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Photosensitized Oxidations of Substituted Pyrroles: Unanticipated Radical-Derived Oxygenated Products

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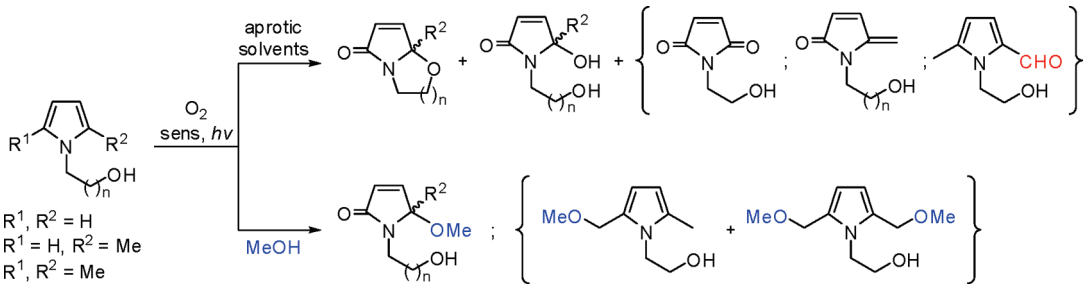

Photooxidation of pyrrole adducts **7**−**10** has been investigated in order to establish a general reaction pattern and mechanism for the formation of the resulting oxygenated products. The reactions were performed in several solvents utilizing both type I and type II sensitizers. In most cases, photooxidations gave complex mixture of products. Among these products, 5,5- or 6,5-bicyclic lactams (**11**, **15**, and **19**), maleimide **12** unsaturated γ-lactams (**16** and **20**), 5-hydroxylactams (**13**, **17**, and **21**), and 5-methoxylactams (**14**, **18**, and **22**) were isolated and characterized. Photooxidation of 2,5-dimethyl-substituted pyrrole **10** in aprotic solvents unexpectedly afforded aldehyde **23** as the major product. Moreover, photooxidation of pyrrole adduct **10** in protic solvents exclusively gave the unprecedented solvent-trapped products **24**−**27**. The formation of products **11**−**22** was rationalized by the intermediacy of a common endoperoxide intermediate, which could be formed by both type I and type II mechanisms. Compounds **23**−**27** were most probably formed via an electron-transfer mechanism.

Introduction

Singlet oxygen ($^1O_2$)[1,2]-mediated oxidation of pyrroles is of significant interest due to the widespread occurrence of pyrrole derivatives in natural products and the well-established sensitivity of these heterocyclic compounds under photooxidation conditions.[3] In this context, pyrrole derivatives often require special handling in order to minimize their oxidative decomposition. Initial interest in the photocatalytic oxidation of pyrroles has been driven by the developments in phototherapeutic methods treating neonatal jaundice.[4] Recently, attention has been focused on the role of porphyrins in the so-called photodynamic action.[5] One of the problems associated with the photooxidation of pyrrole derivatives is the

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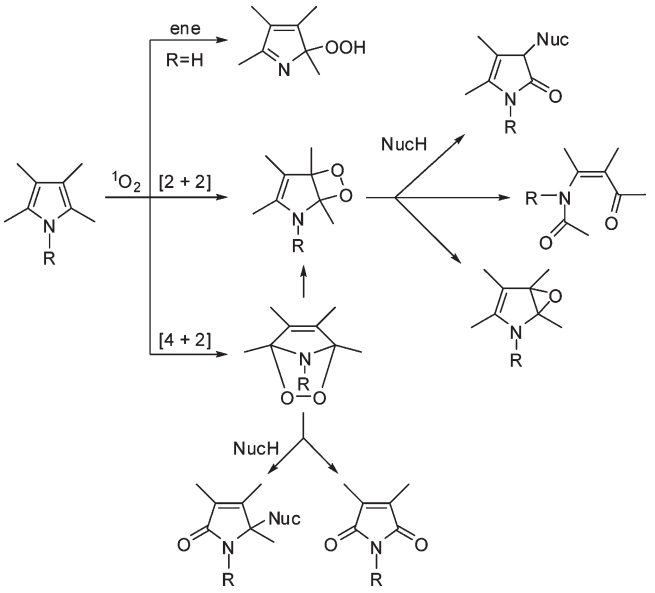
SCHEME 1. Most Common Oxygenated Products Detected from the Photooxidations of Pyrroles (Nuc = Nucleophile)



low chemoselectivity. Thus, their photosensitized oxidation often gives rise to a complex mixture of oxygenated products. This complexity has been mainly attributed to the multiple available pathways for the decomposition of primary oxygenated products such as hydroperoxides, dioxetanes, and endoperoxides. The most common isolated products are shown in Scheme 1. Remarkably, reaction conditions and the substitution pattern on the pyrrole ring play a significant role in determining the nature of the oxygenated products.

Wasserman and Boger reported an interesting study on the photooxidation of N-substituted[6] and N-unsubstituted[7] pyrroles. In particular, they showed that when the heterocyclic ring is substituted by both electron-releasing and electron-withdrawing groups, oxidation reactions can be controlled. This unique behavior has been utilized to synthesize the *d*,*l*- and *meso*-isochrysohermidin[8] as well as the A and B rings of the prodigiosin.[9] It is also worth mentioning that the photooxidation of *N*-arylpyrroles has led to the formation of hydroxy- or methoxylactams.[10] In the same work, it was proposed that the oxygenated products of these reactions may encompass features related to the mitomycin antibiotics.

In 2002, Demir and co-workers showed that the photooxidation of homochiral 2-methylpyrrole derivatives **1** can

SCHEME 2. Photosensitized Oxidation of Homochiral 2-Methylpyrroles

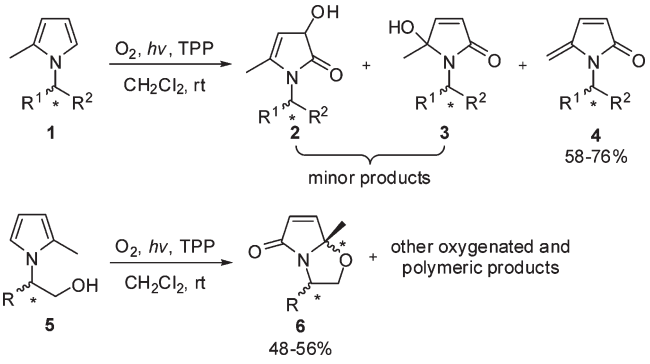
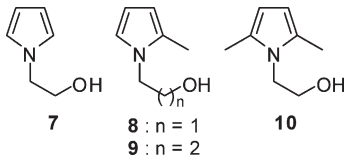


