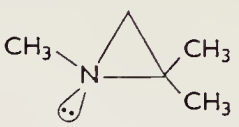
1

THREE-MEMBERED RINGS WITH ONE HETERO ATOM

THE OUTSTANDING CHARACTERISTIC of the three-membered hetero rings is their reactivity to a wide variety of reagents, an effect undoubtedly resulting from the necessary compression of bond angles in these molecules. The introduction of a double bond serves to further increase the strain of the particular system under study. Thus, aziridines are far more reactive than ordinary amines, and 1H-azirines remain to be synthesized (although 2H-azirines are known, see pp. 16–19).

Of the three saturated analogs, epoxides, aziridines, and episulfides, the second group is intrinsically interesting because the substituent on nitrogen does not lie in the plane of the ring, leading to the possibility that suitably constructed derivatives may be subject to resolution into optically active enantiomers, for example, [**1a**] and [**1b**]. However, because of the ease with which nitrogen undergoes inversion of configuration, [**1**] exists at room temperature as a rapidly interconverting mixture[1]; in fact, the rate of the inversion process is such that

[1a]



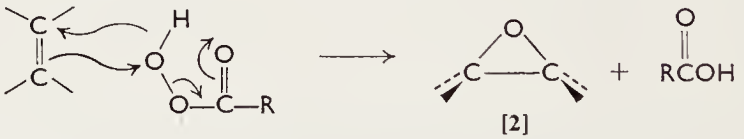
[1b]

substituted aziridines with molecular asymmetry attributable to trivalent nitrogen are likely only to be resolvable at temperatures below $-50°$.[2] On the other hand, nitrogen inversion in aziridines occurs sufficiently slowly (in a relative sense) below room temperature that direct determination of the inversion frequency by nuclear magnetic resonance (n.m.r.) spectroscopy is feasible.[2, 3]

SYNTHETIC APPROACHES

Direct Insertion of the Hetero Atom into a Carbon-Carbon Double Bond

The direct preparation of epoxides [2] from olefins can be carried out by a number of methods, the most frequently employed and generally applicable of which is peracid oxidation.[4] Of the variety



[2]

of peracids that have been used for this purpose, *m*-chloroperbenzoic acid has recently emerged as the most convenient oxidizing agent.[5] This reagent is commercially available,[6] reacts at a somewhat faster rate than either peracetic or perbenzoic acids, and is ideally suited for epoxidations which require long reaction times due to its excellent stability. Because epoxides readily undergo ring cleavage (see p. 25) in the presence of sufficiently acidic carboxylic acids, reactions performed with performic, trifluoroperacetic, monopermaleic, and peracetic acids (in nonbuffered solutions) generally result in the formation of monoesters of 1,2-diols[7]; these reagents are therefore less satisfactory.

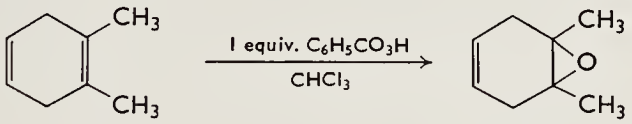
The epoxidation reaction proceeds by an electrophilic attack of the peracid upon the double bond as indicated above.[8] In agreement with this mechanism, it has been widely demonstrated that the rate of epoxidation is very sensitive to the electron density at the olefinic

site (Table 1–1). Thus, whereas, alkyl substitution is attended by pronounced rate enhancement (cyclic olefins are epoxidized at rates comparable to open chain analogs), double bonds which are conjugated with aromatic rings react more slowly. Selectivity is therefore very easily achieved.

TABLE 1–1 ▪

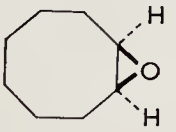
Rate Sequence for Reaction with Peracetic Acid[9]

Compound	Rate	Compound	Rate
$CH_2{=}CH_2$	1	$R_2C{=}CH_2$	500
$RCH{=}CH_2$	24	$R_2C{=}CHR$	6500
$RCH{=}CHR$	500	$R_2C{=}CR_2$	Very fast

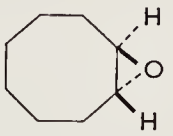


(61%) (*Ref. 10*)

The peracid oxidation of olefins is highly stereospecific as demonstrated by the fact that *cis*-cyclooctene affords [**3**] and *trans*-cyclooctene gives rise to [**4**].[11]



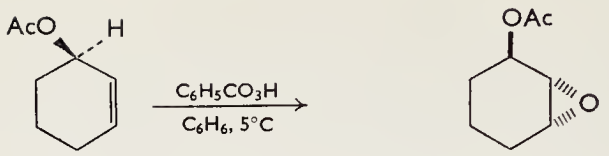
[3]



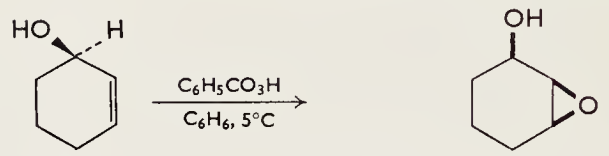
[4]

Because of the bulkiness of the peracid in the transition state leading to epoxidation, attack generally proceeds from the less hindered side (e.g., [**5**]).[12] However, the direction of attack by the peracid may be influenced by polar groups. In the case of [**6**], for example, hydrogen bonding between the hydroxyl group and the peracid not only reverses the stereochemistry of the electrophilic attack, but also results in a significant rate increase.[12a, b]

When the olefinic bond is conjugated with a strongly electron-withdrawing group such as carbonyl or cyano, the rate of epoxidation is either slow or fails completely. For such systems, epoxidation by means of alkaline hydrogen peroxide is very useful. The reaction

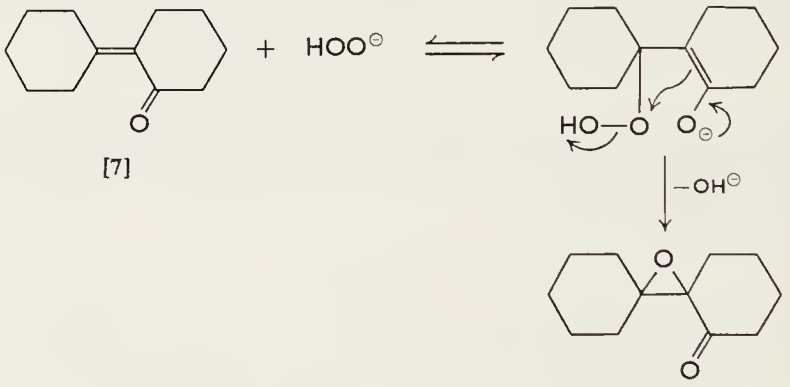


[5] ($k = 2.90 \times 10^{-4}$ mole^{-1} liter second^{-1})



[6] ($k = 34.5 \times 10^{-4}$ mole^{-1} liter second^{-1}) (*Ref. 12a*)

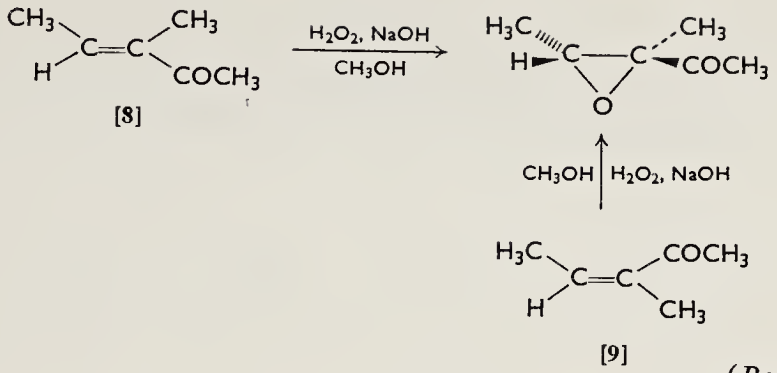
proceeds by Michael addition of hydroperoxide anion to the unsaturated system followed by intramolecular displacement of hydroxide ion,[14] as illustrated in the case of [7]. A fundamental difference exists between alkaline hydrogen peroxide oxidation and



[7] (*Ref. 13*)

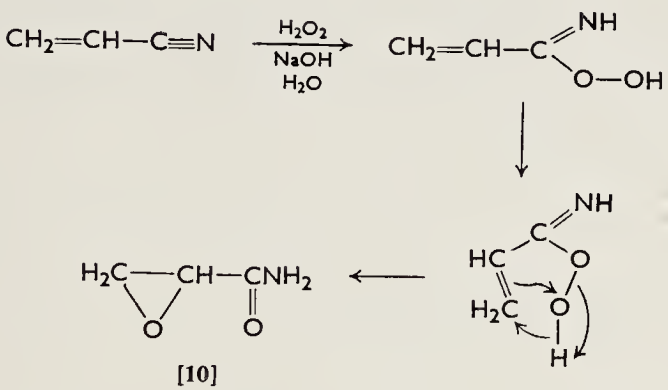
peracid epoxidation. Whereas, the latter is stereospecific, the former is not; generally, however, a single epoxide is formed, but it bears no stereochemical relationship to the reactant[4c]; for example, the alkaline peroxide oxidation of the isomeric ketones **[8]** and **[9]** gives rise to the same epoxide.[4c,15]

With α,β-unsaturated nitriles under these conditions, α,β-epoxyamides (e.g., **[10]**) generally result. The reaction very likely proceeds via a peroxyimidic acid intermediate which functions as the electrophilic reagent.[16] The intermediate peroxyimidic acid derived from benzonitrile readily epoxidizes olefins under neutral conditions and shows promise in the preparation of acid-sensitive epoxides.[16]



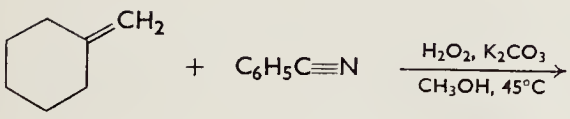
[8] [9]

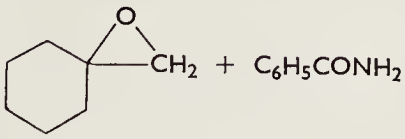
(*Ref. 15*)



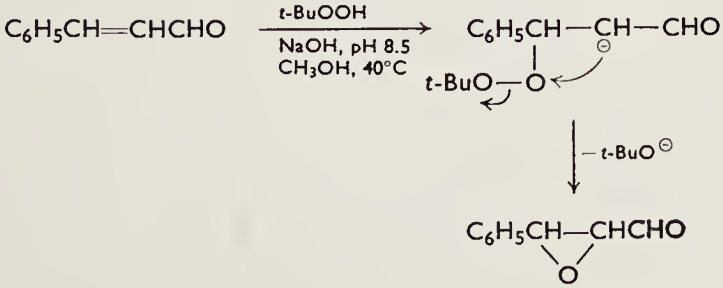
[10]

(*Ref. 16*)



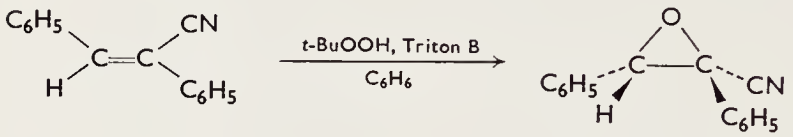


(73%) (*Ref. 16*)



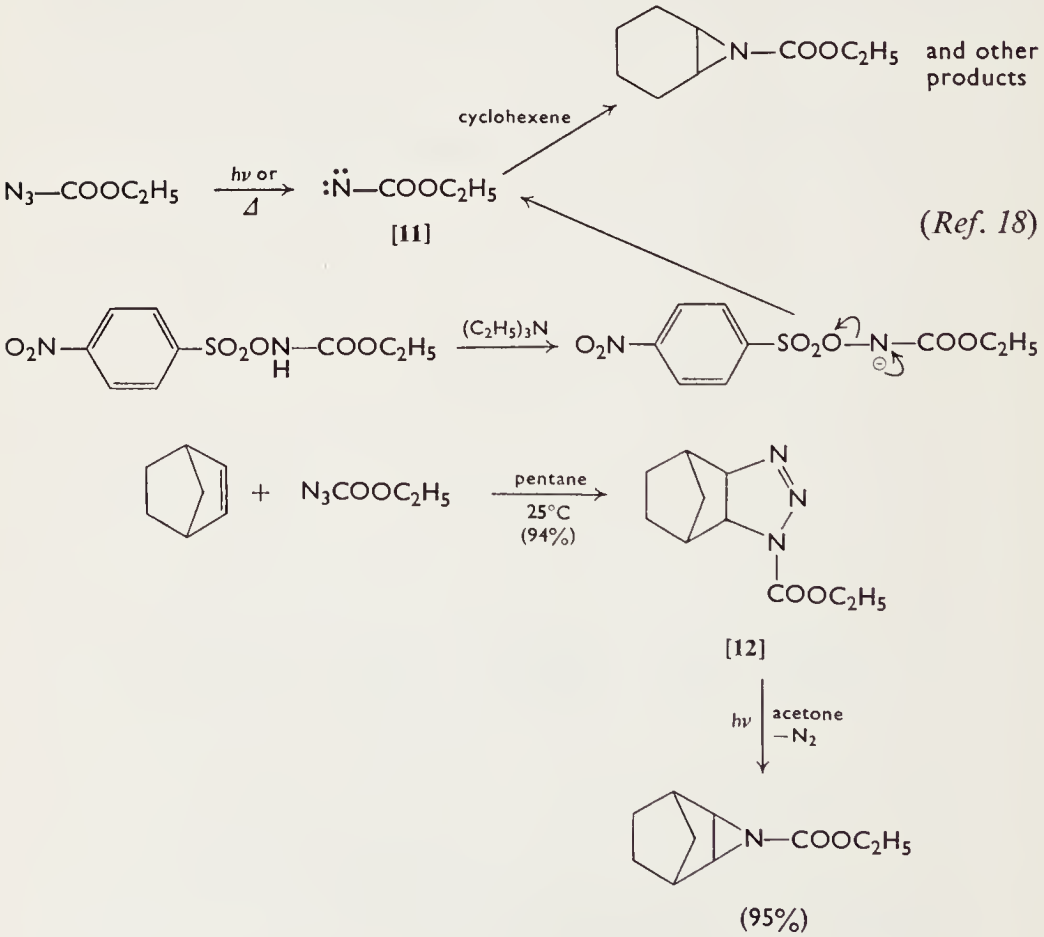
(73%) (*Ref. 16*)

An important variation of the alkaline hydrogen peroxide method makes use of *tert*-butyl hydroperoxide.[16,17] With this reagent, epoxidation of α,β-unsaturated nitriles does not result in hydration of the cyano function.



(76%) (*Ref. 16*)

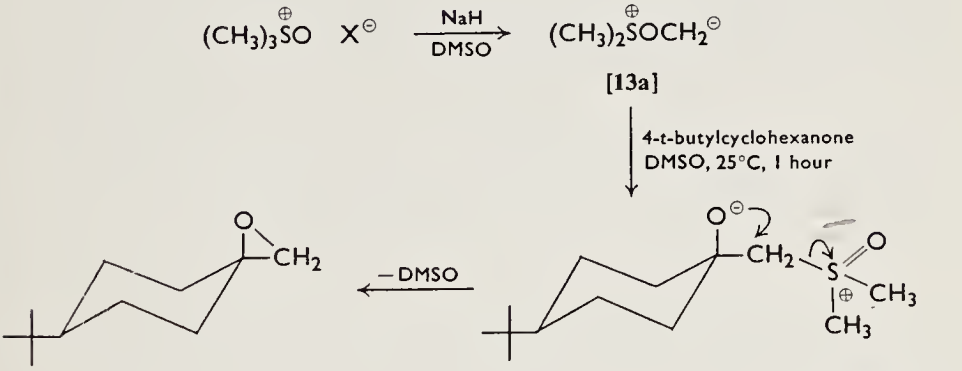
Aziridines can be prepared by the direct insertion of nitrenes (e.g., **[11]**) into olefinic linkages.[18] However, the use of such energy-rich nitrenes results in the formation of substantial quantities of side



products. By contrast, a pure aziridine can be prepared by initially permitting the azide to react with the olefin by 1,3-dipolar addition[19] to afford a 1,2,3-triazoline (e.g., **[12]**) which subsequently can be decomposed quantitatively by ultraviolet irradiation.[20]

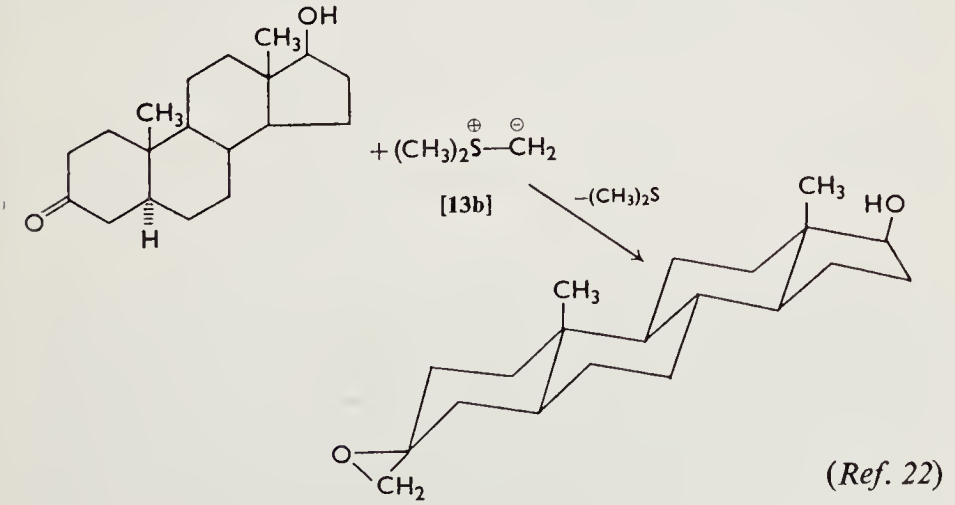
Methylene Insertion Reactions

The reaction of dimethyloxosulfonium methylide **[13a]** with aromatic and nonconjugated aldehydes and ketones results in the



(Ref. 21a)

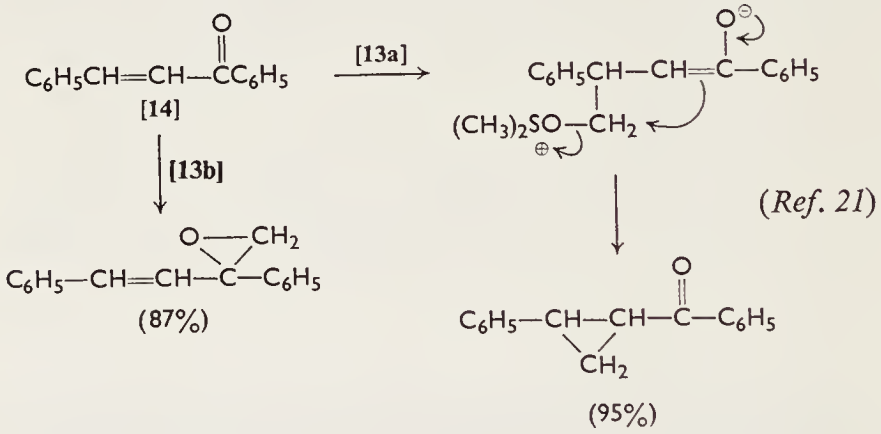
transfer of a methylene group from the ylide to the carbonyl group and yields epoxides.[21] Methylene transfer likewise occurs with the more reactive dimethylsulfonium methylide **[13b]**, but an important



(Ref. 22)

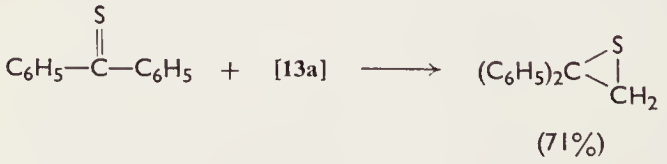
difference is observed between the two reagents. Whereas nucleophilic attack by **[13a]** upon the carbonyl group generally proceeds from the less hindered side to produce a new carbon-carbon bond which is equatorial, **[13b]** reacts stereospecifically in the opposite direction. This reversal in stereochemistry has been attributed to the greater stability, lesser reactivity, and greater bulk of **[13a]** relative to **[13b]**.[22]

An additional fundamental divergence of these ylides appears in their reaction with α,β-unsaturated ketones. Thus, reaction of **[13b]** with benzalacetophenone leads only to the corresponding epoxide; however, **[13a]** gives exclusively the cyclopropyl ketone because of its preference to undergo initial Michael addition.[21]



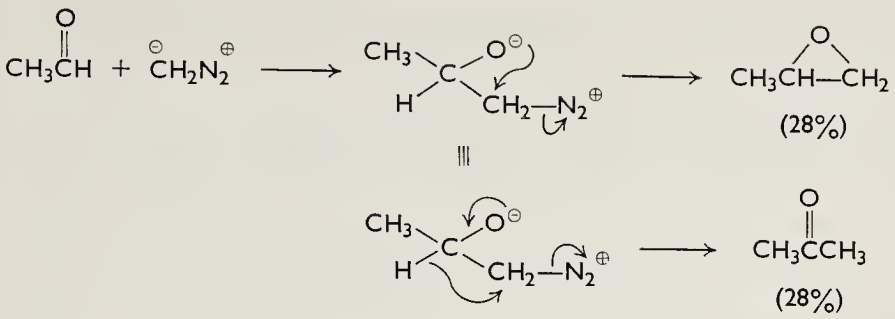
(*Ref. 21*)

Episulfides can be prepared by methylene transfer to thioketones, but similar attempts with $>C{=}N-$ bonds has given several products only one of which is an aziridine.[21a]



(*Ref. 21a*)

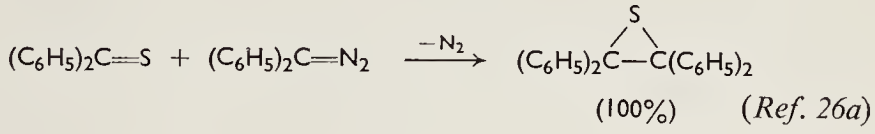
Diazomethane and its derivatives react with many aldehydes and ketones to produce epoxides, but longer-chained aldehydes and ketones are also formed and the desired oxide may be difficult to separate from the mixture. The reaction is very sensitive to the nature of the substituent and prediction of the products is often difficult. The procedure has seen widespread use, however, and the



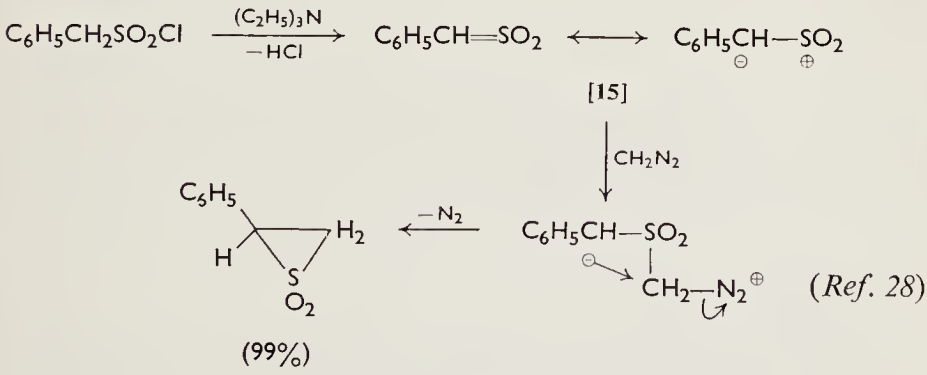
(*Ref. 23*)

results have been extensively summarized.[7a, 24] Treatment of α,β-unsaturated aldehydes with diazomethane does not result in epoxide formation but generally yields pyrazolines.

