

Oxirenes

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I. Introduction

This review is a critical summary of the oxirene literature from its inception to the 1982 April issues of *Chemical Abstracts*, inclusive. An attempt has been made to refer directly to most of the papers on this subject (including all the main ones) and through the leading references therein to the entire oxirene literature, with the exception of papers that make only passing references to this system.

Oxirene (1) is one of a number of heterocycles in which the CH₂ group of cyclopropane has been replaced by a group or atom associated with groups 5 or 6 of the periodic table. Replacement of the CH₂ group of cy-



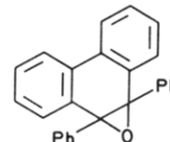
clopropane by an NH group gives 1*H*-azirine (2), while replacement by a sulfur atom results in thiirene (3). These currently favored names for heterocycles 1, 2, and 3 are based on the cumbersome Hantzsch-Widman system,¹ which at present eclipses the simple, effective and elegant system of replacement nomenclature.¹ In the latter, 1, 2, and 3 are, respectively, oxacyclopropane, aza-2-cyclopropane, and thiacyclopropane. The oxirene appellation will be used in this review, but I hope that increasing acceptance of replacement nomenclature will eventually relegate it to the status of a chemical colloquialism.

The reader should be warned that *Chemical Abstracts*, in keeping with its practice of naming polycyclic fused-ring systems as derivatives of a fully conjugated



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parent system, bestows the term oxirene on some compounds which are actually *oxiranes* (epoxides), derivatives of oxacyclopropane. An example is "1a,9a-dihydro-1a,9b-diphenylphenanthro[9,10-*b*]oxirene":²



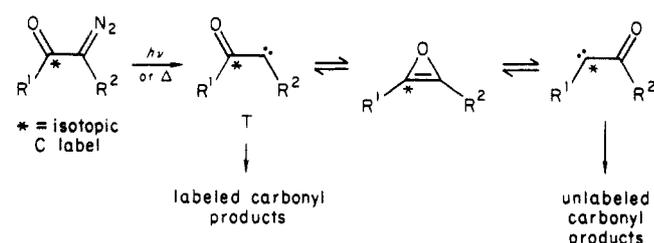
This compound is really a phenanthrene 9,10-oxide, a benzene oxide rather than a benzyne oxide.

Compounds 1, 2, and 3 have been by far the most intensively investigated heterocyclopropenes. While 1 and 2 remain elusive, 3 has recently been observed spectroscopically at low temperatures.³ The interest attached to these systems derives from the challenge they pose to synthesis, to theory, and to the unraveling of their involvement in reaction mechanisms. Brief reviews have appeared on 1, 2, and 3,⁴⁻⁶ and on 1, 3, and silacyclopropane.^{5,6}

The study of oxirenes may be divided into three phases. The first phase is marked by three reports of the synthesis of this system. Oxirenes made their debut in the chemical literature in 1870, when Berthelot claimed that oxidation of propyne with chromium trioxide gave methyloxirene.⁷ They reappear again half a century later, with the report by Madelung and Oberwegner that the reaction of an α-chloro ketone with base gave diphenyloxirene.⁸ In 1952, Schubach and Franzen reported that 5-decyne (dibutylacetylene) reacted with peroxyethanoic acid (peracetic acid) to give dibutyloxirene.⁹ All these claims have been shown to have been in error.

The second, and current, phase of oxirene chemistry began in 1968 with the demonstration by Strausz and

Scheme I



co-workers,¹⁰ as outlined in Scheme I, that a species with the symmetry of an oxirene is involved in the decomposition of α -diazo ketones (the Wolff rearrangement). The reality of this species (the central dogma of oxirene chemistry, the interconversion of oxirenes and oxo carbenes—e.g., from diazo ketone decomposition—has recently been challenged;¹¹ this heresy is briefly discussed in IIIA1 and IIID1) has been abundantly confirmed by further work by the research groups of Strausz and of Zeller (IIID1). However, no oxirene has ever been isolated or spectroscopically observed (see ref 110); there is but one problematic example of the trapping of an oxirene (IIID1), and it is not known if the species 4 is a real intermediate or merely a transition state. This distinction, although important, has only rarely been explicitly recognized in experimental work on oxirene; see, for example, the perceptive comments by Greenberg and Liebman⁵ and by Zeller.¹²

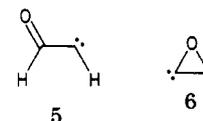
There now exists a significant body of experimental facts (section III), supported by increasingly sophisticated theoretical work (section II), which strongly indicate that the parent oxirene and its simple alkyl and aryl derivatives are, at best, of low stability. The available evidence, then, does not allow us to decide if these species are relative minima (intermediates) or maxima (transition states or activated complexes) on the potential energy hypersurface. Should the latter situation obtain, then simple oxirenes, at least, are forever beyond the grasp of preparation and direct observation, and chemists must be reconciled to consigning them to those but indirectly accessible regions inhabited by such species as the pentavalent carbon of the S_N2 transition state (pace Sneen¹³). Of course, as has been pointed out by one who was not inexperienced in the art and science of synthesis (R. B. Woodward¹⁴), mere coyness toward the advances of the experimenter is no proof of inability to exist; and indeed there appears to be at present no example of a molecule for which can be drawn a conventional Kekulé structure with normal octets that has been shown to be incapable of existence.

We may now be on the verge of the third phase of oxirene chemistry, in which modern matrix-isolation techniques¹⁵ will permit the spectroscopic observation of this system, theory will serve as a guide to the synthesis of relatively stable oxirenes (cf. a fairly stable thiirene¹⁶), and these elusive heterocycles may even become recognized as genuine, albeit transient, natural products (IIIA3).

II. Theoretical Investigations

The simplest, qualitative, theoretical understanding of the nature of oxirene is provided by Breslow's concept of antiaromaticity. Whatever criticisms may be leveled at this notion,¹⁷ it did correctly predict that

oxirene should be unusually unstable. Quantitative information on this question was adduced by Dewar and Ramsden¹⁸ who concluded, on the basis of semi-empirical molecular orbital calculations, that the antiaromatic destabilization of 1 should be small. These workers found oxirene to be 100 kJ mol⁻¹ stabler than methanoylcarbene (formylcarbene) (5) and predicted that this carbene should rearrange to oxirene without an activation energy barrier. The cyclic carbenic iso-



mer of oxirene, carbenaioxirane (oxiranylidene) (6), was calculated to be ca. 65 kJ mol⁻¹ stabler than oxirene. Of particular significance was the prediction that oxirene should be "stable", that is, a true intermediate and not a mere transition state. Similar results were obtained by Hopkinson¹⁹ using ab initio molecular orbital methods. Other workers, using such methods, also found 6 to be ca. 40 kJ mol⁻¹ lower in energy than 1.

Sophisticated ab initio molecular orbital calculations with full geometric optimization indicate that oxirene is less stable than was suggested by some of the earlier computations. The results of such work are presented in a recent review of 1, 2, and 3⁴ and, along with leading references, in an excellent report on state-of-the-art calculations on 1.²⁰ The salient conclusions of these more recent computations are summarized in Figure 1. Oxirene is predicted to be a true intermediate, but with an activation barrier of only 8 kJ mol⁻¹ (31 kJ mol⁻¹ according to ref 4; even an activation of 31 kJ mol⁻¹ corresponds to a room-temperature lifetime of only ca. 10⁻⁸ s). The surmounting of this small barrier converts oxirene into methanoylcarbene (5), which is predicted to be merely a transition state on the way to ketene (7) as shown in Figure 1, or at best⁴ an unstable intermediate that isomerizes to ketene with an activation energy of only 24 kJ mol⁻¹. The reverse process, the conversion of the oxo carbene to oxirene, requires vibrationally excited carbene. This is accessible photochemically by an electronically excited oxo carbene falling to an upper vibrational level of its electronic ground state (internal conversion), or, less efficiently, by generating the carbene at elevated temperatures (IIID1). The oxirene-oxo carbene interconversion, and other potential routes to oxirene, are limited to the singlet hypersurface.

