Photooxygenations of Nitrogen Heterocycles

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I. Introduction

Photooxygenations of organic substrates have been extensively studied in recent years. Singlet oxygen, for example, is known to react with different types of organic compounds, giving rise to a variety of products. Numerous publications have appeared in the literature, which highlight some of the salient features of these studies.[3-10]

Of particular interest to us are the photooxygenation reactions of heterocyclic systems. The reactions of singlet oxygen with heterocyclic compounds often give rise to a complex mixture of products. The diverse transformations that have been observed in these cases have been primarily attributed to the multitude of pathways that are available for the decomposition of the primary photooxygenation products such as the peroxides and hydroperoxides. These secondary reactions are highly dependent on several factors such as the nature of the substrate, the functional groups in the immediate environment of the newly formed peroxide functionality, the solvent, temperature, and other reaction conditions. A large number of papers and a few review articles dealing with some aspects of these studies have appeared in the literature.[11-13] In this brief survey, we have tried to focus our attention on the photooxygenations of different nitrogen heterocycles, primarily from the point of view of synthetic utility and also to illustrate some of the varigated transformations which occur in these systems. The literature has been covered up to September 1978, except in few cases where some of the later references have also been cited.

II. Photooxygenation of Three-Membered Heterocycles

Three-membered heterocycles have received only scant attention as far as sensitized photooxygenation studies are concerned. Quite recently, it has been shown that aziridines undergo sensitized photooxygenation reactions, leading to several products.[14,15] 1,2,3-Triphenylaziridine (**1a**), for example, on photooxygenation in a mixture of benzene and acetone and in the presence of Rose Bengal gives a mixture of products consisting of benzoic acid (**5**, 41%) and benzanilide (**6**, 40%), whereas the photooxygenation of either *trans*- or *cis*-1-cyclohexyl-2-phenyl-3-benzoylaziridines (**1b** and **1c**) in benzene–methanol mixture gives the same mixture of products consisting of benzoic acid (**5**), *N*-cyclohexylbenzamide (**7**), and benzamide (**8**). Similarly, *trans*-2-phenyl-3-benzoylaziridine (**1d**) gives a mixture of benzoic acid (**5**, 54%) and benzamide (**8**, 29%). Some of the dibenzoylaziridines such as *trans*- and *cis*-1-cyclohexyl-2,3-dibenzoylaziridines (**1e** and **1f**), as well as *trans*-1-benzyl-2,3-dibenzoylaziridine (**1g**), on photooxygenation give, in each case, only benzoic acid as the end product. Formation of the various products in the photooxygenations of aziridines **1a–g** has been rationalized in terms of the pathway shown in Scheme I.

Sensitized photooxygenations of a few bicyclic aziridines have been studied recently.[15] The photooxygenation of 1-cyclohexyl-6-(cyclohexylimino-)-1a-phenylindano[1,2-*b*]aziridine (**9**) is reported to give a 51% yield of 2-cyclohexyl-3-hydroxy-3-phenylphthalimidine (**14**), and the formation of this product has been rationalized in terms of the intermediates **10, 11, 12,** and **13** as shown in Scheme II. It is pertinent to observe that Padwa and Vega[16] had suggested earlier that the photolysis of **9** in presence of oxygen gives rise to a 10% yield of **13**. It is likely that singlet oxygen is generated in this system through the reaction of the triplet state of either **9** or **10** with ground-state (triplet) oxygen. The singlet oxygen thus formed may then combine with **10** to give the intermediate **11** and ultimately **13,** as shown in Scheme II. A similar case of the involvement of

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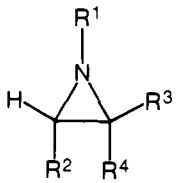
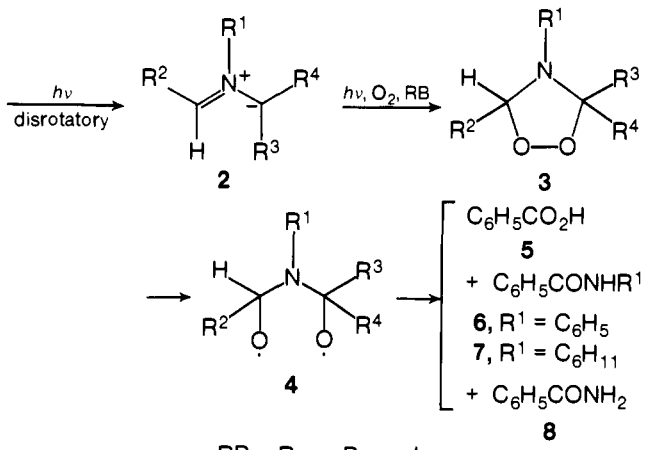
SCHEME I

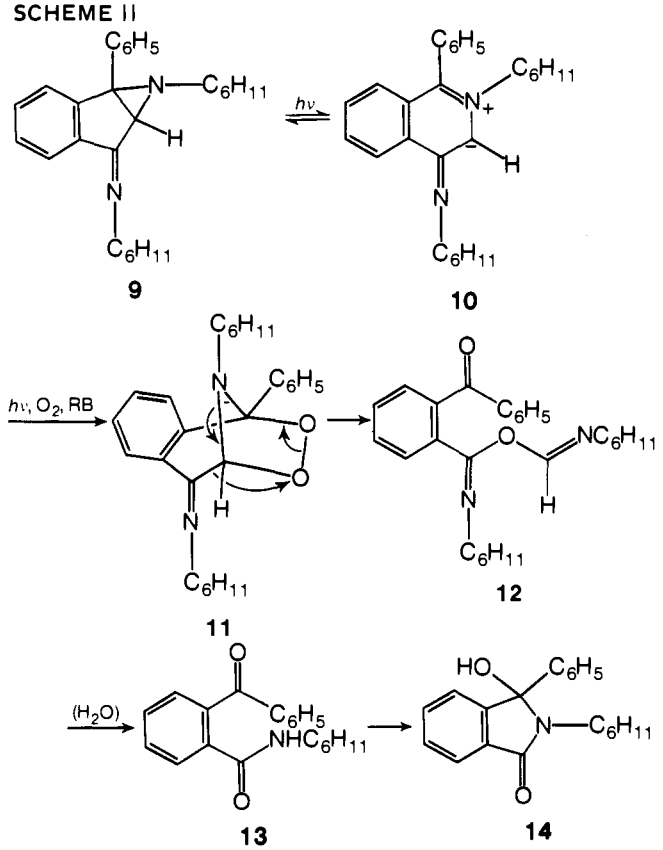


1a, $R^1 = R^2 = R^4 = C_6H_5$; $R^3 = H$
b, $R^1 = C_6H_{11}$; $R^2 = C_6H_5CO$; $R^3 = C_6H_5$; $R^4 = H$
c, $R^1 = C_6H_{11}$; $R^2 = C_6H_5CO$; $R^3 = H$; $R^4 = C_6H_5$
d, $R^1 = R^4 = H$; $R^2 = C_6H_5CO$; $R^3 = C_6H_5$
e, $R^1 = C_6H_{11}$; $R^2 = R^3 = C_6H_5CO$; $R^4 = H$
f, $R^1 = C_6H_{11}$; $R^2 = R^4 = C_6H_5CO$; $R^3 = H$
g, $R^1 = C_6H_5CH_2$; $R^2 = R^3 = C_6H_5CO$; $R^4 = H$



RB = Rose Bengal

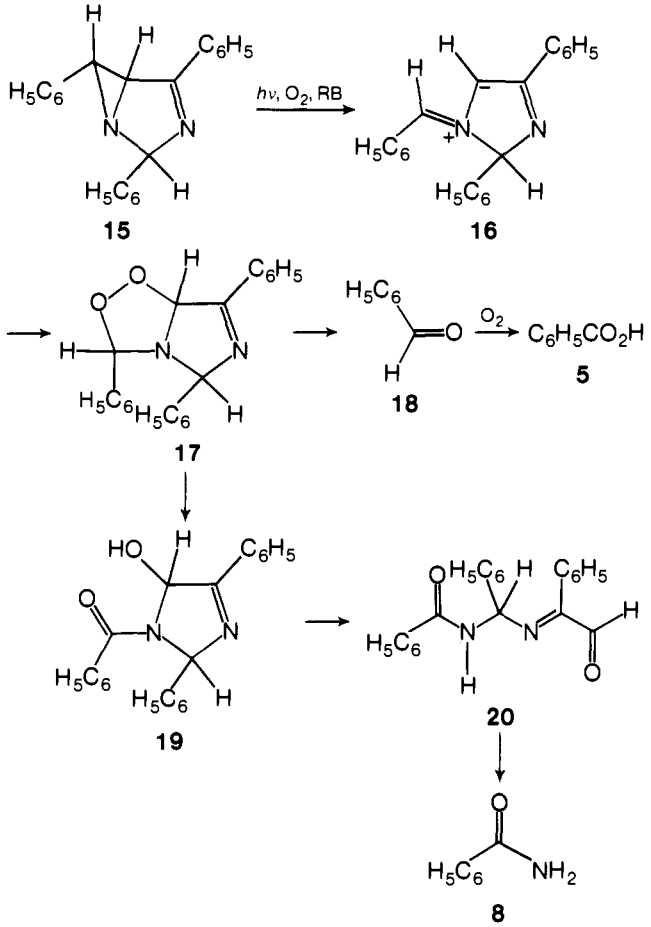
SCHEME II



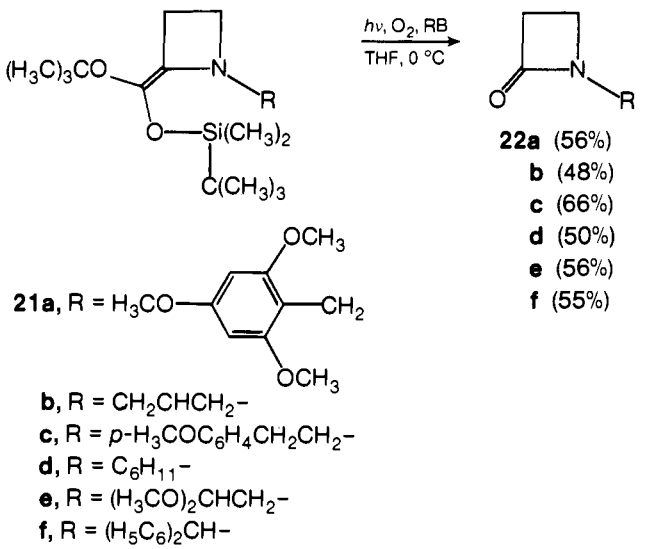
singlet oxygen has been invoked recently in the photooxidation of tetraphenyl-*p*-dioxin, leading to benzil.[17]

Sensitized photooxygenation of *endo*-2,4,6-triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene (**15**), on the other hand, gives a mixture of products consisting of benzaldehyde (**18**, 5%), benzoic acid (**5**, 16%), and benzamide (**8**, 7%) (Scheme III).

SCHEME III



SCHEME IV



22a (56%)
b (48%)
c (66%)
d (50%)
e (56%)
f (55%)

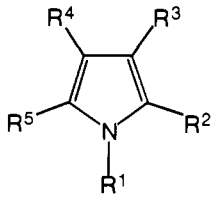
21a, R = H_3CO-

b, R = CH_2CHCH_2-
c, R = *p*-$H_3COC_6H_4CH_2CH_2$-
d, R = C_6H_{11}-
e, R = $(H_3CO)_2CHCH_2$-
f, R = $(H_5C_6)_2CH$-

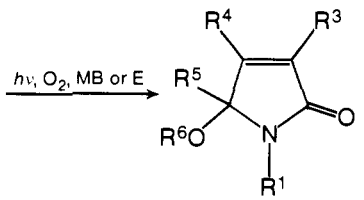
III. Photooxygenation of Four-Membered Heterocycles

One of the few examples of the sensitized photooxygenation of four-membered nitrogen heterocycles involves the reaction of enamino ketene acetals. It has been observed by Wasserman and co-workers[18] that the enamino ketene acetals, **21a–f**, undergo Rose Bengel sensitized photooxygenations, around 0 °C to give the corresponding β-lactams **22a–f**, in good yields (Scheme IV).

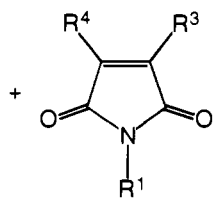
SCHEME V



23, $R^1 = R^2 = R^3 = R^4 = R^5 = H$
25, $R^1 = CH_3$; $R^2 = R^3 = R^4 = R^5 = H$
29, $R^1 = R^2 = R^5 = H$; $R^3 = R^4 = C_2H_5$
32, $R^1 = R^5 = H$; $R^2 = CH_3$; $R^3 = R^4 = C_2H_5$
35, $R^1 = R^3 = R^4 = R^5 = H$; $R^2 = CH_3$
36, $R^1 = R^3 = R^5 = H$; $R^2 = R^4 = CH_3$



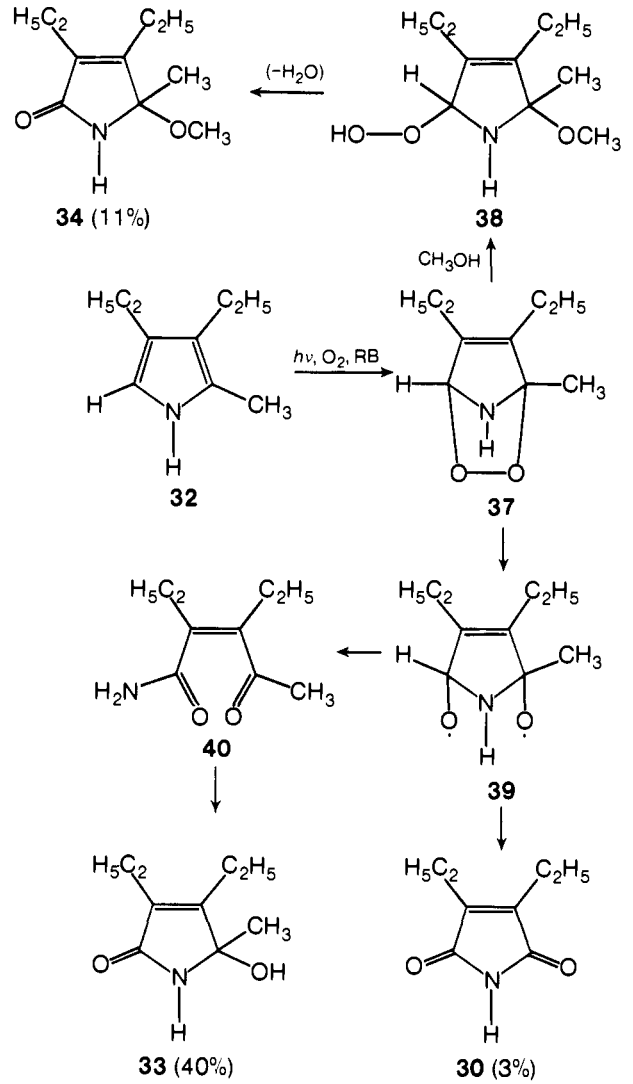
24, $R^1 = R^3 = R^4 = R^5 = R^6 = H$
26, $R^1 = CH_3$; $R^3 = R^4 = R^5 = R^6 = H$
27, $R^1 = R^3 = R^4 = R^5 = H$; $R^6 = CH_3$
31, $R^1 = R^5 = H$; $R^3 = R^4 = C_2H_5$; $R^6 = CH_3$
33, $R^1 = R^6 = H$; $R^3 = R^4 = C_2H_5$; $R^5 = CH_3$
34, $R^1 = H$; $R^3 = R^4 = C_2H_5$; $R^5 = R^6 = CH_3$



28, $R^1 = R^3 = R^4 = H$
30, $R^1 = H$; $R^3 = R^4 = C_2H_5$

MB = Methylene Blue; E = Eosin

SCHEME VI



IV. Photooxygenation of Five-Membered Heterocycles

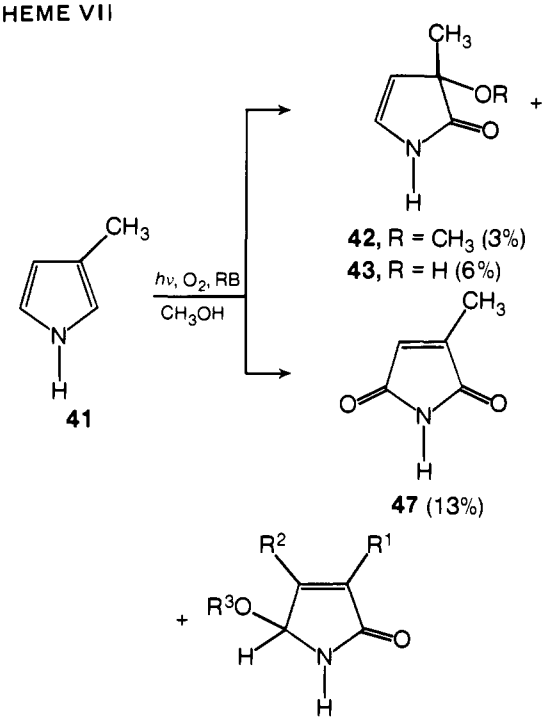
A. Five-Membered Heterocycles Containing One Nitrogen Atom

1. Pyrroles

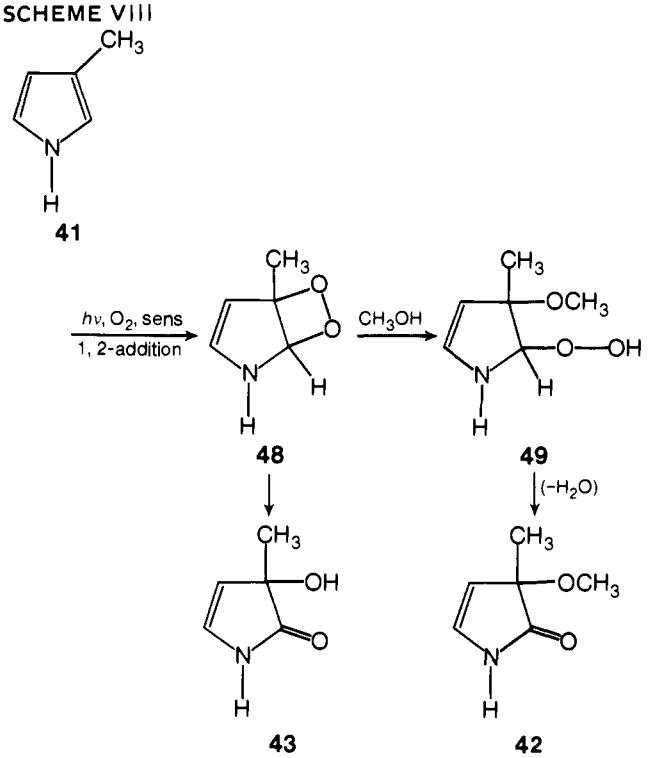
Dye-sensitized photooxygenations of pyrroles have been extensively investigated by several groups of workers.[19] Earlier studies have pointed out that tarry products are formed in the photooxygenation of pyrroles. Bernheim and Morgan,[20] for example, have shown that the pyrrole **23** in water, ethanol, or acetone solution and in the presence of Methylene Blue or Eosin, absorbs 1 mol of oxygen on irradiation to give a mixture of unidentified products. One of these products, however, has been subsequently characterized as the hydroxylactam **24**.[21] Under similar conditions, 1-methylpyrrole (**25**) gives the lactam **26** (Scheme V). Subsequent studies by Quistad and Lightner[22] have shown that the photooxidation of **23** in methanol gives 5-methoxy-Δ^3-pyrrolin-2-one (**27**), as the major product, along with a small amount of maleimide (**28**). Similarly, 3,4-diethylpyrrole (**29**) has been found to give a mixture of diethylmaleimide (**30**) and 3,4-diethyl-5-methoxy-Δ^3-pyrrolin-2-one (**31**). It has been observed that none of **30** is formed when the photooxygenation of **29** is carried out in aqueous medium. Likewise, the photooxygenation of 2-methyl-3,4-diethylpyrrole (**32**) in methanol gives a mixture of products consisting of the Δ^3-pyrrolinones **33** and **34** and diethylmaleimide (**30**) (Scheme V).[23] The formation of the maleimide **30** from **32** is an example of the photooxygenative dealkylation of a pyrrole derivative and several such examples are reported in the literature.[24,25] It has been shown that other pyrrole derivatives such as 2-methylpyrrole (**35**) and 2,4-dimethylpyrrole (**36**) also undergo photooxygenation reactions, similar to the reactions of the pyrroles **23, 25, 29,** and **32**.[26] The formation of the various products in the photooxygenations of the above pyrroles has been rationalized in terms of the initial formation of the corresponding endoperoxides, which in turn can undergo subsequent transformations.[21-23] The photooxygenation of the pyrrole **32,** for example, has been assumed to give the endoperoxide **37,** which is then transformed to products such as **30, 33,** and **34,** through the different intermediates shown in Scheme VI.

An interesting case of the photooxygenation of pyrroles is that of 3-methylpyrrole (**41**) which gives a mixture of products consisting of 3-methoxy-3-methyl-Δ^4-pyrrolin-2-one (**42**), 3-hydroxy-3-methyl-Δ^4-pyrrolin-2-one (**43**), 5-methoxy-3-methyl-Δ^3-pyrrolin-2-one (**44**), 5-methoxy-4-methyl-Δ^3-pyrrolin-2-one (**45**), 5-hydroxy-3-methyl-Δ^3-pyrrolin-2-one (**46**), and citraconimide (**47**) (Scheme VII).[24] The formation of the Δ^3-pyrrolin-2-ones **44-46** from **41** can be understood in terms of a pathway similar to the one shown in Scheme VI. The formation of the Δ^4-pyrrolin-2-ones **42** and **43,** on the other hand, can be rationalized in terms of a 1,2-addition of a singlet oxygen to the pyrrole **41,** leading to the dioxetane intermediate **48,** which in turn can undergo further transformation as shown in Scheme

SCHEME VII



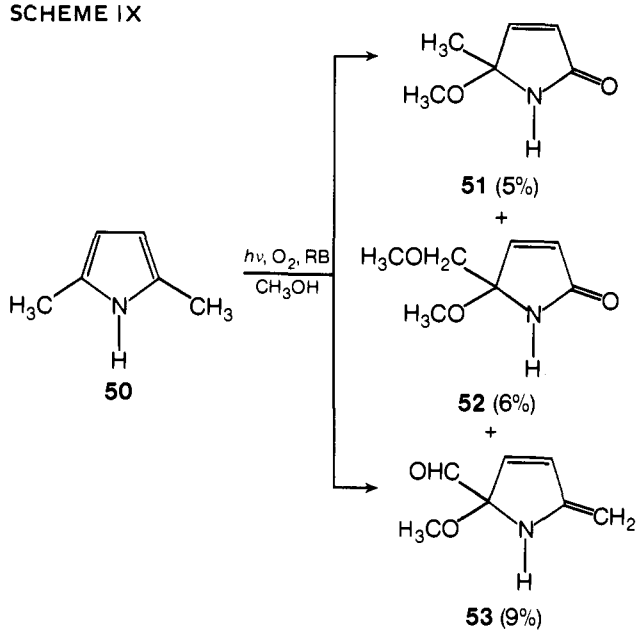
SCHEME VIII



VIII. In this connection, mention may be made that such Δ^4- and Δ^3-pyrrolin-2-ones have been reported to be formed in the photooxygenations of some hemopyrroles such as 3-ethyl-4,5-dimethylpyrrole and 4-ethyl-3,5-dimethylpyrrole.[27]

Some unusual products have been observed in the Rose Bengal sensitized photooxygenation of 2,5-dimethylpyrrole (**50**) in methanol which gives a mixture of 5-methoxy-5-methyl-Δ^3-pyrrolin-2-one (**51**), 5-methoxy-5-(methoxymethyl)-Δ^3-pyrrolin-2-one (**52**), and 2-formyl-2-methoxy-5-methylidene-Δ^3-pyrroline (**53**) (Scheme IX).[28] The formation of products

SCHEME IX

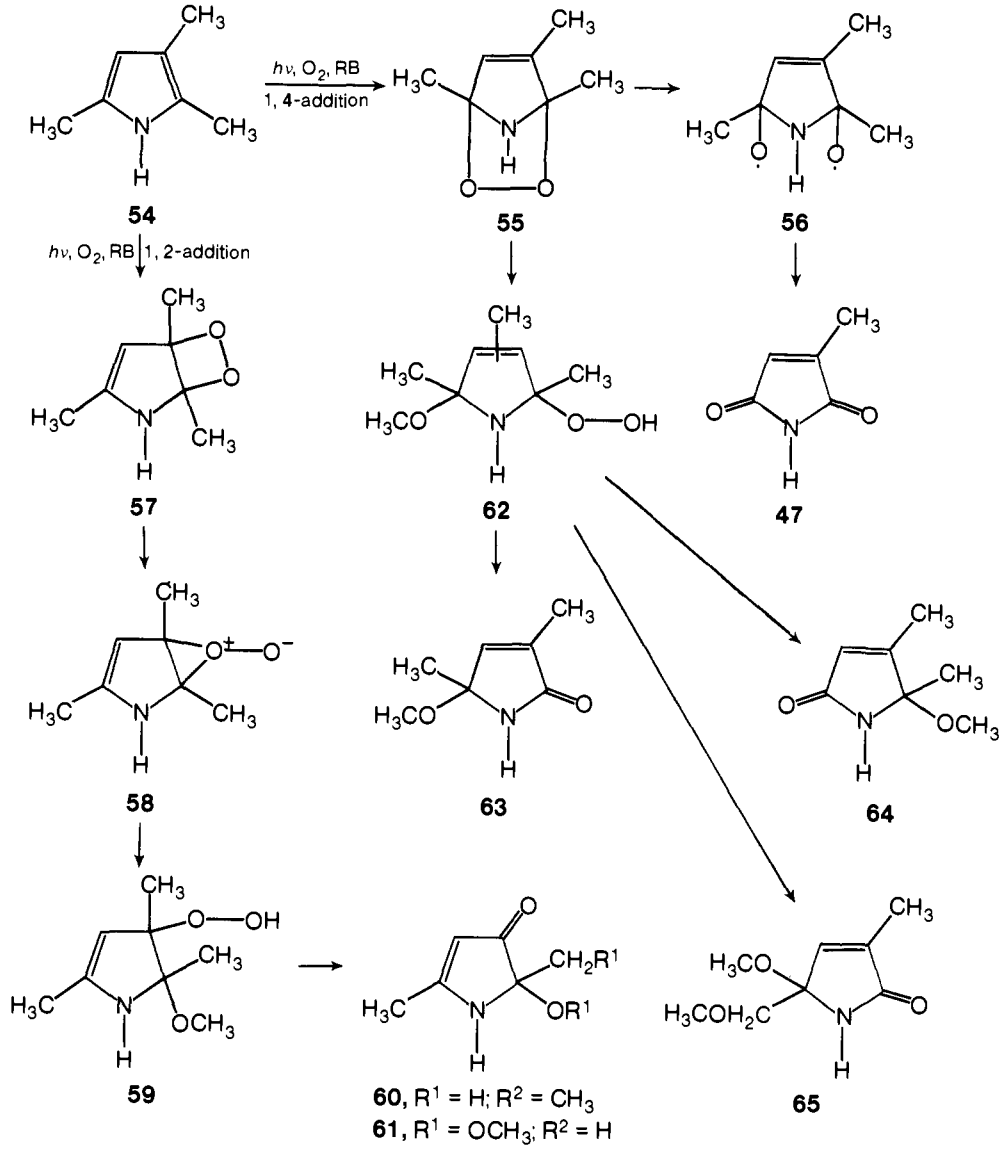


such as **52** and **53** in this reaction would imply that an α-alkyl substituent in a pyrrole derivative is undergoing oxygenation under these conditions.

