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SYNTHESIS AND SPECTROSCOPIC PROPERTIES OF N,N-BRIDGED DIPYRRINONES

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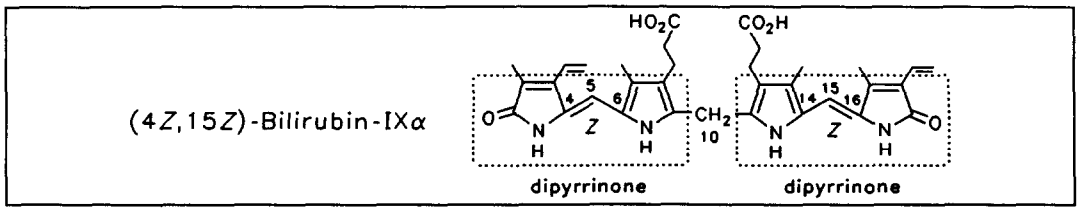
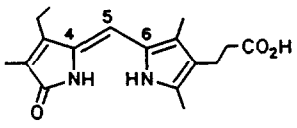
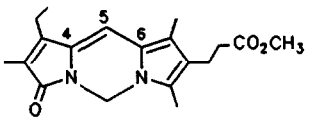
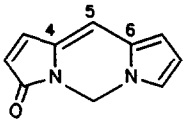
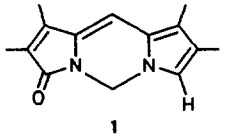
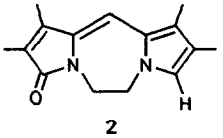
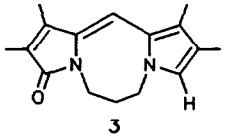
Abstract: 3,4-Dimethylpyrrole-2-aldehyde was converted into methano (**1**), ethano (**2**) and 1,3-propano N_{10},N_{11}-bridged dipyrrinones. At room temperature in cyclohexane the large fluorescence quantum yield associated with **1** ($\phi_F \simeq 0.81$) falls off significantly with increasing bridge length (**2** : $\phi_F = 0.26$, **3** : $\phi_F = 0.0012$).

Bilirubin, the cytotoxic yellow-orange pigment of jaundice,[1] consists of two dipyrrinone chromophores (shown in dashed boxes below) linked to a $-CH_2-$ group. Each dipyrrinone contains an isomerizable carbon-carbon double bond, at C_4 and at C_{15}, with the *Z*-configuration being the more stable.[2] The *E*-isomers are accessible by irradiation of the pigment with visible light and are important to the success of phototherapy for jaundice in newborn babies.[2] $Z \rightarrow E$ isomerization is the fastest and most quantum-efficient photochemical reaction in bilirubin.[3,4] Although bilirubin photochemistry involves an ultrafast (rate = 19 $\pm$ 2 ps^{-1}) twisting about the C_4 or C_{15} carbon-carbon double bonds for relaxation of the singlet excited state pigment,[3,4,5,6] in aqueous solutions of human serum albumin (HSA)) at room temperature the quantum yields are only modest ($\phi_{Z \rightarrow E} \simeq 0.1$)[4,7,8] and fluorescence is weak ($\phi_F \simeq 0.003$, $\tau_F = 18 \pm 3$ ps^{-1}). In organic solvents, the quantum yields drop ($\phi_{Z \rightarrow E} \simeq 0.003$ and $\phi_F \simeq 0.0002$).[8] Other photochemical reactions of bilirubin, *e.g.*, lumirubin (L) formation and photodegradation were found to have even lower quantum yields



