On the Photooxygenation and Autoxidation of Dipyrrylmethenes and Dipyrrylmethanes

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The dye-sensitized photooxygenations of 4,4′-diethyl-3,5,3′5′-tetramethyldipyrrylmethene and 4,4′-diethyl-3,5,3′5′-tetramethyldipyrrylmethane have been investigated in neutral, basic and acidic methanol solution. Several photoproducts are common to the photooxygenation of both substrates. The dipyrrylmethene was detected as an intermediate in the photooxygenation of the dipyrrylmethane; however, it was determined not to be an important precursor to monopyrrole products. Autoxidations of the two dipyrrole compounds were also investigated and were found to be slower than the corresponding photooxygenation. Autoxidation and photooxygenation were both found to be faster in basic than in acidic methanol with the dipyrrylmethane faster than with the dipyrrylmethene in the same solvent.

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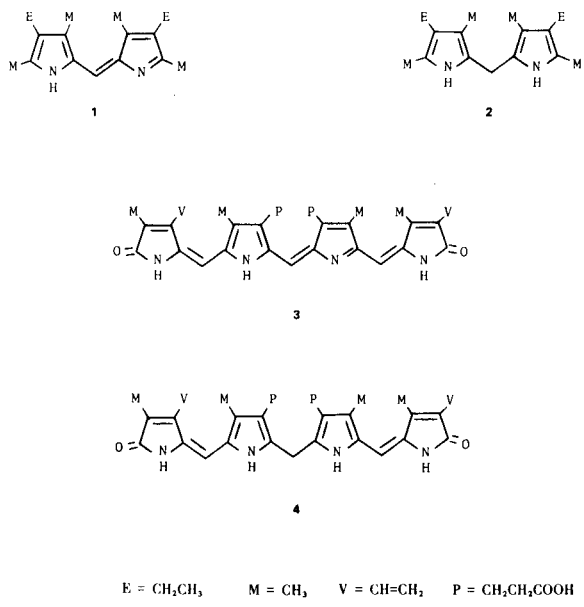
In recent years, interest in the photosensitized oxygenation of bilirubin (1) has arisen because of its relevance to the phototherapy treatment of neonatal jaundice (2,3). *In vitro* photo-reactions of bilirubin, while seemingly less complex than *in vivo* reactions, show rate and product selection dependencies with solvent variation (1) and may also compete with autoxidation (4). In order to provide an understanding of the photochemistry associated with bilirubin and biliverdin, part of our research efforts has been directed at exploring simpler systems such as mono and dipyrroles. From those studies we have elucidated several product types with some correlation between reactivity and product distribution and pyrrole substitution (5,6). Recently, by low-temperature nmr, we have detected pyrrole *endo*-peroxide intermediates and have shown by oxygen-18 incorporation studies that the final product formation can proceed through unimolecular rearrangement or by reaction with indigenous water (7). Investigations have also been extended to dipyrrole systems (8). For these we chose dipyrrylmethene (**1**) and dipyrrylmethane (**2**) because the structural relationship of **1** to **2** is formally the same as the relationship of biliverdin (**3**) to bilirubin (**4**). In either of these dipyrrole or tetrapyrrole systems, the more unsaturated compound (**1** or **3**) can, under some conditions, become a product or an intermediate of the photooxidation of the corresponding **2** or **4** (1,9). Consequently, we studied the conversion of **2** to **1**, determined their relative rates of autoxidation and photooxidation, and determined the photoproducts from both **1** (8) and **2**.

Chart I



Photooxygenation in Basic Methanol.

Photo-irradiation of **1** in oxygenated methanolic ammonia with Rose Bengal (singlet oxygen, $^1O_2$) sensitizer resulted in a decrease in the long wavelength absorbance maximum and gave products **7-11** (Table I). Under the same conditions the photooxygenation of **2** gave **6**, **8-12** (Table I). Although **8-11** were isolated from both reactions, their total yields differed significantly, originating from the different starting materials: 66% from **1** but only 33% from **2**. Compounds **8-11** are identical to the major products isolated from the singlet oxygen sensitized photooxygenation of kryptopyrrole (**5**) in methanol (10,11). Thus, those photoproducts (**8-11**) were conveniently identified by comparison (tlc, nmr, uv, ir and mass spectroscopy) with known, available samples. Although **8-10** seem to be primary products, **11** could be shown to arise from dehydration of **9** and **10** and/or loss of methanol from **8** simply by warming the samples to 45°

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Table I

Physical and Spectroscopic Data for the Photooxygenation Products of 4,4′-Diethyl-3,5,3′,5′-tetramethyl(2•2′)-dipyrrylmethene (**1**) and 4,4′-Diethyl-3,5,3′,5′-tetramethyl(2•2′)dipyrrylmethane (**2**) in Methanolic Ammonia