Schiff bases usually yield 1,2,3-triazolines when treated with diazomethane,[25] but aromatic thioketones have been successfully converted to episulfides by interaction with aryldiazomethanes.[26a]



(100%) (*Ref. 26a*)



(99%) (*Ref. 28*)

The generation of sulfenes (e.g., **[15]**), a group of reactive intermediates known to undergo nucleophilic attack by electron-rich reagents,[27] in the presence of diazomethane leads to the formation of episulfones.[28] Episulfones can, moreover, be produced directly by reaction of diazomethane and its derivatives with sulfur dioxide.[29] The mechanism of this latter condensation probably involves initial

formation of a sulfene, followed by a similar nucleophilic addition of a second molecule of the diazo compound.

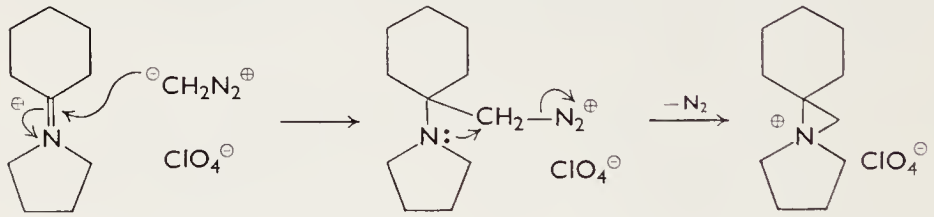
$$(p\text{-}CH_3OC_6H_4)_2C{=}N_2 \xrightarrow[-N_2]{SO_2} (p\text{-}CH_3OC_6H_4)_2C{=}SO_2 \longrightarrow$$

$$(p\text{-}CH_3OC_6H_4)_2C(SO_2)C(C_6H_4OCH_3\text{-}p)_2$$

(70%)

(*Ref. 29b*)

Treatment of ternary iminium perchlorates (e.g., [**16**]) and fluoroborates with diazomethane yields aziridinium salts.[30] The perchlorate and fluoroborate anions were selected because of their low order of nucleophilicity which results in their inability to open the



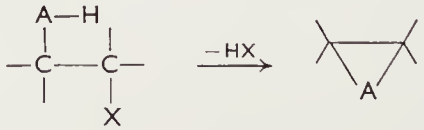
[16] (88%)

(*Ref. 30a*)

very reactive positively charged three-membered ring (see p. 35). The reaction is of wide applicability, and can be used to prepare a variety of aziridinium salts.[30]

Cyclization Methods

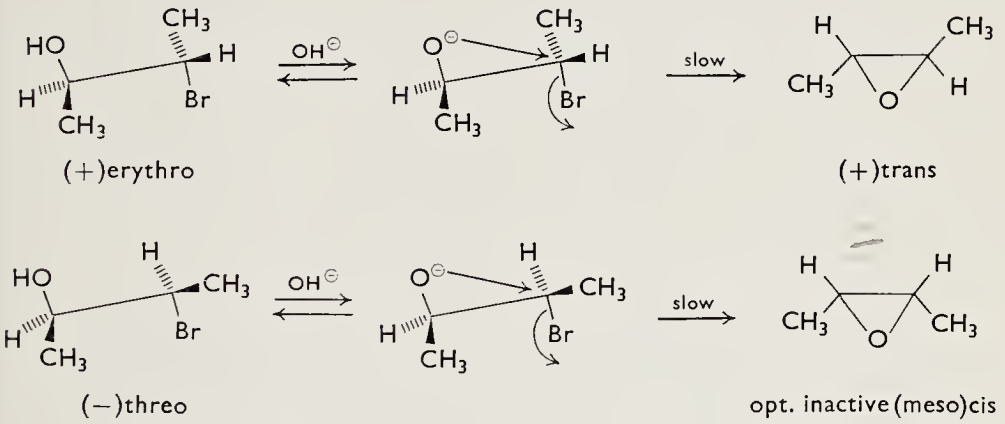
The preparation of three-membered heterocycles by a variety of cyclization reactions is convenient, general, and, often (except perhaps



A=O, NH, S

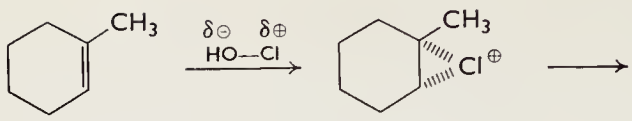
in the case of epoxides)[31] the method of choice. Although a wide range of such reactions are available, they all proceed according to the same mechanistic scheme; that is, cyclization occurs by backside attack of the hetero atom (O^-, NH_2, S^-, etc.) at the carbon atom bearing the leaving group. Therefore, inversion of configuration takes place at the latter site.

The reaction of a halohydrin with alkali is kinetically second order, first order in each component, and proceeds by rapid formation of an alkoxide anion followed by the slower rate-determining cyclization.[32]

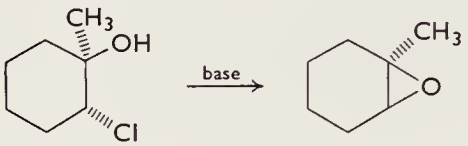


(*Ref. 33*)

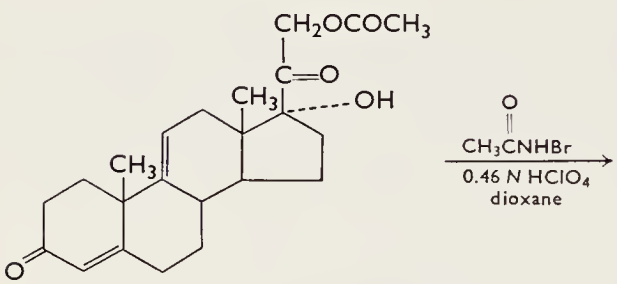
The displacement reaction is not limited to halogen atoms, but may be effected with any good leaving group such as tosylate or trimethylamine. However, since *trans*-halohydrins are readily available through the addition of hypohalous acids[34] to olefins, such substances are most often employed. The hypohalogenation reaction is believed to proceed by an electrophilic attack of the positively charged halogen atom upon the site of unsaturation and results in the formation of a halonium ion intermediate (e.g., [**17**]), which is subsequently attacked by water at the site of greatest incipient carbonium ion stabilization to give *trans*-halohydrins. The reaction is stereospecific and proceeds by addition of halonium ion from the less hindered side[36, 37]; since subsequent epoxide formation results in inversion of configuration at one center, the overall result locates the oxygen atom on the more hindered side (e.g., [**18**]). This result is in direct contrast to peracid oxidation which generally (see p. 4) inserts the oxygen from the less hindered side (e.g., [**19**]).[38, 39]

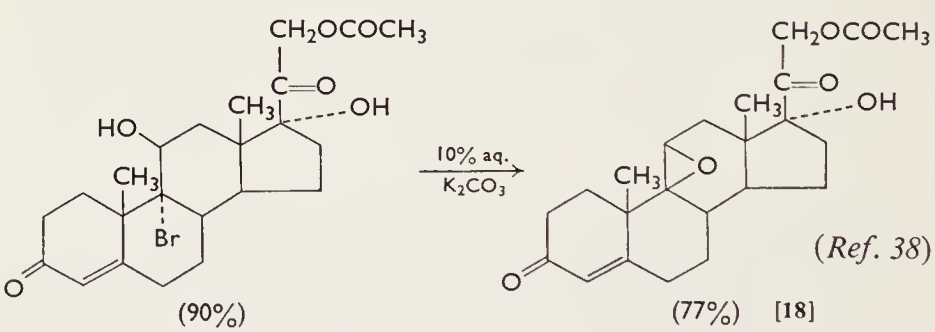


[17]



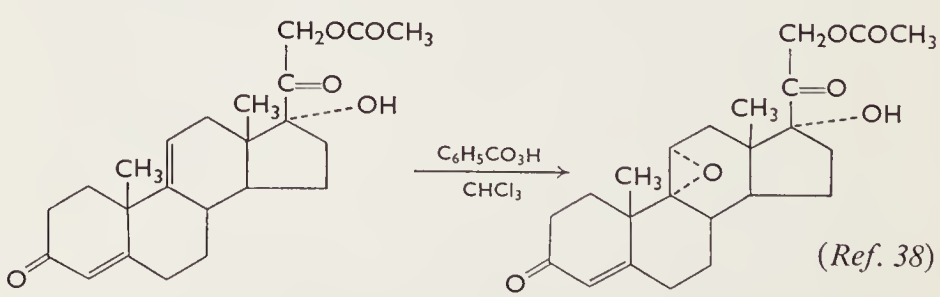
(*Ref. 36*)





(*Ref. 38*)

[18]



(*Ref. 38*)

[19]

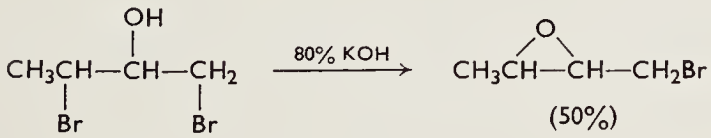
The rate of formation of epoxides from halohydrins can be enhanced by the introduction of substituents (Table 1–2). That the closure of small rings is favored by such substitution is made evident

TABLE 1–2 ▪

Rate Sequence for Reaction with Alkali[40]

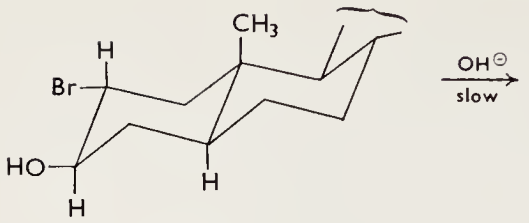
Compound	Rate	Compound	Rate
$HO—CH_2CH_2Cl$	0.31	$HO—CH_2C(CH_3)Cl—CH_3$	77
$HO—CH_2CH(CH_3)Cl$	1.7	$HO—C(CH_3)_2—CHCl—CH_3$	424
$HO—CH(CH_3)CH_2Cl$	6.5	$HO—CH(CH_3)—CCl(CH_3)_2$	633
$HO—C(CH_3)_2CH_2Cl$	78	$HO—C(CH_3)_2—C(CH_3)_2Cl$	3600

in the case of [**20**].[41] The nature of the halohydrin-epoxide reaction is most dramatically demonstrated by halohydrins derived from cyclic olefins. Thus, epoxide formation occurs several thousand

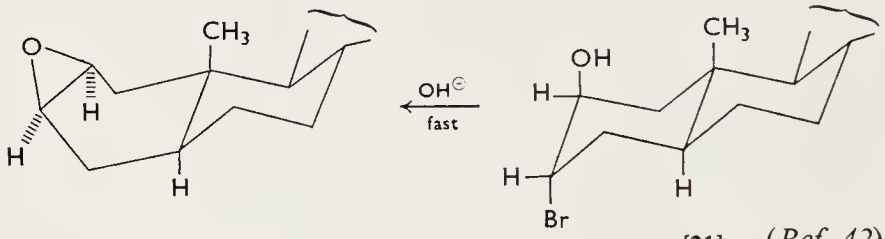


[**20**] (*Ref. 41*)

times faster in the diaxial isomer [**21**] than in the diequatorial isomer [**22**].[42] Whereas *trans*-halohydrins of the above type cyclize via trans ring closure and Walden inversion at the site of displacement to the *cis*-epoxide, *cis*-halohydrins react only very slowly with alkalies, and the reaction when it does occur gives rise to carbonyl compounds.[43]

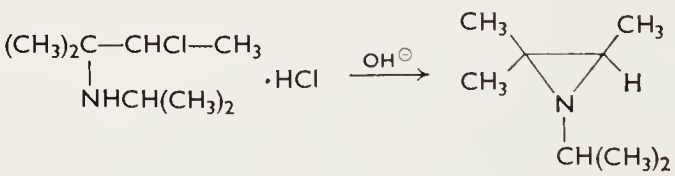


[22]

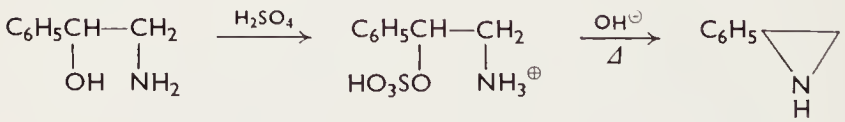


[21] (*Ref. 42*)

The best preparative methods for aziridines involve cyclization reactions. The time-honored syntheses consist in the conversion of a β-amino alcohol (available generally from the reaction of epoxides with ammonia or primary amines, see p. 25) to a β-haloamine (Gabriel method[44]) or to a β-amino hydrogen sulfate (Wenker method[45]) followed by treatment with alkali.[46] The Gabriel synthesis fails,



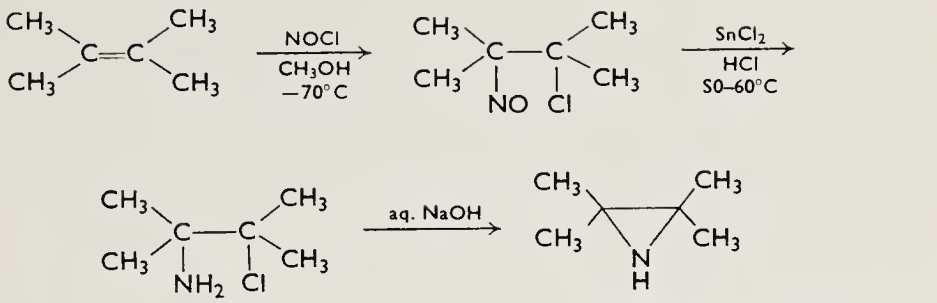
(73%) (*Ref. 47*)



(100%) (90%)

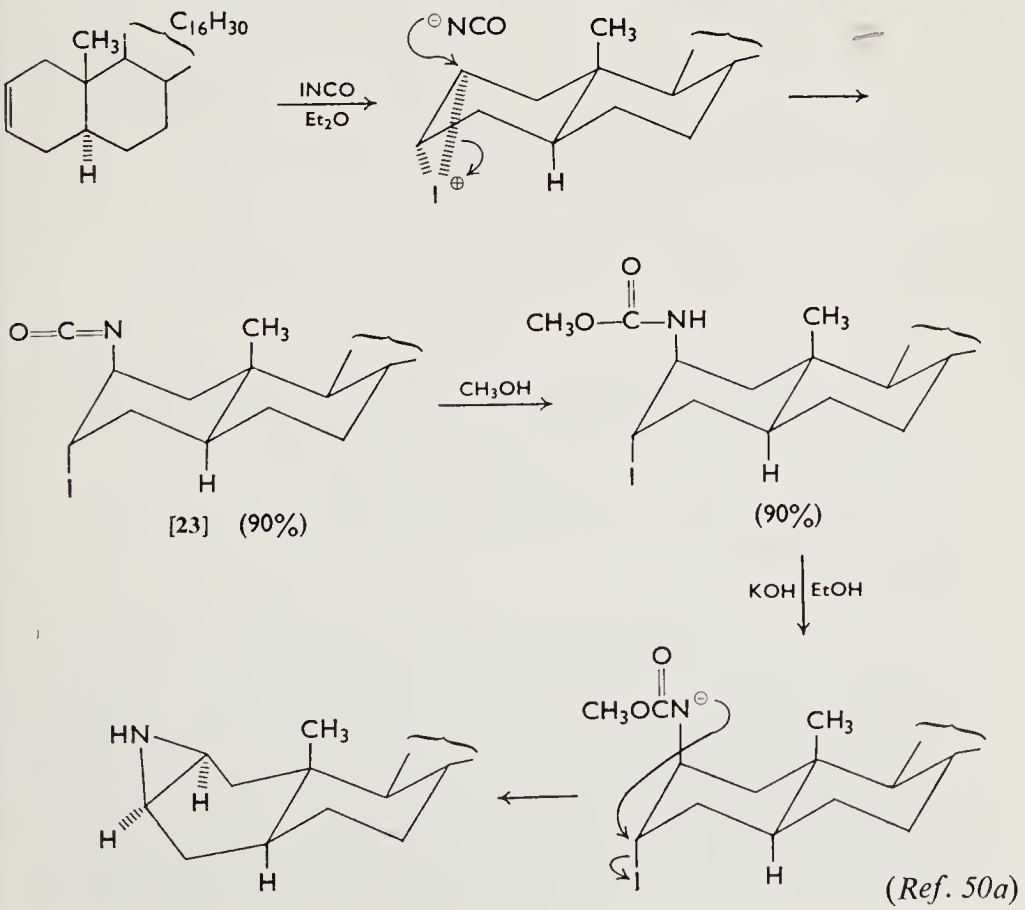
(*Ref. 48*)

however, in the preparation of 2,2,3,3-tetraalkylaziridines because of the difficulty of obtaining the necessary chloroamines. A unique preparation of such heterocycles (which, however, appears to fail when less substituted alkenes are used) consists in a three-step sequence involving chloronitrosation of a tetraalkylethylene, reduction of the nitrosochloride, and cyclization with base.[49] A more recent



(*Ref. 49a*)

preparative scheme, which appears to be of general utility, is effective in converting olefins of any degree of substitution to aziridines.[50] The olefin is treated with iodine isocyanate, a reagent which is known to react via an iodonium ion and to give rise to the trans-diaxial β-iodo isocyanate [**23**]; the latter substance on heating with methanol



[23] (90%)

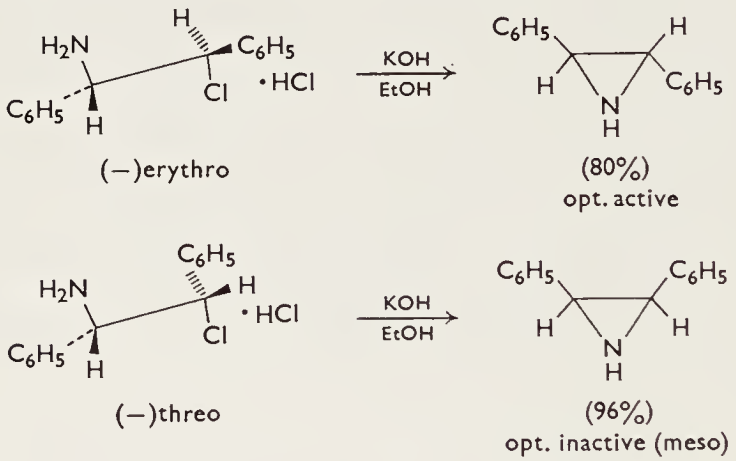
(90%)

(88%)

(*Ref. 50a*)

affords the related β-iodocarbamate. Treatment of the β-iodocarbamate with alcoholic alkali results in aziridine formation in good yield. The kinetics of this cyclization indicate[50c] that ring formation proceeds by rapid abstraction of the carbamate proton followed by the rate-determining ring closure. The intermediate N-carbalkoxy aziridine is rapidly saponified and decarboxylated as it is formed.

The Gabriel ring closure proceeds according to first-order kinetics, in agreement with an intramolecular displacement of the halogen atom by the free amino group.[51] The cyclizations are stereospecific and occur with inversion at the carbon bearing the leaving group.[52]

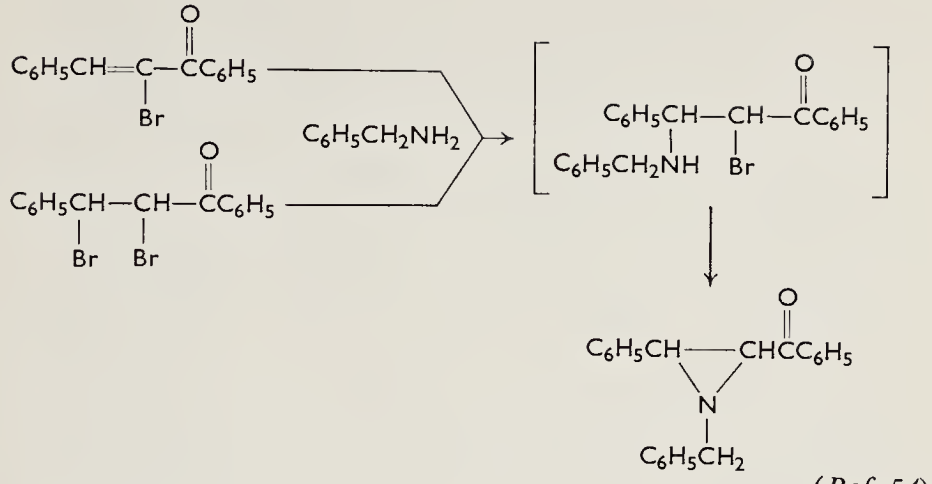


(*Ref. 53*)

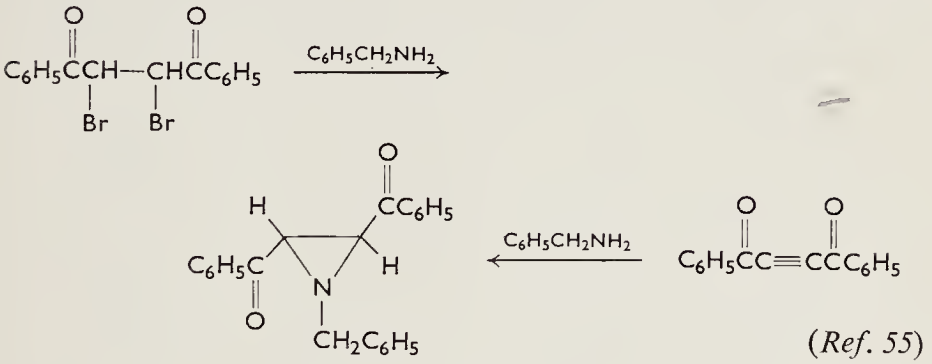
Several variants of the Gabriel synthesis are illustrated in the following reactions. The physical and chemical properties of the resulting benzoylaziridines have been summarized.[56]

Stable aziridinium perchlorates have been synthesized from β-chloroethylamines by treatment with silver perchlorate[57] (for further discussion, see p. 35).

