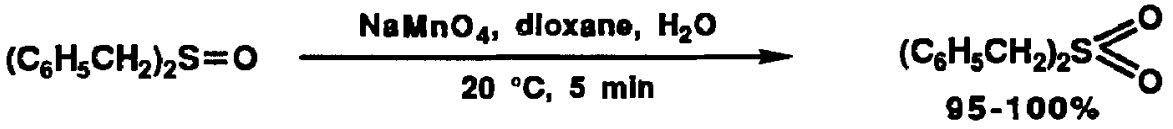
The oxidation of ***sulfoxides to sulfones*** is accomplished with **air** in the presence of noble metal salts [*10*] or with sodium permanganate [*837*] (equations 578 and 579).

[*10*]



578

[*837*]

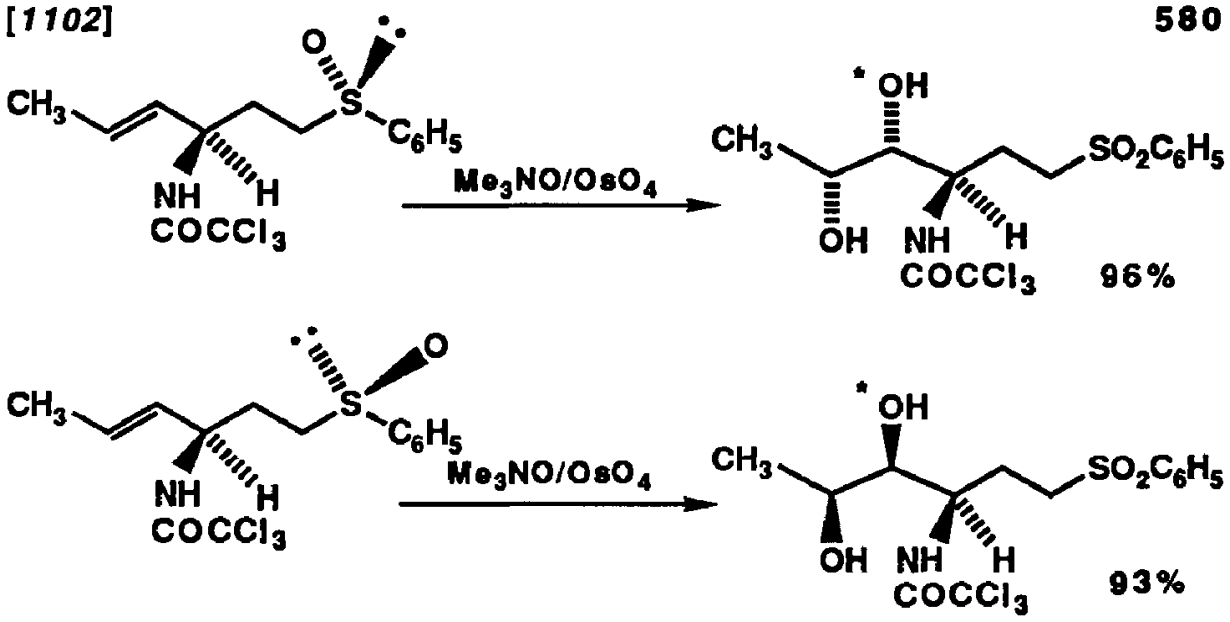


579

Sodium permanganate and, especially, **osmium tetroxide** oxidize sulfoxides to sulfones but do not oxidize sulfides [*837*]. When a mixture of equimolar amounts of diphenyl sulfide, diphenyl sulfoxide, and osmium tetroxide is refluxed in ether for 48 h, the sulfoxide is oxidized in 96% yield to the sulfone, whereas the sulfide is completely recovered [*837*].

Certain unsaturated sulfoxides treated with a catalytic amount of osmium tetroxide and **trimethylamine oxide** as a reoxidant are not only oxidized to sulfones but also hydroxylated at the double bond. The sulfoxide group exerts a steric influence in the hydroxylation: two stereoisomers of a sulfoxide yield, by *syn* hydroxylation, two different stereoisomeric diols (equation 580) [*1102*].

[*1102*]



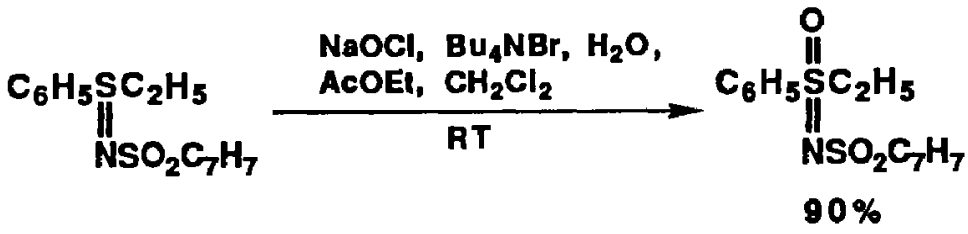
580

*The products were isolated as the diacetates.

Nitrogen analogues of sulfoxides, ***sulfilimines,*** when protected by a tosyl group at the nitrogen, are converted into nitrogen analogues of sulfones, ***sulfoximines,*** by **tetrabutylammonium hypochlorite,** which is pre-

pared in situ from tetrabutylammonium bromide and an excess of sodium hypochlorite (equation 581) [*1200*].

[*1200*]

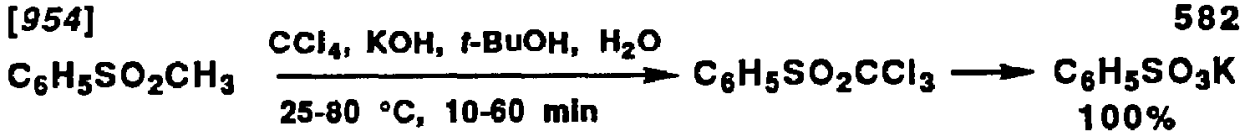


581

Oxidation of Sulfones

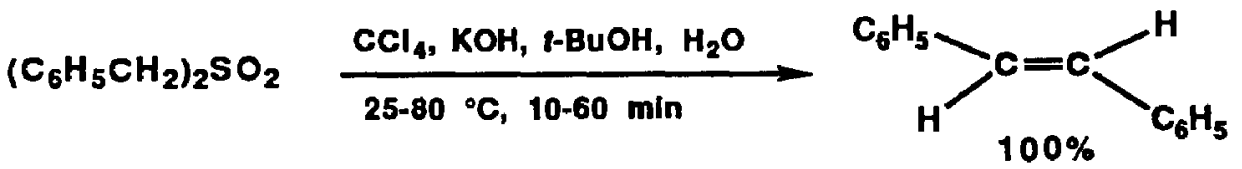
Sulfones undergo peculiar reactions on treatment with carbon tetrachloride and potassium hydroxide in aqueous *tert*-butyl alcohol at 25–80 °C. Methyl phenyl sulfone yields phenyl trichloromethyl sulfone, which is hydrolyzed to benzenesulfonic acid [*954*]. Dibenzyl sulfone is quantitatively converted into *trans*-stilbene, and dicyclohexyl sulfone is converted into a mixture of bicyclohexylidene and 1,1-dichloro-2,3-dicyclohexylcyclopropane [*954*] (equations 582–584).

[*954*]



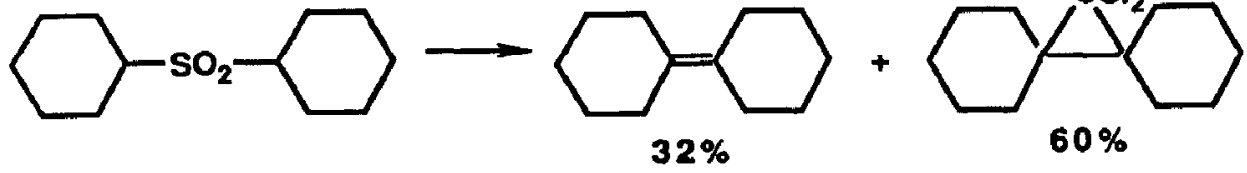
582

[*954*]



583

[*954*]



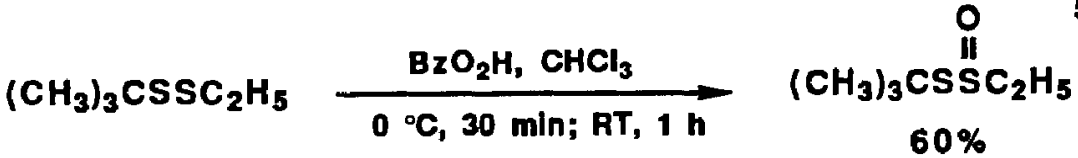
584

Oxidation of Disulfides

Disulfides are oxidized to ***monosulfoxides (alkyl thiolsulfinates)*** with peroxybenzoic acid (equation 585) [*308*].

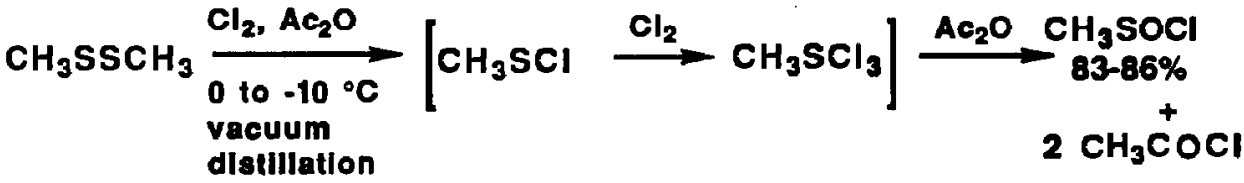
Under anhydrous conditions, **chlorine** converts dimethyl disulfide into ***methanesulfinyl chloride*** by a sequence of reactions (equation 586) [*687*].

[*308*]

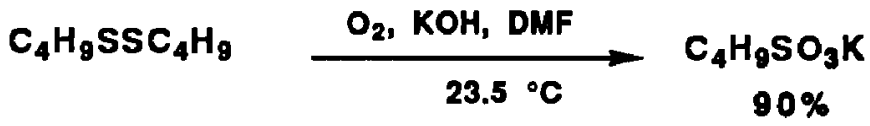


585

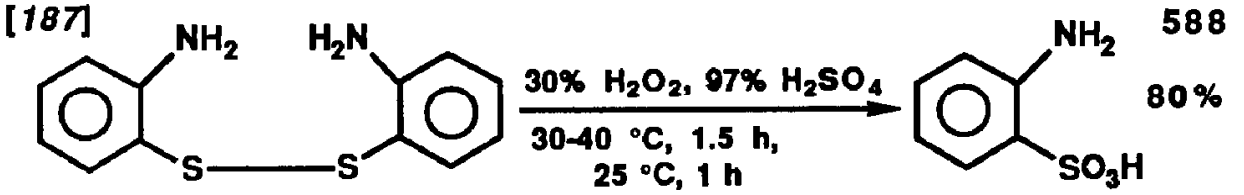
[687] 586



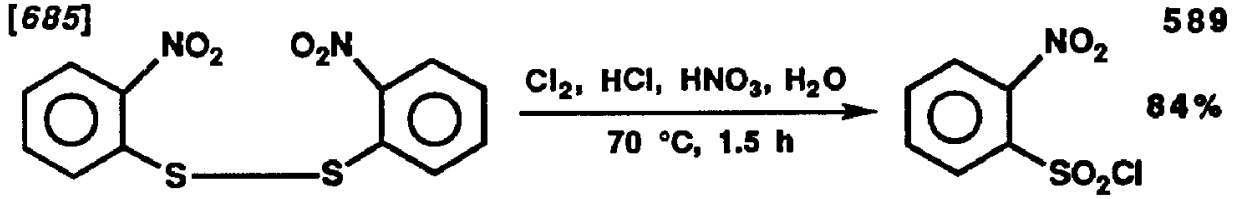
The oxidation of disulfides with **oxygen** in solutions of potassium hydroxide in dimethylformamide at 23.5 °C gives ***sulfonic acids*** in 90% yields (equation 587) [*53*].

[53] 
 587

2,2′-Diaminodiphenyl disulfide, when treated with **peroxysulfuric acid,** is oxidized to *o*-anilinesulfonic acid in 80% yield (equation 588) [*187*].

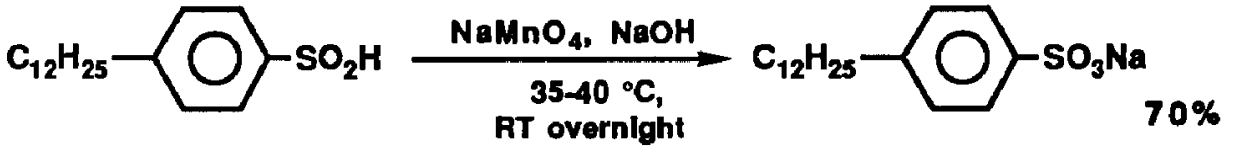
[187] 
 588 80%

Chlorine in the presence of water converts disulfides into ***sulfonyl chlorides*** (equation 589) [*685*].

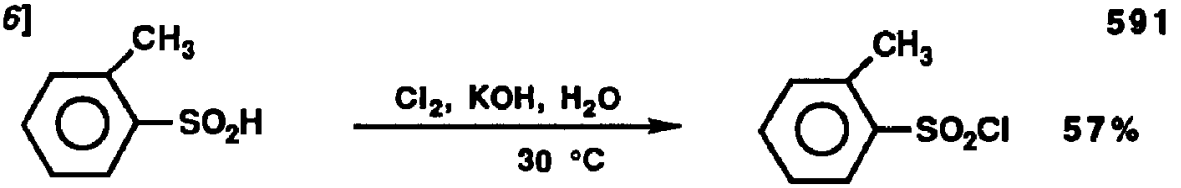
[685] 
 589 84%

Sulfonic acids and sulfonyl chlorides can also be prepared from ***sulfinic acids*** by oxidation with **sodium permanganate** (equation 590) [*836*] and **chlorine** in water (equation 591) [*686*], respectively.

[836] 590



[686] 591



SELENIDES

Like sulfides, ***selenides*** can be oxidized to the corresponding oxides, ***selenoxides,*** or to ***selenones.*** Oxidation to selenoxides is much faster and, with some oxidants, final. Reaction conditions are specified in equation 592 for the oxidation of methyl phenyl selenide [*325, 711, 773, 1034*].

592

[*325*]	CF_3CO_3H, CH_2Cl_2, 20 °C, 30 min		70%
[*325*]	*m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 20 °C, 2 h		40%
[*711*]	*t*-BuOCl, MeCN, C_5H_5N, MeOH, -25 °C, 40 min	80%	
[*325*]	$KMnO_4$, CH_2Cl_2, 20 °C, 30 min		75%
[*773*]	$NaIO_4$, MeOH, H_2O, 0 °C	79%	
[*1034*]	cyclohexanone oxygenase (*Acinetobacter* sp.)	*	

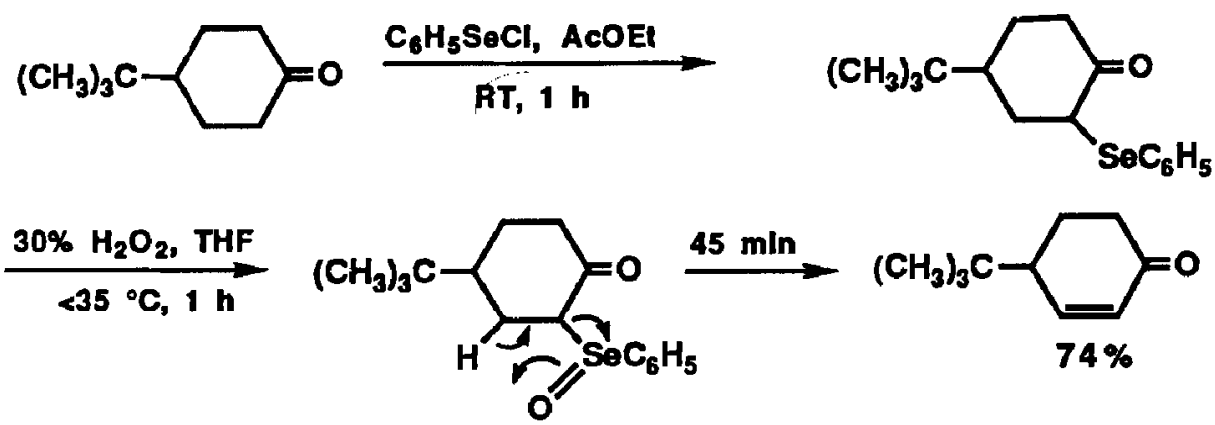
*The yield is not reported.

Diphenyl selenide is oxidized with **peroxyacetic acid** at room temperature to diphenyl selenoxide hydrate, $C_6H_5Se(OH)_2$, in 43% yield after 2 h [*1198*]. Benzyl phenyl selenide is oxidized to benzyl phenyl selenoxide by **sodium periodate** in aqueous methanol at 0 °C in 95% yield and by **iodobenzene dichloride** in aqueous pyridine at –40 °C in 85% yield [*773*].

