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ON THE SYNTHESES AND SINGLET OXYGEN REACTIVITY OF OXODIPYRROMETHENE MODELS FOR BILIRUBIN

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Abstract—Various oxodipyrromethenes with varying β-substituents have been synthesized and their reaction with singlet oxygen studied. The rates of chemical reactivity (k_R) and physical quenching (k_Q) of singlet oxygen by those substrates approach the diffusion threshold in both chloroform and methanol solvents, with k_Q generally larger than k_R in chloroform but of comparable magnitude in methanol. The range of $(k_Q + k_R)$ values is $0.2–4.2 \times 10^9\ M^{-1}\ s^{-1}$.

The phototherapy method[1] for treating physiologic jaundice in newly born infants owes its success, in part, to photodestruction of bilirubin IXα (BR).[2,3] BR can undergo photodestruction *in vitro* under either anaerobic[2,4] or aerobic[2–6] conditions. Photodestruction with visible light is more rapid under aerobic conditions,[4] and the reaction involves BR-sensitized production of singlet oxygen [$^1O_2$] followed by rapid reaction with it.[7,8] Since the light selection in phototherapy is invariably visible or blue light,[9,10] it becomes important to know the quantitative aspects of BR photoreactivity and its reactivity toward $^1O_2$, especially since $^1O_2$ is implicated in photodynamic action.[10,11] Foote and Ching[12] have reported on this subject as have Matheson *et al.*[13] and Stevens and Small.[14] Our approach toward understanding this and other aspects of BR photochemistry and photooxidation has involved the use of model substrates, viz. oxodipyrromethenes.[2,5,15–17] Studies involving such models allowed us to predict and isolate the products of reaction of $^1O_2$ with BR,[2,5,15] and they have provided the key to recognizing and elucidating the Z→E photoisomerization of BR.[2,18] In this work we report on the $^1O_2$ reactivity of model substrates **3–8** and the relationship to BR.

Syntheses

The preparations of oxodipyrromethanes (**3**, **4**, **7** and **8**) follow a general pattern in which an alkylated pyrrole aldehyde is condensed with a pyrrolinone under base catalysis. For **5** and **6** a bromovinyl pyrrolinone is condensed with an alkylpyrrole. Syntheses of the pyrrolinone (left half) components are outlined in Scheme 1, and syntheses of pyrrole and pyrrole aldehyde components (right half) are described in Scheme 2. Thus, as shown in Scheme 1, pyrrolinones are generally obtained following H_2O_2 oxidation of the corresponding pyrrole, which had been prepared following a classical Knorr synthesis. Preparation of pyrrolinone **9** involved cyclization according to Plieninger and Kurze. For the right halves, in Scheme 2 pyrrole aldehydes were prepared by Vilsmeier reactions on pyrroles obtained following a Knorr synthesis or by elaboration of pyrrole itself as a starting material. The coupling reactions (Scheme 3) leading to oxodipyrromethenes were either base-catalyzed condensations of a pyrrolinone and pyrrole aldehyde or reaction of a bromovinyl pyrrolinone with an alkyl pyrrole.

Reaction with singlet oxygen

Singlet $^1O_2$ was produced by excitation of Rose Bengal (RB) (Matheson) or Rose Bengal-18-crown-6 ether (RBCE)[19] (eqns 1 and 2) with monochromatic light, 10 nm bandpass, from a Bausch and Lomb Model 33-86-07 monochromator and a 15 W tungsten-halogen source. RB was used to produce $^1O_2$ in methanol solutions by excitation at 557 nm (λ_{max}) and RBCE was used to produce $^1O_2$ in chloroform solution by excitation at 560 nm (λ_{max}). These excitation wavelengths are sufficiently far removed from the BR long wavelength λ_{max} (450 nm) that excitation of the dye-sensitizer with 10 nm bandpass light involves no direct excitation of BR.

$$^1RB_0 \text{ or } ^1RBCE_0 \xrightarrow[\lambda = 557 \text{ or } 560\text{ nm}]{h\nu} {}^3RB \text{ or } {}^3RBCE \quad (1)$$

$$^3RB \text{ or } {}^3RBCE + {}^3O_2 \longrightarrow {}^1O_2 + {}^1RB_0 \text{ or } {}^1RBCE_0. \quad (2)$$

The $^1O_2$ produced in this way may decay (k_d), be physically quenched (k_Q) by substrate (S), or chemically react (k_R) with S (eqns 3–5). Singlet oxygen reactivity ($k_Q' + k_R'$) with the dye sensitizer is much slower than k_d, k_Q or k_R.[11,12]

$$^1O_2 \xrightarrow{k_d} {}^3O_2 \quad (3)$$

$$S + {}^1O_2 \xrightarrow{k_Q} {}^3O_2 + S \quad (4)$$

$$S + {}^1O_2 \xrightarrow{k_R} \text{Products} \quad (5)$$

The steady-state approximation gives (eqn 6), for the rate of substrate disappearance:

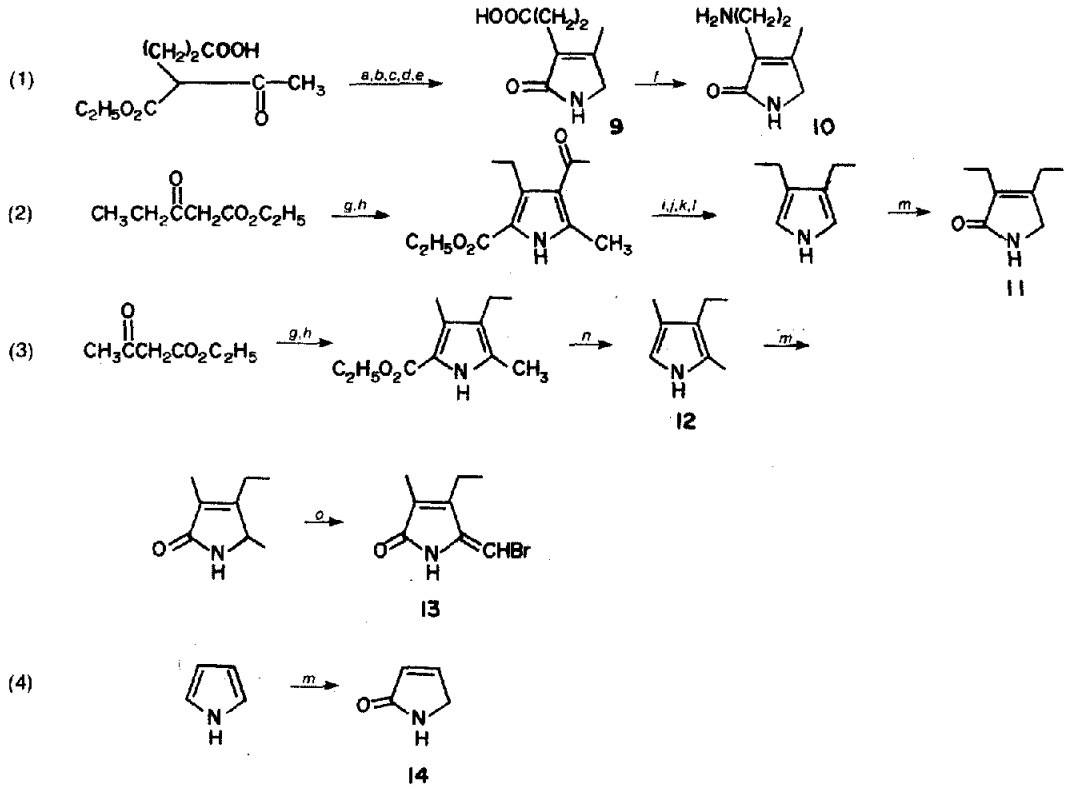
$$-d[S]/dt = K \cdot k_R[S]/\{(k_Q + k_R)[S] + k_d\} \quad (6)$$

