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Metal-catalysed Oxidation of Organic Compounds by Hydroperoxides

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Information on the oxidation of various alkenes by hydroperoxides, as well as that of nitrogen- and sulphur-containing compounds, is summarised. Aspects of the catalysis of such oxidations are considered, and their mechanism and stereochemistry are discussed. A list of 166 references is included.

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I. INTRODUCTION

The oxidising properties of hydroperoxides have long attracted the attention of research workers. Their great reactivity promises the development of highly effective methods of preparative organic chemistry and potentially successful industrial processes. We shall not attempt to survey all the reactions of hydroperoxides, especially in view of the vastness of the literature on this subject [1-7]: we shall restrict our discussion to reactions of various organic compounds with hydroperoxides in the presence of metals to yield oxidised products. Attention will be paid only to work published during the past 5–8 years. In particular, Section II will give a detailed account of the oxidation of alkenes by hydroperoxides in the presence of metals to give α-oxides, alcohols, ketones, and other oxygen-containing compounds. The mechanism and the stereochemistry of the hydroperoxide epoxidation of alkenes will be discussed.

The rest of the Review will examine hydroperoxide oxidation as an extremely promising method of organic chemistry. A reagent comprising a hydroperoxide with a metal salt resembles a peroxy-acid in its mode of action, but also exhibits several interesting novel features. Oxidations of the peroxy-acid type include the epoxidation of enol ethers, the *N*-oxidation of amines, the formation of oxaziridines from azomethines, and the oxidation of organosulphur compounds. Among reactions of a second type are the direct formation of α-hydroxyketones from alkenes, the oxidation of alcohols and quinols, the dehydrogenation of 1,4-dihydropyridines, and others.

II. EPOXIDATION OF ALKENES BY HYDROPEROXIDES CATALYSED BY METALS

1. History

Hawkins [8] discovered in 1950 that cyclohexene oxide was obtained when the cycloalkene was treated with cumenyl hydroperoxide in benzene solution in the presence of vanadium pentoxide. Under the same conditions oct-1-ene was converted into 1,2-epoxyoctane. However, the yields of the oxides were low. Their formation was explained by the addition of $RO_2^{\bullet}$ radicals at the double bond [9].

Investigation of the thermal breakdown of hydroperoxides in solutions of alkenes established [10,11] that the yields of the oxides were independent of the structure of the alkene. The effective activation energy of the reaction of oct-1-ene with t-butyl hydroperoxide was 30 kcal mole^{-1}, from which it was concluded that the reaction had a polar mechanism.

A little later the same workers [12], studying the epoxidation of oct-1-ene, 4-vinylcyclohexene, oct-2-ene, and 2,2,4-trimethylpent-1-ene by t-pentyl hydroperoxide in the presence of metal acetylacetonates, found that the highest yields of α-oxides could be obtained if the reaction were catalysed by the acetylacetonates of vanadium, molybdenum, and chromium. Significantly, the cobalt, copper, and manganese complexes were far less active. Aluminium, iron, nickel, titanium, zinc, magnesium, and zirconium acetylacetonates decompose the hydroperoxide completely, with no formation of α-oxides.

The above work formed a starting point for researches by Halcon International Inc. [13], who patented the production of α-oxides by oxidising alkenes with hydroperoxides in the presence of compounds of molybdenum, vanadium, tungsten, titanium, zirconium, tantalum, and other metals.

2. Catalysts

Compounds of molybdenum, vanadium, tungsten, and chromium are recognised to be the best catalysts for epoxidation, but even among these metals differences in activity are clearly evident. Table 1 shows the dependence on the type of catalyst of the rate and extent of the epoxidation of 2-methylpent-2-ene by cumenyl hydroperoxide [14]. The most active catalysts are hydrocarbon-soluble compounds of molybdenum, e.g. the octanoate, naphthenate [15], di-t-butylbenzoate [16], molybdic esters [17,18], and also the tetra- and para-molybdenates of pyridine and piperidine [19]. A porous ceramic obtained by sintering the oxides—alumina, silica, and molybdenum sesquioxide—has been patented as a catalyst [20]. Metallic molybdenum

can serve as catalyst when it forms the walls of the reaction vessel [21,22]. Molybdenum compounds including other active elements, e.g. heteropolyacids [23], cobalt molybdate [24], etc., have given good results.

Table 1. Epoxidation of 2-methylpent-2-ene by cumenyl hydroperoxide.

Catalyst	Time, min	Yield of oxide, %
None	930	29
$NaMoO_3$	930	70
$NaVO_3$	930	52
MoO_2	90	88
$NaSiMo_{12}O_{40}+NaMoO_3$	45	85
$MoO_2(C_5H_7O_2)_2$	45	86
$VO(C_5H_7O_2)_2$	60	75

Some patents, however, must be approached with caution. In particular, the statement that a mixture of molybdenum and nickel acetylacetonates must be used for successful epoxidation, as these catalysts are inactive when used separately [25], does not correspond to reality. Molybdenum, while more active than vanadium in the oxidation of alkenes, retreats to second place as catalyst for the epoxidation of allyl alcohols, where vanadium compounds are most active [26].

With regard to other catalysts, mention may be made of patents describing the use of compounds of tungsten [27,28] as well as of titanium, chromium, niobium, zirconium, tellurium, rhenium, and other elements [29]. It is extremely interesting that boric esters catalyse the reactions [30,31] with metaborates the most active [32]. A recent paper [33] has described the use of carbonyl and phosphine complexes of rhodium, ruthenium, and iridium as catalysts.

Table 2. Effect of solvent on oxidation of oct-1-ene.

Solvent	Conversion of t-BHP*, %	Yield of oxide, %
Ethyl acetate	100	89.3
Di-isopropyl ketone	98.7	88.0
Acetophenone	98.6	67.8
Benzene	99	63
Methanol	69.6	42.4
Acetone	50.4	23.8
Dioxan	29.6	21.2

*t-BHP = t-butyl hydroperoxide.

3. Solvents

A hydrocarbon or a tertiary alcohol is generally used as solvent for epoxidation. Primary alcohols and ketones inhibit oxidation [14]. As illustration Table 2 lists results obtained for the epoxidation of oct-1-ene by t-butyl hydroperoxide [in various solvents] in the presence of sodium molybdophosphate.

The percentage conversions of ethylbenzene hydroperoxide in the oxidation of propene varies [35] in different solvents—ethylbenzene 99, 2-phenylpropanol 98.8, methanol 54.7, ethanol 62.8, propan-1-ol 67.8, n-butanol 78.0, and n-octanol 87.5.

Thus the successful choice of solvent depends on the specific conditions and should take into account the structure of the alkene and the hydroperoxide, together with the type of catalyst.

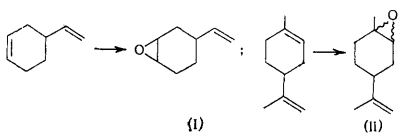
4. Effect of Structure of the Alkene and of the Hydroperoxide

Investigations on epoxidation have been reported mainly in patents and have been concerned with relatively simple alkenes. Only during the past three or four years have papers begun to appear in journals. The rate of epoxidation increases with the number of electron-donor substituents adjacent to the double bond. Table 3 illustrates the dependence of rate of oxidation on degree of branching of the alkene [14,34]. Both structural and geometrical isomers differ in reactivity. Thus the relative reactivities of *cis*-but-2-ene, *trans*-but-2-ene, and but-1-ene are 36.6, 14.2, and 1.0. [35,36]

Table 3. Oxidation of alkenes by t-butyl hydroperoxide.

