Syntheses and Properties of Benzodipyrrinones

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2,3-Benzannelated dipyrrinone analogs (**1** and **2**) of xanthobilirubic acid (**3**) are prepared by base-catalyzed condensation of isoindolinone (**5**) and indolin-2-one (**6**) respectively, with methyl 3-(2-formyl-3,5-dimethyl-1*H*-pyrrol-4-yl)propanoate (**4**). Nuclear Overhauser effect H-nmr studies indicate that both **1** and **2** adopt preferentially a *syn-Z* configuration. The former forms a hydrogen-bonded homodimer in nonpolar solvents; the latter is intramolecularly hydrogen bonded.

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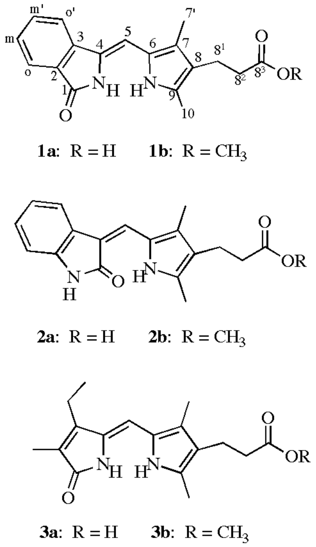
Introduction.

Porphyrins with aromatic rings fused at the β-positions have been a subject of recent syntheses and investigations [1]. Although linear tetrapyrroles have been prepared with aromatic rings attached [2], those with fused aromatic rings are largely unknown. In the following, we report the first 2,3-benzodipyrrinone analog (**1**, Figure 1) of methyl xanthobilirubinate (**3b**) [3], a synthetic precursor to mesobilirubin-XIIIα and its verdin [4] and related linear tetrapyrroles [5]. In addition, we report on **2**, a lactam moiety reversed constitutional isomer of **1**, and compare the properties of these two dipyrrinones.



1a: R = H **1b**: R = CH_3

2a: R = H **2b**: R = CH_3

3a: R = H **3b**: R = CH_3

Figure 1. Structures, numbering system and preferred conformations of benzo analogs **1** and **2** of xanthobilirubic acid **3a**.

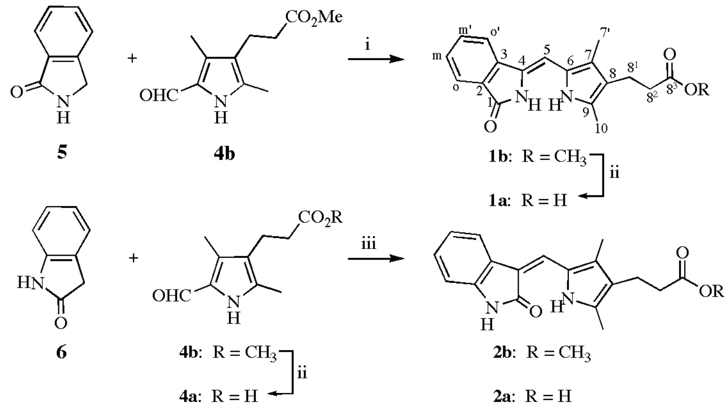
Synthesis.

The common pyrrole reactant for the syntheses of **1** and **2** is pyrrole aldehyde **4b** [6] which was condensed with isoindolinone **5** (prepared from *o*-toluic acid, as reported previously [7]) to give **1b** and 2-indolinone (**6**) to give **2b** (Scheme 1). The condensation to give **2b** proceeded rapidly and smoothly in high yield (79%) from reaction of commercially available **6** with 1.1 equivalents of **4b** in methanol at reflux in the presence of 0.5 equivalents of piperidine. Condensation of the free propionic acid-aldehyde **4a** with **6** was conducted at a higher temperature in ethanol (reflux), using excess (2 equivalents) of piperidine. Condensation of **4b** with **5** proved to be unexpectedly difficult, suggesting that **5** was less reactive than 3,4-alkyl-substituted pyrrolinones in the same reaction. Although a literature report [8] that various salicylaldehydes condense in high yields with **6** in aqueous sodium hydroxide at reflux, reaction of **4b** or **4a** with **5** in the same type of condensation conditions afforded only a 6% yield of **1b** after treatment with diazomethane. Numerous combinations of bases (1,8-diazabicyclo[5.4.0]undec-7-ene, diethyl amine, piperidine) and solvents (*t*-butanol, 1,2-dimethoxyethane, dimethylsulfoxide, acetonitrile), with or without *t*-Boc protection on the nitrogen of **4b** or **5** were ineffective, affording only low yields of **1b** or inducing decomposition. The best yields (21-32%) of **1b** were obtained by carrying out the condensation of **4b** and **5** in dry, deoxygenated dimethylformamide with 2.5 equivalents of piperidine at 85-90 °C for 48 hours.