where K is the rate of $^1O_2$ production and defined as $K = I_a \cdot \phi_{isc} \cdot f^1O_2$ (with I_a = rate of absorption of light by the sensitizer in mol. quanta/sec, ϕ_{isc} = sensitizer triplet quantum yield and f^1O_2 = yield of $^1O_2$ from triplet sensitizer = 1.0.[12,20,21]

For $\Delta[S] \ll [S_0]$, the solution of eqn (6) can be approximated as (eqn 7):

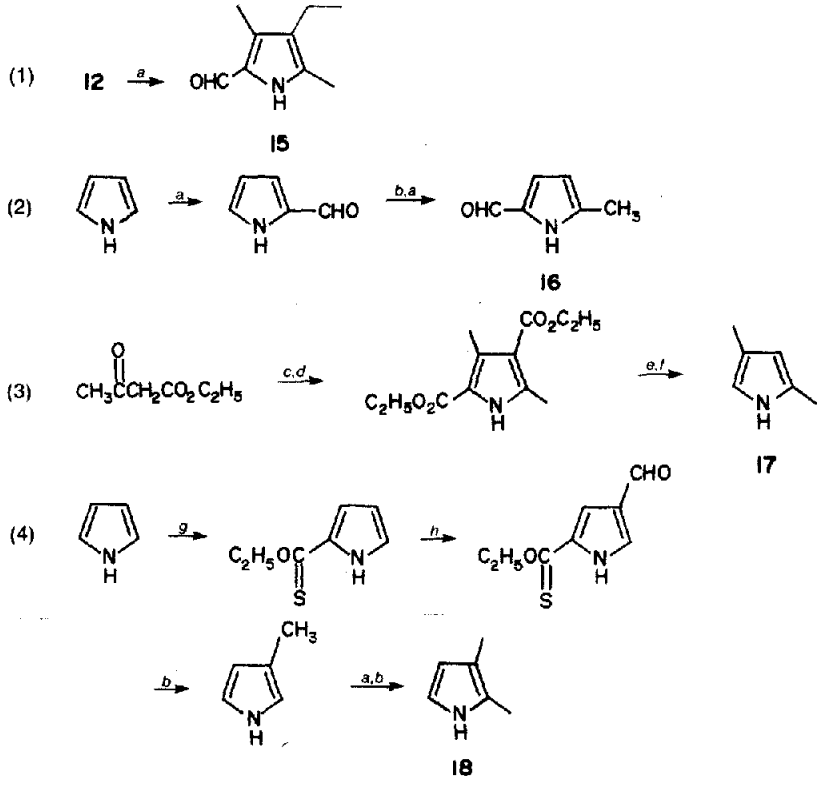
$$\{\Delta[S]/I_a\Delta t\}^{-1} = \phi_{isc}^{-1}\{(k_Q + k_R)/k_R + k_d[S_0]^{-1}/k_R\} \quad (7)$$

where $\Delta[S] = [S_0] - [S]$ and $[S_0]$ is the initial substrate



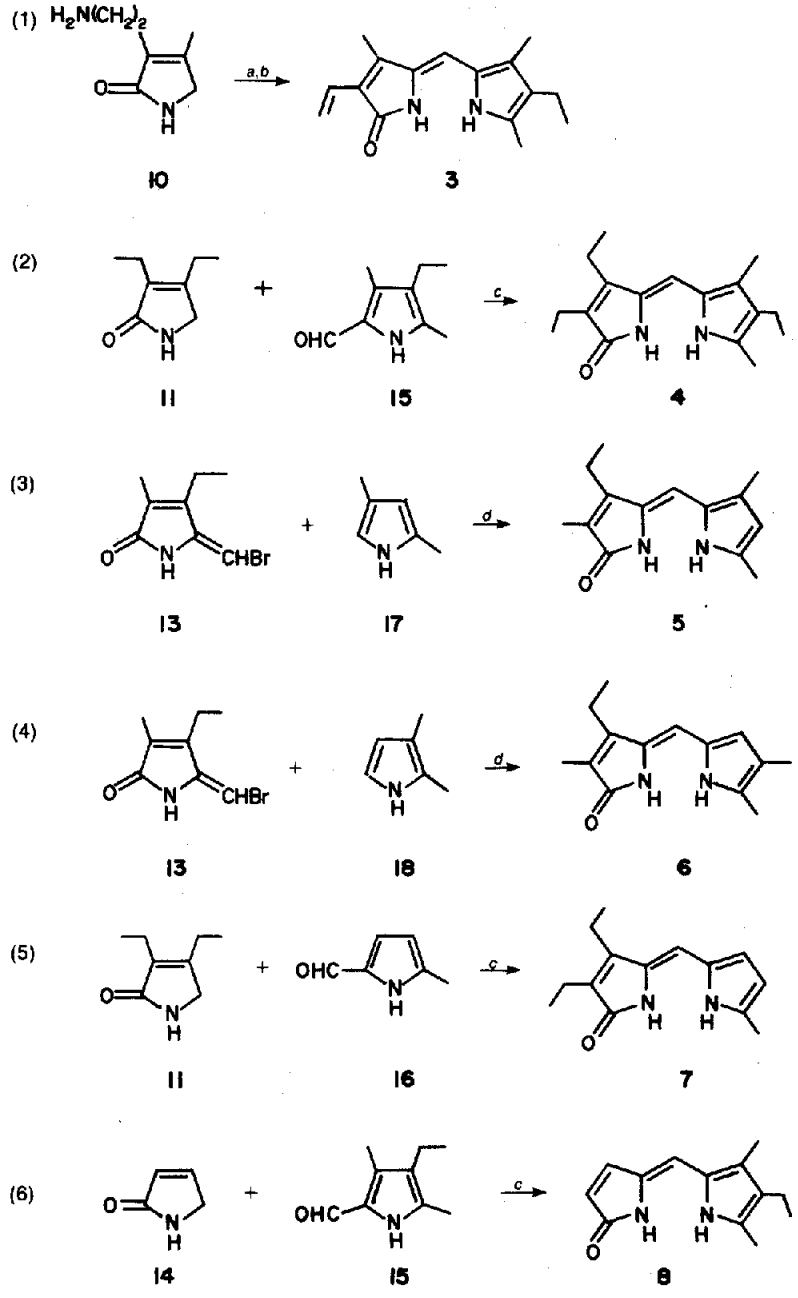
Scheme 1. Left halves.