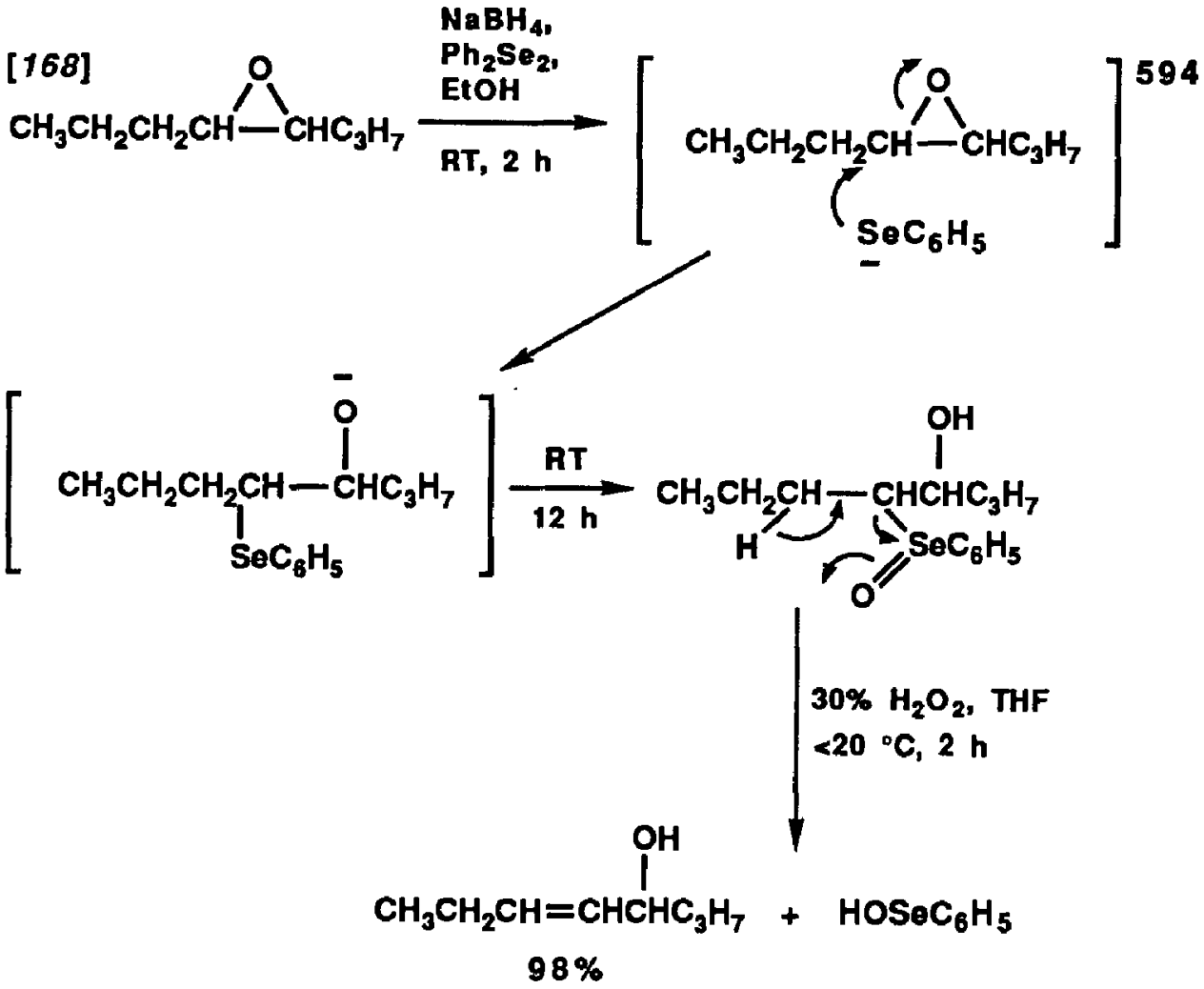
Selenoxides are useful intermediates in the preparation of α,β-unsaturated carbonyl compounds and esters. The treatment of aldehydes, ketones, or esters with benzeneselenyl chloride, C_6H_5SeCl, followed by the oxidation of the selenides to selenoxides by **hydrogen peroxide, peroxy acids,** or **sodium periodate,** gives α,β-unsaturated aldehydes, ketones, or esters. Thus, dehydrogenation with the formation of a carbon–carbon double bond is accomplished under very mild conditions [*167, 169*] (equation 593).

[*167*]

593



Another synthetic application of selenoxides is the conversion of epoxides into allylic alcohols (equation 594) [*168*]. Dehydrogenation occurs almost exclusively away from the hydroxyl group.

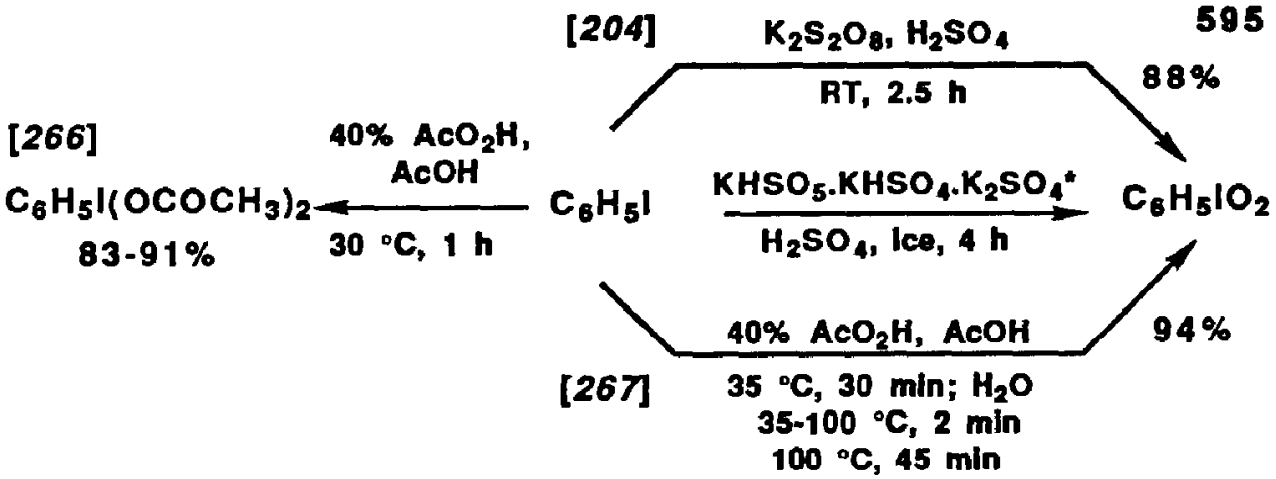


IODO COMPOUNDS

Iodo compounds can be oxidized to ***iodoso compounds*** or to ***iodoxy compounds***. Iodobenzene treated with **peroxyacetic acid** at 30 °C gives an 83–91% yield of iodosobenzene diacetate [*266*]. 2-Iodo-4,5-dinitrobenzoic acid, when heated for 3 min at 100 °C with fuming **nitric acid,** is transformed into 2-iodoso-4,5-dinitrobenzoic acid in 92% yield [*475*]. Under more energetic conditions, the oxidation products are iodoxy compounds [*204, 205, 267*] (equation 595).

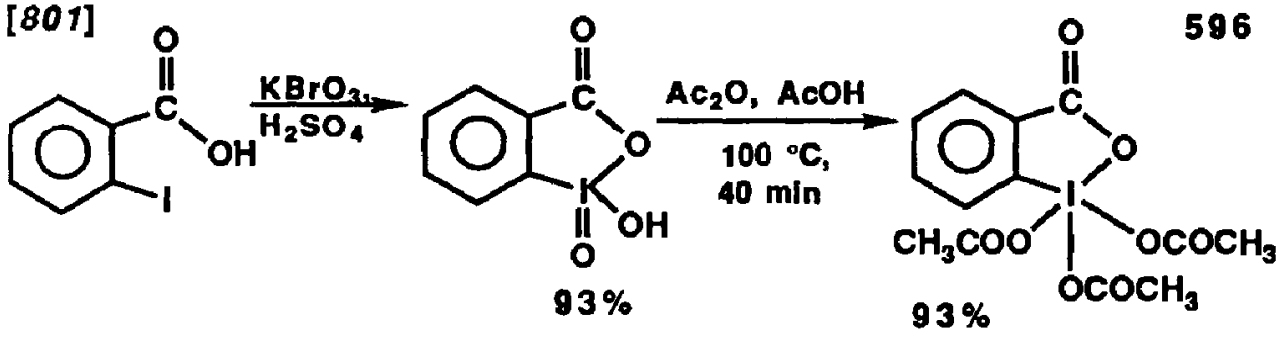
o-Iodosobenzoic acid is converted into *o*-iodoxybenzoic acid in 81% yield by heating at 100 °C with potassium permanganate in dilute sodium hydroxide [*893*].

Both iodoso and iodo compounds are oxidizing agents. The newest iodine-containing oxidant is the **Dess–Martin periodinane,** whose structure



*Oxidation with Oxone is described in reference 205 and gives a 72% yield of iodoxybenzene.

and preparation are shown in equation 596 [*801*]. This reagent oxidizes alcohols to aldehydes or ketones under mild conditions [*801*].



BORON COMPOUNDS

The oxidation of carbon–boron bond converts ***boranes*** into alkyl or aryl ***borates,*** which may be hydrolyzed subsequently to ***alcohols*** and boric acid [*991*]. The oxidation is carried out with **hydrogen peroxide** [*183, 1201, 1202*] or **trimethylamine oxide** [*991, 992*]. Phenylboronic acids are oxidized to phenols ***biochemically*** [*1034*].

A general scheme for the conversion of alkylboranes into alcohols is given in equation 597 [*991*].

[991]

$$(C_4H_9)_3B \xrightarrow{Me_3NO} (C_4H_9)_2BOC_4H_9 \xrightarrow{Me_3NO} C_4H_9B(OC_4H_9)_2 \xrightarrow{Me_3NO} B(OC_4H_9)_3 \qquad 597$$

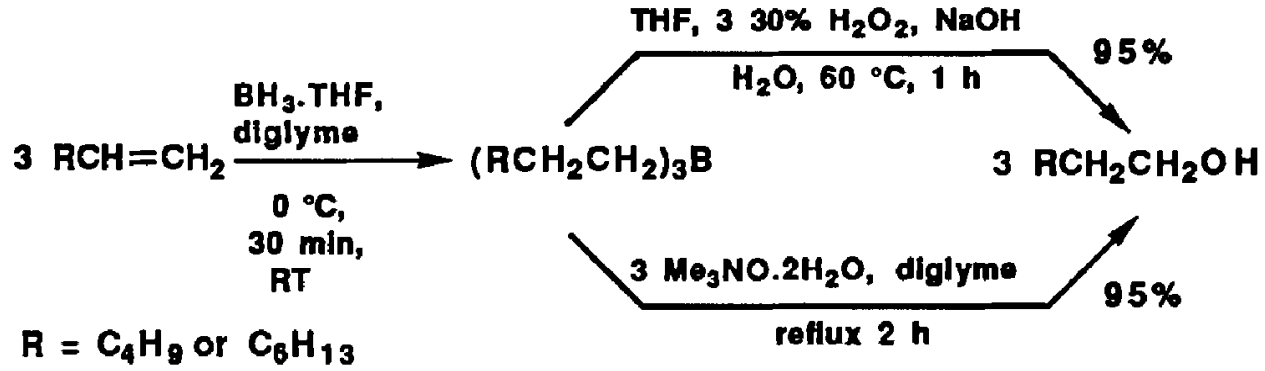
The transformation of tributyl borane with trimethylamine oxide in chloroform into dibutyl borinate is exothermic and rapid at 0 °C, and the transformation of dibutyl borinate into butyl boronate takes place at 25 °C. However, the final conversion of the butyl boronate into tributyl

borate requires refluxing in chloroform for 24 h [*991*]. The alcohols are isolated by transesterification of the alkyl borates, for example, by distillation with decanol [*991*].

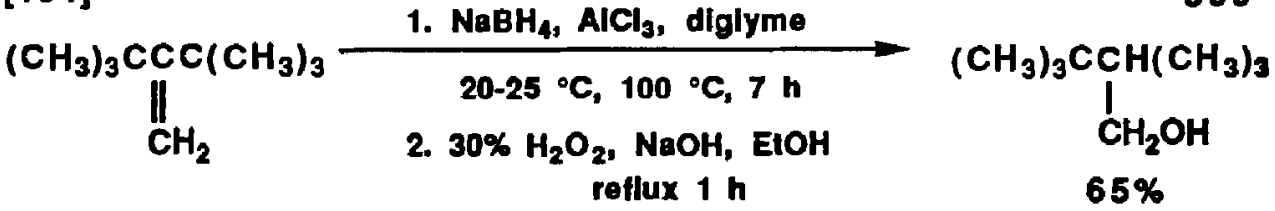
To prepare alcohols by the oxidation of alkyl boranes, borane, diborane, alkyl and dialkyl boranes, and dialkoxy boranes are added to alkenes or alkynes. The addition takes place in the anti-Markovnikov mode because boron is more electrophilic than hydrogen.

Borane, which is used as a complex with tetrahydrofuran [*992*] or dimethyl sulfide [*611, 992*] or generated in situ from lithium borohydride with boron trifluoride etherate [*646*] or sodium borohydride with aluminum chloride [*184*], reacts with 3 mol of an alkene to form a tertiary borane. The oxidation with alkaline hydrogen peroxide [*183, 992, 1201*] or with trimethylamine oxide [*991, 992*] yields an alcohol (equations 598 and 599).

[*992*] 598



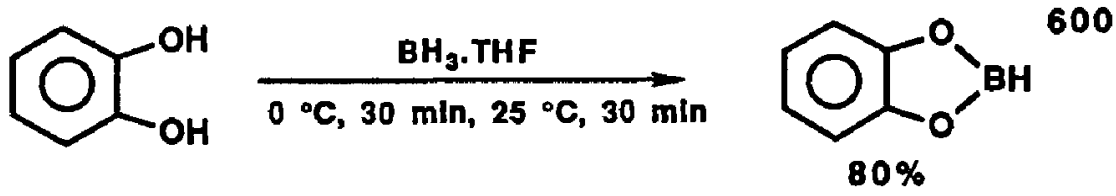
[*184*] 599



Secondary boranes (dialkylboranes) react with alkenes in a 1:1 ratio. "Disiamylborane," which is prepared in situ from borane–dimethyl sulfide with 2 mol of 2-methyl-2-butene, converts 1-octene into 1-octyldisiamylborane in ether at 0 °C in 2 h [*611*] (vide infra).

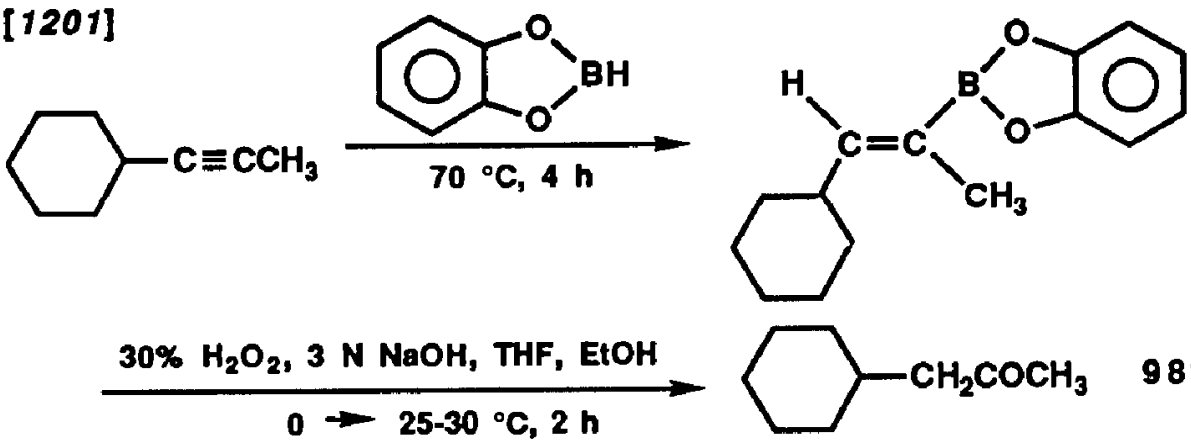
Another secondary borane useful for the conversion of alkenes into alcohols and of alkynes to aldehydes or ketones is catecholborane (1,3,2-benzodioxaborole), which is prepared from catechol and borane in tetrahydrofuran [*1201*] (equations 600 and 601).

[*1201*]



600

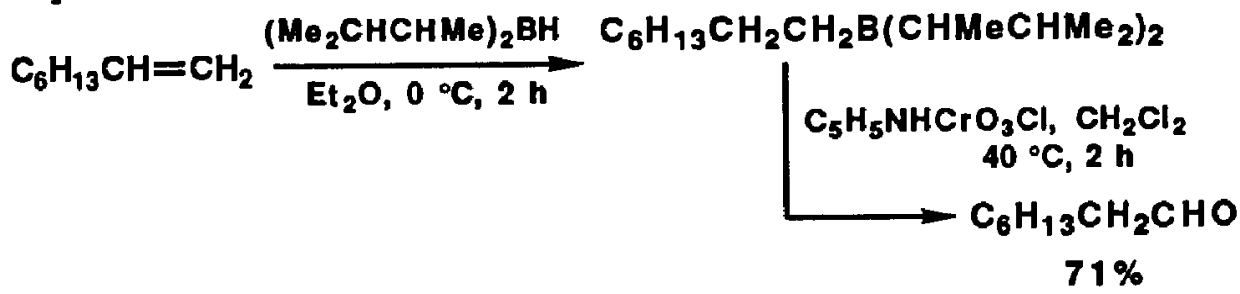
[1201]



601

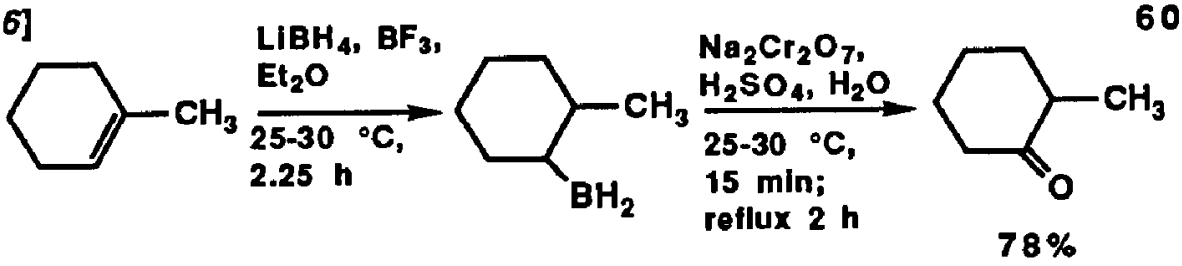
If the oxidation of the boranes is carried out by hexavalent chromium compounds, the products are aldehydes (equation 602) [*611*] or ketones (equation 603) [*646*].

[611]



602

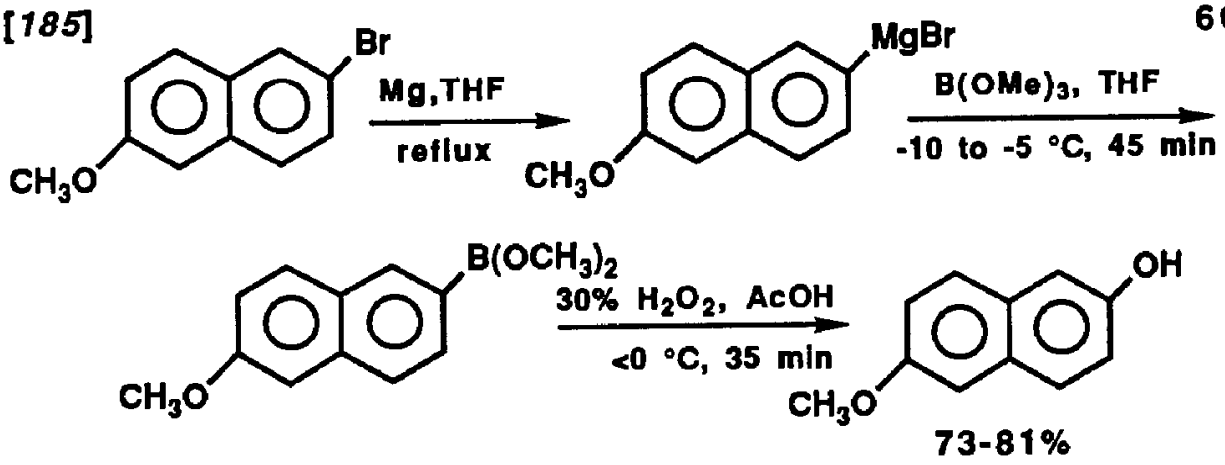
[646]



603

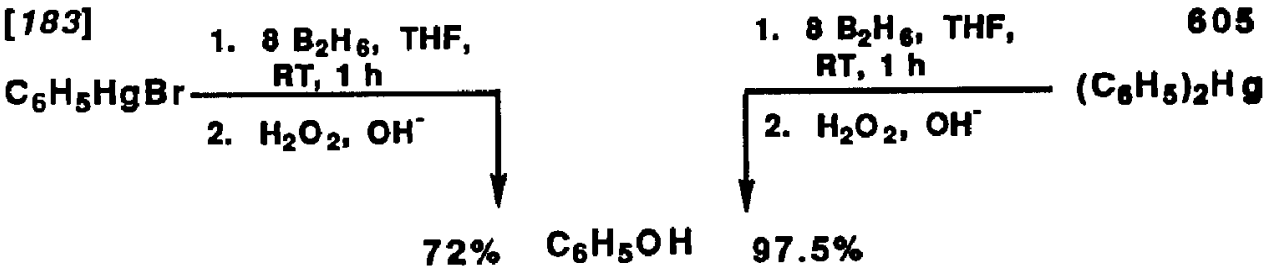
Aromatic boranes are synthesized from diborane and arylmagnesium halides [*185*], arylmercury halides [*183*], or diarylmercury compounds [*183*]. Their oxidation furnishes phenols in variable yields. A large excess (up to 16 mol) of BH_3 is necessary for high yields [*183*] (equations 604 and 605).

