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Synthesis, Structure, and Fluorescence of Isomeric Indolizinediones. Carbonyl-Bridged Isodipyrrinones

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Summary. In "one-pot" reactions, pyrrole-α- and β-aldehydes condense readily with 4-ethyl-3-methyl-3-pyrrolin-2-one to give isodipyrrinone analogs, which undergo intramolecular cyclization when the pyrrolealdehyde possesses an α or β-CO_2R group. The resulting regioisomeric pyrroloindolizinediones, with structures confirmed by NMR analysis, exhibit strong fluorescence, with quantum yields (ϕ_F) as high as 0.91 at $\lambda_{em} \sim 450$–550 nm.

Keywords. Pyrrole; Indolizinedione; Fluorescence quantum yield.

Introduction

Dipyrrinones, such as xanthobilirubic acid (*XBR*, Fig. 1A), are yellow pigments with *UV*-visible absorption ($\varepsilon \sim 30000\,dm^3 \cdot mol^{-1}\,cm^{-1}$) near 410 nm and the important chromophore of bilirubin (*BR*), the yellow pigment of jaundice and a bisdipyrrinone [1]. In both *XBR* and *BR*, the dipyrrinone chromophore has the (4*Z*) exocyclic configuration and adopts the *syn* conformation (Fig. 1B). The lowest lying (singlet) excited state of *XBR* and of *BR* relaxes rapidly by $Z \rightarrow E$ diastereomerization, with only extremely weak fluorescence at room temperature [1]. However, when $Z \rightarrow E$ isomerization is inhibited by linking the two nitrogens – by a carbonyl group, as in xanthoglow [2] (Fig. 1B), or by a methylene group – the pigment becomes strongly fluorescent [3–5].

Recently, we explored the possibility of synthesizing xanthoglow [2, 6] analogs with the *anti*- rather than the *syn*-(*Z*) stereochemistry (Fig. 1B) of the dipyrrinone core [7]. From the *anti*-(4*Z*) stereochemistry, the lactam nitrogen and C(7) of the pyrrole are linked to a carbonyl, thereby giving the $\alpha\alpha\beta$-type of skeleton (Fig. 1C), in contrast to the $\alpha\alpha N$ skeleton of xanthoglow (Fig. 1B), where the two nitrogens

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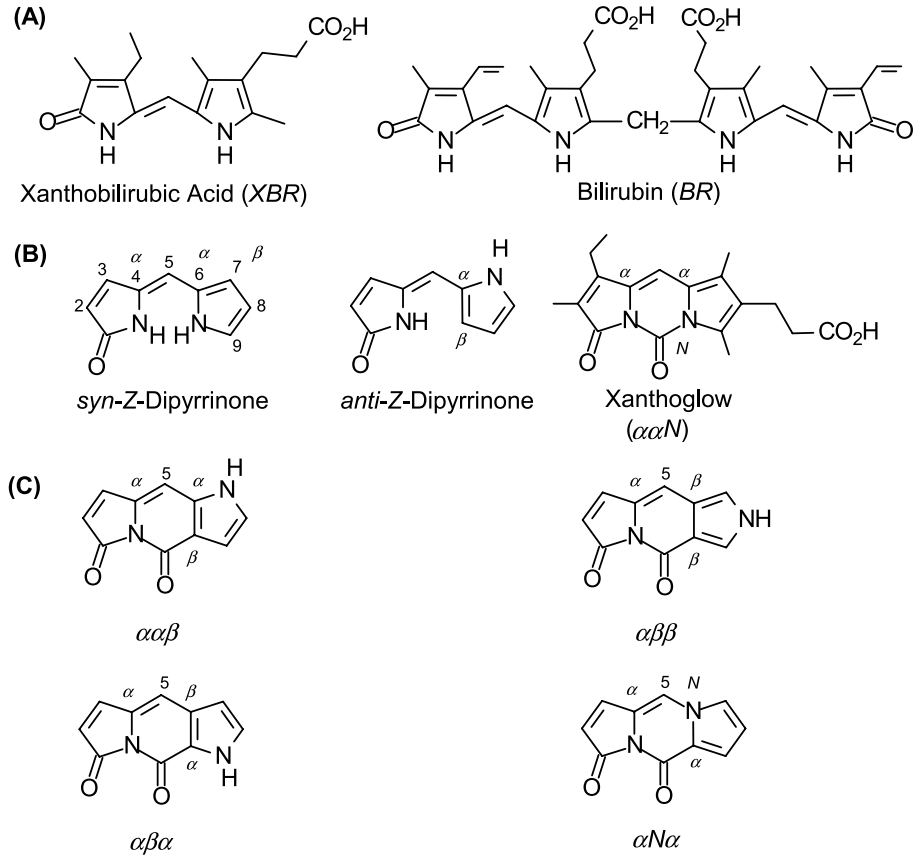