[a]HCN; [b]2,3-dihydrofuran; [c]Ni(R)/H_2; [d]acetic anhydride; [e]H_2SO_4; [f]HN_3; [g]$NaNO_2$/HOAc–H_2O; [h]2,4-pentanedione, Zn/HOAc; [i]B_2H_6; [j]SO_2Cl_2; [k]^-OH; [l]quinoline, Δ/–CO_2; [m]H_2O_2, ^-OH; [n]H_2NNH_2/KOH/Δ; [o]Br.



Scheme 2. Right halves.

[a]$POCl_3$–$HCON(CN_3)_2$; [b]H_2NNH_2/KOH/Δ; [c]$NaNO_2$/HOAc–H_2O; [d]acetoacetic ester, Zn/HOAc; [e]^-OH; [f]H_3O^+/Δ; [g]C_2H_5MgBr/$ClCoSc_2H_5$; [h]Cl_2CHOCH_3/$AlCl_3$/CH_3NO_2.



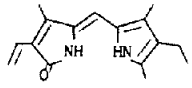
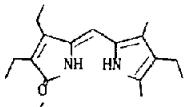
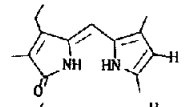
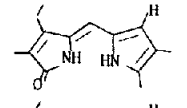
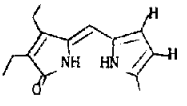
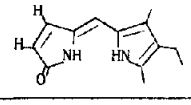
Scheme 3. Coupling to oxodipyrromethenes.

[a]Excess CH_3I/Δ; [b]$KOH/H_2O/\Delta$; [c]$NaOH/CH_3OH/\Delta$; [d]CH_3OH/Δ.

concentration. The value of I_a is determined by actinometry using Reinecke's salt,[22] and a plot of $\{\Delta[S]/I_a\Delta t\}^{-1}$ vs $[S_0]^{-1}$ for a fixed time period will give a linear plot. The ratio of the slope to the intercept of such a plot is $k_d/(k_Q+k_R)$, and the reciprocal of the intercept is $\phi_{isc}k_R/(k_Q+k_R)$. Since the k_d values for $^1O_2$ are known in methanol ($k_d = 1.4\times10^5\ s^{-1}$) and chloroform ($k_d = 1.67\times10^4\ s^{-1}$),[20] the values of (k_Q+k_R) can be determined. They are summarized in Table 1 for BR, aetiobilirubin and the oxodipyrromethenes. In order to separate k_Q and k_R, the values of ϕ_{isc} are required. The value of ϕ_{isc} for RB in methanol is 0.76.[21] Since RB is insoluble in chloroform, RBCE was used, and its ϕ_{isc} value was determined by measuring the reaction rate of, 1,3-diphenylisobenzofuran (DPBF), which is known to be a good $^1O_2$ acceptor but not a quencher.[12] By plotting $(\Delta[DPBF]/I_a\Delta t)^{-1}$ vs $[DPBF_0]^{-1}$, the reciprocal of the intercept, $\phi_{isc}k_R/(k_Q+k_R)$, was found to be 0.36. Since DPBF does not quench $^1O_2$, $k_Q = 0$ and $\phi_{isc} = 0.36$. By way of comparison, ϕ_{isc} for RBCE in methanol was found to be 0.63 (vs 0.76 for RB in methanol[12]).

The derived values of k_R and (k_Q+k_R) for BR, aetiobilirubin (ABR) and the oxodipyrromethenes are presented in Table 1 along with reference values from other work for BR. As has been noted previously,[12] the published[13] k_R value for Nd-YAG laser-produced $^1O_2$ is an

Table 1. Physical (k_Q) and reactive (k_R) rate constants for substrate-singlet oxygen reactivity

Substrate (10^{-5}M)	Value x $10^9 M^{-1}s^{-1}$ in $CHCl_3$[a]		Value x $10^9 M^{-1}s^{-1}$ in CH_3OH[b]	
	$(k_Q + k_R)$	k_R	$(k_Q + k_R)$	k_R
1 Bilirubin IXα	2.8 2.5[d] 2.5[e,f] - -	0.38 0.43[d] 0.17[f,g] 0.01[h,i] 0.10[i,j]	2.1[c] 1.3[d,e]	0.28[c] 0.43[d,e]
2 Aetiobilirubin IVγ[k]	3.0	2.3	2.2[l]	0.85[l]
3 	2.2	1.9	3.1	1.2
4 	4.2	3.2	2.7	1.4
5 	2.4	1.6	1.1	0.6
6 	2.5	1.7	2.3	0.9
7 	1.5	0.8	0.8	0.3
8 	4.4	3.0	0.2	0.1

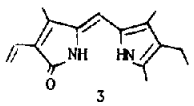
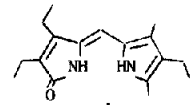
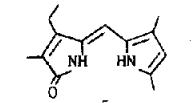
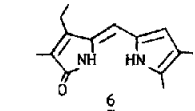
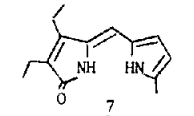
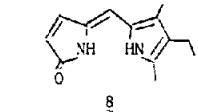
[a] 18-Crown-6 Rose Bengal Sensitizer
[b] Rose Bengal Sensitizer
[c] With 0.2% (vol.) conc. NH_4OH
[d] Data of C. S. Foote and Y-T. Ching, *J. Amer. Chem. Soc.*, 97, 6209 (1975)
[e] $CH_3OH:CHCl_3$ - 1:9
[f] Data of B. Stevens and R. D. Small, *Photochem., Photobiol.*, 23, 33 (1976)
[g] CCl_4 solvent
[h] Data of I. B. C. Matheson, N. V. Curry and J. Lee, *J. Amer. Chem. Soc.*, 96, 3348 (1974)
[i] Freon -113 solvent using Nd-YAG laser direct production of $^1O_2$ at high $^1O_2$ pressures.
[j] Recent data of I. B. C. Matheson, reference 23.
[k] Sample provided by Prof. Kevin M. Smith, University of California at Davis.
[l] $CH_3OH:CHCl_3$ - 9:1 (v/v) solvent

