HETEROCYCLIC COMPOUNDS WITH THREE- AND FOUR-MEMBERED RINGS

In Two Parts

PART ONE

This is Part One of the nineteenth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER, *Consulting Editor*

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Part One

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Research Laboratories, Eastman Kodak Company, Rochester, New York

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The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds and accommodate the specific interests of the authors.

Research Laboratories
Eastman Kodak Company
Rochester, New York

ARNOLD WEISSBERGER

Preface

Compounds with three and four ring members play a considerable role in the rapid and still accelerating development of heterocyclic chemistry. There are two closely related aspects of heterocyclic chemistry: the investigation of different derivatives of the respective nuclei, and that chemistry in which the nuclei themselves undergo changes. The latter aspect attains particular importance with the heterocyclic compounds with less than five ring members, some of which belong to the most reactive compounds in organic chemistry. Consequently, these compounds are playing a role of ever increasing importance as intermediates in reactions including polymerizations.

The lack of a comprehensive and reasonably complete presentation of the field was keenly felt, and we hope that the present volume, written by experts in the various branches, will fill a real need.

The three- and four-membered ring compounds have in common the property of bond-angle strain. Dr. Scott Searles, Jr., one of the authors of the present treatise, points out that the high degree of strain in three-membered rings results in many properties of the compounds such as high reactivity in ring cleavage reactions and low electron-donor ability in coordination with electron acceptors. These properties may be associated with different orbital hybridization, for both bonding and non-bonding electrons, in three-membered ring compounds as compared with 'strainless' analogs, as well as with the relief of angle strain in reaction transition states. 'The chemistry of four-membered ring heterocycles is generally quite different from that of their three-membered analogs, as well as of their five- and six-membered ring analogs. Although in many respects the chemical properties of four-membered heterocyclics are intermediate between those of the corresponding three- and five-membered analogs, this situation is by no means always true. For example, the electron-donor ability associated with the four-membered ether ring of oxetanes is definitely greater than that of other ethers, cyclic or non-cyclic. A different combination of geometric, transannular and probably orbital

hybridization factors may lead to somewhat unique results in four-membered ring heterocyclics.'

I want to thank the authors for their efforts which made this volume possible, and the publishers and their staff for their expert and efficient handling of the production of this treatise.

My wife, Dr. Louise Harris Weissberger, took a special part in this volume by translating from the French original the chapters on Thietanes and β-Lactones. I am following Dr. Etienne's request to honor her memory by mentioning her competent and painstaking effort in representing the authors' original thoughts in faultless English. In my life and in my editorial work, she has played an infinitely larger role by encouraging my efforts, by her ability to acquire and to communicate an understanding of complex problems, by her mastery of the English language, by her sincerity and warmth of personality, and by patience, devotion and love.

Research Laboratories
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Rochester, New York

ARNOLD WEISSBERGER

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CHAPTER I

Ethylene Oxides

ANDRÉ ROSOWSKY
*Harvard University**

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'. . . This compound exhibits certain of the characteristics of aldehydes and represents the first of a new series of substances possessing with respect to aldehydes proper the most curious isomeric relationships.' It was with these singularly prophetic remarks that the celebrated French chemist Wurtz announced in 1859 the isolation of a new substance isomeric with acetaldehyde, which he called ethylene oxide.[1884] In the 100 years after its discovery, ethylene oxide grew from a mere laboratory curiosity into one of the most widely utilized research and industrial chemicals, and the preparation and investigation of its higher homologs came to constitute a considerable segment of organic chemical literature.[185, 1136, 1717, 1857]

Ethylene oxide itself is the lowest member of a class of substances formally termed 'oxiranes',[864] but more commonly designated 'epoxides' or 'ethylene oxides'. Sometimes encountered also are such variants as 'α-oxides' and '1,2-epoxides', to name but two. In deference to common usage the present chapter will retain the terms

'epoxide' and 'ethylene oxide' to describe any substance incorporating in its structure one or more three-membered rings containing one oxygen and two carbon atoms each.

Epoxides are at present the simplest known oxygen-containing heterocycles. Dioxiranes, three-membered rings containing one carbon and two oxygen atoms, were at one time believed to be among the peroxidic products formed from carbonyl compounds on reaction with oxygen. Reference to such compounds can frequently be encountered in the older literature. It is likely, however, that the dioxiranes in question are in fact dimeric or polymeric peroxides. Walsh has called attention to the improbable nature of the dioxirane molecule on the basis of the molecular-orbital theory.[1798]

Acetylene oxide is likewise unknown at present, although certain of its alkyl derivatives were recently postulated as products of the addition of peroxyacids to the corresponding alkylacetylenes.[1538, 1539] Other investigations have cast doubt on the validity of this postulate.[578] More tangible evidence than is currently available seems necessary before such substances can be included among the three-membered oxygen heterocyclic compounds.

The present chapter will be devoted to the chemistry of epoxides, and will be divided into five principal sections. These will deal respectively with the following topics: **I**, physical properties; **II**, occurrence in nature; **III**, synthesis; **IV**, chemical reactions; **V**, analytical methods.

I. Physical Properties

Ethylene oxides, like other three-membered ring systems, possess many singular features that invite a basis in theory. To satisfy this demand, much effort has been devoted to the task of determining with precision such fundamental properties of the molecule as bond lengths, bond angles, and bond energies. With the advent of modern instrumental methods it has been possible to develop a dependable physical basis for theoretical speculations on the electronic structure of ethylene oxide. The present section is concerned with this aspect of epoxide chemistry.

1. Molecular Geometry

The molecular geometry of ethylene oxide has been studied primarily by means of electron diffraction and microwave spectroscopy, together with classical techniques of dipole-moment measurement.

The dipole moment of ethylene oxide is the result of non-uniform electron distribution in σ-bonds, and is caused by the presence of an

electronegative atom in the ring. In benzene solution ethylene oxide has a dipole moment of approximately 1.8–1.9 debye,[25, 32, 631, 632, 768] and of about 1.9 debye in the gaseous state.[32, 631, 632, 1430, 1664] Substitution of an electron-repelling methyl group, as in propylene oxide, causes a slight elevation in dipole moment to 1.9–2.0 debye.[25,390,768,1481] On the other hand, the electron-attracting vinyl group, as in 1,2-epoxy-3-butene, appears to produce little increase if any.[1481] The dipole moments of cyclopentene oxide and cyclohexene oxide were found by Canals and co-workers to be 1.8 and 1.7 debye respectively, whereas 1-methyl-1,2-epoxycyclohexane gave a value of 1.8 debye.[285]

The group moment for an epoxide function has been taken to be 1.3 debye for calculating the expected dipole moments of 4-bromo-2,3-epoxycyclopentanol and 5-bromo-2,3-epoxycyclopentanol respectively.[982] The dipole moments predicted in this fashion are in accord with experimental values.

Microwave spectroscopy has been an exceedingly useful tool for elucidating the molecular geometry of epoxides.[391, 393, 696, 1578] In addition to confirming the above-mentioned trend of dipole moments

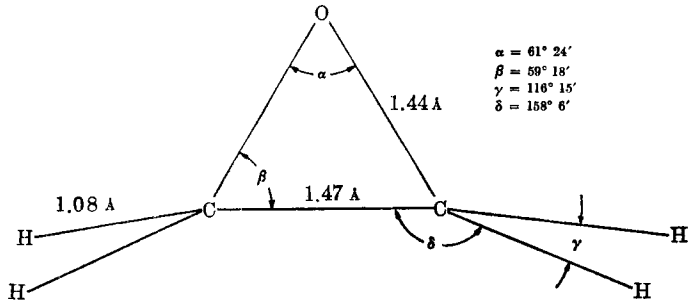


Fig. 1. Detailed structure of ethylene oxide.

for ethylene oxide and propylene oxide, for which values of 1.9 and 2.0 debye respectively were obtained,[392, 1770, 1674] this valuable technique has yielded information concerning bond angles and force constants. Electron-diffraction studies [8, 1836, 850, 851] likewise provide a picture of simple epoxides which is in accordance with other investigations. The results of these various studies are summarized in Fig. 1.

Fig. 1 shows that the plane formed by the carbon and hydrogen atoms is perpendicular to that of the ring. The hydrogens are situated above and below the ring, and the two carbons are raised above the plane formed by the four hydrogens. The C—C bond length is intermediate between that of a normal C—C bond (1.54 Å) and that of a C=C bond (1.33 Å), while the H—C—H bond angle is intermediate

between the tetrahedral (109° 28′) and trigonal (120°) configuration. It can thus be imagined that the oxygen atom is somehow 'lifting' the two carbons out of the plane formed by the four hydrogens, the plane in which they would lie if they were genuine olefinic sp^2-hybridized carbons. These geometrical features become more important when theoretical models are considered in a subsequent section.

2. Energetics

Ethylene oxide is a gas at room temperature and atmospheric pressure, its boiling point being only about 10.5°.[1081, 635] Addition of a methyl group, as in propylene oxide, raises the boiling point to 35°, whereas stilbene oxide, because of the combined influences of molecular weight and structural symmetry, is a solid at room temperature. Ethylene oxide is higher-boiling than cyclopropane (b.p. −32.9°), a fact which is consistent with its more polar character. Similarly, its melting point of −112.5°[635] is higher than that of cyclopropane (m.p. −127.5°) for the same reason.

Crog and Hunt[375] found the heat of combustion of ethylene oxide to be 312.55 ± 0.20 kcal./mole. The heats of fusion and vaporization, determined with great precision by Giauque and Gordon,[635] are 1236 and 6101 kcal./mole respectively. An approximate value for the strain energy of ethylene oxide has been computed by Nelson and Jessup.[1229] The experimental heat of formation, derived by combustion calorimetry, was subtracted from the calculated total bond energy, obtained by summation of Pauling C—C, C—H, and C—O bond energies. The difference, 13 kcal./mole was assigned to strain energy. The corresponding values for cyclopropane, ethyleneimine, and ethylene sulfide were estimated to be 25, 14, and 9 kcal./mole respectively.

The enthalpy of ethylene oxide, measured calorimetrically, has been reported[1617] to be 498 kcal./mole. Measurement of the enthalpy of ethylene oxide over a wide range of pressures has been conducted in at least two laboratories,[325, 1166] and entropy calculations have been made from these results. The entropy of ethylene oxide vapor was likewise determined by Giauque and Gordon.[635] Their experimental value of 57.38 cal./degree-mole after a suitable correction for deviation from ideality is not far from the value 57.56 calculated from theory.

The critical temperature above which ethylene oxide gas cannot be liquefied has been listed variously as 192° and 196°.[1081, 1799] The critical pressure is subject to much more disagreement, however, since an early estimate to 49.1 atm.[939] has given way to a later one of 70.9 atm.[1799]

Perhaps of interest at this point are certain studies involving rupture of the ethylene oxide ring by pyrolysis or photolysis.

Thermal decomposition of ethylene oxide is known to yield methyl radicals, together with such products as carbon monoxide, methane, ethylene, and ketene.[1047, 1204, 1205] Lossing, Ingold, and Tickner have studied the course of ethylene oxide pyrolysis at 800–1000°, using mass spectrometry, and found that no CH_2 is formed.[1047] Their finding rendered untenable a previous proposal by Fletcher and Rollefson[549, 550] that this elusive species might be produced. Operating at about 400° Mueller and Walters[1204, 1205] investigated the effect of methyl radicals from dimethylmercury on the product composition, particularly with respect to acetaldehyde and ketene formation. Although suggestions have appeared that ethylene oxide decomposition takes place by way of intermediate species like $\cdot CH_2CH_2O\cdot$ or even $\cdot CH_2OCH_2\cdot$,[1092, 1911] it would seem that further work is required before the details are understood. On the basis of available evidence the most probable course for the pyrolysis of ethylene oxide, as postulated by Mueller and Walters,[1204, 1205] appears to be as shown in Eq. (1).

$$\begin{aligned}
&(a)\ \underset{\diagdown\,\diagup}{\overset{O}{CH_2—CH_2}} \xrightarrow{\text{pyrolysis}} [?] \longrightarrow CH_3\cdot + HCO\cdot \\
&(b)\ \underset{\diagdown\,\diagup}{\overset{O}{CH_2—CH_2}} + CH_3\cdot \longrightarrow CH_4 + C_2H_3O\cdot \\
&(c)\ C_2H_3O\cdot \longrightarrow CH_3\cdot + HCO\cdot
\end{aligned} \qquad (1)$$

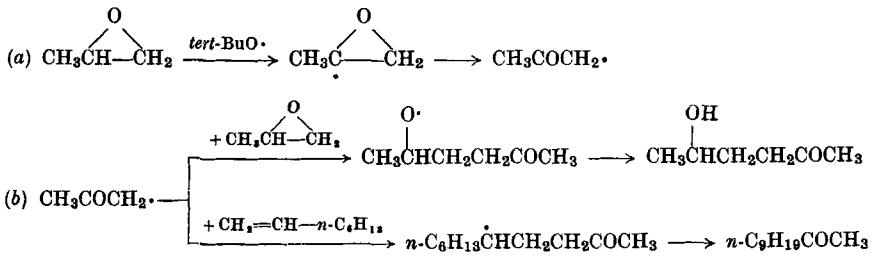
Ketene could be formed in the above scheme by abstraction of hydrogen from $C_2H_3O\cdot$, whereas acetaldehyde is presumably formed in a separate but still not clarified isomerization step.

Photolysis of ethylene oxide has likewise been studied, both directly[657] and by the mercury-photosensitization technique.[399] In each case the first step is considered to be as shown in Eq. (2).

$$\underset{\diagdown\,\diagup}{\overset{O}{CH_2—CH_2}} \xrightarrow{h\nu} CH_3\cdot + HCO\cdot \qquad (2)$$

The exact order of events leading to these familiar species still remains obscure, however. Cvetanovic has called attention to the similarity between the photolytic decomposition of ethylene oxide and the fate of energy-rich intermediates formed during high-temperature catalytic ethylene oxidation.[400, 401]

A recent communication by Gritter and Wallace discloses initiation of a study of the free-radical chemistry of epoxides. Under the influence of *tert*-butoxy radicals, formed by thermal decomposition of di-*tert*-butyl peroxide, propylene oxide is believed to yield an epoxy radical as shown in Eq. (3). The latter undergoes isomerization to $CH_3COCH_2\cdot$ and further reaction with unreacted propylene oxide or other available substrates, such as 1-octene, toluene, cyclohexene, and ethanol,[673] as shown in Eq. (3).



(3)

3. Miscellaneous Physical Properties

Among the miscellaneous physical properties of ethylene oxide meriting brief mention are solvation,[1912] parachor,[1201] thermal conductivity,[1792] magnetic susceptibility,[989] and ionization potential.[1040, 1811, 1048]

4. Spectroscopic Properties

The spectral properties of ethylene oxides are among the most important, not only for the information derivable from them concerning the intimate structure of the three-membered oxide ring, but also in connexion with the detection and identification of this function in complex molecules of unknown constitution, *e.g.* natural products. The present review is concerned with the following three types of spectroscopy: (*A*) infrared spectroscopy, (*B*) ultraviolet spectroscopy, and (*C*) nuclear magnetic resonance spectroscopy.

A. Infrared Spectroscopy

The infrared spectrum of ethylene oxide itself has been studied in the gas phase by Lord and Nolin,[1046] and by Pierson and coworkers.[1365] A very strong band centered at 877 cm.$^{-1}$ and a

weaker one at 1270 cm.$^{-1}$ are the principal features of its spectrum. Completely deuterated ethylene oxide has likewise been investigated.[1046] Vibrational frequencies for ethylene oxide were calculated from theory by Stone[1657] and found to agree with experimental values.[759, 1713, 1046, 1365]

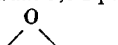
It is convenient to divide the infrared spectroscopy of substituted ethylene oxides into two aspects. The first is location of characteristic bands attributable to the epoxide ring; the second is the effect of an epoxide ring on the absorption bands of other functional groups which might be present in its vicinity. From several deliberate investigations, as well as from numerous incidental contributions to the literature, it is possible to build up an extensive collection of infrared data for a wide variety of substituted epoxides. Leading references may be found in reviews by Bellamy,[118] and by Jones and Sandorfy.[885]

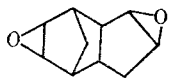
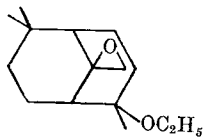
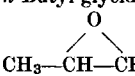
Although little can be said as yet about the relation between the positions of epoxide bands and stereoelectronic factors that might be expected to govern them, there appear to be at least three regions of the infrared spectrum in which epoxide rings can absorb. These are situated within the limits 7.8–8.1, 10.5–11.6, and 11.5–12.7 μ respectively. Because not all authors agree that all three bands are typical, however, they are unfortunately seldom all specified in casual literature citations. The data presented in Table 1, although incomplete in this one respect, is a representative sample of the available literature.

Henbest and co-workers[737] called attention to the existence of an additional characteristic absorption band in the 3.3 μ region, but its usefulness appears limited, since, for most compounds where infrared spectroscopy might facilitate detection of an epoxide ring, there are too many other interfering C—H vibrations in the same region. Goddu and Delker,[653] on the other hand, have examined the first overtone of this band, which is located near 1.65 μ. Although it requires special optics, this technique affords a high degree of resolution and may hold considerable promise for the detection of terminal epoxides.

The second important aspect of infrared spectroscopy which will be considered here is the effect of an epoxide ring on the absorption bands of other functional groups situated in its vicinity, particularly carbonyl groups or phenyl rings. Because the three-membered oxide ring has been shown to exhibit certain properties typical of olefins it might be supposed that the carbonyl stretching frequency of an α,β-epoxyketone should be intermediate between those of the corresponding saturated and α,β-unsaturated ketones. The fact is, however, that, though there is enough excited-state interaction between the

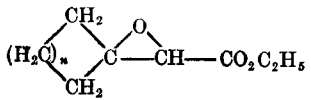
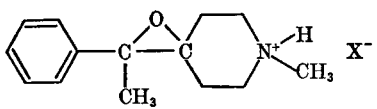
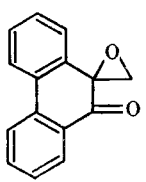
TABLE 1. Infrared Absorption of Epoxides

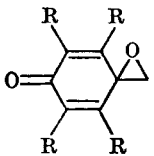
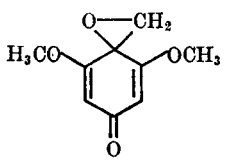
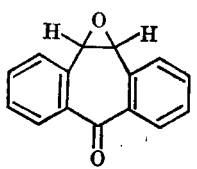
Compound	8 μ region	11 μ region	12 μ region	Reference
Propylene oxide	7.9	10.5	12.1	1306, 1576
*iso*Butylene oxide		11.1	12.6	1306
cis-2,3-Epoxybutane	7.8	11.3	12.9	1306
trans-2,3-Epoxybutane	7.8	11.3	12.3	1306
 (n = 5, 7, 9, 11)		10.9	12.0	1306, 1576
2,3-Epoxy-2-methylheptane	8.0	11.1	11.8	435
1,2-Epoxy-2,4,4-trimethylpentane	8.0	11.1 11.3	12.6	215, 620
2,3-Epoxy-2,4,4-trimethylpentane	7.9		12.3 (13.3)	620
1,1-Di-*tert*-butylethylene oxide	8.2		11.9 12.2	1237
Cyclohexylethylene oxide		10.6	11.9	1306
Cyclopentene oxide			11.9	1306, 1926
Cyclohexene oxide	7.9	11.2	12.3	1306
Methylenecyclohexane oxide	8.0	11.0	12.0–12.3	1487
l-Menthene oxide	8.0		11.9 (13.1)	215
Limonene dioxide	8.0		11.8 12.5 12.0 13.1	215
α-Pinene oxide	7.9		11.9 (13.0)	215
9,10-Epoxyoctalin	7.8	10.9 11.4	12.5	343
2,3-Epoxybicyclo[2.2.1]heptane		11.9		1602, 1926
1,2;4,5-Diepoxycyclohexane	7.9	10.7	12.3	1306

Compound	8 μ region	11 μ region	12 μ region	Reference
	7.9	11.8	12.1	215
	8.0	11.0	12.1	1655
cis-Cyclooctene oxide		10.9	12.1	341
trans-Cyclooctene oxide		10.8–10.9	11.9	341
cis-Cyclodecene oxide		11.1	12.5	1403
trans-Cyclodecene oxide		11.2	12.2	1403
Cyclododecene oxide (*cis*- and *trans*-) and others				1403
Epichlorohydrin	7.9	10.8	11.8	1306
Glycidol		11.1	11.8	1576
			12.0	
n-Butyl glycidyl ether	8.0	10.9	11.8	1306
	8.0	11.3	12.6	1436
1,2;3,4-Diepoxybutane	8.0	10.9	12.3	1306
		11.5		
1,2;5,6-Diepoxypentane		10.9	12.1	1306
		11.8		
1,2-Epoxy-3-butene	8.0		12.2	1306, 1576
1,2-Epoxy-3-hexyne	8.0	10.8		16
Styrene oxide	8.0	11.4	12.3	1306, 1576
		11.6	12.8	1306
α-Methylstyrene oxide				
Glycidaldehyde	8.2		11.8	1311
1,2-Epoxy-3-butanone		10.8	11.5	1893
1,2-Epoxy-2-methyl-3-butanone		10.8	11.9	1893

(*Table continued*)

TABLE 1 (*continued*)

Compound	8 μ region	11 μ region	12 μ region	Reference
2,3-Epoxy-2-methyl-4-pentanone		10.8 11.4	12.0	1893
Glycidonitrile	8.1		12.0	1311
Glycidic esters	8.0	11.1	11.8	1306, 134
 (n = 1, 2, 3)	7.9	10.8	11.8	310
1-Cyanocyclohexene oxide	8.0	11.1	11.6	1865
2,3-Epoxycyclohexanone			12.2	1893
1-Acetoxycyclohexene		11.3	12.2	1576
2,3-Epoxy-1-methoxybutane	7.9	10.5 11.2		1636
1,2-Epoxy-1-methoxy-2-methyl-1-phenylbutane		10.9		1709
	7.8 8.2			1058
Benzalacetophenone oxide		11.2		1893
		10.4 11.2		487

Compound	8 μ region	11 μ region	12 μ region	Reference
Quinone derivatives:				
				
R = OCH_3	7.8	10.4 11.3		486
R = O_2CCH_3	7.8	10.8	11.6	486
R = Cl	7.9	10.8	11.8	486
	7.8	10.9 11.3		486
	7.9	11.2 11.4	11.7	1462
1,2-Epoxy-1,2-dimesitoylcyclohexane	8.2 8.5		11.9	608
1,2-Epoxy-2,3-dimesitoylcyclohexane	(9.1)	11.1		608
Miscellaneous sugar epoxides			12.5	27, 1874

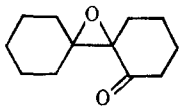
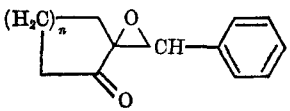
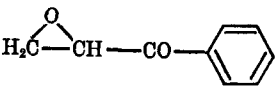
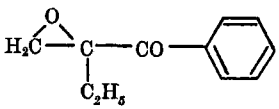
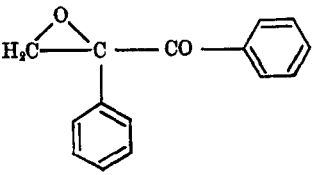
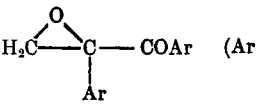
(*Table continued*)

TABLE 1 (*continued*)

Compound	8 μ region	11 μ region	12 μ region	Reference
Steroid epoxides:				
2β,3β-Epoxy-			12.4	679
2α,3β-Epoxy-			12.3	679
3β,4β-Epoxy-		11.2		679
5β,6β-Epoxy-		11.5		679
1α,2α-Epoxy-3-oxo		10.8		
		11.1	11.5	1517
5α,6α-Epoxy-7-oxo			12.5	137
8α,9α-Epoxy-7-oxo-		10.9	12.3	763
		11.1		
8α,14α-Epoxy-7-oxo-			12.4	773
16α,17α-Epoxy-20-oxo-		11.1	12.3	137, 1135
2β,3β-Epoxy-3α-cyano-	8.0	11.5		1865
2β,3β-Epoxy-3α-carbamino-		11.6		1865

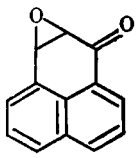
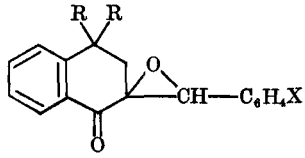
epoxide ring and the carbonyl group to cause exaltation in the ultraviolet spectrum (see section **I.4.***B*), there is too little ground state interaction to produce much change in the infrared carbonyl-stretching frequency,[282, 380, 381] Table 2 shows that the presence of an epoxide

TABLE 2. Carbonyl Stretching Frequencies of α,β-Epoxyketones

Compound	Stretching frequency (cm.$^{-1}$) C=O	Solvent	Reference
1,2-Epoxy-3-butanone	1718	None	1893
1,2-Epoxy-2-methyl-3-butanone	1721	None	1893
2,3-Epoxy-3-methyl-4-pentanone	1718	None	1893
2,3-Epoxycyclohexanone	1718	None	1893
	1700	CCl_4	827
			
$n = 1$	1730	CCl_4	827
$n = 2$	1715 1730	CCl_4	827
$n = 3$	1710	CCl_4	827
	1675	$CHCl_3$	823
	1675 1683, 1691(s)	$CHCl_3$ CCl_4	824 817
	1690	CCl_4	823
 (Ar = mesityl)	1700	$CHCl_3$	823

(*Table continued*)

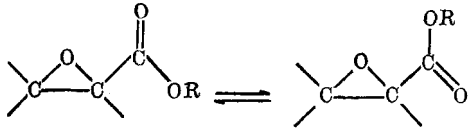
TABLE 2 (*continued*)

Compound	Stretching frequency (cm.$^{-1}$) C=O	Solvent	Reference
trans-Benzalacetophenone oxide	1686	KBr disk	1893
	1687	Nujol mull	380, 381
β-Ethyl-*cis*-benzalacetophenone oxide	1688	$CHCl_3$	824
	1679, 1691(s)	CCl_4	817
β-Ethyl-*trans*-benzalacetophenone oxide	1680	$CHCl_3$	824
	1680, 1691(s)	CCl_4	817
	1676	Nujol mull	282
	1683	CCl_4	282
			
R = H; X = *p*-Cl	1694	CCl_4	378
o-NO_2	1697	CCl_4	378
m-NO_2	1695	Nujol mull	378
	1687	Dioxan	378
p-NO_2	1685	Nujol mull	378
	1687	Dioxan	378
R = CH_3; X = *p*-Cl	1693	CCl_4	378
o-NO_2	1695	CCl_4	378
m-NO_2	1693	CCl_4	378
	1670	Nujol mull	378
p-NO_2	1697	CCl_4	378
	1675	Nujol mull	378
Steroid epoxides:			
1α,2α-Epoxy-3-oxo-	1712	CS_2	1517
5α,6α-Epoxy-7-oxo-	1695	CS_2	137, 138

ring does produce in certain instances a change in the carbonyl-stretching vibration. This effect is probably better explained, however, not on the basis of π-electron delocalization, but by simply assuming modification of the sp^2 character of the C=O bond as a result of steric or inductive phenomena.

One additional special aspect of the infrared spectroscopy of epoxides merits brief mention. It has been observed in at least three laboratories[310, 1176, 817] that the carbonyl-stretching frequency in

glycidic esters is consistently split into a doublet. This effect has been ascribed to the existence of two conformational isomers for glycidic esters,[310, 817] as depicted in Eq. (4).



(4)

Since the C=O and C—O dipoles are oriented in opposite directions in the second isomer, a normal ester band at 1730–1740 cm.$^{-1}$ is to be expected. On the other hand, the first isomer, having parallel C=O and C—O dipoles, should exhibit a higher frequency (*i.e.* increased carbonyl character) than the first. A second peak does in fact appear about 20 cm.$^{-1}$ higher for a number of glycidic esters.[310, 817] The situation is in complete agreement with that of α-haloesters,[118] α,β-epoxyketones,[817] and α-haloketones.[118]

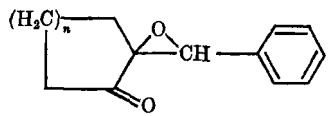
Finally, a few epoxides have been examined also by Raman spectroscopy.[1201, 1008]

B. Ultraviolet Spectroscopy

The ultraviolet spectroscopy of epoxides has received relatively little attention in the literature, since their ability to delocalize π-electrons in a chromophore, although detectable, is even smaller than that of the cyclopropane ring.[1481] A representative selection of λ_{max} values is shown in Table 3. For additional references from the field of steroid chemistry an excellent review by Dorfman[462] should be consulted.

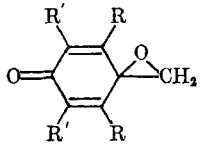
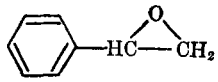
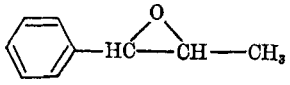
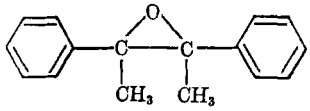
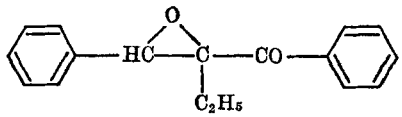
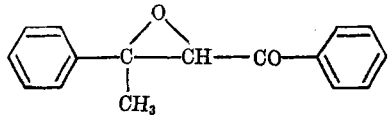
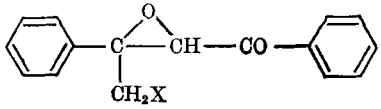
In a study of the far-ultraviolet absorption spectrum of propylene oxide, Walsh reported a strong continuous band beginning at 175 mμ, reminiscent of olefins rather than of paraffins.[1798]

TABLE 3. Ultraviolet Absorption of Epoxides

Compound	λ_{max} (mμ)	log ε	Reference
			
$n = 1$ (not pure)	229	2.7	827
$n = 2$	224	3.1	827
$n = 3$	226	3.0	827

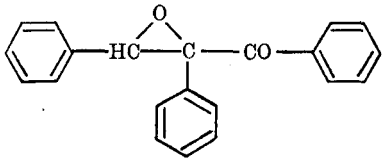
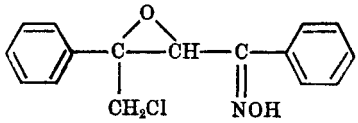
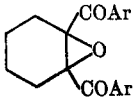
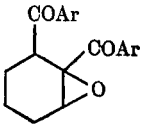
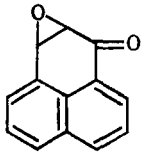
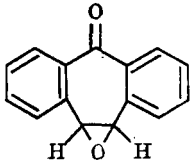
(*Table continued*)

TABLE 3 (*continued*)

Compound	λ_{max} (mμ)	log ε	Reference
			
R = R′ = Cl	267	4.2	486
R = R′ = OCH_3	265.3	4.2	486
R = OCH_3, R′ = H	252	4.2	486
	289	3.8	486
	260	2.2	1481
	247	2.7	283
	260	2.4	1481
cis-Benzalacetophenone oxide	248	4.1	1805
trans-Benzalacetophenone oxide	250–252	4.2	282, 812, 1805
cis-o-Nitrobenzalacetophenone oxide	253	4.3	382
trans-o-Nitrobenzalacetophenone oxide	253	4.3	382
			
cis-	250	4.1	824
trans-	248	4.2	824
			
cis-	247	4.1	1805
trans-	249	4.2	1805
 (X = Cl, Br, I)			

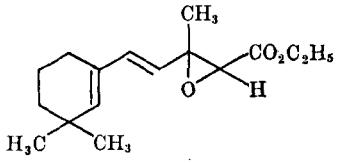
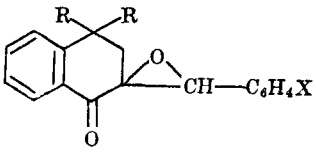
(*Table continued*)

TABLE 3 (*continued*)

Compound	λ_{max} (mμ)	log ε	Reference
cis-	247–250	4.1	1629, 1807
trans-	249–252	4.2–4.3	1629, 1807
			
cis-	253	4.2	822
trans-	252	4.2	822
			
cis-	245	4.0	1643
trans-	247	4.1	1643
 (Ar = mesityl)	270	4.0	608
	235	4.1	608
	243, 244 320, 335	4.0 3.9	282, 380, 381
	258 297 335	4.1 3.4 2.7	1462

(*Table continued*)

TABLE 3 (*continued*)

Compound	λ_{max} (mμ)	log ε	Reference
	286	4.3	730
			
R = H; X = *p*-Cl	258	4.2	378
o-NO_2	258	4.3	378
m-NO_2	259	4.3	378
p-NO_2	264	4.3	378
R = CH_3; X = *p*-Cl	260	4.2	378
o-NO_2	260	4.3	378
m-NO_2	258	4.4	378
p-NO_2	268	4.4	378
Steroid epoxides:			
1α,2α-Epoxy-3-oxo-	300–302	1.4	1517, 1663
8α,9α-Epoxy-7-oxo-	300	1.9	1517
8α,14α-Epoxy-7-oxo-	302.5	1.4	1517
16α,17α-Epoxy-20-oxo-	292	1.5–1.8	1517
16α,17α-Epoxy-20-acetoxy-	292	1.7	1517

C. Nuclear Magnetic Resonance Spectroscopy

The nuclear magnetic resonance spectrum of ethylene oxide itself has been examined in at least two laboratories.[692, 1153] Protons β to oxygen in ethylene oxide exhibit a very strong chemical shift when compared with protons β to oxygen in larger cyclic ethers. This phenomenon has been attributed to shielding by an unusually high electron density in the region of these protons, and a correspondingly low electron density in the region of oxygen.[692] It has been predicted on this basis that the decreasing order of basicities for cyclic orders should be: oxetane, tetrahydrofuran, tetrahydropyran, ethylene oxide.[692, 1556] Experimental verification was secured by studies of hydrogen bonding[1556] and iodine-complex formation.[235, 1693]

Evidence collated from several sources indicates that epoxide

protons will generally be found in the region of the nuclear magnetic resonance spectrum extending from 7.0 to 8.0 τ.[348, 809, 825, 1487, 1694] Systematic data concerning the stereoelectronic influence of various substituents on the chemical shift of epoxide protons is unfortunately still lacking.

Holm[798] reported that spin–spin interaction for ^{13}C nuclei is detectable under high resolution, and the ^{17}O resonance line of epichlorohydrin has recently been described as well.[1919]

5. Theoretical Models

A satisfactory theoretical model for ethylene oxide should take into account as many as possible of the physical properties discussed above, but should be able to predict or explain its chemical properties as well. Three such models have been proposed which are based on molecular-orbital theory,[381, 392, 1667, 1910] and two more which conform rather to the valence-bond representation of chemical structure.[1556,1667] The relative merits of all these models have been discussed in recent reviews.[867, 1301]

The Walsh model[1798] is founded on the premise that carbon atoms in ethylene oxide approach the sp^2 state, its CH_2 units being therefore pseudo-ethylenic in character. Four sp^2-like carbon valencies, directed above and below the plane of the ring, participate in bonding to hydrogen. The remaining two sp^2-like carbon valencies lie in the plane of the ring and are directed toward its center. Overlap of the latter with one of the oxygen atomic orbitals generates a set of three molecular orbitals (one bonding, and two antibonding). There remain two p-like carbon valencies directed perpendicularly to the sp^2-like valencies. These produce, on overlap with a second oxygen atomic orbital, another set of three molecular orbitals (two bonding, and one antibonding). The six electrons constituting three ring bonds can thus be accommodated among the three bonding molecular orbitals available. Because it does not lend itself to representation by means of classical chemical symbols the Walsh structure is best left in the form of an electron-density plot[1798,1301] (Fig. 2).

The effectiveness of the second type of overlap presumably determines the extent of olefinic character of the epoxide. That ethylene oxides are less 'unsaturated' in character than the corresponding cyclopropane derivatives is then attributable to a less favorable oxygen atomic-orbital orientation. The Walsh model is a satisfactory one in that it predicts accurately the C—H bond force constants,[907, 1798]

C—C bond distance,[1798] conjugating power,[280, 381, 1481] and magnetic susceptibility[989] of ethylene oxide.

The second important theoretical model of ethylene oxide, based on the model of cyclopropane developed by Coulson and Moffitt, was constructed independently by Cromwell and co-workers,[282, 380, 381] and by Cunningham and co-workers.[392] Briefly, this approach sets out to vary the carbon hybridization from sp^3 to a value intermediate between sp^2 and sp^3 in such a way that loss of overlap energy is just

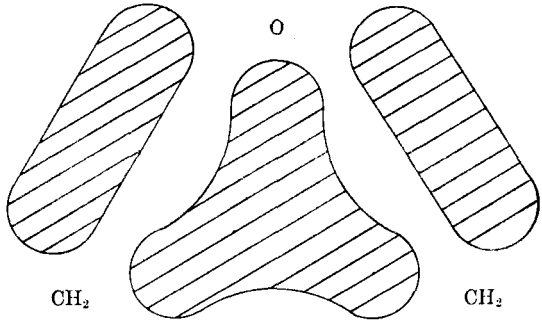
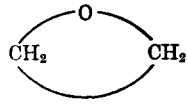


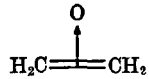
Fig. 2. Ethylene oxide structure (Walsh[1798]).

offset by gain of energy through relief of ring strain. As carbon hybridization gradually passes from sp^3 to sp^2 there is a tendency for the CH_2 hydrogens to spread apart, the 120° ethylenic H—C—H bond angle being approached as a limit. Correspondingly, there is a tendency for the O—C—C bond angle to depart from the optimum tetrahedral value of 109° 5′. Since accurate values are available for these angles by microwave spectroscopy and electron diffraction, it is possible to calculate the actual hybridization state of the ethylene oxide carbons. Cunningham and co-workers found this to be $sp^{2.22}$. The chief structural consequence of this fractional hybridization state is that the atomic orbitals of carbon are not directed along the internuclear axis but away from it, to the extent of 31° for the C—C axis and 14° for the C—O axis. In effect the bonds in ethylene oxide can thus be spoken of as 'bent bonds', and its formula represented as (I).



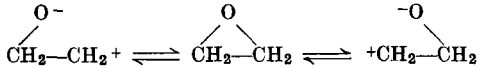
(I)

The most recent attack on this problem is that by Jaffé,[867] who concludes basically that ethylene oxide resembles the π-complexes formulated by Dewar for the interaction of olefins with metal cations, bromonium ions, and even protons. This approach assumes ethylenic carbon atoms at the outset, and proceeds to estimate the extent of departure from ethylenic character when the atomic orbital of oxygen is allowed to interact with the π-orbital linking the two carbons. From this point of view ethylene oxide could be depicted as (II).



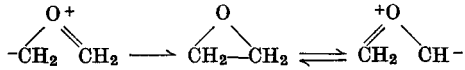
(II)

In addition to the molecular-orbital treatments just discussed there have been various structural proposals emphasizing one or more valence-bond canonical formulas at the expense of others. Thus, on the basis of intrinsic electronegativities, Zimakov[1910] regarded ethylene oxide to be a hybrid of the three limiting structures (IIIa), (IIIb), and (IIIc).



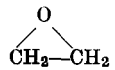
(IIIa) (IIIb) (IIIc)

On the other hand, Searles and co-workers,[1556] arguing on the basis of the low electron density on oxygen indicated by nuclear magnetic resonance and basicity data, favored a hybrid composed of limiting structures (IVa), (IVb), and (IVc).



(IVa) (IVb) (IVc)

In justifying structure (II) Jaffé[816] criticized the hybrid proposed by Searles and co-workers for requiring improper geometry at CH_2. Other authors have commented on the problem,[907, 1069, 1478] but thus far no general agreement can be said to exist regarding the correctness of any proposed structures for ethylene oxide. Since molecular-orbital representations and other devices are not typographically convenient, the classical formula (V) must suffice here and will be retained throughout the remainder of this chapter.



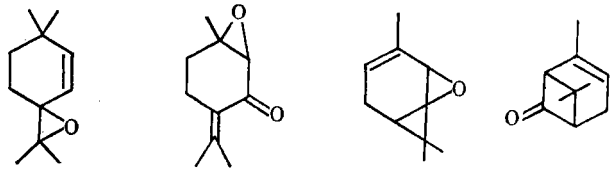
(V)

II. Occurrence of Epoxides in Nature

The occurrence of epoxides in substances of natural origin is not a common phenomenon, although it is becoming increasingly evident from the literature of recent years that such structural units are by no means so rare as had once been thought. The growing importance of epoxides in the field of natural products has in fact warranted a recent review by Cross.[385]

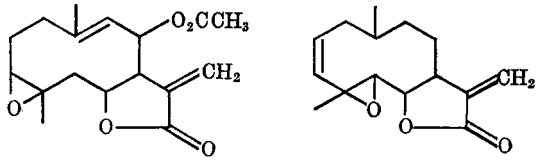
Although examples of the ability of biological systems to synthesize epoxide rings are relatively few, a number of examples are known, particularly in the plant kingdom. The substances cited in the present section obviously represent a broad range of structural complexity. Further, the wide variety in source of origin of these natural products bespeaks the rather generalized capacity of living organisms to construct epoxide rings by means of their enzyme apparatus.

Two simple constituents that appear to contain epoxide units have been detected in essential oils. These are linalool epoxide (VI)[1218] and 1,2-epoxypulegone (VII).[1447] The substance once formulated as 5,6-epoxycar-3-ene (VIII) by Penfold and Simonsen[1322] has recently been reformulated as chrysanthenone (IX) by Blanchard,[169] however.



(VI) (VII) (VIII) (IX)

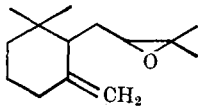
Pyrethrosin (X), an active component of extracts from *Chrysanthemum* species, was recently discussed by Barton and co-workers,[90, 96] as was the related substance parthenolide (XI) in another laboratory.[755]



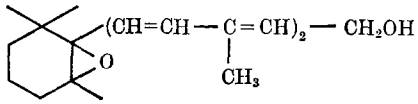
(X) (XI)

A simple epoxide related to ionone has been isolated from amber oil by Ruzicka and Seidel, and the structure (XII) tentatively assigned to it.[1513] Vitamin A epoxide (XIII) is believed to coexist with vitamin

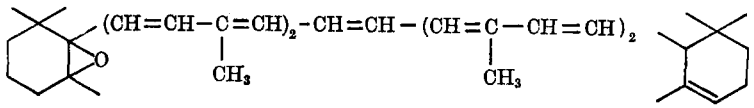
A in fish-liver oil and other sources.[909] Also believed to be a genuine naturally-occurring epoxide is the substance α-carotene monoepoxide (XIV).[911]



(XII)

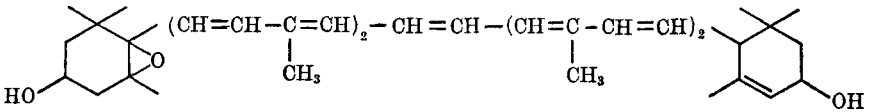


(XIII)



(XIV)

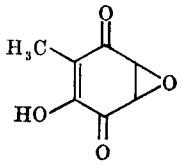
Similarly, Karrer and co-workers discovered that the carotenoid flower pigment trollixanthin (XV),[1039] as well as the related substances antheroxanthin,[908, 914] violaxanthin,[915] and epoxylutein,[910, 916] all contain epoxide units. The subject of naturally-occurring carotenoid epoxides has been reviewed recently,[444, 385] and attention called to the possible need for revision in certain of the structural assignments made by Karrer and his associates.[385]



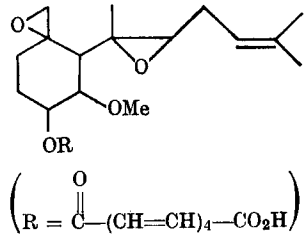
(XV)

A number of naturally-occurring fatty acid epoxides have been isolated from various sources. Among these are *cis*-9,10-epoxyoctadecanoic acid,[1768] *cis*-9,10-epoxyoctadec-12-enoic (coronaric) acid,[1596] *cis*-12,13-epoxyoctadec-9-enoic (vernolic) acid,[100, 677] and *cis*-15,16-epoxyoctadeca-9,12-dienoic acid.[678]

An antibiotic mould metabolite from a species of *Aspergillus* was recently found by Sheehan and co-workers[1567] to incorporate an epoxide unit in its structure, which was formulated as (XVI). Another antibiotic from an *Aspergillus* species is the unusual bisepoxide fumagillin, whose structure was recently established by Tarbell and co-workers to be (XVII).[1694, 1695]

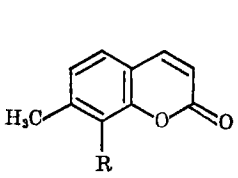


(XVI)

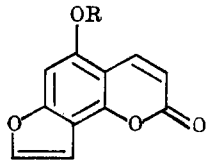


(XVII)

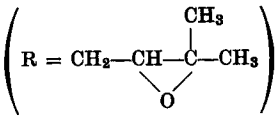
Several plant substances of the coumarin type have been discovered to contain epoxide rings. Among these are auropten (XVIII), a bitter principle occurring in orange-peel oil ;[208] oxypeucedanin (XIX), a potent fish poison found in certain plant rhizomes ;[1615] a related toxin known variously as ferulin or byakangelicol (XX) ;[219, 428] and aculeatin (XXI).[472]

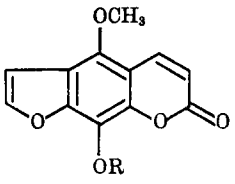


(XVIII)

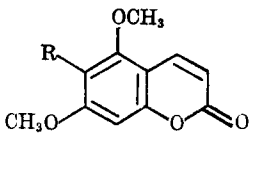


(XIX)

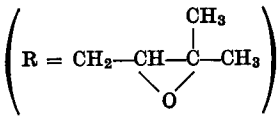




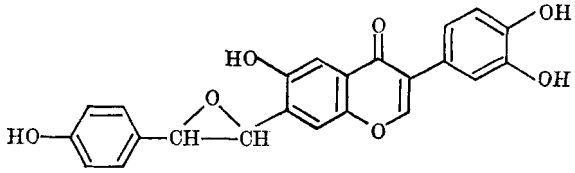
(XX)



(XXI)

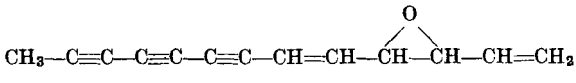


Still another epoxide-containing plant pigment is the flavone fukugetin (XXII), also known as garcinin.[980]

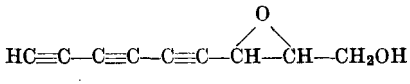


(XXII)

Bohlman and co-workers[207] recently isolated from an *Artemisia* species a polyacetylenic epoxide formulated as (XXIII). The same substance, known as 'pontica epoxide', has been described also by Hemmer and co-workers.[1956] Jones and Stephenson[881] had previously reported the isolation of a polyacetylenic fungal metabolite containing a *trans*-substituted epoxide ring (XXIV). Their discovery of the corresponding olefin and 1,2-diol in the same culture is biogenetically significant, since it suggests the possible intermediacy of epoxide functions in the biological conversion of olefins into 1,2-diols. It may be recalled that Bloom and co-workers[174, 175] have succeeded in converting certain unsaturated steroids into the corresponding epoxysteroids by incubation in the presence of suitable micro-organisms.

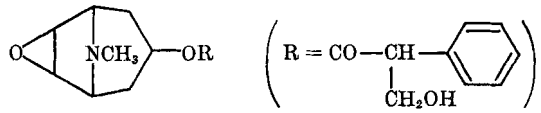


(XXIII)



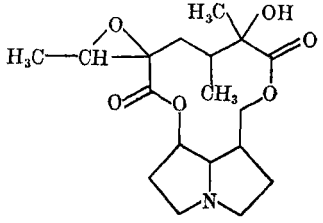
(XXIV)

The alkaloid scopolamine, recently synthesized by Fodor and collaborators,[512] has long been considered to incorporate an epoxide unit,[879] and is now known with certainty to possess structure (XXV).

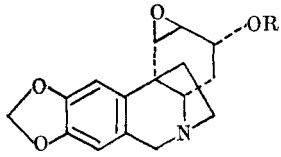


(XXV)

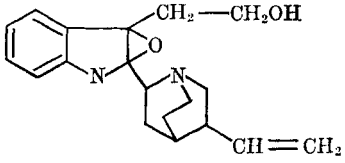
At least two other classes of alkaloids are known at present to include representatives containing epoxide functions. Mention may be made here of jacobine (XXVI)[231, 628] and other *Senecio* alkaloids,[385] and of the *Amaryllidaceae* alkaloids undulatine (XXVIIa) and crinamidine (XXVIIb).[515, 1804] The *Cinchona* alkaloid quinamine was once formulated as an epoxide (XXVIIIa),[661] but now appears to possess a structure (XXVIIIb) containing no epoxide ring.[1867, 385] It is very probable that the number of epoxide alkaloids will grow with time, as investigations of minor members of the various families of alkaloids are pursued.



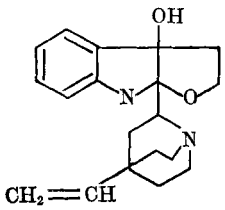
(XXVI)



(XXVIIa: R = H; XXVIIb: R = CH_3)

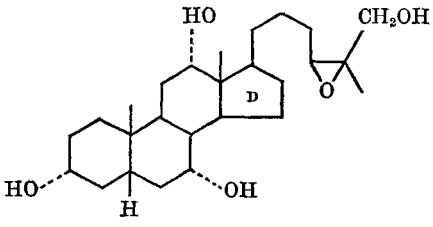


(XXVIIIa)

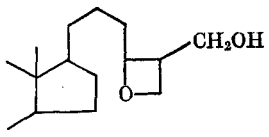


(XXVIIIb)

The bile alcohol scymnol, a characteristic constituent of the bile of certain sharks, was at one time believed to contain an epoxide function, as in (XXIX).[139] Experimental evidence recently published by Cross,[384, 1971] however, has confirmed a suspicion already expressed earlier by Fieser and Fieser[534] that this assignment was in error. The correct structure of scymnol is probably (XXX).

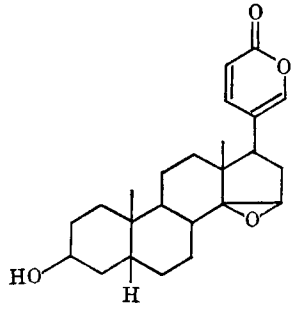


(XXIX)



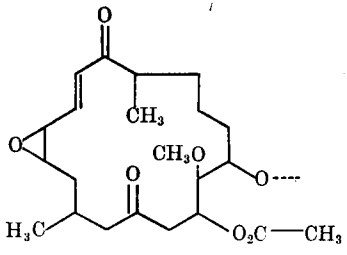
(XXX)

Other members of the steroid class which do contain epoxide rings, on the other hand, are certain bufogenins, *e.g.* resibufogenin (XXXI).[794, 1711] Others in the same family are cinobufagin, marinobufagin, bufatolinin, and jamaicobufagin.[75, 1034, 793, 1547, 1548, 1033]

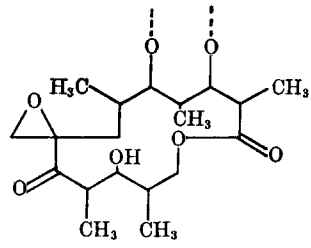


(XXXI)

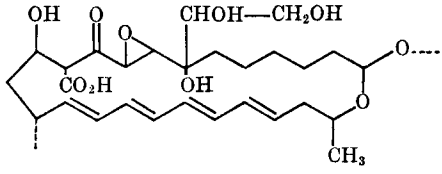
Three macrolide antibiotics have been assigned epoxide rings. These are magnamycin (XXXII),[1877] oleandomycin (XXXIII),[791] and pimaricin (XXXIV),[1305] all derived from species of *Streptomyces* and possessing high activity against pathogenic micro-organisms.



(XXXII)



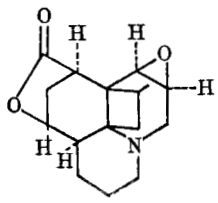
(XXXIII)



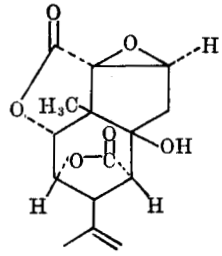
(XXXIV)

A few other complex natural products containing epoxide rings have been reported. These include the alkaloid annotinine

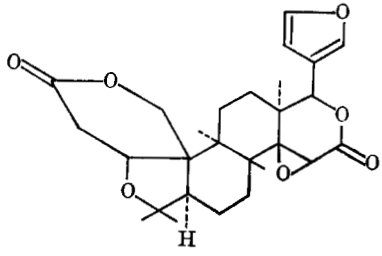
(XXXV);[1838, 1961] the fish poison picrotoxinin (XXXVI),[331] as well as coriamyrtin[1273] and related substances;[266] the citrus bitter principle limonin (XXXVII) and the related substances nomilin and obacunone;[40, 49] and the terpenoid substances clerodin[1957,1958] and cedrelone.[1959, 1960]



(XXXV)



(XXXVI)



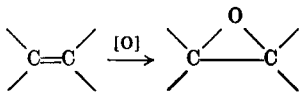
(XXXVII)

It is very probable that future work by organic chemists interested in natural products will bring to light many more examples of substances containing one or more epoxide rings. That such structures are not found more frequently in nature, in spite of the fact that they may well occur very widely as unisolable biogenetic intermediates, is a reflection of the labile character of the epoxide function even under 'physiological conditions'. It would not be unreasonable to expect the most likely candidates for discovery to be substances in which the epoxide function is chemically deactivated, either by virtue of steric inaccessibility or of electronic effects. Such substances should also, moreover, exhibit a correspondingly lower degree of physiological activity.

III. Synthesis of Epoxides

1. Olefin Oxidation

Among the numerous approaches available to chemists for the synthesis of epoxides, perhaps none could be more direct than oxidation of the corresponding olefins, as shown in Eq. (5).



(5)

A. Peroxy Acid Oxidation

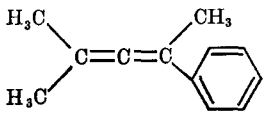
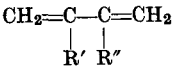
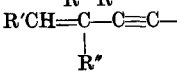
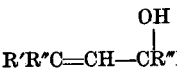
Of all the many techniques currently in use for epoxide synthesis, peroxy acid oxidation of a suitable olefin is probably the most frequently encountered. Its advantages over other methods are considerable. Conditions are always mild, the reaction time is seldom long, and yields are usually high. On the other hand, some side-products are occasionally formed, abnormal reactions sometimes create confusion, and reagent preparation on a large scale is not devoid of danger. For the most part, however, this procedure is of great importance and usefulness in all areas of organic chemistry involving epoxides.

(1) Scope. The scope of the peroxy acid technique has been amply demonstrated in two encyclopedic reviews by Swern,[1678, 1679] himself one of the leading contributors in the field. Inasmuch as these reviews encompass the literature up to 1952, their duplication here would be fruitless. Moreover, the number of references that could be collected even since 1952 is so immense as to render complete tabulation impracticable in the present article. A representative sampling of the literature of recent years is presented in Table 4. Additional examples will be found in the text, and in the reviews by Swern.

Several peroxy acids are used in the conversion of olefins into epoxides. Their properties and preparations have been described by Swern.[1678, 1679] Included among them are performic acid, peracetic acid, perbenzoic acid, monoperphthalic acid, and percamphoric acid. More recently trifluoroperacetic acid has attained some prominence.[501, 1146, 1778] Certain desirable features have been discovered in *p*-nitroperbenzoic acid as well.[1790]

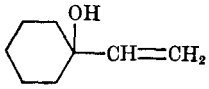
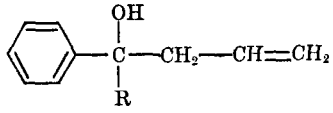
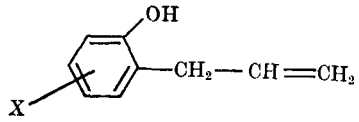
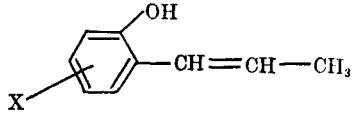
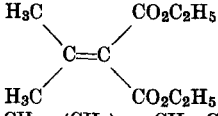
Preference for one or another of these reagents rests on its accessibility or ease of preparation, on the absence of interfering processes, and on the general convenience and safety of handling and work-up.

TABLE 4. Peroxyacid Oxidation of Olefins

Compound		Reference
A. Acyclic olefins		
$R'R''C{=}CR''R''''$	$R' = R'' = R''' = R'''' = H$	1756
	$R' = R'' = R''' = H$; $R'''' = n\text{-}C_5H_{11}$	1022
	$R' = R''' = H$; $R'' = C_2H_5$; $R'''' = n\text{-}C_3H_7$	522
	$R' = R'' = CH_3$; $R''' = H$; $R'''' = tert\text{-}C_4H_9$	273
	$R' = R'' = H$; $R''' = CH_3$; $R'''' = neoC_5H_{11}$	274
	$R' = R'' = H$; $R''' = R'''' = neoC_5H_{11}$	84
	$R' = R'' = R''' = R'''' = CH_3$	492, 774, 1409
	$R' = R'' = R''' = H$; $R'''' = C_6H_5$	901, 1060
	$R' = R''' = H$; $R'' = CH_3$; $R'''' = C_6H_5$	125
	$R' = R'' = H$; $R''' = CH_3$; $R'''' = C_6H_5$	125
	$R' = R'' = CH_3$; $R''' = H$; $R'''' = C_6H_5$	1026
	$R' = R'' = H$; $R''' = R'''' = C_6H_5$	1816
	$R' = R''' = H$; $R'' = R'''' = C_6H_5$	280, 813, 919, 1060
	$R' = H$; $R''' = CH_3$; $R'' = R'''' = C_6H_5$	920, 1743
	$R' = H$; $R'' = R''' = R'''' = C_6H_5$	992, 1060, 1817
	$R' = H$; $R'' = R''' = C_6H_5$; $R'''' = C_6H_5CH_2$	920
	$R' = R'' = R''' = R'''' = C_6H_5$	1020, 1060
$CH_2{=}CH{-}(CH_2)_n{-}CH{=}CH_2$	(n = 1–6, and alkyl-substituted analogs)	511, 1843
		1291
	$R' = R'' = H, CH_3$	
	$R' = H$; $R'' = CH_3$	511
	$R' = R'' = CH_3$	
	$R' = C_2H_5$; $R'' = n\text{-}C_3H_7$	1089
	$R' = R'' = R''' = R'''' = H$	547
	$R' = CH_3$; $R'' = R''' = R'''' = H$	868
	$R' = C_6H_5$; $R'' = R''' = R'''' = H$	868, 1289, 1666

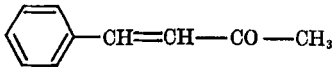
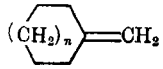
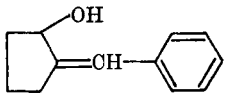
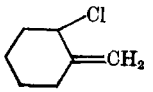
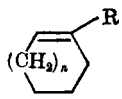
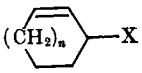
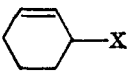
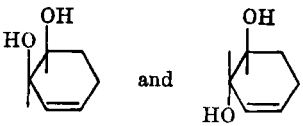
(*Table continued*)

TABLE 4 (*continued*)

Compound		Reference
	$R' = C_6H_5$; $R'' = R''' = H$; $R'''' = CH_3$	
	$R' = C_6H_5$; $R'' = H$; $R''' = R'''' = CH_3$	
	$R' = R'' = R''' = R'''' = CH_3$	1287
	$R' = R'' = R''' = CH_3$; $R'''' = C_2H_5$	1287
	$R' = R'' = R''' = CH_3$; $R'''' = n\text{-}C_3H_7$	1287
	$R' = R'' = R''' = CH_3$; $R'''' = n\text{-}C_4H_9$	1287
	$R' = R'' = R''' = CH_3$; $R'''' = iso C_5H_{11}$	1287
	$R' = R'' = H$; $R''' = CH_3$; $R'''' = C_6H_5CH_2$	1288
		1220
	R = H, CH_3	1289
	X = *o*-CH_3O, *m*-CH_3, *p*-CH_3	1292
	X = *o*-CH_3O, *m*-CH_3, *p*-CH_3	1292
$R'R''CH—CH=CH—CH_3$	$R' = R'' = CH_3CO_2$	259
	$R' = R'' = n\text{-}C_4H_9O$	767
	$R'R'' = —OCH_2CH_2O—$	1364
$H_3C—CH=CH—CO_2H$		239, 347
		1313
$CH_3—(CH_2)_{10}—CH=CH—(CH_2)_4—CO_2H$	(*cis*- and *trans*-)	893
$H_3C—(CH_2)_7—CH=CH—(CH_2)_7—CO_2H$	(*cis*- and *trans*-)	1868
$H_3C—(CH_2)_3—CH=CH—(CH_2)_{11}—CO_2H$	(*cis*- and *trans*-)	893

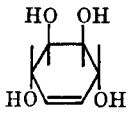
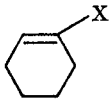
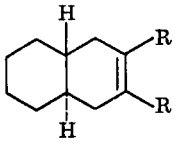
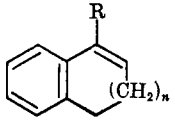
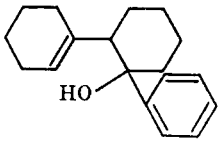
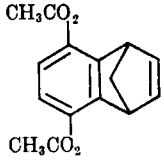
(*Table continued*)

TABLE 4 (*continued*)

Compound		Reference
		1410
B. Semicyclic and alicyclic olefins		
	$n = 1$	1951
	$n = 3$	1923
	$n = 4$	1923
		827
		1198, 1203
	$n = 0$	369
	$n = 1$	190
	$n = 2$	190
	$n = 3$	194
	$n = 4$ (*cis*- and *trans*-)	340, 341, 344
	$n = 5$ (*cis*- and *trans*-)	1404
	$n = 6$ (*cis*- and *trans*-)	1402, 1403
	$n = 7$ (*cis*- and *trans*-)	1401, 1405
	$n = 8$ (*cis*- and *trans*-)	1401, 1405
	R = CH_2=CH; $n = 1$	511
	R = C_6H_5C≡C; $n = 1$	1088
	R = C_6H_5; $n = 0, 1$	190, 1024 1946
	X = Cl, $n = 0$	
	X = Cl, $n = 1$	1193
	X = OH, CH_3CO_2, CH_3O, C_2H_5O	741
		1400

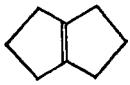
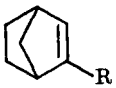
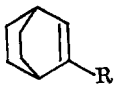
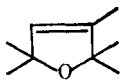
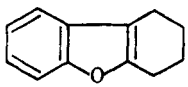
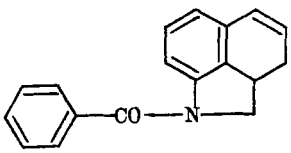
(*Table continued*)

TABLE 4 (*continued*)

Compound		Reference
		1545
	X = Cl	1198, 1201, 1203
	X = CH_3CO_2	1188, 1194, 1488
	R = H, CH_3	739
	n = 1, R = C_6H_5	1163
	n = 2, R = H	363
	n = 3, R = H	841
	n = 1	962
	n = 2	1400
	n = 4	349
		338
		348, 350, 588, 1448, 1832
		76
		1146

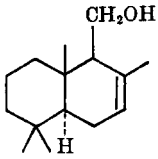
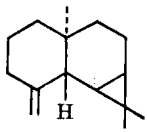
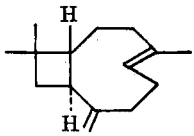
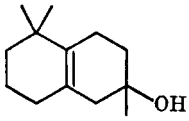
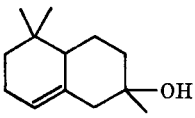
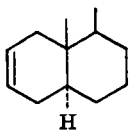
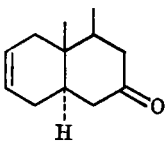
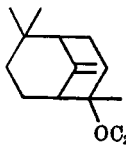
(*Table continued*)

TABLE 4 (*continued*)

Compound		Reference
		343
	R = H, C_6H_5	986, 1602, 1795
	R = H, C_6H_5	614
C. Heterocyclic olefins		
		1519
		1144
		1864
		963
		423
		1610
D. Miscellaneous terpenes		
l-Menthene		1233
Limonene		1948, 1962
Car-3-ene		39
Camphene		512
α-Pinene		1412
β-Pinene		512

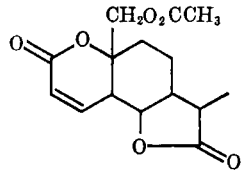
(*Table continued*)

TABLE 4 (*continued*)

Compound	Reference
	36
	260
	89, 92, 95, 1428
	259
	259
	1901
	1900
	1655

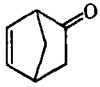
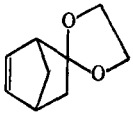
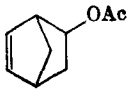
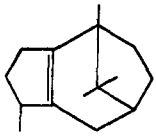
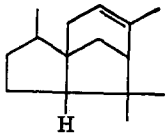
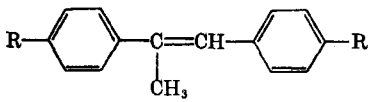
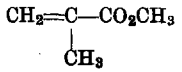
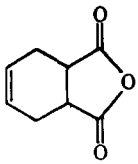
(*Table continued*)

TABLE 4 (*continued*)

Compound	Reference
	1777
E. Steroids	
$\Delta^{1,2}$-Steroids	18, 741, 1371, 1663
$\Delta^{2,3}$-Steroids	603, 738, 1071
$\Delta^{3,4}$-Steroids	1574, 1903, 604
$\Delta^{4,5}$-Steroids	54, 741, 936, 1896
$\Delta^{5,6}$-Steroids	224, 226, 267, 268, 281, 580, 906, 1375, 1376, 1378, 1466, 1484, 1501, 1904
$\Delta^{5,10}$-19-Norsteroids	1504, 1904, 1972
$\Delta^{6,7}$-Steroids	225, 831, 869, 871, 1167
$\Delta^{7,8}$-Steroids	455, 536, 542
$\Delta^{8,9}$-Steroids	1071
$\Delta^{8,14}$-Steroids	536
$\Delta^{11,12}$-Steroids	950
$\Delta^{9,11}$-Steroids	790
$\Delta^{13,14}$-18-Norsteroids	1484
$\Delta^{14,15}$-Steroids	1607
$\Delta^{16,17}$-Steroids	996, 1167, 1823
$\Delta^{17,20}$-Steroids	299, 1167, 1601
$\Delta^{16,17}$-D-Homosteroids	1826, 1830
$\Delta^{4,5;6,7}$-Steroids	937, 1258
$\Delta^{7,8;9,11}$-Steroids	165, 262, 298, 456, 457, 493, 761, 1003, 1544, 1608, 1658
$^{1,2;4,5}$-Steroids	1973

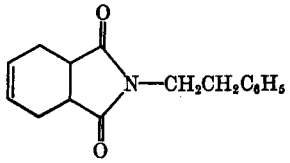
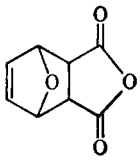
(*Table continued*)

TABLE 4 (*continued*)

Compound		Reference
F. Miscellaneous olefins		
4-*tert*-butylcyclohexene		1963
		1964
		1964
		1964
		1965
		1966
$RCH_2CH{=}CH_2$	R = Br, Cl, OH, CN, C_6H_5O, *iso*C_3H_7O, C_6H_5, *n*-C_4H_9	1967
$RCH_2CH{=}CHCH_2R'$	R = R′ = Br, C_6H_5, C_6H_5O R = Br, R′ = C_6H_5O	1967
	R = H; R′ = H, Cl, CH_3, CH_3O R = Cl, CH_3, CH_3O; R′ = H	1968
		1983
		1969

(*Table continued*)

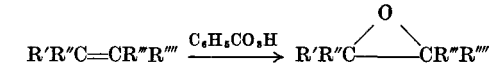
TABLE 4 (*continued*)

Compound	Reference
	1969
	1970

Detailed preparative directions are available for perbenzoic and monoperphthalic acid, the reagents now most in favor for synthetic or degradative work in the field of natural products. On the other hand, the commercial availability of stable, standardized peracetic acid solutions in bulk renders this reagent attractive. It is important to note, however, that peracetic and performic acids are generally not satisfactory for epoxidation unless addition is conducted in a buffered medium to prevent rupture of the oxide ring by excess of acid. Although trifluoroperacetic acid likewise requires the use of a buffer, this reagent appears to possess certain advantages over peracetic acid, for example. Among the desirable characteristics claimed for *p*-nitroperbenzoic acid[1790] are that it is highly reactive, that it can be stored safely for prolonged periods as a solid, and that it does not cause epoxide rupture or isomerization, as even perbenzoic and monoperphthalic acids do on occasion.[546, 1216]

The following classes of olefins have been satisfactorily converted into epoxides with one or more peroxy acids: (1) acyclic olefins bearing only aliphatic substituents; (2) acyclic olefins carrying at least one olefinic, acetylenic, or aromatic substituent; (3) monocyclic olefins bearing aliphatic, olefinic, acetylenic, or aromatic substituents; (4) various polycyclic olefinic hydrocarbons; (5) olefins carrying at least one carbon singly bonded to a polar atom; (6) olefins attached directly to polar atoms; and (7) olefins bearing at least one carbon multiply bonded to a polar atom. These several types will now be illustrated briefly.

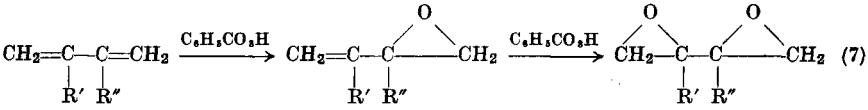
Variously alkyl-substituted acyclic olefins (Eq. 6) have been reported to yield epoxides on treatment with perbenzoic acid, such as ethylene itself,[1756] 1-heptene,[1022] 3-heptene,[522] 2,4,4-trimethyl-1-pentene,[274] 2,4,4-trimethyl-2-pentene,[273] 2,3-dimethyl-2-butene,[1409, 492, 774] and 1,1-di*neo*pentylethylene.[84]



(6)

R′ = R″ = R‴ = R⁗ = H, CH_3
R′ = R″ = R‴ = H; R⁗ = *n*-C_5H_{11}
R′ = R″ = H; R‴ = C_2H_5; R⁗ = *n*-C_3H_7
R′ = R″ = H; R‴ = Me, *neo*C_5H_{11}; R⁗ = *neo*C_5H_{11}
R′ = R″ = CH_3; R‴ = H; R⁗ = *tert*-C_4H_9

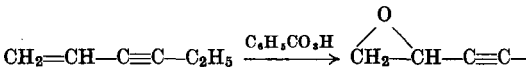
1,3-Butadiene, 2-methyl-1,3-butadiene (isoprene), and 2,3-dimethyl-1,3-butadiene can yield mono- or diepoxides depending on the reactant ratio employed.[511] With isoprene the most substituted double bond is attacked first (Eq. 7).



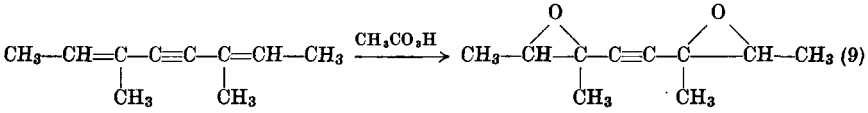
(7)

R′ = R″ = H, CH_3
R′ = H; R″ = CH_3

Illustrative of the preparation of epoxyacetylenes are the reactions of perbenzoic acid with 1-ethyl-3-buten-1-yne[16] and of peracetic acid with 3,6-dimethyl-2,4-octadien-4-yne,[1089] as shown in Eqs. (8) and (9).



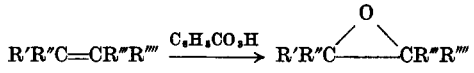
(8)



(9)

Among the phenyl-substituted ethylenes convertible into epoxides by treatment with perbenzoic acid are styrene,[901, 1060] 1-phenyl-1-propene,[125] 2-phenyl-1-propene,[125] 2-methyl-1-phenyl-1-propene,[1026] 1,1-di-*p*-tolylethylene,[1429] 1,1-diphenyl-1-propene,[1816] 1,2-diphenyl-1-propene,[1743, 920] stilbene,[1060, 919, 280, 813] triphenylethylene,[1060, 1817, 992]

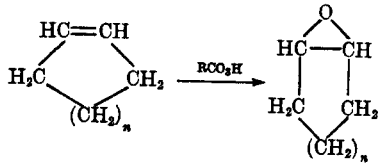
1,2,3-triphenyl-2-propene,[920] and tetraphenylethylene,[1060, 1020] as shown in Eq. (10).



(10)

$R' = R'' = H$; $R'' = H, CH_3, C_6H_5$; $R''' = C_6H_5$
$R' = R''' = H$; $R'' = CH_3, C_6H_5$; $R'''' = C_6H_5$
$R' = R'' = CH_3$; $R''' = H$; $R'''' = C_6H_5$
$R' = H$; $R'' = CH_3$; $R''' = R'''' = C_6H_5$
$R' = R'' = R''' = R'''' = C_6H_5$

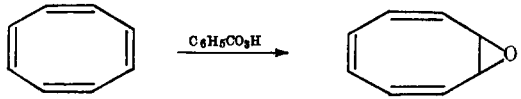
Unsubstituted monocyclic olefins that have been converted into the corresponding epoxides by the peroxyacid technique include cyclobutene,[369] cyclopentene,[190] cyclohexene,[190] cycloheptene,[194] *cis*- and *trans*-cyclooctene,[340, 341, 344] *cis*- and *trans*-cyclononene,[1404] and *cis*- and *trans*-cyclodecene,[1402, 1403] In addition, the *cis*- and *trans*-isomers of cycloundecene[1401, 1405] and cyclododecene[1401, 1405] give products derivable from the corresponding epoxides by performic acid-catalyzed rearrangement (Eq. 11).



(11)

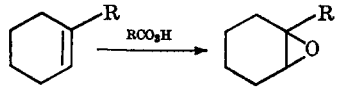
$n = 0$–8

The product obtained on oxidation of cyclooctatetraene with perbenzoic acid[1448] has been a subject of some controversy,[350, 588, 1832] but its structure now appears to be a settled issue[348] (Eq. 12).



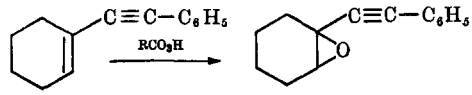
(12

Simple illustrations of monocyclic olefins bearing unsaturated substituents (Eqs. 13 and 14) are 1-vinylcyclohexene,[511] 1-phenylethinylcyclohexene,[1088] and 1-phenylcyclohexene.[190, 1024]



(13)

$R = -C_6H_5, -CH=CH_2$

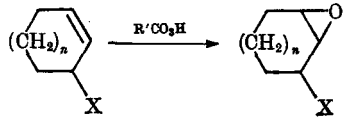


(14)

The array of polycyclic olefins that have been epoxidized with peroxy acids defies complete documentation. A very comprehensive listing may be found in the reviews of Swern,[1678, 1679] and a few recent examples have been collected in Table 4.

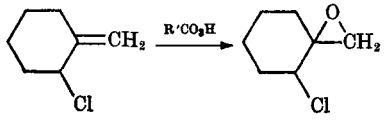
Familiar instances of the conversion of terpenes into epoxides include camphene,[512] car-3-ene,[39] and α- and β-pinene.[1412, 512] Examples of peroxy acid epoxidation are even more plentiful among the higher terpenes,[1131] particularly in the field of steroids.[1679, 532] Epoxide functions have now been introduced in virtually every conceivable site of the cyclopentaperhydrophenanthrene skeleton, as indicated in Table 4.

Peroxy acid treatment of olefins carrying one or more carbon atoms singly bonded to polar atoms like halogens or oxygen (Eqs. 15–17) proceeds satisfactorily with 1-chloro-2-cyclopentene,[1193] 1-chloro-2-cyclohexene,[1193] 2-chloro-1-methylenecyclohexane,[1203, 1198] allyl and crotyl alcohols,[547, 868] 1-hydroxy-2-cyclohexene,[741] and others.[1679,1967] The well-known susceptibility of amino groups and of bivalent sulfur to oxidation by peroxy acids naturally renders these reagents unsuitable for the preparation of epoxides in which intact amino or bivalent sulfur functions are desired.[552]

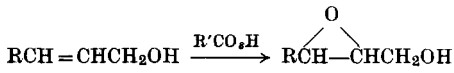


(15)

$n = 0, 1$; X = Cl
$n = 1$; X = OH

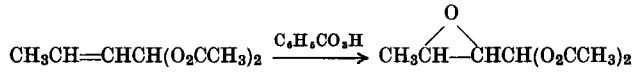


(16)

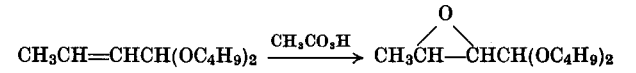


R = H, CH_3, C_6H_5 (17)

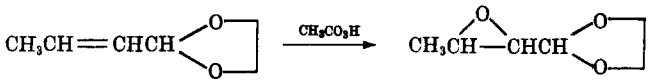
Illustrative of the epoxidation of olefins bearing a carbon substituent bonded to two electronegative atoms are the three examples depicted in Eqs. (18)–(20).[767, 1364]



(18)

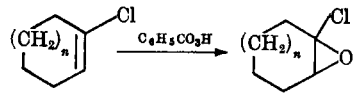


(19)



(20)

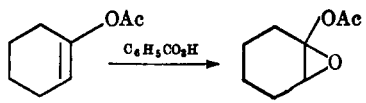
There have also been prepared several epoxides carrying a polar atom directly on one of the ring carbon atoms. Thus, 1-chloro-1-cyclopentene and 1-chloro-1-cyclohexene (Eq. 21) reportedly give the corresponding chloroepoxides on treatment with perbenzoic acid.[1198, 1201, 1203]



(21)

$n = 0, 1$

Shine and Hunt[1488] reported treatment of 1-acetoxycyclohexene with perbenzoic acid (Eq. 22) to yield the desired epoxide, which is different from the substance earlier described by Mousseron and co-workers.[1188, 1194]



(22)

Epoxyacetates have also been prepared from steroid enol acetates by Hirschmann and Wendler,[790] Soloway and co-workers,[1601] and Leeds and co-workers.[996] Moffett and Slomp[1167] have found, with certain unsaturated steroid enol acetates, that where a choice of reaction sites exists perbenzoic acid attacks a simple olefinic double bond preferentially. At higher temperatures and with excess of peroxy acid, however, there occurs epoxidation of the enol acetate

double bond as well. Similar views regarding the selectivity of peroxy acid attack have been expressed in a different context by Van Tamelen and Hildahl.[1778]

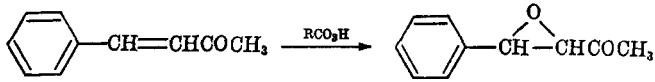
The synthesis of epoxy ethers by peroxy acid treatment of suitable vinylic ethers, on the other hand, is complicated by the acid-sensitivity of epoxy ethers. For example, Bergmann and Mickeley[135] claimed in 1921 to have prepared 1-ethoxy-1,2-epoxyethane by the oxidation of ethyl vinyl ether with perbenzoic acid, but 8 years later modified their structure to a dioxane type of dimer.[136] In 1950 Mousseron and co-workers[1188, 1194] reported the preparation of an epoxy ether from 1-ethoxy-1-cyclohexene, but 4 years later Stevens and Tazuma[1642] showed the compound obtained in this oxidation not to have the structure initially assigned to it.

Although Paul and Tchelitcheff[1309] demonstrated in 1947 that 2,3-dihydropyran did not yield the desired epoxy ether with perbenzoic acid, Hurd and Edwards[843] claimed in 1949 to have obtained this elusive substance. More recently, however, Barker and co-workers[78] reported once again the failure of perbenzoic acid to produce an epoxy ether from 2,3-dihydropyran, and Wood and Fletcher confirmed this observation in the sugar series.[1875]

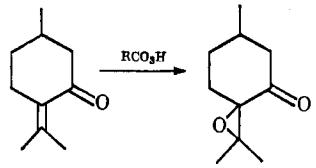
Again in the carbohydrate field, Raphael and Roxburgh[1434] described the preparation of a labile intermediate assumed to possess a monomeric epoxy ether structure but too reactive to allow its isolation. Unsuccessful attempts by Huffman and Tarbell[840] to prepare an epoxide from 2-benzhydrylidenetetrahydrofuran constitute additional evidence of the instability of bicyclic epoxy ethers.

It is generally recognized that when an olefin bears one or more carbon atom multiply bonded to a polar atom like oxygen, the reactivity of the olefinic double bond is considerably depressed, though not entirely extinguished, if an alkyl or phenyl substituent is also present.[1676] Acid and ester functions are apparently more deactivating than ketones or aldehydes. Thus, although maleic and fumaric esters[189, 213] are virtually inert with respect to perbenzoic acid or peracetic acid, crotonic acid,[347, 239] benzalacetone,[1410] and pulegone[1411] do slowly undergo epoxidation in moderate yield (Eqs. 23–25).

$$CH_3CH{=}CHCO_2H \xrightarrow{RCO_3H} CH_3\overset{O}{\overset{/\backslash}{C}}H{-}CHCO_2H \qquad (23)$$



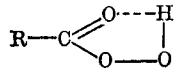
(24)



(25)

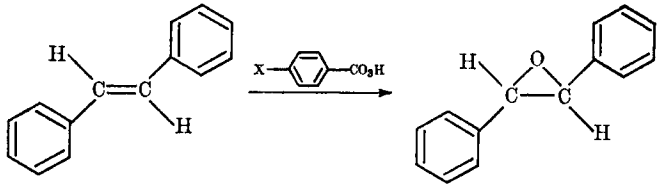
(2) Mechanism. The following types of evidence are pertinent in selecting an acceptable mechanism for olefin epoxidation by means of peroxy acids : (1) the nature of the peroxy acid and the electronic effect of substituents on its reactivity ; (2) the electronic effect of substituents on the reactivity of the olefin component ; (3) stereochemical factors affecting the reactivity of the olefin ; (4) the possibility of acid catalysis ; (5) solvent effects ; and (6) neighboring group effects.

Infrared measurements[426, 636, 1165] indicate that peroxy acids are present in solution largely in the monomeric, intramolecularly hydrogen-bonded form (XXXVIII), in accordance with the fact that they are more volatile than the corresponding carboxylic acids.



(XXXVIII)

Lynch and Pausacker[1060] studied the kinetics of *trans*-stilbene epoxidation with several substituted perbenzoic acids (Eq. 26), and found that electron-donating substituents depress the rate of reaction, *p*-nitroperbenzoic acid attacking *trans*-stilbene more than 30 times faster than does *p*-methoxyperbenzoic acid. Satisfactory linear relationships were obtained between the logarithms of the rate constants and Hammett σ constants. It can be concluded from this that the peroxy acid is an electrophilic reagent.

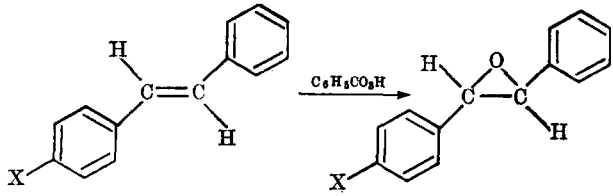


(26)

X = H, CH_3, Cl, CH_3O, NO_2

Swern[1676, 1679] has discussed the effect of substituents on the susceptibility of olefins to peroxy acid attack, on the basis of kinetic

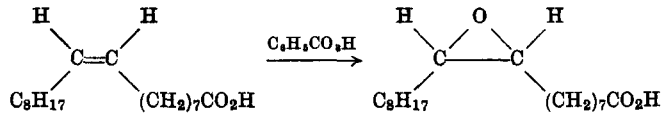
measurements conducted by himself and also by previous authors, notably Böeseken and his students.[198, 201, 203] Swern pointed out convincingly that alkyl substitution is attended by pronounced rate enhancement, whereas attachment of a carboxyl or other carbonyl function diminishes the reaction rate. In the former case the inductive alkyl substituent effect increases electron density at the double bond; in the latter, the combination of inductive and mesomeric effects causes the opposite change. Lynch and Pausacker[1060] made a similar observation during a study of the reactivity of substituted *trans*-stilbenes (Eq. 27) toward perbenzoic acid, *p*-methoxy-*trans*-stilbene reacting some 30 times faster than *p*-nitro-*trans*-stilbene. Again linearity was found in the Hammett plot, especially when the modified σ values of Brown and Okamoto[249] were utilized.[280] Similar investigations have been published recently by Ogata and Tabushi,[1968] who oxidized a number of methylstilbenes carrying various substituents in one or both phenyl rings and found electron-releasing groups to enhance the rate of peroxy acid attack. The same authors[1967] also studied the kinetics of epoxidation of a series of 3-substituted 1-propenes and 1,4-disubstituted 2-butenes containing polar groups. The olefinic component thus clearly appears to function as a nucleophile in this reaction.



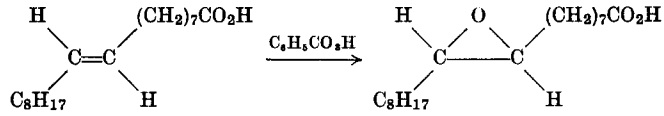
(27)

X = H, CH_3, Cl, CH_3O, NO_2

Witnauer and Swern[1868] demonstrated the remarkable stereospecificity of peroxy acid oxidation by converting oleic acid into *cis*-9,10-epoxystearic acid, and elaidic acid to *trans*-9,10-epoxystearic acid (Eqs. 28, 29). Julietti and co-workers recently obtained similar results with the *cis*- and *trans*-isomers of octadec-6-enoic acid and octadec-13-enoic acid.[893]

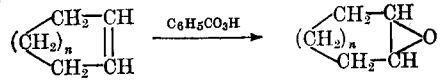


(28)



(29)

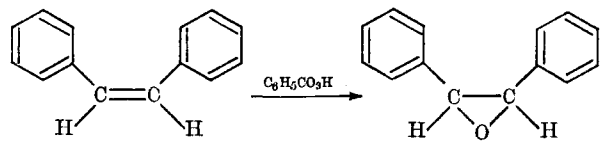
The stereospecificity of peroxy acid oxidation was further demonstrated by oxidative studies of Prelog and co-workers,[1401, 1404, 1405] and also of Cope and co-workers,[340, 341, 344] on the *cis*- and *trans*-isomers of cyclooctene, cyclononene, and cyclodecene (Eq. 30). These olefins all yield epoxides with retention of configuration.



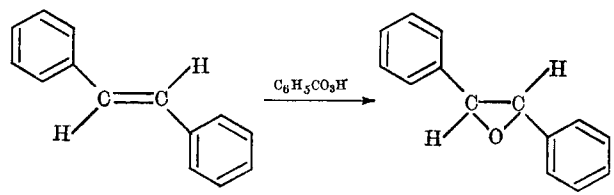
(30)

$n = 4, 5, 6$

Lynn and Pausacker[1060] likewise observed stereospecific epoxidation with perbenzoic acid in the case of *cis*- and *trans*-stilbene, which afford *cis*- and *trans*-stilbene oxide respectively (Eqs. 31 and 32).

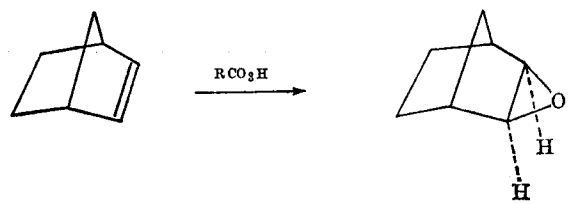


(31)



(32)

The effect of stereochemistry on the mode of addition of peroxy acids to olefins is made clear in the selective epoxidation of bicyclo-[2.2.1]heptene (Eq. 33). Several investigators have reported the

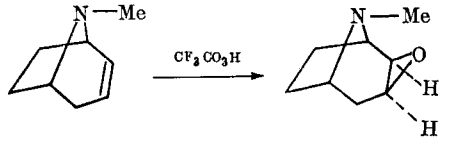


(33)

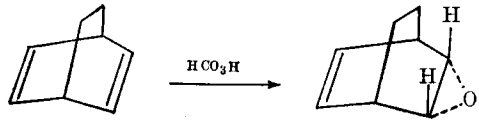
R = CH_3, C_6H_5, *o*-$C_6H_5CO_2H$

exclusive formation of *exo*-2,3-epoxybicyclo[2.2.1]heptane, regardless of the reagent used.[986, 1602, 1795] Attack from the least hindered side occurs preferentially here, and in other instances as well.[93, 530, 1964, 1970]

Additional illustrations of stereospecificity include the epoxidations of tropidine[423] and of bicyclo[2.2.2]hexadiene[614] with trifluoroperacetic acid and performic acid respectively (Eqs. 34 and 35).

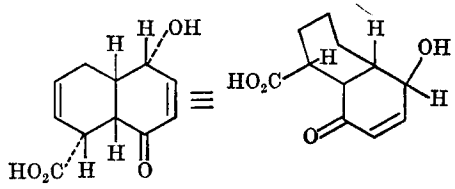


(34)

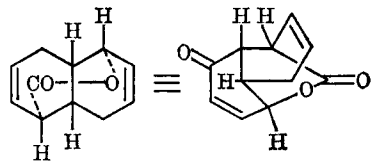


(35)

An enlightening example illustrating the subtle interplay of electronic and stereochemical effects governing olefin reactivity toward peroxy acids is that provided by Woodward and co-workers in connexion with their synthesis of reserpine.[1878] Of the two compounds (XXXIX) and (XL), the former reacts smoothly with perbenzoic acid, whereas the latter reacts slowly and gives poorly defined products. Favored conformational representations of these two substances are shown also.

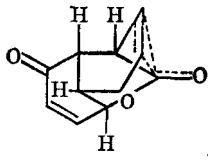


(XXXIX)



(XL)

The explanation advanced by the above authors for the relative inertness of (XL) with respect to (XXXIX) involves electron depletion by non-classical resonance. The conformation allowing such resonance is one of high energy in the case of the hydroxy acid (XXXIX), but is forcibly present in lactone (XL) by virtue of its bridged structure. The non-classical structure envisaged by Woodward and co-workers[1878] appears to be of the type (XLI).



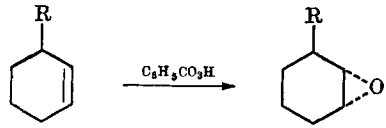
(XLI)

The question of acid catalysis in peroxy acid oxidation of olefins is one which still awaits a definitive answer. Studies made by Böeseken and co-workers,[198, 201, 203] Lynch and Pausacker,[1060] and Campbell and co-workers[280] indicate that no acid catalysis exists. Evidence cited in support of this view include: (1) clean second-order kinetics; and (2) the absence of rate increase on deliberate addition of benzoic acid to a reaction involving perbenzoic acid. On the other hand, Swern[1679] has expressed the opinion that the reaction is acid-catalyzed, and that the attacking species is a complex of peroxy acid and general acid HA. Very recently Berti and Bottari[151, 152, 153] have discovered that peroxybenzoic acid epoxidation of stilbenes is catalyzed by trichloroacetic acid, a more acidic catalyst than had been examined by previous investigators. It thus appears possible that two reaction paths are available, depending on the presence or absence of a sufficiently strong acid to effect catalysis.

Lynch and Pausacker[1060] reported that oxidation of *trans*-stilbene and of cyclohexene with perbenzoic acid occurred faster in benzene than in ether, and that the reaction in ether was unaffected by the addition of magnesium perchlorate. This evidence would point to a non-ionic mechanism, at least in the absence of trichloroacetic acid.

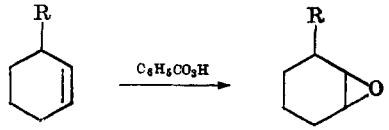
Before the alternative mechanisms at present in favor are presented, it will be convenient to introduce the topic of neighboring group influence. Henbest and Wilson[741] recently made the interesting discovery that though 3-alkoxy- or 3-acetoxycyclohexene gives on treatment with perbenzoic acid predominantly the product in which the epoxide ring and the substituent are on opposite sides of the

cyclohexane ring, the converse holds for 3-hydrocyclohexene (Eqs. 36 and 37). The latter, moreover, undergoes epoxidation at a significantly greater rate.



(36)

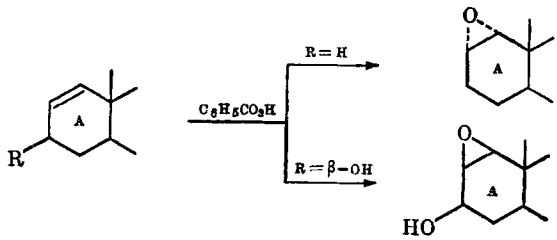
$R = CH_3O, C_2H_5O, CH_3CO_2$



(37)

R = OH

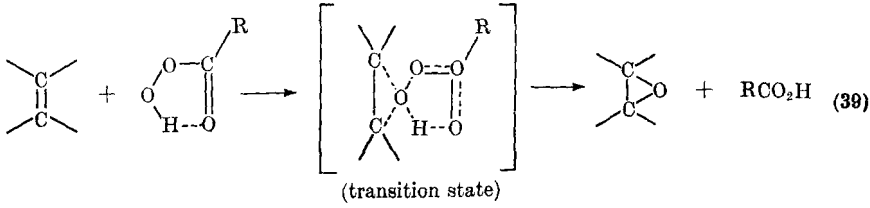
Extending their investigations into the steroid field, Henbest and Wilson[741] noted that cholest-1-ene gave an α-epoxide, whereas 3β-hydroxycholest-1-ene yielded the corresponding β-epoxy steroid (Eq. 38). Their observation was supported independently by Albrecht and Tamm[18] in other work.



(38)

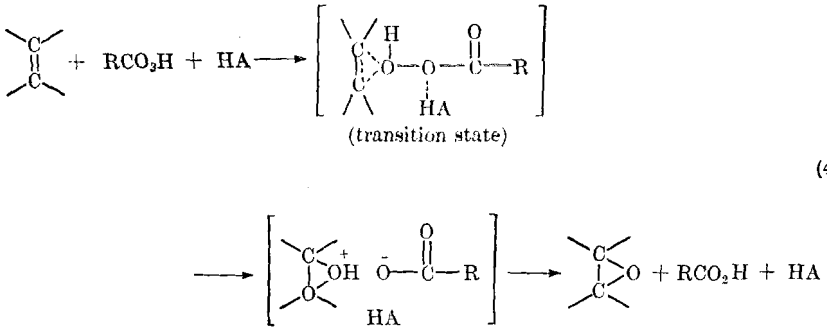
In a similar manner, cholest-4-ene, 3β-acetoxycholest-4-ene, and 3β-methoxycholest-4-ene suffer attack from the expected less hindered α-side,[530] whereas 3β-hydroxycholest-4-ene undergoes β-epoxidation.[741] The same phenomenon appears to operate with 7α- and 7β-hydroxycholest-5(6)-ene derivatives,[741] and also with 7α-hydroxycholest-8(14)-ene.[536]

The mechanism currently favored for non-acid-catalyzed peroxy acid oxidations was postulated by Bartlett[82] and subsequently invoked by Lynn and Pausacker,[1060] by Campbell and co-workers,[280] and, with allowance for neighboring-group participation, by Henbest and Wilson,[741] by Albrecht and Tamm,[18] and also by Sassiver and English.[1522] Schematically this reaction may be depicted as in Eq. (39).



(transition state) (39)

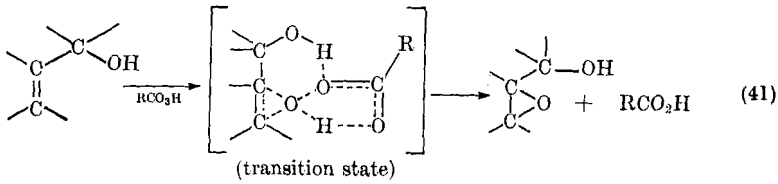
An alternative mechanism, proposed by Swern,[1592] and recently given some experimental substance by Berti and Bottari,[151, 152, 153] may be represented as in Eq. (40).



(transition state) (40)

Whether the mechanism shown in Eq. (40) really does operate in the presence of a strong acid like trichloroacetic acid awaits further experimental study. The influence of solvent polarity, which constitutes a good criterion for the existence of truly ionic or ion-pair intermediates, would provide important evidence on this point.

The first mechanism, with one small refinement, explains satisfactorily the neighboring-group effect discussed above. The transition state for allylic epoxidation is represented by Henbest and Wilson,[741] by Albrecht and Tamm,[18] and also by Sassiver and English,[1522] as shown in Eq. (41).

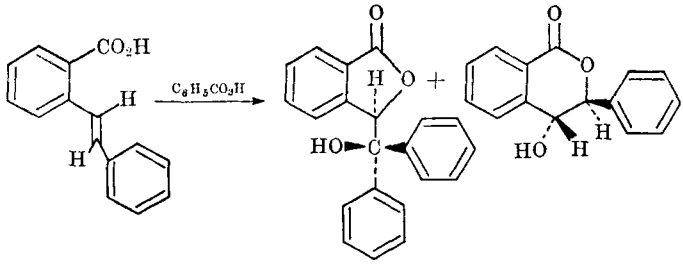


(transition state) (41)

(3) Special aspects. Five special features of peroxy acid epoxidation will be mentioned briefly at this point: (1) formation of lactones

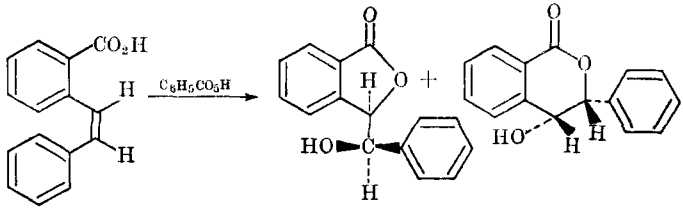
when carboxyl groups are suitably located in the molecule undergoing attack; (2) formation of cyclic ethers when hydroxyl groups are present; (3) formation of lactones when ketones are present which are more reactive than the olefinic double bonds present; (4) formation of α,β-epoxy alcohols from olefins instead of the expected epoxides; and (5) miscellaneous abnormal reactions yielding unexpected products.

Berti and Bottari[151,152,153] reported that epoxidation of *o*-carboxy-*trans*-stilbene with perbenzoic acid is a stereospecific reaction that can yield either of two lactones (XLII) and (XLIII), depending on the temperature (Eq. 42). Two lactones (XLIV) and (XLV) can likewise be formed from the corresponding *cis*-stilbene derivative, the predominance of one over the other being again temperature-dependent (Eq. 43). The five-membered lactones (XLII) and (XLIV) appear to be favored at low temperatures.



(42)

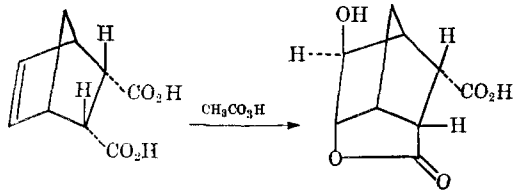
(XLII) (XLIII)



(43)

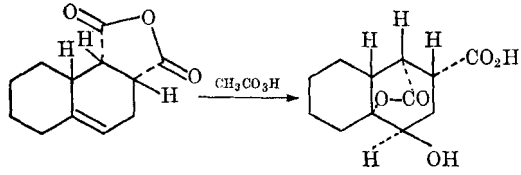
(XLIV) (XLV)

Nazarov and co-workers[1224] observed lactone formation also in the reaction of 2,3-di-*endo*-carboxybicyclo[2.2.1]hept-5-ene with peracetic acid (Eq. 44).



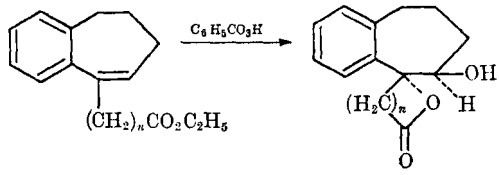
(44)

Nazarov and co-workers[1155] likewise noted lactone formation with the octahydronaphthalene derivative indicated in Eq. (45).

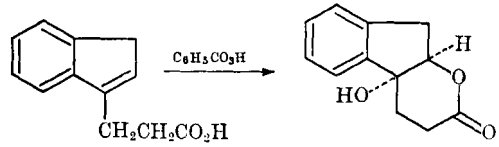


(45)

In a similar manner Crabb and Schofield[362] have described the lactonization effect in the perbenzoic acid epoxidation of certain substituted benzocycloheptene derivatives, and Howell and Taylor[829] did so for the reaction of an indene, as shown in Eqs. (46) and (47).

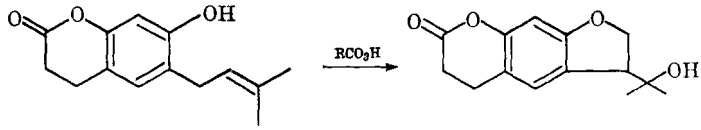


(46)



(47)

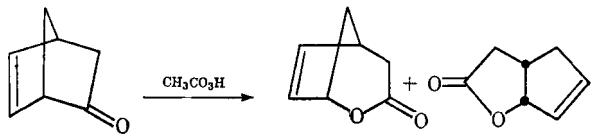
A pertinent related example was published by King and co-workers,[929] illustrating the formation of a five-membered ether instead of a lactone (Eq. 48). A similar instance of ether-ring formation during peroxy acid treatment of 2-allylphenol has been described by Tinsley[1974] and more recently by Harrison and Aelony.[1975]



(48)

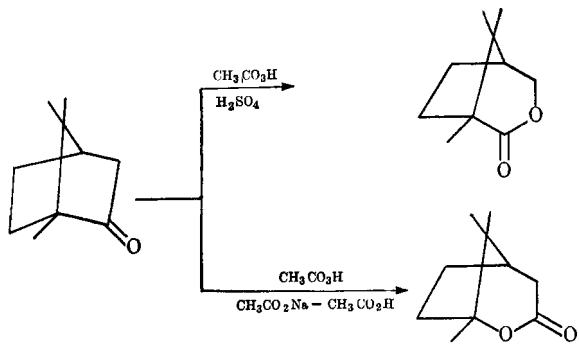
Another special aspect of peroxy acid oxidation concerns rupture reactions occasionally encountered when ketone groups are present in the substrate. Thus Meinwald and co-workers[1147] obtained no epoxide

on treatment of 2-oxobicyclo[2.2.1]heptene (dehydronorcamphor) with peracetic acid, but rather the two lactones shown in Eq. (49).

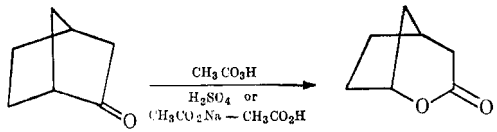


(49)

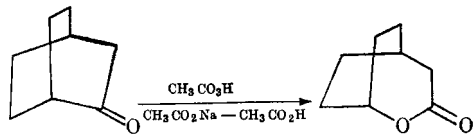
In a related study Sauers[1524] reported that camphor responds differently with respect to the sense of ring rupture, depending on whether buffered peracetic acid or a peracetic acid–sulfuric acid mixture is utilized. Insertion of an oxygen atom near the bridgehead appears more favored in a buffered reaction medium (Eq. 50). For the simple case of 2-oxobicyclo[2.2.1]heptane, however, Meinwald and Frauenglass[1145] found oxygen-insertion to occur preferentially near the bridgehead regardless of the reaction conditions (Eq. 51). Rupture was found to take a similar course (Eq. 52) in the homologous substance 2-oxobicyclo[2.2.2]octane.[1145]



(50)

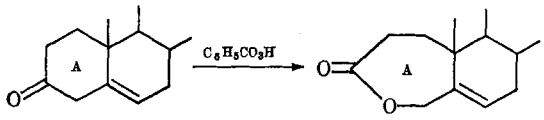


(51)



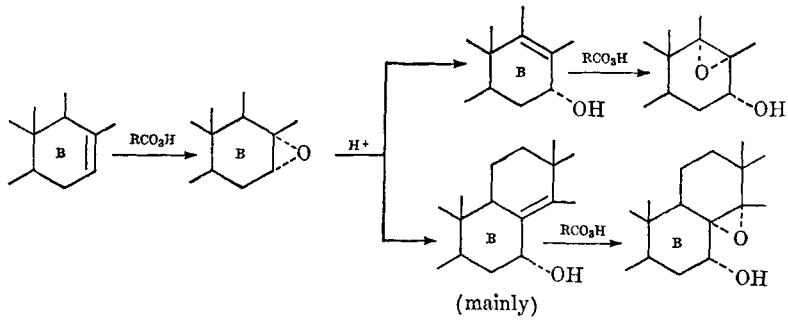
(52)

In the same vein, Mori and Mukawa[1174] reported that a product previously mistaken for an epoxide is in fact a lactone (Eq. 53). Genuine epoxides were, however, also found to accompany this unexpected product.



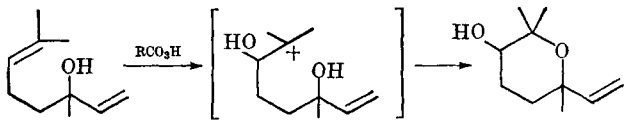
+ epoxides (53)

The fourth topic to be discussed in the present section is an interesting reaction described recently by Fieser and Goto,[536] in a clarification of previous work. Treatment of 3β-acetoxycholest-7-ene with perbenzoic acid in chloroform in the usual manner yields two epoxy alcohols, whereas monoperphthalic acid in ether gives the desired α-epoxy steroid. When the latter is shaken with chloroform containing a minute trace (0.2 mg./100 ml.) of sulfuric acid, an allylic alcohol is formed. It was concluded, therefore, by Fieser and Goto that the course of perbenzoic acid oxidation is as shown in Eq. (54), sufficient acid being present in the chloroform solution of perbenzoic acid to produce rearrangement of the initially formed epoxide.



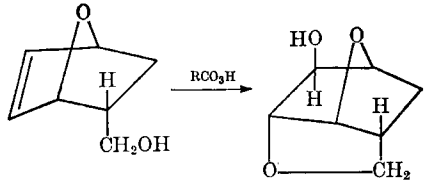
(mainly) (54)

Mention should be made, lastly, of occasional rearrangements encountered when peroxy acid oxidation is attempted on substances containing reactive centers suitably disposed in the molecule. As an example may be cited the recent report by Mousseron and Levallois[1199] of an unexpected cyclization presumably taking place by way of a carbonium ion, as shown in Eq. (55).



(55)

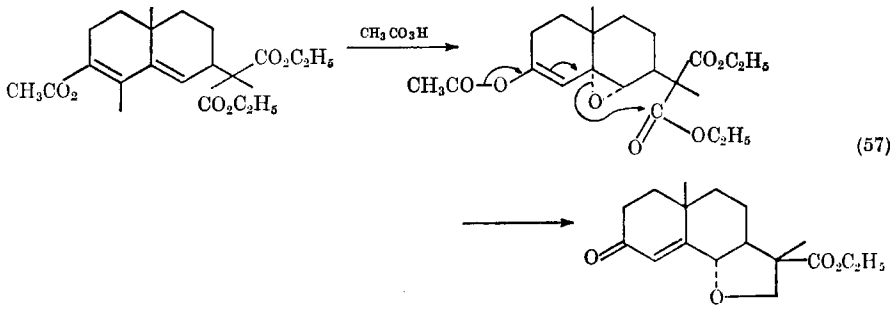
A similar situation appears to exist in the attempted epoxidation[983] of the unsaturated bicyclic alcohol depicted in Eq. (56).



(56)

R = *o*-$C_6H_5CO_2H$

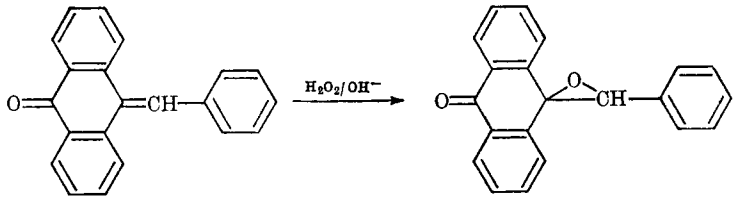
In the course of an ingenious scheme designed to gain access into the santonin series, Abe and co-workers[6] noted the following lactone-generating transformation (Eq. 57), a very useful one in this particular instance.



(57)

B. Alkaline Hydrogen Peroxide Oxidation

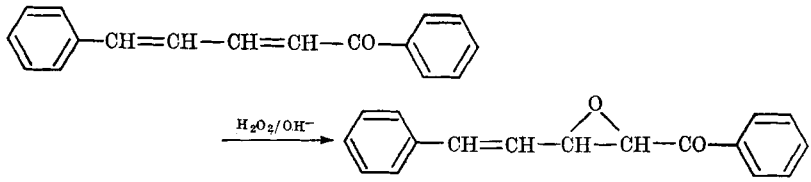
(1) Scope. The earliest reference to the use of alkaline hydrogen peroxide for epoxide synthesis is the report by Weitz and co-workers[1822] that 9-benzalanthrone could be transformed into the corresponding oxide by this method (Eq. 58).



(58)

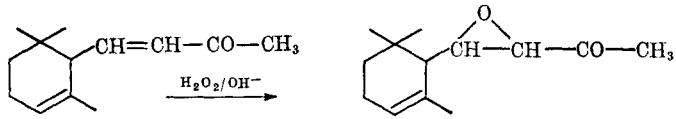
Two years after this discovery Weitz and Scheffer,[1820] in the classic paper on this subject, proposed that alkaline hydrogen peroxide

is a reagent selective for double bonds linked to electron-withdrawing substituents. This was demonstrated clearly by the fact that treatment of 4-benzoyl-1-phenylbuta-1,3-diene with alkaline hydrogen peroxide (Eq. 59), even in excess, yielded only the monoepoxide corresponding to attack on the carbonyl-conjugated double bond.



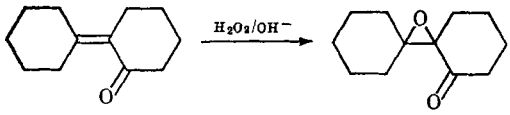
(59)

Karrer and Sturzinger[917] provided further support for this premise when they showed that α-ionone undergoes epoxidation only at the carbonyl-conjugated double bond (Eq. 60).



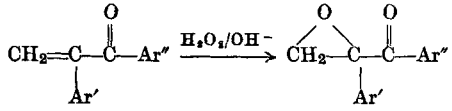
(60)

A notable feature of alkaline hydrogen peroxide is its ability to epoxidize heavily substituted and sterically inaccessible double bonds, provided that they are linked to a carbonyl function. For example, Reese[1441] obtained an excellent yield of the tetrasubstituted epoxide derived from cyclohexylidenecyclohexanone, as shown in Eq. (61).



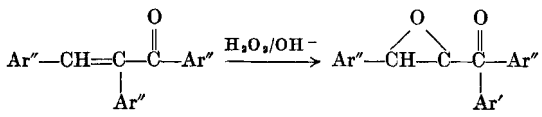
(61)

Fuson and co-workers[607] prepared a number of α,β-epoxy ketones bearing massive groups like mesityl, 2,4,6-triethylphenyl, duryl, and *iso*duryl (Eqs. 62 and 63). Little or no effect attributable to the bulk of these substituents could be discerned on the basis of yields obtained from the reactions.



(62)

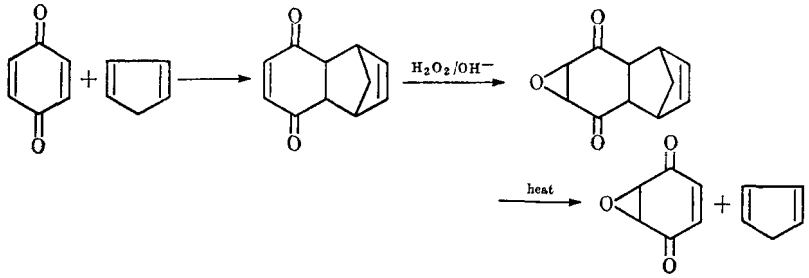
Ar′ = mesityl;
Ar″ = triethylphenyl, duryl, *iso*duryl



(63)

Ar′ = phenyl, mesityl;
Ar″ = mesityl, duryl, isoduryl

Alder and co-workers[19] have described an ingenious technique for preparing benzoquinone monoepoxide by taking advantage of the reversible character of the Diels–Alder condensation (Eq. 64). Several related substances were obtainable by this seemingly indirect route, which was necessitated, however, by the fact that direct oxidation of benzoquinone with alkaline hydrogen peroxide gives maleic acid.[621,1822]

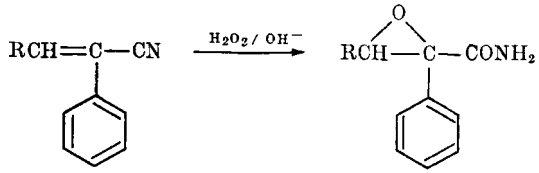


(64)

A large number of epoxidations has been carried out with alkaline hydrogen peroxide and a variety of α,β-unsaturated ketones, both aliphatic and aromatic. A sizeable catalog of these reactions is contained in Table 5, supplementing the ones cited in the text.

Although used predominantly with α,β-unsaturated ketones thus far, the alkaline hydrogen peroxide reagent has also been found to react with α,β-unsaturated nitriles[1209, 1315, 1317] and more recently with α,β-unsaturated aldehydes[963, 1311] and esters.[1310, 1313]

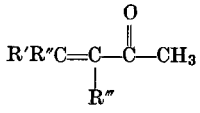
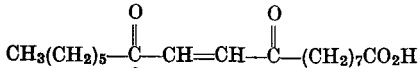
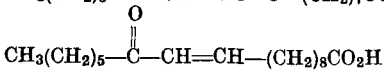
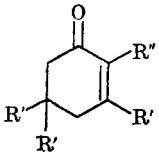
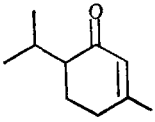
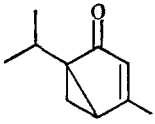
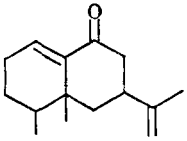
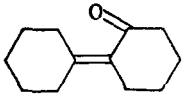
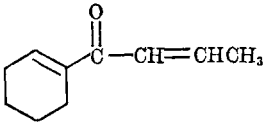
The reaction of alkaline hydrogen peroxide with α,β-unsaturated nitriles was first explored by Murray and Cloke,[1209] who found that certain of these compounds (Eq. 65), when subjected to the Radziszewski amidation procedure, yielded α,β-epoxyamides instead of the anticipated α,β-unsaturated amides.



(65)

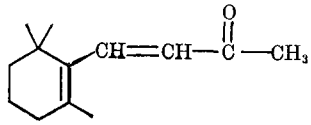
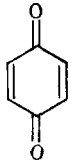
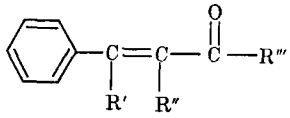
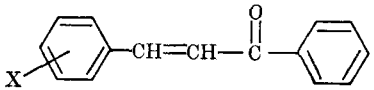
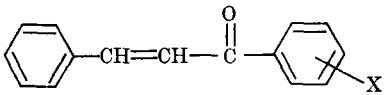
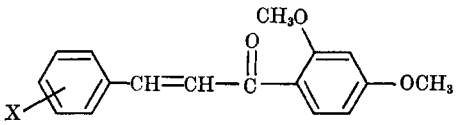
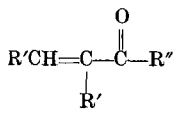
R = CH_3, n-C_3H_7, C_6H_5

TABLE 5. Alkaline Hydrogen Peroxide Oxidation of Olefins

Compound		Reference
A. Ketones		
	$R' = R'' = R''' = H$	1844
	$R' = R'' = H$; $R''' = CH_3$	1844
	$R' = CH_3$; $R'' = R''' = H$	264
	$R' = R'' = CH_3$; $R''' = H$	264, 1820, 1844
	$R' = R''' = CH_3$; $R'' = H$	825, 1219
		1249
		1249
	$R' = R'' = H$	1219
	$R' = H$; $R'' = CH_3$	1219
	$R' = CH_3$; $R'' = H$	821
		966
		477
		1132
		827, 1441
		1219

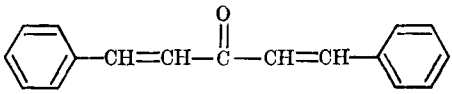
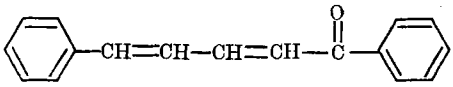
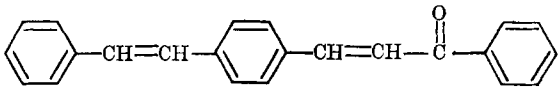
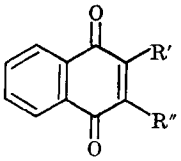
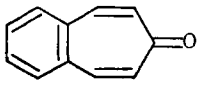
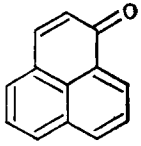
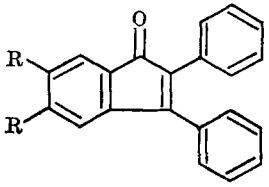
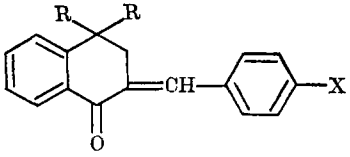
(*Table continued*)

TABLE 5 (*continued*)

Compound		Reference
		917
		19
	R′ = R″ = H; R‴ = CH_3	1820, 1844
	R′ = R″ = H; R‴ = C_6H_5	163, 958, 1805, 1820, 1844
	R′ = CH_3; R″ = H; R‴ = C_6H_5	1219, 1914
	R′ = H; R″ = CH_3; R‴ = C_6H_5	1914
	R′ = H; R″ = C_2H_5; R‴ = C_6H_5	824
	R′ = H; R″ = R‴ = C_6H_5	822
	R′ = R‴ = C_6H_5; R″ = H	822
	X = *o*-NO_2	382, 1219
	X = *o*-Cl, *p*-Cl, *p*-NO_2, *p*-OCH_3	744, 1820
	X = H, *p*-OCH_3	65
	R′ = C_6H_5; R″ = mesityl, duryl, isoduryl	607
	R′ = mesityl; R″ = mesityl, duryl, isoduryl	

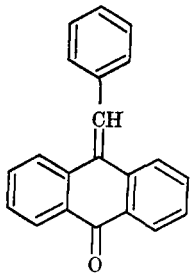
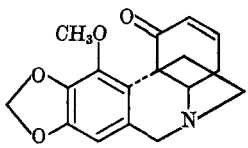
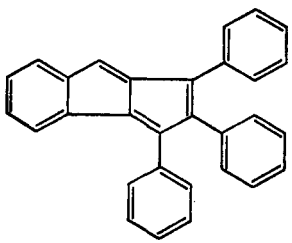
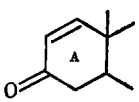
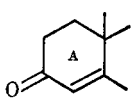
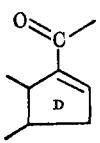
(*Table continued*)

TABLE 5 (*continued*)

Compound		Reference
		1219
		1820
		1820
	R′ = R″ = H R′ = CH_3, farnesyl, phytyl; R″ = H, CH_3, cinnamyl	1822 545
		1820
		541
	R = H, CH_3	818, 1820
	R = H, CH_3; X = Cl, NO_2	378

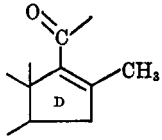
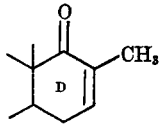
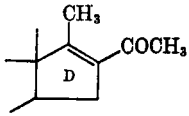
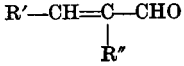
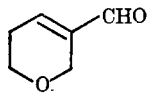
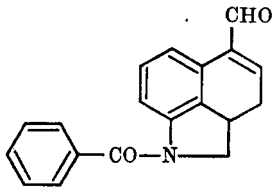
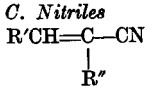
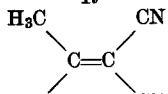
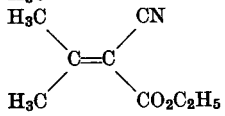
(*Table continued*)

TABLE 5 (*continued*)

Compound	Reference
	1819
	1929
	1976
Steroids	
	1071, 1517
	154, 279
	891, 1133, 1135, 1352, 1494, 1517, 1697, 1931

(*Table continued*)

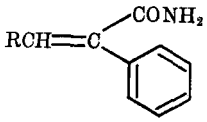
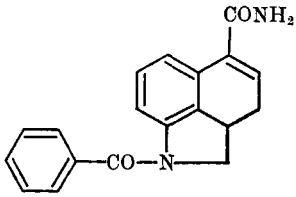
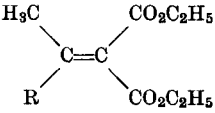
TABLE 5 (*continued*)

Compound		Reference
		1103, 1254, 1691
		1826, 1830
		1977
B. Aldehydes		
	$R' = R'' = H$	1311
	$R' = H$; $R'' = CH_3$	1311
	$R' = CH_3$; $R'' = H$	1243[a]
	$R' = C_6H_5$; $R'' = H$	1243[a]
		1311
		963
C. Nitriles		
	$R' = R'' = H$	1311
	$R' = R'' = C_6H_5$	1317
		1313
		1313

[a] With alkaline *tert*-butyl hydroperoxide.

(*Table continued*)

TABLE 5 (*continued*)

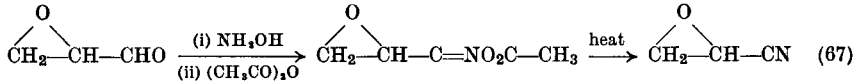
Compound		Reference
D. Amides		
	R = CH_3, n-C_3H_7, C_6H_5	1209
		963
E. Esters		
	R = H, CH_3	1310

When the nitrile group was hydrolyzed with sulfuric acid and the resulting α,β-unsaturated amide was subjected to Radziszewski conditions, however, no epoxidation took place. This is easily understood if one considers that the carbonyl group can satisfy its need for electrons by withdrawing them from the nitrogen and is therefore not very electron-withdrawing with respect to the double bond. Murray and Cloke also found that when the α-phenyl group was replaced with hydrogen, as in cinnamonitrile, no epoxidation occurred. This is additional evidence of the preference of alkaline hydrogen peroxide for electron-deficient double bonds.

Payne and co-workers[1313, 1315, 1317] found that rigid pH control is of critical importance in the epoxidation of α,β-unsaturated nitriles with alkaline hydrogen peroxide. Acrylonitrile, for example, may be converted smoothly into glycidamide in good yield (Eq. 66) provided that the pH is carefully regulated at 7.0–7.5 throughout.[1317]

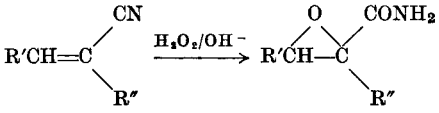
$$CH_2{=}CH{-}CN \xrightarrow{H_2O_2/OH^-} CH_2{-}\underset{\diagup\,\diagdown}{O}{-}CH{-}CONH_2 \qquad (66)$$

Glycidonitrile itself has not been prepared directly from acrylonitrile, but was synthesized recently[1311] from glycidaldehyde by pyrolysis of the corresponding oxime acetate, as shown in Eq. (67).



(67)

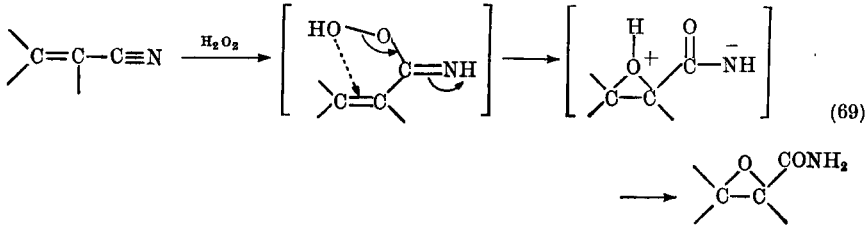
Other α,β-unsaturated nitriles (Eq. 68) converted into the corresponding epoxides by hydrogen peroxide oxidation under controlled pH include α-phenylcinnamonitrile, α-cyano-β-methylcrotononitrile, and ethyl α-cyano-β-methylcrotonate.[1313, 1317]



(68)

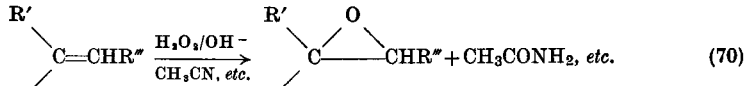
$R' = R'' = C_6H_5$ (pH 7.0–7.5)
$R' = CH_3$, $R'' = CN$ (pH 5.0–6.0)
$R' = CH_3$, $R'' = CO_2C_2H_5$ (pH 9.5–10.0)

Evidence has been secured by Payne and Williams[1317] pointing to the existence in this reaction of a hydroperoxyimide intermediate, which undergoes intramolecular oxidation–reduction as shown in Eq. (69).



(69)

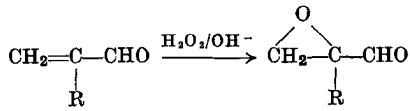
Advantage of the ability of such hydroperoxyimide intermediates to function as oxidizing agents was taken by Payne and co-workers[1315] in developing a new technique of olefin epoxidation. Their procedure involves addition of hydrogen peroxide in alkaline solution to an olefin in the presence of a nitrile, such as acetonitrile, trichloroacetonitrile, or benzonitrile (Eq. 70). Among olefins oxidized in this fashion so far have been 1-hexene, 2-methyl-2-butene, cyclohexene, styrene, and acrolein diethylacetal.



(70)

$R' = n\text{-}C_4H_9$, C_6H_5, $(C_2H_5O)_2CH$; $R'' = R''' = H$
$R' = R'' = R''' = CH_3$

The synthesis of glycidaldehyde, as well as that of other simple α,β-epoxy aldehydes, had proved impossible until recently, when it was reported[1311, 1978] that careful pH control at 8.0–8.5 during the epoxidation of acrolein and α-methylacrolein allows the isolation of glycidaldehyde and α-methylglycidaldehyde in good yield (Eq. 71).

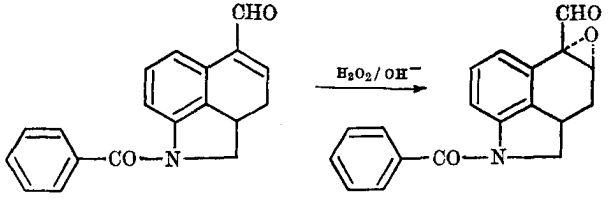


(71)

R = H, CH_3

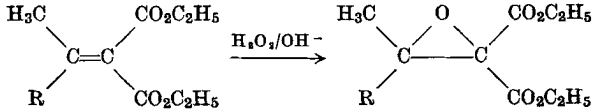
Initial failures by Weitz and Scheffer[1820] to obtain epoxides from cinnemaldehyde or crotonaldehyde were presumably caused by excessive alkalinity in the reaction medium, and may be rectifiable by suitable pH control.

The presence of an α-phenyl group in α,β-unsaturated aldehydes might be expected to facilitate epoxidation, in analogy to α,β-unsaturated nitriles. That this may indeed be the case can be seen from the work of Kornfeld and co-workers[963] in connexion with their lysergic acid synthesis (Eq. 72).



(72)

The reaction of α,β-unsaturated esters has thus far been restricted to diesters derived from malonic acid, presumably because a single ester group is insufficiently electron-withdrawing. Payne[1312] found that, with the pH rigorously controlled at about 8.0, diethyl ethylidenemalonate and diethyl *iso*propylidenemalonate (Eq. 73) can be converted to their respective epoxides with alkaline hydrogen peroxide.

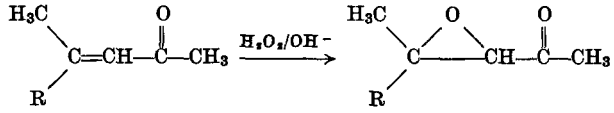


(73)

R = H, CH_3

That the reaction of the *iso*propylidene ester was considerably slower than that of the ethylidene was attributed to a steric effect,[1312]

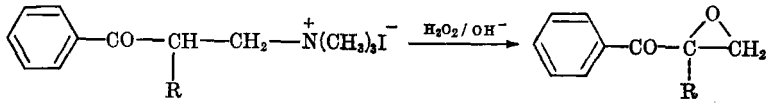
but could also be related to the observation of Bunton and Minkoff[264] that ethylideneacetone is epoxidized much more slowly than *iso*propylideneacetone (mesityl oxide) (Eq. 74). The latter effect was ascribed to enhanced electron density on the double bond by induction, rather than to a steric factor.



(74)

R = H, CH_3

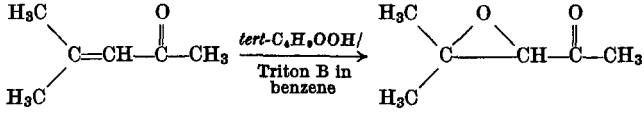
A modified process, described recently by House and co-workers,[823] consists of treating certain β-(*N*,*N*-dimethylamino)propiophenone methiodides with alkaline hydrogen peroxide as shown in Eq. (75). Hofmann elimination and epoxidation take place in a single operation.



(75)

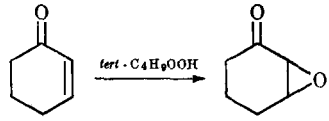
R = H, C_2H_5, C_6H_5

An important variation of the alkaline hydrogen peroxide method will be included at this point, since it is considered to proceed by a very similar mechanism. Yang and Finnegan[1893] established in 1958 that α,β-epoxy ketones could be obtained in excellent yield by treating certain acyl- or aroyl-substituted olefins with solutions of *tert*-butyl hydroperoxide in non-polar media in the presence of a suitable base. For instance, with Triton B as a catalyst and benzene as solvent, mesityl oxide gave a good yield of the corresponding epoxide at room temperature (Eq. 76).

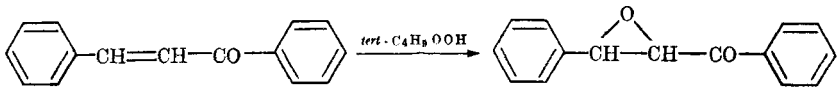


(76)

Similarly, 2-cyclohexenone (Eq. 77) gave the desired epoxide in 66% yield, and benzalacetophenone (Eq. 78) gave the corresponding epoxide nearly quantitatively.

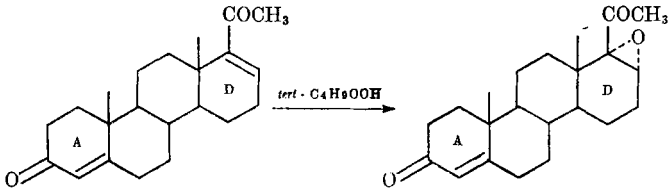


(77)



(78)

The steric selectivity of this reagent is indicated by the fact that the A-ring double bond of progesterone remains intact, whereas the D-ring double bond readily undergoes attack, as shown in Eq. (79).



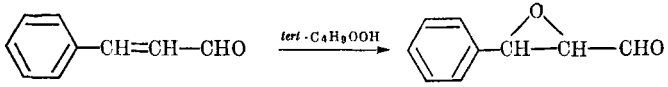
(79)

Methyl acrylate and acrylonitrile (Eq. 80), on the other hand, were reported by Yang and Finnegan[1893] to give no epoxides, but instead the peroxides corresponding to Michael addition of *tert*-butyl hydroperoxide anion to the conjugated systems.

$$CH_2{=}CH{-}R \xrightarrow{tert\text{-}C_4H_9OOH} tert\text{-}C_4H_9OOCH_2CH_2R \qquad (80)$$

$$R = -CO_2CH_3, -CN$$

Further progress in the use of *tert*-butyl hydroperoxide was made recently by Payne,[1312] who conducted the reaction under carefully controlled pH conditions. Cinnemaldehyde, which had previously failed to yield the desired epoxide with alkaline hydrogen peroxide, gave this substance in good yield (Eq. 81) when the reaction was carried out at pH 8.5 in methanol.

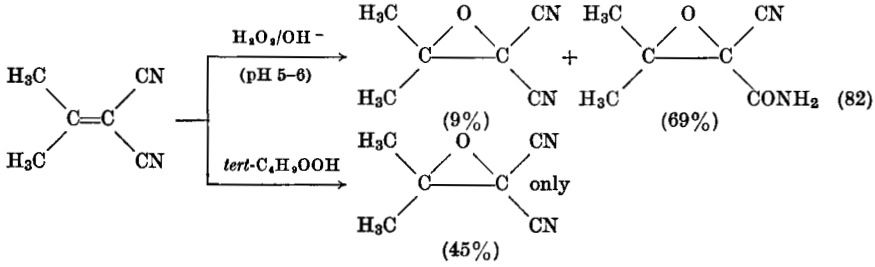


(81)

When no precautions were taken to maintain constant alkalinity, the product appeared to be the peroxide formed by Michael addition. In the light of this finding, the previous report (Yang and Finnegan[1893]) with methyl acrylate and acrylonitrile may be in need of revision.

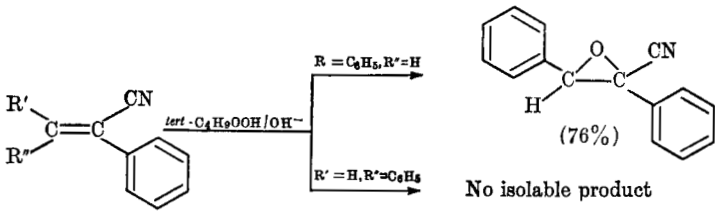
Epoxidation of α-cyano-β-methylcrotononitrile has likewise been

found by Payne[1313] to occur smoothly with *tert*-butyl hydroperoxide in benzene, giving a single product as indicated in Eq. (82).



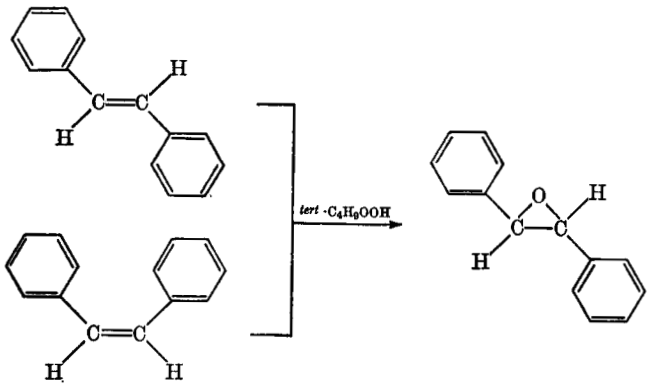
(82)

Payne and Williams[1317] reported the curious observation that whereas *trans*-α-phenylcinnamonitrile gave a high yield of the corresponding epoxide on treatment with alkaline *tert*-butyl hydroperoxide (Eq. 83) *cis*-α-phenylcinnamonitrile gave no isolable products under comparable conditions.



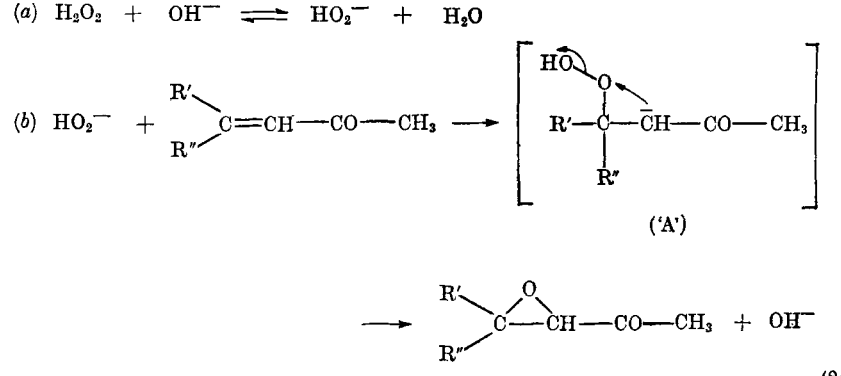
(83)

Finally may be mentioned the report by Maruyama and co-workers[1799] that *cis*- and *trans*-stilbene both yield the *trans* epoxide on treatment with *tert*-butyl hydroperoxide (Eq. 83a), the latter reacting more rapidly.



(83a)

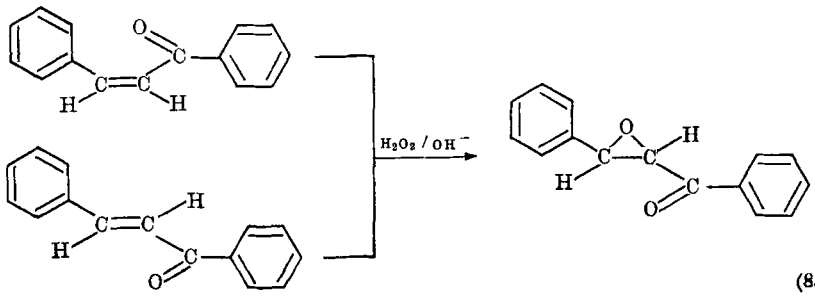
(2) Mechanism. The earliest mechanistic interpretation of alkaline hydrogen peroxide epoxidation was given by Bunton and Minkoff,[264] who found, for the case of ethylideneacetone and mesityl oxide, first-order kinetics with respect to both the unsaturated ketone and the hydroperoxide anion. Accordingly, the reaction was presumed to occur by the path shown in Eq. (84), step (*b*) being rate-determining. The



(84)

authors stressed, however, that it was not possible to decide on the basis of their kinetic data alone whether an anionic intermediate ('A') was actually formed, or whether instead formation of a new C—O bond and rupture of an O—O bond were synchronous. Nevertheless the reaction may be placed with confidence in the Michael category, inasmuch as no attack by HO^- ion on the carbonyl function was discernible.

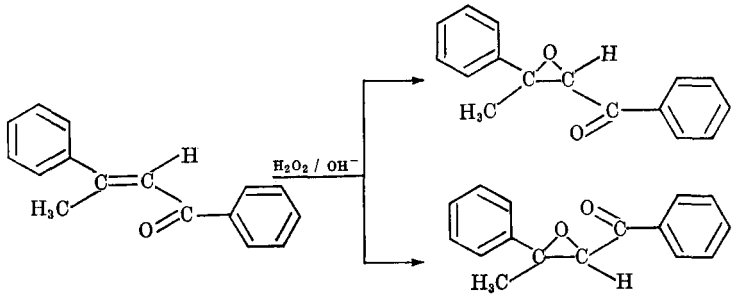
An early clue into the details of the above mechanism was the observation of Black and Lutz[163] that both *cis*-benzalacetophenone and its *trans*-isomer yielded the same epoxide, subsequently shown by Wasserman and Aubrey[1805] to possess the *trans*-configuration (Eq. 85)



(85)

and that the reactants themselves underwent no equilibration under the alkaline conditions used in the reaction.

Concurrent work by Wasserman and co-workers[1807] indicated, on the other hand, that epoxidation of β-methyl-*trans*-benzalacetophenone yielded not just the *trans*-oxide, but its *cis*-isomer as well (Eq. 86).



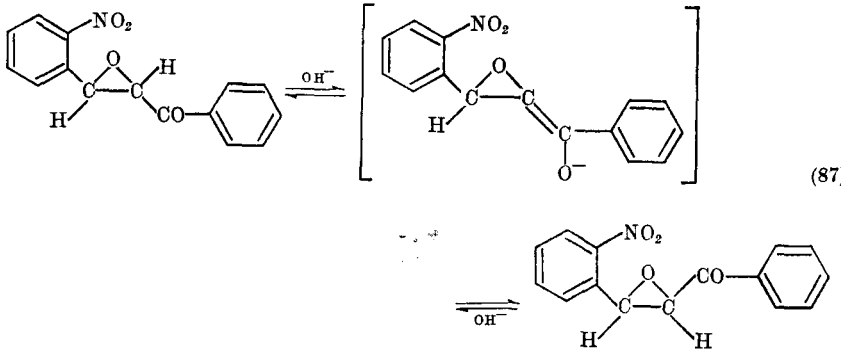
(86)

It might be argued at first glance that the results of Black and Lutz,[163] together with those of Wasserman and co-workers,[1805, 1807] constitute sufficient evidence to validate the long-lived anionic intermediate ('A') postulated by Bunton and Minkoff.[264] If ('A') is reasonably stable, its equilibration to the most stable conformation before collapse would lead primarily to a *trans*-oxide in the case of the isomeric benzalacetophenones (Eq. 85). On the other hand, the presence of a bulky β-methyl substituent would raise the rotational energy barrier in intermediate ('A') sufficiently to allow formation of both possible epoxides from β-methyl-*trans*-benzalacetophenone (Eq. 86).

Such a conclusion cannot be made, however, as House and Ro[825] have pointed out, until it has been established that no equilibration takes place by enolization of the product in the alkaline epoxidation medium. Wasserman and co-workers[1807] had indeed shown previously that treatment of β-methyl-*cis*-benzalacetophenone oxide with alcoholic base caused epimerization to occur, the thermodynamically more stable *trans*-oxide being produced. In contrast, Cromwell and Setterquist[382] had demonstrated the rather surprising alkaline epimerization of *trans*-*o*-nitrobenzalacetophenone oxide to the thermodynamically less stable *cis*-isomer. The accumulation of *cis*-oxide in the latter instance is explicable, however, on the basis of the lower solubility of the *cis*-oxide in the equilibration medium.

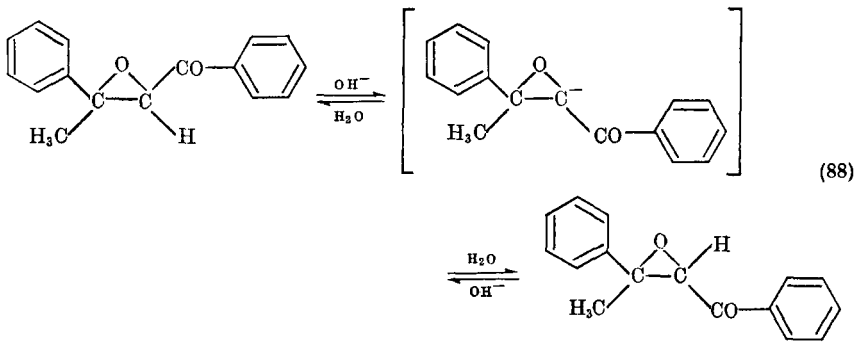
Two mechanisms have been advanced to explain the alkaline epimerization of α,β-epoxy ketones. Cromwell and Setterquist[382] sug-

gested, in connexion with their study of *o*-nitrobenzalacetophenone oxides, that proton abstraction by a base led to an intermediate carrying a negative charge on oxygen, according to the path shown in Eq. (87).



(87)

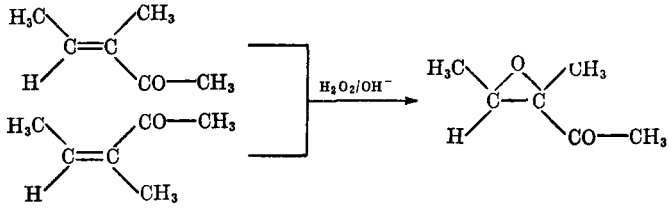
The above authors rationalized formation of the more hindered isomer by assuming the equilibrium to be displaced in its favor by virtue of the lower solubility of this isomer relative to the other. House and Ro,[825] on the other hand, showed by deuteration experiments and nuclear magnetic resonance spectroscopy that the epimerization observed by Wasserman and co-workers[1805, 1807] proceeds by way of an unusual oxide anion in which negative charge resides on carbon as shown in Eq. (88).



(88)

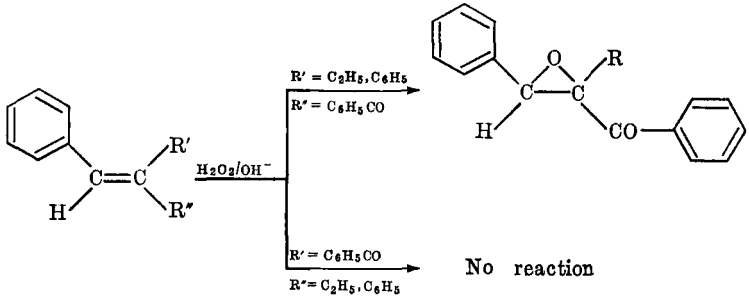
To circumvent the complication introduced by these product equilibration effects, House and Ro[825] studied epoxidation of *cis*-3-methyl-3-penten-2-one and its *trans*-isomer, since the resulting epoxides

contain no enolizable hydrogen atoms. In this instance, as in the previous investigation of Black and Lutz,[163] only a *trans*-oxide is formed (Eq. 89) and a straightforward interpretation is possible.



(89)

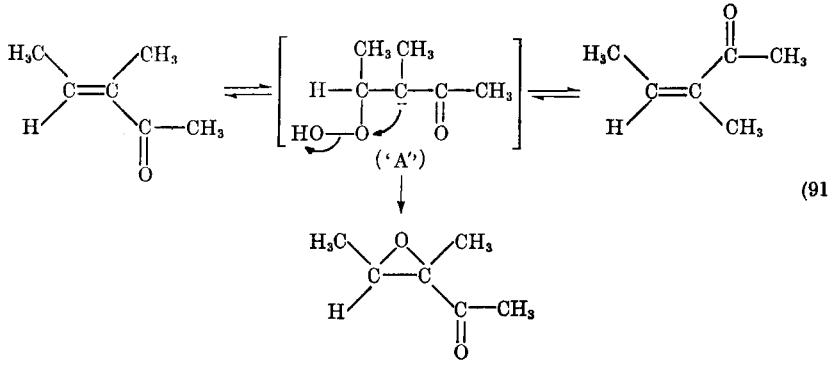
Previous work[822, 824] had shown that when bulkier groups are present at the α-position, only *trans*-olefins undergo epoxidation (Eq. 90). Thus, α-phenyl-*trans*-benzalacetophenone is epoxidized to the corresponding *trans*-oxide, whereas its *cis*-isomer fails to react.[824] Similar results attend the epoxidation of α-ethyl-*trans*-benzalacetophenone and its *cis*-isomer.[822] This effect was attributed to steric inhibition of olefin–carbonyl coplanarity, which appears to be a requirement in this process. Evidently an α-methyl substituent is small enough to permit attainment of requisite coplanarity in both isomers of 3-methyl-3-penten-2-one (Eq. 89).



(90)

House and Ro[825] further made the significant observation that although *cis*- and *trans*-3-methyl-3-penten-2-one do not equilibrate appreciably when the only base present is OH^- ion, in harmony with previous findings of Black and Lutz[163] with *cis*- and *trans*-benzalacetophenone, there is nevertheless a decided tendency for equilibration before epoxidation in the presence of the basic hydroperoxide anion HO_2^-. This was shown by examining the *cis* : *trans* ratio in recovered 3-methyl-3-penten-2-one, which was found to decrease by a factor of about 50 at 90% conversion. Since the *trans*-isomer is oxidized more

rapidly than the *cis*- it must be concluded that gradual accumulation of the former in the reaction mixture is due to a rapid equilibration step that does not require OH^- ion. The most convincing rationalization of all these facts is that the reaction occurs according to the scheme shown in Eq. (91).



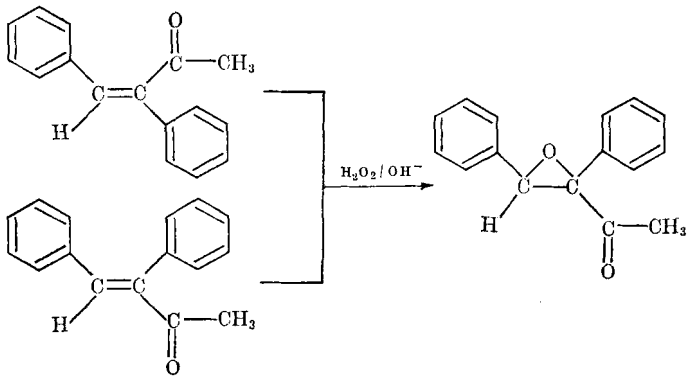
(91)

Intermediate ('A'), the same type of anion as that previously postulated by Bunton and Minkoff,[264] must then be sufficiently long-lived to allow rotation to the stable conformation before collapsing to give the product.

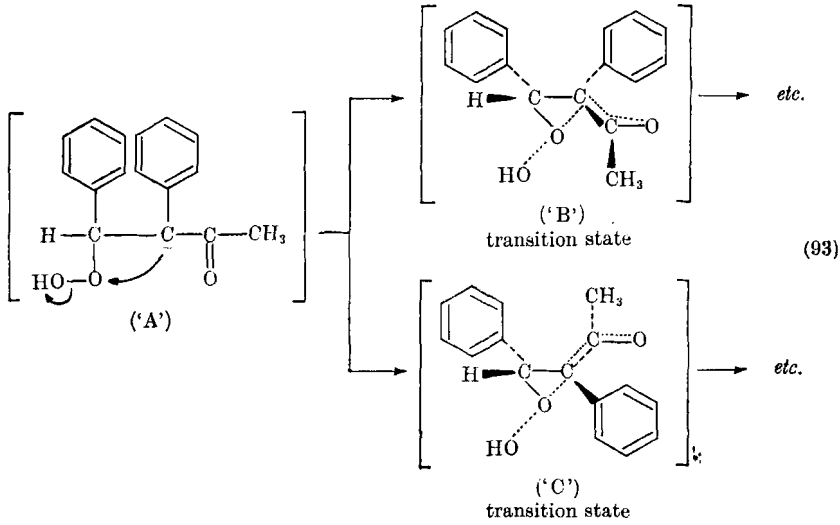
Significant insight into the factors governing the stereochemistry of alkaline hydrogen peroxide epoxidation may be gained from the studies of Zimmerman and co-workers.[1914] These authors noted the anomaly in a previous observation by House and Reif[822] that α-phenyl-*trans*-benzalacetophenone yields the *trans*-oxide with *cis*-oriented bulky substituents (Eq. 90). Since a phenyl group is considered bulkier than a benzoyl, the *cis*-oxide might actually be anticipated if a non-stereospecific process were operative.

To clarify this point, Zimmerman and co-workers[1914] investigated epoxidation of α-phenyl-*cis*-benzalacetone and its *trans*-isomer with alkaline hydrogen peroxide. Since there is no ambiguity regarding the relative bulk of phenyl and acetyl substituents, a truly non-stereospecific process would lead to an oxide with *trans*-oriented phenyl groups. The facts appeared to be in dramatic contrast with expectations, however, only the isomer containing *cis*-oriented phenyl groups being produced (Eq. 92).

The mechanism envisaged by Zimmerman and co-workers[1914] is one in which collapse of anionic intermediate ('A') is dictated by the energies of various possible transition states leading to products, and



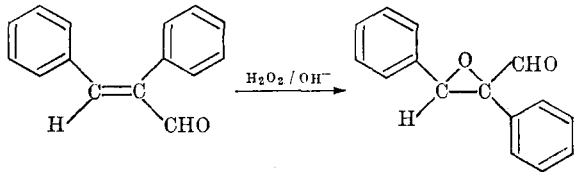
is consistent with the general theory of overlap control for stereoselective processes. According to this point of view, intermediate anion ('A') can collapse by way of two most probable transition states ('B') and ('C'), as shown in Eq. (93).



While *cis*-interaction of phenyl groups in ('B') can be accommodated by a slight twisting of the α-phenyl ring without affecting electron-delocalization involving the carbonyl function, the incipient C—O bond, and the departing OH^- group, the same cannot be said for ('C'). In the latter, any twisting of the acetyl group to relieve *cis*-interaction with the α-phenyl substituent will be done at the expense

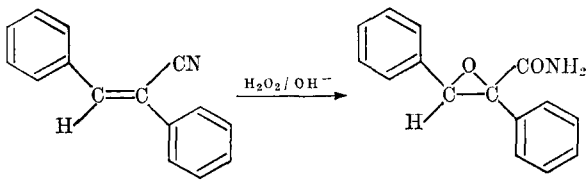
of electron-delocalization, and will therefore be energetically unfavorable. Of the two most probable transition states ('B') and ('C'), therefore, the former is the one of choice, and the collapse of ('A') will lead to the oxide in which phenyl groups are *cis*-oriented. For every instance examined in the literature, Zimmerman and co-workers succeeded in predicting the configuration of the product on the basis of their overlap control theory, since an epoxide with the least hindered acetyl group is always formed. The same principles are presumably operative with other α,β-unsaturated ketones on treatment with alkaline hydrogen peroxide.

Little need be said concerning the mechanism of epoxidation for α,β-unsaturated aldehydes, nitriles, and esters. Payne has proposed extension of the mechanism of Bunton and Minkoff[264] to the epoxidation of acrolein and crotonaldehyde,[1311] as well as of diethyl ethylidenemalonate and diethyl *iso*propylidenemalonate.[1310] Zimmerman and co-workers[1914] have applied overlap control principles to α-phenyl-*cis*-cinnemaldehyde (Eq. 94), which gave the oxide with *trans*-oriented phenyl substituents on treatment with alkaline hydrogen peroxide.



(94)

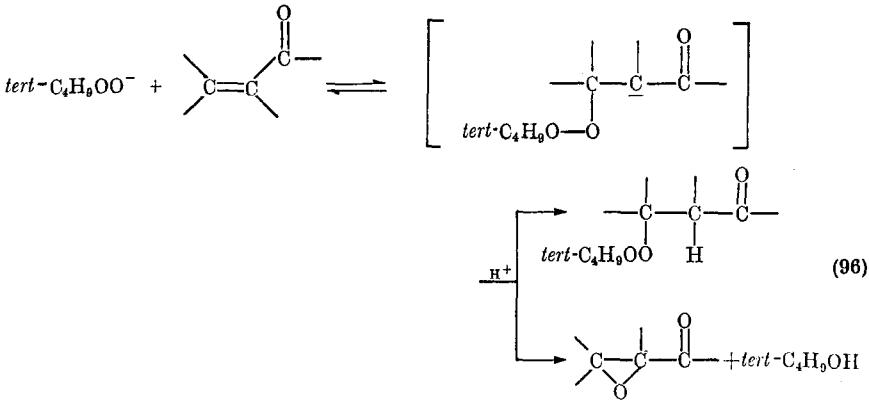
The above result indicates that for the smaller formyl group *cis*-interaction of phenyl groups becomes the dominant factor in selecting between transition states ('B') and ('C'). Similarly[1914] epoxidation of α-phenyl-*cis*-cinnamonitrile gave only the epoxide with *trans*-oriented phenyl substituents (Eq. 95), although this need not be



(95)

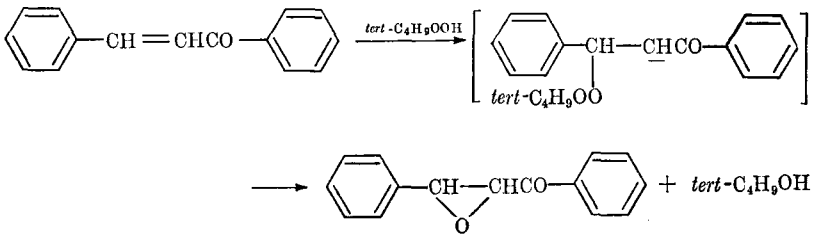
interpreted on the basis of overlap control theory, since the axial symmetry of the nitrile group imposes no special conformational requirement for overlap.

It will be convenient to return at this point to the *tert*-butyl hydroperoxide epoxidation reaction investigated by Yang and Finnegan.[1893] The mechanism advanced by these authors was straightforward. Reversible Michael addition of *tert*-butyl hydroperoxide anion to the conjugated system is considered to be the initial event. The anion thus formed can now follow one of two courses (Eq. 96). Abstraction of a proton from any available source, in another reversible step, yields the Michael product. Alternatively, the anion can collapse irreversibly into an epoxide, with concommitant release of *tert*-butoxide anion. The latter represents, in effect, an intramolecular nucleophilic displacement on oxygen.



(96)

The preponderance of one pathway over the other is governed by the equilibrium concentration of the intermediate anion—*i.e.* on its stability. The more stable the anion, the greater will be the rate of ring closure with respect to proton abstraction. Thus, a very stable anion, such as that resulting from benzalacetophenone, gives a high yield of epoxide (Eq. 97). A less stable one, such as that formed from



(97)

acrylonitrile, on the other hand, readily picks up a proton and gives the Michael product (Eq. 98).

$$CH_2{=}CHCN \xrightarrow{tert\text{-}C_4H_9OOH} [tert\text{-}C_4H_9OOCH_2\bar{C}HCN] \longrightarrow tert\text{-}C_4H_9OOCH_2CH_2CN \quad (98)$$

C. Direct Oxygen Addition

A method of considerable industrial importance for the large-scale preparation of ethylene oxide is direct oxidation of ethylene at elevated temperatures over a suitably prepared metallic silver catalyst. Although the reaction may be written as indicated in Eq. (99), in actual practice only about half the ethylene is converted into ethylene oxide, the remainder being oxidized further to carbon dioxide and water. In spite of this seeming disadvantage, catalytic oxidation appears at present to be economically competitive with chlorohydrin formation as a means for the commercial production of ethylene oxide.[1385] Unfortunately, other olefins, such as propylene and *iso*-butylene for example, apparently give only carbon dioxide and water under the usual oxidation conditions,[1210] so that until now the parent substance ethylene oxide has been the only representative accessible by this route.

The design of reactors, preparation of catalysts, control of temperature, and other topics of practical importance are summarized by Pokrovskii in excellent reviews[1384, 1385] which encompass the literature up to 1955. Reference should be made to these sources for numerous patent disclosures that will not be considered in the present discussion. Among the significant problems examined by Pokrovskii from the standpoint of industrial technology are relative merits of fixed and 'fluidized' catalyst beds, optimum composition of the reaction mixture in terms of both yield and safety, and properties of catalysts—selectivity, activity, durability, *etc.*—that are vital to the success of the enterprise.

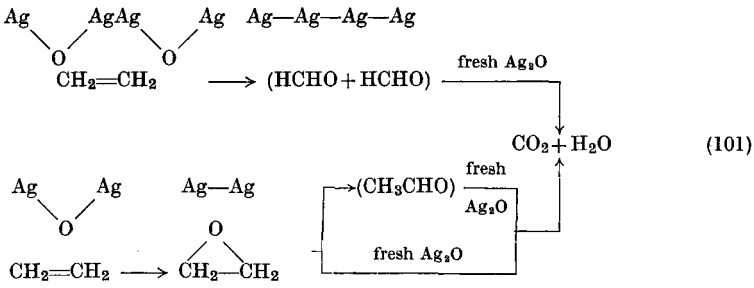
The first thorough investigation of the mechanism of ethylene oxidation on silver surfaces was undertaken by Twigg,[1771] who passed a mixture of air and ethylene at 200–350° over fine glass wool coated with metallic silver and obtained ethylene oxide, carbon dioxide, and water vapor. The reaction appeared to consist of two independent overall processes, which could be depicted separately as shown in Eq. (99) and (100). Of the two reactants, only oxygen was actually

$$CH_2{=}CH_2 + O_2 \longrightarrow \underset{\diagdown\,\diagup}{\overset{O}{CH_2{-}CH_2}} \quad (99)$$

$$CH_2{=}CH_2 + 3O_2 \longrightarrow 2CO_2 + 2H_2O \quad (100)$$

adsorbed, and the reaction rate, though dependent on the square of the atomic oxygen concentration on the catalyst surface, was practically independent of ethylene. This peculiarity evidently sets the process of catalytic olefin epoxidation somewhat apart from most surface-catalyzed reactions.

A rate expression was proposed by Twigg[1771] which could not be solved analytically, but which yielded rate constants for the two separate processes envisioned by him, if it were assumed that the adsorbed oxygen concentration remained constant. It was suggested that gaseous ethylene could collide with adsorbed oxygen in two ways. Collision with two atoms of adsorbed oxygen simultaneously would lead to two molecules of adsorbed formaldehyde, which would in turn be rapidly oxidized further to carbon dioxide and water. On the other hand, collision with a single atom of adsorbed oxygen would give ethylene oxide. The latter could isomerize to acetaldehyde on the surface of the catalyst, or could undergo direct oxidation. The acetaldehyde would be oxidized as rapidly as it was formed, and thus only carbon dioxide and water would be isolated from the reaction in addition to the desired epoxide (Eq. 101).



(101)

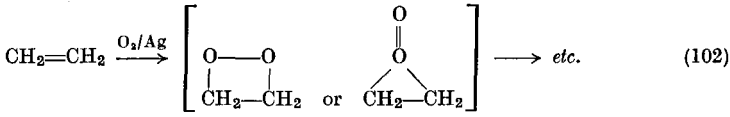
A subsequent investigation by Murray,[1210] conducted at 220–280° in a high-flow-rate reactor over metallic silver deposited on a barium carbonate support, gave results consistent with the picture delineated by Twigg, although the later author obtained a lower apparent energy of activation of 11–12 kcal./mole, instead of the 27 kcal./mole found by Twigg.[1771]

Similar studies were also conducted during this period by McBee and co-workers,[1063] by McKim and Cambron,[1075] and by Shen-wu Wan.[1802]

Schultze and Teil[1550] then carried out a study of the temperature variation over different regions of the catalyst surface as the reaction mixture flowed over them. From the observation that the surface

temperature gradually decreased and then once more increased further along the catalyst, they surmised that some reaction product functioning as an inhibitor was gradually accumulating on the catalyst surface, while other products flowed on and reacted on a fresh surface. This inhibitor could presumably be ethylene oxide, other investigators having also noted the inhibitory effect of this substance on ethylene oxidation.

Schultze and Teil expressed the idea that oxygen was not really chemically adsorbed in the conventional sense, but might instead be bound in a manner intermediate between true chemical adsorption and physical adsorption. In other words, the oxygen on the silver surface might still be 'partially' diatomic. Reaction with ethylene was then pictured as a complexing to form a transient peroxide species $C_2H_4O_2$, which could have one of two structures (Eq. 102), and which would react further very quickly, either on the surface or after desorption. The intermediacy of this peroxide was unfortunately not established experimentally, however.



(102)

Todes and Andrianova[1752, 1753] examined the effect of varying the catalyst on the kinetics of ethylene oxidation, as well as of ethylene oxide oxidation. Whereas ethylene oxide was oxidized faster than ethylene itself on a copper chromite surface, the reverse was true on a silver surface. The unique quality of metallic silver for effecting high conversion of ethylene into ethylene oxide was thus attributed to the high ratio between the rates of oxidation of ethylene and of ethylene oxide on this type of surface. The isomerization of ethylene oxide on the catalyst, earlier advanced by Twigg,[1771] was now rejected by Todes and Andrianova on the ground that ethylene oxide is oxidized at a rate proportional to the partial pressure of oxygen, a variable that should have no effect on the presumed isomerization. Although they had initially taken the position that ethylene oxide is a necessary intermediate in the conversion of ethylene into carbon dioxide and water on silver surfaces,[1752] Todes and Andrianova subsequently concluded,[1753] in agreement with Twigg,[1771] that two parallel and independent pathways exist for this process.

With the advent of isotopic techniques, further knowledge concerning catalytic olefin epoxidation became accessible. Roginskii and

Margolis,[1482] for instance, oxidized a mixture of ^{14}C-labeled ethylene and unlabeled ethylene oxide over metallic silver at 265°, and determined the kinetics of ethylene oxide and carbon dioxide formation by measuring the change in radioactivity of ethylene oxide and carbon dioxide isolated from the reactor after regular time intervals. The radioactivity of ethylene oxide was found to come to a maximum value, whereas that of carbon dioxide increased continuously, a pattern which pointed to the existence of some ethylene oxide-consuming process. Kinetic curves obtained by Roginskii and Margolis were said by them to suggest some autocatalysis. Carbon dioxide formation was felt to occur either on the catalyst surface or in the gas phase. It was noted also that the introduction of ethylene oxide into the reactor depressed the conversion of ethylene into ethylene oxide, though promoting its conversion into carbon dioxide.

In a separate investigation Margolis and Roginskii[1107] carried out catalytic oxidation of ethylene at 350° over vanadium pentoxide, reportedly similar to metallic silver in catalytic properties. They ascertained that carbon dioxide was formed faster from ethylene oxide, or from acetaldehyde under comparable conditions, than from ethylene itself. Further, they noted the formation of carbon monoxide, and determined that its rate of formation was considerably greater than that of carbon dioxide, increasing still more in the presence of added ethylene oxide. The addition of ethylene oxide also appeared to depress both ethylene oxide and acetaldehyde formation. They concluded that reactions leading to carbon dioxide and water did not proceed by way of ethylene oxide, but by way of some other intermediates, and that this process could occur either on the catalyst surface or in the gas phase.

Trotsenko and Polyakov[1766] came to similar conclusions in a concurrent study dealing with heterogeneous–homogeneous aspects of the reaction leading to carbon dioxide and water.

Additional knowledge regarding the kinetics of ethylene oxide formation came from an extensive program of investigation reported by Orzechowski and MacCormack.[1276] Operating on the premise that reliable kinetic data could not be obtained unless catalyst of standard activity was used, they discovered that reproducible results depended on the conditioning or 'training' to which the catalyst was subjected before measurement. Proper 'training' consisted of passing ethylene and oxygen through the reactor at the desired measurement temperature for about 150 hr. before actual measurement. Once the catalyst was standardized in this manner, the slightest change in any of several

critical variables invalidated the measurement. The variables included temperature, flow rate, feed composition, and catalyst state.

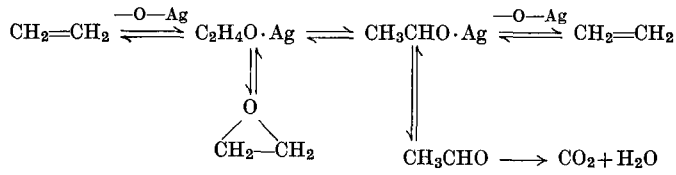
Aside from pioneering rigid catalyst control in this connexion, Orzechowski and MacCormack[1276] explored the significance of so-called 'slow processes', little account of which had been taken by previous workers. The competition of various processes was visualized as a race for available catalyst surface sites by molecules capable of undergoing further reaction and molecules incapable of it. Unreactive molecules can in this manner poison the catalyst, either by taking up space on the metal surface or by occupying space inside the crystal lattice of the catalyst. Such a poisoning effect had been noted earlier by other authors in this field.

Orzechowski and MacCormack[1276] put forward an empirical relationship for the overall rate and also proposed a rate equation for the initial step. Like Twigg,[1771] these authors arrived at the conclusion that adsorption of oxygen on the catalyst surface was followed by two parallel processes—one leading to ethylene oxide, the other leading directly to carbon dioxide and water—and that there also existed a pathway for further oxidation of ethylene oxide.

The selectivity of ethylene oxidation was found to be independent of feed composition at zero conversion.[1276] This was interpreted to mean that each of the two parallel processes is initiated by a similar type of transformation. Selectivity at zero conversion appeared to approach a value considerably different from 100%. Therefore the initial rate of carbon dioxide formation does not approach zero, as it should if it has to arise exclusively from ethylene oxide. The initial rate of ethylene oxide oxidation was found to depend on the partial pressure of both ethylene oxide and oxygen. Orzechowski and MacCormack concluded from this, in conflict with Twigg's earlier proposal,[1771] that isomerization of ethylene oxide to acetaldehyde is not a significant step in its further oxidation. Ethylene oxide could undergo oxidation either on the catalyst surface or in the gas phase by collision with an adsorbed oxygen atom.[1276]

Orzechowski and MacCormack envisaged the process of ethylene oxidation somewhat differently from Twigg,[1771] or from Schultze and Teil.[1550] After the initial adsorption of oxygen on the silver surface, a molecule of gaseous ethylene could collide with a single atom of adsorbed oxygen in two ways, involving two activated complexes of different energies. The product of one type of collision would be ethylene oxide; that of a second type would be an isomer, presumably acetaldehyde. Both types of collision involve adsorbed states of

ethylene oxide and acetaldehyde which are interconvertible, as shown in Eq. (103).



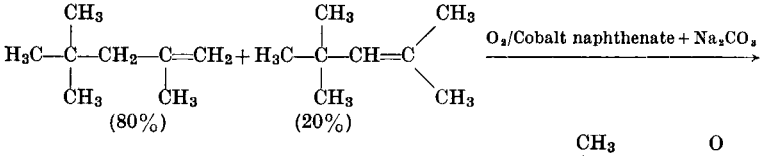
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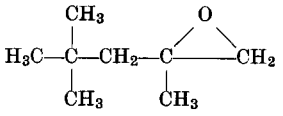
A number of other publications have appeared in this field, which will only be alluded to in the present discussion. Zimakov,[1911] for instance, has speculated on the possibility that a diradical $\cdot CH_2OCH_2\cdot$ is formed during silver-catalyzed ethylene oxide oxidation. Endler and Mazzolini have examined the reaction rate for silver-catalyzed ethylene oxidation from the standpoint of diffusion theory.[502] Gorokhovatskii and co-workers[659] have redetermined the apparent energy of activation for the silver-catalyzed formation of ethylene oxide and obtained a value of 18 kcal./mole, which is intermediate between previous measurements. Kurilenko and co-workers,[984] and also Gorokhovatskii and co-workers,[66] have studied the inhibitory effect of reaction products and found this to vary in the decreasing order: ethylene oxide, carbon dioxide, water. Similar results have been reported very recently by Hayes,[728] who is advancing the possibility that oxygen is adsorbed on metallic silver in the form of O^- or O_2^- ions.

Mention should be made, in addition, of a fourth approach in addition to those of Twigg, Orzechowski–MacCormack, and Schultze–Teil. This approach was taken by Pokrovskii,[1385] and stipulates that collision of a molecule of gaseous ethylene with an oxygen molecule, adsorbed in the diatomic state as suggested by Schultze and Teil,[1550] leads to a peroxy radical. This can in turn collide with a second molecule of ethylene to give two molecules of ethylene oxide, or can first collapse into the Schultze–Teil peroxide and then undergo further transformations. In Pokrovskii's scheme the formation of carbon dioxide and water can occur either by way of ethylene oxide (through acetaldehyde) or by way of other intermediates postulated to arise from the Schultze–Teil peroxide (ketene, or the Zimakov diradical $\cdot CH_2OCH_2\cdot$). A more complete discussion of these various possibilities can be found in Pokrovskii's excellent review article.[1385]

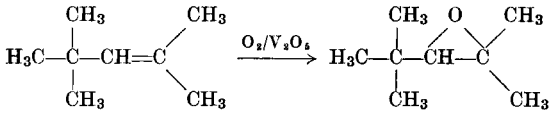
The preceding discussion has been restricted to oxidation of gaseous ethylene at elevated temperatures, little mention having been made of other olefins or other reaction conditions. The fact is, however, that few illustrations of liquid phase catalytic epoxidation are known.

Gasson and co-workers[620] have described a process for the conversion of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene into epoxides with air at 130–140° and 200 lb./in.^{2} over a catalyst of cobalt, manganese, lead or iron naphthenate in base, or of vanadium pentoxide (Eqs. 104 and 105). Some uncertainty is cast on this process, however, by the authors' own admission that comparable yields of epoxides were obtainable without catalysts.





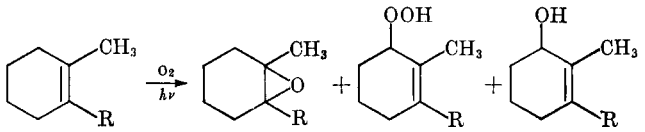
(104)



(105)

Ellis,[495] Dorée and Pepper,[461] Feuell and Skellon,[529] and Gold[654] have all examined the effect of passing gaseous oxygen through hot solutions of various unsaturated fatty acids, esters, and alcohols in the presence of cobalt catalysts. Among other products formed were the corresponding epoxides. Although interesting for other reasons, this process does not, however, constitute a practical synthetic method.

Of related interest is the fact that the passage of oxygen through irradiated 1-methyl-1,2-dimethylcyclohexene (Eq. 106) gives among



(106)

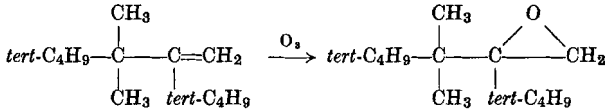
R = H, CH_3

other products the corresponding epoxides.[518] That this reaction probably involves hydroperoxides is indicated by the fact that thermal decomposition of 3-hydroperoxy-1-cyclohexene in the presence of cyclohexene yields a small amount of cyclohexene oxide along with other products.

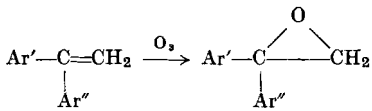
It may be mentioned briefly that direct addition of oxygen to olefins in the presence of suitable enzymes is a very significant biological process. Bloom and co-workers have in fact succeeded in preparing by enzymic methods 9β-11β-epoxy steroids[175] and 14α,15α-epoxy steroids[174] *in vitro* from the corresponding unsaturated steroids.

Chiefly of theoretical interest at the present time are investigations conducted by Cvetanovic and his collaborators,[399, 400, 401, 874, 1523] dealing with the direct addition of oxygen atoms to olefins. Atomic oxygen can be generated by mercury-photosensitized nitrous acid decomposition, nitrogen dioxide photolysis, or electric-discharge-initiated molecular oxygen dissociation. Appreciable yields of 1,2-epoxybutane and of *cis*- and *trans*-2,3-epoxypentane have been obtained in this manner, along with other products.

In conclusion of the present section may be cited reports from two laboratories[87, 368] that certain highly branched olefins give epoxides on ozonolysis,[57] as shown in Eqs. (107) and (108).



(107)



(108)

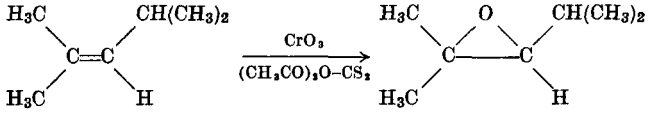
Ar′ = mesityl
Ar″ = phenyl, mesityl

D. Oxidation by Inorganic Reagents

Epoxides have been prepared on occasion by the action of certain inorganic oxidizing agents on suitable olefins. A notable example is chromic oxide in anhydrous media. Knowledge concerning the exact mode of action of such reagents is still incomplete, and for the purpose of epoxide synthesis they are of limited utility. For this reason only a brief discussion will be presented here.

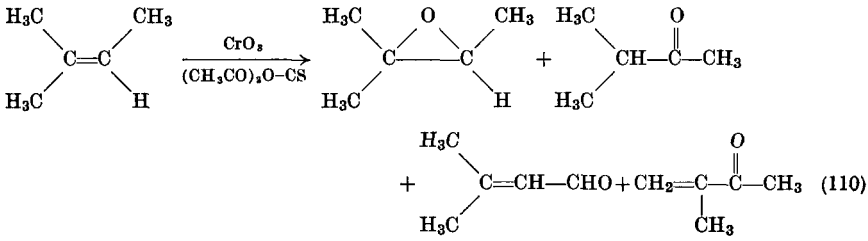
Hickinbottom and co-workers have reported several instances in which olefins were converted into epoxides with chromic oxide in acetic anhydride.[275, 425, 775–779] Rarely were the desired epoxides the only products formed, however. Two or more carbonyl compounds were usually produced as well. A few illustrations will suffice to demonstrate the subtleties of the structure–reactivity relationship for this reaction.

Oxidation of 2,4-dimethyl-2-pentene gave the desired epoxide in high yield (Eq. 109), and no other products were isolated.[777] The reaction was conducted at 0° in a mixture of acetic anhydride and carbon disulfide. Under these conditions 2-methyl-2-butene, in which a



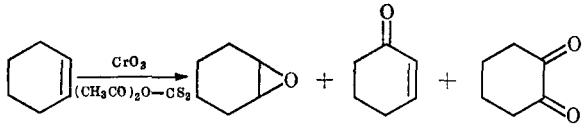
(109)

methyl group replaces an *iso*propyl, gives a mixture of four products.[777] These are the desired epoxide, 2-methyl-3-butanone, 2-methyl-2-butenal, and 2-methyl-1-buten-3-one (Eq. 110).



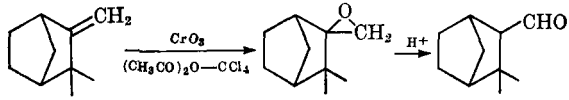
(110)

Epoxide formation is nearly suppressed when massively substituted olefins, such as 2,2,4-trimethyl-3-hexene among others, are subjected to the chromic oxide–acetic anhydride reagent.[425] Cyclohexene yields primarily 2-cyclohexenone and cyclohexane-1,2-dione[777] although some cyclohexene oxide appears to be formed also (Eq. 111).



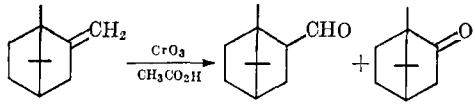
(111)

Camphene yields camphene oxide on oxidation with chromic oxide in acetic anhydride at $-10°$[779] (Eq. 112), but 1-methyl-α-fenchene gives in acetic acid at 25–90° a mixture of α-fenchone and



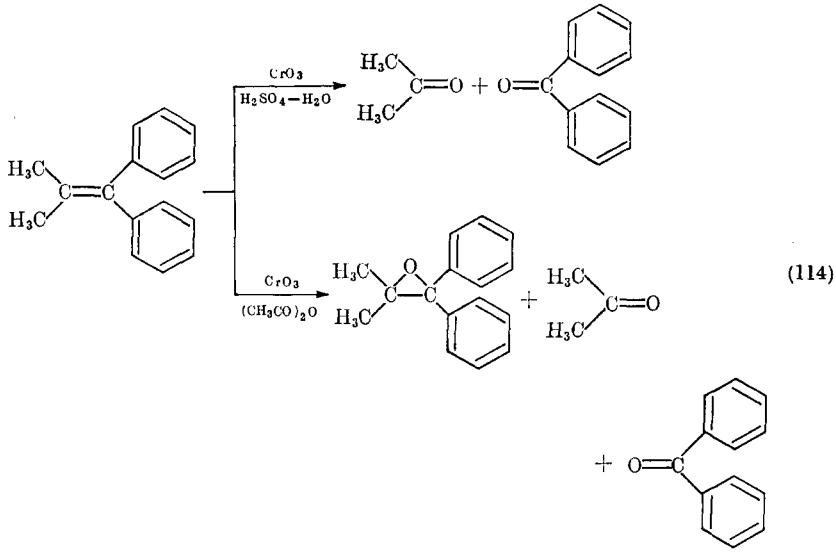
(112)

camphor, the latter predominating[1908] (Eq. 113). Since camphene oxide readily undergoes rearrangement to camphenilanaldehyde on treatment with mineral acid,[779] it is not improbable that 1-methyl-α-fenchene gives the corresponding epoxide under milder, anhydrous, and acid-free conditions.



(113)

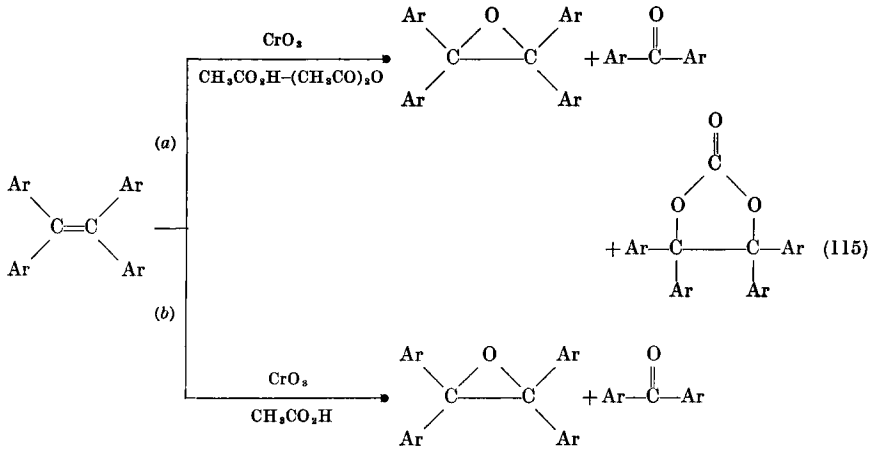
Hickinbottom and co-workers have recently published evidence casting doubt on earlier beliefs that epoxides were intermediates in the formation of carbonyl compounds during olefin oxidation by chromic acid. For example, 2-methyl-1,1-diphenyl-1-propene (Eq. 114) gave a good yield of the corresponding epoxide in acetic anhydride along with



(114)

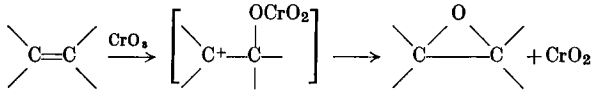
some acetone and benzophenone.[776] In aqueous sulfuric acid, however, only the two ketones were obtained. That the epoxide is not the primary product in sulfuric acid was indicated by the fact that simple acid-catalyzed hydration of the epoxide occurred more slowly than chromic acid oxidation of the original olefin in solutions of comparable acidity.[776]

Other tetrasubstituted olefins (Eq. 115) have recently been reported[1934, 1944] to yield the corresponding epoxides on oxidation with chromic acid in glacial acetic acid. Mosher and co-workers also noted in addition the formation of significant proportions of cyclic carbonates when all traces of water were excluded from the reaction medium by addition of acetic anhydride.[1944]



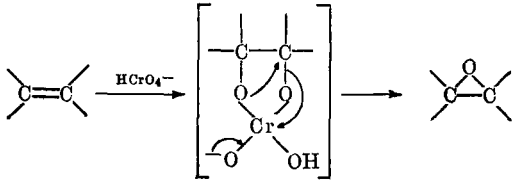
(115)

The importance of epoxide formation relative to other competing processes in anhydrous media appears to depend on the preference of some intermediate for direct collapse to an oxide ring relative to alternative pathways. The nature of this intermediate is not completely known, but Hickinbottom and co-workers[425, 776, 777] incline toward an open carbonium ion which can expel chromium of lower oxidation state in the form of CrO_2 or some other species (Eq. 116).



(116)

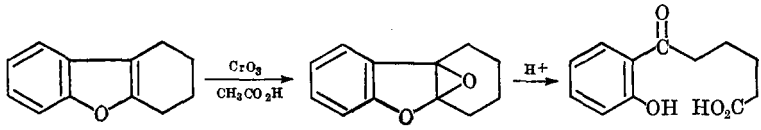
In aqueous media a different intermediate may well exist, especially since chromic oxide itself does not remain intact under these conditions. Zeiss and co-workers have proposed that in aqueous acid solution the rate-determining step is oxidative addition of the chromate ion $HCrO_4^-$ to the double bond, forming a cyclic chromate ester.[1906–1908] This could then conceivably rearrange as indicated in Eq. (117).



(117)

Hickinbottom and co-workers[425] have criticized this postulated cyclic intermediate on a number of grounds, notably its failure to explain formation of epoxides in anhydrous media.[425] For a general discussion, reference may be made to the review article of Waters.[1813]

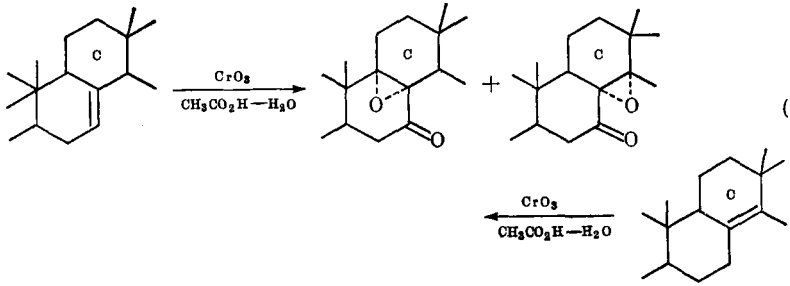
It has been reported[1864] that chromic oxide in acetic acid converted 2,3-tetramethylenebenzofuran into the corresponding epoxy ether (Eq. 118), identified by further acid-catalyzed degradation. This



(118)

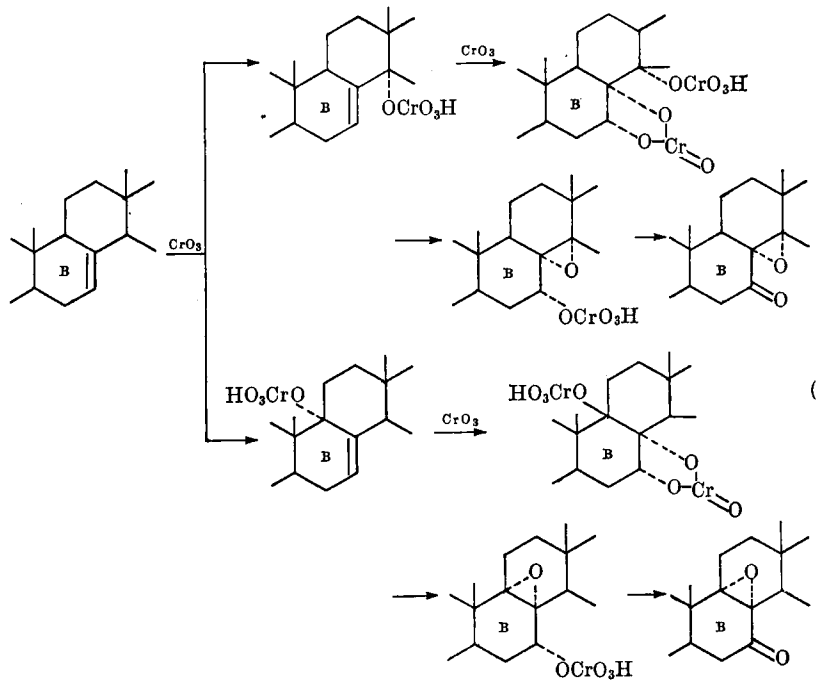
epoxy ether could not be prepared by peroxy acid oxidation, a diol being formed instead. Apparently the conditions used were sufficiently mild to permit isolation of the epoxide in this instance.

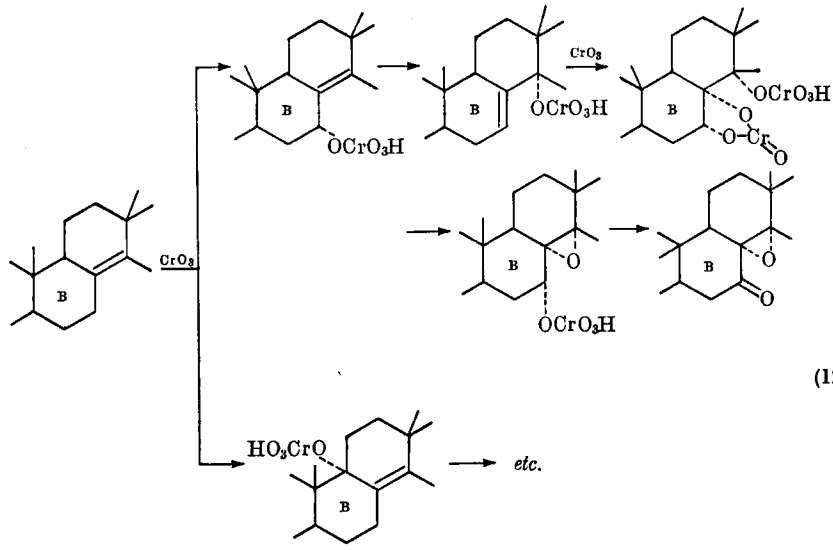
In the field of steroids, attention may be directed to a significant anomaly recently clarified by Fieser and Goto.[536] Treatment of Δ^7-cholestenyl acetate with chromic acid in aqueous acetic acid at 25°



(119)

has long been known[1866] to yield an easily resolvable mixture of 7-oxo-8α,9α-oxide and 7-oxo-8α,14α-oxide (Eq. 119). The latter is also formed by oxidation of $\Delta^{8(14)}$-cholestenyl acetate.[1866] The course of this reaction is delineated by Fieser and Goto[536] as shown in Eqs. (120) and (121).

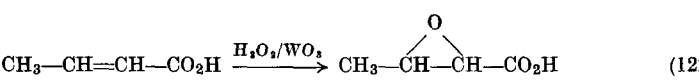

CrO3
B
OCrO3H
HO3CrO
O
Cr
(120)


CrO3
B
OCrO3H
HO3CrO
etc.
(121)

Other related examples in the steroid field have appeared in the literature,[98, 147, 455, 524, 537, 538, 540, 763, 1443, 1571, 1972] and may be referred to in this connexion.

A second element that has proved useful in converting olefins into epoxides has been tungsten. When olefins are treated with a mixture of hydrogen peroxide and catalytic amounts of tungstic acid (WO_3), epoxides are frequently obtained, although generally they are insufficiently stable to permit prolonged exposure to the reagent. Unless the epoxide is isolated quickly, hydration to a 1,2-diol and subsequent oxidation occur.

Payne and Williams[1316] discovered the superiority of the hydrogen peroxide–tungstic acid technique for certain purposes in the course of re-examining previous failures to expoxidize unsaturated acids, *e.g.* crotonic acid, maleic acid, and fumaric acid, with peroxy acids. They attributed these failures to inadequate pH control. When unsaturated acids were treated at 65° with hydrogen peroxide containing 2 moles percent of sodium tungstate, under conditions of rigorous pH control (pH 4.0–5.5), excellent yields of epoxides could be isolated with no difficulty (Eq. 122). The authors expressed the opinion that the actual oxidizing agent in this useful process is an 'inorganic peroxy acid'—presumably pertungstic acid—rather than hydrogen peroxide. Several patent disclosures from the same[287] and other[104] laboratories contain similar findings for other types of olefins, as does also a publication by Sergeev and Bukreeva.[1560]

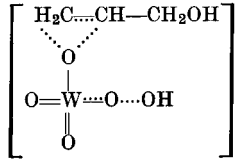


$$CH_3—CH{=}CH—CO_2H \xrightarrow{H_2O_2/WO_3} CH_3—\underset{\diagdown\,O\,\diagup}{CH—CH}—CO_2H \qquad (122)$$

Raciszewski[1426] reported a detailed kinetic study of the epoxidation of allyl alcohol by the hydrogen peroxide–tungstic acid reagent, under conditions that gradually destroyed the glycidol, presumably with the formation of glycerol and other products.[1560] The kinetics were interpreted in terms of a rapid, reversible oxidation of tungstic acid to pertungstic acid by hydrogen peroxide, followed by slow addition of pertungstate ion to allyl alcohol or its conjugate acid, and collapse of the transition state to glycidol with expulsion of regenerated tungstic acid, according to Eq. (123). Results of a similar character have also been published by Sulima for allyl alcohol,[1980] and by Saegebarth for crotyl alcohol.[1981] Substitution of molybdic and selenious acids for tungstic acid has also been discussed.[1980]

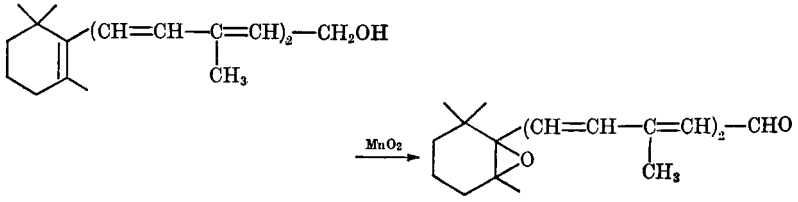
Support for the idea that the attacking species is a nucleophile

(*a*) $H_2O_2 + H_2WO_4(WO_3 + H_2O) \rightleftharpoons H_2O + H_2WO_5$

(*b*) $CH_2{=}CHCH_2OH + H_2WO_5 \xrightarrow{\text{slow}}$  $\longrightarrow$ Products (123)

comes from the enhanced reactivity of olefins bearing electron-withdrawing substituents. But not all such olefins react satisfactorily, as shown by the reported failure of acrolein to yield glycidaldehyde, affording instead acrylic acid.[1560]

Manganese dioxide, finally, has been claimed to function as an oxidizing agent in one very novel example,[1152] the conversion of vitamin A alcohol into an epoxide, retinene oxide, in the dark in the presence of light petroleum (Eq. 124).

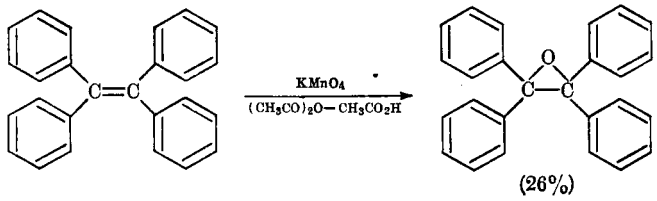


(124)

Some doubt was cast on these observations, however, when it was shown[355] that vitamin A alcohol undergoes autoxidation in the dark to give the epoxide of vitamin A alcohol. The ability of manganese dioxide to produce epoxides from olefins is therefore still open to question.

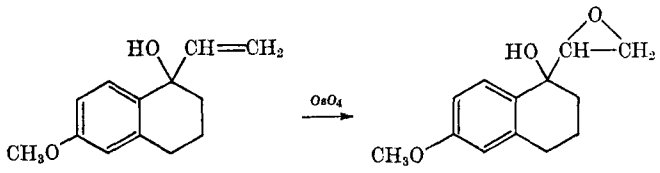
Mosher and co-workers[1944] have, on the other hand, recently published the first known instance of epoxidation with potassium permanganate, whereby tetraphenylethylene is converted into tetraphenylethylene oxide (Eq. 125).

It has recently been claimed also that osmium tetroxide is capable



(125)

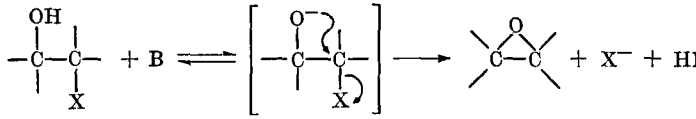
of converting, in at least one instance (Eq. 125a), an allylic alcohol into the corresponding epoxide instead of the expected triol.[1982]



(125a)

2. Cyclodehydrohalogenation

'Cyclodehydrohalogenation' is the term which will be used in the present section to describe collectively reactions whereby a β-halo alcohol, or halohydrin, is cyclized in alkali to produce an epoxide. Schematically the course of such reactions is depictable as shown in Eq. (126), where X is a halogen and B is a base.



(126)

Evidence for the above mechanism, particularly for the presence in appreciable concentration of an anionic intermediate, has been sought by several workers.[70, 1067, 1253, 1398, 1673, 1772, 1861] Twigg and co-workers[1772] demonstrated by means of kinetic, conductomeric, and spectroscopic measurements that the concentration of the intermediate anion is unexpectedly high. Ballinger and Long,[70] and also Swain and co-workers,[1673] subsequently arrived at a similar conclusion on the basis of kinetic isotope-effect studies. The effect of alkyl-substitution on the cyclization rate was investigated by Nilsson and Smith,[1253] Forsberg,[556] and Croisier and Fierens,[376] as well as by Kadesch[900] for the case of vinyl-substitution. The reaction rates of allyl- and phenyl-substituted chlorohydrins, along with those of *cis*- and *trans*-2-chlorocyclohexanol, were determined by Bergkvist.[127] For the case of *cis*- and *trans*-indene chlorohydrins the kinetics were examined by Suter and Milne.[1669] It appears generally that the reaction is approximately second-order overall, deviation from second-order kinetics being a measure of the equilibrium constant for the initial reversible step that precedes the slower rate-determining cyclization.

Empirical rules for cyclodehydrohalogenation have been formulated by Winstein and Henderson.[1857] Briefly, they are: (1) ring closure

occurs preferentially by backside attack on the least-substituted halogen-bearing carbon; (2) halogens follow the customary decreasing order (I, Br, Cl, F) in ease of displacement; and (3) cyclization is favored by alkyl-substitution on the carbons destined to form the ring. The pre-eminence of one or the other of these rules in conflicting cases is a problem that deserves more systematic study than has been hitherto accorded to it.

Winstein and Henderson[1857] have likewise enunciated the stereochemical requisites for cyclodehydrohalogenation. Ring closure demands backside attack by an alkoxide ion on the halogen-bearing carbon, with attendant Walden inversion at that site. The configuration of the halohydrin must therefore be such as to permit attack from the rear. Illustrative of this principle are stereospecific ring closures of *threo*- and *erythro*-2-chloro-3-hydroxysuccinic acid,[981] of *trans*-2-chlorocyclohexanol,[81] and of numerous other β-halo alcohols included elsewhere in the present text. Complex conformational effects sometimes also exercise a significant influence, however. This additional complication is exemplified by recent work of Curtin and Harder,[396] who examined the behavior of the four possible isomers of 2-bromo-4-phenylcyclohexanol toward alkali and toward silver oxide.

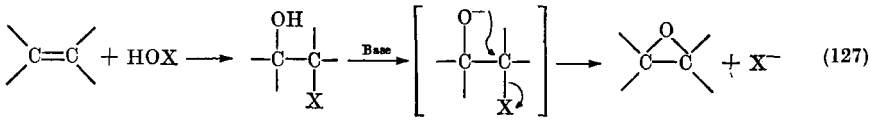
More recent discussions of the kinetics and mechanism of cyclodehydrohalogenation may be found in articles by Frost and Pearson,[593] and by Streitwieser.[1662]

Together with oxidation of olefins with peroxy acids, cyclodehydrohalogenations constitute the bulk of epoxide syntheses known at the present time. In addition the latter reactions possess the eminence of antiquity, since Wurtz himself[1884] made use of cyclodehydrohalogenation in the very first recorded ethylene oxide synthesis.

Below are described five approaches to epoxide synthesis by way of halohydrins. These halohydrins may be isolable purifiable intermediates; or they may be transient, unstable species that undergo spontaneous ring closure under the conditions used to generate them. The former are typical of: (1) addition of hypohalous acids to olefins; (2) chemical reduction of α-halocarbonyl compounds, and (3) addition of organometallic reagents to α-halocarbonyl compounds; the latter, of (4) Darzens condensation; and (5) epoxy ether synthesis.

A. Addition of Hypohalous Acids to Olefins

Conversion of olefins into epoxides has been achieved in a great number of cases through halohydrin intermediates generated by addition of hypohalous acids across the olefinic double bond (Eq. 127).



(127)

It was nearly a century ago—in fact only a few years after Wurtz discovered ethylene oxide[1884]—that Carius[286] effected the earliest additions of hypohalous acids to olefins. In the years that followed, many celebrated chemists were among those who investigated this reaction, which has been of great interest because of the parallelism between it and olefin halogenation.

No attempt will be made here to cite every recorded instance of the preparation of a halohydrin from an olefin. It will be sufficient to consider: (1) the various means employed to generate hypohalous acids; (2) the mechanism of the reaction; and (3) a few representative examples of its application.

(1) Hypohalous acid sources. When chlorine or bromine is bubbled into water an equilibrium is gradually established (Eq. 128).

$$X_2 + H_2O \rightleftharpoons HOX + H^+ + X^- \qquad (128)$$

If an extremely reactive olefin is available the concentration of hypohalous acid, although relatively small, will be sufficient to initiate addition. The equilibrium will be continually re-established to compensate for ensuing HOX depletion, provided that the external X_2 supply is maintained.

In most cases this method is not very satisfactory, however, since (1) olefins are generally insoluble in water; and (2) many olefins are relatively unreactive. A number of devices have been used to raise the effective concentration of hypohalous acid in reaction mixtures, to enhance its potency once formed, and to achieve homogeneity.

The hypohalous acid-generating equilibrium can be displaced to the right if there is present in the water a substance which will capture halide ion irreversibly as it is formed. This has been realized by adding mercuric oxide.[81, 85, 88, 304, 324, 1110, 1860]

Two methods have been utilized to circumvent the low solubility of organic compounds in water. The first is use of emulsifying agents, such as common household detergents, from which the product can be separated readily by steam-distillation.[499, 707, 1669] The second is use of a suitable mutual solvent, *e.g.* acetone,[1277] *tert*-butanol,[741, 797] or dioxan.[80, 143, 144, 146, 480, 581, 582, 584–586, 1004, 1275, 1476, 1583, 1826, 1829]

When it was discovered that hypohalous acid addition is acid-catalyzed—*i.e.* that attack is led by a protonated species H_2OX^+—various amounts of foreign acids were introduced, such as boric acid,[73] acetic acid,[120, 443, 1192, 1241, 1433] sulfuric acid,[780, 1521, 1801] and perchloric acid.[80, 143, 144, 146, 480, 581, 582, 584–586, 741, 797, 1004, 1275, 1476, 1583, 1826, 1829]

Numerous efforts have been directed toward development of reagents that would release hypohalous acids on exposure to aqueous acid without requiring the use of any gaseous halogens. Examples are *N*-chloroacetanilide,[120] *N*-chlorourea,[443, 1241] *N*,*N*-dichlorobenzene sulfonamide,[1032] sodium hypochlorite,[1435, 1563] potassium hypochlorite,[662] calcium hypochlorite,[499, 900, 1870] *tert*-butyl hypochlorite,[500, 707, 859, 1171, 1172, 1173] and other alkyl hypochlorites,[303, 799, 1700] *N*-bromoacetanilide,[1584] *N*,*N*-diboromobenzenesulfonamide,[799, 1353] *N*-bromoacetamide,[1277, 1353, 1360, 1854, 1859, 1861, 1863] and *N*-bromosuccinimide.[80, 143, 144, 146, 480, 581, 582, 584–586, 687, 797, 1004, 1275, 1360, 1433, 1476, 1583, 1801, 1826, 1829, 1855]

Monochlorourea (*N*-chlorourea) is formed when chlorine is allowed to react with urea in the cold. The product thus formed liberates hypochlorous acid vigorously on contact with water containing a trace of acid. The original procedure of Detoeuf[443] was later modified by Newman and Vander Werf,[1241] but on the whole this reagent is troublesome to prepare, its action not uniformly reproducible, and its handling quite hazardous.

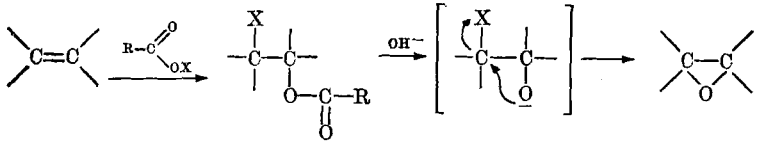
The use of *tert*-butyl hypochlorite with olefins was disclosed first in the patent literature,[993] and was subsequently reported also by Emerson,[499] and by Hanby and Rydon.[707] Hennion and co-workers too have examined this reagent, although they used alcohols as solvents rather than water, thereby obtaining chloro ethers instead of chlorohydrins.[859, 500] Unfortunately *tert*-butyl hypochlorite can be disconcertingly temperamental,[1703] and its usage has therefore been relatively infrequent.

The *N*-halophthalimides, *N*-haloacetanilides,[120] and *N*-halobenzenesulfonamides[1032, 799, 1353] have seen only limited service as reagents for the preparation of halohydrins.

When an aqueous solution of calcium hypochlorite is gradually acidified by passing gaseous carbon dioxide through it or by adding solid carbon dioxide, hypochlorous acid is generated in quantity. This procedure, variously described by Emerson,[499] Kadesch,[900] Wittcoff and co-workers,[1870] Hillyer and Edmonds,[785] and most recently in the steroid field by Mori and co-workers,[1171–1173] is convenient, safe, and

adaptable to large-scale organic synthesis. For the epoxidation of α,β-unsaturated aldehydes Shaer has also reported the successful use of sodium hypochlorite.[1563]

A variation of the general procedure discussed in this section consists of using acyl hypohalite addition to double bonds, according to Eq. (129).



(129)

The acyl hypohalite reaction with iodine as a halogen component is the well-known Prevost reaction,[1850] which has found some application during recent years in the field of natural products.[643, 79, 454, 950, 1879] In this case the acyl hypohalite is acetyl hypoiodite, generated by reaction of iodine with silver nitrate in glacial acetic acid (Eq. 130).

$$I_2 + CH_3CO_2Ag \xrightarrow{CH_3CO_2H} CH_3COOI + AgI \qquad (130)$$

Levine and Wall[1016] have explored the potential of acetyl hypobromite and acetyl hypochlorite in this connexion, obtaining epoxides satisfactorily from several steroids.

Reports concerning the use of *N*-bromoacetamide and *N*-bromosuccinimide have been abundant and favorable (see Table 6), so that at present these are evidently reagents of choice for converting olefins into epoxides by way of bromohydrin intermediates.

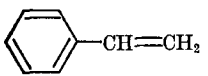
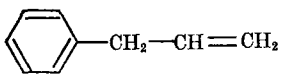
A special technique whose net effect is the addition of hypohalous acid, but which nevertheless differs significantly from the conventional methods, may be given separate consideration at this point.

Cristol and Eilar[372] reported in 1950 that certain olefins (Eq. 131), on treatment with chromyl chloride (CrO_2Cl_2) at low temperature in an inert solvent like carbon tetrachloride, form isolable adducts, which in turn give varying yields of chlorohydrins on hydrolysis. Significantly, however, the sense of addition of the reagent is the reverse of that observed normally with hypohalous acids.

$$R{-}CH{=}CH_2 \xrightarrow[(ii)\ H_2O]{(i)\ CrO_2Cl_2} R{-}\underset{\displaystyle Cl}{\underset{|}{CH}}{-}CH_2OH \qquad (131)$$

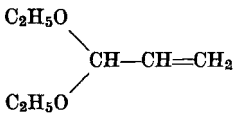
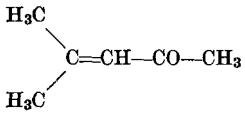
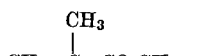
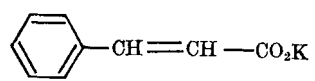
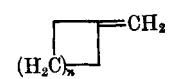
$$R = CH_3,\ C_2H_5,\ n\text{-}C_3H_7,\ n\text{-}C_4H_9$$

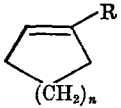
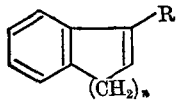
TABLE 6. Addition of Hypohalous Acids to Olefins

Compound		Reagent	Reference
$R'R''C{=}CR'''R''''$	$R' = R'' = R''' = R'''' = H$	*N*-Bromosuccinimide	1801
	$R' = R''' = H$; $R'' = R'''' = CH_3$	*N*-Bromoacetamide	1854, 1861, 1863
	$R' = R'' = H$; $R''' = R'''' = CH_3$	HOCl	1106
	$R' = R'' = R'''' = CH_3$; $R''' = H$	*N*-Bromoacetamide, *N*-bromosuccinimide	687, 1859
		$Ca(OCl)_2$	499
		*N*-Bromosuccinimide	687
$CH_2{=}CH{-}CH{=}CH_2$		$Ca(OCl)_2$, HOCl	510, 900
$R{-}C{\equiv}C{-}CH{=}CH_2$	R = H, CH_3	*N*-Bromoacetamide	1360
$ClCH_2{-}\underset{\displaystyle R}{\underset{\vert}{C}}{=}CH_2$	R = H, CH_3	HOCl	862, 863
$ClCH{=}CH{-}CH{=}CH_2$		HOBr	10
$HO{-}\underset{\displaystyle R}{\overset{\displaystyle R}{\overset{\vert}{\underset{\vert}{C}}}}{-}CH{=}CH_2$	R = H	HOCl, *N*-bromosuccinimide	862, 863, 1855
	R = CH_3	*N*-Bromosuccinimide	1855
$ROCH_2{-}CH{=}CH{-}CH_2OR$	R = H	HOCl	1568
	R = CH_3CO	*N*-Bromosuccinimide	1433

(*Table continued*)

TABLE 6 (*continued*)

Compound		Reagent	Reference
		HOCl	1818, 1882
		*N*-Bromosuccinimide	328, 687
$RCH{=}CH{-}CHO$	R = H	HOCl	1797
	R = CH_3	HOCl	1486, 1563
	R = C_6H_5	*tert*-C_4H_9OCl	1313
$R'R''C{=}CH{-}CO_2H$	R′ = H; R″ = C_6H_5	HOCl	1505
	R′ = H; R″ = CH_3	HOCl	239
	R′ = R″ = CH_3	HOCl	5
	R′ = H; R″ = $CH_3CH{=}CH$	HOCl	176
	R′ = H; R″ = CO_2H	HOCl	981
	R′ = H; R″ = CO_2Na	*N*-Bromosuccinimide	687
		*N*-Bromoacetamide	1983
		*N*-Bromosuccinimide	687
	n = 1, 2, 3, 4	HOBr	1762, 1763

Compound	Reagent	Reference
		
$n = 1$, R = H	*N*-Bromosuccinimide	658
$n = 1$, R = CH_3	HOCl	88
$n = 2$, R = H	*N*-Bromosuccinimide, HOCl	81, 687, 1854, 1861, 1863
		
$n = 1$, R = H	*N*-Bromosuccinimide	687
$n = 2$, R = H	*N*-Bromosuccinimide	687
$n = 2$, R = C_6H_5	*N*-Bromoacetamide	1950
$\Delta^{1,2}$-Steroids	*N*-Bromosuccinimide	1923
$\Delta^{2,3}$-Steroids	*N*-Bromosuccinimide	480, 1275, 1476, 1583
$\Delta^{4,5}$-Steroids	*N*-Bromosuccinimide	327
$\Delta^{5,6}$-Steroids	*N*-Bromoacetamide	497
	$Ca(OCl)_2$	1171–1173
$\Delta^{9,11}$-Steroids	*N*-Bromosuccinimide, *N*-bromoacetamide	80, 143–146, 581, 582, 584–586, 797, 1004
$\Delta^{11,12}$-Steroids	*N*-Bromoacetamide	902, 1277
$\Delta^{16,17}$-Steroids	*N*-Bromoacetamide	1016
$\Delta^{16,17}$-D-Homosteroids	*N*-Bromosuccinimide	1826, 1829

Probably the most striking example of the successful application of the bromohydrin method to epoxide synthesis has been preparation of 9α,11α-epoxy steroids. Although other workers had previously used hypohalous acids in steroid work,[780, 1277, 1521] credit for establishing *N*-bromosuccinimide as the reagent of choice in this case goes to Fried and Sabo,[584] who conducted the reaction in aqueous dioxan containing some perchloric acid as catalyst. Their method, incidentally, paved the way for the convenient synthesis of the highly potent 9α-fluoro steroid hormones by cleavage of the epoxide ring with hydrofluoric acid.

A particularly significant aspect of hypohalous acid addition is the fact that it can lead to epoxides isomeric in configuration to those obtained by peroxy acid epoxidation (compare Tables 5 and 6 for illustrations of this principle).

An impressive number of recent publications by various groups of workers[80, 143–146, 480, 581, 582, 585, 586, 741, 797, 1004, 1275, 1476, 1583, 1826, 1829] continues to retain the excellent procedure of Fried and Sabo,[584] which promises to be of great service in the steroid field. Occasional failures with *N*-bromosuccinimide have been recorded, however, particularly with olefins attached to electron-withdrawing functions that depress the electrophilic susceptibility of the double bond.[687]

(2) Scope. Collected in Table 6 is a representative list of references dealing with hypohalous acid addition to olefins. Where the authors did not convert the halohydrin into its corresponding epoxide, the latter is omitted. Table 6 shows that this method is applicable to the synthesis of a wide variety of epoxides.

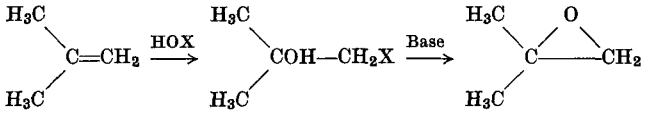
(3) Mechanism. Addition of hypohalous acids to olefinic double bonds is generally regarded as a typical electrophilic substitution reaction, and therefore subject to the same governing principles as others of the same type.

Detailed kinetic studies have been carried out by Shilov and co-workers,[1568] Israel and co-workers,[364, 862, 863, 1450] and most recently de la Mare and co-workers.[71, 1105, 1106]

A few significant illustrations have been selected to call attention to: (1) the directive influence of substituents; (2) the stereospecific mode of addition; and (3) the existence of an 'abnormal' reaction.

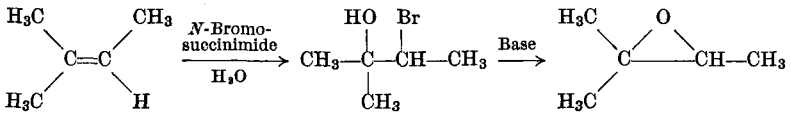
Treatment of *iso*butylene with aqueous hypohalous acids has been observed to yield predominantly 1-halo-2-methyl-2-propanol

(Eq. 132), none of the isomeric halohydrins being detectable even after careful search.[1106]



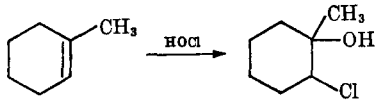
(132)

Similarly, addition of hypobromous acid, in the form of aqueous *N*-bromosuccinimide, to trimethylethylene (Eq. 133) appears to yield only 3-bromo-2-methyl-2-butanol.[1859]

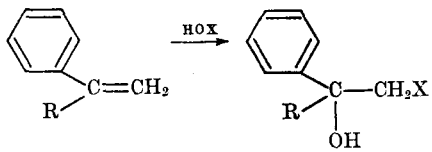


(133)

With styrene[1192] and α-methylstyrene,[492] the halohydrin also seems to be that in which the hydroxyl resides on the most-substituted carbon (Eq. 134), and an analogous situation has been reported for 1-methylcyclohexene[85, 328] (Eq. 135).



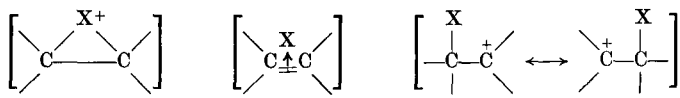
(134)



(135)

X = Cl, Br
R = H, CH_3

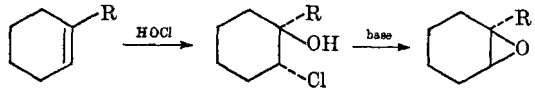
These and other facts point to a mechanism of the type envisaged by Roberts and Kimball,[1470] and frequently invoked by Winstein and co-workers,[1854, 1855, 1859, 1861, 1864] in which an intermediate halonium ion ('A') is formed, and subsequent attack by a nucleophile occurs at the site of greatest incipient carbonium ion stabilization. Alternative suggestions have also been advanced by Dewar[451] and by de la Mare.[1104] The former postulated a π-complex intermediate ('B'), the latter an 'open carbonium ion' intermediate ('C').



('A') ('B') ('C')

Evidence regarding the stereospecific character of hypohalous acid addition may be drawn from the classic works of Bartlett,[81, 85, 88] Winstein,[1854, 1855, 1859, 1861, 1864] and others.[1433]

Addition of hypochlorous acid to cyclohexene or 1-methylcyclohexene, for example, gives only two chlorohydrins from which the corresponding epoxides are readily prepared by heating with alkali. This observation led Bartlett[81, 85] to assign the *trans* configuration to the chlorohydrins (Eq. 136).

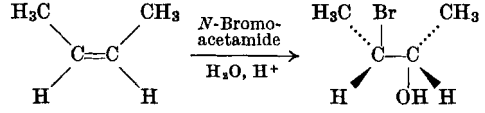


(136)

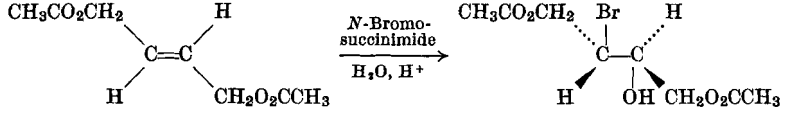
R = H, CH_3

Since addition of a halonium ion can be presumed to take place from the less-hindered side of a double bond, subsequent ring closure will lead to products in which oxygen is on the opposite, or more-hindered, side. This is of course in contrast with the action of peroxy acids, which effectively function by *cis*-addition and afford products in which oxygen assumes the less-hindered position. This difference acquires particular significance in the steroid field (see Table 6).

Treatment of *cis*-2-butene with an acidic aqueous *N*-bromoacetamide (Eq. 137) yields only the corresponding *threo*-bromohydrin.[1854, 1861, 1864] Similarly, treatment of *trans*-1,3-diacetoxy-2-butene with *N*-bromosuccinimide (Eq. 138) gives the corresponding *erythro*-bromohydrin.[1433]



(137)

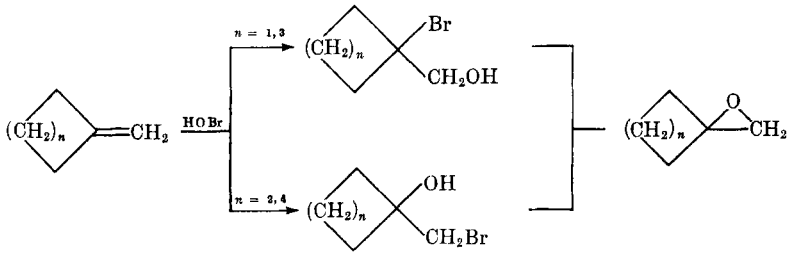


(138)

The above observations too are interpretable on the basis of a cyclic halonium intermediate, since attack by OH^- ion on the bridged ion, with attendant Walden inversion, would give the isolated products.

The concluding illustration to be cited here concerns an unusual effect noted recently by Traynham and Pascual[1762, 1763] on the addition of hypohalous acids to methylenecycloalkanes of different ring

size. Though addition appeared to occur normally with methylenecyclopentane and methylenecycloheptane on treatment with hypobromous acid (Eq. 140), the direction of addition was reversed with methylenecyclobutane and methylenecyclohexane (Eq. 139).



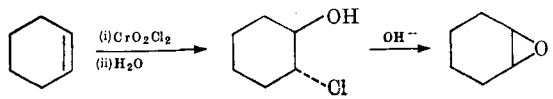
This unexpected event was ascribed to the strain involved in forming a trigonal carbon atom on four- and six-membered rings, compared to their five- and seven-membered homologs. The importance of the size or reactivity of the attacking species, was also indicated, moreover, by the fact that 'abnormal' addition products were not observed with hydrogen bromide, and were mixed with 'normal' products on treatment of the olefins with hypochlorous acid. Of course the nature of the halohydrin intermediate is of little consequence as far as the ultimate epoxide is concerned, provided that cyclization is rapid with respect to 1,4-elimination of the tertiary halogen.

Reference has already been made to the addition of chromyl chloride to olefins, which gives 'abnormal' halohydrins.[372] Propylene, 1-butene, 1-pentene, and 1-hexene, for example, all yield primary alcohols, as shown in Eq. (141).

$$\mathrm{R{-}CH{=}CH_2} \xrightarrow[\text{(ii) } H_2O]{\text{(i) } CrO_2Cl_2} \mathrm{R{-}\underset{\displaystyle Cl}{\underset{|}{CH}}{-}CH_2OH} \qquad (141)$$

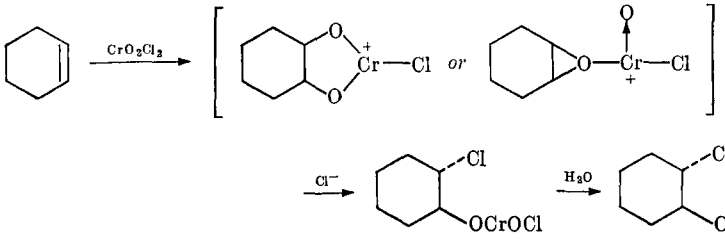
$$\mathrm{R = CH_3,\ C_2H_5,\ \textit{n}\text{-}C_3H_7,\ \textit{n}\text{-}C_4H_9}$$

*iso*Butylene, styrene, and stilbene gave polymeric products on work-up and tetrachloroethylene failed to react. Cyclohexene gave *trans*-2-chlorocyclohexanol, identified by its transformation into cyclohexene oxide in alkali (Eq. 142).



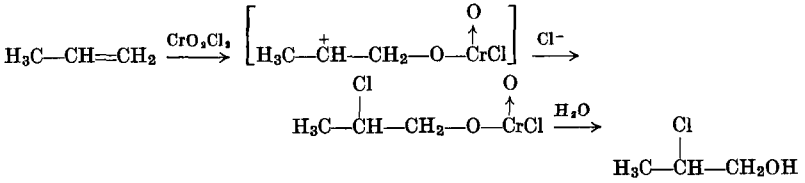
(142)

Cristol and Eilar[372] considered the reaction to be an electrophilic attack, since tetrachloethylene failed to react. Accordingly, the course of events for cyclohexene was pictured as shown in Eq. (143), a cyclic intermediate being invoked to explain the observed stereochemistry of the reaction.



(143)

With propylene, attack by Cl^- ion on the corresponding cyclic intermediate would not produce the observed product. An open carbonium ion is therefore the preferred representation for acyclic olefin intermediates (Eq. 144).

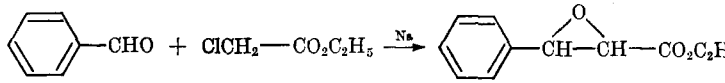


(144)

Although interesting, this method of generating chlorohydrins offers little synthetic advantage over others discussed above, and the literature dealing with it still consists only of the original report of Cristol and Eilar.[372]

B. Darzens Condensation—Glycidic Esters

The most frequently used method for synthesizing glycidic esters is Darzens condensation, which is based on a discovery in 1892 by Erlenmeyer[506] that sodium-catalyzed condensation between benzaldehyde and ethyl α-chloroacetate yields the α,β-epoxy ester ethyl β-phenylglycidate (Eq. 145).



(145)

It is largely by virtue of a massive 30-year study by Darzens, however, that this method, sometimes suitably modified, has come into

general use. The early literature dealing with the Darzens reaction has been excellently reviewed by Newman and Magerlein,[1236] and it will therefore not be of value to duplicate their efforts here. The mechanistic aspects of the reaction have also been discussed more recently by Ballester.[67]

The Darzens condensation may be formulated for the general case as shown in Eq. (146). As this equation indicates, there are three



(146)

components in the reaction, the base B^- being used up along with the reactants. It will be convenient to speak first of the carbonyl component R′R″CO, and then to consider in turn the halogen component XCHR‴R⁗, the base B^-, and finally the overall mechanism and stereochemistry of the reaction.

(1) Carbonyl component. Although the initial discovery by Erlenmeyer[506] was concerned with an aromatic aldehyde, Darzens promptly found other carbonyl compounds that could serve in this type of reaction. Thus aromatic ketones related to acetophenone,[411, 412] simple aliphatic aldehydes,[413] and aliphatic ketones[411–413, 418] were all found suitable, although giving varying yields of glycidic esters.

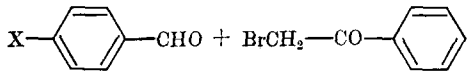
Later workers[67, 1095, 1175, 1228, 1236, 1704, 1708, 1847, 1899, 1984] have greatly expanded the catalog of carbonyl components effective in the Darzens condensation, although occasional disappointments are also on record.[1061, 1177] Efforts to study the reaction kinetically have unfortunately been few, and little can be gained from the all too numerous literature references that fail to specify yields.

It can nevertheless be said in general that the carbonyl component should fulfill the following requirements: (*a*) it should condense more rapidly with the halogen component than with itself; (*b*) it should condense rapidly enough so that the halogen component itself will not undergo autocondensation; and (*c*) it should undergo no appreciable *C*- or *O*-alkylation by the halogen component. The yield of glycidic ester is determined by the relative importance of these side-reactions, as well as of others occurring after the condensation itself.

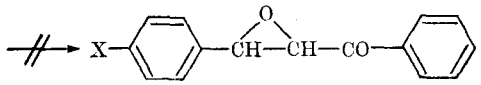
The reactivity of the carbonyl component is of course dictated by the usual electronic factors, electron-attracting substituents tending to render the carbonyl carbon rather positive and hence susceptible to nucleophilic attack.

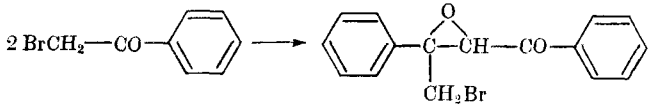
An excellent demonstration of these principles is the work of Bodforss,[182] who subjected several substituted benzaldehydes to

Darzens conditions, using phenacyl bromide (α-bromoacetophenone) as the halogen component. When electron-donating *p*-methyl, *p*-methoxy, or 3,4-methylenedioxy substituents were present, benzaldehyde reacted only sluggishly with phenacyl bromide (Eq. 147), the latter preferring instead to condense with itself to give what was subsequently shown to be a mixture of *cis*- and *trans*-β-phenyl-β-bromomethylbenzalacetophenone oxides (Eq. 148).[1629, 1808]



(147)

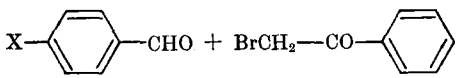




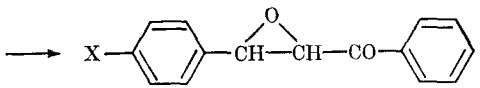
(*cis* and *trans*)

(148)

On the other hand, when electron-attracting *p*-nitro, *p*-chloro, or *p*-phenyl groups were present, the benzaldehyde carbonyl was sufficiently activated to give the expected products, *p*-nitro, *p*-chloro-, and *p*-phenylbenzalacetophenone oxide respectively (Eq. 149).

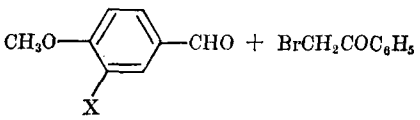


(149)

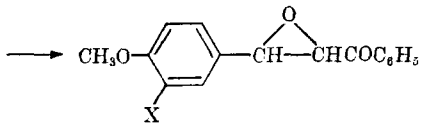


X = NO_2, Cl, C_6H_5

Further, when *o*-bromoanisaldehyde and *o*-nitroanisaldehyde were subjected to the same treatment, the desired epoxy ketones were satisfactorily obtained (Eq. 150).

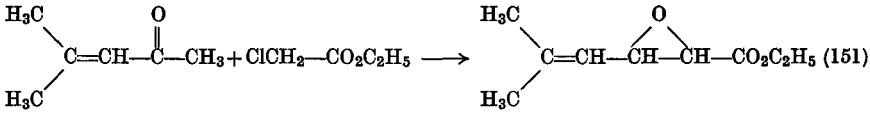


(150)



X = NO_2, Br

In several instances[402, 860, 1294] the carbonyl of α,β-unsaturated ketones has been found active enough to undergo the Darzens condensation. For example, mesityl oxide and ethyl α-chloroacetate give the corresponding glycidic ester in respectable yield (Eq. 151).



(151)

Ballester[67] has pointed out the parallelism of the aldol and Darzens reactions with respect to electronic effects. It is conceivable that steric effects can also play an important role in the reactivity of the carbonyl component, but there is insufficient evidence in the literature at present to warrant any definitive conclusion on this subject.[1236]

(2) Halogen component. The second component of the Darzens condensation will now be considered. The chief requirements that must be fulfilled by a substance functioning in this role are: (*a*) that it should contain at least one activated hydrogen on the halogen-bearing carbon; (*b*) that alkylation by nucleophilic halogen displacement should not occur in place of proton abstraction. Since halogen substituents are themselves somewhat activating by virtue of their electronegativity, it is sufficient to have only one other activating group present, provided that a suitable base is used to abstract the activated proton.

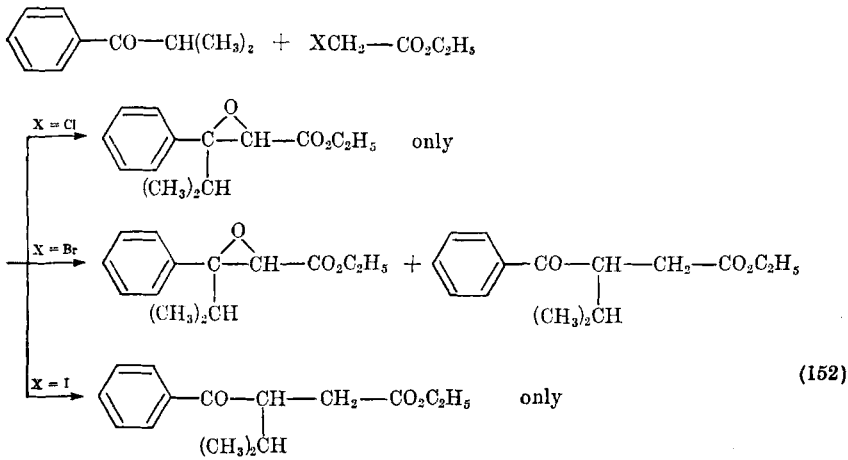
It was shown very early by Haller and Bauer[700, 701] that the most satisfactory halogen in this reaction is chlorine, with bromine and iodine following in that order. When *iso*butyrophenone was condensed with ethyl-α-chloroacetate the expected Darzens product was obtained. With ethyl α-iodoacetate, however, the product was ethyl 3-benzoyl-4-methylvalerate, and ethyl α-bromoacetate gave a mixture of the two (Eq. 152).

Newman and Magerlein[1238] have succeeded in using the toluene-*p*-sulfonate group in place of a halogen, but there is little advantage to this variation.

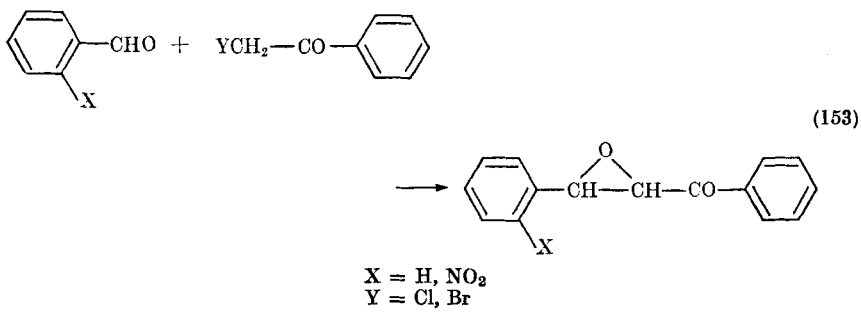
One of the most often used halogen components in Darzens reactions is phenacyl chloride or phenacyl bromide, which condenses for example with benzaldehyde[182, 1913, 1914] and *o*-nitrobenzaldehyde[182, 382] to yield the corresponding oxides shown in Eq. (153). Stereochemical aspects of this reaction are considered later.

Activation of hydrogen in the halogen component is achieved by a variety of functional groups in addition to the classic ester groups and the benzoyl group of phenacyl halides.

Temnikova and co-workers[1704, 1708] have carried out Darzens condensations between benzaldehyde and several α-haloketones, such as α-chloroacetone, 1-chloro-2-butanone, and 1-chloro-3,3-dimethyl-2-butanone (α-chloropinacolone). Similarly, Martynov[1115] has condensed furfural with 3-chloro-2-butanone. Kwart and Kirk[985] have reported that α-chloroacetone yields only one product on condensation with



(152)



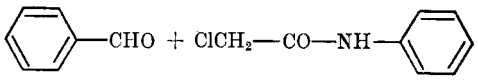
(153)

benzaldehyde, and that the product appears to have the *trans* configuration. In contrast, Temnikova and co-workers[1704, 1708] found that condensation of 1-chloro-3,3-dimethyl-2-butanone with benzaldehyde could be made to yield one or both isomeric oxides, depending on the relative proportion of base used.

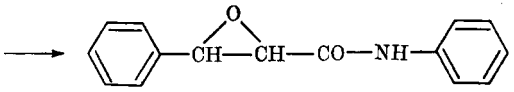
Bodforss,[184] Schickh,[1531] and later Fourneau and co-workers[566] successfully used a variety of α-chloroacetamides in the Darzens condensation. Examples are the preparations of the respective oxides

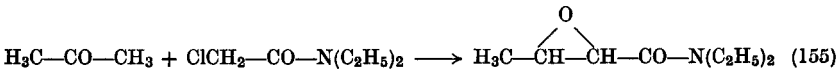
from acetone, cyclohexanone, and benzaldehyde, as shown in Eqs. (154) to (156).

Benzyl halides have in certain cases been sufficiently activated to take part in Darzens condensations. Although benzyl chloride itself gave poor results, *p*-nitrobenzyl chloride condensed readily with

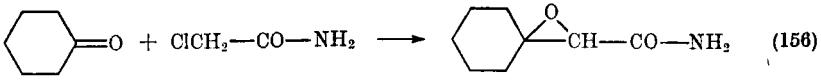


(154)



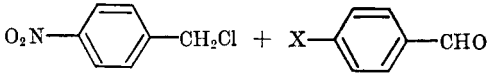


(155)

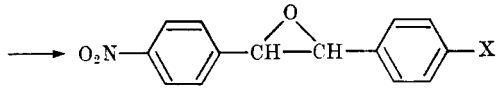


(156)

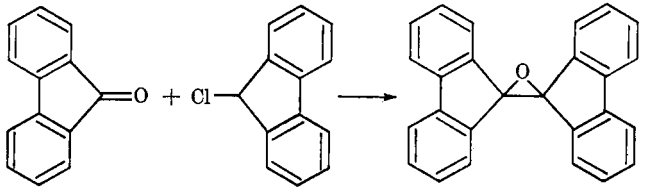
benzaldehyde or *p*-nitrobenzaldehyde (Eq. 157) to give the corresponding oxides.[132] The *p*-nitro group of the halogen component exercised a dominant influence even when a deactivating *p*-nitro substituent was present in the carbonyl component. Bergmann and Hervey[132] also condensed 9-chlorofluorene with fluorenone to obtain the interesting epoxide shown in Eq. (158).



(157)

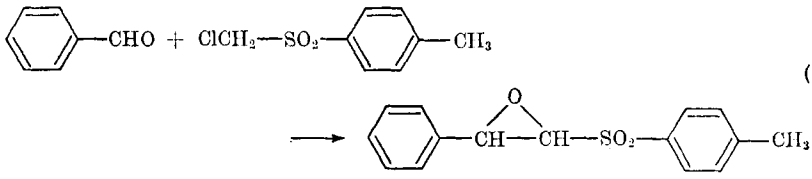


X = H, CH_3O, NO_2



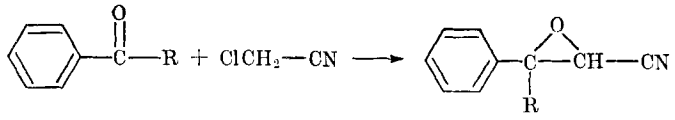
(158)

It has been stated by Ballester[67] that the sulfone group is a suitable activator for the halogen component, as for instance in the Darzens condensation of benzaldehyde and chloromethyl *p*-tolyl sulfone shown in Eq. (159).



(159)

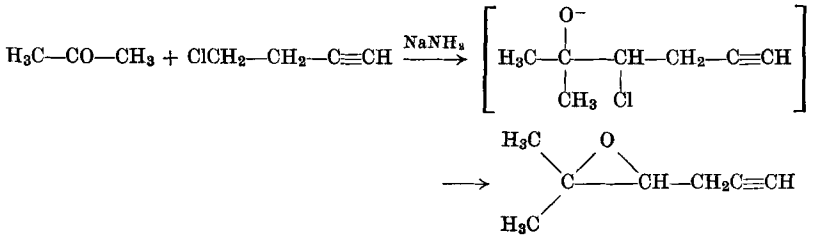
A recent patent disclosure[842] describes the use of α-chloroacetonitrile to prepare epoxides by Darzens condensation with benzaldehyde and propiophenone (Eq. 160). Similarly Stork and co-workers have recently described condensations of α-chloroacetonitrile and α-chloropropionitrile with such carbonyl components as cyclopentanone, cyclohexanone, 1-indanone, and others,[1659] and Blicke and Faust[171] have reported the condensation of α-chloroacetonitrile with benzophenone (Eq. 160).



(160)

R = H, C_2H_5, C_6H_5

Perveev and Shchelnukov[1347] have recently disclosed the application of a β-chloroacetylene as the halogen component in Darzens condensation (Eq. 161). When the reaction is conducted with sodium in liquid ammonia, the halide is sufficiently acidic to afford a β,γ-epoxyacetylene in good yield.



(161)

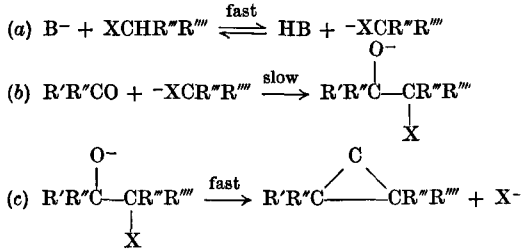
Dihalo compounds have been used occasionally in the Darzens condensation, but an additional activating group is required with these substances. Darzens[415, 416, 419] showed, for example, that treatment of certain ketones with ethyl α,α-dichloroacetate in the presence of magnesium amalgam yielded on hydrolysis a chlorohydrin cyclizable to a glycidic ester in alkali. The reaction can be carried out in benzene or in ether, and other amalgams can be substituted for that of magnesium. Newman and Magerlein[1236] have advocated more extensive application of the dihaloacetate method, particularly for carbonyl compounds that give poor yields under ordinary Darzens conditions, *e.g.* aliphatic aldehydes. To date, however, this potentially interesting modification of the Darzens reaction has remained unexplored.

It might be pointed out, as has been done by Ballester,[67] that chloroform and bromoform do not lead to epoxides when allowed to react with aldehydes or ketones, trihalomethylcarbinols being obtained instead. Halonitromethanes appear to behave similarly. These halogen components have not, however, been examined as carefully as others cited above, particularly with respect to the effect of varying the base B^-.

(3) Base. The third component of Darzens condensation that needs to be considered is the base B^-, which becomes gradually used up during the reaction. Sodium ethoxide was initially prescribed by Darzens,[412] especially where an ethyl ester was employed. Claisen,[314] on the other hand, preferred the stronger base sodium amide, which must of course be used in aprotic solvents. Other bases also requiring aprotic solvents have been metallic sodium in various states of subdivision[946, 947, 1510] and sodium hydride.[1150] The strong catalysts potassium *tert*-butoxide[878, 963] and sodium *tert*-pentoxide[134] have in some instances been claimed to give superior yields. Other bases that have been used include potassium and sodium hydroxide,[1238, 66] potassium carbonate,[132] sodium cyanide,[904, 905] sodium acetate,[904, 905] and diethylamine.[904, 905] The use of magnesium amalgam[415, 416, 419] has already been cited in connexion with the dihaloacetate modification of Darzens condensation.

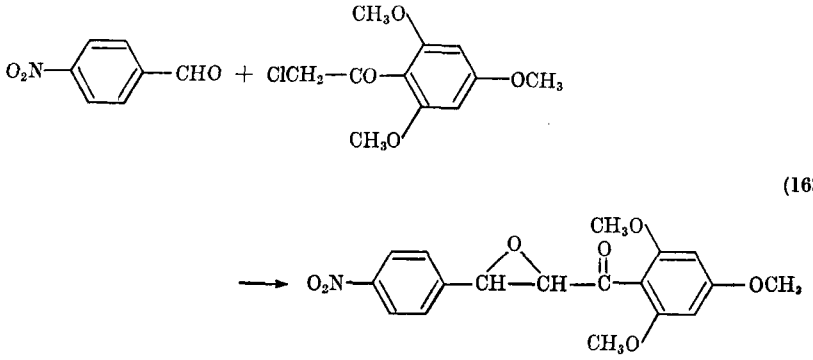
(4) Mechanism. The mechanism of the Darzens condensation has been thoroughly discussed in a review by Ballester,[67] who considers a number of older proposals and cogently discards each of them in turn. Although his arguments will not be reproduced here in their entirety, the preferred mechanism for the general case appears to be as shown in Eq. (162).

If the above mechanism is operative, third-order kinetics should be observed. This has indeed been done by Ballester and Bartlett,[68] who found for the condensation of phenacyl chloride and benzaldehyde in the presence of OH^- ion that the reaction is first-order with respect to each of these, or third-order overall.



(162)

In addition, Ballester and Perez-Blanco[69] have actually isolated two epimeric chlorohydrins from condensation of *p*-nitrobenzaldehyde and 2,4,6-trimethophenacyl chloride (Eq. 163). These intermediates could be cyclized in alkali to the respective epoxides in nearly quantitative yield.

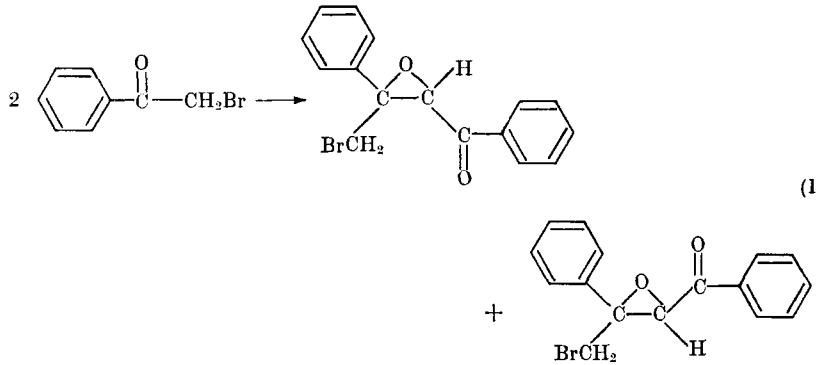


(163)

Evidence that the second, rather than third, step of the proposed mechanism is slow was obtained ingeniously by Ballester,[67] again for the case of benzaldehyde and phenacyl chloride. If the third step were rate-determining, and the second rapid and reversible, it should be possible to prepare the chlorohydrin intermediate by some suitable route, and to establish an equilibrium corresponding to the second step by treating it with alkali. If the second step were reversible, an alkaline solution of chlorohydrin should contain some benzaldehyde and some halocarbanion. If a more reactive carbonyl component, *e.g.* *p*-nitrobenzaldehyde, were introduced, a competition might ensue between

benzaldehyde and *p*-nitrobenzaldehyde for the available halocarbanion. On the addition of *p*-nitrobenzaldehyde to an alkaline solution of phenacyl chloride and benzaldehyde only benzalacetophenone oxide was isolated. This evidence pointed strongly to the second as the slow irreversible step in the reaction.

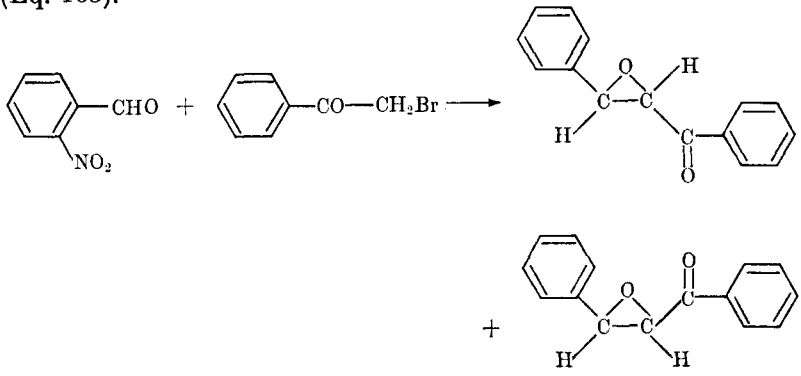
The stereochemistry of the Darzens condensation has received considerable attention in the literature. Early papers devoted to this aspect of the reaction were those of Berson,[150] Wasserman and co-workers,[1807, 1808] and Stevens.[1629, 1643] From the work of these authors



(164)

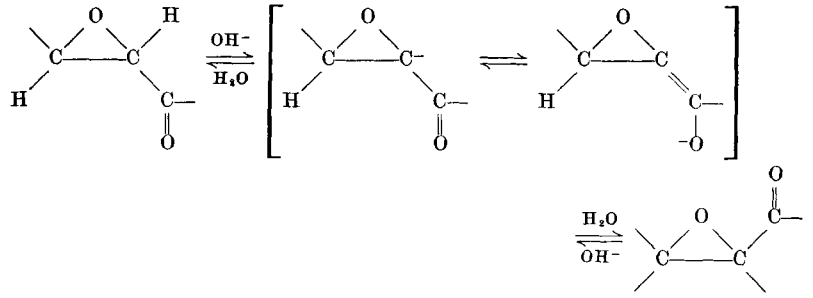
it could be concluded that phenacyl bromide initially undergoes autocondensation stereospecifically to give β-bromomethyl-*trans*-benzalacetophenone oxide, but that prolonged exposure of this product to alkali produces epimerization to the *cis*-oxide (Eq. 164).

Cromwell and Setterquist[382] re-examined earlier condensations of *o*-nitrobenzaldehyde and phenacyl bromide, and likewise obtained a mixture of *trans*-*o*-nitrobenzalacetophenone oxide and its *cis*-isomer (Eq. 165).



(165)

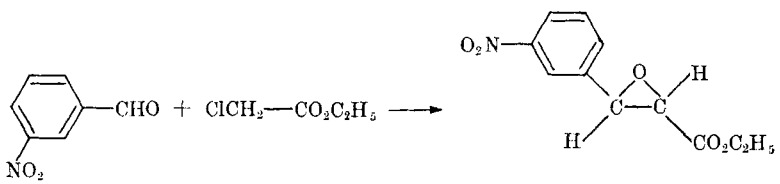
Again it was shown that alkaline treatment caused gradual epimerization of the *trans*-oxide to its *cis*-isomer. Cromwell and Setterquist[382] postulated the *trans*-isomer to be the kinetically favored product and therefore predominant in early stages of the reaction. The *cis*-isomer, however, because it is less soluble than the *trans*, is thermodynamically favored in this instance, in spite of the 1,2-interactions of *cis*-oriented phenyl and benzoyl groups. In other words, the equilibrium



(166)

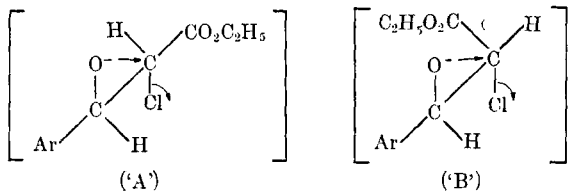
shown in Eq. (166) is displaced to the right by the low solubility of the right-hand product.

Dahn and Loewe[403] have performed a similar experiment with *m*-nitrobenzaldehyde and ethyl α-chloroacetate (Eq. 167), isolating only one product identified as ethyl *trans*-*m*-nitrocinnamate.



(167)

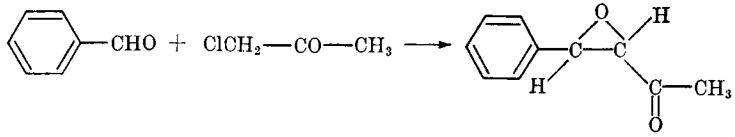
The stereoselectivity of this reaction was attributed by Dahn and Loewe[403] to a preference by the intermediate anion for conformation ('A') rather than ('B'), the former yielding the observed oxide on collapse.



('A') ('B')

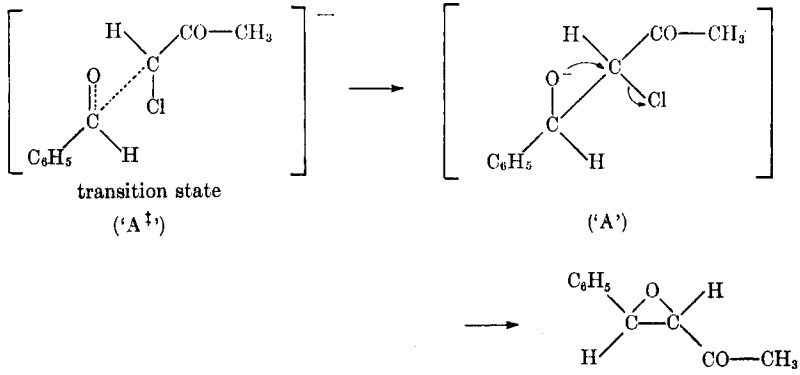
Ar = *m*-$O_2NC_6H_4$

Kwart and Kird[985] examined the condensation of benzaldehyde and α-chloroacetone (Eq. 168), noting that only *trans*-benzalacetone oxide was formed.



(168)

The above authors explained their results on the basis of steric effects also, but preferred to consider not intermediate anions, but transition states for the rate-determining collision between benzaldehyde and α-chloroacetone carbanion. Thus, of the two most probable 'collision orientations' for transition states ('$A^{\ddagger}$') and ('$B^{\ddagger}$'), the first is less sterically crowded, and hence only the corresponding anion ('A') will be formed, rapidly yielding the ultimate product on collapse



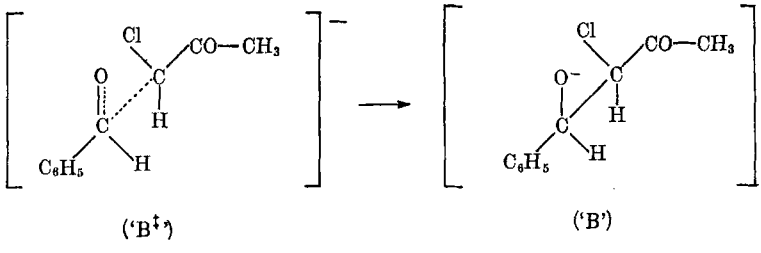
transition state ('$A^{\ddagger}$') ('A')

(169)

(Eq. 169). Further, the intermediate ion ('B'), formed by way of ('$B^{\ddagger}$'), is not in a favorable conformation for backside Cl^- ion displacement and must undergo a 120° rotation [to anion ('C')] before the isomeric epoxide could ever be obtained (Eq. 170).

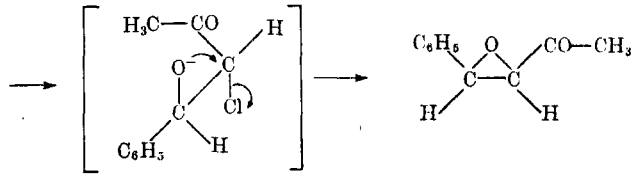
Whereas the ideas of Kwart and Kirk are primarily founded on the theory of steric effects, or non-bonded interactions, Zimmerman and co-workers[1913, 1914] have recently made the suggestion that product composition in Darzens condensations may be under stereoelectronic control. If this theory, amply supported by experiments in other systems, is correct, the concepts of Kwart and Kirk would need only slight adjustment to accommodate the overlap requirements of the carbonyl function in ('$A^{\ddagger}$') and ('$B^{\ddagger}$').

Attention may be drawn, finally, to an interesting variation of the conventional Darzens condensation, and especially to a recent correction of earlier findings. Wasserman and Gorbunoff[1809] found, on reinvestigation of a previous report by Kao and Fuson,[904, 905] that



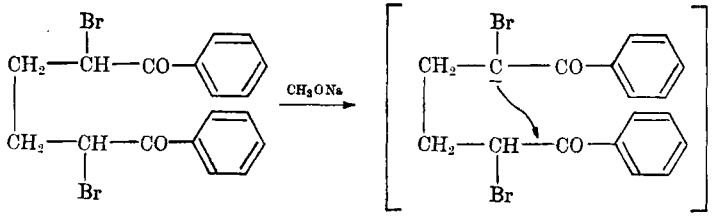
('B‡') ('B')

(170)

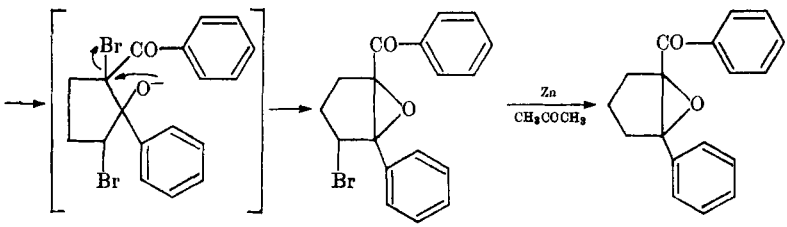


('C')

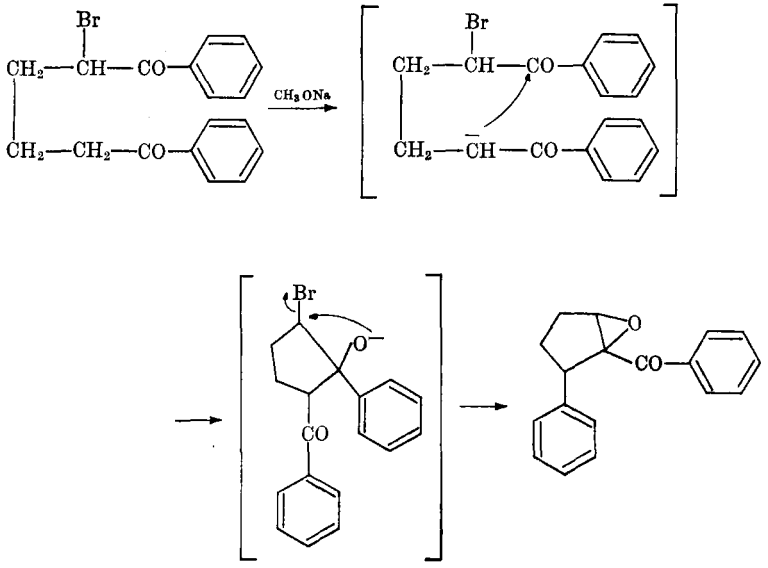
1,4-dibenzoyl-1,4-dibromobutane yields on treatment with alkali not 5-benzoyl-5-bromo-1-phenylcyclopentene oxide as reported earlier, but instead 2-benzoyl-5-bromo-1-phenylcyclopentene oxide, as shown in Eq. (171). Their finding was strengthened by the discovery that



(171)



treatment of 1,4-dibenzoyl-1-bromobutane with alkali gives directly 5-benzoyl-1-phenylcyclopentene oxide (Eq. 172). Since protons activated by a benzoyl group and a bromine atom should in principle be more acidic, it is not entirely clear at present why the reaction of 1,4-dibenzoyl-1-bromobutane proceeds as it does.



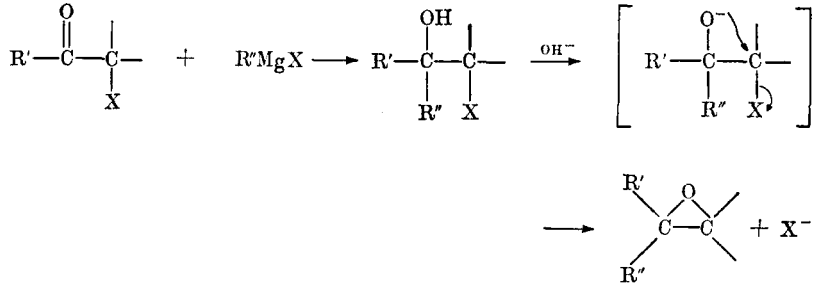
(172)

C. Grignard Reactions of α-Haloketones—Epoxyacetylenes

Among the less often used routes to epoxides based on intramolecular chlorohydrin dehydrohalogenation is the reaction of α-haloketones with Grignard reagents and the subsequent treatment of the product with alkali. This transformation is represented schematically in Eq. (173). Although the number of α-haloketones thus far reported to react satisfactorily with Grignard reagents is small, this route, when applicable, is a convenient method for the preparation of 1,1-disubstituted epoxides.

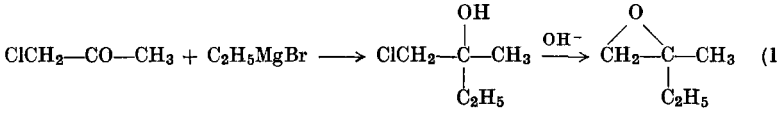
An excellent review of the massive and frequently polemical older literature on the present subject has been written by Kharasch and Reinmuth.[927] Subsequent contributions by Geissman and Akawie,[629] and also by Huang,[832, 833] have also been helpful in understanding the reaction. A long series of papers by Perveev and co-workers[1325–1350] finally has underscored its potential usefulness, particularly in the synthesis of epoxyacetylenes.

Fourneau and Tiffeneau[572] were apparently the first to prepare an epoxide by the route described above. Treatment of α-chloroacetone with excess of ethylmagnesium bromide led in their initial experiments to a mixture of 1-chloro-2-methyl-2-butanol and 3-methyl-4-hexanol



(173)

(Eq. 174). When the mixture was heated with potassium hydroxide the desired epoxide was formed and could be readily separated from 3-methyl-4-hexanol. The origin of the latter will be considered again later.



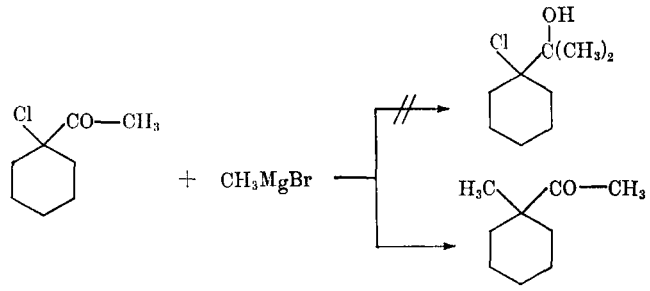
(174)

Kyriakides[987] improved the synthesis devised by the French authors by maintaining rigidly mild conditions throughout the reaction, and cyclizing the crude chlorohydrin without prior purification. A 65% yield of epoxide was obtainable in this manner. Korshak and Ivanova,[965] as well as Johnson and co-workers,[1985] have recently made use of this modified procedure in the preparation of a number of 1,1-dialkylethylene oxides. Cornforth and co-workers[356] have explored the stereospecific character of *n*-butylmagnesium bromide addition to α-chlorobutyraldehyde, in an effort to devise a stereospecific epoxide synthesis.

A disheartening note was struck very early, however, when it was discovered that branched α-haloketones, in which access to the carbonyl group is difficult, are prone to undergo simple halide displacement rather than give the desired chlorohydrin. Examples of this effect are numerous and well chronicled.[927] It will be sufficient, therefore, to cite the work of Sackur,[1516] who found that 1-chloroacetylcyclohexane yielded on treatment with a molar amount of methylmagnesium

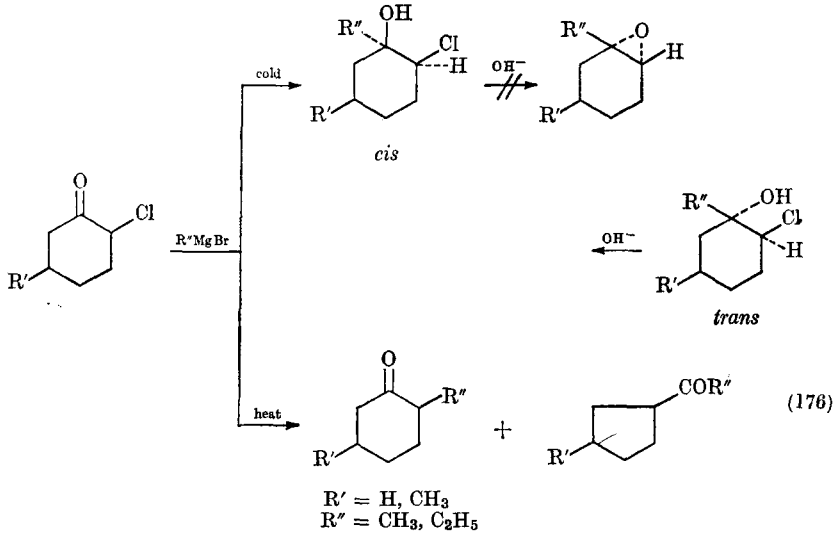
bromide only 1-methyl-1-acetylcyclohexane (Eq. 175). Careful search revealed no trace at all of the desired chlorohydrin.

The reaction of 2-chlorocyclohexanone with alkyl Grignard reagents was first investigated by Tiffeneau and co-workers[1744, 1746] in



(175)

a fruitless attempt to discover a convenient route to trisubstituted alicyclic epoxides. Treatment of 2-chloro- or 2-chloro-5-methylcyclohexanone with methylmagnesium bromide or ethylmagnesium bromide in the cold yielded the corresponding chlorohydrins (Eq. 176). If the



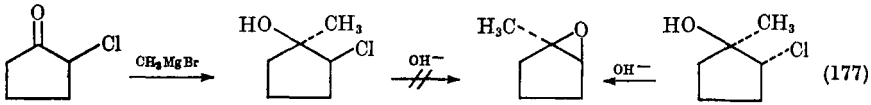
R′ = H, CH_3
R″ = CH_3, C_2H_5

(176)

reaction mixture was heated before hydrolysis, however, there were formed only 2-alkyl- or 2,5-dialkylcyclohexanones together with ring-contraction products.

