Stefan E. Boiadjiev and David A. Lightner*

Department of Chemistry, University of Nevada
Reno, NV 89557-0020
Received June 18, 2004

Bright yellow N,N′-carbonyl-bridged dipyrrinones (substituted 3*H*,5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*]pyrimidine-3,5-diones) were synthesized by reaction of the parent dipyrrinone with carbonyldiimidazole. Their solutions in organic solvents fluoresced strongly, with fluorescent quantum yields (ϕ_F) 0.32-0.92.

J. Heterocyclic Chem., **41**, 1033 (2004).

Dipyrrinones (Figure 1A) typically exhibit only weak fluorescence at room temperature, with fluorescence quantum yields (ϕ_F) of the order of 0.001 at room temperature [1]. The dipyrrinone excited state relaxes to a new ground state by rapid $Z \longrightarrow E$ double bond isomerization (Figure 1A), but when this relaxation mode is inhibited by bridging the lactam and pyrrole nitrogens, strong fluorescence is observed [2-4]. One of the easiest bridges to build is the carbonyl, in a reaction discovered recently [5] to give 3*H*,5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*]pyrimidine-3,5-diones (Figures 1B and C) in high yield from the parent dipyrrinone by reaction with 1,1′-carbonyldiimidazole (CDI) in the presence of a non-nucleophilic amine base, *e.g*., 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Thus, xanthoglow (Figure 1C) is a highly-fluorescent, bridged dipyrrinone analog of the linear tetrapyrrole of jaundice, bilirubin [6], *e.g*., xanthoglow methyl ester was found to exhibit $\phi_F = 0.80$ in cyclohexane [7]. In the following, we describe the syntheses and fluorescence properties of nine new "xanthoglow" derivatives (Figure 1E), with various substituents at C(8) of the dipyrrinone.

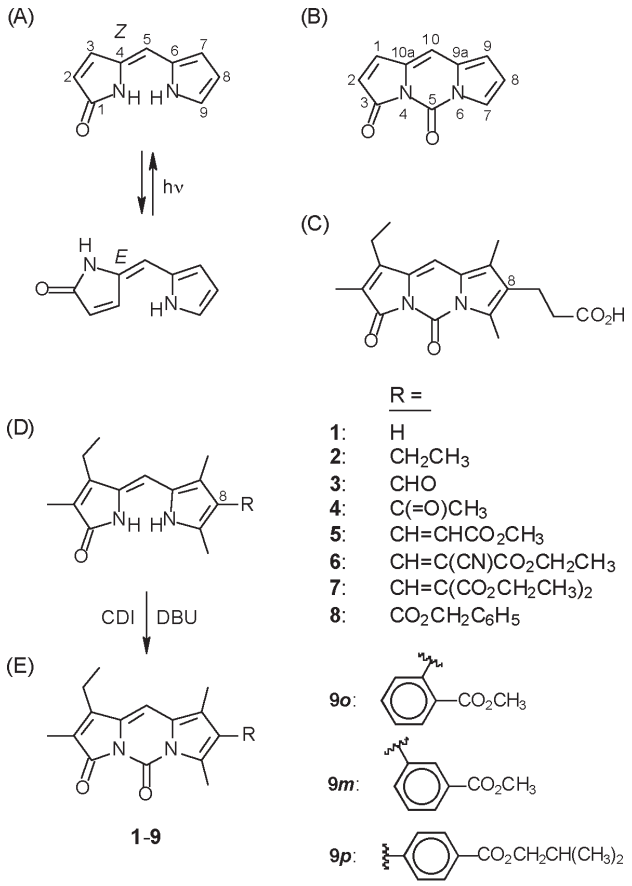
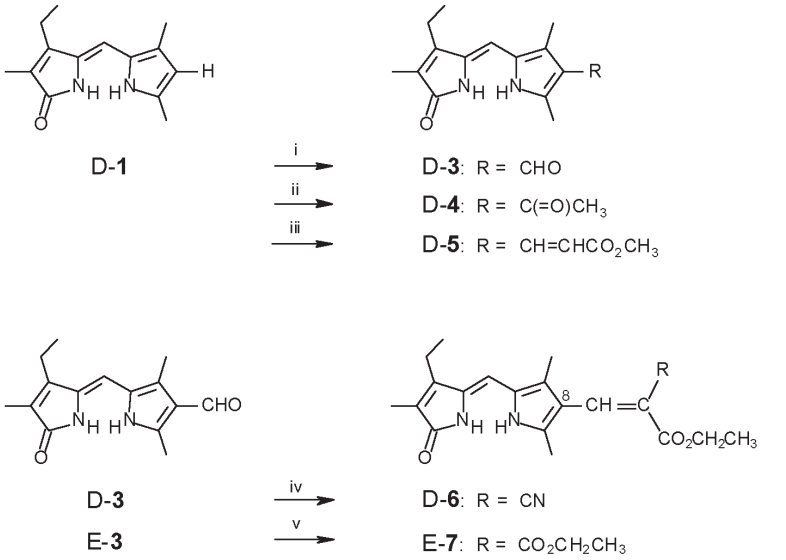