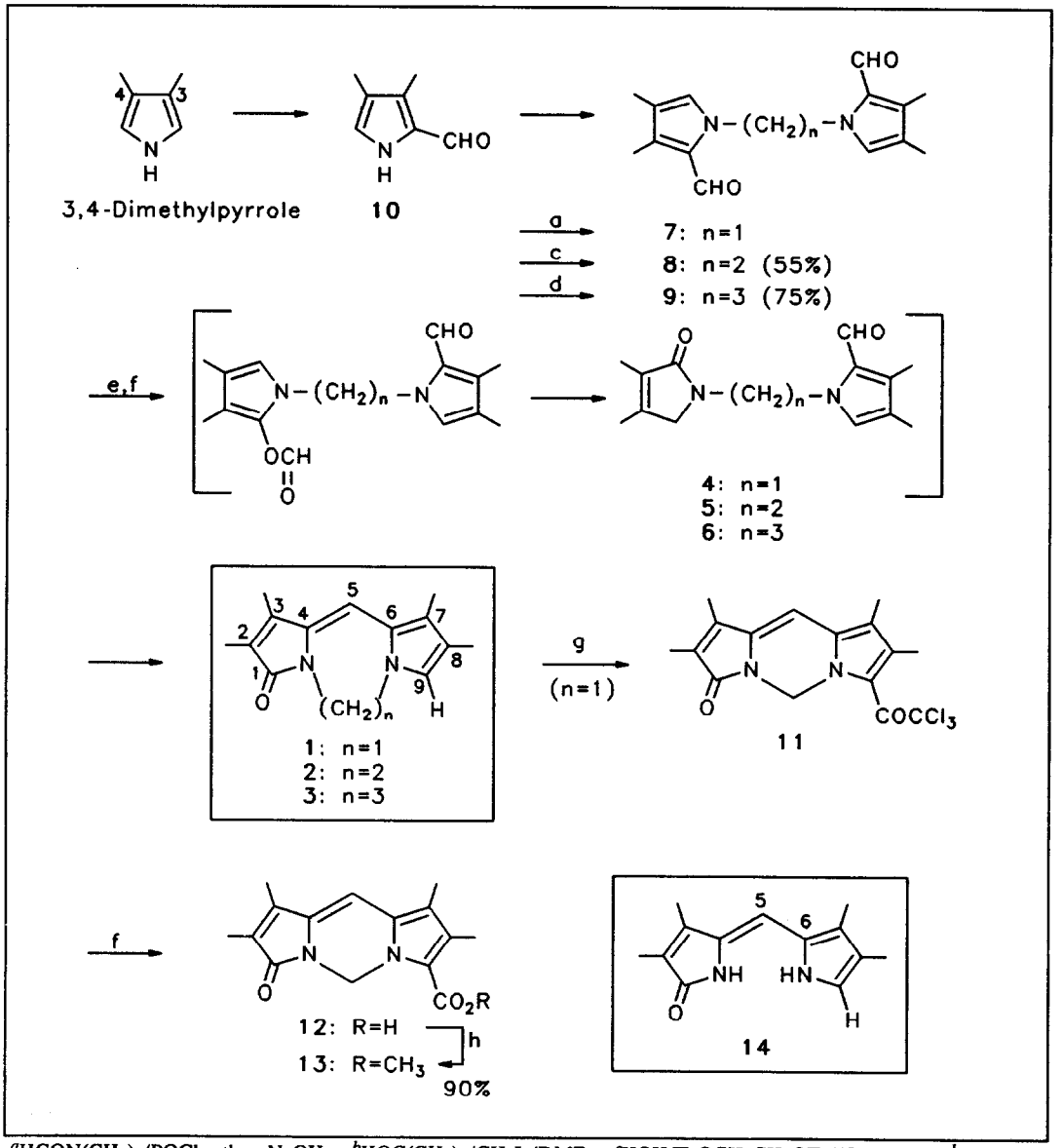
($\phi_{Z\to L} \simeq 10^{-4}$).[8] Consequently, non-radiative deexcitation pathways involving internal conversion are thought to predominate at room temperature as the major pathways for deactivation of photo-excited bilirubin.[4a] When the viscous drag of the microenvironment for bilirubin *increases*, the efficiency of photoisomerization *decreases*: $\phi_{Z\to E} < 0.01$ at 77°K for bilirubin in 50% aqueous ethylene glycol + HSA,[9] and the fluorescence quantum yield *increases* markedly, $\phi_F = 0.92$ (*vs* $\phi_F = 0.006$ at 22°C).[3] Similarly, in a rigid environment, as in polymers such as polymethylmethacrylate at room temperature, the fluorescence quantum yield increases dramatically, $\phi_F = 0.71$ (*vs* $\phi_F < 0.0005$ in ethyl acetate).[3]

When examined at the level of the isolated dipyrrinone chromophore, the quantum yield for $Z \to E$ photoisomerization for xanthobilirubic acid increases somewhat (relative to bilirubin): $\phi_{Z\to E} \simeq 0.2$ in aqueous buffered HSA at 22°C[10] and $\phi_{Z\to E} \simeq 0.22$ in EPA (ether-isopentane-ethanol, 5:5:2, v/v/v) at 20°C[5]; and the fluorescence quantum yields remain low: $\phi_F \simeq 0.003$ in aqueous buffered HSA at 22°C[11] and $\phi_F \leq 10^{-3}$ in EPA.[5] But at very low temperatures (77°K), the dipyrrinone fluorescence quantum yields rise ($\phi_F \simeq 0.33$ in EPA), and the $Z \to E$ quantum yields decrease ($\phi_{Z\to E} < 5\times10^{-4}$).[5] When methyl xanthobilirubinate is constrained to a *Z* configuration by bridging the lactam and pyrrole nitrogens with a methylene group, the room temperature fluorescence quantum yield becomes very large ($\phi_F = 0.85$ in cyclohexane),[12] analogous to its parent dipyrrinone with no alkyl substituents ($\phi_F = 1.0 \pm 0.5$ in *n*-hexane).[13] Thus, it would seem that the major excited state deactivation pathways in bilirubin and in xanthobilirubic acid involve internal molecular motion, predominantly around the C_5-C_6 (C_{14}-C_{15}) single bonds as opposed to motion in the alkyl substituents or translational motion.[4a] This concept was explored through the synthesis and spectroscopic analysis of N,N bridged dipyrrinones with increasing bridge lengths, from methano to 1,2-ethano to 1,3-propano (**1**, **2** and **3**), and thus with increasing rotational flexibility about C_5-C_6.

 Xanthobilirubic Acid	 N,N-Methano Bridged Bridged Xanthobilirubinate	 N-N-Methano Bridged Dipyrrinone
$\phi_F \leq 10^{-3}$ in EPA[5]	$\phi_F = 0.85$ in cyclohexane[12]	$\phi_F = 1.0\pm0.5$ in *n*-hexane[13]
 **1**	 **2**	 **3**

Synthesis. Unlike our previous work on N,N-methano methyl xanthobilirubinate (above), where the parent dipyrrinone methyl xanthobilirubinate was reached with CH_2I_2, the syntheses of **1**, **2** and **3** all start from 3,4-dimethylpyrrole rather than from parent dipyrrinone **14** (Synthetic Scheme). The pyrrole was

SYNTHETIC SCHEME



[a]$HCON(CH_3)_2/POCl_3$, then NaOH; [b]$KOC(CH_3)_3/CH_2I_2$/DMF; [c]KOH/$TsOCH_2CH_2OTs/(CH_3)_2SO$; [d]KOH/$BrCH_2CH_2CH_2Br/(CH_3)_2SO$; [e]*m*-chloroperbenzoic acid/THF/K_2CO_3; [f]NaOH; [g]CCl_3COCl/pyr.; [h]CH_2N_2.

converted[13] in a few steps first to its α-aldehyde (**10**) via a Vilsimeier reaction, then to the dipyrrylalkanes (**7**, **8** and **9**) by deprotonation of the N-*H* with a suitable base, followed by reaction with diidomethane to give **7**, ethylene glycol di-*p*-toluenesulfonate to give **8**, and 1,3-dibromopropane to give **9**, all in acceptable yields.