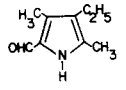
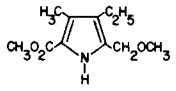
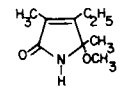
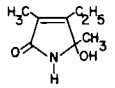
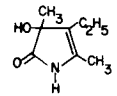
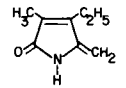
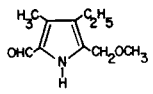
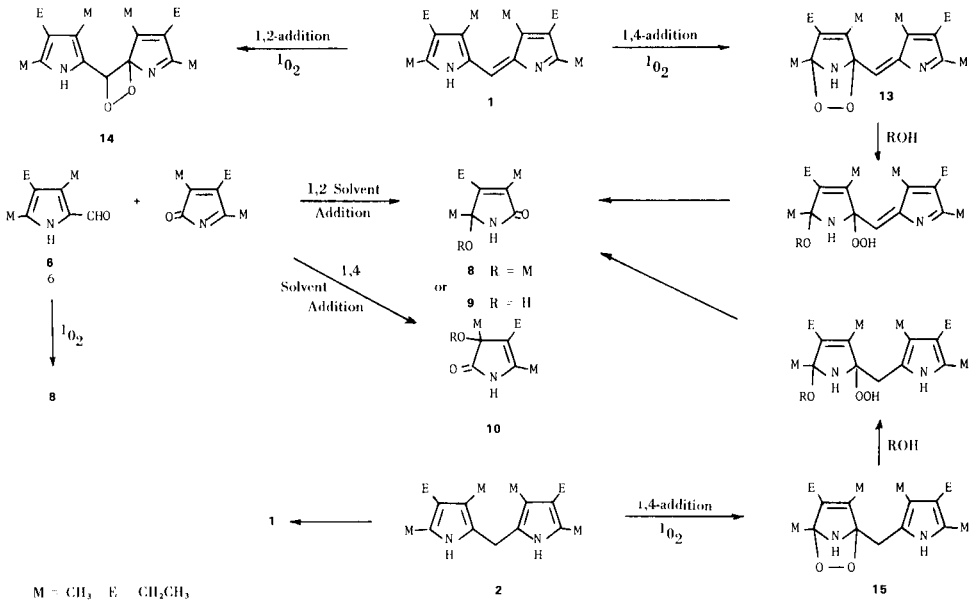
Compound Yield (%) M.p. (°C)	Mass Spectrum m/e (Relative Intensity)	^{1}H-Nmr (Deuteriochloroform, TMS reference, δ in ppm)	Ir (Potassium Bromide, cm^{-1})
 **6** 0% from **1** 0.5% from **2** 101.5-102.9°	151.1040 (52%) [M$^+$] $C_9H_{13}NO$: 151.0997 136 (100%) [M-CH_3] 122 (14%)	1.07 (t, 3H, CH_2CH_3, J = 8 Hz) 2.24 (s, 3H, CH_3) 2.27 (s, 3H, CH_3) 2.39 (q, 2H, CH_2, J = 8 Hz) 9.49 (s, 1H, CHO)	1608 (ν C=O)
 **7** 8% from **1** 0% from **2** 85-86°	211.1204 (67%) [M$^+$] $C_{11}H_{17}NO_3$: 211.1208 196 (7%) [M-CH_3] 180 (100%) [M-OCH_3] 166 (11%) [M-CH_2OCH_3] 148 (41%) 134 (14%) 120 (13%)	1.02 (t, 3H, CH_2-CH_3, J = 8 Hz) (a) 2.20 (s, 3H, CH_3) 2.37 (q, 2H, CH_2, J = 8 Hz) 3.22 (s, 3H, OCH_3) 3.78 (s, 3H, OCH_3) 4.33 (s, 2H, OCH_2-) 9.63 (br, 1H, NH)	
 **8** 31% from **1** 16% from **2** 84-85°	169.1105 (15%) [M$^+$] $C_9H_{15}NO_2$: 169.1103 154 (11%) [M-CH_3] 140 (28%) [M-C_2H_5] 138 (100%) [M-OCH_3] 122 (25%)	1.14 (t, 3H, CH_2CH_3, J = 8 Hz) 1.48 (s, 3H, CH_3) 1.79 (s, 3H, CH_3) 2.24 (q, 2H, CH_2, J = 8 Hz) 2.95 (s, 3H, OCH_3) 7.68 (br, 1H, NH)	1689 (ν C=O)

Table I (continued)