[185]



604

[183]



605

Phenols are also obtained by oxidation of phenylboronic acids with **cyclohexanone oxygenase** produced by ***Acinetobacter*** strain NCIB 9871 (equation 606) [*1034*].

[*1034*]

$$C_6H_5B(OH)_2 \xrightarrow{\text{cyclohexanone oxygenase}} C_6H_5OH \qquad 606$$

Alkyldichloroboranes are oxidized by oxygen to alkyl hydroperoxides (equation 607) [*51*].

[*51*]

$$C_6H_{13}BCl_2 \xrightarrow[H_2O,\ RT]{O_2,\ Et_2O,\ -180\ ^\circ C,\ 20\ min;} C_6H_{13}OOH\ 94\% \qquad 607$$

SILICON AND TIN COMPOUNDS

The silicon–silicon bond is oxidatively cleaved in phenylpentamethyldisilane, which is converted by **peroxybenzoic acid** into phenyldimethylsilyl trimethylsilyl ether in 86% yield (equation 608) [*1203*].

[*1203*]

$$C_6H_5(CH_3)_2SiSi(CH_3)_3 \xrightarrow[RT,\ overnight]{BzO_2H,\ CH_2Cl_2} C_6H_5(CH_3)_2SiOSi(CH_3)_3 \quad 86\% \qquad 608$$

The oxidative cleavage of the ***carbon–tin bond*** takes place in the reaction of alkylstannanes with **lead tetraacetate.** Phenoxymethyltributylstannane, when refluxed in dichloromethane with an equimolar amount of lead tetraacetate for 32 h, is converted into phenoxymethyl acetate in 58% yield (equation 609) [*1204*].

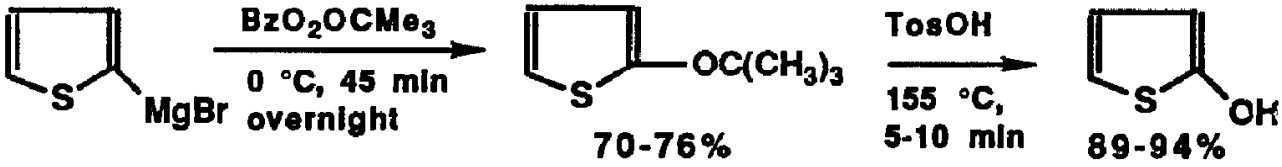
[*1204*]

$$C_6H_5OCH_2Sn(C_4H_9)_3 \xrightarrow[\text{reflux 32 h}]{Pb(OAc)_4,\ CH_2Cl_2} C_6H_5OCH_2OCOCH_3 \quad 58\% \qquad 609$$

ORGANOMAGNESIUM AND ORGANOMERCURY COMPOUNDS

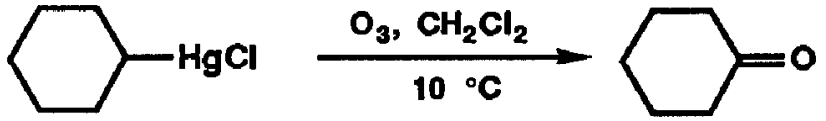
The reaction of ***2-bromomagnesiumthiophene*** with ***tert*-butyl peroxybenzoate** gives 2-*tert*-butoxythiophene, which, on acid-catalyzed thermal decomposition, yields ***2-hydroxythiophene*** (equation 610) [*235*].

[*235*] 610



Secondary ***organomercury chlorides*** are oxidized with ozone to ***ketones*** in fair yields. Primary organomercurials usually give mixtures of acids resulting from deeper oxidation (equation 611) [*114*].

[*114*]



60% 611

Safety Advisory

THE SAFETY INFORMATION is included within this book by the American Chemical Society as a precaution to the readers.

The following chapter discusses the preparation and the use of various oxidizing agents. Strong oxidizing agents are among the most hazardous materials used in the laboratory. The extreme caution required when preparing and using these reagents cannot be overemphasized. The hazards generally associated with the preparation, handling, and use of oxidizing agents are explosion, fire, and uncontrolled and violent exothermic reaction resulting in possible equipment failure and physical injury to the operator. To minimize the potential for any of these occurrences, chemists must prudently exercise all safe practices at their disposal.

All new reactions should be conducted on the smallest possible scale with clean glassware that has been carefully inspected for defects. If at all possible, all reactions should be conducted in an adequate laboratory fume hood with the sash closed. This measure will provide the operator with a physical barrier against fires, explosions, and chemical splashes, as well as provide for the removal of potentially toxic, flammable, or offensive vapors. The laboratory should possess the basic safety facilities necessary to handle and use oxidizing agents, including approved and periodically inspected and tested eye wash stations, safety showers, and fire suppression equipment. To keep personal exposure to a minimum, chemists must wear appropriate and adequate personal protective equipment when conducting oxidation experiments. Essential safety apparel includes chemical splash goggles, full face shields, chemically impervious gloves, and laboratory coats or aprons.

Before following the procedures outlined in this chapter, readers should refer to the original reference for any specific handling practice that may be cited. Chemists should also refer to the manufacturer's material safety data sheet for any additional handling precautions.

Although many oxidation reactions and oxidizing agents have some degree of hazard associated with their use, the procedures marked with the hazard symbol  may require special caution.

Chapter 4
Preparative Procedures

1. PREPARATION OF ANHYDROUS HYDROGEN PEROXIDE IN ETHER [*126*]

A 2.5 M solution of anhydrous hydrogen peroxide in ether is prepared by repeated extraction of 30% aqueous hydrogen peroxide with ether. The ether extracts are dried over anhydrous magnesium sulfate, and the concentration of hydrogen peroxide is determined by iodometric titration.

2. PREPARATION OF 90% HYDROGEN PEROXIDE AND OF 90% PEROXYACETIC ACID [*1198*]

In an ***absolutely clean*** apparatus consisting of a sidearm flask fitted with a ground-glass capillary, a short column, and a condenser fitted with a ground-glass thermometer, 29% hydrogen peroxide is brought to boiling. First, water distills at 29 °C at 18 mm of Hg. Then, at 55 °C at 18 mm of Hg, hydrogen peroxide condenses as an oily liquid sticking to the walls. The residue in the flask is 90% hydrogen peroxide.

The mixing of 64 g (1.69 mol) of 90% hydrogen peroxide, 88 g (0.86 mol) of acetic anhydride, and 18 g of concentrated sulfuric acid and distillation in the apparatus just described gives 122 g (85%) of 90% peroxyacetic acid distilling at 25 °C at 12 mm of Hg and 10 g (7.8%) of 69% peroxyacetic acid distilling at 22 °C at 10 mm of Hg.

All the operations must be carried out with strict safety measures.

3. PREPARATION OF THE JONES REAGENT [*585*]

Chromium trioxide (267 g, 2.67 mol) is dissolved in 400 mL of water, and 230 mL of concentrated sulfuric acid is added with cooling. The cold solution is diluted with water up to 1 L to form an 8 N reagent. The reagent is added dropwise to a solution of the compound to be oxidized in acetone (distilled from potassium permanganate) at 20 °C.

4. PREPARATION OF CHROMIUM TRIOXIDE–PYRIDINE COMPLEX, $CrO_3 \cdot 2C_5H_5N$ (COLLINS REAGENT) [*593*]

A 3-L, three-necked flask equipped with a sealed mechanical stirrer and a drying tube filled with Drierite (calcium sulfate) is charged with 946 mL of dry pyridine and cooled in an acetone–ice bath to −15 to −18 °C. Chromium trioxide (90 g, 0.9 mol) dried previously over phosphorus pentoxide for 12 h under reduced pressure is added portionwise through the neck by using glazed paper cones (a new cone for each added portion) over a period of 5 min while the flask contents are stirred intensively. With these precautions, ignition of the reaction mixture, which would occur had pyridine been added to chromium trioxide, is avoided. After the addition of the chromium trioxide, stirring is continued for 6 h, during which time no further ice is added to the acetone bath. The initially formed bright-yellow viscous mixture turns into a bright-red crystalline slurry.

The complex $CrO_3 \cdot 2C_5H_5N$ is filtered with suction through a sintered-glass funnel, washed immediately with 300 mL of dry reagent-grade petroleum ether, and stored immediately in a desiccator over phosphorus pentoxide at 15–30 mm of Hg. The yield is 180 g (80%). The entire operation starting with the filtration should be performed within less than 3 min to minimize hydration of the extremely hygroscopic complex, which, when stored in this way, is still active after 10 days. The dry complex does not cause any fires.

5. PREPARATION OF PYRIDINIUM CHLOROCHROMATE ADSORBED ON ALUMINA [*604*]

To a solution of 6 g (0.06 mol) of chromium trioxide in 11 mL of 6 N hydrochloric acid is added 4.75 g (0.06 mol) of pyridine within 10 min at 40 °C. The mixture is kept at 10 °C until a yellow-orange solid forms and then reheated to 40 °C to dissolve the solid. Alumina (50 g) is added with stirring at 40 °C. After evaporation in a rotary evaporator, the orange solid is dried in vacuo for 2 h at room temperature. The reagent can be kept under vacuum for several weeks in the dark without losing its activity.

6. PREPARATION OF TETRABUTYLAMMONIUM CHROMATE [*618*]

To a stirred solution of 1.0 g (10 mmol) of chromium trioxide in 25 mL of water, an aqueous solution of 2.92 g (10.5 mmol) of tetrabutylammonium chloride in 50 mL of water is rapidly added at room temperature. A yellow-orange solid precipitates immediately. The mixture is cooled to 0 °C, and the solid is filtered with suction through a sintered-glass funnel. It is carefully washed with cold water, dried under vacuum over phosphorus pentoxide, and stored over calcium chloride. The yield of the tetrabutylammonium chromate is 2.76 g (77%).

7. PREPARATION OF ACTIVE MANGANESE DIOXIDE [*805*]

A solution of 1110 g (5 mol) of manganese sulfate tetrahydrate in 1500 mL of water and a solution of 1170 mL of 40% sodium hydroxide (16 mol) are added

simultaneously over a period of 1 h to a hot stirred solution of 960 g (6.1 mol) of potassium permanganate in 6 L of water. Manganese dioxide starts precipitating as a fine brown solid. Stirring is continued for an additional hour, the mixture is centrifuged, and the solid is washed with water until the washings are colorless. The solid is dried in an oven at 100–120 °C and ground to a fine powder before use. The yield is 920 g (95%).

8. DEHYDROGENATION BY 2,3-DICHLORO-5,6-DICYANO-*p*-BENZOQUINONE (DDQ) [*970*]

A solution of 0.65 g (0.005 mol) of **tetralin** and 1.14 g (0.005 mol) of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in 5 mL of benzene is refluxed for 45 min, during which period the initially red solution becomes colorless. A solution of an additional 1.14 g (0.005 mol) of the quinone in 2 mL of benzene is added, and the refluxing is continued for an additional 75 min. After dilution with light petroleum, the solution is filtered, passed through a column of alumina, and evaporated to give 0.42 g **(70%)** of **naphthalene,** mp 79–80 °C. The petroleum-insoluble residue yields 0.7 g **(61%)** of colorless 2,3-dichloro-5,6-dicyanohydroquinone, mp 263 °C (dec), after crystallization from aqueous ethanol.

9. DEHYDROGENATION VIA SELENOXIDES [*167*]

To a solution of 5.50 g (14.2 mmol) of **3-cholestanone** in 125 mL of ethyl acetate is added 3.30 g (17.2 mmol) of benzeneselenyl chloride (C_6H_5SeCl), and the red-orange solution is stirred for 1 h until it turns pale yellow. Water (25 mL) is added to the stirred mixture, the aqueous layer is drained, and to the organic phase is added 55 mL of tetrahydrofuran and, dropwise, 3.5 mL (34.3 mmol) of 30% hydrogen peroxide while the mixture is stirred for an additional hour at a temperature below 35 °C. The reaction mixture is washed with water and a solution of sodium carbonate, dried, and evaporated to give 5.25 g (96%) of crude product, which on recrystallization from ethanol furnishes 2.43 g **(45%)** of **1-cholesten-3-one,** mp 95–97 °C.

10. OXYGENATION WITH SINGLET OXYGEN

Photochemical Generation [*33*]

To a solution of 6.4 g (0.097 mol) of **cyclopentadiene** in 1.8 L of distilled methanol cooled to 0 °C is added 5 g of thiourea and 0.2 g of rose bengal. Oxygen is bubbled through the solution for 5 min, and the mixture is cooled with ice and water to 15 °C and irradiated with a 450-W high-pressure mercury immersion lamp (Hanovia 679 A36, cooled by running water) with a Pyrex filter while the passage of oxygen is continued for 2.5 h. After 12 h at room temperature in the dark, the solvent is evaporated in vacuo, the residue is treated with water, and the mixture is extracted with benzene until the aqueous layer becomes clear. The aqueous layer is then evaporated, and the residue is fractionated in vacuo to give 5.7 g **(60%)** of ***cis*-2-cyclopentene-1,4-diol** distilling at 100–102 °C at 1.3 mm of Hg, mp 59–60 °C.

Generation from Hydrogen Peroxide and Sodium Hypochlorite [*13*]

A solution of 0.17 g (0.44 mmol) of **tetraphenylcyclopentadienone** in 125 mL of dioxane cooled in ice water is first treated with 5.0 mL (44 mmol) of 8.8 M hydrogen peroxide and subsequently with a solution of 32.8 mL (22 mmol) of 0.67 M sodium hypochlorite added dropwise with stirring. Extraction of the solution with benzene and evaporation of the solvent gives 0.085 g **(50%)** of crystalline ***cis*-dibenzoylstilbene,** mp 215.9–216.3 °C.

Generation from Triphenyl Phosphite Ozonide [*19*]

A solution of 9.3 g (0.03 mol) of **triphenyl phosphite** in 100 mL of dichloromethane is ozonized to form **triphenyl phosphite ozonide.** After the excess ozone is purged with nitrogen, a cold solution of 1.60 g (0.02 mol) of **1,3-cyclohexadiene** in 45 mL of dichloromethane is added from a dropping funnel while the mixture is stirred by a stream of nitrogen and cooled with a dry-ice–acetone bath. After the removal of the bath, the mixture is allowed to warm to room temperature. The solution is concentrated on a rotary evaporator, and the residue is distilled at less than 0.1 mm of Hg in a short-path still to give 1.51 g **(67.4%)** of pale-yellow semisolid **3,6-endooxocyclohexene,** which, after three recrystallizations from pentane, melts at 90–91 °C.

11. OZONIZATION

Ozonolysis of Double Bonds [*81*]

In a 2-L round-bottom reactor cooled to −20 °C, 120.4 g (0.40 mol) of **methyl oleate** is dissolved in 1800 mL of reagent-grade methanol, and oxygen containing 1.092 mmol of ozone per liter is passed through the solution at the rate of 1.94 L/min. After 195 min, ozone is no longer absorbed, as indicated by the liberation of iodine from a solution of potassium iodide at the reactor exit. Glacial acetic acid (150 mL) is added; the solution is warmed to 30 °C, and zinc dust is added, a small amount at a time, until a total of 60 g (0.92 mol) has been used, while the temperature is maintained at 30–35 °C by cooling. The mixture is filtered with suction, and the filtrate is distilled on a steam bath until about one-half of the methanol has been removed. Then 500 mL of dichloromethane and 500 mL of water are added, the aqueous layer is separated, and the dichloromethane layer is washed with water (each wash is back-washed with a small amount of dichloromethane) until all the acid has been removed. The methylene chloride is distilled off on a steam bath, and the residue is fractionated through a small Vigreux column with a nitrogen capillary ebullator. **Pelargonaldehyde** distills at 37–47 °C at 0.35 mm of Hg. The total yield (43.9 g in the main fraction and 2.27 g in the dry-ice trap) is 46.17 g **(81%). Methyl azelaldehydate** distills at 94–96 °C at 0.75 mm of Hg (65.3 g) and at 96–120 °C at 0.30 mm of Hg (4.87 g). The crude yield is **94%** (an **85.4%** yield of the pure compound is obtained on redistillation).

12. ELECTROLYTIC DECARBOXYLATIVE COUPLING OF CARBOXYLIC ACIDS [*118*]

The electrolytic cell is a water-jacketed tube 6 in. (15 cm) long and 1.5 in. (3.8 cm) in diameter and is stoppered with a rubber stopper fitted with a dropping

funnel, a reflux condenser, and two platinum foil electrodes (5 by 2.5 cm) placed about 1–2 mm apart. The cell is charged with a cooled solution of 0.1 g (0.0043 mol) of sodium in 80 mL of methanol, and 10 g (0.083 mol) of **5-fluorovaleric acid** is added. A direct current of 1.5 A at 110 V is passed through the cell for 3 h while the temperature is maintained below 50 °C. The methanolic solution is diluted with water, neutralized with acetic acid, and extracted several times with ether. The combined ether extracts are washed twice with a 5% solution of sodium carbonate, dried over anhydrous sodium sulfate or magnesium sulfate overnight, and evaporated. The residue is refluxed for 1 h with 50 mL of concentrated hydrochloric acid to remove esters formed during the electrolysis. The mixture is cooled and extracted with ether, and the extracts are washed with a 5% solution of sodium carbonate and with water. After the extracts have been dried and the solvent has been evaporated, 2.8 g **(45%)** of **1,8-difluorooctane,** bp 75–75.5 °C at 13 mm of Hg, is obtained.