The constitutional structures of **1b** and **2b** follow from the structures of the reactants and the reaction mechanism, and they are confirmed by their carbon-13 nmr spectral assignments, assisted by HMQC and HMBC 2D experiments. Switching the orientation of the lactam (–NH–C=O) moiety in going from **1** to **2** strongly affects most of the carbon-13 nmr chemical shifts. Only a few remain constant: lactam C=O, 7′–CH_3, 10–CH_3, 8^1–CH_2, 8^2–CH_2, 8^3 C=O and OCH_3. All benzo ring carbons of **1b** are more deshielded than their counterparts in **2b**, except C(2), which is ~10 ppm more shielded. In contrast, the pyrrole ring carbons and C(5) are generally more shielded in **1b** than the corresponding carbons in **2b**.

Distinctions also appear in comparing the H-nmr spectra of **1b** and **2b**: the methine hydrogen at C(5) is ~0.8 ppm more shielded in **1b** than in **2b**, and the aromatic ring hydrogens of **1b** are all more deshielded than in **2b**. The pyrrole and lactam NHs of **1b** appear in the typical places for dipyrrinones that form hydrogen-bonded dimers in deuteriochloroform. However, in **2b**, the pyrrole NH is very

Scheme 1 [a]



[a] Reagents and conditions: i, piperidine in *N,N*-dimethylformamide at 90 °C; ii, aqueous sodium hydroxide in methanol; iii, piperidine in methanol at 65 °C, or in ethanol at 78 °C.

strongly deshielded, which suggests a strong intramolecular hydrogen bond (to the nearby lactam carbonyl).

The *syn*-*Z* configuration in both **1b** and **2b** is revealed by nuclear Overhauser effect (nOe) nmr measurements (Figure 2). Thus, the strong nOe seen between the C(5) methine and the *ortho′* ring hydrogen confirms a *Z* configuration in both **1b** and in **2b**. In the former, the nOe seen between the pyrrole and lactam NHs is also consistent with the *Z*. A *syn* orientation is confirmed by nOe's observed between the C(5) methine and the C(7′)-methyl in both **1b** and **2b**. The likelihood that **1b** is actually present as an intermolecularly hydrogen-bonded dimer is suggested by the weak nOe seen between the C(10)-methyl and the *ortho* hydrogen, consistent with studies of other dipyrrinones [9].

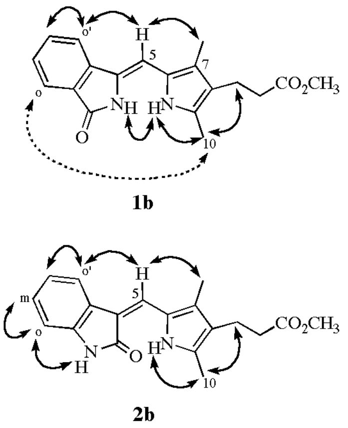


Figure 2. Nuclear Overhauser effect enhancements observed for **1b** and **2b** in deuteriochloroform solvent are shown by double headed curved arrows. A weak nOe is denoted by the dotted arrow.