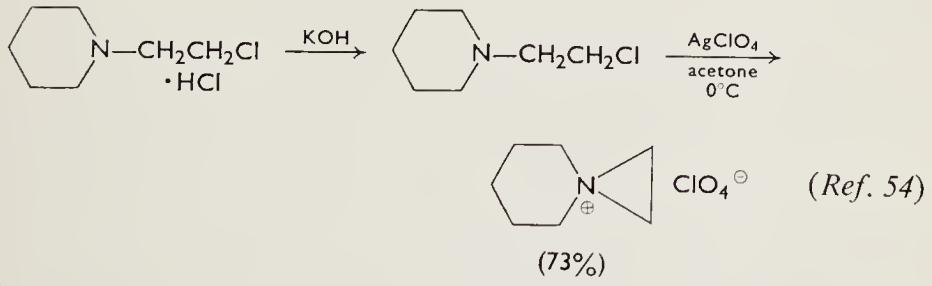
A ketoxime arylsulfonate (e.g., [**24**]), when treated with base followed by acid hydrolysis, is transformed into an α-aminoketone (the Neber rearrangement).[58, 59] The mechanistic course of this rearrangement is believed to involve initial α-proton abstraction by base to give a carbanion, followed by loss of tosylate affording an α,β-unsaturated nitrene (e.g., [**26**]), which then attacks the double bond to give an azirine (e.g., [**27**]).[60, 61] The Neber rearrangement, therefore, does not conform to the general mechanistic trends for



(*Ref. 54*)

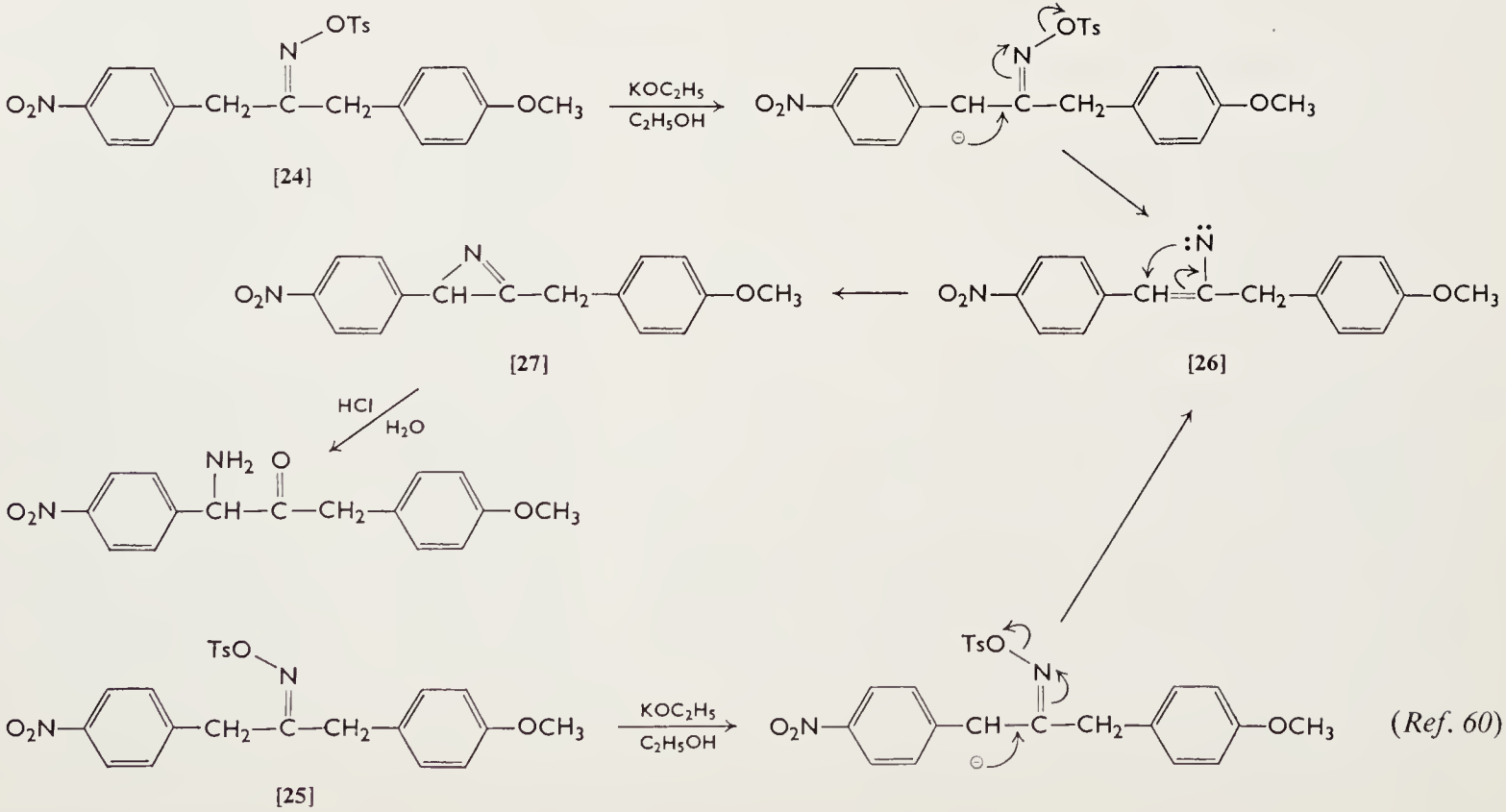


(*Ref. 55*)



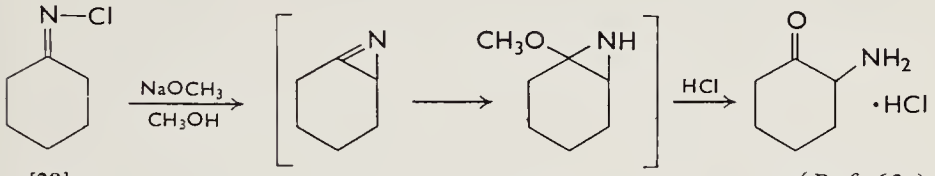
(*Ref. 54*)

cyclization reactions outlined earlier (see p. 10). The above scheme is required by the observation that the configuration of the ketoxime tosylate (syn or anti) has little, if any, influence upon the direction of reaction.[59b, 60] As is illustrated in the cases of [**24**] and [**25**], the incipient amino group is inserted exclusively upon that carbon bearing the more acidic hydrogen atom (i.e., the more stable enolate carbanion).[62]


OTs
N
O_2N
CH_2
C
CH_2
OCH_3
[24]
KOC_2H_5
C_2H_5OH
CH
⊖
:N
[26]
[27]
HCl
H_2O
NH_2
O
TsO
[25]

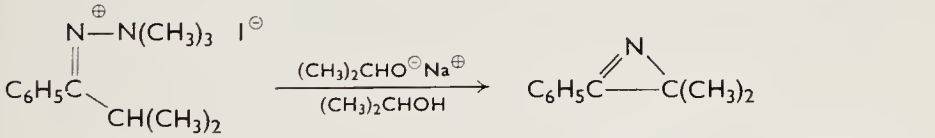
(*Ref. 60*)

From the synthetic point of view, it appears difficult to isolate azirines from the Neber rearrangement; this is also the case in the base-catalyzed rearrangement of N-chloroketimines (e.g., [**28**]) to

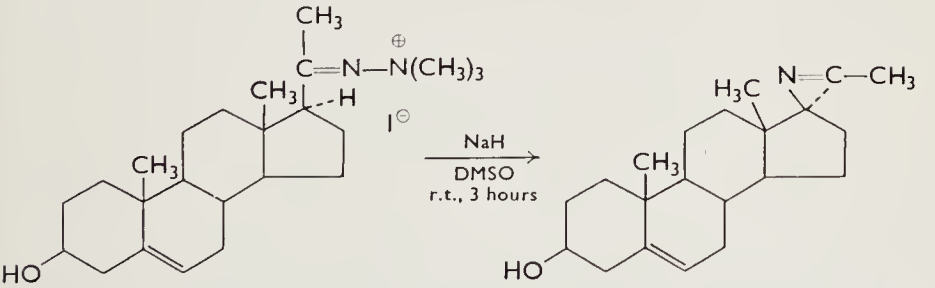


[28] (*Ref. 63a*)

α-aminoketones.[63] More recently, however, a modification of these reactions has been introduced in which a methiodide salt of a ketone dimethylhydrazone (e.g., [**29**] and [**30**]) is used rather than an oxime tosylate or N-chloroketimine.[64] Because of the highly activated nature of the leaving group, this reaction can be performed under conditions sufficiently mild to permit isolation of the azirine.[64]



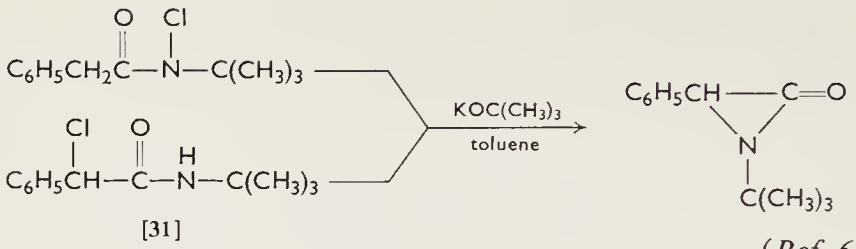
[29] (85%) (*Ref. 64a*)



[30] (67%) (*Ref. 64b*)

α-Lactams, or aziridinones, can be prepared by the cyclization of N-halo- or α-halo *tert*-butylamides with strong base.[65] This reaction may be considered formally analogous to the Favorskii reaction.[66, 67] When [**31**] was prepared in optically active form, it was possible to obtain an optically active aziridinone.[65b]

A variety of cyclization reactions leading to episulfides has been reported, among which may be cited the dehydrohalogenation of

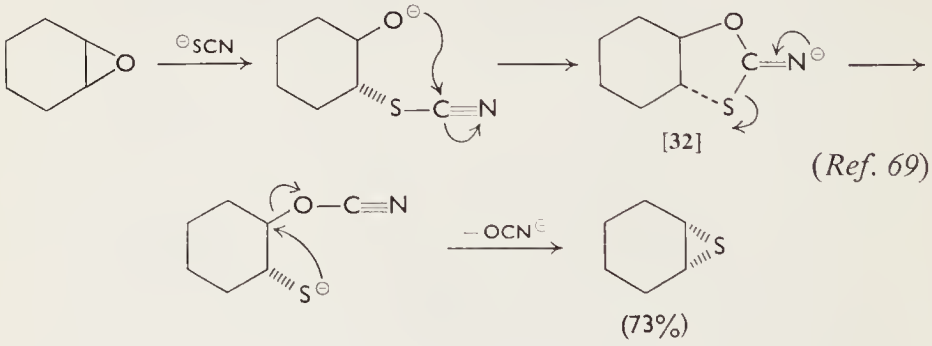


[31]

(*Ref. 65a, b*)

(*Ref. 65c*)

2-haloethanethiols and the dehydration of 2-hydroxyethanethiols[68]; however, the most widely used synthesis is the direct conversion of epoxides to episulfides with thiocyanate salts.[69] The illustrated mechanism has been suggested for this transformation, and has



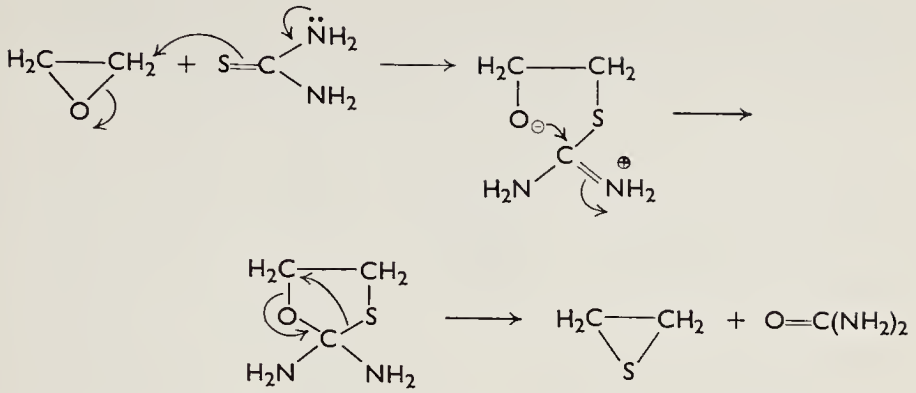
[32]

(*Ref. 69*)

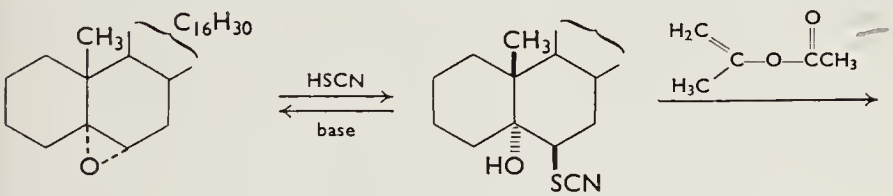
(73%)

received strong corroboration from the observation that cyclopentene oxide is unaffected by the customary reaction conditions because of the considerable strain required to form a trans-fused bicyclo[3.3.0] intermediate analogous to [**32**].[69, 70] Epoxides react with thiourea by a mechanism analogous to the above sequence.[71] Both mechanisms demand that the resultant episulfide possess a configuration opposite to that of the starting epoxide.

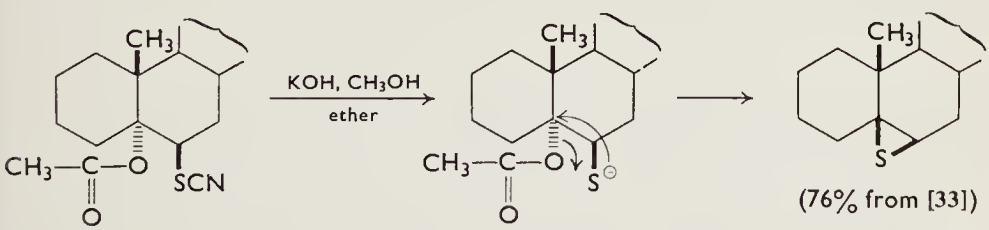
In situations where the above reactions fail or give low yields, it has proven advantageous to initially cleave the epoxide ring to an α-hydroxy xanthate, thiocyanate, or thiol acetate.[72, 73] However, in



certain cases, such as with [**33**], direct treatment of the hydroxy thiocyanate with base results in the displacement of the thiocyanate group by the oxide anion in a manner analogous to the reaction of halohydrins and the starting epoxide is recovered. This situation



[33]



(76% from [33])

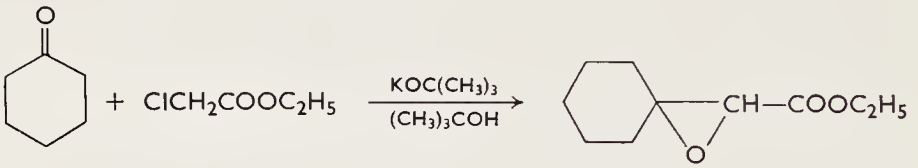
(*Ref. 72b*)

can be easily remedied by first converting the hydroxyl group to its acetate ester; subsequent base treatment results in the kinetically preferred hydrolysis of the thiocyanate moiety to produce the sulfide anion which displaces the acetate ion to furnish the episulfide of inverted configuration.

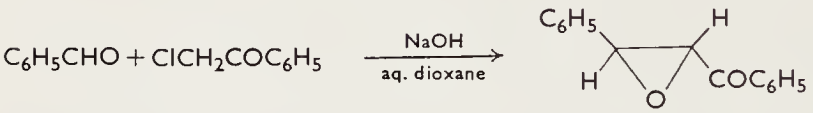
Condensation Reactions

The condensation of a ketone or aromatic aldehyde with an α-halo ester or ketone[74] in the presence of a strong base (the Darzens

reaction) yields an α,β-epoxy carbonyl derivative.[75] The reaction is kinetically third order, first order in each of the three components.[76] The Darzens reaction proceeds in a stereoselective manner to yield

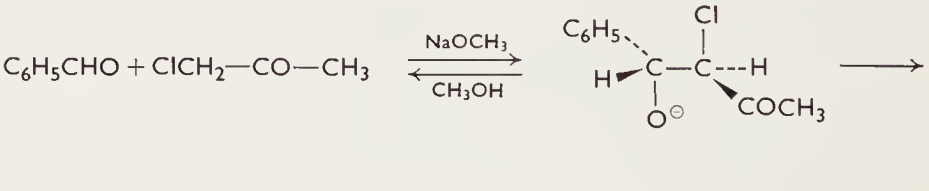


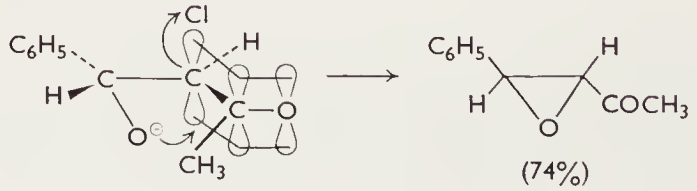
(83–95%) (*Ref. 77*)



(95%) (*Ref. 76*)

trans-epoxides. Although the trans-isomers are the kinetically favored products, prolonged exposure of such compounds to alkali may result in epimerization to the *cis*-epoxides.[78] This stereochemistry has been most recently justified on the basis of stereoelectronic control in the rate-determining collapse of the α-halohydrin anion[79]; thus, in the condensation of benzaldehyde with chloroacetone, the carbonyl group assists in the ring-closure step (e.g., [**34**]).



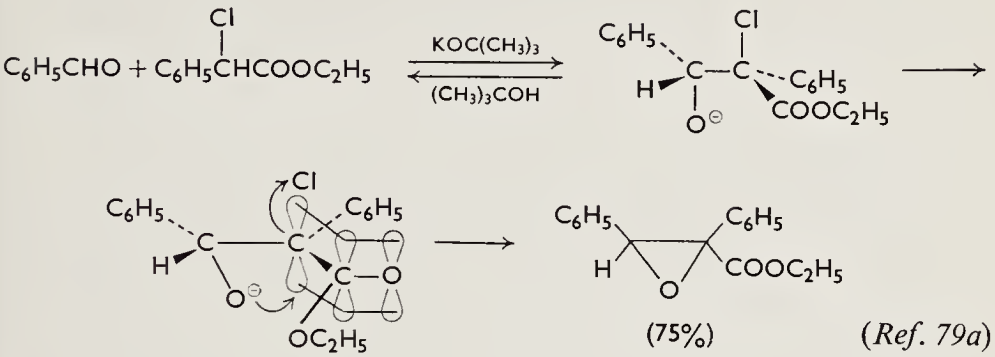


[34]

(74%) (*Ref. 80*)

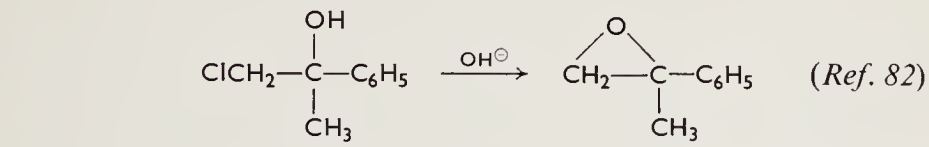
When the resulting epoxide has three substituents, the stereoisomer which results generally possesses the carbonyl function trans to the larger group at the β-carbon atom. In both of the above situations, the stereoelectronic assistance in the cyclization reaction is sterically

unfavorable when the carbonyl function and a large β-substituent are cis to each other.



(*Ref. 79a*)

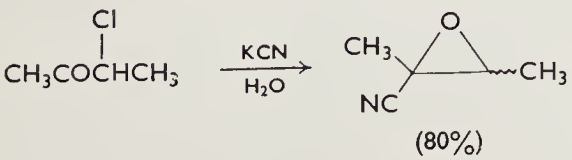
The reaction of α-haloketones with Grignard reagents and subsequent dehydrohalogenation of the resulting halohydrins with alkali also affords epoxides.[81] The process often, however, gives rise to abnormal rearrangement products.[43, 81b, 83] Furthermore, branched



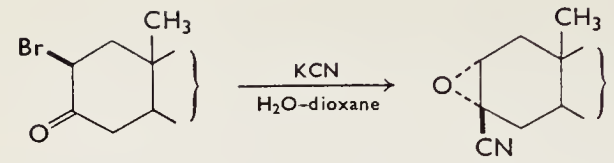
(*Ref. 82*)

α-haloketones with hindered carbonyl groups do not furnish the desired chlorohydrin, but rather undergo simple halide displacement.[81a] It is evident, therefore, that this approach to the synthesis of 1,1-disubstituted epoxides lacks generality.

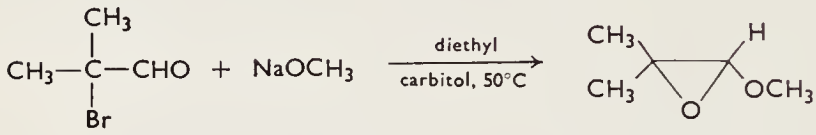
Other reactions which proceed by analogous mechanisms are found in the addition of cyanide and alkoxide ions to α-halocarbonyl compounds; several examples are described by the accompanying equations.