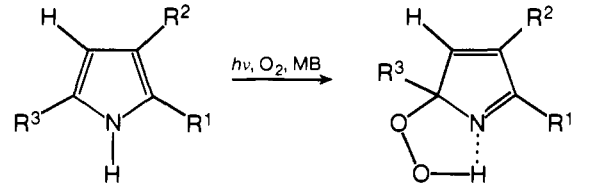
Yet another interesting case of the photooxygenation of pyrroles has been observed in the case of 2,3,5-trimethylpyrrole (**54**).[29] Sensitized photooxygenation of **54** in methanol gives a mixture of products consisting of 5-methoxy-3,5-dimethyl-Δ^3-pyrrolin-2-one (**63**, 5%), 5-methoxy-4,5-dimethyl-Δ^3-pyrrolin-2-one (**64**, 12%), 5-methoxy-5-methoxymethyl-3-methyl-Δ^3-pyrrolin-2-one (**65**, 4%), 2-methoxy-2,5-dimethyl-Δ^4-pyrrolin-3-one (**60**, 13%), 2-hydroxy-2-methoxymethyl-5-methyl-Δ^4-pyrrolin-3-one (**61**, 9%), and citraconimide (**47**, 4%). The formation of these various products in the photooxygenation of **54** has been rationalized in terms of the pathway shown in Scheme X. The formation of the methoxylactams **63** and **64**, for example, has been assumed to involve the endoperoxide **55**, which in turn is formed through the 1,4-addition of singlet oxygen to **54**. On the other hand, the formation of products such as **60** and **61** may be explained in terms of the dioxetane intermediate **57** or the isomeric, peroxirane intermediate **58** (Scheme X).[29]

Sensitized photooxygenations of different *tert*-butylpyrroles have been studied in detail.[30,31] It has been shown, for example, that both 2,5-di-*tert*-butylpyrrole (**66**) and 2,3,5-tri-*tert*-butylpyrrole (**68**) are converted to the corresponding 2-hydroperoxides **67** and **69**, respectively (Scheme XI).[30] In contrast, the photooxygenations of mono-*tert*-butylpyrroles follow a different pathway.[31] Thus, 1-*tert*-butylpyrrole (**70**) on photooxygenation in methanol and using Rose Bengal gives a mixture of products consisting of 5-methoxy-1-*tert*-butyl-Δ^3-pyrroline-2-one (**71**), 5-hydroxy-1-*tert*-butyl-Δ^3-pyrrolin-2-one (**72**), and *N*-*tert*-butylmaleimide (**73**). The Methylene Blue sensitized photooxygenations of **70** in acetone, however, gives a mixture of **72** and β-(*N*-*tert*-butylformamido)acrolein (**74**) (Scheme XII). Similarly, the photooxygenation of 2-*tert*-butylpyrrole (**75**) in methanol yields a mixture of the 5-methoxylactam **76**, the 5-hydroxylactam **77**, and pivalamide (**78**), whereas the photooxygenation of **75** in acetone gives a mixture of **77**, **78**, the keto amide **79**, and the hydroxy ketone derivative **80** (Scheme XII).[31] The photooxygenation of 3-*tert*-butylpyrrole (**81**) in methanol gives a mixture of products consisting of the methoxylactams **82**, and **83**, the hydroxylactam **86**, and 3-*tert*-butylmaleimide (**84**), whereas the same pyrrole (**81**) on photooxygenation in acetone gives a mixture of **84**, **85**, **86**, and 3-hydroxy-3-*tert*-butyl-Δ^4-pyrrolin-2-one (**87**) (Scheme XII).[31] The formation of the various

SCHEME X



SCHEME XI



66, $R^1 = R^3 = t$-Bu; R^2 = H
68, $R^1 = R^2 = R^3 = t$-Bu
67, $R^1 = R^3 = t$-Bu; R^2 = H
69, $R^1 = R^2 = R^3 = t$-Bu

products in the photooxygenation of the different, isomeric *tert*-butylpyrroles **70, 75,** and **81** has been explained in terms of the corresponding unstable endoperoxides which are formed through the 1,4-addition of a singlet oxygen to the starting pyrroles.

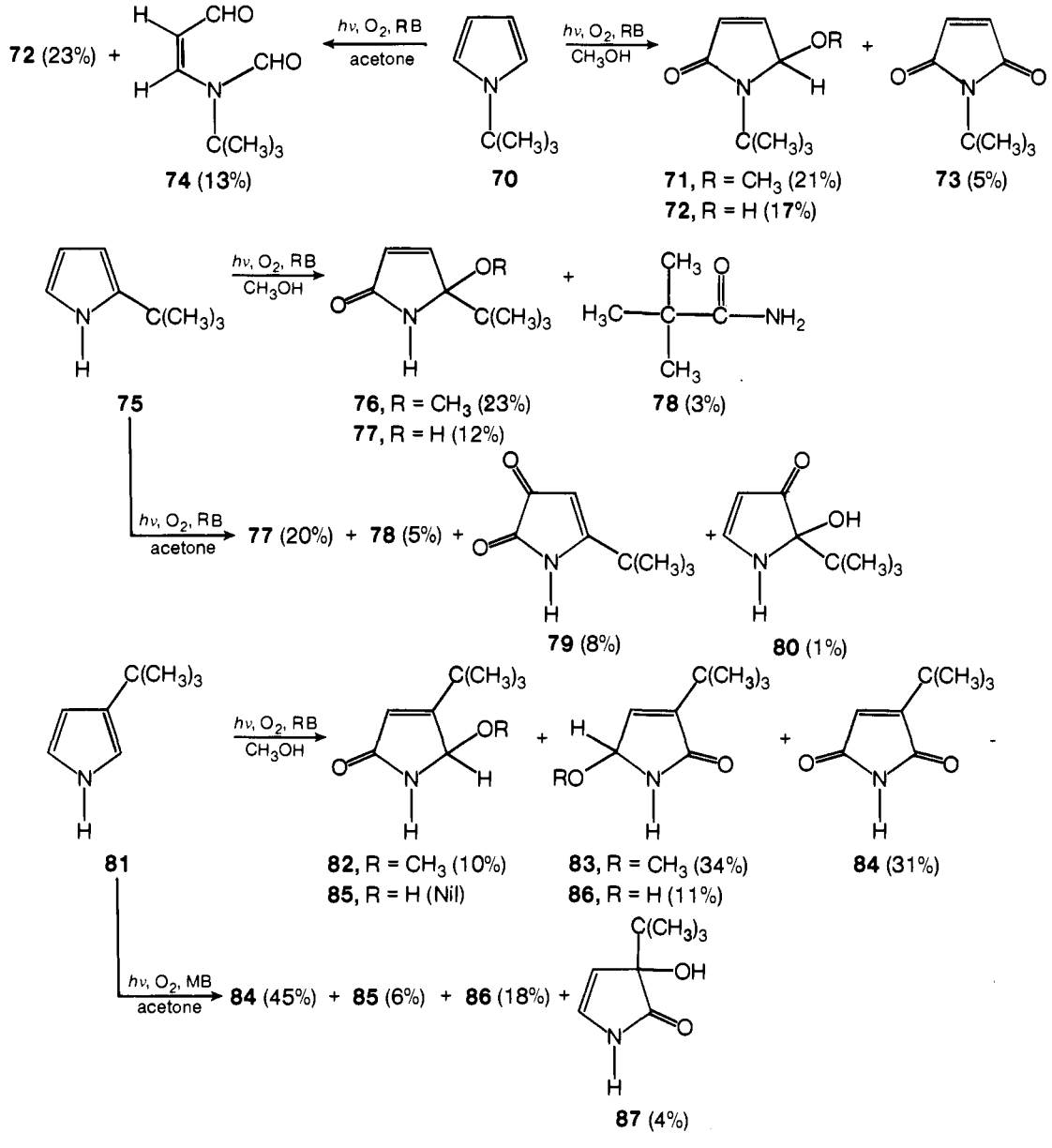
It is pertinent to observe that the actual formation of an endoperoxide such as **88** in the photooxygenation of **70,** for example, has been confirmed through NMR studies, when the reaction is carried out in acetone-d_6 at −78 °C.[31] Further, it has been observed that when the solution of **70** is warmed from −78 °C to room temperature and worked up subsequently, a mixture of products consisting of **71, 72,** and **73** is isolated (Scheme XIII).

Several investigators have examined in detail the photooxygenation of different phenyl substituted pyrrole derivatives.[32-41] Franck and Auerbach,[32] for example, have reported that *N*-phenylpyrrole (**90**), on photooxidation, gives a 15% yield of 5-hydroxy-*N*-phenyl-Δ^3-pyrrolin-2-one (**93**). Subsequent studies by Lightner et al.,[33] however, have shown that the photooxidation of **90** in methanol gives a mixture of products consisting of **93** (18%), 5-methoxy-*N*-phenyl-Δ^3-pyrrolin-2-one (**94,** 22%), and methyl β-(*N*-phenyl-*N*-formamido)acrylate (**95,** 16%). The formation of these various products has been rationalized in terms of the intermediates **91** and **92,** as shown in Scheme XIV.[33]

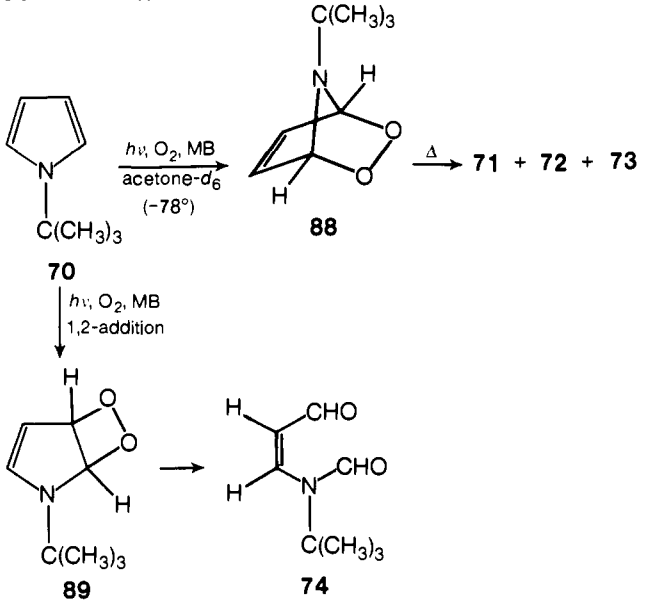
Wasserman and Liberles[34] have shown that the Methylene Blue sensitized photooxygenations of 2,3,4,5-tetraphenylpyrrole (**96**) in methanol gives a mixture of products consisting of 5-methoxy-3,4-epoxy-2,3,4,5-tetraphenyl-Δ^1-pyrroline (**97,** 55%) and α-*N*-benzoylamino-β-benzoylstilbene (**98, 30%**). When the same photooxygenation has been carried out in methanol containing some potassium hydroxide, the product formed is 3,3,4,5-tetraphenyl-Δ^4-pyrrolin-2-one (**99,** 35%) (Scheme XV).

Rio et al.[35-37] have suggested that the products **97, 98,** and **99,** formed from **96,** arise through the hydroperoxide intermediate **101,** which in turn is derived from the endoperoxide **100,** as shown in Scheme XVI. They have shown that the hydroperoxide **101,** when heated in less polar solvents, is converted back to the starting pyrrole **96,** together with molecular oxygen and a small amount of the lactam **99.** Heating of **101** in methanol,

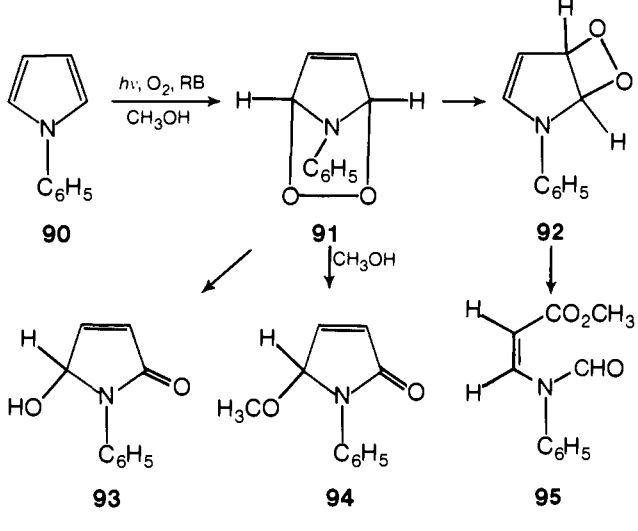
SCHEME XII



SCHEME XIII

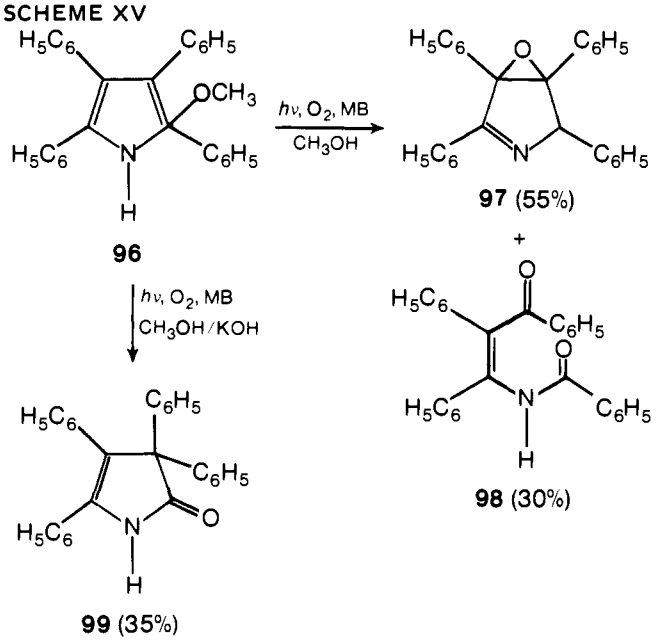


SCHEME XIV



however, gives **97,** along with small amounts of **98,** whereas heating of **101** in methanol, containing potassium hydroxide,

SCHEME XV

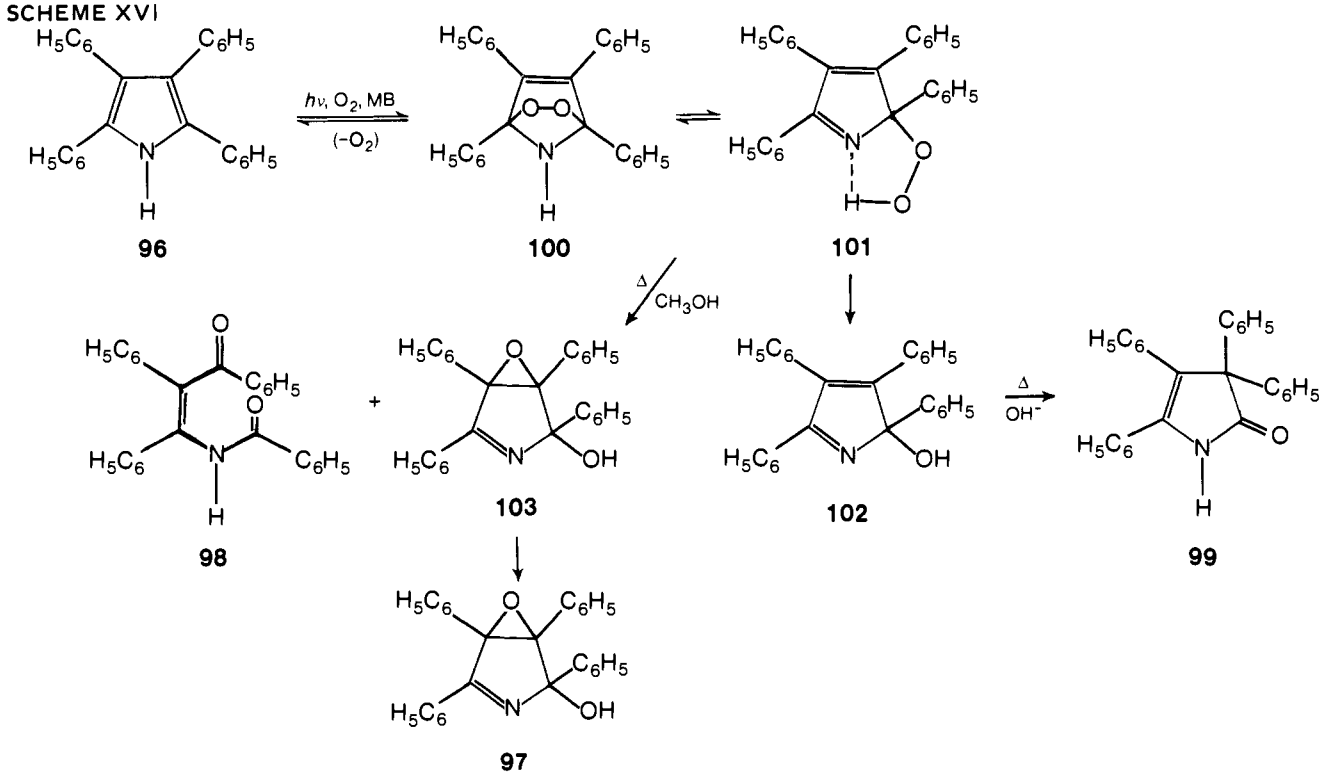


96 97 (55%) + 98 (30%) 99 (35%)

results in the formation of **99** as the major product, together with a small amount of the hydroxy derivative **102** (Scheme XVI). The formation of **98** can be understood in terms of the intermediate **104,** which in itself may arise through the hydroperoxide **101,** as shown in Scheme XVII. Under basic conditions and in the presence of polar solvents, the hydroperoxide **101** could undergo normal decomposition to the hydroxy derivative **102,** the anion of which could undergo further rearrangement to the lactam **99** (Scheme XVII).[35]

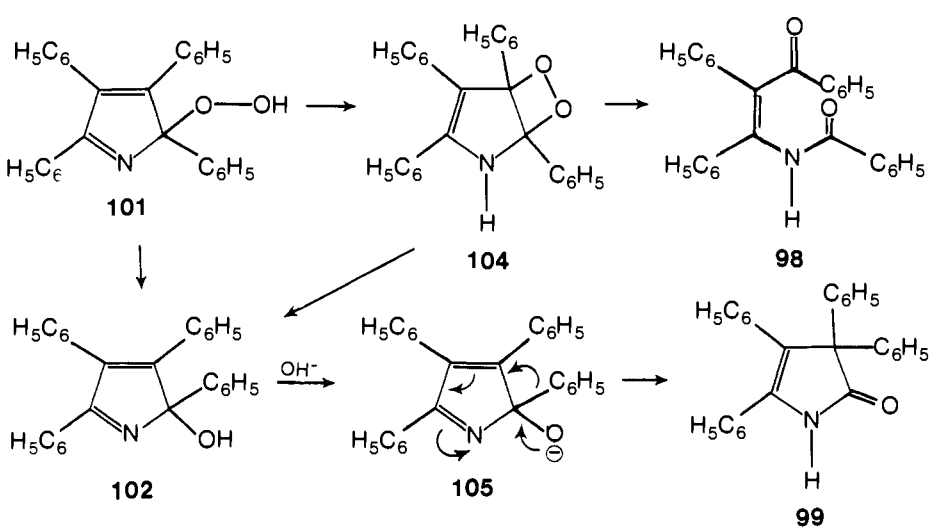
The photooxygenation of 2,5-diphenylpyrrole (**106**), on the other hand, gives rise to the hydroperoxide **107,** which is subsequently transformed to the hydroxy derivative **108,** on treatment with triphenylphosphine (Scheme XVIII).[36] Wasserman and Miller[39] have shown that both *N*-methyl- and *N*-phenyl-2,3,5-triphenylpyrroles (**109** and **111,** respectively) readily react with singlet oxygen to give different products. The reaction of **109,** for example, gives rise to a mixture of products consisting of benzoic acid (**5,** 12%) and *cis*-dibenzoylstyrene oxide (**110,** 65%), whereas a mixture of the Schiff bases **112** and **113** has been obtained in a 70% yield from the photooxygenation of **111** (Scheme XVIII). These authors have suggested that the Schiff bases **112** and **113** may be arising through the endoperoxide

SCHEME XVI



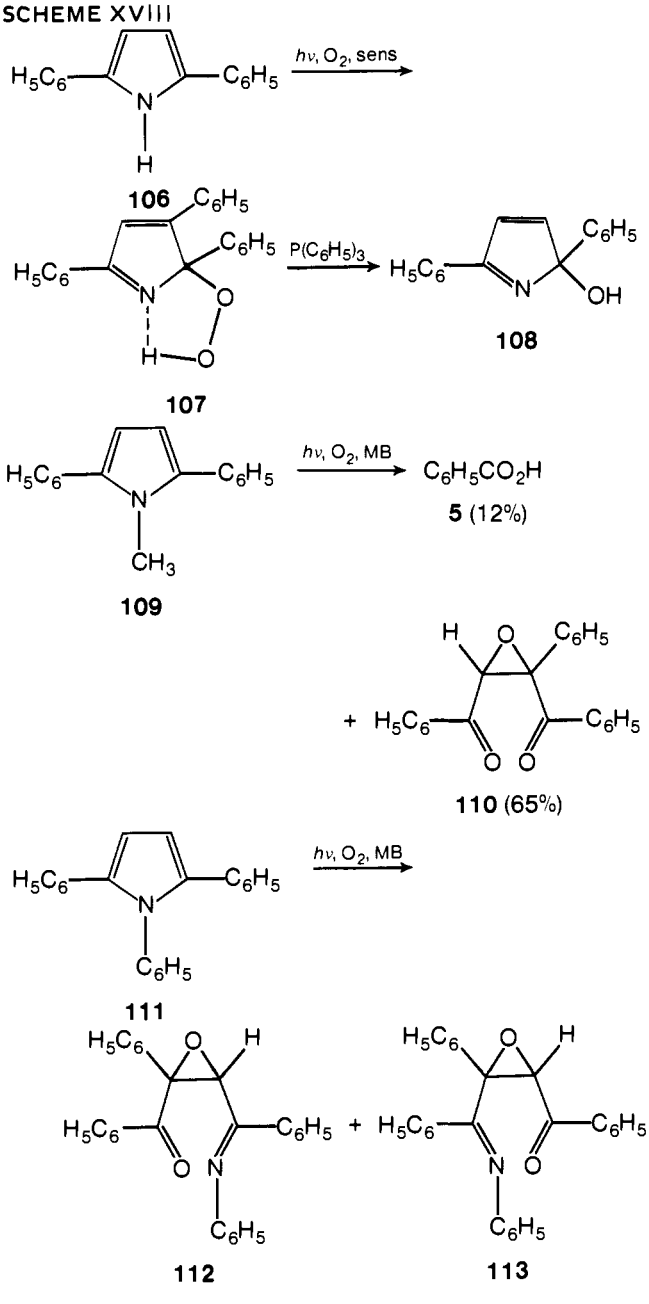
96 100 101 98 103 102 99 97

SCHEME XVII



101 104 98 102 105 99

SCHEME XVIII



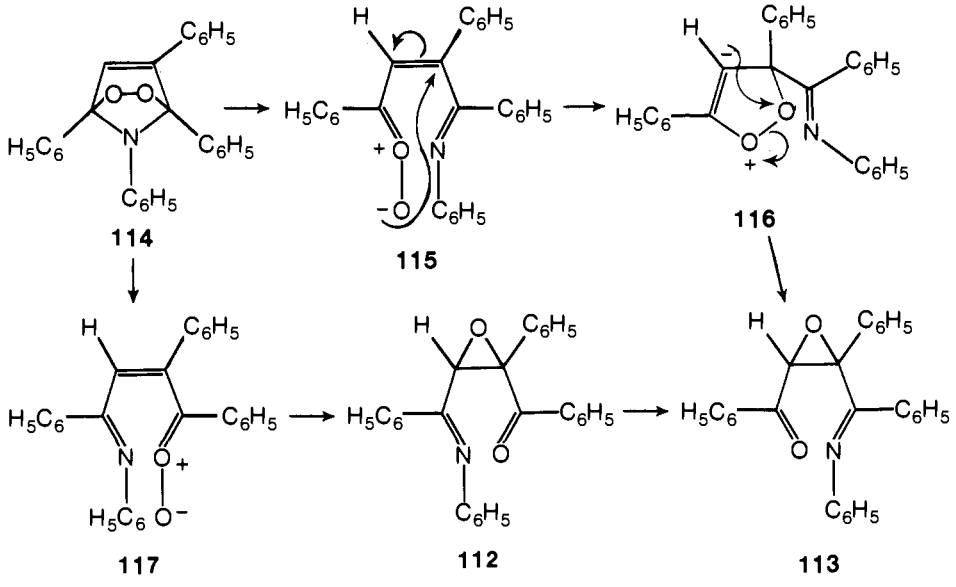
114, as shown in Scheme XIX.

Several derivatives of pyrroles such as 1-benzoyl-2,3,4,5-tetraphenylpyrrole (**118**),[40] 1-hydroxy-2,3,4,5-tetraphenylpyrrole (**122**),[41] and pyrrole α-carboxaldehydes[42] have been shown to undergo ready photooxygenations leading to a variety of products. Thus, the photooxygenation of **118** in chloroform, for example, is reported to give *cis*-1-benzoylimino-2,3-epoxy-1,2,3,4-tetraphenyl-4-butanone (**121**) as the only product. It is quite likely that the initially formed endoperoxide **119** in this reaction is transformed to the dioxetane intermediate **120,** which subsequently rearranges to give **121** (Scheme XX). In contrast, the photooxygenation of **118** in diethyl ether at room temperature does not result in any product formation. Photooxygenation of 1-hydroxypyrrole **122,** on the other hand, gives the corresponding hydroperoxide **123** (Scheme XX).

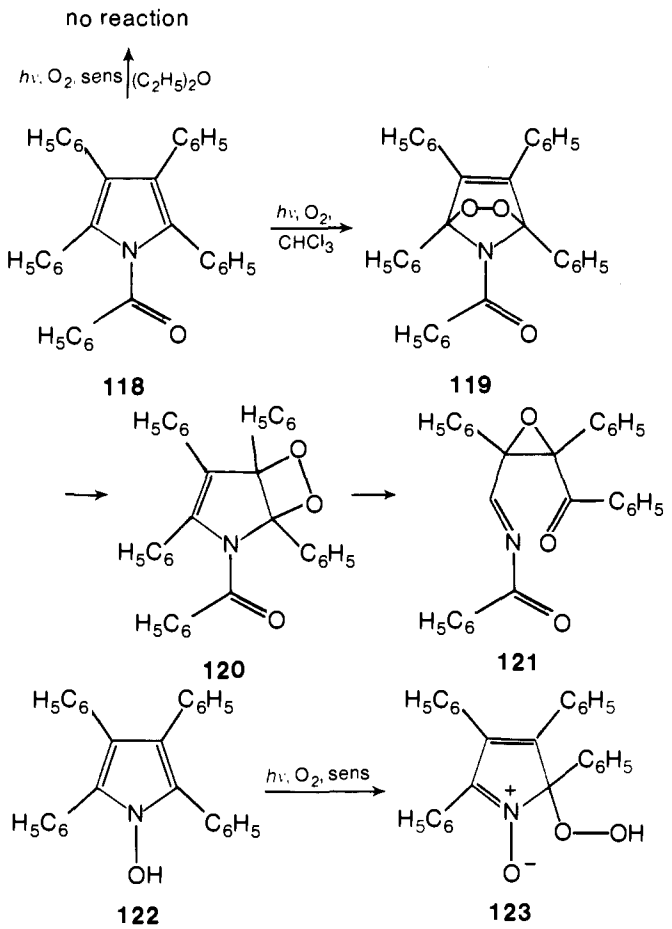
The photooxygenations of several pyrrole-2-carboxaldehydes have been examined recently.[42] It has been shown that the pyrrole-2-carboxaldehydes **124a–e** undergo photooxygenation to give the corresponding 5-methoxylactams **125a–e.** In contrast, the photooxygenation of **124f** gives a mixture of **125f** and citraconimide (**47**). However, the photooxygenation of **124g** does not give rise to any isolable product (Scheme XXI).