Figure 1. (A) $Z \rightarrow E$ Dipyrrinone photoisomerization. (B) The parent N,N'-carbonyldipyrrinone chromophore, 3*H*,5*H*-dipyrrolo[1,2-*c*:2',1'-*f*]-pyrimidine-3,5-dione. (C) Xanthoglow. (D) The dipyrrinone precursors to (E). (E) The xanthoglow target analogs (**1**-**9**) of this work. The latter are prepared from the former in high yield simply by reaction with carbonyldiimidazole (CDI) in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU).

All of the N,N′-carbonyl-bridged dipyrrinones of this work were prepared simply and directly from the parent dipyrrinones (Figure 1D $\longrightarrow$ E) by reaction with 5 equivalents of CDI in refluxing dichloromethane for 16-18 hours in the presence of 5 equivalents of DBU. The product yields were invariably good to excellent (Table 1), and the products were much more soluble in organic solvents than the starting dipyrrinones, some of which (Figure 1D **1**, **2**, **9**) were available from previous studies [8-10]. The others (Figure 1D **3**-**7**) were prepared starting from the 8-H dipyrrinone (Figure 1D **1**) as outlined in Scheme 1. (Reactions designed to convert the N,N′-carbonyl-bridged 8-H dipyrrinone (Figure 1E **1**) directly into the substituted analogs **3** and **4** by ethyl orthoformate – trifluoroacetic acid (TFA) formylation and Friedel-Crafts acylation reactions, respectively, failed.) Dipyrrinone D-**3** served as the precursor to dipyrrinone D-**6**, but the N,N′-carbonyl-bridged products proved to exhibit very different stabilities under the reaction conditions. Whereas the acrylate ester (E-**5**) was stable and isolated in high yield, the cyano ester (**6**) was rather unstable and isolated in only 40% yield after carefully adjusting the reaction conditions by increasing the CDI to ten equivalents and decreasing the DBU to three equivalents and terminating the reaction after only 3 hours – or as soon as the starting dipyrrinone had disappeared. Difficulties were also encountered in the synthesis of D-**7** from D-**3**. Thus, treatment of dipyrrinone D-**3** with diethyl malonate under Knoevenagel conditions in the presence of piperidine gave only a modest yield of dipyrrinone D-**7**, of 85% purity. Insertion of the carbonyl bridge afforded yellow crystalline product E-**7**

Scheme 1 [a]



[a] Reagents and conditions: i, $HC(OCH_2CH_3)_3$, TFA; ii, $(CH_3CO)_2O$, $SnCl_4$; iii, $(CH_3O)_2CHCH_2CO_2CH_3$, TFA; iv, $CH_2(CN)CO_2CH_2CH_3$, piperidine; v, $CH_2(CO_2CH_2CH_3)_2$, piperidine.

Table 1

N,N'-Carbonyl-bridged dipyrrinones **1**-**9**, precursors, yields and spectral data.