Fig. 1. (A) Xanthobilirubic acid, a dipyrrinone obtained from heating bilirubin in molten resorcinol, and bilirubin, a naturally-occurring bis-dipyrrinone; (B) the dipyrrinone skeleton in *syn*- and *anti*-conformations, and xanthoglow, a derivative of xanthobilirubic acid with both nitrogens connected to a carbonyl bridge; (C) the parent chromophores of carbonyl-bridged dipyrrinones with C(5) connecting the lactam α-carbon with a pyrrole α- or β-carbon, or the nitrogen, and with the carbonyl bridge connecting the lactam nitrogen and the pyrrole α- or β-carbon; the atom connectivity can be described in terms of α, β, and *N*, *e.g.*, xanthoglow belongs to the $\alpha\alpha N$ connectivity, with the lactam C(4) α-carbon connected to C(5), which is connected to the pyrrole α-carbon 6, an α-carbon, and with the carbonyl bridge connected to the pyrrole nitrogen; in contrast, the $\alpha\alpha\beta$ skeleton would be the same as $\alpha\alpha N$, except the carbonyl bridge would be to the pyrrole β-carbon (the original (4*Z*)-dipyrrinone in the *anti*-conformation)

are linked to a common carbonyl group. The $\alpha\alpha\beta$ tricyclic skeletal designation signifies that the lactam and pyrrole rings are connected to =C(5), which links the lactam α-carbon to a pyrrole α-carbon, and the pyrrole β-carbon is linked to the lactam N by a C=O group. The $\alpha\alpha\beta$-type carbonyl-bridged dipyrrinone (called: pyrrolo[3,2-*f*]indolizine-4,6-dione) is strongly fluorescent [7], but many simple $\alpha\alpha\beta$-type bridged dipyrrinones were found to be much less soluble in organic solvents than the $\alpha\alpha N$-type (called: 3*H*,5*H*-dipyrrolo[1,2-*c*:2′,1′-*f*]pyrimidine-3,5-dione), exemplified by xanthoglow and its analogs [2, 6]. In order to explore fluorescence from new types of carbonyl-bridged configurationally-restricted

