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THE DYE-SENSITIZED PHOTOOXIDATION OF IMIDAZOLES

TRAPPING OF INTERMEDIATES BY NUCLEOPHILES

HARRY H. WASSERMAN*, MARY S. WOLFF, KENNETH STILLER,
ISAO SAITO and JAMES E. PICKETT
Department of Chemistry, Yale University, New Haven, CT 06520, U.S.A.

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Abstract—The reactions of a series of imidazoles with singlet oxygen have been investigated. While there is evidence that 2,5-endoperoxides or zwitterionic intermediates may be initially formed, the isolated products appear to arise from the decomposition of hydroperoxides or dioxetanes. Nucleophiles such as methanol and diphenyl sulfide serve to intercept unstable intermediates. Based on the photooxidation of model 5-substituted imidazoles, a rationale is presented for the destruction of histidine residues by two equivalents of oxygen in the "photodynamic" process.

Singlet oxygen, as an electrophilic species, reacts readily with electron-rich heterocyclic compounds such as furans, oxazoles, pyrroles and imidazoles.[1,2] Among these substances, imidazoles have been of special interest because of the involvement of this system in the so-called photodynamic effect.[3] Thus, it is well known that enzymes such as insulin, lysozyme and ribonuclease are inactivated by exposure to oxygen and light in the presence of sensitizing dyes such as methylene blue, and this inactivation has been correlated with the oxidative destruction of certain amino acid residues in the polypeptide chain. More specifically, it has been postulated that the loss of activity at histidine sites can be associated with the reaction of the imidazole portion of the molecule with singlet oxygen.[4]

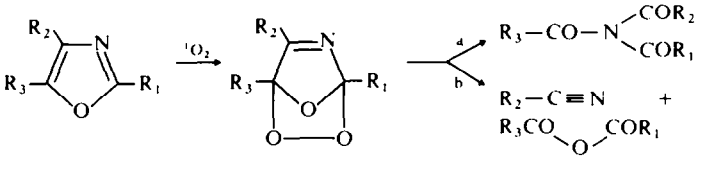
Early investigations on imidazole photooxidation were limited to 2-methylimidazole,[5] histidines,[6] and 2,4,5-triaryl derivatives.[7] More recently,[8,9] information has been provided on the structure of the initially formed peroxides in alkyl imidazole–singlet oxygen reactions. Working at low temperatures two groups have found evidence for the formation of hydroperoxides[8] and 2,5-endoperoxides[9] as unstable intermediates.

In the studies described here, we report on the photooxidation of a series of alkyl- and aryl-substituted imidazoles using methanol and methylene chloride as solvents. Methanol was used for most of the oxidation studies because it provided a polar medium for the reactions, and also served as an efficient nucleophile for reaction with initially formed peroxidic products and for addition to reactive imino intermediates. Our investigation of transient species in these oxidations has also been aided by other trapping methods. These have included the introduction of diphenyl sulfide as a scavenger for intermediate dioxetanes,[10] and the use of alkyl carboxylate side chains substituted at the 2-position of the imidazole for intramolecular interception of 2,5-endoperoxides.

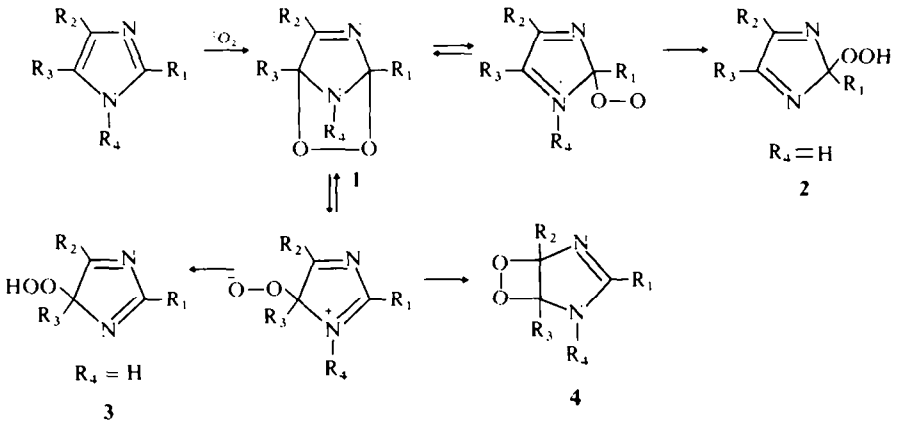
The oxidative changes taking place in the imidazoles differed markedly from those observed in the oxazole series (Scheme 1) where rearrangements to triamides (path a) or cleavage to nitriles (path b) have been reported.[1] As will be outlined in the following discussion, imidazole photooxidation products appeared to result from initial endoperoxide (**1**) formation followed by ring-opening to form hydroperoxides (**2**), (**3**) or dioxetanes (**4**). (Scheme 2). The observed reaction products may then be derived from subsequent decomposition of the peroxidic species (**2**, **3** or **4**). In general, the oxidations were carried out at room temperature using methylene blue as the sensitizing dye and a 150-watt tungsten floodlamp as a source of visible light. Oxygen was bubbled through the solutions until the starting materials were completely consumed as indicated by tlc monitoring of the reaction mixture.

Photooxidation of the parent system, imidazole, and 4-methylimidazole (**5**, R=Me) in methanol took place rapidly, along with considerable decomposition. In both cases, the isolated products, (4,5-dimethoxyimidazolidin-2-ones (**6**)) showed incorporation of one molecule of oxygen and two molecules of solvent. A likely reaction pathway is pictured in Scheme 3.

The reactions of a series of phenyl-substituted imidazoles with singlet oxygen under similar conditions are summarized in Table 1. In the case of 4,5-diphenylimidazole (entry no. 1), the reaction course parallels that outlined in Scheme 3, although the formation of dibenzoylurea indicates a second-stage process involving an additional equivalent of oxygen. This more complex type of oxidation, also shown by 5-phenylimidazole (entry no. 2), will be

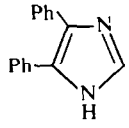
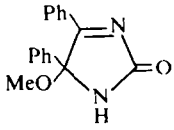
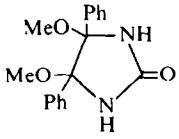
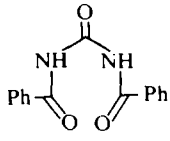
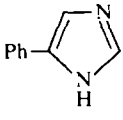
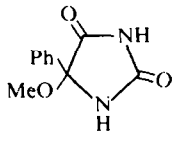
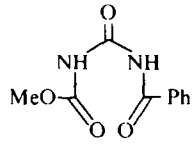
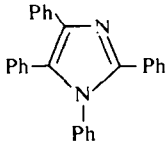
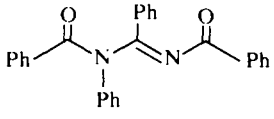
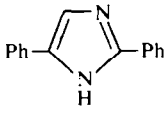
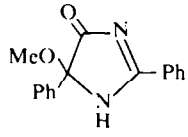


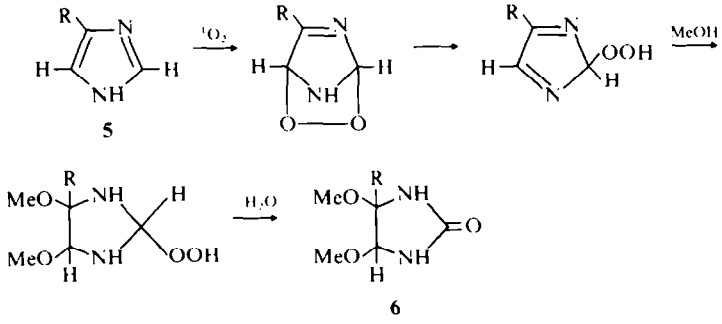
Scheme 1.