Although potassium *tert*-butoxide was used successfully for the conversion of **10** to **7**, it was unsuccessful for the conversions of **10** to **8** and **9** because as competing elimination reactions destroyed the alkyl linker reaction component. Use of the weaker base, potassium hydroxide, was successful, however. As illustrated earlier,[13] Baeyer-Villiger oxidation of **7-9** with one equivalent of *m*-chloroperbenzoic acid gave the corresponding α-hydroxypyrrole formate esters, which were converted to dipyrrinones **1-3** during saponification, without isolation, *via* intermediates (**4-6**) where the pyrrolinone is linked to the α-pyrrole aldehyde through different length (n=1-3) polymethylene units. (These intermediates led to the desired dipyrrinones (**1-3**) through intramolecular base-catalyzed aldol-like condensations.) Conversion of **7** to **1** (via **4**) proceeded smoothly at room temperature, but with increasing length of alkyl linker, the cyclization reaction slowed, and more forcing reaction conditions were required (reflux), with somewhat lower yields being achieved. Dipyrrinone **1** was further functionalized by acylation with trichloroacetyl chloride at the alkyl-free α-position to give trichloromethyl ketone **11**, which could be converted to the corresponding α-acid **12** or ester **13**.

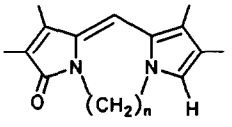
Spectroscopic Properties. Solutions of the methano-bridged dipyrrinone **1** were strongly blue-green fluorescent to the naked eye — in marked contrast to the parent dipyrrinone **14**, from which fluorescence is not detectable ($\phi_F < 10^{-4}$ in cyclohexane). The fluorescence quantum yield of **1** at room temperature in cyclohexane, determined *vs* 9,10-diphenylanthracene standard ($\phi_F = 0.90$), was very large ($\phi_F \simeq 0.81$), consistent with fluorescence deexcitation being the major relaxation path for return of singlet excited **1** to the ground state. The fluorescence emission λ^{max} of **1** was centered near 440 nm in cyclohexane, 470 nm in chloroform solvent, and near 490 nm in methanol. The extremely large fluorescence quantum yield correlates well with previously prepared N,N-methano-bridged dipyrrinones at room temperature[12,13] and is consistent with one major deexcitation pathway: radiative emission. Alternative non-radiative deexcitation pathways cannot be accessed, e.g., photoisomerizates from 4*Z* to 4*E* and molecular motion by rotation about the C_5-C_6 single bond. The behavior of **14** *vs* **1** is analogous to that found by Saltiel *et al.*[14] for stilbene ($\phi_F \simeq 0.05$) and its restricted rotation analog, indenoindene, ($\phi_F \simeq 1.0$) in methylcyclohexane at 298°K.

The ethano (**2**) and propano (**3**) N,N-bridged dipyrrinone analogs, while still more restricted in internal motion than the parent (**14**), have less restricted rotation about the C_5-C_6 single bond than the methano bridged analog (**1**). The methano bridge constrains the dipyrrinone to adopt a fairly rigid planar conformation, but the ethano and propano bridges leave the dipyrrinone in nonplanar conformations twisted about the C_5-C_6 single bond by ~14° and 27°, respectively, as computed by PCMODEL molecular mechanics calculations. These conformations of **2** and **3** are not only twisted but they are also more flexible than that of **1**. It is this mode of internal motion (rotation about C_5-C_6) that is apparently responsible for the lower fluorescence quantum yield in **2** ($\phi_F \simeq 0.26$) and the much reduced fluorescence quantum yield in **3** ($\phi_F \simeq 0.0012$), where internal motion is more facile. Since none of the bridged dipyrrinones of this study can undergo $Z \rightarrow E$ double bond isomerization (at C_4), it would appear that an internal conversion deexcitation pathway involving motion about C_5-C_6 becomes increasingly important in going from **1** to **2** to **3**. These data suggest that

motion about C_5-C_6 (and C_{14}-C_{15}) in bilirubin may also be major contributor to the internal conversion deexcitation pathway which predominates at room temperature or at physiologic temperature (37°C).

The UV-visible spectra of **1-3** differ, with dipyrrinone **1** typically exhibiting longer wavelength λ^{max} for the long wavelength transition (Table 1). This is probably due to more effective conjugation in the dipyrrinone chromophore in planar **1** as opposed to twisted **2** and **3**. In hydrocarbon solvents the long wavelength absorption band is split by ~20 nm, possibly due to exciton splitting in π-stacking dimers. Dreiding molecular models indicate that the π-system of **1** is held planar, that of **2** is twisted about C_5-C_6 by ~30° and that of more flexible **3** is twisted by ~50°. In contrast, the parent dipyrrinone (**14**) does not necessarily adopt a planar conformation and may easily be rotated about the C_5-C_6 bond. From LIS-NMR studies in dilute solutions, Falk *et al.*[5,15] have shown that dipyrrinones like **14** adopt twisted conformations with the C_5-C_6 bond rotated by about ~40° in non-polar solvents such as $CDCl_3$. Although their preferred conformation in polar solvents such as $(CH_3)_2SO$ is unclear, solvent-solute hydrogen bonding[16] may play a role in stabilizing a more planar dipyrrinone conformation, such as attends the self-association of dipyrrinones through intermolecular hydrogen bonding in nonpolar solvents and in the crystal.[5,17] The reduced ϵ value of the bridged dipyrrinone **1** in $(CH_3)_2SO$ is apparently characteristic of a planar dipyrrinone. Whether the data can also be correlated from molecular orbital calculations remains to be examined.