Neither ground-state ethynol (8, hydroxyacetylene) nor carbenaioxirane (6) appear to be viable points of ingress to the oxirene-methanoylcarbene system, as both 8 and 6 can isomerize to ketene by lower energy pathways. The limited experimental information available on carbenaioxirane (IIID2) indicates that it is indeed largely isolated from the oxirene-methanoylcarbene manifold (but note the work of Russell and Rowland, IIID1); appropriate labeling experiments with (the unknown) ethynol have not been performed.

As was mentioned in the Introduction, isotopic labeling experiments with α -diazo ketones have confirmed that labeled oxo carbenes can interconvert through a species with the symmetry of an oxirene (Scheme I). Furthermore, experimental evidence has been obtained²¹ that methanoylcarbene is indeed a species of very low kinetic stability, or even a mere transition state on the route to ketene. There thus appear to be sound

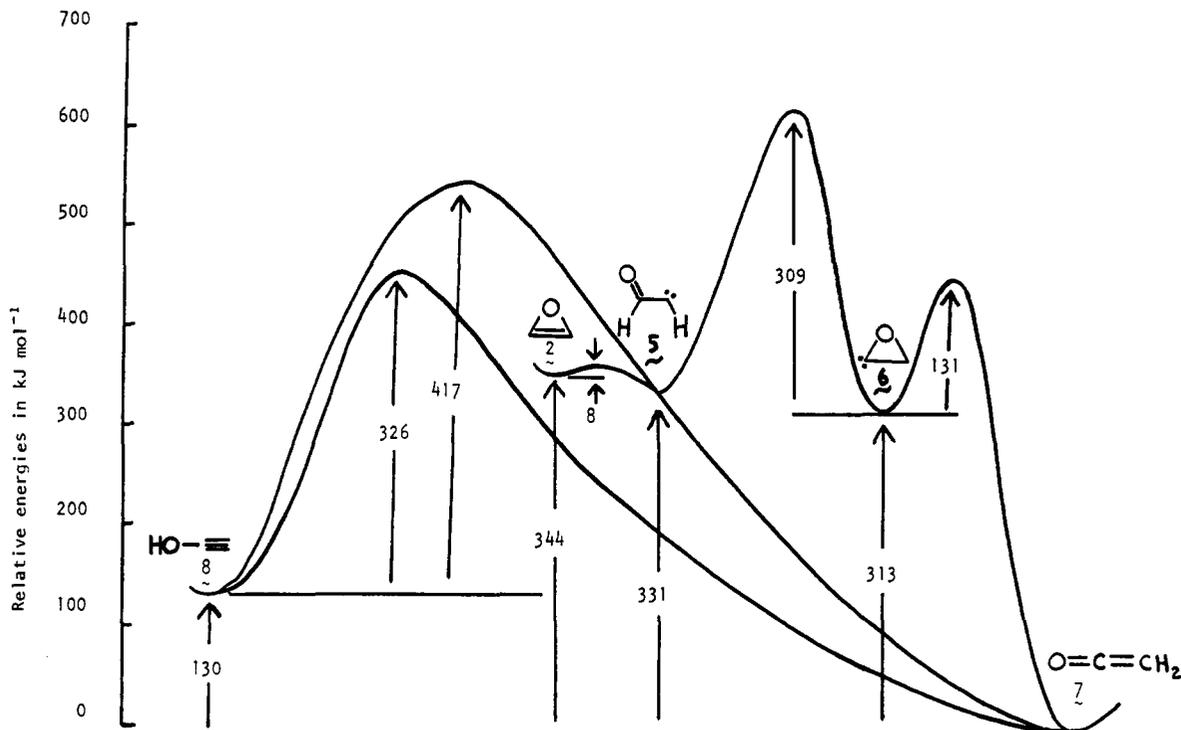


Figure 1. The C_2H_2O energy surface.

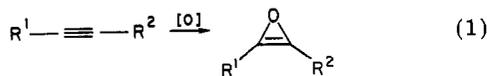
grounds for accepting as essentially correct the relative thermodynamic stabilities and the activation barriers shown in Figure 1. The significance of the heights of the relevant energy barriers (and thus the corresponding rate constants) for experiments designed to detect or isolate oxirene (or azirine, or thiirene) has been subjected to a kinetic analysis by Meier and Kolshorn,²² and their conclusions are in general agreement as to the validity of oxygen scrambling tests (sections I, IIIA, IIIB, and IIIC) for the intermediacy of oxirene.

III. Reactions Possibly Involving an Oxirene, or with the a Priori Potential of Generating an Oxirene

A. Oxidation of Alkynes

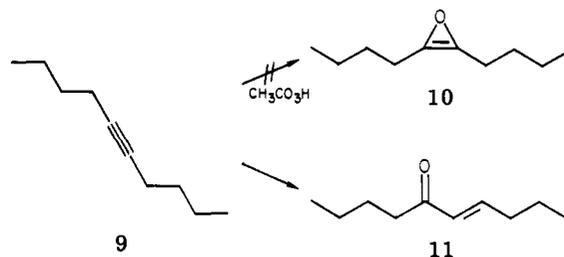
1. Oxidation by Peroxy Acids

Perhaps the most obvious putative route to the oxirene system is the addition of an oxygen atom across the carbon-carbon triple bond (eq 1), and indeed the

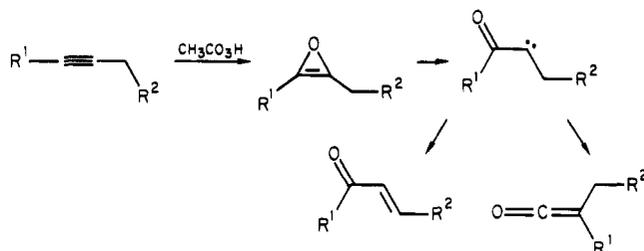


literature on oxirene owes its inception to Berthelot's claim⁷ to have thus synthesized methyloxirene (eq 2). This compound, however, should certainly not be isolable under normal conditions, and the reaction of alkynes with strong oxidants is known to give other products.²³ The next claim of a successful oxirene synthesis⁸ involved a nonoxidative approach (IIID1), but in 1952 Shubach and Franzen⁹ claimed the oxidation of 5-decyne (9) to dibutyloxirene (10) with peroxyethanoic acid²⁴ (Scheme II). However, Franzen soon showed that the product of the oxidation was in

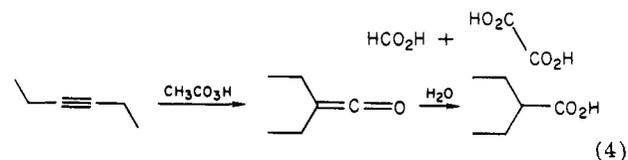
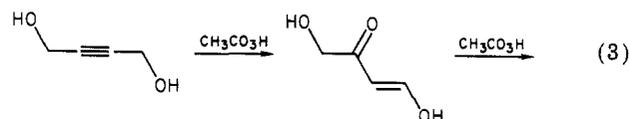
Scheme II



Scheme III

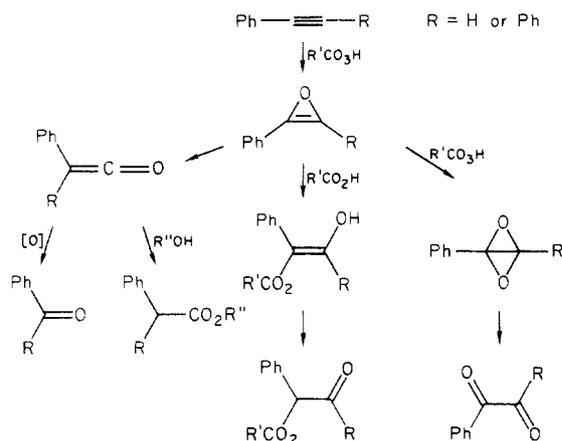


fact 6-decen-5-one (11) (Scheme II), and went on to show that the oxidation of alkynes with peroxyethanoic acid can produce, besides α,β -unsaturated ketones, products plausibly derivable from them (eq 3)²⁵ or from ketenes (eq 4).²⁶ These latter compounds can be ra-



tionalized as arising from an oxo carbene, possibly formed by rearrangement of an oxirene (Scheme III; cf.