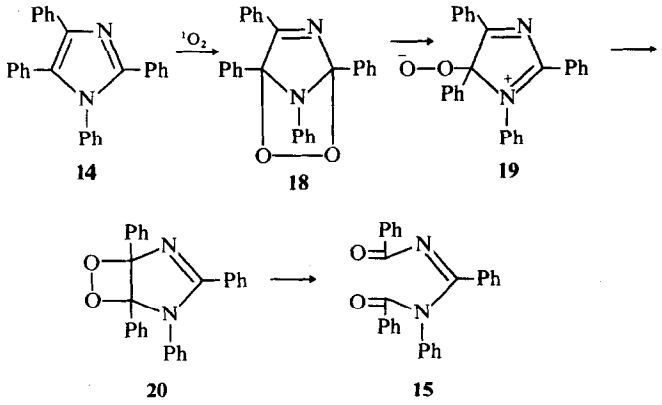
Scheme 2.

Table 1 Photooxidation of imidazoles

	Imidazole	Products (Yields)		
1.	 **7**	 **8** (36%)	 **9** (6%)	 **10** (3%)
2.	 **11**	 **12** (15%)	 **13** (2%)	
3.	 **14**	 **15** (97%)		
4	 **16**	 **17** (29%)		



Scheme 3.



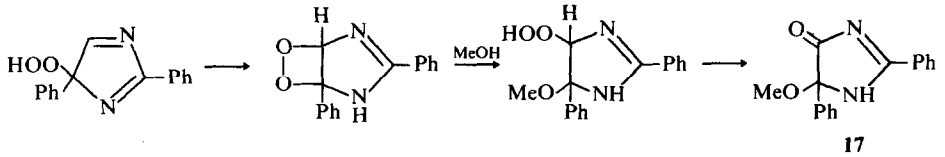
Scheme 4.

discussed in the section on histidine oxidation. Tetraphenylimidazole (**14**), on the other hand, underwent reaction to form the cleavage product (**15**). The latter most probably arises from the dioxetane (**20**), formed by the sequence shown in Scheme 4. The generation of **20** from initially formed 2,5-endoperoxide (**18**) is consistent with the recent findings of Foote *et al.* on low temperature photooxidations of imidazoles[9] and may involve the zwitterionic product (**19**) as a non-isolable intermediate. Dioxetane formation also accounts for the oxygenation at the 4- and 5-positions of 2,5-diphenylimidazole in the formation of **17** (entry no. 4) as outlined in Scheme 5.

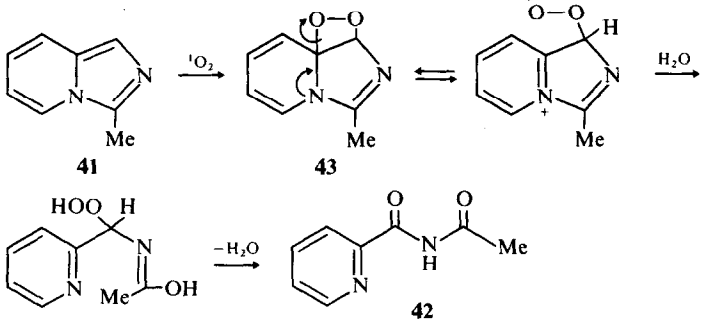
Table 2 lists a series of fused-ring imidazoles yielding photooxidation products by processes corresponding closely to those outlined above. Thus, in entries nos. 1–3, the products are formed by solvent trapping as in Scheme 3 while the reactions in entries nos. 4–9 involve dioxetane intermediates as in Scheme 4. Formation of the pyridinodiamide (**22**; entry no. 10) also appears to involve a dioxetane (**43**) as shown in Scheme 6.

The solvent effects in the photooxidation of the 2-phenyl-4,5-pentanoimidazole (entry no. 9) are of particular interest in studying the intermediate steps leading to the ring-expanded product (**39**). It appears quite probable that the 4,5-dioxetane (**44**) is a key intermediate. In methanol, the dioxetane undergoes ring-opening to the imino hydroperoxide (**45**) which readily reacts with solvent at the 5-position. Subsequent decomposition of the hydroperoxide (**46**) takes place by a Witkop-type fragmentation[11] (Scheme 7). In the non-polar medium (CH_2Cl_2) decomposition of the dioxetane by oxygen-oxygen bond rupture is the preferred reaction pathway leading to **40**.

Histidine-related photooxidations. Particular attention has been paid to the photooxidation of imidazoles because of the correlation of enzyme deactivation by air and light with the destruction of histidine residues.[3,4] Two equivalents of oxygen are required for the inactivation of each histidine residue in the polypeptide chain. In early work on the photooxidation of histidine derivatives, complex mixtures were obtained.[6] Our own investigations on the methylene blue-sensitized photooxidation of N-benzoylhistidine methyl ester (**47**) in methanol also yielded a mixture of products. Hydrolysis of this

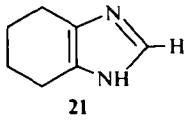
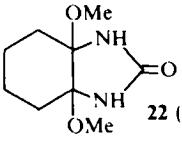
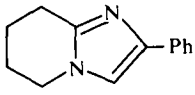
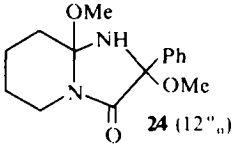
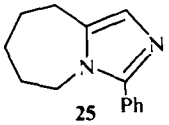
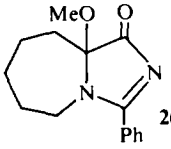
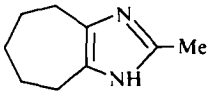
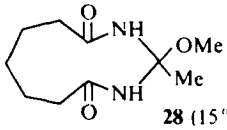
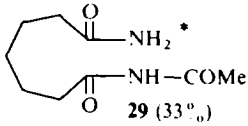
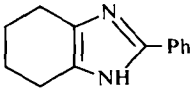
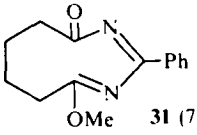
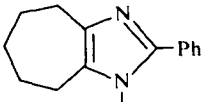
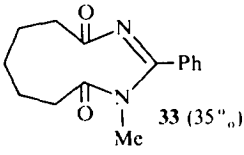
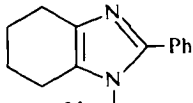
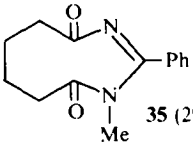
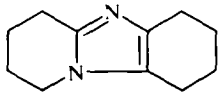
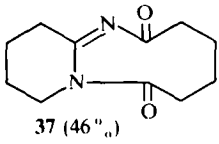
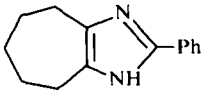
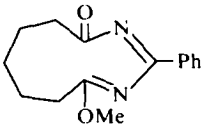
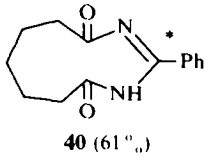
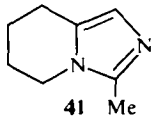
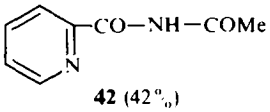


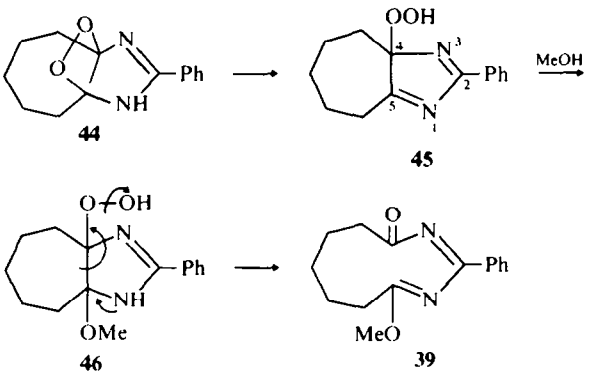
Scheme 5.