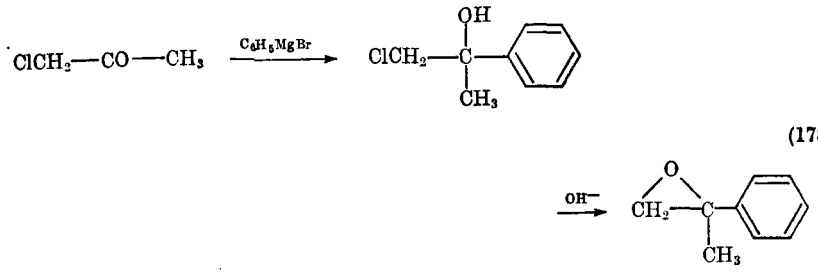
Bartlett and Rosenwald[85] simultaneously published similar results, pointing out in addition that the chlorohydrin prepared by Tiffeneau and Tchoubar[1744] did not give an epoxide on treatment with alkali. The configuration of the chlorohydrin was therefore *cis* and unsuitable for preparation of an alicyclic epoxide. A further unforeseen limitation of the Tiffeneau method lay in the failure of bulky Grignard reagents to yield the desired chlorohydrins, simple reduction of the carbonyl function occurring instead.[81]

In the five-membered series, Bartlett and White[88] converted 2-chlorocyclopentanone into a chlorohydrin on treatment with methylmagnesium bromide, but this product too failed to yield an epoxide because of the *cis*-disposition of hydroxyl and chlorine substituents (Eq. 177).



cis *trans* (177)

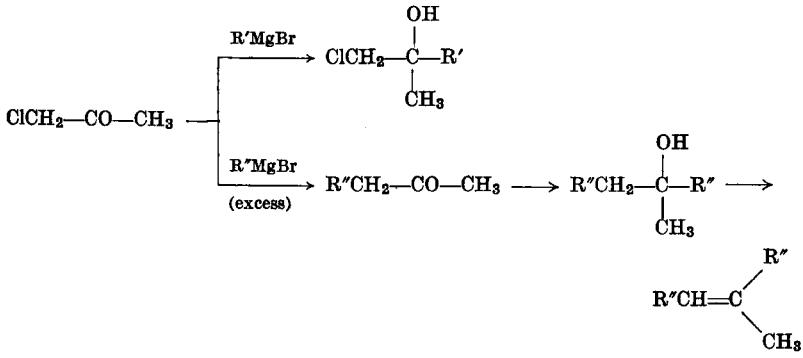
The use of aryl Grignard reagents was initially described in this connexion by Tiffeneau,[1718] who succeeded by carefully controlling the experimental conditions in isolating a chlorohydrin from the reaction of α-chloroacetone and phenylmagnesium bromide. Conversion to α-methylstyrene oxide was accomplished by heating with alkali (Eq. 178).



(178)

Even greater care needs to be exercised in the alicyclic series to prevent phenyl-migration. Fourneau and Tiffeneau,[572] and also Tiffeneau and Tchoubar,[1745] did prepare a chlorohydrin by condensing 2-chlorocyclohexanone with phenylmagnesium bromide, but this product is extremely unstable and presumably possesses incorrect geometry for ring closure in any case.[1723, 1724]

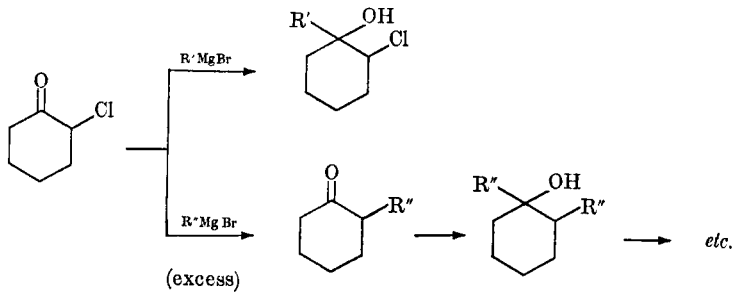
When the migratory aptitude of a phenyl group is modified by suitable substitution, it is possible to isolate moderately stable chlorohydrins, as was shown clearly by Huang[832, 833] in harmony with earlier findings of Bachman and co-workers.[57] When α-chloroacetone was



(179)

$R' = o\text{-}CH_3OC_6H_4,\ m\text{-}ClC_6H_4,\ p\text{-}ClC_6H_4$
$R'' = p\text{-}CH_3OC_6H_4,\ p\text{-}C_2H_5OC_6H_4$

treated with *o*-methoxy-, *m*-chloro-, or *p*-chlorophenylmagnesium bromide, the corresponding chlorohydrins were formed. Likewise, treatment of 2-chlorocyclohexanone with these reagents or with 1-naphthylmagnesium bromide afforded the corresponding chlorohydrins.



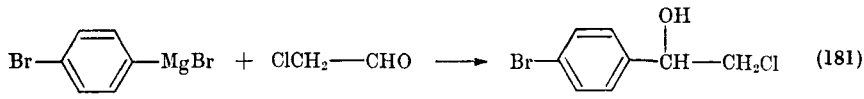
(180)

$R'' = p\text{-}C_2H_5OC_6H_4,\ o\text{-}CH_3C_6H_4,\ p\text{-}CH_3C_6H_4$

But addition of *p*-methoxy- or *p*-ethoxyphenylmagnesium bromide to α-chloroacetone (Eq. 179), or of *p*-ethoxy-, *o*-methyl-, or *p*-methylphenylmagnesium bromide to 2-chlorocyclohexanone (Eq. 180), yielded no chlorohydrins, giving rearrangement products instead.

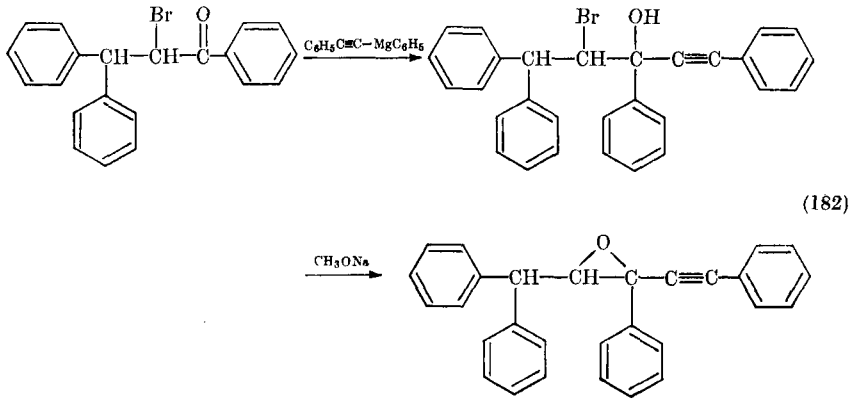
Application of aryl Grignard reagents with α-haloaldehydes is

exemplified by the synthesis (Eq. 181) of *p*-bromophenyl chloromethyl carbinol from *p*-bromophenylmagnesium bromide and α-chloroacetaldehyde.[128]



(181)

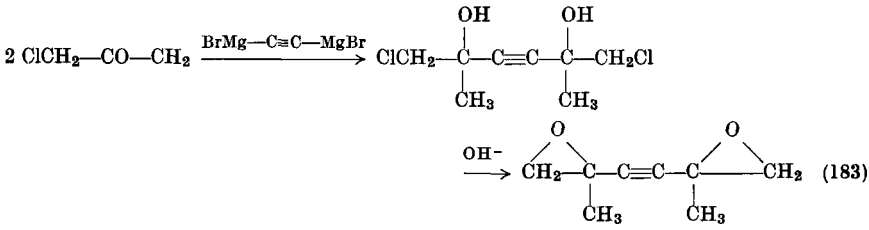
An interesting discovery by Kohler and Tishler,[959] which accidentally opened the most fruitful field of application for the present reaction, concerned the behavior of acetylenic Grignard reagents with α-haloketones. Whereas α-bromo-β,β-diphenylpropiophenone did not give halohydrins on treatment with normally active Grignard reagents like methyl- or phenylmagnesium halides, a bromohydrin was formed satisfactorily with phenylethinylmagnesium bromide (Eq. 182). The latter was in turn readily cyclizable to the corresponding epoxyacetylene.



(182)

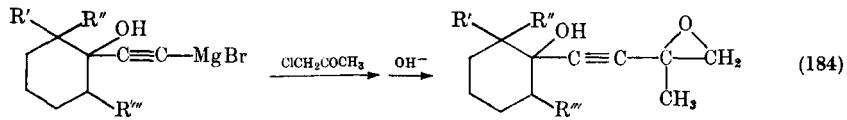
Shortly after, Herstein[757] prepared an unusual bisepoxide by condensing 2 molar equivalents of α-chloroacetone with the difunctional Grignard reagent derived from acetylene, and heating the resulting bischlorohydrin with alkali (Eq. 183). Perveev and Statsevich[1348] have recently confirmed the structure of this novel substance. It is noteworthy that the bisepoxide is so reactive that acid-catalyzed hydration occurs explosively. Ammonolysis, which normally requires elevated temperatures and pressures with ordinary epoxides, takes place smoothly at room temperature.

An important example of the usefulness of the acetylenic Grignard reagent in synthetic organic chemistry involving epoxides is the

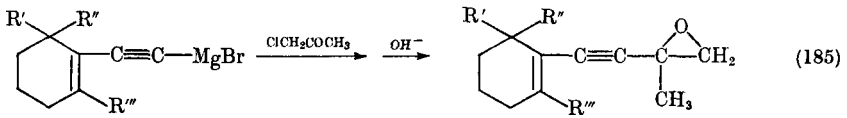


(183)

preparation of products related to vitamin A (Eqs. 184 and 185) by Milas, MacDonald, and Black.[1160]



(184)



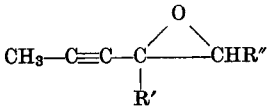
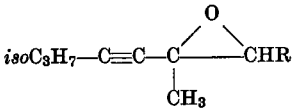
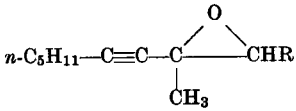
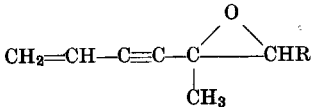
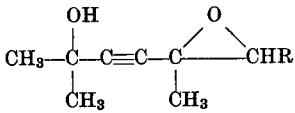
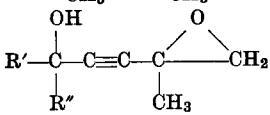
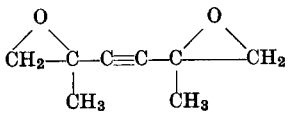
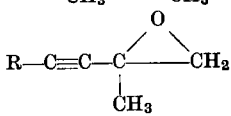
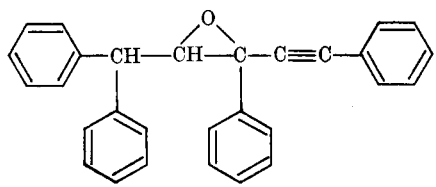
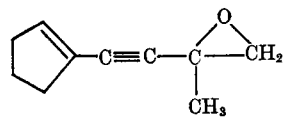
(185)

R′ = R″ = R‴ = H, CH_3
R′ = R″ = H; R‴ = CH_3

Extensive recent research by Perveev and his collaborators[1325–1350] has resulted in a modest but steadily growing catalog of α,β-epoxyacetylenes that display interesting chemical properties and may possess unusual biological properties as well. The α,β-epoxyacetylenes known at present have been collected in Table 7.

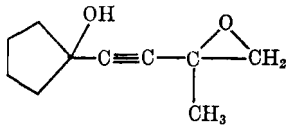
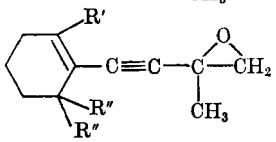
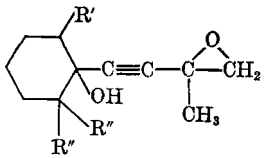
As may be evident from the foregoing discussion, preparation of chlorohydrin precursors by the Grignard reagent route is not at all a general approach to the synthesis of 1,1-disubstituted epoxides. It is of some service, however, where the following requisites are fulfilled: (*a*) the carbonyl function of the α-haloketone should be free of bulky neighboring groups; (*b*) the Grignard reagent itself should not be bulky; (*c*) substituents with high migratory aptitudes should not be introduced by way of the Grignard reagent, and should not be adjacent to the carbonyl function of the α-haloketone; (*d*) the chlorohydrin formed should have the proper configuration for ring closure by back-side alkoxide displacement of Cl^- ion.

TABLE 7. Epoxyacetylenes

Compound		Reference
	$R' = CH_3$, $R'' = H$ $R' = CH_3$, C_2H_5; $R'' = CH_3$	1327, 1338
	R = H, CH_3	1325, 1326
	R = H, CH_3	1725[a]
	R = H, CH_3	1334
	R = H, CH_3	1340
	$R' = CH_3$; $R'' = C_2H_5$, *sec*-C_4H_9 $R' = R'' =$ *iso*-C_3H_7	1340, 1350
		757, 1348
	R = *n*-C_4H_9, *iso*-C_5H_{11}, C_6H_5	1939, 1940
		959
		1344

(*Table continued*)

TABLE 7 (*continued*)

Compound		Reference
		1344
	R′ = H, CH_3; R″ = H	1160, 1344, 1598
	R′ = R″ = CH_3	1160
	R′ = H, CH_3; R″ = H	1160, 1344, 1598
	R′ = R″ = CH_3	1160

[a] Only the chlorohydrin corresponding to the epoxide is described.

The mechanism of the reaction has been discussed amply by Kharasch and Reinmuth.[927] Other pertinent reviews are those of Gaylord and Becker[625] and of Parker and Isaacs.[1301]

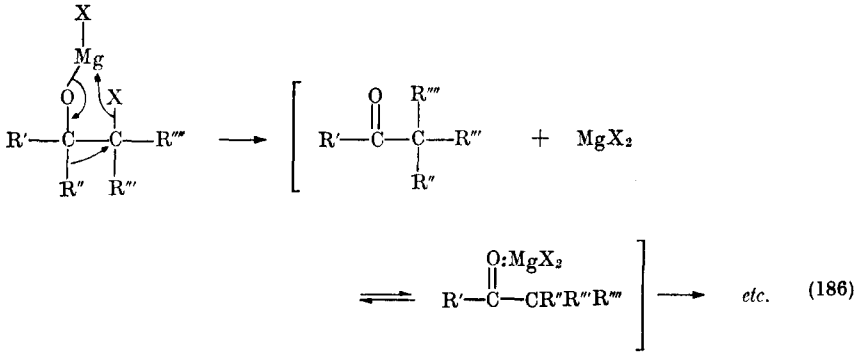
Abnormal products that sometimes accompany desired chlorohydrins have been shown compellingly by Tiffeneau[1723, 1724] to arise, not by direct metathetical exchange, but by a genuine rearrangement of the initial addition complex. Geissman and Akawie[629] have outlined two plausible mechanisms for the formation of abnormal products.

In the first mechanism the addition product undergoes a skeletal rearrangement initiated by electrophilic attack of the MgX group on the neighboring carbon, in analogy to the pinacolic migration. The resulting carbonyl compound can then react further with Grignard reagent (Eq. 186).

In the second, the halogen is displaced nucleophilically by oxygen and a transient epoxide species is formed which, in the presence of MgX_2, rearranges to a carbonyl compound. The latter in turn reacts with Grignard reagent to give the observed products. A similar mechanism has been advanced by House[813, 814] in a related problem (Eq. 187).

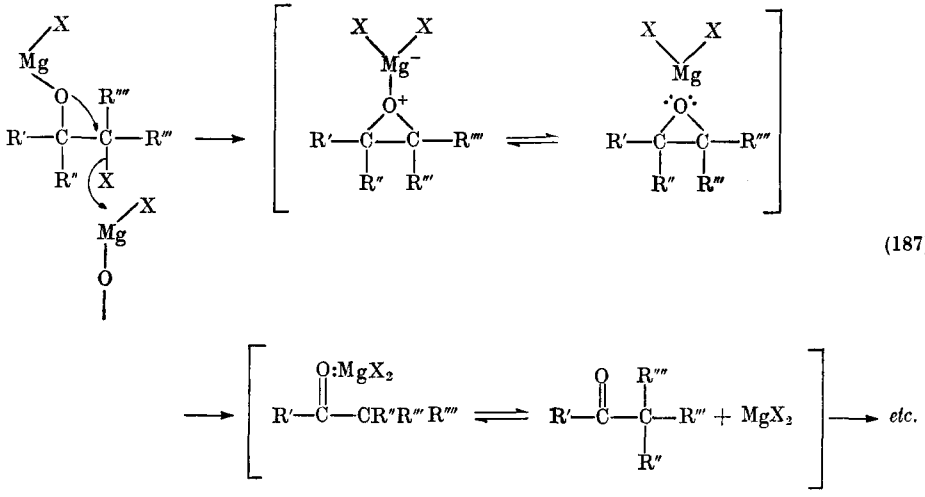
In each instance, the events indicated by curved arrows can occur synchronously or discretely. If substituents have high migratory aptitudes, or can facilitate halide abstraction by resonance-stabilization, the first route should be favored. If the substituents lack this

capacity, the other path might be preferred. A primary halide should more readily be displaced by way of the S_N2-like second path, whereas secondary and tertiary halides should be better suited to the S_N1-like



(186)

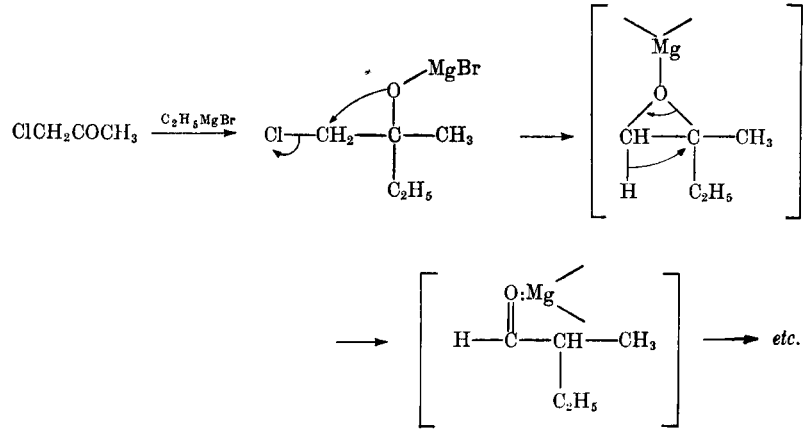
first path. The second route demands that the oxygen and chlorine atoms be *trans*-oriented to permit backside attack. If this condition cannot be met, the first route might conquer by default. It is thus evident that complex steric and electronic factors govern the course



(187)

of the rearrangement. Abnormal products isolated by Fourneau and Tiffeneau[572] in their early explorations, as well as those obtained later by other workers,[927] can be satisfactorily rationalized, however, on the basis of the two mechanisms delineated by Geissman and Akawie.[629]

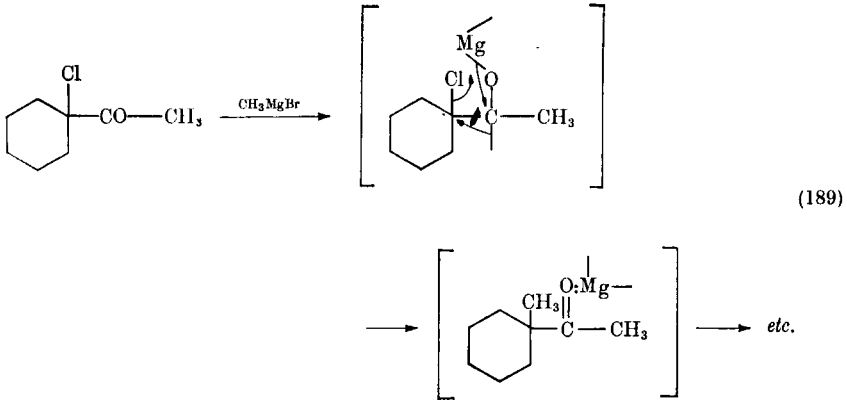
For example, Fourneau and Tiffeneau[572] reported the isolation of 3-methyl-4-hexanol on treatment of α-chloroacetone with excess of ethylmagnesium bromide. It is possible, though not yet completely demonstrable, that this product is formed by way of a transient epoxide intermediate, as shown in Eq. (188).



(188)

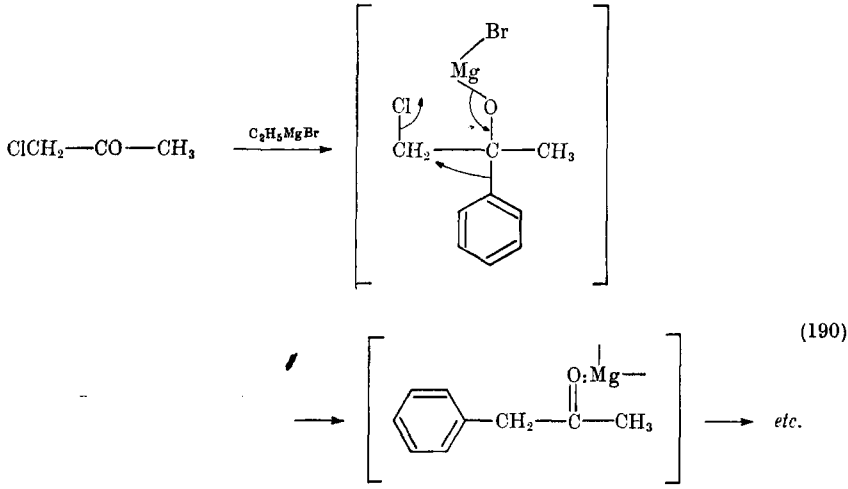
To what extent the putative epoxide in such an abnormal reaction is a long-lived species cannot be inferred from this example, since Fourneau and Tiffeneau[572] observed that 1,2-epoxy-2-methylbutane yields the same product on treatment with ethylmagnesium bromide.

The abnormal product reported by Sackur[1516] from 1-acetyl-1-chlorohexane and methylmagnesium bromide, and that isolated by Tiffeneau[1718] from α-chloroacetone and phenylmagnesium bromide, are probably best explained by the first path as shown in Eqs. (189) and (190).



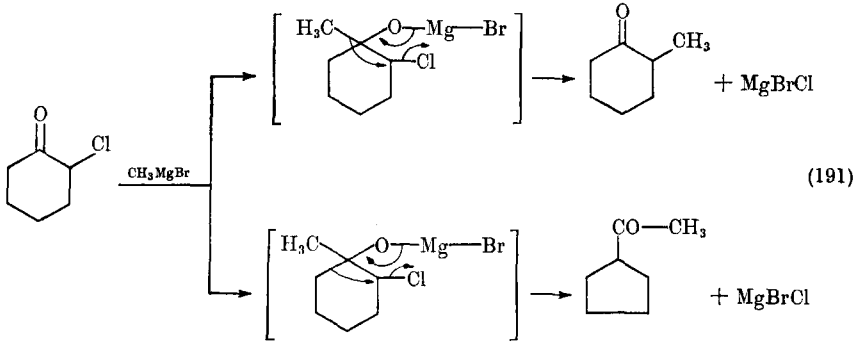
(189)

In the alicyclic series 2-chlorocyclohexanone yields two abnormal products on treatment with methylmagnesium bromide, namely 2-methylcyclohexanone and acetylcyclopentane.[1744] This observation



(190)

also can now be explained, to a first approximation, as shown in Eq. (191). The gross scheme takes no account of modern conformational concepts. Tiffeneau and Tchoubar[1748] found that halomagnesium derivatives of *cis*- and *trans*-2-chloro-1-methylcyclohexanol rearrange

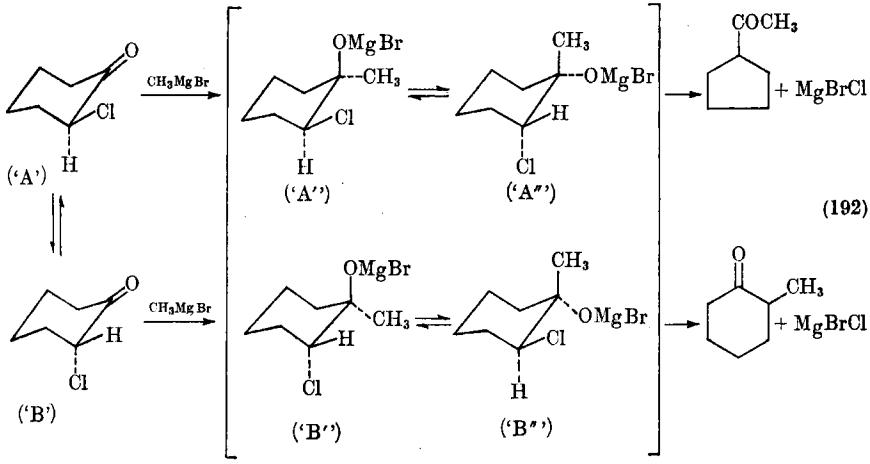


(191)

differently, the *cis*-isomer giving 2-methylcyclohexanone predominantly and the *trans*- only acetylcyclopentane. These halomagnesium derivatives are of course nothing more than the addition products in the Grignard reaction that constitutes the subject of the present

section. It may therefore be instructive to correlate the findings of Tiffeneau and co-workers[1744, 1748] in terms of conformational theory.

If it is assumed that 2-chlorocyclohexanone exists in two conformations ('A') and ('B'), and that the Grignard reagent attacks preferentially from the equatorial side, the course of events may be depicted as shown in Eq. (192).



(192)

Of the four possible conformations for intermediate adducts, the most probable are ('A'') and ('B''), since these two contain only one bulky axial substituent each. These states are therefore probably the most highly populated, and will react fastest to give products. Backside attack on the halogen-bearing carbon is best accomplished by a migrating methyl group in ('B'') and by movement of a ring bond in ('A'') bringing about ring-contraction.

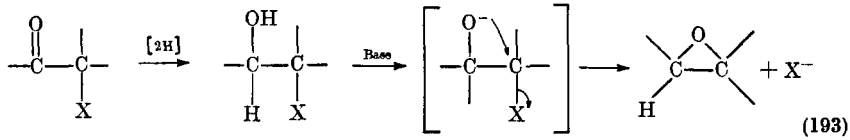
Tiffeneau and co-workers[1744, 1748] obtained similar results with halomagnesium derivatives of *cis*- and *trans*-2-chloro-1,4-dimethylcyclohexanol, and their findings were corroborated and extended by Geissman and Akawie.[629]

Important related studies have been published by House,[813, 814] and by Naqvi and co-workers,[1216] on the subject of magnesium bromide-initiated epoxide isomerizations. Their results, discussed in section **IV.3.***A*, suggest that abnormal addition of Grignard reagents to alicyclic α-haloketones does not proceed by way of an ephemeral epoxide intermediate, in accordance with the view expressed previously by Geissman and Akawie.[629]

Rearrangement of several substituted chlorohydrins of fixed conformation has recently been reported by Curtin and Harder,[396] and attention is directed to this interesting paper, since it is related to the abnormal reaction of α-haloketones with Grignard reagents and hence pertinent to epoxide chemistry.

D. Reduction of α-Halocarbonyl Compounds

Conversion of α-halocarbonyl compounds into halohydrins, followed by alkaline cyclodehydrohalogenation, constitutes still another route to epoxides. This process is depicted in Eq. (193) for the general



(193)

case. As this scheme indicates, the required addition of a hydrogen atom precludes application of this approach for the synthesis of tetrasubstituted epoxides. The ready reductive cleavage of C—X bonds (X = halogen) on metal surfaces, *e.g.* nickel, platinum, or palladium, generally excludes catalytic reduction. The advent of chemical reducing agents, however, has conveniently surmounted this obstacle. Of course the stereochemical requisite amply mentioned elsewhere still applies: reduction must lead to a configuration allowing backside attack in the subsequent cyclization. Space will be devoted in the following discussion only to: (*a*) lithium aluminium hydride (lithium tetrahydroaluminate); (*b*) sodium borohydride (sodium tetrahydroborate); (*c*) the moderately bulky Grignard reagent *iso*butylmagnesium chloride; (*d*) aluminum *iso*propoxide.

The use of lithium aluminum hydride was examined initially by Trevoy and Brown[1764] in connexion with this problem, but because an excess of reagent was used the final product was one that had undergone halogen hydrogenolysis. Thus, phenacyl bromide, *p*-bromophenacyl bromide, and *p*-chlorophenacyl bromide yielded respectively α-phenyl-, α-(*p*-bromophenyl)-, and α-(*p*-chlorophenyl)ethanol. Repetition of this work by Lutz and co-workers,[1055] this time with only slightly more than stoichiometric amounts of reagent, led to the desired bromohydrins in excellent yield (Eq. 194). Bodot and coworkers[186] have reported that lithium aluminum hydride reduction of phenacyl chloride is stereospecific, attributing this effect to the steric

demands of the reagent in the various possible ground state conformations of the substrate.

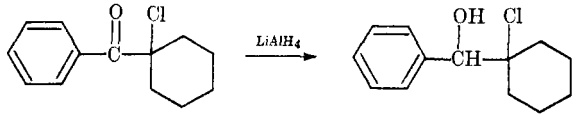
Felkin[487] showed that a lower but still satisfactory yield was



(194)

obtainable when the α-halogen was on a branched carbon atom, as in 1-benzoyl-1-chlorocyclohexane for example (Eq. 195).

The presence of a second phenyl ring, as in α-halodesoxybenzoins,[527] did not prevent isolation of the corresponding halohydrins



(195)

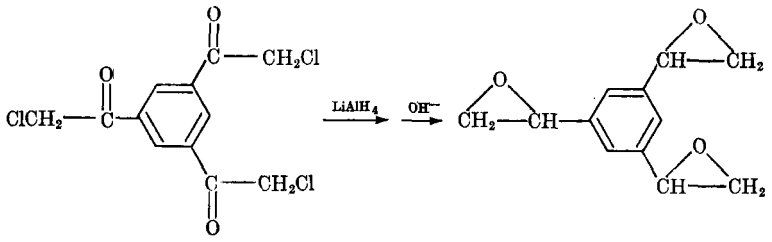
(Eq. 196). Felkin's contention[527] that the product is composed of equal quantities of *erythro*- and *threo*-isomers should be accepted with caution, however, since Lutz and co-workers[1055] reported in the same year the isolation of the *erythro*-product only.



(196)

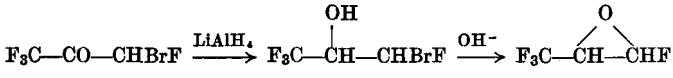
A number of interesting aromatic epoxides (Eq. 197 for example) have been synthesized in this manner by Hopff and co-workers,[804–807] in a program aimed at the preparation of possible cytotoxic agents.

Satisfactory results have likewise been obtained with aliphatic ketones. Thus, Schlenk and Lamp[1533] prepared 1,3-dichloro-2-propanol by lithium aluminum hydride reduction of 1,3-dichloroacetone. McBee

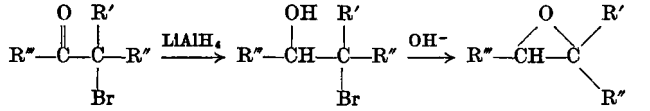


(197)

and co-workers[1066] reduced 1-bromo-1,3,3,3-tetrafluoroacetone to the corresponding bromohydrin, which could then be cyclized to 1,2-epoxy-1,3,3,3-tetrafluoropropane (Eq. 198). Rausch and co-workers[1436] used a similar approach to synthesize other fluorine-containing epoxides (Eq. 199).



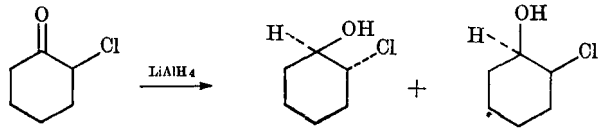
(198)



(199)

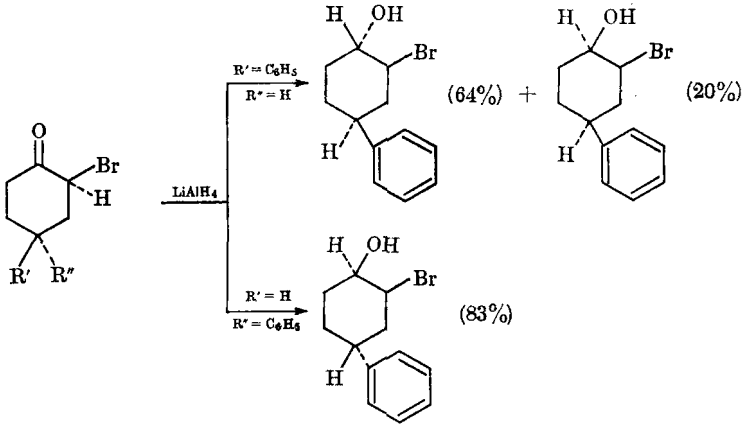
$R'' = C_3F_7$; $R' = H$; $R'' = CH_3$, C_2H_5
$R'' = C_3F_7$; $R' = R'' = CH_3$
$R'' = CF_3$; $R' = H$; $R'' = CH_3$, C_2H_5
$R'' = CF_3$; $R' = R'' = CH_3$

In the alicyclic series, Felkin[527] reduced 2-chlorocyclohexanone to a mixture of *cis*- and *trans*-2-chlorocyclohexanol (Eq. 200) and very recently Curtin and Harder[396] reported interesting observations with isomeric 2-bromo-4-phenylcyclohexanones. Treatment of *cis*-2-bromo-



(200)

4-phenylcyclohexanone with lithium aluminum hydride, for example, led to a mixture of two bromohydrins, the isomer with *trans*-oriented hydroxyl and bromide groups predominating as shown in Eq. (201).

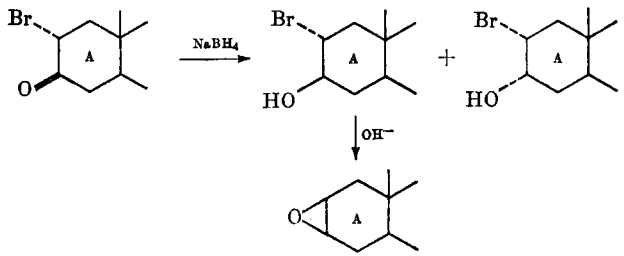


(201)

Reduction of *trans*-2-bromo-4-phenylcyclohexanone, on the other hand, yielded only the bromohydrin with *cis*-oriented hydroxyl and bromide. This puzzling stereospecificity still awaits explanation.

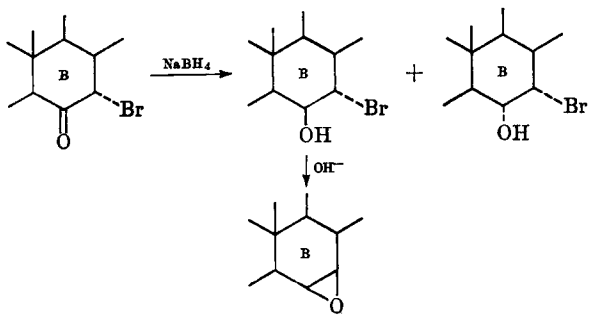
Other α-halocarbonyl compounds that have been reduced successfully with lithium aluminum hydride include α-chlorobutyric acid,[705] ethyl α-chloroacetate,[1620] and diethyl dichloromalonate.[142]

Although its lower reducing power relative to lithium aluminum hydride should render it more desirable for this purpose,[623] sodium borohydride has seen only limited use with simple α-halocarbonyl compounds,[296, 1062] the most notable examples of its application being in the steroid field.[352, 353, 357, 514, 535, 539, 583, 870, 882, 1543, 1823]



(202)

Fieser and co-workers[535, 539] and Corey[352] reduced 2α-bromocholestanone with sodium borohydride to a mixture of *cis*- and *trans*-bromohydrins, and the *trans*-isomer was isolated and cyclized to 2β,3β-epoxycholestane (Eq. 202).

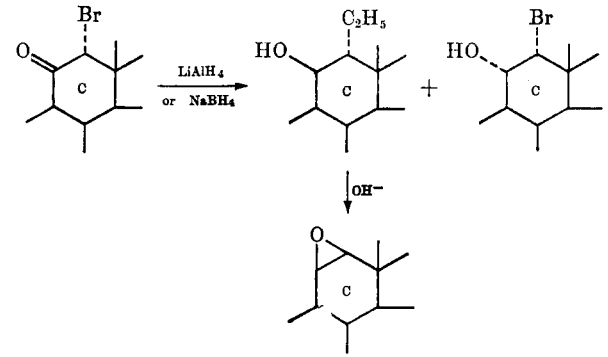


(203)

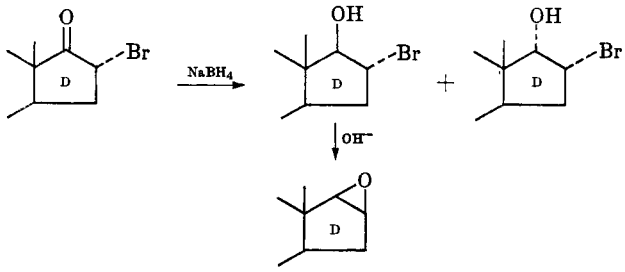
Similarly, James and Shoppee[870] and also Corey[352] reduced a 7α-bromo-6-oxo steroid to a mixture of *cis*- and *trans*-bromohydrins, from which the *trans*-isomer could be separated. Alkaline treatment of the latter gave the corresponding 6β,7β-epoxy steroid (Eq. 203).

Jones and Wluka[882] likewise converted a 12α-bromo-11-oxo steroid

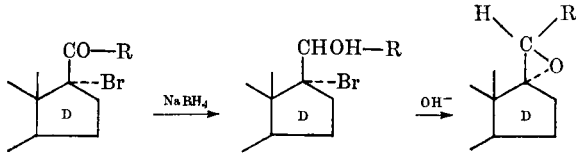
into the corresponding 11β,12β-epoxide (Eq. 204), Fajkos[514] obtained a 16β,17β-epoxide from a 16α-bromo-17-oxo steroid (Eq. 205), and Wendler and co-workers[1823] prepared a 17α,20β-epoxide from a 17α-bromo-20-oxo steroid (Eq. 206).



(204)



(205)

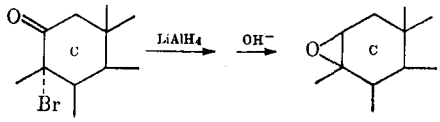


(206)

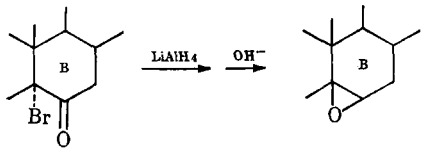
R = CH_3, $CH_3CO_2CH_2$, *etc.*

Henbest and co-workers[736, 742] used controlled amounts of lithium aluminum hydride with success in the synthesis of steroid epoxides. Thus, 5β,6β-epoxides (Eq. 208), 9β,11β-epoxides (Eq. 207), and 11β,12β-epoxides (Eq. 208) were obtainable by reduction of 5α-bromo-6-oxo, 9α-bromo-11-oxo, and 12α-bromo-11-oxo steroid precursors respectively.

Lithium borohydride has also received some support as a reagent in this connexion, but offers little advantage over sodium borohydride.[186, 311, 1698, 1699]



(207)



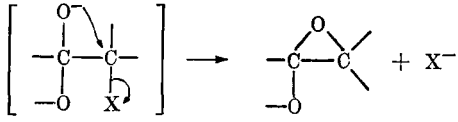
(208)

Although Bartlett[81] demonstrated as early as 1935 that treatment of 2-chlorocyclohexanone with cyclohexylmagnesium chloride, *iso*-propylmagnesium chloride, and *tert*-butylmagnesium chloride led predominantly to *cis*-2-chlorocyclohexanol, which is configurationally unsuited for epoxide formation, Curtin and Harder[396] were recently inspired to examine a slightly less bulky Grignard reagent, namely *iso*butylmagnesium bromide. Reduction of *cis*-2-bromo-4-phenylcyclohexanone with this reagent yielded a mixture in which the bromohydrin with *trans*-oriented hydroxyl and bromine substituents predominated. Similarly, *trans*-2-bromo-4-phenylcyclohexanone yielded only the bromohydrin with *cis*-oriented hydroxyl and bromine substituents. Their results parallel those observed with lithium aluminum hydride and cited above, although small differences appear in yields and isomer ratios. Whether they are to be ascribed to the peculiar nature of the substrate or to that of the reagent remains to be clarified, however.

The last reducing agent that will be mentioned in the present section is aluminum *iso*propoxide, for which only limited application is recorded in the literature of epoxide synthesis.[127, 128, 186, 1062] It is doubtful, however, whether this reagent offers any advantage over those considered above.

E. Addition of Alkoxide and Cyanide Ions to α-Halocarbonyl Compounds—Epoxyethers and Glycidonitriles

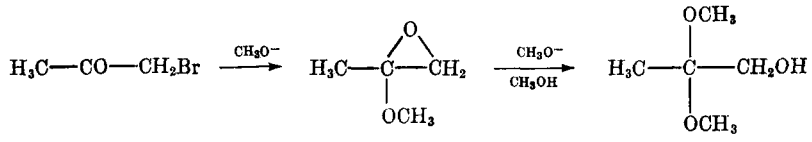
Internal nucleophilic displacement of a halogen with attendant epoxide ring closure has been utilized in the synthesis of epoxy ethers, according to the general transformation depicted in Eq. (209).

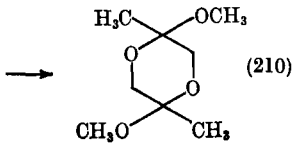


(209)

The requisite halohydrin anion intermediate is normally secured by the treatment of an appropriate α-haloketone or α-haloaldehyde with alkoxide ion under suitable conditions.

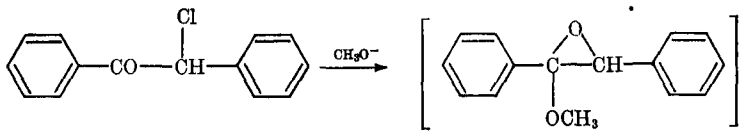
Simple epoxy ethers were postulated as early as 1921 by Bergmann and Miekeley,[135] who believed that oxidation of ethoxyethylene (ethyl vinyl ether) with perbenzoic acid yielded ethoxyethylene oxide. In a



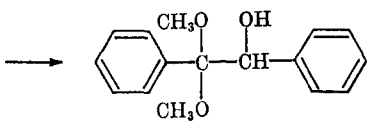


(210)

subsequent re-examination of their own results, however, these authors came to prefer a dimeric structure.[136] They did maintain, nevertheless, that formation of the same type of dimer on treatment of α-bromoacetone with base involved a labile epoxy ether intermediate, which underwent cleavage to a monomeric hydroxy ketal as shown in Eq. (210). The latter could actually be isolated under mild conditions.



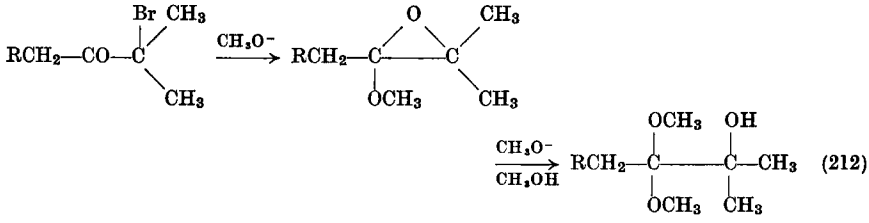
(211)



Ward[1803] found that treatment of phenyl α-chlorobenzyl ketone (α-chlorodesoxybenzoin, or 'desyl' chloride) with base yielded the corresponding hydroxyketal (Eq. 211), and proposed the intermediacy of an epoxy ether in this reaction.

Aston and Greenburg[51] obtained hydroxyketals on treatment of 3-bromo-3-methyl-2-butanone and 2-bromo-2-methyl-3-pentanone with

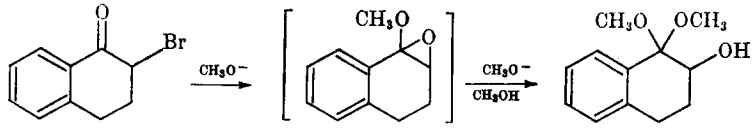
cold methanolic potassium methoxide (Eq. 212). These products too were said to arise from the corresponding unstable epoxy ethers, but higher homologs could not be prepared.



(212)

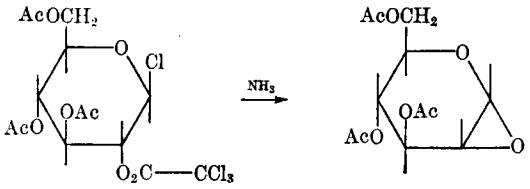
R = H, CH_3

Stevens and co-workers[1628] likewise obtained a hydroxyketal from 2-bromo-1-tetralone on treatment with base, again presumably by way of a labile epoxy ether (Eq. 213).



(213)

The well-known sugar derivative 'Brigl's anhydride', or 1,2-anhydro-3,4,6-tri-*O*-acetyl-α-D-glucopyranose, is an epoxy ether prepared by the action of ammonia on 3,4,6-tri-*O*-acetyl-2-*O*-trichloroacetyl-α-D-glucopyranosyl chloride in benzene solution.[245, 1245]



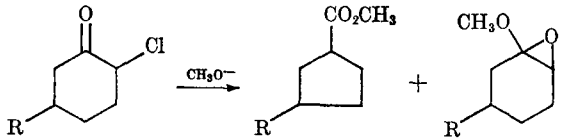
(214)

Ac = CH_3CO

The possibility that epoxy ethers are intermediates in Favorskii-type rearrangements has been raised by a number of authors,[51, 1194] and considerable disagreement existed for a time in the literature.[1635]

For example, Mousseron and co-workers[1194] studied the effect of cold methanolic sodium methoxide on 2-chlorocyclohexanone and 2-chloro-5-methylcyclohexanone (Eq. 215), and reported isolating the Favorskii products, along with equal quantities of what were believed to be epoxy ethers.

Subsequent repetition of this work by Stevens and Tazuma[1642] seemed to indicate the epoxy ether assignment of Mousseron and co-workers[1194] to have been in error, since the products actually obtained from 2-chlorocyclohexanone were carbomethoxycyclopentane and 2-hydroxycyclohexanone dimethyl ketal. To the extent that the latter

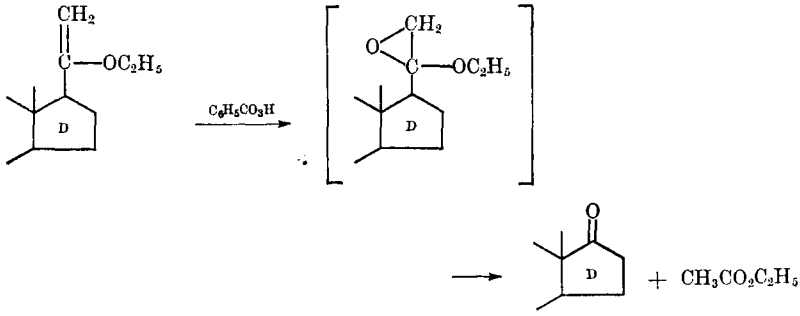


(215)

R = H, CH_3

could be formed from a labile epoxy ether, therefore, the results of Mousseron and co-workers remain acceptable. But Stevens and co-workers[1628-1646] have shown compellingly that Favorskii products are not formed on subjecting epoxy ethers even to stringent Favorskii conditions. Moreover, the work of Loftfield[1041, 1042] on the mechanism of the Favorskii rearrangement seems to have definitively disproved the postulate that epoxy ethers are involved in this reaction.

Another reaction in which epoxy ethers have been suggested to be intermediates is the oxidation of enol ethers with perbenzoic acid. This topic need only be mentioned briefly here, since olefin oxidation with perbenzoic acid has been taken up in greater detail in section **III.1.*A***.

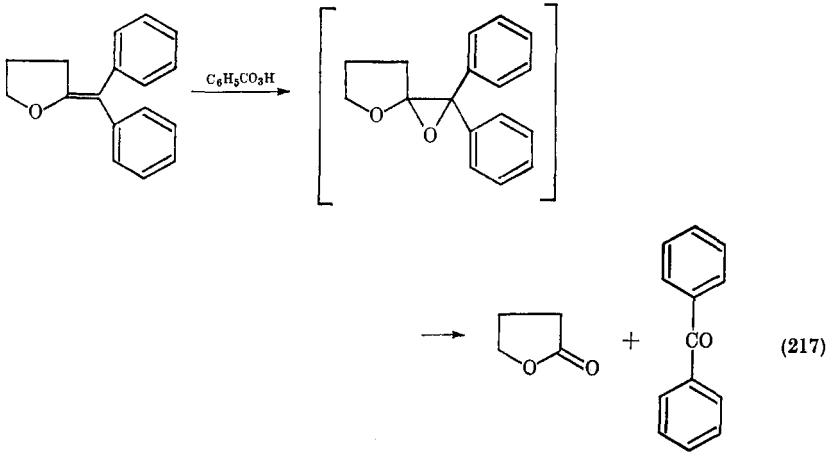


(216)

Although Hurd and Edwards[843] have reported the isolation of an epoxy ether from perbenzoic acid oxidation of 2,3-dihydropyran, no other instance of this sort is known. In fact it is known[119] that treatment of 20-oxo steroid enol ethers with perbenzoic acid gives an unisolable epoxy ether, which readily undergoes cleavage to give 17-oxo steroids as shown in Eq. (216).

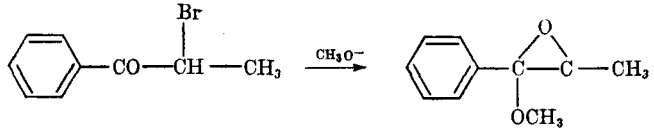
Stevens and Tazuma[1642] have also reported that epoxy ethers are unstable in the presence of perbenzoic acid.

Huffman and Tarbell[840] recently recorded unsuccessful attempts to synthesize a novel spiroepoxy ether by the oxidation of benzhydrylidenetetrahydrofuran with perbenzoic and perphthalic acids. It is conceivable that a labile epoxy ether was formed, but that it underwent rearrangement. The authors observed that the crude product contained benzophenone and probably a γ-lactone which could be γ-butyrolactone (Eq. 217).



(217)

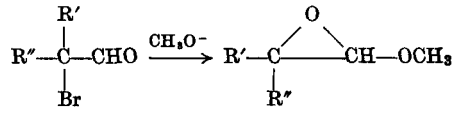
Temnikova and Kropacheva[1705] found that phenyl-substituted epoxy ethers are stable enough to permit their isolation under moderate conditions, a discovery made independently by Stevens and coworkers.[1639] Thus treatment of α-chloro- or α-bromopropiophenone with base in the cold gave a good yield of the corresponding epoxy ether (Eq. 218).



(218)

Temnikova and co-workers[1709] have carried out this reaction also with α-bromo*iso*butyrophenone, α-bromobutyrophenone, α-bromo-α-methylbutyrophenone, and α-bromo-α-*n*-butylpropiophenone.

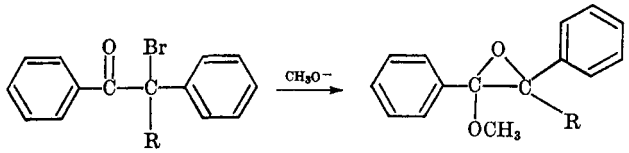
Stevens and co-workers[1636, 1637, 1647] have examined the scope of the reaction forming epoxy ether more exhaustively. Thus it was found that certain α-haloaldehydes yield epoxy ethers even though they lack stabilizing phenyl substituents (Eq. 219).



(219)

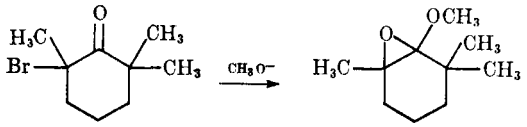
$R' = H$; $R'' = C_2H_5$, n-C_5H_{11}
$R' = R'' = CH_3$

Epoxy ethers bearing more than one phenyl substituent were also prepared[1631, 1644] (Eq. 220), as well as one severely encumbered with alkyl substituents[1646] (Eq. 221).



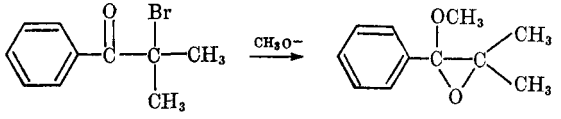
(220)

R = H, C_6H_5



(221)

The effect of varying the alkoxide ion was likewise investigated, several new epoxy ethers being prepared in this manner[1634, 1641] (Eq. 222).



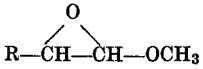
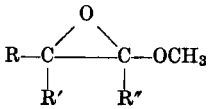
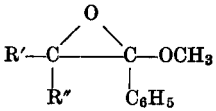
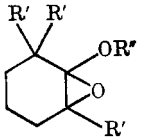
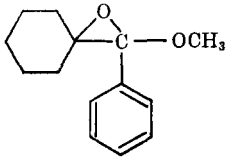
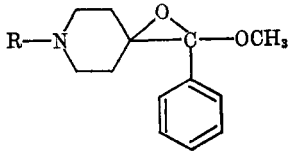
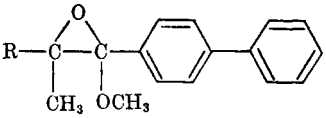
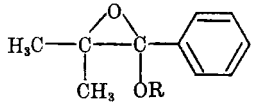
(222)

R = *iso*C_3H_7, n-C_4H_9, *sec*-C_4H_9, $CH_2{=}CHCH_2$, cycloC_6H_{11}, $CH_3OCH_2CH_2$, $C_6H_5CH_2$, $(CH_3)_2NCH_2CH_2$

A representative compilation of epoxy ethers found in the literature of the past 10 years is shown in Table 8. Original references cited therein may be consulted for further details.

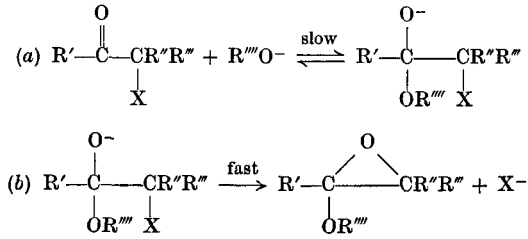
No precise kinetic studies of the reaction yielding epoxy ethers from α-halocarbonyl compounds has been published to date. Presumably

TABLE 8. Epoxyethers

Compound		Reference
	R = C_2H_5, n-C_4H_9	1636
	R′ = H; R″ = cycloC_6H_{11}	1194[a]
	R′ = CH_3; R″ = H	1637, 1647
	R′ = H; R″ = CH_3, C_2H_5, C_6H_5	1639, 1644, 1705, 1709
	R′ = CH_3; R″ = C_2H_5, n-C_4H_9	1709
	R′ = R″ = C_2H_5, C_6H_5	1630, 1631
	R′ = H; R″ = CH_3, cycloC_6H_{11}	1194[a]
	R′ = R″ = CH_3	1646
		1635
	R = CH_3, $C_6H_5CH_2$	1058
	R = CH_3, C_2H_5	1633
	R = *iso*C_3H_7, n-C_4H_9, *sec*-C_4H_9, $CH_2CH=CH_2$, cycloC_5H_{11}, $C_6H_5CH_2$, $(CH_3)_2NCH_2CH_2$, $CH_3OCH_2CH_2$	1634, 1641

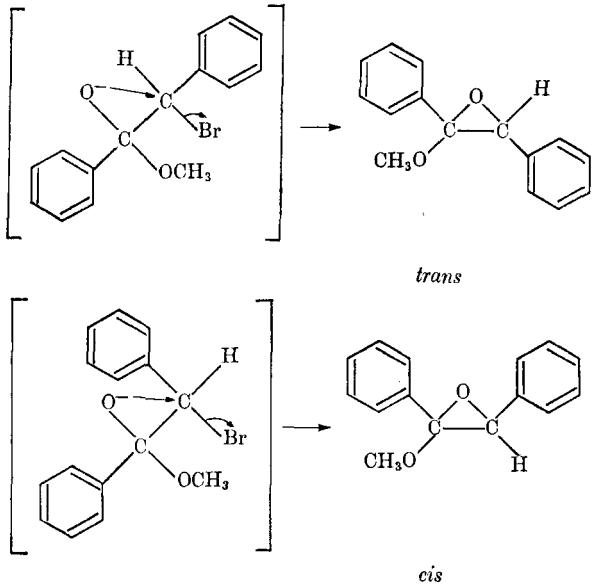
[a] Structures open to doubt.

the course of events may be represented as shown in Eq. (223). If this mechanism is correct, second-order overall kinetics should be observed.



(223)

The stereochemistry of epoxy ethers should follow readily from steric considerations if the intermediate possesses an appreciable lifetime. Stevens and Coffield[1630] examined the product formed from 'desyl' chloride in detail, and concluded that only the *trans*-epoxy



trans

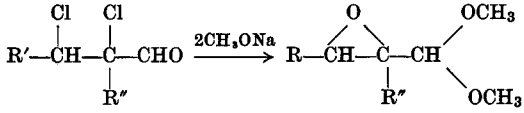
(224)

cis

ether was present. The apparent stereospecificity of this reaction is explicable on the basis of most probable intermediate anion conformations. Of the two most likely structures for this anion (Eq. 224), the first is less sterically hindered, and hence only the *trans*-oxide is produced.

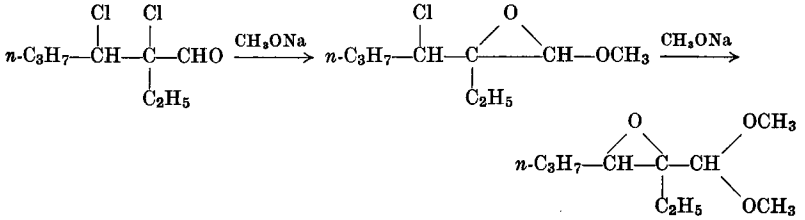
Searles and co-workers[1555] have described a novel reaction involving an epoxy ether as the isolable intermediate. Specifically, they clarified a long-standing misconception[977, 1028] that treatment of

2-alkyl-2,3-dichloroaldehydes with 2 molar equivalents of sodium methoxide gives 3-alkyl-2,3-dimethyloxetanes. Repetition and extension of previous investigations led Searles and co-workers[1555] to conclude that products obtained from such reactions are in fact glycidaldehyde and dimethylacetals (Eq. 225).



$R' = C_2H_5$, $R'' = CH_3$
$R' = n\text{-}C_3H_7$, $R'' = C_2H_5$ (225)

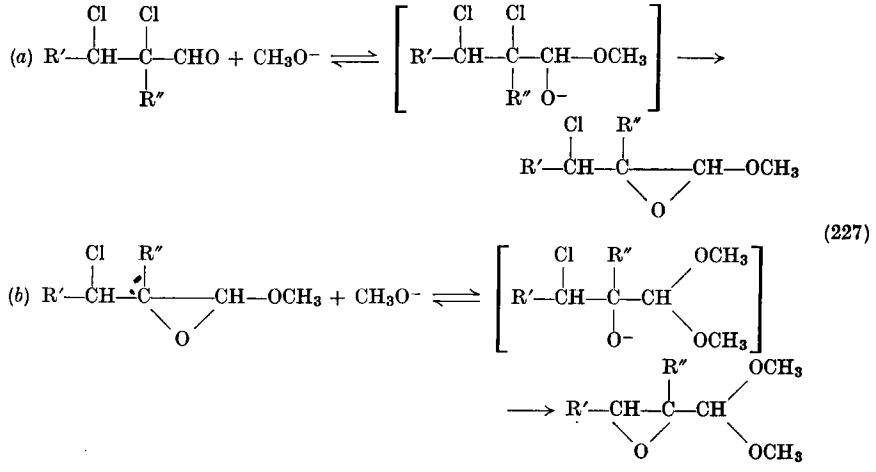
Important evidence concerning the course of this novel transformation was secured by Searles and co-workers[1555] on limiting the amount of sodium methoxide to 1 molar equivalent. There was isolated in this manner from 2,3-dichloro-2-ethylhexanal the epoxy ether shown



(226)

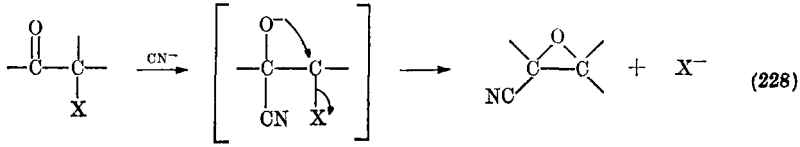
in Eq. (226). Further treatment of the latter with sodium methoxide gave the corresponding glycidaldehyde derivative in good yield.

The authors postulated the mechanism shown in Eq. (227) on the basis of the above and other information.



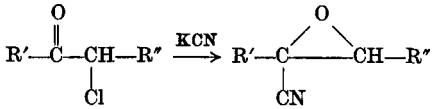
(227)

Related to the epoxy ether preparations is another reaction, involving the same precursors and an essentially identical mechanism. When certain α-haloketones are treated with potassium cyanide in aqueous alcoholic media, there are obtained, among other products, glycidonitriles. In this instance the carbonyl function suffers attack by a CN^- ion, rather than a methoxide, and the intermediate anion collapses quickly to a glycidonitrile by ejecting a halide ion as shown in Eq. (228).



(228)

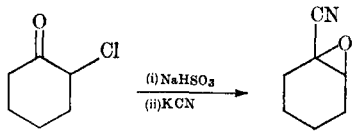
Examples of this reaction are the conversions of α-chloroacetone[895] and 2-chloro-3-butanone[896] into 2-cyanopropylene oxide and 2-cyano-2,3-epoxybutane respectively; of α-chloro-α-phenylacetone[1454] and α-chlorodesoxybenzoin ('desyl' chloride)[957, 1454] into the corresponding phenyl-substituted derivatives; and of ethyl 2-chloro-3-oxobutyrate[523] and 4-chloro-3-oxobutyrate[953] to the corresponding ester derivatives of glycidonitrile (Eq. 229).



(229)

$R' = CH_3$; $R'' = H$, CH_3, C_6H_5, $C_2H_5O_2C$
$R' = R'' = C_6H_5$
$R' = C_2H_5O_2CCH_2$; $R'' = H$

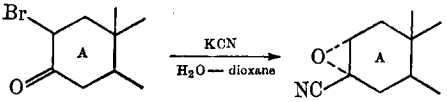
Mousseron and co-workers,[1197] as well as others,[1865] have carried out the synthesis of 1-cyano-1,2-epoxycyclohexane by addition of sodium bisulfite (sodium hydrogen sulfite) to 2-chlorocyclohexanone, and treatment of the resulting adduct with potassium cyanide (Eq. 230).



(230)

Application of this technique to natural products may be illustrated by the conversion of 2β-bromo-3-oxo steroids into the corre-

sponding glycidonitrile derivatives described recently by Winternitz and co-workers[1865] (Eq. 231).

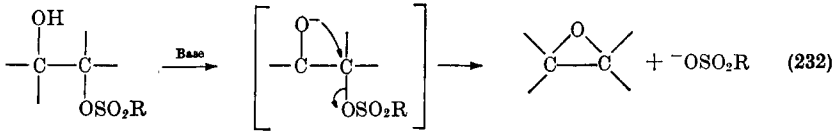


(231)

3. Cyclizations Involving Other Leaving Groups

A. Alkaline Hydrolysis of 1,2-*Diol Monoalkyl- and Monoarylsulfonates*

Although the intramolecular alkoxide displacement of a halide ion discussed above is by far the most common example of that general type of reaction, another cyclization of considerable synthetic importance involves monoalkyl- or monoarylsulfonate esters of 1,2-diols, shown in the following general case in Eq. (232).

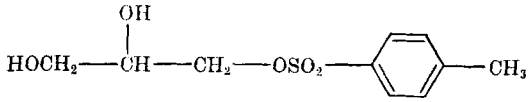


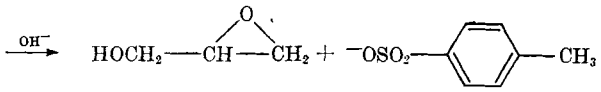
(232)

The most frequently encountered representative of the RSO_2O^- class of leaving groups is probably the toluene-*p*-sulfonate anion (commonly abbreviated to 'tosylate'), but others are occasionally employed as well. The latter include the methylsulfonate ('mesylate') and the *p*-bromobenzenesulfonate ('brosylate') anions.

In general, arylsulfonate anions are considered better leaving groups than halide ions because of their greater affinity for bonding electrons—*i.e.* the higher polarizability of the C—OSO_2Ar than of the C—X bond. A further advantage of arylsulfonate derivatives is their relatively high molecular weight, which occasionally permits their isolation and purification as crystalline solids. Also notable, finally, are the mild conditions sufficient to bring about esterification of alcohols with toluene-*p*-sulfonyl chloride and related reagents. The last is a feature that commends itself especially to chemists working with sensitive natural products like nucleosides.[28, 62, 122, 1528]

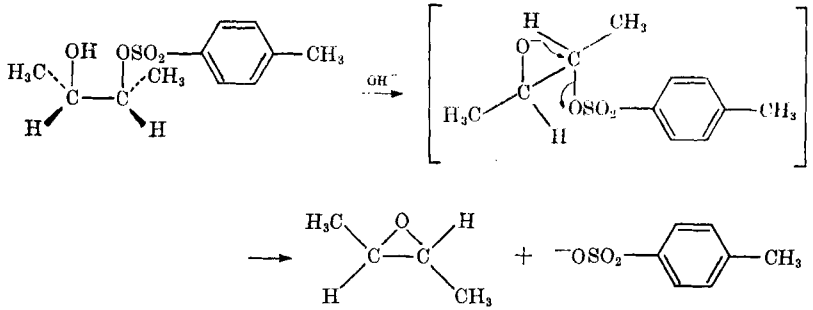
Among the simplest epoxides prepared by way of a 1,2-diol monotosylate are glycidol, synthesized by Sowden and Fischer[1613]





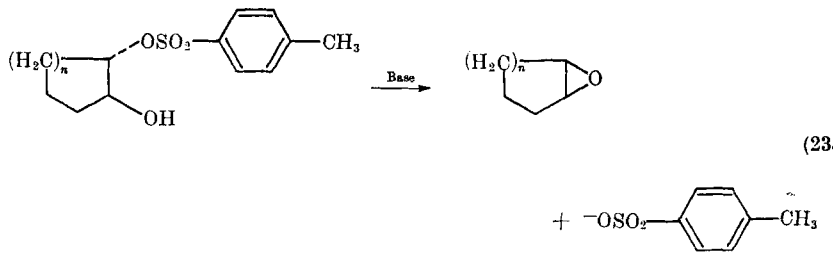
(233)

from glycerol monotosylate (Eq. 233) and *trans*-2,3-epoxybutane, obtained by Eliel and Delmonte[491] from *meso*-2,3-butanediol monotosylate (Eq. 234).



(234)

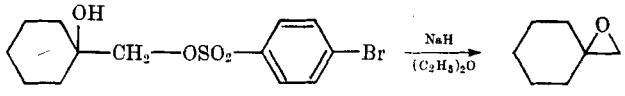
Simple alicyclic epoxides accessible by this route include cyclopentene, cyclohexene, and cycloheptene oxides, prepared by Owen and co-workers[315, 1280, 1282] by treating the corresponding *trans*-1,2-cycloalkane diol monotosylates with various bases (Eq. 235).



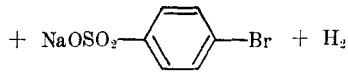
(235)

Likewise, treatment of 1-hydroxymethylcyclohexanol monobrosylate with sodium hydride in a non-polar medium[1487] gives a moderate yield of the corresponding spiroepoxide (Eq. 236). Similar reactions have been conducted in the field of steroid chemistry[1827, 1828] to prepare spiroepoxides.

Optically active styrene oxide has been synthesized[491] from optically active α-hydroxyphenylacetic acid by lithium aluminum

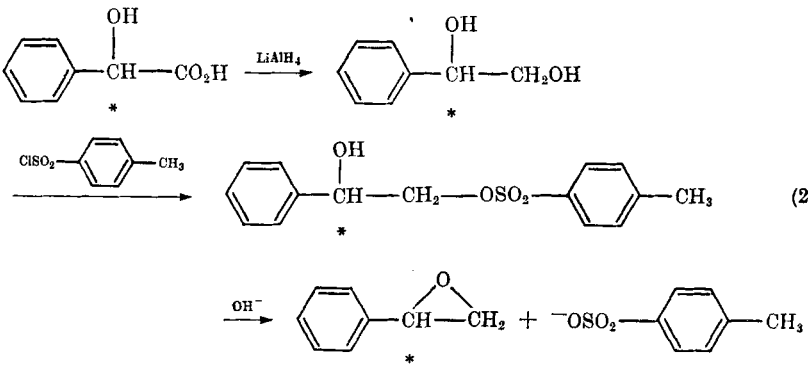


(236)



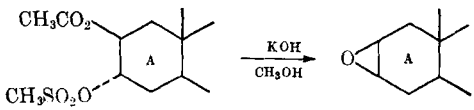
hydride reduction, selective tosylation, and treatment with base (Eq. 237).

The preparation of 1,1-diphenylethylene oxide by intramolecular tosylate displacement has likewise been reported.[491]

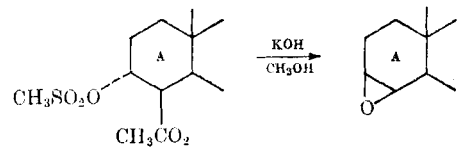


(237)

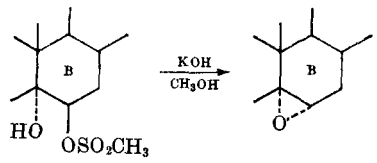
Illustrative of the use of methylsulfonate esters for epoxide synthesis are several preparations drawn from the steroid literature[602–604, 1302, 1823] and depicted in Eqs. (238)–(241). Although other



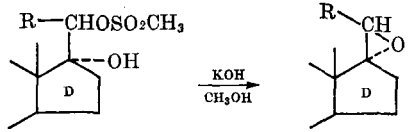
(238)



(239)



(240)

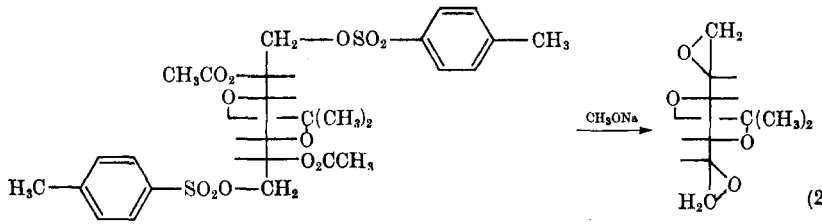


(241)

epoxy steroids should in principle be equally accessible by this route, alternative techniques are more in favor at the present time.

Examination of the literature reveals that the value of the reaction described in the present section lies chiefly in the domain of sugar chemistry. The largest number of illustrations will therefore be understandably derived from that field. The older literature has been reviewed elsewhere,[1245, 1612] and reference may be made to these reviews for discussions beyond the scope of the present article.

Treatment of 2,5-di-*O*-acetyl-3,4-*iso*propylidene-1,6-di-*O*-tosylmannitol with sodium methoxide causes deacetylation, followed by cyclization to 1,2;5,6-dianhydro-3,4-*O*-*iso*propylidenemannitol,[1840] as shown in Eq. (242). Similar reactions were carried out for the preparation of 1,2;3,6-dianhydro-4,5-*O*-*iso*propylidenemannitol[558, 559] and 5,6-anhydro-1,3;2,4-di-*O*-ethylidenesorbitol.[166, 1841] The two isomeric bis-

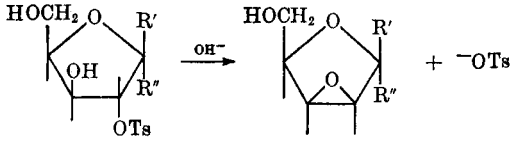


(242)

epoxides 1,2;5,6-dianhydro-3,4-*O*-*iso*propylidene-D-sorbitol and 1,2;5,6-dianhydro-3,4-di-*O*-*iso*propylidene-D-iditol have likewise been obtained from the corresponding tosylate esters.[1783]

Certain furanose sugars have been transformed into epoxy derivatives by a similar process. Thus, 1,2-*O*-*iso*propylidene-6-*O*-

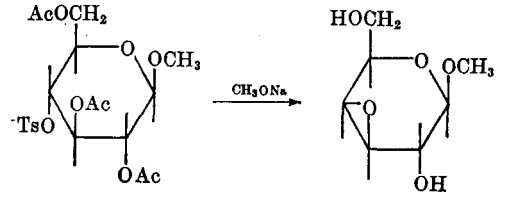
tosyl-α-D-glucofuranose can be cyclized to 5,6-anhydro-1,2-*O*-*iso*-propylidene-α-D-glucofuranose.[407, 1269, 1834] Methyl 2-*O*-tosyl-α-D-xylofuranoside[1324] and methyl 2-*O*-tosyl-β-D-xylofuranoside[29, 64] give methyl 2,3-anhydro-α-D-lyxoside and -β-D-lyxoside respectively, as shown in Eq. (243). Other 2,3-anhydropentafuranoside derivatives have been synthesized as well.[427, 1527]



(243)

Ts = *p*-$CH_3C_6H_4SO_2$
R′ = H, R″ = CH_3O
R′ = CH_3O, R″ = H

Conversion of pyranose sugars into epoxide derivatives can be illustrated amply. Alkaline treatment of 2,3,6-tri-*O*-acetyl-4-*O*-tosyl-β-D-glucoside (Eq. 244) gives the corresponding deacetylated 3,4-anhydro compound,[1207, 1208] and methyl 4-*O*-tosyl-β-D-glucoside and its 2,3-di-*O*-benzoyl derivative give methyl 3,4-anhydro-β-D-glucoside.[258] Although it had been reported previously[723] that methyl



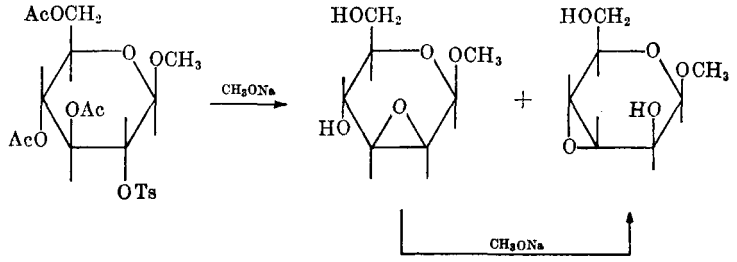
(244)

Ac = CH_3CO; Ts = *p*-$CH_3C_6H_4SO_2$

3,4,6-tri-*O*-acetyl-2-*O*-tosyl-β-D-glucoside simply gives the expected 2,3-anhydro derivative, later work[936] has shown simultaneous formation of a certain amount of the 3,4-epoxy sugar as well (Eq. 245). It is probable that the latter arises by secondary intramolecular opening of the original 2,3-epoxide.[1245] Other instances of 'epoxide migration' will be presented later in this discussion.

When the methoxyl substituent at $C_{(1)}$ is of the inverted configuration, 'epoxide migration' appears to take place in the opposite sense. Thus, although it had been reported previously[988, 1274] that the

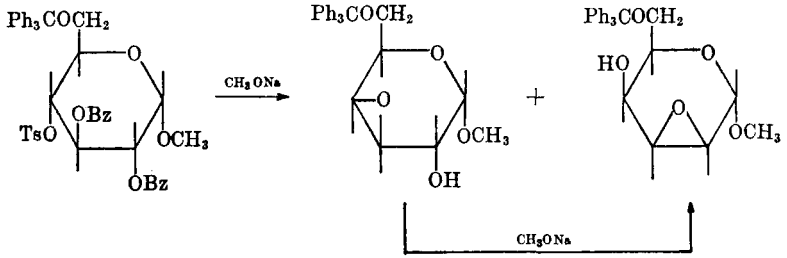
sole product obtainable from methyl 2,3-di-*O*-benzoyl-4-*O*-tosyl-6-*O*-trityl-α-D-glucoside was the corresponding 3,4-anhydro sugar,



(245)

Ac = CH_3CO; Ts = *p*-$CH_3C_6H_4SO_2$

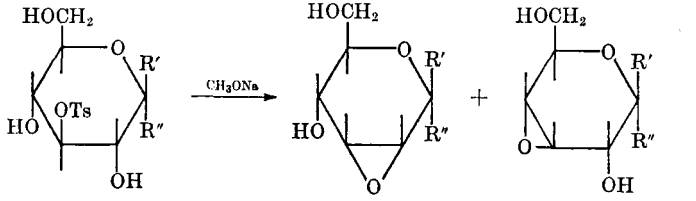
Buchanan[257] subsequently demonstrated a small quantity of 2,3-anhydro isomer to be formed as well (Eq. 246).



(246)

Ph = C_6H_5; Bz = C_6H_5CO; Ts = *p*-$CH_3C_6H_4SO_2$

Where the two hydroxyl groups are so situated that epoxide formation is possible in two directions, both products can sometimes be isolated. For example (Eq. 247), methyl 3-*O*-tosyl-β-D-glucoside yields

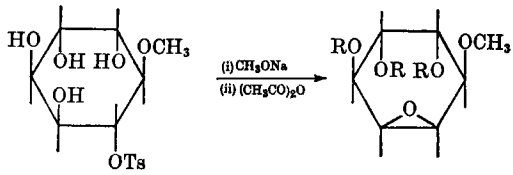


(247)

R′ = CH_3O, R″ = H
R′ = H, R″ = CH_3O
Ts = *p*-$CH_3C_6H_4SO_2$

a mixture of 2,3- and 3,4-anhydro-β-D-alloside,[1319] and methyl 3-*O*-tosyl-α-D-glucoside gives 2,3- and 3,4-anhydro-α-D-alloside.[257, 562, 725, 1271, 1320] In these instances the stereochemistry is unfavorable for 'epoxide migration'.

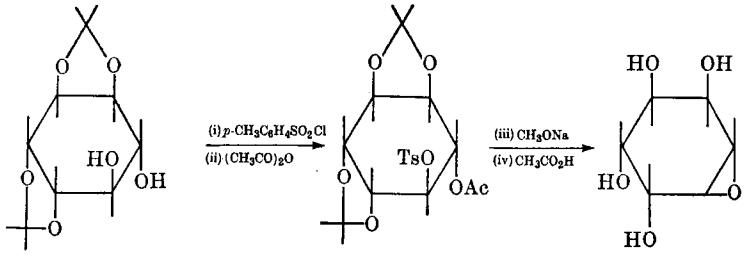
In the inositol series Angyal and co-workers[33, 34] have synthesized a number of epoxides by the same approach. For instance, 3-*O*-methyl-4-*O*-tosyl-(+)-inositol yielded 4,5,6-tri-*O*-acetyl-2,3-anhydro-1-*O*-methyl-*allo*-inositol on treatment with sodium methoxide and subsequent acetylation (Eq. 248).



(248)

R = CH_3CO; Ts = *p*-$CH_3C_6H_4SO_2$

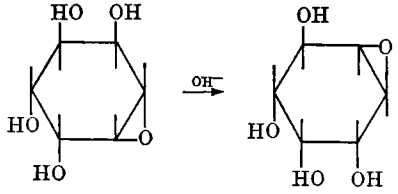
Synthesis of 1,2-anhydro-*allo*-inositol was accomplished from 3,4;5,6-di-*O*-*iso*propylidene-*allo*-inositol in four steps, as indicated in Eq. (249). Certain isomeric anhydroinositols were prepared analogously.[33]



(249)

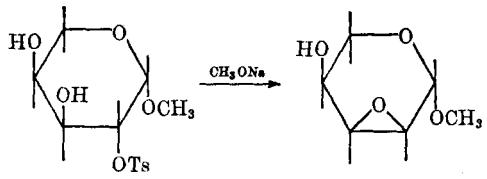
Ac = CH_3CO; Ts = *p*-$CH_3C_6H_4SO_2$

The phenomenon of 'epoxide migration' is directly demonstrable with 1,2-anhydro-*allo*-inositol,[34] which gives on treatment with dilute alkali at room temperature the isomeric substance 1,2-anhydro*neo*-inositol (Eq. 250).



(250)

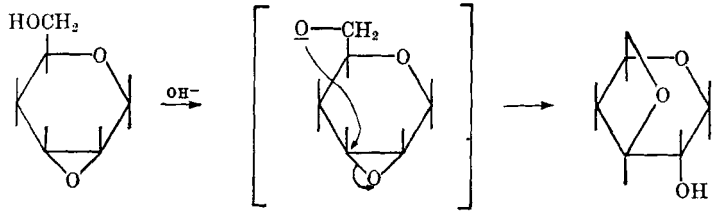
In the pentapyranose series Baker and Schaub[61] reported the preparation of methyl 2,3-anhydro-β-L-ribopyranoside from methyl 2-*O*-tosyl-β-L-arabopyranoside in a similar manner (Eq. 251).



(251)

Ts = p-$CH_3C_6H_4SO_2$

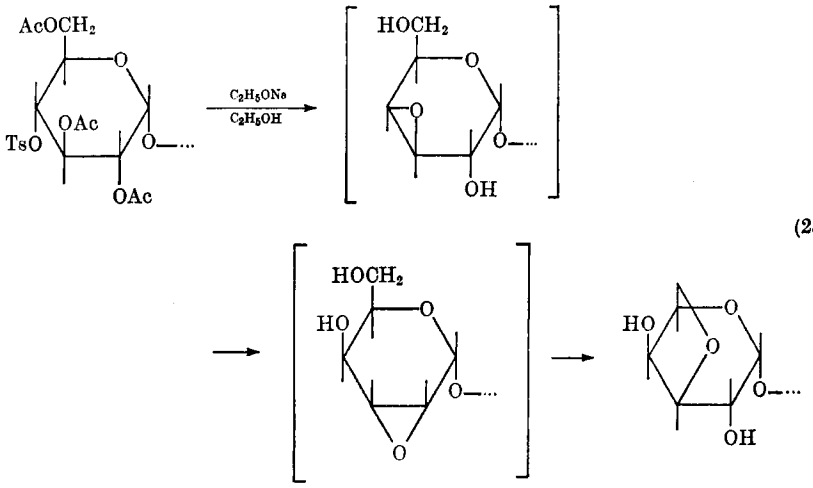
Where several cyclic ethers can be formed by intramolecular tosylate ion displacement, epoxide formation usually occurs in preference to formation of larger ether rings. This is particularly true when the alternatives are four- or six-membered. There are often formed, however, five-membered oxides by attack of the $C_{(6)}$ hydroxyl on a 2,3-anhydro function,[562, 1272, 1319] according to the general scheme depicted in Eq. (252). Prolonged exposure of 2,3-anhydro sugars containing free hydroxyl functions at $C_{(6)}$ to alkaline conditions is obviously undesirable for this reason.



(252)

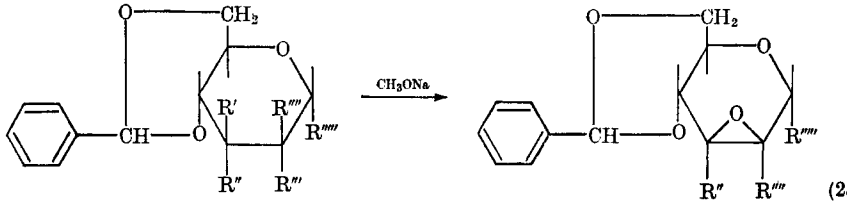
Occasionally a reaction becomes so unexpectedly complex that the desired epoxide is not obtained at all. In the rearrangement sequence shown in Eq. (253), observed by Lemieux and Barrette,[999] the indicated epoxide intermediates are not isolable, and may in fact be merely transient stages in a concerted transformation.

A number of benzylidene derivatives of simple sugars have been converted into epoxides in similar fashion (Eqs. 254 and 255). These reactions are of considerable interest because they involve structures that are conformationally related to *cis*- and *trans*-decalins.[1459] For example, methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucoside and methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-tosyl-α-D-glucoside



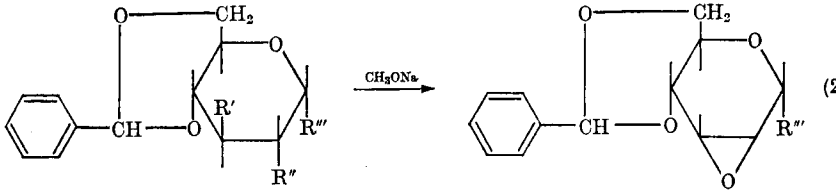
(253)

Ac = CH_3CO; Ts = p-$CH_3C_6H_4SO_2$



(254)

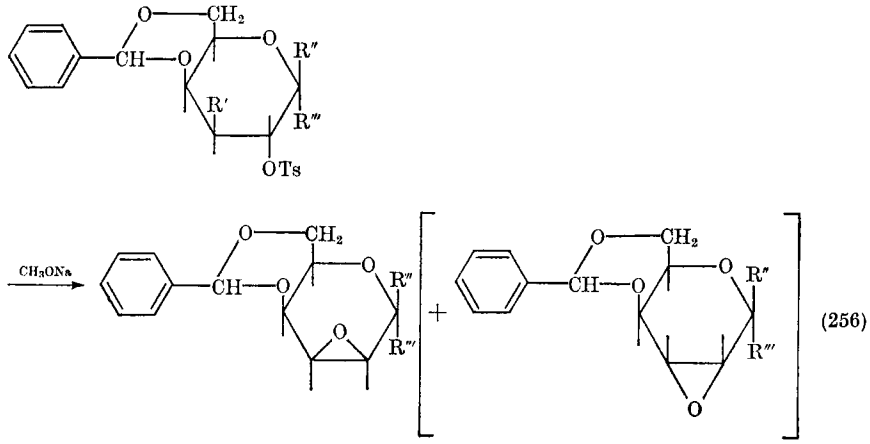
R′ = C_6H_5CO; R″ = R‴ = H; R⁗ = p-$CH_3C_6H_4SO_2O$; R⁗′ = CH_3O
R′ = OH; R″ = R‴ = R⁗ = H; R⁗′ = p-$CH_3C_6H_4SO_2O$
R′ = R⁗′ = p-$CH_3C_6H_4SO_2O$; R″ = R‴ = R⁗ = H



(255)

R′ = p-$CH_3C_6H_4SO_2O$; R″ = C_6H_5CO, p-$CH_3C_6H_4SO_2O$; R‴ = CH_3O
R′ = R‴ = p-$CH_3C_6H_4SO_2O$; R″ = H

yield respectively methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannoside and methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-alloside.[1393] Conversion of the related substance 1,5-anhydro-4,6-*O*-benzylidene-2-*O*-tosyl-D-glucitol into 1,5;2,3-anhydro-4,6-*O*-benzylidene-D-allitol has likewise been described.[257, 725] Epoxides can still be obtained on occasion even when both hydroxyl functions in the 1,2-diol system are sulfonylated. Thus methyl 4,6-*O*-benzylidene-2,3-di-*O*-tosyl-α-D-glucoside[1472] and the analogous α-D-altroside derivative[1474] give methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-alloside and -α-D-mannoside respectively. Similarly, 1,5-anhydro-4,6-*O*-benzylidene-2,3-di-*O*-tosyl-D-glucitol yields 1,5;2,3-dianhydro-4,6-*O*-benzylidene-D-allitol.[1244, 1915]



(256)

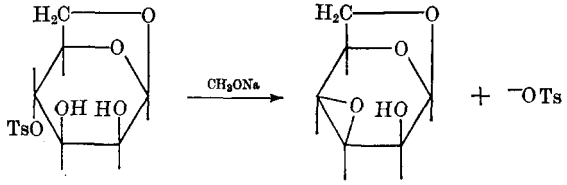
Ts = p-$CH_3C_6H_4SO_2$
R′ = OH, p-$CH_3C_6H_4SO_2O$; R″ = CH_3O; R‴ = H
R′ = OH; R″ = H; R‴ = CH_3O

(when R′ = p-$CH_3C_6H_4SO_2O$; R″ = H, R‴ = CH_3O)

In the galactose series (Eq. 256) methyl 4,6-*O*-benzylidene-2-*O*-tosyl-β-D-galactoside and -α-D-galactoside give methyl 2,3-anhydro-4,6-*O*-benzylidene-β-D-taloside and -α-D-taloside respectively,[1243, 1842] and methyl 4,6-*O*-benzylidene-2,3-di-*O*-tosyl-β-D-galactoside likewise yields the above β-D-taloside derivative.[1611] The ditosylate of the α-D-galactoside derivative, on the other hand, gives a mixture of α-D-taloside and α-D-guloside.[697] In this case the 2- and 3-*O*-tosyl groups undergo hydrolysis at comparable rates, whereas in the glucose series hydrolysis of the 3-*O*-tosyl ester was preferential.

Mention may be made, finally, of several bridged 1,6-anhydro sugars which have been transformed into epoxides by the tosylate

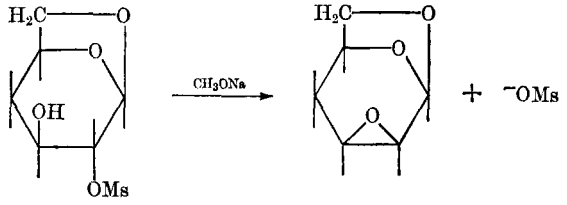
displacement technique. For example, 1,6-anhydro-4-*O*-tosyl-β-D-mannose,[709] 1,6-anhydro-2-*O*-mesyl-β-D-galactose,[873] and 1,6-anhydro-3-*O*-tosyl-β-D-altrose[1243] have been converted into the corresponding epoxides, as indicated in Eqs. (257)–(259). The last example illustrates



(257)

once again the phenomenon of 'epoxide migration' from the 2,3- to the 3,4-position, already discussed above.[33, 34, 1245]

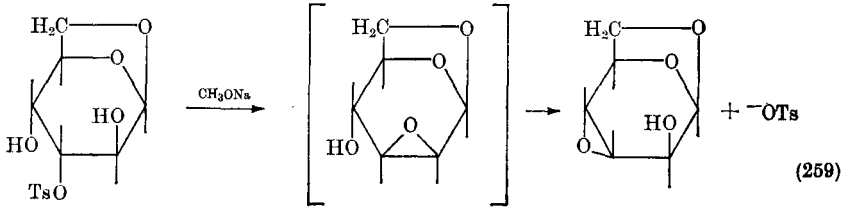
It has been reported by Newth[1243] that 1,6-anhydro-3,4-di-*O*-tosyl-β-D-altrose and 1,6-anhydro-2-*O*-tosyl-β-D-altrose are singularly



(258)

resistant to all attempts at epoxide ring formation. A conformational rationalization for this noteworthy effect has been proposed.[1243]

If a sugar sulfate containing a suitably disposed hydroxyl function is treated with alkali it is possible in principle to displace a SO_4^{2-} ion,

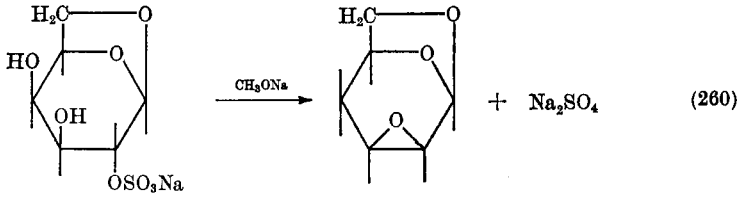


(259)

Ts = *p*-$CH_3C_6H_4SO_2$; Ms = CH_3SO_2

forming an anhydro derivative. Equation (260) illustrates such an intramolecular displacement.[466] A review article by Percival[1323] may be consulted for further discussion of the chemistry of sugar sulfates.

Reference may be made, finally, to previous discussion devoted to cyclodehydrohalogenation for a presentation of the stereochemical principles governing intramolecular tosylate anion displacement as a



(260)

method of epoxide synthesis. Attention is also directed in particular to an admirable review by Newth,[1245] dealing specifically with certain conformational subtleties not touched upon in the present article.

B. Addition of Diazoalkanes to Carbonyl Compounds

A technique that has proved to possess considerable usefulness in epoxide synthesis is addition of diazoalkanes, particularly of the parent substance diazomethane, to suitable carbonyl groups.

The ability of diazomethane to replace hydrogen atoms in acidic compounds like carboxylic acids, phenols, and enols has long been known. Although this aspect need not be dealt with extensively here, it should be stressed that with a polyfunctional substrate diazomethane can function at several reaction sites. Some discrimination is therefore necessary in selecting this reagent for epoxide synthesis.

That epoxides could be formed under certain conditions from carbonyl compounds was not fully realized for many years. Although it had been known for nearly half a century that diazoalkanes did react with certain carbonyl compounds, the nature of the products and the factors governing their formation only began to emerge with the extensive studies of Arndt, Meerwein, and others. Many references to the early literature of this subject may be found in two excellent review articles, by Eistert[485] and more recently by Gutsche.[693]

(1) Scope. Epoxides have been prepared from a wide variety of carbonyl compounds by diazomethane synthesis, in yields ranging from a few percent to nearly quantitative. No attempt will be made here to present a complete catalogue of reactions, inasmuch as this has been done elsewhere.[485, 693] A few additional examples have appeared since then, which are included in the present text. Reference

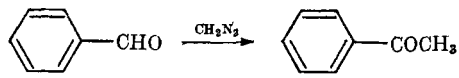
should be made to the articles of Eistert[485] and Gutsche,[693] for exhaustive compilations of the literature before 1951, as well as counsel in the use of diazoalkane reagents.

Simple aliphatic aldehydes react with diazomethane to give epoxides, but these are decidedly minor products, ketones usually predominating. For example (Eq. 261), acetaldehyde reportedly yields

$$CH_3{-}CHO \xrightarrow{CH_2N_2} \underset{(28\%)}{CH_3{-}CO{-}CH_3} + \underset{(28\%)}{CH_3{-}\overset{O}{\overset{/\backslash}{CH}}{-}CH_2} \qquad (261)$$

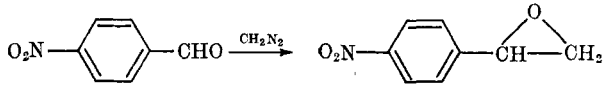
nearly equal quantities of acetone and acetaldehyde.[1382] The reactivity of aldehydes toward diazomethane appears to decrease with increasing chain-length. Presence of electron-attracting substituents on the carbon adjacent to the carbonyl function favors oxide formation, as with chloral (Eq. 262), which affords primarily the desired epoxide.[41, 42, 1139, 1537]

$$Cl_3C{-}CHO \xrightarrow{CH_2N_2} \underset{(54\text{–}64\%)}{Cl_3C{-}\overset{O}{\overset{/\backslash}{CH}}{-}CH_2} \qquad (262)$$



(263)

The electronic influences affecting the course of this reaction are further illustrated by the behavior of *p*-nitrobenzaldehyde (Eq. 264), which yields *p*-nitrostyrene oxide in moderate amounts,[41, 44] whereas benzaldehyde itself (Eq. 263) gives acetophenone exclusively.[159,1180,1536]



(31–46%)

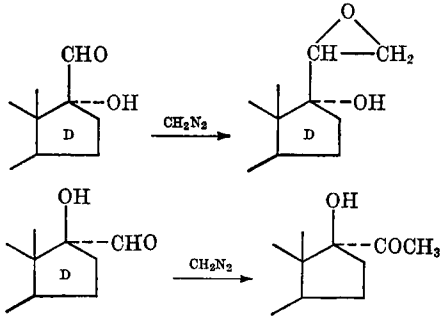
(264)

+ $O_2N{-}C_6H_4{-}CO{-}CH_3$

(24–29%)

The stereochemical demands of the reaction can be demonstrated best in the steroid field (Eq. 265). Though 17-formyl-4-androsten-17α-ol-3-one can be epoxidized in 30% yield with diazomethane, the

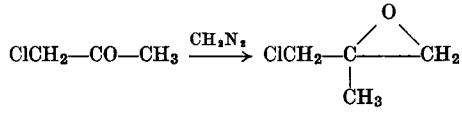
epimeric substance 17α-formyl-4-androsten-17β-ol-3-one gives only a carbonyl compound under comparable conditions.[1415]



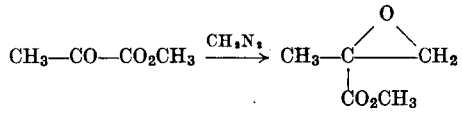
(265)

Treatment of α,β-unsaturated aldehydes with diazomethane generally yields pyrazolines, and therefore needs not be considered further as a method of epoxide synthesis.

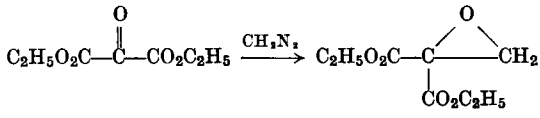
Simple aliphatic ketones like acetone,[1139] methyl ethyl ketone,[1382] and others usually give mixtures of epoxides and homologous carbonyl derivatives, but it is often possible to achieve satisfactory product fractionation. Higher yields can be secured by adding a hydroxylic solvent like water or ethanol[1139, 1140] or to a smaller extent by using a polar solvent like formamide.[1139] A minute positive salt effect has been reported as well.[1382] As with simple aldehydes, ketone reactivity falls off with increasing chain-length, and rises with substitution of electronegative functions at the α-position. Examples of the latter include α-chloroacetone,[41] methylpyruvate,[47] and diethyloxomalonate,[44] which all give good yields of the corresponding epoxides (Eqs. 266–268).



(266)



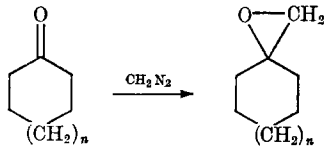
(267)



(268)

Additional instances are found with 1,3-dichloroacetone,[1985] trifluoroacetaldehyde,[1986] 1,1,1-trifluoroacetone,[1986] 1,3-dichloro-1,1,3,3-tetrafluoroacetone,[1987] and other fluorine-containing ketones.[1987]

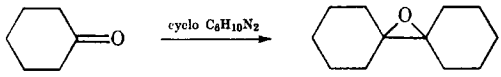
Alicyclic ketones vary considerably in reactivity and in product composition. Susceptibility to diazomethane attack appears to parallel the general reactivity of carboxylic ketones toward conventional



(269)

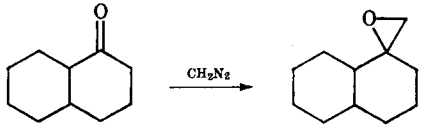
$n = 1, 2$

carbonyl reagents, which passes through a maximum with cyclohexanone,[13, 897, 960, 1179, 1480] dips toward a minimum in the medium-sized rings,[13, 897, 960] and then rises gradually as the macro rings are



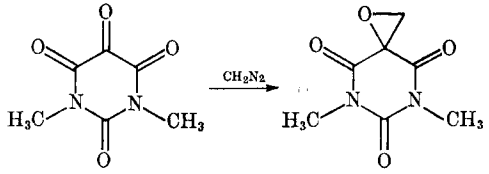
(270)

reached.[1546] Among spiroepoxides synthesized in this manner (Eqs. 269 and 270) are 1-oxabicyclo[2.5]octane, 1-oxabicyclo[2.6]nonane, and 13-oxadispiro[5.0.5.1]tridecane.[764] In addition, spiroepoxides have been



(271)

prepared (Eq. 271), together with other products, from *cis*- and *trans*-1-decalone.[694] Other procedures, perhaps not as rapid but surely safer for large-scale synthesis, may commend themselves for the preparation of such substances.

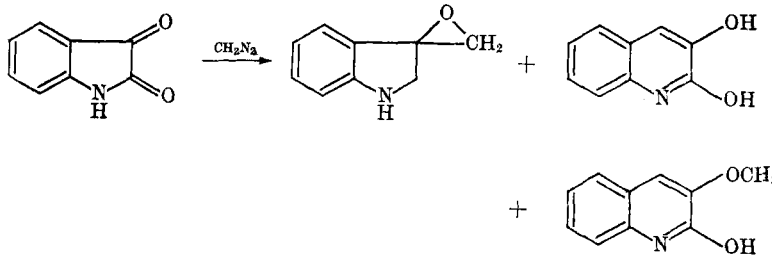


(272)

Among heterocyclic ketones which are reported to give epoxides on treatment with diazomethane are *N*,*N*′-dimethylalloxan[44, 159] (Eq. 272) isatin[44, 732] (Eq. 273), and 4-oxotetrahydrothiopyran[1278]

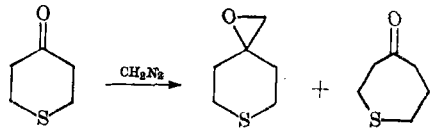
(Eq. 274). Other products are formed as well, of course, and yields vary from very small in the first instance to moderate in the last.

Aromatic ketones, like aldehydes, sometimes yield small amounts



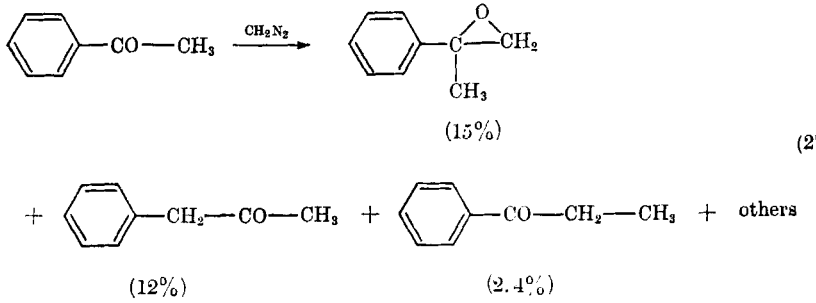
(273)

of the corresponding epoxides, but these are invariably accompanied by larger quantities of ketonic material. Acetophenone, for example, yields at least two homologous ketones in addition to the desired



(274)

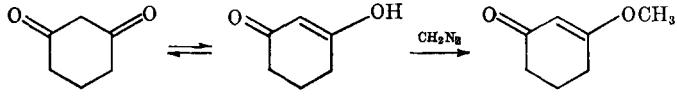
product, as well as recovered starting material[820, 1181] (Eq. 275). Restraint should be exercised in applying this synthetic route, therefore, if alternate and superior routes are available.



(275)

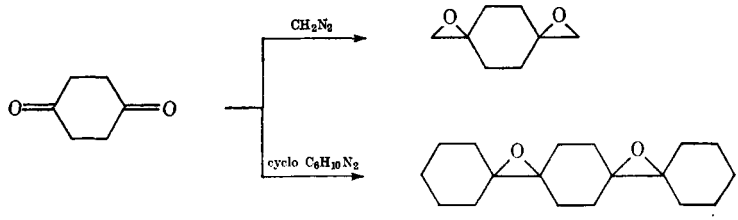
An important exception to the applicability of diazomethane for epoxide synthesis will be apparent when it is recalled that this reagent is exceedingly potent in replacing acidic hydrogens in enols.[485, 693]

It is consequently not possible to form a spiroepoxide from cyclohexane-1,3-dione, for example, since this substance is probably almost wholly enolic.[488] The exclusive product isolated on treatment with diazomethane[44] is the corresponding enol ether (Eq. 276).



(276)

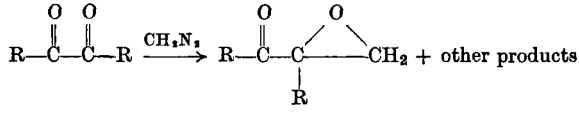
In contrast, cyclohexane-1,4-dione affords, in addition to other products, small quantities of the bisspiroepoxides shown in Eq. (277), with diazomethane[1791] and diazocyclohexane[765] respectively.



(277)

Treatment of α,β-unsaturated ketones with diazomethane generally gives pyrazolines, as with α,β-unsaturated aldehydes.[485, 693] Although it has recently been found possible to cause addition of diazomethane directly to the carbonyl function of such compounds through the use of catalytic amounts of boron trifluoride,[820, 879] it is not possible as yet to prepare anything but a homologous α,β-unsaturated ketone in this manner.

A significant correction of earlier literature was published recently by Eistert and co-workers.[487] Whereas it had been held previously that biacetyl and benzil give only methylenedioxy derivatives on treatment



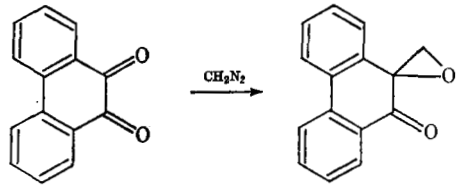
(278)

R = CH_3, C_6H_5

with diazomethane,[159, 485, 693] it now appears that α,β-epoxy ketones are formed in good yields from these two substances, along with other products, none of which are methylenedioxy derivatives (Eq. 278).

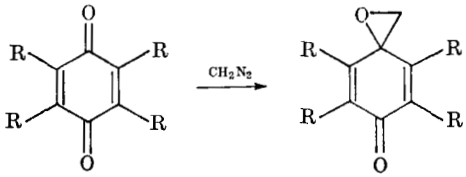
Consistent with the above findings is a recent corroboration of

previous work[41] by Eistert and co-workers.[487] Condensation of 9,10-phenanthrenequinone with diazomethane does yield an epoxide (Eq. 279) as claimed previously.



(279)

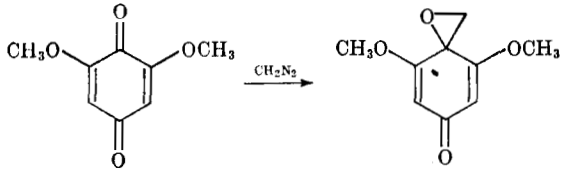
Further progress has been made in recent years with 1,4-quinones, which were formerly considered to yield either pyrazolines in the manner of α,β-unsaturated ketones, or oxapyrazolines by 1,2-addition to the carbonyl function.[485, 693]



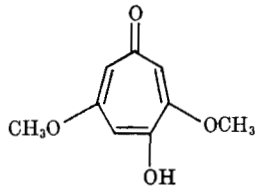
(280)

R = Cl, CH_3O, CH_3CO_2

Eistert and Bock,[486] for example, have found monoepoxides to be accessible by treatment of 2,3,5,6-tetrachloro-, 2,3,5,6-tetramethoxy-, or 2,3,5,6-tetraacetoxybenzoquinone with diazomethane (Eq. 280). Previous speculations[1593] on the nature of the nitrogen-free products isolated from 2,3,5,6-tetramethylbenzoquinone may thus require revision. Eistert and Bock also reported that 2,6-dimethoxybenzoquinone yielded a monoepoxide (Eq. 281), in contrast with the ring-



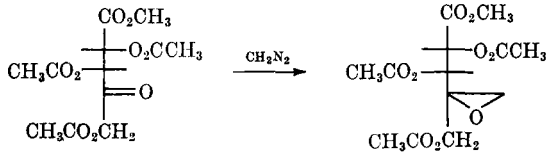
not



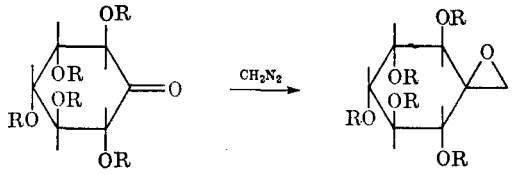
(281)

expansion product postulated by Marini-Bettolo and Paoloni[1108] for the same reaction.

Diazomethane was used to form epoxides in the sugar field in at least two instances,[1399, 1831] shown in Eqs. (282) and (283).



(282)



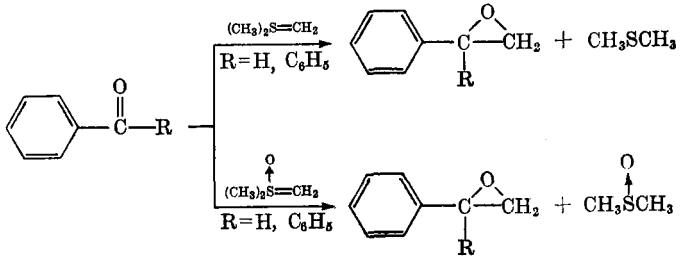
(283)

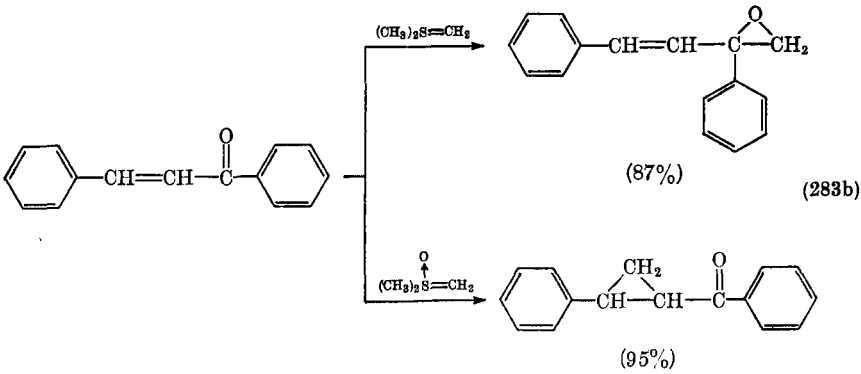
R = CH_3CO

An interesting paper published recently by Gutsche and Smith[695] describes several reactions involving condensation of cycloalkanones with bisdiazoalkanes. Although a number of novel bicyclic ketones were formed, no epoxides could be isolated. This is consistent with previous findings that cycloalkanones give no epoxides on treatment with diazoalkanes higher than diazomethane itself, *e.g.* diazoethane,[13] phenyldiazomethane,[265, 693] and others.[13, 693, 1257]

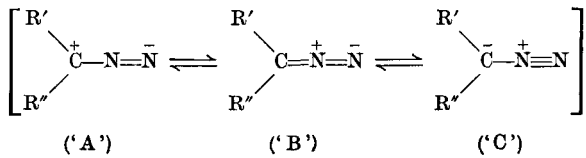
It may be concluded in summary that, although a moderate number of epoxides can be isolated from carbonyl compounds on treatment with diazomethane, this technique suffers from several serious drawbacks as a synthetic tool in epoxide chemistry. Corey and Chaykovsky[1988, 1989] have recently disclosed, however, the ingenious application of dimethylsulfonium and dimethylsulfoxonium methylides as methylene transfer agents for epoxide synthesis. Insertion of methylene into the carbonyl groups of benzaldehyde and benzophenone, for example, can be effected in high yield with either of the above ylide reagents, with the concomitant release of dimethylsulfide and dimethylsulfoxide respectively (Eq. 283a). Examplifying an interesting difference between the two reagents, on the other hand, is the fact that whereas carvone, eucarvone, and benzalacetophenone (Eq. 283b) undergo facile epoxide formation with dimethylsulfonium methylide, the corresponding cycloprane derivatives are generated in high yield

when dimethylsulfoxonium methylide is used. Although substances which readily form enolates, such as desoxybenzoin, do not undergo this reaction, it is likely that these elegant ylide reagents will see increasing popularity in epoxide synthesis.



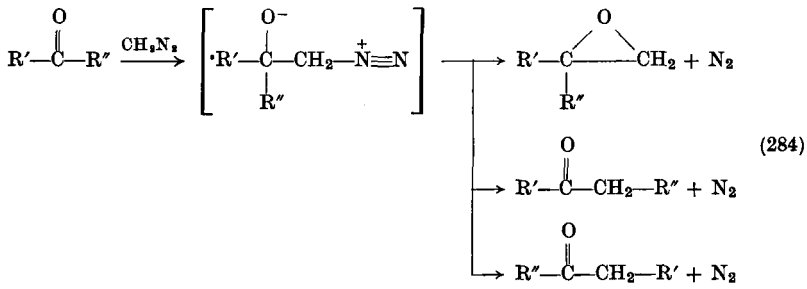


(2) **Mechanism.** Of great importance in permitting chemists to explain rationally the reactivity of carbonyl compounds toward diazomethane was the elucidation of its electronic structure. It is now accepted that a diazoalkane can be represented by a set of canonical structures ('A')-('C'), none of which is an adequate representation by itself.[693] Evidence for the linear nature of diazoalkanes has been obtained by various types of physical measurements, including electron diffraction and infrared spectroscopy.[187, 365, 1432]



Despite the fact that electronegativities might lead to the opposite conclusion, canonical structure ('C') is believed to predominate insofar as the course of reaction with a carbonyl function is concerned. It is evident that in response to the demands of the substrate, and probably under the influence of solvents as well, the carbon atom of diazomethane can sustain a negative charge long enough to allow it to function as a nucleophile, in the manner of more conventional carbonyl reagents.[693]

Evidence for the nucleophilic character of diazomethane in this condensation can be drawn from the enhanced reactivity of chloral[42, 1139, 1537] and α-chloroacetone[41] relative to acetaldehyde and acetone respectively, and of *p*-nitrobenzaldehyde[41, 44] relative to benzaldehyde.[159, 1180, 1536] In the former, halogen atoms exert an electron-withdrawing effect by simple induction, thereby enhancing the positive character of the carbonyl carbon. In the latter, the nitro group operates inductively and by resonance as well to increase the nucleophilic susceptibility of the carbonyl function. Further evidence may be derived from the relative reactivities of diazomethane and ethyl diazoacetate, the latter being a weaker nucleophile by virtue of the electron-delocalizing ability of the carbethoxy group.[693]

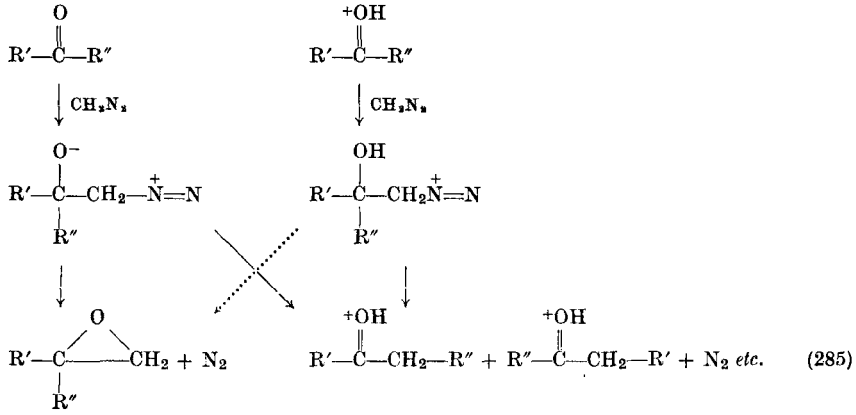


(284)

It was amply emphasized above that the formation of homologous ketones is the principal competing reaction in this condensation.[485, 693] To explain this observation it has become customary to invoke a transient intermediate zwitterion, termed by Arndt and Eistert[43, 485] a 'diazonium betaine', which can collapse into an epoxide with attendant nitrogen expulsion, or can undergo rearrangement to one or two possible carbonyl compounds. The process may be represented schematically as shown in Eq. (284).

The nature of the transition states involved here is not yet fully understood. Although it has been suggested for instance that departure

of nitrogen is completely synchronous with ring closure or rearrangement,[1480] it is also possible that nitrogen is expelled separately, a second zwitterion being thereby formed which undergoes further reactions.[693] Another way of expressing the same thought is to say that the extent of C—N bond-breaking in the transition state is uncertain. It may vary with the dielectric constant of the medium, and in fact may not be the same for ring closure as for alternative processes. House and co-workers have recently suggested, moreover, that alcohols promote condensation of diazomethane with ketones by functioning as acid catalysts.[820] According to these authors it is the free ketone, and



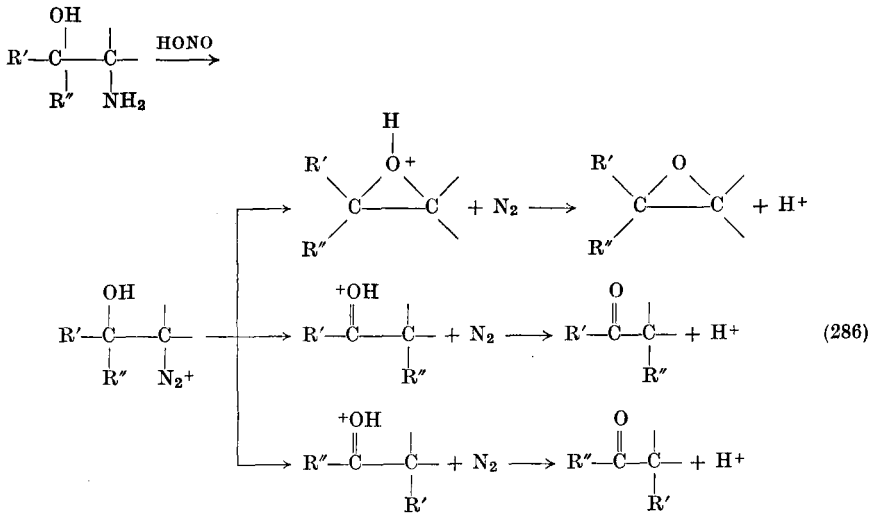
(285)

not its conjugate acid, that leads to epoxide formation (Eq. 285), in harmony with the relative nucleophilicities of alkoxide and hydroxyl functions.

Since the conjugate acid of the ketone yields little or no epoxide by condensation with diazomethane, it seems of doubtful value to conduct the reaction in pure alcohol insofar as epoxide synthesis is concerned. Further speculation regarding details of the reaction mechanism will undoubtedly be forthcoming when more experimental information is available.

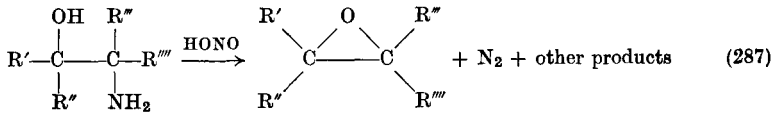
It may be seen in the above scheme of House and co-workers[820] that the protonated form (*i.e.* the conjugate acid) of the Arndt–Eistert 'diazonium betaine' is actually the intermediate that one would anticipate in the diazotization of a β-amino alcohol. For the general case, therefore, it might be expected that treatment of a β-amino alcohol with nitrous acid, or some other diazotizing reagent, would proceed according to the scheme shown in Eq. (286).

In fact, however, the literature contains rather few instances of the conversion of β-amino alcohols into epoxides by this route. These



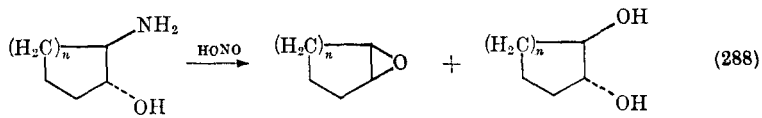
(286)

include (Eqs. 287–289) *p,p'*-dimethoxy-*cis*-stilbene oxide,[1438] 1,1,2-triphenylpropylene oxide,[1074] cyclopentene oxide, [650] cyclohexene oxide,[1851] and more recently the spiroepoxide from 4-aminoethyl-4-hydroxytetrahydrothiapyran 1,1-dioxide.[1278]

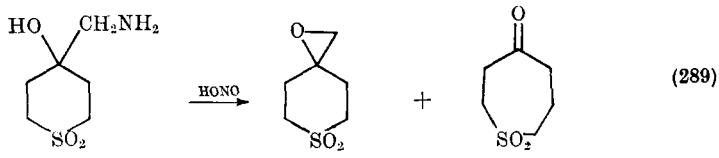


(287)

$R' = R'' = p\text{-}CH_3OC_6H_4$; $R'' = R'''' = H$
$R' = R'' = R''' = C_6H_5$; $R'''' = CH_3$

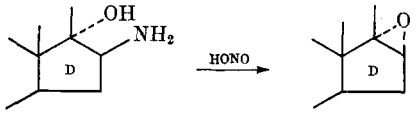


(288)



(289)

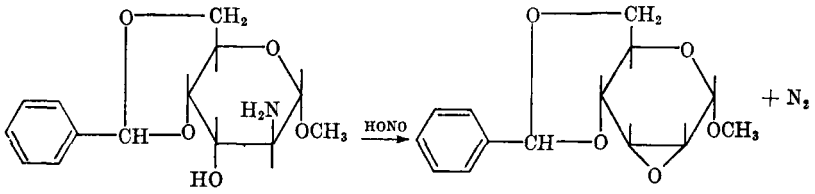
In the steroid field a rare instance of epoxide formation by diazotization of a β-amino alcohol is the conversion of certain D-homosteroid derivatives into the corresponding 17α,17aα-epoxy D-homo-



(290)

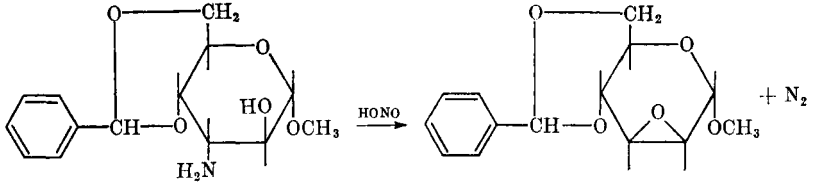
steroids (Eq. 290), first reported by Ruzicka and Meldahl[1511] and subsequently reinvestigated by Cremlyn and co-workers.[366]

In the sugar field may be cited the transformations of methyl 2-amino-4,6-*O*-benzylidene-2-desoxy-α-D-altroside,[1839] methyl 3-amino-



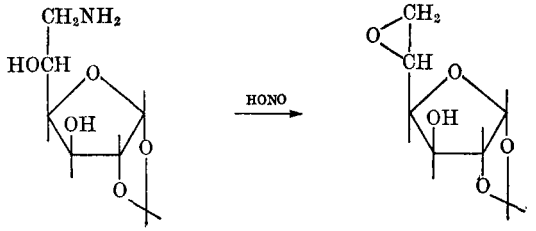
(291)

4,6-*O*-benzylidene-3-desoxy-α-D-altroside,[1839] 6-amino-6-desoxy-1,2-*iso*-propylidene-α-D-glucofuranose,[102] and 4-amino-1,6-anhydro-4-desoxy-β-D-mannose[102] to their respective anhydro derivatives on diazotization (Eqs. 291–294).



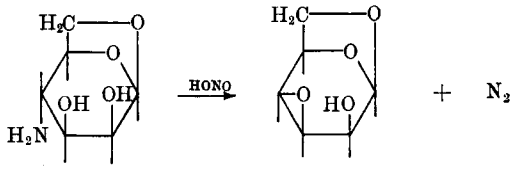
(292)

There is overwhelming evidence, however, that under conventional diazotization conditions epoxides are seldom produced in greater than trace amounts.[123, 395, 528, 820, 1701] Since 1,2-diols and chlorohydrins



(293)

or β-acetoxy alcohols frequently accompany the principal ketonic products when acids like hydrochloric or acetic are used in the diazotization, it is possible that some epoxides are produced but are opened

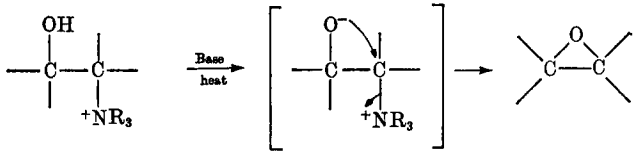


(294)

immediately. That such may indeed be so is indicated by the observation of Curtin and Schmukler[398] that subjection of an epoxide to diazotization conditions resulted in formation of a mixture of non-ketonic products, which was similar to that obtained in the diazotization of the β-amino alcohol itself. At the present time, therefore, diazotization of β-amino alcohols cannot be said to constitute a general approach to epoxide synthesis.

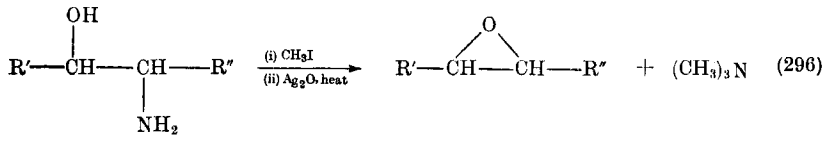
C. Hofmann Reaction of β-Amino Alcohols

It is well known that when a quaternary amine salt containing a suitably disposed hydroxyl group is subjected to the conditions of Hofmann elimination, the hydroxyl function can operate as a proton source, thereby forming a dipolar intermediate which can subsequently collapse into an epoxide ring.[351] As in conventional Hofmann eliminations, evolution of gaseous trialkylamine provides substantial driving force for the cyclization process. For the case of a general quaternary β-amino alcohol the reaction may be depicted as shown in Eq. (295).



(295)

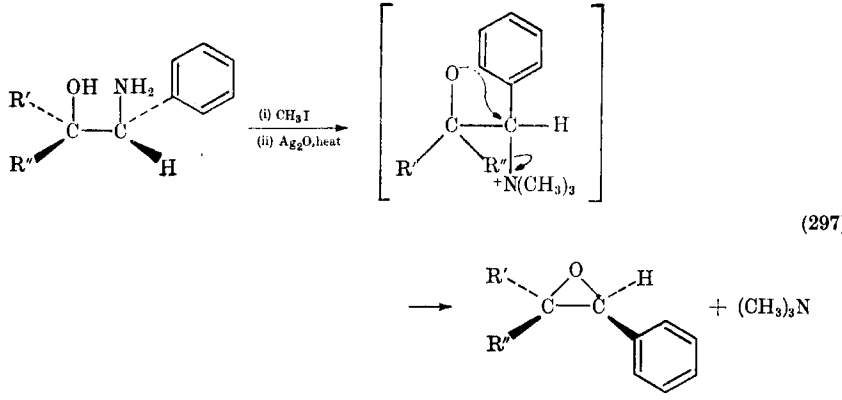
Several simple alkyl- and phenyl-substituted ethylene oxides have been prepared in good yield by this procedure (Eq. 296). These include 1-heptene oxide,[241] 1-octene oxide,[1616] 1-hexadecene oxide,[240] cyclohexylethylene oxide,[240] 1,2-epoxy-4-phenylbutane,[240] and 1,2-epoxy-1-phenylpropane.[240, 1930, 1932, 1954]



(296)

R′ = H; R″ = *n*-C_5H_{11}, *n*-$C_{14}H_{29}$, cycloC_6H_{11}, $C_6H_5CH_2CH_2$
R′ = C_6H_5; R″ = CH_3

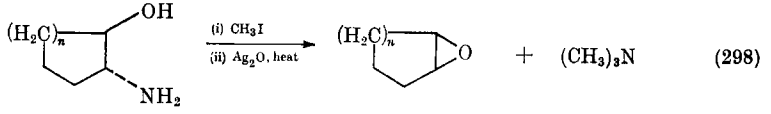
threo- and *erythro*-1,2-Diphenylethanolamines yield *cis*- and *trans*-stilbene oxide respectively (Eq. 297), and several analogous stereospecific epoxide formations have been accomplished in the same manner.[1424]



(297)

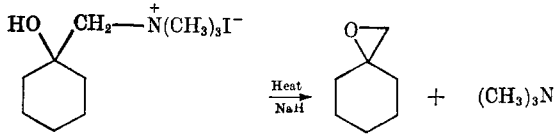
R′ = H; R″ = C_6H_5
R′ = C_6H_5; R″ = H

Cyclopentene and cyclohexene oxides have been synthesized[148,1851] from *trans*-2-aminocyclopentanol and *trans*-2-aminocyclohexanol respectively (Eq. 298), and the bicyclic spiroepoxide 1-oxaspiro[2.5]-octane has been formed[1487] in a similar manner (Eq. 299). Larger rings



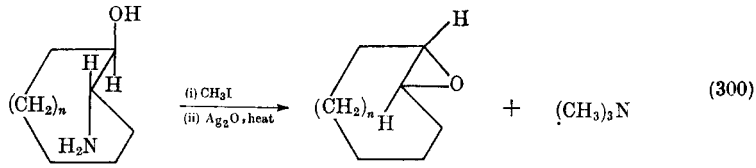
(298)

n = 1, 2, 6, 8, 9, 12



(299)

containing epoxides have been prepared[1672] and when the ring-size exceeds ten carbon atoms, it is even possible to prepare both *cis*- and *trans*-substituted epoxides (Eq. 300). Additional examples may be found in the recent review of Cope and Trumbull.[351]



(300)

$n = 6, 7, 10$

The mechanism of this reaction clearly involves backside alkoxide attack on the neighboring carbon atom with synchronous displacement of trimethylamine. Such a process requires acyclic precursors to assume *trans*-conformation, and for the same reason precludes formation of cyclopentene or cyclohexene oxide from *cis*-2-aminocyclopentanol or *cis*-2-aminocyclohexanol. Because it is so similar to cyclodehydrohalogenation and intramolecular tosylate displacement, which have been considered elsewhere in the present chapter and in previous reviews,[593, 1662, 1857] no further attention need be accorded to it here.

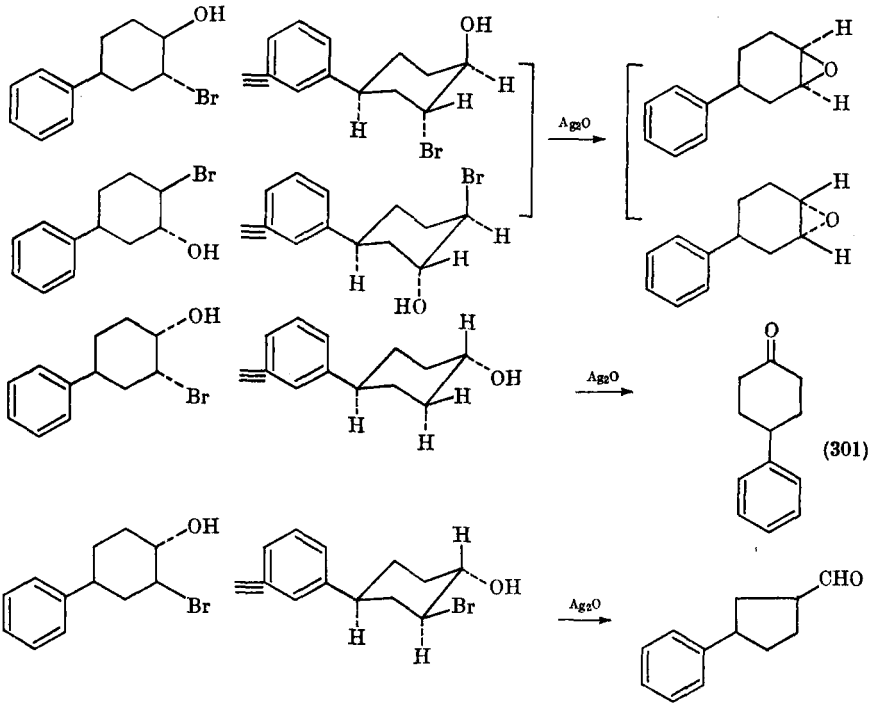
4. Miscellaneous Methods

It is the purpose of this section to present a number of miscellaneous reactions which have been reported to give epoxides, but which are not utilized with sufficient frequency to justify separate treatment.

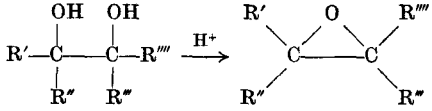
The use of Ag^+ ion to effect cyclization of halohydrins is a reaction that has received but little attention until now, since cyclodehydrohalogenation is customarily conducted with alkali, and results obtained in this fashion are entirely satisfactory for most synthetic purposes. An early example of this reaction was the conversion of 2-hydroxy-1-iodo-3-phenylpropane into 1,2-epoxy-3-phenylpropane with silver nitrate.[1397] A more recent instance, reported by Curtin and Harder,[396] involves the formation of *cis*- and *trans*-4-phenylcyclohexene oxides from a mixture of bromohydrins, as shown in Eq. (301). The stereochemical requisites for cyclization, *trans-axial–axial* disposition of reacting groups, are illustrated by the failure of the isomeric bromohydrins to yield any epoxides; they give carbonyl compounds instead.

Epoxides have been reported to form occasionally during pinacol rearrangements, but they have to possess considerable stability due to

substitution before they can survive the acidic conditions used in this reaction. Examples include dehydration of 3-phenyl-3,4-hexanediol[1732]

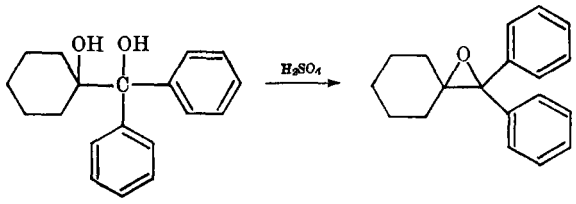


and of 1,2-diphenyl-1,2-di-*p*-tolylethylene glycol[1714–1716] to the corresponding epoxides (Eq. 302), and of 2-pentamethylene-1,1-diphenylethylene glycol[1137] to 1-oxa-2,2-diphenylbicyclo[2.5]octane (Eq. 303).



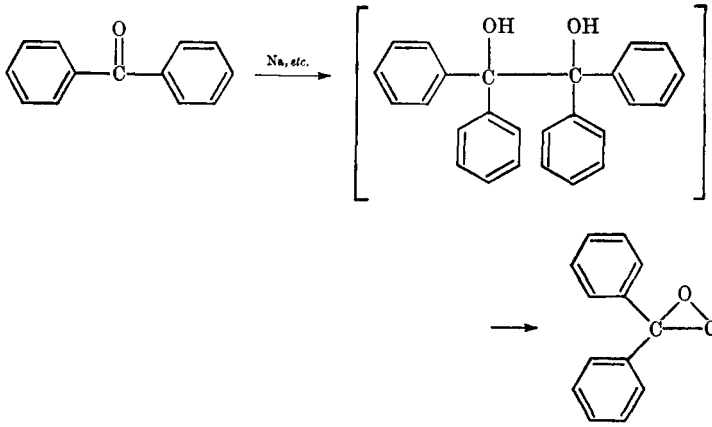
(302)

$R' = H; R'' = R''' = C_2H_5; R'''' = C_6H_5$
$R' = R'''' = p\text{-}CH_3C_6H_4; R'' = R''' = C_6H_5$



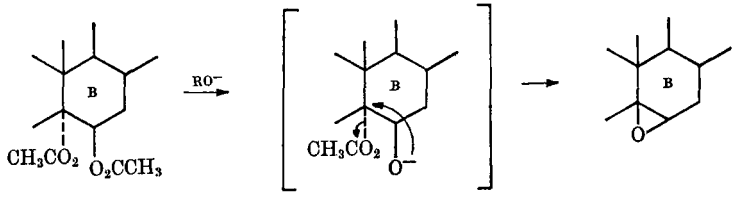
(303)

Isolation of some tetraphenylethylene oxide (Eq. 304) during various bimolecular reductions of benzophenone[933, 1283, 1714–1716] has been attributed likewise to intramolecular dehydration of initially-formed tetraphenylethylene glycol.[1857]



(304)

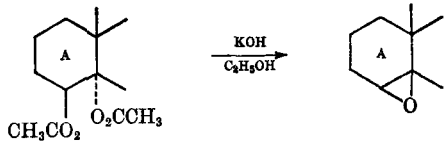
Treatment of 1,2-diol diacetate with alkali has been observed to give epoxides in a number of steroids, particularly 5α,6β-diacetoxy derivatives (Eq. 305) from which are formed 5β,6β-epoxy steroids.[424, 533, 870, 1501] Thus far, this potentially attractive synthesis has been



(305)

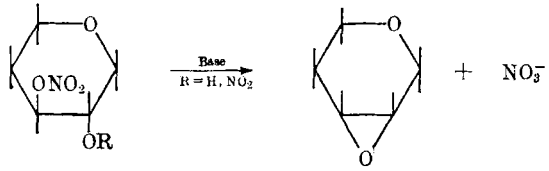
$$+ CH_3CO_2^- + CH_3CO_2R$$

extended[1573] only to the 4β,5β-position of the steroid nucleus (Eq. 306). A related example is the conversion of a 5α-hydroxy-6β-acetoxy-steroid derivative into the corresponding 5α,6α-epoxide on treatment with vinylmagnesium bromide.[1990]



(306)

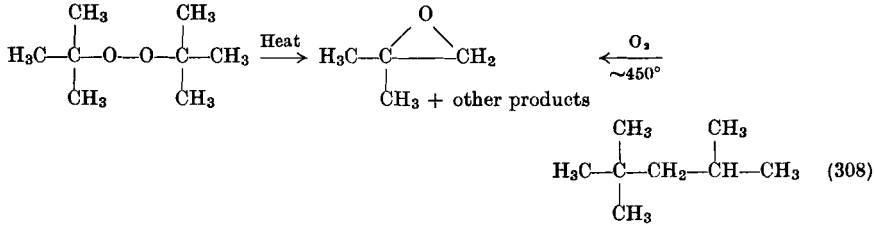
In the same connexion may be cited the work of Honeyman and co-workers[35, 802, 803] in the sugar yield, involving cyclization of certain nitrate esters to 2,3-anhydro derivatives (Eq. 307).



(307)

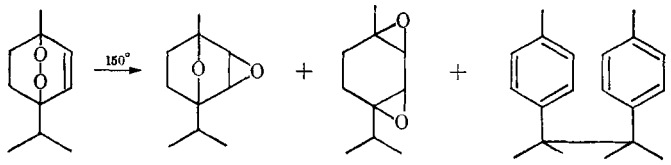
R = H, NO_2

Epoxides can apparently be obtained in trace amounts, together with numerous other products, in the high-temperature (about 450°) oxidation of certain saturated hydrocarbons. The only example existing in the literature until now is that of 2,4,4-trimethylpentane (Eq. 308), which gives a minute yield of *iso*butylene oxide under these conditions.[1508] Related to this observation, however, is the report that di-*tert*-butyl peroxide and di-*tert*-heptyl peroxide (Eq. 308) yield small quantities of *iso*butylene oxide and 1,2-epoxy-1,1-dimethylhexane respectively, along with many other products, during liquid-phase thermal decomposition.[117, 435] McMillan has reported that irradiation of di-*tert*-butyl peroxide generates, among numerous other products, small quantities of *iso*butylene oxide,[1991] but that similar treatment of di*iso*propyl peroxide yields no propylene oxide.[1992]



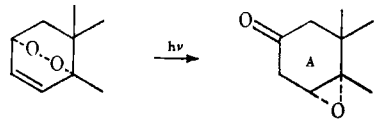
(308)

Thermal decomposition of ascaridole[1129] is reportedly to give, among other products, the two epoxides shown in Eq. (309).



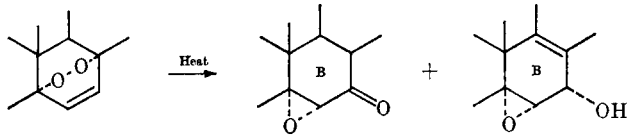
(309)

In the same connexion the photochemical decomposition of certain Δ^3-2α,5α-peroxido steroids in sunlight (Eq. 310) has been used for synthetic purposes, 4α,5α-epoxy-2-oxo steroids being thereby



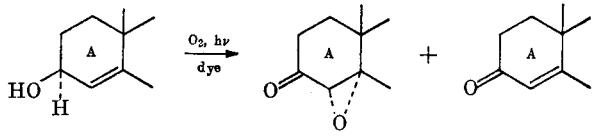
(310)

obtained.[307] Similarly, Bergmann and Myers have recently described the pyrolytic conversion of Δ^6-5α,8α-peroxido steroids (Eq. 311) to 5α,6α-epoxy steroids.[137]

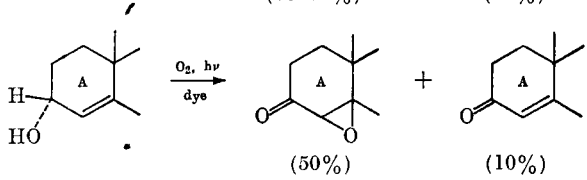


(311)

A stereospecific photocatalyzed epoxidation has been reported recently in the steroid field by Nickon and Mendelson,[1993] using the epimeric allylic alcohols shown in Eqs. (311a) and (311b).



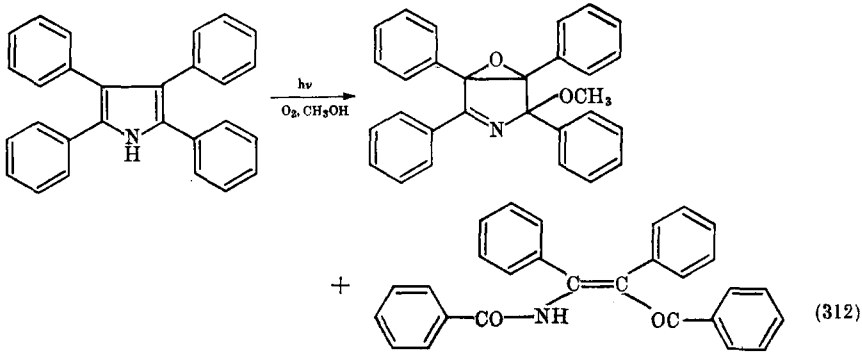
(311a)



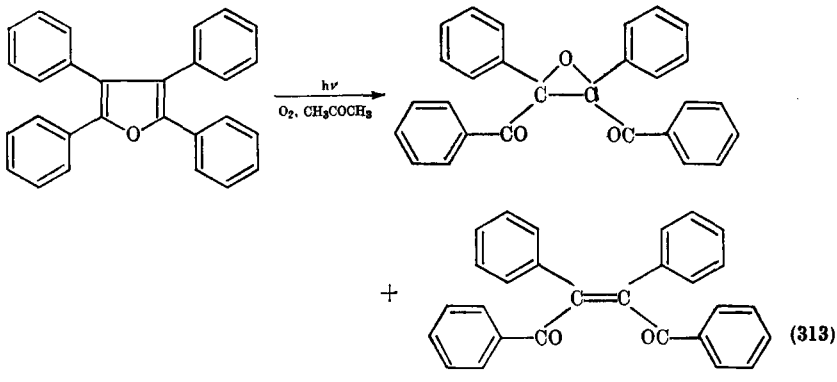
(311b)

Attention may be drawn here to the experiments of Wasserman and Liberles[1810] which involve irradiation of methanolic solutions of tetraphenylpyrrole in the presence of air. The principal product appears to be the epoxide shown in Eq. (312), accompanied by a ring-cleavage product.

A more complex situation is manifest with tetraphenyltetrahydrofuran, which gives two fragmentation products in acetone.[1810] One of these, however, has been formulated as an epoxide (Eq. 313).

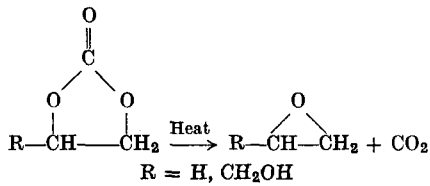


(312)



(313)

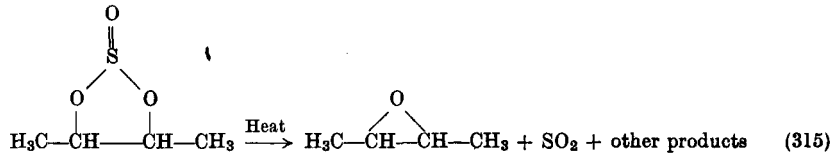
Pyrolytic decomposition of cyclic carbonate esters of 1,2-diols has been utilized on occasion for epoxide synthesis. Ethylene oxide and glycidol, for example, have been prepared[256, 1710] from ethylene carbonate and glyceryl carbonate respectively (Eq. 314).



(314)

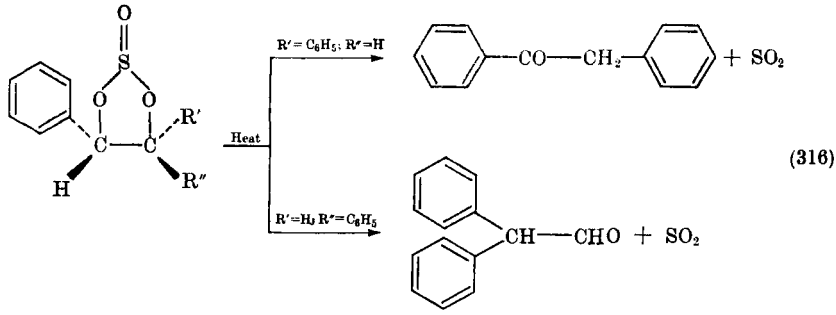
The work of Pattison,[1307] and more recently of Searles and co-workers,[1554] indicates considerable generality for the above reaction in preparing cyclic ethers of various ring sizes. Its scope in epoxide synthesis has been limited so far to the two illustrations cited.

Of related interest in this connexion is the discovery of Denivelle[439] that the cyclic sulfite ester of 2,3-butanediol gives on heating 2,3-epoxybutane and sulfur dioxide, along with other products (Eq. 315).



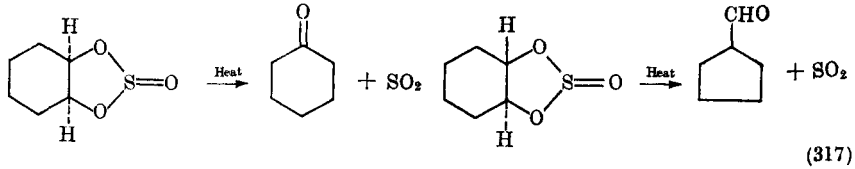
(315)

Subsequent work by Price and Berti,[1407] on the other hand, failed to produce epoxides from the cyclic sulfites of either *cis*- or *trans*-1,2-diphenylethylene glycol. A similar lack of epoxide formation



(316)

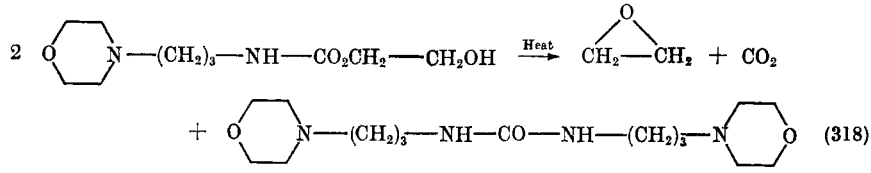
attended the pyrolysis of *cis*- and *trans*-1,2-cyclohexanediol sulfites. The products isolated instead were carbonyl compounds, as shown in Eqs. (316) and (317).



(317)

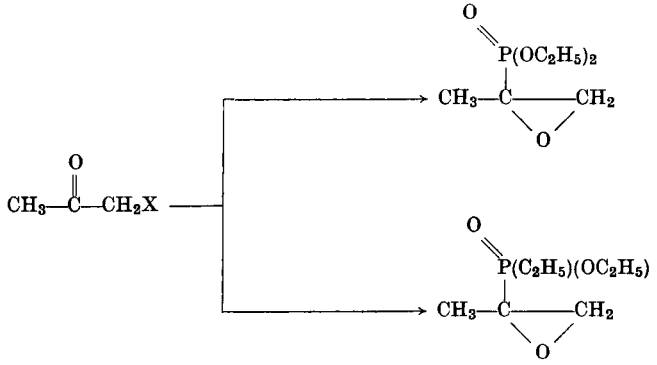
Still another decomposition giving rise to ethylene oxide involves the pyrolysis of β-hydroxyethyl *N*,*N*-dialkylaminopolymethylene carbamates. A specific illustration (Eq. 318) is β-hydroxyethyl γ-morpholinopropyl carbamate, which on heating at 130–140° yields ethylene oxide, carbon dioxide, and a urea derivative.[434] Although interesting, this decomposition is of little preparative value in epoxide synthesis.

A new and interesting class of phosphorus compounds containing the epoxide function has been described by Arbuzov and co-workers.[2007-2011] In a process reminiscent of the epoxy ether synthesis



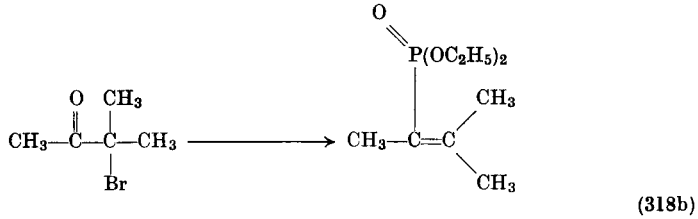
(318)

described previously (see section **III.2.***E*.), an α-haloketone is condensed with the phosphonic and phosphinic acid derivatives shown in Eqs. (318a) and (318b). Two possible products may be formed, depending on



(318a)

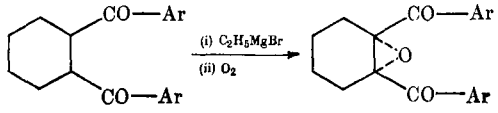
the nature of the halogen and on the degree of substitution of the halogen-bearing carbon. The same reactions have also been reported with 2-chloro- and 2-bromocyclohexane, 2-chloro-2-methylcyclohexane, and 2-chlorocyclopentane.



(318b)

In conclusion of the present section may be mentioned the novel epoxidation described recently by Fuson and co-workers,[608] which involves *cis*-1,2-dimesitoylcyclohexane. Treatment of this substance

with ethylmagnesium bromide, followed by passage of oxygen through the reaction mixture, gives a good yield of the corresponding epoxide (Eq. 319). Further progress in the exploration of the scope of this unusual reaction will probably be forthcoming.



(319)

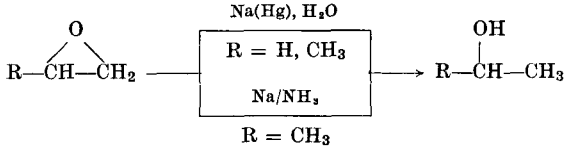
Methods for the preparation of epoxides will undoubtedly occupy the minds of chemists for many years, as improvement of existing techniques and development of new approaches are sought in this important field of heterocyclic chemistry.

IV. Chemical Reactions of Epoxides

1. Reduction

A. Reduction of Epoxides with Metals

(1) Sodium. Most time-honored among all processes for reduction of ethylene oxides is that used by Wurtz himself[1888, 1889] as early as 1862 for the conversion of ethylene oxide into ethanol. The method used by Wurtz involved treatment of the epoxide with sodium amalgam in water, and was alike in all respects to reductions conducted even earlier with other functional groups. A few years after Wurtz published his results, Linnemann[1036] utilized the same technique to obtain 2-propanol from propylene oxide. Some 70 years later Birch[161] substituted sodium in liquid ammonia for sodium amalgam in water, thereby substantially improving the previous procedure (see Eq. 320).

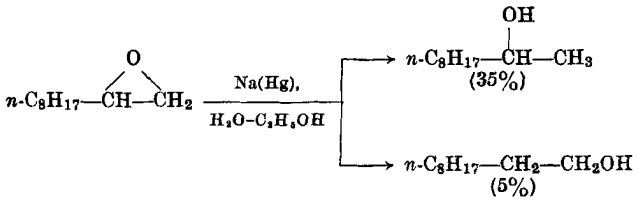


(320)

Newman and co-workers[1240] conducted a careful product analysis after reduction of 1,2-epoxydecane with sodium amalgam in aqueous

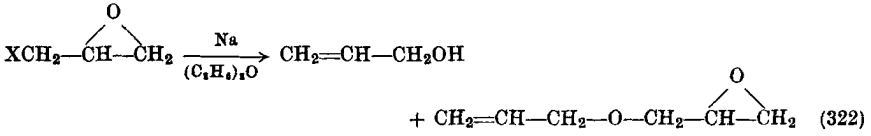
ethanol, and found a detectable quantity of 1-decanol in addition to the anticipated 2-decanol (Eq. 321).

As in so much of its chemistry, epichlorohydrin reduction caused confusion and frustration for many years.[317, 836] After considerable trouble it was at last concluded by Kischner[938] that treatment of



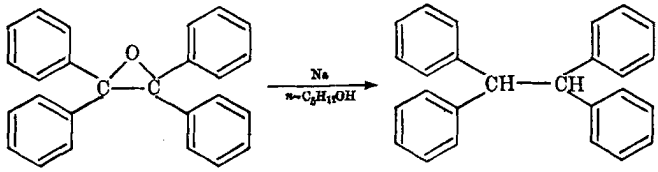
(321)

epichlorohydrin with sodium in absolute ether gives primarily two products (Eq. 322), along with much polymer. The first, already detected by previous investigators,[317, 836] was allyl alcohol. The second, once considered to be 1,2;5,6-diepoxyhexane, was now formulated as allyl glycidyl ether. Bijot[156] has extended this reaction to include epibromohydrin and epiiodohydrin, obtaining the same products as with epichlorohydrin, but was unable to arrive at a complete product analysis.



(322)

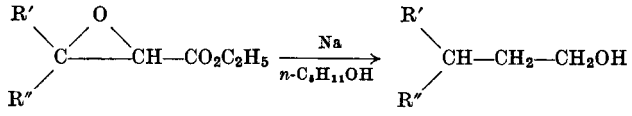
Pentanol was first used in conjunction with sodium reduction of epoxides in 1896 by Klinger and Lonnes,[943] who converted tetraphenylethylene oxide into tetraphenylethane (Eq. 323). The known facility



(323)

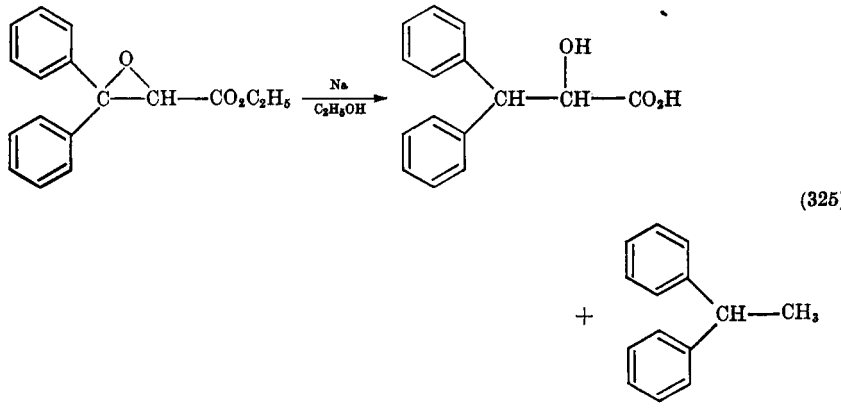
with which benzylic alcohols undergo hydrogenolysis makes perfectly understandable the fact that no 1,1,2,2-tetraphenylethanol could be isolated under these conditions.

Several glycidic esters have been found[158, 161] to give alcohols on reduction with sodium in pentanol or ethanol (Eqs. 324 and 325). Intermediate stages in the reduction process can be isolated in certain instances, but these provide little insight into the detailed course of reaction.



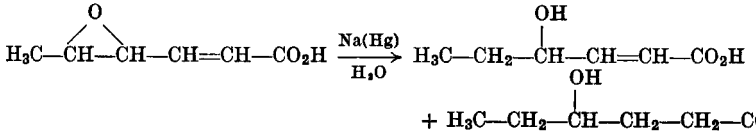
(324)

$R' = n\text{-}C_3H_7, C_6H_5; R'' = H$
$R' = CH_3; R'' = C_2H_5$



(325)

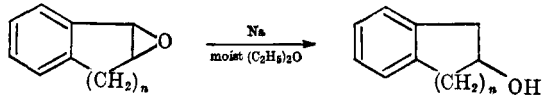
Reduction of 4,5-epoxy-2-hexenoic acid with sodium amalgam has been reported[1775] to yield a mixture of 4-hydroxy-2-hexenoic acid and 4-hydroxyhexanoic acid (Eq. 326).



(326)

Cyclohexene oxide was found to be quite inert by Brunel[255] both toward sodium amalgam in aqueous ethanol, and toward sodium in absolute ethanol. This is rather remarkable in the light of subsequent findings by Mousseron and co-workers[1135] that cyclohexene oxide undergoes rearrangement to a sodium enolate on treatment with metallic sodium in refluxing benzene.

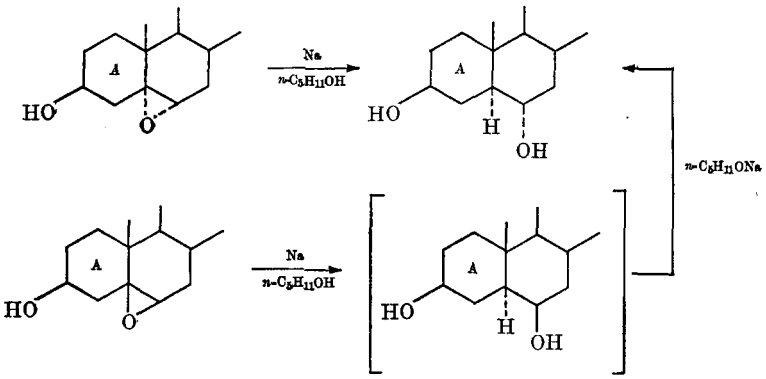
On the other hand, indene oxide and 1,2-epoxytetralin (Eq. 327) undergo reduction with no difficulty on treatment with sodium in moist ether.[837, 1661] The phenyl ring not only greatly enhances the susceptibility of the epoxide function to attack by hydrogen, but also directs addition exclusively to the benzylic position. Similar results were obtained when reduction was conducted with sodium in liquid ammonia.[1670]



(327)

$n = 1, 2$

Urushibara and Chuman[1774] utilized sodium in pentanol to effect reductive cleavage of cholesterol α-oxide and cholesterol β-oxide. Whereas the former gave the anticipated 6α-ol, the latter unexpectedly gave the same product (Eq. 328). The authors showed, however, that dihydro-6β-hydroxycholesterol undergoes epimerization to the 6α-hydroxy isomer on heating with sodium pentylate.

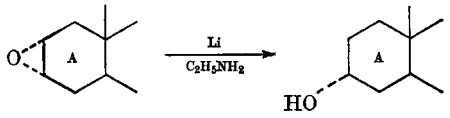


(328)

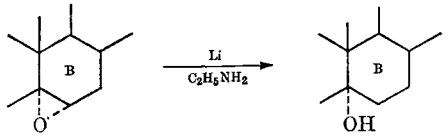
(2) Lithium. Credit for applying lithium–aliphatic amine systems to epoxide reduction, particularly in the steroid field, belongs chiefly to Hallsworth and Henbest.[704] This powerful reagent is capable of cleaving epoxide rings that are left intact by lithium aluminum hydride, but its scope has as yet been little explored.

Addition of 2α,3α-epoxy steroids to lithium in ethylamine gives a 3α-hydroxy derivative, in accordance with the principle of diaxial opening.[704] This principle will be amply invoked throughout subsequent

discussions of the chemical reactions of epoxides. In this instance it is believed that amine-solvated electrons constitute the incoming nucleophile. Other steroid epoxides likewise found[704] to give axial alcohols on

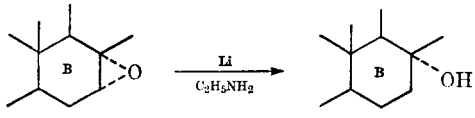


(329)

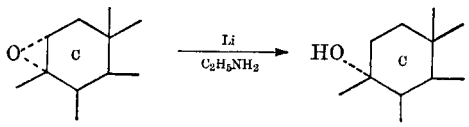


(330)

reduction with lithium in ethylamine are various 5α,6α-, 7α,8α-, and 9α,11α-epoxy steroids (Eqs. 329–332). The last two remain intact in the presence of lithium aluminum hydride.[453, 458, 543, 880]

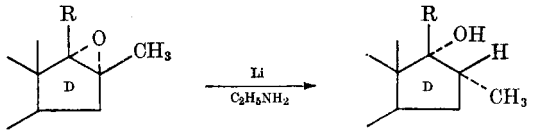


(331)



(332)

An illustration of the potency of lithium–ethylamine reduction was recently provided by Nomine and co-workers,[1254] who succeeded in opening the tetrasubstituted 16α,17α-epoxy steroid shown in Eq. (333).

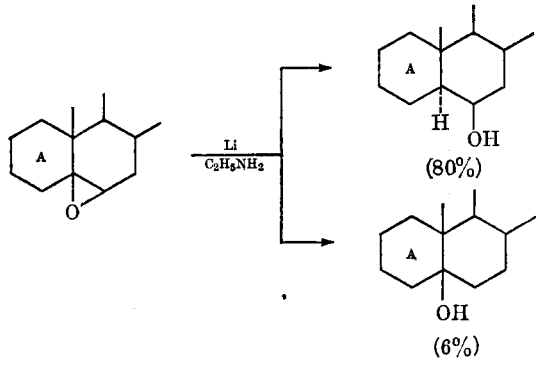


(333)

R = CH_3, *etc.*

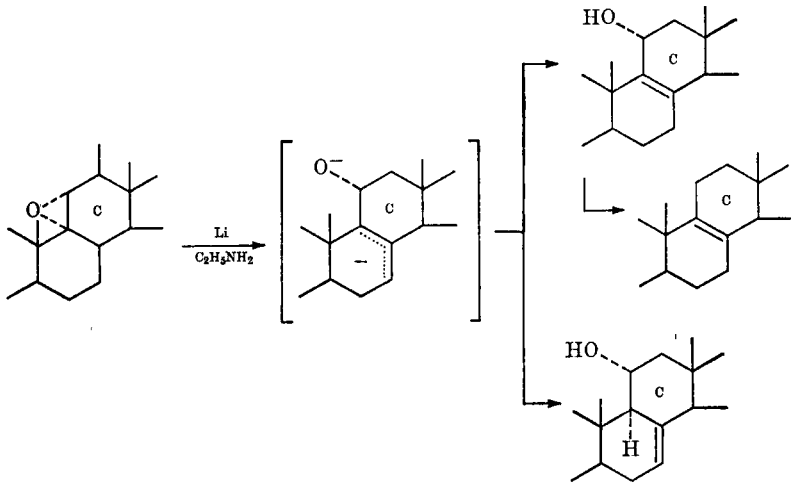
It is not always true that a unique product is formed during reduction with lithium, however, just as it is not true in other modes of reduction. Illustrating this is the fact that Hallsworth and Henbest[704]

obtained a mixture of alcohols on reduction of a 5β,6β-epoxy steroid (Eq. 334). It appears characteristic of 5β,6β-epoxy steroids (see below) that they give rise to mixtures of isomeric alcohols on reduction by any of the known procedures.



(334)

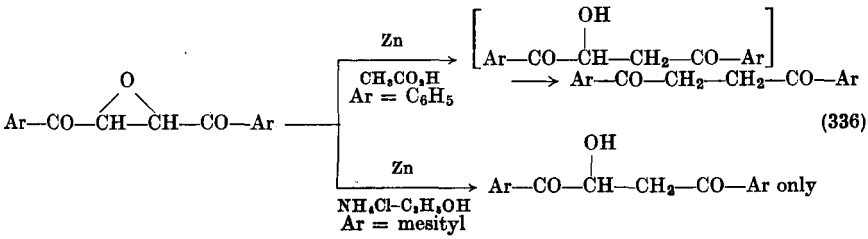
Finally may be mentioned the observation of Hallsworth and Henbest[704] that reduction of a Δ^7-9α,11α-epoxy steroid with lithium in ethylamine gave, in addition to the expected alcohol, a $\Delta^{8(9)}$-steroid.



(335)

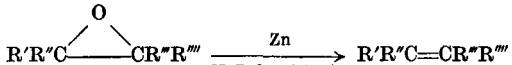
The transformation was believed to involve participation of a mesomeric anion as shown in Eq. (335). Formation of an olefin from the intermediate allylic alcohol is reasonable in view of the recognized lability of allylic C—O bonds.

(3) Zinc. Reduction of ethylene oxides with zinc is scarcely ever used, but a few illustrations may be cited briefly. Lutz and co-workers[1056, 1057] used zinc to cause reductive cleavage of 1,2-dibenzoyl- and 1,2-dimesitoylethylene oxides in acetic acid and ethanolic ammonium chloride respectively (Eq. 336).



(336)

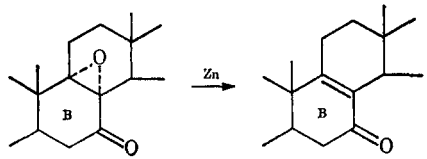
Cornforth and co-workers[356] employed zinc in a solution of sodium iodide and sodium acetate in acetic acid to effect reduction of several alkyl-substituted ethylene oxides to the corresponding olefins (Eq. 337).



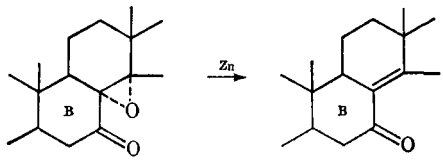
(337)

R′ = CH_3, C_2H_5; R″ = CH_3; R″ = n-C_4H_9; R‴ = H
R′ = R″ = R‴ = CH_3; R″ = n-C_4H_9

In the steroid field, finally, a number of workers[453, 455, 763] have reported conversion of 8α,9α-epoxy-7-oxo steroids and 8α,14α-epoxy-7-oxo steroids into the corresponding α,β-unsaturated derivatives with zinc (Eqs. 338 and 339).



(338)



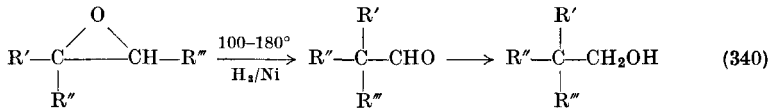
(339)

B. Catalytic Hydrogenation

Before the introduction of complex metal hydrides, the most commonly utilized process for reducing ethylene oxides was catalytic hydrogenation. Recent years, however, have seen a sharp decline in the frequency of application of this technique, because of several serious drawbacks. Among the defects characteristic of catalytic hydrogenation are the following: (1) mechanical inconveniences associated with the handling of pressure equipment and the preparation of Raney nickel catalyst; (2) an often-noted tendency for over-reduction leading to alkanes in place of the desired alcohols; (3) the low degree of stereochemical specificity of the reaction, depending as it does on catalyst surface uniformity and other factors equally difficult to control.

There have been used essentially only three catalysts for the hydrogenation of ethylene oxides: nickel, palladium on charcoal, and platinum black. Solvents normally employed include ethanol with nickel, and ethanol, ethyl acetate, or acetic acid with the others. Reduction over platinum or palladium catalysts is usually conducted at room temperature and low pressure, whereas nickel catalysts have been employed in autoclaves at temperatures ranging from 30° to nearly 200° and high pressures. For excellent general discussions of catalytic reduction any of several outstanding sources[14, 961, 1031] may be consulted.

According to Sabatier and Durand,[1515] ethylene oxide readily undergoes isomerization to acetaldehyde on heating at 125–150° over a nickel catalyst in the presence of hydrogen. By way of comparison, ethylene oxide[1227] reportedly does not isomerize below 400° in the absence of catalyst though alumina lowers the isomerization temperature to about 200°.[859] Reduction of propylene oxide,[516] *iso*butylene oxide,[517] 2,3-epoxybutane,[517] and 1,2-epoxy-2,4,4-trimethylpentane[663] is reported to give only primary alcohols when conducted at elevated temperatures over nickel catalysts (Eq. 340), in marked contrast with the results obtained with lithium aluminum hydride (see section **IV.1.***C*). The formation of primary alcohols is readily explained if one

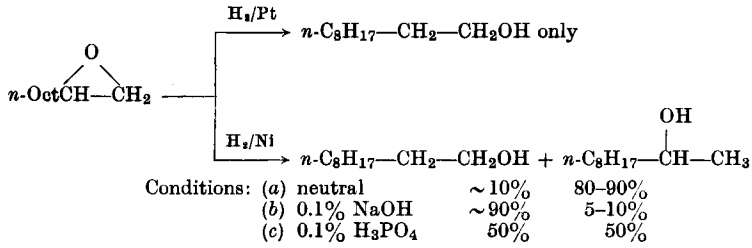


(340)

$R' = R'' = R''' = H$
$R' = CH_3$; $R'' = H$, CH_3; $R''' = H$
$R' = R''' = CH_3$; $R'' = H$
$R' = tert\text{-}C_4H_9$; $R'' = CH_3$; $R''' = H$

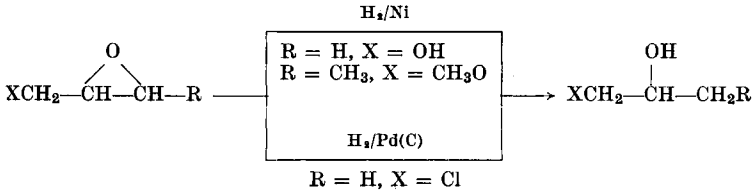
assumes preliminary isomerization of epoxides to the corresponding aldehydes before reduction.

Newman and co-workers[1240] published in 1949 a careful study of the variation in production composition when 1,2-epoxyoctane was reduced over Raney nickel at 150° under neutral, alkaline, and acidic conditions. Their results, summarized in Eq. (341), are rather striking.



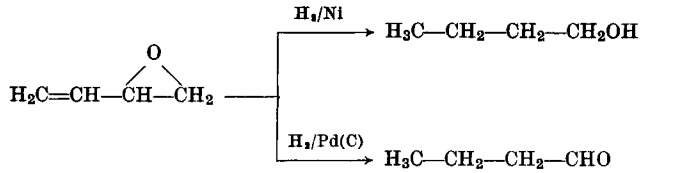
(341)

The presence of a polar atom on the carbon directly attached to an ethylene oxide ring exerts a dramatic influence on the course of reduction (Eq. 342). Epichlorohydrin[511] and glycidol,[967] for instance, yield the corresponding secondary alcohols over nickel and palladium on charcoal respectively. By contrast, propylene oxide is reported to give only *n*-propanol over nickel.[516, 517] Similarly, addition of hydrogen to 2,3-epoxy-1-methoxybutane over nickel occurs at the site furthest from the polar methoxyl substituent as shown.[1812]



(342)

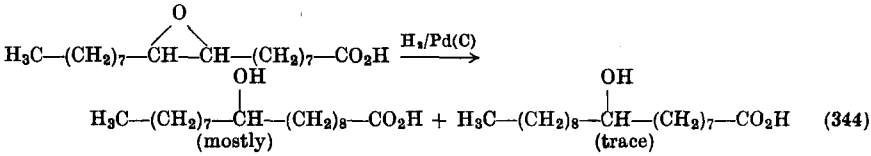
Reduction of 1,2-epoxy-3-butene over Raney nickel at 76° gives *n*-butanol, whereas palladium on charcoal merely causes reduction of the double bond and isomerization to *n*-butyraldehyde[785] (Eq. 343). Reduction of 3-chloro-1,2-epoxy-3-butene over palladium on calcium



(343)

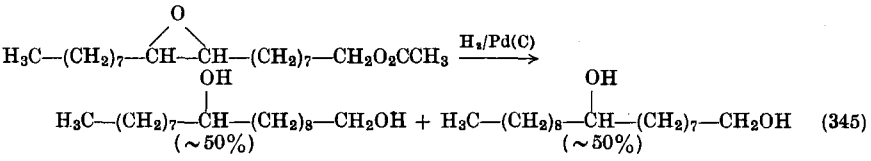
carbonate, on the other hand, reportedly gives mainly 3-chloro-3-buten-1-ol.[1994]

A considerable amount of work has been devoted to the catalytic reduction of fatty acid and fatty alcohol epoxides. Hydrogenation of *cis*- and *trans*-9,10-epoxyoctadecanoic acid, for example, has been reported[1082, 1367, 1488] to give isomeric 10-hydroxyoctadecanoic acids exclusively (Eq. 344). Preferential attack of hydrogen on $C_{(9)}$ was



(344)

attributed to the electron-withdrawing character of the carboxyl group. It is remarkable that this effect should be sufficiently high, in spite of the substantial distance separating the epoxide and carboxyl functions, to cause a significant difference in the electron densities at $C_{(9)}$ and $C_{(10)}$.[1488] It has been stated recently, on the other hand, that some isomeric 9-hydroxyoctadecanoic acids are in fact also formed, so that the hydrogenation may not be quite so specific as was once believed.[893] Nevertheless, *cis*- and *trans*-9,10-epoxyoctadecyl acetates (Eq. 345), in which the electron-attracting influence of a terminal

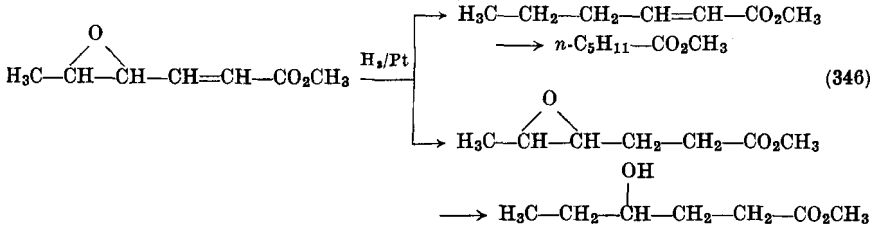


(345)

carboxyl group is absent, give approximately equal mixtures of the corresponding 9- and 10-hydroxyoctadecanols.[555] Recent studies involving *cis*- and *trans*-6,7-epoxy and 13,14-epoxy octadecanoic acids have been conducted also, but it is not known as yet whether reductive cleavage occurs uniquely at the carbon nearest the carboxyl function or not.[893]

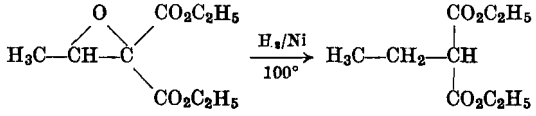
Reduction of methyl 4,5-epoxy-2-hexenoate over platinum has been reported to give methyl 4-hydroxyhexanoate and methyl hexanoate itself.[1775] Incomplete reduction likewise yields these products, but in addition also methyl 2-hexenoate. It was concluded that two parallel processes are operative (Eq. 346). The first involves reduction of the double bond, followed by opening of the epoxide ring; the second, direct

removal of oxygen, followed by reduction of the remaining double bond.



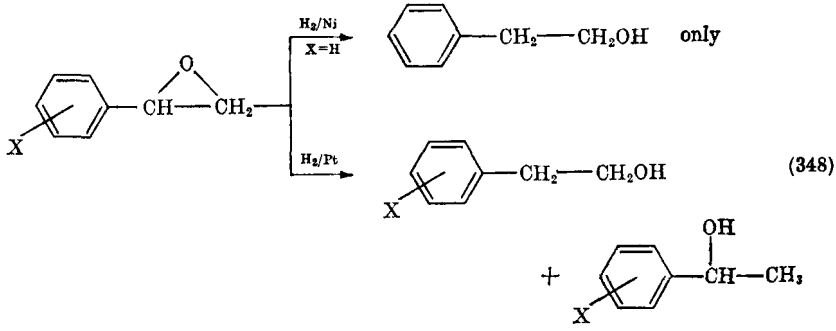
(346)

Hydrogenation of 1,1-dicarbethoxy-1,2-epoxypropane over Raney nickel leads to the formation of 1,1-dicarbethoxypropane exclusively[1310] (Eq. 347).



(347)

Styrene oxide is reduced selectively to β-phenylethanol over Raney nickel.[517, 1240] On the other hand, substituted derivatives containing electron-withdrawing groups yield substantial proportions of secondary alcohols,[1300] as shown in Eq. (348). These electronic effects

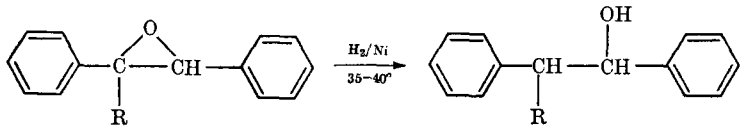


(348)

X =	H	CH$_3$	*m*-CH$_3$O	*p*-Br
	100%	100%	88%	82%
	0%	0%	12%	18%

are considered to militate against any mechanism involving simultaneous addition of two hydrogen atoms per molecule, and to indicate instead participation of an intermediate exhibiting appreciable carbonium ion character.[1300]

Reduction of α-methylstilbene oxide,[920] α-benzylstilbene oxide,[920] triphenylethylene oxide,[1817] and others[1817] has been carried out over Raney nickel at relatively moderate temperatures (Eqs. 349 and 350).

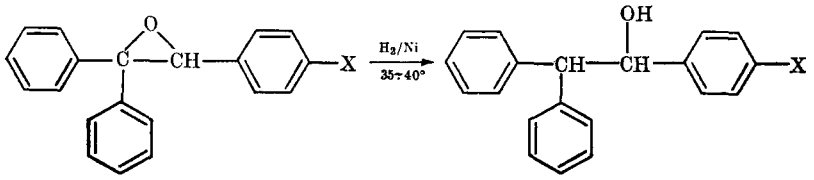


(349)

R = CH_3, $C_6H_5CH_2$

No evidence of aryl migration was detectable, although preliminary hydride shift preceding reduction could of course not be ruled out.

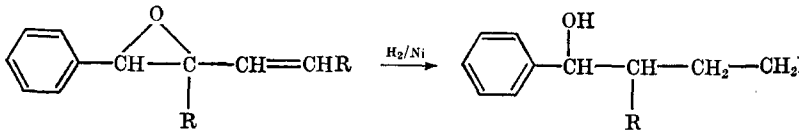
Similarly, hydrogenation of the 1-phenyl-2-vinylethylene oxides gave no evidence of the phenyl-migration known to occur on thermal



(350)

X = H, *p*-CH_3O

isomerization of these substances.[7, 445] The products isolated, however, were secondary benzylic alcohols exclusively (Eq. 351). Reduction of the double bond apparently follows that of the epoxide ring, otherwise the isomeric alcohol might be anticipated.

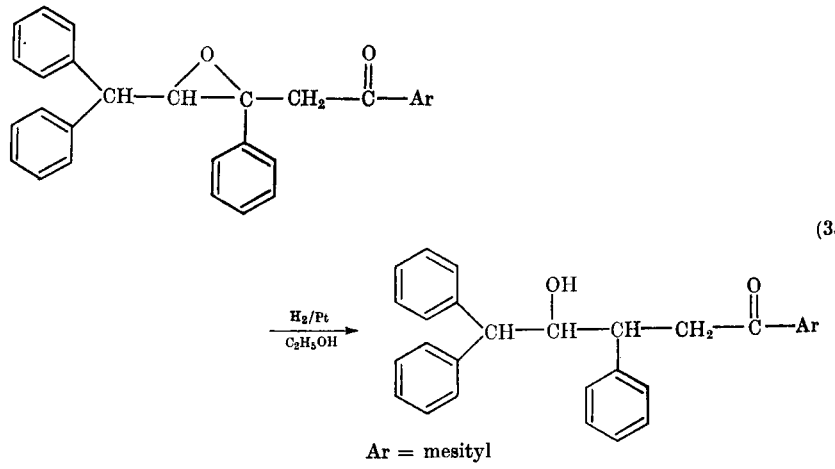


(351)

R = H, CH_3

Kohler and Tishler[959] reduced 2,3-epoxy-4-mesitoyl-1,1,3-triphenylbutane over platinum, and obtained an alcohol formulated as shown in Eq. (352). Here addition of hydrogen again occurs preferentially at the benzylic, or most-highly substituted, epoxide carbon. Steric hindrance evidently prohibits reduction of the carbonyl function.

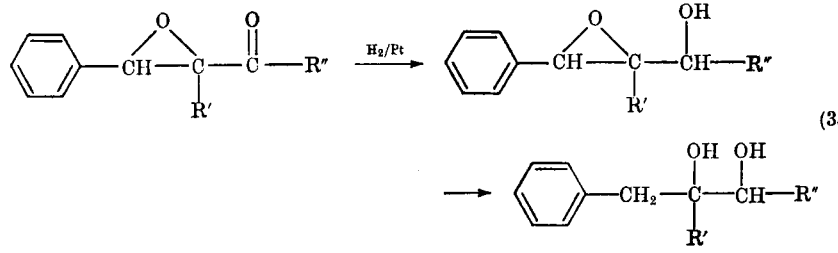
Benzalacetone oxide and several related substances have been hydrogenated over platinum.[1708] In these instances reduction of the



(352)

Ar = mesityl

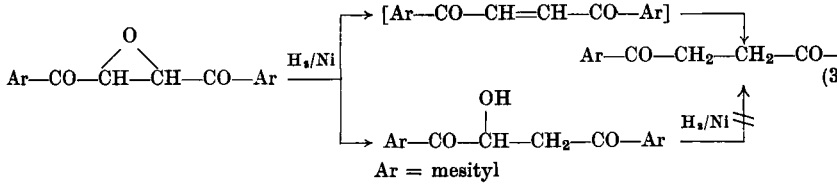
carbonyl function is believed to precede reduction of the epoxide ring. The products ultimately formed are 1,2-diols (Eq. 353).



(353)

R′ = H; R″ = CH_3, C_2H_5
R′ = R″ = CH_3

Similarly, hydrogenation of 1,2-dimesitoylethylene oxide over Raney nickel was reported by Lutz and Wood[1057] to give approximately equal amounts of 1,2-dimesitoylethanol and 1,2-dimesitoylethane (Eq. 354). The authors were of the opinion that the latter was formed separately by way of 1,2-dimesitoylethylene. In support of this

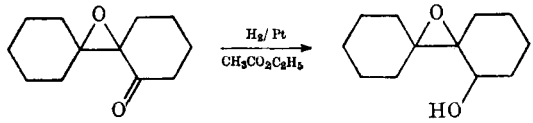


(354)

Ar = mesityl

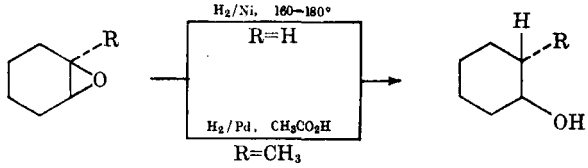
argument, they showed 1,2-dimesitoylethanol to be incapable of undergoing reduction under these conditions.

Hydrogenation of the α,β-epoxy ketone shown in Eq. (355) over platinum in ethyl acetate was found by Reese[1441] to leave the epoxide ring intact. Tetrasubstituted ethylene oxides are notoriously unreactive toward most reagents, and catalytic reduction proves to be unexceptional in this respect.



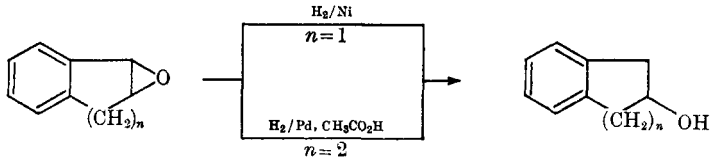
(355)

Cyclohexene oxide and several methyl-substituted analogs have been reduced catalytically over nickel at 160–180°, or over platinum in acetic acid at lower temperatures.[254, 255, 966] It is noteworthy that 1,2-epoxy-1-methylcyclohexane yields *trans*-2-methylcyclohexanol, inasmuch as lithium aluminum hydride is known to give the isomeric tertiary alcohol 1-methylcyclohexanol.[1186, 1195, 1196] Also significant, however, is the fact that addition appears to be of the *cis* type, incoming hydrogen and departing oxygen being on the same side of the cyclohexane ring (Eq. 356).



(356)

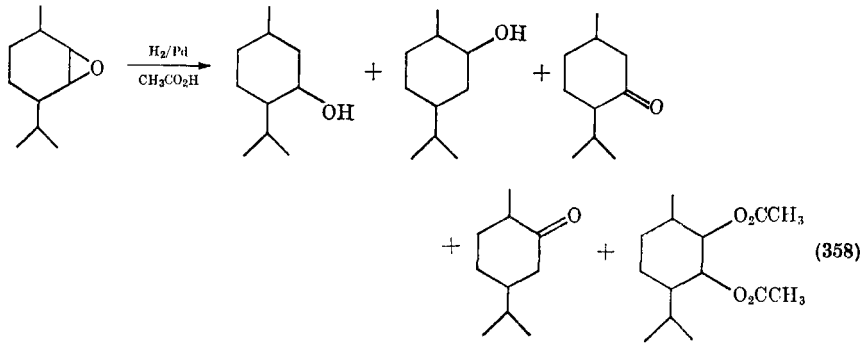
Hydrogenation of indene oxide and 1,2-epoxytetralin has been shown[837, 966, 1833] to proceed exclusively by hydrogen attack on the benzylic epoxide carbon (Eq. 357).



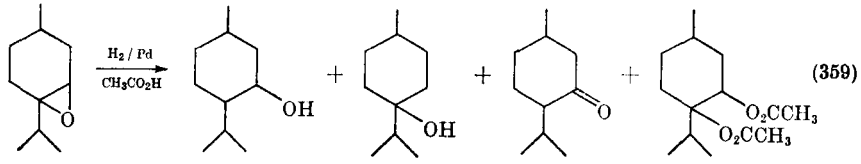
(357)

Russian workers[1366] have conducted a thorough investigation of the composition of product mixtures derived from 1,2-, 2,3-, and 3,4-epoxymenthanes by hydrogenation over palladium in acetic acid.

Surprisingly complex mixtures were obtained, consisting of isomeric alcohols, ketones, acetolysis products, and hydrocarbons. The accompanying formulas (Eqs. 358 and 359) take no account of stereochemistry,



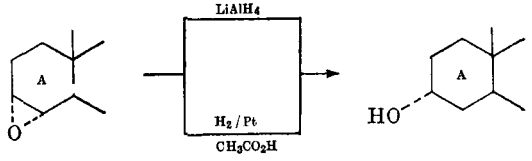
(358)



(359)

inasmuch as the stereochemical homogeneity of the epoxides was unfortunately not specified by the authors.

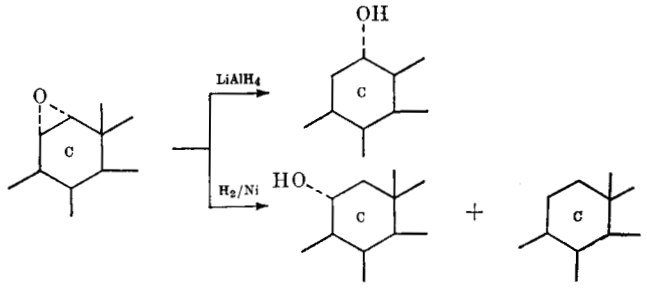
Catalytic reduction of steroid epoxides received considerable attention before the development of complex metal hydride reducing agents. Hydrogenation of 3α,4α-epoxy steroids over platinum in acetic acid (Eq. 360), for example, gives rise to a mixture of 3α-hydroxy and 3α-acetoxy steroids.[604] Reductive cleavage thus occurs in the same direction as with lithium aluminium hydride in this particular instance —*i.e.* it gives an axial alcohol.



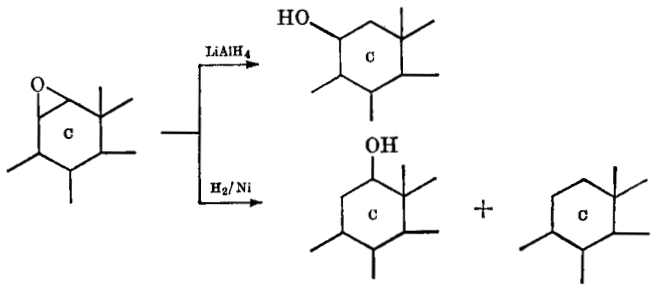
(360)

On the other hand, 11α,12α- and 11β,12β-epoxy steroids (Eqs. 361 and 362) have been reported[1928] to yield on hydrogenation over Raney nickel the corresponding 12β- and 11α-hydroxy derivatives, in contrast

with what takes place with lithium aluminum hydride. In addition to alcohols, however, there are also isolated appreciable quantities of completely reduced hydrocarbons.

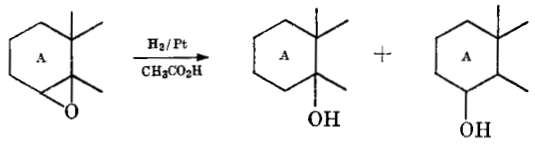


(361)



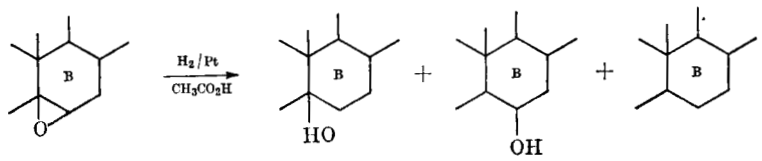
(362)

Lack of specificity of a different sort is exhibited by 4β,5β- and 5β,6β-epoxy steroids (Eqs. 363 and 364), which yield mixtures of isomeric alcohols on reduction over platinum in acetic acid.[888, 1375, 1377,



(363)

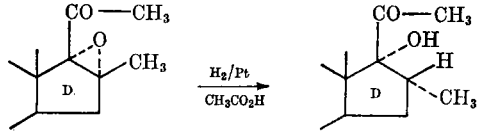
1379, 1512, 1774] By contrast, 5α,6α-epoxy steroids tend to give only one alcohol.[888, 1372, 1379, 1512, 1774] Similar differences between 5α,6α- and



(364)

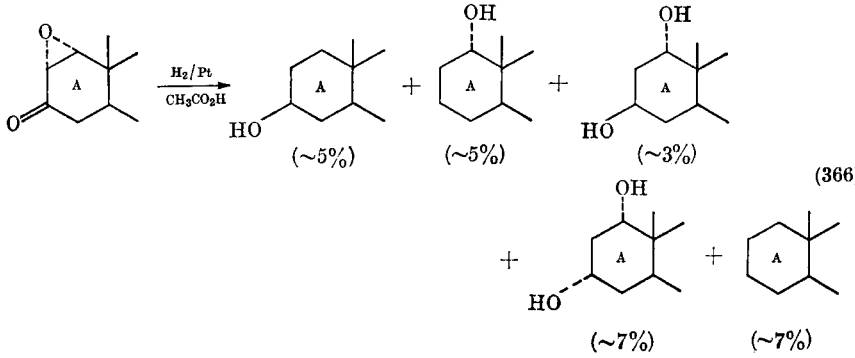
5β,6β-epoxy steroids have been noted on reductive cleavage with lithium aluminum hydride (see section **IV.1.***C.*).

Catalytic hydrogenation of 16α,17α-epoxy-16β-methyl steroids has been found[1254] to involve hydrogen attack at $C_{(16)}$ exclusively (Eq. 365).



(365)

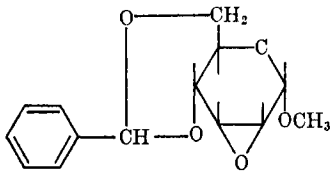
Perhaps no example can better illustrate the defects associated with catalytic reduction in epoxide chemistry than a hydrogenation reported by Striebel and Tamm,[1663] involving the 1α,2α-epoxy-3-keto steroid shown below (Eq. 366). It is seen that the anticipated diol mixture constitutes a mere ten percent of the total product. The remainder has fallen prey to over-reduction.



(366)

Also may be cited several illustrations from the field of sugar chemistry. The 2,3-anhydro-4,6-*O*-benzylidene α-glycosides of D-allose, D-mannose, D-talose, and D-gulose (Eqs. 367–370) yield on catalytic reduction over Raney nickel the corresponding desoxy derivatives,[210, 876, 1414] whereas lithium aluminum hydride yields diametrically opposite results[718, 1414] (see section **IV.1.***C.*).

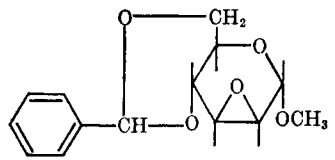
Along the same line, on the other hand, methyl 2,3-anhydro-β-L-riboside gives rise to a mixture of methyl 3-desoxy-β-L-xyloside and methyl 2-desoxy-β-L-arabinoside (Eq. 371), of which the 3-desoxy sugar is the principal constituent.[1206] Analogous results were obtained separately in the D-series by other investigators[302] using lithium aluminum hydride.



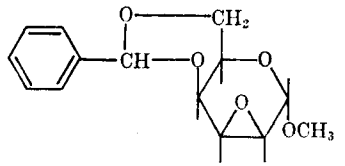
(54%) (367)

+

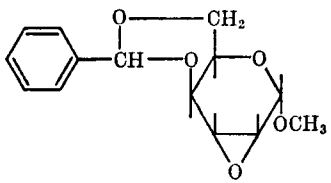
(3·5%)



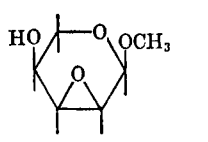
(368)



(369)

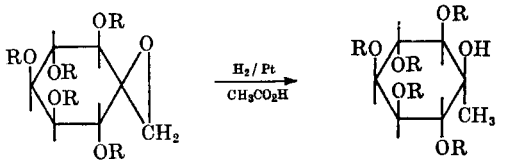


(370)



(mostly) + (371)

In the inositol series, finally, Posternak[1399] has utilized catalytic hydrogenation to effect the transformation shown in Eq. (372).



(372)

R = CH_3CO

A recent paper by Kwiatek and co-workers[1995] discloses the use of a homogeneous catalysis system for the hydrogenation of epoxides. Reduction of cyclohexene oxide to cyclohexanol, and of styrene oxide to 2-phenylethanol, was carried at atmospheric pressure, using $K_3[Co(CN)_5]$ to catalyze the reaction.

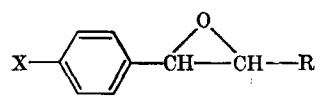
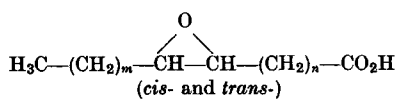
C. Reduction with Complex Metal Hydrides

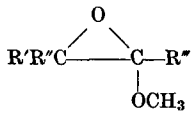
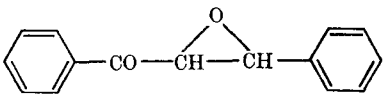
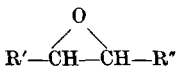
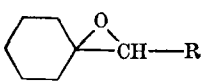
Reductive fission of ethylene oxide rings can best be accomplished at present by using lithium aluminum hydride or one of the other complex metal hydrides. Older literature methods, especially catalytic hydrogenation over Raney nickel, have been shown to be less desirable for a variety of reasons. Among these are the gentleness and directional selectivity of complex metal hydrides, as well as the fact that reduction usually ceases at the alcohol stage, whereas more stringent processes like metal reduction or catalytic hydrogenation frequently lead to deoxygenated products (see sections **IV.1.***A.* and **IV.1.***B.*).

General aspects of the lithium aluminum hydride reduction of epoxides have been discussed briefly by Eliel[490] and also by Parker and Isaacs[1301] within a broader context of nucleophilic reactions. Excellent reviews covering the literature up to 1955 are those of Brown,[252] Gaylord,[623] and also Micovic and Mihailovic.[1155] No attempt to encompass fully the voluminous literature of this topic will be made in the present article, although a representative sampling has been collected in Table 9, to which reference may be made for further details.

According to Trevoy and Brown,[1764] who were among the first to investigate this reaction, reduction of epoxides with lithium aluminum hydride is a bimolecular nucleophilic substitution of the classical S_N2 type, involving backside approach and Walden inversion. The attacking species is believed to be the aluminohydride ion AlH_4^- at

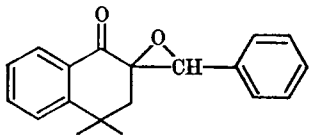
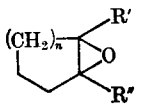
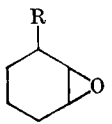
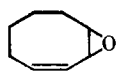
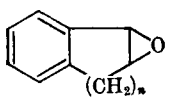
TABLE 9. Reduction of Epoxides with Complex Metal Hydrides

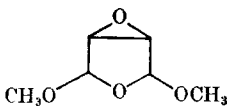
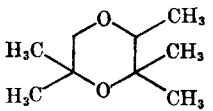
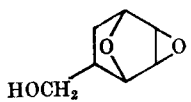
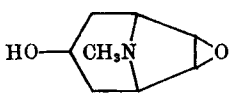
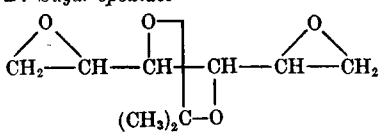
Compound		Reference
A. Acyclic epoxides		
	$R' = R'' = R''' = R'''' = H$	360
	$R' = CH_3$; $R'' = R''' = R'''' = H$	492
	$R' = C_2H_5$; $R'' = R''' = R'''' = H$	596
	$R' = R'' = CH_3$; $R''' = R'''' = H$	492
	$R' = R'' = R''' = CH_3$; $R'''' = H$	492
	$R' = R'' = R''' = R'''' = CH_3$	492, 774
	$R' = R'' = CH_3$; $R''' = iso\text{-}C_3H_7$; $R'''' = H$	492
	$R' = neo\text{-}C_5H_{11}$; $R'' = CH_3$; $R''' = R'''' = H$	492
	$R' = R'' = neo\text{-}C_5H_{11}$; $R''' = R'''' = H$	778
	$R' = R''' = CH_3$; $R'' = R'''' = H$	734, 1004
	$R' = C_6H_5$; $R'' = R''' = R'''' = H$	491, 492, 1261, 1764
	$R' = R''' = C_6H_5$; $R'' = R'''' = H$	397, 526
	$R' = R'' = R''' = C_6H_5$; $R'''' = H$	492, 1996
	$R' = R'' = R''' = R'''' = C_6H_5$	492
	R = H; X = *p*-Br, *p*-NO_2, *p*-CH_3O, *p*-CH_3, *m*-CH_3O	491, 492, 594, 596, 1261, 1299, 1764
	R = C_6H_5; X = *p*-Cl, *p*-CH_3	397, 526
 (*cis*- and *trans*-)	$m = 4$, $n = 10$ $m = 7$, $n = 7$ $m = 11$, $n = 3$	893

Compound		Reference
	$R' = R'' = CH_3, C_2H_5, C_6H_5$; $R''' = C_6H_5$ $R' = H$; $R'' = CH_3$; $R''' = C_6H_5$ $R' = n\text{-}C_5H_{11}$; $R'' = R''' = H$	1630
		758, 1764
	$R' = H$; $R'' = ClCH_2$ $R' = H$; $R'' = CH_3CHBr$ $R' = H$; $R'' = F_3C$ $R' = H$; $R'' = (C_2H_5O)_2CH$ $R' = H$; $R'' = CHO$ $R' = H$; $R'' = CH_2{=}CH$	1764 1812 1064 1882 1847 595, 1764
	$R' = H$; $R'' =$  $R' = CH_3$; $R'' = BrCH_2$ $R' = CH_3$; $R'' = CH_3OCH_2$ $R' = CH_3$; $R'' = C_2H_5O_2C$ $R' = F_3C$; $R'' = C_2H_5O_2C$	1843 1812 1812 1794 1794
B. Semicyclic and alicyclic epoxides		
	$R = H, CH_3$	266, 1186, 1195, 1196
	$R = C_2H_5O_2C$	157, 1196

(*Table continued*)

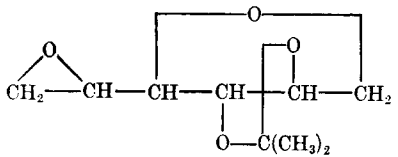
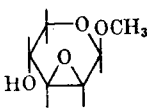
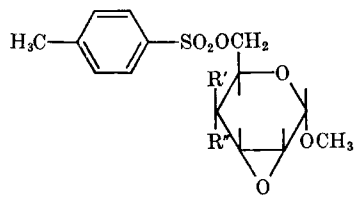
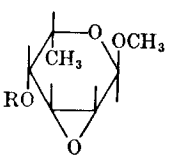
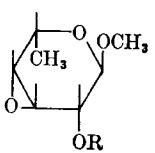
TABLE 9 (*continued*)

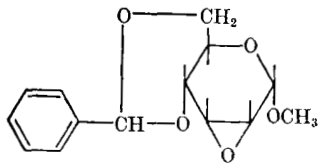
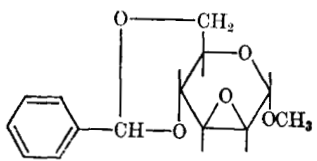
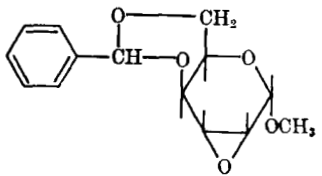
Compound		Reference
		378
	$n = 1$; R′ = R″ = CH_3	1764
	$n = 2$; R′ = R″ = H, CH_3	1186, 1188, 1195
	$n = 2$; R′ = H; R″ = CH_3, CH_3CO_2, Cl, CN, $(CH_3)_2N$	1570, 1764
	R = *cis*-Cl	1186
	R = *cis*-OH	741
	R = *trans*-OH	741
	R = *trans*-CH_3O; *trans*-C_2H_5O	1002, 1186, 1188, 1195
		349
	$n = 3$	363
	$n = 4$	841

Compound	Reference
C. Heterocyclic epoxides	
	1566, 1997, 1998
	1519
	983
	553
D. Sugar epoxides	
	1843

(*Table continued*)

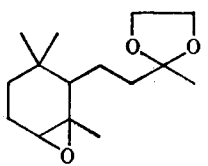
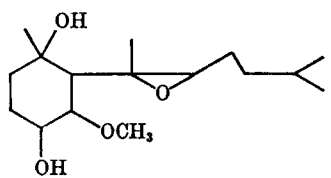
TABLE 9 (*continued*)

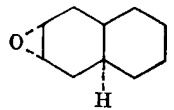
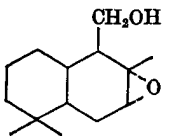
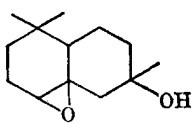
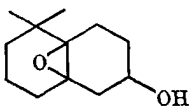
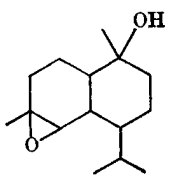
Compound		Reference
		559
		26
	R′ = $CH_3C_6H_4SO_2O$; R″ = H R′ = H; R″ = *p*-$CH_3C_6H_4SO_2O$	211, 213
 and 	R = H, CH_3	302

Compound	Reference
 	1414
	718
E. Steroid epoxides	
1α,2α-Epoxy steroids	740, 1371, 1663
2α,3α- and 2β,3β-Epoxy steroids	336, 603, 1302, 1371, 1575, 1825, 1903
3α,4α- and 3β,4β-Epoxy steroids	604
A-Nor-3β,4β-epoxy steroids	1542
4α,5α- and 4β,5β-Epoxy steroids	278, 330, 741, 889, 1372, 1374, 1376, 1377, 1469, 1696, 1896, 1973
5α,6α- and 5β,6β-Epoxy steroids	889, 1372, 1374, 1469, 1572, 1696
B-Nor-5α,6α-steroids	420

(*Table continued*)

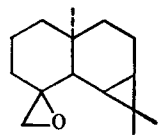
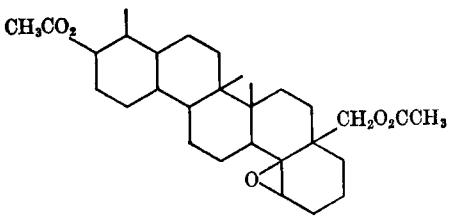
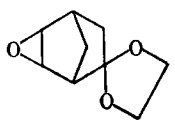
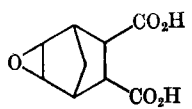
TABLE 9 (*continued*)

Compound	Reference
6α,7α- and 6β,7β-Epoxy steroids	353, 354, 858, 869, 870
7α,8α-Epoxy steroids	880
8α,14α-Epoxy steroids	540
9α,11α-Epoxy steroids	453, 458, 543
11α,12α- and 11β,12β-Epoxy steroids	604, 950
16α,17α-Epoxy steroids	12, 390, 392, 458, 762, 1254, 1373, 1514
17α,20-Epoxy steroids	600, 996, 1259, 1370, 1601, 1823
20,21-Epoxy steroids	1518
F. Miscellaneous terpenes	
	1653
	1694, 1695

Compound	Reference
	1901
	36
 and 	259
	756, 1182

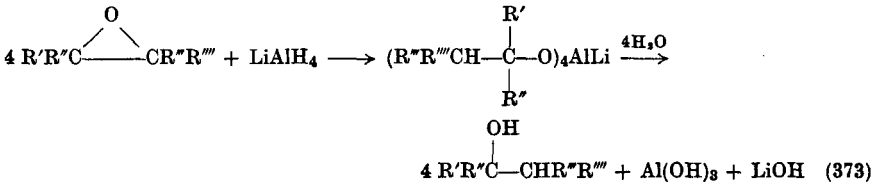
(*Table continued*)

TABLE 9 (*continued*)

Compound	Reference
	260
	91
G. Miscellaneous epoxides	
	1964
 (No reaction)	1999, 2000

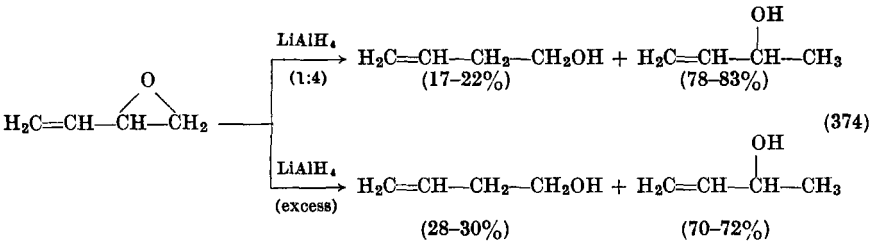
Compound	Reference
	2001
	1966

the outset, but to gradually involve also various alkoxyaluminohydride ions $AlH_{4-n}(OR)_n$, where $n = 1, 2, 3$. The latter can function equally well or better as hydride donors, although they exhibit greater steric requirements in certain instances. The overall reaction may be written as indicated in Eq. (373), decomposition of the 'saturated' alkoxyaluminohydride complex with water giving the desired product.



$$4\,R'R''C(O)CR'''R'''' + LiAlH_4 \longrightarrow (R''R''''CH{-}C(R')(R'')O)_4AlLi \xrightarrow{4H_2O} 4\,R'R''C(OH){-}CHR'''R'''' + Al(OH)_3 + LiOH \quad (373)$$

Evidence for the significant role of the alkoxyaluminohydride ions postulated by Trevoy and Brown[1764] has been secured experimentally by Fuchs and Vander Werf,[595] who examined the effect on product composition of altering the lithium aluminum hydride–ethylene oxide ratio. In the reaction of 1,2-epoxy-3-butene with approximately stoichiometric quantities of reducing agent, the principal product, 1-buten-3-ol, was accompanied by a certain amount of the isomeric substance 1-buten-4-ol (Eq. 374). The proportion of the latter increased



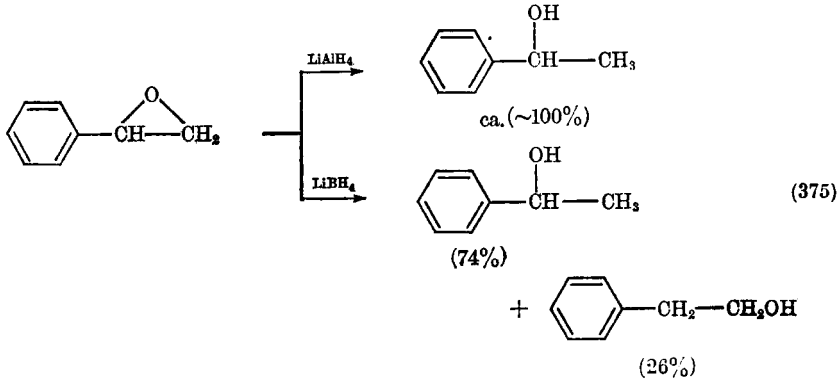
$$H_2C{=}CH{-}CH(O){-}CH_2 \xrightarrow[(1:4)]{LiAlH_4} H_2C{=}CH{-}CH_2{-}CH_2OH\ (17\text{–}22\%) + H_2C{=}CH{-}CH(OH){-}CH_3\ (78\text{–}83\%) \quad (374)$$

$$H_2C{=}CH{-}CH(O){-}CH_2 \xrightarrow[(excess)]{LiAlH_4} H_2C{=}CH{-}CH_2{-}CH_2OH\ (28\text{–}30\%) + H_2C{=}CH{-}CH(OH){-}CH_3\ (70\text{–}72\%)$$

appreciably, however, when a large excess of lithium aluminum hydride was used. This effect was attributed to an increased concentration of the sterically less discriminating species AlH_4^- ion, which can approach more effectively the slightly hindered secondary epoxide carbon than can the larger alkoxyaluminohydride ions. Similarly, reduction of styrene oxide with lithium aluminum hydride (Eq. 375) gave almost none of the sterically unfavored product, 2-phenylethanol, whereas the less bulky reagent lithium borohydride allowed isolation of this product in appreciable quantities.[596]

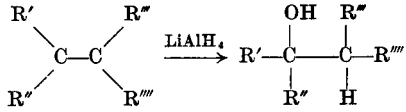
The importance of steric effects in the lithium aluminum hydride

reduction of epoxides has been further emphasized by Eliel and coworkers,[491, 492, 2002] who investigated the product composition obtained



(375)

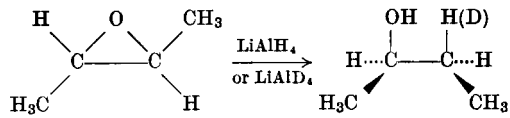
with several alkyl-substituted ethylene oxides (Eq. 376). Attack was found in all cases to take place almost completely on the less-hindered carbon atom of the epoxide ring, and the overall yield was found to diminish sharply with increasing alkyl-substitution.



(376)

$R' = CH_3$; $R'' = R''' = R'''' = H$
$R' = R'' = CH_3$; $R''' = H$; $R'''' = H$, *iso*C_3H_7, *tert*-C_4H_9
$R' = R'' = R''' = CH_3$; $R'''' = H$, CH_3
$R' = R'' = H$; $R''' = CH_3$; $R'''' =$ *neo*C_5H_{11}

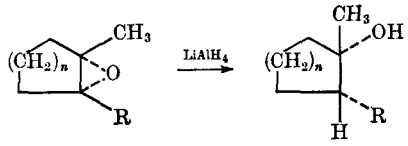
The stereochemically specific character of lithium aluminum hydride reduction was first indicated by the conversion of *trans*-2,3-epoxybutane into optically active 2-butanol (Eq. 377), reported by Leroux and Lucas,[1007] and conducted recently in the same manner with lithium aluminum deuteride by Helmkamp and Schnautz.[734]



(377)

Further evidence of the stereospecificity of this reaction lies in results secured with certain simple alicyclic epoxides (Eq. 378) such as 1-methylcyclohexene oxide[1186, 1187, 1195] and 1,2-dimethylcyclohexene

oxide,[1764] which yield 1-methylcyclohexanol and *trans*-1,2-dimethylcyclohexanol respectively. Similar results have been reported in the cyclopentane series.[1764]



(378)

$n = 1$; R = CH_3
$n = 2$; R = H, CH_3

Similarly, reduction of the spiroepoxide 1-oxabicyclo[5.2]octane with lithium aluminum hydride (Eq. 379) gives 1-methylcyclohexanol.[1186, 1187, 1195] 2-Methyl-1-oxabicyclo[5.2]octane reportedly yields methyl cyclohexyl carbinol according to Mousseron and co-workers,[1186, 1187, 1195, 1196] or 1-ethylcyclohexanol according to Burgstahler.[266] The latter alternative appears more consistent with the rest of the literature, since it involves attack by a hydride donor on the less-substituted epoxide carbon atom.



(379)

R = H, CH_3

A number of epoxides containing polar substituents have been opened with lithium aluminum hydride (Eq. 380). Epichlorohydrin, for example, gives 2-propanol.[1764] According to Trevoy and Brown,[1764] epoxide ring reduction precedes hydrogenolysis of the C—Cl bond, but this should not be regarded as an inviolable rule. Substances in which the epoxide ring is not terminal, *e.g.* 1-bromo-2,3-epoxybutane,[1812] may suffer loss of halogen before ring-opening, so that the polar effect of the polar substituent is lost anyhow. Other related simple epoxides possessing electronegative substituents are shown in Table 9.

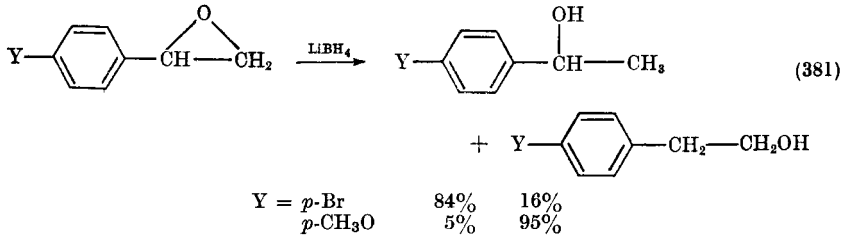


(380)

R = H, X = Cl
R = CH_3, X = Br

That polar substituents can affect the direction of reductive cleavage has been demonstrated by Fuchs and co-workers[594, 596, 1299]

in a study of the reaction of lithium borohydride with various substituted styrene oxides. It was found, for example, that a dramatic reversal of product composition occurs in going from *p*-bromostyrene oxide to *p*-methoxystyrene oxide, as shown in Eq. (381). The enormous preference for attack on the benzylic carbon atom of the latter is attributable to the capacity of the *p*-methoxyl to stabilize by resonance an incipient positive charge at that position in the transition state.[596] The ability of the *p*-bromo substituent to participate in such a manner is evidently not sufficient to offset the preference of the hydride donor for the least-hindered reaction site.



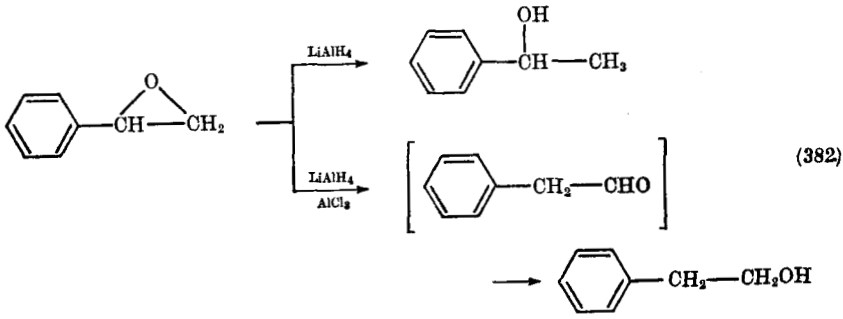
(381)

Y = *p*-Br	84%	16%
p-CH_3O	5%	95%

The directive influence of the *p*-nitro group is likewise evident in the reaction of *p*-nitrostyrene oxide, which gives, however, a preponderance of the sterically least-favored product.[596] This is difficult to accommodate, unfortunately, with the view that the transition state for the reaction of aryl-substituted epoxides with nucleophiles involves more bond breaking than bond forming—*i.e.* that the benzylic epoxide carbon atom possesses a certain degree of carbonium ion character in the transition state—since a *p*-nitro group should destabilize such a transition state and thereby favor normal product. Because the *p*-nitro group does not obey the otherwise satisfactory Hammett-type correlation between the proportion of 'abnormal' product and σ-values for the other substituents examined, Fuchs[594] has concluded that *p*-nitrostyrene oxide cannot be compared mechanistically with other styrene oxides, but should be treated as a special case.

The use of Lewis acids, such as magnesium bromide or aluminum chloride, to cause a change in product composition has been investigated by Park and Fuchs,[1299] and also by Eliel and coworkers.[491, 492, 2002] Evidence secured by the latter with lithium aluminum hydride–aluminum chloride points to preliminary epoxide isomerization to a carbonyl compound, followed by reduction. With styrene oxide (Eq. 382), for instance, isomerization with aluminum chloride leads to phenylacetaldehyde, which on further reaction yields

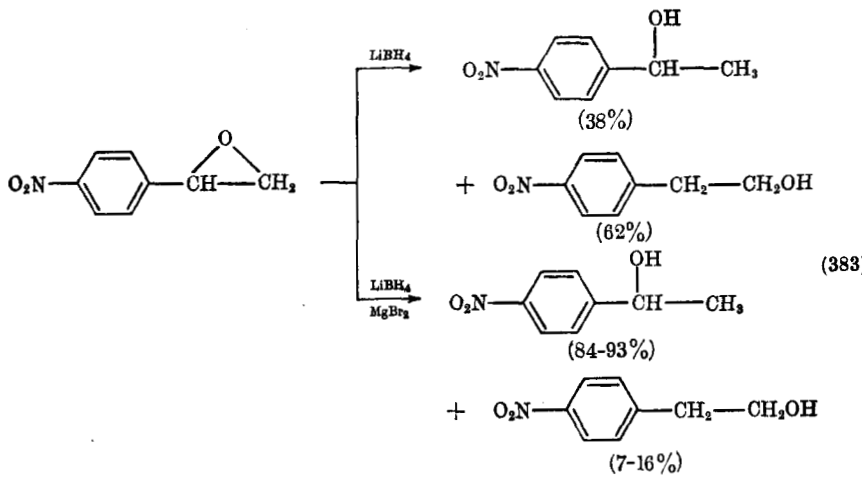
the 'abnormal' product 2-phenylethanol.[492] In the absence of aluminum chloride reduction proceeds normally, phenyl methyl carbinol being formed almost exclusively.[492, 1261, 1764] Such a product inversion



(382)

effect was likewise noted by Eliel and co-workers[491, 492] for a series of methyl-substituted ethylene oxides, as well as for triphenylethylene oxide.[2002]

Although Park and Fuchs[1299] found the same trend in the reduction of *p*-methylstyrene oxide with lithium borohydride–magnesium

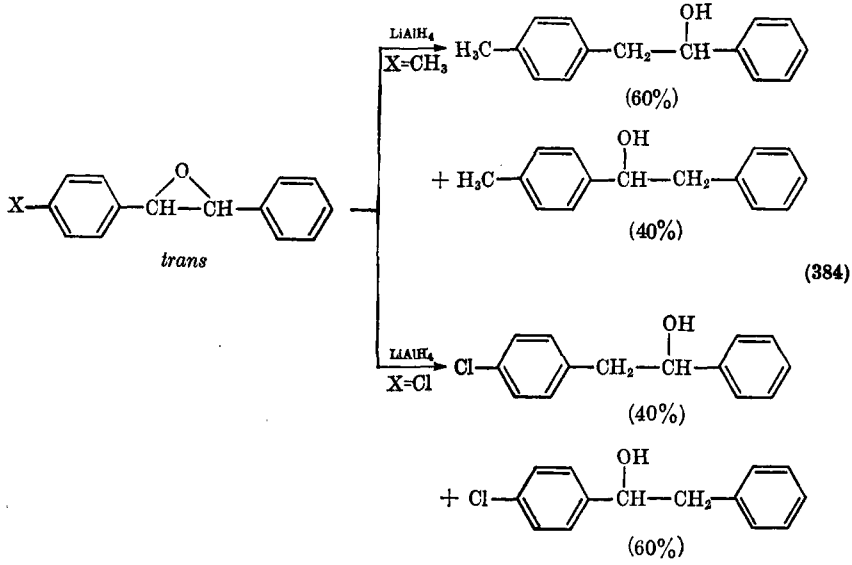


(383)

bromide, the *p*-nitro derivative (Eq. 383) led, surprisingly, to an increased proportion of normal product.[594]

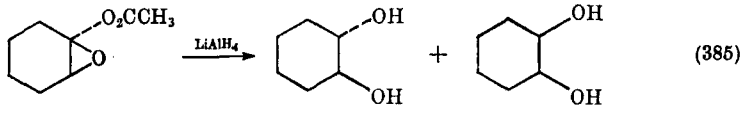
Feldstein and Vander Werf[526] have published evidence of a similar nature dealing with *p*-chloro-*trans*-stilbene oxide and *p*-methyl-*trans*-stilbene oxide (Eq. 384). The electron-releasing methyl substituent

apparently favors formation of phenyl *p*-methylbenzyl carbinol, whereas the electron-withdrawing chlorine substituent favors benzyl *p*-chlorophenyl carbinol. More highly aryl-substituted epoxides become



progressively less reactive toward lithium aluminum hydride, tetraphenylethylene oxide being actually stable toward this reagent.

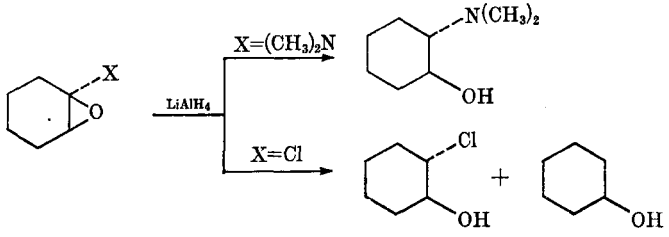
Several alicyclic epoxides substituted with polar atoms have been reduced with lithium aluminum hydride, largely by Mousseron and coworkers, although subsequent investigators[266, 1570] have expressed disagreement with certain of their results. Experimental difficulties in



the preparation of the epoxides themselves and in the isolation, purification, and characterization of reduction products should inspire caution in acceptance of results published in this area of epoxide chemistry.[490, 1301]

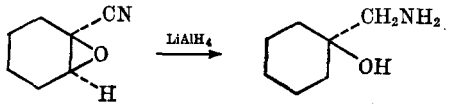
It is reported that 1-acetoxycyclohexene oxide yields a mixture of *cis*- and *trans*-1,2-cyclohexanediol (Eq. 385) on treatment with lithium

aluminum hydride.[1186, 1188, 1195, 1570] On the other hand, 1-chlorocyclohexene oxide is reported to give only *cis*-2-chlorocyclohexanol (Eq. 386), together with the predominant product cyclohexanol



(386)

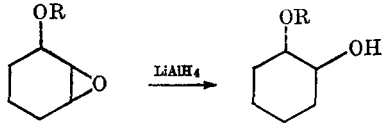
itself,[1186, 1188, 1195] whereas 1-*N*,*N*-dimethylaminocyclohexene oxide allegedly gives only *trans*-2-*N*,*N*-dimethylaminocyclohexanol.[1186–1188, 1195] It appears, therefore, that these polar substituents promote reductive fission of the C—O bond nearest to them, but the stereochemical aspects of the reaction remain obscure at this time. By



(387)

contrast, 1-cyanocyclohexene oxide suffers cleavage of the C—O bond furthest from the nitrile group,[1186–1188, 1195] giving 1-aminomethylcyclohexanol (Eq. 387).

Reduction of 2,3-epoxy-1-methoxycyclohexane[947] and 2,3-epoxy-1-ethoxycyclohexane[1186, 1188, 1195] leads to *trans*-2-methoxy- and *trans*-



(388)

R = CH_3, C_2H_5

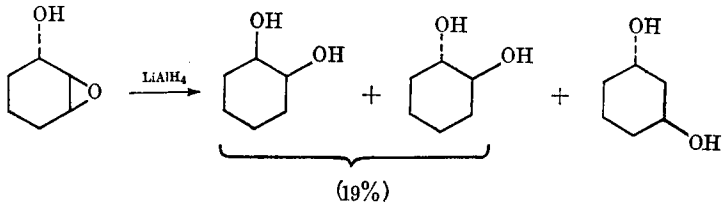
2-ethoxycyclohexanol respectively, indicating the probable *trans* disposition of the alkoxyl substituents relative to the epoxide function in the starting substances (Eq. 388). Similar reasoning leads to the deduction that the 1-chloro-2,3-epoxycyclohexane isomer giving *cis*-2-chlorocyclohexanol and cyclohexanol on reduction probably possessed the *cis* configuration.[1186, 1188, 1195]

Henbest and Wilson[741] have examined carefully the products formed on the reduction of *cis*- and *trans*-1,2-epoxy-3-hydroxycyclohexane with lithium aluminum hydride (Eqs. 389 and 390). The former



(389)

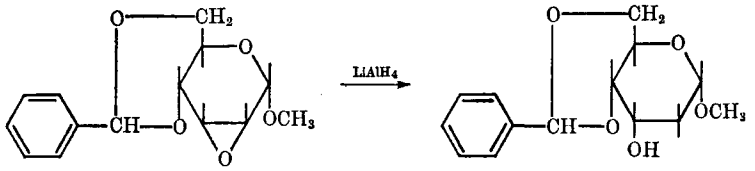
yields only *cis*-1,2-cyclohexanediol, whereas the latter gives a mixture of *trans*-1,3-cyclohexanediol, *cis*-1,2-cyclohexanediol, and *trans*-1,2-cyclohexanediol, in which the 1,3-diol predominates. The above authors point out that the principal products in every instance examined are those anticipated from the Fürst–Plattner rule of diaxial



(390)

epoxide cleavage[603] which allows the most linear distribution of charge in the transition state. In addition, Henbest and Wilson proposed a mechanism which accounts satisfactorily for the formation of the axial–equatorial product *cis*-1,2-cyclohexanediol.

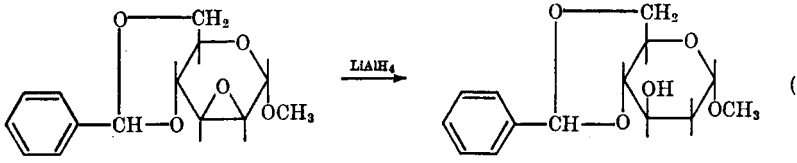
Several 2,3-anhydro sugars have been reduced with lithium



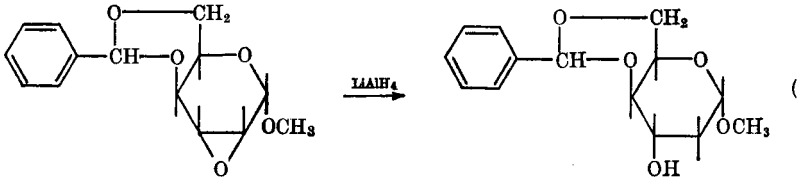
(391)

aluminum hydride, among them methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-guloside, -mannoside, and -alloside,[718, 1414] which yield the corresponding 2-desoxy derivatives (Eqs. 391–393). On the other hand, methyl 2,3-anhydro-β-D-riboside (Eq. 394) apparently yields a mixture of methyl 2-desoxy-β-D-arabinoside and 3-desoxy-β-D-xyloside in which

the latter predominates.[302] It is likely that approach of the hydride donor toward $C_{(3)}$ is completely blocked by the bulky benzylidene group. A more complete list of epoxy sugars reducible with lithium aluminum hydride is given in Table 9.

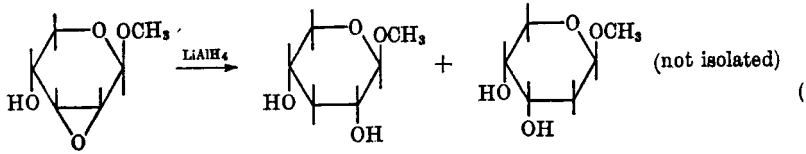


(392)



(393)

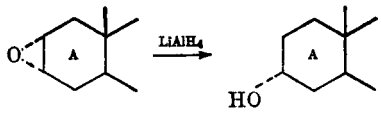
Examples of the reductive cleavage of steroid epoxides are extremely abundant, since these substances serve as excellent synthetic intermediates for introducing various functions into the steroid nucleus.



(394)

(86%)

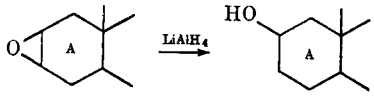
Almost invariably, the direction and stereochemistry of ring fission follow the diaxial principle. For instance, 2α,3α-epoxy steroids (Eq. 395) are reduced to 3α-hydroxy derivatives, whereas their 2β,3β-



(395)

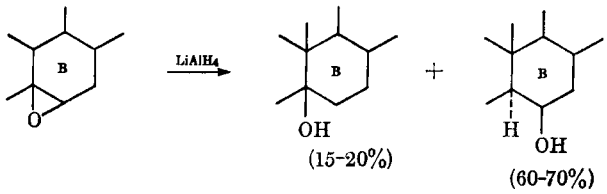
counterparts (Eq. 396) lead to 2β-alcohols.[336, 603, 1302, 1371, 1575, 1825] In both cases, the hydroxyl function assumes the axial disposition in the product.

Further illustrations, among them α- and β-Δ^3-, Δ^4-, Δ^5-, Δ^{11}-, and Δ^{16}-epoxy steroids and related substances, are listed in Table 9. Certain epoxy steroids are not amenable to lithium aluminum hydride



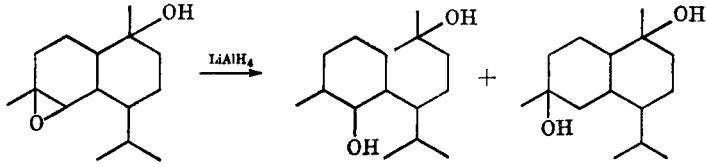
(396)

cleavage, however, either by virtue of the high degree of substitution of the epoxide or because of steric hindrance to the approach of the reagent. These include $\Delta^{7(8)}$-, $\Delta^{10(11)}$-, $\Delta^{8(14)}$-, and other steroid epoxides.[453, 458, 540, 543, 880] Reduction of highly substituted epoxy steroids has been accomplished in certain instances by using lithium in ethylamine (see section **IV.1.***A*.).



(397)

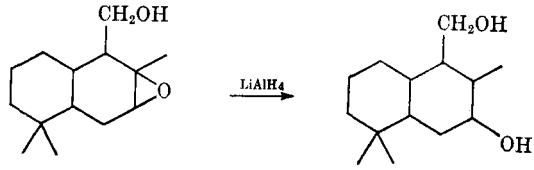
The formation of a unique product is not without exception, although lithium aluminum hydride reduction is far superior to catalytic hydrogenation in this respect. Illustrative of the isolation of more than one product from lithium aluminum hydride reduction are 5β,6β-epoxy steroids. These yield, according to Plattner and coworkers,[1372, 1374] mixtures of 7β- and 5β-hydroxy steroids, in which the former predominate (Eq. 397).



(398)

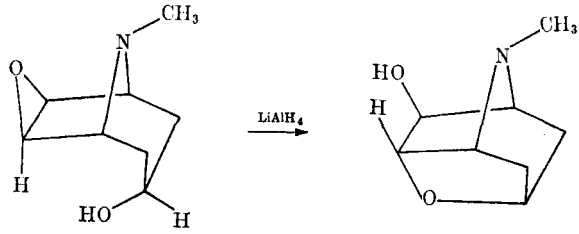
In the field of natural products it is occasionally observed that reduction of an epoxide derivative leads to the sterically less-favored product—*e.g.* to a secondary instead of the expected tertiary alcohol. It is of course impossible to find every example of this occurrence in the literature, but the cases shown below[36, 756, 1182] suffice to illustrate this important phenomenon (Eqs. 398 and 399). In all probability these abnormal cleavages can be accounted for by assuming hydroxyl

participation of the type suggested by Henbest and Wilson[741] for the reduction of *trans*-2,3-epoxy-1-hydroxycyclohexane to *cis*-1,2-cyclohexanediol (Eqs. 389 and 390).

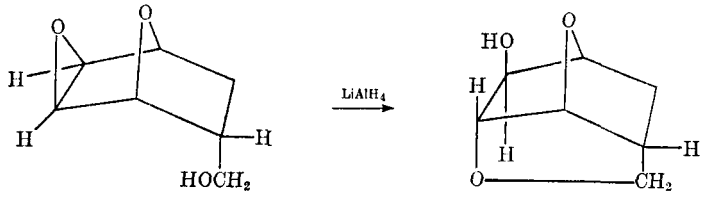


(399)

Hydroxy participation during the reductive epoxide cleavage can also result in formation of new ether rings, [553, 983] as indicated in the two examples shown in Eqs. (400) and (401).



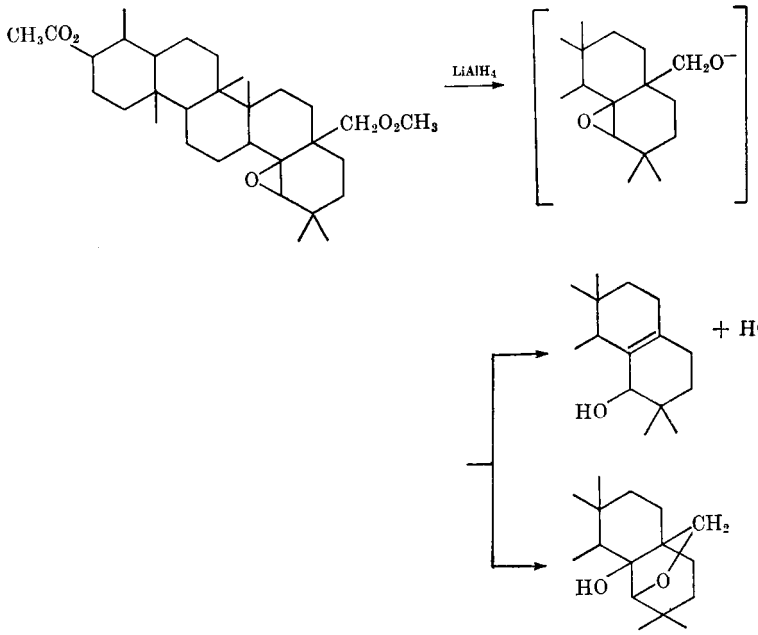
(400)



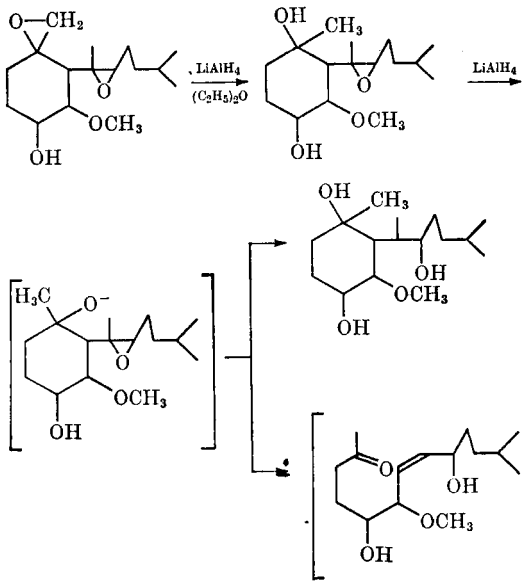
(401)

Deep-seated rearrangements have likewise been known to occur during lithium aluminum hydride reduction of epoxides. Among these is the interesting reaction reported by Barton and Brooks[91] involving the morolic acid derivative shown in Eq. (402).

A further example illustrating complications that can arise in this reaction is given by recent work of Tarbell and co-workers[1694] involving a derivative of the antibiotic fumagillin that contains two epoxide rings, one of which is highly hindered and resists treatment with lithium aluminum hydride in refluxing ether. Although the hindered epoxide ring is finally opened by operating at a higher temperature (in refluxing tetrahydrofuran), two unexpected products are formed, as shown (Eq. 403).


CH3CO2
CH2O2CH3
O
LiAlH4
CH2O−
O
HO
+ HCHO
CH2
HO
O

(402)

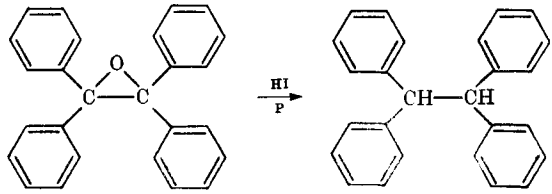

O—CH2
OCH3
OH
LiAlH4
(C2H5)2O
OH
CH3
O
OCH3
OH
LiAlH4
OH
CH3
OH
OCH3
OH
H3C
O−
O
OCH3
OH
O
OH
OCH3
OH
OH
OH
OCH3
OH

(403)

D. Miscellaneous Reducing Agents

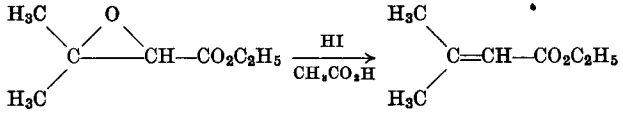
There exists, in addition to the three principal methods of reduction presented above, a number of interesting but seldom-used techniques for converting epoxides into olefins or even into alkanes. This section will be devoted to a brief survey of these reactions.

Perhaps the earliest recorded illustration of the use of hydrogen iodide is the reaction of tetraphenylethylene oxide (Eq. 404), which yields 1,1,2,2-tetraphenylethane in the presence of phosphorus.[1716]



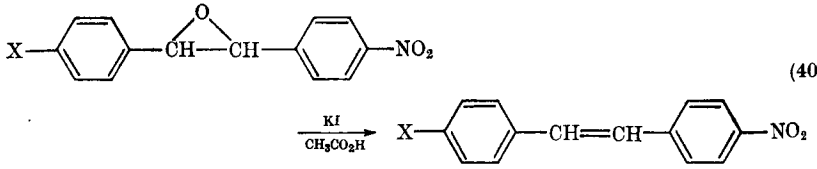
(404)

Darzens[414] discovered the capacity of hydriodic acid for reducing glycidic esters, as in the conversion of ethyl β,β-dimethylglycidate into ethyl β,β-dimethylacrylate in acetic acid (Eq. 405).



(405)

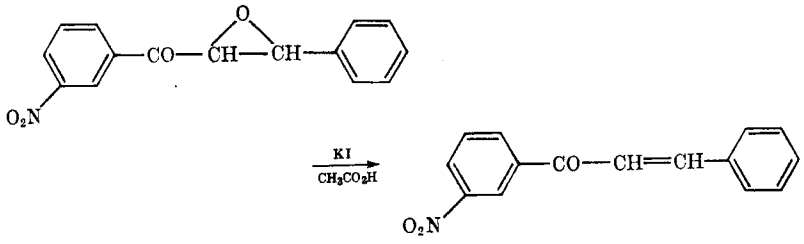
Bergmann and Hervey[132] carried out reduction of *p*-nitro- and *p,p'*-dinitrostilbene oxides with potassium iodide in acetic acid (Eq. 406). Both the *cis*- and *trans*-epoxides gave the same olefin. Precise stereochemical studies have not as yet been performed in this area, however.



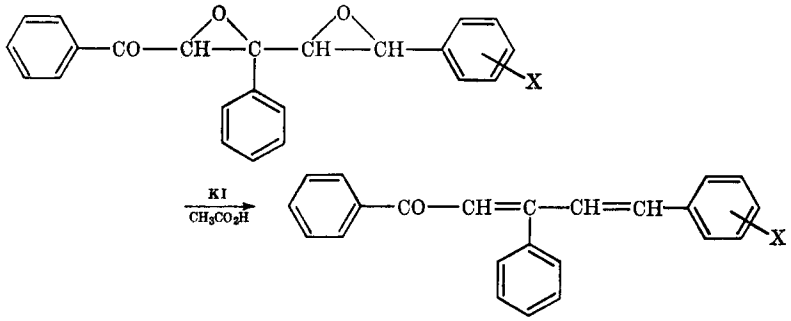
(406)

X = H, NO_2

Three α,β-epoxy ketones reported by Bodforss[182,183] to undergo reduction to the corresponding α,β-unsaturated ketones on treatment with potassium iodide in acetic acid are shown in Eqs. (407) and (408).



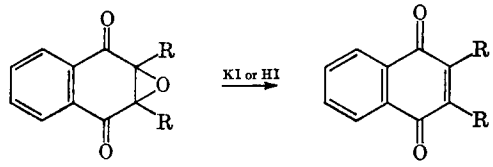
(407)



(408)

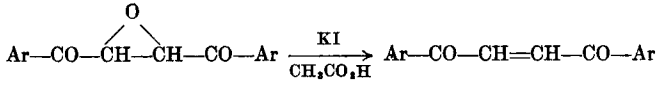
X = *m*-NO_2, *p*-Cl

Lutz and Wood,[1057] moreover, obtained 1,2-dimesitoylethylene on treatment of 1,2-dimesitoylethylene oxide with potassium iodide in acetic acid (Eq. 409), and Shemyakin and co-workers[2003] reduced the epoxybenzoquinones shown in Eq. (408a) to the parent benzoquinones



(408a)

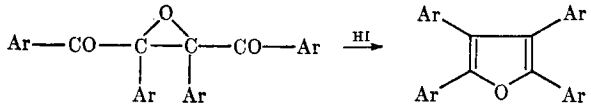
R = H, CH_3, C_6H_5



(409)

Ar = mesityl

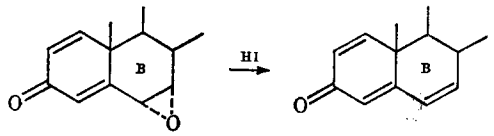
with potassium iodide or hydrogen iodide. More recently, Wasserman and Liberles[1810] used hydrogen iodide to convert 1,2-dibenzoyl-1,2-diphenylethylene oxide into tetraphenyltetrahydrofuran (Eq. 410).



(410)

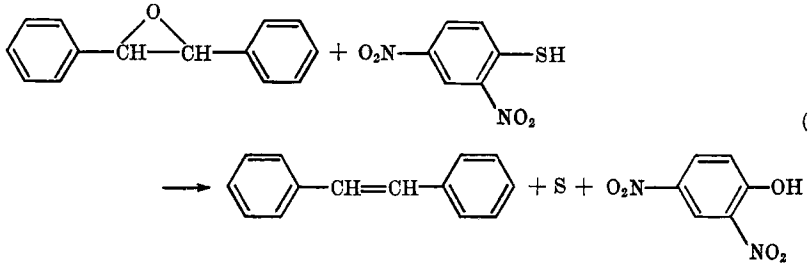
Ar = C_6H_5

Hydrogen iodide reduction has recently been used[1258] also in the steroid field to effect reduction of the 6β,7β-epoxide derivative shown in Eq. (411).



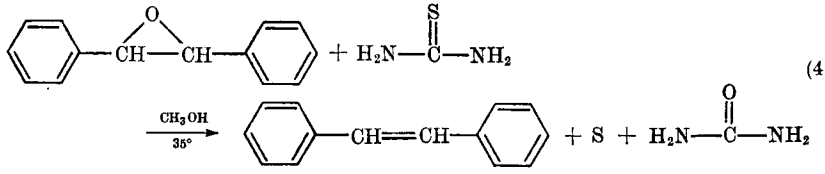
(411)

Attention has already been drawn (see section **IV.4.***C.*) to the observation of Culvenor and co-workers[389] that 2,4-dinitrothiophenol is capable of converting stilbene oxide into stilbene (Eq. 412).



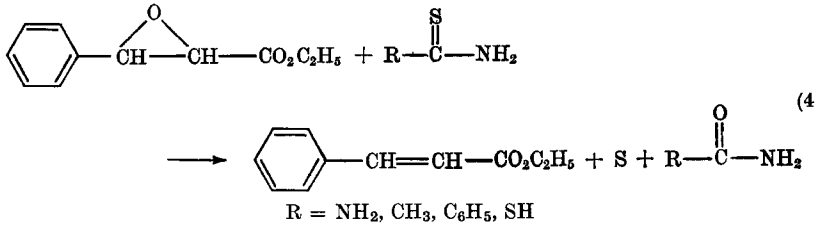
(412)

Other sulfur nucleophiles found to transform epoxides into olefins were thiourea, thioacetamide, thiobenzamide, xanthamide, and thiobarbituric acid. Epoxides reduced in this manner[386] included stilbene



(413)

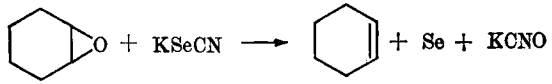
oxide and ethyl β-phenylglycidate (Eqs. 413 and 414). High yields and ease of operation make this little-explored technique worthy of further attention.



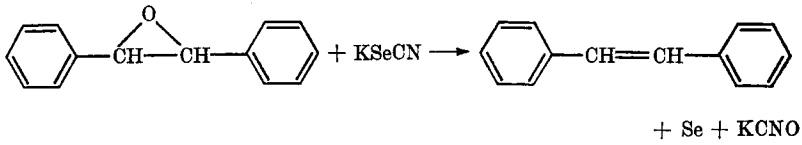
(414)

R = NH_2, CH_3, C_6H_5, SH

Culvenor and co-workers also examined the action of potassium selenocyanate with cyclohexene oxide and stilbene oxide.[386,387] Cyclohexene and stilbene are regenerated in high yield, accompanied by liberation of metallic selenium (Eqs. 415 and 416).

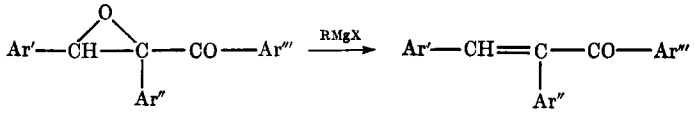


(415)



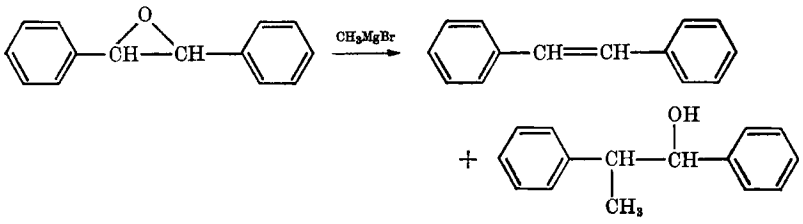
(416)

It has already been mentioned (see section **IV.4.*E*.**) that certain massively substituted α,β-epoxy ketones undergo abnormal reaction on treatment with Grignard reagents (Eq. 417), yielding the corresponding α,β-unsaturated ketones instead of anticipated α-hydroxyketones.[607] Addition of methylmagnesium bromide to stilbene oxide (Eq. 418) likewise yields substantial quantities of stilbene, along with the desired alcohol.[920]



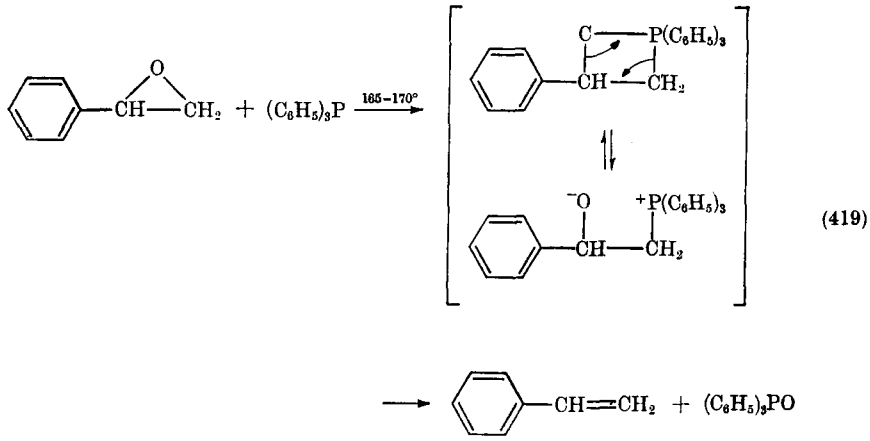
(417)

R = CH_3, X = I
R = C_2H_5, X = Br

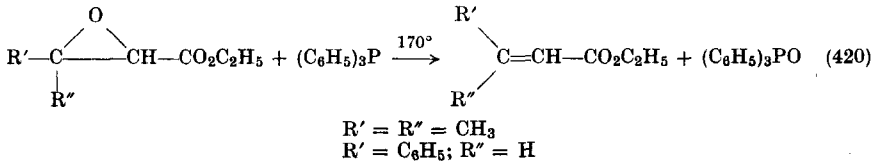


(418)

Wittig and Haag[1871] succeeded in reducing styrene oxide, ethyl β,β-dimethylglycidate, and ethyl β-phenylglycidate by heating them with triphenylphosphine (Eqs. 419 and 420). A cyclic intermediate was postulated.



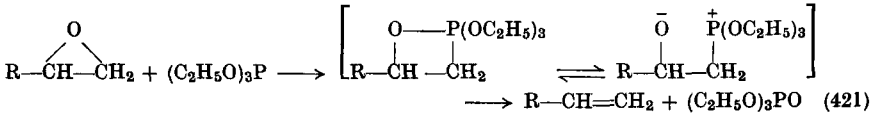
(419)



(420)

$R' = R'' = CH_3$
$R' = C_6H_5$; $R'' = H$

A similar reaction is that published by Scott[1552] involving triethyl phosphite as the reducing agent and ethylene oxide or propylene oxide (Eq. 421). A cyclic intermediate was likewise proposed in this instance.



(421)

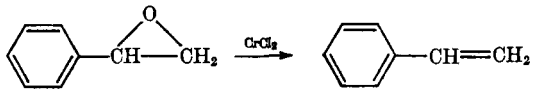
The use of Cr^{2+} ion to effect reduction of various α,β-epoxy ketones to α,β-unsaturated ketones was explored by Cole and Julian[323] with several simple epoxides. Particular success has been encountered with this technique. (Eqs. 425a and 425b), however, in the steroid field.[277, 323, 1258] A paper by Barton and co-workers also describes this method in connexion with the reduction of a tetrasubstituted α,β-epoxy ketone diterpene.[98]

Cyclohexene itself yields only *trans*-2-chlorocyclohexanol (Eq. 422), but styrene oxide and 2,3-epoxy-2-methyl-4-butanone (epoxy-mesityl oxide) give high yields of styrene and mesityl oxide respectively



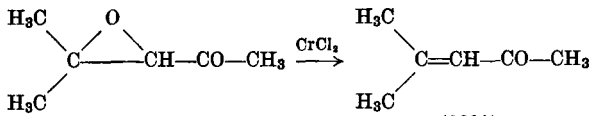
(422)

(Eqs. 423 and 424). Benzalacetophenone oxide, on the other hand, gives only a small amount of benzalacetophenone, unexpectedly leading instead to 1,2-dibenzoyl-1,2-diphenylethane (Eq. 425). Salts



(423)

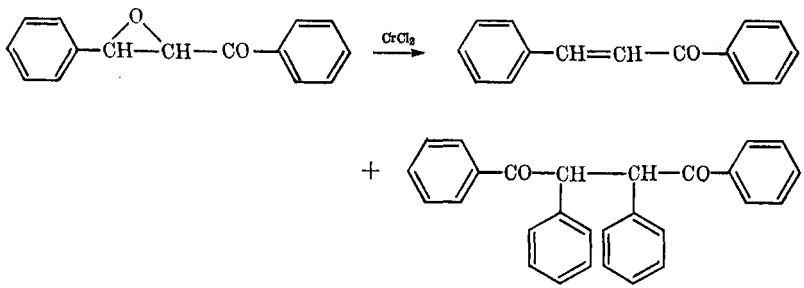
(80%)



(424)

(80%)

which may be utilized in this reaction are chromous chloride and chromous acetate. Operation under an inert atmosphere is desirable to preserve the efficacy of the reagent.

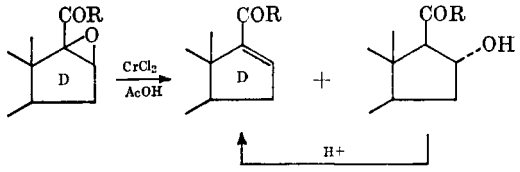


(425)

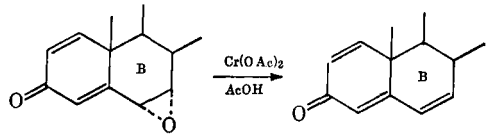
(mostly)

Attention may be drawn, finally, to recent disclosures that α,β-epoxy ketones are converted to the corresponded allylic alcohols on

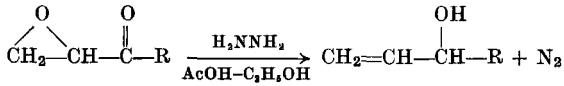
treatment with hydrazine, either at room temperature (Eqs. 425c–425d)[2004] or under Huang–Minlon conditions (Eq. 425f).[2005]



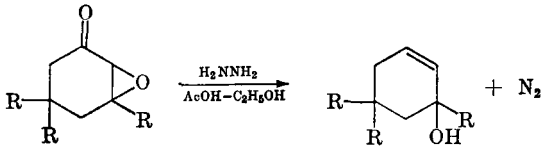
(425a)



(425b)

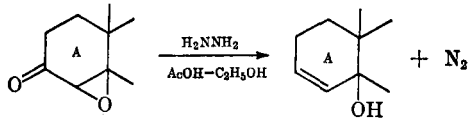


(425c)

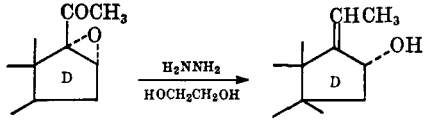


(425d)

R = H, CH_3



(425e)

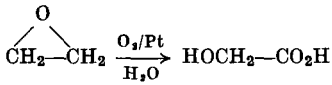


(425f)

2. Oxidation

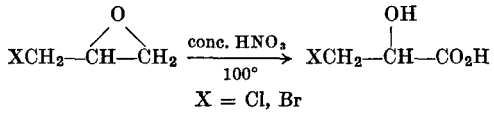
The existing literature contains surprisingly few references dealing with controlled oxidation of ethylene oxides. Mention has been made (see section **III.1.***C.*) of the catalytic oxidation of ethylene oxide to carbon dioxide and water at high temperatures. This section will be devoted to the relatively few known publications describing milder oxidative reactions.

Wurtz himself[1889] noted as early as 1863 that ethylene oxide could be converted into glycollic acid by passing oxygen through aqueous ethylene oxide containing platinum black (Eq. 426).



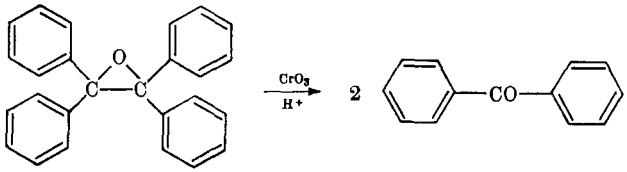
(426)

A related oxidation is that employed by Richter[1458] and later by Fischer and Leuchs,[548] and also by Abderhalden and Eichwald,[3] to convert epichlorohydrin and epibromohydrin into the corresponding α-hydroxy acids (Eq. 427).

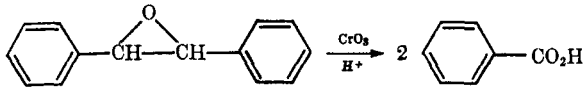


(427)

Thorner and Zincke[1714, 1716] utilized hot chromic acid to carry out oxidative cleavage of tetraphenylethylene oxide and related substances (Eq. 428). In a similar manner Rabe and Hallensleben[1424] oxidized stilbene oxide to benzoic acid with chromic acid (Eq. 429).

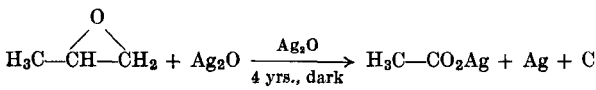


(428)



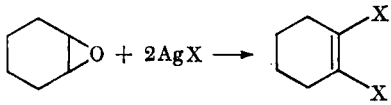
(429)

Although it is obviously of no practical synthetic significance, mention may be made of Linnemann's observation[1037] that sealing propylene oxide in the dark for 4 years in the presence of silver oxide caused deposition of a silver mirror and formation of silver acetate (Eq. 430). Formic acid underwent complete oxidation to carbon dioxide and water.



(430)

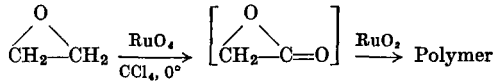
It has been reported by Cauquil and Barrera[293] that treatment of cyclohexene oxide with two molar equivalents of silver perchlorate leads to the formation of metallic silver and a diperchlorate ester formulated as shown in Eq. (431). Similar unsaturated dinitrate esters, which are extremely explosive, were reported to be formed with silver nitrate.[293]



(431)

$X = ClO_4, NO_3$

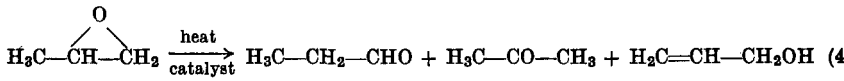
Mention may be made, finally, of an unsuccessful attempt, recently described by Berkowitz and Rylander,[141] to prepare the still unknown substance glycollic lactone by ruthenium tetroxide oxidation of ethylene oxide in carbon tetrachloride at 0°. Tarry products were obtained, which could have been formed by ruthenium dioxide-catalyzed polymerization of this highly strained α-lactone.



(432)

3. Isomerization

The singular tendency of ethylene oxides to undergo isomerization to carbonyl compounds (Eq. 433) was recognized many years ago by a number of distinguished chemists. Wurtz himself,[1884] in his classic publication announcing the discovery of ethylene oxide, stated that this substance was related to acetaldehyde, with which it appeared to share certain chemical properties. Conversion of ethylene oxide into



(433)

acetaldehyde was realized by Ipatieff and Leontovitch[857] in 1903 by passing the gas over alumina at 200–300°, or at 500° in the absence of catalyst. Under these conditions propylene oxide was reported to undergo rearrangement mainly to propionaldehyde.[857] Robeson and Springer,[1475] however, recently observed at 555–650°, with a bed of Fuller's earth as catalyst, that in addition to the main product, propionaldehyde, there was formed also some acetone and allyl alcohol.

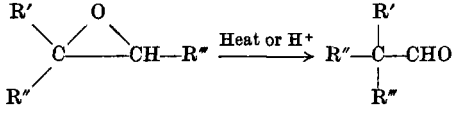
At lower temperatures and with a variety of catalysts (Li_3PO_4, Cr_2O_3, SnO_2, UO_3, and others) it is possible to cause allyl alcohol to become the principal isomerization product.[575, 1052] Still other catalysts (*e.g.* CdO–$CdCl_3$ or WO_3–Fe_2O_3 on dehydrated chromia) are known to lead almost exclusively to propionaldehyde.[866]

The ability of ethylene oxide to undergo rearrangement to acetaldehyde was mentioned (see section **I.2.**) in connexion with the thermal decomposition and photolysis of ethylene oxide, and also (see section **III.1.***C.*) in connexion with catalytic ethylene oxidation at elevated temperatures. This characteristic property is discussed again below with regard to reactions of epoxides with Grignard reagents (see section **IV.4.***E.*). For the purposes of this section the subject of epoxide isomerization can be divided into two parts. The first, and most extensive, is concerned with thermal and acid-catalyzed ethylene oxide isomerization; the second involves base-catalyzed rearrangement.

A. Thermal and Acid-Catalyzed Isomerization

Rearrangement of simple alkyl-substituted epoxides has been studied most extensively by Tiffeneau and his associates in an investigation of the migratory aptitudes of various groups. The isomerization was a convenient means for simulating pinacolic rearrangements, other examples of which were diazotization of β-amino alcohols and treatment of iodohydrins with Ag^+ ion. In recent years, however, it has also received growing recognition in the steroid field as a useful synthetic method for the conversion of olefinic into carbonyl functions (see Table 10 for numerous examples).