The photooxygenation of bilirubin IXα (**126**), a yellow bile pigment, has been the topic of detailed investigations in recent years.[43] It has been observed that some of the cases of jaundice in newborn infants (neonatal hyperbilirubinemia) could be effectively treated by irradiation with a light source in the wavelengths absorbed by bilirubin.[44] Studies have shown that singlet oxygen formed through bilirubin sensitization is the reactive species and hence responsible for the destruction of **126.**[45] The photooxygenation of **126** either in the presence or absence of any sensitizer, for example, gives rise to a variety of products depending on the nature of the solvent and reaction conditions. Some of the products formed from **126** under protic conditions (methanolic or ethanolic ammonia or aqueous ammonia) include biliverdin IXα (**127**),[19a,46] methylvinylmaleimide (**128**),[46a,b,d,e,g,47] hematinic acid imide (**129**),[47a,d] the hydrolysis products **128a** and **129a** of **128** and **129,** respectively,[46g] the dipyrrole dicarboxaldehyde **130,**[46b,48] and various propentdyopents (**131**) (Scheme XXII).[46a,b,d,e,g,47a,48,49] It has been generally observed that the propentdyopents (**131**) are formed in relatively greater amounts in protic solvents than in aprotic solvents. In a recent investigation, Bonnett and Stewart[46b] have shown that the photooxygenation of **126** in methanol containing anhydrous ammonia (0.2%), for example, gives rise to a mixture of products consisting of **128** (7%), **131a** (19%), **131b** (25%), and **131c**

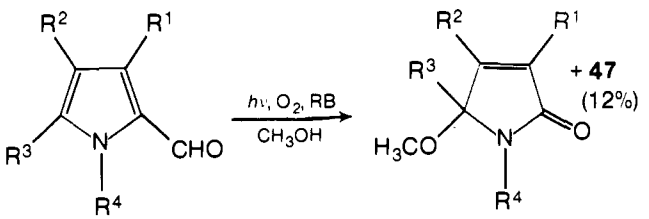
SCHEME XIX



SCHEME XX



SCHEME XXI

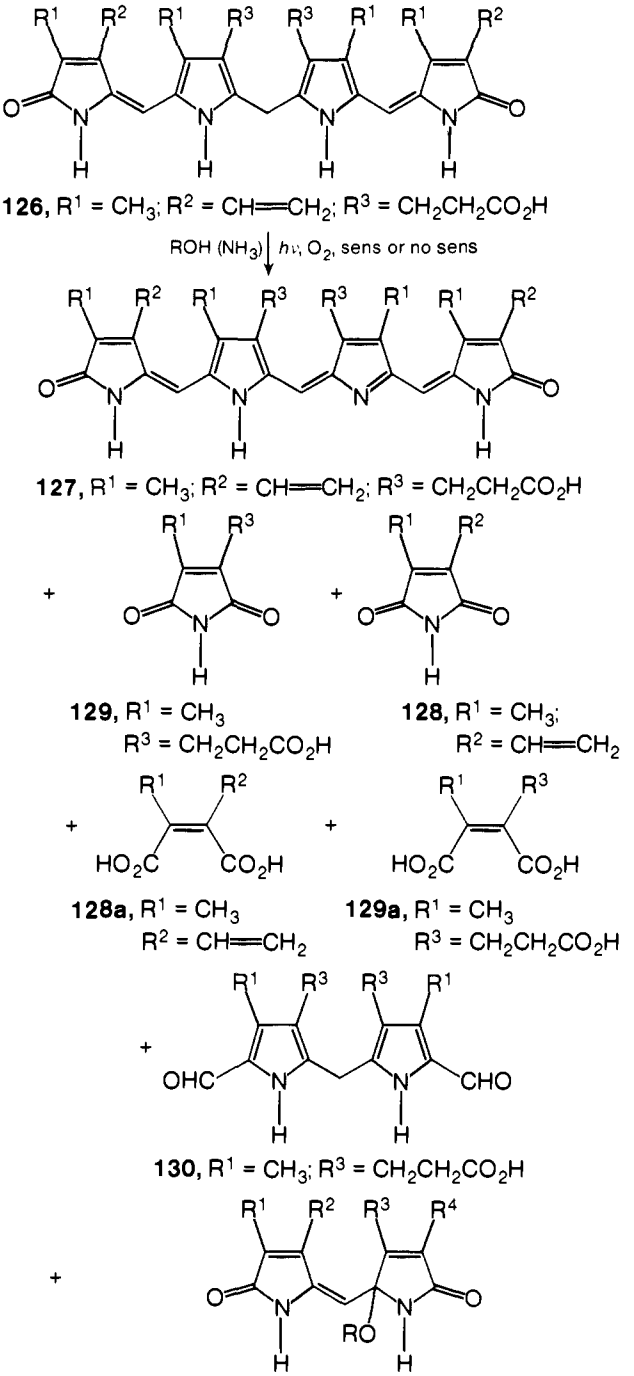


124a, $R^1 = R^3 = CH_3$; $R^2 = C_2H_5$; $R^4 = H$ **125a** (53%)
b, $R^1 = R^2 = C_2H_5$; $R^3 = CH_3$; $R^4 = H$ **b** (53%)
c, $R^1 = R^2 = R^3 = H$; $R^4 = CH_3$ **c** (10%)
d, $R^1 = R^2 = R^4 = H$; $R^3 = CH_3$ **d** (7%)
e, $R^1 = R^3 = CH_3$; $R^2 = R^4 = H$ **e** (41%)
f, $R^1 = CH_3$; $R^2 = R^3 = R^4 = H$ **f** (10%)
g, $R^1 = R^2 = R^3 = R^4 = H$ **g** (Nil)

(31%). The photooxygenation of **126** in aprotic solvents such as chloroform, however, leads to a greater yield of biliverdin (**127**).[46a] Higher yields of **127** have also been observed with increasing bilirubin concentration in methanolic ammonia and chloroform. The formation of biliverdin (**127**) from **126** may involve radical intermediates, whereas products such as **128, 129, 130,** and **131** may be rationalized in terms of the initial photosensitized generation of singlet oxygen, followed by its reaction with **126** to give endoperoxide intermediates.[46a] Further transformation of these endoperoxides to the different products would be analogous to the transformations of various pyrrole endoperoxides.

The photooxygenation of several compounds related to bilirubin has also been studied. In contrast to bilirubin (**126**), biliverdin (**127**) has been shown to be a quencher (and not a sensitizer) of singlet oxygen.[50,51] Biliverdin (**127**), however, undergoes slow photodegradation in presence of oxygen to give methylvinylmaleimide (**128**) as one of the products.[52a] On the other hand, the Rose Bengal sensitized photooxygenation of the methyl ester of biliverdin (**132**) is known to give a mixture of products consisting of the methanol propentdyopent adduct methyl ester **133** (10%) and the methyl ester of hematinic acid

SCHEME XXII



126, $R^1 = CH_3$; $R^2 = CH{=}CH_2$; $R^3 = CH_2CH_2CO_2H$

127, $R^1 = CH_3$; $R^2 = CH{=}CH_2$; $R^3 = CH_2CH_2CO_2H$

129, $R^1 = CH_3$; $R^3 = CH_2CH_2CO_2H$

128, $R^1 = CH_3$; $R^2 = CH{=}CH_2$

128a, $R^1 = CH_3$; $R^2 = CH{=}CH_2$

129a, $R^1 = CH_3$; $R^3 = CH_2CH_2CO_2H$

130, $R^1 = CH_3$; $R^3 = CH_2CH_2CO_2H$

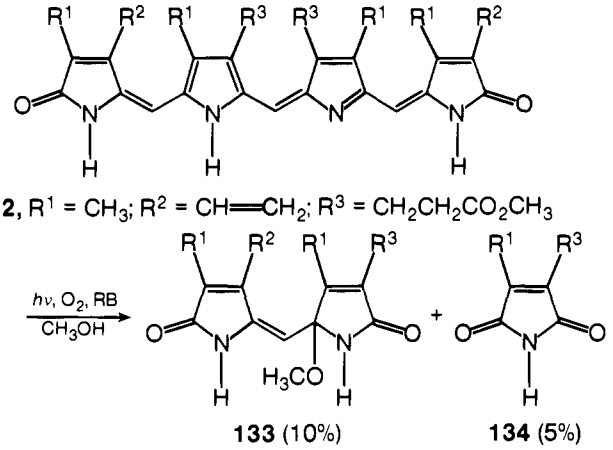
131 (R = H, CH_3 or C_2H_5; $R^1 = CH_3$, $CH{=}CH_2$ or $CH_2CH_2CO_2H$; $R^2 = CH_3$ or $CH{=}CH_2$; $R^3 = CH_3$ or $CH{=}CH_2$; $R^4 = CH_3$, $CH{=}CH_2$, $CH_2CH_2CO_2H$)

131a, R = CH_3; $R^1 = CH_2CH_2CO_2H$; $R^2 = R^3 = CH_3$; $R^4 = CH{=}CH_2$

b, R = CH_3; $R^1 = CH{=}CH_2$; $R^2 = R^3 = CH_3$; $R^4 = CH_2CH_2CO_2H$

c, R = CH_3; $R^1 = CH_2CH_2CO_2H$; $R^2 = R^4 = CH_3$; $R^3 = CH{=}CH_2$

SCHEME XXIII



134 (5%) (Scheme XXIII).[52b]

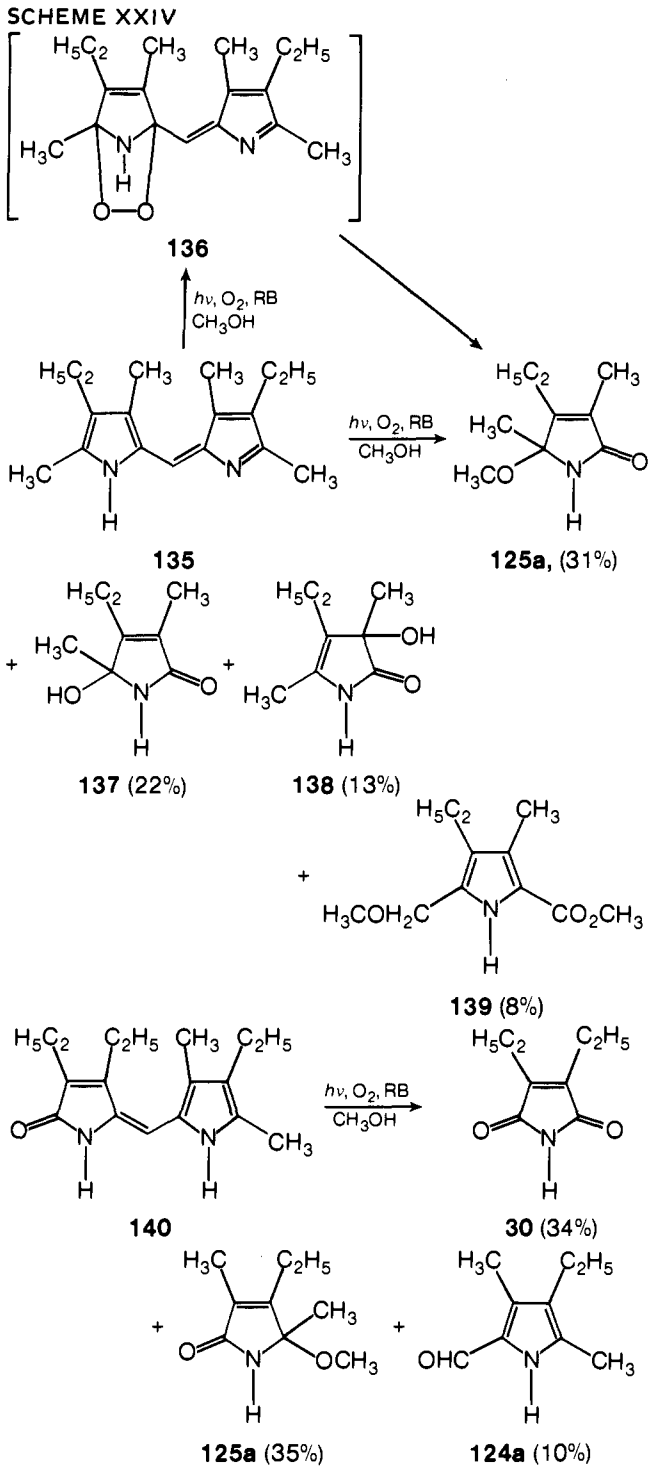
The photooxygenations of several model compounds related to bilirubin such as dipyrrylmethenes and oxopyrromethenes have also been investigated by different workers. Thus, it has been shown that Rose Bengal sensitized photooxygenation of **3**,4,3′,5′-tetramethyl-4,4′-diethyldipyrrylmethene (**135**) gives a mixture of products consisting of 4-ethyl-5-methoxy-**3**,5-dimethyl-Δ^3-pyrrolin-2-one (**125a,** 31%), 4-ethyl-5-hydroxy-3,5-dimethyl-Δ^3-pyrrolin-2-one (**137,** 22%), 4-ethyl-3-hydroxy-3,5-dimethyl-Δ^4-pyrrolin-2-one (**138,** 13%), and methyl 4-ethyl-5-methoxymethyl-3-methylpyrrole-2-carboxylate (**139,** 8%). It has been suggested that at least some of these products such as **125a** may arise via the endoperoxide **136** (Scheme XXIV).[52b] Rose Bengal sensitized photooxygenation of the oxopyrromethene **140,** however, gives a mixture of 3,4-diethylmaleimide (**30,** 34%), 3,5-dimethyl-4-ethyl-5-methoxy-Δ^3-pyrrolin-2-one (**125a,** 35%), and the kryptopyrrole carboxaldehyde **124a** (10%) (Scheme XXIV).[52c]

2. *Indoles and Their Derivatives*

Several interesting examples of the photooxygenations of indoles have appeared in the literature in the last few years.[53-57] 1,2,3-Trimethylindole (**141a**), for example, is known to undergo photooxygenation to give a 92% yield of the keto derivative **142a** (Scheme XXV).[53] Under analogous conditions, 3-methylindole (**141b**) gives a mixture of *o*-formamidoacetophenone (**142b,** 16%) and *o*-aminoacetophenone (**143,** 7%).[54] Similarly, several 3- or 2,3-disubstituted-*N*-methylindoles such as **141c-f** are known to give the corresponding 2-acylaminophenyl ketones **142c-f** in excellent yields (80-90%).[55] Likewise, 3-acylindoles **141g** and **141h** have been shown to give the corresponding keto derivatives **142g** and **142h,** respectively (Scheme XXV).[55] The formation of the different keto products **142a-h** in the photooxygenations of the indole derivatives **141a-h** has been rationalized in terms of the pathway shown in Scheme XXVI. It has been assumed that the keto derivatives are formed through the corresponding dioxetane intermediates **145,** which in turn may be formed through the corresponding peroxy derivatives **144**.[53-55]

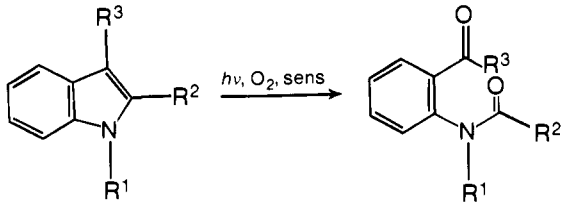
Nakagawa et al.[58] have reported that the photosensitized oxidation of 2,3-diphenylindole (**146a**) gives a mixture of products consisting of 2,3-diphenyl-3-hydroxyindolenine (**152,** 40%), 2-benzamidobenzophenone (**153a,** 11%), and 9*H*-dibenzo[*a*,*c*]carbazole (**156a,** 4.5%). The photooxygenation of *N*-acetyl-2,3-diphenylindole (**146b**) in methanol under similar conditions gives a mixture of the diol **154a** (54%) and the keto derivative **153a** (2%). When the photooxygenation of **146b** is carried out in benzene, however, only traces of **154b** and **153a** are formed. The photooxygenation of 2,3-diphenyl-*N*-methylindole (**146c**), likewise, gives a mixture of products consisting

SCHEME XXIV



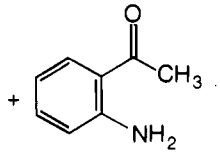
of **153c** (59%), 2,3-dihydro-1,4-benzoxazine (**155,** 15%), and dibenzocarbazole (**156c,** 4%) (Scheme XXVII). The different products formed in the photooxygenations of the indole derivatives, **146a-c,** can be rationalized in terms of the pathway shown in Scheme XXVII. The formation of **152** from **146a,** for example, would suggest that the hydroperoxy intermediate **149** may be involved in this reaction. The hydroperoxy intermediate **149,** besides giving rise to **152,** could also lead to the dioxetane intermediate, **150.** Simple fragmentation of the dioxetane **150** would account for the keto products **153a** and **153c.** The products **154** and **155,** on the other hand, can be best rationalized in terms of the zwitterionic intermediate **147** or the peroxirane derivative, **148.** Addition of methanol to either **147** or **148,** for example, will lead to **151,** which in turn can give rise to both **154** and **155.** The benzoxazine derivative **155** may be formed through

SCHEME XXV



141 a-h **142 a-h**

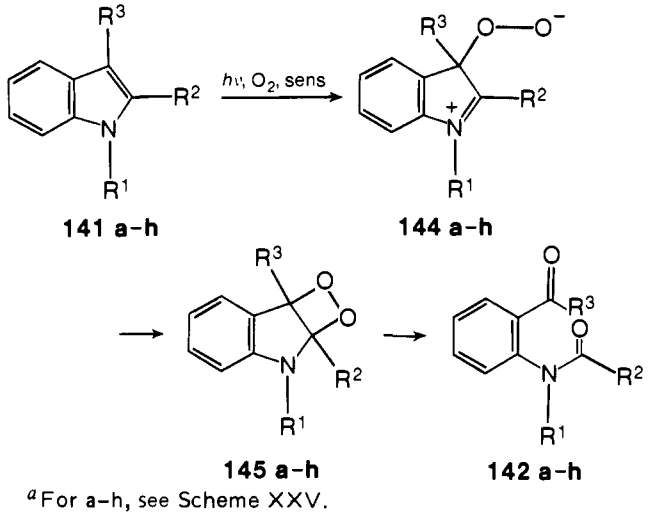
a, $R^1 = R^2 = R^3 = CH_3$
b, $R^1 = R^2 = H$; $R^3 = CH_3$
c, $R^1 = R^3 = CH_3$; $R^2 = H$
d, $R^1 = R^3 = CH_3$; $R^2 = C_6H_5$
e, $R^1 = CH_3$; $R^2 = H$; $R^3 = CH_2CH_2OCH_3$
f, $R^1 = CH_3$; $R^2 = H$; $R^3 = CH_2CH_2CO_2C_2H_5$
g, $R^1 = R^2 = CH_3$; $R^3 = COC_3H_7$-*n*
h, $R^1 = R^2 = CH_3$; $R^3 = COC_6H_5$



143

a rearrangement of the hydroperoxide **151**, involving a ring-enlargement reaction.[59,60] Formation of products such as **156a** and **156c**, on the other hand, could arise through a simple dehydrocyclization pathway, occurring under photochemical conditions (Scheme XXVII).[61]

SCHEME XXVI[a]



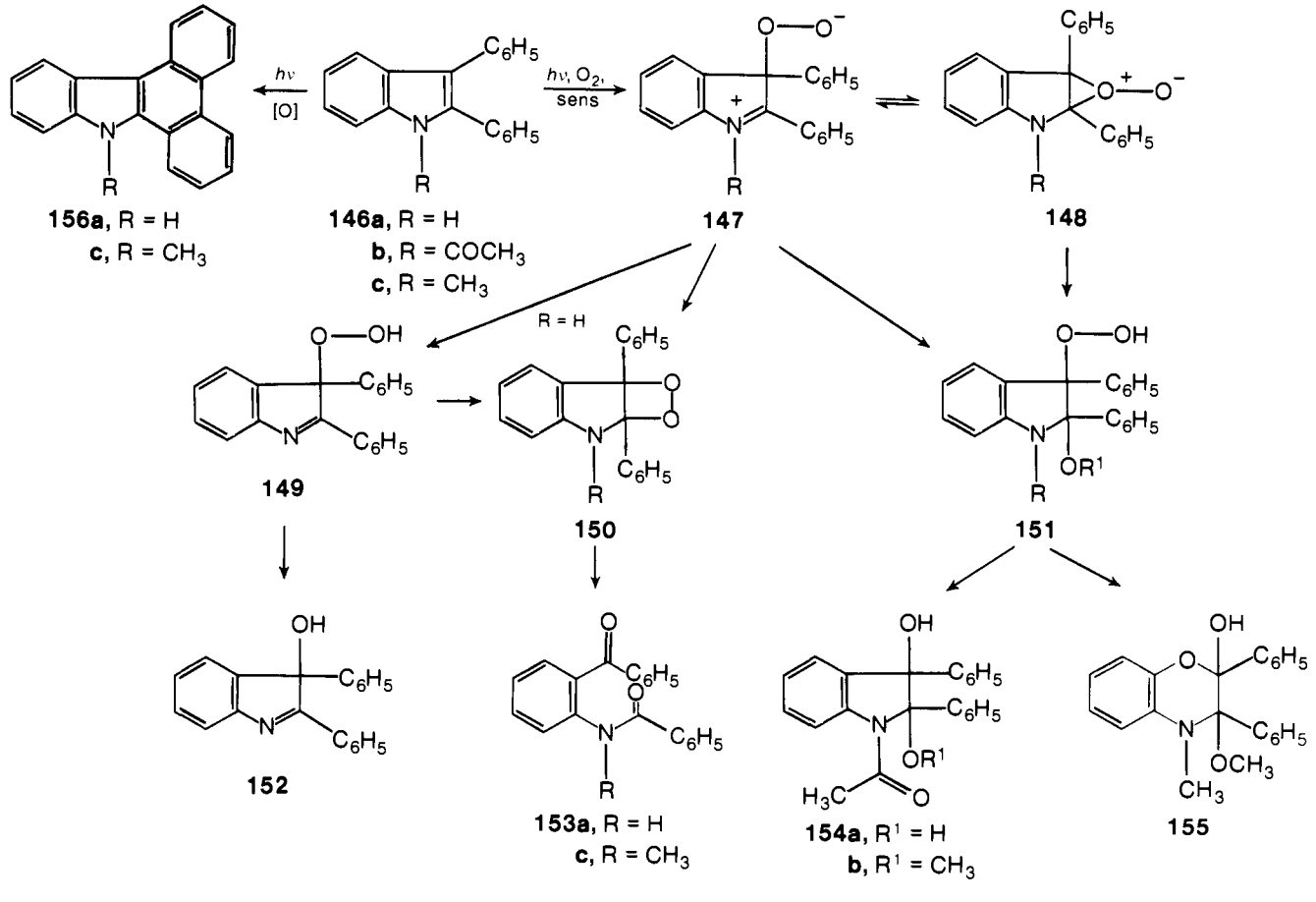
141 a-h **144 a-h**

145 a-h **142 a-h**

[a] For a-h, see Scheme XXV.

Maeda et al.[62] have reported that several indole derivatives give rise to quinazolines, on photooxygenation in the presence of ammonium acetate. Thus, it has been shown that the indoles **157a-f**, on photooxygenation in aqueous methanol containing ammonium acetate, are converted to the quinazolines **161a-f**, respectively (Scheme XXVIII). It is quite likely that the indoles in these reactions are initially converted to the corresponding hydroperoxy derivatives **158**, which may then give rise to the corresponding keto derivatives **160**. These keto derivatives (**160**) in presence of ammonium acetate will subsequently give the quinazolines **161** as shown in Scheme XXVIII.[62]

SCHEME XXVII



156a, R = H
c, R = CH_3

146a, R = H
b, R = $COCH_3$
c, R = CH_3

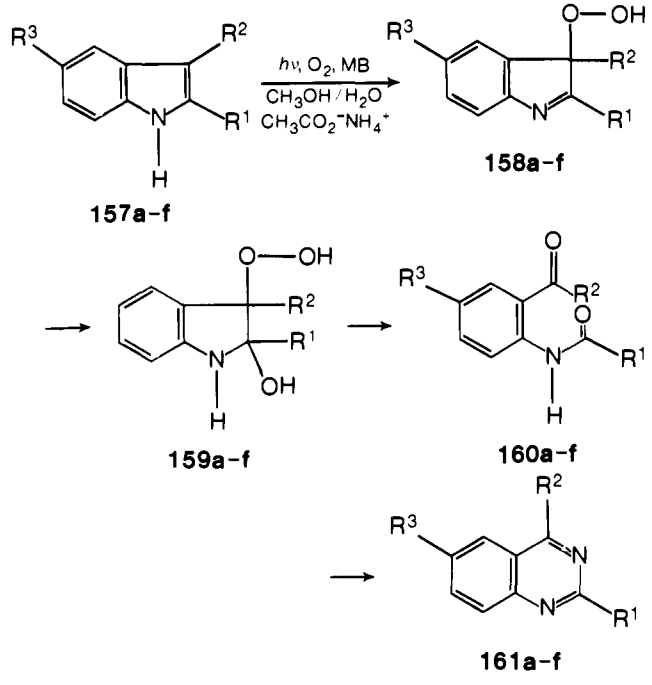
147 **148** **149** **150** **151** **152**

153a, R = H
c, R = CH_3

154a, R^1 = H
b, R^1 = CH_3

155

SCHEME XXVIII



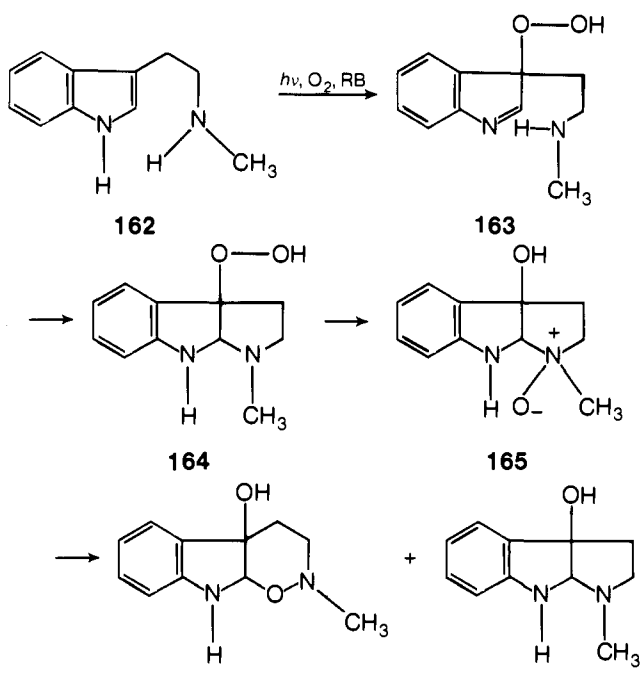
157a-f 158a-f 159a-f 160a-f 161a-f

a, $R^1 = R^2 = C_6H_5$; $R^3 = H$
b, $R^1 = R^2 = R^3 = CH_3$
c, $R^1 = R^2 = CH_3$; $R^3 = Cl$
d, $R^1 = R^2 = CH_3$; $R^3 = OCH_3$
e, $R^1 = C_6H_5$; $R^2 = CH_3$; $R^3 = H$
f, $R^1 = R^2 = C_6H_5$; $R^3 = CH_3$