Scheme 6.

Table 2. Photooxidation of Imidazoles

	Imidazole	Solvent	Products (Yields)
1.	 **21**	MeOH	 **22** (42%)
2.	 **23**	MeOH	 **24** (12%)
3.	 **25**	MeOH	 **26** (60%)
4.	 **27**	MeOH CH_2Cl_2*	 **28** (15%)  **29** (33%)
5.	 **30**	MeOH	 **31** (72%)
6.	 **32**	CH_2Cl_2	 **33** (35%)
7.	 **34**	CH_2Cl_2	 **35** (29%)
8.	 **36**	MeOH	 **37** (46%)
9.	 **38**	MeOH CH_2Cl_2*	 **39** (75%)  **40** (61%)
10.	 **41**	MeOH	 **42** (42%)

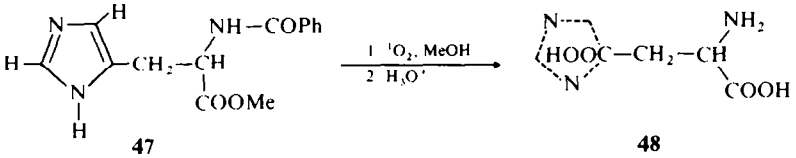


Scheme 7.

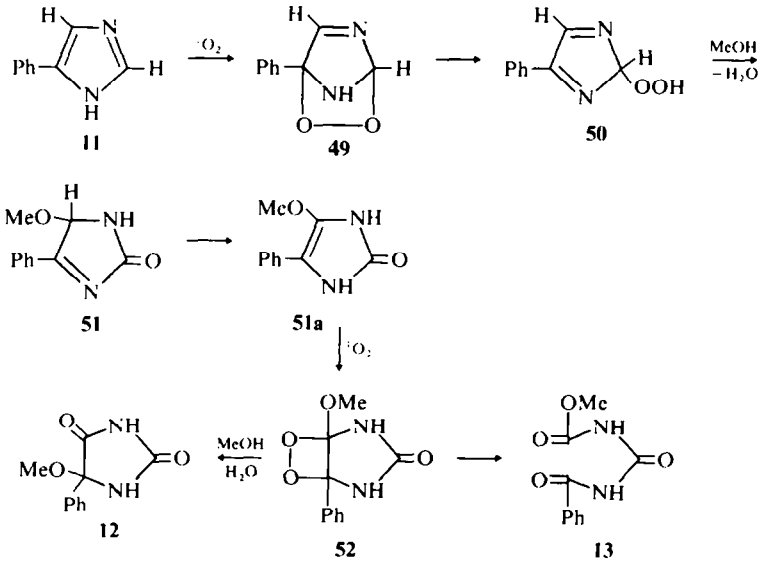
reaction mixture with 6N HCl yielded aspartic acid (**48**) in 65% yield (Scheme 8).

Evidence bearing on the mode of formation of aspartic acid in the above process and, more generally, on the oxidative cleavage of 5-substituted imidazoles by two equivalents of singlet oxygen was derived from the photooxidation of 5-phenylimidazole leading to **12** and **13** (Table 1, entry no. 2). A rationale for the more complex oxidation leading to these products is given in Scheme 9. The first equivalent of oxygen adding to **11** yields an endoperoxide (**49**) which decomposes with loss of water to the diimino derivative (**50**). Addition of methanol and dehydration then leads to the imidazolinone (**51**) which undergoes tautomerization and oxidation to **52** by a second mole of singlet oxygen. The dioxetane (**52**) may undergo cleavage to form **13**, or solvolysis in wet methanol to form **12**. Model imidazolinones undergo rupture of the double bond similar to the conversion of **51a** to **13** under similar conditions of photooxygenation as summarized in the oxidations of **53** to **54** (Table 3).

Diphenyl sulfide as a dioxetane trapping agent. Photooxidation of tetraphenylimidazole in benzene-acetone (9:1) leads, nearly quantitatively, to the dibenzoyl derivative (**15**), presumably by cleavage of the intermediate dioxetane (**55**) as shown in Scheme 10. Evidence for the intermediacy of a dioxetane was obtained by carrying out the photooxygenation in the presence of diphenyl sulfide (0.16 M). Under these conditions the rearranged lactam (**56**) appears to form by attack of the diphenyl sulfide on the oxygen–oxygen bond of the dioxetane, followed by a

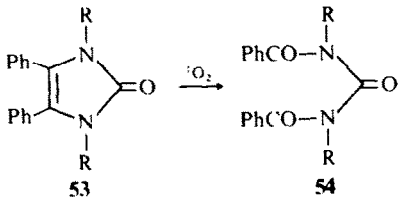


Scheme 8.



Scheme 9.

Table 3.

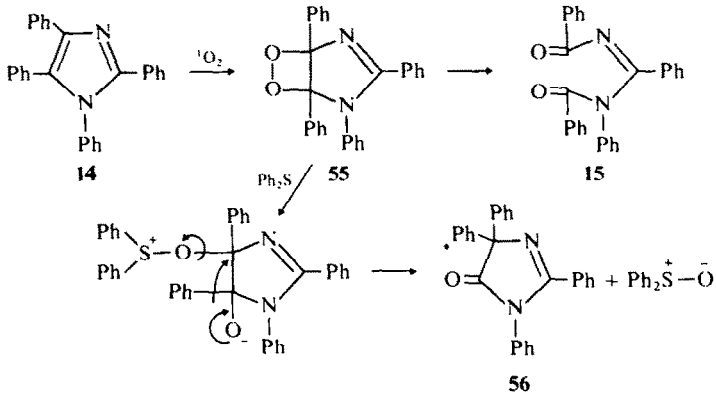


Yields of Dibenzoylureas

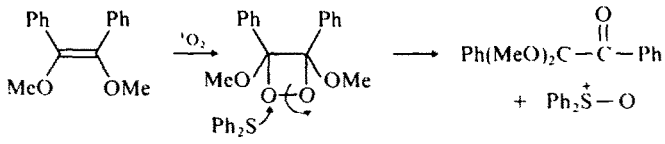
	R	MeOH	CH_2Cl_2
a.	H	55	47
b.	Me	55	70
c.	Ph	–	80

rearrangement involving a 1,2-shift of a phenyl group with release of diphenyl sulfoxide. Our studies on the action of diphenyl sulfide on stable model dioxetanes[10] have shown analogous rearrangements accompanied by the formation of diphenyl sulfoxide (Scheme 11).