Table 1

Nmr Spectral Assignments for Dipyrrinone **1b** and Its Isomer **2b** in Deuteriochloroform at 25 °C

Assignment	**1b** (δ, ppm)		**2b** (δ, ppm)	
	^{13}C	^1H	^{13}C	^1H
lactam CO	170.39		170.02	
2	126.94		137.13	
3	139.28		126.53	
4	123.84		111.92	
5	99.14	6.55	123.37	7.39
6	122.08		126.34	
7	122.89		130.02	
$7'$–CH_3	9.61	2.19	9.74	2.28
8	119.02		121.72	
9	130.95		134.75	
10–CH_3	11.68	2.52	12.22	2.36
o	123.05	7.76	109.28	6.89
o'	118.96	7.79	117.21	7.47
m	126.83	7.39	125.41	7.12
m'	131.60	7.57	121.38	7.04
8^1–CH_2	19.89	2.77	19.84	2.78
8^2–CH_2	35.13	2.49	34.78	2.48
8^3–CO	173.75		173.46	
OCH_3	51.57	3.70	51.60	3.68
pyrrole NH		10.25		13.19
lactam NH		11.82		8.35

A concentration-dependence of the NH H-nmr chemical shifts in **1b** and **2b** (Table 2) further suggests the presence of a monomer-dimer equilibrium in deuteriochloroform solvent. In **1b**, both the lactam and pyrrole chemical shifts drift upfield with increasing dilution, as has been seen previously with **3b** [9a]. In **2b**, only the lactam NH moves upfield with increasing dilution; the pyrrole NH remains at a nearly constant chemical shift. These observations are consistent with a tightly intramolecularly hydrogen bonded pyrrole NH and a lactam to lactam type intermolecularly hydrogen-bonded dimer. The observation that the lactam chemical shift levels out at approximately 10^{-3} *M* concentration indicates that the dimer association constant in **2b** is much less than that of **1b** (Figure 3).

Table 2

Concentration Dependence of Lactam and Pyrrole NH Chemical Shifts of **1b** and **2b** in Deuteriochloroform Solvent at 25 °C

	1b			**2b**	
Concentration (moles/liter)	Lactam NH δ (ppm)	Pyrrole NH δ (ppm)	Concentration (moles/liter)	Lactam NH δ (ppm)	Pyrrole NH δ (ppm)
4.84×10^{-2}	11.832	10.251	3.78×10^{-2}	8.913	13.211
2.75×10^{-2}	11.785	10.245	2.28×10^{-2}	8.352	13.190
1.04×10^{-2}	11.795	10.240	1.02×10^{-2}	7.699	13.158
1.04×10^{-3}	11.495	10.059	1.02×10^{-3}	7.508	13.148
1.04×10^{-4}	10.686	9.535	1.02×10^{-4}	7.484	13.148
1.04×10^{-5}	9.75 – 8.68		1.02×10^{-5}	7.482	13.149

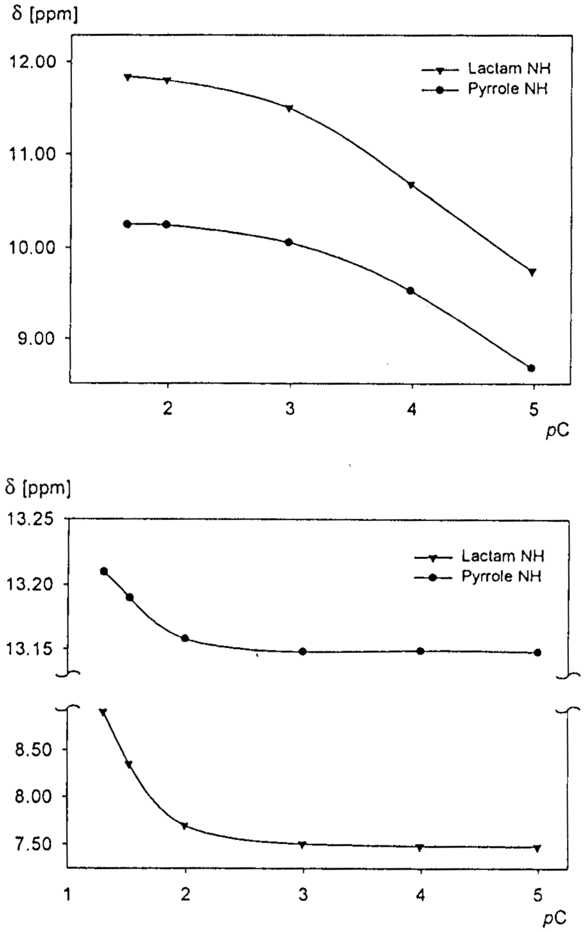


Figure 3. Concentration dependence of NH chemical shifts of dipyrrinone **1b** (upper) and its regioisomer **2b** (lower) in $CDCl_3$ solution at 25 °C (pC = $-\log_{10}$ concentration).