13. OXIDATION WITH HYDROGEN PEROXIDE

Conversion of Alkenes into Alcohols by Hydroboration Followed by Oxidation [*184*]

To a solution of 9.5 g (0.25 mol) of sodium borohydride in 250 mL of purified diglyme is added 70 g (0.50 mol) of 90–92% pure **1,1-di-*tert*-butylethylene** followed by a solution of 11.2 g (0.084 mol) of anhydrous aluminum chloride in 50 mL of diglyme. After the mixture has been stirred for 1 h at 20–25 °C and 7 h on a steam bath, most of the diglyme is removed under reduced pressure, and the residue is treated with excess hydrochloric acid. The organic material (73.8 g), which is isolated by the usual procedure, is dissolved in 100 mL of ethanol containing 8 g (0.2 mol) of sodium hydroxide. To this solution, 68 g of 30% hydrogen peroxide (0.6 mol) is added at a rate sufficient to maintain reflux. After 1 h, 350 mL of water is added, and the organic product is isolated in the usual manner after excess hydrogen peroxide has been destroyed with sodium bisulfite. Fractional distillation gives 51.5 g **(65%)** of **2,2-di-*tert*-butylethanol,** bp 105–110 °C at 29 mm of Hg, mp 52–54 °C (54–55 °C after recrystallization from low-boiling petroleum ether).

anti Hydroxylation of a Double Bond [*131*]

A solution of 8.2 g (0.1 mol) of **cyclohexene** in 45 mL of acetic acid is stirred for 10 h at 50 °C with a solution of 0.2 g of WO_3 in 13 g (0.11 mol) of 30% hydrogen peroxide. Some solvent is removed under reduced pressure, the residue is refluxed for 1 h with an excess of 2 N sodium hydroxide, and the product is obtained by continuous extraction with ether. Distillation of the extract gives a **71%** yield of ***trans*-1,2-cyclohexanediol** boiling at 130–140 °C at 30 mm of Hg.

14. OXIDATION WITH *tert*-BUTYL HYDROPEROXIDE

Oxidation of Tertiary Amines to Amine Oxides [*226*]

To a stirred mixture of 106 g (0.5 mol) of **dimethyldodecylamine** and 3 g of vanadium pentoxide in 400 mL of benzene, 60 g (0.5 mol) of 75% *tert*-butyl hy-

droperoxide is added at 25 °C over a period of 30 min. After having been stirred for 4 h at 40–45 °C, the warm mixture is filtered, the filtrate is evaporated in a vacuum of a water aspirator at a temperature not exceeding 70 °C, and the residue is diluted with 2 volumes of ethyl acetate. The precipitated crystals are filtered with suction, washed with petroleum ether, and dried in vacuo to yield 92 g **(80%)** of **dimethyldodecylamine oxide,** mp 115–117 °C (120–121 °C after recrystallization from ethyl acetate).

Asymmetric Oxidation of Sulfides to Sulfoxides [*224*]

Isopropyl orthotitanate, $Ti(O\text{-}i\text{-}Pr)_4$, (1.49 mL, 5 mmol) and diethyl (*R,R*)-tartrate (1.71 mL, 10 mmol) are dissolved in 50 mL of dichloromethane at room temperature under nitrogen. Water (0.09 mL, 5 mmol) is injected by means of a microsyringe, the mixture is stirred for 15–20 min until it becomes homogeneous, and finally, 0.7 g (5 mmol) of **methyl *p*-tolyl sulfide** is added. The solution is stirred at –20 °C, and 5.5 mmol of a 2 M solution of *tert*-butyl hydroperoxide in dichloromethane is introduced. After 4 h, 10 mol equiv of water is added dropwise via a microsyringe at –20 °C, and vigorous stirring is maintained for 1 h at –20 °C and for an additional 1 h at room temperature. The white gel is filtered after the addition of a small amount of alumina and washed thoroughly with dichloromethane. The filtrate is stirred with 5% sodium hydroxide and brine for 1 h, and the layers formed are separated. The organic phase is dried over anhydrous sodium sulfate and evaporated to give the crude product free of sulfone. Chromatography on silica gel and elution with cyclohexane–ethyl acetate (1:1) gives 0.70 g **(90%)** of **methyl *p*-tolyl sulfoxide,** $[\alpha]_D^{20}$ +131° (*c* 2, acetone) (90% enantiomeric excess).

15. OXIDATION WITH POTASSIUM PEROXYSULFATE

Selective Oxidation of Sulfides to Sulfones [*207*]

A solution of 18.44 g of Oxone (49.5% $KHSO_5$) in 40 mL of water is added to a cooled (0 °C) solution of 1.24 g (0.01 mol) of **methyl phenyl sulfide** in 40 mL of methanol. The resulting cloudy slurry is stirred for 4 h at room temperature, diluted with water, and extracted 3 times with chloroform. The combined extracts are washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a quantitative yield of methyl phenyl sulfone as a white solid. Recrystallization yields **95%** of pure **methyl phenyl sulfone,** mp 85–88.5 °C.

16. OXIDATION WITH ORGANIC PEROXY ACIDS

Oxidation of Primary Aromatic Amines to Nitroso Compounds with Peroxyacetic Acid [*153*]

A solution of 16.2 g (0.10 mol) of **2,6-dichloroaniline** in a mixture of 400 mL of glacial acetic acid and 80 mL (0.70 mol) of 30% hydrogen peroxide is allowed to stand at room temperature for 48 h. The straw-colored crystals are filtered with suction and recrystallized from a minimum amount of glacial acetic acid to give

16.1 g **(91.3%)** of almost white **2,6-dichloronitrosobenzene,** melting at 173–175 °C to a pale-green liquid.

Epoxidation of Alkenes with Peroxytrifluoroacetic Acid [*283*]

To a dispersion of 8.2 mL (0.3 mol) of 90% hydrogen peroxide in 50 mL of dichloromethane cooled in an ice bath is added over a 10-min period 50.8 mL (0.36 mol) of trifluoroacetic anhydride. The solution of peroxytrifluoroacetic acid so obtained is stirred in the cold for 15 min and transferred to a pressure-equalizing dropping funnel, from which it is added over a 30-min period with good stirring to a mixture containing 95 g (0.9 mol) of sodium carbonate, 14.0 g (0.2 mol) of **1-pentene,** and 200 mL of dichloromethane in a flask fitted with an ice-cooled reflux condenser. During the addition, the solvent boils vigorously. After the addition has been completed, the mixture is refluxed for 30 min. The mixture is centrifuged for 15 min at 3000 rpm, the salt is triturated with 300 mL of dichloromethane, and the resulting mixture is centrifuged again. The combined dichloromethane solutions are fractionated in an efficient column (90 by 1.2 cm) packed with 4-mm glass helices and equipped with a variable-reflux-ratio head. After the removal of most of the solvent, the residue is fractionated through a microcolumn to give 14.0 g **(81%)** of **1,2-epoxypentane,** bp 89–90 °C.

Oxidation of Ketones to Esters (Baeyer–Villiger Reaction) with Peroxybenzoic Acid [*305*]

Cyclohexyl methyl ketone (10.2 g, 0.081 mol) is mixed with 0.11 mol of peroxybenzoic acid in a standardized chloroform solution, and the reaction mixture is allowed to stand at room temperature for 77 h. The benzoic acid and the unreacted peroxybenzoic acid are removed by extraction with 1 M sodium bicarbonate. The chloroform solution is washed with water, and the aqueous solutions are extracted with ether. The combined chloroform and ether solutions are dried, and the solvents are removed by evaporation. Distillation of the residual oil at 63–64 °C at 13 mm of Hg yields 8.3 g **(72%)** of **cyclohexyl acetate.**

17. OXIDATION WITH CUPRIC ACETATE

Coupling of Terminal Alkynes [*58*]

To a solution of 2 g (0.01 mol) of cupric acetate in 200 mL of pyridine–methanol–ether (1:1:4), 0.400 g (0.0048 mol) of **2-ethyl-3-butyn-2-ol** is added, and the mixture is refluxed for 20 min. After evaporation of most of the solvent in vacuo, the residue is acidified and extracted with ether, and the extract is evaporated to give 0.350 g **(88%)** of **2,7-dimethylocta-3,5-diyne-2,7-diol,** mp 128–130 °C.

18. OXIDATION WITH SILVER OXIDE (IN SITU) [*365*]

To a solution of 25.5 g (0.15 mol) of silver nitrate in 50 mL of water in a 300-mL bottle, a solution of 5.5 g (0.05 mol) of **3-cyclohexenecarboxaldehyde** in

10 mL of ethanol is added followed by a solution of 17 g (0.3 mol) of potassium hydroxide in 50 mL of water over a period of 1 h. The bottle is cooled with ice and water, and the mixture is stirred intensively. After the mixture has been shaken at room temperature for an additional 2–3 h, the deposited silver is filtered off and washed with a small amount of water, and the filtrate is cooled and acidified with dilute sulfuric acid. The mixture is extracted with ether, and the ether extract is washed with water, dried with sodium sulfate, and distilled to give 4 g **(62.5%)** of **3-cyclohexenecarboxylic acid,** bp 125–126 °C at 13 mm of Hg.

19. OXIDATION WITH MERCURIC OXIDE

Oxidation of Hydrazones to Diazo Compounds [*387*]

A mixture of 13 g (0.066 mol) of **benzophenone hydrazone,** 15 g of anhydrous sodium sulfate, 35 g (0.16 mol) of yellow (or red) mercuric oxide, 200 mL of dry ether, and 5 mL (10 mL if red mercuric oxide is used) of ethanol saturated with potassium hydroxide is shaken for 75 min in a pressure bottle wrapped in a wet towel. The reaction mixture is filtered, and the solvent is evaporated under reduced pressure at room temperature. The dark red oil thus obtained is dissolved in petroleum ether (bp 30–60 °C), and the solution is filtered again. Removal of the solvent from the filtrate under reduced pressure at room temperature gives an oil, which crystallizes when frozen in a stoppered flask in dry ice. After the flask has warmed to room temperature, the dark-red crystals are spread over a porous plate to give 11.4 g **(89%)** of **diphenyldiazomethane,** mp 29–30 °C.

Oxidation of Vicinal Dihydrazones to Alkynes [*394*]

In a three-necked flask equipped with a stirrer and a reflux condenser with a water-separating adapter, 23 g (0.106 mol) of mercuric oxide, 1 g of finely ground potassium hydroxide, and 20 g of anhydrous sodium sulfate in 100 mL of toluene are heated to a gentle reflux. While the suspension is stirred vigorously, 11.0 g (0.056 mol) of finely powdered **1,2-cyclodecanedione dihydrazone** is added in six portions over a period of 30 min. After refluxing for 2 h, the black mixture is filtered. The yellow toluene solution is passed through a column of 10 g of aluminum oxide (activity II–III), and the colorless filtrate is evaporated and distilled to give 5.12 g **(67%)** of **cyclodecyne,** bp 78.5 °C at 12 mm of Hg (after fractionation through a Vigreux column).

20. OXIDATION WITH THALLIUM TRINITRATE

Oxidation of Acetylenes to α-Diketones [*413*]

A solution of 1.78 g (0.01 mol) of **diphenylacetylene** in 20 mL of glyme is added to a solution of 8.9 g (0.02 mol) of thallium trinitrate in 10 mL of water containing 5 mL of 70% perchloric acid. The mixture is gently refluxed for 3 h. After the mixture has been cooled, thallium mononitrate is filtered off, and the filtrate is diluted with 100 mL of water. The mixture is extracted with two 25-mL portions of chloroform. The chloroform extract is dried with anhydrous sodium

sulfate, the solvent is evaporated, and the residue is freed from traces of inorganic thallium salts by passage through a short column (2 by 10 cm) of acid-washed alumina. Elution with benzene–chloroform (1:1) and evaporation of the eluent gives 1.78 g **(85%)** of **benzil,** mp 93–94 °C.

21. OXIDATION WITH CERIC AMMONIUM NITRATE

Oxidation of Sulfides to Sulfoxides [*426*]

Ceric ammonium nitrate (1.10 g, 0.002 mol) is added in one portion to a stirred solution of 0.093 g (0.0005 mol) of **diphenyl sulfide** in 8 mL of 75% aqueous acetonitrile. After 3 min at room temperature, the mixture is quenched with 5 mL of water, and the product is obtained by extraction with two 20-mL portions of ether and evaporation of the solvents. **Diphenyl sulfoxide,** mp 68–70 °C, is obtained in **82%** yield.

22. OXIDATION WITH LEAD TETRAACETATE

Cleavage of Vicinal Diols in Anhydrous Medium [*1155*]

Under a nitrogen atmosphere, 20 g (0.17 mol) of ***cis*-1,2-cyclohexanediol** is dissolved in 200 mL of dry benzene. Anhydrous potassium carbonate (50 g) is added, and the mixture is stirred vigorously while 76 g (0.17 mol) of lead tetraacetate is added in 5-g portions over a period of 1 h. After an additional hour of stirring, the mixture is filtered with suction, and the salts are extracted with benzene. The combined benzene solutions are dried over anhydrous sodium sulfate and evaporated in vacuo. The residue is distilled under a nitrogen atmosphere to give 13.4 g **(68%)** of colorless **adipic aldehyde,** bp 68–70 °C at 3 mm of Hg.

23. OXIDATION WITH NITRIC ACID

Oxidation of Alcohols to Acids [*1206*]

In a 250-mL flask fitted with a magnetic stirring bar and a reflux condenser, nitric acid prepared by diluting 40 mL (0.89 mol) of concentrated nitric acid (*d* 1.4) with 40 mL of water is heated almost to boiling. **Cyclohexanol** (10 g, 0.1 mol) is added dropwise from a separatory funnel through the reflux condenser while the mixture is stirred without further heating. Each drop of cyclohexanol brings the mixture to boiling, and additional cyclohexanol is added only when the effervescence has subsided. After the addition has been completed, the mixture is gently refluxed for an additional 30 min and then transferred into a porcelain dish and evaporated to one-half of its volume on a steam bath in a hood. After cooling, crystals of **adipic acid** are filtered with suction and recrystallized from a minimum amount of water. The yield is 7–8 g **(48–55%),** mp 151 °C.

24. OXIDATION WITH AMMONIUM NITRATE

Oxidation of α-Hydroxy Ketones to α-Diketones [*476*]

In a 100-mL flask fitted with a reflux condenser are placed 0.1 g (0.0005 mol) of cupric acetate monohydrate (as a catalyst), 5 g (0.0625 mol) of ammonium nitrate, 10.6 g (0.05 mol) of **benzoin,** and 35 mL of 80% aqueous acetic acid. The mixture is heated with occasional shaking of the flask. Soon a vigorous evolution of nitrogen commences. After a 1.5-h reflux, the solution is cooled and seeded with a crystal of benzil (or by scratching the walls of the flask with a glass rod) until crystallization takes place. Water is added to the mixture to precipitate the residual benzil. The crystals are filtered with suction and washed with water containing about 20% of ethanol. The yield of **benzil** is **quantitative.** The melting point of the product after recrystallization from 70% ethanol is 95 °C.

25. OXIDATION WITH LEAD NITRATE

Conversion of Haloalkyl Group into Carbonyl [*477*]

To 110 g (1.0 mol) of ***o*-fluorotoluene,** 58 mL (182 g, 1.14 mol) of bromine is added over a period of 1 h at 105–120 °C while the mixture is irradiated with a 500-W bulb from a distance of 5–10 cm. After the addition of bromine has been completed, the ***o*-fluorobenzyl bromide** thus formed is heated in the course of 15 min to 150 °C. The cooled mixture is added in two portions to a solution of 175 g (0.53 mol) of lead nitrate in 1000 mL of boiling water, and the mixture is heated under reflux with occasional shaking. After the first 0.5 h of heating, nitrogen oxides start to evolve, and crystals of lead bromide begin to deposit. After 5–6 h of refluxing, the mixture is steam distilled. The distillate (94 g) is treated with a 5 N solution of sodium bisulfite. The aldehyde–bisulfite compound thus formed (139.5 g, 61.2%) is decomposed with a solution of sodium carbonate, and the aldehyde is steam distilled. The organic layer of the steam distillate is dried and distilled to give 55 g of ***o*-fluorobenzaldehyde**, bp 172–174 °C, n_D^{20} 1.5216. This amount represents a **78.5%** yield based on the aldehyde–bisulfite compound or a **48%** yield based on ***o*-fluorotoluene.**

26. OXIDATION WITH SULFUR

Willgerodt Oxidation of Ketones to Carboxylic Acids (Kindler Modification) [*504*]

A mixture of 373 g (2.2 mol) of **methyl 2-naphthyl ketone,** 105 g (3.3 mol) of sulfur, and 290 g (3.3 mol) of morpholine is refluxed gently for 14 h and briskly for 2 h in a hood. While still hot, the mixture is poured into 1.2 L of warm ethanol. After the mixture has been cooled, 534 g **(89.6%)** of pale-buff crystals of **2-naphthylacetic acid thiomorpholide,** mp 100–106 °C, is obtained. A mixture of 388 g (1.61 mol) of the thiomorpholide, 800 mL of acetic acid, 120 mL of concentrated sulfuric acid, and 180 mL of water is refluxed for 5 h and then poured into 6 L of water. A considerable amount of tar is left in the flask. After the mixture has been allowed to stand overnight, the solid is collected, washed with water, and digested

with a solution of 150 g of sodium hydroxide in 3 L of water. The dark insoluble substance is removed by filtration, and 2-naphthylacetic acid is precipitated as a cream-colored product by acidification. After this material has been washed with water, dried, and digested with several portions of a mixture of benzene with petroleum ether, **2-naphthylacetic acid** is obtained as a purplish-tinged solid, mp 138–141 °C, in **89.5%** yield. Recrystallization from benzene raises the melting point to 142.2–143 °C.

27. OXIDATION WITH SELENIUM DIOXIDE

Oxidation of Ketones to α-Diketones [*516*]

A solution of 72.9 g (0.66 mol) of selenium dioxide, 10 mL of water, and 107.1 g (0.66 mol) of **2-acetylmesitylene** in 600 mL of dioxane is stirred and refluxed for 5 h. After separation from selenium by filtration, the dioxane is evaporated, and the residue is distilled at 130–134 °C at 20 mm of Hg to give an **82.5%** yield of **mesitylglyoxal** as a heavy yellow oil, bp 105–106 °C at 4 mm of Hg.

28. OXIDATION WITH CHROMIUM TRIOXIDE

Oxidation of Alcohols to Aldehydes and Ketones with Chromic Acid Adsorbed on Silica Gel [*537*]

To a solution of 2.0 g (0.02 mol) of chromium trioxide in 50 mL of water, 20 g of silica gel is added with stirring. The mixture is evaporated in vacuo, and the yellow solid is dried overnight at 100 °C. If kept under vacuum in the dark, the reagent retains its activity for at least a week.

The reagent (3 g) is suspended in 5 mL of ether, the mixture is stirred magnetically, and a solution of 0.158 g (1 mmol) of **1-decanol** is added. After 5 min, the solid is filtered off and washed with three 10-mL portions of ether. The combined filtrates are evaporated to give 0.135 g **(86%)** of **decanal,** mp 102–104 °C.

Oxidation of Acetylenic Alcohols to Ketones by the Jones Reagent [*578*]

A solution of 10.3 g (0.103 mol) of chromium trioxide in 30 mL of water and 8.7 mL of concentrated sulfuric acid is added over a period of 2 h to a stirred solution of 15 g (0.126 mol) of **3-octyn-2-ol** in 30 mL of acetone at 5–10 °C. After being stirred for an additional 30 min, the mixture is diluted with water to 250 mL, and the ketone is isolated by extraction with ether. Distillation of the ether solution gives 11.5 g **(73.6%)** of **3-octyn-2-one,** bp 70.5–71.5 at 11 mm of Hg.