order of magnitude lower for BR. However, more recent work by Matheson[23] leads to a value closer to that found in this and other work. Several important conclusions may be deduced from the data of Table 1 and related data. (i) BR, ABR and the oxodipyrromethanes all quench $^1O_2$ enormously fast, with $(k_Q + k_R)$ approaching the diffusion limit. (ii) The $(k_Q + k_R)$ rate constants are fairly solvent insensitive, especially in $CHCl_3$, with the greater spread being found in CH_3OH. In $CHCl_3$, the k_R values of **1–8** vary from 3.2 to 0.38 with the larger values belonging to substrates possessing more highly alkylated pyrrole rings. The exception to this observation is BR (**1**), which has the lowest k_R value of the set. It is tempting to argue that its k_R is somehow tied to its H-bond dependent secondary structure,[24,25] since none of **2–8** can easily achieve that conformation. In CH_3OH, the values of k_R vary from 1.4 to 0.1 and are generally correspondingly smaller than those found in $CHCl_3$. For BR (**1**), however, the k_R values seem to be independent of the choice of these two solvents. This, too might be an expected consequence of intramolecular H-bonding in both solvents, in either of which the long wavelength visible absorption maximum (452 nm) is identical. If a change in the long wavelength λ_{max} is used to detect conformational changes, **3–8** all exhibit λ_{max} shifts to longer wavelength in going from $CHCl_3$ to CH_3OH (Table 2). The greatest λ_{max} shift is found for **8**, the compound with the greatest solvent dependence on k_R. (iii) Recent studies have shown that oxodipyrromethene **4** is a $^1O_2$ sensitizer.[26] BR (**1**) is also a known $^1O_2$ sensitizer[7,8] with a recently established low-lying triplet at ~37 kcal/mole above the ground state.[27] It thus seems improbable that **1** or **4** should quench $^1O_2$ (22 kcal/mole above its ground state) by (resonance) energy transfer. Rather, a more probable quenching mechanism would involve an electron transfer reaction (eqn 8).[14]

$$S + {}^1O_2 \longrightarrow [S^{+\cdot}\ O_2^{-\cdot}] \longrightarrow S + {}^3O_2. \qquad (8)$$

This type of mechanism is, in principle, available to all substrates **1–8**; however, the extent to which it participates will depend on their one electron oxidation (half-wave potentials).[17,28] Thus, substrates with lower half wave potentials are expected to exhibit greater $(k_Q + k_R)$ values according to eqn (8). Since Falk *et al.*[28] have shown that less highly alkylated oxodipyrromethanes have higher half-wave potentials, e.g. $E_{1/2}$ for **7** would be ~0.6V and for **4** ~0.4V, a rough correlation may be

Table 2. Spectroscopic properties of oxodipyrromethenes

Compound	^{1}H-Nmr (Deuteriochloroform TMS, in ppm)	Ms m/e (Relative Intensity)	Uv (λ, ϵ_{max}, methanol)	Ir (Chloroform)
 3 mp 223-224°(d)	1.03 (t, 3H, J=7 Hz, CH_3) 2.10 (s, 3H, CH_3) 2.17 (s, 3H, CH_3) 2.30 (s, 3H, CH_3) 2.43 (q, 2H, J=7 Hz, CH_2) 5.27 (2d, 1H, J=10 Hz, J=3 Hz, vinyl H) 5.93 (2d, 1H, J=18 Hz, J=3 Hz, vinyl H) 6.17 (s, 1H, methine H of bridge) 6.37 (d, 1H, J=10 Hz) 10.20 (br. s, 1H, NH)	256(100%) [M^+] 241(43%) 212(23%)	438 (40,000) [a]433 (36,000)	3361 (NH) 1668 (C=O) 1628 (C=C)
 4 mp 223-4°(d)	1.06 (t, 3H, J=7.5Hz, CH_3) 1.13 (t, 3H, J=7.5Hz, CH_3) 1.20 (t, 3H, J=7.5Hz, CH_3) 2.13 (s, 3H, =C-CH_3) 2.38 (s, 3H, =C-CH_3) 2.43 (q, 4H, J=7.5Hz, $2CH_2$) 6.10 (s, 1H, =CH)		417 (36,000) [a]408 (34,000)	[b]3410 (NH) 3000 (CH) 1670 (C=O) 1640 (C=C) [c]3400 (NH) 3200 (NH hydrogen bonded) 1650 (C=O) 1625 (C=C)
 5 mp 245-6°	1.13 (t, 3H, J=8 Hz, CH_3) 1.93 (s, 3H, =C-CH_3) 2.15 (s, 3H, =C-CH_3) 2.43 (s, 3H, =C-CH_3) 2.45 (q, 2H, J=8 Hz, CH_2) 5.77 (m, 1H, CH of pyr ring) 6.05 (s, 1H, =CH)	230(100%) [M^+] 215(57%) 200(36%) 187(21%)	407 (34,000) [a]398 (33,000)	3400 (NH) 1670 (C=O) 1640 (C=C) [c]3370 (NH) 1660 (C=O) 1625 (C=C)
 6 mp 242-3°(d)	1.13 (t, 3H, J=8 Hz, CH_3) 1.90 (s, 3H, CH_3) 2.00 (s, 3H, CH_3) 2.33 (s, 3H, CH_3) 2.47 (q, 2H, J=8 Hz, CH_2) 6.00 (s, 1H, =CH, methine H) 6.13 (m, 1H, =CH of pyr ring)	230(100%) [M^+] 215(38%) 200(23%) 187(23%)	408 (34,000) [a]400 (30,000)	3460 (NH) 3000 (CH) 1660 (C=O) 1630 (C=C)
 7 mp 188-190°	1.13 (t, 3H, J=7.5Hz, CH_3) 1.18 (t, 3H, J=7.5Hz, CH_3) 2.48 (s, 3H, =CCH_3) 2.50 (q, 4H, J=7.5Hz, $2CH_2$) 5.98 (m, 1H, =CH of pyr ring) 6.12 (s, 1H vinyl H) 6.35 (m, 1H, =CH of pyr ring) 10.6 (br. s, 1H, NH) 11.3 (br. s, 1H, NH pyrrolinone)	231(44%) [MH^+] 230(100%) [M^+] 299(44%) 215(62%) 201(10%)	400 (31,000) [a]386 (31,000)	3350 (NH) 2980 (CH) 1664 (C=O) 1640 (C=C) 1483 (CN)
 8 mp 216-218°	1.05 (t, 3H, J=8Hz, CH_3) 2.14 (s, 3H, =C-CH_3) 2.37 (s, 3H, =C-CH_3) 2.42 (q, 2H, J=8Hz, CH_2) 5.97 (d, 1H, J=6Hz, =CH of pyrrolinone) 6.14 (s, 1H, =CH 7.01 (d, 1H, J=6Hz, =CH of pyrrolinone)	216(100%) [M^+] 201(50%) 187(25%) 173(25%)	430 (39,000) [a]424 (34,000)	3340 (NH) 3000 (CH) 1664 (C=O) 1622 (C=C)