CHART 1



be converted into unsaturated γ-lactams **4** in high yields (Scheme 2);[11] note that lactams **3** and **4** are important synthons for the preparation of a variety of biologically active compounds.[12] More recently, Demir and Aydoyan showed that the $^1O_2$-mediated oxidation of homochiral 2-methylpyrroles **5** produced chiral bicyclic lactams **6** in good diastereoselectivity and moderate to high chemical yields (Scheme 2).[13] It should be also mentioned that chiral bicyclic lactams are frequently used as synthons in the total synthesis of certain natural products.[14,15] The high chemoselectivity in the photooxidation of homochiral 2-methylpyrrole derivatives **1** and **5** prompted us to study the photosensitized oxidation of a family of related substrates. Herein, we report the structure as well as the stereochemistry of a series of novel products formed in the reactions of pyrrole adducts **7**−**10** (Chart 1) with photoreactive molecular oxygen species. We also thoroughly discuss mechanistic possibilities in these photocatalytic oxidations.

Results and Discussion

Photosensitized Oxidation of Pyrrole Derivative 7. The photooxidation of **7** (prepared by a known procedure)[16]

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(11) Demir, A. S.; Aydoyan, F.; Akhmedov, I. M. *Tetrahedron: Assymetry* **2002**, *13*, 601–605.

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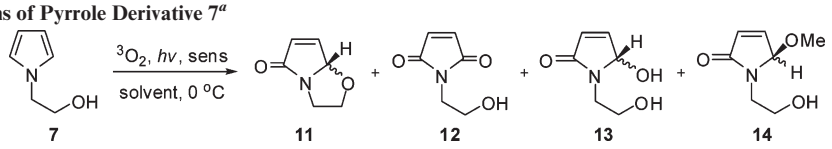
TABLE 1. Photooxidations of Pyrrole Derivative 7[a]



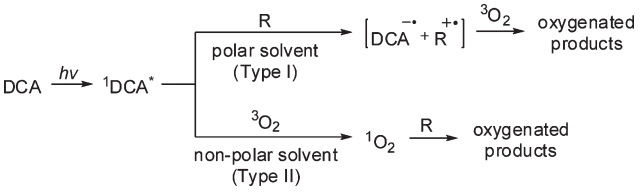
entry	solvent (radical scavenger)	ε[b] (20 °C)	sens[c]	**11**[d]	**12**[d]	**13**[d]	**14**[d]
1	CCl_4	2.24	TPP	17	24	59	
2	benzene	2.28	TPP	14	38	48	
3	CH_2Cl_2	9.14	TPP	16	43	41	
4	$(CH_3)_2CO$	21.0	RB	24	46	30	
5	CH_3CN	36.64	RB	24	45	31	
6	MeOH	33.0	RB	< 5	26	19	~50
7	CH_2Cl_2 (galvinoxyl)	9.14	TPP	18	40	42	
8	MeOH (galvinoxyl)	33.0	RB	< 5	26	24	~45
9	CH_3CN	36.64	DCA	23	51	26	
10	CH_3CN	36.64	$W_{10}O_{32}^{4-}$	6	76	18	

[a]All photooxidations were run up to 70−80% conversion of pyrrole **7**. [b]Dielectric constant.[17] [c]Sens = sensitizer. [d]Relative product yield (%) was determined by ^{1}H NMR analysis of the crude reaction mixtures (average of four runs, error ± 4%).

was initially carried out in oxygen-saturated CH_2Cl_2, at 0 °C in the presence of tetraphenylporphyrin (TPP, principally a type II sensitizer) with a 300 W xenon lamp (> 300 nm) as the light source (Table 1 , entry 3). The reaction was monitored by ^{1}H NMR spectroscopy, while the product distribution was found to be independent of the conversion. In particular, irradiation of **7** for 2 min (78% conversion) exclusively gave three products: 5,5-bicyclic lactam **11**, maleimide **12**, and 5-hydroxylactam **13** (Table 1, entry 3). Surprisingly, unlike the previously reported formation of lactam **6** (Scheme 2) as the major isolated product,[13] in our case 5,5-bicyclic lactam **11** was the minor product. When the photooxidation of **7** was performed using identical conditions with those described previously[11,13] (i.e., in oxygen-saturated CH_2Cl_2 solution, at rt, in the presence of TPP under irradiation with a 100 W sodium lamp), the product distribution was again identical with our first run. Next, three control experiments were carried out: (1) irradiation of **7** in the presence of TPP under anaerobic conditions; (2) irradiation of **7** in the absence of TPP under aerobic conditions; and (3) a solution of **7** was left in the dark in the presence of TPP and molecular oxygen. In all cases, pyrrole derivative **7** remained unreacted. These results clearly indicate that products **11**−**13** are formed via a photosensitized process.

In order to explore the mechanism of adduct formation we then performed the same photosensitized oxidation in a variety of solvents and sensitizers. As can be seen in Table 1, photooxidation of pyrrole **7** in the presence of TPP (entries 1−3) and Rose Bengal (RB) (entries 4 and 5) in polar and nonpolar solvents afforded adducts **11**−**13**. In all cases, 5,5-bicyclic lactam **11** was the minor product. Note that for the first four runs as the solvent polarity increases the relative yield of product **13** decreases with simultaneous increase of product **12**. When methanol was used as the solvent, apart from oxygenated products **11**−**13**, 5-methoxylactam **14** was also obtained (Table 1, entry 6). Furthermore, the presence of galvinoxyl as a radical scavenger/inhibitor in the photooxidation of pyrrole **7** in CH_2Cl_2 or MeOH did not significantly affect the product distribution (Table 1, compare entries 3 and 6 with 7 and 8, respectively). Therefore, it seems reasonable to assume that the formation of products **11**−**14** and their distribution are independent of the presence of a radical scavenger.

SCHEME 3. Type I and Type II DCA-Sensitized Photooxidation Mechanisms (R = Unsaturated Substrate)



Control experiments showed that product **13** does not interconvert to **11**, **12**, or **14**, either photochemically or in the dark. In addition, when we used pyridine as cosolvent (along with CH_2Cl_2 as solvent), we found that the yield of pyrrolinone products decreased compared to the reaction in the absence of pyridine. Therefore, taking into account previous findings,[18] it appears logical to assume that the endoperoxide, between pyrrole **7** and $^1O_2$, is precursor to the isolated photoproducts **11**−**14**.