Scheme IV

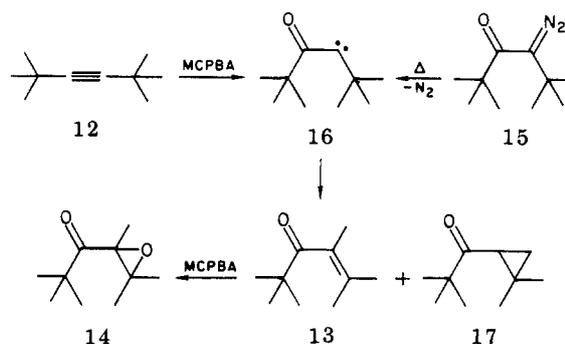


Scheme I and section IIID1).

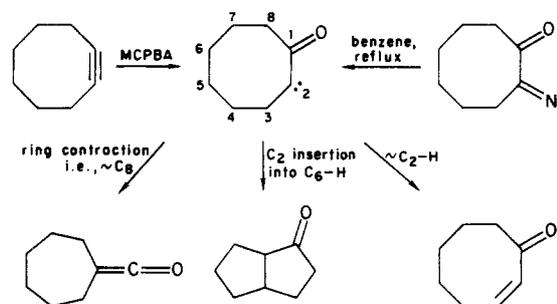
Further evidence concerning the role of oxirene in peroxy acid oxidations of alkynes was sought by later workers who employed phenylethyne²⁷ (in the hope of stabilizing the oxirene system by resonance with the benzene ring) and diphenylethyne²⁸ (with the intention of thwarting isomerization of the oxirene to an α,β -unsaturated ketone, cf. Scheme III). The precise results obtained depended on the reaction conditions, but the essential features of these reactions, as interpreted by these workers, are shown in Scheme IV. An oxo carbene was not postulated for the oxidation of phenylethyne, and was explicitly rejected for the reactions of diphenylethyne since $\text{PhCOCH}(\text{OEt})\text{Ph}$, the expected product of ethanol trapping of benzoylphenylcarbene, was not isolated.²⁹

The demonstration of the involvement in α -diazo ketone decompositions of an oxirene species (I, II, IIID1) opened up the possibility of probing the involvement of oxirenes in peroxy acid oxidations of alkynes by attempting to generate the same oxirene in these two quite different ways. The obtention of similar product distributions would be consistent with the common formation of an oxirene, and oxygen scrambling (cf. Scheme I) would require the intervention of this symmetrical (or pseudosymmetrical, $R^1 \neq R^2$) species. Such experiments were reported in 1970 by Ciabattini and co-workers.³⁰ They showed that the oxidation of 2,2,5,5-tetramethyl-3-hexyne (di-*tert*-butylacetylene) (12) with 3-chloroperoxybenzoic acid (*m*-chloroperbenzoic acid, MCPBA) gave (allowing for further reaction of the enone 13 with peroxy acid to give 14) a product distribution virtually identical with that from thermolysis of the diazo ketone 15 (Scheme V). The products of these reactions can be rationalized as arising from a common oxo carbene 16 (which may arise from di-*tert*-butyloxirene, although the results do not require this) which can undergo a 1,2-methyl migration to give the enone 13, or effect insertion of the carbene carbon into a carbon-hydrogen bond on the adjacent *tert*-butyl group, giving the cyclopropane 17.

Ciabattini and co-workers also reported product comparison studies of the oxidation of cyclic alkynes and the thermal decomposition of cyclic diazo ketones.³¹ Although both types of reaction gave the same products, the relative yields in this case (in contrast to the acyclic, di-*tert*-butyl compounds, above) were considerably different. The main results of this investigation are summarized in Table I. For simplicity, cyclononyne

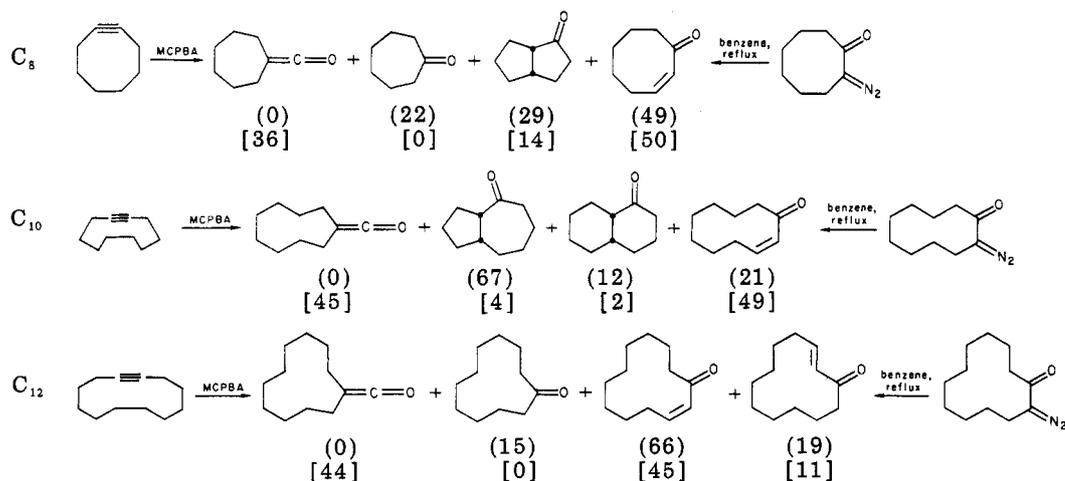
Scheme V^a

^a MCPBA = 3-chloroperoxybenzoic acid.

Scheme VI^a

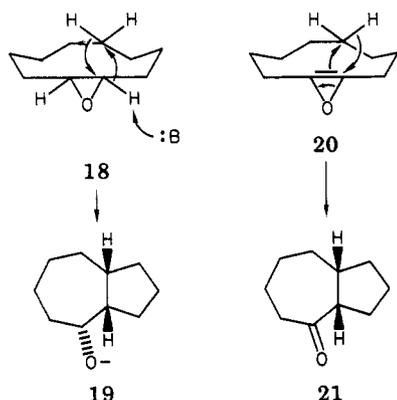
^a MCPBA = 3-chloroperoxybenzoic acid.

and 2-diazocyclononone have been omitted since they gave results similar to those obtained from cyclodecane derivatives. The products are of three types: ring-contracted ketenes (or the ketenes derived from them by peroxy acid oxidation), bicyclic ketones, and enones. The diazo ketones gave mainly ring-contracted products and enones, but the cycloalkynes yielded as their major products enones and, in the cases of cyclooctyne and cyclodecyne, bicyclic ketones as well. All three kinds of products can be explained in terms of a common oxo carbene, e.g., as shown for cyclooctyne in Scheme VI. However, the fact that the two kinds of reaction gave very significantly different ratios of ring-contracted product, bicyclic ketone, and enone shows that this must be an oversimplification. The authors suggest four possible explanations for their results: (1) Both types of reaction may proceed through oxo carbenes, but these may be formed in different conformations and energies. This assumes that rearrangement of the carbene can complete with its conformational and energetic relaxation. Since the cycloalkynes are rigid than the diazoalkanes, insertion of the carbene center into a C-H bond on a distal carbon could be a more prominent process for conformationally unrelaxed carbenes from the cycloalkynes than for carbenes from the diazo ketones, because of the smaller drop in entropy in the former case. (2) The cycloalkynes may be oxidized to oxirenes which then open to oxo carbenes, but the diazo ketones may form their products in processes concerted with the loss of nitrogen, no free carbene arising. (3) The products of cycloalkyne oxidation, in contrast to those from the diazo ketones, may arise directly from intramolecular trapping of oxirenes. An analogy was drawn between the insertion of a carbenoid carbon into a transannular C-H bond (18 \rightarrow 19) and the hypothetical trapping of an oxirene by such a bond, as shown

TABLE I. Products of Cycloalkyne Oxidation and Cyclic Diazo Ketone Decomposition^a

^a The numbers in parentheses are the relative yields from the cycloalkynes; those in brackets are the relative yields from the diazo ketones. MCPBA = 3-chloroperoxybenzoic acid.