TABLE 1. Comparison of UV-Visible Spectral Data of N,N-Bridged Dipyrrinones **1-3** and the Parent Dipyrrinone **14**.[a]



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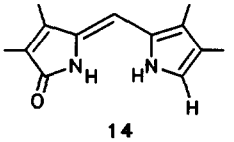


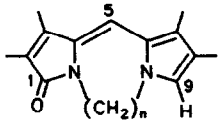
14

Solvent	λ^{max} (ϵ^{max}) Values for Dipyrrinone[b]			
	1	**2**	**3**	**14**
n-Hexane	396 (20,400)[c] 417 (20,200)	386 (26,500)[e] 406 (25,800)	385 (20,500)[f] 402[sh] (19,000)	390 (20,500)[d] 410[sh] (12,000)
Benzene	403 (19,100)[c] 418 (18,700)	393 (24,600)[f] 409 (24,100)	390 (18,800)[d] 406[sh] (17,200)	392 (23,000)[d]
Chloroform	409 (19,300)[d]	398 (25,800)[f]	392 (21,200)[g]	394 (25,300)[d]
Dichloromethane	406 (20,000)[d]	394 (25,900)[f]	390 (20,500)[d]	387 (22,900)[g]
Methanol	412 (20,100)[c]	403 (27,500)[d]	397 (21,600)[d]	396 (27,200)[g]
Dimethylsulfoxide	410 (19,900)[c]	395 (26,300)[g]	394 (26,200)[c]	395 (26,300)[d]

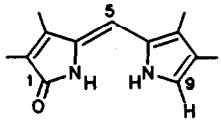
[a]At room temperature for 10^{-5} *M* solutions. [b]Band half-widths (nm) at 1/e th height. [c]36. [d]35. [e]32. [f]33. [g]34.

Torsional deformation from the planar conformation of the N,N methano-bridged dipyrrinone (**1**) upon lengthening the bridge by one (**2**) or two (**3**) methelyne groups can also be detected by changes in the NMR spectra. Thus, the C_5 resonance in the ^{13}C-NMR spectrum shows sensitivity to twisting about C_5-C_6, as may be noted in Table 2, as do ring carbons at the extremities of the molecule, C_9 and C=O. In the planar molecule (**1**), with apparently more effective π-conjugation, these carbon resonances all appear at higher field than those of the twisted molecules (**2** and **3**) with less effective conjugation.

TABLE 2. Comparison of ^{13}C-NMR Chemical Shifts of C_1, C_5 and C_9 in Dipyrrinones **1-3** and **14**.



1: n = 1, **2**: n = 2, **3**: n = 3



14

Carbon	^{13}C Chemical Shift of Dipyrrinone[a]			
	1	**2**	**3**	**14**
C_5	96.92	98.52	98.19	101.06
C_9	119.76	122.99	121.13	119.46
C=O	169.18	169.43	171.06	174.29

[a]Measured in $CDCl_3$, 10^{-2} *M* at 22°C in δ, ppm downfield from $(CH_3)_4Si$.

The ^1H-NMR resonances at C_5-H and C_9-H (Table 3) are also sensitive indicators of conformation and even better predictors of (C_5-C_6) twist deformation from planarity. Here the ^1H-resonances appear at lower field for the planar N,N-methano-bridged dipyrrinone (**1**) than for the twisted ethano (**2**) and propano (**3**) bridged analogs. The more twisted analog (**3** typically exhibits the most shielded signal in $(CD_3)_2SO$ and $CDCl_3$ solvents, with the set of signals from **1**, **2** and **3** being correspondingly more shielded in the latter solvent. As might be expected, these qualitative trends persist in C_6D_6 solvent, except for planar **1** where more effective solvation produces a larger solvent-induced shielding.

The ^{13}C and ^1H-NMR resonances observed for the N,N-bridged dipyrrinones (**1-3**) may be compared to those of the unbridged parent (**14**). The large differences in the ^{13}C resonances (Table 2) are to some extent attributable to substituent effects on replacing N-C with N-H bonds. The rather smaller differences seen in the ^1H-resonances (Table 3) may be more reflective of changes in conformation through rotation about C_5-C_6 and intermolecular hydrogen bonding to give dimers, which predominate in $CDCl_3$ and C_6D_6 solvents. Such hydrogen-bonded dimers cannot be formed in the N,N bridged dipyrrinones.

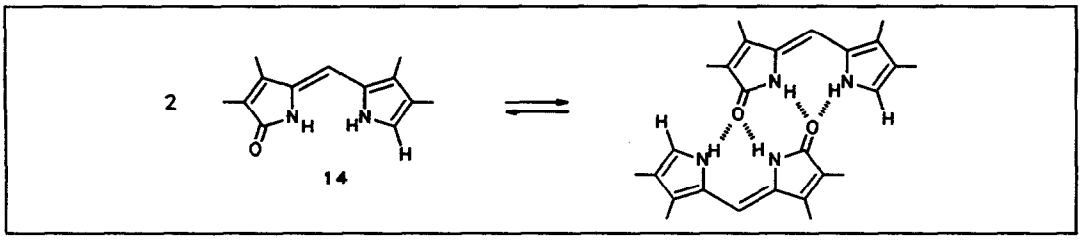
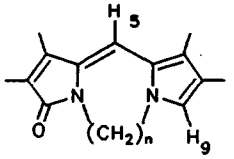


TABLE 3. Comparison of ^{1}H-NMR Chemical Shifts of Hydrogens at C_5 and C_9 in Dipyrrinones **1-3** and **11**.



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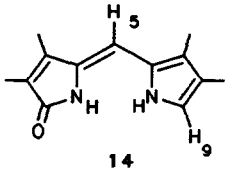

14

Solvent	H_5 - Chemical Shift (δ, ppm)[a]			
	1	**2**	**3**	**14**
$(CD_3)_2SO$	6.51	6.11	6.06	5.94
$CDCl_3$	6.14	6.05	5.99	6.23
C_6D_6	5.83	5.90	5.79	6.11[b]
Solvent	H_9 - Chemical Shift (δ, ppm)[a]			
	1	**2**	**3**	**14**
$(CD_3)_2SO$	6.79	6.70	6.65	6.72
$CDCl_3$	6.56	6.48	6.48	6.85
C_6D_6	5.87	5.92	6.00	6.14[b]

[a]Measured in $4x10^{-2}$ M solutions at 22°C in δ, ppm downfield from $(CH_3)_4Si$.
[b]Value uncertain due to insolubility of pigment.