Alkene	Yield of oxide, %
$C_9H_7-C(CH_3)=CH_2$	63.2
$C_9H_{11}-CH=CH-CH_3$	72.7
	76
$(CH_3)_2C=CH-CH_3$	80.5

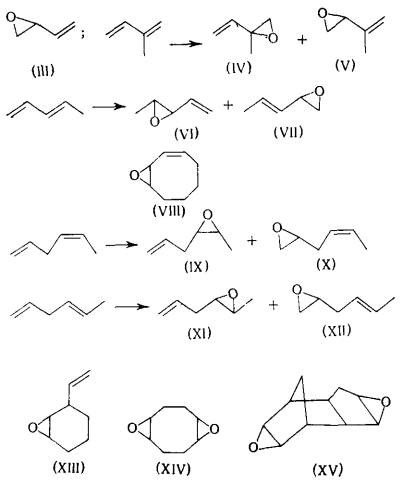
A cyclic double bond usually reacts more readily, as is shown by the epoxidation of alkenylcyclohexenes. Thus 4-vinylcyclohexene gives the theoretical yield of 1,2-epoxy-4-vinylcyclohexane (I) when oxidised with t-butyl [34], t-pentyl, or cumenyl [37] hydroperoxide. Under the same conditions *p*-mentha-1,8-dienes give the monoxides (II). [38]



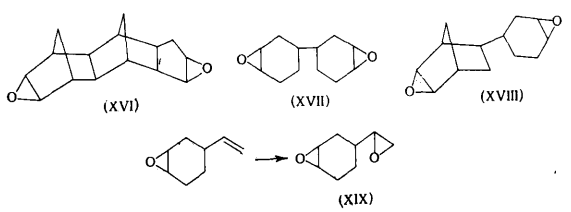
(I) (II)

Examination of the oxidation of dienes has established several empirical rules linking the completeness of oxidation with the structure of the alkene. Conjugated dienes form only monoxides [26]. Thus butadiene gives (III), [26,29] while isoprene and penta-1,3-diene form mixtures of structural isomers (IV)–(VII). [26,40] A monoxide (VIII) has been reported from cyclo-octa-1,3-diene [34]. Aliphatic 1,4-dienes, e.g. *cis*- and *trans*-hexa-1,4-dienes, are able to give only isomeric monoxides (IX)–(XII). A dioxide

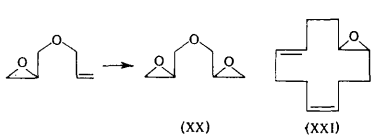
could not be obtained from 3-vinylcyclohexene, since reaction ceases at the monoxide (XIII) stage.



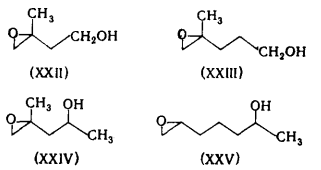
However, 1,5-dialkenes are able in most cases to react with two moles of a hydroperoxide. Cyclo-octa-1,5-diene, for example, is converted into the dioxide (XIV) by t-butyl hydroperoxide in the presence of trisodium dodecamolybdophosphate or tetrasodium dodecamolybdosilicate. The farther apart are the double bonds, the more complete is the epoxidation. This is well illustrated by bi- and tercyclopentadienes, bi(cyclohexenyl), and cyclohexenylnorbornene, which give the dioxides (XV)–(XVIII) in almost quantitative yields when oxidised by t-pentyl hydroperoxide in the presence of molybdenum pentachloride[41]. 4-Vinylcyclohexene dioxide (XIX) cannot be obtained by the direct reaction of two moles of the hydroperoxide with one mole of the diene, since the process is completely inhibited after formation of the monoxide. However, epoxidation of the latter, freed by distillation from inhibiting impurities, will give a satisfactory yield of the dioxide. The same procedure was used to obtain the dioxide of diallyl ether (XX).[26]



The oxidation of trienes by hydroperoxides has not been investigated systematically. It is known merely that *cis,trans,trans*-1,5,9-cyclododecatriene forms a monoxide (XXI).[42]



Smooth progress of the reaction is not prevented by polar groups and heteroatoms sufficiently remote from the double bond. Thus oxides of unsaturated alcohols



have been obtained by the action of t-butyl hydroperoxide in the presence of hexacarbonylmolybdenum. The best catalysts for the oxidation of allyl alcohols were vanadium compounds, but satisfactory yields of oxides can be obtained also with molybdenum catalysts (Table 4)[26]. Allylic diols are oxidised quite smoothly[26] to the oxides

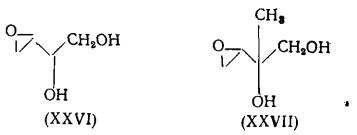


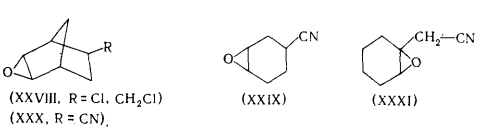
Table 4. Oxidation of allyl alcohols and ethers.

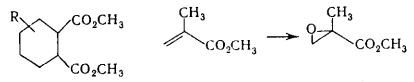
Compound*	Catalyst	Temp., °C	Time, min	Conversion of t-BHP, %	Yield of oxide, %
ROH	$Mo(CO)_6$	100	60	100	70
ROH	$V(C_5H_7O_2)_3$	100	25	92	93
$CH_2=C(CH_3)CH_2OH$	$V(C_5H_7O_2)_3$	80	30	97	100
$CH_2=C(CH_3)CH_2OH$	$Mo(CO)_6$	80	30	82	69
ROEt	$Mo(CO)_6$	95	120	73	77
R_2O	$Mo(CO)_6$	95	120	89	85
R_2O	$Mo(CO)_6$	100	180	88	58

*R = $CH_2:CH.CH_2$–.

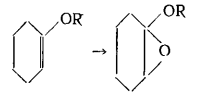
Oxidation of chlorine-containing alkenes gives yields of oxides depending on the position of the chlorine atom relative to the double bond. Thus allyl and methylallyl chlorides are converted into α-oxides in moderate yield. *trans*-1,4-Dichlorobut-2-ene is oxidised with great difficulty to give a 20% yield of the oxide[26]. However, 2-chloro- and 2-chloromethyl-norbornenes form the oxides (XXVIII) in high yield[43].

Epoxidation is not appreciably impeded by the presence of a nitrile group sufficiently remote from the double bond. In t-butyl alcohol solution at 80°C, for example, 4-cyanocyclohexene is oxidised by t-butyl hydroperoxide to give an 89% yield of the oxide (XXIX).[44] 2-Cyanonorbornene is oxidised smoothly to the oxide (XXX), and cyanomethylcyclohexene is converted not quite so well into (XXXI). Acrylonitrile is not epoxidised at all[26].





(XXXII, R = H, Me) (XXXIII)



R = Et, $COCH_3$ (XXXIV)

Few data are yet available on the epoxidation of unsaturated acids and their derivatives. However, quantitative yields of derivatives of cyclohex-4-ene-1,2-dicarboxylic acid (XXXII) have been obtained by means of t-pentyl hydroperoxide in the presence of molybdenum pentachloride or hexacarbonylmolybdenum [39,45]. A process for the epoxidation of vegetable oils has been patented, but details are not reported [46].

Mention must be made of the formation of methyl epoxymethylpropionate (XXXIII) from methyl methacrylate [26], an observation of fundamental importance, since it indicates the powerful oxidising properties of a reagent comprising a hydrogen peroxide and a molybdenum salt. Incidentally, ordinary peroxy-acids do not oxidise esters of $\alpha\beta$-unsaturated acids: only such strong oxidants as trifluoroperacetic and *m*-chloroperbenzoic acids are sufficiently reactive.

