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ON THE ROLE OF SINGLET OXYGEN IN THE SELF-SENSITIZED PHOTO-OXYGENATION OF BILIRUBIN AND ITS PYRROMETHENONE MODELS

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Abstract—4-Ethyl-3-methyl-5-(4-ethyl-3,5-dimethylpyrrolyl-2-methylidene)-3-pyrrolin-2-one (**1**), 3,4-diethyl-5-(4-ethyl-3,5-dimethylpyrrolyl-2-methylidene)-3-pyrrolin-2-one (**2**) and xanthobilirubinic acid (XBR) undergo self-sensitized photo-oxygenation, as does bilirubin. The reaction products of **1** consist of methylethylmaleimide, kryptopyrrole aldehyde and its photo-oxygenation product and oxygenated dipyrroles. The same products are formed from **2**, except xeronimide is found instead of methylethylmaleimide. Kinetic studies indicate that singlet oxygen is not necessarily involved in the photo-oxygenation reactions. Geometric photoisomerization ($Z \rightleftarrows E$) of **1** and **2**, and XBR proceeds at an even faster rate than photosensitized oxygenation.

THE mechanism of photo-oxidation of bilirubin IXα (**BR, L6**) has assumed importance during the past ten years because of its relevance to the excretion of water-soluble BR photodegradation products formed during phototherapy for unconjugated hyperbilirubinemia, especially physiologic jaundice of newborn babies.[1] Although it now seems clear that BR geometric configurational photoisomerization ($Z \rightleftarrows E$)[1,2] is the principal mechanism which allows the body to rid itself of BR during phototherapy,[1,3] the less rapid photodegradation is apparently responsible for the formation of new water-soluble products appearing in phototherapy bile and urine,[4] e.g. the pentdyopent reaction of the latter becomes intensified during phototherapy.[5] Both photoisomerization and photo-oxidation pathways emanate from excited states, as do other photochemical reactions,[1] e.g. constitutional photoisomerization[6] and photoaddition to vinyl groups.[7-9] Therefore, brief reviews of electronic excited states and their reactivities are given in the following.

Electronic excited states and radiative decay

The electronic absorption spectrum of BR in solution (Fig. 1) exhibits an intense absorbance ($\varepsilon \sim 60{,}000$) in the visible region centered near 450 nm with relatively little variation in the position of λ_{max} in organic solvents.[1,8] Shorter wavelength maxima can also be detected near 300 nm, and 200 nm with an inflection near 220 nm. BR dimethyl ester in acetonitrile (Fig. 1) exhibits a shifted long wavelength absorption $\lambda_{max} = 393$, $\lambda_{sh} = 440$ nm due to aggregation,[10] with shorter wavelength maxima appearing at 275 nm and 205 nm with an inflection near 230 nm. Excitation of

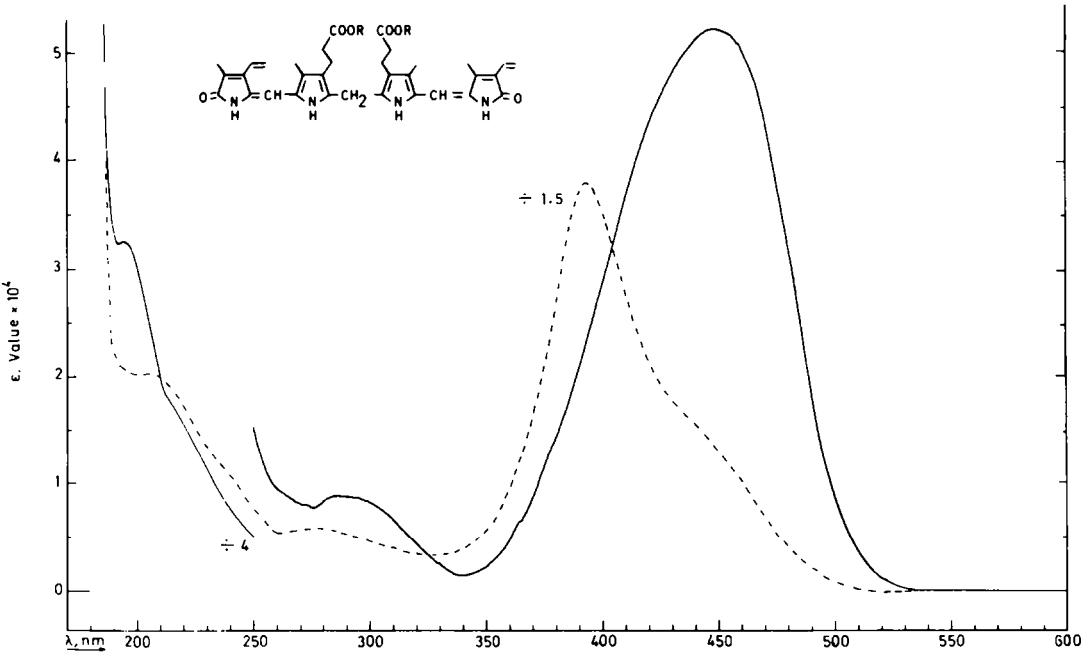


Fig. 1. Electronic absorption spectra of bilirubin IXα (———) 9.0×10^{-6} M and 5.2×10^{-6} M, and its dimethyl ester (– – – – –) 1.3×10^{-5} M, in acetonitrile at 26°C.

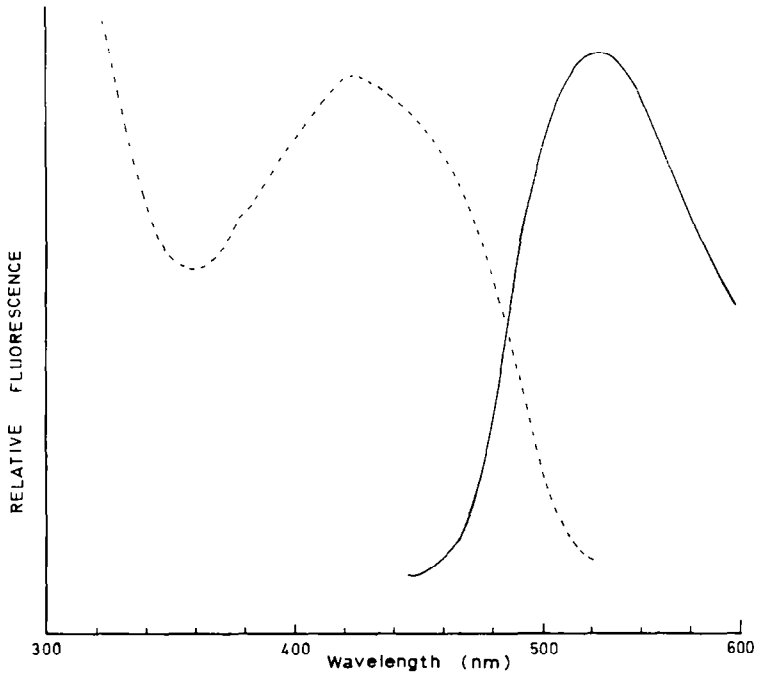


Fig. 2. Fluorescence emission (— —) and excitation (· · · · ·) spectra of bilirubin IXα (1.4×10^{-5} M) in chloroform at 25°C. The excitation wavelength was 450 nm.

BR with 450 nm visible light should lead directly to the lowest energy singlet excited state, one different, in principle, from those directly accessible by excitation near 300 or 200 nm. Different chemical reactivity might be expected from different excited states.[11] Radiative decay from the low-lying excited states, which are accessible by visible (blue) light irradiation has been of considerable photophysical interest in connection with the now widely used phototherapy for neonatal jaundice.[1,2a] It is unclear whether the lowest triplet state of BR has been observed in phosphorescence.[12] BR luminesces from its low energy singlet excited state under a variety of conditions:[1,2,b,c,e,f,h,m,8,13] weak fluorescence can be observed at room temperature in chloroform (Fig. 2) and in selected other organic solvents,[14] as well as from low temperature glasses, with emission near 525 nm.[8,12a-17] Curiously, the fluorescence excitation spectrum of BR (Fig. 2) does not coincide with its absorption spectrum, tempting one to think that only more conformationally restrained structures of BR (e.g. *syn*-4*Z*,*syn*-15*Z*, Fig. 4) fluoresce sufficiently to