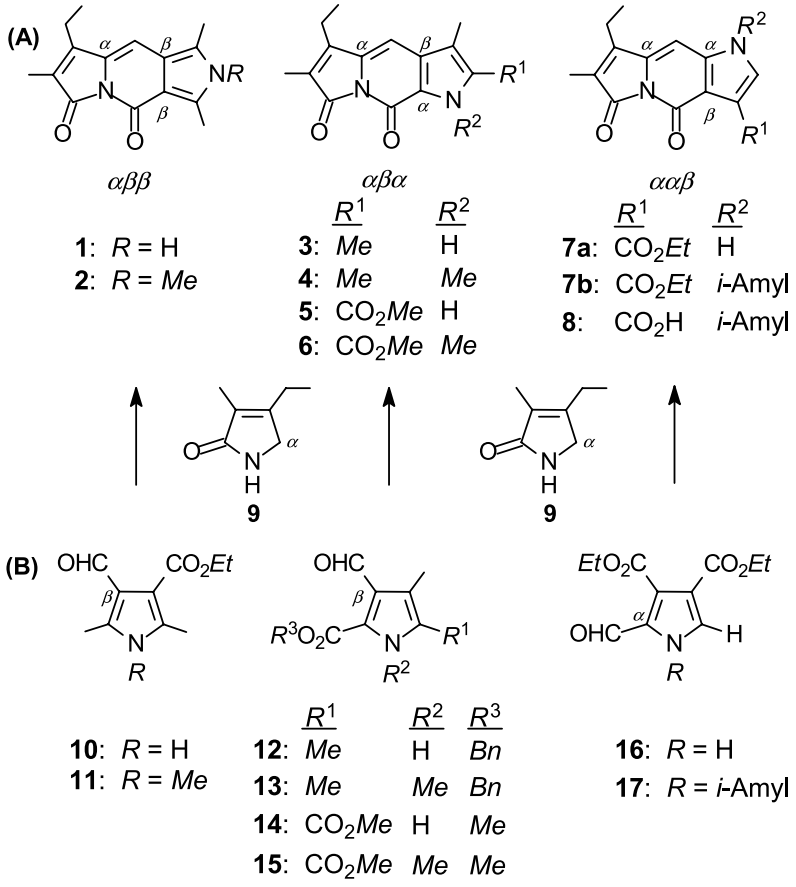

Fig. 2. (A) The target tricyclic compounds and (B) their monopyrrole precursors for the ''one-pot'' syntheses of carbonyl-bridged dipyrrinones **1**–**8**

dipyrrinones, we considered three new types of tricyclic skeletons: $\alpha\beta\beta$, $\alpha\beta\alpha$, $\alpha N\alpha$ (Fig. 1C). The first two have the unusual isodipyrrinone skeleton, with C(5) linked to a pyrrole β-carbon rather than the typical α-carbon linkage found in bilirubin, porphyrins, and dipyrrinones. The last, the $\alpha N\alpha$ skeleton is an enamine type, and that system is not reported herein. The fluorescence and other spectroscopic properties of novel $\alpha\beta\beta$ and $\alpha\beta\alpha$ and new $\alpha\alpha\beta$ target compounds of this work (**1**–**8**, Fig. 2A), are compared with those of the recently reported $\alpha\alpha\beta$ and $\alpha\alpha N$ analogs [2, 6, 7].

Results and Discussion

Mechanism

The syntheses of the $\alpha\beta\beta$, $\alpha\beta\alpha$, and $\alpha\alpha\beta$ tricyclic, dipyrrinone-based compounds were inspired by the observation of *Clezy* and *Liepa* [8] that acid-catalyzed condensation of 4-acetyl-5-formyl-3-methyl-1*H*-pyrrole-2-carboxylic acid with

