Advances in

HETEROCYCLIC CHEMISTRY

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Edited by

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Preface

This, the eleventh volume of *Advances in Heterocyclic Chemistry*, includes surveys of the chemistry of the following groups of heterocyclic compounds: benzo[*b*]thiophenes (B. Iddon and R. M. Scrowston), naphthyridines (W. W. Paudler and T. J. Kress), and quinuclidines (L. N. Yakhontov). In addition, R. A. Jones covers the application of physical methods to pyrrole chemistry and a very topical subject, the photochemistry of heterocycles, is reviewed by S. T. Reid.

Suggestions are welcomed for contributions to future volumes; they should be in the form of short synopses.

Thanks are due to the Editorial Board, the publisher, and the authors for their cooperation.

A. R. KATRITZKY
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Physicochemical Properties of Pyrroles

R. Alan Jones

Quinuclidine Chemistry

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The Photochemistry of Heterocycles

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I. Introduction

The current interest in organic photochemistry[1–4] is reflected in the increase in the number of publications concerned with the photochemistry of heterocyclic systems. Although it has long been known

[1] J. G. Calvert and J. N. Pitts, "Photochemistry." Wiley, New York, 1966.
[2] R. O. Kan, "Organic Photochemistry." McGraw-Hill, New York, 1966.
[3] A. Schönberg, "Preparative Organic Photochemistry." Springer, Berlin, 1968.
[4] N. J. Turro, "Molecular Photochemistry." Benjamin, New York, 1965.

that many heterocycles are light-sensitive and that ready photodecomposition does occur, only recently have detailed investigations illustrated the complexity of the rearrangements and other transformations that occur. Furthermore, as later sections of this review will show, considerable use is now being made of photochemically induced reactions in synthesis. The formation of heterocycles, both by photoaddition and photocyclization, is rapidly becoming not only an acceptable, but in some cases, a preferable method of synthesis.

No review of a fast-growing field of this nature can ever hope to be comprehensive, nor, in fact, would the achievement of this be of any lasting value. It is our intention, therefore, to bring to the attention of the reader the more important recent contributions, and in particular to illustrate the generality and scope of many of the processes discussed. The mechanism of each individual photoreaction will not be considered in detail except insofar as it can be seen to impose limitations on the use of the reaction or to affect directly the nature of the photoproduct.

II. Mechanism of Photochemical Reactions

The mechanism of photochemical transformations has been the subject of many articles and monographs and will be discussed only briefly.

Absorption of ultraviolet (UV) or visible light by an organic molecule results in the excitation of an electron to a higher energy level, the energy level difference ΔE being given by the equation $\Delta E = h\nu$. The electron is, in general, promoted to an antibonding orbital, and the process can be accompanied by quantized increases in vibrational and rotational energy levels.

There are two types of electronic transition commonly responsible for photochemically induced reactions in organic molecules. The first of these is the $n \rightarrow \pi^*$ transition in which an electron in a nonbonding atomic orbital is excited to an antibonding π orbital, the excited state being referred to as n, π^*. This occurs in nitrogen-, oxygen-, and sulfur-containing molecules, and the nature of the n, π^* state of the carbonyl function has been the subject of considerable study.[5, 6] Excitation to the n, π^* state in aldehydes and ketones occurs at approximately 290 nm.

[5] D. C. Neckers, "Mechanistic Organic Photochemistry." Reinhold, New York, 1967.

[6] P. J. Wagner and G. S. Hammond, *Advan. Photochem.* 5, 21 (1968).

The second type of excited state is written as π, π^* and results from a transition in which a π electron is excited to an antibonding π orbital. The light absorbed to produce this transition is generally of shorter wavelength than that for the $n \rightarrow \pi^*$ transition, and the process requires higher energies. The $\pi \rightarrow \pi^*$ transition in ethylene is the result of absorption at 180 nm.

A third transition of less significance is the $n \rightarrow \sigma^*$ transition; this is observed in the photolysis of halogenated compounds.[7] The σ^* energy level is unusually unstable and the molecule undergoes bond cleavage with the formation of free-radical species. Many photoreactions can, in fact, be thought of in radical terms, and close analogies exist between certain photochemical reactions and free-radical processes.