Photooxygenations of several indole derivatives such as tryptophan, tryptamine, tryptophol, etc., have been extensively investigated by different groups of workers.[63-75] The Rose Bengal sensitized photooxygenation of *N'*-methyltryptamine (**162**) in a mixture of benzene and methanol at room temperature, for example, has been shown to give a mixture of products consisting of 4a-hydroxy-2-methyl-2,3,4,4a,9,9a-hexahydro-1,2-oxazino[6,5-*b*]indole (**166**) and 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**167**).[64,65] When the reaction, however, is carried out in methanol at 0 °C, followed by rapid work-up, 3a-hydroperoxypyrroloindole (**164**) is obtained as the major product. It has been observed that the hydroperoxide **164**, on standing in solvents like pyridine, methanol, or benzene, at room temperature, is converted to **166**, indicating thereby that the formation of **166** in the photooxygenation of **162** may involve the intermediates **163**, **164**, and **165**, shown in Scheme XXIX.[65]

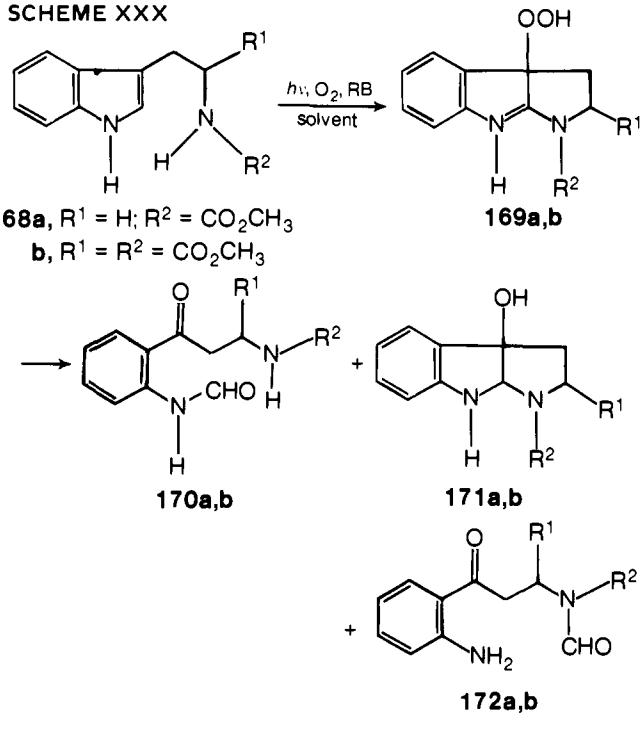
The photooxygenation of *N'*-methoxycarbonyltryptamine (**168a**) in polar solvents like acetone, *tert*-butyl alcohol, or a mixture of pyridine and methanol, on the other hand, leads to a mixture of products consisting of the formylkynurenine derivative **170a** (9%), the 3a-hydroxypyrroloindole **171a** (18%), and the *N'*-formylkynurenine derivative **172a** (18%).[60] It has been shown that the photooxygenation of **168a**, when carried out at low temperatures, gives the hydroperoxide **169a** as one of the isolable products. Further, it has been observed that the hydroperoxide **169a** is converted to a mixture of products consisting of **170a**, **171a**, and **172a** in the presence of silica gel or on refluxing in benzene (Scheme XXX).[66] The hydroperoxides **164** and **169a** can be easily reduced to the corresponding 3a-hydroxypyrroloindoles **167** and **171a**, respectively, providing thereby a convenient synthetic route to the biogenetic-like transformation of indoles to the corresponding 3a-hydroxypyrroloindoles, which are frequently found in natural products such as sporidesmins,[76] brevianamide E,[77] and hunteracine chloride (or bromide).[78]

SCHEME XXIX



162 163 164 165 166 167

SCHEME XXX



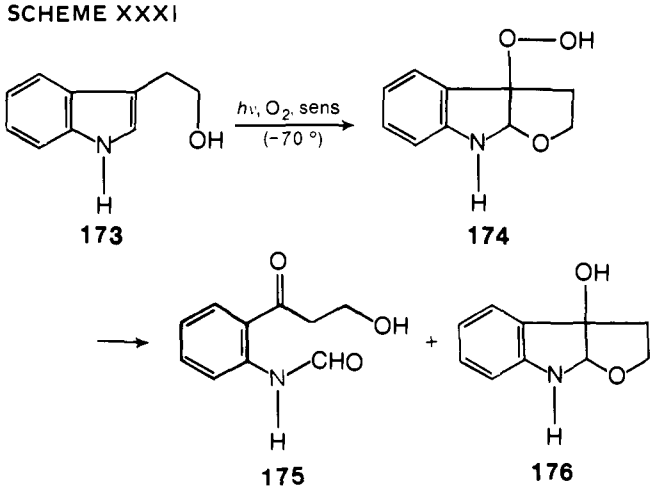
168a, R^1 = H; $R^2 = CO_2CH_3$
b, $R^1 = R^2 = CO_2CH_3$

169a,b 170a,b 171a,b 172a,b

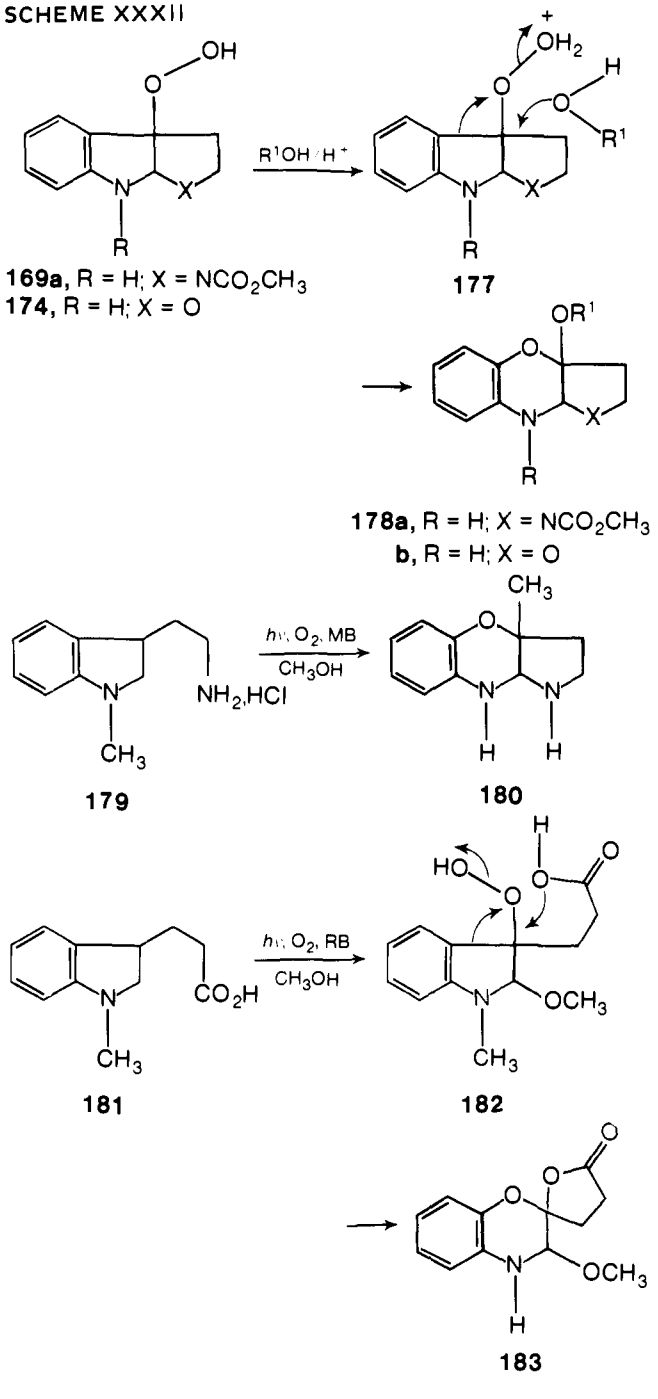
Likewise, the photooxygenation of **168b** under conditions similar to those of **168a** gives a mixture of **170b** (18%), **171b** (14%), and **172b** (8%).[60] The formation of products such as **170b** and **171b** from **168b** would suggest that the hydroperoxide **169b** is involved in these reactions,[60] although attempts at isolating **169b** have been unsuccessful.[63] The photooxygenation of tryptophol (**173**) at −70 °C likewise gives a nearly quantitative yield of the hydroperoxide **174**, which readily decomposes to a mixture of products consisting of **175** and **176**, under a variety of conditions (Scheme XXXI).[63]

The 3-hydroperoxyindolines, which are formed in the photooxygenation of indoles, undergo facile acid-catalyzed rearrangement to give 2,3-dihydro-1,4-benzoxazines.[59,60] Treatment of the hydroperoxides **169a** and **174** with methanol containing catalytic amounts of HCl gives the corresponding benzoxazine

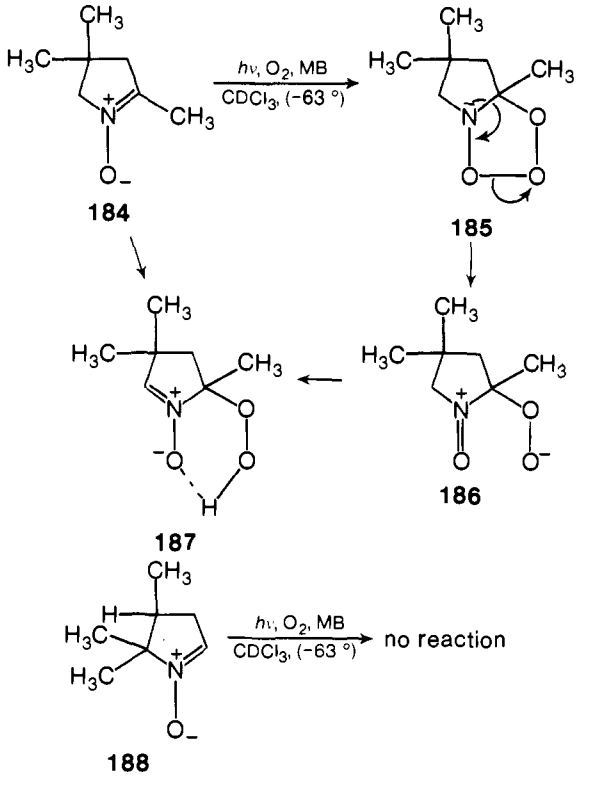
SCHEME XXXI



SCHEME XXXII



SCHEME XXXIII



derivatives **178a** and **178b**, respectively, in high yields (Scheme XXXII).[57,59,60,66]

An interesting case of the photooxygenation of an indole derivative has been that of tryptamine hydrochloride (**179**), which under Methylene Blue sensitized conditions in methanol gives **180**, as the exclusive product, whereas the photooxygenation of the indole **181** gives **183**, as the only isolable product.[59] The formation of **183** from **181** may involve a hydroperoxy intermediate **182**, as shown in Scheme XXXII.

3. Δ^1-Pyrroline N-Oxides

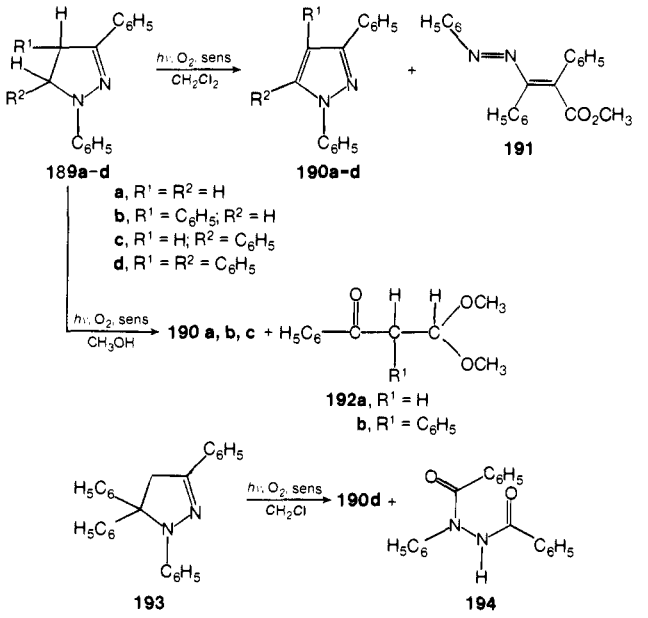
Ching and Foote[79] have reported that 2,4,4-trimethyl-Δ^1-pyrroline *N*-oxide (**184**) on photooxygenation in $CDCl_3$ at −63 °C results in a quantitative yield of 5-hydroperoxy-3,3,5-trimethyl-Δ^1-pyrroline *N*-oxide (**187**), whereas, under similar conditions, 4,5,5-trimethyl-Δ^1-pyrroline *N*-oxide (**188**) is unaffected. A probable mechanism for the transformation of **184** to **187** involves an initial 1,3-dipolar addition of singlet oxygen to **184** to give the intermediate **185**, which will then lead to **187** via the intermediate **186** as shown in Scheme XXXIII. However, the unreactivity of **188**, under analogous conditions, would cast some doubts on this pathway. An alternative pathway for the conversion of **184** to **187** will be through an "ene" reaction, although such "ene" reactions, involving double bonds attached to heteroatoms, are somewhat rare.

B. Five-Membered Heterocycles Containing Two Nitrogen Atoms

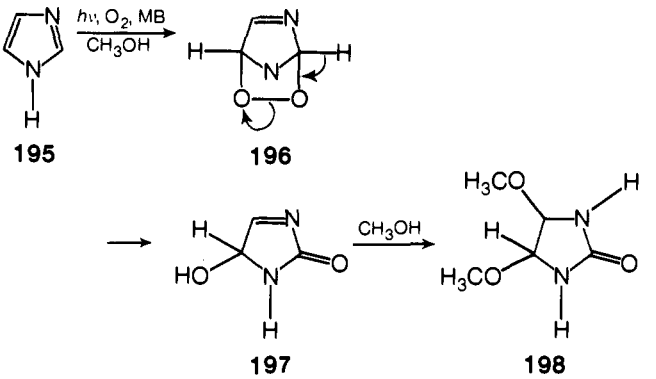
1. Pyrazolines

Evans and Leaver[80] have reported that Methylene Blue sensitized photooxygenation of 1,3-diphenyl-2-pyrazoline (**189a**) in methylene chloride gives 1,3-diphenylpyrazole (**190a**, 76%) as the only isolable product, whereas the photooxygenation of **189a** in methanol results in a mixture of products consisting of **190a** (47%) and β,β-dimethoxypropiophenone (**192a**, 42%). Similarly, Evans[81] has observed that substituted pyrazoles on photooxygenation give rise to different products, depending upon the reaction conditions. Thus, it has been observed that 1,3,4-

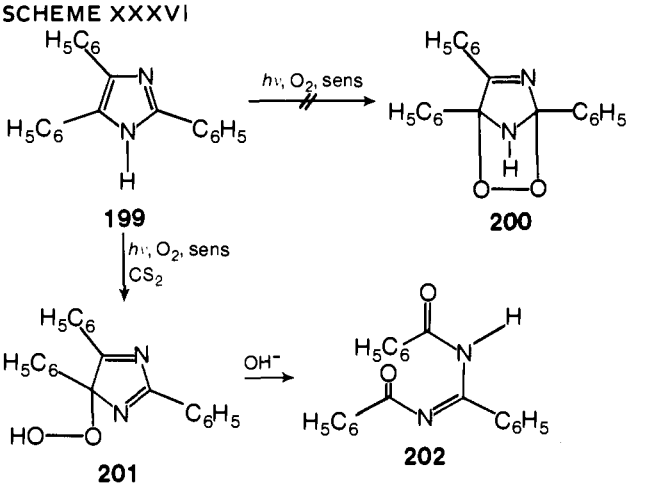
SCHEME XXXIV



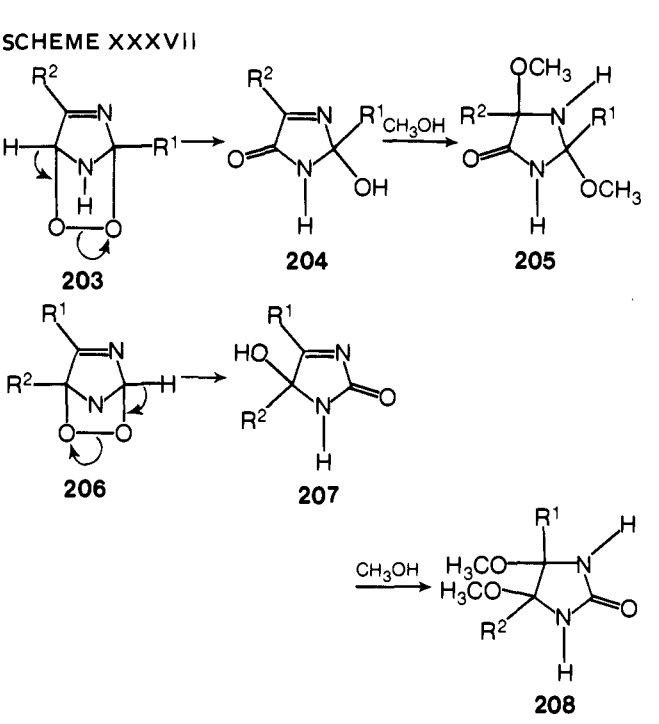
SCHEME XXXV



SCHEME XXXVI



SCHEME XXXVII



triphenylpyrazoline (**189b**), on photooxygenation in methylene chloride, for example, gives a 70% yield of 1,3,4-triphenylpyrazole (**190b**), whereas in methanol, a mixture of **190b** and benzoylphenylacetaldehyde dimethyl acetal (**192b**) is obtained. Similarly, the photooxygenation of 1,3,5-triphenylpyrazoline (**189c**) in methylene chloride gives a mixture of 1,**3**,5-triphenylpyrazole (**190c,** 67%) and the azo compound **191,** whereas in methanol, only **190c** (67%) is obtained.[81] Likewise, the photooxygenation of 1,3,4,5-tetraphenylpyrazoline (**189d**) in methylene chloride gives rise to the corresponding pyrazole, **190d** (99%). In contrast, the photooxygenation of 1,3,5,5-tetraphenylpyrazoline (**193**) in methylene chloride gives a mixture of products consisting of **190d** (61%) and *N,N'*-dibenzoylphenylhydrazine (**194**) (Scheme XXXIV).[81] It has been suggested that the pyrazoles (**190a-d**) formed in these reactions arise through the reaction of singlet oxygen with the corresponding pyrazolines (**189a-d**). The formation of products like **192** in the photooxygenation of pyrazolines, however, has been attributed to the interaction of the dye triplet with the starting pyrazolines (**189a-d**), followed by further transformations.[80] The pathway for the transformation of the azo derivative **191,** however, is still not clearly understood.

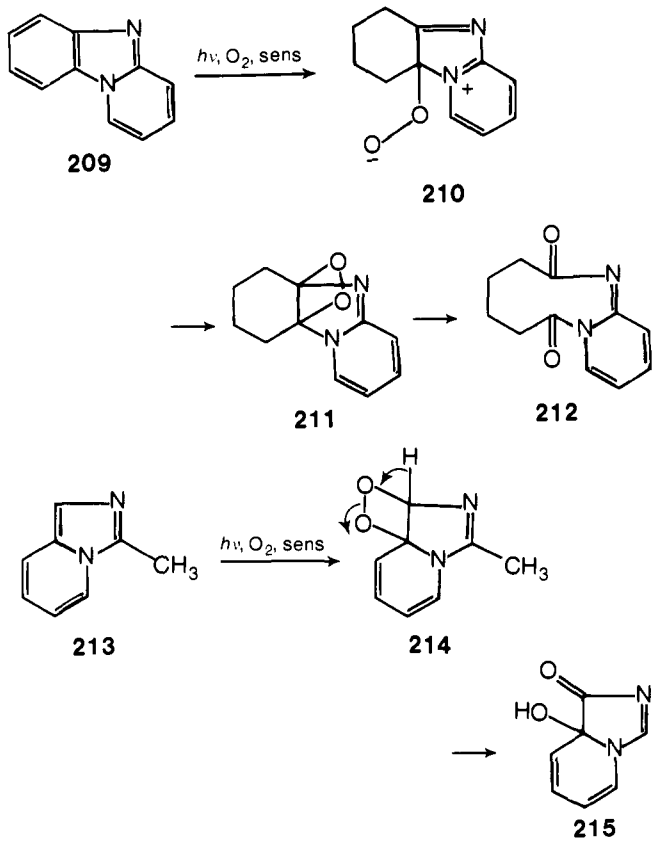
2. Imidazoles

Photooxygenation reactions of imidazoles have gained considerable importance in view of the significant biological implications of these heterocycles.[82] It has been observed that imidazoles behave in many respects like furans and pyrroles on photooxygenation. As a rule, however, imidazoles are prone to cleavage through reactions resembling the oxidation of enamines with singlet oxygen.[83]

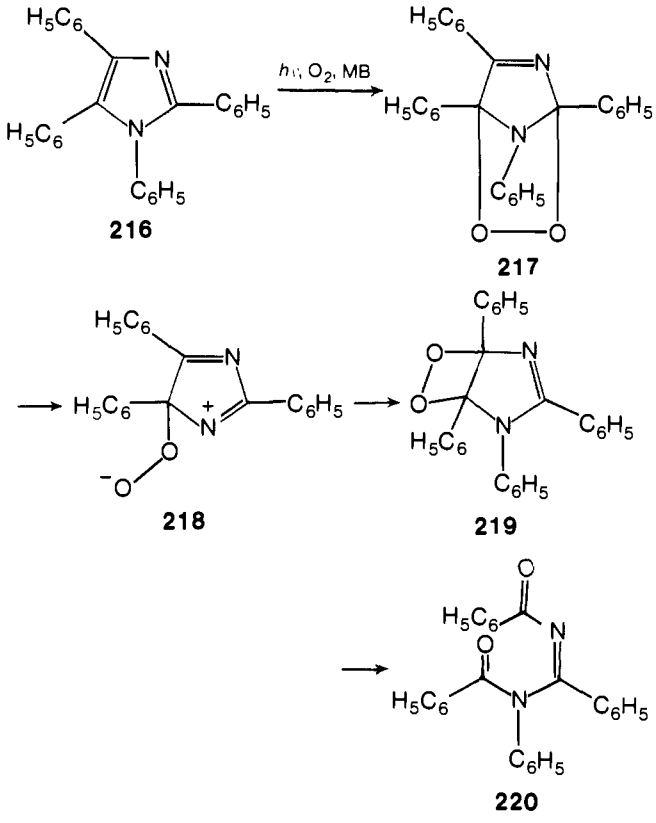
Imidazole (**195**) itself has been reported to undergo very slow photooxidation in methanol leading to the formation of the dimethoxy derivative **198** (30%) as per the pathway shown in Scheme XXXV.[83] Sensitized photooxygenation of 2,4,5-triphenylimidazole (lophine) (**199**) has been reported earlier to give the endoperoxide **200**.[84] Subsequent investigations, however, have shown that the product formed in this reaction is the hydroperoxide **201** and not **200** (Scheme XXXVI).[85,86] The lophine hydroperoxide **201** has been postulated as the intermediate involved in the chemiluminescence of lophine, and this endoperoxide decomposes in alkaline media to yield *N,N'*-dibenzoylbenzamidine (**202**), accompanied by an emission of light at 530 nm (Scheme XXXVI).[37,84,85,87,88]

Studies have shown that the presence of a proton at either the 2 or 5 position of the imidazole ring faciliates a β-elimination type of fragmentation of the initially formed endoperoxide, leading to the formation of hydroxyimidazolone derivatives, as shown in Scheme XXXVII. However, if both 2 and 5 positions of the imidazole are substituted by groups other than hydrogen

SCHEME XXXVIII

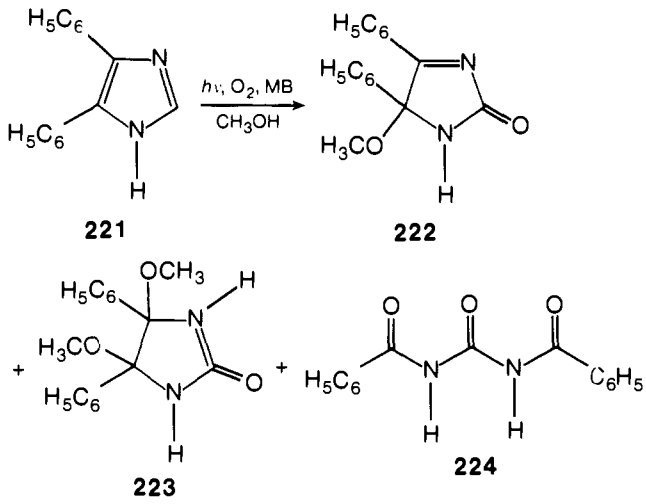


SCHEME XXXIX



as in the case of the imidazole **209,** the normal reactions of an enamine system with singlet oxygen are observed. Thus, it has been shown that the imidazole **209,** on photooxygenation, gives the keto derivative **212,** probably arising through the intermediates **210** and **211** (Scheme XXXVIII).[89] However, if both 2 and 5 positions are substituted and a proton is available at position 4 as in **213,** then the initially formed peroxy derivative **214** may fragment through a β-elimination mode, leading to the formation of **215** (Scheme XXXVIII).[89]

SCHEME XL



The photooxygenation of tetraphenylimidazole (**216**) has been shown to give exclusively *N,N'*-dibenzoyl-*N*-phenylbenzamidine (**220**), and it is assumed that the initially formed endoperoxide **217** in this reaction undergoes transformation to the dioxetane intermediate **219,** which subsequently fragments to **220** (Scheme XXXIX).[83] In contrast, the photooxygenation of 4,5-diphenylimidazole (**221**) gives a 45% yield of a mixture of products consisting of 5-methoxy-4,5-diphenylimidazolin-2-one (**222**), 4,5-dimethoxy-4,5-diphenylimidazolin-2-one (**223**), and a 5% yield of *N,N'*-dibenzoylurea (**224**) (Scheme XL).[83] The photooxygenation of 2,5-diphenylimidazole (**225**) gives 4-methoxy-2,4-diphenylimidazolin-5-one (**226**) as the only product,[90] whereas 4-phenylimidazole (**227**), under similar conditions, yields a mixture of both 5-phenyl-5-methoxyhydantoin (**228**) and *N*-benzoyl-*N'*-carbomethoxyurea (**229**) (Scheme XLI).[83,90] Benzimidazoles are found to be inert under the same photooxidation conditions.[90] Matsuura and Ikari[91] have shown that the Rose Bengal sensitized photooxidation of 1,2-dimethylimidazole (**230**) gives a mixture of products consisting of **231, 232,** and **233** (Scheme XLI). In contrast, the photooxygenation of 4-methylimidazole (**234**) gives acetylurea (**235**) (Scheme XLI).[92]