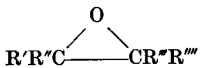
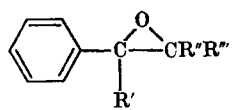
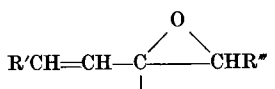
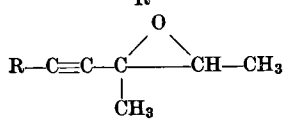
Migratory aptitudes in epoxide rearrangements appear to follow the general trend established in other reactions.[1739, 1740, 1746] Hydride shift is evidently favored by a substantial margin over migration of alkyl groups, as in 1,2-epoxy-2-methylbutane and 2,3-epoxy-2-methylbutane (Eq. 434), which give only the corresponding aldehydes on thermal or acid-catalyzed isomerization.[573, 968, 1721]

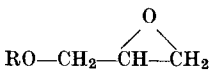
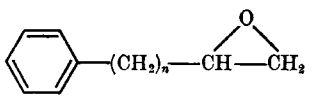
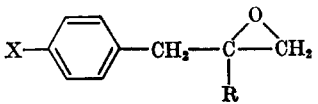
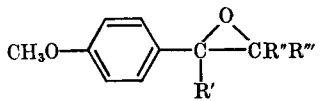
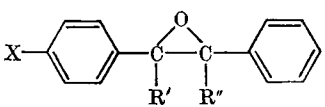
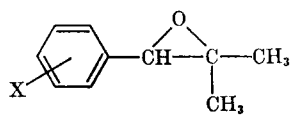


(434)

Alexander and Dittmer[20] have secured evidence of perceptible stereochemical specificity in the isomerization of *cis*- and *trans*-2,3-epoxybutane with phosphoric acid as catalyst. Although the *cis*-isomer

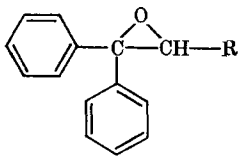
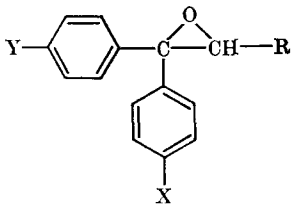
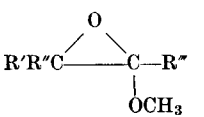
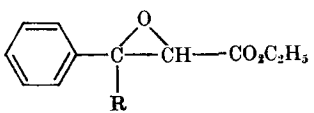
TABLE 10. Thermal and Acid-Catalyzed Epoxide Isomerizations

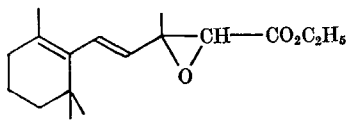
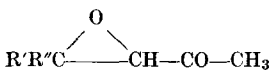
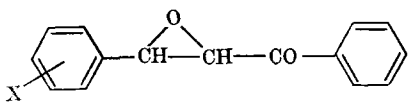
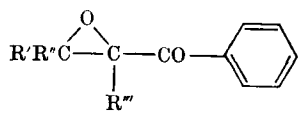
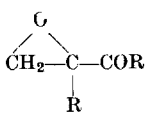
Compound		Reference
A. Acyclic epoxides		
	$R' = R'' = R''' = R'''' = H$	857
	$R' = R'' = R''' = H$; $R'''' = CH_3$, *n*-C_5H_{11}, *iso*C_5H_{11}	491, 575, 857, 866, 1022, 1052, 1475
	$R' = R'' = H$; $R''' = CH_3$; $R'''' = CH_3$, C_2H_5, *neo*C_5H_{11}	274, 275, 491, 573, 619, 814, 857
	$R' = R''' = H$; $R'' = R'''' = CH_3$ (*cis* and *trans*)	20, 814
	$R' = R''' = H$; $R'' = R'''' =$ *tert*-C_4H_9, *neo*C_5H_{11}	778, 1237
	$R' = H$; $R'' = CH_3$, *tert*-C_4H_9; $R''' = R'''' = CH_3$	491, 619, 773, 857, 968
	$R' = R'' = R''' = H$	242, 491, 571, 1023
	$R' = H$; $R'' = CH_3$; $R''' = CH_3$, C_2H_5, *n*-C_3H_7, *iso*C_3H_7	1018, 1025, 1026, 1381, 1733
	$R' = H$; $R'' = C_6H_5CH_2$; $R''' = CH_3$, C_2H_5, *n*-C_3H_7, $C_6H_5CH_2$	1025, 1026
	$R' = CH_3$; $R'' = H$; $R''' = H$, C_2H_5	116, 1720, 1721
	$R' = R'' = H$; $R''' =$ cycloC_6H_{11}, Δ^1-cycloC_6H_9	214, 1729
	$R' = H$; $R'' = R''' = C_6H_5$	2002
	$R' = H$; $R'' = H$, CH_3, C_2H_5; $R''' = C_6H_5$	7, 446–450
	$R' = CH_3$; $R'' = H$, CH_3, C_2H_5; $R''' = C_6H_5$	
	$R = CH_3$, $H_2C{=}CH$, C_6H_5	1330

Compound		Reference
	R = CH_3, C_2H_5, *iso*C_3H_7, *n*-C_4H_9	1390
	*n* = 1, 2, 3, 4	1023
	R = H; X = CH_3O R = $C_6H_5CH_2$; X = H	421, 570 1731
	R′ = H; R″ = R‴ = CH_3, C_2H_5, *n*-C_3H_7, $C_6H_5CH_2$ R′ = R″ = H; R‴ = CH_3 R′ = H; R″ = CH_3; R‴ = C_2H_5 R′ = CH_3; R″ = H; R‴ = C_2H_5	1735, 1741 792 1815 1720, 1815
	R′ = R″ = H; X = H, CH_3 R′ = C_6H_5; R″ = H; X = H, CH_3 R′ = H; R″ = C_6H_5; X = CH_3 R′ = R″ = C_6H_5; X = H	1730, 1734, 1743 338, 491, 618, 990, 1019 338 627
	X = *p*-CH_3, *p*-CH_3O, *m*-CH_3O, *o*-CH_3O	1021, 1735, 1742

(*Table continued*)

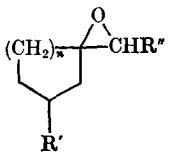
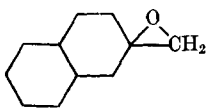
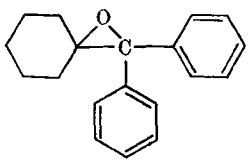
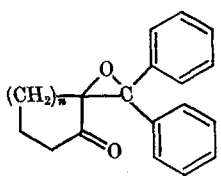
TABLE 10 (*continued*)

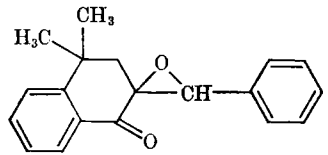
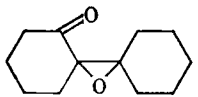
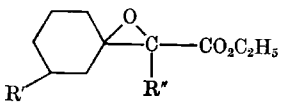
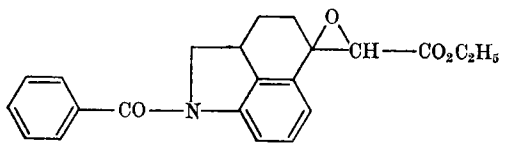
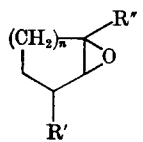
Compound		Reference
	R = H, CH_3, C_2H_5, *n*-C_3H_7, *iso*C_3H_7, *n*-C_4H_9, *iso*C_4H_9, $C_6H_5CH_2$	990, 1019
	R = H, CH_3, C_2H_5; X = CH_3O; Y = H, CH_3O, C_6H_5	438, 1816
	R′ = *n*-C_5H_{11}; R″ = R‴ = H	1633
	R′ = CH_3; R″ = CH_3, C_2H_5; R‴ = *p*-$C_6H_5C_6H_4$	1633
	R′ = H; R″ = CH_3, C_2H_5, C_6H_5; R‴ = C_6H_5	1633, 1644, 1705, 1709
	R′ = CH_3; R″ = CH_3, C_2H_5, *n*-C_4H_9; R‴ = C_6H_5	1705, 1709
	R′ = R″ = R‴ = C_6H_5	1631, 1633
	R′R″ = $(CH_2)_5$; R‴ = C_6H_5	1633
	R = H, C_6H_5	958, 1383, 1737, 1765

Compound		Reference
		730, 861, 1159
	$R' = R'' = CH_3$ $R' = H$; $R'' = C_6H_5$	719, 822, 827, 1184
	X = H, *p*-CH_3O, *o*-CH_3O	21, 812, 815, 1821
	$R' = R'' = R''' = H$ $R' = R'' = H$; $R''' = C_6H_5$ $R' = C_6H_5$; $R'' = H$; $R''' = CH_3$ $R' = C_6H_5$; $R'' = CH_3$; $R''' = H$ (*cis* and *trans*) $R' = R'' = C_6H_5$; $R''' = H$ $R' = R''' = C_6H_5$; $R'' = H$ (*cis* and *trans*)	823 823 822 812 812, 822 812, 822
	R = mesityl	609, 823

(*Table continued*)

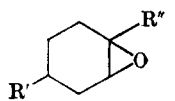
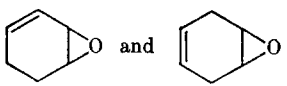
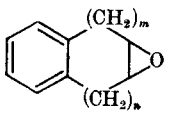
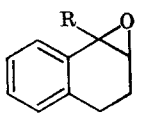
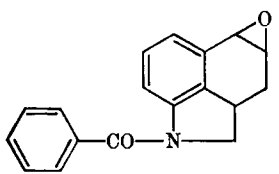
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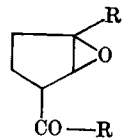
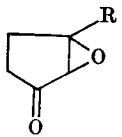
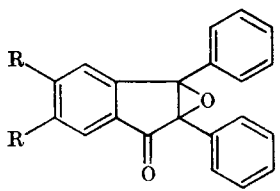
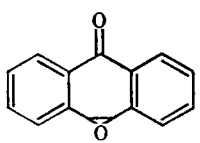
Compound		Reference
B. Semicyclic and alicyclic epoxides		
	$n = 1$; $R' = CH_3$; $R'' = H$ $n = 2$; $R' = CH_3$; $R'' = H, CH_3$ $n = 2$; $R' = H$; $R'' = p\text{-}CH_3OC_6H_4$	1191 1202 1722
		1191
		295
	$n = 1, 2, 3$	822

Compound		Reference
		378
		822, 1441
	R′ = H, CH_3; R″ = H R′ = H, CH_3; R″ = CH_3 R′ = CH_3; R″ = C_2H_5	1191, 1202 1202, 1894 1202
		963
	n = 1, 2; R′ = H; R″ = H n = 13; R′ = H, CH_3; R″ = H n = 1; R′ = H; R″ = C_6H_5	113, 1651, 1652, 1746, 1946

(*Table continued*)

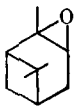
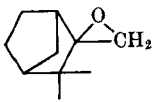
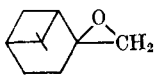
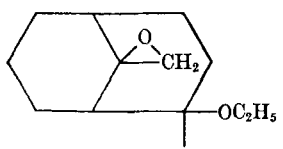
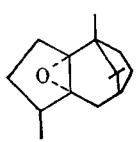
TABLE 10 (*continued*)

Compound		Reference
	R′ = R″ = H R′ = H; R″ = C_2H_5 R′ = H, CH_3; R″ = C_6H_5 R′ = H, CH_3CO_2; R″ = CH_3	110, 1216, 1746 1216 1024 236, 1216, 1746, 1749
		1747
	*m* = 0; *n* = 1, 2, 3, 4 *m* = 1; *n* = 1	318, 363, 841, 1702 1702
	R = C_6H_5, *p*-$CH_3C_6H_5$	1163
		963

Compound		Reference
	R = C_6H_5	609, 1809
	R = CH_3, C_6H_5	828
	R = H, C_6H_5	24, 74, 818, 954
		1462

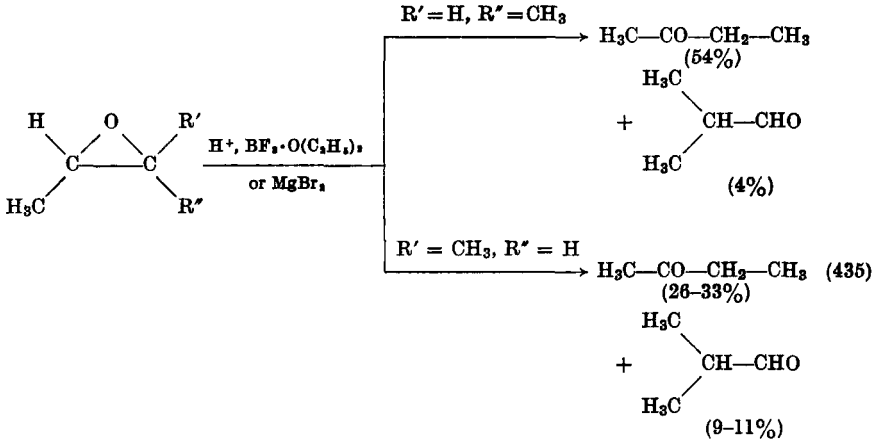
(*Table continued*)

TABLE 10 (*continued*)

Compound	Reference
C. Miscellaneous terpene epoxides	
	37, 38, 1468
	37
Limonene monoxide	1948
	37
	1655
	2006

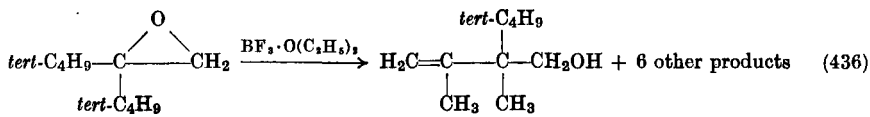
Compound	Reference
D. Steroid epoxides	
2α,3α-Epoxy steroids	336
4α,5α-Epoxy steroids	742
5α,6α-Epoxy B-nor-steroids	420
5α,6α-Epoxy steroids	221–224, 226, 742, 743, 1164, 1904
5β,6β-Epoxy steroids	742, 743, 1904
5β,10β-Epoxy 18-nor-steroids	1904
7α,8α-Epoxy steroids	536, 742
8α,9α-Epoxy steroids	742
8α,14α-Epoxy steroids	742
9α,11α- and 9β,11β-Epoxy steroids	164, 742, 761, 1824
14β,15β-Epoxy steroids	1033
16α,17α-Epoxy steroids	350, 1103, 1254, 1691

yielded mostly 2-butanone by the expected hydride shift, the *trans*-isomer yielded a substantial proportion of *iso*butyraldehyde by methyl migration (Eq. 435). In this type of 1,1-dialkylethylene oxide, methyl migration can evidently compete successfully with hydride migration, provided that the migrating methyl group can effect back-side attack as the C—O bond is breaking. This is in line with numerous other rearrangement reactions involving electron-deficient centers, and suggests that the intermediate in epoxide isomerization is not an open carbonium ion but some type of bridged species.[1301] Similar results were obtained by House[814] on substitution of boron trifluoride or magnesium bromide for phosphoric acid.



(435)

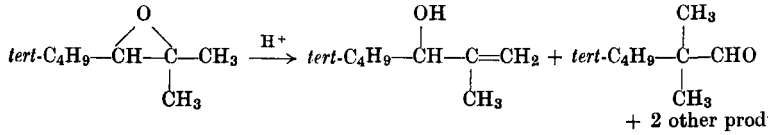
Where a very stable carbonium ion is possible, bridged intermediates are less likely to participate in epoxide isomerization. With 2-*tert*-butyl-1,2-epoxy-3,3-dimethylbutane no less than seven products are formed, according to Newman and co-workers.[1237] These presumably arise from the initially generated di-*tert*-butylcarbonium ion. The chief product, isolable in 40–60% yield, is 2-*tert*-butyl-2,3-dimethyl-3-buten-1-ol (Eq. 436).



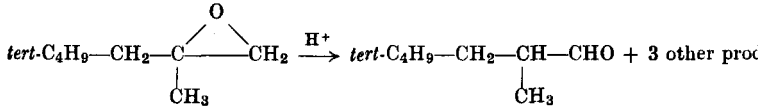
(436)

Complex product mixtures have also been secured by isomerization of 1,2-epoxy-2,4,4-trimethylpentane, 2,3-epoxy-2,4,4-trimethylpentane, and 1,1-di*neo*pentylethylene oxide under acidic conditions.[274,

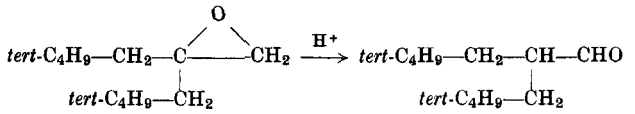
275, 619, 773, 778 The principal product in each of these instances, however, is an aldehyde rather than an unsaturated alcohol (Eqs. 437–439).



(437)

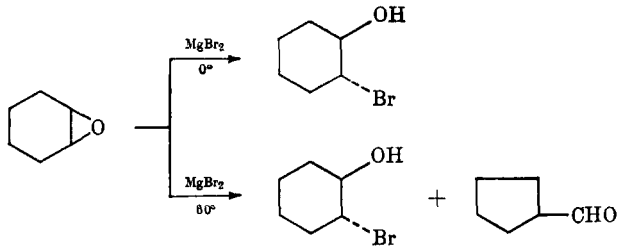


(438)



(439)

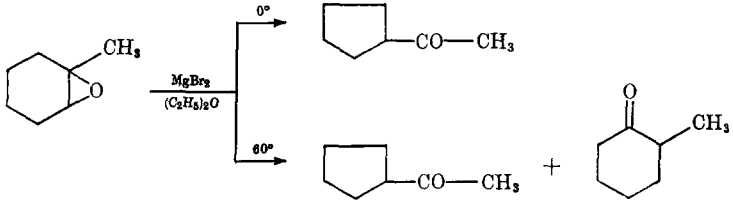
The isomerization of alicyclic epoxides presents an interesting problem, since alkyl migration can cause ring contraction. Bedos,[110, 113] as well as Tiffeneau and Tchoubar,[1746] and more recently Naqvi and co-workers,[1216] converted cyclohexene oxide into formylcyclopentane by heating with magnesium bromide at 60°. The rearrangement product is accompanied by an approximately equal quantity of *trans*-2-bromocyclohexanol at this temperature. At 0°, however, formation of the latter occurs exclusively (Eq. 440).



(440)

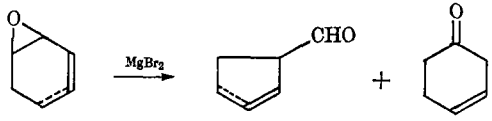
Conflicting observations have been published for 1,2-epoxy-1-methylcyclohexane. On the one hand, Tiffeneau and Tchoubar[1746] allegedly isolated a mixture of isomeric bromohydrins on treatment with magnesium bromide at 0°. On the other, Naqvi and co-workers[1216] reported failing to duplicate the previous work, acetylcyclopentane being the only recognizable product according to these authors.

Thermal isomerization at 220° in the absence of catalyst,[1749] or isomerization at 60° in the presence of magnesium bromide,[1216] gives a mixture of 2-methylcyclohexanone and acetylcyclopentane (Eq. 441).



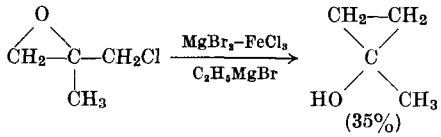
(441)

Isomerization of 1,2-epoxy-3-cyclohexene and 1,2-epoxy-4-cyclohexene over magnesium bromide has been reported by Tiffeneau and Tchoubar[1747] to yield two products in each case (Eq. 442).



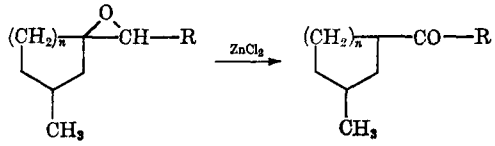
(442)

DePuy and co-workers[2012] have reported a novel isomerization reaction, wherein 1-chloro-2,3-epoxy-2-methylpropane was converted to 1-methylcyclopropanol on treatment with ethylmagnesium bromide in the presence of magnesium bromide and ferric chloride (Eq. 442a).



(442a)

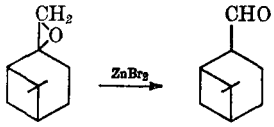
Several spiroepoxides, among them the substances shown in Eq. (443), have been subjected to zinc chloride treatment at elevated temperatures.[1191, 1202] Aldehydes or ketones were invariably formed,



(443)

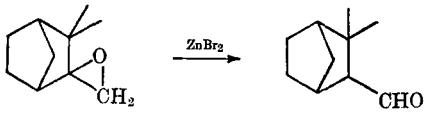
$n = 1$; R = H
$n = 2$; R = H, CH_3

but in no case could ring enlargement be demonstrated. Evidently, hydride shift involves substantially less energy expenditure than alkyl migration in these examples. Similar observations have been published recently by Cope and Burton[1923] for the case of methylenecyclooctene oxide, which gives mainly formylcyclooctane on treatment with formic acid.



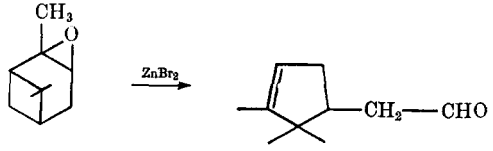
(444)

Arbuzov[38] has described the isomerization of β-pinene oxide (Eq. 444) and camphene oxide (Eq. 445) to the corresponding aldehyde derivatives in the presence of zinc bromide.



(445)

The same author,[37, 38] and also Ritter and Russel,[1468] reported that α-pinene oxide, on the other hand, undergoes a deep-seated skeletal rearrangement under the same conditions, as shown in Eq. (446).



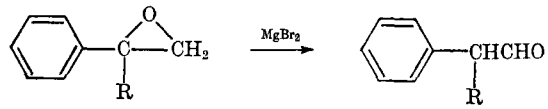
(446)

A large number of alkyl-substituted styrene and *p*-methoxystyrene oxides have been isomerized in various laboratories, notably those of Tiffeneau, Eliel, and Cope. Among the catalysts found to be effective in this connexion are magnesium bromide, aluminum chloride, and boron trifluoride. Only a few illustrative examples are cited in the text, although a larger compilation may be found in Table 10.

Styrene oxide and α-methylstyrene oxide undergo exclusive isomerization to phenylacetaldehyde and methylphenylacetaldehyde respectively (Eq. 447) under the action of various Lewis acids.[242, 491, 571, 1023, 1721] Hydride shifts are clearly dominant here.

Further alkyl substitution, on the other hand, leads to product

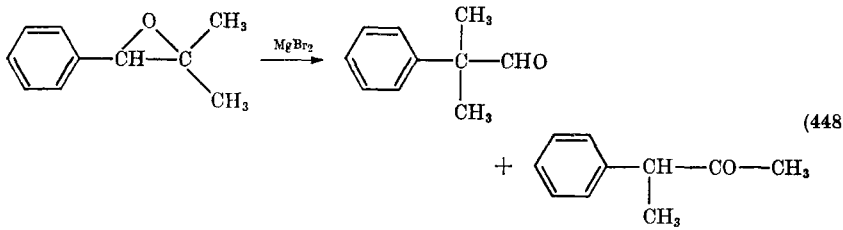
mixtures in which the migratory aptitude of substituents depends on the overall type of substitution present on the epoxide ring. Thus,



(447)

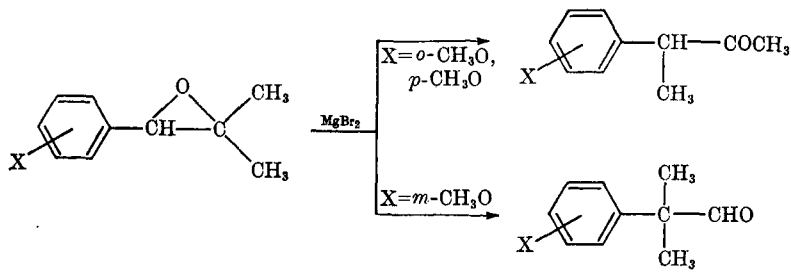
R = H, CH_3

β,β-dimethylstyrene oxide undergoes isomerization to a mixture of dimethylphenylacetaldehyde and 2-phenyl-3-butanone (Eq. 448), in which the former is the principal constituent.[1025, 1381, 1733]



(448)

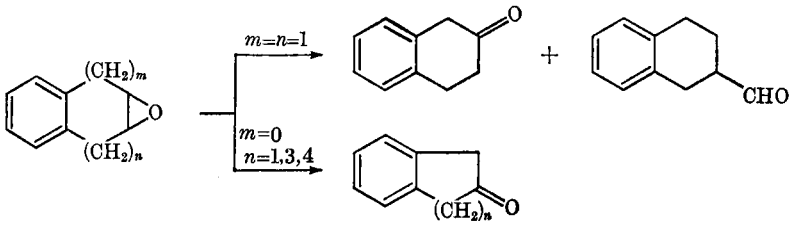
The influence of *o*-, *m*-, and *p*-methoxy substituents is clearly evident from isomerization of correspondingly substituted styrene oxides (Eq. 449). Thus, β,β-dimethyl-*o*-methoxystyrene oxide and its *p*-methoxy isomer give only a ketone, whereas the *m*-methoxy isomer



(449)

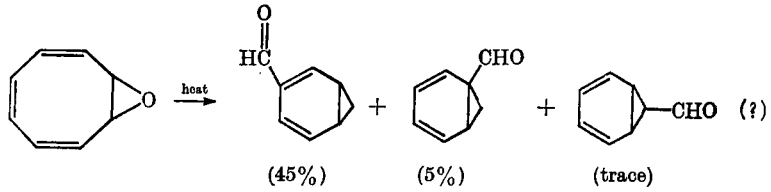
yields an aldehyde exclusively.[1021, 1733, 1735] It appears, therefore, that mesomeric participation by an electron-donating substituent in the transition state lowers the activation energy for methyl migration sufficiently to allow this process to overcome the normally favored process of aryl migration. A further likelihood is that isomerization of

the *o*- and *p*-methoxy derivatives involves a transition state exhibiting substantial carbonium ion character on the benzylic epoxide carbon, whereas the *m*-methoxy derivative involves a bridged transition state.



(450)

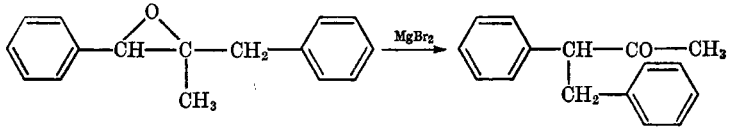
Epoxides derived from indene,[318] 1,2- and 1,4-dihydronaphthalene,[1702] 3,4-benzo-1,3-cycloheptadiene,[363] and 3,4-benzo-1,3-cyclooctadiene[841] are all reported to undergo isomerization to ketones in the presence of magnesium bromide (Eq. 450). That the carbonyl function is separated in every instance from the benzene ring by a methylene group may be taken to indicate probable existence of an open carbonium ion in these processes. Ring contraction has been noted in one



(450a)

case also, namely 1,4-dihydronaphthalene oxide,[1702] which gives a mixture of 2-tetralone and 2-formylindane.

The thermal isomerization of cyclooctatetraene epoxide has been studied at 260° by Büchi and Burgess,[2013] who observed the formation of three isomeric aldehydes (Eq. 450a), one of which may be the elusive compound norcaradiene carboxaldehyde.

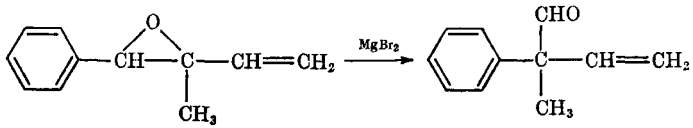


(451)

Migration of a benzyl group appears to occur in preference to hydrogen, alkyl, or aryl migration, as with 1,3-diphenyl-2-methyl-1,2-epoxypropane (Eq. 451), which yields 3,4-diphenyl-2-butanone exclusively.[1025, 1026] Of some interest, incidentally, is the report that

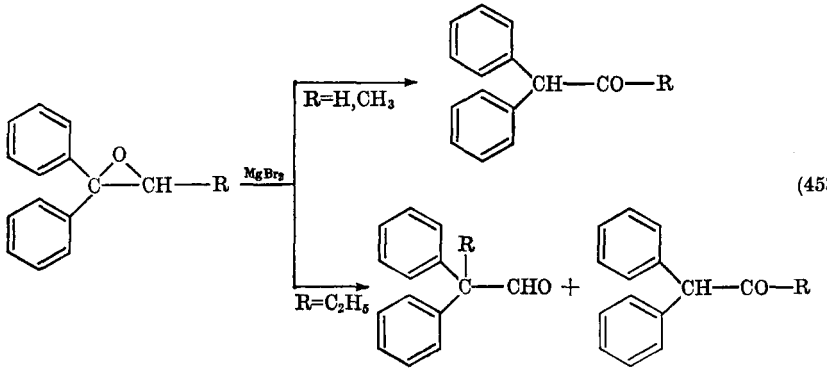
1,1-dibenzylethylene oxide is singularly inert in the presence of sulfuric acid, according to Levy and Tabart.[1025, 1026]

Aryl migration in preference to vinyl or methyl migration is evident with 1,2-epoxy-2-methyl-1-phenyl-3-butene, which gives the corresponding aldehyde exclusively,[446] as shown in Eq. (452).



(452)

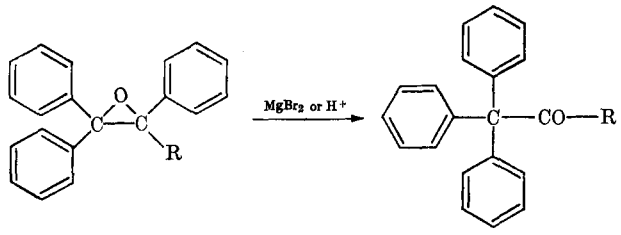
Several 1,1-diarylethylene oxides have been subjected to the action of magnesium bromide or boron trifluoride (Eq. 453). Again, migratory aptitude in the epoxide-isomerization process appears to be a function of the overall substitution pattern. Thus, 1,1-diphenylethylene oxide[338] and 2-methyl-1,1-diphenylethylene oxide[990, 1019] suffer hydride shifts exclusively. On the other hand, 2-ethyl-1,1-diphenylethylene oxide reportedly undergoes hydride shift and ethyl migration.[990, 1019]



(453)

Under the influence of various catalysts triphenylethylene oxide[338, 491, 618] and tetraphenylethylene oxide[627] have been reported to form triphenylacetaldehyde and triphenylacetophenone respectively (Eq. 454). That no diphenylacetophenone was isolated in the former case indicates the preference of phenyl migration over hydride migration with this particular substitution pattern.

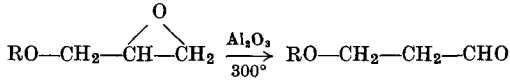
Several glycidic ethers have been isomerized to the corresponding aldehydes, as seen in Table 10. Methyl glycidyl ether, for instance, affords some 3-methoxypropionaldehyde on heating to 300° over



(454)

R = H, C_6H_5

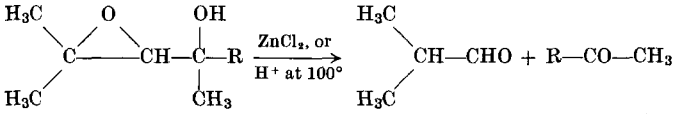
alumina (Eq. 455). It is curious that substantial quantities of starting material are recoverable even under such rigorous conditions.[1390]



(455)

R = CH_3, C_2H_5, *iso*C_3H_7, *n*-C_3H_7

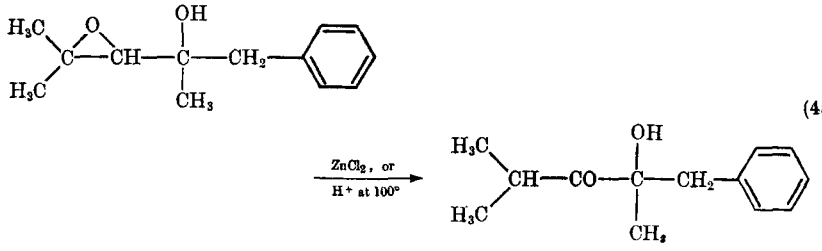
Isomerization of an extensive series of α,β-epoxy alcohols with hot acid or zinc chloride produces rather complex mixtures of aldehydes and ketones.[1287, 1288] As shown in Eq. (456), this reaction usually



+ other products (456)

R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *iso*C_4H_9

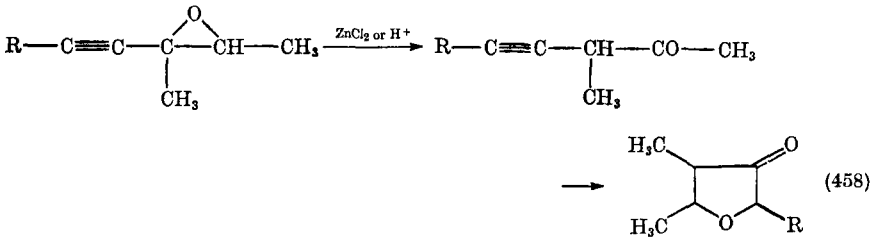
involves fragmentation of the molecule, although at least one exception is known (Eq. 457). Reference to other cleavage reactions of α,β-epoxy alcohols will be made elsewhere (see section **IV.4.*E***.).



(457)

Epoxy acetylenes undergo novel and useful rearrangements under the influence of mineral acid or zinc chloride. Unfortunately not enough cases have been investigated as yet to state whether the reaction

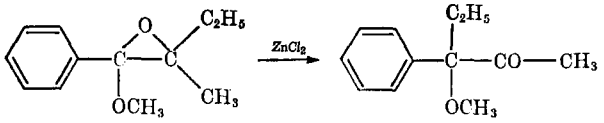
involves alkinyl migration or hydride shift. Initial products can undergo further reaction to give 3-ketotetrahydrofuran derivatives,[1330, 1341] as shown in Eq. (458).



(458)

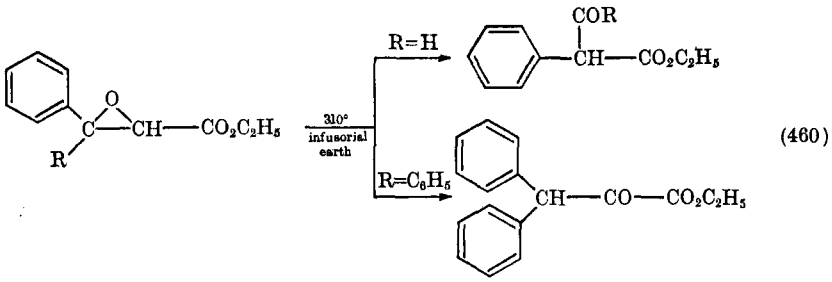
R = CH_3, CH_2=CH, C_6H_5

Magnesium bromide, zinc chloride, and other Lewis acids are capable of cleaving epoxy ethers with great facility,[1705, 1709] the presence of a polar substituent on the epoxide ring promoting rupture



(459)

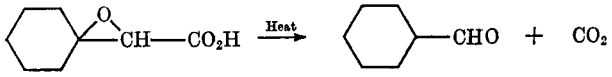
of the nearest C—O bond, as with 1,2-epoxy-1-methoxy-2-methyl-1-phenylpropane for example (Eq. 459). Hydrolysis of the methoxyl group occurs as well when a mineral acid catalyst is substituted for the Lewis acid.



(460)

It has been reported[958, 1383, 1737, 1765] that β-phenyl- and β,β-diphenylglycidic esters suffer rearrangement on heating, at 310° over a bed of infusorial earth for instance (Eq. 460). Phenyl migration occurs in the first case, and hydride shift in the second.

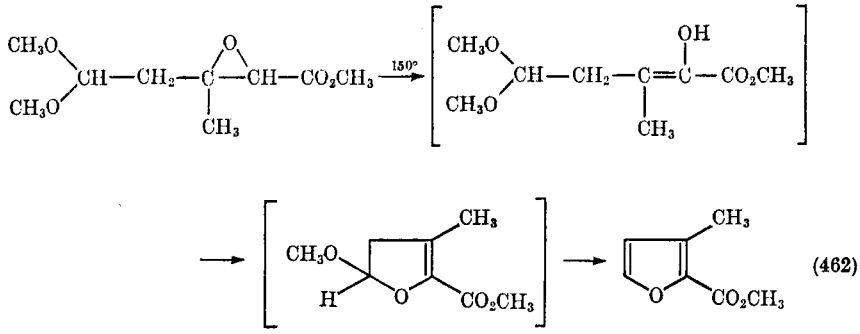
Thermal decarboxylation of glycidic acids or glycidic salts obtained by hydrolysis of Darzens condensation products constitutes an important practical application of epoxide isomerization in chemical synthesis. A simple example (Eq. 461) is decarboxylation of 3,3-pentamethyleneglycidic acid, which gives formylcyclohexane and carbon dioxide in good yield.[1136] Significant applications of this procedure in the field of natural products include synthetic approaches to vitamin A[730, 861, 1159] and lysergic acid.[963] Reference to these publications will



(461)

illustrate adequately the variety of experimental techniques suitable for the isomerization. Newman and Magerlein[1236] and Ballester[67] have reviewed the Darzens condensation (see also section **III.2.***B.*). Their excellent discussions may be consulted for additional details on isomerization of glycidic acids.

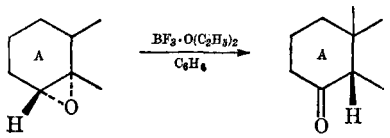
Glycidic esters do not always undergo immediate decarboxylation if an energetically favorable alternative exists. For example, Burness[269] has isolated a furan derivative on heating methyl 2,3-epoxy-5,5-dimethoxy-3-methylvalerate, and has postulated the following course of events for the reaction (Eq. 462):



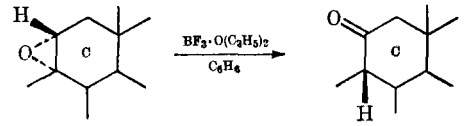
(462)

In the steroid field, Henbest and Wrigley[742, 743] have examined a number of epoxides with reference to boron trifluoride, which is a much stronger Lewis acid than magnesium bromide and hence requires much milder operating temperatures. In all instances studied, hydride shifts took place in preference to ring contraction. The product stereochemistry indicated unequivocally a Walden inversion at the site of

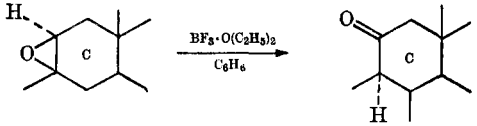
departure of the epoxide oxygen atom. Among the substances smoothly isomerized to ketones in this manner were 4α,5α-, 9α,11α-, and 9β,11β-epoxy steroids, as shown in Eqs. (463)–(465).



(463)

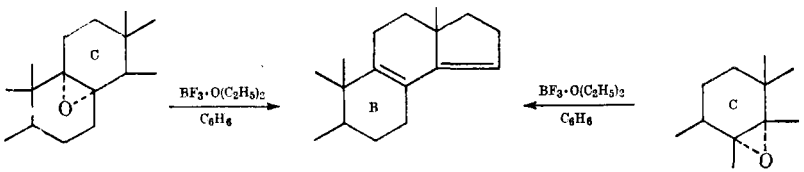


(464)

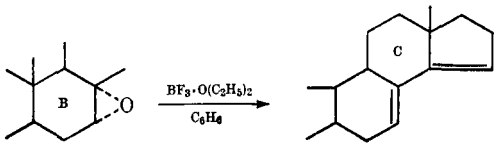


(465)

Certain epoxy steroids, however, yielded dienes rather than ketones,[742] apparently by proton loss from the initially generated carbonium ion, subsequent elimination of water from the resultant allylic alcohol, and finally double-bond migration. Among epoxides



(466)

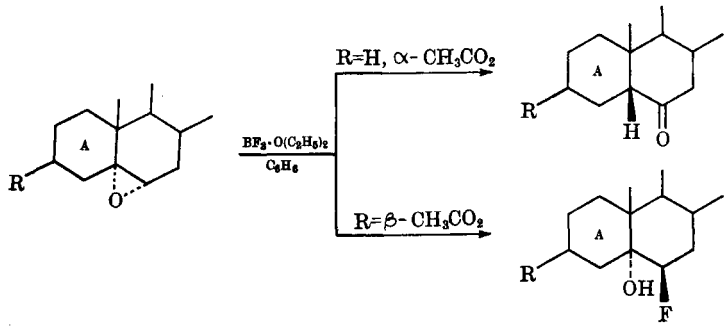


(467)

that appear to undergo this type of isomerization are 8α,9α-, 8α,14α-, and 7α,8α-epoxy steroids, as shown in Eqs. (466) and (467).

Henbest and Wrigley[742] noted the reaction of epoxy steroids with boron trifluoride to be markedly solvent-dependent, since the use of

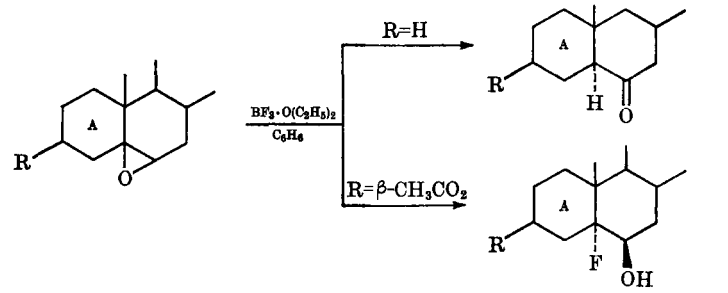
ether instead of benzene caused fluorohydrins to be produced instead of the expected ketones. It was proposed that in the presence of ether, which is more basic than benzene, boron trifluoride is unable to complex so effectively as in benzene with the epoxide oxygen. A similar argument was advanced by House and Reif[822] to explain the greater



(468)

effectiveness of boron trifluoride in cyclohexane than in ether for α,β-epoxy ketone isomerization.

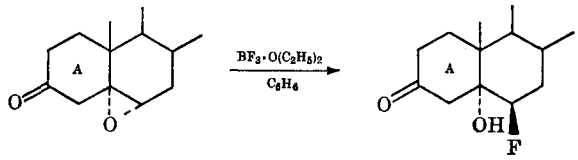
Particularly interesting observations were made by Henbest and Wrigley[743] for $5\alpha,6\alpha$- and $5\beta,6\beta$-epoxy steroids variously substituted at $C_{(3)}$, isomerization to 6-oxo steroids taking place smoothly. Rearrangement of the $5\alpha,6\alpha$-epoxide is somewhat slower, presumably because of



(469)

unfavorable non-bonded ring B interactions. But with a β-acetoxy substituent at $C_{(3)}$, neither $5\alpha,6\alpha$- nor $5\beta,6\beta$-epoxides give the expected ketones, yielding instead 6β-fluoro-5α-hydroxy and 5α-fluoro-6β-hydroxy derivatives respectively. In a similar fashion, $5\alpha,6\alpha$-epoxy-3-oxo steroids give 6β-fluoro-5α-hydroxy derivatives as shown in Eqs. (468)–(470).

The abnormal behavior of 3β-acetoxy-5α,6α-epoxy steroids can be ascribed to the electronegativity of the $C_{(3)}$ substituent, which causes the $C_{(5)}$—O bond to be firmer. Rupture of the $C_{(6)}$—O bond and fluorohydrin formation at the expense of ketone formation are correspondingly enhanced.[743] With 3α-acetoxy-5α,6α-epoxy steroids, this effect is evidently offset by the fact that isomerization results in a conformational change that transforms the configuration of the $C_{(3)}$

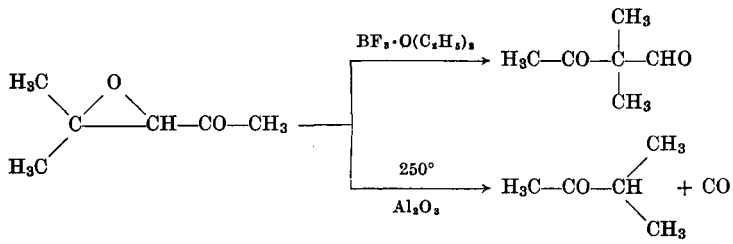


(470)

substituent from axial to equatorial. On the other hand, this second effect is not sufficient to offset the first with 3β-acetoxy-5β,6β-epoxy steroids. Finally, with respect to 3-oxo-5α,6α-epoxides, in which conformational effects are negligible to a first approximation, the electron-withdrawing influence of the carbonyl dipole is the dominant directive factor, causing fluorohydrin formation exclusively.

Subsequent authors have noted a large number of similar effects in the steroid field, and have advanced substantially identical rationalizations for them (see Table 10 for numerous references).

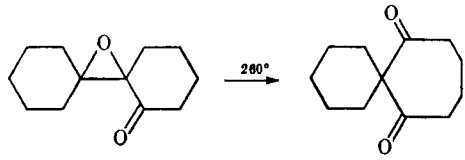
Isomerization of α,β-epoxy ketones has been accorded most intensive study at the hands of House and co-workers.[812, 815, 818, 822, 823, 827, 828, *etc.*]



(471)

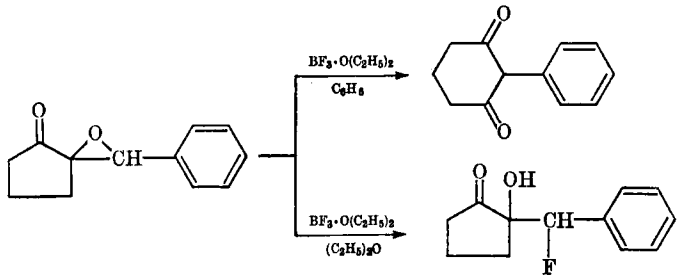
Treatment of 2,3-epoxy-2-methyl-4-butanone with boron trifluoride etherate in benzene (Eq. 471) gives a good yield of 2,2-dimethyl-3-oxobutyraldehyde.[827] This product can only be formed by migration of an acyl group. When rearrangement was conducted at 250° over alumina, methyl isopropyl ketone was isolated, not 4-methylpentane-2,3-dione as claimed previously.[719] Deformylation appears to occur readily on the surface of the alumina catalyst.

Thermal isomerization of α-cyclohexylidenecyclohexanone oxide (Eq. 472) was likewise found to proceed by acyl migration,[827] rather than by alkyl migration as formerly believed.[1441] Curiously, boron trifluoride failed to give recognizable products.



(472)

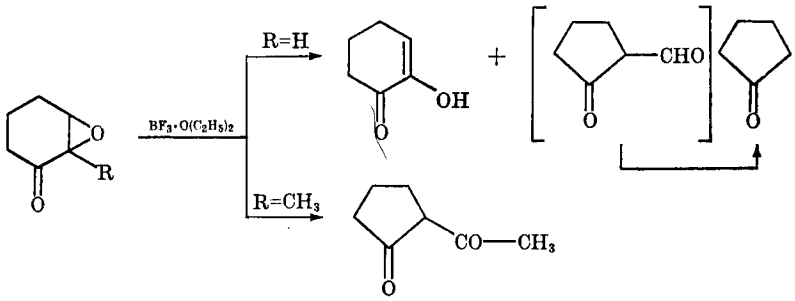
House and Wasson[827] also examined the rearrangements of several α-benzalcycloalkanone oxides in the presence of boron trifluoride, both in benzene and in ether. In the non-basic solvent, α-benzalcyclopentanone oxide underwent ring expansion to 2-phenylcyclohexane-1,3-dione, whereas in ether, which is basic relative to benzene, only a



(473)

fluorohydrin was produced (Eq. 473). Similar solvent effects had been noted by Henbest and Wrigley[743] in the steroid field, as already noted.

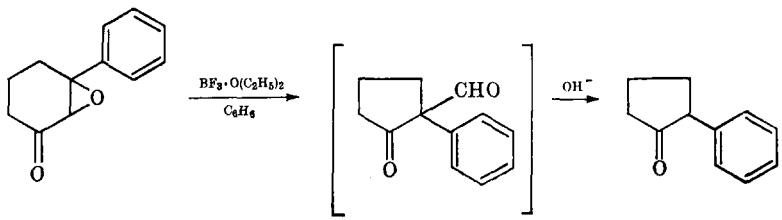
Isomerization of 2,3-epoxycyclohexanone gave a mixture of cyclohexane-1,2-dione and 2-formylcyclopentanone (Eq. 474), in which



(474)

the former was the principal constituent.[828] The minor product underwent ready loss of the aldehyde function in base, so that it was ultimately isolated as cyclopentanone. Rearrangement of 2,3-epoxy-2-methylcyclohexane, in which generation of a 1,2-dione by hydride transfer is obviously excluded, yielded only 1-acetylcyclopentanone.[829]

Presence of a phenyl substituent at $C_{(3)}$, as in 2,3-epoxy-3-phenylcyclohexanone, caused a preponderance of acyl migration (Eq. 475), presumably by stabilizing the carbonium ion generated by $C_{(3)}$—O bond rupture. Formation of a carbonium ion at $C_{(3)}$ rather than $C_{(2)}$ is favored also on electrostatic grounds by the proximity of $C_{(2)}$ to the positive terminal of the carbonyl dipole.[828]



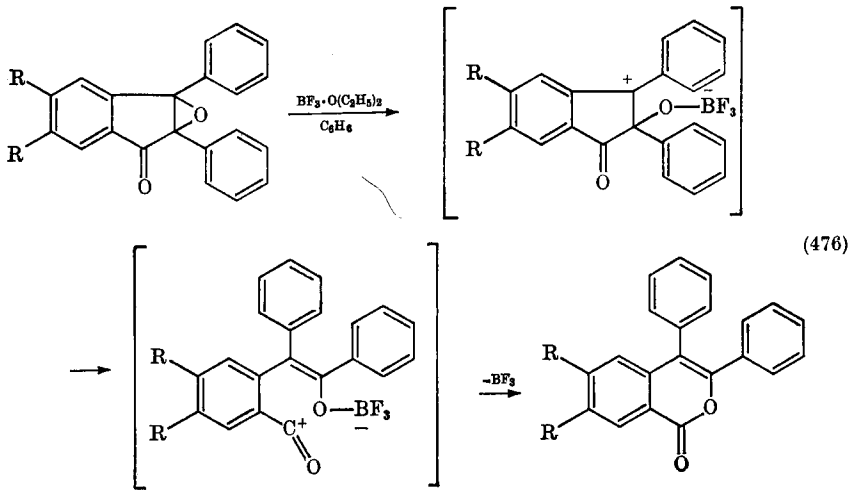
(475)

Treatment of 2,3-epoxy-3-phenylcyclopentanone with boron trifluoride under similar conditions, on the other hand, yielded not the hoped-for cyclobutanone derivative, but 3-phenylcyclopentane-1,2-dione.[828] The high activation energy associated with formation of a four-membered ring evidently causes hydride shift to become the dominant process.

Isomerization of 2,3-diphenyl-1-indanone follows still a third type of reaction path (Eq. 476), yielding a lactone by ring fission and recyclization,[74, 818, 954, 1821] and 2,3,5,6-tetraphenyl-1-indanone undergoes a similar transformation,[818] in contrast with a previous report.[24]

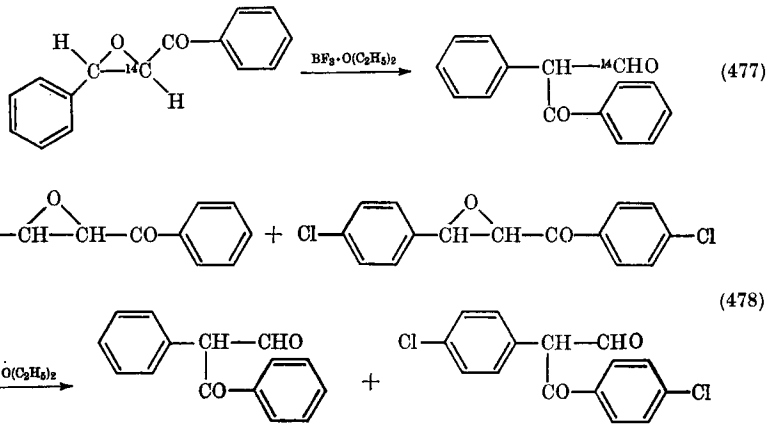
It has long been known that under the influence of mineral acids *trans*-benzalacetophenone oxide (*trans*-chalcone oxide) undergoes rearrangement to an aldehyde.[1821] To determine whether phenyl or benzoyl migration attends this isomerization, House[815] subjected labeled *trans*-benzalacetophenone oxide to the action of boron trifluoride, and examined isotopic distribution in the product. Incorporation of 98% of the ^{14}C label into the aldehyde carbon (Eq. 477) clearly established that benzoyl migration is involved.

To ascertain whether the benzoyl group migrates concertedly or as a separate detached entity, House[815] conducted the isomerization of benzalacetophenone oxide in the presence of an equivalent amount of



(476)

R = H, C_6H_5

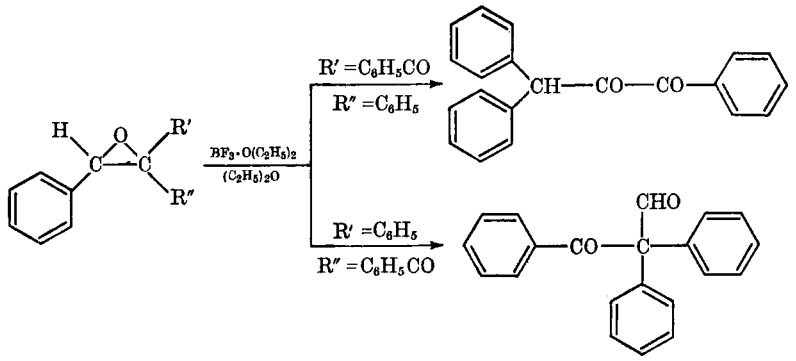


(477)

(478)

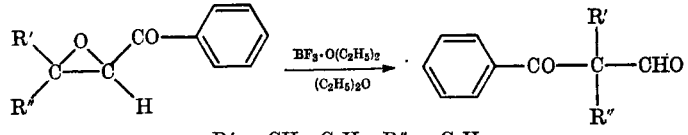
p,p'-dichlorobenzalacetophenone oxide. That rearrangement is a one-step synchronous process was indicated by formation of only two, rather than four, products (Eq. 478). The two epoxides undergo isomerization at comparable rates.

Whether phenyl or benzoyl migration occurs appears to be a function of the overall substitution pattern of the epoxide. Thus, *cis*- and *trans*-α-phenylbenzalacetophenone oxide suffer phenyl migration (Eq. 479), yielding 1,1,3-triphenylpropane-2,3-dione and 2-benzoyl-2,2-diphenylacetaldehyde respectively.[822]



(479)

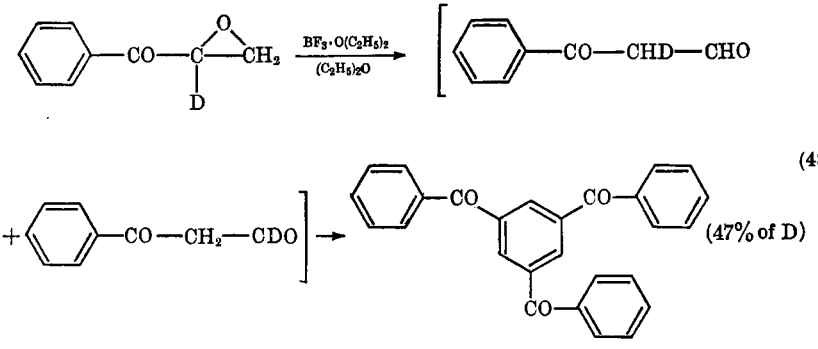
On the other hand, *cis-* and *trans-β*-methylbenzalacetophenone oxide (dypnone oxide) and also *β*-phenylbenzalacetophenone oxide (*β*,*β*-diphenylacrylophenone oxide) yield 2-benzoyl-2-phenylpropionaldehyde and 2-benzoyl-2,2-diphenylacetaldehyde respectively[812] (Eq. 480). In these instances benzoyl migration appears to be the energetically favored pathway.



(480)

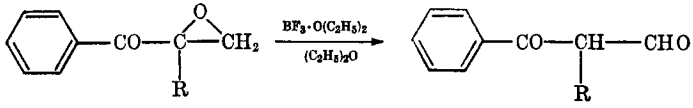
R′ = CH_3, C_6H_5; R″ = C_6H_5
R′ = C_6H_5; R″ = CH_3

There exists an appreciable tendency for aldehyde formation by 1,2-hydride shift, however, when a terminal epoxide is involved. With acrylophenone oxide, for example, House and Wasson[823] demonstrated isotopically that benzoyl migration and 1,2-hydride transfer occur to a comparable extent (Eq. 481).



(481)

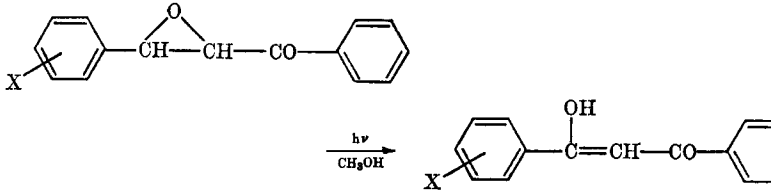
Related terminal epoxides undergoing exclusive isomerization by 1,2-hydride transfer (Eq. 482) include α-ethyl- and α-phenylacrylophenone oxide.[823]



(482)

R = C_2H_5, C_6H_5

Brief mention may be made here, incidentally, of an interesting photochemical epoxide isomerization reported by Bodforss[182] to give β-diketones in small yield from several substituted benzalacetophenone oxides, as shown in Eq. (483).



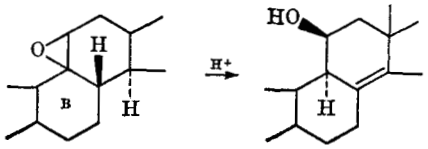
(483)

X = H, *m*-NO_2, *p*-Cl

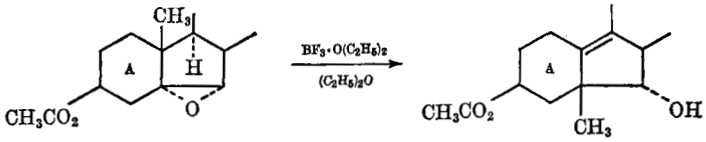
Preliminary results have recently been disclosed by Zimmerman and co-workers[1955] in connexion with the photoisomerization of *trans*-dypnone oxide and α-phenylbenzalacetophenone oxide. As in the work of Bodforss,[182] the latter gives a β-diketone, 1,2,3-triphenylpropane-1,3-dione, among other products. It is probable that numerous other epoxide isomerizations will be reported in the future by chemists active in the growing field of organic photochemistry.

Several instructive illustrations taken from the field of natural products will serve to conclude the present discussion of acid-catalyzed epoxide isomerization. Much has been said about the occurrence of simple 1,2-hydride transfers in boron trifluoride-catalyzed epoxy steroid rearrangements. Although initiated by a mineral acid rather than a Lewis acid, an instance of transannular hydride transfer has been reported for a 9β,11β-epoxy steroid,[1824] as shown in Eq. (484). Such migrations can in principle occur elsewhere.

A second curious example taken from the steroid field concerns the reaction of 5α,6α-epoxy-B-norcholesteryl acetate with boron trifluoride,[420] which gives an unsaturated alcohol in which the $C_{(19)}$-methyl has migrated in the manner depicted in Eq. (485).

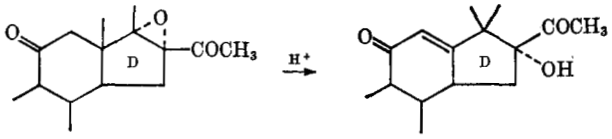


(484)



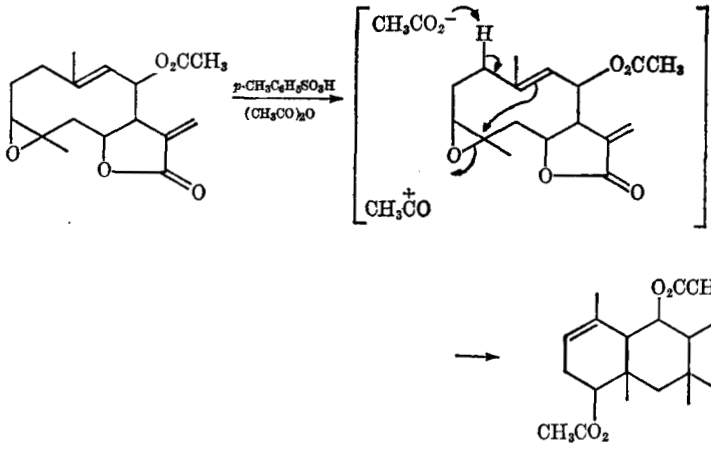
(485)

The acid-catalyzed isomerization of α,β-epoxy ketones in the steroid field is further exemplified by the novel rearrangement shown in Eq. (485a), which was investigated by Taub and co-workers.[1977]



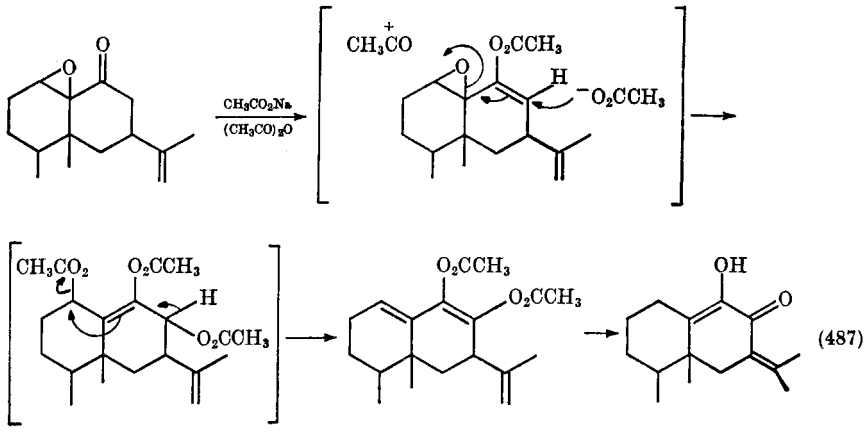
(485a)

Attention may be drawn, moreover, to acid-catalyzed rearrangements of pyrethrosin described by Barton and co-workers,[90-96] involving migration of a double bond (π-electrons) instead of the more customary hydride ion or alkyl group (σ-electrons). The transformation shown in Eq. (486) illustrates this point.



(486)

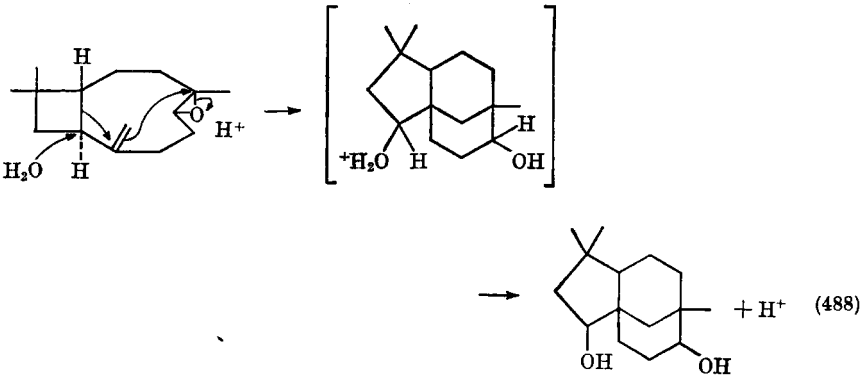
A somewhat related instance of double-bond migration initiating epoxide rearrangement is the multiple transformation of eremophilone oxide[1132] represented in Eq. (487).



(487)

The acid-catalyzed transformation of caryophyllene oxide[97] illustrates the same principle (Eq. 488).

It may be noted parenthetically that species functioning as bases (acetate ions or water) have been included in the last three examples.

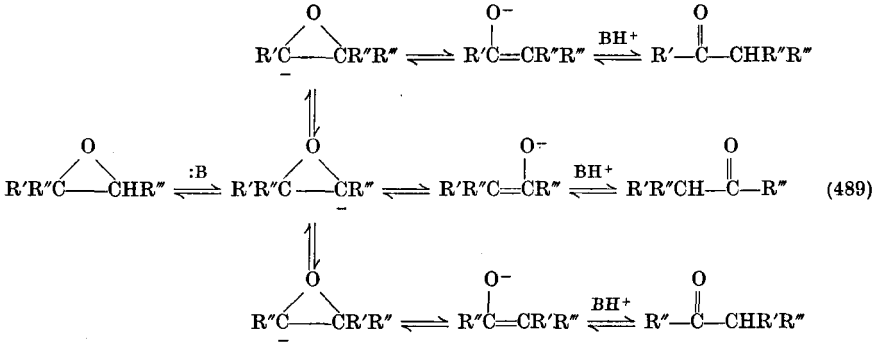


(488)

These isomerizations may therefore be classified as 'base-catalyzed', as well as acid-catalyzed; or, more accurately perhaps, as obeying the 'push–pull' principle. That bases can play a significant role in epoxide rearrangements will be seen in greater detail in the next section.

B. Base-Catalyzed Isomerization

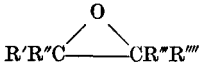
Base-catalyzed rearrangement of ethylene oxides is a topic that has, until now, received only limited attention in the literature, chiefly because epoxides undergo simple nucleophilic attack rather than isomerization with most bases. Strictly speaking, a base-catalyzed epoxide isomerization is one in which the initial event is direct proton abstraction from the oxide ring. This may be followed by redistribution of bonding electrons in any of several possible ways, to give ultimately one or more carbonyl compounds. For the general case the course of such a reaction may be depicted as in Eq. (489).



(489)

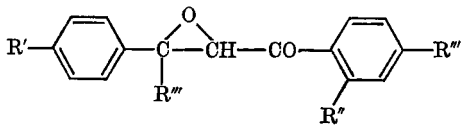
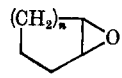
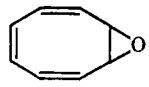
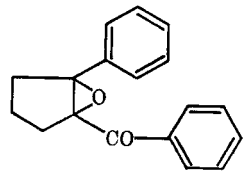
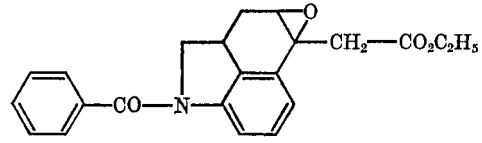
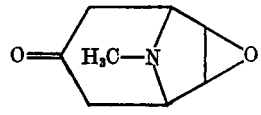
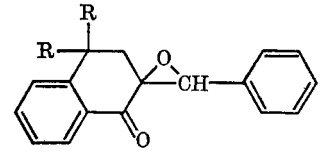
In this discussion, however, the term 'base-catalyzed epoxide isomerization' is given a somewhat broader meaning, to include also certain rearrangements initiated by proton abstraction from carbon atoms not directly part of the oxide ring. These will be taken to include not only α-carbon atoms, but also, with certain alicyclic epoxides, transannular carbon atoms as well. Table 11 lists a number of examples.

TABLE 11. Base-Catalyzed Epoxide Isomerization

Compound		Reference
	$R' = R'' = R''' = H$; $R'''' = C_6H_5CH_2$	729
	$R' = R'' = H$; $R''' = R'''' = C_6H_5$	338
	$R' = R''' = H$; $R'' = R'''' = C_6H_5$	338
	$R' = H$; $R'' = R''' = R'''' = C_6H_5$	338
	$R' = H$; $R'' = p\text{-}CH_3C_6H_4$; $R''' = R'''' = C_6H_5$	338

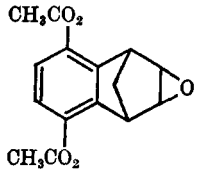
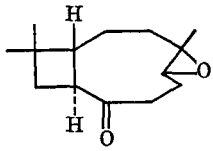
(Table continued)

TABLE 11 (*continued*)

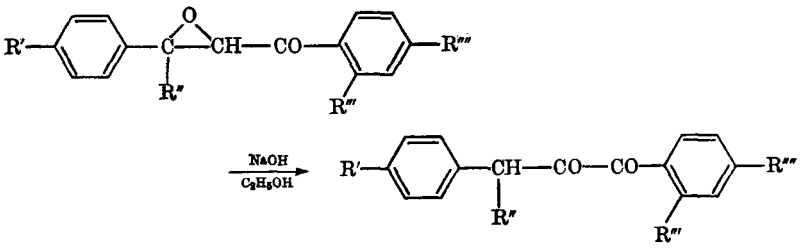
Compound		Reference
	R′ = H; R″ = R‴ = R⁗ = C_6H_5	338
	R′ = R‴ = C_6H_5; R″ = H	326, 744, 887
	R′ = R‴ = C_6H_5; R″ = Me	1809
	R′ = C_6H_5; R″ = H; R‴ = p-$CH_3OC_6H_4$	326, 744, 887
	R′ = C_6H_5; R″ = H; R‴ = 2,4-$(CH_3O)_2C_6H_5$	65
	R′ = p-$CH_3OC_6H_4$; R″ = H; R‴ = 2,4-$(CH_3O)_2C_6H_3$	65
	n = 1	1201
	n = 2	1011, 1201
	n = 3	1201
	n = 4 (*cis* and *trans*)	338, 346
	n = 6 (*cis* and *trans*)	338, 339
		350
		1809
		963
		1143
	R = H, CH_3	378

(*Table continued*)

TABLE 11 (*continued*)

Compound	Reference
	1146
	97

It was known many years ago that benzalacetophenone oxide undergoes rearrangement in ethanolic sodium hydroxide solution, giving 1,3-diphenylpropane-1,2-dione.[991] Several methoxy-substituted analogs of benzalacetophenone have likewise been isomerized to the corresponding 1,2-diones under alkaline conditions.[65, 326, 744, 1231] In each

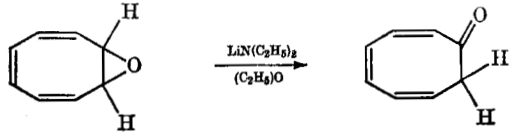


(490)

$R' = R'' = R''' = H$; $R'' = H, CH_3$
$R'' = R'' = R''' = H$; $R' = CH_3O$
$R' = R'' = R'' = H$; $R''' = CH_3O$
$R' = R'' = H$; $R'' = R''' = CH_3O$

instance the benzoyl-activated proton is probably removed first, as indicated by the smooth isomerization of *trans*-β-methylbenzalacetophenone oxide (dypnone oxide), in which no other dissociable proton exists.[1809] Bond redistribution, followed by proton abstraction from the solvent, yields the observed products (Eq. 490). Alternatively, the process might involve intramolecular proton transfer, but to date no experiments have been conducted to distinguish between these possibilities.

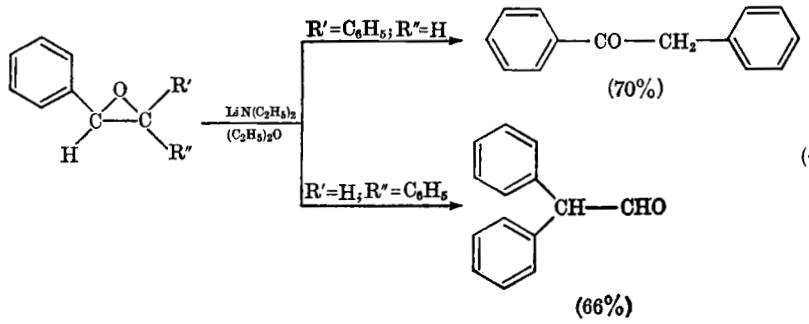
That a carbonyl function is not essential to activate epoxidic protons was demonstrated by Cope and Tiffany[350] for cyclooctatetraene oxide, which was shown to rearrange to 2,4,6-cyclooctatrienone in the presence of lithium diethylamide in non-polar media (Eq. 491).



(491)

Cope and co-workers[338] succeeded, in a subsequent investigation, in causing isomerization of several aryl-substituted ethylene oxides, among them *cis*- and *trans*-stilbene oxides and triphenylethylene oxide. The last proved to be somewhat unreactive, but could be rearranged on replacement of ether with benzene as the reaction medium. In contrast, 1,1-diphenylethylene oxide and tetraphenylethylene oxide failed to undergo isomerization even in benzene.

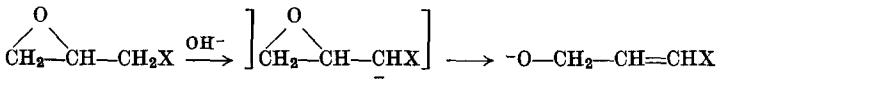
The stereospecific character of this reaction was indicated by the nature of products secured from *cis*- and *trans*-stilbene oxides. Whereas the former afforded only desoxybenzoin, the latter yielded diphenylacetaldehyde exclusively (Eq. 492). Unlike acid-catalyzed migrations to electron-deficient centers, therefore, the base-catalyzed epoxide isomerizations under scrutiny appear to involve *cis*-migration and frontal attack upon an anionic center.[338]



(492)

Culvenor and co-workers[388] contributed two interesting illustrations of base-catalyzed epoxide isomerization (Eq. 493). The first consists of the rearrangement of glycidonitrile to 3-cyanoallyl alcohol

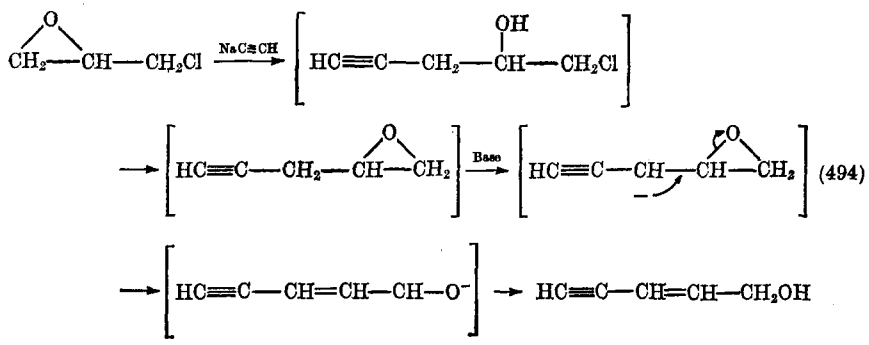
in alkali; the second, of the rearrangement of phenyl glycidyl sulfone to the corresponding allyl alcohol.



$$\longrightarrow HOCH_2—CH=CHX \quad (493)$$

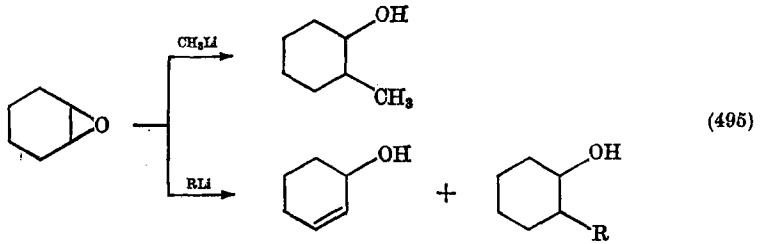
X = CN, $C_6H_5SO_2$

A related process had been invoked previously[729] to rationalize the formation of 1-hydroxy-2-penten-4-yne on condensation of epichlorohydrin with sodium acetylide. The steps represented in Eq. (494) were postulated.



(494)

Mention should be made here of an interesting observation made by Letsinger and co-workers[1011] while attempting to add various alkyllithium reagents to cyclohexene oxide (Eq. 495). Methyllithium

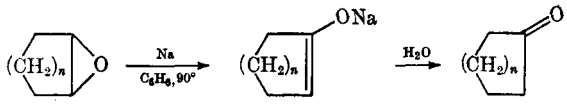


(495)

R = n-C_3H_7, n-C_4H_9

condensed normally to give 2-methylcyclohexanol. On the other hand, n-propyllithium and n-butyllithium gave mainly cyclohexen-3-ol, together with small quantities of the desired products, even when the

reaction was conducted in the absence of lithium halides (for the complicating effects of halide salts on Grignard and related condensations see section **IV.4.*E.***). These unexpected results must presumably be attributed not to the base strength of the reagent alone, but also to the capacity of lithium to co-ordinate with the epoxide oxygen and

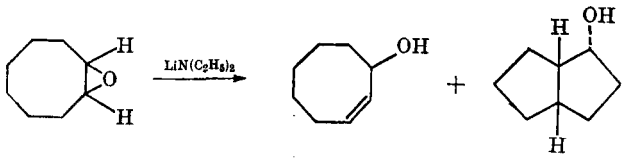


(496)

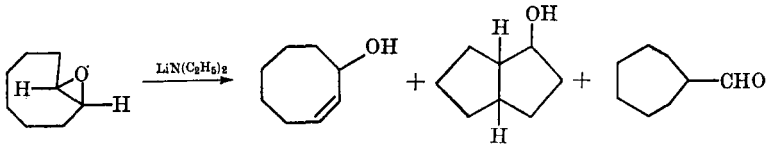
$n = 1, 2, 3$

thereby assist ring rupture. In this respect the reaction might, in fact, be better regarded as a 'push–pull' type of rearrangement.

It had actually been demonstrated earlier by Mousseron and co-workers[1201] that certain alicyclic epoxides give sodium enolates on treatment with metallic sodium in refluxing benzene (Eq. 496). Ketones obtained in this fashion, after hydrolysis of the sodium



(497)



(498)

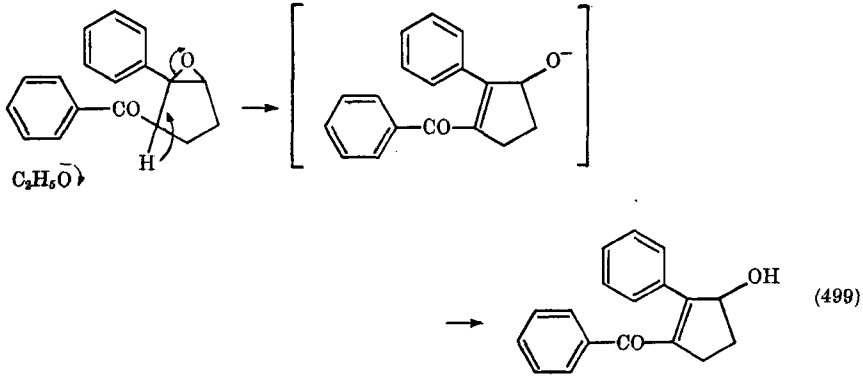
enolates, include cyclopentanone, cyclohexanone, cycloheptanone, and others. Not all epoxides were found capable of undergoing this base-catalyzed isomerization, however.[1201]

Cope and co-workers[338, 346] conducted elegant studies of the effect of strong bases like lithium diethylamide and phenyllithium on the *cis*- and *trans*-isomers of cyclooctene oxide (Eqs. 497 and 498). Complex

product mixtures were obtained with each isomer, but the composition of these mixtures plainly indicated that the simple mechanism outlined previously was inadequate in this case, and proved transannular effects to be operative.

Additional experiments conducted by Cope and co-workers[338, 339] on the *cis*- and *trans*-isomers of cyclodecene oxide yielded similar results. Detailed mechanistic aspects of these transannular epoxide isomerizations have recently been further clarified by Cope and co-workers[338, 342] by deuterium labeling.

Wasserman and Gorbunoff[1809] have published a good illustration of base-catalyzed epoxide isomerization in which the activated proton

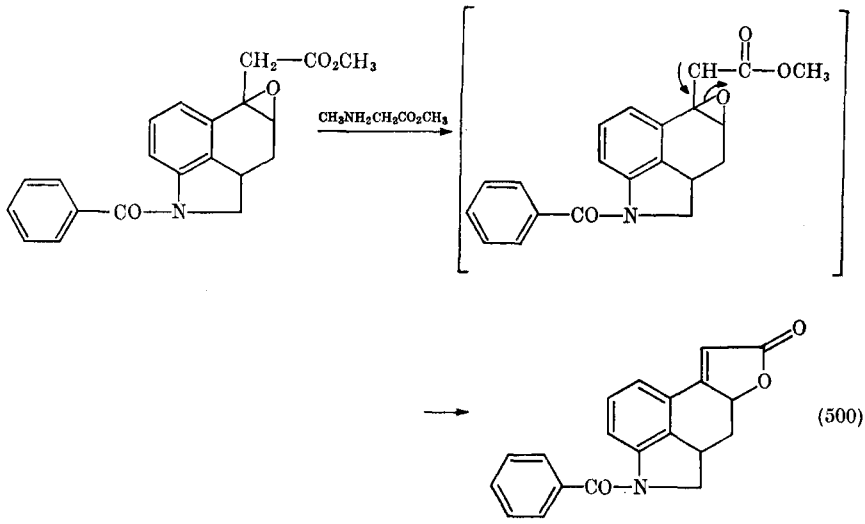


(499)

is on the α-carbon atom, instead of directly on the epoxide ring. Treatment of 1,2-epoxy-3-benzoyl-2-phenylcyclopentane with ethanolic sodium ethoxide gave 1-benzoyl-2-phenylcyclopenten-3-ol by the process depicted in Eq. (499).

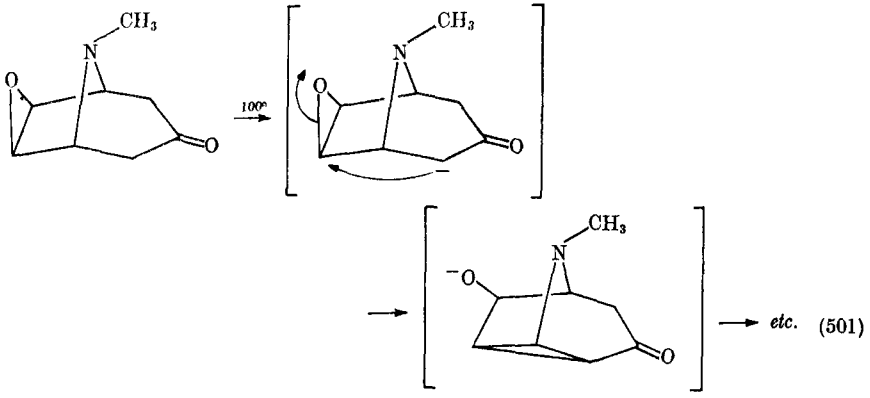
A further example of the same type of rearrangement is provided by the observation of Kornfeld and co-workers,[963] drawn during their synthesis of lysergic acid, that treatment of the β,γ-epoxy ester derivative shown in Eq. (500) with the base sarcosine (the ethyl ester of *N*-methylglycine) led to a lactone instead of the desired nucleophilic addition product.

A novel reaction of scopinone, yielding *m*-hydroxybenzaldehyde, may be mentioned to illustrate still another type of 'base-catalyzed epoxide isomerization', always within the rather liberal definition adopted for this term here. Meinwald and Chapman[1143] have postulated the first step in this deep-seated rearrangement to be proton abstraction from the activated methylene group (doubly activated by the carbonyl



(500)

function and the neighboring electronegative nitrogen atom). The anion generated in this fashion (Eq. 501) opens the epoxide ring intramolecularly, and the unstable bridged species thus produced can undergo further bond redistribution to give the final aromatic product. The

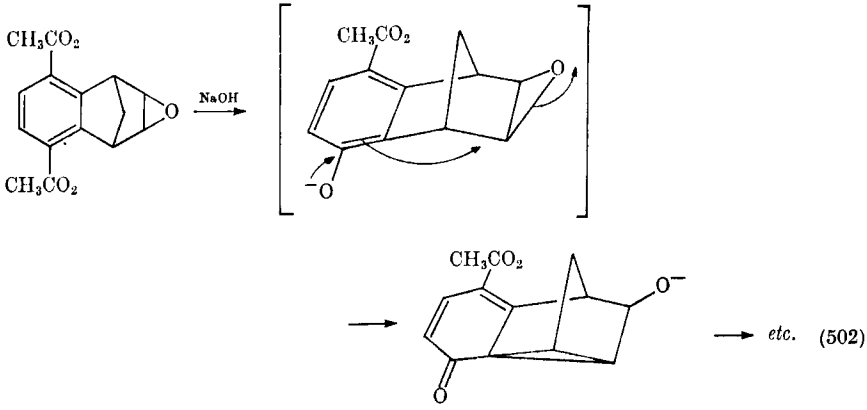


(501)

exact course of reaction following the initial proton abstraction is not, however, known with certainty.

Reference may also be made, in the same connexion, to a related base-catalyzed rearrangement mechanism, suggested also by Meinwald

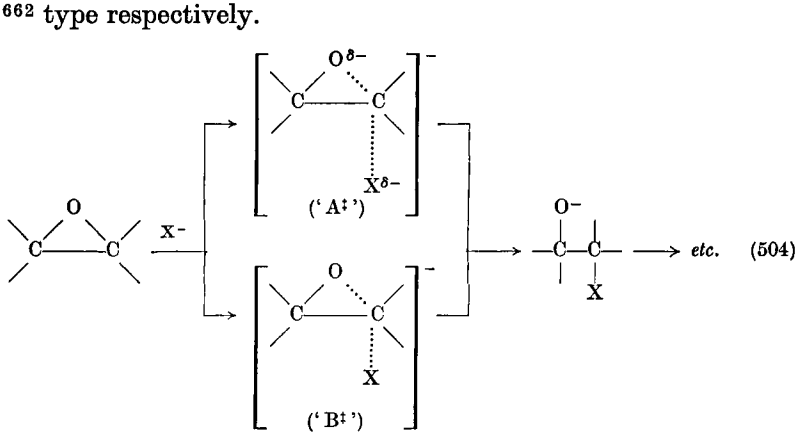
and co-workers,[1146] and involving participation by a pair of aromatic π-electrons instead of σ-electrons (Eq. 502).


CH3CO2
NaOH
CH3CO2
CH3CO2
O
O
O

catalysis. The singularly complex interplay of these forces in epoxide chemistry will become amply evident during the subsequent discussion.

Several significant reviews have appeared in recent years which contributed greatly to current knowledge of epoxide reaction mechanisms. Among them may be cited excellent discussions by Winstein and Henderson,[1857] Eliel,[490] and Parker and Isaacs.[1301] Older articles of an encyclopedic nature include those of Bodforss,[185] Meerwein,[1136] and Tiffeneau.[1717] The well-known review by Streitwieser[1662] may be consulted for a broader treatment of nucleophilic displacement reactions in general.

Parker and Isaacs[1301] have formulated what appears to be the most acceptable theoretical model yet devised to account for the enormous variety of reactions to which epoxides may be subjected. According to these authors, ethylene oxides react by either or both of two limiting processes, which are of the true S_N2 and of the 'borderline S_N2'[1662] type respectively.



(504)

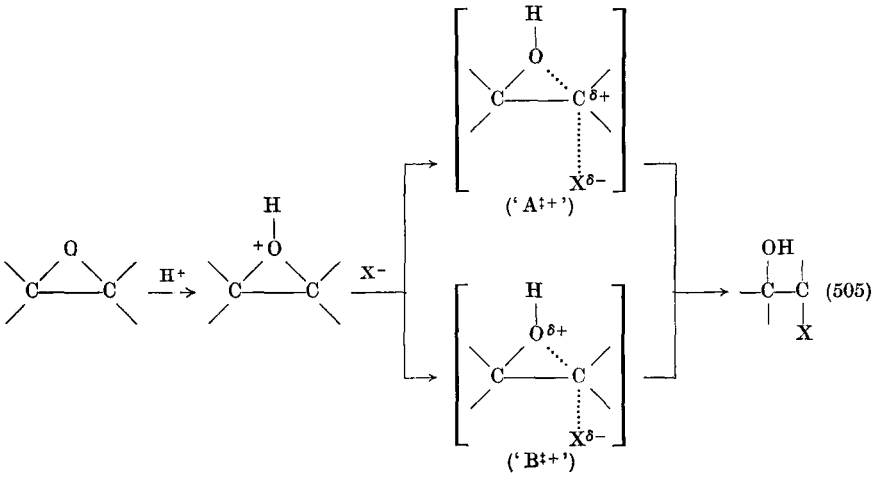
Unlike the classical S_N1 and S_N2 mechanisms of nucleophilic substitution, these processes both involve Walden inversion at the reaction site. It appears, moreover, that both are bimolecular as well, although some conflict exists in the literature on this particular point.[1027, 1045, 1301, 1416, 1417, 1673] Where they do differ, however, is in relative proportions of bond forming and bond breaking in the transition states involved. The latter may be depicted as shown in Eq. (504) for the general case, where X^- is a nucleophilic anion but could equally well be replaced by some neutral species X.

Of the two transition states ('A‡') and ('B‡'), the first clearly entails less bond forming than does the second, and therefore more nearly resembles a conventional S_N1 transition state in that respect.

Somewhat like a S_N1 transition state also, ('A‡') is stabilized by inductive or mesomeric electron release from nearby substituents. That a fully developed carbonium ion is not generated, however, has been firmly established by numerous stereochemical studies demonstrating inversion at the reaction site. There appears, generally, to be sufficient evidence to justify the designation of transition state ('A‡') as a 'borderline S_N2' transition state.[1301]

The second transition state ('B‡') evidently resembles rather closely the true S_N2 transition state. Increasing alkyl substitution, for example, causes a corresponding increase in the activation energy required to form it. Non-polar solvents, on the other hand, lower the activation energy, in line with their recognized ability to accommodate dispersal of like change. Where ('B‡') does presumably differ from a pure S_N2 transition state, however, is in the fact that the geometry of the epoxide ring renders unattainable one of the cardinal conditions for a classical S_N2 transition state, namely, linear disposition of the incoming nucleophile, the carbon atom undergoing substitution, and the departing epoxide oxygen atom.

As will become amply evident in subsequent discussion, acid-catalysis promotes epoxide ring cleavage to a singular degree. Protonation of the epoxide oxygen atom gives an oxonium ion, in which C—O bond rupture is facilitated by the positive charge on the oxygen terminal atom. As in the uncatalyzed case, epoxide reactions may be imagined to proceed by one or both of two limiting pathways in the presence of acid, involving the transition states ('A‡+') and ('B‡+') shown in Eq. (505).



Although perhaps an over-simplification, the Parker–Isaacs model satisfactorily explains the vast majority of the known reactions of epoxides. A number of experimental observations are difficult to reconcile with it, as Parker and Isaacs themselves point out.[1301] Certain of these alleged inconsistencies are the results of faulty experimentation, and can perhaps be eliminated on repetition of the work in question. Others will vanish, it is to be hoped, as further refinements of the present model are developed.

A. Hydroxylic Nucleophiles

Condensations of hydroxylic nucleophiles with ethylene oxides, when considered as a whole, probably constitute the largest single body of epoxide reactions. Included among these nucleophiles are water itself, the aliphatic alcohols, and the aromatic alcohols or phenols. The present section will be devoted to the reactions of these substances.

(1) Water. Among the first reactions of ethylene oxide discovered by Wurtz during his pioneering studies in this field was hydration.[1889] Condensation of ethylene oxide and water in a sealed tube at 100–120° was found to give mainly ethylene glycol. But it was already evident even then, however, that substances of high molecular weight also tend to be produced in such reactions. Wurtz correctly formulated these by-products as poly(ethylene glycols) (Eq. 506).

$$\underset{\diagdown\,\diagup}{\overset{O}{}}\!\!\mathrm{CH_2{-}CH_2} \xrightarrow[100\text{–}120^\circ]{H_2O} \mathrm{HOCH_2{-}CH_2OH} + \mathrm{HOCH_2{-}CH_2{-}O{-}CH_2{-}CH_2OH} + \mathrm{HOCH_2{-}CH_2{-}O{-}CH_2{-}CH_2{-}O{-}CH_2{-}CH_2OH}\ \textit{etc.} \quad (506)$$

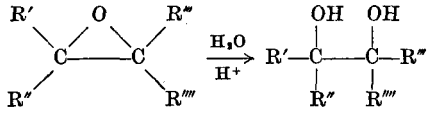
Addition of an acid catalyst allows hydration of ethylene oxide to be accomplished under much milder conditions and at a markedly faster rate.[248, 250] Numerous kinetic studies have been conducted for the reactions of ethylene oxide and several simple homologs with water, in the presence as well as the absence of acid catalysts.[248, 250, 1027, 1301, 1416, 1417, 1418, 1673, 2014, 2015]

Generally epoxide hydrations cited here will be of two types. The first involves heating the epoxide with water alone at 100–125°, frequently in a sealed tube. The second, treating it with water at moderate temperatures in the presence of a trace of acid. Most commonly employed for this purpose is sulfuric acid, although perchloric acid has likewise been reported on occasion. Acetic acid, formic acid, hydrochloric acid, hydrobromic acid, and hydroiodic acid can be used

as well, but must be very dilute to avoid formation of 1,2-diol monoesters or halohydrins (see section **IV.4.***D.* for reactions of epoxides with mineral acids and carboxylic acids).

Treatment of epoxides with concentrated formic acid or acetic acid, followed directly by alkaline hydrolysis of the resultant 1,2-diol monoester, is sometimes regarded as a 'hydration' on the basis of the final product secured in this manner. Inasmuch as reactions of epoxides with carboxylic acids are accorded separate treatment in this chapter (see section **IV.4.***D.*), however, such two-step sequences will not be included among the hydration reactions of this section.

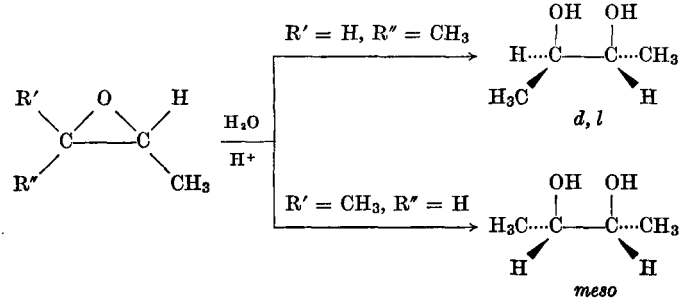
Among the many alkyl-substituted epoxides that have been reported to undergo hydration under various conditions are propylene oxide, *iso*butylene oxide, 1,2-epoxybutane, trimethylethylene oxide, and others[498, 619, 752, 1015, 1027, 1140, 1616, 1800, 1849] shown in Eq. (507).



(507)

$R'' = R''' = R'''' = H$; $R' = CH_3$, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *n*-C_6H_8, cycloC_6H_{11}
$R''' = R'''' = H$; $R' = R'' = CH_3$, C_2H_5, *n*-C_3H_7, *n*-C_4H_9
$R' = R'' = CH_3$; $R''' = H$; $R'''' = CH_3$, C_2H_5, *tert*-C_4H_9
$R'' = R'''' = H$; $R' = CH_3$; $R''' = CH_3$, C_2H_5, *n*-C_3H_7
$R' = CH_3$; $R'' = C_2H_5$, *tert*-$C_4H_9CH_2$; $R''' = R'''' = H$

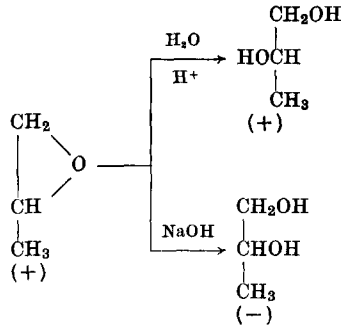
Wilson and Lucas[1849] noted the stereospecific nature of this reaction from the hydration of *cis*- and *trans*-1,2-epoxybutane, which yielded a racemic mixture and a single *meso* compound respectively on treatment with dilute aqueous sulfuric acid (Eq. 508).



(508)

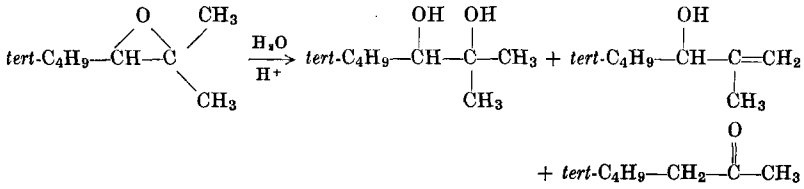
Levene and Walti[1026] have studied the course of hydration of dextrorotatory propylene oxide in acid and in alkali. Acid-catalyzed cleavage was found to involve Walden inversion at the optically active center, whereas base-initiated ring opening was attended by retention

of configuration at that site (Eq. 509). Nucleophilic attack thus appears to take place at the more highly substituted carbon atom in acid, and at the less highly substituted one in base.



(509)

Hydration of massively substituted epoxides in acid can be expected to yield significant amounts of elimination and/or rearrangement products derivable from an intermediate carbonium ion. This expectation is amply fulfilled with 2,3-epoxy-2,4,4-trimethylpentane (Eq. 510), which yields in addition to the desired 1,2-diol, an unsaturated alcohol, a ketone, and several other products.[619]

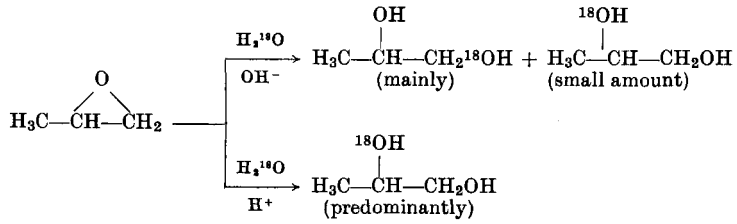


(510)

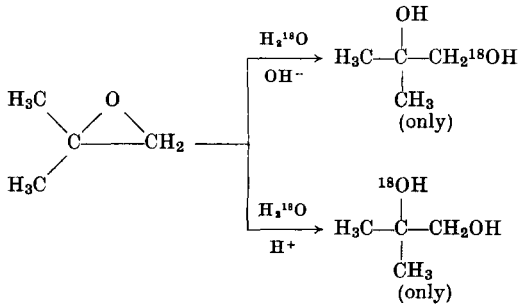
Attempts to hydrate 1,1-dibenzylethylene oxide[1025, 1026] and 1,1-di*neo*pentylethylene oxide[84] were frustrated by the singular stability of these substances under conventional hydrolysis conditions. Under forcing conditions no 1,2-diol was formed, because the carbonium ion thereby generated underwent elimination and/or rearrangement.

Pritchard and Long[1416–1418] studied the distribution of ^{18}O in products obtained on hydration of propylene oxide and *iso*butylene oxide in $H_2{}^{18}O$, both in alkaline and in acid solutions (Eqs. 511 and 512). Their results are consistent with the premise that attack by water occurs predominantly on the terminal epoxide carbon atom, unless an

acid is present, in which case the trend is sharply reversed. Hydrolysis of propylene oxide in $H_2{}^{18}O$ has likewise been investigated by Swain and Thornton.[2014]

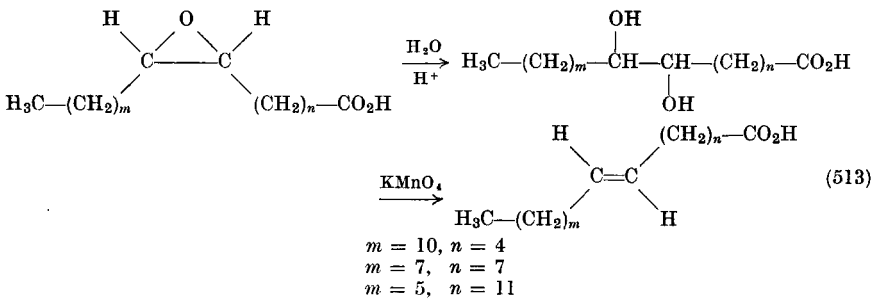


(511)



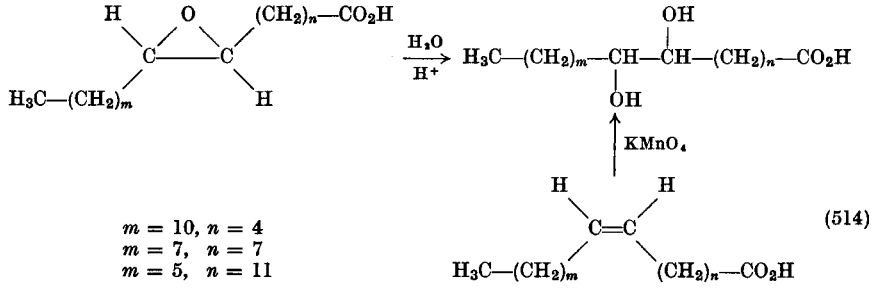
(512)

Hydration of epoxides derived from long-chain unsaturated acids or esters has been studied very extensively in a number of laboratories.[52, 930, 1623, 1677, 1689, 1868, *etc.*] Acid-catalyzed hydration of *cis*- and *trans*-2,3-epoxyoctadecanoic acid, *cis*- and *trans*-6,7-epoxyoctadecanoic acid, *cis*- and *trans*-9,10-epoxyoctadecanoic acid, and *cis*- and



(513)

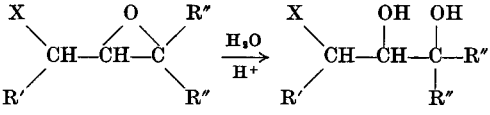
trans-13,14-docosanoic acid give 1,2-diols isomeric with those secured directly from the corresponding olefins by potassium permanganate or osmium tetroxide *cis*-hydroxylation (Eq. 513).



$m = 10, n = 4$
$m = 7, n = 7$
$m = 5, n = 11$

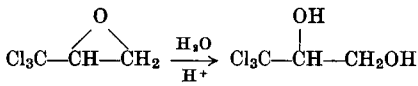
(514)

Several simple alkyl-substituted epoxides containing one or more polar atoms in the vicinity of the epoxide ring (Eqs. 515 and 516) have been hydrated to corresponding 1,2-diols.[2,199,568,1010,1139,1295,1392,1461] Two of these in particular, epichlorohydrin and glycidol, have figured prominently in the now classic kinetic study of Brønsted and co-workers,[248] and in the more recent investigation of Ross.[1491]



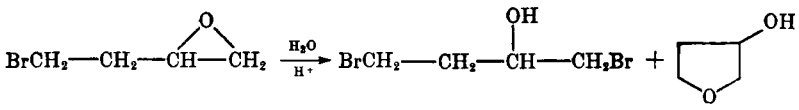
(515)

$R' = R'' = H$; X = Cl, Br, OH, *iso*C_4H_9O, C_2H_5S
$R' = H$; $R'' = CH_3$; X = Br, I
$R' = H$, CH_3; $R'' = C_2H_5$; X = Br



(516)

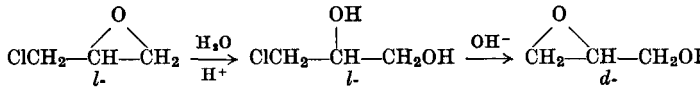
Hydration of 4-bromo-1,2-epoxybutane is unusual in that it yields not the desired 1,2-diol (Eq. 517), but instead a mixture of 1,4-dibromo-2-butanol and 2-hydroxytetrahydrofuran.[1295, 1297]



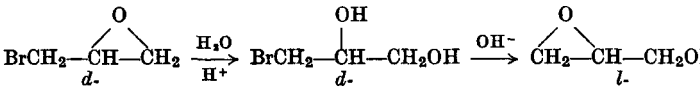
(517)

Abderhalden and Eichwald[2] examined the stereochemical consequences of acid-catalyzed *l*-epichlorohydrin and *d*-epibromohydrin

hydration (Eqs. 518 and 519). Results obtained in this study supported the premise that attack occurs at the central carbon atom under acidic conditions, and is accompanied by Walden inversion.

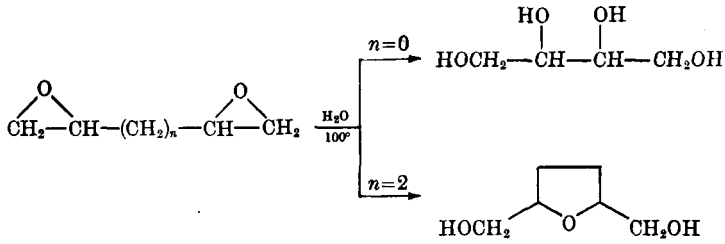


(518)



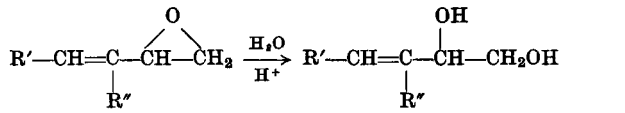
(519)

Hydration of *meso*- and *dl*-1,2;3,4-diepoxybutane has been reported[115, 525, 672, 1491] to give *meso*- and *dl*-1,2,3,4-tetrahydroxybutane respectively, in the absence of added acid or alkali (Eq. 520). The homologous bisepoxide 1,2;5,6-diepoxyhexane, on the other hand,



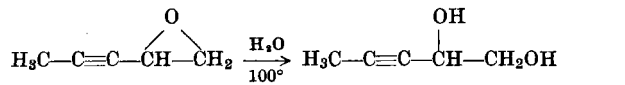
(520)

gives a tetrahydrofuran derivative rather than a tetrol, both in the presence and the absence of added acid.[1491] Kinetic measurements on the hydration rate of both these bisepoxides have been conducted by Ross,[1491] in connexion with a broad study of the relation between the nucleophilic susceptibility and biological activity of various epoxides.



(521)

R′ = R″ = H
R′ = Br; R″ = H
R′ = H; R″ = Br

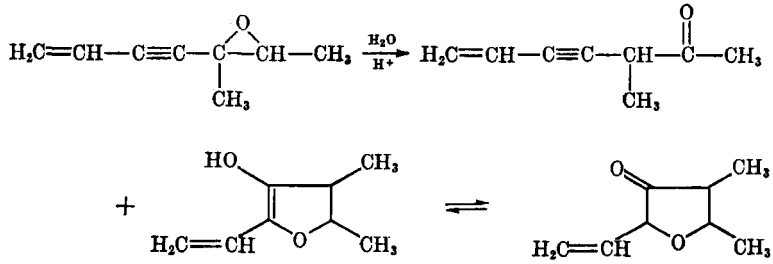


(522)

Representative of ethylenic and acetylenic epoxides that are reported to condense with water are 1,2-epoxy-3-butene[1297] and 1,2-epoxy-3-pentyne,[1010, 1360] as shown in Eqs. (521) and (522). Acid-

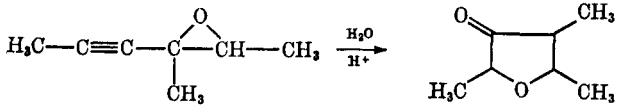
catalyzed hydration of 4-bromo- and 3-bromo-1,2-epoxy-3-butene has likewise been claimed to yield the corresponding 1,2-diols.[1354, 1356]

A more complex situation appears to exist with 2,3-epoxy-3-methyl-6-hepten-4-yne,[1342] which allegedly yields no 1,2-diol on treatment with dilute aqueous sulfuric acid, but instead the two products indicated in Eq. (523).



(523)

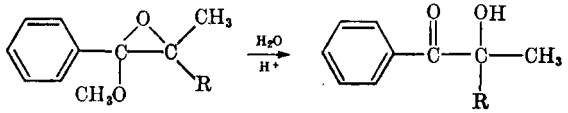
In a similar vein, acid-catalyzed hydration of 2,3-epoxy-3-methyl-4-pentyne (Eq. 524) is reported to give a tetrahydrofuran derivative rather than a 1,2-diol.[1330, 1342] The marked effect of two methyl groups will be noted on comparison with 2,3-epoxy-3-pentyne,[1010, 1360] which gives the desired 1,2-diol satisfactorily under the same conditions (Eq. 522).



(524)

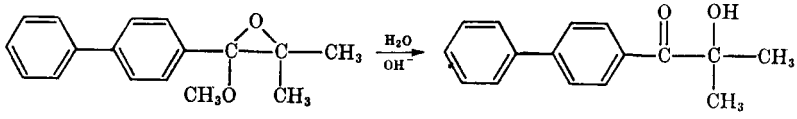
Hydration of epoxyethers has been found in three laboratories[1058, 1059, 1632, 1633, 1707] to yield α-hydroxyketones by attack of water on the methoxyl-substituted epoxide carbon atom (Eqs. 524 and 525).

Singular stability has been noted by Lyle and co-workers,[1058, 1059] on the other hand, with the epoxy ether shown in Eq. (527), which



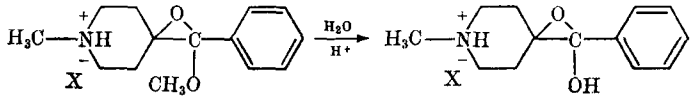
(525)

R = C_2H_5, n-C_4H_9



(526)

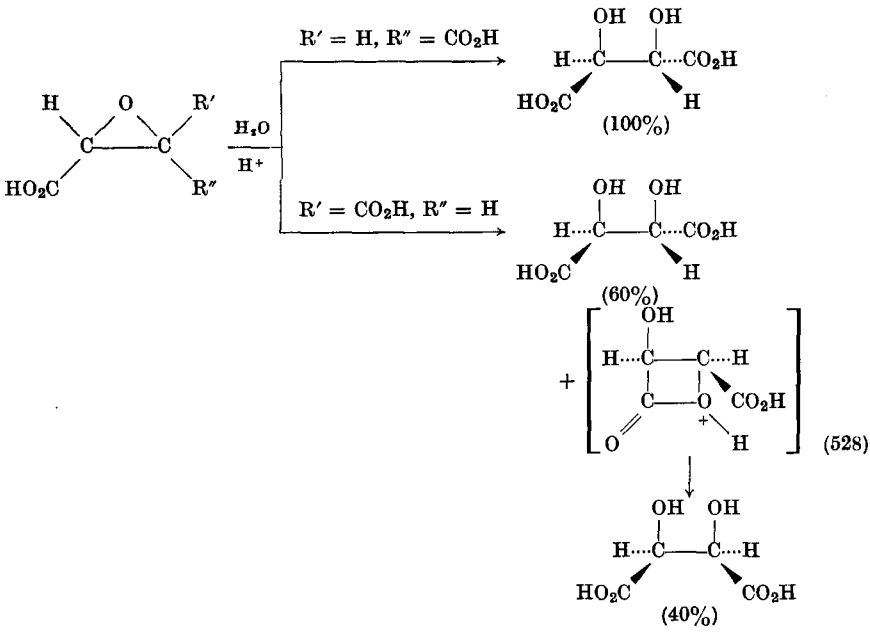
gives on treatment with aqueous acid a product formulated as an α-hemiketal, a type of epoxide virtually unique in the entire literature.



(527)

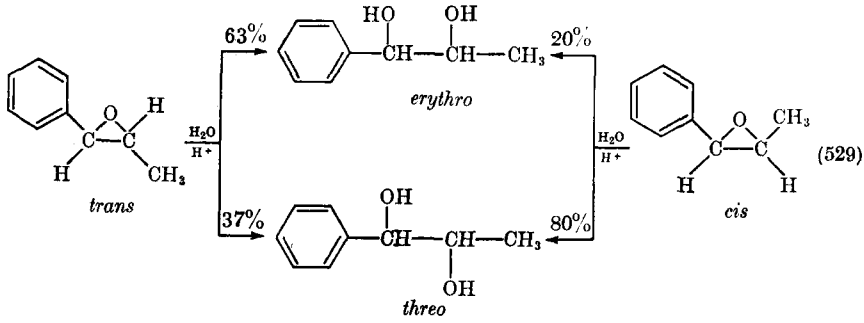
X = Br, I

A classic stereochemical investigation by Kuhn and Ebel[981] involved hydration of *cis*- and *trans*-2,3-epoxysuccinic acid (epoxymaleic acid and epoxyfumaric acid) in the presence of acid or alkali. Though the *cis*-isomer gave *erythro*-2,3-dihydroxysuccinic acid exclusively, the *trans* gave an approximately equal mixture of *threo*- and *erythro*-1,2-diols. This observation is attributable to the simultaneous operation of a normal addition process and of an 'abnormal' one leading to overall retention of configuration. The *threo*-isomer is generated by direct nucleophilic displacement, with attendant Walden inversion at the site of attack. The *erythro*-isomer, on the other hand, appears to be evolved by preliminary β-lactone formation, followed by nucleophilic ring opening. Since two Walden inversions are associated with this process, as shown in Eq. (528), no net inversion at the site of attack is to be expected.



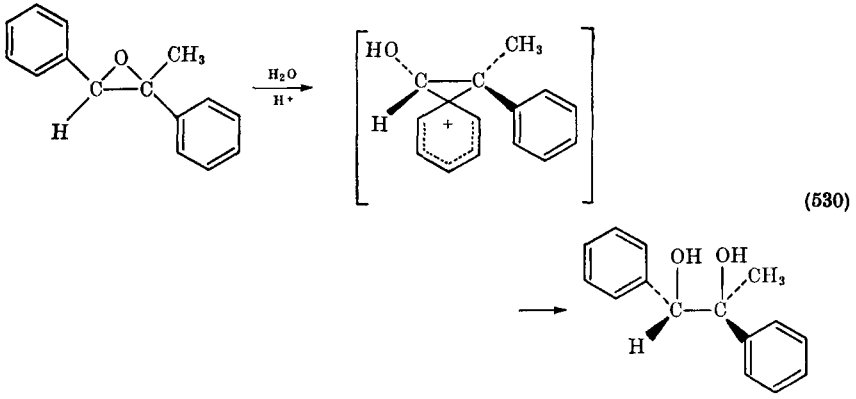
(528)

Several aryl-substituted ethylene oxides may be cited in connexion with epoxide hydration. For instance, α-methylstyrene oxide gives 1,2-dihydroxy-2-phenylpropane on careful treatment with cold dilute hydrochloric acid.[409] The isomeric substance β-methylstyrene oxide, which can exist in two geometric modifications, is reported to



give mixtures of stereoisomeric 1,2-dihydroxy-1-phenylpropanes having the compositions shown in Eq. (529).[1671, 1930, 1932, 1954]

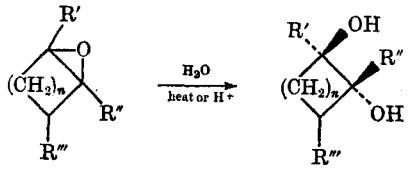
Acid-catalyzed hydration of α-methyl-*trans*-stilbene oxide has been reported by Tiffeneau and Levy,[1736] and more recently by Brewster,[243] to give a 1,2-diol whose structure likewise suggests



retention of configuration on ring opening. The most reasonable explanation for this anomalous addition, according to Parker and Isaacs,[1301] involves anchimeric assistance by the phenyl group, and nucleophilic attack by water on the bridged phenonium intermediate thereby generated. Since two Walden inversions are required by such a scheme (Eq. 530), the observed net retention of configuration at the

reaction center is satisfactorily accounted for. The possibility of a rather fully developed carbonium ion reacting stereospecifically by asymmetric induction has been intimated as well.[243]

Among the simple alicyclic epoxides known to undergo hydration readily (Eq. 531) are cyclobutene oxide,[369] cyclopentene oxide and

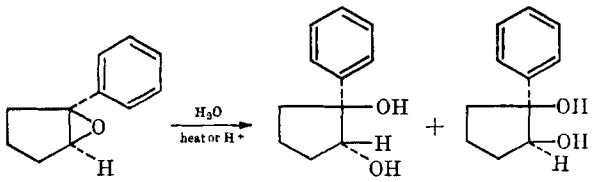


(531)

$n = 1$; R′ = R″ = R‴ = H
$n = 2$; R′ = R‴ = H; R″ = H, CH_3
$n = 2$; R′ = R″ = H; R‴ = CH_3
$n = 2$; R′ = R″ = C_2H_5; R‴ = H
$n = 3$; R′ = R‴ = H; R″ = H, CH_3
$n = 3$; R′ = R‴ = H; R″ = CH_3
$n = 3$; R‴ = H; R′ = R″ = CH_3, C_2H_5

several alkylated derivatives,[188, 442, 651, 652, 1080, 1788] and cyclohexene oxide and several alkylated derivatives.[85, 188, 204, 254, 1080, 1200, 1214, 1215, 1788, 1853] All these substances yield *trans*-1,2-diols exclusively.

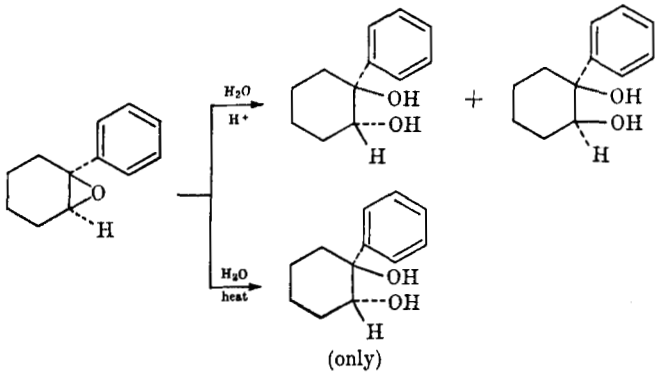
Special comment is warranted with 1,2-epoxy-1-phenylcyclopentane and 1,2-epoxy-1-phenylcyclohexane, which again represent situations in which hydration appears to occur, at least in part, with retention of configuration at the site of water attack (Eqs. 532 and



(532)

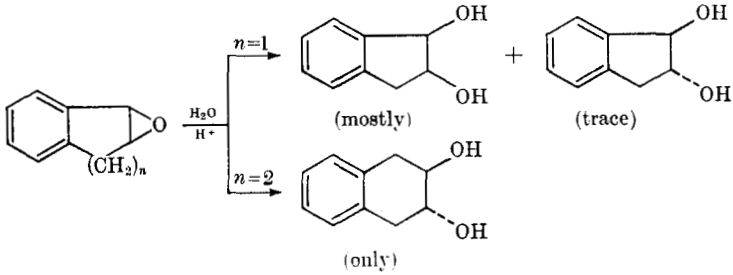
533). The first gives mixtures of *cis*- and *trans*-1,2-diols both in the presence and in the absence of acid catalyst.[188, 442, 1080, 1788] Condensation of 1,2-epoxy-1-phenylcyclohexane with water in the presence of acid likewise yields a mixture of *cis*- and *trans*-1,2-diols,[188, 1080, 1788] although allegedly giving only the *trans*-1,2-diol in the absence of acid.[1214]

Addition of water to indene oxide,[190] 1,2-dihydronaphthalene oxide,[1788] and 1,4-dihydronaphthalene oxide,[1788] in the presence of



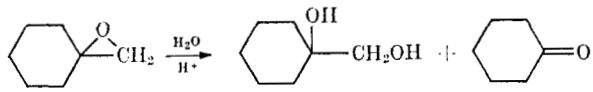
(533)

acid has been reported (Eq. 534). The first two appear to give chiefly the *cis*-1,2-diol, by some mechanism involving over-all retention of configuration. The last, on the other hand, gives a *trans*-1,2-diol exclusively.



(534)

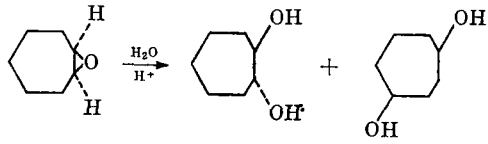
Hydrolytic cleavage of the semicyclic epoxide 1-oxaspiro[2.5]-octane has been shown[1701] to give a mixture of the expected 1-hydroxymethylcyclohexanol and the pinacolic rearrangement product cycloheptanone (Eq. 535).



(535)

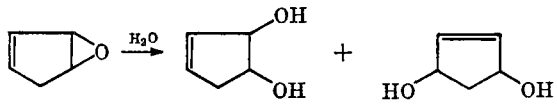
Cycloheptene oxide has long been known to undergo acid-catalyzed hydration to *trans*-1,2-dicloheptanediol.[194, 442, 649] More recent work by Cope and co-workers,[345] however, has uncovered in addition the presence of *cis*-1,4-cycloheptanediol (Eq. 536). The latter can be

derived by intramolecular hydride migration, either before or concurrent with attack by water.



(536)

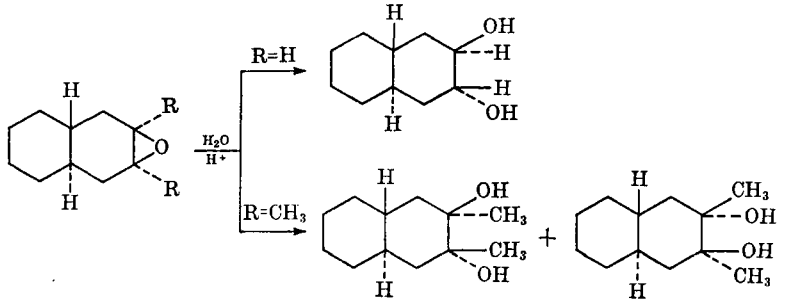
Similarly, Cope and co-workers[340, 344] identified *trans*-1,2-cyclooctanediol and *cis*-1,4-cyclooctanediol among the products obtained on treatment of *cis*-cyclooctene oxide with dilute hydrochloric acid. The 'hydration' of cyclooctene oxides by the two-step process of formic acid addition and subsequent hydrolysis will be considered at greater length elsewhere (see section **IV.4.***D*).



(536a)

Hydration of 1,2-epoxycyclopent-3-ene has been found by Korach and co-workers[962] to give a mixture of two isomeric *cis* diols, as shown in Eq. (536a). The reaction is reported to be singularly facile.

Interesting results have been obtained with 2,3-epoxy-*trans*-decalin and 2,3-epoxy-2,3-dimethyl-*trans*-decalin (Eq. 537). Whereas

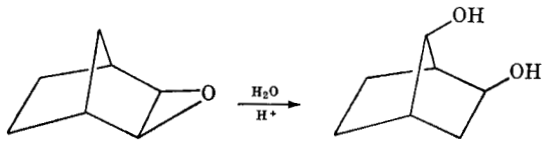


(537)

the former gives only one *trans*-2,3-dihydroxytetralin, identified as the diaxial isomer,[739] the latter yields two, shown to be diaxial and diequatorial *trans*-2,3-dihydroxy-2,3-dimethyltetralin respectively.[23]

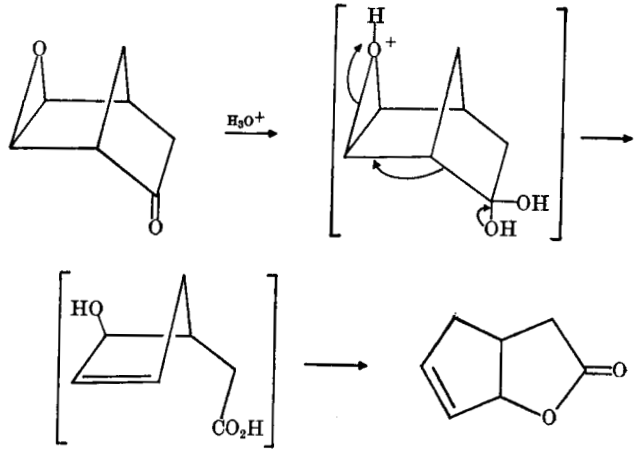
Walborsky and Loncrini,[1795] and also Kwart and Vosburgh,[986] demonstrated that hydration of 2,3-*endo*epoxybicyclo[2.2.1]heptane in

dilute aqueous sulfuric acid gives rise to skeletal rearrangement with formation of 2,7-dihydroxybicyclo[2.2.1]heptane (Eq. 538).



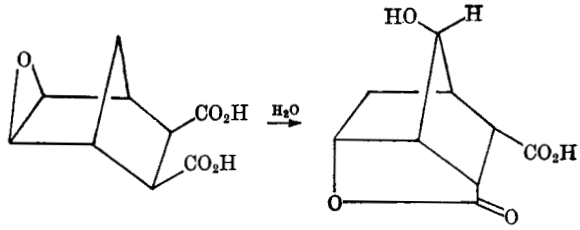
(538)

Meinwald and Cadoff[1964] have studied the acid-catalyzed hydration of 2,3-*endo*epoxy-4-oxobicyclo[2.2.1]heptane, which was found to yield the lactone according to the route shown in Eq. (538a).



(538a)

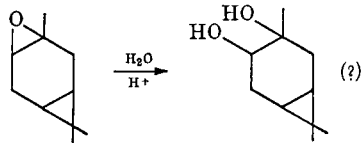
Berson and Suzuki[1999] carried out the hydration of *exo*-1,2-epoxy bicyclo[2.2.1]octane *exo*-4,5-dicarboxylic acid, and isolated a lactone believed to be the skeletal rearrangement product depicted in Eq. (538b).



(538b)

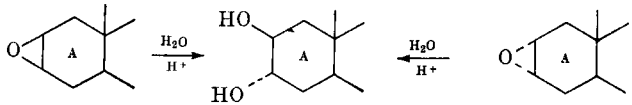
Condensation of water with several epoxides derived from monoterpenes has been reported on numerous occasions, but considerable uncertainty surrounds some of the published results, since complex rearrangements are the rule more often than not.

Pillay and Simonsen[1368] have stated, for example, that a substance formulated by them as *d*-Δ^3-carene oxide is stable to aqueous sulfuric acid. Arbuzov and Michailov,[39] on the other hand, also claim to have prepared this epoxide, but report success in forming the corresponding 1,2-diol on exposure to conventional hydrolysis conditions (Eq. 539). To date this question apparently remains unresolved, although the physical properties reported for the two supposed epoxides are different.



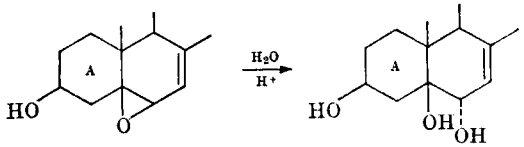
(539)

Addition of water to steroids may be illustrated by the observation of Shoppee and co-workers[1574] that treatment of 2β,3β- and 2α,3α-epoxy steroids with dilute acid yields identical diaxial products (Eq. 540).



(540)

A more recent example[289] involves hydration of a Δ^7-5β,6β-epoxy steroid to the corresponding 5β,6α-diol as shown in Eq. (541).



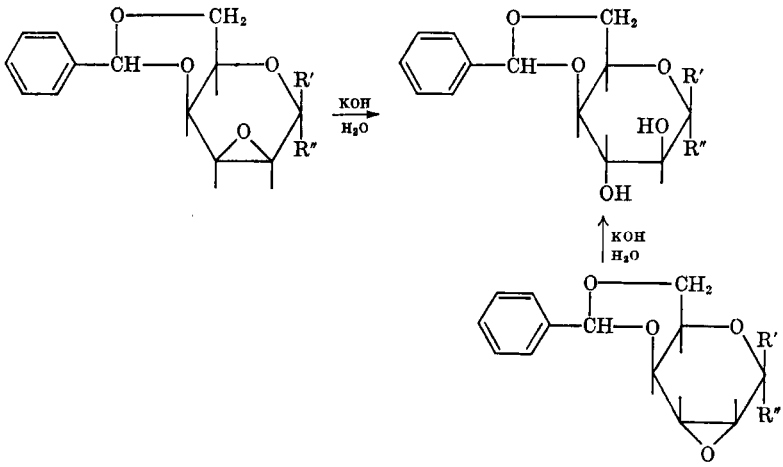
(541)

Numerous epoxy sugars have been hydrolyzed in aqueous base, among them almost all the possible 2,3-anhydro-4,6-*O*-benzylidene α- and β-methyl glycosides of D-talose,[697, 1611] D-gulose,[697, 1611] D-mannose,[674] and D-allose[674, 1320, 1459, 1474] as indicated in Eq. (542).

Similarly, 2,3-anhydro-4,6-di-*O*-methyl α- and β-methyl glycosides of D-allose (Eq. 544) give the corresponding derivatives of D-altrose,[1320, 1471] attack occurring at $C_{(2)}$ as above.

Honeyman[801] has reported, on the other hand, that addition of water to methyl 2,3-anhydro-β-D-ribopyranoside (Eq. 545) takes place at $C_{(3)}$, rather than $C_{(2)}$, giving methyl β-D-xyloside.

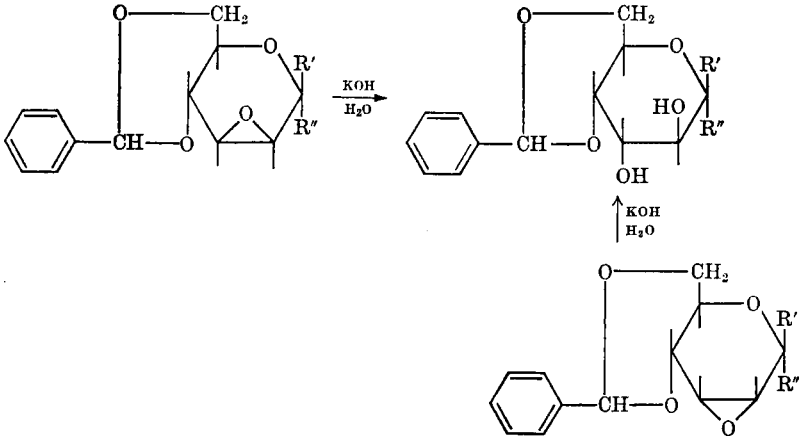
Acid-catalyzed sugar epoxide hydration has also been carried out in a few instances. Müller[1207, 1208] and more recently Buchanan,[258]



(542)

$R' = CH_3O$, $R'' = H$
$R' = H$, $R'' = CH_3O$

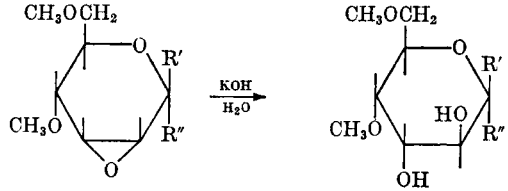
$R' = CH_3O$, $R'' = H$
$R' = H$, $R'' = CH_3O$



(543)

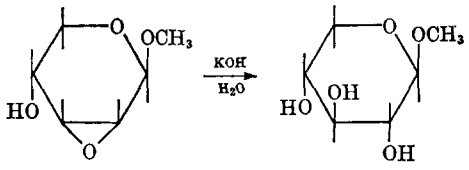
$R' = H$, $R'' = CH_3O$

$R' = H$, $R'' = CH_3O$



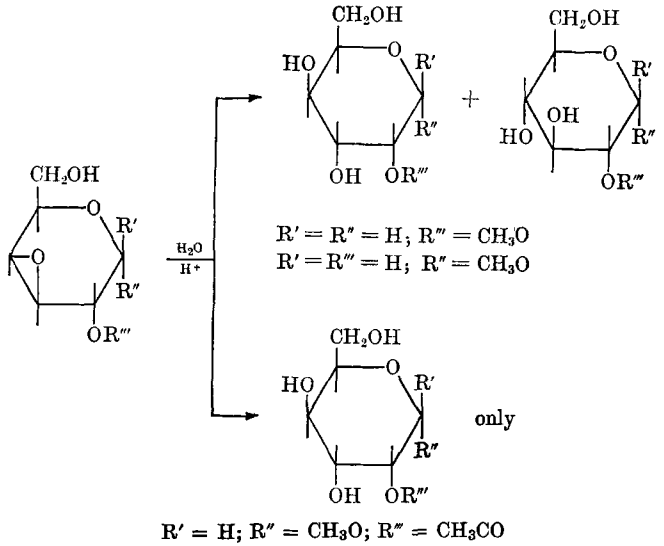
(544)

$R' = CH_3O$, $R'' = H$
$R' = H$, $R'' = CH_3O$



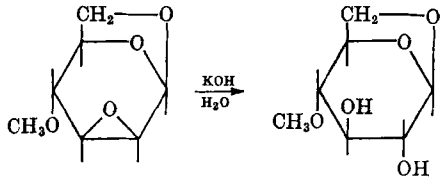
(545)

for example, have converted the α- and β-methyl glycosides of 3,4-anhydro-D-galactose to the corresponding derivatives of D-gulose and D-glucose, as shown in Eq. (546). Buchanan[258] incidentally also demon-



(546)

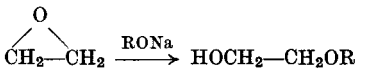
strated that the presence of an *O*-acetyl substituent in methyl 3,4-anhydro-α-D-galactoside directs the attacking nucleophile exclusively to $C_{(3)}$, so that only methyl 3-*O*-acetyl-α-D-guloside is produced.



(547)

Jeanloz,[1941] finally, has reported the cleavage of 4-*O*-methyl 2,3;1,6-dianhydro-β-D-mannose with base to 4-*O*-methyl-2,3;1,6-dianhydro-β-D-glucose, as shown in Eq. (547).

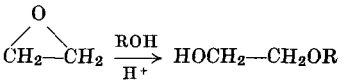
(2) Alcohols. The reaction between ethylene oxide and ethanolic alkali has been used for at least 60 years to prepare monoalkyl ethers of ethylene glycol, and was probably known much earlier but somehow remained neglected. In 1894 Roithner[1483] published the observation that sodium ethoxide and ethylene oxide undergo condensation to give β-ethoxyethanol. Then 30 years later Cretcher and Pittenger[367] extended the scope of the reaction to include all alcohols up to *n*-pentanol (Eq. 548).



$$\underset{\diagup\,\text{O}\,\diagdown}{\text{CH}_2\text{—CH}_2} \xrightarrow{\text{RONa}} \text{HOCH}_2\text{—CH}_2\text{OR} \qquad (548)$$

R = CH_3, C_2H_5, *n*-C_3H_7, *iso*C_3H_7, *n*-C_4H_9, *iso*C_4H_9, *n*-C_5H_{11}

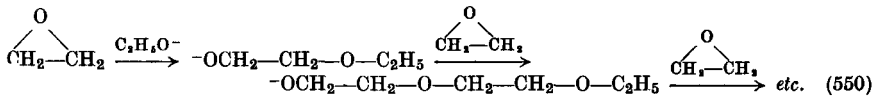
A profound catalytic effect by traces of mineral acid was first noted by Ashburn and co-workers,[50] who exploited this observation to the fullest in the preparation of an impressive series of ethylene glycol monoalkyl ethers (Eq. 549).



$$\underset{\diagup\,\text{O}\,\diagdown}{\text{CH}_2\text{—CH}_2} \xrightarrow[\text{H}^+]{\text{ROH}} \text{HOCH}_2\text{—CH}_2\text{OR} \qquad (549)$$

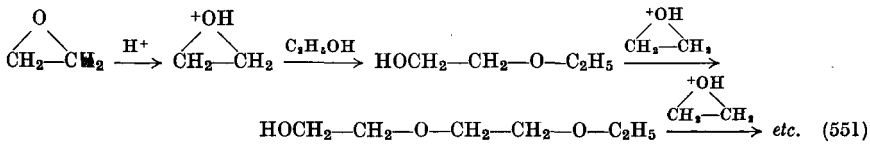
R = CH_3, C_2H_5, *n*-C_3H_7, *iso*C_3H_7, *n*-C_4H_9, *sec.*-C_4H_9, *tert*-C_4H_9, *n*-C_5H_{11}, *etc.*

The kinetics of the reaction between ethylene oxide and various alcohols has been a subject of some interest as an application of the theory of consecutive reactions.[593, 1162, 1217, 1303] With ethanol, for example, a sequence of steps may be written in the manner depicted in Eq. (550), and a complex kinetic expression derived for the rate of ethylene oxide disappearance.



$$\underset{\diagup\,\text{O}\,\diagdown}{\text{CH}_2\text{—CH}_2} \xrightarrow{C_2H_5O^-} {}^-\text{OCH}_2\text{—CH}_2\text{—O—}C_2H_5 \xrightarrow{\underset{\diagup\,\text{O}\,\diagdown}{\text{CH}_2\text{—CH}_2}} {}^-\text{OCH}_2\text{—CH}_2\text{—O—CH}_2\text{—CH}_2\text{—O—}C_2H_5 \xrightarrow{\underset{\diagup\,\text{O}\,\diagdown}{\text{CH}_2\text{—CH}_2}} \textit{etc.} \qquad (550)$$

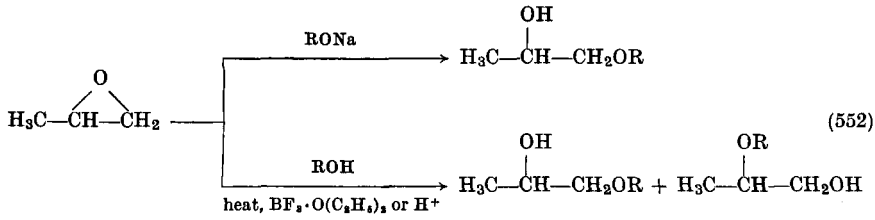
When condensation is brought about in the presence of catalytic amounts of acid, a similar series of steps may be envisaged (Eq. 551).



$$\underset{\diagup\,\text{O}\,\diagdown}{\text{CH}_2\text{—CH}_2} \xrightarrow{\text{H}^+} \underset{\diagup\,{}^+\text{OH}\,\diagdown}{\text{CH}_2\text{—CH}_2} \xrightarrow{C_2H_5OH} \text{HOCH}_2\text{—CH}_2\text{—O—}C_2H_5 \xrightarrow{\underset{\diagup\,{}^+\text{OH}\,\diagdown}{\text{CH}_2\text{—CH}_2}} \text{HOCH}_2\text{—CH}_2\text{—O—CH}_2\text{—CH}_2\text{—O—}C_2H_5 \xrightarrow{\underset{\diagup\,{}^+\text{OH}\,\diagdown}{\text{CH}_2\text{—CH}_2}} \textit{etc.} \qquad (551)$$

The practical consequence of these consecutive reactions is that higher condensation products are invariably formed when ethylene oxide is passed continuously through alcoholic solutions, whether they be alkaline, neutral, or acidic. Monoalkyl ethers of ethylene glycol can normally be removed without difficulty from such higher condensates by straightforward fractional distillation. From a commercial point of view, higher-boiling products are of course also of considerable interest, and their fractionation constitutes one of the important processes of industrial chemistry.

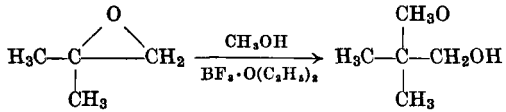
When propylene oxide (Eq. 552) is treated with sodium alkoxides, attack appears to occur exclusively on the terminal epoxide carbon atom, the only β-alkoxyalcohols recoverable from higher condensates being 1-alkoxy-2-propanols.[309, 681, 1079, 1358, 1561] In contrast, however, heating propylene oxide with an alcohol in an autoclave, in the absence of added alkali, yields a mixture of primary and secondary alcohols.[338, 1530] The use of catalytic amounts of sulfuric acid or boron trifluoride likewise causes formation of such mixtures.[309, 1358]



(552)

R = CH_3, C_2H_5, *iso*C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}

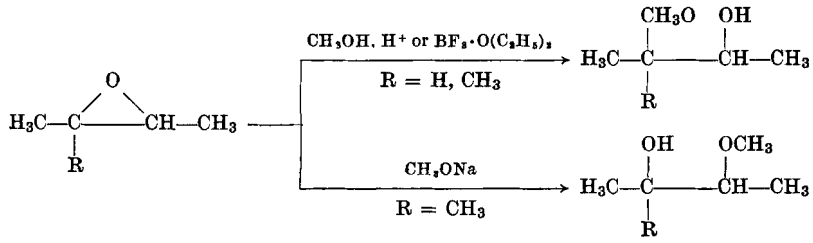
Treatment of *iso*butylene oxide with methanol (Eq. 553) in the presence of a trace of boron trifluoride is reported to give only 2-methoxy-2-methyl-1-propanol, along with polymerization products and *iso*butyraldehyde (isolated as its dioxolane derivative).[1355] It is perhaps surprising that no 1-methoxy-2-methyl-2-propanol was formed at all under these conditions.



(553)

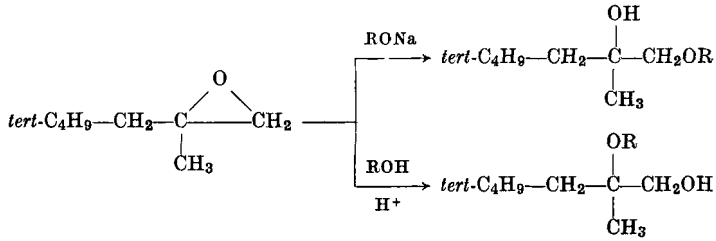
Addition of methanol to 2,3-epoxybutane yields 2-methoxy-3-butanol in the presence of boron trifluoride catalyst.[345, 1355] Attack of sodium methoxide takes place at the terminal epoxide carbon atom of

2,3-epoxy-2-methylbutane, giving 3-methoxy-2-methyl-2-butanol (Eq. 554). The same epoxide gives chiefly 3-methoxy-3-methyl-2-butanol, however, when the addition of methanol is catalyzed by boron trifluoride or sulfuric acid.[1361, 1859]



(554)

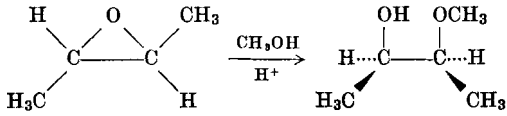
A similar reversal in the sense of alcohol addition has been noted by Graham and co-workers[663] with 1,2-epoxy-2,4,4-trimethylpentane (Eq. 555).



(555)

R = CH_3, C_2H_5

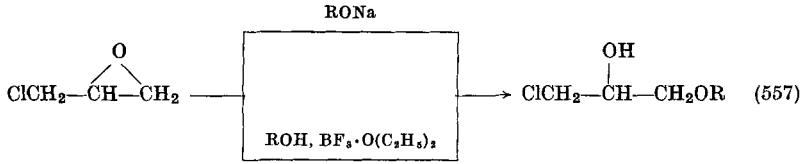
Evidence of the stereospecific character of this reaction was secured by Helmkamp and Lucas[733] through condensation of methanol with dextrorotatory *threo*-2-3,epoxybutane in the presence of catalytic amounts of acid (Eq. 556). The sole product was shown to be optically active *erythro*-3-methoxy-2-butanol, since methylation afforded *meso*-2,3-dimethoxybutane.



(556)

Several ethylene oxides containing one or more polar atoms on carbon atoms adjacent to the epoxide ring have been condensed with alcohols under various conditions. Greatest attention has been given to epichlorohydrin in this connexion.

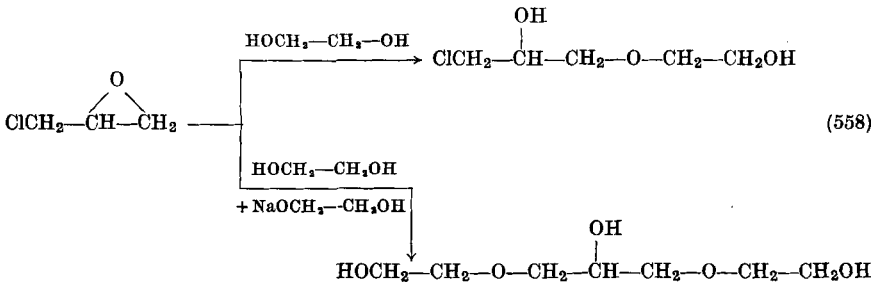
Cretcher and Pittenger,[367] and also Fairbourne and co-workers,[513] have described the addition of various alkoxide ions to epichlorohydrin. The reaction is rather slow, but products are formed as anticipated by attack on the terminal epoxide carbon (Eq. 557). The same products have been reported by several authors[513, 551, 569, 1355, 1388, 1782] to form likewise under acid conditions. Apparently the electronegativity of the chlorine atom overcomes the normal tendency for attack at the most highly alkylated carbon atom under acidic conditions.



(557)

R = CH_3, C_2H_5, *n*-C_3H_7, *iso*C_3H_7, *n*-C_4H_9, *iso*C_4H_9, *n*-C_5H_{11}

Ethylene glycol has likewise been found to condense with epichlorohydrin.[926] In the absence of alkali, simple addition at the terminal epoxide carbon atom occurs, but in the presence of the monosodium glycolate a halogen-free product is isolated, which appears to be 1,3-di-β(-hydroxyethoxy)-2-propanol, as shown in Eq. (558).

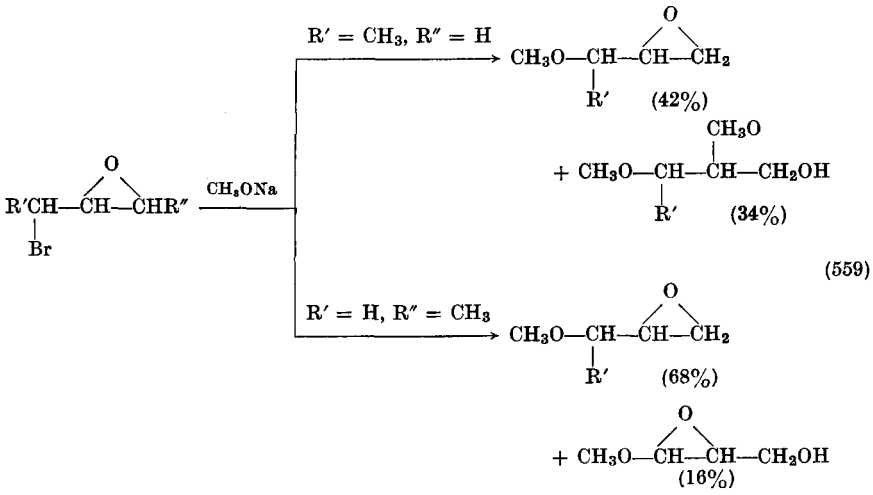


(558)

Waters and VanderWerf[1812] have published an ingenious study of the reactions of 3-bromo-1,2-epoxy- and 1-bromo-2,3-epoxy-propane with sodium methoxide and sodium ethoxide (Eq. 559). There appears in each case to be preliminary Br^- ion displacement under the conditions used, followed by cleavage of the resultant glycidic ether.

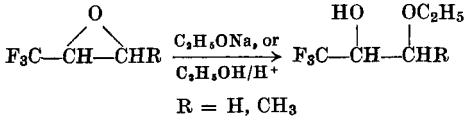
Addition of ethanol to 2,3-epoxy-1,1,1-trifluoropropane was examined by McBee and co-workers[1064, 1065] to ascertain what effect the strongly electron-withdrawing trifluoromethyl group might have

on the direction of ring rupture. The sole product isolated with both sodium ethoxide and acidic ethanol was 1,1,1-trifluoro-3-methoxy-2-propanol, formed by attack upon the epoxide carbon atom furthest



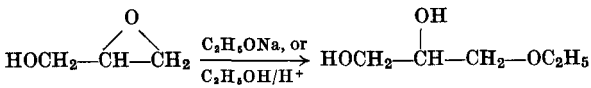
(559)

from the trifluoromethyl group (Eq. 560). Similar results were observed with 2,3-epoxy-1,1,1-trifluorobutane.[1064, 1065] Analogous observations had been recorded many years earlier by Meerwein and co-workers[1139] for 1,1,1-trichloro-2,3-epoxypropane.

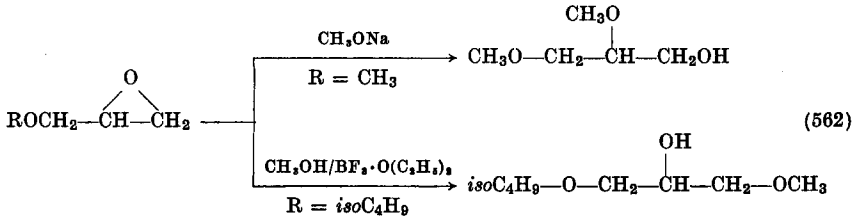


(560)

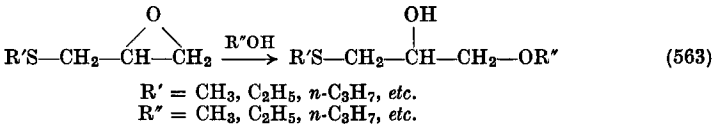
Glycidol has been converted into 1-ethoxy-2,3-propanediol (Eq. 561) by treatment with sodium ethoxide or with acidic ethanol.[852] Similarly, methyl and isobutyl glycidyl ethers (Eq. 562) have been reported to undergo cleavage with methanol under various conditions.[1392, 1812] The last substance named reacted poorly, however, and the structure assigned to its fission product may be open to question.



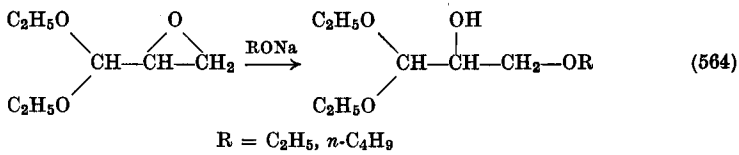
(561)



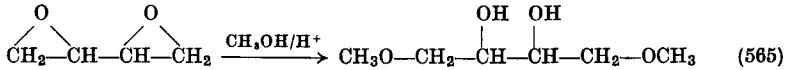
Rietz and co-workers[1461] have condensed several aliphatic alcohols with alkyl glycidyl sulfides, thereby securing the β-alkoxy-β-hydroxypropylsulfides shown in Eq. (563).



Glycidaldehyde diethylacetal yields on treatment with alcoholic alkali (Eq. 564) the product to be anticipated on the basis of preferential attack on the terminal epoxide carbon atom.[1882]

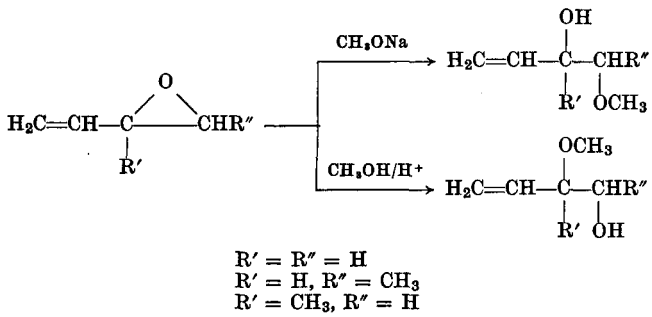


In the same manner, treatment of *meso*-1,2;3,4-diepoxybutane with acidic methanol (Eq. 565) predictably yields *meso*-1,4-dimethoxy-2,3-butanediol.[115]



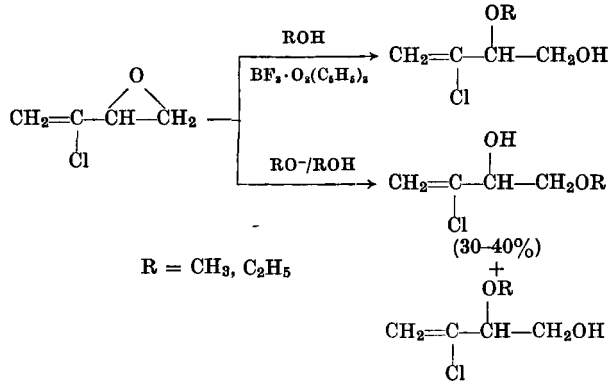
Several epoxides bearing multiply-bonded substituents have been subjected to alcohol addition. Treatment of several vinyl-substituted ethylene oxides with sodium methoxide, for example, has been reported to yield alcohols corresponding to attack on the epoxide carbon atom furthest from the unsaturated function.[86, 1393, 1419, 1461] In the presence of a trace of mineral acid, however, methanol adds to the opposite terminal of the epoxide ring (Eq. 566).

Albitskaya and co-workers[2016] observed the formation of both possible products, however, when 3-chloro-1,2-epoxy-3-butene was



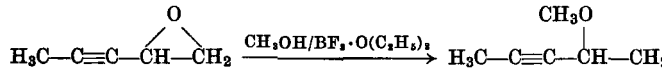
(566)

treated with sodium methoxide or ethoxide (Eq. 566a). The boron trifluoride-catalyzed addition of methanol and ethanol still yielded only the primary alcohol derived from attack on the epoxide carbon nearest to the unsaturation.



(566a)

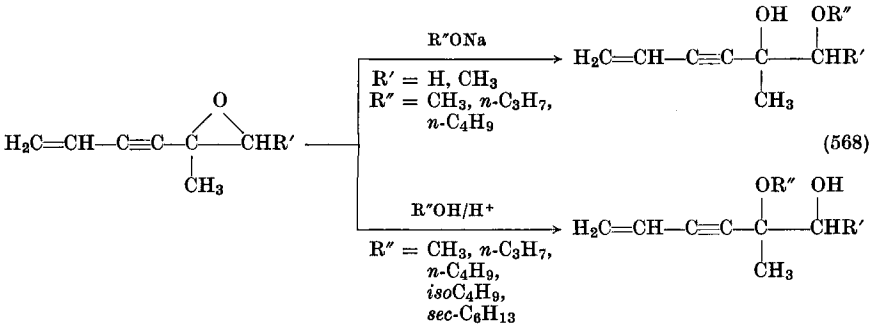
Several acetylenic epoxides have been observed to condense with methanol and other alcohols. Addition of methanol to 1,2-epoxy-3-pentyne in the presence of boron trifluoride (Eq. 567), for example, gives



(567)

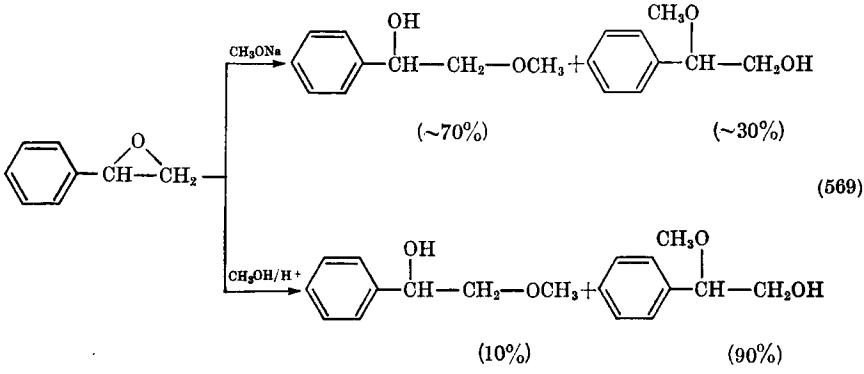
2-methoxy-3-pentyne-1-ol.[1360] Perveev and co-workers[1333, 1335, 1350] have examined, moreover, the reactions of various alcohols with epoxy alkenynes, with the usual results as shown in Eq. (568).

Among the phenyl-substituted ethylenes that have been cleaved with alcohols are styrene oxide,[1442] β-methylstyrene oxide,[1073] and stilbene oxide.[1437] Sodium methoxide is capable of adding to either of



(568)

the epoxide carbon atoms in styrene oxide. In contrast with a previous claim,[499] however, terminal attack has been shown to be preponderant.[1442] But in the presence of mineral acid methanol does add primarily to the epoxide terminal carbon atom nearest the phenyl substituent, as shown in Eq. (569). Condensation of methanol with 9-benzalfluorene oxide likewise is reported to occur at the most arylated carbon.[132]

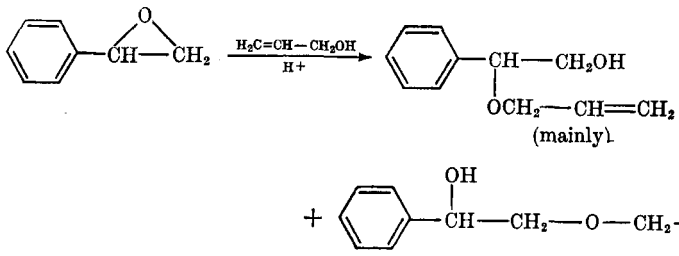


(569)

Acid-catalyzed addition of allyl alcohol to styrene oxide has also been a subject of conflict. Swern and co-workers[1680] reported obtaining a mixture of alcohols, of which the principal constituent was considered to be 2-allyloxy-1-phenylethanol. Hayes and Gutberlet,[727] however, subsequently showed the chief product in the mixture to be

in fact 2-allyloxy-2-phenylethanol (Eq. 570), as might be expected in the light of results secured with other alcohols.

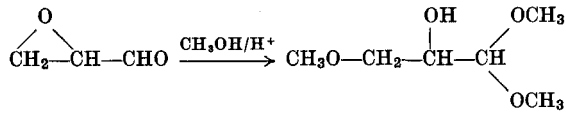
Treatment of 2,3-epoxy-1-phenylpropane with methanol also is reported to give a mixture of 1-methoxy-3-phenyl-2-propanol and 2-methoxy-3-phenyl-1-propanol.[1451]



(570)

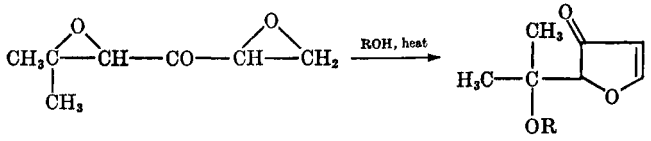
Kohler and Tishler[959] carried out addition of methanol to 2,3-epoxy-1,1,3,5-tetraphenylpent-4-yne without specifying the sense of addition. One might anticipate on the basis of existing evidence that condensation would occur at $C_{(2)}$ in alkali and $C_{(3)}$ in acid.

Glycidaldehyde condenses with three molar equivalents of methanol in the presence of a trace of acid (Eq. 571), giving 1,1,3-trimethoxy-2-propanol.[1847] Attack thus appears to be favored at the epoxide terminal carbon atom furthest from the carbonyl function (or from the acetal function if acetal formation is the primary step in this reaction).



(571)

Puzzling circumstances attend the addition of methanol and other alcohols to 2,3;5,6-diepoxy-2-methyl-4-hexanone.[1221] Whereas one might expect attack to take place preferentially at $C_{(6)}$ (less hindered than $C_{(2)}$, which should be the second choice) in the absence of added acid, condensation actually occurred at the most alkylated site, as shown in Eq. (572). The first cleavage product is not isolated,

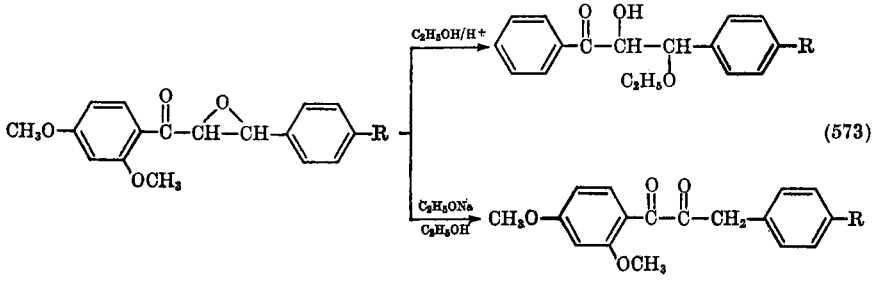


(572)

R = CH_3, C_2H_5, *iso*C_3H_7

intramolecular alkoxide attack on the remaining epoxide ring and subsequent elimination of water giving a furan derivative.

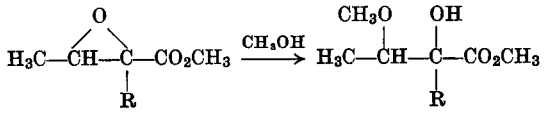
In this connexion, Baker and Robinson[65] also noted, in a different case, that acid-catalyzed nucleophilic attack occurs preferentially at the epoxide carbon atom furthest from the carbonyl function of an α,β-epoxyketone (Eq. 573). Interestingly, however, under alkaline conditions a rearrangement took place instead of the anticipated ring-opening reaction.



(573)

R = H, CH_3

The epoxide ring of methyl crotonate has been reported to undergo addition of methanol on the carbon atom furthest from the ester function (Eq. 574), giving methyl 2-hydroxy-3-methoxybutyrate.[465] Alcoholysis of 1,1-dicarbethoxy-1,2-epoxypropane in the presence of acid has also been carried out.[1310] Although not definitely established, it is nevertheless probable that addition likewise takes place at the epoxide carbon atom furthest removed from the ester substituents.

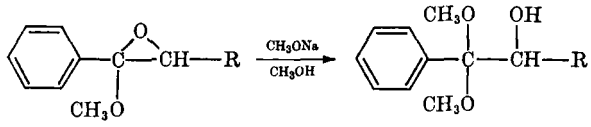


(574)

R = H, CH_3O_2C

Many epoxy ethers have been opened with alcohols, notably by Stevens and co-workers,[1631, 1635–1637, 1639, 1641, 1644] and by other authors as well.[1707, 1773] Attack, when it occurs, takes place exclusively on the epoxide carbon atom bearing the ether substituent. Treatment of 1,2-epoxy-1-methoxy-1-phenylpropane with sodium methoxide in methanol, for example, gives the dimethylacetal of α-hydroxyethyl phenyl ketone. The cleavage of 1,2-epoxy-1-methoxy-1,2-diphenylethane follows a similar course, as shown in Eq. (575).

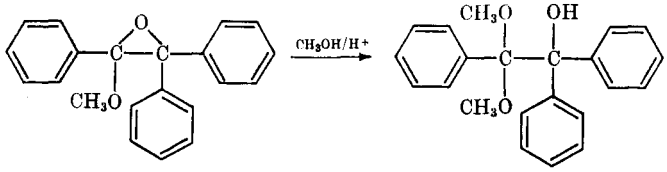
Increasing stability of the epoxy ether is produced with increasing phenyl substitution, as shown by the fact that 1-methoxy-1,2,2-triphenylethylene oxide resists attempts to condense it with methanol,



(575)

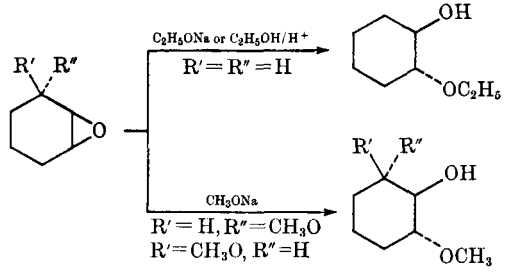
R = CH_3, C_6H_5

either in the absence or in the presence of added alkali.[1631] In the presence of a trace of mineral acid, however, cleavage occurs, not unexpectedly, to give the desired dimethylacetal of benzoyl diphenyl carbinol (Eq. 576).



(576)

Addition of alcohols to simple alicyclic epoxides has received surprisingly little attention, but it is certain to proceed normally in the manner of other nucleophiles. Thus, cyclohexene oxide has been

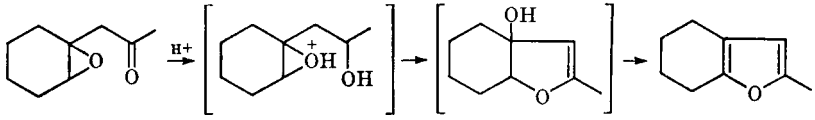


(577)

R′ = H, R″ = CH_3O
R′ = CH_3O, R″ = H

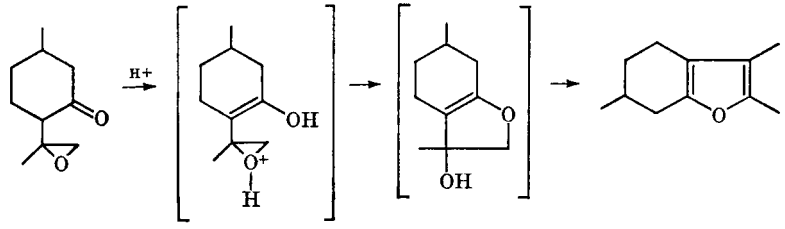
cleaved with ethanol, both in acid and in base,[966, 1355, 1856] to *trans*-2-ethoxycyclohexanol. Similarly, *cis*- and *trans*-1,2-epoxy-3-methoxycyclohexane undergo *trans* opening to give the derivatives shown in Eq. (577).

An interesting furan synthesis based on acid-catalyzed intramolecular condensation has been reported by Fritel and Baranger,[589] using 1,2-epoxy-1-(2-oxopropyl)-cyclohexane. Attack is believed by these authors to be led by the enolic form of the ketone, as shown in



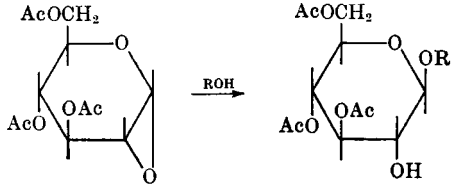
(578)

Eq. (578). A similar pathway was postulated by Fritel and Fetizon[590] to explain the ready, albeit low-yield, cyclization of isopulegone oxide to a furan derivative, as shown in Eq. (579).



(579)

The renowned sugar epoxide 'Brigl's anhydride'[245] has been cleaved with a number of alcohols (Eq. 580) among them methanol, ethanol, and benzyl alcohol.[771]

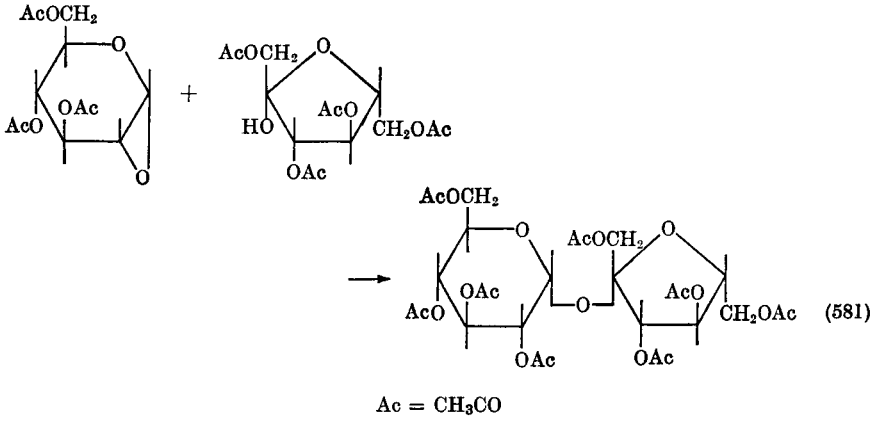


(580)

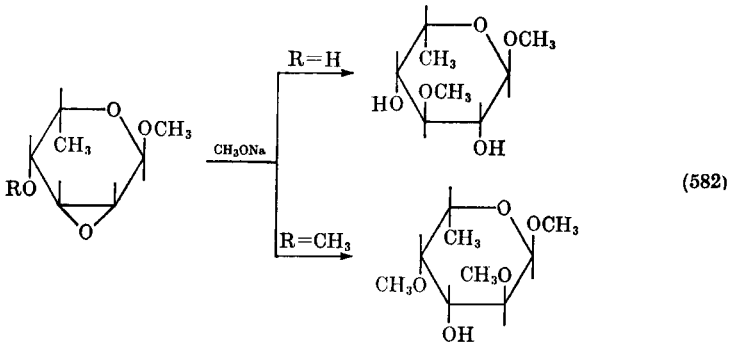
Ac = CH_3CO; R = CH_3, C_2H_5, $C_6H_5CH_2$

This technique of generating glycosidic linkages has received extensive application in the synthesis of disaccharides. Sucrose octa-*O*-acetate, for example, can be formed by condensing Brigl's anhydride with 1,3,4,6-tetra-*O*-acetyl-D-fructose (Eq. 581), although the yield is only 5%.[1001]

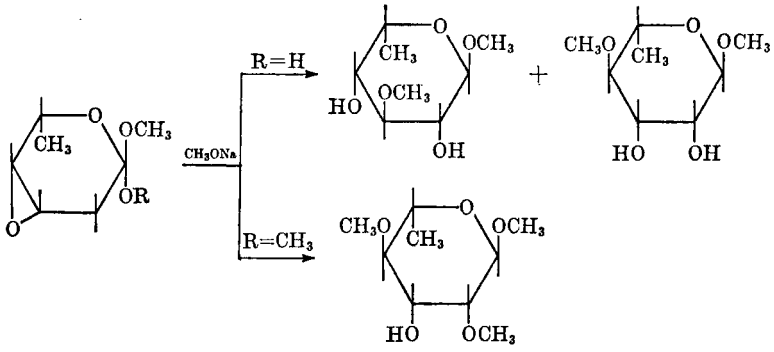
The literature contains several other illustrations of the use of Brigl's anhydride in this type of reaction,[772, 998, 1000] but further attention will not be given to them here.



Several instructive examples from the field of sugar chemistry may be cited to illustrate the subtle interplay of steric and electronic factors governing the direction of epoxide ring cleavage by an alcohol, generally methanol.

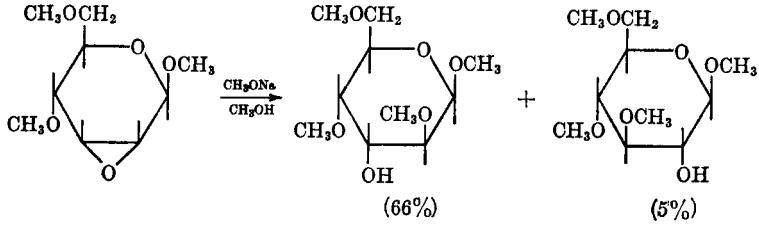


Charalambous and Percival[302] observed that addition of methanol to certain 2,3- and 3,4-anhydro-6-desoxy-D-taloside derivatives proceeds differently depending on the presence or absence of an *O*-methyl group on the carbon atom neighboring the epoxide ring, as shown in Eqs. (582) and (583).



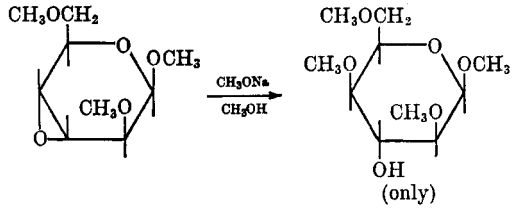
(583)

It had been shown some 15 years earlier by Peat and Wiggins[1320] that methyl 2,3-anhydro-4,6-di-*O*-methyl-β-D-alloside (Eq. 584) and



(584)

methyl 3,4-anhydro-2,6-di-*O*-methyl-β-D-altroside (Eq. 585) behave somewhat differently on treatment with methanolic sodium methoxide. Whereas the former gave a mixture of methyl 2,4,6-tri-*O*-methyl-β-D-altroside (66%) and methyl 2,4,6-tri-*O*-methyl-β-D-glucoside (5%), the

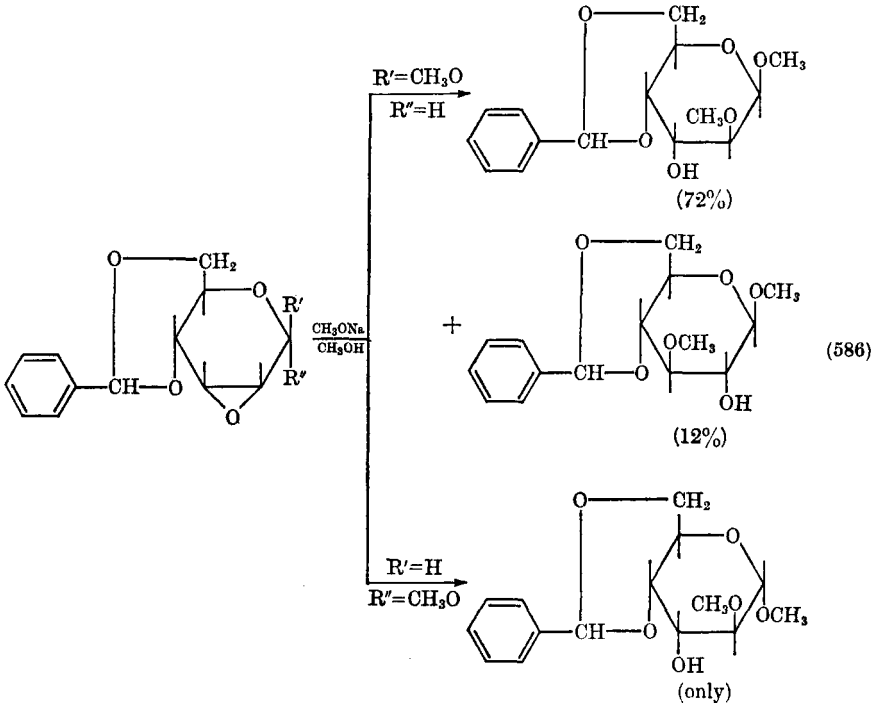


(585)

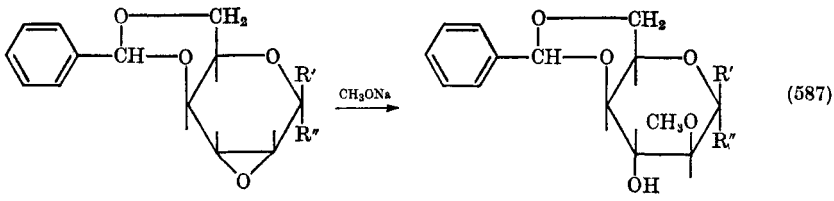
latter gave methyl 2,4,6-tri-*O*-methyl-β-D-idoside as the only isolable product. This observation apparently reflects a greater steric hindrance to approach of incoming nucleophiles at $C_{(3)}$ with the altrose derivative.

Nearly all possible methyl 2,3-anhydro-4,6-*O*-benzylidene α- and β-glycosides of D-talose,[697, 1611, 1842] D-gulose,[697, 1611] D-mannose,[674]

and D-allose[674, 1320, 1473] have been condensed with sodium methoxide in methanol. Results of these condensations are summarized in Eqs. (586)–(589).



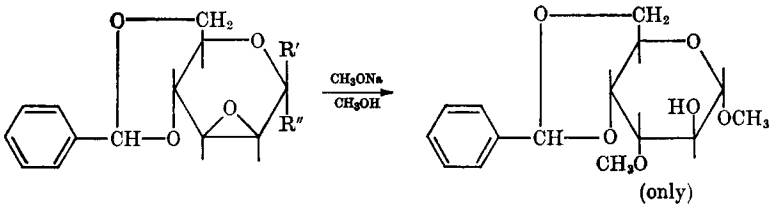
(586)



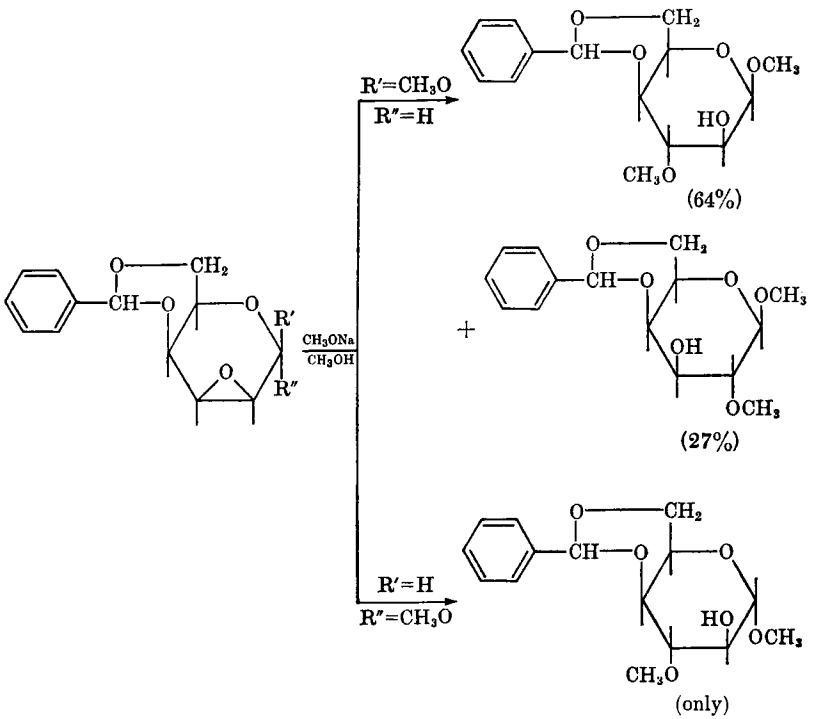
(587)

R′ = CH_3O, R″ = H
R′ = H, R″ = CH_3O

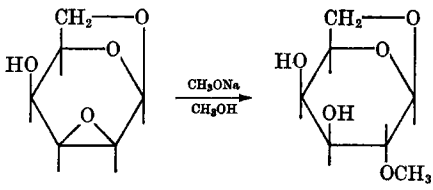
Mention may also be made of the reactions of 2,3;1,6- and 3,4;1,6-dianhydro-β-D-talose (Eqs. 590 and 591), which are reported to give only 1,6-anhydro-2-*O*-methyl-β-D-galactose and 1,6-anhydro-4-*O*-methyl-β-D-mannose respectively.[873]


CH3ONa
CH3OH
HO
OCH3
CH3O
(only)

(588)

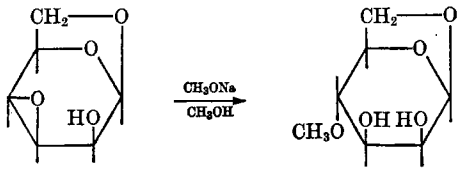

R′=CH3O
R″=H
(64%)
CH3ONa
CH3OH
OH
OCH3
(27%)
R′=H
R″=CH3O
(only)

(589)


CH3ONa
CH3OH
HO
OH
OCH3

(590)

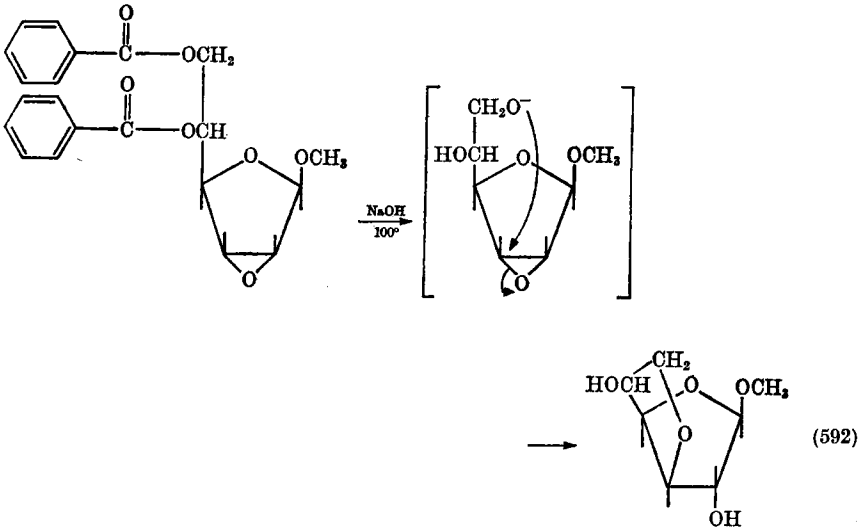
Several epoxy sugars containing a suitably disposed free hydroxyl group have been shown to yield new anhydro sugars on treatment with aqueous base or acid. When the free hydroxyl group is on a carbon atom



(591)

adjacent to the epoxide ring, a process termed 'epoxide migration' frequently occurs in base. Epoxide migrations have already been considered at some length (see section **III.3.***A*), and therefore need not be discussed further.

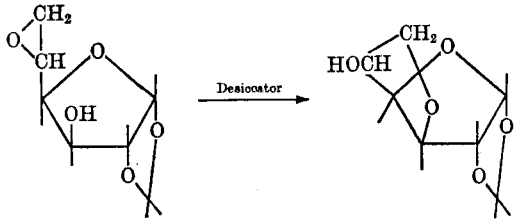
Intramolecular alkoxide attack on an ethylene oxide ring may also be illustrated by two examples involving furanose sugars, in which the epoxide ring is fused to a five- rather than a six-membered ring. Ohle and Wilcke[1272] reported the formation of a 3,6-anhydro derivative on treatment of methyl 5,6-di-*O*-benzoyl-β-D-*allo*furanoside with hot alkali (Eq. 592).



(592)

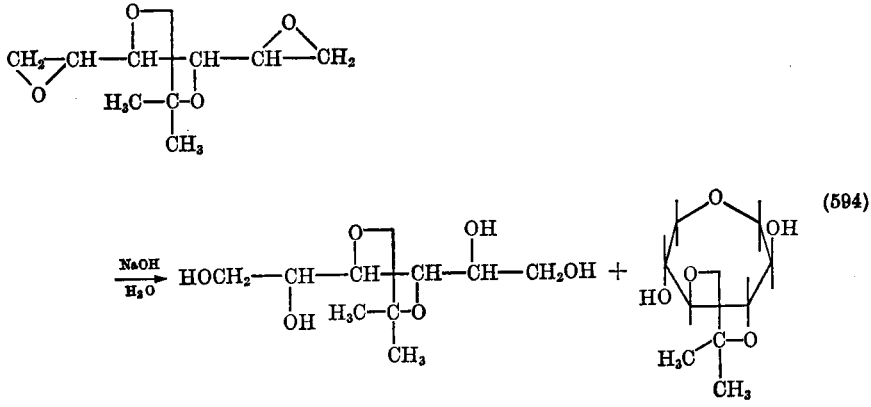
Similarly, but under singularly mild conditions, Seebeck and coworkers[1557] noted the conversion of 5,6-anhydro-1,2-*O*-*iso*propylidene-α-D-glucofuranoside into a 3,6-anhydro derivative simply on standing in a desiccator containing acid (Eq. 593).

Finally, certain curious observations published recently by Vargha and Kasztreiner[1783, 1784] are of interest. Treatment of the 1,2;5,6-dianhydro-3,4-*O-iso*propylidene derivatives of D-mannitol, D-sorbitol, and L-iditol with alkali unexpectedly gave the corresponding

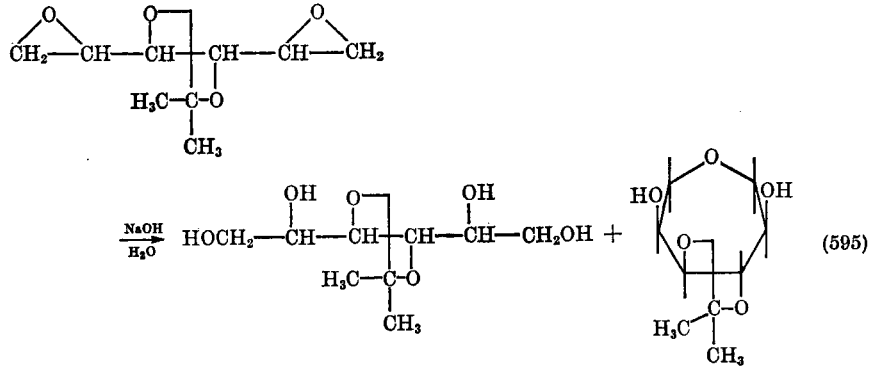


(593)

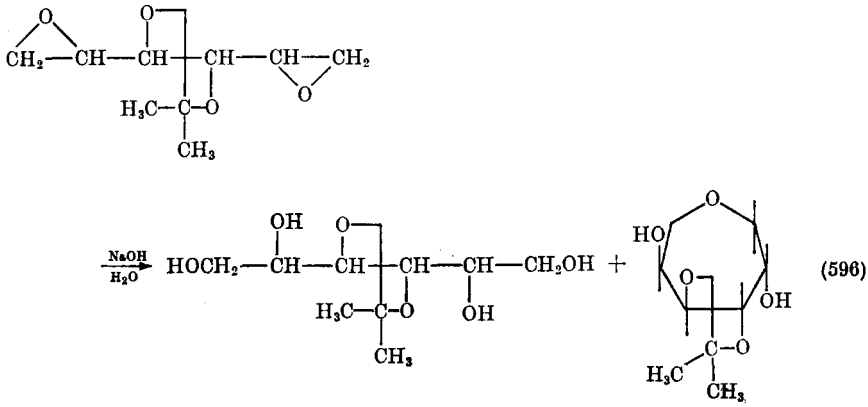
seven-membered 1,6-anhydro sugars, along with the desired hydration products 3,4-*O-iso*propylidene-D-mannitol, -D-sorbitol, and -L-iditol (Eqs. 594–596).



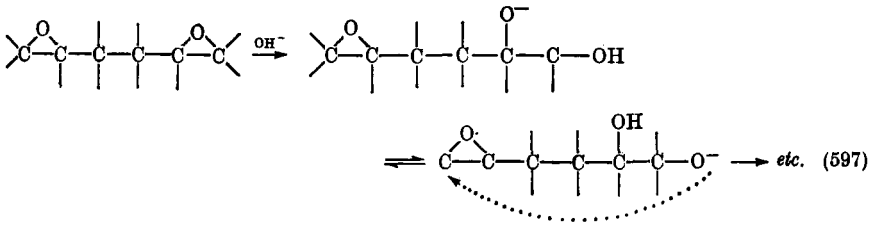
(594)



(595)

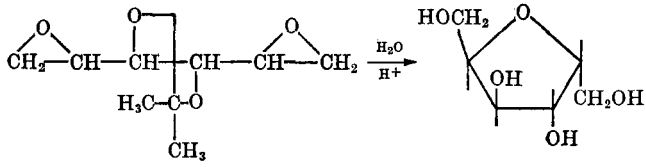


Yields of 1,6-anhydro derivatives, after removal of the 3,4-*O*-*iso*propylidene blocking group, were 5–7% for the D-mannitol series, 15–20% for the D-sorbitol series, and 55–60% for the L-iditol series. The authors ascribed this trend to the fact that formation of these 1,6-anhydrides produced two, one, and zero axial hydroxyl substituents respectively. That seven- in preference to five- or six-membered anhydrides were generated was attributed to the presence of the 3,4-*O*-*iso*propylidene function. The products were formulated on the assumption that no inversion had occurred either at $C_{(2)}$ or $C_{(5)}$, and that initial attack of an OH^- ion at $C_{(1)}$ or $C_{(6)}$ was followed by a tautomeric proton transfer to the adjacent secondary alkoxide oxygen (Eq. 597).



In acidic solution, on the other hand, Vargha and Kasztreiner observed formation of five- rather than seven-membered anhydro sugars. With 1,2;5,6-dianhydro-3,4-*O*-*iso*propylidene-D-sorbitol, for example, there was formed 2,5-anhydro-D-iditol (isolated and characterized as its 1,3;4,6-di-*O*-benzylidene derivative), along with a hexitol which was not fully identified (Eq. 598). The other possible anhydride, 2,5-anhydro-D-mannitol, evidently does not form under these conditions. The inversion at $C_{(5)}$ is noteworthy.

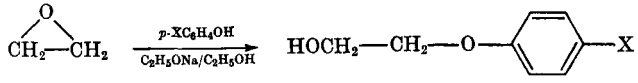
In acidic solution, according to Vargha and Kasztreiner,[1784] the 3,4-*O*-*iso*propylidene blocking function must be removed before hydration of the epoxide ring, otherwise a seven-membered anhydro sugar would be generated as in alkaline solution.



+ $HOCH_2(CHOH)_4CH_2OH$ (598)

(3) Phenols. The condensation of ethylene oxides with phenols has not been investigated so extensively as that of alcohols, but generally follows a similar course.

Boyd and Marle[229] have conducted a thorough study of the ease of addition of various substituted phenols to ethylene oxide in alkaline solution (Eq. 599). Using no less than 25 different phenols, these authors



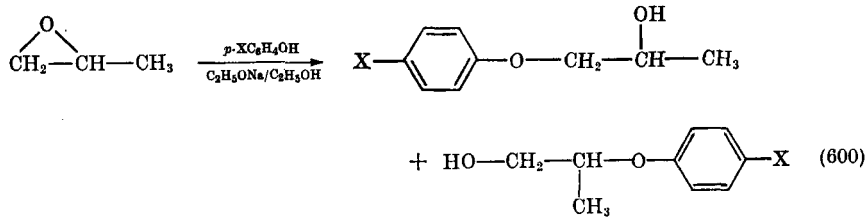
(599)

X = H, CH_3, Cl, CH_3O, NO_2, *etc.*

demonstrated clearly that the rate of reaction was increased by the presence of substituents tending to decrease the acidity of the phenol, *i.e.* of substituents which increase the base strength of the corresponding phenoxide ion.

Careful analysis by two groups of investigators[180, 1162, 1303] has shown that the initial addition product can react further with excess of ethylene oxide in the presence of base, giving a range of higher-boiling adducts as with ordinary alcohols.

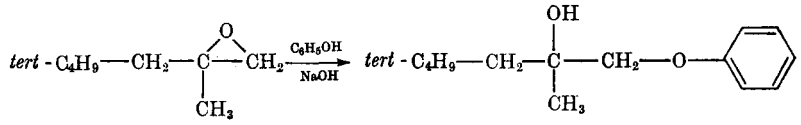
Substitution of propylene oxide for ethylene oxide (Eq. 600)



(600)

X = H, CH_3, Cl, CH_3O, NO_2, *etc.*

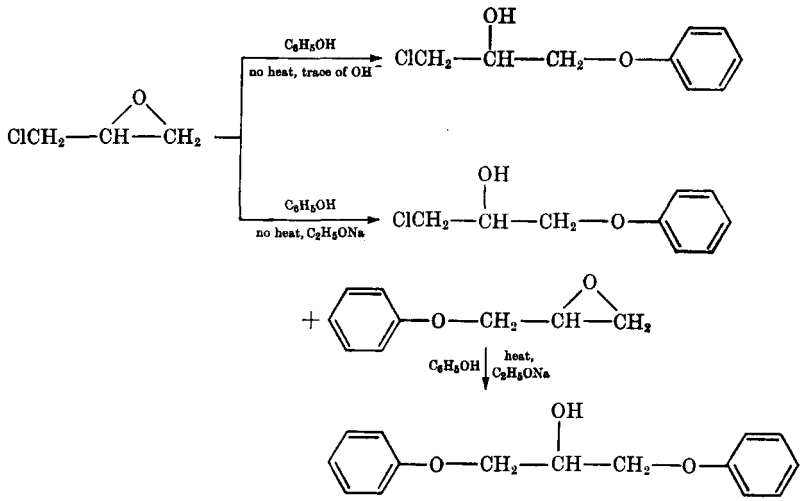
causes formation of mixtures of isomeric 1,2-diol monoaryl ethers, but no attempt has been made to establish product ratios for the substituted phenols.[229, 1561] In every instance, however, the rate of addition to propylene oxide was lower than that to ethylene oxide.[229] Phenol has also been condensed with 1,2-epoxyhexane in the presence of boron trifluoride,[1782] but only the isomer generated by terminal attack was isolated from the product mixture.



(601)

Addition of phenol and naphthol in alkaline solution has been carried out also with 1,2-epoxy-2,4,4-trimethylpentane (Eq. 601), attack occurring exclusively at the unhindered terminal epoxide carbon atom.[663]

The course of addition of phenols to epichlorohydrin has been a subject of some controversy, since one might suppose the strongly nucleophilic character of phenoxide ion to cause indiscriminate attack on the chlorine-substituted carbon atom and the epoxide ring.

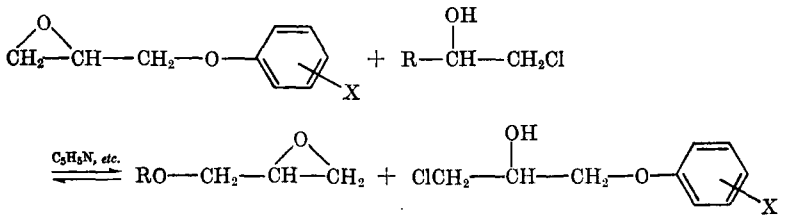


(602)

Among the earliest reports in this area was that of Lindemann,[1035] who claimed that three products could be produced under various conditions, namely, 1-chloro-3-phenoxy-2-propanol, phenyl glycidyl ether, and 1,3-diphenoxy-2-propanol (Eq. 602). The last could be

prepared by condensation of phenol with glycidyl ether in the presence of alkali. Although conflicting results had been published by other workers, Boyd and Marle[228, 229] confirmed and extended Lindemann's findings to several other phenols. Under mild conditions and in the presence of only catalytic quantities of base, the chlorohydrin could be made predominantly. When larger proportions of base were used, although still in the cold, phenyl glycidyl ether could be obtained, along with the chlorohydrin. But in the presence of excess of base at high temperature the product isolated was phenyl glycidyl ether exclusively. Similar results have been reported by Van Zyl and co-workers.[1782]

More recently Bradley and co-workers[233] demonstrated a fourth significant product in this reaction to be 1,3-dichloro-2-propanol, formed by addition of hydrochloric acid to epichlorohydrin. These authors then showed that under suitable conditions phenyl glycidyl ether can be made to react with a chlorohydrin. There are formed in this manner a new epoxide and 1-chloro-3-phenoxy-2-propanol, as



(603)

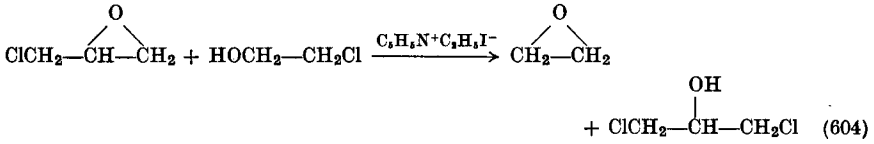
X = H, *o*-CH_3, *p*-CH_3, *p*-Cl
R = $HOCH_2$, $CH_3CO_2CH_2$, $ClCH_2$, $HOCH_2CH_2OCH_2$, $C_6H_5OCH_2$, *etc.*

shown in Eq. (603). A number of catalysts were found to be satisfactory for bringing about this reversible hydrogen chloride transfer, among them potassium carbonate, pyridine, quinoline, triethylamine, piperidine, and others. The method was applied to a variety of aryl glycidyl ethers and chlorohydrins.

Bradley and co-workers[233] advanced the attractive premise that certain difficultly accessible epoxides might be synthesized conveniently by this approach, provided that the glycidyl ether used is a good hydrogen chloride acceptor and that the desired products can be removed readily from the equilibrium mixture.

A perhaps still more general type of conversion was incidentally uncovered by Bradley and co-workers[233] during the same work, when epichlorohydrin was found to react with ethylene chlorohydrin in the

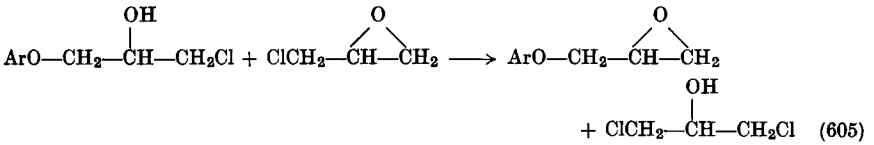
presence of *N*-ethylpyridinium iodide. Although the authors failed to state whether or not epichlorohydrin was converted into 1,3-dichloro-2-propanol as anticipated (Eq. 604), the catalyst was said to be recovered unchanged. The scope of this interesting transformation does not seem to have been explored further.



(604)

The effect of substituents on the reactivity of phenols with epichlorohydrin has been examined also by Bradley and co-workers.[233] In contrast with earlier observations made by Boyd and Marle with ethylene oxide and propylene oxide,[228, 229] the most acidic phenols are the ones giving maximum yields with epichlorohydrin. This indicated that in this particular reaction the relative concentration of phenoxide ions rather than their nucleophilicity is the overriding factor in determining the rates of addition.

Stephenson[1627] has developed a convenient procedure for preparing 1-chloro-3-phenoxy-2-propanols from epichlorohydrin and phenols, which is economical of reagents and minimizes the formation of undesirable side-products (Eq. 605). He has also greatly extended the applicability of hydrogen chloride transfer for the preparation of epoxides.

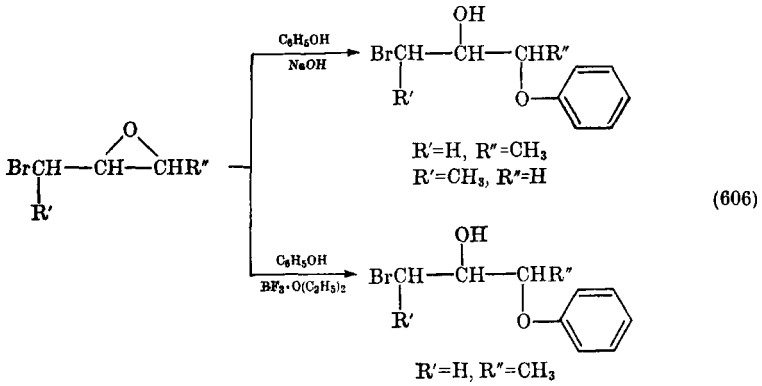


(605)

Ar = C_6H_4X (X = H, CH_3, Cl, Br, I, NO_2, CN, $CO_2C_2H_5$, CHO), α-$C_{10}H_7$, β-$C_{10}H_7$

Acid-catalysis was demonstrated for the addition of phenol to epichlorohydrin by Levas and Lefebre,[1013] using boron trifluoride. Although some unidentified higher-boiling products accompanied the desired adduct, this procedure was deemed superior to that reported by Boyd and Marle[228, 229] under alkaline conditions, which requires as much as 6 weeks for completion. Bradley and co-workers[233] have objected, on the other hand, that the boron trifluoride-catalyzed process involves an excessively large phenol : epichlorohydrin ratio and is therefore uneconomical.

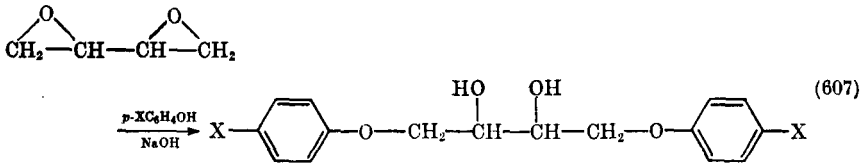
The boron trifluoride-catalyzed condensation of phenol with epihalohydrins has recently been extended by Bridger and Russell[244] to 1-bromo-2,3-epoxybutane, which appears to yield chiefly 1-bromo-3-phenoxy-2-butanol, although the presence of a small amount of the other possible isomer was not excluded. By contrast, Rowton and Russell[1502] had previously reported that the addition of sodium phenoxide to 3-bromo-1,2-epoxybutane and 2-bromo-3,4-epoxypentane gave only 3-bromo-1-phenoxy-2-butanol and 2-bromo-4-phenoxy-3-pentanol respectively. Attack thus occurs at the epoxide carbon atom furthest from the halogen regardless of the presence or absence of added acid (Eq. 606).



(606)

R′ = H, R″ = CH_3

Beech has reported that the addition of alkaline phenol, *p*-chlorophenol, and β-naphthol occur smoothly at the terminal positions of *meso*-2,3-diepoxybutane, yielding the corresponding *meso*-1,4-diaryloxy-2,3-butanediols (Eq. 607).

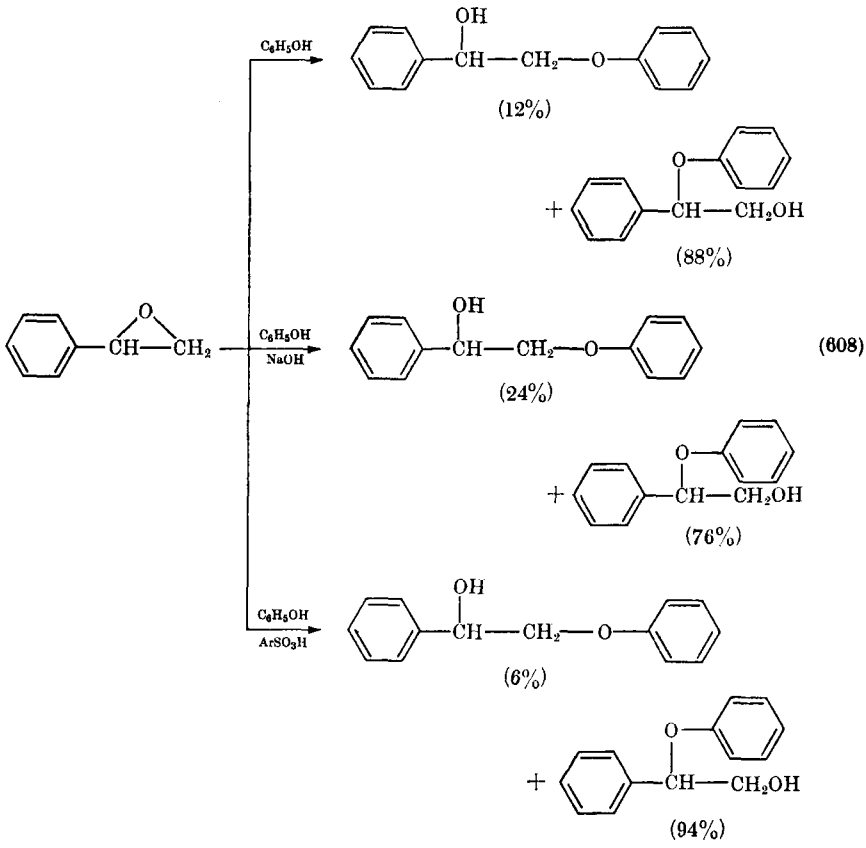


(607)

X = H, Cl

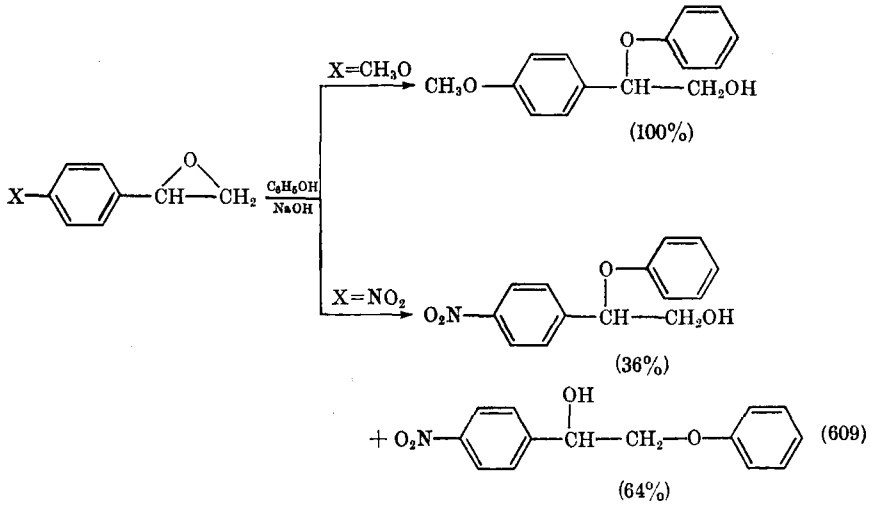
Guss and co-workers[682-689] have examined the addition of phenol to styrene oxide under various conditions (Eq. 608), and found, as with alcohols, that phenol itself yields two products with this epoxide. The

proportion of products could be varied by altering the reaction temperature or the medium polarity. In addition, terminal attack occurred to a greater extent in the presence of sodium hydroxide than in its absence, whereas arylsulfonic acids promoted the opposite trend.[682, 688, 689]



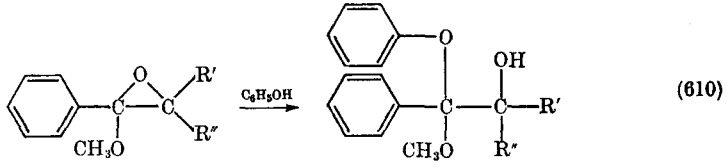
(608)

The effect of introducing substituents into the styrene oxide system was also investigated by Guss and co-workers.[683, 684, 686] As expected, the electron-withdrawing *p*-methoxy substituent greatly favors attack of the reagent on the epoxide carbon atom nearest the benzene ring, whereas the *p*-nitro group exerts the opposite effect (Eq. 609). Other substituents examined in this connexion were *o*- and *m*-nitro groups.



$R' = R'' = CH_3$
$R' = H$; $R'' = C_2H_5$, n-C_3H_7

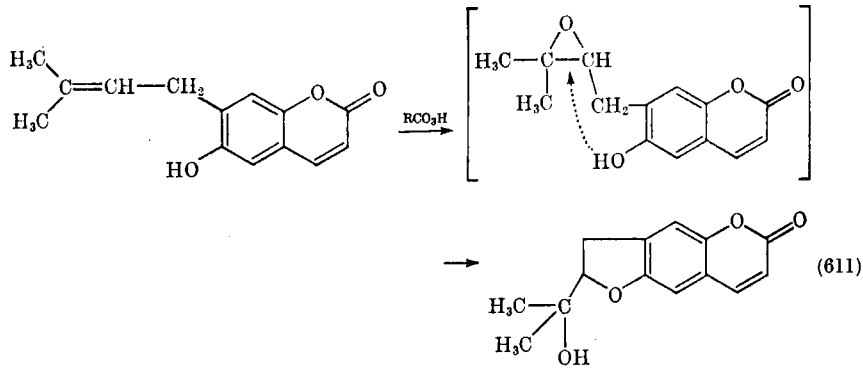
Ugolnikov[1773] has studied addition of phenol to such epoxy ethers as 1,2-epoxy-1-methoxy-1-phenylbutane (Eq. 610), finding that attack occurs exclusively at the methoxy-substituted epoxide carbon atom as with simple alcohols.



Mention may be made, finally, of two types of rearrangements caused by intramolecular attack of a phenolic oxygen on an epoxide ring.

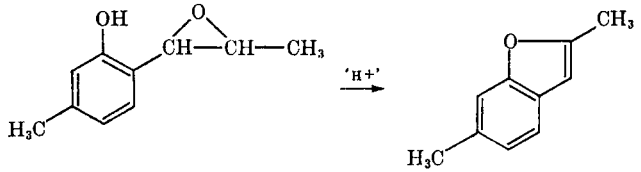
The first concerns the report of King and co-workers[929] that treatment of the coumarone derivative shown in Eq. (611) with monoperphthalic acid gives rise not to the expected epoxide, but instead to a cyclic substance derivable from it.

The second, described by Pansevich-Kolyada and Idelchik,[1292] deals with the epoxide of 2-propenyl-*m*-cresol, which undergoes rearrangement simply on standing at room temperature in a desiccator over sulfuric acid. The product obtained is 2,6-dimethylbenzofuran



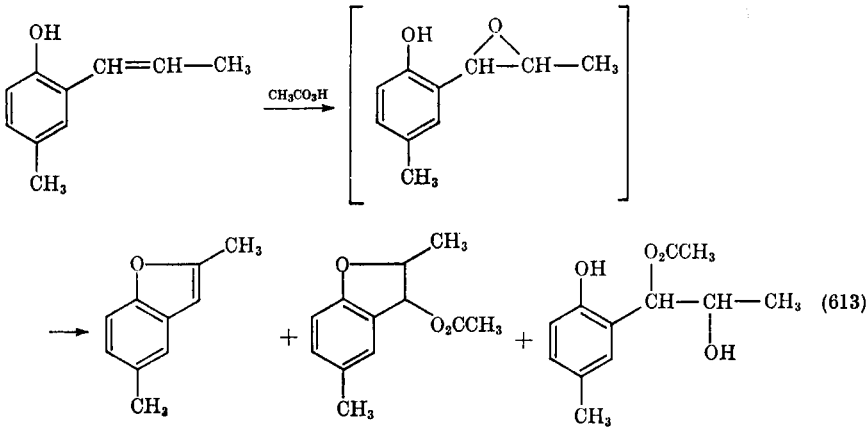
(611)

(Eq. 612). Similarly, attempted epoxidation of 2-propenyl-*p*-cresol proved unsuccessful because the intermediate epoxide suffered ready rearrangement in the epoxidation medium, giving 2,5-dimethylbenzo-



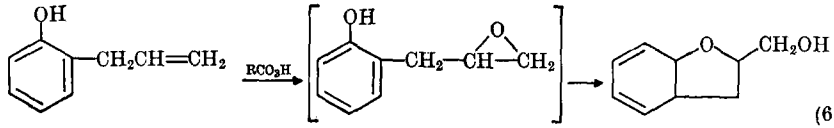
(612)

furan and other products (Eq. 613). Likewise, peroxy acid epoxidation of 2-allylphenol has been reported[1974, 1975] to lead only to formation of a five-membered ether by attack of the phenolic hydroxyl on the



(613)

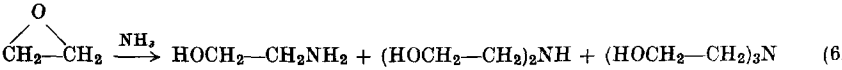
nearest epoxide carbon (Eq. 613a). Curiously, there appears to be formed none of the six-membered ether that would result from terminal carbon attack.



(613a)

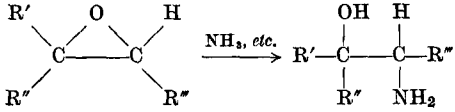
B. Ammonia and Amines

The vigorous interaction of ethylene oxide with ammonia was noted as early as 1863 by Wurtz,[1891] 4 years after his initial publication announcing the discovery of ethylene oxide,[1884] and was reported again somewhat later by Gabriel[611] and again by Knorr.[948] The last investigated the composition of the product mixture more thoroughly than had been done before, and demonstrated the formation of di- and triethanolamine alongside the principal product (Eq. 614). Further condensation of the epoxide with the primary product constitutes, in fact, the chief side process in the reactions of all amines with ethylene oxides.



(614)

During their extensive studies of the sense of addition of nucleophiles to epoxides, Krassusky and his collaborators[969-976, 979] conducted a large number of reactions involving ammonia, ethylamine, dimethylamine, diethylamine, *iso*pentylamine, and piperidine, among others. Substrates included propylene oxide and *iso*butylene oxide, 2,3-epoxybutane, 2,3-epoxy-2-methylbutane, and 1,2-epoxy-2-methylbutane. In every instance the only products isolated were those formed



(615)

$R' = CH_3$, *iso*C_3H_7; $R'' = R''' = H$
$R' = R'' = CH_3$; $R''' = H, CH_3$
$R' = H$; $R'' = R''' = CH_3$

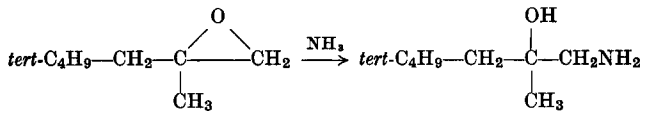
by attack of the amine on the least substituted epoxide carbon (Eq. 615), as would be anticipated if condensation were of the conventional S_N2 type.[1301]

Numerous subsequent publications emanating from other laboratories concerned with addition of ammonia and simple amines to

epoxides are generally in substantial agreement with previous findings.[218, 240, 610, 1014, 1023, 1024, 1102, 1170, 1380, 2017] Among the many other amines also utilized to cleave simple alkyl-substituted epoxides have been ethylene diamine,[941] hydrazine,[125, 612, 634, 886, 1332] hydroxylamine,[184,884] phenylhydrazine,[886,1332] ethyleneimine,[601,1931,2018] aniline and various *N*-substituted or phenyl-substituted derivatives,[1072, 1111, 1112, 1116, 1118–1122, 1362, 1665, 1933] tetrahydroquinoline,[964] decahydroquinoline,[1130] and others.[655, 934, 1332, 1898, 1920, 1921] This section is concerned chiefly with reactions of ammonia, simple alkylamines, and anilines. Reference should be made to the original literature for more detailed information on the course of addition of less commonly used reagents of the amine class, such as those cited above.

Mention may be made briefly of the studies of Malinovskii and co-workers,[1091, 1093, 1097] involving addition of ammonia to ethylene oxide, propylene oxide, and styrene oxide under stringent conditions. At 400–450° over an alumina catalyst, for example, ethylene oxide and ammonia are reported to give a moderate yield of pyridine (16.6–19.4%). With styrene oxide an exceedingly complex mixture of products is formed, among which are various pyrrole and pyridine derivatives, benzene, toluene, ethylbenzene, benzaldehyde, acetophenone, phenylacetaldehyde, and others.

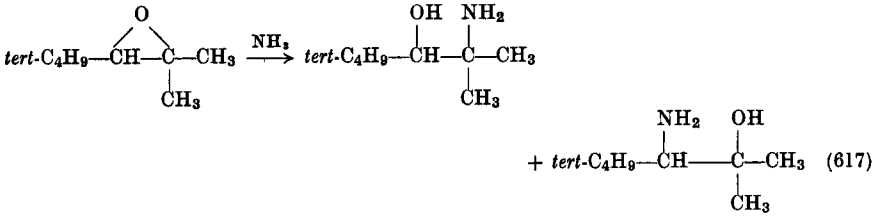
An interesting recent study illustrating the complex interplay of steric and electronic factors governing the direction of ring opening was reported by Graham and co-workers.[663] Treatment of 1,2-epoxy-2,4,4-trimethylpentane with ammonia, diethylamine, and several other reagents yielded the expected adducts, together with some secondary condensation products (Eq. 616). On the other hand, 2,3-epoxy-2,4,4-



(616)

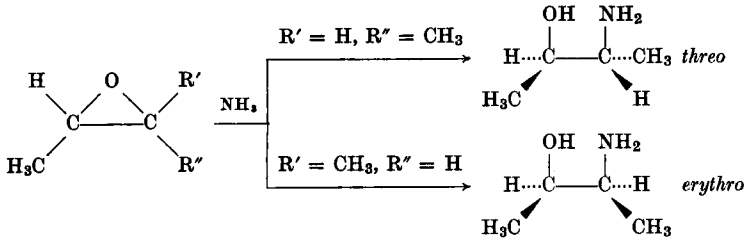
trimethylpentane, in which access to the epoxide function is more severely hindered, failed to react with diethylamine under comparable conditions (ethanolic solution at 180° in a sealed tube). The less bulky ammonia molecule did react, but unexpectedly gave a mixture of isomeric β-amino alcohols, as shown in Eq. (617). In this case the least alkylated epoxide carbon atom should be the electronically favored target for a nucleophile operating by a classical S_N2 process. This effect might well be outweighed, on the other hand, by the fact that the particular lone substituent in this instance is a bulky *tert*-butyl group. If the nucleophile were operating according to a 'borderline S_N2'

process,[1301] electronic factors might be expected to direct attack toward the most alkylated epoxide carbon atom, *i.e.* that carbon atom most capable of sustaining transient carbonium ion character. To what



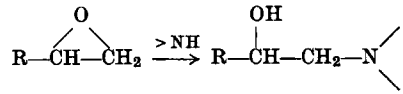
extent one or the other limiting process is predominant in this instance unfortunately remains a subject of conjecture.

The stereochemically specific character of the reaction of amines with simple alkyl-substituted epoxides was established by Dickey and co-workers[452] in an investigation of ammonia addition to *cis*- and *trans*-2,3-epoxybutane. Products of this condensation were found to be *threo*- and *erythro*-3-amino-2-butanol respectively (Eq. 618).



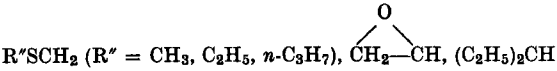
(618)

Addition of ammonia and amines to epoxides containing one or more polar atoms in the vicinity of the oxide ring has been found to occur more rapidly for the most part than with the corresponding alkyl-substituted analogs. Glycidol,[949, 1099, 1460] epichlorohydrin,[300, 464, 519, 633, 640, 766, 951, 1072, 1498] and 1,2-epoxy-3,3,3-trifluoropropane,[1064]



(619)

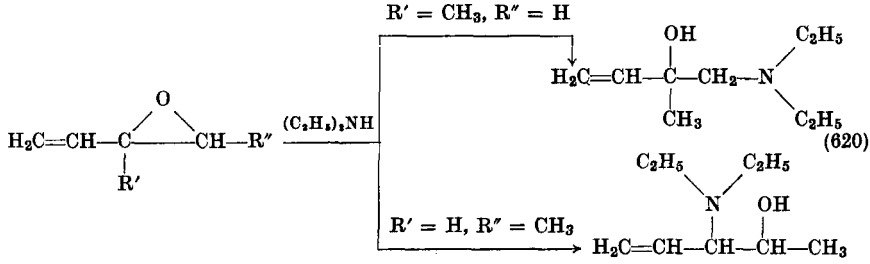
R = $ClCH_2$, $HOCH_2$, F_3C, $R'OCH_2$ (R′ = CH_3, C_2H_5, *iso*C_3H_7, *n*-C_4H_9, C_6H_5, *etc.*),



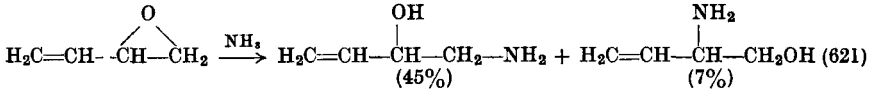
for example, all undergo ammonolysis more rapidly than propylene oxide itself, but continue to suffer fission of the bond joining the oxygen atom to the terminal epoxide carbon atom (Eq. 619). Other

epoxides of this class that have been opened in the same fashion include glycidyl ethers,[227, 875, 1386, 1389, 1392, 1394, 1396, 1565] glycidyl alkyl sulfides,[1230, 1754] glycidaldehyde diethylacetal,[1818, 1883] and 1,2;3,4-diepoxybutane.[115]

The effect of vinyl and ethinyl substituents on the direction of ring opening has been examined by a number of Russian workers.[17, 1329, 1336, 1346, 1350, 1393, 2018] These unsaturated functions allegedly deactivate the carbon atom to which they are attached, as in 1,2-epoxy-2-methyl-3-butene (Eq. 620), which undergoes attack at the terminal epoxide carbon atom only.[1393, 2018] This could of course have been foreseen on steric grounds alone. The picture is further obscured, moreover, by the report,[15] that 2,3-epoxy-4-pentene opens in the opposite sense (Eq. 620). A careful study by Ettlinger[508] has shown that 1,2-epoxy-3-butene itself reacts with ammonia chiefly at the primary carbon atom, although a small quantity of the isomeric product is formed as well (Eq. 621).

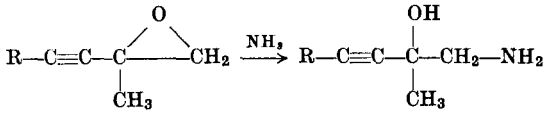


(620)



(621)

Ring cleavage of acetylenic epoxides may be illustrated by the reactions of the substituted 1,2-epoxy-3-butyne derivatives represented in Eq. (622) with ammonia, ethylamine, diethylamine, and others.[1345, 1346, 1350]

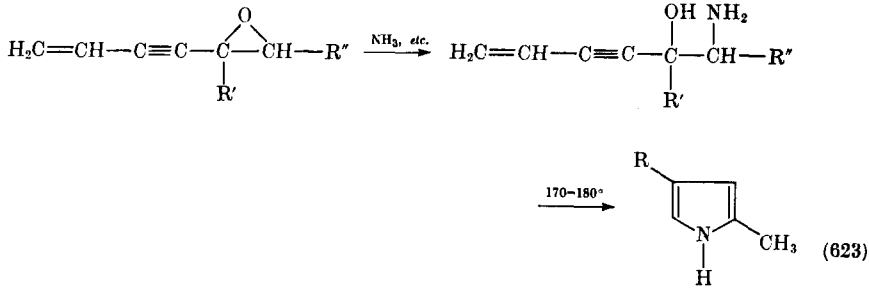


(622)

R = CH_3, C_6H_5, *etc.*

The addition of primary amines to 1,2-epoxy-3-alken-5-ynes, as shown in Eq. (623), constitutes a useful *N*-substituted pyrrole synthesis. Attack of the amine nucleophile occurs exclusively at the

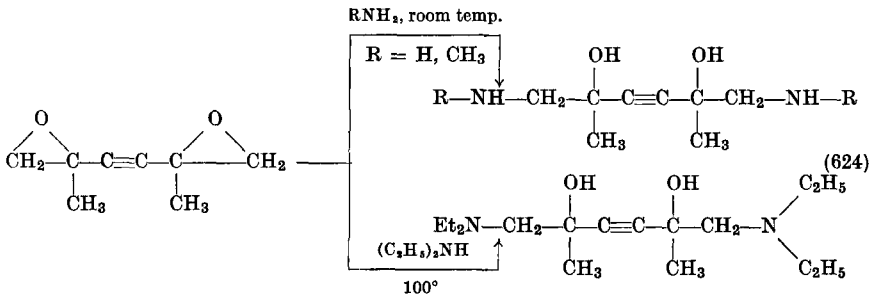
epoxide carbon atom furthest from the unsaturation, regardless of steric effects. Heating the β-amino alcohols generated in this manner causes cyclization and elimination.[1329, 1336, 1345] Addition of diethylamine to 1,2-epoxy-2-methyl-4-phenyl-3-butyne likewise occurs at the terminal position.[1939]



(623)

R′ = H, CH_3; R″ = CH_3
R′ = CH_3; R″ = H

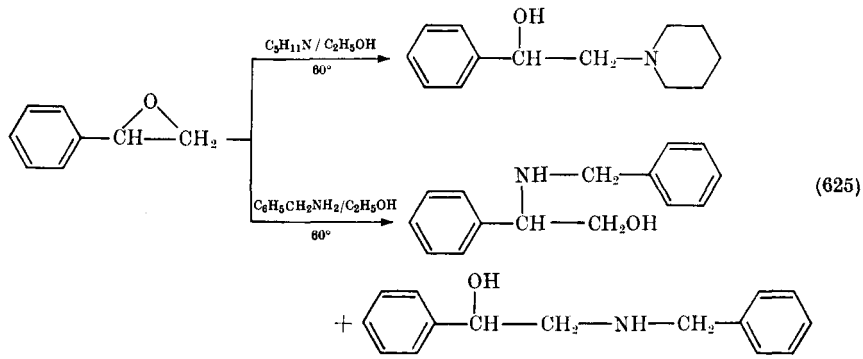
The singularly labile bisepoxide 1,2;5,6-diepoxy-2,5-dimethylhex-2-yne has been found[1348] to undergo ring opening readily at room temperature with ammonia or methylamine (Eq. 624), and at 100° with diethylamine.[1349]



(624)

Styrene oxide has received considerable attention in this connexion.[941, 1728] Chapman and co-workers[1301, 301] found the proportion of normal to abnormal ('normal' refers, in their parlance, to terminal attack) products to depend on the nature of the amine, the reaction temperature, the presence or absence of an acid catalyst, and the presence or absence of solvent. Ethanolic piperidine at 60°, for instance, gave almost exclusively normal attack, whereas benzylamine under comparable conditions gave a significant proportion of abnormal

product (Eq. 625). The ratio of abnormal to normal product with ethanolic benzylamine progressively decreased, moreover, as the reaction temperature was lowered from 60° to 20°. Addition of acid also appears to favor abnormal fission, particularly in the presence of ethanol as solvent.[253] Other amines which have been condensed with styrene oxide include ammonia itself,[290] ethylenimine,[601] 2-aminopyridine,[1935] and benzylamine.[1917]



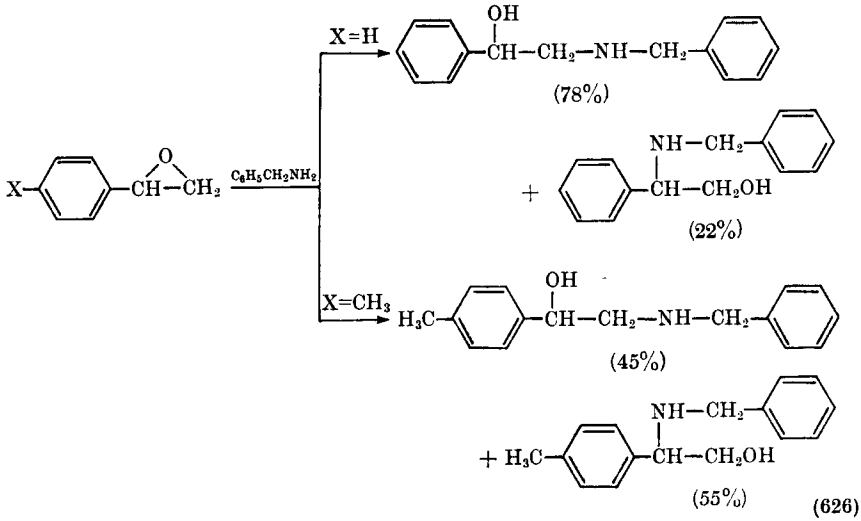
(625)

Several other phenyl-substituted ethylene oxides have been condensed with amines, among which may be cited β-methylstyrene oxide,[181, 563, 601, 1931] epoxycinnamyl alcohol and its *p*-nitro derivative,[181, 606, 1666] 2,3-epoxy-1,1,3-triphenyl-1-propanol,[77] and benzylethylene oxide and *p*-nitrobenzylethylene oxide.[291, 567] Inasmuch as the phenyl group exercises a decidedly disruptive influence on the orientational specificity of epoxide ring fission, a substantial proportion of abnormal product should be anticipated whenever a phenyl-substituted ethylene oxide is cleaved with an amine. It is well to bear in mind also the cautionary words of Parker and Isaacs[1301] concerning the abundance in the literature of yield results of questionable validity.

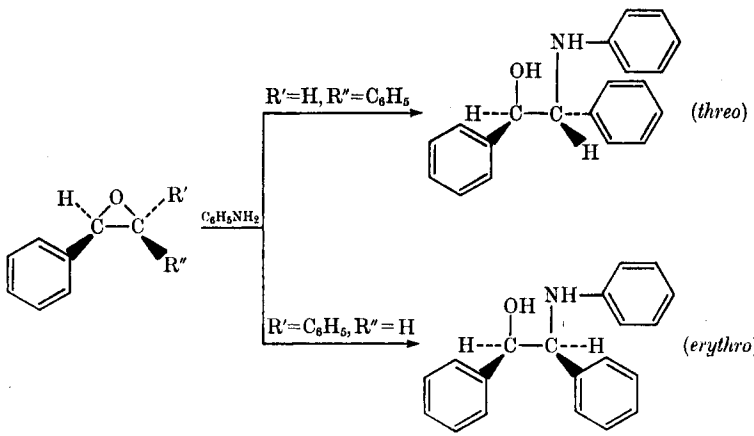
Interesting recent work by Addy and co-workers[1917] sheds additional light on the directive effect of substituents for the reaction of benzylamine with various styrene oxides. The pronounced tendency of a *p*-methyl substituent to foster abnormal attack, as shown in Eq. (626), is especially noteworthy.

Stühmer and Messwarb[1665] have reported addition of aniline, 1-naphthylamine, and others to *cis*- and *trans*-stilbene oxide to afford *threo* and *erythro* adducts respectively, as shown in Eq. (627). Their observations are consistent with the premise that ring-opening is accompanied by Walden inversion at the site of nucleophilic attack.

Addition of amines to 1,2-dihydronaphthalene oxide has been claimed[1661] to yield products corresponding to attack at the epoxide carbon atom furthest from the benzene ring. The validity of this claim



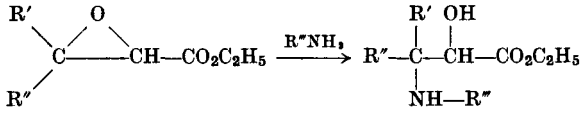
(626)



(627)

has been questioned, however, by Van Tamelen and co-workers,[1780] who favor instead attack on the benzylic epoxide carbon atom. The case of 1,4-dihydronaphthalene oxide is presumably an unambiguous one.[332]

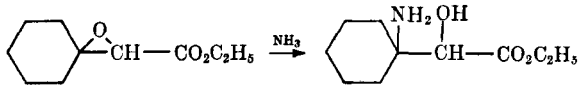
Addition of amines to glycidic esters and glycidamides has been the subject of a massive study during the last decade by Martynov and his collaborators.[408, 1111–1113, 1116–1118, 1120–1123, 1126, 2019] Alkyl- as well as aryl-substituted glycidic esters were examined with reference to several amines, among them ammonia, cyclohexylamine, and aniline. All the alkyl-substituted glycidic esters tested were found to undergo nucleophilic attack at the most-alkylated carbon atom in preference to the carbon atom bearing the electron-withdrawing ester function (Eq. 628). This is consistent with the mechanistic picture delineated by Parker and Isaacs,[1301] in which the transition state is 'borderline S_N2',[1662] *i.e.*, in which the carbon atom undergoing substitution assumes considerable positive character, but does not ever become a fully developed carbonium ion.



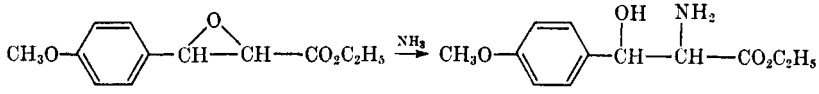
(628)

$R' = CH_3$; $R'' = CH_3$, C_2H_5
$R' = R'' = C_2H_5$
$R'R'' = (CH_2)_4$, $(CH_2)_5$
$R''' = H$, C_6H_5, *etc.*

Less straightforward are results secured with aryl-substituted glycidic esters. Difficult to reconcile with the Parker–Isaacs model, for instance, are the reactions (Eqs. 629 and 630) of ethyl 3,3-pentamethylene glycidate[1116, 1117, 1120] and ethyl 3-*p*-anisylglycidate.[1123]



(629)

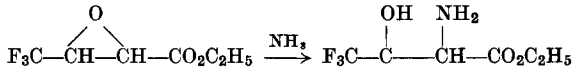


(630)

If the premise of an electron-deficient carbon atom in the transition state is valid, then one might expect the *p*-anisyl function (Eq. 630) to be surely at least as effective as two methylene groups (Eq. 629) in stabilizing this charge deficiency, while being of comparable steric bulk. That is, one might anticipate 'normal' (this term is used here to

denote attack at the epoxide carbon atom furthest from the ester function) product with ethyl 3-*p*-anisylglycidate and 'abnormal' product perhaps only with ethyl 3-*p*-nitrophenylglycidate (electronic destabilizing effect) or ethyl 3,3-diphenylglycidate (steric hindrance to the approach of reagent). Yet according to Martynov and Olman,[1123] amines condense with ethyl 3-*p*-anisylglycidate at the epoxide carbon atom nearest the ester function.

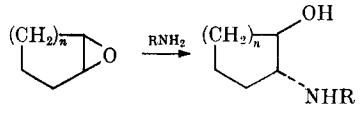
A second observation which appears incompatible with the simple Parker–Isaacs model is the report that ethyl β-trifluoromethylglycidate suffers attack at the carbon atom nearest the ester function (Eq. 631) in spite of the greater electronegativity of the trifluoromethyl group.[1895]



(631)

These and other inconsistencies have been discussed more amply by Parker and Isaacs.[1301] It is not inconceivable that amines react with glycidic esters by a more complex mechanism than has been envisaged until now. Of interest in this connexion is a proposal advanced by Sullivan and Williams [1668] to rationalize the anomalous addition of hydrogen sulfide to certain α,β-epoxycarbonyl compounds, and considered in detail in section **IV.4.***C*.

Mousseron and Granger,[1191] and other authors as well,[839,1068,2020,2021] have studied the direction and stereochemistry of ring opening with alicyclic epoxides. It was concluded that the configuration of products arising from condensation of epoxides (*e.g.* cyclopentene, cyclohexene, cycloheptene, and cyclooctene oxides) with amines (*e.g.* methylamine, cyclohexylamine, diethylamine, aniline, and others) is *trans* in every instance (Eq. 632). This is of course in harmony with a

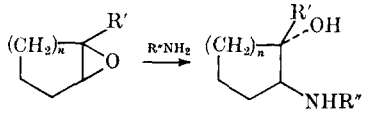


(632)

mechanistic model involving backside approach of the incoming nucleophile.

Condensations of ammonia and methylamine with 1-alkyl-1,2-epoxycycloalkanes were likewise examined thoroughly by Mousseron and Granger[1191] to test the directive effect of alkyl substituents on the sense of ring opening. In every instance ring cleavage followed the

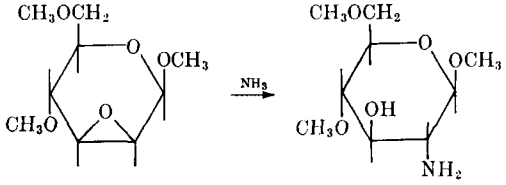
expected course, yielding the most highly substituted alcohol (Eq. 633). Similar results were noted by Newhall[1233] for the reaction of 1-menthene with ammonia and other amines.



(633)

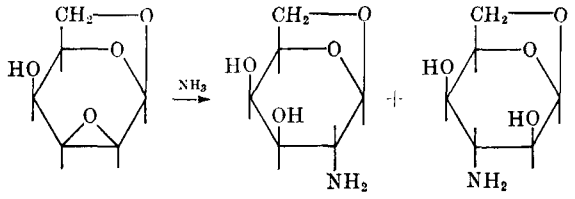
$n = 1, 2$
$R' = CH_3, C_2H_5, n\text{-}C_3H_7, iso\text{-}C_3H_7, n\text{-}C_4H_9$
$R'' = H, CH_3$

The stereospecific character of epoxide ammonolysis has allowed significant contributions to be made in the field of sugar chemistry. Ammonolysis of methyl 2,3-anhydro-4,6-di-*O*-methyl-β-D-mannoside, for example, led Haworth and co-workers[724] to the synthesis of an



(634)

O-methyl derivative of glucosamine (Eq. 634) providing a final structure proof for that biologically important substance. Similarly, ammonolysis of 1,6;2,3-dianhydro-D-talose gave two products (Eq. 635), one of which was shown to be a derivative of chondrosamine, another amino sugar of biological importance.[872]

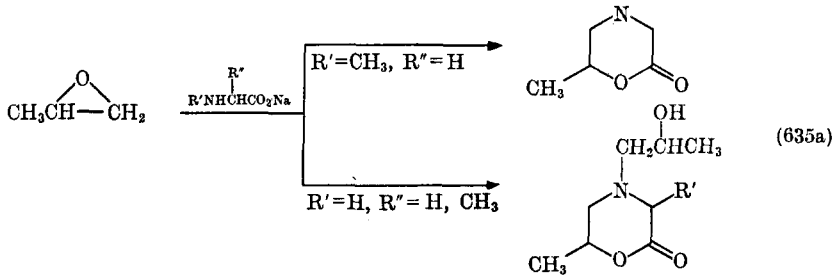


(635)

The reaction of amino acid derivatives with epoxides has been explored to some extent in a recent study by Pascal.[2022] Cyclic products are obtained, as shown in Eq. (635a).

Among the numerous sugar epoxides which have been subjected

to the action of ammonia may be mentioned the 1,2;5,6-dianhydro-3,4-*O*-*iso*propylidene derivatives of D-mannitol, D-sorbitol, and L-iditol,[1783, 1840] methyl 2,3-anhydro-α-L-ribopyranoside,[61] methyl 2,3-anhydro-4,6-*O*-benzylidene-β-D-taloside,[1842] methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-alloside and methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannoside,[504, 561, 1319, 1320, 1839] 1,6;2,3-dianhydro-4-*O*-methyl-D-mannose,[1942] methyl α- and β-D-lyxoside,[63, 64] methyl α- and β-D-riboside,[27] and others.[29,167,407,427,713,1264,1266,1267,1269,1324,1527,1834,1841]



(635a)

Mention may be made, finally, of several kinetic studies performed with amines and epoxides and treated elsewhere in considerable detail.[1301]

Barker and Cromwell[72] have measured the rate of reaction of morpholine with benzalacetophenone oxide. Second-order kinetics were observed, in conformity with a bimolecular process.

Eastham and co-workers[473] have determined the velocity of the reaction of ethylene oxide itself with diethylamine, aniline, and pyridine in aqueous solutions of pH 4–14. The reaction rate could be expressed by a second-order equation, amine and epoxide terms each appearing to the first power. Rate constants for the various amines examined were, however, remarkably similar, showing little relation to their structure or basicity. Qualitatively similar trends had been reported previously by Smith and co-workers.[1587, 1588]

Eastham and Darwent[474] have also studied the kinetics of the perchloric acid-catalyzed reaction of ethylene oxide with pyridine. In excess of pyridine the rate was found to be dependent on the concentrations of ethylene oxide and perchloric acid. Addition of stronger bases, *e.g.* ammonia, triethylamine, or benzylamine, depressed the rate of cleavage, presumably by competing with ethylene oxide for the available proton source, believed to be pyridinium perchlorate in this case. Other acids examined included nitric acid and hydroiodic acid, and it was found that the reaction rate depended to a certain extent

on the anions involved. Acid-catalysis has also been noted by Browne and Lutz[253] for the addition of benzylamine to styrene oxide.

Andersson[30] has determined pseudo first-order rate constants for the reaction of excess ammonia with a variety of epoxides, ranging from ethylene oxide itself to tetramethylethylene oxide, and including also cyclohexene oxide, styrene oxide, and glycidol. The least reactive substance studied, tetramethylethylene oxide, was found to react 600 times more slowly than ethylene oxide. Curiously enough, on the other hand, glycidol, styrene oxide, and ethylene oxide all reacted at comparable rates.

Hannson[710-712] has measured reaction rates for a large assortment of aliphatic amines and pyridines, using propylene oxide, epichlorohydrin, and glycidol, in an effort to correlate these rates by means of a Hammett–Taft type of equation involving both electronic and steric terms. In contrast with the work of Eastham,[473, 474] a sizable variation in rate was found among the amines examined, allowing a valid correlation to be established between structure and reactivity.

Most recently Addy and co-workers[1917] made the notable discovery that the 'normal' reaction (*i.e.* terminal attack) of benzylamine with *p*-substituted styrene oxides exhibits a positive ρ-value in the Hammett plot, while the 'abnormal' reaction (*i.e.* benzylic attack) exhibits a negative ρ-value. These facts are consistent with a transition state of appreciable carbonium ion character for the latter reaction.

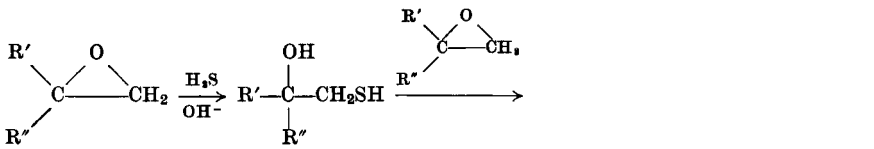
C. Sulfur-Containing Nucleophiles

A sizable collection of sulfur-containing compounds has been utilized to cleave epoxide rings.[1446] The reagents considered in this section are: (1) hydrogen sulfide, alkylmercaptans, and thiophenols; (2) thiocyanate salts; (3) carbon disulfide, thiourea and related reagents; (4) thioacids; (5) sulfite and bisulfite salts, and sulfinate salts; (6) thiosulfate salts and miscellaneous other reagents.

Epoxides are generally very susceptible to attack by sulfur nucleophiles, in accordance with the recognized nucleophilicity of these reagents.[1662] The direction of ring fission is governed by the same electronic and stereochemical principles as those operating in other related reactions, *e.g.* the additions of hydroxylic nucleophiles discussed in section **IV.4.*A***.

(1) Hydrogen sulfide, alkylmercaptans, and thiophenols. Hydrogen sulfide was first reported[307, 1230] to add to ethylene oxide only in 1935,

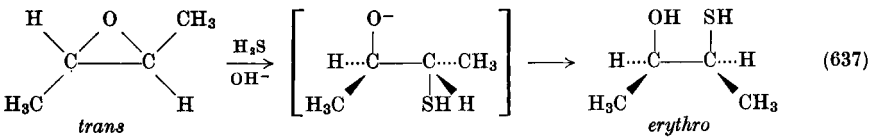
more than 60 years after the discovery of ethylene oxide by Wurtz.[1884] Condensation is accompanied by considerable heat evolution, but with suitable precautions 2-mercaptoethanol is obtainable in good yield. As in addition of water or ammonia (see section **IV.4.***B*), the initial product can condense with unchanged ethylene oxide, giving bis-(2-hydroxyethyl) sulfide. In practice, this secondary process can easily be controlled by operating at moderate temperatures and by using bis-(2-hydroxyethyl) sulfide as solvent.[708, 1876] Kinetic studies, such as that of Berbé,[126] have shown the attacking nucleophile to be HS^- ion rather than undissociated hydrogen sulfide. Propylene oxide,[126, 1128, 1846] 1,2-epoxy-2-methylbutane,[1124] and α-methylstyrene oxide[1124] undergo addition in the same fashion, giving in each case the most alkylated alcohol (Eq. 636).



(636)

$R' = R'' = H$
$R' = CH_3$; $R'' = H$, C_2H_5, C_6H_5

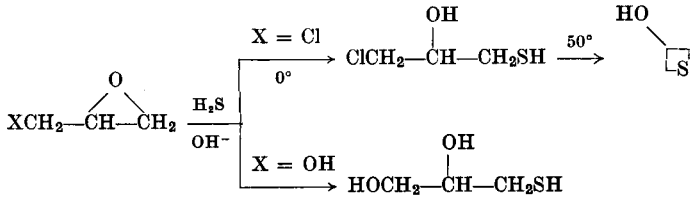
Isolation of *erythro*-2-mercapto-3-butanol by Price and Kirk[1408] from the condensation of hydrogen sulfide with *trans*-2,3-epoxybutane illustrates the stereochemically specific character of the reaction (Eq. 637). In this, as well as other reactions involving epoxides less reactive than ethylene oxide, it is necessary to operate in the presence of base. Failure to do so leads to a low reaction rate because of the small HS^- ion concentration in neutral solution.



(637)

Addition of hydrogen sulfide to epichlorohydrin is reported to follow one of two courses depending on temperature.[1581, 1925] Whereas 3-chloro-1-mercapto-2-propanol is formed at 0°, a chlorine-free substance is secured at 50°, which has been formulated on the basis of its

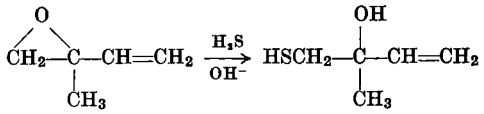
chemical stability as 3-hydroxythietane rather than the alternative product 1,2-epoxy-3-mercaptopropane (Eq. 638). Glycidol reacts in the same manner as epichlorohydrin, giving 1-mercapto-2,3-propanediol by attack of HS^- ion on the primary epoxide carbon atom.[1582] Cyclization



(638)

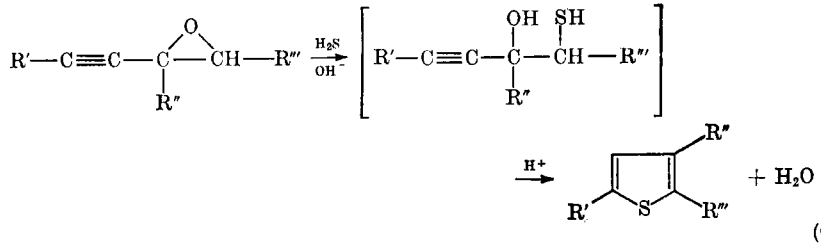
to a thietane derivative is of course precluded in this case by absence of a suitable leaving group.

Hydrogen sulfide has been found[2023] to attack the terminal epoxide carbon of 1,2-epoxy-2-methyl-3-butene as expected (Eq. 638a).



(638a)

Cleavage of epoxides with hydrogen sulfide has been exploited advantageously by Perveev and co-workers[1331, 1337–1340] in the synthesis of certain substituted thiophenes from acetylenic epoxides. Addition of hydrogen sulfide occurs, as anticipated, by attack on the epoxide carbon atom furthest from the triple bond. The resulting



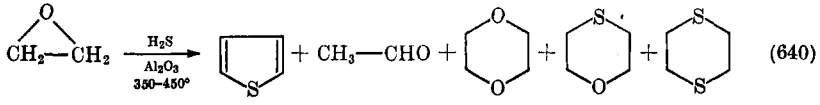
(639)

R′ = CH_3, C_2H_5, CH_2=CH, $(CH_3)_2COH$, $C_2H_5C(CH_3)OH$, C_6H_5
R″ = H, CH_3, C_2H_5
R‴ = H, CH_3

acetylenic β-mercaptoethanol may be cyclized readily on treatment with acid (Eq. 639).

Thiophene is also formed in small quantities, according to several authors,[1091, 1097, 1098, 1897] when a mixture of ethylene oxide and

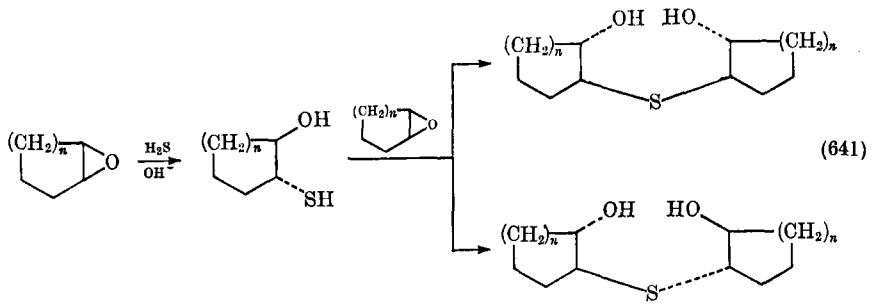
hydrogen sulfide is passed over alumina at 350–450°. Other substances produced by this vigorous technique are acetaldehyde, 1,4-dioxan, 1,4-dithian, and 1,4-oxathian (Eq. 640). Methyl-substituted derivatives are formed analogously when propylene oxide is substituted for ethylene oxide.



(640)

Martynov and Rozepina[1125] have reported addition of alkaline hydrogen sulfide to occur at the carbon atom nearest the ester function in ethyl β,β-dimethylglycidate. This is in notable contrast to Martynov's own observations with amines (see section **IV.4.***B*), which appear to add primarily to the most alkylated carbon atom of this substance (*i.e.* to the epoxide carbon atom furthest from the ester function). Addition of HS^- ions and amines may perhaps be suspected of following different mechanistic courses.

Illustrative of the behavior of alicyclic epoxides toward attack by hydrogen sulfide are reactions of cyclopentene oxide[658, 1777] and cyclohexene oxide.[391, 1185] Passage of hydrogen sulfide through alkaline solutions of these substances (Eq. 641) causes first the formation of

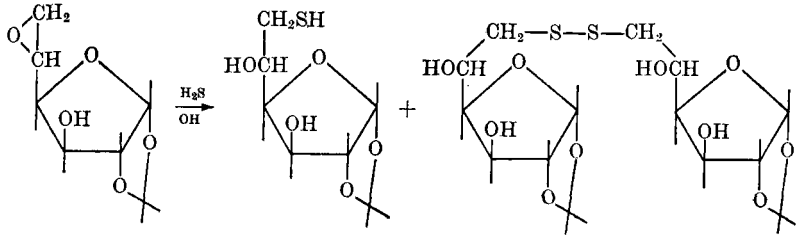


(641)

$n = 1, 2$

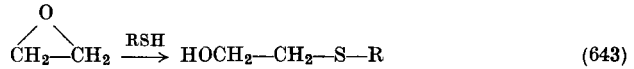
trans-2-mercaptocyclopentanol and *trans*-2-mercaptocyclohexanol respectively. These are accompanied by small quantities of bis-(2-hydroxycyclopentyl) sulfide and bis-(2-hydroxycyclohexyl) sulfide, each of which can in principle exist in two geometrical modifications. Mousseron and co-workers[1185] in fact did report the isolation of two isomeric sulfides from the reaction of cyclohexene oxide, but made no final distinction between them.

From the field of sugar chemistry may be cited the conversion of 5,6-anhydro-1,2-*O*-*iso*propylidene-α-D-glucose (Eq. 642) to 1,2-*O*-*iso*-propylidene-6-mercapto-6-deoxy-α-D-glucose on treatment with alkaline hydrogen sulfide.[1268, 1270]



(642)

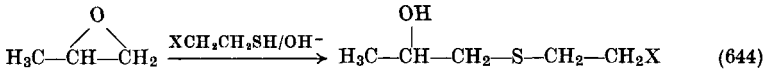
Addition of alkylmercaptans to ethylene oxide has been reported on numerous occasions (Eq. 643). Among substances utilized for this purpose have been ethyl-, *n*-butyl, *iso*pentyl-, benzyl-, and *n*-dodecylmercaptans.[391, 591, 1230] Certain mercaptans possessing other functional groups and similarly condensable with ethylene oxides (Eq. 643) have included β-mercaptoacetic acid, β-mercaptoethanol, and β-mercaptoethylamine.[307, 405] Kinetic studies conducted with several of these reagents led Danehy and Noel[405] to conclude that the attacking species is, not unexpectedly, the mercaptide ion, and that the reaction rate is proportional, as a rule, to the pK_a of the mercaptan. This is consistent with findings cited elsewhere in connexion with the addition of phenols to ethylene oxides (see section **IV.4.***A*.).



(643)

R = C_2H_5, *n*-C_4H_9, *iso*C_5H_{11}, *n*-$C_{12}H_{25}$, C_6H_5, HO_2CCH_2, $HOCH_2CH_2$, $H_2NCH_3CH_2$

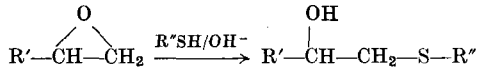
Propylene oxide has been subjected to the action of β-mercaptoethanol.[1281] In each case, nucleophilic attack takes place at the terminal epoxide carbon atom exclusively (Eq. 644).



(644)

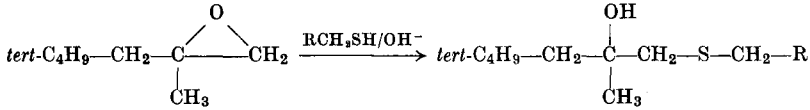
The highly-branched mercaptan 2,4,4-trimethyl-2-pentanethiol has been reported[479] to condense with ethylene oxide and propylene

oxide (Eq. 645). Similarly, the highly-branched epoxide 1,2-epoxy-2,4,4-trimethylpentane (Eq. 646) has been condensed with methyl- and benzylmercaptans.[663]



(645)

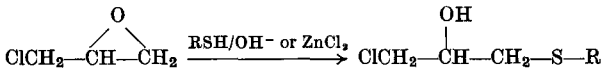
R′ = H, CH_3; R″ = $(CH_3)_3CCH_2C(CH_3)_2$



(646)

R = H, C_6H_5

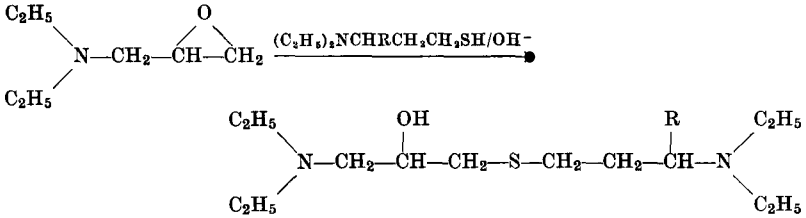
Among the epoxides possessing one or more polar atoms near the ring may be mentioned epichlorohydrin (Eq. 647), which has been cleaved with a number of alkylmercaptans.[592, 642, 1230, 1582] Of interest is the fact that in addition to the conventional alkaline catalysts, zinc chloride has also been found effective in promoting this particular reaction.[1754] Attack takes place at the terminal epoxide carbon atom furthest from the polar atom in every instance.



(647)

R = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, n-C_5H_{11}, n-C_6H_{13}, $C_6H_5CH_2$

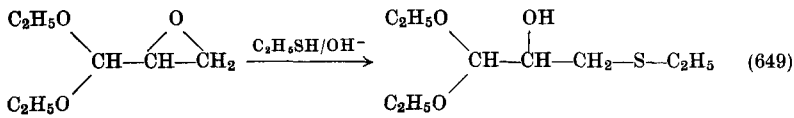
Terminal condensation products are likewise formed preferentially (Eq. 648) in the reaction of 1,2-epoxy-3-(*N*,*N*-diethylamino)propane



(648)

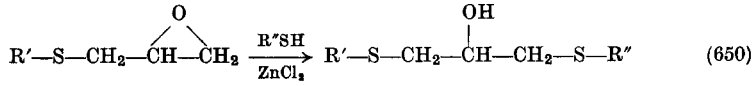
R = H, CH_3

with 3-(*N*,*N*-diethylamino)-1-propanethiol or 3-(*N*,*N*-diethylamino)-1-butanethiol.[638] Similarly condensation of 1,2-epoxy-3,3-diethoxypropane with ethylmercaptan occurs exclusively at the primary carbon atom (Eq. 649), giving 3,3-diethoxy-1-ethylthio-2-propanol.[1882]



(649)

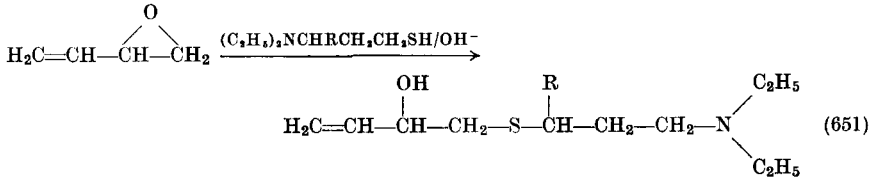
Finally may be cited the zinc chloride-catalyzed reactions of various 3-alkylthio-1,2-epoxypropanes with alkylmercaptans,[1752] as shown in Eq. (650).



$$R'—S—CH_2—\underset{\diagdown\,O\,\diagup}{CH}—CH_2 \xrightarrow[ZnCl_2]{R''SH} R'—S—CH_2—\underset{OH}{CH}—CH_2—S—R'' \qquad (650)$$

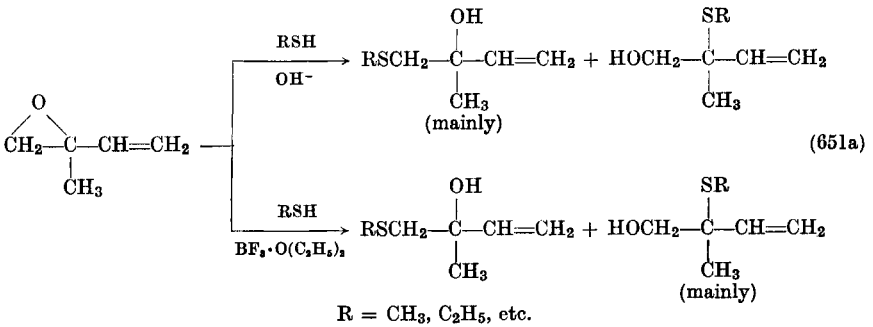
$R' = CH_3, C_2H_5, n\text{-}C_3H_7$, *etc.*
$R'' = CH_3, C_2H_5, n\text{-}C_3H_7$, *etc.*

Treatment of 1,2-epoxy-3-butene with 3-(*N*,*N*-diethylamino)-1-propanethiol or 3-(*N*,*N*-diethylamino)-1-butanethiol (Eq. 651) has likewise been reported to yield only products derived from attack on the terminal epoxide carbon atom.[638] The same epoxide yields with ammonia a detectable quantity of product corresponding to attack at the epoxide carbon atom nearest the double bond, whereas the mercaptans evidently do not.



$$H_2C{=}CH—\underset{\diagdown\,O\,\diagup}{CH}—CH_2 \xrightarrow{(C_2H_5)_2NCHRCH_2CH_2SH/OH^-} H_2C{=}CH—\underset{OH}{CH}—CH_2—S—\underset{R}{CH}—CH_2—CH_2—N\begin{matrix}C_2H_5\\C_2H_5\end{matrix} \qquad (651)$$

It has been found by Pudovik and Orlova,[2023] on the other hand, that whereas 1,2-epoxy-2-methyl-3-butene yields on treatment with alkylmercaptans in base a mixture in which the product formed by terminal attack is preponderant, the use of boron trifluoride to catalyze the reaction reverses the trend (Eq. 651a).



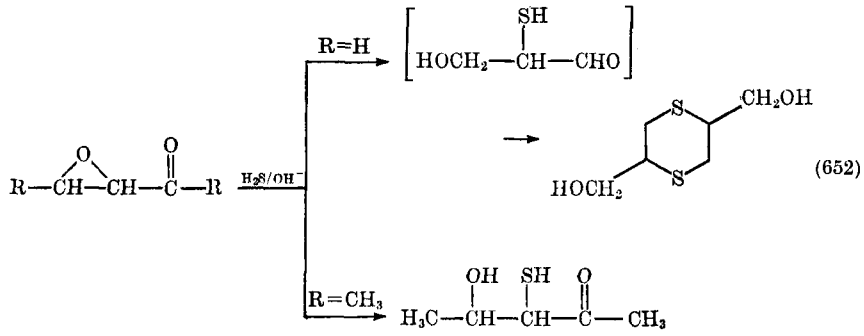
$$\underset{\diagdown\,O\,\diagup}{CH_2}—C(CH_3)—CH{=}CH_2 \xrightarrow[OH^-]{RSH} RSCH_2—\underset{CH_3}{\overset{OH}{C}}—CH{=}CH_2 + HOCH_2—\underset{CH_3}{\overset{SR}{C}}—CH{=}CH_2 \quad \text{(mainly)}$$

$$\xrightarrow[BF_3\cdot O(C_2H_5)_2]{RSH} RSCH_2—\underset{CH_3}{\overset{OH}{C}}—CH{=}CH_2 + HOCH_2—\underset{CH_3}{\overset{SR}{C}}—CH{=}CH_2 \quad \text{(mainly)} \qquad (651a)$$

R = CH_3, C_2H_5, etc.

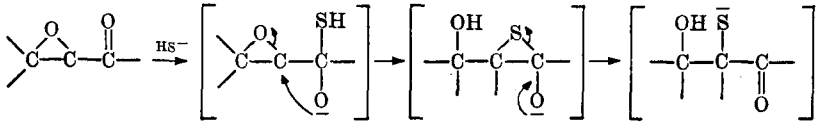
Condensation of hydrogen sulfide has also been reported to take place smoothly with glycidaldehyde and 2,3-epoxy-4-pentanone in alkaline solutions.[1668] In the first case the initial product, formulated

as 3-hydroxy-2-mercaptopropionaldehyde, undergoes rapid cyclization to a 1,4-dithiane derivative, as shown in Eq. (652). In the second, the product isolated is 2-hydroxy-3-mercapto-4-pentanone. That attack occurs at the epoxide carbon atom nearest the carbonyl function, instead of the furthest as with other reagents (*e.g.* see section **IV.4.***B*), recalls the observations recorded by Martynov and Rozepina[1691] for hydrogen sulfide addition to ethyl β,β-dimethylglycidate.



(652)

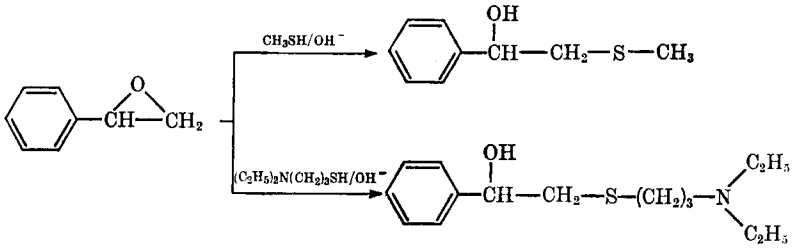
Sullivan and Williams[1668] have proposed that the novel course of events involved here may be rationalized by assuming HS^- ion attack at the carbonyl rather than the epoxide function. The unstable adduct generated in this manner is then postulated to undergo the transformations depicted in Eq. (653), giving the observed α-mercaptocarbonyl products.



(653)

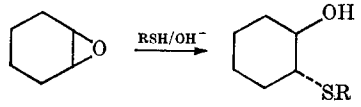
Styrene oxide (Eq. 654) illustrates the reaction of the aryl-substituted class of ethylene oxides with alkylmercaptans.[638] In this case ring opening allegedly occurs only by attack of the nucleophile on the terminal carbon atom, in contrast with the direction of fission obtained with amines (see section **IV.4.***B*.).

Addition of alkylmercaptans to alicyclic epoxides is exemplified by the reactions of β-hydroxyethylmercaptan, 1,3-ethanedithiol, and



(654)

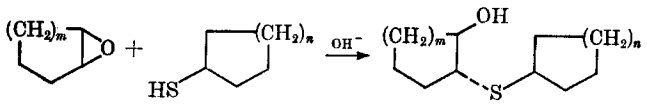
1,2,3-propanetrithiol with cyclohexene oxide,[1281] which give the corresponding *trans*-adducts (Eq. 655).



(655)

R = $HOCH_2CH_2$, $HSCH_2CH_2$, $HSCH_2CH(SH)CH_2$

Mousseron and co-workers[1185] have condensed cyclopentene oxide and cyclohexylmercaptan (Eq. 656), isolating what may be supposed to be *trans*-β-hydroxycycloalkyl sulfides.

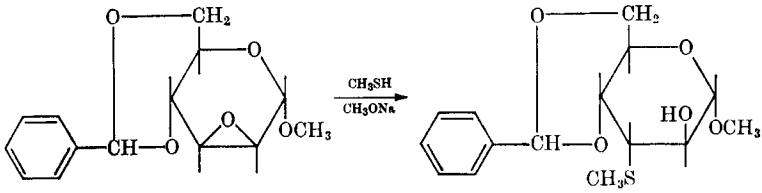


(656)

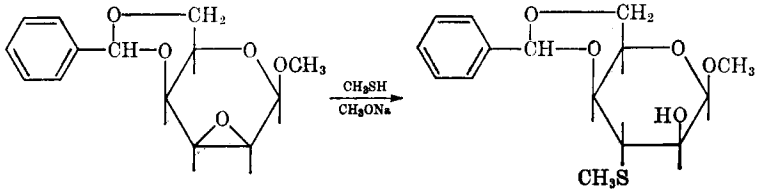
$m = 1, 2$
$n = 1, 2$

Addition of alkylmercaptans to anhydro sugars was at one time explored with interest as a means of synthesizing deoxy sugars, since the adducts thus secured could be desulfurized with Raney nickel.[427, 691, 875, 1084] Examples include the 2,3-anhydro-4,6-*O*-benzylidene derivatives of methyl α-D-mannoside,[875, 1084] β-D-taloside,[691] and α-D-guloside,[1084] which give the corresponding sulfide derivatives on treatment with methylmercaptan in base (Eqs. 657–659). Ring opening occurs in such a direction as to give diaxially disposed hydroxyl and methylthio substituents in each case.

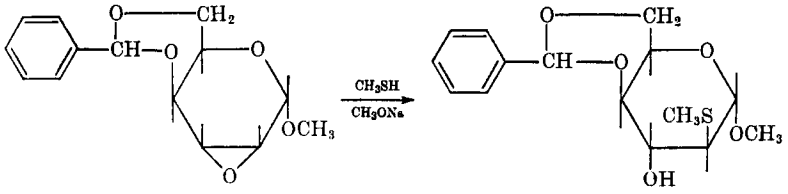
Two further illustrations, one from the sugar[1206] and the other from the steroid field,[1520] complete this presentation of the reactions of ethylene oxides with alkylmercaptans. As seen in Eqs. (660) and (661), attack follows the general sense indicated above with respect to direction and stereochemistry.



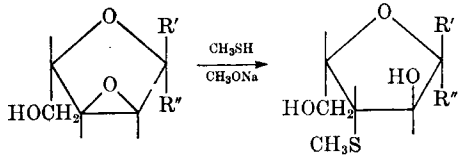
(657)



(658)

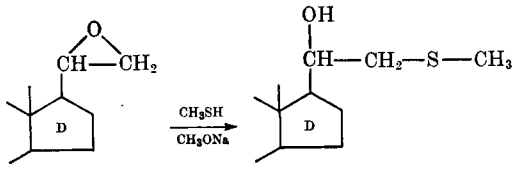


(659)



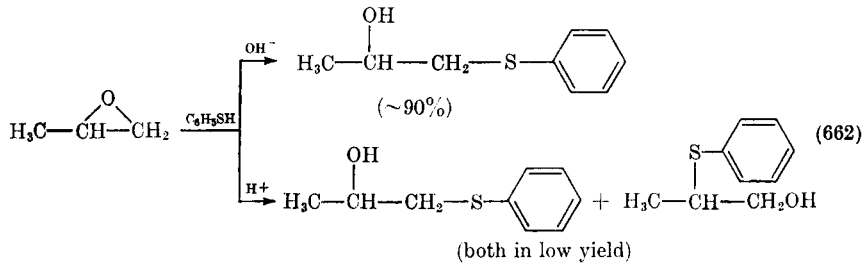
(660)

R′ = CH_3O, R″ = H
R′ = H, R″ = CH_3O



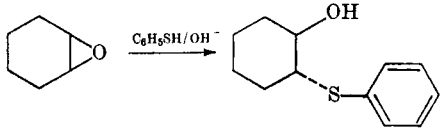
(661)

Attention may now be directed to the reactions of aromatic thiols with epoxides. Schuetz,[1549] for example, has investigated the course of addition of thiophenol to propylene oxide, both in alkaline and in acidic solutions. Significantly lower yields obtained in acid tended to confirm the premise that thiophenoxide ion rather than undissociated thiophenol is the attacking nucleophile. Likewise predictable was the isolation of two isomeric phenylthiopropanols under acid conditions, but of only one in base (Eq. 662).

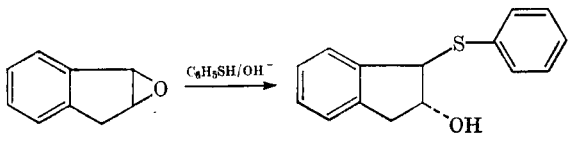


(662)

In a similar manner, thiophenol has been condensed with ethylene oxide itself,[1230] with cyclohexene oxide,[1230] and more recently with indene oxide.[584] The last undergoes addition preferentially at the benzylic epoxide carbon atom. Both alicyclic epoxides (Eqs. 663 and 664) are cleaved to 2-phenylthiocycloalkanols possessing *trans*-configuration.



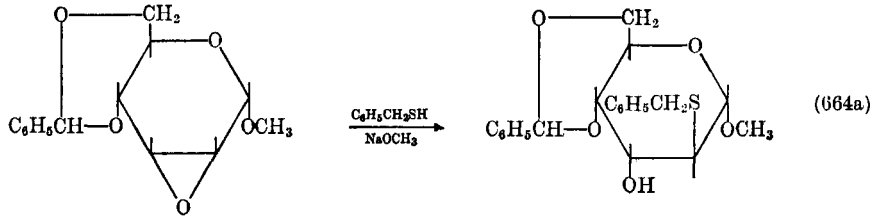
(663)



(664)

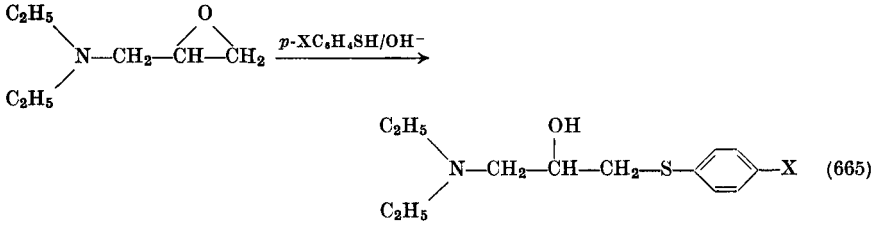
Christensen and Goodman[2024] have carried out the cleavage of methyl 2,3-anhydro-4,6-*o*-benzylidene-α-D-alloside with alkaline benzyl mercaptan. Attack takes place at $C_{(2)}$ to produce diaxially disposed hydroxyl and benzylthio substituents as expected (Eq. 664a).