The excited molecule initially formed from the ground state by absorption of light is in the singlet state; two electrons with antiparallel spins are in orbitals of different energy. Direct excitation to the triplet does not occur. The energy associated with the excited singlet species can be dissipated in one of three ways, by fluorescence (emission of radiation of wavelength similar to that absorbed), by radiationless transitions, and by chemical reaction. Radiationless transitions are of two kinds. The excited species first undergoes internal conversion to the energetically lowest singlet excited state; this is followed either by further internal conversion to a vibrationally excited ground state, or by intersystem crossing to a triplet state involving a change of spin orientation in one electron. The excited triplet state has lower energy than the corresponding singlet state, and also has a significantly longer life (at least 10^{-4} seconds compared with about 10^{-9} seconds for the singlet). Energy is dissipated by the excited triplet in a number of ways; these are phosphorescence (emission of light of longer wavelength than that absorbed), further radiationless transitions including energy transfer to other molecules, and chemical reactions. The exact details of the mechanism of many photochemical reactions are far from clear; in general, most reactions appear to take place in the excited triplet state, although there are authentic examples of reactions occurring in the singlet state and in a vibrationally excited ground state.

In addition to direct excitation, photochemical reactions can be induced by "sensitization." This is the result of energy transfer from an excited molecule and occurs on molecular collision, provided that the energy level to which the acceptor is excited is lower. The use of

[7] J. R. Majer and J. P. Simons, *Advan. Photochem.* **2**, 137 (1964).

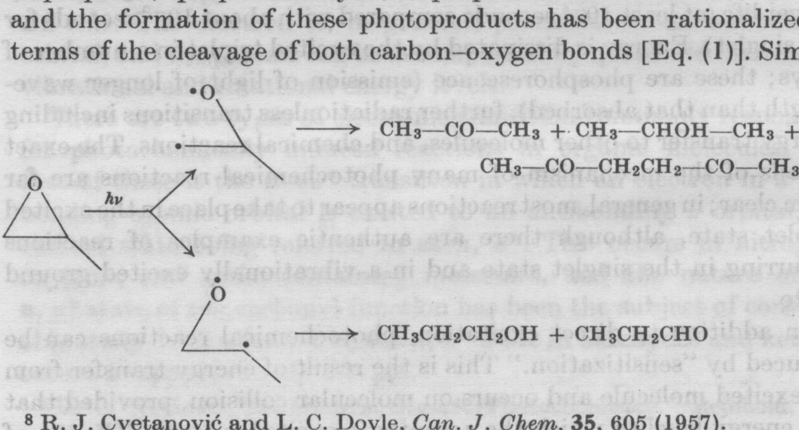
singlet–singlet and, in particular, triplet–triplet energy transfer is of considerable value both in the study of the mechanism of a photoreaction and in inducing photoreactions in molecules such as alkenes which are difficult to excite directly.

III. Bond Cleavage and Rearrangement

The increase in energy in a molecule on absorption of UV light is sufficient to bring about bond cleavage. As a result, fragmentation and rearrangement of the molecule can occur. The effect on heterocycles is discussed in this section and, for simplicity, the transformations are classified, somewhat arbitrarily, on the basis of ring size; pyrazolines are treated separately. Heterocyclic dienes and heteroaromatic compounds are also discussed separately, and the section is completed by consideration of the photochemistry of heteroaromatic *N*-oxides.

A. Three-Membered Heterocycles

Early work[8] on the gas phase photolysis of oxiranes led to the postulation that diradical species resulting from carbon–oxygen bond cleavage were involved in their decomposition. Recent studies[9] in the liquid phase support the concept of homolytic cleavage of the carbon–oxygen bond, and suggest that this process is followed by a series of radical reactions. In this way, methyloxirane is converted into acetone, isopropanol, propionaldehyde, *n*-propanol, and hexane-2,5-dione; and the formation of these photoproducts has been rationalized in terms of the cleavage of both carbon–oxygen bonds [Eq. (1)]. Similar

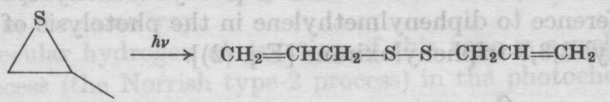


(1)

[8] R. J. Cvetanović and L. C. Doyle, *Can. J. Chem.* **35**, 605 (1957).
[9] R. J. Gritter and E. C. Sabatino, *J. Org. Chem.* **29**, 1965 (1964).

effects are observed in alicyclic epoxides, the principal products of photolysis of cyclohexene oxide being cyclohexanone and cyclohexanol. Oxiranes are also reported[10] to undergo photochemically induced alcoholysis; cyclohexene oxide in this case affording *trans*-2-methoxycyclohexanol in high yield on irradiation in methanol.