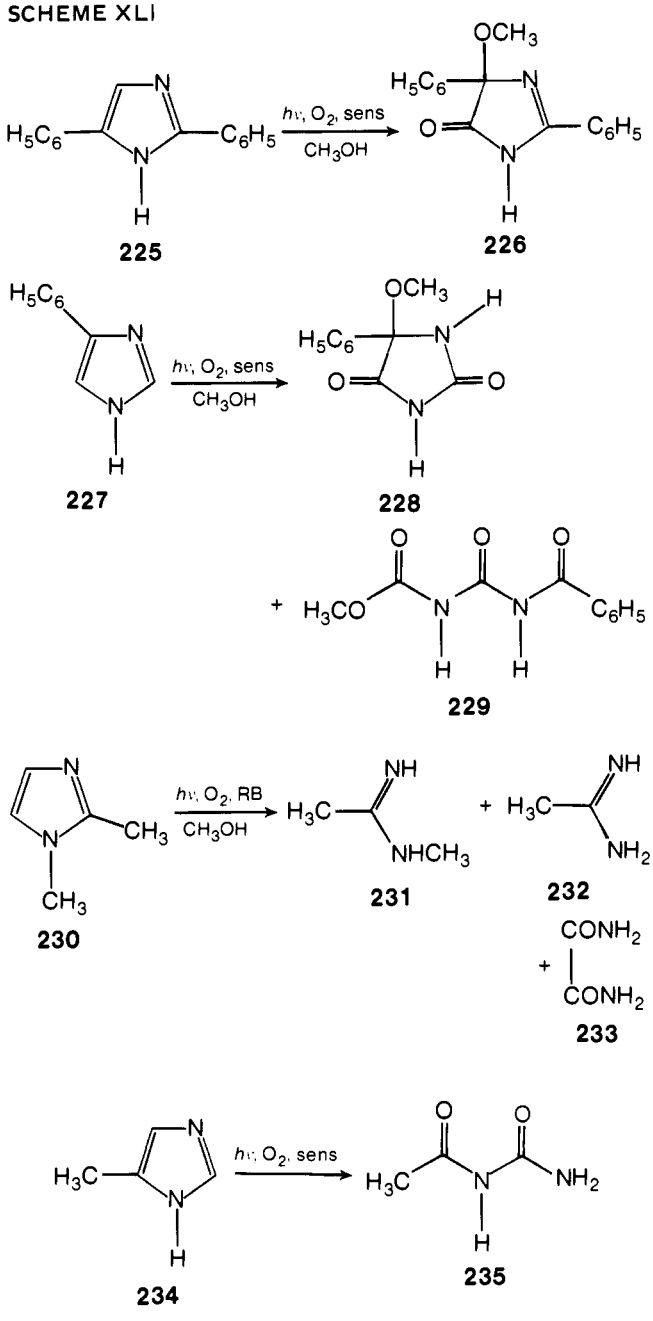
Sensitized photooxygenation of histidine needs special mention in view of its relation to the photodynamic destruction of histidine residues in proteins. Histidine (**236**) on photooxygenation gives products of cleavage of the imidazole ring; the initial products have not been isolated, but model studies on other imidazoles suggest that the cleavage of the enamine double bond is the likely primary pathway, followed by the hydrolytic cleavage to give aspartic acid (**237**). *N*-Benzoylhistidine (**238**) also, on photooxygenation, gives a complex mixture of products, one of them being **239** (Scheme XLII).[12,83,93]

Phenyl-substituted imidazolones (**240a,b**) undergo facile cleavage of their enamine double bonds on photooxygenation to give *N,N'*-diacylureas (**243a,b**), similar to the formation of **229** from the imidazole **227** (Scheme XLIII).[89,94]

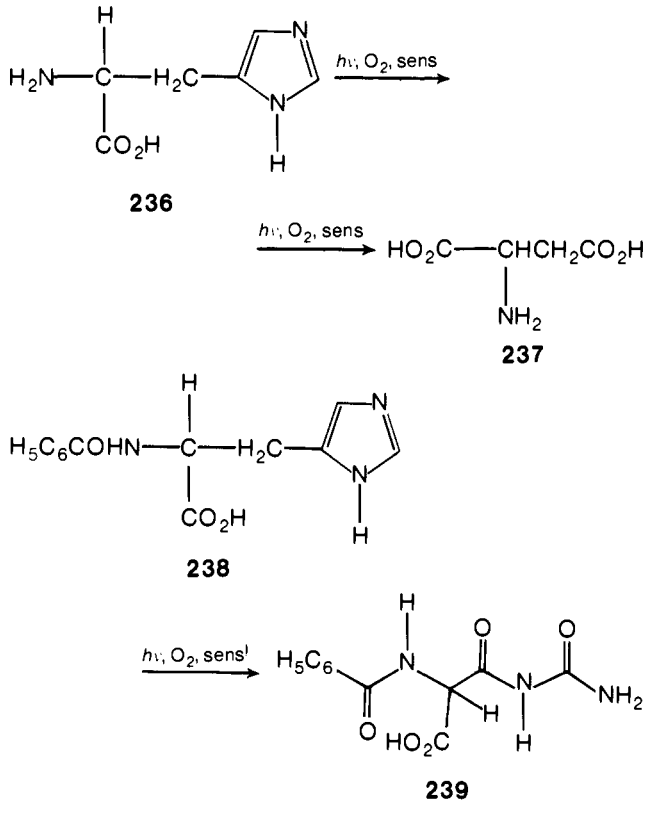
3. Purines

Photodynamic inactivation of biological systems involving nucleic acid has been found to be chiefly due to the selective degradation of guanine residues in nucleic acids, under sensitized photooxygenation.[95-97] In spite of detailed investigations, the primary products of oxidation of nucleic acids have not been well characterized. It has been observed that guanine is the principal

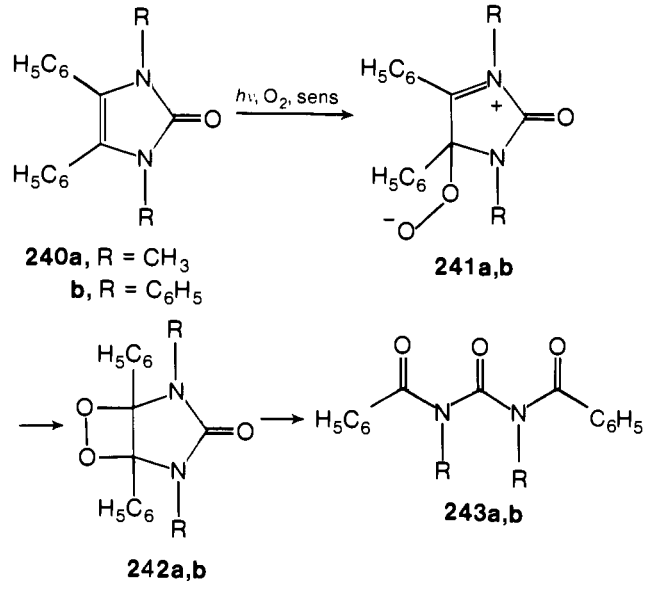
SCHEME XLI



SCHEME XLII



SCHEME XLIII



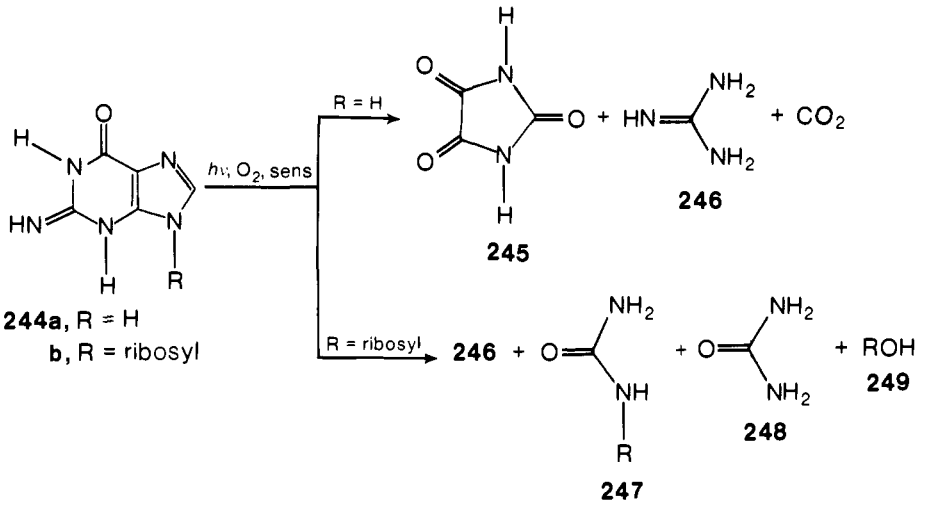
base unit that is readily destroyed in oxidation.[98-104] Studies on model systems suggest that the enamine double bonds in the heterocyclic bases are most susceptible to oxidative cleavages.

Sussenbach and Behrends,[100,101,105] for example, have reported that the sensitized photooxygenation of guanine (**244a**) gives a mixture of products consisting of **246**, ribosylurea (**247**), urea (**248**), and ribose (**249**) (Scheme XLIV).[104]

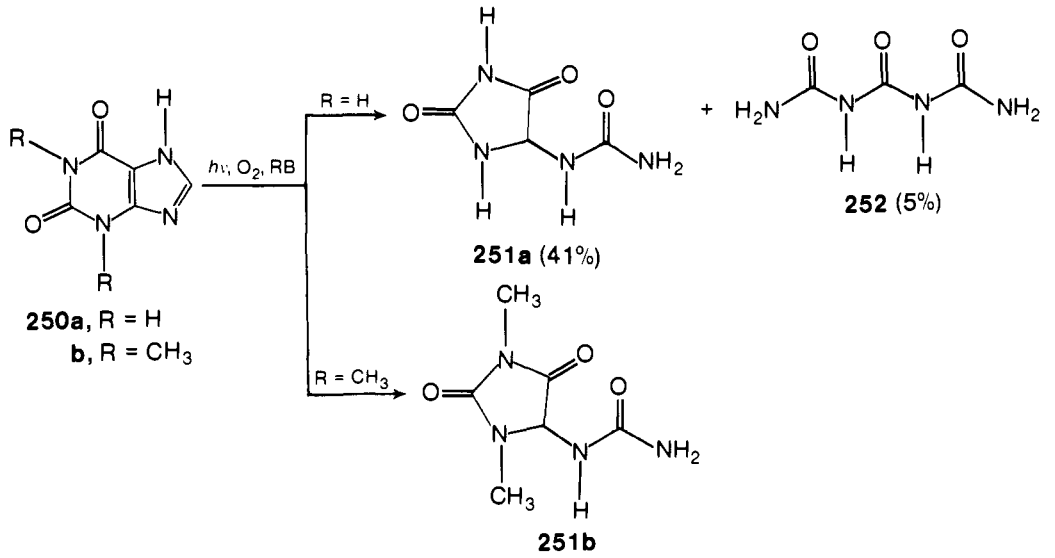
In view of the ease with which the primary photooxidation products undergo further reactions, the photooxygenations of free bases and nucleosides have resulted in complex mixtures, arising through extensive degradations.[98-104] However, it is generally agreed that the initial reaction in most of these cases involves either a 1,4- or 1,2-addition of singlet oxygen to give the corresponding endoperoxide or oxetane, respectively. These in turn undergo further transformations to give the various products. Thus, it has been found that chemically produced singlet oxygen reacts with free bases and nucleosides around pH 7 and above, and that these reactions are quenched by 1,4-diazabicyclo[2.2.2]octane (Dabco), which is a singlet oxygen quencher.[106-108] Nilsson et al.[109] have found that the reaction of singlet oxygen with guanosine monophosphate to be extremely slow in unbuffered methanol–water mixture, whereas Knowles et al.[110,111] have shown that the photooxygenation is inhibited by oxygen around pH 6.9.

Sensitized photooxygenation of several purine derivatives has been examined by several workers. When an aqueous, alkaline solution of xanthine (**250a**) is photooxygenated in presence of Rose Bengal and the reaction mixture is acidified, a mixture of products consisting of allantoin (**251a**, 41%) and triuret (**252**, 5%) is obtained (Scheme XLV).[112] The photooxygenation of theophylline (**250b**), on the other hand, gives 1,3-dimethylallantoin (**251b**) as the major product (Scheme XLV).[99] The formation of allantoin (**251a**) and 1,3-dimethylallantoin (**251b**) in the photooxygenations of **250a** and **250b** may be rationalized in terms of the cyclic peroxide **253** and its further transformations (Scheme XLVI).

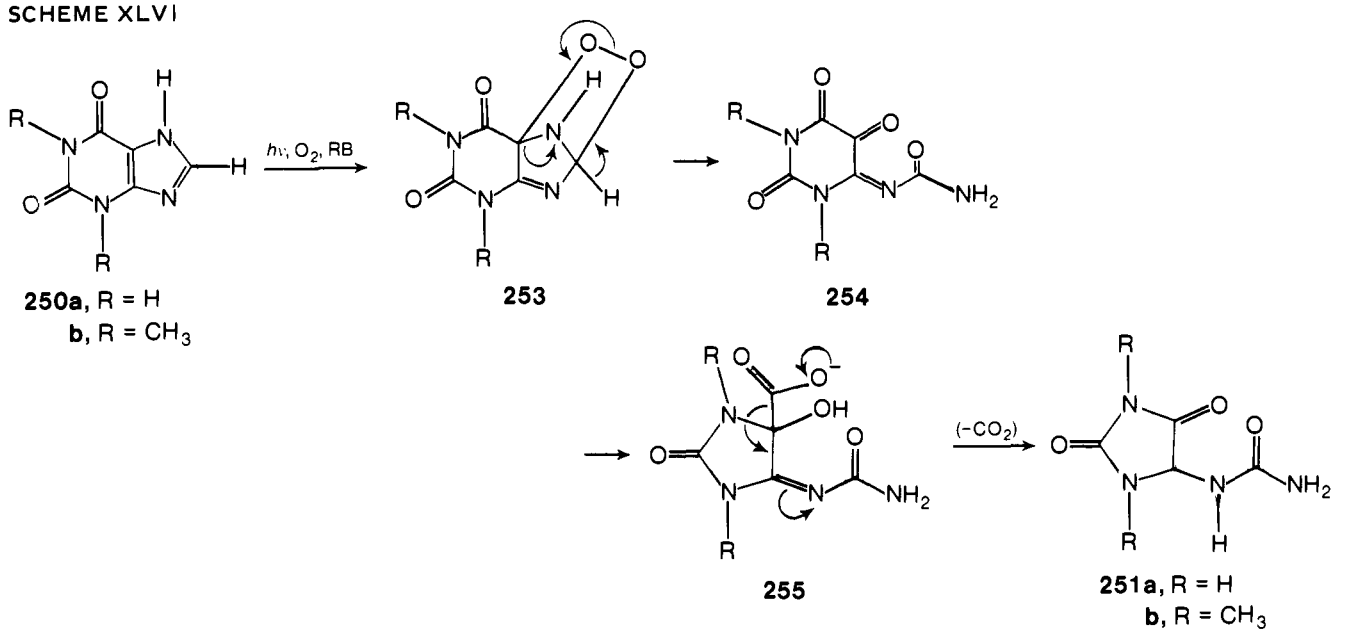
SCHEME XLIV



SCHEME XLV

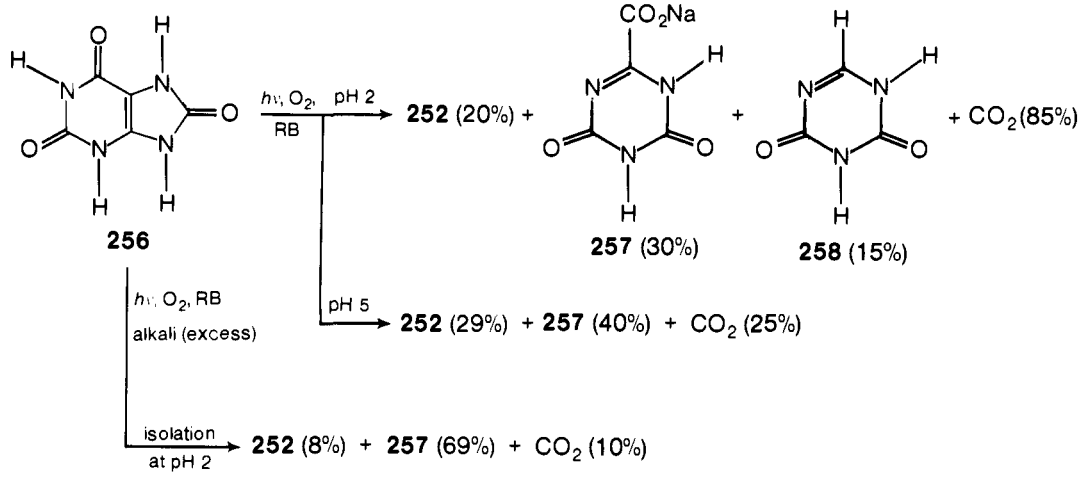


SCHEME XLVI

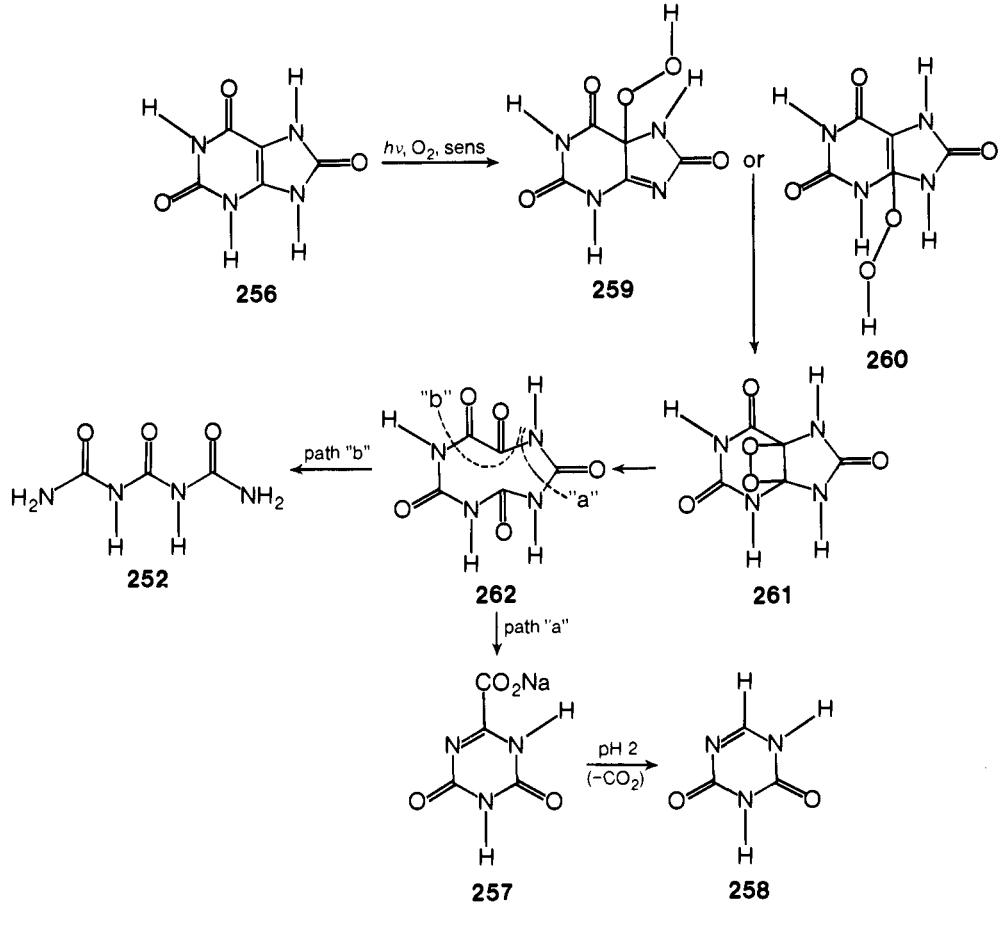


The photooxygenation of uric acid (**256**) has been found to be pH dependent. Isolation of the products at pH 2 yields a mixture of triuret (**252**, 20%), sodium oxonate (**257**, 30%), allantoxaidin (**258**, 15%), and carbon dioxide (85%).[112] At pH 5, however, the yield of sodium oxonate (**257**) increases to about 40% and none of **258** has been isolated. On the other hand, photooxy-

SCHEME XLVII

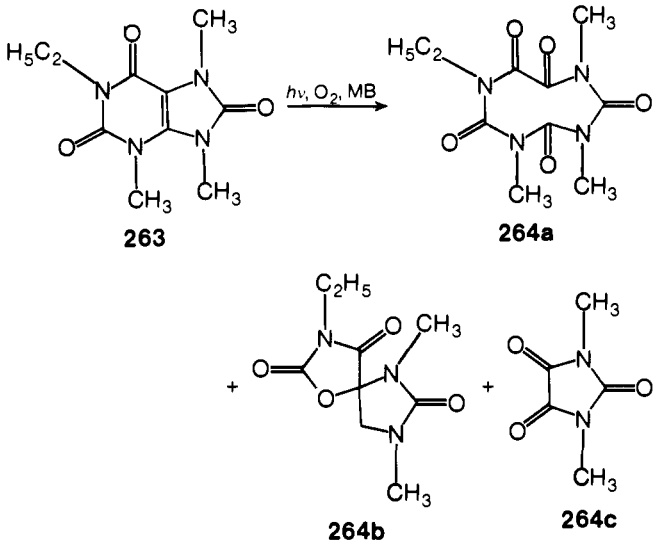


SCHEME XLVIII

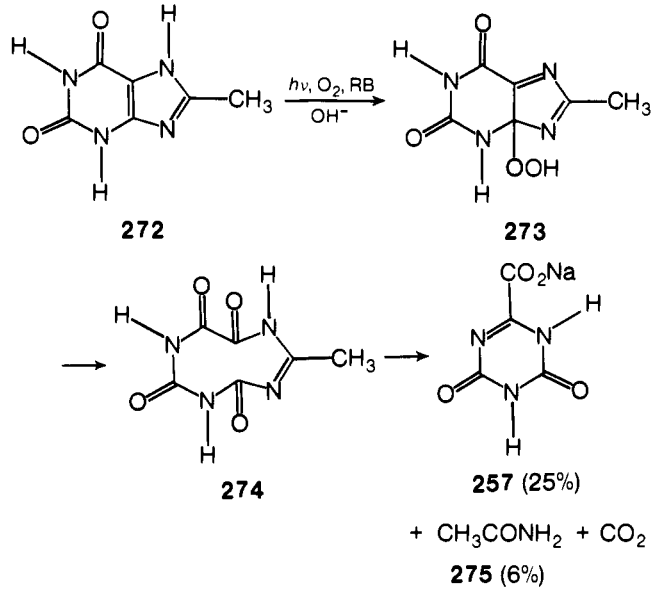


genation of **256** in the presence of a large excess of alkali, followed by the isolation of products at pH 5, after acidification with acetic acid gives a mixture of **252** (8%), **257** (69%), and carbon dioxide (10%) (Scheme XLVII). Since it is known that sodium oxonate (**257**) is converted to **258** on treatment with strong acids,[113,114] it has been inferred that **258** is formed in a secondary reaction, occurring under the acidic conditions of work-up, of the reaction mixture. The various products formed in the photooxygenation of **256** can be understood in terms of the pathway shown in Scheme XLVIII. Attack of singlet oxygen on **256** would result in the formation of the hydroperoxide **259** (or **260**). The 4,5 bond of **259** (or **260**) can be cleaved either concertedly or through the four-membered cyclic peroxide **261,** to form the nine-membered intermediate **262,** which would then be hydrolyzed to give sodium oxonate (**257**), as per path "a" and the triuret **252,** through path "b" (Scheme XLVIII). It may be mentioned in this connection that a fully N-alkylated uric acid such as 1-ethyl-**3**,7,9-trimethyluric acid (**263**), undergoes photooxygenation in presence of Methylene Blue to give the corresponding nine-membered cyclic product **264a,** along with 1,**3**-dimethyl-7-ethylcaffolide (**264b**) and 1,**3**-dimethylparabanic acid (**264c**) (Scheme XLIX).[115] Matsuura and Saito[116] have shown that the Rose Bengal sensitized photooxygenation of 1,3,7,9-tetramethyluric acid (**265**) in methanol yields a mixture of 4,5-dimethoxy-1,3,7,9-tetramethyluric acid (**268,** 35%) and allocaffeic acid (**269,** 5%). On the contrary, Methylene Blue sensitized photooxygenation of **265** in chloroform gives 1,3,7-trimethylcaffolide (**271**) as the major product (42%), along with a 7% yield of 1,3-dimethylparabanic acid (**264c**). The formation of these products in the photoxygenation of **265** has been

SCHEME XLIX



SCHEME LI



rationalized in terms of the zwitterionic intermediate **266** and its further transformations (Scheme L).[116]

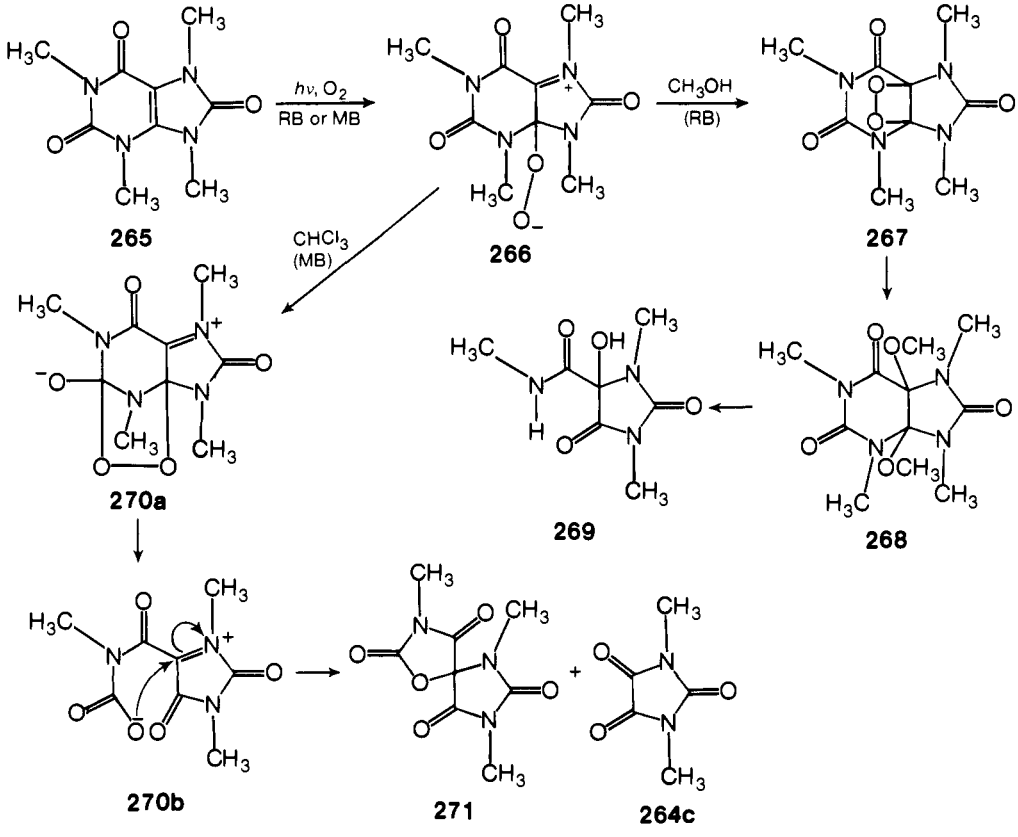
Sensitized photooxygenation of 8-methylxanthine (**272**) in the presence of 1.1 mol equiv of alkali results in a mixture of products consisting of **257** (25%), acetamide (**275,** 6%), and carbon dioxide (53%).[112] The formation of these products is readily understood in terms of the intermediates **273** and **274,** shown in Scheme LI.