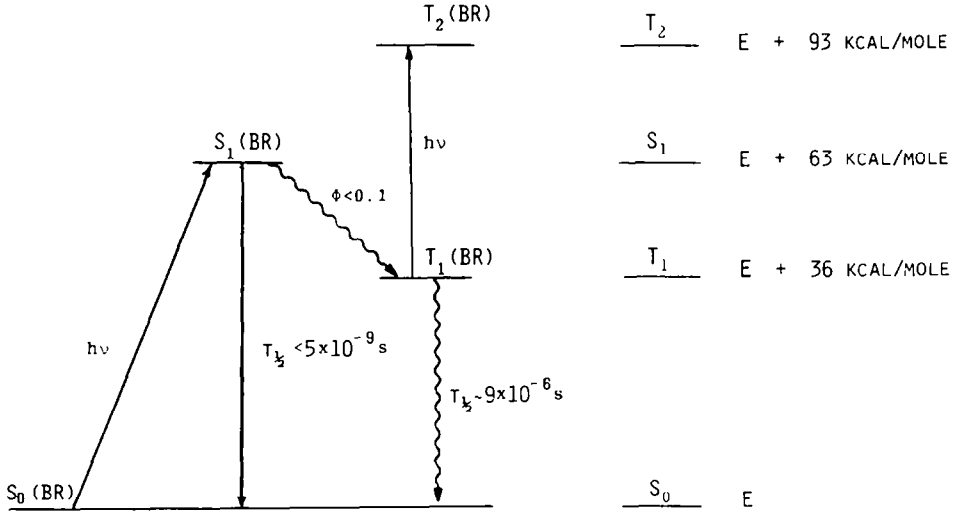


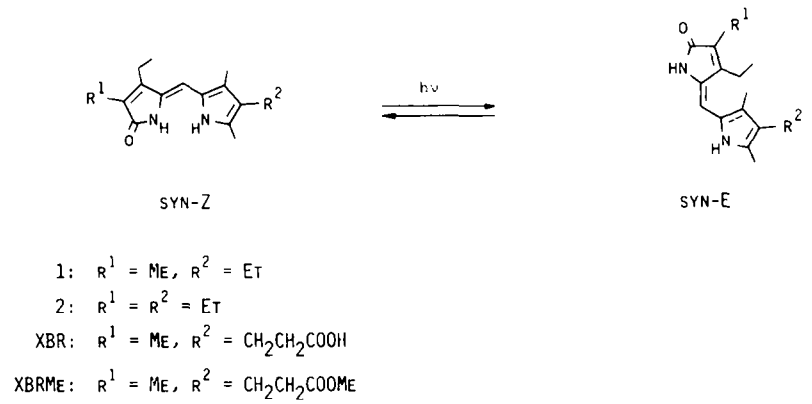
Fig. 3. Photochemical reaction cycle for electronic excitation of ground state bilirubin IXα (S_0) to its first excited singlet (S_1) which can decay to (S_0) with fluorescence or undergo intersystem crossing to the lowest lying triplet excited state (T_1). (T_1) can be excited to T_2 by nonradiative intersystem crossing as shown or by phosphorescence (not shown). Phosphorescence of T_1 has not been detected, but the half-life of T_1 is ~9 μs. The data are taken from Land[18] and Bonnett *et al.*[12]

be observed;[2b,c,e,f] whereas, conformationally mobile structures, e.g. BR dimethyl ester, dissipate energy more efficiently by molecular motion and do not fluoresce as well. The quantum yield for fluorescence of BR is about 0.05 in 77 K glasses with a half-life of $< 5 \times 10^{-9}$ s.[16,17]

As shown in Fig. 3, the energy of the lowest singlet excited state (S_1) of BR lies ~63 kcal/mol (450 nm) above its ground state. The lowest lying triplet state (T_1) was determined to be ~36 kcal/mol above the ground state, with a half-life in benzene of 9×10^{-6} s.[18] Intersystem crossing from S_1 to T_1 bilirubin is small, $\phi < 0.1$;[18] consequently, the formation of T_1 is not readily accessible by direct irradiation.[19] Measurements of triplet state properties of BR by Land[18] were achieved by direct excitation to T_1 using the pulse radiolysis technique and by anthracene-sensitized energy transfer. Significantly, a triplet for the pyrromethenone, xanthobilirubinic acid (XBR) methyl ester, is even shorter-lived and weaker in intensity.[20] Recently, direct irradiation of BR by a 347 nm ruby laser source has been reported to yield triplets (quantum yield <0.005 in aqueous and methanolic basified solution and ~0.01 in benzene).[19]

Non-radiative decay (Here, two major types of non-radiative decay are of interest)

1. *Geometric configurational isomerization.* Aside from the perceptive recognition by Lemberg[21] that natural BR should possess the 4*Z*, 15*Z* configuration



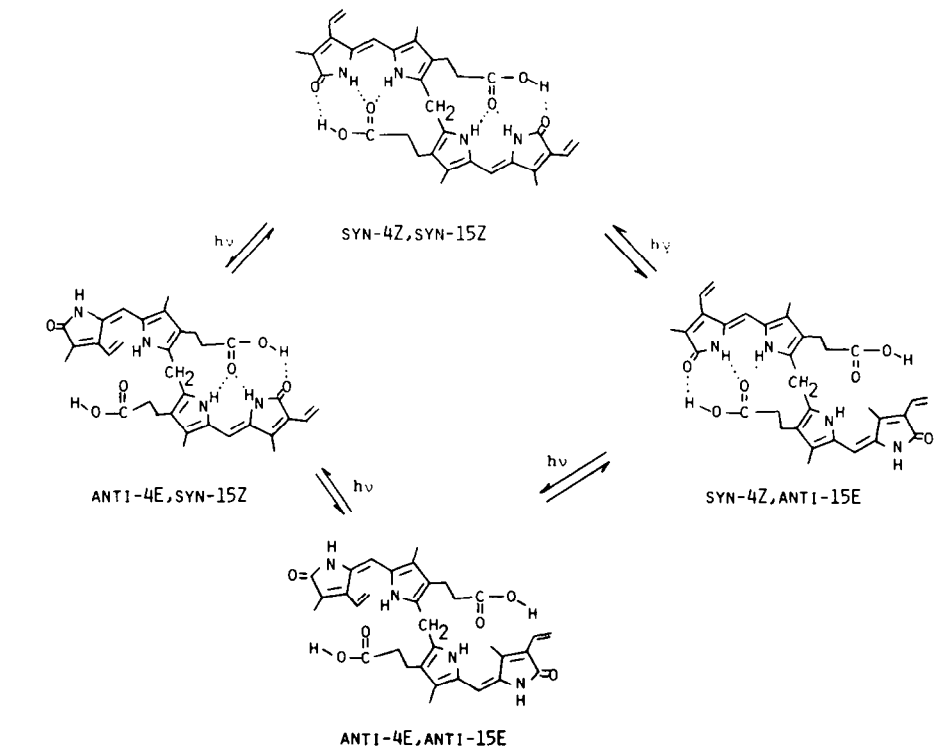


Fig. 4. Photochemical configurational isomerizations ($Z \rightleftarrows E$) of pyrromethenones and bilirubin IXα. The photochemical reaction cycle shows the consequences of $Z \rightarrow E$ double bond geometric isomerization: disruption of intramolecular hydrogen bonds. Photobilirubin is a mixture of the 4*Z*/15*E*, 4*E*/15*Z* and 4*E*/15*E* structures.

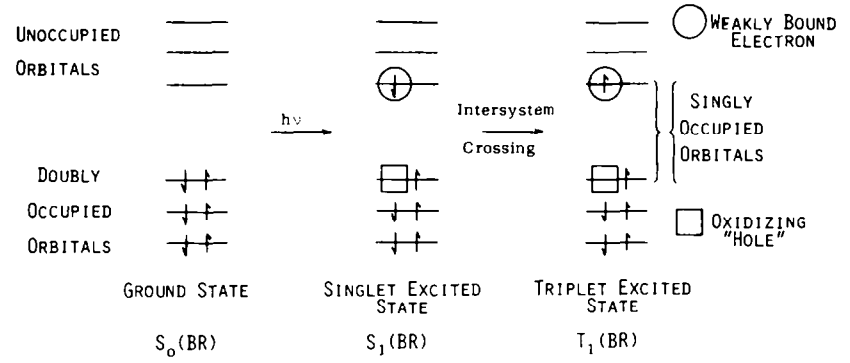


Fig. 5. Schematic diagram illustrating electron excitation in bilirubin and oxidizing and reducing properties of the excited states, according to Foote.[36]

rather than the commonly written 4*E*,15*E* configuration, the question of geometric isomers about Δ^4 and Δ^{15} of BR was not raised again until recently and then at first only in connection with jaundice phototherapy for the newborn.[1-3,22-24] Photochemical isomerization about C=C double bonds is a well studied phenomenon, approachable from either the *E* or *Z* isomer.[25] It involves: (1) absorption of a photon with the requisite energy to give a π π^* excited state with planar geometry; (2) relaxation of the excited state to a lower energy metastable state with a twisted C=C conformation; and (3) decay of the twisted conformation either back to the planar starting olefin or to the geometrically isomerized planar olefin. Application of these principles to the pyrromethenones, (**1**, **2**, and XBR) of this work leads to a photoequilibrium mixture of *Z* and *E* isomers (Fig. 4).[2a,3a,24,26] Similarly, irradiation of BR is observed to give a photoequilibrium mixture of the original 4*Z*, 15*Z* isomer in addition to the three possible remaining configurational isomers: 4*E*,15*Z*; 4*Z*,15*E*; and 4*E*,15*E* (Fig. 4).[2a,3,27] The latter three isomers, taken collectively, have been called photobilirubin[2k] and are accessible by direct irradiation of bilirubin with blue light by a photochemical isomerization proceeding mainly through excited singlet states.[28,29] Ample precedent for the geometric configurational photoisomerization may be found in the structurally related pyrromethenones and benzalpyrrolinones, whose $Z \rightleftarrows E$ photoisomerizations are well documented.[30,31]

Geometric configurational isomerization of BR (Fig. 4), now widely appreciated,[2,3] is apparently the most important photochemical event associated with phototherapy for jaundiced infants with unconjugated hyperbilirubinemia (physiologic jaundice of the newborn).[3] Newborn babies develop unconjugated hyperbilirubinemia and often become jaundiced because the hepatic apparatus for conjugating BR is functionally immature at birth.[32] Consequently, neurotoxic BR accumulates in the circulation and extravascular tissues with increased risk of irreversible brain damage. Phototherapy is now a well-established method for reducing serum bilirubin levels, thereby decreasing the risk of BR encephalopathy. Phototherapy causes a net increase in the elimination of BR via formation of BR photoproducts that are readily excreted in bile and urine. Although accurate determination of the ratio of hepatic to renal excretion of BR photoproducts is not yet determined, it is clear from available data that hepatic excretion is by far the major route.[3a e,j,l,m,n] The key to hepatic excretion of BR is photochemical geometric configurational isomerization,[1,2] which affords *E* isomers[27,33] that are more polar that the natural, thermodynamically more stable 4*Z*,15*Z* isomer and sufficiently hydrophilic to cross the liver into bile without resort to conjugation.[3,34,35] Renal excretion of BR photoproducts[4] implicates a competing photo-oxidation mechanism. We turn our attention to decay of BR excited states with the intervention of oxygen.