[a] in $CHCl_3$ [b] in CCl_4 [c] KBr pellet

drawn. By way of contrast, 3,4 - diethyl - 5 - (phenylmethylidene) - 3 - pyrrolin - 2 - one[29] has $E_{1/2} \approx 1.2V$[28] and is non-interactive (k_Q or k_R) with $^1O_2$. The radical ion pairs $[S^{+\cdot}O_2^{-\cdot}]$ postulated in the quenching mechanism (eqn 8) can also account for the observed products either by collapse to give dioxetanes or *endo*-peroxides[17] which decompose to products (eqn 9), or, in addition for **1** and **2**, by H· abstraction *en route* to biliverdin-like products (BV) (eqn 10).[5,14] The comparatively slow rate (k_R) of product formation from **1**, **7** and **8** (in CH_3OH) could thus be ascribed to non-involvement of radical ion pairs or to a less favorable partioning of the radical ion pair in eqns like 9 and 10.

$$[S^{+\cdot}O_2^{-\cdot}] \longrightarrow \text{Dioxetanes/}\textit{Endo}\text{peroxides} \longrightarrow \text{Products} \quad (9)$$

$$[S^{+\cdot}O_2^{-\cdot}] \longrightarrow [S\text{–H}]^{\cdot}O_2H \longrightarrow BV + H_2O_2. \quad (10)$$

Other evidence for electron transfer reactions with $^1O_2$ may be found in enamine cleavages which appear to go through an electron-transfer or charge-transfer mechanism involving collapse of an ion-radical pair.[29] The reaction products were examined following RB-sensitized photooxygenations of **3–8** in methanol solution using monochromatic excitation of RB at 557 nm. The major identifiable products in each instance were imides, pyrrole aldehydes and methoxypyrrolinones. They originate, presumably from unstable dioxetane intermediates at the exocyclic ene-amide carbon–carbon double bonds.[17] Other detectable products seem to arise from oxidation of the pyrrole ring.[2,4,15,26]

Summary

The first order rates of reaction, as measured by k_Q and k_R, for oxodipyrromethenes **3–8** and $^1O_2$ are very similar to those of bilirubin IXα and aetiobilirubin IVγ. The values of $(k_Q + k_R)$ approach the diffusion threshhold; hence, these substrates are among the most reactive known for $^1O_2$. The reaction with $^1O_2$ appears to involve an important component of electron transfer leading to radical ion pairs. These may in turn decay (k_Q) or react (k_R), and the overall rate constant $(k_Q + k_R)$ generally follows the half-wave oxidation potentials of the substrates. The reaction products of substrates + $^1O_2$ include those from exocyclic ene-amide C=C bond scission (via a dioxetane?) and attack at the pyrrole ring.

EXPERIMENTAL

General. All m.ps were determined on a Thomas–Hoover Unimelt capillary apparatus and are uncorrected. NMR spectra were measured in $CDCl_3$ on a unless otherwise specified Perkin–Elmer R-24B spectrometer. Chemical shifts are reported in ppm (δ) downfield from TMS as an internal standard. The following descriptive abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; br, broad; m, multiplet. Mass spectra (ms) were determined on a Jeol JMS-07 instrument at 12 eV or 70 eV. Visible and UV spectra were recorded on a Cary 14 spectrophotometer. IR spectra were obtained from samples in $CHCl_3$ or in KBr pellets using a Beckman IR-8 spectrophotometer. The plates used for preparative tlc (20 cm × 20 cm) were prepared with *ca.* 8 g of absorbent (0.05–0.2 mm silica gel F, M. Woelm, Eschwege) giving a layer thickness of 1 mm. Preparative photochemistry was carried out in a water-cooled Pyrex immersion well apparatus with circulating O_2 using a 500 W tungsten-halogen lamp (Sylvania 500 Q/CL). Kinetic photoisomerization studies were carried out at 10° in quartz NMR tubes using a Hanovia 100 W, 1.2 A high pressure mercury lamp, model SH. Kinetic photooxygenation studies were accomplished in a UV cell (1 cm path, 3 ml) using 10 nm bandpass monochromatic light from a Bausch and Lomb monochromator (model 33-86-07) equipped with a 15 W tungsten lamp or a 200 W super pressure Hg lamp. For degassed experiments, a pyrex to quartz fuzed 10 mm quartz cell was subjected to at least three cycles of freeze-pump-thaw treatment at a pressure of $< 4.0 \times 10^{-6}$ Torr. Light intensities at each excitation wavelength used were determined by actinometry[22] with potassium Reinecke's salt. Solvents were reagent grade, distilled, unless otherwise specified. Microanalyses were performed by Chemalytics, Tempe, Arizona.

The left halves

3 - (*β* - *Carboxyethyl*) - 4 - *methyl* - 3 - *pyrrolin* - 2 - *one* (**9**) was prepared by the method of Plieninger *et al.*[31] in 51% yield, m.p. 167–169° (lit.[31] m.p. 166°); NMR (pyridine-d_5) δ 1.87 (s, 3H, CH_3), 2.83 (s, 4H, $-CH_2CH_2-$), 3.63 (s, 2H, CH_2 in pyrrolinone), 9.86 (br.s, 1H, NH) ppm.

3,4 - *Diethyl* - 3 - *pyrrolin* - 2 - *one* (**11**) was prepared by the method of Lightner *et al.*[32] in 30% yield, b.p. 126°/0.15 Torr (lit.[32] b.p. 115–118°/0.2 Torr); NMR δ 1.07 (5, 3H, CH_3, J-8 Hz), 1.15 (t, 3H, J = 8 Hz, CH_3), 2.30 (q, 4H, J = 8 Hz, $2CH_2$), 3.80 (s, 2H, CH_2), and 7.00 (br.s, 1H, NH) ppm.

2 - *Bromomethylene* - 3 - *ethyl* - 4 - *methyl* - 3 - *pyrrolin* - 5 - *one* (**13**) was prepared by bromination[33] of 4 - ethyl - 3,5 - dimethyl - 3 - pyrrolin - 2 - one in 58% yield, m.p. 137–141° (lit.[33] 139–141°); NMR δ 1.11 (t, 3H, J = 7.0 Hz, CH_3), 1.83 (s, 3H, CH_3), 2.40 (q, 2H, J = 8 Hz, CH_2), 5.90 (s, H, =CH), 7.40 (br.s, 1H, NH) ppm; UV (95% EtOH), $\lambda_{max} = 282$ nm, $\epsilon = 1.9 \times 10^4$ (lit.[33] $\lambda_{max} = 282$ nm, $\epsilon = 1.8 \times 10^4$); and IR ($cm^{-1}$, $CHCl_3$), 3475 (NH), 3125 (=CH), 1710 (C=O), 1650 (C=C) cm^{-1}.