Concluding Comments. Methano (**1**), ethano (**2**) and propano (**3**) N,N-bridged dipyrrinones cannot undergo $4Z \rightarrow 4E$ photochemical double bond isomerization, and internal motion is restricted to different extents in the C_5-C_6 single bond. Excitation in the long wavelength absorption band near 400 nm give a strongly fluorescing excited states for the most rigid isomer, planar **1** ($\phi_F \simeq 0.81$) and decreasing fluorescence from the excited states of **2** ($\phi_F \simeq 0.26$) and **3** ($\phi_F = 0.0012$), which can experience increasing greater motion about the C_5-C_6 single bond. Here, internal conversion by twisting about the C_5-C_6 bond is thought to be the main deexcitation mode.

Acknowledgement. We thank the National Institutes of Health (HD-17779) for generous support of this work.

EXPERIMENTAL

General Procedures. All ultraviolet-visible spectra were recorded on a Perkin-Elmer 3840 diode array or Cary 219 spectrophotometer, and all infrared (IR) spectra were recorded on a Perkin-Elmer instrument. Nuclear magnetic resonance (NMR) spectra were determined on a GE QE-300 300-MHz spectrometer in $CDCl_3$ solvent (unless otherwise specified) and reported in δ ppm downfield from $(CH_3)_4Si$. Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ. Analytical thin layer chromatography was carried out on J.T. Baker silica gel IB-F plates (125 μ layers). Flash column chromatography was carried out using Woelm silica gel F, thin layer chromatography grade. Radial chromatography was carried out on preparative thin layer grade Merck silica gel PF-254 with $CaSO_4$, using a Chromatotron (Harrison Research, Inc., Palo Alto, CA). HPLC analyses were carried out on a Perkin-Elmer Series 4 high performance liquid chromatograph with an LC-95 UV-visible spectrophotometric detector (set at 410 nm) equipped with a Beckman-Altex ultrasphere-IP 5 μm C-18 ODS column (25 x 0.46 cm) and a Beckman ODS precolumn (4.5 x 0.46 cm). The flow rate was 1.0 mL/minute, and the elution solvent was 0.1 *M* di-*n*-octylamine acetate in 3% aqueous methanol (pH 7.7, 31°C).

Spectral data were obtained in spectral grade solvents (Aldrich or Fisher). Ethylene glycol, *p*-toluenesulfonylchloride diidomethane, 1,3-dibromopropane, tetrahydrofuran, N,N-dimethylformamide, phosphorous oxychloride, potassium *tert*-butoxide, *m*-chloroperbenzoic acid, and trichloroacetyl chloride were from Aldrich. Tetrahydrofuran was dried by distillation from sodium.

2-Formyl-3,4-dimethyl-1*H*-pyrrole (10). In a 500 mL three-neck round bottom flask equipped with dropping funnel and a thermometer were added 3,4-dimethylpyrrole (24.23 g) and N,N-dimethylformamide to anhydrous ethyl ether (250 mL). Phosphorous oxychloride (39.78 g, 0.26 mol) was added dropwise at 0°C. The reaction mixture was stirred overnight at room temperature. Then the solvent was removed (roto-vap) and the residue was dissolved in 200 mL of cold water. To this mixture sodium hydroxide (65 g) was added slowly with stirring in a cooling bath. After stirring the mixture for 1 hour, a precipitate was collected by filtration, washed with cold water several times and dried. Further purification can be achieved by recrystallization in dichlomethane-*n*-hexane to give 29 g of the aldehyde (92% yield). It had mp 133-134°C (Lit.[28] 134°C); ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.020 (s, 3H), 2.274 (s, 3H), 6.866 (d, 1H, J=2.4 Hz), 9.267 (b, 1H), 9.531 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$) δ: 8.58 (q), 9.46 (q), 121.08 (s), 124.85 (d), 129.59 (s), 131.27 (s), 177.21 (d) ppm; GC/MS (*m/z*): 123 [M^+], 122 (100%), 94 [M-CHO] amu.

Bis-(3,4-dimethyl-2-formyl-pyrrol-1-yl) methane (7). 3,4-Dimethyl-2-formyl-1*H*-pyrrole (1.23 g, 10 mmol) was dissolved in N,N-dimethylformamide (20 mL, dried over magnesium sulfate and distilled) under a nitrogen atmosphere. Potassium *tert*-butoxide (1.7 g) was added, and the mixture was stirred for 1 hour. Diiodomethane (0.35 mL) was then added dropwise using a syringe. (Heat evolved!) After stirring the mixture for 10 minutes, another portion (0.35 mL) of diiodomethane was added dropwise, and the reaction mixture was stirred for an additional 2 hours at room temperature. The reaction was quenched by pouring into ice and water (200 mL) then extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with saturated sodium chloride solution (3 x 50 mL), dried over anhydrous sodium sulfate, filtered and evaporated. *n*-Hexane was added to the residue, and the solution placed in refrigerator to effect a precipitation. Further purification was carried out by flash chromatography on silica gel (dichloromethane-methanol 100:2 R_F 0.8), and recrystallization from ethyl acetate-*n*-hexane gave **7** (1.0 g, 80% yield). The product had mp 176-177°C; IR ($CHCl_3$) ν: 2925, 2863, 1649 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.914 (s, 6H), 2.209 (s, 6H), 6.764 (s, 2H), 7.273 (s, 2H), 9.682 (s, 2H) ppm; ^{13}C-NMR ($CDCl_3$) δ: 8.78 (q), 9.42 (q), 56.22 (t), 120.39 (s), 126.61 (s), 130.53 (d), 135.69 (s), 178.07 (d) ppm; and GC/MS: R_t=19.46 minutes *m/z*=258 [M^+], 229 [M-CHO], 136 (100%, 109, 93, 41 amu.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$ (258.2): %C. 69.75; %H, 7.02; %N, 10.84
Found: %C, 69.67; %H, 7.07; %N, 10.71