2. *Photo-oxidation and the role of singlet oxygen.* Photo-oxidation reactions of BR occur from an electronically excited state, either the singlet (S_1) or the triplet (T_1). Absorption of light, e.g. at 450 nm, promotes an electron to a higher energy orbital without change of spin, thereby producing the first singlet excited state (S_1) having no unpaired spins, but two singly occupied orbitals (Fig. 5). Under the proper conditions, a non-spin-paired electron of the excited singlet (S_1) may undergo spin inversion to give the triplet state (T_1) which has two unpaired spins and two singly occupied orbitals. The single electron found in the high energy orbital of S_1 and T_1 is less strongly bound, and hence is more easily removed by oxidizing agents than in S_0. Moreover, the "hole" left in the formerly doubly occupied orbital of S_0 when the electron was promoted is in an orbital which would be expected to bind electrons comparatively strongly, with the effect that both S_1 and T_1 would be more readily reduced than S_0. Excited states are thus expected to be both oxidized and reduced more easily than the ground state.[36] Oxidizing behavior is particularly common, and with only a few exceptions photosensitized oxidations proceed via the longer-lived triplet excited state.[37] Where T_1 is either inaccessible or very short lived, however, bimolecular reactions via S_1 may become competitive.

Photo-oxidation reactions may go through S_1 or through T_1 excited states. Reactions via T_1 fall into two broad mechanistic classes: Type I or Type II.[37] Singlet and Type I triplet photo-oxidations of BR might involve interaction of excited BR with another molecule ($^3O_2$ or BR) directly, usually with electron or hydrogen atom transfer, to give BR radical ions [$BR^+ \cdot$] or radicals [$BRH \cdot$] which might undergo the reactions shown in Fig. 6. Type II photo-oxidation of BR involves quenching of T_1(BR) to give singlet excited oxygen [$^1O_2$] and ground state BR, S_0(BR).

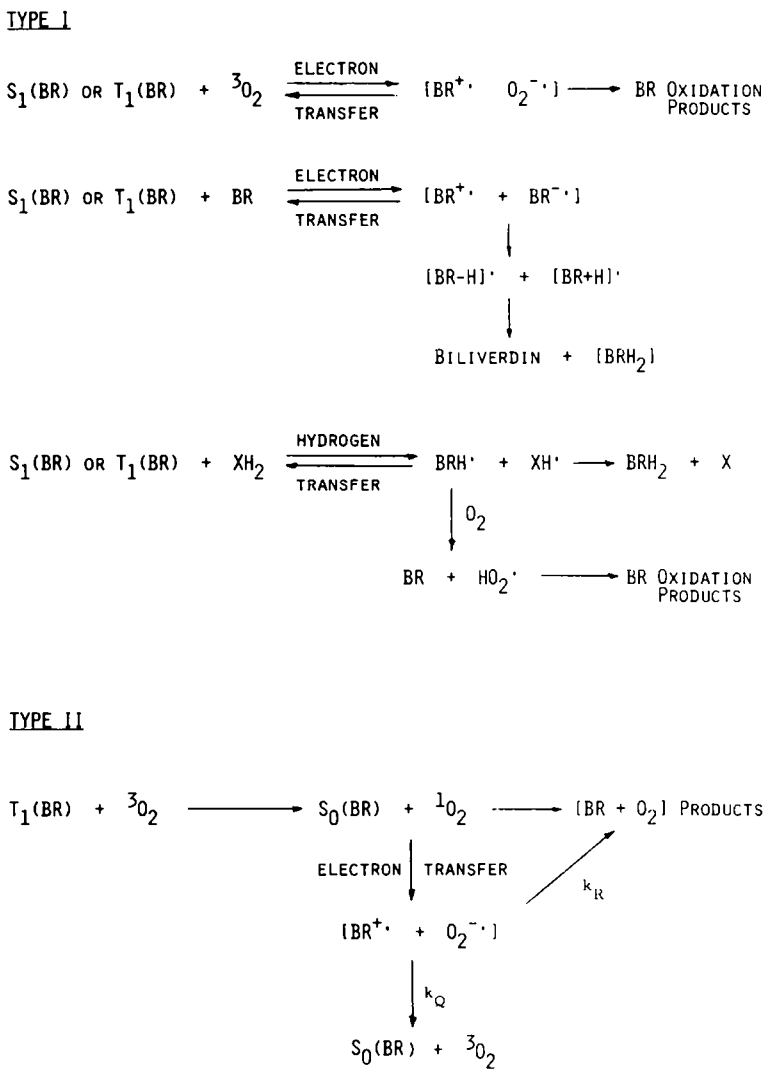


Fig. 6. Reaction schemes for the fate of singlet excited [S_1(BR)] and triplet [T_1(BR)] excited bilirubin involving electron transfer, hydrogen transfer and energy transfer photo-oxidation mechanisms.[39]

In view of its poor intersystem crossing quantum yield ($\phi < 0.1$) and short T_1(BR) lifetime,[18] BR is expected to be an inefficient sensitizer for $^1O_2$. This has been observed.[8,38] Type I photo-oxidation of BR is probably the mechanism followed in the self-sensitized formation of biliverdin IXα (BV, **L4**), especially since the yields of BV are considerably enhanced in aprotic and deoxygenated solvents, and the reaction is promoted by radical quenchers or electron-transfer acceptors.[11,38] It may well turn out that most self-sensitized photo-oxidation reactions of BR follow a singlet or Type I mechanism, *including even self-sensitized photo-oxygenation*, which has generally been ascribed to a Type II $^1O_2$ mechanism.[38] For example, in the Type I reaction with ordinary (triplet) oxygen ($^3O_2$), formation of reactive superoxide ion ($O_2^{-\cdot}$) by electron transfer is possible, and the course of reaction of the superoxide ion-BR radical ion pair [BR^+ $O_2^{-\cdot}$] could lead to the same products as reaction of $^1O_2$ with BR either directly or indirectly by the radical ion-pair (see under Type II, Fig. 6).[24,29,31,38] It is difficult to distinguish between the various types of photo-oxygenation mechanisms, especially because the radical ion pair [BR^+ O_2^-] is expected to give $^1O_2$-type products, and the various kinetic and competitive quenching reactions do not allow for facile distinction between $^1O_2$ as a reactant *vs* $O_2^{-\cdot}$.[39] BR is known to react chemically with $^1O_2$ but at a rate ($k_R = 0.1–0.4 \times 10^9\ M^{-1}\ s^{-1}$) that is approximately an order of magnitude less than the quenching rate ($k_Q = 2.1–2.8 \times 10^9\ M^{-1}\ s^{-1}$).[39] Since $^1O_2$ quenching by BR probably involves electron transfer, radical ion pair [$BR^{+\cdot}O_2^{-\cdot}$] formation[40] is probably the first process with the radical ion pair partioning into the chemically reactive (k_R) and physically quenching (k_Q) pathways. In view of the evidence, doubt is cast on the uniqueness of an *ordinary* $^1O_2$ mechanism in the self-sensitized photo-oxygenation of BR. The formation of BV during BR photo-oxidation.[11,41,42] the observation that k_Q exceeds k_R for reaction with $^1O_2$,[39] and the observation that spin-trapping agents form stable radical species during self-sensitized but not Rose Bengal-sensitized photo-oxygenation[46] point to an electron-transfer component in both the self-

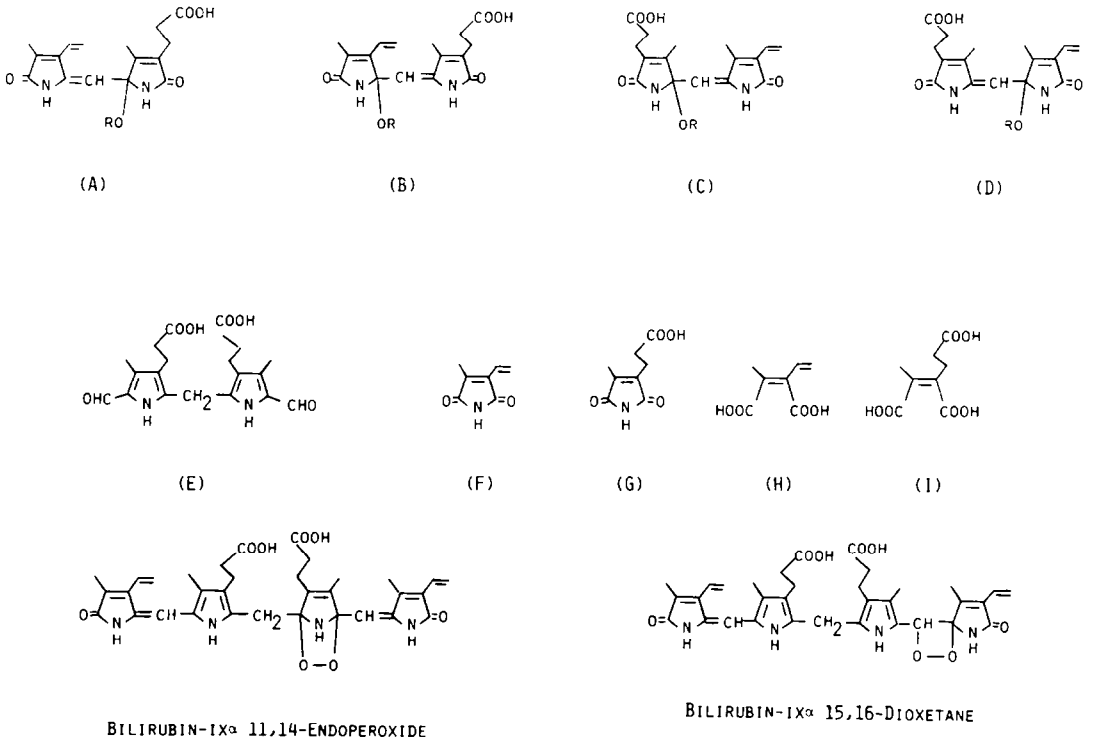


Fig. 7. Photodegradation (via photo-oxidation) products of bilirubin IXα. E I presumably obtain from a dioxetane intermediate. Propentdyopent adducts (**B**, **C** and **D**) apparently arise from an *endo*-peroxide intermediate. The 11,14-*endo*-peroxide would be expected to give **C**, which can undergo allylic rearrangement to **D**. The propentdyopent (**A**) expected to arise from bilirubin IXα 6,9-*endo*-peroxide has not been isolated. (R = alkyl or hydrogen.)

sensitized and probably in dye-sensitized photo-oxygenation reactions of BR. Whether $^1O_2$ is formed at all, or to what extent it participates in the self-sensitized photo-oxygenation of BR has not been unequivocally ascertained. The various methods used in detecting $^1O_2$,[36,43] e.g. competitive reaction,[40,44,45] quenching[40,44-46] and rate effects in deuterated solvents[45,48] respond in a similar way to O_2^{-} [47] and thus cannot be used to exclude its intermediacy.