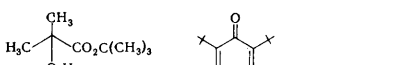
Enol ethers give high yields of oxides. Thus ethoxycyclohexene and cyclohex-1-enyl acetate are converted into the oxides (XXXIV). [47]

The influence of the structure of the hydroperoxide on the rate and the completeness of the epoxidation of alkenes has been less fully studied. Thus alkylated aromatic hydroperoxides have exhibited high activity in the epoxidation of oct-2-ene in benzene solution catalysed by hexacarbonylmolybdenum [14]. In particular, the percentage conversion of *p*-nitrocumenyl, cumenyl, and t-butyl hydroperoxides was respectively 83, 60, and 54. Hence an electron-accepting substituent in the benzene ring tends to increase the rate of oxidation.

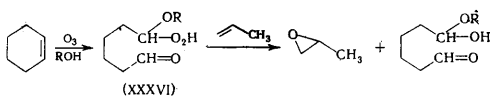
The relative reactivities of ethylbenzene, t-butyl, and cumenyl hydroperoxides in the epoxidation of propene have been given [48] as 2.4 : 1.3 : 1. t-Butyl α-hydroperoxy-α-methylpropionate (XXXV), obtained by oxidising t-butyl isobutyrate [49], is an excellent reagent for obtaining methyloxiran [50]: in the presence of molybdenum and sodium naphthenates the yield of the oxide is 78–84%.

Application of the hydroperoxides of ionol (XXXVa), di-isopropyl ketone, and tetralin has been patented [34], but their activities were not compared.

It has recently been established that smooth epoxidation of propene and cyclohexene is accomplished by means of alkoxy-ω-formylalkyl hydroperoxides (XXXVI), which are formed when cyclohexene is ozonised in solutions of primary alcohols [51].

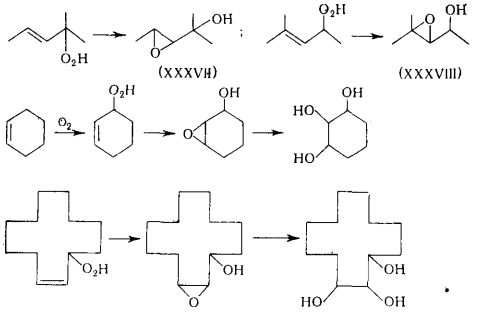


(XXXV) (XXXVa)



(XXXVI)

An interesting variety of hydroperoxide oxidation is based on the principle of the "self-epoxidation" of alkenyl hydroperoxides. In particular, the epoxyalkanols (XXXVII) and (XXXVIII) have been obtained from the hydroperoxides of 4- and 2-methylpent-2-enes:



(XXXVII) (XXXVIII)

The best catalysts for the process are compounds of tungsten [52] and vanadium [53]. Processes for obtaining cyclohexanetriols and cyclododecanetriols (above) have been based on the same principle [54,55].

5. Mechanism and Stereochemistry

Kinetic aspects of epoxidation have recently been surveyed quite fully [56]. Certain fundamental principles may be recalled here to provide a link with the above discussion. Over the range of cyclohexene concentrations 0.087–1.79 M reaction with t-butyl hydroperoxide in the presence of molybdenum acetylacetonate is initially first order with respect to the substrate and the hydroperoxide [57]. In contrast to earlier work [12] the first order with respect to the catalyst was established. Over the temperature range 24–51 °C the activation functions are $\Delta H = 12.7 \pm 0.4$ kcal mole^{-1} and $\Delta S = -19.8 \pm 1.9$ e.u. The Michaelis–Menten equation has been applied [58,59] to the initial stages of formation of an α-oxide on the basis of the considerable analogy with enzymic catalysis.

Epoxidation has been considered [57-60] to comprise the stages—(1) oxidation of the metal by the hydroperoxide to a higher (most probably the highest) valency with an increase in the number of vacant 4*d* orbitals, (2) coordination of the hydroperoxide with the catalyst involving a lone pair of electrons on an oxygen atom in the hydroperoxide and 4*d* orbitals of the metal, (3) weakening of the oxygen–oxygen bond with migration of electron density to the metal as a result of coordination, the enhancement of the electrophilic character of the hydroperoxide facilitating rupture of this bond as a result of nucleophilic attack on the alkene, (4) redistribution of the proton, (5) exchange of ligands, and (6) competitive inhibition due to the formation of catalytically inactive molybdenum–inhibitor complexes.

Epoxidation is inhibited by water, ketones, and alcohols. In particular, the inhibiting effect falls in the sequence—water, 1-phenylethanol, t-butyl alcohol, 2-phenylpropan-2-ol—and is greater the greater the stability of the molybdenum–inhibitor complex, which is determined by the nature of the inhibitor as ligand. More highly polar alcohols form more stable complexes, a relation which has been expressed quantitatively: for aliphatic alcohols the polar Taft factors σ^* were found to correlate with the dissociation constants of the complexes (Scheme 1). Thus there is no doubt about the electrophilic character of the

reaction. This conclusion was supported by a kinetic investigation of the oxidation of *para*- and *meta*-substituted styrenes, which showed that the rate-determining stage was electrophilic attack on the alkene (Table 5). This is indicated by the negative value of the constant $\rho = 1.4 \pm 0.6$.[59]

Scheme 1

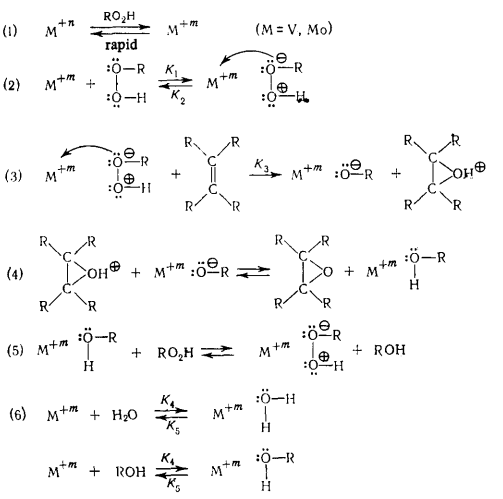
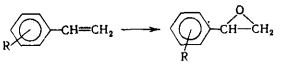


Table 5. Rate constants of the oxidation of *meta*- and *para*-substituted styrenes by t-butyl hydroperoxide

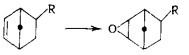


Substituent R	H	*m*-Cl	*p*-Cl	*m*-Br	*p*-Br	*m*-NO_2	*p*-CH_3
10^4 x rate constant, M^{-1} min^{-1}	26.7	21.8	30.5	26.1	31.0	3.10	89.6

The present Reviewers had found that the initial rates of oxidation by t-pentyl hydroperoxide of a series of norbornene derivatives in the presence of molybdenum pentachloride varied with the electronegativity of the 6-substituent. Table 6 shows that compounds having electron-donating substituents show higher initial rates of oxidation, whereas electron-accepting substituents lower the rate[43].