Product	Yield	UV-visible [a]	Infrared	^{1}H-NMR [b]	^{13}C-NMR [b]	Combustion [c]	%C	%H	%N
1 [5]	95	421 (18,300)	1761, 1680,	1.20, 1.94, 2.13,	8.4, 10.6, 13.8, 15.6, 17.9, 97.2, 117.2,	E-T:	70.29	6.29	10.93
		270 (10,500)	1636, 1610, 1521	2.52, 2.65, 5.99,	120.9, 126.2, 126.8, 130.4, 135.0,	E-F:	70.11	6.07	11.01
				6.38	143.4, 146.5, 167.7				
2 [5]	94	433 (18,100)	1760, 1683,	1.05, 1.19, 1.93, 2.10,	8.4, 8.9, 12.7, 13.8, 14.7, 17.1, 17.9,	E-T:	71.81	7.09	9.85
		278 (10,700)	1639, 1612, 1538	2.39, 2.51, 2.62,	97.0, 120.7, 125.9, 126.1, 129.5,	E-F:	72.00	7.03	9.80
				6.37	130.1, 130.7, 143.4, 146.4, 167.8				
3	66	411 (18,500)	1771, 1695,	1.23, 1.99, 2.39, 2.57,	8.5, 10.0, 13.0, 13.7, 18.0, 96.5, 120.2,	E-T:	67.59	5.67	9.85
		395 (18,800)	1668, 1615,	3.01, 6.45, 10.17	125.2, 127.4, 127.7, 131.9, 143.1,	E-F:	67.60	5.83	9.92
		249 (27,700)	1586, 1530		143.7, 146.9, 167.2, 186.5	D-T:	69.74	7.02	10.85
						D-F:	69.55	6.72	10.83
4	92	405 (18,900)	1774, 1762,	1.23, 1.97, 2.31, 2.50,	8.5, 11.3, 13.7, 14.7, 18.0, 31.9, 96.6,	E-T:	68.44	6.08	9.39
		264 (19,000)	1685, 1662,	2.56, 2.96, 6.44	119.6, 127.0, 127.3, 128.6, 131.5,	E-F:	68.11	6.03	9.38
			1620, 1577		138.8, 143.3, 146.7, 167.3, 196.9	D-T:	70.56	7.40	10.29
						D-F:	70.32	7.55	10.37
5	89	417 (20,100)	1770, 1755,	1.22, 1.95, 2.28, 2.54,	8.5, 11.1, 13.4, 13.7, 18.0, 51.6, 96.3,	E-T:	67.04	5.92	8.23
		288 (28,700)	1716, 1690,	2.80, 3.80, 6.21, 6.41,	118.1, 119.3, 122.6, 127.2, 127.4,	E-F:	66.82	5.94	8.10
			1634, 1557	7.68	131.4, 135.9, 136.8, 143.0, 146.6,	D-T:	68.77	7.06	8.91
					167.3, 167.7	D-F:	68.35	7.20	8.59
6	40	409 (24,300)	1769, 1724,	1.23, 1.40, 1.98, 2.25,	8.5, 10.6, 13.7, 14.1, 15.8, 18.0, 62.7,	E-T:	66.48	5.58	11.08
		308 (20,900)	1711, 1605, 1595	2.57, 2.79, 4.38, 6.43,	96.3, 107.2, 115.1, 119.4, 122.0,	E-F:	66.30	5.29	11.07
				8.25	127.7, 127.9, 131.9, 137.2, 142.8,	D-T:	67.97	6.56	11.89
					146.8, 148.8, 162.1, 167.2	D-F:	67.78	6.61	11.60
7	60	414 (21,800)	1713, 1689,	1.16, 1.29, 1.33, 1.90,	8.5, 10.5, 13.0, 14.0, 14.2, 14.9, 17.9,	E-T:	64.77	6.15	6.57
		282 (17,400)	1656, 1609, 1579	2.12. 2.41, 2.51, 4.28,	61.1, 61.2, 100.3, 116.5, 122.3, 123.5,	E-F:	64.63	6.12	6.74
				4.30, 6.07, 7.76, 10.72,	124.0, 125.2, 128.6, 136.9, 138.9,				
				11.23	148.7, 165.5, 167.1, 174.3				
8	93	404 (19,200)	1774, 1701,	1.21, 1.95, 2.30, 2.54,	8.5, 11.1, 13.7, 14.4, 17.9, 66.2, 96.7,	E-T:	70.75	5.68	7.18
		255 (20,100)	1639, 1584	3.02, 5.31, 6.42, 7.33,	118.6, 121.3, 126.7, 127.2, 128.2,	E-F:	70.89	5.79	7.11
				7.38, 7.43	128.3, 128.6, 131.3, 135.9, 141.3,	D-T:	72.50	6.64	7.69
					143.1, 146.7, 164.6, 167.3	D-F:	72.56	6.65	7.69

