Bicyclic Endoperoxides and Synthetic Applications

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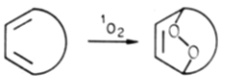
I. Introduction

Although the existence of singlet molecular oxygen has been recognized since 1924,[1] its chemistry has developed dramatically during the last two decades. Not only have chemists contributed to the exponentially growing chemistry of singlet oxygen, but other scientist such as biologists and biochemists have also shown substantial interest in this field. This interest has grown considerably since the recognition of the biochemical roles[2] of the excited state of oxygen in certain blood diseases, in cancer-inducing mechanisms, in a possible free-radical-like aging mechanism, in the role of bacterial activities of phagocytes, and in metabolic hydroxylation. In addition to investigations into the role of singlet oxygen in these phenomena and the mechanism of its reactions, its synthetic applications have also been explored and their utility has been demonstrated.

One can roughly categorize the reactions of singlet oxygen into two classes: (1) cycloaddition to form cyclic peroxides and (2) ene reactions to form hydroperoxide. The 1,4 cycloaddition of singlet oxygen to a cyclic diene results in the formation of a bicyclic endoperoxide (eq 1). This cycloaddition provides an excellent opportu-



(1)

nity to introduce two oxygen functions in the 1,4-positions of 1,3-dienes.

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Metin Balci was born in Erzurum, Turkey, in 1948. He went to school in Turkey and then in Germany, where he did his undergraduate work at the University of Cologne. He received his "Diplom-Chemiker" degree in 1972 followed by a Ph.D. degree i976 from the University of Cologne where he worked with Professor E. Vogel. After military service in Turkey, he did postdoctoral work with Professors H. Günther at the University of Siegen (Germany), W. Adam at the University of Puerto Rico, and W. M. Jones at the University of Florida. He has worked on annulenes, NMR spectroscopy applied to organic chemistry, cycloheptatriene–norcaradiene problems, singlet oxygen, cyclic strained allenes, and carbene–carbene rearrangements.

In recent years, several excellent reviews[3] concerning the reactions of singlet oxygen have been published. The primary focus of this review will therefore be on recent applications of bicyclic endoperoxides to synthetic problems which demonstrate the generality of the synthetic methodology involving singlet oxygen; some other applications will also be briefly discussed.

II. Reduction of Bicyclic Endoperoxides

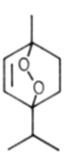
A. Diimide Reduction

Unsaturated bicyclic endoperoxides can be synthesized readily by photooxygenation of cyclic 1,3-dienes[4] and are important precursors for saturated endoperoxides (eq 2). The peroxide linkage is highly suscep-

(2)

tible to reductive cleavage by a variety of reductants. It is therefore not suprising that in the catalytic hydrogenation of unsaturated endoperoxides, the peroxide bond as well as the double bond is reduced.

In contrast to this, ascaridole (1) is one of the few



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cyclic peroxides in which catalytic hydrogenation does not attack the peroxide linkage.[5] If the problem of

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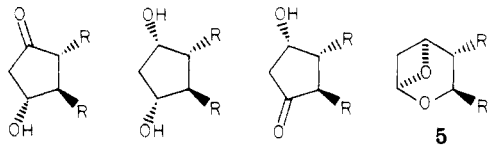
concurrent peroxide bond reduction could be circumvented in a general and efficient way, a novel route to the prostaglandin endoperoxides and saturated bicyclic endoperoxides could be implemented.

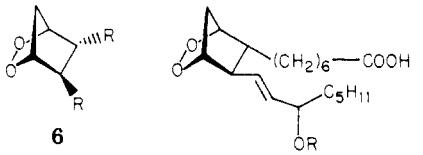
Prostaglandin (PG) endoperoxides[6] are the immediate biological precursors of prostaglandins[6] such as prostaglandin E_2 (2), prostaglandin $F_{2\alpha}$ (3), prostaglandin D_2 (4), and thromboxane A_2 (5).[7] These are derivatives of the strained 2,3-dioxabicyclo[2.2.1]hep-



2 3 4 5

R = $CH_2CH{=}CH(CH_2)_3COOH$, $CH_2CH{=}CHCH(OH)C_5H_{11}$

tane heterobicyclic ring system 6.

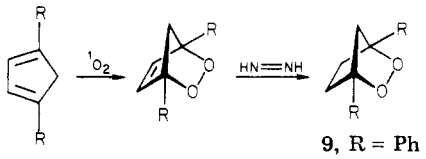


6

7, PGG, R = OH
8, PGH, R = H

Recently, the isolation of the two prostaglandin bicyclic endoperoxides PGG (7) and PGH (8)[8] has initiated considerable synthetic interest in the 2,3-dioxabicyclo[2.2.1]heptane structure. These endoperoxides have not only been identified as intermediates in prostaglandin formation but they have also been shown to exhibit strong and independent physiological effects. The synthesis of this interesting and biologically important endoperoxide structure could be facilitated by introducing the diimide reduction.

A variety of methods have been used for generation of diimide in reaction mixtures containing reducible substrates.[9] The use of potassium azodicarboxylate and acetic acid for the generation of diimide[10] appears to be the most useful technique. the first nonenzymatic synthesis of the bicyclic ring system 9, which presents the prostaglandin structure, was achieved by Salomon and Coughlin[11] using the combination of singlet oxygenation and subsequent diimide reduction described above (eq 3). It has been shown that diimide selectivly

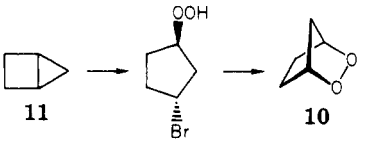


(3)

9, R = Ph
10, R = H

reduces the carbon–carbon double bond of unsaturated dialkyl peroxides. This selective reduction has been extended to provide an efficient synthesis of the parent compound (10).[12]

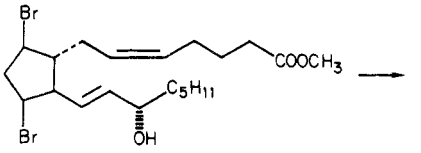
The saturated endoperoxide 10, which is a key compound in the study of the chemistry associated with prostaglandin endoperoxides, has been synthesized by other groups using different approaches. Porter and Gilmore[13] were successful in the synthesis of 10 using silver acetate cyclization of the *trans*-3-bromocyclopentane hydroperoxide (12) which was obtained by reaction of bicyclopentane (11) with 98% H_2O_2 and *N*-bromosuccinimide (eq 4). The extension of this



(4)

11 12 10

cyclization to dibromide 13 gave the prostaglandin endoperoxide 14[14] in a yield of 20–25% (eq 5). Salomon



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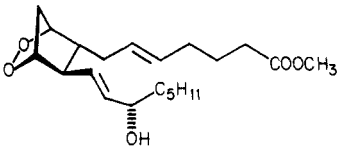

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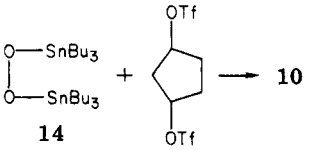
14

and Salomon[15] obtained 10 by an independent route using the condensation of 14 with bistriflate 15 (eq 6).

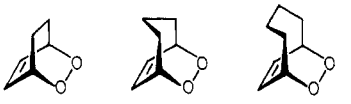


(6)

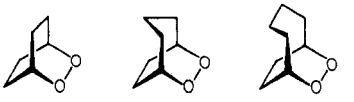
14 15

A new homologous series of endoperoxides related to the prostaglandin endoperoxides bearing bromo substituents has recently been synthesized by Bloodworth and Eggelte.[16]

The selected diimide reduction has been extended to a series of unsaturated bicyclic [*n*.2.2] peroxides. The singlet oxygen adducts 16,[17] 17,[18] and 18[19] from 1,3-cyclohexadiene, 1,3-cycloheptadiene, and 1,3-cyclooctadiene upon reduction with diimide gave the saturated bicyclic endoperoxides 19,[12] 20,[12,20] and 21,[12,21] respectively.



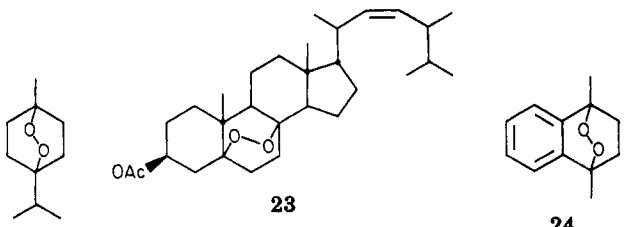
16 17 18



19 20 21

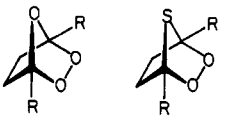
The generality of diimide reduction under very mild conditions has been demonstrated by Adam and Eggelte. Dihydroascaridole (22), epidoxyergosterol acetate (23), and 1,2,3,4-tetrahydro-1,4-*epi*-dioxynaphthalane (24) have been synthesized from the corresponding unsaturated precursors in high yield.[22]

Selective diimide reduction not only serves as an access to the unknown saturated bicyclic endoperoxides but also facilitates the trapping of the unstable singlet oxygen adducts by running photooxygenation at low



22 23 24

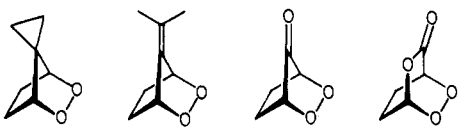
temperature (−78 °C), followed by diimide reduction at the same temperature. By application of this technique, unstable ozonide[23] structures (**25**) and thiaozonides (**26**)[24] have been isolated.



25 **26**

R = CH_3, $C(CH_3)_3$

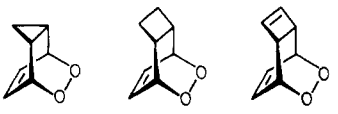
In view of this convenient technique of trapping unsaturated endoperoxides, Adam and Erden reinvestigated the photooxygenation of spiro[2.4]hepta-4,6-diene[25] and 6,6-disubstituted fulvenes.[26] By succesful isolation of **27**[27] and **28**[28] the intervention of the earlier



27 **28** **29** **30**

postulated endoperoxides, which lead to a complex mixture of products, has been confirmed. The ozonolysis of **28** gave endoperoxide **29**[28] which turned out to be unstable. However, the interesting saturated bicyclic endoperoxide **30**,[29] obtained by photooxygenation of α-pyrone followed by reductive trapping, was stable. An interesting feature of **29** and **30** is their emission of light during the decarbonylation and decarboxylation, respectively.

The reactivity of diimide with olefins is influenced by the number and nature of the alkyl substituents present. Trans olefins are usually reduced slightly more rapidly than cis olefins, and the ease of olefin reduction diminishes as the number of alkyl substituents is increased. These reactivity differences have been attributed to the differences in strain (torsion, bond angle, and eclipsing) with the more strained olefins reacting more rapidly.[30] The diimide reduction of the following interesting endoperoxides **31**,[31] **32**,[32] and **33**,[33] which

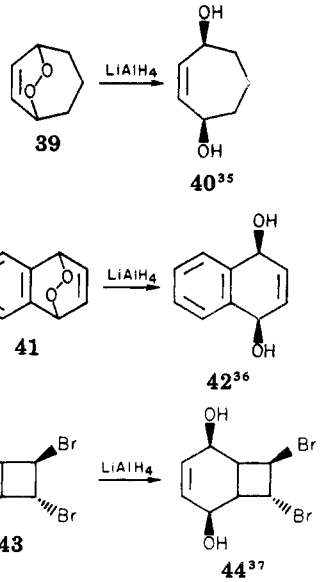


31 **32** **33**

possess the additional strain of annelation with cyclopropane, cyclobutane, and cyclobutene, proceeded smoothly, affording the corresponding saturated endoperoxides in high yield.