N_{10},N_{11}-Methano-(2,3,7,8-tetramethyl)dipyrrinone(1). To a solution of bis(2-formyl-3,4-dimethyl-pyrrol-1-yl) methane (7) (2.58 g, 10 mmol) and K_2CO_3 (1 g) in tetrahydrofuran (50 mL) with stirring under a nitrogen atmosphere, *m*-chloroperbenzoic acid (80%, 1.42 g, 6.6 mmol) in tetrahydrofuran (50 mL) was added dropwise during 1 hour. Aqueous NaOH solution (4*N*, 10 mL) was added to the mixture, and stirring was continued for an additional 3 hours. Water (20 mL) and sodium sulfite were then added to the mixture. After stirring for 20 minutes, the mixture was extracted with dichloromethane until the aqueous layer became colorless. The combined organic layers were washed with water, saturated NaCl solution (50 mL), dried over anhydrous sodium sulfate, filtered and evaporated. The residue was chromatographed by radial chromatography on silica gel (Chromatotron, 2 mm layer; eluent: CH_2Cl_2-CH_3OH 100:1) to afford uncoupled oxopyrrole 4 (R_f=0.2), desired product 1 (R_f=0.42), and starting material 7 (R_f=0.65). The fluorescent yellow product (1) was recrystallized to give 0.48 g of yellow needles from ethyl ether-petroleum ether (or ethanol-water) in 20% yield. It had mp 164-165°C; IR ($CHCl_3$) ν: 2920, 2861, 1667, 1612 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.927 (s, 3H), 2.017 (s, 3H), 2.074 (s, 3H), 2.085 (s, 3H), 5.536 (s, 2H), 6.144 (s, 1H), 6.562 (b, 1H) ppm; and ^{13}C-NMR ($CDCl_3$) δ: 8.49 (q), 8.75 (q), 9.43 (q), 10.00 (q), 55.66 (t), 96.92 (d), 119.12 (s), 119.76 (d), 121.03 (s), 124.39 (s), 126.65 (s), 131.74 (s), 137.73 (s), 169.18 (s) ppm.

Anal. Calcd. for $C_{14}H_{16}N_2O$ (228.1): %C, 73.66; %H, 7.06; %N, 12.27
Found: %C, 74.00; %H, 7.05; %N, 12.12

Bis-1,2-(3,4-dimethyl-2-formyl-pyrrol-1-yl)ethane (8). Crushed potassium hydroxide (1.1 g) and 3,4-dimethyl-2-formyl-1*H*-pyrrole (615 mg, 5 mmol) were added to absolute dimethylsulfoxide (20 mL) and stirred for 4 hours under a nitrogen atmosphere at room temperature. The reaction temperature was increased to 65°C, and to the warm solution was added 1,2-ethylene glycol di-*p*-toluenesulfonate (2.96 g, 8 mmol, see below) in small portions over 10 minute intervals. The mixture was stirred for an additional 3 hours at 65°C. After cooling the reaction to room temperature, it was quenched by pouring into cold water (200 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with cold water (5 x 200 mL), saturated sodium chloride solution (50 mL), dried over anhydrous potassium carbonate, filtered and evaporated. The residue was chromatographed on TLC grade silica gel by radial chromatography chromatotron, 4 mm layer; eluent: dichloromethane-methanol, 100:2.5, R_f=0.65) to give 0.35 g (55%) of the desired product. It had mp 184-185°C; IR ($CHCl_3$) ν: 2924, 2864, 1645 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.89 (s, 3H), 2.24 (s, 3H), 4.42 (s, 4H), 6.38 (s, 2H), 9.66 (s, 2H) ppm: ^{13}C-NMR ($CDCl_3$) δ: 8.77 (q), 9.18 (q), 49.66 (t), 118.96 (s), 127.08 (s), 130.69 (d), 134.07 (s), 177.41 (d), 177.54 (d) ppm; GC-MS (*m/z*) = 272 [M^+], 243, 200, 185, 149, 121 (100%), 93, 41 amu.

Anal. Calcd. for $C_{16}H_{20}N_2O_2 \cdot ¼\ H_2O$ (276.9): %C, 69.42; %H, 7.46; %N, 10.11
Found: %C, 69.46; %H, 7.14; %N, 10.34

Ethylene glycol di-*p*-toluenesulfonate. To a mixture of anhydrous ethylene glycol (6.2 g, 0.1 mol) and dry pyridine (64 mL) was added *p*-toluenesulfonyl chloride (38 g, 0.2 mol) portion-wise, keeping the temperature at about 0°C. The resulting slurry was stored in a refrigerator overnight. The mixture was then poured into 400 mL of ice and water, and the resulting white precipitate was collected by filtration and washed with cold water (3 x 200 mL). The solid was then recrystallized from ethanol to give 30 g (80%) of the desired product. It had mp 126-127°C (Lit.[18] 126-129°C); ^{1}H-NMR ($CDCl_3$) δ: 2.454 (s, 6H), 4.179 (s, 4H), 7.338 (d, 4H, J=8.4 Hz), 7.331 (d, 2H, J=8.4 Hz) ppm; ^{13}C-NMR ($CDCl_3$) δ: 21.66 (q), 66.66 (t), 127.94 (d), 129.94 (d), 132.30 (s), 145.25 (s) ppm; GC/MS: 370 [M^+] amu.