(*Ref. 84*)

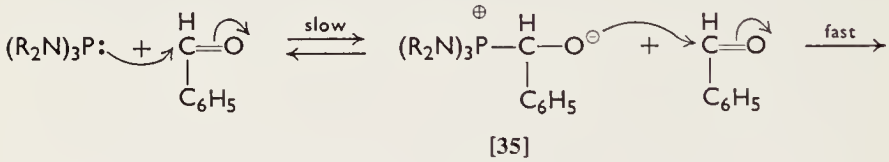


(20%) (*Ref. 85*)

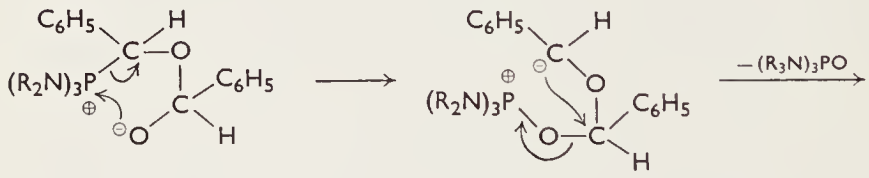


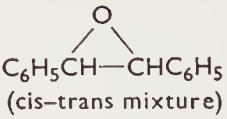
(53%) (*Ref. 86*)

Finally, the reaction of aromatic aldehydes with phosphorus triamides has been observed to furnish epoxides.[87] The following mechanism has been proposed for the transformation. The presence

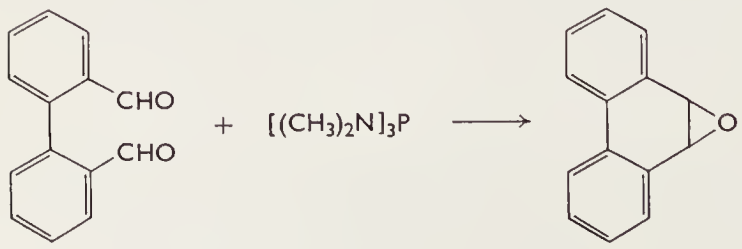


[35]





(cis–trans mixture) (*Ref. 87*)



(89%) (*Ref. 88*)

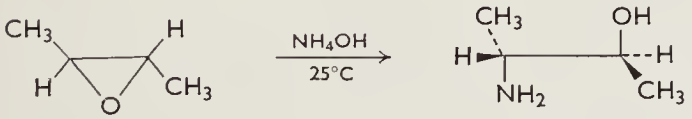
of an electronegative group on the aromatic ring enhances epoxide formation, whereas electron-releasing substituents favor instead the formation of intermediate adducts of type [**35**].[87]

REACTIONS

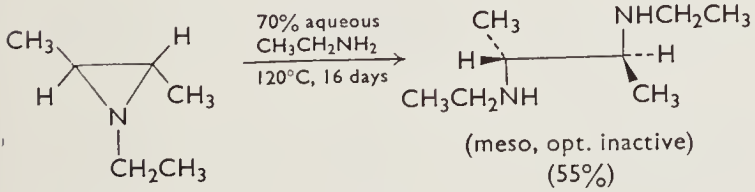
The monohetero atomic, three-membered rings are extremely susceptible to cleavage reactions because of the favourable release of strain energy involved. For this reason, these substances may be converted to a wide variety of functionalized compounds. With the exceptions to be noted below, aziridines exhibit behavior characteristic of secondary aliphatic amines; such reactions, because they are not peculiar to the three-membered ring, will not be considered here.[89]

Nucleophilic Ring Openings

Ring opening processes initiated by nucleophilic reagents have been shown to proceed with extensive, if not complete, inversion of configuration at the point of attack:



(76%) (*Ref. 90*)

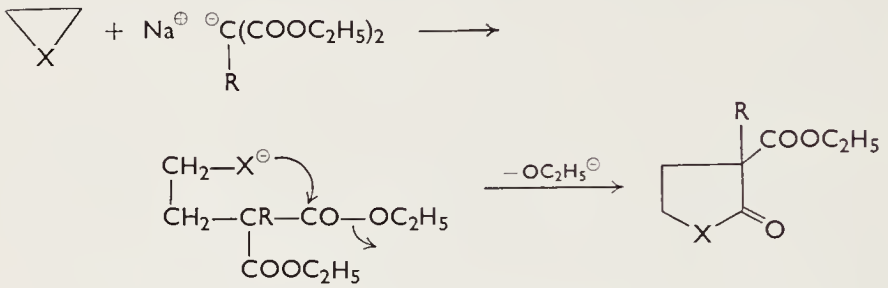


(opt. active)

(meso, opt. inactive)
(55%) (*Ref. 91*)

(35%) (*Ref. 92*)

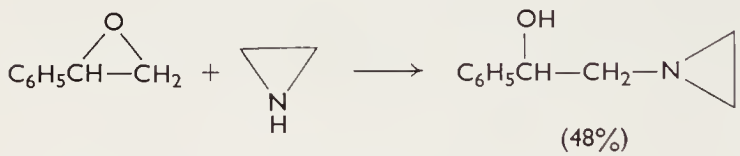
In certain situations, further reactions of the reactive ring-opened intermediates may occur, for example:



X=O, R=H (*Ref. 93*)

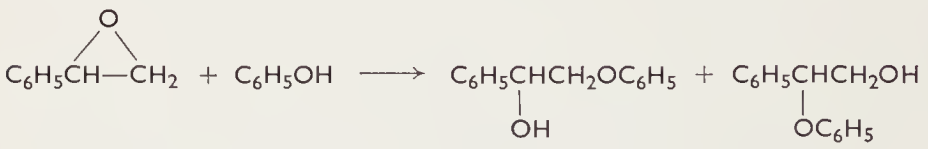
X=NH, R=C_6H_5 (25%) (*Ref. 94*)

When unsymmetrical three-membered rings are involved, ring opening can occur in either of two different directions. Frequently, the nucleophile attacks the less hindered carbon atom preferably with



(48%) (*Ref. 95*)

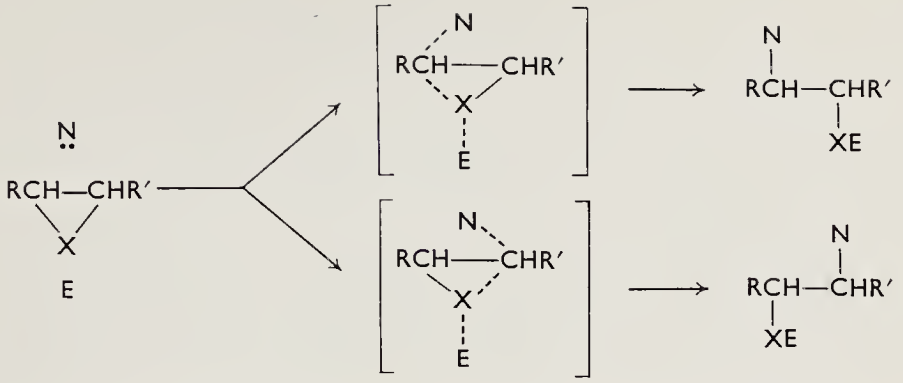
the result that one direction of ring opening is predominant.[7b] However, such reactions are generally difficult to predict because the product ratio can easily be affected by changes in the solvent and in



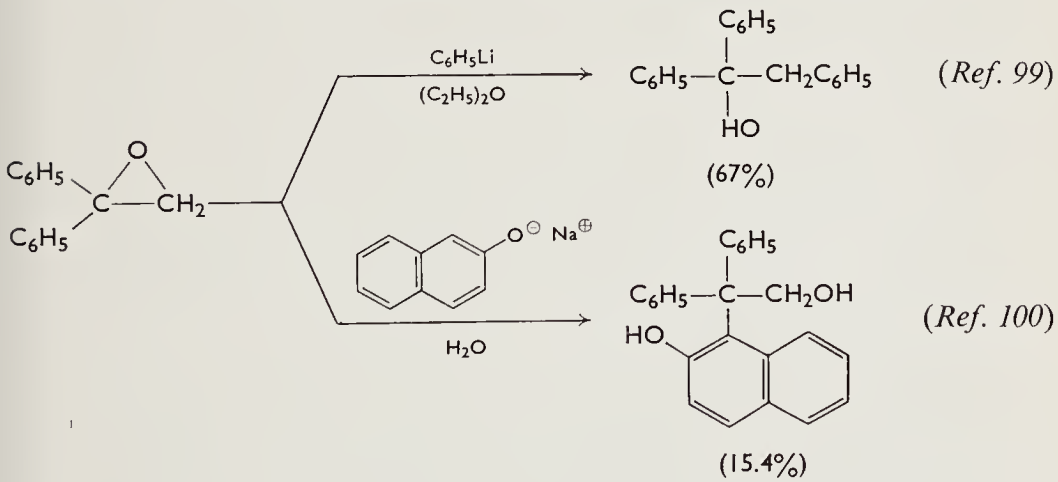
NaOH, H_2O	(20%)	(65%)
$NaOC_6H_5$, dioxane	(41%)	(36%)

(*Ref. 97*)

the proportion of the reagents.[96] The diverse and often seemingly contradictory facts relating to the opening of these strained rings can be correlated in terms of a "push-pull" mechanism.[98] According to this concept, the major factors involved in such processes are approach



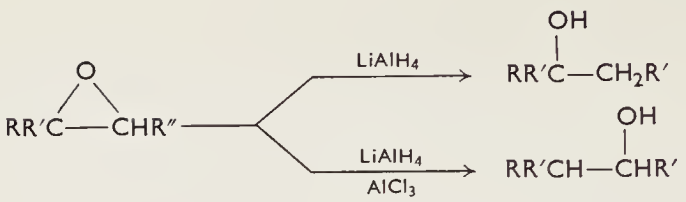
of the nucleophilic reagent (N), the rupture of the C—X bond, and the effect of the electrophilic reagent (E, solvent in nucleophilic displacements or proton in electrophilic reactions). As a result, steric factors are less influential than usual, while sensitivity to factors such as solvent, resonance, and the presence of electron-releasing substituents is substantially increased. In 1,1-diphenylethylene oxide, for example, steric considerations would promote attack at the methylene carbon, but bond breaking is facilitated by resonance stabilization of the incipient carbonium ion and renders attack at the tertiary carbon very feasible.[96] The latter mode of reaction is, as



(*Ref. 99*)

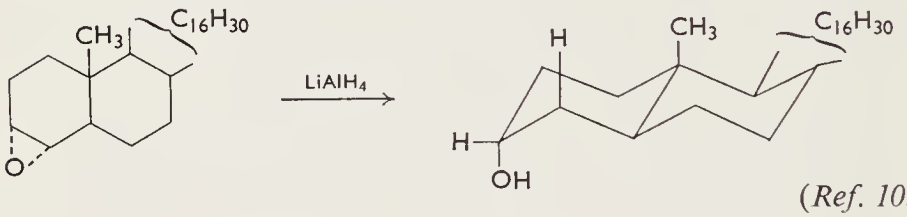
(*Ref. 100*)

expected, enhanced by solvents of high ionizing power. Of a similar nature, lithium aluminum hydride reduction of unsymmetrical epoxides affords the more highly substituted carbinols, whereas similar reduction in the presence of aluminum halides gives the less highly substituted carbinols.[101]

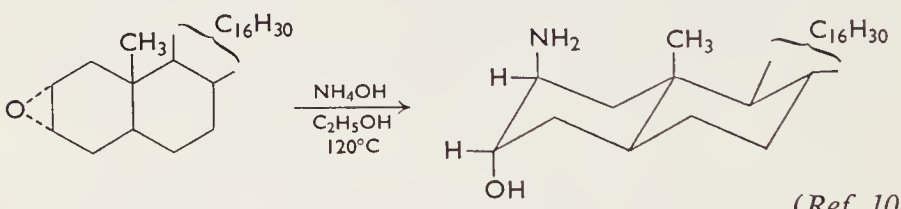


(*Ref. 101*)

Rigid systems (steroids have been most widely studied) containing three-membered hetero rings are attacked by nucleophilic reagents in a remarkable conformationally-specific manner from the axial side to give rise to products arising from trans-diaxial addition.[102] Such



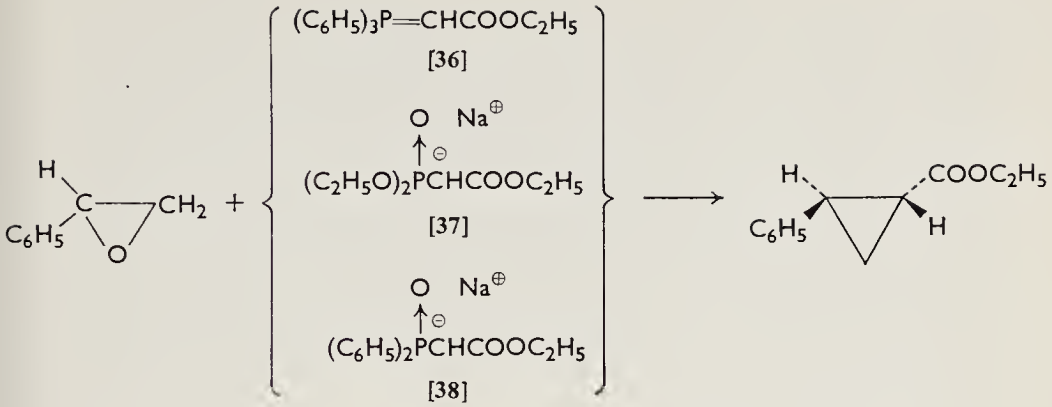
(*Ref. 103*)

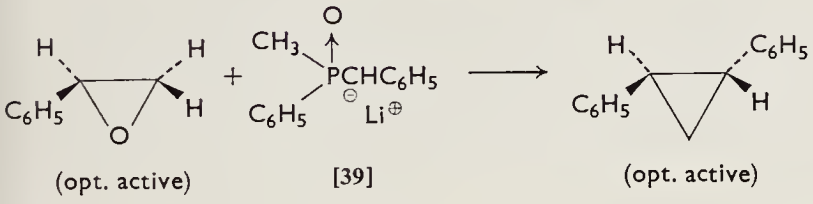


(*Ref. 104*)

diaxial cleavages presumably result because they proceed by way of a favorable linear distribution of charge in the transition state. In systems which are not rigid, and interconversion of chair forms is occurring, prediction of the product by the principle of axial attack is clearly impossible since either point of attachment of the heterocyclic ring may become axial.

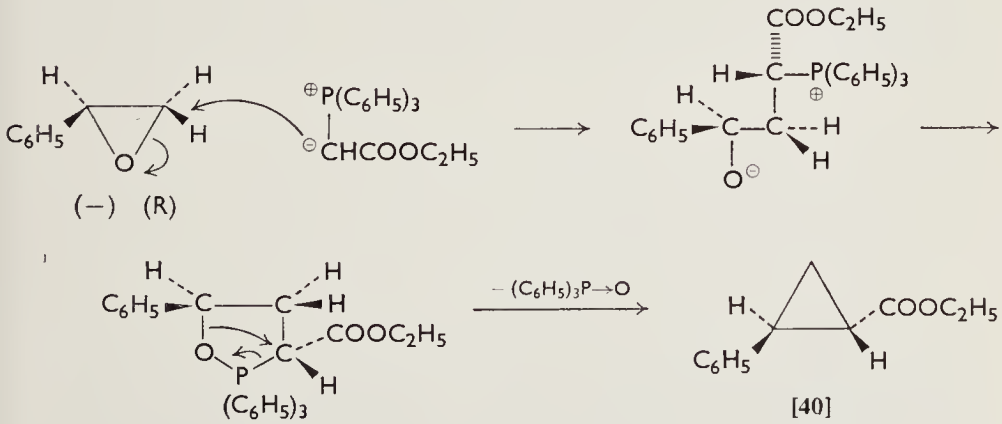
A series of interesting and synthetically useful processes is embodied in the conversion of epoxides to cyclopropanes upon reaction with carbalkoxymethylenephosphoranes [**36**],[105] or with phosphonate [**37**],[106] phosphinate [**38**],[107] and phosphine oxide [**39**] carbanions.[107, 108] Phosphonate carbanions [**37**] are more reactive than [**36**], thus enabling syntheses to be carried out at considerably lower temperatures (85°C instead of 200°C) with the result that higher yields are generally achieved with the former reagents. The use of nucleophiles of types [**36**], [**37**], and [**38**] is restricted to those derivatives





(*Ref. 108*)

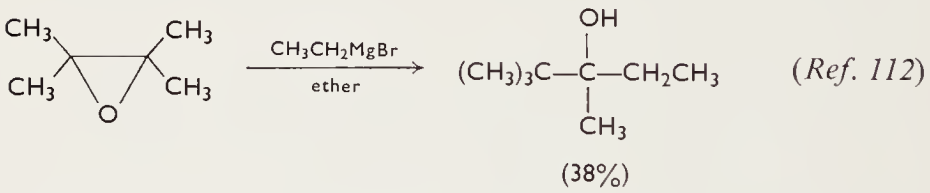
which contain a carbanion-stabilizing substituent such as carbethoxy or cyano. The utility of phosphine oxide carbanions **[39]**, where such restrictions are not present, is immediately apparent. Of particular importance in these reactions is the finding that optically active epoxides yield optically active cyclopropane derivatives; furthermore, as illustrated below, the overall reaction proceeds



(*Ref. 110*)

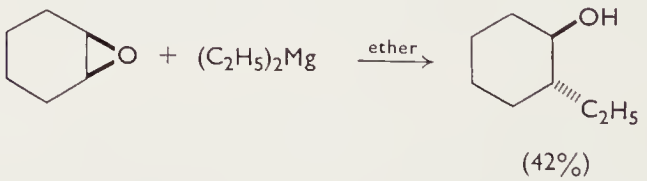
predominantly with inversion of configuration.[109, 110] The mechanism of this group of reactions which involve the same fundamental processes (although, some differences in transient electronic distributions undoubtedly exist) involves initial S_N2 attack at the less hindered epoxide carbon by the nucleophilic carbanion to cause ring cleavage. The resulting zwitterion probably undergoes ring closure to a five-membered, phosphorus-containing ring which subsequently collapses (in one or more steps) to give the observed product. The formation of cyclopropanes is not stereospecific, but trans isomers do predominate and, in the case of **[40]**, the trans isomer is the only cyclopropane observed.

The reaction of Grignard reagents with epoxides has been employed extensively as a route to primary alcohols containing two additional carbon atoms[111]; however, rearrangements under these conditions are very commonly observed.[7c] Such rearrangements have been found to result because of the halide component of the Grignard reagent



(Ref. 112)

which isomerizes (see p. 41) the epoxide to an aldehyde or ketone which subsequently reacts normally with the Grignard reagent. Replacement of the Grignard reagent with a dialkylmagnesium usually eliminates such rearrangements when they are prone to occur.[113]

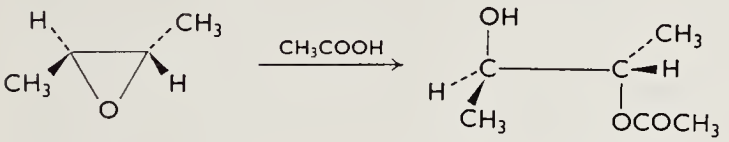


(Ref. 114)

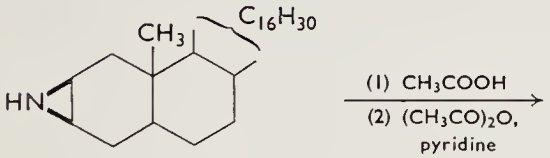
Electrophilic Ring Openings

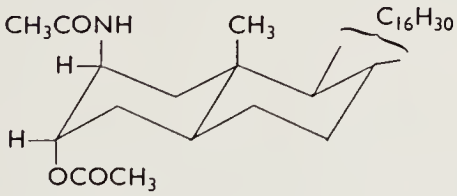
Ring opening reactions of monohetero atomic, three-membered rings are greatly accelerated in acidic media as exemplified by the observations that hydrobromic acid adds readily to ethylene oxide at

−78°C to yield ethylene bromohydrin[115] and that ethyleneimine and ethylene sulfide polymerize readily, and sometimes explosively, in the presence of acids under noncontrolled conditions. From the stereochemical point of view, these processes generally occur stereospecifically with inversion of configuration at the point of attack Such evidence reflects the fact that fully developed carbonium ions are customarily not generated in such electrophilic processes,[116] and agrees with a mechanistic interpretation based on the "push-pull" theory described earlier (see p. 26).