By submitting the [2 + 4] adduct **34** (isolated by photooxygenation of cycloheptatriene)[20,31] to diimide reduction, the more strained double bond incorporated into the six-membered ring was reduced readily. However, achieving the complete reduction caused some

SCHEME I



39 **40**[35]

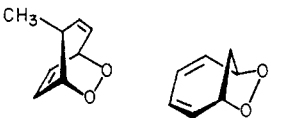
41 **42**[36]

43 **44**[37]

difficulties, since the double bond in **35** is incorporated into the seven-membered ring and the strain in the molecule was also reduced due to the reduction of the first double bond. Repetitive reduction with diimide was necessary in order to obtain **36** (eq 7).

34 **35** **36** (7)

Diimide reductin of **37**, which is readily accessible by photooxygenation of 7-methylcycloheptatriene,[34] could be completed only with 40–50-fold excess of diimide.

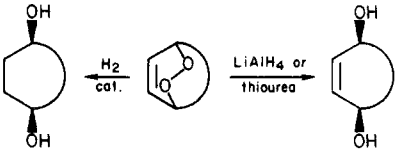


37 **38**

A similar effect was also observed by the saturation of the second double bond of the [2 + 6] adduct from cyloheptatriene.[20,31]

B. $LiAlH_4$, Thiourea, and Catalytic Reduction

Bicyclic endoperoxides can be readily reduced by lithium aluminum hydride or thiourea to give 2-ene-1,4-diols. Catalytic hydrogenation normally leads to further reduction to 1,4-diols (eq 8). Therefore the

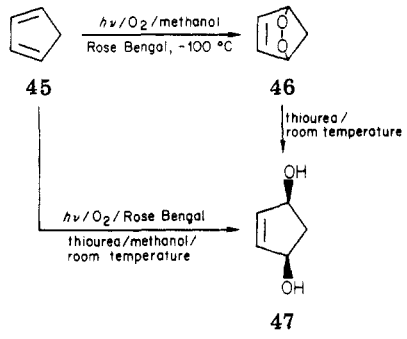


(8)

combination of singlet oxygenation of 1,3-dienes followed by reduction provides convenient and efficient access to the 2-ene-1,4-diols and 1,4-diols both with the syn configuration. These are not readily obtainable by other routes. A few interesting examples are listed in Scheme I.

Thiourea reduction has some advantages over both catalytic hydrogenation and lithium aluminum hydride

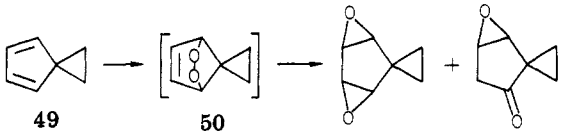
reduction in that it reduces only the oxygen–oxygen bond and thus preserves most other functional groups in the molecule. For example, Schenck and Dunlap[38] synthesized endoperoxide **46** by 1,4-addition of singlet oxygen to cyclopentadiene (**45**) and after isolation reduced it with thiourea to the diol **47** (eq. 9). Kaneko et al.[17b] reported that the diol **47** can be obtained in one step by reaction of the diene **45** with singlet oxygen in the presence of thiourea. Under these conditions, irradiation can be conducted conveniently at room temperature without isolation of the endoperoxide **46**. In



45 46 47 (9)

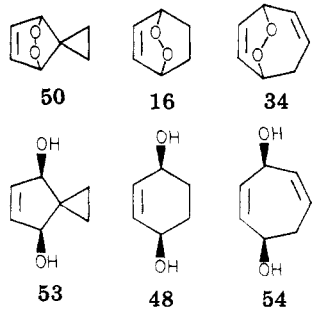
the same manner, *cis*-2-cyclohexene-1,4-diol (**48**) was obtained from cyclohexadiene.

The singlet oxygenation of spiro[2.4]hepta-4,6-diene has been reported.[25] The endoperoxide **50** could not be isolated. The intervention of **50** has been postulated by isolation of the bisepoxide **51** and keto epoxide **52** which are derivatives of **50** (eq. 10). The postulated



49 50 51 52 (10)

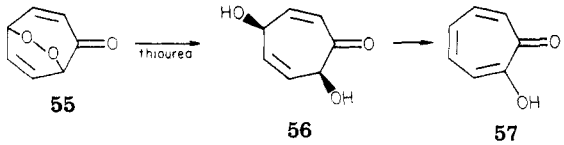
endoperoxide **50** has been trapped[27] by conducting a dye-sensitized photooxygenation in the presence of thiourea to give the *cis*-diol **53**. This method therefore



50 16 34 53 48 54

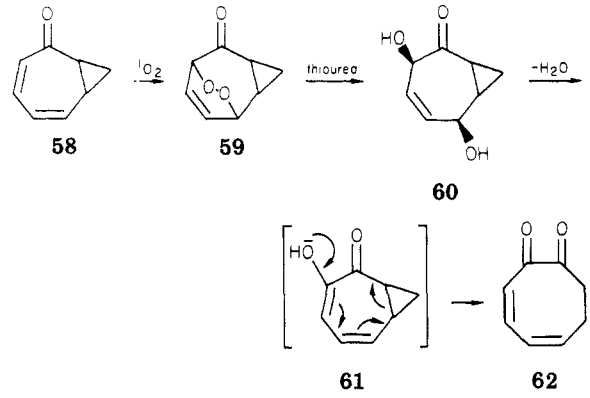
seems to be applicable to the synthesis of the diols by trapping of the corresponding labile endoperoxides. The thiourea reduction of **34** in methanol proceeded smoothly, affording the labile *cis*-diol **54**.[20]

Oda and Kitahara[39] described a simple method for the preparation of tropolone. Selective reduction of the endoperoxide **55** with thiourea gave tropolone (**57**) in 72% yield instead of the possible intermediate **56** (eq 11).



55 56 57 (11)

Ito et al.[40] reported the photooxygenation of 2,3-homotropone. Photooxygenation of **58** in acetone using hematoporphyrin as the sensitizer gave the endoperoxide **59** in 90% yield. Selective reduction of the peroxide linkage of **59** with thiourea provided the dihydroxy ketone **60** which slowly underwent dehydration to form **62** (eq 12). The dehydration was probably catalyzed by a trace amount of hydrogen chloride that was present in the chloroform. In the formation of **62** the intermediate 7-hydroxy-2,3-homotropone (**61**) has

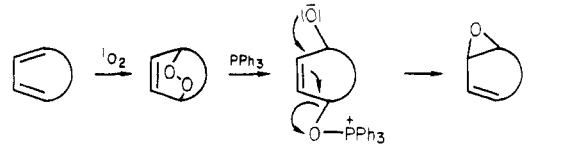


58 59 60 61 62 (12)

been suggested as a transient species which isomerizes spontaneously to **62**.

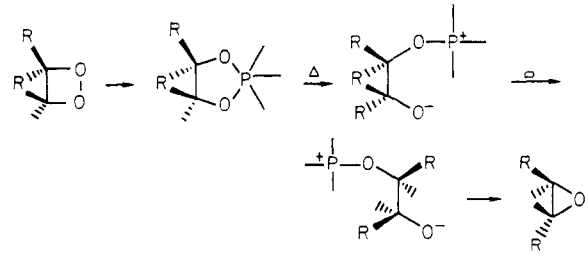
C. Triphenylphosphine Deoxygenation

1,4-Cycloaddition of singlet oxygen to 1,3-dienes followed by reductive extrusion of one oxygen atom with trivalent phosphorus compounds such as phosphines and phosphites provides a convenient entry to the unsaturated epoxides (eq 13). The mechanism is



(13)

analogous to that of the triphenylphosphine reduction of the dioxetanes which leads to phosphoranes.[41] Phosphoranes are known to undergo thermal decomposition to give epoxides (eq 14). Bartlett et al.[41c] have



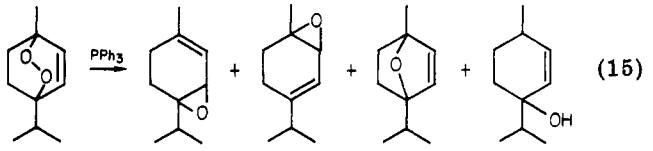
(14)

shown that this reaction is stereospecific; the *trans*-diphenyldioxetane gives only *cis*-stilbene oxide. The nature of the final products depends on the structure of the starting dioxetane. For open-chain dioxetanes, epoxides are the major products since free rotation around the C–C bond allows the two oxygen functions of the zwitterionic intermediate to be in the trans configuration which is necessary for the elimination. For the cyclic system where free rotation is hindered, elimination occurs instead to give allylic alcohols or diketones.[42]

It is interesting that bicyclic endoperoxides, in which

backside displacement is precluded, can form the unsaturated epoxide by S_N2' displacement. However, in some cases the displacement is accompanied by side reactions such as the formation of allylic alcohol (66) or bicyclic ether (65).

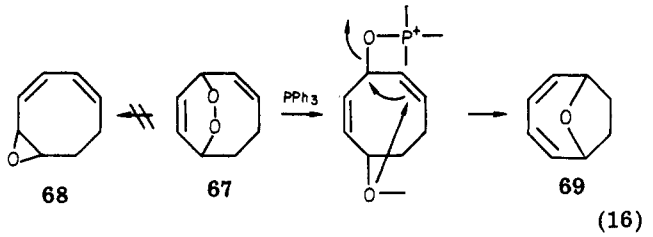
Triphenylphosphine deoxygenation of ascaridole (1) has been reported to give a complex mixture of products (63–66), with 63 being the major product (eq 15).[43] When the desired sterochemical arrangement for a S_N2' displacement cannot be achieved, the side reactions



(15)

1 63 64 65 66

would determine the final product. Triphenylphosphine deoxygenation of 67 and 70 gave the cyclic ethers 69[32] and 72[44] instead of the epoxides 68 and 71, repectively (eq 16 and 17). Oda et al.[45] utilized the



68 67 69

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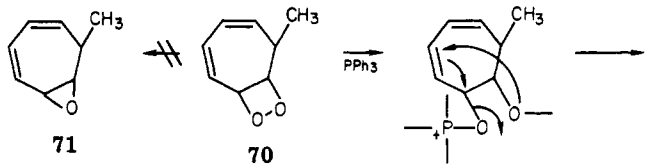
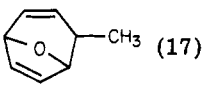


71 70



(17)

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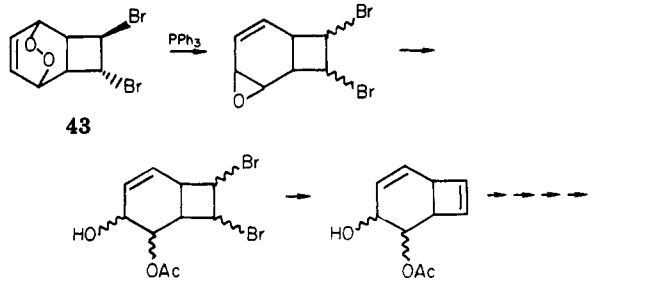
triphenylphosphine reduction in the synthesis of the interesting diketone 73 which is the valence isomer of the 3,5,7-cyclooctatriene-1,2-dione (eq 18).



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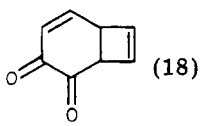
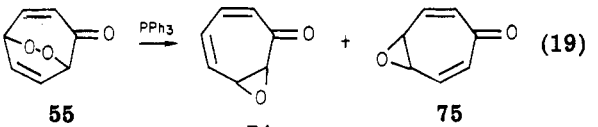


(18)

73

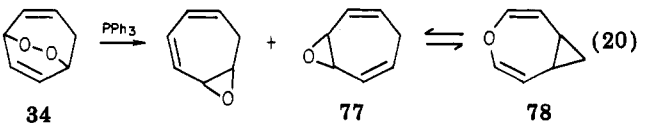
Tropone oxides 74 and 75 being the oxygen analogues of homotropone are interesting in view of oxide group participation in the homoconjugation. Their synthesis[46] has been established by deoxygenation of the troponeendoperoxide (eq 19).