The colors of **1b** and **2b** differ, with the latter being more reddish. Thus, the long wavelength uv-visible absorption in **2b** is typically strongly red-shifted relative to that of **1b**, which is only slightly red-shifted relative to that of **3b** (Figure 4). The absorption intensitities are comparable, and quite similar uv-visible spectral differences are found for the corresponding carboxylic acids (**1a**, **2a** and **3a**).

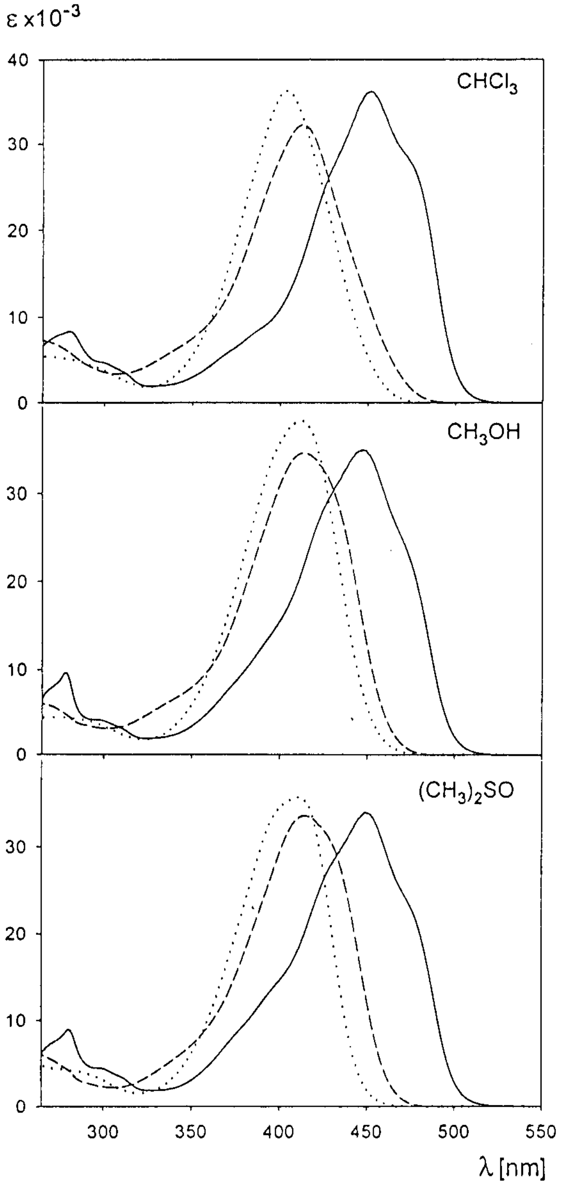


Figure 4. UV-vis spectra of dipyrrinone **1b** (- - - - -), **2b** (———) and **3b** (ÆÆÆÆÆ) in chloroform (upper), methanol (middle) and dimethyl sulfoxide (lower).

EXPERIMENTAL

Nuclear magnetic resonance (nmr) spectra were obtained on a Varian Unity Plus spectrometer operating at 500 MHz (proton) and 125 MHz (C-13) in dimethylsulfoxide-d_6 solvent, unless otherwise indicated. Chemical shifts are reported in ppm referenced to the residual dimethylsulfoxide-d_5 proton signal at 2.49 ppm and the C-13 signal at 39.5 ppm. Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected. Analytical thin layer chromatography was performed on J.T. Baker silica gel IB-F plates (125 µm layers). Radial chromatography used Merck silica gel PF_{254} with calcium sulfate binder. All solvents were reagent grade obtained from Fisher. *N*,*N*-Dimethylformamide and methanol were from Fisher; piperidine and 2-indolinone (**6**) were purchased from Acros. Deuterated chloroform and dimethylsulfoxide-d_6 were from Cambridge Isotope Laboratories. Oxisoindole (**5**) [7] and 3,5-dimethyl-4-(2-methoxycarbonylethyl)-1*H*-pyrrole-2-aldehyde [6] were prepared according to modified literature procedures.