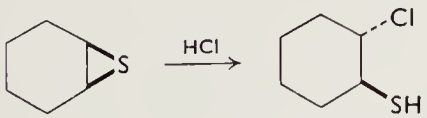


(52%) (*Ref. 117*)



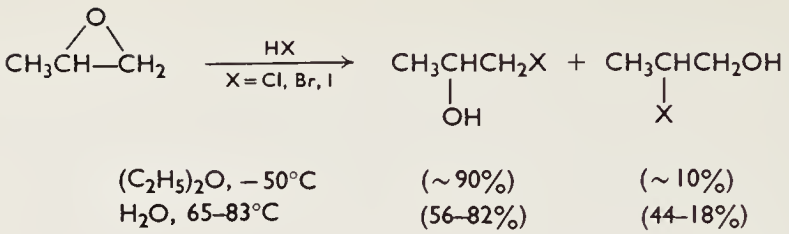


(60%) (*Ref. 104*)



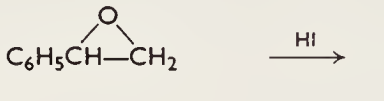
(57%) (*Ref. 69, 118*)

In reactions with unsymmetrically substituted epoxides, two products are possible and the mode of ring cleavage is again strongly controlled by such factors as solvent and electron distribution in the substrate (see p. 27). In the following example, the product ratio is markedly altered in favor of the more highly substituted carbon atom on passing from nonpolar ether to polar water as the reaction medium:

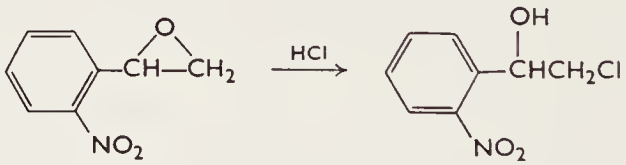


(*Ref. 119*)

Substituents exert a powerful effect on the course of ring opening as illustrated by the cleavage of styrene oxide with hydrogen iodide in the direction of the incipient benzylic carbonium ion. In contrast, hydrochloric acid adds to *o*-nitrostyrene oxide in the opposite sense because of the powerful electron-withdrawing capability of the nitro group, which raises the activation energy of the transition state in



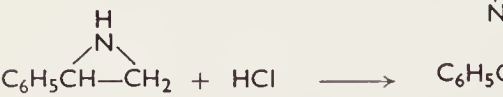
(*Ref. 120*)



(*Ref. 121*)

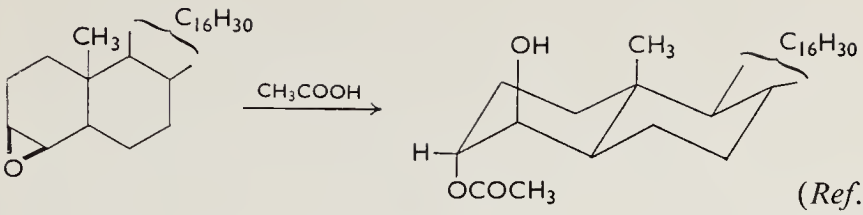
which the benzylic carbon atom exhibits partial positive character above that for reaction at the primary carbon atom. A similar phenomenon has been observed in the aziridine series as demonstrated by the following examples:

(*Ref. 122*)

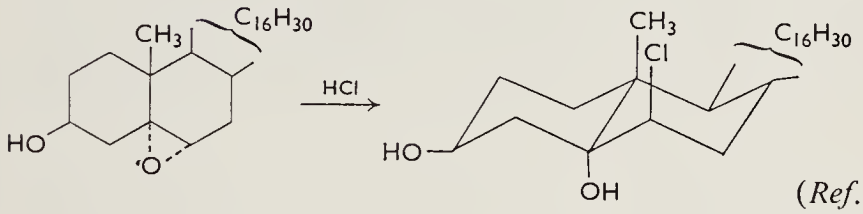


(*Ref. 123*)

The principle of axial attack in ring-opening processes is also operative under electrophilic conditions (see also aziridine example, p. 31).

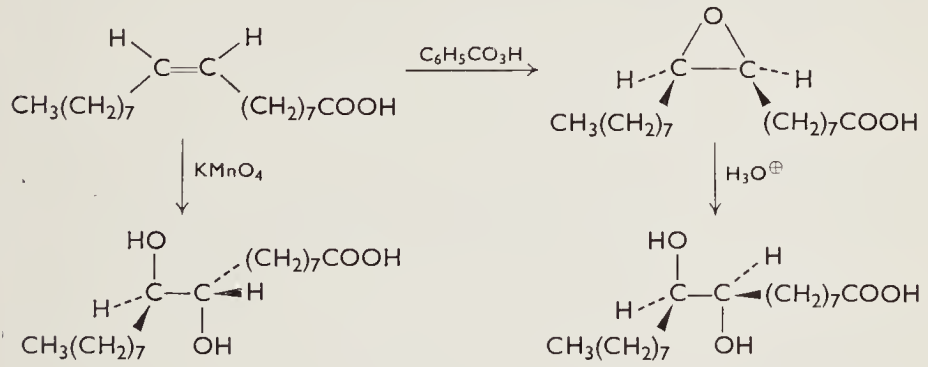


(*Ref. 103*)



(*Ref. 124*)

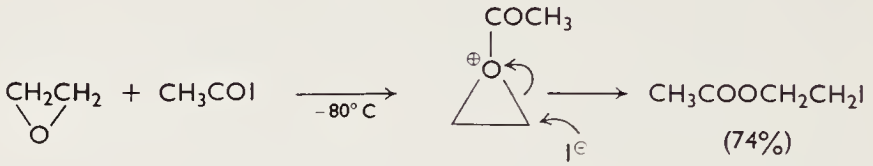
It may be readily seen that epoxides, aziridines, and episulfides are cleaved by hydrohalogen acids to halohydrins, haloethylamines, or haloethylmercaptans, respectively, from which the respective heterocycles can be resynthesized on treatment with base. This stereospecificity has been utilized advantageously in the case of epoxides, to prepare glycols which are isomeric with those glycols which result from treatment of olefins with such reagents as potassium permanganate (which give *cis* addition). Such an application is shown below.



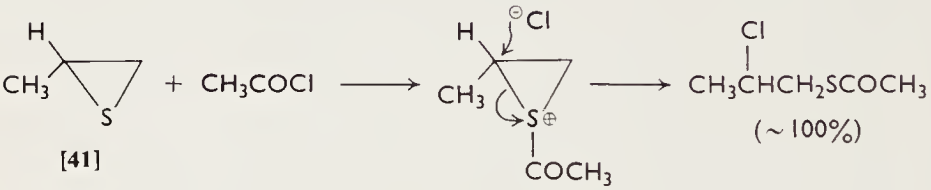
(*Ref. 125*)

The reaction of epoxides and episulfides with acid chlorides is believed to proceed by electrophilic attack of the latter reagent at the hetero atom to produce an intermediate onium salt which, because of its extremely high reactivity, is easily and rapidly attacked by the

anion at the carbon atom with rupture of the ring. The stereochemical course of such reactions follows the usual pattern of trans

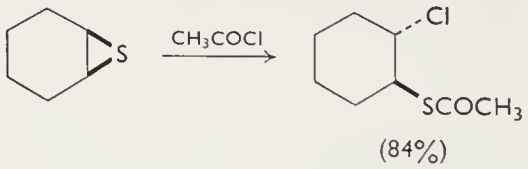


(*Ref. 126*)

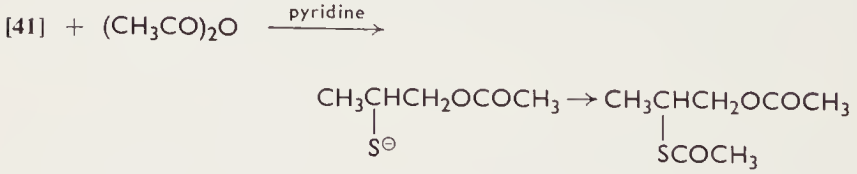


(*Ref. 127*)

addition.[69] It is interesting to note that the episulfide [**41**] reacts with acetic anhydride in pyridine to open in the direction opposite to



(*Ref. 69*)

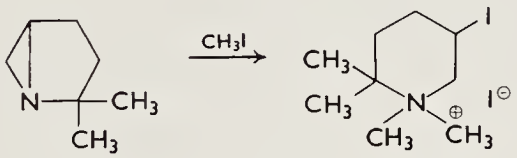


(*Ref. 127*)

that encountered with acetyl chloride. It appears that, in contrast to the latter situation in which the onium salt is probably directly involved and therefore the transition state favoring attack at the more highly substituted carbon atom is preferred, the reaction in pyridine proceeds by direct attack of acetate ion on the free episulfide and steric hindrance becomes the important criterion.

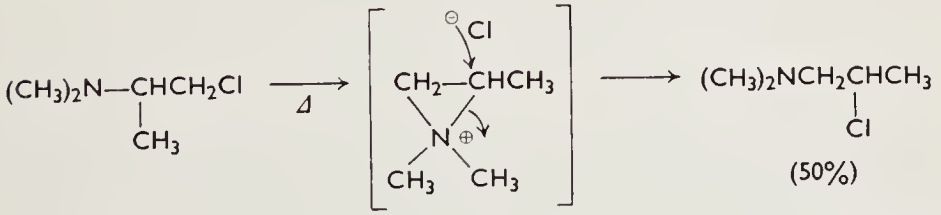
Other Ring Opening Processes

Protonated aziridines or quaternary aziridinium salts are exceptionally reactive toward nucleophiles, and attempts to prepare them generally result in ring cleavage (see **[42]**, for example). Generally, however, isolation of such compounds has proven feasible when anions of low nucleophilicity such as picrylsulfonate,[128] perchlorate,[30] fluoroborate,[30] and *p*-toluene sulfonate[129] are employed, although a few examples of stable monomeric aziridine methiodides have been cited.[130]

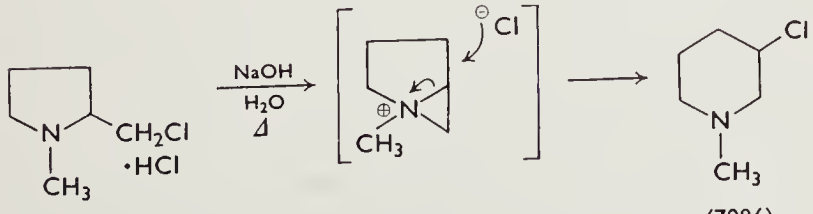


[42] (100%) *(Ref. 131)*

The reverse process, namely the cyclization of a β-haloethylamine to an aziridinium cation, has been found by kinetic methods to occur during the solvolysis of such amines.[132] In addition, other reactions of these substances such as the rearrangements shown below can only be explained as proceeding through aziridinium intermediates.



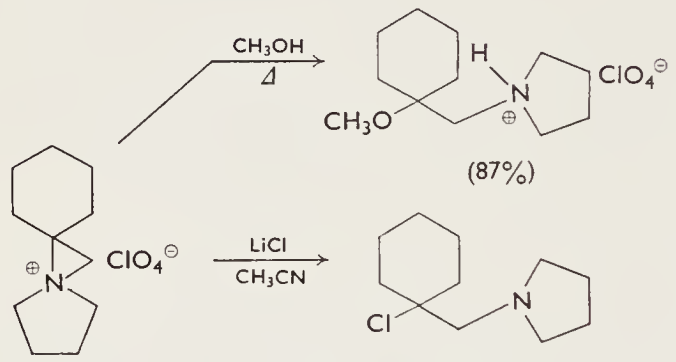
(50%) *(Ref. 133)*



(70%) *(Ref. 134)*

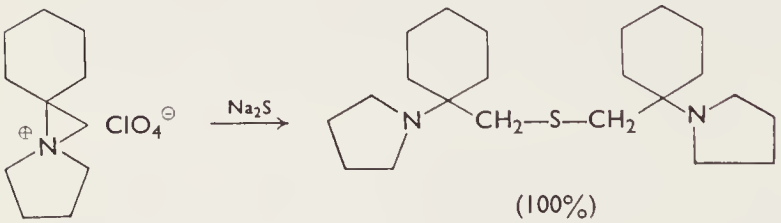
Furthermore, the mechanism of biological action of nitrogen mustards is believed to involve the alkylation of functional groups of metabolic importance by intermediate aziridinium salts.[135] In fact, stable aziridinium perchlorates can be readily isolated from the reaction of β-chloroethylamines with silver perchlorate in cold acetone (see p. 17).[57, 136]

The reaction of aziridinium salts with various nucleophilic reagents results as expected in the formation of ring cleavage products. Several examples are given below.



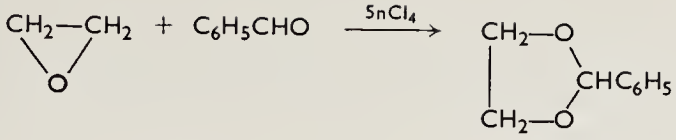
(*Ref. 30a*)

(*Ref. 57*)



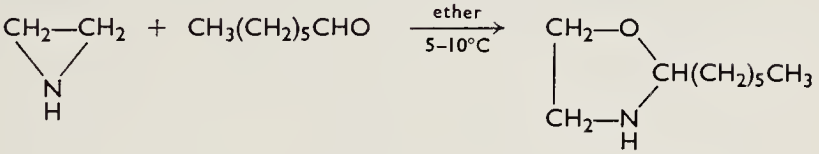
(*Ref. 137*)

Epoxides and aziridines condense readily with carbonyl compounds to give dioxolanes [**43**] and oxazolidines [**44**], respectively.[138, 139] By analogy, aziridinium salts likewise condense with aldehydes, ketones, and nitriles at moderate temperatures with expansion of the aziridinium ring.[30c, d] The reactions of aziridinium salts can be generally described according to the nucleophilicity of the attacking reagent. If the attacking species is very nucleophilic, the product will be that in which cleavage of the less substituted C—N bond of the three-membered ring occurs. If the attacking species is a relatively poor nucleophile, the reaction can be viewed as an ionization with cleavage of the three-membered ring to yield the most stable carbonium ion (e.g., [**45**]) which then reacts with the poor nucleophile.



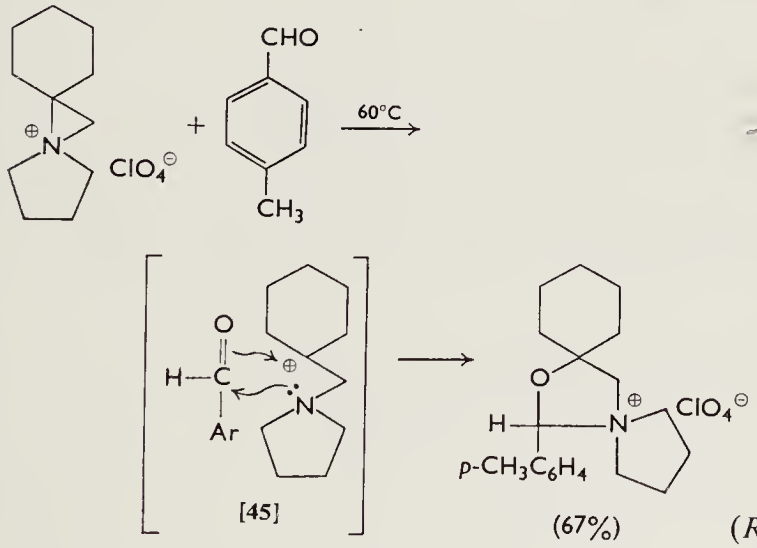
(35%)

[43] (*Ref. 138*)

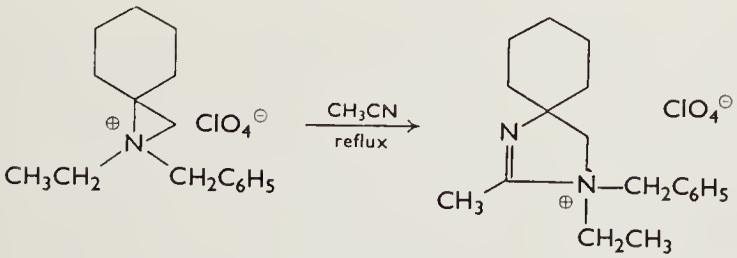


(95%)

[44] (*Ref. 139*)



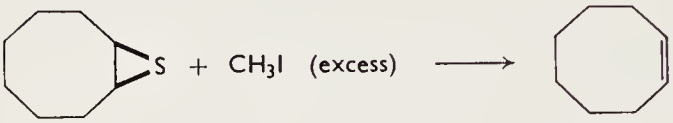
(67%) (*Ref. 30c*)



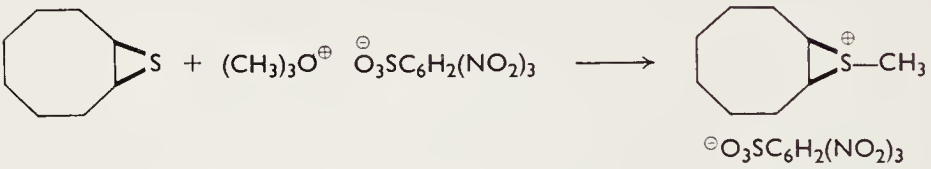
(57%) (*Ref. 30e*)

Ring cleavages have also been observed during the attempted alkylation of episulfides with methyl iodide; olefins generally result (see p. 40 for a further discussion of this reaction). Stable epi-

sulfonium salts can be isolated, however, by again resorting to anions of low nucleophilicity such as the 2,4,6-trinitrobenzenesulfonate anion.[141] Such salts are rapidly cleaved by nucleophilic reagents with net trans addition.[142]



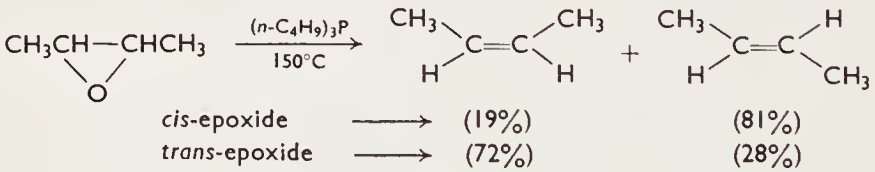
(Ref. 140)



(Ref. 141)

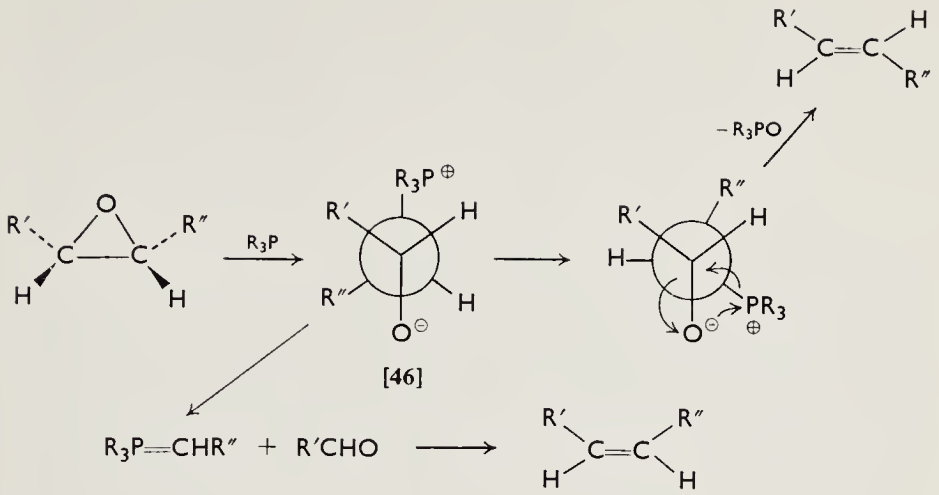
Reactions Involving Extrusion of the Hetero Atom

Epoxides are smoothly deoxygenated by tertiary phosphines at elevated temperatures (150–200°C) and give rise to olefins.[143]. Pre-

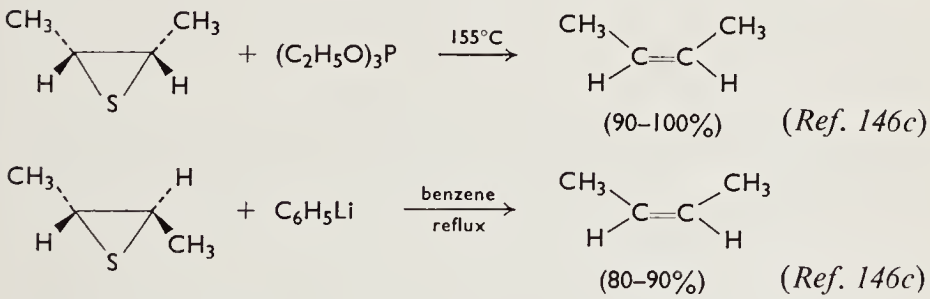


(Ref. 143a)

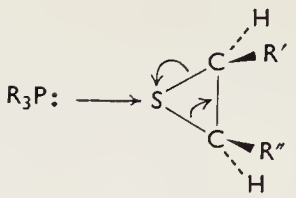
sumably, the reaction occurs by nucleophilic attack of the tertiary phosphine at an epoxide carbon atom, thus affording a betaine of type [**46**] which, after rotation of the central carbon-carbon bond by 180°, collapses with the liberation of *tert*-phosphine oxide to yield as the predominant product an olefin of configuration opposite to that of the starting epoxide. The minor olefinic product probably arises because of the propensity of ylids to form betaines reversibly[144]; thus, decomposition of [**46**] to an ylide and an aldehyde followed by a Wittig-type recombination of these two moieties would be expected to lead to a certain amount of *cis*-olefin formation.[145] Control experiments showed that isomerization of the 2-butenes did not occur under the reaction conditions.[143a]



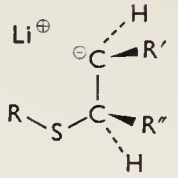
In contrast, the treatment of episulfides with tertiary phosphines[143a, 146b] or phosphites[146a, c, d] leads to greater than 97% stereospecific removal of sulfur from the three-membered ring with the formation of olefins possessing the original configuration of the



heterocycle. Similar stereospecificity was obtained with phenyllithium.[146c, 147] The reaction of tertiary phosphines with episulfides is bimolecular, first order in each reactant, and the rate is unaffected by solvents of varying dielectric constant, thus indicating that charge separation is of little importance in the transition state of the rate-controlling step. These results rule out a mechanism such as that which prevails in the case of epoxides, but favor a concerted process involving nucleophilic attack by phosphorus on sulfur as pictured in [**47**]. The organolithium desulfurization reaction has been formulated as proceeding through [**48**],[147] but because the geometry of the starting heterocycle is maintained, this postulated intermediate must have a very brief lifetime, if it exists at all.