N_{10},N_{11}-1,2-Ethano-(2,3,7,8-tetramethyl)dipyrrinone (2). To a solution of bis(2-formyl-3,4-dimethyl-pyrrol-1-yl)-1,2-ethane (8) (3 mmol, 0.816 g) and K_2CO_3 (0.5 g) in 25 mL of tetrahydrofuran-dichloromethane, 25:1 with stirring under nitrogen, was added dropwise *m*-chloroperbenzoic acid (0.7 g, 80%) in 15 mL of tetrahydrofuran over 1 hour. Stirring was continued for 2 hours after final addition. To the mixture was

added 6 *N* aq. NaOH (2 mL), and stirring was continued for 20 minutes. Water (15 mL) and sodium sulfite (1 g) were added, and stirring was continued overnight. The solution was extracted with CH_2Cl_2 (5 x 50 mL) and the combined organic extracts were washed with cold water (3 x 100 mL) and sat. NaCl solution (50 mL). After drying the organic layer over anhydrous Na_2SO_4 and filtration, the solvent was evaporated. Radial chromatography eluting with *n*-hexane-acetone (8:2) gave three major products: Starting material (**8**) R_f=0.62, bridged dipyrrinone (**2**) R_f=0.46, and uncoupled intermediate (**5**) R_f=0.1. Resubmission of the uncoupled product (**5**) to 6 *N* aq. NaOH (2 mL) and methanol (2 mL) at reflux gave more yellow dipyrrinone (**2**), which precipitated from the reaction solution after cooling to 4°C for 1 hour. This was collected, combined with chromatographed dipyrrinone and recrystallized from alcohol-water to give **2**, 130 mg, (17% yield). It had mp 128-130°C; IR ($CHCl_3$) ν: 2922, 2863, 1626 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.914 (s, 3H), 1.986 (s, 3H), 2.084 (s, 3H), 2.101 (s, 3H), 4.072 (b, 4H), 6.045 (s, 1H), 6.478 (s, 1H) ppm and ^{13}C-NMR ($CDCl_3$) δ: 8.85 (q), 9.42 (q), 9.66 (q), 9.85 (q), 41.40 (t), 49.44 (t), 98.52 (d), 118.67 (s), 122.99 (d), 123.08 (s), 125.06 (s), 125.94 (s), 133.37 (s), 139.48 (s), 169.43 (s) ppm.

Anal. Calcd. for $C_{15}H_{18}N_2O$ (242.1): %C, 74.34; %H, 7.49; %N, 11.57
Found: %C, 74.29; %H, 7.66; %N, 11.67

Bis-1,3-(3,4-dimethyl-2-formyl-pyrrol-1-yl)propane (9). 3,4-Dimethyl-2-formyl-1*H*-pyrrole (1.23 g, 10 mmol) in 20 mL of absol. dimethylsulfoxide was stirred with crushed potassium hydroxide (1.7 g) for 3 hours at room temperature under a nitrogen atmosphere. To the mixture, 1,3-dibromopropane (0.7 mL, 7 mmol) was added portion-wise as follows: (i) 0.4 mL was added dropwise using a syringe holding the reaction temperature below < 18°C and stirring for 20 minutes; (ii) additional 1,3-dibromopropane (0.2 mL) was added dropwise at a temperature < 18°C and stirring was continued for 30 minutes; (iii) finally 0.1 mL of 1,3-dibromopropane was added and stirring was continued for 2 hours at room temperature. The reaction mixture was then poured into ice and water (total 200 mL) and extracted with dichloromethane (4 x 50 mL). The combined organic layers were washed with cold water (5 x 200 mL), saturated sodium chloride solution (100 mL), dried over anhydrous potassium carbonate, filtered and evaporated. To the resulting sticky dark mixture were added ethyl acetate (1-2 mL) and n-hexane (50 mL), and the solution was kept in a refrigerator overnight. The precipitated solid was filtered, washed with cold *n*-hexane and dried under vacuum to afford 1.07 g, (75% yield) of white product (99% purity on GC/MS analysis). It had mp 97-98°; IR ($CHCl_3$) ν: 2927, 2864, 1651 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.951 (s, 6H), 2.134 (m, 2H, J=7.2 Hz), 2.228 (s, 6H), 4.203 (t, 4H, J=7.5 and 6.9 Hz), 6.650 (s, 2H), 9.632 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 8.82 (q), 9.38 (q), 32.86 (t), 46.42 (t), 118.97 (s), 127.32 (s), 129.74 (d), 133.76 (s), 177.46 (d) ppm; GC/MS: R_t=21.66 min.; (*m/z*)=286 [M^+], 258, 163 (100%), 122, 108, 94, 41 amu.

Anal. Calcd. for $C_{17}H_{22}N_2O_2$ (286.4): %C, 71.30; %H, 7.74; %N, 9.78
Found: %C, 71.23; %H, 7.33; %N, 9.68

N_{10},N_{11}-1,3-Propano-(2,3,7,8-tetramethyl)dipyrrinone (3). To a solution of bis(2-formyl-3,4-dimethyl-pyrrol-1-yl)-1,3-propane (**9**) (2.86 g, 10 mmol) in 50 mL of tetrahydrofuran and K_2CO_3 (1.6 g) was added dropwise *m*-chloroperbenzoic acid (1.72 g, 80%) in 50 mL of THF over 1 hour with stirring under nitrogen. Stirring was continued for 2 hours after addition was complete. To the mixture, 4 *N* aq. NaOH (12 mL) was added, and stirring was continued for 20 minutes. The water (30 mL) and sodium sulfite (2 g) were added to the mixture. After stirring for 1 hour, the mixture was extracted with CH_2Cl_2 (5 x 50 mL). The combined organic extracts were washed with cold water (3 x 200 mL) and sat. aqueous NaCl (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated (roto-vap). Chromatography indicated two major products, bis-1,3-(2-oxopyrro-1-yl)propane and 1-(2-oxo-pyrrol-1-yl)-3-(2-formyl-3,4-dimethylpyrrol-1-yl) propane (**6**), and the only mixture was resubmitted to 2 mL of 4 *N* aq. NaOH in methanol (3 mL) and heated at reflux for 2 hours under nitrogen. After cooling to room temperature, the mixture was kept at 4°C overnight to afford a yellow precipitate. The solid was collected by filtration, washed with water (3 x 30 mL)