Sensitized photooxygenations of 9-phenylxanthine (**276a**) in presence of Rose Bengal gives 4,5-dimethoxy-9-phenyluric acid (**280a**) in a 58% yield.[117] Similarly, 1,3-dimethyl-9-phenylxanthine (**276b**) gives 1,3-dimethyl-4,5-dimethoxy-9-phenyluric acid (**280b,** 23%) (Scheme LII).[117] Likewise, 9-phenyluric acid (**281a**) on photooxygenation gives **280a,** whereas, 1,3-dimethyl-9-phenyluric acid (**281b**) gives a mixture of **280b** and 1,3-dimethyl-4-hydroxy-5-methoxy-9-phenyluric acid (**284**).[117]

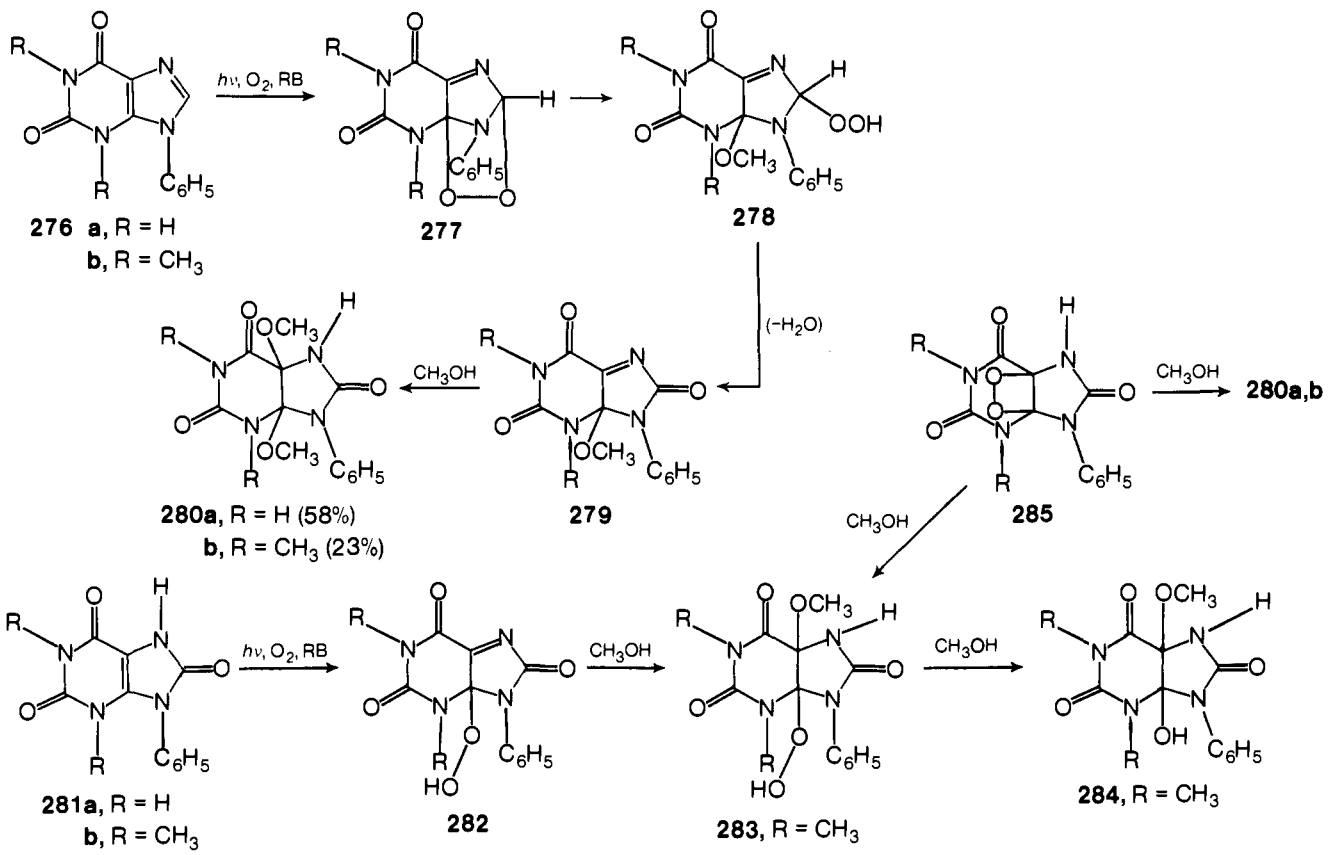
The formation of both **280a** and **280b** in the photooxygenations of **276a** and **276b** can be accounted for in terms of the endoperoxide **277,** which can then undergo subsequent transformations (Scheme LII). In contrast, the formation of both **280a** and **280b** from **281a** and **281b,** respectively, can be rationalized in terms of the hydroperoxide **282** (Scheme LII).[117]

It has been shown that 8-methoxycaffeine (**286**), on photooxygenation in alcoholic solvents, in the presence of Rose Bengal gives 1-methyl-2,2-dimethoxy-4-methylamino-3-imidazolin-5-one (**288,** 78%) along with the carbamate **287** and carbon dioxide.[118] Both the endoperoxide **289** and the hydroperoxide **290** have been invoked as intermediates in the transformation of **286** to **287** and **288** (Scheme LIII).[118]

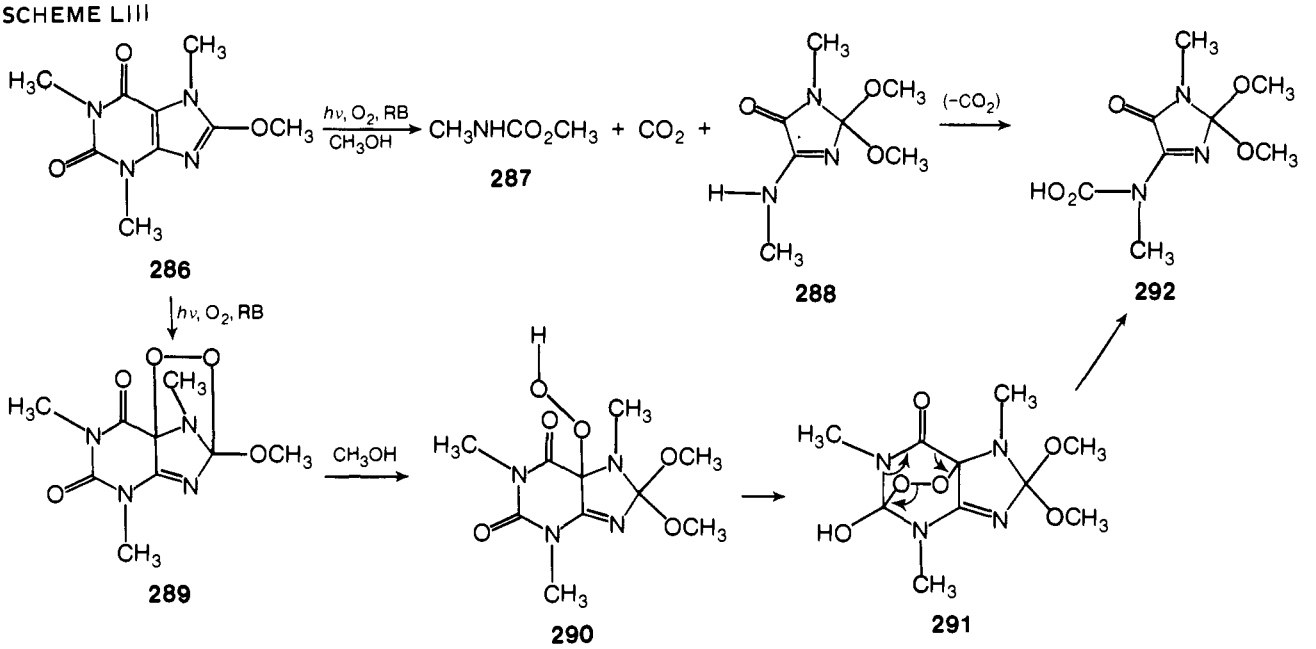
SCHEME L



SCHEME LII



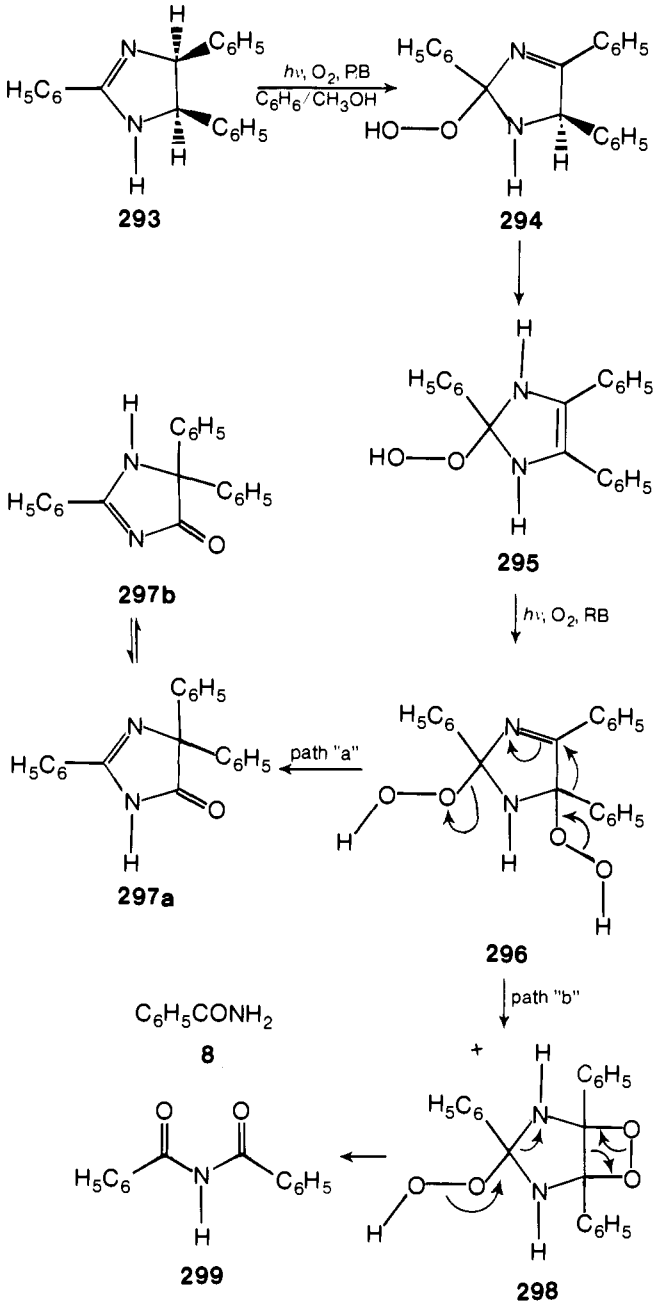
SCHEME LIII



4. Imidazolines

Recent studies have shown that imidazolines undergo photooxygenation to give a variety of products.[15] The Rose Bengal sensitized photooxygenation of *cis*-2,4,5-triphenylimidazoline (**293**), for example, gives a mixture of products consisting of 2,5,5-triphenylimidazolin-4-one (**297**, 7%), dibenzamide (**299**, 8%), and benzamide (**8**, 21%). The formation of these different products is understood in terms of the reaction pathway shown in Scheme LIV. It has been assumed that **293** undergoes an "ene" type of reaction with singlet oxygen to give the hydroperoxy intermediate **294**, which can be subsequently transformed to the bishydroperoxy intermediate **296**, through further reaction with singlet oxygen. The intermediate **296** can undergo a fragmentation, accompanied by a rearrangement involving a phenyl group migration as per path "a" shown in Scheme LIV, to give the imidazolone **297**, which can exist in equilibrium between its two tautomeric forms, **297a** and **297b**. An alternative mode of transformation is through path "b", which involves the formation of an intermediate **298**, which can undergo fragmentation to dibenzamide (**299**) and benzamide (**8**) (Scheme LIV).

SCHEME LIV



C. Five-Membered Heterocycles Containing One Oxygen and One Nitrogen Atom

1. Oxazoles

Oxazoles are known to undergo photooxygenation reactions leading to a variety of products, depending on the nature of the substrates and the reaction conditions.[119-125] The photooxygenation of 2-methyl-5-phenyloxazole (**300**) in methanol, for example, gives a mixture of benzoic acid (**5**, 83%) and α-acetamido-α-methoxyacetophenone (**301**, 10%) (Scheme LV).[119] It has been assumed that the ozonide-like peroxide **302** is involved as the initial intermediate in this reaction, which is then transformed to **301**, through the pathway indicated in Scheme LV. A different mode of reaction, however, has been observed in the case of 2,4,5-triphenyloxazole (**305**), which gives the tribenzoyl derivative **308** when photooxygenated either in methanol or chloroform (Scheme LV).[119] It has been suggested that the peroxy intermediate **306**, undergoes rearrangement to give *N*-benzoylisoimide (**307**), which is then transformed to **308** (Scheme LV). Similarly, the reactions of both 2-methyl-4,5-diphenyloxazole (**309a**) and 4-methyl-2,5-diphenyloxazole (**309b**) give rise to dibenzoylacetamide (**310**), in each case.[119,120]

Oxazoles with no substituents at the 4 position could lead to *N*-formyl derivatives on photooxygenation. Thus, it has been observed that 2,5-diphenyloxazole (**311**) gives the *N*-formyl derivative **312** (Scheme LVI).[121,122]

In the case of fused-ring oxazoles, isoimides similar to **307** have been isolated, although they have not been obtained in the case of simple oxazoles. Thus, the photooxygenation of **313** in methanol has been shown to give exclusively **314** (65%) (Scheme LVI).[12,123,124]

The photooxygenation of a fused-ring oxazole derivative such as **315**, which is unsubstituted in position 2, appears to proceed through the peroxy intermediate **316**, which subsequently undergoes rearrangement to form the cyano anhydride **317**. Loss of carbon monoxide from **317** would give the ω-cyanocarboxylic acid **318**, which has been isolated as the exclusive product in this reaction (Scheme LVI).[123]

Graziano et al.[126] have reported the effect of alkoxy substituents on the dye-sensitized photooxygenation of oxazoles. Thus, the photooxygenations of 2-phenyl-4-methyl-5-methoxyoxazole (**319a**), 2-phenyl-4-methyl-5-ethoxyoxazole (**319b**), and 2-ethoxy-4-methoxy-5-phenyloxazole (**319c**) give the corresponding diacylcarbamates (**324a-c**) in good yields. Further, it has been observed that under appropriate conditions, 3*H*-1,2,4-dioxazoles (**321a-c**) are formed. It has been suggested that the 3*H*-1,2,4-dioxazoles in these oxidations are formed through the peroxirane intermediates **320**, formed through a 1,2-addition of singlet oxygen to the starting oxazoles (**319a-c**), analogous to the addition of singlet oxygen to alkenes or dienes[127,128] (Scheme LVII). Irradiation of the dioxazole **321a** under conditions similar to the photooxygenation reactions of **319a** gives a small amount of **324a**, indicating thereby that **321** could be a possible intermediate in the transformation of **319** to **324**. However, the low yields of **324** from the irradiation of **321** would suggest that alternative pathways may likely be involved for the conversion of **319** to **324**. These authors have suggested that an alternative pathway for the photooxygenation of **319** involves the formation of the endoperoxide **322**, formed through a 1,4-addition mode, and its subsequent transformation to **324** (Scheme LVII). In addition to **324**, the photooxygenations of the alkoxyoxazoles **319a-c** give small amounts of the keto imines **325a-c**. However, the actual mode of formation of **325** in these reactions is not clearly understood.

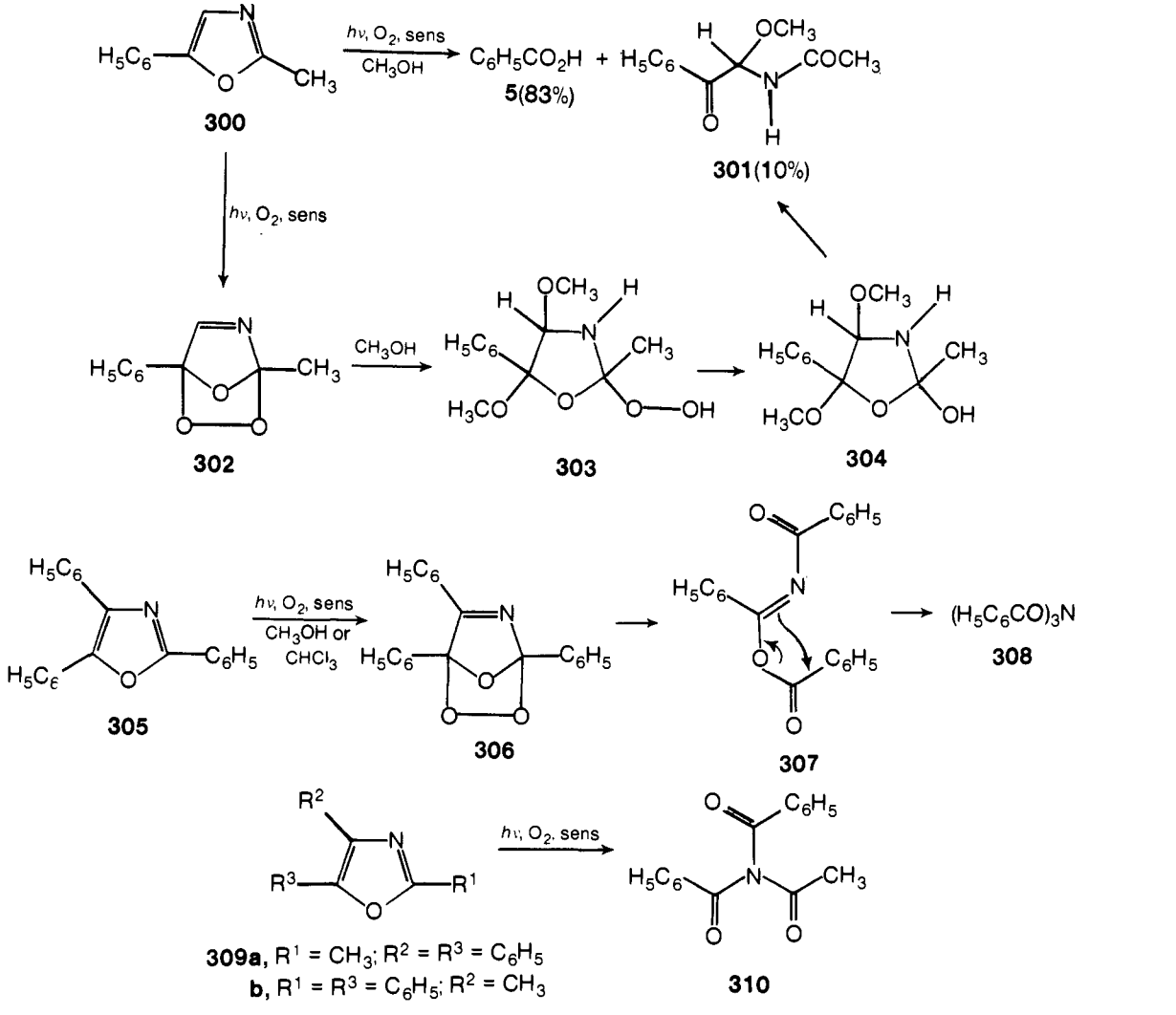
Subsequent studies by Graziano et al.[129] have shown that 1,2,4-dioxazoles (**321a,b,d-i**) are obtained in excellent yields, when the photooxygenations of **319a,b,d-i** are carried out in the presence of small amounts of Dabco (Scheme LVIII). However, the exact role of Dabco in these reactions has not been clearly understood.

2. Oxazolines and Oxazolinones

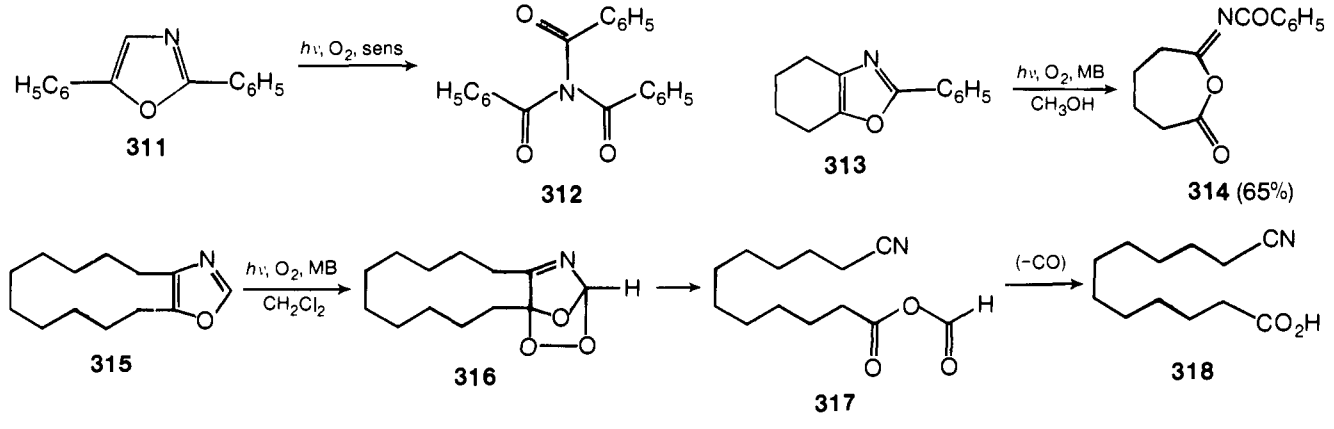
Tsuge et al.[130] have reported that the sensitized photooxygenation of **3**,4,5-triphenyl-4-oxazolin-2-one (**326**) gives a mixture of products consisting of benzoic acid (**5**), benzanilide (**6**), and *o*- and *p*-benzamidobenzophenones (**332** and **333**) (Scheme LIX). It has been assumed that singlet oxygen reacts with **326** to give the zwitterionic intermediate **327**, which then rearranges to the dioxetane intermediate **328**. Loss of carbon dioxide from **328** could result in **329**, whereas the further fragmentation of either **328** or **329** could give rise to the various products that have been observed in the photooxygenation of **326** (Scheme LIX).[130]

Quite recently, it has been shown that Rose Bengal sensitized photooxygenation of an oxazoline derivative such as 4-benzoyl-3-cyclohexyl-5- (*cis*-1,2-diphenylvinyl)-2-phenyl-4-oxazoline (**334**) in a mixture of benzene and methanol gives a mixture of products consisting of *N*-cyclohexylbenzamide (**7**, 19%) and benzoic acid (**5**, 52%).[15] The formation of both **7** and **5** from **334**

SCHEME LV



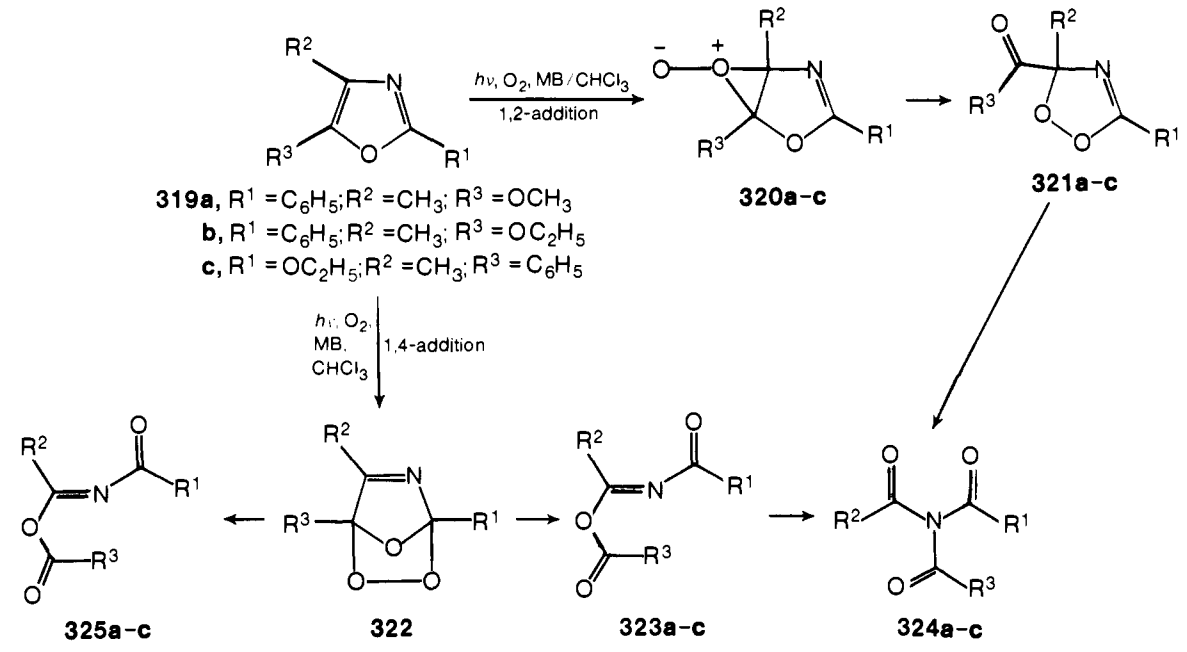
SCHEME LVI



may be understood in terms of the fragmentations of the initially formed dioxazoline intermediate **336** (Scheme LX).