Previous studies have shown that the photooxidation of pyrroles in the presence of molecular oxygen and type II sensitizers produces 5-hydroxy or 5-methoxylactams and maleimides. Specifically, these products are obtained when a hydrogen atom[18a,19] or an alkyl group[19c,20] is placed at the α-position of the reactant pyrrole.[19c,20] Furthermore, the oxygenation of organic compounds photosensitized by 9,10-dicyanoanthracene (DCA) has been extensively studied

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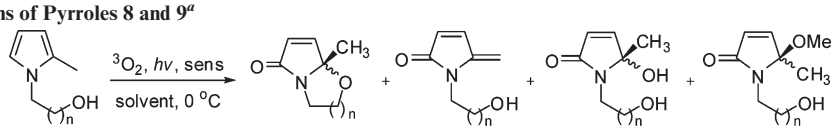
TABLE 2. Photooxidations of Pyrroles 8 and 9[a]



entry	n	solvent ($^1O_2$ quencher or radical scavenger)	sens[b]	**15**, n = 1[c] **19**, n = 2[c]	**16**, n = 1[c] **20**, n = 2[c]	**17**, n = 1[c] **21**, n = 2[c]	**18**, n = 1[c] **22**, n = 2[c]
1	1	CCl_4	TPP	9	41	50	
2	1	Benzene	TPP	15	47	38	
3	1	CH_2Cl_2	TPP	11	70	19	
4	1	$(CH_3)_2CO$	RB	10	46	44	
5	1	CH_3CN	RB	10	57	33	
6	1	MeOH	RB	8	15	15	62
7	1	CH_2Cl_2 (DABCO)	TPP	17	55	28	
8	1	CH_2Cl_2 (galvinoxyl)	TPP	19	49	32	
9	1	MeOH (galvinoxyl)	RB	< 5	15	25	~55
10	1	CCl_4	DCA	11	26	63	
11	1	CH_3CN	DCA	11	43	46	
12	1	CH_3CN (DABCO)	DCA	17	31	52	
13	1	CH_3CN	$W_{10}O_{32}^{4-}$	18	48	34	
14	2	CH_2Cl_2	TPP	36	45	19	
15	2	MeOH	RB	14	9	17	60
16	2	CH_2Cl_2 (galvinoxyl)	TPP	35	52	13	
17	2	MeOH (galvinoxyl)	RB	16	10	24	50

[a]All photooxidations were run up to 70−80% conversion of pyrrole **8** or **9**. [b]Sens = sensitizer. [c]Relative product yield (%) was determined by ^1H NMR analysis of the crude reaction mixtures (average of four runs, error ± 4%).

and has been shown to occur by two competing mechanisms: type I and II (Scheme 3).[21] The relative contribution of these two pathways depends on solvent polarity and the nature of the substrate. It is generally accepted that, in polar solvents, ion pairs diffuse apart to give solvent-separated radical ions, which can react further.[22] On the other hand, in the presence of $^1O_2$-acceptors and nonpolar solvents, the corresponding $^1O_2$-adducts appear to be the mainly formed products.[23] Moreover, photocatalyzed reactions induced by polyoxometalates such as decatungstate ($W_{10}O_{32}^{4-}$) have been explored extensively over the past several years.[24,25] It is generally accepted that illumination of $W_{10}O_{32}^{4-}$ leads to the formation of a charge-transfer excited state $W_{10}O_{32}^{4-*}$ that decays in less than 30 ps to an extremely reactive transient, which is designated as wO.[26] In general, wO reactivity provides an interesting mechanistic tool for studies of light-induced oxidations, since it proceeds *exclusively* via free-radical pathways (electron or hydrogen transfer).[27]

In this context, and in order to get further information on the reaction mechanism, we examined the photooxidation of **7** under type I conditions (electron and/or hydrogen transfer). In particular, the photooxidation reactions of **7** were carried out in CH_3CN, at 0 °C, with either DCA or $W_{10}O_{32}^{4-}$ as photosensitizers. In this case, products **11**−**13** were exclusively formed, and their relative yields are shown in Table 1 (entries 9 and 10). Note that these entries show an increased relative yield of maleimide **12** in comparison to that of entry 5 (with CH_3CN as the solvent).

Photosensitized Oxidations of 2-Methylpyrroles 8 and 9. Compounds 1-(2-hydroxyethyl)-2-methylpyrrole (**8**) and 1-(3-hydroxypropyl)-2-methylpyrrole (**9**) were prepared from the reactions of 5-chloro-3-penten-2-one with the corresponding amino alcohols.[28] The photooxidation reactions of **8** (under mainly type II conditions) were carried out in several solvents, at 0 °C, in the presence of molecular oxygen and TPP or RB (Table 2, entries 1−5). The conversion and product distribution in these reactions were measured by integrating the appropriate peaks in the ^1H NMR spectra. It was again found that the product distribution was independent of the conversion. In all cases, three oxygenated products were formed (Table 2, entries 1−5). In particular, irradiation of **8** gave 5,5-bicyclic lactam **15**, unsaturated

(21) For two related reviews, see: (a) Foote, C. S. In *Free Radicals in Biology*; Pryor, W. A., Ed.; Academic Press: New York, 1976; pp 85−133. (b) Foote, C. S. *Tetrahedron* **1985**, *41*, 2221–2227.

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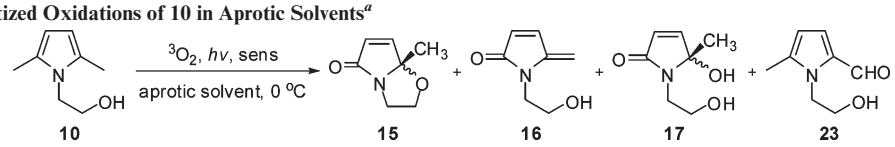
(28) (a) Barbry, D.; Faven, C.; Ayana, A. *Synth. Commun.* **1993**, *23*, 2647–2658. (b) Demir, A. S.; Akhmedov, İ. M.; Tanyeli, C.; Gerçek, Z.; Gadzhili, R. A. *Tetrahedron: Asymmetry* **1997**, *8*, 753–757. (c) Demir, A. S.; Akhmedov, İ. M.; Şeşenoğlu, Ö.; Alptürk, O.; Apaydin, S.; Gerçek, Z.; İbrahimzade, N. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1162–1167.