Compound Yield (%) M.p. (°C)	Mass Spectrum m/e (Relative Intensity)	^{1}H-Nmr (Deuteriochloroform, TMS reference, δ in ppm)	Ir (Potassium Bromide, cm^{-1})
 9 22% from **1** 11% from **2** 135-137.5°	155.0943 (27%) [M^+] $C_8H_{13}NO_2$: 155.0946 140 (54%) [M-CH_3] 138 (19%) [M-OH] 126 (100%) [M-C_2H_5] 122 (32%)	1.17 (t, 3H, CH_2-CH_3, J = 8 Hz) 1.51 (s, 3H, CH_3) 1.73 (s, 3H, CH_3) 2.35 (q, 2H, CH_2, J = 8 Hz) 2.90-3.50 (br, 1H, OH) 6.83 (br, 1H, NH)	1670 (ν C=O)
 10 13% from **1** 0% from **2** 120-122.5°	155.0941 (7%) [M^+] $C_8H_{13}NO_2$: 155.0946 140 (10%) [M-CH_3] 138 (100%) [M-OH] 126 (25%) [M-C_2H_5] 122 (17%)	1.16 (t, 3H, CH_2-CH_3, J = 8 Hz) 1.51 (s, 3H, CH_3) 1.80 (s, 3H, CH_3O) 2.34 (q, 2H, CH_2, J = 8 Hz) 7.17 (br, 1H, NH)	1701 (ν C=O) 1625 (ν C=C)
 11 0.5% from **1** 2% from **2** oil	137.0871 (100%) [M^+] $C_8H_{11}NO$: 137.0841 122 (88%) [M-CH_3] 108 (46%) 94 (55%)	1.14 (t, 3H, CH_2CH$_3$, J = 7 Hz) 1.89 (s, 3H, CH_3) 2.44 (q, 2H, CH_2, J = 7 Hz) 4.80 (1H, = CH_2) 4.86 (1H, = CH_2) 8.12 (br, 1H, NH)	uv (methanol): ϵ max 262, 8.8 x 10^3, ϵ max 212, 4.9 x 10^3
 12 0% from **1** 0.5% from **2**	181.1119 (4%) [M^+] $C_{10}H_{15}NO_2$: 181.1103 166 (11%) [M-CH_3] 150 (100%) [M-OCH_3]	1.08 (t, 3H, CH_2CH$_3$, J = 8 Hz) 2.28 (s, 3H, OCH_3) 2.42 (q, 2H, CH_2, J = 8 Hz) 3.38 (s, 3H, OCH_3) 4.42 (s, 2H, OCH_2-) 9.58 (s, 1H, CHO)	3420 (ν N-H) (b) 1710 (ν C=O)

(a) In carbon tetrachloride. (b) In deuteriochloroform.

Scheme I



in a glass container. The 5-hydroxylactam (**9**) can be distinguished from its less polar 3-hydroxy isomer (**10**) by analytical tlc and by comparison of their infrared spectra when obtained as potassium bromide pellets. We have consistently found the carbonyl stretching mode of 3-hydroxylactams to appear at longer wavenumbers than the equivalent absorption band of the corresponding 5-hydroxylactams (in this case: 1701 cm^{-1} for **10** and 1670 cm^{-1} for **9**).

Kryptopyrrole aldehyde **6** and compound **12** were formed only from **2** in small isolated yield and were identified by comparison (tlc, nmr, ir, uv, and mass spectroscopy and (for **6**) comparison with an authentic sample. Compound **7** was formed only from **1** and was assigned its structure from spectral data and comparison with a synthetic sample. The mass spectrum (parent ion 211.1204) confirmed that it was a monopyrrole with molecular formula of $C_{11}H_{17}NO_3$. The nmr spectrum indicated that the ethyl group and one methyl group were intact and attached to a pyrrole ring rather than to a hydroxylactam. Furthermore, two different methoxy groups and a deshielded methylene group were also evident. The similarity of the nmr spectrum of **12** with the nmr spectrum of **7** (nearly identical except for s 9.58, CHO in place of s 3.78, CO_2CH_3) suggested a structure like **12**, and the mass spectrum and infrared spectrum were in agreement. The relative oxidation states of **7** and **12** parallel the relative oxidation states of **1** and **2**.

When the Rose Bengal-sensitized photooxygenation of **2** in methanolic ammonia was monitored by uv-visible absorption spectroscopy, an absorbance at 443 nm appeared, grew in intensity and disappeared. We attribute this absorption to the conversion of **2** to **1**, followed by subsequent photooxygenation of **1**. That the observed absorbance at 443 nm was due to formation of **1** was confirmed by the nmr spectrum obtained from a reaction mixture which was not allowed to proceed to completion. The amount of **1** observed during the early stages of the photooxygenation of **2** ranged from 10 to 20% of the initial concentration of **2** (Table II). The concentration of **1** then decreased after two minutes by which time 90% **2** had been consumed. Under the reaction conditions **1** disappeared with a half-life eight times longer than that observed for **2**.

When methylene blue was used as the singlet oxygen sensitizer, the photooxygenations of **1** and **2** proceeded

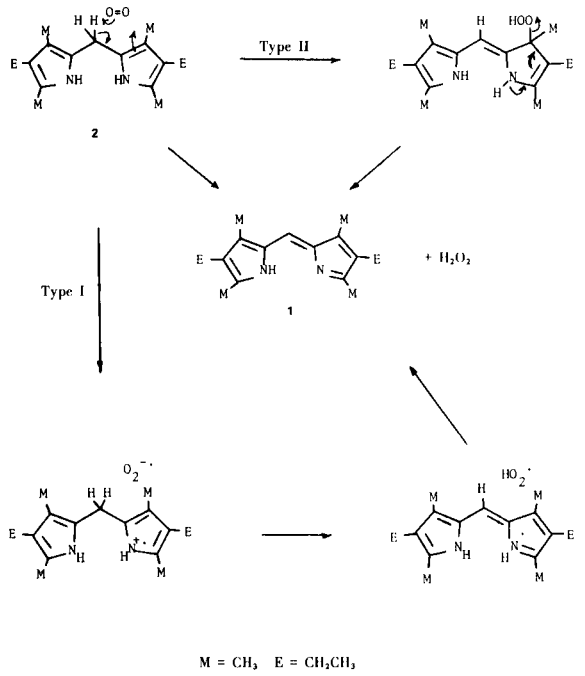
Table II

Photooxidation of Dipyrrylmethene **1** and Dipyrrylmethane **2** in Basic Methanol with Rose Bengal Sensitizer (a)

Time (minutes)	Reaction of **1** % **1**	Reaction of **2** % **1**	% **2**
0 (b)	100	20	100 (c) (80) (d)
¼		8	100 (80)
½		22	41 (33)
1	90	19	35 (28)
2	74	17	11 (9)
4	46	12	8 (7)
8	8	4	5 (4)
16	1		

(a) From optical densities at 443 nm. (b) Approximately 3 minutes transpired before this measurement was obtained. (c) Based on the concentration of **2** at time zero. (d) Based on the total concentration of **2** and **1** at time zero.