3 - *Pyrrolin* - 2 - *one* (**14**) was prepared by the method of Bocchi *et al.*[34,35] in 15% yield; NMR δ 4.10 (s, 2H), 6.17 (d, 1H, =CH), 7.18 (d, 1H, =CH), 8.10 (s, NH) ppm.

The right halves

4 - *Ethyl* - 2 - *formyl* - 3,5 - *dimethylpyrrole* (**15**) was prepared by a Vilsmeier reaction[36] on kryptopyrrole (**12**) in 73% yield, m.p. 105–106° (lit.[37] m.p. 105–106°); NMR ($CDCl_3$) δ 1.05 (t, 3H, J = 7 Hz, CH_3), 2.27 (s, 6H, $2CH_3$), 2.40 (q, 2H, J = 7 Hz, CH_2), 9.43 (s, 1H, CHO) ppm; mass spectrum, *m/e* (rel. intens.) 151 (M^+, 50%), 136 (100%).

2 - *Formyl* - 2 - *methylpyrrole* (**16**) was prepared as above by a Vilsmeier reaction[36] on a 2-methylpyrrole[38] in 97% yield, m.p. 67–68° (lit.[37] m.p. 70°); NMR (CCl_4) 2.38 (s, 3H, CH_3), 5.95 (t, 1H), 5.82 (t, 1H), 9.45 (s, 1H, CHO) ppm; mass spectrum, *m/e* (rel. intens. 109 (M^+, 100%), 80 (91%), 53 (89%).

2,4 - *Dimethylpyrrole* (**17**)[39] was obtained from base-catalyzed hydrolysis and decarboxylation of 2,4 - dimethyl - 3,5 - decarboethoxypyrrole[37] in 33% yield, b.p. 60–68°/11 Torr (lit.[37] 58°/9 Torr).

3 - *Methylpyrrole*[39,40] was synthesized by Huang–Minlon reduction and base-catalyzed decarboxylation of ethyl-4-formyl, 2-pyrrolethiocarboxylate in 76% yield, b.p. 47–48°/13 Torr (lit.[39,40] 44–45°/10 Torr); NMR ($CDCl_3$) δ 2.10 (s, 3H, CH_3), 6.00 (m, 1H, CH=), 6.40 (m, 1H, CH=), 6.50 (m, 1H, CH=), 7.50 (br.s, 1H, NH) ppm.

3 - *Methyl* - 2 - *pyrrole aldehyde.*[39] Into a 50 ml round-bottom flask equipped with teflon stirring bar, pressure equalized addition funnel and blanketed with N_2 was placed 7.6 g of $POCl_3$ in 20 ml anhyd ether. A soln of 3.6 g dry DMF in 10 ml ether was added in one portion and the mixture allowed to stir for 5 min. The viscous $POCl_3$–DMF complex (colorless) was separated from the ether and transferred to a 100 ml 3-neck round-bottom flask fitted with reflux condenser, addition funnel and stirring bar. CH_2Cl_2 (20 ml) was added. Then a soln of 2.8 g (0.035 mole) of 3-methylpyrrole in 10 ml CH_2Cl_2 was added dropwise, and the mixture was stirred for 2 hr. The solvent was removed under vacuum, and the residual red oil was poured into 50 ml ice water and neutralized with NaOAc to Congo red paper. A slight excess of NaOAc was added to insure that the soln was buffered since acidic conditions cause the aldehyde to undergo acid-catalyzed condensation reactions to give dimeric or polymeric side products. The neutralized mixture was heated on a steam bath for 15–30 min, gravity filtered hot and stored overnight at 5° to yield brown needles, 45% yield. Sublimation (oil bath 70°, 0.05 Torr) of the crude product gave long colorless needles in 35% yield, m.p. 90°–92° (lit.[37] m.p. 92°); NMR ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 6.06 (t, 1H, J = 3 Hz, CH=), 6.97 (t, 1H, J = 2 Hz, CH=), 9.53 (br.s, 1H, CHO) ppm.

2,3 - *Dimethylpyrrole* (**18**)[39] was prepared by a Huang–Minlon reduction of 3 - methyl - 2 - pyrrole aldehyde, b.p. 63–64°/13 Torr (lit.[37] 65°/14 Torr) in 63% yield; NMR ($CDCl_3$) δ 1.97 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 5.83 (t, 1H, J = 3 Hz, CH=), 6.33 (t, 1H, J = 3 Hz, CH=), 7.30 (br.s, 1H, NH) ppm.

Oxodipyrromethenes

5' - *Oxo* - 4' - *vinyl* - 4 - *ethyl* - 3',3,5 - *trimethyl* - 1',5' - *dihydro* - (2.2') - *dipyrromethene* (**3**) was prepared by the method of Plieninger and Kurge[31] from **9** and **15** in 27% yield, m.p. 223–224° (d), (yellow crystals). Physical/Spectroscopic constants are in Table 2. (Found: C, 75.03; H, 7.80; N, 10.78. Calc. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93%).

5' - *Oxo* - 3',4',4 - *triethyl* - 3,5 - *dimethyl* - 1',5' - *dihydro* - (2.2') - *dipyrromethene* (**4**) was synthesized by the method of Lightner

et al.[32] in 52% yield, m.p. 238–240° (lit.[32] 233° (d)). Physical/Spectroscopic data are in Table 2.

5' - Oxo - 3' - ethyl - 4',3,5 - trimethyl - 1',5' - dihydro - (2.2') - dipyrromethene (**5**). Compound **13** (4 g, 18.8 mmole) in 83 ml MeOH was added to 2,4-dimethylpyrrole (2.0 g, 21 mmole) in a 150 ml flask. The mixture was heated at reflux for 1.5 hr under N_2 and then cooled to −5°. The fish egg-like solid was filtered and dried (2.6 g, 60%). The crude product (1.3 g) was dissolved in $CHCl_3$ (360 ml) and extracted with 10 mM NaOH aq. The $CHCl_3$ soln was dried by addition of Na_2SO_4. After evaporation of the solvent, the residue was crystallized from benzene to give yellow needles, m.p. 245–246°. Physical/Spectroscopic properties are given in Table 2. (Found: C, 73.06; H, 7.94; N, 12.36. Calc. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16%).

5' - Oxo - 4',4,5 - trimethyl - 3' - ethyl - 1',5' - dihydro - (2.2') - dipyrromethene (**6**). The condensation of **13** with **18** as above gave **6** in 56% yield, m.p. 243° (d) (yellow needles). Physical/Spectroscopic data are in Table 2. (Found: C, 73.14; H, 7.61; N, 11.92. Calc. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16%).