If the photo-oxygenation reaction mechanism is in doubt, the structures of the reaction products are more clearly established.[38] The product type and distribution vary with solvent.[1,8,38] Thus, in protic solvents, e.g. methanolic ammonia or aqueous ammonia, BR photo-oxidation products[1,8,38] include (Fig. 7): BV (**L4**)[11,41,42] various propentdyopents (**B**, **C**, **D**),[40,41,49-51] a dipyrrylmethane dialdehyde (**E**),[40,50,52] methylvinylmaleimide (**F**),[40,41,50-53] hematinic acid imide (**G**),[41,51,52] and acyclic hydrolysis products (**H** and **I**)[41] of the cyclic imides. Of these various products, propentdyopents form the majority and account for nearly 60 wt.% of the total photoproducts. Structure proofs of the various isomeric propentdyopents derived from BR photo-oxygenation[38] presented difficulties which were elegantly resolved by Bonnett and Stewart.[40] The propentdyopents apparently arise from unstable *endo*-peroxides[54] (Fig. 7) formed at the pyrrole rings of BR.[1,38,40,41,52] BR-6,9-*endo*-peroxide should give **A** directly, whereas, BR-11,14-*endo*-peroxide should give **C**. Both **A** and **C** are capable of allylic rearrangement to **B** and **D**, respectively. Actually, only three of the propentdyopents (**B**, **C**, and **D**) are isolated since the more sterically hindered isomer **A** is completely rearranged to **B**.[40] Hematinic acid imide (**G**) probably also arises from either BR *endo*-peroxide; whereas methylvinylmalimide (**F**) and the dipyrrylmethane dialdehyde probably arise from unstable BR-dioxetane precursors (Fig. 7).[1,38,40,41,52]

In order to understand better the photochemistry of BR, we have made use of pyrromethenones as model substrates. Both the kinetics and products of their photo-oxygenation have been studied.[24,29,55] In this work, we report on the photochemical reactions of 4-ethyl-3-methyl-5-(4-ethyl-3,5-dimethyl-pyrrolyl-2-methylidene)-3-pyrrolin-2-one (**1**)[30d] and 3,4-diethyl-5-(4-ethyl-3,5-dimethylpyrrolyl-2-methylidene)-3-pyrrolin-2-one (**2**)[57] with reference to their ability to sensitize $^1O_2$ formation, reaction with $^1O_2$, and an even faster $Z \rightarrow E$ photoisomerization.

RESULTS AND DISCUSSION

Pyrromethenones (**1** and **2**), XBR, and XBRME (Fig. 4), which have been shown to undergo the expected[26,28,31] rapid $Z \rightleftarrows E$ configurational photoisomerization, also undergo slower photo-oxygenation reactions. The same reaction products appear in both the self-sensitized and Rose Bengal-sensitized photo-oxygenations, but in either case when oxygen is carefully excluded, only a $Z \rightleftarrows E$ photoisomerization can be observed. In the photo-oxygenation reactions, pyrromethenone (**2**), which possesses

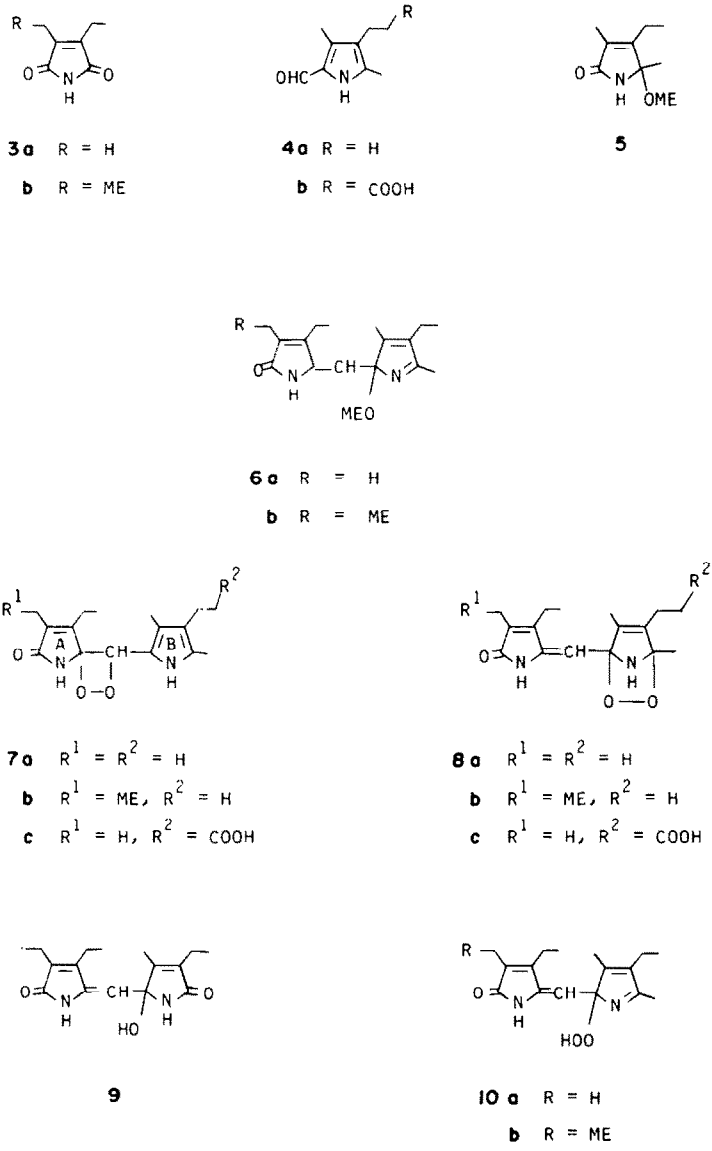


Fig. 8. Photo-oxygenation products (**3**–**6**) of pyrromethenones (Fig. 4) with presumed intermediate dioxetanes (**7**) and *endo*-peroxides (**8**). The pyrromethenedione (**9**) arises from silica-catalyzed oxygenation.[75] Dipyrroles **10** are possible precursors of **6**.

different types of pyrrole β-substituents (two Et's in ring A, Me and Et in ring B) compared with **1** (Me and Et in each of rings A and B), was the earlier and present choice for relating product structure with mechanism. Thus, when 3,4-diethyl-maleimide (**3b**) (Fig. 8) was isolated as a photo-oxygenation product of **2** it clearly originated from ring A; whereas, in the photo-oxygenation of **1**, the imide **3a** might have come from either ring. Both **1** and **2** give kryptopyrrole aldehyde (**4a**), originating from ring B, as a photo-oxygenation product. Equivalent products have been found following self-sensitized or methylene blue-sensitized photo-oxygenation of XBR:[59] methylethyl-maleimide (**3a**) and 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-propanoic acid (**4b**) (Fig. 8). The suggested mechanism for the formation of such products has implicated a dioxetane intermediate (**7**);[38,59] however, evidence for radical pathways in photo-oxygenation of pyrromethenones has also been forthcoming.[24,29,59] Pyrromethenone **2** has been observed to oxidize in the dark to water-propentdyopent (**9**) on a silica surface exposed to air—a reaction which presumably involves radicals.

Other major photo-oxygenation products arising from **1** and **2** include pyrrolinone (**5a**) and pyrromethenones (**6a** and **6b**) (Fig. 8). Whether equivalent products occur following photo-oxygenation of XBR is currently being investigated. The monopyrrole (**5**) might be thought to originate from the *endo*-peroxide (**8**), although that is not entirely clear because intermediates such as **8** (or even **7**) have not yet been observed, and **4** is known to undergo dye-sensitized photo-oxygenation to give **5**.[60] The pyrromethenones (**6**) might arise from the *endo*-peroxides (**8**), assuming

an abnormal decomposition mechanism[54,61] leading to **10**, and its subsequent reaction. Since *endo*-peroxides like **8** have been implicated in BR photo-oxygenation as precursors of propentdyopents, and since propentdyopents (e.g. **9**) are not observed in the photo-oxygenation of **2**, the mechanism of formation of **6** probably involves other types on intermediates (e.g. **10**).

Although much of the product analysis work with pyrromethenones was valuable in elucidating some of the products of BR photo-oxygenation, the fact that the models did not give propentdyopents, which are the major products from BR, was cause for puzzlement. It appeared that, aside from the mechanistic problems posed in the photo-oxygenation of pyrromethenones *per se*, different mechanisms (or a different mix of mechanisms) were operating in BR photo-oxidation as opposed to that of its model pyrromethenones. The questions of mechanism revolve around the role of Type II singlet oxygen [$^1O_2$] *vs* Type I radical-type photo-oxidations (*vide supra*).[37] The implications of radical-type photo-oxidations became especially apparent when it was found that the formation of the (ene-amide) double bond cleavage products (those like **3** and **4**) of pyrromethenones became considerably reduced when some of the pyrrole β-alkyl substituents were replaced by hydrogen. Not only did the less alkylated pyrromethenones fail to undergo the enamide C=C cleavage reaction, but they were resistant to self-sensitized and Rose-Bengal-sensitized photo-oxygenation and exhibited only the $Z \rightleftarrows E$ photoisomerization.[24] That behavior is paralleled by benzalpyrrolinones, which are also resistant to photo-oxygenation.[31] The extent of involvement of photo-oxygenative cleavage of the enamide double bond parallels the ease of one electron oxidation of the substrate,[62] i.e. the most highly alkylated pyrromethenone has the lowest half-wave potential and hence the greatest reactivity toward oxygen, either $^1O_2$ or $^3O_2$, in an electron-transfer type mechanism.[24,63] Consequently, whether $^1O_2$ was involved at all in the self-sensitized photo-oxygenation reactions of **1**, **2**, XBR, and even BR, became a point of interest to us.