Scheme 2



more rapidly than with the same molar equivalent of Rose Bengal. The use of methylene blue typically led to formation of **1** from **2** even before irradiation. Consequently, Rose Bengal (or hematoporphyrin in acidic solutions) was used in all studies and the phenomenon with methylene blue is under study separately.

Photooxygenations in Acidic Methanol.

The dye-sensitized photooxygenations of **1** and **2** in acidic methanol proceeded slower than in basic methanol (Tables II-IV) for each of the sensitizers investigated. Hematoporphyrin was used as the singlet oxygen sensitizer in acidic methanol because Rose Bengal is ineffective in acidic media and because of the difficulties with methylene blue discussed earlier.

In acidic methanol the hematoporphyrin-sensitized photooxygenation of **2** is more than one hundred times faster than the photooxygenation of **1** (Table IV). Unlike the photooxygenation of **2** in basic methanol, irradiation of **2** in the presence of a sensitizer in acidic methanol did not result in any noticeable growth and decline of the absorbance due to **1** during the reaction course. Since **2** did not appear to be converted to **1** during photo-irradiation and since the photooxygenation of **2** was much faster than **1**, we concluded that any photoproducts isolated from the hematoprophyrin sensitized photooxygenation of **2** in acidic methanol could not arise from intermediate **1**. We, therefore, attempted the isolation of the products from photooxygenation of **2** in acidic methanol and chose conditions which would favor photooxygenation over autoxidation (*vide infra*).

Irradiation of **2** with a higher than normal lamp voltage (100 volts) was initiated immediately upon acidification and was continued for ten minutes. Work-up under mildly basic conditions resulted in a 20% yield of **8**. Under these conditions **1** underwent less than 5% reaction and attempts to isolate **8** were unsuccessful.

Autoxidation.

The disappearance of substrate is considerably slower in the absence of light and sensitizer for either **1** or **2** in both acidic and basic methanol (Tables IV-VI). Such reactions may be classified as autoxidation reactions although there may also be concurrent acid or base catalyzed decomposition occurring, *e.g.*, in basic methanol **1** might undergo a retro-aldol condensation and **2** might be expected to exhibit typical pyrrole acid sensitivity.

The autoxidation of **2** in ammoniacal methanol proceeded with a half-life of approximately 230 minutes or three orders of magnitude slower than its Rose Bengal sensitized photooxygenation in the same solvent (Table IV). The rate of autoxidation of **2** is *p*H sensitive; the reaction is extremely slow at *p*H 7 and proceeds faster as small amounts of base are added.

During the course of the autoxidation of **2** there were observed visible absorbances at 443 nm and 480 nm. We attribute the origin of the former absorbance, at least in part, to conversion of **2** to **1**. The rate of subsequent disappearance of the absorption at 443 nm is similar to that found for the autoxidation of **1** in basic methanol (Table V). The identity of the specie responsible for the absorbance at 480 nm has not been established, but it may be due to a trace of boron complex (12) of **1** (**2** is prepared from **1** by sodium borohydride reduction, and

Table III

Photooxidation of Dipyrrylmethene **1** and Dipyrrylmethane **2** in Acidic Methanol with Hematoporphyrin Sensitizer (a,b)

Time (minutes)	Reaction of **1** %**1**	Reaction of **2** % **1**	% **2**
0 (c)	100	19	100 (d) (81) (e)
1		19	34 (28)
5		19	27 (22)
10		20	8 (6)
20	92	22	4 (3)
40		19	
80	77	16	

(a) From optical densities at 443 nm. (b) With methylene blue sensitizer the reaction proceeds about 10% slower. (c) Approximately 20 seconds transpired prior to obtaining these readings. (d) This column lists the % of **2** as referenced to the measurement at time zero. (e) This column lists the % of **2** compared to total of **1** and **2** at time zero.

Table IV

Kinetic Data for Oxidations of Dipyrrylmethene **1** and Dipyrrylmethane **2** (a)

Solvent Reaction	**1** $\tau_{1/2}$ (sec)	**1** k_d (sec^{-1}) (b)	**2** $\tau_{1/2}$ (sec)	**2** k_d (sec^{-1}) (b)
Basic Methanol				
Autoxidation	5.4×10^4	3.0×10^{-4}	1.4×10^4	1.2×10^{-3}
Photooxidation	2.2×10^2	9.5×10^{-2}	22	1.0
Acidic Methanol				
Autoxidation	1.5×10^5	1.3×10^{-4}	7.1×10^2	2.0×10^{-2}
Photooxidation	1.4×10^4	1.1×10^{-3}	4.0	0.45

(a) Determined from log concentration *vs* time. (b) Pseudo-first order rate constants for disappearance of substrate.