(19)

55 74 75

The triphenylphosphine deoxygenation of endoperoxide 34 gave rise to a mixture of 3,4-epoxy-1,5- and 5,6-epoxy-1,3-cycloheptadiens, respectively (76 and 77)[47] (eq 20). At room temerature the epoxy diene 77 was in equilibrium with its valence tautomer, as confirmed

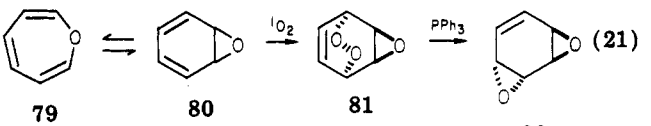


(20)

34 76 77 78

by ^1H NMR. This tautomeric equilibrium has already been described by Grimme et al.[48]

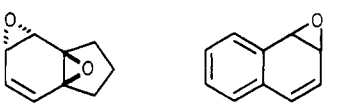
Since benzene cannot be oxidized by peracids to form epoxides, the photooxygenation of the oxepin or benzene oxide derivatives followed by triphenyl phosphite or triphenylphosphine reduction provides a unique entry into the biologically important arene oxides. The oxepin–benzene oxide system (79 ⇌ 80) readily undergoes a 1,4 Diels–Alder addition with singlet oxygen generated from hypochlorite–hydrogen peroxide[49] to form 1,4-epoxy endoperoxide 81[50,51] which has been deoxygenated[52] to the known *trans*-benzene dioxide[53] 82 (eq 21).



(21)

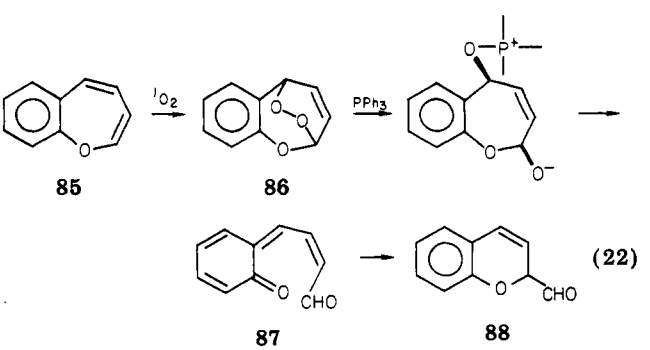
79 80 81 82

Foster and Berchtold[52] have synthesized *anti*-indene dioxide (83) in a similar way by reduction of the corresponding endoperoxide with triphenyl phosphite. Vogel et al.[36] provided a novel example of the applicability of this synthetic methodology by synthesizing the naphthalene monoepoxide 84 via the deoxygenation of the endoperoxide 41 with triphenylphosphine.



83 84

Since benzoxepin (85) is not in equilibrium with its valence isomer, the sensitized photooxygenation of 85 gave the [2 + 4] oxepin adduct 86, which on deoxygenation with trimethyl phosphite undergoes an unusual rearrangement ot the aldehyde 88. This probably goes via quinone methide 87[54] (eq 22).



(22)

85 86 87 88

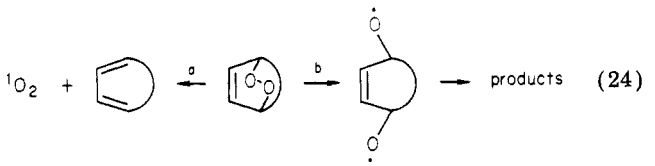
Deoxygenation of the norcaradiene endoperoxides[55] (89) (obtained by tetraphenylporphirine-sensitized photooxygenation of 7-substituted cycloheptatriene derivatives) provides a convenient synthesis of stable epoxy olefins (90) (eq 23). Structurally these norcaradiene monoepoxides are extremly interesting because the isomers with the epoxide ring and the cyclopropane ring in a anti relationship possess a "locked-in" planar cyclohexene conformation, as suggested by inspection of Dreiding models and ^1H NMR analysis.[56]

89 90 (23)

a, X = H
b, X = $COOCH_3$
c, X = CN (endo)
d, X = CN (exo)
e, X = Ph

III. Thermolysis of Bicyclic Endoperoxide

At least two different decomposition modes must be considered in the thermochemical reaction of endoperoxides: (1) loss of molecular oxygen in a process which is similar to the reverse of the formation process and (2) cleavage of the O–O bond[57,58] (eq 24).



(24)

Thermal dissociation leading to diradical formation (path b) will be favored over thermal dissociation into parent hydrocarbon and molecular oxygen (path a) simply because the activation energy for the O–O cleavage appears to be lower than for dissociation reaction (38 kcal).[59] Loss of molecular oxygen is expected to be more important in those endoperoxides which, upon loss of molecular oxygen, gain significant resonance stabilization. Kearns and Khan[60,61] have stated that resonance stabilization of the parent hydrocarbon is presumably the reason why endoperoxides of many polycyclic aromatic hydrocarbons are observed to thermally decompose by loss of molecular oxygen rather than by O–O bond cleavage.

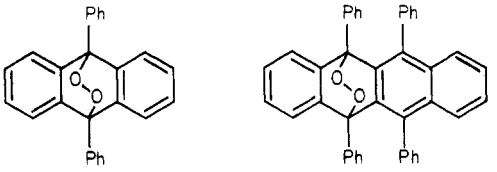
A. Loss of Molecular Oxygen

Since the synthesis of rubrene peroxide (92)[62] by Dufraisse, over 100 such polycyclic aromatic endoperoxides have been described in the literature.[4b] It has been shown that the ease of release of molecular oxygen by polyacene peroxides upon thermolysis depends primarily on the nature of the aromatic system and on the type of substituents in the meso position. In general, it appears that peroxides in the anthracene series give higher yields of oxygen than those in the naphthacene series and that aryl substituents in the meso position lead to increased oxygen release relative to alkyl or hydrogen.[63]

Wasserman et al.[64] studied the thermal decomposition of 91 and 92 in the presence of a variety of known singlet oxygen acceptors. The structures of the oxygenated products were the same as those observed in

TABLE I. $\Delta S^{\ddagger}$ Values and $^1O_2$ Yield for 100–103

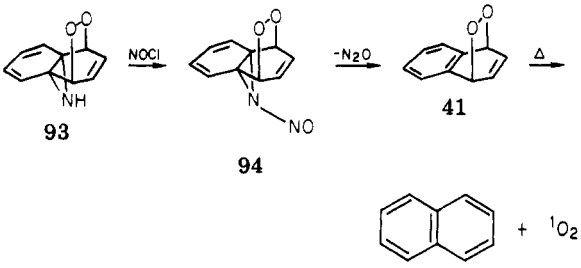
compd	$\Delta S^{\ddagger}$	$^1O_2$, % yield	solvent
100	9.6 ∓ 0.5	35	dioxane
101	7.4 ∓ 0.8	50	dioxane
102	−1.8 ∓ 0.8	95	dioxane
103	−0.3 ∓ 0.7	95	dioxane



91 92

parallel dye-sensitized photooxygenation reactions. This method thus provides a synthetically useful chemical technique for carrying out singlet oxygen reactions.

The interesting feature of some cyclic endoperoxides forming molecular oxygen and parent hydrocarbon by a retro-Diels–Alder reaction has also been observed recently in naphthalene-derivatives. Suitable substituted alkyl derivatives of naphthalene readily undergo dye-sensitized photooxygenation to give the corresponding endoperoxides. However, parent naphthalene shows hardly any tendency to react with singlet oxygen.[65] This lack of reactivity has been circumvented by employing a different approach. Thus, Vogel et al.[36] found (an alternative route to obtain naphthalene endoperoxide (41)) the *N*-nitrosoaziridine 94[66] to eliminate N_2O at very low temperatures to form 41 (eq 25). The

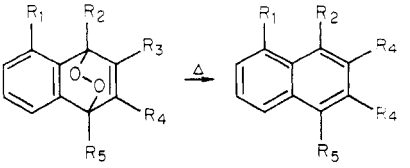


93 94 41

(25)

endoperoxide 41 undergoes thermal cleavage to naphthalene and oxygen with comperative ease. The activation entropy $\Delta S^{\ddagger}$ = 0.2 ∓ 1.1 kcal/mol points to a concerted cleavage (see below). Evidence that oxygen released by 41 is $^1O_2$ is found in products from the thermolysis of 41 with $^1O_2$ acceptors such as diphenylisobenzofuran or tetramethylethylene.

Recently, Wasserman and Larsen[67] synthesized some alkyl-substituted naphthalene 1,4-endoperoxides (95–99) (eq 26). Their thermal stabilities vary appre-



95-99 (26)

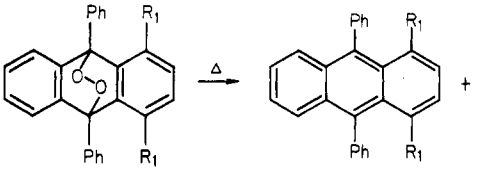
	R_1	R_2	R_3	R_4	R_5
95	H	Me	H	H	Me
96	Me	Me	H	H	H
97	Me	Me	H	H	Me
98	H	Me	Me	H	Me
99	H	Me	Me	Me	Me

ciably, and their decomposition in solution follows first-order kinetics. That the oxygen formed is probably

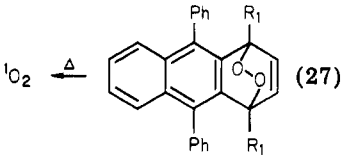
in the singlet state was shown by allowing one of the peroxides to decompose in the presence of 2,5-diphenyl-4-methyloxazole, an efficient singlet oxygen acceptor.

Hart and Oku[68] obtained octamethylnaphthalene 1,4-endopeoroxide which was also converted into the starting material and presumably singlet oxygen.

Turro et al.[69] recently studied the thermal decomposition of the 9,10- and 1,4-anthracene endoperoxides (**100**–**103**). They release nearly quantitative (95%) molecular oxygen and form the parent hydrocarbon (eq 27). The thermal decomposition process to generate



100, R_1 = H
101, R_1 = CH_3



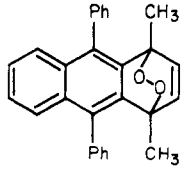
(27)

102, R_1 = CH_3
103, R_1 = OCH_3

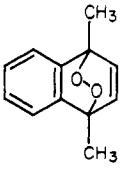
singlet oxygen approaches 100% for **102** and **103**, whereas **100** and **101** yielded only 35% and 50% singlet oxygen, respectively. Futhermore, it was found that a correlation exists between $\Delta S^{\ddagger}$ for thermolysis and the yield of $^1O_2$ (Table I).

By comparison with a classical concerted fragmentation, the retro [4 + 2] cycloaddition of dicyclopentadiene,[70] the $\Delta S^{\ddagger}$ values in Table I suggest a concerted reaction for the thermolysis of **102** and **103**.

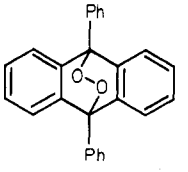
To further investigate the decomposition mechanism of endoperoxides, Turro and Chow[71] studied the effect of magnetic field on the thermolysis of endoperoxides of aromatic compounds. An interesting consequence of radical reactions involving singlet–triplet interconversions is the possibility of observing a variation in product distribution with application of a steady external magnetic field.[72] The rate of singlet–triplet conversion is expected to increase proportionally to the strength of magnetic field.[73] The thermolysis of the compound **102**, **95**, **100**, and **97** was carried out in a variable magnetic field.