Gilman and Fullhart[638] have investigated the action of several



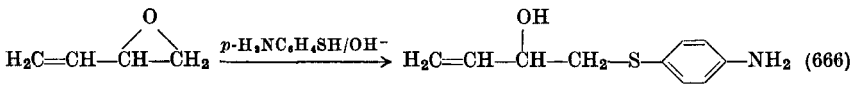
(664a)

p-substituted thiophenols on 1,2-epoxy-3-butene (Eq. 665) and 1,2-epoxy-3-(*N*,*N*-diethylamino)propane (Eq. 666). Among the thiols utilized in this study were *p*-methyl-, *p*-chloro-, *p*-amino-, and *p*-*N*,*N*-diethylamino-ethiophenol. Once more, terminal attack appeared to be predominant, although minute quantities of isomeric products might well have escaped detection.



(665)

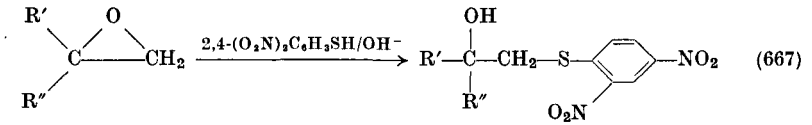
X = CH_3, Cl, NH_2, $(C_2H_5)_2N$



(666)

Treatment of *meso*-1,2;3,4-diepoxybutane with 2-thionaphthol in alkaline solution causes formation of *meso*-1,4-di-(2-thionaphthoxy-)-2,3-butanediol by terminal addition.[115]

Culvenor and co-workers[389, 422] have utilized 2,4-dinitrothiophenol to cleave a number of ethylene oxides. Notable examples include ethylene oxide itself, propylene oxide, *iso*butylene oxide, epichlorohydrin, and glycidol (Eq. 667). All undergo addition to the

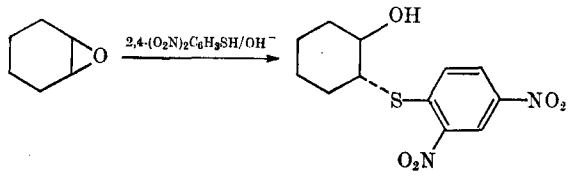


(667)

R′ = H, CH_3, $ClCH_2$, $HOCH_2$; R″ = H
R′ = R″ = CH_3

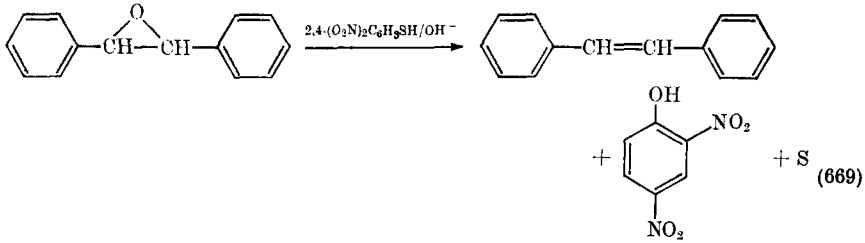
terminal epoxide carbon atom. Cyclohexene oxide (Eq. 668) likewise undergoes ring opening readily, giving a *trans*-adduct.

Culvenor and co-workers[389] made the curious observation that addition of 2,4-dinitrothiophenol to stilbene oxide, on the other hand,



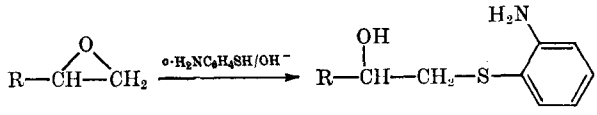
(668)

gives stilbene, 2,4-dinitrophenol, and free sulfur (Eq. 669). The reductive capacities of certain other sulfur-containing reagents toward epoxides was also noted by these authors, and has already been considered at greater length in section **IV.1.***D*.



(669)

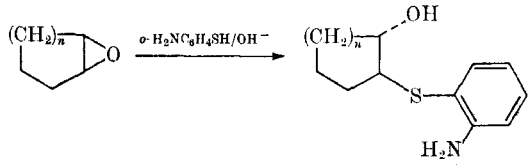
Meriting special comment on account of certain recent findings is the reagent *o*-aminothiophenol. This substance was reported, first in 1949 and again on several subsequent occasions,[292, 294, 391, 605] to yield 2,3-dihydrophenothiazine on condensation with ethylene oxide in base, and the corresponding substituted 2,3-dihydrophenothiazines with propylene oxide, cyclohexene oxide, and styrene oxide respectively. It has now been established, however, in three laboratories,[598, 830, 923] that previous reports were in error. The products formed are in fact normal open-chain adducts, as shown in Eqs. (670)–(672). Styrene



(670)

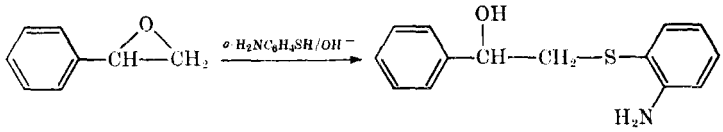
oxide yields a mixture of isomeric products,[923] in harmony with its customary behavior with nucleophiles. Danehy and Noel[405] have reported, incidentally, that *p*-aminothiophenol exhibits an anomalously high reactivity toward epoxides in relation to its pK_a value.

Culvenor and co-workers[391] have also carried out addition of *o*-aminothiophenol to 2-benzoyl-1-phenylethylene oxide and 2-acetyl-1-phenylethylene oxide, and to the oxides of ethyl 2-methylcrotonate

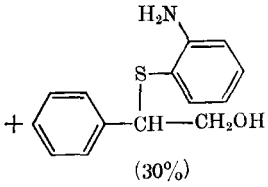


(671)

$n = 1, 2$



(38%)



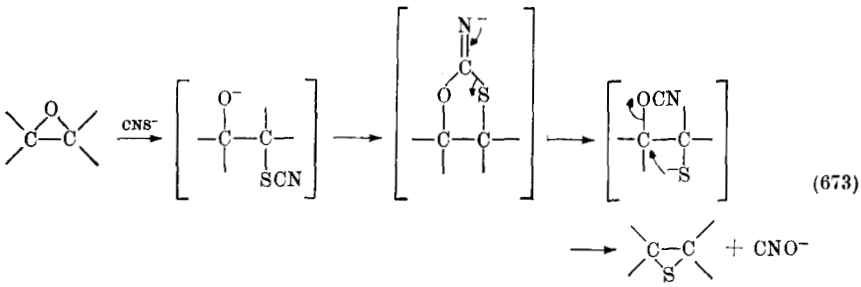
(672)

(30%)

and ethyl cinnamate as well. Incomplete product characterization by these authors, together with corrective finds made with simpler epoxides in other laboratories, may render desirable a re-examination of the results obtained with such α,β-epoxy ketones and α,β-epoxy esters.

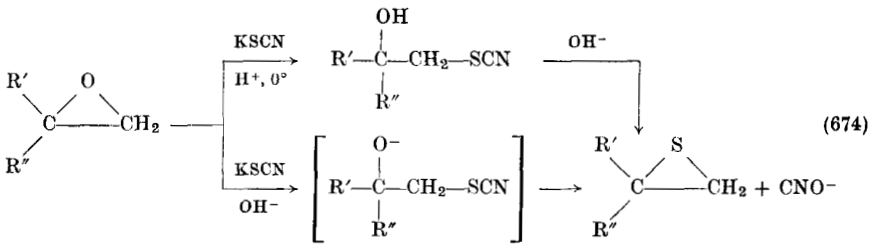
(2) Thiocyanate salts. The earliest publication describing addition of a thiocyanate salt to an epoxide appeared in 1946 from the Culvenor laboratory.[387] Since then a number of papers have dealt with this useful reaction, which may be utilized to transform ethylene oxides into ethylene sulfides conveniently in a single operation. It is generally agreed[714, 1408, 1777] that the course of events may be depicted as shown in Eq. (673) for the general case.

Ethylene oxide, propylene oxide, and *iso*butylene oxide yield β-thiocyanato alcohols on treatment with ice-cold, slightly acidified solutions of ammonium or potassium isothiocyanate.[1408, 1793] These



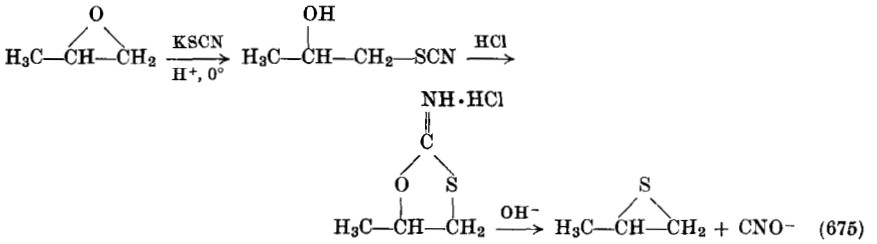
(673)

derivatives are quite unstable, being transformed into ethylene sulfides on exposure even to traces of alkali (Eq. 674). Recyclization is accompanied by expulsion of a good leaving group, the CNO^- ion. Addition of alkaline potassium isothiocyanate to the above epoxides give rise to ethylene sulfides directly.[1408, 1597]



(674)

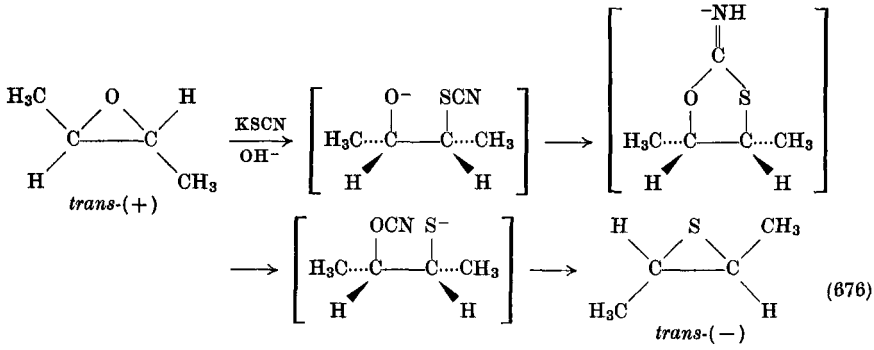
Concrete evidence for the existence of a cyclic intermediate of the type postulated by Van Tamelen,[1777] and also by Harding and coworkers,[714] was sought by Price and Kirk[1408] with propylene oxide. Careful treatment of 1-thiocyanato-2-propanol with hydrogen chloride yielded a salt for which the cyclic imine hydrochloride structure shown in Eq. (675) was formulated. Conversion of this salt into propylene sulfide was then readily accomplished in base.



(675)

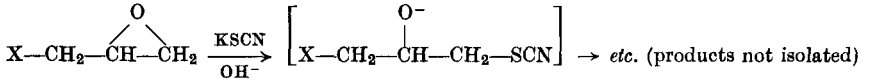
An indication of the stereochemically specific character of this reaction was obtained also by Price and Kirk[1408] with dextrorotatory

trans-2,3-epoxybutane, which gave levorotatory *trans*-2,3-dimethylethylene sulfide (Eq. 676). Intervention of a racemizable open carbonium ion was thereby clearly excluded.



(676)

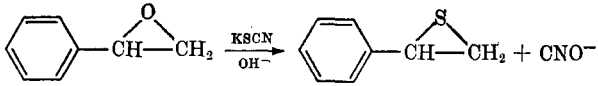
Nichols and Ingham[1250] have published kinetic studies involving addition of CNS^- ions to a large assortment of substituted ethylene oxides. Among the substances examined in this connexion were epihalohydrins, glycidol and its derivatives, and others (Eq. 677). Terminal addition appeared to take place preponderantly, if not exclusively, in every case.



(677)

X = Cl, Br, I, Me, OH, *iso*C_3H_7O, O_2NO, $H_2C{=}CHCH_2O$

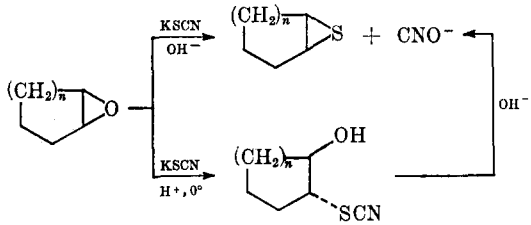
In spite of a previous report to the contrary, Guss and Chamberlain[685] discovered that styrene oxide could be converted directly into styrene episulfide by the thiocyanate route (Eq. 678).



(678)

Treatment of cyclopentene oxide and cyclohexene oxide with ice-cold slightly-acidic potassium isothiocyanate or ammonium isothiocyanate yields *trans*-2-thiocyanatocyclohexanols.[387, 658, 1597, 1777] In spite of a previous contention that formation of cyclopentene sulfide by such a route is unlikely because of the reputedly high energy of

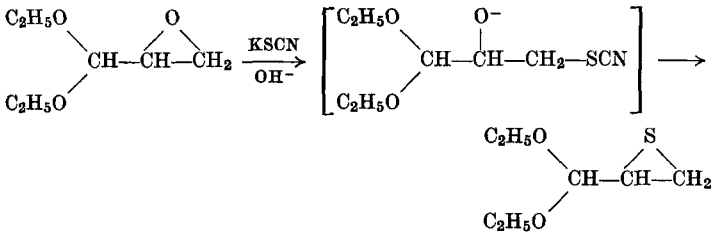
cyclic intermediates composed of two *trans*-fused five-membered rings,[1777] it is now known that both cyclopentene sulfide[658] and cyclohexene sulfide[387, 1777, 1597] are obtainable on treatment of the corresponding epoxides with alkaline potassium isothiocyanate (Eq. 679).



(679)

$n = 1, 2$

Addition of potassium isothiocyanate to 1,2-epoxy-3,3-diethoxypropane has been found by Wright[1882] to yield 3,3-diethoxy-1,2-propylene sulfide (Eq. 680). A recent publication by Hall and co-workers[1936] discloses the use of potassium isothiocyanate for the conversion of certain sugar epoxides into the corresponding sugar episulfides. Other authors have now also reported the preparation of *trans*-β-isothiocyanotoalcohols from the corresponding epoxides, both in the sugar series[2024] and in the steroid field as well.[2025]

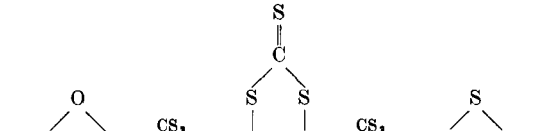


(680)

(3) Carbon disulfide, thiourea, and related reagents. Culvenor and co-workers[386, 387] have examined the action on ethylene oxides of several interesting sulfur-containing nucleophiles in addition to those already considered.

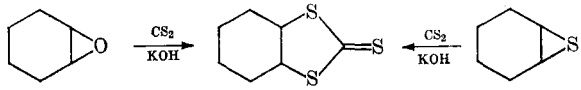
Alkaline carbon disulfide, for example, gives rise to cyclic trithiocarbonate derivatives on addition to ethylene oxide, cyclohexene oxide, and styrene oxide (Eqs. 681 and 682). The same derivatives were obtainable from the corresponding episulfides, which led the authors to

conclude that the latter might be intermediates in the conversion of ethylene oxides into cyclic trithiocarbonates.[387]



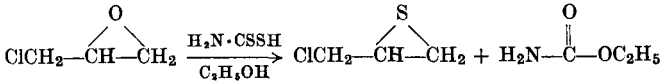
(681)

R = H, C_6H_5



(682)

A second reagent explored briefly by Culvenor and co-workers[386] was xanthamide, which transformed epichlorohydrin into 3-chloro-1,2-propylene sulfide in moderate yield (Eq. 683).

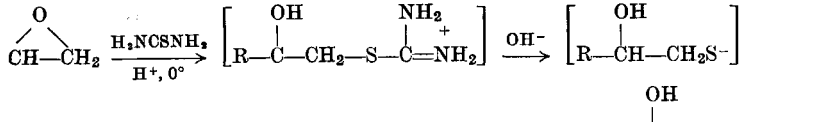


(683)

(low yield)

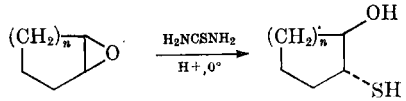
Related substances examined casually were thioacetamide and thiobarbituric acid, but products secured with them were only incompletely characterized.[386]

Thiourea was investigated with several epoxides, and found to be a fairly satisfactory replacement for hydrogen sulfide in the preparation of β-mercapto alcohols.[386] Thus, propylene oxide, cyclopentene oxide, cyclohexene oxide, and 1,2-epoxy-3-butene could be converted into the corresponding β-mercapto alcohols (Eqs. 684 and 685). An improved



(684)

R = CH_3, $H_2C{=}CH$

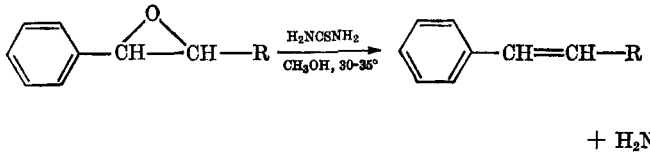


(685)

$n = 1, 2$

process minimizing polymer formation was subsequently devised by Bordwell and Anderson.[216]

Curious observations were made[386] on attempted condensation of certain phenyl-substituted ethylene oxides with thiourea and related reagents, among them acetamide, benzamide, and thiobarbituric acid. Stilbene oxide and ethyl epoxycinnamate, for example, underwent remarkably ready reduction on treatment with thiourea (Eq. 686), giving stilbene and ethyl cinnamate respectively, together with urea and free sulfur.



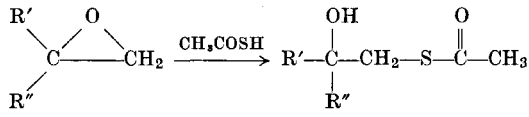
(686)

$$+ H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2 + S$$

R = C_6H_5, $CO_2C_2H_5$

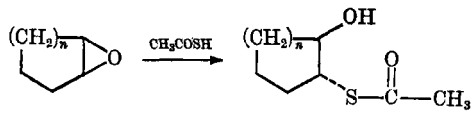
(4) Thiocarboxylic acids. A reagent used on occasion to cause rupture of ethylene oxide rings is thioacetic acid, almost the sole representative of its class of substances to have received any attention in this connexion.

Originally reported in 1941 by Nylen and Olsen[1260] to condense with ethylene oxide to give β-hydroxyethyl thioacetate, thioacetic acid



(687)

R′ = H; R″ = CH_3, $ClCH_2$, $HOCH_2$, H—C(=O)—
R′ = R″ = CH_3

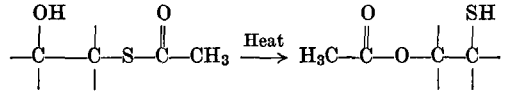


(688)

n = 1, 2

has since also been utilized (Eqs. 687 and 688) with propylene and *iso*-butylene oxide,[422, 1581, 1582] epichlorohydrin and glycidol,[422, 1581, 1582] cyclopentene oxide and cyclohexene oxide,[658, 715, 1161] and glycidaldehyde.[1668]

A characteristic feature of these β-hydroxyethyl thioacetate derivatives is their powerful tendency to undergo thermal rearrangement to the isomeric β-mercaptoethyl acetates,[1260, 1582] as shown in Eq. (689) for the general case.



(689)

The only other thiocarboxylic acid examined thus far in this reaction has been thiobenzoic acid, reported by Nylen and Olsen[1260] to give only a poor yield of β-hydroxyethyl thiobenzoate on addition to ethylene oxide.

(5) Sulfite and bisulfite salts; sulfinic acid salts. Passage of ethylene oxide through concentrated aqueous sodium bisulfite has long been known to cause formation of an adduct. Yet it was not until 1936 that Lauer and Hill[995] obtained conclusive proof of the structure of this adduct (Eq. 690) as sodium isethionate,[391] by conversion into taurine. It appears, therefore, that treatment of an epoxide with sodium bisulfite results in establishment of a C—S linkage, and that the attacking species must actually be SO_3^{2-} ion rather than undissociated HSO_3^- ion, which possesses no unshared sulfur electrons capable of bond formation.[995]

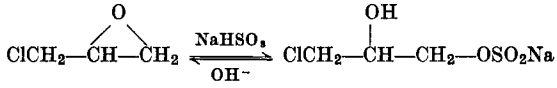


(690)

Among alkyl-substituted ethylene oxides known to undergo cleavage on treatment with sodium sulfite are propylene oxide, *iso*-butylene oxide, 1,2-epoxybutane, 1,2-epoxyoctane, and 2,3-epoxybutane.[1675] These reactions with sodium sulfite constitute the basis for an analytical method developed by Swan[1675] for the estimation of epoxide titer (see section **V.1.***B.*).

In 1868 Darmstaedter[410] published a paper stating that the bisulfite addition product of β-chloropropionaldehyde was formed on treatment of epichlorohydrin with sodium bisulfite, and Pazschke expressed the same belief again in 1870.[1318] In 1929 Fromm and coworkers[588] asserted, however, that epichlorohydrin reacts with a molar equivalent of sodium bisulfite to give a ring-cleavage product formulated as the monosodium sulfonate ester of 3-chloro-1,2-propanediol (Eq. 691).

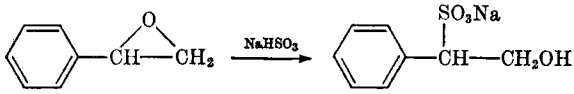
Support for this structure was drawn from the fact that epichlorohydrin was regenerated on treatment with base. It remains unclear, however, why SO_3^{2-} ion should prefer to attack ethylene oxide in one fashion and epichlorohydrin in another.



(691)

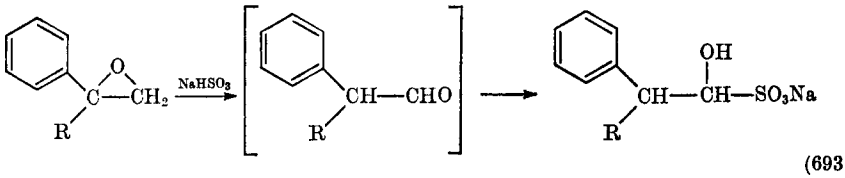
The adduct of sodium bisulfite and cyclohexene oxide was formulated by Brunel[255] as sodium *cis*-2-hydroxycyclohexyl sulfonate. No subsequent comment has appeared in the literature regarding this curious stereochemical assignment. Suter and Milne[1670] reported that indene oxide yielded a mixture of *cis*- and *trans*-indanediols, together with 1-monosodiumsulfonyl 2-hydroxyindane of undefined stereochemistry. Further work is clearly desirable in both instances.

Schenck and Kaizerman[1529] have condensed styrene oxide with sodium bisulfite, thereby obtaining only the sodium salt of β-hydroxy-α-phenylethane sulfonic acid (Eq. 692). Location of the sulfur atom on the benzylic epoxide carbon atom is consistent with the trend usually observed for acid-catalyzed nucleophilic attack on styrene oxide.



(692)

On the other hand, Tiffeneau[1720] noted as early as 1907 that α-methylstyrene oxide is isomerized under the influence of sulfurous acid itself, and slowly yields the bisulfite addition product of methylphenylacetaldehyde on treatment with sodium bisulfite (Eq. 693). It



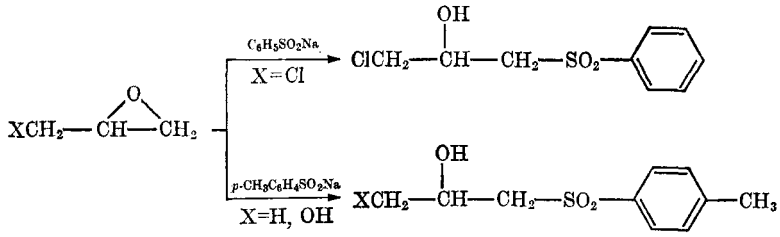
(693)

$R = CH_3, C_6H_5$

appears, therefore, that if nucleophilic attack by SO_3^{2-} ion is slow with respect to acid-catalyzed rearrangement to a carbonyl compound, the product secured from treatment of an epoxide with aqueous sodium bisulfite may well be a bisulfite addition product. Such an adduct has

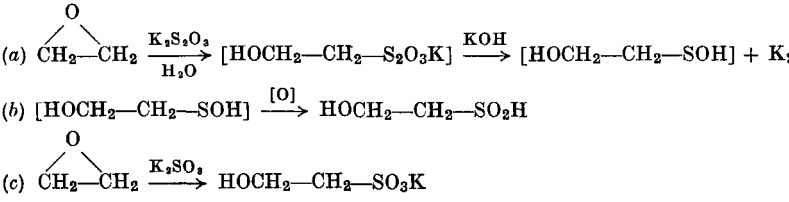
also been isolated from 1,1-diphenylethylene oxide,[942] but no other illustrations exist so far in the literature. Ethyl epoxycinnamate fails to react with sodium sulfite;[1675] the behavior of this substance with sodium bisulfite has unfortunately not been reported.

Related work by Culvenor and co-workers[388] has dealt with addition of sodium salts of arylsulfinic acids, which attack epoxide rings in the same manner as sodium sulfite. Products thereby obtained are sulfones. Examples of this interesting reaction include the condensation of sodium benzenesulfinate with epichlorohydrin, and of sodium toluene-*p*-sulfinate with propylene oxide and glycidol (Eq. 694).



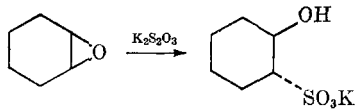
(694)

(6) Miscellaneous sulfur-containing reagents. Culvenor and co-workers[391] were the first to examine briefly the action of alkaline potassium thiosulfate on ethylene oxide. The products isolated by them were potassium isethionate (potassium β-hydroxyethanesulfonate) and β-hydroxyethane sulfinic acid. The course postulated for this process was as shown in Eq. (695).



(695)

Although a sulfinic acid could not be isolated from the condensation of potassium thiosulfate with cyclohexene oxide, the authors did obtain potassium 2-hydroxycyclohexane sulfonate, presumably possessing the *trans* configuration (Eq. 696).

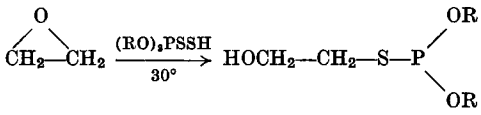


(696)

Ross[1491] subsequently developed a dependable qualitative test for the presence of epoxide functions in substances of unknown constitution (see section **V.1.***A.*). Liberation of base in the first stage is easily detected by use of an indicator. Among the numerous ethylene oxides examined by Ross in this connexion were propylene oxide, epichlorohydrin, glycidol, 1,2-epoxy-3-butene, 1,2;3,4-diepoxybutane and several alkyl derivatives, cyclohexene oxide, and a number of bisepoxides of interest for their cytotoxic properties. The action of $S_2O_3^{2-}$ ion was also examined kinetically in the same study.

Application of the qualitative thiosulfate reaction in structural investigations of epoxide-containing natural products may be illustrated by the work of Tarbell and co-workers[1490, 1694, 1698] on the antibiotic fumagillin.

Mention may be made, in conclusion, of the report of Kabachnik and co-workers[898] that dialkyl dithiophosphate esters condense with ethylene oxide as indicated in Eq. (697). Higher polymers are said to form readily unless careful temperature control is exercised throughout the reaction.



(697)

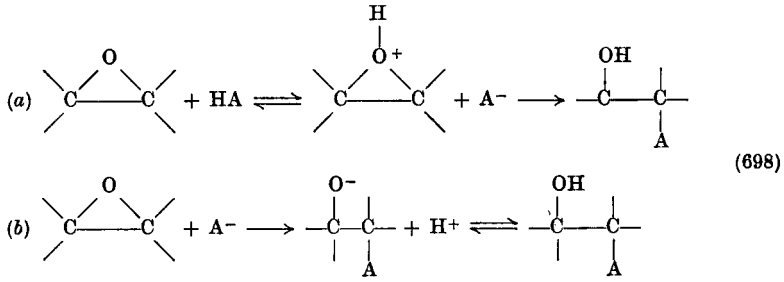
Future work in the growing field of sulfur chemistry may well disclose numerous other powerful sulfur-containing nucleophiles capable of cleaving epoxide rings under mild conditions.

D. Reactions of Epoxides with Acids

This section is devoted to the addition of acids to ethylene oxides. To facilitate its presentation the material will be divided into two principal categories: (1) condensation with mineral acids; (2) condensation with organic acids. The first will include halogen acids and other strong mineral acids; the second will include carboxylic acids, sulfonic acids, and hydrocyanic acid (hydrogen cyanide).

Two modes of addition may be depicted for the reaction of acids to epoxides, corresponding formally to uncatalyzed and acid-catalyzed nucleophilic substitution processes. These may be represented as in Eq. (698). Although the situation is probably more complicated in actual fact, the simplified picture presented here will suffice within the framework of the Parker–Isaacs model for epoxide reactions.[1301]

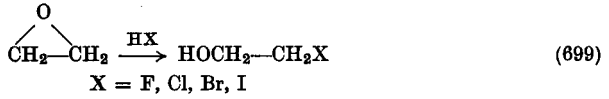
Which of the two types of processes depicted above will preponderate is presumably governed by a number of interrelated variables.



(698)

Among them may be the strength of the acid, the polarity of the reaction medium, the nucleophilicity of the conjugate base, the structure of the epoxide, and other factors.

(1) Mineral acids. The reaction of ethylene oxide itself with hydrochloric acid was first reported by Wurtz,[1886, 1887, 1889] who noted the vigor of the condensation but succeeded in isolating ethylene chlorohydrin. Subsequent investigators extended the reaction (Eq. 699) to include also hydrofluoric acid,[952] hydrobromic acid,[1081] and hydroiodic acid.[248, 476] An important side-process when addition is effected in water is the formation of ethylene glycol and poly(ethylene glycols). If desired, however, the reaction can be conducted in non-aqueous media by passing gaseous hydrogen halides into well-cooled solutions of ethylene oxide in ether, dioxan, or ethanol. It is noteworthy that hydrobromic acid may be added to ethylene oxide at a temperature as low as $-78°$.[1081]

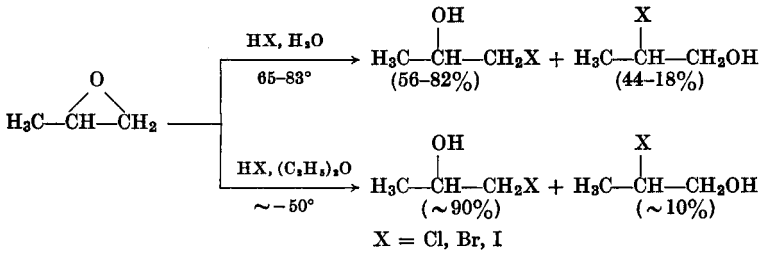


(699)

Several simple alkyl-substituted ethylene oxides undergo addition of hydrogen halide to give the corresponding halohydrins. Wide attention, for example, has been accorded to propylene oxide, particularly in connexion with kinetic studies.[248, 1585, 1586, 1589, 1590]

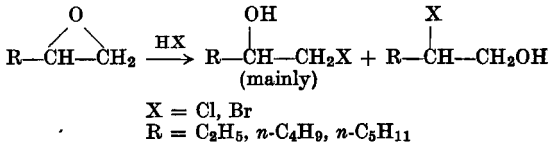
In 1918 Abderhalden and Eichwald[4] made the curious observation that dextrorotatory propylene oxide yields levorotatory 1-bromo-2-propanol on treatment with hydrogen bromide. Subsequent work by Levene and Walti[1015] confirmed this particular finding, but at the same time called attention to certain defects in the previous study. There

does appear to be inversion in the sign of optical rotation on ring opening, and the extent of this trend seems to vary, moreover, with the solvent used. It remained for Stewart and Vander Werf[1649] to produce a really thorough product analysis (Eq. 700) that could be correlated with certain of the parameters cited above. The excellent work of these authors has contributed substantially to the present state of knowledge concerning epoxide reaction mechanisms.[1301]



(700)

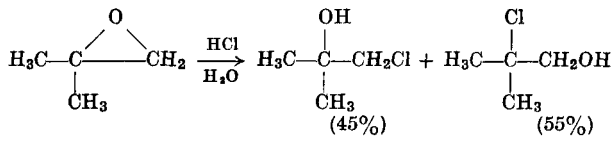
Other monoalkylated ethylene oxides reported to undergo ready cleavage on treatment with halogen acids (Eq. 701) include 1,2-epoxybutane,[1589] 1,2-epoxyhexane,[1800] and 1,2-epoxyheptane.[241] Although the last two have been said to yield only secondary alcohols, corresponding to exclusive attack of halide on the terminal epoxide carbon atom, it is probable that isomeric alcohols are also formed in small undetected quantities.



(701)

*iso*Butylene oxide has been the subject of sharply conflicting observations.[750, 753, 1154, 1359, 1589] Whereas Michael[1154] reported hydrogen chloride to give rise to a mixture of isomeric chlorohydrins in which 1-chloro-2-methyl-2-propanol predominated, Henry[750, 753] and later Petrov[1359] asserted on the contrary that 2-chloro-2-methyl-1-propanol was the principal constituent of the product mixture. Most recent evidence, secured by Smith and Skyle,[1589] indicates that aqueous hydrochloric acid affords a mixture composed of nearly equal proportions of isomeric chlorohydrins (Eq. 702).

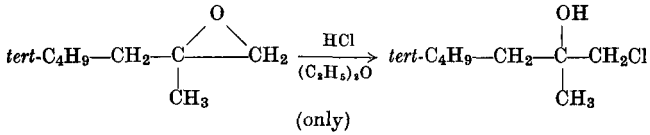
On the other hand, 1,2-epoxy-2,4,4-trimethylpentane has recently been reported to give only one chlorohydrin on treatment with ethereal



(702)

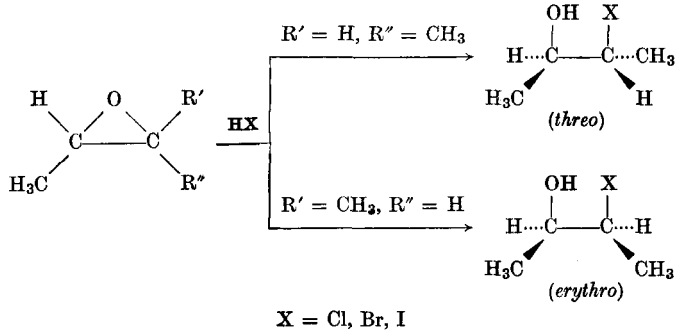
hydrogen chloride (Eq. 703), formulated as 1-chloro-2,4,4-trimethyl-2-pentanol.[663]

Light has been cast upon the stereochemical aspects of this reaction by Lucas and co-workers,[1050, 1051, 1861, 1863] who showed *cis*- and *trans*-2,3-epoxybutane to give *threo*- and *erythro*-halohydrins



(703)

respectively on treatment with hydrochloric acid, hydrobromic acid, or hydroiodic acid (Eq. 704). The stereospecificity of the addition is a reflection of the fact that even under these acid-catalyzed conditions a fully developed carbonium ion is not generated, and is consistent with the view that the process involved here is of the 'borderline S_N2' type.[1301]

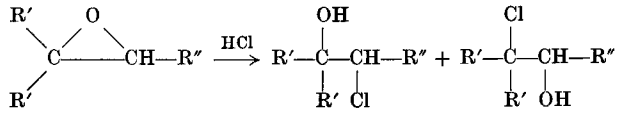


(704)

The action of halogen acids on 2,3-epoxypentane was reported many years ago by Henry,[748] who believed only a single product to have been formed. The validity of this conclusion is questionable, however, and may bear revision.

More heavily alkylated ethylene oxides (Eq. 705) have also been subjected to the action of hydrogen halides.[751, 913, 1183, 1359] Mixtures of isomeric halohydrins are undoubtedly produced, but precise quantitative data still remains to be secured.

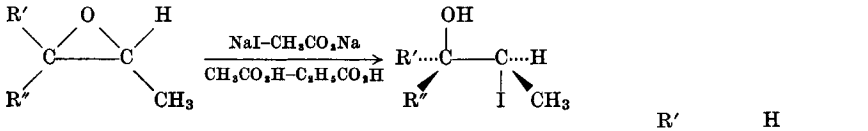
An interesting stereospecific olefin synthesis developed by Cornforth and co-workers[356] initially involves addition of the elements of



(705)

$R' = CH_3$; $R'' = CH_3$, *iso*C_4H_9
$R' = C_2H_5$; $R'' = CH_3$

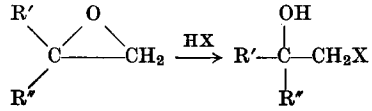
hydrogen iodide to epoxides (Eq. 706). The reagent found most convenient for this purpose is a solution of sodium iodide and sodium acetate in mixed acetic acid and propionic acid. Iodohydrins generated in this manner form single olefins on treatment with stannous chloride and phosphorus oxychloride in pyridine.



(706)

$R' = C_2H_5$; $R'' = CH_3$
$R' = CH_3$; $R'' = C_2H_5$

Very shortly after the discovery of ethylene oxide Reboul,[1439] Markownikov,[1109] Henry,[747] and other investigators[41, 410, 784, 836, 952, 1297, 1585] set out to examine the behavior of epichlorohydrin, epibromohydrin, and epiiodohydrin toward the various halogen acids from a purely qualitative point of view, and later authors[248, 1585] gradually

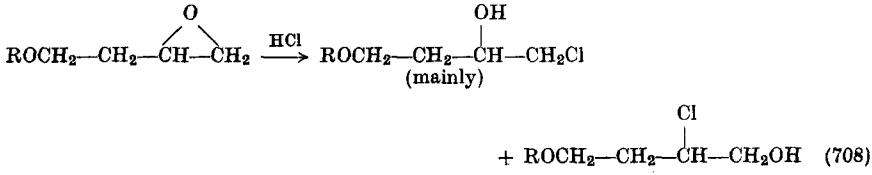


(707)

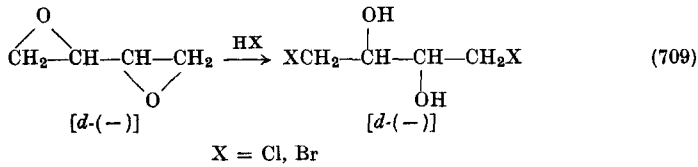
X = F, Cl, Br, I
$R' = H$; $R'' = XCH_2$ (X = Cl, Br, I), $BrCH_2CHBr$
$R' = CH_3$; $R'' = ClCH_2$, Cl_3C

began to concern themselves with precise quantitative measurements of the same reactions. It has been found, in general, that treatment of an epihalohydrin with a halogen acid (Eq. 707) causes formation of an α,α'-dihalohydrin exclusively, indicating preferential nucleophilic attack at the terminal epoxide carbon atom furthest from the polar halogen substituent.

The action of hydrogen halides on miscellaneous other ethylene oxides containing polar atoms in the vicinity of the epoxide ring has been described. Among substances examined in this connexion

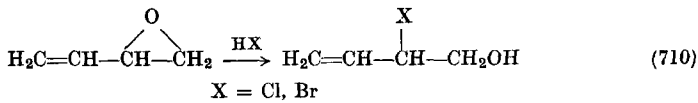


(Eq. 708) are 3,4-epoxy-1-methoxy- and 3,4-epoxy-1-ethoxybutane,[1296,1298,1308] and quite recently *d*-(−)-1,2;3,4-diepoxybutane.[525] The latter (Eq. 709) opens with retention of optical activity, since attack takes place at the terminal epoxide carbon atoms which do not constitute sites of asymmetry.



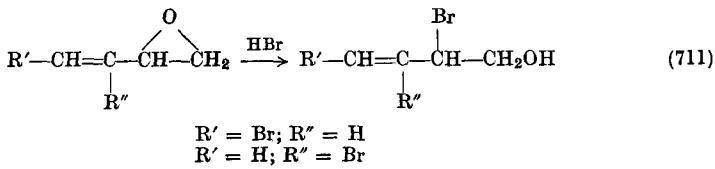
(709)

Addition of hydrochloric acid or hydrobromic acid to 1,2-epoxy-3-butene (Eq. 710) is reported to give only 2-chloro- and 2-bromo-3-buten-1-ol respectively.[899,1357] The decisive influence exerted by the double bond is evident, when it is recalled that the corresponding saturated epoxide is opened in the opposite sense.



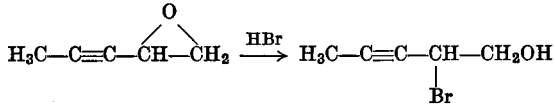
(710)

Petrov[1354,1356] has described the cleavage of 4-bromo-1,2-epoxy-3-butene and 3-bromo-1,2-epoxy-3-butene (Eq. 711) with hydrobromic acid, which allegedly gives primary alcohols as above.



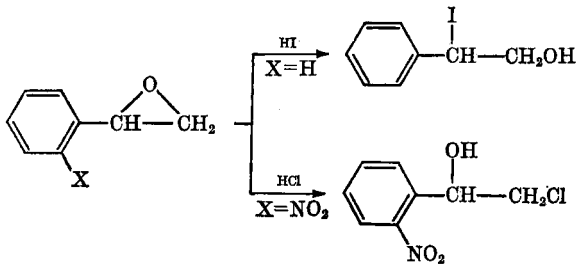
(711)

Similarly, Petrov[1360] has reported addition of hydrogen bromide to 1,2-epoxy-3-pentyne (Eq. 712), which gives rise to 2-bromo-3-pentyn-1-ol exclusively. This and related results are doubtless attributable to the ability of double and triple bonds to stabilize partial carbonium ion character development in the 'borderline S_N2' transition state.[1301]



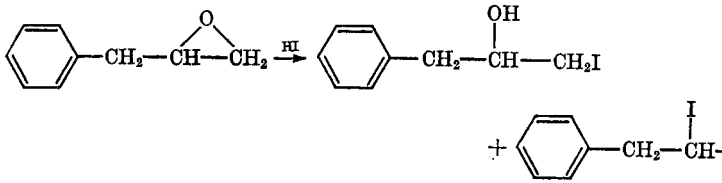
(712)

The effect of phenyl substituents on the course of halogen acid addition to ethylene oxides is exemplified by the reactions of styrene oxide, which is reported to give 2-iodo-2-phenylethanol exclusively on treatment with hydrogen iodide.[1728, 1730] Condensation of *o*-nitrostyrene oxide with hydrochloric acid, on the other hand, gives rise to 2-chloro-1-(*o*-nitrophenyl)ethanol.[41] This inversion in sense of addition (Eq. 713) is ascribable to the electron-withdrawing capacity of the *o*-nitro function, which raises the activation energy necessary to form a transition state in which the benzylic epoxide carbon atom could exhibit partial positive character.



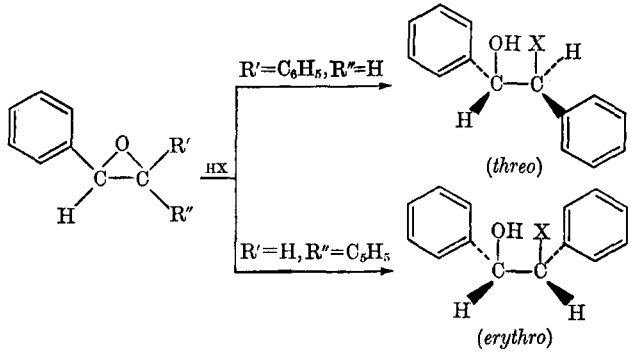
(713)

When the phenyl substituent is one carbon removed from the epoxide ring, as in 2,3-epoxy-1-phenylpropane, nucleophilic attack can evidently occur at either possible reaction sites, since a mixture of iodohydrins (Eq. 714) is obtained on treatment with hydrogen iodide.[1397]



(714)

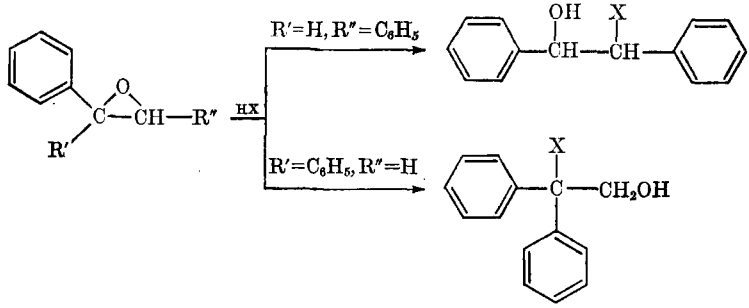
Several instances of higher phenyl-substitution exist in the literature, among them *cis*- and *trans*-stilbene oxides (Eq. 715), which yield *threo*- and *erythro*-halohydrins respectively on addition of halogen



(715)

X = Cl, Br

acids.[1449] Others are 1,2-epoxy-1,2-diphenylpropane[1742] and 1,2-epoxy-1,1-diphenylpropane.[1650] The latter (Eq. 716) appear to yield uniquely products corresponding to nucleophilic attack on the most substituted carbon atom, as might be predicted on the basis of the Parker–Isaacs model[1301]

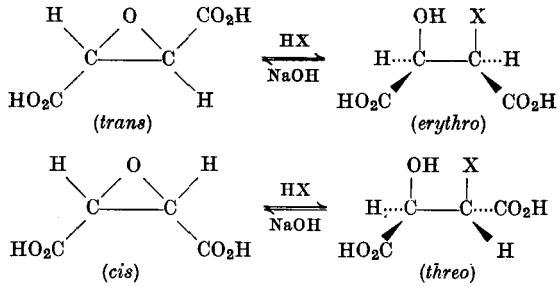


(716)

X = Cl, Br

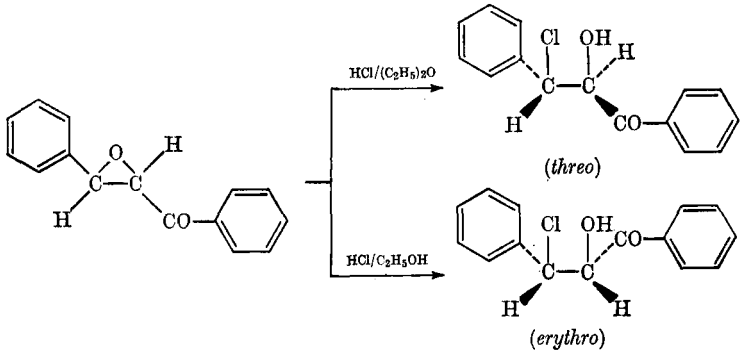
Kuhn and Ebel,[981] in one of the earliest stereochemical investigations involving ethylene oxides, demonstrated that *trans*-2,3-epoxysuccinic acid yields only a halohydrin possessing *erythro* configuration, whereas the corresponding *cis*-oxide yields a *threo*-halohydrin, as indicated in Eq. (717). The halohydrins could be reconverted into the

original epoxides on treatment with alkali, thus establishing their configurations unambiguously.



(717)

Benzalacetophenone oxide and several substances derived from it have been subjected to the action of hydrogen chloride in various solvents.[65, 816, 886, 1835] House[816] has reported, for instance, that *trans*-benzalacetophenone oxide (Eq. 718) gives the corresponding *threo*-chlorohydrin on treatment with hydrogen chloride in ether, indicating either the absence of inversion or an even number of inversions amounting to no net inversion. In ethanol, however, the same epoxide yields the isomeric *erythro*-chlorohydrin, indicating overall inversion

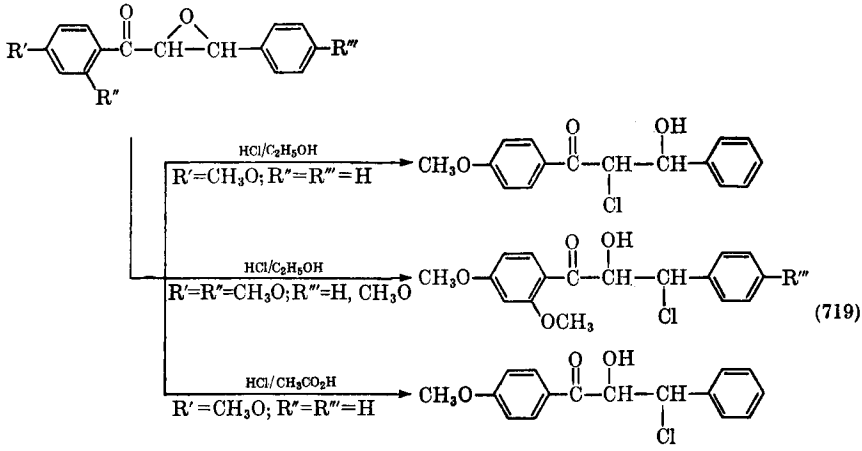


(718)

in the more polar solvent. The C—O bond undergoing rupture is adjacent to the phenyl rather than the benzoyl substituent in each case. This is in line with the greater ability of the former to accommodate development of a nearby positive center in the transition state.

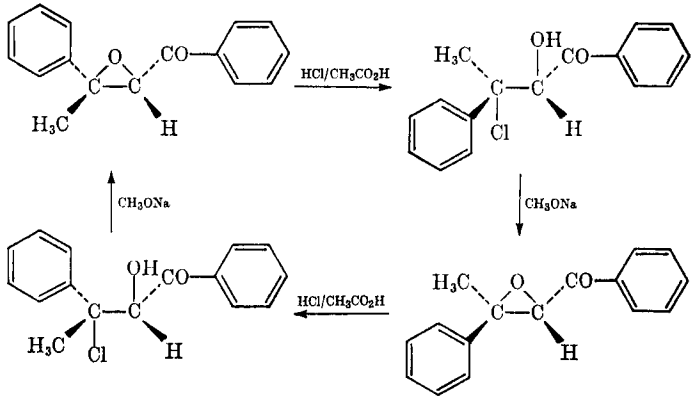
An instance in which the solvent appears to affect not merely the stereochemistry but also the direction of ring cleavage had been described previously by Jorländer.[886] Treatment of 1-(*p*-anisyl-)-2-phenylethylene oxide of unspecified configuration with hydrogen

chloride in ethanol or in acetic acid allegedly led to fission of different C—O bonds (Eq. 719). Baker and Robinson,[65] on the other hand, examined the behavior of 2-(*p*-anisyl)-1-(2,4-dimethoxyphenyl)ethylene oxide and arrived at conclusions in conflict with Jorländer[886] concerning the direction of ring opening in ethanol.



(719)

Wasserman and Aubrey[1806] extended this type of investigation to include the *cis*- and *trans*-isomers of dypnone oxide. Chlorohydrins obtained on treatment of these α,β-epoxy ketones with hydrogen chloride in acetic acid could be recyclized into dypnone oxides of

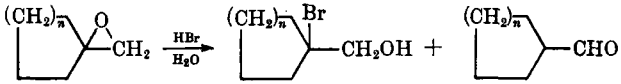


(720)

opposite configuration in base (Eq. 720). It was inferred that halogen acid addition must have taken place with overall retention of configuration, and that an even number of inversions are involved. Once

again, it is seen that attack occurs at the epoxide carbon atom furthest from the carbonyl function.

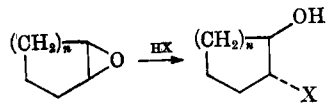
Addition of hydrogen chloride to semicyclic ethylene oxides was first explored by Tiffeneau and co-workers,[1750] who reported formation of 1-chlorocyclohexanemethanol from 1-oxaspiro[2.5]octane (methylenecylohexane oxide). Traynham and Pascual[1763] recently extended this investigation to include also methylenecyclopentane oxide and methylenecycloheptane oxide, using hydrobromic in place of hydrochloric acid. Although principal products in every case, 1-bromocycloalkanemethanols formed in this manner were accompanied by varying amounts of cycloalkanecarboxyaldehydes. The relative proportions of bromohydrin to aldehyde appear to depend on ring size, as shown in Eq. (721). That cyclohexanecarboxyaldehyde may have escaped notice in Tiffeneau's previous studies is understandable, since it merely constituted 5% of the product mixture.



(721)

$n = 1$	65%	35%
$n = 2$	95%	5%
$n = 3$	68%	32%

Cyclopentene oxide,[1151] cyclohexene oxide,[81, 966, 1853] and cycloheptene oxide[1310] have all been reported to undergo addition of halogen acids with ease, giving *trans*-2-halocycloalkanols as anticipated (Eq. 722). Karabinos and Hazdra[2026] recently reported failing to condense cyclohexene oxide with anhydrous hydrogen fluoride in diglyme or



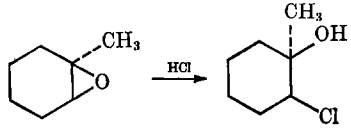
(722)

X = Cl, Br, I
$n = 1, 2, 3$

dimethylformamide, although a modest yield of 2-fluorocyclohexanol could be obtained if the epoxide was heated at 150–180° with sodium fluoride. Fluoroalcohols of higher molecular weight are also produced under these conditions.

Tiffeneau and co-workers[1750] carried out addition of hydrogen chloride to 1,2-epoxy-1-methylcyclohexane and reported the formation

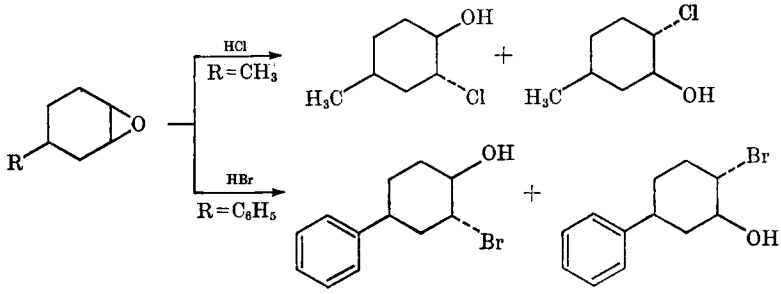
of 2-chloro-1-methylcyclohexanol exclusively (Eq. 723). Curiously, this substance is different from that secured on addition of hypochlorous acid to 1-methylcyclohexene, and yet chemical evidence cited by Tiffeneau is consistent with its formulation as a tertiary alcohol. It would appear, therefore, that ring opening can occur in this case with



(723)

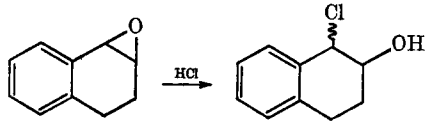
overall retention of configuration even though only alkyl-substitution is involved.

Treatment of 1,2-epoxy-4-methylcyclohexane[966] and 1,2-epoxy-4-phenylcyclohexane with halogen acids has been shown, on the other hand, to give rise to mixtures of isomeric halohydrins (Eq. 724).

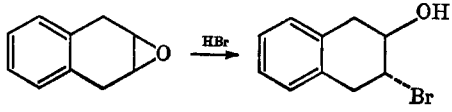


(724)

Ring cleavage of 1,2-dihydronaphthalene oxide[1661] and 1,4-dihydronaphthalene oxide[72] has been carried out with hydrochloric acid and hydrobromic acid respectively. Though it is safe to suppose a *trans*-halohydrin to have been formed in the second case (Eq. 726), the product stereochemistry is somewhat in doubt in the first (Eq. 725).

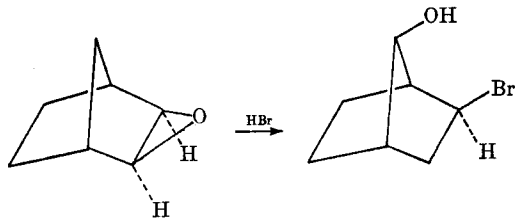


(725)



(726)

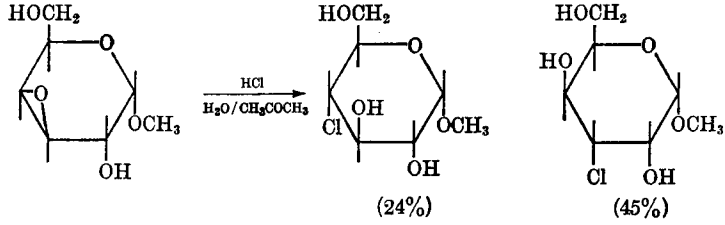
Walborsky and Loncrini[1796] not long ago reported addition of hydrogen bromide to *exo*-2,3-epoxybicyclo[2.2.1]heptane (*exo*norbornylene oxide). The product isolated from this reaction was identified as 2-*exo*bromo-7-hydroxybicyclo[2.2.1]heptane (Eq. 727). The analogous rearrangement has been realized in the case of benznorbornadiene oxide by Bartlett and Giddings.[2001]



(727)

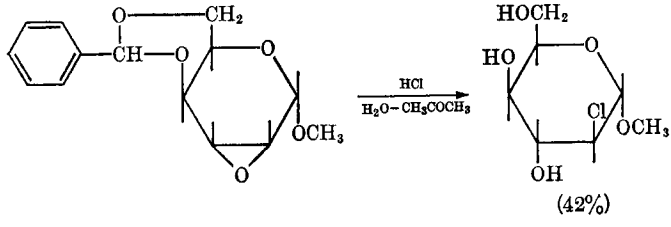
Ample results may be drawn from the sugar series on the subject of hydrogen halide addition to epoxides, some of which has only been recently found to be in error and corrected.

Buchanan[257] has obtained a mixture of methyl 4-chloro-4-desoxy-α-D-glucoside and methyl 3-chloro-3-desoxy-α-D-guloside, as indicated in Eq. (728), on treatment of methyl 3,4-anhydro-α-D-galactoside with hydrogen chloride in aqueous acetone.



(728)

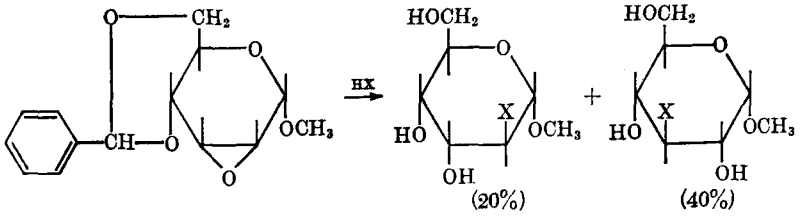
On exposure of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-guloside (Eq. 729) to similar treatment, there was isolated only methyl 2-chloro-2-desoxy-4,6-*O*-benzylidene-α-D-idoside.[258]



(729)

The extent of revision imposed on previous results by these findings has been discussed by Newth in a recent review,[1245] and need not be considered further here.

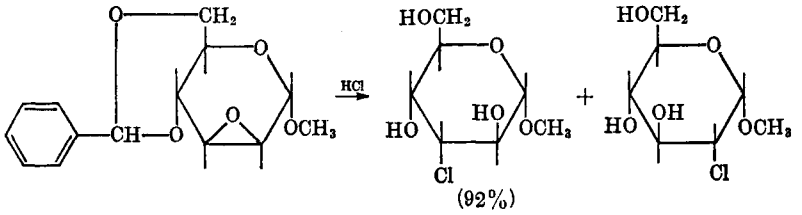
Analogous results have been secured by Newth and co-workers[1246, 1247] with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-glycosides of D-allose and D-mannose (Eqs. 730 and 731). Both epoxides



(730)

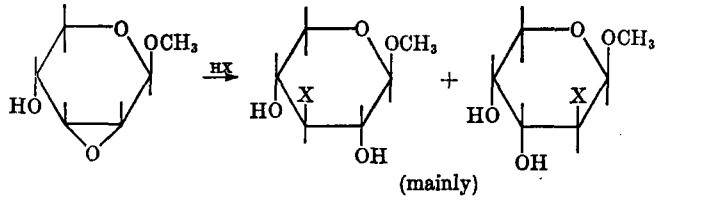
X = Cl, Br

undergo cleavage in two directions, giving mixtures of isomeric chlorohydrins derived from D-altrose and D-glucose, but yield data indicate predominant $C_{(3)}$ attack in each case.



(731)

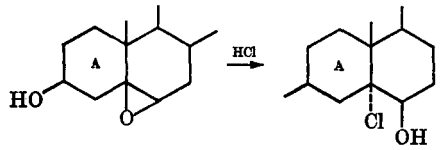
Similarly, treatment of methyl 2,3-anhydro-β-D-riboside with hydrogen halides has been shown by two groups of workers[26, 921] to involve chiefly $C_{(3)}$ attack, yielding a mixture of isomers derived from D-xylose and D-arabinose (Eq. 732).



(732)

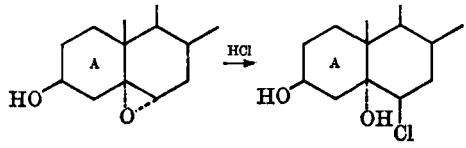
X = Cl, Br

Illustrations of halogen acid addition to epoxides abound in the steroid field. Only a few representative examples need be cited to demonstrate that ring opening usually gives a diaxial product according to the Fürst–Plattner rule.



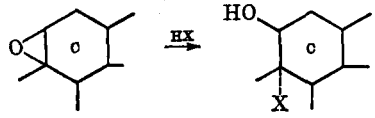
(733)

Treatment of 5α,6α-epoxy-3-β-hydroxy steroids (Eq. 733) and 5β,6β-epoxy-3β-hydroxy steroids (Eq. 734) with hydrochloric acid yields 6β-chloro-3β,5α-dihydroxy and 5α-chloro-3β,6β-dihydroxy derivatives respectively.[106, 297]



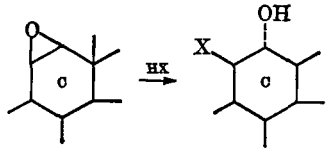
(734)

Addition of halogen acids to 9β,11β-epoxy steroids (Eq. 735) and 11β,12β-epoxy steroids (Eq. 736) leads to 9α-halo-11β-hydroxy and 11β-halo-12α-hydroxy derivatives respectively.[357, 583, 584, 585, 615, 1277, 1543, 1698]



(735)

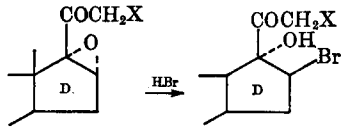
X = F, I



(736)

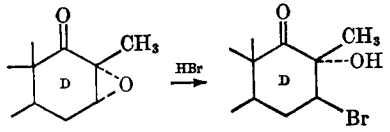
X = F, Br

A modest assortment of steroidal α,β-epoxy ketones (Eqs. 737–740) have been subjected to the action of hydrogen halides, among them

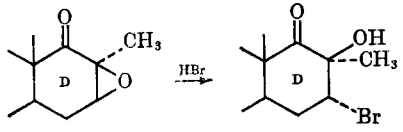


(737)

X = H, CH_3CO_2

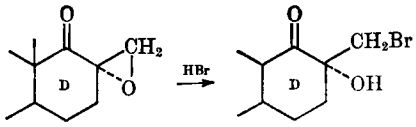


(738)



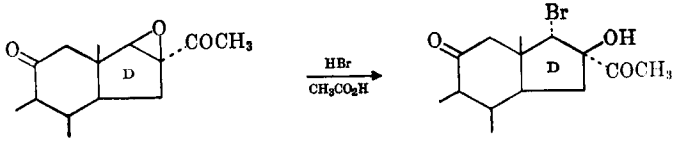
(739)

16α,17α-epoxy-20-oxo steroids,[891, 1465, 1467] 16α,17α-epoxy-17β-methyl-17α-oxo and 16β,17β-epoxy-17α-methyl-17α-oxo D-homosteroids,[599, 1829] and the spiroepoxide[1828] depicted in Eq. (740).

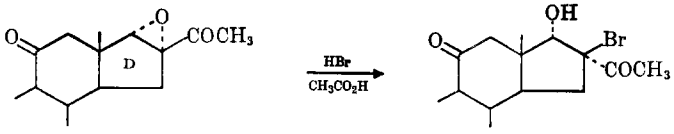


(740)

Interesting stereochemical specificity is displayed during the addition of hydrogen bromide to the 16α-acetyl-16β,17β-epoxy and 16β-acetyl-16α,17α-epoxy steroids studied recently by Taub and co-workers[1977] and shown in Eqs. (740a) and (740b). Steric hindrance to



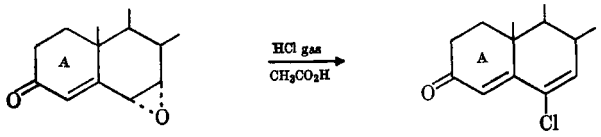
(740a)



(740b)

topside approach of Br^- by the 18-methyl apparently causes the 16α,17α-epoxide to open in this unexpected manner.

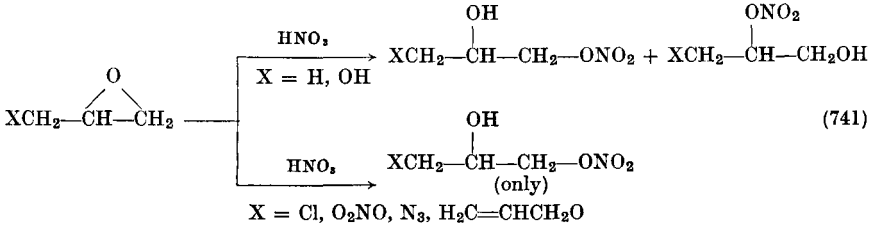
Mention may also be made of a novel type of halogen acid addition which has been noted by Sciaky[2027] with certain 6α,7α-epoxy-Δ^4-3-oxo steroids, as shown in Eq. (740c).



(740c)

In conclusion of the present section, attention may be directed to two other strong mineral acids that have been condensed with ethylene oxides: nitric acid and perchloric acid. These reagents, provided they are used as cold dilute aqueous solutions to avoid oxidative reactions, give 1,2-diol monoesters.

It was reported as early as 1870 by Henry[746] that propylene oxide and epichlorohydrin yield nitrate esters with dilute nitric acid (Eq. 741). Ingham and Nichols[852] extended this observation to glycidol as

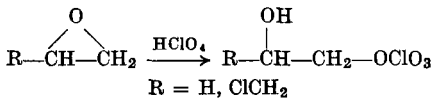


(741)

well, and found that it gave a mixture of isomeric nitratodiols whose composition depended markedly on the polarity of the reaction medium. Not unexpectedly, a medium of high dielectric constant tended to favor attack at the most alkylated epoxide carbon (*i.e.* favored a 'borderline S_N2' pathway in terms of the Parker–Isaacs model). It is likely that a mixture of isomeric nitratoalcohols is produced with propylene oxide as well.[1363] Nichols and co-workers[853, 1251, 1363] have also conducted thorough kinetic studies of the addition of NO_3^- ion to the ethylene oxide ring of various epoxides in neutral or acidic solution. Their results parallel those secured already some years ago by Smith and co-workers,[1590] and also by Brønsted and co-workers.[248]

Perchloric acid was reported in 1909 by Hofmann and co-workers[796] to condense with ethylene oxide and epichlorohydrin,

giving very explosive β-chloratoalcohols (Eq. 742). Investigation of these products has been understandably scanty, however.



$$R{-}CH(O)CH_2 \xrightarrow{HClO_4} R{-}CH(OH){-}CH_2{-}OClO_3 \qquad R = H,\ ClCH_2 \qquad (742)$$

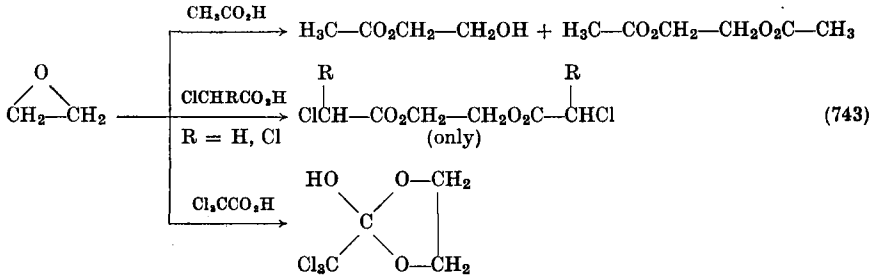
(2) Organic acids: (*a*) **carboxylic acids.** The second major category of acidic nucleophiles commonly used to cause ring opening in ethylene oxides is composed mainly of carboxylic acids, among them formic acid, acetic acid, and benzoic acid. Although deliberate use of such reagents for epoxide cleavage has not been reported often, olefins are well known to give rise to 1,2-diol monoesters on treatment with peroxy acid solutions containing appreciable quantities of free parent acid. Particularly notorious in this respect are solutions of performic acid or peracetic acid.[1678, 1679] This section includes a considerable number of examples of this type of ring opening, inasmuch as it is recognized to involve preliminary epoxide formation followed by further reaction with liberated carboxylic acid. Whenever an epoxide is only an inferred intermediate in the conversion of an olefin into a 1,2-diol monoester, however, attention is called to this by enclosing the epoxide in parentheses in the equations (*e.g.* Eq. 745).

It is often customary to hydrolyze 1,2-diol monoesters isolated from olefins directly to 1,2-diols, without determining the site of attack in the presumed epoxide intermediate. This is regrettable in those instances where information on the direction of ring cleavage might be useful. Where the structure of the 1,2-diol monoesters cannot be specified, only the formula of the 1,2-diol ultimately isolated is shown here (*e.g.* Eq. 747).

Excellent reviews by Swern[1678, 1679] have already been cited in connexion with epoxide synthesis by peroxy acid oxidation of olefins (see section **III.1.***A*.). These papers are equally useful in connexion with the present topic, and should be consulted for many details that cannot be discussed here.

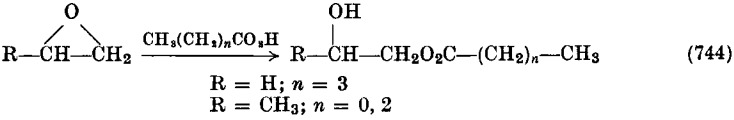
That acetic acid condenses rapidly with ethylene oxide was first noted by Wurtz himself[1886, 1890] as early as 1860. Although 2-acetoxyethanol appeared to be the principal product, there were also formed 1,2-diacetoxyethane and monoacetate esters of various higher molecular weight glycols. Meerwein and Sonke[1142] examined the action of stronger acids like chloroacetic acid and dichloracetic acid, and established that diesters were the preponderant products. Trichloroacetic

acid, on the other hand, behaved as an ortho acid, allegedly yielding the cyclic product shown in Eq. (743).



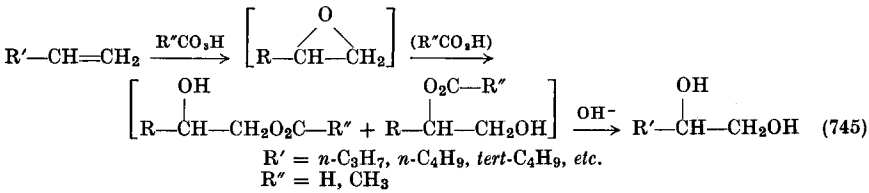
(743)

Longer-chain carboxylic acids have been utilized by Fraenkel-Conrat and Olcott[576] to open ethylene and propylene oxide (Eq. 744), the latter allegedly undergoing exclusive terminal addition.



(744)

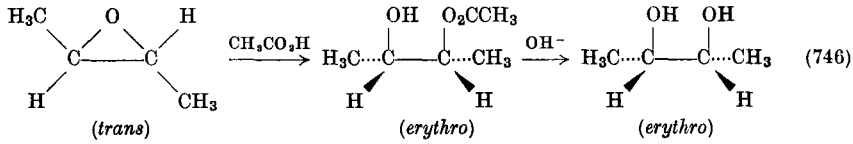
Several other terminal olefins have been reported to give mixtures of isomeric 1,2-diol monoesters from which 1,2-diols are obtained by alkaline hydrolysis (Eq. 745). Although quantitative results are not available, it must be supposed by analogy that the terminal epoxide carbon atom is attacked preferentially, giving the most highly substituted alcohols.[191, 209, 369, 675, 1681, 1682, 1688]



(745)

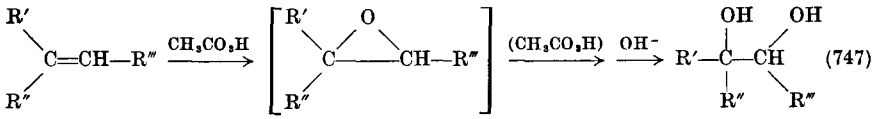
Stereochemical specificity is manifest in the reaction of *trans*-2,3-epoxybutane with acetic acid, which Winstein and Lucas[1862] reported to give only *erythro*-2-acetoxy-3-butanol (Eq. 746). Hydrolysis leads to optically inactive *meso*-2,3-butanediol. Similarly, Böeseken and Cohen[193] had described previously the preparation of racemic *d,l*-2,3-butanediol from *cis*-2-butene and peracetic acid, presumably by way of an epoxide and a 1,2-diol monoacetate which were not isolated. Analogous results

subsequently obtained by Criegee and co-workers[369] with other *cis–trans* olefin pairs likewise indicate that opening of epoxides with carboxylic acids takes place by Walden inversion at the reaction site.



(746)

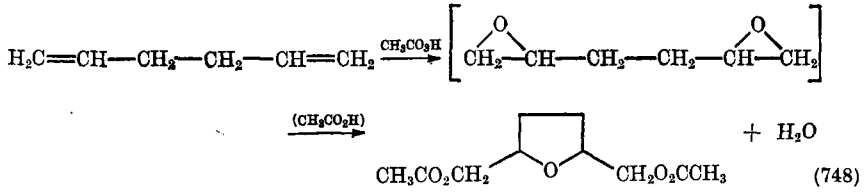
Among other simple alkyl-substituted epoxides either cleaved directly with acetic acid, or assumed to exist as intermediates in the conversion of corresponding olefins into 1,2-diol monoacetates,[191, 272–275, 698, 772] are the substances shown in Eq. (747). The location of acetoxyl groups in the products in these reactions is unknown, hydrolysis to 1,2-diols having been carried out directly.



(747)

R′ = *n*-C_3H_7; R″ = H; R‴ = CH_3
R′ = R″ = CH_3; R‴ = C_2H_5, *tert*-C_4H_9
R′ = *tert*-C_4H_9, *n*-C_4H_9; R″ = CH_3; R‴ = H

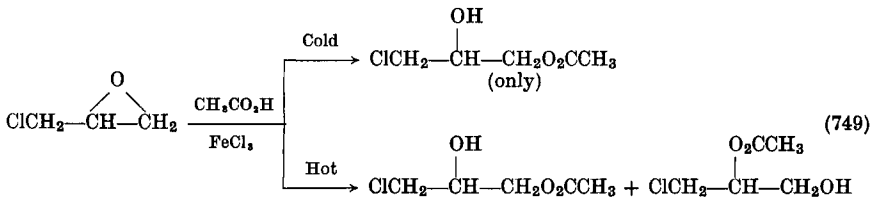
Somewhat more complex is the reaction described by Böeseken,[189] whereby diallyl can be converted into 2,5-diacetoxymethyltetrahydrofuran on treatment with peracetic acid (Eq. 748). This transformation was presumed to occur by way of 1,2;5,6-diepoxyhexane, which reacts further with acetic acid present in the oxidizing solution. Ross[1491] has observed a similar cyclization while attempting acid-catalyzed hydration of authentic 1,2;5,6-diepoxyhexane.



(748)

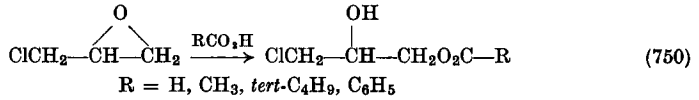
Addition of carboxylic acids to epichlorohydrin has been studied in several laboratories.[1, 248, 945, 1491] Knoevenagel[945] noted, for instance, that acetic acid attacks only the terminal epoxide carbon atom when the reaction is conducted in the cold, but gives a mixture of isomeric

1,2-diol monoacetates on heating (Eq. 749). The effectiveness of ferric chloride as a catalyst for this reaction was also described in passing.



(749)

Abderhalden and Eichwald[1] observed, moreover, that addition of formic acid to levorotatory epichlorohydrin yields levorotatory 3-chloro-1-formoxy-2-propanol, whereas dextrorotatory epibromohydrin gives dextrorotatory 3-bromo-1-formoxy-2-propanol under similar conditions. Condensation of several other carboxylic acids (Eq. 750) was examined kinetically by Brønsted and co-workers.[248] These authors concluded the attacking species to be the anion of the carboxylic acid, rather than the free acid itself, since the reactivity of the acids tested could be correlated to their degree of dissociation. Acids utilized in this classic study were formic acid, acetic acid, trimethylacetic acid, and benzoic acid. In accord with the above is the recent observation of Maerker and co-workers[2028] that epichlorohydrin is attacked faster by the sodium salts of stearic acid or azelaic acid than by the free acids themselves. Benzyl trimethyl ammonium chloride was used as a catalyst in this study.



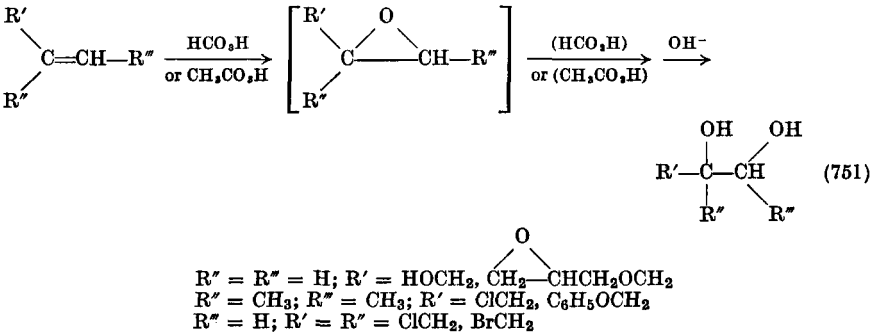
(750)

Other olefins bearing polar atoms in the vicinity of the double bond that have been converted into the corresponding 1,2-diols by treatment with a peroxy acid and subsequent alkaline hydrolysis[140, 233, 1279, 1870] are the substances shown in Eq. (751). In these instances the direction of ring fission is unfortunately not known, since 1,2-diol monoesters thereby generated were for the most part hydrolyzed directly.

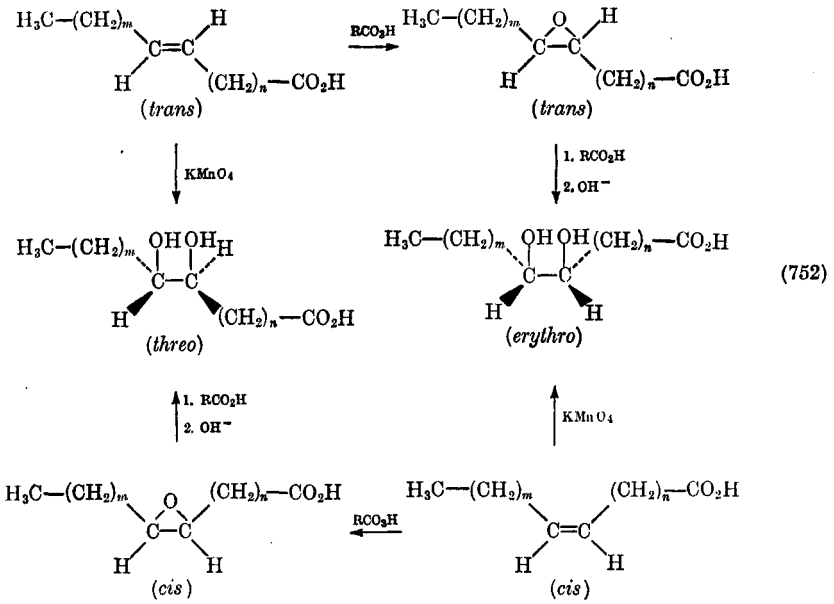
Ross[1491] has published kinetic data for the addition of acetic acid to several epoxides in buffered solution, among them epichlorohydrin, glycidol, 1,2;3,4-diepoxybutane, 1,2;5,6-diepoxyhexane, and diglycidyl ether (diallyl ether diepoxide). Other organic acids found to condense smoothly with 1,2;3,4-diepoxybutane in the presence of their sodium

salts (*i.e.* in buffered solutions) were benzoic acid, tartaric acid, citric acid, and oxalic acid.

Virtually a private domain for this reaction, the field of fatty acid chemistry provides an enormous variety of examples illustrating

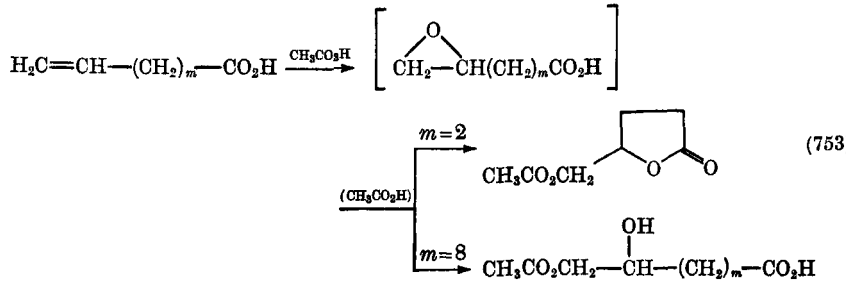


addition of carboxylic acids to epoxides. Cleavage of an assortment of *trans*-substituted fatty acid epoxides with carboxylic acids has been found to yield, after alkaline hydrolysis, 1,2-diols isomeric with those obtained by potassium permanganate oxidation but possessing the opposite configuration (Eq. 752). Entirely analogous results are ob-



tained on replacement of *trans*-substituted fatty acid epoxides with *cis*-substituted isomers (Eq. 752). Although most of the examples cited here involve 1,2-diol monoesters formed directly by peroxy acid oxidation of olefins,[52, 121, 263, 461, 782, 835, 1252, 1677, 1686–1688] a few involve authentic epoxides isolated before cleavage.[100, 678, 1768] It is probable that addition of carboxylic acids to fatty acid epoxides yields mixtures of isomeric 1,2-diol monoacetates, although quantitative results on this point are lacking.

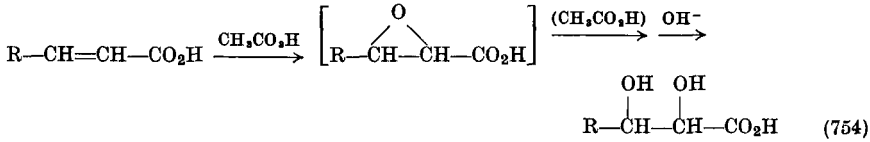
Certain unsaturated fatty acids give lactone esters on treatment with peracetic acid, presumably by intramolecular attack of the carboxyl function on the initially-formed epoxide ring. Thus, 4,5-epoxypentanoic acid generated by peracetic acid oxidation of 4 pentenoic acid undergoes cleavage to give a five-membered lactone as



(753)

shown in Eq. (753), whereas the higher homolog 10,11-epoxyundecanoic acid only gives the open-chain 1,2-diol monoacetate under these conditions.

Several instances are known in which α,β-unsaturated acids yield α,β-dihydroxy acids on treatment with peracetic acid and alkaline hydrolysis of the resultant 1,2-diol monoesters.[237, 239, 503, 1212] Although no information is available concerning the direction of acetic acid

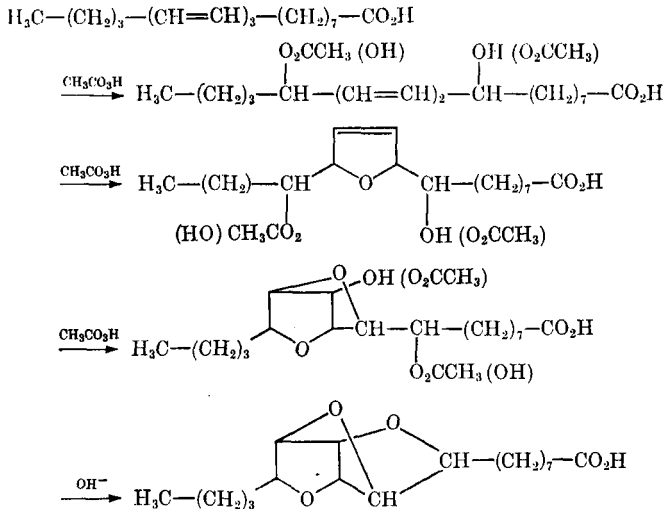


(754)

R = CH_3, C_2H_5, n-C_3H_7, C_6H_5, n-$C_{15}H_{21}$ (*cis* and *trans*), *etc.*

addition, it may be supposed by analogy that attack would occur preferentially at the epoxide carbon atom furthest from the carboxyl function (Eq. 754).

To appreciate the formidable complexities that can arise when such fatty acids as linoleic acid, linolenic acid,[664] ricinoleic acid,[918] or ricinelaidic acid[918] are epoxidized and the resulting intermediates undergo further reactions, it is instructive to examine results obtained with 9,10;11,12;13,14-octadecatrienoic acid by Böeseken and co-workers.[202] Addition of a single molar equivalent of peracetic acid yielded a product formulated as a monoacetate of 9,14-dihydroxy-10,11;12,13-octadecadienoic acid. Addition of a second molar equivalent of oxidizing agent gave a cyclic derivative depicted as a 2,5-dihydrofuran. The third molar equivalent of peracetic acid gave a bicyclic product containing only a single acetoxy group, and yielding on alkaline hydrolysis the tricyclic structure shown in Eq. (755). These



(755)

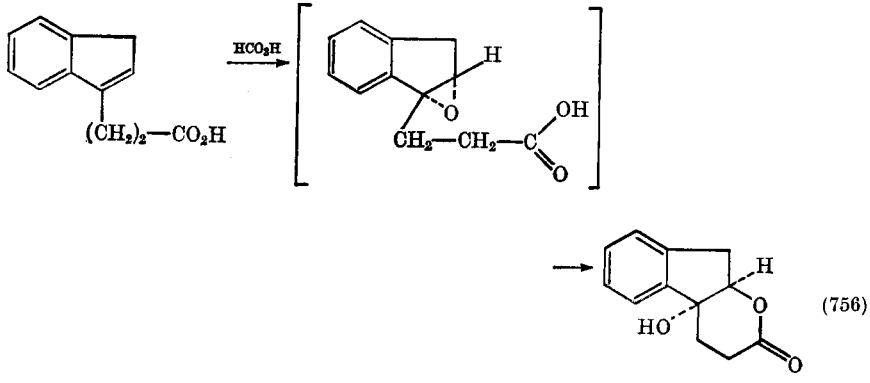
rearrangements all presumably involve epoxide intermediates if the accepted mechanism for the reaction of peroxy acids with olefins is operative here.

Lactone formation on treatment of unsaturated acids with peroxy acids is not confined to the field of fatty acid chemistry. Howell and Taylor[829] obtained a hydroxylactone, for instance, on adding performic acid to the indene derivative shown in Eq. (756). An epoxide was assumed to constitute the intermediate stage of this transformation.

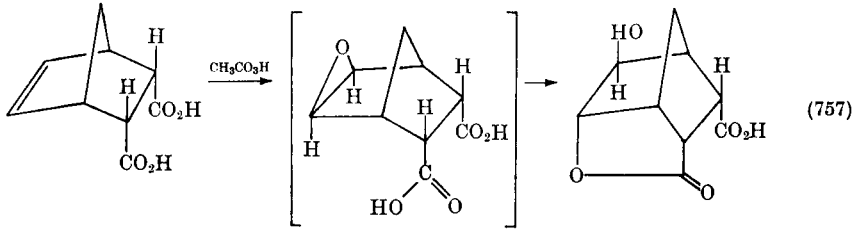
Nazarov and co-workers[1224] have noted intramolecular attack by a carboxyl function on an epoxide ring in the case of the bicyclo[2.2.1]-heptene derivative shown in Eq. (757). Other work of a similar char-

acter by Nazarov and co-workers[1223] has already been cited in section **III.1.*A***.

Crabb and Schofield[362] likewise reported formation of a spirolactone during the attempted epoxidation of certain benzocyclo-



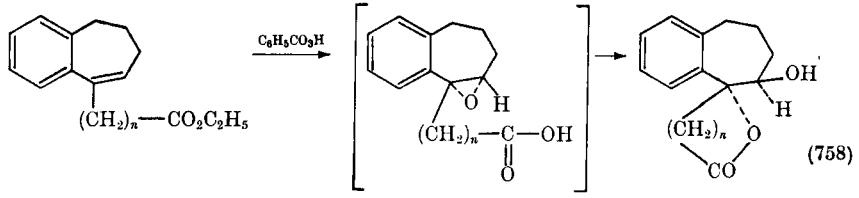
(756)



(757)

heptadiene derivatives with perbenzoic acid (Eq. 758). Hydrolysis of the ester function must evidently precede cleavage of the epoxide ring.

Recent studies of Berti and Bottari[151–153] may be cited, which

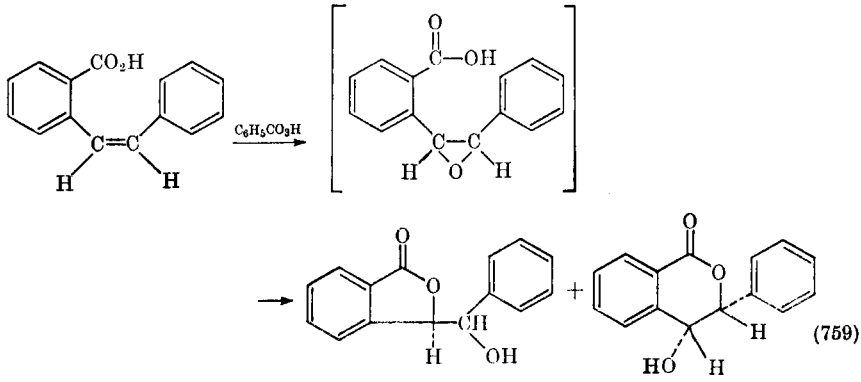


(758)

$n = 3, 4$

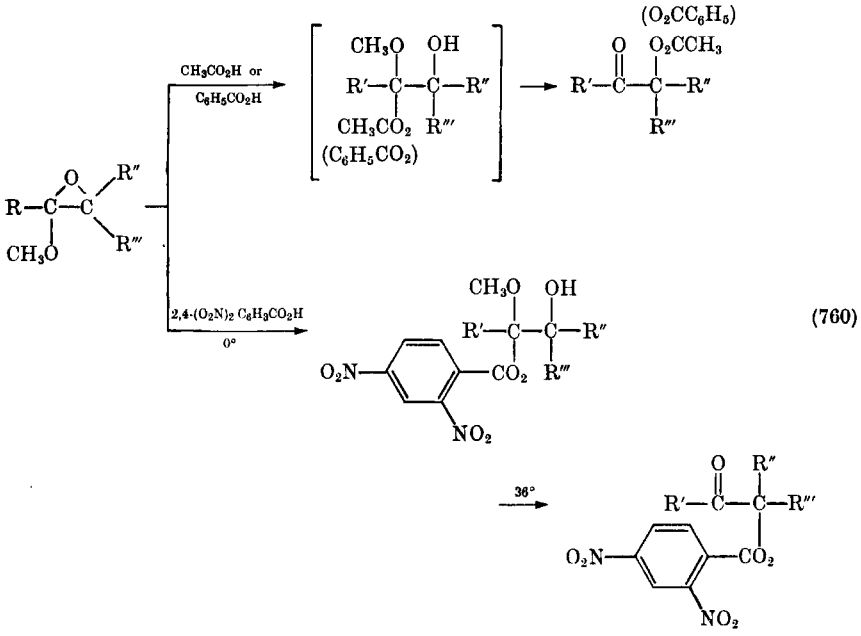
deal with the course of reaction of certain styrene and stilbene derivatives possessing carboxyl substituents suitably disposed for lactone formation. Although several other substances are included in their work, it will be sufficient to consider here the behavior of *o*-carboxy-*cis*-stilbene on treatment with perbenzoic acid (Eq. 759).

Several epoxy ethers have been subjected to the action of acetic acid and 3,5-dinitrobenzoic acid by Stevens and co-workers.[1632, 1636, 1637, 1639] It was established that attack by the



(759)

carboxylic acid occurs exclusively at the methoxyl-substituted epoxide carbon atom, but subsequent rearrangement to the ester of an α-hydroxy ketone takes place with extreme ease (Eq. 760). Only with a

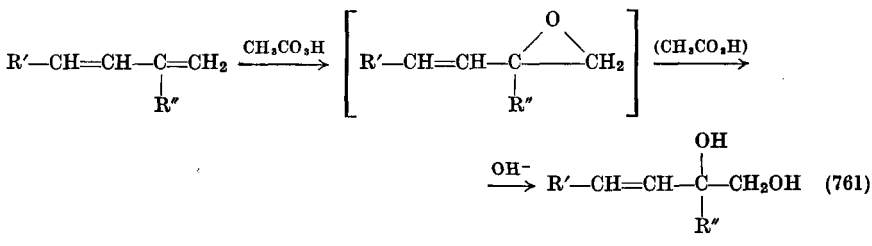


(760)

R′ = H, $C_6H_5C_6H_4$; R″ = R‴ = CH_3
R′ = R″ = H; R‴ = C_2H_5, n-C_5H_{11}
R′ = C_6H_5; R″ = H; R‴ = CH_3, C_6H_5

2,4-dinitrobenzoate ester, and at low temperatures, was it possible to isolate the initial cleavage product.

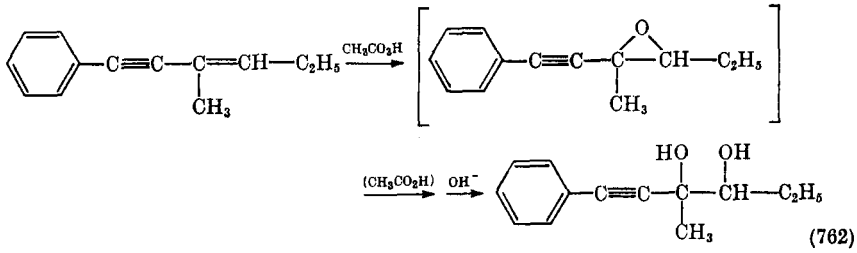
Addition of a carboxylic acid to an epoxide can be regarded as an intermediate stage in the conversion of various dienes into unsaturated 1,2-diols,[191, 787, 1211] as shown in Eq. (761).



(761)

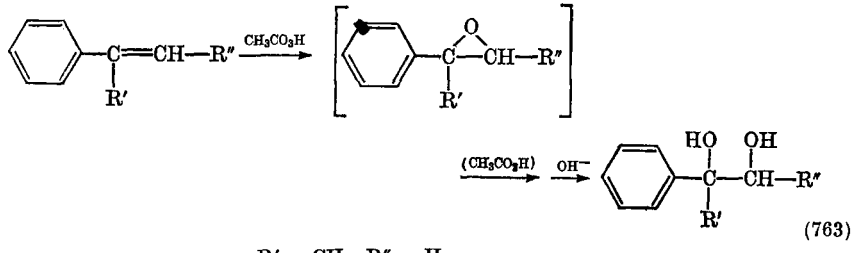
R′ = H; R″ = H, CH_3
R′ = C_6H_5; R″ = H

Addition of a carboxylic acid to an acetylenic epoxide presumably constitutes an intermediate stage in the conversion of 3-methyl-1-phenyl-3-hexen-1-yne into the corresponding 1,2-diol (Eq. 762) by peracetic acid oxidation.[1087]



(762)

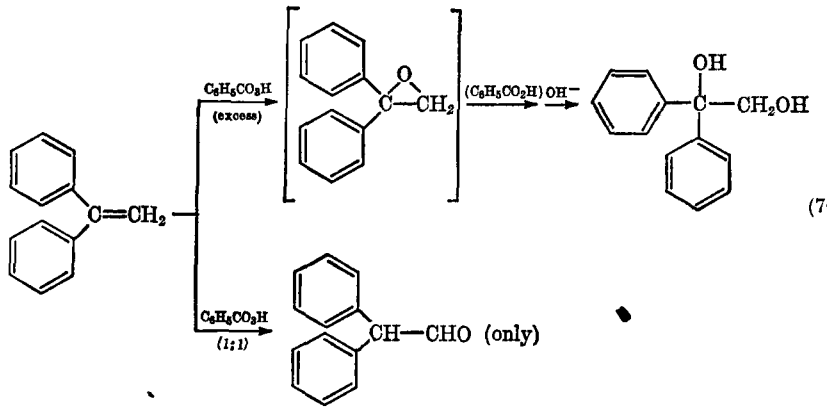
A number of aryl-substituted ethylene oxides have been exposed to the action of carboxylic acids during the peroxy acid oxidation of olefins. Among these (Eq. 763) may be cited β-methylstyrene,[196]



(763)

R′ = CH_3; R″ = H
R′ = H; R″ = $HOCH_2$, HO_2C, *etc.*

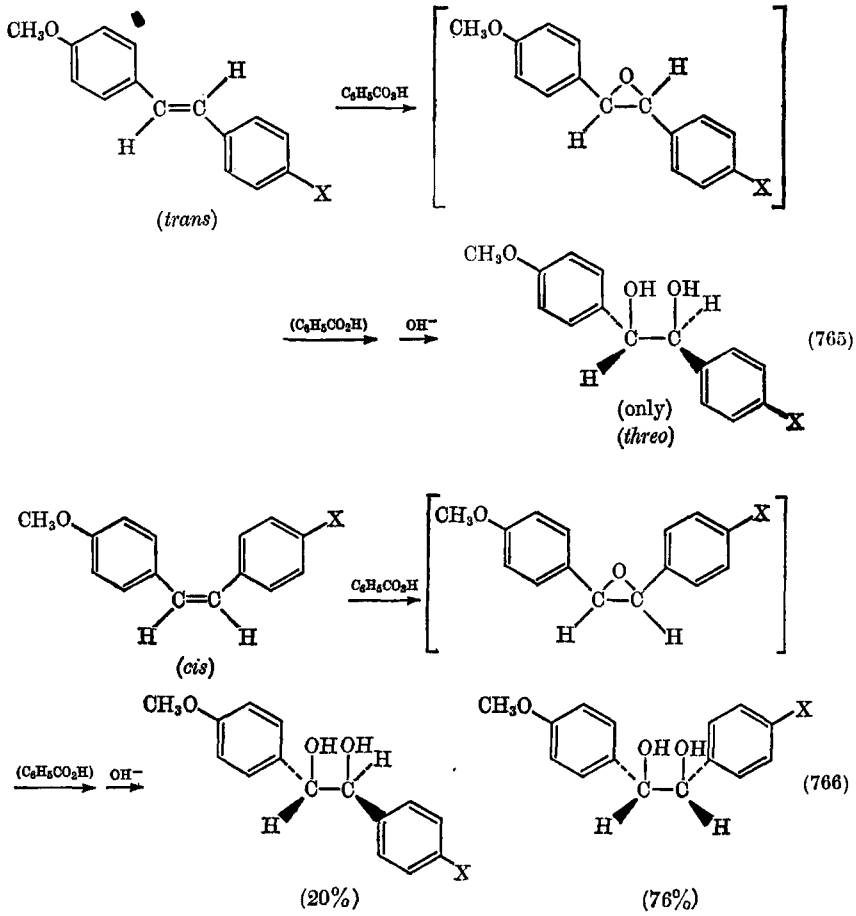
cinnamic acid,[503] cinnamyl alcohol,[1892] and others.[196, 792, 1211] Treatment of α-phenylstyrene with excess of perbenzoic acid has been found[1232] to give a 1,2-diol monobenzoate, from which 1,1-diphenylethylene glycol may be obtained by alkaline hydrolysis, whereas the use of an equivalent amount of reagent gives only diphenylacetaldehyde (Eq. 764).



(764)

Interesting stereochemical aspects of the addition of carboxylic acids to epoxides have been revealed by recent experiments of Curtin and co-workers.[394] Treatment of the *cis*- and *trans*-isomers of *p*-methoxystilbene and *p*-methoxy-*p'*-methylstilbene with perbenzoic acid causes the formation of 1,2-diol monobenzoates. Although the position of attachment of the benzoyloxy substituent was not specified, it is likely on electronic grounds to be the carbon atom nearest the *p*-methoxyphenyl group. Of particular interest, however, was the observation that the *trans*-olefins, which presumably yield *trans*-substituted epoxides, give rise uniquely to 1,2-diols of *threo* configuration on alkaline hydrolysis of the monobenzoate ester (Eq. 765). This indicates that benzoic acid addition occurs entirely with overall retention of configuration, *i.e.* with an even number of Walden inversions. Addition of benzoic acid to an authentic sample of *trans*-substituted epoxide did, in fact, appear to involve no net inversion at the reaction site. Similar experiments conducted with *cis*-olefins gave mixtures of 1,2-diols, indicating the *cis*-epoxides to open in part (20%) with overall inversion and in part (76%) with overall retention of configuration (Eq. 766). Unfortunately the authentic *cis*-epoxides themselves could not be prepared to confirm this premise.

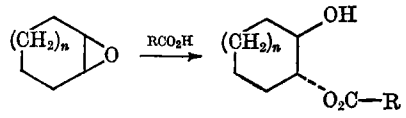
The results obtained by Curtin and co-workers[394] is not interpretable in terms of the simple Parker–Isaacs model,[1301] but can be rationalized by assuming participation of the *p*-methoxyphenyl substituent. Attack by carboxylate anion on the *p*-methoxyphenonium



intermediate thereby formed would give a product in which no apparent inversion had occurred at the epoxide carbon atom undergoing substitution.[1301]

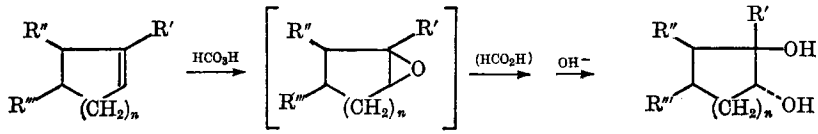
Carboxylic acid cleavage of semicyclic and alicyclic epoxides is amply exemplified in the literature. Oxidation of methylenecyclohexane with performic acid, for example, yields a 1,2-diol monoformate, from which may be obtained 1-hydroxymethylcyclohexanol

on alkaline hydrolysis.[782, 783] Similarly, addition of performic acid to a number of alkyl-substituted cycloalkenes (Eq. 768), and addition of acetic acid or benzoic acid to cyclohexene oxide and cycloheptene oxide (Eq. 767) have been reported from various laboratories.[15, 39, 196, 255, 503, 1054, 1463, 1530] In all instances *trans*-1,2-diols are isolated on alkaline hydrolysis of 1,2-diol monoesters derived from simple alicyclic epoxides. Stereochemical details are unfortunately lacking with many alkyl-substituted derivatives.



(767)

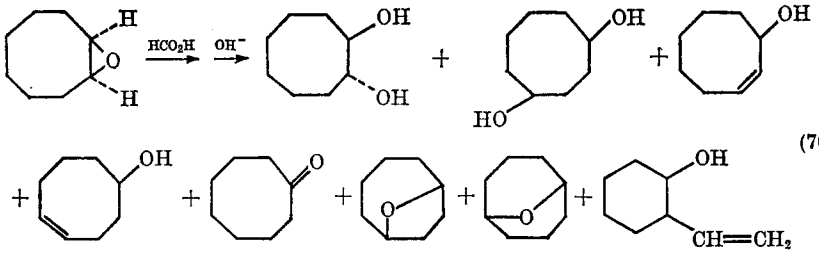
$n = 1, 2$
$R = CH_3, C_6H_5$



(768)

$n = 1, 2$
$R' = CH_3$; $R'' = R''' = H$
$R'' = CH_3$; $R''' = R' = H$
$R''' = CH_3$; $R'' = R' = H$

Addition of formic acid to *cis*- and *trans*-cyclooctene oxide has been studied with admirable precision by Cope and his students,[338, 340–342, 344, 347, 349] with the help of modern vapor-phase chromatographic technique. Hydrolysis of the crude mixture of monoformate esters obtained from *cis*-cyclooctene oxide gave a complex mixture of no less than ten components, eight of which have already been identified (Eq. 769).

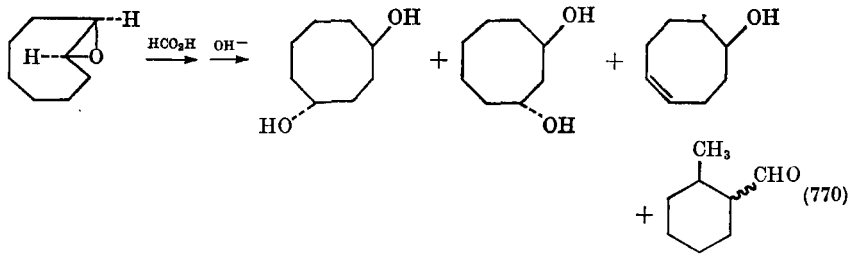


(769)

+ 2 other products

The proportion of 'normal' product (*i.e. trans*-1,2-cyclooctanediol) in the mixture was found to depend on the degree of dissociation of the acid used.[342] The stronger the acid, the larger the proportion of combined 'abnormal' products in the mixture. Included among the acids examined in this connexion were trifluoroacetic acid, trichloroacetic acid, formic acid, acetic acid (as well as sodium acetate–acetic acid buffer), and trimethylacetic acid. Though the strongly dissociated trihaloacetic acids gave virtually no 'normal' product at all, trimethylacetic acid failed to react altogether. The other reagents gave rise to product mixtures of varying composition, sodium acetate–acetic acid buffer giving the maximum yield of desired *trans*-1,2-cyclooctanediol.

On addition of formic acid to *trans*-cyclooctene oxide and hydrolysis of the resultant mixture of formate esters, a diol mixture was likewise obtained, four components of which have been characterized.[341] Only the configuration of the last remains in doubt. None of the desired 1,2-diol is formed at all in this case, only 'abnormal' products.

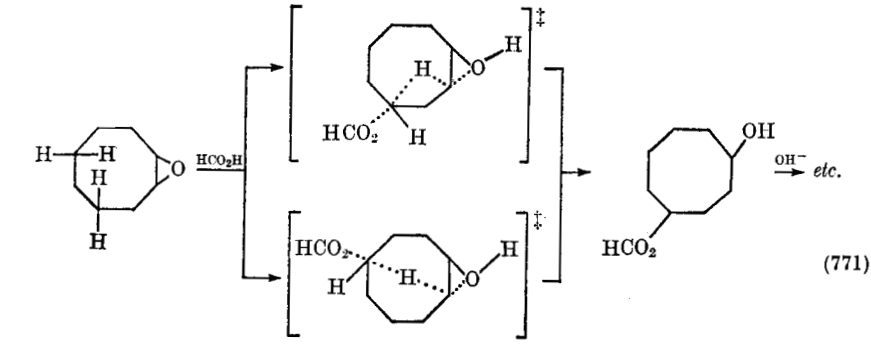


(770)

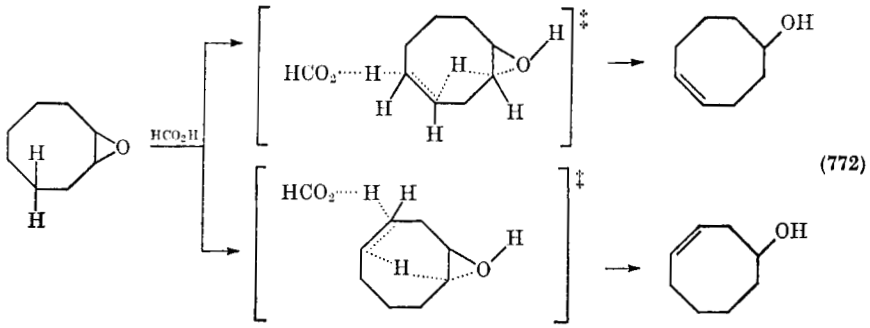
Elegant experiments involving deuterium labeling[338] have established that both 1,3- and 1,5-hydride shifts occur during addition of formic acid to *cis*-cyclooctene oxide, the latter predominating. Cope and co-workers regard these processes as concerted migrations of the type depicted in Eqs. (771) and (772). Although they represent modifications of the simple Parker–Isaacs model, such reaction mechanisms nevertheless conform to the premise that fully developed carbonium ions are not generated in epoxide ring cleavage.

Treatment of *cis*- and *trans*-cycloundecene and cyclododecene with performic acid likewise gives complex mixtures of products derivable by 'abnormal' formolysis of the corresponding epoxides.[1401, 1405] By contrast, methylenecyclooctane oxide yields no diols on treatment with formic acid and subsequent alkaline hydrolysis, the main product being formylcyclooctane.[1923]

In a related vein, Walborsky and Loncrini,[1795] and concurrently

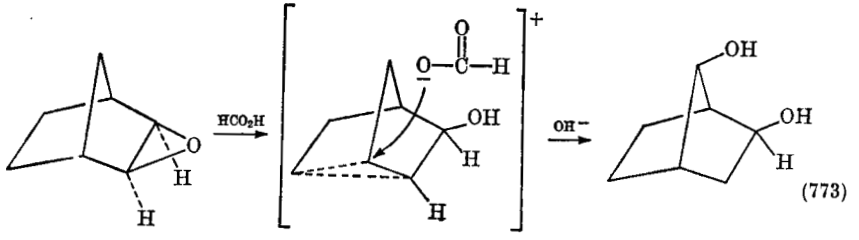


(771)



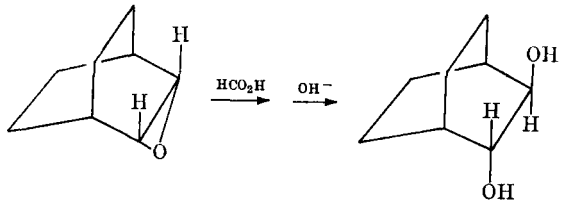
(772)

Kwart and Vosburgh,[986] investigated the reaction of *exo*-2,3-epoxybicyclo[2.2.1]heptane (*exo*norbornylene oxide) with formic acid (Eq. 773). Alkaline hydrolysis of the monoformate ester thus formed gave a diol identified as 2,7-dihydroxybicyclo[2.2.1]heptane, the same substance obtained ten years previously by Birch and co-workers[162] during attempted peracetic acid epoxidation of norbornylene. The skeletal rearrangement observed in this instance is of the conventional norbornyl type, development of positive character at $C_{(2)}$ being facilitated by partial delocalization of the $C_{(1)}$—$C_{(6)}$ bonding electrons.



(773)

Walborsky and Loncrini[1795] demonstrated, on the other hand, that addition of formic acid to 2,3-epoxybicyclo[2.2.2]octane (Eq. 774) does not produce skeletal rearrangement, since alkaline hydrolysis of the monoformate ester yields *trans*-2,3-dihydroxybicyclo[2.2.2]octane only.

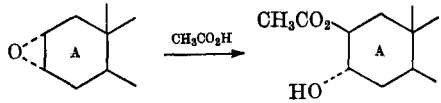


(774)

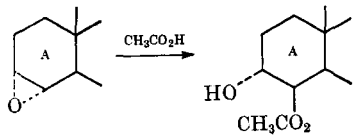
Among monocyclic terpenes which are reported to be converted into mixtures of 1,2-diol monoacetates on treatment with peracetic acid are Δ^3-carene[39, 1368] and β-pinene.[39] Since the authentic epoxides are claimed not to give recognizable products in the presence of acetic acid, however, it must remain an open question whether or not epoxides are really intermediates in the alleged olefin transformations. However, catalytic hydrogenation of epoxides derived from 2-menthene, 3-menthene, and carvomenthene in glacial acetic acid over palladium has yielded 1,2-diol monoacetates, together with numerous other products[1366] (see also section **IV.1.***B.*).

Reference has already been made in section **III.1.***A.* to several peroxy acid olefin epoxidations that fail to give recognizable products. It can be assumed that many of these failures are caused by the sensitivity of initially-formed epoxides to even traces of carboxylic acids present in the epoxidizing solutions.

In conclusion of this section may be cited several illustrations drawn from the field of steroid chemistry. Addition of acetic acid to 2α,3α-epoxy steroids[603] and 3α,4α-epoxy steroids[604] has been reported to give 2β-acetoxy-3α-hydroxy and 4β-acetoxy-3α-hydroxy derivatives respectively (Eqs. 775 and 776). The stereochemical disposition of



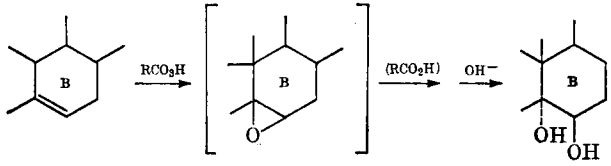
(775)



(776)

substituents in these products is that anticipated on the basis of the principle of diaxial ring opening.[1301]

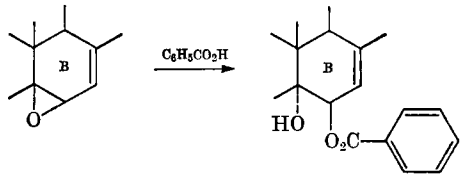
Ring opening of 5β,6β-epoxy steroids (Eq. 777) likewise appears to occur with inversion of configuration at $C_{(5)}$ in the presence of



(777)

R = H, CH_3

formic acid,[483, 1157, 1445] giving diaxial products as expected. Cleavage of a Δ^7-5β,6β-epoxy steroid (Eq. 778) with benzoic acid has been reported, on the other hand, to proceed with overall retention of configuration at $C_{(7)}$.[289]

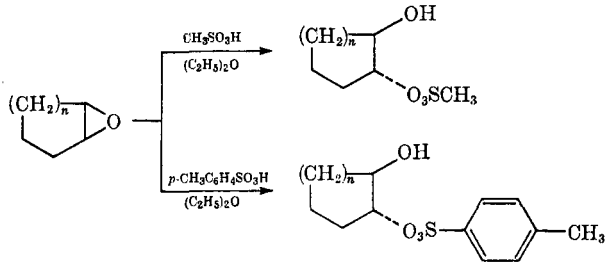


(778)

(*b*) **Sulfonic acids.** Credit for the first recorded condensation of an ethylene oxide with a sulfonic acid appears to belong to Criegee and Stanger,[373] who in 1936 reported the isolation of *trans*-1,2-cyclohexanediol monotosylate on treatment of cyclohexene oxide with toluene-*p*-sulfonic acid in ether. Subsequent publications describing the same reaction have included those of Winstein and co-workers,[1858] and of Clarke and Owen.[315] Methanesulfonic acid was also utilized by the latter authors. Although giving lower yields, cyclopentene oxide[370, 1282] and cycloheptene oxide[1280] likewise undergo cleavage with either methanesulfonic or toluene-*p*-sulfonic acid to the corresponding *trans*-1,2-diol monosulfonate esters (Eq. 779).

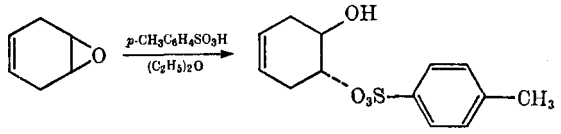
Ali and Owen[22] extended the scope of this reaction by subjecting 1,2-epoxy-4-cyclohexene (Eq. 780) and 2,3-epoxytetralin (Eq. 781) to the action of toluene-*p*-sulfonic acid in ether, obtaining *trans*-1,2-diol monoesters in the usual manner.

Cleavage of ethyl epoxycrotonate and ethyl epoxycinnamate with

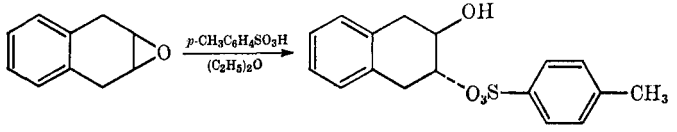


(779)

$n = 1, 2, 3$

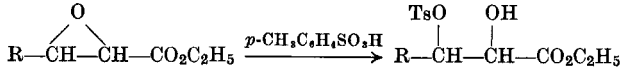


(780)



(781)

toluene-*p*-sulfonic acid (Eq. 782) was examined by Linstead and coworkers.[1038] Attack was found to occur preferentially on the epoxide carbon atom furthest from the ester function, regardless of the nature of the other substituent.

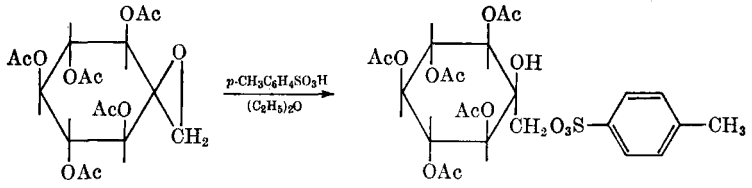


(782)

TsO = H_3C—C6H4—SO_2O

R = CH_3, C_6H_5

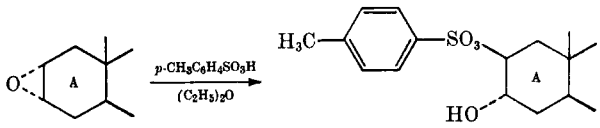
An illustration drawn from the field of sugar chemistry involves addition of toluene-*p*-sulfonic acid to the inositol derivative[1399] shown in Eq. (783).



(783)

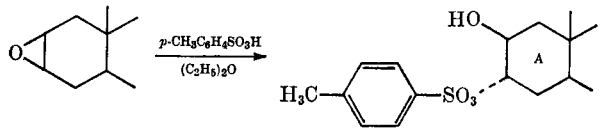
Ac = CH_3CO

Finally may be cited two examples from steroid chemistry, involving diaxial ring opening of 2α,3α-epoxy steroids (Eq. 784) and 2β,3β-epoxy steroids (Eq. 785) with toluene-*p*-sulfonic acid.[1574] Many



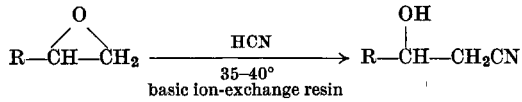
(784)

more instances of this type of reaction can undoubtedly be found in the literature, although no further space will be devoted to them here.



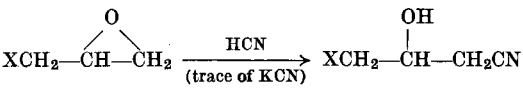
(785)

(*c*) **Hydrogen cyanide.** Ethylene oxide was found to condense with hydrogen cyanide as early as 1878 by the German chemist Erlenmeyer,[505] who obtained β-cyanoethanol in high yield by this method. During subsequent years this condensation was repeated in many laboratories, and appeared in numerous patent disclosures. A recent patent by Luskin,[1053] for example, describes the use of basic ion-exchange resins to promote hydrogen cyanide addition to ethylene oxide or propylene oxide (Eq. 786). This convenient technique, involving aqueous media and temperatures of 35–40°, offers obvious advantages over previous methods utilizing liquid hydrogen cyanide.[1558]



(786)

The early literature of epoxide chemistry contains several accounts of the reaction of hydrogen cyanide with epichlorohydrin,[811,1712] epibromohydrin,[1009] ethyl glycidyl ether,[1009] and related substances. Attack by the nucleophilic species, CN^- ion in this case, occurs uniquely at the site furthest from the polar atom, *i.e.* at the terminal epoxide carbon atom (Eq. 787). An important contribution was made by

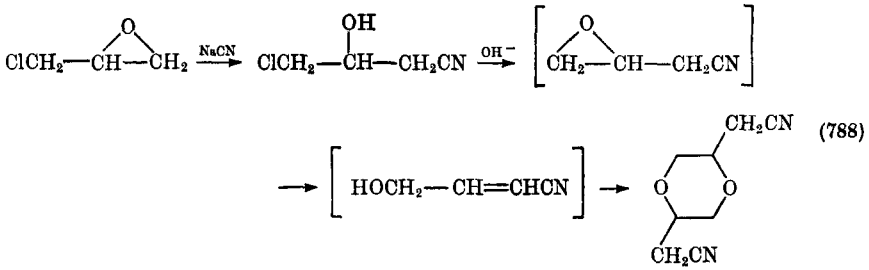


X = Cl, Br, C_2H_5O

(787)

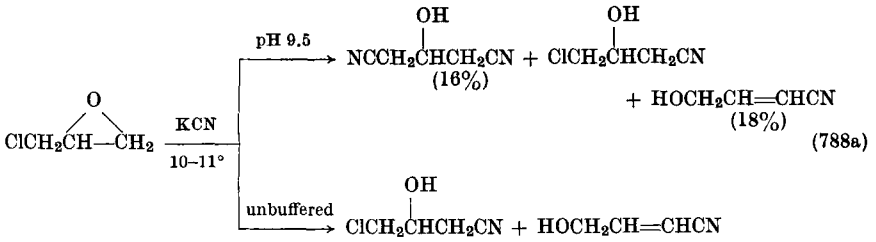
Rambaud,[1431] moreover, when he noted the marked catalytic effect of adding a trace of potassium cyanide to the liquid hydrogen cyanide.

The use of dry sodium cyanide or potassium cyanide was once believed to yield glycidonitrile by direct replacement of the chlorine atom.[717, 1318] Legrand,[997] and again Culvenor and co-workers,[388] demonstrated that the product thought by previous authors to be glycidonitrile was in reality 2,5-dicyanomethyl-1,4-dioxan, the dimer of γ-hydroxycrotononitrile. In 1930 Braun[238] allegedly succeeded in forming 1-chloro-3-cyano-2-propanol in aqueous sodium cyanide. It is not improbable, therefore, that the above 1,4-dioxan derivative arises from the series of steps shown in Eq. (788).



(788)

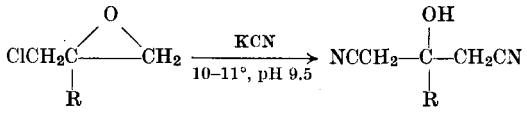
Johnson and co-workers[1985] have helped to clarify the course of this reaction by carefully examining the distribution of products from the condensation of epichlorohydrin with aqueous potassium cyanide in buffered and in non-buffered solution. Although a mixture was formed if a pH of 9.5 was maintained (Eq. 788a), only 1,3-dicyano-2-



(788a)

propanol was isolated in an unbuffered medium; but no glycidonitrile could be obtained at all. Whether γ-hydroxycrotononitrile is generated by way of 2,3-dicyano-1-propanol or by some other route was not established. The same authors also studied the condensation of aqueous potassium cyanide at pH 9.5 with several substituted epichlorohydrins,

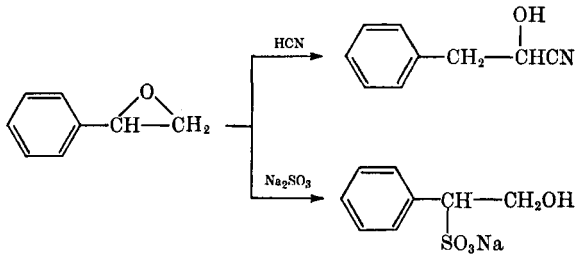
as shown in Eq. (788b). Curiously, treatment of 1,4-dichloro-2,3-epoxybutane with this reagent gave no product, although 2-chloromethylepichlorohydrin yielded 2-cyanomethyl-1,3-dicyano-2-propanol as anticipated.



(788b)

R = CH_3, C_2H_5, C_6H_5, $ClCH_2$

Styrene oxide is reported to give only phenylacetaldehyde cyanohydrin (Eq. 789) on treatment with hydrogen cyanide.[1728] This may be compared with a similar isomerization observed on treatment of α-methylstyrene with sodium bisulfite.[1720] That styrene oxide undergoes addition and not isomerization in the presence of sodium bisulfite,[1529] though undergoing isomerization in the presence of hydrogen cyanide, reflects the unlike nucleophilicities of these reagents.



(789)

Attention may be called, in conclusion, to the observation of Brunel[255] that cyclohexene oxide fails to condense with hydrogen cyanide. This is again compatible with the weakly nucleophilic character of the CN^- ion and the low dissociation constant of its conjugate acid.

E. Organometallic Reagents

The characteristic ease with which ethylene oxides undergo nucleophilic attack or isomerization in the presence of Lewis acids made them obvious substrates for the organometallic reagents introduced by Grignard[667–669] around the turn of the century, and subsequently named in his honor. The earliest disclosure of a reaction between an epoxide and a Grignard reagent, however, bears the name of Blaise,[168] who noted the formation of ethylene bromohydrin on treatment of ethylene oxide with methylmagnesium bromide. In the years

that followed, a number of chemists of the French school became associated with this reaction, among them Grignard himself,[667-669] Henry,[751] Bedos,[107, 108, 111, 112] Godchot,[647, 648] Fourneau,[572, 1641] Tiffeneau,[1719, 1728] and others. Their work, along with later systematic studies by chemists in America, notably Cottle,[358, 359, 656, 1622] Huston,[509, 844-849] and others, has been exhaustively reviewed by Kharasch and Reinmuth,[927] as well as by Gaylord and Becker.[625] These encyclopedic articles should be consulted for a more complete treatment than can be given here.

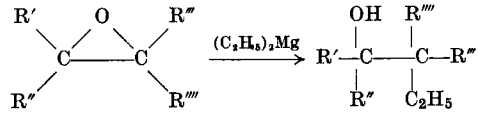
It is convenient to divide the discussion of the present subject into two sections. The first will deal with what may be termed 'simple' organometallic reagents, R_nM, in which n organic radicals, R, are covalently bonded to an atom of metal, M, belonging to the nth column of the periodic table. These are at present quite limited in number, including chiefly organomagnesiums, R_2Mg, organosodiums, RNa, and organolithiums, RLi. The second section will be concerned with Grignard reagents proper, the reactive entities of which are currently believed to be organomagnesiums, R_2Mg, and magnesium halides, MgX_2. The relationship between these two species is commonly expressed in terms of a concept known as the Schlenk equilibrium,[1534, 1535] which may be represented by Eq. (790).

$$2\,RMgX \rightleftharpoons R_2Mg + MgX_2 \qquad (790)$$

In harmony with conventional usage, the symbol 'RMgX' is used here to describe the Grignard reagent, but coordination with basic solvents like diethyl ether or tetrahydrofuran should be assumed to play an important role in the reaction as well. Also, the Schlenk equilibrium is only an approximation of reality, and several authors have voiced objections to it on various grounds. These and other mechanistic considerations are amply discussed by Wright,[1881] Gaylord and Becker,[625] and Kharasch and Reinmuth[927] in their reviews.

(1) Simple organometallic reagents: (*a*) Organomagnesiums. Several simple alkyl-substituted ethylene oxides were treated with diethylmagnesium in 1936 by Norton and Hass,[1256] using the then recently developed technique of removing magnesium halide components of Grignard reagents by precipitation with dioxan. The filtrate remaining after separation of the solid magnesium halide–dioxan complex can be regarded as a solution of simple organomagnesium reagent. In each case an alcohol was obtained, corresponding to an addition of the organic radical R to the least-substituted terminal epoxide carbon

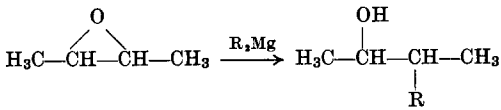
atom (Eq. 791). Epoxides investigated in this manner included ethylene oxide, propylene oxide, *iso*butylene oxide, *cis*- and *trans*-2,3-epoxybutane, 2,3-epoxy-2-methylbutane, and 2,3-epoxy-2,3-dimethylbutane.[1256]



(791)

$R' = R'' = R''' = R'''' = H$
$R' = CH_3$; $R'' = R''' = R'''' = H$
$R' = R'' = CH_3$; $R''' = R'''' = H$
$R' = R'' = R''' = CH_3$; $R'''' = H$

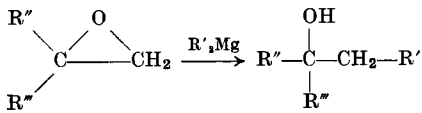
Cottle and co-workers,[358, 359] and more recently Huston and Brault,[846] have studied the effect of varying the organic radical, R, in the organomagnesium reagent, R_2Mg. The former authors treated 2,3-epoxybutane with dimethyl-, diethyl-, and di-*n*-butylmagnesium, and obtained the corresponding 3-alkyl-2-butanols (Eq. 792). The latter



(792)

$R = CH_3$, C_2H_5, n-C_3H_7

treated *iso*butylene oxide with dimethyl-, diethyl-, di-*n*-propyl-, di-*n*-butyl-, and di-*tert*-butylmagnesium (Eq. 793). In each case attack occurred at the terminal epoxide carbon atom exclusively, and yields decreased with increasing bulk of R. Similar results were secured

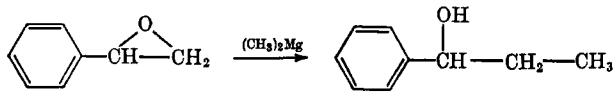


(793)

$R' = CH_3$, C_2H_5, n-C_3H_7, n-C_4H_9, *iso*C_4H_9, *tert*-C_4H_9, cycloC_6H_{11}, C_6H_5, *etc.*;
$R'' = R'' = H$, CH_3; $R'' = CH_3$; $R'' = H$

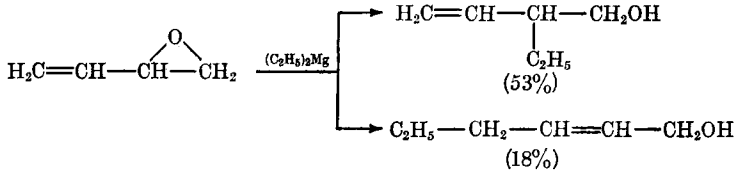
with ethylene oxide[1895] and propylene oxide,[509] although yields realized with the terminal 1,1-dialkylated epoxides were highest (Eq. 793).

Treatment of styrene oxide with dimethylmagnesium (Eq. 794) is reported to give the corresponding secondary alcohol by attack on the



(794)

terminal epoxide carbon atom.[656] When the phenyl ring is replaced by a vinyl function, as in 1,2-epoxy-3-butene (Eq. 795), two products are formed on treatment with diethylmagnesium.[579] These are 2-ethyl-3-buten-1-ol, arising by attack of the reagent on the carbon atom adjacent to the electron-withdrawing vinyl group, and 2-hexen-1-ol, formed either by '1,4-addition' or by normal addition to the terminal carbon atom followed by allylic rearrangement.



(795)

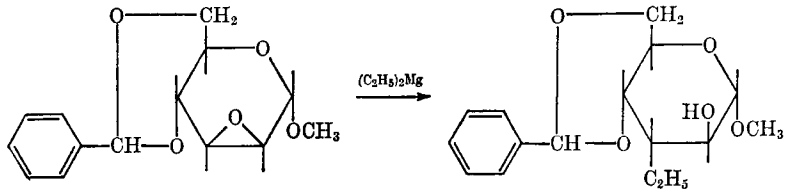
In the alicyclic series Bartlett and Berry[83] demonstrated that cyclohexene oxide yields *trans*-2-alkylcyclohexanols on treatment with dimethyl- or diethylmagnesium (Eq. 796).



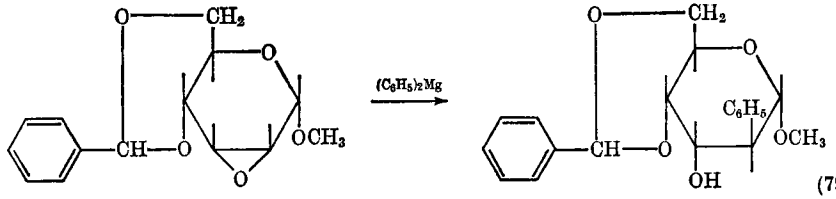
(796)

R = CH_3, C_2H_5

In the field of sugar chemistry Foster and co-workers[560] have found that diethylmagnesium adds to $C_{(3)}$ of methyl 4,6-*O*-benzylidene-2,3-anhydro-α-D-mannoside (Eq. 797), and Richards[1455] has observed $C_{(2)}$ attack with methyl 4,6-*O*-benzylidene-2,3-anhydro-α-D-alloside and diphenylmagnesium (Eq. 798).



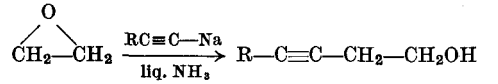
(797)



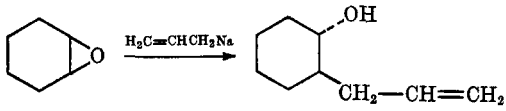
(798)

That the above sugar epoxides undergo cleavage in opposite directions is consistent with the principle of diaxial product control in conformationally frozen systems.[1301]

(*b*) **Organosodiums.** Only a few examples can be found in the literature to illustrate the reaction of organosodium reagents, RNa, with ethylene oxides. These include condensation of ethylene oxide itself (Eq. 799) with several sodium acetylides in liquid ammonia and of cyclohexene oxide (Eq. 800) with allylsodium.[1242, 1540, 1606]

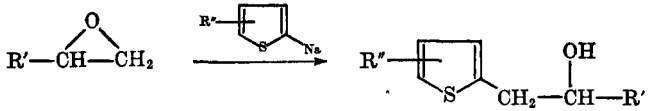


R = H, C_2H_5, *n*-C_3H_7, *n*-C_4H_9 (799)



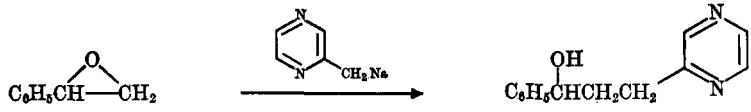
(800)

Several 2-thienylsodiums have likewise been treated with epoxides to obtain the corresponding 2-(β-hydroxyalkyl)thiophenes (Eq. 801). Among the epoxides examined in this connexion are ethylene oxide, propylene oxide, styrene oxide, 1,2-epoxy-3-butene, and epichlorohydrin.[1532]



R′ = H, CH_3, $ClCH_2$, $CH_2{=}CH$, C_6H_5
R″ = H, 4-CH_3, 5-Cl, 5-*tert*-C_4H_9 (801)

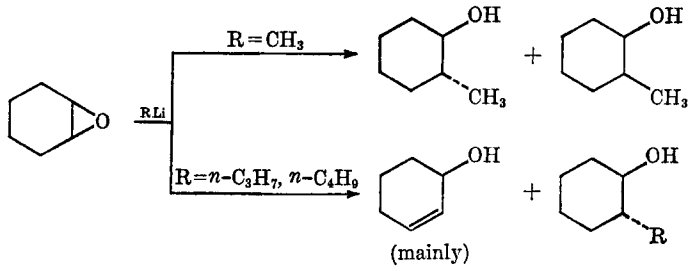
A recent publication by Kamal and Levine[2029] has disclosed the successful addition of the sodio derivative of 2-methylpyrazine to styrene oxide, attack taking place as expected on the terminal epoxide carbon (Eq. 801a).



(801a)

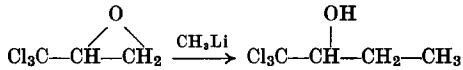
(*c*) **Organolithiums.** Relatively few organolithium reagents, RLi, have been investigated in epoxide chemistry, and the scanty evidence

available suggests, in fact, that they are somewhat less satisfactory in certain cases than dialkylmagnesiums. Thus, although cyclohexene oxide gives *trans*-2-methylcyclohexanol in good yield on treatment with dimethylmagnesium,[83] methyllithium leads to a mixture of *cis*- and *trans*-2-methylcyclohexanols.[1011] Whether the *cis*-isomer is a genuine product or an artifact has not yet been ascertained. Letsinger and co-workers[1011] have also made the disconcerting observation that treatment of cyclohexene oxide with *n*-propyl- or *n*-butyllithium yields primarily cyclohexen-3-ol, and only small quantities of the desired *trans*-2-alkylcyclohexanol (Eq. 802).



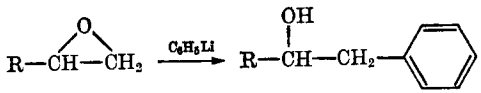
(802)

Cyclopentene oxide is reported to react smoothly with methyllithium,[1769] but higher alkyllithiums have not been examined with this epoxide until now. Methyllithium likewise condenses readily with 3,3,3-trichloro-1,2-epoxypropane[637] to give the corresponding terminal addition product (Eq. 803).



(803)

Cristol and co-workers[371] have reported that propylene oxide and styrene oxide yield respectively β-phenylethanol and 1,2-diphenylethanol on treatment with phenyllithium (Eq. 804). Again attack of the



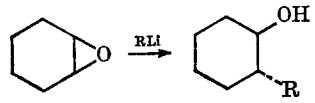
(804)

R = CH_3, C_6H_5

nucleophile occurs preferentially at the least-hindered terminal epoxide carbon atom.

Cyclohexene oxide has been said[334] to give 2-phenyl-, 2-benzyl-,

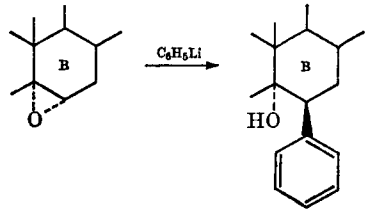
and 2-naphthylcyclohexanol respectively on addition to the corresponding aryllithium reagents (Eq. 805). Huitric and Carr[2030] have recently shown also that addition of *o*-tolyllithium to cyclohexene oxide gives only one product, identified by nuclear magnetic resonance spectroscopy as *trans*-2-*o*-tolylcyclohexanol.



(805)

R = C_6H_5, $C_6H_5CH_2$, 1-naphthyl

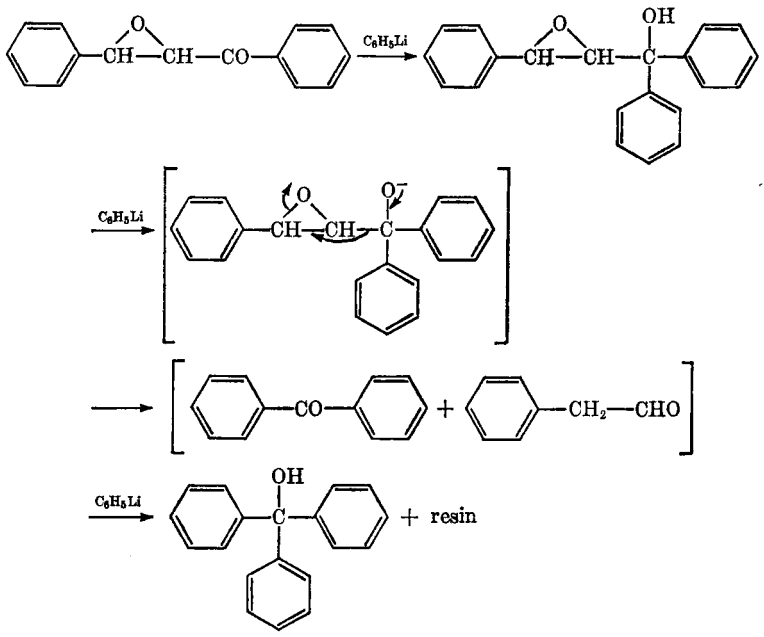
In the steroid field, Zderic and Chavez-Limon[1905] have produced 5α-hydroxy-6β-phenyl derivatives by adding phenyllithium to 5α,6α-epoxy steroids (Eq. 806). Attack of the reagent at $C_{(6)}$ of the steroid skeleton is consistent with the fact that this is the less-alkylated terminal epoxide carbon atom (*i.e.* the least hindered), and also with the fact that a diaxial product is thereby obtained.



(806)

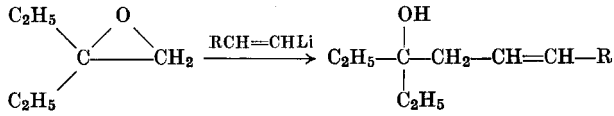
Phenyllithium also occupies a place in epoxide literature in connexion with a curious rearrangement first noted by Bergmann and Wolff,[133] and later elucidated by Kohler and co-workers.[155, 956, 958] Treatment of benzalacetophenone oxide and certain derivatives with 1 molar equivalent of phenyllithium in the cold gives the corresponding α,β-epoxy alcohol in which addition has occurred preferentially at the carbonyl function. Further treatment of this product with excess phenyllithium at room temperature causes rupture of a C—C bond. The product ultimately isolated is triphenylcarbinol, which presumably forms from the initially-generated benzophenone, as shown in Eq. (807). Phenylacetaldehyde polymerizes too rapidly under these conditions to allow its isolation, but other evidence indicates that it is formed in all likelihood at the same time as the benzophenone.

Several reactions illustrating the condensation of alkenyllithiums and lithium acetylides are known.[48] The former include addition of



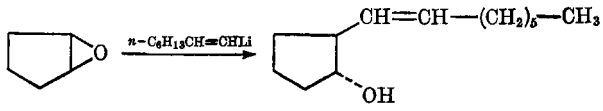
(807)

1-octenyllithium to 1,2-epoxy-2-ethylbutane and cyclopentene oxide (Eqs. 808 and 809), of 1-cyclohexenyllithium to 1,2-epoxyoctane (Eq. 810), and of β-styryllithium to 1,2-epoxy-2-ethylbutane (Eq. 808).

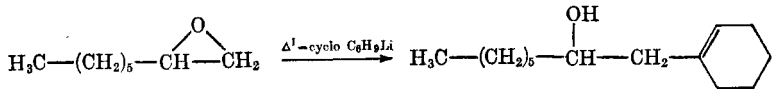


(808)

R = *n*-C_6H_{13}, C_6H_5



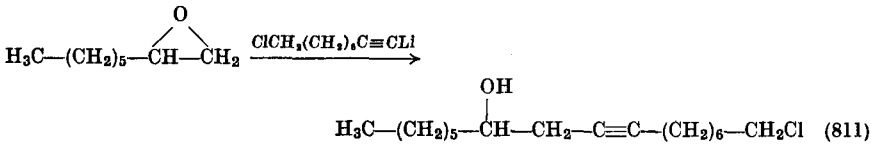
(809)



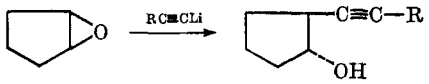
(810)

The reaction of epoxides with lithium acetylides[630] is exemplified by the addition of 9-chlorononinyllithium to 1,2-epoxyoctane (Eq. 811) and of several alkinyllithiums to cyclopentene oxide (Eq. 812).

The lithium salt of ethoxyacetylene has been found by Vollema and Arens[2040] to condense readily with epichlorohydrin in liquid ammonia, yielding 1,2-epoxy-5-ethoxy-4-pentyne. The lithium salt of



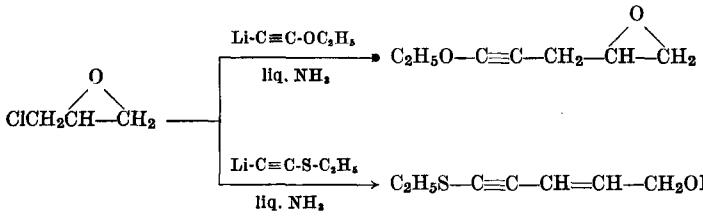
(811)



(812)

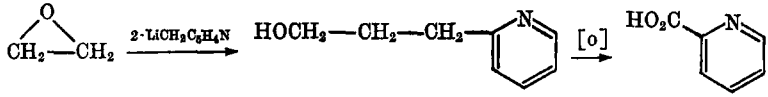
R = n-C_4H_9, n-C_5H_{11}, n-C_6H_{13}

ethylthioacetylene, on the other hand, gave the unexpected product shown in Eq. (812a). Further work on the course of this reaction seems desirable.



(812a)

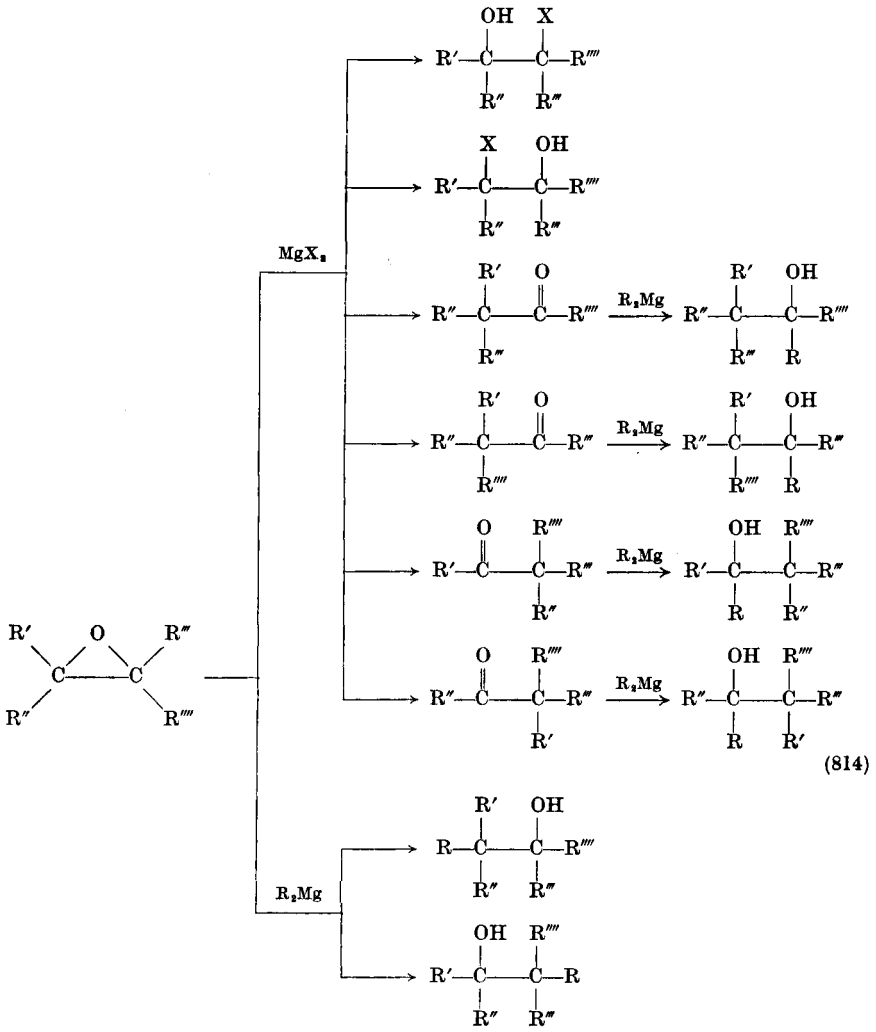
Gilman and Towle,[641] finally, have reported the condensation of ethylene oxide with α-picolyllithium (Eq. 813), which occurs normally to give only 3-(α-picolyl)propanol, as shown by oxidation to α-picolinic acid.



(813)

(2) Grignard reagents. As has already been pointed out, Grignard reagents may be regarded as mixtures of dialkyl- or diaryl-magnesiums and magnesium halides. Depending on relative reaction rates then, an epoxide can undergo reaction either with the dialkyl- or diarylmagnesium component, or with the magnesium halide component, or with both. For the general case these possibilities may be represented as shown in Eq. (814).

Thus two halohydrins and no less than six alcohols are in principle obtainable from condensation of an ethylene oxide with a Grignard reagent. Fortunately, in the majority of cases, only two or three products appear in readily detectable amount. The factors governing



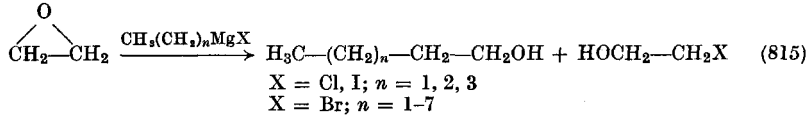
(814)

selection of a reaction path are by no means simple, as will be apparent in subsequent discussion.

Perhaps more frequently used in Grignard reactions than any other representative of its class of substances has been the parent compound

ethylene oxide itself.[927] This reaction constitutes, in fact, one of the most attractive methods of hydroxyethylation available to synthetic chemists at the present time.

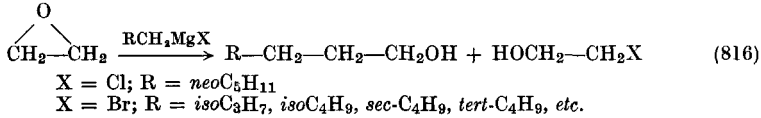
Among alkyl Grignard reagents reported to react with ethylene oxide (Eqs. 815 and 816) are primary alkylmagnesium bromides ranging from methyl- to *n*-octylmagnesium bromide.[358, 844, 845, 1785]



$$\underset{\diagup\,\diagdown}{\overset{O}{CH_2—CH_2}} \xrightarrow{CH_3(CH_2)_nMgX} H_3C—(CH_2)_n—CH_2—CH_2OH + HOCH_2—CH_2X \qquad (815)$$

X = Cl, I; n = 1, 2, 3
X = Br; n = 1–7

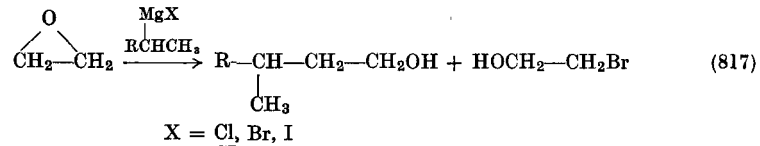
Information is also available for the condensation of methyl- to *n*-butylmagnesium chlorides,[848, 849] and methyl- to *n*-butylmagnesium iodide.[847] In addition, several branched-chain primary alkylmagnesium bromides, chlorides, and iodides have been examined.[844, 847, 1101]



$$\underset{\diagup\,\diagdown}{\overset{O}{CH_2—CH_2}} \xrightarrow{RCH_2MgX} R—CH_2—CH_2—CH_2OH + HOCH_2—CH_2X \qquad (816)$$

X = Cl; R = *neo*C_5H_{11}
X = Br; R = *iso*C_3H_7, *iso*C_4H_9, *sec*-C_4H_9, *tert*-C_4H_9, *etc.*

Most effective among the three types of alkylmagnesium halides are apparently the bromides,[844, 845] chlorides and iodides exhibiting a greater tendency to form halohydrins at the expense of desired Grignard adducts.[844, 847] Chain length seems to have little or no effect on yield and product composition. Reactant ratio, however, and to an even greater extent temperature and reaction time, play profound roles in determining the composition of product mixtures. In all known cases, only primary alcohols are produced, indicating that ethylene oxide does not undergo isomerization to acetaldehyde before condensation with the dialkylmagnesium component of the Grignard reagent.[927]

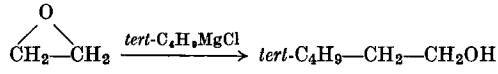


$$\underset{\diagup\,\diagdown}{\overset{O}{CH_2—CH_2}} \xrightarrow{RCHCH_3\,(MgX)} R—\underset{\displaystyle CH_3}{\underset{|}{CH}}—CH_2—CH_2OH + HOCH_2—CH_2Br \qquad (817)$$

X = Cl, Br, I
R = CH_3, C_2H_5, n-C_3H_7, *iso*C_3H_7

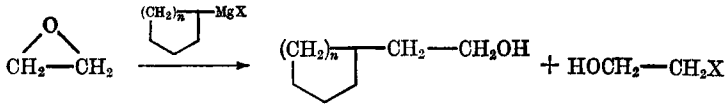
Among secondary Grignard reagents that have been added to ethylene oxide with substantially similar results (Eq. 817) are isopropylmagnesium halides, *sec*-butylmagnesium halides, and several others.[844, 847, 848]

Tertiary alkyl Grignard reagents are extremely unreactive toward ethylene oxide, giving rise exclusively to ethylene halohydrins under conditions normally suitable for reactions with primary or secondary Grignard reagents.[800, 844, 847, 848] In other words, in terms of the Schlenk equilibrium concept set forth above, the magnesium halide component of tertiary alkyl Grignard reagents causes halohydrin formation faster than the dialkylmagnesium component can add. Special conditions have, however, been found, which permit addition of *tert*-butylmagnesium chloride to ethylene oxide (Eq. 818), giving a modest yield of the desired primary alcohol.[1094, 1101]



(818)

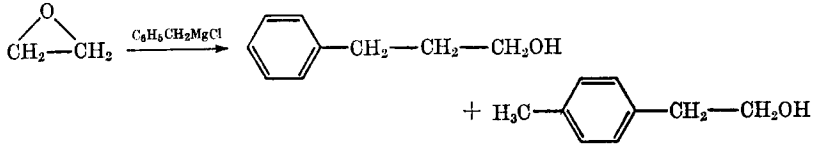
Cyclopentyl- and cyclohexylmagnesium halides have been found[781, 1369] to yield the corresponding β-cycloalkylethanols with no difficulty, together with the usual ethylene halohydrin side-products (Eq. 819).



(819)

X = Cl, $n = 1$
X = Br, $n = 2$

Benzylmagnesium halides constitute an interesting special case, inasmuch as they give rise to small but significant proportions of rearrangement products. Treatment of ethylene oxide with benzylmagnesium chloride, for example, gives a mixture of 3-phenyl-1-propanol and 2-*p*-tolylethanol (Eq. 820), as shown by the isolation of

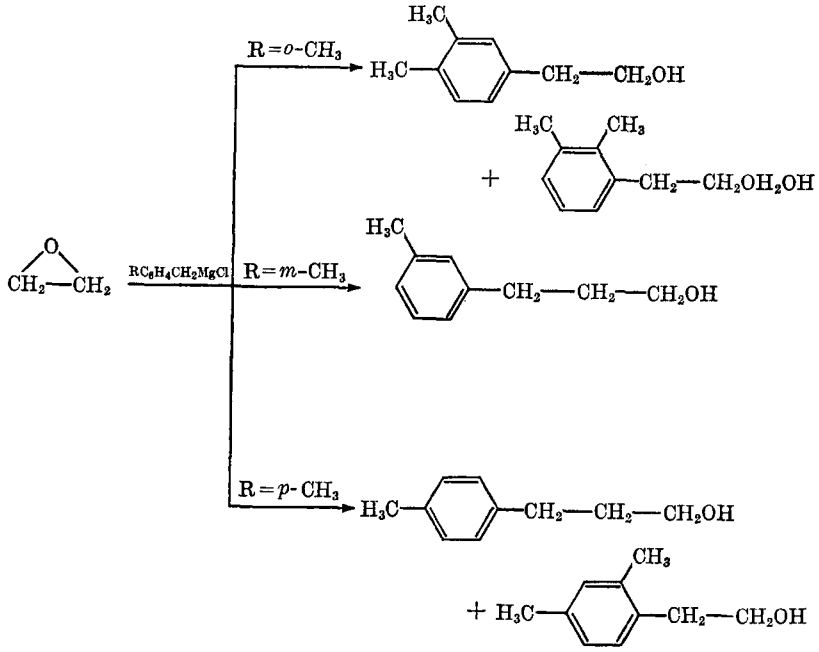


(820)

benzoic acid and terephthalic acid on permanganate oxidation of the mixture.[53, 639]

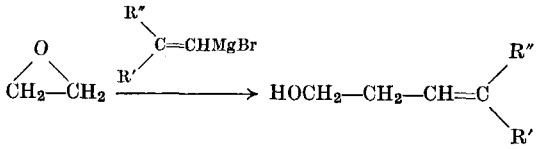
Addition of ethylene oxide to the three isomeric xylylmagnesium bromides, moreover, leads to various mixtures of products,[844, 1190] as

shown in Eq. (821). It is curious that though *o*- and *p*-xylylmagnesium bromide undergo some rearrangement, *m*-xylylmagnesium bromide appears to undergo normal addition only. Ethylene halohydrins are probably formed in all these instances as well.



(821)

Alkenylmagnesium bromides have been reported to condense with ethylene oxide. Vinyl- and *iso*butenylmagnesium bromide, for example, give the expected γ,δ-unsaturated alcohols in good yield (Eq. 822), but β-styrylmagnesium bromide reacts poorly.[1255]



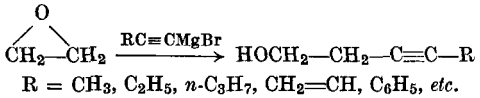
(822)

$R' = H, R'' = C_6H_5$
$R' = R'' = H, CH_3$

A substantial number of acetylenic Grignard reagents (Eq. 823) have been found to participate in this type of addition, giving γ,δ-acetylenic alcohols.[406, 520, 1222, 1242, 1423, 1654]

Only a few illustrations need to be given here of the usefulness of

ethylene oxide for hydroxyethylation of aromatic Grignard reagents.[56, 270, 271, 276, 557, 1591, 1592, 1594, 1692] Many additional examples are given in the reviews cited above.[625, 927]

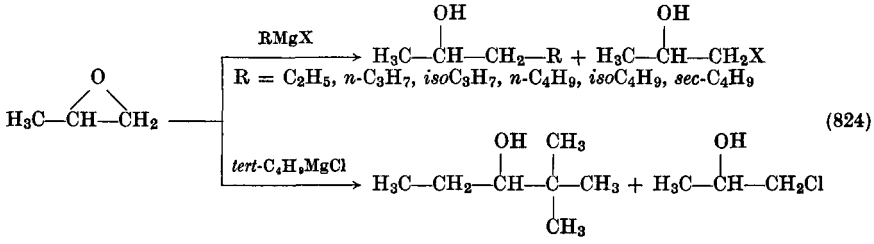


(823)

Carbocyclic aromatic Grignard reagents of note in this connexion are phenylmagnesium halides,[844] the three isomeric tolylmagnesium bromides,[721, 1190] the three isomeric anisylmagnesium bromides,[58, 577, 810, 1127] the two isomeric naphthylmagnesium bromides,[1235, 1609] 2-acenaphthylmagnesium bromide,[333] and 9-phenanthrylmagnesium bromide.[125, 1947] Mention may also be made of several heterocyclic aromatic Grignard reagents, derived from indole[1263] and thiophene[646] respectively, which give β-hydroxyethyl derivatives on treatment with ethylene oxide.

Condensation of Grignard reagents with alkyl-substituted ethylene oxides is fairly complex, particularly if the epoxides involved are asymmetric and massively substituted. The reaction course depends also on the structure of the Grignard reagent, and obviously on experimental conditions used for the condensation.[625, 927]

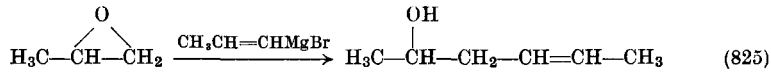
Propylene oxide reacts with a wide assortment of primary and secondary Grignard reagents (Eq. 824), the products being those



(824)

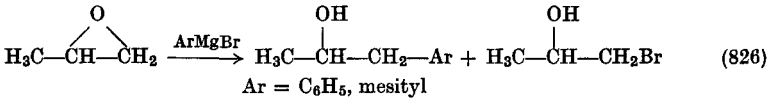
expected from attack of the organic radical, R, on the least-substituted epoxide carbon atom.[509, 751, 845, 849, 1016, 1256] In a clarification of conflicting earlier results,[845, 849] Gaylord and Caul[626] recently demonstrated, on the other hand, that propylene oxide gives on treatment with *tert*-butylmagnesium chloride a mixture of 1-chloro-2-propanol and 2,2-dimethyl-3-propanol. The latter is the product to be expected if propylene oxide undergoes preliminary isomerization to propionaldehyde.

Treatment of propylene oxide with the Grignard reagent derived from 1-bromo-1-propene has been reported[1255] to yield 2-hexen-4-ol (Eq. 825).



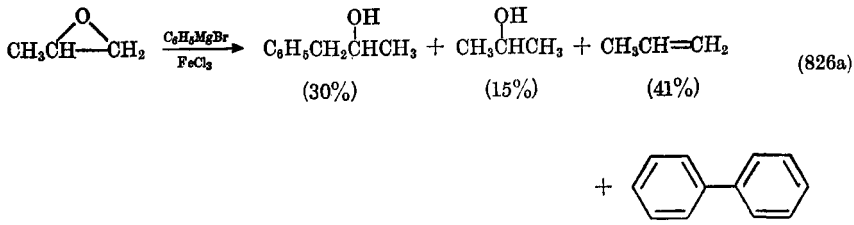
(825)

Phenylmagnesium bromide, a representative example of several aromatic Grignard reagents recorded in the literature in connexion with propylene oxide, also gives normal products (Eq. 826), as does the even bulkier reagent mesitylmagnesium bromide.[509, 845] The reason for the singular behavior of *tert*-butylmagnesium chloride is therefore probably not merely a steric one.



(826)

Kharasch and co-workers[2031] have examined the effect of using ferric chloride to catalyze the condensation of phenylmagnesium bromide with propylene oxide. In addition to the expected products (1-phenyl-2-propanol and 1-bromo-2-propanol), some 2-propanol and propylene was isolated, together with the Grignard coupling product biphenyl (Eq. 826a). The normal halohydrin side product 1-bromo-2-propanol was presumed to give rise to 2-propanol and propylene on further reaction with phenylmagnesium bromide and ferric chloride. Similar results were secured with *n*-propylmagnesium bromide and ferric chloride.[2031]

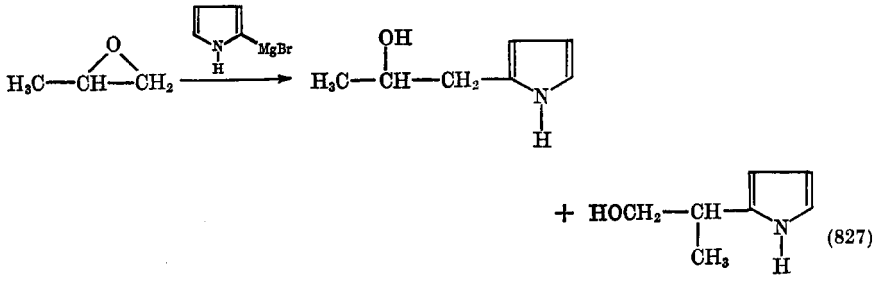


(826a)

On the other hand, 1-pyrrylmagnesium bromide is reported[760] to give a mixture of two isomeric alcohols in low yield (Eq. 827). The minor product, however, is formed simply by attack on the most alkylated epoxide carbon, rather than by preliminary isomerization to propionaldehyde.

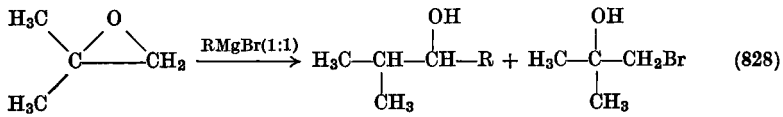
With increasing alkyl-substitution, ethylene oxides tend to undergo isomerization to carbonyl compounds before condensation with the organic radical of the Grignard reagent.[625, 927]

*iso*Butylene oxide, for example, behaves as though it were undergoing preliminary rearrangement to dimethylacetaldehyde even on



(827)

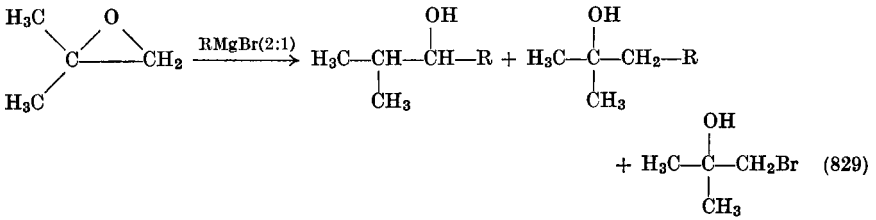
treatment with primary Grignard reagents (Eq. 828). The reactivity of the terminal epoxide carbon atom is evidently offset by the readiness with which the epoxide ring is isomerized by Lewis acids.[751, 846, 1256]



(828)

R = CH_3, C_2H_5, *n*-C_3H_7, *iso*C_3H_7, *n*-C_4H_9

Eq. (828) deals with equimolar proportions of reactants. If an excess of epoxide is utilized, more complex product mixtures are generated, which contain three of the eight products (Eq. 829) obtainable in principle from this reaction. A small amount of normal adduct can, therefore, be secured by using an excess of epoxide.[846]



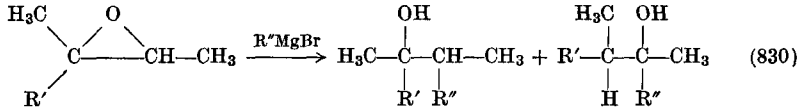
(829)

R = C_2H_5, *n*-C_3H_7

Treatment of 2,3-epoxybutane with several Grignard reagents has been reported to give two alcohols, in varying proportions depending on the nature of the reagent and on reaction conditions.[359, 751, 1256] In addition, a stereochemical dependence can be suspected, on the basis of differences in product yield from the *cis*- and *trans*-isomers of 2,3-epoxybutane. It is probable, however, that the stereochemical purity

of the epoxides and the methods of product analysis used in these investigations were sufficiently uncertain to warrant caution.

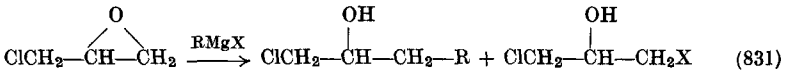
Trimethylethylene oxide gives rise to 2,3-dimethyl-2-butanol and 2,3-dimethyl-2-pentanol respectively (Eq. 830) on condensation with methylmagnesium bromide or ethylmagnesium bromide.[751, 1256] Although nothing can be said about the first reaction (except by inference), the second clearly proceeds by preliminary isomerization to 2-methyl-3-butanone. Similarly isomerization evidently accompanies the addition of alkylmagnesium bromides to tetramethylethylene oxide.[1256]



$R' = H;\ R'' = CH_3, C_2H_5$
$R' = CH_3;\ R'' = CH_3, C_2H_5$

(830)

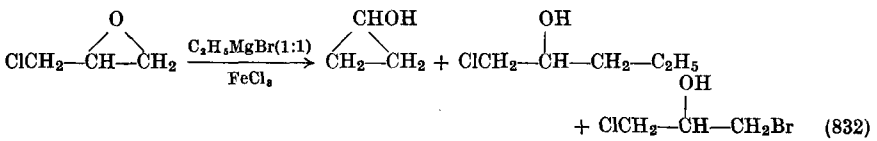
Addition of Grignard reagents to epihalohydrins has been a subject of controversy for many years. Experimental results published by early workers, among them Iotsitch,[855, 856] Fourneau and Tiffeneau,[572] Henry,[751] and Delaby,[433] will not be considered here. The review by Gaylord and Becker[625] gives details of this work. Koelsch and McElvain[955] were the first investigators to take up the problem in America. The authors reported that Grignard reagents give, under suitable conditions, mixtures containing normal products and dihalo alcohols in varying proportions (Eq. 831). Their observations were subsequently confirmed and extended by Ribas and Tapia.[1452]



(831)

X = Cl, Br
R = C_2H_5, *n*-C_3H_7, *iso*C_3H_7, *n*-C_4H_9, *iso*C_4H_9, *sec*-C_4H_9, *n*-C_5H_{11}, C_6H_5, $C_6H_5CH_2$, *etc.*

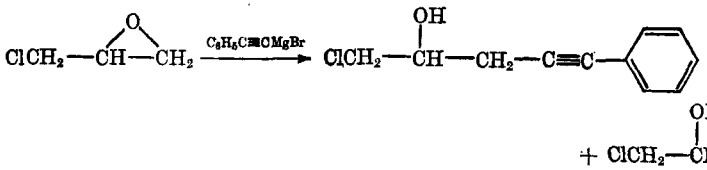
Cottle and co-workers[1086, 1622] have reported the interesting discovery that under certain circumstances addition of ethylmagnesium bromide to epichlorohydrin gives rise to some cyclopropanol, particularly in the presence of a catalytic amount of ferric chloride (Eq. 832).



(832)

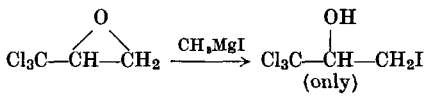
A similar reaction has now also been reported by DePuy and coworkers,[2012] using 1-chloro-2-methyl-2,3-epoxypropane (2-methylepichlorohydrin) to obtain 1-methylcyclopropanol in moderate yield.

Treatment of epichlorohydrin with phenylethinylmagnesium bromide (Eq. 833) gives an acetylenic alcohol of unverified constitution, together with 3-bromo-1-chloro-2-propanol.[406] It is probable that attack of the Grignard reagent takes place, as in other instances, at the terminal epoxide carbon atom on electronic and steric grounds.

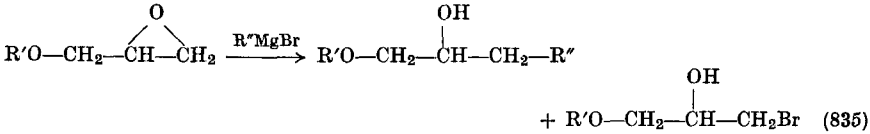


(833)

Other monosubstituted ethylene oxides carrying polar atoms have been treated with various Grignard reagents. Among these epoxides (Eqs. 834–836) may be cited 3,3,3-trichloro-1,2-epoxypropane,[637] 1,2-epoxy-3-methoxy- and 1,2-epoxy-3-phenoxypropane,[230] and certain 3-*N*,*N*-dialkyl-1,2-epoxypropanes.[160]

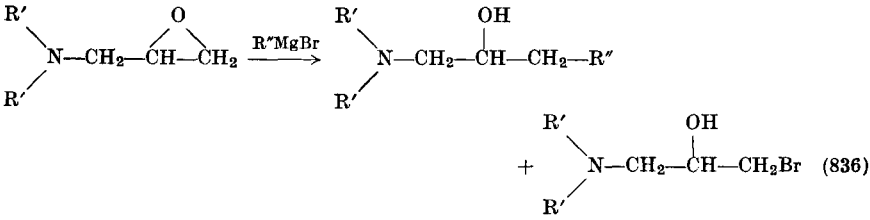


(834)



(835)

$R' = C_2H_5$, C_6H_5; $R'' = CH_3$
$R' = R'' = C_6H_5$

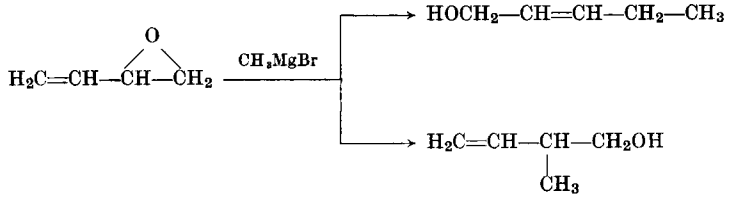


(836)

$R' = C_2H_5$, *n*-C_3H_7, *etc.*
$R'' = CH_3$, C_2H_5

In none of the instances known does substitution of a polar atom for a hydrogen on the methyl group of propylene oxide appear to have much effect. The fact that 3,3,3-trichloro-1,2-epoxypropane yields only a halohydrin (the one recorded instance of such an effect) is probably due merely to the nature of the Grignard reagent, since methylmagnesium iodide is known to favor iodohydrin formation to an overpowering degree in many cases.[625, 927]

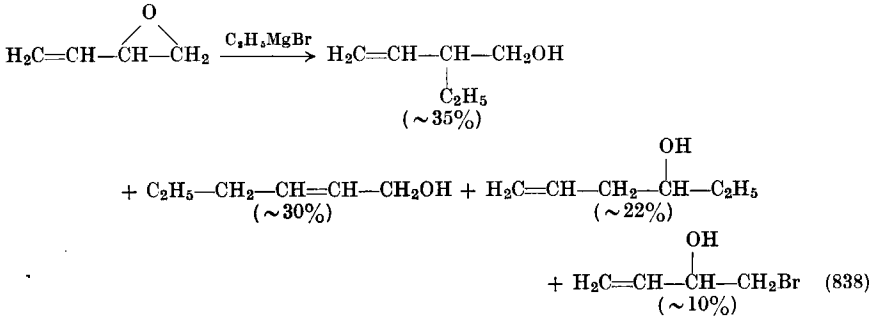
Addition of Grignard reagents to 1,2-epoxy-3-butene gives mixtures of alcohols.[579] Methylmagnesium bromide, for example, gives 2-penten-1-ol as the principal product, together with some 2-methyl-3-buten-1-ol (Eq. 837). The former can be regarded as a



(837)

'1,4-addition' product, or as an allylic rearrangement product arising from 1-penten-3-ol under the acidic work-up conditions. The latter is formed by attack on the carbon atom nearest the strongly electron-withdrawing vinyl group.

Still a third type of product (Eq. 838) is obtained with ethylmagnesium bromide, namely 1-hexen-4-ol.[579] This unsaturated alcohol



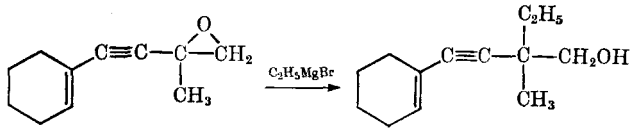
(838)

may be derived by preliminary isomerization to 3-butenal, followed by addition of Grignard reagent.

Among other Grignard reagents also reported to add to 1,2-epoxy-3-butene are cyclohexylmagnesium bromide,[1559] phenylmagnesium

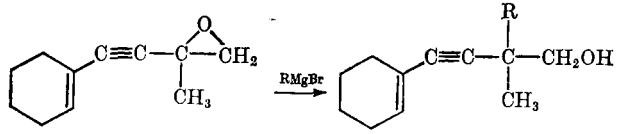
bromide,[1559] α-naphthylmagnesium bromide,[624, 1559] and α-thienylmagnesium bromide.[646] The nature of products secured in certain of these condensations, however, is still a matter of some conjecture at present.

Addition of Grignard reagents to acetylenic epoxides is exemplified by the reported condensations of ethylmagnesium bromide and of 1-bromomagnesyl-5-methoxy-3-methyl-3-penten-1-yne with the epoxide depicted in Eqs. (839) and (840). In each case, products isolated



(839)

from the reaction suggest attack by the Grignard reagent to have occurred at the epoxide carbon atom nearest the highly-electronegative triple bond,[1598] in spite of the greater steric hindrance at this terminal epoxide carbon atom. In terms of the Parker–Isaacs model,

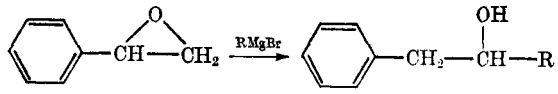


(840)

R = $CH_3OCH_2CH{=}C(CH_3)C{\equiv}C$

this reaction may be considered illustrative of the 'borderline S_N2' process, wherein appreciable positive character is developed in the transition state for nucleophilic substitution.[1301]

When the ethylene oxide contains an aromatic substituent, as in styrene oxide, there is a significant tendency for preliminary isomerization to occur. Thus, treatment of styrene oxide with methylmagnesium bromide or ethylmagnesium bromide yields 1-phenyl-2-propanol and 1-phenyl-2-butanol respectively[1728] (Eq. 841).

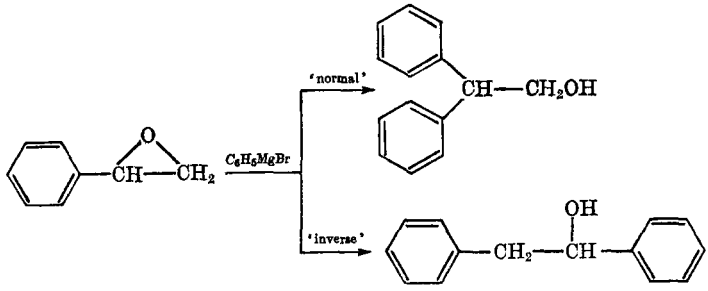


(841)

R = CH_3, C_2H_5

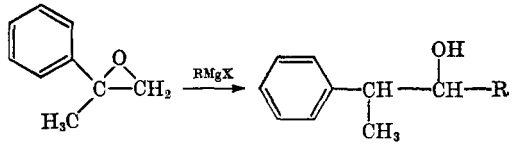
Kharasch and Clapp[925] have published the important observation that the course of reaction of phenylmagnesium bromide with styrene

oxide is governed by the order of addition of the reactants (Eq. 842). Addition of the epoxide to the Grignard reagent ('normal' addition, according to conventional usage) leads to 2,2-diphenylethanol by attack at the epoxide carbon atom nearest the electron-withdrawing phenyl substituent. Addition of the Grignard reagent to the epoxide ('inverse' addition) yields the product derived from addition of the reagent to phenylacetaldehyde, namely 1,2-diphenylethanol.



(842)

Treatment of α-methylstyrene oxide with *tert*-butylmagnesium chloride or phenylmagnesium bromide has been reported[924, 1719] to yield 4,4-dimethyl-2-phenyl-3-pentanol and 1,2-diphenyl-1-propanol respectively (Eq. 843). Both products presumably arise from methylphenylacetaldehyde, formed by preliminary isomerization of α-methylstyrene oxide.

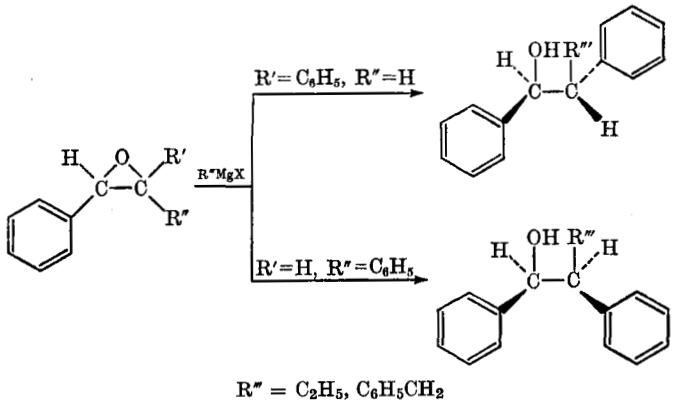


(843)

R = *tert*-C_4H_9, C_6H_5

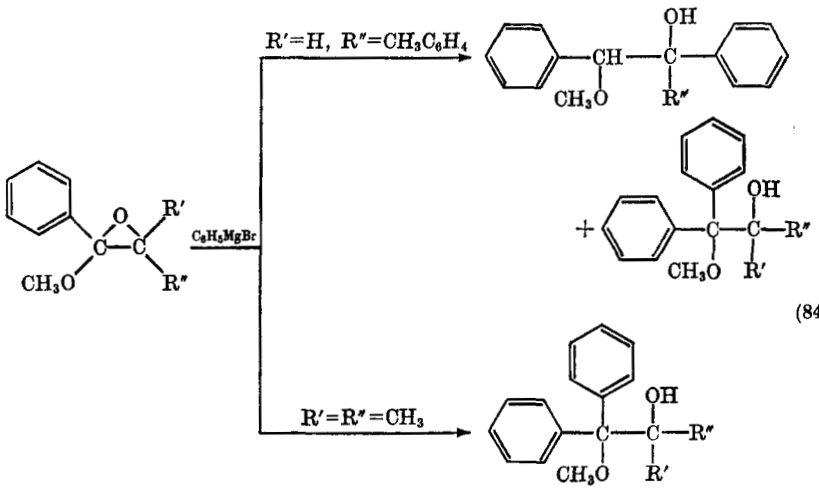
Kayser[919, 1024] conducted one of the earliest modern stereochemical investigations when he examined the products formed on adding ethyl and benzyl Grignard reagents to *cis*- and *trans*-stilbene oxides. On treatment with methylmagnesium bromide, for instance, *cis*- and *trans*-stilbene oxide yielded different stereoisomers of 1,2-diphenyl-1-propanol, each of them a *dl*-pair. Similar results were secured with ethylmagnesium bromide and ethylmagnesium chloride. Although this was not established by Kayser, the products are presumably those shown in Eq. (844) on the basis of other nucleophilic additions to *cis*- and *trans*-stilbene oxides (see, *e.g.* section **IV.4.***B*.).

Several epoxy ethers have been shown to undergo addition by Grignard reagents.[1638, 1645, 1706] Direct addition has been observed, as



(844)

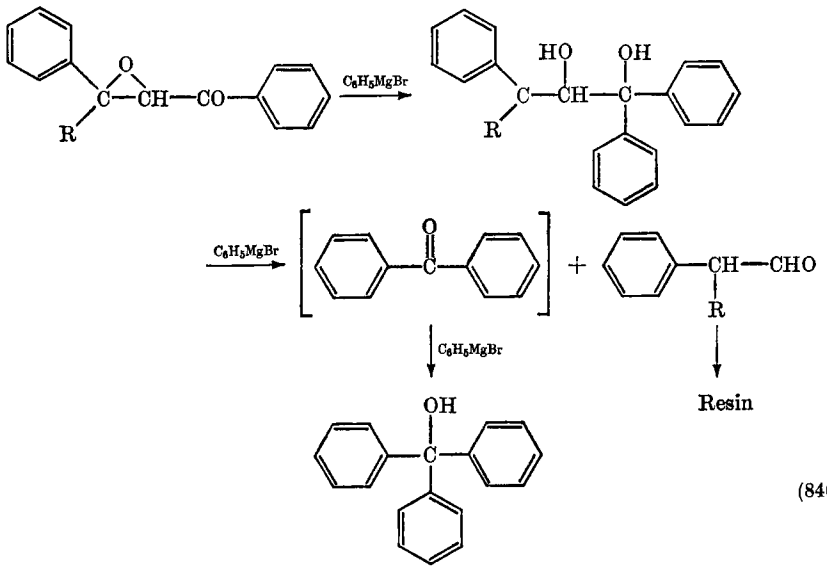
well as addition following preliminary isomerization (Eq. 845). Thus, 1,2-epoxy-1-methoxy-1-phenylpropane and 1,2-epoxy-1-methoxy-1,2-diphenylethane give mixtures of alcohols arising from each of the possible reaction paths. When rearrangement to a carbonyl compound is relatively improbable, as in 1,2-epoxy-1-methoxy-2-methyl-1-phenylpropane, only one alcohol is formed. Direct addition appears to occur preferentially at the epoxide carbon atom to which the phenyl and methoxyl substituents are attached, as would be anticipated from the inductive effects of these groups.



(845)

Special comment is required for reactions of α,β-epoxy ketones and glycidic esters with Grignard reagents.

Kohler and co-workers[155, 956, 958] have conducted a thorough study of the reactions of certain benzalacetophenone oxides with phenylmagnesium bromide, and of benzalacetone oxide with mesitylmagnesium bromide. Treatment of benzalacetophenone oxide itself apparently yields under the mildest conditions an α,β-epoxy alcohol (called an 'oxanol'), which decomposes at higher temperatures under the influence of Grignard reagent. Products ultimately isolated are triphenylcarbinol and a resin formed by polymerization of phenylacetaldehyde (Eq. 846). Similarly, β-phenylbenzalacetophenone oxide gives triphenylcarbinol and diphenylacetaldehyde.



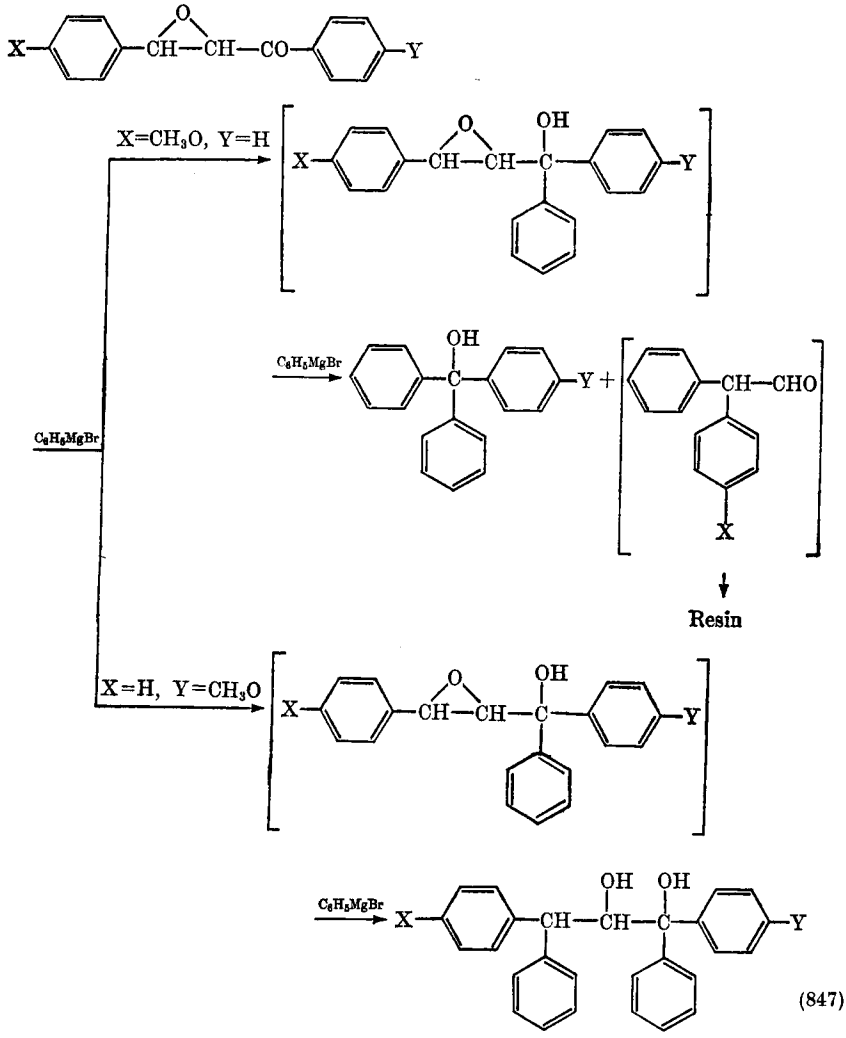
(846)

R = H, C_6H_5

In addition, several other benzalacetophenone oxides substituted in one or the other phenyl rings have been investigated.[59, 133, 155, 958] Anisalacetophenone oxide and phenylmagnesium bromide, for example, yield triphenylcarbinol, presumably by way of the oxanol[958] shown in Eq. (847), whereas benzal-*p*-methoxyacetophenone oxide yields the glycol corresponding to attack of a second molar equivalent of Grignard reagent in preference to cleavage.[155] The influence of a methoxyl substituent on the reactivity of the intermediate oxanol is manifest. A sufficient amount of conflict about the course of these reactions

exists among various authors, however, to warrant caution in accepting present evidence.[625, 927]

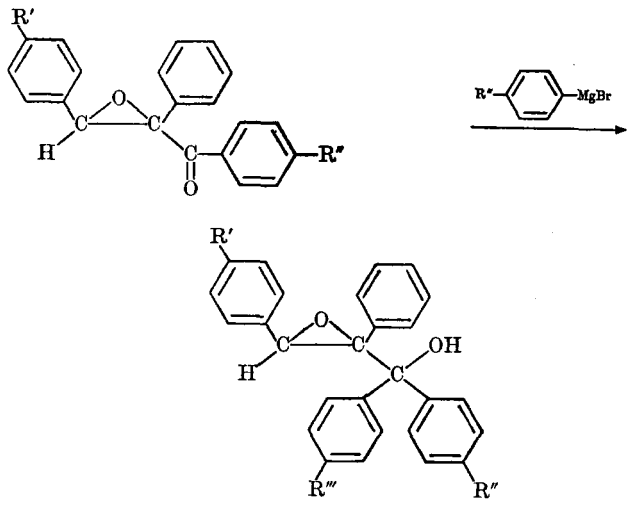
'Oxanols' (α,β-epoxy alcohols) have actually been isolated by



(847)

Dilgen and Hennessy[2032] from the condensation of several aryl α,β-epoxyketones (Eq. 847a) with excess Grignard reagent at room temperature, cleavage occurring at reflux.

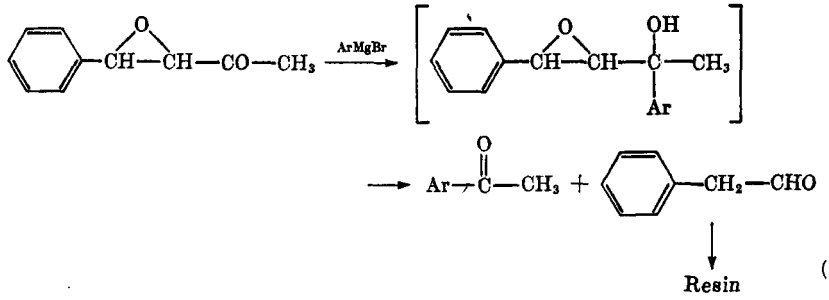
Treatment of benzalacetone oxide with mesitylmagnesium bromide



(847a)

R′ = R‴ = H; R″ = H, CH_3O_2
R″ = R‴ = H; R′ = CH_3O
R′ = R″ = H; R‴ = CH_3O

yields acetylmesitylene and a resin (Eq. 848), indicating that a ketone is probably formed in all cleavage reactions of oxanols.[958] The low reactivity of acetylmesitylene prevents further condensation with Grignard reagent, so that no tertiary carbinol is isolable in this case.

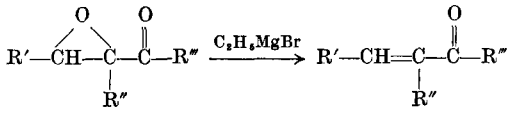


(848)

Ar = mesityl

Fuson and co-workers[607] have published the remarkable observation that certain aryl-substituted α,β-epoxy ketones simply lose oxygen to give α,β-unsaturated ketones on treatment with ethylmagnesium bromide or other Grignard reagents (Eq. 849). Although a mechanism

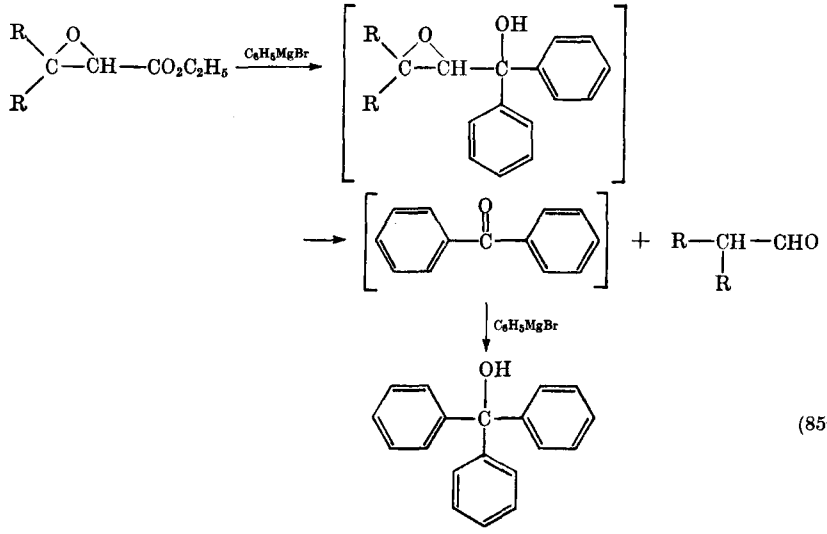
has been advanced to explain this curious effect,[912] no subsequent work has appeared on the subject.



(849)

R′ = H; R″ = mesityl; R‴ = mesityl, duryl, isoduryl
R′ = R″ = C_6H_5; R‴ = mesityl, duryl
R′ = R‴ = mesityl; R″ = H

There has been disagreement among various authors on the subject of glycidic esters. The most recent evidence[958] indicates that β,β-dimethyl- and β,β-diphenylglycidic esters undergo cleavage with excess of phenylmagnesium bromide, yielding triphenylcarbinol and either dimethylacetaldehyde polymers or diphenylacetaldehyde. Glycidic esters must therefore initially form an oxanol, which is then cleaved by excess of Grignard reagent as shown in Eq. (850). The



(850)

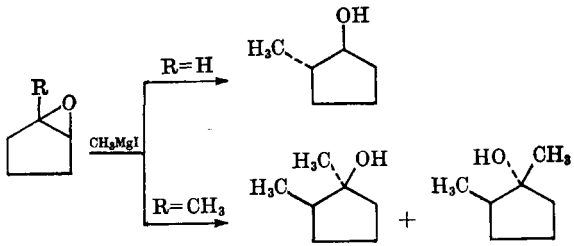
R = CH_3, C_6H_5

reaction is unfortunately complicated, however, by the ready isomerization of glycidic esters to α-keto esters, and subsequent condensation of the latter with Grignard reagent.

Several alicyclic epoxides have been subjected to the action of Grignard reagents. Much of the early literature is unfortunately in

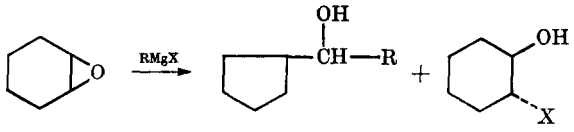
error on this subject,[108, 648] since it was not realized for many years that cyclohexene oxide underwent skeletal rearrangement in the presence of Grignard reagents.

Cyclopentene oxide and 1-methylcyclopentene oxide yield respectively *trans*-2-methylcyclopentanol and a mixture of *cis*- and *trans*-1,2-dimethylcyclopentanol (Eq. 851) on treatment with methylmagnesium iodide.[305, 648, 1769] The latter could in principle be formed either by a preliminary isomerization to 2-methylcyclopentanone, or by direct addition to the least-substituted epoxide carbon atom. These possibilities have not, however, been distinguished until now.



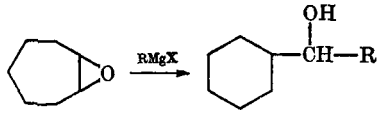
(851)

Cyclohexene oxide yields on treatment with methylmagnesium iodide and several other Grignard reagents (Eq. 852) the corresponding alkyl cyclopentyl carbinols, and in certain cases some *trans*-2-halocyclohexanols as well,[108, 112, 334, 647, 1156, 1477, 1786]



(852)

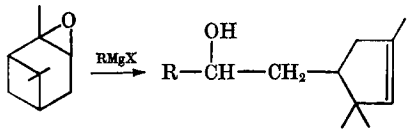
Ring contraction was reported[648] to occur, however, on treatment of the homologous substance cycloheptene oxide with phenylmagnesium bromide (Eq. 853). Although this has not yet been confirmed, Gaylord and Becker[625] have postulated that rearrangement likewise accompanies condensation of cycloheptene oxide with methylmagnesium iodide.[648]



(853)

R = CH_3, C_6H_5

Condensation of α-pinene oxide with methylmagnesium iodide and other Grignard reagents has been shown[1468] to involve rupture of the bridge, giving a variety of campholenols (Eq. 854). The reaction of

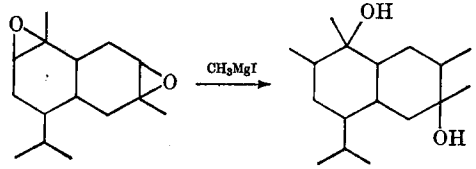


(854)

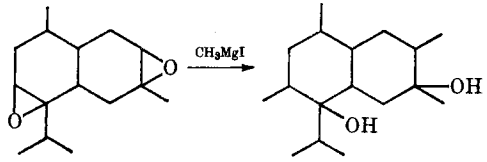
R = CH_3, C_2H_5, *n*-C_3H_7, *iso*C_3H_7, *n*-C_4H_9, *iso*C_4H_9, C_6H_5

β-pinene oxide with methylmagnesium iodide and ethylmagnesium bromide has been described also,[1413] but structures assigned to the isolated products have been questioned.[1579]

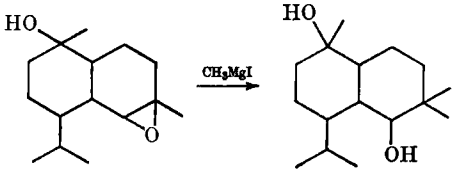
An important method of locating double bonds in unsaturated sesquiterpenes is to convert these into epoxides by oxidation with a peroxy acid, and to condense the resulting epoxide derivatives with methylmagnesium iodide. Further degradations then yield additional structural information. Three illustrations (Eqs. 855–857) of this



(855)



(856)

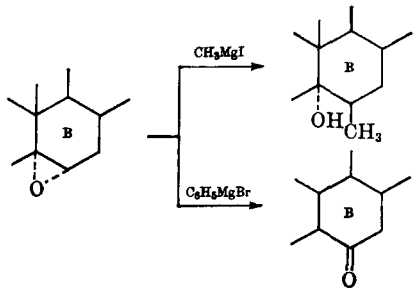


(857)

technique involve the addition of methylmagnesium iodide to cadinene dioxide,[284] isozingiberene dioxide,[1600] and α-cadinol oxide.[1182] The unusual formation of a secondary, rather than the expected tertiary, alcohol, in the last instance is noteworthy, and is presumably caused by conformational effects (*e.g.* the principle of diaxial product control).

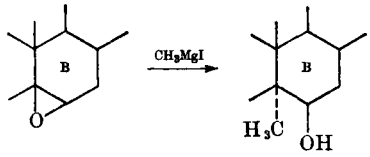
In the field of steroid chemistry, addition of Grignard reagents to

epoxides has been useful chiefly in connexion with the preparation of biologically potent 6β-alkyl-5α-hydroxy derivatives from suitable 5α,6α-epoxide precursors.[9,54,99,225,267,281,312,337,484,544,666,1083,1464,1619] With phenylmagnesium bromide, however, 5α,6α-epoxy steroids (Eq. 858) appear to give only 6-oxo derivatives by isomerization,[308,1905]



(858)

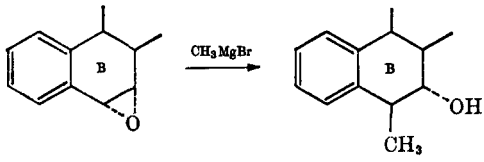
presumably because of the bulky nature of the reagent. The importance of conformational effects is underlined, moreover, by the fact that a 5β,6β-epoxide condenses with methylmagnesium iodide to give a 6β-hydroxy-5α-methyl steroid, rather than a 5β-hydroxy-6α-methyl derivative (Eq. 859). Attack by methylmagnesium iodide is seen to



(859)

conform to the diaxial-product-control principle with respect to ring B in each case.

One instance has been recorded of methylmagnesium bromide addition to 6α,7α-epoxy steroids (Eq. 860) which gives 7α-hydroxy-



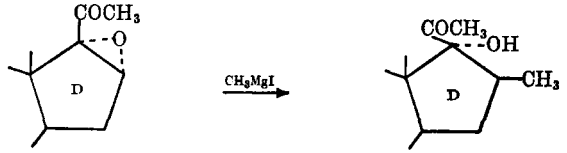
(860)

6β-methyl derivatives,[1787] but few other steroid epoxides appear to have been subjected to this type of transformation until now. It will be noted in this example that attack occurs at the benzylic epoxide carbon atom, as expected on the basis of the Parker–Isaacs model,[1301] that the product configuration corresponds to diaxial control, and that

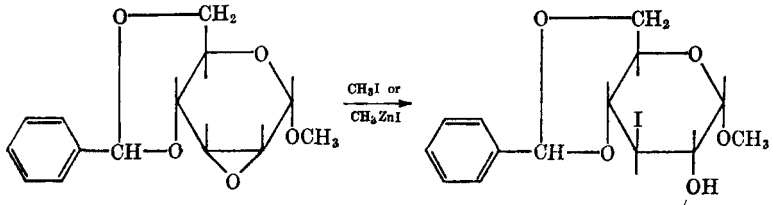
Walden inversion has taken place at the site of addition in spite of its benzylic character.

Addition of methylmagnesium iodide to steroidal α,β-epoxy ketones is exemplified by the work of Sciaky,[2027] using a $16\alpha,17\alpha$-epoxy-20-oxo derivative as shown in Eq. (860a).

Anhydro sugars have only rarely been converted into alkylated or arylated desoxy sugars by treatment with Grignard reagents, halohydrins being formed as a rule instead of the desired adducts. Conformational effects in rigid bicyclic derivatives are very much in evidence in

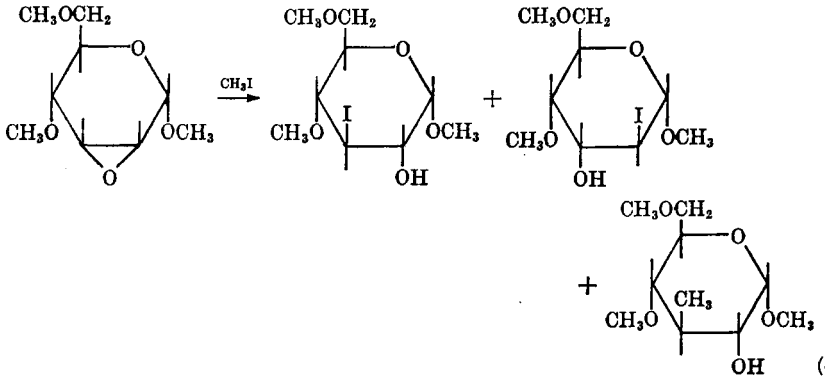


(860a)



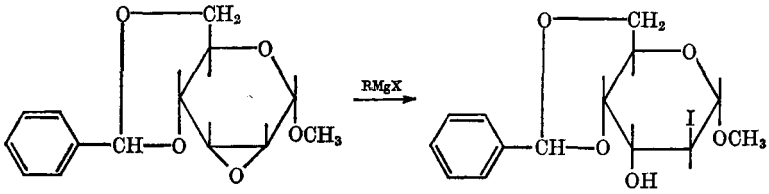
(861)

this field.[625, 1245] Thus, though methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-alloside yields only the 3-iodo-3-desoxy derivative and no alkyl adduct (Eq. 861), 2,3-anhydro-4,6-di-*O*-methyl-α-D-alloside gives isomeric iodohydrins but also a 3-methyl-3-desoxy derivative on treatment with methylmagnesium iodide[1248] (Eq. 862). Operation of the diaxial-control principle is manifest in these examples.



(862)

The effect of varying the Grignard reagent becomes evident on addition of ethylmagnesium iodide to the above 4,6-*O*-benzylidene derivative. Again, only an iodohydrin was obtained, isomeric with the

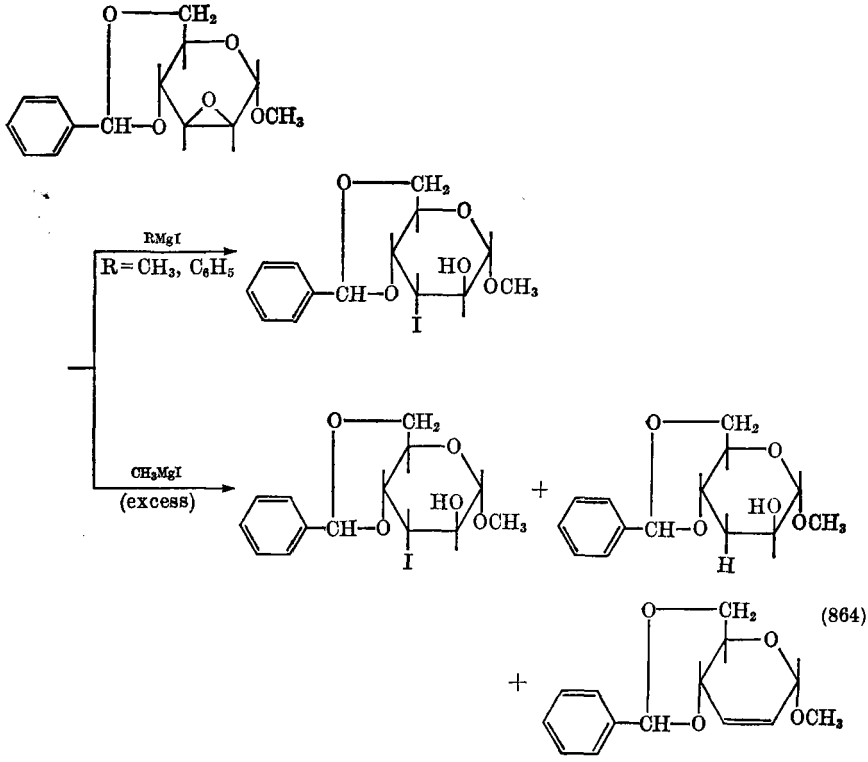


(863)

R = C_2H_5; X = Br, I
R = C_6H_5; X = Br

product obtained with methylmagnesium iodide, but retaining axially disposed iodide and hydroxyl substituents,[1457] as shown in Eq. (863).

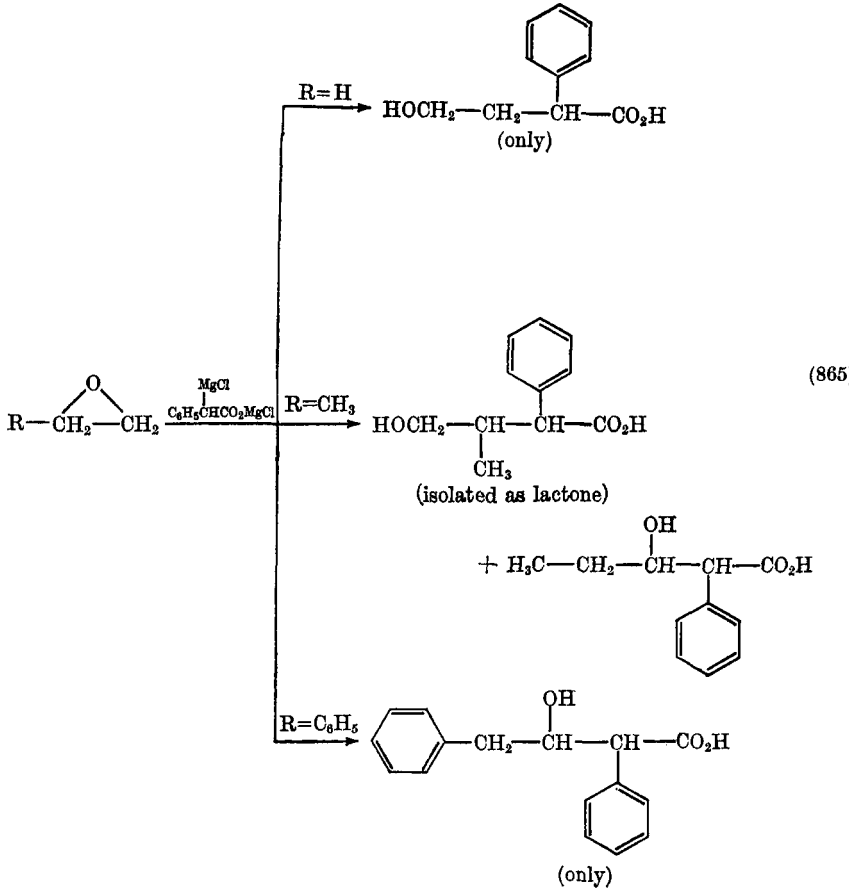
It has been reported[560, 1455] that condensation of 4,6-*O*-benzylidene-2,3-anhydro-α-D-mannoside with methyl- or phenylmagnesium iodide affords only the corresponding diaxial iodohydrin, while a large



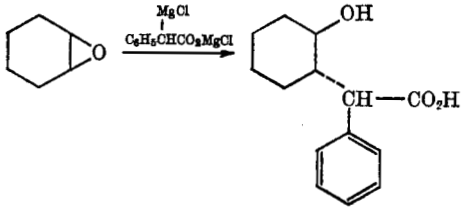
(864)

excess of Grignard reagent results in loss of iodine and elimination of water (Eq. 864).

This section is concluded with a brief mention of a type of Grignard reagent named after the Russian chemist Ivanov, and derived from α-chlorophenylacetic acid.[172, 173] Ethylene oxide yields on treatment with Ivanov reagent the hydroxylated product shown in Eq. (865), but propylene oxide gives a mixture indicating that the epoxide can react by direct addition to the terminal carbon atom or by preliminary isomerization to propionaldehyde. Cyclohexene oxide (Eq. 866) undergoes only terminal attack, without isomerization or ring contraction, whereas styrene oxide (Eq. 865) behaves as though it were reacting exclusively in the form of phenylacetaldehyde.



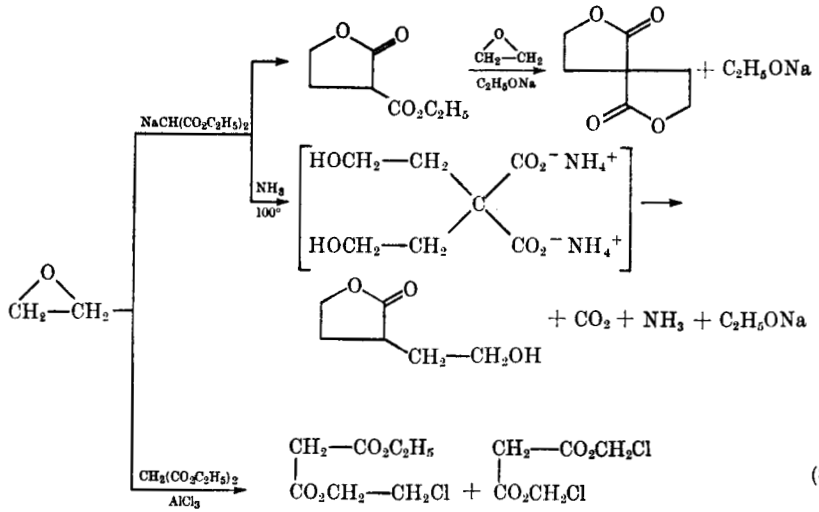
(865)



(866)

F. Carbanions

The addition of a carbanion to an epoxide was first described in 1899 by Traube and Lehman,[1759] who condensed ethylene oxide with diethyl sodiomalonate. Subsequent work by these and other investigators[124, 1285, 1286, 1759] established that any of three products may be formed depending on the particular reaction conditions employed (Eq. 867). At moderate temperatures equimolar quantities of reactants

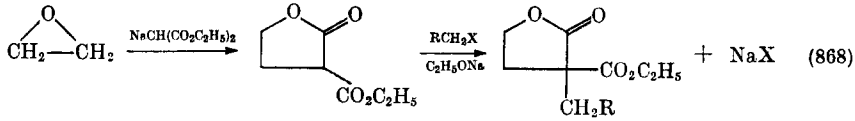


(867)

give primarily α-carbethoxybutyrolactone.[1285, 1286, 1759] Excess of ethylene oxide, on the other hand, leads to further condensation, since the initially-formed lactone ester still possesses an enolizable hydrogen atom. The product obtained in this manner has been shown to be a spirolactone.[124] Finally, if the reaction is conducted in a sealed tube at 120° in the presence of ammonia, piperidine, or other secondary amines, there is formed α-(2-hydroxyethyl)butyrolactone, with attendant liberation of carbon dioxide.[1285, 1286] Recent work,[716] incidentally,

has refuted a previous claim that aluminum chloride functions as a catalyst in this condensation.[1427] The products actually formed in the presence of aluminum chloride appear to be ethyl β-chloroethylmalonate and ethyl di-(β-chloroethyl)malonate, rather than the desired lactone ester.

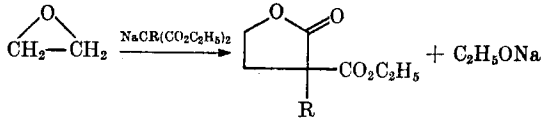
Advantage of the fact that α-carbethoxybutyrolactone still possesses an active proton has been taken by McRae and co-workers.[1077] Condensation of ethylene oxide, diethyl sodiomalonate, and a suitable alkyl halide in equal proportions gives rise to an α,α-disubstituted butyrolactone, as shown in Eq. (868).



(868)

R = $CO_2C_2H_5$; X = Cl, Br
R = C_6H_5; X = Cl

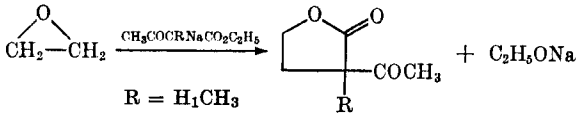
An extensive series of diethyl alkylsodiomalonates was examined by Rothstein,[1495] and found to condense satisfactorily with ethylene oxide, giving the corresponding α-alkyl-α-carbethoxybutyrolactones (Eq. 869).



(869)

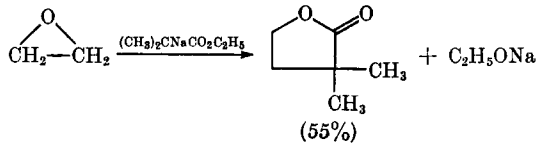
R = *n*-C_6H_{13}–*n*-$C_{12}H_{25}$, *etc.*

Ethyl sodioacetoacetate,[1759] ethyl α-methylsodioacetoacetate,[1625] and ethyl dimethylsodioacetate[838] have likewise been added successfully to ethylene oxide, as indicated in Eqs. (870) and (871).



(870)

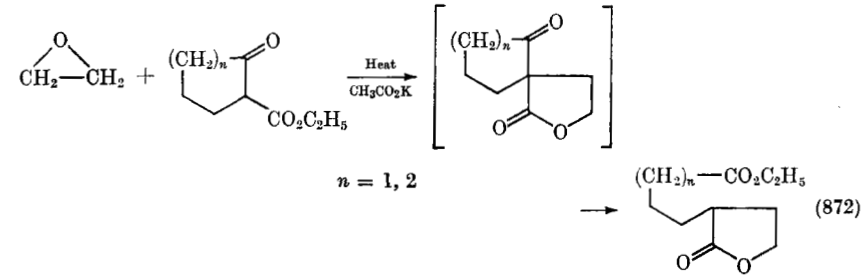
R = H_1CH_3



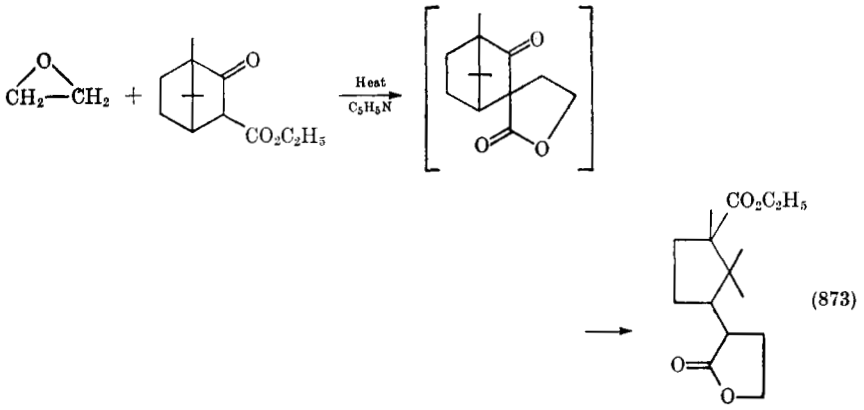
(871)

(55%)

Ethylene oxide has also been condensed with 2-carbethoxycyclopentanone,[1625] 2-carbethoxycyclohexanone,[1625] and α-carbethoxycamphor.[617] The primary products in these reactions undergo cleavage before they can be isolated, yielding lactone esters instead of ketolactones (Eqs. 872 and 873).

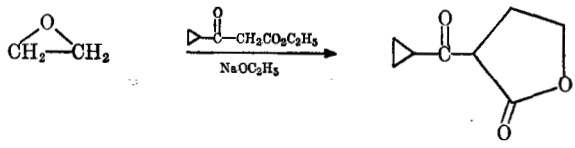


(872)



(873)

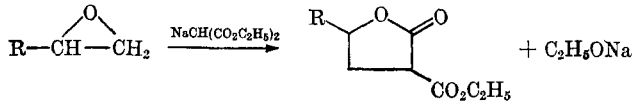
A ketolactone was isolated,[2033] on the other hand, from the condensation of ethylene oxide with carbethoxymethyl cyclopropyl ketone in the presence of sodium ethoxide (Eq. 873a).



(873a)

Many monoalkyl-substituted ethylene oxides have been condensed with diethylsodiomalonate (Eq. 874), giving β-alkyl-α-carbethoxybutyrolactones exclusively.[621, 622, 903, 1077, 1496] The relatively

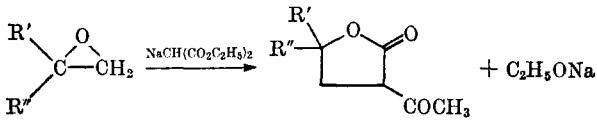
bulky nature of the nucleophile is considered responsible for the complete absence of attack at the secondary epoxide carbon atom.



(874)

R = CH_3, *n*-C_4H_9, *n*-C_5H_{11}, *iso*C_5H_{11}, *iso*C_6H_{13}, *n*-C_7H_{15}–*n*-$C_{11}H_{23}$

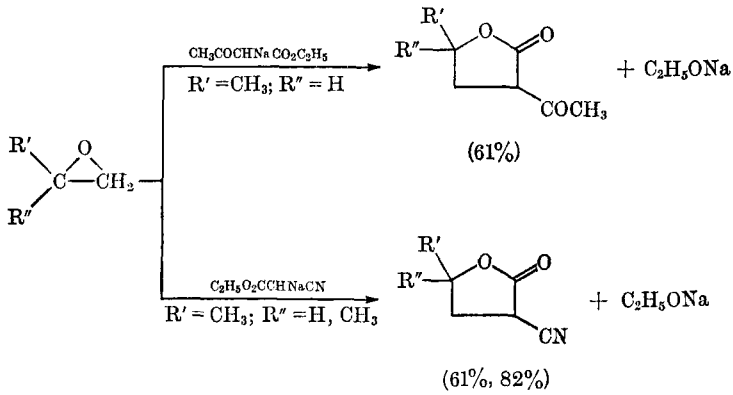
Ethyl sodioacetoacetate (Eq. 875) has likewise been found to react smoothly at the terminal carbon atom of propylene oxide, 1,2-epoxy-2-methylbutane, and related substances.[663, 1496, 1500]



(875)

R′ = CH_3; R″ = H, C_2H_5, *iso*C_3H_7, *n*-C_4H_9, *iso*C_4H_9, *iso*C_5H_{11}, *neo*C_5H_{11}, *n*-C_6H_{13}

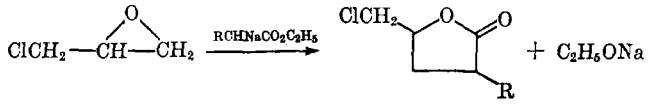
Still another active hydrogen component utilized in this reaction has been ethyl cyanoacetate (Eq. 876), the sodium salt of which was condensed with propylene oxide or *iso*butylene oxide.[645] Similarly, ethyl sodioacetoacetate (Eq. 876) has been added to propylene oxide.[11] Terminal attack is the rule in all these instances.



(876)

Epichlorohydrin and epibromohydrin have been subjected to the action of the greatest variety of carbanion reagents (Eq. 877). These include a number of diethyl sodiomalonates,[1012, 1758, 1759, 1782] ethyl

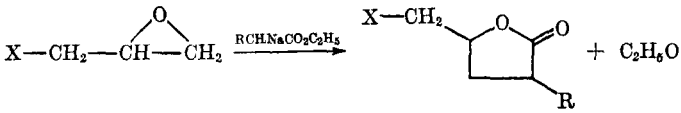
sodioacetoacetate,[1012, 1758, 1759] and the sodium derivative of 1,3-carbethoxy-2-propanone.[703] Although rupture of the epoxide ring occurs more readily than halide displacement in the case of epichlorohydrin and epibromohydrin, Temnikova and Ershov[2034] have recently published the observation that the opposite effect occurs with 1-bromo-2,3-epoxybutane and 3-bromo-1,2-epoxybutane.



(877)

R = $C_2H_5O_2C$, CH_3CO, $C_2H_5O_2CCH_2CO$

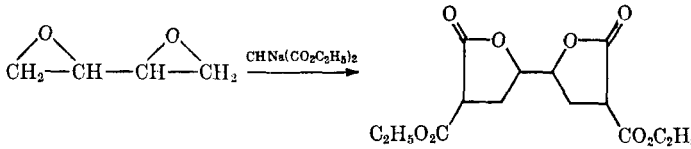
Haller and Blanc[699, 702] have also condensed sodium salts of acetoacetone and ethyl benzoylacetate with epichlorohydrin, but the structures formulated for products thereby secured are open to question.



(878)

X = CH_3O, C_2H_5O, *etc.*; R = $C_2H_5O_2C$, CH_3CO, CN
X = $(CH_3)_2N$, $(C_2H_5)_2N$, $(CH_2)_5N$, *etc.*; R = $C_2H_5O_2C$

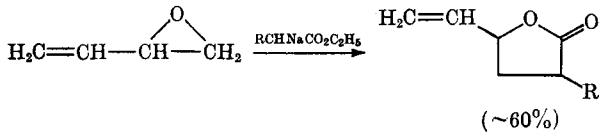
Glycidyl ethers (Eq. 878) behave as do other terminal epoxides on treatment with diethyl sodiomalonate, ethyl sodioacetoacetate, and ethyl sodiocyanoacetate.[1499, 1782] Glycidamines (Eq. 878) act in the same manner in the presence of diethyl sodiomalonate,[1497] as does also 1,2;3,4-diepoxybutane[115] (Eq. 879).



(879)

Condensation of the sodio derivatives of diethyl malonate,[1507] ethyl acetoacetate,[11] and ethyl cyanoacetate[1916] has been found to take place exclusively at the terminal position of 1,2-epoxy-3-butene (Eq. 880). It may be recalled that this substance gives significant proportions of other products on treatment with less bulky nucleophiles.

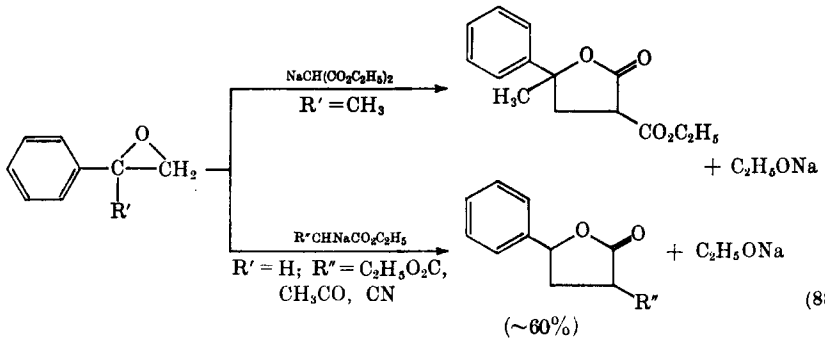
Addition of the same reagents has been reported[11, 1507, 1916] also



(880)

R = $C_2H_5O_2C$, CH_3CO, CN

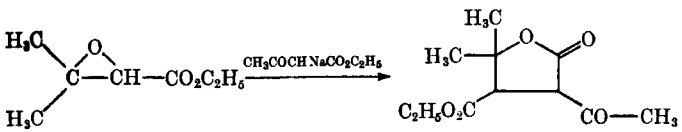
to occur uniquely at the terminal position of styrene oxide (Eq. 881). Diethyl sodiomalonate likewise reacts smoothly with α-methylstyrene oxide,[1500] *p*-nitrostyrene oxide,[373] and 1-allyl-3,4-methylenedioxybenzene epoxide (safrole oxide).[720]



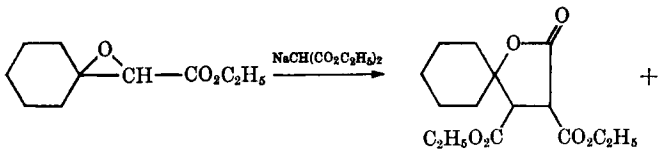
(881)

R′ = H; R″ = $C_2H_5O_2C$, CH_3CO, CN

Diethyl sodiomalonate has been condensed with ethyl cyclohexylideneacetate oxide (Eq. 883), but the structure of the product was not rigorously established.[1201] Ethyl sodioacetoacetate, in contrast



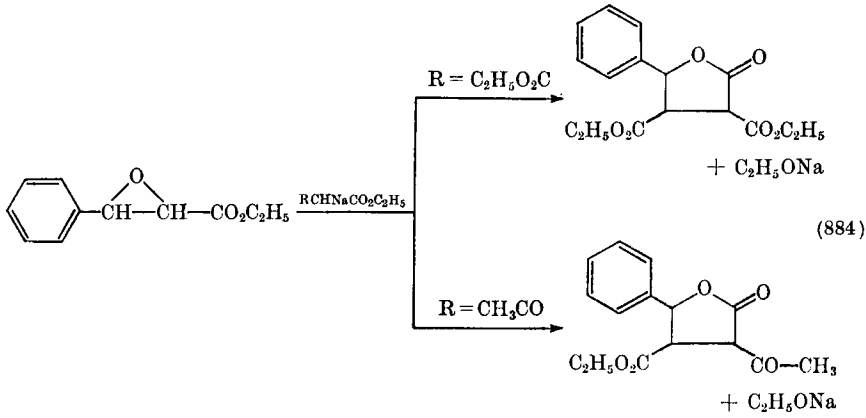
(882)



(883)

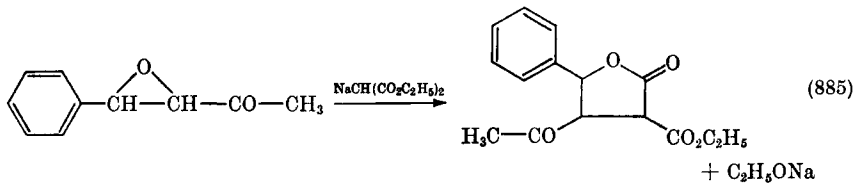
with amines (see section **IV.4.*B.***), is believed[306] to add to the epoxide carbon atom nearest the ester function in ethyl β,β-dimethylglycidate (Eq. 882). If this is correct it is likely that the first reaction follows a

similar course. Ethyl β-phenylglycidate (Eq. 884) has been reported to react with both diethyl sodiomalonate and ethyl sodioacetoacetate.[306]



(884)

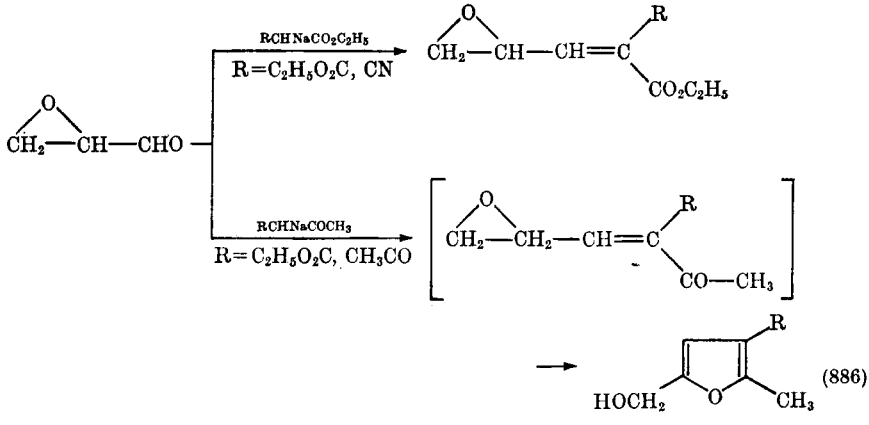
Similarly, addition of diethyl sodiomalonate to benzalacetone oxide has been found to give the corresponding butyrolactone derivative,[966] as shown in Eq. (885). No structure was formulated, but analogy supports the assignment made here.



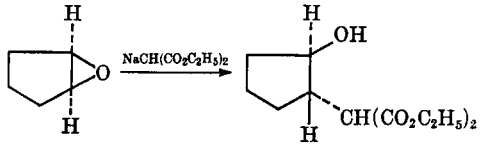
(885)

Condensation of diethyl sodiomalonate and ethyl sodiocyanoacetate with glycidaldehyde (Eq. 886) has been reported to occur preferentially at the aldehyde function.[1847] Ethyl sodioacetoacetate and sodioacetylacetone react likewise (Eq. 886), but the initial adducts cannot be isolated, since they readily undergo cyclization to furan derivatives.

Various alicyclic epoxides have been subjected to the action of carbanionoid reagents. Cyclopentene oxide (Eq. 887) is unique thus far, in that it gives no lactone.[670] Lactone formation is prevented by the high activation energy required to establish *trans*-fusion between two five-membered rings.[670]



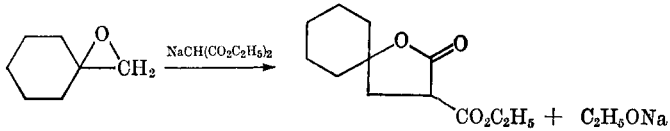
(886)



(887)

(70-75%)

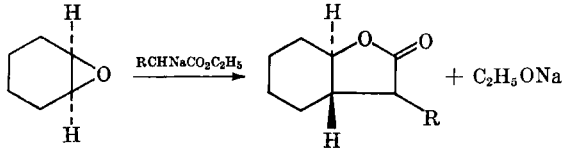
The semicyclic epoxide 2-oxaspiro[2.5]octane reportedly undergoes terminal addition exclusively on treatment with diethyl sodiomalonate, thereby affording a spirolactone[1201] as shown in Eq. (888).



(888)

R = $C_2H_5O_2C$, CH_3CO, CN

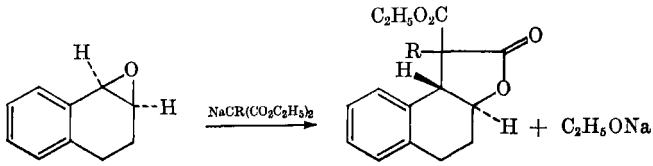
Cyclohexene oxide (Eq. 889) and certain methyl-substituted derivatives have been condensed successfully with diethyl sodiomalonate,[321, 1076, 1201, 1241] ethyl sodioacetoacetate,[966] and ethyl sodiocyanoacetate.[645] Lactone rings are generated in all cases, since *trans*-fused six-membered rings are stable.



(889)

R = $C_2H_5O_2C$, CH_3CO

Treatment of 1,2-epoxytetralin with diethyl sodiomethylmalonate was found to involve attack on the benzylic epoxide carbon atom exclusively (Eq. 890), in spite of the fact that this position is some-

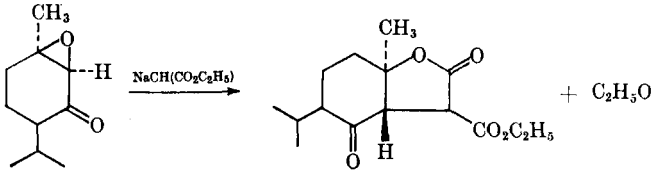


(890)

R = H, CH_3

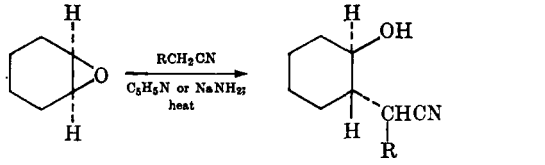
what hindered and the diethyl methylmalonate anion is quite bulky.[1780] It may be supposed by analogy that the reaction of diethyl sodiomalonate itself with 1,2-epoxytetralin, previously claimed to give no recognizable product,[966] should in principle have given the corresponding lactone. Participation of an intermediate exhibiting substantial carbonium ion character in this reaction is indicated by the fact that attachment of the nucleophilic species tends to occur on the benzylic epoxide carbon atom.[1780]

The reaction of diethyl sodiomalonate with 1,2-epoxy-3-menthane was reported in 1925, to give a low yield of an unidentified lactone, $C_{15}H_{22}O_5$.[966] Analogy with all the foregoing suggests the structure indicated in Eq. (891), but rigorous proof is, as yet, lacking.



(891)

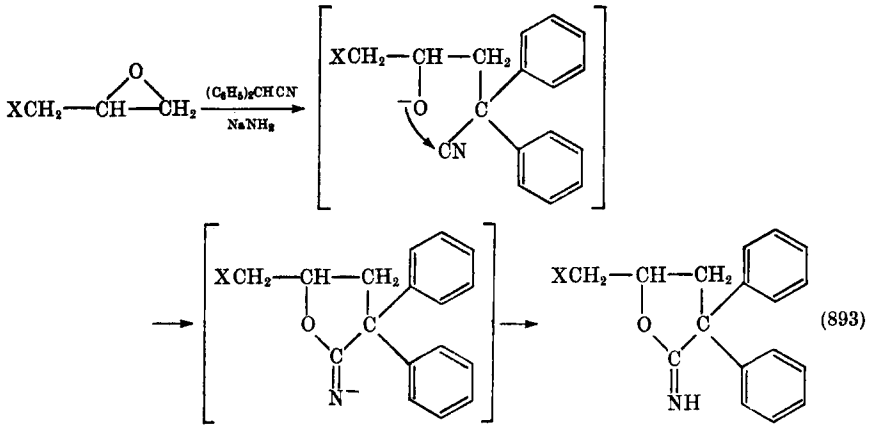
Several other types of carbanions have been utilized to open epoxide rings. Mousseron and Canet,[1189] for example, have reported the use of acetonitrile, proprionitrile, benzyl cyanide, and cyclohexyl cyanide to cleave cyclohexene oxide in the presence of pyridine or sodium amide (Eq. 892).



(892)

R = H, CH_3, C_6H_5

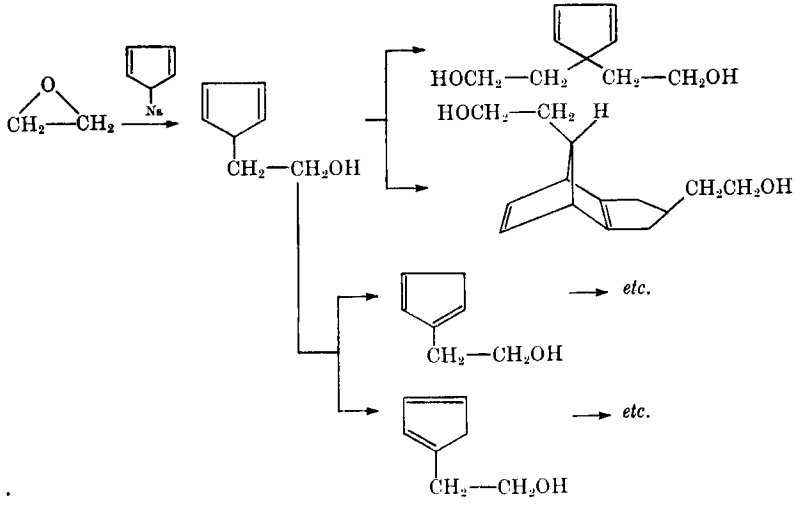
Similarly, Easton and Fish[478] have condensed epichlorohydrin, 1,2-epoxy-3-(*N*,*N*-diethylamino)propane, and allyl glycidyl ether with diphenylacetonitrile in the presence of sodium amide (Eq. 893).



(893)

X = Cl, $(C_2H_5)_2N$, $H_2C{=}CHCH_2O$

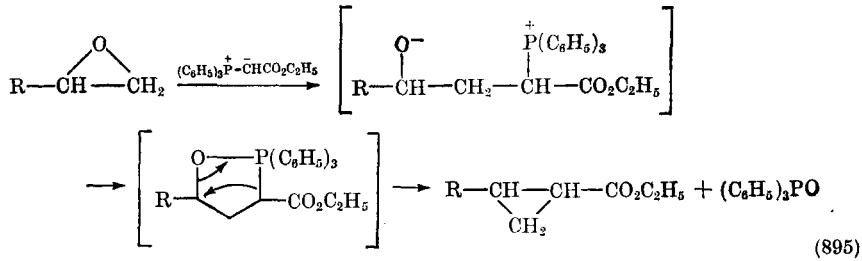
The sodium salt of cyclopentadiene has been reported to condense readily with ethylene oxide, but the reaction appears to be exceedingly complex.[179,1836] The initial adduct shown in Eq. (894) can react further with ethylene oxide, undergo Diels–Alder dimerization, or isomerize to give two more β-hydroxyethylcyclopentadienes. Each of



(894)

these can react further with ethylene oxide, or undergo Diels–Alder dimerization. In Eq. (894) only a fraction of the possible products is shown.

Among miscellaneous carbanions worthy of mention, finally, are those derived from α-, β-, and γ-picoline and γ-collidine,[314] various nitroalkanes,[460] alkyl *N*,*N*-dialkylaminomethyl ethers,[1262] and ethyl β-triphenylphosphonium acetate.[440, 1952] The last is of particular interest, inasmuch as it yields a cyclopropane derivative by the process depicted in Eq. (895).

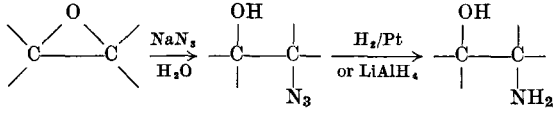


(895)

R = C_2H_5, C_6H_5

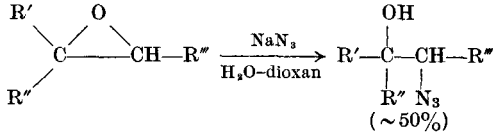
G. Miscellaneous Nucleophilic Additions

(1) Azide ion. The ready cleavage of ethylene oxide rings by N_3^- ion is in accordance with its recognized nucleophilic character. Although so far limited to three,[853, 1070, 1776] publications devoted to this reaction have explored the behavior of a wide assortment of epoxides. It is customary to characterize β-azido alcohols obtained on treatment of epoxides with aqueous sodium azide by reduction to β-amino alcohols,[1070, 1776] as shown in Eq. (896).



(896)

Propylene oxide, *iso*butylene oxide, and 2,3-epoxybutane all undergo cleavage readily on treatment with sodium azide (Eq. 897),

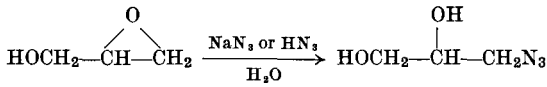


(897)

R′ = CH_3; R″ = H, CH_3; R‴ = H
R′ = R‴ = CH_3; R″ = H

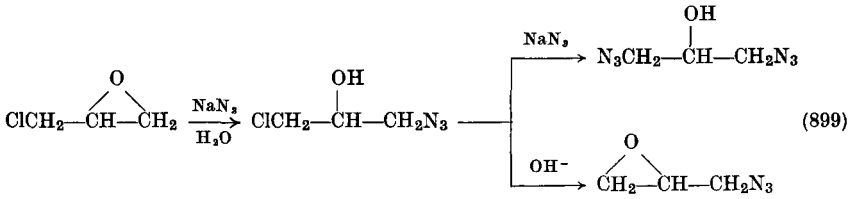
affording the respective β-azidoalcohols.[853, 1776] Where a choice exists the attacking species selects terminal approach almost exclusively.

Glycidol (Eq. 898) has been treated with aqueous sodium azide or aqueous hydrazoic acid.[853] Approach of the reagent occurs toward the least-substituted epoxide carbon atom in both cases. The reaction of



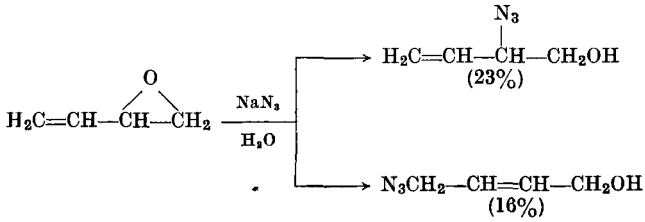
(898)

N_3^- ion with epichlorohydrin (Eq. 899) may involve either simple cleavage,[853] or cleavage accompanied by chlorine replacement,[1776] depending on the amount of nucleophile used. The 1,3-diazido-2-propanol obtained in the latter process is explosive above 150°. Treatment of the simple cleavage product, 1-azido-3-chloro-2-propanol, with alkali yields glycidazide.[853]



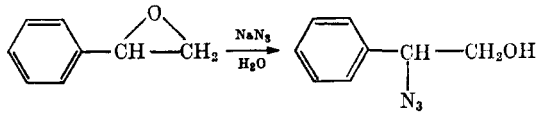
(899)

Addition of N_3^- ion to 1,2-epoxy-3-butene (Eq. 900) provides an interesting illustration of '1,4-addition', since there are isolated approximately equal proportions of 2-azido-3-buten-1-ol and 4-azido-2-buten-1-ol.[1776] Such homoallylic participation is a well-known phenomenon in many solvolytic processes,[1873] and seems to suggest the existence of a carbonium ion-like intermediate in the present case.



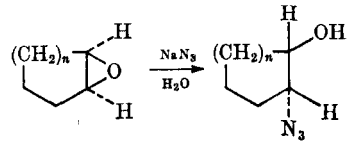
(900)

Styrene oxide undergoes attack at the benzylic epoxide carbon atom exclusively (Eq. 901), giving 2-azido-2-phenylethanol as sole product.[1070, 1776]



(901)

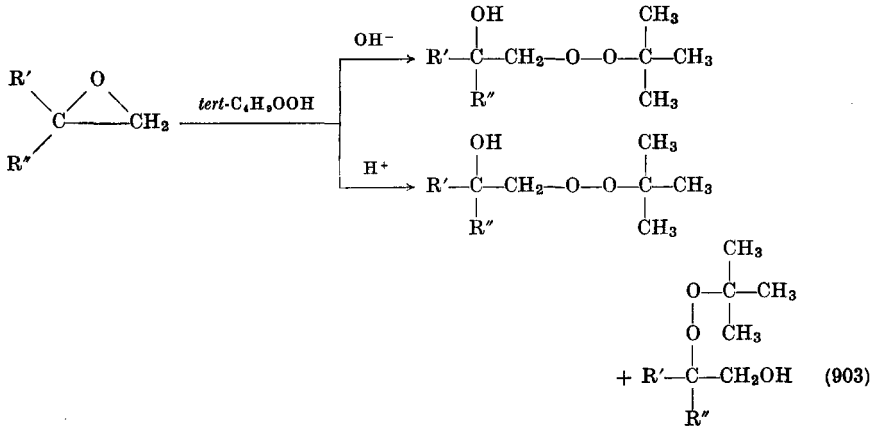
Cyclopentene oxide and cyclohexene oxide, finally, have been found to give the corresponding *trans*-2-azidocycloalkanols (Eq. 902) on treatment with aqueous sodium azide.[1776]



(902)

$n = 1, 2$

(2) Peroxide and hydroperoxide ions. A patent disclosure by Barusch and Payne[101] has described addition of *tert*-butylhydroperoxide to ethylene oxide, propylene oxide, and *iso*butylene oxide in ether, in the presence of either basic or acidic catalysts. The *tert*-butylperoxide ion, like other nucleophiles, apparently prefers to attack

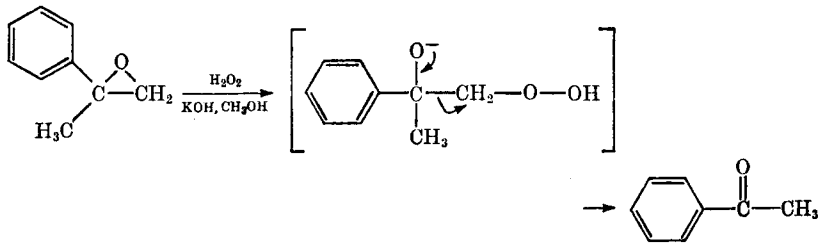


(903)

$R' = R'' = H, CH_3$
$R' = H; R'' = CH_3$

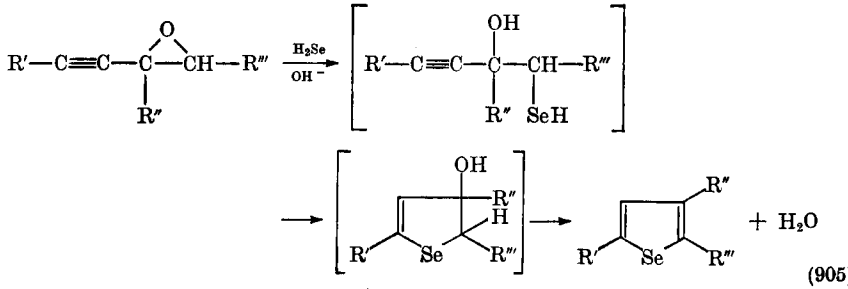
the least-hindered epoxide carbon atom. Again, as with other reactions of epoxides, *tert*-butylhydroperoxide yields in the presence of acids a mixture of peroxides corresponding to attack at both epoxide carbon atoms (Eq. 903).

Similarly, Hoffman[795] recently reported treatment of α-methylstyrene oxide with alkaline hydrogen peroxide to give an almost quantitative yield of acetophenone. It was suggested that attack by OOH^- ion is responsible for this phenomenon, which may be depicted as shown in Eq. (904).



(904)

(3) Hydroselenide ion. The nucleophilicity of the SeH^- ion was utilized advantageously by Perveev and co-workers[1331, 1343] in their synthesis of selenophenes. Appropriate acetylenic epoxide precursors yielded, on treatment with alkaline hydrogen selenide and subsequent acidification, a variety of substituted selenophenes. Intermediate stages in this transformation are presumably β-hydroseleno alcohols and β-hydroxydihydroselenophenes as shown in Eq. (905).



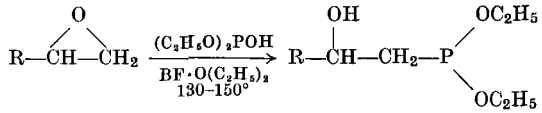
(905)

R′ = CH_3; R″ = C_2H_5; R‴ = H
R′ = R″ = R‴ = CH_3
R′ = C_2H_5; R″ = CH_3; R‴ = H
R′ = C_6H_5; R″ = CH_3, C_2H_5; R‴ = H
R′ = H_2C=CH; R″ = CH_3; R‴ = H, CH_3

This reaction is completely analogous to that involving hydrogen sulfide and leading to the corresponding substituted thiophenes.

(4) Dialkylphosphites. Pudovik and Ivanov[1420] reported in 1952 that ethylene oxide, ethyl glycidyl ether, and cyclohexene oxide

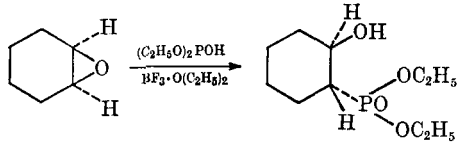
undergo condensation with diethylphosphite in the presence of catalytic amounts of boron trifluoride etherate. The authors considered the products to contain C—P bonds, as shown in Eqs. (906) and (907).



(906)

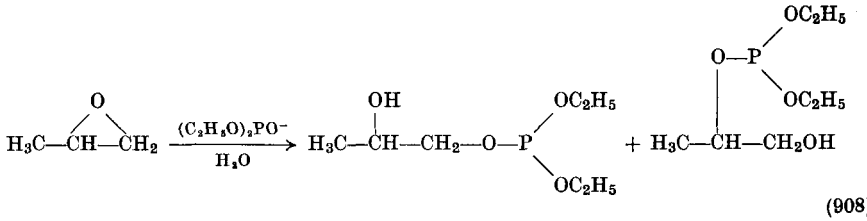
R = H, $C_2H_5OCH_2$

Kreutzkamp,[978] on the other hand, later published a paper stating that epoxides suffer nucleophilic attack by the oxygen rather than the phosphorus atom of dialkylphosphites in basic solution.

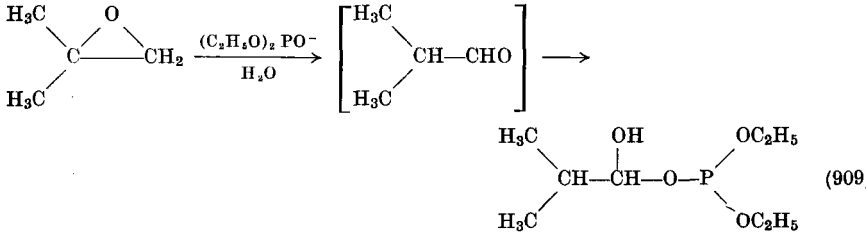


(907)

Unsymmetrical epoxides were said to give rise to mixed products, although experimental details were not included. Eqs. (908) and (909) illustrate the action of diethylphosphite in base on propylene oxide and *iso*butylene oxide. The latter undergoes preliminary isomerization to *iso*butyraldehyde before yielding a conventional carbonyl adduct.



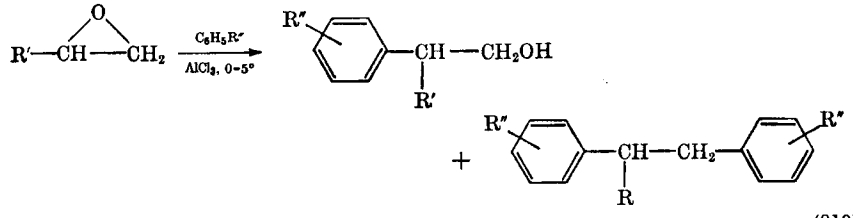
(908)



(909)

(5) Friedel–Crafts reactions. Schaarschmitt and co-workers[1526] published in 1925 a paper describing the use of ethylene oxide as an

alkylating agent under Friedel–Crafts conditions (Eq. 910). In the presence of aluminum chloride and hydrogen chloride the main product was found to be bibenzyl, the hoped-for 2-phenylethanol being produced in trace amounts only. Subsequent investigation by Smith and Natelson[1595] confirmed previous findings, and extended them to include also reactions of ethylene oxide with bromobenzene, and of propylene oxide with benzene. Colonge and Rochas,[329] on the other hand, succeeded in finding reaction conditions favorable for β-arylethanol formation in acceptable yields. The crucial parameters in the condensation appear to be careful temperature control and maintenance of strictly anhydrous conditions. Mixtures of *o*-, *m*-, and *p*-isomers were formed with substituted benzene derivatives. *p*-Chloro-, *p*-bromo-, and *p*-nitrobenzene are reported to fail to condense with ethylene oxide under conditions satisfactory for benzene, toluene, and anisole.[329]



(910)

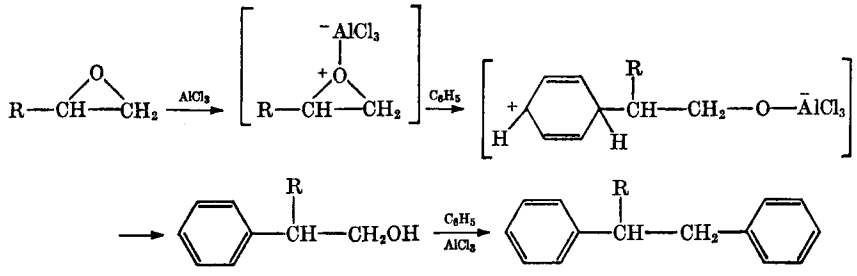
R′ = H; R″ = H, CH_3, C_2H_5, CH_3O, Br
R′ = CH_3; R″ = H

More recent work by Hopff and Koulen[808] further broadened the scope of the reaction by including an assortment of disubstituted benzenes, and also biphenyl and acenaphthene. Somerville and Spoerri,[1603, 1604] moreover, have examined the action of *iso*butylene oxide and 2,3-epoxybutane on benzene in the presence of aluminum chloride. Mixtures of alcohols and hydrocarbons were isolated, as in previous work.

It is likely that β-arylalcohol formation takes place by some sequence as shown in Eq. (910a), further reaction of the alcohol with benzene leading to the observed hydrocarbon.

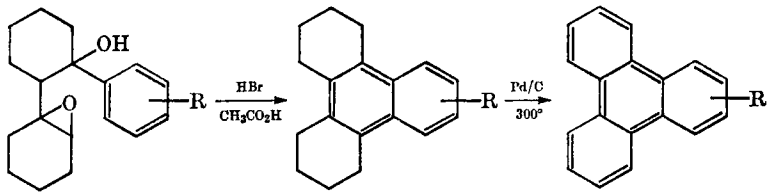
In this respect, the aromatic component of such Friedel–Crafts condensation may be considered to function as a nucleophile, in which π-electrons attack the aluminum chloride-coordinated ethylene oxide ring.

An interesting synthetic illustration of the Friedel–Crafts addition of epoxides to the aromatic nucleus has been provided by Bradsher,[234]



(910a)

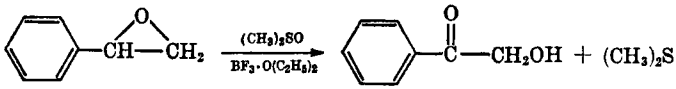
and more recently by Barker and co-workers.[76] This involves intramolecular cyclization of the substances depicted in Eq. (911), followed by catalytic dehydrogenation to the desired polycyclic aromatic products.



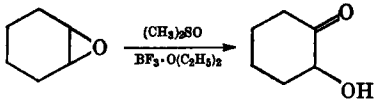
(911)

R = H, *m*-CH_3, *p*-CH_3, *o*-CH_3

(6) Sulfoxides. A recent publication by Cohen and Tsuji[1922] has disclosed a novel transformation involving addition of dimethylsulfoxide to a variety of epoxides in the presence of boron trifluoride etherate as catalyst. Styrene oxide, for example, affords a good yield of α-hydroxyacetophenone (Eq. 912), whereas cyclohexene oxide gives 2-hydroxycyclohexanone (Eq. 913). Dimethylsulfide is evolved concomitantly.



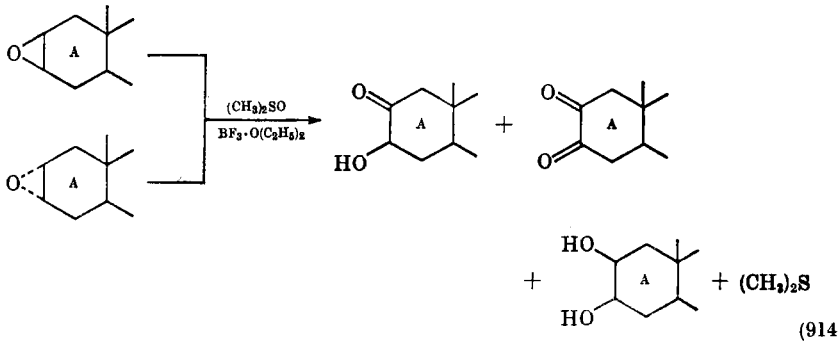
(912)



(913)

That 2α,3α- and 2β,3β-epoxy steroids appear to yield approximately equal amounts of 3β-hydroxy-2-oxo products, together with the

corresponding diols and diones, has been interpreted[1922] to imply a common enol intermediate (Eq. 914). Although the detailed events in this singular oxidation–reduction reaction are not yet understood, it is probable that one stage consists of nucleophilic attack by the oxygen of dimethylsulfoxide on the epoxide ring, facilitated by coordination of the epoxide oxygen with boron trifluoride.

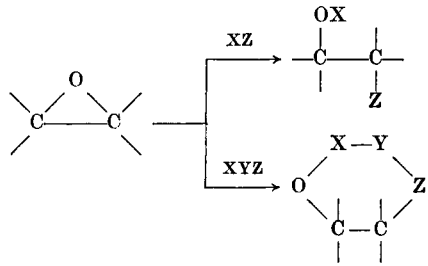


(914)

5. Electrophilic Additions

A significant portion of the epoxide literature deals with reactions which, although ostensibly of widely divergent character, nevertheless do possess the following important property in common: all involve addition to oxygen, as well as to carbon atoms. Products secured from such reactions, in other words, lack free hydroxyl groups, in contrast with those derived from conventional nucleophilic substitutions.[1301] Insofar as the present author is aware, little effort has been made to treat all these epoxide reactions as a unit, and not much is known of their mechanisms.

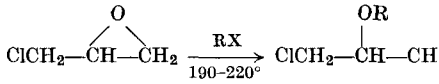
Two types of condensations may be defined, on the basis of the products they yield. The first yields open-chain compounds; the second, cyclic compounds. As shown below, the distinction arises simply out of the nature of the reagents involved. In general, the reactions shown in Eq. (915) may be considered representative of these two types.



(915)

A. Reagents Yielding Open-Chain Products

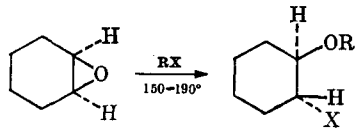
(1) Alkyl halides, acyl halides, anhydrides, and related substances. It was discovered as early as 1861 by Reboul and Lourenco[1440] that epichlorohydrin may be caused to react with ethyl bromide on heating in a sealed tube to an elevated temperature. The product isolated from this condensation was 1-bromo-3-chloro-2-ethoxypropane. Some years later Paal[1284] extended this reaction to include also methyl iodide, ethyl iodide, *n*-propyl iodide, and *iso*propyl iodide (Eq. 916). In each instance an alkyl ether of 1-chloro-3-iodo-2-propanol was formed.



(916)

X = Br; R = C_2H_5
X = I; R = CH_3, C_2H_5, *n*-C_3H_7, *iso*C_3H_7

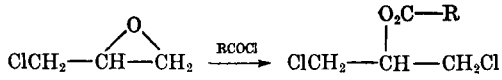
Subsequent work by Bedos[109] demonstrated the reaction to be equally applicable to cyclohexene oxide (Eq. 917), which yielded the corresponding β-haloethers on treatment with methyl, ethyl, or *n*-propyl halides at 150–190°. The stereochemical course of the reaction was of course not explored at the time, but may be supposed to lead to a *trans*-configuration.



(917)

X = Br, I
R = CH_3, C_2H_5, *n*-C_3H_7

Truchot[1767] reported in 1865 that epichlorohydrin (Eq. 918) could likewise be condensed with several acyl chlorides, giving esters of 1,3-dichloro-2-propanol. Bedos[109] later showed that cyclohexene oxide

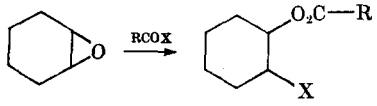


(918)

R = CH_3, *n*-C_3H_7, *n*-C_4H_9, C_6H_5

(Eq. 919) is also attacked by acetyl chloride or bromide, and by propionyl chloride, even at room temperature. Again, stereochemical details were not examined.

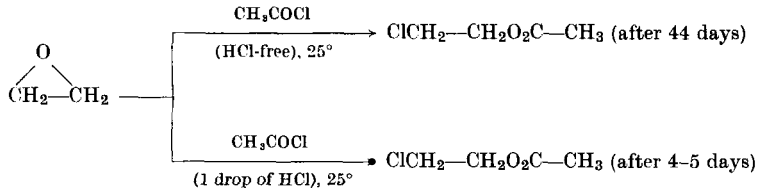
A careful study by Gustus and Stevens,[690] conducted with acetyl chloride scrupulously free of hydrogen chloride and water, showed that



(919)

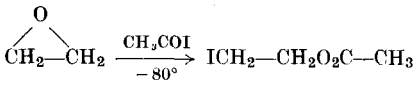
X = Cl; R = CH_3, C_2H_5
X = Br; R = CH_3

the reaction of ethylene oxide itself is exceedingly slow under these conditions, requiring a month or more for completion (Eq. 920). It is possible, therefore, that all previous investigations utilizing acyl halides were in fact dealing with acid-catalyzed reactions. Indeed, it is not unreasonable to suspect the reagents employed by early chemists to have been severely contaminated with carboxylic and halogen acids.



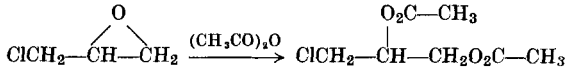
(920)

On the other hand, Gustus and Stevens[690] noted the singular ease with which acetyl iodide condenses with ethylene oxide, even at $-80°$, to give β-iodoethyl acetate (Eq. 921).

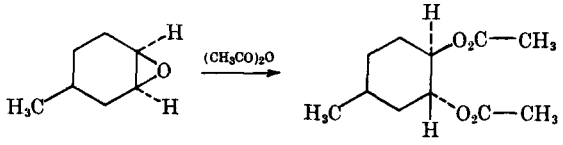


(921)

Acetic anhydride has long been claimed to condense with ethylene oxides (Eqs. 922 and 923), giving thereby diesters of 1,2-diols.[1621, 1767] Whether the reagent was free of acetic acid may be a matter of conjecture, however.

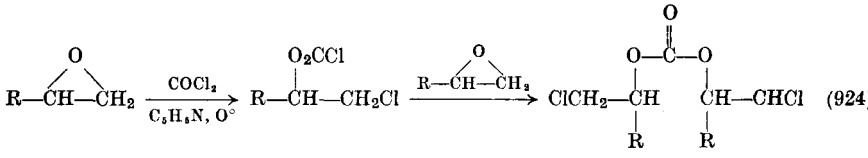


(922)



(923)

Reactions of ethylene oxide, propylene oxide, and epibromohydrin with phosgene (Eq. 924) have been reported recently from two laboratories to give β-chloroacetyl chloroformates.[883, 1096] Excess of

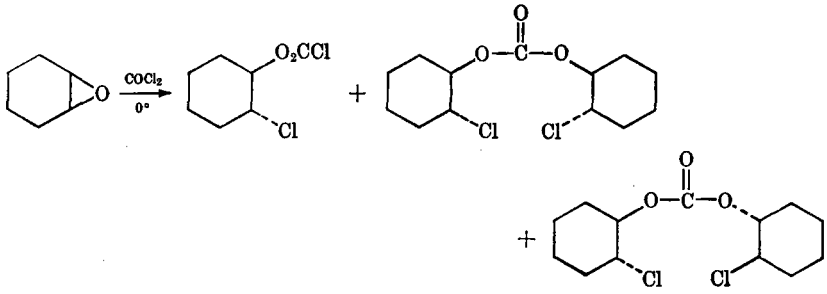


(924)

R = H, CH_3, $ClCH_2$

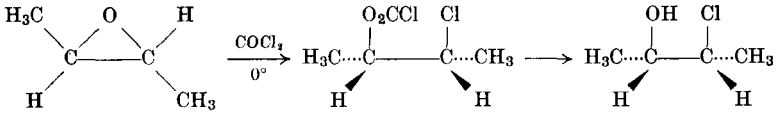
epoxide causes further reaction to take place, giving di-(β-chloroalkyl) carbonates. The presence of a trace of pyridine exerts a catalytic effect, but is not essential.

Stereochemical specificity was demonstrated with cyclohexene oxide (Eq. 925), which opens with Walden inversion to give *trans*-2-



(925)

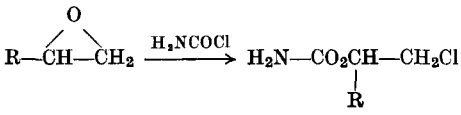
chlorocyclohexyl chloroformate, accompanied by two isomeric carbonates.[883, 1096] Similarly, *trans*-2,3-epoxybutane (Eq. 926) give *erythro*-3-chloro-2-propanol on hydrolysis of the initially-formed ester.