Recent studies have shown that the sensitized photooxygenation of Δ^2-oxazolin-5-one (**337**) in methanol for $\frac{1}{2}$ h, for example, gives a mixture of dibenzamide (**299**, 40%) and benzamide (**8**, 49%). However, when the photooxygenation of **337** is carried out for $\frac{1}{4}$ h, under analogous conditions, a 44% yield of bis[4,4-(2,4-diphenyl-Δ^2-oxazolin-5-one)] (**338**) is formed, along with a small amount of benzamide (**8**, 28%) (Scheme LXI).[131] The formation of the different products in the photooxygenation of **337** can be rationalized in terms of the different pathways shown in Scheme LXII. It has been assumed that one of the possible transformations of **337** will be through its initial conversion to the tautomeric oxazolium 5-oxide **339**, which in turn reacts with singlet oxygen to give the endoperoxide **340** as per path "a" in Scheme LXII. Subsequent loss of carbon dioxide from **340** will result in the formation of dibenzamide (**299**). An alternative pathway (path "b") for the transformation of **337** will be through the initial loss of carbon monoxide to give *N*-benzylidenebenzamide (**342**), which on hydrolysis gives benzamide

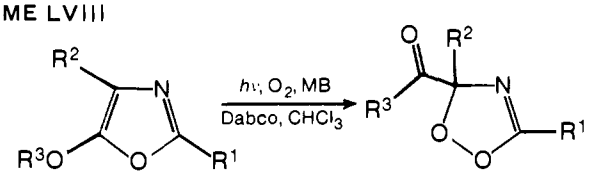
SCHEME LVII



319a, $R^1 = C_6H_5$; $R^2 = CH_3$; $R^3 = OCH_3$
b, $R^1 = C_6H_5$; $R^2 = CH_3$; $R^3 = OC_2H_5$
c, $R^1 = OC_2H_5$; $R^2 = CH_3$; $R^3 = C_6H_5$

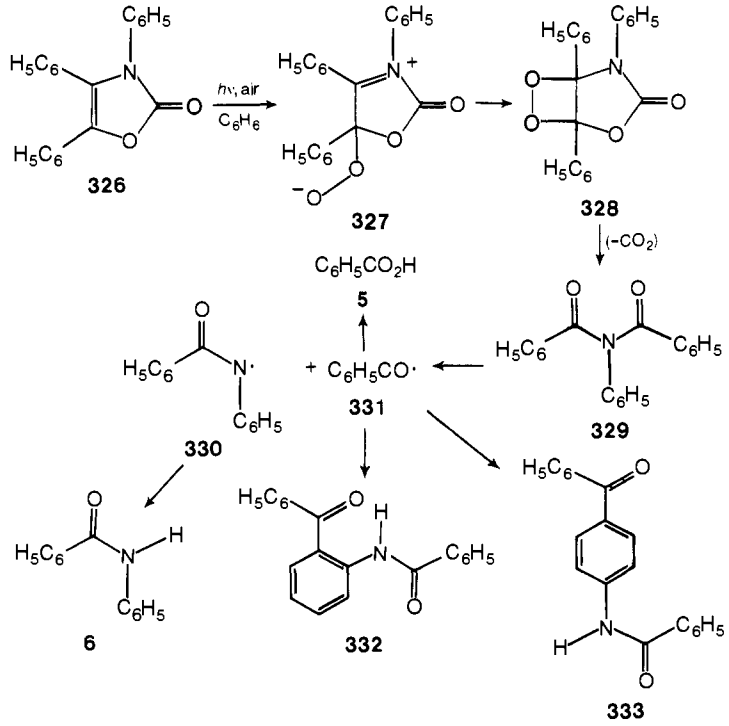
320a-c **321a-c** **322** **323a-c** **324a-c** **325a-c**

SCHEME LVIII



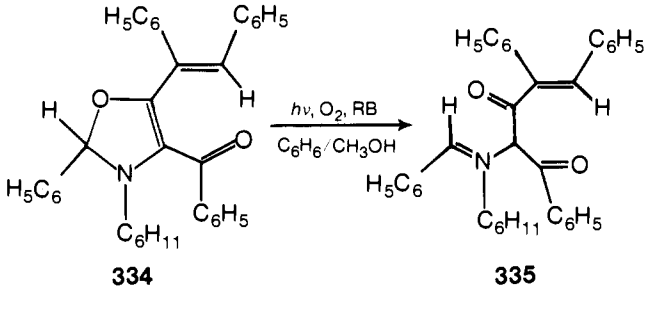
319a, $R^1 = C_6H_5$; $R^2 = R^3 = CH_3$	**321a** (97%)
b, $R^1 = C_6H_5$; $R^2 = CH_3$; $R^3 = C_2H_5$	**b** (98%)
d, $R^1 = C_6H_5$; $R^2 = i\text{-}C_3H_7$; $R^3 = CH_3$	**d** (92%)
e, $R^1 = C_6H_5$; $R^2 = CH_2C_6H_5$; $R^3 = CH_3$	**e** (85%)
f, $R^1 = R^2 = C_6H_5$; $R^3 = CH_3$	**f** (90%)
g, $R^1 = CH_2C_6H_5$; $R^2 = R^3 = CH_3$	**g** (90%)
h, $R^1 = n\text{-}C_5H_{11}$; $R^2 = R^3 = CH_3$	**h** (73%)
i, $R^1 = CH_3$; $R^2 = CO_2CH_3$; $R^3 = CH_3$	**i** (92%)

SCHEME LIX

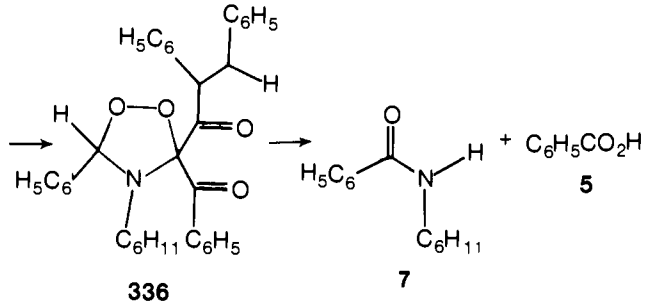


326 **327** **328** **329** **330** **331** **332** **333**

SCHEME LX

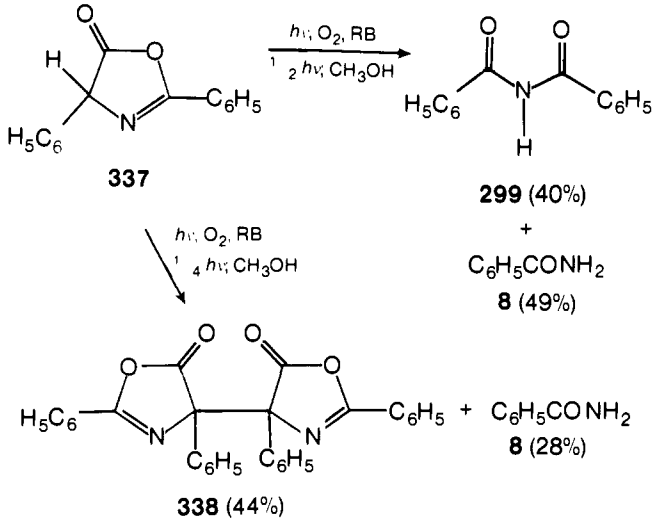


334 **335**



336 **7**

SCHEME LXI

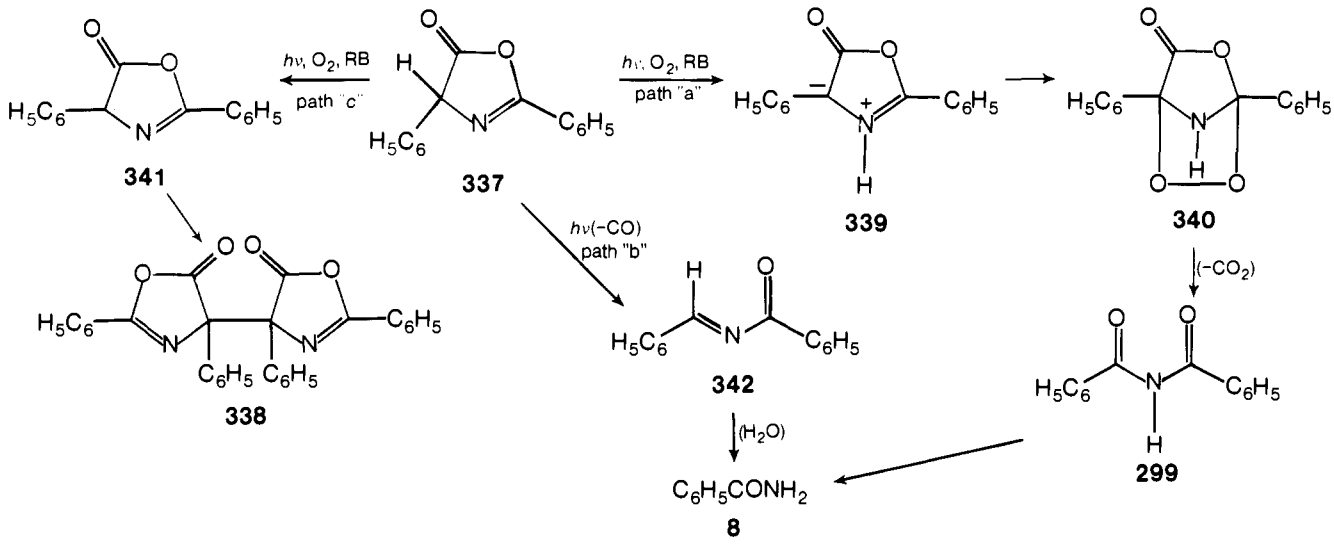


337

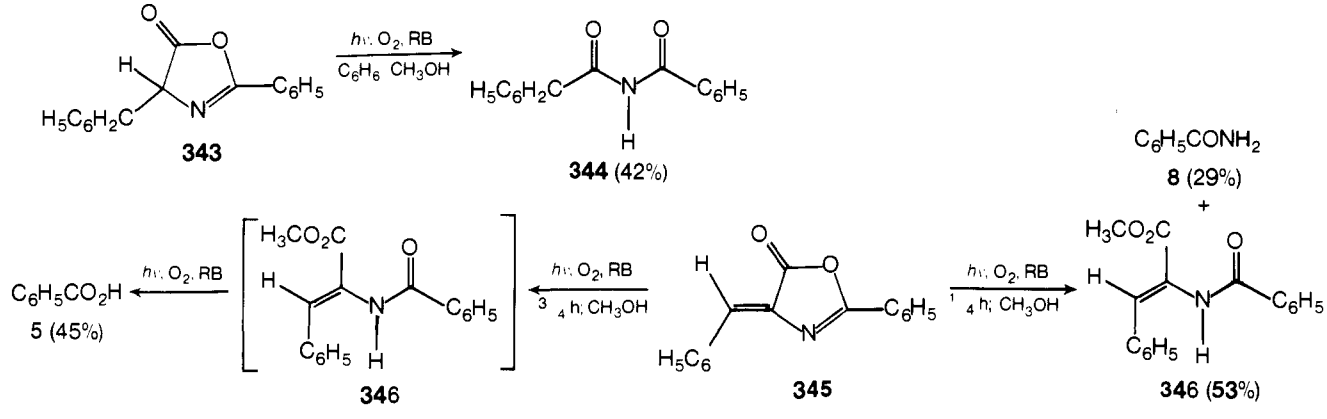
299 (40%) + $C_6H_5CONH_2$ **8** (49%)

338 (44%) + $C_6H_5CONH_2$ **8** (28%)

SCHEME LXII



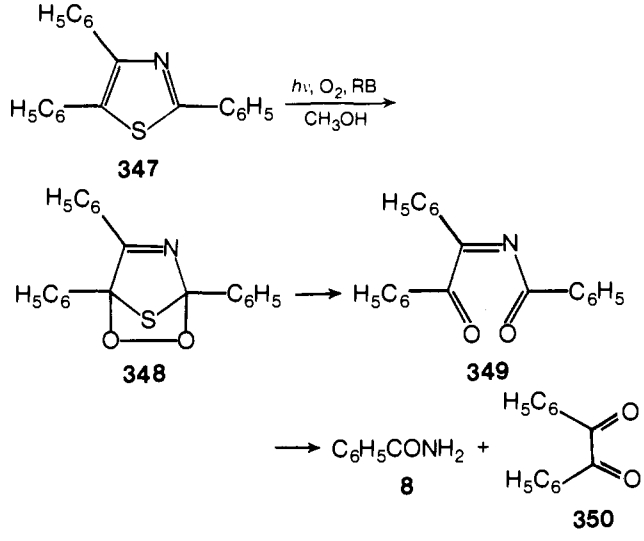
SCHEME LXIII



(8). The formation of the bisoxazolinone **338,** however, can be rationalized in terms of the radical intermediate **341,** formed through the abstraction of a hydrogen atom from the C_4 position of **337** by molecular oxygen (Scheme LXII).

Similarly, the photooxygenation of 4-benzyl-2-phenyl-Δ^2-oxazolin-5-one (**343**) in a mixture of benzene and methanol gives a 42% yield of *N*-benzoylphenylacetamide (**344**) as the only isolable product (Scheme LXIII).[131] In contrast, the photooxygenation of 4-benzylidene-2-phenyl-Δ^2-oxazolin-5-one (**345**) in methanol for $^1/_4$ h gives a mixture of methyl α-benzamidocinnamate (**346,** 53%) and benzamide (**8,** 29%). When the photooxygenation of **345,** however, is carried out in methanol for $^3/_4$ h, a 45% yield of benzoic acid is isolated. It has been suggested that **346** in these reactions arises through the simple addition of methanol to **345,** whereas other products like benzoic acid and benzamide arise through the photooxygenation of **346** (Scheme LXIII).[131]

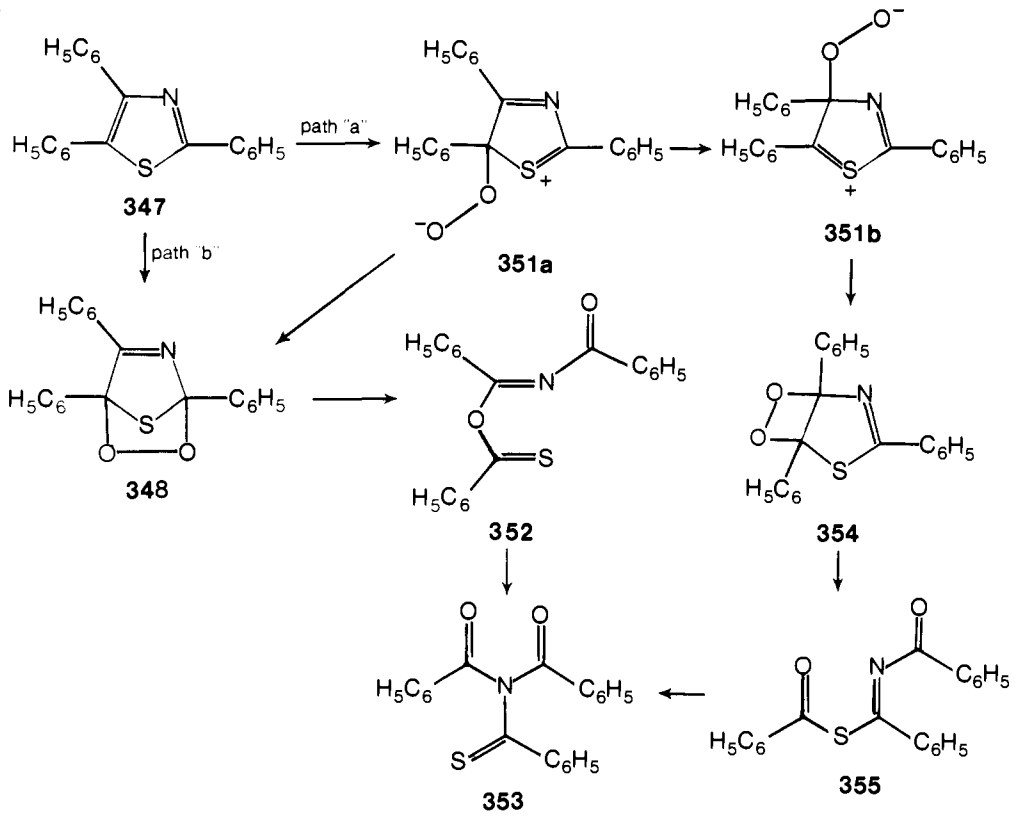
SCHEME LXIV



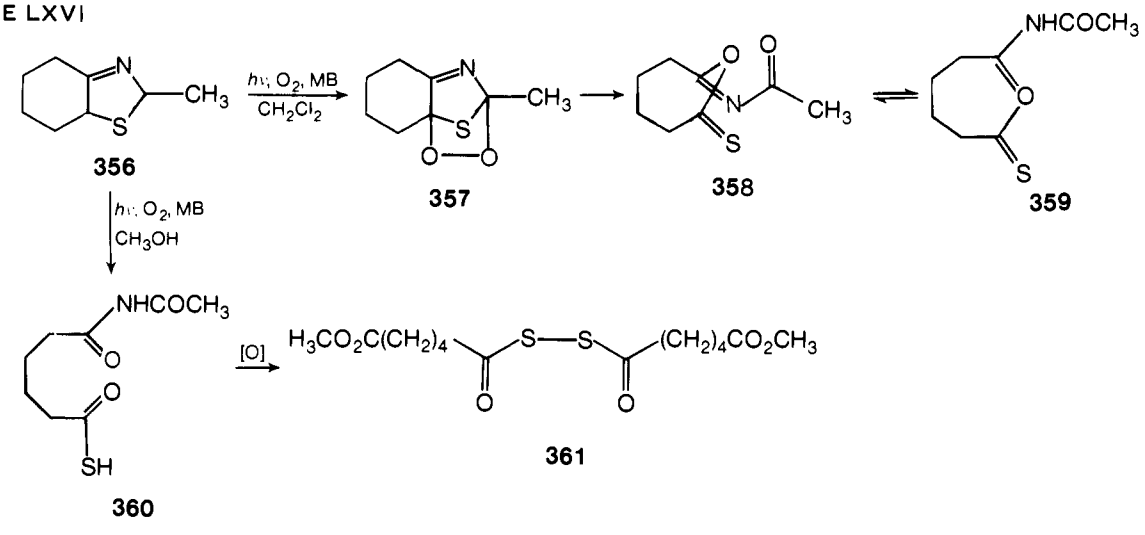
D. Five-Membered Heterocycles Containing One Sulfur and One Nitrogen Atom

Matsuura and Saito[132] have examined the photooxygenation reactions of some thiazoles, in connection with their studies on the photodynamic action of biological systems. The photooxygenation of 2,4,5-triphenylthiazole (**347**) in methanol in the presence of Rose Bengal, for example, gives a mixture of products consisting of benzil (**350**) and benzamide (**8**) (Scheme LXIV). In contrast, the photooxygenation of **347** in chloroform using Methylene Blue as sensitizer gives *N,N*-dibenzoylthiobenzamide (**353**) as the only product. The formation of both benzil (**350**) and benzamide in the photooxygenation of **347** has been rationalized in terms of the endoperoxide **348** and its fragmentation product, **349** (Scheme LXIV). The formation of *N,N*-dibenzoylthiobenzamide (**353**), however, can be rationalized in terms of any one of the pathways shown in Scheme LXV. As per path "a", for example, it has been assumed that the initially formed zwitterionic intermediate **351** is converted to the dioxetane derivative **354,** which then fragments to **355.** A simple rearrangment of **355** under the reaction conditions will lead to **353.** The alternative pathway (path "b") involves the formation

SCHEME LXV



SCHEME LXVI



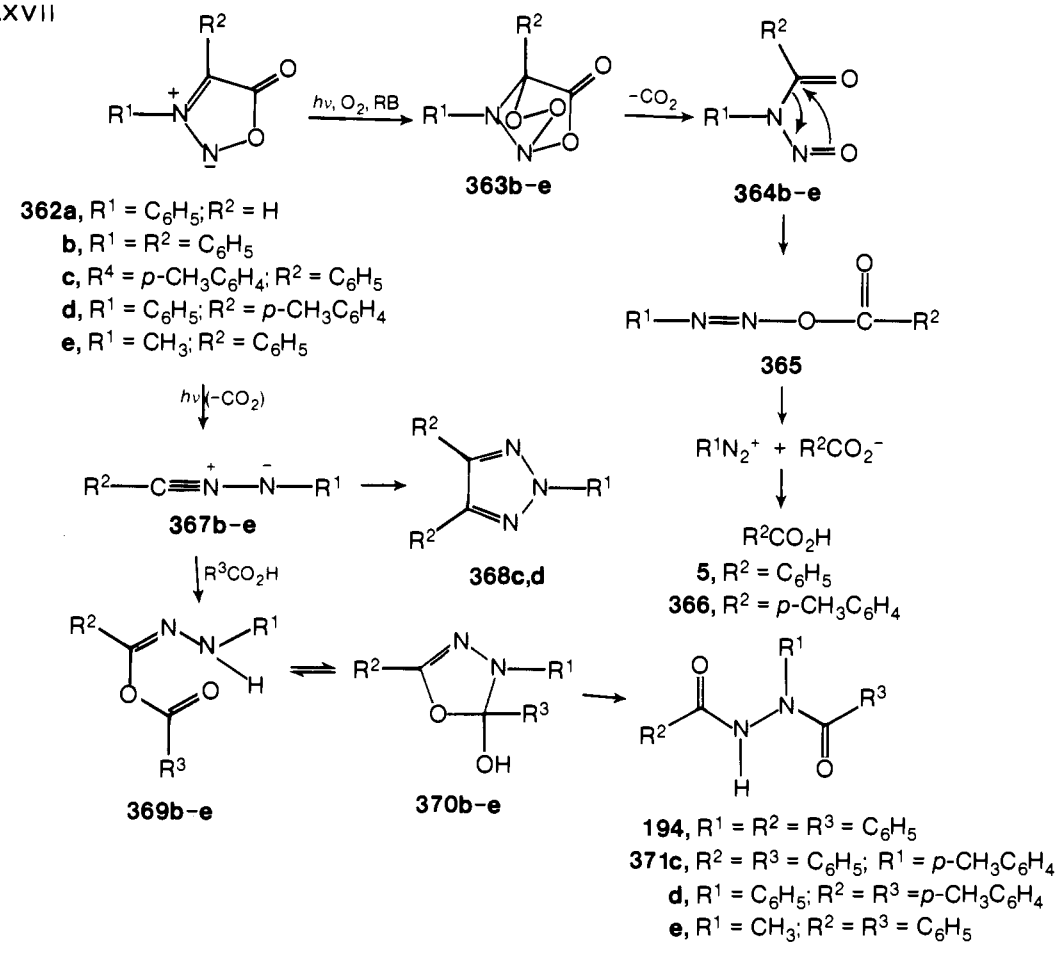
of the endoperoxide **348,** which can cleave to **352,** and subsequent rearrangement of **352** will lead to **353** (Scheme LXV).

Wasserman and Lenz[133] have reported that the Methylene Blue sensitized photooxygenation of 4,5,6,7-tetrahydro-2-methylbenzothiazole (**356**) in dichloromethane gives a 67% yield of **359,** whereas the photoxygenation of **356** in methanol gives the diacyl sulfide **361** (Scheme LXVI). The formation of **359** in this reaction may be explained in terms of the endoperoxide **357** and its rearrangement product **358,** as shown in Scheme LXVI. The formation of **361,** however, can be understood in terms of the initial formation of the thioisoimide **358** or its tautomer, **359,** which is then converted to **360.** Air oxidation of **360,** followed by methanolysis of the product, will result in **361.**[133]

E. Five-Membered Heterocycles Containing One Oxygen and Two Nitrogen Atoms

The photooxygenation of sydnones has been studied quite recently and it has been observed that several products are formed in these reactions.[134] The photooxygenation of 3,4-diphenylsydnone (**362b**), for example, gives a 25% yield of α,β-dibenzoylphenylhydrazine (**194**), whereas the photooxygenation of 4-phenyl-3-*p*-tolylsydnone (**362c**) under similar conditions gives a mixture of 4,5-diphenyl-2-*p*-tolyl-1,2,3-triazole (**368c,** 8%) and α,β-dibenzoyl-*p*-tolylhydrazine (**371c,** 8%). Under analogous conditions, **3**-phenyl-4-*p*-tolylsydnone (**362d**) gives a mixture of products consisting of α,β-di(*p*-toluyl)-phenylhydrazine (**371d,** 10%) and 2-phenyl-4,5-di(*p*-tolyl)-1,2,**3**-triazole (**368d,** 1%). Similarly, the photooxygenation of 3-methyl-4-phenylsydnone (**362e**) in methanol gives a mixture of benzoic acid (**5,** 10%) and α,β-dibenzoylmethylhydrazine (**371e,** 5%). In contrast, the attempted photooxygenation of 3-phenylsydnone (**362a**) in methanol did not lead to any isolable product. A probable route to the formation of the different products in the photooxygenation of the various sydnones **362b–e** is shown in Scheme LXVII. It has been assumed that singlet oxygen adds to sydnones through a 1,3-dipolar mode to give the corresponding endoperoxides **363b–e,** which subsequently lose carbon dioxide to give the *N*-nitroso derivatives **364b–e.** Intramolecular rearrangements of **364b–e** will lead to

SCHEME LXVII



the corresponding diazotates (**365**) which will then decompose to give the corresponding carboxylic acids. An independent mode of transformation of **362b-e** will be their conversion to the corresponding nitrile imines, **367b-e**. The reaction of these nitrile imines (**367b-e**) with the appropriate carboxylic acids (**5** or **366**) will result in the formation of the imido esters, **369b-e**. The rearrangement of these imido esters will give the corresponding diaroylhydrazines (**194, 371c-e**). The formation of the triazoles **368c,d** in these reactions, however, has been rationalized in terms of the further photolysis of the corresponding nitrile imines, through known pathways.[135]

V. Photooxygenation of Six-Membered Heterocycles

A. Six-Membered Heterocycles Containing One Nitrogen Atom

The photooxygenations of several pyridinium betaines have been examined by Takeshita et al.[136] who have shown that a variety of products are formed in these reactions. The Methylene Blue sensitized photooxygenation of *N*-methylpyridinium 3-oxide **372a** in chloroform, for example, gives a mixture of products consisting of *N*-methylmaleimide (**373a,** 3.8%) and 5-(*N*-methylformamido)-2(5*H*)-furanone (**374a,** 26%), whereas irradiation of **372a** in ethanol gives a mixture of 3-hydroxy-*N*-methyl-α-pyridone (**375**), diethyl maleate (**379a**), diethyl fumarate (**379b**), and ethyl *N*-methyloxamate (**377a**). On the other hand, the photooxygenation of a chloroform solution of *N*-benzylpyridinium 3-oxide (**372b**) gives a mixture of *N*-benzylmaleimide (**373b,** 1%), *N*-benzylformamide (**376,** 12%), and 5-(*N*-benzylformamido)-2(5*H*)-furanone (**374b,** 9.3%). When the photooxygenation of **372b** has been carried out in ethanol, however, the products formed include **373b** (2%), **376** (21%), **374b** (14%), ethyl *N*-benzyloxamate (**377b,** 53%), and ethyl *N*-benzylcarbamate (**378,** 8.7%) (Scheme LXVIII). In contrast to the reactions of betaines **372a** and **372b,** 3-hydroxypyridine (**372c**) does not react with singlet oxygen in chloroform solution. However, when the reaction of **372c** has been carried out in ethanol, a mixture of products consisting of diethyl maleate (**379a**), ethyl oxamate (**377c**), and diethyl oxalate (**380**) is obtained (Scheme LXVIII).[136] The formation of the various products in the sensitized photooxygenation of the pyridinium betaines **372a-c** has been rationalized in terms of the pathways shown in Scheme LXIX.