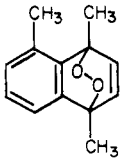
102



95

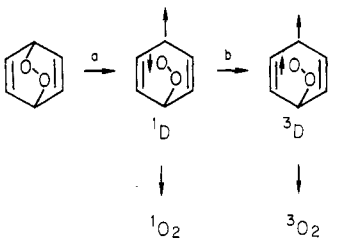


91



97

The external magnetic field should have no significant effect on the singlet oxygen yield of the endoperoxides if they undergo decomposition predominantly via a concerted fragmentation. In fact, the singlet oxygen yield from **102** was unchanged by application of a variable external magnetic field. However, under the same conditions a substantial change in the singlet oxygen yield from **100** has been observed. To explain this the authors suggest the following mechanism: In an initial step **100** forms a singlet diradical intermediate ^1D which competitively fragments to $^1O_2$ and intersystem crosses to ^3D which fragments to $^3O_2$ and diphenylanthracene (eq 28). In this mechanism only step



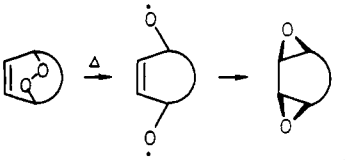
(28)

b should be magnetic field dependent. In the case of **102** the major pathway of reaction may be concerted or may involve a diradical singlet ^1D which is too shortlived to be influenced by magnetic field. The behaviors of **95** and **97** are intermediate to the behaviors of **102** and **101**. Thus, the authors suggest either a mixture of concerted and diradical mechanisms is operating or the derived singlet diradical undergoes a different partitioning to singlet and triplet products.

More recently,[74] ^{17}O-labeling experiments on **101** have been used to study the decomposition mechanism in more detail. Since ^1D species containing ^{17}O (a magnetic isotope) have a higher probability of undergoing intersystem crossing in a magnetic field than molecules containing ^{16}O and ^{18}O (nonmagnetic isotopes), the yield of trapped $^1O_2$ and untrapped $^3O_2$ should vary in a predictable way. Actually, this has been demonstrated, and in this way the proposed mechanism for the thermolysis of **101** via an initial diradicaloid intermediate, ^1D, has been established.

B. Cleavage of the O–O Bond

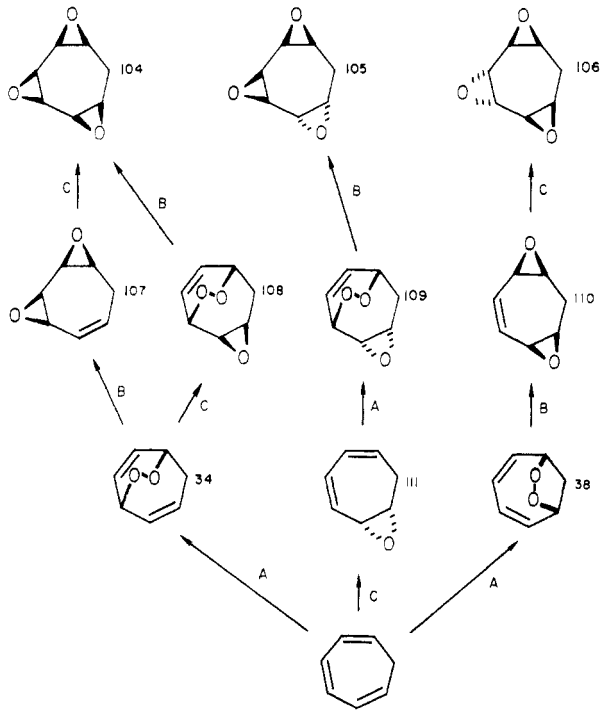
One of the common reactions of unsaturated [*n*.2.2] bicyclic endoperoxides is the cleavage of the weak oxygen–oxygen bond followed by addition of the oxygen radicals to the adjacent double bond to give bisepoxides with syn configuration (eq 29). This method has been



(29)

utilized in the last decade many times to synthesize cyclic bisepoxides. A review has been recently published[75] which discusses the synthesis of cyclic polyepoxides. This includes both the thermal rearrangement of unsaturated endoperoxides and the importance of this synthetic methodology. Thus, epoxide formation will not be discussed here in detail. However, recent developments and the synthetic application of the thermal rearrangement to new system will be summarized.

SCHEME II[a]

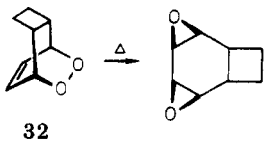


[a] A = $^1O_2$, B = Δ, C = RCO_3H

Recently a combination of photooxygenation of 1,3-dienes, thermal rearrangement, and epoxidation have served as a convenient and effective synthetic approach for the stereospecific synthesis of each of the isomeric trioxides **104**, **105**, and **106**.[76,77,94] As Scheme II reveals, two synthetic pathways to the all-syn isomer **104** have been accomplished. In the first, tropylidene-derived [2 + 4] endoperoxide **34**, readily obtained by the singlet oxygenation of cycloheptatriene,[20,31,79,80] gave the expected bisepoxide **107** upon thermolysis. This was converted into **104** by epoxidation with *m*-chloroperbenzoic acid. In the second, the order of the thermolysis and epoxidation was reversed. The second isomer,[76] syn, anti isomer **105**, was obtained by thermolysis of **109**, which is readily available by photooxygenation of cycloheptatriene oxide (**111**).[81] The [2 + 6] adduct[20,31] served as a starting material for the preparation of the third isomer of **106**. On thermolysis (more conveniently on photolysis at 350 nm obtained bisepoxide **110** gave the desired anti, anti trioxide **106** upon epoxidation with *m*-chloroperbenzoic acid.

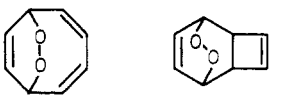
In summary, the basic synthetic tools employed in this design were (a) singlet oxygenation, (b) endoperoxide rearrangement, and (c) epoxidation reactions. However, by appropriate ordering of these transofrmation, it was possible to synthesize each of these three trioxide isomers stereospecifically. This is the first use of such permutations of these reagents for the stereospecific synthesis of polyepoxides.

More recently, bicyclo[4.2.0]octane diepoxide (**112**)[32] was prepared by thermal isomerization of the endoperoxide (**32**) which was obtained by photooxygenation of bicyclo[4.2.0]octa-2,4-diene (eq 30).



32 112 (30)

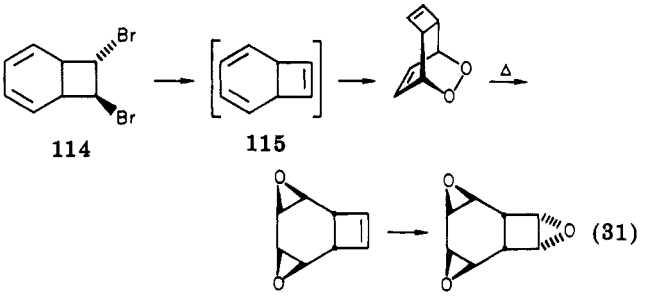
Unfortunately cyclooctatetraene (COT) shows hardly any tendency to react with singlet oxygen[82] to form the potentially valuable endoperoxides **113** and **33**. The



113 33

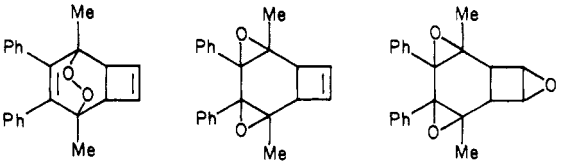
lack of reaction is readily explicable by the fact that the tub conformation of COT does not provide the near-planar diene system necessary for a concerted [4 + 2] Diels–Alder cycloaddition. Although the valence tautomer **115** does provide this necessary geometry, its low equilibrium concentration[83] at ambient temperature precludes trapping. The succesful generation of **115** by Vogel[84] (using low-temperature debromination of the dibromide **114** with disodium phenanthrene) and his finding that isomerization to COT is quenched at −78 °C suggested a solution to this difficulty.

Indeed, when **115** was generated at −78 °C and allowed to react with singlet oxygen, it gave **33** in high yield.[33] This, in turn, was converted on thermolysis to the corresponding *cis*-bisepoxide **116**. Further oxidation of **116** with *m*-chloroperbenzoic acid afforded the all-cis isomer **117** (eq 31).



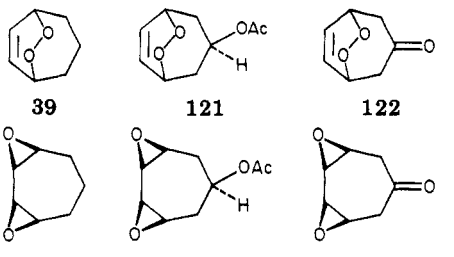
114 115 116 117 (31)

Highly substituted derivatives **118** and **119** have been synthesized by Warrener et al.[85] by thermolysis of the endoperoxide **120** followed by epoxidation. Further-



120 118 119

more, the thermolysis of endoperoxides **39**,[35] **121**,[86] and **122**[87] provided the expected cycloheptadiene bisepoxides **123**,[35,47] **124**, and **125**, respectively. The for-



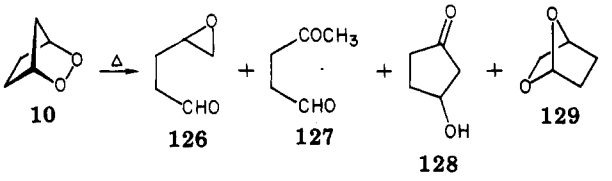
39 121 122

123 124 125

mation of **122** by photooxygenation of cycloheptadienone is suprising in view of the normally low dienic reactivity of 3,5-cycloheptadienone[88] due to the twisted conformation of the diene moiety. Usually,

cycloaddition takes place only at elevated temperatures following the isomerization to the conjugated system.

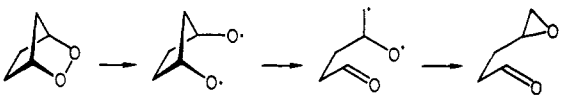
As a model compound for the prostaglandine endoperoxides the thermal chemistry of 2,3-dioxabicyclo-[2.2.1]heptane (**10**) has been studied by Salomon et al.[89] Thermal decomposition of **10** leads to an unusual product mixture of **126–129** (eq 32). The epoxy al-



10 126 127 128 129 (32)

dehyde **126** is an expected product of decomposition[90] and is believed to arise from simple homolysis of the peroxide bond in **10** followed by ring opening to diradical **10b**. Cyclization would produce the observed epoxy aldehyde (eq 33).

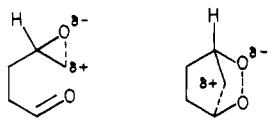
For the formation of **127** and **128**, a polar rearrangement mechanism rather than diradical processes has been suggested, since they are favored by polar and



10 10a 10b 126 (33)

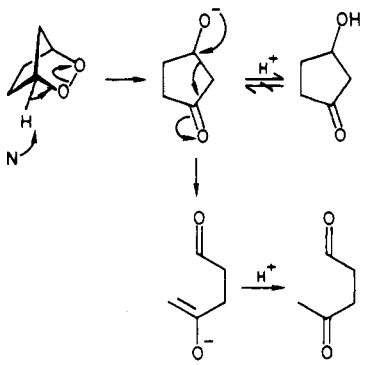
protic solvents. Usually, the formation of ketols such as **128** are rationalized in terms of base-catalyzed isomerization. However, in this case, **128** was formed under nonalkaline condition. This has also been found to be the case with PG-endoperoxides, which rearrange to give D and E prostaglandins in neutral aqueous solution.[91]

The formation of **127** probably arises from a 1,2-hydride shift to the positive carbon in **130** or **131**. More



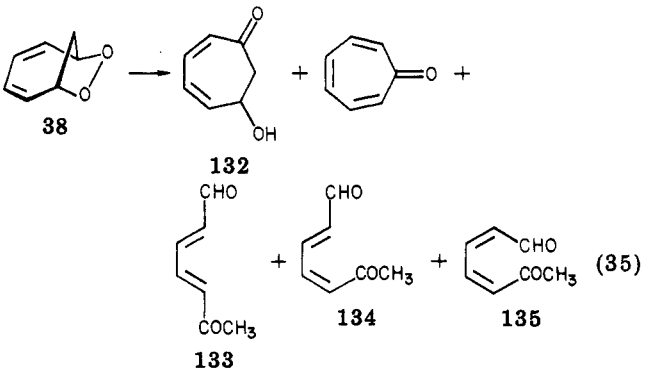
130 131

recently, Salomon and Zagorski[92] have studied the mechanism of amine-catalyzed fragmentation of 2,3-dioxabicyclo[2.2.1]heptane (**10**). The authors suggest from their kinetic data that the amine-catalyzed fragmentation (**10** → **127**) and disproportionation (**10** → **128**) are closely related mechanistically. Rate-determining cleavage of the bridgehead C–H bond generates a keto alkoxide with partitions between retro–aldol cleavage leading to **127** and protonation to **128** (eq 34).