Table 1 (continued)

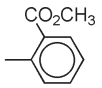
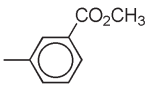
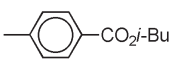
N,N'-Carbonyl-bridged dipyrrinones **1**-**9**, precursors, yields and spectral data.

Product	Yield	UV-visible [a]	Infrared	^{1}H-NMR [b]	^{13}C-NMR [b]	Combustion [c]	%C	%H	%N
9*o* [10]	85	428 (20,100) 280 (12,900)	1763, 1724, 1685, 1638, 1613, 1545	1.23, 1.94, 1.97, 2.48, 2.55, 3.73, 6.45, 7.20, 7.44, 7.56, 7.98	8.4, 9.5, 13.6, 13.8, 17.9, 52.1, 97.4, 120.9, 125.9, 126.3, 127.7, 129.5, 130.3, 130.6, 131.4, 131.5, 131.8, 132.2, 134.5, 143.5, 146.5, 167.4, 167.7	E-T: E-F:	70.75 70.61	5.68 5.59	7.18 7.15
9*m* [10]	92	425 (19,900) 282 (14,400)	1765, 1722, 1689, 1639, 1611	1.24, 1.99, 2.09, 2.57, 2.65, 3.94, 6.46, 7.43, 7.52, 7.93, 8.03	8.5, 9.7, 13.7, 13.8, 18.0, 52.2, 97.0, 119.9, 126.5, 126.6, 128.3, 128.5, 129.1, 130.4, 130.9, 131.1, 131.9, 134.0, 134.5, 143.4, 146.6, 166.9, 167.7	E-T: E-F:	70.75 70.86	5.68 5.43	7.18 7.19
9*p* [10]	87	425 (20,700) 289 (16,500)	1766, 1715, 1611, 1500,	1.04, 1.24, 1.99, 2.09, 2.10, 2.57, 2.67, 4.13, 6.46, 7.32, 8.11	8.5, 9.7, 13.7, 13.8, 18.0, 19.2, 27.9, 71.1, 96.9, 119.7, 126.6, 126.7, 129.1, 129.2, 129.6, 130.0, 130.9, 131.9, 138.4, 143.4, 146.6, 166.4, 167.6	E-T: E-F:	72.20 72.31	6.53 6.89	6.48 6.57

[a] In chloroform, concentration ~5 x 10^{-5} M; [b] In deuteriochloroform; [c] Combustion analyses: Theoretical (T); Found (F) for the pigments of Figure 1D (D-T, D-F) and Figure 1E (E-T, E-F). Where D-F and D-T values are absent, the dipyrrinones have appeared previously in the literature.

Table 2

Fluorescence quantum yields (ϕ_F) and wavelength (nm) of excitation and emission maximum of the N,N′-carbonyl-bridged dipyrrinones **1**-**9** [a].