5' - Oxo - 3',4' - diethyl - 5 - methyl - 1',5' - dihydro - (2.2') - dipyrromethene (**7**). Compounds **11** (1 g, 0.007 mole), **16** (0.8 g, 0.007 mmole), 4N NaOH aq (20 ml) and MeOH (11 ml) were added to a 50 ml flask. When the mixture was heated at reflux, a yellow solid appeared. After 40 min reaction, the yellow solid was filtered and recrystallized from pyridine-water to yield fine yellow needles, m.p. 188–190°, 47% yield. Physical/Spectroscopic properties are given in Table 2. (Found: C, 72.85; H, 7.82; N, 11.91. Calc. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16%).

5' - Oxo - 4 - ethyl - 3,5 - dimethyl - 1',5' - dihydro - (2.2') - dipyrromethene (**8**) was prepared as above by base-catalyzed condensation of **15** with **14** in 59% yield, m.p. 216–218. Physical/Spectroscopic data are in Table 2. (Found: C, 72.26; H, 7.25; N, 12.94. Calc. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95%).

Kinetic studies

Ammonium Reinecke's salt, $NH_4[Cr(SCN)_4(NH_3)_2]\cdot H_2O$ was prepared by the method of Schlessinger.[41]

Potassium Reinecke's salt, $KCr(NH_3)_2(SCN)_4$. Ammonium Reinecke's salt (5 g) was dissolved in 100 ml water and heated to 40–50°. KNO_3 (13 g) was added to the soln and the soln was stirred for 10 min. After cooling in an ice bath a red solid was isolated by filtration. This red solid was crystallized from warm water containing a few percent of KNO_3. The red crystals were collected and dried over P_2O_5 in a vacuum desiccator to give anhydrous product (1.5 g). These operations were done in dim red light in a dark room. The ligand field band was 392 nm, $\epsilon_{392} = 92.1$ (lit.[22] 392 nm, $\epsilon_{392} = 935$). $\lambda_{max} = 520$ nm (108.4) in water (lit.[22] $\lambda_{max} = 520$ nm, $\epsilon_{520} = 106.5$).

18-Crown-6[42] was prepared from triethylene glycol and thionyl chloride; m.p. 35–36° (lit.[42] 36.5–38°); NMR ($CDCl_3$) δ 3.56 (s) ppm; IR (cm^{-1}, chloroform), 2860, 1450, 1355, 1250; mass spectrum, *m/e*, 265 [$M^+ + 1$], 264 [M^+], 221, 177, 133, 117, 110, 89, 59.

Actinometry at 557 nm and 560 nm. Potassium Reinecke's salt (140 mg) was dissolved in a 25 ml flask with water (0.016 M) and acidified with 1 drop of 0.5 M H_2SO_4 (pH = 3.5–5.0). The soln (2 ml) was irradiated in a 10 mm quartz cuvette at 557 nm or 560 nm for 2 hr before and after photooxygenation of the substrates (the absorption maximum of rose bengal in MeOH is at 557 nm and at 560 nm in $CHCl_3$/18-crown-6). Before irradiation one should make sure the soln absorbs 100% of the light at 557 nm by running UV spectra (if $A \gg 1$, f, fraction of light absorption, ≈ 1). During irradiation, the soln in the UV cuvette was shaken every 5 min. After 2 hr of irradiation, the actinometry soln was taken to the dark room, and shaken again. A 0.5 ml aliquot of the irradiated soln was diluted in a clean cuvette with 1.5 ml of 0.1 M $Fe(NO_2)_3\cdot HClO_4$ soln (4.04 g $Fe(NO_3)_3\cdot 9H_2O$ dissolved in a 100 ml volumetric flask with 0.5 M $HClO_4$). A reference standard was prepared with 0.5 ml of unirradiated Reinecke's salt actinometry soln (0.016 M) and 1.5 ml of 0.1 M $Fe(NO_3)_3\cdot HClO_4$ soln. The photo-released thiocyanate was determined by differential spectrophotometry at 450 nm, using $\epsilon = 4.3 \times 10^3$.

$$Cr(NH_3)_2(NCS)_4^- + H_2O \xrightarrow{h\nu} Cr(NH_3)_2(NCS)_3\cdot H_2O + NCS^-.$$

In one study, the optical density difference was found to be 0.297 at 450 nm. The known quantum yield of SCN^- from potassium Reinecke's salt is 0.280 at 557 nm and 0.279 at 560 nm; so, the light intensity may be calculated from the data as shown below.

$$I = \frac{6.023 \times 10^{20} \times \frac{0.297}{4.3 \times 10^3} \times 2 \times 2 \times \frac{1}{0.5}}{0.28 \times 7237 \text{ sec}}$$

$$= 1.64 \times 10^{14} \text{ q/sec.}$$

Quantum yield of intersystem crossing (Φ_{isc}) of Rose Bengal-crown ether in chloroform. Diphenylisobenzofuran (DPBF) (*ca.* 1.5 mg) was dissolved in $CHCl_3$ in a 25 ml volumetric flask. Several different aliquots of the soln (e.g. 0.5–3.0 ml) were taken and diluted to 10 ml with a $CHCl_3$ soln of Rose Bengal-18-crown-6 complex (RBCE) (1 ml), prepared by dissolving 10 mg of Rose Bengal and 14 mg of 18-crown-6 in $CHCl_3$ in a 25 ml volumetric flask. The sample concentration was determined by absorption spectroscopy before photooxygenation. ($\lambda_{max} = 413$ nm, 263 nm, $\epsilon_{413} = 2.2 \times 10^4$, for DPBF in chloroform, [RB]–4.0×10^{-5} M [18-crown-6] = 2.6×10^{-4} M).

The final DPBF solution (2 ml was placed in a 1 cm path-length quartz cuvette and irradiated for 60 sec at 24° by monochromatic light at 560 nm for which the incident intensity had previously determined. The concentration change of the substrate, Δ [DPBF] upon irradiation was determined by measuring the absorbance difference of the DPBF at 410 nm. The light intensity at 557 nm for the monochromatic light was 1.64×10^{14} q/sec as determined above; therefore, $I_a\Delta t = 1.62 \times 10^{-5}$ mol quanta, where I_a is the rate of light absorption by the RB sensitizer in mol quanta/sec. The data used in determining Φ_{isc} for RBCE are located in Table 3.

A least squares plot of $(\Delta[DPBF]/I_a\Delta t)^{-1}$ vs $[DPBF]^{-1}$ gave a slope of 3.1×10^{-5} with an intercept of 2.79 (correlation coefficient = 0.968). Since $(k_R\Phi_{isc})/(k_R + k_Q) = (\text{intercept})^{-1} = 0.36$, a value of $\Phi_{isc} = 0.36$ may be determined for RBCE in chloroform. Φ_{isc} for Rose Bengal in methanol was also determined (0.63) (lit.[21] 0.76) by the above method.