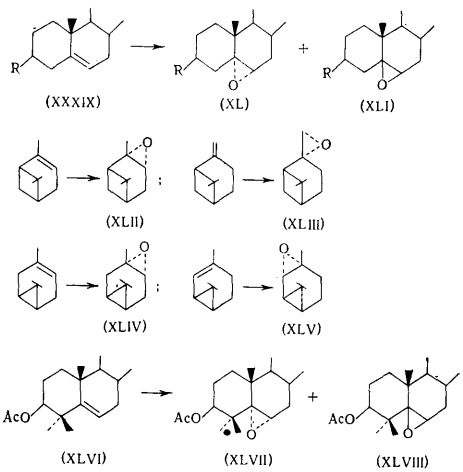
The activation energy of epoxidation can vary with the structure of the alkene and the hydroperoxide, as well as with the type of catalyst. Thus the oxidation of propene by ethylbenzene, t-butyl, and cumenyl hydroperoxides has effective activation energies of 15–15.5 kcal $mole^{-1}$,[48] but the corresponding value for the reaction between 2-methylpent-2-ene and cumenyl hydroperoxide is 23.8 kcal $mole^{-1}$.[60] The very low activation energy of 5.6 ± 0.5 kcal $mole^{-1}$ was found[43] for the reaction between norbornene and t-pentyl hydroperoxide in the presence of molybdenum(V) chloride. Introduction of an electron-accepting group into the hydroperoxide lowers the effective activation energy; in particular, a value of 11.7 ± 0.5 kcal $mole^{-1}$ was obtained[49] for the oxidation of propene by t-butyl α-hydroperoxy-α-methylpropionate [(XXXV)]. The catalyst may cause very marked changes in activation energy. In the oxidation of oct-1-ene by t-butyl hydroperoxide, for example, use of different metal acetylacetonates gave the values (in kcal $mole^{-1}$)—Cr^{III} 23, VO^{II} 15, MoO_2 12, and V^{III} 9.[12] Aspects of the mechanism of hydroperoxide epoxidation are discussed also in several other papers[61–63].

Table 6. Rates of oxidation of 6-substituted norbornene derivatives by t-pentyl hydroperoxide



Substituent R	H	CH_3	OH	OAc	*endo*-CN	*exo*-CN	CH_2OH	CH_2OAc	CO_2CH_3	Cl
$10^7 W$, $M\,s^{-1}$	35	116	7	6	9	8	23	5	2	15

An all-round assessment of a reagent is unthinkable without examination of the stereochemistry of its reactions. Among epoxidising agents the stereochemistry of epoxidation by peroxy-acids has been most widely investigated. It has been reliably established that peroxy-acids attack an alkene mainly on the less shielded side. The configuration of the resulting oxide coincides with the direction of attack by the reagent. These principles can be seen especially clearly with cyclic alkenes, such as steroids, terpenes, etc. For example, the epoxidation of Δ^5-steroids (XXXIX) by peroxy-acids produces a mixture of oxides in which the 5α,6α-isomer (XL) predominates[64,65]. Relatively slight shielding of the double bond permits the peroxy-acid to approach the opposite side also, with formation of the 5β,6β-oxide (XLI). Until recently almost nothing was known of the stereochemistry of epoxidation by hydroperoxides. It has been reported only that *cis*- and *trans*-but-2-enes formed the corresponding oxides[14].

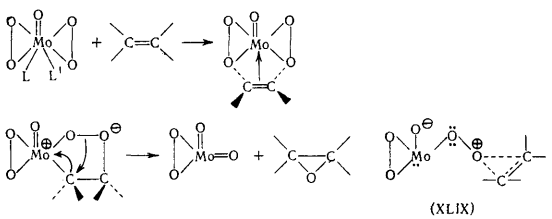


The present Reviewers investigated the stereochemistry of the epoxidation of certain steroids and terpenes[38,66], and established that it depends both on steric factors and on the presence of complexing groups in the reactant molecule. In the oxidation of unsaturated cyclic hydrocarbons and alkenes not containing these groups near the double bond

the stereospecificity of epoxidation by t-pentyl hydrogen peroxide is limited only by steric factors. Thus epoxidation of Δ^5-steroids (XXXIX: R = H, Cl, OH) occurs mainly by attack by the reagent at the less shielded α-side, which as in the experiments with peroxy-acids leads to predominance of the 5α,6α-oxides (XL) in the mixture of epimers. The bicyclic hydrocarbons—pin-2-ene, pin-2(10)-ene, car-2-ene, and car-3-ene—have such effective shielding of the double bond that, when oxidised with t-pentyl hydroperoxide in the presence of molybdenum pentachloride, only the oxides (XLII)–(XLV) are formed, whose configuration coincides with the direction of attack by the reagent. The same oxides were obtained by oxidising these monoterpenes with perbenzoic acid [66-70].

Thus epoxidation by a hydroperoxide involves a stage in which the double bond is attacked by a "molybdenum–hydroperoxide" complex, whose size governs control of the reaction solely by steric factors. This stage, it seems to us, can be modelled on the oxidation of cycloalkenes by the molybdenum pentoxide–hexamethylphosphoramide MoO_5.HMPA complex [71]. This reagent quantitatively epoxidises Δ^5-steroids (XXXIX: R = H, Cl, OH, OCOCH), to form the almost pure 5α,6α-oxides [72,73]. The above monoterpenes undergo stereospecific oxidation, being converted by this complex into the oxides (XLII)–(XLV). [74] Epoxidation by this reagent is evidently still more strictly controlled by steric factors, which follows also from experiments on 3β-acetoxy-4,4-dimethylsteroids (XLVI), also not oxidised by the reagent owing to steric hindrance by the geminal methyl groups. Hydroperoxides in the presence of molybdenum pentachloride or hexacarbonylmolybdenum are also unable to oxidise compounds of type (XLVI), whereas perbenzoic acid reacts quite readily to give a mixture of the 5α,6α- and 5β,6β-oxides (XLVII) and (XLVIII) in the proportions 82 : 18 [Table 7].

The highly stereospecific action of the MoO_5.HMPA reagent is an important argument, in the opinion of the Reviewers, for interpreting the mechanism of epoxidation as ambipolar 1,3-addition [75]. In any case, it is difficult to accept the possibility of completely stereoselective oxidation if the recently suggested [76] scheme



(XLIX)

involving a three-membered transition state (XLIX), is adopted. Anomalous results were obtained when Δ^5-steroids having oxygen-containing groups attached to $C_{(3)}$ were oxidised with t-pentyl hydroperoxide in the presence of molybdenum pentachloride (or hexacarbonylmolybdenum). Thus 3β-acetoxy-Δ^5-steroids (L) were converted mainly (55–80%) into 5β,6β-oxides. Owing to conformational distortions of rings A and B the double bond in 3-ethylenedioxy-Δ^5-steroids (LI) is accessible to attack on the β-side. Oxidation by perbenzoic acid therefore yields mainly the 5β,6β-oxides (proportions of 5α,6α- and 5β,6β-oxides 35 : 65). The ethylene acetal (LI) undergoes completely stereospecific β-epoxidation both with t-pentyl hydroperoxide in the presence of molybdenum pentachloride and with the peroxide complex MoO_5.HMPA: both reagents give the pure 5β,6β-oxides (LII).

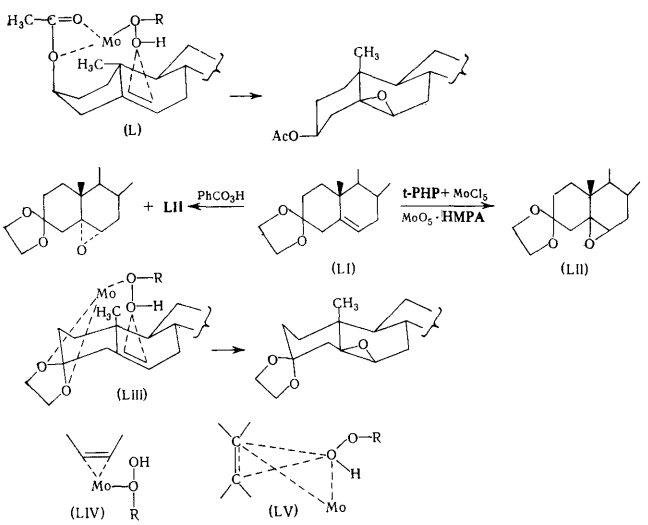


Table 7. Composition of mixtures of 5,6-oxides obtained by the epoxidation of Δ^5-steroids.