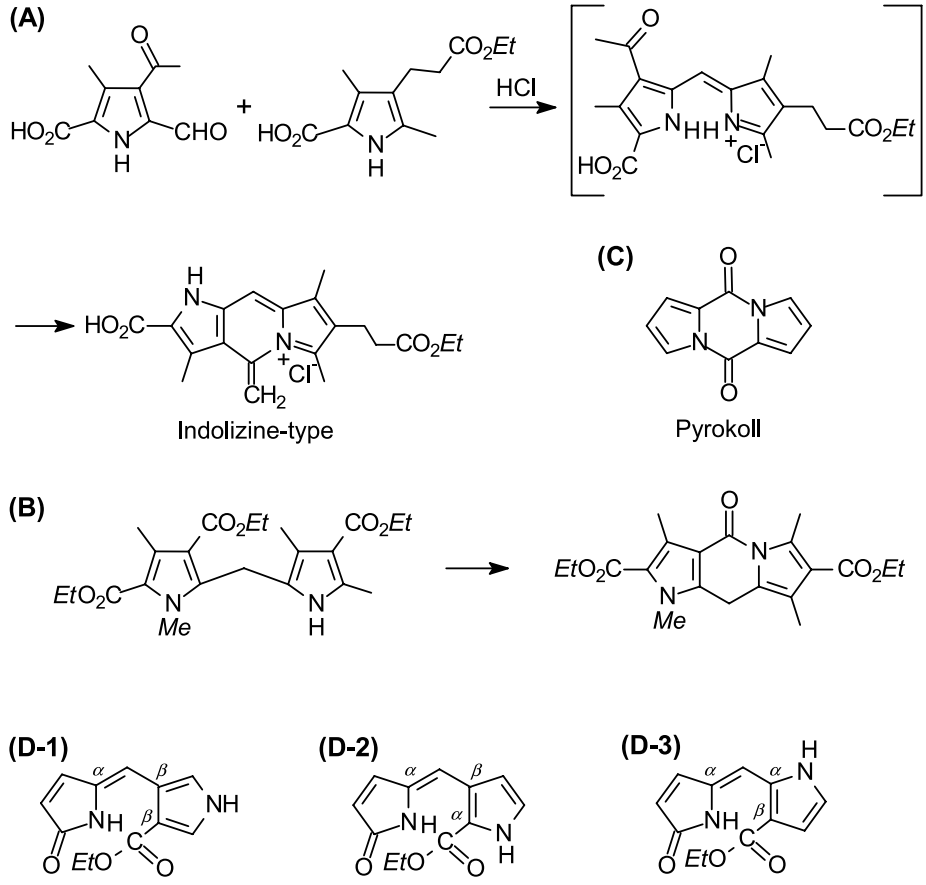

Fig. 3. (A) Unexpected indolizine formation by condensation of two pyrroles; (B) intramolecular cyclization of a dipyrrylmethane from a deprotonated pyrrole nitrogen to the neighboring pyrrole β-CO_2Et group; (C) pyrokoll, from 1880; (D) the minimum components and orientations required for intramolecular cyclization between a (deprotonated) lactam nitrogen and neighboring CO_2Et group to produce indolizinediones **1**–**8**

4-(ethoxycarbonylethyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid afforded not the expected dipyrrylmethene product, but rather an unexpected product, the indolizine formed by intramolecular cyclization of the dipyrrylmethene intermediate (Fig. 3A). Studies of similar acid-catalyzed condensations leading to 6-methylenepyrrolo[3,2-*f*]indolizines were reported by *Mironov et al*. [9].

Even earlier work by *Corwin* and *Ellingson* [10] showed the feasibility of using a (deprotonated) pyrrole nitrogen-nucleophile to accomplish an intramolecular cyclization with a neighboring pyrrole β-carboethoxy group (Fig. 3B). Here, the *N*-methylated nitrogen does not react, and if both pyrroles are *N*-methylated, no reaction proceeds. Such a N−C(=O)−C bridged system was not without precedence and had been described (pyrokoll, Fig. 3C) in 1880 by *Ciamician* [11]. Accordingly, for the syntheses of the $\alpha\beta\beta$ compounds of this work (**1** and **2**) the $\alpha\beta\alpha$ (**3**–**6**) and the $\alpha\alpha\beta$ (**7** and **8**) (Fig. 2), we envisioned

intramolecular cyclizations emanating from the dipyrrinone skeletons oriented as in Fig. 3D.

Synthesis

It appeared to us that the most economical routes to the target compounds would be one-pot syntheses (Fig. 2) in which 4-ethyl-3-methyl-3-pyrrolin-2-one (**9**) [12] was condensed with a pyrrole-β-aldehyde (to form **1**–**6**) or pyrrole-α-aldehyde (to form **7** and **8**) to give first the appropriate isodipyrrinone or dipyrrinone (Fig. 3D), to be followed by lactam NH deprotonation and cyclization with a neighboring carboalkoxy group. A non-nucleophilic base such as *DBU* (1,8-diazabicyclo[5.4.0] undec-7-ene) seemed appropriate to the task while avoiding saponification of the important carboalkoxy group. Thus, by reacting **9** with pyrrolealdehydes **10** and **11** (Fig. 2B) under these conditions, we obtained $\alpha\beta\beta$ products **1** and **2**, in good yield (62–73%), proving that the method works – even in the face of steric hindrance due to the ''ortho'' effect. Similarly, **9** reacted smoothly i) with **12**–**15** to afford **3**–**6** in 35–75% yield, and ii) with **16** and **17** to afford **7a** and **8** in 88 and 7% yield. The *N*-methylated aldehydes (**13** and **15**) afforded much lower yields of tricyclic products than those from the N-H aldehydes **12** and **14** – possibly due to decreased electrophilicity at the α-ester carbonyl carbon reaction center. The very low yield of **8** is unexplained but is possibly related to steric hindrance from the *iso*-amyl group in the dipyrrinone-forming condensation step. Since **7a** was too insoluble for spectroscopic measurements, it was *N*-alkylated to give **7b**. The required monopyrrolealdehydes were prepared by formylation of known β-H or α-H precursors. *N*-Methyl and *N-iso*-amyl pyrroles **11**, **13**, **15**, and **17** were synthesized from the N-*H* pyrrole by methylation using potassium *tert*-butoxide plus methyl or *iso*-amyl iodide.