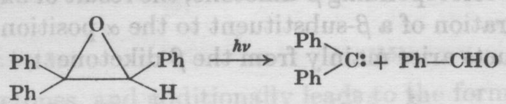
Thiiranes appear[9] to undergo carbon–sulfur bond cleavage more readily, but this process is less well investigated. The only photoproduct so far obtained from methylthiirane (**1**) is the dimeric allyl



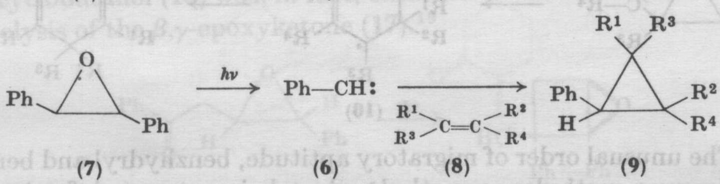
(**1**) (**2**)

disulfide (**2**). The photosensitized decomposition of aziridine has also been studied.[11]

Photofragmentation of phenyl-substituted oxiranes has been shown[12] to result in the formation of carbenes; triphenyloxirane (**3**) on irradiation in methylcyclohexane at 77°K affords benzaldehyde (**4**) and diphenylmethylene (**5**), identified by fluorescence and electron paramagnetic resonance (EPR) absorption studies. The most convenient precursor of phenylcarbene (**6**) is stilbene oxide (**7**),[13] and the



(**3**) (**5**) (**4**)



(**7**) (**6**) (**8**) (**9**)

stereospecific addition of phenylcarbene to alkenes (**8**) has been employed as a useful synthesis of phenylcyclopropanes (**9**).[13] Phenylcarbene, generated in this way, can also be added in high yield to

[10] K. Tokumaru, *Bull. Chem. Soc. Japan* **40**, 242 (1967).

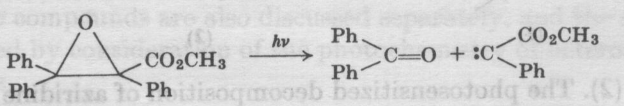
[11] R. F. Klemm, *Can. J. Chem.* **45**, 1685 (1967).

[12] A. M. Trozzolo, W. A. Yager, G. W. Griffin, H. Kristinnsson, and I. Sarkar, *J. Am. Chem. Soc.* **89**, 3357 (1967).

[13] H. Kristinsson and G. W. Griffin, *J. Am. Chem. Soc.* **88**, 1579 (1966).

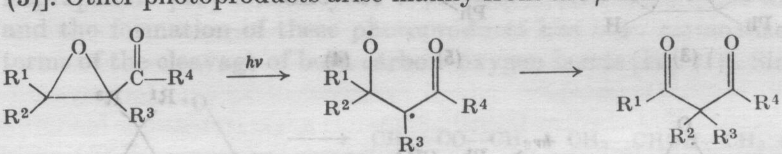
but-2-yne to give the phenyl-substituted cyclopropene,[13] and undergoes insertion reactions with *n*-pentane to form the three possible phenyl-substituted alkanes.[14]

Formation of these carbenes may well involve a two-step homolytic cleavage, but the extension of this process to the formation of phenylcyanocarbene and phenylmethoxycarbonylcarbene from the appropriately substituted oxirane led to the suggestion that heterolytic cleavage of the carbon–carbon bond might be the initial step.[15] This would account for the formation of phenylmethoxycarbonylcarbene in preference to diphenylmethylene in the photolysis of 2-methoxycarbonyl-2,3,3-triphenyloxirane [Eq. (2)].



(2)

Recently, considerable interest has been shown in the photochemistry of α,β-epoxyketones.[16] Although the photochemistry of this system is undoubtedly the result of an $n \to \pi^*$ excitation in the carbonyl function, the orbital overlap with the "bent bonds" of the three-membered ring, for which there is considerable evidence,[16] is also implicated in the process. The major product of irradiation of an α,β-epoxyketone is the corresponding β-diketone, the result of oxirane ring cleavage and migration of a β-substituent to the α-position [Eq. (3)]. Other photoproducts arise mainly from the β-diketone.