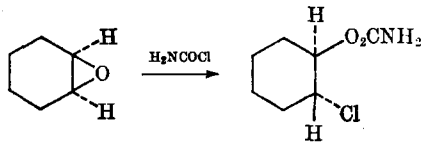
(926)

A related condensation is that of chloroformamide with epoxides, reported recently by Boberg and Schultze[178] to give urethans with ethylene oxide, epichlorohydrin, and cyclohexene oxide (Eqs. 927 and 928).

A patent disclosure by Pechukas[1321] describes the condensation of methyl chlorocarbonate in pyridine at 85° with ethylene oxide and propylene oxide, epichlorohydrin, and styrene oxide. Products formed

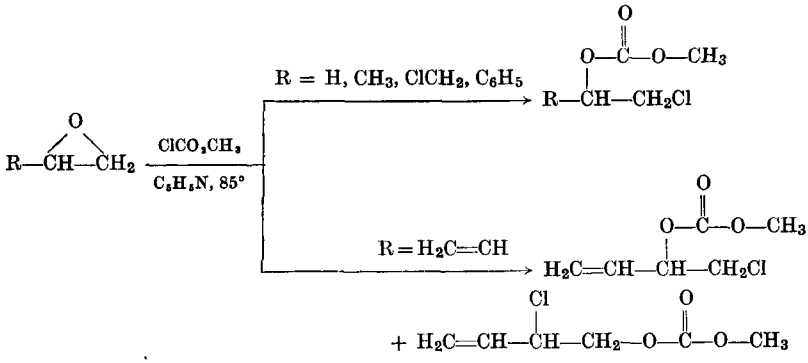


(927)



(928)

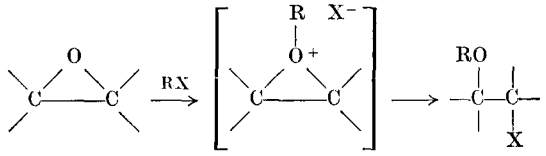
in this manner are methyl β-chloroalkyl carbonates. 1,2-Epoxy-3-butene is reported to give a mixture of isomeric carbonates (Eq. 929).



(929)

(929)

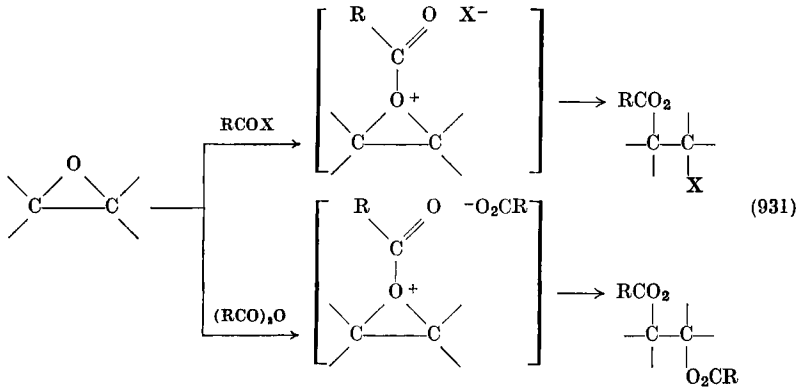
The detailed mechanism of these condensations is at present a matter of speculation, but it is attractive to imagine the involvement of oxonium-type intermediates, in which transient alkyl or acyl cations



(930)

are functioning as protons. According to this view, condensation of an ethylene oxide with an alkyl halide would be pictured as shown in Eq. (930).

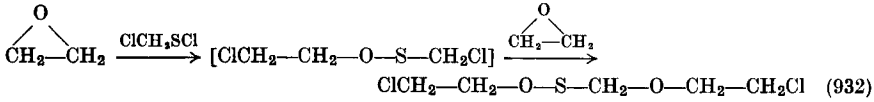
Similarly, addition of an acyl halide or an anhydride could be depicted as shown in Eq. (931).



(931)

Analogous mechanisms could be envisaged for the additions of phosgene, chloroformamide, and methyl chlorocarbonate to epoxides.

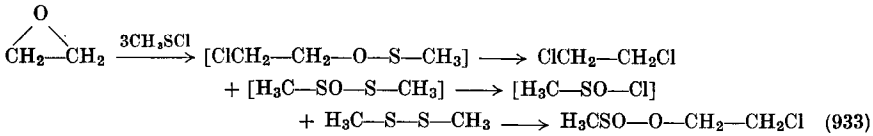
(2) Sulfenyl chlorides. Brintzinger and co-workers[246] have reported the condensation of chloromethylsulfenyl chloride with 2 molar equivalents of ethylene oxide to give the product shown in Eq. (932).



(932)

Subsequent publications have described two other aliphatic sulfenyl chlorides, namely methylsulfenyl chloride[463] and trichloromethylsulfenyl chloride.[994]

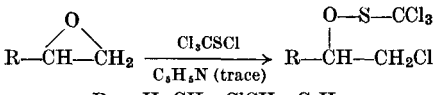
Douglas and Douville[463] observed the formation of three products on treating ethylene oxide with 3 molar equivalents of methylsulfenyl chloride, as shown in Eq. (933).



(933)

Langford and Kharash[994] noted the ready reaction of trichloromethylsulfenyl chloride with ethylene oxide in the presence of a trace of pyridine. Other epoxides examined in the same connexion included

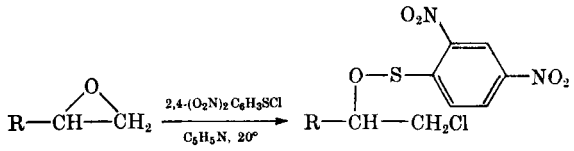
propylene oxide, epichlorohydrin, cyclohexene oxide, styrene oxide, and *meso*-1,2;3,4-diepoxybutane (Eq. 934).



(934)

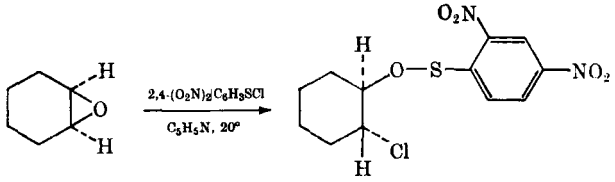
R = H, CH_3, $ClCH_2$, C_6H_5

Peters and Kharash had previously described the reaction of 2,4-dinitrophenylsulfenyl chloride with ethylene oxide in pyridine.[1351] Although propylene oxide, styrene oxide, and cyclohexene oxide likewise underwent addition (Eqs. 935 and 936), *cis*- and *trans*-stilbene oxide were inert under the same conditions.[1351]



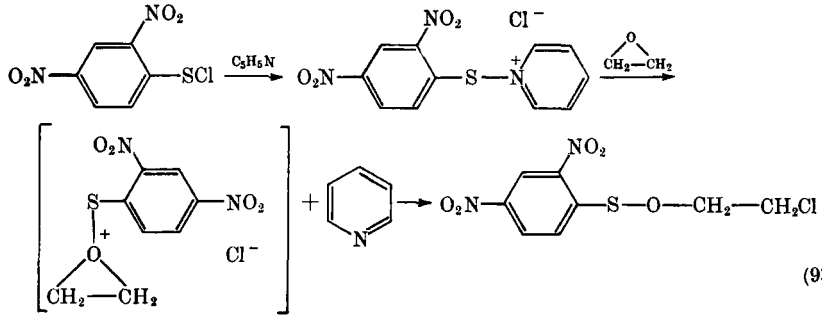
(935)

R = CH_3, C_6H_5



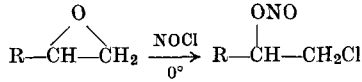
(936)

It is clear from existing evidence that this reagent suffers S—Cl bond rupture, and may consequently be regarded as an analog of hydrogen chloride in which the place of the proton has been taken by a 2,4-dinitrophenylsulfenyl cation. The fact that pyridine is a required catalyst suggests that its function is to assist dissociation of the reagent, perhaps by the process depicted in Eq. (937).



(937)

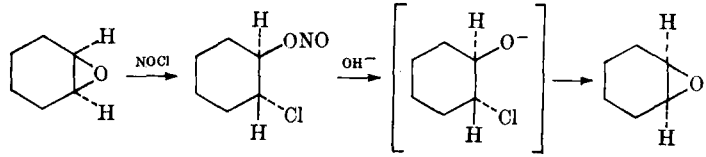
(3) Nitrosyl chloride and dinitrogen tetroxide. Malinovskii and co-workers[1095] published in 1953 an interesting study of the addition of nitrosyl chloride to several epoxides to give β-chloroalkyl nitrites (Eq. 938).



(938)

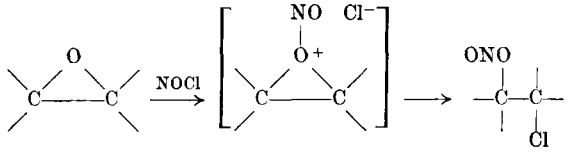
R = H, CH_3, $ClCH_2$

The stereochemically specific character of this condensation is evident from the fact that cyclohexene oxide yields *trans*-2-chloro-1-cyclohexyl nitrite (Eq. 939), which on treatment with alkali regenerates cyclohexene oxide.[1095]



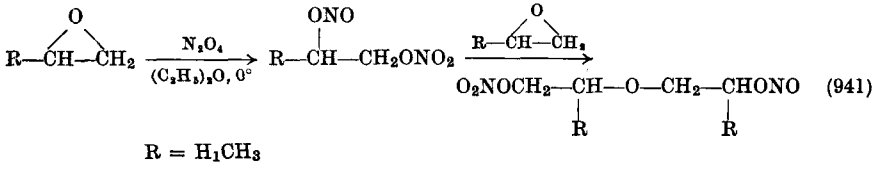
(939)

Although the above authors did not advance a detailed mechanism, it appears probable that nitrosyl cation can in effect function as a proton, forming an oxonium-type intermediate (Eq. 940). Attack by Cl^- ion is thereby facilitated and occurs with Walden inversion, as in the cleavage of epoxides with hydrogen chloride itself.



(940)

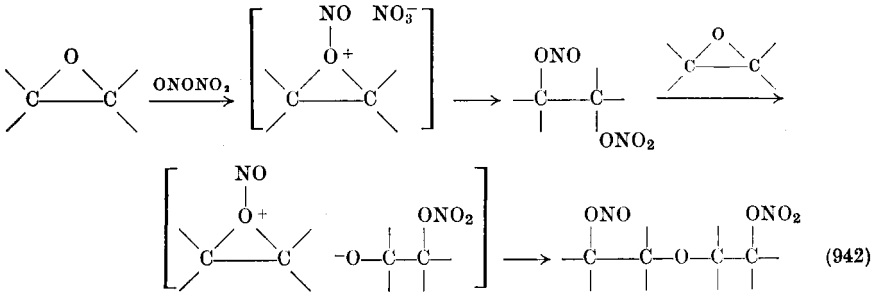
Dinitrogen tetroxide, the dimer of nitrogen dioxide, has been found to add smoothly to ethylene oxide and propylene oxide (Eq. 941), thereby giving β-nitratoalkyl nitrites,[1421, 1422, 1492] and not β-nitroalkyl nitrites as proposed previously by Darzens.[415]



(941)

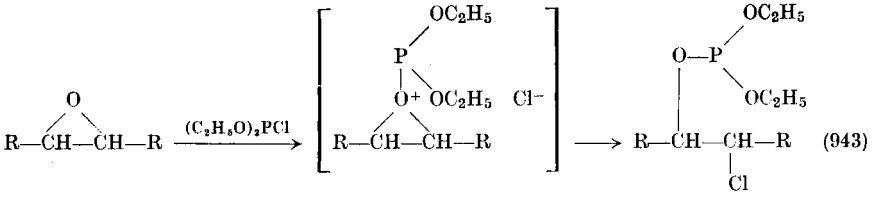
R = H, CH_3

It appears that dinitrogen tetroxide functions as nitrosyl nitrate, in analogy with nitrosyl chloride, forming an oxonium-type intermediate (Eq. 942). Attack by nitrate ion upon the latter gives rise to the observed product, which in turn reacts further by the same process.



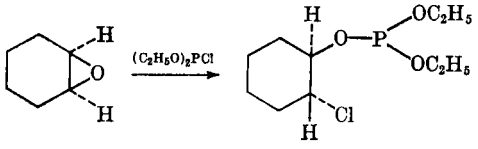
(942)

(4) **Dialkoxychloro- and alkyldichlorophosphines.** It was reported in 1952 by Pudovik and Ivanov[1420] that diethoxychlorophosphine condenses with ethylene oxide and 2,3-epoxybutane (Eq. 943). Since a new O—P bond is formed during this reaction it is plausible that an oxonium-type complex constitutes an intermediate state in the process.



(943)

R = H, CH_3

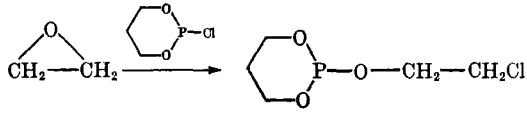


(944)

Insight into the stereochemical aspects of the addition may be derived from the reaction of cyclohexene oxide (Eq. 944), which yields a *trans* adduct.[1420]

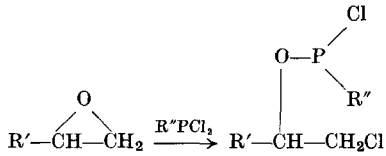
Trimethylenedioxychlorophosphine was found to condense in a

similar fashion with ethylene oxide,[1420] yielding the trialkylphosphite derivative shown in Eq. (945).



(945)

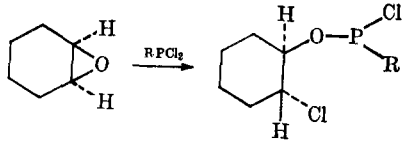
A related reaction is that recently described by Ivin and Karavanov,[865] involving alkyldichlorophosphines and epoxides (Eq. 946). Although the direction and stereochemistry of ring opening were not specified, they are in all probability analogous to those of cleavage with diethoxychlorophosphine.[142] The same reactions have also been investigated by Gefter,[2035] and by Kamai and Tsivuni.[2036]



$R' = H, CH_3$
$R'' = CH_3, C_2H_5, C_6H_5$

(946)

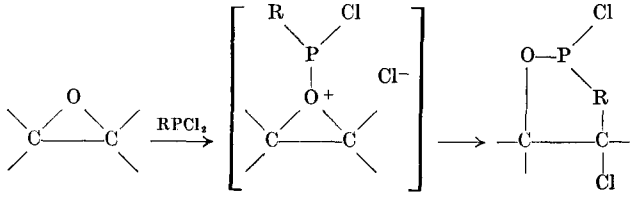
Cyclohexene oxide presumably gives a *trans* adduct as formulated in Eq. (947) on treatment with methyldichloro- and ethyldichlorophosphine.[865]



$R = CH_3, C_2H_5$

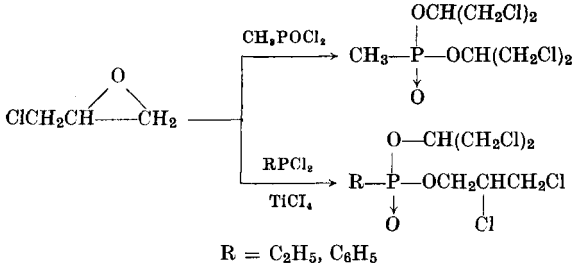
(947)

If an oxonium-type intermediate participates in the additions of alkyldichlorophosphines to epoxides as proposed, it may be pictured as in Eq. (948).



(948)

A different mode of addition was discovered by Rizpolozhenskii and Muslinkin,[2037] however, with epichlorohydrin and ethyl or phenyl dichlorophosphine in the presence of catalytic amounts of titanium tetrachloride, which gave the unexpected product shown in Eq. (948a). The same authors[2037] also investigated the reaction of epichlorohydrin with methyl dichlorophosphine oxide (Eq. 948a).

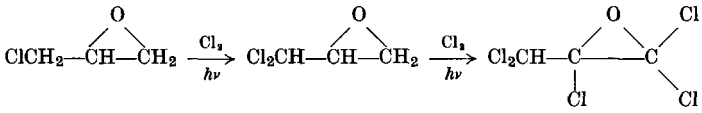


(948a)

R = C_2H_5, C_6H_5

(5) Halogens and halogenating agents. Addition of halogens to ethylene oxides has been reported on a number of occasions, but little is known of the scope or mechanism of this reaction, as it is of no synthetic importance.

Chlorination of propylene oxide and epichlorohydrin has been conducted in the presence of sunlight or a suitable substitute, but the course of the reactions remains obscure. Propylene oxide is reported to give a complex mixture of products, two of which are 1,3-dichloro-2-propanol and chloroacetone.[459] Epichlorohydrin (Eq. 949) appears to form 1,1-dichloro-2,3-epoxypropane initially, and then to react further, giving finally 1,1,2,3,3-pentachloro-2,3-epoxypropane.[320]



(949)

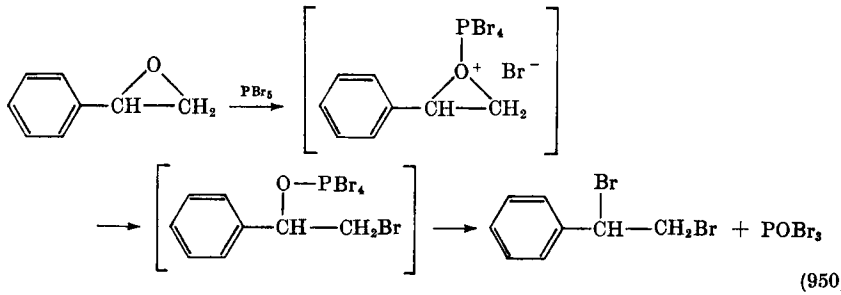
Phosphorus pentachloride too has received some attention as a halogenating agent with such epoxides as ethylene oxide,[1885] 1,2-epoxy-2-methylbutane,[1562] and 2,3-epoxyhexane.[748] The nature of products formed in these reactions is not known with certainty, however.

Maas and Boomer[1081] have studied the formation of oxonium complexes between ethylene oxide and chlorine at −80°. Freezing-point results led them to conclude that two complexes are produced, which were formulated as $C_2H_4O \cdot Cl$ and $C_2H_4O \cdot 3Cl$. Detailed structures for these unstable complexes were not, however, put forward. A

violent explosion ensued on allowing a 30% mixture of chlorine and ethylene oxide to come from $-80°$ to room temperature.

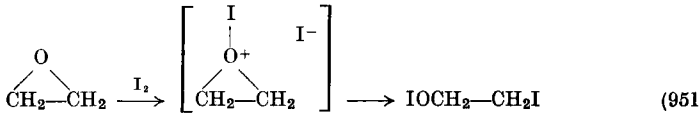
Bromination of ethylene oxide was reported as early as 1862 by Wurtz[1887] to give a red solid of unknown constitution. Maas and Boomer[1081] obtained the same red solid on warming to room temperature oxonium complexes of ethylene oxide and bromine prepared at $-80°$. Freezing-point results indicated for these complexes the empirical formulas $C_2H_4O \cdot Br$ and $C_2H_4O \cdot 2Br$. No explosion occurs on warming to room temperature, however.

Tiffeneau and Fourneau[691] obtained 1,2-dibromo-1-phenylethane on treatment of styrene oxide with phosphorus pentabromide. This transformation could be imagined to proceed by way of oxonium complex formation, followed by Br^- ion attack as shown in Eq. (950).



(950)

It may be mentioned, finally, that Gustus and Stevens[690] have reported an ill-fated attempt to condense ethylene oxide, acetyl chloride, and iodine. On warming from $-80°$ to room temperature a violent detonation occurred, attributed by these authors to formation

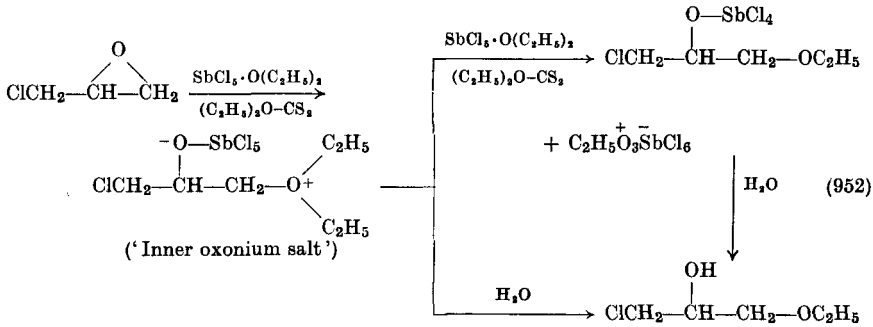


(951)

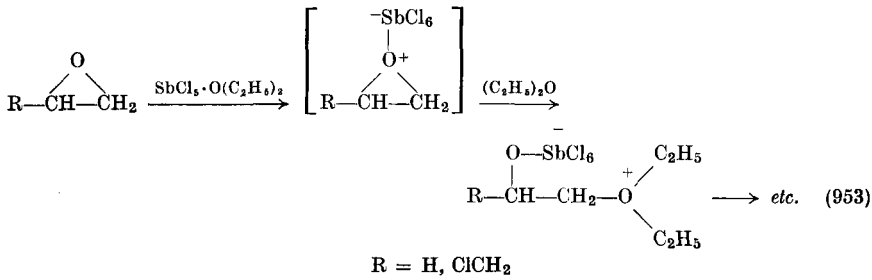
of β-iodoethyl hypoiodite (Eq. 951). This substance could be envisaged to arise out of an oxonium complex, acetyl chloride perhaps playing an as yet undefined accessory role as well.

(6) Metallic halide salts. The present state of knowledge concerning reactions of epoxides with metallic halide salts is due in large measure to the work of Meerwein and co-workers[1138, 1141] in the field of oxonium compounds.

When epichlorohydrin was added to excess of antimony pentachloride etherate in cold ethereal carbon disulfide, heat evolution occurred and a precipitate of triethyloxonium hexachloroantimonate was formed.[1138, 1141] After removal of this salt, the organic filtrate was found to contain a tetrachloroantimony derivative of 1-chloro-3-ethoxy-2-propanol. When excess of epichlorohydrin was used, however, there precipitated from solution not triethyloxonium hexachloroantimonate, but an 'inner oxonium salt'. This, on treatment with more antimony pentachloride etherate, gave rise to the same tetrachloroantimony derivative, hydrolysis of which gave 1-chloro-3-ethoxy-2-propanol. These various transformations are depicted in the accompanying scheme (Eq. 952). A completely analogous sequence of reactions was carried out, incidentally, with ethylene oxide itself.[1138,1141]



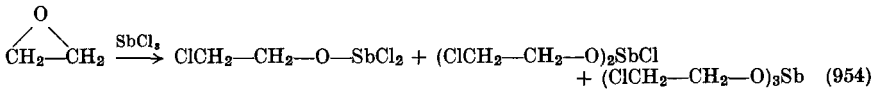
Formation of the 'inner oxonium salt' may be preceded by an intermediate oxonium state (Eq. 953) of the type considered above. Cleavage of the oxonium ring is then accomplished by nucleophilic



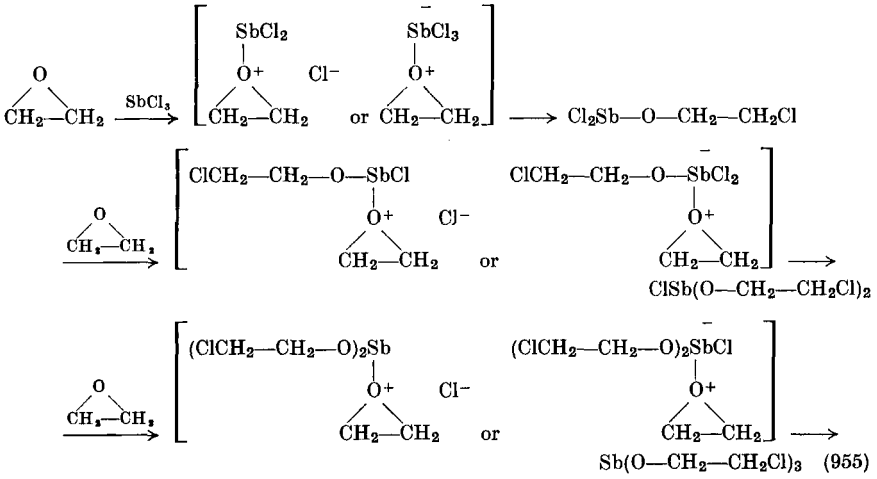
attack of diethyl ether on the terminal epoxide carbon atom. This process remains speculative at present, however.

Malinovskii and Romantsevich[1100] have examined the action of antimony trichloride on ethylene oxide at room temperature. Three

products could be isolated (Eq. 954), their relative proportions depending on the excess of ethylene oxide utilized. Thermal decomposition of the adducts gives ethylene chlorohydrin.

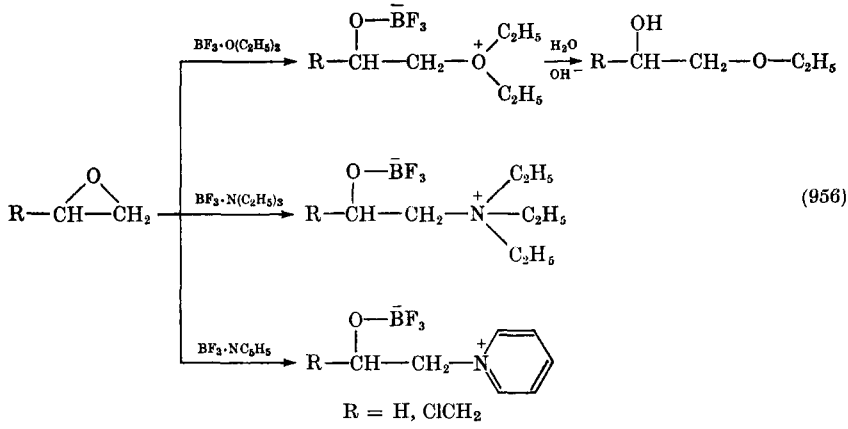


The course of this reaction can be imagined to consist of the three stages depicted in Eq. (955), where the exact nature of the intermediates is as yet uncertain.



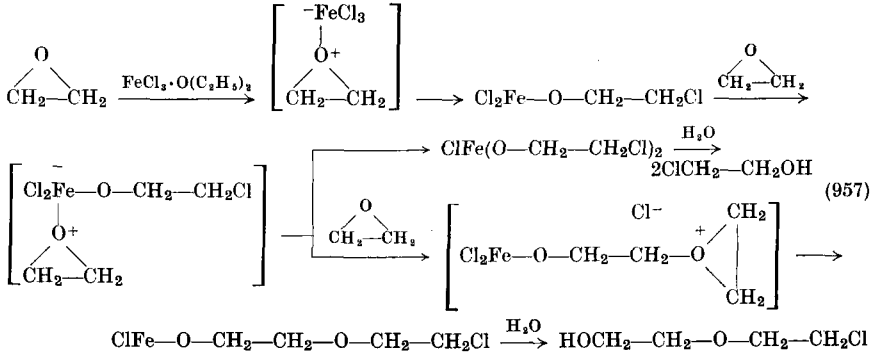
Meerwein and co-workers[1138, 1141] have also studied the addition of diethyl ether, pyridine, and triethylamine complexes of boron trifluoride to epichlorohydrin and ethylene oxide. Once more, 'inner oxonium salts' were isolable from the reactions, and could be purified and characterized by further transformations.

Similarly, Meerwein and co-workers[1138, 1141] investigated the action of ferric chloride etherate on ethylene oxide and epichlorohydrin, and Borkovec[217] has recently done likewise for ethylene oxide and propylene oxide in a study of 'internal polymerization'. Ethylene oxide reacts very rapidly, and it is not possible to isolate intermediate stages leading to the ultimate products. Hydrolysis of the latter yields ethylene chlorohydrin and also ethylene glycol mono-(β-chloroethyl) ether, in contrast with the situation existing with adducts from antimony pentachloride for example. It is this distinction which led to



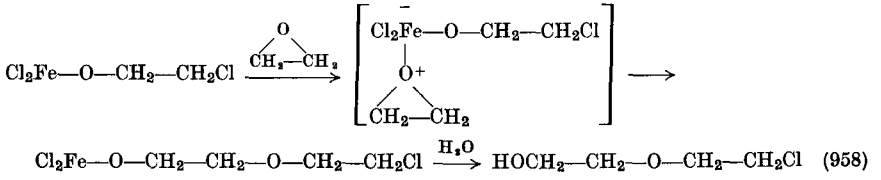
(956)

formulation of the 'internal polymerization' concept. depicted in Eq. (957) for ethylene oxide. Propylene oxide behaves similarly, but reacts more sluggishly.[217]



(957)

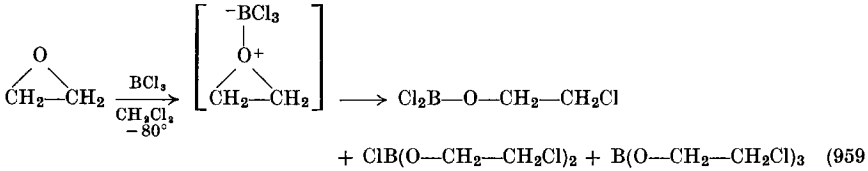
An alternative approach, similar to one advanced in a later paper by Robinson,[1479] would involve migration of a β-chloroethoxide ion as shown in Eq. (958).



(958)

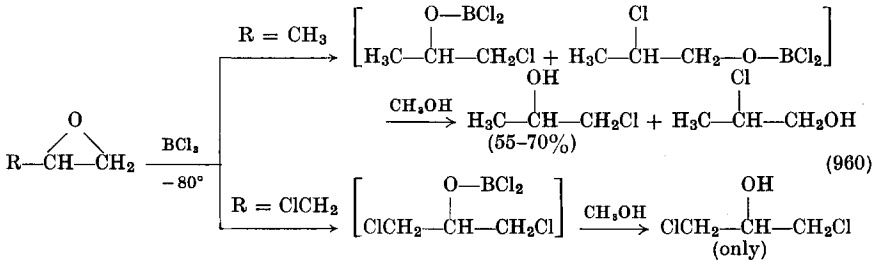
The action of boron trichloride has been examined with several epoxides. Grimley and Holliday[671] claimed to have isolated the oxonium complex of ethylene oxide and boron trichloride by allowing them

to react at $-78.5°$ in the absence of solvent. There was formed, in addition, a non-volatile product whose composition suggested the combination of 2 molar equivalents of ethylene oxide with 1 of boron trichloride. Edwards and co-workers,[481] however, later obtained conflicting results on addition of boron trichloride to ethylene oxide at $-80°$ in methylene chloride. No oxonium complex could be isolated under these conditions, but only open-chain products, as shown in Eq. (959). Methanolysis of the latter gave ethylene chlorohydrin.



$$+ \mathrm{ClB(O{-}CH_2{-}CH_2Cl)_2} + \mathrm{B(O{-}CH_2{-}CH_2Cl)_3} \quad (959)$$

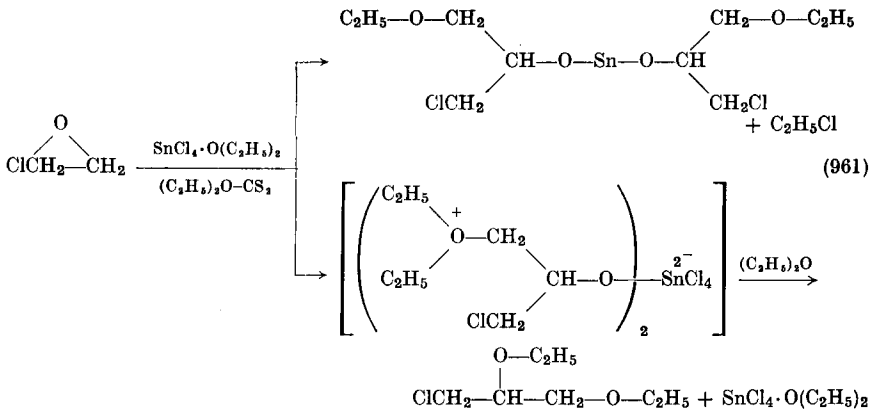
Propylene oxide was found to react at each of its terminals, yielding a mixture of isomeric chlorohydrins on methanolysis of the boron-containing adducts.[482] On the other hand, epichlorohydrin gave only 1,3-dichloro-2-propanol on similar treatment, indicating exclusive attack on the terminal epoxide carbon atom (Eq. 960).



(960)

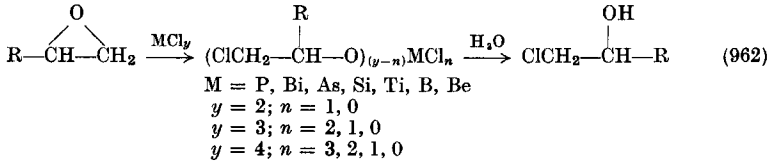
The reaction of epichlorohydrin with stannic chloride etherate produced unexpected results, according to Meerwein and co-workers,[1138, 1141] in that it follows the course outlined in Eq. (961). Worsfold and Eastham[1880] have also recently reported similar observations.

A number of other metallic halide salts have been found to condense with ethylene oxide, propylene oxide, or epichlorohydrin in a similar fashion (Eq. 962). Among them are phosphorus trichloride,[1577, 2037] bismuth trichloride,[1880] arsenic trichloride,[1090] silicon tetrachloride,[1304] titanium tetrachloride,[1509, 1577] beryllium chloride,[1138] and boron trifluoride.[482] Depending on their reactivity, on the reactant ratio, and



(961)

on the temperature, these salts can give varying proportions of mono-, di-, and tri-(β-chloroalkoxy) derivatives. Hydrolysis of the adducts yields β-chloroalcohols.

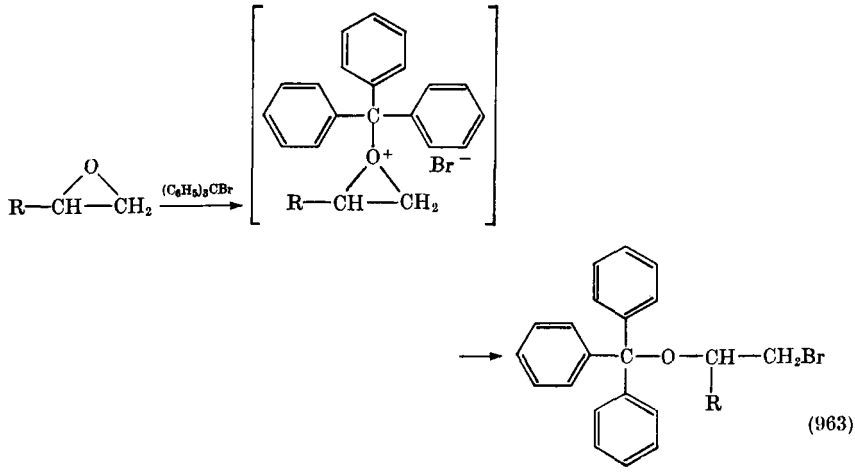


(962)

(7) Miscellaneous reagents. Jensen and co-workers[877] have developed a useful procedure for epoxide cleavage, applicable also to the opening of other cyclic ethers. Addition of triphenylmethyl bromide ('trityl' bromide) to ethylene oxide or propylene oxide, as well as cyclohexene oxide or styrene oxide, yields the corresponding β-chloroalkyl trityl ethers (Eq. 963). Oxonium ions may constitute intermediate stages in this reaction, in harmony with the general tenor of this section.

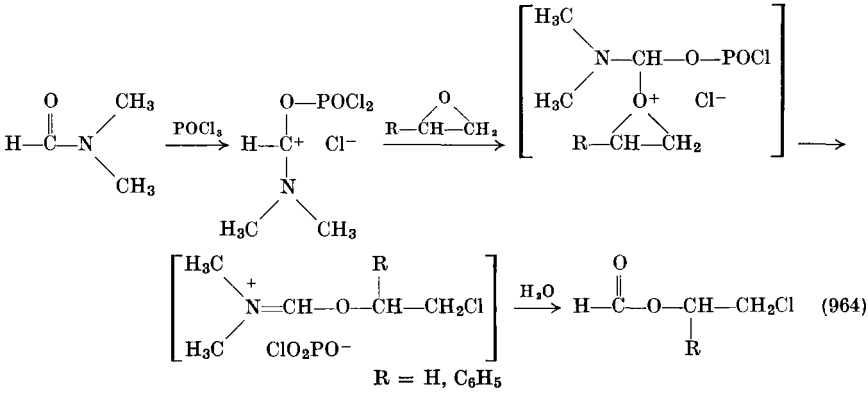
Addition of the Vilsmeier reagent (phosphorus oxychloride plus dimethylformamide) to ethylene oxide, cyclohexene oxide, and styrene oxide has been reported by Ziegenbein and Franke[1909] to give β-chloroalkyl formate esters in good yield (Eq. 964). It may be assumed that oxonium intermediates participate in this type of ring-opening as well.

Dermer and Durr[441] published in 1954 an interesting paper describing the reaction between ethylene oxide and formaldehyde dimethylacetal in the presence of catalytic amounts of boron trifluoride etherate. There were isolated two open-chain compounds, in addition



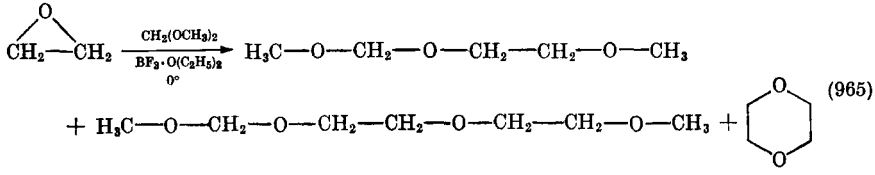
(963)

R = H, CH_3, C_6H_5



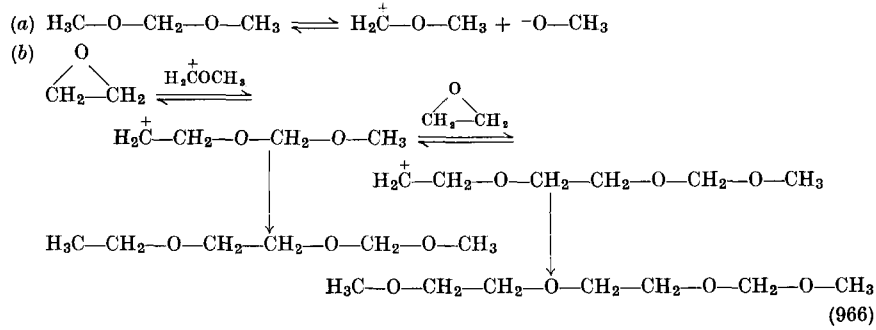
(964)

to 1,4-dioxan formed by ethylene oxide dimerization (see below) and polymers. Acid degradation permitted formulation of these products as mixed acetals of formaldehyde, as shown in Eq. (965). The relative proportions of ethylene oxide and formaldehyde dimethylacetal determined the composition of the product mixture.



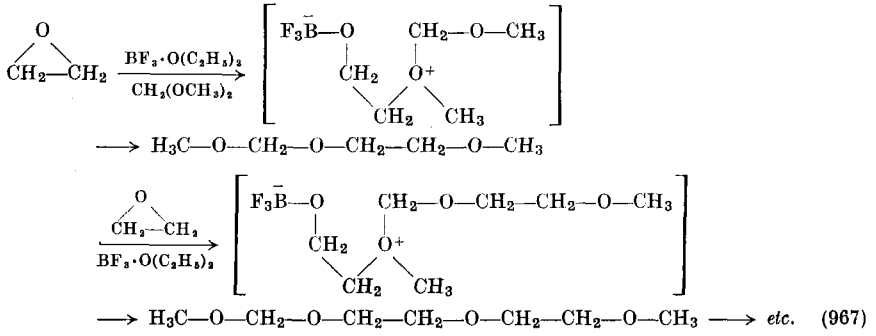
(965)

The authors presented no detailed discussion of the possible course of this reaction, beyond proposing a carbonium ion mechanism of the type shown in Eq. (966) without precisely defining the role of the catalyst.



(966)

If one is disinclined to accept the existence of methoxymethyl carbonium ions, a more attractive picture might involve formation of an 'inner oxonium salt' of the Meerwein type, followed by internal bond redistribution, as shown in Eq. (967).



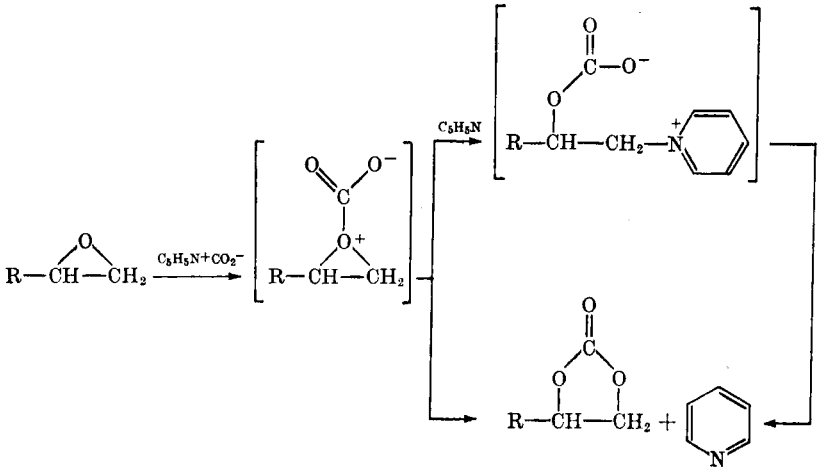
(967)

B. Reagents Yielding Cyclic Products

(1) Carbon dioxide. The patent literature contains a number of disclosures describing addition of carbon dioxide to ethylene or propylene oxide for the preparation of cyclic carbonate esters.[319, 1030, 1168, 1169]

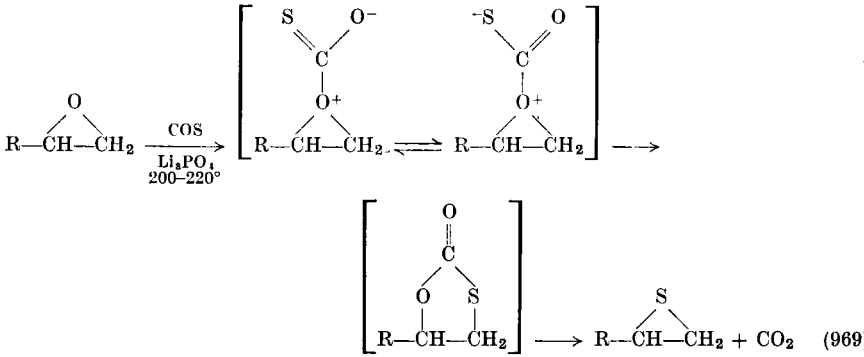
One such process utilizes catalytic amounts of anhydrous calcium bromide, magnesium bromide, or tetraethylammonium bromide at 180–210°,[1030, 1168, 1169] whereas the other employs pyridine, trimethylamine, or other tertiary nitrogenous bases.[319] Although detailed

mechanisms have not been published, it may be supposed that oxonium ions are involved, possibly in some fashion as shown in Eq. (968).



(968)

A recent publication by Durden and co-workers[1927] describes the lithium phosphate-catalyzed addition of carbon oxysulfide to ethylene oxide, propylene oxide, and cyclohexene oxide. Although final products

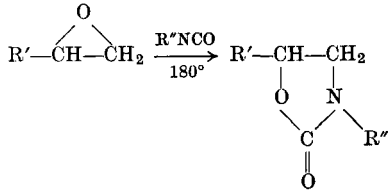


(969)

isolated under the conditions developed by these authors are episulfides (Eq. 969), it may be assumed that cyclic thiocarbonate intermediates precede them during the reaction.

(2) Isocyanates. It has been reported recently from three laboratories[676, 1618, 1953] that ethylene oxide and styrene oxide condense with certain organic isocyanates, among them cyclohexyl,

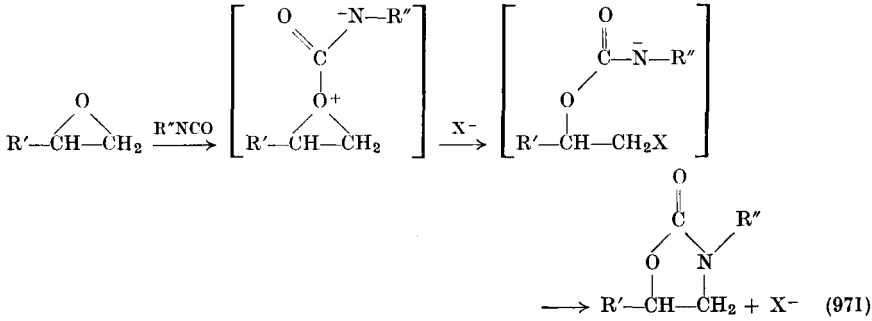
phenyl, and benzyl isocyanate. Products thereby formed have been formulated as derivatives of 2-oxazolidone (Eq. 970). The presence of benzyldimethylamine, tetramethylammonium bromide, potassium iodide, or lithium chloride exerts a marked catalytic influence on the reaction.



(970)

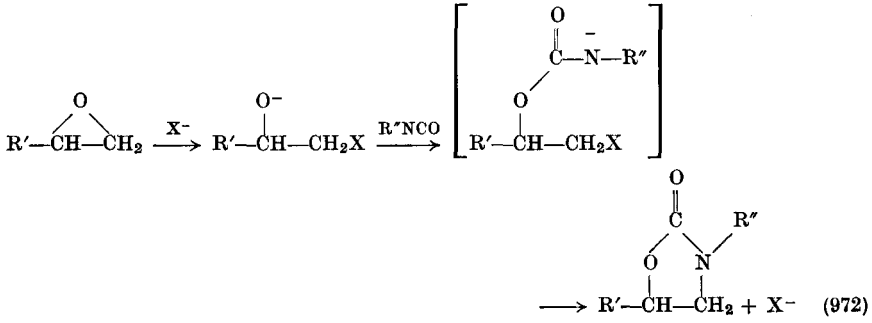
$R' = H, C_6H_5OCH_2$; $R'' = C_6H_5$
$R' = C_6H_5$; $R'' = cyclo C_6H_{11}, C_6H_5CH_2$

An oxonium intermediate may be involved here, in a manner directly analogous to the reaction wherein carbon dioxide takes the place of the isocyanate component (Eq. 971).



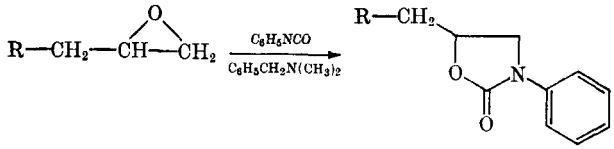
(971)

An alternative explanation,[1618] is that halide ion opens the epoxide ring, and that the resultant β-chloroalkoxide ion attacks the carbon atom of the isocyanate function, as shown in Eq. (972).



(972)

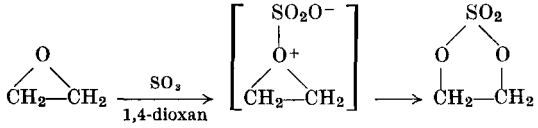
Condensation of phenyl isocyanate has also been reported recently[1953] to occur with phenyl glycidyl ether and 1,2-epoxy-3-phenylbutane in the presence of catalytic amounts of benzyldimethylamine (Eq. 973).



(973)

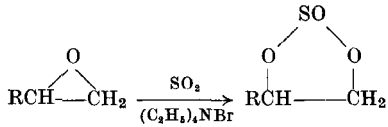
R = C_6H_5O, C_6H_5

(3) Oxides of sulfur. Ham[706] has recently disclosed a method for preparing ethylene glycol sulfate in modest yield by the addition of sulfur trioxide to ethylene oxide in dioxan solution. The course of this condensation presumably involves, likewise, an oxonium complex (Eq. 974).



(974)

The analogous reaction with sulfur dioxide has also been reported by Razuvaev and co-workers,[2038] using ethylene oxide, propylene oxide, epichlorohydrin, and glycidol, and triethylammonium bromide or other salts as catalysts (Eq. 974a).

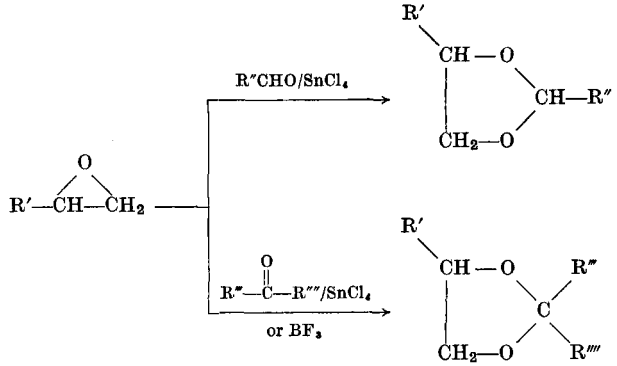


(974a)

R = H, CH_3, $ClCH_2$, $HOCH_2$

(4) Aldehydes and ketones. The usefulness of ethylene oxide, propylene oxide, and epichlorohydrin in preparing cyclic acetals and ketals from aldehydes and ketones respectively has been known for some time. Bogert and Roblin,[206] for instance, condensed ethylene oxide and propylene oxide with *n*-heptaldehyde, benzaldehyde, 2-octanone, and acetophenone respectively in the presence of stannic chloride (Eq. 975). In the same manner, Bersin and Willfang[149, 1845] utilized epichlorohydrin to obtain acetals and ketals from acetaldehyde, crotonaldehyde, chloral, benzophenone, 3-pentanone, cyclopentadecanone, camphor, and other carbonyl compounds. The use of boron

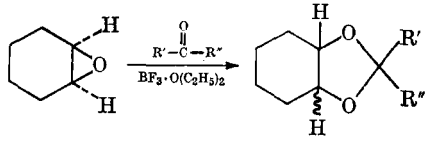
trifluoride etherate in the condensation of acetone with an assortment of ethylene oxides (Eq. 975) was recently explored further by Ponomarev.[1391]



(975)

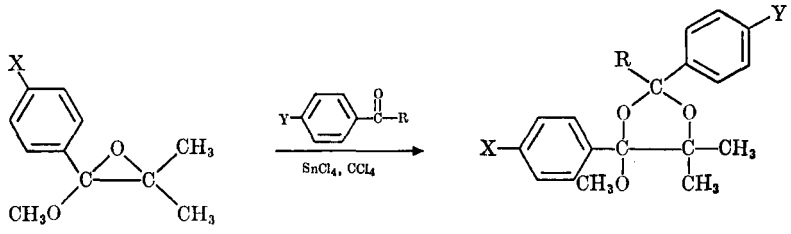
R′ = H, CH_3, $ClCH_2$, $HOCH_2$, $H_2C{=}CH$, C_6H_5, CH_3OCH_2; R″ = CH_3, n-C_3H_7, n-C_4H_9, n-C_7H_{15}, n-C_8H_{17}, n-$C_{10}H_{21}$, n-$C_{12}H_{25}$, $CH_3CH{=}CH$, Cl_3C, C_6H_5; R‴ = R⁗ = CH_3, C_2H_5, C_6H_5 or R‴ = CH_3; R⁗ = n-C_6H_{13}, C_6H_5

Petrov[1355] prepared cyclic ketals from cyclohexene oxide (Eq. 976), but the stereochemistry of ring fusion was unfortunately not elucidated. Oxonium-type intermediates are probably involved in these reactions, although their exact nature has not been established.



(976)

The condensation of benzaldehyde, p-methoxybenzaldehyde, p-nitrobenzaldehyde, and benzophenone with 1,2-epoxy-1-methoxy-1-phenyl-2-methylpropane in the presence of stannic chloride (Eq. 976a)

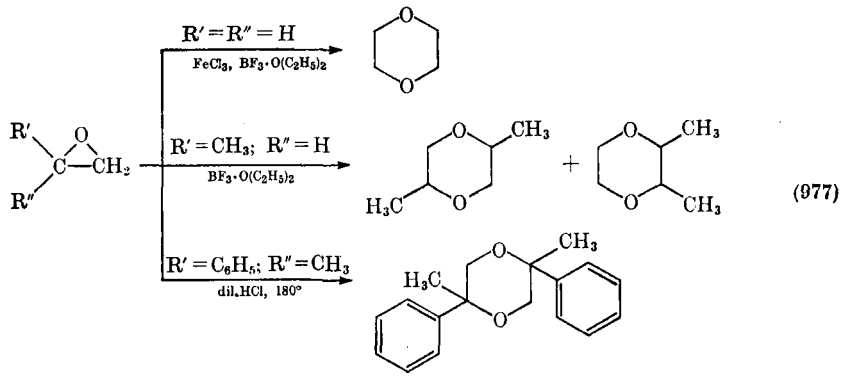


(976a)

X = H; R = H; Y = H, CH_3O, NO_2
X = Cl; R = H, C_6H_5; Y = H
X = Y = CH_3O

has also recently been described.[2039] Other epoxyethers examined in this study were 1,2-epoxy-1-methoxy-1-(*p*-chlorophenyl)- and 1,2-epoxy-1-methoxy-1-(*p*-methoxyphenyl)-2-methylpropane. Although these epoxides all produced cyclic adducts with benzaldehyde, 1,2-epoxy-1-methoxy-1-phenylpropane, in which a methyl substituent is lacking, gave no isolable product.

(5) **Ethylene oxides.** It was demonstrated as early as 1907 by Favorskii[521] that ethylene oxide undergoes dimerization on treatment with zinc chloride or concentrated sulfuric acid, yielding 1,4-dioxan (Eq. 977). This product was also obtained in appreciable quantities

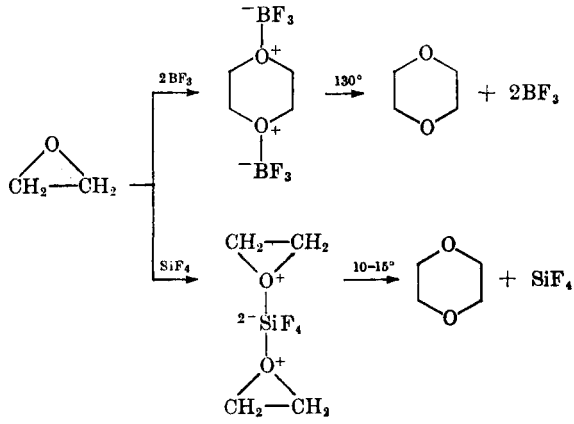


(977)

during the reaction of ethylene oxide with ferric chloride,[217] and also by depolymerization of the initial adduct secured on treatment of boron trifluoride with excess of ethylene oxide at $-80°$.[1656] Since acetaldehyde would give 2-methyl-1,3-dioxolane on condensation with ethylene oxide (see above), this particular reaction path is evidently not involved here. That isomerization to an aldehyde can occur, however, was indicated by the observation of Cohen and co-workers[322] that α-methylstyrene oxide produces 2,5-dimethyl-2,5-diphenyl-1,4-dioxan and 2-phenylpropionaldehyde on heating with dilute hydrochloric acid (Eq. 977). Dermer and Durr,[441] during an investigation cited above, noted formation of 2,5-dimethyl- and 2,3-dimethyl-1,4-dioxan on treating propylene oxide with boron trifluoride etherate.

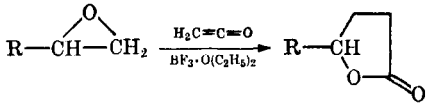
Schmeisser and Jenkner[1541] noted that 1,4-dioxan formation can involve participation by one of two isolable intermediate oxonium complexes. The first is a fairly stable bisoxonium complex of 1,4-dioxan itself, whereas the second appears to be a very labile bisoxonium

complex containing intact ethylene oxide (Eq. 978). Whether the second type passes through the first in yielding 1,4-dioxan has not, however, been established.



(978)

(6) Ketenes. Brief mention may be made, finally, of a recent report published by Oda and co-workers[1945] concerning the addition of ketene to various ethylene oxides in the presence of boron trifluoride



(979)

R = H, CH_3, $ClCH_2$, C_6H_5

as catalyst. The products are γ-lactones (Eq. 979), but are obtained only in rather low yields.

V. Analytical Aspects of Epoxide Chemistry

One of the important problems confronting chemists ever since the discovery of ethylene oxide has been a growing need for reliable and expedient analytical methods, both at the qualitative and at the quantitative level.

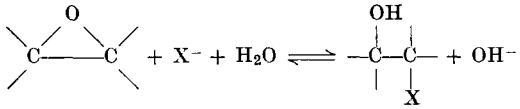
It is the object of this section to consider briefly the existing analytical procedures of epoxide chemistry at each of these levels. More detailed discussions are given in two excellent recent reviews.[103,894]

1. Qualitative Tests

Qualitative tests for the detection of epoxide functions belong in any comprehensive system of organic analysis. They may be used to follow approximately the course of epoxide-forming reactions, *e.g.* addition of peroxy acids to olefins. Conversely, of course, they may be used to follow the gradual breakdown of epoxide functions under the action of nucleophiles or other reagents. An area of growing interest, finally, is the qualitative detection of epoxide rings in substances of natural origin. Reference has already been made elsewhere (see section **II.**) to the expanding catalog of epoxide-containing natural products.

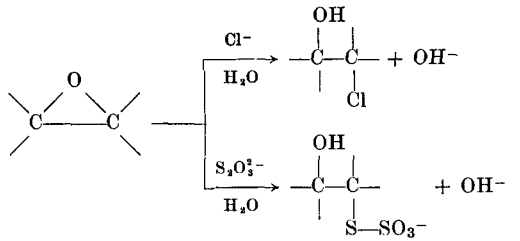
There are at present three general types of qualitative tests for the epoxide function. The first depends on the fact that treatment of an epoxide with concentrated aqueous solutions of nucleophilic salts releases OH^- ions into solution. The second is based on hydration and oxidative cleavage of the resulting 1,2-diol with a suitable reagent. The last depends on the ability of various tertiary aromatic bases like pyridine to form intensely-colored complexes with epoxides. These three approaches will now be considered in turn.

Liberation of OH^- ions on treatment of an epoxide with a nucleophilic anion in water, or in a suitable organic solvent containing dissolved water, may be seen readily from the general equation (Eq. 980).



(980)

When ethylene oxide is passed through concentrated aqueous sodium chloride containing a trace of hydrochloric acid there is soon a marked increase in pH, which may be followed by means of a suitable

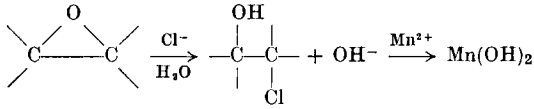


(981)

indicator (Eq. 981).[402] The same principle constitutes the basis of the often-used Ross thiosulfate test, which takes advantage of the strong nucleophilic character of $S_2O_3^{2-}$ ion (Eq. 981).[1491] The more labile

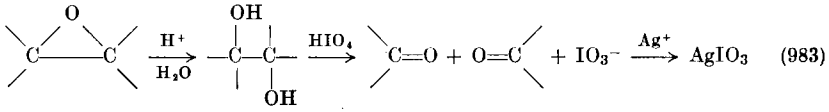
epoxides give an almost instantaneous pink color on the addition of sodium thiosulfate in the presence of phenolphthalein indicator. Others may require a few minutes or longer.

A variation of the above tests is that devised by Lenher,[1005] which depends on the low solubility of certain metal ions in alkaline solution. Treatment of an epoxide with concentrated aqueous manganous chloride, for example, causes the gradual appearance of a manganous hydroxide precipitate as OH^- ions are liberated (Eq. 982). Other halides examined by Lenher but found to be less effective were zinc chloride, ferrous chloride, and stannous chloride.



(982)

The second of the three types of qualitative tests mentioned above involves acid-catalyzed cleavage of an epoxide with periodic acid.[36] The IO_4^- ion then oxidizes the resulting 1,2-diol in the usual manner, while itself undergoing reduction to iodate. In the presence of Ag^+ ion, the gradual formation of iodate will be marked by precipitation of silver iodate (Eq. 983). An obvious drawback to this procedure is that any other functional groups capable of reducing IO_4^- ion will interfere with epoxide detection.



(983)

The remarkable capacity of pyridine and related bases to form brilliantly-colored dyes with various ethylene oxides has been explored by Lohmann,[1043, 1044] Giua,[644] and earlier authors. Colors ranging from one end of the visible spectrum to the other were obtained with a variety of bases, among them pyridine, 2-picoline, 3-picoline, 2,6-lutidine, quinoline, isoquinoline, quinaldine (2-methylquinoline), and acridine. An exceedingly sensitive color test developed by Gunther and co-workers[680] utilizes lepidine (4-methylquinoline) in ethylene glycol at 170°. As little as 1 μg. of ethylene oxide is detectable under optimum conditions.

A ferric thiocyanate test paper has been developed by Deckert[432] for the detection of ethylene oxide in the atmosphere or in other gas mixtures. A positive test is given, however, by any basic gas, *e.g.* ammonia.

2. Quantitative Assay

According to Jungnickel and co-workers,[894] a satisfactory procedure for epoxide assay should conform to the following four basic criteria: (1) applicability to a wide variety of epoxides; (2) precision and accuracy; (3) absence of interference; and (4) operational expediency.

With very few exceptions, quantitative epoxide assay techniques currently in use are derived from the reaction of ethylene oxides with halogen acids, notably hydrochloric acid and hydrobromic acid, in a variety of solvents. Acid uptake may be determined by any of several reliable procedures. These include titration with standard base[894] or back-titration with standard acid.[745] The end-point may be detected visually in the presence of suitable acid–base indicators, or by the more precise technique of potentiometry.[467, 468, 470] A useful alternative, applicable in the presence of easily hydrolysed substances or of amines that buffer the end-point, is the technique of argentiometry. In this procedure excess of halide ion is titrated with silver nitrate in the presence of ferric thiocyanate indicator,[470, 1624] or potentiometrically.[1595]

Several solvent systems have been utilized for epoxide titration. Desirable properties for a solvent in this connexion are: (1) that it be easy to purify and store; (2) that it be unreactive towards both the epoxide and the epoxide reagent; and (3) that it not be excessively volatile, noxious, or toxic.

Aqueous epoxide titration suffers from two serious defects. The first is the limited solubility of many epoxides in water, a handicap sometimes overcome by replacement of water by ethanol. The second is the competing acid-catalyzed hydrolysis, equally troublesome in ethanol since ethanolysis constitutes a side-reaction as much as does hydrolysis. Partial suppression of these interfering processes is achieved at high halide concentration, as reported for example by Deckert,[429,431] Kerckow,[922] Lubatti,[1049] and others.[251, 475, 894]

Anhydrous epoxide titrations have been conducted in a variety of organic solvents. Ethereal hydrogen chloride, for example, has been used in several laboratories,[620, 894, 931, 1252, 1684] but is not always satisfactory on account of solvent evaporation on prolonged standing[894] and other difficulties.[620] Solutions of hydrogen chloride in anhydrous dioxan have likewise been utilized,[475, 894, 931] but dioxan is difficult to purify and store, gives a weak indicator end-point, and possesses undesirable physiological properties. A recent publication describes a reagent prepared by mixing *n*-propanolic hydrogen chloride and

carbon tetrachloride.[745] Hydrochlorination has also been carried out in boiling pyridine containing pyridine hydrochloride,[232, 665, 894] and also in chloroform solution.[894] These procedures are generally satisfactory if one is not averse to the odor of pyridine. The use of hydrogen chloride in *N,N*-dimethylformamide has likewise been reported.[1565] Glacial acetic acid has been found to possess a number of features that commend its use over other solvents.[468] If desired, benzene or chloroform may be used to dissolve the epoxide.[467] Titration is carried out by adding hydrogen chloride or hydrogen bromide in glacial acetic acid directly, either to an indicator or a potentiometric end-point.[467, 468, 470] The use of glacial acetic acid as solvent allows titration of epoxy acid salts and epoxy amines, substances not previously amenable to direct assay in other solvents.[470, 894, 1565] Glacial acetic acid solutions give sharp indicator end-points, cause few undesirable side reactions if titrated rapidly at room temperature, and are suitable for all epoxides.

Styrene oxide and certain di- and trisubstituted epoxides cannot be assayed satisfactorily by titration with acid on account of their tendency to undergo isomerization to carbonyl compounds.[84,469,620,894] Other trisubstituted epoxides are extraordinarily resistant to acid treatment and fail to give accurate titers for that reason.[620, 778]

Gasson and co-workers developed an analytical method suitable for the determination of 1,2-epoxy-2,4,4-trimethylpentane.[620] The epoxide was heated at 100° in a sealed tube with di-*n*-butylamine, and the resulting product acetylated with acetic anhydride. Titration with perchloric acid in acetic acid containing a suitable indicator gave the amount of tertiary amine formed.

Durbetaki has devised a convenient procedure for assaying epoxides that contain tertiary carbon atoms.[469] Advantage was taken of their tendency to undergo rapid isomerization on heating in the presence of a Lewis acid. Treatment of α-methylstyrene oxide, for instance, with zinc bromide in benzene at 98° gave α-phenylpropionaldehyde, which was assayed gravimetrically by precipitation with 2,4-dinitrophenylhydrazine. Satisfactory analyses were likewise obtained with α-pinene oxide and camphene oxide, which suffer rearrangement to campholenic aldehyde and camphenilanaldehyde respectively in nearly quantitative yield. Zinc chloride and ferric chloride were also employed, though with less success. Analysis of 1,2-epoxy-2,4,4-trimethylpentane was carried out satisfactorily in the presence of its isomer 2,3-epoxy-2,4,4-trimethylpentane, since the latter remains intact in the presence of zinc bromide at 98°.

Several analytical procedures are based on the hydration rather than hydrohalogenation of epoxides. The resulting 1,2-diols are assayed by oxidative titration with periodic acid in aqueous sulfuric acid or perchloric acid.[475] Alternatively, carbonyl compounds formed on periodic acid oxidation of 1,2-diols may be determined colorimetrically with phenylhydrazine or other suitable reagents.[247, 374]

Addition of certain sulfur-containing nucleophiles constitutes the basis of several analytical procedures. Among these nucleophiles are sodium sulfite,[1675] sodium thiosulfate,[1491] and hydrogen sulfide.[935] In each case, OH^- ions released after attack of the nucleophile on the epoxide can be titrated continuously with standard acid to maintain a constant pH.[1491]

Gunther and co-workers have developed an exceedingly sensitive colorimetric assay for ethylene oxide based on the intensely-blue dye formed in the presence of lepidine (4-methylquinoline).[680] Other authors,[247, 374] however, have called attention to certain inadequacies in this method.

Finally, Willits and co-workers[1848] have examined the technique of polarography as a tool for quantitative epoxide assay. No polarographic reduction was obtained, however, with any of the several types of epoxides tested.

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CHAPTER II

Aziridines

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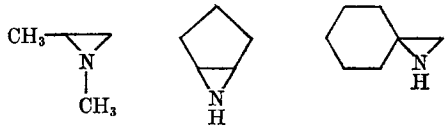
I. Introduction

This chapter is concerned with all compounds having a three-membered ring containing two carbon atoms and one nitrogen atom. The parent compound of this heterocyclic system is the unsaturated ring, which has two isomeric forms, 1-azirine (I) and 2-azirine (II). Very few authentic examples of the azirines are known, and this review is therefore concerned almost wholly with the chemistry of the saturated derivative, aziridine (III).



(I) (II) (III)

Many aziridines are conveniently named as derivatives of a parent alkene, *e.g.* ethylenimine (III), *N*-methylpropylenimine (IV) and cyclopentenimine (V). However, *Chemical Abstracts* uses the word ethylenimine only for the parent compound (III), and all derivatives are indexed as aziridines, *e.g.* 1,2-dimethylaziridine for (IV). Fused-ring derivatives are indexed and named by the Ring Index system,[289] *e.g.* 6-azabicyclo[3.1.0]hexane for (V) and 1-azaspiro[2.5]octane for (VI).



(IV) (V) (VI)

To avoid confusion, it is recommended that names such as ethylene imine, ethyleneimine, azacyclopropane, and dimethylenimine no longer be used.

II. Aziridines

Aziridines have attracted considerable attention in recent years because of fundamental academic interest in such compounds as

examples of highly-strained reactive rings. Further, ethylenimine and some of its simple derivatives are produced commercially and have found considerable use in many branches of applied chemistry, such as textiles, plastics, coatings, and pharmacologically active substances. As a result of this interest, the chemistry of aziridine has been the subject of several brief[236, 29, 1] and more extensive reviews.[151, 31]

Aziridine derivatives in which the nitrogen atom occupies a bridgehead position have been reviewed in an earlier volume in this series.[272]

In 1888, Gabriel[156, 157] obtained from the treatment of β-bromoethylamine with potassium hydroxide a reactive product which he formulated as vinylamine. In several subsequent papers,[158–160] reactions of the presumed vinylamine were interpreted as additions to the carbon–carbon double bond. Soon after, Marckwald observed that the supposed primary unsaturated amine formed an alkali-insoluble benzenesulfonamide, characteristic of secondary amines; and, further, did not decolorize aqueous potassium permanganate instantaneously as would be expected for vinylamine.[217, 260] Marckwald pointed out that these facts were better accommodated by the cyclic structure (III), which was accepted after a brief polemic.[130, 261] The previous observations of Gabriel were later reinterpreted[162] as ring-opening reactions characteristic of the three-membered ring.

In subsequent years, other methods for the synthesis of aziridines have been developed, and a wide variety of derivatives are now known.

1. Physical Properties and Structure

The lower molecular weight volatile aziridines are colorless liquids with a characteristic ammoniacal odor. Special care must be used in the preparation and handling of such compounds because of their high toxicity. Higher molecular weight aziridines are less dangerous, but contact with the skin should still be avoided. The boiling points and melting points of a variety of alkyl- and aryl-substituted aziridines are given in Table 2.

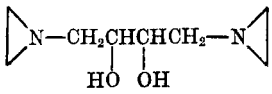
The dimensions of the three-membered ring as determined by measurement of the microwave spectrum[225, 352, 367] and electron-diffraction spectrum[220a] of ethylenimine vapor and the X-ray diffraction of a crystalline derivative (VII)[185] are summarized in Table 1. Since the bond lengths are very nearly equal, the internal bond angles must be close to 60°, compared with 111.3° for the C—N—C bond angle in dimethylamine.

Although the values found by the three methods are not in perfect agreement, they all show that in particular the carbon–carbon bond length is much smaller than that observed in open-chain compounds.

TABLE 1. Bond Lengths in Å

Bond	From microwave spectrum	From electron diffraction	From X-ray diffraction	Normal values for open-chain amines
C—C	1.480	1.48	1.463	1.54
C—N	1.488	1.49	1.510, 1.468	1.47

The resulting ring strain is also reflected in an increase in the C—H vibrational frequency and a decrease in the N—H vibrational frequency as determined by measurement of the infrared and Raman



(VII)

spectra.[214, 322] From heat of combustion data, the strain energy has been estimated at 14 kcal./mole for ethylenimine, compared with 25, 13 and 9 kcal./mole for cyclopropane, ethylene oxide, and ethylene sulfide respectively.[282]

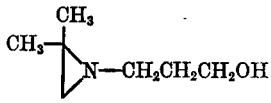
The fact that ethylenimine is a relatively weak base has been described and discussed in terms of the aromaticity or electron delocalization of the three-membered ring.[285, 323] A variety of alkyl aziridines have pK_a in the range 7.93–9.47, whereas for ammonia it is 9.5 and for dimethylamine 10.7.[67] Especially revealing is a comparison of the pK_a values of a series of cyclic imines $(CH_2)_nNH$ and $(CH_2)_nNCH_3$, which showed that the order of basicity with ring size is $3 \ll 6 < 4 < 5$.[318] The same order was found for hydrogen-bonding ability with CH_3OD by a spectrophotometric technique.

Further evidence for the relatively weakly basic character of the aziridine nitrogen atom was provided by a proton magnetic resonance study of a series of cyclic amines,[191] and measurements of the basicity of cyclic and branched amines toward the Lewis acid trimethylboron.[63]

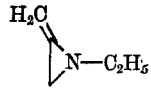
The proton magnetic resonance spectrum has also been used to characterize 2,2,3,3-tetramethylaziridine (which shows a single sharp line revealing the equivalence of the four methyl groups[87]) and 1-ethyl-2-methyleneaziridine (IX) (which shows bands characteristic of the

vinylic hydrogens and the cyclic methylene hydrogens of the aziridine ring[52]).

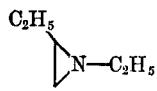
In spite of considerable effort, no compound which owes its asymmetry solely to a non-planar trivalent nitrogen has been resolved into optical isomers.[325] In 1939, several research groups suggested that the additional rigidity of the three-membered ring might permit the resolution of suitably substituted aziridines, such as (VIII).[3, 266, 270] This idea received further support from a calculation of the energy barriers for inversion of nitrogen in 1-methylaziridine.[235] However, only unsuccessful attempts at resolution were reported, and the question of the resolvability of aziridines remained unanswered for many years.



(VIII)



(IX)



(X)

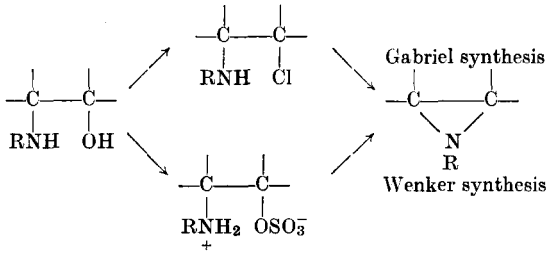
An elegant solution to the problem has been provided by the measurement of the nuclear magnetic resonance spectra, which permits a direct determination of the inversion frequency. The spectra of *N*-substituted aziridines such as (VIII), (IX), and (X) showed that the substituent on the nitrogen does not lie in the plane of the ring. However, the inversion frequency is so high that resolution of such molecules in the most favorable case is likely to be possible only at temperatures below $-50°$.[52, 257]

2. Methods of Preparation

A. The Gabriel and Wenker Reactions

The preparation of an aziridine derivative is most frequently accomplished in a two-step synthesis from a suitably substituted β-amino alcohol. When the reaction is carried out via the β-haloamine, it is called the Gabriel synthesis (Eq. 1), in honor of the discoverer of the prototype reaction. A convenient modification of this sequence, called the Wenker synthesis (Eq. 2), was published in 1935[366] and almost simultaneously reported independently in the patent literature.[354, 355] This involves the conversion of the amino alcohol into the β-amino hydrogen sulfate (which undoubtedly exists as the zwitterion)

followed by treatment with alkali. In both the Gabriel and Wenker reactions, piperazine formation may be an important side reaction.[196]



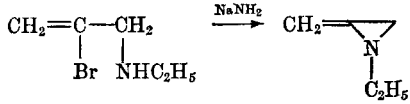
(1)

(2)

(R = H, alkyl, aryl)

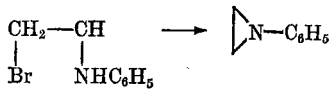
These two reactions have been used for the preparation of a wide variety of aziridines, as shown in Table 2.

The Gabriel synthesis is surprisingly versatile, since it gives excellent yields of aziridines even when the halogen is at a vinyl



(3)

position[52] (Eq. 3) or on a tertiary carbon atom[87] (Eq. 5), or when the basicity of the amine is greatly lowered by substitution of an aryl group for one of the hydrogen atoms[196] (Eq. 4).



(4)

By the use of an elegant tracer technique, it has been shown that Eq. (3) occurs via an elimination–addition mechanism.[54a, 54b, 54d]

Cyclization of β-amino-α-chloro esters[190] and various N-β-haloalkyl sulfonamides have also been reported and are included in Table 2.

Further examples, noted too late for inclusion in Table 2, are the preparation of 1- and 2-arylaziridines by the Wenker synthesis,[61a] and the preparation of six new 1,2,2,3-tetrasubstituted aziridines by the Gabriel method.[205a]

A limitation in the Gabriel synthesis is the difficulty of obtaining chloroamines from highly substituted amino alcohols. A unique method for the synthesis of 2,2,3,3-tetraalkylaziridines is a three-step sequence involving the chloronitrosation of a tetraalkylethylene, reduction of

TABLE 2. Aziridines Prepared by the Gabriel (G) Reaction (Eq. 1) or the Wenker (W) Reaction (Eq. 2)

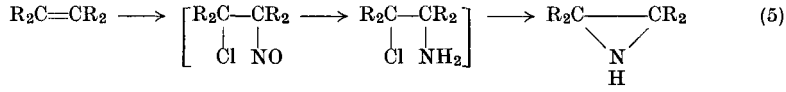
Substituents	Method; yield (%)	B.p. (c°/mm.) or *m.p. (c°)	References
None	G 75	56/760	157, 26
	W 70		8, 324, 310
		*−78	350
1-Methyl	G —	27/764	239, 261
2-Methyl	W 60	66	159, 162, 226 329, 269
1-Ethyl	W 70	—	132
1-(2-Aminoethyl)	W 16	126	226
2-Ethyl	W 46	88	226
1,2-Dimethyl	W 35	42	269
2,2-Dimethyl	W 68	69	65, 69, 75, 226
2,3-Dimethyl (*cis* and *trans*)	W 60	75/746	123, 226
2-Bromomethyl-1-methyl	G —	unstable	361
2,2,3-Trimethyl	W 19	83	226
1-Ethyl-2-methylene	G —	77/745	52
1-*n*-Butyl	W 74	106	132
1-*sec*-Butyl	G 72	96	57
1-*tert*-Butyl	W 27	91/745	52
2,2,3,3-Tetramethyl	G 79	104/744	87
2,2-Dimethyl-3-propyl	W 57	128	226
3-Ethyl-2,2,3-trimethyl	G 71	129/751	87
2,2,3-Trimethyl-3-propyl	G 84	150/747	87
1-Butyl-2,2-dimethyl	W 80	135	132
1-Butyl-2-ethyl	W 70	63/55	132
1-Cyclohexyl	W 32	89/66	52
1-*tert*-Octyl	W 41	94/25	53
2-Methyl-1-*tert*-octyl	W 76	113/25	53
1-Phenyl	G 68	70/13	145, 154, 196
2-Phenyl	G —	—	161, 372
1-(*o*-Tolyl)	G 57	73/8	197
1-(*m*-Tolyl)	G 71	73/8	197
1-(*p*-Tolyl)	G 65	76/8	197
1-(*o*-Chlorophenyl)	G 52	92/10	197
1-(*m*-Chlorophenyl)	G 62	94/10	197
1-Benzyl	W 65	86/12	52, 189
2-Benzyl	W 76	73/1	230
1-Benzyl-2-methyl	W —	58/2	334
1-(4-Biphenylyl)	G 93	*98	21
1-[4-(4-Aminobenzenesulfonyl)-phenyl]	G —	*186	224

(*Table continued*)

TABLE 2 (*continued*)

Substituents	Method; yield (%)	B.p. (c°/mm.) or *m.p. (c°)	References
1,2-Dimethyl-3-phenyl	G ---	—	339, 342, 343, 344
2,3-Diphenyl (*cis* and *trans*)	G 96	*83, *46	118, 365
3,3-Dimethyl-2,2-diphenyl	G poor	*193	238
1,2,3-Triphenyl	G —	*99	347
2-Carboethoxy	G 20	53/12	190
1-Arenesulfonyl	G —	—	3, 279
1-Benzenesulfonyl-2-bromomethyl	G 94	*89	173, 174
1-Benzenesulfonyl-2-ethyl	G —	*76	256
1-*p*-Bromobenzenesulfonyl-2,2-dimethyl	G 46	*79	3
1-Benzenesulfonyl-2,3-dimethyl (*cis*)	G —	*42	256
(*trans*)	G —	*77	256
2-Phenyl-1-*p*-toluenesulfonyl	G good	*95	234
1-Benzenesulfonyl-2-benzyl	G 89	*55	175
7-Azaspiro[5.2]octane	W 66	158	340
6-Azabicyclo[3.1.0]hexane	W 61	122	139
1,5-Dimethyl-6-azabicyclo-[3.1.0]hexane	G 73	134	87
7-Azabicyclo[4.1.0]heptane	W 35	149, *20	286, 313
1-Methyl-7-azabicyclo[4.1.0]-heptane	W —	66/25	370
3-Methyl-7-azabicyclo[4.1.0]-heptane	W good	72/39	313
7-Methyl-7-azabicyclo[4.1.0]-heptane	W —	56/42	313, 370
1,6-Dimethyl-7-azabicyclo-[4.1.0]heptane	G 76	165/750	87
7-Propyl-7-azabicyclo[4.1.0]-heptane	W 63	77/31	313
7-Cyclohexyl-7-azabicyclo-[4.1.0]heptane	W 73	109/14	313
7-*n*-Octyl-7-azabicyclo[4.1.0]-heptane	W 65	122/12	313
7-Phenyl-7-azabicyclo[4.1.0]-heptane	W —	86/0.3	313
7-Benzyl-7-azabicyclo[4.1.0]-heptane	W 72	112/4	313
8-Azabicyclo[5.1.0]octane	W 78	171	341
9-Azabicyclo[6.1.0]nonane	W 33	94/25	229
Camphenimine(?)	G —	—	130

the nitrosochloride and cyclization with alkali[87] (Eq. 5). The intermediate products are not isolated in pure form.

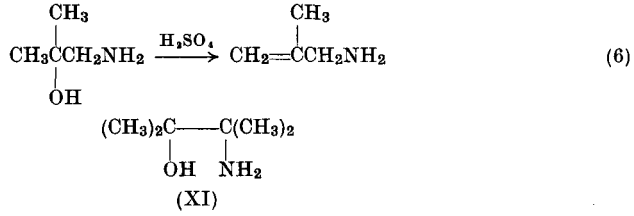


(5)

In the Gabriel synthesis, care must be taken to insure that the product is not contaminated with the volatile chloroamine which may act as a polymerization initiator.

Detailed examples of modifications in the technique of the Gabriel synthesis are to be found in the literature.[26, 11]

The Wenker reaction offers some advantage in ease of handling of the reagents, and lack of volatility of the β-aminoalkyl hydrogen sulfate. Side reactions which are known to interfere with the Wenker procedure are dehydration, which occurs when the hydroxyl group is attached to a tertiary carbon atom[3, 242] (Eq. 6) and pinacol rearrangement, which occurs when highly branched amino alcohols such as (XI) are treated with acid reagents.[87]

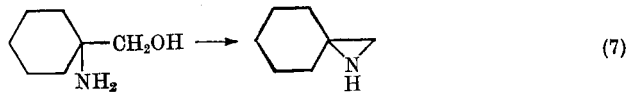


(6)

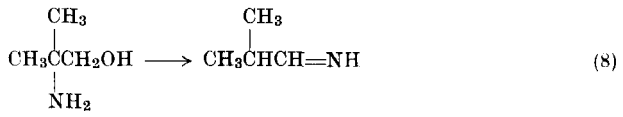
(XI)

The literature should be consulted for various modifications in the technique of the Wenker synthesis.[38, 253, 298, 8, 324]

Although formally aziridines may be considered anhydrides of β-amino alcohols, only one instance is reported in which direct dehydration of an amino alcohol over hot alumina gives an aziridine in rather



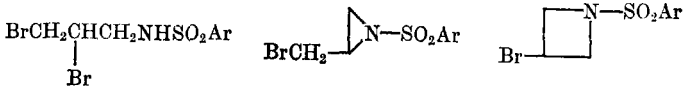
(7)



(8)

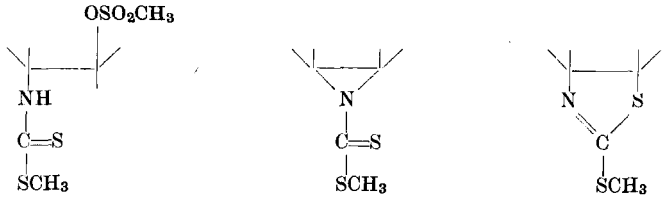
poor yield[316] (Eq. 7). A similar treatment of 2-amino-2-methyl-1-propanol gave no aziridine, but *iso*butylidenimine as the principal product[86a] (Eq. 8).

In the Gabriel reaction, cyclization to the three-membered aziridine is strongly favored over the four-membered azetidine, since treatment of (XII) with sodium hydroxide gives (XIII) and not (XIV).[173]



(XII) (XIII) (XIV)

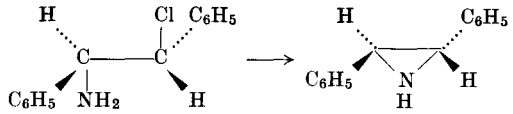
Surprisingly, cyclization of 3-amino-2-methansulfonylaltroside dithiocarbamate (part structure XV) with base gave the aziridine derivative (XVI) rather than the isomeric less-strained thiazoline (XVII).[82]



(XV) (XVI) (XVII)

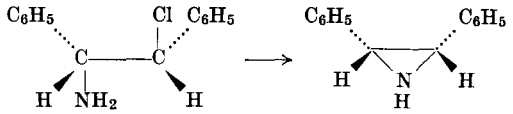
B. Stereochemistry and Mechanism of Ring Closure

Weissberger and Bach first demonstrated that the Gabriel ring closure occurs with inversion at the substituted carbon atom, since an optically active *trans*-2,3-diphenylaziridine was formed by cyclization



(9)

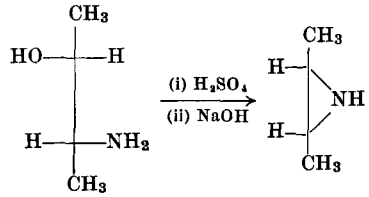
of (−)-*erythro*-α-amino-α′-chlorobibenzyl (Eq. 9); and an optically inactive *cis*-2,3-diphenylaziridine was formed by cyclization of the corresponding (−)-*threo*-α-amino-α′-chlorobibenzyl[365] (Eq. 10).



(10)

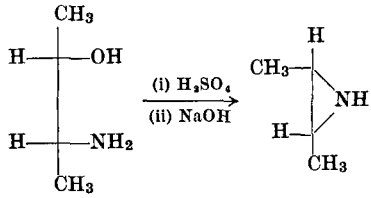
Similarly, Lucas and co-workers showed that the Wenker ring closure is accompanied by inversion at the substituted carbon atom,

since an optically active *threo*-3-amino-2-butanol gave a *meso*-2,3-dimethylaziridine (Eq. 11); and an optically active *trans*-2,3-dimethylaziridine was obtained from an optically active *erythro*-3-amino-2-



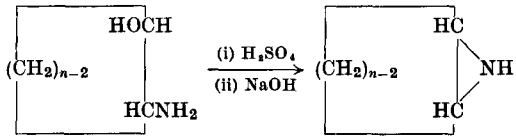
(11)

butanol (Eq. 12). Evidence was provided that the first step of the Wenker synthesis, formation of the sulfate ester, occurred with retention of configuration.[123]



(12)

The preparation of a series of *cis*-cycloalkenimines from the *trans*-2-aminocycloalkanols further illustrates inversion at the substituted carbon atom in the Wenker ring closure[139, 286, 341, 229, 379] (Eq. 13).

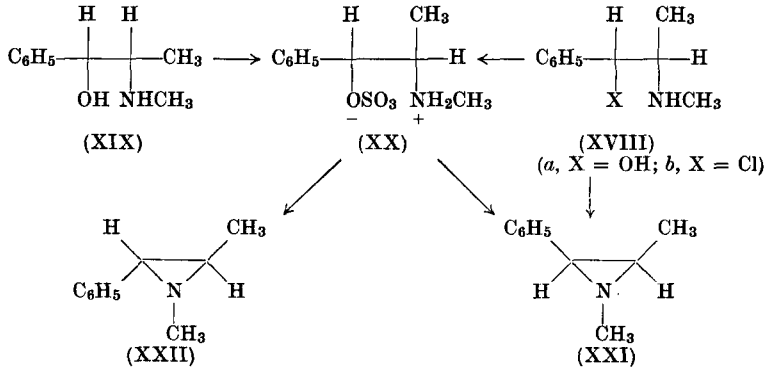


(13)

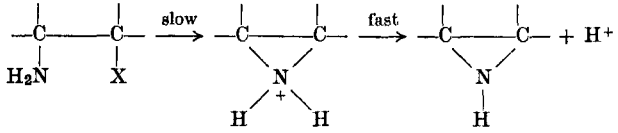
(n = 5, 6, 7, 8)

The Wenker synthesis is not stereospecific when the hydroxyl group of the amino alcohol is on a benzyl-type carbon atom. L-Ephedrine (*erythro*) (XIX) and L-ψ-ephedrine (*threo*) (XVIIIa) give the same (*threo*) sulfate (XX) on treatment with chlorosulfonic acid. Treatment of (XX) with sodium hydroxide gives a mixture of *erythro*-(XXI) and *threo*-(XXII) aziridines. The analogous Gabriel ring closure is stereospecific, since the *threo*-chloroamine (XVIII*b*) on treatment with sodium hydroxide gives only (XXI).[339, 342–344]

Freundlich, Salomon, and their co-workers found that the Gabriel ring closure proceeds according to first-order kinetics, in agreement



with internal nucleophilic displacement of the halogen by the amino group[149, 308] (Eq. 14).

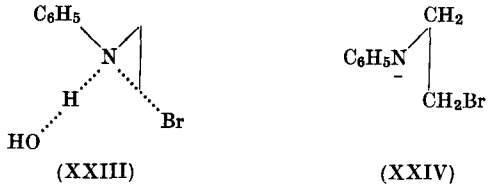


(14)

In the alkaline solvolysis of *N*-β-bromoethylaniline, the rate of appearance of bromide ion was dependent on sodium hydroxide concentration and satisfied Eq. (15). The second-order component of this

$$d[Br^-]/dt = k'[\text{bromoamine}] + k''[OH^-][\text{bromoamine}] \quad (15)$$

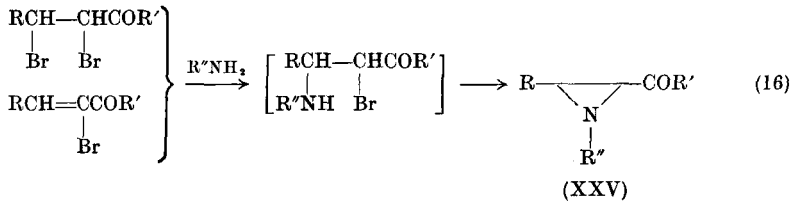
reaction can be pictured as the result of either a concerted mechanism (XXIII) or a two-step process involving formation of an anilino ion (XXIV).[198]



C. Ethylenimine Ketones and Related Syntheses

Closely related to the Gabriel synthesis is the reaction of α,β-dihaloketones or α-halo-α,β-unsaturated ketones with primary amines

to give ethylenimine ketones (2-acylaziridines) (Eq. 16). The probable intermediate in this reaction, a β-amino-α-haloketone, is not isolated.



(16)

(XXV)

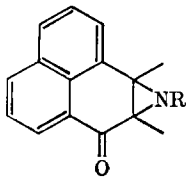
The development of this field is reported almost entirely in a series of papers by Cromwell and his group over a period of nearly 20 years.[93-114] Many syntheses as well as detailed studies of three-ring

TABLE 3. Aziridines Prepared by the Reaction of α,β-Dibromo- and α-Bromo-α,β-unsaturated Ketones with Primary Amines according to Eq. (16)

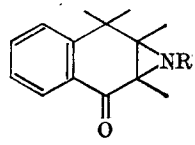
2-Substituent	3-Substituent	1-Substituent	References
Acetyl	*p*-Biphenylyl	Cyclohexyl	111
Benzoyl	Hydrogen	Cyclohexyl	102
Benzoyl	Methyl	Cyclohexyl	101
Benzoyl	Phenyl	Hydrogen	93
Benzoyl	Phenyl	Methyl	94
Benzoyl	Phenyl	Cyclohexyl	93, 102
Benzoyl	Phenyl	Benzyl	93, 96, 102
Benzoyl	*o*-Nitrophenyl	Cyclohexyl	110
Benzoyl	*m*-Nitrophenyl	Benzyl	95
Benzoyl	*p*-Nitrophenyl	Hydrogen	110
Benzoyl	*p*-Tolyl	Benzyl	95
Benzoyl	*p*-Anisyl	Cyclohexyl	114
p-Toluyl	Phenyl	Hydrogen	102
p-Toluyl	Phenyl	Methyl	102, 113
p-Toluyl	Phenyl	Cyclohexyl	102
p-Toluyl	Phenyl	Benzyl	95, 97, 102
p-Phenylbenzoyl	Hydrogen	Cyclohexyl	102
p-Phenylbenzoyl	Methyl	Methyl	109
p-Phenylbenzoyl	Methyl	Cyclohexyl	108, 109
p-Phenylbenzoyl	Phenyl	Methyl	106, 109, 113
p-Phenylbenzoyl	Phenyl	Cyclohexyl	106, 109

carbonyl hyperconjugation, stereochemistry, mechanisms of ring cleavage and absorption spectra–structure relationships are described, and have been summarized in a brief review.[112] Aziridines prepared according to Eq. (16) are listed in Table 3.

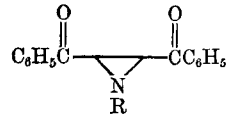
Similarly, fused polycyclic aziridines (XXVI, XXVII) have been obtained by reaction of the corresponding haloketones with primary amines.[103, 104]



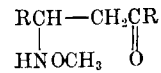
(XXVI)



(XXVII)



(XXVIII)



(XXIX)

Aziridinyl ketones of structure (XXV) are also formed by the reaction of an α,β-unsaturated ketone with a primary amine and iodine,[331, 109] and by the treatment of β-methoxyaminoketones (XXIX) with sodium methoxide.[51]

1,2-Dibenzoyl-1,2-dibromoethane reacts with primary amines to give a 2,3-dibenzoylaziridine derivative (XXVIII).

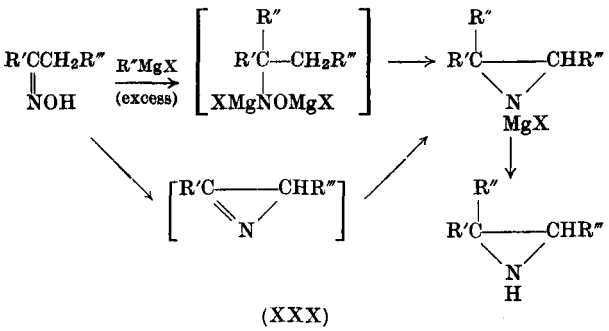
α,β-Dibromo- and α-bromo-α,β-unsaturated esters, amides and nitriles also react with primary amines to give aziridines. Compounds prepared in this way are listed in Table 4.

TABLE 4. Aziridines Prepared by the Reaction of α,β-Dibromo- and α-Bromo-α,β-unsaturated Esters, Amides, and Nitriles with Primary Amines

2-Substituent	3-Substituent	1-Substituent	References
Carbomethoxy	Hydrogen	Benzyl	330, 234a
Carbomethoxy	Hydrogen	Benzohydryl	330
Carboethoxy	Phenyl	Alkyl	273
Carboalkoxy	Methyl	Benzyl	297, 334
Cyano	Hydrogen	Cyclohexyl	363, 363a
Cyano	Hydrogen	Alkyl	15, 363a
Carbamoyl	Phenyl	Hydrogen	376

D. The Hoch–Campbell Synthesis

The reaction of a ketoxime with excess of Grignard reagent is a useful general method for the preparation of 2,2-disubstituted aziridines. The procedure was introduced by Hoch[213] and further developed by Campbell,[72, 74] and has been formulated as shown in Eq. (17). An alternative intermediate (XXX) provides a better rationalization of the observation that the carbon atom incorporated in the ring is derived from the oxime and not from the Grignard reagent.[206] Care



(17)

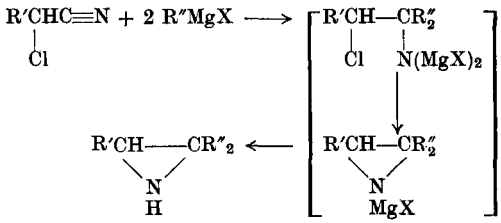
(XXX)

must be observed in the hydrolysis of the magnesium derivative of the aziridine to avoid ring opening.[70, 71] Examples of aziridines prepared by the Hoch–Campbell synthesis are listed in Table 5.

TABLE 5. Aziridines Prepared by the Reaction of Ketoximes with Grignard Reagents (Hoch–Campbell Synthesis) According to Eq. (17)

2-Substituent, R′, derived from oxime	2-Substituent, R″, derived from R″MgX	3-Substituent, R‴	References
Methyl	Butyl	Hydrogen	206
Ethyl	Ethyl	Methyl	206
Ethyl	Phenyl	Methyl	206
Propyl	Propyl	Ethyl	206
Phenyl	Methyl	Methyl	206
Phenyl	Ethyl	Hydrogen	74
Phenyl	Ethyl	Methyl	74, 213
Phenyl	Propyl	Hydrogen	74
Phenyl	Propyl	Methyl	206
Phenyl	Propyl	Ethyl	206
Phenyl	Phenyl	Methyl	72, 213
Phenyl	Phenyl	Ethyl	72
Phenyl	Phenyl	3,3-Dimethyl	238

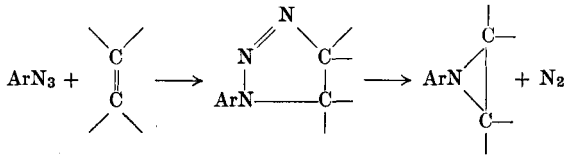
A related little-known reaction giving 2,2,3-trisubstituted aziridines results on treatment of α-chloronitriles with a Grignard reagent[120, 348] (Eq. 18).



(18)

E. Pyrolysis of Triazolines

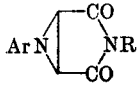
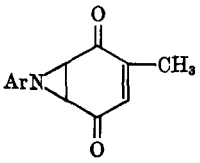
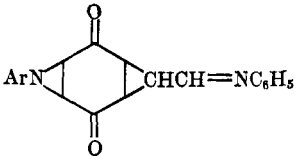
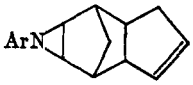
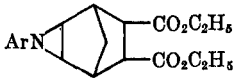
The synthesis of aziridines by the addition of an azide to an alkene followed by pyrolysis of the resulting triazoline was first observed by Wolff[371, 4, 5] (Eq. 19). The reaction is successful when



(19)

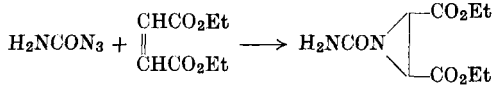
applied to a variety of polycyclic and highly polar olefins, but fails with relatively simple compounds such as styrene.[228b] Aziridines prepared in this way are listed in Table 6.[380]

TABLE 6. Aziridines Formed by the Pyrolysis of Triazolines

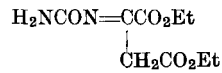
Aziridine	References
	119, 275, 238a
	81
	371
	6
	6

The analogous reaction of carbamic acid azide with diethyl fumarate yields a product which was formulated as an aziridine

(XXXI)[115] but is probably the isomeric open-chain compound (XXXII).[23]



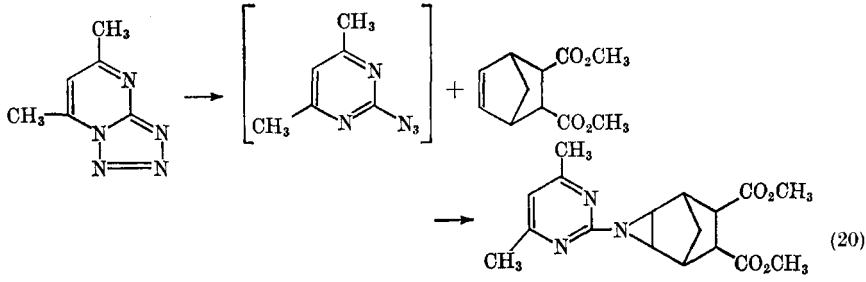
(XXXI)



(XXXII)

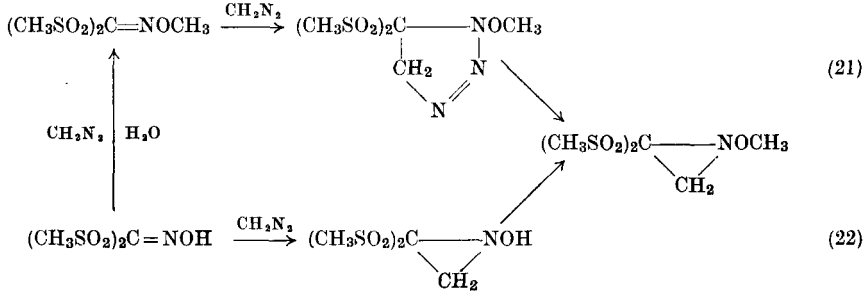
By analogy, an aziridine has also been proposed as the intermediate in the reaction of sulfuryl hydrazide with *p*-xylene.[116]

The product of the pyrolysis of a pyrimidotetrazole (isomeric with an arylazide) in the presence of a polycyclic alkene has been formulated as an aziridine[219] (Eq. 20).



(20)

It is reported that the triazolines formed by addition of diazomethane to a variety of anils do not yield aziridines on pyrolysis.[228b] However, the *O*-methyl ether of isonitrosobis(methylsulfonyl)methane reacts with diazomethane to give a triazoline which may be pyrolyzed to a unique 1-methoxyaziridine (Eq. 21). The same aziridine is also obtained by methylation of the corresponding 1-hydroxyaziridine, which is formed in a similar way, but without isolation of a triazoline intermediate[16] (Eq. 22).

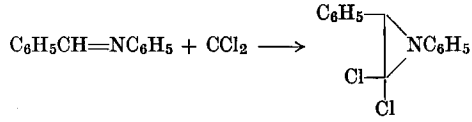


(21)

(22)

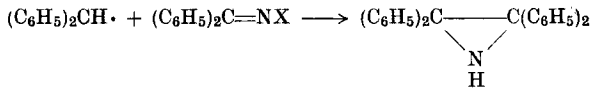
F. Miscellaneous Ring Closures

The addition of a carbene to an anil would appear to be a simple method for the preparation of an aziridine. Thus far, few examples of such a reaction are known[144, 228a, 90a] (Eq. 23) (however, see section **II.4** below).



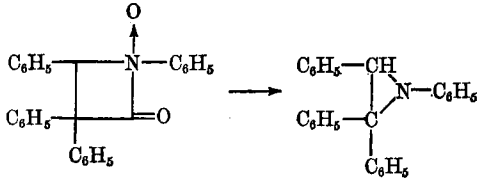
(23)

The reaction of diphenylmethyl radical with benzophenone azine or benzophenone hydrazone gives 2,2,3,3-tetraphenylaziridine[364a] (Eq. 23a).



(23a)

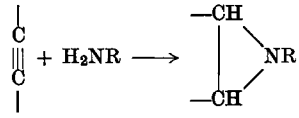
A compound believed to be an azetidinone *N*-oxide on heating gives a tetraphenylaziridine[347] (Eq. 24).



(24)

Treatment of bis-(2-chloroethyl)amine with sodium metal gives 1-ethylaziridine among other products.[290]

Formation of ethylenimine by the pyrolysis of 2-oxazolidone has been claimed.[228, 336] The evidence is based on the isolation of polymeric products and is of doubtful validity.



(25)

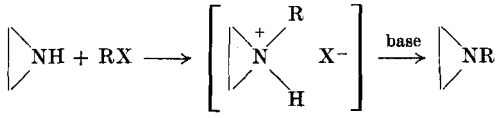
Addition of a primary amine to an alkyne would provide a simple aziridine synthesis (Eq. 25). Although no such reaction has been achieved,[224] the formation of an aziridine by the addition of a nitrene to an alkene has recently been demonstrated.[381]

3. Functional Derivatives

In this section are considered all reactions of aziridines which do not result in quaternization of the nitrogen atom or opening of the three-membered ring (see sections **II.4** and **II.5** below). In general, aziridines exhibit the behavior characteristic of secondary aliphatic amines. However, frequently special precautions are needed to prevent side-reactions due to opening of the ring.

A. Alkylation

(1) Alkyl halides. The alkylation of 1-unsubstituted aziridines with alkyl halides must be conducted in the presence of a base (Eq. 26), since the aziridinum ion which is an intermediate in the reaction



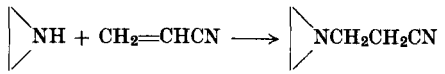
(26)

is highly susceptible to ring opening by nucleophilic reagents. The classes of alkyl halides which have been used for the alkylation of aziridines are listed in Table 7.

TABLE 7. Types of Alkyl Halides Used in the Alkylation of *N*-Unsubstituted Aziridines

Halide	References
Primary alkyl halides	78, 313, 386
Chloromethyl arenes	268, 326, 328
α-Haloketones	327
α-Haloacids and derivatives	29, 188, 294, 335

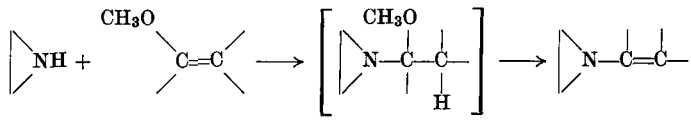
(2) Addition to alkenes. Aziridines add to a wide variety of alkenes, with or without the use of a basic catalyst.[29] The mode of



(27)

addition to unsymmetrical alkenes is as expected if the aziridine is a nucleophile (Eq. 27). Reactions in which the aziridinyl group replaces the methoxyl group of enol methyl ethers may be formulated as

addition–elimination reactions[125, 353] (Eq. 28). Aziridines have been added to the various types of alkenes listed in Table 8.

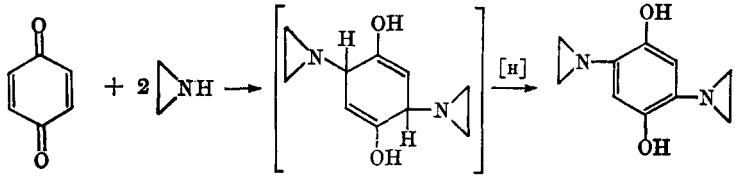


(28)

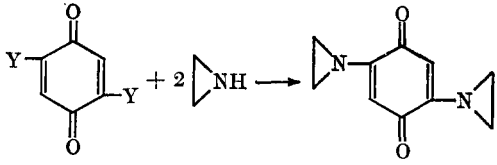
TABLE 8. Types of Alkenes to Which Aziridines Have Been Added

Alkene	References
Styrene	37, 136
Various alkenes	50, 337a
α,β-Unsaturated esters	13, 39, 48, 180, 237, 375, 377, 137
α,β-Unsaturated nitriles	40, 345, 249a
1-Cyano-1,4-butadiene	333
Alkyne	236a

(3) Addition to quinones. The addition of aziridines to quinones has been of particular interest because in this way polyaziridinyl compounds are formed which have carcinotoxic activity.[168–170, 142] When benzoquinone is treated with ethylenimine in the presence of oxidizing agents (or a sufficient excess of quinone), the 2,5-diaziridinyl quinone is formed: in the presence of reducing agents the corresponding hydroquinone is produced (Eq. 29).[262, 263] 2,5-Dimethoxy- or dihaloquinones react similarly with elimination of methoxyl or halogen (Eq. 30). A variety of such aziridine derivatives have been prepared



(29)

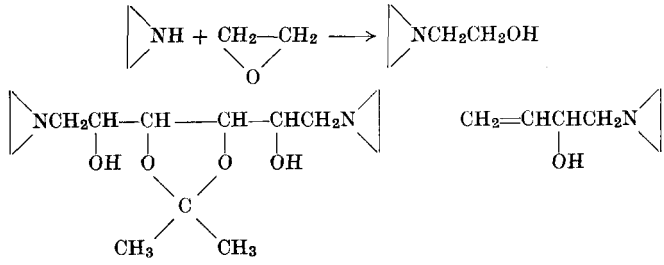


(30)

(Y = OCH_3 or halogen)

and tested for pharmacological activity. *o*-Benzoquinone reacts with ethylenimine in an analogous fashion.[216]

(4) Addition to epoxides. The addition of aziridines to epoxides proceeds in the normal fashion to give β-hydroxyalkyl aziridines[25,153,313,369] (Eq. 31). With unsymmetrical epoxides, the aziridinyl group becomes attached to the less-substituted carbon atom.[299] The products of the

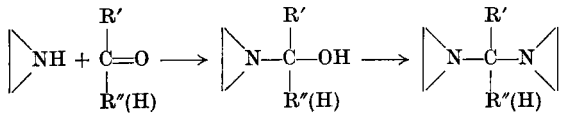


(31)

(XXXIII) (XXXIV)

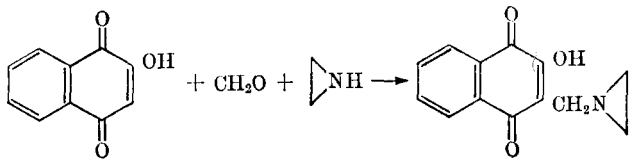
addition of ethylenimine to epoxides derived from sugars and sugar alcohols[358, 359] (*e.g.* XXXIII) and to butadiene monoxide[17] (XXXIV, 'Tetramin') are of particular interest as tumor growth inhibitors.[54b, 54c, 331a]

(5) Addition to carbonyl compounds. The addition of ethylenimine at low temperatures to the carbonyl group of aldehydes and



(32)

ketones gives moderately stable α-hydroxyalkyl derivatives; reaction with a second molar proportion of ethylenimine gives the diaziridinyl compound[124, 241, 360, 297a] (Eq. 32).

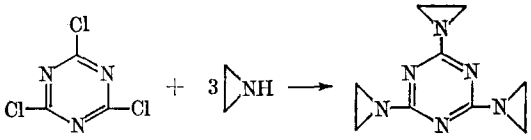


(33)

A single example of the use of ethylenimine in the Mannich reaction has been reported[359a] (Eq. 33).

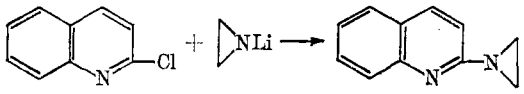
B. Arylation

Ethylenimine reacts with halogen derivatives of many aromatic nitrogen-containing heterocyclic compounds to form aziridinyl or polyaziridinyl derivatives. The best-known example of this type of reaction is the preparation of 2,4,6-triaziridinyl-1,3,5-triazine (also called triethylenemelamine, TEM) (Eq. 34) which has been extensively tested as a cancer chemotherapy agent.



(34)

With less-reactive aryl halides, the use of 1-lithioaziridine is advantageous[182] (Eq. 35).



(35)

Ethylenimine can also react with 2,4,6-trinitroanisole to give 1-(2,4,6-trinitrophenyl)aziridine.[29]

Arylation reactions are classified in Table 9.

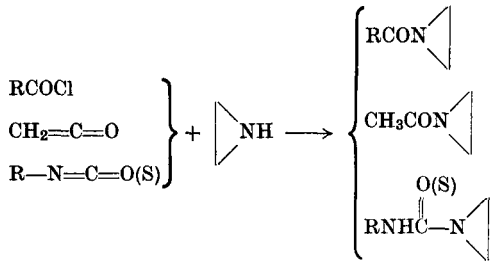
TABLE 9. Types of Aryl Halides Used in the Arylation of Aziridines

Aryl halide	References
Halotriazines	58, 205, 209, 311, 315, 373
Trichloromethyltriazine	29
Halopyrimidines	203, 204, 240
Chloropurine	301a
Chloroquinoline	182

C. Acylation

Acylation of aziridines may be accomplished by treatment with acid chlorides, with precautions to keep the reaction under alkaline

conditions. Acetylation with ketene is particularly convenient. With isocyanates and isothiocyanates, ureas and thioureas are formed.



Many such acyl derivatives have been prepared and no attempt has been made to provide a complete list. Selected examples are classified in Table 10.

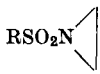
TABLE 10. Types of Reagents Used for the Acylation of Aziridines

Types of reagent	Class of product	References
Acid chlorides	Amides	61, 29
Ketenes	Amides	33, 47, 291, 221, 227
Isocyanates	Ureas	36, 41, 42, 54, 133, 146, 171, 267, 332, 357
Isocyanic acid	Ureas	43
Isothiocyanates	Thioureas	141, 351, 121, 158
N-Chloroamide	Ureas	284
Thiophosgene	Thiocarbonyl chloride	301
Carbamyl chloride	Ureas	27
Carbodiimide	Guanidines	314
N-Carboxylic anhydride	Amides	290

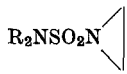
D. Formation of Bonds with Heteroelements

(1) Nitrogen–sulfur bonds. Aziridines react normally with sulfonyl chlorides to form sulfonamides (XXXV).[252, 292] Such derivatives have been frequently employed in the characterization of *N*-unsubstituted aziridines[217] and no attempt is made here to list such examples.

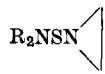
Similarly, sulfamides (XXXVI) are formed by the reaction of aziridines with dialkylsulfamyl halides,[293] and sulfenamides (XXXVII)[150] from sulfenyl chlorides.



(XXXV)

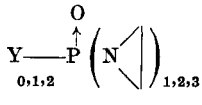


(XXXVI)

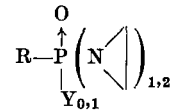


(XXXVII)

(2) Nitrogen–phosphorous bonds. Ethylenimine reacts with compounds containing one, two or three halogens attached to phosphorous to give the corresponding mono-, di- or triaziridinyl derivative. In this way a great variety of phosphoramides (XXXVIII), phosphonamides (XXXIX) and the sulfur (thio) analogs have been prepared. Many such



(XXXVIII)



(XXXIX)

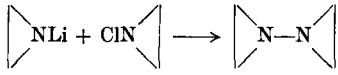
(Y = R_2N or RO)

compounds have been tested for carcinotoxic and other biological activity. The types of aziridinyl–phosphorous compounds reported are classified in Table 11.

TABLE 11. Aziridinyl–Phosphorous Compounds

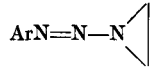
Types of compound	References
Phosphoramides	208, 210, 211, 244, 287, 288, 320, 362
Thiophosphoramides	245
Phosphonamides	28, 148, 187, 251
Thiophosphonamides	246

(3) Nitrogen–nitrogen bonds. Diaziridine has been prepared by the reaction of lithioaziridine with 1-chloroaziridine[186] (Eq. 36). Support for the structure assigned to this product was obtained from the infrared-absorption spectrum, which showed absence of NH and C=N bonding, and the proton magnetic resonance spectrum, which indicated that all of the hydrogens are equivalent.



(36)

An unstable triazene (XL) is obtained when ethylenimine is treated with a diazonium salt.[302, 202b]



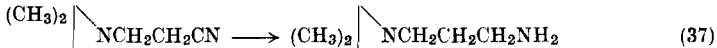
(XL)

(4) Nitrogen–silicon bonds. The reaction of ethylenimine with chlorosilanes gives products in which the aziridine ring is attached to silicon.[207]

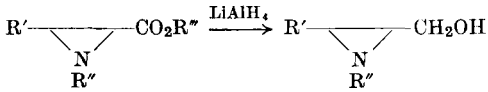
E. Reactions of Functional Groups in the Side-Chain

In aziridine derivatives, the ring is usually the most reactive part of the molecule. However, a few instances are known in which functional groups elsewhere in the molecule react without ring opening.

A nitrile group in the side-chain may be catalytically hydrogenated[29, 345] (Eq. 37), and an ester group can be reduced to a primary alcohol with lithium aluminum hydride[76] (Eq. 38).

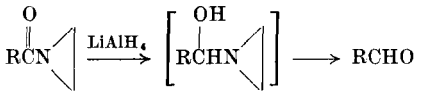


(37)



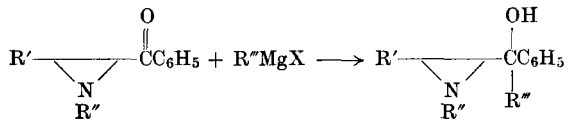
(38)

Reduction of *N*-acylaziridines with lithium aluminum hydride provides a novel method for the preparation of aldehydes, presumably via the readily hydrolyzed aminohydrin, which is not isolated[64] (Eq. 39).



(39)

Phenyllithium or Grignard reagents add to the carbonyl group of *N*-substituted 2-acylaziridines to give the expected aziridinyl carbinols[95, 101, 105] (Eq. 40).

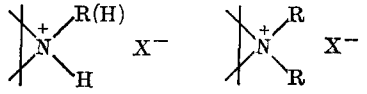


(40)

4. Aziridinium Salts

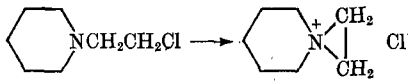
When an aziridine is treated with an acid, the resulting protonated aziridine (XLI) is usually too reactive to be isolated, and rapidly undergoes solvolysis, isomerization or polymerization. Thus the isolation of stable crystalline aziridine hydrohalides is seldom mentioned in the literature.[328]

Many aziridines form picrates and other salts which are stable in the crystalline state.[86, 24] Attempts to recrystallize such compounds frequently result in decomposition. The quaternary aziridinium salts (XLII) are somewhat more stable,[239] and have been much studied in connexion with the reactions of the β-chloroalkyl tertiary amines ('nitrogen mustards').



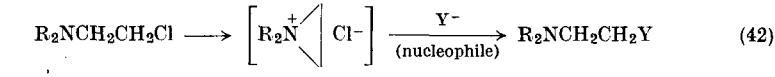
(XLI) (XLII)

The formation of a quaternary aziridinium salt was proposed many years ago by Marckwald[261] (Eq. 41) to account for observations of the properties of *N*-(β-chloroethyl)piperidine. Later, the reactivity of nitrogen mustards with biological systems was recognized,[152] and led



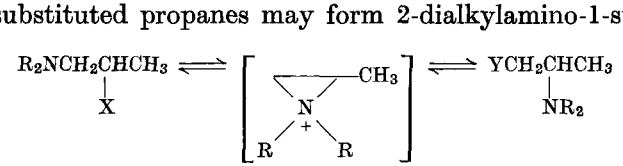
(41)

to detailed studies of the kinetics and mechanism of reaction of such compounds with solvent and other nucleophiles.[19, 88, 306, 349] These investigations support the view that the reaction proceeds via a quaternary aziridinium ion (Eq. 42), which may sometimes be isolated in the form of a relatively insoluble salt such as the picrylsulfonate.[79, 80, 194, 295a]



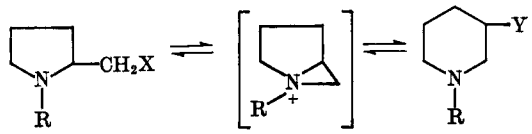
(42)

An intermediate aziridinium ion accounts for the observation that alkylations with β-haloalkyl tertiary amines frequently lead to products with a rearranged carbon–nitrogen skeleton. For example, 1-dialkylamino-2-substituted propanes may form 2-dialkylamino-1-substituted



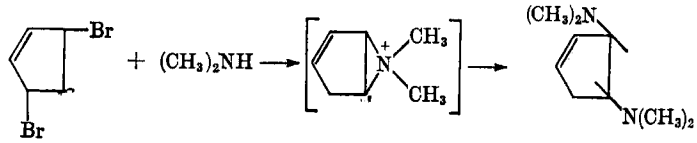
(43)

propanes and *vice versa*[91, 151, 305] (Eq. 43), and the 2-(substituted methyl)-1-alkylpyrrolidine skeleton may be reversibly rearranged to a 3-substituted 1-alkylpiperidine[55, 155, 300] (Eq. 44).



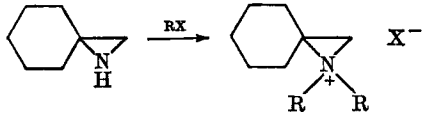
(44)

An aziridinium ion intermediate also accounts for the stereochemical course of the reaction of *cis*- or *trans*-3,5-dibromocyclopentene with dimethylamine[91a, 122] (Eq. 45).



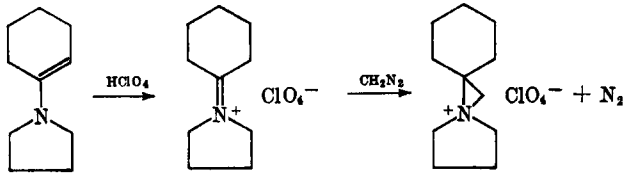
(45)

One of the few aziridines which is readily alkylated to give a stable quaternary aziridinium salt is 1-azaspiro[5.2]octane[165, 166] (Eq. 46). Some unsuccessful attempts to obtain stable quaternary aziridinium salts by alkylation of an aziridine with alkyl halides have been reported.[189]



(46)

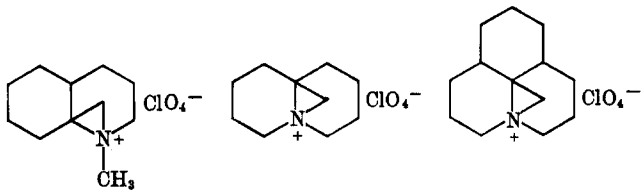
A novel synthesis of relatively stable quaternary aziridinium salts has been introduced by Leonard.[254] Ternary iminium perchlorates (obtained by treatment of the corresponding enamine with perchloric acid) react with diazomethane to give the aziridinium perchlorate



(47)

(Eq. 47). A band in the nuclear magnetic resonance spectrum corresponding to the methylene hydrogens of the aziridinium ring provided particularly valuable evidence for the structure of the product. The method seems to be very general, and has been utilized for the pre-

paration of a variety of polycyclic aziridinium salts, *e.g.* (XLIII), (XLIV) and (XLV).



(XLIII) (XLIV) (XLV)

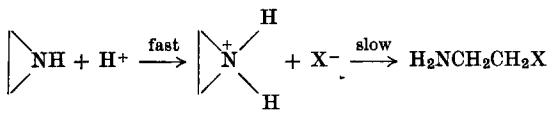
5. Ring-Opening Reactions

Most of the ring-opening reactions of aziridines may be formulated as nucleophilic substitution reactions, in which one of the carbon–nitrogen bonds is broken and a new bond with carbon is formed. In this section, ring-opening reactions are classified on the basis of the element which is joined to the carbon atom in the newly formed bond of the reaction product.

A. Formation of Carbon–Halogen Bonds

The reaction of an aziridine with a halogen acid is more properly to be regarded as reaction of halide ion with an intermediate aziridinium ion. Such reactions are usually of little preparative value, since they represent essentially the reversal of the Gabriel ring closure. However, they have been of considerable interest in providing evidence concerning the mechanism of the acid-catalyzed ring-opening reactions of aziridines.

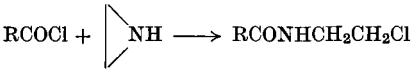
Evidence provided by kinetic measurements supports the view that the reaction is a second-order (S_N2) process when a nitrogen–primary carbon bond is broken[131] (Eq. 48).



(48)

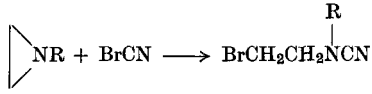
When the aziridine ring is more highly substituted the mechanism of the reaction becomes more complicated, perhaps involving a mixture of S_N1 and S_N2 processes.[14, 94, 98]

In the absence of alkali, acid chlorides add to ethylenimine to give *N*-(β-chloroethyl)amides[29] (Eq. 49).



$$\text{RCOCl} + \text{HN}(\text{CH}_2\text{CH}_2) \longrightarrow \text{RCONHCH}_2\text{CH}_2\text{Cl} \tag{49}$$

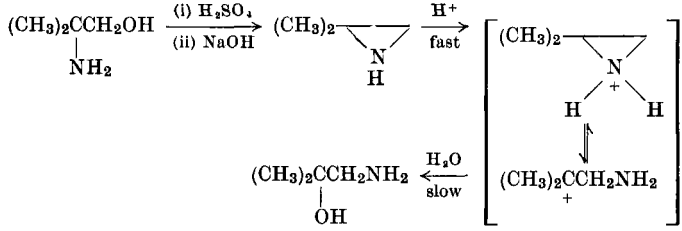
Cyanogen bromide adds to 1-alkylaziridines to give good yields of the β-bromoethylcyanamides (Eq. 50). More highly substituted aziridines give mixtures of products.[132]



$$\text{RN}(\text{CH}_2\text{CH}_2) + \text{BrCN} \longrightarrow \text{BrCH}_2\text{CH}_2\overset{\text{R}}{\underset{|}{\text{N}}}\text{CN} \tag{50}$$

B. Formation of Carbon–Oxygen Bonds

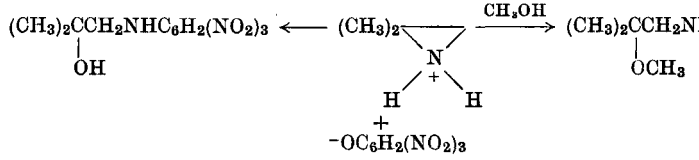
The acid-catalyzed hydrolysis of aziridines is usually of little preparative value. In certain instances such a reaction may represent the final step in the isomerization of a β-amino alcohol[312, 340] (Eq. 51). Kinetic studies show that when a nitrogen–tertiary carbon bond is present in the aziridine, this bond is hydrolyzed in an S_N1-type reaction[312] (Eq. 51).



$$(\text{CH}_3)_2\overset{\text{NH}_2}{\underset{|}{\text{C}}}\text{CH}_2\text{OH} \xrightarrow[\text{(ii) NaOH}]{\text{(i) H}_2\text{SO}_4} (\text{CH}_3)_2\text{C}(\text{CH}_2)\text{NH} \xrightarrow[\text{fast}]{\text{H}^+} \left[(\text{CH}_3)_2\text{C}(\text{CH}_2)\overset{+}{\text{N}}\text{H}_2 \rightleftharpoons (\text{CH}_3)_2\overset{\text{OH}}{\underset{|}{\text{C}}}\text{CH}_2\overset{+}{\text{N}}\text{H}_2\right] \xrightarrow[\text{slow}]{\text{H}_2\text{O}} (\text{CH}_3)_2\overset{\text{OH}}{\underset{|}{\text{C}}}\text{CH}_2\text{NH}_2 \tag{51}$$

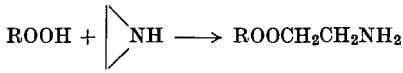
When a nitrogen–secondary carbon bond is broken in the hydrolysis, the reaction occurs with inversion of configuration as shown by studies of the hydrolysis of the 2,3-dimethylaziridines[123] and cycloalkenimines.[340]

Aziridines react with other compounds containing the hydroxyl group similarly.[84, 346] For example, refluxing the picrate of 2,2-dimethylaziridine in methanol gave the amino ether, whereas heating in an inert solvent gave the picramide derivative[86] [Eq. (52)].



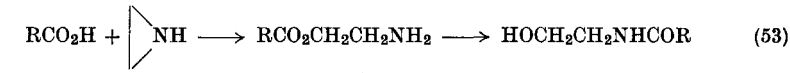
$$(\text{CH}_3)_2\overset{\text{OH}}{\underset{|}{\text{C}}}\text{CH}_2\text{NHC}_6\text{H}_2(\text{NO}_2)_3 \longleftarrow (\text{CH}_3)_2\text{C}(\text{CH}_2)\overset{+}{\text{N}}\text{H}_2 \;{}^-\text{OC}_6\text{H}_2(\text{NO}_2)_3 \xrightarrow{\text{CH}_3\text{OH}} (\text{CH}_3)_2\overset{\text{OCH}_3}{\underset{|}{\text{C}}}\text{CH}_2\text{NH}_2 \tag{52}$$

Hydroperoxides react with ethylenimine to give the β-aminoalkyl peroxides[134] (Eq. 52a).



(52a)

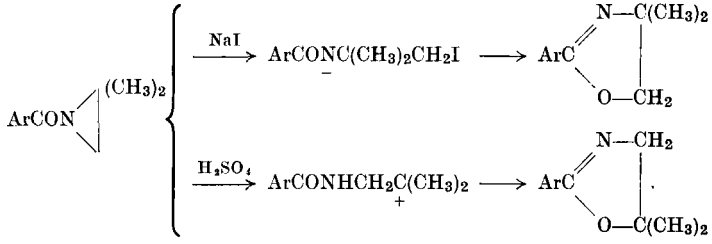
Carboxylic acids react with aziridines to give β-aminoalkyl benzoates which readily rearrange to the isomeric *N*-(β-hydroxyalkyl)-amides[296] (Eq. 53). The ring opening occurs with inversion when a nitrogen–secondary carbon bond is broken.[179] The kinetics of the reaction of a series of substituted benzoic acids with several aziridines was studied to obtain the Hammett rho constant for the ring opening.[296]



(53)

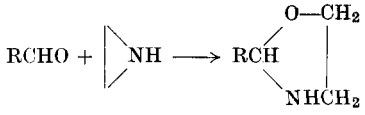
The formation of tris-(β-aminoethyl)phosphate by the reaction of ethylenimine with phosphoric acid has been claimed in a patent.[2]

On treatment with aluminum chloride or sodium iodide, *N*-acyl derivatives of aziridines rearrange to the isomeric oxazolines.[202] When an unsymmetrical aziridine such as 1-benzoyl-2,2-dimethylaziridine is used, treatment with sodium iodide gives the oxazoline resulting from nitrogen–primary carbon fission (S_N2-type reaction), whereas treatment with sulfuric acid gives the isomeric oxazoline resulting from nitrogen–tertiary carbon fission (S_N1-type reaction).[199, 200]



On treatment with nitrous acid, ethylenimine gives ethylene glycol.[138] According to recent evidence, *N*-nitrosoethylenimine may be an intermediate when nitrosation is conducted under neutral conditions.[378]

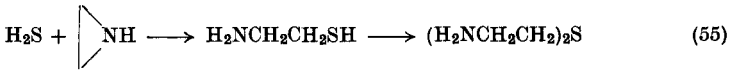
Aldehydes and some ketones give oxazolidines on prolonged heating with ethylenimine[126] (Eq. 54).



(54)

C. Formation of Carbon–Sulfur Bonds

Depending on the conditions, ethylenimine reacts with hydrogen sulfide to give either β-aminoethyl mercaptan or β,β′-diaminodiethyl sulfide[160, 32, 276] (Eq. 55). Other examples of the reaction of organic



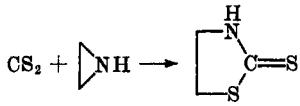
(55)

compounds containing the thiol group with aziridines to give the β-aminoalkyl derivative are listed in Table 12.

TABLE 12. Reactions of Aziridines with Thiols to Give β-Aminoalkyl Derivatives

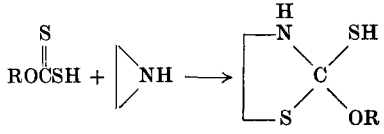
Thiol	References
Hydrogen sulfide	32, 147, 182, 184, 249, 274, 276, 338, 370, 27a
Alkyl mercaptans	27, 221, 370
Thiophenol	265, 370
Thiolcarboxylic acids	190, 247, 248, 317, 337, 338

The reaction of ethylenimine with carbon disulfide to give thiothiazolidone was discovered by Gabriel[159] and later extended to other aziridines[85, 370] (Eq. 56).

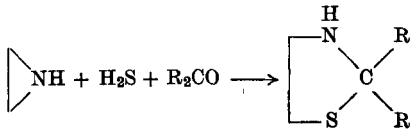


(56)

Ethylenimine reacts with xanthates to give a thiazolidine derivative[220] (Eq. 57) and with hydrogen sulfide plus various ketones to give dialkyl thiazolidines[35] (Eq. 58).

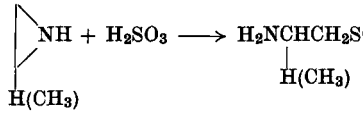


(57)



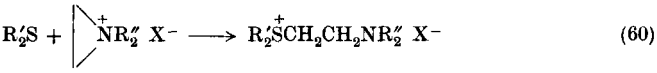
(58)

Ethylenimine and 2-methylaziridine react with sulfurous acid to give taurine and 2-aminopropane-1-sulfonic acid respectively[157, 162] (Eq. 59). However, a sulfonic acid did not give the expected sulfone.[183]



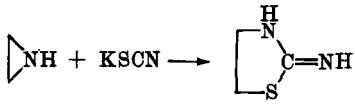
(59)

Some examples have been reported of the reaction of sulfides with quaternary aziridinium salts to give sulfonium salts[152] (Eq. 60).



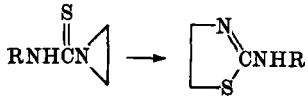
(60)

With potassium thiocyanate, aziridines give 2-iminothiazolidine derivatives[131, 161] (Eq. 61).



(61)

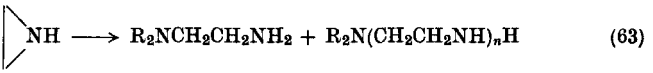
A variety of aziridine thiocarbanilides have been isomerized to 2-amino-2-thiazolines[121, 202, 222, 351] (Eq. 62).



(62)

D. Formation of Carbon–Nitrogen Bonds

Ammonia and primary and secondary amines react with aziridines to give diamines and polymers[368, 44] (Eq. 63). An acid catalyst, heat



(63)

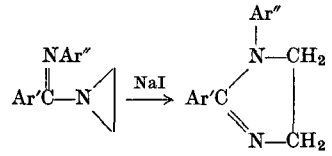
and pressure are frequently required to obtain a good yield of desired product.[83, 89, 212] The reaction occurs more readily with 1-sulfonylaziridines, probably because electron withdrawal by the sulfonyl group

makes the aziridine ring carbon atoms more susceptible to nucleophilic attack.[231, 278, 280] As expected, the reaction occurs with inversion of configuration when a nitrogen–secondary carbon bond is broken.[179, 370] Examples of the reaction are collected in Table 13.

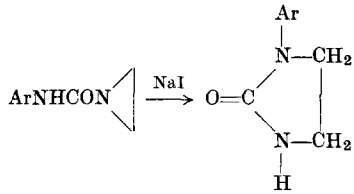
TABLE 13. Reactions of Aziridines with Ammonia and Amines Leading to the Formation of diamines and Polymers

Aziridine	References
Unsubstituted and alkylaziridine	29, 44, 59, 60, 83, 89, 179, 212, 368
1-Acylaziridine	223, 280, 295
1-Arylsulfonylaziridine	167, 231, 278, 280
7-Azabicyclo[4.1.0]heptane	370

1-(*N*-Arylbenzimidoyl)aziridines are isomerized by treatment with sodium iodide to give 1,2-diarylimidazolines[201] (Eq. 64), and 1-aziridinecarboxanilide is isomerized to 1-phenyl-2-imidazolidinone[202,223,275] (Eq. 65).

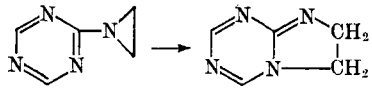


(64)



(65)

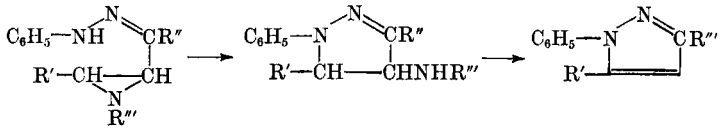
Further examples of such isomerizations have been reported;[202b, 202c] the whole topic of isomerization of aziridines has been reviewed in detail.[202a]



(66)

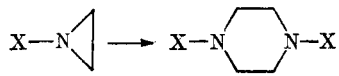
1-Aziridinyl-*sym*-triazines rearrange in the presence of sodium iodide or acid catalysts to form dihydroimidazo-[1,2-a]-*sym*-triazines[202] (Eq. 66).

Somewhat more complicated is the rearrangement of 2-aroyl-aziridine phenylhydrazones to pyrazolines, which readily lose a molecule of amine to give pyrazoles[99, 102, 106, 108, 111] (Eq. 67).



(67)

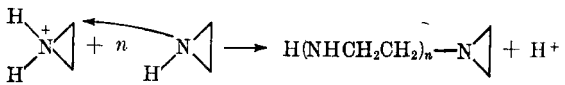
1-Aryl- and 1-arylsulfonyl-aziridines on treatment with sodium iodide are dimerized to piperazines[202] (Eq. 68).



(68)

E. Polymerization

Although many aziridines are quite stable and may be stored for a long time in the pure state or in the presence of alkali, contact with acidic or alkylating reagents frequently leads to rapid polymerization. This acid-catalyzed polymerization may be considered the particular instance of nucleophilic attack on an aziridinium ion by a molecule of aziridine.[193, 232, 255] Repetition of this reaction n times followed by loss of a proton leads to a polymer (Eq. 69).

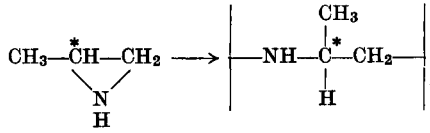


(69)

In addition to the propagation and termination steps shown, various chain-transfer and chain-branching reactions may occur, which lead to a highly branched structure. Such alternative reactions are diminished, and a more strictly linear product is obtained, by the polymerization of 1-alkyl- or 1-benzenesulfonyl-aziridines.[31]

The interpretation of the mechanism of polymerization is supported by studies of the kinetics of the reaction and the determination of the structure of low molecular weight polymers.[18, 226] For example, from the polymerization of ethylenimine, products have been identified corresponding to Eq. (69) where n = 1, 2 and 3.[31]

Although polymerization of racemic 2-methylaziridine gave only an oily product, the corresponding optically active monomer formed a solid optically active polymer of relatively low molecular weight. This observation suggests that the reaction involved ring opening at the primary carbon atom, leading to a chain with a high degree of steric regularity[269] (Eq. 70).



(70)

(Retention of configuration at *)

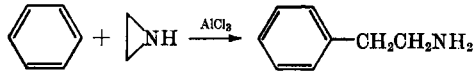
Because of the well-established industrial applications of polyethylenimine, and the potential value of other polymers of aziridine derivatives, many claims regarding such materials are to be found in the patent literature. Only those patents which are concerned with products of fairly well-defined structure are included in this review. Table 14 provides a key to the literature on aziridine polymers.

TABLE 14. Selected List of Aziridines Which Have Been Polymerized

Aziridines	References
Unsubstituted, alkyl-, and aryl-aziridines	18, 30, 44, 45, 49, 188, 197, 226, 232, 255, 269, 356
1-Acylaziridine	34, 46, 227, 243
1-Sulfonylaziridine	281
Copolymer with ethylene carbonate	128

F. Formation of Carbon–Carbon Bonds

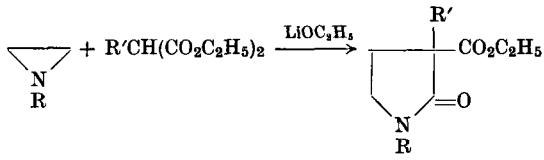
In the presence of aluminum chloride, benzene adds to aziridines to give β-aminoalkyl derivatives[56] (Eq. 71).



(71)

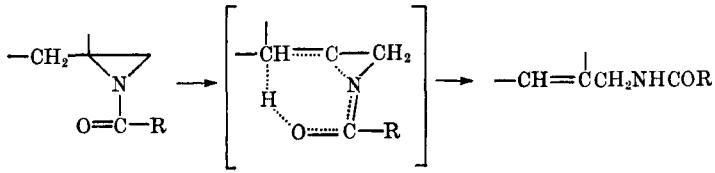
Similarly, the magnesium derivative of indole reacts with ethylenimine to give tryptamine in about 50% yield.[66a]

By heating *N*-substituted aziridines with lithium ethoxide and an excess of monoalkylated diethyl malonate, substituted pyrrolidones are formed[331b] (Eq. 71a).



(71a)

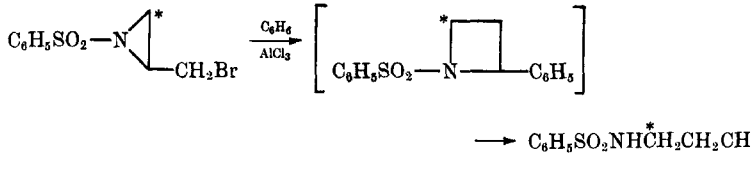
A general reaction of 1-acyl-2-*prim*-alkylaziridines is the pyrolytic rearrangement to an unsaturated amide[140, 340, 229] (Eq. 72). Stereochemical evidence supports the view that the reaction involves the intramolecular *cis*-elimination of a proton concerted with the opening of the aziridine ring (transition state, XLVI).[230]



(72)

(XLVI)

On treatment with aluminum chloride in benzene, 1-benzenesulfonyl-2-bromomethylaziridine gives an open-chain benzenesulfonamide (Eq. 73). Evidence provided by an isotopic-tracer study (discussed in further detail in the accompanying chapter on azetidines) is that the reaction occurs by way of an azetidine.[176, 177]

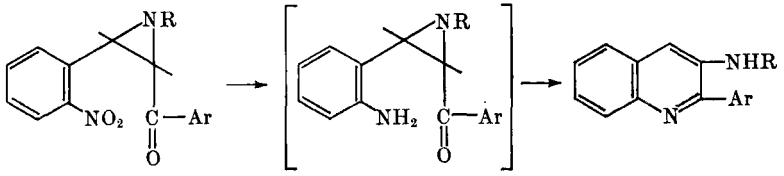


(73)

(* = isotopically labelled carbon atom)

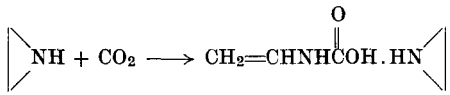
Catalytic hydrogenation of a 1-alkyl-2-aroyl-3-*o*-nitrophenylaziridine gives a 3-alkylamino-2-arylquinoline. The reaction may be

formulated as occurring via cyclization and rearrangement of an intermediate amine, which is not isolated[110] (Eq. 74).



(74)

Ethylenimine is alleged to react with carbon dioxide at low temperatures to give a vinylamine derivative, but the product is extremely unstable and not well characterized[319] (Eq. 75).



(75)

G. Hydrogenolysis

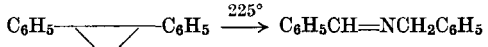
Unexpectedly, hydrogenolysis of aziridines does not consistently result in cleavage of the bond between the nitrogen atom and the less-substituted carbon atom of the ring. Examples of hydrogenolysis, collected in Table 15, do not permit any further generalization about the scope of the reaction.

TABLE 15. Hydrogenolysis of Aziridines

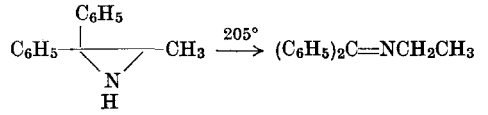
Aziridine	Catalyst or reagent	Product	References
Ethylenimine	Ni	Ethylamine	29
2,2-Dimethylaziridine	Ni	*tert*-Butylamine	75
1-Ethyl-2-methylene-aziridine	Pt	*N*-Ethyl-*n*-propylamine	52
1,2-Dimethyl-3-phenyl-aziridine	Pd	2-Methylamino-1-phenyl-propane	192
2-Carbamoyl-3-phenyl-aziridine	Pt	β-Phenylalanine amide	376
2-Phenyl-1-toluene-sulfonylaziridine	Pd	*N*-(β-Phenylethyl-*p*-toluenesulfonamide	234
7-Azabicyclo[4.1.0]-heptane	$LiAlH_4$	Cyclohexylamine	370

H. Other Ring-Opening Reactions

At high temperatures, some phenylated aziridines rearrange in an anomalous manner which corresponds to the cleavage of the carbon–carbon bond of the ring[90, 73] (Eqs. 76 and 77).

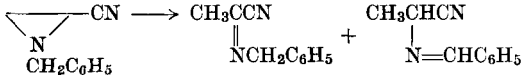


(76)



(77)

At 100°, 1-benzyl-2-cyanoaziridine is isomerized to a mixture of Schiff bases[190] (Eq. 77a).

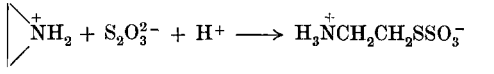


(77a)

With diborane, ethylenimine is cleaved to give $C_2H_5NHB_2H_5$ and other products,[68] and with fluorine complete fragmentation of the molecule is observed.[178]

6. Methods of Analysis

Although colorimetric[135, 303] and polarographic[258] methods for the determination of aziridines have been described, a more specific procedure is based on the consumption of 1 mole of acid per aziridine ring, which is very rapid in the presence of thiosulfate ion at pH 4[9, 311] (Eq. 78).



(78)

7. Toxicology: Industrial and Pharmacological Applications

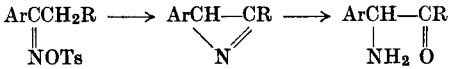
The toxicity of ethylenimine was noted by Gabriel and evaluated quantitatively by Ehrlich even before the structure was elucidated.[157, 159] Subsequent investigators reported further details of toxicological studies, and noted that skin, eyes, respiratory system and kidneys are attacked.[12, 77, 117] Several cases of poisoning of humans have been described.[226, 286]

The observation that aziridines exhibit a radiomimetic type of toxic action[181] led to extensive programs of synthesis and testing of aziridines and β-chloroalkylamines for pharmacological activity.[304, 307, 364] Some of these substances have reached advanced stages of evaluation as cancer chemotherapeutic agents,[7, 143, 215, 283] and a few are in regular clinical use.[22, 163]

The ability of ethylenimine to function as an alkylating agent has resulted in a number of industrial applications. Nucleophilic centers in cellulose,[127, 164] starch[233] and protein[10] react with ethylenimine to give products containing β-aminoalkyl groups.

III. Azirines, *C*-Alkoxyaziridines, and Aziridinones

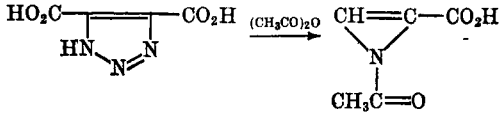
In a reinvestigation of the Neber rearrangement[277] of oxime tosylates to aminoketones it has been conclusively demonstrated that a 1-azirine is an intermediate (Eq. 79). When the reaction was run under slightly different conditions, an unstable alkoxyaziridine was obtained.[92, 195]



(79)

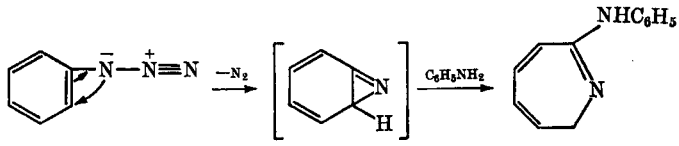
An alkoxyaziridine has also been proposed as an intermediate in a more complex rearrangement of 2-acetylcoumarone oxime tosylate.[172]

A 2-azirine structure has been assigned to a by-product of the reaction of acetic anhydride with the triazoledicarboxylic acid obtained from the treatment of acetylenedicarboxylic acid with hydrazoic acid[374] (Eq. 80).



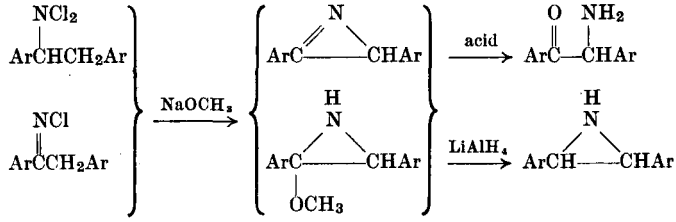
(80)

A resonance-stabilized azirine has been proposed as an intermediate in the reaction of phenylazide with aniline to give 2-anilino-7*H*-azepin[218] (Eq. 81).



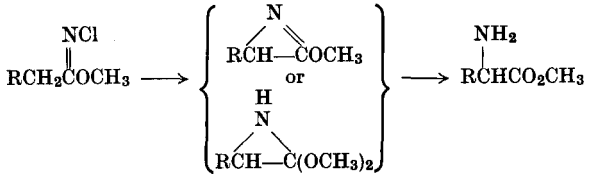
(81)

The reaction of *N*,*N*-dichloro-*sec*-alkylamines or *N*-chloroketimines with base gives an azirine (or related alkoxyaziridine) intermediate, which may be hydrolyzed to an aminoketone or reduced to an aziridine[20] (Eq. 82).



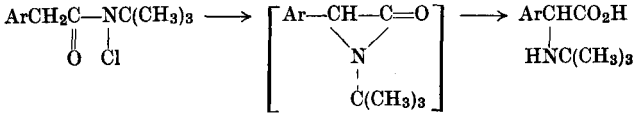
(82)

Similarly, an alkoxyazirine or a dialkoxyaziridine may be an intermediate in the formation of α-amino acid esters from *N*-chloroketimino esters by treatment with base followed by acid[20] (Eq. 83).



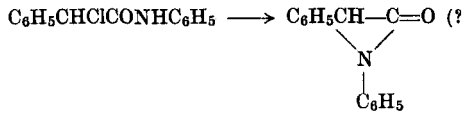
(83)

Infrared-spectral evidence indicates that an aziridinone is an intermediate in the formation of *N*-*tert*-butylamino acids from *N*-*tert*-butyl-*N*-chloroamides by treatment with base[20] (Eq. 84).



(84)

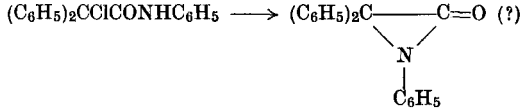
The preparation of 1,3-diphenyl-2-aziridinone by the treatment of α-chloro-α-phenylacetanilide with sodium hydride (Eq. 85) and 1,3,3-triphenyl-2-aziridinone by the treatment of α-chloro-α,α-diphenyl-



(85)

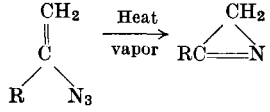
acetanilide with sodium hydride (Eq. 86) was reported briefly.[309] Doubt was cast on the validity of this report by a detailed reinvestigation, which showed that the conditions specified for Eq. (86) resulted

only in the formation of oxindole- and indoxyl-type compounds.[321] The formation of such five-membered ring compounds may be rationalized by means of the aziridinone intermediate.



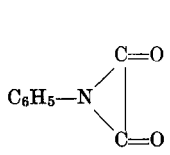
(86)

The vapor phase pyrolysis of vinyl azides leads to the formation of 2-substituted-1-azirines[329a] (Eq. 87).

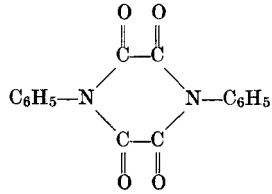


(87)

A compound previously thought to be an aziridinedione (XLVII) was later shown to be (XLVIII).[66]



(XLVII)



(XLVIII)

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CHAPTER III

Ethylene Sulfides

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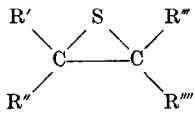
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I. Introduction

The ethylene sulfides (I) are known as olefin sulfides, thiiranes, and



(I)

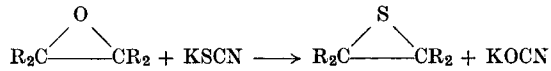
thiacyclopropanes. The olefin sulfide type of nomenclature is widely used in naming specific compounds, *e.g.* ethylene sulfide, propylene sulfide, cyclohexene sulfide, *etc.* The name thiirane is in accord with good nomenclature, but it has been slow to find a place in the literature. The thiacyclopropane terminology is not widely used. The general term 'episulfide' may have a broad meaning. However, it is to be understood that, as used herein, it refers only to the three-membered ring structure. Likewise, 'epoxide' implies an ethylene oxide structure.

An attempt has been made in this chapter to cover the literature pertaining to ethylene sulfide cited in *Chemical Abstracts* up to January, 1961.

II. Methods of Preparation

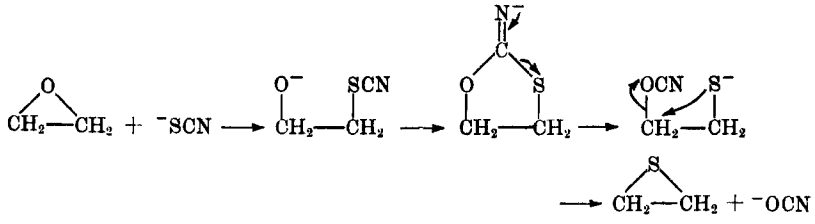
1. From Epoxides and Salts of Thiocyanic Acid

Epoxides react with salts of thiocyanic acid to yield the corresponding episulfides and a salt of cyanic acid:



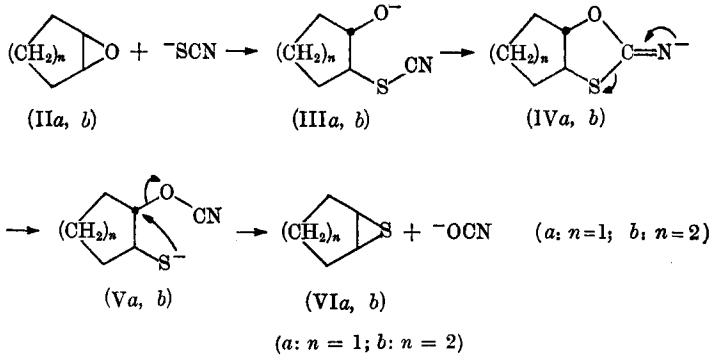
This method has been applied for the synthesis of ethylene sulfide,[5, 11, 22, 67] propylene sulfide,[62] *cis*- and *trans*-2-butene sulfides,[75, 78] *iso*butylene sulfide,[107] cyclohexene sulfide,[19, 107] 3-bisethoxypropylene sulfide,[122] and styrene sulfide.[50] A modification of this reaction has been used for the synthesis of carbohydrates possessing episulfide structures.[48]

The mechanism shown in Eq. (1) has been suggested for the reaction of ethylene oxide with the thiocyanate ion.[42]



(1)

Van Tamelen[118] proposed that if such a mechanism is operative, one might expect the conversion of cyclopentene oxide (II*a*) into cyclopentene sulfide (VI*a*) (Eq. 2) to be difficult since it would involve a strained intermediate (IV*a*) possessing two five-membered rings fused in a *trans* sense. Experimentally, treatment of (II*a*) with potassium

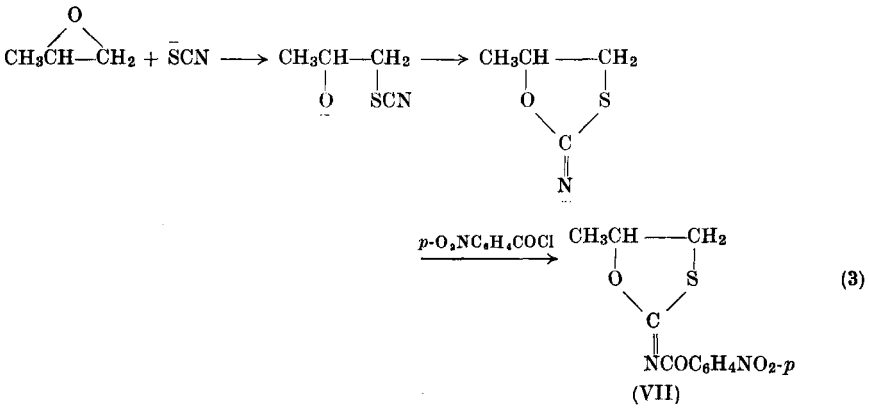


(2)

(II*a*, *b*) (III*a*, *b*) (IV*a*, *b*) (V*a*, *b*) (VI*a*, *b*)

(*a*: $n = 1$; *b*: $n = 2$)

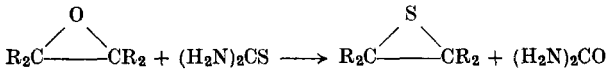
thiocyanate under conditions equivalent to, or more vigorous than, those which brought about a 73% yield of cyclohexene sulfide (VI*b*) from cyclohexene oxide (II*b*) gave only recovered cyclopentene oxide. Further, alkaline treatment of *trans*-2-hydroxycyclopentylthiocyanate (protonated III*a*) did not yield cyclopentene sulfide, although *trans*-2-hydroxycyclohexylthiocyanate (protonated III*b*) was readily converted into cyclohexene sulfide by treatment with base. Support for the oxathiolane structure (such as IV*a*) as an intermediate has come from the isolation of 2-(*p*-nitrobenzimino)-5-methyl-1,3-oxathiolane (VII) when propylene oxide and potassium thiocyanate were reacted in the presence of *p*-nitrobenzoyl chloride[78] (Eq. 3).



(3)

2. From Epoxides and Thiourea or Other Thioamides

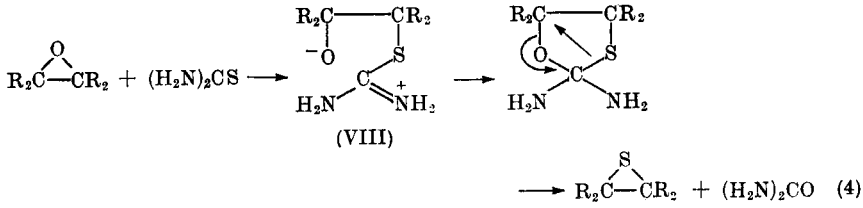
Epoxides react with thiourea in a manner analogous with their reaction with thiocyanate ion.



This, the most generally used method for preparing episulfides from the corresponding epoxides,[8, 9, 15, 53, 56, 69, 101] has given good yields of ethylene,[80] propylene,[8, 19] 3-chloropropylene,[19] *iso*butylene,[19] and cyclohexene sulfides.[19] The mechanism shown in Eq. (4) has been suggested[16, 20] for the reaction.

When the reaction is conducted in the presence of at least an equimolar quantity of acid, the isothiuronium salt (IX) may be obtained in yields up to 80%. The nature of the products obtained on

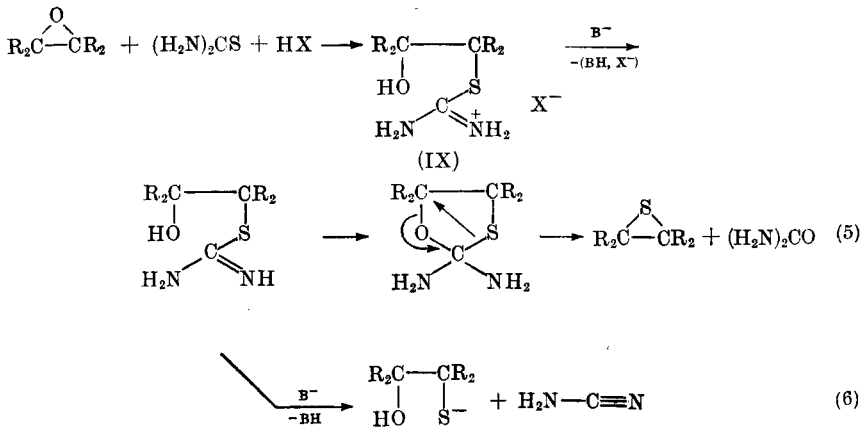
alkaline hydrolysis of (IX) depends on the procedure used.[8, 61] When excess of aqueous alkali is added to an acidic solution of (IX), the



(VIII)

(4)

major product is the corresponding episulfide (Eq. 5). When an aqueous solution of (IX) is added to an excess of aqueous alkali, the major product is the corresponding 2-hydroxyethanethiol (Eq. 6).

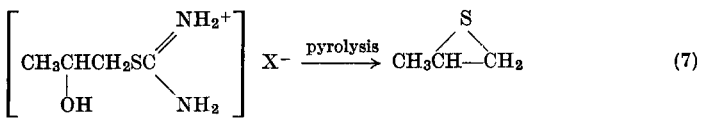


(IX)

(5)

(6)

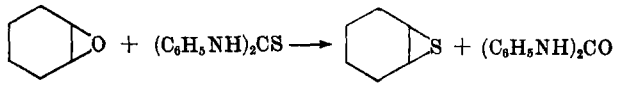
S-Hydroxyethylisothiuronium salts may be thermally decomposed to episulfides.[8] Propylene sulfide is formed by heating an aqueous or a dioxan solution of *S*-2-hydroxy-1-propylisothiuronium acetate, or by pyrolysis of the dry benzoate (Eq. 7). Aqueous solutions of the chloride or sulfate do not yield propylene sulfide on heating.



(X = acetate or benzoate)

(7)

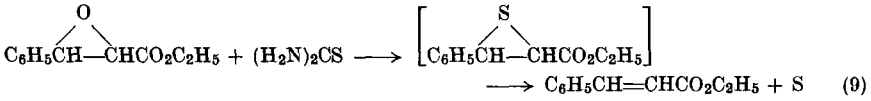
Thiocarbanilide reacts with cyclohexene oxide to yield (37%) cyclohexene sulfide[19] (Eq. 8). Thioacetamide, thiobenzamide, xanth-



(8)

amide, and thiobarbituric acid react similarly[17] to form episulfides and the oxygen analog of the thio reactant. The oxygen analogs were found in high yields but polymerization prevented isolation of the episulfides.

Thiourea, as well as the other thioamides, reacts with ethyl phenylglycidate to yield ethyl cinnamate, sulfur and the *o*-amide (Eq. 9). This is in accord with the fact that other aromatic-substituted

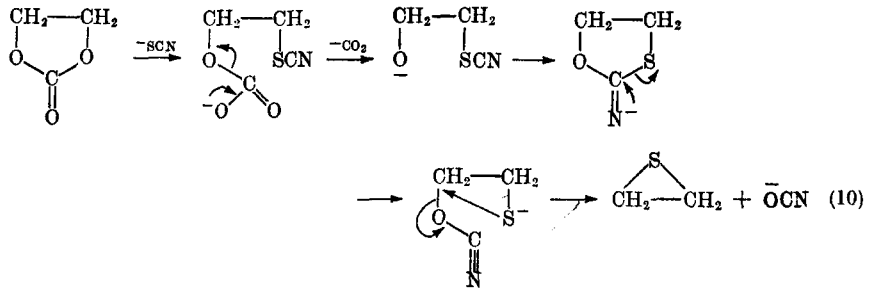


(9)

ethylene sulfides lose sulfur readily to form the corresponding unsaturated compound.

3. From Ethylene Carbonate and Potassium Thiocyanate

The fusion of ethylene carbonate with potassium thiocyanate at 95° produces ethylene sulfide in 65% yield.[102]

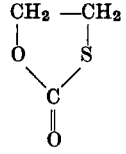


(10)

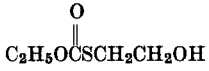
It has been suggested that the reaction proceeds by a mechanism (Eq. 10) similar to that proposed for the formation of episulfides from epoxides and thiocyanates.

4. By Pyrolysis of Certain Thiolcarbonates and 2-Mercaptoalkyl Carbonates

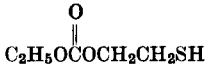
Ethylene monothiolcarbonate (X), ethyl 2-hydroxyethylthiolcarbonate (XI), and ethyl 2-mercaptoethylcarbonate (XII) are readily pyrolyzed to yield ethylene sulfide.[84, 89] At atmospheric pressure (X)



(X)



(XI)

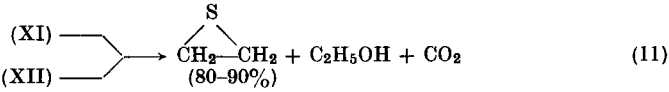


(XII)

and (XII) require alkaline catalyst for smooth decomposition. The highest yield of ethylene sulfide from (XI), however, is obtained in the absence of catalyst.

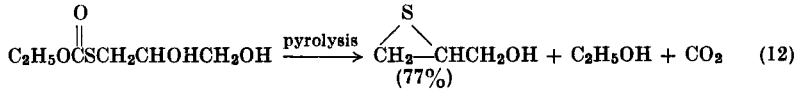
Ethylene monothiolcarbonate (X) is a convenient source of ethylene sulfide since the only by-product is carbon dioxide. When 1 mole of ethylene monothiolcarbonate is pyrolyzed in the presence of 1 mg. of sodium methoxide, the yields of ethylene sulfide range between 70 and 80%.

Ethylene sulfide is obtained with an equimolar amount of ethanol when (XI) and (XII) are precursors (Eq. 11).



(11)

The generality of the pyrolysis of ethyl 2-hydroxyalkylthiolcarbonate is further illustrated[89] by preparation of 2-hydroxymethylethylene sulfide (XIII) by pyrolysis of (XIV) (Eq. 12).



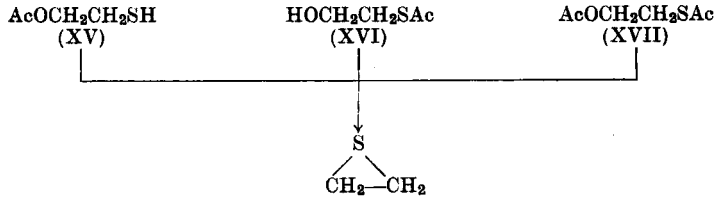
(12)

(XIV) (XIII)

5. By Alkaline Hydrolysis of Acylated Vicinal Hydroxy–Thiols

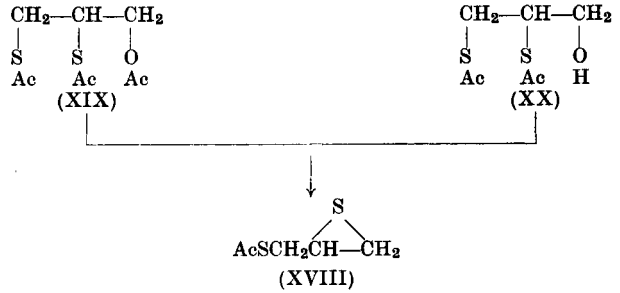
The deacetylation of vicinal hydroxy–thiol acetates proceeds abnormally owing to competitive episulfide formation.[54, 68] 2-Mercaptoethyl acetate (XV), the isomeric *S*-acetyl compound (XVI), and the diacetate (XVII) yield ethylene sulfide when treated with dilute alkali (Eq. 13).

Similarly, the *S*-acetyl, the *O*-acetyl, as well as the diacetyl derivatives of *trans*-2-mercaptocyclohexanol, give good yields of cyclohexene sulfide.



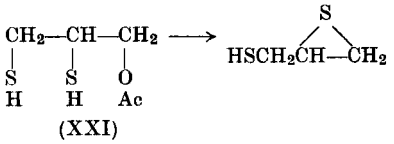
(13)

Under mild alkaline conditions 3-acetylthiopropylene sulfide (XVIII) can be prepared from 2,3-di(acetylthio)propyl acetate (XIX), as well as from 2,3-di(acetylthio)propanol (XX) (Eq. 14).



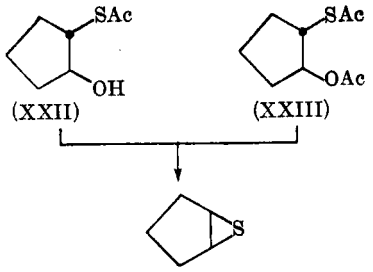
(14)

2,3-Dimercaptopropyl acetate (XXI) gives 3-mercaptopropylene sulfide (Eq. 15).



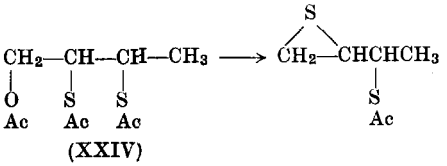
(15)

Cyclopentene sulfide is obtained by the reaction of *trans*-2-acetylthiocyclopentanol (XXII) with sodium bicarbonate and by the reaction of *trans*-2-acetylthiocyclopentyl acetate (XXIII) with aqueous sodium hydroxide (Eq. 16). Use of methanolic sodium methoxide[47] instead of sodium hydroxide reduced the yield.

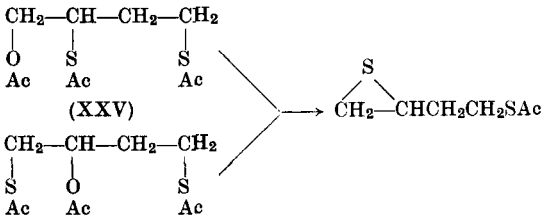


(16)

The reactions of the triacetates of 2,3-dimercapto-1-butanol (XXIV), 2,4-dimercapto-1-butanol (XXV), 1,4-dimercapto-2-butanol (XXVI), 3,4-dimercapto-2-butanol (XXVII), 1,3-dimercapto-2-methyl-2-propanol (XXVIII), 2,5-dimercapto-1-pentanol (XXIX), 1,6-dimercapto-2-hexanol (XXX), and 2,11-dimercapto-1-undecanol (XXXI) with sodium bicarbonate give good yields of the respective episulfides.[39]

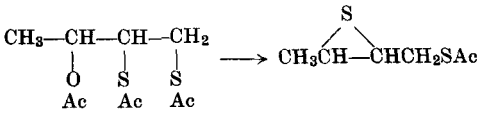


(XXIV)

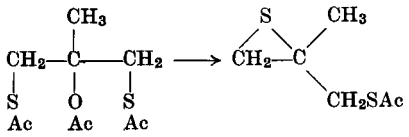


(XXV)

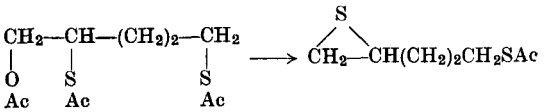
(XXVI)



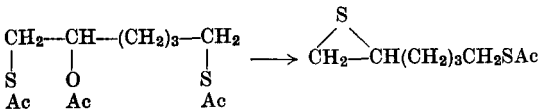
(XXVII)



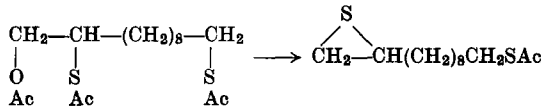
(XXVIII)



(XXIX)

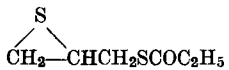


(XXX)



(XXXI)

Under the same reaction conditions the tripropionates and tributyrates of 2,3-dimercaptopropanol yield 3-propionylthiopropylene sulfide (XXXII) and 3-butyrylthiopropylene sulfide (XXXIII) respectively.

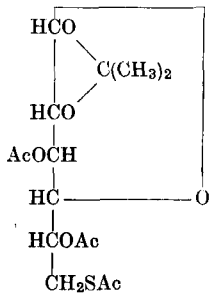


(XXXII)

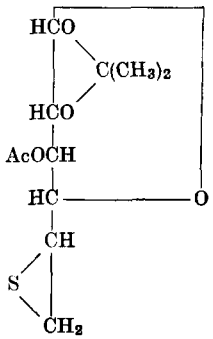


(XXXIII)

3,5-Di-*O*-acetyl-6-acetylthio-6-deoxy-1,2-*O*-*iso*propylidene-α-D-glucose (XXXIV) yields the episulfide (XXXV) when treated with sodium methoxide in a chloroform–methanol mixture[15] (Eq. 17).



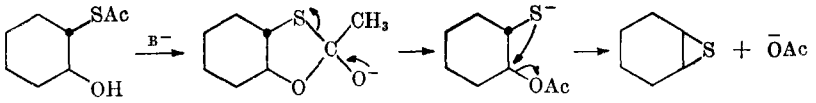
(XXXIV)



(XXXV)

(17)

A detailed study[68] of this method of synthesis has been made during which cyclohexene sulfide was prepared. The fact that cyclohexene sulfide is formed from both the *S*- and *O*-monoacetates of



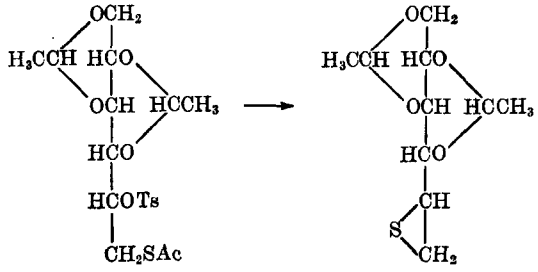
(XXXVI) (XXXVII)

(18)

trans-2-mercaptocyclohexanol supports the generally accepted mechanism that (XXXVII) is the true precursor of the episulfide and that (XXXVI) undergoes an isomerization, as shown in Eq. (18).

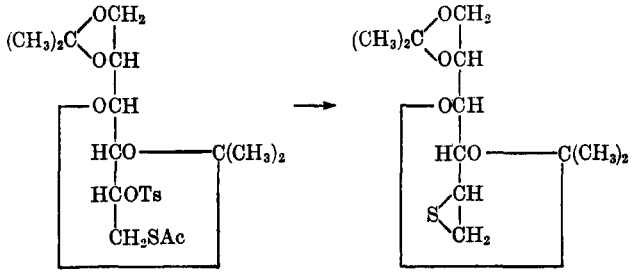
6. By Alkaline Hydrolysis of Vicinal Tosylates–Thiolacetates

The most successful application of this method has been in the synthesis of carbohydrate episulfides.[15] 5,6-Dideoxy-5,6-epithio-1,3:2,4-di-*O*-ethylidene-L-iditol (XXXVIII) is obtained by reacting 6-acetylthio-6-deoxy-1,3:2,4-di-*O*-ethylidene-5-*O*-tosyl-D-glucitol (XXXIX) with sodium methoxide.



(XXXIX) (XXXVIII)

Similarly, 5,6-dideoxy-5,6-epithio-1,2:3,4-di-*O*-*iso*propylidene-L-glucitol (XL) is obtained from 6-acetylthiol-6-deoxy-1,2:3,4-di-*O*-*iso*propylidene-5-*O*-tosyl-D-mannitol (XLI).

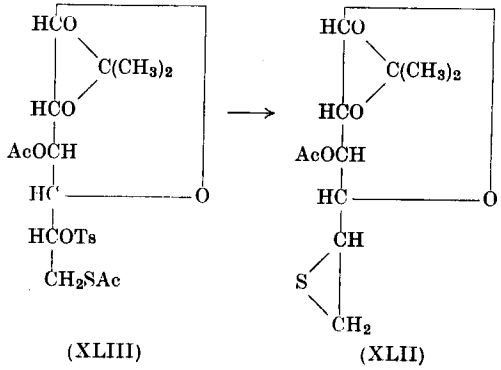


(XLI) (XL)

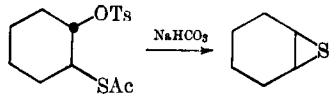
3-*O*-Acetyl-5,6-dideoxy-5,6-epithio-1,2-*O*-*iso*propylidene-α-L-idose (XLII) is obtained from 3-*O*-acetyl-6-acetylthio-6-dioxy-1,2-*O*-*iso*propylidene-5-*O*-tosyl-α-D-glucose (XLIII).

Cyclohexene sulfide results from the reaction of *trans*-2-acetylthiocyclohexyl *p*-toluenesulfonate with sodium bicarbonate[55] (Eq. 19).

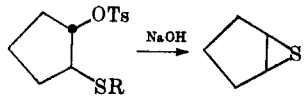
trans-2-Acetylthiocyclopentyl *p*-toluenesulfonate and *trans*-2-benzoylthiocyclopentyl *p*-toluenesulfonate are converted to cyclo-



(XLIII) (XLII)



(19)

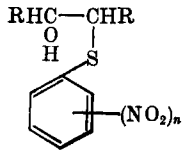


(20)

(R = acetyl or benzoyl)

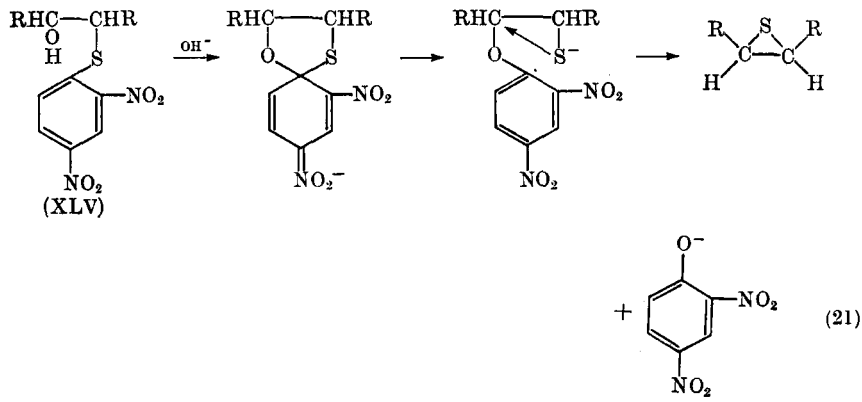
pentene sulfide by sodium hydroxide in triethylene glycol or its dimethyl ether (Eq. 20).

7. From 2-(Nitrophenylthio)ethanols and Alkali



(XLIV)
(n = 1–3)

Compounds of the type (XLIV) are converted by dilute alkali into the corresponding nitrophenol and episulfide.[20] The reaction mechanism depicted in Eq. (21) has been suggested.



(21)

8. From 2-Chloroethylthiocyanate or Ethylenedithiocyanate and Sodium Sulfide

These preparations, as represented by Eqs. (22) and (23), are of historical interest since they were used by Delépine in the early syntheses of ethylene sulfide.[33-37]

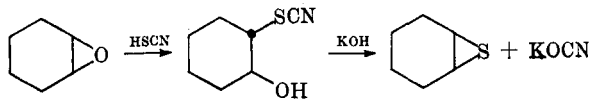
$$ClCH_2CH_2SCN + Na_2S \longrightarrow \underset{CH_2—CH_2}{\overset{S}{\diagup\diagdown}} + NaCl + NaSCN \qquad (22)$$

Cyclohexene sulfide,[73] 2-cyclohexylethylene sulfide,[73] and tetramethylethylene sulfide[123] are reported to be formed in poor yields from the corresponding dithiocyanates.

$$NCSCH_2CH_2SCN + Na_2S \longrightarrow \underset{CH_2—CH_2}{\overset{S}{\diagup\diagdown}} + 2NaSCN \qquad (23)$$

9. From Vicinal Hydroxy-Thiocyanates

trans-2-Hydroxycyclohexyl thiocyanate (XLVI) may be prepared by the ring opening of cyclohexene oxide with thiocyanic acid. Slow

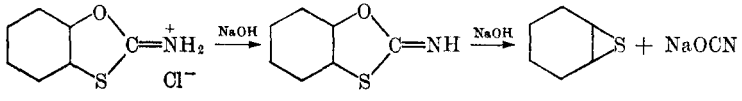


(24)

(XLVI)

addition of dilute potassium hydroxide to (XLVI) yields cyclohexene sulfide[118] (Eq. 24).

The crystalline hydrochloride (XLVII) is formed by saturating (XLVIII) with dry hydrogen chloride. The slow addition of 2 molar equivalents of alkali to (XLVII) gives cyclohexene sulfide,[118] in good yield (Eq. 25).



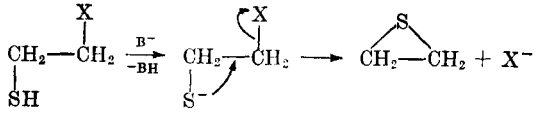
(25)

(XLVII) (XLVIII)

These reactions support the postulated reaction mechanism for formation of cyclohexene sulfide from cyclohexene oxide and potassium thiocyanate (Eq. 2).

10. By Dehydrohalogenation of 2-Haloethanethiols

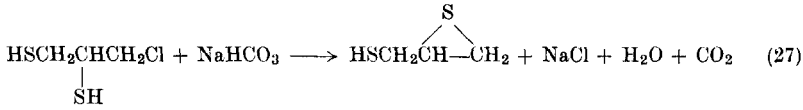
2-Haloethanethiols react with base to yield episulfides according to Eq. (26). Optimum yields of the episulfides are obtained by main-



(26)

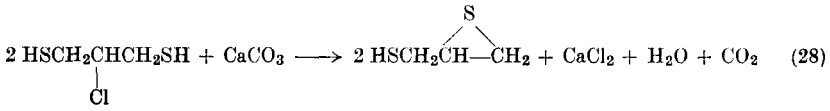
taining the pH between 7.5 and 9.5.[12] Satisfactory reagents are sodium borate, sodium bicarbonate, sodium acetate, or a buffer composed of sodium hydrogen phosphate and sodium dihydrogen phosphate.

3-Mercaptopropylene sulfide is obtained by treating 2,3-dimercaptopropyl chloride with sodium bicarbonate[39] (Eq. 27). A less



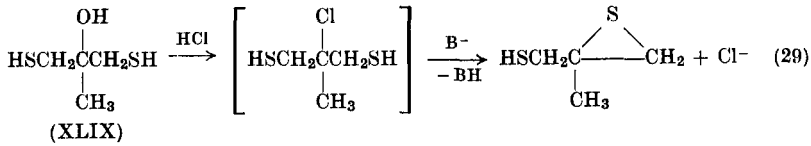
(27)

satisfactory procedure involves the reaction of 2-chloro-1,3-dimercaptopropane with calcium carbonate (Eq. 28).



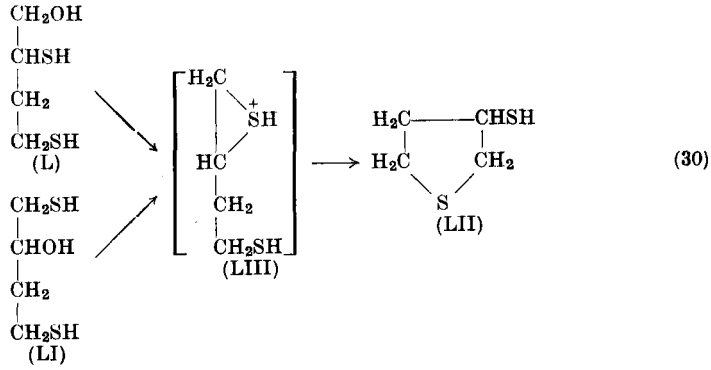
(28)

Crude 1,3-dimercapto-2-methyl-2-propanol (XLIX) gives 2-mercaptomethyl-2-methylethylene sulfide (Eq. 29).



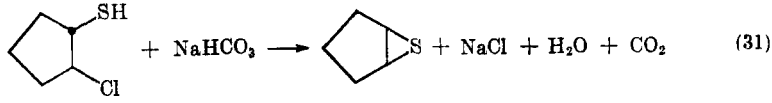
(29)

Interestingly, the action of cold concentrated hydrochloric acid on 2,4-dimercapto-1-butanol (L) and 1,4-dimercapto-2-butanol (LI) does not give the chloro dithiol as does 2,3-dimercaptopropanol. Instead, the product is 3-mercaptothiophane (LII), which may be formed via the cyclic sulfonium ion (LIII) (Eq. 30).



(30)

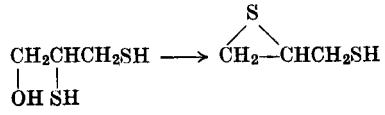
Cyclopentene sulfide was first prepared by the reaction of sodium bicarbonate on *trans*-2-chlorocyclopentanethiol[118] (Eq. 31).



(31)

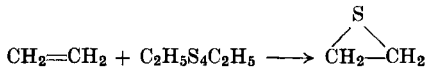
11. By Dehydration of 2-Hydroxyethanethiols

One application of this reaction is known.[105] 2,3-Dimercaptopropanol is dehydrated by heat to give 3-mercaptopropylene sulfide.



12. By Addition of Sulfur to Unsaturated Compounds

Ethylene, propylene, and cyclohexene are converted in low yields into the corresponding episulfides by reacting the olefin with ethyl tetrasulfide at approximately 150°.[60] The ethyl tetrasulfide serves as a source of free sulfur.

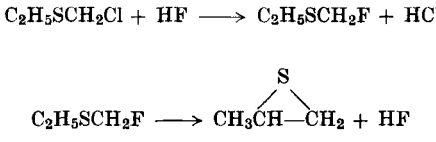


$$CH_2{=}CH_2 + C_2H_5S_4C_2H_5 \longrightarrow \overset{S}{\overset{/\quad\backslash}{CH_2{-}CH_2}}$$

Unsaturated fatty acids and unsaturated glycerides are transformed into episulfides by adding sulfur at the site of unsaturation.[29-32] The procedure involves heating the acid or glyceride with an excess of sulfur at a temperature in the range 135–200°. The use of iodine as a catalyst shortens the reaction time.

13. From Ethyl Chloromethyl Sulfide and Hydrogen Fluoride

Propylene sulfide is formed by the reaction of hydrogen fluoride with ethyl chloromethyl sulfide.[77]

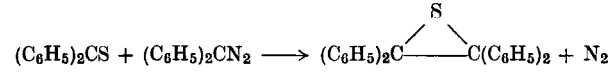


$$C_2H_5SCH_2Cl + HF \longrightarrow C_2H_5SCH_2F + HCl$$

$$C_2H_5SCH_2F \longrightarrow \overset{S}{\overset{/\quad\backslash}{CH_3CH{-}CH_2}} + HF$$

14. From Diazomethanes and Thioketones

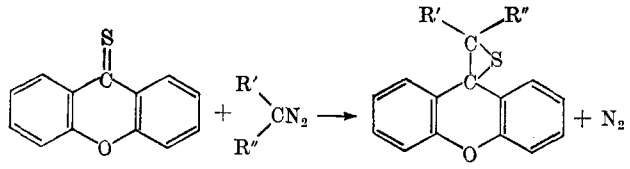
Aryldiazomethanes react with aromatic thioketones to yield episulfides.[113] An illustrative example is the reaction of diphenyldiazomethane with thiobenzophenone:



$$(C_6H_5)_2CS + (C_6H_5)_2CN_2 \longrightarrow \overset{S}{\overset{/\quad\backslash}{(C_6H_5)_2C{-}C(C_6H_5)_2}} + N_2$$

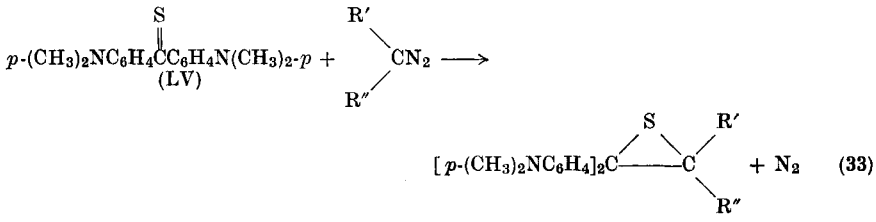
The non-carbonyl-substituted aliphatic diazo compounds, *e.g.* diphenyldiazomethane, phenyldiazomethane, biphenylenediazomethane, *etc.*, react very readily. Monocarbonyl-substituted compounds, *e.g.* diazoacetic esters and phenylbenzoyldiazomethane, react more slowly, and the dicarbonyl-substituted compounds, *e.g.* diazomalonic ester, benzoyldiazoacetic esters, *etc.*, do not react with benzothiophenone.

The behavior of different thioketones toward a given diaryldiazomethane also varies widely. Xanthione (LIV) and Michler thioketone (LV) are transformed into episulfides by reaction with diazomethanes[100] (Eqs. 32 and 33).



(32)

(LIV)

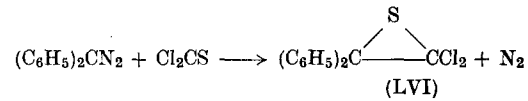


(33)

(LV)

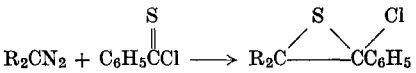
15. From Diazomethanes and Thioacid Chlorides

Thiophosgene reacts vigorously with certain diazo compounds even in the cold.[114] For example, diphenyldiazomethane and thiophosgene yield an episulfide of structure (LVI).



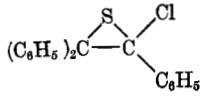
(LVI)

The reaction of thiobenzoyl chloride with the aliphatic diazo compounds is quite analogous with that of thiophosgene (Eq. 34). It reacts rapidly with noncarbonyl-substituted diazo compounds, slowly with monocarbonyl derivatives, and not at all with dicarbonyl-substituted diazo compounds.

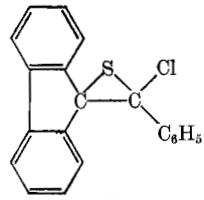


(34)

Diphenyl diazomethane and biphenylene diazomethane yield episulfides (LVII) and (LVIII) respectively.

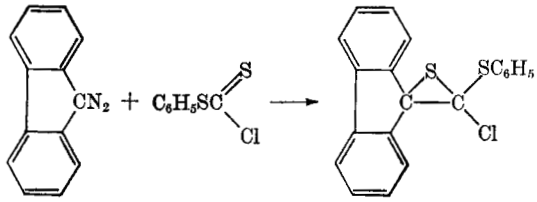


(LVII)

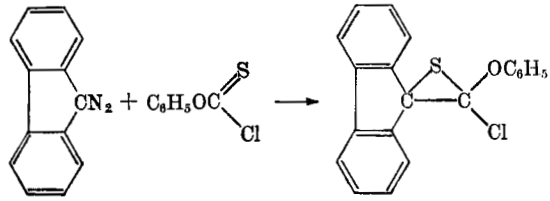


(LVIII)

Biphenylene diazomethane reacts with the phenyl chlorothiocarbonates as indicated in Eqs. (35) and (36).[96]



(35)

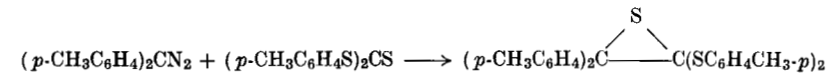


(36)

16. From Diaryldiazomethanes and Thioesters

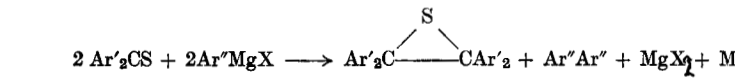
Diaryldiazomethanes react with aryltrithiocarbonates to yield 2,2-diaryl-3,3-diarylthioethylene sulfides.[96] These reactions have been applied in the following preparations:





17. From Aromatic Thioketones and Grignard Reagents

Aromatic thioketones react vigorously with Grignard reagents to yield substituted ethylene sulfides:[95]

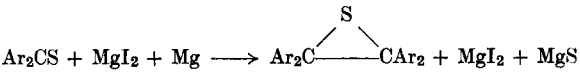


From a given thioketone one obtains the same tetraarylethylene sulfide regardless of the Grignard reagent. The yield of episulfide depends both on the type of thioketone and Grignard reagent used.

This method has been used to prepare tetraanisylethylene sulfide and *p,p',p'',p'''*-tetraethoxytetraphenylethylene sulfide.

18. From Aromatic Thioketones, Magnesium and Magnesium Iodide

Aromatic thioketones react with a mixture of magnesium and magnesium iodide in ether to yield a tetraarylethylene sulfide:[94]

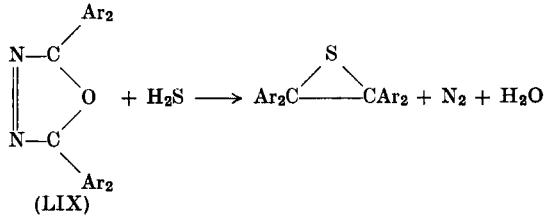


$$2\,Ar_2CS + MgI_2 + Mg \longrightarrow Ar_2C\overset{S}{\diagdown\diagup}CAr_2 + MgI_2 + MgS$$

Tetraanisylethylene sulfide has been prepared by this method.

19. From 2,2,5,5-Tetraaryl-2,5-dihydro-1,3,4-oxadiazoles and Hydrogen Sulfide

When dry hydrogen sulfide is passed into a boiling ethanolic solution of a tetraaryldihydrooxadiazole (LIX), a tetraarylethylene sulfide is formed.[99]



$$\underset{\text{(LIX)}}{\text{N,N-dihydro-1,3,4-oxadiazole, 2,2,5,5-tetraaryl}} + H_2S \longrightarrow Ar_2C\overset{S}{\diagdown\diagup}CAr_2 + N_2 + H_2O$$

This reaction has been used for the preparation of tetraphenylethylene sulfide, tetra-*p*-tolylethylene sulfide, and tetraanisylethylene sulfide.

III. Properties

1. Physical Properties

A. Spectra

The first spectral studies of ethylene sulfide[43] were made in the region of 0.7–1.2 microns. The range was later extended to 1–17 microns.[51, 116, 117] The Raman spectrum has been examined also.[116, 117]

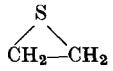
A determination of bond distances and angles from microwave spectra has been applied to structural studies of ethylene sulfide.[21]

The ultraviolet spectra of the several episulfides studied[26] in both solution and in the gas phase are characterized by one band in the region of 2600 Å (38,460 cm.$^{-1}$). Studies have been made on ethylene sulfide, propylene sulfide, and cyclohexene sulfide. The solution spectra have inflections in the region of 2450 Å (40,820 cm.$^{-1}$). The gas-phase spectrum reveals a distinct second transition.

Comparative studies[27] with the 4-, 5-, and 6-membered ring homologs of ethylene sulfide have shown that the absorption shifts to longer wavelengths as the electron density on the sulfur increases. A correlation of ring size and electron distribution in the ring is the subject of an earlier study.[104]

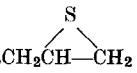
B. Tabulation of Physical Properties

TABLE 1. Ethylene Sulfide



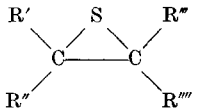
B.p.	n_D^{20}	d_4^{20}	Molar refraction	Dipole moment	References
55–56°	1.4914	1.0046	17.33	1.66 ± 0.03D	26, 34, 36, 49, 65, 84

TABLE 2. Substituted Propylene Sulfides



R—	B.p. (°C)	n_D	References
H—	75–77	n_D^{19} 1.4730	8, 19, 23, 26, 36, 60, 77
CH_3—	104–105	n_D^{15} 1.475	36
n-C_3H_7—	—	—	9
n-C_5H_{11}—	83/5 mm.	n_D^{20} 1.4702	69
CH_2=CH—	103–104	—	17
Cl—	79–81/114 mm.	n_D^{20} 1.5280	19
HS—	66–67/20 mm.	n_D^{18} 1.5810	39, 68, 54, 63, 105
CH_3O—	—	—	101
C_2H_5O—	79/65 mm.	n_D^{20} 1.4734	2
C_6H_5O—	94/4 mm.	n_D^{20} 1.5742	62
CH_3S—	98–99/35 mm.	n_D^{20} 1.5600	2
C_2H_5S—	85/13 mm.	n_D^{20} 1.5450	2
$(C_2H_5)_2N$—	72/14 mm.	n_D^{20} 1.4857	2
$C_6H_5\overset{\displaystyle CH_3}{\overset{|}{N}}$—	107–108/0.1 mm.	n_D^{11} 1.606	24

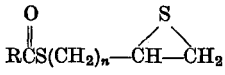
TABLE 3. Aliphatic-Substituted Ethylene Sulfides



R′—	R″—	R‴—	R⁗—	B.p. or *m.p. (°C)	n_D	References
CH_3—	H—	CH_3—	H—	51–51.5°/130 mm.	n_D^{20} 1.4765	75
CH_3—	CH_3—	H—	H—	84–86°	n_D^{20} 1.4641	19, 107
CH_3—	H—	H—	CH_3—	88–89°/735 mm.	n_D^{25} 1.4587[a]	56, 78, 75
CH_3—	CH_3—	CH_3—	CH_3—	127° / *76.1–76.6°		123
n-C_6H_{17}—	H—	$HO_2C(CH_2)_7$—	H—	—	—	29, 31, 32
n-C_5H_{11}—	H—	$HO_2C(CH_2)_7CH{=}CHCH_2$—	H—	—	—	30
CH_3COSCH_2—	CH_3—	H—	H—	41°/0.15 mm.	n_D^{20} 1.5397	39
CH_3COSCH_2—	H—	CH_3—	H—	42°/0.08 mm.	—	39
$CH_3COSCH(CH_3)$—	H—	H—	H—	64°/0.1 mm.	n_D^{20} 1.5401	39
$C_2H_5O_2C$—	H—	CH_3—	C_2H_5—	77–79°/7 mm.	n_D^{23} 1.4683	41
CH_3—	$HSCH_2$—	H—	H—	66–67°/17 mm.	n_D^{24} 1.5534	39
$(C_2H_5O)_2CH$—	H—	H—	H—	84°/14 mm.	n_D^{20} 1.4613	122

[a] Other properties are: d_4^{25} 1.4587; MR_D 27.08; $[\alpha]_D^{25} - 129.0°$.

TABLE 4. Acylthioalkylethylene Sulfides



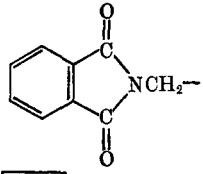
R—	n	B.p. or *m.p. (°C)	n_D^{25}	References
CH_3—	1	46°/0.1 mm.	1.5530	2, 39, 44, 54, 55, 68
C_2H_5—	1	45–47°/0.01 mm.	—	39
n-C_3H_7—	1	61–65°/0.15 mm.	1.5365	2, 39
C_6H_{11}—	1	89°/0.05 mm.	1.5476	2
n-$C_{15}H_{31}$—	1	*59–60°	—	2
$ClCH_2$—	1	88°/0.2 mm.	1.5836	2
Cl_2CH—	1	86°/0.1 mm.	1.5858	2
Cl_3C—	1	111°/0.4 mm.	1.5830	2
$ClCH_2CH_2$—	1	98°/0.2 mm.	1.5645	2
$C_2H_5SCH_2$—	1	112°/0.025 mm.	1.5810	2
$CH_3SCH_2CH_2$—	1	122°/0.01 mm.	1.5789	2
$CH_3COCH_2CH_2$—	1	106°/0.01 mm.	1.5440	2
$C_2H_5O_2CCH_2$—	1	110°/0.15 mm.	1.5286	2
$CH_3O_2CCH_2CH_2$—	1	120–124°/0.1 mm.	1.5382	2
C_2H_5OCO—	1	116–118°/0.3 mm.	1.5407	2
CH_3O—	1	65°/0.25 mm.	1.5432	2
C_2H_5O—	1	60°/0.01 mm.	1.5296	2
n-C_4H_9O—	1	103°/0.01 mm.	1.5164	2
$C_6H_5CH_2O$—	1	140°/0.05 mm.	1.5828	2
C_6H_5—	1	130°/0.01 mm.	1.6242	2
p-ClC_6H_4—	1	*74°	—	2
p-$NO_2C_6H_4$—	1	*62	—	2
p-$CH_3CONHC_6H_4$—	1	*163°	—	2
p-$(CH_3)_2NC_6H_4$—	1	*78–81°	—	2
$HO_2CCH_2CH_2$—	1	*78–80°	—	2
p-$C_6H_4N{=}NC_6H_4$—	1	*81–82°	—	2
C_6H_4(1,4-bis)—	1	*112–113°	—	2
$C_6H_5CH_2$—	1	137–138°/0.3 mm.	1.5981	2
$(C_6H_5)_2CH$—	1	*63°	—	2
C_6H_5CHCl—	1	*69–71°	—	2
p-$ClC_6H_4CH_2$—	1	*32–34°	—	2
p-$ClC_6H_4OCH_2$—	1	*42–42.5°	—	2
$C_6H_5CH_2OCONHCH_2$—	1	*69°	—	2
$C_6H_5CONHCH_2$—	1	*121°	—	2
$C_6H_5CH_2CH(C_6H_5CONH)$—	1	*130°	—	2
	1	*102°	—	2
	1	120°/0.1 mm.	1.6180	2
CH_3—	2	66°/0.05 mm.	1.5504	39
CH_3—	3	78–80°/0.15 mm.	1.5428	39
CH_3—	4	78°/0.05 mm.	1.5382	39

TABLE 5. Alicyclic Ethylene Sulfides

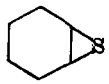
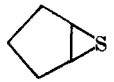
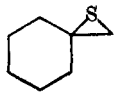
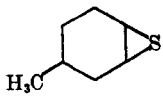
Episulfide	B.p. (°C)	n_D	References
	69–70/65 mm.	n_D^{25} 1.5222	47, 55, 118
	67–68/16 mm.	n_D^{20} 1.5309	8, 19, 20, 26, 55, 60, 68, 73, 118, 119
	—	n_D^{25} 1.5310	74
	85–86/25 mm.	n_D^{25} 1.5097	17

TABLE 6. Carbohydrate Ethylene Sulfides

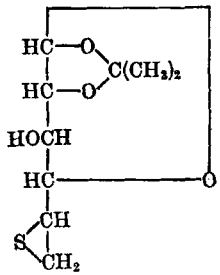
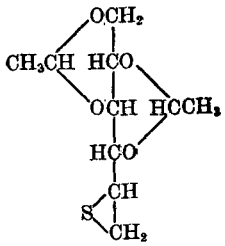
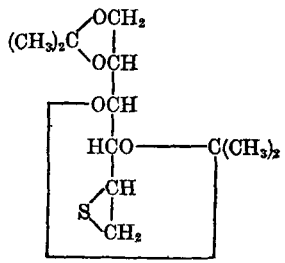
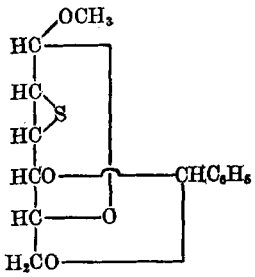
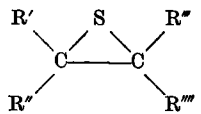
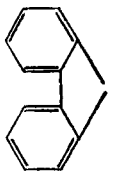
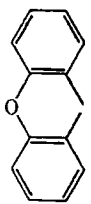
Episulfide	B.p. or *m.p. (°C)	$[\alpha]_D^{23}$	References
	*164–165	−16°	15
	*150–151	+3°	15
	90–92/0.01 mm.	+30°	15
	*166	—	48

TABLE 7. Aromatic-Substituted Ethylene Sulfides



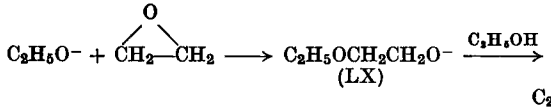
R′—	R″—	R‴—	R⁗—	B.p. or *m.p.°(C)	References
C_6H_5—	H—	H—	H—	25–28/0.01 mm.	50
C_6H_5—	C_6H_5—	CH_3—	H—	*64–67	98
C_6H_5—	C_6H_5—	C_6H_5—	C_6H_5—	*178–179	99, 113
C_6H_5—	C_6H_5—	p-$CH_3OC_6H_4$—	p-$CH_3OC_6H_4$—	*100 (decomp.)	113
C_6H_5—	C_6H_5—	p-$(CH_3)_2NC_6H_4$—	p-$(CH_3)_2NC_6H_4$—	*164–165	113
CH_3—	C_6H_5—	p-$(CH_3)_2NC_6H_4$—	p-$(CH_3)_2NC_6H_4$—	*134	100
CH_3—	p-$CH_3C_6H_4$—	p-$(CH_3)_2NC_6H_4$—	p-$(CH_3)_2NC_6H_4$—	*124	100
p-ClC_6H_4—	p-ClC_6H_4—	p-$(CH_3)_2NC_6H_4$—	p-$(CH_3)_2NC_6H_4$—	*180	100
2,5-$(CH_3)_2C_6H_3$—	C_6H_5—	p-$(CH_3)_2NC_6H_4$—	p-$(CH_3)_2NC_6H_4$—	*189	100
p-$CH_3C_6H_4$—	p-$CH_3C_6H_4$—	p-$(CH_3)_2NC_6H_4$—	p-$(CH_3)_2NC_6H_4$—	*164	100
p-$CH_3C_6H_4$—	p-$CH_3C_6H_4$—	p-$CH_3C_6H_4$—	p-$CH_3C_6H_4$—	*194–195	99
p-$CH_3OC_6H_4$—	p-$CH_3OC_6H_4$—	p-$CH_3OC_6H_4$—	p-$CH_3OC_6H_4$—	*210 (decomp.)	94, 95, 99
C_6H_5—	C_6H_5—	C_6H_5S—	C_6H_5S—	*135	96
p-$CH_3C_6H_4$—	p-$CH_3C_6H_4$—	p-$CH_3C_6H_4S$—	p-$CH_3C_6H_4S$—	*134–135	96
p-$C_2H_5OC_6H_4$—	p-$C_2H_5OC_6H_4$—	p-$C_2H_5OC_6H_4$—	p-$C_2H_5OC_6H_4$—	*156	95
C_6H_5—	C_6H_5—	Cl—	Cl—	*89–90	114
C_6H_5—	C_6H_5—	C_6H_5—	Cl—	*70–71	114
C_6H_5—	C_6H_5—	C_6H_5O—	Cl—	*78	97
C_6H_5—	C_6H_5—	C_6H_5S—	Cl—	*99–100	97

R′—	R″—	R‴—	R⁗—	B.P.° or *M.p.°(c)	References
		Cl—	Cl—	*97	114
		C_6H_5—	Cl—	*125–126	114
		C_6H_5S—	Cl—	*110	96
		C_6H_5—	C_6H_5—	190–200 (decomp.)	113
		*p*-ClC_6H_4—	*p*-ClC_6H_4—	*170	100
		o-ClC_6H_4—	C_6H_5—	*195	100
		p-$NO_2C_6H_4$—	C_6H_5—	*182	100
		p-$C_6H_5C_6H_4$—	C_6H_5—	—	100
		CH_3—	C_6H_5—	*105	100
		p-$CH_3C_6H_4$—	*p*-$CH_3C_6H_4$—	*176	100

2. Chemical Properties

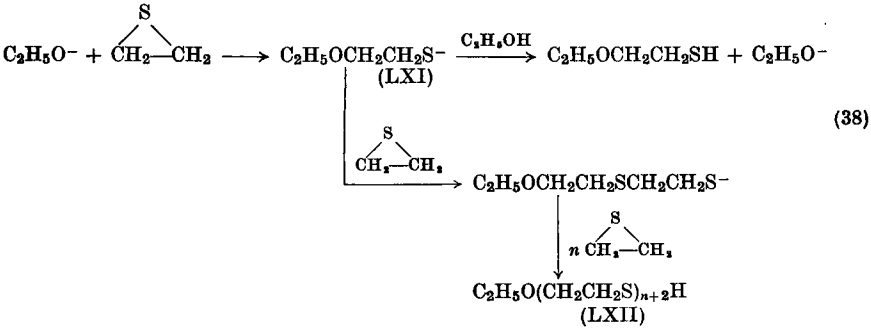
A. Displacement Reactions

Analogous with epoxide chemistry, the vast majority of the episulfide reactions which have been studied have involved the opening of the episulfide ring and the addition of a molecule of reagent. Thus ethylene sulfide readily undergoes ring opening with a variety of reagents, both under acidic and basic reaction conditions. However, owing to their relative ease of polymerization, the ethylene sulfides have not found as broad application as mercaptoethylating agents as have the ethylene oxides as hydroxyethylating agents.



$$C_2H_5O^- + \underset{\diagdown\,\diagup}{\overset{O}{CH_2—CH_2}} \longrightarrow \underset{(LX)}{C_2H_5OCH_2CH_2O^-} \xrightarrow{C_2H_5OH} C_2H_5OCH_2CH_2OH + C_2H_5O^- \quad (37)$$

Under basic reaction conditions, especially in the presence of polarizing solvents, ring opening of episulfides and epoxides is similar. For example, the reaction of ethoxide ion involves the attack of this nucleophile on one of the epoxide or episulfide carbon atoms and ring opening to form the intermediate nucleophiles (LX) and (LXI) (Eqs. 37 and 38).



$$C_2H_5O^- + \underset{\diagdown\,\diagup}{\overset{S}{CH_2—CH_2}} \longrightarrow \underset{(LXI)}{C_2H_5OCH_2CH_2S^-} \xrightarrow{C_2H_5OH} C_2H_5OCH_2CH_2SH + C_2H_5O^- \quad (38)$$

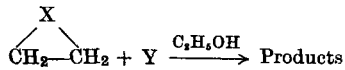
$$\underset{(LXI)}{C_2H_5OCH_2CH_2S^-} + \underset{\diagdown\,\diagup}{\overset{S}{CH_2—CH_2}} \longrightarrow C_2H_5OCH_2CH_2SCH_2CH_2S^- \xrightarrow{n\ \underset{\diagdown\,\diagup}{\overset{S}{CH_2—CH_2}}} \underset{(LXII)}{C_2H_5O(CH_2CH_2S)_{n+2}H}$$

In the epoxide sequence (Eq. 37) the reaction is completed by the solvent and the ethoxide ion is regenerated. The reaction is referred to as a base-catalyzed addition of ethanol.

In a similar environment, the episulfide reaction (Eq. 38) is not readily terminated by solvent, but instead, a polyethylene sulfide (LXII) is formed. This is understandable when one notes that although the mercaptide ion is a weaker base than the alkoxide ion, it is a much stronger nucleophile. Thus the alkoxide ions are depleted in the formation of mercaptide ions, and the newly generated mercaptide ions react

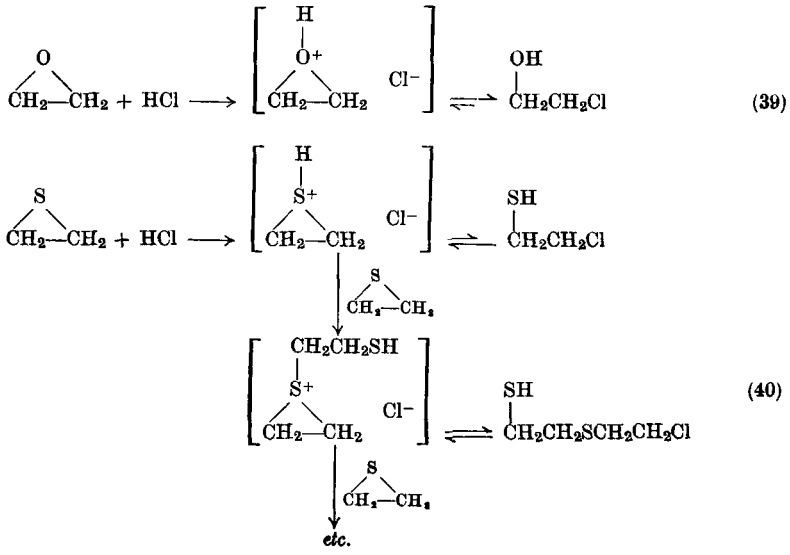
with the unchanged ethylene sulfide to give polyethylene sulfide as the major, if not exclusive, reaction product under these conditions. This is illustrated in Table 8.

TABLE 8. Comparison of Reactions of Ethylene Oxide and Ethylene Sulfide with Nucleophiles in Ethanol



Y	X = O Product (yield)		X = S Products (yield)	
$C_2H_5O^-$	$C_2H_5OCH_2CH_2OH$	(95%)	$C_2H_5O(CH_2CH_2S)_nH$	(100%)
$C_2H_5S^-$	$C_2H_5SCH_2CH_2OH$	(91%)	$C_2H_5SCH_2CH_2SH$ + $C_2H_5S(CH_2CH_2S)_nH$	(25%) (75%)
$(C_2H_5)_2NH$	$(C_2H_5)_2NCH_2CH_2OH$	(85%)	$(C_2H_5)_2N(CH_2CH_2S)_nH$	(100%)

The polymerization tendencies of episulfides are also encountered under acidic reaction conditions. Dilute hydrochloric acid, for example, instantly polymerizes ethylene sulfide to an amorphous powder. Under the same conditions ethylene oxide gives 2-chloroethanol in good yield. This may be attributed to the greater tendency of sulfur as compared with oxygen to form 'onium' ions. A comparison of the two reactions may be pictured as shown in Eqs. (39) and (40).

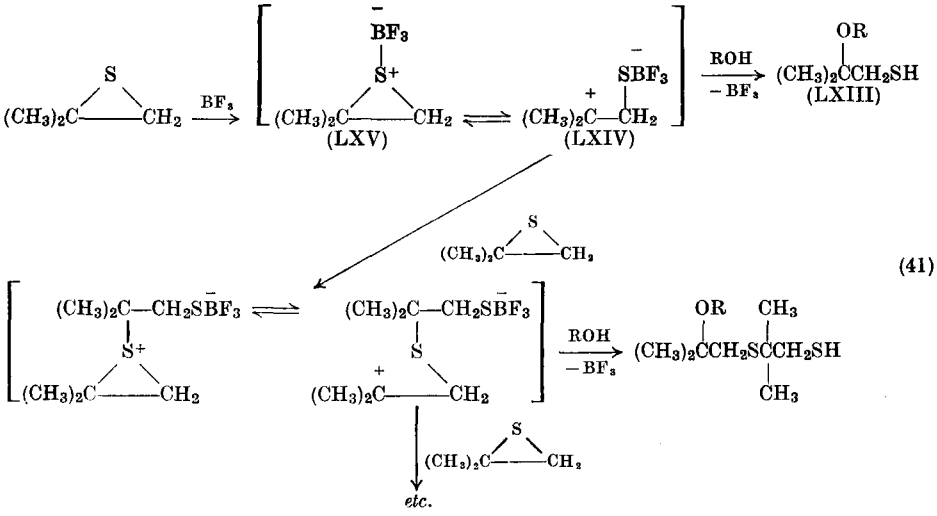


(39)

(40)

Thus, owing to their tendency toward polymerization and the difficulties often encountered in their preparation, systematic investigations of the chemistry of episulfides have been rare indeed. The nucleophilic displacement reactions reviewed in this section are often by necessity related to specific examples. Generalizations of a given reaction should be viewed cautiously until more detailed investigations are reported.

(1) By alcohols. In the absence of acid or base catalyst, episulfides are not prone to react with alcohols. In the presence of a catalytic quantity of boron trifluoride, *iso*butylene sulfide reacts when



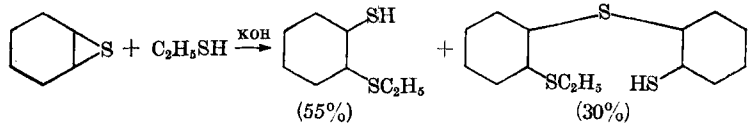
(41)

heated with an excess of a primary saturated alcohol to give a 2-alkoxyethanethiol (LXIII) in 20–40% yields in addition to higher boiling materials[108, 111] (Eq. 41). This reaction applied to *iso*butylene sulfide, and secondary alcohols such as 2-octanol and cyclohexanol gives only higher molecular weight materials. This is also true in reactions between primary alcohols and propylene sulfide or cyclohexene sulfide. The isolable alkoxy mercaptans derived from *iso*butylene sulfide and primary alcohol have been shown to be essentially primary thiols resulting from the fission of the tertiary carbon–sulfur bond. Cleavage in the opposite direction would lead to tertiary thiols. These results may be explained by the reaction sequence depicted in Eq. (41).

Apparently, the aliphatic alcohol is competitive with the episulfide for carbonium ion (LXIV) (or sulfonium ion, LXV) only when the steric requirements of the alcohol are much less than those of the episulfide.

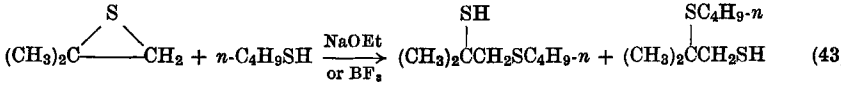
In a basic environment the reaction of alcohols with alkylene sulfides generally leads exclusively to polymeric materials,[76,64] as previously discussed [see Eq. (38)]. The quantitative estimation of ethylene sulfide has been based on its polymerization to easily isolable polyethylene sulfide by reaction of an ethanolic solution of the episulfide with a catalytic quantity of diethylamine[11] or sodium methoxide.[89]

(2) By mercaptans and hydrogen sulfide. As with alcohols, free thiols do not easily open the episulfide ring;[18] *e.g.* cyclohexene sulfide and ethanethiol may be recovered virtually unchanged after being heated in a sealed tube at 120° for 6 hr. In fact, thiols have been suggested as polymerization inhibitors for ethylene sulfide.[11,13,107] In the presence of base or acid catalyst, however, reaction readily occurs and 2-mercaptoethyl thiolethers and higher condensation products of the types shown in Eqs. (42) and (43) are obtained.[1,18,67,81,82,108,109,110]



(42)

The direction of ring opening of unsymmetrical episulfides by thiols in the presence of either acid or base catalyst appears to be rather non-selective.[108] Mixtures of primary and tertiary mercaptans have been obtained by reaction of *iso*butylene sulfide with some of the simple aliphatic thiols such as *n*-butanethiol in the presence of catalytic quantities of either boron trifluoride or sodium ethoxide (Eq. 43).



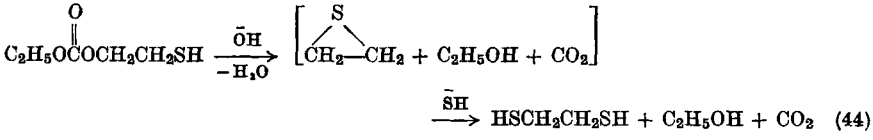
(43)

The total yields are about 75% when the mercaptan is used in 100% excess, compared with about 40% when the theoretical amount of mercaptan is employed. Attempts to effect the simple addition of mercaptans to tetramethylethylene sulfide have been unsuccessful.[108]

Methanolic hydrogen sulfide reacts smoothly at 60° with ethylene sulfide to produce 1,2-ethanedithiol.[67] Potassium hydrogen sulfide has

been employed to convert cyclohexene sulfide and propylene sulfide to the corresponding dithiols in poor yields.[18]

Ethyl 2-mercaptoethylcarbonate decomposes in the presence of base to yield ethylene sulfide, carbon dioxide, and ethanol. When this carbonate was reacted with ammonium hydroxide saturated with hydrogen sulfide, a 74% yield of ethanedithiol was obtained[14] (Eq. 44).

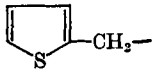


$$C_2H_5OCOCH_2CH_2SH \xrightarrow[-H_2O]{\bar{O}H} \left[\begin{array}{c} S \\ / \quad \backslash \\ CH_2—CH_2 \end{array} + C_2H_5OH + CO_2\right] \xrightarrow{\bar{S}H} HSCH_2CH_2SH + C_2H_5OH + CO_2 \quad (44)$$

TABLE 9. Aminothiols from Ethylene Sulfide and Primary Aliphatic Amines



$$RNH_2 + \begin{array}{c} S \\ / \quad \backslash \\ CH_2—CH_2 \end{array} \longrightarrow RNHCH_2CH_2SH$$

R—	B.p. (°c/mm.) or *m.p. (°c)	n_D^{25}	References
C_2H_5—	75/63	1.4751	88, 121
$HOCH_2CH_2$—	—	—	88
$CH_3OCH_2CH_2$—	57/3	1.4770[a]	52
$(C_2H_5)_2NCH_2CH_2$—	92/5	1.4795[a]	52, 11
CH_2=$CHCH_2$—	68/19	1.4936	88
n-C_3H_7—	82/46	1.4720	88, 121
iso-C_3H_7—	81/64 *34–35	—	88
n-C_4H_9—	81/18	1.4694	88, 91, 121
iso-C_4H_9—	76/23	1.4652	88
sec-C_4H_9—	83/33	1.4676	88
tert-C_4H_9—	71/28 *41–43	—	88
C_6H_{11}—	99/7	1.5040	88, 80
n-C_6H_{13}—	97/9	1.4680	88, 11
n-C_7H_{15}—	70/2.5	1.4703	107
n-C_8H_{17}—	83/0.3	1.4691	88
n-$C_{10}H_{21}$—	120/0.6	1.4674	88
$C_6H_5CH_2$—	84/0.1	1.5585	88, 11
$C_6H_5CH_2CH_2$—	108/2	1.5540[a]	80
$C_6H_5CH_2CH(CH_3)$—	111/2	1.5462[a]	80
	139/6	1.5776[a]	80

[a] Measured at 20°.

(3) By amines. Whereas the reactions of episulfides with alcohols and mercaptans have found limited use in synthesis, their reaction with amines has become the most general route to 2-aminoethanethiols (see Tables 9–14):

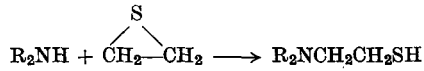
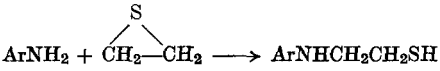
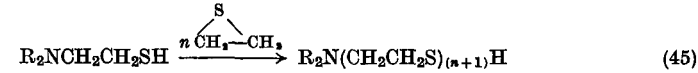


TABLE 10. Aminothiols from Ethylene Sulfide and Primary Aromatic Amines



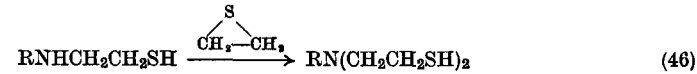
Ar—	B.p. (°C/mm.) or *m.p. (°C)	n_D^{20}	References
C_6H_5—	138/12	1.6057	107, 128, 83, 81, 11, 80
o-$CH_3C_6H_4$—	132/5	1.5895	128, 80
m-$CH_3C_6H_4$—	133/5	1.5874	80
p-$CH_3C_6H_4$—	130/5	1.5862	128, 80
o-$CH_3OC_6H_4$—	146/5	1.5918	128, 80
m-$CH_3OC_6H_4$—	163/5	1.5930	80
p-$CH_3OC_6H_4$—	151/4	1.5910	128, 80
o-$NH_2C_6H_4$—	152/1.5	1.6320	80
m-$NH_2C_6H_4$—	165/1.5	1.6483	80
o-$CH_3OCOC_6H_4$—	151/2	1.6019	124
m-$CH_3OCOC_6H_4$—	182/3	1.5936	124
p-$C_2H_5OCOC_6H_4$—	185/3 *58–58.5	—	124
p-ClC_6H_4—	130/1.5	1.6132	125

This reaction, first described by Reppe and Nicolai[83] in 1936, has been extensively investigated in the case of ethylene sulfide, both with



(45)

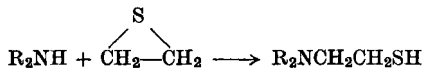
aliphatic and with aromatic primary and secondary amines. The two principal side-reactions encountered are further alkylation of thiol (Eq. 45) and bisalkylation of the primary amines (Eq. 46). Non-

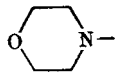
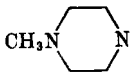
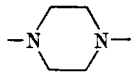


(46)

polar reaction conditions should be employed with the strongly basic amines if extensive polymerization is to be avoided. The use of two- to three-fold excess of the amine and elevated temperatures favor

TABLE 11. Aminothiols from Ethylene Sulfide and Secondary Amines



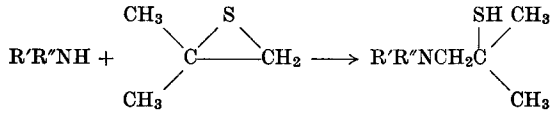
R_2N—	B.p. (°c/mm.)	n_D^{25}	References
$(CH_3)_2N$—	58–59/63	1.4630	53, 80
$(C_2H_5)_2N$—	85/56	1.4636	88, 121, 46, 11, 80
$(n\text{-}C_3H_7)_2N$—	77/10	1.4614	88, 80
$(iso\text{-}C_3H_7)_2N$—	73/13	1.4686	88, 80
$(n\text{-}C_4H_9)_2N$—	66/0.7	1.4620	88, 80, 107, 121
$(iso\text{-}C_4H_9)_2N$—	91/10	1.4572	88, 80
$(sec\text{-}C_4H_9)_2N$—	93/8	1.4723	88
$(n\text{-}C_5H_{11})_2N$—	91/0.8	1.4629	88, 107
$(iso\text{-}C_5H_{11})_2N$—	85/1	1.4600	88, 11
$(n\text{-}C_7H_{15})_2N$—	127/2	1.4660	107
$(n\text{-}C_8H_{17})_2N$—	146/2	1.4658	107
$(CH_2{=}CHCH_2)_2N$—	90/17	1.4895	88, 11
	79/10	1.4991	88, 107, 52
	92/10	1.5021	88, 52, 11
	95/10	1.5040	88
	96/0.03	—	88
$HOCH_2CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle \vert}{N}}$—	78/0.9	1.4977	88
$(C_6H_5CH_2)_2N$—	196–198/2	1.5760[a]	80
	81/22	1.5004[a]	128, 52

[a] Measured at 20°.

monomercaptoethylation. Although only polyethylene sulfide results when a mixture of diethylamine and ethylene sulfide in methanol is allowed to stand at room temperature for several hours, a 55% yield of 2-diethylaminoethanethiol has been obtained by employing ether as a solvent and by conducting the reaction at room temperature for

4 days. This yield is further raised to 75–80% by employing a two-fold molar excess of the amine, with benzene as a solvent and conducting the reaction at 100° for 2 hr.[11]

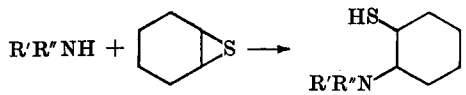
TABLE 12. Aminothiols from Isobutylene Sulfide and Amines



R′—	R″—	B.p. (°C/mm.) or *m.p. (°C)	n_D^{25}	References
n-C_7H_{15}—	H—	83–86/2	1.4630	112, 107
n-$C_{12}H_{25}$—	H—	138/3	—	112, 107
C_2H_5—	C_2H_5—	94/52	1.4597	112, 107
n-C_4H_9—	*n*-C_4H_9—	89/2	1.4748	112, 107
n-C_5H_{11}—	*n*-C_5H_{11}—	85–90/2	1.4653	112, 107
iso-C_5H_{11}—	*iso*-C_5H_{11}—	83–86/2	1.4677	112, 107
n-C_7H_{15}—	*n*-C_7H_{15}—	126/2.5	—	112
Morpholino-		81/6.5	1.4886	112, 107
Piperidino-		47/2.5	1.4840	112, 107
3-Methylpiperidino-		51–53/2	1.4782	112, 107
4-Ethylpiperidino-		74–76/2.5	1.4894	112, 107
Piperazino-		*127–131	—	112, 107

In the monomercaptoethylation of the weakly basic aromatic amines, the reaction is slow and is often facilitated by the use of ionizing solvents and by heating.[80, 11] Ethylene sulfide reacts with

TABLE 13. Aminothiols from Cyclohexene Sulfide and Amines



R′R″N—	B.p. (°C/mm.)	n_D^{25}	References
Piperidino—	97–99/1	1.5190	112, 107
$C_6H_5N(CH_3)$—	175/16	—	18

aniline at room temperature and gives 2-phenylaminoethanethiol in good yield after standing for 5 days.[11] The presence of electron-donating substituents such as methyl or methoxy in the *o*- or *p*-positions of the primary aryl amine does not affect the course of this

reaction.[128] More drastic conditions such as prolonged heating of the reaction mixture at 100°, however, are required for alkylation of the more weakly basic substituted anilines such as esters of *o*-, *m*-, and *p*-carboxyanilines.[124]

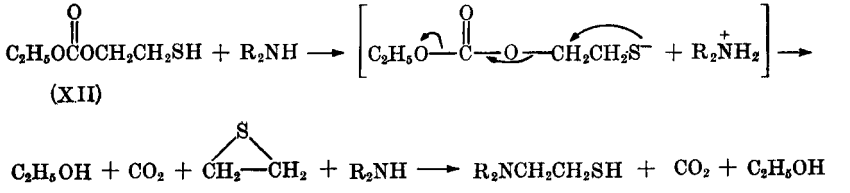
TABLE 14. Aminothiols from Propylene Sulfide[a] and Amines



R—	B.p. (°C/mm.)	n_D^{25}	References
n-C_5H_{11}—	86–87/2	1.4634	107

[a] has been reacted with diethylamine to give  , m.p. 148–150° after acid hydrolysis.[122]

In lieu of preparing and handling large amounts of ethylene sulfide, ethyl 2-mercaptoethylcarbonate (XII) has been employed with advantage in the mercaptoethylation of primary and secondary amines.[88] Introduction of this carbonate into a refluxing solution of amine in toluene promotes its decomposition to ethylene sulfide, carbon dioxide and ethanol. The ethylene sulfide reacts with the amine to give the 2-aminoethanethiol (Eq. 47).



(XII)

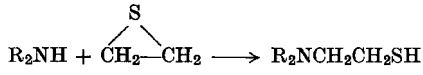
(47)

When a two-fold molar excess of amine at reaction temperatures of about 100° (an autoclave is employed for the low-boiling primary aliphatic amines) was used, yields of 85–95% were quite common for the alkylation of a number of aliphatic and heterocyclic secondary amines, and 65–75% for several primary aliphatic amines. The yields of some of the 2-aminoethanethiols obtained by this procedure are recorded in Table 15.

These data give some insight into the steric effect encountered in alkylations of aliphatic amines with ethylene sulfide. The lack of a

definite trend in yields in the mercaptoethylation of the primary amines indicates there is no pronounced steric effect, even with the comparatively hindered *tert*-butylamine. Evidently, serious steric interaction is encountered only with amines possessing a higher degree

TABLE 15. Steric Effects

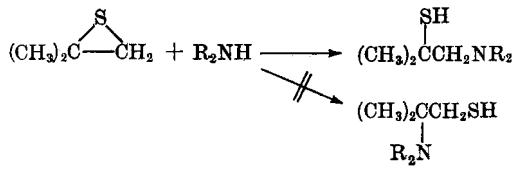


R_2NH	Yield (%)	R_2NH	Yield (%)
n-$C_3H_7NH_2$	75	(*n*-C_3H_7)$_2$NH	88
iso-$C_3H_7NH_2$	77	(*iso*-C_3H_7)$_2$NH	10
n-$C_4H_9NH_2$	66	(*n*-C_4H_9)$_2$NH	91
iso-$C_4H_9NH_2$	72	(*iso*-C_4H_9)$_2$NH	89
sec-$C_4H_9NH_2$	68	(*sec*-C_4H_9)$_2$NH	20
tert-$C_4H_9NH_2$	64		

of branching near the site of reaction (on the carbon alpha to the nitrogen) as observed with di*iso*propyl- (10%) and di-*sec*-butylamines (20%). Similar branching on the beta-carbon, as in di*iso*butylamine, had no apparent adverse effect on the yield (90%) of 2-(di*iso*butylamino)ethanethiol.

Ethylene monothiolcarbonate,[85] 2-mercaptoethyl carbamates,[86] and 2-hydroxyethylthiolcarbonates[87] have also been studied as mercaptoethylating agents for amines.

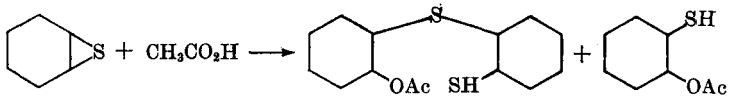
The reaction of amines with other episulfides has received only superficial study, and any generalizations concerning relative reactivi-



(48)

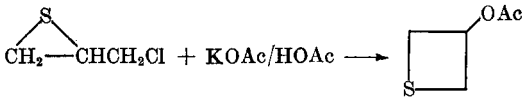
ties should be withheld until more data are available. Apparently the reactions of secondary amines with *iso*butylene sulfide occur less readily than with ethylene sulfide.[107] The aminothiols prepared from *iso*butylene sulfide are exclusively tertiary thiols, as indicated in Eq. (48).

(4) By carboxylic acids and anhydrides. With excess of boiling glacial acetic acid, cyclohexene sulfide gives 2-mercaptocyclohexyl-2′-acetoxycyclohexyl sulfide (LXVI) as the major product.[18, 118] The simple addition product, 2-mercaptocyclohexyl acetate (LXVII), has also been reported.[18] 2-Acetoxytrimethylene sulfide results from a ring

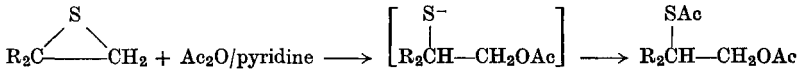


(LXVI) (LXVII)

expansion when 3-chloropropylene sulfide is heated with potassium acetate in glacial acetic acid:[2]

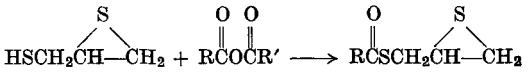


Ethylene sulfide reacts with acetic anhydride in the presence of pyridine to give the diacetate of 2-mercaptoethanol.[4] Propylene sulfide[23] and *iso*butylene sulfide[25] undergo similar ring opening with the ring fission occurring at the primary carbon–sulfur bond. This may be attributed to attack by the acetate anion in a conventional S_N2-type reaction:

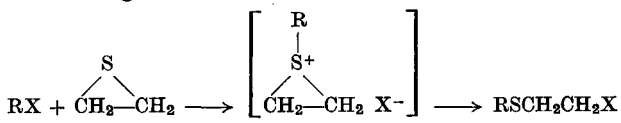


Cyclohexene sulfide yields the *trans*-diacetate.[118]

3-Mercaptopropylene sulfide may be acylated by means of acetic anhydride, succinic anhydride, or the more reactive mixed anhydrides, without apparent rupture of the episulfide ring:[2, 4]



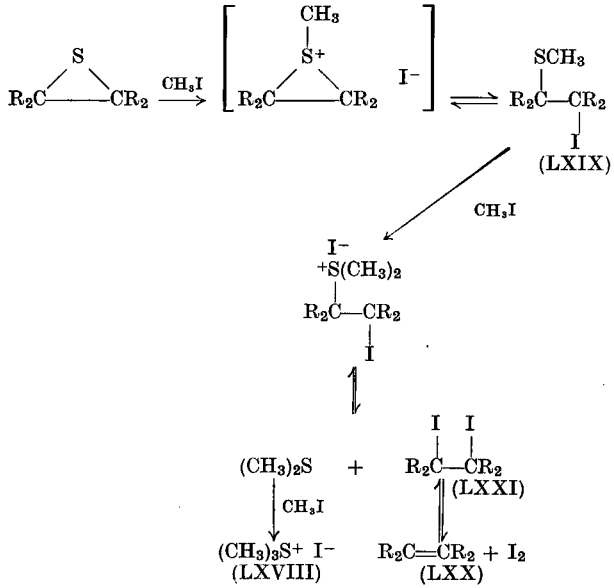
(5) By hydrogen halides, alkyl halides, and acyl halides. Hydrogen halides, alkyl halides, and acyl halides in general readily cause rupture of the episulfide ring:



(R = H, alkyl, acyl; X = Cl, Br, I)

Ethylene sulfide,[35] propylene sulfide,[23] 3-chloropropylene sulfide,[18] and cyclohexene sulfide[18] have been converted into 2-chlorothiols in 33, 50, 72, and 57% yields respectively by reaction with concentrated hydrochloric acid. Dilute hydrochloric acid, however, leads to more extensive polymerization.[35]

The reaction of episulfides with alkyl halides has thus far been limited to methyl iodide. With the more highly substituted episulfides, the commonly isolated product is trimethylsulfonium iodide (LXVIII), which may be formed as shown in Eq. (49).



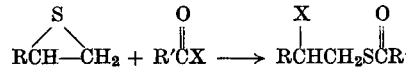
(49)

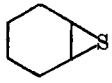
Thus cyclohexene sulfide reacts slowly at room temperature in the presence of a slight excess of methyl iodide to form (LXVIII) in about 50% yield.[18] With the simpler episulfides, *e.g.* ethylene sulfide and propylene sulfide, a complex mixture of salts is obtained unless a large excess of methyl iodide is employed to suppress the competitive quaternization of the episulfide by intermediate iodo compounds such as (LXIX). Apparently no simple methyl 2-iodoethyl sulfide (LXIX) has been isolated from this type of reaction, nor have other expected fragments such as the olefin (LXX) or the diiodide (LXXI).

The majority of the acyl halide reactions with episulfides have involved ethylene sulfide and propylene sulfide with C_1–C_4 aliphatic acyl halides and have given 2-haloalkyl thiolesters in good yields. A survey of these reactions is summarized in Table 16.

The reaction of propylene sulfide or 3-chloropropylene sulfide with acetyl halides or hydrogen halides leads to good yields of the 2-haloalkyl compound (LXXII) which results from cleavage of the secondary

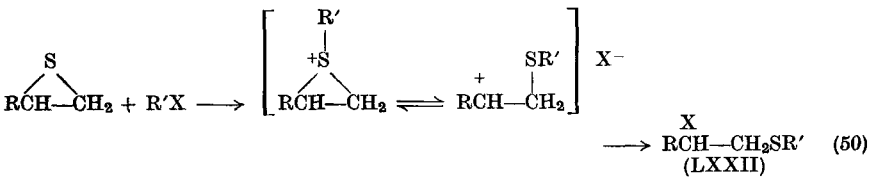
TABLE 16. Reactions of Episulfides and Acyl Halides



R—	R'—	X—	Yield (%)	References
H—	CH_3—	Cl—	75	4
H—	CH_3—	Br—	70	53, 59
H—	CH_3—	I—	74	58
H—	$ClCH_2$—	Cl—	—	67
H—	$ClCH_2$—	Br—	—	67
H—	$BrCH_2$—	Br—	65	59
H—	Cl_3C—	Cl—	75	59
H—	C_2H_5—	Br—	90	59, 53
H—	n-C_3H_7—	Br—	76	59, 53
H—	n-C_4H_9—	Br—	70	53
H—	C_6H_5—	Br—	90	59, 53
CH_3—	CH_3—	Cl—	—	18, 23
CH_3—	CH_3—	Br—	95	23, 59
CH_3—	CH_3—	I—	71	59
CH_3—	$ClCH_2$—	Cl—	67	59, 77
CH_3—	$BrCH_2$—	Br—	49	59
CH_3—	Cl_2CH—	Cl—	63	59
CH_3—	Cl_3C—	Cl—	67	59
CH_3—	C_2H_5—	Br—	73	59
CH_3—	n-C_3H_7—	Br—	71	59
CH_3—	C_6H_5—	Cl—	—	18
CH_3—	C_6H_5—	Br—	43	59
$ClCH_2$—	CH_3—	Cl—	—	18, 25
	CH_3—	Cl—	—	18, 118

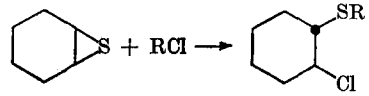
carbon–sulfur bond[23, 25, 59] (Eq. 50). This would be predicted of a reaction following an S_N1 mechanism in which the carbon–sulfur bond-breaking of the sulfonium ion intermediate is far more nearly complete in the transition state than the bond-making step with the attacking nucleophile.

On this basis it would be predicted that the direction of ring opening of unsymmetrical episulfides by acidic reagents will depend on the ability of groups attached to the episulfide ring to stabilize the positive charge which is developing on the adjacent carbon.



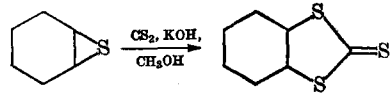
(R = CH_3, $ClCH_2$; R′ = H, CH_3CO; X = Cl, Br, I)

The only stereochemical study[118] of ring opening of episulfides by these reagents has been confined to reactions with cyclohexene sulfide. *trans*-2-Chlorocyclohexyl thiolacetate and *trans*-2-chlorocyclohexanethiol have been isolated from the reaction of cyclohexene sulfide with acetyl chloride and hydrochloric acid respectively, with no indication of the corresponding *cis* product having been formed:

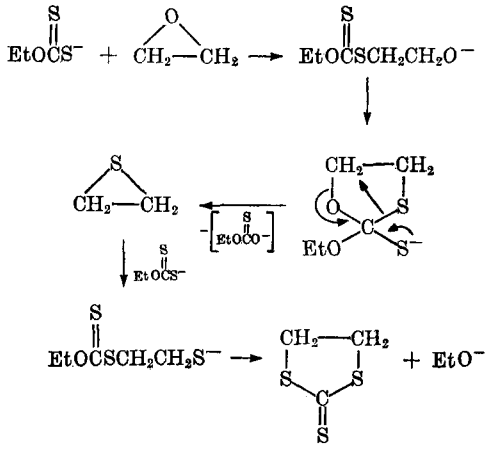


(R = H, CH_3CO)

(6) By xanthates. Cyclohexene sulfide has been converted in 95% yield to the corresponding trithiocarbonate by its reaction with a methanolic solution of carbon disulfide and potassium hydroxide:[19]



Episulfides are considered to be intermediates in the formation of trithiocarbonates from metallic xanthates and epoxides[19, 57] (Eq. 51).



(7) By dialkyl dithiophosphates. Dialkyl 2-mercaptoethyl dithiophosphates (LXXIII) have been obtained in approximately 50% yield by heating the strongly acidic dialkyl dithiophosphates with ethylene sulfide:[66]

$$(RO)_2PSSH + \underset{\diagdown\,\diagup}{\overset{S}{CH_2—CH_2}} \longrightarrow \underset{(LXXIII)}{(RO)_2PSSCH_2CH_2SH}$$

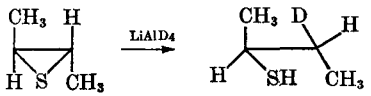
(R = CH_3, C_2H_5, *n*-C_3H_7, *iso*-C_3H_7, *iso*-C_4H_9)

(8) By lithium aluminum hydride. The reaction of several episulfides with lithium aluminum hydride has been shown to proceed with reductive ring cleavage to give thiols as their lithium mercaptides in about 75% yields. The secondary thiols, rather than the corresponding 1-thiols, were obtained from the reduction of propylene sulfide and 1-hexene sulfide:[9]

$$\underset{\diagdown\,\diagup}{\overset{S}{RCH—CH_2}} + LiAlH_4 \longrightarrow \overset{SLi}{\underset{|}{RCH}}CH_3 + AlH_3$$

(R = CH_3, *n*-C_4H_9)

The reduction of L-2,3-dimethylethylene sulfide with lithium aluminum deuteride has been demonstrated to proceed with inversion of configuration:[56]

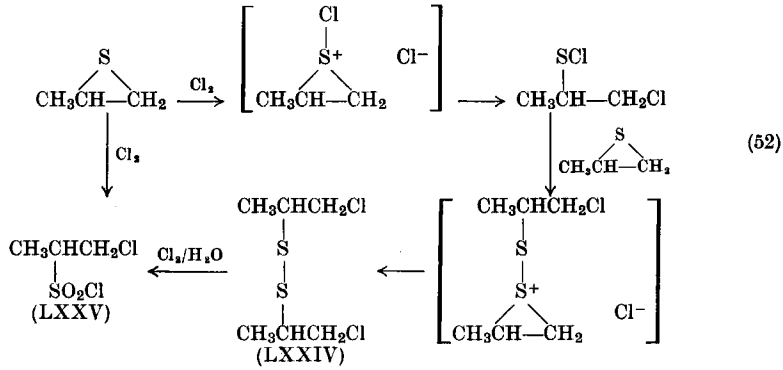


Polymer was the major product obtained in an attempted lithium aluminum hydride reduction of 1-octene sulfide.[69]

(9) By chlorine and bromine. Addition of chlorine or bromine to propylene sulfide in anhydrous solvents causes ring cleavage at the primary carbon–sulfur bond to give 1-methyl-2-haloethyl disulfides (LXXIV)[115] (Eq. 52). 1-Halo-2-propanesulfonyl halide (LXXV) may be obtained by reversing the manner of addition. Aqueous chlorine also cleaves the sulfide ring at the primary carbon to give 1-chloro-2-propanesulfonyl chloride.

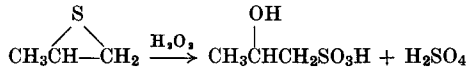
These observations are interesting since it is an instance in which an unsymmetrical aliphatic episulfide, reacting through a probable sulfonium ion intermediate, has undergone fission at the least substituted carbon–sulfur bond.

1,2-Dichlorocyclohexane has been isolated from the reaction of cyclohexene sulfide with chlorine in carbon tetrachloride.[18]



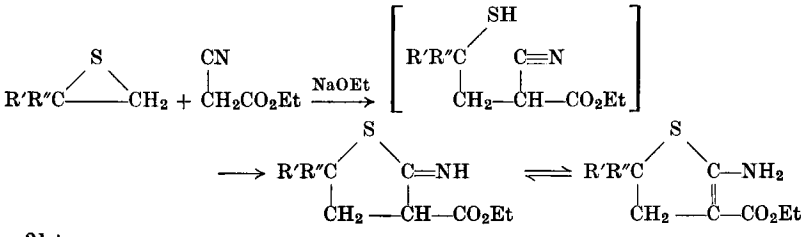
(52)

(10) By hydrogen peroxide. Oxidative ring cleavage of propylene sulfide with 30% hydrogen peroxide has afforded 2-hydroxy-1-propanesulfonic acid and sulfuric acid as the only identified products:[115]



(11) By nitric acid and sulfuric acid. The oxidation of ethylene sulfide with concentrated nitric acid leads to sulfoacetic acid, $HO_3SCH_2CO_2H$, and other condensed acids.[35] Sulfuric acid, dilute or concentrated, appears to have only a polymerizing influence.[18]

(12) By ethyl cyanoacetate. Attempted base-catalyzed condensations of ethyl malonate and ethyl acetoacetate with the simple episulfides have been unsuccessful. However, 2-iminothiophanes are obtainable from ethyl cyanoacetate and alkene sulfides.[106] In the alkylation of ethyl cyanoacetate with propylene sulfide and isobutylene sulfide, nucleophilic attack by the carbanion is on the primary carbon atom of the episulfide (Eq. 53).



(53

Styrene sulfide has also been reacted with ethyl cyanoacetate to give presumably 2-imino-3-carbethoxy-5-phenylthiophane[50] (R′ = C_6H_5; R″ = H).

B. Desulfurization Reactions

As has been discussed, the reaction of episulfides with many nucleophilic reagents proceeds with ring opening and formation of a mercaptide ion or a mercaptan. In some instances, however, olefins are formed by the removal of sulfur from the episulfide. Reagents which have been effective for this are the organolithium compounds, Grignard reagents, and tervalent phosphorous compounds such as triphenylphosphine and triethylphosphite. Some episulfides have also been thermally degraded to an olefin and sulfur.

(1) By phosphites and phosphines. Triethyl phosphite[75, 28, 101, 18] and triethyl-,[18] tributyl-,[38] and triphenylphosphines[10, 38, 28, 18] have been reacted with a number of episulfides to yield practically quantitative amounts of triethyl thionophosphate and trialkyl- or triarylphosphine sulfides, respectively, and the olefin resulting from desulfurization of the episulfide (Eqs. 54 and 55).

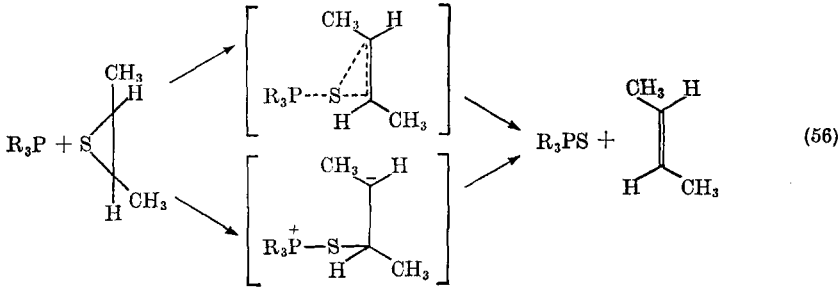
$$(EtO)_3P + R_2C\overset{S}{\diagup\diagdown}CR_2 \longrightarrow (EtO)_3PS + R_2C{=}CR_2 \qquad (54)$$

Interestingly, the desulfurization is stereospecific. Pure *cis*- and pure *trans*-2-butenes have been obtained in over 99% yields from their respective episulfides by reaction with triethyl phosphite at 105–155°.[75] Similar stereospecific results have also been effected with triphenyl phosphine and tributyl phosphine.[38]

$$R_3P + R_2C\overset{S}{\diagup\diagdown}CR_2 \longrightarrow R_3PS + R_2C{=}CR_2 \qquad (55)$$

The kinetics of the reactions of triphenyl phosphine with *cis*- and *trans*-2-butene sulfides and with 1-butene sulfide have been measured and each of the reactions was found to be bimolecular, first order in each reactant. Further, the rates were found to be relatively insensitive to large changes in the dielectric constant of the medium. Such results suggest that charge separation is not important in the transition state for the rate-controlling step, and that the desulfurization proceeds by

a nucleophilic attack by the phosphine on the sulfur to give the phosphine sulfide and olefin in one step rather than involving an intermediate such as (LXXIV) (Eq. 56).



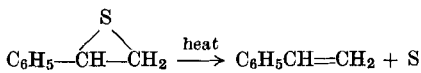
(56)

(LXXIV)

(2) By organometallics. Alkyl- and aryllithium reagents also remove sulfur from the episulfides to form quantitative yields of alkyl and aryl mercaptides and olefins.[75, 9] A study of the desulfurization of *cis*- and *trans*-2-butene episulfides demonstrated at least a 97% stereoselective removal of sulfur from the *cis*-episulfide to give *cis*-2-butene and from the corresponding *trans*-episulfide to yield *trans*-2-butene.

Reaction of aliphatic episulfides with Grignard reagents appears to be less well defined, although olefin formation seems to be the main course of reaction.[9]

(3) By thermal decomposition. Heating of an episulfide may cause decomposition leading to olefin and sulfur. Styrene sulfide decomposes to styrene and sulfur when distilled at temperatures above 88°/4 mm.:[50]



Similar decompositions have been observed with 3-acylthiopropylene sulfides,[2] 1-octene sulfide,[69] and a number of aryl-substituted ethylene sulfides.[93, 96, 97, 100, 113, 114]

When ethylene sulfide was passed over aluminum oxide at 220°, 1,4-dithiane was isolated and ethylene gas was evolved.[126]

IV. Uses

The greatest use of episulfides is as chemical intermediates. In addition, certain other applications have been suggested in the literature. For instance, ethylene sulfide imparts unshrinkability to wool

when the fabric is treated with dilute alkali followed by immersion in an aqueous alcoholic solution of the sulfide. Similar effects are produced by treating the wool with ethylene sulfide vapor and water at 50°.[5] The shrink temperatures of collagen and modified collagens have been raised by similar treatment.[45]

A recent study has led to a variety of episulfides which have antituberculosis activity against human-type tuberculosis.[1, 2, 3, 39] The episulfides prepared from unsaturated fatty acids and esters are reported to be useful as insecticides and fungicides.[29] This type of sulfur compound is also utilized in cosmetic preparations.[31, 32] New compounds, useful as lubricants,[30] have been prepared from the metal salts of these episulfides.

3-Phenoxypropylene sulfide increases the resistance of vinyl halide polymers to decomposition by light.[62]

3-Mercaptopropylene sulfide has been used to modify the physical and chemical properties of polymeric materials.[63]

Ethylene sulfide has been employed as an intermediate in polymeric compositions from cyanamide,[70] biguanide,[72] and guanylurea,[71] which are claimed to be useful as insecticides, rubber addenda, and dehairing agents.

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CHAPTER IV

Oxaziranes

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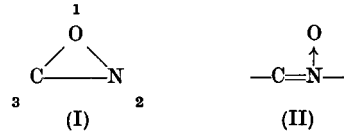
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I. Introduction

The synthesis of the oxazirane system, a three-membered ring containing carbon, oxygen, and nitrogen, was independently announced in 1956–1957 by three different research groups.[3, 10, 13] Krimm in Germany was undoubtedly the first to prepare these compounds, which he named isonitrones. The oxazirane nomenclature would appear to be more descriptive, however, and is employed throughout this chapter. The numbering of this system is shown in (I). The oxazirane ring is very frequently found in the older chemical literature as representing the structure of nitrones; in recent years, however, the

structure (II) has been firmly established for nitrones. The structural assignment of the oxazirane ring also may be considered to be unambiguous on the basis of both chemical and physical evidence, the



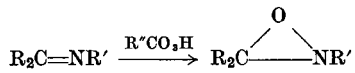
(I) (II)

most striking of which is the partial resolution of an unsymmetrically substituted oxazirane.[4]

II. Preparation of Oxaziranes

1. Oxidation of Imines

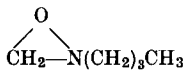
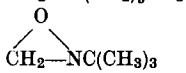
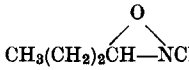
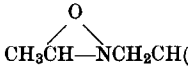
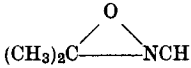
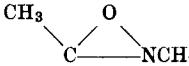
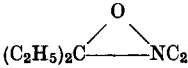
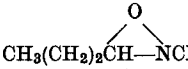
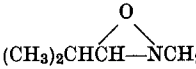
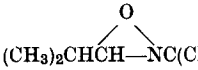
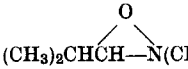
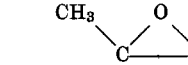
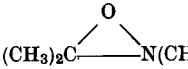
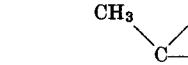
The most useful preparation of oxaziranes is the very ready oxidation of imines with organic peracids. This is a remarkably general reaction, and, since imines of widely varying structure can easily be



prepared, this oxazirane synthesis is a versatile one. The major limitation of the synthesis is the extremely labile nature of some oxaziranes. For example the 2-phenyloxaziranes are quite unstable, particularly in the presence of acid, and their preparation is accordingly quite difficult by this method.

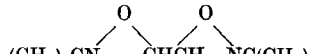
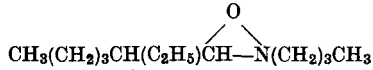
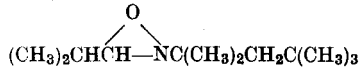
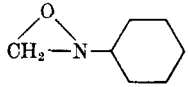
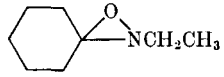
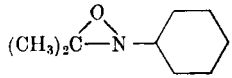
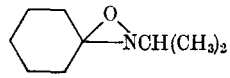
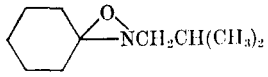
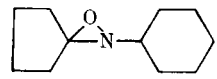
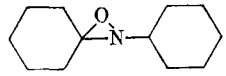
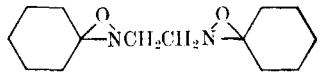
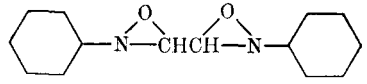
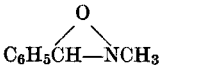
For laboratory purposes oxaziranes are conveniently prepared by addition at 10–20° of an anhydrous solution of peracetic acid in methylene chloride to the imine dissolved in the same solvent.[4] The peracetic acid can be readily prepared at ice-bath temperatures by reaction of acetic anhydride with 90% hydrogen peroxide in the presence of a catalytic amount of sulfuric acid. However, the presence of water in the reaction medium does not appear to have a deleterious effect in many cases, and good yields of oxaziranes are frequently obtained from such systems.[13] Laboratory yields of the oxaziranes generally range from 50 to 90%, depending on the properties and stability of the particular compound obtained. The oxaziranes are usually distillable liquids boiling at slightly higher temperatures than the imines from which they are derived. Table 1 lists those oxaziranes which have been prepared by the oxidation of imines, and the wide applicability of this synthesis is self-evident.

TABLE 1. Preparation of Oxaziranes from Imines

Oxaziranes	Yield (%)	B.p. °C	B.p. mm.	References
	74	43	20	4
	46	52	75	4
	35	42	32	13
	53	40	32	13
	59	58	60	13
	49	51	6	4
	56	62	19	4
	71	43	13	13
	50	53	12	4
	71	68	39	4
	65	65	10	4
	64	60	15	4
	14	58	3	4
	69	70	6	4
	73	61	8	4

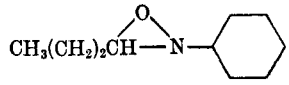
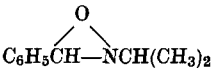
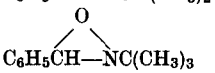
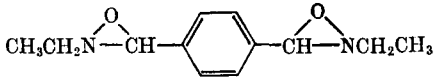
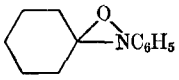
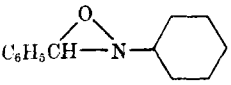
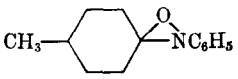
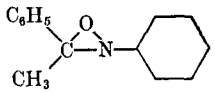
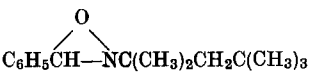
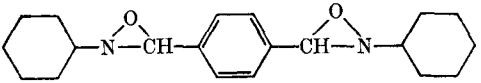
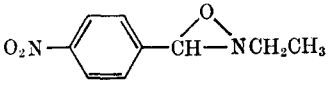
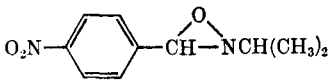
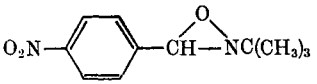
(*Table continued*)

TABLE 1 (*continued*)

Oxazirane	Yield (%)	B.p. °C	B.p. mm.	References
	51	53–56[a]		4
	83	—	—	4
	78	—	—	4
	66	45	5	13
	52	76	14	10
	83	72	8	13
	85	72	8	13
	89	55	0.6	13
	87	74	4	13
	89	95	0.3	10, 13
	39	106[b]		13
	80	123[b]		10
	65	70	2.5	13

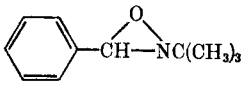
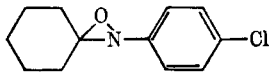
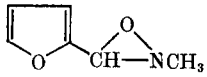
(*Table continued*)

TABLE 1 (*continued*)

Oxazirane	Yield (%)	B.p. °C	B.p. mm.	References
	65	69	0.01	13
	67	64	0.9	13
	71	61	0.3	4
	45	93[b]		10
	86	75[b]		13
	80	47[b]		10
	86	65[b]		13
	61	117	0.8	13
	67	—	—	4
	70	161[b]		10
	97	34[b]		4
	60	46[b]		4
	78	65[b]		4

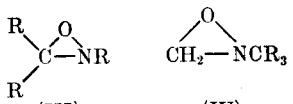
(*Table continued*)

TABLE 1 (*continued*)

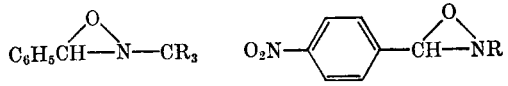
Oxazirane	Yield (%)	B.p. °C	B.p. mm.	References
	75	68	0.4	4
	—	69[b]		13
	53	44	0.6	13

[a] Melting point of mixture of *meso*- and *dl*-isomers.
[b] Melting point.

Typical examples of easily prepared oxaziranes are trialkyloxaziranes (III), 2-*tert*-alkyloxaziranes (IV), 2-alkyl-3-(dialkylcarbinyl)-oxaziranes (V), 2-*tert*-alkyl-3-phenyloxaziranes (VI), and 2-alkyl-3-(*p*-nitrophenyl)oxaziranes (VII). In all cases cited here the parent imines are readily available.

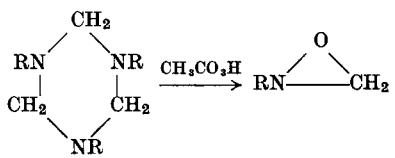


(III) (IV) (V)



(VI) (VII)

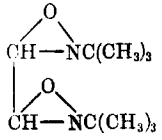
The conversion of imines into oxaziranes is a reasonably selective oxidation and may be carried out in the presence of functional groups, *e.g.* ethylenic unsaturation, which normally react with peracids. Also, 1,3,5-trialkyl perhydro-*s*-triazines obtained from condensation of formaldehyde and primary amines can be oxidized to oxaziranes.



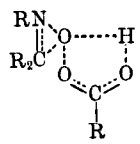
(VIII)

Under these conditions the peracetic acid reagent apparently depolymerizes the triazine to the imine which is then converted to the oxazirane. Thus 2-*n*-butyloxazirane was prepared by application of this synthesis.[4]

Most oxaziranes are fairly stable and can be readily purified by fractional distillation or crystallization provided that exposure to high temperatures for extended periods of time is avoided. The purification of oxaziranes can be followed by iodimetric titration since they are active oxygen compounds and can readily be titrated as such.[4] It should be emphasized, however, that the oxazirane ring is an energy-rich system and that the same precautions should be taken with these compounds in laboratory work as are employed with organic peroxides. Compounds in which the oxazirane ring makes up a relatively large portion of the molecule and bifunctional oxaziranes should be handled with special care. Indeed an explosion of unknown cause has been observed during the preparation of the oxazirane (IX).[15]

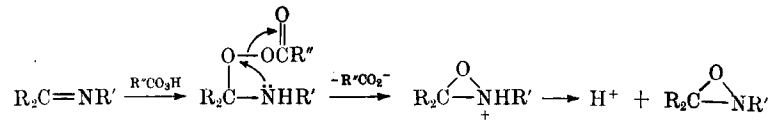


(IX)



(X)

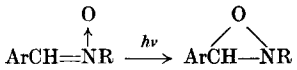
It is of some interest to speculate briefly concerning the nature of the peracid–imine reaction. It is quite possible that this reaction is analogous to the epoxidation of olefins with peracids and involves a similar cyclic transition state (X). An equally attractive if less obvious possibility is that the imine reaction proceeds through addition of the peracid to the azomethine followed by internal nucleophilic displacement of the basic nitrogen atom on the peroxide bond. This reaction



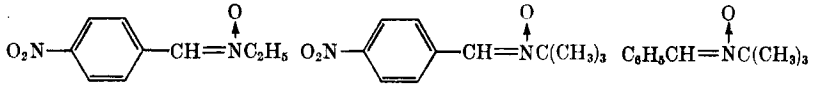
has an obvious analogy with the reaction of secondary amines with diacyl peroxides described by Gambarjan.[9] In any event the oxidation of an imine with a peracid is, at least qualitatively, a much faster reaction than oxidation of olefins of comparable structure.