Properties

All of the bridged dipyrrinones of this work were yellow and had rather high melting points, with the N-alkylated compounds having lower values (211–250°C) and the others having higher values (298–367°C) and poorer solubility in organic solvents, especially **7a**. The solubility and melting point properties stand in strong contrast to the $\alpha\alpha N$ series of bridged dipyrrinones related to xanthoglow [2], which are quite soluble in organic solvents over a wide range of polarity. The ^{1}H NMR, ^{13}C NMR (APT), and gHMBC spectra provided firm proof of structure of **1**–**8**, which followed logically from the method of synthesis. The *UV*-visible spectra (Table 1) of **1**–**8** show multiple bands centered near 400 nm with $\varepsilon \sim 15000$, weaker bands centered near 300–350 nm ($\varepsilon \sim 5000$), and a more intense band located near 250–300 nm ($\varepsilon \sim 25000$). The position and composition of the bands varies with the structural types and type of number substituents on the pyrrole ring. One might distinguish the $\alpha\beta\beta$ type ($\lambda_{max} \sim 380$–410, ~ 300, $\sim$250 nm) from the $\alpha\beta\alpha$ type ($\lambda_{max} \sim 410$–420, ~ 350, ~ 250–300 nm) and $\alpha\alpha\beta$ type ($\lambda_{max} \sim 400$–420, ~ 240–260 nm) on the basis of their *UV*-visible spectral profiles.

Table 1. Solvent dependence of the *UV*-visible spectra of **1–8**

Compound	λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1})									
	n-C_6H_{14}		C_6H_6		$CHCl_3$		CH_3OH		$(CH_3)_2SO$	
1	insoluble		404	(16200)	407	(15300)	409	(16200)	403	(16700)
			384	(16800)	389	(16000)				
			318	(4500)	308	(4800)	309	(3900)	308	(4300)
			305	(4600)	253	(23500)	252	(26400)		
					246	(23600)	245	(27300)		
2	403	(17800)	409	(17200)	413	(15700)	409	(16400)	404	(17100)
	381	(18400)	389	(17800)	395	(16600)				
	316	(4600)	319	(4200)	321	(4100)				
	301	(5000)	305	(4600)	307	(4700)	299	(4500)	300	(4700)
	253	(25100)			256	(28500)	253	(30800)		
	245	(25500)			249	(27000)	248	(30100)		
3	sh 410	(4600)	sh 413	(5000)	sh 412	(4300)	sh 415	(4300)	sh 411	(5100)
	355	(10000)	355	(9500)	356	(9700)	361	(10900)	361	(10700)
	294	(2100)	293	(2300)	293	(2500)	295	(2800)	296	(2900)
					267	(18500)				
4	416	(6400)	sh 418	(6400)	sh 415	(5600)	sh 411	(5700)	sh 413	(6200)
	394	(6900)	397	(6900)						
	356	(9200)	361	(9500)	365	(9900)	366	(10400)	366	(10100)
	280	(8800)							sh 273	(13800)
	270	(12500)			245	(26700)	244	(29500)		
5	insoluble		403	(7100)	405	(6100)			406	(6900)
			382	(7400)	386	(6400)	393	(6300)	390	(7100)
			335	(3900)	336	(3900)	336	(4100)		
			293	(36400)	293	(42900)	292	(39800)	295	(37300)
			283	(31900)	283	(37300)	283	(38000)	285	(34700)
6	404	(8900)	409	(8200)	411	(7200)	407	(7000)	411	(7400)
	382	(9200)	387	(8500)	392	(7500)	393	(7100)	393	(7700)
	340	(4600)	342	(4400)	340	(4400)	339	(4300)	sh 339	(4400)
	293	(29600)	296	(29100)	296	(32000)	291	(31700)	296	(31100)
	285	(32600)	290	(29100)	290	(32500)	287	(32100)	289	(30800)
7b	422	(11100)	424	(12300)	424	(11200)	420	(10200)	425	(11100)
	397	(12500)	399	(13100)	400	(12000)	400	(10600)	402	(11600)
	sh 298	(3200)	sh 300	(3200)	sh 298	(4100)	sh 299	(4600)	sh 298	(4500)
	261	(15000)			263	(17300)	260	(19300)	261	(19300)
8	425	(7300)	427	(10000)	426	(9700)	sh 422	(8800)	sh 426	(9100)
	401	(9200)	404	(10800)	404	(10500)	403	(9300)	407	(9700)
	sh 297	(3900)	sh 299	(4400)	sh 300	(5100)	sh 299	(5800)	sh 301	(5600)
	sh 256	(15100)			261	(19800)	261	(21400)	261	(21700)
					244	(22800)	243	(25300)		