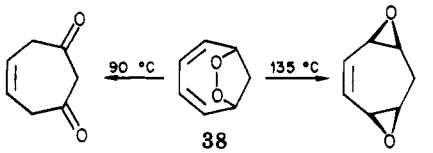
(34)

Rearrangement of an endoperoxide to a ketol and acetyl-aldehyde has been observed recently by Adam and Balci.[47] Thus, methanolysis of the [2 + 6] photoadduct of cycloheptatriene[47] (**38**) at room temperature gave an unusual product distribution (eq 35). The rate



38 132 133 134 135 (35)

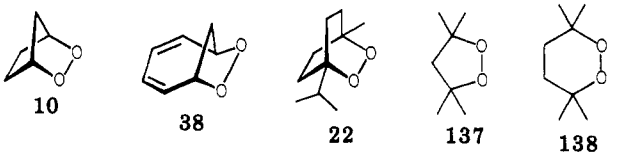
acceleration in polar solvents indicates that a polar mechanism is responsible for this transformation. Thermolysis of **32** in toluene at 135 °C gave the bisepoxide **110** and tropone in addition to three of the four possible ring-opened dienes (**133–135**). These were formed in 32%, 6–8%, and 44% yields, respectively (eq 36). However, the formation of enedione **136** at 90 °C



136 38 110 (36)

is most intriguing since twofold hydrogen migration is preferred at lower temperatures.

Inspection of Dreiding models[93] suggests an explanation for the similar thermal behavior in polar solvent of **10** and **38**; these two endoperoxides are rigid and

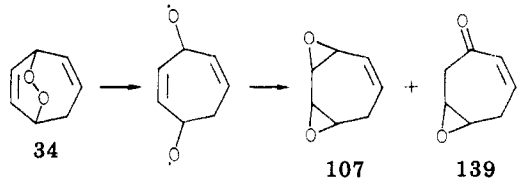


10 38 22 137 138

$\phi = 0 \pm 5°$ $0 \pm 5°$ $15 \pm 5°$ $30 \pm 5°$ $75 \pm 5°$

possess a –C–O–O–C– dihedral angle of $\phi = 0°$. By comparison[12,93] **22**, **137**, and **138** have corresponding dihedral angles of $\Phi = 15 \pm 5°$, $30 \pm 5°$, and $75 \pm 5°$, respectively. Consistent with this suggestion is Brown's observation[93] of a decrease in the separation of the first two peroxide bands in the photoelectron spectra as the dihedral angle progresses from 0 to 90°.[94]

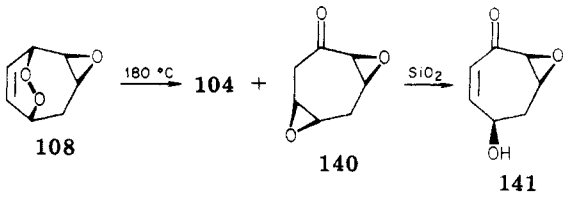
It was pointed out earlier that, upon thermolysis, unsaturated bicyclic endoperoxides readily form the corresponding bisepoxides. However, in strained molecules like [2.2.1] systems thermolysis is always accompanied by side reactions.[25,26] One of these side reactions is the formation of epoxy ketones. Such side reactions have been observed recently also in cycloheptatriene systems. For example, thermolysis of 1,3-cycloheptadiene endoperoxide (**39**) gave a quantitative yield of bisepoxide **123**.[35,47] In contrast, **34**, which differs from **39** by an additional double bond, forms the bisepoxide **107** in only 11% yield.[47] The major product of this reaction is the epoxyenone **139** (eq 37). Control



(37)

experiments reveal that both **107** and **139** are stable to the thermolysis conditions. Therefore, the intermediate-formed diradical either transposes an alkoxy α hydrogen by β scission, affording epoxy enone **139**, or cycloadds into ene bisepoxide **107**.

The driving force of this rearrangement is not the formation of α,β-unsaturated ketones, since blocking of the double bond in **34** by epoxidation does not prevent the rearrangement to form **140**, formed in addition to **104**[94] (eq 38).

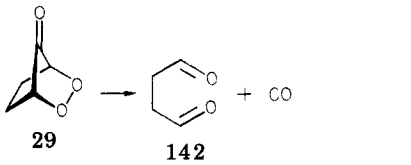


(38)

In summary, bisepoxides can be formed from bicyclic endoperoxides in nearly quantitative yield. However, if the molecules are highly strained or perturbed by double bonds or epoxides, other reactins become important.

IV. Fragmentation of Bicyclic Endoperoxides

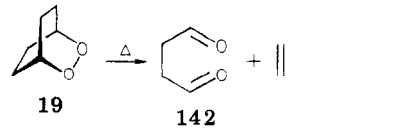
An interesting example of decarbonylative fragmentation of a cyclic endoperoxide[28] is found in **29** which is cleanly transformed at −10 °C into succinaldehyde (**142**) (eq 39). Analogous fragmentation by addition



(39)

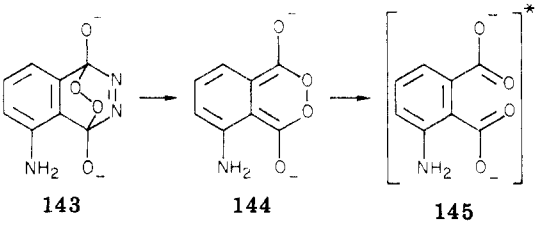
of singlet oxygen to tetraphenylcyclopentadienone[95] had been observed earlier.

The thermal reactivity of the bicyclic endoperoxides changes dramatically from the [2.2.1] to the [2.2.2] system. In contrast to **10**, the thermal decomposition of **19** varies slightly with changes in solvent polarity. Decomposition of **19**[96] gave succinaldehyde (**142**) and ethylene which was trapped by bromine (eq 40).



(40)

Probably the best known example of chemiluminescence results from the oxidation of luminol (5-amino-2,3-dihydro-1,4-phthalazinedione) which gives an intense blue light. This was first reported by Albrecht[97] in 1928. It is generally agreed that the excitation-producing step is nitrogen extrusion from a dianion of an azo compound[98] for which Michl[99] has proposed an endoperoxide structure (**143**). According to his suggestion, loss of N_2 occurs from **143** with preservation of the peroxide linkage to afford xylylene peroxide (**144**). The latter affords electronically excited 3-aminophthalate which is responsible for light emission (eq 41). Following this proposal, considerable attention

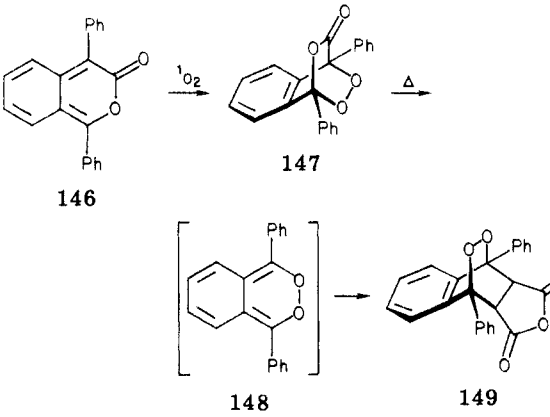


(41)

has been directed toward the synthesis of *o*-xylylene peroxides.

For instance, Smith and Schuster[100] submitted 1,4-diphenyl-2-benzopyron-3-one to sensitized photooxygenation and isolated the interesting benzopyrone endoperoxide (**147**) which upon thermal decomposition gave *o*-dibenzoylbenzene and phenyl *o*-benzoylbenzoate. The *o*-xylylene peroxide **148** (the first reported example of this interesting hetero ring system) was suggested as a thermolysis intermediate to rationalize these products.

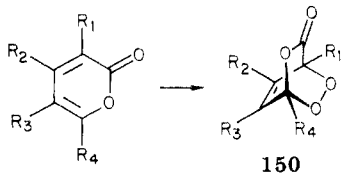
Isolation of **149** from pyrolysis of **147** in the presence of maleic anhydride is convincing support for this proposal (eq 42). In addition to its interesting chem-



(42)

istry, **148** presented an example of a potentially important new class of chemiluminescent reagents. In fact, thermolysis of **147** does not produce a detectable luminescence. However, in the presence of biacetyl, phosphorescence from the triplet excited biacetyl was detected. Addition of rubrene, perylene, or one of several easily oxidized aromatic hydrocarbons resulted in readily detected luminescence. In this case, the luminescence is arising from the singlet excited state of the added hydrocarbon. Furthermore, the authors showed by fluorescence that the Chemically Initiated Electron-Exchange Luminescence mechanism[101] (CIEEL) is operating.

More recently, the synthesis of some α-pyrone endoperoxides (**150**) has been accomplished[102] (eq 43). On



(43)

	R_1	R_2	R_3	R_4
150a	H	H	H	H
150b	Ph	Ph	Ph	Ph
150c	H	H	COOH	H
150d	H	H	COOMe	H

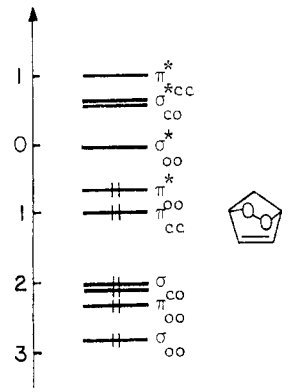
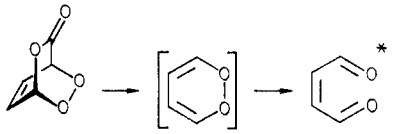


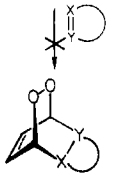
Figure 1. Orbital energies of the cyclopentadiene endoperoxide. Energies are in units of β.

thermal decomposition, these endoperoxides lose CO_2 quantitatively to afford the respective 1,2-diacylethylenes (**152**) (eq 44). All efforts to trap the possible



(44)

151 **152**



intermediate *o*-dioxin (**151**) with maleic anhydride or *N*-phenyltriazolinedione failed. It is therefore likely that in this case decarbonylation takes place concurrently with peroxide bond cleavage to afford **152** directly without the intervention of the *o*-dioxin (**151**).

The endoperoxides **150** also undergo fluorescer-enhanced chemiluminescence for which chemiluminescence measurement clearly indicate an electron-exchange mechanism. A fluorescer like rubrene catalyzes the decarboxylation of the endoperoxides (**150**). This is in contrast to the benzoannelated endoperoxide **147**.