Table V

Autoxidation of Dipyrrylmethene **1** and Dipyrrylmethane **2** in Basic Methanol (a)

Time (hours)	Reaction of **1** % **1**	Reaction of **2** % **1**	% **2**
0 (b)	100	39	100 (c) (61) (d)
½	100		
1	99		
2	95	49	60 (37)
4	89	42	50 (31)
6	80	30	36 (22)
8			
21		24	13 (8)

(a) From optical densities at 443 nm. (b) Approximately 2 minutes transpired before this measurement was obtained. (c) Based on the concentration of **2** at time zero. (d) Based on the total concentration of **1** and **2** at time zero.

Table VI

Autoxidation of Dipyrrylmethene **1** and Dipyrrylmethane **2** in Acidic Methanol (a)

Time (hours)	Reaction of **1** % **1**	Reaction of **2** % **1**	% **2**
0 (b)	100	30	100 (c) (67) (d)
1/12		24	61 (41)
¼		26	45 (30)
½		25	33 (22)
1	100	27	30 (20)
2	99	28	27 (18)
3	95	23	22 (15)
5	94	25	22 (15)

(a) From optical densities at 443 nm. (b) This measurement was obtained at approximately 2 minutes after mixing. (c) Based on the concentration of **2** at time zero. (d) Based on the total concentration of **1** and **2** at time zero.

the complex of **1** with boron trifluoride has λ max 480, ε, 59,000). It is four times slower than for the same reaction of **2** and three hundred times slower than the rose bengal sensitized photooxygenation of **1** in basic methanol (Table IV). During the course of the autoxidation of **1**, new absorbances at 480 nm and 360 nm were observed.

The autoxidation of **2** in acidic methanol is complex. When a few drops of dilute (10%) hydrochloric acid were added to a solution of **2** in neutral methanol, the solution darkened and eventually turned black. The intensity of a visible absorbance at 483 nm increased gradually over a period of 2-3 hours and then slowly decreased. The absorbance at 483 nm was probably due to the presence of at least two species as evidence by the observation that two absorptions, 443 nm (**1**) and 475 nm (unknown), were obtained when an aliquot from the acidic autoxidation of **2** was made basic. The shift in absorbance from 480 nm in acidic methanol to 443 nm in basic methanol was consistent with formation of **1** (Table VII). Analytical tlc indicated the presence of **1** and several other species and, indeed, **1** was isolated by preparative tlc. The substance absorbing at 660 nm has not been identified. The darkening of the solution is speculated to originate from a polymerization similar to that observed for pyrrole in acidic media (13).

The autoxidation of **1** in acidic methanol is slow (Table VI); only 1% of **1** reacted after 60 minutes and only 6% after 300 minutes. In acidic media the rate of autoxidation of **1** is seven times slower than the rate of its hematoporphyrin-sensitized photooxidation (Table IV).

The autoxidation and photooxidaiton of **2** in basic methanol are sensitive to the method of preparation of **2**. When the excess sodium borohydride was destroyed with dilute hydrochloric acid, a visible absorbance near 500 nm was observed in addition to that observed at 443 nm. An absorbance near 500 nm was also detected when **1** was dissolved in ammoniacal methanol which had been stored in a pyrex vessel. This latter phenomenon may be

Table VII

Wavelengths (nm) of Visible Absorbance Maxima of Dipyrrylmethene **1**

Compound	Methanol (a)			Chloroform	Benzene
	acid	neutral	base		
1	480	480	443	487	487 (445)
1·HBr	481	481	443	487	489

(a) ϵ in acid depends on *p*H. The absorbance gradually decreases from *p*H 3 to approximately *p*H 8.5 at which point a shift to 443 nm occurs.

explained as a result of the known extraction of boron from Pyrex (14).

Origin of Photoproducts.

We view the dye-sensitized photooxidaiton products of dipyrrylmethene **1** as arising principally from an intermediate *endo*-peroxide (**13**) or dioxetane (**14**) as shown in Scheme 1. In the absence of added dye sensitizer, no photooxygenation occurs in our reaction time periods. There is ample precedence for the formation of pyrrole *endo*-peroxides during their dye-sensitized photooxygenation (5-7), and the implications of dioxetanes in imidazole (15,16), enamine (17,18) and bilirubin (1,19) photooxygenations are now well known. Thus, the formation of major photoproducts **8**, **9** and **10** can be rationalized in a straightforward way, as in Scheme 1. An alternative or competitive mechanism might involve a retro-aldol reaction of **1** to its two components, kryptopyrrole aldehyde and kryptopyrrole as a first step. Subsequent photooxygenation of these two components could lead to **8-10**. Kryptopyrrole aldehyde is known (20) to yield **8** (but not **9** or **10**) under the reaction conditions, and kryptopyrrole is known to photooxygenate in methanol to give a 1:1·5:1 isolated mixture of **8**:**9**:**10** (10). However, the facts that **1** gives a 3:2:1 mixture of **8**, **9** and **10** and that we could not detect even small quantities of kryptopyrrole aldehyde argues against the *major* involvement of the alternative mechanism proposed here.