29. OXIDATION WITH CHROMIUM TRIOXIDE–PYRIDINE COMPLEX

Oxidation of Primary Alcohols to Aldehydes [*598*]

A solution of 5 g (0.043 mol) of **2-ethyl-2-methyl-1-butanol** in 5 mL of dry pyridine is added to a stirred slurry of chromium trioxide–pyridine complex (***Pro-***

cedure 4) in 50 mL of pyridine, and the mixture is allowed to stand overnight at room temperature. After a 3-h reflux, the mixture is poured into cold dilute sulfuric acid, and the product is extracted with ether. Evaporation of the dried ether extract and fractionation of the residue under atmospheric pressure yields 4.4 g **(88%)** of **diethylmethylacetaldehyde,** bp 132–133 °C.

30. OXIDATION WITH CHROMIUM TRIOXIDE–3,5-DIMETHYLPYRAZOLE COMPLEX

Oxidation of Secondary Alcohols to Ketones [*602*]

3,5-Dimethylpyrazole (0.580 g, 0.006 mol) is added to a suspension of 0.600 g (0.006 mol) of chromium trioxide in 20 mL of dichloromethane, and the mixture is stirred under argon at room temperature for 15 min. To the dark-red solution, 0.263 g (0.0022 mol) of **α-phenylethanol** in 2 mL of dichloromethane is added in one portion, and the reaction mixture is stirred at room temperature for 30 min. The progress of the reaction is monitored by vapor-phase chromatography with a 6-ft (~1.8-m) 5% Carbowax 20 M (a polyethylene glycol compound) column. The solvent is removed under reduced pressure, the residue is extracted with 50 mL of ether, and the resulting mixture is filtered. The residue after concentration is dissolved in pentane, the solution is filtered through a short column packed with silica, and the filtrate is evaporated to give 0.260 g **(100%)** of **acetophenone.**

31. OXIDATION WITH PYRIDINIUM CHLOROCHROMATE (PCC)

Oxidation of Primary Alcohols to Aldehydes [*605*]

To a stirred suspension of 32.3 g (0.1 mol) of pyridinium chlorochromate in 200 mL of methylene chloride is added rapidly at room temperature a solution of 11.6 g (0.1 mol) of **1-heptanol** in 100–150 mL of dichloromethane. A black precipitate is formed shortly. After 2 h, the mixture is diluted with 5 volumes of anhydrous ether, the solvents are decanted, and the black solid is washed twice with ether. The organic solution is filtered through Florisil (magnesium silicates), and the solvent is evaporated at reduced pressure. **Heptanal** (10.1 g), bp 153 °C, is obtained in **78%** yield.

32. OXIDATION WITH PYRIDINIUM CHLOROCHROMATE ADSORBED ON ALUMINA

Oxidation of Unsaturated Primary Alcohols to Unsaturated Aldehydes [*604*]

A solution of 0.51 g (3.8 mmol) of **cinnamyl alcohol** in 10 mL of hexane is stirred with 9.3 g (7.6 mmol) of the pyridinium chlorochromate reagent (***Procedure 5***) at room temperature for 24 min. The solid is filtered off and washed with three 10 mL-portions of ether. The combined filtrates are evaporated, and the residue is distilled in vacuo to give 0.42 g **(84%)** of **cinnamaldehyde,** bp 130 °C at 20 mm of Hg.

33. OXIDATION WITH TETRABUTYLAMMONIUM CHROMATE

Oxidation of Secondary Alcohols to Ketones [*618*]

A solution of 1.58 g (5.68 mmol) of tetrabutylammonium chloride in 28 mL of water is added rapidly with stirring to a solution of 0.54 g (5.4 mmol) of chromium trioxide in 14 mL of water at room temperature. The tetrabutylammonium chromate is extracted with 200 mL of chloroform. The chloroform solution is concentrated to 6 mL, and a solution of 0.5 g (2.71 mmol) of **benzhydrol** in 4 mL of chloroform is added with stirring. After 3 h at 60 °C, the mixture is diluted with ether, and the solution is poured into 1 N sodium hydroxide. The ether layer is washed with a saturated solution of sodium chloride, dried with anhydrous sodium sulfate, and evaporated to give 0.450 g **(91%)** of **benzophenone,** mp 45–47 °C.

34. OXIDATION WITH SODIUM DICHROMATE

Oxidation of Secondary Alcohols to Ketones [*642*]

In a 2-L, three-necked flask fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser, a solution of 120 g (0.400 mol, 20% excess) of sodium dichromate dihydrate and 135 g (1.33 mol) of 96% sulfuric acid in 500 mL of water is added over a 40-min period to a well-stirred mixture of 128.0 g (1.00 mol) of **4-ethylcyclohexanol** in 200 mL of water. Within 2 min, the mixture becomes greenish-black, and the temperature rises from 30 to 68 °C during the addition of the first half of the oxidizing solution. Immediately after the addition has been completed, the temperature starts dropping and, within 5 min, decreases to 55 °C. The mixture is cooled and extracted twice with 400 mL of ether–pentane (3:1). The extracts are washed several times with water, dried, and evaporated to yield 113.6 g **(90%)** of **4-ethylcyclohexanone,** bp 109–112 °C at 50 mm of Hg.

35. OXIDATION WITH SODIUM HYPOCHLORITE

Epoxidation of Unsaturated Ketones [*691*]

To a solution of 1.0 g (0.048 mol) of **benzalacetophenone** in 7.5 mL of pyridine is added 11 mL of a fresh 5.25% solution of sodium hypochlorite (Clorox). An exothermic reaction is accompanied by the almost immediate fading of the yellow color of the solution. When the mixture becomes almost colorless, 25 mL of water is added. The precipitated white crystals of the epoxide are filtered with suction, washed thoroughly with water, and recrystallized from ethanol to give 1.0 g **(94%)** of **1,3-diphenyl-2,3-epoxy-1-propanone,** mp 89–90 °C.

36. OXIDATION WITH SODIUM CHLORITE

Oxidation of Aldehydes to Carboxylic Acids [*1162*]

Solutions of 1.52 g (0.01 mol) of **vanillin** in 19 mL of *tert*-butyl alcohol, of 1.43 g (0.013 mol) of resorcinol (as chlorine scavenger) in an acetate buffer of

pH 3.93, and of 13 mL (0.012 mol) of sodium chlorite in water are mixed. The precipitate of vanillic acid (0.84 g) is filtered with suction. The filtrate is extracted with dichloromethane, and an additional crop (0.52 g) is obtained by extraction with a solution of sodium hydrogen carbonate followed by acidification. The total yield of **vanillic acid** is **81%.**

37. OXIDATION WITH SODIUM HYPOBROMITE

Conversion of Methyl Ketones into Carboxylic Acids with One Less Carbon [*736*]

A solution of sodium hypobromite, prepared by dissolving 42 g (1.05 mol) of sodium hydroxide in 200 mL of water and adding 15 mL (47 g, 0.29 mol) of bromine at 0 °C, is added over a 30-min period to a stirred solution of 15.0 g (0.066 mol) of **4-(*p*-methoxyphenyl)acetophenone** in 150 mL of dioxane. During the addition, the temperature is allowed to rise to 35–40 °C. After being stirred for an additional 15 min, the mixture is treated with enough sodium bisulfite to destroy the excess of sodium hypobromite. Water (1 L) is added, and 200 mL of water is distilled off to remove the bromoform and some dioxane. Acidification of the hot solution and subsequent cooling yields 13.8 g **(91%)** of **4-(*p*-methoxyphenyl)benzoic acid,** mp 247–248 °C.

38. OXIDATION WITH *N*-BROMOACETAMIDE

Selective Oxidation of Secondary Alcohols in Preference to Primary Alcohols [*743*]

To a solution of 13.05 g (0.095 mol) of *N*-bromoacetamide in 233 mL of methanol, 3.6 mL of pyridine, and 12.7 mL of water, 15.00 g (0.023 mol) of **20-cyano-3α,21-dihydroxy-17-pregnen-11-one** is added. The mixture, while protected from light, is stirred overnight at room temperature. After this time, a considerable amount of crystals accumulates. To destroy the excess of *N*-bromoacetamide, 4.2 mL of allyl alcohol is added, followed by 4.4 mL of 6 N hydrochloric acid to neutralize the pyridine. Crystallization is completed by the addition of 900 mL of water over a period of 20 min. After the mixture has been left in an ice bath for 30 min, the crystals are filtered with suction, washed with water, and dried to furnish 14.3 g **(96.5%)** of **20-cyano-21-hydroxy-17-pregnene-3,11-dione,** mp 254.1–255.1 °C.

39. OXIDATION WITH ACETYL HYPOIODITE

syn Hydroxylation of Double Bonds (Woodward Method) [*782*]

A mixture of 0.82 g (0.01 mol) of **cyclohexene,** 3.67 g (0.022 mol) of silver acetate, and 2.54 g (0.01 mol) of iodine in 65 mL of glacial acetic acid is shaken for 4.5 h at room temperature. Wet acetic acid (10 mL), containing 0.2 mL (0.011 mol) of water, is added, and the mixture is refluxed for 1 h. After the mixture has been cooled, the precipitated silver salts are filtered off and washed with a small

amount of acetic acid. The combined filtrate and washings are evaporated at 100 °C under reduced pressure. The residue is diluted with water, the solution is extracted with ether, and the ether extract is washed with concentrated ammonium hydroxide and with water. After the removal of ether, the residue is refluxed for 1 h with an excess of 3 N aqueous potassium hydroxide. The mixture is neutralized with concentrated hydrochloric acid and evaporated to dryness, and the residue is extracted with chloroform. Evaporation of the solvent gives 0.83 g **(66%)** of crude ***cis*-1,2-cyclohexanediol.** Recrystallization from ethyl acetate yields 0.52 g **(41%)** of pure product, mp 94–97 °C.

40. OXIDATION WITH PERIODIC ACID

Cleavage of Vicinal Diols to Carbonyl Compounds in Aqueous Medium [*759*]

A solution of 5.4 g (0.015 mol) of **glucose phenylosazone** in 2 L of warm 66% ethanol is cooled to room temperature and treated with a solution of 10 g (0.044 mol) of paraperiodic acid in 70 mL of water. The yellow-orange precipitate appears at once. After dilution of the mixture with 500 mL of water, the precipitate is filtered with suction, and the crystals are washed with 66% ethanol and dried in vacuo. Two recrystallizations of the residue (3.4 g, **85%**) from 66% ethanol give yellow-orange needles of **mesoxaldehyde osazone,** mp 198 °C (dec).

41. OXIDATION WITH SODIUM PERIODATE

Oxidation of Sulfides to Sulfoxides [*770*]

Thioanisole (methyl phenyl sulfide) (12.4 g, 0.1 mol) is added to 210 mL (0.105 mol) of a 0.5 M solution of sodium metaperiodate at 0 °C, and the mixture is stirred in an ice bath overnight. The precipitated sodium iodate is filtered, and the filtrate is extracted with chloroform. The extract is dried over anhydrous magnesium sulfate, and the solvents are evaporated under reduced pressure. The residue (13.9 g, **99%** yield) is distilled at 83–85 °C at 0.1 mm of Hg to give pure **methyl phenyl sulfoxide,** mp 29–30 °C.

42. OXIDATION WITH ALUMINA-SUPPORTED SODIUM PERIODATE

Preparation of the Supported Oxidant [*771*]

Acidic aluminum oxide (Merck 90) for column chromatography (100–325 mesh) (33.4 g) is added in one portion to a magnetically stirred solution of 21.4 g (0.1 mol) of **sodium metaperiodate** in 60 mL of water at 60 °C. The mixture is stirred for 20 min at 60 °C and then dried in a rotary evaporator. The white residue is heated at 120 °C for 16 h to a constant weight. The concentration of the oxidant is 3 mmol/g of alumina.

Oxidation of Sulfides to Sulfoxides [*771*]

To a solution of 6.2 g (0.05 mol) of **methyl phenyl sulfide** in 50 mL of 95% ethanol is added 54.8 (0.1 mol) of the supported oxidant in one portion at room temperature. The mixture is stirred vigorously until the sulfide has been completely consumed, as detected by gas-liquid chromatography with a 5% Carbowax 20 M (a polyethylene glycol compound) column (5 h). After filtration of the solid and removal of most of the ethanol by evaporation of the filtrate, 25 mL of dichloromethane is added. The solution is dried with anhydrous sodium sulfate and evaporated to dryness to give 5.54 g **(88%)** of **methyl phenyl sulfoxide,** bp 98–102 °C at 1 mm of Hg.

43. OXIDATION WITH SODIUM PERIODATE AND POTASSIUM PERMANGANATE

Cleavage of Alkenes by Lemieux–Rudloff Reagents [*763*]

A mixture of 0.2824 g (1 mmol) of **oleic acid,** 0.414 g (3 mmol) of potassium carbonate, 1.712 g (8 mmol) of sodium metaperiodate, and 0.021 g (0.134 mmol) of potassium permanganate in 400 mL of water is kept at 20 °C for 20 h. The solution is strongly acidified with 10% sulfuric acid and extracted with ether. Evaporation of the extract gives 0.354 g of a residue, which on trituration with petroleum ether gives 0.161 g of oily pelargonic acid and 0.193 g of crystalline **azelaic acid,** mp 102–104.5 °C. Pure **pelargonic acid** is obtained by vacuum distillation, and pure azelaic acid (mp 106.5–107.5 °C), by recrystallization, first from water and then from ethyl acetate. Yields of both crude acids are **quantitative,** but the yields of purified products are not stated.

44. OXIDATION WITH MANGANESE DIOXIDE

Oxidation of Allylic Alcohols to α,β-Unsaturated Aldehydes [*805*]

Cinnamyl alcohol (5 g, 0.037 mol) is stirred for 30 min with a suspension of 50 g (0.57 mol) of active manganese dioxide (***Procedure 7***) in 250 mL of carbon tetrachloride. The mixture is filtered, and the filtrate is evaporated. The residue is treated with a solution of 7.5 g (0.067 mol) of semicarbazide hydrochloride and 9 g (0.066 mol) of sodium acetate trihydrate in aqueous ethanol. The mixture is heated to 60 °C and kept at room temperature for 2 h. The **semicarbazone of cinnamaldehyde,** mp 212–215 °C, is obtained in **71.5%** yield.

Oxidation of Vicinal Diols to Ketones [*817*]

A solution of 1 g (0.0058 mol) of ***cis*-9,10-decalindiol** in 50 mL of dichloromethane is stirred at room temperature with 20 g of active manganese dioxide for 1 h. The mixture is filtered through Celite (diatomaceous earth), and the filtrate is evaporated in a rotary evaporator under vacuum generated by a water aspirator.

The residue is distilled to give 0.9 g **(90%)** of **1,6-cyclodecanedione,** mp 92–95 °C, on crystallization from acetone.

45. OXIDATION WITH POTASSIUM PERMANGANATE

Cleavage of Alkenes to Carboxylic Acids [*869*]

In a 5-L, three-necked round-bottom flask equipped with a gas-tight (Trubore) stirrer, an efficient reflux condenser connected to a dry-ice trap, a dropping funnel, and a thermometer reaching almost to the bottom of the flask are placed 460 g (2.6 mol) of potassium permanganate, 315 g (5.5 mol) of potassium hydroxide, and 3500 mL of water. The solids are dissolved by heating to 60 °C and constant stirring. **2,3-Dichlorohexafluoro-2-butene** (473 g, 2.03 mol) is added dropwise at such a rate as the capacity of the reflux condenser permits. After the addition has been completed, the solution is heated until the temperature of the liquid reaches 95 °C (8–10 h). The mixture is then cooled to 40 °C, and a stream of sulfur dioxide is passed through the liquid with stirring and cooling below 60 °C until the permanganate color just fades. The solution is acidified with just enough of 50% sulfuric acid to neutralize the potassium hydroxide used, and sulfur dioxide is passed again through the mixture until all the manganese dioxide is dissolved. Continuous extraction with ether and fractionation of the extract through an efficient column yield 480 g of the 80:20 azeotropic mixture of trifluoroacetic acid and water boiling at 103–105 °C at 745 mm of Hg. The yield of **trifluoroacetic acid** is **87%.**

Oxidation of Acetylenes to α-Diketones [*864*]

Into a solution of 5.6 g (0.02 mol) of **stearolic acid** in 3 L of water containing 1.5 g (0.027 mol) of potassium hydroxide, carbon dioxide is introduced until pH 7.5 is reached. A solution of 6.3 g (0.04 mol) of potassium permanganate in 300 mL of water is added all at once. The temperature of the reaction mixture is kept at about 25 °C, and the pH is maintained between 7.0 and 7.5 by the gradual bubbling of carbon dioxide into the mixture as the oxidation proceeds. After 1 h, the excess of potassium permanganate is destroyed by the addition of sodium bisulfite, and hydrochloric acid is added to precipitate the product. **9,10-Diketostearic acid** is filtered with suction and recrystallized from 200 mL of absolute ethanol at 0 °C. The total yield is 5.7–6.0 g **(92–96%)** of the product, mp 84.5–85.0 °C.

Oxidation of Secondary Alcohols to Carboxylic Acids [*1147*]

To a vigorously stirred mixture of 120 g (0.42 mol) of crystalline sodium carbonate (decahydrate) in 500 mL of water and 60 g (0.6 mol) of **cyclohexanol,** 270 g (1.71 mol) of potassium permanganate is added portionwise while the mixture is cooled to maintain the temperature between 15 and 30 °C. After removal of the manganese dioxide by filtration and acidification of the filtrate with 120 g of concentrated hydrochloric acid, 61 g **(70%)** of **adipic acid,** mp 151 °C, is obtained.

46. OXIDATION WITH POTASSIUM-PERMANGANATE-COATED MOLECULAR SIEVES

Oxidation of Secondary Alcohols to Ketones [*863*]

A 2-L, round-bottom flask is charged with 500 mL of a 0.06 M aqueous solution of potassium permanganate, and 20 g of Linde 13X molecular sieves (1/16-in. [0.16-cm] pellets) is added in one portion. The water is removed under reduced pressure in a rotary evaporator, and the coated pellets are separated from the nonadsorbed potassium permanganate by screening (20 mesh). The reagent contains 0.27 mmol of potassium permanganate per gram.

A suspension of 15.0 g (4.05 mol) of the reagent in 20 mL of freshly distilled benzene containing 0.250 g (1.36 mmol) of **cyclododecanol** is heated to 70 °C for 1.5 h. The solution is filtered through Celite (diatomaceous earth), the pellets are washed with 70 mL of benzene, and the combined filtrates are evaporated under reduced pressure to yield 0.226 g **(90%)** of **cyclododecanone** as colorless crystals, mp 56–59 °C. The pure compound melts at 59–61 °C.