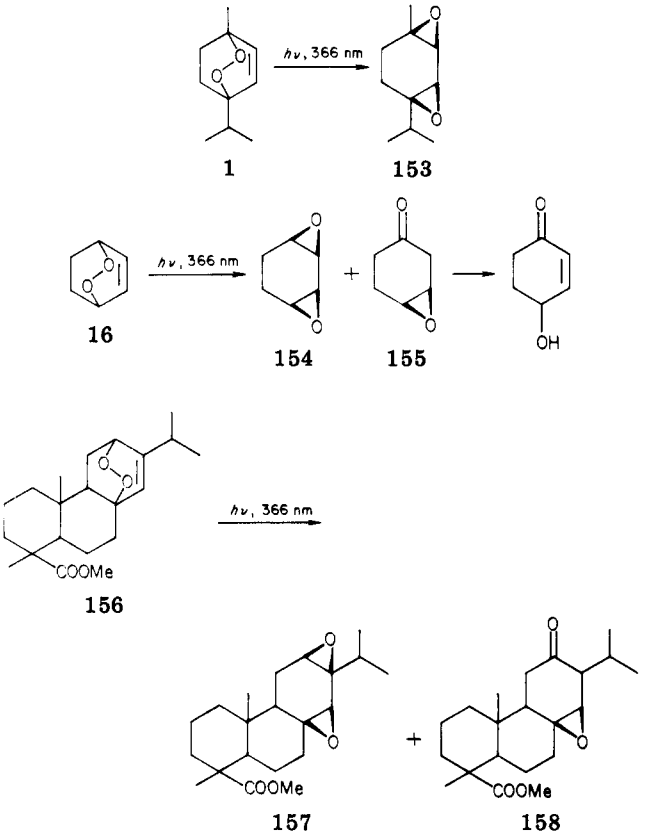
V. Photolysis of the Bicyclic Endoperoxides

To date, the only theoretical study concerning the photochemical decomposition of bicyclic endoperoxides is that reported by Kearns.[59] In this report it was concluded that the first excited singlet and triplet states have the electronic configurations $\pi^2_{CC}\pi^{*1}_{OO}\sigma^{*1}_{OO}$. It would therefore be predicted that long-wavelength photolysis should lead to cleavage of the oxygen–oxygen bond since the electron is transferred into the oxygen–oxygen antibonding orbital (Figure 1). Besides, these states correlate with the low-lying states of the diradical.

According to Kearns' analysis, the second excited/state corresponds to transfer of an electron from π^*_{OO} to σ^*_{CO} antibonding orbital. In contrast to the lower energy transition, this should actually strengthen the O–O bond while weakening the C–O bond. It would therefore be predicted that, at shorter wavelengths, carbon–oxygen cleavage should be observed.

Although there is relatively little information on the photolysis of bicyclic endoperoxides, one can make some comparison with the properties of simple dialkyl and

SCHEME III



diaryl peroxides.[103] In this case absorption in the long-wavelength region leads to the primary photodissociation process which involves cleavage of the weak peroxide bond. For this process, a relatively large excess of energy is available (56 kcal/mol at 313 nm, 78 kcal/mol at 254 nm). At wavelengths below about 230 nm, a second dissociative mode appears: cleavage of the C–O bond (eq 45). Upon irradiation with wave-

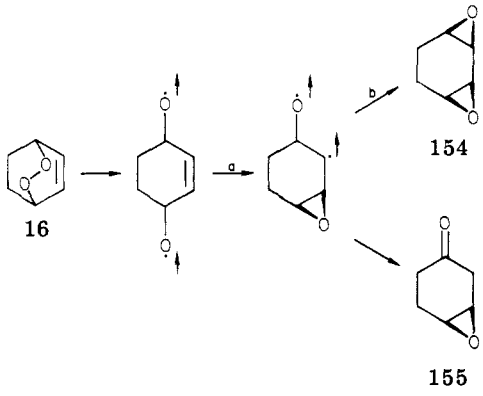
$$^1O_2 + 2R\cdot \xleftarrow{\lambda < 250\ nm} ROOR \xrightarrow{\lambda > 250\ nm} RO\cdot + RO\cdot \quad (45)$$

lengths greater than 250 nm, one would therefore expect unsaturated bicyclic endoperoxides to give products resulting from oxygen–oxygen diradicals. Irradiation with wavelengths less than 250 nm should also cause extrusion of molecular oxygen to give products from R.

Maheshwari et al.[104] have shown that irradiation at 366 nm of bicyclic endoperoxides such as ascaridole (**1**) and those derived from cyclohexadiene and levopimaric acid, methyl ester (**156**) give rearrangement products expected of O–O cleavage (Scheme III). The bisepoxides are the same products as those obtained in the thermal rearrangement. In the case of **16** and **156** the keto epoxides **155** and **158** were also observed. It was further found that irradiation of solutions of ascaridole (**1**) or **16** in the presence of any of the sensitizers Michler's ketone, phenanthrene, or trimethylamine gave the same products faster than was the case with direct irradiation. Although the quenching experiments did not reveal the nature of the intermediate, a likely mechanism involving the triplet is therefore a possible pathway for product formation, though not necessarily the only one.

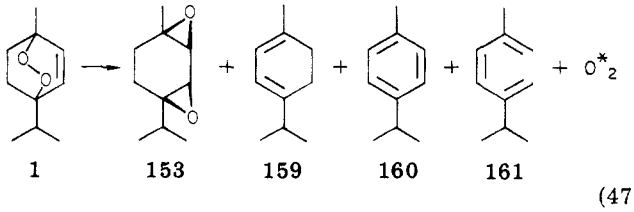
The diradical can either add to the double bond to form the bisepoxide or undergo hydrogen shift to give

the epoxy ketone. Of course if the reaction proceeds via a triplet, a spin inversion is required for the second step (b) (eq 46). It may be that this delays the closure



(46)

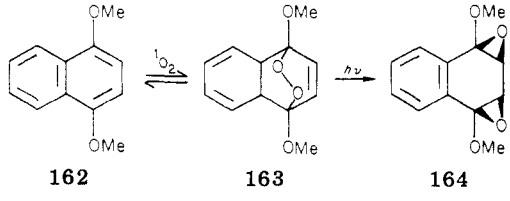
to the bisepoxide sufficiently to allow the hydrogen migration to compete and to form the keto epoxide. Consistent with the alkyl peroxide analogy discussed above, Srinivasan et al.[105] have recently reported that the photolysis of ascaridole gives a different product composition at 185 nm than at 366 nm.[104] Besides the isoascaridole (**153**), α-terpine (**159**), the triene **161**, a trace of *p*-cymene (**160**), and oxidation products derived from solvent such as cyclohexyl hydroperoxide, cyclohexanol, and cylohexanone (when the solvent was cyclohexane) were also isolated (eq 47). Because of the



(47)

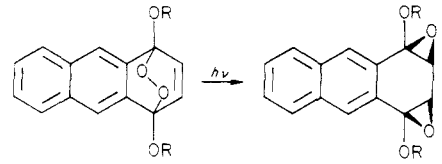
fact that no trace of oxygen was observed in the solution and in view of the 40-fold weaker absorption of oxygen at 185 nm compared with the absorption of ascaridole at the same wavelengths, the possibility that released oxygen undergoes secondary photolysis is excluded. The oxygen formed by a retro-Diels–Alder reaction must be in the excited state. The results do not shed light onto the character of the oxygen formed by this reaction.

As I have shown in section III, thermolysis of some endoperoxides derived from aromatic hydrocarbons gave preferentially the parent hydrocarbons rather than the corresponding bisepoxides. In such cases, photolysis serves as a convenient way to circumvent these fragmentation reactions. For instance, reaction of 1,4-dimethoxynaphthalene with singlet oxygen affords the expexted endoperoxide which, upon photolysis, is cleanly transformed into the naphthalene diepoxide **164**. In comparison, heating the endoperoxide leads to oxygen extrustion to give only starting material[106] (eq 48).



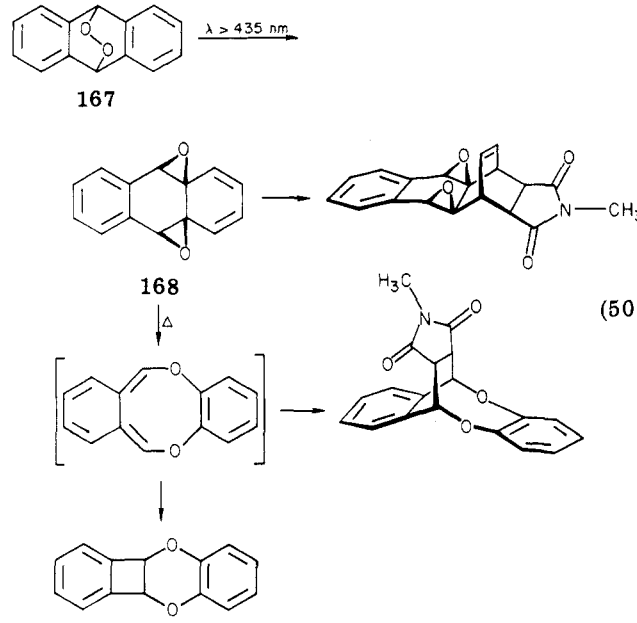
(48)

Another example, photolysis of 1,4-endoperoxides of anthracene substituted with alkoxy groups at C_1 and C_4, gives the isolable bisepoxides upon irradiation[106] (eq 49). In contrast, the bisepoxide **168** formed from



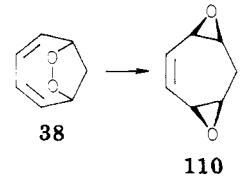
(49)

thermolysis and photolysis of 9,10-anthracene endoperoxide (**167**) could not be isolated. Their formation has been established by trapping with *N*-methylmaleicimide.[107] Recently, Rigaudy et al.[108] were succesful in isolating the anthracene bisepoxide **168** by prolonged irradiation at wavelengths greater than 435 nm (eq 50).



(50)

As can be appreciated from eq 35, the thermolysis of tropylidene 1,6-endoperoxide (**38**) gave a complex mixture of products. In contrast, its photochemistry is simple. Thus, irradiation at 350 nm (presumably n,π^* transition originating at the peroxide moeity) cleanly converted **38** into the *syn*-bisepoxide[20] (eq 51). Irradiation in benzene at 300 nm (π,π^* excitation of the dienic moiety) results only in recovery of the endoperoxide.

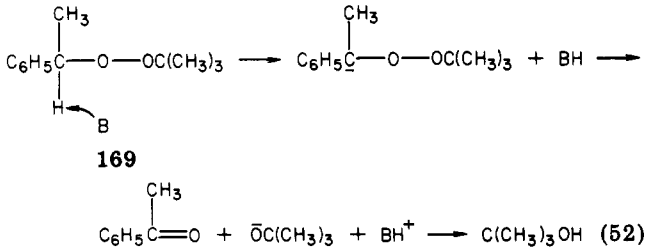


(51)

VI. Rearrangement of Endoperoxides

A. Base- and Acid-Catalyzed Rearrangements

Kornblum and de la Mare[109] reported the first base-catalyzed decomposition of a dialkyl peroxide in 1951. They found that bases such as potassium hydroxide, sodium ethoxide, or piperidine catalyze the decomposition of 1-phenylethyl *tert*-butyl peroxide (**169**) (eq 52).

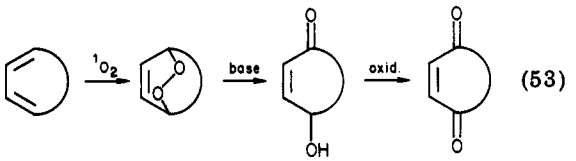


169

(52)

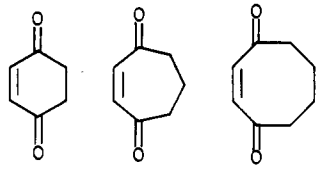
In view of this mechanism, only those dialkyl peroxides and alkyl hydroperoxides having a hydrogen on the carbon attached to the peroxide linkage should undergo base-catalyzed rearrangement.