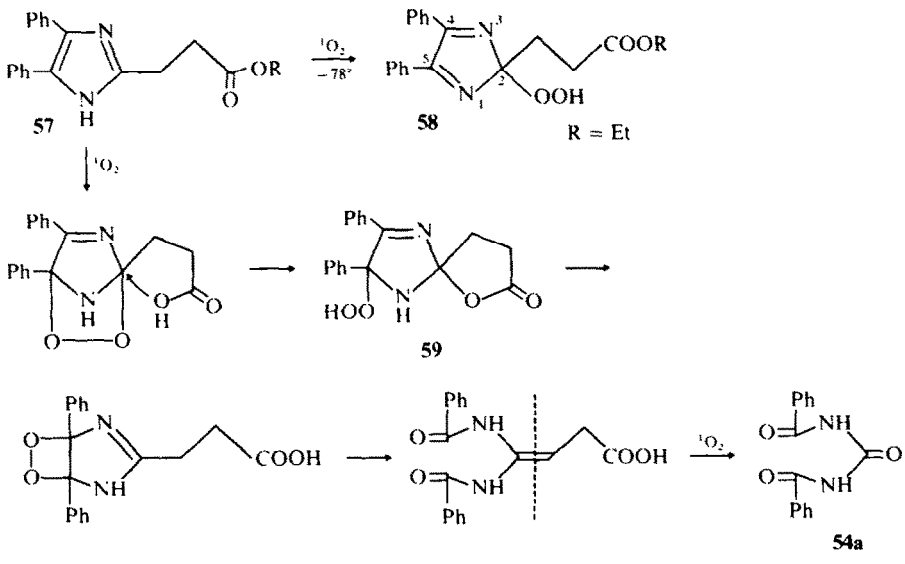
Intramolecular interception of peroxides. In order to learn more about transient products formed at early stages of imidazole photooxidation we investigated the possibility of intramolecular trapping of peroxidic intermediates. For this purpose we utilized 4,5-diphenylimidazole-2-propionic acid and its ethyl ester as substrates for singlet oxygen reactions. The ethyl ester (**57**, R=Et) reacted readily with exactly one equivalent of singlet oxygen to give a product showing typical behavior of a hydroperoxide (immediate starch-iodide coloration). This product was stable in



Scheme 10.



Scheme 11.



Scheme 12.

solution at −78° but gradually decomposed on warming above 0°. The structure of this peroxide was uniquely defined as **58** by the ^{13}C NMR spectrum which showed equivalent carbons for C-4 and C-5 and only one set of phenyl carbon resonances. The isomeric 5-hydroperoxide or any cyclic peroxide would not provide the symmetry required for the observed NMR spectrum. The acid (**57**, R=H), on the other hand, reacted with two equivalents of singlet oxygen to yield dibenzoylurea (**54a**). We suggest that in contrast to the ester case (**57**, R=Et) where the 2-hydroperoxide is formed, the carboxyl group in **57**, R=H, assists in opening the 2,5-endoperoxide yielding the 5-hydroperoxide (**59**). The further reactions of **59** leading to dibenzoylurea would then include carbon–carbon bond cleavage by a second-stage singlet oxygen-enamine reaction as outlined in Scheme 12.

EXPERIMENTAL

Methods. Mops are uncorrected. Microanalyses were performed by Dr. R. Rittner, Olin Corp., New Haven. IR spectra were run as KBr pellets on a Perkin-Elmer model 337 spectrophotometer and are calibrated to polystyrene. NMR spectra were taken on a Varian model A60-A spectrophotometer; chemical shifts are reported as δ values with TMS internal standard, using $CDCl_3$ as solvent unless otherwise indicated. UV spectra were taken on a Bausch and Lomb 550 instrument. Mass spectra were obtained on a Hitachi RMU-6 spectrometer.

The standard photooxidation reaction was carried out in a 3-neck round-bottom flask at room temp with methylene blue as sensitizer. O_2 was passed through the magnetically stirred soln during irradiation with a 150 watt tungsten lamp. The reactions were followed by tlc and were terminated when the starting material was exhausted.

Photooxidation of imidazole. A sample of 4.45 g (65 mmol) imidazole was dissolved in 4500 mL MeOH with 4 mg methylene blue. The standard photooxidation was allowed to proceed slowly in this very dilute soln for 14 days. In more concentrated soln, considerable tarring took place. After removal of the solvent *in vacuo*, the residue was dissolved in a small amount of EtOAc and chromatographed on 200 g silica gel. The column was eluted with $CHCl_3$–MeOH, 9:1. 4,5-Dimethoxyimidazolone-2 was isolated from the mixture and was crystallized from EtOAc, 977 mg, 9%, m.p. 112–114°. (Found: C, 41.09; H, 7.04; N, 19.20. Calc. for $C_5H_{10}O_3N_2$: C, 41.09; H, 6.90; N, 19.17%). IR ($CHCl_3$): 1728 cm^{-1}; NMR ($CDCl_3$): δ 3.40 (s, 6 H), 4.82 (s, 2 H), 7.5 (bs, 2 H).

Photooxidation of 4-methylimidazole (**5**). 4-Methylimidazole[12] (4.5 g, 55 mmol) was photooxidized in 3 L MeOH for 24 hr. The residue, after evaporation of the solvent, was chromatographed on 400 g silica gel. Elution with ether and with 4% MeOH–ether gave a thick oil (1.5 g) which crystallized from ether to give 0.56 g 5-methoxy-5-methylhydantoin, m.p. 120–130°, 7%. Recrystallization from ether provided an analytical sample, m.p. 132.5–134°. (Found: C, 41.70; H, 5.61; N, 19.22. Calc for $C_5H_8N_2O_3$: C, 41.67, H, 5.59; N, 19.44%); NMR: δ 1.63 (s, 3 H), 3.27 (s, 3 H), 6.00 (bs, 2 H); IR: 3220, 1780, 1725 cm^{-1}; MS: *m/e* 144 (M^+), 116, 113, 101, 73, 42, 41

Elution with 10% MeOH–ether gave an oil (1.2 g) which solidified on standing, providing **6**, m.p. 100–109°, 13%. Recrystallization from EtOAc provided an analytical sample, m.p. 131–133°. (Found: C, 44.98; H, 7.64; N, 17.40. Calc for $C_6H_{12}N_2O_3$: C, 44.99; H, 7.55; N, 17.49%); NMR. δ 1.45 (s, 3 H), 3.26 (s, 3 H), 3.38 (s, 3 H), 4.58 (b, 1 H), 7.44 (b, 1 H), 7.15 (b, 1 H); IR: 3250, 3120, 1710 cm^{-1}; MS: *m/e* 145, 129, 60, 43. Further elution with 30% MeOH–ether provided an intractable oil (1.8 g, *ca* 18%).

Photooxidation of 4,5-diphenylimidazole (**7**). A sample of the imidazole (1.269, 5.7 mmol) was dissolved in 1800 mL MeOH with 4 mg methylene blue. The standard photooxidation was carried out for 24 hr at a temp of 32°. Following the removal of solvent *in vacuo*, the residue was dissolved in $CHCl_3$ and chromatographed on 200 g silica gel. Elution of the column with $CHCl_3$ yielded a yellow oil which was crystallized from benzene. Compound **8** was recrystallized from benzene to yield 525 mg (36%), m.p. 180–2°, lit. 179–80°.[27] The IR and UV spectra were superimposable on those of an authentic sample. (Found: C, 72.16; H, 5.20; N, 10.52. Calc for $C_{16}H_{14}O_2N_2$: C, 71.96; H, 5.52; N, 11.92%); NMR: ($CDCl_3$): δ 8.0–7.2 (m, 2 H), 7.2–7.6 (m, 8 H), 3.35 (s, 3 H); IR: (KBr): 1728 cm^{-1}; UV: $\lambda_{max}^{CHCl_3}$ (log ε 276 mμ (4.2.).

Elution of the column with $CHCl_3$ also yielded an oil whose bis-2,4-dinitrophenylhydrazone was identical with that of benzil as shown by its superimposible IR spectrum and its mixture m.p. The yield of the hydrazone was 74 mg (2%), m.p. 188–89°.

Elution of the column with $CHCl_3$–MeOH, 98:2, yielded two compounds. The first compound was recrystallized from benzene to yield 40 mg (3%) of **10**. The IR spectrum of the urea was superimposable on that of an authentic sample.[26] An analytical sample was prepared by repeated recrystallization from benzene. (Found: C, 67.15; H, 4.51, N, 10.44. Calc. for $C_{15}H_{12}O_3N_2$: C, 66.95; H, 4.48; N, 10.37%).