Earlier we and others had noted that BR was a more effective physical quencher than a reactive quencher for $^1O_2$, $k_Q = 2.1\text{–}2.8 \times 10^9\ M^{-1}\ s^{-1}$ *vs* $k_R = 1\text{–}4 \times 10^8\ M^{-1}\ s^{-1}$. Although the data say little about the ability of BR to sensitize $^1O_2$, they suggest, however, that BR can undergo electron-transfer reactions with $^1O_2$.[39] Similarly, pyrromethenone (**2**) has been observed to quench $^1O_2$ at a rate approaching the diffusion limit, with $k_Q \approx k_R \approx 1 \times 10^{-9}\ M^{-1}\ s^{-1}$.[39,56,64] Here again the evidence suggests that pyrromethenones, like BR, react with $^1O_2$ by electron-transfer processes. With respect to self-sensitized photo-oxidation and the possible formation of $^1O_2$ from BR or pyrromethenone triplets, it should be noted that BR triplet is formed very inefficiently (with a quantum yield >0.1)[18] and is especially short-lived (9 μsec).[18] Furthermore, the triplet of the structurally related pyrromethenone XBRME is even shorter-lived.[20] The latter findings are hardly compelling for the expectation of a self-sensitized photo-oxidation mechanism involving formation of $^1O_2$, despite the nearly diffusion-controlled rates of reaction with $^1O_2$ generated independently. Even if $^1O_2$ were generated in the self-sensitized photo-oxidations, there are also indications that reaction with $^1O_2$ takes place by electron-transfer.

With these thoughts in mind, we began investigations of the mechanism of self-sensitized photo-oxygenation with a study of the effects of various inhibitors[40,44–46] on the rates. Similar, earlier experiments with BR involved the observations that ($^1O_2$ physical quencher) β-carotene had a pronounced effect in inhibiting self-sensitized photodestruction; diazabicyclo[2.2.2]octane (DABCO), also a $^1O_2$ physical quencher, had a less pronounced effect.[40,44,45] The reactive quencher, tetramethylethylene, was about as effective as DABCO; the radical chain inhibitor, 2,6-di-*t*-butylphenol had little or no effect.[44] The rate of self-sensitized photodestruction of BR was accelerated two-fold in methanol-d_4 (*vs* methanol solvent),[45] and BR was able to sensitize the slow photo-oxygenation of 2,5-dimethylfuran to give 2-hydroperoxy-5-methoxy-2,5-dimethyl-2,5-dihydrofuran.[45] These data implicate $^1O_2$, although not necessarily uniquely.[47]

When a 10^{-5} M, oxygen-rich methanolic solution (2 ml) of pyrromethenone (**1** or **2**) was irradiated in a 10 mm pathlength quartz cuvette at 417 nm with monochromatic light, the absorbance maximum peak decreased and new absorbances appeared at 320 nm and 265–268 nm. A time study of the changes of absorbance at 417 nm and the emergence of new peaks at 320 and 265 nm are summarized in Table 1. An initially rapid $Z \rightleftarrows E$ photoisomerization slowed after an irradiation period of 10–80 min and then accelerated with continued irradiation. Product analysis of the first (photoisomerization) stage was achieved by HPLC and showed only the formation of an *E* isomer. Product analysis of the later (photo-oxygenation) stage was achieved on 10^{-5} M methanolic solutions of **2** contained in 10 cm pathlength cells following irradiation with 417 nm monochromatic light until 90% disappearance of the 417 nm absorbance (50 hr). Evaporation of the solvent followed by TLC using chloroform-ether (6 : 4) allowed isolation of xeronimide (**3b**),[55] kryptopyrrole aldehyde(**4a**)[56,60] and 5-methoxy-4-ethyl-3, 5-dimethyl-3-pyrrolin-2-one (**5**)[65] in addition to pyrromethenone (**6b**) (Fig. 8). With pyrromethenone (**1**), the principle products were **3a**, **4a**, **5** and **6a**. Products **3**, **4**, and **6** were identical with known comparison samples. Both **4** and **6** have λ_{max} near 315 nm, but only **4** can be detected (TLC) in the early stages of the reaction. Studies have shown that **4a** will undergo a dye-sensitized (but not a self-sensitized) photo-oxygenation to **5**.[60] Although the Rose Bengal-sensitized photo-oxygenation (with monochromatic light irradiation at 557 nm) of **1** or **2** is a much faster (90% reaction in 30 min) and somewhat cleaner reaction, the major products are the same as from the self-sensitized reaction.

The rapid formation of a photoproduct absorbing at 265 nm (Table 1) is attributed to photoisomerization of *Z*-**2** to its *E* isomer[24,30b,d,66]—a fast reaction which reaches photoequilibrium in less than 10 min (Fig. 4). When the photochemistry was carried out in deoxygenated methanol, the only new absorbance found was that at 265 nm. When that solution was examined by HPLC or TLC, only two compounds could be detected, one corresponding to the starting *Z* isomer, the other to the *E* isomer. Upon standing in the dark overnight, most of the *E* isomer reverted to the thermo-

dynamically more stable *Z* configuration (Table 2). The nearly complete $E \rightarrow Z$ reversion took only minutes with an added drop of trifluoroacetic acid. It is important to note that in the course of irradiation of **1** or **2**, either in the presence or absence of oxygen: (1) disappearance of starting pyrromethenone reaches a plateau of 20–25% during the first 10 min, (2) only minor changes are noted during the next hour, and (3) a subsequent stage leads to substantial photo-destruction of pyrromethenone. In the first stage only the new absorbance at 265 nm can be seen, and it rapidly reaches a constant value (Table 1). The reaction at this stage is nearly completely reversible thermally (Table 2) or by acid catalysis. Significant absorbance at 315 nm (assigned to **4a**) cannot be detected until the onset of the second stage (Table 1, 143 min), at which point both the new absorbance at 265 nm (*E* isomer) and the band due to the starting pyrromethenone at 417 nm (*Z* isomer) decline in an irreversible reaction leading to increasing absorbance at 315 nm.

The photochemical reactions of **1** and **2** show a solvent effect on the rate of disappearance of pyrromethenone. Thus, when a $CHCl_3$ or $CDCl_3$ solution of **2** (or **1**) was irradiated at 408 nm ($\lambda_{max}^{CHCl_3}$) and compared to irradiation of **2** (or **1**) ($\lambda_{max}^{CH_3OH}$ 417 nm) in CH_3OH or CD_3OD by measuring the % decline in the corresponding λ_{max}, normalized to equivalent incident light intensity, the rate of disappearance of **2** (or **1**) in the first 10 min is ten times faster in the hydroxylic solvents. This solvent effect suggests that the intermediate in the isomerization is more polar than the ground state.[25] Furthermore, essentially no solvent deuterium isotope effect can be found during that time but becomes manifest subsequently, e.g., the rate of disappearance of **2** is about six times faster in CD_3OD as compared to CH_3OH *after* the first 10 min of reaction. The second stage of the reaction appears to have the characteristics of a self-sensitized photo-oxidation involving either $^1O_2$ or OOH.[47]

In order to examine more carefully the possibility of a $^1O_2$ reaction in the second stage of irradiation of **2**, use was made of quenchers as shown in Table 3. Strikingly, the added quenchers exert only minimal effects on the rate of photo-oxygenation. The well-known $^1O_2$ quencher, β-carotene,[36,67,68] retards the reaction only very slightly;[44] DABCO, also a $^1O_2$ quencher,[67,68] is only slightly more effective.[44,45] Other additives such as the radical chain inhibitor 2,6-di-*t*-butylphenol,[11,44] or the electron acceptor, phenyl-*t*-butylnitrone,[11] had essentially no effect on the rate. Tetraphenylethylene, which might be implicated in charge transfer,[43] had only a small effect in increasing the rate; 2,5-dimethylfuran, a reactive substrate for $^1O_2$ and radicals,[67] exhibited a comparable small increase in rate. In view of the previously established ability of BR to sensitize the photo-oxygenation of 2,5-dimethylfuran,[45] we investigated this substrate further. Under conditions of prolonged irradiation in methanol with blue light, products from the pyrromethenone-sensitized photo-oxygenation of 2,5-dimethylfuran could be isolated and were shown to consist mainly of 2-hydroxy-5-methoxy-2,5-dimethyl-2,5-dihydrofuran and a small amount of 2-hydroperoxy-5-methoxy-2,5-dimethyl-2,5-dihydrofuran. With shorter irradiation times, using 500 W visible light, the major product was 2-hydroperoxy-5-methoxy-2,5-dimethyl-2,5-dihydrofuran. These are the expected products from reaction of 2,5-dimethylfuran with $^1O_2$ to give an *endo*-peroxide, which undergoes ground state reaction with methanol to yield the hydroperoxide, reduction of which can lead to the hydroxy compound. However, *endo*-peroxides have also been shown to arise in non-$^1O_2$ photo-oxidations involving electron transfer mechanisms;[43c] consequently, here, too, the evidence can support either mechanism.