TABLE 3. Photosensitized Oxidations of 10 in Aprotic Solvents[a]



entry	solvent ($^1O_2$ quencher or radical scavenger)	sens[b]	15[c]	16[c]	17[c]	23[c]
1	CCl_4	TPP	< 5	~25	< 5	65
2	benzene	TPP	8	nd[d]	33	59
3	CH_2Cl_2	TPP	8	9	30	53
4	$(CH_3)_2CO$	RB	8	10	20	62
5	CH_3CN	RB	8	32	9	51
6	CH_2Cl_2 (galvinoxyl)	TPP	10	35	40	15
7	CH_2Cl_2 (DABCO)	TPP	5	7	25	63
8	CCl_4	DCA	9	nd[d]	25	66
9	CH_3CN	DCA	nd[d]	11	33	56
10	CH_3CN (DABCO)	DCA	13	nd[d]	18	69
11	CH_3CN	$W_{10}O_{32}^{4-}$	15	28	12	45

[a]All photooxidations were run up to 70−80% conversion of pyrrole **10**. [b]Sens = sensitizer. [c]Relative product yield (%) was determined by ^1H NMR analysis of the crude reaction mixtures (average of four runs, error ± 4%). [d]Not detected.

γ-lactam **16**, and 5-hydroxylactam **17**. It is worth mentioning that the addition of a catalytic amount of *p*-TsOH to a solution of **17** in toluene/CH_3CN (3:1, v/v) at 70−80 °C led after 1 h to the formation of compound **16**. This observation further confirms the structure of compound **17**.

In the aforementioned cases (Table 2, entries 1−5), solvent polarity did not have any considerable effect on the product distribution; 5,5-bicyclic lactam **15** was the minor product (9−15%), whereas unsaturated γ-lactam **16** and 5-hydroxylactam **17** were the major products (85−91% combined yield). When the solvent was methanol, methanol-trapped compound **18** was obtained as the major product (Table 2, entry 6). When TPP was used as the photosensitizer in CH_2Cl_2 and in the presence of a catalytic amount of DABCO, a well-established $^1O_2$ physical quencher,[29] products **15**−**17** were exclusively formed (Table 2, entry 7) suggesting that their formation is independent of the presence of $^1O_2$ quenchers. Moreover, we examined the photooxidation of pyrrole **8** in CH_2Cl_2 or MeOH in the presence of galvinoxyl as a radical inhibitor (Table 2, entries 8 and 9). In accordance with our previous findings (Table 1, entries 7 and 8), products **15**−**18** were mainly observed.

As an extension of our studies we also performed the photosensitized oxidations of **8** with DCA in both polar and nonpolar solvents (Table 2, entries 10 and 11). In addition, we carried out the photooxidation of **8** in CH_3CN with either DCA in the presence of DABCO or with $W_{10}O_{32}^{4-}$ (Table 2, entries 12 and 13). In these cases, 5,5-bicyclic lactam **15** was the minor product (11−18%), whereas unsaturated γ-lactam **16** and 5-hydroxylactam **17** were the major adducts (82−89% combined yields).

The photooxidation of pyrrole **9** in CH_2Cl_2 at 0 °C with TPP as the sensitizer afforded 6,5-bicyclic lactam **19**, unsaturated γ-lactam **20**, and 5-hydroxylactam **21** (Table 2, entry 14). Note that 6,5-bicyclic lactam **19** was formed in 36% relative yield, and in this case, the minor product was 5-hydroxylactam **21** (19% relative yield). These findings, in conjunction with our results on the photooxidation of pyrroles **7** and **8**, demonstrate that the formation of the 6,5-bicyclic lactam is generally preferred compared to the 5,5-bicyclic lactam. When methanol was used as the solvent, 5-methoxylactam **22** was obtained in 60% relative yield (Table 2, entry 15) besides oxygenated products **19**−**21**. Ultimately, when galvinoxyl was used as radical inhibitor in the photooxidation of pyrrole **9** in CH_2Cl_2 or MeOH, products **19**−**21** or **19**−**22** were observed, respectively (Table 2, entries 16 and 17).

Photosensitized Oxidations of Pyrrole 10. 1-(2-Hydroxyethyl)-2,5-dimethylpyrrole (**10**) was prepared by the Paal−Knorr condensation of 2,5-hexanedione and ethanolamine.[30,31] The photooxidations of **10** were initially carried out in several aprotic solvents under conditions similar to that for pyrroles **7** and **8** (Table 3, entries 1−5), while the conversion and the product distribution were measured as described above. It was once again found that the product distribution was independent of the conversion; in particular, irradiation of **10** in CH_2Cl_2 furnished a complex mixture of four oxygenated products: 5,5-bicyclic lactam **15**, unsaturated γ-lactam **16**, 5-hydroxylactam **17**, and aldehyde **23**. Solvent polarity did not have a considerable impact on product distribution (Table 3, entries 1−5). Interestingly, aldehyde **23** was the major product (51−65%), whereas oxygenated products **15**−**17** were generally detected in small quantities. On the basis of what is known for the photooxidation products of substituted pyrroles,[3c,e,f,11,13] the formation of **23** was completely unprecedented.

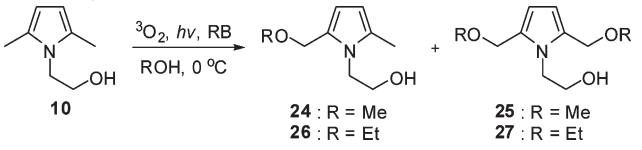
In order to understand the origin of aldehyde **23**, we performed the photooxidation of **10** in CH_2Cl_2 using TPP as sensitizer, along with a catalytic amount of either galvinoxyl, a radical scavenger, or DABCO, a $^1O_2$ quencher (Table 3, entries 6 and 7). The photooxidation of **10** in CH_2Cl_2 in the presence of galvinoxyl furnished aldehyde **23** in 15% relative yield (entry 6), while, in the absence of galvinoxyl, aldehyde **23** was formed in 53% relative yield (entry 3). This result strongly supports a free-radical process

(29) (a) Ouannes, C.; Wilson, T. *J. Am. Chem. Soc.* **1968**, *90*, 6527–6528. (b) Foote, C. S. In *Quenching of Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Ed.; Academic Press: New York, 1979; pp 139−173.

(30) (a) Paal, C. *Chem. Ber.* **1884**, *17*, 2756–2767. (b) Knorr, L. *Chem. Ber.* **1884**, *17*, 1635–1642.