Determination of k_R and k_Q for oxodipyrromethenes (**3–8**) *and bilirubins* (**1**) *and* (**2**)

About 1 mg of substrates (oxodipyrromethene or bilirubin) was dissolved in MeOH or $CHCl_3$ in a 25-ml volumetric flask.

Table 3. $(\Delta[DPBF]/I_a\Delta t)^{-1}$ vs $[DPBF]^{-1}$ in chloroform

DPBF Aliquot	[DPBF] M	$[DPBF]^{-1}M^{-1}$	Δ[DPBF] M	$(\Delta[DPBF]/I_a\Delta t)^{-1}$
1	2.82×10^{-5}	3.55×10^{4}	4.12×10^{-6}	3.93
2	3.50	2.86	4.47	3.63
3	4.27	2.34	4.65	3.48
4	5.70	1.74	4.95	3.27
5	7.10	1.41	4.91	3.30
6	8.38	1.19	5.12	3.36

Aliquots of 1 ml, 1.5–3.5 ml of the soln were withdrawn and diluted to 10 ml with the Rose Bengal/MeOH soln (10 mg RB in 25 ml MeOH) or the Rose Bengal-18-crown-6/$CHCl_3$ soln (10 mg RB, 14 mg CE in 25 ml $CHCl_3$). The final concentration of substrate was determined by its absorption spectrum and previously determined molar extraction coefficient. The concentration of RB for all solns was the same (4.0×10^{-5} M, and the fraction of absorption of light at 557 nm ≈ 1), and the concentration of 18-crown-6 was 2.6×10^{-4} M. Exactly 2 ml of each soln was placed in a 10 mm pathlength quartz cuvette, and the UV or visible spectrum was taken. The absorbance of the substrate was corrected by subtracting the absorbance of RB, even though the RB absorption was weak at the absorption maximum of all substrates (2.5–5.0%). The soln in the cuvette was then irradiated at 557 nm with monochromatic light, 10 nm bandpass in MeOH or at 560 nm in $CHCl_3$ for an appropriate time period, for a substrate concentration change of 5–10%. The emitted light intensity was determined by potassium Reinecke's salt actinometry before and after the photooxygenation reaction as described above.

By way of an example, k_R and k_Q were determined for oxodipyrromethenes in MeOH as shown below. Six different concentrations of **5** (with constant concentration of Rose Bengal) were prepared as above. Each soln (2 ml) was placed in a cuvette (1 cm path-length), and the visible absorption spectrum was run to determine the concentration of **5**. Next, the solution was irradiated with 557 nm monochromatic light for 120 sec. The concentration of the **5** could be measured spectrophotometrically after irradiation since the photooxidation reaction products are colorless. The results are tabulated in Table 4 and are used to determine k_R and k_Q below.

$I_a\Delta t$ for RB was determined to be 3.29×10^{-5} mol quanta by actinometry. Equation (7) in the text was used, and a least squares plot of $(\Delta[5]/I_a\Delta t)^{-1}$ vs $[5]^{-1}$ gave a slope of 2.87×10^{-4} and an intercept of 2.36. The correlation coefficient was 0.9959. Since $k_d = 1.4 \times 10^5\ s^{-1}$ for $^1O_2$,[20] and, from eqn (7) in the text, $k_d/(k_R + k_Q)$ = slope/intercept = 1.23×10^{-4}, $(k_R + k_Q) = 1.14 \times 10^9\ M^{-1}\ s^{-1}$. The expression $(k_R + k_Q)$ can be separated and the values of k_R and k_Q determined using the expression (from equation (7) of the text) $(\phi_{isc}k_R)/(k_R + k_Q)$ = intercept^{-1} = 2.36^{-1}. Since $\phi_{isc} = 0.76$ for RB in CH_3OH, $k_R = 6.4 \times 10^8\ M^{-1}\ s^{-1}$.

Product studies of RB-sensitized photooxygenation of oxodipyrromethenes with monochromatic light

In a typical experiment, 1 mg of oxodipyrromethene was dissolved in 57 ml of MeOH and to this soln was added 3 ml of a stock soln of Rose Bengal in MeOH (2×10^{-4} M). The resultant soln was placed in two 10 cm pathlength quartz cells (30 ml in each) and irradiated with monochromatic light at 557 nm (until 90% decrease in absorbance). After evaporation of the solvent, the photoproducts were compared with authentic samples of imides, pyrrole aldehydes and pyrrolinones using analytical tlc with $CHCl_3$/ether (6:4) as the irrigating solvent. Products were observed by fluorescence quenching on the plates. Imides were detected on the analytical tlc plates by a color reaction.[43] The plate was placed in a Cl_2 atmosphere chamber for 5 min and then removed. The excell Cl_2 was blown off with an air stream. The plates were then sprayed with a soln of 300 mg of benzidine in 100 ml of 50% EtOH containing a KI granule. Imides appear dark blue on a colorless background.

The photooxygenation products obtained from **3–8** are summarized as follows: from **3**, methylvinylmaleimide[44] and kryptopyrrole[36] aldehyde; from **4**, xeronimide,[45] kryptopyrrole aldehyde[36] and 5 - methoxy - 3,5 - dimethyl - 4 - ethyl - 3 - pyrrolin - 2 - one;[36] from **5**, methylethylmaleimide,[46] 2 - formyl - 3,5 - dimethylpyrrole[36] and 5 - methoxy - 3,5 - dimethyl - 3 - pyrrolin - 2 - one;[36] from **6**, methylethylmaleimide,[46] 2 - formyl - 3,5 - dimethylpyrrole[36] and 5 - methoxy - 4,5 - dimethyl - 3 - pyrrolin - 2 - one;[36] from **7**, xeronimide[45] and 5 - methoxy - 3,5 - dimethyl - 4 - ethyl - 3 - pyrrolin - 2 - one;[36] and from **8**, maleimide, kryptopyrrole aldehyde and 5 - methoxy - 3,5 - dimethyl - 4 - ethyl - 3 - pyrrolin - 2 - one.

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Table 4. Kinetic parameters for oxodipyrromethene **5** reacting with $^1O_2$

Aliquot	Concentration of 5 [5], M	$[5]^{-1}$	$\Delta[5]$	$(\Delta[5])^{-1}$	$(\Delta[5]/I_a\Delta t)^{-1}$
1	9.9×10^{-6} M	1.0×10^5	1.0×10^{-6}	9.7×10^5	31.9
2	1.5×10^{-5} M	6.7×10^4	1.6	6.4	21.1
3	2.1	4.8	2.2	4.6	15.1
4	3.6	2.8	3.2	3.1	10.3
5	4.2	2.4	3.5	2.9	9.5
6	5.3	1.9	4.0	2.5	8.3

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