(10)

(3)

The unusual order of migratory aptitude, benzhydryl and benzyl > hydrogen > methylene > methyl ≫ phenyl, is accounted for in terms of the intermediate (**10**) formed directly from the excited singlet state.[17]

[14] H. Dietrich, G. W. Griffin, and R. C. Petterson, *Tetrahedron Letters* 153 (1968).

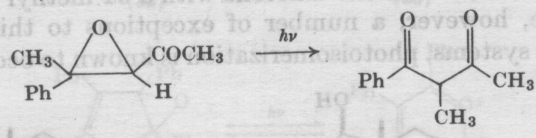
[15] P. C. Petrellis and G. W. Griffin, *Chem. Commun.* 691 (1967).

[16] A. Padwa, *in* "Organic Photochemistry" (O. L. Chapman, ed.), Vol. 1, p. 91. Dekker, New York, 1967.

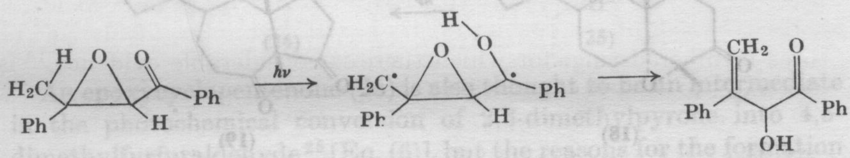
[17] C. S. Markos and W. Reusch, *J. Am. Chem. Soc.* **89**, 3363 (1967).

Other factors including the environment of the carbonyl group also appear to influence the course of this rearrangement. While 3,4-epoxy-4-phenylpentan-2-one (**11**) is rearranged to the diketone (**12**) in the usual manner, *trans*-1-benzoyl-1,2-epoxy-2-phenylpropane (**13**) undergoes a different rearrangement to give 1,3-diphenyl-2-hydroxybut-3-en-1-one (**14**),[18] presumably via an initial intramolecular hydrogen abstraction from the γ-carbon atom (**15**), followed by ring cleavage. The corresponding *cis* isomer, in which hydrogen abstraction by the benzoyl group from the methyl group is no longer possible, is not rearranged in the same way.

Intramolecular hydrogen abstraction of this type is a well-documented process (the Norrish type-2 process) in the photochemistry

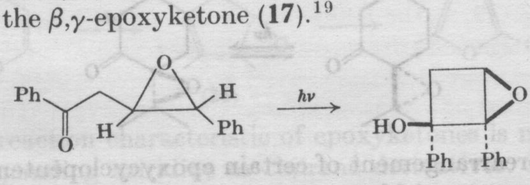


(**11**) (**12**)



(**13**) (**15**) (**14**)

of ketones, and additionally leads to the formation of cyclobutanols. The cyclobutanol (**16**) was, in fact, obtained as one of the products of photolysis of the β,γ-epoxyketone (**17**).[19]



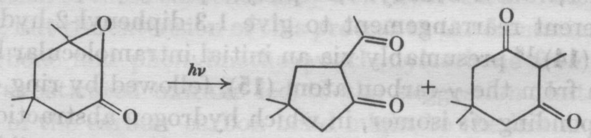
(**17**) (**16**)

The study of the photochemical rearrangements of α,β-epoxyketones has been extended to include cyclic systems and, in particular,

[18] H. E. Zimmerman, B. R. Cowley, C. Y. Tseng, and J. W. Wilson, *J. Am. Chem. Soc.* **86**, 947 (1964).

[19] A. Padwa, D. Crumrine, R. Hartman, and R. Layton, *J. Am. Chem. Soc.* **89**, 4435 (1967).