The second compound which was eluted from the column was recrystallized from acetone to yield 109 mg (6%) of **9** with MeOH of crystallization, m.p. 209–212°, dec., lit. 214–214°, dec.[28] The IR spectrum was superimposable on that of an authentic sample.[28] (Found: C, 68.44; H, 6.08; N, 9.39. Calc. for $C_{17}H_{18}O_3N_2$: C, 68.71; H, 6.07; N, 9.10%).

Photooxidation of 5-phenylimidazole (**11**). A sample of 5-phenylimidazole[24] (4.5 g, 31 mmol) was dissolved in 4500 mL MeOH with 4 mg methylene blue. The standard photooxidation was carried out for 32 hr. After removal of the solvent *in vacuo*, the residue was dissolved in a small amount of $CHCl_3$ and chromatographed on silica gel. The column was eluted with $CHCl_3$ and the first 600 mL were collected. This fraction was then rechromatographed on 200 g silica gel, and the column eluted with ether. Two compounds were isolated from the chromatography. The first, compound **12**, was crystallized from $CHCl_3$–ether: yield, 971 mg, 15%, m.p. 167–170°. (Found: C, 58.22; H, 4.85; N, 13.58. Calc for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59%); NMR (deuteroacetone): δ 3.1 (br, 1 H), 3.37 (s, 3 H), 7.5 (m, 5 H), 8.0 (br, 1 H); UV: λ^{MeOH} 269 (log ε 2.4), 263 (log ε 2.8), 258 (log ε 2.9), 245 (log ε 3.1) nm: IR (KBr): 1792, 1723 cm^{-1}.

The second compound **13** isolated from the chromatography, m.p. 169–172°, yield 105 mg, 2%, was recrystallized from trichloroethylene. (Found: C, 54.06; H, 4.54; N, 12.61. Calc. for $C_{10}H_{10}N_2O_4$: C, 54.19, H, 4.64; N, 12.57%); NMR ($CDCl_3$): δ 3.84 (s, 3 H), 7.55–7.65 (m, 3 H), 8.1 (m, 2 H), IR (KBr): 1797, 1703, 1668 cm^{-1}.

Photooxidation of 1,2,4,5-tetraphenylimidazole (**14**). The imidazole[29] (2.08 g, 5.6 mmol) was dissolved in 1700 mL MeOH with 5 g methylene blue. The standard photooxidation reaction was carried out for 24 hr. The MeOH was removed under reduced pressure, and the solid which resulted was recrystallized twice from MeOH yielding 2.20 g (97%) of **15**, m.p. 145–146.5°, identical with an authentic sample.[30]

Photooxidation of 2,5-diphenylimidazole (**16**). 2,5-Diphenylimidazole was prepared according to the method of Aines.[23]

A sample of 1.339 g (6.1 mmol) of imidazole was dissolved in 1400 mL MeOH with 4 mg methylene blue. The standard photooxidation was carried out for 30 hr at 32°. After removal of the solvent *in vacuo*, the residue was dissolved in a small amount of $CHCl_3$, chromatographed on 200 g silica gel, and the column was eluted with a 7:3 soln of benzene–EtOAc. The crystalline residue was recrystallized from benzene to yield 451 mg of **17** m.p. 154–157°, 29%. The analytical sample was prepared by repeated recrystallization from benzene, m.p. 156–157°. (Found: C, 72.32; H, 5.18; N, 10.68. Calc. for $C_{16}H_{14}O_2N_2$: C, 72.17; H, 5.30; N, 10.52%); NMR ($CDCl_3$).

δ 7.9–8.2 (m, 2H), 7.2–7.8 (m, 8H), 3.40 (s, 3H); UV: λ^{MeOH} 258 (log ε 3.97), 238 (log ε 4.18); IR (KBr): 1763, 1617 cm^{-1}; ($CHCl_3$): 1747, 1730 cm^{-1}.

Photooxidation of tetrahydrobenzimidazole (**21**). Tetrahydrobenzimidazole was prepared by the general method of Bredereck and Theilig,[13] m.p. 147–149°, lit[14] 149–150°. Photooxidation of the imidazole (1.13 g, 0.93 mmol) for 24 hr in MeOH with NaOAc (20 mg) was followed by dissolution of the residue in $CHCl_3$ and clarification with charcoal. The soln was evaporated *in vacuo*, triturated three times with MeOH and evaporated, and crystallized as its methanolate from 4 mL MeOH to give hard cubic crystals of **22** (480 mg, m.p. 167–169°). A second crop was obtained, 300 mg, m.p. 156–160°; overall yield, 42%. A run without NaOAc gave the product in 37% yield, m.p. 113–127°. Recrystallization from EtOH–EtOAc gave pure material, m.p. 156–157°, which was further recrystallized for analysis. (Found: C, 54.13; H, 8.31; N, 14.09. Calc. for $C_9H_{16}N_2O_3$: C, 53.99; H, 8.05; N, 13.99%); NMR: δ 1.00–1.60 (b, 8H), 3.38 (s, 3H), 6.39 (b, 2H); IR: 3240, 3200, 3100, 1710 cm^{-1}; MS: *m/e* 200 (M^+), 184, 168, 136.

Photooxidation of 4-phenyl-1(1,2α)pyrimidazole (**23**). The imidazole (Aldrich, 1.5 g, 7.7 mmol) was photooxidized for 18 hr in 1.5 L MeOH, and the residue after evaporation of the solvent was chromatographed on 200 g silica gel. The fraction eluted with ether crystallized to give **24**, m.p. 83–85° (0.25 g, 12%). An analytical sample was obtained by recrystallization from ether–hexane, m.p. 85–89°, long flat prisms. (Found: C, 65.97; H, 5.78; N, 10.17. Calc. for $C_{15}H_{16}N_2O_3$: C, 66.19; H, 5.92; N, 10.29%); NMR: δ 8.18 (bd, 1H), 7.73 (m, 3H), 7.32 (m, 3H), 6.60 (m, 2H), 3.71 (s, 3H), 3.33 (s, 3H); IR: 3440, 1740 cm^{-1}; UV: λ^{MeOH} 230 (log ε 4.5), 288 (log ε 4.2) nm; MS: *m/e* 272 (M^+), 257, 241, 226, 212, 198, 181, 169, 134, 122, 94.

Photooxidation of 2-phenyl-(1,5)imidazepine (**25**). The imidazole (1.50 g, 7.1 mmol) was photooxidized in MeOH with NaOAc (200 mg) for 8 hr. The residue, after clarification with charcoal, crystallized from EtOAc–ether to give **26**, m.p. 112–120° (1.1 g, 60%). Photooxidation without NaOAc gave the product, m.p. 95–110°, in 36% yield. Recrystallization from EtOAc provided pure **26**, m.p. 121–125°. (Found: C, 69.06; H, 7.02; N, 10.84. Calc. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 6.85; N, 10.65%); NMR: δ 7.55 (m, 5H), 3.40–4.20 (m, 2H), 3.15 (s, 3H), 1.20–2.10 (b, 8H); IR: 1730, 1603 cm^{-1}; UV: λ^{MeOH} 252 (log ε 3.8), 286 (log ε 3.5) nm; MS: *m/e* 258 (M^+), 243, 215, 127, 96.