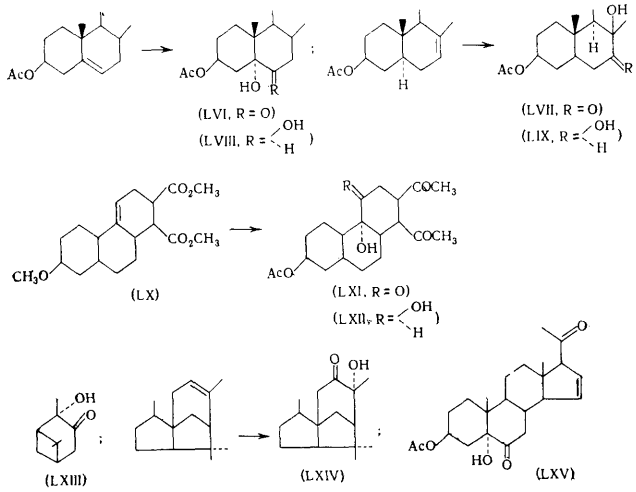
Δ^5-Steroid	Oxidising agent					
	C_6H_5COOH		t-PHP + Mo		MoO_5 + HMPA	
	5α, 6α	5β, 6β	5α, 6α	5β, 6β	5α, 6α	5β, 6β
3β-Acetoxyandrost-5-en-17-one	65	35	20	80	100	0
3β-Acetoxycholest-5-ene	70	30	45	55	80	20
3β-Acetoxyspirost-5-ene	65	35	35	65	95	5
3β-Acetoxypregna-5,16-dien-20-one	65	35	35	65	90	10
3β-Acetoxy-4,4-dimethylcholest-5-ene	82	18	no reaction takes place			
Cholest-5-ene	90	10	55	45	100	0
3α-Chlorocholest-5-ene	85	15	60	40	95	5
Cholest-5-en-3β-ol	90	10	70	30	90	10
Spirost-5-en-3β-ol	90	10	55	45	90	10
3-Ethylenedioxyspirostene	35	65	0	100	0	100

Whereas the results of epoxidation by MoO_5.HMPA can be explained by stereospecificity in the action of the reagent, the outcome of the experiments with 3-pentyl hydroperoxide and molybdenum pentachloride is somewhat unexpected. Formation of the "anomalous" 5β,6β-oxides in the oxidation of 3β-acetoxy-Δ^5-steroids and that of the "normal" 5β,6β-oxides by the epoxidation of ethyleneacetals most probably have the same origin: complexing groups combine with the metal and thereby orient the hydroperoxide for attack on the β-side. This is especially clearly evident with ethylene acetals, where steric factors and the orienting effect of the oxygen group act in harmony (LIII).

Thus the stereochemistry of the epoxidation of unsaturated cyclic hydrocarbons and of compounds containing no metal-complexing groups is determined by the direction of attack by the "metal–hydroperoxide" complex. Such attack occurs predominantly on the less shielded side and involves the formation of π-complexes of type (LIV) [63-73] or (LV). [62]

III. "HYDROXYKETONISATION" OF ALKENES

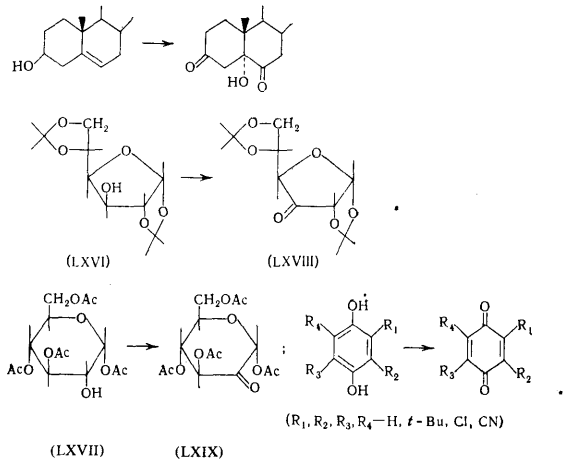
It has recently been shown [38,66,77,78] that trisubstituted alkenes can be converted directly into α-hydroxy-ketones by excess of a hydroperoxide in the presence of molybdenum, tungsten, and vanadium compounds. The yields are usually 60–90%. Thus Δ^5- and Δ^7-steroids are converted in one stage, when treated with two moles of t-pentyl hydroperoxide, into 85–90% yields of 5α-hydroxy-6-ones (LVI) and 8β-hydroxy-7-ones (LVII) respectively. The glycols (LVIII) and (LIX) were found as by-products. A double bond conjugated with an aromatic ring readily undergoes this reaction. For example, the compound (LX) gives a mixture of the hydroxy-ketone (LXI) and the glycol (LXII). It is significant that the new method enables the hydroxy-ketones (LXIII) and (LXIV) to be obtained from pin-2-ene and cedr-8-ene, whose oxides isomerise very readily [67,79].



The reaction has its limitations, since it extends only to trisubstituted alkenes. Attempts at the hydroxyketonisation of compounds containing a disubstituted double bond have been unsuccessful. Oxidation does not affect the double bond in αβ-unsaturated ketones, as is exemplified by the conversion of dehydropregnenolone acetate into 3β-acetoxy-5β-hydroxypregn-16-ene-6,20-dione (LXV).

IV. OXIDATION OF SECONDARY ALCOHOLS AND QUINOLS

Although the formation of ketones from secondary alcohols by the action of hydroperoxides is well known [80], this method has no preparative value. However, it has recently been established [38,81] that diverse secondary alcohols are easily oxidised by t-pentyl hydroperoxide in the presence of a catalyst (molybdenum pentachloride), without which hardly any oxidation occurs. The completeness of conversion varies between 40% and 90% depending on the structure of the alcohol. The new method of oxidation can be regarded as preparative in view of the high selectivity of the process. Among oxidations achieved in this way are those (percentage conversion indicated in parentheses) of cyclohexanol into cyclohexanone (95), cholestanol into cholestanone (85), 5α,22α-spirostan-3β-ol into the spirostanone (85), 18β-methyl glycyrrhetate into 3-oxomethyl glycyrrhetate (40), cholest-4-en-3β-ol into cholesten-3-one (60), *trans*-cyclohexanediol into hydroxycyclohexanone (85), pinane-2β,3α-diol into hydroxypinocamphone (80), and 3β-acetoxy-5α,6α-dihydroxysteroids into 3β-acetoxy-5α-hydroxy-6-oxosteroids (85). Oxidation of a hydroxy-group may be combined with hydroxyketonisation: thus 3β-hydroxy-Δ^5-steroids are converted in a single stage into 5α-hydroxy-3,6-diones:

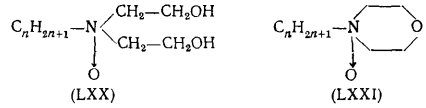


Hydroperoxide oxidation is extremely promising as a convenient method of obtaining keto-sugars [82,83], e.g. the smooth conversion of glucofuranose (LXVI) and glucopyranose (LXVII) derivatives into ketones (LXVIII) and (LXIX). Quinols are oxidised to quinones in high yields (70–95%). [38]