47. OXIDATION WITH TETRABUTYLAMMONIUM PERMANGANATE (PURPLE BENZENE)

Cleavage of Alkenes to Carboxylic Acids [*845*]

Potassium permanganate (4.8 g, 0.03 mol) and 50 mL of water are vigorously stirred for 10 min, and the mixture is cooled in a water bath. Then 30 mL of benzene, 0.5 g (0.0016 mol) of tetrabutylammonium bromide, and 2 g (0.011 mol) of ***trans*-stilbene** are added. The mixture is stirred for 3 h at room temperature and then treated sequentially with sodium bisulfite and acid. The benzene layer is separated, dried, and evaporated to give 2.49 g **(92%)** of **benzoic acid.**

48. OXIDATION WITH FERRIC CHLORIDE

Dehydrogenation of Hydroquinones to Quinones and of Thiols to Disulfides [*907*]

To a solution of 0.285 g (0.002 mol) of **2-mercaptohydroquinone** in 10 parts of alcohol is added 3.5 mL (0.007 mol) of a 2 N solution of ferric chloride. The **disulfide of *p*-benzoquinone** deposits in the form of a yellow precipitate. It is collected and recrystallized from glacial acetic acid to give yellow crystals, mp 178 °C, in **quantitative** yield.

49. OXIDATION WITH OSMIUM TETROXIDE

syn Hydroxylation of Double Bond with an Equivalent Amount of Osmium Tetroxide [*949*]

1,2-Dimethylcyclopentene (6.4 g, 0.067 mol) is added portionwise to a solution of 17 g (0.089 mol) of osmium tetroxide in 300 mL of ether with 11 mL of pyridine

as a catalyst. After 1 h, the dark deposit (20.5 g) is collected, dissolved in chloroform, and decomposed by shaking with a solution of 30 g of mannitol in 300 mL of a 10% solution of potassium hydroxide (added in four portions during a 24-h period). The combined aqueous solutions are continuously extracted with chloroform, the chloroform and pyridine are distilled off through a small column, and the viscous residue is distilled at 90 °C at 9 mm of Hg to give 6.1 g **(70%)** of ***cis*-1,2-dimethyl-1,2-cyclopentanediol,** bp 86 °C at 8 mm of Hg (mp 25–25.2 °C after recrystallization from ethyl acetate).

syn Hydroxylation of Double Bond with a Catalytic Amount of Osmium Tetroxide [*130*]

A solution of hydrogen peroxide in *tert*-butyl alcohol is prepared by adding 400 mL of pure *tert*-butyl alcohol (free of isobutylene) to 100 mL of 30% hydrogen peroxide. The solution is treated with small portions of anhydrous sodium sulfate until two layers separate. The alcohol layer is removed and dried with anhydrous sodium sulfate and finally with anhydrous calcium sulfate (Drierite). The solution contains 6.3% of hydrogen peroxide in *tert*-butyl alcohol.

To 6.1 g (0.105 mol) of **allyl alcohol** is added 54.6 mL (0.1 mol) of 6.3% hydrogen peroxide in *tert*-butyl alcohol followed by 1 mL of a 0.5% solution of osmium tetroxide in *tert*-butyl alcohol. The reaction is exothermic and requires cooling with tap water. After 3 h, the reaction mixture is fractionated to remove the solvent, the catalyst, and the unreacted allyl alcohol (1.7 g). The residue is 4.2 g **(60%)** of **glycerol.**

50. OXIDATION WITH RUTHENIUM TETROXIDE

Oxidation of Amides to Imides [*1205*]

A solution of 2.4 g (0.012 mol) of **ethyl 1-acetylpiperidine-2-carboxylate** in 40 mL of ethyl acetate is added to a mixture of 0.240 g of hydrated ruthenium dioxide and 120 mL of 10% aqueous solution of sodium periodate (0.056 mol). The mixture is vigorously stirred at room temperature for 14 h. The organic layer is separated, the aqueous layer is extracted with three 40-mL portions of ethyl acetate, and the combined organic solutions are stirred with 2 mL of isopropyl alcohol for 2–3 h to destroy the excess of ruthenium tetroxide. The black ruthenium dioxide that precipitates from the solution is filtered, and the filtrate is washed with 40 mL of water, dried with anhydrous sodium sulfate, and evaporated in vacuo to give 2.42 g **(95%)** of crude **ethyl 1-acetyl-6-oxopiperidine-2-carboxylate.**

All operations should be done ***in the hood,*** because ruthenium tetroxide possesses an unpleasant ozone-like smell. Commercially available ruthenium dioxide may differ in its properties, especially in its reaction with sodium periodate, depending on the way it is prepared and on the content of water in its hydrated form [*1207*].

51. OXIDATION WITH DIETHYL AZODICARBOXYLATE

Demethylation of Tertiary Amines [*980*]

***N*-Methylisopelletierine** (6 g, 0.039 mol) and diethyl azodicarboxylate (6.8 g, 0.039 mol) are dissolved in 15 mL of methanol. The heat of the reaction brings

the solution to boiling so that moderate cooling with water has to be applied. After the reaction is over, the methanol is evaporated. The residue, a thick amber-colored syrup, is then refluxed with 80 mL of 1 N hydrochloric acid for 3 h while formaldehyde is evolved and the solution darkens. After the solution has been allowed to stand for 2 days, diethyl hydrazodicarboxylate, mp 131 °C, settles at the bottom of flask. The isopelletierine is liberated by concentrated alkali and extracted with ether. The solution is dried with potassium carbonate. Distillation of the solution yields 4.4–4.5 g **(80–82%)** of **isopelletierine,** bp 101–102 °C at 12 mm of Hg.

52. OXIDATION WITH POTASSIUM NITROSODISULFONATE (FREMY SALT)

Conversion of Aromatic Amines into Quinones [*490*]

A solution of 0.605 g (0.005 mol) of **2,6-dimethylaniline** in 25 mL of acetone is mixed with a solution of 3 g (0.01 mol) (10% excess) of potassium nitrosodisulfonate in 50 mL of 0.6 M potassium dihydrogen phosphate and 100 mL of water. After 75 min, the oxidant has reacted. The solution is extracted several times with a total of 120–150 mL of chloroform. The combined extracts are dried with anhydrous sodium sulfate, and the solvent is evaporated in vacuo at 40–50 °C to yield as a residue 0.560 g **(82%)** of **2,6-dimethyl-*p*-benzoquinone,** mp 63–65 °C (dec).

53. OXIDATION WITH *p*-NITROSODIMETHYLANILINE

Oxidation of Activated Methylene Group to Carbonyl [*986*]

To a boiling solution of 24 g (0.24 mol) of **acetylacetone** and 36 g (0.24 mol) of *p*-nitrosodimethylaniline in 120 mL of ethanol is added 4.4 mL (0.15 mol) of a solution of sodium hydroxide (*d* 1.36) all at once. After about 1 min, the color of the solution changes, and the mixture keeps on boiling even after removal of the water bath. If the boiling becomes too vigorous, the mixture is cooled intermitently without suppressing the boiling. The reaction is finished when the reaction mixture becomes bright red. The mixture is cooled and mixed with 400 mL of ether, which causes the precipitation of sodium acetate, resulting from the cleavage of the acetylacetone. The mixture is filtered, and the filtrate is treated with a solution of 150 mL of dilute sulfuric acid (*d* 1.16) in 50 mL of water and, finally, extracted with six 300–500-mL portions of ether. The combined ether extracts are distilled and then evaporated in vacuo to remove the alcohol. The residue is fractionated at 12 mm of Hg at 54–55 °C to give 15 g **(55%)** of **triketopentane (pentanetrione).**

54. SOMMELET OXIDATION

Oxidation of Aralkyl Halides to Aldehydes [*956*]

Equivalent quantities of **2,4-bis(chloromethyl)anisole** and hexamethylenetetramine (small excess) in chloroform are mixed and refluxed for 2–3 h until precipitation of the salt is complete. The crystals are filtered with suction to give an essentially quantitative yield.

A solution of 59 g (0.12 mol) of the salt in 500 mL of water is refluxed for 4 h and filtered while hot. The filtrate is cooled in an ice bath. The white needles that separate are collected and washed with cold water to give 14 g **(70%)** of **4-methoxyisophthalaldehyde,** mp 117–118 °C. One recrystallization from 60% alcohol gives 12.6 g (63%) of the compound, mp 119–120 °C.

55. OXIDATION WITH DIMETHYL SULFIDE AND *N*-CHLOROSUCCINIMIDE

Oxidation of Secondary Alcohols to Ketones [*1138*]

To a stirred solution of 0.400 g (3.0 mmol) of *N*-chlorosuccinimide in 10 mL of analytical-grade toluene is added, at 0 °C, 0.3 mL (4.1 mmol) of dimethyl sulfide under argon. A white precipitate is formed immediately after the addition. The mixture is cooled to −25 °C with carbon tetrachloride–dry ice. A solution of 0.312 g (2.0 mmol) of **4-*tert*-butylcyclohexanol** (a mixture of *cis* and *trans* isomers) in 2 mL of toluene is added dropwise while the mixture is stirred for 2 h at −25 °C. Then a solution of 0.303 g (3.0 mmol) of triethylamine in 0.5 mL of toluene is dropped in, the cooling bath is removed, and after 5 min, 20 mL of ether is added. The organic layer is washed with 5 mL of water, dried with anhydrous magnesium sulfate, and evaporated to give 0.310 g **(~100%)** of **4-*tert*-butylcyclohexanone** as white plates, mp 44–47 °C.

56. OXIDATION WITH DIMETHYL SULFOXIDE

Oxidation of Acetylenic Alcohols to Acetylenic Aldehydes [*1015*]

To a refluxing solution of 4 g (0.033 mol) of **4,6-octadiyn-1-ol** and 21 g (0.10 mol) of dicyclohexylcarbodiimide in 200 mL of absolute ether, a solution of 1.7 g of crystalline phosphoric acid in 100 mL (110 g, 1.41 mol, 43× molar excess) of dimethyl sulfoxide is added dropwise. After an additional heating for 4 h, 100 mL of 4 N sulfuric acid is added. The precipitated crystals of *N,N'*-dicyclohexylurea are filtered with suction and washed with ether. The filtrate is washed until neutral with a solution of sodium hydrogen carbonate. The dried ether solution is evaporated, and the residue is distilled at 60 °C at 0.001 mm of Hg to give a **73%** yield of **4,6-octadiynal** as a colorless oil.

Oxidation of α-Bromo Ketones to Dicarbonyl Compounds [*1003*]

A solution of 15.98 g (0.065 mol) of ***p*-bromophenacyl bromide** in 100 mL (110 g, 1.41 mol, 38.5 equiv) of dimethyl sulfoxide is kept at room temperature for 9 h. It is then poured into an ice–water mixture and extracted with ether. The extracts are washed with water, dried with anhydrous magnesium sulfate, and evaporated in vacuo. The residual pasty pale-yellow solid is recrystallized from butyl ethyl ether to give 11.2 g **(84%)** of ***p*-bromophenylglyoxal hydrate,** mp 123–124 °C.

57. BIOCHEMICAL OXIDATION

Asymmetric Oxidation of Sulfide to Sulfoxide [*1046*]

Mycelia of *Aspergillus niger* from two malt slopes are transferred to four 500-mL Erlenmeyer flasks, each containing 100 mL of Czapek Dox liquid medium and 2 mL of corn steep liquor (Dista Products Ltd). The four flasks are used to inoculate 57 1-L flasks, each containing 100 mL of Czapek Dox medium at pH 4–5. The flasks are shaken on a platform shaker (180 rpm) at 30 °C for 2 days. **Benzyl *tert*-butyl sulfide** (30 mg dissolved in 1 mL of ethanol) is injected into each flask, and the flasks are shaken for 4 days at 30 °C. The mycelia are filtered off and extracted with boiling dichloromethane. The filtrate is continuously extracted with dichloromethane for 6 days. Evaporation of the extract and chromatography of the residues on deactivated alumina give sulfide, sulfoxide, and sulfone in this sequence. The sulfoxide fraction is recrystallized to give a **61%** yield of **(–)-benzyl *tert*-butyl sulfoxide** of 77% optical purity, mp 75–76 °C, [α] –265 ° (after six recrystallizations from pentane). *tert*-Butyl *p*-tolyl sulfide furnishes *tert*-butyl *p*-tolyl sulfoxide in 24% yield and 94% optical purity.

CORRELATION TABLES

THE PURPOSE of the correlation tables is to show what oxidants are suitable for the oxidation of compounds to their various oxidation products and where in the book such oxidations can be found. Abbreviations used in the tables are explained in footnotes or in the list of abbreviations on pages 319 and 320.

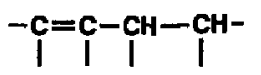
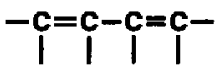
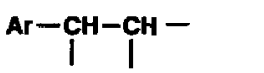
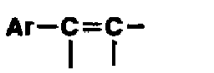
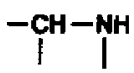
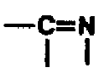
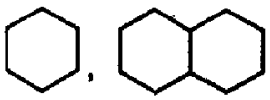
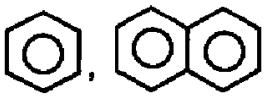
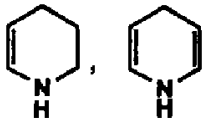
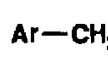
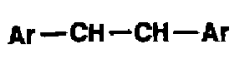
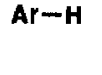
The absence of a reagent in the column "Oxidants" means that the reagent was not used in examples shown in this book. It does not mean that oxidants not listed here cannot be used successfully for a particular oxidation.

Numbers in italics in the "Page" column refer to pages in Chapter 4, Preparative Procedures.

CORRELATION TABLES

Table 1

DEHYDROGENATION

Starting Compound	Product	Oxidants	Page
		$Hg(OAc)_2$, H_2O_2, DDQ* $PhIO_2/Ph_2Se_2$, *m*-$HO_2C_6H_4IO_2/Ph_2Se_2$ H_2O_2/PhSeCl, biochemical oxidation	47,48 48,49 49,*275*
		ZnO-Cr_2O_3, *o*-$C_6Cl_4O_2$, DDQ	49
		$Hg(OAc)_2$, Ag_2O, *t*-BuOCl	49,50
		Pt, Pd, S, Se, *o*-$C_6Cl_4O_2$ DDQ*, $AlCl_3$	50-52 *275*
		HNO_3, As_2O_3, MnO_2 $K_3Fe(CN)_6$, $PhNO_2$	52
		O_2/KOH, MnO_2, $KMnO_4$	53
		$AlCl_3$, H_2CrO_4, H_2SO_4/Fe_2O_3, H_5IO_6, $FeCl_3$ $K_3Fe(CN)_6$, biochemical oxidation	53-55

*DDQ is 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

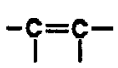
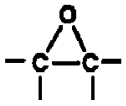
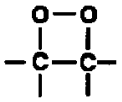
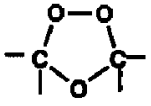
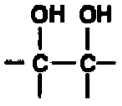
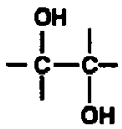
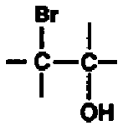
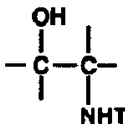
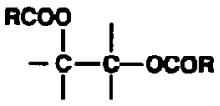
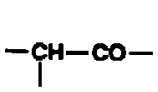
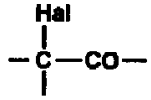
Table 2

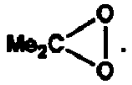
OXIDATION OF ALKANES AND CYCLOALKANES

Starting Compound	Product	Oxidants	Page
$-CH_3$	$-CO_2H$	biochemical oxidation	58
$-CH_2-$	$-\underset{\displaystyle OH}{\underset{\vert}{CH}}-$	biochemical oxidation	58
$-\underset{\vert}{CH}-$	$-\overset{\displaystyle OH}{\overset{\vert}{\underset{\vert}{C}}}-$	O_3, CrO_3, $PhCH_2NEt_3MnO_4$ p-$O_2NC_6H_4CO_3H$	58,59
$-\underset{\vert}{CH}-$	$-\overset{\displaystyle OOH}{\overset{\vert}{\underset{\vert}{C}}}-$	O_2	60

Table 3

OXIDATION OF ALKENES AND CYCLOALKENES

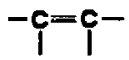
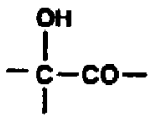
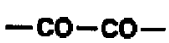
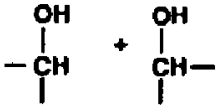
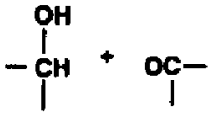
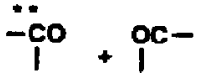
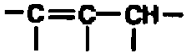
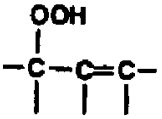
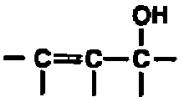
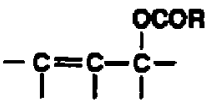
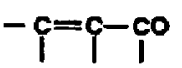
Starting Compound	Product	Oxidants	Page
		O_2, O_3, H_2O_2, *t*-BuOOH RCO_3H, Me_2CO_2* $Tl(OAc)_3$, CrO_3, $CrO_2(NO_3)_2$ NaOCl, $Ca(OCl)_2$, NBS** I_2/Ag_2O, $I(OCOCF_3)_3$ electrolysis, biochemical oxidation	60-62 61-64,*279* 61,62 61,63 62,63 61,62
		O_2, $(PhO)_3PO_3$	64-65
		O_3	65-67
		$KMnO_4$, OsO_4 $Ph_3MePMnO_4$, $PhCH_2NEt_3MnO_4$ $OsO_4 + H_2O_2$, $NaClO_3$, or $KClO_3$ $OsO_4 + AgClO_3$, $Ba(ClO_3)_2$ or R_3NO I_2 + AgOAc, AgOBz or TlOAc + H_2O biochemical oxidation	68,71-73,*290* 72,73 68,69,*291* 68,69,72,73 70,*286* 71
		H_2O_2/V_2O_5, SeO_2, MoO_3, WO_3 RCO_3H, I_2 + AgOAc, AgOBz or TlOAc	69,72,*277* 69-72
		AcNHBr, NBS**	73,74
		TosNClNa/OsO_4	74
		$Tl(OAc)_3$, $Pb(OAc)_4$, $Bz_2O_2 + I_2$ AgOAc, AgOBz or TlOAc + I_2	74,75
		air, electrolysis, H_2O_2, HCO_3H CrO_3, CrO_2Cl_2 + Zn, DDQ*	75,76
		CrO_2Cl_2, $Ag_2CrO_4 + I_2$	76

* Me_2CO_2 is dimethyldioxirane  .