Similarly, we suggest that photoproducts **8** and **9** from dipyrromethane **2** originate from an *endo*-peroxide intermediate (15). Minor photoproducts from **1** and **2** include methoxymethyl compounds **7** and **12**. Their origin is obscure at present, and they probably arise in radical pathways, initiated perhaps in electron transfer (Type I) photooxidation mechanisms involving sensitizers.

The observed conversion of **2** to **1** during photooxygenation could also account for the formation of **6**, **8**, **9** and **10** by the pertinent mechanisms discussed above. The extent of participation of **1** in the formation of photoproducts from **2** is limited as evidenced by the following observations: (i) Only 10-20% of **1** is observed during photooxygenation of **2**. (ii) The rate of photooxygenation of **2** is approximately ten times faster than that of **1**. (iii) The methoxymethyl compound **7** was not isolated from photooxygenation of **2** while it was isolated in 8% yield from **1**. (iv) Less than 1% of the 3-hydroxylactam **10** resulted from photooxygenation of **2** as compared to 13% from photooxygenation of **1**. Due to its lability and possible rearrangement to **9**, the lack of significant amounts of **10** must be viewed cautiously.

The conversion of **2** to **1** might be viewed as resulting from a singlet oxygen "ene" reaction followed by loss of hydrogen peroxide (Scheme 2). Alternatively, the formation of **2** from **1** may involve a Type I photooxidation mechanism (21,22). The conversion of **2** to **1** is formally analogous to the conversion to bilirubin (**4**) to biliverdin (**3**), which also occurs during sensitized photooxygenation (1,23). Some of our current work on the mechanism of the photooxygenation of bilirubin indicates that biliverdin may arise from a Type I mechanism (23,24).

Reaction Rates.

The rates of autoxidation of **1** and of **2** were much slower than the rates of photooxygenation under identical conditions. The photoproducts that we have isolated were thus not significantly contaminated with products from autoxidation.

In general, the rates of autoxidation and photooxidation of **1** and **2** were slower in acidic than in basic methanol. The exception to this is the autoxidation of **2** in acidic methanol. The difference is probably due to its (2) pyrrole-like acid sensitivity (13) rather than to its actual reaction with oxygen.

The slower rates of photoxygenation and autoxidation of **1** in acidic methanol compared to basic methanol are due to the protonation of **1**. By means of visible absorption spectroscopy, we have observed that the protonated from predominates below *p*H 9, but some free base exists even until *p*H 5. In the *p*H range 5-9 both protonated and unprotonated **1** will exist and reaction rates will be sensitive to the relative concentration of each specie. That protonation might slow down the photooxygenation of **1** is not unexpected. It is known that pyrroles containing electron withdrawing groups are more stable to photooxygenation, *etc.* than pyrrole or alkyl-substituted pyrroles (25). Thus, since **1** is a stronger base

than **2**, the rates of photooxidation and autoxidation of **1** are more greatly affected by changing from basic to acidic methanol (Table IV) than are the corresponding rates of **2**. In addition, protonation of **1** may also cause changes in conformation which, in turn, could affect reaction rates.

In summary, the dye-sensitized photooxygenations of dipyrrylmethane (**2**) and dipyrrylmethene (**1**) in basic methanol and of (**2**) in acidic methanol gave primarily the expected methoxy and hydroxylactams. Other products obtained in basic methanol include two pyrrole aldehydes from **2** and a pyrrole carboxylic acid ester from **1**. The lactams are most likely formed from intermediate pyrrole *endo*-peroxides. The mechanisms which lead to aldehydes and carboxylate ester remain unexplained. Conversion of **2** to **1** during photooxygenation may arise from a Type I photooxidation mechanism, but does not represent a major pathway to products. Autoxidation reactions are slow with respect to photooxygenation and do not contribute to the formation of the isolated photoproducts. The rates of photooxygenation and autoxidation, especially those of **1**, are *p*H dependent. Protonation of **1** markedly reduces its reactivity towards auto- or photooxidation. The less basic dipyrrylmethane (**1**) is less sensitive to *p*H changes.

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EXPERIMENTAL

General.

Methanol was distilled Baker-Analyzed anhydrous reagent grade. Rose bengal and methylene blue were obtained from Matheson, Coleman and Bell. Hematoporphyrin was obtained from Nutritional Biochemical Inc. Column chromatography was performed using silica gel (M. Woelm, Eschwege, 70-235 mesh ASTM). Silica gel F (M. Woelm) was used for all thin layer chromatography (tlc). Preparative plates (1 mm thickness) were prepared from ethanol slurries. The ethanol was evaporated at room temperature and the plates activated at 110° for 1-2 hours. Photochemistry was carried out either in 1 cm pathlength quartz cuvettes (Pyrocell) or in a water-cooled pyrex immersion well apparatus (26). The light sources were either a Westinghouse or Sylvania tungsten-halogen quartz lamp, 120 V, 500W, no. Q/CL, run at 80 volts except where indicated. A Cary 14 spectrophotometer was used to determine the ultraviolet-visible (uv-vis) absorption spectra. Mass spectra were determined on CEC 491-21, AEI MS-9, Varian Mat 311 or Jeolco JMS-07 mass spectrometers at 70 eV ionization voltage. Infrared (ir) spectra were obtained using a Perkin-Elmer 421 or Beckman IR-8 instrument. All nuclear magnetic resonance (nmr) data were obtained on a Varian XL-100, EM-360 or A-60 nmr instrument. All melting points were obtained on a Thomas Hoover capillary apparatus and are uncorrected.