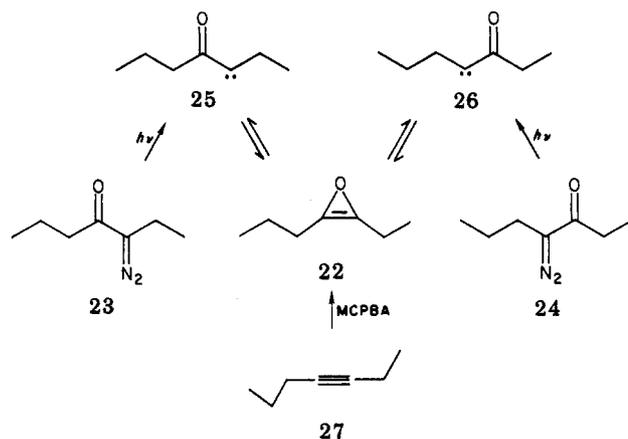
Scheme VII



for the C_{10} system in Scheme VII. That there may be more transannular insertion from the relatively rigid oxirene than from an oxo carbene is plausible for the reasons similar to those advanced in (1), above. It appears however that for the carbenoid-oxirene analogy to hold, the oxirene need not be a true intermediate: oxirene character in a transition state may promote transannular reactions in a manner analogous to that in which a transition state with carbene character can effect transannular insertion, as implied for $18 \rightarrow 19$ in Scheme VII. Thus, rather than the full-fledged oxirene **20** being formed, delivery of an oxygen atom to the triple bond by the peroxy acid (see below) may be concerted with insertion of an incipiently electron-deficient carbon into a transannular C-H bond, leading to **21**. (4) Either or both types of reaction may proceed by more than one mechanistic pathway. Whichever of the suggested rationalizations (1)-(4) is correct, presumably the failure of the C_{12} system to form bicyclic products (Table I) is due to those conformational factors that make large rings less prone than medium ones to undergo transannular reactions.

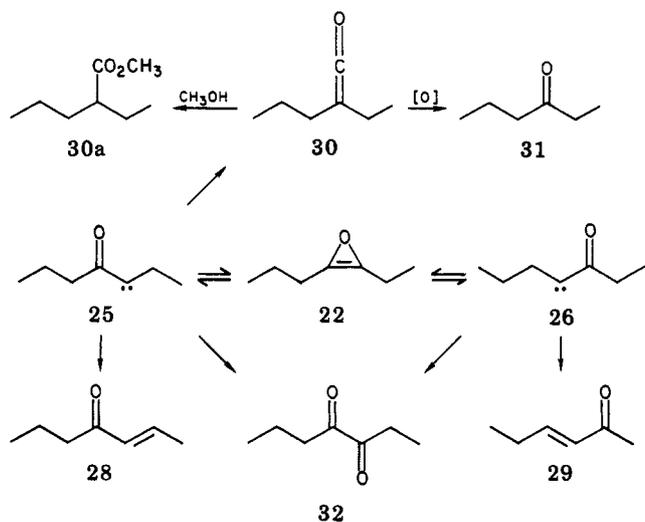
More definitive evidence for the formation of an oxirene species (intermediate or transition state) was presented recently by Cormier,³² in an extension of his earlier work on diazo ketones.³³ This approach was based on the realization that, in principle, the oxirene **22** could be generated from the diazo ketones **23** or **24**, (via the oxo carbenes **25** or **26**), or from the alkyne **27** (Scheme VIII). The results of these investigations are

Scheme VIII



MCPBA = 3-chloroperoxybenzoic acid

Scheme IX



summarized in Scheme IX and Table II, for the case of reactions conducted in ether (other solvents gave similar results). If the carbenes **25** (from **23**) and **26** (from **24**) equilibrate through the oxirene **22**, and if **22** is also the initial product of epoxidation of **27**, then essentially the same mixture of products should be formed on decomposition of the diazo ketones and on oxidation of the alkyne. As Table II shows, this is the

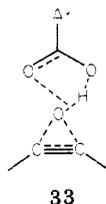
TABLE II. Yields of Products from Diazo Ketone Decomposition and Alkyne Oxidation

starting material	yields, %						oxirene participation, %
	28Z	28E	29Z	29E	31	30a	
23	13	17	11	11	13	0	ca. 85 ^a
24	11	9	13	15	16	0	ca. 82 ^b
27	11	15	11	14	18	3	?

^a % oxirene participation = $2 \times [(28Z + 28E)/(28Z + 28E + 29Z + 29E)] \times 100$. ^b % oxirene participation = $2 \times [(29Z + 29E)/(28Z + 28E + 29Z + 29E)] \times 100$.

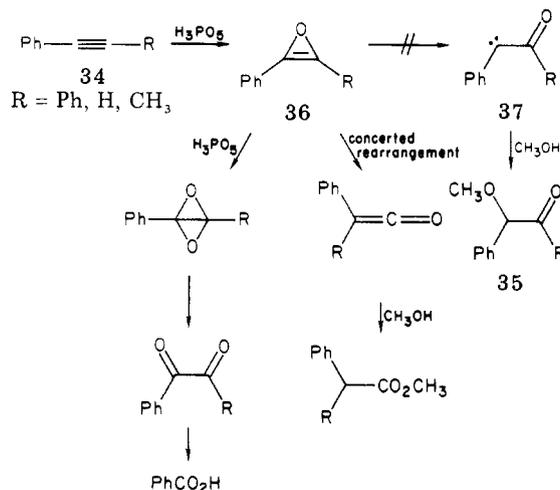
case. The extent of oxirene participation in the case of diazo ketone decomposition can be estimated from the ratio of oxygen-shifted enone to total enone, as indicated in Table II; the factor of 2 takes into account the reversion of oxirene to the carbene from which it was originally formed. This calculation makes the (reasonable) assumption that the pseudosymmetrical oxirene **22** does not discriminate between its C₃ and its C₄ side when it opens to an oxo carbene. Besides forming the α,β -unsaturated ketones **28** and **29** by 1,2-hydrogen migration, the carbenes can undergo alkyl migration to give the ketene **30**, which undergoes oxidation to 3-hexanone (**31**) by peroxy acid or adventitious oxygen (or in the presence of methanol forms the methyl ester **30a**). The diketone **32** was suggested to arise from oxidation of the oxo carbenes, although it could perhaps have been formed from direct oxidation of the oxirene **22** to a dioxabicyclobutane followed by double ring cleavage (cf. Scheme IV). These results show that an oxirene species **22** equilibrates the carbenes **25** and **26** in the diazo ketone photodecompositions, but they do not reveal whether for the oxidation of the alkyne **22** is the initial product, is derived from cyclization of first-formed oxo carbenes, or is not formed at all, the two carbenes being formed from the pseudosymmetrical alkyne in a ratio which mimics ring opening of the **22** from the diazo ketones.

That some kind of oxirene species is the first-formed entity in the oxidation of alkynes by peroxy acids was strongly indicated by kinetic studies³⁴ that showed that changes in the solvent have a very similar effect on the reaction rates for oxidation of 3-octyne and of cyclohexene with 3-chloroperoxybenzoic acid. Since the logarithm of the rate constant is proportional to the free energy of activation, the effect of solvent on the energies of the two transition states is virtually identical (the effects of solvation of the peroxy acid cancel out, since this reagent is common to all the oxidations, and the solvation energies of the two hydrocarbons should be small). This rate constant correlation, and the effect of the nature of the solvent on the enthalpy and entropy of activation are in complete accord with a transition state **33**, completely analogous to that in alkene epoxidation. Although the authors concluded that the

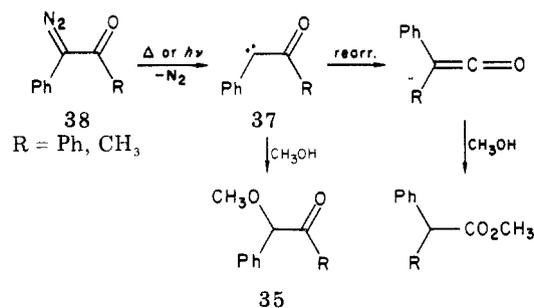


oxirene-like transition state does indeed lead to oxirenes

Scheme X



Scheme XI

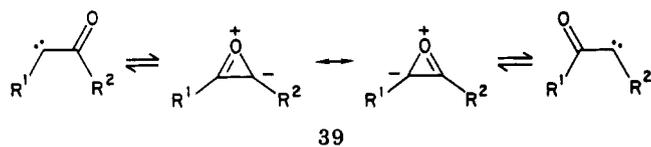


(which quickly decompose), it is not clear that this is necessarily the case: it seems conceivable that the incipient oxirene, still partially bonded to the departing carboxylic acid moiety, might begin to suffer the ring-opening reactions which lead to the observed products of alkyne epoxidation. If this is the case then an oxirene-like transition state, but not an intermediate, is involved in alkyne epoxidation.