Base-catalyzed decomposition of peroxides and hydroperoxides exemplify a general type of elimination reaction which may be anticipated for compounds in which an anion or group X (capable of giving a relatively stable anion X^-) is attached to oxygen. The application of this mechanism to bicyclic endoperoxides and the oxidation of the resulting monocyclic hydroxy ketones should provide an efficient way to convert cyclic 1,3-dienes into the corresponding 1,4-diones (eq 53). This convenient synthetic pathway has recently been demonstrated with some interesting systems.



(53)

The triethylamine-catalyzed rearrangement of 1,3-cycloheptadiene endoperoxide (17) gave the hydroxy ketone which upon oxidation with manganese dioxide formed 1,4-cycloheptenedione 171 in high yield.[35] Using this method Kitahara et al.[110] have succeeded in synthesizing cyclooctenedione 172, and synthesis of cyclohexenedione 170[111] has been claimed, but the initially

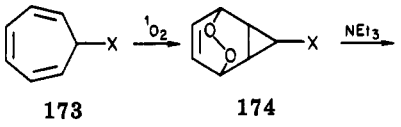


170 171 172

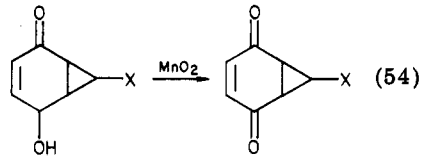
formed intermediate tautomerized to *o*-catechol.[35]

Homobenzoquinones are significant compounds because they have interesting structural features and are expected to show unusual properties. However, their preparation has been difficult. The classical way via either addition of diazoalkanes to *p*-benzoquinone and thermolysis of the resulting adducts[112] or addition of carbenes to *p*-benzoquinone[113] have been limited to substituted derivatives. The unsubstituted parent hydrocarbon has been synthesized by Chaples and Dreiding[114] in eight steps.

Since singlet oxygenation of cycloheptatrienes affords norcaradiene-type [2 + 4] endoperoxides, base-catalyzed rearrangement followed by oxidation provided a convenient way to obtain 7-substituted *p*-homobenzoquinones in high yield.[115] This synthetic sequence has the further advantage of stereospecific functionalization of the cyclopropane ring in the *p*-homobenzoquinones (eq 54).



173 174

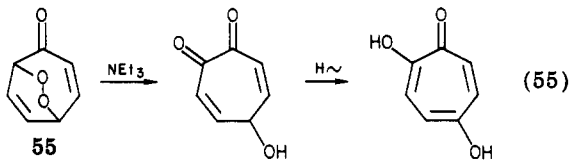


(54)

175 176

X = H, CHO, $COOCH_3$, CN (endo and exo), CH_3[116]

Treatment of tropone endoperoxide[117] (55) (obtained by sensitized photooxygenation) with triethylamine in ethanol at room temperature resulted in a facile cleavage of the epidioxy linkage to give 5-hydroxytropolone (178) (presumably from tautomerization of 177) in quantitative yield (eq 55). This procedure may

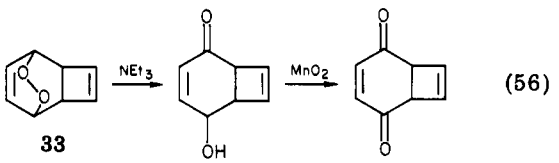


(55)

55 177 178

be the most convenient method for synthesis of 178 reported[118] to date.

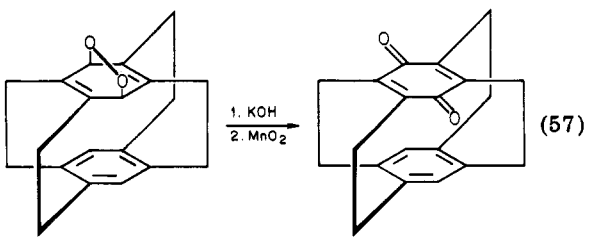
Bicyclo[4.2.0]octa-3,7-diene-2,5-dione, which is a valence isomer of 2,5,7-cyclooctatriene-1,4-dione,[119] has been synthesized by Kitahara et al.[120] in seven steps. Triethylamine-induced rearrangement of the endoperoxide 33 provides a short and efficient synthesis[33] for this interesting dione (180) (eq 56).



(56)

33 179 180

The strained benzene ring in cyclophanes readily undergoes Diels–Alder reactions. Singlet oxygen addition to the [2.2.2.2]-(1,2,2,5)cyclophane has been demonstrated by Gray and Boekelheide.[121] Treatment of the endoperoxide 181 with methanolic potassium hydroxide effected a clean rearrangement to the expected hydroxy ketone which was converted smoothly into the quinone 182 in high yield. This synthetic approach provides a possible general route for obtaining quinone cyclophanes (eq 57).

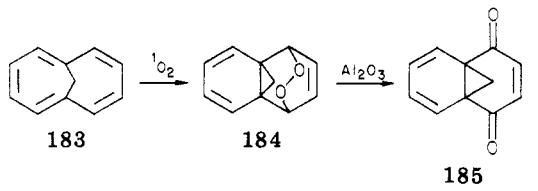


(57)

181 182

Some unusual conversions of bicyclic endoperoxides into diketones have been observed by Vogel et al.[122] 1,6-Methano[10]annulene (183) undergoes rapid oxi-

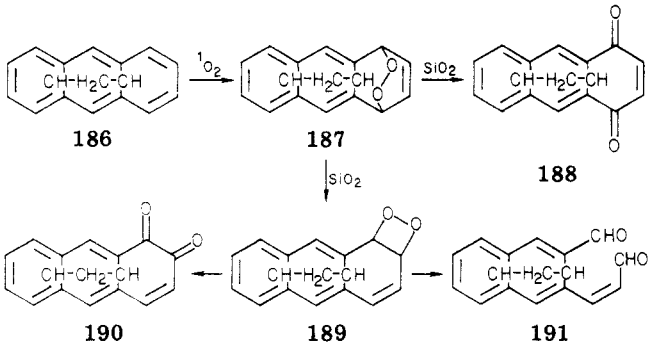
dation to form the endoperoxide **184**. An attempt to purify this by column chromatography with alumina gave tricyclic[4.4.1.0^{1,6}]undeca-3,7,9-triene-2,5-dione (**185**) (eq 58). This presumably resulted from base-



183 **184** **185** (58)

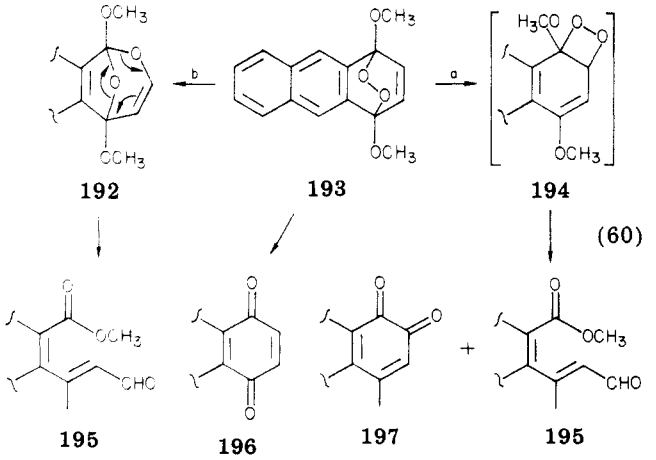
induced rearrangement followed by dehydrogenation.

Aromatic bridged [14]annulenes having anthracene perimeters are also amenable to photooxygenation. The isolated endoperoxide **187** rearranges over silica gel to form **188**, **190**, and **191**. The formation of the dialdehyde **191** can be explained in terms of 1,4-endoperoxide–dioxetane rearrangement and subsequent cleavage of **189** (eq 59). Both **190** and **191** are indicative of acid-induced rearrangement.[122] The acid-catalyzed 1,4-endoperoxide–dioxetane rearrangement has been previously postulated in the anthracene system. Rigaudy[123] and Baldwin et al.[124] independently showed that under acid condition **193** can undergo rearrangement. Thus, although Baldwin et al. found only the *p*-quinone **196** when **193** was treated with aqueous acid,



186 **187** **188** **190** **189** **191** (59)

reaction in anhydrous acidic media (ethereal hydrogen chloride or hydrogen chloride in benzene) gave a mixture of the *o*-quinone and the aldehyde ester **195** (eq 60). For this transformation Baldwin suggested the

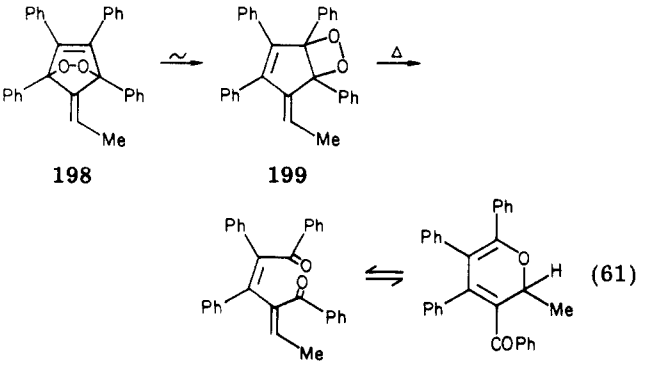


192 **193** **194** (60)

195 **196** **197** **195**

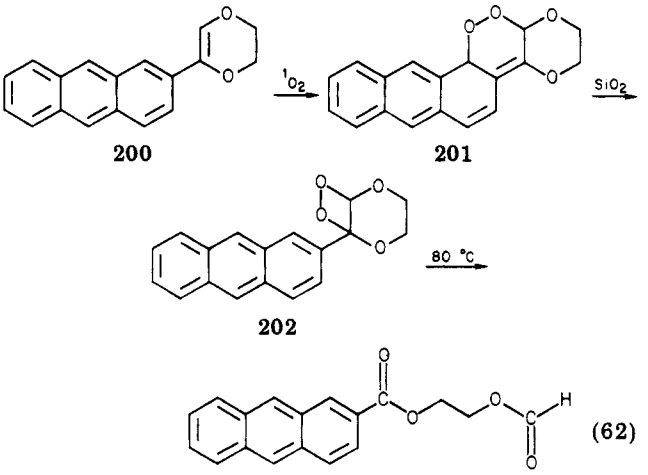
dioxetane **194** as a possible intermediate (pathway a). An alternative mechanism for formation of **195** which does not include the intermediacy of a 1,2-dioxetane has been proposed by Rigaudy[125] (pathway b). An investigation of the chemiluminescence which accompanies the acid-catalyzed decomposition of the endoperoxide **193** has provided indirect evidence for the intermediacy of a 1,2-dioxetane in that reaction.[126]

Le Roux and Goasdoue[127] reported the first isolation and characterization of dioxetanes formed by acid-catalyzed rearrangement of 1,4-endoperoxides. Sensitized photooxygenation of polyarylfulvenes gives the corresponding 1,4-endoperoxides (**198**), which when treated with acid rearrange into 1,2-dioxetanes (**199**). These undergo thermally induced luminescence (eq 61).



198 **199** (61)

More recently a silica gel catalyzed rearrangement of a monocyclic endoperoxide to a 1,2-dioxetane has been demonstrated by Schaap et al.[128] The 2-(2-anthryl)-1,4-dioxene (**200**) gave upon photooxygenation **201** in 31% yield as one of the three products. The endoperoxide **201** was isolated and converted quantitatively into the dioxetane **202** by means of silica gel (eq 62).