2,4-Dimethyl-3-ethylpyrrole (Kryptopyrrole) (**5**).

This can be more easily prepared than described earlier (27,28). In a 2 l. 3-neck, round bottom flask equipped with a mechanical stirrer, thermometer, distillation head with condenser, and heating mantle, were placed 180 g. (0.86 mole) of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole (27), 210 g. (3.19 moles) of potassium hydroxide, 156 g. of hydrazine hydrate (3.12 moles) and 1 l. of diethylene glycol. The mixture was heated gradually to 200° for 8 hours under nitrogen and the biphasic distillate was collected. At 240° distillation was terminated and the distillate extracted with ether (3 x 100 ml.). After drying over anhydrous sodium sulfate and evaporation of solvent, vacuum distillation (96-100°/-19 Torr) gave 62.2 g. (59%) of a pale yellow liquid, [lit. b.p. 92.5-94°/18 Torr, 50-58%, (27)].

2,4-Dimethyl-3-ethylpyrrole-5-aldehyde (**6**).

This was prepared by an improved procedure over that described earlier (29). To a 1 l. 3-neck, round bottom flask fitted with mechanical stirrer, condenser, and dropping funnel was added 17.9 g. (0.25 mole) of dry *N,N*-dimethylformamide, and the flask was cooled in an ice bath to about 10°. Phosphorus oxychloride (37.6 g., 0.25 mole) was added slowly, then the ice bath was removed and stirring continued 15 minutes. 1,2-Dichloroethane (70 ml.) was added and the temperature was lowered to 5°. Kryptopyrrole (27.4 g., 0.22 mole) in 50 ml. ethylene dichloride was added dropwise to the reaction mixture and the solution was then refluxed 15 minutes. Sodium acetate trihydrate (152 g., 1.12 moles) in 200 ml. of water was added to the solution. The mixture was heated at reflux for 30 minutes with vigorous stirring, cooled and transferred to a separatory funnel. After removal of the ethylene chloride layer, the aqueous phase was extracted with ether (3 x 100 ml.), and the combined organic portions were washed with saturated aqueous sodium carbonate (2 x 80 ml.). After drying over anhydrous magnesium sulfate, evaporation of the solvent gave a crude black aldehyde; 33.6 g. This material could be purified in 80-85% yield by first crystallizing from aqueous ethanol, then subliming (75°/0.2 Torr) and recrystallizing to give pale yellow needles, m.p. 101.5-102.5° [lit. (29) m.p. 105-106°, 42%].

4,4′-Diethyl-3,5,3′,5′-tetramethyl(2•2′)dipyrrylmethene Hydrochloride (**1**•HCl).

Anhydrous ether (100 ml.) was saturated with hydrogen chloride while cooling in a 250 ml. 3-neck flask with mechanical stirrer, calcium sulfate trap, and dropping funnel. To the ice-cooled reaction flask were added kryptopyrrole aldehyde (**6**) (5.0 g., 0.033 mole) and kryptopyrrole (**5**) (4.1 g., 0.033 mole) dissolved together in ether (75 ml.). Hydrogen chloride was bubbled into the reaction mixture an additional 15 minutes to insure complete reaction. The solid was filtered, washed with ether, and dried to yield the dipyrrylmethene hydrochloride (9.3 g., 96%, m.p. 209° dec.); nmr (deuteriochloroform): δ ppm 1.08 (3H, t, J = 7 Hz), 2.28 (3H, s), 2.37 (2H, q, J = 7 Hz), 2.62 (3H, s), 7.05 (1 H, s); uv (methanol); ε, 98,000. A previous report of this compound omitted the physical properties (30). The dipyrrylmethene hydrochoride when first filtered was orange, then darkened on standing.

4,4′-Diethyl-3,5,3′,5′-tetramethyl(2•2′)dipyrrylmethene (**1**).

One hundred and fifty mg. (0.51 mmole) of the corresponding hydrochloride (**1**•HCl) was placed in each of six 250 ml. flasks along with 200 ml. water. The mixtures were boiled quickly on a hot plate to dissolve the solid and 4 ml. concentrated ammonium hydroxide was quickly added to each flask. A yellow precipitate appeared immediately. The flasks were allowed to stand 4 hours at room temperature, then at 5° for one day.

Filtration and drying under vacuum gave a yellow powder, m.p. 137-137° [lit. (31) m.p. 151°]; nmr (deuteriochloroform): δ ppm 1.05 (3H, t, J = 7.5 Hz), 2.13 (3H, s), 2.30 (3H, s), 2.37 (2H, q, J = 7.5 Hz), 6.66 (1H, s), 7.9 (1H, brs); (benzene): δ ppm 1.00 (3H, t, J = 7.5 Hz), 2.02 (3H, s), 2,08 (3H, s), 2.20 (2H, q, J = 7.5 Hz), 6.19 (1H, s); ms: m/e (relative intensity) 256 [M^+] (53%), 241 (100), 227 (8), 226 (10), 212 (53), 197 (15); uv-vis (methanol): λ max 442 nm, ε, 40,000.

4,4′-Diethyl-3,5,3′,5′-tetramethyl(2•2′)dipyrrylmethane (**2**).