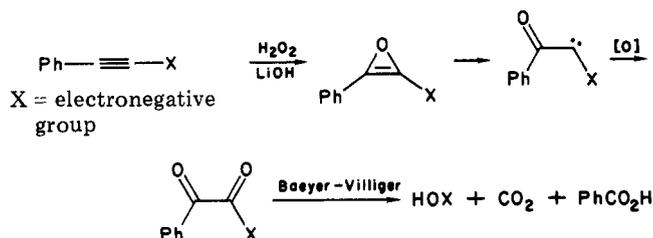
In other kinetic studies, the effect of ring substituents on the rate of reaction of phenylethyne with peroxybenzoic acid was investigated.³⁵ The reaction was accelerated by electron-donating groups (a good linear $\log k_{rel}/\sigma^+$ correlation was obtained), showing that the peroxy acid attacks the alkyne as an electrophile, rather than as a nucleophile, the latter being an a priori possibility for alkynes which, unlike alkenes, are susceptible to attack by nucleophiles.³⁶

Quite recently, the results of the oxidation of phenylethyne and derivatives by peroxyphosphoric acid (H₃PO₅)¹¹ have provided the basis of a challenge to the traditional view that oxirenes rearrange to oxo carbenes. The alkynes **34** reacted with the peroxy acid to give a mixture that did not include the methoxy ketone **35**, a product that would be expected had the oxirene **36** been formed and rearranged to the oxo carbene **37**; the authors' interpretation of these results is outlined in Scheme X. In support of the contention that **35** should have been formed had **37** intervened, thermal or photochemical decomposition of the α -diazo ketones **38** (IID1), a process for which the intermediacy of oxo carbenes seems to be well established, indeed gave rise to **35**; the essential features of the diazo ketone decompositions are summarized in Scheme XI. The two sets of results were interpreted as showing that an

Scheme XII



Scheme XIII



oxirene, formed in the peroxy acid reaction, rearranges in a concerted manner (Scheme X) to a ketene, without forming a carbene. This raises the question of how the well-established interconversion of oxo carbenes occurs in diazo ketone decompositions (I, IID1), and as an alternative to an oxirene the authors propose the species **39** (Scheme XII; cf. Scheme I). To accommodate the possibility of there being more than one entity with the symmetry required for oxo carbene interconversion, the somewhat noncommittal term "oxirene species" has generally been used in this review to denote a species (transition state or intermediate) with the chemical symmetry of an oxirene. The work with peroxymonophosphoric acid, while clearly important, requires some suspension of judgment since (1) it is not clear how **39** differs from oxirene resonance structures, (2) it is not yet known if these results can be generalized to other oxidants and alkynes, and (3) it has *not* been established (cf. earlier parts of this section) that oxirenes are formed in the peroxy acid oxidation of alkynes. A viable interpretation of these results is that oxo carbenes interconvert through oxirenes (IID1), but that oxirenes are not formed by attack of peroxy acids on alkynes, at least in the case of compounds **34**.

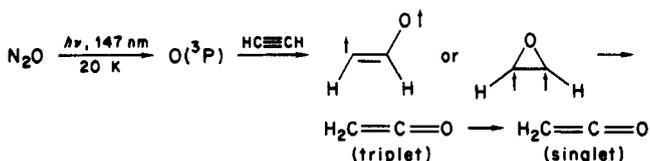
The molybdenum-catalyzed oxidation of alkynes by *tert*-butyl hydroperoxide has been investigated³⁷ (the epoxidation of *alkenes* by this system has become an important reaction³⁸). The formation of oxirenes was excluded since there were no ketene products, and the reaction, which gave 1,2-diketones and their oxidative cleavage products, was suggested to proceed through a metal-oxo carbene complex.

Oxidation of electron-deficient alkenes by alkaline hydrogen peroxide (a nucleophilic oxidant, in contrast to the electrophilic ones discussed so far in this section) gives products that have been suggested to arise from an oxirene, e.g., Scheme XIII.³⁹ However, although carbenes are implicated as intermediates in these reactions, there is no independent evidence that they arise from oxirenes under these conditions.

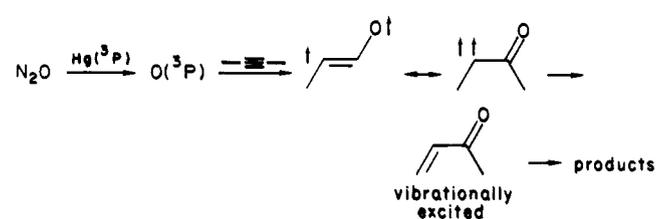
2. Oxidation by O₂ or O

Ethyne is oxidized to ketene by hot air.⁴⁰ This reaction probably proceeds by a hydroperoxide radical, as seems to be general for the oxidation of hydrocarbons by molecular oxygen at elevated temperatures.⁴¹ Oxirene is probably not involved since molecular oxygen is not a donor of singlet-oxygen atoms (see the remarks on this point in ref 27, p 4866).

Scheme XIV



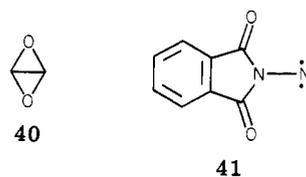
Scheme XV



In an experiment that might have appeared propitious for the synthesis and detection of oxirene, Haller and Pimentel⁴² irradiated a mixture of ethyne and nitrous oxide, N₂O, in an argon matrix at 20 K. The N₂O was decomposed with 147-nm light, conditions under which ground-state, triplet, oxygen atoms are formed. Only ketene was detected, and the authors favored diradical intermediates over oxirene (Scheme XIV), since formation of the latter would not conserve spin (cf. ref 43).

Avery and Heath⁴⁴ irradiated 2-butyne and N₂O in the gas phase (mercury photosensitization to decompose the N₂O). The main products were carbon monoxide, propene, ethane, 3-buten-2-one, and polymer. This reaction, too, was considered to involve a diradical rather than an oxirene (Scheme XV).

In earlier work the reaction of (presumably triplet) oxygen atoms with ethyne at liquid oxygen (sic) temperature was suggested to form dioxabicyclobutane (**40**),⁴⁶ but this is unlikely as it would probably have



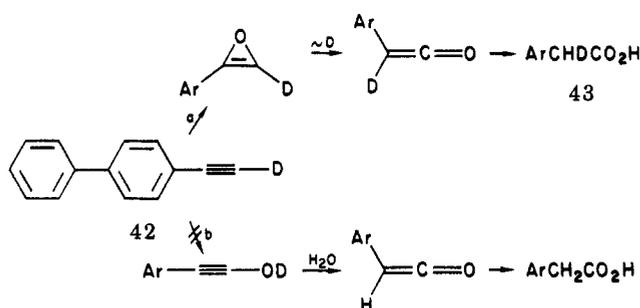
violated spin conservation; other work on the reaction of alkynes with oxygen atoms⁴⁶ probably did not involve oxirenes either, for the same reason.