			Solvent				
			Cyclohexane	Benzene	Chloroform	Methanol	Dimethyl-sulfoxide
1	H	ϕ_F	0.85	0.76	0.68	0.35	0.69
		λ_{em}	456	479	491	521	500
		λ_{exc}	407	414	421	421	421
2	CH_2CH_3	ϕ_F	0.80	0.71	0.62	0.32	0.63
		λ_{em}	475	489	502	533	509
		λ_{exc}	414	421	421	421	421
3	CHO	ϕ_F	0.68	0.78	0.76	0.52	0.80
		λ_{em}	449	457	459	500	482
		λ_{exc}	413	399	399	399	399
4	$C(=O)CH_3$	ϕ_F	0.79	0.79	0.74	0.45	0.73
		λ_{em}	454	459	476	507	489
		λ_{exc}	398	399	414	411	413
5	$CH=CHCO_2CH_3$	ϕ_F	0.68	0.66	0.63	0.44	0.62
		λ_{em}	461	482	491	525	504
		λ_{exc}	405	411	411	412	412
6	$CH=C(CN)CO_2CH_2CH_3$	ϕ_F	0.10	0.08	0.02	2.6 x 10^{-3}	1.8 x 10^{-3}
		λ_{em}	472	521	536	514	493
		λ_{exc}	400	413	412	412	413
7	$CH=C(CO_2CH_2CH_3)_2$	ϕ_F	0.02	0.02	0.03	0.04	7.8 x 10^{-3}
		λ_{em}	453	481	489	518	497
		λ_{exc}	403	421	415	414	415
8	$CO_2CH_2C_6H_5$	ϕ_F	0.92	0.87	0.82	0.51	0.79
		λ_{em}	455	459	476	504	485
		λ_{exc}	395	396	410	407	409
9*o*		ϕ_F	0.75	0.71	0.61	0.34	0.65
		λ_{em}	478	487	502	532	505
		λ_{exc}	414	421	421	421	421
9*m*		ϕ_F	0.83	0.75	0.67	0.39	0.67
		λ_{em}	458	482	494	526	504
		λ_{exc}	411	421	421	421	421
9*p*		ϕ_F	0.78	0.76	0.66	0.38	0.66
		λ_{em}	456	481	493	524	503
		λ_{exc}	410	421	421	421	421

[a] Concentrations 2.4-3.0 x 10^{-6} *M*.