2. Photolysis of Nitrones

One of the more interesting oxazirane preparations is the photolysis of nitrones. Several authors have commented on the fact that nitrones are degraded on exposure to ultraviolet light.[11,14] This phenomenon has been investigated in some detail by Calvin and Splitter,[18] who found that ultraviolet radiation converts nitrones into the isomeric oxaziranes which in some cases can be isolated in fairly good yields. Thus irradiation of (XI)–(XIII) gave the corresponding

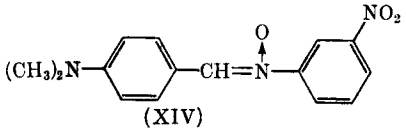


oxaziranes in yields of 35, 40, and 95% respectively. The nitrone (XIV)

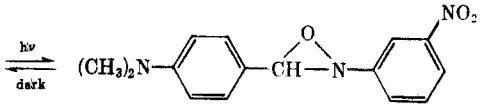


(XI) (XII) (XIII)

on irradiation was converted into an unstable product, presumably the



(XIV)



(XV)

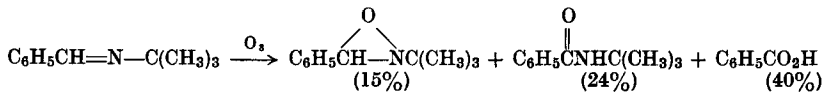
oxazirane (XV), which on standing in the dark overnight returned largely to (XIV).

From a preparative point of view the photochemical oxazirane synthesis has a number of obvious limitations, but in some cases it may be possible to obtain oxaziranes which are not sufficiently stable to obtain by other methods; thus (XV) could not be synthesized by oxidation of the parent imine at least under ordinary conditions.

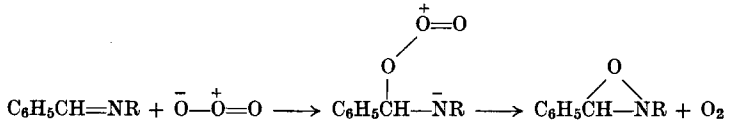
3. Ozonization of Imines

Recent work has indicated that the ozonization of imines gives oxaziranes in relatively poor yield. Thus the reaction of *N-tert*-butylphenylazomethine with ozone gave a 15% yield of the oxazirane along

with the other products indicated. Investigation of this reaction has indicated that it is of very limited value as a preparative method for

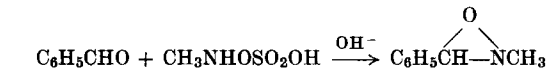


oxaziranes and often fails completely.[1,16] However, the reaction has been pictured as a nucleophilic attack of ozone on the azomethine linkage:

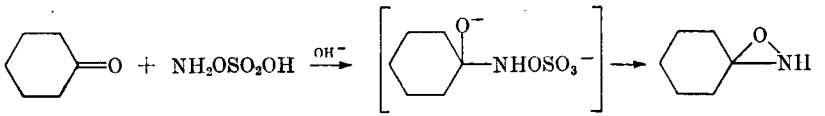


4. Reaction of Hydroxylamine-*O*-sulfonic Acids with Carbonyl Compounds

One of the more useful oxazirane syntheses is that described by Schmitz.[17] It is based on the discovery that hydroxylamine-*O*-sulfonic acids react in alkaline solution with aldehydes and ketones to form oxaziranes in 20–40% yield. Thus benzaldehyde and *N*-methylhydroxylamine-*O*-sulfonic acid give the oxazirane in 38% yield:



Since many oxaziranes have limited stability in alkaline solutions this synthesis is not characterized by high yields in most cases. It does, however, extend the spectrum of available oxaziranes considerably, and a dramatic example of this is the preparation of the isomeric



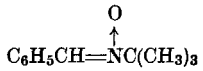
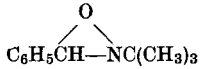
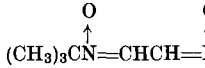
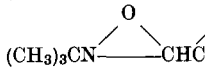
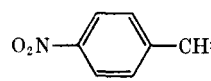
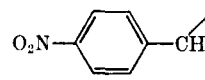
cyclohexanone oxime. The latter compound is the first oxazirane prepared without a substituent on the ring nitrogen.

III. Physical Properties

Most oxaziranes are liquids whose boiling points are somewhat above those of the imines from which they are derived. They have, however, much lower boiling points than the isomeric highly polar nitrones, and those oxaziranes which are solids have substantially lower melting points than the corresponding nitrones. In general oxaziranes have very limited water solubility in contrast again with the nitrones.

It has been claimed that there is characteristic oxazirane absorption in the infrared at 6.8–7.0 μ.[13] However, since the carbon–hydrogen bending vibration of alkyl groups appears in this same region, this is a

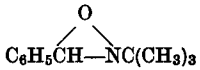
TABLE 2. Ultraviolet Spectra of Isomeric Nitrones and Oxaziranes

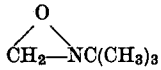
Compounds	λ_{max} (mμ)	ϵ_{max}
	295	16 700
	249	930
	336	20 800
	None	
	252; 362	11 400; 15 800
	268	11 900

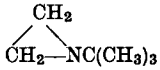
tenuous conclusion and of little value for diagnostic purposes. In contrast with nitrones, oxaziranes show only end-absorption in the ultraviolet, and indeed this fact is one of the more important pieces of evidence for their structure. The striking differences in the spectra of oxaziranes and nitrones are demonstrated by Table 2.

Nuclear magnetic resonance spectra were also obtained for 2-*tert*-butyl-3-phenyloxazirane (XVI) and 2-*tert*-butyloxazirane (XVII).[4] The former compound had three absorption peaks with chemical shifts, $(H_{H_2O}-H_0)/H_{H_2O}$, equal to $+0.28$ (phenyl protons), -0.01 (oxazirane proton) and -0.40 (*tert*-butyl protons). In the latter compound the

oxazirane protons were found at −0.09 and the *tert*-butyl protons at −0.38. The oxazirane-ring proton absorption was also split into two peaks under high resolution as might be expected for two slightly

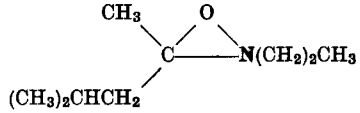

(XVI)


(XVII)


(XVIII)

different protons (*cis* and *trans* to the alkyl group on an almost tetrahedral nitrogen atom). This is in accord with the oxazirane structure and suggests that inversion of the *N*-alkyl group does not take place rapidly at room temperature in this compound. The slow inversion of *tert*-butyloxazirane compared with 1-*tert*-butylaziridine (XVIII) has been ascribed by Bottini and Roberts to diminished repulsions of ring hydrogens and substituent hydrogens in (XVII) as compared with (XVIII).[2]

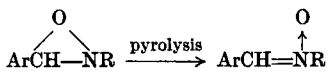
One of the more salient points concerning an unsymmetrically substituted oxazirane ring is that it has an asymmetric carbon atom and should be capable of resolution into optically active forms. The oxazirane (XIX) has in fact been partially resolved (α_D^{22} −3.94°) by treating it with the alkaloid brucine under the correct conditions.[4]


(XIX)

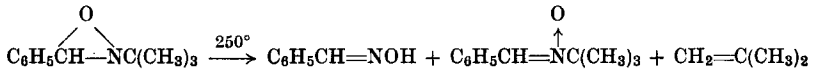
This resolution formed the cornerstone of the assignment of the oxazirane structure to these compounds. Complete resolutions of these products has not as yet been achieved, however.

IV. Pyrolysis and Thermal Decomposition of Oxaziranes

As mentioned above, the oxazirane ring has limited stability. The products of its thermal decomposition vary considerably with the structure of the oxazirane and also with the pyrolysis conditions. The products of thermal decomposition of the 3-aryloxaziranes are the isomeric nitrones. This is apparently a general reaction and may be conveniently accomplished by heating solutions of the oxazirane in

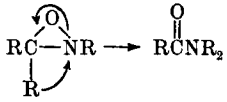


acetonitrile or diethyl carbitol at 80–100° for an appropriate time. This reaction has been studied in detail for 2-*tert*-butyl-3-phenyloxazirane and proceeds in quantitative yield.[8] The extreme lability of some oxaziranes with respect to this isomerization is illustrated by the conversion of 3-(*p*-dimethylaminophenyl)-2-(*m*-nitrophenyl)oxazirane (XV) into the nitrone when this compound is allowed to stand in the dark overnight at room temperature. The reversion of this oxazirane, prepared originally by photolysis of the nitrone, to the nitrone clearly indicates that the oxazirane is a higher energy species than the nitrone. This reaction is, accordingly, of considerable interest since it is a rare example of the interconversion of electromagnetic and chemical energy.[18] The behavior of 2-*tert*-butyl-3-phenyloxazirane in a pyrolysis tube at 250° has also been investigated.[4] Under these conditions the major products were *iso*butylene, benzaldoxime, and nitrone. At this temperature olefin and oxime are apparently formed from nitrone, a

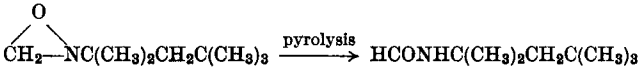


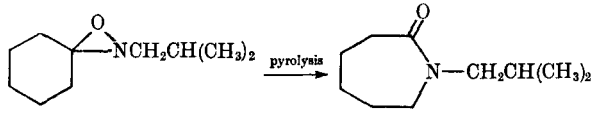
reaction somewhat analogous to thermal decomposition of amine oxides.

The behavior of various alkyloxaziranes at elevated temperatures under pyrolysis conditions has also been studied. Under these conditions amides generally are obtained in good yield. These reactions are carried out in the gas phase at 200–300° and are a direct consequence of the relatively weak oxygen–nitrogen bond. Whether unpairing of the electrons of this bond occurs is uncertain but the reaction may best be described as a concerted rearrangement as indicated below:

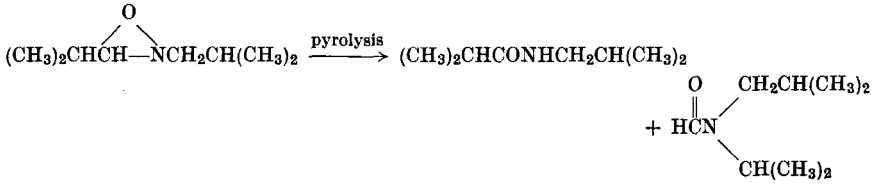


Several examples of oxazirane pyrolyses have been reported.[4, 13] Typical illustrations of this phenomenon include the pyrolysis of 2-*tert*-octyloxazirane and 2-*iso*butyl-3,3-pentamethyleneoxazirane. The latter example is of some interest in that it involves ring expansion and is the basis of a convenient synthesis of *N*-alkylcaprolactams. In



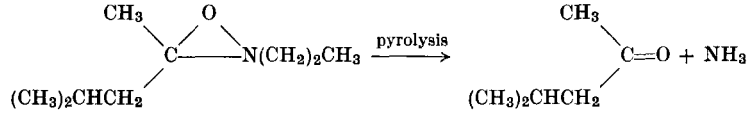


the pyrolysis of unsymmetrically substituted oxaziranes it is obvious that two isomeric amides can be formed. Thus pyrolysis at 300° of 2-*iso*butyl-3-*iso*propyloxazirane gave *N*-*iso*butyl*iso*butyramide (25%) and *N*-*iso*butyl-*N*-*iso*propylformamide (49%). In this case the *iso*propyl group migrated preferentially to the hydrogen atom. In other examples

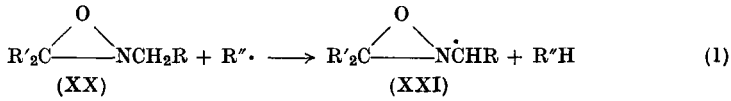


of this pyrolysis methyl has been shown to be a better migrating group than either *iso*butyl or *iso*propyl by a factor of about two. In a general sense, however, there do not appear to be large differences among alkyl groups in their migratory aptitudes in this reaction. At the fairly high temperatures employed and considering the high energy content of the oxazirane ring, this relative lack of discrimination in terms of which group migrates is not surprising.

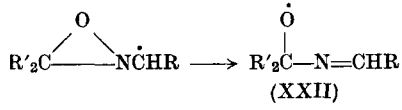
Thermal decomposition of oxaziranes in the liquid phase normally takes a different course than observed in vapor-phase pyrolysis.[4] Thus when 3-*iso*butyl-3-methyl-2-*n*-propyloxazirane was heated under reflux (170°) in a nitrogen atmosphere the major products were methyl *iso*butyl ketone (92%) and ammonia (32%). In addition a 4% yield of



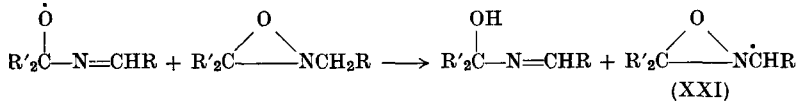
amide mixture was obtained which was identical with the amide mixture from vapor-phase pyrolysis of the same oxazirane. It is probable that thermal decompositions of this type are radical chain-reactions possibly involving the following steps:



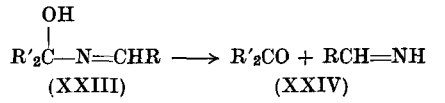
(1)



(2)



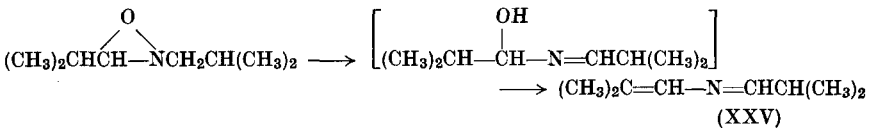
(3)



(4)

In this sequence a radical, possibly a biradical derived from unpairing the electrons of the oxazirane oxygen–nitrogen bond, abstracts the α-hydrogen atom of the *N*-alkyl group to form (XXI) which subsequently isomerizes to (XXII). Alternatively the formation of (XXII) may take place directly by a concerted reaction. In either event the iminoalkoxy radical (XXII) carries the chain. The ammonia which is formed presumably comes from aldol-like condensations of the imine (XXIV). The fact that vapor-phase pyrolysis does not take this course simply reflects the low probability of a chain reaction in the vapor phase.

The decomposition of 2-*iso*butyl-3-*iso*propyloxazirane was also examined under comparable conditions. Here the major products were water and the unsaturated imine (XXV). The imine presumably comes from dehydration of the iminoalcohol (XXIII) which is formed by the



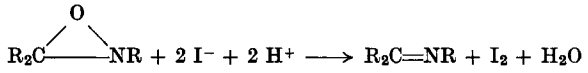
same type of chain-reaction described above. It is obvious, of course, that oxaziranes without α-hydrogens on the *N*-alkyl group would not be subject to this type of chain-reaction, and indeed they are not. Thus thermal decomposition of *N-tert*-octyloxazirane in solution gives *N-tert*-octylformamide. Here there is no difference between vapor-phase pyrolysis and thermal decomposition in solution.

Finally, many oxaziranes decompose at room temperature over a period of days. This decomposition, although it has not been studied in detail, appears to be grossly comparable to solution decompositions at

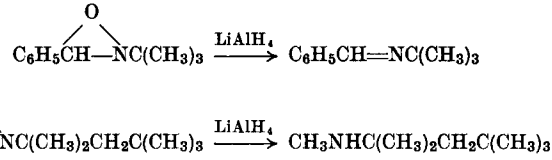
elevated temperatures and probably proceeds through a similar radical chain-reaction. Again it is observed that the *N-tert*-alkyloxaziranes are not subject to this reaction and can be kept for years without decomposition. The susceptibility of some oxaziranes to this decomposition at room temperature is particularly great. Thus 2,3-dialkyloxaziranes and 2-*n*-alkyloxaziranes, though they can be distilled, will on standing for 1–2 weeks at room temperature decompose to an appreciable extent.

V. Reactions of Oxaziranes with Reducing Agents

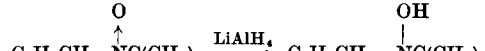
Oxaziranes are active oxygen compounds and react with a wide variety of reducing agents. The most important of these is the reaction with potassium iodide since this reaction is the basis of the iodimetric procedure for assay of oxazirane purity.[4] The reaction has also been examined preparatively and forms a basis for reduction of oxaziranes



to imines. The reduction of oxaziranes can also be carried out with lithium aluminum hydride. Here the product normally obtained is the imine and in some cases the amine. Thus 2-*tert*-butyl-3-phenyloxazirane is reduced by lithium aluminum hydride in ether to *N*-benzylidene-*tert*-butylamine. However, 2-*tert*-octyloxazirane is converted under comparable conditions into *tert*-octylmethylamine. In contrast with these results the isomeric nitrones under the same conditions are

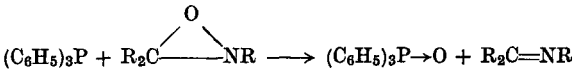


reduced to hydroxylamines with the oxygen–nitrogen bond remaining intact. The reduction of oxaziranes to amines has also been carried out with hydrogen at low pressures using a platinum catalyst at room temperature.[10]

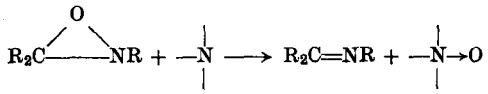


A second group of oxazirane reductions is characterized by transfer of the ring oxygen atom to an oxidizable substrate. Thus

reaction of triphenylphosphine with oxaziranes gives triphenylphosphine oxide in excellent yield.[10] The reaction of trialkyloxaziranes



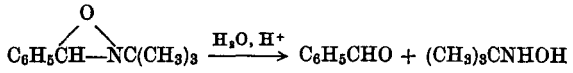
with brucine to give brucine *N*-oxide also goes very smoothly.[4] This reaction has already been mentioned in reference to the partial resolu-



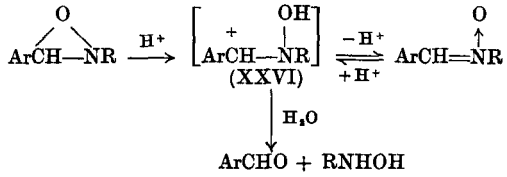
tion of a trialkyloxazirane. The reaction is also of considerable interest in that it goes under very mild conditions and may represent a convenient synthesis of amine oxides under anhydrous conditions. Its generality has not been investigated as yet, however. Finally, the reaction of phenylmagnesium bromide with 2-*tert*-butyl-3-phenyloxirane gives phenol in yields of 40% but there are indications this may be a complicated redox reaction.[5]

VI. Reactions of Oxaziranes with Acidic Reagents

The hydrolysis of 3-aryloxaziranes takes place readily in the presence of a strong mineral acid. Thus 2-*tert*-butyl-3-phenyloxazirane is converted by sulfuric acid in aqueous methanol into benzaldehyde and *tert*-butylhydroxylamine in quantitative yield.[4] Indeed this method is certainly the procedure of choice for preparation of *tert*-butylhydroxylamine. It is probable that to some extent the nitrone is

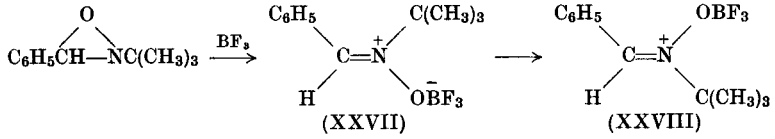


involved as an intermediate in this reaction. The unstable intermediate (XXVI) by loss of a proton is converted into nitrone, and by reaction



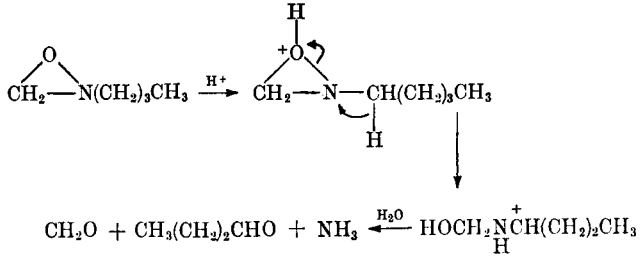
with water the final hydrolysis products are obtained. The nitrone itself is, of course, also hydrolyzed under these conditions to give the same products.

The behavior of 2-*tert*-butyl-3-phenyloxazirane with boron fluoride etherate under anhydrous conditions has also been examined in some detail.[4] From this reaction a crystalline boron fluoride complex was obtained which was spectroscopically characterized as that of the *cis*-isomer (XXVII) of *N*-*tert*-butylbenzaldoxime. On standing or recrystallization from solvent this isomer was converted to the *trans*-form (XXVIII). Separation of the *N*-ethers of oximes into *cis*- and



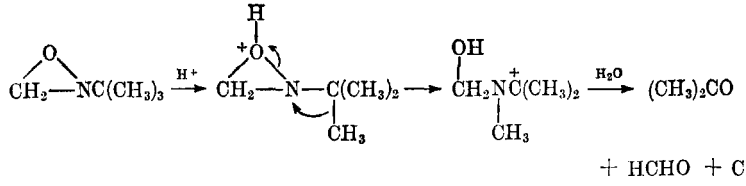
trans-forms has never been accomplished with any degree of certainty. Apparently the energy barrier between these isomers is sufficiently small that only the stable *trans*-form is normally obtained. The formation of the unstable *cis*-nitrone complex from the oxazirane–boron fluoride reaction is not surprising since oxaziranes are very high-energy species and the transition state for this reaction is almost certainly very close in its geometry to the oxazirane itself.[7]

The reaction of alkyloxaziranes with aqueous acid takes quite a different course. In this case the oxygen–nitrogen bond of the protonated oxazirane is cleaved via a concerted reaction with concurrent migration of one of the groups on the α-carbon atom of the *N*-alkyl substituent. In the transition state for this reaction the nitrogen atom



is electron-deficient, and this provides the driving force for the rearrangement. Thus the products of this reaction are aldehydes or ketones and an amine. In the case of *n*-butyloxazirane, hydrogen migrates, and ammonia, formaldehyde and butyraldehyde are formed

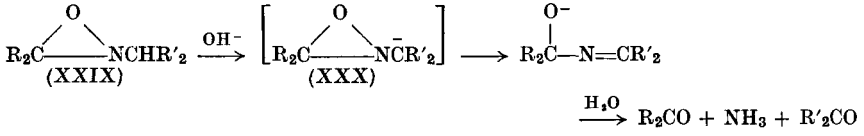
in excellent yield. With *N-tert*-butyloxazirane, methyl migrates. On the basis of examination of a limited number of compounds in this reaction it appears that the migratory aptitudes to nitrogen are in the



following order: phenyl > hydrogen > alkyl. Also there is a striking difference in the acidic hydrolysis of the 3-phenyloxaziranes and the 3-alkyloxaziranes. In the former, the ring opens with cleavage of the carbon–oxygen bond to form a resonance-stabilized carbonium ion (XXVI). In the latter the relatively weak oxygen–nitrogen bond is broken to give an electron-deficient nitrogen atom which can fill its octet by migration of one of the available groups.

VII. Reaction of Oxaziranes with Basic Reagents

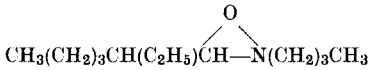
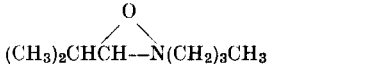
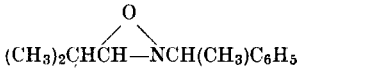
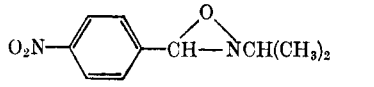
The oxazirane ring itself is not very reactive toward basic reagents, at least at ordinary temperatures. Thus *N-tert*-alkyloxaziranes do not react with sodium methoxide or potassium hydroxide under a variety of conditions.[4] In contrast with these observations, however, oxaziranes with an α-methylene or α-methinyl substituent such as (XXIX) react vigorously with aqueous ethanolic alkali solution to give ammonia as a major product. Indeed the reaction is often suitable as an analytical procedure for determination of oxazirane purity since in most cases the



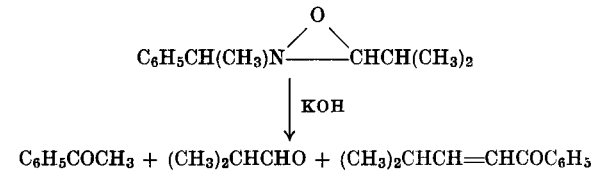
yield of ammonia is almost quantitative. This reaction presumably involves the abstraction of a proton to form a carbanion (XXX) which is then degraded to carbonyl compounds as indicated. Proton-abstraction may well be concerted with ring cleavage, in which case the carbanion (XXX) would not have a discrete existence. Table 3 shows the yields of ammonia obtained from four typical oxaziranes; only in the case of the *p*-nitrophenyloxazirane was the reaction not quantitative.

The aldehydes and ketones formed in this reaction are subject to secondary condensation reactions, and so the isolation of products normally is difficult. However, the reaction of potassium hydroxide in

TABLE 3. Ammonia Assays of Oxaziranes

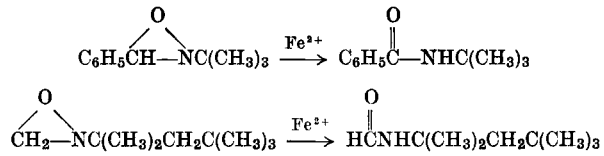
Oxaziranes	Yield of NH_3 (%)
	96
	93
	92
	59

moist ethylene glycol with 2-(α-phenylethyl)-3-*iso*propyloxazirane gave a 57% yield of *iso*butyraldehyde, a 9% yield of *iso*butylideneacetophenone and a 25% yield of acetophenone. Though the material balance of this experiment was not very satisfactory, all of the products were readily explicable on the basis of the mechanism proposed.

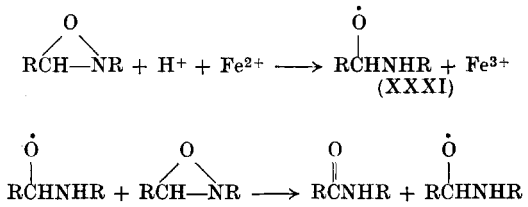


VIII. One-Electron Transfer Reactions of Oxaziranes

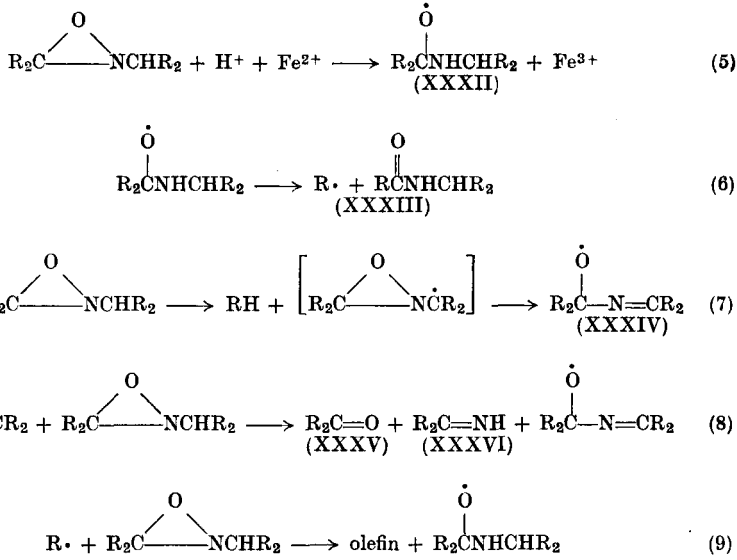
In common with organic peroxides, oxaziranes show some rather interesting one-electron transfer reactions. Thus 2-*tert*-butyl-3-phenyloxazirane is converted by a catalytic amount of ferrous ion into *N*-*tert*-butylbenzamide in quantitative yield. Comparable results are



obtained with 2-*tert*-octyloxazirane. The mechanism of these transformations is uncertain at present but may be formulated as a radical chain-reaction in which the aminoalkoxyl radical (XXXI) is the chain-carrying species.[4] The second step then involves the transfer of a hydrogen atom from (XXXI) to give amide and regenerate the amino-

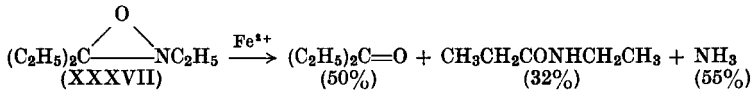


alkoxyl radical. Other mechanisms can be considered for this reaction which also involve (XXXI) as an intermediate, but this one has the virtue of being the least complex and in the absence of more detailed information appears quite reasonable.

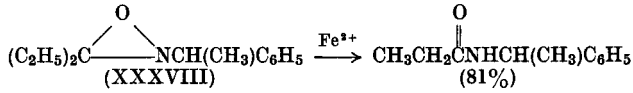


The reaction of trialkyloxaziranes with ferrous ion is considerably more complex but undoubtedly also involves the aminoalkoxyl radical. Some of the more important reactions which occur under these circumstances are indicated in Eqs. (5)–(9). Here the chain-carrying species

(XXXII) can fragment to give amide (XXXIII) and an alkyl radical which can then dimerize or disproportionate. The alkyl radical generated in this process can transfer hydrogen atom to continue the chain as in Eq. (9) or can initiate a new chain-reaction by abstracting the α-hydrogen atom of the *N*-alkyl group. The iminoalkoxyl radical (XXXIV) so formed is the chain-carrying species of this second chain-reaction which gives rise to the ketone (XXXV) and the imine (XXXVI). The latter imine in water would of course hydrolyze to ammonia. This sequence is very similar to that postulated for the thermal decomposition of oxaziranes in solution described in section IV above. A specific example of the type of reaction described here is observed with triethyloxazirane (XXXVII), where the products isolated were ethane, ethylene, diethyl ketone, ammonia, and *N*-ethyl-



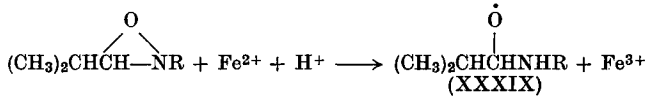
propionamide. The comparable reaction of 3,3-diethyl-2-(α-phenylethyl)oxazirane (XXXVIII) was also investigated and gave *N*-(α-phenylethyl)propionamide, ethane, ethylene, and only trace amounts of ammonia and acetophenone. The difference between the behavior of these two oxaziranes is striking and is presumably because attack of ethyl radical on the α-hydrogen atom of the *N*-*a*-phenylethyl group of



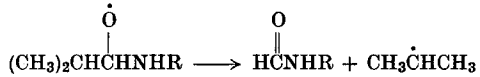
(XXXVIII) (Eq. 7) is restricted by steric strain in the transition state. These results are of some interest since *a priori* one might expect that the benzylic hydrogen involved in this case would be very active in chain-transfer reactions. Actually, the transition state for this chain-transfer reaction probably closely resembles reactants, and the reactions themselves are accordingly governed by steric factors.[7]

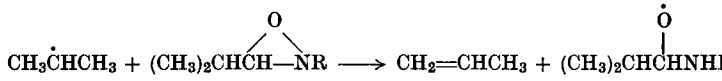
The behavior of 2,3-dialkyloxaziranes in this reaction was also studied. Thus 2-*iso*butyl-3-*iso*propyloxazirane gave with ferrous ion *N*-*iso*butylformamide (83%), propane, and propylene. Similarly 2-*tert*-butyl-3-*iso*propyloxazirane yielded only *N*-*tert*-butylformamide (82%), propane, and propylene. These results can also be represented in terms of the chain-reactions described above. The chain-carrying species (XXXIX) reacts by fragmentation to give an *iso*propyl radical when a carbon–carbon bond is ruptured. This process occurs to the

complete exclusion of carbon–hydrogen bond breaking, since the latter reaction would give as a product *N*-alkyl*iso*butyramides and these were not found. This observation is in agreement with the behavior

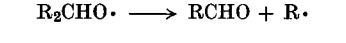


(XXXIX)





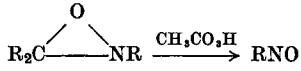
of alkoxyl radicals where a carbon–carbon bond normally is broken before a carbon–hydrogen bond.[12] Finally it should be pointed out



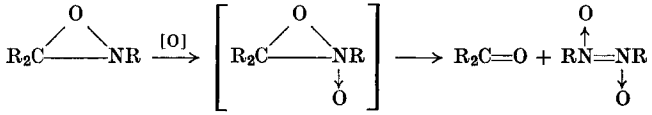
that the one-electron transfer reactions of oxaziranes are poorly understood at present and much additional work is required for a real understanding of these reactions.

IX. Oxidation of Oxaziranes to Nitrosoalkanes

From a preparative point of view one of the more important oxazirane reactions is their oxidation to nitrosoalkanes.[6] This is con-

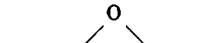
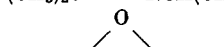
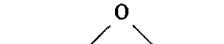
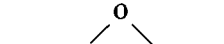
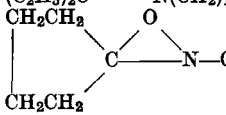
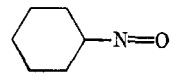
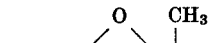
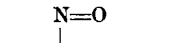
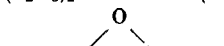


veniently carried out with peracetic acid at room temperature or below and proceeds in yields of 30–90%. The nitrosoalkanes are obtained as the *trans*-dimers which are normally crystalline solids. The exact nature of this reaction is uncertain but it may be formulated as follows:



The yields obtained in the oxidation of several oxaziranes are tabulated in Table 4. The synthesis of nitrosoalkanes via oxazirane intermediates

TABLE 4. Preparation of Nitrosoalkane Dimers

Oxazirane	Nitrosoalkane dimer	Yield (%)
	$(CH_3)_2CHN{=}O$	33
	$C_6H_5CH_2N{=}O$	37
	$CH_3(CH_2)_{11}N{=}O$	37
	$CH_3(CH_2)_{17}N{=}O$	60
		68
		83
	$C_6H_5(CH_2)_2N{=}O$	71

is of considerable importance in that it is the only convenient laboratory procedure for the preparation of these compounds.

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CHAPTER V

Thietane and Its Derivatives

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I. General Discussion

1. History of Thietane

Although Mansfield[50] had suspected its existence in 1886, thietane was actually first isolated and identified in 1916 by Gryszkiewicz-Trochimowski[39] who prepared it by the reaction of trimethylene bromide with sodium sulfide. Probably Lilienfeld[46] in 1911 obtained another compound with a ring containing three atoms of carbon and one of sulfur, 3-thietanol. This author, however, treated the technical dichlorohydrin of glycerol with sodium sulfide to give a mixture of products which he polymerized to a rubbery mass without preliminary fractionation.[46, 47]

Unlike the tetra- and pentamethylene sulfides which are found in Iranian and American oils, trimethylene sulfide does not seem to occur naturally.[36b]

Among those who have made a special study of thietane and its derivatives are the group at the American Petroleum Institute,[16–22, 40, 41, 43, 61] who are concerned with the precise determination of the physical properties of the unsubstituted ring, and the Dutch school of Backer,[6–12] who have described several spirocyclic compounds.

Except for the use of a very impure polymerization product by Lilienfeld in 1911, it appears that compounds containing the thietane ring have had no industrial application to this day.

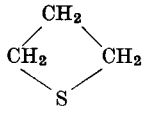
2. Nomenclature

A. The Nucleus

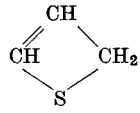
Thietane is a four-membered heterocyclic compound which can be considered as derived from a 1,3-dithiol by the elimination of one molecule of hydrogen sulfide. The sulfur atom can be thought of as replacing a methylene group, in which case the compound would be called thiacyclobutane. One can also consider the presence of the heteroatom as a result of the addition of sulfur to a hydrocarbon chain, hence the terms trimethylene sulfide, 1,3-thiopropane, *n*-propylene sulfide and propane α,γ-sulfide as given in *The Ring Index*, number 40. The name epithio-1,3-propane has also been used.[48]

The term thietane is recommended by the International Union of Pure and Applied Chemistry; this name was made up by combining the prefix 'thia-', the designation for bivalent sulfur, with the syllable '-et-' and the suffix '-ane' indicating the presence of a saturated, four-membered ring containing no nitrogen. In French, the suffix '-anne' is recommended to avoid possible confusion with saturated hydrocarbons and with heterocyclics containing elements in the fourth column of the Periodic Table.[48]

The derivative containing one double bond is called thiete:

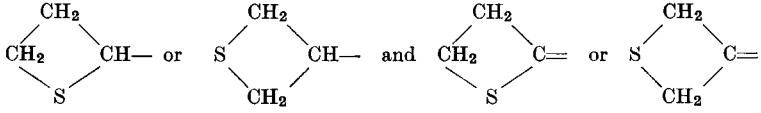


Thietane

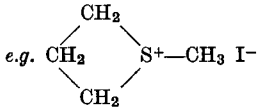


Thiete

The terms 'thietanyl' and 'thietanylidene' can be used, respectively, to designate the radicals:

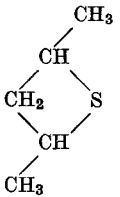
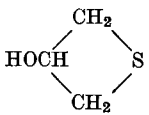
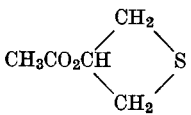
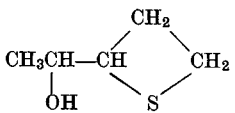
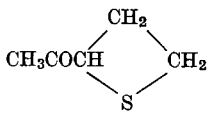


The sulfonium salts[48] can be designated by the prefix 'thiania-' to indicate the replacement of a carbon by an ionized sulfur atom:



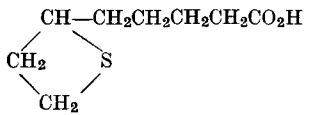
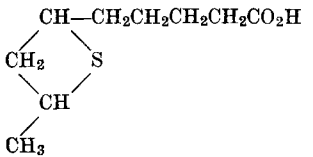
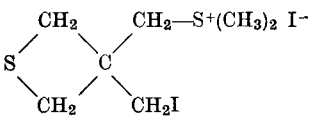
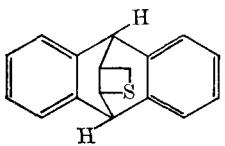
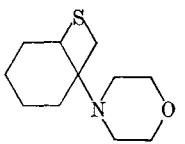
This compound, which actually occurs in equilibrium with γ-iodopropylmethyl sulfide would be 1-methyl-1-thianiacyclobutane iodide.

TABLE 1. Nomenclature of Some Thietane Derivatives

Formula	Name	Other names
	2,4-Dimethylthietane	α,α′-Dimethyltrimethylene sulfide
	3-Thietanol	3-Hydroxythietane
	3-Thietanyl acetate	3-Acetoxythietane
	α-Methyl-2-thietanemethanol[a]	1-(2-Thietanyl)ethanol; 2-(1-hydroxyethyl)thiacyclobutane
	Methyl 2-thietanyl ketone[a]	2-Acetylthietane

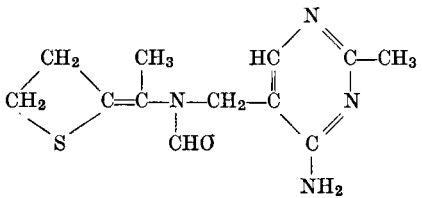
(*Table continued*)

TABLE 1 (*continued*)

Formula	Name	Other names
	2-Thietanevaleric acid[a]	5-(2-Thietanyl)valeric acid; 2-(4-Carboxybutyl)trimethylene sulfide
	4-Methyl-2-thietanevaleric acid	5-(4-Methyl-2-thietanyl)valeric acid; 4-methyl-2-(4-carboxybutyltrimethylene sulfide
	3-Iodomethyl-3-methylthiomethylthietane iodomethylate	
	9,10-Dihydroanthracene-9,10-*endo*-2′,3′-thietane	
	4-(7-Thiabicyclo[4.2.0]oct-1-yl) morpholine	

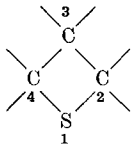
(*Table continued*)

TABLE 1 (*continued*)

Formula	Name	Other names
	*N*-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-*N*-[1-(2-thietanylidene)ethyl]formamide[a]	

[a] From *Chemical Abstracts*.

B. Substitution Derivatives



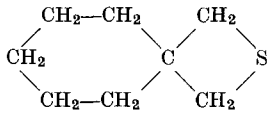
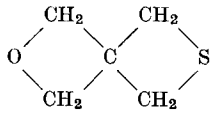
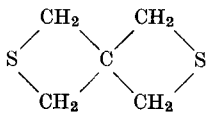
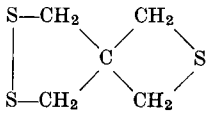
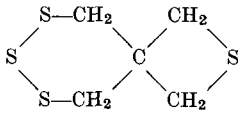
The sulfur atom is always number 1; formerly, however, the letters α, β, and α' were used with the term 'trimethylene sulfide' to designate carbon atoms 2, 3, and 4, respectively.

Some typical thietane derivatives are listed in Table 1.

C. Spirocyclic Derivatives

The 'oxa', 'thia' nomenclature is the most practical for designating spirocyclic derivatives containing the thietane ring. The numbering must then follow the general rules (see Table 2).

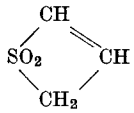
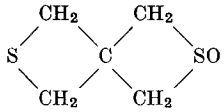
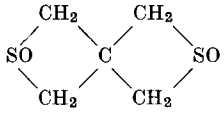
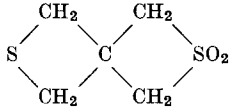
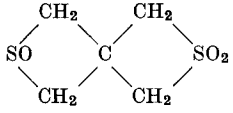
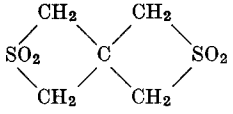
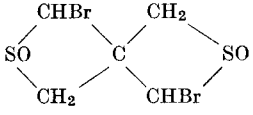
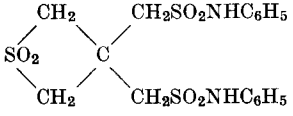
TABLE 2. Nomenclature of Some Spirocyclic Compounds Containing the Thietane Ring

Formula	Name
	2-Thiaspiro[3.5]nonane
	2-Oxa-6-thiaspiro[3.3]heptane
	2,6-Dithiaspiro[3.3]heptane
	2,6,7-Trithiaspiro[3.4]octane
	2.6,7,8-Tetrathiaspiro[3.5]nonane

D. Sulfoxides and Sulfones

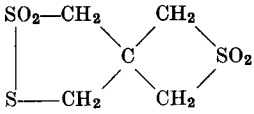
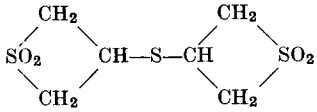
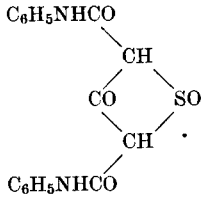
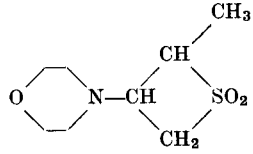
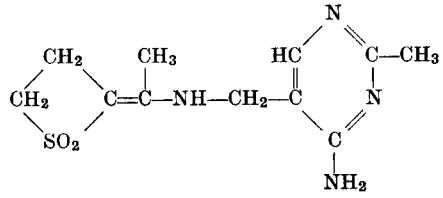
These are designated by the terms 'oxide' and 'dioxide', respectively, preceded by the number of the oxidized sulfur atom, or, if there is no ambiguity, by '*S*'. Table 3 gives some examples which illustrate the application of the rule to compounds containing several sulfur atoms.

TABLE 3. Nomenclature of Some Sulfones and Sulfoxides Containing the Thietane Nucleus

Formula	Name
	Thiete 1,1-dioxide
	2,6-Dithiaspiro[3.3]heptane 2-oxide
	2,6-Dithiaspiro[3.3]heptane 2,6-dioxide
	2,6-Dithiaspiro[3.3]heptane 2,2-dioxide
	2,6-Dithiaspiro[3.3]heptane 2,2,6-trioxide
	2,6-Dithiaspiro[3.3]heptane 2,2,6,6-tetraoxide
	1,5-Dibromo-2,6-dithiaspiro[3.3]-heptane 2,6-dioxide
	3,3-Thietanedimethanesulfonanilide 1,1-dioxide

(Table continued)

TABLE 3 (*continued*)

Formula	Name
	2,6,7-Trithiaspiro[3.4]octane 2,2,6,6-tetraoxide
	Bis-(3-thietanyl 1,1-dioxide) sulfide
	3-Oxo-2,4-thietanedicarboxanilide 1-oxide; or 2,4-bis(phenylcarbamoyl)-3-thietanone 1-oxide
	4-(2-Methyl-3-thietanyl) morpholine *S,S*-dioxide
	4-Amino-2-methyl-5-[{[1-(2-thietanylidene)ethyl]amino}-methyl]pyrimidine *S,S*-dioxide

II. Physical Properties

1. Thietane

A. Solid State

The melting point has been given as $-64°$,[53] $-68°$[67] and $-73.25°$C.[61, 40] The heat of fusion, $\Delta H_{fus.}$, is 1971 cal./mole.[61] The cryoscopic constant has been stated to be 0.023/°K[40] or 0.0248°K.[61]

The study of the specific heats between 12.22 and 194.70°K has revealed the existence of two kinds of thietane crystals, I and II, which are stable, respectively, below and above 176.7°K (transition

temperature); the enthalpy of transition between the crystalline varieties is 159.8 cal./mole at this temperature.[61] The heat capacities of crystals I and II at different temperatures are shown in Table 4.

TABLE 4. Heat Capacity of Thietane Crystals I and II

Crystal I		Crystal II	
Temperature (°K)	Heat capacity (cal. deg.$^{-1}$ mole^{-1})	Temperature (°K)	Heat capacity (cal. deg.$^{-1}$ mole^{-1})
12.22	0.445	180.20	18.886
20.16	1.892	182.43	19.223
32.34	4.902	185.13	19.662
43.31	7.253	187.99	20.101
52.66	8.828	188.70	20.227
64.46	10.343	194.15	21.081
76.26	11.431	194.70	21.146
88.86	12.401		
101.73	13.144		
114.22	13.840		
127.13	14.584		
142.39	15.547		
159.30	16.857		
171.63	18.181		

B. Liquid and Gaseous States

The calculated molecular weight is 74.144. The boiling points at various temperatures are listed in Table 5.

TABLE 5. Boiling Point of Thietane

Pressure (mm. of Hg)	B.p. (°C)	References
249	61.2 ± 0.03	67
738	93.7 ± 0.1	67
752	94.0 ± 0.2 (corr.)	39, 4
760.00	94.968	61, 40
762	94.7	67
'atmospheric'[a]	93–95	21
'atmospheric'[a]	93.6	53
'atmospheric'[a]	92–94	19
'atmospheric'[a]	94	43d
'atmospheric'[a]	94–94.5	33
'atmospheric'[a]	94–95	41a, 62a
'atmospheric'[a]	95–96	26a

[a] Not specified.

Between 48 and 132°C, the values obtained for the vapor tension verify one of the following equations:[61]

$$\log_{10} p(\text{mm. of Hg}) = 7.01667 - 1321.331/(t + 224.513);$$

$$\log_{10} p(\text{atm.}) = A(1 - 368.128/T),$$

where

$$\log_{10} A = 0.802678 - 5.9283 \times 10^{-4}T + 5.5834 \times 10^{-7}T^2.$$

The heat of vaporization, $\Delta H_{\text{vap.}}$, at 327.53°K has been given as 6636 cal./mole[67] and 8234 cal./mole.[61]

Values which have been obtained for the density of liquid thietane are listed in Table 6.

TABLE 6. Density of Liquid Thietane

Temperature (°C)	Density (d_4^t)	References
0	1.0371	53
20	1.0228	43d
20	1.0224	67
20	1.02000	40
23	1.0284	39
25	1.01472	40, 43
30	1.00957	40
40	1.0017	43d
60	0.9817	43d
85	0.9566	43d

The molar volume, V, of thietane has been determined to be 78.6 cm.^{3};[40] the calculated value is 88.6 or 89.2.[40]

The absolute viscosity at various temperatures is given in Table 7.

TABLE 7. Absolute Viscosity of Thietane

Temperature (°C)	η (centipoise)	References
20	0.638 ± 0.001	40
25	0.607	40
30	0.576	40

Table 8 gives values obtained for the refractive index in the temperature range 20–30°C. Further results are shown in Table 9. The 'refractivity intercept', defined as $n_D^{20} - 0{\cdot}5\, d_4^{20}$, has the value 1.00020.[40]

TABLE 8. Refractive Index of Thietane

Temperature (°C)	Refractive index (n_D^t)	References
20	1.51020	40
20	1.5072	53
20	1.5097	67
20	1.5096	62a
20	1.5094	26a
20	1.5070	66
23	1.5059	39
25	1.50738	40
25	1.5027	33
30	1.50448	40

TABLE 9. Refractive Index of Thietane with Monochromatic Light of Different Wavelengths

Temperature (°C)	Lines	Wavelength (Å)	n	References
20	Hg(g)	4358.3	1.52648	40
25			1.52362	40
30			1.52059	40
20	H(F)	4861.3	1.5185	67
20			1.51922	40
25			1.51635	40
30			1.51337	40
20	He(v)	5015.7	1.51737	40
25			1.51453	40
30			1.51154	40
20	Hg(e)	5460.7	1.51330	40
25			1.51050	40
30			1.50755	40
20	H(C)	6562.8	1.5061	67
20			1.50660	40
25			1.50379	40
30			1.50093	40
20	He(r)	6678.1	1.50603	40
25			1.50318	40
30			1.50035	40

The specific optical dispersion, $10^4 \times [n(H_F) - n(H_C)]/d_4$, is 123.72 at 20°C;[40] this value is of the same order of magnitude as that observed for the olefins.

Values for the molar refraction, R, are given in Table 10.

TABLE 10. Molar Refraction (Sodium D line, λ 5892.6 Å) of Thietane

$R_{obs.}$(cm.^{3})	$R_{calc.}$ (cm.^{3})	References
(21.44)	21.65	39
21.67		67
21.71	21.85	40

The atomic refractivity, R_D, of the sulfur atom in thietane is 7.81 cm.^{3} Sunner,[67] who investigated the molar refraction of some aliphatic cyclic molecules $(CH_2)_nS$, noticed an increase in the atomic refraction of the sulfur atom with decreasing strain of the ring.

Details of the surface tension are given in Table 11.

TABLE 11. Surface Tension of Thietane

Temperature (°C)	σ (dynes/cm.)	References
20	34.70	43d
20	36.3	40
25	35.6	40
30	35.0	40

The parachor, $P = M\sigma^{1/4}/(D - d)$, at 20°C was observed to be 178.1[40] or 177.0[43d]; the calculated value is 176.8 or 176.0.[40]

The heat capacity of the liquid[61] is shown in Table 12.

TABLE 12. Heat Capacity of Liquid Thietane

Temperature (°K)	Heat capacity (cal. deg.$^{-1}$ mole^{-1})	Temperature (°K)	Heat capacity (cal. deg.$^{-1}$ mole^{-1})
201.98	24.490	260.43	25.667
211.32	24.572	269.93	25.981
221.33	24.689	285.16	26.546
231.25	24.876	303.46	27.280
241.08	25.113	312.44	27.661
250.81	25.374	321.29	28.037

The entropy, S^0, of thietane is given in Table 13.

TABLE 13. Entropy of Liquid Thietane

Temperature (°K)	S^0 (cal. deg.$^{-1}$ mole^{-1})	References
298.16	44.72 ± 0.10	61
327.53	47.32 ± 0.10	61

Thermodynamic functions[61] (in cal. deg.$^{-1}$ mole^{-1}, except for $H^0 - H_0^0$ which is expressed in kcal./mole), calculated from infrared and Raman data, are listed in Table 14.

TABLE 14. Thermodynamic Functions of Thietane

Temperature (°K)	$-(F^0-H_0^0)/T$	$(H^0-H_0^0)/T$	$(H^0-H_0^0)$	S^0	C_p^0
0	0	0	0	0	0
273.16	55.86	10.87	2.970	66.73	15.31
298.16	56.85	11.29	3.367	68.14	16.57
300	56.92	11.33	3.398	68.24	16.66
400	60.44	13.32	5.327	73.76	21.89
500	63.64	15.51	7.756	79.16	26.56
600	66.67	17.69	10.61	84.35	30.45
700	69.55	19.75	13.83	89.30	33.69
800	72.31	21.67	17.33	93.98	36.40
900	74.97	23.43	21.09	98.40	38.70
1000	77.52	25.06	25.06	102.59	40.67

The heat capacity of the vapor at 377.20°K and 190 mm. of Hg is 20.8 cal. deg.$^{-1}$ mole^{-1}.[61] The entropy of the gas (observed) is shown in Table 15.

TABLE 15. Entropy of Thietane Vapor

Temperature (°K)	S^0 (cal. deg.$^{-1}$ mole^{-1})	References
298.16	68.17 ± 0.25	61
327.53	69.75 ± 0.25	61

2. Derivatives of Thietane

A. Physical Properties

The melting and boiling points, densities and refractive indices of derivatives of thietane are listed in Table 16.

TABLE 16. Physical Properties of Thietane Derivatives

Name	M.p. (°C) [solvent of recrystallization]	B.p. (°C/mm.)	d_4^t	n_D^{20}	References
		103–105/740		1.4881	62a, 41a
2-Methylthietane		105.5–107.5/747	0.9571_4^{20}	1.4831	39
		101–102		1.4852	62
		105–105.5/773	0.9531_4^{20}	1.4888	2
		108	0.9439_4^{25}		49
3-Methylthietane		108–109		1.4840 (25°)	17
			1.0164_{20}^{20}	1.4865	35, 41a
2,4-Dimethylthietane		112.5–113.5/757	0.8710_4^{18}	1.4502 (18°)	39
cis		113–115/740		1.4739	62a, 41a
trans		113–115/740		1.4712	62a, 41a
3,3-Dimethylthietane		120		1.4739 (18°)	9
				1.4640 (35°)	
		115–116		1.4738 (18°)	62
		116		1.4733	62a, 41a
3,3-Diethylthietane		170.5–173		1.4833	62
		172		1.4831	62a, 41a
		90/60			34
3-Ethyl-2-propylthietane *cis*		185–188/740		1.4804	62a, 41a
trans		185–188/740		1.4731	62a, 41a
2-Isopropyl-3,3-dimethylthietane		173–174/740		1.4600	62a, 41a
2-Thiaspiro[3.2]hexane		141–142/740		1.5192	62a, 41a
2-Thiaspiro[3.3]heptane		149–150/740		1.5145	62a, 41a
2-Thiaspiro[3.4]octane		92–93/23		1.5191	62a, 41a
2-Thiaspiro[3.5]nonane		96/18			10
3-3-Dibenzylthietane	57–58	156/0.1			62a, 41a
9,10-Dihydroanthracene-9,10-*endo*-2′3′-thietane	175–175.5 [2-propanol]				31

Name	M.p. (°c) [solvent of recrystallization]	B.p. (°c/mm.)	d_t^t	n_D^{20}	References
3-Thietanol		57/1.3	1.2130^{20}	1.5433	63, 64
		86/16		1.5398 1.5393	1
		51–52/0.9	1.2129^{25}	1.5476 1.5408 (25°)	30
		90/20			27[a]
3-Thietanyl acetate		80/17 82/20		1.4904 1.4898	1
3-Thietanyl 3,5-dinitrobenzoate	112–113 [95% ethanol]				30
3-Methyl-3-thietanemethanol		78–79/2		1.5143	62a, 41a
— α-naphtylurethane	108–109				62a, 41a
α-Methyl-2-thietanemethanol		97/22 95/18			69
3,3-Bis(hydroxymethyl)thietane	72–74	sublimed/0.01			15
3,3-Dimethoxythietane		62–63/12		1.4760 (25°)	51a
3-Thietanone	62–63				51a, 56b
— semicarbazone	188–189 (dec.)				56b
— 2,4-dinitro-phenylhydrazone	175–176				51a
Methyl 2-thietanyl ketone		49/7 77/30			69 43b
3-Dimethylaminothietane chlorohydrate	180.5–182.5 [abs. ethanol + ether]				31
3-Dimethylaminothietane picrate	210–212 (decomp.) [abs. ethanol]				31

(*Table continued*)

TABLE 16 (*continued*)

Name	M.p. (°C) [solvent of recrystallization]	B.p. (°C/mm.)	n_t^t	n_D^{20}	References
3-Dimethylaminothietane methylsulfate	166–170 [2-propanol]				31
4-(7-Thiabicyclo[4.2.0]oct-1-yl)morpholine	165–167				66a
2-Oxa-6-thiaspiro[3.3]heptane		60/3			25
		85/15			26
2,6-Dithiaspiro[3.3]heptane	31.5 [ether]	108–109/16			7
	31–32 (spontaneously)	103–104/12			59
	31	116–118/15	1.2281_4^{35}		45
2,6-Dithiaspiro[3.3]heptane 2-oxide	81.5 [benzene]				7
2,6-Dithiaspiro[3.3]heptane 2,2-dioxide	116.5 [ethanol]				7
2,6,7-Trithiaspiro[3.4]octane	55.5–56.5				6
	53–54 [ether + hexane]				59
2,6,7,8-Tetrathiaspiro[3.5]-nonane	78.5 [alcohol]				6[c]
	77–77.5 [hexane]				60
3-Iodomethyl-3-methylthio-methylthietane iodomethylate	145–146 [water or ethanol]				8
	143 [methanol]				7[d]
2-Thietanevaleric acid		136–150/0.15			23
		120–135/0.1			74

Name	M.p. (°C) solvent of recrystallization	B.p. (°C/mm.)	d_t^t	n_D^{20}	References
Methyl 2-thietanevalerate		89–96/0.15			74
Ethyl 2-thietanevalerate		95–101/0.25			74
4-Methyl-2-thietanevaleric acid		134–146/0.2			23
		120–127/0.2			74
N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-*N*-[1-(2-thietanylidene)ethyl]formamide	135				69, 43a
	113				55, 55a
	136 and 162 (dimorphic)				70
N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-*N*-[1-(2-thietanylidene)ethyl]formamide	135				69, 43a
	136 and 162 (dimorphic)				71, 70, 43c
	166–168 (dec.)				67b
	113				55, 55a
— hydrate	109.5				43c
— picrate	153				71
N-[(4-Amino-2-ethyl-5-pyrimidinyl)methyl]-*N*-[1-(2-thietanylidene)ethyl]formamide	80				71
N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-*N*-[α-(2-thietanylidene)benzyl]formamide	186				71

[a] Reported as 'hydroxypropylene sulfide'.[1]
[b] Density of solid, $d_4^{15} = 1.2439$.[45]
[c] Reported as '2-thio-2,6,7-trithiaspiro[3.4]octane'.[60]
[d] Reported as '2,6-dithiaspiro[3.3]heptane bisiodomethylate'.[8]

B. Crystallographic Properties

The only compound containing the thietane ring for which we have crystallographic information is 2,6-dithiaspiro[3.3]heptane.[11] For the crystal system (monoclinic), $\beta = 89° 45'$; $b : a : c = 0.499 : 1 : 0.340$.

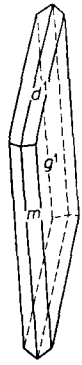


Fig. 1. Crystal form of 2,6-dithiaspiro[3.3]heptane.

The forms are $g^1 = (010)$; $d^1 = (111)$; $m = (110)$. The angles (observed) are $g^1 : m = 63° 31'$; $g^1 : d^1 = 74° 24'$; $(001) : (\bar{1}01) = 55° 18'$. The crystals consist of plates which are parallel at g^1 (Fig. 1).

III. Physicochemical Properties of Thietane and Its Derivatives

1. Geometry of the Thietane Molecule

Recently Goldish[37, 38] has examined the vapor of thietane by electron diffraction and determined the spatial configuration of the molecule (Fig. 2). The thietane molecule should be virtually planar,

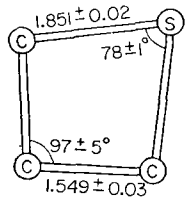


Fig. 2. Spatial configuration of thietane molecule.

although the author is not precise about this point. As expected[65] for a small ring, the angles C—C—C and C—S—C differ considerably from

those found in non-cyclic molecules: thus C—C—C = 109° 28′ in alkanes and C—S—C = 105° in dimethyl sulfide.*

Scott *et al.*[61] have postulated a planar structure for the thietane molecule, for the calorimetric and spectroscopic values calculated from such a model agree most closely with the experimental values.

The moments of inertia have been calculated,[61] assuming the distances: C—S = 1.82 Å; C—C = 1.54 Å; H—C = 1.09 Å; and the angles: C—S—C = 79°; H—C—H = H—C—C = H—C—S (for the methylene in the α-position); H—C—H = H—C—C (for the methylene in the β-position); the principal moments of inertia of the molecule, in 10^{-38} g. cm.^{2}, are then: $I_a = 0.824$; $I_b = 1.234$; $I_c = 1.893$.

2. Dipole Moments

The dipole moments of thietane and its derivatives are listed in Table 17.

TABLE 17. Dipole Moments of Thietane and Its Derivatives

Compound	Temperature (°C)	Solvent	μ (Debyes[a])	Reference
Thietane	25°	Benzene	1.78	28
2-Methylthietane	25°	Benzene	1.79	49
3,3-Dimethyl-thietane	?	Not specified	1.76	42
3-Thietanol	20°	Benzene	1.93	64
2,6-Dithiaspiro-[3.3]heptane	?	Not specified	1.12	42

[a] 1 Debye (D) = 10^{-18} c.g.s.e.s.

A. Thietane, 2-Methylthietane and 3,3-Dimethylthietane

The moments of these three compounds are practically the same, since the moment of the methyl group is equal to that of the C—H bond.

It may be interesting to compare the moments of thietane, a cyclic aliphatic molecule, with that of a non-cyclic aliphatic molecule, *e.g.* dimethyl sulfide, whose moment in benzene solution is 1.45 D (see ref. 49).

* Siebert, H., *Z. anorg. Chem.*, **271**, 65 (1952); see also Maccoll, A., *Progr. Stereochem.*, **1**, 361 (1954).

The value of the angle C—S—C in the dimethyl sulfide molecule is 105°, which suggests hybridization (nearly of the sp^3 type) of the orbitals occupied by *all* the electrons, bonding or not, of the sulfur atom, so that the axes of the orbitals occupied by the bonding electrons of the sulfur atom must be co-linear with the C—S linkages. On this hypothesis, an hybridization moment of the sulfur atom directed away from this atom is likely to be present. Its value is very high indeed, since it reaches 2.8 D,* so that the *intrinsic* moment of the dimethyl sulfide molecule would be no more than -1.3 D.

In the thietane molecule the C—S—C angle is about 90° or even less (see Fig. 2). A s–p hybridization of the orbitals occupied by the bonding electrons of the sulfur atom does not seem to be necessary, since the p_x and p_y atomic orbitals are perpendicular to each other. If this is so, the hybridization moment of the sulfur atom would disappear. It is then impossible to understand the actual value of the moment of the thietane molecule, $+1.77$ D, and its sign as indicated by the moment determined for the thietane derivative, 3-thietanol, which is discussed below. Therefore, in spite of the value of the C—S—C angle, we must assume a s–p hybridization of the sulfur atom, probably nearly sp^3 as in the dimethyl sulfide molecule (in spite of the value of the C—S—C angle). Consequently the C—S bonds in the thietane molecule are *bent*, the angle of bending being about 10°[38].†

B. 3-Thietanol

According to Sjöberg,[64] the moment of this compound ($\mu = 1.93 \pm 0.01$ D) would differ from that calculated on the basis of free rotation of the COH group around the C—O axis, and also from the moment calculated on the basis of a mixture (in equal proportions) of all the possible rotational isomers derived from the various positions of minimum energy of the O—H bond (Fig. 3); the two calculations give the same numerical result. If, as Sjöberg has done, one takes $\mu_{COH} = 1.7$ D with $\psi_1 = 88°$ and $\mu_{thietane} = 1.9$ D, directed along the line which bisects the C—S—C angle, the calculated moment is 2.5 D.

In fact, the data for this calculation are rather questionable; the best values‡ are $\mu_{COH} = 1.7$ D at 61° of the C—O bond axis and

* See, for example, Fyfe, W. S., *J. Chem. Phys.*, **21**, 2 (1953); Gibbs, J. H., *J. Phys. Chem.*, **59**, 644 (1955).

† Gomel, M., and H. Lumbroso, *Bull. soc. chim. France*, **1962**, 2212; see footnote to p. 2214.

‡ See, for example, Lumbroso, H., and G. Dumas, *Bull. soc. chim. France*, **1955**, 651.

$\mu_{thietane}$ = 1.78 D, which give $\mu_{calc.}$ = 2.09 D, a result which is in better agreement with the observed moment (1.93 D).

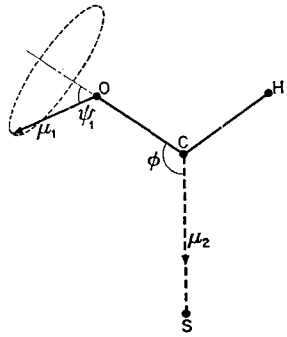


Fig. 3. Partial dipole moments of 3-thietanol.

C. 2,6-*Dithiaspiro*[3.3]*heptane*

A finite dipole moment, 1.12 D,[42] for such a symmetrical molecule (see Table 2) seems to be anomalous. It may be due to thermal flexibility or to a large atom polarization of the molecule. Anomalous high dipole moments have been also observed for apparently symmetrical molecules having two opposed finite dipoles, *e.g.* benzoquinone.*

3. Infrared and Raman Spectra

A. Thietane

The infrared-absorption spectrum of the vapor has been studied by Vernon Thornton of the Phillips Petroleum Company (quoted in ref. 61), and that of the liquid has been measured at the Laramie Station of the Bureau of Mines as part of A.P.I. Research Project 48 A (see refs. 61 and 40). The Raman spectrum has been measured by E. J. Rosenbaum of the Sun Oil Company (*cf.* ref. 61).

The complete analysis of these spectra was made by D. W. Scott *et al.*[61] The vibrational assignment of the bands has been discussed in terms of a planar-ring structure of the molecule (point group symmetry C_{2v}). In Table 18, A_1, B_1, A_2 and B_2 refer to the symmetry species into which the various vibration modes are divided.

Thiacyclobutane polymerizes at an appreciable rate when exposed

* See, for example, Sutton, L. E., *Ann. Reps. Progr. Chem.* (*Chem. Soc. London*), **37**, 61 (1940).

to ultraviolet light, and some polymerization of the sample is induced by the exciting light used for the Raman spectrum. For this reason, some of the weaker Raman lines included in Table 18 are probably

TABLE 18. Spectra[a] of Thiacyclobutane below 1500 cm.$^{-1}$

Raman liquid	Infrared		Assignment
	Liquid	Vapor	
215 *ww*			?
245 *ww*			?
272 *ww*			?
467 (1)			?
528 (24)			Fundamental A_1
580 (1)			?
609 (3)			528 + 73 = 601 B_2[b]
670 (32)*b*	672 *s*	675 *s*	Fundamental B_1
698 (16)	701 *s*	698 *s*	Fundamental A_1
768 (2)		770 *ww*	698 + 73 = 771 B_2
840 (8)	844 *s*	844 *s*	Fundamental B_2
878 (3)			Fundamental A_2
932 (30)		932 *m*	Fundamental A_1
		958 *w*	878 + 73 = 951 B_1
969 (12)*b*, *d*	969 *s*	969 *s*	Fundamental B_2
991 (5)			Fundamental B_1
	~1015 *ww*		932 + 73 = 1005 B_2
1031 *ww*			?
1042 *ww*			969 + 73 = 1042 A_1
	1055 *ww*		2 × 528 = 1056 A_1
	1090 *ww*		?
1137 (1)			Fundamental A_2
1175 (6)	1170 *s*	1173 *s*	Fundamental B_1
1205 (3)			528 + 675 = 1203 B_1
1217 (3), 1236 (5)	1224 *s*	1222 *s*, 1236 *s*	Fundamental A_1 and 528 + 698 = 1226 A_1
1276 (2)		1270 *s*	Fundamental B_2
1303 *ww*			Fundamental A_2
1326 (1)			Fundamental B_1
1358 (2)*b*			2 × 675 = 1350 A_1
		1370 *ww*	675 + 698 = 1373 B_1
1395 (3)			2 × 698 = 1396 A_1
1437 (10)	1441 *s*	1440 *s*	Fundamental A_1 & B_1
1464 (9)	~1458 *m*	1460 *s*	Fundamental A_1

[a] Symbols *s* (strong), *m* (medium), *w* (weak), *ww* (very weak) indicate the intensity of the band; *b* (broad), *d* (diffuse), *sh* (sharp) the shape.

[b] 73 cm.$^{-1}$ is the frequency (assumed) of the out-of-plane bending mode of species B_2.

those of polymers which had accumulated in the sample and not those of the pure compound.

In Table 19 are summarized the vibrational frequencies (in cm.$^{-1}$) for the various modes of vibration of the molecule.

TABLE 19. Modes of Vibration of the Thietane Molecule

Mode of vibration	A_1	B_1	A_2	B_2
Ring deformation	528[a]			73[b]
C—S stretching	698	675		
CH_2 rocking			878	844 and 969
C—C stretching	932	991		
CH_2 wagging	1226	1173 and 1326		
CH_2 twisting			1137 and 1303	1272
CH_2 bending	1440 and 1460	1440		
C—H stretching	2950(2)	2950	2950	2950(2)

[a] Refers to the in-plane bending mode of deformation of the thietane ring.

[b] Assumed to refer to the out-of-plane bending mode of deformation of the thietane ring (see Ref. 61).

The infrared spectrum of thietane has been examined by other authors.[40, 33, 1, 41a] Lord[47a] has attributed low vibrational frequencies

TABLE 20. Raman Spectrum of Thietane

Frequency (cm.$^{-1}$) $\Delta\nu$	Differential intensity	Frequency (cm.$^{-1}$) $\Delta\nu$	Differential intensity
249	2	1122	3
276	2	1144	12
306	2	1177	30
345	2	1223	22
447	3	1270	7
502	5	1293	7
528	120	1364	10
671	179	1406	7
702	60	1440	45
846	27	1467	30
935	135	2864	125
970	50	2916	178
1023	3	2946	325
1032	3	2980	210
1091	8		

at 56, 63 and 68 cm.$^{-1}$ to ring puckering of the thietane molecule in the vapor phase. Its Raman spectrum was studied independently by Akishin *et al.*,[3, 4, 3a] who reported results given in Table 20.

B. Thietane Derivatives

Akishin *et al.*[2, 3, 3a] described the Raman spectrum of 2-methylthietane (see Table 21).

TABLE 21. Raman Spectrum of 2-Methylthietane

Frequency (cm.$^{-1}$) $\Delta\nu$	Differential intensity	Frequency (cm.$^{-1}$) $\Delta\nu$	Differential intensity
236	4	1017	21
286	29	1062	4
406	8	1091	18
516	31	1135	0
539	24	1149	36
579	5	1170–1183	20
592	5	1219	26
628 or 630	90	1270	5
644 or 648	20	1335	12
700	85	1364	14
715	20	1439	30
803	23	1451	45
880	9	2864	147
914	8	2920	310
938	0	2953	262
914	8	2920	310
938	0	2953	262
961	43	2980	145
996	35		

For many of the saturated heterocyclic sulfur-containing compounds the sum of the intensities of the lines between 600 and 740 cm.$^{-1}$, which are characteristic of the C—S bond, is almost constant.[4]

The infrared absorption spectra of 3-thietanol,[1] methyl 2-thietanyl ketone,[69] α-methyl-2-thietanemethanol,[69] and of *N*-[(4-amino-2-methyl-5-pyrimidinyl)methyl-*N*-[1-(2-thietanylidene)ethyl]formamide[69, 71] are given in Figs. 4–7. Two characteristic absorption bands at 1150–1190 cm^{-1} (strong) and 1240–1300 cm^{-1} (variable) appear in the spectra of 19 other thietanes discussed by Hays;[41a] 3-thietanone has also been examined.[55b]

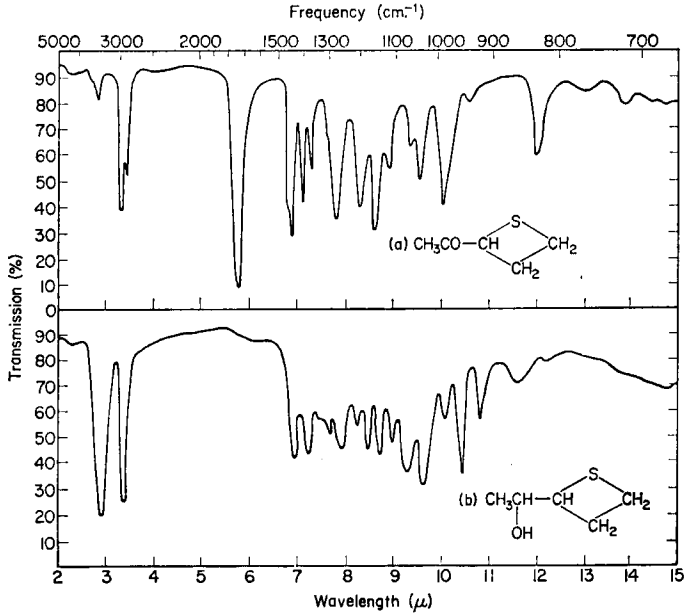


Fig. 4. Infrared spectra of: (a) methyl 2-thietanyl ketone;[69] (b) α-methyl-2-thietanemethanol.[69]

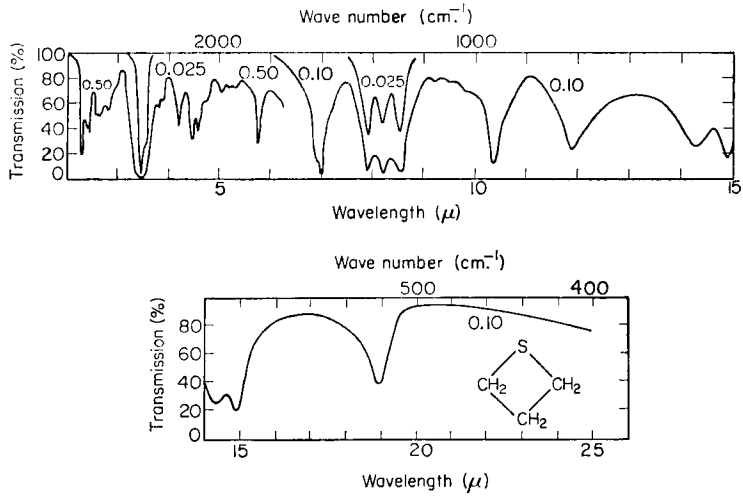


Fig. 5. Infrared spectrum of thietane.[40]

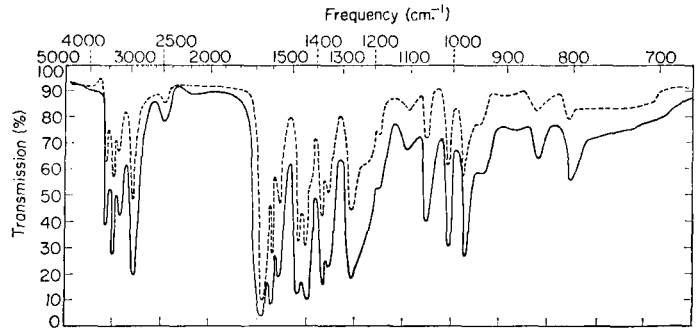


Fig. 6. Infrared spectrum of *N*-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-*N*-[1-(2-thietanylidene)ethyl]formamide,[69, 71] in two forms, since this compound is dimorphic: —, m.p. 136°C; – – –, m.p. 162°C.

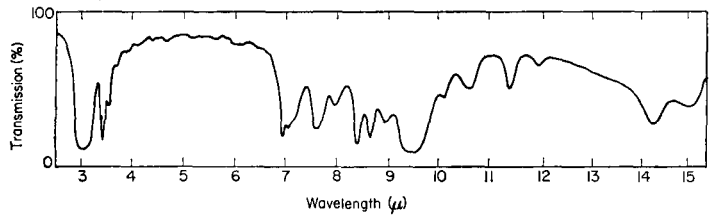


Fig. 7. Infrared spectrum of 3-thietanol (J. H. C. Nayler, personal communication).

4. Ultraviolet Spectrum

A. Thietane

The ultraviolet spectrum of thietane has been studied by Haines, Helm, Bailey and Ball,[40] and by Davis[29] (see Fig. 8).

In an attempt to explain the spectra of small cyclic sulfur compounds, Davis[29] has related the position of the ultraviolet absorption maximum of various linear and cyclic sulfur compounds to the ability of the sulfur atom in these molecules to donate electrons to the boron atom of boron trifluoride. This ability decreases in the following order:* 4-membered ring > 5-membered ring > 6-membered ring > acyclic derivative > 3-membered ring.[41a]

* Searles, S., M. Tamres, and E. R. Lippincott, *J. Am. Chem. Soc.*, **75**, 2775 (1953); Tamres, M., S. Searles, and R. F. Vanco, *Abstr.* 123*rd Mtng. Am. Chem. Soc.*, Los Angeles (1953).

In connexion with the preceding series, the nuclear magnetic resonance δ-values for the hydrogens adjacent to the sulfur atom were found to decrease in the order:* 4-membered ring > 3-membered ring > 5-membered ring > 6-membered ring.

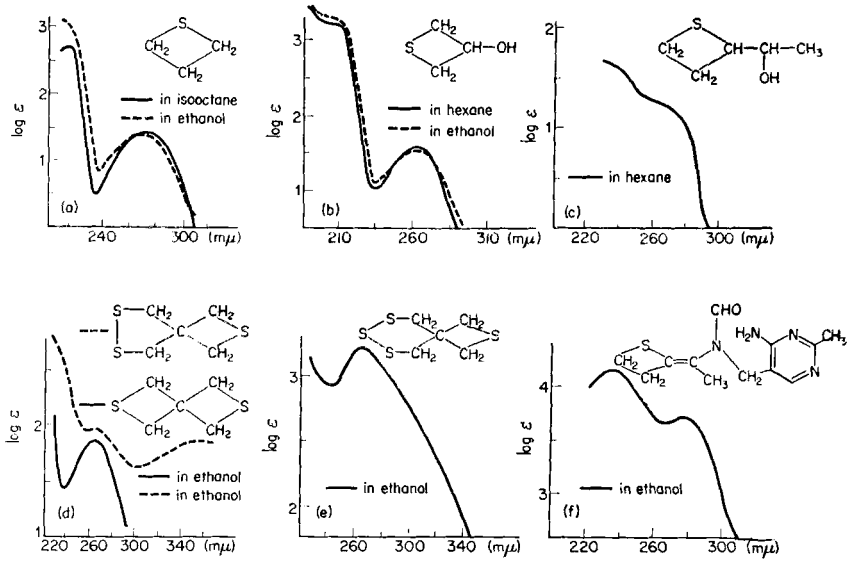


Fig. 8. Ultraviolet spectra of: (a) thietane;[40, 29, 13] (b) 3-thietanol;[64] (c) α-methyl-2-thietanemethanol;[69] (d) 2,6-dithiaspiro[3.3]heptane and 2,6,7-trithiaspiro[3.4]-octane;[59] (e) 2,6,7,8-tetrathiaspiro[3.5]nonane;[60] (f) *N*-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-*N*-[1-(2-thietanylidene)ethyl]formamide.[69]

According to Davis, the characteristics of the ultraviolet spectrum, reactivity, and nuclear magnetic resonance spectrum of the small cyclic sulfur compounds may be explained by their inherent electronic structure rather than by steric considerations. The data suggest the following limiting structures:



Other properties of small-ring compounds† have been explained in terms of the delocalization of *p* electrons.

* Gutowsky, H. S., R. L. Ritedge, M. Tamres, and S. Searles, *J. Am. Chem. Soc.*, **76**, 4242 (1954).

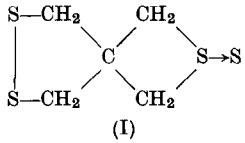
† Rogers, M. T., and J. D. Roberts, *J. Am. Chem. Soc.*, **68**, 843 (1946); Roberts, J. D., and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5031 (1951).

B. Thietane Derivatives

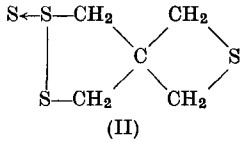
The derivatives of thietane show a strong absorption of long radiation with a maximum around 260–275 mμ (Fig. 8).

Sjöberg[64] has investigated the spectrum of 3-thietanol. The ultraviolet spectrum of α-methyl-2-thietanemethanol, reported by Yonemoto,[69] shows a shoulder at 270 mμ. That of *N*-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-*N*-[1-(2-thietanylidene)ethyl]-formamide [69, 43c] has a maximum at about 275 mμ and another around 230–235 mμ. Schotte[59] described the ultraviolet spectrum of 2,6,7-trithiaspiro-[3.4]octane; it has two peaks, at 264 and 354 mμ.

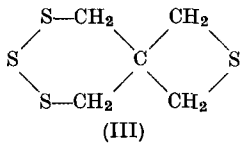
Schotte[60] also investigated the compound considered by Backer and Evenhuis[6] to be 2-thio-2,6,7-trithiaspiro[3.4]octane (I). As its ultraviolet spectrum does not show the absorption characteristics of the dithiolane ring, formula (I) was ruled out. This compound is probably either 6-thio-2,6,7-trithiaspiro[3.4]octane (II) or 2,6,7,8-tetrathiaspiro[3.5]nonane (III); formula (III) seems preferable.



(I)



(II)



(III)

TABLE 22. Mass Spectrum of Thietane

Mass number	Intensity	Mass number	Relative intensity
122–77	0	46	100.0
76	1.86	45	24.6
75	1.71	42	0.42
74	42.0	41	8.35
70	0.17	39	9.59
61	0.09	35	0.79
60	0.17	34	0.40
58	1.89	33	0.81
57	0.96	32	1.85
48	4.57	29	0.64
47	7.23	27	8.08

5. Mass Spectrum

The mass spectrum of thietane was studied by Haines *et al.*[40] (current intensity, 8.0 μA; temperature of the chamber of ionization, 300 °C). Ions of mass number (*m/e*) 76 to 27 were found (Table 22).

More recently, Gallegos and Kiser[36a] have reported the appearance potentials and relative abundances for the principal positive ions in the mass spectrum of thietane, the purity of which was estimated at 99.8 mole %. Their results are summarized in Table 23.

TABLE 23. Mass Spectrum and Appearance Potentials at the Principal Ions of Thietane

m/e	Percent relative abundance	Appearance potential (e.v.)	Process	ΔH_f^+ (kcal./mole)
26	4.9	17.1 ± 0.4	$(CH_2)_3S \rightarrow C_2H_2^+ + CH_3S + H$ (?)	319
			$\rightarrow C_2H_2^+ + CH_2S + H_2$ (?)	333
27	9.5	16.7 ± 0.2	$\rightarrow C_2H_3^+ + CHS + H_2$ (?)	285
28	3.5	13.6 ± 0.2	$\rightarrow C_2H_4^+ + CH_2S$ (?)	253
37	2.0			
38	2.9			
39	13.5	15.3 ± 0.4	$\rightarrow C_3H_3^+ + H_2 + H + S$	262
41	11.7	12.2 ± 0.2	$\rightarrow C_3H_5^+ + SH$	265
45	25.8	13.9 ± 0.2	$\rightarrow CHS^+ + C_2H_4 + H$	271
			$\rightarrow CHS^+ + C_2H_3 + H_2$	271
46	100.0	11.8 ± 0.2	$\rightarrow CH_2S^+ + C_2H_2 + H_2$	233
47	11.3	12.3 ± 0.15	$\rightarrow CH_3S^+ + C_2H_3$	235
48	5.9	11.6 ± 0.15	$\rightarrow (CH_2{}^{34}S)^+ + C_2H_2 + H_2$	228
59	1.8			
73	2.0			
74	52.3	8.9 ± 0.15	$\rightarrow C_3H_6^+$	220

IV. Preparations of Thietanes

1. From a Dihalo Derivative and Sodium Sulfide

A. Unsubstituted Thietane

This is the oldest method, which was used by Gryszkiewicz-Trochimowski.[39] Although he varied the experimental conditions, he was unable to obtain a yield of thietane better than 10%. Solid and oily polymerization products, which cannot be steam-distilled, are formed simultaneously (Section **VII**). The authors who reinvestigated

and perfected this method always use ethanol as the principal solvent and an excess of sodium sulfide (see Table 24).

TABLE 24. Preparation of Thietane from Trimethylene Halides and Sodium Sulfide

Halogen derivative $X(CH_2)_3X$	Sulfide	Solvent	Extraction method	Yield (%)	References
X = Br	$Na_2S,9H_2O$	Ethanol + water	Steam distillation	10	39
X = Br	$Na_2S,9H_2O$	Ethanol + water	Extraction with ether	35–45	14
X = Br				45	66
X = Br	Na_2S (anhydrous)	Anhydrous ethanol	Salting out; extraction with pentane	48	67
X = Br	Na_2S (anhydrous)	Anhydrous ethanol		33	53
X = Cl	Na_2S (anhydrous)	Anhydrous ethanol	Salting out; extraction with light petroleum	30	21
X = Br	Na_2S_2	Water + ethanol		very low	13

The use of the anhydrous sulfide, prepared from sodium ethoxide and dry hydrogen sulfide,[67] eliminates the possibility of hydrolysis:

$$Na_2S + H_2O \rightleftharpoons NaHS + NaOH$$

but it does not seem to improve the yields. Nevertheless it facilitates the isolation of thietane, for the distillation or steam-distillation of a non-anhydrous mixture usually gives one or two phases containing an homogeneous mixture of water + ethanol + thietane. Under these conditions, the sulfur compound must be separated by recirculation which involves considerable loss, or by extraction with light petroleum after salting out with sodium chloride. The sulfur derivative could be separated from the distillate by precipitation of the mercuric chloride complex, as described for the recovery of tetramethylene sulfide and selenetane,[54] followed by treatment with a base to regenerate the thietane.

B. Other Compounds Containing the Thietane Ring

Those which have been prepared from metallic sulfides and dihalogenated derivatives are listed in Table 25. Several comments should be made about this Table:

TABLE 25. Compounds Containing the Thietane Ring Prepared from Dihalogenated Derivatives and Alkali Sulfides or Hydrosulfides

Name	Halogen derivative	Sulfide	Solvent	Yield (%)	References
2-Methylthietane	$BrCH_2CH_2CHBrCH_3$	$Na_2S,9H_2O$	Ethanol + water		39
2,4-Dimethylthietane	$(CH_3CHBr)_2CH_2$	$Na_2S,9H_2O$	Ethanol + water		39
3,3-Dimethylthietane	$(CH_3)_2C(CH_2Br)_2$	K_2S	Ethanol + water	60	9
		KHS	Ethanol + water	55	9
	$(CH_3)_2C(CH_2Cl)_2$	K_3HS_2	Anhydrous glycol	50	34
		Na_2S		23	34
3,3-Diethylthietane	$(C_2H_5)_2C(CH_2Cl)_2$	K_3HS_2	Anhydrous glycol	20	34
2-Thiaspiro[3.5]nonane	$(CH_2)_5C(CH_2Br)_2$	K_2S	Ethanol + water	54	10
		Na_2S_2		very low	10
3-Thietanol	$ClCH_2CHOHCH_2Cl$ (impure)	$Na_2S,9H_2O$	None		46
		Na_2S (100% excess)	Methanol	40	56b
α-Methyl-2-thietanemethanol	$ClCH_2CH_2CHClCHOHCH_3$	K_2S	Ethanol + water		69
3,3-Dimethoxythietane	$(CH_3O)_2C(CH_2Br)_2$	$Na_2S,9H_2O$	Ethanol + water	75–80	51a
3,3-Bis(chloromethyl)thietane (55%) and 2,6-Dithiaspiro[3.3]heptane (45%)	$(ClCH_2)_3CCH_2Br$	KSH	Ethanol	54	41a
2,6-Dithiaspiro[3.3]heptane	$C(CH_2Br)_4$	K_2S or KHS	Ethanol + water	60–70	7, 59
	$C(CH_2Br)_4$	Na_2S	Anhydrous ethanol	37	45
	$C(CH_2Br)_4$	$Na_2S,9H_2O$	Ethanol + water	very low	45
	$C(CH_2Cl)_4$	NaHS	Anhydrous pentanol	very low	35

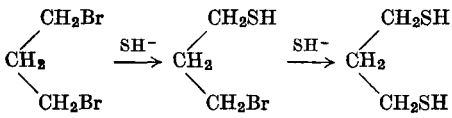
(*Table continued*)

TABLE 25 (*continued*)

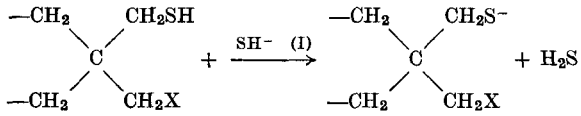
Name	Halogen derivative	Sulfide	Solvent	Yield (%)	References
2-Oxa-6-thiaspiro[3.3]-heptane	$CH_2OCH_2C(CH_2Cl)_2$	Na_2S	Anhydrous ethanol	20	25, 26
2,6,7,8-Tetrathiaspiro-[3.5]nonane[a]	$C(CH_2Br)_4$	K_2S_2	Ethanol + water	23	6, 60
		Na_2S_2	Ethanol alone or + water	31	6
2-Thietanevaleric acid	$ClCH_2CH_2CHCl(CH_2)_4COOCH_3$	K_2S	Ethanol + water	47	74
		$Na_2S_2O_3$, $5H_2O$	Ethanol + water	27	74
		$Na_2S,9H_2O$	Ethanol	47	74
	$BrCH_2CH_2CHBr(CH_2)_4COOC_2H_5$	$Na_2S,9H_2O$	Ethanol	57	74
4-Methyl-2-thietane valeric acid	$CH_3CHBrCH_2CHBr(CH_2)_4COOC_2H_5$	$Na_2S,9H_2O$	Ethanol	42	74

[a] Reported as 2-thio-2,6,7-trithiaspiro[3.4]octane.[60]

(1) Although the reaction of trimethylene bromide with the alkali hydrosulfides[5,53] normally yields 1,3-propanedithiol:

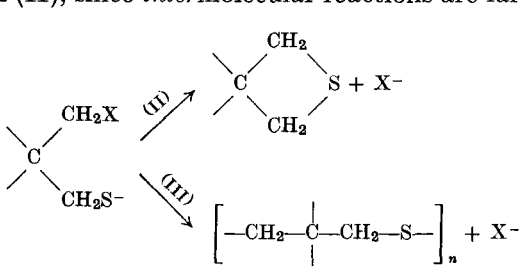


the 3,3-dialkylthietanes—or spirocyclic compounds with C-3 as the center atom—are formed equally well by the action of an alkali *sulfide* or *hydrosulfide* on the corresponding dihalo derivative. Contrary to the opinion of Franke and Dworzak,[36] no thiol derivative is formed under these conditions. One can assume that the 3-halogenated thiol intermediate reacts preferentially according to mechanism (I).



(2) In general the yields of the 3,3-dialkyl derivatives are superior to those of unsubstituted thietane. This occurs as though the alkyl radicals or the pre-existing ring repel the two halomethyl groups, pushing them toward each other and thus facilitating cyclization with the alkali sulfides.

The presence of substituents must impede the formation of ions $XCH_2-\overset{|}{\underset{|}{C}}-CH_2S^-$ to a much greater extent than their disappearance by cyclization (II), since *inter*molecular reactions are far more sensitive



to steric hindrance than are *intra*molecular reactions.[33] For the same reason, the concentration of these ions is too low for the 'parasitical' reaction (III), which yields linear polymers, to be predominant (dilution principle). Reaction (III), however, becomes important when the ion concentration is increased by a change in the solvent; thus, in the

presence of water, tetrakis(bromomethyl)methane reacts with sodium sulfide to give polymers as the principal product.[45]

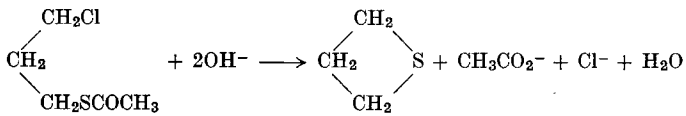
(3) It is not possible to isolate 3,3-bis(bromomethyl)thietane from the products of the reaction of tetrakis(bromomethyl)methane with sulfide or alkali hydrosulfide.[7] 2,6-Dithiaspiro[3.3]heptane is formed even when an excess of the halogen derivative is used.

(4) Unlike the corresponding bromo derivatives, the hindered dichloro compounds, *e.g.* 1,3-dichloro-2,2-dimethylpropane, do not react appreciably with sodium sulfide at the boiling point of ethanol. The use of glycol[34] gives a much higher reaction temperature without recourse to pressure; further, it facilitates the preparation of anhydrous sodium sulfide from the commercial sulfide, and the recovery of the final product (see the Appendix).

2. Cyclization of a γ-Halothiol or Its Esters

A. Thietane

Thioacetic acid condenses readily with allyl chloride in the presence of ultraviolet light. The resulting 3-chloropropyl thioacetate undergoes ring closure in the presence of potassium hydroxide; the yield of thietane is 24% and no oxetane is formed:[33, 26a]



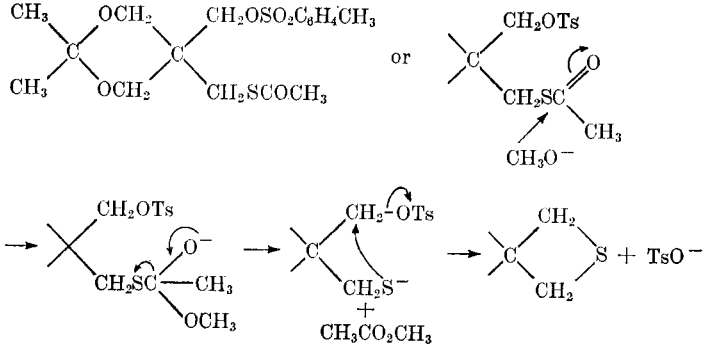
It would be interesting to compare the yield obtained in this reaction with that given by the cyclization of 3-chloropropanethiol itself.[64]

B. Other Compounds Containing the Thietane Ring

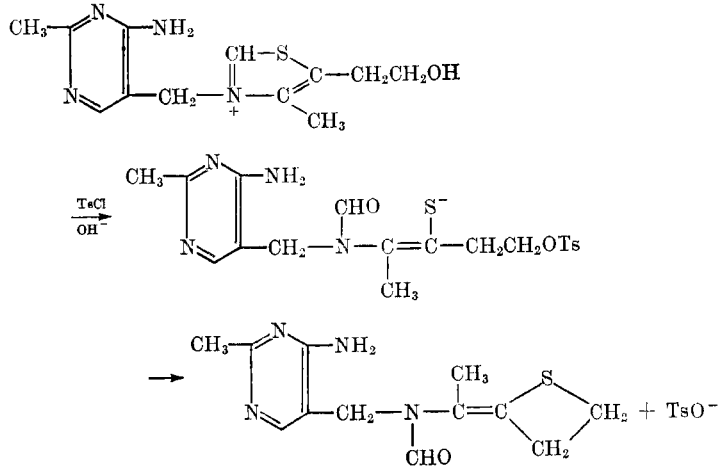
(1) 3-Methylthietane. 3-Methylthietane has been obtained in excellent yield (80%) by the treatment of 3-chloro-2-methylpropyl thioacetate with sodium hydroxide; it is separated by steam-distillation.[17]

(2) 3,3-Bis(hydroxymethyl)thietane. Bladon and Owen[15] prepared 3,3-bis(hydroxymethyl)thietane from a derivative of pentaerythritol. Although a molecule of *p*-toluenesulfonate is eliminated instead of one of an alkali halide, the reaction is entirely comparable to the preceding ones. The two hydroxymethyl groups are simultaneously

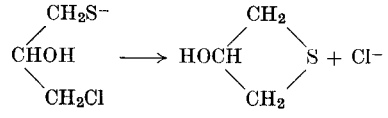
liberated from their ketal by the solution of sodium methylate in the methanol–chloroform mixture used in this reaction.



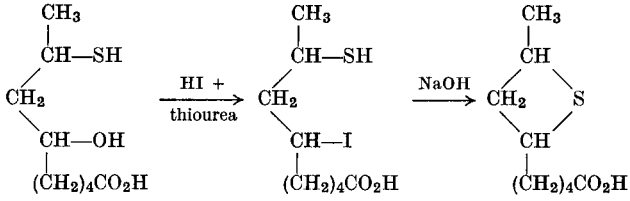
(3) Thietane derivative from thiamine. Motoyama[55, 43b] cyclized thiamine in the course of dehydration with *p*-toluenesulfochloride in an alkaline medium:



(4) 3-Thietanol. When 3-chloro-2-hydroxyl-1-propanethiol is treated with an aqueous solution of sodium bicarbonate, ring closure occurs with the formation of 3-thietanol in 90% yield.[1, 64] This is a first-order reaction.[63]



(5) 2-Thietanevaleric acid and 4-methylthietanevaleric acid. Bullock[23] obtained 2-thietanevaleric acid and 4-methylthietanevaleric acid as by-products in the preparation of 6,8-dithioloctanoic acid and 6,8-dithiolnonanoic acid.



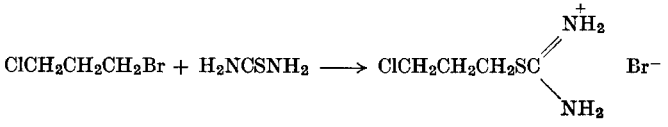
2-Thietanevaleric acid has also been prepared by cyclization of the *p*-toluenesulfonic esters of 6-hydroxy-8-thiolvaleric and 8-hydroxy-6-thiolvaleric acids.[74]

3. From a Halogen Derivative and Thiourea

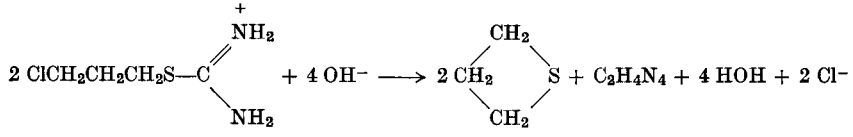
A. Thietane

Recently Bordwell and Pitt[19] proposed an excellent method for the synthesis of thietane from trimethylene chlorobromide. The latter is prepared industrially by the addition of hydrobromic acid to allyl chloride in the presence of a peroxide which orients the fixation of the bromine atom to the end of the chain.

The chlorobromide is first converted into the thiuronium salt by heating with an alcoholic solution of thiourea:[40]

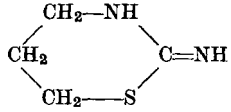


This salt is isolated and subjected to alkaline decomposition which is accompanied by cyclization:

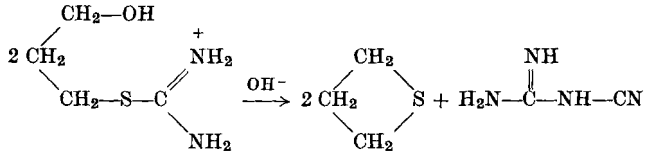


The mechanism of this reaction could involve the cyclization of a 3-halo-1-propanethiol, progressively liberated in the reaction medium as in (**2**) and (**3**) above (section **IV.2.***B*); on the other hand, the reaction

might proceed through a six-membered-ring intermediate identical with that formed in the reactions discussed in section **IV.4.***C*. Although



the yields are somewhat lower, considerable time is saved if the 1-bromo-3-chloropropane is treated directly with thiourea in aqueous alkaline solution.[19] An oil which cannot be steam-distilled is formed simultaneously. According to Kienle,[44] one should be able to carry out a similar reaction starting with 3-chloropropanol, which combines with thiourea in alcoholic solution. The resulting salt is isolated and treated



with an aqueous solution of potassium carbonate. Unlike the decomposition of *S*-(2-hydroxyethyl)isothiuronium chlorohydrate to give thiirane,[44] the decomposition of *S*-(3-hydroxypropyl)isothiuronium chlorohydrate to thietane is not spontaneous.

B. Other Compounds Containing the Thietane Ring

Etienne and Soulas[35] have extended the preceding method to the preparation of 3-methylthietane (yield 45%) from 1-bromo-3-chloro-2-methylpropane, and particularly to the preparation of 2-methylthietane (yield 70%) from 1,3-dichlorobutane. Although the two halogen atoms in this compound are identical, they differ in reactivity since one is attached to a primary carbon and the other to a secondary carbon atom; only one of them forms the thiuronium salt (see the Appendix).

Yurugi *et al.*[74] have described the preparation of 2-thietanevaleric acid from methyl 8-bromo-6-hydroxyoctanoate, thiourea, thionyl chloride and sodium hydroxide.

Campbell[25] has reported that thiourea reacts with 3,3-bis(chloromethyl)oxetane to give 2-oxa-6-thiaspiro[3.3]heptane.

4. By the Elimination of a Cyanate Ion

In this section we are dealing with processes which apparently differ in reaction conditions but which probably proceed by the same mechanism. Although oxirane reacts spontaneously with thiocyanic acid or its alkali salts to give thiirane,[68] the only example of a direct reaction between an oxetane and potassium thiocyanate is a classic double exchange:[25]

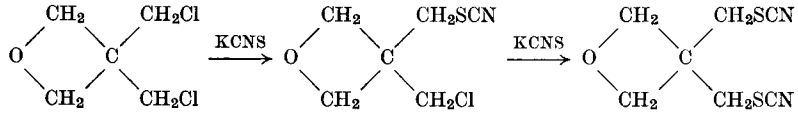


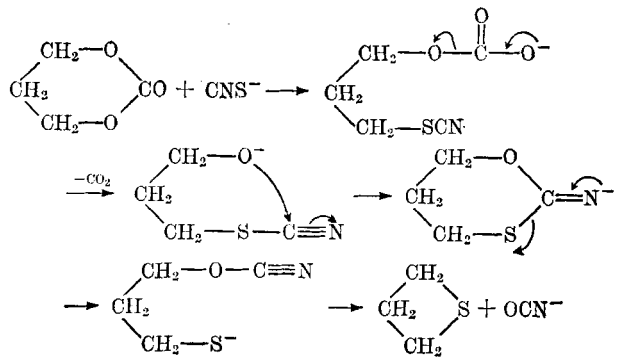
TABLE 26. Decomposition of Cyclic Carbonates of 1,3- and 2,4-Diols in the Presence of Alkali Thiocyanate[62, 62a, 41a]

Substituents of 1,3,2-dioxanone	Reaction temperature (°C)	Product	Yield (%)
None	140	Thietane	3
4-Methyl	170–180	2-Methylthietane	16
5,5-Dimethyl	175–185	3,3-Dimethylthietane	56–58
5,5-Diethyl	190–195	3,3-Diethylthietane	43.8–63
5-Hydroxymethyl-5-methyl	170–180 (130–140 mm.)	3-Methyl-3-thietane-methanol	50
5,5-Dibenzyl	220–240	3,3-Dibenzylthietane	29
	(20–35 mm.)	3,3-Dibenzyloxetane	12
4-Isopropyl-5,5-dimethyl	240–250	2-Isopropyl-3,3-dimethylthietane	13
		2-Isopropyl-3,3-dimethyloxetane	35
4,6-Dimethyl	180–200	*cis*-2,4-Dimethylthietane	4
		trans-2,4-Dimethylthietane	3
		2-Penten-4-ol	9
5-Ethyl-4-propyl	210–220	*cis*-3-Ethyl-2-propylthietane	9
		trans-3-Ethyl-2-propylthietane	7
		Unsatd. alcohols (unidentified)	
4,4,6-Trimethyl	190–200	2-Methyl-2-penten-4-ol	63
		4-Methyl-2-penten-4-ol	8
5-Ethyl-5-phenyl	170–180	α-Ethylstyrene	20
5,5-Pentamethylene	220–230	2-Thiaspiro[3.5]nonane	57
5,5-Tetramethylene	220–230	2-Thiaspiro[3.4]octane	50
5,5-Trimethylene	210–220	2-Thiaspiro[3.3]heptane	33
5,5-Ethylene	170–180	2-Thiaspiro[3.2]hexane	8
5-Methylene	150–160	Polymer	

A. Decomposition of Cyclic Carbonates of 1,3- *and* 2,4-*Diols in the Presence of Thiocyanate*

Oxetane is prepared *in situ* by the thermal decomposition of a cyclic carbonate of a 1,3-diol, but Searles and Lutz [62] and Hays[41a] have observed the formation of the thiacyclobutane ring when the cyclic carbonate is fused in the presence of an equimolecular quantity of potassium thiocyanate. The yield is low in the case of unsubstituted thietane but the process is very interesting for the preparation of certain homologs (Table 26).

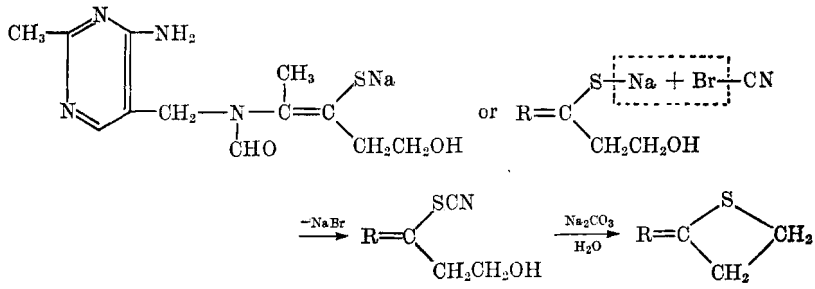
The mechanism involves a thiocyanhydrin intermediate in the form of an ion:



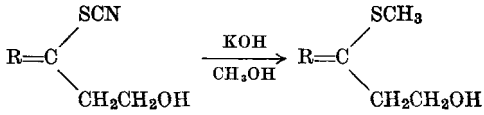
The effect of steric hindrance at the α-carbon atom is evident in several of the cases studied: higher temperatures are required for the reaction and the expected thietane products are accompanied by the corresponding oxetanes, formed from the attack of the carbonyl-carbon atom by the thiocyanate ion. The yields and purity of the thietanes possessing β-hydrogen atoms were poor, due to thermal decomposition of the cyclic carbonates to allylic alcohols.

B. Decomposition of Thiocyanhydrins of 1,3-*Diols*

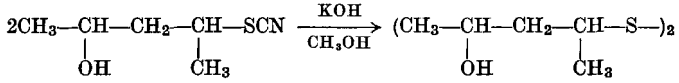
The alkaline decomposition of the thiocyanhydrins of 1,3-diols seems to constitute a general method for the closure of the thietane ring, except for the synthesis of unsubstituted thietane. Yonemoto[69, 71, 43c] has applied it to cyanothiamine, the product resulting from the action of cyanogen bromide on the S—Na derivative of the corresponding hydroxythiol. This cyclization proceeds equally well in neutral



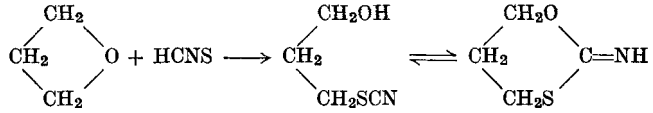
solution.[70] If the solvent contains methanol, a methyl thioether is also formed. The formation of methyl cyanate as an intermediate is likely.[71]



In certain cases, the alkaline decomposition of a thiocyanhydrin yields a disulfide.[71] Wagner-Jauregg and Häring[68] showed that oxetane



reacts slowly with hydrogen thiocyanate in ether solution. The resulting thiocyanhydrin is in equilibrium with 2-imino-1,3-oxathiacyclohexane,



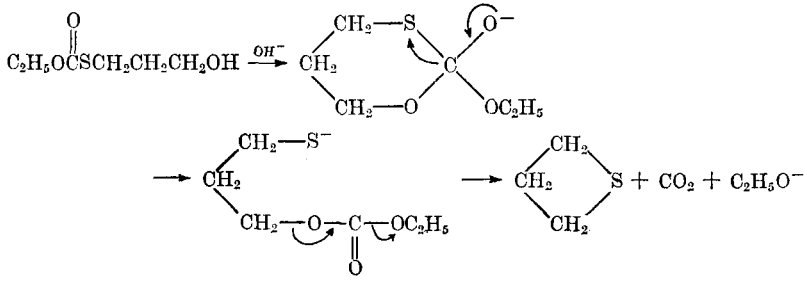
the chlorohydrate of which is stable. The existence of this six-membered ring supports the mechanism proposed above for the reaction of Searles and Lutz.

A mixture of α-lipoic acid and 2-thietanevaleric acid has been obtained from the reaction product of methyl 6,8-dichlorooctanoate and potassium thiocyanate, cyclized by sodium hydroxide or sulfide.[74]

C. Decomposition of Product of Reaction of 3-Hydroxypropanethiolate with Ethyl Chloroformate

Also in this group of methods for the synthesis of the thietane ring is the reaction of Reynolds, Fields and Johnson,[57] who decomposed

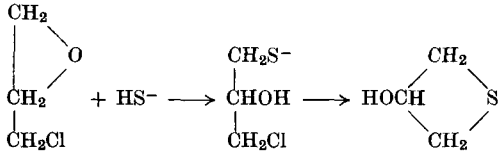
the product of the reaction of sodium 3-hydroxypropanethiolate with ethyl chloroformate at about 200° in the presence of a trace of sodium hydroxide under reduced pressure (13 mm. of Hg).



5. From Compounds Containing a Three-Membered Ring

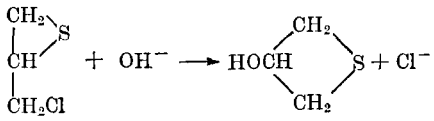
A. From Epichlorohydrin

Sjöberg[64] and later Dittmer and Christy[30] prepared 3-thietanol from epichlorohydrin and sodium hydrosulfide (yield 33%) or the barium salt (yield 39%) at about 50°c. The fact that 3-chloro-2-hydroxy-1-propanethiol is the principal product when the reaction is carried out at 0° suggests that the preceding transformation proceeds through this thiol intermediate.



B. From 2-(Chloromethyl)thiirane

On the other hand, Nayler[1] assumes that the formation of 3-thietanol from 2-(chloromethyl)thiirane and sodium carbonate (yield

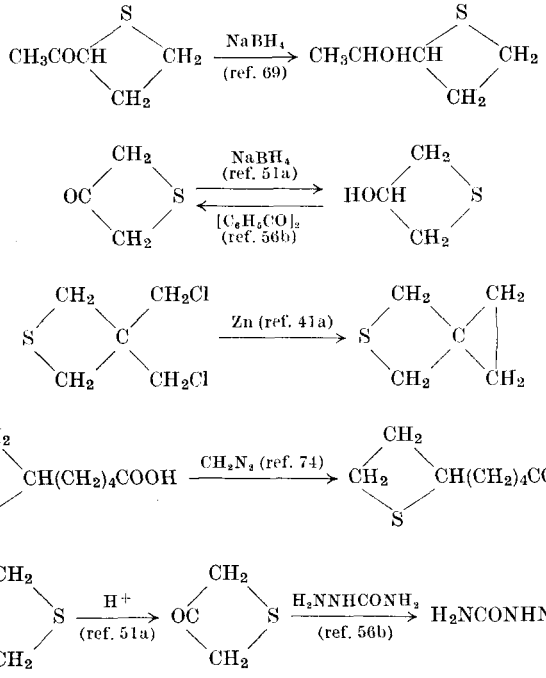


45%) proceeds via the displacement of an electron; this results in the attachment of an hydroxyl group to C-2 with enlargement of the ring.

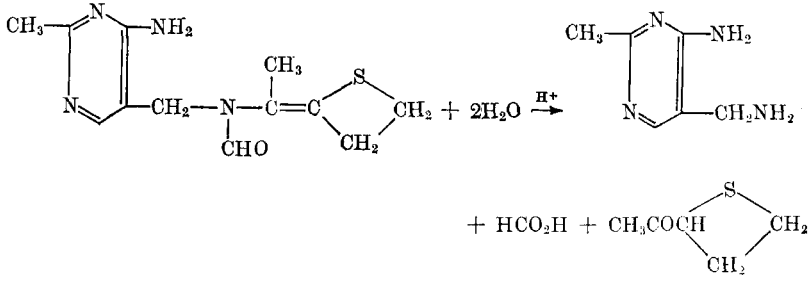
6. Miscellaneous Methods

A. Chemical Transformations

Some functional derivatives of thietane can undergo reduction, oxidation, esterification or hydrolysis without change in the ring:

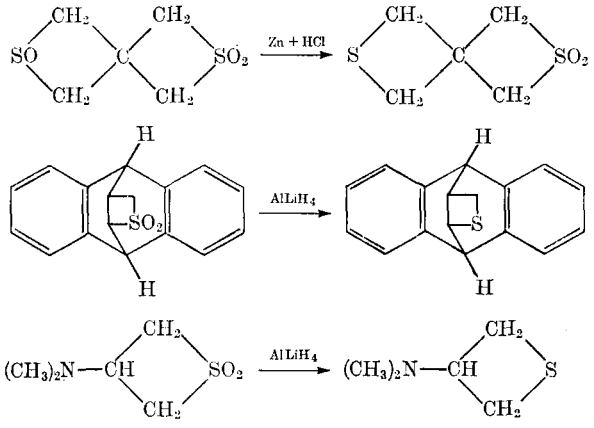


Yonemoto[69, 43b] obtained acetylthietane by the degradation of *N*-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-*N*-[1-(2-thietanylidene)-ethyl]formamide with hydrochloric acid:



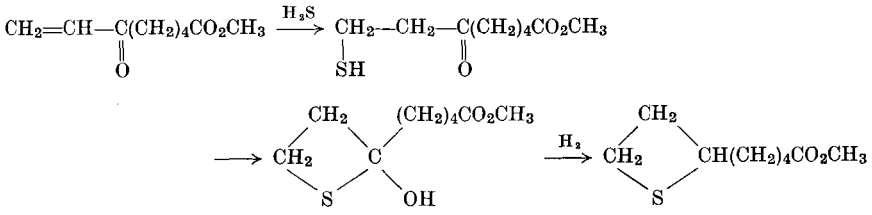
B. Reduction of Sulfoxides or Sulfones

Certain thietanes which cannot be prepared directly can be obtained by the reduction of the corresponding sulfoxides[7] or sulfones:[31, 66a]



C. Hydrogenation of Methyl 6-Oxa-7-octenoate

Bullock[24] believes that compounds containing the thietane ring are formed during the hydrogenation of methyl 6-oxa-7-octenoate in the presence of cobalt polysulfide:

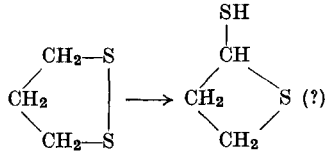


D. Addition of Periodate to 1,3-Propanedithiol

The gradual addition of potassium periodate to a dilute solution of 1,3-propanedithiol in sodium hydroxide yields thietane or its polymers; sulfur precipitates.[5] In acid solution, the product is usually 1,2-dithiolane.[13] Methyl 6,8-dithioloctanoate and potassium periodate yields 2-thietanevaleric acid.[74]

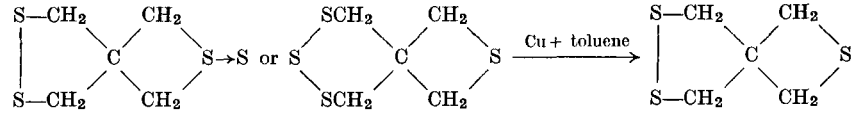
E. Photochemical Transformation of 1,2-*Dithiolane*

Barltrop[13] has postulated that 3-thietanethiol is formed in the course of the primary photochemical transformation of 1,2-dithiolane:



F. Ring Contraction of 2,6,7,8-*Tetrathiaspiro*[3.5]*nonane*

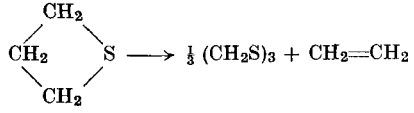
The reaction below, which Backer[6] considers as the desulfuration of 2-thio-2,6,7-trithiaspiro[3.4]octane by powdered copper, is more probably due to the contraction of the ring of 2,6,7,8-tetrathiaspiro-[3.5]nonane:[60]



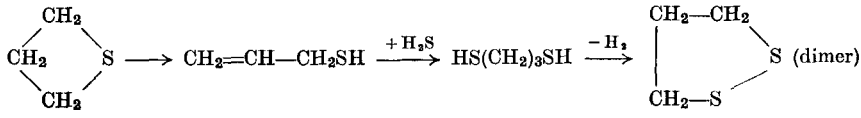
V. Chemical Reactivity of Thietane and Its Derivatives

1. Stability

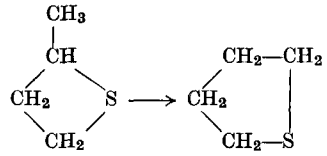
The polymerization of thietane under the influence of various catalysts is discussed below (section **VII**). On exposure to light, only the following decomposition seems to occur:[41]



The effect of heat on thietane has been studied by Yur'ev and Levi.[73] At 250°C in the presence of alumina and in a current of nitrogen, thietane decomposes to give principally a mixture of hydrogen, hydrogen sulfide, an olefin, and a solid (12%) containing a trace of the dimer of dithiolane.[13] Decomposition at 250°C in a current of hydrogen sulfide yields a larger proportion of the dithiolane dimer, the formation of which can be explained[73] by the reaction:



When 2-methylthietane vapor is carried over the surface of alumina by a current of hydrogen sulfide at 350°C, it isomerizes partially to give thiacyclopentane[72] and derivatives containing the thiol group:



This isomerization does not take place in the presence of glass wool, nor when 2-methylthietane is refluxed for 45 hr. in the presence of alumina.[72]

2. Heats of Combustion and Formation of Thietane

For reactions (I) and (II) the enthalpies at constant volume, ΔU^0, and at constant pressure, ΔH^0, are (at 25°C) shown in Table 27.

$$C_3H_6S\ (\text{liquid}) + 6\ O_2\ (\text{gas}) + (n-2)\ H_2O\ (\text{liquid}) = 3\ CO_2\ (\text{gas}) + (H_2SO_4, nH_2O)(\text{liquid}) \quad (\text{I})$$

$$C_3H_6S\ (\text{liquid}) + 4\tfrac{1}{2}\ O_2\ (\text{gas}) = 3\ CO_2\ (\text{gas}) + 3\ H_2O\ (\text{liquid}) + S\ (\text{rhombic}) \quad (\text{II})$$

TABLE 27. Enthalpies of Combustion of Thietane

Purity of thietane (mole %)	$-\Delta U^0$ (I) (kcal./mole)	$-\Delta U^0$ (II) (kcal./mole)	$-\Delta H^0$ (II) (kcal./mole)	References
—	635.30 ± 0.30	492.12	493.01	67
99.95	635.23 ± 0.20	492.42	493.31	43

Values of enthalpies, free energies and entropies of formation of thietane are summarized in Table 28.

3. Reactions

Although only some of the possible reactions of thietane have been investigated, it appears to be an active compound, largely because the ring opens easily to undergo addition and polymerization reactions. The only reactions which occur without opening of the ring are the additions of oxygen, of iodine, and of certain salts (see section VI below).

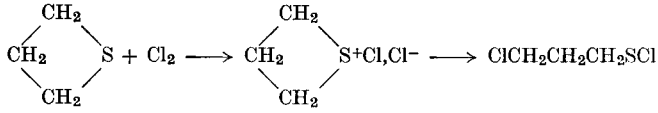
TABLE 28. Heats of Formation of Thietane

Initial state	Final state	ΔH° (kcal./mole)	ΔF° (kcal./mole)	ΔS° (cal. deg.$^{-1}$ mole^{-1})	References
C (graphite), S (rhombic), H_2 (gas)	C_3H_6 (liquid)	5.90 ± 0.32 (25°c)	—	—	67
C (graphite), S (rhombic), H_2 (gas)	C_3H_6 (liquid)	6.20 ± 0.29 (25°c)	—	—	43
C (graphite), S (rhombic), H_2 (gas)	C_3H_6 (liquid)	6.20 ± 0.29 (20°c)	24.27	−60.62	61
C (graphite), S (rhombic), H_2 (gas)	C_3H_6 (gas)	14.78 (20°c)	25.37	−37.20	61
C (graphite), S (rhombic), H_2 (gas)	C_3H_6 (gas)	14.78 ± 0.30 (25°c)	—	—	43

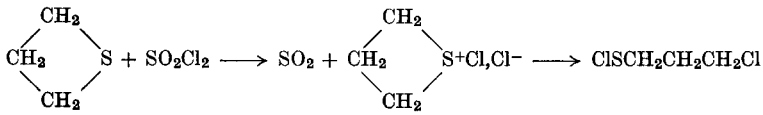
In general the thietane ring is particularly susceptible to attack by electrophilic agents, but it undergoes mercaptoacylation with compounds containing a mobile hydrogen less readily than ethylene sulfide. It seems to be stabilized by bases.

A. Action of Halogens

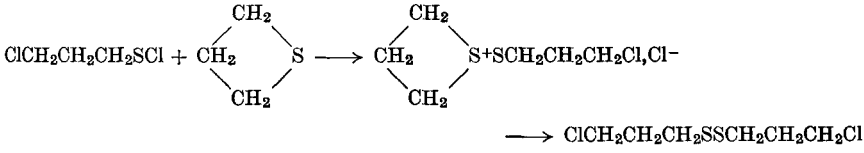
(1) Chlorine. Thietane reacts with chlorine in a manner similar to thiirane, but more slowly and with lower yields.[66]



(*a*) When thietane is added to an equimolecular solution of chlorine in chloroform (cooled to −50°) containing a small amount of hydroquinone as a chlorination inhibitor, 3-chloropropanesulfenyl chloride is formed in a yield of 30%.[66] The same product (yield 69%) is obtained when thietane is treated with sulfuryl chloride in hot

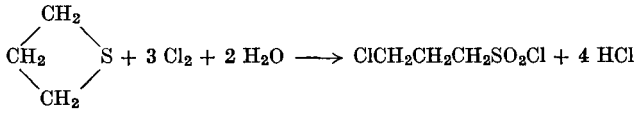


pentane solution in the presence of a trace of iodine. 3-Chloropropanesulfenyl chloride can react with another molecule of thietane in chloroform to give bis-(3-chloropropyl) disulfide.



(*b*) When chlorine gas is passed through a cold solution of thietane in chloroform, bis-(3-chloropropyl) disulfide is formed directly (yield 49%). It was identified as the piperidine addition product.[66]

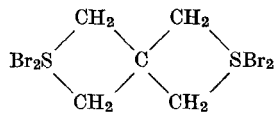
(*c*) The addition of thietane to a cold water–acetic acid mixture, which is kept saturated with chlorine, gives 3-chloro-1-propanesulfonyl chloride.[66]



(*d*) 3-Chlorothietane can be isolated as the sulfone[30] or the sulfoxide[32, 51] (see section **VI** below).

(2) Bromine. (*a*) The addition of a solution of bromine in carbon tetrachloride to cold thietane diluted with heptane yields a yellow-orange precipitate which decomposes rapidly, even at −15°C, with the liberation of hydrobromic acid.[20] This compound is probably bis-(3-bromopropyl) disulfide which cannot be distilled without decomposition.[66]

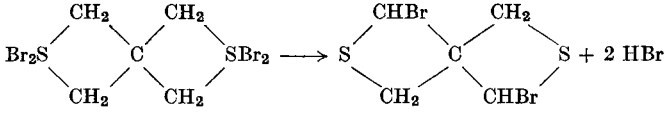
(*b*) The two thietane rings of 2,6-dithiaspiro[3.3]heptane seem to stabilize each other, for Backer and Keuning[8] obtained an addition compound, stable in dry air, by exposing this spirocyclic compound to a large excess of bromine vapor at room temperature in a desiccator.



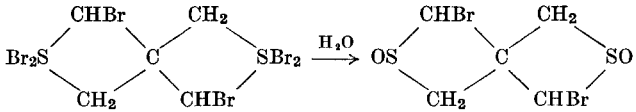
The excess bromine which impregnates the tetrabromide is drawn off by suction until the composition of the product is constant. The product is a brownish-red oil which gives off hydrobromic acid fumes in humid

air, but only decomposes superficially when it is moistened because of the formation of a protective coating.[8]

(*c*) When a benzene solution of dry bromine is added to a solution of 2,6-dithiaspiro[3.3]heptane in benzene, and then an aqueous solution of sodium carbonate is added to decompose the soluble product 1,5-dibromo-2,6-dithiaspiro[3.3]heptane-2,6-dioxide (melting at 126.5°) is obtained[7]. One can assume that the addition product originally formed undergoes the following rearrangement:



and that the resulting product takes up more bromine. The hydrolysis can then be written as:



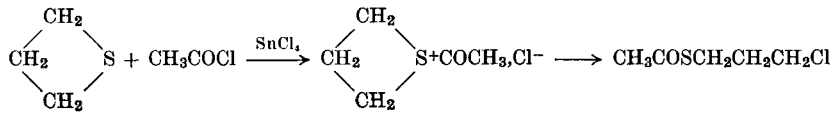
The reactivity of this disulfoxide is discussed below (section **VI.2.***C*). The impossibility of further bromination is interpreted as evidence for the 1,5-position of the bromines on both rings.

(3) Iodine. This halogen forms relatively stable addition products with 2,6-dithiaspiro[3.3]heptane and 2-thiaspiro[3.5]nonane; with thietane and its homologs, the addition products are polymerization initiators which are discussed below (section **VI.3.**).

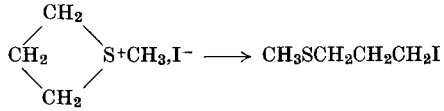
B. Reaction with Halogen Compounds

(1) Inorganic halides. Hydrochloric acid and certain metal and metalloid halides bring about the polymerization of thietane and its homologs (see section **VII** below).

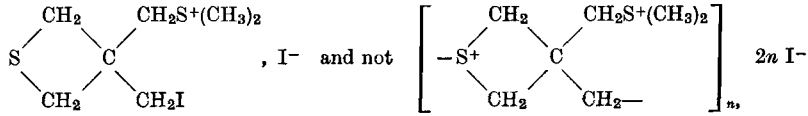
(2) Acetyl chloride. Acetyl chloride reacts with a benzene solution of thietane in the presence of stannic chloride to yield 3-chloropropyl thioacetate.[66] 2-Methylthietane reacts similarly.[66]



(3) Methyl iodide. Organic sulfides can usually add an equimolecular quantity of methyl iodide to form the sulfonium salts. According to Gryskiewicz-Trochimowski,[39] two molecules of methyl iodide combine with one molecule of thietane; Bennet and Hock[14] undertook the elucidation of the structure of this compound, the existence of which posed a theoretical problem. They showed that the action of methyl iodide on thietane results in opening of the ring, and on this basis the reaction can be regarded as similar in its mechanism to that of the polymerizations which are catalyzed by electrophilic agents. It first forms the normal sulfonium iodide which would be stable if the thietane ring were not strained (the analogous derivative of tetrahydrothiophene is stable). As the carbon–sulfur linkage in sulfonium salts is relatively labile, the strain of the ring brings about

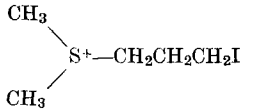
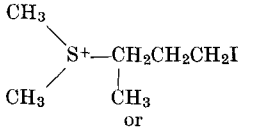
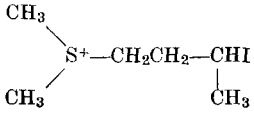
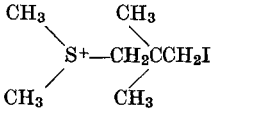
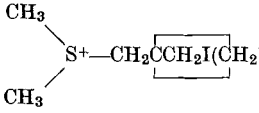
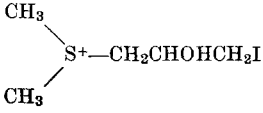
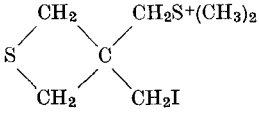
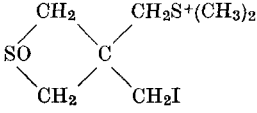


its cleavage and the 1-iodo-4-thiapentane molecule so formed adds another molecule of methyl iodide. Thus the product of the reaction of methyl iodide with thietane is dimethyl-(3-iodopropyl)sulfonium iodide, $(CH_3)_2S^+CH_2CH_2CH_2I,I^-$. This formula explains the fact that only part of the iodine contained in the product is ionized[14] and that the reaction is relatively slow.[39, 14, 20] This structure was demonstrated by the formation of the chloroplatinate and the chloroaurate by double decomposition, and by the fact that the compound was identical with a sample prepared by an unequivocal synthesis.[14] It is reasonable to assume that the products of the reaction of substituted thietanes with methyl iodide have the same structure.[8] For example, the product of the reaction of two molecules of methyl iodide with one molecule of 2,6-dithiaspiro[3.3]heptane is:



for only part of the iodine which it contains reacts with thallium sulfate.[8] The impossibility of opening the second thietane ring can be attributed to the insolubility of the product in the reaction medium.[8] Since these compounds are often obtained as well-formed crystals, they can be considered as characteristic derivatives useful for identification (Table 29).

TABLE 29. Physical Properties of the Sulfonium Salts resulting from Ring-Opening of Substituted Thietane Derivatives by Methyl Iodide

Compound reacting with CH_3I	Salt obtained (anion I^-)	M.p. (°C)	Recrystallization solvent	References
Thietane		98.5–99	Ethanol	39
		98–100[a]	Ethanol	20
		97–98	Anhydrous ethanol	14, 33
2-Methylthietane	 or 	123–124		39
3,3-Dimethylthietane		130–131		8
2-Thiaspiro[3.5]nonane		92[b]		10
3-Thietanol		105–106	Ethanol	64
		114	Ethanol	1
		110–110.5	Anhydrous ethanol	30
2,6-Dithiaspiro[3.3]heptane		145–146 (decomp.)	Ethanol or water	8
		143 (decomp.)	Methanol + water	7
2,6-Dithiaspiro[3.3]heptane 2-oxide		133–134 (decomp.)	Ethanol	8

[a] Formula reported, no doubt in error, as C_4H_9SI.

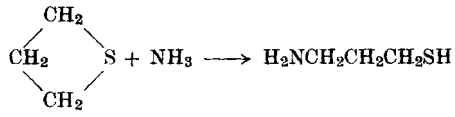
[b] The picrate prepared by double decomposition melts at 117°C.

9,10-Dihydroanthracene-9,10-*endo*-2′,3′-thietane adds only *one* molecule of methyl iodide in benzene;[31] the product melts at 125.5–127.5° (yield 75%).

C. Reaction with Compounds Possessing a Mobile Hydrogen Atom

Acids and even water[39] can bring about polymerization (see section **VII** below).

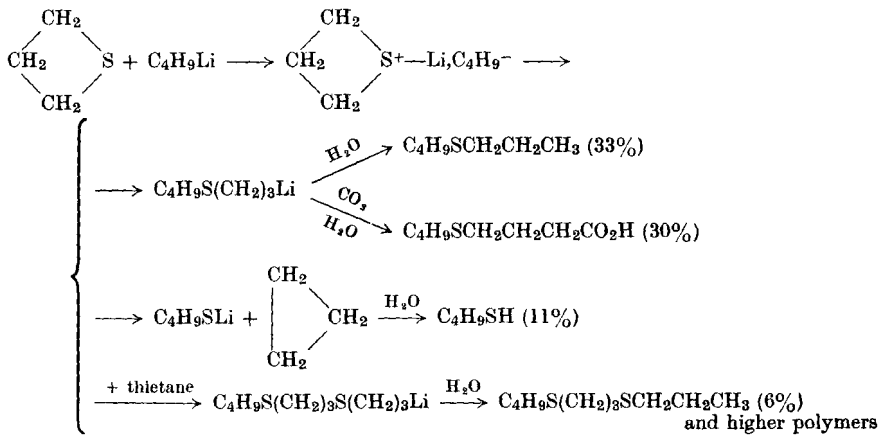
(1) Ammonia. To obtain 3-aminopropanethiol from thietane and ammonia, a 10% ethanolic solution of the reactants must be heated for 8 hr. at 200°C in a closed flask; the product is isolated as the chloroplatinate.[39]



(2) Amines. No reaction occurred when thietane was in contact with aniline for 3 months at room temperature,[35] or when it was refluxed with dibutylamine.[72] Therefore, one can assume that 'mercaptopropylation' requires much more drastic conditions than does the 'mercaptoethylation' which occurs with ethylene sulfide.

D. Reaction of Thietane with Organolithium Compounds

This reaction[16] is entirely different from that observed with ethylene sulfide or oxetane. In the first stage, a derivative is formed



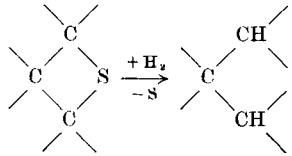
which contains a carbon–lithium bond, and therefore has the character of an organometallic compound; it can react with another molecule of thietane and so on.

With phenyllithium, the reaction is more complicated because the medium contains an excess of bromobenzene which participates in exchange reactions.[16]

E. Removal and Addition of Sulfur

Sulfur is removed from 3-thietanol by Raney nickel in boiling water; acetone is isolated as 2,4-dinitrophenylhydrazone after chromic oxidation of the distillate.[1]

Many other reductive desulfurizations have taken place in boiling benzene.[62a, 41a]



From previously known data,[61] Girelli and Burlamacchi[36b] have calculated the equilibrium constant for the hydrodesulfurization reaction:

$$\text{Thietane} + 2\ H_2 \rightleftharpoons \text{Propane} + H_2S$$

The value of log K is given in Table 30.

TABLE 30. Equilibrium Constant for the Hydrodesulfurization Reaction of Thietane

$T°K$	298.16	500	700	900
Log K	28.88	15.61	9.90	6.67

α-Lipoic acid or its esters has been obtained by heating 2-thietanevaleric acid or its esters with sulfur at 160–180°C for 30 minutes.[74]

Several other reactions of thietanes have been reported (section **IV.6.***A* above).

VI. Sulfoxides, Sulfones, and Addition Compounds of Thietanes

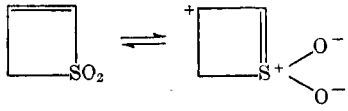
Though the thiiranes are usually decomposed by oxidizing agents, the thietanes normally yield sulfones and some sulfoxides. This reaction and the addition of mercuric chloride or iodide are the only reactions

with those discussed in section **IV.6.***A* above which occur without opening the ring, since the 'iodomethylates' actually are formed with cleavage of the carbon–sulfur bond,[14] and in general the bromine addition products are very unstable (see section **V.3.***A*.(**2**) above).

1. Sulfones

A. Physical Properties

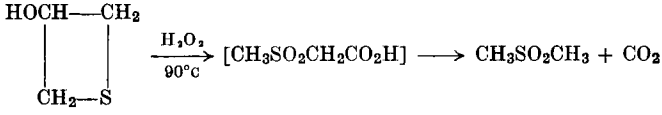
These properties are collected in Table 31. The structure of thiete 1,1-dioxide has been confirmed by nuclear magnetic resonance measurements.[30] The electron density on C-3 seems to be weaker than that on C-2, which suggests a displacement of electrons according to the following scheme:



Thiete 1,1-dioxide absorbs ultraviolet radiation between 220 and 420 mμ. Its infrared spectrum shows vibration frequencies at 3165 cm.$^{-1}$ (C—H) and at 1543cm.$^{-1}$ (C=C).[30]

B. Preparation of Sulfones

(1) **From the corresponding thietane derivative.** The reagent most commonly used to convert thietane or its derivatives into sulfones is hydrogen peroxide in acetic acid. It is advisable to cool the reaction flask during the process. This is a necessary condition for the oxidation of 3-thietanol as it yields dimethyl sulfone at 90–100°:[30]



Aqueous permanganate has been used to oxidize thietane,[39] 2-methylthietane and the dimethylthietanes[39, 9] to the sulfones, but the yields are lower than those obtained with hydrogen peroxide.[20] On treatment with potassium permanganate, 2,6-dithiaspiro[3.3]heptane gives the disulfone directly in 60% yield, and peracetic acid gives a quantitative yield; in the latter case the oxidation intermediates can be isolated.[7]

TABLE 31. Physical Properties of Cyclic Sulfones Containing a Four-Membered Ring

Name[a]	M.p. (°c)	Recrystallization solvent	Remarks	References
Thietane 1,1-dioxide	75.5–76	Water		39
	75	Ethanol		20
	77–78	Petr. ether		26a
	73–75	Ethyl acetate		31
			Dipole moment 4.49 (25°c)	28
Thiete 1,1-dioxide	52–54	Ether + ethanol	Vesicant	30, 31
2-Methylthietane 1,1-dioxide	(liquid at −20°)		B.p. = 251.5–253.5° $n_D^{16.5} = 1.4700$ $d_4^{16.5} = 1.2174$	39
2,4-Dimethylthietane 1,1-dioxide	(liquid)		B.p. (758 mm.) = 255–255.5° $n_D^{17.5} = 1.4653$ $d_4^{17.5} = 1.1589$	39
3,3-Dimethylthietane 1,1-dioxide	54–55			9
2-Thiaspiro[3.5]nonane 1,1-dioxide	72.5–73	Water		10
3-Chlorothietane 1,1-dioxide	136.5–137.5	Water		30
3-Thietanol 1,1-dioxide	101–102	Ethyl acetate	3,5-Dinitrobenzoate m.p. = 197–198°; *p*-toluenesulfonate m.p. = 129–131°	30
3-Thietanol 1,1-dioxide	98	Ethanol		64
3-Ethoxythietane 1,1-dioxide	50–53	Ether + hexane		31
3-Aminothietane 1,1-dioxide	93–96	Ethyl acetate		31
3-Dimethylaminothietane 1,1-dioxide	~0°		Picrate m.p. 177–178 (decomp.) Iodomethylate m.p. 188–190° (decomp.)	31
3-Phenylthio-thietane 1,1-dioxide	72–74	Isopropanol		31
Bis-(3-thietanyl 1,1-dioxide sulfide)	226–227	Acetic acid		31
9,10-Dihydroanthracene-9,10-*endo*-2′,3′-thietane 1′,1′-dioxide	226–267.5	Acetic acid		31
2-Oxa-6-thiaspiro[3.3]heptane 6,6-dioxide	161–162	Toluene		25, 26

Name[a]	M.p. (°C)	Recrystallization solvent	Remarks	References
3,3-Thietanedimethanesulfonic acid 1,1-dioxide		(Crystallizes with $2H_2O$	Acid chloride m.p. 144–146° (decomp.); dianilide m.p. 200–202°	6
2,6-Dithiaspiro[3.3]heptane 2,2-dioxide	116.5	Ethanol		7
2,6-Dithiaspiro[3.3]heptane 2,2,6-trioxide	156	Water		7
2,6-Dithiaspiro[3.3]heptane 2,2,6,6-tetraoxide	244.5	Water		7
2,6,7-Trithiaspiro[3.4]octane 2,2,6,6-tetraoxide	257 (decomp.)	Water	Obtained by oxidation of 2,6,7,8-tetrathiaspiro[3.5]-nonane	6
N-(2,2-Dimethyl-3-thietanyl) pyrrolidine *S,S*-dioxide	68		Obtained by method 6 Yield 80%	56[a]
N-(2,2-Dimethyl-4-phenyl-3-thietanyl) pyrrolidine *S,S*-dioxide	161		Obtained by method 6 70%	56[a]
N-(2-Methyl-3-thietanyl) piperidine *S,S*-dioxide[b]	b.p. (10^{-3}mm) = 121		Obtained by method 6 90%	56[a]
N-(4-Ethyl-2-propyl-3-thietanyl) piperidine *S,S*-dioxide			Obtained by method 6 88%	56[a]
4-(2-Ethyl-3-thietanyl) morpholine *S,S*-dioxide	114		Obtained by method 6 83%	56[a]
4-(2-Ethyl-4-phenyl-3-thietanyl) morpholine *S,S*-dioxide	170		Obtained by method 6 65%	56[a]
4-(2-Methyl-3-thietanyl) morpholine *S,S*-dioxide	107–108		Obtained by method 6 (very good)	66[a]
4-(6-Thiabicyclo[3.2.0]hept-1-yl) morpholine *S,S*-dioxide	122–123		Obtained by method 6 77%	66[a]
4-(7-Thiabicyclo[4.2.0]oct-1-yl) morpholine *S,S*-dioxide	139–140		Obtained by method 6 (very good)	66[a]
4-Amino-2-methyl-5-[{[1-(2-thietanylidene)-ethyl]amino}methyl]pyrimidine *SS*-dioxide	183 (decomp.)			69
N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-*N*-[1-(2-thietanylidene)ethyl]formamide *S,S*-dioxide	132 (decomp.)	Ethanol, Acetone		69, 55a
	176–178 (dec.)			67b

[a] See structural formulae given in Table 3.
[b] Hydrochloride m.p. = 210, Picrate m.p. = 190, Methiodide m.p. = 164.

The presence of sulfuric acid in the reaction product shows that the permanganate oxidation goes too far. Likewise, the treatment of thietanol with permanganate in an aqueous acetone solution, even at room temperature, results in considerable decomposition;[30] the only product which can be isolated is dimethyl sulfone (yield 2%).

(2) **From the corresponding sulfoxides.** The preparation of the sulfoxide–sulfone derivative of 2,6-dithiaspiro[3.3]heptane is rather difficult; when 3 molecules of peroxide are used per molecule of this derivative containing two thietane rings, one obtains four of the possible oxidation products plus a product whose melting point is too high to be determined.[7] Therefore, 2,6-dithiaspiro[3.3]heptane 2,2,6-trioxide is best prepared in two steps:

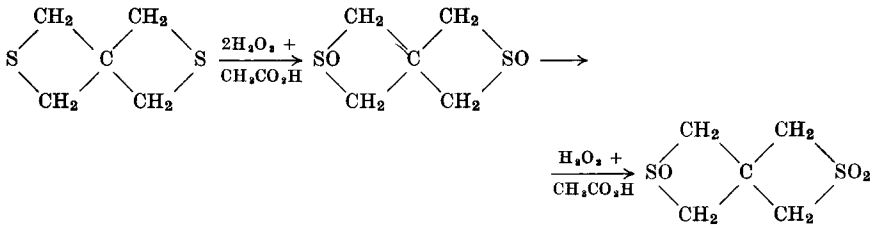


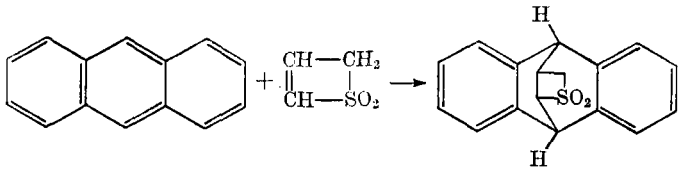
TABLE 32. Addition Reactions of Thiete 1,1-Dioxide

Reagent	Conditions: Solvent	Conditions: Temperature	Conditions: Time	Product	Yield (%)
C_2H_5OH	Ethanol[a]	Reflux	35 min.	3-Ethoxythietane 1,1-dioxide	68
NH_3	Ethanol	Room	5 days	3-Aminothietane 1,1-dioxide	48
$(CH_3)_2NH$	Benzene	Room	6 days	3-Dimethylamino thietane 1,1-dioxide	99
H_2S	Water[b]	50°c	30 min.	Bis-(3-thietanyl 1,1-dioxide) sulfide	64
C_6H_5SH	Ethanol[c]	Reflux	90 min.	3-Phenylthiothietane 1,1-dioxide	92.5

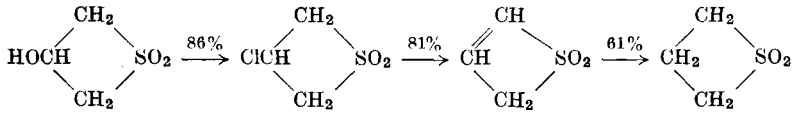
[a] In the presence of sodium ethylate.
[b] In the presence of barium hydrosulfide.
[c] In the presence of triethylamine.

One can obtain the disulfone by the addition of more peroxide or permanganate.

(3) From thiete 1,1-dioxide. This unsaturated sulfone readily adds various reagents[31, 26c] in alkaline solution (Table 32). Like 3-thietanol 1,1-dioxide, thiete 1,1-dioxide decomposes to dimethyl sulfone when it is refluxed for 30 min. with an aqueous solution of barium hydroxide in the presence of air.[31] When thiete 1,1-dioxide is in contact with a toluene solution of anthracene for 5 days at 147° in a sealed tube, the Diels–Alder addition compound is usually formed; this product does not dissociate even at 200°C under 35 mm. of Hg.[31]



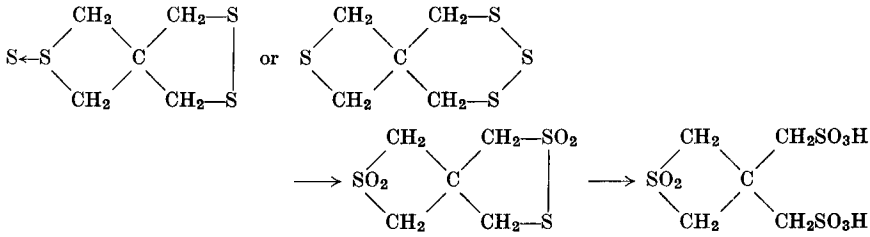
(4) By chemical transformation. 3-Thietanol 1,1-dioxide, which contains an hydroxyl group, can be converted to 3-chlorothietane 1,1-dioxide by thionyl chloride in the presence of pyridine or, better, of 2,4,6-collidine.[30] On treatment with triethylamine in benzene at 40°C, this derivative loses hydrochloric acid to form thiete sulfone, which in turn is reduced by sodium borohydride[31] into thietane 1,1-dioxide:



Thietane-3,3-dimethanesulfonic acid 1,1-dioxide is converted into the disulfanilide by the action of phosphorus pentachloride, followed by aniline[6] [see also section **VI.2.***C*.(**2**) below].

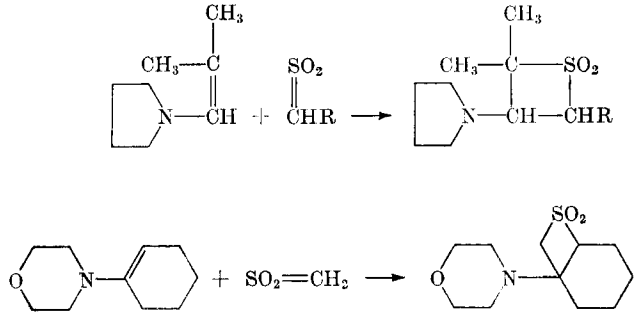
(5) By oxidative degradation of various substances containing the thietane ring. When Backer and Evenhuis[6] oxidized 2-thio-2,6,7-trithiaspiro[3.4]octane, or rather 2,6,7,8-tetrathiaspiro[3.5]nonane,[60] with perbenzoic acid or with hydrogen peroxide in acetic acid, they first obtained 2,6,7-trithiaspiro[3.4]octane 2,2,6,6-tetraoxide, and then

thietane-3,3-dimethanesulfonic acid 1,1-dioxide; several salts and derivatives of the latter were prepared:



The permanganate degradation of *N*-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-*N*-[1-(2-thietanylidene)ethyl]formamide yields 4-amino-2-methyl-5-[{[1-(2-thietanylidene)ethyl]amino}methyl]pyrimidine *SS*-dioxide.[69*]

(6) By cycloaddition of sulfenes to enamines.[56a, 66a]



The enamine is kept over night at room temperature with the theoretical quantities of an aliphatic sulfonyl chloride and triethylamine in ether or dioxane.[56a, 66a] The yields are usually good.

C. Chemical Properties

Like the linear sulfones, the sulfones containing a four-membered ring are characterized by their chemical stability.[56a]

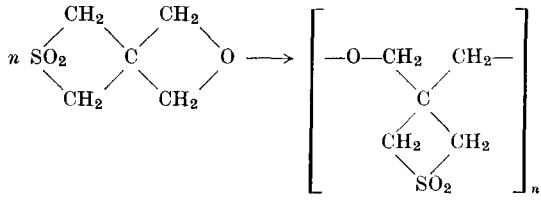
2,6-Dithiaspiro[3.3]heptane 2,2,6,6-tetraoxide is particularly inert; it does not react with potassium permanganate even in the presence of sulfuric acid at 100°C.[7] It dissolves in pure nitric acid; on evaporation of this solution, the crystalline disulfone is recovered quantitatively.

* See structural formulae in Tables 1–3.

This disulfone undergoes no transformation when heated to 150°C with bromine in a sealed tube, even in the presence of a catalyst (iron, sulfur) or of a solvent (water, carbon tetrachloride).

2,6-Dithiaspiro[3.3]heptane 2,2,6,6-tetraoxide is equally stable to reducing agents. It is unaltered by heating in acetic acid solution with a large excess of zinc and hydrochloric acid. It does not react with hydrazine hydrate at 150°C nor with sulfur at 250°C,[7] and it gives no addition product with mercuric chloride.

2-Oxa-6-thiaspiro[3.3]heptane 6,6-dioxide, which contains an oxetane ring, has been polymerized by boron fluoride[25] or by phosphorus pentafluoride[26] in liquid sulfur dioxide to give a low-molecular-weight polyether which melts at 220°C:



Incidentally, thietane 1,1-dioxide could not be polymerized in the presence of various catalysts.[35]

Thietane 1,1-dioxide, 3-dimethylaminothietane 1,1-dioxide, and 9,10-dihydroanthracene-9,10-*endo*-2′,3′-thietane 1′,1′-dioxide are easily reduced by lithium aluminum hydride;[31] the corresponding sulfide is regenerated.

However, thiete 1,1-dioxide does not give thiete under these conditions, and thiophenol is the only product identified from the reduction of 3-phenylthiothietane 1,1-dioxide.[31]

Thiete 1,1-dioxide is hydrogenated by hydrogen gas at 1.75 kg/cm^2 in chloroform in the presence of palladium or by sodium borohydride in aqueous methanol to give thietane 1,1-dioxide.[31] It is decomposed by aqueous barium hydroxide into dimethylsulfone and barium formiate; this ring cleavage may be analogous to a reverse aldol condensation.[31]

Some other reactions of sulfones containing a four-membered ring are described in section **VI.1.***B*.(**2**)–(**4**) above.

2. Sulfoxides

A. Physical Properties

The physical properties of the sulfoxides are given in Table 33.

TABLE 33. Physical Properties of Cyclic Sulfoxides Containing a Four-Membered Ring

Name	M.p. (°c)	Recrystallization solvent	Remarks	Addition compound with $n HgCl_2$		References
				n	M.p. (°c)	
Thietane 1-oxide			B.p. (0.1 mm.) = 36–38°c			32
			B.p. (14 mm.) = 91–92°c $n_D^{20} = 1.5156$			26a
			B.p. (25 mm.) = 102°c $n_D^{25} = 1.5146$			67b
3,3-Dimethylthietane 1-oxide	liquid			1	127	9
3-Chlorothietane 1-oxide	84–87		α-Isomer			32
	56–58		β-Isomer			51
3-Thietanol 1-oxide	76–78.5		3,5-Dinitrobenzoate m.p. = 171–173°c			32
2-Thiaspiro[3.5]nonane 1-oxide	room temperature		B.p. (5 mm.) 148–151°c	1	161.5	10
2,6-Dithiaspiro[3.3]heptane 2-oxide	81.5	Benzene	Hygroscopic	1.5	decomp.	7
2,6-Dithiaspiro[3.3]heptane 2,6-dioxide	146	Acetone	Very hygroscopic	2	185 (decomp.)	7
2,6-Dithiaspiro[3.3]heptane 2,2,6-trioxide	156	Water	Slightly hygroscopic	1	186–187	7
1,5-Dibromo-2,6-dithiaspiro-[3.3]heptane 2,6-dioxide	126.5	Benzene		0.5	120 (decomp.)	8

Name	M.p. (°c)	Recrystallization solvent	Remarks	Addition compound with $nHgCl_2$		References
				n	M.p. (°C)	
3-Oxo-2,4-thietanedicarboxanilide 1-oxide	170 (decomp.)		Fine rosy; softens at 140°c			56
2,4-Bis-(*o*-tolylcarbamoyl)-3-thietanone 1-oxide	174 (decomp.)		Pink; softens at 155–156°c			56
2,4-Bis-(*p*-tolylcarbamoyl)-3-thietanone 1-oxide	208–210 (decomp.)		Pink; softens at 185°c			56
2,4-Bis-(α-naphthylcarbamoyl)-3-thietanone 1-oxide	155		Greenish-brown; softens at 137°c			56
2,4-Bis-(β-naphthylcarbamoyl)-3-thietanone 1-oxide	207		Crimson; softens at 185°c			56

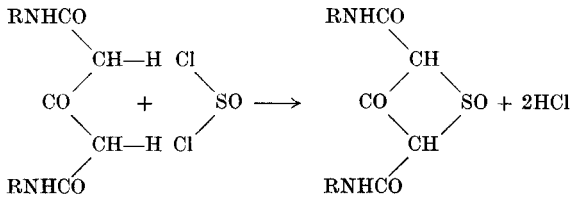
B. Preparation of Sulfoxides

(1) From the corresponding thietanes. The oxidizing agent which is always used is hydrogen peroxide generally in acetic acid; the first seven sulfoxides listed in Table 33 were thus obtained from the corresponding sulfides. Nitric acid brings about the polymerization of thietane, accompanied by decomposition.[20] 2,6-Dithiaspiro[3.3]heptane, which is more stable, gives the disulfoxide in a low yield on reaction with nitric acid; with chromic anhydride in acetic acid solution, it gives a very low yield of the disulfoxide.[7] It is rather difficult to obtain the pure sulfoxides corresponding to thietane and its derivatives. Only the 3,3-disubstituted derivatives have been described before 1959, and those of 3,3-dimethylthietane and of 2-thiaspiro[3.5]nonane can only be conveniently purified as the mercuric chloride addition compounds.[9, 10]

Cerniani *et al.*[26a] have shown by spectrophotometric studies that the oxidation of thietane by hydrogen peroxide in 0.1 M perchloric acid is kinetically a second-order reaction.

As there are several oxidation products which can be formed when 2,6-dithiaspiro[3.3]heptane is treated with hydrogen peroxide in acetic acid, a smaller quantity of oxidizing agent than that theoretically required is recommended for the preparation of the monosulfoxide.[7] For the same reason, 2,6-dithiaspiro[3.3]heptane 2,2,6-trioxide is best prepared in two steps [section **VI.1.***B.*(**2**) above]. The preparation of 1,5-dibromo-2,6-dithiaspiro[3.3]heptane 2,6-dioxide is treated in section **V.3.***A.*(**2**) above.

(2) By the action of thionyl chloride on an amide of 3-oxoglutaric acid. When a solution of an aromatic diamide of 3-oxoglutaric acid in benzene is refluxed with thionyl chloride, hydrochloric acid is liberated and the color of the solution changes.[56] Even with excess thionyl chloride, no compound containing two $\rangle C{=}S{=}O$ groups is observed; the reaction can be written as:



Methyl 3-oxoglutarate itself reacts in the same way with thionyl chloride;[35] the reaction product, which melts at too low a temperature

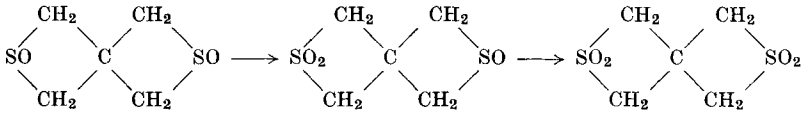
to be purified by crystallization and boils at too high a temperature to be distilled without decomposition, can only be isolated as the mercuric chloride addition complex.

The derivatives of 3-thietanone-2,4-dicarboxylic acid 1-oxide have been little studied; their structure has not been definitely established.

C. Reactivity of Sulfoxides Containing a Four-Membered Ring

Like the linear sulfoxides, these compounds are readily reduced or oxidized to give, respectively, the corresponding sulfides or sulfones.

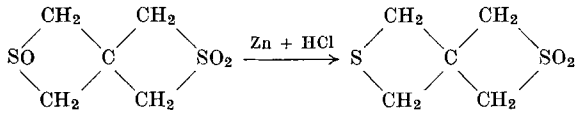
(1) Oxidation. The oxidation of 2,6-dithiaspiro[3.3]heptane 2,6-dioxide is discussed in section **VI.1.***B.***(2)** above:



Hydrogen peroxide in acetic acid, however, decomposes 1,5-dibromo-2,6-dithiaspiro[3.3]heptane 2,6-dioxide with the production of sulfuric acid, and the corresponding disulfone cannot be isolated.[8]

(2) Reduction. A solution of 2,6-dithiaspiro[3.3]heptane 2,6-dioxide is reduced by a large excess of powdered zinc and hydrochloric acid to give 2,6-dithiaspiro[3.3]heptane.[7]

The reduction of 2,6-dithiaspiro[3.3]heptane 2,2,6-trioxide by zinc and hydrochloric acid in boiling water gives a good illustration of the difference in reactivity of the sulfoxide and sulfone groups, since this



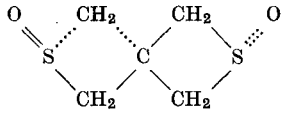
reaction yields 2,6-dithiaspiro[3.3]heptane 2,2-dioxide. This is the only method by which this compound can be obtained, since, with the direct oxidation of 2,6-dithiaspiro[3.3]heptane or its monosulfoxide by hydrogen peroxide in acetic acid, the sulfide is first oxidized to the disulfoxide, and then derivatives containing more oxygen atoms per molecule are formed.[7]

(3) Addition compounds. The hydrogen-bonding ability of the oxygen atom in thietane 1-oxide has been studied by Tamres and

Searles.[67a] The addition compounds of the four-membered cyclic sulfoxides with mercuric chloride are listed in Table 33. They are prepared in and recrystallized from ethanol. Backer and Keunig[8] have described several addition compounds of 2,6-dithiaspiro[3.3]-heptane 2,6-dioxide with metal salts.

The cobalt salt of *d*-camphorsulfonic acid forms the most interesting addition product by means of which the disulfoxide can be resolved into its two optical isomers; this constitutes a new method called '*active addition*'—the formation of an addition product with an optically active compound.

Although it does not contain an asymmetric atom, 2,6-dithiaspiro-[3.3]heptane 2,6-dioxide can have as an element of symmetry only one

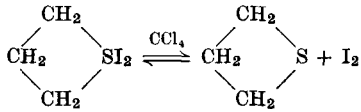


perpendicular binary axis connecting the two sulfur atoms. This compound has a '*spiro*' isomerism since both oxygen atoms are outside the plane occupied by the two other sulfur valences.

The addition compound, prepared in absolute alcohol, can be fractionated into samples of different solubility and rotatory power; the levorotatory enantiomorph is finally separated as the chloroplatinate. No racemization was observed in the presence of N hydrochloric acid at 100°C or of sodium hydroxide. On oxidation with hydrogen peroxide in acetic acid, the levorotatory disulfoxide gives an inactive disulfone in accord with theory.[8]

3. Addition Compounds of the Thietanes with Iodine

The addition compound of iodine with thietane (see also ref. 41a) is strongly dissociated, as the spectrophotometric measurements of McCullough and Mulvey[52, 33a] have shown; it is dissociated to a lesser extent, however, than the addition compound of iodine with dimethyl sulfide.



This addition compound catalyzes the polymerization of thietane.[5, 52] The dissociation of similar compounds has been discussed in connexion with the oxidizability[26a] or the basicity[41a] of the corresponding thietane.

TABLE 34. Physical Properties of Addition Compounds of Mercuric Chloride with the Thietanes

Name	Moles of $HgCl_2$/mole of compound	M.p. (°c)	Recrystallization solvent	Yield (%)	References
Thietane	1	decomp. > 95			39
		92–95 (decomp.)	Ethanol		20
2-Methylthietene	1	decomp. > 104			39
2,4-Dimethylthietane	1	90–91 (followed by decomp.)			39
3,3-Dimethylthietane	1	118 (decomp.)	Ethanol	80	9
2-Thiaspiro[3.5]nonane	1[a]	161 (slight decomp.)	Ethanol		10
3-Thietanol	$1 + 1H_2O$	80 (softens) 100 (decomp.)	(Insoluble)	91	64
2,6-Dithiaspiro[3.3]heptane	2	(decomp.)	Sol. CH_3CO_2H	100	7
2,6-Dithiaspiro[3.3]heptane 2-oxide	$1\frac{1}{2}$[b]	(decomp.)	Ethanol	65	7
2,6-Dithiaspiro[3.3]heptane 2,2-dioxide	1	177–178	Ethanol	80	7
2,6,7,8-Tetrathiaspiro[3.5]-nonane	1[c]		Ethanol	73	6

[a] Combination with 1 mole of $HgBr_2$; m.p. = 157.5°c.[10]

[b] On oxidation it gives the addition compound of 2,6-dithiaspiro[3.3]heptane 2,6-dioxide with 2 moles of $HgCl_2$; m.p. (decomp.) = 185°c.[7]

[c] It combines as readily with 1 mole of $HgBr_2$.

Iodine reacts with 3,3-dimethylthietane without the formation of a crystalline diiodide.[9] In acetic acid, iodine adds to 2-thiaspiro[3.5]-nonane. The 2,2-diiodide obtained (yield 65%), which melts at 83–84°C, is unstable, and after several days it changes into a brown sirup.[10]

Only 2,6-dithiaspiro[3.3]heptane reacts with iodine dissolved in carbon disulfide to give a relatively stable addition compound, the 2,2,6,6-tetraiodide, in 60% yield. This product decomposes at about 100°C; it is oxidized by silver oxide and the disulfoxide cannot be isolated from the reaction products. Iodine is completely removed by prolonged treatment with a concentrated solution of sodium thiosulfate.[7]

4. Addition Compounds of the Thietanes with Mercuric Chloride

Like the aliphatic sulfides, the thietanes, with the exception of 9,10-dihydroanthracene-9,10-*endo*-2′,3′-thietane,[31] add mercuric chloride from ethanol solution, occasionally from a hydrocarbon–ethanol mixture,[20] and rarely from aqueous solution.[64] Precipitation can occur even from a very dilute solution.[20] The melting point of some of these crystalline products is so precise that the compounds can be considered as characteristic derivatives for identification, but many decompose below their melting temperatures.

Unlike tetramethylene and pentamethylene sulfide, thietane does not add mercuric iodide.[20]

The physical properties of these addition compounds are listed in Table 34.

VII. Oligomers and Polymers of Thietane

1. Oligomers

Two types of by-products appear during the preparation of thietane, principally when the method employed is the cyclization of a dihalo derivative with an alkali sulfide.[39, 67]

A. Linear Oligomers

The formation of linear oligomers containing both the halogen, X, and sulfur can be explained by the following reactions:[22]

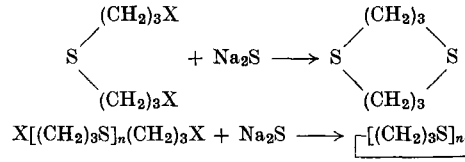
$$2\ X(CH_2)_3X + Na_2S \longrightarrow X(CH_2)_3S(CH_2)_3X$$

$$2\ X(CH_2)_3S(CH_2)_3X + Na_2S \longrightarrow X[(CH_2)_3S]_3(CH_2)_3X \quad \text{or}$$

$$X(CH_2)_3S(CH_2)_3X + X(CH_2)_3X + Na_2S \longrightarrow X[(CH_2)_3S]_2(CH_2)_3X$$

B. Cyclic Oligomers

Cyclic oligomers result from the reaction of these dihalo derivatives with the alkali sulfide:[22]



In fact, only the cyclic oligomers have been investigated. Their yield, which can be as high as 36%,[22] and the distribution of products of different molecular weights seem to vary within wide limits according to the conditions used;[22] this explained the lack of agreement among the various authors. Meadow and Read[53] separated a dimer of thietane (yield 2%; m.p. −15°C; b.p. 245–246°C), the existence of which had been suspected by Mansfield;[50] Bost and Conn,[22] using quite similar experimental conditions, identified a hexamer which gave a constant melting point (51–52°C) after several reprecipitations by ether from a chloroform solution maintained at about −10 to −15°C.

As the melting point of the tetramer[53] is 46°C, the relatively high softening temperature (83–85°C) of the polymer mixtures obtained by different authors[39, 72] during the preparation of thietane, can only be explained by the presence of *linear* polymers.

The formation of oligomers or of polymers has been observed in the course of the synthesis of several derivatives containing the thietane ring.[19, 25, 35, 39, 45]

The condensation of 1,1-bis(chloromethyl)cyclopropane with sodium sulfide[26b] in anhydrous glycol gives only the 5,11-dithiadispiro-[2.3.2.3]dodecane (yield: 32%; b.p. (15 mm.) = 142°), the disulfone of which melts at 130°C. No 2-thiaspiro[2.3]hexane[41a] is obtained.

2. Polymers

Insoluble flakes appear gradually in samples of thietane and some of its homologs which have been stored in the light.[29, 35, 40, 41, 61] The reaction involved is a decomposition to give an unsaturated hydrocarbon and thioformaldehyde (see section **V.1** above) rather than a polymerization.[40]

A number of products favor or set off a polymerization which can be slow or rapid and exothermic, depending on the temperature and the proportion of impurities or catalyst (Table 35). Etienne and Soulas[35] investigated the conditions which give polymers of the highest possible

molecular weight; the monomer should be freshly distilled and perfectly dry. Lowering of the temperature to below 0°c generally has the effect of stopping the polymerization.

TABLE 35. References Concerning the Polymerization of Thietane and Its Derivatives by Various Agents

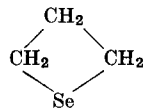
Name	Heat alone	Iodine	Water	Mineral acids	Catalysis (Friedel–Craft)
Thietane	67[a]	5, 52	72[b]	20, 72	35
2-Methylthietane	72			72	35, 72
3,3-Dimethylthietane					35
2-Thiaspiro[3.5]nonane		10			
2,6-Dithiaspiro[3.3]-heptane					35[c]
2-Oxa-6-thiaspiro[3.3]-heptane					25[c]
3-Thietanol	47[a]			58	46
	46			46	
				64	

[a] The monomer was not purified.
[b] In a closed flask at 125°c.
[c] The polymer obtained is tridimensional.

Bases seem to stabilize thietane; the organolithiums, however, initiate stepwise polyaddition reactions.[16]

VIII. Selenetane

The selenium analogue of thietane is called selenetane:



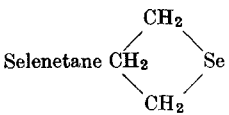
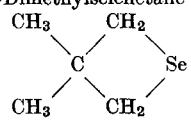
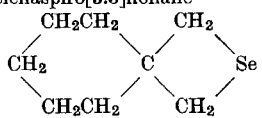
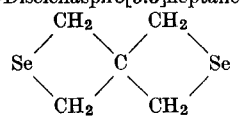
Morgan and Burstall[54] prepared selenetane in 1930 by a method analogous to that previously used for the preparation of thietane. Backer and Winter[11] subsequently made a rather detailed study of some of its homologs.

1. Physical Properties, Nomenclature and Crystallography

A. Physical Properties

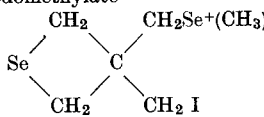
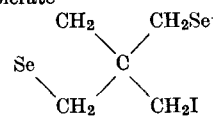
Seletane is a liquid with an extremely irritating vapor; it can be distilled with ethanol, ether and some other volatile solvents.[54] Its homologs also have a very disagreeable odor.[11] Their properties are listed in Table 36.

TABLE 36. Physical Properties of the Selenetanes

Name and Formula	M.p. (°C) (and recrystallization solvent)	B.p. °C	B.p. mm of Hg	Refractive Index n_D^t n	Refractive Index n_D^t t	Density (d_4^t) d	Density (d_4^t) t	References
Selenetane 		118–119	779	1.5612	15	1.525[a] 1.510 1.498 1.484	20 29 37.5 47	54
3,3-Dimethylselenetane 		56 139–140 (polymer)	40 760	1.5117	21	1.3120	21	11
2-Selenaspiro[3.5]nonane 	−46 (en masse)	103.5–104	13	1.5498	15			11
2,6-Diselenaspiro[3.3]heptane 	67 (hexane)	(distil- lable)	5					11

(*Table continued*)

TABLE 36 (*continued*)

Name and Formula	M.p. (°C) (and recrystallization solvent)	B.p. °C	B.p. mm of Hg	Refractive Index n_D^t n	Refractive Index n_D^t t	Density (d_4^t) d	Density (d_4^t) t	References
3-Iodomethyl-3-methylselenomethylselenetane iodomethylate 	112–113 (decomp.) (ethanol + water)							
3-Iodomethyl-3-methylselenomethylselenetane picrate 	113–113.5 (water)							11

[a] The density of selenetane varies with the temperature, t, according to the formula: $d_4^t = 1.554 - 0.001493t$.

B. Crystallographic Properties

2,6-Diselenaspiro[3.3]heptane has been studied by Terpstra,[11] who compared it with the corresponding sulfur derivative. The crystals are isomorphic. The melting point of 2,6-dithiaspiro[3.3]heptane (31.5°C) is raised by the addition of 2,6-diselenaspiro[3.3]heptane (m.p. 67°C).

TABLE 37. Angles of Monoclinic Crystals of 2,6-Diselenaspiro[3.3]heptane

	Observed	Calculated
$g^1 : m$ = (010) : (110)	63° 54′	—
$g^1 : d^1$ = (010) : (111)	74° 4′	—
[001] : [10$\bar{1}$]	54° 18′	—
$m : d^1$ = (110) : (111)	51° 23′	51° 21′
[10$\bar{1}$] : [101]	71° 0′	71° 18′

The crystallographic system is monoclinic, with $\beta = 89° 56'$ and $b : a : c = 0.4899 : 1 : 0.3512$. The forms are $g^1 = \{010\}$; $a^1 = \{\bar{1}01\}$; $d^1 = \{111\}$; $m = \{110\}$. The angles are shown in Table 37. The crystals are plates which are parallel to the plane $g' = \{010\}$ (Fig. 9).

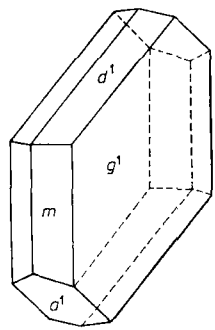


Fig. 9. Crystal form of 2,6-diselenaspiro[3.3]heptane.

2. Preparation

Selenetane, 3,3-dimethylselenetane, 2-selenaspiro[3.5]nonane, and 2,6-diselenaspiro[3.3]heptane have been prepared by the addition of the corresponding bromo derivatives to a suspension or solution of alkali selenide in ethanol in an inert atmosphere (Table 38). Under these

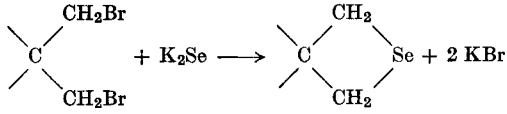
TABLE 38. Preparation of Selenetanes

Name	Selenide	Solvent	Atmosphere	Isolation method[a]	Yield (%)	References
Selenetane	Na_2Se	Absolute ethanol	H_2	A	5	11, 54
3,3-Dimethylselenetane	K_2Se	Ethanol	N_2	B	40	11
2-Selenaspiro-[3.5]nonane	K_2Se	Ethanol	N_2	B	68	11
2,6-Diselenaspiro[3.3]heptane	K_2Se	Ethanol + benzene	N_2	C	very good	11

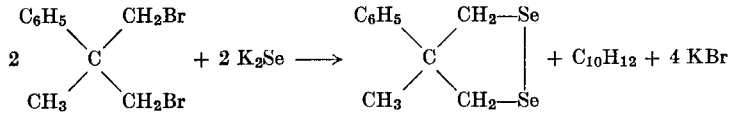
[a] Isolation methods:

A. Water is added to the concentrated solution, and the product extracted with light petroleum.
B. To the solution obtained is added an aqueous saturated solution of sodium chloride, and the mixture 'extracted with ether'.
C. The concentration residue is taken up in hexane to precipitate KBr. After distillation under 5 mm., the product is separated from $C(CH_2Br)_4$ as the mercuric chloride addition compound.

conditions, however, 1,3-dibromo-2-methyl-2-phenylpropane forms 4-methyl-4-phenyl-1,2-diselenacyclopropane and a hydrocarbon[12]



which is probably 1-methyl-1-phenylcyclopropane or an isomer containing a double bond.



3. Chemical Properties

A. Selenetane

Selenetane is a labile compound which can be stored under cool dark conditions, but which polymerizes to a large extent on distillation

even in an atmosphere of carbon dioxide.[54] Even if any elevation of the temperature is avoided during its preparation, yellow gummy polymers are formed, notably a cyclic hexamer (m.p. 38–40°C), the chemical and physical properties of which have been studied by Morgan and Burstall.[54]

(1) Reaction with methyl iodide. Methyl iodide in alcoholic solution reacts with selenetane to open the ring and to yield a brown oil.[54]

(2) Addition compounds. Only the following two addition compounds of selenetane have been identified:

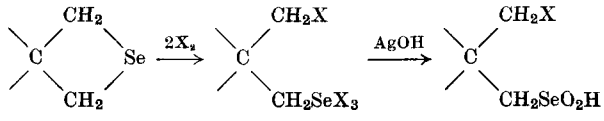
(*a*) When selenetane is treated with an alcoholic iodine solution, selenetane 1,1-diiodide (m.p. 98°C) precipitates as fine violet-red needles which are soluble in benzene. At the same time there appears an amorphous violet polymer, of the same percentage composition, which is insoluble in all organic liquids.[54]

(*b*) The addition compound with one molecule of mercuric chloride, which precipitates from alcoholic solution, softens at 80°C and decomposes at about 105°C. On treatment with sodium hydroxide, selenetane is regenerated. This addition compound decomposes on heating in mercury selenide and 1,3-dichloropropane.[54]

B. Substituted Selenetanes

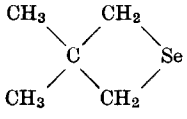
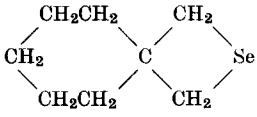
Like the corresponding sulfur derivatives, the 3,3-disubstituted selenetanes and 2-selenaspiro[3.5]nonane are considerably more stable than selenetane itself.[11] Although these compounds are prepared at the reflux temperature of the solvent, there is little or no polymeric material formed, and the yields, therefore, are reasonably satisfactory (Table 36).

(1) Action of halogens and halogenated compounds. (*a*) At room temperature a molecule of 3,3-dimethylselenetane or 2-selenaspiro-[3.5]nonane takes up 4 atoms of bromine, or 2 and then 4 atoms of



chlorine, with cleavage of the ring.[11] The resulting halogen derivative yields a seleninic acid on hydrolysis with silver hydroxide (Table 39).

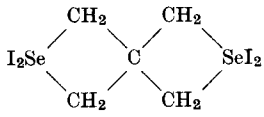
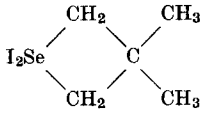
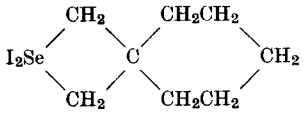
TABLE 39. Reactions of 3,3-Disubstituted Selenetanes with Chlorine or Bromine[11]

Formula	Halogen	Solvent	Tetrahalo derivative obtained		Acid formed by hydrolysis	
			Yield (%)	M.p. (°C)	Yield (%)	M.p. (°C)
	Br	CH_3CO_2H		103 (decomp.)	54	91
	Cl	$CHCl_3$	97	100 (decomp.)	70	90–91
	Br	CCl_4	83	121–122 (decomp.)	70	102.5–103
	Cl	CCl_4	46	102–104	77	100–100.5

(*b*) Reaction with iodine gives unstable addition products which decompose or polymerize rapidly (Table 40).

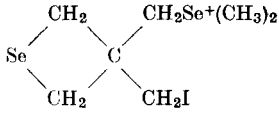
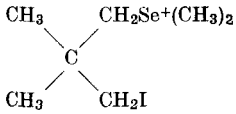
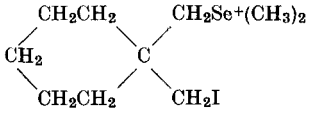
(*c*) The reaction of the substituted selenetanes with methyl iodide

TABLE 40. Addition Compounds of Substituted Selenetanes with Iodine[11]

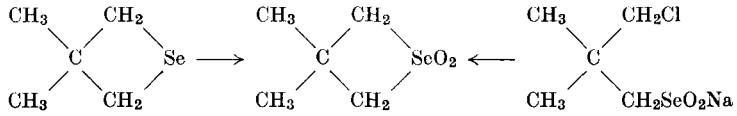
Formula	Reaction medium	Yield (%)	Remarks
	CS_2		Decomposes rapidly
	CH_3CO_2H	94	Polymerizes rapidly
	CH_3CO_2H	90	Polymerizes rapidly; m.p. 59°C (decomp.)

is similar to that of the corresponding sulfur derivatives (Table 41); the structure of the products has been demonstrated by the formation (by double decomposition) of the picrate or other selenonium salts.

TABLE 41. Products Resulting from the Action of Methyl Iodide on the Substituted Selenetanes[11]

Formula of the cation (anion I^-)	Solvent	Yield (%)	M.p. (°C)
	None or absolute ethanol	40	112–113 (decomp.)
	Absolute ethanol	95	105
	Absolute ethanol		Cannot be crystallized

(2) Action of oxygen. 3,3-Dimethylselenetane has been oxidized by hydrogen peroxide, preferably in acetone, to give a selenone melting at 132–132.5°C (yield 44%). The aqueous solution of this product is acidic, but that of 3,3-dimethylthietane 1,1-dioxide is neutral. The same selenone is obtained by the cyclization of sodium 3-chloro-2,2-dimethylpropane-1-seleninate, a reaction which occurs when this compound is heated in absolute ethanol for 24 hr. at 85°C in a sealed tube:[11]



(3) Addition compounds with the mercuric halides. In an ethanolic medium 3,3-dimethylselenetane and 2-selenaspiro[3.5]nonane add an equimolecular quantity of mercuric chloride or bromide; the yield of precipitate is around 100%. One molecule of 2,6-diselenaspiro[3.3] heptane adds 2 molecules of mercuric chloride. The analysis of these compounds presents difficulties.[11]

IX. Appendix

1. Preparation of 3,3-Dimethylthietane[34]

A. Method 1

A solution containing 150 g. of potassium hydroxide pellets in 500 ml. of neutral colorless technical glycol was saturated with hydrogen sulfide which had been washed with glycol. The gas delivery tube was replaced by a capillary supplied with nitrogen, the vessel fitted with a small distillation column, and the pressure in the apparatus reduced with a water pump to eliminate the excess of hydrogen sulfide gas. Distillation was carried out by heating the flask gradually over an oil bath until the temperature reached the boiling point of glycol under the pressure selected (15–50 mm.). If one tries to distil the reaction mixture under normal pressure, the temperature so attained is such that the solvent reacts with the alkali sulfide to form organic sulfur compounds.

Owing to loss of hydrogen sulfide during dehydration, the composition of the salt remaining in solution corresponded approximately to the formula KHS,K_2S. To this sulfide solution was added 141 g. (1 mole) of 2,2-dimethyl-1,3-dichloropropane.* Then the distillation column and capillary were removed and the vessel was equipped with a reflux condenser, a thermometer immersed in the liquid, and an efficient stirrer. The mixture was refluxed gently for about 20 hr. in an atmosphere of nitrogen; the temperature was 125–135°C, and the stirring such that the two liquids were intimately mixed.

The cold mixture was rapidly filtered through sintered glass, and the precipitate washed with a little dry glycol. The two liquid layers (L and U) were separated in a separatory funnel. The lower layer, L, was distilled at atmospheric pressure with a small column, until the boiling point of pure glycol was attained. The distillate consisted of two layers, L_u and L_e; the top layer L_u (8 g.) was combined with liquid U (76 g.) and dried over potassium carbonate.

This crude dry product (82 g.) was rectified under nitrogen at reduced pressure to yield 51 g. of dimethylthietane (yield 50%) which distilled at 45°C under 51 mm. pressure; it was collected in a cold flask. The next fraction, which distilled at 100–105°C under 52 mm. pressure, did not contain the thiol group. Distillation at atmospheric pressure should be avoided because of foaming.

* Etienne, Y., and R. Soulas, *Bull. soc. chim. France*, **1957**, 978.

B. Method 2

The same procedure can be used with the substitution of an anhydrous solution of Na_2S in glycol for the glycol solution of the salt KHS,K_2S; the anhydrous solution of Na_2S was obtained by the distillation of 530 g. of sodium sulfide nonahydrate in 1 l. of glycol under reduced pressure (15–50 mm. of nitrogen) until the elimination of water was complete. 3,3-Dimethylthietane can be recovered from the unfiltered reaction product by steam-distillation (yield 23%).

2. Preparation of 2-Methylthietane[35]

Into a three-necked flask equipped with a reflux condenser and protected from atmospheric carbon dioxide were introduced 450 g. of water, 92 g. of thiourea (1.2 mole), 127 g. of 1,3-dichlorobutane (1 mole), and 144 g. of sodium hydroxide pellets (3.6 moles). The mixture was stirred vigorously overnight at room temperature. The solid material dissolved rapidly; the fine emulsion obtained had separated as a white precipitate by the next day. After the reaction mixture had been refluxed vigorously with stirring for about 12 hr., it was steam-distilled and the aqueous layer was recycled. The organic part of the distillate was decanted, dried over potassium carbonate and fractionated in the presence of calcium hydride (b.p. at 760 mm. 107–108°C).

The yields are better than 70%. The yield is lower if the stirring is inefficient (in which case the product contains some of the chloro derivative), or if one reduces the length of time during which the reactants are in contact at room temperature.

3. Preparation of α-Methyl-2-thietanemethanol[69]

A cold solution containing 15 g. of potassium hydroxide pellets in 60 ml. of water was saturated with hydrogen sulfide; then 15 g. of potassium hydroxide dissolved in 20 ml. of water was added, and the solution made up to 180 ml. with ethanol. A portion of this solution (60 ml.) was heated under reflux, and the remaining 120 ml. of the potassium sulfide solution together with 30 g. of 3,5-dichloro-2-pentanol were added slowly over a period of 30 min. Refluxing and stirring were continued for 1–1½ hr.; then 50 ml. of water was added and the mixture concentrated by distillation. The aqueous residue was extracted with ether. After the extract had been dried, the ether was driven off and the remainder distilled. The fraction distilling at 99–102°C (23 mm.) was collected: after redistillation (b.p. 18 mm. 95°C), the yield was 12 g. (53%).

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CHAPTER VI

β-Lactones

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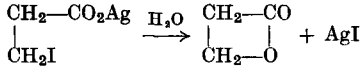
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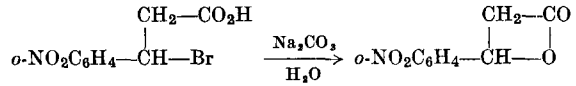
I. General

1. Historical

The β-lactones, internal esters containing a strained four-membered ring, differ from the five- and six-membered lactones by the irreversibility of their transformation into hydroxy acids; for this reason they can only be obtained by indirect methods. The simplest β-lactone, propiolactone, was first prepared in 1916 by Johansson[210] who treated an aqueous solution of sodium β-iodopropionate with silver nitrate (yield 9%):



Earlier, Einhorn[65] had identified a substituted β-lactone which, owing to its insolubility in water and convenient melting temperature, could be easily separated and purified by crystallization:



The β-lactones, in fact, are very reactive, rather labile compounds. Although their existence as intermediates in a large number of reactions had been reported as early as the last century,[5, 48, 65, 67, 70] only those could be characterized which melt at a temperature sufficiently high to permit purification by crystallization, or boil at a low enough

temperature to permit distillation, sometimes at reduced pressure. The industrial preparation of ketene, which has made it possible to obtain β-propiolactone cheaply by the addition of formaldehyde,[141, 234] has led to a renewed interest in this compound and its simple homologs. Gresham and his collaborators at the B. F. Goodrich Company have published a series of papers and notes on the reactions of these compounds. Numerous other β-lactones, which cannot be isolated but whose decomposition products are of industrial interest, are also prepared from ketene or methylketene and carbonyl compounds.

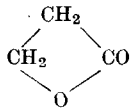
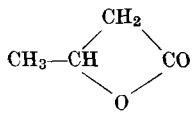
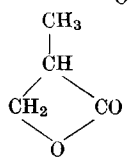
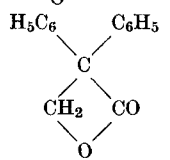
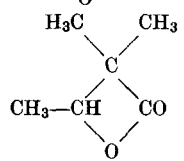
Among the reviews which have been published in the last ten years on the β-lactones, we should mention that of Zaugg,[363] which is very complete up to 1952, and the interesting articles of Hayao[169] and Machell,[257] which are less comprehensive. The dimer of ketene[410, 543] and its simple homologs,[546] some of which have a β-lactone structure, are treated in several recent reviews; in addition, they are mentioned in general articles concerning the ketene monomers.[434, 459, 510a, 548, 596]

2. Nomenclature

The lack of a systematic nomenclature for the β-lactones is to be deplored. Although the term 'lactone' has been used universally for a long time by the workers in the field, it was not retained by the Commission of Liège and the Geneva Convention which preferred the term '-olide' to which is added the name of the corresponding hydrocarbon. The International Union of Chemistry, in its turn, has not recognized the suffix '-olide'. Nor does the designation 2-oxetanone, which stems from the general system established for the heterocyclic compounds, seem to have been adopted. In view of this lack of agreement, *Chemical Abstracts* designates the β-lactones as products of the cyclization of the corresponding hydroxy acids, whereas the authors rather name the simple β-lactones as substitution derivatives of β-propiolactone.

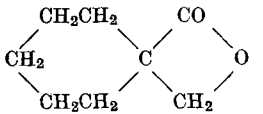
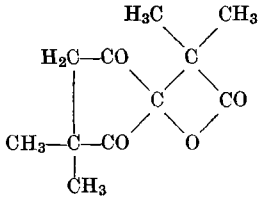
This has led to the four principal nomenclatures given in Table 1. Number 1 is assigned to the carboxyl carbon in the Geneva system, and to the hetero atom (oxygen) in the general heterocyclic system, a situation which gives rise to confusion. The system employed by *Chemical Abstracts* uses 'butyrolactone' to designate the γ-lactone of 4-hydroxybutyric acid, but keeps the term 'hydracrylic acid, β-lactone' for propiolactone. For the sake of conciseness we have kept the latter term and along with the *Chemical Abstracts* terminology, we have sometimes used the common system which is more convenient for simple derivatives.

TABLE 1. Nomenclature of the β-Lactones

Formula	Usual name (scientific journals)	Name derived from the acid (*Chem. Abstr.*)	Geneva system	General heterocyclic system
	β-propiolactone[a]	Hydracrylic acid, β-lactone	3,1-propanolide	2-oxetanone
	β-methyl-β-propiolactone[b]	3-hydroxybutyric acid, β-lactone	3,1-butanolide	4-methyl-2-oxetanone
	α-methyl-β-propiolactone	3-hydroxy-2-methylpropionic acid, β-lactone	2-methyl-3,1-propanolide	3-methyl-2-oxetanone
	α,α-diphenyl-β-propiolactone	2,2-diphenylhydracrylic acid, β-lactone	2,2-diphenyl-3,1-propanolide	3,3-diphenyl-2-oxetanone
	α,α,β-trimethyl-β-propiolactone	3-hydroxy-2,2-dimethylbutyric acid, β-lactone	2,2-dimethyl-3,1-butanolide	3,3,4-trimethyl-2-oxetanone

(*Table continued*)

TABLE 1 (*continued*)

Formula	Usual name (scientific journals)	Name derived from the acid (*Chem. Abstr.*)	Geneva system	General heterocyclic system
	α,α-pentamethylene-β-propiolactone	1-(hydroxymethyl)-cyclohexanecarboxylic acid, β-lactone	cyclohexano-3-spiro-3,1-propanolide	2-oxaspiro[3.5]-1-nonanone
		1-hydroxy-α,α,3,3-tetramethyl-2,5-dioxocyclopentaneacetic acid, β-lactone	2,2-dimethyl-(1′,1′-dimethyl-2′,4′-dioxocyclopentano)-3-spiro-3,1-propanolide	3,3,6,6-tetramethyl-oxa-1-spiro[3.4]-octane-2,5,8-trione

[a] Also called propionolactone or betaprone.

[b] Also called β-butyrolactone. This name leads to confusion with butyrolactone which is a γ-lactone, and the nomenclature cannot be used for the higher homologs. In our opinion this nomenclature should be rejected as should that of *iso*valerolactone which is sometimes used for the β-lactone of 3-hydroxy-3-methylbutyric acid.

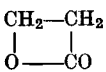
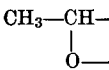
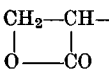
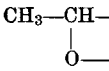
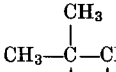
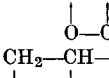
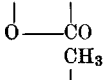
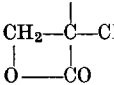
II. Physical Properties

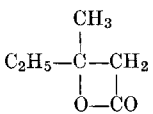
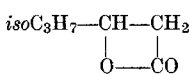
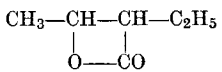
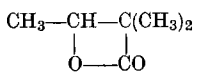
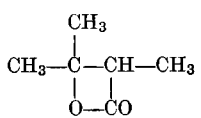
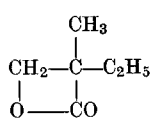
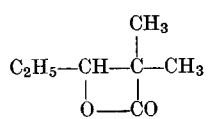
The melting and boiling points of the aliphatic β-lactones are listed in Table 2, and those of the aromatic β-lactones in Table 3. We have mentioned those β-lactones which have been definitely isolated even if their purification has not been accomplished. On the other hand, we have not included the β-lactones which have been reported in patents but for which precise preparative procedures are not given.

Compounds containing more than one β-lactone function are given in Table 4.

Much work has been done on the physical properties of the dimer of ketene which has the structure of the β-lactone of 3-hydroxy-3-butenoic acid; these values are given in Tables 5–7. Tables 8 and 9 are concerned with the dimers of the substituted ketenes for which a β-lactone structure has been demonstrated.

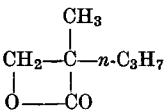
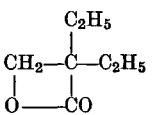
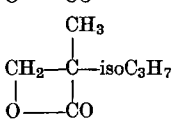
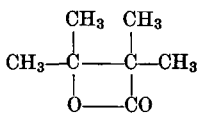
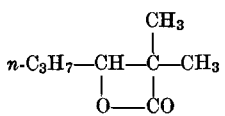
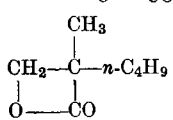
TABLE 2. Physical Properties of Aliphatic β-Lactones

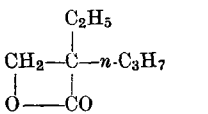
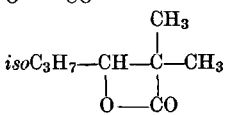
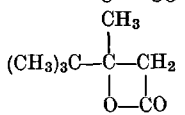
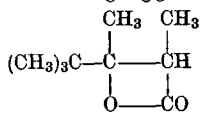
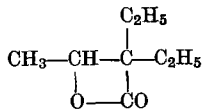
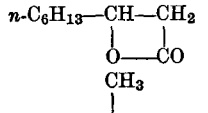
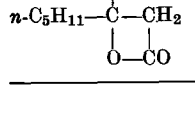
Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	Hydracrylic acid	−33.6	51/10	1	*b*, *c*
			83/45–50	2	
	3-Hydroxybutyric acid		72–74/29	1	212
				2	141
				5	210[a]
	2-Methylhydracrylic acid		49–50/10	1	210
	3-Hydroxy-2-methylbutyric acid	−24	67–67.5/21[d]		213
			63–64/12[d]		159
	3-Hydroxy-3-methylbutyric acid		62/12	1	159
			58/12	2	241
		−26.5			114, 141[e]
	2-(Hydroxymethyl)butyric acid		64–65/13		159
	2,2-Dimethylhydracrylic acid		58/15	1	159
		−13.5	50/12		86
		−13	53.5/15	2	167, 167b
	3-Hydroxyhexanoic acid		62–63/5	2	360, 141

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	3-Hydroxy-3-methylvaleric acid		60–61/10	2	141
	3-Hydroxy-4-methylvaleric acid		110–113/10	2	38, 40
	2-Ethyl-3-hydroxybutyric acid	−25	79–81/18 75/13	1 1	213 296
	3-Hydroxy-2,2-dimethylbutyric acid	16	63–65/14 73/20 115–116/110	1 2	296 86, 323
	3-Hydroxy-2,3-dimethylbutyric acid				
	2-(Hydroxymethyl)-2-methylbutyric acid		63/16	1	86, 71
	3-Hydroxy-2,2-dimethylvaleric acid	25	58/4.4	2	167

(*Table continued*)

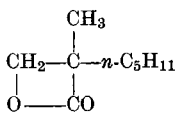
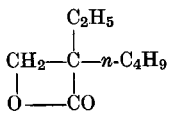
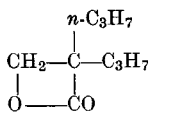
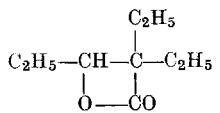
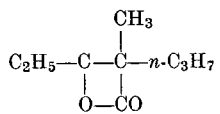
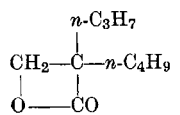
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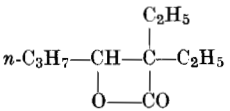
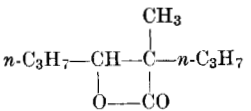
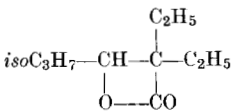
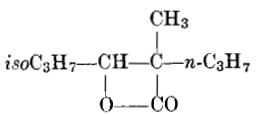
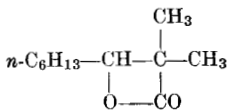
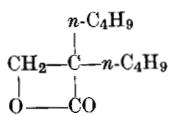
Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	2-(Hydroxymethyl)-2-methylvaleric acid		64/5 55/1	2 1	167 86, 71
	2-Ethyl-2-(hydroxymethyl)butyric acid		65–70/7 100/35 49/2	3, 4 1 2	331 71 86, 167
	2-(Hydroxymethyl)-2,3-dimethylbutyric acid		84/18	1	72, 73
	3-Hydroxy-2,2,3-trimethylbutyric acid				278
	3-Hydroxy-2,2-dimethylhexanoic acid		68/5 101/26	2	167 86
	2-(Hydroxymethyl)-2-methylhexanoic acid		60/1.5	1	72, 73

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	2-Ethyl-2-(hydroxymethyl)valeric acid		74/2	1	71
	3-Hydroxy-2,2,4-trimethylvaleric acid	13.5	73–75/8	2	167, 86
			75–82/9	5	67a, 67b
	3-Hydroxy-3,4,4-trimethylvaleric acid	100		6	94b
	3-Hydroxy-2,3,4,4-tetramethylvaleric acid	46–47		4	30a
	3-Hydroxy-2,2-dimethylbutyric acid		47/0.9	2	167
	3-Hydroxynonanoic acid			2	10
	3-Hydroxy-3-methyloctanoic acid			2	25

(*Table continued*)

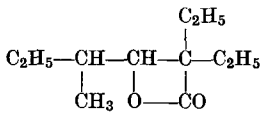
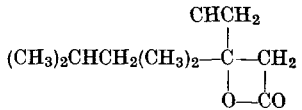
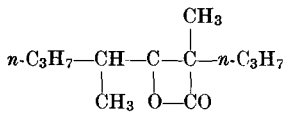
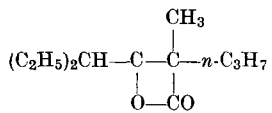
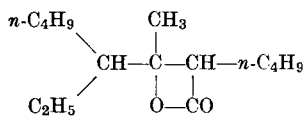
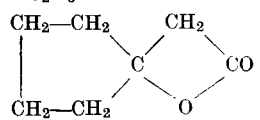
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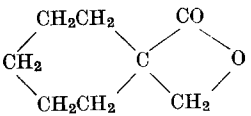
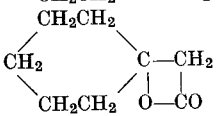
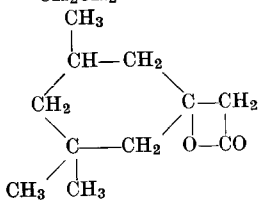
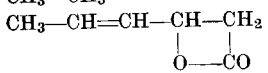
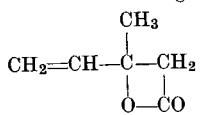
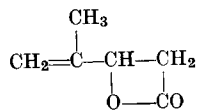
Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	2-(Hydroxymethyl)-2-methyl-heptanoic acid		75/1.5	1	72, 73
	2-Ethyl-2-(hydroxymethyl)-hexanoic acid			1	71
			75/1	4	85
			74/2	2	167
	2-(Hydroxymethyl)-2-*n*-propyl-valeric acid		68/1	1	72, 73
			86–88/5	3	328
	2,2-Diethyl-3-hydroxyvaleric acid		32/0.1	2	167
	3-Hydroxy-2-methyl-2-propyl-valeric acid		37/0.3	2	167
	2-(Hydroxymethyl)-2-propyl-hexanoic acid		90/1.5		72, 73

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	2,2-Diethyl-3-hydroxyhexanoic acid		65/0.7	2	167
	3-Hydroxy-2-methyl-2-propyl-hexanoic acid		62/0.6	2	167
	2,2-Diethyl-3-hydroxy-4-methyl-valeric acid		29/0.1	2	167
	3-Hydroxy-2,4-dimethyl-2-propyl-valeric acid		60/1	2	167
	3-Hydroxy-2,2-dimethylnonanoic acid		105–107/4	2	167
	2-Butyl-2-(hydroxymethyl)-hexanoic acid		90/1 98–100/3	1 3	71, 86 328

(*Table continued*)

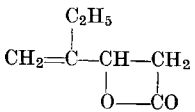
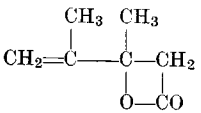
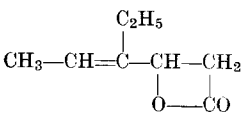
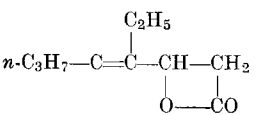
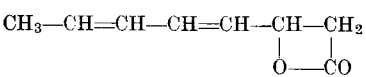
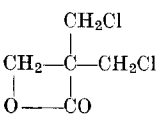
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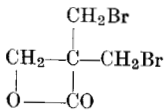
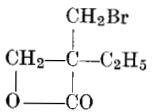
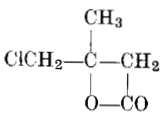
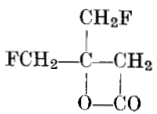
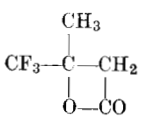
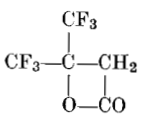
Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	2,2-Diethyl-3-hydroxy-4-methyl-hexanoic acid		31/0.1	2	167
	3-Hydroxy-3-*iso*butyl-5-methyl-hexanoic acid			2	25
	3-Hydroxy-2,4-dimethyl-2-propyl-heptanoic acid		32/0.08	2	167
	4-Ethyl-3-hydroxy-2-methyl-2-propylhexanoic acid		32/0.1	2	167
	2-Butyl-4-ethyl-3-hydroxy-3-methyloctanoic acid		136–137/1.5	6	358
	1-Hydroxycyclopentaneacetic acid	81		1	218

Formula	Corresponding hydroxy acid	M.p. (°c)	B.p. (°c/mm.)	Method of preparation[a]	References
	1-(Hydroxymethyl)cyclohexane-carboxylic acid	16.4	75.5/1	1	71
	1-Hydroxycyclohexaneacetic acid	129		1, 2	218 25, 295a
	1-Hydroxy-3,3,5-trimethylcyclo-hexaneacetic acid			2	25
	3-Hydroxy-4-hexenoic acid			2	26, 39, 162, 141[c]
	3-Hydroxy-3-methyl-4-pentenoic acid			2	141
	3-Hydroxy-4-methyl-4-pentenoic acid		64/10	2	151, 141

(*Table continued*)

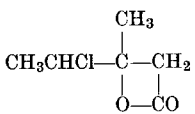
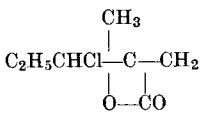
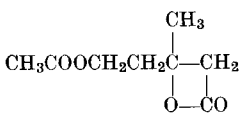
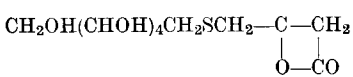
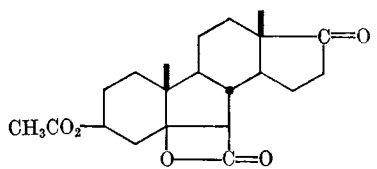
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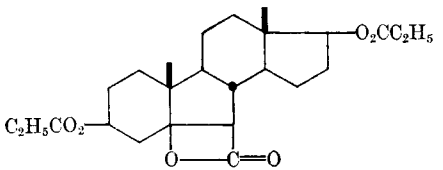
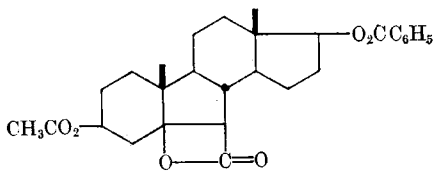
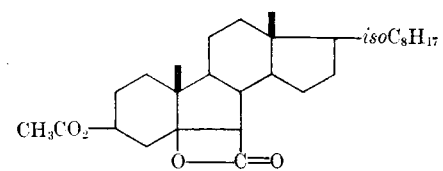
Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	4-Ethyl-3-hydroxy-4-pentenoic acid			2	141
	3-Hydroxy-3,4-dimethyl-4-pentenoic acid			2	151, 141
	4-Ethyl-3-hydroxy-4-hexenoic acid			2	26
	4-Ethyl-3-hydroxy-4-octenoic acid			2	82
	3-Hydroxy-4,6-octadienoic acid			2	26
	2,2-Bis(chloromethyl)hydracrylic acid	35–36	distils at <0.3 mm.	1	291, 339, 72

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	2,2-Bis(bromomethyl)hydracrylic acid	oil	distils at <0.3 mm.	1	72
	2-(Bromomethyl)-2-(hydroxymethyl)butyric acid		125(decomp.)/24	1	72
	4-Chloro-3-hydroxy-3-methylbutyric acid	24–25	36–42/0.003	2	46a
	4-Fluoro-3-(Fluoromethyl)-3-hydroxybutyric		105–107/16	2	19a
	4,4,4-Trifluoro-3-hydroxy-3-methylbutyric acid				225a
	4,4,4-Trifluoro-3-(trifluoromethyl)-3-hydroxybutyric acid		94.5–95/775	2, 4	225

(*Table continued*)

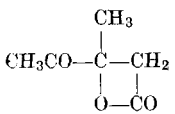
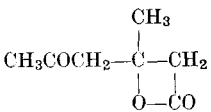
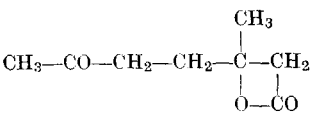
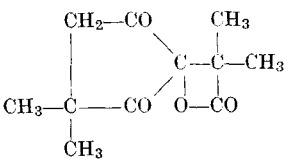
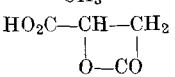
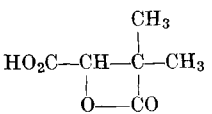
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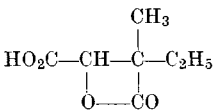
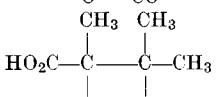
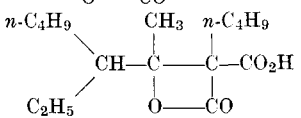
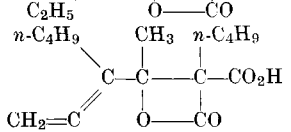
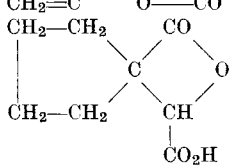
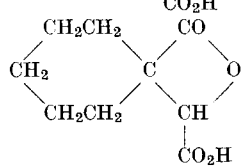
Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	4-Chloro-3-hydroxy-3-methyl-valeric acid[d]	56–57 71–72		2	46a
	4-Chloro-3-hydroxy-3-methyl-hexanoic acid (mixture of isomers)		45–50/0.001	2	46a
	3,5-Dihydroxy-3-methylvaleric acid 5-acetate		(unstable)	2	46b
	3,7,8,9,10,11-Hexahydroxy-5-thiaundecanoic acid			5	332
 or $C_{21}H_{28}O_5$	3β,5ξ-Dihydroxy-17-oxo-B-norandrostane-6-carboxylic acid 3-acetate	172–173		4	216a, 26a

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
 or $C_{25}H_{36}O_6$	3β,5ξ,17β-Trihydroxy-B-norandrostane-6-carboxylic acid 3,17-dipropionate	141–144		4	216b
 or $C_{28}H_{34}O_6$	3β,5ξ,17β-Trihydroxy-B-norandrostane-6-carboxylic acid 3-acetate 17-benzoate	153–154		4	295b
 or $C_{29}H_{46}O_4$	3,5-Dihydroxy-B-norcholestane-6-carboxylic acid 3-acetate	125		4	26a, 277b

(Table continued)

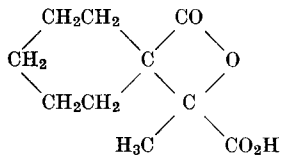
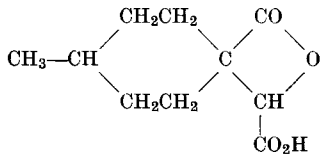
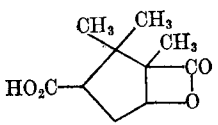
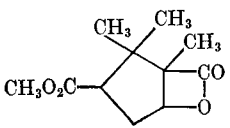
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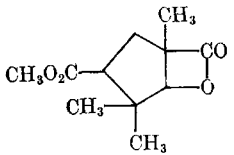
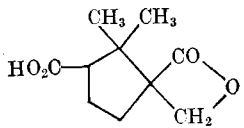
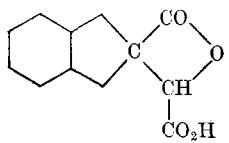
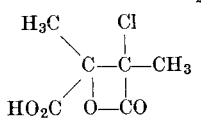
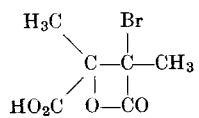
Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	3-Hydroxy-3-methyllevulic acid			2	144, 141, 37
	3-Hydroxy-3-methyl-5-oxohexanoic acid			2	32, 40, 141[c]
	3-Hydroxy-3-methyl-6-oxo-heptanoic acid			2	144, 141
	1-Hydroxy-3,3,α,α-tetramethyl-2,5-dioxocyclopentaneacetic acid	133–134 (decomp.)		1 6	334
	Malic acid	64–65 (liq.)[d]		1	175, 177–179, 140a
	3,3-Dimethylmalic acid	45–47 56(+ $1H_2O$)		1	5 218, 285

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	3-Ethyl-3-methylmalic acid	(liq.)		1	218
	2,3,3-Trimethylmalic acid	118–120 120		1	230 218
	Butyl-(2-ethyl-1-hydroxy-1-methyl-hexyl)malonic acid			6	358
	Butyl-(2-butyl-1-hydroxy-1-methyl-2,3-butadienyl)malonic acid	99–100		6	358
	1-Carboxycyclopentaneglycolic acid	81		1	218
	1-Carboxycyclohexaneglycolic acid	129		1	218

(*Table continued*)

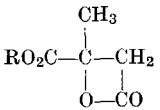
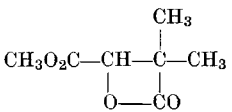
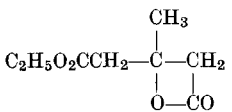
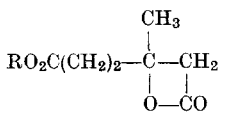
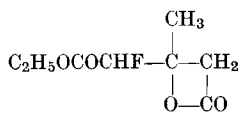
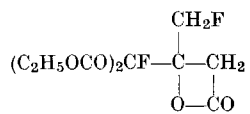
TABLE 2 (*continued*)

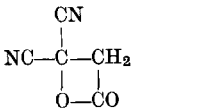
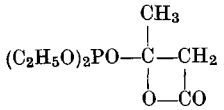
Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	1-Carboxy-α-methylcyclohexane-glycolic acid	46		1	218
	1-Carboxy-4-methylcyclohexane glycolic acid	110		1	56
	5-Hydroxycamphoric acid	209–210		4	335a
	5-Hydroxycamphoric acid (methyl ester)	101–102		4 5	335a

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	5-Hydroxyisofenchocamphoric acid (methyl ester)	89–90[d] 125–127[d]		4	171a 335b
	α^1-Hydroxycamphoric acid	151–152		1	230a
	2-Carboxy-α-hydroxyhexahydro-2-indaneacetic acid[d]	125[d] 116[d]		1	218
	3-Chloro-2,3-dimethylmalic acid[d]	92–94[d] 141–142[d]		6	326
	3-Bromo-2,3-dimethylmalic acid[d]	95–96[d] 148–150[d]		6	326

(*Table continued*)

TABLE 2 (*continued*)

Formula	Corresponding hydroxy acid	M.p. (°c)	B.p. (°c/mm.)	Method of preparation[a]	References
	Citramalic acid (ester)			2[e]	141, 142, 147, 158
	3,3-Dimethylmalic acid (ester)		70–72/0.04	5	285
	3-Hydroxy-3-methylglutaric acid (ester)			2	32, 141[c]
	3-Hydroxy-3-methylhexanedioic acid (ester)			2[f]	38, 158, 141
	2-Fluoro-3-hydroxy-3-methylglutaric acid 1-ethyl ester		108–110/0.2	2	19a
	1-Fluoro-2-(Fluoromethyl)-2-hydroxy-1,1,3-propanetricarboxylic acid 1,1-diethyl ester		149–150/0.5	2	19a

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	3,3-dicyanohydracrylic acid	182		2 6	1 260
	3-Diethylphosphono-3-hydroxy-butyric acid		86–112/0.7	2	267

[a] Methods of preparation: 1, decomposition of a salt of the β-halo acid; 2, addition of a ketene to a carbonyl compound; 3, and following other procedures (see section **IV.3** *et seq.*).

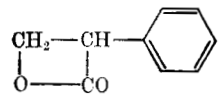
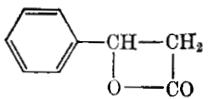
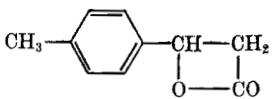
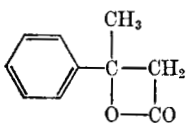
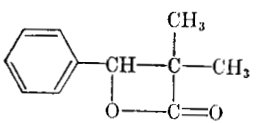
[b] Proposed values: m.p. (°C) -33.4,[107] -31.2,[141] -33.36 ± 0.01,[337] b.p. (°C/mm.) 28/3,[141] 45.8/8, 51/10;[107, 141, 210, 243] d_4^{20} 1.1460,[107] d_0^{20} 1.1489,[141] d_D^{20} 1.4131[107] or 1.4135;[141] n_D^{25} 1.4104[243] or 1.4117.[300]

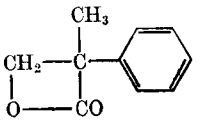
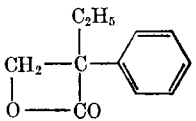
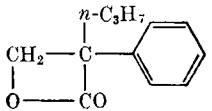
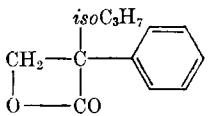
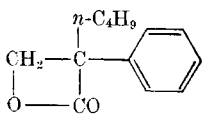
[c] List of references is not complete.

[d] Two isomers have been isolated.

[e] R = CH_3 or C_2H_5.

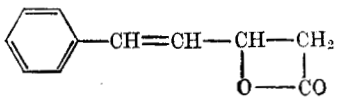
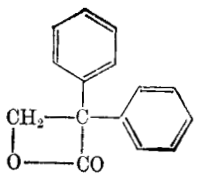
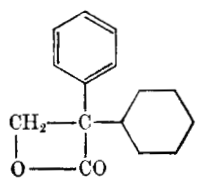
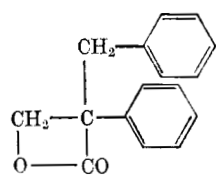
TABLE 3. Physical Properties of Aromatic and Heterocyclic β-Lactones

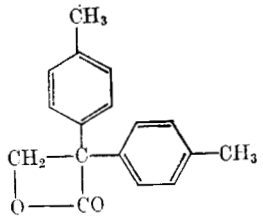
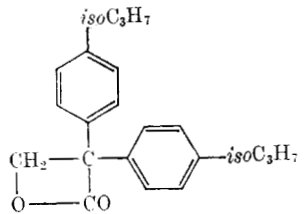
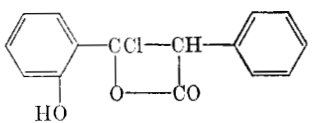
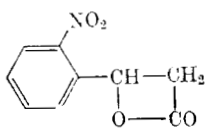
Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	Tropic acid		95–100/1	3	328
	3-Phenylhydracrylic acid			2	26, 149, 155
	3-*p*-Tolylhydracrylic acid			2	48a
	3-Hydroxy-3-methyl-3-phenylbutyric acid			2	25, 155
	2,2-Dimethyl-3-phenylhydracrylic acid				273a 278a

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	2-Methyl-2-phenylhydracrylic acid		75–80/0.6 91/0.6	3	328 330
	2-(Hydroxymethyl)-2-phenyl-butyric acid		105–108/1 105/0.8	3[b]	329 330
	2-(Hydroxymethyl)-2-phenylvaleric acid		100–110/0.5	3 4	330 331
	2-(Hydroxymethyl)-3-methyl-2-phenylbutyric acid		95–105/0.6	3	330
	2-(Hydroxymethyl)-2-phenyl-hexanoic acid		118–120/1	3	328 330

(*Table continued*)

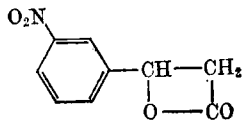
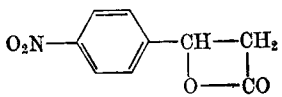
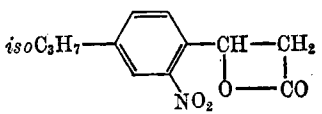
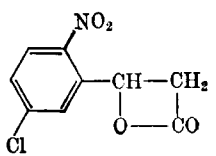
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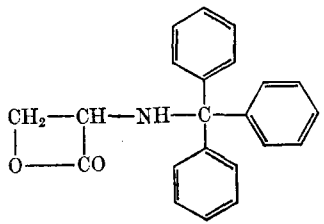
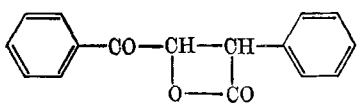
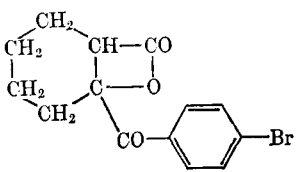
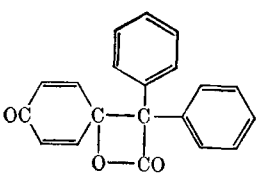
Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	3-Hydroxy-5-phenyl-4-pentenoic acid			2	26
	2,2-Diphenylhydracrylic acid	94–96		3 1	330 361
	2-Cyclohexyl-2-phenylhydracrylic acid	97–98		3	330a
	2-Benzyl-2-phenylhydracrylic acid	124–125		3	328, 330

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	2,2-Ditolylhydracrylic acid (*para*?)	92		1	71, 72
	2,2-Di-*p*-cumenylhydracrylic acid	86		1	71, 72
	3-Chloro-2-phenyl-3-(*o*-hydroxyphenyl)hydracrylic acid	132			273b
	3-(*o*-Nitrophenyl)hydracrylic acid	124 (decomp.)		1	65

(*Table continued*)

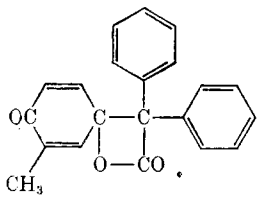
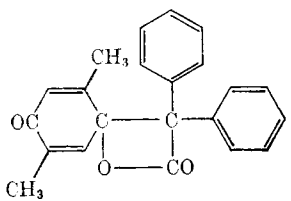
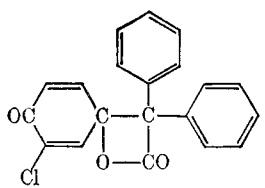
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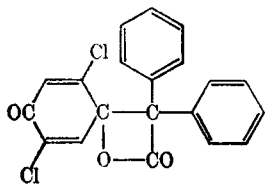
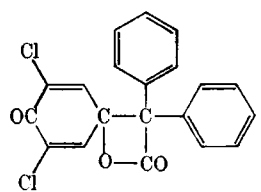
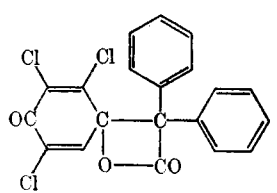
Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	3-(*m*-Nitrophenyl)hydracrylic acid	98 (decomp.)		1	287, 186
	3-(*p*-Nitrophenyl)hydracrylic acid	91.9		1	14, 61, 140a
	3-(4-*iso*Propyl-2-nitrophenyl)-hydracrylic acid	73 (decomp.)		1	66
	3-(5-Chloro-2-nitrophenyl)hydracrylic acid	147 (decomp.)		1[e]	64

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	*N*-Trityl-L-serine	193–194		4	306
	3-Hydroxy-4-oxo-2,4-diphenyl butyric acid	75[d] 95[d] 130[d] 148[d]		1	21 226 228 229
	2-(*p*-Bromobenzoyl)-2-hydroxy-cyclohexanecarboxylic acid	83		1	12, 227
	1-Hydroxy-4-oxo-α,α-diphenyl-2,5-cyclohexadiene-1-acetic acid	143 (decomp.)[f]		2	152, 313

(*Table continued*)

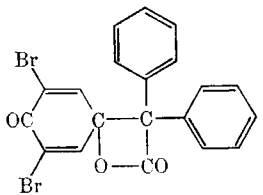
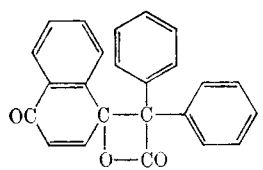
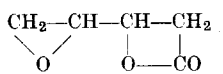
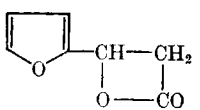
TABLE 3 (*continued*)

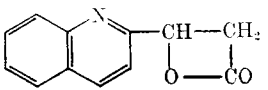
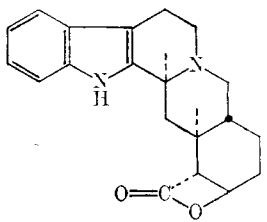
Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	1-Hydroxy-3-methyl-4-oxo-α,α-diphenyl-2,5-cyclohexadiene-1-acetic acid	123 (decomp.)		2	316
	1-Hydroxy-2,5-dimethyl-4-oxo-α,α-diphenyl-2,5-cyclohexadiene-1-acetic acid	123–124 (decomp.)		2	316
	3-Chloro-1-hydroxy-4-oxo-α,α-diphenyl-2,5-cyclohexadiene-1-acetic acid	129–130 (decomp.)		2	316

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	2,5-Dichloro-1-hydroxy-4-oxo-α,α-diphenyl-2,5-cyclohexadiene-1-acetic acid	180–192 (decomp.)		2	316
	3,5-Dichloro-1-hydroxy-4-oxo-α,α-diphenyl-2,5-cyclohexadiene-1-acetic acid	143 (decomp.)		2	316
	2,3,5-Trichloro-1-hydroxy-4-oxo-α,α-diphenyl-2,5-cyclohexadiene-1-acetic acid	220 (decomp.)		2	316

(*Table continued*)

TABLE 3 (*continued*)

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	3,5-Dibromo-1-hydroxy-4-oxo-α,α-diphenyl-2,5-cyclohexadiene-1-acetic acid	141 (decomp.)		2	316
	1,4-Dihydro-1-hydroxy-4-oxo-α,α-diphenyl-1-naphthaleneacetic acid	127 (decomp.)		2	316
	4,5-Epoxy-3-hydroxyvaleric acid		84–86/1–2 84–86/3	2	355 323a
	β-Hydroxy-2-furanpropionic acid			2	141, 149[c]

Formula	Corresponding hydroxy acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	References
	β-Hydroxy-2-quinolinepropionic acid	83[g]		1	67
	Yohimbic acid	173–175		4[b]	57

[a] Methods of preparation: 1, decomposition of a salt of the β-halo acid; 2, addition of a ketene to a carbonyl compound; 3 and following, other procedures (see section **IV.3** *et seq.*).

[b] Dextrorotatory.

[c] List of references is not complete.

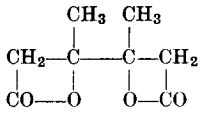
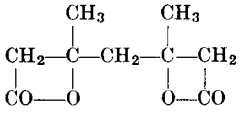
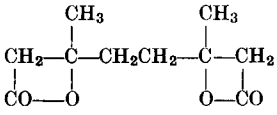
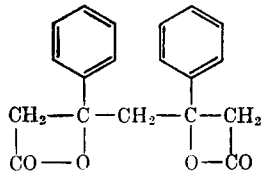
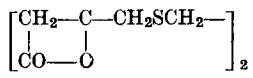
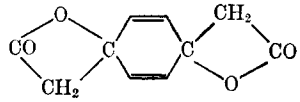
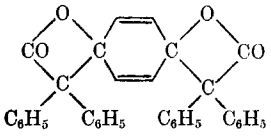
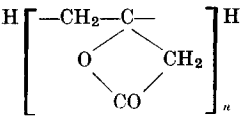
[d] Two isomers have been isolated.

[e] For crystallographic properties, see ref. 64.

[f] Phenylhydrazone, m.p. 180°C.

[g] Chlorohydrate, m.p. 138°C; the corresponding picrate has also been described.[67]

TABLE 4. Compounds Containing Several β-Lactone Rings (Excluded are Condensation Derivatives of Compounds Containing two Ketene Groups)

Formula	Corresponding hydroxy acid	Method of preparation	References
	3,4-Dihydroxy-3,4-dimethylhexanedioic acid	2[a]	141, 144
	3,5-Dihydroxy-3,5-dimethylheptanedioic acid	2[a]	40, 41, 144
	3,6-Dihydroxy-3,6-dimethyloctanedioic acid	2[a]	144
	3,5-Dihydroxy-3,5-diphenylheptanedioic acid	2[a]	144
	3,10-Dihydroxy-5,8-dithiadodecanedioic acid	5[b]	332
	1,4-Dihydroxy-2,5-cyclohexadiene-1,4-diacetic acid	2[a]	74, 152
	1,4-Dihydroxy-α,α,α′,α′-tetraphenyl-2,5-cyclohexadiene-1,4-diacetic acid	2[a]	152
	Poly[(3:4)-3-hydroxybutyric acid]	5[b]	45, 200, 352, 533b

[a] Addition of a ketene to a carbonyl compound.

[b] See section **IV.5.**

TABLE 5. Physical Properties of the Ketene Dimer (Solid State)

(*a*) Freezing point

	°C	Reference
Observed	−6.5	410–446
	−6.7	430
	−7.6	488
	−7	525
	−7 to −8	401

(*b*) Freezing point depressions for 1 mole of substance dissolved in 100 moles

	°C	Reference
Calculated	0.406	560

(*c*) Latent heat of fusion at the melting point

	Cal./mole	Reference
Calculated	3450	560

Property	Data	Reference
(*d*) Crystallographic properties (see Fig. 1)		
System determined by X-ray diffraction	Monoclinic	494
Space group	$P2_{1/C}$	
Number of molecules per unit	4	

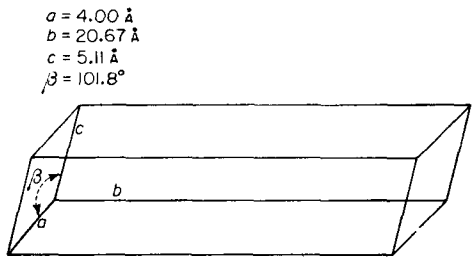


Fig. 1. Unit cell of ketene dimer.

TABLE 6. Physical Properties of the Ketene Dimer (Liquid State)

(*a*) Vapor pressure

	mm.Hg	°C	Reference
Calculated			560
Observed	8	20	410
	23	38.5	401
	28	43	42
	30	42	478
	41	50.5	401
	48	43.5	525
	80	63.5–64.5	451
	92	67–69	592, 462b
	99	69.4–69.5	488
	100	70.0	401
	400	96	557
	760 (?)	126–127	430
		127	589
		127.4	410

(*b*) Boiling point elevation for 1 mole of substance dissolved in 100 moles

	°C	Reference
Calculated	0.33	560

(*c*) Density

	°C	d_4^t	d_{20}^t	Reference
Calculated				560
Observed	20		1.0897	410
		1.0943		488
	25	1.0626		555

(*d*) Viscosity

	°C	Centipoise	Reference
Calculated	25	0.72	560

TABLE 6 (*continued*)

(*e*) Refractive index for the sodium D line

	°C	n_D^t	Reference
Observed	20	1.4376	525
		1.4378	488
		1.4379	410
Calculated	25	1.422	560
Observed		1.436	410
		1.4313	555
		1.4345	451

(*f*) Molar refraction

	Molar refraction	Reference
Calculated	19.659	560
Observed	20.14	431

(*g*) Surface tension

	°C	dynes/cm.	Reference
Calculated	25	21.9	560
		20.3	555
Observed		20.49	555

(*h*) Parachor [$P = M\sigma^{\frac{1}{4}}/(D - d)$]

	°C	Parachor	Reference
Calculated		182.4	560–479
Observed	20.4	183.2	410, 186
	24	181.5	

(*i*) Average specific heat of the liquid between 25°C and its boiling point

	Cal.g.$^{-1}$°C^{-1}	Reference
Calculated	0.476	560

(*j*) Molar volume

	°C	Molar volume	Reference
Calculated	25	84.4	560
	127	96.0	560

TABLE 6 (*continued*)

(*k*) Thermal conductivity at 25°C

	B.t.u.(hr.)$^{-1}$(sq.ft.)$^{-1}$(°F./ft)$^{-1}$	Reference
Calculated	0.089	560

TABLE 7. Physical Properties of the Ketene Dimer (Vapor State)

(*a*) Critical constants (calculated)

Critical pressure (atm.)	Critical volume	Critical temperature (°K)	Reference
54.0	246	583	560

(*b*) Latent heat of vaporization

	°C	Cal./mole	Cal./g.	Reference
Calculated	127	9 600		560
	25	11 100		560
	25	13 870	165	410

(*c*) Viscosity

	°C	Centipoise	Reference
Calculated	25	0.00796	560

(*d*) Specific heat

Cal. g.$^{-1}$ °C^{-1}	Reference
$(C_p)_0 = 3.89 + 72\ 245 \times 10^{-3}T - 34\ 325 \times 10^{-6}T^2$	560

(*e*) Thermal conductivity at 25°C

	B.t.u.(hr.)$^{-1}$(sq.ft.)$^{-1}$(°F/ft.)$^{-1}$	Reference
Calculated	0.0057	560

(*f*) Diffusivity in air at 1 atm.

	°C	cm.^{2}/sec.$^{-1}$	Reference
Calculated	25	0.081	560

TABLE 8. Physical Properties of Alkylketene Dimers with a β-Lactone Structure

$$2\ RCH{=}C{=}O \longrightarrow RCH{=}C{-}CH{-}R \quad (O{-}CO)$$

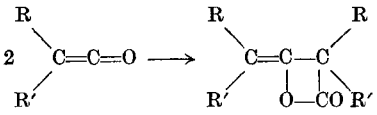
Substituent (R)	B.p. (°c/mm.)	n_D^t	t (°C)	Remarks	Reference
CH_3	50–52/9				465
	57–58/12	1.4280	25		557, 559
	48–48.5/13	1.4365	20	m.p. = −49.4°; d_4^{20} = 0.9926	488
		1.4322	25	d_4^{25} = 0.9864	555, 487, 442a
C_2H_5	92–95/31	1.4385	24		583
	95–96/32	1.4387	25		557, 442a
n-C_3H_7	135/30	1.4433	25		557
iso-C_3H_7	108–110/35	1.4343	25		557, 552, 442a
C_4H_9	115–116/4	1.4513		d_4^{20} = 0.9170	465
	127–129/10	1.4478	25		557
	139–140/26				475
C_5H_{11}	128–130/8	1.4330	20	$d_{22.5}^{20}$ = 0.8463	464
	106/0.4	1.4501	22.5	$d_{22.5}^{22.5}$ = 0.9096	445
C_6H_{13}	148/1.3	1.4517	25	d_4^{25} = 0.8959	555
	132–133/2	1.4489	25		
$C_{10}H_{21}$				m.p. = 41–42°; 41–41.6°	557–559 579a
$C_{12}H_{25}$				m.p. = 42–44°; 49.5–50°	557–559 579a
$C_{14}H_{18}$				m.p. = 54–56°; 57–57.5°	544 579a
$C_{16}H_{33}$				m.p. = 62–63°; 62.3–63.3°	557, 559 579a
H, $C_{10}H_{21}$ [a]					557
CH_3, C_4H_9 [a]	111–116/30				557
CH_3, C_6H_{13} [a]	86–89.5/1.3	1.4453	25	d_4^{25} = 0.9130	555
C_6H_{11} [b]	108–111/2	1.5001	20		466, 468
$C_6H_{11}CH_2$ [b]	190–191/6	1.4925	20		466, 468
$C_6H_{11}(CH_2)_2$ [b]	115–120/2	1.4850	20		466, 468
$C_6H_{11}(CH_2)_3$ [b]	150–152/1	1.4860	20	m.p. = 16–17°	466, 468
$C_6H_{11}(CH_2)_4$ [b]	128–130/1			m.p. = 33–35°	466, 468
$CH_3O_2C(CH_2)^n$, $C_2H_5O_2C(CH_2)_8$	see section V			n = 3 and 7	407

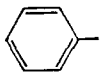
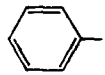
[a] Resulting from the codimerization of two different alkylketenes.

[b] C_6H_{11} represents the cyclohexyl radical.

[c] Cyclic and linear products arising from the condensation of the diketenes $O{=}C{=}CH(CH_2)_nCH{=}C{=}O$ (not isolated).[408, 409, 557, 448]

TABLE 9. Physical Properties of Dialkylketene Dimers with a β-Lactone Structure



Substituents R	Substituents R′	B.p. (°C/mm.)	n_D^{20}	Remarks	Reference
CH_3	CH_3	119.5–120/150	1.4380		431a, 462
		105–110/110			67c
		110–111/101	1.4382		462
		83–85/40	1.4381		524a
CH_3	C_2H_5	82–84/11	1.448		67c, 431a, 524a
C_2H_5	C_2H_5	121–123/24			67c
C_2H_5	C_4H_9	104–106/3			524a
				m.p. (decomp.) = 148°	400

III. Physicochemical Properties of the β-Lactones

1. Structure of the Dimer of Ketene (Historical)

The history of the establishment of this structure is summarized in Table 10 which includes only a part of the work of C. D. Hurd and his school. We have also not mentioned some of the work of G. Schroeter,[562–564] of H. Staudinger[568–571] and of others[439] who have discussed the structure of the ketene dimer incidentally without furnishing any new evidence.

A β-lactone configuration was accepted for most of the alkylketene dimers not long after that for the dimer of unsubstituted ketene.[465, 466, 475, 488, 546, 555, 567, 583, 595] Recently it has been shown that several dimers of dialkylketenes also have this structure.[462]

2. Geometry of the Molecule

Bregman and Bauer[27] have studied propiolactone by electron diffraction; Kay and Katz[496] have investigated the structure of the ketene dimer and shown it to be the β-lactone of 3-hydroxy-3-butenoic acid by X-ray diffraction. Schematic diagrams[94] showing the interatomic distances and the angles of these two compounds are given in

TABLE 10. Structure of the Dimer of Ketene (Historical)

Authors	Year	Evidence	Conclusions as to Formulas[a]			References
			Rejected	Possible	Preferred	
F. Chick & N. T. Wilsmore	1908	Reactions giving acetoacetic acid derivatives		(I)	(IV)	430
H. Staudinger & S. Bereza	1909	Analogy with the dimers of substituted ketenes[b]		(I)⇄(II)	(II)	571a
F. Chick & N. T. Wilsmore	1910	Reactions, notably with bromine			(I)	431
G. Schroeter	1916 1920	Comparison of physical and chemical properties with those of the cyclobutanediones	(I)		Aggregate	562–564
G. C. Lardy	1924	Ultraviolet spectrography	(VI)		(I)⇄(II)⇄(III)	515
C. D. Hurd, A. D. Sweet & C. L. Thomas	1933	Dimerization to dehydroacetic acid and bromination[b]			(IV)	481
W. R. Angus, A. H. Leckie C. G. LeFevre, R. J. W. LeFevre & A. Wassermann	1935	Dipole moment; molecular refraction	(I) or (III) alone	(II)[+(I)+(III)]	(II)	401
C. D. Hurd & J. W. Williams	1936	Parachor; results of pyrolysis and of ozonization	(I)	(IV)⇄(V)	(IV)	186
P. F. Gross	1936	Hydrogenation			(V) or (VI)	455
K. W. Kohlrausch & R. Skrabal	1938	Raman spectrography		(I), (II) or (III)		504
C. D. Hurd & A. S. Roe	1939	Chemical[c]			(IV)⇄(V)	479
A. B. Boese, Jr. & A. L. Wilson	1940	Halogenation; hydrogenation[c]	(IV)		(VI)	410
C. D. Hurd & J. L. Abernethy	1940	Chlorination; chemical[c]			(IV)⇄(V)	474
M. Calvin, T. T. Magel & C. D. Hurd	1941	Ultraviolet spectrography		(IV)⇄(V)	(V)	42
P. F. Oesper & C. P. Smyth	1942	Dipole moment[c]	(I), (III)	(IV), (V) or (VI)	(V)	535

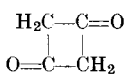
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TABLE 10 (*continued*)

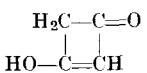
Authors	Year	Evidence	Conclusions as to Formulas[a]			References
			Rejected	Possible	Preferred	
E. C. Hurdis & C. P. Smyth	1943	Dipole moment	(I)			482
F. O. Rice & R. Roberts	1943	Results of pyrolysis[c]	(V)		(I)	554
H. Z. Lecher, R. P. Parker & R. C. Conn	1944	Bromination[b]			(IV)⇄enol	518
H. J. Taufen & M. J. Murray	1945	Raman spectrography	(I), (II), (V)		(IV) or (VI)	327
D. H. Whiffen & H. W. Thompson	1946	Infrared spectrography[c]	(I), (II), (IV)	(V), (VI) or (V)+(VI)	(VI)	588
J. T. Fitzpatrick	1947	Results of pyrolysis			(VI)	446
A. T. Blomquist & F. H. Baldwin	1948	Reaction with *N*-bromosuccinimide			(VI)	406
F. A. Miller & S. D. Koch, Jr.	1948	Infrared spectrography of the vapor	(IV), (II)	(I)⇄(V)⇄(VI)	(V)⇄(VI)	526
A. Wassermann	1948	Conductivity and potentiometry in anhydrous acetone[c]		(V) and (VI)	(VI)	582
H. J. Hagemeyer, Jr.	1949	Analogy with formation of β-lactone from ketene[d]			(VI)	141
J. D. Roberts, R. Armstrong, R. F. Trimble, Jr., & M. Burg	1949	Dipole moments; ultraviolet spectrography		(V) or (VI)	(VI)	555
C. D. Hurd & C. A. Blanchard	1950	Ozonolysis (new results)		(IV)[d] (V)[d]	(VI)	475
L. Katz & W. N. Lipscomb	1952	X-ray diffraction			(VI)	494
J. R. Johnson & V. J. Shiner	1953	Addition of deuteromethanol			(VI)	488
Y. Ikeda & T. Higashigaito	1953	Ultraviolet and infrared spectrography			(VI)	484
F. A. Long & L. Friedman	1953	Mass spectrography			(VI)	522
P. T. Ford & R. E. Richards	1955	Proton resonance			(VI)	447
J. Bregman & S. H. Bauer	1955	Electron diffraction		(V) or (VI)		27

Authors	Year	Evidence	Conclusions as to Formulas[a]			References
			Rejected	Possible	Preferred	
A. R. Bader, H. S. Gutowsky, G. A. Williams & P. E. Yankwich	1956	Nuclear magnetic resonance			(VI)	403
F. A. Miller & G. L. Carlson	1957	Infrared spectrography (new results)			(VI)	525
M. I. Kay & L. Katz	1958	X-ray diffraction			(VI)	496
A. Kawasaki, J. Furukawa *et al.*	1960	Infrared spectrography			(VI)	495

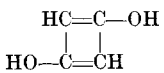
[a] Formulas:



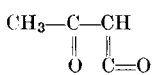
(I)



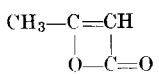
(II)



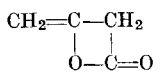
(III)



(IV)



(V)



(VI)

[b] Essentially a discussion of the literature; no new experimental facts are described.
[c] Evidence based partially on a discussion of the literature.
[d] Structure which may possibly be present in trace amounts.

Figs. 2 and 3. The ring of the ketene dimer would be planar;[27] the planarity of the propiolactone ring was only established later by Kwak, Goldstein and Simmons[238] from the microwave spectrum in the

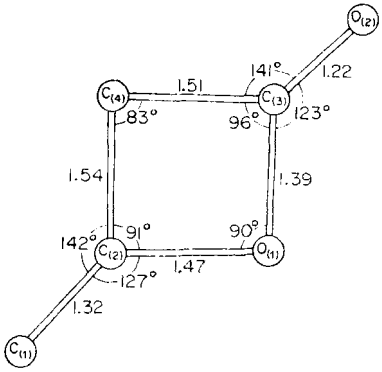


Fig. 2. Interatomic distances and angles of propiolactone.

region 18–34 kmcyc. The protons are located symmetrically on both sides of the plane of symmetry formed by the carbon and oxygen atoms.[4]

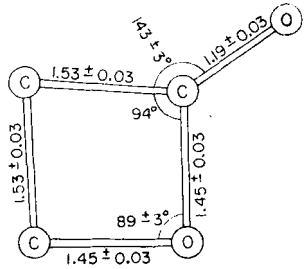


Fig. 3. Interatomic distances and angles of ketene dimer.[496]

If one assumes that the strain[161] of a cyclic molecule increases as the square of the deformation of the valence angles (section **III.4.***B*), the energy required to deform the angles of propiolactone by a total of 36° can be estimated as 25.6 cal./mole.

3. Dipole Moments

Those of propiolactone and of several ketene dimers are listed in Table 11. The calculated partial moments are in good agreement with

TABLE 11. Dipole Moments of β-Lactones

Compound	μ (Debye)	Temperature (°C)	Solvent	Author (year)	Reference
Propiolactone	3.85	30	Benzene	Miller (1953)	247, 273
	4.18		(Vapor)	Kwak (1956)	238
Dimer of ketene	3.15	25	Benzene	Angus (1935)	401
	3.30	25	Carbon tetrachloride	Angus (1935)	401
	3.31	25	Benzene	Oesper (1942)	535
	3.53		(Vapor)	Hurdis (1943)	482
	3.23	25	Benzene	Roberts (1949)	555
Dimer of methylketene	3.30	25	Benzene	Roberts (1949)	555
Dimer of hexylketene	3.58	25	Benzene	Roberts (1949)	555
Mixed dimer of methylketene and hexylketene	3.42	25	Benzene	Roberts (1949)	555

experiment and with the planarity of the structure of propiolactone.[238] The dipole moment of ketene dimer, a finite value, has frequently been cited to rule out several of the symmetrical structures which have been considered for that molecule (Table 10).

4. Spectrography of the β-Lactones

Like the other physicochemical methods, spectrography has played an important role in the establishment of the structure of the ketene dimer (see Table 10).

A. Ultraviolet-absorption Spectrum

(1) Propiolactone and its homologs. Linnell and Noyes[243] have reported that chloroform, which does not react with propiolactone under the influence of ultraviolet radiation, is the only solvent suitable for such studies; its own absorption unfortunately makes the results difficult to interpret. One can only state that the ratio between the light transmission of the solution and that of pure chloroform decreases regularly between 280 and 250 mμ. The corresponding curve for the lactone of 3-hydroxybutyric acid, which seems to be parabolic, shows a maximum at about 251 mμ.[42]

(2) Ketene dimers. Investigators, who have recently studied ketene dimer dissolved in cyclohexane[555] (see Fig. 4) or *iso*octane,[42] have not found the three maxima observed by Lardy[515] who used hexane, ether or acetone as the solvent. A single absorption maximum

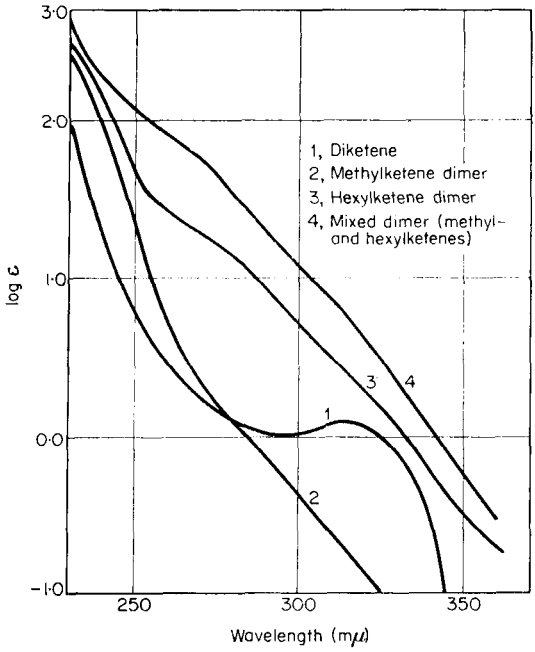


Fig. 4. Ultraviolet-absorption spectra of several ketene dimers in cyclohexane.[555]

with a small extinction coefficient was observed at 312 or 313 mμ rather than at 285 mμ;[484] one can understand this by the effect of the double bond $\rangle C{=}C\langle$ on the $\rangle C{=}O$ linkage, an effect which is transmitted through the heterocyclic oxygen atom. The absorption of the dimers of methylketene and hexylketene and the mixed dimer decreases almost continuously with increasing wavelength.[555] The disappearance of the maximum confirms the stabilizing effect of alkyl groups.

B. Infrared-absorption Spectrum

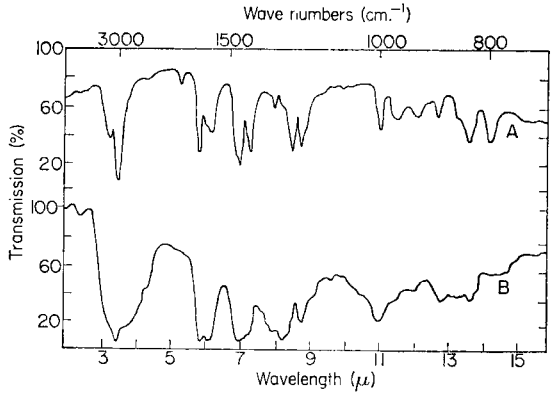
The infrared-absorption spectra of some β-lactones are shown in Fig. 5.

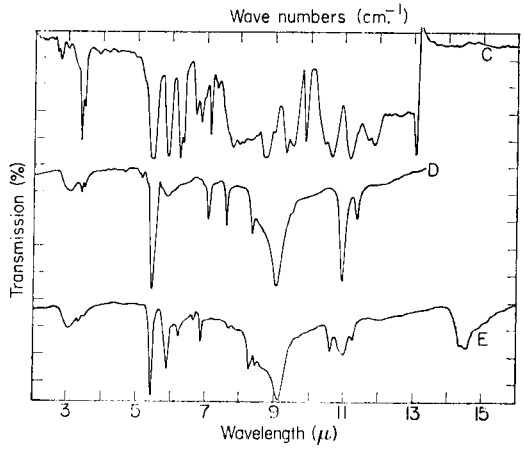
(1) Propiolactone. Linnel and Noyes[243] have observed that this spectrum, which in other respects is very simple, shows strong absorption at 1835 cm.$^{-1}$ (liquid) or at 1866 cm.$^{-1}$ (gas) corresponding to the absorption frequency of the carbonyl group; this maximum occurs about 100 cm.$^{-1}$ above that of the corresponding linear ester.[161] In general, when one compares the spectra of a series of cyclic compounds containing the same function, the displacement of frequency appears to be proportional to the deformation of the valence angles.[45b, 161] It should be noted, in this respect, that the absorption frequency of the carbonyl group in the β-lactones is near that found in the 3-oxetanones.[57] The complete infrared spectrum of propiolactone has been published by Bartlett and Rylander.[12]

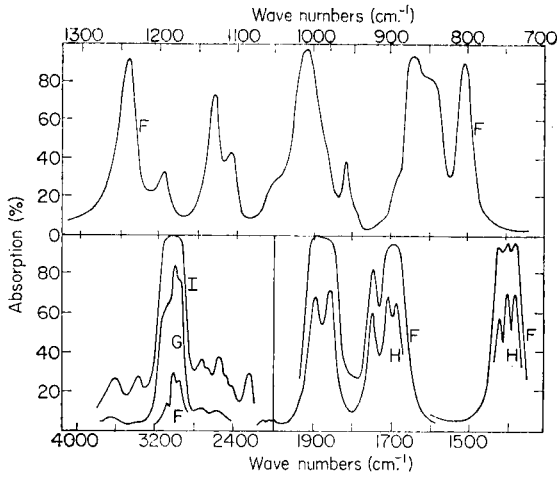
If an equimolecular quantity of methanol is added to propiolactone dissolved in 10 vol. of carbon tetrachloride, the maximum shifts from 1831 to 1834 cm.$^{-1}$ Searles, Tamres and Barrow[300] have deduced from this that the hydrogen bonding occurs principally with the oxygen atom of the carbonyl group rather than with the heterocyclic oxygen. The possibility of resonance between these two oxygen atoms is reduced when the ring is strained, a condition which limits the increase in electron density on the oxygen atom of the carbonyl group.[45b] These results are in agreement with the observed values for the dipole moment, and they explain the fact that the heat of mixing of the lactones with chloroform and the shift in the extinction band of deuteromethanol in the presence of a given lactone increase with the number of atoms forming the ring. On the other hand, the ability of the cyclic ethers to donate electrons increases with the strain of the ring.

(2) Other β-lactones. The vibration band of the carbonyl group appears at about 5.45 μ (1835 cm.$^{-1}$) for most of the β-lactones[12, 19a, 26a, 171a, 267, 295b, 300, 255a, 355, 533b] it occurs at 5.49–5.53 μ (1820–1805 cm.$^{-1}$)[30a] when the α-carbon is particularly crowded[30a, 295a, 306, 330, 331] and occasionally at 5.55 μ (1801 cm.$^{-1}$)[57, 216b] or even 5.74 μ.[358] If the substituents on the α-carbon are strongly electronegative, the absorption maximum is shifted to 5.39 μ[1] or below.[225] The Raman spectrum of the lactone of 3-hydroxybutyric acid has been published.[327]

(3) Ketene dimer (β-lactone of 3-hydroxy-3-butenoic acid). A comparison of the infrared-absorption spectra of this substance in the solid,[525] liquid[484] and gaseous[525] states confirms the existence of only one and the same structure, although the contrary seemed possible on the basis of earlier work.[526] Table 12 contains the results of infrared-


Wave numbers (cm.⁻¹)
3000
1500
1000
800
100
60
20
100
60
20
Transmission (%)
A
B
3
5
7
9
11
13
15
Wavelength (μ)


Wave numbers (cm.⁻¹)
C
D
E
Transmission (%)
3
5
7
9
11
13
15
Wavelength (μ)


Wave numbers (cm.⁻¹)
1300
1200
1100
1000
900
800
700
80
60
40
20
0
F
F
Absorption (%)
I
G
F
F
H
F
H
F
4000
3200
2400
1900
1700
1500
Wave numbers (cm.⁻¹)

and Raman spectrographic studies which have been published by various authors; those of Miller and Koch,[526] which have already been discussed by Miller and Carlson,[525] are not included, nor are those of Lord, McDonald and Slowinski[555, 525] which differ from the preceding only with respect to a double peak in the infrared around 1060 cm.$^{-1}$ instead of a shoulder at 1020 cm.$^{-1}$ The most interesting part of these spectra is the double-bond absorption region (1676–1922 cm.$^{-1}$) which has been analyzed by Miller and Carlson (Table 13). It has been stated that the vibration frequency of the carbonyl group in the ketene dimer is still higher than in propiolactone, and that this corresponds to the still greater strain of the ring. The vibration frequency of the double bond $>C=C<$, which with the pure liquid cannot be distinguished from the band immediately below it, is very high because of its exocyclic nature and of remarkable intensity.[525] The three other bands in this region, at 1689, 1744 and 1864 cm.$^{-1}$, would be due to various combinations.

The infrared spectrum of solutions of ketene dimer has also been studied. Kawasaki *et al.*,[495] who observed only four strong bands in the double-bond region in the spectrum of the liquid, found five such bands in chloroform solution. The band at about 1895 cm.$^{-1}$ in carbon tetrachloride appeared to be stronger than the band at 1865 cm.$^{-1}$, but the opposite occurred in chloroform.[588] On the other hand, the shoulder observed at 848 cm.$^{-1}$ in the liquid becomes a band at 835 cm.$^{-1}$ in carbon disulfide. These variations undoubtedly arise from molecular association.

(4) Dimers of methylketene and hexylketene and the mixed dimer. The Raman and infrared spectra of these compounds, which were investigated by Roberts *et al.*,[555] are in accordance with the β-lactone structure which was established on the basis of the chemical evidence. The $>C=O$ vibration frequency of diphenylketene dimer appears at 1850 cm.$^{-1}$ in carbon tetrachloride.[400] Three bands were observed, at 1880, 1825 and 1745 cm.$^{-1}$ in the spectra of dimethylketene dimer.[431a]

Fig. 5. Infrared-absorption spectra of β-lactones from the following acids:
A, Butyl-(2-butyl-1-hydroxy-1-methyl-2,3-butadienyl)malonic acid;
B, Butyl-(2-ethyl-1-hydroxy-1-methylhexyl)malonic acid;
C, 2-(*p*-Bromobenzoyl)-2-hydroxycyclohexanecarboxylic acid;
D, Hydracrylic acid (in CCl_4);
E, 3-Hydroxy-4-oxo-2,4-diphenylbutyric acid (in CCl_4);
F, G and I: Ketene dimer (containing a trace of acetic anhydride[525]); respectively 0.14, 0.10 and 0.25 mm of liquid;
H, Ketene dimer (in CCl_4).

TABLE 12. Spectra[b] of the Dimer of Ketene between 150 and 400 cm.$^{-1}$

Infrared			Raman		
Solid (Miller & Carlson[526])	Liquid (Miller & Carlson[526])	Liquid (Whiffen & Thompson[588])	(Taufen & Murray[527])	(Kohlrausch & Skrabal[504])	(Angus *et al.*[401])
			154(44)	149(4)	
			324(8)	324(2)	334
			444(15)	438(3)	450
			504(7)	501(1)	
			531(20)	523(3)	532
					613
			670(100)	671(8)	674
812	810 SS	805 S	803(3)	800(0)	
862, 884	840 sh	846 S	840(6)	844(1)	
	870 SS b	868 S	870(9)	864(2)	865
959	960 S	957 m	951(3)	951(0)	
		986 w	986(10)	984(2)	984
1024	1011 SS b	1009 S	1017(4)	1016(1)	
1060	1050 m	1055 w			
1115	1100 m	1106 m	1104(1)	1099(1)	1104
1143	1130 w	1130 m[a]			
1173	w				
1196	1193 m	1194 m			1185
1247	1237 SS b	1239 S			
					1270
				1313(0)	
1365	1347	1375 m	1374(20)	1373(3)	1374
1396	1391 S	1393 m			
1416	1408	1417 m			
1458–1474	1463 m				
1520	1517 w				
	1538 w				
1555	1555 w				1547
1572	m				
	1689 SS	1685 S	1689(10b)	1686(11)	
1704	b	1705 S			1721
	1744 m	1745	1760		
			1791		
1847	1864 SS	1865 S	1859(20)	1856(3)	
1886	1897 SS b	1895 S	1896(14)	1891(2)	1888
1946	1957 sh				1933
2030	2010 m	2010 w			
		2040 w			
2079	2073 m	2110 w			
2222	2213 w	2230 w			

(*Table continued*)

TABLE 12 (*continued*)

Infrared			Raman		
Solid (Miller & Carlson[525])	Liquid (Miller & Carson[525])	Liquid (Whiffen & Thompson[588])	(Taufen & Murray[327])	(Kohlausch & Skrabal[504])	(Angus *et al.*[401])
2348	2337 m	2420 ww			
		2480 ww			
		2560 w			
		2660 ww			
		2710 w			
		2970 m	2958(61)	2966(10b)	2962
3020		3010 m	3019(43)	3019(10b)	3019
3065	3075 } m	3082 w	3072		
3181	3163 }		3127	3131	3127
				3213 (b)	
		3370 w			
		3620 w			

[a] Probably re-enforced by the presence of an impurity.

[b] Remarks:

Intensity: SS, very strong; S, strong; m, medium; w, weak; ww, very weak. Band: b, broad; sh, shoulder.

The broad bands around 1704 and 1875 cm.$^{-1}$ should be resolved by a study of thin layers (see Table 13). The studies of Whiffen and Thompson[588] indicate the possibility of infrared bands (liquid) at 893, 914 and 946 cm.$^{-1}$ Kawasaki *et al.*[495] have observed four strong bands in the spectrum of ketene dimer liquid (at 1675, 1727, 1848 and 1883 cm.$^{-1}$) in the double-bond absorption region.

C. Nuclear Magnetic Resonance

(1) Propiolactone. This spectrum, which was determined by Anderson,[4, 94c] is in accordance with the presence of two equivalent groups of protons each of which consists of two protons. If one selects an initial wave function which preserves the symmetry of the molecule, one cannot establish the presence of additional lines in the spectrum. Three other β-lactones have been studied.[140, 235b]

(2) Dimer of ketene. Bader *et al.*[403, 447] observed two lines of equal intensity both of which are due to CH_2 groups; this confirms the structure as that of the β-lactone of 3-hydroxy-3-butenoic acid.[529a] For the β-lactone of 3-hydroxy-2-butenoic acid, there would be two

TABLE 13. Attribution of Bands of Strong Intensity between 1676 and 1922 cm.$^{-1}$ in the Spectrum of Ketene Dimer[525]

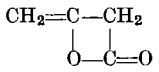
Vapor between 40 and 180°			Solution in CCl_4			Liquid at about 25°	
Wave number (cm.$^{-1}$)	Intensity[a]	Attribution[b]	Wave number (cm.$^{-1}$)	Intensity[a]	Attribution[b]	Wave number (cm.$^{-1}$)	Intensity[a]
1676	S	2 × 838 = 1676 803 + 887 = 1690 670R + 1007 = 1677	1675	S	2 × 840 = 1680 804 + 875 = 1679 670R + 1006 = 1676	1689	SS (broad)
1720	SS	Vibration $\rangle C{=}C\langle$	1708	SS	Vibration $\rangle C{=}C\langle$		
1776	m	2 × 887 = 1774	1752	S	2 × 875 = 1750	1744	m
1875	S	887 + 1007 = 1894[c]	1867	S	875 + 1006 = 1881[c]	1864	SS
1922	SS	Vibration $\rangle C{=}O\langle$	1900	SS	Vibration $\rangle C{=}O$	1897	SS

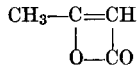
[a] Intensity: SS, very strong; S, strong; m, medium.

[b] Raman frequency.

[c] Fermi resonance with the vibration $\rangle C{=}O$.

proton-resonance lines, one of intensity 3 due to the CH_3 group and the other of intensity 1 due to the CH group:





Anet[400] recently published the nuclear-magnetic-resonance spectrum of the β-lactone dimer of diphenylketene.

D. Mass Spectrum

(1) Propiolactone. Friedman and Long,[93] who studied this spectrum, found ions of mass 14–55 (Table 14). The absence of ions of

TABLE 14. Mass Spectrum of Propiolactone[93]

Mass	Relative intensity of the ion	Corresponding fragment
14	20.1	CH_2
15	30.5	CH_3
18	2.9	
26	16.5	C_2H_2
27	11.8	C_2H_3
28	64.2	C_2H_4; CO
29	19.2	HCO
41	4.0	C_2HO
42	100.0	C_2H_2O
43	31.7	C_2H_3O
44	5.5	CO_2;C_2H_4O
55	1.8	C_3H_3O

mass 72 corresponding to propiolactone itself confirms the instability of the β-lactone structure. On the basis of these results the authors arrived at the following conclusions. The two most intense peaks are those resulting from cleavage of two opposite linkages in the ring; for example, the fragment $C_2H_2O^+$ of mass 42, and the fragment $C_2H_4^+$ of mass 28 (part of this peak can just as well be attributed to the fragment CO^+). The ionic radicals thus formed rearrange into more stable ions with an even number of electrons: CH_3^+ (from CH_2) of

mass 15, and $C_2H_3O^+$ of mass 43. The peak at mass 29 can only represent the ion HCO^+ (from the dissociation of H_2CO^+); those of mass 26 and 27 result from the dissociation of the ion $C_2H_4^+$. That the bonds next to the methylene groups have some tendency to break is shown by the moderate intensity of the peaks of mass 14 and 15.

(2) Dimer of ketene. The mass spectrum of the dimer of ketene has been studied by the same authors[522] (Table 15). These cleavages

TABLE 15. Mass Spectrum of the Dimer of Ketene[522]

Mass	Relative intensity of the ion	Corresponding fragment
12	1.3	C
13	3.7	CH
14	14.5	CH_2
15	4.9	CH_3
24	0.4	C_2
25	2.7	C_2H
26	11.5	C_2H_2
27	9.8	C_2H_3
28	19.9	$CO;C_2H_4$
29	3.9	COH
36	1.0	C_3
37	6.1	C_3H
38	8.3	C_3H_2
39	16.9	C_3H_3
40	16.2	$C_3H_4;C_2O$
41	3.4	C_2HO
42	100	C_2H_2O
43	11.7	C_2H_3O
44	2.9	$CO_2;C_2H_4O$
56	19.2	$CH_2—CH_2—C=O$
57	1.1	
60	0.5	
69	0.5	
84	5.2	Ketene dimer

occurred under conditions entirely comparable to those employed in the study of propiolactone. The high intensity of the peaks of mass 42 and 14 in comparison with that of mass 15 was interpreted as evidence in favor of the accepted structure (see formulas at the end of Table 10).

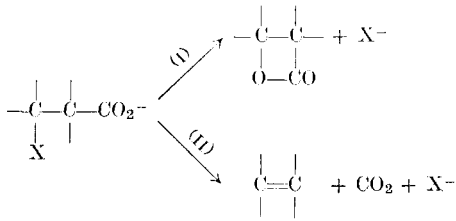
IV. Preparation of β-Lactones

Until recently only two methods were available for obtaining the β-lactones: cyclization of the salts of β-halo acids and the reaction of the ketenes with aldehydes or ketones. Other procedures of more-or-less general applicability have been published recently.

1. From Salts of β-Halo Acids

A. Aqueous Medium

The salts of β-halo acids in aqueous solution or in an ionizing medium decompose according to the following schemes:

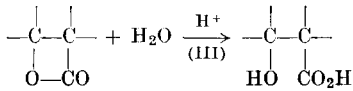


Since it was known that the thermal decomposition of the β-lactones yields an ethylene hydrocarbon and carbon dioxide, the appearance of these products during the neutralization of the β-halo acids[14, 90, 286, 357] was at first attributed to the degradation of an intermediate lactone.[70,80]

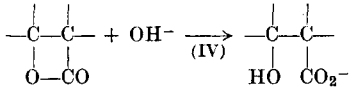
Later on it appeared that the two types of reaction, (I) and (II), take place simultaneously and independently;[213] the mechanism of the formation of the ethylene hydrocarbon has been elucidated.[139,229,280,363] Several authors have published monographs on this subject.[5, 139, 218]

(1) Factors influencing the yields of β-lactones. In practice, the salt to undergo cyclization is prepared *in situ* from the β-halo acid and an alkaline reagent—an oxide, hydroxide or metal carbonate, occasionally potassium acetate.[334] Several factors affect the yield of β-lactone which one can hope to obtain.

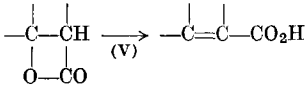
The pH of the medium in which the reaction takes place must be carefully adjusted.[159, 210–213] Excessive acidity can accelerate hydrolysis of the lactone:

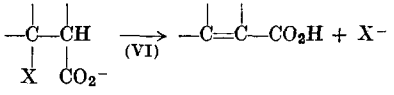


whereas with alkaline a medium, the yield of lactone is reduced by saponification:



and at the same time, if the nature of the substituents permits, by the formation of the α,β-unsaturated acid by the two side reactions (V) and (VI):





The synthesis is usually carried out at room temperature, never above 50°, as the rate of the side reactions, such as hydrolysis (III), tends to increase more rapidly with increasing temperature than that of the desired reaction.[159]

The length of time in which the β-lactone is in contact with the reaction medium must be controlled, not only because the lactone hydrolyzes by reaction (III) but also because reaction (I), by which the lactone is formed, is reversible. Since reaction (II) is irreversible, one would finish (owing to displacement of the equilibrium) with the ethylene hydrocarbon and carbon dioxide as the only end-products. For this reason, the soluble lactones must be rapidly extracted with a solvent which is not miscible with water. The chlorinated hydrocarbons of high density are more convenient to use than ether,[212, 296] a finding which has led to the rather general procedure described by Hagman.[159, 71] If the extraction is difficult, which is true for propiolactone itself[210] and for other lactones with a carboxyl group,[5,79,177,178,230,230a] it may be worthwhile to use a silver salt to render reaction (I) irreversible, and possibly to work in a non-aqueous medium (section **IV.1.***B.*).