In sum, the evidence is hardly compelling for an exclusive $^1O_2$ mechanism in the photo-oxygenation; yet, neither can it be ruled out. Only the change to a deuterated solvent had a pronounced effect on the reaction an effect which might be associated with the increased lifetime of $^1O_2$ normally observed with deuterated solvents.[45,48,68,69] However, such solvent isotope effects need not be associated exclusively with an increased lifetime of $^1O_2$[43c,68] but might also effect an increased lifetime of other reactive (oxygen) species.[47] As with the results from pyrromethenone-sensitized photo-oxygenation of 2,5-dimethylfuran, either a $^1O_2$ mechanism or one involving electron transfer is tenable. Nonetheless, we found it puzzling that the photo-oxygenation reaction should become strongly accelerated in methanol-d_4 when other evidence (Table 3) appeared to rule out a major $^1O_2$ pathway. In order to explore further the questionable implication of $^1O_2$, we resorted to a kinetic investigation of the effect of 1,4-diazabicyclo[2.2.2]octane (DABCO) on the rate of photo-oxygenation.

For substrates (A), which are known to react only with $^1O_2$, Foote[68] has used a kinetic method to determine two limiting events, whether a quencher, Q, deactivates only $^1O_2$ or whether it quenches excited sensitizer (^{3}Sens or ^{1}Sens) exclusively. If the irradiation time and [Q] are kept constant, and if the amount of A converted to photo-oxygenation products $(AO_2)^{-1}$ is kept to less than about 10%, then a plot of $[AO_2]^{-1}$ (or $\{\Delta[A]\}^{-1}$) *vs* $[A]^{-1}$ will give a straight line. The family of such lines generated with different [Q] will share a common intercept (constant intercept) if Q deactivates $^1O_2$ only. On the other hand, if Q affects the lifetime of ^{3}Sens or ^{1}Sens*, the plots will have [Q]-dependent intercepts, but the ratio of slope to intercept will be a constant. We used DABCO as a quencher; it physically quenches singlet oxygen but does not react chemically with it,[67,68] and it has also been shown to quench *Sens.

The results are plotted in Fig. 9. The lines for [Q] = [DABCO] = 150 μM and 750 μM bear a greater similarity to the behavior expected for $^1O_2$ quenching only that to the pattern for exclusive quenching of ^{3}Sens. However, the plots do not exhibit the constant intercept required for exclusive $^1O_2$ quenching. Whether this is due to imprecision in our accounting for the $Z \rightleftarrows E$ photoisomerization is difficult to know, especially since that difficulty may have even brought the plots close to a common intercept. On the other hand the ratio of slope to intercept (16 for [Q] = 750 μM and 8 for [Q] = 150 μM) is not constant either—an observation which is inconsistent with DABCO quenching of sensitizer only. Curiously, the plot for no added DABCO falls between the two plots for [Q] = 150 μM and [Q] = 750 μM. At relatively low ratios of [Q] to original pyrromethenone concentration the influence of quencher is seen to be negligible, if not slightly accelerating on the photo-

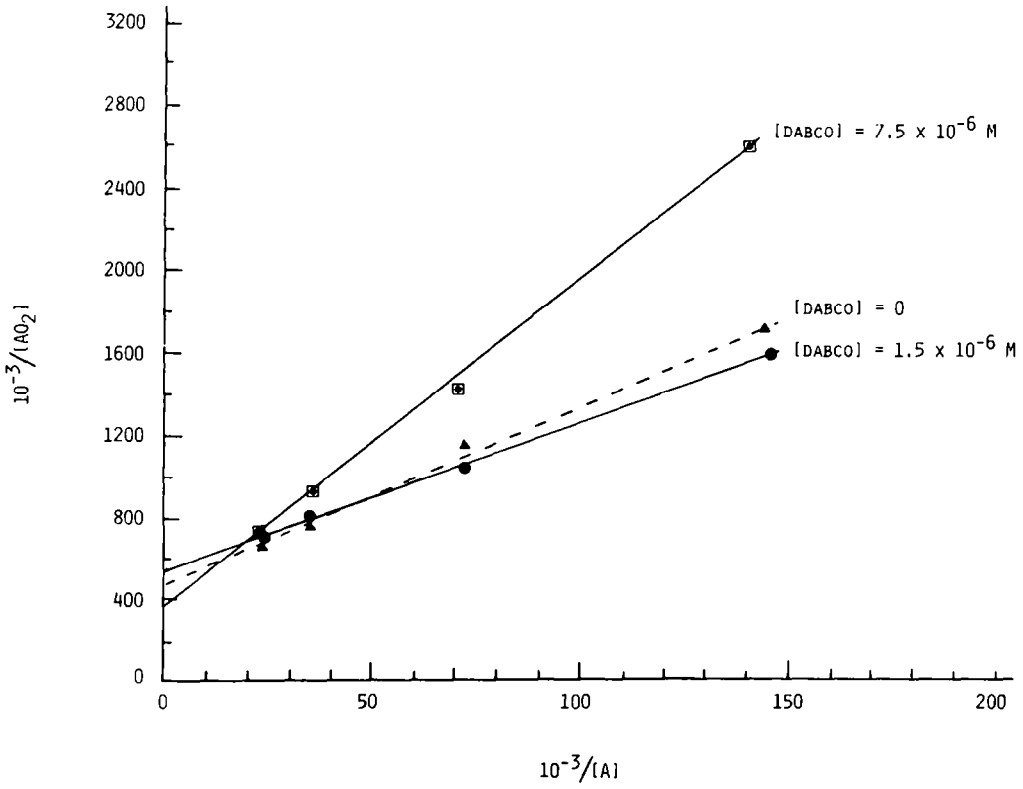


Fig. 9. Plot of reciprocal disappearance of pyrromethenone (1) ($10^{-3}/[AO_2]$) *vs* reciprocal initial concentration of pyrromethenone (1) ($10^{-3}/[A]$) for a range of initial pyrromethenone concentrations. The three different plots indicate either no added quencher, DABCO, or two different DABCO concentrations in each kinetic run. See experimental section.

oxygenation. At relatively higher ratios the photodestruction rate is retarded. We suggest that the data of Fig. 9 indicate that a $^1O_2$ pathway is not uniquely implicated in self-sensitized pyrromethenone photooxidation and, in addition, there is probable cause to believe that electron-transfer is an important component of the reaction.[70]

CONCLUSION

Evidence in the foregoing that does not unequivocally rule out $^1O_2$ in the self-sensitized photooxygenation of pyrromethenones is, we believe, more consistent with an electron-transfer radical mechanism (Fig. 6). Additional support for a radical (Type I) photo-oxidation mechanism may be found elsewhere.[24,39,56] In particular, the work of Grunewald *et al.*[59] on self-sensitized XBR photo-oxygenation strongly implicates a radical mechanism, in which, for example, DABCO can act as an electron donor. We therefore view the photochemistry to proceed by an initial rapid photoequilibration of *Z* and *E* configurational isomers of the pyrromethenone (P), equation (1). In this step,

$$(Z-P)_0 \overset{h\nu}{\rightleftharpoons} (Z-P)_1 \quad (E-P)_1 \overset{h\nu}{\rightleftharpoons} (E-P)_0 \qquad (1)$$

singlet excited $P(P_1)$ either decays to starting isomer or to the configurationally inverted diastereomer. The equilibrium is established rapidly from either direction, predominantly via singlet excited states, whose principal anaerobic de-excitation modes are isomerization about the exocyclic carbon–carbon double bond and vibrational interconversion as opposed to fluorescence.[28] The intersystem crossing to the triplet state is apparently extremely low.[20] Consequently, it would appear that self-sensitized photo-oxygenation proceeds mainly by the singlet excited state along radical-like Type I pathways involving either reaction of excited pyrromethenone with oxygen (equation (2)) or with a second pyrromethenone (equation (3)).

$$P_1 + {}^3O_2 \overset{\text{e-transfer}}{\rightleftharpoons} [P^+ \cdot O_2^{-}\cdot] \longrightarrow \text{products} \qquad (2)$$

$$P_1 + P_0 \overset{\text{e-transfer}}{\rightleftharpoons} (P+H)^{\cdot} + (P-H)\cdot \xrightarrow{{}^3O_2} \text{products} \qquad (3)$$

The implications of the foregoing for the self-sensitized photo-oxidation and photo-oxygenation of BR become apparent in the following. Although BR undergoes rapid $Z \rightleftarrows E$ configurational photoisomerization,[1,2] proceeding mainly through the singlet excited state,[1,28,29,38] it has also been shown to have a difficultly accessible, short-lived triplet[18] and to undergo radical reactions in its photo-oxidation.[1,11,38,71] Kinetic studies of BR photo-oxidation implicate $^1O_2$ through quenching experiments[40,44,45] as well as deuterated solvent experiments[45] – experiments

which, however, do not uniquely support $^1O_2$ but are also consistent with photo-oxidation reactions involving other dioxygen species, e.g. $O_2^{\cdot-}$ (or $^{\cdot}OOH$[47]). We suggest that the available data support an electron-transfer radical photo-oxidation mechanism for both BR and pyrromethenones.[39,56,71] The composite data suggest photo-oxidation pathways for BR as shown in Fig. 6. Further studies with XBR and BR are in progress to determine the extent of the involvement of singlet oxygen.