3,5-Dimethyl-4-(2-methoxycarbonylethyl)-1*H*-pyrrole-2-aldehyde (**4b**).

To a solution of 5.62 g (20 mmoles) *tert*-butyl 3,5-dimethyl-4-(2-methoxycarbonylethyl)-1*H*-pyrrole-2-carboxylate [10] in 15 ml of anhydrous dichloromethane was added 40 ml of trifluoroacetic acid, and the mixture was stirred for 20 minutes while cooling with an ice bath. Then triethylorthoformate (11 ml, 100 mmoles) was added at 4 °C during 5 minutes and stirring was continued for 15 minutes more. The mixture was poured into 100 ml of water-ice and then diluted with a solution of 12.0 g of sodium hydroxide in 30 ml of water. The product was extracted into chloroform (3 x 100 ml). The combined extracts were washed with 5% aqueous sodium bicarbonate (2 x 50 ml), water (3 x 50 ml) and dried over anhydrous sodium sulfate. After filtration through a short pad of silica gel, the solvent was evaporated under vacuum, and the residue was recrystallized from hexane-dichloromethane to afford 3.65 g (87%) of aldehyde **4b**. It had mp 129-130 °C (lit [6a] 123-125 °C); ^{1}H nmr (deuteriochloroform): δ 2.26 (3H, s), 2.27 (3H, s), 2.45 (2H, t, *J* = 7.8 Hz), 2.71 (2H, t, *J* = 7.8 Hz), 3.66 (3H, s), 9.43 (1H, s), 10.29 (1H, br.s) ppm; ^{13}C nmr: δ 8.71, 11.5, 19.2, 34.6, 51.6, 120.9, 127.9, 132.4, 136.4, 173.3, 175.7 ppm.

3,5-Dimethyl-4-(2-carboxyethyl)-1*H*-pyrrole-2-aldehyde (**4a**).

A mixture of 1.05 g (5 mmoles) ester **4b**, 10 ml of methanol, 1.00 g (25 mmoles) of sodium hydroxide, and 3 ml of water was heated at gentle reflux for 3.5 hours under Ar. After cooling, the mixture was diluted with 10 ml of water, and the methanol solvent was evaporated under vacuum. The residue was cooled in an ice bath and slowly acidified with 10% aqueous hydrochloric acid to pH <4. The separated solid was collected by filtration, washed with cold water (3 x 20 ml) and dried overnight under vacuum (over P_2O_5) to afford 0.86 g (88%) of acid **4a**; mp 157-158 °C; ^{1}H nmr: δ 2.14 (3H, s), 2.19 (3H, s), 2.29 (2H, t, *J* = 7.6 Hz), 2.55 (2H, t, *J* = 7.6 Hz), 9.40 (1H, s), 11.39 (1H, br.s), 12.04 (1H, s) ppm; ^{13}C nmr: δ 8.52, 11.0, 18.9, 34.5, 120.4, 127.5, 130.7, 135.3, 174.0, 175.5 ppm.

(*Z*)-[(3,5-Dimethyl-4-(2-methoxycarbonylethyl)-1*H*-pyrrol-2-yl)-methylidenyl]-isoindolinone (**1b**).