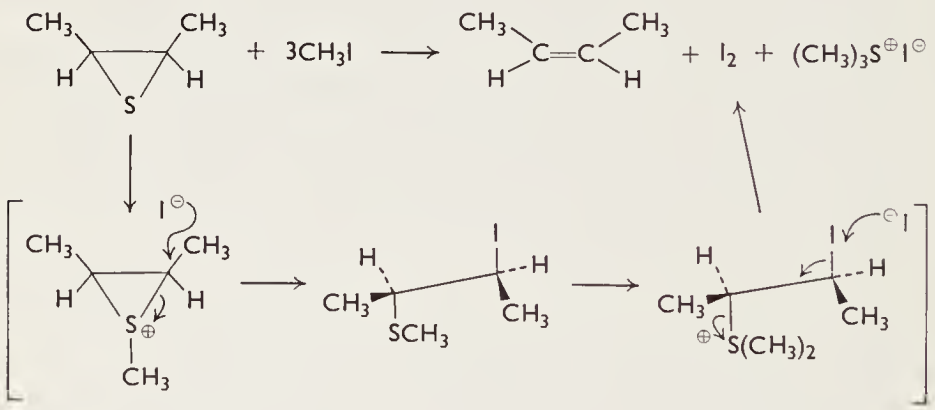


[47]



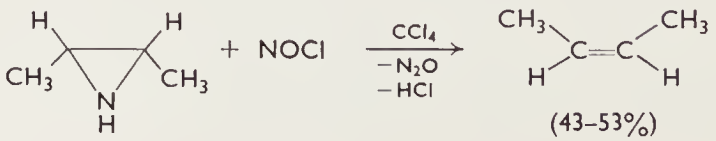
[48]

It has already been mentioned (p. 37) that the reaction of episulfides with methyl iodide results in the formation of olefins. Of intrinsic interest is the fact that this reaction proceeds with greater than 97% stereoselectivity.[140] The principal route for this transformation involves the initial formation of an episulfonium salt, and is illustrated in the accompanying equations. Firm evidence for this



mechanistic pathway has been obtained by utilizing methyl bromide as the alkylating agent which permits the isolation of the β-bromosulfide and β-bromosulfonium bromide; these latter substances can in turn be converted to olefin when treated with iodide ion or iodine under the original reaction conditions.[148]

The reaction of aziridines with nitrosating agents such as nitrosyl chloride or methyl nitrite results in the formation of olefins with greater than 99% stereoselective deamination.[149, 150] Such trans-

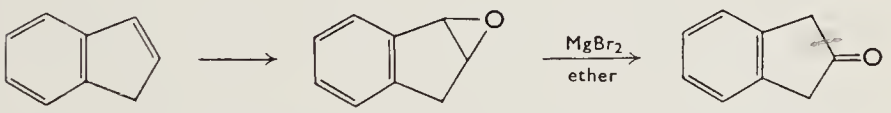


(43–53%) (*Ref. 149*)

formations proceed via N-nitrosoaziridine intermediates which are isolable at temperatures below −20°C, but which decompose to the observed products at higher temperatures.

Rearrangements

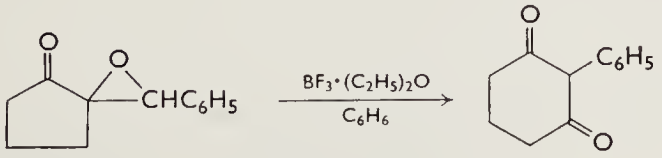
Although certain simple epoxides are known to undergo thermal isomerization to carbonyl compounds, epoxide rearrangements are, in general, most readily and conveniently effected with such acid catalysts as aqueous mineral acid, boron trifluoride etherate in benzene, or anhydrous magnesium bromide in benzene or ether.[7] These conversions are of special interest since they provide a simple means of converting olefins to carbonyl compounds. Which carbonyl-containing product is formed from a particular epoxide is dependent



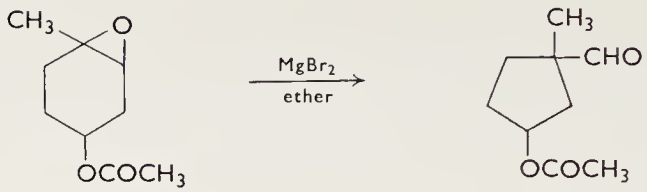
[49] (~100%)

(*Ref. 151*)

upon the ease of cleavage of one or the other of the carbon-oxygen bonds, and on the relative migratory aptitudes of the different substituent groups. For example, in indene oxide [**49**] rupture of the C—O bond which leads to an incipient benzylic carbonium ion is to be preferred and therefore, 2-indanone results.[152] In fact, monoaryl-substituted epoxides invariably rearrange to give non-conjugated ketones. The relative migratory aptitudes of groups appears generally to be in the order of aryl>acyl>H>ethyl>methyl (note that hydride shifts are favored by a considerable margin over migration of alkyl groups). In certain cases, the rearrangement may be accompanied by ring expansion or contraction.

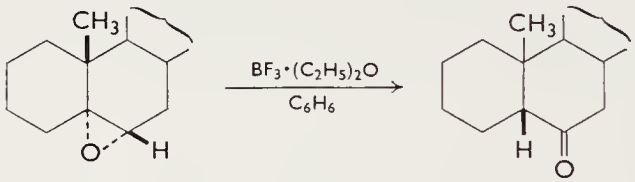


(71%) (*Ref. 153*)



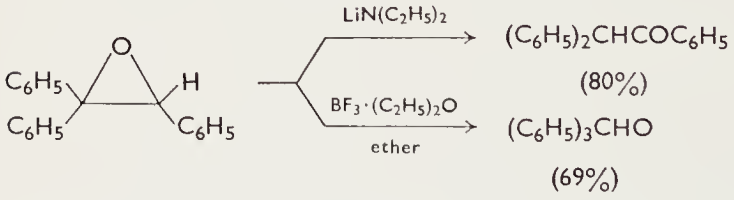
(15%) *(Ref. 154)*

The rearrangement of epoxides to ketones under the influence of Lewis acids has been shown to be stereospecific.[155] For example, the steroidal epoxide [**50**] gives only the less stable 5β,6-ketone on treatment with boron trifluoride etherate in benzene.



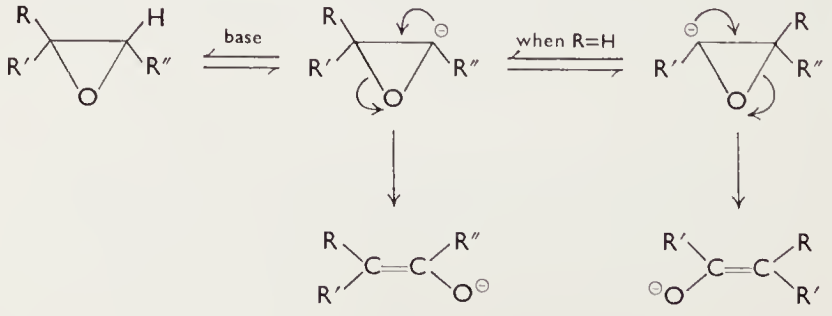
[50] (30%)

Strong bases may also effect the rearrangement of certain epoxides (bases must not be those which will preferentially rupture the ring by nucleophilic attack at an epoxide carbon atom), and the products frequently differ from those isolated under acidic conditions, as

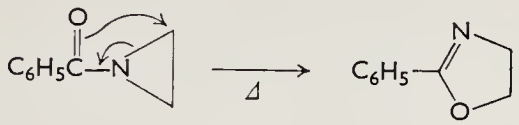


(Ref. 156)

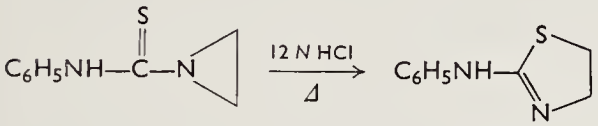
illustrated below. The course of such base-catalysed isomerizations may be depicted as follows:



N-Acyl derivatives of ethyleneimine are readily converted upon distillation to 2-substituted-2-oxazolines (e.g., [**51**]). The rearrange-

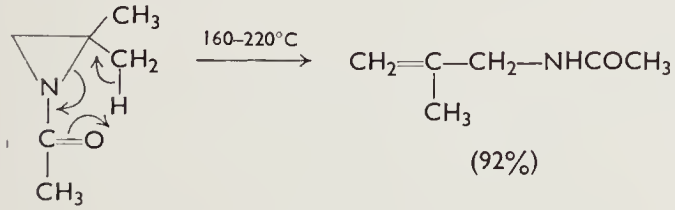


[51] (*Ref. 157*)

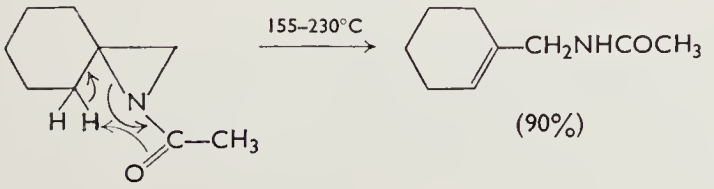


(91%) (*Ref. 158a*)

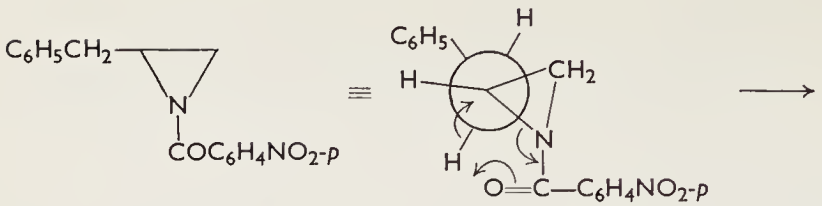
ment occurs by intramolecular attack of the carbonyl oxygen at a ring carbon to cause rupture of the system. The driving force for this process is found in the relief of strain which the opening of the three-membered ring provides. Similar rearrangements occur under the influence of acid catalysts.[158] Pyrolysis of N-acyl derivatives of homologous aziridines, in contrast, results in isomerization to N-allyl amides.[159] Sucn rearrangements proceed via transition states in which intramolecular proton transfer from a side chain carbon to oxygen occurs concomitantly with cleavage of the three-membered hetero ring (as depicted), and involve stereospecific cis-elimination (see [**52**]) as is observed in the Chugaev reaction and the Cope amine oxide pyrolysis.



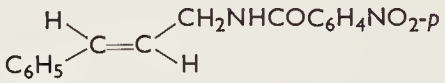
(92%) (*Ref. 159a*)



(90%) (*Ref. 159b*)

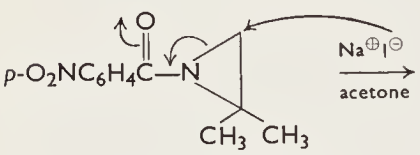


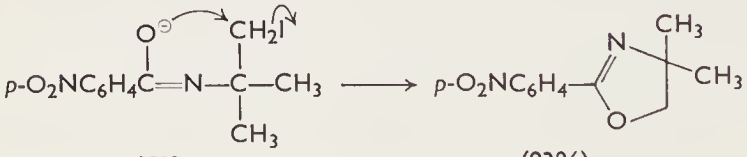
[52]



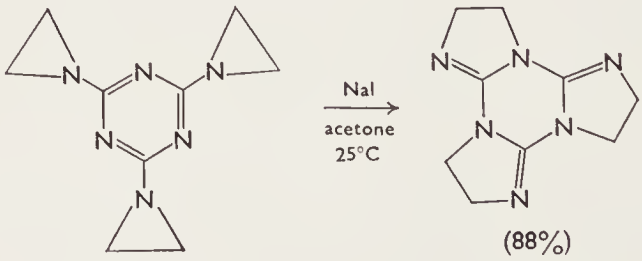
(91%) (*Ref. 159d*)

Iodide ion (and thiocyanate ion) is an effective catalyst for the isomerization of aziridine derivatives.[160] Such rearrangements are envisioned as proceeding by nucleophilic attack on the least substituted aziridinyl carbon atom by iodide ion to give an iodoethyl



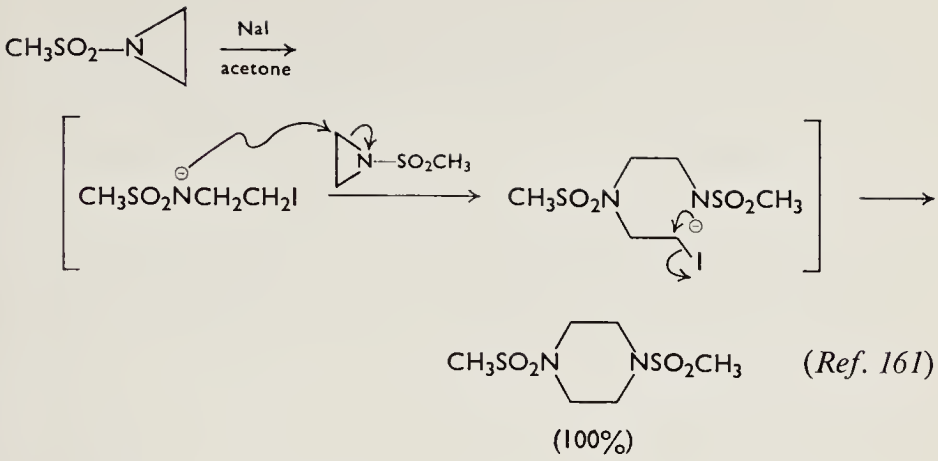


[53] (93%) (*Ref. 158b*)



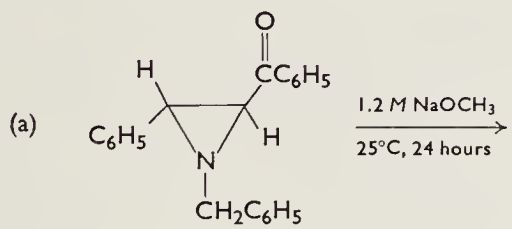
(88%) (*Ref. 161*)

intermediate such as **[53]** which is converted to product in the manner shown. When an intermediate such as **[53]** is difficult to form, dimerization generally occurs.

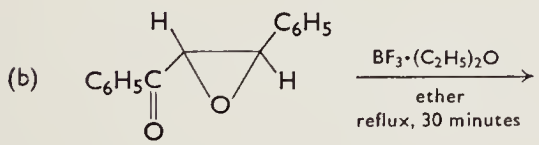


Exercises

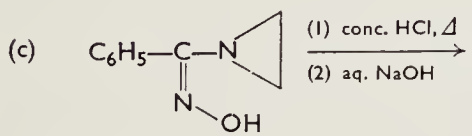
1. Predict the major product of the following reactions:



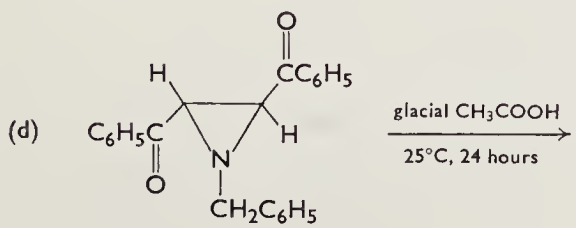
(*Ref. 162*)



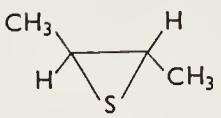
(*Ref. 163*)



(*Ref. 164*)

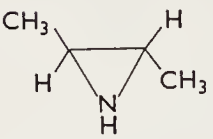


(*Ref. 162*)

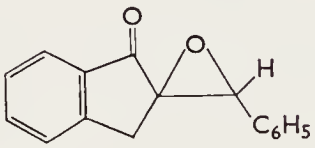
(e) 

(SS) (−)

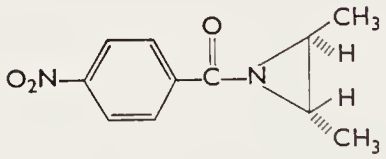
$\xrightarrow[H_2SO_4]{CH_3CN}$ $C_6H_{11}NS$ (opt. active?) *(Ref. 165)*

(f) 

(SS) (−) + $CH_3\overset{\overset{S}{\|}}{C}NH_2$ $\xrightarrow[\Delta]{C_6H_6}$ $C_6H_{11}NS$ (opt. active?) *(Ref. 165)*

(g) 

$\xrightarrow[0°C]{H_2SO_4}$ *(Ref. 166)*

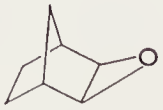
(h) 

$\xrightarrow[acetone]{NaI}$ (stereochemistry?) *(Ref. 167)*

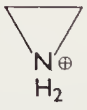
(i) $ClCH_2SO_2Cl + CH_2N_2 \xrightarrow[ether,\ -10°C]{(C_2H_5)_3N}$ *(Ref. 168)*

(j) $C_6H_5CH{=}N{-}N{=}CHC_6H_5 + (CH_3)_2\overset{\oplus}{S}CH_2\overset{\ominus}{\underset{\|}{}}O \xrightarrow{(CH_3)_2S{=}O}$

(1 equiv.) *(Ref. 169)*

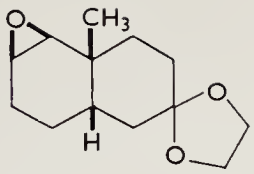
(k) 

$\xrightarrow[10–15°C]{48\%\ HBr}$ *(Ref. 170)*

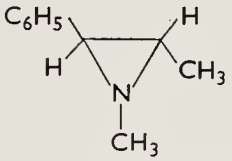
(l) $C_6H_5C{\equiv}N$ + 

$BF_4^{\ominus}$ $\xrightarrow{100°C}$ *(Ref. 171)*

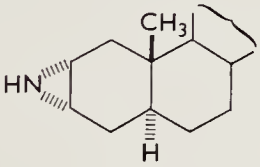
(m) $C_6H_5CHBr{-}SO_2{-}CHBrC_6H_5 + (C_2H_5)_3N \xrightarrow{CH_2Cl_2}$ *(Ref. 172)*

(n) 

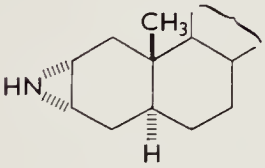
1 *N* $C_6H_5CH_2ONa$ / $C_6H_5CH_2OH$ (*Ref. 173*)

(o) 

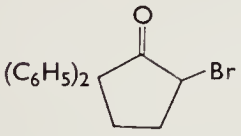
D(+)
HCl → (configuration?; opt. active?) (*Ref. 174*)

(p) 

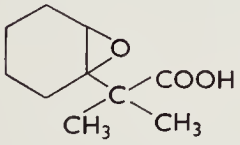
(1) CH_3SO_2Cl, pyridine, 0°C, 24 hours
(2) $LiAlH_4$,  , reflux, 12 hours (*Ref. 175*)

(q) 

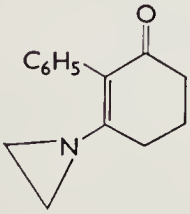
+ C_6H_5COCl → (acetone, reflux, 5 hours) (*Ref. 175*)

(r) 

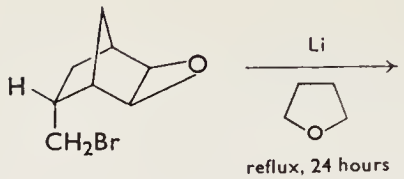
KCN / C_2H_5OH, reflux, 24 hours (*Ref. 176*)

(s) 

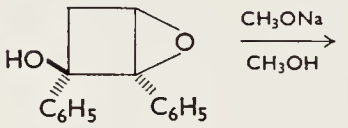
CH_3COOH (*Ref. 177*)

(t) 

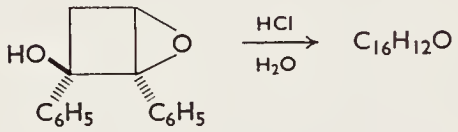
NaI, in melt (*Ref. 178*)

(u) 

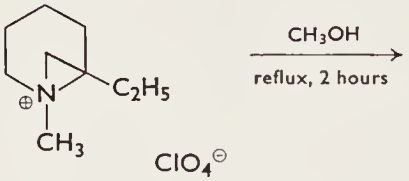
(Ref. 179)

(v) 

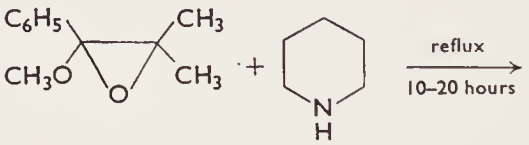
(Ref. 180)

(w) 

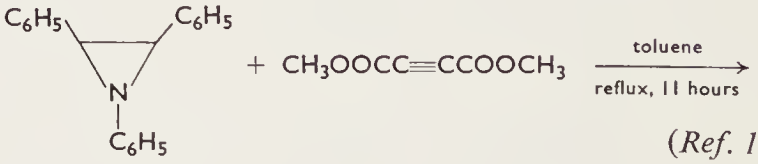
(Ref. 180)

(x) 

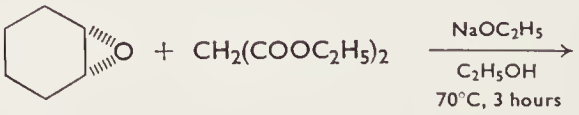
(Ref. 181)

(y) 

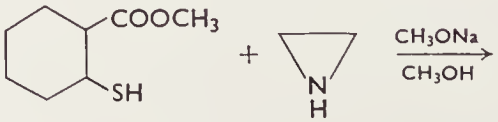
(Ref. 182)

(z) 

(Ref. 183)

(a′) 

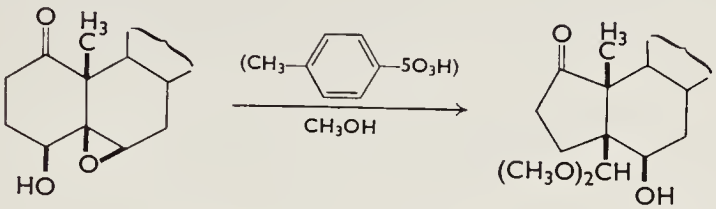
(Ref. 184)

(b′) 

(Ref. 185)

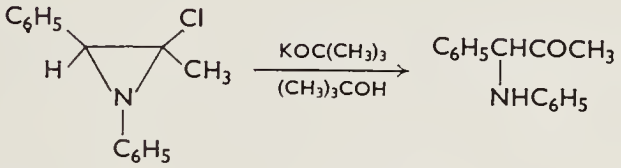
2. Suggest a reasonable mechanism for each of the following transformations:

(a)



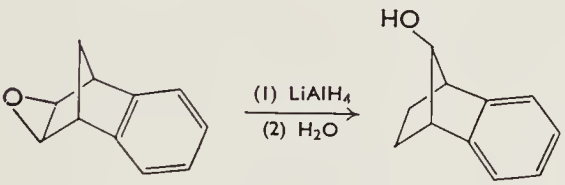
(*Ref. 186*)

(b)