Preparation of 2-methyl-4,5-pentanoimidazole (**27**). 2-Acetoxycycloheptanone (45 g) was refluxed in 300 mL formamide at 180–190° for 6 hr. Aqueous base was added and the resultant alkaline (pH 10) mixture was extracted with $CHCl_3$. The dried extracts were evaporated to dryness and the solid residue crystallized from $CHCl_3$–pet ether, yield: 19 g (42%), m.p. 228–236°. An analytical sample was prepared by recrystallization from EtOH–EtOAc–ether, m.p. 233°. (Found: C, 72.46; H, 9.46; N, 18.31. Calc. for $C_9H_{14}N_2$: C, 71.96; H, 9.39; N, 18.65%); NMR: δ 1.70 (b, 6H), 2.30 (s, 3H), 2.60 (m, 4H), 7.93 (1H); IR: 3500, 1603 cm^{-1}; UV: λ^{MeOH} 222 (log ε 3.8), 268 (log ε 2.4) nm; MS: *m/e* 150 (M^+), 44.

Photooxidation of 2-methyl-4,5-pentanoimidazole (**27**). The imidazole (1.25 g, 8.3 mmol) was photooxidized in 2 L MeOH for 18 hr in the presence of NaOAc (15 mg). The clarified residue was crystallized from $CHCl_3$–CCl_4 to give **28**, m.p. 142–145° (250 mg, 15%). A run without NaOAc gave 12% of product, m.p. 78–90°. Recrystallization from MeOH–EtOAc (1:10) gave pure **28**, m.p. 140–148°. (Found: C, 56.13; H, 8.78; N, 13.60. Calc. for $C_{10}H_{18}N_2O_3$: C, 56.06; H, 8.47; N, 13.06%); NMR: δ 3.40 (s, 3H), 1.90 (s, 3H), *ca* 2 (9–12H); IR: 3230, 3100, 1660 cm^{-1}; UV: λ^{MeOH} 214 (log ε 3.1) nm; MS: *m/e* 214 (M^+), 199, 183, 171, 100.

Photooxidation in CH_2Cl_2 and acidic work up gave the hydrolysis product, **29**, in 33% yield, m.p. 139–142°. The same product was obtained from hydrolysis of **28**. (Found: C, 53.99; H, 8.05; N, 13.99. Calc. for $C_9H_{16}N_2O_3$: C, 54.03; H, 7.94; N, 13.53%); NMR (DMSO-d_6): δ 6.70 (b, 2-3H), 2.50 (s, 3H), 2.10 (b, 10H); IR: 3410, 3350, 3270, 3210, 1730, 1640, 1620 cm^{-1}; MS: *m/e* 200 (M^+), 142, 100, 59, 43.

Preparation of 2-phenyltetrahydrobenzimidazole (*2-phenyl-4,5-butanoimidazole*, (**30**)). According to the method of Weidenhagen,[15] a soln of adipoin (15 g, Aldrich) in MeOH (500 mL) was added to a mixture of copper acetate (63 g), conc ammonia (560 mL), and benzaldehyde (20 g). The soln was heated on a steam bath for 2–3 hr and allowed to cool to room temp. The Cu- complex of the imidazole (25–30 g) was removed by filtration and freed of Cu by treatment of an alcohol suspension with gaseous H_2S. The mixture was then heated with Norit and filtered and the red-brown soln evaporated to dryness *in vacuo*. The solid (crude imidazole) was suspended in EtOAc and filtered with suction, yield 10–15 g (50–58%). Recrystallization from alcohol provided pure imidazole, m.p. 250–255°. (Found: C, 78.39; H, 7.20; N, 14.26. Calc. for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13%); IR: 3400, 1650 cm^{-1}; UV: λ^{MeOH} 210 (log ε 3.6), 294 (log ε 4.0) nm; MS: *m/e* 198 (M^+).

Photooxidation of 2-phenyltetrahydrobenzimidazole (**30**). The imidazole (0.715 g, 3.6 mmol) was photooxidized in 1 L MeOH with NaOAc (10 mg) for 15 hr. After the usual work-up, the residue was crystallized from ether as clusters of rhombic prisms, yielding **31** (0.61 g) m.p. 85.5–88°, which was twice recrystallized for analysis. The first recrystallization provided 466 mg, m.p. 86–88°. The combined mother liquors provided a second crop, 160 mg, m.p. 80–84°; overall yield, 72%. (Found: C, 69.05; H, 6.80; N, 10.85. Calc. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47%); NMR: δ 1.8–2.3 (bm, 8H), 3.8 (s, 3H), 7.7–7.8 (m, 5H); IR: 1680, 1660, 1630 cm^{-1}; UV: λ^{MeOH} 209 (log ε 4.1), 246 (log ε 4.2) nm; MS: *m/e* 244 (M^+), 229, 215, 99, 59, 45.

Preparation of 1-methyl-2-phenyl-4,5-pentanoimidazole (**32**). 2-Phenyl-4,5-pentanoimidazole (3.8 g) was dissolved in dry THF, 100 mL. NaH (0.5 g) was added and the mixture heated. MeI (3 g) was added dropwise and the mixture heated for 30 min at 80°. A few drops of water were added, and the THF was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$, washed with water, and evaporated. The residue was crystallized in two crops from cyclohexane by addition of EtOAc, total wt. 2.1 g, m.p. 110–116°. Recrystallization from ether provided material melting at 119–123°. (Found: C, 79.81; H, 8.02; N, 12.58. Calc. for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38%); UV: λ^{MeOH} 209 (log ε 3.9), 278 (log ε 4.1) nm.

Photooxidation of 1-methyl-2-phenyl-4,5-pentanoimidazole (**32**). The imidazole (0.50 g, 2.2 mmol) was photooxidized for 2 hr in CH_2Cl_2. The residue, after clarification in ether with charcoal, crystallized on standing at room temp for 15 hr. Crystallization from cyclohexane afforded **33** m.p. 84–87° (0.20 g, 35%), which was further recrystallized for analysis. (Found: C, 70.24; H, 7.02; N, 10.94. Calc. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84%); NMR: δ 7.7 (m, 5H), 3.3 (s, 3H), 2.5 (m, 4H), 1.6 (m, 6H); IR: 1630, 1680 cm^{-1}; UV: λ^{MeOH} 209 (log ε 4.2), 258 (log ε 4.2) nm; MS: *m/e* 258 (M^+), 243, 241, 215, 181, 161, 118.

Preparation of 1-methyl-2-phenyltetrahydrobenzimidazole (**34**). Compound **34** was prepared exactly as for **32**, m.p. 128–129° (cyclohexane). (Found: C, 79.04; H, 7.95; N, 13.39. Calc. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20%); UV: λ^{MeOH} 209 (log ε 3.8), 278 (log ε 4.0) nm; MS: *m/e* 212 (M^+).

Photooxidation of 1-methyl-2-phenyltetrahydrobenzimidazole (**34**). The imidazole (0.39 g, 1.8 mmol) was orange photooxidized in CH_2Cl_2 for 3.5 hr. The residue crystallized on standing several days at room temp. Recrystallization from benzene–hexane afforded **35**, m.p. 101–106° (0.13 g, 29%), which was further recrystallized for analysis. (Found: C, 68.65; H, 6.82; N, 11.64. Calc. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47%); NMR: δ 7.50 (m, 5H), 3.19 (s, 3H), 2.95 (m, 4H), 2.03 (m, 4H); IR: 1710, 1670 cm^{-1}; UV: λ^{MeOH} 209 (log ε 4.0), 243 (log ε 3.9) nm; MS: *m/e* 244 (M^+), 215, 161, 118.