**NBS is *N*-bromosuccinimide.

Continued on next page

Table 3 (continued)

Starting Compound	Product	Oxidants	Page
		$KMnO_4$	76,77
		SeO_2, $KMnO_4$	76
		$O_3/LiAlH_4$	77,78
		$O_3/NaBH_4$	77,78
		O_3/Pd or Raney Ni O_3/Zn, $O_3/(MeO)_3P$, O_3/Me_2S	77,78 *276*
		$O_2/h\nu$, H_2O_2, CrO_3 $CrO_2(OAc)_2$, $NaIO_4$ $OsO_4/NaIO_4$, $KMnO_4$	78-80
		O_3/H_2O_2 or RCO_3H; Ag_2O, HNO_3 CrO_3, $K_2Cr_2O_7$, $NaMnO_4$, $KMnO_4$ Bu_4MnO_4, $NaIO_4/KMnO_4$, RuO_4	81-84 *289* *288,290*
		$O_2/h\nu$, $(PhO)_3PO_3$, $H_2O_2/NaOCl$	84,85
		SeO_2	85,86
		*t*-BuO_2Ac, *t*-BuO_2Bz, $Hg(OAc)_2$ $Pb(OAc)_4$	86
		O_2/Cu(II), $HgBr_2/h\nu$, CrO_3 $PhIO_2/(RSe)_2$	86,87

* DDQ is 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

** If the vinylic carbon is linked to hydrogen, the product of the reductive ozonolysis is an aldehyde.

***Carboxylic acids are formed only when hydrogen or halogen are present at the carbon of the double bond.

Table 4

OXIDATION OF DIENES

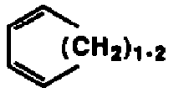
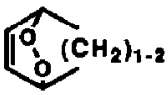
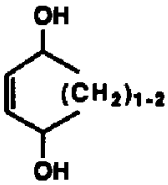
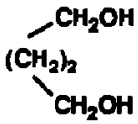
Starting Compound	Product	Oxidants	Page
		$O_2/h\nu$, $H_2O_2/NaOCl$, $H_2O_2/Br_2/KOH$ RCO_3K/OH^-, $(PhO)_3PO_3$	87-89
		$O_2h\nu$ H_2O_2/OsO_4, $KMnO_4$	*275* 89
		$O_3/LiAlH_4$	90

Table 5

OXIDATION OF ALKYNES

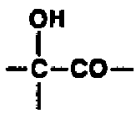
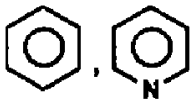
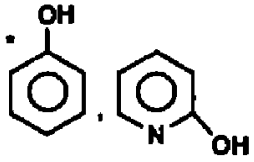
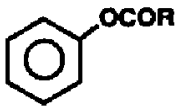
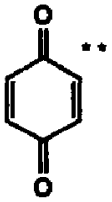
Starting Compound	Product	Oxidants	Page
$-C\equiv CH$	$-C\equiv C-C\equiv C-$	O_2/Cu(I), Cu(II)	90,91 *279*
	$-CO_2H$	$Tl(NO_3)_3$, $KMnO_4$, PhIO, $C_6F_5I(O_2CR)_2$	91,92
$-C\equiv C-$		$Tl(NO_3)_3$	91
	$-CO-CO-$	O_3, $Tl(NO_3)_3$, SeO_2, $ZnCr_2O_7$ $Mo(O_2)_2$, $KMnO_4$, $Zn(MnO_4)_2$, OsO_4 RuO_4, DMSO, PhIO	91,92 *289*

Table 6

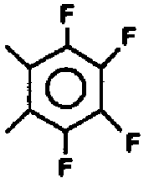
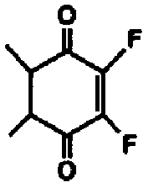
OXIDATION OF AROMATIC HYDROCARBONS AND NONFUNCTIONALIZED HETEROCYCLES

Starting Compound	Product	Oxidants	Page
	 *	KOH CF_3CO_3H, biochemical oxidation	92 93
		RCO_3H, $Pb(OCOR)_4$, $(i\text{-}PrO_2)_2CO$ $Bz_2O_2 + I_2$	93,94
	 **	O_2, H_2O_2, RCO_3H, $Ce(SO_4)_2$ SeO_2, CrO_3, $Na_2Cr_2O_7$, $K_2Cr_2O_7$ $ZnCr_2O_7$, HIO_4, $Mn_2(SO_4)_3$	94-96
	—CHO	O_3	96,97
	$—CO_2H$	O_2, O_3/H_2O_2, electrolysis, RCO_3H HNO_3, CrO_3, $Na_2Cr_2O_7$, $KMnO_4$ RuO_4/NaOCl *or* $NaIO_4$	96-98
$ArCH_2—$		$O_2/h\nu$	99
		H_2O_2, $Hg(OAc)_2$, $(NH_4)_2Ce(NO_3)_6$ $Pb(OAc)_4$	100,101
	ArCHO, ArCO—	O_2, AgO, $HgBr_2$, $(NH_4)_2Ce(NO_3)_6$, $K_2S_2O_8$ SeO_2, CrO_3, CrO_2Cl_2, $Na_2Cr_2O_7$, $K_2Cr_2O_7$ HIO_4, $NaIO_4$, MnO_2, $KMnO_4$, RONO	101-105
	$ArCO_2H$	O_2, O_3, electrolysis, $KHSO_5$ HNO_3, CrO_3, $Na_2Cr_2O_7$ NaOCl, $KMnO_4$, NiO_2, biochemical oxidation	105-109

* This product is obtained only when the ring contains nitro groups.
**This product is obtained only with condensed aromatic hydrocarbons.

Table 7

OXIDATION OF HALOGEN DERIVATIVES AND TOSYLATES

Starting Compound	Product	Oxidants	Page
$-CH_2\overset{*}{Hal}$	$-CHO$	R_3NO, DMSO (Me_2SO)	109,110
$-CH_2OSO_2C_7H_7$	$-CHO$	DMSO	109,110
$-\overset{|}{C}=\overset{|}{C}-CH_2Hal$	$-CHO$	H_2CrO_4, $Na_2Cr_2O_7$, $C_6H_{12}N_4$	109-111
$ArCH_2Hal$	ArCHO	$Pb(NO_3)_2$, H_2CrO_4, $K_2Cr_2O_7$ Bu_4NIO_4, $C_6H_{12}N_4$, RNO $Me_2C=N(O)ONs$	110-112,*282,292*
$-CH_2Hal$	$-CO_2H$	N_2O_4**, biochemical oxidation	112,113
$-\overset{|}{C}H-Hal$	$-\overset{|}{C}O$	CrO_3 $Na_2Cr_2O_7$, Bu_4NOCl	112
$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}H-Hal$	$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}O$	$C_6H_{12}N_4$	110
$Ar\overset{|}{C}H-Hal$	$Ar\overset{|}{C}O$	CrO_3, Bu_4NOCl	112
		HNO_3	113,114

* Hal = Cl, Br, or I.
**N_2O_4 was also used to convert the groups $-CHF_2$ and $-CF_2I$ to $-CO_2H$.

Table 8

OXIDATION OF PRIMARY ALCOHOLS

Starting Compound	Product	Oxidants	Page
$-CH_2OH$	$-CHO$ *	Cu, CuO, $CuCr_2O_4$ O_2/Cu, Ag, Co_2O_3, Pt, PtO_2	114,115,123,126
$-C=C-CH_2OH$	$-C=C-CHO$ *	AgO, $(NH_4)_2Ce(NO_3)_6$ $Pb(OAc)_4$, N_2O_4	115,124,126, *283,284*
$ArCH_2OH$	$ArCHO$ *	CrO_3**, H_2CrO_4 $Na_2Cr_2O_7$, $K_2Cr_2O_7$ $(R_4N)_2CrO_4$	115-118,123-126
$ArC=C-CH_2OH$	$ArC=CCHO$ *	$(C_5H_5NH)_2Cr_2O_7$, $Ag_2Cr_2O_7$	
		CrO_2Cl_2, $(t\text{-}Bu)_2CrO_4$, KOCl t-BuOCl, NBS, NCS	119,123,125,125
		MnO_2, $KMnO_4$, $BaMnO_4$	119,120,124-126,*288*
		K_2FeO_4, NiO_2, RuO_4	120,125-127
		$C_6Cl_4O_2$, DDQ, $EtO_2CN{=}NCO_2Et$	120,125,126
		Me_2S + Cl_2 or NBS, DMSO	120-123,125,126,*293*
		$(PhSeO)_2O$, periodinane***	123,124,126
$-CH_2OH$	$-CO_2H$	O_2/Pt, PtO_2, electrolysis KOH, NaOH/Ag_2O, HNO_3	127,128,130,*281*
$-C=C-CH_2OH$	$-C=C-CO_2H$	CrO_3**, $ZnCr_2O_7$ $(t\text{-}Bu)_2CrO_4$, $(C_5H_5NH)_2Cr_2O_7$	128,130
$ArCH_2OH$	$ArCO_2H$ *	MnO_2, $NaMnO_4$, $KMnO_4$, $(CuMnO_4)_2$ Bu_4NMnO_4, NiO_2, Na_2RuO_4, K_2RuO_4	129,130
$ArC=C-CH_2OH$	$ArC=C-CO_2H$	biochemical oxidation	130
$-CH_2OH$	$-CO_2R$	MnO_2, NaCN	131
	$-CONH_2$	NiO_2, NH_3	132
$2-CH_2OH$	$-COOCH_2-$	$KHSO_5$, $Na_2Cr_2O_7$, $(t\text{-}Bu)_2CrO_4$ Br_2 + $NaBrO_3$, MnO_2	131

* In the preparations of the compounds marked with asterisks, more specific oxidants are shown in the text.

** CrO_3 includes its complexes such as $CrO_3 \cdot 2C_5H_5N$ and $C_5H_5NHCrO_3Cl$.

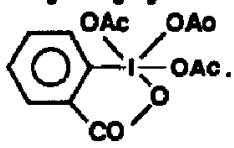
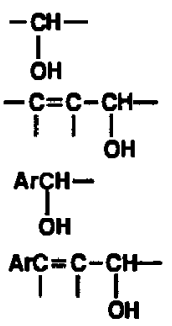
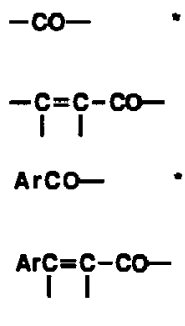
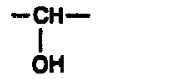
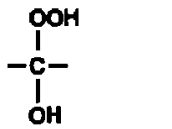
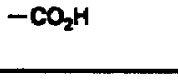
***Periodinane (Dess-Martin reagent) is 

Table 9

OXIDATION OF SECONDARY ALCOHOLS

Starting Compound	Product	Oxidants	Page
	 *	Cu, $CuCr_2O_4$, Raney Ni $O_2/h\nu$, O_2/Cu, Ag, Pd, Pt, PtO_2	132,133,147,149
		electrolysis, H_2O_2, $KHSO_5$, RCO_3H CuO, Ag_2O, Ag_2CO_3, AgO	133,147,148
		$(NH_4)_2Ce(NO_3)_6$, $Ce(SO_4)_2$ $Pb(OAc)_4$, N_2O_4	133,149
	*	CrO_3**, H_2CrO_4, $Na_2Cr_2O_7$, $K_2Cr_2O_7$ $ZnCr_2O_7$, $(Bu_4N)_2CrO_4$ Bu_4NHCrO_3Cl, CrO_2Cl_2	133,147-149 *283,284,285*
		Cl_2, Br_2, NaOCl, $Ca(OCl)_2$ Bu_4NOCl, t-BuOCl $NaBrO_2$, $NaBrO_3$	138-140,147-149
		MnO_2, $NaMnO_4$, $KMnO_4$, $BaMnO_4$ $(Bu_4N)MnO_4$	140-142,147-149,*290*
		K_2FeO_4, RuO_4, Na_2RuO_4, K_2RuO_4	142,148,149
		Oppenauer oxidation, DDQ	142-144,149,261
		$EtO_2CN{=}NCO_2Et$	144,149
		NCS, Me_2S + NCS, DMSO	144-146,147,148,*293*
		Ph_3CBF_4, $(PhSeO)_2O$	146-149
		biochemical oxidation	146,216
		$O_2/h\nu$	150
		HNO_3, CrO_3, $KMnO_4$	150,*289*

* In the preparation of the compounds marked with asterisks, more specific oxidants are shown in the text.
**CrO_3 includes all its complexes such as $CrO_3.2C_5H_5N$ and $C_5H_5NHCrO_3Cl$.

Table 10

OXIDATION OF TERTIARY ALCOHOLS

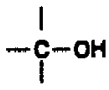
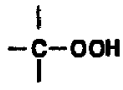
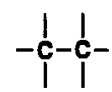
Starting Compound	Product	Oxidants	Page
		H_2O_2/H_2SO_4	150,151
	—CO—	$Pb(OAc)_4$, AcOI	151
	$-CO_2H$ + —CO—	CrO_3	151

Table 11

OXIDATION OF UNSATURATED ALCOHOLS AT DOUBLE BONDS

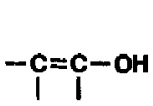
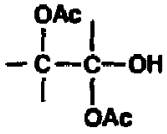
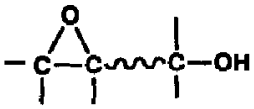
Starting Compound	Product	Oxidants	Page
		$Pb(OAc)_4$	151,152
		t-BuOOH, RCO_3H Sharpless reagent CrO_3, Na_2CrO_4	152-154

Table 12

SELECTIVE OXIDATION OF ALCOHOLS AND DIOLS

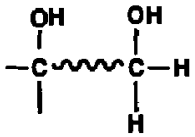
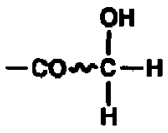
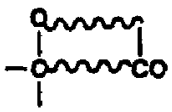
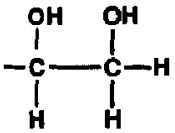
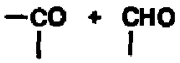
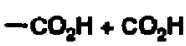
Starting Compound	Product	Oxidants	Page
		$Ce(SO_4)_2$,$(NH_4)_2Ce(NO_3)_6$ CrO_3, Cl_2, NaOCl, AcNHBr, $BaMnO_4$ Me_2S + Cl_2 or NCS, DDQ biochemical oxidation	155 *286*
		$CuCr_2O_4$, Ag_2CO_3	157-159
			
		$(NH_4)_2Ce(NO_3)_6$ $Pb(OAc)_4$ $NaBiO_3$, CrO_3, $K_2Cr_2O_7$ HIO_4, $NaIO_4$, KIO_4 MnO_2, $KMnO_4$ PhIO, $PhI(OAc)_2$, $PhIO_2$	159-162,*281* *286* *288*
		O_2/Co, electrolysis	163

Table 13

OXIDATION OF PHENOLS

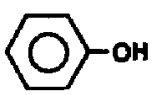
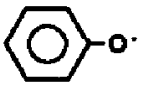
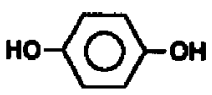
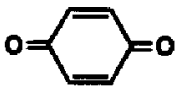
Starting Compound	Product	Oxidants	Page
		$K_2Cr_2O_7$, $FeCl_3$	163
		$K_3Fe(CN)_6$	163
		$K_2S_2O_8$	163,164
		HgO, $Hg(OCOCF_3)_2$, $(NH_4)_2Ce(NO_3)_6$ CrO_3, Br_2, DDQ $(KO_3S)_2NO^{\cdot}$, biochemical oxidation + H_2O_2	164,165
		Ag_2O, HgO, $(NH_4)_2Ce(NO_3)_6$ PbO_2, $Pb(OAc)_4$, N_2O_4, $Na_2Cr_2O_7$ $NaClO_3$, $NaIO_3$, $BaMnO_4$, $FeCl_3$ $Fe_2(SO_4)_3$	165-168 *290*
		RCO_3H	168

Table 14

OXIDATION OF ETHERS AND EPOXIDES

Starting Compound	Product	Oxidante	Page
$-CH_2O-$	$-CHO-$ (OOH)	O_2	168,159
	$-COO-$	O_3, CrO_3, $ZnCr_2O_7$ Br_2, $KMnO_4$, $Zn(MnO_4)_2$ $PhCH_2NEt_3MnO_4$, RuO_4	169,170
$-C=C-O-$	$-C(O)-C-O-$	RCO_3H	170
	$-C(-)-CO-O-$	HNO_3, $C_5H_5NHCrO_3Cl$	171
$-C=C-C-O-$	$-C(O)-C-C-O-$	RCO_3H	171
	$-C=C-CHO$	SeO_2	171,172
$-C\equiv C-O-$	$-CO-COO-$	PhIO	172
$-CH_2-OSi-$	$-CO-O-$	CrO_3, NBS/*hv*	172
$-CH-OSi-$	$-CO$	NBS	172
$-C=C-OSi-$	$-C(OH)-CO-$	O_2, RCO_3H, CrO_2Cl_2	172,173
$-C(O)-C-$	$-C(OOH)-C-OH$	H_2O_2	173,174
	$-CO-C(OH)-$	DMSO	173,174
	$-CO$ + $OC-$	HIO_4	173,174

Table 15

OXIDATION OF ALDEHYDES AND THEIR DERIVATIVES

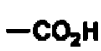
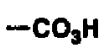
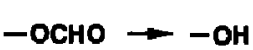
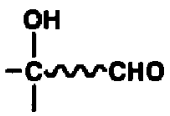
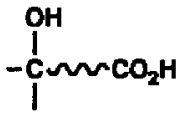
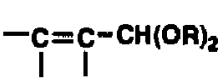
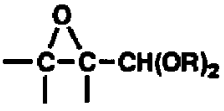
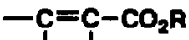
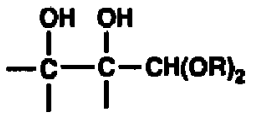
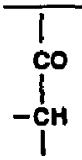
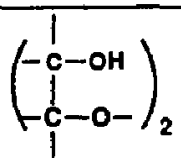
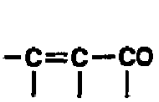
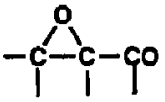
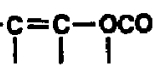
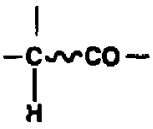
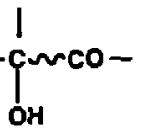
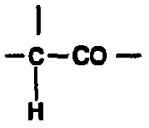
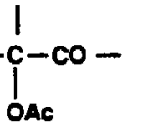
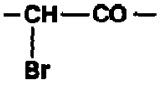
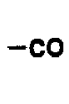
Starting Compound	Product	Oxidants	Page
		O_2, H_2O_2, ROOH, H_2SO_5, Ag_2O AgO, HNO_3, NaOH, KOH $K_2Cr_2O_7$, $NaClO_2$, MnO_2 $KMnO_4$, R_4NMnO_4, NiO_2, RuO_4 K_2RuO_4, DMSO, PhIO	174-180 *279* *285*
		O_2	180
		H_2O_2, RCO_3H	180,181
		H_2O_2, *t*-BuOOH	182
		O_2, Br_2	182,183
		$KMnO_4$, biochemical oxidation	182,183
		HNO_3	183,184
		O_3, RCO_3H	184,185
		RCO_3H	184,185
		RCO_3H	184,185
		$KMnO_4$	185