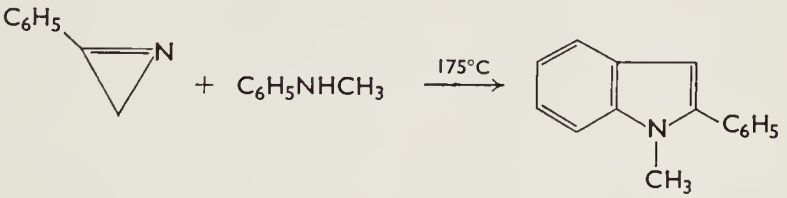
(*Ref. 187*)

(c)



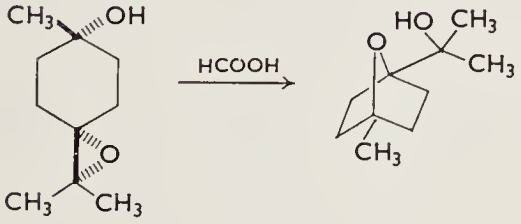
(*Ref. 188*)

(d)



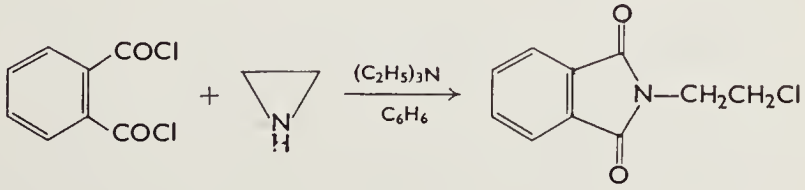
(*Ref. 189*)

(e)

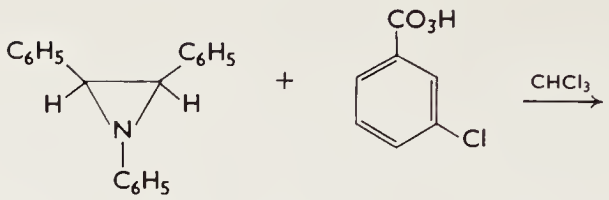


(*Ref. 190*)

(f)

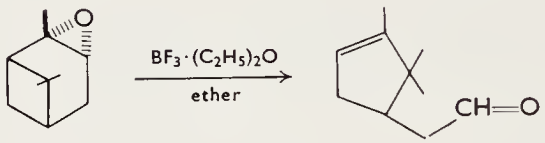


(*Ref. 191*)

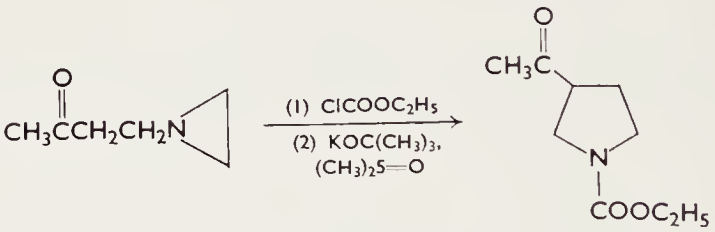
(g) 

$C_6H_5N{=}O + C_6H_5CH{=}CHC_6H_5 +$
$C_6H_5CHO + C_6H_5CH{=}NC_6H_5$

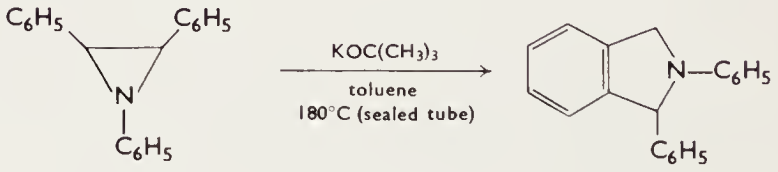
(Ref. 192)

(h) 

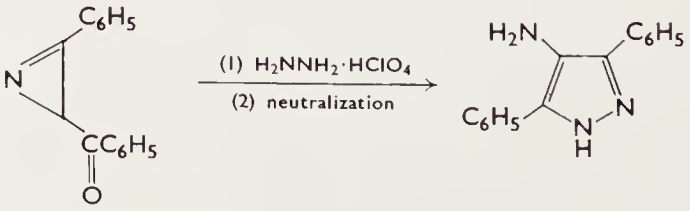
(Ref. 193)

(i) 

(Ref. 194)

(j) 

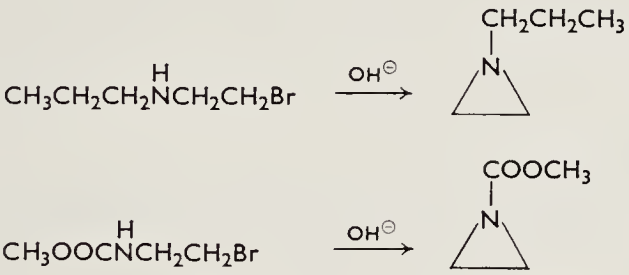
(Ref. 195)

(k) 

(Ref. 196)

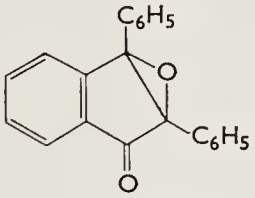
3. Explain each of the following results:

(a) Reaction (1) proceeds with first-order dependence on the organic substrate and zero-order dependence on alkali, while reaction (2) is first-order in each component:



(*Ref. 197*)

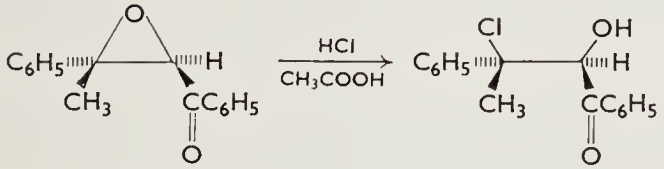
(b) Epoxyketone [**I**] upon irradiation or heating is converted to an isomeric red compound. When either source of energy is removed, the colorless [**I**] is reformed. What is the structure of the red isomer?



[**I**]

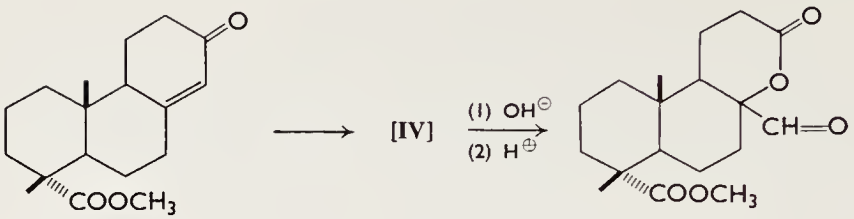
(*Ref. 198*)

(c) Ring cleavage of epoxyketone [**II**] proceeds with *retention* of configuration instead of the usual inversion of configuration.



[**II**] (*Ref. 199*)

(d) Treatment of [**III**] with excess *m*-chloroperbenzoic acid in methylene chloride results in the uptake of *two* atoms of oxygen to give [**IV**] ($\nu_{max}^{CCl_4}$ 1754 and 1709 cm^{-1}). In base, [**IV**] undergoes a facile rearrangement to [**V**]. What is the structure of [**IV**], and depict the mechanism by which it is transformed to [**V**].



(*Ref. 200*)

References and Notes

(1) The reader should satisfy himself that inversion in configuration of the nitrogen atom in **[1a]** followed by rotation of the resulting structure by 180° gives **[1b]**.

(2) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 5126 (1956); *ibid.*, **80**, 5203 (1958); A. Loewenstein, J. F. Neumer, and J. D. Roberts, *ibid.*, **82**, 3599 (1960); A. T. Bottini, R. L. VanEtten, and A. J. Davidson, *ibid.*, **87**, 755 (1965).

(3) A similar examination of the n.m.r. spectra of azetidine, pyrrolidine, piperidine, and morpholine derivatives showed that inversion of nitrogen configuration in these larger rings was too rapid for measurement even at −77°C.

(4) (a) D. Swern, *Chem. Revs.*, **45**, 1 (1949); (b) D. Swern, *Org. Reactions*, **7**, 378 (1953); (c) H. O. House, *Modern Synthetic Reactions*, W. A. Benjamin, Inc., New York, 1965, Chapter 5.

(5) N. N. Schwartz and J. H. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).

(6) The F.M.C. Corp., New York, N.Y.

(7) (a) A. Rosowsky in A. Weissberger (ed.), *The Chemistry of Heterocyclic Compounds*, Vol. 19, Part I, Interscience, New York, 1964, Chapter 1; (b) R. E. Parker and N. S. Isaac, *Chem. Revs.*, **59**, 737 (1959); (c) S. Winstein and R. B. Henderson in R. C. Elderfield (ed.), *Heterocyclic Compounds*, Vol. 1, Wiley, New York, 1950, Chapter 1.

(8) (a) P. D. Bartlett, *Rec. Chem. Progr. (Kresge-Hooker Sci. Lib.)*, **11**, 51 (1950); (b) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, **1955**, 1525.

(9) D. Swern, *J. Am. Chem. Soc.*, **69**, 1692 (1947).

(10) W. Hückel and V. Wörffel, *Chem. Ber.*, **88**, 338 (1955).

(11) A. C. Cope, S. W. Fenton, and C. F. Spencer, *J. Am. Chem. Soc.*, **74**, 5884 (1952); A. C. Cope, A. Fournier, Jr., and H. E. Simmonds, Jr., *ibid.*, **79**, 3905 (1957).

(12) (a) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, **1957**, 1958; (b) H. B. Henbest, *Proc. Chem. Soc.*, **1963**, 159; (c) B. Rickborn and S. Y. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).

(13) J. Reese, *Chem. Ber.*, **75**, 384 (1942).

(14) C. A. Bunton and G. J. Minkoff, *J. Chem. Soc.*, **1949**, 665.

(15) H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *J. Am. Chem. Soc.*, **81**, 108 (1959); H. O. House and R. S. Ro, *ibid.*, **80**, 2428 (1958).

(16) G. B. Payne and P. H. Williams, *J. Org. Chem.*, **26**, 651 (1961); G. B. Payne, P. H. Deming, and P. H. Williams, *ibid.*, **26**, 659 (1961); G. B. Payne, *ibid.*, **26**, 663, 668 (1961); G. B. Payne, *Tetrahedron*, **18**, 763 (1962); Y. Ogata and Y. Sawaki, *ibid.*, **20**, 2065 (1964).

(17) N. C. Yang and R. A. Finnegan, *J. Am. Chem. Soc.*, **80**, 5845 (1958).

(18) W. Lwowski and T. W. Mattingly, Jr., *ibid.*, **87**, 1947 (1965); W. Lwowski and T. J. Maricich, *ibid.*, **86**, 3164 (1964); K. Hafner and C. König, *Angew. Chem.*, **75**, 89 (1963) and references cited therein.

(19) R. Huisgen, *Angew. Chem. Intern. Ed.*, **2**, 565, 633 (1963).

(20) P. Scheiner, *J. Org. Chem.*, **30**, 7 (1965).

(21) (a) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345, 1353 (1965) and references cited therein; (b) V. Franzen and H. E. Driessen, *Tetrahedron Letters*, 661 (1962).

(22) C. E. Cook, R. C. Corley, and M. E. Wall, *ibid.*, 891 (1965).

(23) P. Pöhls, Inaug. diss. Univ. Marburg, Germany, 1934.

(24) B. Eistert in *Newer Methods of Preparative Organic Chemistry*, Interscience, New York, 1948, pp. 513–570; C. D. Gutsche, *Org. Reactions*, **8**, 364 (1954).

(25) A. Mustafa, *J. Chem. Soc.*, **1949**, 234; G. D. Buckley, *ibid.*, **1954**, 1850; see, however, A. L. Logothetis, *J. Org. Chem.*, **29**, 3049 (1964) where the reaction of diazomethane with fluoro-substituted imines has been found to occur readily and give rise to aziridines.

(26) (a) H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 833 (1920); (b) the direct interaction of diazo compounds with sulfur also yields episulfides: N. Latif and I. Fathy, *J. Org. Chem.*, **27**, 1633 (1962); N. Latif, I. Fathy, and B. Haggag, *Tetrahedron Letters*, 1155 (1965). It is likely that such condensations occur via the intermediacy of a thioketone.

(27) L. A. Paquette, *J. Org. Chem.*, **29**, 2851 (1964) and references cited therein.

(28) G. Opitz and K. Fischer, *Angew. Chem.*, **77**, 41 (1965).

(29) (a) H. Staudinger and F. Pfenninger, *Chem. Ber.*, **49**, 1941 (1916); (b) L. v. Vargha and E. Kovacs, *ibid.*, **75**, 794 (1942); (c) G. Hesse, E. Reichold, and S. Majmudar, *ibid.*, **90**, 2106 (1957); (d) G. Hesse and S. Majmudar, *ibid.*, **93**, 1129 (1960); (e) N. P. Neureiter and F. G. Bordwell, *J. Am. Chem. Soc.*, **85**, 1209 (1963).

(30) (a) N. J. Leonard and K. Jann, *ibid.*, **82**, 6418 (1960); **84**, 4806 (1962); (b) N. J. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.*, **28**, 1499 (1963); (c) N. J. Leonard, E. F. Kiefer, and L. E. Brady, *ibid.*, **28**, 2850 (1963); (d) N. J. Leonard, J. V. Paukstelis, and L. E.

Brady, *ibid.*, **29**, 3383 (1964); (e) N. J. Leonard and L. E. Brady, *ibid.*, **30**, 817 (1965); (f) N. J. Leonard, *Rec. Chem. Progr.* (*Kresge-Hooker Sci. Lib.*), **26**, 211 (1965).

(31) The epoxidation of olefins is sometimes preferred; however, this reaction and the cyclodehydrohalogenation of ethylene halohydrins constitute the majority of epoxide syntheses.

(32) For a summary of various kinetic investigations, see ref. 7a, p. 94.

(33) S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, **61**, 2845 (1939).

(34) The reagents which have emerged as those of choice for generating hypohalous acids *in situ* are the N-haloacetamides and N-halosuccinimides in the presence of aqueous perchloric acid, see R. Filler, *Chem. Revs.*, **63**, 21 (1963).

(35) (a) S. Winstein and L. Goodman, *J. Am. Chem. Soc.*, **76**, 4368, 4373 (1954) and references cited therein; (b) Unusual effects have, however, been noted: J. G. Traynham and O. S. Pascual, *ibid.*, **79**, 2341 (1957); J. G. Traynham and O. S. Pascual, *Tetrahedron*, **7**, 165 (1959).

(36) P. D. Bartlett and R. H. Rosenwald, *J. Am. Chem. Soc.*, **56**, 1990 (1934); P. D. Bartlett, *ibid.*, **57**, 224 (1935).

(37) P. D. Bartlett and R. V. White, *ibid.*, **56**, 2785 (1934); S. Winstein and R. E. Buckles, *ibid.*, **64**, 2780, 2787, 2791, 2796 (1942); S. Winstein and L. L. Ingraham, *ibid.*, **74**, 1160 (1952); S. Winstein and H. J. Lucas, *ibid.*, **61**, 1576, 2845 (1939); R. A. Raphael, *J. Chem. Soc.*, **1952**, 401.

(38) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

(39) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, *Conformational Analysis*, Interscience, New York, 1965, p. 284.

(40) H. Nilsson and L. Smith, *Z. Physik. Chem.*, **166A**, 136 (1933) and earlier references cited therein.

(41) A. A. Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 713 (1941); *Chem. Abstr.*, **36**, 404 (1942).

(42) D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, **1957**, 2907.

(43) See, for example, D. Y. Curtin and R. J. Harder, *J. Am. Chem. Soc.*, **82**, 2357 (1960).

(44) S. Gabriel, *Chem. Ber.*, **21**, 1049 (1888); S. Gabriel and R. Stelzner, *ibid.*, **28**, 2929 (1895).

(45) H. Wenker, *J. Am. Chem. Soc.*, **57**, 2328 (1935).

(46) (a) J. S. Fenton in R. C. Elderfield (ed.), *Heterocyclic Compounds*, Vol. 1, Wiley, New York, 1950, Chapter 2; (b) P. E. Fanta in A. Weissberger (ed.), *The Chemistry of Heterocyclic Compounds*, Vol. 19, Part I, Interscience, New York, 1964, Chapter 2.

(47) G. F. Hennion and P. E. Butler, *J. Org. Chem.*, **27**, 2089 (1962).

(48) S. J. Brois, *ibid.*, **27**, 3532 (1962).

(49) (a) G. L. Closs and S. J. Brois, *J. Am. Chem. Soc.*, **82**, 6068 (1960); (b) J. Meinwald, Y. C. Meinwald, and T. N. Baker, III, *ibid.*, **86**, 4074

(1964); E. Vogel, M. Biskup, W. Pretzer, and W. A. Böll, *Angew. Chem. Intern. Ed.*, **3**, 642 (1964).

(50) (a) A. Hassner and C. Heathcock, *Tetrahedron Letters*, 393 (1963); 1125 (1964); (b) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964); (c) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 3640 (1964).

(51) H. Freundlich and G. Salomon, *Z. Physik. Chem.*, **166A**, 161, 179 (1933) and previous papers; G. Salomon, *Helv. Chim. Acta*, **16**, 1361 (1933); **19**, 743 (1936); P. L. Levins and Z. B. Papanastassiou, *J. Am. Chem. Soc.*, **87**, 826 (1965) and pertinent references cited therein.

(52) The Wenker synthesis has been found not to be stereospecific when the hydroxyl group of the amino alcohol is on a benzyl-type carbon atom, see ref. 46b, p. 534.

(53) A. Weissberger and H. Bach, *Chem. Ber.*, **64**, 1095 (1931); **65**, 631 (1932).

(54) N. H. Cromwell, R. D. Babson, and C. E. Harris, *J. Am. Chem. Soc.*, **65**, 312 (1943).

(55) A. B. Turner, H. W. Heine, J. Irving, and J. B. Bush, Jr., *ibid.*, **87**, 1050 (1965).

(56) N. H. Cromwell, *Rec. Chem. Progr.* (*Kresge-Hooker Sci. Lib.*), **19**, 215 (1958).

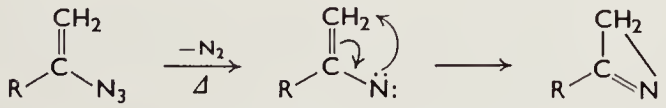
(57) N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **30**, 821 (1965).

(58) (a) C. O'Brien, *Chem. Revs.*, **64**, 81 (1964); (b) D. J. Cram and M. J. Hatch, *J. Am. Chem. Soc.*, **75**, 33 (1953).

(59) Aldoxime tosylates on reaction with base undergo *E*2 elimination of *p*-toluenesulfonic acid with the formation of nitriles or isonitriles: (a) E. Mueller and B. Narr, *Z. Naturforsch.*, **16B**, 845 (1961); (b) M. S. Hatch and D. J. Cram, *J. Am. Chem. Soc.*, **75**, 38 (1953).

(60) H. O. House and W. Berkowitz, *J. Org. Chem.*, **28**, 2271 (1963).

(61) The insertion of unsaturated nitrenes into double bonds as a preparative route to azirines has been reported: G. Smolinsky, *J. Am. Chem.*



Soc., **83**, 4483 (1961); G. Smolinsky, *J. Org. Chem.*, **27**, 3557 (1962); L. Horner, A. Christmann, and A. Gross, *Chem. Ber.*, **96**, 399 (1963).

(62) Although a direct 1,3-displacement of tosylate by the carbanion in a concerted process has not been definitely ruled out,[60] the process may be considered unlikely because (a) an S_N2 displacement at a multiply bonded atom would be involved, and (b) frontside displacements, as would be required in the case of **[25]**, are quite unfavorable.

(63) (a) G. H. Alt and W. S. Knowles, *J. Org. Chem.*, **25**, 2047 (1960); (b) H. E. Baumgarten and J. M. Petersen, *ibid.*, **28**, 2369 (1963); H. E.

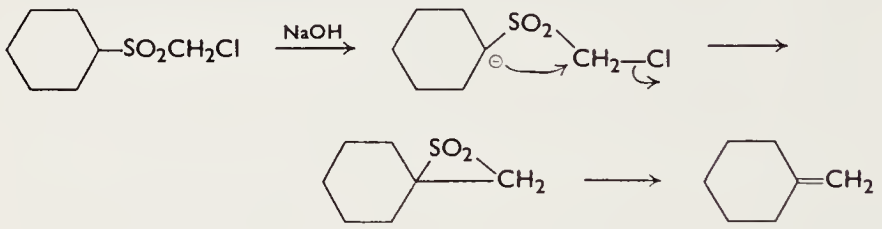
Baumgarten, J. E. Dirks, J. M. Petersen, and D. C. Wolf, *J. Am. Chem. Soc.*, **82**, 4422 (1960); H. E. Baumgarten and J. M. Petersen, *ibid.*, **82**, 459 (1960); H. E. Baumgarten and F. A. Bower, *ibid.*, 76, 4561 (1954).

(64) (a) R. F. Parcell, *Chem. Ind. (London)*, **1963**, 1396; (b) D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *J. Org. Chem.*, **30**, 579 (1965).

(65) (a) H. E. Baumgarten, *J. Am. Chem. Soc.*, **84**, 4975 (1962); (b) H. E. Baumgarten, J. F. Fuerholzer, R. D. Clark, and R. D. Thompson, *ibid.*, **85**, 3303 (1963); (c) J. C. Sheehan and I. Lengyel, *ibid.*, 86, 746 (1964) and other pertinent references cited in these papers.

(66) A. S. Kende, *Org. Reactions*, **11**, 261 (1960).

(67) Another process related in nature to the Favorskii reaction is the Ramberg-Bäcklund rearrangement of α-halosulfones, for example,

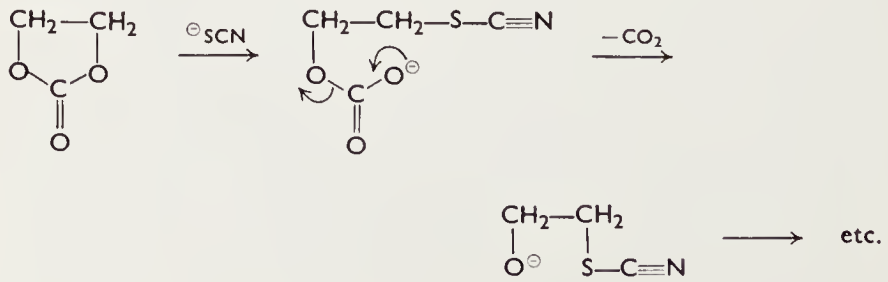


which proceeds via an episulfone intermediate to an olefin. This reaction cannot be used for the synthesis of episulfones, however, because the latter compounds lose rapidly the elements of sulfur dioxide (to produce olefins) in the alkaline medium required for the rearrangement; see L. A. Paquette, *J. Am. Chem. Soc.*, 86, 4085, 4089, 4383 (1964) for leading references.