(31) Zhu, M.; Spink, D. C.; Bank, S.; Chen, X.; DeCaprio, A. P. *J. Chromatogr.* **1993**, *628*, 37–47.

TABLE 4. Photooxidations of Pyrrole 10 in Protic Solvents (MeOH and EtOH)



entry	R	irradiation time	conversion (%)[a]	**24**, R = Me[a] **26**, R = Et[a]	**25**, R = Me[a] **27**, R = Et[a]
1	Me	1 min	20	100	nd[b]
2	Me	1.5 min	40	79	21
3	Me	2 min	50	73	27
4	Me	2.5 min	68	59	41
5	Me	4 min	100	16	84
6	Me	5 min	100	nd[b]	100
7	Et	40 s	25	100	nd[b]
8	Et	1.5 min	40	100	nd[b]
9	Et	2 min 40 s	48	100	nd[b]
10	Et	3 min	72	84	16
11	Et	3.5 min	100	59	41
12	Et	4.5 min	100	nd[b]	100

[a]Conversion and relative product yield (%) were determined by ^{1}H NMR analysis of the crude reaction mixtures (average of three runs, error ± 4%). [b]Not detected.

for the formation of aldehyde **23**. On the other hand, the photooxidation of **10** in the presence of DABCO furnished aldehyde **23** in 63% relative yield (entry 7). Moreover, we performed the photosensitized oxidation of **10** with DCA in both polar and nonpolar solvents (Table 3, entries 8 and 9). Additionally, we carried out the photooxidation of **10**, in CH_3CN, with DCA in the presence of DABCO as well as with $W_{10}O_{32}^{4-}$ (Table 3, entries 10 and 11). In all these cases, aldehyde **23** was the major product (45−69%).

When pyrrole **10** was photooxidized in MeOH using RB as sensitizer, at 0 °C for 1 min, an unprecedented, methanol-trapped product (**24**) was formed quantitatively (Table 4, entry 1). Product **24** is very reactive and, under the photooxidation conditions, can be readily transformed into diether **25**. Indeed, when **10** was photooxidized in MeOH for 5 min (in the presence of a catalytic amount of RB, at 0 °C), diether **25** was formed quantitatively (Table 4, entry 6). The relative yields of these adducts in various irradiation times are shown in Table 4 (entries 2−5). In order to be certain that compounds **24** and **25** are indeed derived through photosensitized oxidations, we performed two control experiments: (1) irradiation of **10** under oxygen but in the absence of a sensitizer and (2) irradiation of **10** with a sensitizer under anaerobic conditions. Both experiments failed to afford either **24** or **25**. Furthermore, we performed the photooxidation of **10** in MeOH with a catalytic amount of galvinoxyl. In this case, ^{1}H NMR analysis of the crude photooxidation mixtures (obtained after 1, 2 and 4 min) showed consumption of starting material and formation of unidentified highly polar side products. These results clearly demonstrate that methanol-trapped products, **24** and **25**, are formed through a radical-mediated process.

In a similar manner, we performed the photooxidation of pyrrole **10** in EtOH. In accordance to the findings obtained using MeOH as a solvent, we were able to isolate and characterize ethanol-trapped products **26** and **27**. The relative yields of these compounds were dependent on the pyrrole conversion (Table 4, entries 7−12).

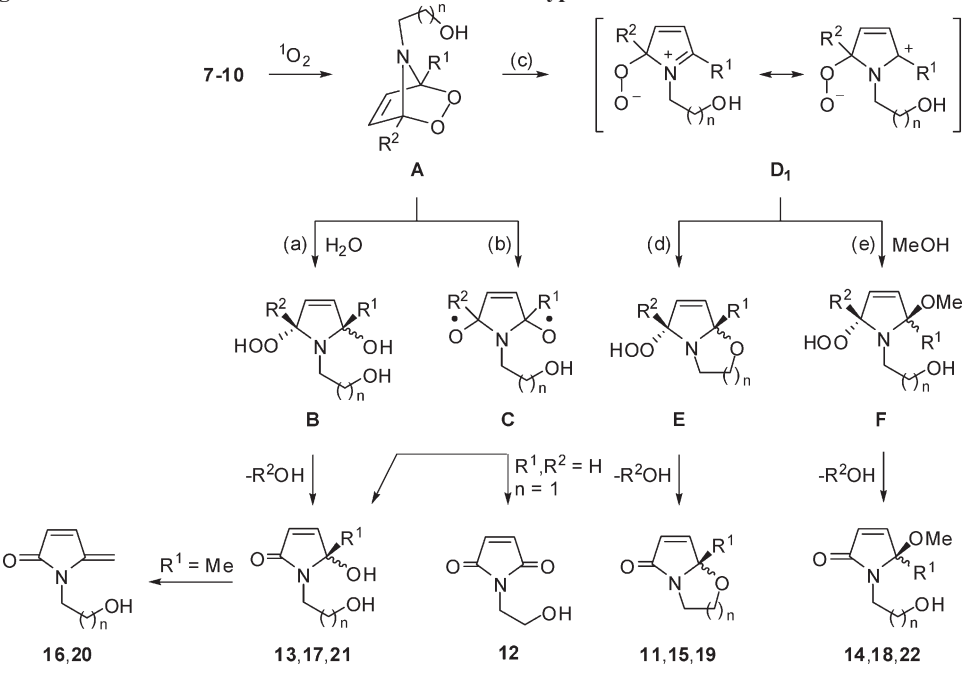
To the best of our knowledge, there are no reports regarding the formation of such trapped products (**24**−**27**) in the photooxidation of substituted furans[3d−f,32] or pyrroles. In fact, the photooxidation of 2,5-dimethylpyrrole in methanol has been reported to afford 5-methoxy-5-methyl-3-pyrrolin-2-one, 5-methoxy-5-methoxymethyl-3-pyrrolin-2-one, and 2-formyl-2-methoxy-5-methylidene-3-pyrroline.[33]