V. OXIDATION OF NITROGEN-CONTAINING COMPOUNDS

1. Aliphatic Amines

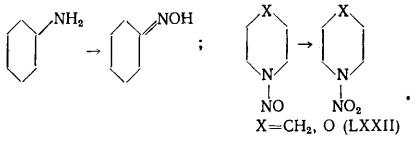
Tertiary aliphatic and cycloaliphatic amines are converted by hydroperoxides in the presence of vanadium, molybdenum, and titanium compounds into 75–80% yields of *N*-oxides [84]. *N*-Oxidation goes smoothly with bis-hydroxyethylamine and morpholine derivatives



The influence of the catalyst and of the solvent on the completeness of conversion of amines has been investigated with the oxidation of tributylamine, triethylamine, and dimethylaminoethanol by t-butyl and cumenyl hydroperoxides as examples [85]. The best catalysts are vanadium and molybdenum compounds, tungsten and niobium compounds are less active, chromium salts exhibit little activity, and cobalt, manganese, and iron salts are almost inactive. It is noteworthy that the latter completely decompose the hydroperoxide, but the yield of *N*-oxides is only 3–10%.

The oxidation of tertiary amines is less demanding on the choice of solvent. Thus in the presence of vanadium compounds high (84–96%) yields of *N*-oxides were obtained by using t-butyl alcohol, methanol, oxolan, ether, and acetone as solvents.

According to the patent literature [86] primary amines are converted by hydroperoxides, in the presence of molybdenum, vanadium, and titanium, into ketoximes, the most satisfactory results being obtained with cyclohexylamine:



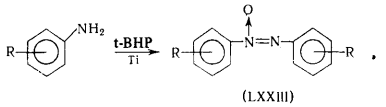
X=CH_2, O (LXXII)

The reaction of cyclohexylamine with ethylbenzene and t-butyl hydroperoxides obeyed a second-order rate equation [87]; oxidation to the ketoxime took place with high yields in the presence of titanium, vanadium, molybdenum, and tungsten compounds.

The interesting potentialities of the hydroperoxide method are demonstrated by the recently reported [45,88] examples of the conversion of nitrosamines into nitramines. In particular, nitramines (LXXII) have been obtained by the action of t-pentyl hydroperoxide on *N*-nitroso-morpholine and -piperidine in the presence of molybdenum pentachloride.

2. Aromatic Amines

Depending on the dosage of the oxidant, primary aromatic amines can be converted into azoxy-compounds or nitro-derivatives. In the presence of titanium compounds aniline, *o*- and *p*-toluidines, and *m*-nitroaniline are converted by t-butyl hydroperoxide almost quantitatively [89] into the corresponding azoxy-compounds (LXXIII):



(LXXIII)

p-Chloro-, 2,4,6-tribromo-, and *o*- and *p*-nitroanilines give unidentified products under the same conditions.

Kinetic investigation of the oxidation of *para*- and *meta*-substituted anilines to nitrobenzenes has shown [90] that the best catalysts are vanadium compounds, molybdenum being less active, and tungsten and cobalt salts completely inactive. Under optimum conditions (with t-butyl hydroperoxide and vanadyl trisacetylacetonate) the rates of oxidation of the anilines correlate well with the Hammett σ-constants and the Brown–Okamoto σ^*-constants, the values found for the ρ-constant being respectively -1.63 and -1.42. It is significant that a value of ρ of the same order (-1.86) was found for the oxidation of substituted anilines by peracetic acid [91]. The reaction mechanism in Scheme 2 has been suggested [90].

The oxidation of secondary aromatic amines has been investigated with cobalt salts as catalyst. Under these conditions the oxidant is $RO_2^{\cdot}$, which makes such reactions fundamentally different from ionic oxidation [92,93].

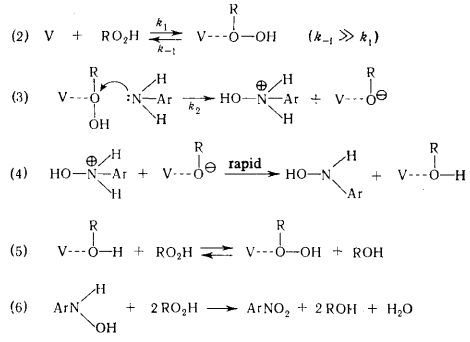
3. *N*-Oxidation of Aromatic Nitrogen Heterocycles

The oxidation of diverse compounds of this class has been investigated [38,45,88,94]. Almost quantitative *N*-oxidation is possible with pyridines containing one to five substituents, including such difficultly oxidisable compounds as 3,5-dibromopyridines and acetamidopyridines.

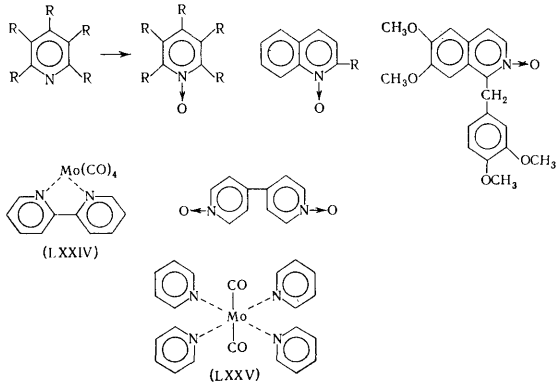
The reaction is conducted in benzene solution in the presence of t-pentyl hydroperoxide with molybdenum pentachloride or hexacarbonylmolybdenum. The advantages of the proposed method can be demonstrated by the oxidation of acridine, which is converted quantitatively into the *N*-oxide after only 2 h, whereas perbenzoic acid gives merely 50% conversion after several days. Derivatives of quinoline, isoquinoline (papaverine), and naphthoquinoline are oxidised very smoothly. The possibility of obtaining the dioxides in at least 85% yield in a single stage has been shown for the oxidation of 4, 4′-bipyridyl, 2,3,5,6-tetramethylpyrazine, and phenazine.

Scheme 2

(1) Activation of catalyst (rapid)



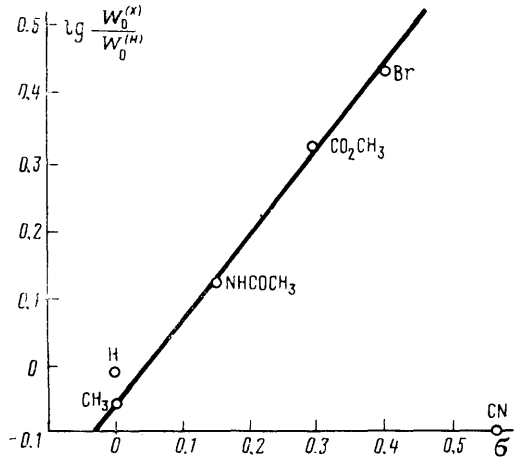
2,2′-Bipyridyl, 1,10-phenanthroline, and 8-hydroxyquinoline stand apart in being completely unoxidised. The catalyst is firmly bound by these reactants, and does not undergo the complex formation which would activate the hydroperoxide. An investigation was therefore made of the dependence of the rate of oxidation of alkenes and pyridine on the strength of binding of the molybdenum, by conducting oxidation in the presence of complexes hexacarbonylmolybdenum, tetracarbonylbipyridylmolybdenum (LXXIV), and dicarbonyldibipyridylmolybdenum (LXXV). The catalytic activity of molybdenum dropped sharply in this sequence: whereas (LXXIV) still had a catalytic effect, the complex (LXXV) was completely inactive. It is readily seen that substituting four coordination positions with such an active ligand as 2,2′-bipyridyl prevents complex formation either with the hydroperoxide or with the substrate.