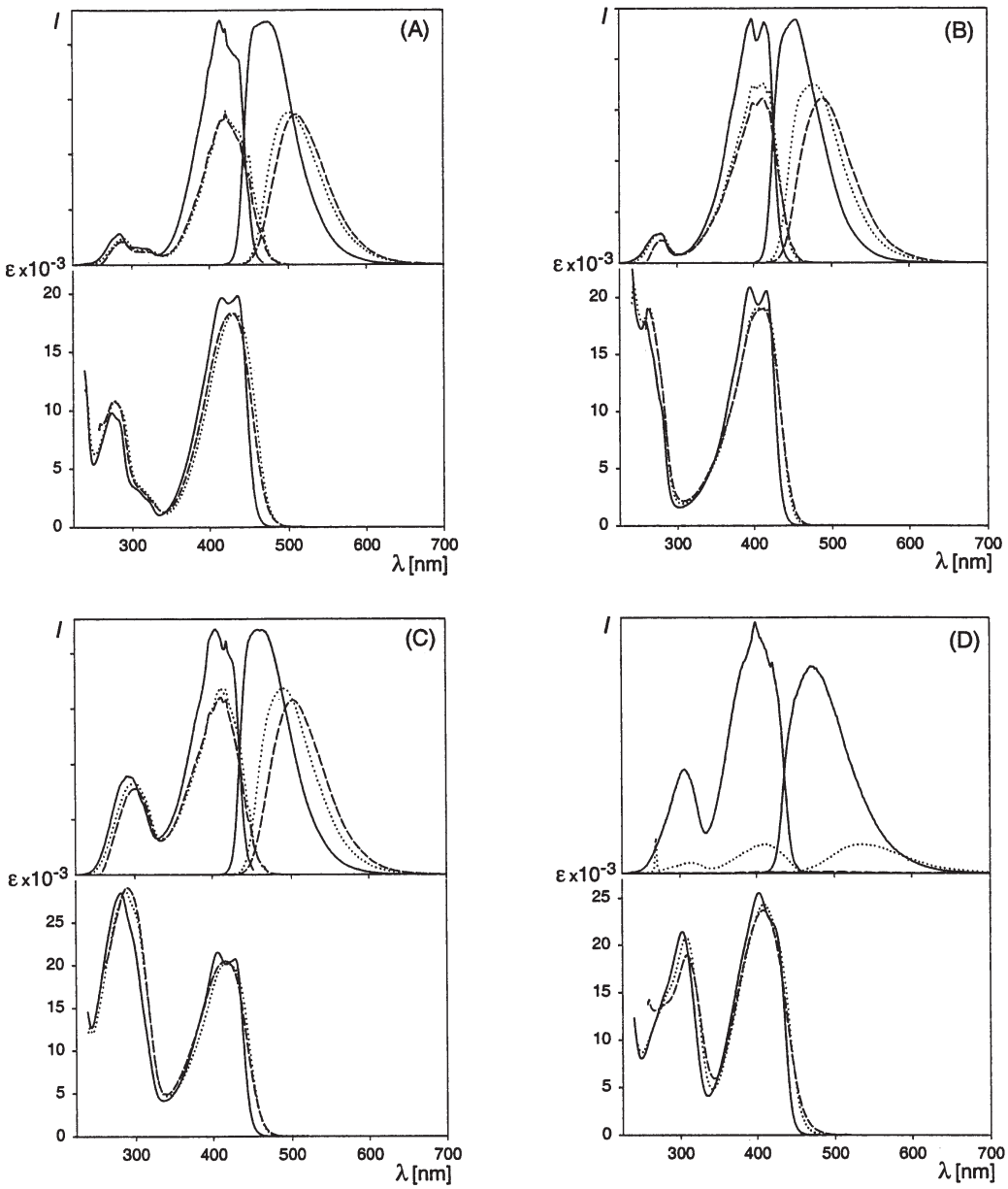


Figure 2. Fluorescence excitation and emission spectra (upper panels) and ultraviolet-visible spectra (lower panels) of N,N′-carbonyl-bridged dipyrrinones **2** (A), **4** (B), **5** (C) and **6** (D) in cyclohexane (——), $CHCl_3$ (···) and $(CH_3)_2SO$ (– – –) at 20 °C. Fluorescence spectra were run at ~3 x 10^{-6} *M* concentration; ultraviolet-visible spectra at ~5 x 10^{-5} *M*.

containing ~15% of the mono-ethyl ester analog, E-**5**. A successful synthesis of E-**7** was achieved from E-**3**, the cyclized aldehyde, by reaction with diethylmalonate in the presence of piperidine.

The structures of the N,N′-carbonyl-bridged dipyrrinones (E-**1**-**9**) follow from the structures of the dipyrrinone precursors and were confirmed by 2D nmr spectroscopic analysis (Table 1), and in one case (E-**9*o***), the structure was confirmed by X-ray crystallography [11]. Compounds E-**1**-**5**, **8** and **9** all exhibit strong fluorescence from excitation of the long wavelength absorption band in both nonpolar (cyclohexane, benzene) and polar ($(CH_3)_2SO$) solvents, whereas the fluorescence of E-**6** is very weak. Whether the weak fluorescence of E-**6** is due to the presence of the cyano (replacing the acrylic ester α-H) was unclear, until we examined the malonylidene analog, E-**7**, which also showed a very weak fluorescence. Apparently, it is the presence of a second ester (or cyano) group on the vinyl group at C(8) that causes the fluorescence quenching, but the exact mechanism is unclear.

The fluorescence quantum yields of E-**1**-**9** are summarized in Table 2.