Photooxidation of 4,5-butano-(1,2α)pyrimidazole (**36**). 4,5-Butano(1,2α)pyrimidazole[17] (1.7 g, 10.5 mmol) was photooxidized for 15 hr in 2 L MeOH. The residue was clarified

with charcoal ($CHCl_3$), triturated with a little benzene, and filtered. The solid (0.90 g, 46%, m.p. 156–164°) was recrystallized from $CHCl_3$–pet ether to give pure **37**, m.p. 162–163.5°. The same product, m.p. 160–164°, was obtained on photooxidation in CH_2Cl_2 for 1 hr (52%). (Found: C, 64.31; H, 5.91; N, 13.36. Calc. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72%); NMR: δ 3.00 (b, 4 H), 2.00 (b, 4 H), 7.35 (qd, 2 H), 7.90 (td, 1 H), 8.72 (bd, 1 H); IR: 1690, 1640 cm^{-1}; UV: λ^{MeOH} 215 (log ε 4.0), 260 (log ε 3.6), 263 (sh, log ε 3.0), 283 (sh, log ε 3.0) nm; MS: *m/e* 204 (M^+), 176, 94.

Preparation of 2-phenyl-4,5-pentanoimidazole (**38**). The imidazole was prepared as for 2-phenyltetrahydrobenzimidazole using 2-acetoxycycloheptanone, m.p. 273–277°. (Found: C, 78.80; H, 7.83; N, 13.16. Calc. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20%); IR: 3420, 1590 cm^{-1}; UV: λ^{MeOH} 294 (log ε 4.3), 212 (log ε 3.9) nm; MS: *m/e* 212 (M^+).

Photooxidation of 2-phenyl-4,5-pentanoimidazole (**38**). The imidazole (0.50 g, 2.36 mmol) was photooxidized in the usual manner for 2.5 hr in MeOH. An ether soln of the residue, on seeding, deposited crude **39** m.p. 71–80° (440 mg, 73%). A pure sample from ether gave m.p. 86–88°. (Found: C, 70.33; H, 6.91; N, 10.69. Calc. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84%); NMR: δ 1.6, (b, 6 H), 2.4 (b, 4 H), 3.8 (s, 3 H), 7.4 (m, 3 H), 7.8 (m, 2 H); IR: 1680, 1620 cm^{-1}; UV: λ^{MeOH} 208 (log ε 4.2), 247 (log ε 4.0) nm; MS: *m/e* 258 (M^+), 242, 229, 215, 201.

3-Phenyl-2,4-diazacyclodec-3-en-1,5-dione (**40**) was obtained from the photooxidation of **38** in CH_2Cl_2 (61%), m.p. 168–170° from EtOAc. (Found: C, 69.02; H, 6.81; N, 11.33. Calc. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47%); NMR: δ 1.6 (b, 6 H), 2.4 (b, 4 H), 7.4 (m, 3 H), 7.8 (m, 2 H); IR: 3200, 1710, 1660, 1630 cm^{-1}; UV: λ^{MeOH} 209 (log ε 4.2), 253 (log ε 4.1) nm; MS: *m/e* 244 (M^+), 215, 201, 147, 103, 104.

Hydrolysis of **39** *and* **40** *gave N-benzoylpimelamide*, m.p. 153–156° (water). (Found: C, 63.86; H, 6.85; N, 10.42. Calc. for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68%); IR: 3390, 3300, 3190, 1740, 1680, 1640 cm^{-1}; MS: *m/e* 262 (M^+), 245.

Photooxidation of 2-methylimidazo-(1,5α)pyridine (**41**). The imidazole[15] (1.7 g, 14 mmol) was photooxidized in 2 L MeOH for 4 hr. The residue, after clarification with charcoal, was crystallized from ether to give lustrous plates of **42**, m.p. 68–70° (0.90 g, 42%). Recrystallization from ether gave an analytical sample, m.p. 78–79°, lit[16] 81–82°; identical in all respects to that prepared from picolinamide and Ac_2O. (Found: C, 58.61; H, 4.89; N, 17.11. Calc. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06%); NMR: δ 2.61 (s, 3 H), 7.60 (m, 1 H), 8.20–7.95 (m, 2 H), 8.63 (bd, 1 H), 10.15 (b, 1 H), IR: 3300, 1725, 1705, 1690, 1660 cm^{-1}; UV: λ^{MeOH} 230 (log ε 4.2), 268 (log ε 3.8) nm; MS: *m/e* 164 (M^+), 149, 106, 78, 43.

Photooxidation of the methyl ester of N-benzoylhistidine (**47**). A sample of N-benzoylhistidine[25] (110 mg, 0.4 mmol) was dissolved in 100 mL MeOH with 1 mg methylene blue. The standard photooxidation was carried out for 30 hr. After removal of the solvent *in vacuo*, the residue was hydrolyzed in 10 mL 6 N HCl. The solvent was removed *in vacuo* with mild heating (60°), and the residue analyzed using a Spinco amino acid analyzer with the following results: residual histidine, 3%; aspartic acid (**48**) 62%; two peaks in the hydroxy acid region, ~10% and ~15%.

A control experiment was run in which 100 mg of the starting material was hydrolyzed in 10 mL 6*N* HCl. The solvent was removed *in vacuo* and the residue was chromatographed as before. Only one peak corresponding to histidine was obtained.

Photooxidation of 4,5-diphenylimidazolinone (**53a**). The imidazolinone[19] (2.0 g, 8.5 mmol) was suspended in 2 L MeOH and photooxidized for 18 hr. The residue was clarified with charcoal in $CHCl_3$. The residue was triturated with ether yielding, **54a** (1.2 g, 55%).

Photooxidation of 1,3-dimethyl-4,5-diphenylimidazolinone (**53b**). The imidazolinone[20] (0.50 g, 1.9 mmol) was photooxidized in MeOH for 12 hr. The residue was crystallized from EtOAc–hexane to give **54b**, m.p. 157–159° (0.31 g, 55%). A yield of 70% was obtained using CH_2Cl_2 as solvent. Recrystallization from EtOAc provided the analytical sample, m.p. 160–161°, lit[21] m.p. 162–163°. (Found: C, 68.98; H, 5.70; N, 9.56. Calc. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45%); NMR: δ 1.30 (10 H), 2.9 (s, 6 H); IR: 1725, 1680, 1655 cm^{-1}; MS: *m/e* 296 (M^+), 191, 105, 77.

Photooxidation of tetraphenylimidazolinone (**53c**). The imidazolinone[22] (2.0 g, 5.2 mmol) was photooxidized in CH_2Cl_2 for 5 hr. The usual work-up gave *sym*-**54c**, 1.7 g, m.p. 160–180°, 80%. Recrystallization from alcohol afforded 1.35 g lustrous plates, m.p. 196–200°, identical with an authentic sample,[22] m.p. 197–199°, lit[22] 200°.

Photooxidation of tetraphenylimidazole (**14**) *in the presence of diphenyl sulfide*. Compound **14** (744 mg, 2 mmol) and diphenyl sulfide (2.9 g, 16 mmol) were dissolved in benzene–acetone (9:1) and photooxidized for 30 min with methylene blue as sensitizer. Two mmol of O_2 were consumed. After evaporation of the solvent and chromatography on silica gel the mixture yielded **56** (244 mg, 33%, m.p. 157–158°). (Found: C, 83.71; H, 4.97; N, 7.27. Calc. for $C_{27}H_{20}N_2O$: C, 83.48; H, 4.19; N, 7.21%); IR: 1725, 1610, 1590, 1570 cm^{-1}; MS: *m/e* 388 (M^+), 360, 269, 257, 180, 165.

Also isolated were diphenyl sulfoxide (41%) and **15** (12%).