A mixture of 627 mg (3.00 mmoles) of aldehyde **4b**, 532 mg (4.00 mmoles) of oxisoindole **5** [7], 4 ml of anhydrous *N*,*N*-dimethylformamide, and 1.0 ml (10.0 mmoles) of piperidine was purged with Ar for 15 minutes, then sealed in a thick wall glass tube and heated at 85-90 °C for 48 h. After cooling, the mixture was diluted with 100 ml of chloroform and washed with 5% aqueous hydrochloric acid (100 ml) and water (3 x 100 ml). After drying over anhydrous sodium sulfate, filtration and removal of the solvent under vacuum, the residue was purified by radial chromatography (eluent 2.5-3.5% vol/vol methanol in dichloromethane). The pure fractions, after evaporation, were recrystallized from dichloromethane-methanol to afford 309 mg (32%) of bright yellow **1b**; mp 248-249 °C; ^{1}H nmr: δ 2.09 (3H, s), 2.19 (3H, s), 2.39 (2H, t, *J* = 7.6 Hz), 2.60 (2H, t, *J* = 7.6 Hz), 3.57 (3H, s), 6.51 (1H, s), 7.40 (1H, dd, ^3J = 7.5; 7.6 Hz), 7.59 (1H, dd, ^3J = 7.5; 7.6 Hz), 7.68 (1H, d, ^3J = 7.6 Hz), 8.03 (1H, d, ^3J = 7.6 Hz), 10.39 (1H, s), 10.52 (1H, s) ppm; ^{13}C nmr: δ 9.21, 10.9, 19.4, 34.6, 51.2, 96.5, 118.3, 119.6, 121.5, 121.9, 122.5, 123.1, 126.9, 127.1, 129.2, 131.5, 139.0, 168.0, 172.9 ppm; uv-visible (carbon tetrachloride): λ sh 450, ε, 20600; λ_{max} 420, ε, 38200; λ sh 400, ε, 26600; (N-methylformamide): λ_{max} 415, ε, 33200.

Anal. Calcd for $C_{19}H_{20}N_2O_3$ (324.4): C, 70.35; H, 6.22; N, 8.64. Found: C, 70.44; H, 6.34; N, 8.60.

(*Z*)-[(3,5-Dimethyl-4-(2-carboxyethyl)-1*H*-pyrrol-2-yl)-methylidenyl]-isoindolinone (**1a**).

A mixture of 162 mg (0.50 mmoles) of methyl ester **1b**, 20 ml of dichloromethane, 7 ml of methanol and 5 ml of 1 *M* aqueous sodium hydroxide (5.00 mmoles) was heated at reflux, and the dichloromethane was removed completely by distillation. The homogeneous residue was heated at reflux for 3 hours. After cooling, water (10 ml) was added, and the methanol solvent was evaporated under vacuum. The residue was cooled in an ice bath and acidified with 10% aqueous hydrochloric acid to pH <4. The precipitated product was collected by filtration, washed with water (3 x 5 ml) and dried under vacuum for 24 hours (P_2O_5) to afford 146 mg (94%) of acid **1a**; mp 303-305 °C (dec.); ^{1}H nmr: δ 2.10 (3H, s), 2.20 (3H, s), 2.29 (2H, t, *J* = 7.7 Hz), 2.57 (2H, t, *J* = 7.7 Hz), 6.52 (1H, s), 7.40 (1H, dd, ^3J = 7.6; 7.4 Hz), 7.59 (1H, dd, ^3J = 7.8; 7.4 Hz); 7.68 (1H, d, ^3J = 7.6 Hz), 8.03 (1H, d, ^3J = 7.8 Hz), 10.38 (1H, s), 10.52 (1H, s), 12.01 (1H, br.s) ppm; ^{13}C nmr: δ 9.27, 11.0, 19.5, 35.0, 96.6, 118.7, 119.6, 121.4, 122.0, 122.5, 123.0, 126.9, 127.1, 129.2, 131.5, 139.0, 168.0, 174.1 ppm; uv-visible (dichloromethane): λ_{max} 413, ε, 33100; (N-methylformamide): λ_{max} 419, ε, 32700.

(*Z*)-3-[(3,5-Dimethyl-4-(2-methoxycarbonylethyl)-1*H*-pyrrol-2-yl)-methylidenyl]-indolin-2-one (**2b**).