Mechanistic Considerations. As we already mentioned, it is generally accepted that type I and type II photooxidation mechanisms (Scheme 3) are often competitive. When RB, DCA, or $W_{10}O_{32}^{4-}$ are used in polar solvents, the type I mechanism predominates, whereas in the case of TPP as the sensitizer in nonpolar solvents, the type II process (energy transfer) is more likely to occur. Consistent to this hypothesis, the photooxidation of **7**−**10** in CH_2Cl_2 in the presence or in the absence of galvinoxyl (Tables 1−3) gave rise to the same oxygenated products and in similar relative yields. However, similar oxygenated products were observed (a) when the photooxidation of **7**−**10** in polar solvents (using RB, DCA, or $W_{10}O_{32}^{4-}$ as sensitizers) was carried out in the presence or in the absence of galvinoxyl (Tables 1−3) and (b) when the photooxidation of **8** or **10** in CH_2Cl_2 (using TPP as sensitizer) was examined in the presence or in the absence of DABCO (Tables 2 and 3). Taking into account the data obtained from the TPP-sensitized photooxidations of pyrroles **8** and **10** in CH_2Cl_2, it seems likely that these reactions proceed with both type I and type II mechanisms. Considering the reduction potential of ^{1}TPP* (E_{red} = 0.81 V vs SCE),[34] an electron-transfer mechanism[35] should be possible for substrates with negative oxidation potentials. Although there are no literature data available, we believe that pyrroles **8** and **10** comply with this requirement. More generally, on the basis of our results (from the sensitized photooxidations of pyrroles **7**−**10**), we suggest that oxygenated products **11**−**22** can be formed by either of the two mechanisms or, most probably, by both of them operating simultaneously: (a) a type I electron transfer (ET) or hydrogen abstraction transfer (HAT) process and (b) a type II energy-transfer process via $^1O_2$. The distinction between these two mechanistic pathways is not always straightforward.

The formation of oxygenated products **11**−**22** under energy-transfer conditions (type II) is outlined in Scheme 4. It is known that in the $^1O_2$ reactions of pyrroles, the oxygenated products are derived from a common reactive endoperoxide intermediate. Lightner and co-workers observed the formation of this endoperoxide intermediate by using low-temperature ^{1}H NMR spectroscopy.[18a,19c] The origin of the oxygenated products can be then explained by ground- and excited-state reactions of these unstable endoperoxides. In the present case, we suggest that the initially formed endoperoxide **A** can be followed by five different mechanistic pathways (Scheme 4, pathways a−e). Hydrolysis of endoperoxide **A** affords hydroperoxide **B**, a proper precursor to 5-hydroxylactams **13**, **17**, and **21** (pathway a);

(32) Foote, C. S.; Wuesthoff, M. T.; Wexler, S.; Burstain, I. G.; Denny, R.; Schenck, G. O.; Schulte-Elte, K. −H. *Tetrahedron* **1967**, *23*, 2583–2599.
(33) Low, L. K.; Lightner, D. A. *J. Chem. Soc., Chem. Commun.* **1972**, 116–117.
(34) Darwent, J. R.; Douglas, P.; Harriman, A.; Porter, G.; Richoux, M.-C. *Coord. Chem. Rev.* **1982**, *44*, 83–126.
(35) (a) Kavarnos, G. J.; Turro, N. *J. Chem. Rev.* **1986**, *86*, 401–449. (b) Kavarnos, G. J. Fundamental Concepts of Photoinduced Electron-Transfer. In *Top. Curr. Chem.*; Springer: Berlin-Heidelberg, 1990; Vol. 156, pp 21−58.

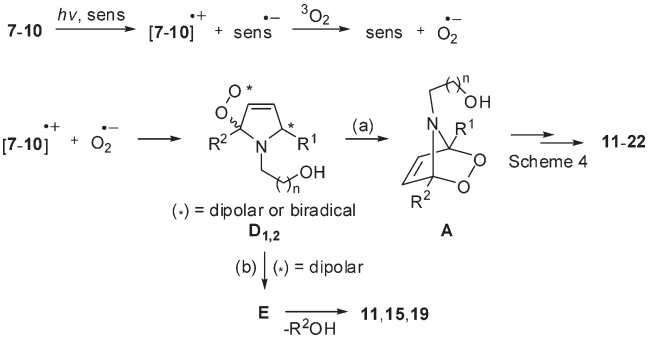
SCHEME 4. Suggested Mechanism for the Formation of 11−22 under Type II Conditions



however, it has been reported that in nonaqueous solvents the major pathway for the formation of 5-hydroxylactams is *a*-H abstraction either intramolecularly, from biradical **C** (pathway b), or by other agents (e.g., an excited molecule of the sensitizer).[18a] Also note that the role of the pyrrole *a*-hydrogen is very important in the mechanism of endoperoxides decomposition via nonhydrolytic pathways.[11,18a,19c,20a,c−e] We believe that in case of the photooxidation of pyrrole **10**, 5-hydroxylactam **17** originates from the hydrolysis of the corresponding endoperoxide followed by the loss of one *a*-methyl group. A similar dealkylation reaction was reported in 1972.[20b]

Oxygenated products **17** and **21** can undergo elimination of H_2O to form unsaturated γ-lactams **16** and **20**, respectively. 1-(Hydroxyethyl)maleimide **12**, on the other hand, may originate from biradical **B**, formed either by thermal or photochemical O−O homolysis of **A** followed by hydrogen loss from the alkoxy radicals (pathway b).[36] The formation of bicyclic hydroperoxide **E** from **A** involves the intramolecular nucleophilic attack of the hydroxyl group either directly or through an open dipolar $\mathbf{D_1}$,[37] shown in pathway c (Scheme 4).[13] The bicyclic hydroperoxide **E** decomposes yielding bicyclic lactams **11**, **15**, and **19** (pathway d). In a similar manner, methanolysis of the endoperoxide **A**, either directly or via pathway c, gives hydroperoxide **F**, a precursor to 5-methoxylactams **14**, **18**, and **22** (pathway e).