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 deuteriochloroform and hexadeuteriodimethyl-sulfoxide solvents. Chemical shifts are reported in ppm referenced to the residual chloroform proton signal at 7.26 ppm and C-13 signal at 77.00 ppm unless otherwise noted. Infrared spectra were recorded on a Perkin-Elmer FT-IR Spectrum 2000 spectrophotometer. Gas-chromatography-mass spectrometry analyses were carried out on a Hewlett-Packard Model 5890A capillary gas chromatograph (30 m DB-1 column) equipped with Hewlett-Packard 5970 mass selective detector. Combustion analyses were carried out by Desert Analytics, Tucson, AZ and gave results reported in Table 1. All ultraviolet-visible and fluorescence spectra were recorded on a Perkin-Elmer Lambda-12 spectrophotometer and on a Jobin Yvon Fluorolog 3 model FL3-22 fluorimeter, respectively, in 1 cm quartz cells at 20 °C. Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected. Analytical thin layer chromatography (tlc) was carried out on J.T. Baker silica gel IB-F plates (125 μm layer). Preparative chromatographic separations were achieved by radial chromatography on 2 or 4 mm thick rotors using Merck silica gel PF_{254} with $CaSO_4$ binder. All solvents were reagent grade obtained from Fisher or Aldrich. 1,1′-Carbonyldiimidazole (CDI) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were obtained from Acros and deuterated chloroform and dimethylsulfoxide were from Cambridge Isotope Laboratories. The spectral data were obtained in spectral grade solvents, and hplc grade solvents were dried and purified according to standard procedures [12]. Dipyrrinones D-**1** [8], D-**2** [9] and D-**9*o***, **9*m***, **9*p*** [10] were available in our lab from previous studies.

General Method of Synthesis of E-**1**-**9**.

A mixture of 1 mmol of dipyrrinone, 0.81 g (5 mmoles) of 1,1′-carbonyldiimidazole (CDI), 0.75 mL (5 mmoles) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 80 mL of anhydrous methylene chloride was heated under nitrogen at reflux for 16 hours. (In a few cases we modified the procedure: for E-**3**, – 1 hour at reflux using 5 equivalents of CDI and 2 equivalents of DBU, and for E-**6** and **7** – 3 hours at reflux using 10 equivalents of CDI and 3 equivalents of DBU.) After cooling, the mixture was washed with 100 mL of 1% aqueous hydrochloric acid, then with water (3 x 100 mL), and the solution was dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent under vacuum, the residue was purified by radial chromatography on silica gel. The fractions containing a nonpolar fluorescent band were combined, the solvent was evaporated under vacuum and the residue was recrystallized from ethyl acetate or ethyl acetate-hexane (added during cooling) to afford pure bright yellow tricyclic compounds.

Acknowledgments.

We thank the U.S. National Institutes of Health (HD 17779) for generous support of this work. S.E. Boiadjiev is on leave from the Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia.

REFERENCES AND NOTES

[1] H. Falk, The Chemistry of Linear Oligopyrroles and Bile Pigments, Springer Verlag, Vienna, 1989.

[2] J. J. G. S. van Es, J. H. Koek, C. Erkelens and J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas*, **105**, 360 (1986).

[3] J. S. Ma and D. A. Lightner, *Tetrahedron*, **47**, 3719 (1991).

[4] K. O. Hwang and D. A. Lightner, *Tetrahedron*, **50**, 1955 (1994).

[5] J. O. Brower and D. A. Lightner, *J. Org. Chem*., **67**, 2713 (2002).

[6] J. R. Chowdhury, A. W. Wolkoff, N. R. Chowdhury, I. M. Arias, in The Metabolic and Molecular Bases of Inherited Disease, Vol. **II**, C. R. Scriver, A. L. Beaudet, W. S. Sly, D. Valle, eds, McGraw-Hill Inc., NY, 2001, pp. 3063-3101.

[7] S. E. Boiadjiev and D. A. Lightner, *J. Phys. Org. Chem.* **17**, 675 (2004).

[8] H. Falk, A. Leodolter and G. Schade, *Monatsh. Chem*., **109**, 183 (1978).

[9] F. R. Trull, R. W. Franklin and D. A. Lightner, *J. Heterocyclic Chem*., **24**, 1573 (1987).

[10] S. E. Boiadjiev and D. A. Lightner, *J. Org. Chem*., **68**, 7591 (2003).

[11] Crystal coordinates of **9*o***, tables of bond lengths, bond angles and torsion angles are available from the Cambridge Structural Data File CCDC No. 248957.

[12] D. D. Perrin and W. L. F. Armarego, Purification of Laboratory Chemicals, 3rd ed, Pergamon Press, England, 1988.