A mixture of 460 mg (2.2 mmoles) of aldehyde **4b**, 266 mg (2.0 mmoles) of indolin-2-one (**6**), 0.1 ml (1.0 mmole) of piperidine, and 20 ml of anhydrous methanol was heated at reflux for 8 hours. After cooling, the mixture was chilled at -20 °C overnight. The separated product was collected by filtration and washed with cold methanol. Purification by radial chromatography (eluent 2.0-3.5% v/v methanol in dichloromethane) and recrystallization from dichloromethane-methanol afforded 513 mg (79%) of deep orange **2b**; mp 216-217 °C; ^{1}H nmr: δ 2.24 (3H, s), 2.27 (3H, s), 2.44 (2H, t, *J* = 7.6 Hz), 2.66 (2H, t, *J* = 7.6 Hz), 3.57 (3H, s), 6.85 (1H, d, ^3J = 7.6 Hz), 6.95 (1H, dd, ^3J = 7.6, 7.6 Hz), 7.07 (1H, dd, ^3J = 7.6, 7.6 Hz), 7.54 (1H, s), 7.69 (1H, d, ^3J = 7.6 Hz), 10.73 (1H, s), 13.39 (1H, s) ppm; ^{13}C nmr: δ 9.35, 11.8, 19.4, 34.2, 51.2, 109.2, 112.4, 117.9, 120.7, 121.5, 123.2, 125.5, 125.7, 125.9, 129.5, 133.8, 138.0, 169.3, 172.8 ppm; uv-visible (carbon tetrachloride): λ sh 476, ε, 26400; λ_{max} 451, ε, 36200; λ sh 428, ε, 26700; λ_{max} 278, ε, 8300; (N-methylformamide): λ sh 476, ε, 22200; λ_{max} 449, ε, 34100; λ sh 430, ε, 28400; λ_{max} 280, ε, 8900.

Anal. Calcd for $C_{19}H_{20}N_2O_3$ (324.4): C, 70.35; H, 6.22; N, 8.64. Found: C, 70.49; H, 6.26; N, 8.64.

(*Z*)-3-[(3,5-Dimethyl-4-(2-carboxyethyl)-1*H*-pyrrol-2-yl)-methylidenyl]-indolin-2-one (**2a**).

A mixture of 390 mg (2.0 mmoles) of aldehyde **4a**, 253 mg (1.9 mmoles) of indolin-2-one (**6**), 0.4 ml (4 mmoles) of piperidine, and 10 ml of anhydrous ethanol was heated at gentle reflux for 15 hours. After cooling, acetic acid (1 ml) was added slowly followed by 0.2 ml of 10% aqueous HCl, and the mixture was chilled at -20 °C for 6 hours. The separated product was collected by filtration, washed with cold ethanol-water (9:1 v/v) and dried overnight under vacuum (over P_2O_5) to afford 515 mg (87%) of bright orange **2a**; mp 265-267°C; ^{1}H nmr: δ 2.25 (3H, s), 2.28 (3H, s), 2.34 (2H, t, J = 7.7 Hz), 2.63 (2H, t, J = 7.7 Hz), 6.85 (1H, br.d, ^3J = 7.6 Hz), 6.95 (1H, ddd, ^3J = 7.6, 7.6 Hz, ^4J = 1.0 Hz), 7.07 (1H, ddd, ^3J = 7.6, 7.6 Hz, ^4J = 1.0 Hz), 7.54 (1H, s), 7.69 (1H, br.d, ^3J = 7.6 Hz), 10.72 (1H, s), 12.05 (1H, br.s), 13.38 (1H, s) ppm; ^{13}C nmr: δ 9.40, 11.9, 19.5, 34.6, 109.2, 112.3, 117.9, 120.7, 121.9, 123.2, 125.5, 125.7, 126.0, 129.6, 133.8, 137.9, 169.3, 173.9 ppm; uv-visible (dichloromethane): λ sh 473, ε, 26200; λ_{max} 451, ε, 35400; λ sh 430, ε, 28000; λ_{max} 281, ε, 8500; (N-methylformamide): λ sh 475, ε, 26100; λ_{max} 452, ε, 34900; λ sh 431, ε, 27300; λ_{max} 281, ε, 8900.

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