SCHEME 5. Proposed Mechanistic Pathways for the Formation of 11−22 under Type I Conditions



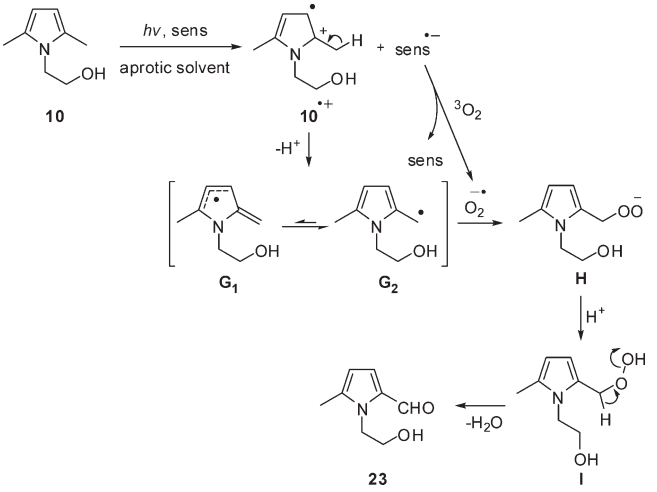
A reasonable mechanistic rationalization for the sensitized photooxidation of pyrroles **7**−**10** under ET conditions (type I) is presented in Scheme 5. Initially, an electron is transferred from the pyrrole to the photoexcited sensitizer to form the radical ions. Subsequent oxidation of $sens^{\bullet-}$ by ET to molecular oxygen furnishes the superoxide radical anion ($O_2^{\bullet-}$). Reaction of the latter with $[\mathbf{7-10}]^{\bullet+}$ gives rise to dipolar or biradical $\mathbf{D_1}$ or $\mathbf{D_2}$, respectively. The intermediate or transition state $\mathbf{D_{1,2}}$ is expected to yield endoperoxide **A** (Scheme 5, pathway a).[38] Eventually, oxygenated products **11**−**22** are generated according to the mechanism shown in Scheme 4. Alternatively, dipolar species $\mathbf{D_1}$ is intramolecularly attacked by the hydroxyl moiety, forming the bicyclic hydroperoxide which decomposes to bicyclic lactams **11**, **15**, and **19** (Scheme 5, pathway b).

(36) Storey, P. R.; Morrison, W. H.; Butler, J. M. *J. Am. Chem. Soc.* **1969**, *91*, 2398–2400.

(37) In the case that the exciplex has a zwitterionic character, the bicyclic lactams and the 5-methoxylactams could also be formed without the intermediacy of the endoperoxide **B**. Also note that 1,4-dipolars and 1,4-biradicals are often suggested as intermediates in singlet oxygen [4 + 2] cycloaddition reactions. For some representative examples, see: (a) Clennan, E. L.; Nagraba, K. *J. Org. Chem.* **1987**, *52*, 294–296. (b) O'Shea, K. E.; Foote, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 7167–7170. (c) Kwon, B.-M.; Foote, C. S.; Khan, S. I. *J. Org. Chem.* **1989**, *54*, 3378–3382. (d) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 3330–3343. (e) Motoyoshiya, J.; Okuda, Y.; Matsuoka, I.; Hayashi, S.; Takaguchi, Y.; Aoyama, H. *J. Org. Chem.* **1999**, *64*, 493–497. (f) Bobrowski, M.; Liwo, A.; Oldziej, S.; Jeziorek, D.; Ossowski, T. *J. Am. Chem. Soc.* **2000**, *122*, 8112–8119. (g) Sevin, F; McKee, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 4591–4600.

(38) For the formation of endoperoxides via an electron-transfer pathway, see: (a) Eriksen, J.; Foote, C. S.; Parker, T. L. *J. Am. Chem. Soc.* **1977**, *99*, 6455–6456. (b) Santamaria, J. *Tetrahedron Lett.* **1981**, *22*, 4511–4514. (c) Jianxin, C.; Yi, C.; Baowen, Z.; Yangfu, M. *Acta Chim. Sin.* **1985**, *43*, 601–602.

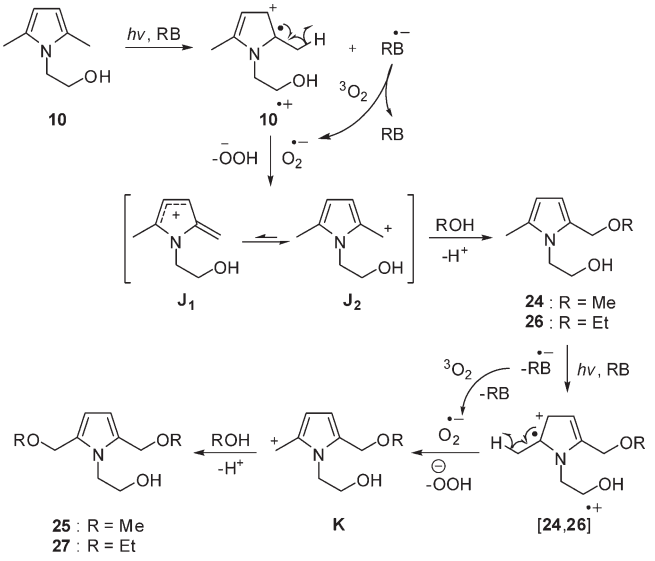
SCHEME 6. Suggested Mechanism for the Formation of 23 under Type I Conditions



According to the data in Table 3, aldehyde **23** is generated to a greater extent in aprotic solvents via an ET process. The suggested mechanism for this novel photooxidation reaction is shown in Scheme 6. Electron transfer from pyrrole **10** to the excited state of the sensitizer affords radical cation $\mathbf{10}^{\bullet+}$ and $\text{sens}^{\bullet-}$. Oxidation of $\text{sens}^{\bullet-}$ via ET to molecular oxygen furnishes the superoxide radical anion ($O_2^{\bullet-}$), while a simultaneous proton loss from $\mathbf{10}^{\bullet+}$ affords radical **G**. The preferential site for radical recombination between **G** and the superoxide radical anion is the *a*-carbon atom given that the aromaticity is restored in species $\mathbf{G_2}$. This radical intermediate leads to hydroperoxy anion **H**, the protonation of which affords hydroperoxide **I**. At the last step, **I** undergoes dehydration to yield aldehyde **23**.

RB is a well-known photosensitizing dye of xanthine origin. This powerful photosensitizer is known for its high efficiency in generating singlet oxygen.[39] However, it has been reported that it can also form radicals in the presence of many electron-donating molecules.[40] Considering the data obtained from the RB-sensitized photooxidations of pyrrole **10** in MeOH in the presence or in the absence of galvinoxyl, we strongly suggest that solvent-trapped products **24**−**27** are formed via an ET mechanism. This mechanism is outlined in Scheme 7. In particular, ET from **10** to the excited state of RB leads to the formation of the radical ions $\mathbf{10}^{\bullet+}$ and $\text{RB}^{\bullet-}$. Since the radical anion of RB is a reducing species, it can form superoxide radical anion ($O_2^{\bullet-}$) under aerobic conditions. Superoxide radical anion may then abstract a hydrogen atom from $\mathbf{10}^{\bullet+}$, affording cation **J**. The possibility of a hydrogen atom abstraction from $\mathbf{10}^{\bullet+}$, by the excited stated of RB, cannot be excluded. The *a*-carbon atom should be the preferential site for methanol or ethanol attack (the resonance structure $\mathbf{J_2}$ predominates). This leads to the formation of products **24** and **26**, which are even better electron donors than **10**. Further ET from **24** or **26** to the excited stated of RB and subsequent HAT of $\mathbf{24}^{\bullet+}$or $\mathbf{26}^{\bullet+}$ affords cation **K**. This cation can be trapped by methanol or ethanol to form products **25** and **27**, respectively.