Of relevance to the possibility of synthesizing oxirene by the reaction of oxygen atoms with ethyne in a matrix at low temperature are experiments involving the addition of nitrenes to alkynes to give 1*H*-azirines. The singlet nitrene **41** apparently reacts with alkynes to form a short-lived 1*H*-azirine.⁴⁷ However, the parent reaction, between nitrene itself (NH) and ethyne, gave keteneimine, H₂C=C=NH, with no sign of the azirine, although the reaction was conducted at 4 K;⁴⁸ it was suggested that initially formed singlet nitrene, from the photolysis of HN₃, was deactivated to the triplet state before reacting with the ethyne, since the photolysis of HN₃ with ethene (which is more reactive than ethyne toward electrophiles) under the same conditions gave aziridine.

3. Oxidation by Biochemical Systems

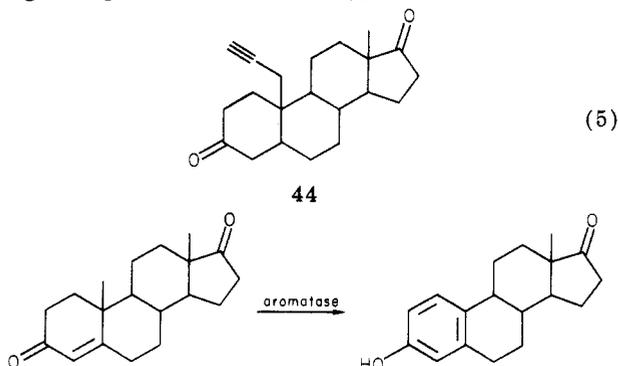
Probably the most surprising aspect of the putative oxidation of alkynes to oxirenes is the fact that evidence

Scheme XVI



has recently been obtained that oxirenes may be formed, enzymatically, in living cells. The oxidation of 4-ethynylbiphenyl (42) to the carboxylic acid 43 (Scheme XVI) may involve an oxirene, since the labeled alkyne shown gave acid with complete deuterium retention (path a); path b should have given unlabeled acid.⁴⁹

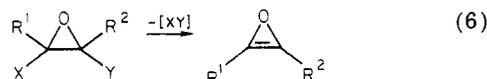
The alkynyl steroid 44 inactivates aromatase, an enzyme that catalyzes the conversion of androgen to estrogen (eq 5). It has been suggested⁵⁰ that the inac-



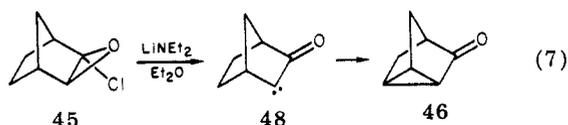
tivation process involves the oxidation of 44 to an oxirene that rearranges to an oxo carbene which then binds to the enzyme prosthetic group, thus inactivating it. That 44 did not act, as had been previously suggested, by forming an alkynyl ketone (HC≡CCH₂ → HC≡CCO) was shown by the fact that authentic alkynyl ketone did not significantly inhibit aromatase, and that the C₁₉-d₂ alkyne (C≡CCD₂) inactivated aromatase at essentially the same rate as the undeuterated alkyne.

B. β-Elimination Reactions

Little work seems to have been done on the introduction of a double bond into a preformed oxirane ring by β-elimination (eq 6). The most obvious candidates

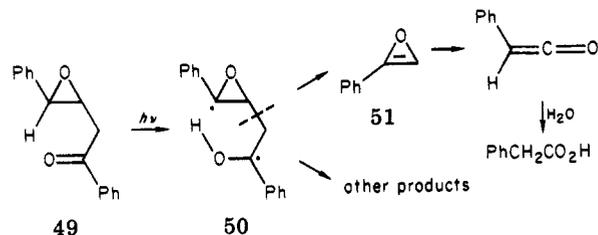


for this transformation, halooxiranes, have not been subjected to a systematic study of their reactions with nonnucleophilic bases,⁵¹ although the chlorooxirane 45 has been shown to give on dehydrohalogenation the cyclopropane 46 (eq 7).⁵² Griesbaum and co-workers

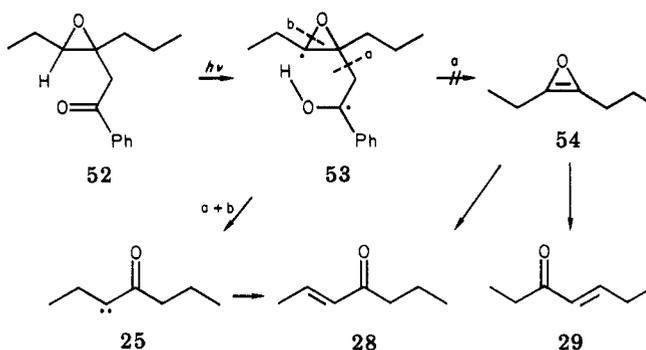


have prepared a series of vicinal dichlorooxiranes with the express intention of investigating their dehalogen-

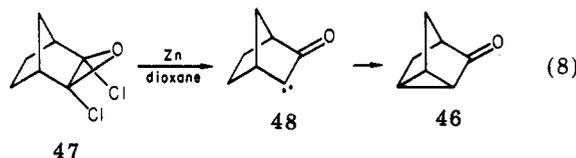
Scheme XVII



Scheme XVIII



ation to oxirenes,⁵³ and Lewars and co-workers have found that the dichlorooxirane 47 can be dechlorinated to 46 (eq 8).⁵⁴ The formation of 46 from 45 and 47

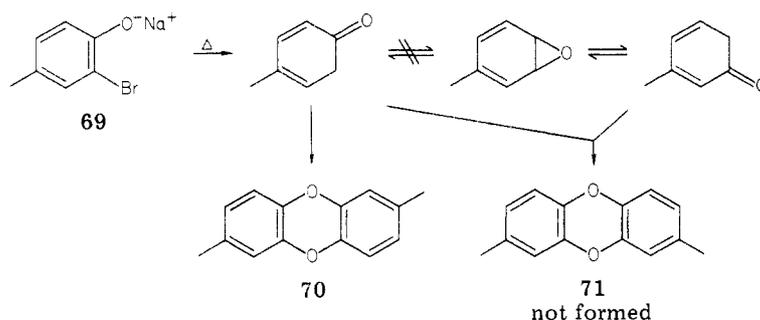


probably proceeds through an oxo carbene (or carbenoid) 48, but it is not known if an oxirene is the precursor of, or equilibrates with, the carbene. The relationship of oxo carbenes to oxirenes is discussed further in IIID1.

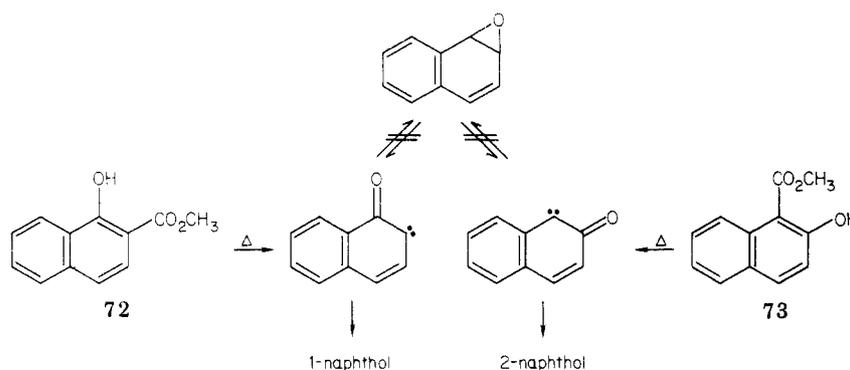
The situation seems to be similar, too, for the β-elimination of other simple groups,⁵⁵ although Padwa and co-workers have rationalized some of the products from photolysis of a β,γ-epoxy ketone by invoking an oxirene intermediate (Scheme XVII).⁵⁶ A Norrish type II photoreaction of 49 was suggested to lead to formation of the diradical 50 and thence to phenyloxirene (51), which on aqueous workup gave rise to phenylacetic acid, one of the observed products. The validity of this mechanism has, however, been called into question by Cormier who in his paper comparing alkyne epoxidation and diazo ketone decomposition³² also investigated the photolysis of 52 (Scheme XVIII). If the diradical 53 resulting from γ-hydrogen abstraction had suffered 1,4-fragmentation to an oxirene 54, then the enones 28 and 29 should have been formed (cf. Scheme IX, IIIA1); however, only 28 was obtained. It was suggested that cleavage of bonds a and b is concerted, leading without the intervention of 54 to the oxo carbene 25 which isomerizes to 28.