(LXXIV) (LXXV)

Several quantitative characteristics have been obtained for the *N*-oxidation of pyridine and its 3-substituted derivatives by t-pentyl hydroperoxide in the presence of

molybdenum pentachloride [95]. In particular, it has been established that the reaction is first order with respect to substrate and hydroperoxide on conversion of up to 20% of the former. The activation energies of the oxidation of pyridine and methyl pyridine-3-carboxylate over the range 40–80°C were respectively 9.1 ± 0.2 and 7.7 ± 0.2 kcal mole^{-1}.

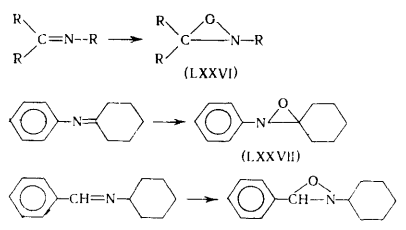


Dependence of rate of oxidation of substituted pyridines on the σ-constants.

The dependence of the rate of reaction of 3-substituted derivatives on the σ-constant was very characteristic. The diagram shows that the rate increases with decrease in the electron density on the reaction centre (series constant $\rho = +1.2$). 3-Cyanopyridine is out of line with the general sequence, and has the lowest rate of oxidation. This was attributed to enhanced complexing activity of the nitrile group, resulting in blocking of the catalyst.

4. Synthesis of Oxaziridines

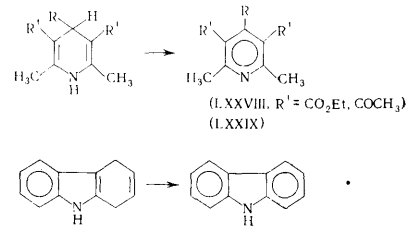
Oxaziridines are formed in yields of 40–90% when azomethines are oxidised with peroxy-acids [96]. It has recently been shown that these interesting compounds can be obtained by oxidising azomethines with t-pentyl hydroperoxide in the presence of molybdenum compounds [38,45,88]. Azines obtained from aliphatic aldehydes or ketones and amines react especially easily. Reaction goes very smoothly to give at least 80% yields of oxaziridines (LXXVI):



Oxaziridines (LXXVII) containing aromatic and aliphatic substituents are formed smoothly. Attempts to obtain purely aromatic oxaziridines were completely unsuccessful. Thus oxidation of benzylidenaniline is accompanied by vigorous rearrangement to benzanilide.

5. Dehydrogenation of 1,4-Dihydropyridines

One stage in the Hantzsch method for the preparation of pyridines involves the dehydrogenation of 1,4-dihydropyridines by means of various oxidising agents [97,98]. It has recently been found [99] that dehydrogenation by the action of t-pentyl hydroperoxide in the presence of molybdenum pentachloride is far more convenient. For example, diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate is converted quantitatively into (LXXVIII):

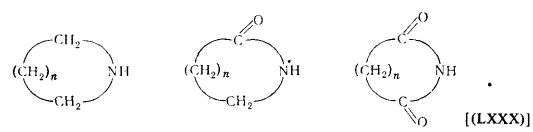


However, the conversion of 4-substituted dihydropyridines into pyridines (LXXIX) requires milder conditions, since in boiling benzene *N*-oxides are formed simultaneously. If excess of the hydroperoxide is used, *N*-oxides of the corresponding pyridines are formed in at least 80% yield in a single stage.

Dihydrocarbazole is converted quantitatively into carbazole.

6. Oxidation of Cyclic Amines to Imides

Interesting new potentialities for hydroperoxide oxidation are revealed by recent publications. It has been shown in particular that piperidine can be converted into 2-oxopiperidine [100], and caprolactam, 2-oxopiperidine, and 2-oxopyrrolidine are oxidised by t-butyl hydroperoxide to the corresponding imides [101] (LXXX)

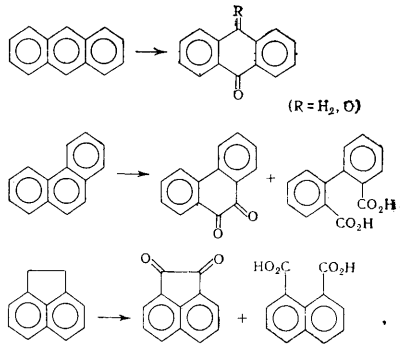


The reactions are catalysed by bivalent and tervalent manganese salts. The yields of the imides are 65–85%, which confers preparative value on the method.

VI. OXIDATION OF FUSED AROMATIC HYDROCARBONS

Anthracene, phenanthrene, and acenaphthene can be oxidised by means of t-pentyl hydroperoxide in the presence of molybdenum pentachloride [102]. Anthracene is converted into a mixture of anthrone and anthraquinone, and phenanthrene and acenaphthene give phenanthraquinone

and acenaphthenequinone together with diphenic and naphthalic acids:

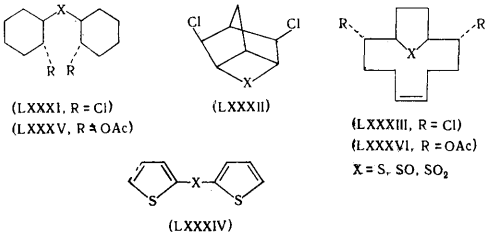


Thus the reaction involves rupture of a carbon–carbon bond. Up to 90% conversion of the hydrocarbons can be achieved by using excess of hydroperoxide. If vanadium compounds are used as catalysts, the same oxidation products are formed, but conversion of the initial compounds does not exceed 25%.

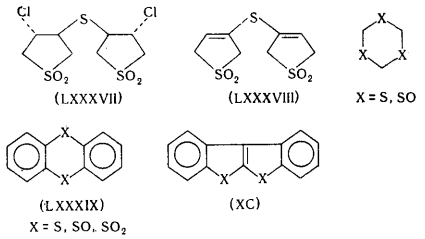
VII. OXIDATION OF ORGANOSULPHUR COMPOUNDS

Inorganic oxidising agents and peroxy-acids are generally employed to oxidise a sulphur atom in an organic compound [103,104]. The reaction between a sulphide and a hydroperoxide is very slow in the absence of a catalyst: for example, cyclohexyl methyl sulphide is converted into the sulphoxide by the action of t-butyl hydroperoxide at 60°C over a period of 64 h. [105] Some years later it was shown that aliphatic sulphides could be oxidised quantitatively to the sulphones by the action of hydroperoxide in the presence of molybdenum acetylacetonate [106]. A process of oxidation of sulphides to sulphoxides and sulphones by the action of hydroperoxides in the presence of metals of Groups IV and VII has been patented, and the partial and complete oxidation of dialkyl (diphenyl) sulphides has been described [107].

The hydroperoxide oxidation of organosulphur compounds has been most fully investigated [28,108,109]. The new method is applicable generally, since it can be used to oxidise organosulphur compounds of diverse structure. Its chief merit is extraordinarily high selectivity, not possible with the usual oxidising agents. The high rate of oxidation and the preparative simplicity are noteworthy. Hydroperoxide oxidation combines mildness of action, permitting the oxidation of compounds which undergo changes in the presence of such a reagent as hydrogen peroxide, with strong oxidising power, allowing the oxidation of sulphides and aromatic sulphur heterocycles that do not react with other oxidants. For example, the dichlorinated sulphides (LXXXI)–(LXXXIII), whose chlorine atoms are extremely labile, and dithienyl sulphide (LXXXIV) give very low yields of sulphoxides and sulphones when treated with hydrogen peroxide, whereas oxidation with t-pentyl hydroperoxide and molybdenum pentachloride in benzene solution produces almost quantitative yields of the oxidised products. The introduction of two acetoxy-groups, as in the sulphides (LXXXV) and (LXXXVI), almost completely prevents oxidation by hydrogen peroxide by shielding the sulphur atom, but high yields of sulphoxides and sulphones were obtained by means of the above hydroperoxide and catalyst.