(**2**) **Kinetics.**[139] During the decomposition of a salt of a β-halo acid in aqueous solution, it is easy to follow the concentration of halogen ion formed by potentiometry or by simple argentometry.[159,211,239] Thus one can determine the overall kinetics of reactions (I), (II) and (VI), all of which yield the ion X^-, without,

however, being able to draw any conclusions concerning reaction (I) alone. In this way Simpson[310] has shown that sodium β-chloropropionate in aqueous solution at 70° decomposes much less rapidly than its bromo and iodo homologs. Other authors[159, 212, 213, 239, 280, 282, 356] have discussed the effect of hydrocarbon substituents on reaction rates.

With an α,α-disubstituted β-halopropionic acid, reactions (V) and (VI), which require the presence of at least one hydrogen atom on the α-carbon, are impossible. Then only reactions (I) and (II) are responsible for the formation of ion X^-. If by measuring the carbon dioxide liberated one can determine the part of X^- due to reaction (II), the kinetics of the formation of the lactone can be determined from the rate of appearance of ion X^-. This was done by Johansson[212] and Hagman[159] and more recently by Fischer and Etienne.[71, 86] It is necessary to work with a neutral buffered solution as the rate of reaction (I) is sensitive to variations of pH.[212] The proportion of the secondary reaction (II) is practically negligible in the cases studied. With the α,α-dialkyl-β-halopropionates, the more crowding are the α-alkyl groups, the more rapid is the cyclization.[86] The experiments were largely concerned with the β-bromo acids; the cyclization of the salts of the β-chloro acids, which have been studied, is considerably slower; β-chloropivalic acid cannot be used for the preparation of α,α-dimethyl-β-propiolactone[86] as there is loss by hydrolysis [reaction (III)] owing to the very long half-time of the reaction. However, 2-chloromethyl-2-ethylhexanoic acid, which is very crowded, cyclizes at a reasonable rate so that it can be used to obtain the corresponding β-lactone in a 70% yield.[72]

For the preparation of α,α-diphenyl-β-propiolactone, which is completely insoluble in water and therefore does not undergo hydrolysis [reaction (III)], the β-chloro acid gives the highest yield[361] although the reaction is much slower.

B. Non-aqueous Medium

Etienne, Soulas and René[73] have tried to cyclize β-halo acids in ionizing media other than water; the salt was prepared *in situ* with potassium carbonate. Only methyl ethyl ketone gave acceptable yields which, however, were lower than those obtained in an aqueous medium.

Certain β-lactones, notably those with a carboxyl group in the β-position,[218] have been prepared by the action of moist silver oxide on the corresponding β-bromo acid in ether solution; aqueous sodium

carbonate cannot be used. This procedure was used to synthesize ^{14}C-labeled propiolactone.[354]

A few lactones, with at least one halomethyl group in the α-position, have been obtained by dry distillation of the corresponding (finely-powdered) silver salt.[291, 339, 72] On the other hand, an aqueous solution of alkali 3-chloro-2,2-bis(chloromethyl)propionate does not give the β-lactone, but tends to become acidic with time and to deposit a polymer.[72]

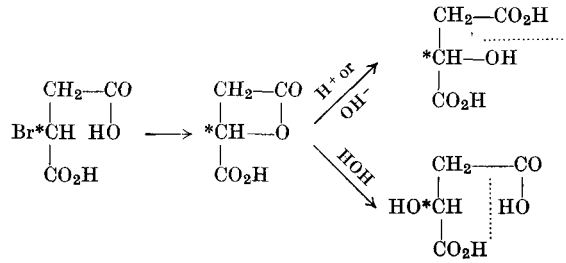
However, most of the β-halo acids, which readily give lactones in aqueous solution, on treatment with alkali carbonate yield little or no lactone if the silver salt is heated alone or stirred with ether.[296]

β-Propiolactone is formed when silver isocyanate is reacted with trimethylsilyl 2-bromopropionate.[21a]

C. Stereochemistry of the Cyclization of the Salts of β-Halo Acids

The intermediate formation of β-lactones plays an important role in the Walden inversion which occurs in various reactions of the optically active β-halo acids.[47, 282, 363] Several of these reactions have been subjected to thorough investigation: the hydrolysis of the halosuccinic acids to malic acid,[7, 173–180, 252, 293, 347–349] of the β-halobutyric acids[84, 282, 283] (section **VI.5**), of the bromophenylpropionic acids,[301, 269] of the 2-bromo-2-(*p*-bromobenzoyl)cyclohexanecarboxylic acids,[12, 227] of 3-benzoyl-3-bromo-2-phenylpropionic acids,[12,21,226,228, 229] and also the action of amines on halosuccinic acids[83, 252–255, 349] and on other β-halo acids,[269, 301] and the reaction of the alkali xanthates with halosuccinic acids.[176]

According to Holmberg,[180] the pH of the solution is the only factor which can determine the nature of the optical antipode of a hydroxy acid formed from a halo acid. Contrary to what Walden had suggested, the only effect of silver oxide would be to facilitate the formation of the β-lactone.[174, 175] For example, the hydrolysis of

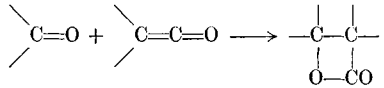


l-bromosuccinic acid always occurs through the intermediate β-lactone of *d*-malic acid.[173, 177] In basic or acidic solution, cleavage of the ring of this lactone occurs between the carbon of the carboxyl group and the lactone oxygen; the *d*-isomer is obtained.[174] In a neutral medium, the elements of water enter between the asymmetric carbon and the lactone oxygen to give the *l*-isomer.[174]

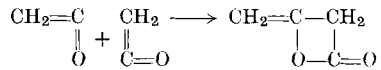
Winstein and Grunwald[356] have discussed the mechanism of the closure of small rings, which explains the optical inversion which occurs on the conversion of a β-halo acid into the β-lactone. In accordance with this mechanism, only the *trans*-form of a 2-halocyclohexanecarboxylic acid can give a β-lactone.[12, 21] One of the two optical isomers of a β-halo acid can form a β-lactone[228] much more rapidly than the other[229] and with a higher yield.[159]

2. From Ketenes and Carbonyl Compounds

In 1911 Staudinger and Bereza[316] found that diphenylketene reacts with carbonyl compounds to give β-lactones.[29] Kung[234] in 1944 showed that ketene itself reacts in this way providing a catalyst is present, as Hurd and Thomas[185] had suggested.



The spontaneous dimerization of ketene, which was described as early as 1910, is only a particular case of this general reaction; the β-lactone structure of the ketene dimer, however, was not recognized until much later:[410]



The preparation of ketene dimers which have a β-lactone structure is treated in section **V**.

A. Aliphatic Ketenes

(1) Catalysts. Hagemeyer[141] has discussed the catalysts to be used for the preparation of a β-lactone by the addition of ketene to an aldehyde.

In the absence of a catalyst, except in the special case of glycidaldehyde,[323a] an α,β-unsaturated ketone is formed:

$$2\ CH_2{=}C{=}O + RCH_2CHO \longrightarrow RCH_2CH{=}CHCOCH_3 + CO_2$$

The reaction probably takes place through the ketene dimer; it is discussed in section **VII.**

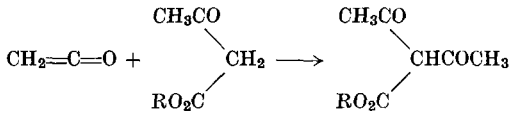
In an acid medium, particularly with the lower aldehydes, this reaction gives the acetate in the enol form:

$$CH_2{=}C{=}O + RCH{=}CHOH \longrightarrow RCH{=}CHOCOCH_3$$

In the presence of potassium acetate,[48a, 185, 186] ketene reacts with aromatic aldehydes to give a little β-lactone, but the principal product is a mixed anhydride. It has been definitely shown[186] that this anhydride does not come from the reaction of ketene with the lactone which may be formed in a first step:

$$ArCH{=}O + 2\ CH_2{=}C{=}O \longrightarrow ArCH{=}CH{-}CO{-}O{-}CO{-}CH_3$$

In regard to the enolic ketones,[19a, 141] they form the acetates in their enol form equally well in acid medium; the β-diketones and the β-keto esters, in the presence of metals or bases, give compounds with an acetyl group on the carbon atom of the active methylene group:

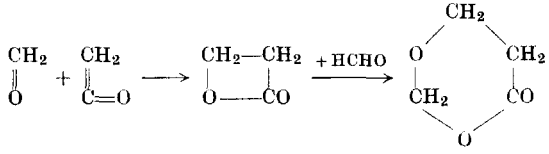


Salts which are strongly acid in aqueous solution and compounds which are able to form co-ordination complexes with the hydroxyl groups, are good catalysts for the formation of β-lactones except when they are insoluble in the reaction medium.[141]

The zinc salts have been widely used for this purpose: chloride,[19a, 141, 151, 152, 158, 167a, 234, 322] perchlorate,[32] nitrate,[34] thiocyanate,[33] trifluoroacetate,[40] fluophosphate,[37] fluoborate,[145] as well as the boron compounds boric acid,[150, 152, 158] boron acetate,[152, 158] borate esters,[150, 152] boron trifluoride[25, 26, 36, 46b, 166] or its ether complex[46a, 142, 144, 147, 151, 157, 158, 234, 295a] and metal fluoborates,[145] and the aluminum compounds aluminum chloride alone[26, 36] or in a mixture (*e.g.* with zinc salts[319, 320, 346]), alumina,[41] and aluminum silicate.[91, 360]

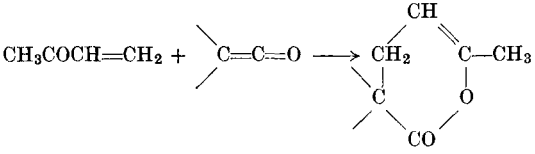
Salts of magnesium,[32] cadmium,[37] cobalt,[32, 37] mercury[26, 146, 149] and uranium,[38] phosphate esters,[143] various salts of organic acids[149, 153, 155, 185] and even organic peroxides[10] have likewise been proposed as catalysts.

With formaldehyde (which is very reactive as it gives the lactone in a 7% yield even in the absence of a catalyst) or the lower aldehydes, one must not use too active a catalyst which would bring about polymerization of the lactone and dimerization of the ketene, especially if the reaction is run as a continuous process in the absence of a solvent.[141] A small amount of 1,3,4-dioxanone can also be formed:



The ketones are less reactive, as is shown by the fact that they can be used as solvents for the addition of ketene to formaldehyde or acetaldehyde;[234] they will react with ketene only in the presence of more powerful catalysts.[363]

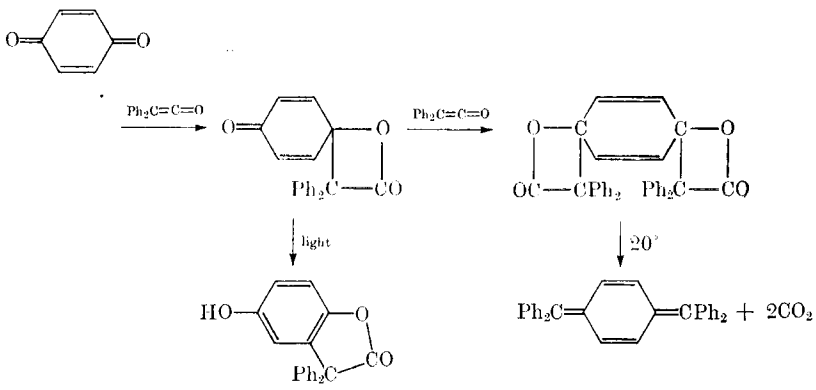
(2) Other factors. The reaction with aldehydes usually takes place between 0 and 15° in a solvent such as ether or acetone in the cases mentioned above, or in β-lactone itself if the process is continuous.[157, 319, 322] Cyclohexanone reacts in ether solution between −10° and 0°.[295a] For the reaction with other ketones, which if present in excess serve as the solvent, ketene is often added at room temperature. This is true also for the quinones.[74, 152] Cornforth[46a] studied the stereoselectivity of the addition of ketene to 3-chloro-2-butanone.



Methyl vinyl ketone and some unsaturated aldehydes[145, 151] react with ketene to give only a δ-lactone[359] in the absence of a catalyst; some δ-lactone is formed even in the presence of a substance which favors the formation of β-lactone.[141]

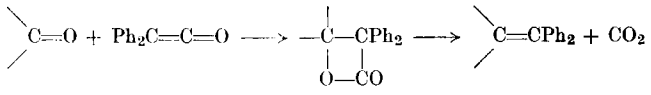
B. Diphenylketene

Staudinger[313–316] has shown that benzoquinone in ether solution adds diphenylketene at room temperature in the absence of light to give a monolactone (72% yield); if the ketene is present in excess, the dilactone formed is decarboxylated spontaneously to give a hydrocarbon.



The other quinones react in a comparable way. The mono-β-lactones obtained rearrange to give γ-lactones in the light;[316, 298] *o*-benzoquinone,[69] however, gives a γ-lactone directly, even if the reaction occurs in the dark. If one of the carbonyl groups is crowded, the reaction at room temperature in the presence of an excess of diphenylketene will not go beyond the monolactone stage. If both carbonyl groups are crowded, the reaction only takes place at a higher temperature and yields the decarboxylation product of the dilactone directly.[313]

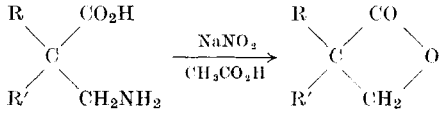
The aldehydes, except for benzaldehyde,[313] and the ketones, except for benzophenone, are alike in respect to their reaction with diphenylketene.[315, 318] For convenience diphenylketene is used in the form of the quinoline complex which dissociates above its melting point; the reaction, therefore, is run at 120–160°, and under these conditions only the ethylene hydrocarbon resulting from the decomposition of the β-lactone can be isolated:[314]



Sometimes only the liberation of carbon dioxide is observed.[318] An aldehyde or a β-unsaturated ketone will usually react with diphenylketene to give a δ-lactone.[317]

3. By Diazotization of α,α-Dialkyl-β-aminopropionic Acids

Testa and his collaborators[328–330b] have recently shown that the diazotization of an α,α-dialkyl-β-aminopropionic acid at about 0° in acetic acid gives the corresponding β-lactone and not the hydroxy acid:



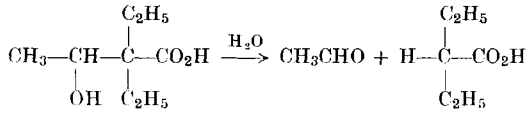
If the β-lactone does not separate spontaneously, it is extracted with ether. An optically active acid gives a lactone of opposite rotation.[329] This method, which is also useful if one of the R groups is aromatic, seems to have been tried only for the preparation of β-lactones which are substituted in α-position.

4. From β-Hydroxy Acids

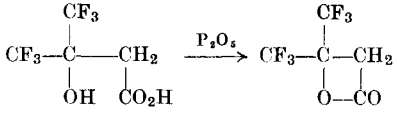
Several methods have been developed recently for preparing β-lactones from β-hydroxy acids; whether these methods are generally applicable cannot be decided at this point as they have only been used in special cases.

A. Direct Dehydration of β-Hydroxy Acids

Unless lactonization with ring enlargement occurs,[30a, 167] the direct dehydration of β-hydroxy acids[24] usually yields: (*a*) either an α,β-unsaturated acid or its decarboxylation products[80, 85, 336] if there is at least one hydrogen atom on the α-carbon; (*b*) either a polyester[2,22,362] or the products resulting from cleavage of the bond between the α- and β-carbons[24, 214, 296, 297] if the α-carbon is completely substituted:



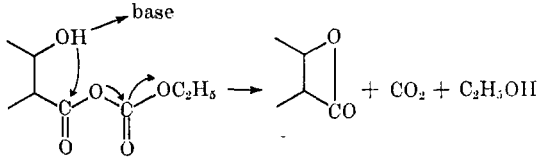
Although the intermediary formation of β-lactones from β-hydroxy acids has been accepted in order to explain some reactions,[80,85,222,256,336,342] it cannot be said to be the general case;[296,363] in the presence of electronegative substituents, ring closure does occur:[225,260]



However, on recrystallization from acetic anhydride, 5-hydroxycamphoric acid gives the corresponding β-lactone directly,[335a] and a similar compound[335b,171a] is lactonized by acetyl chloride at room temperature.

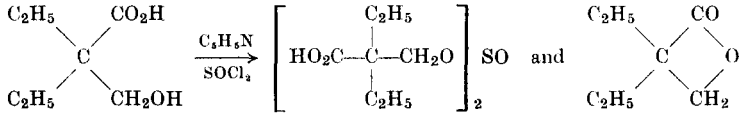
B. Reaction of Yohimbic Acid with Ethyl Chloroformate

When yohimbic acid is treated with excess of ethyl chloroformate in pyridine solution* at room temperature, a β-lactone is formed (yield, 37%).[57] This reaction is interpreted as confirmation for the *cis* position assigned to the carboxymethyl and hydroxyl groups of yohimbine:



C. Reaction of 2-Ethyl-3-hydroxymethylbutyric Acid with Thionyl Chloride

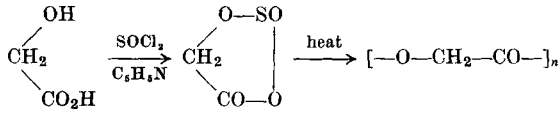
When a cold benzene solution of 2-ethyl-3-hydroxymethylbutyric acid containing pyridine is treated with thionyl chloride, the chief product is a sulfite ester, but a β-lactone is also isolated in an 8.5% yield:[331]



* *Cf.* the formation of the β-thiolactones (section **X.4**).

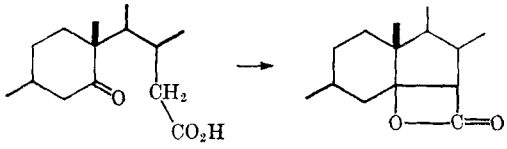
With 2-hydroxymethyl-2-phenylvaleric acid, 5.3% of lactone is formed and the sulfite ester cannot be isolated.

These two reactions (*B* and *C*) can be compared to the formation of cyclic anhydro carbonates or sulfites from α-hydroxy acids; these cyclic derivatives decompose to give α-lactone polymers:



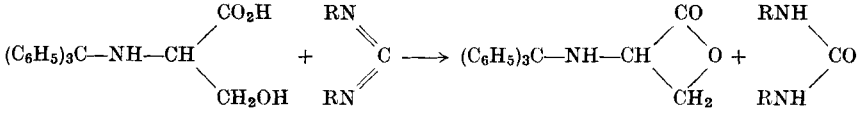
D. Reaction of Keto Acids of Steroids with Benzoyl Chloride and Pyridine

On reaction with benzoyl chloride and pyridine, some keto acids of steroids give a β-lactone, and thus two new rings appear in the molecule.[26a, 216c, 295c] It can be assumed that an acid chloride and then a ketene are formed as intermediates; the ketene group can react with the carbonyl group:



E. Dehydration of N-(*Triphenylmethyl*)-L-*serine*

N-(Triphenylmethyl)-L-serine gives a crystalline β-lactone in 15% yield upon dehydration with *N*,*N*′-di*iso*propylcarbodiimide:



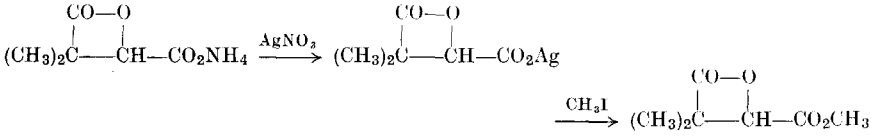
The direction of optical rotation is the same for the acid and its lactone.[306] This process has been used[30a] with 3-hydroxy-2,3,4,4-tetramethylvaleric acid.

5. By Chemical Transformation of a Compound containing a Pre-existing β-Lactone Ring

This is an exceptional case in view of the ease with which the β-lactone ring opens under the influence of the most varied reactions.

A. Transformation of β-Lactones with a Functional Group

β-Lactones containing an acid group can give salts and esters:[285, 335a, 358]

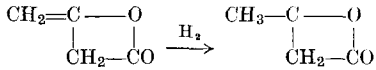


or even undergo decarboxylation.[358]

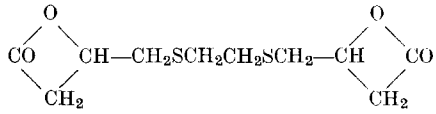
β-(2-Quinolyl)-β-propiolactone, as a result of its amine function, gives a picrate and a chlorohydrate;[67] the keto-β-lactones yield phenylhydrazones.[313]

B. From Ketene Dimer

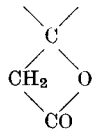
Ketene dimer can be hydrogenated to β-butyrolactone;[3, 141, 154, 189, 311] too extensive reduction gives butyric acid:[36, 154]



It adds thiols in the presence of substances which initiate the formation of free radicals. Thus with ethanedithiol it forms:[332]



Ketene dimer, by virtue of its double bond, can participate in copolymerizations[45, 200, 352, 449a, 533b] with vinyl, acrylic and diene monomers. The β-lactone ring is retained in the macromolecule which contains the units:

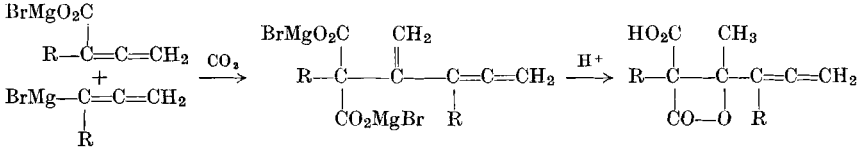


The hydrogenation of other unsaturated β-lactones has been described.[67b, 358]

6. Miscellaneous Methods

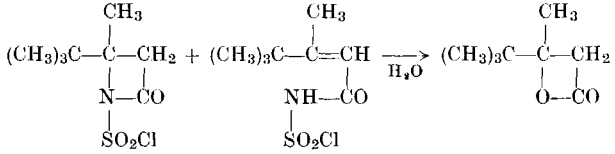
A. Cyclization of Carbonylated Organomagnesium Derivatives of Primary Propargyl Bromides

Wotiz and Matthews[358] found a lactone acid among the products resulting from the uptake of carbon dioxide by organomagnesium derivatives of primary propargyl bromides. They attributed its formation to a series of reactions terminating in the cyclization of a β,γ-unsaturated dicarboxylic acid:



B. Hydrolysis of the Products of Reaction between Trimethylbutene and N-Carbonylsulfonamidyl Chloride

The β-lactone of 3-hydroxy-3,4,4-trimethylpentanoic acid has been obtained by hydrolysis of the products resulting from the addition of trimethylbutene to *N*-carbonylsulfonamidyl chloride:[94b]

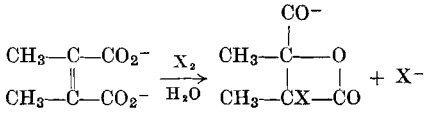


C. Steam-Distillation of 2-Bromomethyl-2-ethylhexanoic Acid

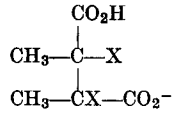
When a sample of technical 2-bromomethyl-2-ethylhexanoic acid, prepared by the nitric acid oxidation of 2-bromomethyl-2-ethyl-1-hexanol, is steam-distilled, a trace of α-butyl-α-ethyl-β-propiolactone is found in the distillate.[72] The formation of a β-lactone in a strongly acid medium is exceptional.

D. Reaction of Chlorine or Bromine with an α,β-Dimethylmaleate

When chlorine or bromine reacts with a salt of α,β-dimethylmaleic acid[326] in aqueous solution, a β-lactone is formed in a yield of 41 or 33% respectively:



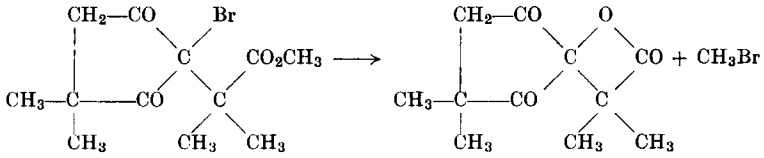
It has not been possible to prepare this lactone by direct cyclization of the β-halo acid:



which eliminates the halide ion only after 24 hr., whereas the preceding reaction takes place in a few minutes. Under the same conditions, dimethylfumaric acid gives an isomer of this β-lactone.

E. Ring Closure of Methyl 1-Bromo-α,α,3,3-tetramethyl-2,5-dioxocyclopentaneacetate

Methyl 1-bromo-α,α,3,3-tetramethyl-2,5-dioxocyclopentaneacetate, in which the halogen atom is activated by two adjacent carbonyl groups, undergoes ring closure merely on heating:[334]



F. Reaction of Acetic Anhydride with Mesoxalonitrile

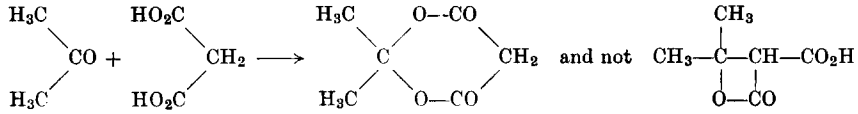
The compounds produced by the reaction of acetic anhydride with Mesoxalonitrile[260] would be the β-lactone of 3,3-dicyanohydracrylic acid.[1]

G. From 3-Benzyloxypropionic Acid and Thionyl Chloride[24a]

H. Reactions Giving Compounds now Known not to be β-Lactones

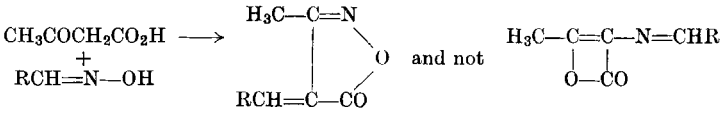
Some compounds which were originally believed to be β-lactones do not have this structure.

The condensation of aldehydes or ketones with malonic acid or alkylmalonic acid[218, 221, 270–272, 284, 285, 308, 309, 340–344, 353] or their derivatives[59] gives a diketodioxane:[53, 67b, 183]

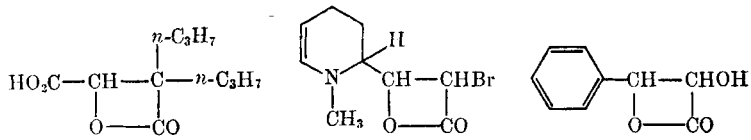


Citraldehyde under certain conditions gives a tricyclic dilactone[20] which does not contain a β-lactone ring.[140, 345]

The reaction of the aldoximes with the esters of β-keto acids yields, not unsaturated β-lactones,[274, 275] but 4-arylidene-5-*iso*oxazolones:[60]



The structure of three other 'β-lactones' which have been reported in the literature[6, 63, 68] has been questioned[363] or ruled out.[242, 58, 70]



7. Purification and Determination of Propiolactone

The principal impurities in technical propiolactone prepared from ketene and formaldehyde are ketene dimer and acetic anhydride.[208] These compounds favor the rearrangement of propiolactone during distillation to acrylic acid.[89] The methods of purification which have been proposed comprise either the injection of water[89] or alcohol,[106] or the removal of the acidic products by washing with dilute sodium hydroxide[208] preceded by instantaneous vaporization. These purification procedures require rigorous precautionary measures as propiolactone itself can participate in the reaction. Water can be removed with isocyanic esters.[42]

The determination of propiolactone with thiosulfate has been described by Tyler and Reesing;[337] it cannot as a rule be applied to the homologs (see section **VI.4.***C*). The determination of acrylic acid with a mixture of potassium bromate and bromide and that of the total acidity by direct titration with sodium methylate in anhydrous methanol have been discussed in the booklets edited by members of the Celanese Corporation of America. They recommend mass spectrography for the evaluation of the lactone content of commerical products and for the detection of certain impurities.

Propiolactone must be stored under cool conditions (0°) in the dark in the presence or absence of a stabilizer; the greatest care must

be exercised to prevent contact with a compound capable of initiating an explosive polymerization (see section **VIII**).

Tetramethylcyclobutanedione is removed from the β-lactone of 2,2-dimethylhydracrylic acid by partial hydrogenation.[167b]

V. Preparation of Ketene Dimers having a β-Lactone Structure

1. Unsubstituted Ketene

In 1908 Chick and Wilsmore,[595] independently of Staudinger and Klever,[574] noticed the tendency of ketene to polymerize under certain conditions to form a liquid dimer which boiled at about 127° under atmospheric pressure. The structure of this dimer was the subject of an extremely long and often impassioned discussion which is not solely of historical interest. As the configuration of the β-lactone of 3-hydroxy-3-butenoic acid was not definitely established until 1946,[459] most of the mechanisms published before that date concerning the formation and properties of ketene dimer must be revised. Since liquid ketene dimerizes spontaneously in the neighborhood of its boiling temperature[553, 554] and ketene vapor dimerizes reversibly above 400°,[593] the dimer has been noted by most of the authors who have worked with the monomer,[436, 531, 532] and it is not practical to give an exhaustive bibliography for this compound.

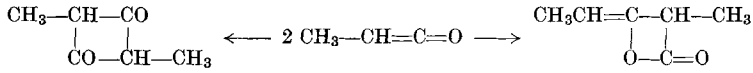
Several industrial procedures[529, 589] have been described which bring about the dimerization of ketene with a high yield, or which can be operated as continuous processes; it is necessary, in general, to keep the temperature and the monomer concentration of the medium within certain limits. Acetone[451, 592] is a convenient solvent for the dimerization, which is catalyzed by metals or bases, for ketene monomer is often recovered in acetone solution[462b, 517, 533] owing to the method of preparation; the dimer itself,[579] possibly diluted with acetic anhydride,[511a] is an interesting medium especially for a continuous process.[561, 537, 530] The use of acid catalysts has been described.[530]

Rice and Greenberg[553] found that the dimerization of ketene in solution is bimolecular; the rate increases with the dielectric constant of the solvent and does not seem to be affected by the presence of oxidants or antioxidants.

2. Alkylketenes ('Aldoketenes')

Some of the lower monoalkylketenes like methylketene[595] can dimerize in two ways to yield either a symmetrical cyclobutanedione or the β-lactone of a β,γ-unsaturated acid:[487, 488]

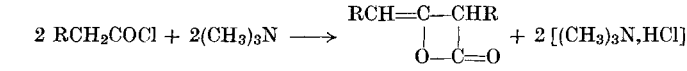
On the basis of spectrographic studies[555] and investigations with labeled elements, pyrolysis,[546] hydrogenation[464, 465] or cleavage with ozone,[466, 475] it is now established that the β-lactone structure is much



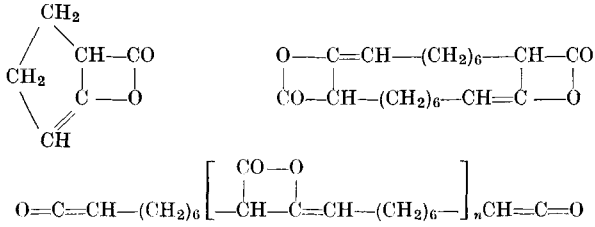
The melting point is 140°.[575] Liquid[595]

more frequent than the symmetrical structure for the dimers of the other alkylketenes.[552] The conditions of dimerization can influence the structure of the product; the dimerization can yield a mixture of the two isomers, not to mention the isomers due to the presence of several asymmetric carbon atoms. With phenylketene and some others[568, 571, 576] the problem does not seem to have been definitely solved. Owing to the presence of a catalyst or to a favorable temperature, several methods[422, 423, 467, 477, 527, 566] which were expected to give an alkylketene yielded only the dimer.

The most general method for preparing the dimers of the alkylketenes, and possibly the mixed dimers,[529, 555, 557] consists of treating an acid chloride with a carefully selected tertiary base.[401a, 559, 541, 584] It is often claimed that the amine hydrochloride formed catalyzes the dimerization of the alkylketene, but one can think of mechanisms[400] by which the dimer would be formed directly:



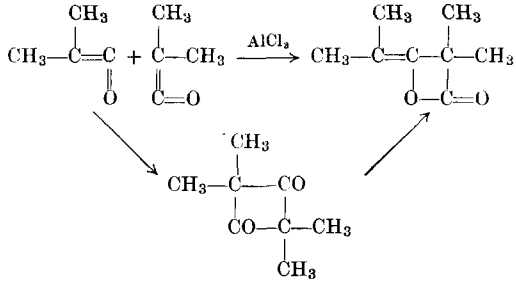
Depending on the distance between the carbonyl chloride groups and the reaction conditions, notably the dilution, the chlorides of dicarboxylic acids seem to give bicyclic compounds having the same empirical formula as the monomer, tricyclic dimers, linear polymers or a mixture:



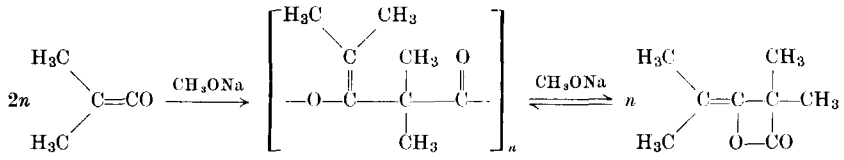
However, the structure necessary for the explanation of certain reactions have not been established beyond question (see Table 8, footnote *c*).

3. Dialkylketenes

The best known dimer of dimethylketene is 2,2,4,4-tetramethyl-1,3-cyclobutanedione, a volatile stable solid which sublimes at 115–116° and has an agreeable camphor-like odor. In 1907 Staudinger and Klever[573] had described a liquid isomer which boiled at 170–171°, had a pungent odor and was a lachrymator; it could be saponified by sodium hydroxide to give a water-soluble acid.[443, 460, 584] Hasek[462] has shown recently that this substance is the β-lactone dimer, a rather stable compound as it can be refluxed for 24 hr. without appreciable decomposition. This β-lactone of 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid is obtained either by the dimerization of dimethylketene in the presence of aluminum chloride[524a] or by the rearrangement of tetramethylcyclobutanedione by heating with aluminum chloride.[431a]



One can also prepare this β-lactone by heating a polyester obtained from dimethylketene in the presence of sodium methylate:[67c, 462]



Other polymers of dimethylketene with a polyketone structure, *e.g.* those prepared in the presence of triethylamine, evidently do not undergo this degradation.

Hasek, Clark, Elam and Martin[462] likewise obtained the β-lactone dimer of methylethylketene and of diethylketene from the corresponding monomers and aluminum chloride. The rearrangement of the symmetrical dimer (which always has the higher melting point and volatility) to the β-lactone is much more difficult.[431a]

Recently Anet[400] was able to prepare a β-lactone by dimerization of diphenylketene in benzene at 80° in the presence of a trace of sodium methylate.

4. Purification of Ketene Dimer

Among other impurities, ketene dimer prepared in acetone solution[520] can contain acetic anhydride formed by the accidental hydrolysis of the monomer. This product, which can be determined by infrared spectrophotometry,[556a] is separated by distillation,[440] preferably below 80–100 mm.,[592] followed by fractional crystallization.[523b, 525]

Ketene dimer can only be kept for several weeks at 0 ± 5° in the dark in the presence of a stabilizer (see section **VIII**). As a trace of mineral acid or base can initiate an explosive reaction, the containers used must be carefully cleaned; vessels of aluminum, stainless steel and glass which does not have an alkaline reaction are suitable.

VI. Reactions of the β-Lactones

1. General Remarks

The strained ring of the β-lactones makes them extremely reactive; most of them react, for example, with aqueous solutions of mineral salts to give compounds containing both ions, an exceptional reaction in organic chemistry.[98] The numerous reactions described in the literature in which the salts of β-halo organic acids and mineral salts participate can be considered as taking place through a β-lactone intermediate.

The reactions of the β-lactones almost always result in opening of the ring; cleavage of one of the oxygen bonds occurs, the bond broken depending on the reagent and the conditions. The few cases in which certain β-lactones react to give compounds which retain the β-lactone ring are treated in section **IV.5.**

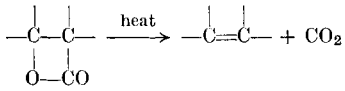
Most of the reactions of β-lactones in the literature concern propiolactone itself. Since there is an understandable tendency to consider these reactions of propiolactone as general reactions, one must bear in mind in working with substituted β-lactones that substituents can exert a profound influence, not only on the reaction rate, but sometimes even on the nature of the reactions.[114, 241] As the reactivity of the ketene dimers with a β-lactone structure differs from that of the other β-lactones, they are treated separately in section **VII.**

For several reactions it is possible to use impure β-lactones,

often because they cannot be purified; this justifies their inclusion in Tables 2–4.

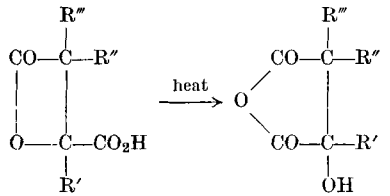
2. Effect of Heat

The β-lactones which can be isolated at about room temperature are easily decomposed (see section **IV.1**) by heat to give an ethylene hydrocarbon and carbon dioxide,[14, 30a, 46a, 185, 216a, 216b, 225, 230a, 295b, 313, 335, 335a] sometimes in the presence of water.[65, 66, 114, 159, 287] The photolysis of propiolactone[243] gives these products and some others:



This is why it is impossible to use distillation, even under reduced pressure, to purify several β-lactones of relatively high molecular weight which do not crystallize easily.[363] However, these lactones in a crude state have several industrial uses, specifically the preparation of ethylene hydrocarbons by the preceding reaction.[34,37,38,40,41,48a,143–147, 149–152, 158] The reaction of diphenylketene with certain carbonyl compounds, which only occurs above 120°, gives these decomposition products directly (see section **IV.2**). Because of its instability to heat, propiolactone is best purified by instantaneous distillation.[208] The β-lactone of 2,2-diphenylhydracrylic acid, which distils at about 175–180° under 15 mm. almost without decomposition, is exceptional in this respect.

The β-lactones are polymerized by heat; the resulting polyesters are susceptible to pyrolytic degradation to give the unsaturated acids (see section **VIII**). Special precautions, therefore, are necessary for the preparation of pure unsaturated hydrocarbons by decomposition of the β-lactones. Likewise, in the pyrolysis of the product of the reaction of a ketene with certain unsaturated carbonyl compounds, the diene derivatives formed by the decomposition of the β-lactone and the δ-lactone, which may be present, are not necessarily identical.[145, 151] Some lactone acids rearrange without decomposition upon heating to give an isomer of hydroxysuccinic anhydride:[5, 79, 218, 230]

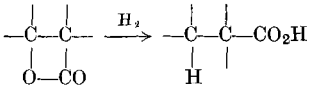


but the decarboxylation by heat of a β-lactone containing a carboxylic acid group has been reported.[358]

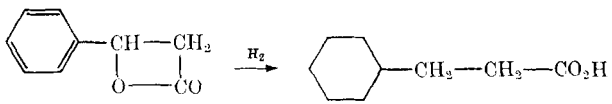
3. Hydrogenation and Combustion

A. Hydrogen

The catalytic hydrogenation of the β-lactones in the presence of Raney nickel, a process which is frequently carried out industrially with impure products, yields organic acids,[36, 142, 153–156] which can be optically active,[171a] according to the general scheme:

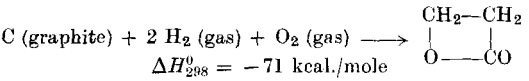


The presence of polymerization products of the lactone[156] in the starting material makes no difference, as the dimers[155] and polyesters[153] are hydrogenated to give the same final product. With β-lactones containing aromatic substituents, hydrogenation of the aromatic ring sometimes occurs simultaneously:[155]



B. Oxygen

The heat of combustion of propiolactone has been evaluated by Linnell and Noyes[243] to be 349 ± 7 cal./mole, from which one can estimate the heat of formation:

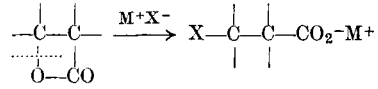


C. Chlorine

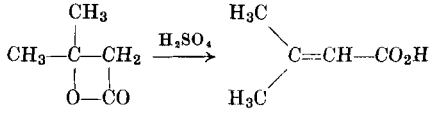
An α-chlorinated polyester results from the action of chlorine on monomeric propiolactone.[285a]

4. Action of Mineral Acids and their Derivatives

The β-lactones, which often polymerize in the presence of anhydrous salts, add the ions resulting from the dissociation of mineral acids or their salts in a polar liquid, according to the general scheme:



Several 'parasitical' reactions can occur simultaneously: (*a*) the solvent may react; in an aqueous medium the lactone is partially hydrolyzed to the hydroxy acid (section **VI.5**); (*b*) if the pH of the medium is too basic or too acidic, polymerization occurs (section **VIII**); (*c*) where M^+ is the ion of an alkali metal, the salt of the β-halo acid formed initiates the polyaddition of unchanged lactone molecules (section **VIII**) to give an oligomer. On the other hand, in pure sulfuric acid or in certain boron fluoride complexes, lactones with at least one hydrogen atom in the α-position and one or two alkyl groups in the β-position give the corresponding substituted acrylic acid by an exothermic reaction:[19, 166, 187, 225]



A rearrangement with enlargement of the ring can also occur,[167] when an *iso*propyl substituent is in the β-position.

A. Halogen Acids[66, 159, 225, 278d]

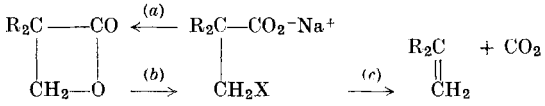
The yield of 3-halopropionic acid formed by the addition of a halogen acid to propiolactone in an aqueous or acetic acid medium decreases in the order: HI; HBr; HCl.[110, 124] The addition of hydrofluoric acid does not seem to have been accomplished. For the addition of these acids in the presence of alcohol, see section **VI.6**.

B. Alkali Halides

(1) Propiolactone. To minimize the hydrolysis of the lactone, the salts must be used in concentrated aqueous solution. The 'parasitical' polyaddition reaction (see section **VIII**) is avoided[98, 117] by addition

of the lactone in an excess of saline solution, which has the effect of displacing the equilibrium, the addition of alkali halides to propiolactone being reversible (section **VI.1.**). These are second order reactions.[13, 62, 324] The yields are slightly higher with the iodides and bromides than with the alkali chlorides,[98, 117] which can be classified in the decreasing order: LiCl; NH_4Cl; NaCl; $CaCl_2$. The excellent yields obtained with lithium chloride can be explained by the low solubility of the salt lithium 3-chloropropionate in the medium in which it is formed; this suppresses the polyaddition reaction.[98] The hydrochloric acid–sodium chloride mixture which has been used[98] gives 3-chloropropionic acid directly. In every case the addition product has been isolated as the 3-halopropionic acid after acidification of the reaction mixture.

(2) Other β-lactones. The lactones of yohimbic acid[57] and malic acid[175] give the expected reactions, but the lactone of 3-hydroxy-3-methylbutyric acid, which is somewhat less stable in water,[114] only gives addition products with the alkali halides in low yield. The addition of sodium chloride, bromide and iodide to the lactone of 2,2-diphenylhydracrylic acid does not give the corresponding acid but rather diphenylethylene in a yield of 6, 54, and 86%, respectively:[361]



as reaction (*c*) is much more rapid than (*a*). Although the α,α-dialkyl-β-halopropionic acids have only a slight tendency to give ethylene hydrocarbons, a study of these acids showed that reaction (*b*) is reversible, a fact that had escaped Hagman;[159] when a mixture of α,α-dimethyl-β-propiolactone and an aqueous solution of 1 *M* sodium bromide (50% excess) was kept in a thermostat at 50°, *iso*butylene was slowly liberated.[323] It has been verified that the pressure above a mixture of lactone and distilled water remains constant under these conditions.

C. Other Mineral Salts (of Acids containing Sulfur)

(1) Propiolactone. The action of oxidizing salts (halogenates, perchlorates, hypochlorites, persulfates, *etc.*), which can involve radical decomposition of the lactone, has not been considered.[98] The

TABLE 16. Addition of Salts of Mineral Acids containing Sulfur to Propiolactone

Salt used	Molecules of β-propiolactone/ molecule of salt	Salt formed	Remarks	Yield (%)	References
Ammonium sulfite	1	$HO_3SCH_2CH_2CO_2NH_4$	Can be isolated only as the barium salt		98
Sodium thiosulfate		$NaO_3SSCH_2CH_2CO_2Na$	$HSCH_2CH_2CO_2H$ + (—$SCH_2CH_2CO_2H)_2$[a]	14 29	98 117
Sodium hydrosulfide	1	$HSCH_2CH_2CO_2Na$ +	Best yields at −25°	68–67	100
	2	$S(CH_2CH_2CO_2Na)_2$		6–7	117
Sodium sulfide		$HSCH_2CH_2CO_2Na$ +	Low yields due to high pH	10	100
		$S(CH_2CH_2CO_2Na)_2$		22	117
Sodium disulfide		(—$SCH_2CH_2CO_2Na)_2$		94	117
Sodium selenide		$HSeCH_2CH_2CO_2Na$	(—$SeCH_2CH_2CO_2H)_2$ + H_2Se[a]	61	258
Sodium dithionite	2	$S_2O_4(CH_2CH_2CO_2Na)_2$	$SO_2(CH_2CH_2CO_2H)$ + SO_2[a]	43	92, 116
Ammonium thiocarbamate	1	$H_2NC(O)SCH_2CH_2CO_2NH_4$		85	202
Ammonium dithiocarbamate	1	$H_2NCS_2CH_2CH_2CO_2NH_4$	Acid can be cyclized to give 4-keto-2-thiono-1,3-thiazane	92	104, 108
Ammonium dithiocarbazate	1	$N_2NNHCS_2CH_2CH_2CO_2NH_4$		53	262
Sodium thiocyanate	1	$NCSCH_2CH_2CO_2Na$		81	98, 116

[a] After acidification.

addition reactions, which have received the most attention, are those which occur with the acid derivatives of sulfur because of the interest of the products for the rubber industry and the manufacture of plastics and fungicides, and also because the propiolactone ring has a tendency to open with the formation of a C—S bond. One encounters this tendency in the reaction of propiolactone with organic compounds containing both nitrogen and sulfur (section **VI.11**) or with mixtures of alkali hydrosulfides and chlorides.[117] It also accounts for the fact that oligomers[206] are not formed from the primary reaction products as long as an excess of the sulfur compound is present with which the lactone can react preferentially.

The products which have been prepared from propiolactone and the salts of inorganic acids containing sulfur or selenium are listed in Table 16. Bartlett and Small[13, 62, 324] studied the kinetics of some of these reactions. The addition reactions of the β-lactones and organic acids containing sulfur or phosphorus are treated in section **VI.11.**

(2) Other β-lactones. Some examples of reactions between β-methyl- or dimethylpropiolactone and salts of mineral acids containing sulfur have been published.[114, 282] Although propiolactone reacts very rapidly with the thiosulfates,[13, 337] this is not true of the other β-lactones which, therefore, cannot be determined by means of this reagent.[241] It can be assumed that the reactions, which have been described in the literature, of various organic β-halo acids with alkali sulfides,[95] thiosulfates[245] or xanthates[176, 248] take place through the β-lactone intermediate.

D. Other Mineral Salts

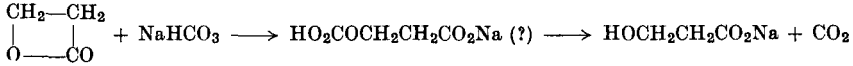
(1) Sodium cyanide. As it is difficult[98, 116] to isolate the 3-cyanopropionic acid, which results from the addition of propiolactone to sodium cyanide at about $-10°$, it is usually hydrolyzed to succinic acid[99] without preliminary purification:

$$\begin{array}{l}CH_2\text{—}CO\\ |\quad\ |\\ CH_2\text{—}O\end{array} + NaCN \longrightarrow \begin{array}{l}CH_2\text{—}CO_2Na\\ |\\ CH_2\text{—}CN\end{array} \xrightarrow{H^+} \begin{array}{l}CH_2\text{—}CO_2H\\ |\\ CH_2\text{—}CO_2H\end{array}$$

(2) Potassium nitrite. Although the preceding additions occur at room temperature or below, the reaction of potassium nitrite with propiolactone[98, 167c] gives a good yield only at a high temperature:[116]

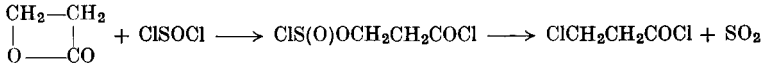
$$\begin{array}{l}CH_2\text{—}CO\\ |\quad\ |\\ CH_2\text{—}O\end{array} + KNO_2 \xrightarrow[H^+]{\text{then}} \begin{array}{l}CH_2\text{—}CO_2H\\ |\\ CH_2\text{—}NO_2\end{array}$$

(3) Sodium bicarbonate. Treatment with sodium bicarbonate or alkaline salts results in saponification[98] (section **VI.5**):



E. Chlorides of Mineral Acids

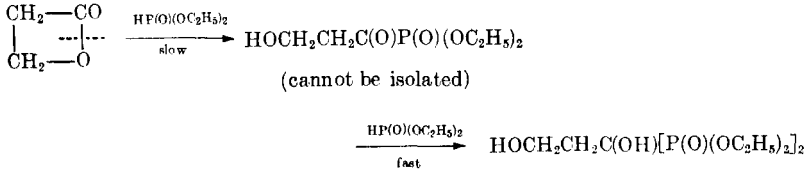
Thionyl chloride reacts rather slowly with propiolactone to give 3-chloropropionyl chloride,[110, 120] probably through a chlorosulfinate intermediate. β,β-Dimethyl-β-propiolactone behaves similarly.[114] The presence of a little sulfuric acid[204] or zinc chloride[217] speeds up the reaction, particularly if technical thionyl chloride is used:



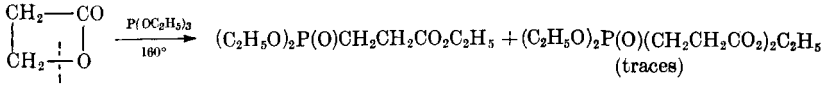
Sulfuryl chloride, SO_2Cl_2, and phosphoryl chloride, PCl_5, give the same product.[110, 120]

F. Esters of Mineral Acids

Propiolactone adds diethyl phosphite at about 155° in the absence of a solvent, or at room temperature if the reaction is catalyzed by triethylamine or if the sodium salt is used:[265, 268]



With triethyl phosphite, however, it is the bond between the methylene group and the lactone oxygen which is broken:[46,231,266,268]



Basic catalysts and excess of propiolactone favor the formation of telomers. Ethyl metaphosphate, without a catalyst at a temperature

below 40°, reacts with propiolactone to give a polymer[299] which probably has the structure:

$$[—P(O)(OC_2H_5)OCH_2CH_2C(O)O—]_n$$

and contains no P—C linkages.

The addition of propiolactone at 0–5° to an equimolecular quantity of diethyl sulfate results eventually in the formation of an acrylic ester:[126]

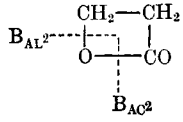
$$\begin{matrix}CH_2—CO\\ |\quad\ |\\ CH_2—O\end{matrix} + R_2SO_4 \longrightarrow \underset{\text{(cannot be isolated)}}{ROSO_2OCH_2CH_2OR} \longrightarrow RHSO_4 + CH_2{=}CH—CO_2R$$

Treatment with a mixture of sulfuric acid and alcohol gives the same result with a somewhat lower yield but the mechanism of the reaction is not necessarily identical.[233, 237, 303]

5. Hydrolysis of β-Lactones

A. Mechanism of Hydrolysis

The β-lactones react with excess of water to give β-hydroxy acids. The mechanism of this hydrolysis (or hydration) is particularly interesting as it differs from that usually encountered in the hydrolysis of esters.[54, 246] In a neutral or slightly acid medium, a bimolecular alkyl–oxygen heterolysis ($B_{AL}2$) occurs, whereas in a basic medium[62] or its opposite, a strongly acid solution, the reaction occurs through the classic mechanism of bimolecular acyl–oxygen heterolysis ($B_{AC}2$ or $A_{AC}2$, respectively):



This anomaly can be attributed to the strain of the ring which confers unsaturation characteristics on the constituent groups. The position of the cleavage was determined from the hydrolysis of the lactone of 3-hydroxybutyric acid by ^{18}O-labeled water:[281, 282]

$$\begin{matrix}CH_3—CH—CH_2\\ \quad\ |\quad\ |\\ \quad O—CO\end{matrix} + H_2{}^{18}O \xrightarrow{\text{neutral}} \begin{matrix}CH_3—CH—CH_2\\ \quad\ |\quad\ |\\ {}^{18}OH\ CO_2H\end{matrix} \longrightarrow \begin{matrix}CH_3—CH{=}CH\\ \quad\ |\\ CO_2H\end{matrix} + H_2{}^{18}O$$

This mechanism is particularly important in the Walden inversion of β-lactones containing an asymmetric carbon atom, when the corresponding hydroxy acid is formed.[282, 283] This was shown clearly by Olson and Miller[282] who measured the percentage of dextrorotatory 3-hydroxybutyric acid in the hydrolysis products of the corresponding dextrorotatory β-lactone as a function of the pH of the original solution. The experimental points are in good agreement with the curve (Fig. 6) which was calculated on the assumption that hydrolysis by molecular water occurs without optical inversion, and that attack by H^+ or OH^- ions leads to an optically active acid of opposite sign.

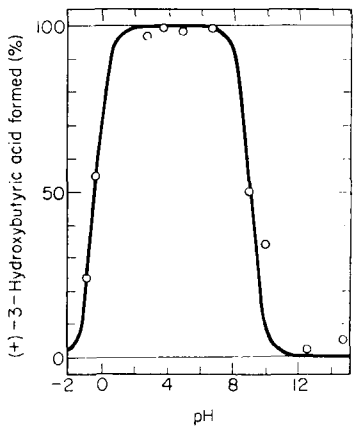


Fig. 6. Percentage of the dextrorotatory form of 3-hydroxybutyric acid produced by the hydrolysis of the dextrorotatory lactone at various pH values.[282] For the determination of the pH, the H^+ ion activity was arbitrarily fixed at 7.87 for 7.87 *N* sulfuric acid.

The mechanism of the hydrolysis has also been confirmed by a kinetic study carried out with propiolactone[246] and the lactones of 3-hydroxybutyric acid[212, 282, 283] (Fig. 7) and malic acid.[47, 178, 179] The hydrogen ion concentration necessary for mechanism A_{AC^2} is much higher with propiolactone than with the β-methyl homolog.

The hydrolysis (possibly enzymatic[30]) of various β-lactones[362, 330b] has been studied. The hydrolyses of the lactone of 3-hydroxy-2-methylbutyric acid[159] and of α′-hydroxy camphoric acid[230a] are very slow. On the other hand, the hydrolysis rate of the lactone of 3-hydroxy-3-methylbutyric acid is very rapid and increases with the hydrogen ion concentration due to perchloric acid; the reaction yields only 37% of

the expected hydroxy acid because of decomposition to *iso*butylene and carbon dioxide.[114, 159, 241] With pure sulfuric acid, this lactone

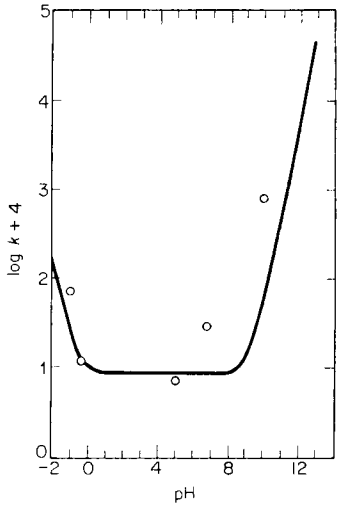


Fig. 7. Rate of hydrolysis of the β-lactone of 3-hydroxybutyric acid at various pH values. For the determination of the pH, the H^+ ion activity was arbitrarily fixed at 7.87 for 7.87 *N* sulfuric acid. The difference between the experimental points and the theoretical curve is attributable to a side-reaction of the lactone with the anions of the salts used as buffers.

gives dimethylacrylic acid (section **IV.4**). The hydrolysis of β-lactones can be used industrially for the manufacture of unsaturated acids (section **VIII**).

B. Hydrolysis with Small Amounts of Water

By using a relatively small amount of water at 80–100°, Hagemeyer[148] was able to convert several β-lactones into substituted or

$$2\ \begin{array}{l} RCH{-}CH_2 \\ | \quad\ | \\ O{-}{-}CO \end{array} + H_2O \longrightarrow O(CHRCH_2CO_2H)_2$$

unsubstituted 3,3-oxydipropionic acids. However, small quantities of water[89] added to technical propiolactone react preferentially with acetic anhydride,[30b] the principal impurity present, and this serves as a method for its elimination.

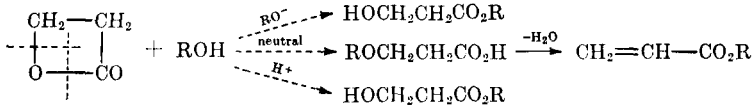
C. Saponification

The saponification of various β-lactones has been carried out either to verify their structure,[57, 221, 287, 335] or to prepare the hydroxy acids[19a, 82, 147, 157, 362] or their dehydration products.[162, 273b] Matusak[263] has made a detailed study of the saponification of propiolactone. The high value of the enthalpy of activation, which is unexpected in view of the strain of the valence angles in the ring, seems to indicate the importance of antagonistic factors; it explains the possibility of purifying technical propiolactone by washing with sodium hydroxide (pH 9)[208] without appreciable decomposition. Potassium hydroxide was used in trace amount as a catalyst for the polymerization of propiolactone[220d] (section **VIII**).

6. Alcoholysis

A. Propiolactone and Monoalcohols

The alcoholysis of propiolactone proceeds by the same mechanisms as the hydrolysis, a fact which supports the mechanisms proposed for the latter.[11, 118] One can easily deduce which linkage has been broken from the nature of the final products.



In the presence of a trace of an alkaline catalyst, a 3-hydroxypropionate ester is formed in a good yield; as the reaction with the primary alcohols is very rapid, it is advantageous to run the reaction at a low temperature[97] with excess of alcohol to cut down the polymerization. This is difficult to avoid with the secondary alcohols which, therefore, give rather low yields of hydracrylic ester.

The addition of methanol to propiolactone in the presence of an equimolecular quantity of sodium methylate gives 3-methoxypropionic acid in a high yield. Bartlett and Rylander[11] have explained the mechanism of this reaction which does not differ from the preceding one:

$$HOCH_2CH_2CO_2CH_3 \xrightarrow{CH_3O^-} CH_2{=}CH_2{-}CO_2CH_3 + H_2O$$

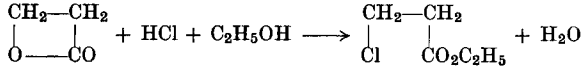
$$CH_2{=}CH{-}CO_2CH_3 \xrightarrow{CH_3OH} CH_3OCH_2CH_2CO_2CH_3$$

$$CH_3OCH_2CH_2CO_2CH_3 \xrightarrow{HO^-} CH_3OCH_2CH_2CO_2^- + CH_3OH$$

The water liberated in the first step is responsible for the saponification.

As the reaction of propiolactone with even the primary alcohols in the absence of a catalyst is very slow, alcohols can be used to remove acetic anhydride[337] from the technical product.[106] Heating brings about the formation of polymers or the esterification of the alkoxy acids.[118,233] The reaction of propiolactone with alcohol in the vapor phase[321] at 150–200° gives an acrylic ester.[88]

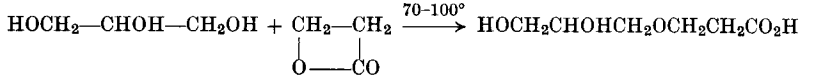
In a weakly acidic solution, the addition of propiolactone to alcohols gives a mixture of hydracrylic ester, 3-alkoxypropionic acid and its ester, or polymers derived from these products;[24a, 118] the proportions vary with the reaction conditions. As methanol is a more basic solvent than water, the minimum acidity at which mechanism $A_{AC}2$ can be observed appears to be higher. If the medium is saturated with anhydrous hydrochloric acid, an ester of 3-chloropropionic acid is formed:[121]



Mudrak and Stevick have described the addition of propiolactone on aluminium or titanium alcoholates.[277a]

B. Propiolactone and Polyalcohols

Propiolactone reacts with glycerol and polyalcohols of this type[360a] to give interesting polymers[35] which are comparable to the alkyd resins. Apparently an hydroxy acid is first formed:[277d]



This hydroxy acid can be converted into polyesters by heating with an acidic catalyst; the resulting macromolecules, which contain lateral hydroxyl groups, can either be cross-linked by the formation of ether bridges, or combined with a melamine resin.[232]

Some oxyalkylated phenol–formaldehyde resins have been modified by treatment with propiolactone[55a] to improve their surfactant properties.

The fixation of propiolactone by cellulose has been studied by Daul, Reid and Reinhardt.[45a, 49–51, 288, 289, 291b] The amount taken up reaches 60% for the purified cotton, and 200% for crude cotton owing to the presence of salts which act as catalysts. Although it is not easy to orient the fixation selectively, the use of a xylene solution in the presence of a basic catalyst favors esterification. Etherification, which

predominates when cellulose is exposed to propiolactone vapor in the absence of a catalyst, is accompanied by polymerization of the lactone with the acid groups thus formed, a reaction which gives a grafted polymer.[289] The duration of contact, the temperature and concentrations evidently affect the course of the reaction, which does not occur if a large amount of water or certain natural waxes are present, or if the cotton has been mercerized or twisted. The transformed cotton fiber, especially the esterified fiber, shows wool-like properties and increased resistance to hydrophilic reactions, to heat and to creasing. Some authors consider this treated fiber principally as a starting material which can be further modified.[93a, 279] The improvement reported in dyeing properties[87] has not been confirmed.[338] For the difference in the reactivity of propiolactone with linen and cotton, see Gokal and Skelly.[93b]

The reaction has been carried out with flax,[93d] with modified cellulose fibers[52, 289a] and with cellulose xanthate,[76] but in these cases functions other than the hydroxyl groups can be involved.

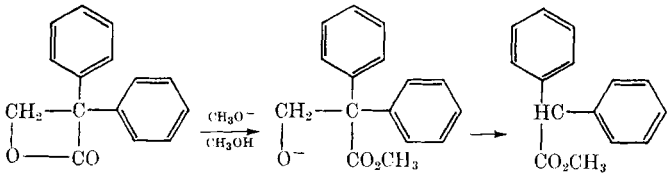
Another polysaccharide, amidon, has been treated with propiolactone. Although this treatment causes cross-linking of part of the polymer, the soluble part has a high viscosity and great stability to ageing during which the risk of gel formation is greatly reduced.[31, 220]

Propiolactone improves the resistance of wood to decay without reducing its strength.[94a]

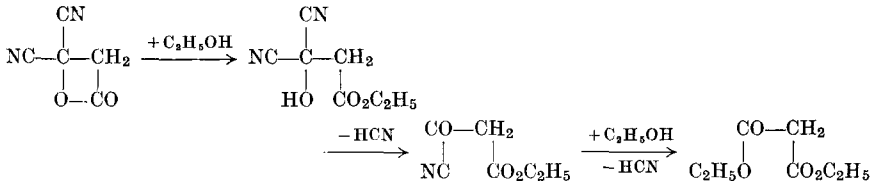
Silicic acid behaves similarly to a polyalcohol.[300a, 351]

C. Other β-Lactones

The β-lactone of 2,2-diphenylhydracrylic acid reacts with sodium methylate in methanol to give methyl diphenylacetate:[362]



With the same reagent, the two isomeric β-lactones of 4-chloro-3-hydroxy-3-methylvaleric acid yield respectively the *cis*- and *trans*-esters of 3,4-epoxy-3-methylvaleric acid,[46a] whereas the β-lactones of the steroids give the ester corresponding to the original keto acid.[26a] The lactone of 3,3-dicyanohydracrylic acid reacts[1] in a special manner:



The other β-lactones[57, 67a, 114, 147, 157, 323a] behave like propiolactone with the lower alcohols; the β-disubstituted lactones have a tendency to form β-hydroxy esters.[225] In strong acid solution the hydroxy ester is generally dehydrated to give the acrylic ester.

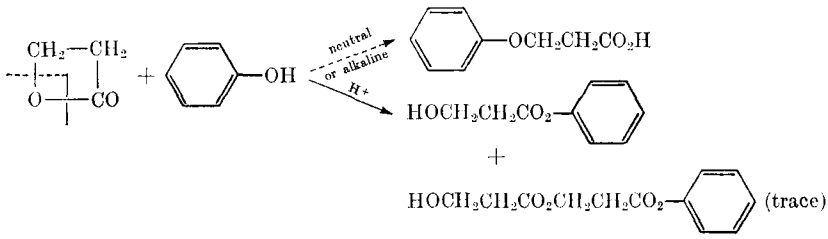
The reaction of cotton with the α,α-dialkyl-β-propiolactones has been studied by Valls and Devroe.[338] A sample of wet linters will take up 12% by weight of the β-lactone of 2,2-dimethylhydracrylic acid if it is refluxed for 2 hr. with a 20% xylene solution of the lactone. Under the same conditions, only 1% of the β-lactone of 2-ethyl-2-hydroxylmethylhexanoic acid reacts. These lactones then are appreciably less reactive than propiolactone for which the values reported by Daul have been confirmed.[338] The addition of 12% of the β-lactone of 2,2-dimethylhydracrylic acid brings about a profound modification in the crystal lattice of the cellulose without significant change in mechanical properties. The addition of the lactone of 3-hydroxy-3-methylbutyric acid to cellulose has also been investigated.[288]

7. Phenolysis

If one tries to apply the mechanisms shown for the hydrolysis of propiolactone to the reaction between the lactone and phenol, one must bear in mind that phenol is an extremely acid solvent.[11]

In the absence of a catalyst, β-phenoxypropionic acid is formed; the reaction is slow, and polymerization occurs if heat is applied to speed it up.[112, 122]

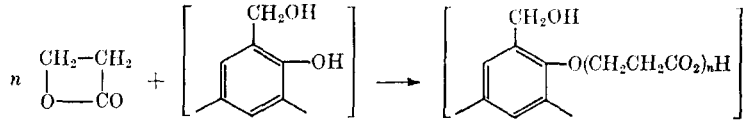
A trace of sulfuric acid is sufficient to bring about phenolysis by cleavage of the O—CO bond with the formation of phenyl hydracrylate;[11] under these conditions a small amount of dimer is formed due to the side-reaction, auto alcoholysis:[16, 17]



With the lactone of 3-hydroxy-3-methylbutyric acid, phenyl dimethylacrylate is obtained instead of the expected hydroxy ester.[114]

Sodium phenolate in aqueous solution behaves like the strongly basic salts; the chief reaction is saponification of the propiolactone to sodium hydracrylate.[112] A little 3-phenoxypropionate, however, can be isolated under these conditions.[122] On the other hand, the strongly acidic chloro- or nitrophenols in the form of the alkali phenolates in aqueous solution react with propiolactone to give addition products in excellent yield.[122, 224]

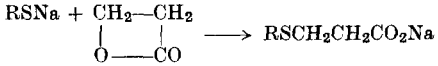
The phenolic resins can be modified by propiolactone[55a, 165] to give ion-exchange resins, for example. The starting material is the solution resulting from the condensation of phenol with formaldehyde in an alkaline medium:



8. Reaction of the β-Lactones with Sulfur Compounds

A. Thiols and Thiophenols

This addition is best accomplished by pouring propiolactone into an aqueous solution of alkali mercaptide;[112, 123, 277] the yields are particularly high. Dithioresorcinol adds two molecules of lactone.[123]



As in the general case, the salt of 3-(alkylthio)propionic acid thus formed can add additional molecules of lactone to give oligomers. 3-Mercaptopropionic acid behaves in a manner analogous to the other thiols and yields 3,3′-thiodipropionic acid;[123, 127, 358a] this explains the formation of this product in the reaction of sodium hydrosulfide with propiolactone (section **VI.4.***C*). The yields are usually lower when the free thiol[277d] is used rather than its salt.

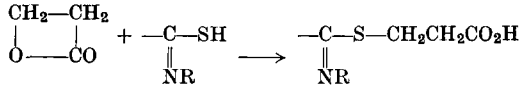
The reactions of propiolactone with thioglycolic acid,[170] or albumins,[233a] of the β-lactone of 3-hydroxybutyric acid with coenzyme A[55], and of the β-lactone of 2,2-diphenylhydracrylic acid with various thiols[364] have been described.

B. Sulfinates, Sulfonates and Xanthates

The arylsulfinates,[96, 116] arylsulfonates[182] and the xanthates,[75, 176, 248] including cellulose xanthate,[76] behave like the corresponding inorganic salts (Table 16).

C. Compounds containing Sulfur and Nitrogen (see Table 16)

When propiolactone is placed in contact with an organic compound containing a S=C(NHR)— group in a polar medium, a C–S linkage is always formed according to the scheme:

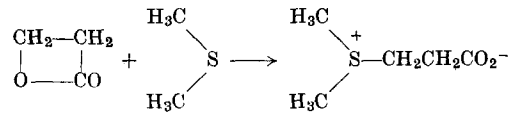


This reaction occurs with thiourea;[108, 128] the yield is excellent and the product is converted into sodium 3-mercaptopropionate by saponification; this reaction also takes place with phenyl- and allylthiourea,[137] dithiobiuret,[137] thiosemicarbazide[137] and rodanine,[136] preferably in an alkaline medium.

The thiols derived from nitrogen-containing heterocyclic compounds[206] react normally with propiolactone by virtue of their thiol groups, and the *N*-substituted mono-[202] or dithiocarbamates[104, 108] and phenyl dithiocarbazate[262] behave in a manner analogous to the inorganic salts from which they are derived.

D. Alkyl Sulfides

Dimethyl-β-propiothetine, which can be isolated as the hydrochloride, has been prepared[23, 23a, 292] by the treatment of methyl sulfide with the theoretical quantity of propiolactone in nitromethane at 20°:

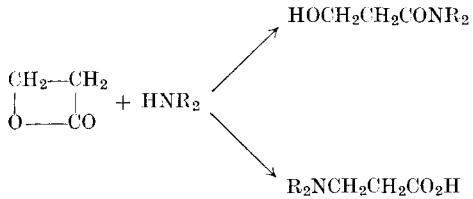


9. Reaction of the β-Lactones with Ammonia and Primary or Secondary Amines

A. Propiolactone

The relative proportion of the two possible products, the amide of hydracrylic acid and the amino acid, depends on the nature of the

amine and of the solvent, as well as on the order in which the reactants are added.[101, 113] Unlike some of the preceding reactions, neither polymer nor oligomer is formed in a significant amount. These reactions



are much more difficult to interpret than the hydrolysis and alcoholysis of the β-lactones. For example it is impossible to relate their course to the basic dissociation constant of the amine used.[113] Sodium ethylate and sulfuric acid have no catalytic effect.[181]

On the basis of the numerous known examples collected by Zaugg[363] in tabular form, one can state that with the primary aliphatic amines in general, the use of water as solvent and excess ammonia under pressure[236] both favor the formation of amides.[134] In acetonitrile or *tert*-butanol, one obtains the amino acid[129] which is frequently insoluble in this medium. The secondary aliphatic amines, with the exception of dimethylamine,[131] and hydrazine,[101] yield chiefly hydracrylamides or hydrazides irrespective of the experimental conditions.[135] It is impossible to drawn any other simple conclusion in regard to the behavior of the aliphatic amines.[131, 133, 135, 168, 333a, 333b]

The aromatic (or cyclic) amines react more slowly than the aliphatic amines and generally yield amino acids,[1b,102,130,138,181,182,240] although there are exceptions; *p*-toluidine, the naphthylamines, phenylhydrazine, benzylamine and aniline itself furnish a significant percentage of hydracrylamide, particularly with ether as the solvent.[189] Moreover, with phenylhydrazine, the substituted hydrazide obtained can undergo ring-closure to form 3-pyrazolidone. The nitrogen of mono- and di-ethanolamine reacts;[132] this is to be expected as propiolactone adds amines even in the presence of a solvent containing an hydroxyl group;[129] the corresponding substituted amino acid is obtained.

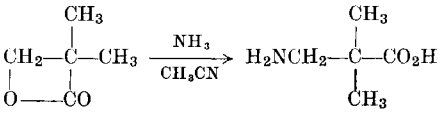
B. Other β-Lactones

Iwakura *et al.*[188, 189] have shown that the β-lactone of 3-hydroxybutyric acid and aniline yield 3-amino-*N*-phenylbutyric acid if the

addition is carried out in the presence of water.[138] If the solvent is acetonitrile, benzene or ether, one obtains—in that order—a higher and higher proportion of 3-hydroxy-*N*-phenylbutyramide. The β-lactone of 3-hydroxy-3-methylbutyric acid[114, 240] and its hexafluoro analog[225] give hydroxyamides selectively.

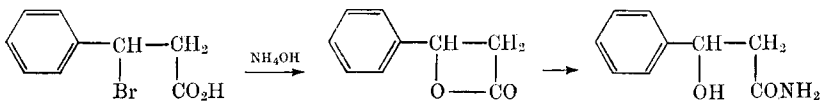
The addition of amines to the β-lactone of 3-(*p*-nitrophenyl)-hydracrylic acid yields chiefly the hydracrylamides,[15] although benzylamine and cyclohexylamine can give the amino acid under certain conditions.[61] The formation of an amide from ammonia and some β-lactones which have an aromatic substituent in the β-position[64, 65] or from various other β-lactones[1, 167a, 175, 306] has been described. On the other hand, the β-lactone of 2,2-diphenylhydracrylic acid has given the corresponding *N*-substituted β-alanines in all the cases studied.[364]

Among the results published since the appearance of Zaugg's summary tables,[363] the synthesis of 3-amino-2,2-dimethylpropionic acid should be mentioned:[73, 167]



and also the study of the reactions of hydrazine with the α-substituted β-lactones.[278b–d, 330b]

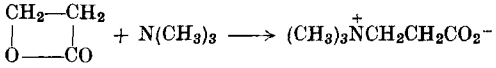
Finally, stereochemical or simply chemical considerations have led several authors to postulate the formation of a β-lactone whenever they have had to deal with a reaction involving ammonia or an amine in aqueous or alcoholic solution and a β-halo acid.[83] Some of the older literature on this subject[252–256,349] has been discussed by Darapsky[48] and others,[269, 301] notably the formation of 3-phenylhydracrylamide by the reaction of ammonium hydroxide with 3-bromo-3-phenyl-propionic acid:



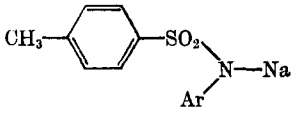
The conversion of the β-lactones in a solvent into β-lactams by ammonia under pressure has been suggested.[328]

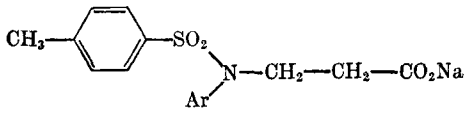
10. Reaction of β-Lactones with Other Organic Nitrogen Compounds

In the presence of water, the addition of tertiary amines gives quaternary ammonium hydroxides; in its absence[54b, 81, 113, 276a, 302a, 355a] a betaine can be isolated:



The same reaction occurs with the nitrogen heterocyclic compounds,[113, 184, 336a] even with those containing amino groups. As the betaines are effective in initiating the polymerization[71] of the β-lactones, their isolation sometimes requires that precautions be taken.[336a] The *N*-sodium derivatives of succinimide[116, 307] and the *N*-aryltoluenesulfamides[182] also add propiolactone. Pyrrole and indole react in a special way with propiolactone (section **VI.14**).





The aromatic isocyanates react with propiolactone in the presence of a trace of tertiary amine: phenyl isocyanate yields principally diphenylurea and acrylic anhydride, products of the decarboxylation of a hypothetical mixed acrylic–phenylcarbamic anhydride. The diisocyanates give spongy cross-linked polymers under these conditions.[312a, 336a]

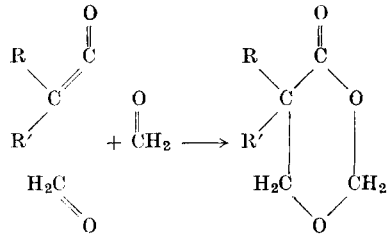
The modification of polyamide fibers with propiolactone has been patented.[93e, 333c]

11. Reactions of β-Lactones with Wool

The addition of propiolactone to various macromolecular compounds, polyglucosides and phenolic resins, has been treated in the chapters dealing with the reactions with alcohols and phenols. Wool presents a more complicated case, as it contains amino, imido, carboxyl and hydroxyl groups.[216] The exact nature of the reactions are difficult to elucidate.[215] However, the conditions for treating wool with propiolactone in the presence of traces of water[251, 294] or ethanol[78] have been selected so as to reduce the static electrical charge[250] during elaboration of the fiber, while at the same time improving the technical and aesthetic properties.[78, 216, 249, 251, 295]

12. Reaction of β-Lactones with Aldehydes

During the preparation of certain β-lactones from substituted ketenes and formaldehyde, compounds containing a six-membered ring are formed as by-products:



These cyclic compounds are comparable with the lactone of 3-(hydroxymethoxy)butyric acid obtained by Lobry de Bruyn and Van Ekenstein[244] from 3-hydroxybutyric acid and formaldehyde. When propiolactone is heated with an aqueous solution of formaldehyde in the presence of a zinc salt, the non-alkylated homolog is obtained (R = R′ = H).[73]

13. Reaction of β-Lactones with Organic Acids and their Derivatives

A. Alkali Salts of Organic Acids

The addition of the alkali salts of organic acids in aqueous solution to propiolactone[62] is similar to that of the salts of inorganic acids and, like the latter, the organic salts bring about the formation of oligomers[103, 109] unless present in excess. The side-reaction, hydrolysis of the lactone, also occurs.[109] Diassi and Dylion[57] have studied the reaction of sodium acetate in acetic acid solution with the lactone of yohimbic acid.

B. Free Organic Acids

The free organic acids in the presence of a trace of sulfuric acid give the same products but by a different mechanism; the cleavage occurs between the carbonyl group and the oxygen atom of the lactone.[110, 201, 360a] The ester-acids formed are likely to decompose[109] when distilled under atmospheric pressure:

$$CH_3CO_2CH_2CH_2COOH \xrightarrow{\text{heat}} CH_3CO_2H + CH_2{=}CHCO_2H$$

C. Acetic Anhydride

Acetic anhydride, which apparently does not react with propiolactone in the absence of a catalyst,[30b, 89, 108, 208] gives β-acetoxypropionic anhydride in the presence of a trace of sulfuric acid, after a number of rearrangements:[110, 201]

$$(CH_3CO)_2O + \begin{array}{l} CH_2—CH_2 \\ | \quad\quad | \\ O——CO \end{array} \xrightarrow{H^+} CH_3CO_2CH_2CH_2COOCOCH_3$$

$$\xrightarrow{\text{distillation}} (CH_3CO_2CH_2CH_2CO)_2O + (CH_3CO)_2O$$

D. Acetyl Chloride

Likewise propiolactone adds acetyl chloride[110, 125] at an appreciable rate only in the presence of sulfuric acid:

$$CH_3COCl + \begin{array}{l} CH_2—CH_2 \\ | \quad\quad | \\ O——CO \end{array} \xrightarrow{H^+} CH_3CO_2CH_2CH_2COCl$$

E. Ketene

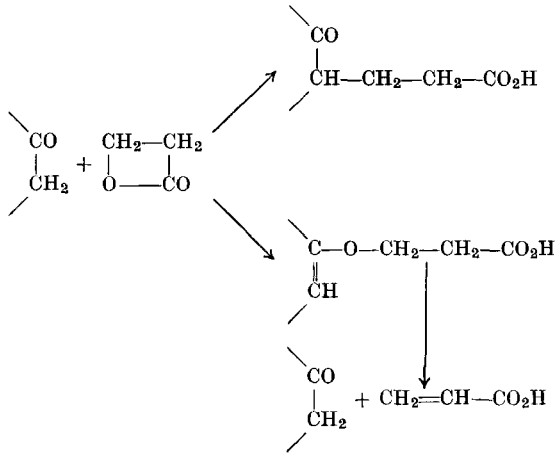
Ketene does not react with the lactone of 3-(*m*-nitrophenyl)-hydracrylic acid;[186] this indicates that the mixed anhydride, which has been observed when an aromatic aldehyde is reacted with ketene under certain conditions, is not formed via a β-lactone intermediate.

14. Reaction of β-Lactones with Compounds containing an Active Methylene Group

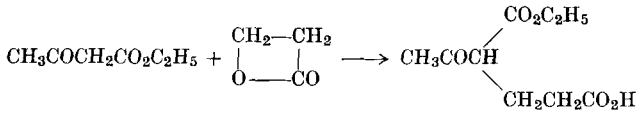
The addition of propiolactone to the sodium derivatives of ethyl acetoacetate,[9, 18, 115] of 2,4-pentanedione, of 1-phenyl-1,3-butanedione[18, 115] and of cyanoacetamide[115] can occur in an aqueous or a non-anhydrous alcoholic medium. The reactions of malonic ester[9, 115] and acetamidomalonic ester[325] and the ester of *N*-acetyl-2-cyanoglycine[325] are run in absolute ethanol in the presence of sodium ethylate, but with the decahydrophenanthrone derivatives[77] it is preferable to use ether in the presence of a metallic amide.

Two main reactions are possible: carboxyethylation of the carbon, and addition to the oxygen in the enol form. As a matter of fact, only the first reaction can be observed as the carboxyethoxy derivatives are too unstable and give the original carbonyl compound and acrylic

acid on distillation. Under these conditions, the existence of the second reaction is shown by the decrease in the yield of the first which never exceeds 40% and can even be zero in the case of the nitroalkanes:[115]

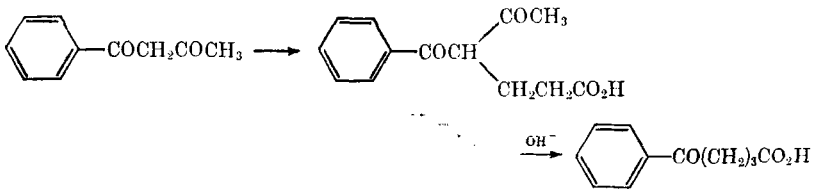


In addition, there are side-reactions, for example, the formation of oligomers by polyaddition on the ionized carboxyl group of the carboxyethylation product, and possibly decomposition of the lactone by the solvent. Nevertheless, the carboxyethylation reaction is of interest as there are no other practical methods available for the preparation of some of the derivatives obtained:



Malonic ester can add two carboxyethyl groups.

During the treatment of the reaction mixture, the product can undergo a transformation; the most frequent is an hydrolysis which yields a δ-keto acid:

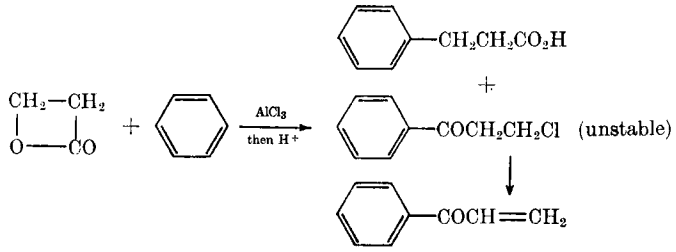


The reaction with cyanoacetamide and cyanacetic ester is more complex.[115]

The addition of propiolactone to pyrrole[163] and its derivatives[164] and to indole[164] is similar to the preceding reactions; carboxyethylation of the carbon in the 3-position occurs, if it is free, and there is no reaction with the nitrogen atom. In the presence of trifluoroacetic acid, the 4-pyrones are acylated in position 6.[357a]

15. Friedel–Craft Reaction with β-Lactones

A reaction mixture containing 1 molar equivalent of propiolactone, an aromatic hydrocarbon in excess and 2 molar equivalents of aluminum chloride gives, after hydrolysis, an α,β-unsaturated ketone and phenylpropionic acid in a yield which is usually higher than that of the ketone; a trace of 3-chloropropionic acid is also present:[304]

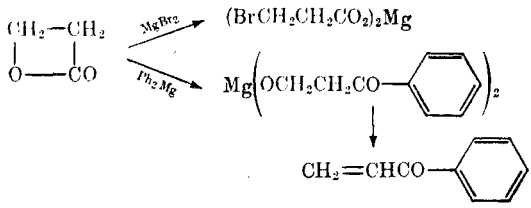


The use of a larger quantity of aluminum chloride (3 molar equivalents) brings about cyclization of the ketone to indanone with a yield which can be as high as 80%.[291a] The experimental conditions are rather specific.[44, 291a] With less aluminum chloride, one obtains chloropropionic acid—the lower the reaction temperature, the higher the yield;[277c] at the same time, the percentage of phenylpropionic acid and of 3-hydroxypropiophenone formed increases.

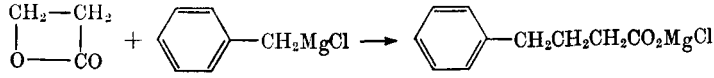
16. Action of Metal Hydrides and Organometallic Compounds on β-Lactones

A. Grignard Reagents

It is important to pour the propiolactone into the organometallic compound to avoid the preponderant formation of polymers. The action of magnesium bromide and that of diphenylmagnesium in the presence of ether have been studied independently:[111]



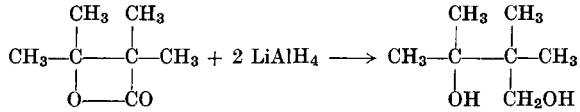
In addition to the product above, the second reaction yields a high proportion of polymers. Phenylmagnesium bromide and methylmagnesium iodide give a mixture of the halopropionic acid and α,β-unsaturated ketone.[8, 111] Benzylmagnesium chloride behaves differently: besides chloropropionic acid and a polymer, it gives 4-phenylbutyric acid which is undoubtedly formed by an addition reaction:



The polymerization of propiolactone induced by organometallic compounds[43a, 93c, 186a] is discussed in section **VIII.**

B. Lithium Aluminum Hydride

Natta *et al.*[278] have used this reagent to reduce the lactone of 3-hydroxy-2,2,3-trimethylbutyric acid:



The impure lactone of 1-hydroxycyclohexaneacetic acid and that of 2,2-dimethyl-3-phenylhydracrylic acid react in the same way to give 1-hydroxycyclohexane-ethanol[295a] and 2-methyl-1-phenyl-1,2-propanediol[273a] respectively. The lactone of 2,2-diphenylhydracrylic acid, which is crowded, does not react with methylmagnesium iodide,[365] but is reduced by lithium aluminum hydride to 2,2-diphenyl-1,3-propanediol with a yield of 84%.

17. Solubility of Some Macromolecular Materials in Propiolactone

Propiolactone can be used as a solvent for polyvinyl fluoride,[28] polyacrylonitrile[171, 324a, 350] and probably for several other macropolymers which are less difficult to dissolve. Longster and

Walker[1a, 247, 350] have related this solubilizing power of propiolactone to the high value of the component dipoles and the cohesion energy of the cyclic esters.

VII. Reactions of Ketene Dimers with a β-Lactone Structure

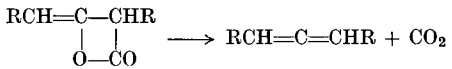
1. General Remarks

The presence of a double bond on the carbon opposite to the carbonyl group confers special reactivity on the β-lactone obtained by the dimerization of ketenes. As Gibaud and Willemart[452] have noted, the reactions of unsubstituted ketene dimer[410] can often be better explained in terms of the 'old' formulas (see Table 10) than by the β-lactone structure which is now accepted, and it is understandable that these reactions have been advanced as arguments at various times in favor of one configuration or another. Perekalin,[543] Piekarski[546] and Wiley,[591] however, have proposed mechanisms which permit the interpretation of the reactions of these heterocyclic compounds with the aid of modern theory. It should be noted also that some monosubstituted ketene dimers, owing to the presence of a rather large substituent, would be susceptible to preliminary dissociation in certain reactions.[534] But, in general, the lower ketene dimers display a tendency to polymerize rather than to dissociate, a tendency which is even more marked than that of the saturated β-lactones.

2. Effect of Heat

The substituted ketene dimers are relatively stable to heat and can be distilled without significant decomposition at rather high temperatures. Regeneration of the corresponding ketene monomer[400,459] has been observed at a high temperature (about 650°[419, 446, 479, 554]) with the unsubstituted compound and ketenes containing lower alkyl substituents.

More moderate heating brings about[433, 446, 524a] decomposition according to the general scheme mentioned in section **VI.2**:

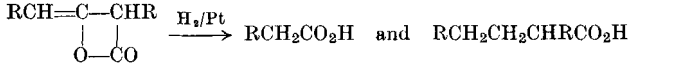


This can be accompanied by isomerization or polymerization[546] of the allene formed. A more profound decomposition can occur yielding methane, carbon and carbon monoxide.[479]

3. Action of Chemical Elements

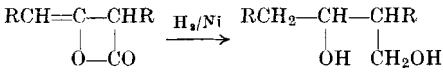
A. Hydrogen[546]

The unsubstituted dimer can undergo saturation of the double bonds without destruction of the β-lactone structure, followed by opening of the ring (section **IV.5.***B*), but the lactone of 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid yields mostly 2,2,4-trimethylvaleric acid.[67c, 462] Hill and Hill,[465] in their hydrogenation of the dimers of methyl- and *n*-butylketene, observed this reaction and, in addition, the formation of an acid, which can be explained by preliminary dissociation to the monomer:



$$RCH{=}C(O{-}CO){-}CHR \xrightarrow{H_2/Pt} RCH_2CO_2H \text{ and } RCH_2CH_2CHRCO_2H$$

At higher pressure (2900–3700 lb./in.^{2}) and in the presence of Raney nickel, diols are formed in variable yields which are sometimes excellent:[464, 466]

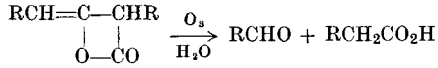


$$RCH{=}C(O{-}CO){-}CHR \xrightarrow{H_2/Ni} RCH_2{-}CH(OH){-}CHR(CH_2OH)$$

B. Oxygen and Ozone

The heat of total combustion of unsubstituted ketene dimer in the gaseous state, is equal to 447 cal./mole,[401, 410] a value which is in excellent agreement with the calculated one[560] but which does not correspond[560] to the published values for the heat of formation.[410]

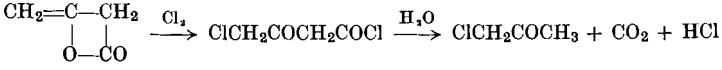
Treatment with ozone, followed by hydrolysis of the ozonide, brings about cleavage of the double bond as one would expect:[466, 475]



$$RCH{=}C(O{-}CO){-}CHR \xrightarrow[H_2O]{O_3} RCHO + RCH_2CO_2H$$

C. Halogens and Halogenating Agents

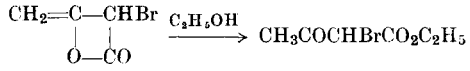
Chlorine and bromine[410, 474] add to unsubstituted ketene dimer to form the haloacetoacetyl halide which hydrolyzes to the haloacetone:[417]



$$CH_2{=}C(O{-}CO){-}CH_2 \xrightarrow{Cl_2} ClCH_2COCH_2COCl \xrightarrow{H_2O} ClCH_2COCH_3 + CO_2 + HCl$$

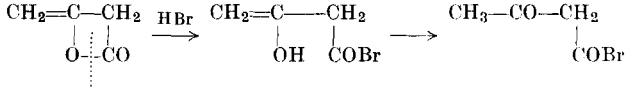
Bromine reacts in the same way with the dimer of methylketene[465] and its higher homologs,[579a] a reaction which can be used as a method of determination.

N-Bromosuccinimide, which is a specific brominating agent for allyl methylene groups, gives a very unstable bromo derivative[406] which on ethanolysis yields the bromoacetate:



4. Action of Mineral Acids

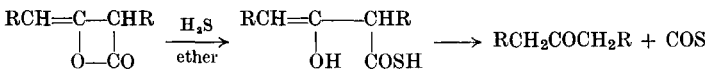
When the β-lactone of 3-hydroxy-3-butenoic acid is treated with dry hydrochloric acid at $-7°$ and then at $-50°$, acetoacetyl chloride is formed; this compound, which is an acetoacetylating agent, decomposes above $-20°$ to dehydroacetic acid.[478, 539] The same reaction occurs with hydrobromic acid:[545, 546]



and with dry hydrofluoric acid at $-5°$.[535a] Unlike the saturated β-lactones, the ketene dimers cannot add the ions formed by the dissociation of acids and salts in aqueous solution, for they react preferentially with water itself.[546] Magnesium iodide in ether solution behaves like a dehydrating agent.[452] Other salts, such as mercuric chloride or aluminum chloride, act as polymerization catalysts[93c] (section **VIII**).

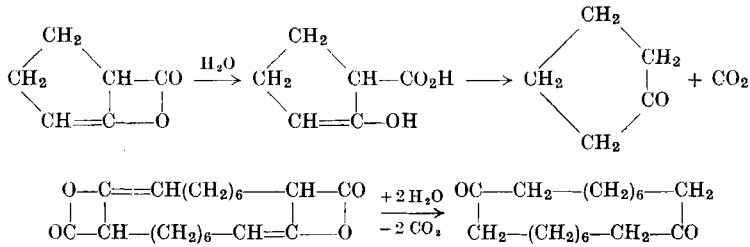
5. Action of Water and Hydrogen Sulfide

It has long been known that water slowly decomposes ketene dimer to give acetoacetic acid, and then acetone and carbon dioxide.[410] If one assumes[545, 546] that the addition proceeds by the same mechanism as that of hydrogen sulfide, the cleavage occurs between the carbonyl group and the lactone oxygen:



The substituted ketene dimers are the less sensitive to hydrolysis the larger the R group; on the addition of water or saponification, they

give keto acids[484c] which can be easily decarboxylated to ketones.[400, 548a, 557] This reaction is particularly interesting for the preparation of ketones or of cyclic polyketones[408, 409] from the cyclization products of compounds containing two ketene groups:



It has been extended to the preparation of mono-[407] and poly-keto[448] dicarboxylic acids which can be converted into α,ω-dicarboxylic acids.[448]

Fields and Zopf[445a] have shown that liquid motor fuels containing a trace of water cease to be corrosive after treatment with a trace of alkylketene dimer.

6. Action of Organic Compounds containing a Mobile Hydrogen Atom

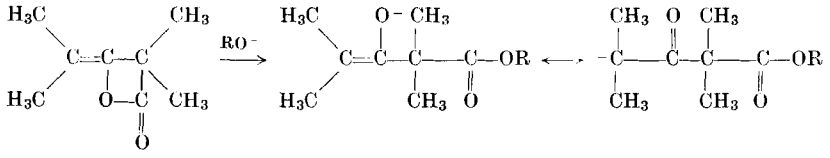
The reaction[410, 545, 591] is much less complex than is generally the case with the β-lactones (section **VI.5**). With the exception of the dimer of diphenylketene[400] cleavage always occurs between the carbonyl group and the oxygen atom to which the mobile hydrogen (or deuterium) of the reagent AH becomes linked.[591] After rearrangement of the enol, a substituted acetoacetic derivative is obtained. This reaction has been applied, in some cases in the presence of catalysts: to alcohols,[416, 462, 484c, 485, 502, 547, 557, 598] including deuteromethanol[488, 591] alcohols containing a carbonyl group,[505, 506, 513] unsaturated alcohols,[428, 501] polyalcohols[435, 472] and their derivatives,[416] including castor oil,[403b] polyesters,[523a] cellulose,[425, 438, 445b, 564b] poly(vinyl alcohol),[432, 490, 491a, 523, 572, 581b] the esters of hydroxy acids,[402] alcoholates of polyvalent metals,[470] and dioxyindole;[542] to thiols;[462, 547] to phenols[421, 454, 484c, 541a, 547, 549, 551,] and to phenols containing an aldehyde or ketone group;[549] to ammonia;[431] to aliphatic,[414, 426, 442, 483, 484c, 485, 544, 557] aromatic[67c, 430, 462, 492, 493, 503a, 509, 512, 516, 524, 533, 539, 554a] and unsaturated[491, 491a] amines, aminophenols,[415, 462b] phenylhydrazine,[489, 518, 519, 521] pyrrole,[580] indoles;[542] to gelatin,[581b] zein,[457] wool,[564b] amides,[530b, 540] imines,[534b] and ureas.[413, 453, 486, 499, 500, 507, 508, 511]

There are two important industrial applications of this reaction: the synthesis of acetoacetic esters and amides from unsubstituted ketene dimer, and the water-proofing of leather[565] and of cellulose materials,[445b,463,558,579b,584c,590] *e.g.* paper,[437,438,461,463b,528,530c,554b,586,586a,587] by ketene dimers containing sufficiently long-chain hydrocarbon substituents. The latter is often carried out in an emulsion.[401a,405,425,429a,438,441,484a,498,536,556,564a,582a,585,586b,587,587b]

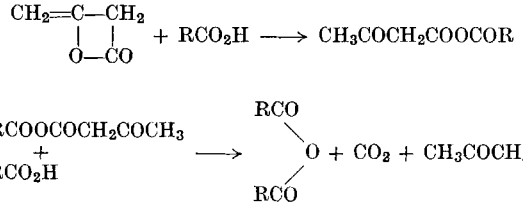
The kinetics of the addition of ketene dimer to aromatic amines have been investigated.[524] The dimers of the higher alkylketenes do not react with secondary amines or with phenylhydrazine,[546] but their quantitative reaction with ethylamine has been used for their determination.[546] 2,3-Dihydro-*N*,*N*-dimethyl-*p*-toluidine reacts in a particular way with ketene dimer[527a] to form 7,8-dihydro-2,6-dimethylchromone.

It is well known that the reaction of ketene dimer with phenols,[510,538,541,550,551] phenylhydrazine,[483,489,518,519,521,581] enamines,[473a] *o*-phenylenediamine,[554a] and ureas,[511] can be followed or accompanied by a cyclization to give coumarins, pyrazolones, 4*H*-pyran-4-ones, 1,3-dihydro-4-methyl-2*H*-1,5-benzodiazepin-2-one and pyrimidones, respectively.

The β-lactone of 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid with sodium methoxylate in tetrahydrofuran yields a sodium enolate, several reactions of which were described by Hasek.[462a]



The organic acids are added according to the general scheme to form the mixed anhydride;[456] with excess of carboxylic acid, rearrangement and decomposition occur:

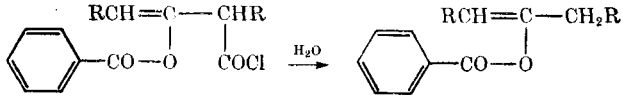


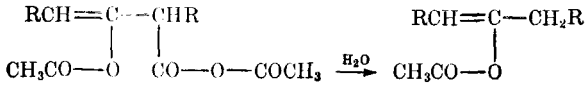
Isocyanic esters can be obtained from hydroxamic acids:[530a]

$$R{-}\underset{\underset{O}{\|}}{C}{-}NHOH \xrightarrow[\text{dimer}]{+\text{ketene}} R{-}\underset{\underset{O}{\|}}{C}NHOCOCH_2COCH_3 \xrightarrow{350^\circ C} RNCO + CH_3COCH_3 + CO_2$$

7. Reaction with Acid Chlorides or Anhydrides and Chloro Ethers

The addition of benzoyl chloride or acetic anhydride, present in excess, to an alkylketene dimer gives an enol ester after hydrolysis; the yields are low:[546]

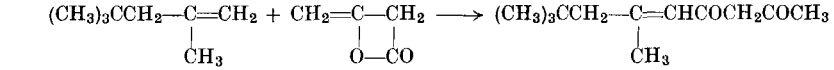


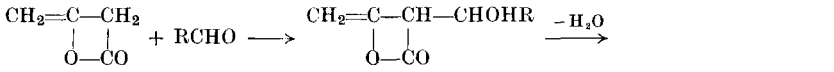


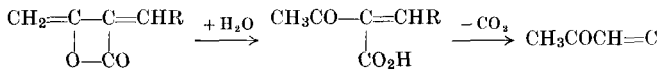
Unsubstituted ketene dimer does not react with maleic anhydride.[480] In the presence of aluminum chloride, it would add chloromethyl ether[577] to give 2-acetyl-3-methoxypropionyl chloride.

8. Addition Reactions

We are dealing here with special reactions of ketene dimers which the saturated β-lactones do not undergo. Thiol groups can add to the $CH_2{=}C\langle$ double bond of unsubstituted ketene dimer (section **IV.5.***B*). On the other hand, with certain olefins[424, 497] and with aldehydes,[410, 412, 479] except for formaldehyde,[411, 479] there is opening of the ring and addition as with compounds containing a mobile hydrogen atom:



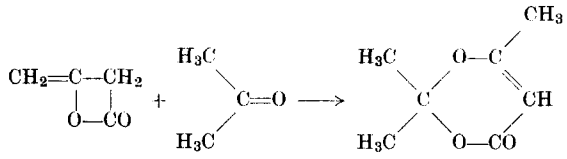




The addition of ketene dimer to 1,1-diethoxyethane yields ethyl 2-(1-ethoxyethyl)acetoacetate.[504a, 597]

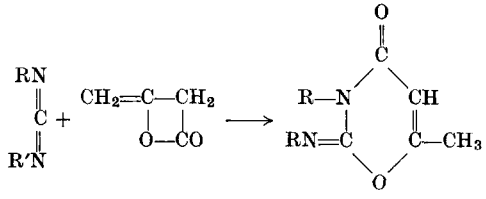
9. Reactions with Carbonyl Compounds

Just as the β-lactones can add aldehydes to form dioxanones, the ketene dimers add certain carbonyl compounds to yield heterocyclic compounds containing a six-membered ring. The condensation of acetone, for example, with unsubstituted ketene dimer proceeds rather easily;[404, 427, 429] the structure of the resulting 2,2,4-trimethyl-6-oxo-1,3-dioxene has been demonstrated by proton resonance[403a] and by reduction with lithium aluminum hydride:[450]



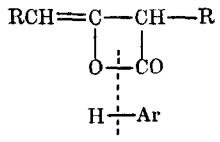
These compounds are of interest as they possess, although to a lesser degree, some of the properties of the ketene dimer from which they are derived.[427–429]

The addition of carbodiimides,[471] which has been studied by Lacey and Ward,[514] can be compared with that of the ketones:[458]



10. Friedel–Craft Reaction with Ketene Dimers

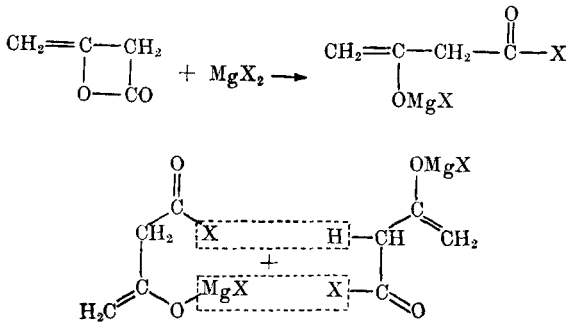
This occurs in accordance with the general scheme:[410,418,444,478,546]



to give a 1-aryl-1,3-butanedione in a usually low yield.

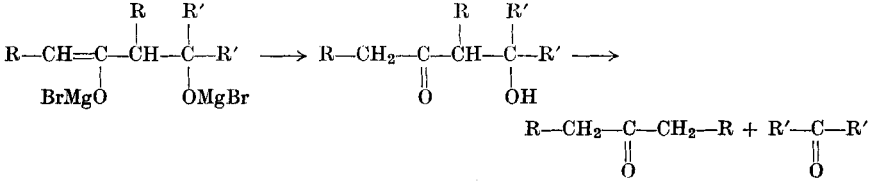
11. Reaction with Organomagnesium Compounds and Lithium Aluminum Hydride

Anhydrous ethereal solutions of magnesium halides convert unsubstituted ketene dimer quantitatively into dehydroacetic acid; this is also the principal reaction which occurs with mixed organomagnesium compounds.[452] On the other hand, a fraction of the magnesium compound decomposes with the formation of a hydrocarbon by way of the hydrogen halide which appears during the condensation. The liberation



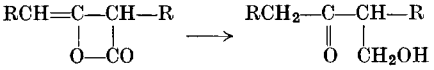
of hydrocarbon should not be interpreted as a measure of the degree of enolization of the ketene dimer.[479]

Besides these reactions, with methylmagnesium iodide and especially with phenylmagnesium bromide one observes the formation of the ketone and tertiary alcohol corresponding to the addition product of the organometallic compound and the ketene monomer. The alkylketene dimers should normally yield keto alcohols with excess of Grignard reagent.[533a] These compounds, however, have been isolated only in the case of phenylmagnesium bromide; the aliphatic organomagnesium compounds R′MgBr give only ketones by means of a retro aldol condensation:



Lithium aluminum hydride theoretically reduces ketene dimers to diols identical with those obtained by hydrogenation under high

pressure (section **VII.3.***A*); actually the reaction often stops with the formation of the keto alcohol:[462, 567, 583]



Diethylzinc was used as a catalyst for the polymerization of ketene dimer into a polyketone[93c] (section **VIII**).

VIII. β-Lactone Polymers

1. Saturated β-Lactones (General)

The β-lactones containing a strained ring polymerize[160, 312] easily and irreversibly under the influence of a large variety of acidic and basic reagents and salts. A radical process does not seem to be involved, but rather a stepwise polyaddition or an ionic mechanism which can be cationic or anionic according to the nature of the initiator used.[43, 43a] As the latter—or its decomposition products—remains attached to the end of each chain, the product obtained is similar to an oligomer or telomer[109] if it is made up of only a few units, in which case the terminal radical is of predominant importance; the product resembles a polyester if the molecular weight is so large that one can consider the end groups to be negligible.

One should mention in passing the lateral growth of polymer chains which occurs in the graft of the β-lactones on amidon,[31] cellulose[49–52, 279, 291b, 338] and other macromolecules (section **VI.11**).

For a number of years the polymers derived from β-lactones were regarded only as starting materials largely for the preparation of unsaturated products by pyrolytic or hydrolytic decomposition. They were not useful directly because of their chemical and thermal instability and mediocre mechanical properties which are attributable to their low molecular weight. Further, their melting temperature was often below 90°.

Recently with α,α-disubstituted monomers[71, 72, 86, 290, 333, 339] and improved polymerization techniques, macromolecular materials have been obtained which are interesting in themselves and chemically and thermally stable; these products have satisfactory mechanical characteristics and melting points as high as 250°.

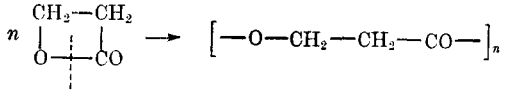
Important progress was made in 1962, in the field of the polymerization of β-propiolactone itself,[43, 43a, 93b, 93c, 280d] and high

molecular weight products are now obtainable from this unsubstituted monomer.

A. Mechanism

There are several conceivable mechanisms of polymerization which are in accordance with the general scheme of opening of the β-lactone ring given in section **VI.4.5** *et seq.* One must bear in mind, however, that the β-lactones are basic and can, therefore, prevent even a strongly acidic catalyst from being effective since there would be a large excess of lactone present in relation to the catalyst.

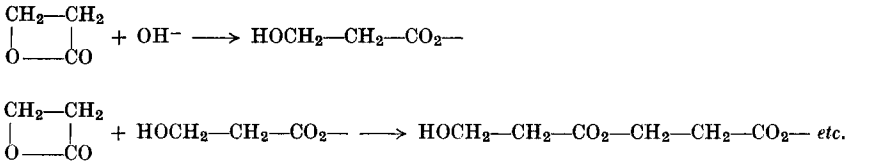
Acid reagents (sulfuric acid, metal and metalloid halides) bring about cleavage of the O—CO bond. With propiolactone and the lower β-lactones, a violent, exothermic polymerization occurs in the absence of a solvent. In general, it is difficult to obtain products which have a high molecular weight, although Cherdron[43] recently succeeded, using acetyl perchlorate or aluminum chloride as catalysts:



Nevertheless, if the operation is carried out at a low temperature (*e.g.* −30°) in the presence of a diluent such as nitromethane or a chlorinated hydrocarbon over a period of 30–50 hr., monomers containing two alkyl groups in the α-position can be polymerized to give products which can be easily drawn into fibers at their melting temperature.[71] At too low a temperature, however, the reaction is blocked;[72] nor does it occur if the amount of catalyst is too small or if the catalyst is neutralized by a basic diluent such as an ether.[72, 86, 107]

It was mentioned in sections **VI.4** and **13** that most alkali salts in aqueous solution,[98, 99] particularly the halides[117] and salts of carboxylic acids,[103, 109] bring about the formation of oligomers when they are added to a β-lactone. No products of high molecular weight appear under these conditions because of competition for each molecule of lactone added, between the two possible reactions: combination with the salt or addition to a growing chain. In the absence of a solvent and in some organic solvents, these salts, if used in small amounts, bring about polymerization of β-lactones,[280d] cleavage probably occurring between the oxygen and the methylene group.[43] The stepwise addition mechanism observed in this case recalls that described by Perry and

Hibbert* in 1940 with regard to ethylene oxide. The bases themselves can react in the same way,[280d] as a salt of a carboxylic acid is first formed by saponification:



With the tertiary amines,[228] the propagation reaction is preceded[323] by an initiation reaction (actually the formation of a betaine) the kinetics of which are influenced by temperature and retarded by the basicity of the medium which tends to inhibit the rupture of the oxygen–alkyl linkage of the lactone.

The tertiary amines in which the nitrogen atom is not screened and is, therefore, easily accessible, like trimethylamine, quinuclidine and especially triethylenediamine, are particularly effective catalysts which bring about rapid polymerization.[333] N. Fischer[86] has determined the initiation and propagation reaction constants of two α,α-dialkyl-β-lactones whose polymerization had been initiated by triethylamine. The kinetic results are in accordance with those which one would expect from Bauer and Magat's† theory of 'type two polycondensation'; there is no termination reaction, a situation which facilitates the formation of copolymeric sequences, nor is there any reaction between growing chains.

The rate of conversion and the mean molecular weight increase with time, the latter to a limiting value which is higher, the lower the initial concentration of the catalyst. Moreover, the reaction rate evidently increases with the temperature.

The polymerization of propiolactone by organic derivatives of zinc,[93c] cadmium or aluminum[448a] requires the presence of a co-catalyst, water or oxygen; this is not so[186a] with organic derivatives of lithium, sodium,[43a] potassium or magnesium.

Recently some Japanese[169a, 169b, 280a, 280b, 280c] and Belgian[52a] investigators were able to induce ionic polymerization of propiolactone by irradiation of the crystalline monomer with γ-rays of ^{60}Co or by bombardment with electrons. The polymerization rate as a function of

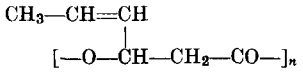
* See, for example, S. Perry and H. Hibbert, *J. Am. Chem. Soc.*, **62**, 2599 (1940); A. K. Gupta, *J. Soc. Chem. Ind.*, **68**, 179 (1949).

† E. Bauer and M. Magat, *J. Chim. Phys.*, **47**, 841 (1950).

the temperature passes through a maximum just below the melting point of the monomer; it is proportional to the radiation dose per unit time and the yield is rather low.

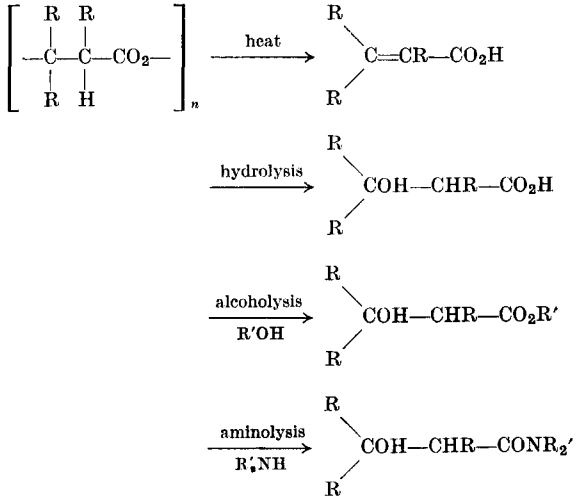
Copolymers of propiolactone with ethylene,[243, 264] styrene,[239a] acrylic derivatives,[259, 280b] butadiene,[223] trioxane,[56a] tetrahydrofurane[295c] and metaphosphate esters[299] have been described; some of these may have been produced by a radical catalysis. Pivalolactone, the β-lactone of 2,2-dimethylhydracrylic acid, has been used in some aromatic polyesters compositions.[221a] On the other hand the intermediate formation of propiolactone has been postulated in the reaction of carbon monoxide with oxirane[302] and in that of carbon dioxide with ethylene,[261] a reaction which yields oligomers.

Some polymers of unsaturated lactones have been used to modify drying oils:[305]



B. Properties[107]

(1) Polymers of low molecular weight. The chemical properties of the low and medium molecular weight polymers (*e.g.* below 1500), derived from lactones containing at least one hydrogen on the α-carbon, have been the subject of considerable investigation. The reactions can be summarized as follows:



The decomposition of these polyesters to acrylic monomers takes place between 150 and 200°.[235] The presence of a triaryl phosphate favors this reaction.[209] Often polymerization and pyrolysis occur simultaneously when the monomer is heated with the catalyst which had brought about formation of the monomer from ketene and a carbonyl compound;[88, 89, 166, 187, 346] several patents[25, 39] and a paper[48a] do not mention the intermediate polymer, whose formation, however, seems likely. Sometimes even the formation of a lactone monomer is not expressly suggested, or even that it is a mixture of polymer and the dehydration product of the lactone which undergoes pyrolysis.

Several workers have made use of this method of preparing acrylic acid to carry out Diels–Alder syntheses.[119, 207, 172] Propiolactone is heated in an autoclave with a diene, possibly in the presence of a catalyst which favors the polymerization. Sometimes an inhibitor such as hydroquinone is added which can prevent the polymerization of the acrylic acid formed.

The hydrolysis can be carried out industrially on a mixture of the lactone and its polymer.[26] As a matter of fact, the strong acid medium and the high temperature used[205] cause dehydration to the hydroxy acid, and this method, which is a variant of the preceding ones, is used for the preparation of unsaturated derivatives. Sorbic acid and its esters have been prepared in this way[26] from ketene and crotonaldehyde.

The alcoholysis of the polyesters of propiolactone[105] and their aminolysis by dimethyl- or diethylamine[203] take place in the presence of a trace of sulfuric acid; this makes it possible to obtain the esters and amides of hydracrylic acid, which are difficult to prepare from the acid itself.

The hydrogenation of the β-lactone polymers, which like the corresponding monomers yield saturated acids, was accomplished by Hagemeyer.[155] He noted the presence of dimers which do not seem to have been mentioned elsewhere in the literature. The chlorination[285a] gives an α-chloro polyester.

(2) Thermally stable polyesters of high molecular weight. Up to now high molecular weight polyesters, which can be used as plastics, have been prepared only from α,α-disubstituted or α,α,β-trisubstituted β-lactones.[61a, 71, 72, 86, 160, 290, 312, 333, 339] The substitution in β-position lowers the melting point of the polymer appreciably[114, 186a, 225] and even seems to limit the degree of polymerization obtainable with the usual catalysts.

The transitory formation of a β-lactone does not seem to be

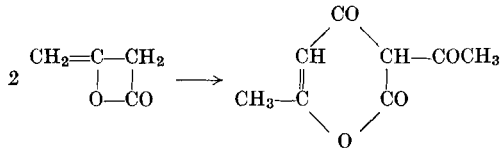
involved in the preparation of polyesters from dimethylketene and aldehydes.[273a, 278a]

2. Ketene Dimers

It is known that ketene dimer, which is stable at 0°, polymerizes slowly at room temperature and rapidly at higher temperatures. The alkalinity of some types of glass is sufficient to accelerate this process.

A. Formation of Dehydroacetic Acid and Stabilization of Ketene Dimer

If ketene dimer is added to an inert solvent containing a little pyridine,[420, 476, 431, 480, 481] trimethylamine[421a, 543a] or alkali phenolate,[578] or if it is treated with an acid,[410, 520, 591] dehydroacetic acid is formed. This also occurs during various reactions of ketene dimer, *e.g.* with mixed or symmetrical organomagnesium compounds,[452] and even during distillation[592] under insufficiently low pressure:



Under the influence of acids or bases, the dehydroacetic acid can undergo further reactions.

One can stabilize ketene dimer stored in the dark with 0.5–1% copper or anhydrous magnesium sulfate, with boric acid,[469] and also by dilution with acetone.[410] It has been claimed that zinc, calcium and aluminum sulfate[503] and picric acid[520] also have a stabilizing effect (section **V.4**).

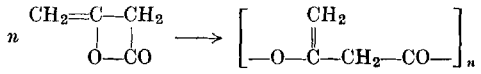
2,6-Dimethyl-4-pyrone and 2,6-bis-(6-methyl-4-oxo-2-pyranylmethyl)pyrone have been reported[578] among the products of the polymerization of ketene dimer by sodium phenolate.

The base-catalyzed conversion of substituted ketene dimers to ketene trimers has been described.[442b, 443a, 462a]

B. Formation of Linear Polyesters

In 1960 Furukawa *et al.*,[93c 449] using mercuric chloride in ether as the catalyst, succeeded in obtaining a polyester, melting at 85–87°, from ketene dimer. This polymer (mol. wt. about 1600) has been

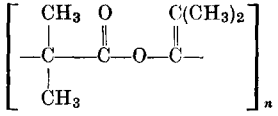
characterized by its infrared-absorption spectrum and alcoholysis products:



An analogous polyester, the ends of which are blocked by a hydrogen and an alkoxy residue, was prepared by the action of a trace of sodium acetate on specially purified ketene dimer dissolved in three or four times its weight of alcohol.[581a] The yield is of interest only if the polymer is separated immediately from the excess of alcohol and acetoacetic ester which is formed simultaneously.

Even more recently some Japanese investigators have induced the polymerization of ketene dimer by radiation according to the method which they used for propiolactone.[169a, 169b, 280a, 503b]

The lactone dimer of dimethylketene has been polymerized,[67c] a polyester of the same structure



was obtained from dimethylketene monomer in the presence of triethylaluminum[531a] or sodium methoxide[462] (section **V.3**).

C. Formation of Other Polymers

In the presence of the etherate of boron fluoride at -8 to $-4°$, ketene or its dimer gives a non-fusible, amorphous polyketone with a molecular weight around 2000 in a yield of 11%.[93c, 448a, 533a]

The copolymerization of vinyl monomers and ketene dimer, during which the lactone ring remains intact, is reported in section **IV.5.***B*.

IX. Toxicity and Biological Properties of β-Lactones*

1. β-Propiolactone

A. Toxicology[700]

Technical β-propiolactone has corrosive and vesicant properties; in contact with the skin it causes painful blisters and, as its action

* We wish to thank Mme. O. Thibault, Maître de Recherches at the Centre National de la Recherche Scientifique, for her help in writing this chapter.

is often delayed, extreme precautions are in order. Repeated exposure of the skin even to dilute solutions can bring about deep chronic lesions which may not be conspicuous. The lachrymatory vapor irritates the eyes and mucous membranes. The maximum tolerable dose has not yet been determined.

For these reasons, suitable ventilation is required in working with β-propiolactone; impermeable gloves and adequate protective clothing should be worn.

In case of accident, it should be remembered that β-propiolactone, which is water-soluble, is hydrolyzed relatively easily to hydracrylic acid which is only slightly toxic; therefore, copious washing is recommended. In the case of ingestion, the subject should drink a great deal of water, an emetic should be given and a physician summoned.

B. Fungicidal, Bactericidal and Viricidal Properties

In spite of these disadvantages, if suitable precautions are taken, β-propiolactone lends itself to interesting medical applications, especially in serology, owing to its fungicidal, bactericidal and viricidal properties. These have been studied by Bernheim and Gale[702] and by Gale[711–713] shortly after the product (Betaprone) became commercially available.

(1) Use as external disinfectant. Propiolactone inhibits the growth of various strains of fungi (*Pseudomonas, Trichophyton, Epidermophytes, Blastomyces dermatitis, Candida albicans, etc.*) by a mechanism which these authors believe to be analogous to that of the antibiotics, *i.e.* by inhibition of the oxidative metabolism.[702, 711–713] This property should make it an interesting compound for the therapy of mycoses. Gale has proposed the use of propiolactone as an external disinfectant; some of it is absorbed by the skin, but some is hydrolyzed to give 3-hydroxypropionic acid which, owing to its acidity, augments the disinfectant affect of the lactone.

Joos[720] has reported that ointments containing 0.1–0.4% of a mixture of propiolactone and aqueous albumin (30%) give excellent cosmetic results with regeneration of the skin. However, if one grants that complete hydrolysis does not occur rapidly, there are objections to its cosmetic application; *in vitro* propiolactone destroys certain enzymes of skin samples stored for use as grafts;[703] it is a vesicant (section **IX.1.***A*) and in addition carcinogenic. It initiates epitheliomas in rats when applied locally.

(2) Use as sterilizing agent. Propiolactone not only prevents the growth of micro-organisms but also destroys bacterial spores;[704] it lowers their resistance to heat.[731b] Both the vapor[708a] and the aqueous solution are bactericidal.[717] It acts more rapidly than formaldehyde and with fewer secondary effects. Walters,[745] Logrippo and Hartman,[726] and Hoffmann and Warshowsky[717] have proposed that it be used for surgical and general hospital supplies.[745]

It has been used as a sterilizing agent[716] in the storage of blood,[723, 745] of plasma (banks),[714, 723] of erythrocytes[721, 722] and of arterial homo-grafts.[727, 745] It cannot be used for skin banks as it destroys the dehydrogenase and cytochrome-oxidase activity of the tissue with the result that skin stored in this way is not viable.[703] On the other hand, it is useful for the storage of vaccines.

(3) Use in immunology. Propiolactone plays an important role in immunology owing to the fact that, in addition to its bactericidal effect, it is a viricide. It inactivates a number of viruses of diseases, *e.g.* encephalitis,[700a, 709] encephalomyelitis,[707a, 726, 726a] enterotoxemia,[733] hepatitis,[710, 732] influenza[747] and bronchitis,[703a] poliomyelitis,[705,706,725] tetanus,[735] Newcastle disease,[724, 730, 731, 742a] brucellosis[718] and others.[707b, 708b, 742a]

There is disagreement with regard to influenza and Newcastle disease,[742] but investigators agree that it is one of the best inactivators for the manufacture of vaccines.[726, 727a, 731a, 733, 734]

In general, the inactivation of viruses by heat, ultraviolet radiation or the usual chemical agents (phenol and formaldehyde) presents problems; it is difficult to obtain complete inactivation of all the virus without a reduction of its antigenic power and deterioration of the plasma proteins, *i.e.* to create immunity without risk of the disease. From this point of view, propiolactone has important advantages: (*a*) It is readily soluble, active at low concentrations and not toxic even at high concentrations; according to Hartman, Kelly and Logrippo,[715] 1 g./l. is sufficient to destroy the 'block-virus', but there are advantages in using 3–4 times this concentration to inactivate the last trace. Even at this level, propiolactone is not toxic. (*b*) Inactivation of the virus occurs rapidly; contact for 10–15 min. at 37° is sufficient[726] instead of the prolonged incubation (several days) necessary with formaldehyde, which results in deterioration.[733] (*c*) It serves to stabilize and conserve the activity of the vaccine which usually falls off rather rapidly, probably owing to enzyme action.[733] (*d*) It makes it possible to obtain vaccines which confer a lasting immunity.[724]

(*e*) It does not destroy the plasma proteins, blood cells or antibodies.[710]

As its inactivation effect is accentuated by ultraviolet light,[740, 726a, 734a] a combination of ultraviolet radiation with propiolactone might be useful. Propiolactone and formaldehyde have been used together.[725]

C. Mutagenic and Carcinogenic Action

Propiolactone is capable of causing chromosome anomalies resulting in mutation[729] in plants,[738, 739, 741a] in bacteria[708, 719] and in yeasts.[741] These mutations confer a resistance to antibiotics.

Since, in addition to its mutagenic effect, propiolactone impedes cellular division in *Saccharomyces* and *Escherichia coli*,[728] it is not surprising that it should be involved with cancer.

Several authors claim that it exerts a carcinogenic effect.[736, 737] Walpole, Roberts, Rose, Hendry and Homer[744] reported that propiolactone causes local sarcomas in the rat. They believe that propiolactone, like ethylenimine, probably owes its carcinogenic effect to its ability to combine with cellular constituents as a prosthetic group; this is in agreement with the general theory according to which the initial step in the chemical production of cancer consists in the inactivation of certain cellular constituents by attachment of foreign residues to the molecule.

It is not impossible that propiolactone exerts both a carcinogenic effect and the opposite, *i.e.* the inhibition of spontaneous tumors, as is true of many chemical carcinogens, but this has not been demonstrated. One can simply classify propiolactone with the alkylating agents[719a] which can have a toxic effect on the chromosomes, specifically on deoxyribonucleic acid; they act by alkylation, *i.e.* by attachment to the side-chains of the long deoxyribonucleic acid molecules or by formation of bridges between molecules, thus altering their physiological behavior.

D. Miscellaneous

Along with other lactones, propiolactone has been studied to test its isotropic action of the isolated hypodynamic papillary muscle of the cat, without positive results.[701]

2. Other Compounds containing the β-Lactone Ring

A. α,α-Dialkyl-β-propiolactones

The α,α-dialkyl-β-propiolactones are lachrymators and irritate the mucous membranes;[71] the odor of the α-alkyl-α-phenyl-β-propio-

lactones is similar to that of the acid chlorides.[330] These products attack the skin severely and cause itching.[278b]

B. Lactone of Yohimbic Acid

According to Diassi and Dylion,[57] it does not have any of the sedative activity of reserpine or deserpidine, but in the anesthetized dog it shows the adrenolytic and transitory hypotensive activity typical of yohimbine.

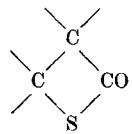
C. Ketene Dimer

The toxicology of ketene dimer and of its homologs[462] which contain a β-lactone ring is outside of the scope of this article. We shall only mention that although it is ten times less toxic than ketene itself,[746] the dimer is very irritating and at a concentration of 2 mg./l. causes opaqueness of the cornea.[707] It can be present at a level of several parts per thousand in products prepared from ketene (β-propiolactone and various esters[707]) and markedly increases the toxicity of these preparations.

X. β-Thiolactones

1. General

The β-thiolactones are characterized by the four-membered ring:



The simplest compound of this series was recently described by Bartlett and Tate,[608] but, shortly before, Lin'kova, Kil'disheva and Knunyants[608] had prepared the β,β-dimethyl homolog. The α-amino derivatives have been studied by Yugoslav[601a, 602, 603] and Russian[605–609] authors.

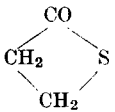
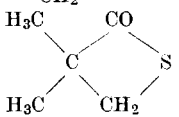
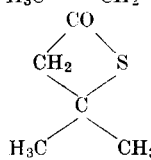
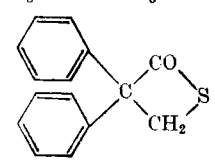
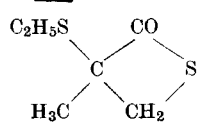
The nomenclature of the β-thiolactones has given rise to the same difficulties as with the β-lactones; *Chemical Abstracts* places these compounds after the corresponding thiol acids.

2. Physical Properties

A. Physical Constants

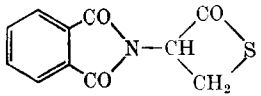
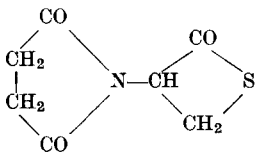
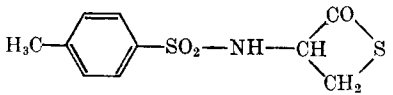
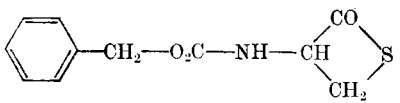
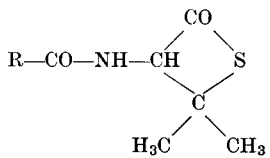
The melting and boiling points, densities and refractive indices of the β-thiolactones are listed in Table 17.

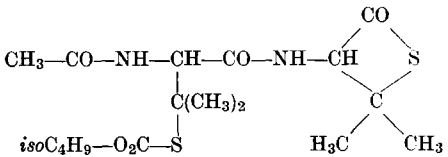
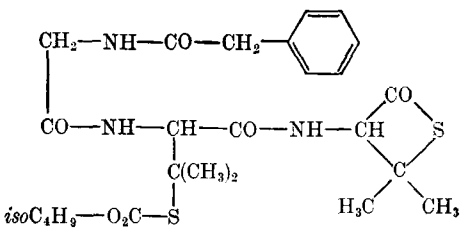
TABLE 17. Physical Properties of the β-Thiolactones

Formula	Corresponding thiol acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	Remarks	References
	3-Mercaptopropionic acid		50–53/12	A	$n_D^{20} = 1.5269$; $d_4^{20} = 1.301$	601
	3-Mercapto-2,2-dimethylpropionic acid		32/3	A		610
	3-Mercapto-3-methylbutyric acid		33–34/1.5	D	$n_D^{20} = 1.4865$; $d_{20}^{20} = 1.0425$	608
	3-Mercapto-2,2-diphenylpropionic acid	55–56		A and C		609 609a
	2-Ethylthio-3-mercapto-2-methylpropionic acid		68–70/0.1	A	$n_D^{20} = 1.5425$; $d = 1.154$	609

(Table continued)

TABLE 17 (*continued*)

Formula	Corresponding thiol acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	Remarks	References
	3-Mercapto-2-phthalimidopropionic acid	141–143 138.5–139		B B	Levorotatory Racemic	602 602
	3-Mercapto-2-succinimidopropionic acid	95–97[b]		B	Racemic	603
	L-3-Mercapto-2-(toluene-*p*-sulfonamido)propionic acid	101–102[c]		B C	Levorotatory	603 601a
	*N*-Benzyloxycarbonyl-L-cysteine	125 (soft. 115)			$[\alpha]_D^{20} = -50°$ (*c*, 1 in $CHCl_3$)	601a
	*N*-Acyl-3-mercaptovaline	93–95[d] 129–130 129–131 194–195		D D D D	R = H R = CH_3 R = $PhCH_2$ R = $PhCH_2$ $CONHCH_2$	605 605 605 605

Formula	Corresponding thiol acid	M.p. (°C)	B.p. (°C/mm.)	Method of preparation[a]	Remarks	References
	*N*-(*N*-Acetyl-3-mercaptovalyl)-3-mercaptovaline *iso*butyl carbonate	196–198[d]		D		606
	3-Mercapto-*N*-(3-mercapto-*N*-phenaceturoylvalyl)valine *iso*butyl carbonate	164–166[e]		D		606

[a] See section **X.4.**
[b] Recrystallized from methanol and then from ethanol.
[c] Recrystallized from benzene and hexane.
[d] Recrystallized from absolute ethanol.
[e] Recrystallized from acetone and water.

B. Crystallographic Properties

The β-thiolactone (*levo* form) of 3-mercapto-2-phthalimidopropionic acid, after recrystallization from ethyl acetate and then from ethanol, was obtained as white orthorhombic prisms (m.p. 141–143°) which were studied with X-rays by Grdenic and Despotovic:[602] the dimensions of the lattice unit (in Å) were *a*, 5.35; *b*, 20.70; *c*, 9.30; the number of molecules per lattice unit, *Z*, was 4; the density of the solid was 1.55 g./cm.^{3}; the space group, D_2^4, was $2_12_12_1$ The space group was determined by the systematic absence of reflexions in the diagrams of the oscillating crystal.

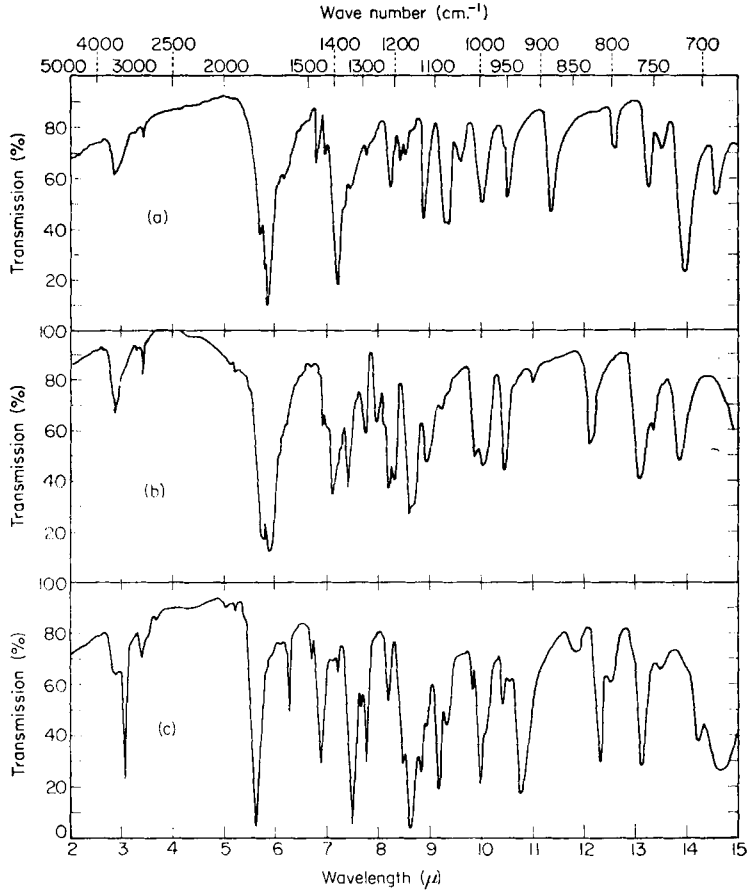


Fig. 8. Infrared-absorption spectra of some β-thiolactones:[603] (a), α-phthalimido-β-propiothiolactone; (b) α-succinimido-β-propiothiolactone; (c) α-(toluene-*p*-sulfonamido)-β-propiothiolactone.

3. Physicochemical Properties (Infrared Spectrography)

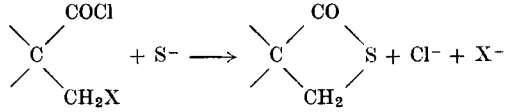
Hadzi[603] has measured the infrared-absorption spectra of three β-thiolactones derived from cysteine (Fig. 8). The vibration frequency of the lactonic carbonyl group—when it is not masked by that of the imidocarbonyl group—appears at about 1770 cm.$^{-1}$ [601, 603] This frequency is of the same order as that found for the γ-lactones, and thus lower than that of the carbonyl group of the β-lactones. This suggests that the β-thiolactone ring is less strained than the β-lactone ring, a conclusion which is confirmed by the ease with which the β-thiolactone ring is formed. The presence of a nitrogen atom in the neighborhood of the lactone carbonyl group seems to be responsible for the infrared band reported at about 1000 cm.$^{-1}$ [603]

4. Methods of Preparation

Because of the limited number of examples, it is not certain that all the methods described for the preparation of β-thiolactones are generally applicable. The method of preparation is indicated for each β-thiolactone described in Table 17 in column 6.

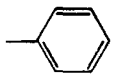
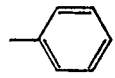
A. Reaction of a β-Halo Acid Chloride with a Metal Sulfide

β-Thiolactones can be prepared from a β-halo acid chloride and a salt of hydrogen sulfide:[601, 609, 610]



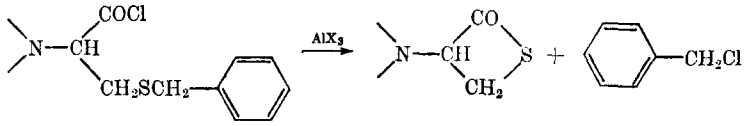
Specific examples are listed in Table 18.

TABLE 18. Preparation of α,α-Disubstituted β-Thiolactones from β-Halo Acid Chlorides

Halogen X	Substituents in α-position		Sulfide	Medium	Maximum yield	Reference
Cl	—H	—H	Na_2S (anhydrous)	CS_2	44	601
Cl	$—CH_3$	$—CH_3$	Na_2S (anhydrous)	CS_2	55	610
Br			$Na_2S.9H_2O$	C_2H_5OH + CH_2Cl_2	100	609
			H_2S + $2(C_2H_5)_3N$	$(C_2H_5)_2O$ + CH_2Cl_2	96	609
Cl	$—CH_3$	$—SC_2H_5$	H_2S + $2(C_2H_5)_3N$	$CHCl_3$	50	609

B. Elimination of Benzyl Chloride

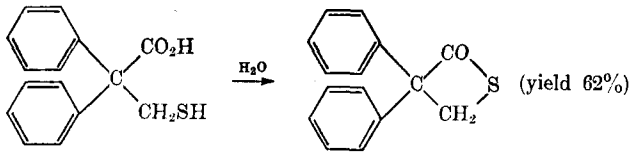
Another method is by the action of at least 2 molar equivalents of aluminum chloride or bromide on a *N*-acyl-*S*-benzyl derivative of cysteine at room temperature:[602, 603]



The yields range from 50 to 67% and appear to pass through a maximum which is a function of the reaction time. The benzyl chloride formed combines with the benzene used as a solvent. The use of 1 molar equivalent of aluminum chloride per molar equivalent of acid chloride results in the formation of a polythioester which in the case of the *N*-phthaloyl derivative[602] has a molecular weight of about 1500 (m.p. 256–260°).

C. Dehydration of a β-Thiol Acid

Dehydration of a β-thiol acid with phosphoric anhydride at about 100° also gives a β-thiolactone:[609]

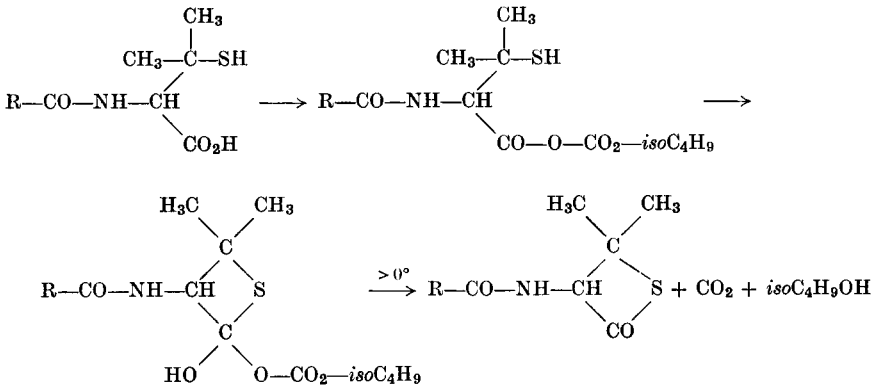


Some *N*-substituted derivatives of cysteine have recently been cyclized by di*iso*propyl- or dicyclohexylcarbodiimide in dioxane at room temperature.[601a]

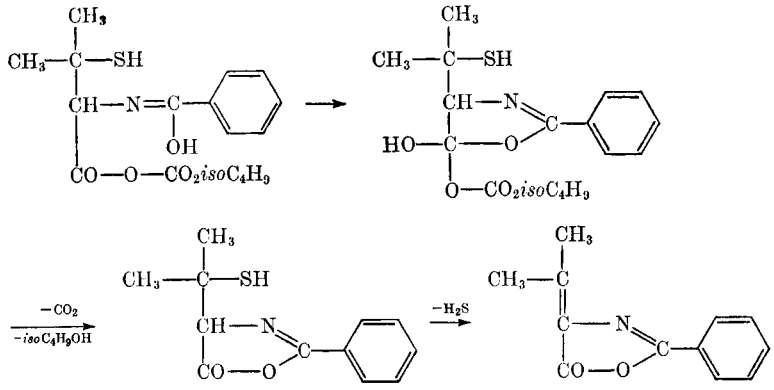
D. Reaction of an Alkyl Chloroformate with a β-Thiol Acid

A further method is by the reaction of ethyl or *iso*butyl chloroformate with a β-thiol acid with 2 molar equivalents of triethylamine.[605–609] The reaction is run in chloroform first at −10 to −5°, then at room temperature. The authors[605] assume that a mixed anhydride inter-

mediate is formed, but substitution on the sulfur atom cannot be ruled out:[604]



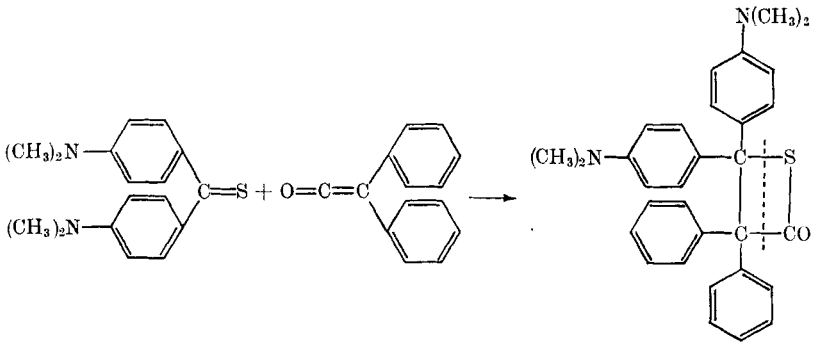
When R represents a phenyl group, however, one ends up with a 4-*iso*-propylidene-2-phenyl-2-oxazolin-5-one rather than with a β-thiolactone, because of the greater acidity of the amide hydrogen:



E. Attempts to combine Ketenes with Thioketones

The β-thiolactones, unlike the β-lactones, cannot be prepared from ketones as the thioaldehydes do not exist in the monomeric form. According to Staudinger,[611] thiobenzophenone reacts with diphenyl ketene to give a compound which decomposes at 180° to regenerate the starting materials; 4,4′-bis(dimethylamino)thiobenzophenone, on the

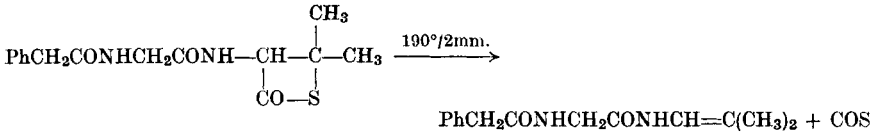
other hand, yields the decomposition products of the β-thiolactone; the latter cannot be isolated:



5. Reactivity of the β-Thiolactones

A. Effect of Heat

The thermal decomposition, which has been studied in only a single case,[605] is similar to that of the β-lactones:



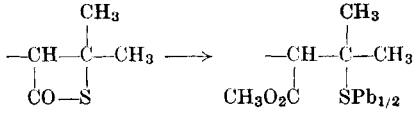
The *N*-2-methylpropenylphenaceturamide obtained was identified by its hydrolysis product, isobutyraldehyde.

B. Desulfuration with Raney Nickel

The β-thiolactone of 3-mercapto-2-phthalimidopropionic acid has been desulfurated[602] by Raney nickel in absolute ethanol under reflux, to give phthalimidopropionaldehyde and the corresponding alcohol.

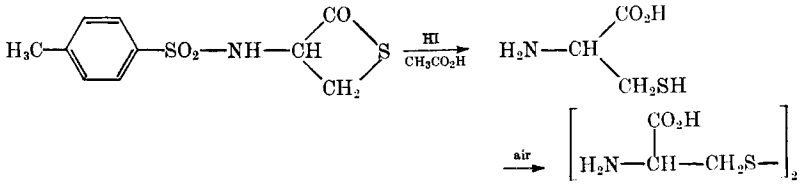
C. Action of Lead Acetate

When the β-thiolactone of *N*-phenaceturyl-3-mercaptovaline was refluxed with lead acetate in methanol, opening of the ring occurred:[605]



D. Hydrolysis, Saponification and Alcoholysis

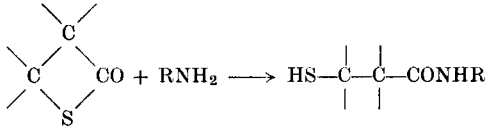
Hydrolysis of the β-thiolactones by cold neutral water is slow.[605] With hot water, the corresponding thiol acid is usually obtained. The β-thiolactone of 3-mercapto-2-(toluene-*p*-sulfonamido)propionic acid, or its polymer, can be hydrolyzed to cysteine which is oxidized in air to cystine:[603]



The β-thiolactone of 3-mercapto-2-phthalimidopropionic acid[602] behaves similarly. Other examples of acid hydrolysis,[602, 603, 608] saponification[603, 605, 608] and alcoholysis[602, 605] have been reported.

E. Reaction with Amines and the Preparation of Polypeptides

The most interesting reaction of the β-thiolactones and the one which has been most thoroughly studied is that which occurs with amines. In most instances benzylamine or aniline was used. In all cases the exclusive formation of a 3-mercaptoamide was observed:[602, 603, 605, 608]



The addition of α-amino acids[601a, 602, 603, 608] to the β-thiolactones, which are acylating agents similar to the mixed anhydrides, has been used for the stepwise synthesis of polypeptides containing up to five amino acid units.[606, 607] Cysteine, as its methyl ester or sodium salt, is first allowed to react with 1 molar equivalent of the β-thiolactone derivative of a *N*-acylcysteine; the crude β-thiolactone is sometimes used:

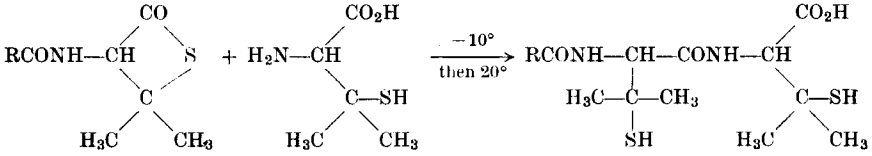
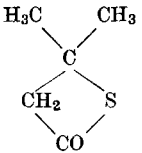
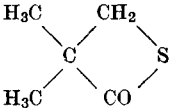
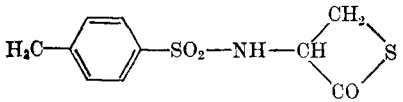
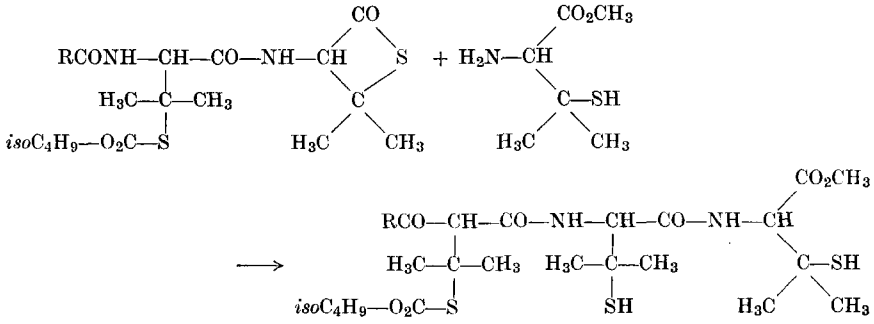


TABLE 19. Polymerization of the β-Thiolactones

Monomer	Initiator	Temperature (°C)	Time	Polythioester	Reference
	Trace of H_2O	Sealed tube			607
	H_2SO_4 (1%)	20	Several days	m.p., 65°	610
	$BF_3(C_2H_5)_2O$ (1%)	20		m.p., 80°	610
	$(C_2H_5)_3N$ (3%)	60		m.p., 85°	610
	Dilute $NaHCO_3$	20	Immediate	m.p., 175–180°; soluble in $(CH_3)_2NCOH$	603, 601a

Treatment with *iso*butyl chloroformate and triethylamine (section **IX.4.***D*) lactonizes the new mercapto acid, whereas the other thiol group is simultaneously esterified by the chloroformate. Then the product is treated with cysteine again, *etc.*:



The yields are high, particularly in view of the small quantities of materials with which these experiments were carried out.

F. Polymerization of the β-Thiolactones

Fles *et al.*[602] have proposed a mechanism to explain the formation of polythioester which occurs when 1 molar equivalent of *N*-acyl-*S*-benzylcysteine is treated with 1 molar equivalent of aluminum halide. The conditions for the formation of polythioesters from β-thiolactone monomers are listed in Table 19.

Like the corresponding β-lactone, the β-thiolactone of 3-mercapto-2,2-dimethylpropionic acid gives higher-molecular-weight polymers with alkaline initiators than with acidic initiators.[610] The polythioester in this case melts at an appreciably lower temperature than the corresponding polyester; the opposite is true if one compares the polyterephthalates with the polythioterephthalates.

XI. References

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CHAPTER VII

Trimethyleneimines

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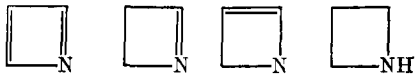
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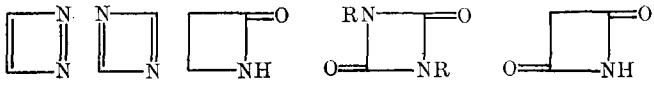
I. Introduction

The systematic name of the parent compound of the four-membered nitrogen heterocyclic series is azete (I) (R.R.I. No. 43), and in the usual way the names 1-azetine (II), 2-azetine (III) and azetidine (IV) are formed for the partially and completely hydrogenated derivatives. The name 'trimethyleneimine' is often used as a synonym for



(I) (II) (III) (IV)

azetidine and as a convenient generic term for the saturated imines, but it should not be used in forming names of more complex compounds. Names based upon the 'a' system (*e.g.* azacyclobutane) should be restricted to fused-ring systems (see section **II.3** below). The names of compounds with two nitrogen atoms are derived from 1,2-diazete (V) (R.R.I. No. 34) and urete (VI) (R.R.I. No. 35). These names are employed in *Chemical Abstracts* indexing, together with the names 2-azetidinone (VII) and uretidinedione (VIII) for the important β-lactams and isocyanate dimers, respectively, but the name malonimide is used for (IX) rather than the systematic 2,4-azetidinedione.



(V) (VI) (VII) (VIII) (IX)

All of these ring systems in all stage of hydrogenation are treated in this chapter. Among the four-membered nitrogen heterocycles the only adequately characterized substances are completely saturated compounds and their oxo derivatives. It is therefore more practical to consider the completely hydrogenated compounds as the parent substances, and the material has been organized on this basis.

II. Azetidines

The azetidines or trimethyleneimines form a limited group of compounds which have received relatively little attention, mainly because of the low yields often encountered in their preparation. In their properties the azetidines may be considered to occupy a position intermediate between that of the highly reactive ethyleneimines and the pyrrolidines. The compounds unsubstituted on nitrogen behave as typical secondary amines in most reactions, but the strained hetero-ring is fairly susceptible to cleavage.

The parent compound azetidine was the first member of the series to be described. In 1888 Gabriel and Weiner[70] obtained an impure preparation by treatment of γ-bromopropylamine with alkali, and correctly formulated the product as the four-membered cyclic imine.

Another preparation, obtained by dry distillation of 1,3-diaminopropane dihydrochloride, was recorded in 1890.[139] The compound was not thoroughly characterized until a more efficient synthesis, namely formation and reductive cleavage of the *N*-*p*-toluene-sulfonamide, was developed by Marckwald.[159, 111]

Additional preparations of azetidine and of a few simple alkyl homologs were described in the ensuing three decades, and it was recognized that, in accordance with findings in the carbocyclic series, the presence of substituents, particularly in position 3, facilitated closure of the ring and imparted enhanced stability. More recent activity in the investigation of the four-membered cyclic imines has been stimulated considerably by findings in the ethyleneimine series, and an interest in the relationship of ring-size and reactivity.

1. Azetidine

Azetidine is a colorless mobile liquid which fumes in moist air and is completely miscible with water. The b.p. is recorded as 62°/730 mm.[184] and 62.5/747 mm.[192] Vapor pressures at various temperatures have been measured;[28] at 0° it is 48.9 mm. The Trouton constant is 23.6.[28] The density is: d_4^{20} 0.8436,[111] d_4^{24} 0.8412;[184] n_D^{20} 1.4229,[192] n_D^{25} 1.4278.[184] Proton magnetic resonance results have been recorded for azetidine and several *N*-alkyl derivatives.[89]

Several studies have been undertaken to correlate the basic strength of cyclic imines and the steric effects of differing ring size, and these reveal that azetidine is one of the strongest bases among simple amines. The dissociation constants for azetidine are pK_A 11.29 (25°) and 11.04 (35°), and for *N*-methylazetidine pK_A 10.40 (25°).[192] These values are nearly identical to those for the corresponding five-membered imines and much higher than those for the ethyleneimines. The electron-donor properties indicated by hydrogen-bonding measurements confirm this relationship. With the Lewis acid trimethylboron, whose steric requirements are somewhat greater, azetidine forms an addition compound $C_3H_6NH—B(CH_3)_3$, m.p. −9° to −6°, which is appreciably more stable than that formed by pyrrolidine or any other cyclic imine.[26] Azetidine also forms an addition compound, $C_3H_6NB_2H_5$, with diborane.[28] Searles *et al.*[192] have interpreted the dissociation constants in terms of ring-size of the imines. The order of base strengths as determined by pK_A and hydrogen-bonding measurements is $4 \simeq 5 > 6 \gg 3$, and as determined by entropies of neutralization is $5 > 4 > 6 > 3$.

The ultraviolet and nuclear magnetic resonance spectra of *N*-nitroso- and *N*-nitroazetidine have been compared with those of acyclic nitrosamines and nitramines.[27a] The lower transition temperature in the nuclear magnetic resonance spectrum of nitrosoazetidine and the shorter wavelength maximum in the ultraviolet spectrum of nitroazetidine are both consistent with a decrease in N=N double-bond character in these derivatives due to the strain imposed by a double bond exocyclic to the four-membered ring.

Table 1 summarizes the properties of salts and functional derivatives of azetidine.

TABLE 1. Derivatives of Azetidine

Compound	M.p. (°C)	Reference
$C_3H_6NH \cdot HAuCl_4$	192 (decomp.)	111
$(C_3H_6NH)_2 \cdot H_2PtCl_6$	203 (decomp.)	70
$C_3H_6NH \cdot$ Picrate	166–167	70
$C_3H_6NCS_2H \cdot C_3H_6NH$	89	111
$C_3H_6NCONC_3H_6$	207	111
$C_3H_6NCONHC_6H_5$	189–190	250
$C_3H_6NCSNHC_6H_5$	110	111, 239
C_3H_6NCSNH-*p*-$C_6H_4CH_3$	144	239
C_3H_6NCSNH-*p*-C_6H_4Cl	146–147	239
C_3H_6NCSNH-*p*-C_6H_4OEt	120	239
$C_3H_6NSO_2CH_3$	81–82	127
$C_3H_6NSO_2C_6H_5$	68	111
$C_3H_6NSO_2$-*p*-$C_6H_4CH_3$	120	159
C_3H_6N–NO	196–197 (b.p.)	111
2,4,6-Tris-(1-azetidinyl)-1,3,5-triazine	256–259	186
2,5-Bis-(1-azetidinyl)-1,4-benzoquinone	255–258	162
2,5-Bis-(1-azetidinyl)-1,4-hydroquinone	250 (decomp.)	162
Bis-(1-azetidinyl)methane	67–69 (b.p.)	250

2. Substituted Azetidines

A. Methods of Preparation

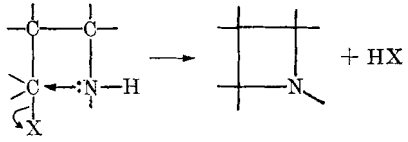
The methods available for the synthesis of azetidines can be broadly divided into two groups: (1) formation of the cyclic imine by ring closure of a suitable acyclic precursor; (2) reduction of β-lactams and malonimides. Azetidine and the homologs listed in Table 2 have all been prepared by direct ring closure of a difunctional chain. This approach is restricted essentially to variations on one reaction, the

TABLE 2. Secondary and Tertiary Azetidines prepared by Direct Ring Closure

Substituents	Method[a] (Yield)	B.p. (°C/mm.)	Derivatives (m.p.)	Reference
1-Methyl	2 (8%)	40/735	Picrate (135–136°) Picrolonate (212–213°)	192
1-Ethyl	2 (13%)	74/743	n_D 1.4090	22
1-*n*-Butyl	2 (24%)	127/748	Methiodide (150°, decomp.) Picrate (109–111°)	22, 48
1-*tert*-Butyl	2 (47%)	116/747	Methiodide (227°, decomp.)	22
1-Benzyl	2 (9%)	71–75/5	Picrate (89–90°)	243
2-Carboxylic acid	1		$[\alpha]_D - 108°$	56
3-Sulfonic acid	1			
2-Methyl	4 (78%)	74/755	*p*-Nitrobenzamide (42–43°) Methanesulfonamide (96–99°)	127, 243
2-Phenyl	4[b]		Benzenesulfonamide	131
2,3-Dimethyl	1	88	*N*-Methyl methiodide 191°)	13
3,3-Dimethyl	3 (low)		Picrate (189–190°)	137
3,3-Bis(amino-methyl)	1		Trihydrochloride (272°)	145
3,3-Bis(toluene-*p*-sulfonamido-methyl)	4[b]		*N*-toluene-*p*-sulfonamide (214°)	145
3-(Aminomethyl)-3-(hydroxy-methyl)	1	203° (m.p.)	*p*-Nitrobenzamide (170–172°)	85
1,3,3-Trimethyl	1 (80%)	73–74	Hydrochloride (150°) Hydrobromide (164–165°)	155
1,2-Dimethyl-4-*iso*propyl	1 (80%)	125–129	Picrate (128–131°)	134
4-*iso*Butyl-1,2-dimethyl	1 (79%)	152–154	Picrate (93–94°); chloroaurate of methochloride (63–64°)	135
2,4,4-Trimethyl	1	86–88	Chloroaurate (124–126°)	133
1,2,4,4-Tetra-methyl	1	93–97	Picrate (196°); chloro-aurate of etho-chloride (161–163°)	133
1-Ethyl-2,4,4-trimethyl	1 (53%)	117–118	Picrate (177°); chloro-aurate (115–116°)	136

[a] Numbers indicate methods 1–4 in the text.
[b] Only 1-arylsulfonamide reported.

internal nucleophilic displacement by an amino group, or the anion of a sulfonamido group, of a suitable leaving group in the γ-position of a three-carbon chain (Eq. 1). Ring closures with the various functional groups are discussed separately below, but certain features and limita-



(1)

tions common to all of these can be recognized. No one method has been found appropriate for all azetidines, nor is this to be expected, since different problems arise with different substituents.

There are several competing reactions which may interfere with or preclude the formation of the four-membered ring in these processes. One of the more obvious side-reactions, and one which was encountered in the earliest work, is the formation of cyclic dimers and polymers. In certain cases solvolysis, elimination, and fragmentation give by-products at the expense of the cyclic imine. Actually a relatively small number of azetidines have been synthesized by direct ring closure, and many of these preparations were recorded before the concepts and consequences of reaction mechanism and conformation were recognized. Yields were often poor, but efforts to determine the exact nature of the side-reactions or by-products were seldom made.

(1) Ring closure of γ-haloamines. The cyclization of γ-bromo- or γ-chloroamines in the presence of strong base, employed in the earliest synthesis of azetidine,[70] has been the most commonly used method for the direct formation of substituted azetidines and quaternary azetidinium salts (Table 3). This reaction has been used also for the preparation of almost all of the conidines and related fused-ring azetidine derivatives discussed below in section **II.3**. Most of the theoretical treatment and structural correlations pertaining to the synthesis of azetidines by ring closure have therefore been made in this series.

The preparation of the parent trimethyleneimine from γ-bromopropylamine is extremely inefficient; a mixture of azetidine and the dimeric bishomopiperazine is obtained, and in the most recent report of this reaction the total yield of crude steam-volatile base ranged from 6 to 26%.[186] The first-order rate constant for the cyclization of

3-bromopropylamine is 0.0005, compared with 0.036 for 2-bromoethylamine and 30 for 4-bromobutylamine.[63] These values are consistent with the generalization[183] that the ease of ring closure depends on both

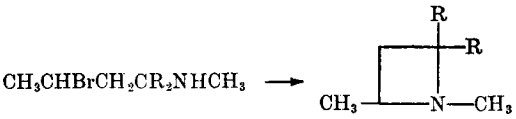
TABLE 3. Quaternary Azetidinium Halides prepared by Ring Closure of γ-Dialkylamino Halides

Substituents	X⁻	M.p. or decomp. (°C)	References
1,1-Dimethyl	Br	240–250	79
1,1-Diethyl	Br	175	78
1,1-Di-*n*-propyl	Br	52–59	78
1,1-Di-*n*-butyl	Br	120–121	78
1,1-Di*iso*amyl	Br	71–73	79
1,1-Pentamethylene (spiro)	I	174	46
1,1,2-Trimethyl[a]	$AuCl_4$	228	155
2-(2-Bromoethyl)-1,1-dimethyl	Br	209–210	30
3-(1-Chloroethyl)-1,1-dimethyl[a]	$AuCl_4$	133	157
1,1,3,3-Tetramethyl[a]	$AuCl_4$	209	155
1,1-Diethyl-3,3-dimethyl[a]	$AuCl_4$	143	155
1-Ethyl-1,2,2,4-tetramethyl[a]	$AuCl_4$	160	136

[a] Ring closure of the iodide followed by conversion to the aurichloride.

the distance between bonding centers and the ring strain of the product. The combination of these two factors operates to produce a minimum for the four-membered ring in a plot of rate *versus* chain-length.[64]

Although the cyclization of a γ-haloamine is inherently less favorable than with the lower or higher homologs, satisfactory yields of substituted azetidines have been realized. Data on the yields of simple alkyl-substituted secondary azetidines are lacking, but Mannich and Baumgarten obtained 1,3,3-trimethylazetidine from the primary bromide in 80% yield.[155] Similarly, in a series of 4-alkyl-2-bromo-4-methylaminobutanes, in which the halogen is secondary, Kohn *et*

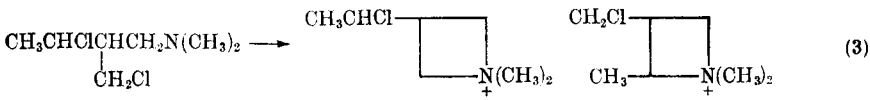


(2)

al.[133–136] reported consistently good yields of tertiary azetidines (Eq. 2). The reactions were generally performed by treating the crude bromoamine hydrobromide, obtained from the alcohol, with alkali followed

by steam-distillation. Degradative evidence for the structures of these imines was obtained, but the purity of the products may be open to question.

In contrast with the behavior of these bromides, γ-dialkylaminoalkyl chlorides, according to Mannich and Baumgarten,[155] give quaternary azetidinium salts only when the halogen is primary; treatment of 3-chloro-1-dimethylaminobutane with base caused elimination instead.[156] An illustration of the greater ease of ring closure with a primary halogen was offered with the dichloroamine (X),[157] which gave the 3-monosubstituted azetidine (Eq. 3). This structure was assigned by virtue of the fact that two different racemates of the dichloride



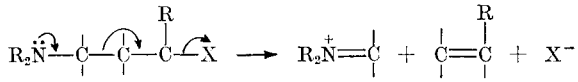
(X) (XI) (XII) (3)

both gave the same quaternary salt (XI), whereas two diastereoisomeric products (XII) would have been expected had the disubstituted azetidinium salt been formed by ring closure at the secondary chlorine atom. This and similar quaternizations, however, were carried out by the addition of sodium iodide, so that the selectivity observed does not reflect the greater ease of displacement of the primary chlorine by the tertiary nitrogen but rather by iodide ion, and the ring closure thus depends on competition between primary iodine and secondary chlorine.

The success of the ring closure with a secondary halide is actually governed by several factors. If the reaction conditions favor a concerted displacement, cyclization (or dimer formation) may be the predominant reaction. If the halide reacts by an S_N1 type process, however, ring closure is only one of several paths available, and may be suppressed by competing reactions of elimination and fragmentation. This latter case will invariably obtain with tertiary halides, and no azetidines have been obtained from γ-amino tertiary halides. These same considerations apply with other leaving groups.

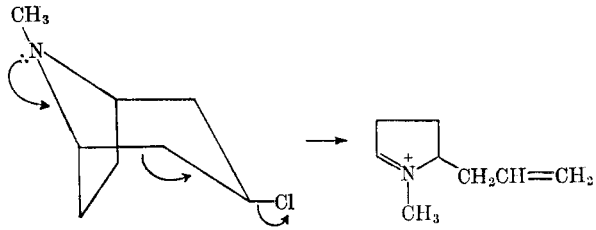
In addition to the nature of the medium, the stereochemistry of the halide may have a profound effect on the course of the reaction. This point has been discussed in detail by Grob[87, 88] in connexion with the fragmentation of γ-amino halides. In this reaction, when the proper conformation can be achieved, cleavage takes place according to

Eq. (4) with formation of an olefin and products derived from the immonium cation. The fragmentation can occur either by a concerted process or in two stages involving a prior dissociation of the halide ion; it is frequently the major reaction with a tertiary or secondary



(4)

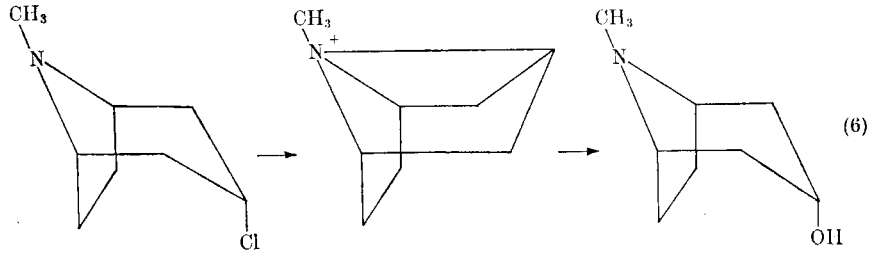
halide, but has not been observed with primary halides. The importance of stereochemical factors is illustrated by the epimeric tropanyl halides.[2] In the 3β-halide (XIII) the C_α—C_β and C_γ—Cl bonds are antiparallel, and fragmentation occurs exclusively (Eq. 5). With the



(5)

(XIII) (XIV)

axial 3α-chloride (XV) this condition is not fulfilled, and the tricyclic azetidinium intermediate (XVI) is formed by displacement in the boat form (Eq. 6); attack of solvent then leads to the tropanol (XVII) with retention of configuration.

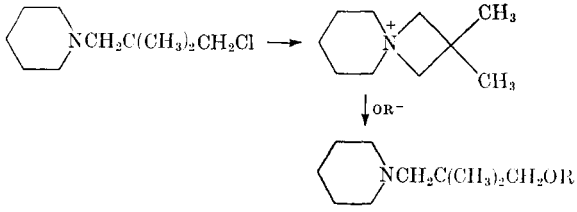


(6)

(XV) (XVI) (XVII)

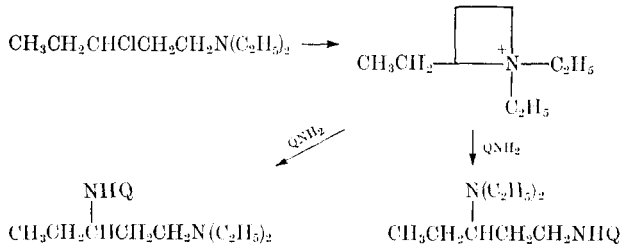
The similar incursion of azetidinium intermediates has been suggested[247] to account for the rate enhancement in the displacement reaction of a primary neopentyl halide (Eq. 7) and the formation of mixed products in the reaction 3-chloro-1-diethylaminopentane with

an 8-aminoquinoline[49] (Eq. 8). A somewhat less clear-cut case is described in the reaction of 1-chloro-3-diethylamino-2-propanol with alkali.[181]



(7)

The effect of substituents on nitrogen or at other positions in the chain cannot be very accurately assessed from the meagre data on yields in individual cases, but a few generalizations can be made. With



(8)

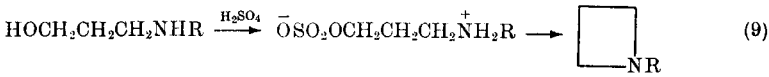
γ-halo primary amines, the formation of secondary azetidines can be expected to be complicated by further alkylation of the imine; this is probably responsible in part for the poor yield of trimethyleneimine. Several secondary azetidines have been obtained in higher yields from primary amino halides in the pentaerythritol series,[145, 161] indicating the beneficial effect of substituents in the β-positions. The effect of substitution on nitrogen has been interpreted[243] in terms of the suppression of fragmentation, a bulky group interfering with the stereoelectronic requirements for this process. This factor is not important, however, with primary halides.

The yield of azetidine in a given case will depend, of course, not only on the relative ease of ring closure but on the stability of the product as well. Thus substitution may depress the rate of formation but impart stabilization to the product. The latter effect, particularly with substituents in the 3-position of the azetidine ring, has been observed in numerous cases and is the subject of further comment

below. One case in point is the ring closure of a series of 3-bromo-1-dialkylaminopropanes studied by Gibbs and Marvel.[78, 79] The 1,1-dimethylazetidinium salt could be isolated only from very dilute solutions, and was much less stable than the quaternary bromides with larger alkyl substituents.

Vaughan *et al.* have considered the effect of substitution on the conformational requirements for azetidine formation.[243] It was suggested that the most favorable case for cyclization will be represented by a 3-aminopropyl system with a bulky group on nitrogen and no substituents on carbon, and that adjacent *threo* substituents or *gem* substituents at the 2-position will have little effect. *Erythro* substituents at C-2 and C-3, which must become eclipsed in going from the ground state to the transition state, will retard the rate of cyclization and decrease stability, whereas the effect of *erythro* substituents at C-1 and C-2 will be reflected mainly in stability.

(2) Ring closure of γ-aminoalkylsulfate or -sulfonate esters. The sulfate esters of γ-amino alcohols have been used on several occasions in place of the γ-halo amine in the preparation of 1-substituted azetidines by internal alkylation.[22] These derivatives are conveniently obtained by treatment of the amino alcohol with concentrated sulfuric acid or treatment of the amine hydrochloride with chlorosulfonic acid.[48] Reaction of the inner salts with alkali and steam distillation furnishes azetidines in yields ranging from 8 to 47%. The yield is not improved



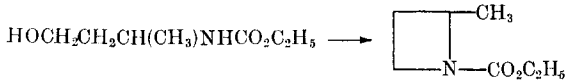
(9)

by conducting the cyclization in dilute solution.[127] It is likely that higher yields would be obtainable by this procedure in the case of azetidines substituted at other positions. In an attempt to use this procedure to prepare a secondary azetidine, γ-aminopropyl hydrogen sulfate was treated with alkali, but the yield of trimethyleneimine was less than 1%.[96] This provides a striking example of the greater difficulty of closure of the four- as compared with the three-membered imine ring; with β-aminoethyl hydrogen sulfate the yield of aziridine is nearly quantitative under optimum conditions.[249]

A modification of this approach is the use of the γ-aminosulfonate ester.[243] In the preparation of 1-benzylazetidine, decomposition of the toluenesulfonate ester of the *sec*-amino alcohol gave a 26% yield of the

imine compared with 5–9% with the alkyl hydrogen sulfate.[243] The usefulness of this alternative is mitigated, however, by the greater difficulty of preparation of the intermediate amino tosylate esters.

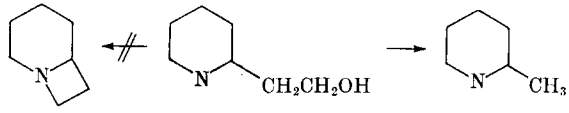
The direct conversion of a γ-amino alcohol into an azetidine has not been accomplished, although the hydroxyurethane (XVIII) is reported[171] to undergo ring closure to the azetidine carboxylate (XIX) at elevated temperatures (Eq. 10). The cyclization of an amino alcohol



(10)

(XVIII) (XIX)

by treatment with Raney nickel has been found to be an effective method for the closure of a five-membered ring in octahydropyrrocoline, but this reaction failed in an attempted synthesis of conidine (XX) from 2-(β-hydroxyethyl)piperidine (XXI), dehydroxymethylation to α-pipecoline occurring instead[141] (Eq. 11). In the special case of 2,2-

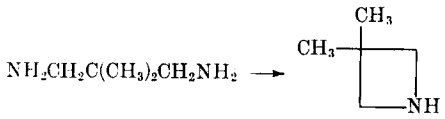


(11)

(XX) (XXI)

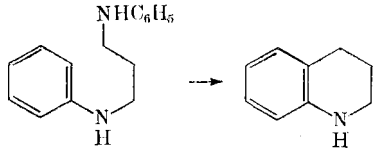
dinitro-1,3-propanediol, treatment with ammonia is claimed to give 3,3-dinitroazetidine.[188]

(3) Ring closure of 1,3-diamines. The thermal decomposition of diamine dihydrochlorides, a method often used for the preparation of five- and six-membered cyclic amines, has found few applications in the azetidine series, and no satisfactory preparations by this reaction have been recorded. Ladenburg and Sieber[139] obtained a very low yield of trimethyleneimine, together with β-picoline, by dry distillation of 1,3-diaminopropane dihydrochloride. A similar preparation of 3,3-dimethylazetidine has been reported to proceed in very low yield[137] (Eq. 12).



(12)

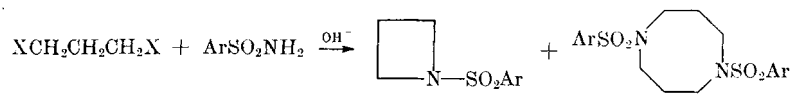
Two reports of the ring closure of 1,3-diamines have been found to be in error. The hydrochloride of tetrakis(aminomethyl)methane was reported[84] to pass readily into a spirocyclic azetidine derivative, but in later work Litherland and Mann[145] found the hydrochloride to be unaffected by treatment with concentrated hydrochloric acid at 160°. Another case in which formation of an azetidine was thought to occur was in the distillation of 1,3-dianilinopropane. Scholtz[190] obtained the diamine from trimethylene dibromide and excess aniline, and on distillation a base, $C_9H_{11}N$, was isolated and assigned the 1-phenylazetidine structure. On reinvestigation of this process,[51] a similar product was obtained, but the compound was shown to be tetrahydroquinoline, arising by an internal Hofmann–Martius reaction.



(13)

Another preparation of 1-phenylazetidine, by distillation of 3-anilino-*n*-propylamine, was also recorded in the early literature.[7] This transformation, which seems unlikely in the light of the uniformly unsuccessful results in other cases, has never been confirmed.

(4) Formation and reduction of 1-arylsulfonazetidides. Although the direct formation of a trimethyleneimine by cyclization of a 1,3-dihalide and an amine or ammonia has not been accomplished, closure of the four-membered ring occurs smoothly on dialkylation of a sulfonamide. This method, originally developed by Marckwald,[159] is particularly useful with the parent azetidine, in which yields by direct cyclization to the base are consistently very low. The related dialkylation of cyanamide with a dihalide was found[186] to give negligible amounts of the *N*-cyanoazetidine.

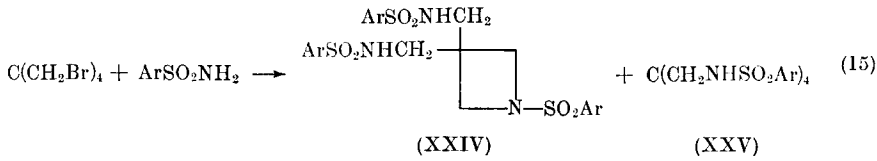


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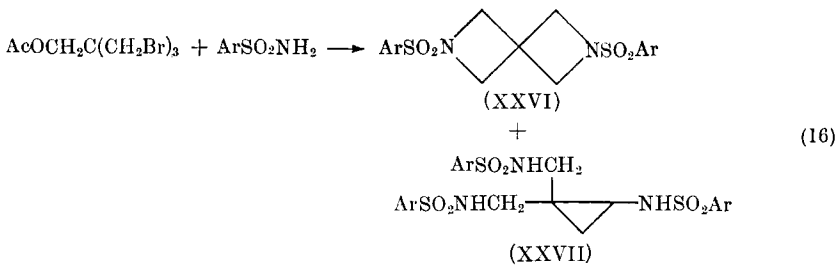
(XXII) (XXIII)

The preparation of azetidine-*p*-toluene-sulfonamide (XXII) from trimethylene chlorobromide proceeds in 55% yield.[192] The product

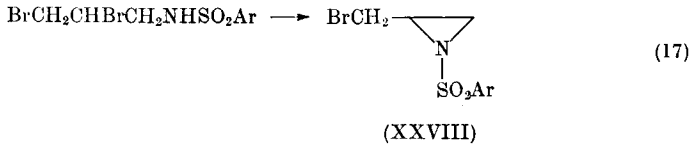
obtained with the dibromide is accompanied by a minor amount of the eight-membered disulfonamide (XXIII). Alkylation of the sodio derivative of *p*-toluene-sulfonamide with pentaerythrityl tetrabromide



(Eq. 15) gave the bis(*p*-toluene-sulfonamidomethyl)azetidine sulfonamide (XXIV) as a by-product together with the tetrakissulfonamide (XXV).[145] With pentaerythrityl tribromide monoacetate (Eq. 16), the reaction with *p*-toluene-sulfonamide leads to a mixture of the spirodisulfonamide (XXVI) and a cyclopropane derivative (XXVII).



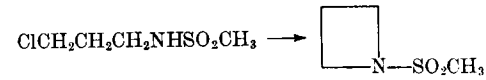
The more facile formation of a three-membered aziridine ring in preference to an azetidine in this reaction was demonstrated by Gensler,[75] who showed that the product obtained from 1-benzenesulfonamido-2,3-dibromopropane and base (Eq. 17) was the ethyleneimine (XXVIII). This observation is interesting in light of the fact that



only the piperazine derivative, and no aziridine sulfonamide, is obtained by alkylation of *p*-toluene-sulfonamide with ethylene dibromide.[159] Several other β-halo sulfonamides, however, also give aziridines (Chapter II).

Cyclization of the readily available γ-*p*-toluene-sulfonamidopropyl

tosylates with sodium ethoxide is also quite efficient,[243] giving an 80% yield in the case of *p*-toluene-sulfonazetidide. High dilution techniques increased the yield markedly in the preparation of the 2-methyl-azetidine sulfonamide. Methanesulfonazetidide (XXX) was isolated in 67% yield by cyclization of the γ-chloropropylsulfonamide (XXIX).



(18)

(XXIX) (XXX)

Conversion of the monocyclic sulfonamides into the free amines can only be accomplished by reductive methods since the azetidine ring does not in general survive drastic hydrolytic treatment. The reduction of *p*-toluene-sulfonazetidide with sodium and pentanol, originally described as nearly quantitative, has subsequently been reported to give widely divergent results, with yields ranging from 14 to 80%.[118, 186, 251] The low yields obtained in some cases may have been due to inadequate precautions against the loss of volatile base. The γ-hydroxy amine has been found as a by-product.[251] The reduction has been accomplished in low yield with sodium–liquid ammonia[28] and also with lithium aluminum hydride;[127] hydrogenation with copper chromite is ineffective.[186]

(5) Reduction of azetidinones and malonimides. The reduction of lactams to the corresponding cyclic imines with lithium aluminum hydride is a highly satisfactory and general method with five-, six-, and seven-membered ring compounds, and several efforts to apply this transformation to the preparation of azetidines from β-lactams have been made. In the earlier attempts[213, 15, 127] azetidinones with a phenyl or benzyl substituent on nitrogen were used, and ring cleavage to the corresponding *sec*-aminopropanol was observed in every case as the major or exclusive reaction. Attempts to effect this reduction with other hydride reagents were equally unproductive.

This approach was brought to fruition as a general method for the preparation of 3,3-disubstituted azetidines, however, by Testa, Fontanella and Cristiani,[232] who found that the corresponding azetidinones without a substituent on nitrogen were reduced with lithium aluminum hydride to the imines (Table 4). The reduction is carried out at very low temperatures, and the yields are usually about 70–80%. The reduction of both carbonyl groups in 3,3-disubstituted-1-unsubstituted malonimides to the azetidines has also found to be a generally useful

TABLE 4. 3-Substituted Azetidines from Azetidinones

Monosubstituted

Substituent	Yield (%)	B.p. (°C/mm.) or m.p. (°C)	M.p. of picrate (°C)	M.p. of *N*-acetyl derivative (°C)	Reference
*iso*Butyl	68	80/51	127		230a
Cyclohexyl	50	90/15			230a
Benzyl	49	98/0.8			230a
Phenyl	54	88/3.5	150	Oil	237
p-Tolyl	40	83/0.4	151		20a
p-Anisyl	45	92/0.3	152		20a
p-Nitrophenyl[a]	67		152	129	20a
p-Aminophenyl[a]	69		205	157	20a
p-Chlorophenyl[a]	81		174	82	20a
p-Bromophenyl[a]	61		173	82	20a
p-Cyanophenyl[a]	65		185	96	20a
p-Hydroxyphenyl[a]	78	140	214	194	20a
α-Naphthyl	45	151/1.0			230a
p-Biphenylyl	42				230a

Disubstituted[b]

Substituents	Yield (%)	B.p. (°C/mm.) or m.p. (°C)	M.p. of picrate (°C)	M.p. of carbamate (°C)
Methyl, phenyl	65	73/0.9	154	176
Ethyl, phenyl	71	86/0.1	163	156
n-Propyl, phenyl	74	89/0.4	198	166
*iso*Propyl, phenyl	75	36–38	179	160
n-Butyl, phenyl	74	85/0.2	175	131
Cyclohexyl, phenyl	75	85–87	218	174
Benzyl, phenyl	86	62–64	201	
Diphenyl	43	95–96	222	
Dimethyl	45	91/760	190	184
Diethyl	71	51/20	128	180
Di-*n*-propyl	73	87/20	138	
Di-*n*-butyl	87	110/15	145	115
Ethyl, benzyl	29	130/0.4	178	

[a] Prepared by substitution of 1-acetyl-3-phenylazetidine; the yield given is that of acetyl derivative in the substitution step.

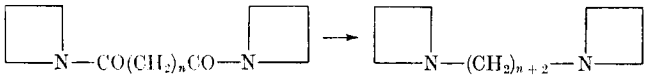
[b] Reference 232.

[c] Reference 236.

reaction.[234] The requirement of an unsubstituted lactam nitrogen atom was confirmed in both series; the presence of an alkyl group completely changed the course of the reaction, leading exclusively to the substituted aminopropanol. This effect of a *N*-substituent is consistent with the generally accepted mechanism of amide reductions (cf. section **III.2.***B* below).

This method is applicable also to 3-monosubstituted azetidinones, 3-phenylazetidine being obtained in 58% yield from the lactam. Since these azetidinones are readily obtained *via* substituted cyanoacetic esters [section **III.1.***A*.(**4**) below], a large series of 3-substituted imines is potentially available. The lithium aluminum hydride reduction should presumably also succeed with 4-substituted-2-azetidinones, but there are as yet no general routes to these precursors in which the nitrogen is unsubstituted.

Although tertiary azetidines cannot be prepared directly from the β-lactams, Testa *et al.* have found[236, 230a] that *N*-acyl-3-substituted azetidines are smoothly reduced with lithium aluminum hydride to the tertiary amines. Several 1,1′-poly(methylene)bisazetidines (XXXI) have also been obtained in this way, and this process should be applicable to a wide series of tertiary azetidines.



(19)

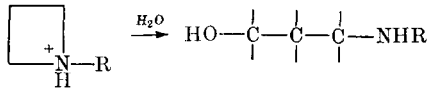
(XXXI)

B. Chemical Properties and Reactions of Azetidines

Excluding the azetidinones and malonimides, only a few azetidine derivatives with functional groups attached directly to ring carbon atoms have been prepared, and of these only the 2-carboxylic acid (section **II.2.***C* below) has been adequately characterized. The possible existence of the 3-keto derivatives is mentioned in section **III.1.***D*.(**1**). Virtually all of the chemistry of azetidines, therefore, concerns the reactions of the imine function or various ring-cleavage processes.

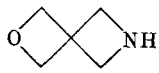
The instability of trimethyleneimine towards mineral acids was noted in the earliest description of the compound,[159] and hydrolysis of the ring has been considered a more-or-less typical property of the class. No systematic studies of the ring cleavage have been made, but Testa *et al.*[236, 237] showed that *C*-substituted azetidines, particularly 3,3-disubstituted compounds, behave as stable secondary amines, and

it is clear that broad generalizations will have little validity. The driving force for the C—N bond breaking, which occurs by attack of a nucleophile on the conjugate acid (Eq. 20), is relief of strain, and as



(20)

strain is reduced by the introduction of geminal substituents, ring-opening becomes increasingly difficult. The lower susceptibility to cleavage of the trimethyleneimine ring as compared with the ethyleneimines is reflected in the absence of alkylating properties, mentioned in section **II.2.***C*.(**1**). The azetidine ring is very stable towards strong acid in the spiro compounds derived from pentaerythrityl amines (section **II.3.***B*), and the imine ring survives conditions which cleave the oxide



(XXXII)

ring in the oxazaspiro system (XXXII).[110] The polymerization of azetidine with boron trifluoride catalyst has been shown by Jones[118] to be much slower than that of ethyleneimine. Azetidine is stated to be largely unchanged by treatment with alumina at 360°.[250]

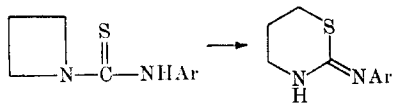
The stability of the four-membered imine ring towards strong base or reducing agents such as sodium in alcohol or metal hydrides is demonstrated by the use of these conditions in several preparative methods. The behavior toward catalytic hydrogenation is less well known. Azetidine has been obtained by the hydrogenolysis of 1-benzylazetidine with palladium–carbon catalyst at room temperature, but the yield was only 50% and some hydrogenolysis of the ring may have occurred.[127] Azetidine *p*-toluene-sulfonamide is unaffected by hydrogenation with Raney nickel at 100°.[127] The only information on oxidation products of azetidine is a statement by Yanbikow[250] that acrolein and ammonia are produced by treatment with hydrogen peroxide.

The conversion of secondary azetidines into amides, carbamates, sulfonamides and ureas is accomplished without difficulty by the usual procedures; a number of these derivatives are listed in Tables 1, 2 and 3. An extensive survey of these reactions has been carried out with 3-phenylazetidine.[237] *N*-Nitroso derivatives are obtained with nitrous acid, and *N*-nitroso-3-phenylazetidine has been reduced with lithium

aluminum hydride to the *N*-amino derivative, which behaves as a typical 1,1-disubstituted hydrazine. Attempted reduction of the nitroso compound with zinc and acid caused hydrolysis to the azetidine.[237] The oxidation of *N*-nitrosoazetidine to the *N*-nitro derivative with peroxytrifluoroacetic acid has been accomplished in 47% yield.[27a] Reduction of *N*-nitrosoazetidine with sodium hydrosulfite results in the formation of cyclopropane, presumably by way of an azene intermediate; the direct deamination of the imine proceeds by a similar path on treatment with difluoramine to give a 40% yield of cyclopropane.[27b]

Except for the reductive cleavage of sulfonamides with sodium and alcohol [section **II.2.***A*.(**4**)], the only report of the hydrolysis of amides and related derivatives to the free bases is that of Bonati *et al.*[20a] A series of *p*-substituted 3-phenylazetidines was prepared by nitration of *N*-acetyl-3-phenylazetidine followed by reduction, diazotization and Sandmeyer reactions. The free azetidines were then obtained by hydrolysis of the amides with refluxing hydrochloric acid. The yields were high, and no ring-cleavage products were observed.

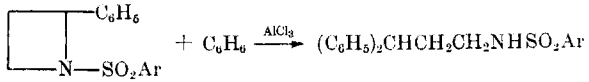
Two rearrangements of *N*-functional azetidines under acid conditions have been recorded. Tisler[239] has observed that arylthioureas (XXXIII) of azetidine are converted in nearly quantitative yield into



(21)

(XXXIII) (XXXIV)

the 2-aryliminotetrahydrothiazines (XXXIV) by warming with concentrated hydrochloric acid (Eq. 21). The other reaction is the conversion in 70% yield of 1-benzenesulfonyl-2-phenylazetidine with benzene and aluminum chloride into 3,3-diphenyl-1-benzenesulfonamidopropane (Eq. 22).[131]



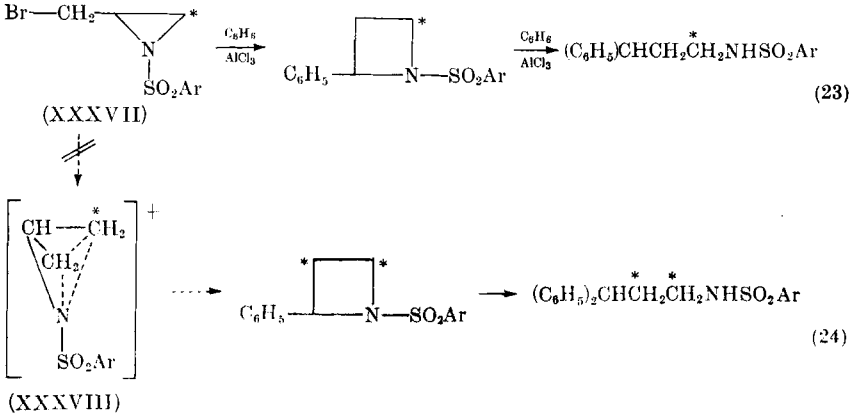
(22)

(XXXV) (XXXVI)

The latter ring cleavage is of importance in connexion with the mechanism of the rearrangement of 2-bromomethyl-1-benzenesulfonylaziridine (XXXVII) in benzene under Friedel–Crafts conditions

to give the diphenylpropylsulfonamide (XXXVI). This unusual reaction was observed by Gensler and Rockett,[76] who ruled out several possible intermediates and suggested a mechanism involving initial ring expansion to the azetidine (XXXV). Such a path recalls similar rearrangements of cyclopropylcarbinyl derivatives, which are known to proceed *via* non-classical bridged carbonium ions.

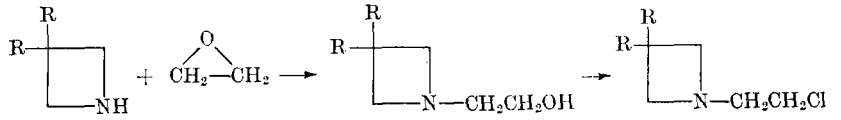
In an investigation of the mechanism, Koehler,[131] using [3-^{14}C]-bromomethylaziridine, found that the final product contained tracer only in the carbon adjacent to the sulfonamide group, and interpreted the results in terms of the mechanism shown in Eq. (23). Had the non-classical ion (XXXVIII) been involved, ^{14}C would have appeared at two places in the final product. Although the azetidine has not been isolated nor identified as a long-lived species in the reaction, the tracer experiment, together with the independent demonstration that (XXXV) does give the final product, provides very convincing evidence for the formation and subsequent cleavage of the azetidine.



The formation of tertiary azetidines from the secondary imines can be accomplished by hydride reduction of the amides[236, 237] or by reductive alkylation of the imine with lithium aluminum hydride in the presence of ethyl acetate. Tertiary azetidines can also be obtained by direct alkylation. Azetidine and methyl iodide in ether solution furnish *N*-methylazetidine hydriodide;[250] a contrary report by Gibson *et al.*[80] is clearly in error. Reaction of the secondary bases with ethylene oxide (Eq. 25) gives the *N*-hydroxyethylazetidines which can

be converted with thionyl chloride into the stable primary chlorides (XXXIX).[238]

The quaternization of tertiary azetidines with alkyl bromides or iodides is uncomplicated, and a number of quaternary azetidinium salts have been obtained in this way in addition to those prepared by

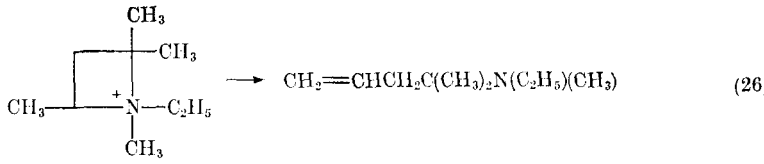


(25)

(XXXIX)

direct cyclization of tertiary amines (Table 3). Methiodides have also been obtained directly from the secondary imines with excess methyl iodide.[133] A low yield of 1,1-dimethylazetidinium iodide, together with a large amount of trimethylene diiodide, was obtained from the reaction of azetidine *p*-toluene-sulfonamide and excess methyl iodide at high temperature.[170]

The data available on the stability of *N*,*N*-dialkylazetidinium salts do not give a completely consistent picture. Mannich and Baumgarten[155] found that several 1,1-dialkyl-3,3-dimethylazetidinium chlorides, including the 1,1-dimethyl derivative, were transformed on heating to the 3-chloro-2,2-dimethylpropyl amines. The corresponding *N*,*N*-diethyliodides on heating gave a mixture of products including ethylene and amine hydriodides. Gibbs and Marvel[78,79] studied a series of 1,1-dialkylazetidinium bromides and observed that the 1,1-dimethyl derivative decomposed rapidly to a linear polymer; the higher homologs polymerized very much more slowly.

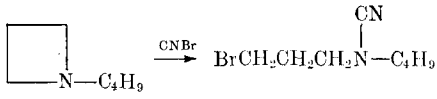


(26)

(XL)

The Hofmann elimination of several quaternary azetidinium hydroxides was carried out by Kohn and Morgenstern[136] and Kohn and Giaconi.[135] Ring cleavage was observed in all cases; with 1-ethyl-1,2,2,4-tetramethyl azetidinium hydroxide (Eq. 26), the normal

product (XL) was obtained. The identification of the methine in certain other cases was not completely unequivocal. The von Braun cyanogen bromide reaction of 1-*n*-butylazetidine also leads to ring opening, with the formation of *N*-(3-bromopropyl)-*N*-*n*-butylcyanamide (XLI) in 85% yield (Eq. 27).[48]

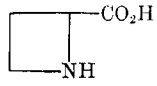


(27)

(XLI)

C. Natural Occurrence and Pharmacological Properties

(1) Naturally occurring azetidines. The only compound containing a trimethyleneimine ring that has been found in nature is (−)-azetidine-2-carboxylic acid (XLII). This compound was isolated by



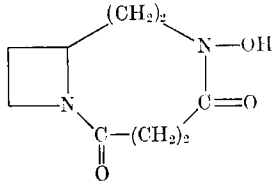
(XLII)

Fowden[56] and by Virtanen and Linko[245] in relatively large amounts from the seeds and leaves of *Convallaria majalis* and the rhizomes of *Polygonatum officianilis*.[57] It is the principal free amino acid in several plants of the Liliaceae and Agavaceae, including species of the genera *Rhodea*, *Bowiea* and *Dracanea*, and has been identified as a constituent of more than 20 of 90 species examined.[59]

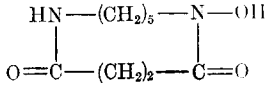
The constitution of the amino acid was recognized from the empirical formula and the instability of the compound under acidic conditions. γ-Amino-α-chlorobutyric acid[56] and homoserine[144] were identified by paper chromatography among the products resulting from treatment with hydrochloric acid, and the structure was then confirmed by comparison with an authentic sample prepared by treatment of γ-amino-α-bromobutyric acid with barium hydroxide. The biogenetic pathway and metabolism of this unusual amino acid are obscure; neither aspartic acid nor α,γ-diaminobutyric acid, which is also present in *P. multiflorum*, serve as precursors for the azetidine. This question is discussed further in section **II.4**.

Another natural product which for some time was thought to be

an azetidine derivative is the actinomycete metabolic product nocardamine,[226] which was considered to be (XLIII) on the basis of preliminary structural studies. A reinvestigation, however, has revealed that the compound is instead the 11-membered cyclic hydroxamic acid (XLIV).[27]



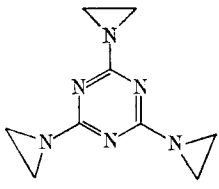
(XLIII)



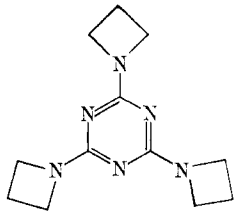
(XLIV)

(2) Pharmacological properties of azetidines. Little has been published on the pharmacological evaluation of azetidines, although several synthetic studies have been prompted by structural analogies of the trimethyleneimine system with other pharmacologically active compounds.

One of the considerations that has attracted attention is the possibility that certain azetidines might display the alkylating properties of the lower aziridine homologs such as triethylenemelamine (XLV) which has shown promise as a chemotherapeutic agent in neoplastic diseases. This nitrogen-mustard type of activity has not, however, been found in an azetidine derivative. The 2,4,6-tris-(1-azetidinyl)-*sym*-triazine (XLVI) shows no appreciable activity,[186] and *N*,*N*-diethylazetidinium ion has been found ineffective in the alkylation of cysteine.[240]



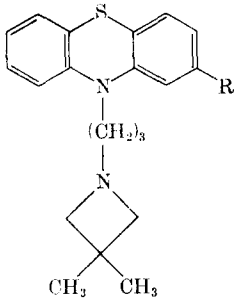
(XLV)



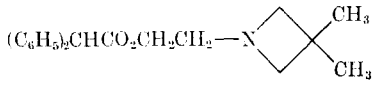
(XLVI)

Another structural relationship has been examined by Testa *et al.*[238] The 3,3-dialkylazetidine ring can be considered as a dialkylamino group with the alkyl radicals tied together, and analogs of a

number of important chemotherapeutic agents were prepared in which the ubiquitous diethylaminoalkyl group was replaced by the 2-[1-(3,3-dimethylazetidinyl)]ethyl unit. Among others were the phenothiazine derivatives (XLVII) and the antispasmodic analog (XLVIII).



(XLVII, R = H, Cl)



(XLVIII)

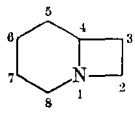
The pharmacological properties of these derivatives were not qualitatively different from those of the respective dialkylaminoalkyl compounds. Azetidine analogs have been included on a few other occasions in series of compounds for biological testing without noteworthy results.[5, 99]

3. Fused-Ring and Spirocyclic Azetidines

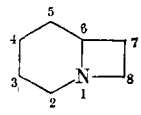
A. Fused-Ring Systems

A number of bi- and polycyclic ring systems which contain at least one four-membered nitrogen-containing ring are recorded in the Ring Index. Some of these, appearing in a single reference in the older literature, are completely implausible and do not warrant comment. Only those systems that are well authenticated or have been widely discussed are treated in this section.

(1) Conidine (1-azabicyclo[4.2.0]octane) (R.R.I. No. 870). The name conidine was coined by Löffler,[149] with the numbering indicated in (XLIX). This numbering is inconsistent with the general rules of



(XLIX)



(L)

nomenclature for bicyclic compounds, which prescribe the numbering shown in (L). Since the original papers by Löffler and co-workers,[146–150] only one article has appeared in which additional derivatives were reported, and the older numbering was retained to avoid confusion.[141] Use of the approved numbering would require revision of the names of every derivative in the literature to date, and it is suggested that the traditional numbering continue to be used with the trivial name 'conidine'; this practice will be followed here. It would seem appropriate to use the official numbering when a name is based on the azabicyclo system.

TABLE 5. Conidine and Homologs

Compound	B.p. (°C)	Derivatives, m.p. (°C)	Reference
Conidine	142–143	Picrate, 241–243; methiodide, 203–204[a]	141
2-Methylconidine	143–145	Chloroaurate, 198–199	146
Iso-2-methylconidine[b]	151–153	Chloroaurate, 166	146
3-Methylconidine	158	Picrate, 194–195	147
8-Methylconidine	154–158	Picrate, 237[150], 242[141]	150
2-Ethylconidine	176–183[c]	Picrate, 198	149
7-Ethylconidine	182		141
6,8-Dimethylconidine	170–172	Picrate, 239	141
6,8,8-Trimethyl-5-dehydroconidine			164

[a] Several other quaternary halides and bis-quaternary salts were also prepared.
[b] Diastereoisomer.
[c] Mixture of diastereoisomers.

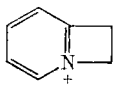
Interest in this bicyclic system, as with the related indolizidines and pyrrolizidines, arose during alkaloid studies. Conhydrine, one of the alkaloids of poison hemlock, was converted by various treatments into mixtures of unsaturated bases called the 'coniceines'.[160] Two of these bases, α-coniceine and ϵ-coniceine, were eventually shown in synthetic work by Löffler to be stereoisomers of 2-methylconidine. The conidine ring system is not found in any of the naturally occurring *Conium* alkaloids.

Conidine and the homologs listed in Table 5 were prepared by treatment of the corresponding 2-(β-haloalkyl)piperidine hydrohalides with aqueous base. The yields in a series of four β-chloroethylpiperidines were 63–73%;[141] much lower yields were obtained at high tem-

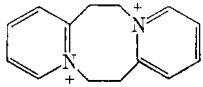
perature in diethylene glycol solution. In a few cases mixtures of diastereoisomers were obtained; these were separated by distillation in the case of 2-methylconidine (ϵ-coniceine).[146] Several conidine derivatives have been synthesized by the sequence described in section **II.3.***A*.(**2**) below for the 1-azabicyclo[3.2.0]heptane system, and this route promises to be a very general one.[164]

Conidine is a strong base (pK_A 10.4)[141] and readily forms quaternary salts. On standing the viscosity gradually increases and a soft polymer is obtained. The polymerization is accelerated by a trace of methyl iodide, and much more effectively by boron trifluoride etherate. With *d*- and *l*-conidine, boron trifluoride-catalyzed polymerization gives crystalline isotactic polymers of high molecular weight.[241]

Unsaturated quaternary conidinium salts. During their work on the preparation of conidines from β-haloethylpiperidines, Löffler and co-workers[147,149] also examined the cyclization of several 2-(β-haloethyl)pyridines with base, and obtained crystalline quaternary salts. These were called 'pyridonium halides' and were assigned the structure (LI). These formulations were called into question by Boekelheide

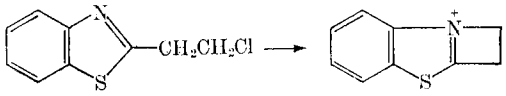


(LI)



(LII)

and Feeley[19] who hydrogenated the supposed conidinium derivative and obtained a high-boiling base which was shown to be dimeric. The pyridine cyclization product is thus presumably the tricyclic bis-diazocinium derivative (LII); the same substance was obtained by heating 2-vinylpyridine hydrobromide. With 2-(β-bromopropyl)-pyridine, in which the halogen is secondary, the product is not the dimer but the elimination product, 2-propenylpyridine hydrobromide.[117]

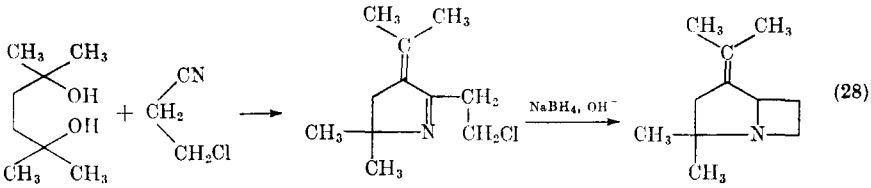


(LIII)

The analogous quaternization of 2-(β-chloroethyl)benzothiazole to give a four-membered ring product (LIII) is claimed in a patent.[12] In the light of Boekelheide's findings the product of this reaction is

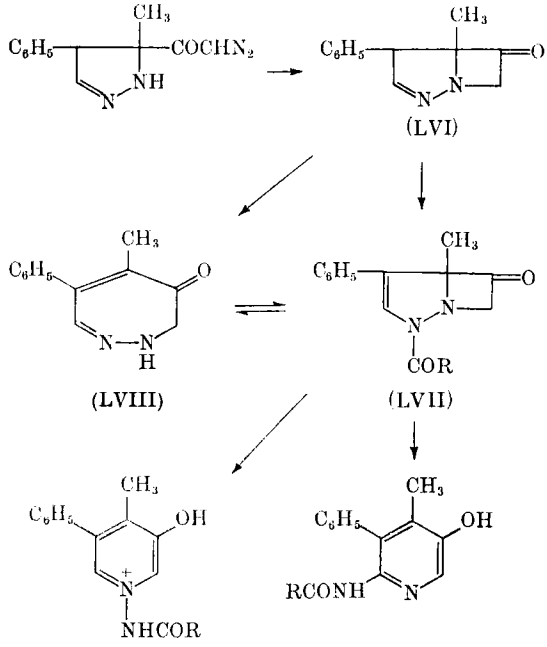
probably best represented as the eight-membered dimer also. In view of the absence of any authenticated example of a system comprising a four-membered ring fused through a quaternary nitrogen atom to an aromatic ring, and the great reactivity implied in this system (section **II.4**), it seems that due caution should be exercised in the attribution of such structures.

(2) 1-Azabicyclo[3.2.0]heptane. The first compound with this ring system was described in 1961 by Meyers and Libano.[165] The synthetic route comprised the cyclization of a 2-(β-chloroethyl) pyrrolidine, which was obtained by an ingenious application of the Ritter reaction using a diol and a β-chloronitrile (Eq. 28). The initially-formed pyrroline (LIV) was reduced with sodium borohydride and the pyrrolidine cyclized under mild alkaline conditions without isolation of either intermediate. The overall yield of the bicyclic base (LV) (b.p. 198°; picrate, m.p. 167°) based on the diol was 60%.



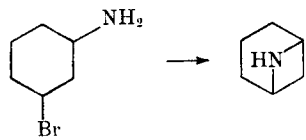
(LIV) (LV) (28)

(3) 1,2-Diazabicyclo[3.2.0]heptane. This system has been obtained in only one series, and is represented by the unsaturated ketones (LVI) and (LVII).[158, 167] The four-membered heterocyclic ring was formed by treatment of the diazoacetylpyrazoline with acetic acid (Eq. 29); this is the only recorded preparation of an azetidine derivative by this reaction. These compounds also represent the only example of a carbonyl group in the β-position of the four-membered imine ring. Acylation of the imino ketone (LVI) (picrate, m.p. 114°) gives the amide (LVII), but most of the reactions of (LVI) and (LVII) involve scission of the bridging C—N bond. An interesting feature is the reversible interconversion of the diazabicycloheptane and diazepine (LVIII) systems, which provides another path for the formation of the bicyclic ketone. Other reactions of the ketone (LVII) under relatively mild conditions lead to a diversity of rearrangement products, among them the two pyridine derivatives indicated in Eq. (29).



(29)

(4) 6-Azabicyclo[3.1.1]heptane (R.R.I. No. 812). This system is represented by a single example. The parent imine (LIX) (picrate, m.p. 158–162°) was obtained by von Braun, Haensel and Zobel[23] by cyclization of 3-bromocyclohexylamine (Eq. 30). The latter was prepared from the alkoxyoxime by reduction and cleavage with hydrogen

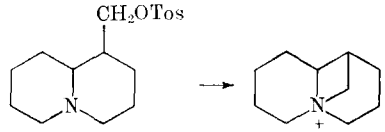


(30)

(LIX)

bromide and was presumably a mixture of isomers. The imine was obtained in admixture with secondary and tertiary amines and tetrahydroaniline; fragmentation products were probably formed as well. The bicyclic imine was separated from the unsaturated amine by destruction of the latter with nitrous acid. The bicyclic base was characterized by formation of an alkali-insoluble sulfonamide and hydrogenation to cyclohexylamine.

(5) 1,5-Methano-2*H*-quinolizinium (R.R.I. No. 2177). The decahydro derivative (LX) (picrate, m.p. 207°) of this interesting tricyclic quaternary system was prepared by Galinovsky and Nesvadba[71] during stereochemical studies in the lupin alkaloid series. The *p*-toluenesulfonate ester of lupinine was found to cyclize spontaneously to the quaternary tosylate (Eq. 31), establishing the *trans* relationship of the hydroxymethyl group and the bridgehead hydrogen atom.



(31)

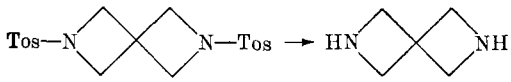
(LX)

(6) 7-Azabicyclo[4.2.0]octane (R.R.I. No. 813). Although this ring system should present no special synthetic difficulty, no authentic members have been recorded. For many years this ring system was thought to represent, in the form of the β-lactam, the acyl derivatives of anthranilic acids. These compounds, the acylanthranils, are discussed in section **III.3**

B. Spirocyclic Systems

The spirocyclic azetidines are of two types, with carbon or quaternary nitrogen as the common atom; none of these systems presents features of special interest or importance.

(1) 2,6-Diazaspiro[3.3]heptane (R.R.I. No. 744). The parent compound of this system was characterized by Litherland and Mann[145] (dihydrochloride, m.p. 275°; di-*o*-nitrobenzamide, m.p. 218°). The



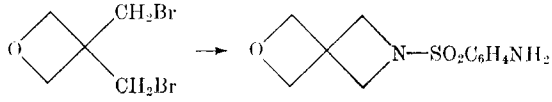
(32)

(LXI)

diamine (LXI) was prepared by acid hydrolysis of the di-*p*-toluenesulfonamide, which was obtained as a by-product in the reaction of pentaerythritol tribromide monoacetate with sodio-*p*-toluene-sulfonamide (Eq. 16). Only the tetrakis(sulfonamidomethyl)methane and the monocyclic azetidine derivative were formed in the corresponding

reaction of pentaerythrityl tetrabromide (Eq. 15). The survival of the spirobisazetidine during vigorous acid hydrolysis attests to the stability conferred by 3,3-disubstitution in the two rings.

(2) 2-Oxa-6-azaspiro[3.3]heptane (R.R.I. No. 745). The *N*-sulfanilyl derivative (LXII) (m.p. 126°) of the parent spirocyclic base was obtained by Hoste and Govaert[110] from the reaction of 3,3-bis(bromomethyl)oxetane with the sodio derivative of sulfanilamide (Eq. 33). Treatment of the bicyclic sulfonamide with hydrobromic acid led to cleavage of the four-membered oxide ring.



(33)

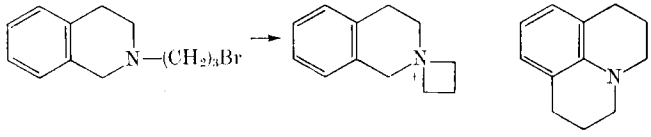
(LXII)

(3) 4-Azoniaspiro[3.5]nonane (R.R.I. No. 811). The unsubstituted trimethylenepiperidinium bromide (LXIII) was first reported by Gabriel and Stelzner,[69] although the dimeric bispiro structure (LXIV) was later advanced[107] on the basis of the elimination products obtained on base treatment, variously reported to be *N*-allylpiperidine, bis-(3-piperidinopropyl) ether and related fragments. The cyclization of *N*-(3-iodopropyl)piperidine was subsequently reported by Dunlop[46] to give the quaternary iodide (LXIII) (m.p. 174°), and the data seem to adequately confirm this structure. Treatment of the iodide with silver hydroxide led to *N*-(3-hydroxypropyl)piperidine. The 2,2-dimethyl-4-azoniaspiro iodide has also been prepared.[155]



(LXIII) (LXIV)

(4) Spiroazetidine[1,2′]-1′*H*-isoquinolinium (R.R.I. No. 2179). The ring-closure of *N*-(3-bromopropyl)tetrahydroisoquinoline was carried out by Jones and Dunlop[119] in connexion with studies on the stereochemistry of spirans; the quaternary azetidine (LXV) (platini-



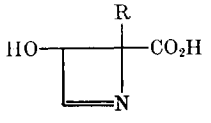
(LXV) (LXVI)

chloride, m.p. 183°) was obtained in admixture with the dimer. An attempt to effect the corresponding cyclization of *N*-(3-bromopropyl)-tetrahydroquinoline led instead to ring-closure at position 8 with the formation of julolidine (LXVI).

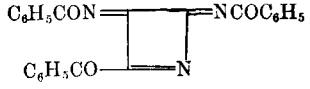
4. Azetines and Azetes

A. Azetines

No adequately characterized compound containing a four-membered ring with a nitrogen atom and a double bond has been recorded. Most of the examples of unsaturated derivatives that have been reported are in polycyclic systems or rings containing more than one nitrogen atom, and are discussed in sections **II.3**, **III.3**, **V**, and **VI.2**. One report of a monocyclic azetine derivative concerns the condensation of an α-amino acid with glyoxal, which produced a red substance considered to be the 3-hydroxy-1-azetine-4-carboxylic acid (LXVII).[176] This formulation seems quite unlikely, as does an earlier azetine structure (LXVIII) suggested[44] for a reaction product of benzoyl bromide and silver cyanide.

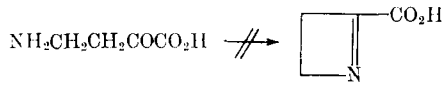


(LXVII)



(LXVIII)

An unsaturated trimethyleneimine derivative must necessarily be either a cyclic Schiff base (1-azetine) or the enamine tautomer (2-azetine). The presence of either of these highly reactive functional systems in a strained four-membered ring may be expected to make the isolation of an azetine a difficult feat. One obvious approach to the formation of an azetine is the cyclization of a β-amino ketone, and this



(LXIX) (LXX)

has been examined by Macholan and Svatek.[153] The behavior of γ-amino-α-ketobutyric acid (LXIX) was compared with that of the five- and six-carbon ω-amino-α-keto acids by several physical and chemical techniques. In contrast with the latter compounds, there was no evidence of any formation of the cyclic Schiff base (LXX) or

carbinol amine with the substituted butyric acid, and the azetine ring thus remains ephemeral. These results do not preclude the possibility that in a more favorable case an azetine might be detected or isolated. In certain reactions discussed elsewhere, such as the hydride reduction of azetidinones (Eq. 63, section **III.2.***B*), unsaturated intermediates or entities with some N—C double-bond character probably play a role.

The possible intermediacy of an azetine derivative is of interest in connexion with the biosynthesis of azetidine-2-carboxylic acid. The formation *in vivo* of proline and pipecolic acid, the five- and six-membered homologs, is thought to occur *via* oxidative deamination of ornithine and lysine, respectively, followed by cyclization to the unsaturated precursors and then reduction. If this path were involved in the enzymic synthesis of the azetidine acid, an azetine intermediate would be required. Although α,γ-diaminobutyric acid is not a direct source of carbon in the biosynthesis of the azetidine, Fowden and Bryant observed an unknown spot in the paper chromatogram of the amino acids present after feeding experiments with this amino acid in *C. majalis*, and discussed the possibility that this was due to 1-azetine-2-carboxylic acid.[58] The evidence was insufficient to establish the point. A plausible biogenetic pathway for azetidine-2-carboxylic acid that does not involve an unsaturated precursor is the direct cyclization of a homoserine derivative, *e.g.* a phosphate ester. This acid is also found in the same plants, and the ring-closure has abundant precedent in the preparation of azetidines from γ-amino sulfate esters [section **II.2.***A*.(**2**)].

B. Azetes

Suggestions of azete structures have been made from time to time; these reports have been discussed and evaluated by Ballard and Melstrom[8] and only one case will be mentioned here. 2,3-Dibromopropylamine was reported by Abderhalden and Paquin[1] to undergo transformation to a compound formulated as a dibromoazetine, which was further transformed with sodium to a compound, C_3H_3N, formulated as the parent substance, azete. In a reinvestigation, Gensler[24] demonstrated that the compounds in question were in fact dibromopropylamine hydrobromide and allylamine.

III. 2-Azetidinones (β-Lactams)

The first authentic 2-azetidinone was described by Staudinger in 1907,[214] and a dozen or more members of the series were prepared in

the ensuing decade by this pioneer and his co-workers. With the exception of a neglected contribution by R. Breckpot in 1923, virtually no further literature on azetidinones appeared until after the second World War. The discovery of a β-lactam ring as a unique structural feature of the penicillin molecule, made during the British–U.S. co-operative wartime program, prompted tremendous activity in the chemistry of azetidinones, and these compounds emerged from the status of curiosities to the best known and most numerous of the azetidine derivatives. Several refined preparative methods for azetidinones were developed by Sheehan and this group in connexion with the total synthesis of a penicillin, which was described in 1959.[200] A broad synthetic program initiated by Testa and co-workers in 1958 has further extended the field. Reviews of the early developments of azetidinone chemistry[9] and of synthetic methods[83,198] have been published.

1. Methods of Preparation

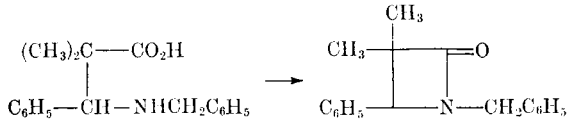
The amide linkage of the azetidinones lends a broader scope to the synthetic approaches than is available in the monofunctional imines. This fact, together with the impetus provided by the problem of penicillin synthesis, has led to a much wider variety of preparative methods for azetidinones. Several of these reactions have been applied only to azetidinones with several complex substituents, and as with the azetidines and all other four-membered nitrogen heterocyclic series, the least substituted compounds are the least accessible. Nearly all of the possible modes of ring closure of the azetidinone ring have been realized, and the synthetic methods are organized according to the final bond formed. A number of reactions that were explored in unsuccessful attempts to form azetidinones during the penicillin program are summarized by Ballard *et al.*[9]

A. Ring Closure at the Amide Bond (N—C-2)

(1) Direct cyclization of β-amino acids. Most of the azetidinone preparations that comprise formation of the amide bond have been carried out with the acid chlorides or esters as starting materials. In many of the reported cyclizations of free β-amino acids, reagents such as thionyl chloride have been employed and the reactions presumably involve the initial formation of the acid chloride; in other cases the mechanism of the ring closure is not clear. The various procedures

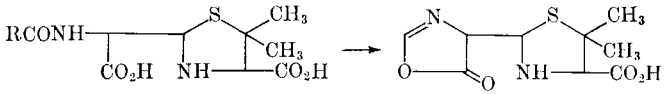
that have been developed for conversion of a free β-amino acid directly into the lactam are dealt with in this section.

The cyclization of a β-amino acid was first carried out by Staudinger, Klever, and Kober[222] to provide an alternative synthetic route for the proof of structure of 1-benzyl-3,3-dimethyl-4-phenyl-2-azetidinone (LXXII), which had been obtained by a cycloaddition reaction [section *D.*(**1**)]. The amino acid (LXXI) was cyclized in 60%



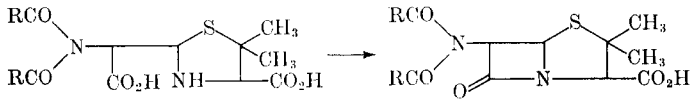
(LXXI) (LXXII) (34)

yield by treatment with acetyl chloride (Eq. 34). No further azetidinones were prepared in this way until the advent of the penicillin program, when the problem of cyclization of penicilloic acid (LXXIII) became of urgent importance. One additional monocyclic β-lactam was obtained in model studies by treatment of an amino acid with thionyl chloride,[9] but many attempts to effect cyclization of a penicilloic acid



(LXXIII) (LXXIV) (35)

were uniformly unsuccessful.[6] A number of these failures were due at least in part to the competing reaction of oxazolone formation (LXXIV), since the reagents used to 'activate' the amino acid were also capable of promoting azlactonization.



(LXXV) (36)

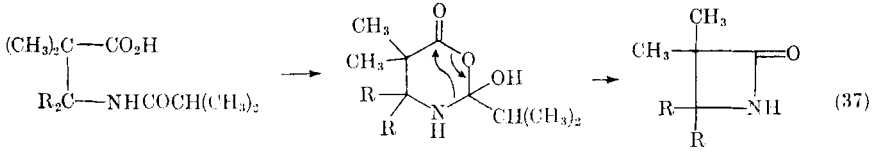
That the penicillin ring-system (LXXV) can be obtained by such a ring closure when azlactonization is blocked was demonstrated by Sheehan and co-workers with α-phthalimido- or sulfonamido-2-thiazolidineacetic acids (Eq. 36), which were cyclized with thionyl

chloride or phosphorus oxychloride;[199] a large series of penicillin analogs was later obtained in this manner.[20] These studies were climaxed by the total synthesis of a natural penicillin,[200] in which the key cyclization step was accomplished by use of *N*,*N*′-dicyclohexylcarbodiimide and in lower yield with several other peptide-forming reagents. The effectiveness of these reagents in the ring closure of acyclic β-amino acids has not been explored.

The preparation of five 1,3,4-triaryl-2-azetidones from the β-arylamino acids by treatment with benzenesulfonyl chloride and alkali has been reported by Spasov *et al.*[212]

(2) Ring closure of β-acylamino acids. Although the cyclization of a β-amino acid by thermal dehydration has never been accomplished, the formation of azetidinones can be smoothly effected by elimination of a molecule of acid on heating an *N*-acyl-β-amino acid (Eq. 37). This method was an outgrowth of early work on the preparation of azetidinones by cycloaddition of dimethylketene and imines, since the piperidinediones formed as byproducts in this reaction [Eq. 43, section *D*.(**1**)] were very readily cleaved to the β-*iso*butyrylamino acids and thus provided a convenient source of starting materials. Several examples of this thermal cyclization with the *iso*butyryl amides of β-alkylamino acids were reported by Staudinger and his associates;[222, 225] the yields of β-lactams were 60–80%.

The method was further explored during the penicillin work, and evidence was obtained that acetic and *n*-butyric acids as well as *iso*butyric acid could be eliminated by dry distillation or by heating in a suitable solvent. The sequence of reactions involving formation of



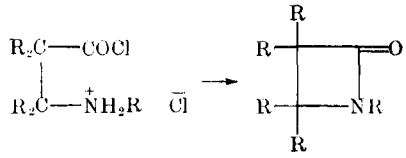
(LXXVI) (LXXVII) (37)

the piperidinedione, cleavage and 'de*iso*butyrylation' was also successfully carried out with 2-substituted thiazolines and dimethylketene as starting materials, and in this way two model thiazolidine-β-lactams were obtained.[9]

Sheehan and Corey[198] have suggested that the ready elimination

of *iso*butyric acid, as contrasted with the failure of the ring closure with the free acid, may occur by a cyclic mechanism in which the four-membered ring is formed by an acyl migration (LXXVII).

(3) Ring closure of β-amino acid chlorides. As mentioned above, β-amino acid chlorides are very probably intermediates in some of the direct cyclization reactions of amino acids, but the preparation and subsequent ring closure of the acid chlorides was not described until 1958. Independently Blicke and Gould[15] and Testa, Fontanella and Fava[235] developed general procedures in which the amino acid chloride hydrochloride is prepared and then cyclized to the azetidinone by treatment with a base (Eq. 38). A summary of the compounds obtained by this method is presented in Table 6.



(38)

The amino acids used by Blicke and Gould were all secondary amines obtained by the addition of benzylamine or alkyl amines to atropic acid or other substituted acrylic acids. The acid chloride salts were prepared by treatment with thionyl chloride, and after removing by-products the crude products were refluxed in benzene solution with excess dimethylaniline. The 1,3- and 1,4-disubstituted azetidinones were isolated in yields of 40–80%. The beneficial influence of substitution was observed with the 1-benzyl-3-methyl-4-phenyl- and 1-benzyl-3,3-dimethyl-4-phenyl-2-azetidinones, both of which were obtained in 90% yield. In an unsuccessful attempt to prepare β-aminodiazoketones several of the acid chloride hydrochlorides were treated with diazomethane; this reaction also furnishes the β-lactams, although in rather low yield.

The lactams prepared by Testa *et al.* were all 3,3-disubstituted derivatives; the acids were synthesized by hydrogenation of a series of disubstituted (mainly α-alkyl-α-phenyl) α-cyano esters followed by acid hydrolysis. The preparation of the acid chloride hydrochlorides was carried out with phosphorus pentachloride in acetyl chloride solution, essentially the conditions that have been used for the direct cyclization of β-amino acids. Although no β-lactams were isolated from this reaction, Testa suggests that the lactam is formed as an intermediate and is then converted into the acid chloride salt by hydrogen

TABLE 6. Monocyclic 2-Azetidinones prepared from β-Amino Acid Derivatives

Substituents						
At N	At C-3	At C-4	Method[a]	Yield (%)	M.p. (°C) or b.p. (°C/mm.)	Reference
Unsubstituted						
			D	0.7	74	105
Monosubstituted						
Methyl			D	11	69/18	104
Phenyl			D		80	9
Benzyl			D	5	110/2	104
	*iso*Butyl		D	67	44	230a
	Cyclohexyl		D	54	128	230a
	Benzyl		D	43	90	230a
	Phenyl		C	4	115	231
			D	52		237
			D	28		15
	p-Tolyl		D	54	69	20a
	p-Anisyl		D	20	136	20a
	α-Naphthyl		D	49	126	230a
	p-Biphenylyl		D	11	222	230a
Disubstituted						
Methyl	Phenyl		C	16	86/0.1	15
Isopropyl	Phenyl		C	80	91/.05	15
Allyl	Phenyl		C	42	103/.15	15
Cyclohexyl	Phenyl		C	39	60	15
Cyclohexanemethyl	Phenyl		C	76	51	15
Benzyl	Phenyl		C	66	72	15
			D	15–40		
β-Phenylethyl	Phenyl		C	57	145/.05	15
Phenyl	Benzamido		D	25	206	9
Phenyl	Acetamido		D	35	225	9
Phenyl	Benzamido		D	25	206	9
Phenyl	Phenylacetamido		D	35	225	9
Benzyl	Methyl		C	45	83/0.1	15
Benzyl	Cyclohexyl		C	81	131/0.05	15
Methyl		Methyl	D			24
Ethyl		Methyl	D	35		24
Benzyl		Phenyl	D	45	160/15	104
			C	75		15
Benzhydryl		Phenyl	D	3	99	104
Phenyl		Phenyl	A	54	155	9
			D	73		9
Benzyl		Methyl	C	75	85/0.1	15
Benzyl		Cyclohexyl	C	79	136/0.07	15
	Methyl, methyl		D	80	70–73/0.8	55

(*Table continued*)

TABLE 6 (*continued*)

Substituents						
At N	At C-3	At C-4	Method[a]	Yield (%)	M.p. (°C) or b.p. (°C/mm.)	Reference
	Ethyl, ethyl		C	32		235
			D	92	91–96/0.8	55
	n-Propyl, *n*-propyl		D	91	103/0.2	55
	n-Butyl, *n*-butyl		D	99	125/0.1	55
	Ethyl, 1-cyclohexenyl		C	51	70	235
	Ethyl, benzyl		C	28		235
			D	64	57	233
	Methyl, phenyl		C	64	95	235
			D	51		233
	Ethyl, phenyl		C	85	70	235
			D	86		55, 233
	n-Propyl, phenyl		D	56	43	233
	*iso*Propyl, phenyl		C			235
			D	79	105	233
	1-(3-Dimethylaminopropyl), phenyl		D	31	158/0.2	233
	n-Butyl, phenyl		C	75	67	235
			D	92		55
	*iso*Butyl, phenyl		C	43	120	235
	Cyclohexyl, phenyl		C	70		235
			D	80	176	55
	Benzyl, phenyl		C	36	130	235
			D	87		55
	Ethyl, *p*-nitrophenyl		C	80	114	54
	Phenyl, phenyl		C	68	173	235
Trisubstituted						
Ethyl	Ethyl, phenyl		D	40	110/0.6	233
Benzyl	Methyl	Phenyl	C	90	141/0.1	15
Phenyl	Phenyl	Phenyl	A		135	212
β-Naphthyl	Phenyl	Phenyl	A		194	212
o-Methoxyphenyl	Phenyl	Phenyl	A		147	212
Phenyl	Phenyl	Tolyl	A		144	212
Phenyl	Phenyl	Piperonyl	A		133	212
Phenyl	Methyl	Phenyl	D		114	9
Tetrasubstituted						
Methyl	Methyl, methyl	Phenyl	B	60		222
Benzyl	Methyl, methyl	Phenyl	A	60		222
			B	70		222
			C	91	38	15
Ethyl	Methyl, methyl	Phenyl	B	87	100/0.2	9

[a] Methods: A, Cyclization of amino acid; B, cyclization of acylamino acid; C, cyclization of amino acid chloride; D, cyclization of amino ester with Grignard reagent.

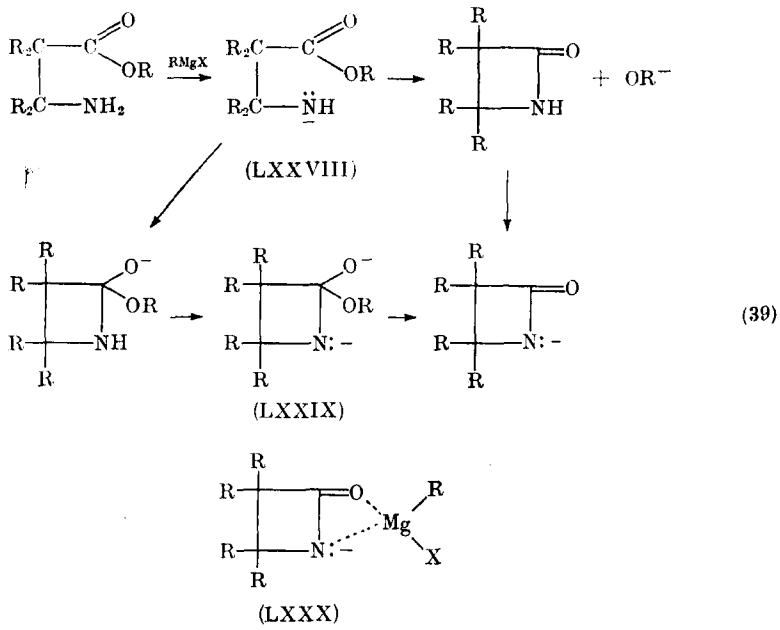
chloride liberated in the ring closure. A low yield of one azetidinone was obtained by treatment of the amino acid with phosphorus pentachloride in chloroform solution. The acid chloride hydrochloride, which in most cases crystallized from the acetyl chloride solution, was isolated and treated in ether suspension with dry ammonia or triethylamine. The β-lactams were isolated in yields ranging from 30 to 85%; the most successful results were obtained with ammonia.

This method when applied to a monosubstituted lactam, 3-phenylazetidinone, gave only a 4% yield,[231] again illustrating the requirement of multiple substitution.

(4) Ring closure of β-amino acid esters. The technique of converting an amine into the conjugate base by reaction with a Grignard reagent to facilitate nucleophilic attack at an ester carbonyl group has been long known.[18] The application of this procedure to the preparation of azetidinones by cyclization of the halomagnesium salts of β-amino acid esters was described by Breckpot in 1923.[24] Twenty years later, chemists on the penicillin team, apparently unaware of Breckpot's paper, studied the reaction in some detail and prepared several additional β-lactams.[9] Several further examples of the reaction were described by Holley and Holley,[104] who obtained the parent 2-azetidinone, β-propiolactam, in 0.7% yield.[105] In the cyclization of *N*-alkyl β-aminopropionates the ratio of β-lactam to total amides was found in three cases to be 0.2–0.3, indicating that a substantial amount of the aminoester was converted to polyamide products. Testa and coworkers[230a, 233] have prepared a number of mono- and disubstituted 2-azetidinones from the β-amino esters and have more closely defined the optimum reaction conditions. The azetidinones prepared by this method are summarized in Table 6.

In the original procedures used for this cyclization,[24] one molar equivalent of ethylmagnesium bromide was added to the β-alkylamino ester, but a study of conditions for the cyclization of methyl β-anilino-α-phenylacetamidopropionate revealed that two molar equivalents of the Grignard reagent gave much higher yields of the azetidinone.[9] A large excess decreased the yield slightly. Methylmagnesium iodide was found to be superior to the ethyl derivative, and other reagents such as dialkylmagnesium or dialkylzinc compounds were ineffective. Gould[83] found that the best yield in the preparation of 1-benzyl-3-phenyl-2-azetidinone was realized with two molar equivalents of the ethyl Grignard reagent, and that the cyclization was more favorable with the *iso*propyl ester of the β-benzylamino acid than

with the methyl or ethyl esters. In their work with β-amino-α,α-disubstituted propionic acid ethyl esters, Testa *et al.*[233] confirmed the requirement of a two molar quantity of Grignard reagent, and later observed,[237] with ethyl β-amino-α-phenylpropionate, that the use of four molar equivalents of Grignard reagent markedly increased the yield of lactam. Methyl-, ethyl- and *n*-butylmagnesium bromides were found to be equivalent.[233] The reaction temperature was found to be crucial in this series. With α-alkyl-β-amino-α-phenyl esters, high yields of the 2-azetidinones were obtained at 0–5°; at 80° only polymeric products were formed. The reaction with α,α-dialkyl-β-amino esters, on the other hand, is incomplete at the lower temperatures, and the best yields of β-lactams with these were obtained in refluxing ether.[55]



(39)

The need for two molar equivalents of Grignard reagent in the cyclization of primary β-amino esters is readily understood (Eq. 39). Testa *et al.* have represented the reaction as occurring *via* the dianion (LXXIX), but the postulation of this presumably high-energy species is unnecessary, since the azetidinone initially formed by displacement of the amide ion (LXVIII) contains a more acidic hydrogen atom than the starting amine, and would immediately consume a second molar

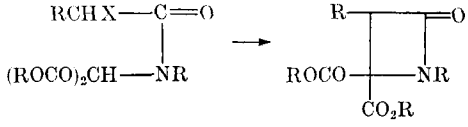
equivalent of Grignard reagent. The beneficial effect of excess Grignard reagent in the reaction of secondary β-amono esters is less obvious. The reaction is usually heterogeneous, and it is possible that formation of an insoluble complex such as (LXXX) removes Grignard reagent from the solution.

This procedure and the cyclization of β-amino acid chlorides are complementary. The two methods appear to be equally suitable for the cyclization of certain polysubstituted β-amino acids, but the Grignard reagent–ester technique seems the more reliable for preparing azetidinones with a free N—H group from primary amino acids.[55, 233] The results of Blicke and Gould, however, indicate that the acid chloride hydrochloride–dimethylaniline method is better suited for preparing azetidinones with substituents at N and C-3 or C-4.

(5) Ring closure of β-amino carboxamides. The only report of the cyclization of a β-amino amide to an azetidinone is that of Talley *et al.*[229] who isolated from the incubation of asparagine at pH 6.7 and 100° a compound which was considered to be 2-azetidinone-4-carboxylic acid. The formation of the β-lactam ring from a carboxamide under these conditions would be difficult to understand, and since no direct evidence for the azetidinone structure was provided, the possibility of an alternative formulation must be considered.

B. Ring Closure at the C-3—C-4 *Bond*

In 1950 Sheehan and Bose[194] reported the formation of an azetidinone by intramolecular alkylation of an α-haloacylaminomalonic ester (Eq. 40). This was the first example of a β-lactam synthesis in which the amide bond was first established, and it is the only case in which any azetidine ring has been formed by cyclization of a heterochain at a C—C bond.



(40)

Diethyl chloroacetanilidomalonate, prepared by the reaction of anilidomalonic ester with chloroacetic anhydride or with the acid in the presence of phosphorus trichloride, was treated with triethyl amine in benzene solution at room temperature to give an 88% yield of

1-phenyl-4,4-dicarbethoxyazetidinone. About 12 β-lactams have been prepared in uniformly good yield by a similar procedure;[21, 194, 195] the compounds are summarized in Table 7. The 1-substituted azetidinone-4,4-dicarboxylates were oils or low-melting solids and were characterized by the infrared spectra (lactam carbonyl band 5.62–5.75 μ) and in one case by comparison with an independently synthesized compound. A number of transformations, including saponification and decarboxylation, were also carried out.

TABLE 7. 2-Azetidinones from α-Haloacylaminomalonic Esters

Substituents				Yield (%)	M.p. (°C) or b.p. (°C/mm.)	Reference
At N	At C-3	At C-4				
Phenyl	H	$CO_2C_2H_5$	$CO_2C_2H_5$	88	39	194
Phenyl	H	CO_2H	$CO_2C_2H_5$	[a]	104	194
Phenyl	H	H	$CO_2C_2H_5$	[a]		194
Phenyl	H	$CO_2CH_2C_6H_5$	$CO_2CH_2C_6H_5$	88	95	194
Phenyl	H	CO_2H	CO_2H	[a]	171	194
Phenyl	H	H	CO_2H	[a]	148	194
Phenyl	H	$CONH_2$	$CONH_2$	80	260	195
Phenyl	H	H	$CONHC_6H_5$	[a]	255	195
p-Tolyl	H	$CO_2C_2H_5$	$CO_2C_2H_5$	90	90	195
Cyclohexyl	H	$CO_2C_2H_5$	$CO_2C_2H_5$	91		195
β-Naphthyl	H	$CO_2C_2H_5$	$CO_2C_2H_5$	95	75	194
Phenyl	Methyl	$CO_2CH_2C_6H_5$	$CO_2CH_2C_6H_5$	97	90	195
Phenyl	Ethyl	$CO_2C_2H_5$	$CO_2C_2H_5$	93		195
Phenyl	Phthalimidomethyl	$CO_2C_2H_5$	$CO_2C_2H_5$	50	154	21
Phenyl	Br	$CO_2C_2H_5$	$CO_2C_2H_5$	90	—	21
p-Tolyl	Cl	$CO_2C_2H_5$	$CO_2C_2H_5$	62	110(.05)	21

[a] Obtained from preformed azetidinone by further reaction.

The reaction is restricted to *sec*-aminomalonates; the *N*-substituent may be either alkyl or aryl. In most of the cases studied the chloroacetamides were used, but α-chloropropionyl and α-chlorobutyryl amides and the dihaloacetamides[21] also give azetidinones with a substituent at C-3. Attempts to extend the reaction to the preparation of azetidinones other than 4,4-dicarbalkoxy derivatives were unsuccessful.[21]

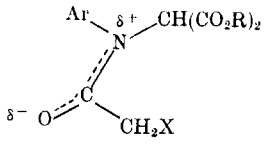
The ring closure is an exceptionally facile process, and can be brought about with a variety of weak bases such as secondary and tertiary amines or potassium carbonate. The mild conditions and high yields are in sharp contrast to the analogous cyclization of γ-bromopropylmalonic ester with strong base, in which intermolecular alkylation seriously competes with the formation of the cyclobutane ring.

Bose and co-workers[21] have examined some related reactions in an effort to define the factors which favor β-lactam formation. Amidomalonic esters cannot be alkylated with alkyl bromides or chlorides with a weak base such as triethylamine. The attempted alkylation of ethyl acetanilidomalonate with ethyl bromoacetate using this base led only to the betaine ester, indicating that the success of the ring closure is not primarily dependent upon the α-haloamide structure. This was confirmed by the finding that the β-chloropropionanilidomalonic ester underwent similar cyclization to the pyrrolidone in the presence of triethylamine, although the yields were not as high as those usually realized in the azetidinone preparations. Six- and seven-membered lactams could not be obtained from the respective γ- and δ-haloacylamidomalonates.

This method for the preparation of azetidinones thus represents a rare case in which cyclization to a four-membered ring is peculiarly favorable. Consideration of the conformation of the haloacylamidomalonic ester provides a plausible explanation for this unusual situation. For attainment of the normal resonance stabilization in an amide bond (LXXXI) the groups attached to nitrogen and to the carbonyl must be coplanar.[248] If it is then assumed that the haloalkyl group is disposed toward the malonate group to avoid carbonyl interactions, the resulting conformation (LXXXII) is seen to be optimum for internal displacement.



(LXXXI)



(LXXXII)

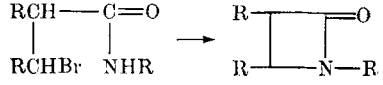
C. Ring Closure at the N—C-4 *Bond*

The formation of azetidinones by cyclization of β-haloamides with strong base was first described by Knunyants and Gambaryan in 1955.[129] Several *N*-substituted β-bromo-β-phenylpropionamides (Table 8), obtained from the bromoacid chloride and cyclohexyl amine or α-aminoesters, were converted into the β-lactams in 75–85% yield by treatment with sodium or potassium amide in liquid ammonia (Eq. 41). The α,β-dibromoanilide was cyclized with sodium hydroxide in liquid ammonia in 96% yield.[130] The yields of β-lactams from β-alkyl-β-bromopropionanilides were about 25%, the major product being the

TABLE 8. 2-Azetidinones from β-Haloamides

Substituents			Yield	M.p. (°C) or	
At N	At C-3	At C-4	(%)	b.p. (°C/mm.)	Reference
Benzyl			40		15
Phenyl		Methyl	26	138/3	130
Cyclohexyl		Phenyl	80	53	129
$-CH_2CONH_2$		Phenyl	80	144	129
$-CH(CO_2C_2H_5)-CH(CH_3)_2$		Phenyl	80	169/1	129
$-C(CO_2C_2H_5)=C(CH_3)_2$		Phenyl	80	51	129
Phenyl		Methyl, methyl	27	43	130
Phenyl	Br	Phenyl	96	203	130

α,β-unsaturated anilide. The unsaturated amides were also obtained in the β-phenyl series with alcoholic base or liquid ammonia alone. Ring closure of *N*-benzyl-β-bromopropionamide was effected in 40% yield by the use of sodium hydride in boiling toluene.[15]



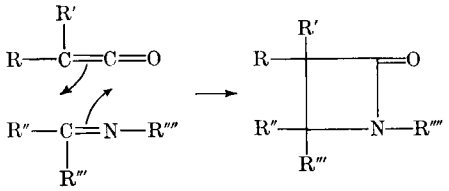
(41)

D. Simultaneous Formation of N—C-2 *and* C-3—C-4 *Bonds*

Three reactions have been used to effect the formation of the azetidinone system by addition of the elements of a ketene unit to a C—N double bond. These methods are distinctly different, with the azomethine serving as electrophile in one case, nucleophile in another and partner in a concerted addition in a third. Since the overall processes are similar and complementary, however, they are appropriately treated as a group.

(1) Cycloaddition of ketenes and azomethines. The direct combination of a ketene and a Schiff base to give a 2-azetidinone is one of the best-known examples of a very general process that is conveniently called cycloaddition. This reaction (Eq. 42), which can be viewed as a concerted process involving simultaneous formation of the two bonds, was systematically studied by Staudinger in his pioneering work on

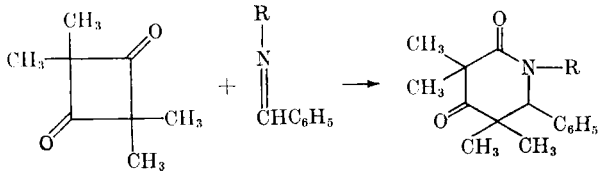
ketenes.[216] Several applications of this cycloaddition process leading to other four-membered nitrogen-containing rings are discussed in later sections.



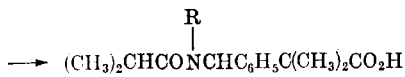
(42)

The first example of this reaction, and the first preparation of an authentic 2-azetidinone, was reported in 1907.[214, 215] The condensation of diphenylketene and benzalaniline was found to proceed smoothly at room temperature to give the tetraphenylazetidinone in 72% yield. A number of additional 2-azetidinones (Table 9) were subsequently prepared by Staudinger and his students from disubstituted ketenes and di- or trisubstituted azomethines. Yields were not recorded in all cases; with *o,o*-biphenyleneketene and diphenylketene, the most reactive members, azetidinones were obtained in yields of 80–100%.

A competing reaction, especially with condensations of dimethylketene, is the formation of piperidinedione derivatives (LXXXIII) from two molar equivalents of the ketene and one of the azomethine[222] (Eq. 43). These compounds, which may be the major products with benzal derivatives of aliphatic or benzyl amines,[9] probably arise by condensation of the azomethine with the ketene dimer. The piperidinediones, which are also obtained in the addition reaction of ketenes with thiazolines, discussed below, are characterized by hydrolysis to the β-(*iso*butyrylamido) acids (LXXXIV), which can then be cyclized to the β-lactam (method *A*.(**2**)).



(LXXXIII)



(LXXXIV)

(43)

TABLE 9. Monocyclic 2-Azetidones from Ketenes and Azomethines

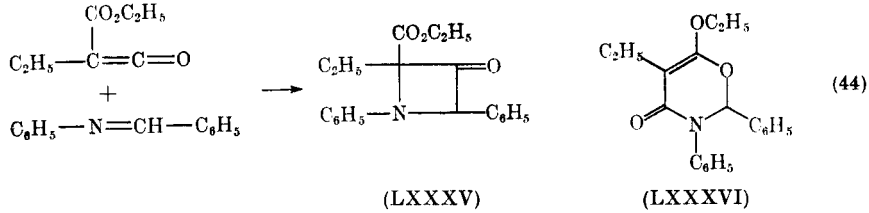
Substituents			Yield	M.p.	
At N	At C-3	At C-4	(%)	(°C)	Reference
Disubstituted					
Phenyl		Phenyl	39	155	217
Phenyl		*o*-Tolyl	11	134	174
Phenyl		*m*-Tolyl	12	87	174
Phenyl		*p*-Tolyl	22	109	174
Phenyl		*o*-Methoxyphenyl	39	108	174
Phenyl		*m*-Methoxyphenyl	16	96	174
Phenyl		*m*-Chlorophenyl	32	148	174
Phenyl		*p*-Dimethylamino-phenyl	62	156	174
o-Tolyl		Phenyl	7	107	174
m-Tolyl		Phenyl	18	91	174
p-Tolyl		Phenyl	13	126	174
p-Methoxy-phenyl		Phenyl	19	86	174
m-Chlorophenyl		Phenyl	34	97	174
Trisubstituted					
Phenyl	Methyl	Phenyl	47	113	126
Phenyl	Ethyl	Phenyl	24	123	126
Phenyl	Phenyl	Phenyl	74	134	126
			35	133	174
Phenyl	Phenyl	*o*-Tolyl	21	138	174
Phenyl	Phenyl	*m*-Tolyl	20	129	174
Phenyl	Phenyl	*p*-Tolyl	14	118	174
Phenyl	Phenyl	*m*-Chlorophenyl	13	131	174
Phenyl	Phenyl	*o*-Methoxyphenyl	25	124	174
Phenyl	Phenyl	*m*-Methoxyphenyl	29	136	174
Phenyl	Phenyl	*p*-Dimethylamino-phenyl	90	153	174
			79	158	126
Phenyl	Phenyl	*p*-Nitrophenyl	78	149	126
Phenyl	Phenyl	2-Pyridyl	56	162	126
Phenyl	*p*-Chlorophenyl	Phenyl	54	175	126
Phenyl	*p*-Methoxy-phenyl	Phenyl	65	199	126
o-Tolyl	Phenyl	Phenyl	12	143	174
m-Tolyl	Phenyl	Phenyl	15	133	174
p-Tolyl	Phenyl	Phenyl	15	180	174
m-Chlorophenyl	Phenyl	Phenyl	28	123	174
o-Methoxy-phenyl	Phenyl	Phenyl	5	139	174
p-Methoxy-phenyl	Phenyl	Phenyl	19	156	174
p-Dimethyl-aminophenyl	Phenyl	Phenyl	70	176	126
Benzyl	Phenyl	*p*-Nitrophenyl	65	140	126

(*Table continued*)

TABLE 10 (*continued*)

Substituents			Yield	M.p.	
At N	At C-3	At C-4	(%)	(°C)	Reference
Tetrasubstituted					
Phenyl	Methyl	Phenyl, phenyl	48	122	126
Phenyl	Phenyl	Phenyl, phenyl	76	146	126
Phenyl	Methyl, methyl	Phenyl		149	221
Phenyl	Ethyl, ethyl	Phenyl	82	73	223
Benzyl	Methyl, methyl	Phenyl	10	36	222
Phenyl	Methyl, methyl	Styryl			216
p-Nitrophenyl	Methyl, methyl	Phenyl			216
Diphenylmethyl	Methyl, methyl	Phenyl			216
Phenyl	Ethyl, carbethoxy	Phenyl		110	217
Phenyl	Methyl, methyl	*p*-Dimethylamino-phenyl			216
Phenyl	Methyl, phenyl	Phenyl			225
Phenyl	Carbomethoxy, phenyl	Phenyl	15 14	159	217 126
Phenyl	Phenyl, phenyl	Phenyl	71	161	126, 214
Phenyl	Phenyl, phenyl	Styryl	70	172	214
Phenyl	Phenyl, phenyl	*o*-Tolyl	52	168	174
Phenyl	Phenyl, phenyl	*m*-Tolyl	63	108	174
Phenyl	Phenyl, phenyl	*p*-Tolyl	72	171	174
Phenyl	Phenyl, phenyl	*m*-Chlorophenyl	71	177	174
Phenyl	Phenyl, phenyl	*o*-Methoxyphenyl	30	236	174
Phenyl	Phenyl, phenyl	*m*-Methoxyphenyl	21	204	174
Phenyl	Phenyl, phenyl	*p*-Dimethylamino-phenyl	67	174	174
Benzyl	Phenyl, phenyl	Phenyl	46	86	126
o-Tolyl	Phenyl, phenyl	Phenyl	72	165	174
m-Tolyl	Phenyl, phenyl	Phenyl	69	166	174
p-Tolyl	Phenyl, phenyl	Phenyl	21	169	174
m-Chlorophenyl	Phenyl, phenyl	Phenyl	98	183	174
o-Methoxy-phenyl	Phenyl, phenyl	Phenyl	55	150	174
p-Methoxy-phenyl	Phenyl, phenyl	Phenyl	16	204	174
Pentasubstituted					
Phenyl	Methyl, methyl	Methyl, phenyl			216
Phenyl	Methyl, methyl	Phenyl, phenyl			216
Phenyl	Methyl, methyl	Methylthio, phenyl	60		103
Phenyl	Methyl, phenyl	Phenyl, phenyl			216
Phenyl	Carbomethoxy, phenyl	Phenyl, phenyl	35	195	126
Phenyl	Phenyl, phenyl	Phenyl, phenyl	71	162	126, 220
p-Dimethyl-aminophenyl	Phenyl, phenyl	Phenyl, phenyl	100		220
Phenyl	3,3-(*o*,*o*′-Bi-phenylene)	Phenyl, phenyl			216

Another complication was encountered by Staudinger in the reactions of ethylcarbethoxyketene and dicarbethoxyketene with benzalaniline.[217] In both cases an unstable product was obtained by condensation at $-10°$, and with the former ketene this substance could be isolated and purified. The compound was shown to be isomeric with the azetidinone and was converted into the azetidinone on heating at 180°; on hydrolysis it gave products corresponding to the ketene and azomethine. These unstable products were regarded by Staudinger as the 3-azetidinones (LXXXV), formed by reverse addition (Eq. 44). A rationalization of this mode of addition is not apparent, and the oxazine structure (LXXXVI) has been suggested[198] as a possible alternative. Since the only well-characterized 3-azetidinone derivatives are bicyclic compounds which undergo very facile valence tautomerism [Eq. (29), section **II.3.***A*.(**3**)], it is difficult to predict whether or not a compound with structure (LXXXV) would exhibit the properties described.



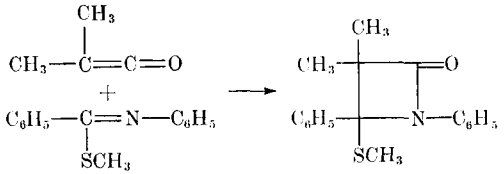
(LXXXV) (LXXXVI) (44)

The scope of this cycloaddition method for preparing azetidinones has been greatly extended by two later reports in which ketenes were prepared by Wolff rearrangement of diazoketones. Kirmse and Horner[126] carried out the reaction by photolytic decomposition of the diazoketone in the presence of the azomethine in benzene solution, with the azomethine always present in excess. Under these conditions, monosubstituted ketenes, which polymerize too readily to permit cycloaddition when prepared in a separate step, can be condensed with azomethines. This technique also suppresses the formation of the piperidinedione. Although monoalkylketenes give rather low yields of the azetidinone, phenylketene, prepared from diazoacetophenone, gave yields comparable with those obtained with diphenylketene. *p*-Chlorophenylketene was found to be less reactive, and no azetidinone was obtained with *p*-nitrophenylketene.

In a similar vein Pfleger and Jäger[174] have examined the reaction of diphenylketene, phenylketene and ketene with a large series of

azomethines. These workers prepared phenylketene *in situ* by the silver-oxide-catalyzed rearrangement of the diazoketone, a technique that had been unsuccessfully tried during the penicillin program.[9] In this case the yields in a series of parallel condensations were consistently higher with diphenylketene (prepared separately, not *in situ*), and most of the reactions with the latter took place at room temperature, whereas with phenylketene slightly elevated temperatures were required. The cycloaddition with ketene itself was first carried out by Staudinger who found a temperature of 200° to be necessary, and this was confirmed in a number of examples by Pfleger and Jäger. Lewis acid catalysts were ineffective in promoting the cycloaddition.

The structural requirements with respect to the azomethine cannot be precisely defined since there are some inconsistencies in the results obtained by the different procedures that have been used. Anils of aliphatic aldehydes,[174] phenylhydrazones, and imidochlorides[9] do not give azetidinones, but *S*-methylisothiobenzanilide gave the azetidinone (LXXXVII) in 60% yield[103] (Eq. 45). Azomethines derived from benzylamines give low and erratic yields.[222, 174] From the work of



(45)

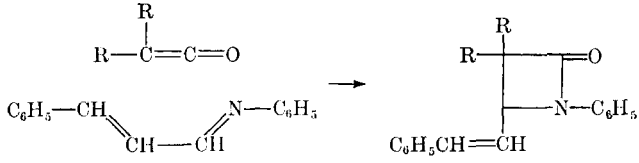
(LXXXVII)

Staudinger[216] it is evident that an electron-releasing group such as dimethylamino in the *N*-aryl moiety of the anil enhances the cycloaddition, whereas a *p*-nitro group suppresses the reaction completely. Kirmse and Horner were able to obtain an azetidinone from *p*-nitrobenzalbenzylamine, but Pfleger and Jäger found that a nitro group in any position in either aryl group of the azomethine prevented the condensation with any of the ketenes used. Methyl and *o*- or *p*-methoxy groups had little effect. Very surprisingly, a chlorine substituent *o*- or *p*- in either ring of the benzalaniline prevented reaction, but a *m*-chloro group in either ring promoted the addition.

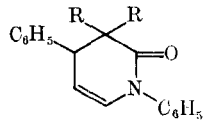
Another modification of this cycloaddition reaction which leads to 3-monosubstituted azetidinones is the use of 1-ethoxyalkynes as precursors for the labile monoalkylketenes.[242a] At elevated temperatures the acetylenic ethers undergo fragmentation to the aldoketene and

ethylene, and in dilute solutions with excess benzalaniline or benzophenoneanil, 1-ethoxypropyne and 1-ethoxyheptyne gave the corresponding 3-methyl- and 3-*n*-pentylazetidinones.

The reaction of dimethylketene and diphenylketene with cinnamylidene aniline (Eq. 46) gives addition products which could be either the azetidinone (LXXVIII) or the dihydropyridone (LXXIX) formed by 1,4-addition to the conjugated azomethine.[214] The structure



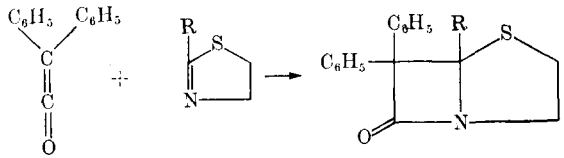
(LXXXVIII) (46)



(LXXXIX)

of these products was not established until the advent of infrared studies during the penicillin program. The spectrum of the triphenyl derivative was found to be quite clearly consistent with the β-lactam formula. In later work corresponding products from ketene and phenylketene and cinnamylideneaniline were assigned dihydropyridone formulas without further evidence or comment.[174] Similar tetrahydropyrazine structures were assigned to the products obtained from the condensation of the dianil of biacetyl with these ketenes.

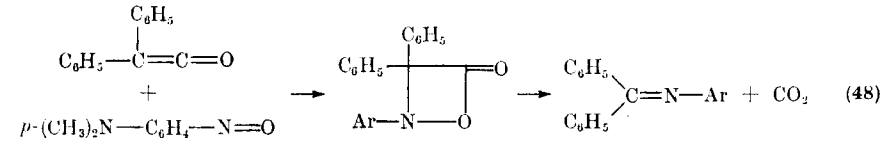
The construction of the basic thiazolidine-β-lactam nucleus of the penicillins by the addition of diphenylketene to 2-phenylthiazoline (Eq. 47) was accomplished during the penicillin program,[6, 9] but numerous attempts to extend the reaction to other thiazolines or other ketenes were unsuccessful, although the corresponding piperidinediones were obtained. Several additional examples have been described



(47)

by Pfleger and Jäger,[174] who found that 2-amino- and 2-mercapto-thiazoline, or the acyl derivatives, were converted into the bicyclic azetidinones in 45–68% yields on treatment with diphenylketene. The addition of ketene to other heterocyclic systems has not been reported.

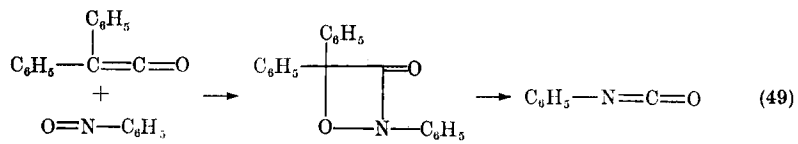
An interesting variant of this addition reaction of ketenes and azomethines is the formation of a 2-azetidinone by condensation of *p*-nitrosodimethylaniline with excess diphenylketene (Eq. 48). This



(48)

(XC)

reaction, described by Staudinger and Jelagin,[220] is considered to involve initial cycloaddition to an oxazetidone (XC) which immediately loses carbon dioxide with formation of the azomethine, the latter then undergoing condensation with a second molar equivalent of ketene. When one molar equivalent of ketene was used the presence of the azomethine was demonstrated by isolation of the characteristic hydrolysis products. The reaction is not general; in the absence of the electron-releasing dimethylamino group the polarity of the —N=O bond is reversed, and with nitrosobenzene the cycloaddition proceeds in the opposite sense (Eq. 49) to give the stable oxalactam (XCI). This structure was established by fission to the isocyanate and by synthesis from *N*-phenyl chlorodiphenylacethydroxamic acid.

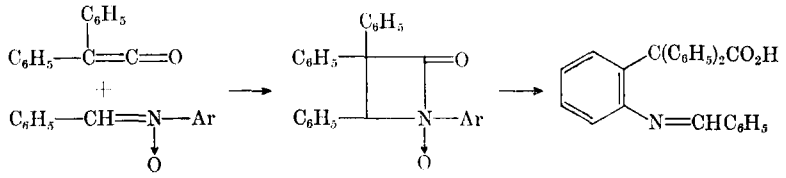


(49)

(XCI)

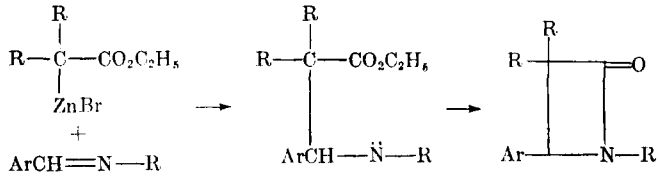
In studies of the reaction of diphenylketene with nitrones Staudinger and Miescher[224] obtained several compounds which were represented as arising by cycloaddition of the ketene and the —N=O group, analogous to that observed with nitrosodimethylaniline. The compounds underwent decarboxylation to furnish a series of so-called nitrenes. The structures assigned all required pentacovalent nitrogen, and these reactions were re-examined and reinterpreted by Taylor,

Owen and Whittaker in 1938,[230] and the azetidinone oxide structure (XCII) was advanced for the initial addition compound. Later work, however, requires further revision of this structure to (XCIII), arising by attack of the ketene at the *ortho* position of the *N*-phenyl ring in the nitrone.[95a]



(XCII) (XCIII) (50)

(2) Reformatsky reaction of α-bromoesters and azomethines. In 1943 Gilman and Speeter[82] observed that the —C=N— bond in an anil is capable of reacting with an α-bromozinc ester under the conditions of the Reformatsky reaction as customarily used with aldehydes. The product obtained, either after the usual acid hydrolysis step or without this treatment, was found to be the azetidinone corresponding to the cycloaddition product of the azomethine and the ketene derived from the bromoester (Eq. 51). The condensation doubtless proceeds by nucleophilic attack of the organozinc compound at the —C=N bond, forming the bromozinc complex of the amine anion which is also an intermediate in the cyclization of β-aminoesters with Grignard reagents (Eq. 39).



(51)

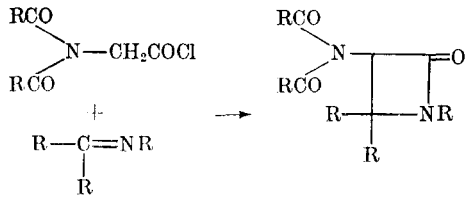
This reaction has been used to prepare the azetidinones listed in Table 10. From the limited data available it appears that the reaction is generally quite satisfactory with α-bromoalkyl esters and benzylidine derivatives of aryl or alkylamines.