One hundred and sixty-eight mg. (0.57 mmole) of the dipyrrylmethene•hydrochloride (**1**•HCl) was added to 30 ml. of methanol under nitrogen. To this stirred solution was added 30 mg. (0.79 mmole) of sodium borohydride over a period of 5 minutes. Hydrogen was evolved, and the solution rapidly changed color from red to pale yellow. Further addition of sodium borohydride (5-10 mg.) induced no further change in color. The solvent was evaporated in a stream of nitrogen, the oxygen-sensitive residue was taken up in degassed chloroform and filtered. Removal of the chloroform gave 134 mg. (91%) of a light tan oil, which was extremely air sensitive and was thus used in autoxidation and photooxidation studies as freshly prepared; nmr (deuteriochloroform): δ ppm 1.07 (3H, t, J = 8 Hz), 1.98 (3H, s), 2.10 (3H, s), 2.37 (2H, q, J = 8 Hz), 3.73 (2H, s); ms: m/e (relative intensity) 258 [M^+] (4%), 256 [M-2], (9%), 241 (15%), 212 (9%), 136 (100%); ir (film): ν 3300 cm^{-1} (N-H) and 1680 cm^{-1} (C=C).

Anal. Calcd. for $C_{17}H_{26}N_2$: 258.2096. Found: 258.2010.

Independent Synthesis of 5-Methoxymethyl-4-ethyl-3-methyl-2-carbomethoxypyrrole (**7**).

5-Bromomethyl-4-ethyl-3-methyl-2-carbomethoxypyrrole (32), 150 mg. (0.58 mmole) was dissolved in 20 ml. of methanol in a 100 ml., 3-neck, round bottom flask fitted with a reflux condenser. Sodium methoxide, 71 mg. (0.58 mmole) was added and the solution heated at reflux for one hour using a water bath and magnetic stirring. After evaporation of methanol, 30 ml. of ether was added and the insoluble material filtered. The filtrate was evaporated and the residue purified by preparative tlc on silica gel. The major band (R_f 0.45, chloroform) was collected and gave 79.3 mg. of a white solid, m.p. 85-86° (66% yield). The nmr and mass spectra match exactly those of photoproduct **7** obtained from dipyrrylmethene (**1**).

Photooxygenation of 4,4′-Diethyl-3,5,3′,5′-tetramethyl(2•2′)dipyrrylmethene (**1**) and 4,4′-Diethyl-3,5,3′,5′-tetramethyl(2•2′)-dipyrrylmethene (**2**) in Basic Methanol with rose bengal Sensitizer.

A methanolic solution of **1** or **2** (0.4 mmole%) containing 3.6 mg.% of rose bengal and 0.5% (v/v) concentrated ammonium hydroxide was placed in a water-cooled pyrex immersion apparatus (26). This apparatus was adapted with a circulating oxygen system which permitted the oxygen consumption to be measured. The solution was irradiated until oxygen uptake ceased (approximately 1 molar equivalent). Methanol was removed on a rotary evaporator at 30-40°. Initial separations were obtained by column chromatography on silica gel using an ethyl acetate-acetone-methanol elution sequence. All structurally identified products were found in the ethyl acetate fraction. Final separations and purifications were done by silica gel tlc. Products (Table I) were identified by their spectral characteristics and, with the exception of **12**, by comparison to samples obtained from photooxidation of monopyrroles (5,6,10,20,25).

Photooxygenation of 4,4′-Diethyl-3,5,3′,5′-tetramethyl(2•2′)dipyrrylmethane in Acidic Methanol.

A 0.4 mmole% solution of **2** was placed in a 25 x 200 mm test tube located 1 inch from the light source. Methanol containing hydrochloric acid (0.5% v/v concentration) and hematoporphyrin was added. The solution was immediately irradiated with a tungsten-halogen lamp (100 volts). A stream of oxygen was continuously passed through the solution. After 10 minutes the irradiation was terminated and the solution made slightly basic. The reaction mixture was then treated as described above for the photooxygenations in basic methanol. Only 5-methoxy-4-ethyl-3,5-dimethyl-3-pyrrolin-2-one (**8**) was obtained (20% yield).

Kinetic Experiments.

Kinetic data were determined with 0.5 mmole% solutions. The reactions were carried out in 18 x 65 mm test tubes. For autoxidation reactions the test tubes were wrapped in aluminum foil. For photooxygenations the test tubes were placed 2 inches from the light source. For both types of oxygenations a continuous fine stream of oxygen was passed through the solution *via* a capillary tube. For slow reactions the solvent level was maintained as necessary. During the course of the reaction aliquots were removed and diluted. A diluted aliquot (basic methanol) served to directly determine the concentration of **1** by uv-visible spectroscopy. Concentrations of **2** were determined from a second aliquot by converting **2** to **1** according to the following procedure and comparison with controls. To 1 ml. of benzene was added 10 μl. of the reaction mixture and a 3-fold excess of 2,3-dichloro-5,6-dicyanoquinone (DDQ). The mixture was allowed to stand for 30 minutes in the dark. The benzene was then removed and the residue taken up in the appropriate amount of basic methanol. The total amount of **1** and **2** present at the time that the aliquot was taken was then determined by uv-visible spectroscopy. The concentration of **2** was determined by difference.

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