and recrystallized from ethanol-water to afford pure 268 mg of **3** (10% yield). It had mp 128-129°C; IR ($CHCl_3$) ν: 2922, 2861, 1664, 1625 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.833 (m, 2H), 1.922 (s, 3H), 2.013 (s, 3H), 2.047 (s, 3H), 2.108 (s, 3H), 3.58 (b, 2H), 3.830 (t, 2H), 5.990 (s, 1H), 6.462 (b, 1H) ppm; and ^{13}C-NMR ($CDCl_3$) δ: 8.85 (q), 9.73 (q), 2 x 10.01 (q), 29.15 (t), 36.67 (t), 44.19 (t), 98.19 (d), 118.67 (s), 120.80 (s), 121.13 (d), 125.71 (s), 126.05 (s), 137.48 (s), 139.86 (s), 171.06 (s).

Anal. Calcd. for $C_{16}H_{20}N_2O_2$ (256.4): %C, 74.97; %H, 7.86; %N, 10.93
Found: %C, 75.23; %H, 7.49; %N, 10.73

N_{10},N_{11}-Methano-(2,3,7,8-tetramethyl-9-trichloroacetyl)dipyrrinone (11). N_{10},N_{11}-Methylene bridged dipyrrinone (**1**) (46 mg, 0.2 mmol) was stirred and dissolved in pyridine under nitrogen while heating to 80°C. To the stirred solution, trichloroacetyl chloride (0.2 mmol) was added dropwise (syringe) during 10 minutes, and stirring was continued for an additional 10 minutes. Pyridine was removed under vacuum and the residue was dissolved in CH_2Cl_2, washed with H_2O (5 x 30 mL) and saturated aq. NaCl. After drying over anhydrous Na_2SO_4, the mixture was filtered and the solvent was evaporated. The residue was flash column chromatographed on Woelm TLC grade silica gel (eluent CH_2Cl_2-CH_3OH 100:1) to give 54 mg of the yellow product (**11**) in 70% yield. It had mp 184-186°C; IR ($CHCl_3$) ν: 2922, 2860, 1686, 1646 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.954 (s, 3H), 2.079 (s, 3H), 2.105 (s, 3H), 2.423 (s, 3H), 5.856 (s, 2H), 6.084 (s, 1H) ppm; and ^{13}C-NMR ($CDCl_3$) δ: 8.73 (q), 8.95 (q), 9.39 (q), 14.28 (q), 56.78 (t), 93.87 (d), 120.36 (s), 123.71 (s), 130.16 (s), 130.21 (s), 133.25 (s), 137.04 (s), 168.93 (s), 175.37 (s) ppm. It was used directly in the next step and analyzed as its carboxylic acid methyl ester.

N_{10},N_{11}-Methano-(2,3,7,8-tetramethyl-9-methoxycarbonyldipyrrinone (13). N_{10},N_{11}-Methano(12,3,7,8-tetramethyl-9-trichloroacetyl)-dipyrrinone (30 mg, 0.08 mmol) was dissolved in a 3 N aqueous NaOH solution (3 mL) with a minimal amount of CH_3OH (several drops). The mixture was refluxed for 1 hour under nitrogen. After cooling the pot to room temperature, the solvent was evaporated under vacuum. Water (15 mL) was added to the residue to dissolve the resulting salt. The mixture was filtered to remove unreacted starting material. The basic solution was then neutralized with 10% HCl at 0°C. The precipitate was centrifuged and washed with water (3 x 20 mL). The yellow product was dried under vacuum in the desiccator over P_2O_5 overnight then used directly in the next step. It had ^{1}H-NMR (d_6-DMSO) δ: 1.803 (s, 3H), 2.005 (s, 3H), 2.061 (s, 3H), 2.151 (s, 3H), 5.804 (s, 2H), 6.539 (s, 2H), 12.26 (b, 1H) ppm.

The dried solid (**12**) was suspended in anhydrous methanol with stirring. Diazomethane in anhydrous ethyl ether was added slowly until all of the solid (acid) was dissolved in solution. After addition of 1 more drop of diazomethane, the mixture was stirred for 1 hour at room temperature. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and flash chromatographed on Woelm TLC grade silica gel (eluent CH_2Cl_2-CH_3OH 100:2) to afford 22 mg of the ester (**13**) in (90% yield). It had mp 184-186°C; IR ($CHCl_3$) ν: 2953, 2922, 2863, 1691, 1643 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.940 (s, 3H), 2.051 (s, 3H), 2.086 (s, 3H), 2.252 (s, 3H), 3.867 (s, 3H, -OCH_3), 5.942 (s, 2H, N-CH_2-N), 6.070 (s, 1H, =C-H) ppm; and ^{13}C-NMR ($CDCl_3$) δ: 8.54 (q), 8.59 (q), 9.31 (q), 11.04 (q), 51.13 (q), 56.45 (t), 94.77 (d), 119.00 (s), 120.46 (s), 128.80 (s), 129.01 (s), 130.00 (s), 134.98 (s), 136.94 (s), 161.76 (s), 168.96 (s) ppm.

Anal. Calcd. for $C_{16}H_{18}N_2O_3$ (286.3): %C, 67.12; %H, 6.34; %N, 9.78
Found: %C, 66.82; %H, 6.20; %N, 9.85

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