(68) (a) D. D. Reynolds and D. L. Fields in A. Weissberger (ed.), *The Chemistry of Heterocyclic Compounds*, Vol. 19, Part I, Interscience, New York, 1964, Chapter 3; (b) A. Schönberg in E. Müller (ed.), *Methoden der Organischen Chemie (Houben-Weyl)*, Georg Thieme Verlag, Stuttgart, Germany, 1955, pp. 153 ff.

(69) E. E. Van Tamelen, *J. Am. Chem. Soc.*, 73, 3444 (1951).

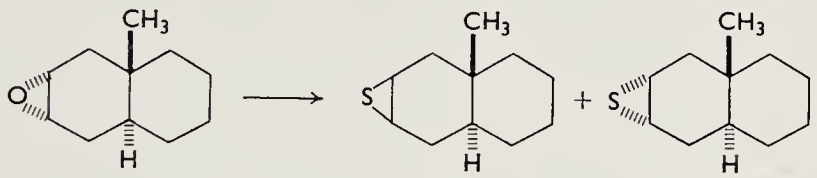
(70) The fusion of ethylene carbonate with potassium thiocyanate yields ethylene sulfide: S. Searles and E. F. Lutz, *J. Am. Chem. Soc.*, **80**, 3168 (1958). A similar mechanistic sequence has been proposed:



(71) C. C. J. Culvenor, W. Davies, and W. E. Savige, *J. Chem. Soc.*, **1952**, 4480, and references cited in this paper.

(72) (a) L. Goodman, A. Benitez, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 1680 (1958); (b) D. A. Lightner and C. Djerassi, *Tetrahedron*, **21**, 583 (1965).

(73) This procedure is also advisable for minimizing the formation of mixtures when higher molecular weight epoxides are involved. For example, reaction of (+)-*trans*-9-methyldecalin-2α,3α-epoxide with potassium thiocyanate in refluxing ethanol proceeds slowly to give a 4 : 1 mixture of the episulfides shown. The latter substance most probably arises from reaction of the initially formed episulfide with thiocyanate.



(4 parts) (1 part)

(74) As a general rule, α-chloro derivatives are preferred to the bromo or iodo analogs because they give rise to fewer side products. In situations where the chloro derivative yields cleanly the desired epoxy compound, the bromo and iodo counterparts give alkylation products or result in the formation of a mixture of the two.

(75) (a) M. S. Newman and B. J. Magerlein, *Org. Reactions*, **5**, 413 (1949); (b) M. Ballester, *Chem. Revs.*, **55**, 283 (1955).

(76) M. Ballester and P. D. Bartlett, *J. Am. Chem. Soc.*, **75**, 2042 (1953).

(77) R. H. Hunt, L. J. Chinn, and W. S. Johnson, *Org. Syn.*, **Coll. Vol. 4**, 459 (1963).

(78) J. A. Berson, *J. Am. Chem. Soc.*, **74**, 5175 (1952); H. H. Wasserman, N. E. Aubrey, and H. E. Zimmerman, *ibid.*, **75**, 96 (1953); H. H. Wasserman and J. B. Brows, *J. Org. Chem.*, **19**, 515 (1954); C. L. Stevens, R. J. Church, and V. J. Traynelis, *ibid.*, **19**, 522 (1954); C. L. Stevens and V. Traynelis, *ibid.*, **19**, 533 (1954); N. H. Cromwell and R. A. Setterquist, *J. Am. Chem. Soc.*, **76**, 5752 (1954).

(79) (a) H. E. Zimmerman and L. Ahramjian, *ibid.*, **82**, 5459 (1960); (b) C. C. Tung, A. J. Speziale, and H. W. Frazier, *J. Org. Chem.*, **28**, 1514 (1963).

(80) H. Kwart and L. G. Kirk, *ibid.*, **22**, 116, 1755 (1957).

(81) (a) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Non-Metallic Compounds*, Prentice-Hall, New York, 1954, pp. 181 *et seq.*, (b) T. A. Geissman and R. I. Akawie, *J. Am. Chem. Soc.*, **73**, 1993 (1951);

(c) R. L. Huang, *J. Org. Chem.*, **19**, 1363 (1954); (d) R. L. Huang, *J. Chem. Soc.*, 2539 (1954); (e) F. Ya. Perveev and F. Ya. Statsevich, *Zh. Obshch. Khim.*, **30**, 3558 (1960) and earlier papers.

(82) M. Tiffeneau, *Compt. Rend.*, **134**, 774 (1902).

(83) Compare (a) H. O. House, *J. Am. Chem. Soc.*, **77**, 3070, 5083 (1955); (b) S. M. Naqvi, J. P. Horwitz, and R. F. Filler, *ibid.*, **79**, 6283 (1957).

(84) R. Justoni, *Gazz. Chim. Ital.*, **69**, 378 (1939).

(85) F. Winternitz, C. Menon, and E. Arnal, *Bull. Soc. Chim. France*, **1960**, 505.

(86) C. L. Stevens and B. T. Gillis, *J. Am. Chem. Soc.*, **79**, 3448 (1957).

(87) V. Mark, *ibid.*, **85**, 1884 (1963).

(88) M. S. Newman and S. Blum, *ibid.*, **86**, 5598 (1964).

(89) For a comprehensive review of this subject, see ref. 46.

(90) F. H. Dickey, W. Fickett, and H. J. Lucas, *J. Am. Chem. Soc.*, **74**, 944 (1952).

(91) R. Ghirardelli and H. J. Lucas, *ibid.*, **79**, 734 (1957).

(92) G. K. Helmkamp and N. Schnantz, *Tetrahedron*, **2**, 304 (1958).

(93) W. Traube and E. Lehmann, *Chem. Ber.*, **32**, 720 (1899).

(94) H. Stamm, *Angew. Chem.*, **74**, 694 (1962).

(95) A. Funke and G. Benoit, *Bull. Soc. Chim. France*, **1953**, 1021.

(96) For a more comprehensive discussion of this point, see E. L. Eliel in M. S. Newman (ed.), *Steric Effects in Organic Chemistry*, Wiley, New York, 1956, pp. 106–114.

(97) C. O. Guss, *J. Am. Chem. Soc.*, **71**, 3460 (1949); C. O. Guss and H. R. Williams, *J. Org. Chem.*, **16**, 1809 (1951).

(98) A. Feldstein and C. A. Vanderwerf, *J. Am. Chem. Soc.*, **76**, 1626 (1954); R. Fuchs and C. A. Vanderwerf, *ibid.*, **76**, 1631 (1954).

(99) S. J. Cristol, J. R. Douglass, and J. S. Meek, *ibid.*, **73**, 816 (1951).

(100) C. O. Guss, R. Rosenthal, and R. F. Brown, *ibid.*, **75**, 2393 (1953).

(101) M. N. Rerick and E. L. Eliel, *ibid.*, **84**, 2356 (1962); E. L. Eliel and M. N. Rerick, *ibid.*, **82**, 1362 (1960); E. L. Eliel and D. W. Delmonte, *ibid.*, **80**, 1744 (1958).

(102) A. Fürst and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

(103) A. Fürst and R. Scotoni, Jr., *ibid.*, **36**, 1332 (1953).

(104) A. Hassner and C. Heathcock, *J. Org. Chem.*, **30**, 1748 (1965).

(105) D. B. Denney and M. J. Boskin, *J. Am. Chem. Soc.*, **81**, 6330 (1959); D. B. Denney, J. J. Vill, and M. J. Boskin, *ibid.*, **84**, 3944 (1962).

(106) W. S. Wadsworth, Jr., and W. D. Emmons, *ibid.*, **83**, 1733 (1961).

(107) L. Horner, H. Hoffmann, and V. G. Toscano, *Chem. Ber.*, **95**, 536 (1962); see also L. Horner, H. Hoffmann, W. Klink, H. Ertel and V. G. Toscano, *ibid.*, **95**, 581 (1962).

(108) I. Tömösközi, *Chem. Ind.* (*London*), 689 (1965).

(109) I. Tömösközi, *Tetrahedron*, **19**, 1969 (1963).

(110) Y. Inouye, T. Sugita, and H. M. Walborsky, *ibid.*, **20**, 1695 (1964).

(111) N. G. Gaylord and E. I. Becker, *Chem. Revs.*, **49**, 413 (1951).

(112) F. H. Norton and H. B. Hass, *J. Am. Chem. Soc.*, **58**, 2147 (1936).

(113) For a comprehensive discussion of the reaction of epoxides with organometallic reagents, see ref. 7a, pp. 386 ff.

(114) P. D. Bartlett and C. M. Berry, *J. Am. Chem. Soc.*, **56**, 2683 (1934).

(115) O. Mass and E. H. Boomer, *ibid.*, **44**, 1709 (1922); for kinetic evidence on this point, see J. N. Brønsted, M. Kilpatrick, and M. Kilpatrick, *ibid.*, **57**, 428 (1929).

(116) A frequently quoted exception to this rule is found in the report that hydrochloric acid reacts with either *cis*- or *trans*-2,3-diphenylethyleneimine to afford a mixture of the two isomeric α-amino-β-chlorodibenzyls (suggesting, of course, that both cis and trans additions have occurred): A. Weissberger and H. Bach, *Chem. Ber.*, **65**, 631 (1932). Such is, however, not the case with the related *cis*- and *trans*-stilbene oxides which open stereospecifically: D. Reulos, *Compt. Rend.*, **216**, 714 (1943); **218**, 795 (1944).

(117) S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, **61**, 1581 (1939).

(118) C. C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, **1949**, 282.

(119) C. A. Stewart and C. A. Vanderwerf, *J. Am. Chem. Soc.*, **76**, 1259 (1954).

(120) M. Tiffeneau and E. Fourneau, *Compt. Rend.*, **146**, 697 (1908); A. Orekhoff and M. Tiffeneau, *Bull. Soc. Chim. France*, **37**, 1410 (1925).

(121) F. Arndt, J. Amende, and W. Ender, *Monatsh. Chem.*, **59**, 202 (1932).

(122) S. Gabriel and H. Ohle, *Chem. Ber.*, **50**, 804 (1917).

(123) F. Wolfheim, *ibid.*, **47**, 1440 (1914).

(124) R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, **1943**, 613; P. N. Chakravorty and R. H. Levin, *J. Am. Chem. Soc.*, **64**, 2317 (1942).

(125) D. Atherton and T. P. Hilditch, *J. Chem. Soc.*, **1943**, 204.

(126) E. L. Gustus and P. G. Stevens, *J. Am. Chem. Soc.*, **55**, 378 (1933).

(127) W. Davies and E. W. Savige, *J. Chem. Soc.*, **1950**, 317.

(128) C. Golumbic, J. S. Fruton, and M. Bergmann, *J. Org. Chem.*, **11**, 518 (1946); N. B. Chapman and J. W. James, *J. Chem. Soc.*, **1954**, 2103; J. F. Allen and N. B. Chapman, *ibid.*, **1960**, 1482.

(129) A. T. Bottini, B. F. Dowden, and R. L. Van Etten, *J. Am. Chem. Soc.*, **87**, 3250 (1965).

(130) P. E. Fanta, L. J. Pandya, W. R. Groskopf, and H.-J. Su., *J. Org. Chem.*, **28**, 413 (1963); A. T. Bottini and R. L. Van Etten, *ibid.*, **30**, 575 (1965); G. K. Helmkamp, R. D. Clark, and J. R. Koskinen, *ibid.*, **30**, 666

(1965). Note especially the fact that such methiodides undergo rapid equilibration with the corresponding 2-iodoalkylamines: A. T. Bottini, B. F. Dowden, and L. Sousa, *J. Am. Chem. Soc.*, **87**, 3249 (1965).

(131) A. L. Logothetis, *ibid.*, **87**, 749 (1965).

(132) P. D. Bartlett, S. D. Ross, and C. G. Swain, *ibid.*, **69**, 2971 (1947); P. D. Bartlett, J. W. Davis, S. D. Ross, and C. G. Swain, *ibid.* **69**, 2977 (1947); P. D. Bartlett, S. D. Ross, and C. G. Swain, *ibid.*, **71**, 1415 (1949).

(133) E. M. Schultz and J. M. Sprague, *ibid.*, **70**, 48 (1948).

(134) R. C. Fuson and C. L. Zirkle, *ibid.*, **70**, 2760 (1948).

(135) W. C. G. Ross, *Biological Alkylating Agents*, Butterworths, London, England, 1962.

(136) N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 3021 (1963).

(137) J. V. Paukstelis, Ph.D. Thesis, University of Illinois, Urbana, 1964.

(138) M. T. Bogert and R. L. Roblin, Jr., *J. Am. Chem. Soc.*, **55**, 3741 (1933).

(139) J. B. Doughty, C. L. Lazell, and A. R. Collett, *ibid.*, **72**, 2866 (1950).

(140) G. K. Helmkamp and D. J. Pettitt, *J. Org. Chem.*, **25**, 1754 (1960), see also ref. 141.

(141) D. J. Pettitt and G. K. Helmkamp, *ibid.*, **28**, 2932 (1963).

(142) G. K. Helmkamp, B. A. Olsen, and D. J. Pettitt, *ibid.*, **30**, 676 (1965), see also D. J. Cram, *J. Am. Chem. Soc.*, **71**, 3883 (1949); N. Kharasch and A. J. Havlik, *ibid.*, **75**, 3734 (1953); N. R. Slobodkin and N. Kharasch, *ibid.*, **82**, 5837 (1960).

(143) (a) M. J. Boskin and D. B. Denney, *Chem. Ind.* (*London*), 330 (1959); (b) D. E. Bissing and A. J. Speziale, *J. Am. Chem. Soc.*, **87**, 2683 (1965).

(144) A. J. Speziale and D. E. Bissing, *ibid.*, **85**, 1888, 3878 (1963).

(145) H. O. House and G. Rasmusson, *J. Org. Chem.*, **26**, 4278 (1961), see also ref. 4c, p. 253.

(146) (a) R. E. Davis, *J. Org. Chem.*, **23**, 1767 (1958); (b) D. B. Denney and M. J. Boskin, *J. Am. Chem. Soc.*, **82**, 4736 (1960); (c) N. P. Neureiter and F. G. Bordwell, *ibid.*, **81**, 578 (1959); (d) R. D. Schultz and R. L. Jacobs, *J. Org. Chem.*, **23**, 1799 (1958).

(147) F. G. Bordwell, H. M. Andersen, and B. M. Pitt, *J. Am. Chem. Soc.*, **76**, 1082 (1954).

(148) G. K. Helmkamp and D. J. Pettitt, *J. Org. Chem.*, **29**, 3258 (1964).

(149) R. D. Clark and G. K. Helmkamp, *ibid.*, **29**, 1316 (1964).

(150) Aziridines can also be deaminated readily with 3-nitro-N-nitrosocarbazole: C. L. Bumgardner, K. S. McCallum, and J. P. Freeman, *J. Am. Chem. Soc.*, **83**, 4417 (1961).

(151) B. Tchoubar, *Compt. Rend.*, **214**, 117 (1942), see also J. E. Horan and R. W. Schiessler, *Org. Syn.*, **41**, 53 (1961).

(152) Magnesium bromide is known to initially convert epoxides to bromohydrin derivatives prior to rearrangement.[83]

(153) H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, **78**, 4394 (1956).

(154) E. A. Braude, A. A. Webb, and M. V. S. Sultanbawa, *J. Chem. Soc.*, **1958**, 3328.

(155) H. B. Henbest and T. I. Wrigley, *ibid.*, **1957**, 4596.

(156) A. C. Cope, P. A. Trumbull, and E. R. Trumbull, *J. Am. Chem. Soc.*, **80**, 2844 (1958).

(157) S. Gabriel and R. Stelzner, *Chem. Ber.*, **28**, 2929 (1895).

(158) (a) A. S. Deutsch and P. E. Fanta, *J. Org. Chem.*, **21**, 892 (1956); (b) H. W. Heine and Z. Proctor, *ibid.*, **23**, 1554 (1958); (c) H. W. Heine, M. E. Fetter, and E. M. Nicholson, *J. Am. Chem. Soc.*, **81**, 2202 (1959).

(159) (a) P. E. Fanta and A. S. Deutsch, *J. Org. Chem.*, **23**, 72 (1958); (b) P. D. Talukdar and P. E. Fanta, *ibid.*, **24**, 526 (1959); (c) D. V. Kashelikar and P. E. Fanta, *J. Am. Chem. Soc.*, **82**, 4927 (1960); (d) D. V. Kashelikar and P. E. Fanta, *ibid.*, **82**, 4930 (1960).

(160) For a review of aziridine rearrangements, see H. W. Heine, *Angew. Chem.*, **74**, 772 (1962); *Angew. Chem. Intern. Ed.*, **1**, 528 (1962). More recent examples have been described by: H. W. Heine and A. C. Brooker, *J. Org. Chem.*, **27**, 2943 (1962); H. W. Heine, *J. Am. Chem. Soc.*, **85**, 2743 (1963); H. W. Whitlock, Jr., and G. L. Smith, *Tetrahedron Letters*, 1389 (1965).

(161) H. W. Heine, W. G. Kenyon, and E. M. Johnson, *J. Am. Chem. Soc.*, **83**, 2570 (1961).

(162) A. B. Turner, H. W. Heine, J. Irving, and J. B. Bush, Jr., *ibid.*, **87**, 1050 (1965).

(163) H. O. House, *ibid.*, **76**, 1235 (1954).

(164) P. Rajagopalan and C. N. Talaty, *ibid.*, **88**, 5048 (1966).

(165) J. R. Lowell, Jr., and G. K. Helmkamp, *ibid.*, **88**, 768 (1966).

(166) J. W. Ager, F. A. Eastwood, and R. Robinson, *Tetrahedron*, **Suppl. No. 7**, 277 (1966).

(167) H. W. Heine, D. C. King, and L. A. Portland, *J. Org. Chem.*, **31**, 2662 (1966).

(168) L. A. Paquette and L. S. Wittenbrook, *Chem. Commun.*, **1966**, 471.

(169) R. Huisgen, R. Sustmann, and K. Bunge, *Tetrahedron Letters*, **1966**, 3603.

(170) H. M. Walborsky and D. F. Loncrini, *J. Org. Chem.*, **22**, 1117 (1957).

(171) E. Pfeil and U. Harder, *Angew. Chem. Intern. Ed.*, **4**, 518 (1965).

(172) L. A. Carpino and L. V. McAdams, III, *J. Am. Chem. Soc.*, **87**, 5804 (1965).

(173) C. Heathcock, *ibid.*, **88**, 4110 (1966).

(174) S. J. Brois and G. P. Beardsley, *Tetrahedron Letters*, **1966**, 5113.

(175) K. Ponsold and D. Klemm, *Chem. Ber.*, **99**, 1502 (1966).

(176) S. S. Kulp, V. B. Fish, and N. R. Easton, *J. Med. Pharm. Chem.*, **6**, 516 (1963).

(177) J. Falbe, H.-J. Schulze-Steinen, and F. Korte, *Chem. Ber.*, **97**, 1096 (1964).

(178) H. W. Whitlock, Jr., and G. L. Smith, *Tetrahedron Letters*, **1965**, 1389.

(179) R. R. Sauers, R. A. Parent, and S. B. Damle, *J. Am. Chem. Soc.*, **88**, 2257 (1966).

(180) A. Padwa, *ibid.*, **87**, 4205 (1965).

(181) N. J. Leonard, K. Jahn, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.*, **28**, 1499 (1963).

(182) C. L. Stevens and C. H. Chang, *ibid.*, **27**, 4392 (1962).

(183) H. W. Heine and R. Peavy, *Tetrahedron Letters*, **1965**, 3123; A. Padwa and L. Hamilton, *ibid.*, **1965**, 4363.

(184) J. A. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 3475 (1965).

(185) F. Jakob and P. Schlack, *Chem. Ber.*, **96**, 88 (1963).

(186) D. Lavie, Y. Kashman, E. Glotter, and N. Danielli, *J. Chem. Soc.* (*C*), **1966**, 1757.

(187) J. A. Deyrup and R. B. Greenwald, *Tetrahedron Letters*, **1966**, 5091.

(188) P. D. Bartlett and W. P. Giddings, *J. Am. Chem. Soc.*, **82**, 1240 (1960).

(189) G. Smolinsky and B. I. Feuer, *J. Org. Chem.*, **31**, 1423 (1966).

(190) R. M. Bowman, A. Chambers, and W. R. Jackson, *J. Chem. Soc.* (*C*), **1966**, 1296.

(191) H. W. Heine, *J. Am. Chem. Soc.*, **85**, 2743 (1963).

(192) A. Padwa and L. Hamilton, *J. Org. Chem.*, **31**, 1995 (1966).

(193) M. P. Hartshorn, D. N. Kirk, and A. F. A. Wallis, *J. Chem. Soc.*, **1964**, 5494.

(194) J. E. Dolfini and D. M. Dolfini, *Tetrahedron Letters*, **1965**, 2053.

(195) H. W. Heine and F. Scholer, *ibid.*, **1964**, 3667.

(196) E. F. Ullman and B. Singh, *J. Am. Chem. Soc.*, **88**, 1844 (1966).

(197) W. J. Gensler and B. A. Brooks, *J. Org. Chem.*, **31**, 568 (1966).

(198) E. F. Ullman and J. E. Milks, *J. Am. Chem. Soc.*, **86**, 3814 (1964).

(199) H. H. Wasserman and N. E. Aubrey, *ibid.*, **78**, 1726 (1956).

(200) C. W. J. Chang and S. W. Pelletier, *Tetrahedron Letters*, **1966**, 5483.