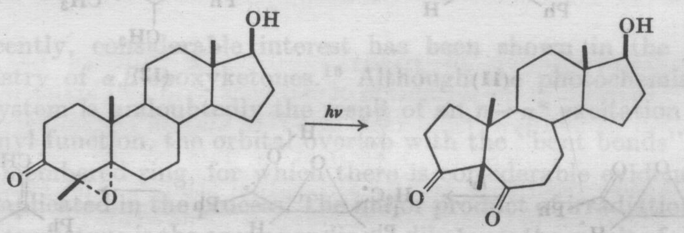
steroidal molecules in which a detailed study of the stereochemistry can easily be made. Isophorone oxide, for example, is converted into the two possible β-diketones [Eq. (4)].[20]



(4)

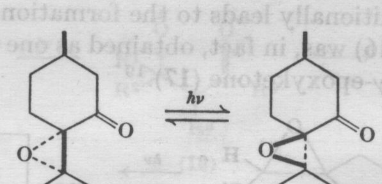
A stereospecific rearrangement is observed in the photolysis of 17β-hydroxy-4α,5α-epoxy-4β-methylandrostan-3-one (**18**) to give the β-diketone (**19**)[21]; the analogous 4β,5β-epoxysteroid is converted in the same manner into the diketone with a 5α-methyl group.

There are, however, a number of exceptions to this specificity; and in some systems, photoisomerization is known to occur. One such



(**18**) (**19**)

example is the reversible isomerization of α- and β-pulegone oxides [Eq. (5)].[20]



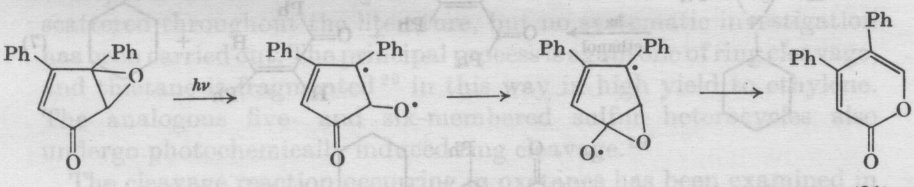
(5)

The photorearrangement of certain epoxycyclopentenones takes a different course to yield 2-pyrone derivatives; one example is the conversion of 3,4-diphenyl-4,5-epoxycyclopent-2-en-1-one (**20**) into 4,5-diphenyl-2-pyrone (**21**), and this can be rationalized by assuming cleavage of the oxirane to give the diradical (**22**) or its equivalent,

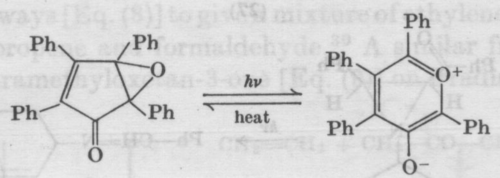
[20] C. K. Johnston, B. Dominy, and W. Reusch, *J. Am. Chem. Soc.* **85**, 3894 (1963).

[21] H. Wehrli, C. Lehmann, K. Schaffner, and O. Jeger, *Helv. Chim. Acta* **47**, 1336 (1964).

followed by rearrangement to the intermediate (**23**).[22] Other epoxycyclopentenones also undergo this photoreaction, and in the case of the tetraphenyl derivative (**24**), an additional product is the pyrylium 3-oxide (**25**)[23]; this is not, however, an intermediate in the formation of the corresponding pyrone. Both processes are observed in the photolysis of substituted 2,3-epoxyindanones.[24]

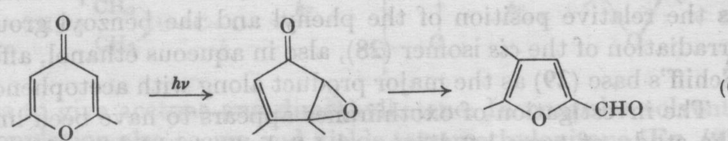


(20) **(22)** **(23)** **(21)**



(24) **(25)**

An epoxycyclopentenone (**26**) is also thought to be an intermediate in the photochemical conversion of 2,6-dimethylpyrone into 4,5-dimethylfurfuraldehyde[25] [Eq. (6)], but the reasons for the formation of the furan rather than a 2-pyrone are not clear.



(6)

(26)

The photoreaction characteristic of epoxyketones is not observed in the corresponding aziridine or thiirane derivatives. In the compounds so far examined, the result of photolysis is usually photoextrusion of the heteroatom. In this way, *trans*-1-cyclohexyl-2-phenyl-3-benzoylaziridine is converted in aqueous ethanol into a

[22] A. Padwa, *Tetrahedron Letters* 813 (1964).
[23] J. M. Dunstan and P. Yates, *Tetrahedron Letters* 505 (1964).
[24] H. E. Zimmerman and R. D. Simkin, *Tetrahedron Letters* 1847 (1964).
[25] P. Yates and I. W. J. Smith, *J. Am. Chem. Soc.* **85**, 1208 (1963).