Table 16

OXIDATION OF KETONES AND THEIR DERIVATIVES

Starting Compound	Product	Oxidants	Page
		H_2O_2	186
–CO–	–COO– and/or –OCO–	H_2O_2/H^+, $(Me_3SiO)_2$, PhSe(O)OOH H_2SO_5, $KHSO_5$, RCO_3H $(NH_4)_2Ce(NO_3)_6$, biochemical oxidation	186-190 195,*279*
		H_2O_2, NaOCl	191,192,*285*
		$(Me_3SiO)_2$, RCO_3H	191,192 194,195
–CO–CO–	–CO–O–CO–	H_2O_2, H_2SO_5, RCO_3H	193,194
		CrO_2Cl_2, MoO_5, ArIO, biochemical oxidation	196-199
		$Pb(OAc)_4$	199
$-CH_2-CO-$	–CO–CO–	SeO_2, H_2SeO_3, CrO_3 RNO, DMSO	199,200,*283* 201,*292*
	–CO–CO–	RNO, DMSO	201,202,*293*
–CO–CH_3	$-CH_2-CO_2H$	$Tl(NO_3)_3$, $S/(NH_4)_2S$, S/HN⟨O⟩ CCl_4/KOH	202-206 *282*
	$-CO-CO_2H$	$KMnO_4$	206
	$-CO_2H$	HNO_3, $KMnO_4$, $Na_2Cr_2O_7$ NaOCl, KOCl, Cl_2/NaOH Br_2/NaOH, I_2/KOH, CCl_4/KOH	205-210 *286*
	$-CO_2H$ + –CO– or $-CO_2H$ + $-CO_2H$	O_2, KO_2, HNO_3, CrO_3, $KMnO_4$	211,212

Continued on next page

Table 16 (continued)

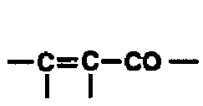
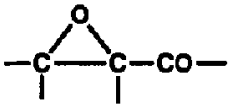
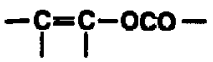
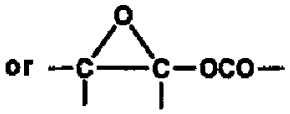
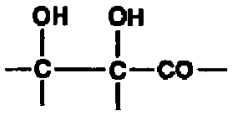
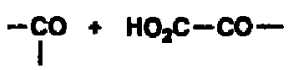
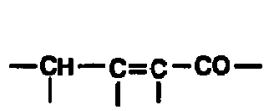
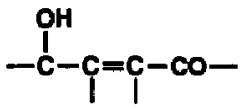
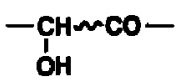
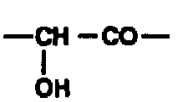
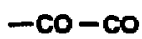
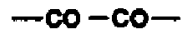
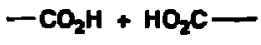
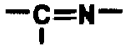
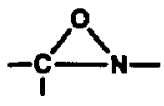
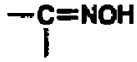
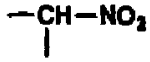
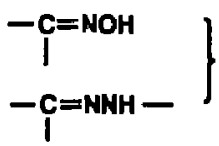
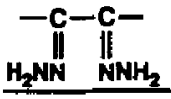
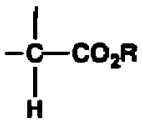
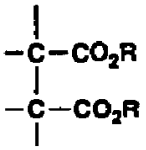
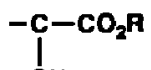
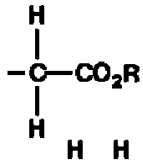
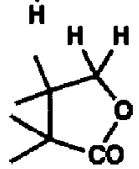
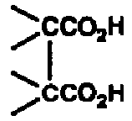
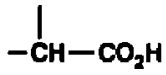
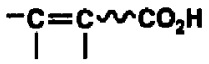
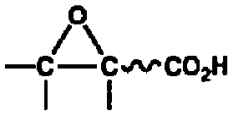
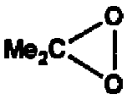
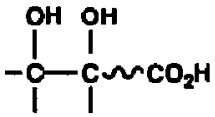
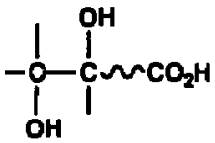
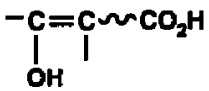
Starting Compound	Product	Oxidants	Page
		H_2O_2, t-BuOOH, RCO_3H, NaOCl $Ca(OCl)_2$, NBS	212-214
		RCO_3H	212-214
	or 		192
		OeO_4	214
		O_3	215
		biochemical oxidation	214
		CrO_3, DMSO, biochemical oxidation	215,216
		O_2, $CuSO_4$, $Cu(OAc)_2$, $(NH_4)_2Ce(NO_3)_6$ $NH_4NO_3/Cu(OAc)_2$, Bi_2O_3 $NaBrO_3$, biochemical oxidation	217,218 *282*
		RCO_3H	218,219
		RCO_3H	219
		MnO_2	219
		O_3, $(NH_4)_2Ce(NO_3)_6$, $ZnCr_2O_7$ $(PhSeO)_2O_2$, MoF_3, $MoOCl_3$, WF_6	219,220
		Ag_2O, HgO, $Pb(OAc)_4$, NiO_2	219-221,*280*
		HgO	221,222,*280*

Table 17

OXIDATION OF CARBOXYLIC ACIDS AND THEIR DERIVATIVES

Starting Compound	Product	Oxidants	Page
$-CO_2H$	$-CO_3H$	H_2O_2	222
		1. LDA*, 2. $FeCl_3$	223
		1. LDA*, 2. MoO_5; camphorylsulfonyloxaziridine; $PhI(OAc)_2$	223
	$-CO-CO_2R$	air, N_2O_3	223
		HNO_3, $KMnO_4$	224
	$-CHO$	Bu_4IO_4	224
$2-CH_2-CO_2H$	$-CH_2-CH_2-$	electrolysis	224,*276*
		H_2O_2, RCO_3H, NBS, 	224,225
		$KMnO_4$, OsO_4	225,226
		RCO_3H	225,226
		biochemical oxidation	225,226
	$-COCO\sim CO_2H$	$KMnO_4$	226

*LDA is lithium diisopropylamide.

Continued on next page

Table 17 (continued)

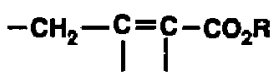
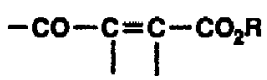
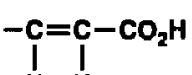
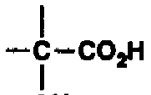
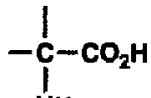
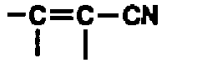
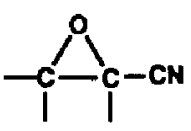
Starting Compound	Product	Oxidants	Page
		CrO_3	226
	—CHO	$KMnO_4$	226
	—CHO + HO_2CCO_2H	$KMnO_4/NaIO_4$	226,227
		$KMnO_4$	226,227
	—CO_2H + HO_2C	O_3/H_2O_2, RCO_3H	226,227
	—CO—CO_2H	Br_2, $KMnO_4$, RuO_4	227,228
	—CHO, —CO—	H_2O_2, R_4NIO_4, NBS, $Pb(OAc)_4$	228,229
	—CHO	NaOCl	229
	—CO_2H	H_2O_2, AgO	229
—CO—CO_2H	—CO_2H	H_2O_2	229
—CO—CO_2R	—CO—OCO_2R	RCO_3H	229
—$CONH_2$	—NCO	$Pb(OAc)_4$	230
—$CONHNH_2$	—CHO	$K_3Fe(CN)_6$	230
	—CO_2H	$(NH_4)_2Ce(NO_3)_6$	230
		H_2O_2	230

Table 18

OXIDATION OF NITROGEN COMPOUNDS

Starting Compound	Product	Oxidants	Page
$-\overset{\displaystyle NO_2}{\underset{\displaystyle |}{C}}H-$	—CHO, —CO—	$KMnO_4$	230,231
—NO	$-NO_2$	H_2O_2, RCO_3H, $K_2Cr_2O_7$	231
—NHOH	$-\overset{\displaystyle \cdot}{N}O$	Ag_2O	232
	—NO	Ag_2O, Ag_2CO_3, $Na_2Cr_2O_7$ $K_2Cr_2O_7$, MnO_2 $EtO_2CN{=}NCO_2Et$	231,232
$-N{=}N-$	$-N(\rightarrow O){=}N-$	RCO_3H	232
$-N_3$	$-NO_2$	1. Ph_3P, 2. O_3	232
—NH—NH—	$-N{=}N-$	air, Ag_2O, CuO, HNO_3, Br_2, NBS MnO_2, $EtO_2CN{=}NCO_2Et$ diphenylpicrylhydrazyl	233
$-NH_2$	$-N{=}N-$	O_2, $NaBO_3$, MnO_2 $BaMnO_4$, $AgMnO_4$ NiO_2	
	$-\overset{\displaystyle O}{\underset{\displaystyle |}{N}}{=}N-$	H_2O_2, RCO_3H	234
	—NO	H_2SO_5, $KHSO_5$, RCO_3H	235,*278*
	$-NO_2$	HBO_3, H_2SO_5, RCO_3H, $Me_2C\overset{O}{\underset{O}{<}}$, $KMnO_4$, biochemical oxidation	235,236
—NH—	$-\overset{\displaystyle OH}{\underset{\displaystyle |}{N}}-$	H_2O_2	236
$-\underset{\displaystyle |}{N}-$	$-\overset{\displaystyle O}{\underset{\displaystyle |}{N}}-$	H_2O_2, t-BuOOH, RCO_3H, $Me_2C\overset{O}{\underset{O}{<}}$	236-239 *277*
$-CH_2-NH_2$	$-CH{=}NH$ $\left(\rightarrow -CH{=}O\right)$	$Na_2S_2O_8$, NaOCl, $KMnO_4$, $BaMnO_4$ $Zn(MnO_4)_2$, K_2FeO_4, $CH_2O/C_6H_{12}N_4$ $NaNO_2$/DMSO	239,240
$-\underset{\displaystyle |}{CH}-NH_2$	$-\underset{\displaystyle |}{C}{=}NH$ $\left(\rightarrow -\underset{\displaystyle |}{C}{=}O\right)$	$Hg(OAc)_2$, MnO_2	240,241

Continued on next page

Table 18 (continued)

Starting Compound	Product	Oxidants	Page
$-CH_2-NH_2$	$-C\equiv N$	AgO, Co_2O_3, NiO_2, $Pb(OAc)_4$, NaOCl $K_3Fe(CN)_6$, K_2RuO_4	241,242
	$-CO_2H$	biochemical oxidation	242
$-CH-NH-$	$-C=N-$	$Hg(OAc)_2$, HNO_3, MnO_2	240,241
$-CH-N-$	$-C(OH)-N-$	biochemical oxidation	242,243
	$-CO-N-$	biochemical oxidation	242
$-CH_2N-$	$-CON-$	RCO_3H, MnO_2, $KMnO_4$, $K_3Fe(CN)_6$ $EtO_2CN{=}NCO_2Et$	242-244 *291*
	$-NH-$	$O_2/h\nu$, $Hg(OAc)_2$, MnO_2, $K_3Fe(CN)_6$	243
	$-CO-$	RO_3H, MnO_2	244
$-C=C-N-$	$-CO-CO-$	$O_2/h\nu$	244,245
$-C\equiv C-N-$	$-COCO-N-$	PhIO	245
$-CH-N-CO-$	$-CO-N-CO$	*t*-BuOOH, RCO_3H, RuO_4	244,245,*291*
NH_2	O=⟨⟩=O	Ag_2O, PbO_2, $Pb(OAc)_4$ $NaNO_2/H_2SO_4$, HNO_3 $Na_2Cr_2O_7$, $K_2Cr_2O_7$, NaOCl $FeCl_3$, $(KO_2S)_2NO^{\cdot}$	246-248,*292*

Table 19

OXIDATION OF COMPOUNDS OF PHOSPHORUS AND ARSENIC

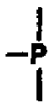
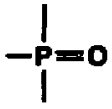
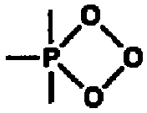
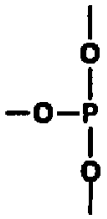
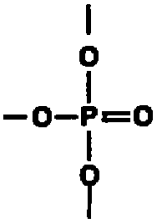
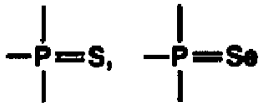
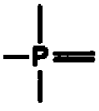
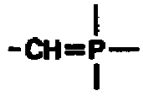
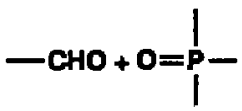
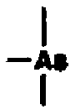
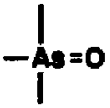
Starting Compound	Product	Oxidants	Page
		O_3, $KHSO_5$, AgO, MnO_2 $BaMnO_4$	248,249
		O_3	2
		O_3, H_2O_2, $(Me_3SiO)_2$ ROOH, AgO, R_3NO	248,249
		O_3, DMSO	249,250
		$NaIO_4$	250
		H_2O_2	250

Table 20

OXIDATION OF COMPOUNDS OF SULFUR AND SELENIUM

Starting Compound	Product	Oxidants	Page
—SH	—S—S—	air, H_2O_2, $(R_4N)_2Cr_2O_7$	250-252
		R_4NCrO_3Cl, MnO_2, $Cu(MnO_4)_2$	
		$FeCl_3$, $EtO_2CN{=}NCO_2Et$	252,*290*
	$-SO_2H$	H_2O_2	251,252
	$-SO_3H$	O_2, $KHSO_5$, HNO_3	252
	$-SO_2Cl$	Cl_2/H_2O	
—SCN, —S—C(=NH)—NH$_2$	$-SO_2Cl$	Cl_2, H_2O	252
—S—	—S(=O)—	H_2O_2, $NaBO_3$, $KHSO_5$, $(R_4N)_2S_2O_8$	253-259
		t-BuOOH, Me_2C(O)O, RCO_3H	261
		$(NH_4)_2Ce(NO_3)_6$, N_2O_4, HNO_3, SO_2Cl_2	*281*
		H_2CrO_4, *t*-BuOCl	
		$NaBrO_2$, $NaIO_4$, R_4NIO_4	*287,288*
		MnO_2, ArIO, $ArI(OAc)_2$, $EtO_2CN{=}NCO_2Et$	257,258
		Sharpless reagent, biochemical oxidation	*278,294*
	—S(=O)(=O)—	H_2O_2, $NaBO_3$, $KHSO_5$, $(R_4N)_2S_2O_8$, RCO_3H	253-257
		NaOCl, RuO_4	261,*278*
—C(SR)$_2$	—C(=O)(SR)$_2$	H_2O_2, RCO_3H, $NaIO_4$	259,260
	—C(=O)(=O)(SR)$_2$	H_2O_2, RCO_3H, $KMnO_4$	260
—S(=O)—	—S(=O)(=O)—	air, $NaMnO_4$, OsO_4/R_3NO	262

Table 20 (continued)

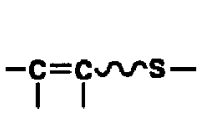
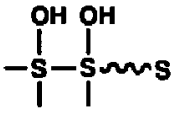
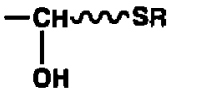
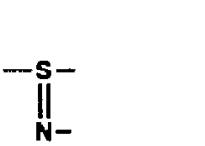
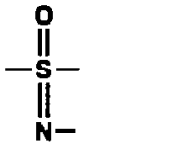
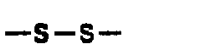
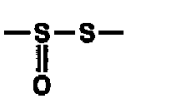
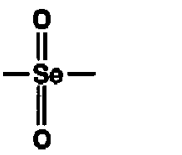
Starting Compound	Product	Oxidants	Page
		OsO_4/R_3NO	262
		CCl_3CHO/Al_2O_3	261
		R_4NOCl	262,263
		RCO_3H	263
	—SOCl	Cl_2/Ac_2O	264
	$—SO_3H$	O_2, H_2SO_5	264
	$—SO_2Cl$	Cl_2/H_2O	264
$—SO_2H$	$—SO_3H$	KOCl, $NaMnO_4$	264
—Se—		H_2O_2, RCO_3H, t-BuOCl $NaIO_4$, $ArICl_2$, biochemical oxidation	265,266
		RCO_3H, $KMnO_4$	265

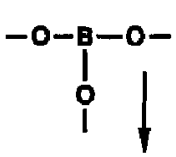
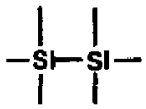
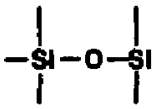
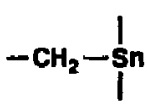
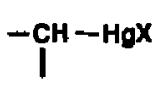
Table 21

OXIDATION OF IODO COMPOUNDS

Starting Compound	Product	Oxidants	Page
—I	—IO	RCO_3H, HNO_3	266,267
	$—IO_2$	$KHSO_5$, $K_2S_2O_8$, RCO_3H $KBrO_3$, $KMnO_4$	266,267

Table 22

OXIDATION OF BORON, SILICON, TIN, MAGNESIUM, AND MERCURY COMPOUNDS

Starting Compound	Product	Oxidants	Page
R_3B			267-270
	3 R-OH + H_3BO_3	H_2O_2, R_3NO biochemical oxidation	277
		RCO_3H	270
	$—CH_2OH$ ($—CH_2OAc$)	$Pb(OAc)_4$	270
—R—MgBr	ROH	BzO_2OCMe_3	271
		O_3	271

ABBREVIATIONS AND GENERIC NAMES

$[\alpha]_D^t$	specific rotation for the D line of sodium light at temperature t (°C)
Amberlyst	ion-exchange macroreticular resin suitable for aqueous or nonaqueous catalysis
bp	boiling point
c	concentration in grams per 100 ml
Carbitol	2-(2-ethoxyethoxy)ethanol or diethylene glycol monoethyl ether
Celite	silicon dioxide (95% SiO_2), diatomaceous earth, infusorial earth, siliceous earth, or kieselguhr
Cellosolve	2-ethoxyethanol
d	density
d^{18}	density (specific gravity) at 18 °C
d_{20}^{20}	density (specific gravity) at 20 °C related to the density of water at 20 °C
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
dec	with decomposition
Diglyme	bis(2-methoxyethyl)ether or diethylene glycol dimethyl ether
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Enz-FAD	enzyme–flavin adenine dinucleotide
Florisil	activated magnesium silicate
HMPA	hexamethylphosphoramide or hexamethylphosphoric triamide
LDA	lithium diisopropylamide
Monoglyme	ethylene glycol dimethyl ether or 1,2-dimethoxyethane
mp	melting point
n_D^{20}	refractive index for the D line of sodium light at 20 °C
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NBA	*N*-bromoacetamide

NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
PCC	pyridinium chlorochromate
rpm	revolutions per minute
RT	room temperature
THF	tetrahydrofuran
Tos	*p*-methylbenzenesulfonyl, *p*-toluenesulfonyl, or tosyl

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