SCHEME 7. Suggested Mechanism for the Formation of 24−27 under Type I Conditions



Conclusion

In this work, we studied the photooxidation of N-substituted pyrroles **7**−**10** using either type I or type II conditions. In all cases, bicyclic lactams **11**, **15**, and **19** were the minor products. Seventeen different products from both protic and polar or nonpolar aprotic solvents were isolated and fully characterized. The formation of products **11**−**22** could be rationalized by both type I and type II mechanisms; the distinction between these mechanistic pathways is not trivial. On the other hand, unprecedented compounds **23**−**27** were most probably formed through an electron-transfer mechanism.

Experimental Section

General Procedures for the Photosensitized Oxidations of Pyrrole Adducts 7−10. A solution of the pyrrole (0.27 mmol) in solvent (50 mL) containing a catalytic amount of sensitizer (10^{-4} M) was placed in a flask, and oxygen was gently bubbled through it. The solution was cooled to 0 °C and irradiated with a xenon 300 W lamp. All photooxidations were stopped at 70−80% pyrrole conversion. When TPP and RB were used as sensitizers, irradiation time varied between 1 and 5 min. On the other hand, when DCA and $W_{10}O_{32}^{4-}$ were used as sensitizers, irradiation time varied between 30 min and 2 h. When DABCO or galvinoxyl were used in the photooxidation, their concentration was 1.2×10^{-3} and 10^{-2} M, respectively. In most cases, photooxidations gave complex mixtures of oxygenated products. These adducts were purified by flash column chromatography using silica gel.

Photosensitized Oxidations of 7. Photolysis of **7** in several solvents and sensitizers (Table 1) gave complex mixtures of oxygenated products **11**−**14**. These adducts were purified by flash column chromatography over silica gel (hexanes/EtOAc = 4:1 → EtOAc/acetone = 3:1 v/v). The spectroscopic data of products **11**−**14** are as follows:

2,3-Dihydropyrrolo[2,1-*b*]oxazol-5(7a*H*)-one (11): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, 1H, J = 6.0 Hz), 6.16 (d, 1H, J = 6.0 Hz), 5.45 (br s, 1H), 4.27 (m, 1H), 4.19 (t, 1H, J = 7.0 Hz),

(39) (a) Gollnick, K.; Schenck, G. O. *Pure Appl. Chem.* **1964**, *9*, 507–525. (b) Murasecco-Suardi, P.; Gassmann, E.; Broun, A. M.; Oliveros, E. *Helv. Chim. Acta* **1987**, *70*, 1760–1766.

(40) For some selected examples, see: (a) Lambert, C.; Sarna, T.; Truscott, G. T. *J. Chem. Soc., Faraday Trans.* **1990**, *86*, 3879–3882. (b) Sarna, T.; Zajac, J.; Bowman, M. K.; Truscott, T. G. *J. Photochem. Photobiol. A: Chem* **1991**, *60*, 295–310. (c) Rózanowska, M.; Ciszewska, J.; Korytowski, W.; Sarna, T. *J. Photochem. Photobiol. B: Biol* **1995**, *29*, 71–77. (d) Lambert, C. R.; Kochevar, I. E. *Photochem. Photobiol.* **1997**, *66*, 15–25.

3.75 (m, 1H), 3.28 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 146.0, 131.3, 93.4, 71.0, 42.8 ppm; MS m/z = 125 (100, m/z = 95).

1-Hydroxyethylmaleimide (12): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 2H), 3.78 (m, 2H), 3.73 (m, 2H), 2.10 (br s, 1H, OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 134.4, 61.0, 40.8 ppm; ESI-MS m/z = 164.3 $[M + Na]^+$.

5-Hydroxy-1-(2-hydroxyethyl)-1*H*-pyrrol-2(5*H*)-one (13): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, 1H, J = 6.0 Hz), 6.11 (d, 1H, J = 6.0 Hz), 5.45 (br s, 1H), 5.26 (br s, 1H, OH), 3.91 (br s, 1H, OH), 3.76 (m, 3H), 3.39 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 146.5, 128.0, 84.8, 61.6, 43.5 ppm; MS m/z = 125 (100, m/z = 40).

1-(2-Hydroxyethyl)-5-methoxy-1*H*-pyrrol-2(5*H*)-one (14): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (d, 1H, J = 6.0 Hz), 6.29 (d, 1H, J = 6.0 Hz), 5.47 (br s, 1H), 3.80 (m, 2H), 3.56 (t, 2H, J = 5.0 Hz), 3.18 (s, 3H), 3.00 (br s, 1H, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 144.0, 130.5, 89.6, 61.8, 51.1, 43.7 ppm; ESI-MS m/z = 180.2 $[M + Na]^+$.

Photosensitized Oxidations of 8 and 9. Photolysis of **8** and **9** in several solvents and sensitizers (Table 2) gave complex mixtures of oxygenated products **15**−**18** and **19**−**22**, respectively. Compounds **15**−**18** were purified by flash column chromatography over silica gel (hexanes/EtOAc = 4:1 → EtOAc/acetone = 2:1 v/v). Compounds **19**−**22** were purified by flash column chromatography over silica gel (hexanes/EtOAc = 4:1 → EtOAc/acetone = 1:1 v/v).

Photosensitized Oxidations of 10. Photolysis of **8** and **9** in several solvents and sensitizers (Tables 3 and 4) gave mixtures of oxygenated products **15**−**17** and **23**−**27**, respectively. These adducts were purified by flash column chromatography over silica gel (hexanes/EtOAc = 4:1 → EtOAc/acetone = 2:1 v/v).

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Supporting Information Available: General experimental considerations and experimental procedures for the synthesis of pyrroles **7**−**10**. Analytical and spectroscopic data for compounds **7**−**10** and **15**−**27**. Copies of ^{1}H and ^{13}C NMR spectra for pyrroles **7**−**10** and the photooxidation products. Copies of HMQC and HMBC spectra for compounds **17** and **23**. Copies of DEPT 135 and HMQC spectra for compounds **24** and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.