EXPERIMENTAL

Photochemical reactions were carried out at 20° in 10 mm spectrophotometric quartz rectangular cuvettes (Pyrocell) using 10 nm bandpass monochromatic light from a Bausch and Lomb monochromator (Model 33-86-07) equipped with a 200 W Hg lamp course. The monochromator entrance slit was adjusted to 2.78 mm and the exit slit 1.56 mm to give 10 nm bandpass light. A Lucite filter ($\frac{3}{8}$" thick) was placed just after the exit slit to remove any light (overtones) emitting below 350 nm. For degassed experiments, a Pyrex-to-quartz fused 10 mm spectrophotometric quartz cell was subjected to at least three cycles of freeze-pump-thaw treatments at a pressure of $<5\times10^{-6}$ Torr. A Beckman 25 UV-visible spectrophotometer was used to record absorbance readings with a probable error of ±0.002 A.U. on the data read-out. A constant temp bath (Neslab No. RT4-4), equipped for closed loop circulation was used to thermostat the cuvettes at 25.0 ± 0.2° during the photolysis and in the Beckman 25. Light emission intensities for the photochemical experiments were determined at the specified wavelengths by ferrioxalate actinometry.[72]

Preparative photochemistry was carried out with monochromatic light (above) in 10 cm cylindrical cells (25–30 ml volume), or in 1 l Erlenmeyer flasks (Pyrex) using Westinghouse "Special Blue" fluorescent lamps (F20T12/BB; 20 W) having 95% of their light emitted in the 425–475 nm range (for a precise distribution, see the Westinghouse lamp sales bulletin). Preparative photochemistry using broad spectrum visible light was carried out in a water-cooled Pyrex immersion well apparatus (with circulating O_2 for photo-oxygenation experiments) using a Sylvania 500 Q/CL 500 W tungsten-halogen lamp.[73,74]

IR spectra were run in $CHCl_3$ or CCl_4 on a Perkin-Elmer 599 spectrophotometer. ^{1}H-NMR spectra were measured in $CDCl_3$ or CH_3OD on a Perkin-Elmer R-24B or JEOL FX-100 spectrometer. Chemical shifts are reported in ppm (δ) downfield from TMS as an internal standard with multiplicities: s = singlet, d = doublet, br = broad and m = multiplet. Mass spectra were determined on a JEOL JMS-07 instrument at 70 ev. Electronic spectra were recorded on a Beckman 25 instrument. High performance liquid chromatography (HPLC) was carried out using a Perkin-Elmer Series 3 liquid chromatograph, unless otherwise specified on a DuPont Zorbax-SIL (4.6 mm ID × 25 cm) column. Silica gel F (M. Woelm, Eschwege) was used for preparative and analytical TLC.

Rose Bengal was obtained from Matheson. 2,6-Di-*t*-butylphenol, tetraphenylethylene (TPE) and 1,4-diazabicyclo-[2.2.2]octane (DABCO) were obtained from Aldrich. Phenyl-*t*-butylnitrone was a gift from Dr. J. D. Cheng (Texas Tech. University). β-Carotene was obtained from Sigma and purified by column chromatography (Woelm neutral alumina, Activity II) using hexane to give deep red crystals. 2,5-Dimethylfuran was prepared from hexane-2,5-dione as previously described.[73] Solvents were Fisher reagent grade, redistilled. The methanol-d_4 was 99.5% from Stohler.

Compound **1** was prepared according to the procedure of Falk *et al.*[33] from kryptopyrrole, and **2** was prepared according to the method of Lightner *et al.*[57] 5-[1,5-didehydro-3-ethyl-4-methyl-5-oxo-2*H*-pyrrol-2-ylidene)-methyl]-2,4-dimethyl-1*H*-pyrrol-3-propanoic acid (xanthobilirubinic acid, XBR) was prepared according to the method of Grunewald *et al.*[58]

Kinetic studies

General procedure. Exactly 1.00 ml of a freshly prepared 3.00×10^{-5} M soln of **1** or **2** in MeOH was added to a thermostatted (20°) standard 10 mm rectangular, stoppered cuvette along with exactly 1.00 ml of MeOH alone or 1.00 ml of a methanolic stock soln of one of the additives (see below). The electronic spectrum of the resulting soln was taken immediately (time zero) then retaken after set intervals (10, 60, 140 and 260 min) of irradiation with 417 nm monochromatic light. The percent decrease in absorbance (Table 1) at 417 nm was calculated as follows:

$$\%\ \text{decrease} = (A_0 - A_t)\times 100/A_0$$

where A_0 = absorbance measured at 417 nm at time zero and A_t = absorbance measured at 417 nm at time = 10, 60, 140 or 260 min. In order to subtract the effects of the rapidly obtained $Z \rightleftarrows E$ configurational isomerization, a different equation was used:

$$\%\ \text{additional decrease} = (A_{10} - A_t)\times 100/A_{10}$$

where A_{10} = absorbance measured at 417 nm after 10 min of irradiation by 417 nm monochromatic light.

Table 1. Quantitative changes in the electronic absorption spectrum of pyrromethenone (**2**) determined at the declining λ_{max} (417 nm) and emerging absorbances (315 and 265 nm) during self-sensitized photo-oxygenation with 417 nm monochromatic light

Irradiation time (min)	%Decrease in absorbance (A) 417 nm	(A_t-A_0)* 417 nm	315 nm	265 nm
0	0	0	0	0
10	21.5	−0.20	+0.000	+0.085
23	21.5	−0.20	+0.000	+0.085
78	21.5	−0.20	+0.000	+0.085
143	30.8	−0.287	+0.050	+0.080
309	51.2	−0.477	+0.125	+0.065
475	68.3	−0.637	+0.205	+0.050
Then Dark Reaction				
18 hr	59.2	−0.552	+0.175	±0.000
24 hr	59.2	−0.552	+0.175	±0.000

*A_t = Absorbance at time t, A_0 = Absorbance at time 0.

Table 2. Quantitative changes in the spectrum of pyrromethenone (2) during irradiation with 417 nm monochromatic light

Irradiation time (min)	% Decrease in 417 nm absorbance	
	aerobic	anaerobic
7	12.3	13.5
20	21.3	24.5
40	24.6	27.8
60	24.6	27.8
Then Dark Reaction		
15 hr	2.5 (90% $E \rightarrow Z$)	15.8 (43% $E \rightarrow Z$)*

*Introduction of air following 60 min anaerobic photoirradiation led, in the subsequent dark reaction to 73% reversion of $E \rightarrow Z$ isomers.

Actinometry[72] on the 417 nm irradiation light was performed before and after each experiment to ensure that the light intensity for separate runs was essentially constant.

The stock solns of additives consisted of: DABCO (1.50×10^{-3} M), TPE (3×10^{-3} M), β-carotene (3.00×10^{-5} M) (since β-carotene absorbs strongly at 417 nm, a 0.29 a.u. subtraction had to be applied to A_0 and A_t in the analysis), 2,5-dimethylfuran (3.00×10^{-5} M), β-carotene as external filter (2.00 ml of 1.50×10^{-5} M β-carotene was placed in a rectangular, stoppered 10 mm cuvette in front of 2.00 ml of 1.50×10^{-5} M **1** or **2** contained in a second 10 mm stoppered cuvette so the irradiation light passed first through the β-carotene solution). For runs in CD_3OD, 1.50×10^{-5} M **1** or **2** in methanol-d_4 were irradiated. The control experiment for all of the foregoing used 1.50×10^{-5} M **1** or **2** in methanol.

Kinetic studies with DABCO

Pyrromethenone (**1**) was dissolved in HPLC grade MeOH to give a 60 μM stock soln. DABCO was also dissolved in HPLC grade MeOH to give either a 6.0 mM or 600 μM stock soln. The freshly prepared solns were combined in the correct proportions in standard 1.0 cm quartz cuvettes, with additional MeOH in some cases, to give 2.00 ml of 45, 30, 15 and 7.5 μM solns of **1** with either 0.00, 150 μM or 750 μM DABCO. Each kinetic run had only one concentration of DABCO and was executed as follows. The initial absorbance (A_0) was determined for a given soln, which was then irradiated with 417 nm monochromatic light at 25.0° for 20 min, a time during which essentially no destruction of pigment was observed, rather, only the formation of a $Z \rightleftarrows E$ photostationary state. The initial A_{20} was read immediately, then the absorbance was monitored each minute for the next 4 min for any readjustments associated with complete reversal of *E* isomers of **1** to the original *Z* configuration. (The $Z \rightleftarrows E$ photostationary state, which is rapidly achieved during irradiation, decays fairly quickly with reversion of *E* to *Z* isomers as determined by HPLC). By this procedure a "true" A_{20} value was reached, a value reflecting only minute irreversible changes in **1**. The "true" A_{20} value was taken as the starting absorbance for these studies because the photostationary state varies with DABCO concentration and essentially no photodestruction of pigment occurs.

Table 3. Percent decrease in absorbance measured at 417 nm when 1.5×10^{-5} M pyrromethenone (**2**) is irradiated with 417 nm monochromatic light in the presence of quenchers or methanol-d_4

Solvents/Additive	% Decrease in absorbance[a] after irradiation for				% Additional decrease[b] calculated after initial 10 min irradiation for irradiation time		
	10 min	60 min	140 min	260 min	60 min	140 min	260 min
MeOH/None[c]	26.2	28.0	31.7	37.2	2.5	7.7	15.0
MeOH/DABCO[d]	26.0	27.4	29.7	32.9	1.9	5.0	9.3
MeOH/2,5-DF[d]	25.4	27.3	32.0	42.0	2.5	8.8	22.2
MeOH/TPE[d]	26.8	29.8	33.4	38.5	4.0	9.0	16.0
MeOH/β-carotene[e]	23.5	26.6	30.2	33.7	4.1	8.8	13.2
(β-carotene as a light filter)[e]	25.3	25.4	26.6	28.1	0.2	1.8	3.8
MeOH/DBP[d]	26.0	28.3	30.7	—	3.1	6.4	
(1.5×10^{-2} M)	26.0	28.3	30.4	—	3.1	5.9	—
MeOH/PBN[d,f]	24.3	26.2	27.9	–	2.5	4.8	·
CH_3OH[g]/None	25.6	28.4	34.8	—	3.7	12.3	—
CD_3OD[g]/None	22.6	37.1	78.9	-	18.8	72.8	—

[a]Calculated according to the expression % decrease = $100(A_t - A_0)/A_0$, where A_0 is the absorbance at time zero and A_t is the absorbance after t min irradiation.