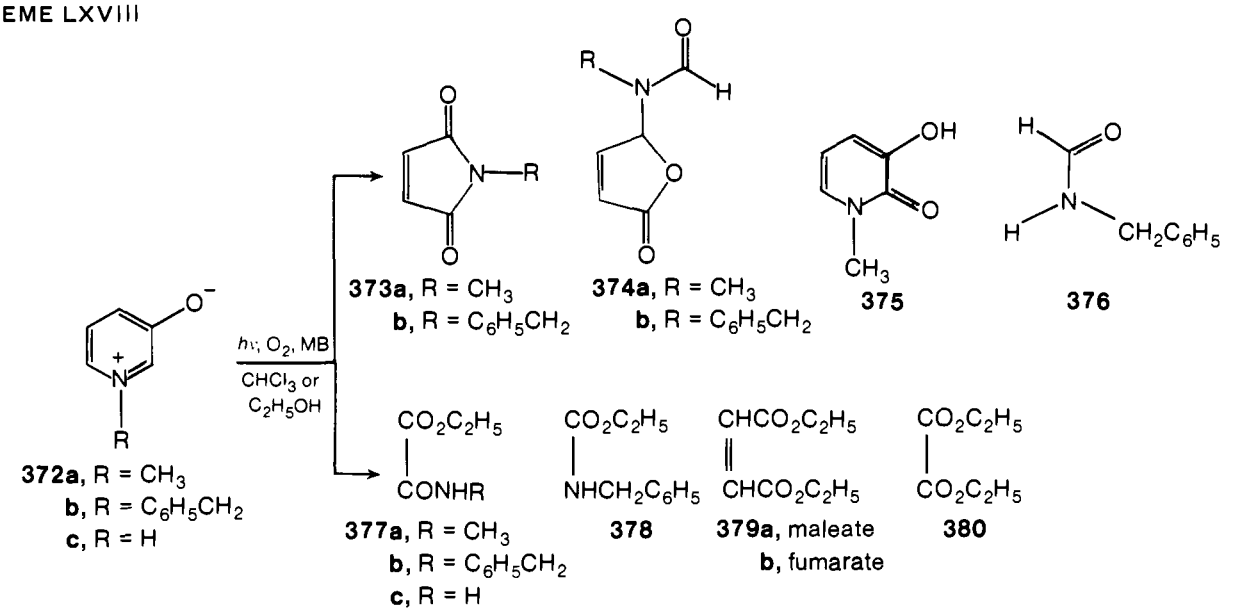
Quite recently, Tamura et al.[137] have shown that the photooxygenation of 5-methoxy-1-methylpyridinium **3**-oxide (**391**) in ethanol at room temperature leads to the formation of a 49% yield of the trione **393.** It appears that in this case, singlet oxygen adds to the starting betaine (**391**) by a 1,**3**-dipolar mode to give the endoperoxide **392,** which then cleaves to give **393** (Scheme LXX). It is interesting to note that when the 6 position of the pyridine ring is substituted by a phenyl group as in the case of **394,** the hydroxy dione **396** is formed, probably through the intermediate **395** (Scheme LXX).[137]

Photooxygenation of polynuclear heteroaromatics such as **397** and **399** gives the corresponding 9,10-endoperoxides **398** and **400,** respectively (Scheme LXXI).[6,138] Some of these peroxides such as **400** on heating liberate singlet oxygen and give rise to the starting aromatic hydrocarbon,[138] analogous to the decomposition of 9,10-diphenylanthracene 9,10-peroxide[94] and certain alkyl-substituted naphthalene 1,4-peroxides.[139]

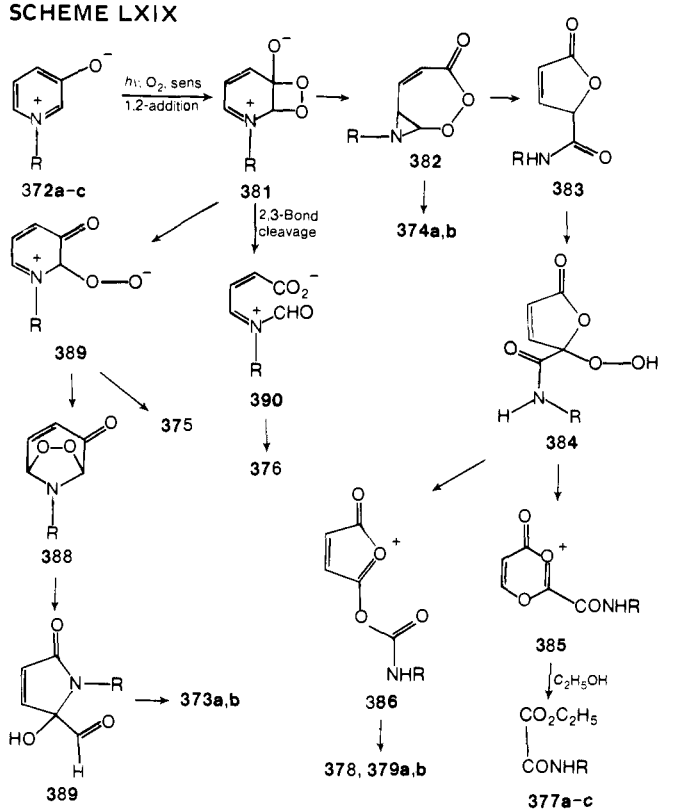
B. Six-Membered Heterocycles Containing Two Nitrogen Atoms

A variety of substituted pyrazines and pyrimidines are known to react with singlet oxygen to form endoperoxides.[140] Irradiation of an oxygenated solution of 2,5-dibenzyl-**3**,6-diethoxypyrazine (**401a**) in dichloromethane, in the presence of Methylene Blue,

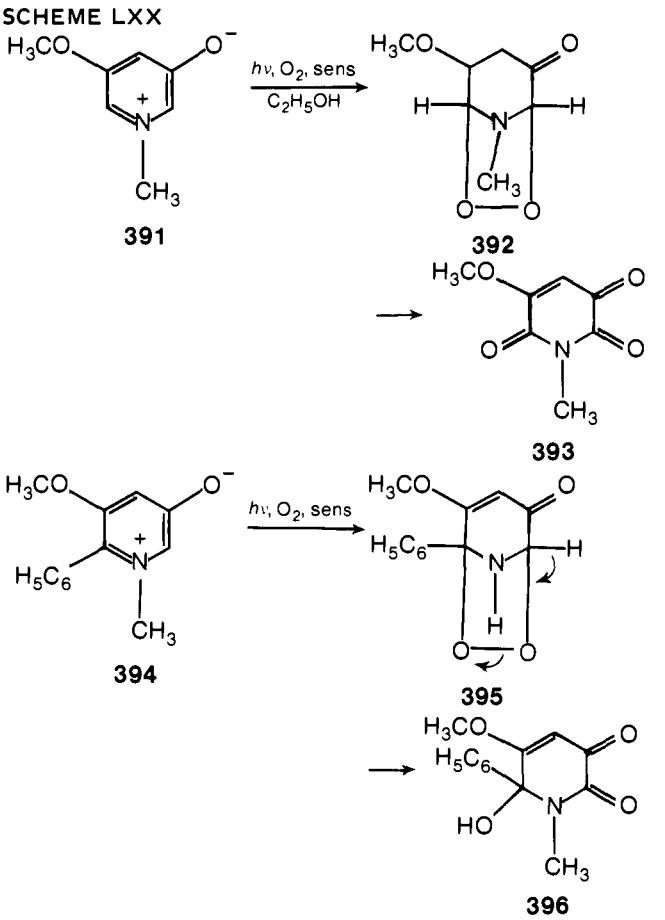
SCHEME LXVIII



SCHEME LXIX



SCHEME LXX



for example, gives a nearly quantitative yield of the stable peroxide **402a** (Scheme LXXII). Similarly, photooxygenations of the pyrazines **401b** and **401c** give the corresponding peroxy derivatives **403** and **402b**, respectively (Scheme LXXII).[140]

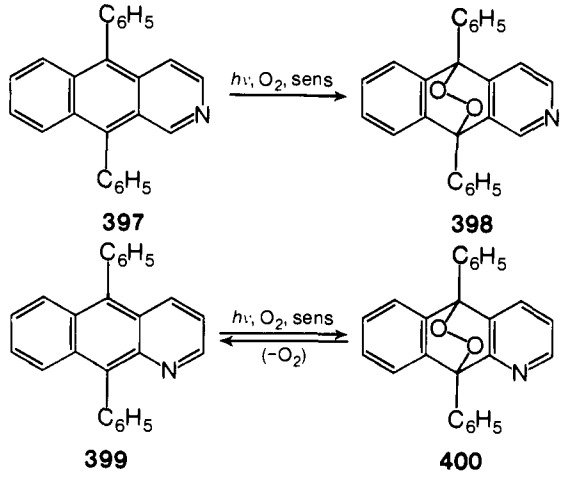
Pyrimidines have been shown to behave like pyrazines, as far as their photooxygenation reactions are concerned. Thus, it has been observed that the pyrimidines **404a** and **404b** give the corresponding endoperoxides **405a** and **405b**, respectively (Scheme LXXII).[140]

Sensitized photooxygenation of diphenyluracil (**406**) in liquid ammonia at −60 °C has been reported to give an unstable peroxy intermediate **407**, which on warming fragments to give **408** (Scheme LXXIII).[141]

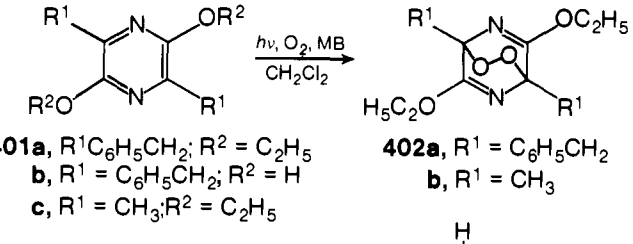
Just recently, it has been shown that the Rose Bengal sensitized photooxygenations of a dihydropyrazine derivative such as 2,3-dihydro-5,6-diphenylpyrazine (**409**) in a mixture of methanol and benzene leads to the formation of 1,3-dibenzoylurea (**224**) (Scheme LXXIV).[15] It has been suggested that under photochemical conditions, **409** is initially converted to 1-methyl-4,5-diphenylimidazole (**413**).[142] Subsequent photooxygenation of **412** leads to the 1,3-dibenzoylurea (**224**), presumably through the intermediates **413–418** as shown in Scheme LXXIV.[15,143–145] In support of this mechanism, it has been shown that the photooxygenations of both 1-methyl-4,5-diphenylimidazole (**412**) and 4,5-diphenylimidazole (**413**), under analogous conditions, give rise to 1,3-dibenzoylurea (**224**).[15]

The photooxygenation of a polynuclear heteroaromatic system such as **419** is reported to give the corresponding 9,10-

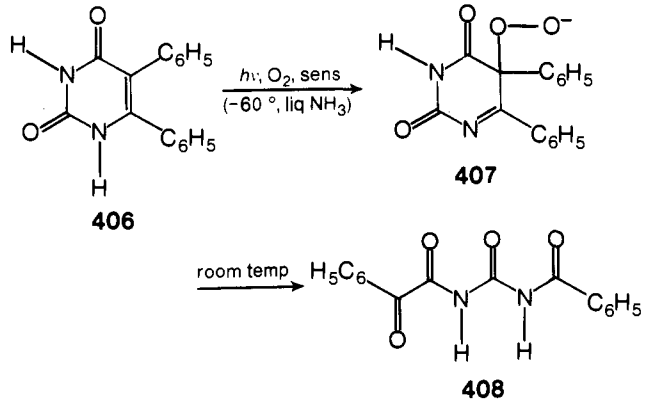
SCHEME LXXI



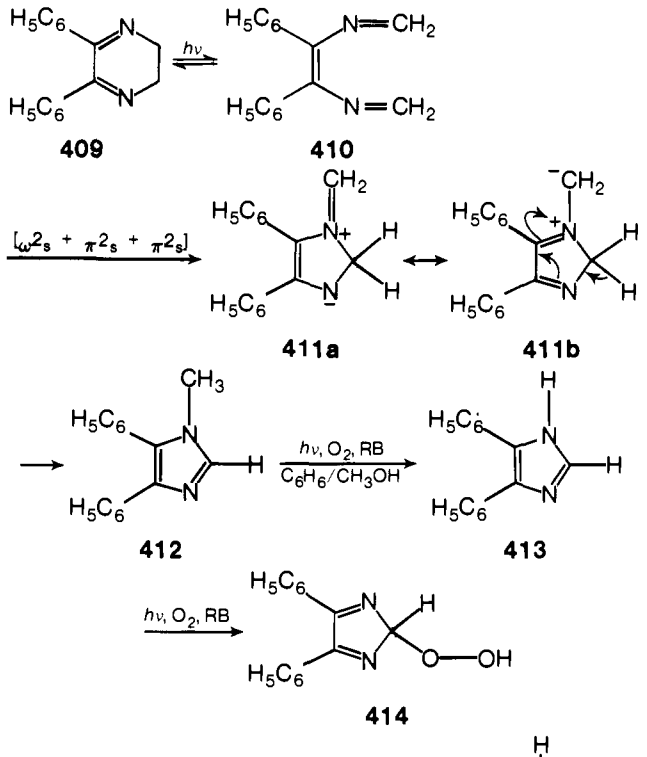
SCHEME LXXII



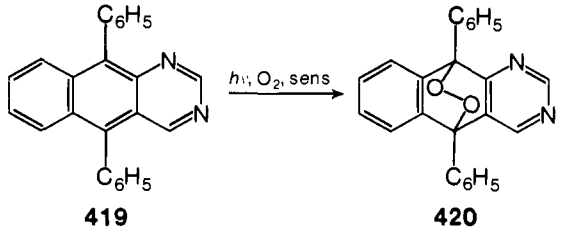
SCHEME LXXIII



SCHEME LXXIV



SCHEME LXXV



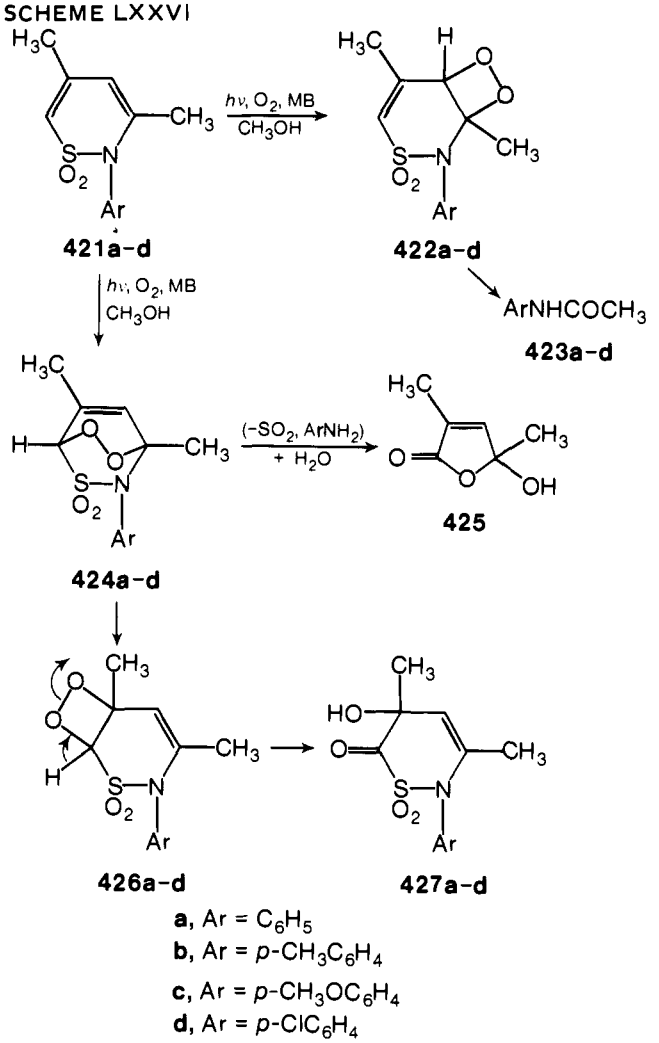
endoperoxide **420**[146] (Scheme LXXV) and this reaction is analogous to those of **397** and **399**, which have been mentioned earlier.

C. Six-Membered Heterocycles Containing One Sulfur and One Nitrogen Atom

Fanghänel et al.[147] have reported that sensitized photooxygenation of the sultams **421a–d** in methanol yields a mixture of products consisting of the cyclic α-ketosulfonamides *N*-aryl-3,5-dimethyl-5-hydroxy-1,1,6-trioxo-5,6-dihydro-2*H*-1,2-thiazines (**427a–d**) (major product), acetylarylamines (**423a–d**), and 2,5-dihydro-2-oxo-3,5-dimethyl-5-hydroxyfuran (**425**) (minor product) (Scheme LXXVI).

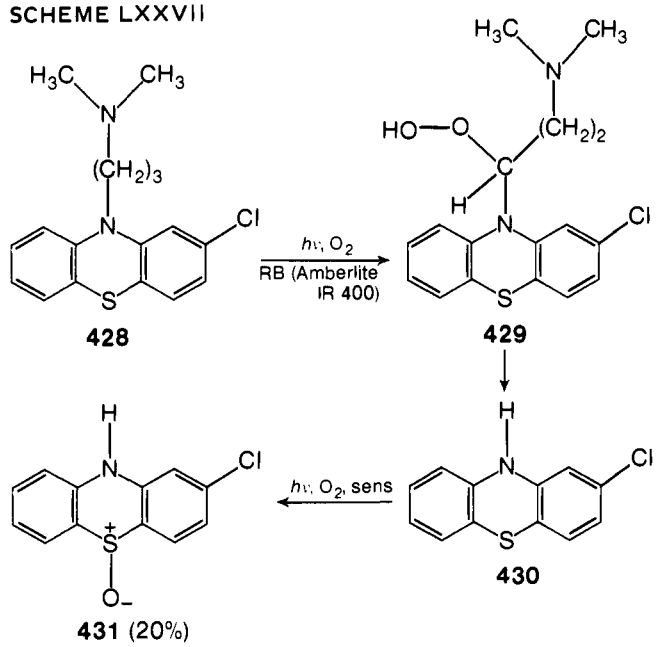
Recently, it has been observed[148] that chloropromazine (**428**) reacts with singlet oxygen, generated photochemically, using

SCHEME LXXVI



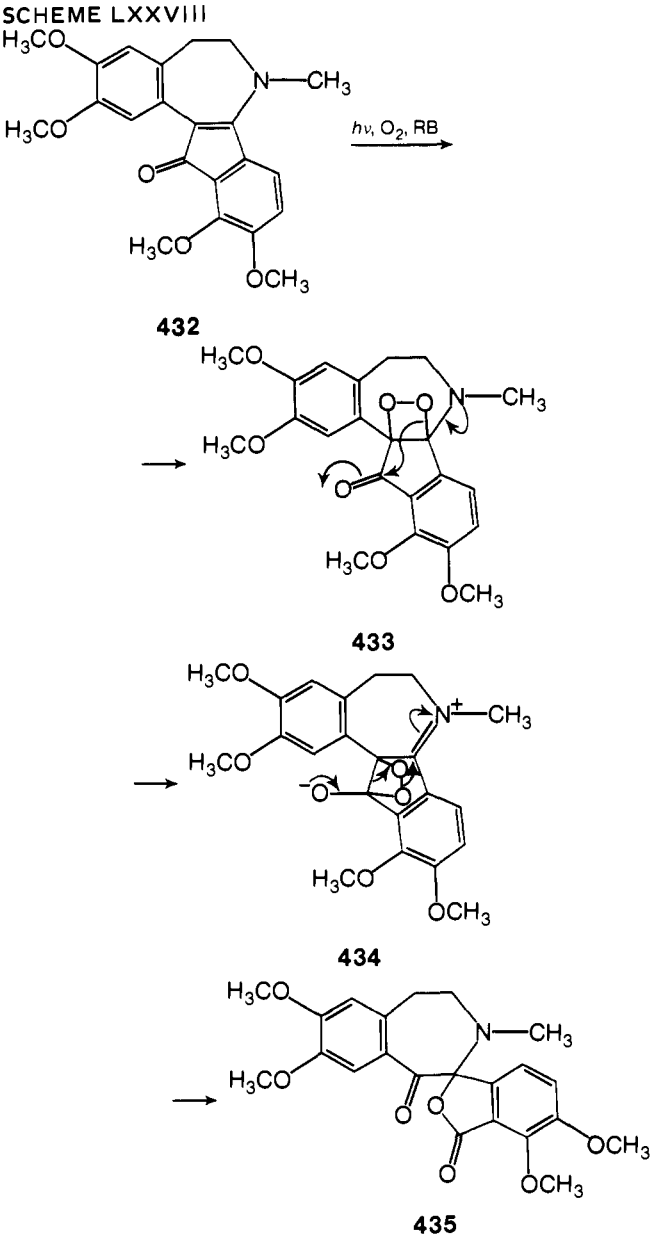
a, Ar = C_6H_5
b, Ar = p-$CH_3C_6H_4$
c, Ar = p-$CH_3OC_6H_4$
d, Ar = p-ClC_6H_4

SCHEME LXXVII



Rose Bengal attached to Amberlite IRA-400, to give 2-chlorophenothiazine 5-oxide (**431**) (Scheme LXXVII). In addition, small amounts of unidentified substances have also been isolated from this reaction. Shorter irradiation times, however, have resulted in the formation of 2-chlorophenothiazine (**430**) in these reactions. It is quite likely that the initial reaction of **428** involves its conversion to the hydroperoxide **429**, which undergoes fragmentation to give the dealkylated product **430**. Subsequent photooxygenation of **430** would be expected to give rise to **431** (Scheme LXXVII).

SCHEME LXXVIII



VI. Photooxygenation of Seven-Membered Heterocycles

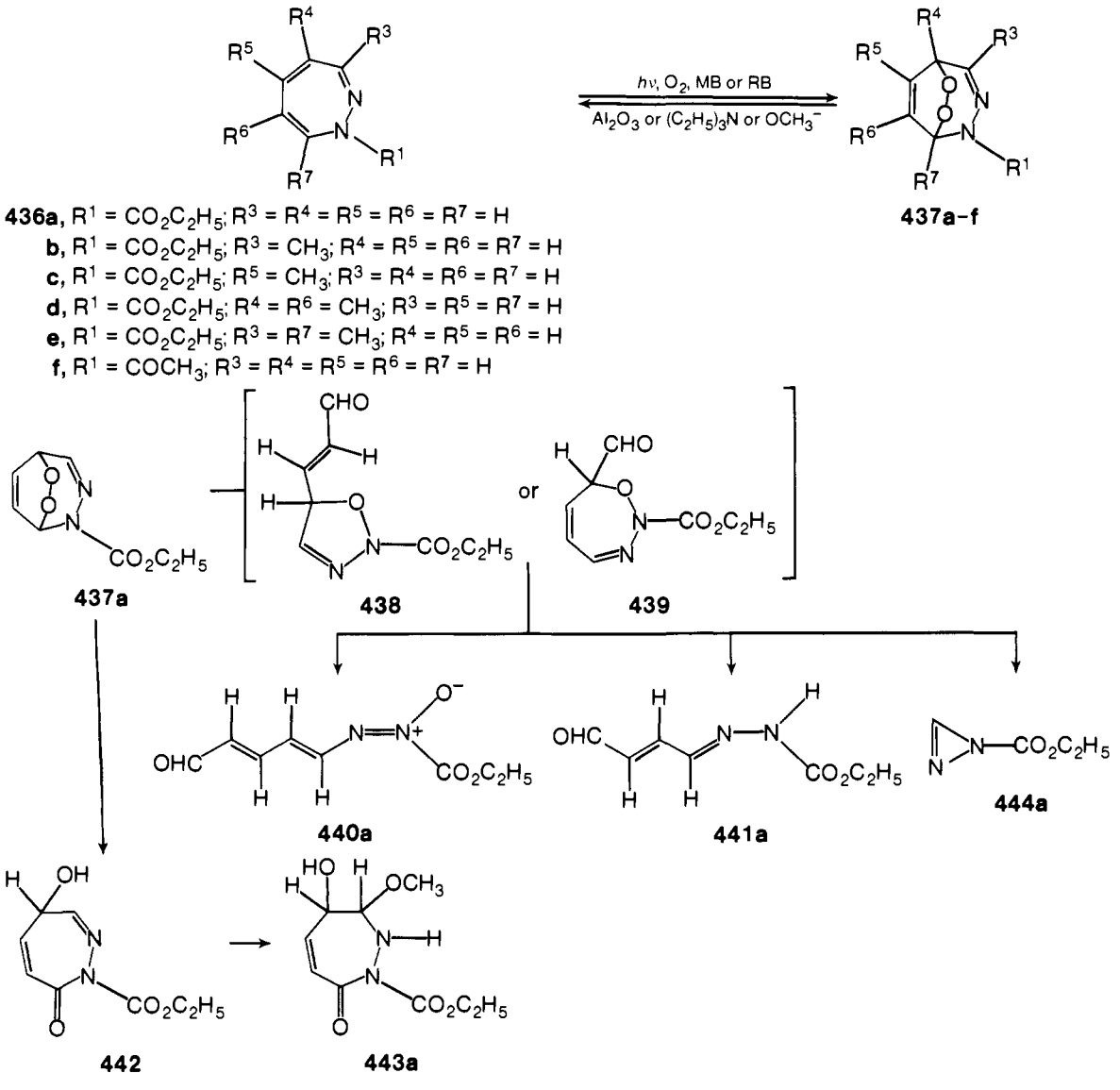
A. Seven-Membered Heterocycles Containing One Nitrogen Atom

An example of the photooxygenation of a seven-membered heterocycle containing one nitrogen atom is found in the case of **432**, reported by Orito et al.[149] They have shown that the Rose Bengal sensitized photooxygenation of **432** leads to the keto lactone **435**, which is a convenient intermediate for the synthesis of rhoeadine alkaloids such as (±)-*cis*-alpinine and (±)-*cis*-alpinigenine (Scheme LXXVIII).[150-155]

B. Seven-Membered Heterocycles Containing Two Nitrogen Atoms

Tsuchiya et al.[156] have examined the photooxygenation of several diazepine derivatives and have shown that different

SCHEME LXXIX



products are formed in these reactions, depending upon the reaction conditions. Thus, it has been shown that the photooxygenation of the diazepine **436a** in dichloromethane, for example, gives rise to the endoperoxide **437a** as the major product, besides small amounts of **440a, 441a,** and **444a** (Scheme LXXIX). When the photooxygenation, however, is carried out in methanol, besides the endoperoxide **437a,** the diazepinone **443a** is also obtained. The formation of products such as **440a, 441a,** and **444a** in the photooxygenation of **436a** has been rationalized in terms of either the oxadiazole intermediate **438,** or the oxadiazepine derivative **439,** as shown in Scheme LXXIX. The formation of the diazepinone **443a,** however, can be understood in terms of the intermediate **442,** formed from **437a** (Scheme LXXIX).[156]

Similarly, the reactions of the diazepines **436b–f** with singlet oxygen, under photooxygenation conditions, give rise to the corresponding endoperoxides **437b–f** in major amounts (Scheme LXXIX). Further, it has been observed that endoperoxides **437a–f** readily revert back to the starting diazepines **436a–f,** by passing them over alumina or by treatment with either sodium methoxide or triethylamine.[156]

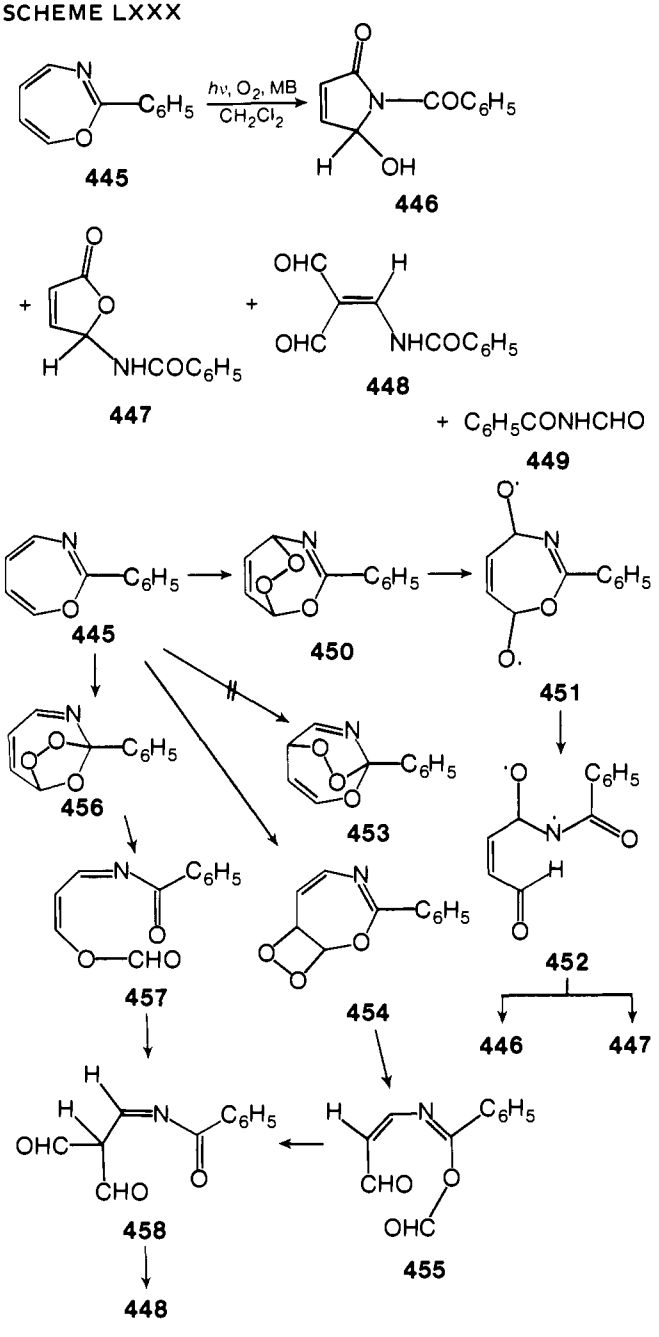
C. Seven-Membered Heterocycles Containing One Oxygen and One Nitrogen Atom

Seshimoto et al.[157] have reported that the photooxygenation of 2-phenyl-1,3-oxazepine (**445**) in dichloromethane gives a mixture of products consisting of the pyrrolinone **446,** the butenolide **447,** the ethylidenemalonaldehyde **448,** and *N*-formylbenzamide (**449**). It is quite likely that the oxazepine **445** in this reaction undergoes a simple 1,4-addition with singlet oxygen to give the endoperoxide **450,** which can subsequently cleave to give products such as **446** and **447,** through the intermediates **451** and **452.** It is interesting to note that the endoperoxide **453** is not formed in the reaction of **445** with singlet oxygen. The formation of the ethylidenemalonaldehyde **448,** on the other hand, can be understood in terms of the dioxetane intermediate **454** or the peroxy derivative **456,** as shown in Scheme LXXX.[157] Further oxidation of **448** in presence of singlet oxygen could lead to *N*-formylbenzamide (**449**), which has been obtained as one of the products from **445.**

VII. Conclusion

In this brief review, we have made an attempt to catalogue some of the reported photooxygenation reactions of different nitrogen heterocycles. In doing so, we have concerned ourselves primarily with the different types of products formed in these reactions and, also, some of the suggested pathways for their formation. Although detailed studies on the mechanism of photooxygenation reactions, in general, have been carried out by several investigators, there is a dearth of such studies in the area of nitrogen heterocycles. The examples that are included in this review are mostly photooxygenation reactions brought

SCHEME LXXX



about in the presence of a sensitizer and these reactions therefore may come under the categories of either type I or type II processes.[4] However, in some cases, the unsensitized photooxidations may also be involved.

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VIII. References

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