The advantages of hydroperoxide oxidation are clearly evident from experiments on the sulphides (LXXXVII) and (LXXXVIII). Oxidation of the former with hydrogen peroxide gives a mixture of the sulphoxide and the sulphone, whereas the latter remains completely unoxidised [110]. However, the Reviewers have been able to obtain sulphoxides and sulphones in at least 90–95% yield by the action of t-pentyl or cumenyl hydroperoxide in the presence of molybdenum pentachloride. The possibility of precise control of the degree of oxidation by measuring out the oxidant has been shown with trithian as example, which is converted quantitatively into mono-, di-, and tri-sulphoxides, as well as with thianthren and 3,4,5,10-tetramethylthianthren (LXXXIX), which are converted respectively into mono- and di-sulphoxides, sulphoxidosulphones, and disulphones. Similarly, benzothiopheno[2,3-*b*]benzothiophen (XC) is converted quantitatively into the monosulphoxide and the mono- and di-sulphones; the disulphone could not be obtained by the action of hydrogen peroxide [111].

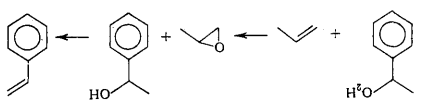


The hydroperoxide method has been applied to the selective oxidation of organosulphur compounds such as dicyclohexyl sulphide, thiadecalin, 13-thiabicyclo[8,2,1]-tridecane, benzothiophen, phenoxathi-in, phenazine, etc.

VIII. POSSIBLE INDUSTRIAL APPLICATIONS OF METAL-CATALYSED HYDROPEROXIDE OXIDATION

The development of processes for the conversion of alkenes originating from the petroleum industry into oxygen-containing compounds—oxides, alcohols, ketones, etc.—is one of the main tasks of petroleum chemistry. From this naturally follows the interest that has been evinced in the hydroperoxide epoxidation of alkenes.

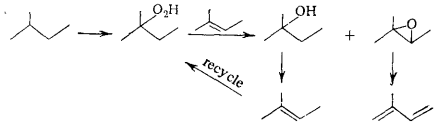
Publication of the firm Halcon International Inc. patents [112–117] on the simultaneous production of methyloxiran and styrene clearly revealed the potentiality of the new method. This process is based on the reactions



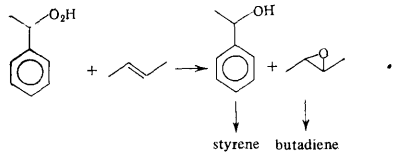
It may compete with the classical method of obtaining styrene by the dehydrogenation of ethylbenzene. A recent report on the starting-up of a plant based on the "Halcon process" states [118] that technical difficulties have been successfully overcome. Information on the production and purification of ethylbenzene hydroperoxide and on the choice of optimum conditions for oxidation will be found in patents [119-127]. The use of cumenyl hydroperoxide enables methyloxiran and α-methylstyrene to be produced together [128,129]. An interesting route has been suggested [50] for the simultaneous production of methacrylic esters and methyloxiran.

The development of improved and economic processes for obtaining isoprene is a most important task of the monomer industry. A process based on isopentane hydroperoxide is undoubtedly of interest in this connection [130-134]; its principle will be clear from Scheme 3.

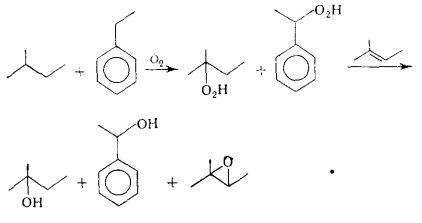
Scheme 3



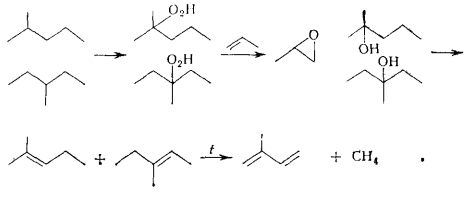
Among processes for the combined production of styrene and dienes—butadiene and isoprene—the first involved oxidation of but-2-ene by ethylbenzene hydroperoxide followed by appropriate reactions [135]:



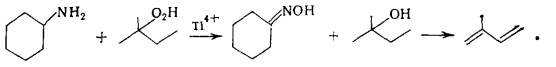
Oxidation of a mixture of isopentane and ethylbenzene is claimed [136] to yield the corresponding hydroperoxides, which are then used to oxidise isopentene to the oxide, after which the reactions are similar to those described above:



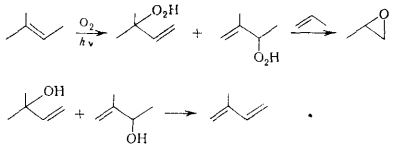
A noteworthy combined process for obtaining isoprene and methyloxiran from 2- and 3-methylpentane hydroperoxides yields tertiary alcohols, which crack to form isoprene [137]:



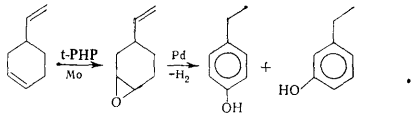
The production of isoprene can be combined with that of cyclohexanone oxime, which is formed by oxidising cyclohexylamine with hydroperoxides in the presence of titanium salts [137,138]:



An extremely interesting process for obtaining isoprene and methyloxiran is based on unsaturated hydroperoxides formed by the photosensitised oxidation of isopentene [139]:

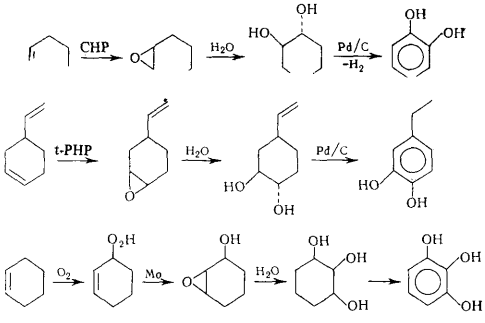


It has been proposed to use hydroperoxide epoxidation as a stage in the production of phenols. In particular, a mixture of *m*- and *p*-ethylphenols is obtained by the scheme [140]

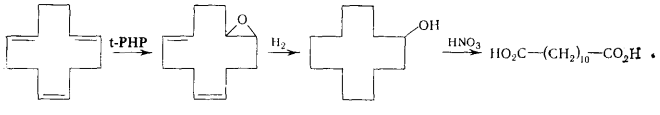


The essential nature of methods developed for obtaining catechol [141,142], ethylcatechol [143], and pyrogallol [144] will be clear from Scheme 4.

Scheme 4



A suggested method for obtaining dodecanedioic acid involves the stages [145]



The application of hydroperoxide epoxidation to the production of various oxygen-containing compounds is considered in periodical communications [146-152] and in patents [153-157].

While the Review was being prepared for press several publications have appeared on the kinetics and the mechanism of hydroperoxide epoxidation [158-163]. Papers clearly showing for the first time that the reaction is catalysed by complexes of sexivalent molybdenum are especially interesting [158,159]. The stereochemistry of oxidation has been examined [164-166].

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