(3) Addition of acid chlorides to azomethines. Another means of elaborating an azetidinone ring from a C=N bond was developed by Sheehan and Ryan[206, 207] as a specific method for the preparation of

TABLE 10. 2-Azetidinones from Reformatsky Reaction of Azomethines

Substituents			Yield (%)	M.p. (°C) or b.p. (°C/mm.)	Reference
At N	At C-3	At C-4			
Disubstituted					
Methyl		Phenyl	52	90/0.6	15
Phenyl		Phenyl	56	154	82
Trisubstituted					
Methyl	Methyl	Phenyl	81	105/0.6	15
Phenyl	Methyl	Phenyl	85	109	82
Benzyl	Methyl	Phenyl	76	142/0.1	9, 83
Phenyl	Phenyl	Phenyl	7	133	15
Phenyl	Methyl	2-(3-Methylthienyl)		112	166
Tetrasubstituted					
Benzyl	Methyl, methyl	Phenyl	84	155/0.5	15

3-acylaminoazetidinones related to penicillin. This reaction (Eq. 52) comprises the addition of a diacylaminoacetyl chloride to a Schiff base or a thiazoline, in the latter case generating directly the 4-thia-1-azabicyclo[3.2.0]heptane system of penicillin.

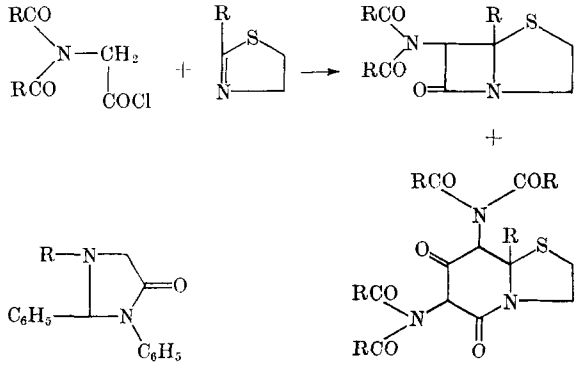


(52)

The reaction of phthalimidoacetyl chloride and benzalaniline in benzene solution with triethylamine gave a 50% yield of 1,4-diphenyl-3-phthalimidoazetidinone (m.p. 230–231°). All of the other recorded examples of this process involve the addition of diacylaminoacetyl chlorides to 2-substituted thiazolines[207, 202, 205] (Eq. 53). In these cases the yield of β-lactam is greatly dependent on reaction conditions and substituents at position 2 of the thiazoline ring, and a second product, considered to be the acylpiperidinedione (XCIV), is also obtained. The formation of this byproduct was suppressed by using methylene chloride or chloroform solvent and a high-dilution procedure.[207, 202]

A variety of complex double-acyl blocking groups for the amino-

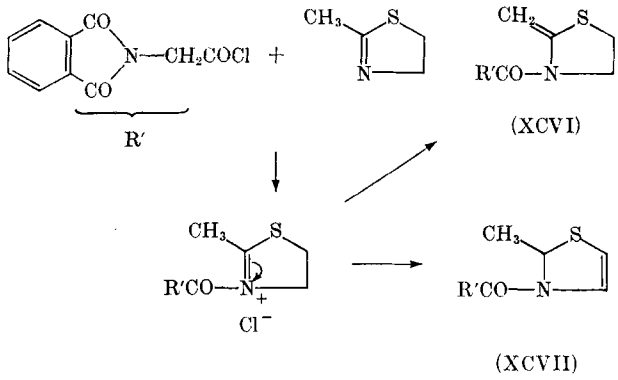
acetyl chloride was devised to permit ready removal and yet prevent azlactonization of the acid chloride.[205, 197] When the carbobenzoxy- or sulfonylamino-acetyl chlorides, both of which contain a free —NH group, were used in the reaction with an imine the product formed was the imidazolidone (XCV) rather than the azetidinone.[198]



(53)

(XCV, R = $ArSO_2$ or $C_6H_5CH_2OCO$) (XCIV)

Although the overall course of the reaction and the formation of piperidinedione derivatives suggest the possibility that an acylamino-ketene intermediate may be formed as a reactive intermediate, the reaction most probably involves initial nucleophilic attack of nitrogen on the acid chloride. This mode of reaction is well-known with acid anhydrides and imines, and is consistent with the results observed in the reaction of phthalimidoacetyl chloride and 2-methylthiazoline[196] (Eq. 54). The products obtained were the 2-methylenethiazolidine (XCVI) and the 4-thiazoline (XCVII), presumably arising from an initially formed 3-acylthiazolinium chloride.

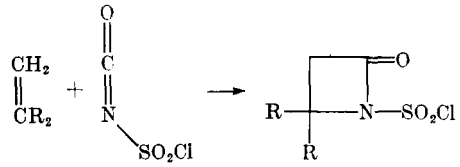


(54)

(XCVII)

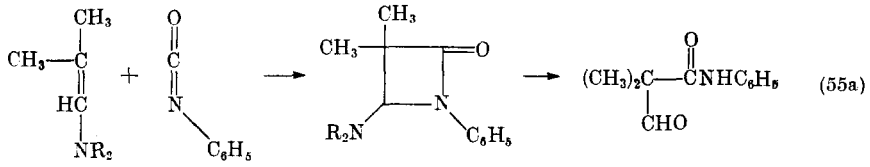
E. Simultaneous Formation of N—C-4 *and* C-2—C-3 *Bonds*

(1) Cycloaddition of isocyanates and olefins. The reaction of an isocyanate and an olefinic double bond, analogous to the combination of the —N=C=O group with a ketene double bond to form the malonimide ring [section **IV.2.***A*.(**1**)] represents the other possible mode of formation of an azetidinone by cycloaddition. This condensation was first reported with chlorosulfonylisocyanate and a series of terminal olefins to give the 4,4-dialkyl-1-chlorosulfonyl-2-azetidinones[86] (Eq. 55). The reaction of phenylisocyanate with simple olefins



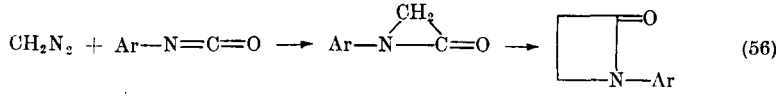
(55)

has not been observed, but Perelman and Mizsak have obtained 4-amino-3,3-dimethyl-1-phenylazetidinones in high yields by cycloaddition of *N*,*N*-disubstituted isobutenylamines with phenylisocyanate; enamines containing a β-hydrogen do not give lactams.[172a] The 4-aminoazetidinones are exceptionally sensitive to hydrolysis with traces of moisture to give β-formylisobutyranilide (Eq. 55a).



(55a)

(2) Condensation of diazomethane and isocyanates. Sheehan and Izzo[204] have observed that the reaction of phenyl- or *p*-bromophenylisocyanate with two molar equivalents of diazomethane gives the 1-phenylazetidinones in 15–20% yield (Eq. 56). This method is of very limited scope; no β-lactams were obtained in the similar reaction of



(56)

(XCVIII)

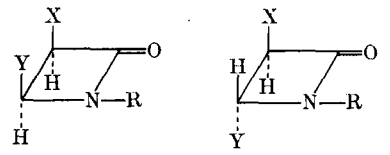
several other arylisocyanates. This reaction, which actually involves the simultaneous formation of three of the four bonds of the azetidinone ring, is reminiscent of the preparation of cyclobutanone from diazomethane and ketene. The condensation probably proceeds by initial formation of an α-lactam (XCVIII) and subsequent expansion of the three-membered ring.

2. Properties and Reactions of 2-Azetidinones

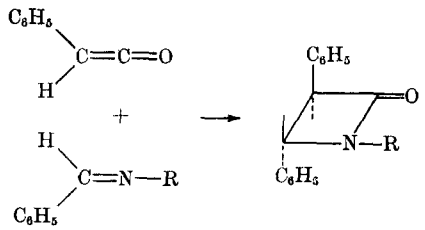
A. Structure and Physical Properties

The reactions that have been used to prepare β-lactams, though frequently proceeding in rather low yields, are nevertheless generally unambiguous from the standpoint of the structure of the product. In several of the preparations discussed in the preceding section, particularly in the first applications of methods in which two bonds are formed simultaneously, the azetidinone structures were confirmed by the facile hydrolysis to the β-amino acid.[82, 206, 222] In most of the subsequent preparations the products were adequately characterized by the nature of the synthetic reaction and the composition indicated by elemental analysis.

A point of structure that has been neglected is the stereochemistry of 3,4-disubstituted 2-azetidinones and 3,3,4- or 3,4,4-trisubstituted 2-azetidinones in which the geminal substituents are unlike. Such compounds can exist in two diastereoisomeric forms [*e.g.* (XCIX) and (C)],



(XCIX) (C)



(57)

but the formation of two diastereoisomers has apparently never been observed in the preparation of monocyclic 2-azetidinones. It is clear that a *cis*-form such as (XCIX), with 3- and 4-substituents eclipsed, would be of much higher energy than the *trans*-isomer, and it is highly probable that the latter is formed exclusively in reactions such as the cycloaddition of phenylketene and benzalanils (Eq. 57). This point has, however, not been examined. An optically active monocyclic β-lactam has been prepared on one occasion. Fontanella and Testa[53] resolved ethyl α-ethyl-α-phenyl-β-alanate and from the (+)-isomer obtained the azetidinone of opposite sign of rotation, $[\alpha]_D$ −78°, by cyclization with Grignard reagent.

The physical state of azetidinones varies widely with the degree and nature of substituents; most of the more highly substituted compounds are readily crystallized (Table 9). One highly characteristic and extremely useful property of these compounds is the infrared absorption spectrum, which can provide a very reliable confirmation of the presence of the four-membered lactam ring. The stretching frequency of the carbonyl group, which in an acyclic amide usually appears at about 6.0 μ, is shifted in the spectra of azetidinones to a much lower wavelength, normally in the range of 5.70–5.76 μ in monocyclic lactams. In the fused ring thiazolidine-β-lactams, because of additional constraint on the —C(O)—N— link, a further hypsochromic shift to about 5.60 μ is observed. Minor variations in these band positions have been observed in azetidinones with additional substituents, and the lactam carbonyl band may be obscured by another group, as in the phthalimido lactams prepared by Sheehan and Ryan.[206] The infrared spectra are, nevertheless, sufficiently characteristic that the demonstration of the strained carbonyl band is obligatory in assigning an azetidinone structure in a questionable case.

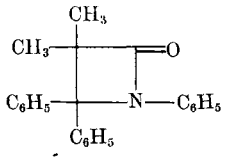
Analytical procedures for the detection and determination of 2-azetidinones have been developed by D'Amato *et al.*[38] These are based upon color reactions of the β-amino acid formed by mild hydrolysis with ninhydrin with sodium nitroprusside, and can be used for the estimation of azetidinones in biological fluids.

B. Chemical Properties and Reactions of Azetidinones

A large part of the literature on the properties and reactions of β-lactams relates to the unique and exceptionally labile penicillin molecule and related thiazolidine-β-lactams. Both the complex chemistry of penicillin itself and the extensive work on model compounds

carried out during the war-time program have been reviewed authoritatively in the penicillin monograph,[32] and these subjects will be dealt with very briefly here.

The thermal stability of azetidinones obtained by cycloaddition reactions was examined by Staudinger,[216] who observed both reversal of the original condensation to give the ketene and azomethine, and also the alternative mode of fission to an isocyanate and an olefin. For example, styrene and phenyl isocyanate were identified in the products obtained by vaporizing 1,4-diphenyl-2-azetidinone over a heated filament. With 3,3-dimethyl-1,4,4-triphenyl-2-azetidinone, obtained from dimethylketene and benzophenone anil, evidence was obtained for the production of both pairs of products (Eq. 58). The

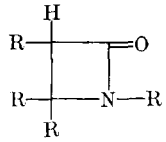


$$\longrightarrow (CH_3)_2C{=}C{=}O + (C_6H_5)_2C{=}NC_6H_5$$

$$+ (CH_3)_2C{=}C(C_6H_5)_2 + C_6H_5N{=}C{=}O \qquad (58)$$

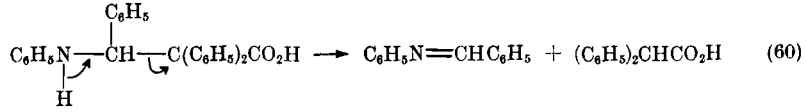
relative importance of the two modes of division (*cf.* section **VI.1**) in a given case is evidently related to the stabilities of the products. The temperature required for the dissociation of the lactams varies widely with the structure; the generalization has been suggested[8] that the higher the temperature required for condensation of the ketene and azomethine, the more stable the lactam.

By far the most extensively studied reaction of 2-azetidinones is their hydrolysis, particularly in alkali. The alkaline hydrolysis is very general, although tremendous differences in reactivity are observed. The β-amino acids are usually obtained in high yield, and this reaction sometimes offers a convenient method of preparing a β-amino acid when the latter is otherwise unavailable and the azetidinone can be obtained by another route such as cycloaddition or a Reformatsky reaction.[15] Occasionally the amino acid undergoes β-elimination under the hydrolysis conditions to give the α,β-unsaturated acid (Eq. 59) or, if an α-hydrogen is lacking, an azomethine may be formed (Eq. 60).



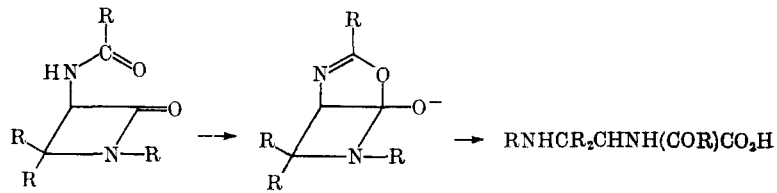
$$\longrightarrow RNHCR_2CHRCO_2H \longrightarrow RNH_2 + R_2C{=}CRCO_2H \qquad (59)$$

The much greater ease of hydrolysis of the penicillins compared to that of polysubstituted monocyclic β-lactams caused some delay in acceptance of the thiazolidine-β-lactam structure, and this marked



(60)

contrast prompted most of the work that has been done on correlation of structure and ease of hydrolysis of azetidinones. A number of qualitative and semi-quantitative comparisons of the rate and extent of hydrolysis of a series of β-lactams were made during the penicillin program and are summarized by Ballard *et al.*[9] 1,4-Diphenyl-2-azetidinone is almost completely hydrolyzed by refluxing for 1 hour in methanolic 0.5 *N* potassium hydroxide. It was observed that the introduction of two methyl groups at C-3 in this lactam greatly lowered the rate of hydrolysis, and that the 1,3,3,4-tetraphenyl derivative was even more resistant to hydrolysis. With this latter compound hydrolysis can be effected with hot concentrated alkali; the products obtained are diphenylacetic acid and benzalaniline, formed by elimination from the β-anilino acid[215] (Eq. 60). A similar depression in the rate of hydrolysis by α-substituents is observed in acyclic acid derivatives, and is attributable to steric interference with the attack of base. An increase in the extent of hydrolysis under standard conditions is observed on going from a 4-cyclohexyl to a 4-phenyl substituent; this has been correlated with the slightly different acid strengths of the



(61)

substituted acetic acids.[9] A substantial acceleration of the rate of alkaline hydrolysis is brought about by an acylamino substituent at C-3. This has also been attributed to the greater acid strength of the derived α-acylamino acid, but it seems more likely that the hydrolysis here involves direct participation of the acylamino group (Eq. 61). Stabilization of the β-lactam ring toward alkali is also imparted by

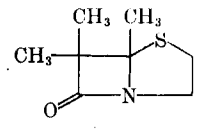
substituents at C-4. 4,4-Dicarbethoxy-1-phenyl-2-azetidinone can be saponified in high yield to the mono ester, and after decarboxylation the second ester group can be hydrolyzed without opening the ring.[194]

Holley and Holley[102] obtained quantitative rate data for the hydrolysis of a number of azetidinones, Table 11, and these confirm

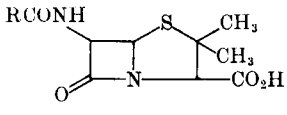
TABLE 11. Apparent Second-Order Rate Constants for Alkaline Hydrolysis of Azetidinones and Related Compounds[a]

Compound	10^{-2} K_2 (l. mole^{-1} sec.$^{-1}$) At 0°C	At 50°C	Reference
2-Azetidinone	0.12	13.0	105
1-Methyl-2-azetidinone	0.0095	1.5	104
1-Benzyl-2-azetidinone		1.7	104
1-Benzyl-4-phenyl-2-azetidinone		1.0	104
1-Benzhydryl-4-phenyl-2-azetidinone		0.3	104
1-Benzyl-3,3-dimethyl-4-phenylazetidinone		0.04	102
2-[1-(3-Phenylacetamido-2-azetidinone)]-*iso*valeric acid (desthiobenzylpenicillin) (CIII)		4.0	102
6,6,7-Trimethyl-4-thia-1-azabicyclo[3.2.0]-heptan-5-one (2-methyl-2-thiazolidine-α-*iso*butyric acid β-lactam) (CI)	0.015		102
Benzylpenicillin (CII)	38		102
2-Pyrrolidone		0.06	105
N-Methylacetamide		0.03	105

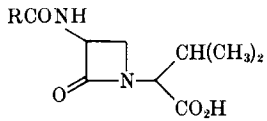
[a] Rates in 0.5 *N* sodium hydroxide in 85% ethanol.



(CI)



(CII)

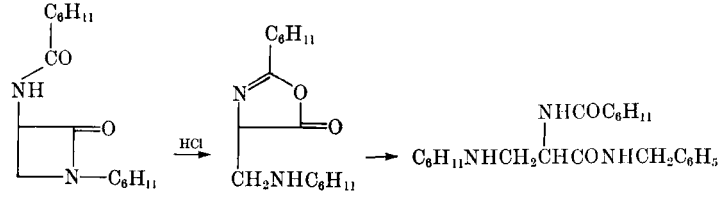


(CIII)

the earlier observations stated above. The retardation in rate caused by 1-alkyl substituents is due presumably to a combination of inductive and steric effects. From these values the rate of hydrolysis of highly substituted 2-azetidinones is comparable with that of the strain-free pyrrolidones and acyclic amides, although the rate for the parent β-propiolactam is 200 times greater than that of the five-membered homolog.

These data and others have been interpreted in terms of the factors responsible for the 'abnormal' rate of hydrolysis of the penicillins. It was shown[103] that a mercapto group at C-4 does not accelerate the hydrolysis, and it is apparent that the exceptional reactivity of penicillin (CII) is due entirely to the additional strain imposed by the fusion of the azetidinone moiety to a five-membered ring. The trimethyl thiazolidine-β-lactam (CI) is thus a very inadequate model compound, lacking the rate-enhancing acylamino group and containing three rate-depressing methyl groups. The effect of the geometry of the bicyclic ring system on the amide resonance in the β-lactam link has been discussed in detail.[248]

The data on acid-catalyzed hydrolysis of azetidinones are much less complete, but numerous examples of the cleavage of the β-lactam ring with alcoholic hydrochloric acid have been recorded.[9] The reaction is stated to be slower than alkaline hydrolysis; 1,4-diphenyl-2-azetidinone is unaffected by refluxing for 1 hour with two molar equivalents of hydrochloric acid. There is indirect evidence that azetidinones are converted by hydrogen chloride in an inert medium into the β-amino acid chloride hydrochloride. One case has been mentioned in section **III.1.***A*.(**3**). The reaction of 3-cyclohexaneacetamido-1-cyclohexyl-2-azetidinone with hydrogen chloride in chloroform followed by addition of benzylamine led to the formation of the *N*-benzyl-β-cyclohexylaminopropionamide.[9] The lactam itself does not react with benzylamine under the conditions used, and either the acid chloride, or, more likely in this case, the oxazoline (CIV), must be formed as an intermediate.

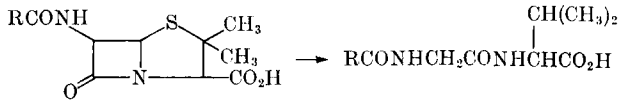


(CIV)

The β-lactam ring can be cleaved with amines, leading to the propionamide, but the reaction with monocyclic azetidinones requires rather drastic conditions. Several benzylamides were obtained by heating trisubstituted azetidinones with benzyl amine at 160°. Sheehan and Bose[195] observed an interesting difference in reactivity between 4,4-dicarbethoxy-1-phenyl-2-azetidinone and the mono ester. The

former was unchanged by refluxing with benzylamine in benzene solution, but the acid underwent decarboxylation and ring cleavage at room temperature to give α-anilinosuccinic acid dibenzylamide. The diethyl ester was converted with ammonia into the 4,4-dicarboxamide, the lactam remaining intact, indicating unusual reactivity in the malonic ester function.

Hydrogenolysis of the β-lactam ring at the N—C-4 bond occurs readily with 4-phenyl-2-azetidinones, which can be considered derivatives of benzylamine and therefore susceptible to cleavage at the C_6H_5CH—N— bond. In two cases the corresponding propionamides were isolated in good yield after treatment of the lactams with Raney nickel.[9] With other azetidinones the ring is generally stable. In the Raney nickel-catalyzed desulfurization of benzylpenicillin (Eq. 62), which was one of the most fruitful degradation reactions, some of the tripeptide (CV) was obtained together with the desthiopenicillin (CIII).[120] It was demonstrated that the tripeptide was not formed



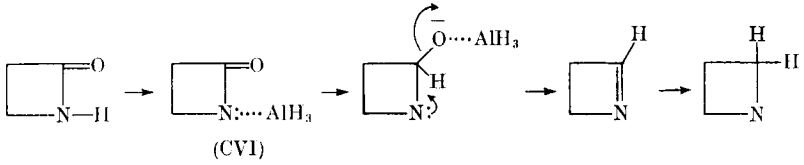
(62)

(CII) (CV)

from the desulfurized β-lactam, but rather directly from the penicillin molecule in a competing reaction, providing another example of the singular behavior of the bicyclic system. Other reactions in which the azetidinone ring remains intact include the catalytic hydrogenolysis of benzyl ester[194] and the catalytic hydrogenation of aromatic rings[9] and nitro groups.[54]

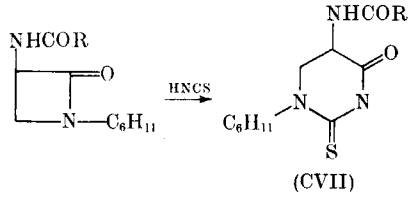
The reduction of 1-unsubstituted azetidinones to azetidines with lithium aluminum hydride is an important synthetic method [section **II.2.***A*.(**5**)]. The ring cleavage leading to the γ-aminopropanol that invariably occurs with 1-substituted azetidinones[213, 232] can be considered a case of 'reductive decomposition'.[72] This cleavage process is the normal one with *N*,*N*-disubstituted acyclic amides when at least one of the groups is electron-withdrawing, and the cleavage of 1-aryl-2-azetidinones is thus unexceptional. With 1-alkyl lactams, the usual reaction in five- and six-membered rings is reduction to the cyclic imine, and the abnormal cleavage with the four-membered lactam is attributable to relief of ring-strain. The situation is saved in the 1-unsubstituted azetidinones apparently by the fact that the negatively charged

nitrogen atom in the initially formed conjugate base (CVI) cannot assume the role of a leaving group even in the strained ring. Displacement of oxygen therefore occurs, presumably assisted by unshared electrons on nitrogen and thus creating some double-bond character between N and C-2 (Eq. 63).



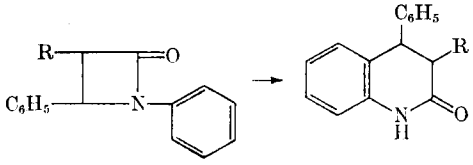
(63)

A formidable array of rearrangements involving the β-lactam ring is encountered in the chemistry of the penicillins. Most of these reactions are peculiar to the bicyclic system and occur because of the juxtaposition of other functional groups. Only a few rearrangements and ring-enlargements characteristic of the azetidinone ring *per se* will be mentioned here. One of the penicillin transformations that was extended to a monocyclic β-lactam is the facile cleavage with thiocyanic acid



(64)

(Eq. 64). This reaction was carried out with 3-cyclohexaneacetamido-1-cyclohexyl-2-azetidinone,[9] giving a product represented as the dihydrothiouracil (CVII). In another model reaction, 1-phenyl-3-phenylacetamido-2-azetidinone was isomerized by heating to the oxazolone (*cf.* Eq. 61). An interesting ring expansion of 1,4-diphenyl-2-azetidinone and the 3-bromo derivative has been described by Knunyants and Gambaryan.[130] In concentrated sulfuric acid the ring is opened at the N—C-4 bond and subsequent ring closure to the 4-phenylcarbostyril occurs (Eq. 65); the 3-bromo derivative was obtained in 72% yield. A

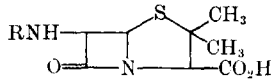


(65)

similar cleavage of the lactam ring was observed with 4-methyl-1-phenyl-2-azetidinone, loss of a proton then giving crotonanilide.

C. Natural Occurrence and Pharmacological Properties

The only azetidinone derivatives thus far found in nature are the penicillins, elaborated by strains of the mold *Penicillium notatum* and other microorganisms. The extraordinary antibacterial action of these compounds revolutionized the treatment of Gram-positive bacterial infections, and their discovery marked the beginning of the age of antibiotics. It was recognized early in the co-operative penicillin program that the antibacterial properties of various fermentation broths were not due to a single chemical entity and eventually six compounds differing in the acyl residue attached to the amino group of 6-aminopenicillanic acid (CVIII, R = H) were isolated from culture



(CVIII)

media.[14] The finding that production of benzylpenicillin (CVIII, R = $C_6H_5CH_2CO$—) was stimulated by the addition of phenylacetic acid derivatives permitted the preparation of a series of biosynthetic penicillins with various substituted phenylacetyl groups by addition of the respective acids to the culture medium. More recently the parent 6-aminopenicillanic acid has been obtained by fermentation[11] and also by synthesis,[201] and the preparation of a wide variety of 'semi-synthetic' penicillins has been undertaken.[112] These compounds are much needed adjuncts to the natural penicillins for therapeutic purposes since the effectiveness of the latter is reduced by development of resistant strains of pathogens.

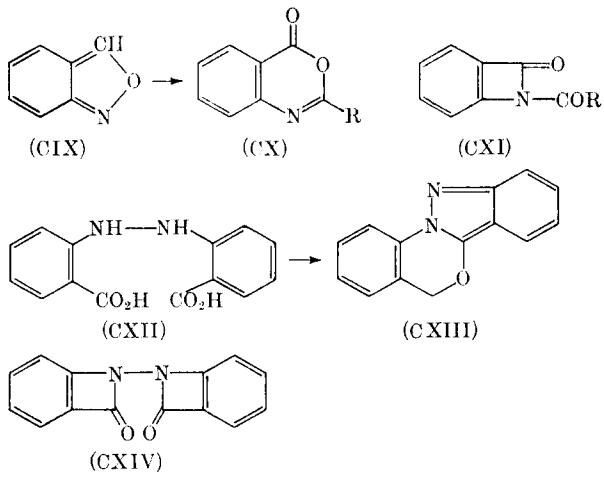
The series of 3,3-disubstituted 2-azetidinones prepared by Testa *et al.*[55, 235] has given several potentially useful drugs. These compounds were examined because of their structural relationship to 5,5-disubstituted barbiturates and hydantoins, and pharmacological evaluation reported by Maffii[154] has revealed sedative and anticonvulsant properties in certain of these β-lactams that resemble those of phenobarbital. The effects on the central nervous system have been studied in detail with 3-ethyl-3-phenyl-2-azetidinone and several other

members. 3-Ethyl-1-methyl-3-phenyl-2-azetidinone displays effects on the central nervous system closely paralleling those of meprobamate.

3. Unsaturated Azetidinones

Products obtained in a variety of reactions have from time to time been assigned, on the basis of the criteria of the period, structures in which an unsaturated β-lactam ring is a prominent feature. None of these formulations can be accepted in the light of contemporary understanding of reaction mechanisms or stability considerations, and it is very doubtful that any presently known techniques would permit of the preparation or characterization of such compounds.

The scattered references to monocyclic 3-azetin-2-one structures[125, 138] need not be considered further, but the so-called benzazetinones deserve brief comment. Throughout the earlier literature and as recently as 1956,[168, 143] the stable products (acylanthranils) obtained by treatment of anthranilic acids or anthranils (CIX) with acylating agents were formulated as the *N*-acyl-β-lactams (CXI). Similar azetinone structures were advanced for the condensation



(CIX) (CX) (CXI)

(CXII) (CXIII)

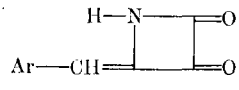
(CXIV)

product of hydrogen cyanide and phenanthraquinone[116] and the dehydration product of *o,o'*-dicarboxyhydrazobenzene (CXII) (Bisanthranil).[97] Definitive evidence has been presented by Zentmoyer and Wagner[252] that the anthranils are [3.1.4]benzoxazine derivatives (XII), and Mosby[168] has shown that Heller's bisanthranil is best represented by structure (CXIII) rather than the benzazetinone (CXIV).

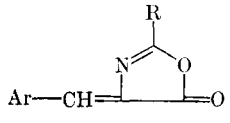
IV. Azetidinediones

1. 2,3-Azetidinediones

The only compound for which a 2,3-azetidinedione structure has been advanced is the condensation product of veratraldehyde and formylglycine.[175] This product was formulated as the ketolactam (CXV) rather than the oxazolone (CXVI, R = H) primarily on the basis of the infrared spectrum. The spectrum was dissimilar to that of the corresponding 2-alkyloxazolones (CXVI, R = CH_3), but the reported carbonyl stretching frequency of 1663 cm.$^{-1}$ is not consistent with the lactam structure. Vigorous hydrolysis of the compound gave the arylpyruvic acid. Both the mode of formation and of hydrolysis of the compound are consistent with oxazolone formulation, and although the question cannot be settled, the azetidinedione structure is not acceptable on the basis of existing evidence.



(CXV)



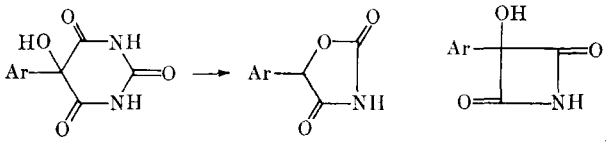
(CXVI)

2. 2,4-Azetidinediones (malonimides)

2,4-Azetidinediones are malonimides, and are indexed as such in *Chemical Abstracts*. Earlier workers for the most part did not recognize the difficulties inherent in the synthesis of the highly strained malonimide ring, and it appears that with one exception, all of the dozen or more compounds described as malonimides in the literature[8] before 1950 were incorrectly formulated. A number of these compounds have been reinvestigated by King, Clarke-Lewis and Morgan, and alternative structures assigned.

The product[52] obtained by heating the phenylhydrazine salt of malonyl monohydrazide was shown[124] to be 1-acetyl-2-phenylhydrazine rather than the 1-anilinoimide. The supposed imide formed in the condensation of α-naphthylamine and ethyl malonate[163] is in fact a dihydroxyquinoline.[124] A similar condensation with benzidine[142] gives a polymeric product rather than the imide.[124] Several compounds assigned the tartronimide structure (CXIX) have been obtained by the vigorous alkaline hydrolysis of dialuric acids (CXVII).[172, 228] These products, which have also been stated to arise from the reaction

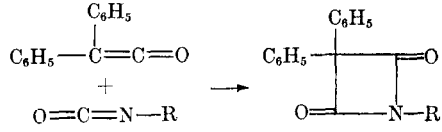
of tartronic esters with urea or ammonia,[180] have been found to be the isomeric oxazolidinediones (CXVIII).[122] A similar imide formation was suggested in the alkaline hydrolysis of the anils obtained from alloxan and a series of *o*-dimethylaminoanilines.[182] Further study of these reactions[123] has revealed that the hydrolysis products are hydantoins, formed from quinoxalines which are the actual products of the alloxan condensation.



(CXVII) (CXVIII) (CXIX)

A. Methods of Preparation

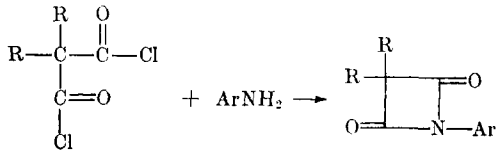
(1) Cycloaddition of ketenes and isocyanates. All of the authentic malonimides recognized to date are 3,3-disubstituted derivatives. The first example, 1,3,3-triphenyl-2,4-azetidinedione, was prepared[219] by the thermal cycloaddition of diphenylketene and phenyl isocyanate (Eq. 66), the condensation closely resembling the better known dimerization of isocyanates (section **VI.3**). The malonimide was obtained at 150° and is stable at this temperature, but at higher temperatures the addition is reversed to give the original components. This process has subsequently been applied to the preparation, in low yield, of 1-methyl- and 1-cyclohexyl-3,3-diphenylmalonimides by condensation of diphenylketene and the respective isocyanates.[47]



(66)

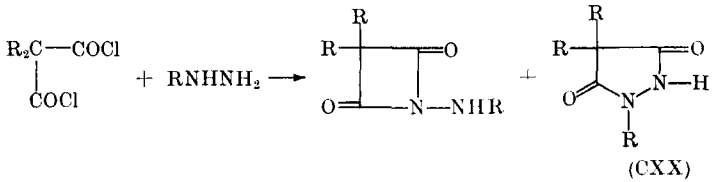
(2) From malonyl chlorides and amines. The first comprehensive study of the preparation and properties of malonimides was reported in 1959 by Ebnöther *et al.*,[47] who synthesized a large number of derivatives by condensation of disubstituted malonyl chlorides with aromatic amines (Eq. 67). This approach was first utilized successfully in the preparation of the 3,3-diethylimides from 6-aminoquinoxalines.[140]

In the general procedure, weakly basic amines, including aniline, *p*-phenylenediamine, 2-aminoindole, 2-aminothiazole and the isomeric aminopyridines are condensed with diphenyl- or dialkyl-malonyl chlorides in the presence of a tertiary amine as the hydrogen chloride acceptor. The yields of the malonimides, which are usually accompanied by the corresponding diamides, vary widely and are often rather poor.



(67)

Ammonia or alkylamines give exclusively the malondiamides. A series of 1-aminomalonimide derivatives was prepared by condensation of 1,1-disubstituted hydrazines, hydrazones and acyl hydrazides with diethyl- and diphenylmalonyl chloride. Again the highest yields were obtained with the more weakly basic hydrazides and hydrazones. A few monosubstituted hydrazines were also converted into malonimides; the pyrazolidinediones (CXX) were obtained as minor by-products (Eq. 68).

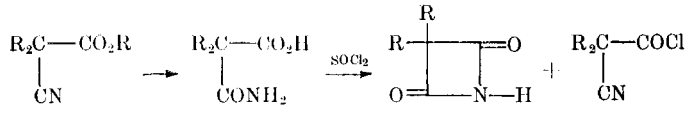


(68)

The yields of azetidinediones are very low with dimethylmalonyl chloride, emphasizing the importance of the bulk of the substituent groups. The very marked influence of the geminal substituents on the course of these acylations can be attributed to a combination of steric shielding to the approach of a second molecule of amine, leading to diamide formation, and a buttressing effect which compresses the valence angle and lowers the entropy of activation for formation of the four-membered imide. The fact that in the reaction with monosubstituted hydrazines, the malonyl dihydrazides, resulting from attack of a second molar equivalent of hydrazine, are obtained in larger amounts than the pyrazolidinediones has been taken as an indication that the deformation of the valence angle is the more important factor.

A total of some 80 malonimides, about half of them 1-amino derivatives, was prepared and characterized by Ebnöther and co-workers; the list of individual compounds will not be duplicated here. Many of the derivatives were obtained by modification of groups in the intact imides. The structures were confirmed by the characteristic infrared-absorption spectra and, in selected cases, hydrolysis or conversion into the unsymmetrical diamides with ammonia.

(3) Ring closure of malonamidic acids. Very shortly after the appearance of the extensive work of Ebnöther *et al.*, another substantial contribution to the chemistry of malonimides was reported by Testa and co-workers,[234] who developed a simple procedure for the ring closure of malonic acid monoamides (Eq. 69). The amides were



(69)

obtained by acid-catalyzed hydration of disubstituted cyanoacetic esters followed by saponification to the acid. Treatment of the amidic acids with pyridine and thionyl chloride then gives the 3,3-disubstituted malonimides in yields ranging from 13 to 25%. The major by-product is substituted cyanoacetyl chloride. Three 3-alkyl-3-phenyl- and three 3,3-dialkylmalonimides were prepared, the lowest yields being obtained in the latter cases.

B. Properties and Reactions

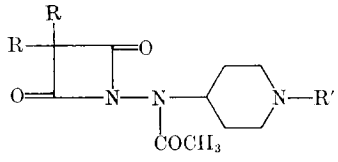
The 3,3-disubstituted malonimides are colorless liquids or low-melting solids, and can be isolated by distillation at reduced pressure. A number of the trisubstituted malonimides prepared by method (**2**) were separated from by-products by chromatography on alumina. The infrared spectra display a typical high-frequency carbonyl stretching band at 1725–1770 cm.$^{-1}$, and occasionally a weaker band at higher frequency. The band in 1-unsubstituted or simple 1-amino or 1-aryl derivatives appears at about 1745 cm.$^{-1}$; acetylation of the 1-amino group shifts the absorption to 1765–1770 cm.$^{-1}$

The four-membered imide ring in all of these azetidinediones is rapidly cleaved by ammonia at room temperature with the formation of the diamide.[47] The 1-unsubstituted derivatives are readily hydrolyzed to the malonamidic acid in alkaline solutions, but are relatively

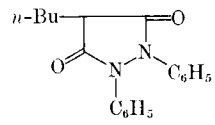
stable towards acid hydrolysis.[234] The 1,3,3-trisubstituted derivatives are in general quite susceptible to cleavage by acid, especially in the 3,3-dialkyl series, although the acetyl group can be preferentially removed in the hydrolysis of 1-acetylamino-3,3-diphenylmalonimides. The imide ring is unaffected by hydrogenation or by acylation at another center. The imide —NH— group can be methylated with diazomethane.

The behavior of malonimides towards lithium aluminum hydride parallels that of azetidinones.[234] With a substituent on the imide nitrogen atom, hydrogenolysis of the ring takes place, with formation of either the 2,2-disubstituted 3-hydroxypropionamide or, on further reduction, the propanolamine. With the 1-unsubstituted compounds, however, reduction of both carbonyl groups occurs without ring opening, and the azetidines are obtained in high yield.

(1) **Pharmacology.** The impetus for the preparation of these extended series of azetidinediones was the possibility that these imides might exhibit useful pharmacological properties. They are structurally related to the succinimides and pyrazolidinediones on one hand and to azetidines and azetidinones on the other, and a variety of pharmacological effects have been observed in members of all of these classes. The anti-inflammatory properties of a number of 3,3-disubstituted 1-aminomalonimides were reported by Ebnöther *et al.*[47] A very high activity was found in the series of derivatives (CXXI) obtained by condensation of dialkylmalonyl chlorides with 1-acetyl-1-(4-N′-alkylpiperidyl)hydrazines; the compound (CXXI, R = *n*-C_3H_7 and R′ = *iso*C_3H_7) was the most active in the series, and was 10-fold more potent than phenylbutazon (CXXII).



(CXXI)



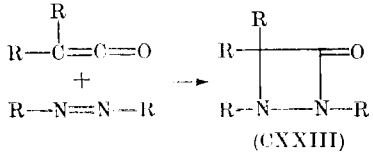
(CXXII)

The 3-alkyl-3-phenylmalonimides prepared from the malonamidic acids showed definite sedative properties, but these were stated to be of a lower order than those of the corresponding azetidinones.[234]

V. Derivatives of 1,2-Diazetidine

1. Diazetidines and Diazetidinones

The only general method for the formation of the diazetidine ring is the cycloaddition of azo compounds and unsaturated compounds with a highly reactive double bond. In all but one case the olefin used has been a ketene, and the products are therefore diazetidinones (CXXIII, Eq. 70); the reaction is analogous to the preparation of β-lactams from ketenes and azomethines.



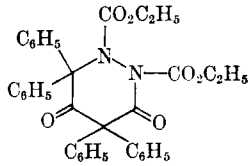
(CXXIII) (70)

The first member of the series (CXXIII, R = C_6H_5) was briefly described by Staudinger[216] from the condensation of diphenylketene and azobenzene. The reaction was extended to phenylazocarboxlic ester by Ingold and Weaver,[115] who obtained the ester (CXXIII, R = CO_2Et) in 70% yield. A major improvement in the method was effected by Cook and Jones,[33] who were studying the differences in chemical properties of the geometrical isomers of symmetrical azo compounds. Whereas the condensation of diphenylketene with *trans*-azobenzene requires elevated temperature, the *cis*-isomer reacts rapidly and exothermically at room temperature, a result consistent with the geometrical requirements of the transition state of the cycloaddition. The preparation of several diazetidinones was accomplished conveniently by irradiation of a ligroin solution of the ketene and normal *trans*-azo compound, the *cis*-isomer being generated *in situ*. The cycloaddition has also been carried out by photolysis of diazoketones in the presence of the azo compound.[108]

The addition reaction has been applied, with diphenylketene, to an arylazocyanide[33] and bisbenzoyldiimide[108] as well as several symmetrical azo compounds (Table 12). Ketene itself reacts with azobenzene under irradiation, but not with ethyl azobisformate ester.[187] With excess diphenylketene, the condensation of the azobisformate leads to a pyridazine derivative (CXXIV).[115] The only simple diazetidines that have been described were obtained by the cycloaddition of tetrafluoroethylene and azobisformates;[34] trifluoroethylene and chlorotrifluoroethylene yield analogous products. Dimethyl 3,3,4,4-

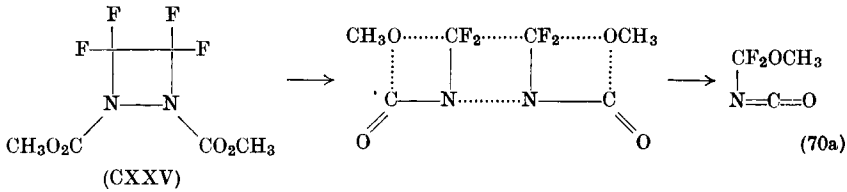
TABLE 12. 1,2-Diazetidin-3-ones

Substituents			M.p. (°C)	Reference
At N-1	At N-2	At C-4		
Phenyl	Phenyl		115	187
m-Tolyl	*m*-Tolyl			187
Phenyl	Phenyl	Phenyl	92	109
Phenyl	Phenyl	Diphenyl	175	108, 33
Phenyl	$-CO_2C_2H_5$	Diphenyl	132	115
p-Chlorophenyl	—CN	Diphenyl	121	33
o-Tolyl	*o*-Tolyl	Diphenyl	162	33
m-Tolyl	*m*-Tolyl	Diphenyl	118	33
p-Tolyl	*p*-Tolyl	Diphenyl	172	33
Benzyl	Benzyl	Diphenyl	154	108
Benzoyl	Benzoyl	Diphenyl	195	108



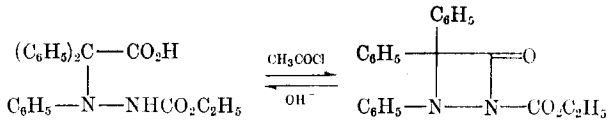
(CXXIV)

tetrafluoro-1,2-diazetidine-1,2-dicarboxylate (CXXV) undergoes a remarkable thermal cleavage reaction to produce methoxydifluoromethyl isocyanate in 70% yield[120a] (Eq. 70a).



(CXXV) (70a)

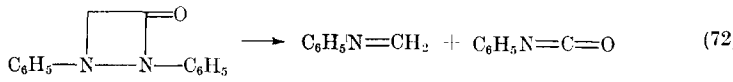
There is one report of the synthesis of a diazetidinone by formation of the amide linkage (Eq. 71). The hydrazinoacetic acid used was



(71)

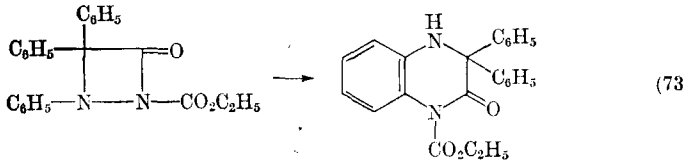
actually prepared by hydrolysis of the four-membered ring obtained by cycloaddition; the ring closure was brought about with acetyl chloride.[115] It is probable that this method would be practical only with highly substituted derivatives, although it does not appear to have been widely explored.

The chemical properties of a few diazetidinones have been reported. At elevated temperature the ring is cleaved with rupture of the lower-energy N—N bond (Eq. 72). In two cases[187, 209] the isocyanate and the



(72)

corresponding imine fragments were isolated or characterized as further reaction products, but azobenzene has also been obtained from the pyrolysis of the 1,2,4,4-tetraphenyl derivative.[33] Azobenzene was also obtained in high yield by warming the tetraphenyl compound with a trace of sodium methoxide, and, in the case of the 1,2-diphenyl derivative, by permanganate oxidation.[187] The cyclic hydrazide ring is usually opened with very mild alkaline hydrolysis to give the substituted hydrazinoacetic acid. The *N*-aryldiazetidines, as tetrasubstituted arylhydrazines, should be susceptible to benzidine- or semidine-type rearrangements, and such a reaction has been realized (Eq. 73). 1-Carbethoxy-2,4,4-triphenyldiazetidinone was converted by mineral acid into an isomer which formed acyl derivatives and was assigned the quinoxaline structure (CXXVI).[115]



(CXXVI)

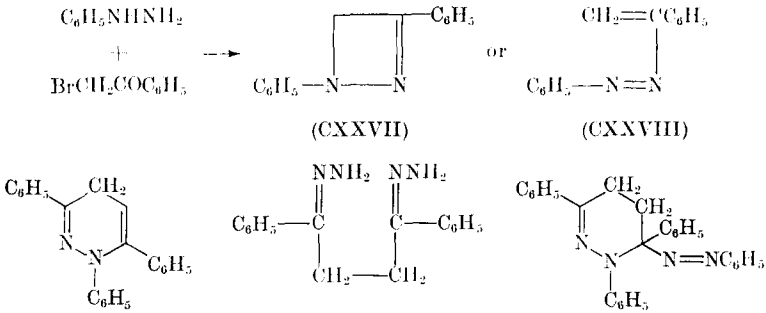
(73)

2. Diazetines

The unsaturated diazetine ring has been invoked as a structural feature in two types of reaction products, and one of these was the subject of intermittent study by a number of investigators for over 60 years. In 1885 Hess[100] described the reaction product of phenacyl bromide and phenyl hydrazine as a yellow substance, $C_{14}H_{12}N_2$, and suggested the Δ^2-diazetine (CXXVII) or the vinylazo compound

(CXXVIII) as possible structures, although a dimeric tetrazocine structure was advanced shortly thereafter.[35] The compound was found[60] to give on treatment with acid a substance that was eventually shown to be the pyridazine (CXXIX).[16] Further reaction with phenyl hydrazine[191] or reduction with sodium amalgam gave the bisphenylhydrazone of diphenacyl (CXXX).[16] After further molecular-weight determinations Bodforss reinstated the monomeric formula, and in two later reports,[17, 242] the diazetine structure was reaffirmed, essentially by elimination of the vinylazo alternative and with no further positive evidence.

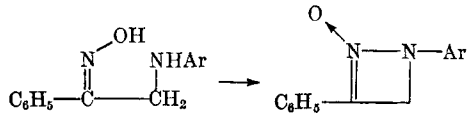
In a thorough re-examination of the question, Curtin and Tristram[36] clearly demonstrated a dimeric formula for the compound and concluded that the only tenable structure is that of the phenylazotetrahydropyridazine (CXXXI). This structure, which may be derived by dimerization of the vinylazo intermediate (CXXVIII), is consistent with the extremely facile conversion into (CXXX), although the mechanism of the acid-catalyzed elimination to (CXXIX) is somewhat obscure. Structure (CXXXI) is compatible with the infrared spectrum[36] and also with the proton magnetic resonance spectrum.[3]



A number of similar halogen-free products obtained from phenacyl halides and phenylhydrazine have been assigned diazetine structures[106, 31, 244] by analogy to the earlier formula for the Hess compound; these clearly require revision in light of the work of Curtin.

Another case in which the diazetine structure has been attributed is that of the 'dehydrophenacylamine oxides' derived by mild oxidation of *N*-arylphenacylamine oximes (Eq. 74), which were formulated as the four-membered nitrones (CXXXII).[227] This structure appears to lack any adequate foundation.

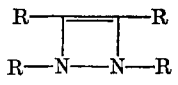
Although no authentic diazetine derivative has been described, theoretical considerations indicate that a Δ^3-diazetine (CXXXIII) will possess a certain degree of aromatic character, and an estimate of a



(74)

(CXXXII)

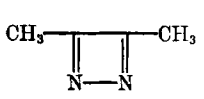
delocalization energy of 0.5 β has been made.[3] In an effort to examine this possibility, attempts have been made to obtain a 3-diazetine by the cycloaddition of an acetylene and an azo compound, and by treatment of a diazetidinone with zinc dust.[3] In neither case have products corresponding to (CXXXIII) been isolated.



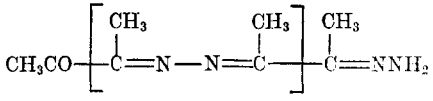
(CXXXIII)

3. Diazetes

The four-membered ring structure (CXXXIV) was considered in an early paper[37] for the high-melting condensation product of biacetyl and hydrazine. The preparation was repeated,[253] and the product was clearly shown to be the expected condensation polymer (CXXXV), which gave the bis-hydrazone on further treatment with hydrazine.



(CXXXIV)



(CXXXV)

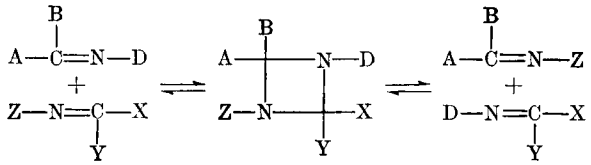
VI. Derivatives of Uretidine (1,3-Diazetidine)

1. Uretidines

Saturated uretidines correspond to the cyclization products of two molecules each of a carbonyl compound and ammonia or a primary amine. They can thus be considered as dimers of Schiff bases and are

closely related to the much better known cyclic trimers, the hexahydro-*sym*-triazines.[210] Although only a few scattered members of the series have been described it is probable that further compounds could be obtained by the methods that have been employed, all of which involve the condensation of a carbonyl compound and amine or of the equivalent azomethine or substituted methylenediamine.

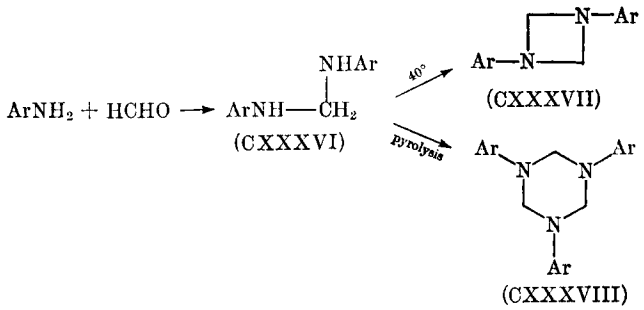
The first uretidines were described by Ingold and Piggott[113] during a systematic study of additive ring formation, as exemplified by the formation of four-membered cyclic products in the dimerization of ketenes and in the related reactions of ketenes with isocyanates, azomethines and azo compounds, and, it was thought at the time, the dimerization of nitroso compounds. On the premise that in any double-bonded compounds there is a tendency for establishment of an equilibrium with the dimeric form, the reversible dimerization of azomethines according to Eq. (75) was examined. A number of pairs of



(75)

anils were warmed or allowed to stand in concentrated solutions and the equilibration was very convincingly demonstrated. In three cases the uretidine was isolated and in others the corresponding anils formed by ring division opposite to the mode of formation were obtained.

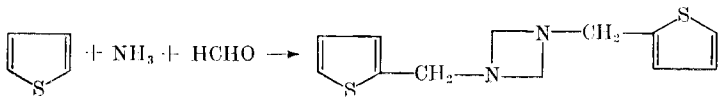
The direct condensation of a primary amine and formaldehyde has been used in the preparation of 1,3-di-*p*-tolyluretidine (CXXXVII)[114] (Eq. 76) and 1,3-bis-(2-hydroxyethyl)uretidine.[173] In



(76)

the reaction with *p*-toluidine, the methylenedi-*p*-tolylamine (CXXXVI) was proven to be an intermediate. This compound was the major product when the reaction was carried out at 0°. At 40–70° the uretidine was obtained in 80% yield; higher temperatures favored the production of the hexahydro-*sym*-triazine (CXXXVIII). In the reaction of aniline and other primary amines with formaldehyde the hexahydro-*sym*-triazines appear to be the only low molecular weight condensation products that have been characterized. Other uretidines could presumably be obtained by proper control of reaction conditions, although complex equilibria among the methylolamine, azomethine, diaminomethane and higher condensation products are involved. The successful isolation of the cyclic dimer will depend on the ease of separation of this product from the mixture and the relative stabilities of the several products.

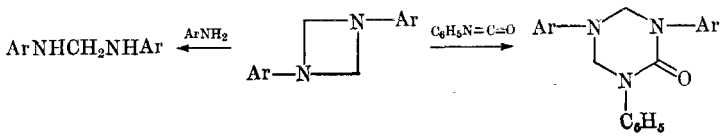
A variation of this approach is the direct formation of the uretidine in the Mannich reaction, which was used to prepare the bis-(2-thienylmethyl) derivative[93] (Eq. 77). This product was also obtained by neutralization of the corresponding aminomethylsulfonic acid.[94] When 2-methylthiophene was subjected to the same conditions the di-(5-methyl-2-thienylmethyl)amine and the corresponding *sym*-triazine, and no uretidine, were isolated.



(77)

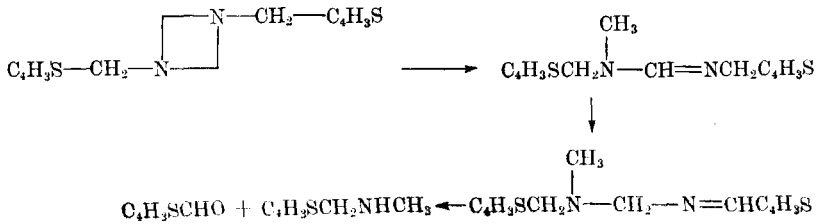
Ring-opening reactions of molecules of the uretidines and similar four-membered cyclic compounds were classified by Ingold and Piggott[113] as either division into two molecules of azomethine, or scission, involving the breaking of only one C—N bond. The division process, or thermal depolymerization, is apparently a general reaction of the series, and presumably intervenes in the formation of trimers and higher polymers,[93] and possibly in other reactions as well.

1,3-Di-*p*-tolyluretidine reacts with *p*-toluidine to give the expected diamine, and with phenylisocyanate at elevated temperatures to yield the hexahydrotriazinone (CXXXIX)[114] (Eq. 78). The dithienylmethyl derivative is quantitatively converted by dilute acid into the aldehyde and secondary amine; the reaction is viewed as proceeding through the tautomeric imines[92] (Eq. 79).



(78)

(CXXXIX)

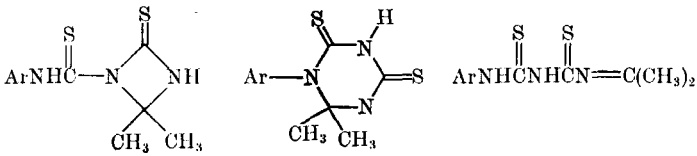


(79)

2. Uretidinones

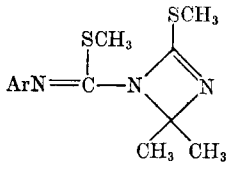
Four-membered cyclic structures for the condensation products of urea and aldehydes were first written in 1869.[189] The high-melting, insoluble products derived from urea and formaldehyde were accepted[98, 151] for some time to be the parent compound of the series, uretidinone or methyleneurea. This structure was subsequently replaced by oligomeric formulas,[45] and after a careful review[90] of the earlier work, Hale and Lange[91] in 1919 were 'forced to the conclusion that no adequate proof of the synthesis of a four-membered cyclic urea from an aldehyde and urea has ever been advanced'. This view appears to remain valid, although a subsequent assignment[95] of a bis-uretidinone structure, to a condensation product of urea and acetone, has been made without structural support.

A dithiouretidinone structure has been retained until more recently for the condensation products of ketones and dithiobiurets. These compounds, named 'dithio-c-keturets', were studied extensively by Fromm[65, 66, 67] who considered the three structural possibilities (CXL), (CXLI) and (CXLII). Since a 'similar' product was obtained

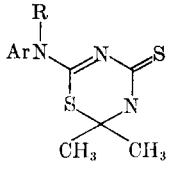


(CXL) (CXLI) (CXLII)

in one case from a 1,1-disubstituted dithiobiuret, excluding the thiazine structure (CXLI), the four-membered formula (CXL) was adopted for the series. In a re-examination of these compounds, Fairfull and Peak[50] subjected the product from 1-phenyldithiobiuret and acetone to *S*-methylation, followed by successive conversion of both —C(SCH$_3$)=N— groups to —CO—N(CH$_3$)— by quaternization and hydrolysis. Final hydrolysis gave aniline rather than *N*-methylaniline, establishing that neither of the enolic thiocarbonyl groups involved the C_6H_5NH— unit, and thus the uretidinone structure (CXLIII) for the dimethylthio ether is ruled out. These authors conclude that the compounds derived from monosubstituted dithiodibiurets have the triazine structure (CXLI), and dismiss all of the uretidinone formulations for the products derived from dithiobiurets and carbonyl compounds. A thiadiazine structure (CXLIV) is suggested for the product obtained from 1-methyl-1-phenyldithiobiuret.

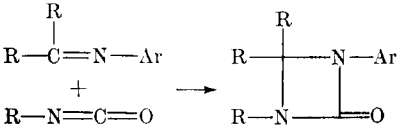


(CXLIII)



(CXLIV)

The only authentic members of the series have been prepared by the cycloaddition of an isocyanate to a C=N bond (Eq. 80), paralleling the formation of β-lactams by the addition of ketenes to azomethines. The reaction of phenyl- or α-naphthylisocyanate with methyleneaniline or its cyclic trimer gave 1,3-diphenyl- and 1-phenyl-3-α-naphthyl-uretidinone respectively.[193] The reaction was extended by

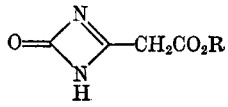


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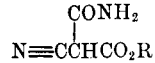
Hale and Lange[91] to the preparation of 1,4-diphenyluretidinone from cyanic acid and benzalaniline. The process is limited in scope; with alkylidene anilines two molar equivalents of cyanic acid add to form a diketopiperidine.

These uretidinones are readily hydrolyzed to the respective urea and aldehyde components.[91, 193] The ring is stable to acylation; the 1,4-diphenyl member gives the 3-acetyl derivative.[91]

A similar addition of cyanic acid, generated *in situ* from urea, was postulated by Frerichs and Hartwig[62] to occur with the —C≡N triple bond of ethyl cyanoacetate, giving an acidic product assigned the uretinone structure (CXLV). Significantly, no analogous product was obtained with monofunctional nitriles. It seems highly probable that the condensation occurred at the active methylene group to give the carboxamidocyanoester (CXLVI), paralleling the reaction of phenylisocyanate with malonic ester.[41]



(CXLV)



(CXLVI)

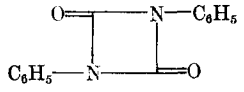
3. Uretidinediones

The uretidinediones, which are the cyclic dimers of isocyanates, form the most extensive series of four-membered heterocyclic compounds with two nitrogen atoms. Their chemistry closely resembles that of the isocyanate monomers with which they are in equilibrium at high temperatures. The parent compound, the dimeric form of cyanic acid, is unknown, and all but one member of the series are 1,3-diaryl derivatives.

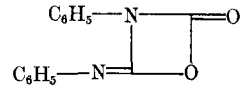
1,3-Diphenyluretidinedione was the first member of the series to be prepared, and has been studied more extensively than any other derivative. The rapid formation of a crystalline product, m.p. 175°, from treatment of phenylisocyanate with a trace of triethylphosphine was observed by A. W. Hofmann in 1859, and the compound was thoroughly characterized as a dimer in 1871.[101] Two other analogous products were obtained shortly thereafter by a similar reaction,[40, 61] and the dimerization was found to occur also in pyridine solution.[211]

The first suggestion of a symmetrical four-membered ring structure (CXLVII) was made by Staudinger,[216] and this remains the accepted formulation. The presence of the uretidinedione ring in the crystalline solid has been confirmed by X-ray measurements, which show a slightly oblique four-membered ring with an —N—CO—N— bond angle of 87°.[25] An alternative structure (CXLVIII) has been

suggested[73] in analogy to the structure of the ketene dimers and to account for the formation of diphenylurea on treatment of the dimer with Grignard reagents. It has been pointed out, however, that this

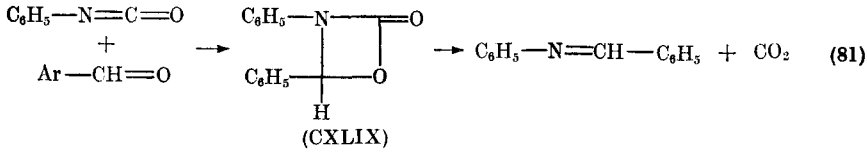


(CXLVII)



(CXLVIII)

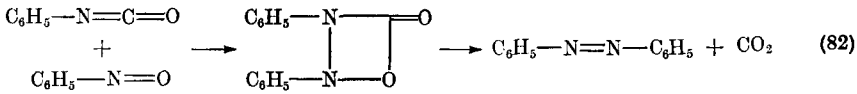
and other reactions can be accounted for equally well with the uretidinedione structure.[4] A further objection may be raised to the oxazetidinone structure (CXLVIII). It has been shown[218] that the reaction of phenylisocyanate with an aldehyde or nitrosobenzene gives directly the imine (Eq. 81) and azobenzene (Eq. 82) respectively. These reactions



(81)

(CXLIX)

were considered to proceed by the intermediate formation of the similarly constituted azalactones (CXLIX) and (CL), although these products were not isolated, and may not be present in measurable concentrations. It would be expected, therefore, that if the phenyliso-

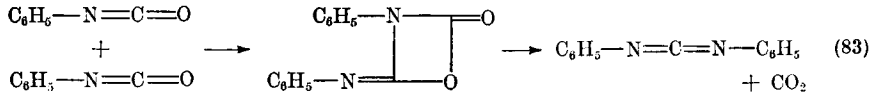


(82)

(CL)

cyanate dimer possessed the structure (CXLVIII), facile thermal decomposition to diphenylcarbodiimide and carbon dioxide would occur, rather than the observed depolymerization to the monomeric isocyanate. It is quite possible that the isomeric dimer (CXLVIII) is involved in the phospholine oxide-catalyzed conversion of isocyanates to carbodiimides (Eq. 83),[29] but the stable products isolated in the trialkylphosphine-catalyzed dimerization seem definitely to be the uretidinediones.

The trialkylphosphine-catalyzed condensation of aryl isocyanates, used in the earliest preparation of 1,3-diphenyluretidinedione, is still the most general synthetic method, and has been extended to a number



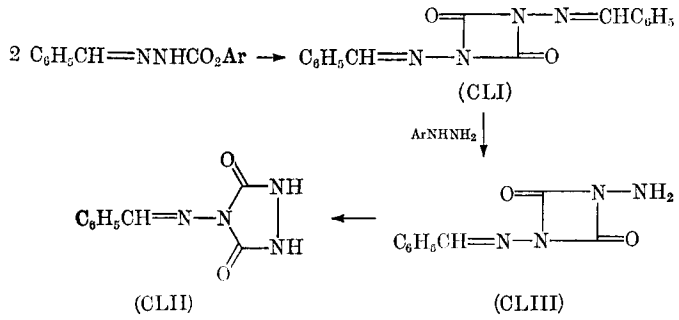
(83)

of other isocyanates.[178] These include the *o*-, *m*-, and *p*-chlorophenyl, *p*-bromophenyl, *p*-nitro, *p*-ethoxyphenyl, α- and β-naphthyl, and *m*- and *p*-tolyl derivatives. The yields are generally high and in a few cases are nearly quantitative. The *o*-chloro member is the only *ortho*-substituted dimer known and was obtained in 37% yield; the *o*-tolyl-uretidinedione could not be isolated.[61] An unsymmetrical dimer was obtained by condensation of *p*-chlorophenyl- and *p*-tolyl-isocyanates in the remarkably high yield of 88%.[178] A summary of the known uretidinediones, with melting points, has been compiled[4] and will not be duplicated here. The condensation of 1-substituted 2,4-diisocyanates proceeds selectively through the *p*-isocyanate groups, giving 4,4′-disubstituted 3,3′-diisocyanato uretidinediones; a series of eight compounds is listed by Siefken.[208]

The equilibrium between monomeric isocyanate and uretidinedione in the presence of catalysts is shifted to the monomer at elevated temperatures, so that the yield of uretidinedione is maximized by using the lowest temperature at which the condensation occurs at a practical rate. Although a variety of tertiary phosphines have been described in the patent literature as catalysts for uretidinedione formation,[4] a striking difference is observed with the cyclic tertiary phospholidines, which lead to the formation of the carbodiimide and carbon dioxide.[10] Tertiary amines have also been used to catalyze the dimerization of isocyanates.[152, 211]

A few cases have been reported of the formation of uretidinediones from carbamates; it is possible that these reactions involve the isocyanate as an intermediate. The action of thionyl chloride on *N*-phenylurethane has been shown to give 1,3-diphenyluretidinedione,[246] but the reaction is not general; with six other urethanes either an unidentified oil or unchanged starting material was obtained.[177] A substituted phenyl carbamate was found to give the uretidinedione on warming in pyridine.[179] The 1,3-diaminouretidinedione (CLI) was prepared by simple pyrolysis of the aryl carbamate[43]

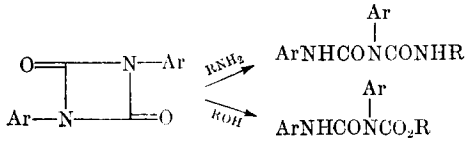
(Eq. 84). The dimeric nature of the product was indicated by reaction with phenylhydrazine, which effected exchange with one of the benzylidene groups, giving a product (CLIII) with one free amino group per $C_6H_5CH{=}N{-}$ unit. Had the product been a trimer, these groups would have been present in a ratio of 1 : 2 or 2 : 1. Several unsymmetrical diarylidene derivatives were prepared by the reaction of (CLIII) with aldehydes. Acid hydrolysis of the dimer led to the urazine (CLII).



(84)

The 1,3-diaryluretidinediones are colorless high-melting solids; their very low solubility in most solvents facilitates their preparation but usually precludes cryoscopic molecular-weight determinations. Although the ring is sufficiently stable to permit reactions such as halogenation and nitration of the aryl substituents in 1,3-diphenylisocyanate dimer,[4] the compounds dissociate on heating, or at low temperature in the presence of catalysts, so that reactions with nucleophiles may be ambiguous.

Evidence for the dimeric structure of the compounds was originally adduced by the reaction with amines to form trisubstituted biurets[40, 101] (Eq. 85) although the disubstituted urea could also be

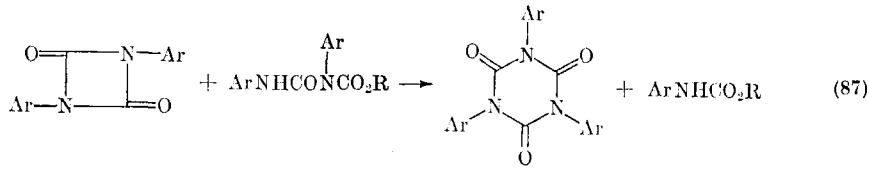


(85)

(86)

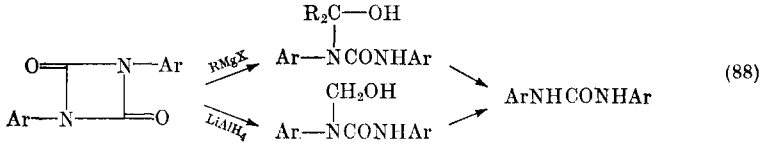
obtained.[101] Both of these reactions have been verified in later work.[4,178] With primary amines the 5-substituted 1,3-diarylbiuret is formed in good yield in refluxing ethanol solutions. In dichlorobenzene solution, however, the dimer of 4-methyl-*m*-phenylenediisocyanate reacts with

dibutylamine to give the diurea.[185] Prolonged boiling of a uretidinedione in alcohol solution gives the allophanate[101] (Eq. 86). Kogon[132] has presented evidence that the trimerization of phenylisocyanate in ethanol solution with a tertiary amine catalyst proceeds by initial formation of the allophanate and the uretidinedione and subsequent reaction of these with elimination of a molar equivalent of ethyl carbanilate (Eq. 87).



(87)

Treatment of 1,3-diphenyluretidinedione with either Grignard reagents[178] or lithium aluminum hydride[73] results in the formation of diphenylurea. In both cases the reaction presumably proceeds *via* the *N*-hydroxyalkyl intermediate[4] (Eq. 88).



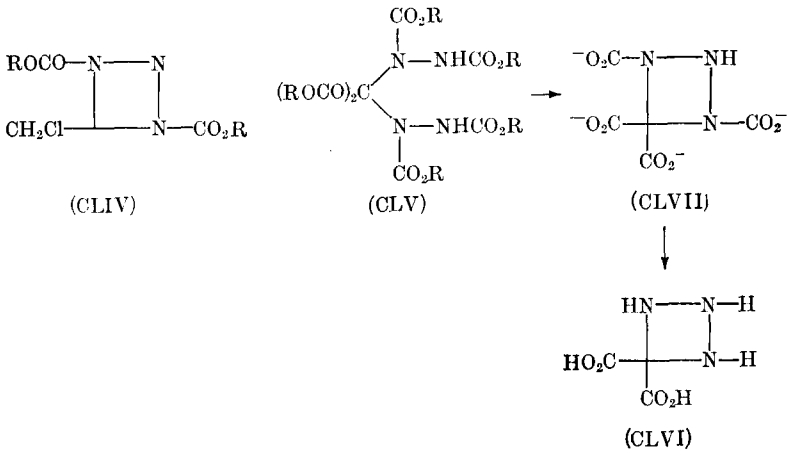
(88)

VII. Other Ring Systems

The monocyclic triazetidine ring (R.R.I. No. 25) has appeared in the literature on two occasions. A product obtained by the action of water or alcohol on *N*-chlorourethane was formulated as the 1,3-dicarbethoxy derivative (CLIV).[39] In the other case, alkaline hydrolysis of the condensation product (CLV) of ethyl malonate and azobisformic ester was thought to give the tetracarboxylate (CLVII) and eventually the acid (CLVI).[42] In neither case was any attempt made to prove the presence of the —N—N—N— chain, and there is no basis for accepting these highly implausible structures in preference to more conventional alternatives.

Besides the monocyclic diazetidine and triazetidine rings, the Revised Ring Index contains some 20 bicyclic and tricyclic systems in

which two or three nitrogen atoms are incorporated in a four-membered ring. Some of these are formal representations of dipolar compounds, and others are archaic valence-bridged structures for well-known polyazole and polyazine derivatives. A few of the systems represent



(CLIV) (CLV) (CLVII) (CLVI)

somewhat casual structural assignments which have not been reinterpreted, but which are clearly untenable in the light of present understanding of the stability and instability of four-membered heterocyclic rings. Since adequate structural evidence is not available for any of these ring systems, further discussion would be unprofitable.

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CHAPTER VIII

Four-Membered Rings Containing Two Heteroatoms

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I. Introduction

A number of four-membered rings containing two heteroatoms have been described in the literature. However, the assignment of structure to many of these compounds has been ambiguous. For this reason only two groups of compounds in this classification will be discussed: β-sultones and the 1,2-oxazetidines. The structural assignments of these materials are on reasonably firm grounds, and, though the number of representative compounds in each class is not large, the systems are of some interest and will be described briefly here.

II. β-Sultones

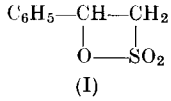
1. Preparation

The preparations of β-sultones which have been described in the literature are all based on the reaction of an olefin and sulfur trioxide. In the hydrocarbon series this reaction has only been successful with

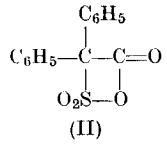
$$R_2C{=}CR_2 + SO_3 \longrightarrow R_2C\text{—}CR_2 \quad (O\text{—}SO_2)$$

two olefins. The adduct (I) of styrene with sulfur trioxide has been prepared by sulfonation of styrene at low temperature with the

dioxane–sulfur trioxide complex in an inert hydrocarbon solvent, and the corresponding adduct (II) from diphenylketene and sulfur trioxide has been reported in the patent literature.[1, 5] Both of these compounds



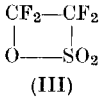
(I)



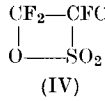
(II)

are extremely labile and can only be obtained by operating under very carefully controlled experimental conditions. Indeed the olefin–sulfur trioxide reaction even in those cases where it can be controlled does not normally give β-sultones as the isolated products.

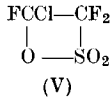
Most β-sultones which have been prepared are obtained from reaction of sulfur trioxide with highly fluorinated olefins.[2–4] These olefins are resistant to oxidation, and the stability of the β-sultone itself appears to be greatly enhanced by the fluorine substituents. The reaction of tetrafluoroethylene with sulfur trioxide proceeds in almost quantitative yield and does not require a diluent or complexing agent for the sulfur trioxide.[3] The product (III) is a liquid which fumes in air and boils at 42°. The reaction is also successful with a variety of



(III)

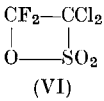


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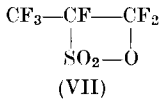


(V)

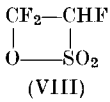
fluorochloroolefins, and with chlorotrifluoroethylene the product obtained again in good yield is a mixture containing approximately equal amounts of the sultones (IV) and (V). Asymmetrical dichlorodifluoroethylene gives only (VI), and from perfluoropropylene the sultone (VII) is obtained in 85% yield. Trifluoroethylene can also be



(VI)



(VII)



(VIII)

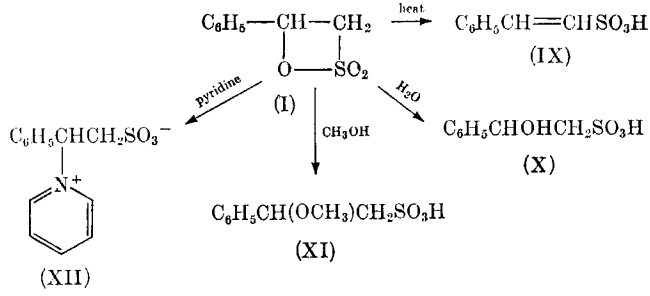
employed in the reaction to give (VIII), but vinylidene fluoride and vinyl fluoride do not appear to give sultones in any appreciable quantity. The sultones which have been described in the literature are summarized in Table 1. Some additional examples of fluorochlorosultones have been described but their structures are in considerable doubt.[4]

TABLE 1. Preparation of β-Sultones

Sultone	Yield (%)	B.p. °C	B.p. mm.	References
$CF_2—CF_2$ | | $O—SO_2$	93	42	760	2, 3
$FCCl—CFCl$ | | $O—SO_2$	80	110	760	3
$CF_2—CCl_2$ | | $O—SO_2$	56	110	760	3
$CF_2—CFH$ | | $O—SO_2$	61	103	760	3
$CF_2—CF—CF_3$ | | $O—SO_2$	85	47	760	2, 3
$CF_2—CF—(CH_2)_3CH_3$ | | $O—SO_2$	72	63	20	3
$CF_2—CF—(CF_2)_6H$ | | $O—SO_2$	90	76	22	3

2. Reactions

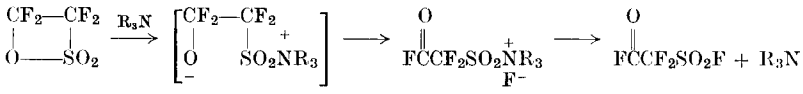
Almost all reactions of sultones involve ring opening. The styrene sultone on heating is converted to the unsaturated sulfonic acid (IX). Nucleophiles will in general attack the β-carbon atom of this species



and thus water, methanol, and pyridine under the appropriate conditions react to give the hydroxyacid (X), the methoxyacid (XI), and the betaine (XII).

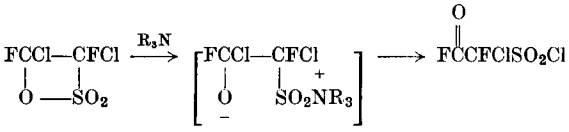
Ring-opening reactions are also observed with the fluorinated

sultones.[3] In these cases, however, the chemistry is complicated by the labile nature of the carbon–halogen bonds of some of the intermediate species. Thus the sultone (III) on treating with a catalytic amount of triethylamine is quantitatively isomerized to (XIV) presumably through the path indicated. Sultones with chlorine in the β-position undergo a comparable reaction. These compounds preferentially expel



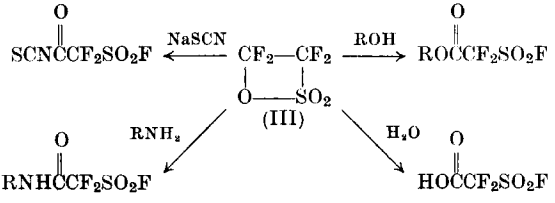
(III) (XIII) (XIV)

chloride ion from the betaine intermediate; thus, (XV) is converted into the sultonic carboxylic halide (XVI).



(XV) (XVI)

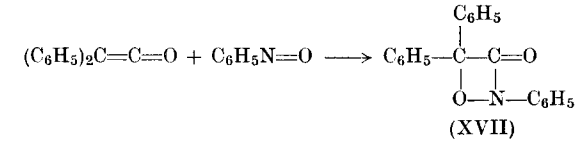
The fluorinated sultones are extremely reactive toward any nucleophile. Tetrafluoroethylene β-sultone reacts with alcohols, sodium methoxide, primary and secondary amines, and potassium thiocyanate to give derivatives of fluorosulfonyldifluoroacetic acid. The reactions may proceed through preliminary rearrangement of the sultone to the fluorosulfonyldifluoroacetyl fluoride, $FCOCF_2SO_2F$, which in turn reacts with the nucleophile. The acyl fluoride group is, of course, much more reactive toward nucleophiles than the sultonyl fluoride.



III. 1,2-Oxazetidines

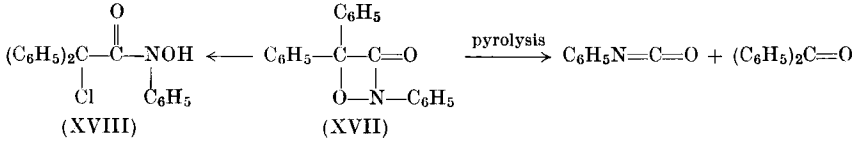
One 1,2-oxazetidine has been described in the literature.[6] It was prepared by Staudinger from the reaction of nitrosobenzene and

diphenylketene. The product (XVII) is a solid melting at 72° and was obtained in 63% yield. On pyrolysis it is converted into phenyl isocyanate and benzophenone. Hydrolysis of (XVII) with hydrochloric



(XVII)

acid gave (XVIII) and so the structure of (XVII) seems reasonably certain. This synthesis of 1,2-oxazetidines is presumably capable of extension to other systems but this has not been investigated as yet.



(XVIII) (XVII)

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CHAPTER IX

Oxetanes

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Department of Chemistry, Kansas State University

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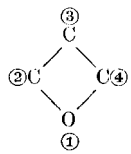
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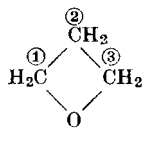
VII. References. 1060

I. Introduction

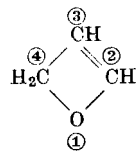
Compounds having a saturated four-membered ring containing one oxygen atom are systematically given the generic name 'oxetane' (R.R.I. No. 44), with the numbering indicated (I). 'Trimethylene oxide' is the generally accepted common name for the parent compound



(I)



(II)



(III)

in the series and the term was formerly used commonly as a generic name, with a different numbering system (II). This numbering system is employed with other 'oxide' names which have been used

occasionally, such as '1,3-propylene oxide', 'α,γ-propylene oxide' and 'symmetrical propylene oxide'. Oxetanes have been named also as 'oxacyclobutanes', with the standard numbering (I), and as epoxy derivatives of the corresponding hydrocarbons or other compounds.

The unsaturated four-membered cyclic ether (III), which is unknown, has been given the name 'oxete' and is numbered as shown.

Trimethylene oxide was the first oxetane reported, having been described by Reboul in 1878.[189] During the next fifty years few papers relating to oxetanes were published, but since then interest has been developing at a steadily increasing rate. In recent years the field of oxetane chemistry has become very active, due in particular to the discovery of commercially interesting polymers[66] and to general interest in four-membered ring compounds. Only one naturally occurring oxetane has been found to date—the tetracyclic mold metabolite, trichothecin.[82] Brief reviews of oxetane chemistry have been published by Winstein and Henderson[257] and by Stevens.[246]

II. Structure and Properties of the Oxetane Ring

1. Molecular Dimensions of Trimethylene Oxide

The intimate structure of trimethylene oxide has recently been studied in detail by infrared, Raman and microwave spectroscopy and by electron diffraction. The results indicate that the ring is essentially planar with C_{2v} symmetry,[71, 261, 262] but a facile ring-bending vibration, to an estimated maximum of 0° 21′ from coplanarity, has been deduced from the far infrared[48] and microwave spectra.[36] The greater tendency for coplanarity in trimethylene oxide than in cyclobutane has been attributed to there being only one-half as many hydrogen–hydrogen interactions between adjacent methylene groups.[104]

Determination of the molecular dimensions of trimethylene oxide by electron diffraction (ED)[5, 93] and microwave (MW)[105] spectroscopy showed the molecule to be not quite square. The smallest internal angle is at the carbon opposite the oxygen, since the largest angle is that at the oxygen atom. This situation is, of course, the result of the greater length of a C—C bond, as compared to a C—O bond. As in other small ring compounds[84] the external bond angles tend to be larger than normal and the distances between atoms in the ring are slightly greater than normal.

TABLE 1. Dimensions of Trimethylene Oxide

Bond lengths		Valence angles	
C—C	1.553 ± 0.03 Å (ED), 1.55 Å (MW)	COC	94.2° ± 2.5° (ED)
C—O	1.457 ± 0.002 Å (ED), 1.44 Å (MW)	CCC	86.8° ± 2.5° (ED), 84° (MW)
C_α—H	1.09 Å (MW)	CCO	89.5° ± 2.5° (ED)
C_β—H	1.08 Å (MW)	HCH	113° 38′ ave. (ED), α 110°, β 111° (MW)

2. Spectral Properties

Oxetanes are generally transparent in the visible and ultraviolet regions, except when a substituent having absorption is present. The ultraviolet absorption spectra for oxetane and 2,2-dimethyloxetane show maxima at 183 and 173 mμ, respectively, there being very little absorption above 220 mμ.[160] The far ultraviolet absorption spectrum of oxetane has been measured and discussed in terms of the possible structure of the excited state.[75]

The molecular vibrations and the thermodynamic properties of oxetane have been calculated from the infrared and Raman data.[262] Infrared absorption spectra have been recorded for numerous oxetanes and it has been found that a strong absorption band at about 10.2 μ is characteristic of this class of compounds and has been useful for diagnostic purposes.[12, 27, 102a, 199] Raman spectra for trimethylene oxide, 3,3-dimethyloxetane and 3.3-bis(cyanomethyl)oxetane have been reported.[76, 77, 262] A strong Raman band observed at 9.7–9.9 μ and attributed to a ring vibration[262] might be of value in identification of oxetanes, but Raman spectra have been used very little for this purpose. An X-ray crystallographic study of 3,3-bis(iodomethyl)-oxetane has been reported.[251]

N.m.r. spectra are also useful in the diagnosis of oxetane rings, as considerably lower electron shielding values (τ) are observed for the α-methylene protons in oxetanes than in any other class of ethers (Table 2).[103, 133, 183, 199, 231, 243, 250] The values for the β-protons are, of course, more nearly normal.

The mass spectrum of trimethylene oxide has been described recently.[84a] An ionization potential of 9.85 ± 0.15 e.v. was found for formation of the parent molecule ion, which may be compared with values of 10.65 ± 0.10 e.v. for ethylene oxide and 9.45 ± 0.15 or 10.1 ± 0.2 e.v. for tetrahydrofuran.

3. Evidence on Electron Distribution

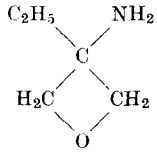
It seems likely that the cause of the lower nuclear magnetic resonance shielding is an unusual electron distribution in the oxetane ring, with the electron density on the oxygen atom higher and that on the ring carbon atoms lower than found at corresponding positions in other ethers. There is considerable supplementary evidence for this. Somewhat greater than normal electronegativity at position 3 is

TABLE 2. Properties of Oxetanes and Other Ethers

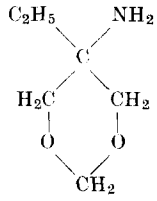
Compound	N.m.r., τ-value[a] α-Protons	ΔH_{mix}[b] with $CHCl_3$, 3°	$\Delta H_f°$ of I_2 complex[c]	μ, D[d]
Trimethylene oxide	5.4	760	6.4	1.92
2,2-Dimethyloxetane		915		1.93
2-Oxabicyclo[4.2.0]octane	5.68			1.92
Ethylene oxide	7.5	365		1.91
Propylene oxide	7.34, 7.71	470	3.8	1.95
Tetrahydrofuran	6.37	750	5.3	1.75
Tetrahydropyran	6.44	640	4.9	1.55
Methyl ether				
Ethyl ether	6.64	650	4.2	1.26

[a] References 95, 123, 181, 211, 225.
[b] References 215, 216.
[c] In *n*-heptane. References 17, 224.
[d] In benzene, except ethylene oxide, which is in gas phase. See references 2, 40, 69, 112.

indicated by the basicity of 3-amino-3-ethyloxetane (IV) which has a pK_a of 7.60, compared to 8.10 for 5-amino-5-ethyl-1,3-dioxane (V), which also has an oxygen β to the amino group in two directions.[220] A similar effect has been observed also in the cycloalkylamines.[194]



(IV)



(V)

There is considerable evidence for abnormally high electron density on the oxygen atom of oxetanes. The electron donor ability

of cyclic ethers in hydrogen bonding, as measured both spectroscopically by the O–D shift of methanol-d solutions and calorimetrically by heat of mixing with chloroform, was found to be greatest for oxetanes and least for ethylene oxides,[235, 236] and varies roughly in inverse proportion to the τ-values.[103] The same was true for the heat of formation of iodine complexes.[23, 248] Typical data are listed in Table 2.

The excellent solvent action of trimethylene oxide for the polymer, Geon 101, has been attributed to its high electron donor ability.[3] Trimethylene oxide and 3,3-dimethyloxetane showed significantly greater solubility in water than other cyclic and acyclic ethers tested, including tetrahydrofuran and tetrahydropyran.[15] Since the importance of hydrogen bonding in water solubility of ethers was indicated by an observed decrease in solubility with increase in temperature in all cases, this is further evidence for the greater electron donor ability of oxetanes in hydrogen bonding.

The reason for the somewhat unique mode of electron distribution in oxetanes is not well understood. The difference from that in ethylene oxides appears to be due to fundamentally different hybridization of orbitals in the three-membered ring,[44, 236] but, according to Coulson and Moffitt's calculations,[44] the difference in hybridization in four- and five-membered rings is very small. Undoubtedly other factors are involved. Arnett and Wu have explained the difference in electron donor abilities of tetrahydrofuran and tetrahydropyran on the basis of the interactions between the electrons in non-bonded orbitals on oxygen and in the adjacent carbon–hydrogen bonds, these being greater when the ring is coplanar than when puckered.[8] Since the tetrahydrofuran ring is, in turn, probably slightly less nearly coplanar than the oxetane ring, the explanation may be extended in some degree to the latter.

4. Dipole Moment Data

If the electron density on oxygen is higher and that on carbon lower in oxetanes than for other ethers, higher carbon–oxygen bond moments might be expected. The dipole moments of oxetanes,[4, 46, 77, 88, 122] however, seem to be interpretable on the basis of a fairly normal carbon–oxygen bond moment. The situation, however, is complicated by lack of knowledge concerning induced dipole moments, which appear to be considerably lower for cyclic than acyclic ethers.[46]

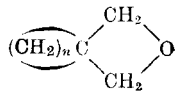
The dipole moments of 3,3-bis(halogenomethyl)oxetanes have been interpreted as indicating that there is considerable free rotation of the halogenomethyl groups of these molecules in benzene solution

at 20–25°, although opposed positions are most stable. The moment of 3,3-bis(bromomethyl)oxetane increased from 1.15 D at 25° to 1.28 D at 81.4°.[77] On the other hand, 3,3-bis(cyanomethyl)oxetane appears to have the cyano groups entirely *trans*.[76] A reported value of 0.8 D for the moment of 2,6-dioxaspiro[3.3]heptane has led Arbuzov[7a] to propose that the oxetane ring is very puckered.

5. Possible Alteration of Bond Angles

Another consequence of the four-membered ring structure in oxetanes appears to be sufficient flexibility of the ring dimensions to allow alteration by appropriate substitution. 3,3-Dialkyloxetanes show *lower* electron donor ability than trimethylene oxide, whereas this property is significantly greater for 2,2-dialkyloxetanes than for trimethylene oxide, as expected from inductive effects of the alkyl groups,[235, 236, 249] the lower basicity may be a consequence of a decreased valency angle at oxygen becoming more like that in ethylene oxides; such a decrease in angle might result from the mutual repulsion of the alkyl groups at position 3 increasing the exterior angle at that point (Thorpe–Ingold effect) and decreasing the interior angle both there and at the oxygen atom opposite. Differences in the reactivity of these oxetanes towards lithium aluminum hydride (section **III.8.***E*) also fit this interpretation.[233]

It was thought that this idea might be tested by observing the effect of smaller than normal exterior angles at position 3. The electron donor ability of a series of 2-oxaspiro[3 *n*]alkanes (VI) was determined by hydrogen-bonding measurements, but the observed order for *n*,



(VI)

$4 > 3 > 2 > 5$, differed from that predicted on the basis of the above reasoning,[230] and the evidence is not conclusive.

III. Reactions of Oxetanes

Oxetanes show many of the reactions of the more familiar epoxides, though frequently with lower degree of reactivity, as might be expected from the lesser degree of ring strain. This may be compensated for, however, by the greater electron ability of the ring oxygen atom (section **II.3**), and additional effects are sometimes

observed as a result of characteristics of the four-membered ring. Reactions of functionally substituted oxetanes which do not directly involve the oxetane ring are discussed in section **V.12.**

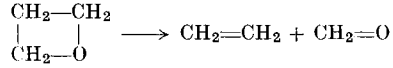
1. Formation of Addition Compounds

The high electron density of the oxygen atom in oxetanes is favorable to the formation of addition compounds with Lewis acids. Trimethylene oxide has been observed to form an iodine complex,[23, 248] a hydrate[244] and two dinitrogen tetroxide adducts, one in mole ratio 1 : 1 and the other 2 : 1.[240] The boron fluoride complex is unstable, decomposing into a polymer.[249]

2,6-Dioxaspiro[3.3]heptane has been reported to form a crystalline mercuric chloride complex, melting at 131–132°, and analyzing as $C_5H_4O_2 \cdot 1.5HgCl_2$.[10]

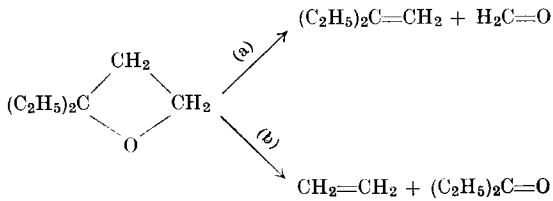
2. Pyrolysis and Photolysis

Oxetanes decompose thermally at about 450°, forming olefins and carbonyl compounds.

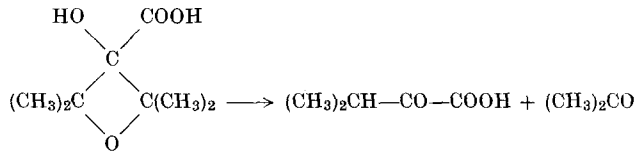


The process is reminiscent of the pyrolysis of cyclobutane to ethylene, which occurs at about the same temperature, and is quite different from the pyrolysis of either ethylene oxide or tetrahydrofuran, which requires temperatures of about 400° and 550°, respectively.

The mechanism of the pyrolysis of trimethylene oxide was studied by Bittker and Walters,[21] who observed a first-order gas phase reaction, most of which was unaffected by the presence of radical traps, indicating that the activated molecule either undergoes a concerted scission of both bonds simultaneously, or scission of the C—O bond only, forming an unstable 1,4-biradical. The report[11] that 2,2-diethyloxetane decomposed predominately to form 2-ethyl-1-butene and formaldehyde (a) seems in agreement with both mechanisms, since these two products would be derived from the more stable biradical possible and are also probably thermodynamically more stable.



Substitution on the ring affects the ease of pyrolysis. 2,2-Diethyloxetane was found to decompose more slowly at 450° than trimethylene oxide, while 3,3-diethyloxetane and other 3,3-dialkyloxetanes pyrolyzed more easily than trimethylene oxide.[220] 2,2,4,4-Tetramethyl-3-hydroxyoxetane-3-carboxylic acid pyrolyzes at unusually low temperatures, 150–300°, to form dimethylpyruvic acid and acetone.[192] No decarboxylation was observed. This cleavage might be mechanistically different from that of oxetane itself, since the carbonyl group may cause acid-catalyzed fragmentation (section **II.7.***G*).



Irradiation by a mercury arc causes oxetanes to decompose photochemically.[75, 160] From oxetane were formed ethylene and formaldehyde, the latter decomposing further to hydrogen and carbon monoxide to some extent. 1,1-Dimethyloxetane decomposed about equally in both directions, to form ethylene and acetone as well as *iso*butylene and formaldehyde.[150] The 1,4-diradicals are formed less selectively here than in pyrolysis, since the radiation absorbed has much greater energy than the bonds in the ring. The radicals must be very unstable since their decomposition was independent of temperature and presence of solvent. 2-Phenyloxetane underwent photolysis to yield predominantly formaldehyde and styrene, the latter undergoing further reactions.[160]

The cracking pattern of trimethylene oxide on electron impact in the mass spectrometer has been reported;[84a] it is basically similar to that in pyrolysis and photolysis.

3. Free Radical Decomposition, Additions and Halogenation

Although pyrolysis and photolysis of oxetanes do not appear to involve free radical chain reactions, these can be initiated by methyl radicals and lead to similar decomposition products. This process has been studied with trimethylene oxide, using methyl radicals generated by photolysis of acetone or by pyrolysis of di-*tert*-butyl peroxide.[160] The principal products were ethylene, hydrogen and carbon monoxide, with only a trace of formaldehyde; in addition, substantial amounts of methane and ethane were found. A plausible mechanism appears to

involve: (1) hydrogen abstraction by the methyl radical to form methane and an oxetanyl radical (probably α-oxetanyl); (2) rapid dissociation of the latter to ethylene and the formyl radical; (3) subsequent reactions of the formyl radical to give carbon monoxide, hydrogen atoms, formaldehyde, oxetanyl radicals, etc.; and (4) secondary reaction of ethylene with hydrogen atoms and with methyl radicals and of hydrogen atoms with oxetane.

$$CH_3 + (CH_2)_3O \longrightarrow CH_4 + \begin{matrix} CH_2{-}CH \\ | \quad | \\ CH_2{-}O \end{matrix}$$

$$\begin{matrix} CH_2{-}CH \\ | \quad | \\ CH_2{-}O \end{matrix} \longrightarrow CH_2{=}CH_2 + HCO$$

$$HCO \longrightarrow CO + H\cdot$$

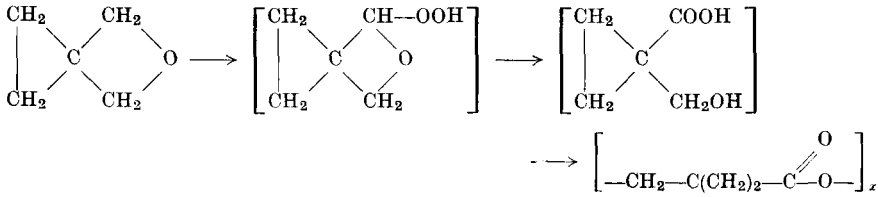
$$HCO + CH_2{=}CH_2 \longrightarrow CO + CH_3CH_2\cdot$$

$$HCO + R\cdot \longrightarrow CO + RH$$

$$HCO + RH \longrightarrow H_2CO + R\cdot$$

The occurrence of a similar process in the reaction with oxygen might be expected, and it is indeed found that oxetanes are very susceptible to autooxidation. This tendency often gives difficulty in obtaining correct elemental analyses on pure compounds, unless oxygen can be excluded from the sample or the analysis can be done at once. Samples exposed to oxygen show a positive potassium iodide test for peroxides and an infrared absorption band at about 900 cm.$^{-1}$ characteristic of such. On heating or standing many hours, the infrared absorption characteristic of the oxetane ring disappears and a viscous, polymeric product results. The reaction is catalyzed by cobalt naphthenate and by benzoyl peroxide.[220]

In the case of 2-oxaspiro[3.2]hexane, the infrared absorption spectrum of the polymeric product indicates it to be a polyester with



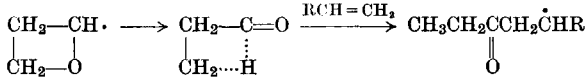
cyclopropane rings present.[229] The process may thus be similar to autooxidation at 120° of tetrahydrofuran[178, 195] and tetrahydropyran,[129] which yield the corresponding lactones; for the intermediate hydroxy acid from an oxetane would polymerize instead of cyclize to a β-lactone.

Autooxidation of 2-phenyloxetane followed a somewhat different course, since the most easily abstracted hydrogen must be tertiary, rather than secondary. The product was a lower polymer with carbonyl absorption characteristic of a phenyl ketone.[220]

Trimethylene oxide has been found to react with 1-octene in the presence of *tert*-butyl peroxide to give a low yield of 3-hendecanone, along with much telomeric material.[253a] Analogous reactions with

$$(CH_2)_3O + C_6H_{13}—CH=CH_2 \longrightarrow CH_3—CH_2—CO—C_8H_{17}$$

1-octene were observed with tetrahydrofuran and tetrahydropyran, although there was much less telomer formation in these cases. An interesting suggestion was made that the initially-formed α-oxetanyl radical may rapidly undergo 'decyclization' to a hydrogen-bridged radical (VII), which may add to the olefin as an acyl radical.



(VII)

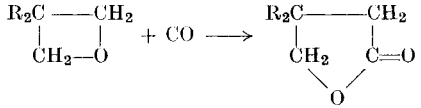
Halogenation of oxetanes has received relatively little study. Bromination is strongly light-catalyzed and proceeds by substitution, the hydrogen bromide evolved subsequently reacting further, undoubtedly with ring cleavage. Both rings of 2-oxaspiro[3.2]hexane were cleaved by light-catalyzed bromination.[229] Hexafluorooxetane has been synthesized by electrolytic fluorination of trimethylene oxide.[139]

4. Catalytic Reactions with Hydrogen and Carbon Monoxide

Unlike oxiranes, oxetanes are difficult to hydrogenate catalytically. Unsuccessful attempts to hydrogenate trimethylene oxide over platinum and Raney nickel catalysts have been reported.[234] With a cobalt carbonyl catalyst, and an equimolar mixture of carbon monoxide and hydrogen, however, trimethylene oxide was found to undergo hydrogenation, isomerization to aldehyde and aldol-type polymerization.[108]

The reaction of trimethylene oxide and of 3,3-dimethyloxetane with carbon monoxide at about 200° and 200–250 atmospheres pressure,

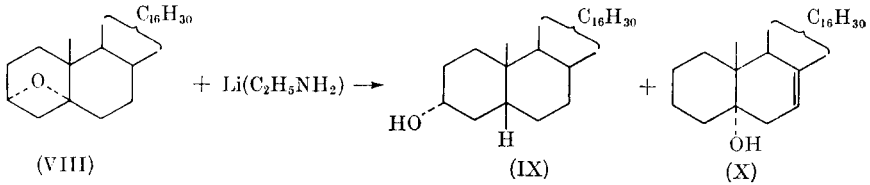
in the presence of cobalt octacarbonyl, is claimed to give the corresponding γ-lactones in 55–60% yields.[172]



[R_2 = H_2, $(CH_3)_2$]

5. Reductive Cleavage with Lithium–Ethylamine

The only example of reduction of an oxetane by a metal in ammonia or an amine appears to be that of 3α,5α-epoxycholestane (VIII) with lithium in ethylamine. Hallsworth and Henbest[107] observed that this reaction gave a quantitative yield of a mixture of 3α-cholestanol (IX) and 5α-cholestanol (X). These were found in a 3 : 7 ratio, showing that the ring opening is not strongly influenced by substitution.



(VIII) (IX) (X)

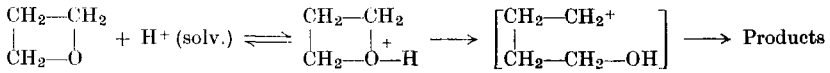
6. Acid-Catalyzed Reactions

Oxetanes are very susceptible to acid catalysis in ring-opening reactions. The specific rate constants for the acid-catalyzed hydrolysis of trimethylene oxide is nearly as great as that of ethylene oxide,[185, 241] and similarity of rates of the two oxides has been observed also for the acid-catalyzed reaction with sodium thiosulfate.[218] In contrast, non-acid catalyzed reactions of oxetanes proceed at an extremely slow rate compared to those of ethylene oxides. Undoubtedly, the formation of a reactive oxonium species is more favored with the oxetanes, because of the considerably higher electron donor ability, and this factor largely compensates for the lower ring strain.

A. Hydrolysis

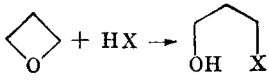
Evidence on the mechanism of hydrolysis of trimethylene oxide has been obtained by the kinetic studies of Pritchard and Long,[185] who found that the ratio, k^D/k^H of the pseudo first-order rate constants

in dilute sulfuric acid (deuterated and not deuterated) had the value 2.2. This is in the range for reactions in which water does not act as a nucleophilic agent. Further support for this view was the observation that the rates of hydrolysis in water and dioxane were found to be proportional to the acidity function, h_0, rather than the hydronium ion activity. These data indicate a mechanism involving preliminary equilibrium of the cyclic ether and hydronium ion with the oxonium ion, followed by a rate-determining cleavage of a carbon–oxygen bond, to form a very reactive carbonium ion. A similar mechanism has been deduced for the acid-catalyzed hydrolysis of ethylene oxide and it is noteworthy that both reactions have similar entropies as well as energies of activation.[185]



B. Nucleophilic Substitutions by Halide Ions, Thiourea, Alcohols and Thiols

There are many acid-catalyzed reactions of oxetanes which seem closely related to this hydrolysis, in that various nucleophilic reagents other than water are capable of reacting with the intermediate carbonium or oxonium ions. Hydrochloric, hydrobromic and hydriodic acids react readily with oxetanes both in water and in benzene solutions to give 1,3-halohydrins.

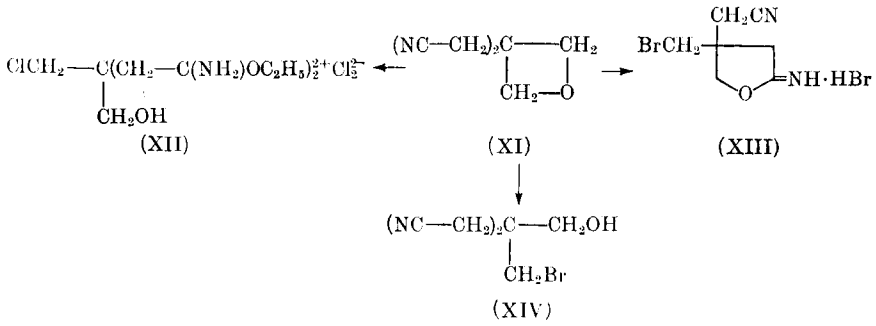


Measurement of the heat of the reaction with hydrochloric acid has been used to distinguish between oxetane and tetrahydrofuran structures,[83] as it is significantly greater for the former. Epoxides, however, show about the same heat of reaction with hydrochloric acid as oxetanes. Like ethylene oxide, trimethylene oxide reacts with aqueous ferric chloride solution, ferric hydroxide precipitating.[52] The reaction of oxetanes with pyridine hydrochloride in pyridine has been developed as a convenient method of quantitative analysis of oxetanes.[140]

Extensive synthetic application has been made of the reactions of hydrobromic and hydriodic acids with various 3,3-disubstituted

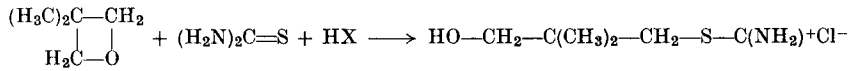
oxetanes, to prepare many halohydrin derivatives of pentaerythritol in excellent yield. This includes the reactions of 3,3-bis(bromomethyl)-oxetane and 3,3-bis(iodomethyl)oxetane with hydrochloric, hydrobromic and hydriodic acids,[98] of 3,3-bis(aminomethyl)oxetane[100] and 3-bromomethyl-3-hydroxymethyloxetane[99] with hydrochloric acid, of 2,6-dioxaspiro[3.3]heptane with hydriodic acid (both rings opening to give the diiododiol),[10] and of 6-sulfanilimyl-2-oxa-6-azaspiro[3.3]-heptane with hydrogen chloride, in which the oxetane ring but not the azetidine ring is cleaved.[100]

With cyanomethyl derivatives, secondary reactions were observed with the cyano group, 3-cyanomethyl-3-hydroxymethyloxetane being converted into 3-chloromethyl-3-hydroxymethylbutyrolactone,[99] and 3,3-bis(cyanomethyl)oxetane (XI) being converted into the diimido-ether (XII) with hydrogen chloride in cold ether and to the lactim (XIII) with hydrogen bromide in ether benzene.[43] A good yield of dicyanobromopentaerythritol (XIV), however, was obtained from



(XII) with aqueous hydrogen bromide.[32, 33] Trimethylene oxide has been converted to 1,3-dibromopropane with hydrogen bromide under heat and pressure.[130]

Thiourea reacts with trimethylene oxide, 2-methyloxetane, 3-methyloxetane, 2,2-dimethyloxetane[220] and 3,3-dimethyloxetane[197] in



aqueous solutions containing an equivalent amount of sulfuric, perchloric or hydrochloric acid to form the corresponding hydroxyalkylthiouronium salts in moderate yields. The yields were diminished, at least in the last case mentioned, by considerable formation of the

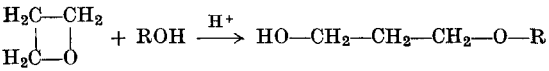
1,3-glycol derived from hydrolysis of the oxetane and also the corresponding chlorohydrin, if hydrochloric acid were used. This low degree of selectivity might be considered evidence for a carbonium ion-nature of the intermediate, although no evidence for rearrangement such as might be expected of a *neo*pentyl-type carbonium ion was observed. The reaction of sodium thiosulfate with oxetanes also is markedly catalyzed by acid and is probably analogous to the thiourea reaction.[218]

The direction of ring cleavage in unsymmetrical oxetanes is not always as would be predicted from a purely S_N1 process. 2-Methyloxetane is converted by aqueous hydrochloric or hydrobromic acids, by thiourea and hydrochloric acid and by hydrogen chloride or hydrogen bromide in benzene predominantly into the product resulting from ring cleavage between the oxygen and the unsubstituted methylene group.[234] The steric effect apparent here would seem to indicate that in these cases, the halide ion tended to react with the oxetane oxonium ion before it could pass into a carbonium ion. 2-Phenyloxetane, however, has been found to give only products resulting from ring cleavage between the oxygen and the benzylic carbon atom.[234] Here carbonium ion formation is apparently more favored by the stabilizing effect of the phenyl group.

TABLE 3. Product Proportions from 2-Methyloxetane[201, 213]

Reagent	$RCH(OH)(CH_2)_2X$	$RCH(X)(CH_2)_2OH$
HCl, aq.	75%	25%
HBr, aq.	90	10
Thiourea, HCl, aq.	100	—
HCl, C_6H_6	94	6
HBr, C_6H_6	98	2

Alcohols react easily with trimethylene oxide in the presence of catalytic amounts of sulfuric or *p*-toluene sulfonic acids to form the 3-hydroxypropyl ethers.[221] (In addition, some low molecular polymeric



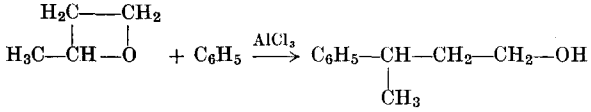
product was also observed, probably polyglycol ether formed by the reaction of the primary product with additional trimethylene oxide.)

The analogous acid-catalyzed reaction of thiols has also been

observed, but it required much more rigorous conditions and gave low yields of 3-hydroxypropyl sulfides,[221] in contrast to the facile reaction of thiols with ethylene oxides.[190]

C. Friedel–Crafts Reaction

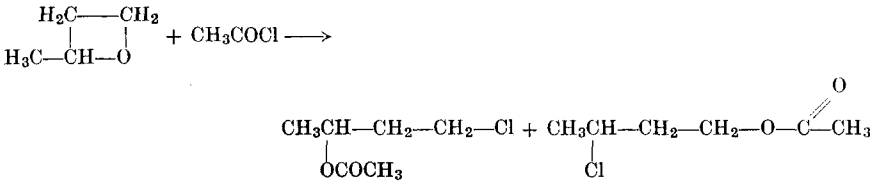
Qualitative analogy with ethylene oxide chemistry is also to be found in the Friedel–Crafts reaction of oxetanes. The aluminum chloride-catalyzed reactions of trimethylene oxide with benzene and with mesitylene,[219] and of 1-methyloxetane and 1-phenyloxetane with benzene[220] gave the corresponding 3-aryl-1-propanols in 50–70% yields



and good purity. In these reactions, also, the reactivity of trimethylene oxide is somewhat less than that of ethylene oxide, as shown by a competition experiment.[219]

D. Acylation

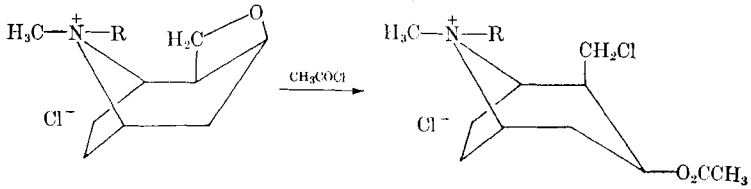
The reaction of oxetanes with acyl chlorides to form 1,3-halohydrin esters appears to be very general. It was first reported by Derick and Bissell[52] with trimethylene oxide and acetyl chloride, which gave a very vigorous reaction yielding 3-chloropropyl acetate. These reactions seem mechanistically similar to the above acid-catalyzed reactions, because of the probable intermediacy of a cyclic acyloxonium ion which may or may not cleave to an acyloxycarbonium ion. 2-Methyloxetane reacted with acetyl chloride in benzene to give a mixture of



40% of 3-chloro-1-butyl acetate and 60% of 4-chloro-2-butyl acetate. The same reaction with 2-phenyloxetane gave only the secondary chloride, 3-chloro-3-phenyl-1-propyl acetate in 75% yield.[234]

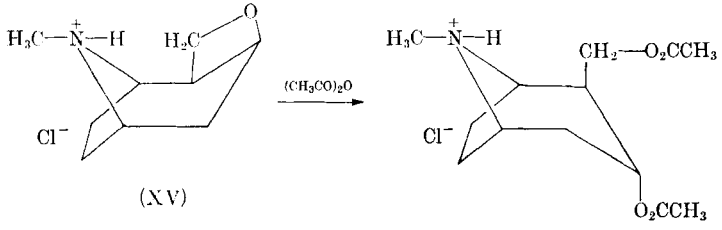
Other examples are the moderately slow reaction of 3,3-bis(chloromethyl)oxetane with benzoyl chloride to form 2,2,2-tris(chloromethyl)ethyl benzoate, and the vigorous reaction of 3,3-bis(bromomethyl)oxetane with benzoyl bromide to form 2,2,2-tris(bromomethyl)-ethyl benzoate.[27] The reaction of trimethylene oxide with phosphorus pentachloride to give 1,3-dichloropropane is probably of similar type.[52]

A study of cleavage of an oxetane ring fused to the tropane ring system by acetyl chloride and acetic anhydride has been reported by Kovacs and collaborators.[150] With both 2,3-anhydro-2β-hydroxymethyl-3β-tropanol hydrochloride (XV) and methochloride (XVI) the reaction of acetyl chloride in acetic anhydride gave ring cleavage between the oxygen atoms and the unsubstituted methylene group

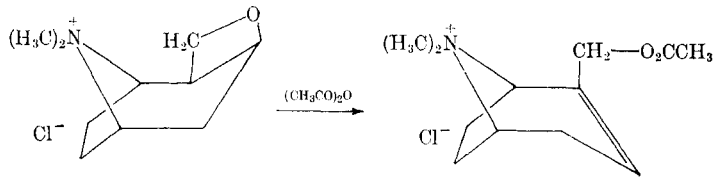


(XV, R = H; XVI, R = CH_3)

with retention of configuration at position 3. The products were obtained in good yields and were identical to those obtained from the corresponding chloroalcohols. These results would be more in accord with an S_N2 mechanism, perhaps involving attack of chloride.



(XV)



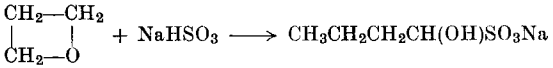
(XVI)

The reaction of (XV) and (XVI) in hot acetic anhydride was found to give solvolysis-type products. The former was converted in good yield to the diacetate having inverted configuration at position 3, and the latter underwent elimination to an allylic acetate.[150]

Such elimination processes, characteristic of carbonium ion intermediates, are frequently observed in acid-catalyzed reactions of oxetanes. Another example is the formation of cinnamyl alcohol, isolated in 30% yield, following the reaction of 2-phenyloxetane with hydrochloric acid in cold aqueous acetone.[233]

E. Rearrangements

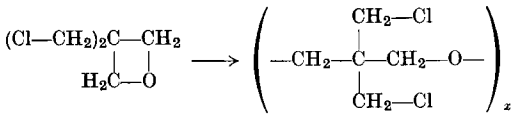
Rearrangements might also be expected but seem to have been seldom observed. The isolation of the sodium bisulfite addition compound of propionaldehyde from the reaction of trimethylene oxide with sodium bisulfite, however, provides an example.[208] It is interesting



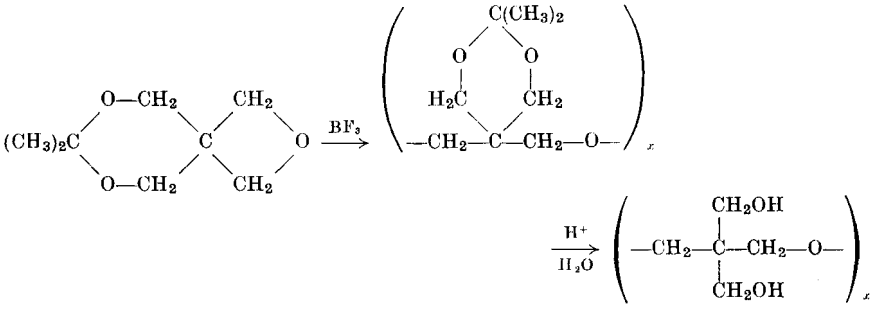
that rearrangements were observed neither in the Friedel–Crafts reaction of oxetanes with aromatic hydrocarbons, nor in the various acid-catalyzed reactions of 3,3-dimethyloxetane,[238] which may proceed by way of neopentyl carbonium ion intermediates. As pointed out by Scott and Gayle,[219] lack of rearrangement is not necessarily inconsistent with carbonium ion character of intermediates, particularly if the mechanism is borderline S_N1–S_N2.[238]

F. Polymerization and Polymers

Polymerization is often observed as a side process in acid-catalyzed reactions of oxetanes. It is especially favored by use of a non-polar solvent, such as ethyl chloride,[146] bromide[67, 159, 130] or sulfur dioxide,[136] and a strong Lewis acid catalyst, such as hydrogen fluoride,[136] boron trifluoride,[136] boron trifluoride etherate,[66, 67, 146] aluminum chloride[91] and phosphorus pentafluoride,[28, 30, 31, 169] with no nucleophilic agent present; when carried out at low temperatures the reaction gives high molecular weight linear polyethers.[67, 68, 69, 91, 214] A polymer of 3,3-bis(chloromethyl)oxetane is prepared commercially

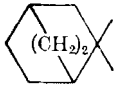


in this way,[37a, 165] and considerable study has been devoted to the production and properties of polymers of oxetanes, particularly 3,3-disubstituted oxetanes. 3,3-Bis(hydroxymethyl)oxetane cannot be polymerized in the same way because of the reactivity of the hydroxyl groups, but its acetonide, 7,7-dimethyl-2,6,8-trioxaspiro[3.5]nonane, may be polymerized and the polymer then hydrolyzed to linear polypentaerythritol.[66, 67]



Poly-3,3-bis(chloromethyl)oxetane (known commercially as 'Penton') has good electrical, molding, dimensional stability and solubility properties.[69, 118, 165, 206] A study of analogous polymers has shown that there is considerable effect of substituents on the properties, as may be seen by the data in Table 4.

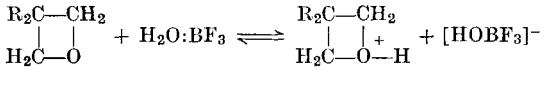
TABLE 4. Properties of Oxetane Polymers $(O—CH_2CR_2—CH_2—)_x$

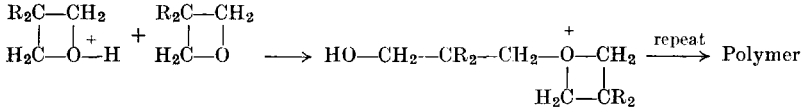
R_2	Cryst. m.p.°	Solubility, *etc.*	Reference
H_2	35	Soluble C_6H_6	198
$(CH_3)_2$	47	Soluble C_6H_6, $(CH_3)_2CO$	67
$(CH_2)_2$	45		31
$(CH_2)_5$	152	Tough film	31
	290	Insoluble, brittle	31
C_2H_5, CH_2Cl	100	Soluble C_6H_6	67
$(CH_2Cl)_2$	180	Generally insoluble [except $((CH_3)N)_3PO$]	67, 28
$(CH_2Br)_2$	220		27
$(CH_2I)_2$	290		27
$(CH_2CN)_2$	175	Soluble C_2H_5OH, $(CH_3)_2CO$	68
$(CH_2F)_2$	125		61
$(CH_2OH)_2$	280	Insoluble	67
$(CH_2OEt)_2$	80		67
$(CH_2OC_6H_5)_2$	85	Amorphous	67

It may be seen that increasing the bulk of hydrocarbon groups causes increase in melting points of the crystalline polymers formed. This has been explained by Campbell and Foldi[31] as being due to the increased opportunity for interactions, such as Van der Waals forces, between polymer chains as the lateral groups become more spherical. The same also applies to the increase in melting point with increase in the size of the halogen in halogenomethyl groups.

The polymer from the very bulky, 3,3-bis(phenoxymethyl)oxetane is low-melting and amorphous, perhaps on account of the non-spherical nature of the phenyl groups. The melting points of polymers of 3,3-bis(fluoromethyl)oxetane and 3,3-bis(cyanomethyl)oxetane, however, are much higher than would be expected from the bulk of these groups, showing that the polarity of substituent groups is also an important factor.[31] Also noteworthy is the very high melting point of the polymer of 3,3-bis(hydroxymethyl)oxetane due possibly to crosslinking by hydrogen bonding. Thus, bulk, polarity and hydrogen bonding ability are all important factors with regard to the melting point of these polymers.

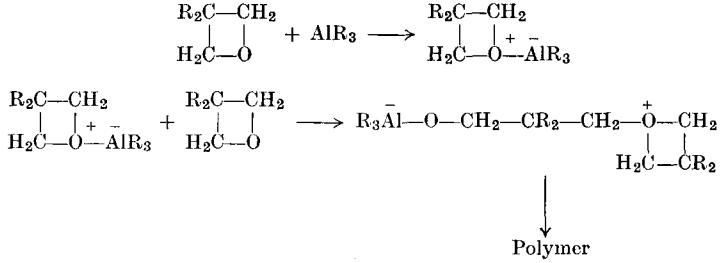
There is little information on the mechanism of polymerization. It would seem possible that it may be a chain process initiated by carbonium ions.[68] Such would involve *neo*pentyl-type carbonium ions, which should be rather subject to rearrangement, but there seems to be no evidence for skeletal rearrangement during polymerization. The data seem in better agreement with a mechanism involving the oxonium ions or Lewis acid complexes.[68] In the case of boron trifluoride catalysis, a kinetic study showed that water is a necessary co-catalyst, suggesting a hydrogen ion-catalyzed process.[198]



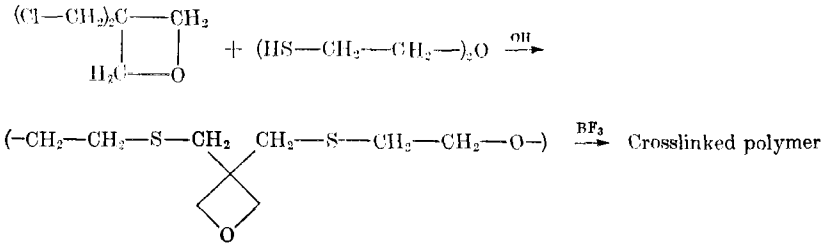


In addition to the strong Lewis catalysts already mentioned, trialkylaluminum and trialkoxyaluminum catalysts,[91, 125, 138, 184] and even aluminum hydride or aluminum amalgam catalysts,[144] may be used for the polymerization of oxetanes. With these a higher temperature, with low catalyst concentration, may be used to convert 3,3-

bis(chloromethyl)oxetane into a high polymer; with 5% triethylaluminum at 40°, however, the polymer was of low molecular weight.[138] It seems reasonable that an oxonium ion mechanism may operate also for the polymerization with trialkylaluminum and related catalysts.



Three additional ways of obtaining polymers from oxetanes have been employed. One is to prepare a polymer containing oxetane rings and then to crosslink by treating with boron trifluoride or other catalyst that will polymerize oxetanes. This has been done with the polymers obtained from the reaction of 3,3-bis(chloromethyl)oxetane with sodium sulfide or with bis(2-mercaptoethyl)ether in base,[27] and also with the polymers from the base-catalyzed reaction of ethylene oxide with 2,2-bis(hydroxymethyl)oxetane.[213] Another example of this



approach is represented by the heat-curing of the polymer from 2,6-dioxaspiro[3.3]heptane,[119] which as normally made apparently contains some unreacted oxetane rings as well as active catalyst. In each case, very hard, insoluble and infusible crosslinked polymers were obtained.

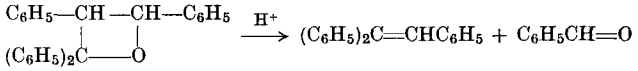
Another method of obtaining crosslinked oxetane polymers is to treat a polyoxetane having free hydroxyl groups with a dibasic acid anhydride. Heating the polymer of 3-hydroxymethyl-3-ethoxymethyloxetane with phthalic anhydride or maleic anhydride has been cited

as an example in a patent on obtaining polymers that are useful metal adhesives.[117]

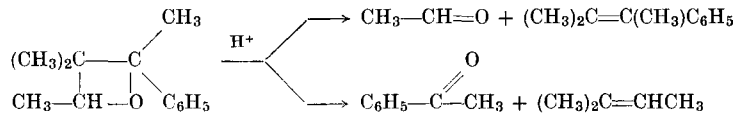
Finally, the copolymerization of a compound with two oxetane rings with another appropriate difunctional compound has been used. Examples cited here are the reactions of 2,6-dioxaspiro[3.3]heptane with phthalic anhydride[145] and with terphthaloyl chloride.[27] The latter polymer appeared to be crosslinked as it was insoluble in all solvents tested and contained considerably less than the theoretical amount of chlorine.

G. Fragmentation

Polysubstituted oxetanes undergo fragmentation to olefins and carbonyl compounds when treated with mineral acid. This reaction was first observed by Kohler and Richtmyer,[147] who observed the scission of 2,2,3,4-tetraphenyloxetane in warm, methanolic hydro-



chloric acid. It was rediscovered independently by Büchi and collaborators,[25] who used it to establish the structures of 2,3,3-trimethyl-4-phenyloxetane and 2,3,3,4-tetramethyl-2-phenyloxetane. In these cases cleavage of the ring occurred in both possible directions and



identification of the two carbonyl products from each permitted the assignment of the oxetane structures. The compound which by analogy was 2,3,3-trimethyl-4-propyloxetane underwent fragmentation apparently in one direction only, as *n*-butyraldehyde was the only carbonyl product observed.

The application of such fragmentation to structure determination of polysubstituted oxetanes is useful as they are quite unreactive towards other reagents, such as lithium aluminum hydride, that might otherwise be used.[25] The reaction was predicted by Büchi by analogy with the well known acid-catalyzed cleavage of polysubstituted 1,3-diols to olefins and carbonyl compounds,[60] and indeed the latter cleavage has been shown by Zimmerman and English to involve a four-membered intermediate similar to an oxetane oxonium ion.[260]

This fragmentation may be compared also to that due to pyrolysis and photolysis (section **III.2**) and the similar cleavage of 2,2,4,4-tetramethyl-3-hydroxyoxetane-3-carboxylic acid on mild heating.[192]

7. Cleavage with Alkyl Halides

Cleavage of trimethylene oxide with triphenylmethyl bromide has been reported by Jensen and Bedard.[133a] This reaction, which probably goes by way of the *O*-(triphenylmethyl)oxetane oxonium ion, appears

$$(C_6H_5)_3C{-}Br + \begin{matrix} CH_2{-}CH_2 \\ | \quad\quad | \\ CH_2{-}O \end{matrix} \longrightarrow (C_6H_5)_3C{-}O{-}CH_2{-}CH_2{-}CH_2{-}Br$$

quite similar to the cleavage of oxetanes by acyl halides (section **III.6.***D*). *O*-Alkyloxetane oxonium ion intermediates have also been postulated for the polymerization of oxetanes with Lewis acid catalysts.[68]

The effect of ring size on the reaction of cyclic ethers with triphenylmethyl bromide was shown by tetrahydrofuran giving incomplete reaction.[133a] The cleavage of tetrahydrofuran, 1,4-dioxane and hexamethylene oxide with methyl iodide at 160°, reported by Müller and co-workers,[168a] could doubtless be extended to many oxetanes.

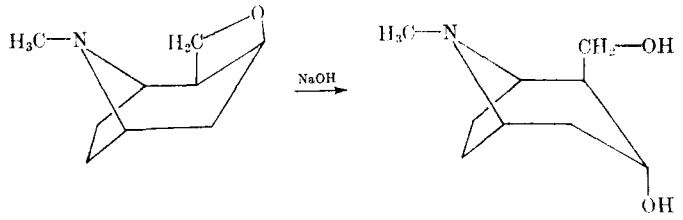
8. Other Nucleophilic Substitutions

Nucleophilic displacement reactions without strong acid catalysts are known with oxetanes but are very much slower than with such catalysts in marked contrast to ethylene oxides.

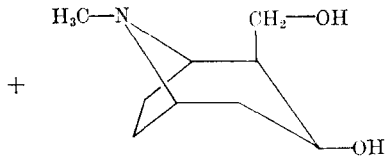
A. Hydroxide and Alkoxides

The rate constant for the reaction of trimethylene oxide with hydroxide ion is 10^{-3} times that of ethylene oxide,[185] and the reaction of sodium alkoxides with trimethylene oxide requires long heating at high temperatures to give moderate yields of 3-alkoxy-1-propanols. Examples of the latter reaction have been reported[221] as well as of the reaction of alkoxides with 2,6-dioxaspiro[3.3]heptane.[75b]

The rate of the reaction of 2,3-anhydro-2β-hydroxymethyl-3β-tropanol with sodium hydroxide has been found to be dependent on the alkali concentration, indicating the process to be of the S_N2 type.[150] The product is, however, predominantly 2β-hydroxymethyl-3α-tropanol (XVIIa), indicating the occurrence of attack of hydroxide at the more substituted carbon atom, and the isomer normally expected from S_N2 attack, 2β-hydroxymethyl-3β-tropanol (XVIIb), was the



(XVIIa)

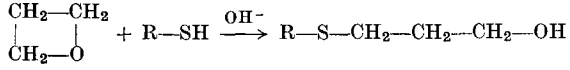


(XVIIb)

lesser product. The possibility of the former arising from an epimerization by the alkali was eliminated, by demonstrating that this gives 2α-hydroxymethyl-3α-tropanol. The result observed may be due to steric effects in this bicyclic ring system.

B. Thiols and Amines

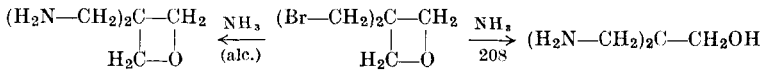
The reaction of thiols with trimethylene oxide, which is itself very slow even at 150°, is markedly catalyzed by alkali, giving the expected 3-hydroxypropyl sulfides in 60–75% yields under mild conditions.[222] A competition experiment showed that trimethylene oxide



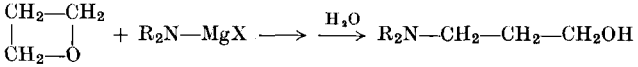
is considerably less reactive than ethylene oxide towards sodium thiophenoxide.

The reaction of primary and secondary amines with trimethylene oxide has been carried out in sealed tubes at 150°, to give 45–67% yields of the expected 3-hydroxypropylamines,[222] in contrast to the very rapid reaction of amines with ethylene oxide in the cold.[190] 3,3-Bis(hydroxymethyl)oxetane,[97] 3,3-bis(aminomethyl)oxetane[96] and 2,6-dioxaspiro[3.3]heptane[94] have been cleaved by heating with ammonia at 200° several hours, to form the expected products in 60–80% yields. The reaction of 3,3-bis(bromomethyl)oxetane with ammonia gave quantitative substitution of the bromine atoms by amino groups, with no ring cleavage, under mild conditions, but use of

high temperature and pressure gave a 70% yield of the triamine of pentaerythritol.[19]



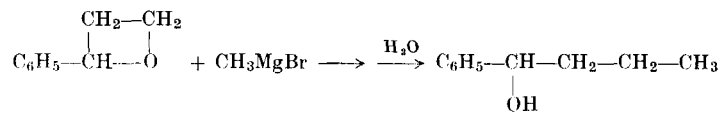
The reaction of several primary and secondary bromomagnesium amides with trimethylene oxide in ether and benzene gave after hydrolysis the expected 3-hydroxypropylamines, without the use of high pressure equipment.[222]



Cleavage with a tertiary amine has been reported in one case. Prolonged treatment of 3,3-bis(bromomethyl)oxetane with trimethylamine in aqueous or alcoholic solution gave 1,1,1-tris(dimethylaminomethyl)ethanol trimethobromide and tetrakis(dimethylaminomethyl)methane tetramethobromide.[34] 3,3-Bis(dimethylaminomethyl)oxetane was undoubtedly the intermediate and was isolated when milder conditions were used.[34]

C. Organometallics

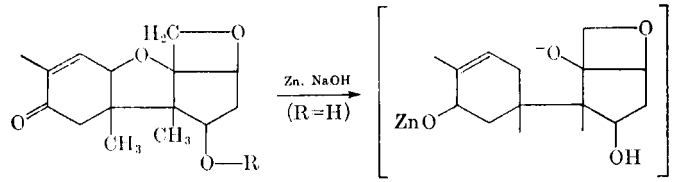
Oxetanes react with Grignard reagents and organolithium compounds in a manner analogous to ethylene oxides, although higher reaction temperatures are required.[217] A side reaction observed with Grignard reagents is the formation of 1,3-halohydrin, presumably from magnesium halide present in the reagent. The Grignard reaction is less satisfactory with substituted oxetanes than with trimethylene oxide, due to decreased rate of reaction and to difficulty in purifying the products, but products were obtained from 2-methyloxetane and 2-phenyloxetane, corresponding to attack of the Grignard alkyl group on the less substituted α-carbon atom of the oxetane.[220] Phenyllithium was found not to react with tetra- and pentasubstituted oxetanes.[25]



Triphenylsilyllithium has been observed to react with trimethylene oxide in the same manner as phenyllithium, giving 3-hydroxypropyltriphenylsilane.[259]

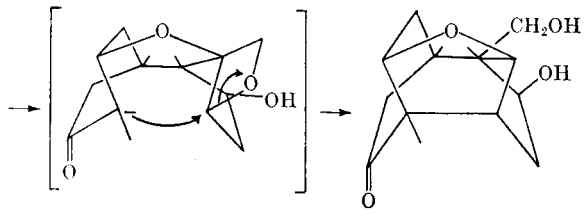
D. Carbanions

Two examples of the reaction of oxetanes with carbanions have been reported in connexion with the work of Jones and collaborators on the structure of the mold metabolite, trichothecin (XVIIIa).[74] The reaction of the derived alcohol, trichothecoone (XVIIIb), with zinc dust in alkali, gave rise to the cage structure (XIX) supported by the infrared and n.m.r. spectra, by acetylation to a diacetate and by oxidation to a diketoacid. This conversion has been interpreted as a series of reactions starting with a reductive conjugate cleavage of the five-membered ring ether linkage and ending with a nucleophilic attack on the oxetane ring by the carbanion form of the enolate of the attached cyclohexanone moiety.



(XVIIIb, R = H;

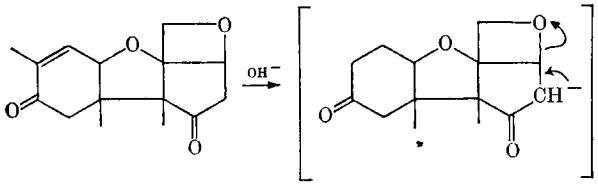
in XVIIIa, R = *cis*-$CH_3CH{=}CH{-}C(=O)-$)



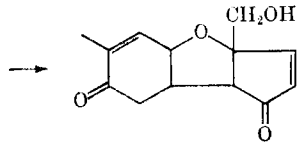
(XIX)

Trichothecodione (XX) obtained from trichothecolone by chromic acid oxidation, was found to be isomerized on treatment with base to a compound (XXI) containing a new double bond and a hydroxyl group but lacking the oxetane ring. This reaction might be considered a nucleophilic attack on the oxetane ring by an adjacent electron pair,

made possible by the presence of the active methylene group on the α-carbon atom of the oxetane ring.



(XX)



(XXI)

E. Lithium Aluminum Hydride

Reductive cleavage of oxetanes by lithium aluminum hydride gives the alcohols resulting from ring scission between the oxygen atom and the least substituted α-carbon atom.[236] The reaction proceeds smoothly without apparent side reactions and gives reasonable yields when carried out in a moderately high boiling solvent such as tetrahydrofuran. It has been useful for proof of structure of some oxetanes but is not completely general, for being subject to steric hindrance it proceeds at an impracticably slow rate with tetrasubstituted and some trisubstituted oxetanes.[25]

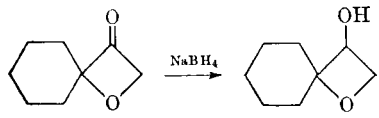
$$\begin{matrix} H_2C{-}CH_2 \\ | \quad | \\ (C_2H_5)_2C{-}O \end{matrix} \xrightarrow[2.\ H_2O]{1.\ LiAlH_4} (C_2H_5)_3C{-}OH$$

The effect of aluminum chloride on lithium aluminum hydride reduction of 2-phenyloxetane has been investigated.[220] The rate of reaction was increased, with little effect on the yield when a 2 : 1 ratio of the hydride to aluminum chloride was used. The product was 80% 1-phenyl-1-propanol, the normal product and 20% hydrocinnamyl alcohol, the 'abnormal' product which resulted from reduction of the more substituted carbon atom. This is a considerably less 'abnormal' product than is obtained from the similar reduction of styrene oxide[58] and shows the greater stability of the intermediate oxetane complex with carbonium ion formation.

It is interesting that *gem*-dialkyl substitution at the β-carbon atom of an oxetane markedly reduces the rate of reaction with lithium aluminum hydride[234] as might be expected from the *neo*pentyl-type structure. Monosubstitution at the β-carbon atom, as in 3-methyloxetane, however, caused little retardation of reductive cleavage of the oxetane ring by lithium aluminum hydride. The reactivity of 2-oxaspiro[3.*n*]alkanes, $(CH_2)_nC(CH_2)_2O$, (VI, p. 989) towards lithium aluminum hydride was in the order, $n = 4 > 3 > 2 > 5$,[230] which is approximately parallel to the order of hydrogen bonding ability of these compounds (section **II.5**).

9. Reactions of 3-Oxetanones

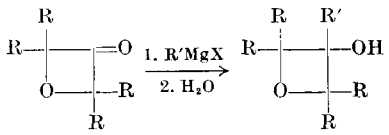
The several 3-oxetanones known show typical ketone properties, as well as some which are not. They form carbonyl derivatives, such as semicarbazones, oximes and 2,4-dinitrophenylhydrazones, in a normal manner and are readily reduced to the corresponding 3-oxetanols. Various reagents have been used; sodium borohydride reacted with 1-oxaspiro[3.5]-3-nonanone (XXII) to give an 85% yield of the oxetanol (XXIII)[226] and 2,2,4,4-tetramethyl- and 2,2,4,4-tetraphenyl-3-oxetanone have been reduced to the corresponding oxetanols with lithium aluminum hydride in 57–58% yields and by *iso*propylmagnesium bromide in 20 and 57% yields, respectively.[111, 123] Tetraphenyl-3-oxetanone was reduced with methanolic sodium methoxide in the oxetanol in 93% yield[123] and also polargraphically, the half-wave potential being considerably less negative than for other aliphatic ketones.[182] Treatment of tetramethyl-3-oxetanone with zinc in acetic anhydride is reported to give reductive cleavage to 2,4-dimethyl-2-acetoxy-3-pentanone, accompanied by the non-reductive cleavage product, 2,4-dimethyl-2,4-diacetoxy-3-pentanone.[170]



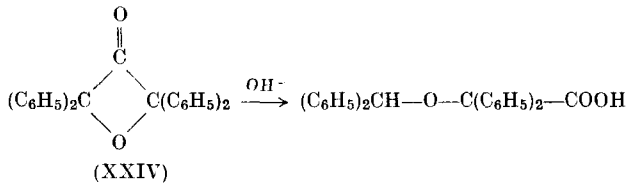
(XXII) (XXIII)

Addition of the methyl Grignard reagent to 2,2,4,4-tetraphenyl-3-oxetanone[123] and to 2,2,4,4-tetramethyl-3-oxetanone[111] has been reported to take place normally, giving the corresponding 3-methyl-3-oxetanols in 89% and 25% yields, respectively. The benzyl Grignard

reagent reacted with tetraphenyl-3-oxetanone to give 3-benzyl-2,2,4,4-tetraphenyl-3-oxetanol in 70% yield.[123]



3-Oxetanones seem much less susceptible to acid-catalyzed ring cleavage than other types of oxetanes, for treatment of the oxetanone acetals (XXXIIIa, b, c, p. 1020) with refluxing dilute sulfuric acid gave the corresponding oxetanones in fair to good yield.[6] On the other hand, 3-oxetanones react markedly with bases. 1-Oxaspiro[3.5]-3-nonanone (XXII) dissolves readily in aqueous alkali, from which it may be precipitated unchanged by carbon dioxide.[162] Its pK_a has been estimated at 12.5, which is much less that of simple ketones and is more like that for β-keto esters.[174] It also shows weak reducing action with Tollen's and Fehling's reagents. Treatment with alkaline sodium hypodite gives a small yield of 1-hydroxycyclohexylglycolic acid, which may be due to iodine substitution in the methylene group followed by a Favorskii rearrangement.[162] Tetraphenyl-3-oxetanone (XXIV) which has no enolizable hydrogen, is cleaved to *O*-benzhydryl-benzilic acid with potassium hydroxide in dioxane.[123]



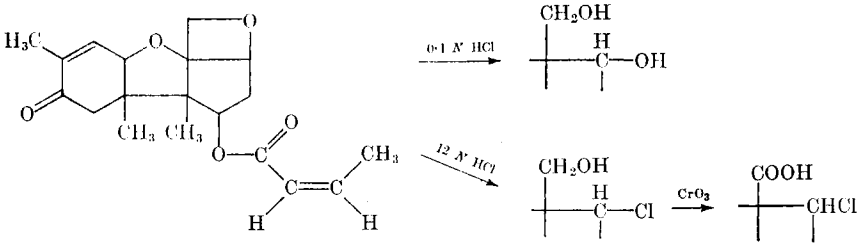
(XXIV)

The infrared absorption spectrum of 3-oxetanones have a strong absorption bond at 5.5–5.6 μ, ascribable to the carbonyl function.[6, 111, 123, 162, 170] The slightly lower wavelength than that found in cyclobutanone (5.63 μ) is in accord with a probably smaller interior angle at the carbonyl group. In compound (XXII) a somewhat less intense band is also observed at 5.84 μ, which may be attributed to the presence of the enol tautomer. The ultraviolet spectrum of (XXII) shows an absorption maximum at 290 mμ, with log = 1.4;[162] these values are slightly greater than for acetone and cyclobutanone and suggest that there may be a slight interaction between the *p* and *pi* orbitals of the oxygen atom and the carbonyl group though less than found with certain β,γ-unsaturated ketones.[153]

IV. Natural Occurrence and Pharmacological Properties

1. Trichothecin

An antifungal substance produced by the fungus *Trichothecium roseum* Link and named accordingly 'Trichothecin', was reported by Freeman and Morrison in 1948.[82] A very intensive study by both Freeman[83] and Jones[73, 74] and their co-workers subsequently showed it to have the pentacyclic structure (XVIIIa) one of the rings being an oxetane ring.

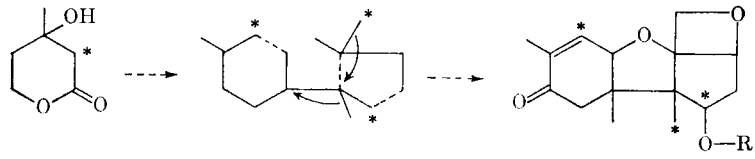


(XVIIIa)

It is beyond the scope of this review to examine the complete structure determination, except for the demonstration of the presence of the oxetane ring. This was done first by showing the presence of an easily hydrolyzed oxide function, which was converted into two hydroxy groups when very dilute acid was used and to a chlorohydrin when concentrated hydrochloric was used. Chromic acid oxidation of the latter to a chlorocarboxylic acid showed that the oxetane structure had an α-methylene group.[83] Measurements of chlorohydrin formation and the rate of reaction with sodium thiosulfate gave results which were reasonable for either an epoxide or oxetane structure,[83] but the infrared absorption spectrum clearly indicated an oxetane, as the typical 10.2 μ band was present, while those characteristic of epoxides were not.[74] All other reactions studied could be interpreted readily in terms of the oxetane structure, including the previously discussed base-catalyzed isomerization of the ring in the derivative trichothecodione (section **III.8.***D*).

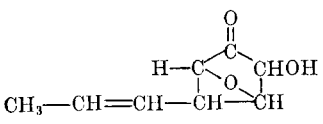
A plausible pathway for the biogenesis of trichothecin, following the Ruzicka isoprene rule, has been proposed by Jones and collaborators.[73] This was verified quickly by Jones and Lowe, by determination

of the distribution of radioactivity in trichothecin formed when the organism was fed 2-^{14}C-mevalonic lactone.[134]

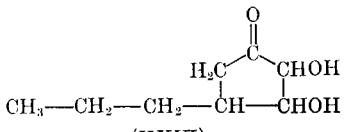


2. Terrein

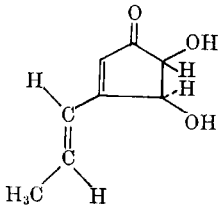
For many years another mold metabolite, terrein, was considered to have the oxetane structure (XXV). This structure was based on a classical study of its reactions which showed it to be an unsaturated, cyclic α-ketol of the formula $C_8H_{10}O_3$.[40] Catalytic hydrogenation rapidly gave a tetrahydro derivative proved to be 2,3-dihydroxy-4-propylcyclopentanone (XXVI). It was decided that terrein had the oxetane structure (XXV) rather than the dienone structure (XXVII) (or a stereoisomer), because at the time the resistance of oxetanes to hydrogenolysis was not known, and efforts to prepare a diacyl derivative and a Diels–Alder adduct had not succeeded.



(XXV)



(XXVI)



(XXVII)

Recent investigations, however, have showed that the dienone structure is actually correct. Spectral evidence for a *trans*-dienone group in both the infrared and ultraviolet regions was described by Grove,[101] who also showed a reaction with maleic anhydride, further

supporting the diene structure. Barton and Miller showed that the DNP derivative of terrein could be diacetylated, and by ozonization of terrein diacetate to diacetoxy-(+)-tartaric acid completed the evidence on the total stereochemistry of this molecule.[13]

3. Pharmacological Activity

3,3-Diethyloxetane has been found to have good anaesthetic, sedative and anticonvulsant activity when administered to rats.[89] Anticonvulsant activity was observed in both pentylenetetrazol and electroshock seizures. Its toxicity is comparable to that of the closely related anticonvulsant drug, 2,2-diethyl-1,3-propanediol (Prenderol), but its action does not seem to be due primarily to hydrolysis to the latter, which would be very slow in the nearly neutral body fluids, for the physiological effect is rapid. Also, it shows different activity, being much more active than the diol against chemical shock and longer acting in its protection against electroshock.

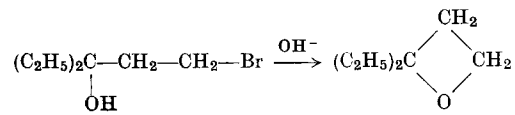
Other oxetanes have also been found to have anaesthetic activity with rats, but the toxic dose was about the same as the effective dose.[89] Capillary rupture was observed. The additional oxetanes thus tested were trimethylene oxide, 2-methyloxetane, 2,2- and 3,3-dimethyloxetane and 3-ethyloxetane.

V. Methods of Synthesis

Oxetanes have been produced by a wide variety of synthetic methods, most of which are quite limited. Methods involving closure of the oxetane ring by carbon–oxygen bond formation are discussed first, followed by methods of ring closure about a carbon–carbon bond and by other methods of ring closure less easily classified. Finally, syntheses of oxetanes from other oxetanes are described.

1. Intramolecular Williamson Reaction

The method most commonly used for the preparation of oxetanes—and the only one presently available for the preparation of the parent compound, trimethylene oxide—is the intramolecular Williamson reaction. Typically it consists of the reaction of 1,3-halohydrins with alkali, forming the cyclic ether with the loss of hydrogen halide.



Numerous variations have been employed in order to improve the scope and yields, so that the method now has fairly wide generality. Although reasonably good yields are often obtained when conditions are properly adjusted, the reaction suffers from the difficulties inherent in closure of four-membered rings in that the rate of cyclization is relatively low, which often permits competing elimination and intermolecular substitution processes to consume much of the starting material.[205] The second-order rate constants have been determined for the reaction of a number of chloroalcohols in alkaline solution; for those which undergo predominately intramolecular substitution the rate constants at 80° are about 10^{-2} times as great as those for comparable β-chloroalcohols at 20°.[62, 78]

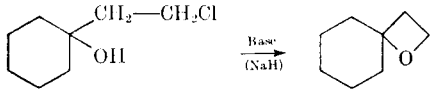
A. Substituent Effects

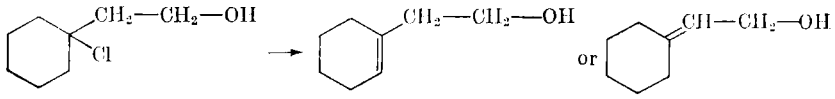
A compilation of oxetanes prepared in this way is given in Table 5. It is apparent that the effect of alkyl substitution depends greatly on the position of substitution. This is in marked contrast to the situation in the analogous syntheses of epoxides and aziridines, where substitution invariably enhances the cyclization process.[57] On the carbinol carbon atom alkyl substitution results in increased yield but on the halogen-bearing or on the middle carbon atoms the effect is to markedly decrease the yields.

Thus, 2-methyloxetane[242] and 2-ethyloxetane[234] were prepared in 60–66% yield compared to a 42–44% yield of trimethylene oxide[174] from the acetates of the corresponding chlorohydrins under very similar conditions; and 2,2-diethyloxetane was prepared in 90% yield from its chlorohydrin.[168] The yield of 2-phenyloxetane was 70% from its chlorohydrin acetate.[234] 2,2-Diphenyloxetane could not be prepared,[220] due to instability of the chlorohydrin.[255] The increase in yield associated with substitution at the carbinol carbon atom may be due to increased nucleophilicity of the alkoxide oxygen, as well as to the possible stabilizing effect of substituents on the ring and the unimportance of steric hindrance in intermolecular displacement reactions.

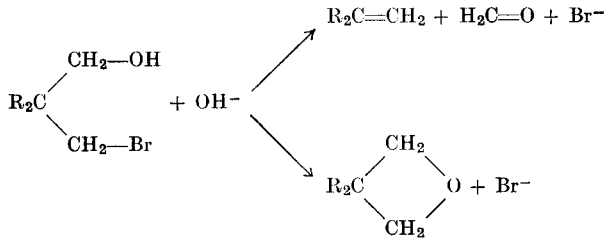
The unfavorable effect of substitution on the carbon atom bearing the halogen atom is shown by the reaction of two chlorohydrins with secondary halogen, 5-chloro-3-hexanol and 4-chloro-1-phenyl-1-butanol, giving the corresponding oxetanes in 25% and 0% yields, respectively.[85] There are no examples of an oxetane prepared by displacement of tertiary halogen. An attempted case, the reaction of 1-chloro-(2-hydroxyethyl)cyclohexane with base, was completely unsuccessful,

due to formation of unsaturated alcohol, whereas the isomeric chlorohydrin, 1-hydroxy-(2-chloroethyl)cyclohexane, reacted with base to give the oxetane in 55% yield.[199]

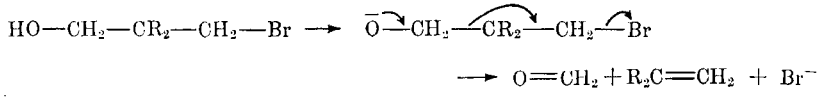




Dialkyl substitution on the central carbon atom of the three-carbon moiety brings about a decrease in the yield of oxetane, while phenyl substitution at that position prevents oxetane formation entirely.[223, 232] The reason is that such substitution promotes a conjugate elimination reaction in the basic medium, due to a tendency of the γ-halogenoalkoxide ion to undergo cleavage or 'fragmentation'.



The effects of β-substituents in promoting this cleavage at the expense of the competing oxetane process are in the order: phenyl > methyl > ethyl, *n*-butyl > H. This order correlates with the thermodynamic stability of the olefin formed. There is a marked effect of solvent on the relative yields of the two processes, dilute aqueous base favoring the cleavage and alcoholic or concentrated aqueous base favoring oxetane formation. These observations suggest that the cleavage process is essentially an ionization of halide ion from the γ-halogenoalkoxide ion.[232]

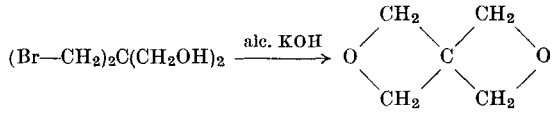


Quite different is the result when hydroxymethyl and halogenomethyl groups are substituted on the β-carbon atom, for unusually good yields of 3,3-disubstituted oxetanes are obtained from the reaction of pentaerythritol halides with alcoholic potassium hydroxide. The synthesis of 3,3-bis(chloromethyl)oxetane in 90% yield from pentaerythritol trichloride[53, 67, 209] in this manner is of commercial importance (section **III.6.***F*).



Cyclization is no doubt kinetically favored in these cases by the presence of more alkoxide oxygen atoms and/or displaceable halogen atoms per molecule and, as a result, fragmentation to olefin and carbonyl compounds occurs to only a small extent.

A double Williamson reaction is observed when pentaerythritol dichloride or dibromide is treated with alcoholic potassium hydroxide, forming 2,6-dioxaspiro[3.3]heptane.[10, 75b, 120] A lower yield here of 20–30% seems to reflect the greater ring strain of this system.



A report that 3-chlorooxetane is formed by the reaction of powdered sodium hydroxide on the allyl alcohol chloroiodides[20] has been found to be incorrect, the material actually being 2-chloroallyl alcohol.[173] The report of 3-iodooxetane from the same reaction is probably also incorrect.

B. Use of Esters

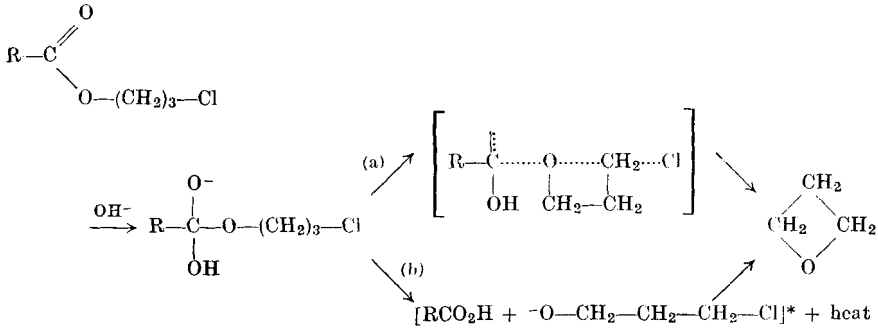
A common method of improving the yields of oxetanes from the intramolecular Williamson reaction of 1,3-halohydrins is to use the acetate esters of the 1,3-halohydrin rather than the halohydrin directly. Thus trimethylene oxide is obtained in 40–45% yield by treating 3-chloro-1-propyl acetate with concentrated potassium hydroxide at 140–150°, whereas only a 20–25% yield is obtained under the same conditions from 3-chloro-1-propanol.[174] Likewise, 2-phenyloxetane

was found in 58% yield from 1-phenyl-3-chloro-1-propanol and in 70% yield from the acetate of the latter.[233]

Such advantage in using esters is not completely general, for approximately the same yields of 3,3-dimethyloxetane and 3,3-diethyloxetane were obtained by the reaction of alkali with the corresponding bromohydrins as with the bromohydrin acetates.[220] The benzoate and propionate esters of 3-chloro-1-propanol gave about the same results as the acetate,[220] but the chloroacetate ester gave only a 24% yield of trimethylene oxide, while the trichloroacetate and trifluoracetate esters gave none.[54]

A cyclic phosphonate ester, *cis*-2-chloromethyl-2-ethyl-1,3-propanediol benzylphosphonate, has been converted to the corresponding oxide, 3-ethyl-3-hydroxymethyloxetane, in good yield.[253] A patent has been issued on the synthesis of 2,6-dioxaspiro[3.3]heptane by the reaction of alkali with the cyclic sulfite ester of pentaerythritol dichloride, which is readily obtained from pentaerythritol, thionyl chloride and pyridine.[64]

The reason that esters frequently give better yields of oxetanes is not known, but it seems likely that reaction of hydroxide ion would be primarily on the carbonyl carbon atom, to form an intermediate of the usual type. This might reasonably decompose either (a) with concerted attack on the halogen-substituted carbon atom, or (b) into a 3-halogenoalkoxide ion which is thermally activated by the heat of decomposition of the intermediate, thus facilitating ring closure.



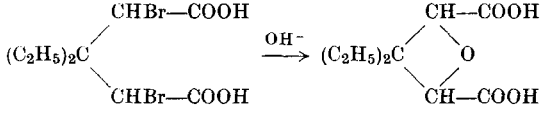
It has been suggested also[54] that the attack of hydroxide on the carbonyl group may be concerted with ring closure, bypassing the usual ortho-ester type intermediate, and that the concentration of 3-chloroalkoxide ion being lower when generated from the ester than from the chlorohydrin, may favor cyclization over polymerization. The resulting advantage of the latter, however, would probably be greatly diminished

by the fact that the chloroalkoxide should be able to react also with the chloroester present, giving polymeric material, and so this explanation seems unlikely.

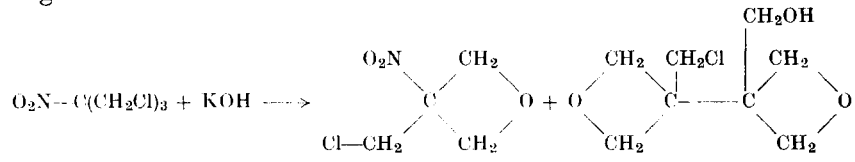
C. Effect of Leaving Group

There has been considerable variation in the nature of the leaving atom or group in the intramolecular Williamson synthesis of oxetanes. 1,3-Chlorohydrins, or their esters, have been most widely used, because of their ready availability by routes involving the Grignard,[47, 168] Friedel–Crafts[234] and Darzens reactions[242] and also by the convenient direct reaction of many 1,3-diols with acetyl chloride.[233] 1,3-Bromohydrins, usually prepared from the corresponding diols and hydrobromic acid, have been employed less often, and 1,3-iodohydrins very seldom.[47] It is difficult to judge which halogen gives the most satisfactory results in the oxetane synthesis, due to lack of comparable data. In the reaction of pentaerythritol chlorobromoiodide with alkali, iodide was preferentially displaced, giving a 65% yield of 3-chloromethyl-3-bromomethyloxetane and showing that ring closure occurs most readily by displacement of the most weakly bound halogen.[98] In most oxetane syntheses, however, this factor may be somewhat compensated for by similar effects on the competing reactions.

1,3-Dihalides may give oxetanes on treatment with alkali, the chlorohydrins being presumably formed first. An interesting example of this process is the formation of 3,3-diethyl-2,4-oxetanedicarboxylic acid from α,α-dibromo-β,β-diethylglutaric acid.[256] Also in this category

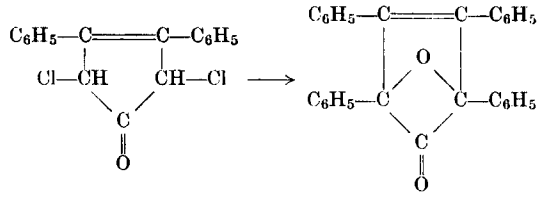


is possibly the reaction of 2-chloromethyl-2-nitro-1,3-dichloropropane with alcoholic potassium hydroxide to give two products, formulated as 3-nitro-3-chloromethyloxetane and 3-chloromethyl-3′-hydroxymethyl-3,3′-bioxetanyl on the basis of elemental analysis and molecular weight.[141]



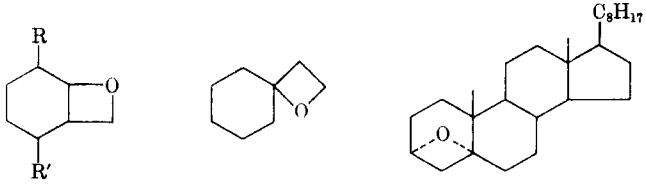
Another reported case is the reaction of tetraphenylcyclopentadienone dichloride, supposedly (XXVIII) with hot methanolic base, to

form a crystalline product formulated as the bicyclic oxetanone (XXIX).[186] Little evidence exists, however, for these structures.



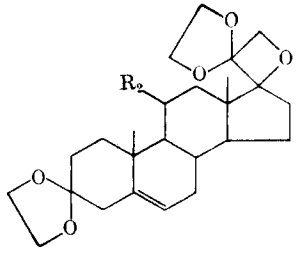
(XXVIII) (XXIX)

Mono-*p*-toluenesulfonates and mono-*p*-bromobenzenesulfonates of 1,3-diols may be used in place of 1,3-halohydrins in the intramolecular Williamson reaction. This variation was used for the preparation of several bicyclic, polycyclic and spirooxetanes, such as the 7-oxabicyclo[4.2.0]octanes (XXX),[113, 199, 231] 1-oxaspiro[3.5]nonane



(XXX) (XXXI) (XXXII)

(XXXa, R = R′ = H;
XXXb, R = CH_3, R′ = $CH(CH_3)$.)



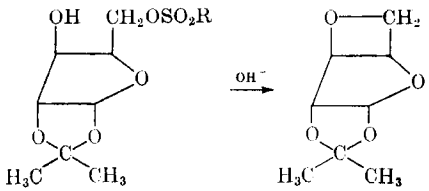
(XXXIIIa, R_2 = H_2;
XXXIIIb, R_2 = H, α-OH;
XXXIIIc, R_2 = H, β-OH;
XXXIIId, R = H.)

(XXXI),[113, 199] 3α,5α-epoxycholestane (XXXII)[38, 39] and some 17α,21-oxide steroids (XXXIIIa, b, c)[6] from the corresponding diols. The yields were in the range of 50–90%. In each case the diol monoarenesulfonate was obtained readily and in high yield by simple treatment of the diol with the arenesulfonyl chloride and pyridine.

The method, however, was not successful with 5β-hydroxy-3α-coprostanyl tosylate, due to the tendency of the monotosylate to undergo conjugate elimination rather than intramolecular substitution. 1β-Hydroxy-3β-cholestanyl tosylate also undergoes only the conjugate elimination process with potassium *tert*-butoxide. It appears that the synthesis of 3α,5α-epoxycholestane may be an unusual case, because of high steric compression in the tosyloxyalkoxide intermediate, which is relieved by the substitution process.[39] This is the only successful synthesis of a compound with the highly strained 1,3-epoxycyclohexane structure. Treatment of the *p*-toluenesulfonate of *trans*-1,3-cyclohexanediol with methanolic sodium methoxide gave 4-cyclohexenol in good yield and no bicyclic oxetane.[37b]

Although the reaction of the mono-*p*-toluenesulfonate of 1,3-propanediol is reported to give no trimethylene oxide when treated with hot caustic, 2,2-dibutyl-1,3-propanediol has been converted to 3,3-dibutyloxetane by treatment of its monobrosylate with potassium *tert*-butoxide.[113] The yield for the cyclization was somewhat better (72%) than that usually obtained for this type of compound from the bromohydrin, but this advantage was offset by the low yield of the monoester from the diol. A higher over-all yield of oxetanes from such *diprimary* diols can be obtained by converting the diols to their di-*p*-toluenesulfonate esters, which are treated with hot, powdered potassium hydroxide.[258] This synthesis undoubtedly occurs by way of the monotosylates, these apparently being less susceptible to fragmentation than the corresponding bromohydrins.

The use of other sulfonate esters of 1,3-diols has been studied less, but available information indicates that similar results may be expected.

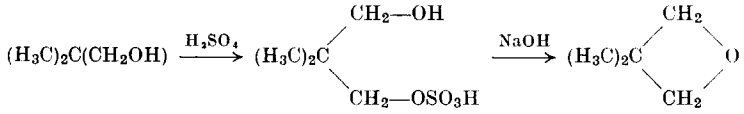


(XXXIV, R = CH_3 or *p*-CH_3—C_6H_4—)

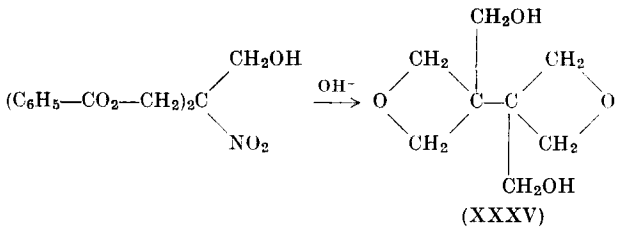
5-Methanesulfonoxy-1,2-*iso*propylidene-D-xylose reacted with alcoholic potassium hydroxide to give the oxetane derivative (XXXIV) in 85% yield,[115] the same result being obtained with the corresponding tosylate.[156]

The use of hydrogen sulfate esters has been reported. The reaction

of alkali with the crude mono(hydrogen sulfate) of 2,2-dimethyl-1,3-propanediol gave a 29% yield of 3,3-dimethyloxetane.[212] In the same manner and in about the same yield 3,3-diethyloxetane, 3-butyl-3-ethyloxetane, 2-propyl-3-ethyloxetane and 2-methyloxetane were also synthesized.[212]

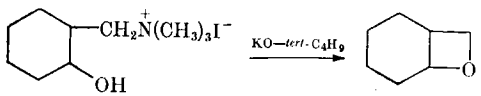


Displacement of carboxylate groups to give oxetanes failed to occur in the cases of the reactions of 3-hydroxypropyl acetate, chloroacetate and trichloroacetate with hot caustic,[54] but one example of such a displacement of a benzoate group has been reported. 2-Nitro-2-hydroxymethyl-1,3-dibenzoxypropane reacted with alcoholic potassium hydroxide to give a compound considered to be 3,3-bis(hydroxymethyl)-3,3′-bioxetanyl (XXXV) on the basis of its analysis.[141]



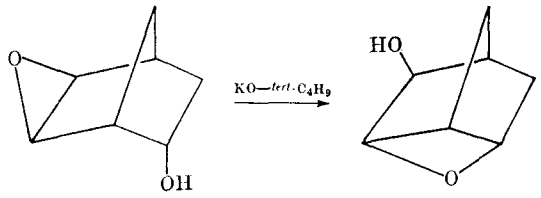
(XXXV)

Other interesting leaving-groups that have been tried in the intramolecular Williamson reaction are the nitrate, trimethylammonium, and epoxide groups. The first was demonstrated by the isolation of 3,3-bis(nitratomethyl)oxetane from the reaction of pentaerythritol trinitrate and sodium ethoxide; the yield, however, was only 15%.[59] An example of oxetane formation with loss of trimethylamine is afforded by the observation that treatment of 2-hydroxy-1-cyclohexylmethyltrimethylammonium iodide with potassium *tert*-butoxide,



gave 7-oxabicyclo[4.2.0]octane in low yield.[252] An interesting example of the displacement of an epoxide oxygen atom by an alkoxide oxygen

atom in an oxetane synthesis, is the reaction of 2,3-epoxy-5-hydroxynorbornane (XXXVI) with potassium *tert*-butoxide in *tert*-butanol to form 3,5-epoxy-2-hydroxynorbornane (XXXVII) in 82% yield.[114]

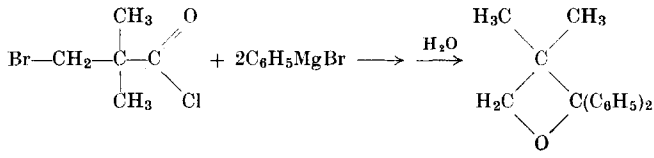


(XXXVI) (XXXVII)

D. Nature of the Base

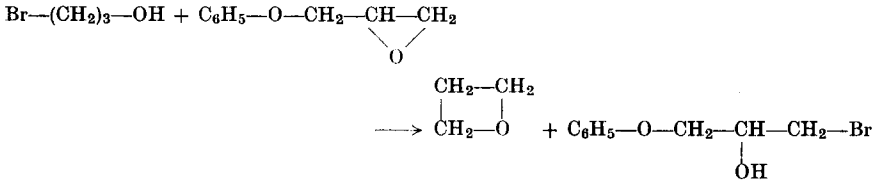
Best results in the intramolecular Williamson synthesis of oxetanes appear to be obtained with the use of strong base. Concentrated, powdered and alcoholic potassium hydroxide have been most commonly used and seem to be roughly equivalent. Differences between dilute, concentrated and alcoholic sodium and potassium hydroxide were mentioned in section **V.1.*A***.[232] The molten sodium hydroxide–potassium hydroxide eutectic has given good results,[217, 233, 234] as have also sodium and potassium methoxide in methanol and potassium *tert*-butoxide in *tert*-butanol;[39, 113, 114, 199, 231] the latter appears to have special advantage with monoarenesulfonates of 1,3-diols, as it causes less conjugate elimination to occur. Sodium hydride in ether or in mineral oil has given similar results.[199] The use of sodium amalgam has been reported by Kleinfeller to cause the conversion of 2-nitro-2-hydroxymethyl-1,3-dibromopropane into 3-chloromethyleneoxetane and 3-methyleneoxetane but the structures of these were not actually established and are probably incorrect. A recent preparation of 3-methyleneoxetane by Applequist and Roberts[7] (section **VI.7**) gave a material with a distinctly different boiling point to that reported by Kleinfeller.

2,2-Diphenyl-3,3-dimethyloxetane has been synthesized in good yield by the reaction of 2,2-dimethyl-3-bromopropionyl chloride with excess phenyl Grignard reagent, the intermediate magnesium alkoxide

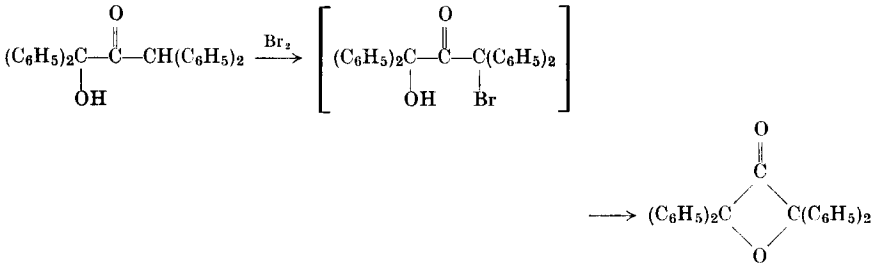


apparently cyclizing as formed. The isolation of the intermediate bromohydrins was avoided, and the high degree of substitution here probably enhanced the ease of ring closure. 2,2,3,3-Tetramethyl-, 2-phenyl-2,3,3-trimethyl- and 2-methyl-2,3-diphenyloxetane were prepared similarly.

It has been reported that phenyl glycidyl ether, in the presence of pyridinium iodide, can serve as the base for conversion of 3-bromo-1-propanol into trimethylene oxide in 92% yield,[22] but an attempt to repeat this reaction was completely unsuccessful.[220]



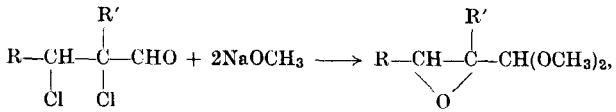
A case of spontaneous loss of hydrobromic acid with closure of an oxetane ring has been apparently observed in one case. The light-catalyzed reaction of bromine with 1,1,3,3-tetraphenylhydroxyacetone in refluxing carbon tetrachloride solution gave a 50% yield of 2,2,4,4-tetraphenyl-3-oxetanone.[123]



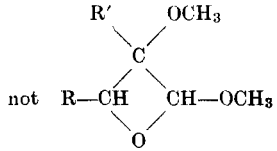
E. Use of β-Chloroaldehydes

2-Alkyl-2,3-dichloroaldehydes undergo smooth substitution of both chlorine atoms when treated with two molecular equivalents of sodium methoxide in methanol, to give products which have been formulated as 2,3-dimethoxyoxetanes (XXXIX).[151] This structure was based on the elemental analysis, acetal-like chemical properties and identification of the products of hydrolysis. The evidence, however,

fits equally well the 2,3-epoxydimethylacetal structure (XXXVIII), and the latter was shown to be indeed the case by isolation of the

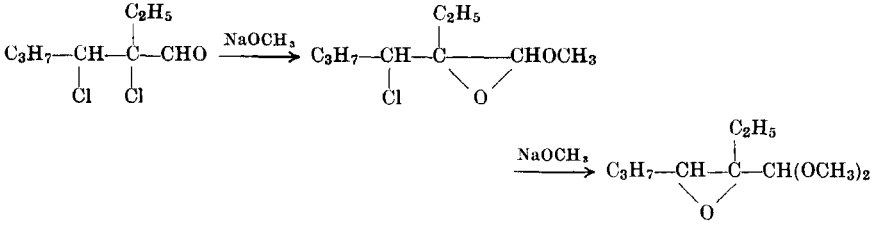


(XXXVIII)



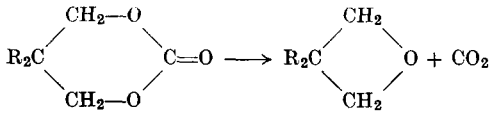
(XXXIX)

epoxy ether intermediate in one case and by the nuclear magnetic resonance spectra and the independent synthesis of the final product in another.[225, 228]



2. Pyrolysis of Carbonate and Sulfite Esters of 1,3-Diols

Carbonate esters of 1,3-diols decompose to form oxetanes and carbon dioxide when heated at 200–250°, generally in the presence of a basic catalyst.[63, 176, 177, 215, 224] This is the method of choice for the synthesis of 3,3-dialkyloxetanes, which are thus obtained in good yields and good state of purity. Carbonate esters of 1,3-diols which



possess β-hydrogen atoms, however, are very prone to suffer a β-elimination process, to form unsaturated alcohols and carbon dioxide; and the presence of a phenyl group between the carbinol groups

TABLE 5. Synthesis of Oxetanes by the Intramolecular Williamson Reaction

Oxetane	Starting material	Base	Yield, %	B.p.[c] (mm.)	Reference
Trimethylene oxide	$Cl(CH_2)_3OH$	conc. KOH	20–25	47–48	4, 52, 174
	$Cl(CH_2)_3OCOCH_2Cl$	conc. KOH	24	47–48	54
	$Cl(CH_2)_3O_2CCH_3$	conc. KOH, KOH—NaOH	42–44	47–48	174, 217
	$Br(CH_2)_3OH$	$C_6H_5OCH_2—CH(O)CH_2$	92	47	22
2-Methyloxetane	$Cl(CH_2)_2CH(O_2CCH_3)CH_3$	conc. KOH	66	60–61	242
	Mixed chloroacetates[a]	KOH–NaOH	52[b]	60	233
	HSO_4 ester of diol	conc. KOH	15[b]	(58–61)	212
2-Ethyloxetane	$Cl(CH_2)_2CH(O_2CCH_3)CH_3$	KOH, KOH–NaOH	60	87, 88–89	154, 234
2-Phenyloxetane	$Cl(CH_2)_2CH(O_2CCH_3)C_6H_5$	conc. KOH	70	87–8 (8)	234
	$Cl(CH_2)_2CH(OH)C_6H_5$	conc. KOH	58	52(0.5)	234
3-Methyloxetane	$BrCH_2CHCH_3CH_2O_2CCH_3$	KOH–NaOH	43	67	234
3-Ethyloxetane	$BrCH_2CHC_2H_5CH_2O_2CCH_3$	conc. KOH	25	98.5–99	232
3-Butyloxetane	$BrCH_2CH(C_4H_9)CH_2O_2CCH_3$	conc. KOH	30	83–85 (85)	232
2,2-Dimethyloxetane	$(CH_3)_2C(OH)(CH_2)_2Cl$	powd. KOH	43, 25	71, 70	15, 234
2,3-Dimethyloxetane	Mixed chloroacetates[a]	KOH–NaOH	45[b]	85–86	233
3,3-Dimethyloxetane	$BrCH_2C(CH_3)_2CH_2OH$	conc. KOH	57	76–77	232
	$BrCH_2C(CH_3)_2CH_2OH$	powd. KOH	—	78(742)	15
	$ClCH_2C(CH_3)_2CH_2OH$	conc. KOH	19	79.5–50	67
	$HOSO_3CH_2C(CH_3)_2CH_2OH$	conc. KOH	29[b,d]	79.2–80.3	212
2-Methyl-4-ethyloxetane	$CH_3CHClCH_2CH(OH)C_2H_5$	conc. KOH	25	98–99	85
2,2-Diethyloxetane	$(C_2H_5)_2C(OH)(CH_2)_2Cl$	powd. KOH	90, 50	129, 124–126	168, 233
	$(C_2H_5)_2C(OH)(CH_2)_2I$	powd. KOH	—	128–130	47
3,3-Diethyloxetane	$BrCH_2C(C_2H_5)_2CH_2OH$	conc. KOH	57	138–140	232
	$HOSO_3CH_2C(C_2H_5)_2CH_2OH$	conc. KOH	34[b]	139–141	212
3-Ethyl-2-propyloxetane	Mixed chloroacetates[a]	KOH–NaOH	33[b]	155	233
	HSO_4 ester of diol	conc. KOH	20[b]	152.5–155.5	212

Oxetane	Starting material	Base	Yield, %	B.p.° (mm.)	Reference
3-Ethyl-3-propyloxetane	$ClCH_2C(CH_3, iso\text{-}C_3H_7)CH_2OH$	$NaOC_2H_5$	80	139–140	245
3-Ethyl-3-*iso*propyloxetane	$BrCH_2C(C_2H_5, iso\text{-}C_3H_7)CH_2CH$	conc. KOH	47	155–157	232
2-Ethyl-2-butyloxetane	$HSO_4CH_2C(C_2H_5, C_4H_9)CH_2OH$	conc. KOH	35[b]	181.2–183.9	212
3,3-Dibutyloxetane	$HOCH_2C(C_4H_9)_2CH_2OBros$	KO-*tert*-C_4H_9	72	105 (15)	113
3,3-Dibenzyloxetane	$BrCH_2C(CH_2C_6H_5)CH_2OH$	$NaOC_2H_5$	47	135 (1)	232
3,3-Bis(bromomethyloxetane)	$(BrCH_2)_3CCH_2OH$	alc. KOH	79	121 (1.8)	19, 77, 90,
			70–80	m.p. 25	96
3,3-Bis(chloromethyloxetane)	$(ClCH_2)_3CCH_2OH$	alc. KOH	90	80 (10)	66, 67, 69
		conc. KOH	65–80	83 (11)	53, 77, 98,
				m.p. 19	209
3-Chloromethyl-3-bromomethyloxetane	$(ClCH_2)(BrCH_2)(ICH_2)CCH_2OH$	KOH	65	m.p. 16	98
3,3-Bis(hydroxymethyloxetane)	$(HOCH_2)_3CCH_2Br$	alc. KOH	70	135–138 (1–2)	131
			81	128 (0.04)	97
				m. 84	
3,3-Bis(nitratomethyloxetane)	$(O_2NOCH_2)_3CCH_2Br$	$NaOC_2H_5$	15	m. 89–91	59
3-Bromomethyl-3-hydroxymethyloxetane	$(HOCH_2)_2C(CH_2Br)_2$	alc. KOH	70	149–150 (13)	99
		$NaOC_2H_5$	71	141–143 (1–2)	132
3-Chloromethyl-3-hydroxymethyloxetane	$(HOCH_2)_2C(CH_2Cl)_2$	KOH	70–80	99–102 (3)	120
		$NaOC_2H_5$	76	142–145 (4–5)	132
3,3-Bis(aminomethyloxetane)	$(BrCH_2)_3CCH_2OH$	NH_3	(low)	122 (1.5)	96
3-Hydroxymethyl-3-diethylaminomethyloxetane	$(BrCH_2)_2C(CH_2OH)_2$	$(C_2H_5)_2NH$	—	132 (14)	80
3-Ethyl-3-hydroxymethyloxetane	$ClCH_2C(C_2H_5)(CH_2O)_2POCH_2C_6H_5$	NaOH	80	87–92 (0.1)	253
3-Nitro-3-chloromethyloxetane	$O_2NC(CH_2Cl)_3$	Na	—	45–6 (9)	141
3,3-Dimethyl-2,2-diphenyloxetane	$BrCH_2C(CH_3)_2COCl + C_6H_5MgBr$	—	68	m. 89–90	171
2,6-Dioxaspiro[3.3]hexane	$(BrCH_2)_2C(CH_2OH)$	alc. KOH	20–25	172	10
	$(ClCH_2)_2C(CH_2OH)_2$	alc. KOH		m. 89	120

(*Table continued*)

TABLE 5 (*continued*)

Oxetane	Starting material	Base	Yield, %	B.p.° (mm.)	Reference
3-Chloromethyl-3′-hydroxymethyl-3,3′-bioxetanyl(?)	O_2N–$C(CH_2Cl)_3$	alc. KOH	60	80 (12)	141
3,3′-Bis(hydroxymethyl)-3,3′-bioxetanyl(?)	O_2N–$C(CH_2OCOC_6H_5)_3$	alc. KOH	—	108–112 (9)	141
2,2,4,4-Tetraphenyl-2-oxetanone	$(C_6H_5)_2COHCOCH(C_6H_5)_2 + Br_2$	None	50	m. 199–201	123
2-Oxaspiro[3.5]nonane	$(CH_2)_5C(CH_2Br)CH_2OH$	$NaOC_2H_5$, conc. KOH	68	173	230, 232
2-Oxaspiro[3.4]octane	$(CH_2)_4C(CH_2Br)CH_2OH$	conc. KOH	48	149–150	232
1-Oxaspiro[3.5]nonane	$(CH_2)_5C(OH)(CH_2)_2OBs$	KO-*tert*-C_4H_9	62	57 (16)	113
	$(CH_2)_5C(OH)(CH_2)_2Cl$	NaH	55	79 (35)	199
	$(CH_2)_5C(CH_2OTs)_2$	KOH–NaOH	20, 45	64 (14)	31, 258
2-Oxaspiro[3.5]-5-nonene	The glycol ditosylate	KOH–NaOH	54	178	31
6-Methyl-2-oxaspiro-[3.5]-nonane	The glycol ditosylate	KOH–NaOH	10	120–121 (81)	31
6-Methyl-2-oxaspiro-[3.5]-5-nonene	The glycol ditosylate	KOH–NaOH	13	74–75 (11)	31
4,7-Endomethylene-2-oxaspiro[3.5]nonane	The glycol ditosylate	KOH–NaOH	33	90–91 (24)	31
4,7-Endomethylene-2-oxaspiro[3.5]-5-nonene	The glycol ditosylate	KOH–NaOH	28	81 (20)	31
4,7-Ethylene-2-oxaspiro-[3.5]nonane	The glycol ditosylate	KOH–NaOH	19	117 (24)	31
7,7-Dimethyl-2,6,8-trioxaspiro[3.5]nonane	$(CH_3)_2C(OCH_2)_2C(CH_2Cl)CH_2OH$	alc. KOH	66	91 (13)	67
7-Oxabicyclo[4.2.0]octane	2-OH-$C_6H_{10}CH_2OBs$	KO-*tert*-C_4H_9	67, 47	35.5 (17)	113, 199
2-Methyl-5-*iso*propyl-7-oxabicyclo[4.2.0]octane	2-OH-3-CH_3-6-*iso*C_3H_7—$C_6H_8CH_2OTs$	NaH	49		199
		KO-*tert*-C_4H_9	30	78 (2.5)	231
2,5-Epoxy-2-hydroxynorbornane	2,3-Epoxy-5-hydroxy-norbornane	KO-*tert*-C_4H_9	82	m. 173–176	114

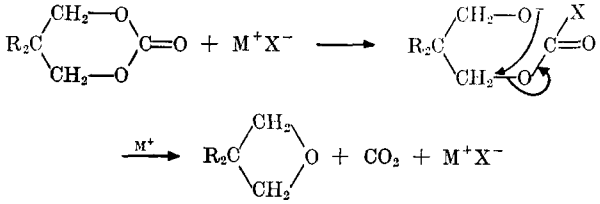
Oxetane	Starting material	Base	Yield, %	B.p.° (mm.)	Reference
2,2-Dimethyl-5*H*-oxeto-[2′,3′:4,5]furo[2,3-d]-1,3-dioxole	1,2-*Iso*propylidene-D-xylose-5-tosylate	$NaOCH_3$	90	m. 16–17	156
	Corr. 5-methanesulfonate	alc. KOH	85	53–54(0.08)	115
3α,5α-Epoxycholestane	5α-Hydroxycholestan-3β-yl tosylate	KO-*tert*-C_4H_9	55	m. 82–86	39
Δ^5-Pregnene-11α-ol-3,20-dione-17α,21 oxide 3,20-bisethylene ketal	The 11α,21-ditosylate	alc. KOH	48, 69	m. 213–214	6
The 11β-isomer of above	The 21-tosylate	alc. KOH	91	m. 241–243	6
Δ^5-Pregnene-3,20-dione-17α,21 oxide 3,20-bisethylene ketal	The 21-tosylate	alc. KOH	90	m. ca. 241	6
Δ^5-Pregnene-3,11,20-trione-17α,21-oxide 3,20-bis(ethylene ketal)	The 21-tosylate	alc. KOH	95	m. 192–195	6
2^1,3-Anhydro-2β-hydroxymethyl-3β-tropanol hydrochloride	2-β-Chloromethyl-3-β-tropanol·HCl	dil. NaOH	56.5	m. 139–141	138
2^1,3-Anhydro-2β-hydroxymethyl-3β-tropanol methiodide	2-β-Chloromethyl-3β-tropanol·CH_3I	dil. NaOH	80	m. 266–268	138

[a] Mixture of isomeric chlorohydrin acetates obtained from acetylation of diol.
[b] Over-all yield from diol.
[c] Crude hydrogen sulfate ester of diol used.
[d] Conversion yield was 47%.

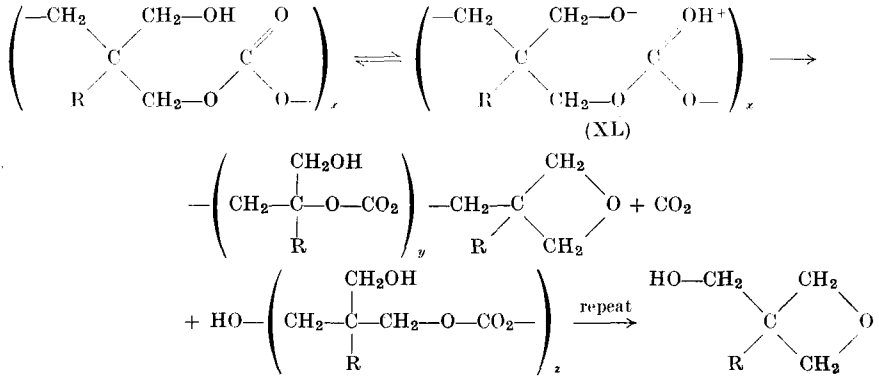
results in conjugate elimination to form olefin and carbonyl compound.[224] The oxetanes so prepared are shown in Table 6.

The carbonate esters are readily available by ester interchange reaction of 1,3-diols and ethyl or ethylene carbonate. They may be used in the cyclic form (1,3-dioxan-2-ones) obtained by distillation, although this is not essential[224] as at the decomposition temperature there is probably an equilibrium between cyclic monomer and polymer.[206a] In a series of bases tested, the best catalysts found were dry potassium cyanide and dry potassium carbonate[224]; lithium bromide is also an effective catalyst[177, 239] and is less prone to cause the β-elimination side reaction.[220] If a free hydroxymethyl group is present, as with 1,1,1-tris(methylol)ethane and pentaerythritol, decomposition to the oxetane and carbon dioxide occurs smoothly without a catalyst.[63, 176]

The available information suggests that the reaction is mechanistically related to the intramolecular Williamson reaction. The catalysts, which are nucleophilic in character, would be expected to attack the carbonyl carbon atom, generating an alkoxide ion which



can give an intramolecular displacement reaction. When a hydroxymethyl group is present, a new route involving interaction in the polymeric carbonate ester, as in (XL), becomes possible, and this accounts for the lower stability of these carbonates.



(XL)

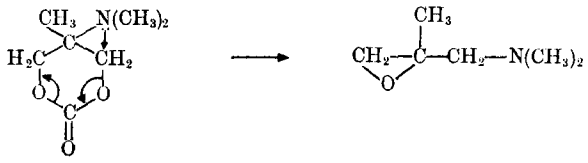
TABLE 6. Synthesis of Oxetanes from Carbonate Esters of 1,3-Diols

Oxetane	Diol	Catalyst	B.p.° (mm.)	Yield, %	Reference
Trimethylene oxide	$HO(CH_2)_3OH$	K_2CO_3	—	0	224
2-Methyloxetane	$CH_3CHOHCH_2CH_2OH$	K_2CO_3	—[a]	15	224
3,3-Dimethyloxetane	$(CH_3)_2C(CH_2OH)_2$	KCN	80–81	66	224
3,3-Diethyloxetane	$(C_2H_5)_2C(CH_2OH)_2$	KCN	139–141	65	224
		$LiNH_2$	136–140.5	31	177
3,3-Dibenzyloxetane	$(C_6H_5CH_2)_2C(CH_2OH)_2$	K_2CO_3	135(0.1)	25	224
2,2,4-Trimethyloxetane	$(CH_3)_2C(OH)CH_2CHOHCH_3$	K_2CO_3	—[a]	10	224
2-*Iso*propyl-3,3-dimethyloxetane	$(CH_3)_2C(CH_2OH)CHOHCH(CH_3)_2$	KCN	135	49	224
3-Methyl-3-hydroxymethyloxetane	$CH_3C(CH_2OH)_3$	None	72(1)	68, 91[b]	64
			80(4)	77[b]	176
3-Ethyl-3-hydroxymethyloxetane	$CH_3C(CH_3OH)_3$	None	96(4)	86[b]	64
			84(2.8)	87[b]	176
3,3-bis(hydroxymethyl)oxetane	$C(CH_2OH)_4$	None	128–130(0.05)	40[b]	37
			122(0.25)	58, 70[b]	64
			155(3.5)	34[b]	176
2,6-dioxaspiro[3.3]heptane	$C(CH_2OH)_4$	None		1–2%[b]	64
2-Oxaspiro[3.3]heptane	$(CH_2)_3C(CH_2OH)_2$	$C_2H_5CO_2K$	110–116	10	229

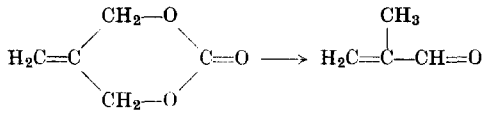
[a] Not obtained pure.

[b] Yield from the diol, the carbonate ester not having been isolated.

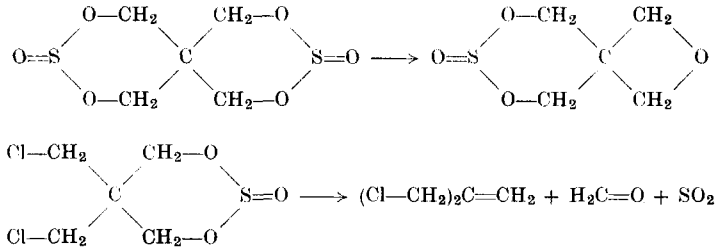
Rearrangement was observed in the thermal decomposition of the carbonate esters of 2-alkyl-2-dimethylamino-1,3-propanediol, which also proceeded very easily with evolution of carbon dioxide and required no added catalyst. The cyclic ether products were shown to be



1-dimethylamino-2-alkyl-2,3-epoxypropanes resulting from a shift of the dimethylamino group.[227] Rearrangement was also observed in the pyrolysis of 4-methylene-1,3-dioxan-3-one, which gave 2-methylacrolein, instead of 3-methyleneoxetanes.[220]



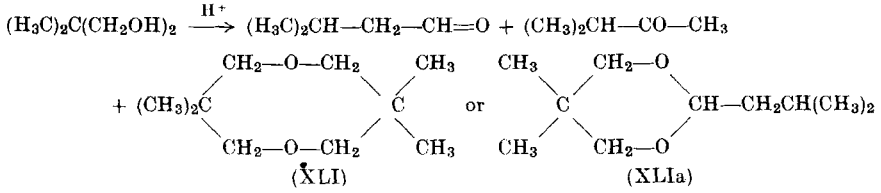
The analogous pyrolysis of cyclic sulfite esters of 1,3-diols appears generally inapplicable to oxetane synthesis. In only one instance has decomposition to an oxetane been observed; that at 260–270° of the bis(cyclic sulfite) of pentaerythritol to the cyclic sulfite of 3,3-bis(hydroxymethyl)oxetane in 25% yield.[253a] No 2,6-dioxaspiro[3.3]heptane was observed, and further heating gave polymeric products. The cyclic sulfite ester of 2,2-dimethyl-1,3-propanediol and of 2-methyl-2-hydroxymethyl-1,3-propanediol were stable at 450–500°,[253] while the cyclic sulfite ester of dichloropentaerythritol decomposed at 500° to formaldehyde, sulfur dioxide and 3-chloro-2-chloromethyl-1-propene.[163]



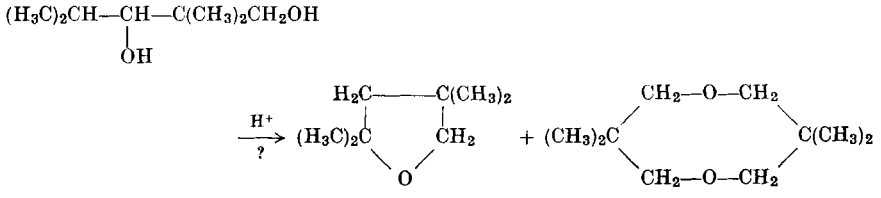
3. Cyclodehydration of 1,3-Diols

Synthesis of oxetanes by treatment of 1,3-diols with acid has been reported several times, but in only one instance has it been well authenticated. That it is not a general method is clear from the studies in the older literature on the reaction of various acyclic 1,3-diols with acids, particularly sulfuric acid.

In none of the acyclic cases did an oxetane appear to be formed, the products being generally carbonyl compounds. Thus, 1,3-propanediol was converted to propionaldehyde and acetone, accompanied by some higher condensation products,[193] and 1,3-butanediol was converted to butyraldehyde and methyl ethyl ketone[14] (or to 1,3-butadiene at higher temperatures).[152] 2,2-Dimethyl-1,3-propanediol with dilute sulfuric acid yielded isovaleraldehyde, methyl isopropyl ketone and a 'cyclic double oxide', formulated (XLI) but is perhaps more likely the cyclic acetal (XLIa).[72, 157] Similar results were obtained from 2-methyl-1,3-propanediol[157] and 1-phenyl-2-methyl-1,3-propanediol.[106, 210] 2,2,4-Trimethyl-1,3-pentanediol and 2,2,5-trimethyl-1,3-

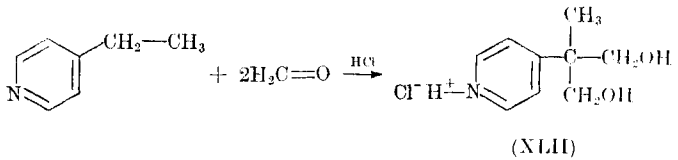


hexanediol are of interest in that a 'monoxide', as well as the 'dioxide' was obtained from each, but it appeared to be not the oxetane but the five- or six-membered cyclic ether that might result from a hydride shift.[157] The evidence for this, however, is not conclusive.

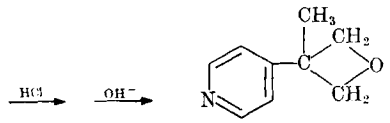


In addition, the cleavage of *ditertiary* 1,3-diols and of some *secondary–tertiary* 1,3-diols to olefins and carbonyl compounds is well known.[60, 259] Many *primary–tertiary* 1,3-diols are dehydrated to unsaturated alcohols.[180]

The one seemingly well established example of the isolation of an oxetane from the direct dehydration of 1,3-diols is the cyclization of 2-methyl-2-(4-pyridyl)-1,3-propanediol (XLII) when heated with formaldehyde and hydrochloric acid.[158,159] The presence of formaldehyde was essential, probably to suppress reversal of the formation of (XLII) from 4-ethylpyridine and formaldehyde. The structure of the product, 3-methyl-3-(4-pyridyl)oxetane (XLIII), was established by analysis, formation of salts, cleavage of the ether function with hydrobromic acid and catalytic hydrogenation of the pyridine ring, followed by cleavage of the oxetane ring with hydrobromic acid and cyclization with alkali to form 3-methyl-3-hydroxymethylquinuclidine.

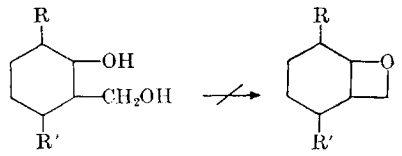


(XLII)



(XLIII)

The reports of Rupe and collaborators that 2-hydroxymethylcyclohexanol[201] (XLIVa) and 2-hydroxymethylcarvomenthol[203] (XLIVb) cyclize to bicyclic oxetanes either in the presence of acid or spontaneously could not be confirmed when reinvestigated



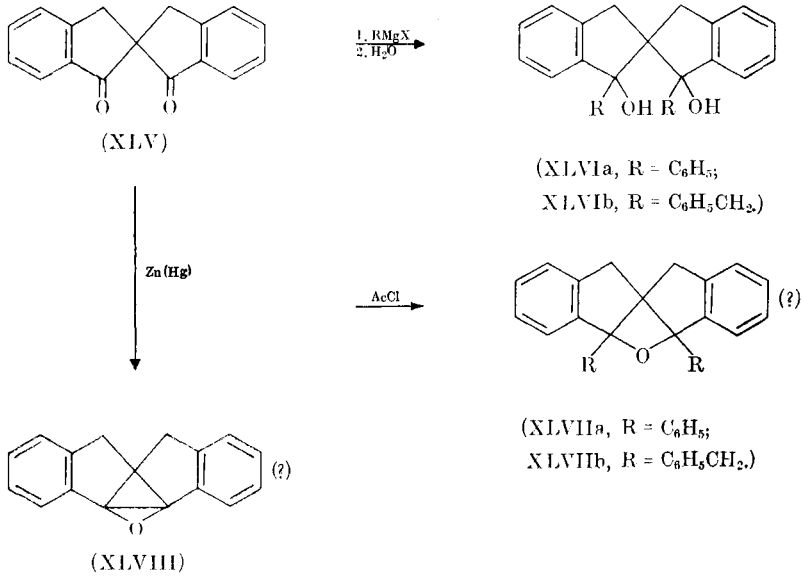
(XLIV)

(a) R = R′ = H
(b) R = CH_3, R′ = $CH(CH_3)_2$

recently.[199,231] Rupe's products cannot be formulated, but they were probably not the 7-oxabicyclo[4.2.0]octanes claimed, as the boiling point of each was about 10° higher than was recently found for pure,

well-characterized specimens of these compounds, prepared by the intramolecular Williamson reaction.[113, 199, 231] Heating 2-hydroxymethylcarvomenthol with a trace of sulfuric acid resulted in dehydration forming 3-methyl-α-terpinene.[231]

Another interesting but unproven report of an oxetane from dehydration of a 1,3-diol is that of Leuchs and Lock,[156] who treated the dihydroxyspirans (XLVI), obtained by reaction of the diketospiran (XLV) with the phenyl or benzyl Grignard reagent, with acetyl chloride and obtained a neutral compound in each case which had the correct analysis for the oxetane structures written (XLVII). In addition, reduction of the diketospiran with amalgamated zinc in acetic



(XLV)

(XLVIa, R = C_6H_5;
XLVIb, R = $C_6H_5CH_2$.)

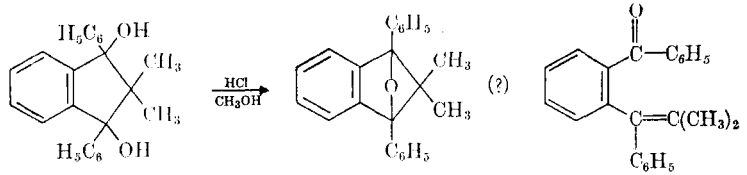
(XLVIIa, R = C_6H_5;
XLVIIb, R = $C_6H_5CH_2$.)

(XLVIII)

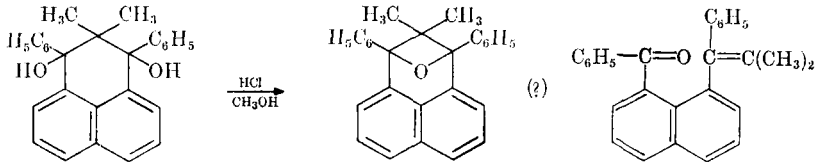
acid gave a 25% yield of a compound formulated as (XLVI). Because of the high degree of strain in these products and the likelihood of the formation of isomeric compounds by rearrangement processes, the structures seem improbable.

A similar situation was reported more recently by Geissman and collaborators.[86, 87] They observed that compounds having the 2,2-dimethyl-1,3-diphenyl-1,3-propanediol grouping attached to a benzene or naphthalene nucleus (XLIXa, b) were converted by heating in methanolic hydrogen chloride into crystalline substances which might be oxetanes (La, b). The evidence presented for these highly strained

oxetane structures consisted of the elemental analyses and, in the case of (Lb), lack of reaction in the 'Grignard machine'. In the light of subsequent work on the cleavage reaction of similar 1,3-diols in acid,[60] it now seems likely that these products were the isomeric ketones, (Lc) and (Ld), the latter being too hindered sterically to react with a Grignard reagent. Compound (Lc) was obtained by Brutcher and Cenci in a non-crystalline form when (XLIXa) was heated in fused potassium bisulfate at 150–160°.[24a]



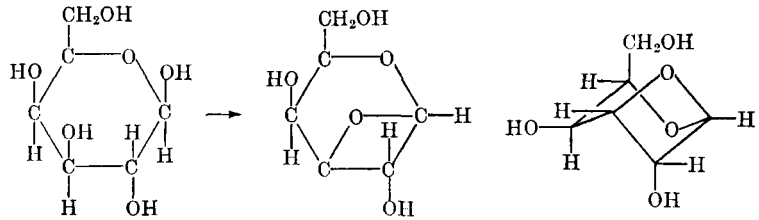
(XLIXa) (La) (Lc)



(XLIXb) (Lb) (Ld)

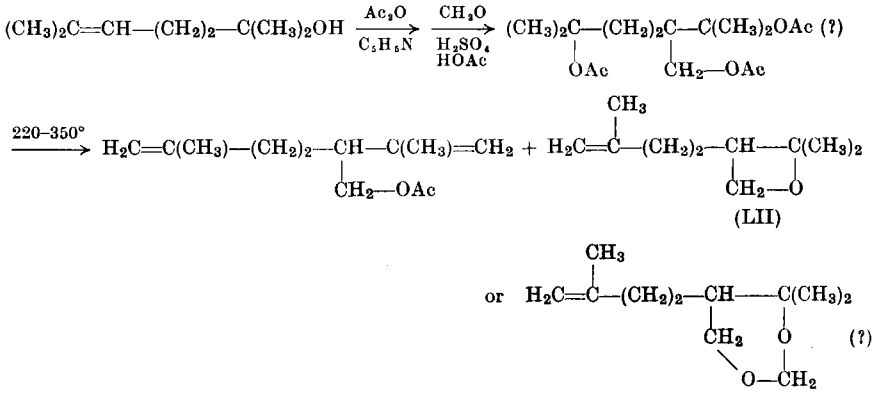
Pyrolysis of β-D-galactose has been reported to give 1,3-anhydro-β-D-galactose (LI), an oxetane in the carbohydrate series.[109] It was obtained as a syrupy distillate with positive rotation which formed an *iso*propylidene derivative, was not oxidized by periodate, did not reduce Fehling's solution and was not affected by long refluxing in dilute alkali. If this is so, the compound would be a second example of a 1,3-epoxide bridge in a six-membered ring (for the other, see page 1021), with the additional strain of an axial 5-hydroxymethyl group (LIa).

Another interesting case is the pyrolysis of the Prins reaction product of 1,6-dimethyl-5-hepten-2-ol, which gave, in addition to a



(LI) (LIa)

low yield of the expected unsaturated ether a material which did not react with phthalic anhydride.[102] It was suggested that this material might be the oxetane (LII), but other structures, such as 2,2-dimethyl-5-*iso*propylidenetetrahydropyran, also seem to be possible.

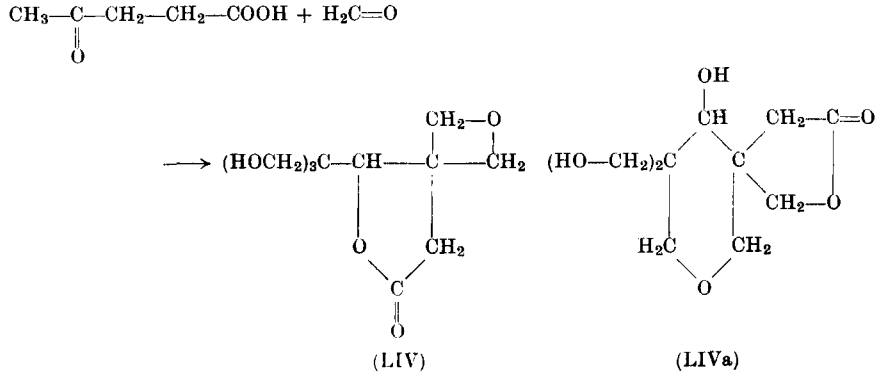


The literature contains unproven examples of oxetane formation from 1,3-diols, such as the patent claim that 1,8-epoxynaphthalene (LIII) is formed by dehydration of 1,8-naphthalenediol under non-



(LIII)

oxidizing conditions. This oxetane, which would surely be highly strained, is said to be a useful gum inhibition agent.

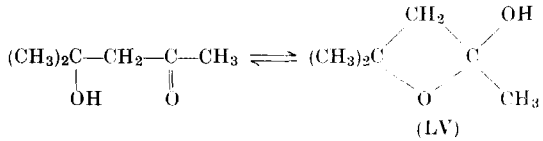


(LIV) (LIVa)

The slow reaction of levulinic acid with formaldehyde in the cold, catalyzed by barium hydroxide, gives a compound with the chemical properties of a trihydroxylactone. An oxetane structure (LIV) has been suggested,[188] although an isomeric bicyclic structure with a tetrahydropyran (LIVa) ring may be more probable.

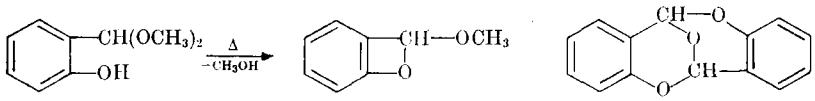
4. Isomerization Methods

It has been proposed that β-hydroxycarbonyl compounds or their derivatives may exist in cyclic forms which would be oxetane derivatives. In 1943 Doeuvre[55] considered that the physical constants of diacetone alcohol indicated the existence of two tautomeric forms, the normal form and 2,2,4-trimethyl-4-hydroxyoxetane (LV), but it would appear that intramolecular hydrogen bonding would be a more acceptable explanation now.



(LV)

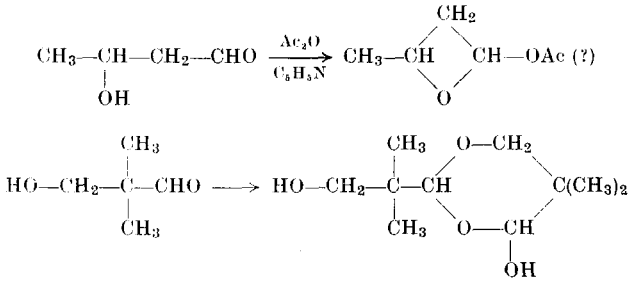
Bergmann and Lippmann[17] observed that salicylaldehyde dimethyl acetal lost methanol on heating in vacuum to form a new compound, melting at 217–218° and formulated as (LVI), but the dimeric structure (LVII) was not ruled out and seems more probable. Bergmann and



(LVI) (LVIa)

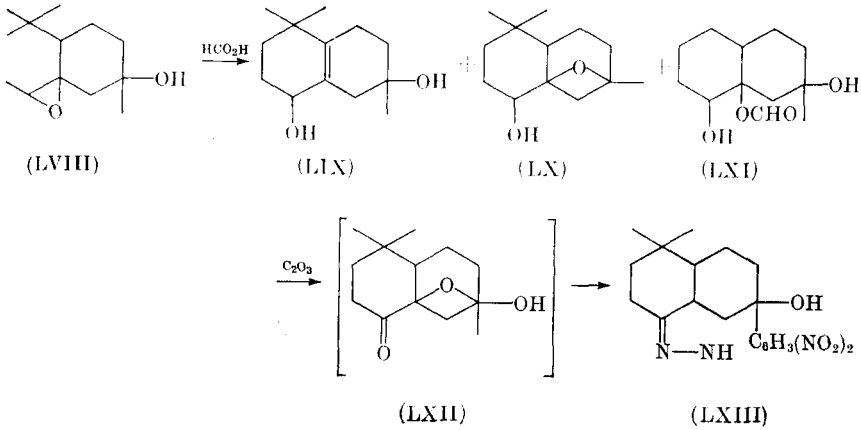
Kann[16] reported that the product of acetylation of aldol with pyridine and acetic anhydride was 4-methyl-2-acetoxyoxetane, because it had a considerably higher boiling point than the expected 3-acetoxybutyraldehyde obtained from acetylation of aldol dimethyl acetal with subsequent acid hydrolysis. The so-called oxetane, however, had twice the expected molecular weight in freezing benzene, phenol and acetic acid (although the expected molecular weight was observed in boiling aniline with which it probably reacted). This fact suggests that the compound was the acetate of aldol dimer. Aldol dimer may have a structure akin to that of the dimer of hydroxypivaldehyde, which has

shown by Spath and Pallan-Raschik[242a] to be the dihydroxy-1,3-dioxane (LVII). Hurd and Abernathy have presented several convincing lines of evidence that aldol, its dimethyl acetal and other β-hydroxyaldehydes exist in the open chain form, rather than in a cyclic form.[127]



(LVII)

The base-catalyzed isomerization of the hydroxyoxirane, 2,3-epoxy-5-hydroxynorbornane, has been discussed earlier (section **V.1.***C*), and seems well substantiated, since it may be viewed as an extension of the intramolecular Williamson reaction. An example of acid-catalyzed isomerization of an epoxyalcohol to a hydroxyoxetane has been claimed recently,[246] but the evidence for it seems incomplete. The epoxide of α-ambrinol (LVIII) reacted exothermically with cold formic acid to form a mixture of products which was not separated but appeared on the basis of elemental analysis and saponification data to consist mainly of composition $C_{13}H_{22}O_2$, probably a mixture of unsaturated diol (LIX) and perhaps the hydroxyoxetane (LX), contaminated with some formate ester (LXI). Since the hydrogen uptake

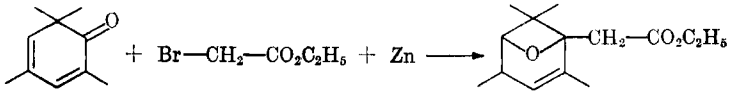


(LVIII) (LIX) (LX) (LXI)

(LXII) (LXIII)

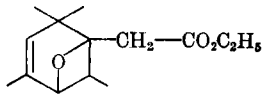
was only about 25% of the theory for the diol, the isomeric oxetane was believed to be a major product. The product was subsequently oxidized by chromic anhydride in an acetic acid–benzene solution. From this reaction the dinitrophenylhydrazone of 4,4,7-trimethyl-7-hydroxy-$\Delta^{9,10}$-1-octalone (LXIII) was obtained, possibly derived from (LXII).

A spontaneous isomerization of a Reformatsky product has been claimed to give a 1,3-epoxycyclohexane structure. Schmitt[211] carried out the reaction of 2,2,4,6-tetramethyl-3,5-cyclohexadienone with ethyl bromoacetate and zinc in benzene, obtaining an ester, $C_{14}H_{22}O_{31}$ which had no free hydroxyl group. On this basis, the structure was considered to be (LXIV) or (LXV). An attempt to confirm the structure by saponification and acidification was unsuccessful, since the structures of the two products obtained, a hydrocarbon and a ketone, were not determined. Because of the high strain of the ring systems in (LXII) and (LXIII) it seems more likely that the product was (LXVI), resulting from conjugate addition of the organozinc intermediate.

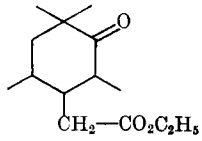


(LXIV)

or



(LXV)



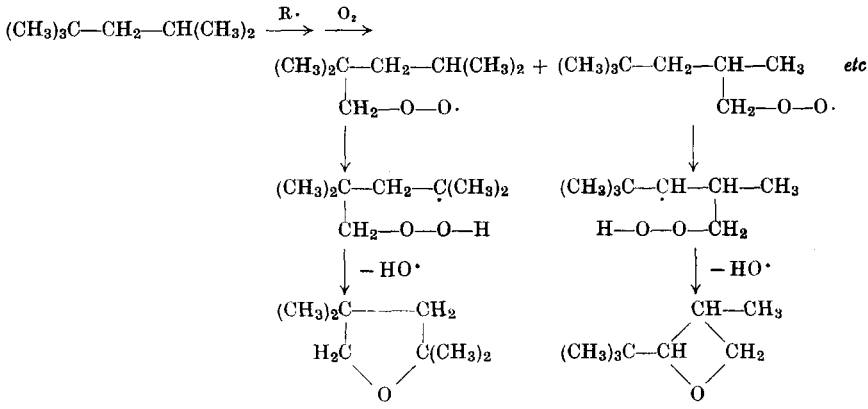
(LXVI)

5. Oxidation Methods and Pyrolysis of Dialkyl Peroxides

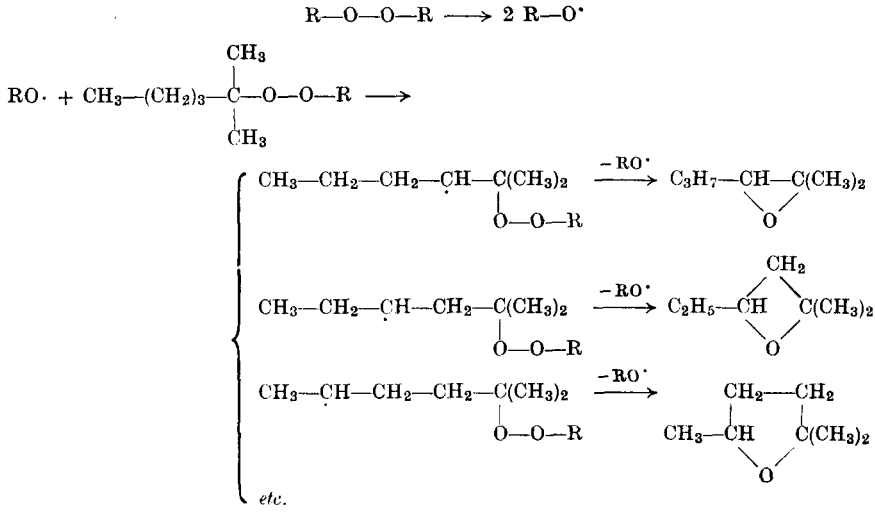
Oxetanes have been found to be among the products of high-temperature oxidation of alkanes. The reaction of isooctane with oxygen at 450–475° gave a small but isolatable amount of 2-*t*-butyl-3-methyloxetane, and from *neo*hexane a similar low yield of 2,3,3-trimethyloxetane was isolated.[204] A cyclic ether believed to be an oxetane was obtained from hexane but the structure was not established. Oxidation of butane has been patented as a method of preparation of 2-methyloxetane, although its direct isolation from the oxidation products

offers difficulty.[35] 2*H*-Pentafluorooxetane has been prepared by the reaction of 1,1,2,2,3-pentafluoropropane with oxygen at 500°.[121]

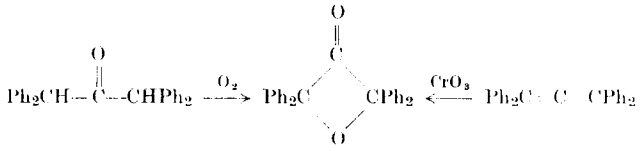
A mechanism for the formation of oxetanes and other cyclic ethers obtained has been proposed by Rust and Collamer and consists of hydroperoxy radical intermediates undergoing intramolecular hydrogen shifts to give hydroperoxy-substituted radicals, which may then undergo intramolecular displacements of hydroxyl radical.[204]



Thermal decomposition of di-*tert*-heptyl peroxide in the liquid phase gave products similar to those from the alkane oxidations, including 2,2-dimethyl-3-ethyloxetane in 4.4% yield. A similar mechanism appears to be involved.[51]



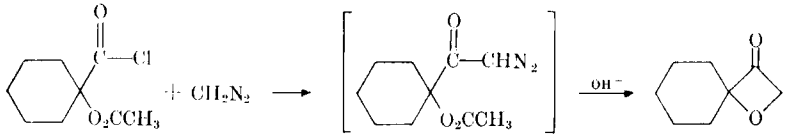
Autooxidation of *sym*-tetraphenylacetone in refluxing aqueous acetic acid gave a 61% yield of 2,2,4,4-tetraphenyl-3-oxetanone.[123] A hydroperoxide intermediate, decomposing by an ionic mechanism, has been postulated; presumably a mechanism analogous to that of Rust and Collamer (above) might also be invoked. This oxetanone was also prepared by oxidation of tetraphenylallene with chromic acid and with nitrogen tetroxide, followed by zinc chloride.



An unsubstantiated claim has been made in a patent that oxidation of α-naphthol may give 1,8-epoxynaphthalene (LIII, p. 1037).[9]

6. Diazoketone Synthesis of Oxetanones

The oxetane ring system may be formed also by the decomposition of diazomethyl α-ketols, yielding 3-oxetanones. The method is analogous to that which has been used for the synthesis of coumaranone from 2-acetoxybenzoyl chloride and diazomethane, followed by hydrolysis.[161] 1-Oxaspiro[3.5]-3-nonanone has been prepared by this route in 30% over-all yield from 1-hydroxycyclohexanecarboxylic



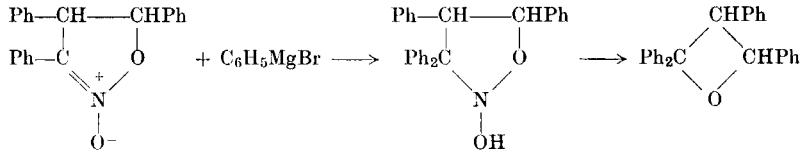
acid.[162, 226] 3-Oxetanone itself was also prepared by this method but was isolated only as its phenylhydrazone and in poor yield.[162]

7. Grignard Reaction with Triphenylisoxazoline Oxide

Kohler and Richtmyer observed that 3,4,5-triphenyl-2-isoxazoline 2-oxide reacted with phenylmagnesium bromide to form an unstable addition compound, formulated as (LXVII).[147] At room temperature in glacial acetic acid it decomposed to 2,2,3,4-tetraphenyloxetane, as shown by the elemental analysis and cleavage with acid to triphenylethylene and benzaldehyde mentioned earlier.

The reaction was not general. The ethyl and benzyl Grignard

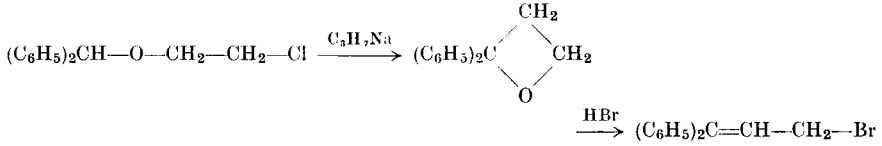
reagents gave reduction processes and the methyl Grignard reagent gave addition, forming 4-hydroxyamino-2,3,4-triphenyl-2-pentanol.



(LXVII)

8. Perkin-type Ring Closure

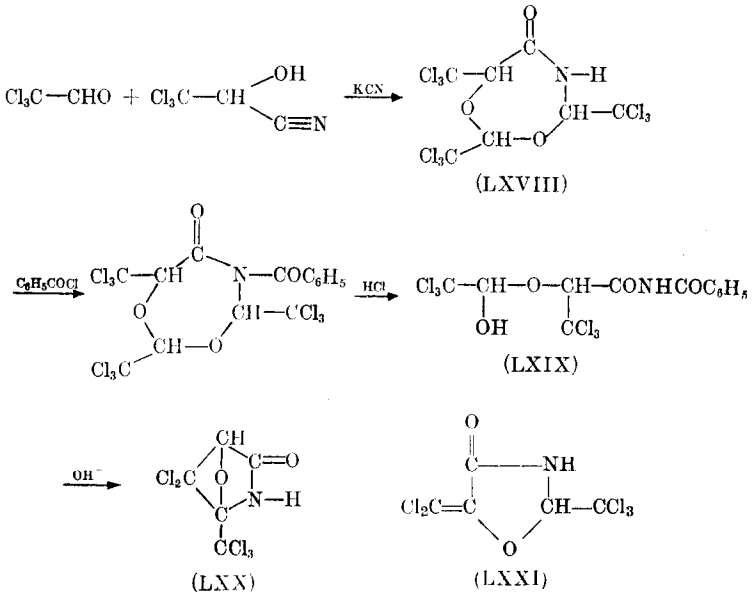
Cyclodehydrohalogenation with formation of a new carbon–carbon bond has been used successfully to synthesize an oxetane.[220] Reaction of propylsodium with benzhydryl 2-chloroethyl ether in decane gave a 44% yield of 2,2-diphenyloxetane. This structure was established by the elemental analysis, infrared spectrum and the cleavage with hydrogen bromide in acetic acid to form 3-bromo-1,1-diphenylpropene.



The method has potential synthetic value, as this compound cannot be made by the intramolecular Williamson method due to instability of the corresponding halohydrin.[225] The chloroethyl ether is easily prepared from benzhydrol and ethylene chlorohydrin in the presence of sulfuric acid. An attempted extension to the reaction of benzyl 2-chloroethyl ether with ethylsodium or propylsodium, however, was unsuccessful, due to the predominating tendency for 1,2-elimination.

Mention should be made of an early claim of oxetane ring closure by a Perkin-type ring closure, although it is doubtful if the product was truly an oxetane. In 1914, Crowther and co-workers[45] reported the formation of the seven-membered lactam (LXVIII) by the reaction of chloral cyanohydrin and chloral in the presence of base and gave reasonably good evidence in support of this structure. The benzoyl derivative of (LXVIII) was hydrolyzed with hydrochloric acid to form an unstable material, which was converted by hot caustic into a new substance, the analysis and general properties of which (solubility in

base, monomethylation, lack of reaction with bromine) appeared to fit the bicyclic oxetane structure (LXX). The structure assumed for the precursor (LXIX), however, seems unlikely in view of the acid medium used; other structures not possessing the oxetane ring, such as (LXXI), also appear to fit the data.



(LXVIII)

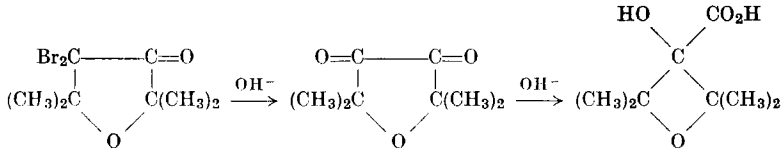
(LXIX)

(LXX)

(LXXI)

9. Ring Contraction of 3,4-Furandiones

A logical method of oxetane synthesis would be ring contraction of a tetrahydrofuran derivative. This approach was first reported by Richet, Dulou and Dupont,[192] who obtained 2,2,4,4-tetramethyl-3-hydroxyoxetane-3-carboxylic acid (LXXIV) by the reaction of 2,2,5,5-tetramethyl-4,4-dibromo-3-furanone (LXXII) with aqueous alkali. It was subsequently shown that the intermediate in the process was the tetramethyl-3,4-furandione (LXXIII), which had undergone the benzilic acid rearrangement in the alkaline medium. Treatment of

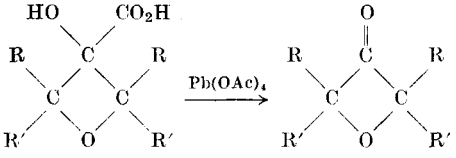


(LXXII) (LXXIII) (LXXIV)

(LXXIII) with aqueous potassium hydroxide gave the oxetane in 79% yield.[170]

The reaction has been extended by Harper and Lester to 2,5-dimethyl-2,5-diethyl- and 2,2,5,5-tetraphenyl-3,4-furandione, which gave the expected tetrasubstituted 3-hydroxyoxetane-3-carboxylic acids.[111] The furandiones were here prepared by selenium dioxide oxidation of the 3-furanones prepared from the appropriately substituted 2-butyne-1,4-diols.

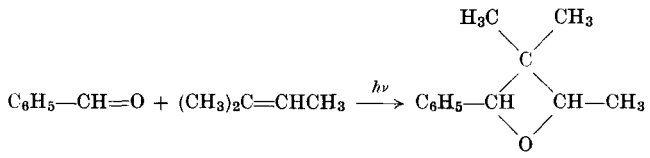
Each of the three 3-hydroxyoxetane-3-carboxylic acids was converted by means of lead tetraacetate oxidation into the corresponding tetrasubstituted 3-oxetanones in approximately 60% yield.[111, 170] The chemistry of these compounds has already been discussed.



R = R′ = CH_3
R = R′ = C_6H_5
R = CH_3; R′ = C_2H_5

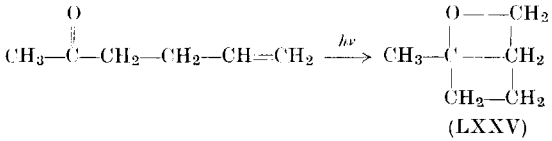
10. Photosynthesis

The photochemical reaction of aldehydes and ketones with olefins was reported by Paterno and Chieffi in 1909[175] and subsequently reinvestigated and confirmed by Büchi and his collaborators.[25] This photosynthesis is the reverse of the photochemical and thermal decomposition of oxetanes (section **III.2**). The structure of the oxetanes formed from 2-methyl-2-butene with benzaldehyde, acetophenone and *n*-butyraldehyde was established in the first two cases by identification of the carbonyl compounds formed by acid-catalyzed scission of the ring (section **III.6.***G*).[19] This showed that the addition reaction took place with the oxygen atom becoming attached to the less-substituted of the doubled bonded carbon atoms. (The product from *n*-butyraldehyde and 2-methyl-2-butene gave an ambiguous result on acid scission, *n*-butyraldehyde being the only carbonyl compound identified; it is therefore uncertain whether it follows the above rule.)



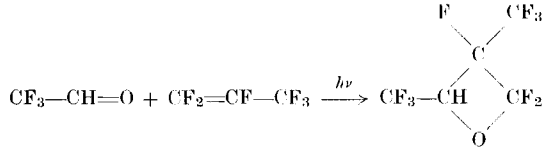
Although the yields of oxetanes are generally only about 5–10% and the reaction is very slow, the simplicity of the method makes it useful. Sunlight or mercury arc irradiation may be used.

Srinivasan[243] has applied this photochemical reaction to the unsaturated ketone, 5-hexen-2-one, which reacted intramolecularly to form the highly strained bicyclic oxetane, 1-methyl-2-oxabicyclo-[2.2.0]hexane (LXXV). This structure was supported by the infrared and n.m.r. spectra of the compound.

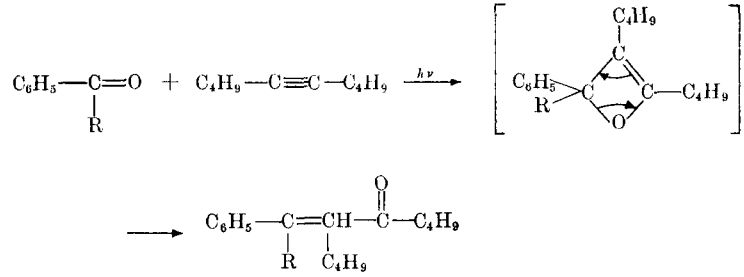


(LXXV)

Very recently an extensive series of polyfluorooxetanes has been prepared by the photochemical reaction of fluoroolefins with fluoroaldehydes, fluoroketones and fluoroacyl fluorides.[110] The yields were generally excellent, the structures of the products being determined by n.m.r. spectroscopy and confirmed in one case by a pyrolysis study. It was then apparent that the reaction took place in the same manner as in Büchi's series, the oxygen becoming attached to the less-substituted (by substituents other than fluorine) carbon atom of the fluoroolefin. Only a few representative polyfluorooxetanes of the series reported are listed in Table 7.

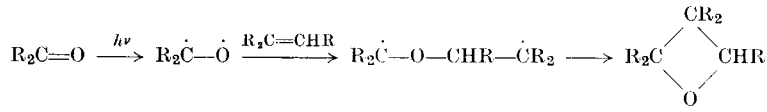


A similar reaction appears to occur between acetylenes and aldehydes or ketones on irradiation, but unfortunately the oxetes that would be expected could not be isolated. Instead, an α,β-unsaturated



ketone, which could conceivably arise from the oxete, was obtained in low yield.[26] Instability of the oxete is not surprising in view of the difficulty of isolating oxetes from other methods of synthesis (section VI).

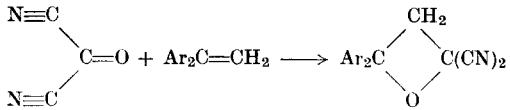
The possible mechanism for the photochemical synthesis of oxetanes has been discussed but not systematically studied. Büchi has suggested a step-wise process, initiated by photoactivation of the carbonyl compound to the diradical triplet state.[25] Subsequent addition to the olefin would give one of four possible diradicals in each case, followed by ring closure.



As it seems reasonable that the most stable diradical would be that with the unpaired electrons on the most substituted carbon atoms possible, this mechanism appears to be in agreement with the structures of the oxetanes obtained. This need not, however, rule out an alternate concerted four-center reaction not involving a triplet state. Srinivasan's observation that oxygen gas had no effect on the photochemical reaction of 5-hexen-2-one[243] would seem to be more in favor of the concerted mechanism.

11. Condensation of Carbonyl Cyanide with Olefins

Achmatowicz and Leplawy[1,2] have recently observed reactions similar to the above photosyntheses, but without requiring irradiation. Carbonyl cyanide was found to condense with 1,1-diphenylethylene and with 1,1-di-*p*-tolylethylene in hexane solution at room temperature, forming 2,2-dicyano-4,4-diaryloxetanes in 58–66% yield. The structures were established by hydrolysis with alkali to form the corresponding oxetanedicarboxylic acids, which yielded on acidification the α-hydroxy-α-carboxyl-γ,γ-diaryl-lactone. Hydrolysis in dilute acid gave β-hydroxyl-β,β-diarylpropionic acids.



Ar = C_6H_5, *p*-$CH_3C_6H_4$

TABLE 7. Synthesis of Oxetanes by Other Cyclization Methods

Oxetane	Method[a]	Yield, %	B.p.° (mm.)	Reference
2,2,3,3,4-Pentafluorooxetane	5			121
2-Methyloxetane	5		59.4–59.7	35
2,3,3-Trimethyloxetane	5	1.4	99–100	204
2,2-Dimethyl-3-ethyloxetane	5	4.4		51
3-Methyl-2-*tert*-butyloxetane	5	1.4	136.5–138	204
3-Methyl-3(4′-pyridyloxetane)	3	95	m. 78–9	159, 160
3,3-Bis(hydroxymethyloxetane), cyclic sulfite ester	2	25	m. 74–75	254
2,2-Diphenyloxetane	8	44	m. 103	220
2,2,3,4-Tetraphenyloxetane	7		m. 162	147
2,2-Dicyano-4,4-diphenyloxetane	11	58	m. 108	1, 2
2,2-Dicyano-4,4-di(*p*-tolyloxetane)	11	66	m. 94–94.5	1, 2
2,2,3-Trimethyl-4-phenyloxetane	10	10	44 (3.5) 230–232	25
2,2,3-Trimethyl-4,4-diphenyloxetane	10	—	305–310 m. 110–111	175
2,2,3-Trimethyl-4-butyloxetane	10	6.5	62–64 (23)	25
2,2,3,4-Tetramethyl-4(2-phenyl-vinyloxetane)	10	—	320–340	175
2,3,3,4-Tetramethyl-2-phenyloxetane	10	4.4	42 (0.05) 232–233	25
1-Methyl-2-oxabicyclo[2.2.0]-hexane	10	—	ca. 90°	243
2,2,3-Trifluoro-3,4-(bistrifluoro-methyl)- (*cis* and *trans*)	10	32	*cis* 41–42 *trans* 38–39	110
2,2,3-Trifluoro-4-trifluoromethyl-3-perfluoropropyl- (*cis* and *trans*)	10	37	*cis* 86	110
2,2,3-Trifluoro-4-trifluoromethyl-3-(4′*H*-octafluorobutyloxetane) (*cis* and *trans*)	10	59	*cis* 128 *trans* 124	110
2,2,3-Trifluoro-4-trifluoromethyl-3-(2′*H*-perfluoroethyloxetane) (*cis* and *trans*)	10	66	*cis* 89 *trans* 72	110
2,2,3-Trifluoro-3-chloro-4-(4′*H*-octafluorobutyloxetane)	10	15	136	110
2,3-Bis(trifluoromethyl)tetra-fluorooxetane	10	38	25	110
3-Trifluoromethyl-2-perfluoro-phenyltetrafluorooxetane	10	91	161	110
2,2-Bis-(chlorodifluoromethyl)-3-trifluoromethyltrifluorooxetane	10	56	107.5	110
3-Trifluoromethylnonafluoro-1-oxaspiro[3.3]heptane	10	33	68–69	110
2,2,4,4-Tetramethyl-3-hydroxyoxet-ane-3-carboxylic acid	9	79–89 70–100	m. 118 m. 123–124	192
2,4-Dimethyl,2,4-diethyl-3-hydroxy-oxetane-3-carboxylic acid	9	30	m. 127–128	111
2,2,4,4-Tetraphenyl-3-hydroxy-oxetane 3-carboxylic acid	9	93	m. 189–190	111

(*Table continued*)

TABLE 7 (*continued*)

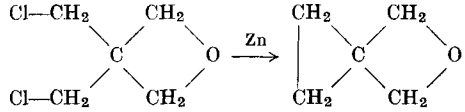
Oxetane	Method[a]	Yield, %	B.p. °(mm.)	Reference
2,2,4,4-Tetraphenyl-3-oxetanone	5	50[b]	m. 198–201	123
2,2,4,4-Tetraphenyl-3-oxetanone	5	61.5[c]	m. 199–201	123
3-Oxetanone-2,4-DNP	6	—	m. 152–155	162
1-Oxaspiro[3.5]-3-nonanone	6	45	86 (28)	162, 226

[a] Numbers correspond to subtitles in section V.
[b] From oxidation of tetraphenylallene.
[c] From autooxidation of *sym*-tetraphenylacetone.

12. Synthesis from Other Oxetanes

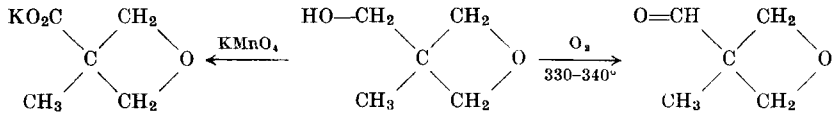
Ring closure need not necessarily be the final step in the synthesis of a desired oxetane, as interconversions of groups attached to the oxetane ring can often be carried out without affecting the latter. Cases where this has been done are as follows:

(*a*) Cyclization of 3,3-bis(chloromethyl)oxetane by means of the Freund reaction, using zinc dust, sodium carbonate and sodium iodide in hot acetamide. 2-Oxaspiro[3.2]hexane was obtained in 25% yield.[229]



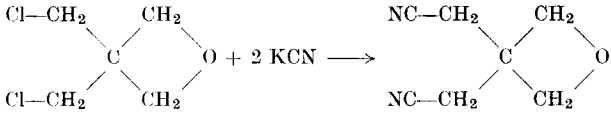
(*b*) Air-oxidation of 3-hydroxymethyl-3-methyloxetanes over a silver–pumice catalyst.[166] At 330–340°, 3-formyl-3-methyloxetane was formed in 35% yield. 3-Ethoxymethyl-3-formyloxetane was also similarly prepared from 3-hydroxymethyl-3-ethoxymethyloxetane. The use of these formyloxetanes as fabric conditioners has been patented.[166]

Potassium permanganate oxidation of 3-hydroxymethyl-3-methyloxetane gave the potassium salt of 3-methyl-3-oxetane carboxylic acid in 56% yield.[220]



(*c*) Carbonyl-addition reactions of 3-oxetanones, as described in section **III.9.**

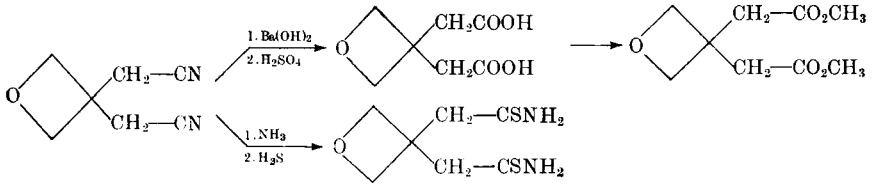
(*d*) Substitution of the halogen atoms in 3,3-bis(chloromethyl)oxetane, 3,3-bis(bromomethyl)oxetane and other 3-halogenomethyloxetanes by other groups, such as the cyano group in the following example:



In spite of the *neo*pentyl-type nature of the halogen atoms, nucleophilic displacements in this type of structure occur with ease, even chlorine being displaced quite readily. The reasons for the ease of reaction may plausibly be (1) the lessened steric hindrance of the methylene groups of the oxetane ring, being restrained by the ring at an angle of less than 90°, and (2) the electronegative nature of the ring, conferring reactivity on the halogenomethyl groups somewhat as in the case of benzyl halides.

A summary of the examples of such substitution reactions is given in Table 8. It will be observed that both halogen atoms in 3,3-bis(chloromethyl)oxetane were generally replaced under the conditions used, but in some cases both mono- and disubstituted products were obtained. It seems conceivable that in some cases substitution of the first halogen atom by a group such as alkoxyl or amino might facilitate the substitution of the second halogen by anchimeric assistance, but there has been no study of the relative rates of the first and second steps of substitution.

(*e*) Interconversions of other groups, by hydrolysis and other reactions. 3,3-Bis(cyanomethyl)oxetane was hydrolyzed with barium hydroxide, followed by precipitation of the barium with sulfuric acid to form 3,3-oxetanediacetic acid which was esterified with diazomethane.[43] Treatment of the dinitrile with alcoholic ammonia and then hydrogen sulfide gave 3,3-bis(thiocarbamoylmethyl)oxetane.



Similar reactions have been carried out with 3-hydroxymethyl-3-cyanomethyloxetane, treatment with refluxing barium hydroxide

TABLE 8. Substitution Reactions of 3-Halogenomethyloxetanes

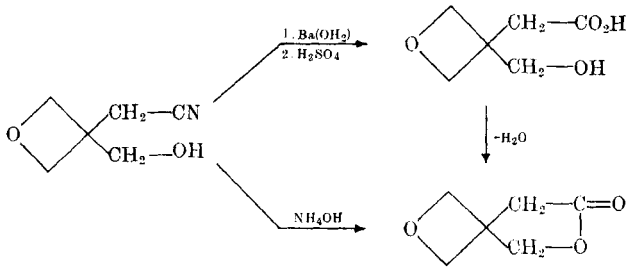
Reagent	Product	B.p.° (mm.)	M.p.	Yield, %	Reference
A. From 3,3-bis(chloromethyl)oxetane					
KO_2CH_3, 180°	$(CH_3CO_2CH_2)(ClCH_2)C_3H_4O$	42–44 (0.05)		30	67
	$(CH_3CO_2CH_2)_2C_3H_4O$	68 (0.05)		60	67
KOC_2H_5, alc.	$(C_2H_5OCH_2)_2C_3H_4O$	81.5–82 (19)		68	67
KOC_6H_5, 125°	$(C_6H_5OCH_2)_2C_3H_4O$	143 (0.05)	68	40	67
KSC_6H_5	$(C_6H_5SCH_2)(ClCH_2)C_3H_4O$	144 (1.3)		43	27
Na_2S, alc.	$S(CH_2)_2C_3H_4O$	60 (3)		20	27
KSCN, alc.	$(NCSCH_2)(ClCH_2)C_3H_4O$	115 (1.5)		17	27
	$(NCSCH_2)_2C_3H_4O$				27
$Na_2S_2O_3$, aq.	$(NaO_3S_2CH_2)_2C_3H_4O\cdot 3H_2O$		81.8–82.1	70	27
NaI, $CH_3COC_2H_5$	$(ICH_2)_2C_3H_4O$		50	89	27
NaCN	$(NCCH_2)_2C_3H_4O$		76.5	40	27
NH_3, 80°	$(H_2NCH_2)_2C_3H_4O$	75.5 (0.5)		55–75	27
Piperidine	$(C_5H_{10}NCH_2)_2C_3H_4O$	145 (3)		32	27
$NaCH(CO_2C_2H_5)_2$	$(C_2H_5O_2C)_2C(CH_2)_2C_3H_4O$	105–107 (1.1)		40	27
B. From 3,3-bis(bromomethyl)oxetane					
NaCN, alc.	$(NCCH_2)_2C_3H_4O$			89	43
NH_3	$(H_2NCH_2)_2C_3H_4O$				19
$(CH_3)_2NH$	$(CH_3)_2NCH_2)_2C_3H_4O$	111–113	62.4	82	32
Piperidine	$(C_5H_{10}NCH_2)_2C_3H_4O$	151.5	38.9	70	37
$(C_2H_5)_2NH$	$(C_2H_5)_2NCH_2)_2C_3H_4O$			77	32
$(CH_3)_3N$	$[((CH_3)_3NCH_2)(ClCH_2)C_3H_4O]Cl$			63	33
	$[((CH_3)_3NCH_2)_2C_3H_4O]Cl_2$			16	33
Sulfanilimide, NaOEt	p-$NH_2C_6H_4SO_2N(CH_2)_2C_3H_4O$		126.5	70	124

(*Table continued*)

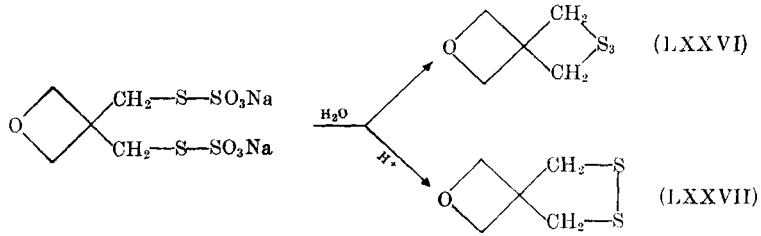
TABLE 9 (*continued*)

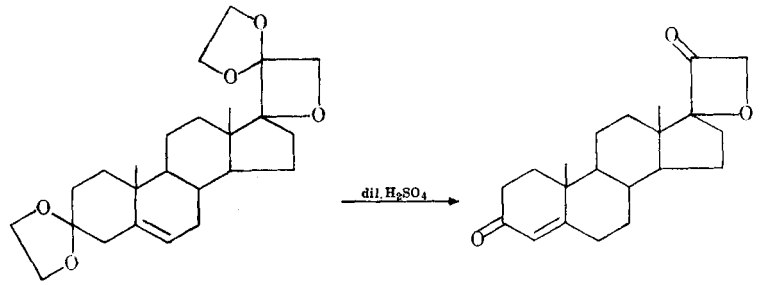
Reagent	Product	B.p.° (mm.)	M.p.	Yield, %	Reference
C. From 3-bromomethyl-3-hydroxymethyloxetane					
NaCN	$(NCCH_2)(HOCH_2)C_3H_4O$			81	99
$(CH_3)_2N$, C_6H_6	$(CH_3)_2NCH_2)(HOCH_2)C_3H_4O$	111–113 (12)	62.4	82	36a
Piperidine	$(C_5H_{10}NCH_2)(HOCH_2)(C_3H_4O)$	151.5 (12)	38.9	70	181
$NaOC_6H_5$	$(C_6H_5OCH_2)(HOCH_2)C_3H_4O$	131–132 (0.07)			181
$NaOC_6H_4CH_3(o\text{-})$	$(o\text{-}CH_3C_6H_4OCH_2)(HOCH_2)C_3H_4O$	118–119 (0.02)		80	181
$NaOC_6H_4OCH_3(o\text{-})$	$(o\text{-}CH_3OC_6H_4OCH_2)(HOCH_2)C_3H_4O$		58°	85	181
$NaO\text{-}\beta\text{-}C_{10}H_7$	$(\beta\text{-}C_{10}H_7OCH_2)(HOCH_2)C_3H_4O$		134–135	76	181
D. From 3-chloromethyl-3-ethyloxetane					
$(p\text{-}NaOC_6H_4)_2C(CH_3)_2$	$(CH_3)_2C(p\text{-}C_6H_4OC(C_2H_5)(CH_2)_2O)_2$			178°	65
$(m\text{-}NaOC_6H_4)_2C(CH_3)_2$	$(CH_3)_2C(m\text{-}C_6H_4OC(C_2H_5)(CH_2)_2O)_2$		188–193 (0.1)		65
$1,3,5\text{-}C_6H_3(OH)_3$	$1,3,5\text{-}C_6H_3(OCH_2C(C_2H_5)(CH_2)_2O)_3$			(visc. oil)	65

solution giving the barium salt of 3-hydroxymethyl-3-carboxymethyloxetane.[99] The free acid was obtained by precipitating the barium with sulfuric acid and converted into its lactone by adding a little hydrochloric acid and then evaporating *in vacuo*. This lactone was also prepared directly from 3-hydroxymethyl-3-cyanomethyloxetane and concentrated aqueous ammonia.



Hydrolysis of the di-Bunte salt derived from 3,3-bis(chloromethyl)oxetane and sodium thiosulfate gave either a trisulfide or a probable disulfide, depending on conditions.[27] The former, obtained by acid hydrolysis of di-Bunte salt contaminated with sodium thiosulfate, was a colorless crystalline compound, considered to be (LXXVI). The latter, from the action of dilute hydrochloric acid on the pure di-Bunte salt, was a yellow oil which polymerized immediately on distillation and therefore no direct evidence on its structure was obtained. Since





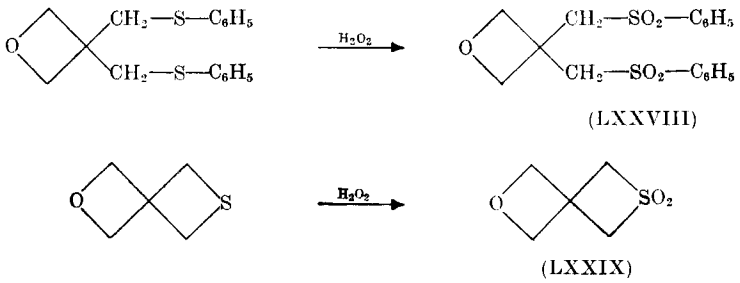
(XXXa)

this behavior was similar to that of trimethylene disulfide, it was considered to be (LXXVII), although survival of the oxetane ring after the acid treatment would be unusual.

Acid hydrolysis of the oxetanone cyclic acetals in the steroid series, such as (XXXa), to the corresponding oxetanones with dilute acid has been observed without serious cleavage of the oxetane ring, but as mentioned earlier oxetanones seem less sensitive to acid-catalyzed ring cleavage than oxetanes.

Alcohol derivatives of hydroxyalkyloxetanes may be prepared without affecting the ring. The acetate, benzoate, *p*-nitrobenzoate and urethane of a 3-hydroxymethyl-3-phenoxymethyloxetane[37] and 3-hydroxymethyl-3-bromomethyloxetane[36a] have been prepared.

The oxetane ring was not affected by treatment of sulfur derivatives with hydrogen peroxide and in this manner, 3,3-bis(benzenesulfonylmethyl)oxetane (LXXVIII) and 2-oxa-6-thiaspiro[3.3]heptane 6,6-dioxide (LXXIX) were made from the corresponding sulfides.[27]



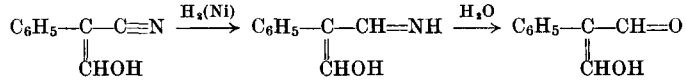
VI. Oxetes

There is, as yet, no well-established case of a compound with an unsaturated four-membered cyclic ether (oxete) ring, although several compounds thought to be oxetes have been reported in the literature. Inspection of the data on each, however, shows insufficient evidence to support the structure and generally the reactions used of the properties of the compound make the oxete structures seem very unlikely.

Two recent attempts to prepare oxetes by the use of established methods have been unsuccessful. One involved the photochemical method and was discussed in section **V.9**; the other is described here together with the other cases. A successful preparation of a four-membered cyclic ether with an *exo*-double bond, 3-methylene oxetane, is also described.

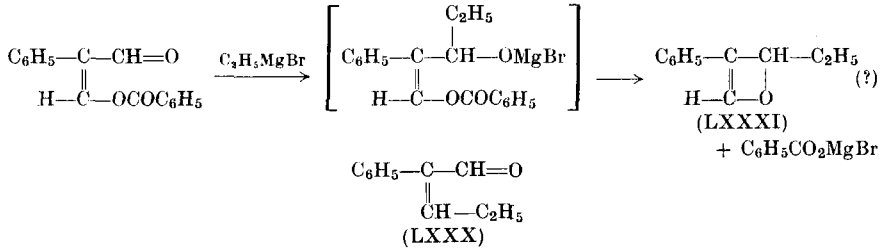
1. 4-Ethyl-3-phenyloxete

Rupe and co-workers[200, 202] reported that catalytic hydrogenation of hydroxymethylenephenylacetonitrile over a nickel catalyst used at that time (1927) gave only one mole of hydrogen absorption, yielding the corresponding imine. Although such hydrogenation of the nitrile group in preference to the latent aldehyde group is surely unusual, the structure was apparently shown by its hydrolysis, in 50–60% yield, to hydroxymethylenephenylacetaldehyde. The latter was purified and characterized by good elemental analysis, qualitative tests and by the



preparation of several derivatives. One of these was the benzoate ester, a pure sample of which was treated with ethylmagnesium bromide in ether solution. After decomposition of the reaction mixture with cold dilute hydrochloric acid, benzoic acid was isolated in 98% yield and a liquid product was obtained by distillation, giving an analysis moderately close to that expected for $C_{11}H_{12}O$.

The failure to show a good Tollens test and failure to form a semicarbazone, seemed to exclude the unsaturated aldehyde (LXXX) that might be expected, and it was therefore considered to be 4-ethyl-3-phenyloxete (LXXXI). The same material was also obtained from the reaction of methoxymethylenephenylacetaldehyde with ethylmagnesium bromide.

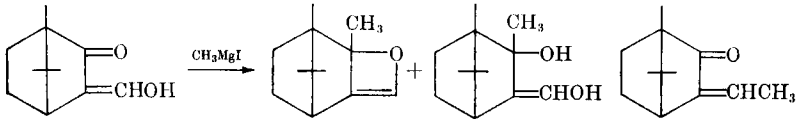


(LXXX)

Unfortunately no further study on this interesting compound was reported. The oxete structure seems inconsistent with its being isolated from an acidic solution, since an allylic vinylic ether should be even more susceptible to hydrolysis than oxetanes, but the boiling point of 98–100° (11 mm.) is too low for a dimeric structure. It may be conceivable that the material is 2-phenyl-2-penten-1-ol, arising from reduction as well as addition by the Grignard reagent, which may have contained excess magnesium.

2. 1,2,9,9-Tetramethyl-3-oxatricyclo[4.2.1.$0^{2,5}$]-5-nonene

A synthesis somewhat similar to that of Rupe appears to have been reported some twenty years earlier by Forster and Judd,[79] who were engaged in a research program on camphor derivatives. Forster and Judd treated hydroxymethylenecamphor with a large excess of methylmagnesium iodide, and obtained a small yield of a liquid product with an elemental analysis intermediate between $C_{12}H_{18}O$ and $C_{12}H_{20}O_2$. This was thought to be a mixture of the diol (LXXXIII) and the oxete (LXXXII) which is the title compound.



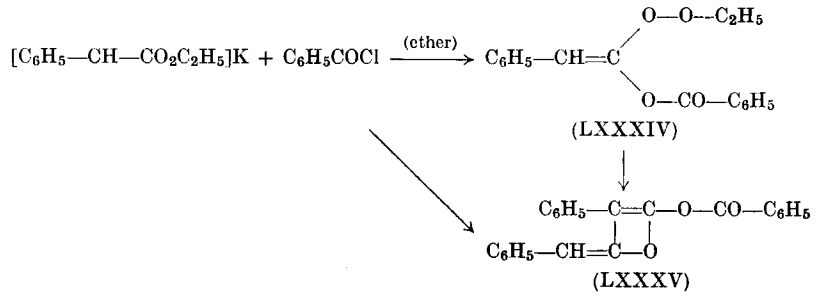
(LXXXII) (LXXXIII) (LXXXIIa)

For purification purposes, the mixture was treated with bromine, forming hydrogen bromide and a material which gave an elemental analysis in agreement with $C_{12}H_{18}OBr_2$. Debromination with zinc dust in alcohol yielded a liquid, boiling at 227–228°, which still gave an analysis somewhat lower (0.8%) in carbon than theory demands for the oxete (but this could be due to probable ease of autooxidation). It reacted with bromine to regenerate the dibromide previously obtained. The structure seems unlikely, however, because of its apparent stability towards hydrogen bromide and the product may have been the isomeric unsaturated ketone (LXXXIIa).

3. 3-Phenyl-4-benzal-2-benzoxyoxete

The enol ester of a β-lactone (LXXXV) was reported in 1930 by Scheibler, Emden and Krabbe[207] to be formed by heating 2-ethoxy-2-benzoxystyrene (LXXXIV) at 300° under reduced pressure and in the presence of a catalytic amount of copper-bronze. Compound (LXXXV) had been obtained by the reaction of benzoyl chloride with the potassium enolate of ethylphenylacetate in ether and was apparently the *O*-acylation product, since its analysis showed it to be isomeric with ethyl benzoylphenylacetate and its melting point and chemical properties were distinctly different. Furthermore, it could be rearranged to ethyl benzoylphenylacetate by heating with sodium ethoxide. The structure of the 'oxete' (LXXXV) was supported by excellent elemental analysis and by the formation of benzoic acid and phenylacetic

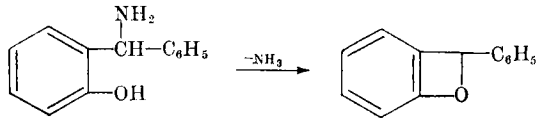
acid on hydrolysis with concentrated potassium hydroxide. A small amount of the compound could also be obtained from the reaction of benzoyl chloride with ethyl potassiophenylacetate if the reaction mixture were processed with aqueous alkali before distillation.



The reactions involved in the formation of (LXXXV) by both methods seem unusual, and it is surprising that an enol benzoate of a β-lactone was not hydrolyzed by the alkali in the second synthesis. Scheibler's work in other areas of ketene acetal chemistry was later discredited by the inability of others to repeat the work,[164] but this work does not seem to have been reinvestigated.

4. 8-Phenyl-7-oxabicyclo[4.2.0]octa-1,3,5-triene

The first oxete claimed is due to Cohn,[41] who in 1895 reported that *o*-hydroxybenzhydrylamine lost ammonia on being heated in dilute acid to give, in 90% yield, a yellow, crystalline substance melting with decomposition at 170–200°. On the basis of an elemental analysis, agreeing with $C_{13}H_{10}O$, it was assigned structure (LXXXVI) although it showed phenolic properties which are clearly inconsistent with this formulation. It was soluble in alkali, and from its reaction with



(LXXXVI)

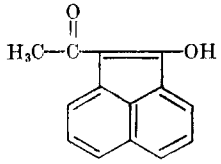
alcoholic sodium ethoxide the salt, $C_{13}H_9NaO$, was isolated, dissolving in water to give an alkaline solution. One hydrogen could be replaced also by acyl and alkyl groups, as shown by the isolation of an ethyl derivative, an acetyl derivative and a benzoyl derivative. These were

all insoluble in alkali and had gradual melting ranges in the proximity of 150–200°. Later it was reported that treatment with fuming hydrogen iodide gave 1,2,3-triphenylpropane.[42]

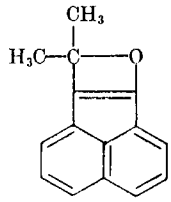
Subsequently the same material was obtained by Darapsky, Berger and Neuhaus[43] from the alkaline hydrolysis of the cyclic urethane resulting from the spontaneous decomposition of *o*-hydroxydiphenylacetyl azide. *o*-Hydroxybenzhydrylamine may well be the intermediate involved in the formation of the supposed oxete here, as in Cohn's work; and Darapsky assumed it to have the structure assigned by Cohn and did not investigate it further.

5. 8*H*-Acenaphth[1,2-*b*]oxetin

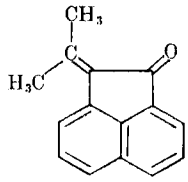
This material (LXXXVIII) has been reported by Ghiga[90] to be formed by the reaction of 7-hydroxy-8-acetylacenaphthalene (LXXXVII) with methylmagnesium bromide. It was a yellow, crystalline substance, m.p. 74–75°, giving an elemental analysis in good agreement with the theoretical. It gave no color with ferric chloride solution and was said to contain no free hydroxyl group. 8-*Iso*propylideneacenaphthenone (LXXXIX) seems to fit the evidence equally well and would seem more likely to have been formed on acidification of the magnesium salts.



(LXXXVII)



(LXXXVIII)

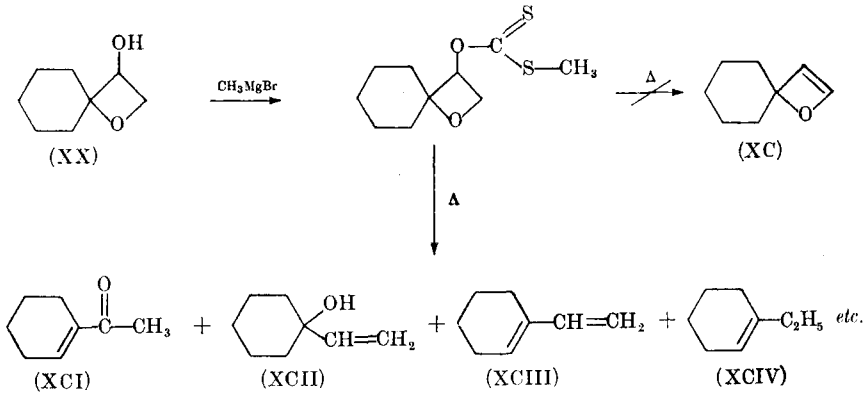


(LXXXIX)

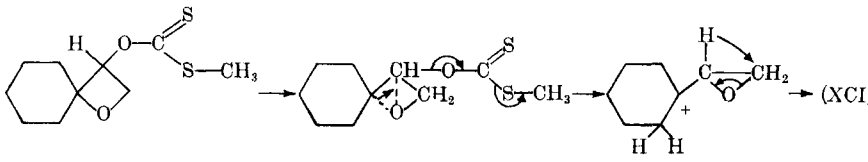
6. Attempted Synthesis of 1-Oxaspiro[3.5]-2-nonene

Since 3-oxetanols are readily available by the reduction of 3-oxetanones (section **III.8**), their dehydration would seem a logical route for the preparation of oxetes. For this purpose, the methyl xanthate ester of 1-oxaspiro[3.5]-3-nonanol was prepared and pyrolyzed it at 220–280° by the Chugaev procedure[226] since this is usually an exceptionally mild method of dehydrating alcohols and is relatively free of rearrangements. A liquid product was obtained which gave an elemental analysis checking closely with the theoretical for 1-oxaspiro[3.5]-2-nonene (XC); moreover, its boiling point (140–141°) and

infrared spectrum were reasonably close to what might have been expected. Difficulty was encountered, however, in further characterizing the product, which was then found by gas chromatography to be a mixture of several components. The fractions collected from the gas chromatographic column were identified by infrared, n.m.r. and mass spectroscopy as 1-acetylcyclohexane (XCI), 1-vinylcyclohexanol (XCII), 1-vinylcyclohexene (XCIII) and 1-ethylcyclohexene (XCIV).



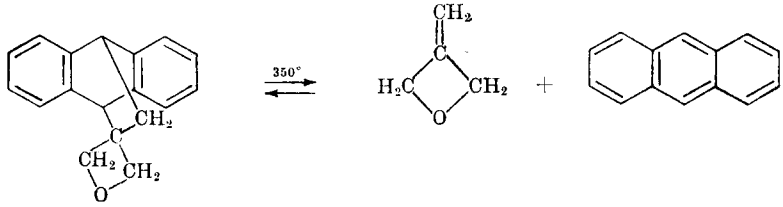
No evidence for any of the oxete could be found, although its presence as a minor product could not be ruled out. It is clear, however, that this is a very abnormal Chugaev reaction. The formation of 1-vinylcyclohexene may be explained by the following sequence of reactions, involving a postulated transannular participation of the ether–oxygen atom in the elimination of the xanthate group. The other products are reduction products possibly arising from the formation of methylmercaptan.



7. 3-Methyleneoxetane

This compound (XCVI) was prepared by Applequist and Roberts[7] by the pyrolysis at 350° of 2,3,5,6-dibenzospirobicyclo[2.2.2]octane-7,3′-oxetane (XCV). The compound was a liquid, b.p. 70°, with an

infrared spectrum in accord with the assigned structure. The elemental analysis was somewhat low for carbon, due apparently to the rapid hydroperoxidation to which it seemed to be subject. Confirmation of the structure was obtained by showing that it recombined with anthracene on heating to form (XCV). No attempt was made to isomerize it to 3-methyloxete.



(XCV)

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