Oxirene derivatives (radical cations, cations, or conjugate acids; the neutral molecule could not, of course, be observed) have been invoked as entities formed eliminatively in mass spectrometric fragmentations. α,β-Epoxy ketones (acyloxiranes) give species that have been assigned the protonated oxirene structure, e.g., 55 (Scheme XIX).⁵⁷ The addition of hydrogen sulfide to ethyne (radical cation chemistry) leads to a species that

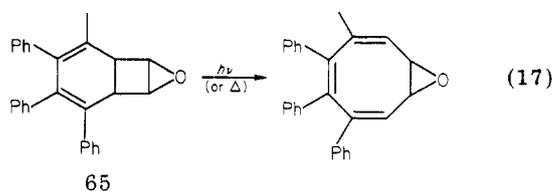
Scheme XXI



Scheme XXII



ketenes (or to metastable oxo carbene intermediates—see II and IIID1). This is in contrast to compounds that are thermodynamically stable even if extraordinarily reactive toward bimolecular processes; such compounds *can* be made by flash thermolysis⁶² (a good example is 1-methylpentalene⁶⁸). In a cleverly conceived and skillfully executed synthesis, Warren and co-workers⁶⁹ prepared the formal [2 + 2] oxirene-arene adduct **65**, a promising-looking potential oxirene precursor. Unfortunately however, photolysis (or thermolysis) of **65** caused conversion to a bicyclic isomer (eq 17) with no indication of oxirene extrusion. Suspecting that this



undesired transformation may have been promoted by substituent stabilization of a biradical-like excited state, these workers tried to prepare the unsubstituted compound **58**, an attempt that was, however, thwarted by the fickleness of reactions that had proved reliable in other contexts.

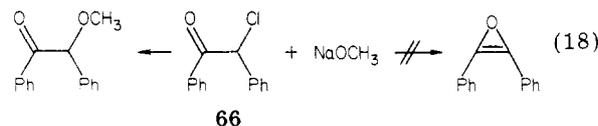
D. Isomerization Reactions

1. Isomerization of Oxo Carbenes ("Keto Carbenes"): The Wolff Rearrangement

The reactions discussed in this section will be treated within the framework of the oxirene-oxo carbene interconvertibility paradigm. However, results from the oxidation of some alkynes with peroxyphosphoric acid¹¹ raise the possibility that this may have to be modified; the point was briefly discussed in IIIA1.

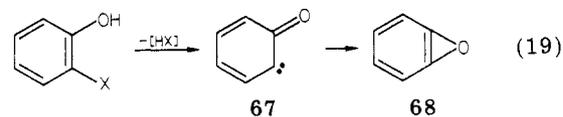
After the initial claim of the synthesis of an oxirene (by the oxidation of propyne: Section I) this system

reappeared after 50 years of quiescence with the claim⁸ that 2-chloro-1,2-diphenylethanone (**66**) reacted with sodium methoxide to give diphenyloxirene (eq 18).



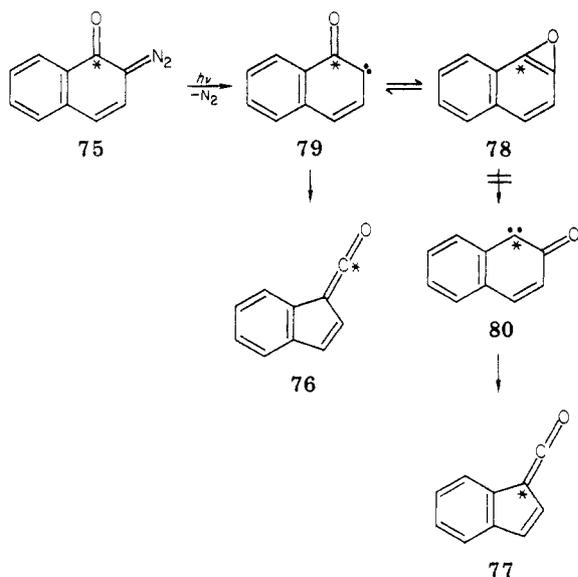
However, it was later shown⁷⁰ that the product was the prosaic methoxy ketone (eq 18). The conversion of an α -halo ketone to an oxirene would be at least formally analogous (both are α -eliminations followed by carbon-oxygen bonding) to the well-established transformation of α -diazo ketones into oxo carbenes and hence into oxirene species (see below). However, even with strong, nonnucleophilic bases, **66** failed to provide evidence of diphenyloxirene formation.²⁷

Related to the dehydrohalogenation of α -halo ketones is a potential route to benzoxirenes by dehalogenation of 2-halophenols (eq 19). This can be envisioned to

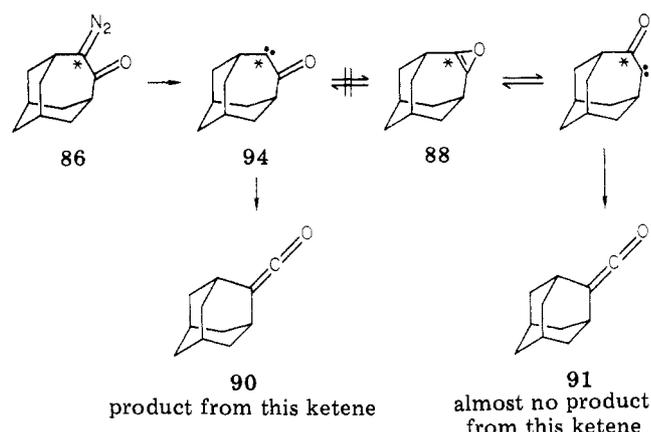


proceed through the oxo carbene **67** that might isomerize to benzoxirene (**68**), although attack of the oxygen on the halogen-bearing carbon with ejection of halide is also conceivable.⁷¹ Attempts to generate benzoxines by this route have provided results that indicate that the oxirene is not formed.^{72,73} For example, thermolysis of the sodium phenoxide **69** gave the bimolecular product **70**, but no **71** (Scheme XXI);⁷³ had a benzoxirene intervened, some **71** should have been formed. Related experiments with naphthols (Scheme XXII)⁷⁴ indicated that **72** and **73** form oxo carbenes that do not cyclize to benzoxirene systems. These results are not absolutely conclusive evidence against the formation of

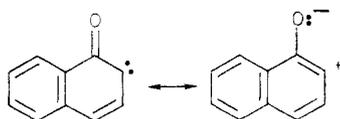
Scheme XXIV



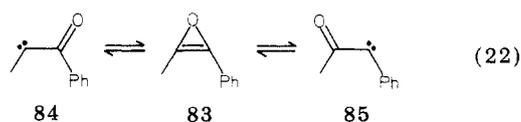
Scheme XXV



ketones might form an oxirene, which then opened exclusively to recreate its parent carbene; this logical possibility is clearly unlikely. The apparent reluctance of 75 and 81 to form oxirenes was suggested to be due either to concerted ketene formation without the intervention of a carbene (carbene formation from *acyclic* α -diazo ketones seems well established⁷⁷), or to stabilization of the oxo carbenes by resonance; the dipolar resonance form has an extra aromatic ring and might stabilize the hybrid considerably, e.g., for 79:

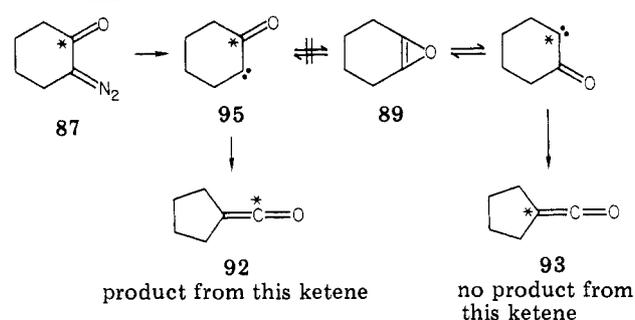


Zeller has shown by labeling experiments that the equilibrium between 2-methyl-3-phenyloxirene (83) and its isomeric parent carbenes 84 and 85 is strongly shifted toward 85 (eq 22).⁸⁷