200 **201** **202** (62)

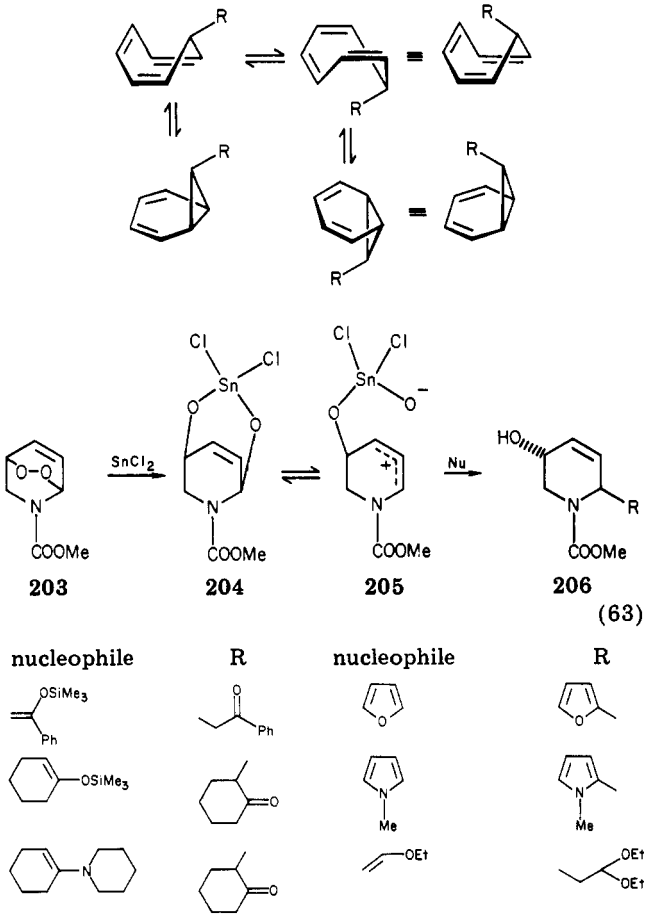
These experiments demonstrate that 1,4-endoperoxides may be transformed by acid catalysis to cleavage products of the type found in aromatic dioxygenase enzymes and therefore suggest the possibility that such species are intermediates in these biological processes.[129]

B. $SnCl_2$-Promoted Rearrangement

A novel type of condensation of nucleophilic alkenes on piperidine and *N*-(methoxycarbonyl)pyrrole rings has been achieved by a stannous chloride effected reaction of the corresponding bicyclic endoperoxides.

Natsume et al.[130] showed that in the presence of $SnCl_2$, endoperoxide **203**[131] (obtained by photooxygenation of the dihydropyridine derivative) reacts with carbon nucleophiles such as trimethylsilylated ketones, vinyl ethers, enamines, indole, *N*-methylpyrrole, and furan to give products as shown in eq 63.

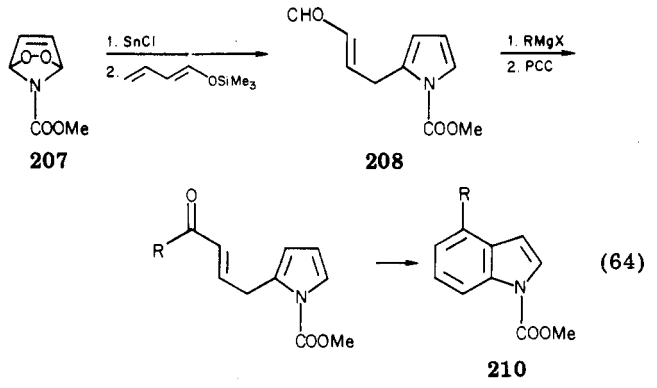
SCHEME IV



(63)

This is novel in that it leads to carbon–carbon bond formation without involving carbanions. The reaction is believed to proceed by a two-electron transfer from bivalent metal to the peroxide to form both diol anion and quadrivalent tin species (**204**). This may be in equilibrium with an allylic cation (**205**) or nucleophiles might attack **204** directly by an S_N2 mechanism to afford trans products.

N-(Methoxycarbonyl)pyrrole endoperoxide[132] (**207**) has been used as a synthon for the synthesis of 2-substituted pyrrole derivatives (**208**). Grignard reaction with **208** followed by oxidation and ring closure provided a convenient synthesis of 4-alkylindoles (**210**) (eq 64). Natsume and Kitagawa[133] utilized the $SnCl_2$-



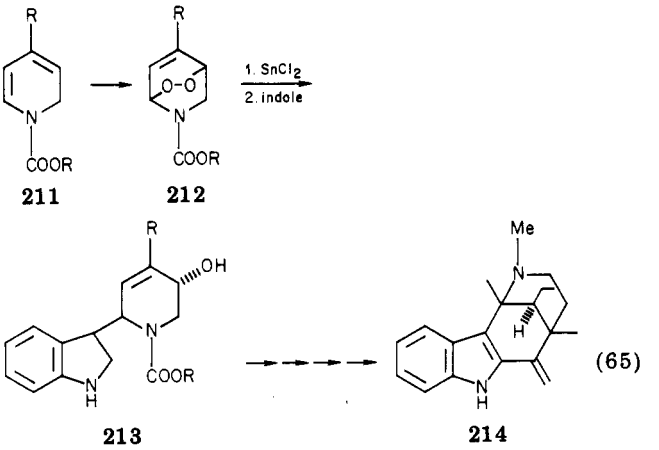
(64)

promoted carbon–carbon condensation as a key step in achieving the stereoselective total synthesis of an indole alkaloid, *dl*-3-epiuleine (**214**) (eq 65).

Figure 2. HOMO(W) + 2p (left) and LUMO(W) + 2p (right).

TABLE II. Product Distribution by Photooxygenation of 7-Substituted Cycloheptatriene Derivatives

R (substituent)	tropylidine-type adduct, % yield	norcaradiene-type adduct, % yield
OCH_3	80	
H	40	3.5
Ph	3	61
CN		75
$COOCH_3$		84
CHO		58



(65)

VII. Application of Bicyclic Endoperoxides To Detect Valence Isomerization

Cycloheptatriene undergoes two dynamic processes (Scheme IV), valence isomerization and ring inversion. The equilibrium for the symmetry-allowed valence isomerization of cycloheptatriene and norcaradiene has been demonstrated.[134] Substituents at C-7 with π-electron acceptor ability, such as CHO, COOR, CN, etc., tend to favor the norcaradiene structure while substituents with π-electron donor ability, such as OR, and NR_2, favor the cycloheptatriene.

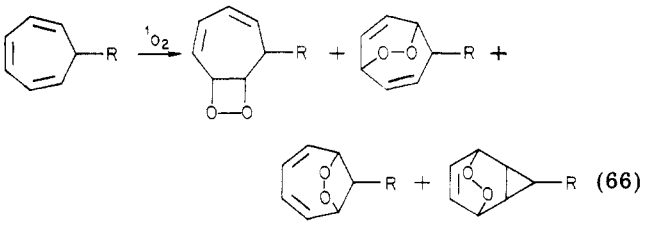
Hoffmann[135] and Günther[136] explained this phenomenon on the basis of HOMO and LUMO interactions. When the ligand π system is a good acceptor, i.e., possesses low-lying unoccupied molecular orbitals, it interacts with the HOMO Walsh orbital in the cyclopropane. This interaction is shown schemetically in Figure 2. The resulting reduction of electron density in the cyclopropane HOMO leads to diminished antibonding between C_1 and C_6. This would predict stabilization of the norcaradiene by π-acceptor groups. On the other hand, an occupied 2p orbital on the substituent R interacts via electron donation into the LUMO Walsh orbital of the cyclopropane ring, leading to increased antibonding between C_1 and C_6. Consequently, OR, and NR_2 substituents should benefit the tropylidine structure. Experimental data confirm this theoretical prediction. For example, no norcaradiene valence tautomer could be detected for the unsubstituted cycloheptatriene by variable-temperature ^1H NMR, even down to −150 °C.[137] However, about 3% norcaradiene was detected for the 7-carboxylic acid[138] and

TABLE III. Product Distribution by Photooxygenation of 7-Alkyl-substituted Cycloheptatriene Derivatives

R (substituent)	tropylidine-type adduct, % yield	norcaradiene-type adduct, % yield
CH_3	44	32
CH_2CH_3	42	32
$CH(CH_3)_2$	25	64
$C(CH_3)_3$	25	64

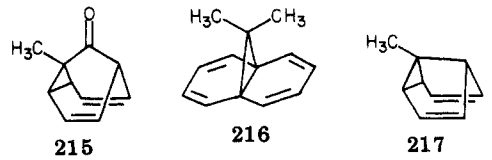
about 7.5% for the 7-carbaldehyde.[139] In cases where valence isomerization could not be detected by NMR spectroscopy, the existence of such valence tautomerization has been surmised from Diels–Alder reaction products. For instance, cycloheptatriene gives in most cases norcaradiene-type addition.[140]

Recently it has been reported that singlet oxygen adds to the 7-substituted cycloheptatriene derivatives to form bicyclic endoperoxides whose structures vary with the nature of the substituents.[55,141] The different products are given in eq 66 and the influcnece of R is given in Table II. In contrast to singlet oxgyen, the



(66)

more typical dienophile *N*-phenyltriazolinedione gave exclusively norcaradiene-type addition products[55] regardless of substituted groups R. The fact that cycloheptatriene with σ-donating OMe substituents leads only to the tropylidine [2 + 4] adduct, those with π acceptors (CN, COOMe, and CHO) afford only the norcaradiene [2 + 4] adducts, and the unsubstituted and monophenyl-substituted gave both adducts was interpreted in terms of singlet oxygen intervening in the tropylidine–norcaradiene equilibrium. This is believed to also qualitatively reflect the stabilizing effect of the substituents. The fact that other dienophiles do not intervene in the valence isomerization is not suprising since the activation free energy for [2 + 4] cycloaddition of singlet oxygen is much less than most (about 6–8 kcal/mol).[142] This activation energy lies within the range of $\Delta G^{\ddagger}$ values for the valence isomerization of cycloheptatriene (2–12 kcal/mol, the lower limit for dicyano derivative[143] and the upper for the unsubstituted cycloheptatriene[144]). By isolation of *endo*- and *exo*-norcaradiene endoperoxides[56] the existence or ring inversion[138] was also confirmed. The effect of the alkyl groups on the valence isomerization of cycloheptatriene has been studied in related systems such as **215**,[145] **216**,[146] and **217**.[147] The results indicate a preference



215 **216** **217**

for isomers with the alkyl group attached to the cyclopropane ring rather than to the corresponding aliphatic ring.

Theoretical considerations[148] predict that σ-donating substituents should favor the norcaradiene structure.

Submitting a series of 7-substituted alkylcycloheptatriene derivatives to the dye-sensitized photooxygenation showed an increase in the yield of the norcaradiene-type adduct on going from CH_3 to $C(CH_3)_3$[34] (Table III). These observations do not reveal whether the increase of the yield of the norcaradiene-type adduct is arising from the stabilization effect of the norcaradiene structure by means of electronic factors or from the more favored conformation of the cycloheptatriene for a Diels–Alder reaction achieved by steric interaction with the bulky substituent.[149]

VII. Conclusions

The collected examples in this review demonstrate clearly the synthetic potential of bicyclic endoperoxides. Thermolysis and photolysis are synthetic tools in achieving two epoxide rings in the syn configuration and have been utilized many times. The recently introduced diimide reduction provides an entry to the prostaglandine-type endoperoxides. However, unstable intermeidates formed by photooxygenation of 1,3-dienes can be trapped, and saturated endoperoxides can be readily synthesized. On the other hand, the combination of photooxygenation and base-catalyzed rearrangement followed by oxidation is an excellent method for converting 1,3-diene units into the 1,4-ene-2-diones. The field appears to hold opportunities for new discoveries and advances which would be of general synthetic interest, and it is hoped that this review will stimulate further work in this area.

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