[b]Calculated according to the expression % additional decrease = $100(A_{10} - A_t)/A_{10}$.

[c]Unless otherwise indicated, the concentration of additive is 1.5×10^{-3} M.

[d]PBN (phenyl-*t*-butylnitrone), BDP (2,6-di-*t*-butylphenol), DABCO (1,4-diazabicyclo[2.2.2]octane), 2,5-DF (2,5-dimethylfuran), TPE (tetraphenylethylene).

[e]1.5×10^{-5} M.

[f]4.5×10^{-5} M.

[g]3.0×10^{-5} M in pyrromethenone (**2**).

The 10 mm cuvette was then returned to the monochromatic light and irradiation recommenced within 5.0 ± 0.1 min after its initial removal. After a total irradiation period of 120 min, the A_{120} was taken and corrected (as above) for the $Z \rightleftarrows E$ photoisomerization by reading the absorbance values at 1 min intervals for 4 min. The change in absorbance, ΔA, is plotted in Fig. 9 according to Foote.[68]

Pyrromethenone-sensitized photo-oxygenation of 2,5-dimethylfuran

(*a*) A soln of pyrromethenone (**1** or **2**) (**1**, 51.6 mg, 0.20 mmol), and 2,5-dimethylfuran (480 mg, 5.00 mmol) in HPLC grade MeOH (200 ml) was placed in a 2 l Erlenmeyer flask. The flask was capped with parafilm and, except for the bottom, covered with Al foil. A 20 × 20 × 0.3 cm glass plate was placed on two horizontally mounted Westinghouse Special Blue fluorescent tubes, and the above Erlenmeyer was placed on the glass plate. The soln was irradiated for 25 days and worked up as follows. To one-tenth of the reaction soln was added 2,4-dinitrophenylhydrazine (158.4 mg, 0.80 mmol) and conc HCl (4 ml). After boiling for 10 min and cooling overnight, 124 mg (52.5% yield based on 2,5-dimethylfuran) of the orange, powdery bis-2,4-dinitrophenylhydrazone of *trans*-1,2-diacetylethylene, m.p. 281–282° dec [lit.[74] m.p. 284°] was obtained.

The other nine-tenths of the mixture was concentrated under reduced pressure at ambient temp to yield 662 mg of a very pale yellow oil, which contained (TLC) mainly 2,5-dimethyl-2-hydroxy-5-methoxy-2,5-dihydrofuran along with some 2,5-dimethyl-2-hydroperoxy-5-methoxy-2,5-dihydrofuran and 2,5-dimethyl-2-hydroperoxy-5-hydroxy-2,5-dimethylfuran, and little or no 1,2-diacetyl-ethylene.

The major component of the oil was isolated as follows. One-half of the oil was chromatographed on two 20 × 20 × 0.1 cm preparative layer silica gel plates with 5% MeOH-$CHCl_3$. A bright blue fluorescent band (254 nm UV detection lamp) at $R_f = 0.4$ was removed and washed with methanol to give 55 mg of colorless, oily 2,5-dimethyl-2-hydroxy-5-methoxy-2,5-dihydrofuran (17%), which exists in soln as an equilibrium mixture with its acylic isomer, *cis*-1,2-diacetylethylene monomethylhemiketal. IR (neat) *ν*: 3370 (br) 1700 (br) cm^{-1}; ^{1}H-NMR ($CDCl_3$) *δ*: 1.60 (6H, s, CH_3), 3.13 (3H, s, OCH_3), 5.08 (1H, br. s, OH), 5.85 (2H, s, =CH) ppm; ^{13}C-NMR data and assignments are shown below in Table 4.

(*b*) A water-cooled Pyrex immersion well photolysis apparatus was charged with 2,5-dimethylfuran (120 mg, 1.25 mmol), pyrromethenone (**2**) (42.2 mg, 0.155 mmol) and MeOH (100 ml). The resulting suspension was sparged with oxygen for 1 hr, then while O_2 was continually being recirculated through the suspension, it was irradiated with a Sylvania 500 Watt tungsten-halogen lamp (W-I_2) for 20 hr at 120 volts. When the measured O_2 uptake was 53 ml or 1.89 × theory and slowly increasing, the resulting soln was essentially completely photobleached and the run was terminated. The solvent was removed at ambient temp leaving a viscous amber oil, 210 mg. G.C. and nmr analysis revealed a quantitative yield of 2,5-dimethyl-2-hydroperoxy-5-methoxy-2,5-dihydrofuran (Table 4).

Self-sensitized photo-oxygenation of pyrromethenone (**2**)

A soln (2.7×10^{-5} M) of **2** in MeOH was irradiated with 417 nm monochromatic light using a 2 cm diam. × 10 cm length air-cooled cylindrical quartz UV cell. The reaction progress was monitored by decrease in intensity at 417 nm while irradiation was continued for 50 hr until **1** was ≥90% reacted. Evaporation of the solvent followed by TLC using $CHCl_3$-ether (6 : 4) gave the following major photo-oxygenation products:

(i) *Xeronimide* (**3b**), 50–60%, m.p. 68–69°. IR ($CHCl_3$) *ν*: 3440, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 1.13 (3H, t, J = 7.5 Hz), 2.38 (2H, q, J = 7.5 Hz). MS, *m/e* (rel. intens.): 153 (M^+, 89%), 138 (100%), 124 (23%), 120 (35%), 110 (42%). λ_{max} (CH_3OH) 220 nm (ε 12,000).

(ii) *Kryptopyrrole aldehyde* (**4a**), 5–10%, m.p. 105–106°. ^{1}H-NMR ($CDCl_3$) *δ*: 1.05 (3H, t, J = 7 Hz), 2.27 (6H, s), 2.40 (2H, q, J = 7 Hz) 9.43 (1H, s). MS, *m/e* (rel. intens.): 151 (M^+, 50%), 136 (100%). λ_{max} (CH_3OH) 312 nm (ε 9,000).

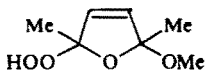
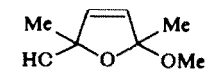
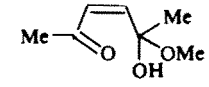
(iii) 4-*Ethyl*-5-*methoxy*-3,5-*dimethyl*-3-*pyrrolin*-2-*one* (**5**). IR (CCl_4) *ν*: 3250, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 1.20 (3H, t, J = 7.5 Hz), 1.53 (3H, s), 1.85 (3H, s); 2.30 (2H, q, J = 7.5 Hz), 3.01 (3H, s). MS *m/e* (rel. intens.): 169 ($M^{+\cdot}$, 15%), 154 (10%), 138 (100%), 122 (25%).

(iv) 3,4-*Diethyl*-5-(3,5-*dimethyl*-4-*ethyl*-5-*methoxy*-2*H*-*pyrrolyl*-2-*methylidene*)-3-*pyrrolin*-2-*one* (**6b**) 17%. ^{1}H-NMR ($CDCl_3$) *δ*: 1.12 (6H, t, J = 7 Hz, 2 × CH_3), 1.19 (3H, t, J = 7 Hz, CH_3), 1.42 (3H, s, CH_3), 1.192 (3H, s, CH_3), 2.35 (6H, q, J = 7 Hz, 3 × CH_2), 2.95 (3H, s, OCH_3), 5.66 (1H, s, =CH). MS, *m/e* (rel. intens.): 302.1993 (M^+, calcd for $C_{18}H_{26}N_2O_2$ 302.1994, 34%), 287 (100%), 273 (28%), 271 (49%). λ_{max} (CH_3OH) 312 nm (ε 16,000); pentdyopent reaction, λ_{max} = 433 nm (fluorescent yellow).

Rose Bengal-sensitized photo-oxygenation of pyrromethenone (**2**)

A soln (2.7×10^{-5} M) of **2** in MeOH containing 8×10^{-2} mg/ml Rose Bengal was irradiated with 557 nm monochromatic light as above. After 30 min irradiation, **2**

Table 4. ^{13}C-NMR spectral assignments for the photo-oxygenation products of 2,5-dimethylfuran

Compound	Carbon-13 assignments[a]			
	Vinyl-C	Quaternary-C	OCH_3	CH_3
 [b]	134.33 (d) 131.58 (d)	113.91 (s) 111.57 (s)	51.38 (q)	25.34 (q) 22.25 (q)
 [c]	134.61 (d) 131.46 (d)	115.25 (s) 113.44 (s)	50.20 (q)	25.04 (q) 21.47 (q)
 [c]	134.79 (d) 131.22 (d)	114.31 (s)	51.01 (q)	25.27 (q) 21.82 (q)

[a] Values in ppm downfield from tetramethylsilane, run in $CDCl_3$.
[b] Sample prepared according to ref. 74.
[c] These are in equilibrium in the $CDCl_3$ used to run the spectra.

was ⩾90% reacted, whereupon work-up as before gave the same major products as in the self-sensitized reaction: **3b** (50%), **4a** (3%), **5** (35%) and **6b** (15%).

Configurational photoisomerization of pyrromethenone **1** *and XBRME*

Solns (0.25 m M) of either **1** or XBRME in EtOH : toluene (1 : 1) were irradiated in standard 10 mm quartz rectangular cuvettes with 415 nm monochromatic light for up to 52 min and the reactions progress was followed by HPLC using a Zorbax-SIL column and EtOH-toluene (15 : 85). At time zero, only one peak could be seen for either XBRME or **1**. Upon irradiation, a new, more polar substance was detected. The new peak increased at the expense of the starting peak until a nearly 1 : 1 photoequilibrium was reached after *ca.* 40 min. The half-life of the new peak was 16 ± 2 hr at 27°, as judged from sampling the photoequilibrated soln (stored in the dark). The newly-formed peak reverted to starting material on standing. In MeOH solvent, photoequilibrium was more rapidly established, and the photoproduct reverted more rapidly to starting material. Consistent with other observations, we assign the *E* configuration to the photoisomer.

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