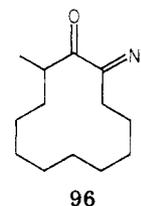


Diazo ketones that clearly did not give rise to significant oxirene formation are 86⁸⁸ and 87;⁸⁹ the oxirenes 88 and 89, by virtue of their symmetry, would

Scheme XXVI



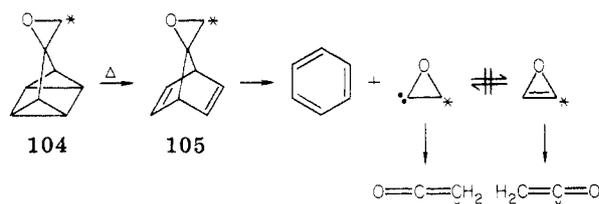
undergo, except for slight isotopic biasing, equal cleavage of their two carbon-oxygen bonds (Schemes XXV and XXVI). However, the product carboxylic acids were derived only from the ketenes 90 (with virtually none from 91) and 92 (with none from 93), respectively. The reluctance of the carbene 94 to cyclize to 88 was ascribed to the extra ring strain that would be incurred. Lack of oxirene formation from the carbene 95 was suggested to be due to its rapid deactivation to a lower energy level, or to incompatibility of the oxirene geometry with fusion to a cyclohexene ring (this latter factor seems to be equivalent to increased ring strain). Not surprisingly, medium³¹ (IIIA1) and large^{31,90} ring (e.g., 96) diazo ketones seem less reluctant to form fused-ring oxirenes.



For the oxygen migration test for oxirene participation to be valid, it must be shown²² that intermolecular oxygen transfer does not occur, and that oxygen scrambling does not happen at the ketene stage. Dilution studies excluded the former for photolysis of simple aliphatic α -diazo ketones^{83b} and it appears to be taken for granted that this complication does not intrude; oxygen scrambling at the ketene stage was ruled out for a series of alkyl/aryl-labeled diazo ketones.⁹¹

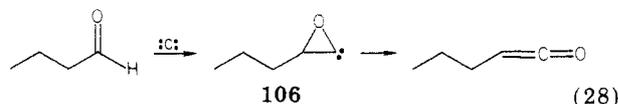
The question of whether the symmetrical or pseudosymmetrical species implicated in the Wolff rearrangement and other reactions is a true intermediate or a mere transition state could be definitively settled in favor of the former, more chemically interesting possibility, by successful trapping experiments or, more dramatically, by the spectroscopic observation of an oxirene. There appear to have been no reports of deliberate attempts to trap oxirenes (cf. closing remarks of ref 83d), but one adventitious case of the possible trapping of such an intermediate has been reported. Photolysis of the diazo amide 97 in methanol gave the methanol adduct 98.^{77a} This was regarded as strong evidence for a true intermediate 99, as depicted in eq 23, but incorporation of methanol at an earlier stage seems to be conceivable, e.g., as outlined in eq 24. Less ambiguous would be the observation of a cycloaddition reaction such as the trapping of an oxirene by a diene to give a Diels-Alder adduct, or the isolation of the dihydro derivative (an oxirane) in the presence of diazene (diimide).

Scheme XXVIII



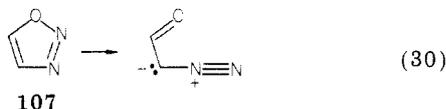
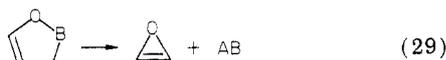
thermolysis (not true high-vacuum flash thermolysis) (Scheme XXVIII). Ready isomerization to a bicycloheptadiene derivative 105 was apparently followed by chelotropic extrusion of 6. ^{14}C labeling showed that 6 opened to ketene without isomerizing to oxirene. This is, of course, what would be expected from the molecular orbital calculations summarized in Figure 1. The appropriate dimethyl analogue of 104 gave dimethylketene, presumably by way of dimethylcarbenaoxirane.

In a study of the deoxygenation of carbonyl compounds by atomic carbon, Dewar and co-workers¹⁰⁰ presented experimental and theoretical evidence that the carbonyl group can react with carbon atoms to form a carbenaoxirane. Butanal gave propylketene, probably via the carbenaoxirane 106 (eq 28).



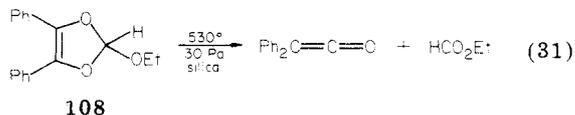
E. Extrusion from Larger Heterocycles

Any heterocycle containing the $\text{OCH}=\text{CH}$ moiety can *in principle* extrude the superfluous fragment and form oxirene, as illustrated for a five-membered ring in eq 29. Probably the most propitious AB fragment-



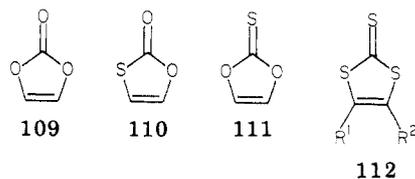
would be nitrogen, but the required 1,2,3-oxadiazole 107 is unknown, presumably because of ready valence tautomerization to diazoethanal (eq 30) (this approach has been spectacularly successful with the sulfur analogue of 107).³ The use of 107 as an oxirene precursor is thus closely linked to the important diazo ketone decompositions discussed in IIID1.

The flash thermolysis of the dioxolane 108 gave among the products diphenylketene and ethyl methanoate (eq 31),¹⁰¹ and it is conceivable that diphenyl-



oxirene is the precursor of the ketene, although this is by no means required.

Of much greater promise than thermolysis for the detection of oxirene is low-temperature photolysis. Clement and Strausz investigated the photolysis in an argon matrix at low temperatures of 1,3-dioxolenone (vinylene carbonate), 109.⁹⁸ However, the only $\text{C}_2\text{H}_2\text{O}$



species detected was ketene. The sulfur derivatives of 109, compounds 110 and 111, behaved similarly, as did the benzo derivatives of 110 and 111. Flow thermolysis of these compounds also provided ketenes, indicating that these cyclic carbonates are a new source of oxo carbenes. The probable greater stability of thiirenes as compared to oxirenes is shown by the fact that photolysis of compounds of the type 112 in a low-temperature matrix is an excellent source of thiirenes.¹⁰²

IV. Conclusions and Speculations

Oxirene is probably a true intermediate, but is separated from ketene by only a very low barrier. Since its instability results from unimolecular isomerization rather than from reactivity in bimolecular processes, the only viable current technique for its direct observation seems to be generation and spectroscopic examination in an inert matrix at temperatures near absolute zero.

Substituted oxirenes may well be more stable. The substituents would be required not to present mere steric hindrance to bimolecular reactions, as in tetra-*tert*-butylcyclobutadiene,¹⁰³ or even to exert the more subtle steric effect which keeps tetra-*tert*-butyltetrahydrofuran from springing open,¹⁰⁴ but to hinder isomerization to the oxo carbene. Electron-withdrawing groups may be of value in this respect,^{5,16} and further information on this point could be gathered by molecular orbital calculations and perhaps by studies of the effects of substituents on thiirene, the closest known³ relative of oxirene.

Another, conceptually straightforward, approach to designing a relatively stable oxirene is to deplete the electron density in the carbon-carbon double bond by utilizing the "push-pull" concept,¹⁰⁵ the affixing of an electron source and an electron sink to opposite ends of the bond. This subterfuge does have the disadvantage that to the extent to which it succeeds one has bypassed the very system sought, and although formal victories should not be disdained, the signal climax to the search for oxirene would no doubt be the securing of the spectroscopic profile of the elusive heterocycle.

Note Added in Proof. Since this review was submitted, five important papers relevant to the subject have appeared.¹⁰⁶⁻¹¹⁰

Acknowledgments. I thank Miss Charlotte Kohn for her fast and accurate typing of this manuscript.

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