4,5-Diphenylimidazole-2-propionic acid, ethyl ester (**57**, R=Et). Desyl bromide (27.5 g, 100 mmol), K_2CO_3 (14 g, 100 mmol), succinimide (10 g, 100 mmol), and Bu_4NBr (20 mg) were stirred and refluxed for 12 hr in 100 mL $CHCl_3$. The mixture was filtered and the solvent evaporated to yield a mass of white crystals that were filtered off and washed with a little ether (yield: 21.0 g, 75%). Without further purification this product was dissolved in 75 mL EtOH and saponified with 5.0 g (78 mmol) KOH dissolved in 50 mL hot EtOH. After refluxing for 1 hr, the mixture was cooled, acidified with conc HCl and refluxed overnight. The mixture was then cooled and filtered to give a white product which was washed with water and dried (yield 20.6 g; 81%; m.p. 135–136°). NMR: δ 1.20 (t, 3 H), 2.59 (br.s, 4 H), 4.08 (q, 2 H), 6.54 (d, 1 H), 7.33 (m, 9 H), 7.93 (br. d, 2 H); IR: 3370, 1735, 1635, 1500 cm^{-1}.

Without further purification the above product was dissolved in 100 mL glacial AcOH with 21 g ammonium acetate and refluxed 6 hr under N_2. The mixture was then poured into ice water, filtered, and the product recrystallized from 2-butanone (yield: 9.5 g; 55%) m.p. 127° (phase transition); 142–143°. NMR: δ 1.23 (t, 3 H), 2.87 (m, 4 H), 4.12 (q, 2 H), 7.30 (m, 10 H); IR: 3420, 1720, 1600, 1420, 1370, 1180 cm^{-1}; (Found: C, 74.93; H, 6.07; N, 8.91. Calc. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74%).

Saponification of the imidazole ester with KOH and acidification gave **57** (R=H) as an amorphous solid m.p. >250°. NMR (DMSO-d_6): δ 2.82 (m, 4 H), 7.30 (m, 10 H); IR (KBr): 3300, 1720, 1600, 1440, 1380, 1185 cm^{-1}.

Photooxidation of 4,5-diphenylimidazole-2-propionic acid (**57**, R=H). The imidazole propionic acid (1.45 g, 5 mmol) was suspended in 150 mL dichloroethane and photooxidized 7 hr at 0° with methylene blue sensitizer. Ten mmol of O_2 were consumed. The mixture was washed with water and evaporated to give a gummy solid yielding 150 mg of crystalline **54a** after trituration with ether and filtration, m.p. 203.5–204.5° (lit[26] 202–203°). IR: 3181, 1759, 1678, 1600, 1524, 1491, 1279 cm^{-1}; NMR ($CDCl_3$ + DMSO-d_6): δ signals only between 7–8; MS: *m/e* 268 ($C_{15}H_{12}N_2O_3$, M.W. 268).

When the photooxidation was carried out in an NMR tube ($CDCl_3$) and the products observed directly in the NMR, only dibenzoylurea resonances were found.

Photooxidation of 4,5-diphenylimidazole-2-propionic acid ethyl ester (**57**, R=Et). The imidazole ethyl ester (320 mg, 1 mmol) was dissolved in 2 mL CH_2Cl_2 and photooxidized with Sensitox (polymer-based Rose Bengal) at −78°. The mixture was decanted and the solvent exchanged to $CDCl_3$ by repeated partial evaporation at −78° under reduced pressure. The carbon NMR was then taken at −78°: 13.7 ($-CH_3$), 28.3, 28.9 (methylene), 60.5 ($-OCH_2-$), 123.9 (C=N), 128.0, 128.7, 129.3, 131.2 (aromatics), 167.2 (NNC(OOH)R),

172.3 (C=O). When warmed above 0° the sample decomposed. In a large scale run (5 mmol) the amount of O_2 taken up in this oxidation was shown to be one molar equivalent.

REFERENCES

[1]H. H. Wasserman and B. H. Lipshutz, Reactions of Singlet Oxygen with Heterocyclic Systems, in *Singlet Oxygen* (Edited by H. H. Wasserman and R. W. Murray). Academic Press, New York (1979).

[2]M. V. George and V. Bhat, *Chem. Rev.* **79**, 447 (1979).

[3a]J. D. Spikes and R. Straight, *Annu. Rev. Phys. Chem.* **18**, 409 (1967); [b]J. D. Spikes and M. McKnight, *Ann. N.Y. Acad. Sci.* **171**, 149 (1970); [c]G. Jou, *Photochem. Photobiol.* **21**, 463 (1975); [d]L. Weil and T. S. Seibles, *Arch. Biochem. Biophys.* **54**, 368 (1955).

[4a]A. Lukton, R. Weisbrod, and J. S. Schlesinger, *Photochem. Photobiol.* **4**, 277 (1965); [b]R. Nilsson, P. B. Merkel and D. R. Kearns, *Ibid.* **16**, 117 (1972); [c]R. Straight and J. D. Spikes, *Ibid.* **27**, 565 (1978); J. R. Fisher, G. R. Julian, and S. J. Rogers, *Physiol. Chem. Phys.* **6**, 179 (1974).

[5]T. Matsuura and M. Ikari, *Kogyo Kagaku Zasshi* **72**, 179 (1969).

[6]M. Tomita, M. Irie, T. Ukita, *Biochemistry* **8**, 5149 (1969).

[7]H. H. Wasserman, K. Stiller and M. B. Floyd, *Tetrahedron Letters* 3277 (1968).

[8]M. L. Graziano, M. R. Iesce and R. Scarpati, *J.C.S. Chem. Comm.* 7 (1979).

[9]H.-S. Ryang and C. S. Foote, *J. Am. Chem. Soc.* **101**, 6683 (1979).

[10]H. H. Wasserman and I. Saito, *Ibid.* **97**, 905 (1975).

[11]B. Witkop, *Ibid.* **72**, 1428 (1950).

[12]Y. Nozaki, F. R. N. Gurd, R. F. Chen and J. T. Edsall, *Ibid.* **92**, 3223 (1970).

[13]H. Bredereck and G. Theillig, *Ber.* **86**, 88 (1953).

[14]H. Schubert and S. Hofmann, *J. Prakt. Chem.* **7**, 207 (1958).

[15]J. D. Bowder and G. R. Ranige, *J. Chem. Soc.* 2834 (1955).

[16]M. Hamana and M. Yamazaki, *Yakugaku Zasshi* **81**, 574 (1961); C.A. 55: 24743d.

[17]N. Campbell and E. B. McCall, *J. Chem. Soc.* 2411 (1951).

[18]R. Weidenhagen, R. Herman and H. Wegner, *Ber.* **70**, 570 (1937).

[19]H. Blitz, *Ann.*, **339**, 265 (1905).

[20]H. Blitz, *Ber.* **40**, 4803 (1907).

[21]H. Blitz, *Ibid.* **41**, 1388 (1908).

[22]H. Blitz, *Ann.*, **368**, 319 (1909).

[23]P. G. Haines and E. C. Wagner, *J. Am. Chem. Soc.* **71**, 2793 (1949).

[24]R. Weindenhagen and R. Herrmann, *Ber.* **68**, 1953 (1935).

[25]O. Gerngross, *Z. Physiol. Chem.*, **108**, 53 (1919); P. Karrer and S. Salman, *Helv. Chim. Acta.* **36**, 570 (1953).

[26]A. Rosenthal and J. P. O'Donnell, *Can. J. Chem.* **38**, 459 (1960).

[27]H. Blitz, *Ann.* **368**, 156 (1909).

[28]H. Blitz, *Ber.* **40**, 2635 (1907).

[29]A. E. Everest and H. McCombie, *J. Chem. Soc.* **99**, 1946 (1911).

[30]D. A. Peak, *Ibid.* 215 (1952).