All of the pigments studied, **1–8**, were fluorescent, in some cases the fluorescence was exceptionally strong with fluorescence quantum yields (ϕ_F) $\sim$0.9 (Table 2). The fluorescence was clearly influenced by the choice of solvent. For

Table 2. Solvent dependence of the fluorescence excitation (λ_{ex}/nm) and emission (λ_{em}/nm) wavelengths and quantum yields (ϕ_F) of **1**–**8**

Compound	Cyclo-C_6H_{12}			C_6H_6			$CHCl_3$		
	λ_{ex}	λ_{em}	ϕ_F	λ_{ex}	λ_{em}	ϕ_F	λ_{ex}	λ_{em}	ϕ_F
1 ($\alpha\beta\beta$)	385	435	0.02	381	449	0.70	388	455	0.86
2 ($\alpha\beta\beta$)	381	441	0.21	408	453	0.75	396	450	0.86
3 ($\alpha\beta\alpha$)	356	474	0.13	355	476	0.22	359	494	0.29
4 ($\alpha\beta\alpha$)	359	466	0.12	361	480	0.27	365	498	0.31
5 ($\alpha\beta\alpha$)	364	407	0.01	396	451	0.09	404	459	0.54
6 ($\alpha\beta\alpha$)	396	449	0.02	408	453	0.10	410	467	0.60
7b ($\alpha\alpha\beta$)	400	453	0.01	400	456	0.06	398	455	0.14
8 ($\alpha\alpha\beta$)	396	465	0.27	400	456	0.82	399	477	0.87

Compound	CH_3OH			$(CH_3)_2SO$		
	λ_{ex}	λ_{em}	ϕ_F	λ_{ex}	λ_{em}	ϕ_F
1 ($\alpha\beta\beta$)	411	489	0.73	411	479	0.91
2 ($\alpha\beta\beta$)	410	492	0.71	397	479	0.88
3 ($\alpha\beta\alpha$)	363	548	0.02	365	514	0.08
4 ($\alpha\beta\alpha$)	369	542	0.04	368	510	0.15
5 ($\alpha\beta\alpha$)	398	508	0.10	397	475	0.59
6 ($\alpha\beta\alpha$)	396	505	0.13	396	476	0.67
7b ($\alpha\alpha\beta$)	397	502	0.56	398	484	0.46
8 ($\alpha\alpha\beta$)	397	513	0.28	407	499	0.71

example, **1** exhibits large ϕ_F values in all solvents studied, except for cyclohexane, in which it was least soluble. In such instances, diminished fluorescence attended **2** (in cyclohexane) and **3** (insoluble in most solvents), **4**, **5**, **6**, and **7** in all but $CHCl_3$ and $(CH_3)_2SO$ (where they are most soluble). The fluorescence is probably quenched by self-association (aggregation). This possibility is supported by the hypsochromic shifts of both λ_{ex} and λ_{em} from weakly fluorescing solutions of **1**–**8**, *vs*. solutions with strong fluorescence: typically $(CH_3)_2SO$ and $CHCl_3$. Selected fluorescence emission and *UV*-visible absorption curves for **1**–**8** may be seen in Fig. 4, and a comparison of the normalized fluorescence emission spectra of **2**, **4**, **7b**, and xanthoglow (*XG*) may be seen in Fig. 5. From the latter, the xanthoglow emission λ_{max} (Fig. 1) is clearly redshifted from those of **1**–**8**, and the most soluble of **1**–**8** tend to give the larger emission intensities (and ϕ_F, Table 2).

Concluding Comments

New tricyclic skeletal types ($\alpha\beta\beta$ and $\alpha\beta\alpha$, **1**–**6**) based on isodipyrrinones are readily prepared in ''one-pot'' syntheses. The new carbonyl-bridged isodipyrrinones are intensely fluorescent ($\phi_F \sim 0.9$, $\lambda_{em} \sim 450$–515 nm) in organic solvents

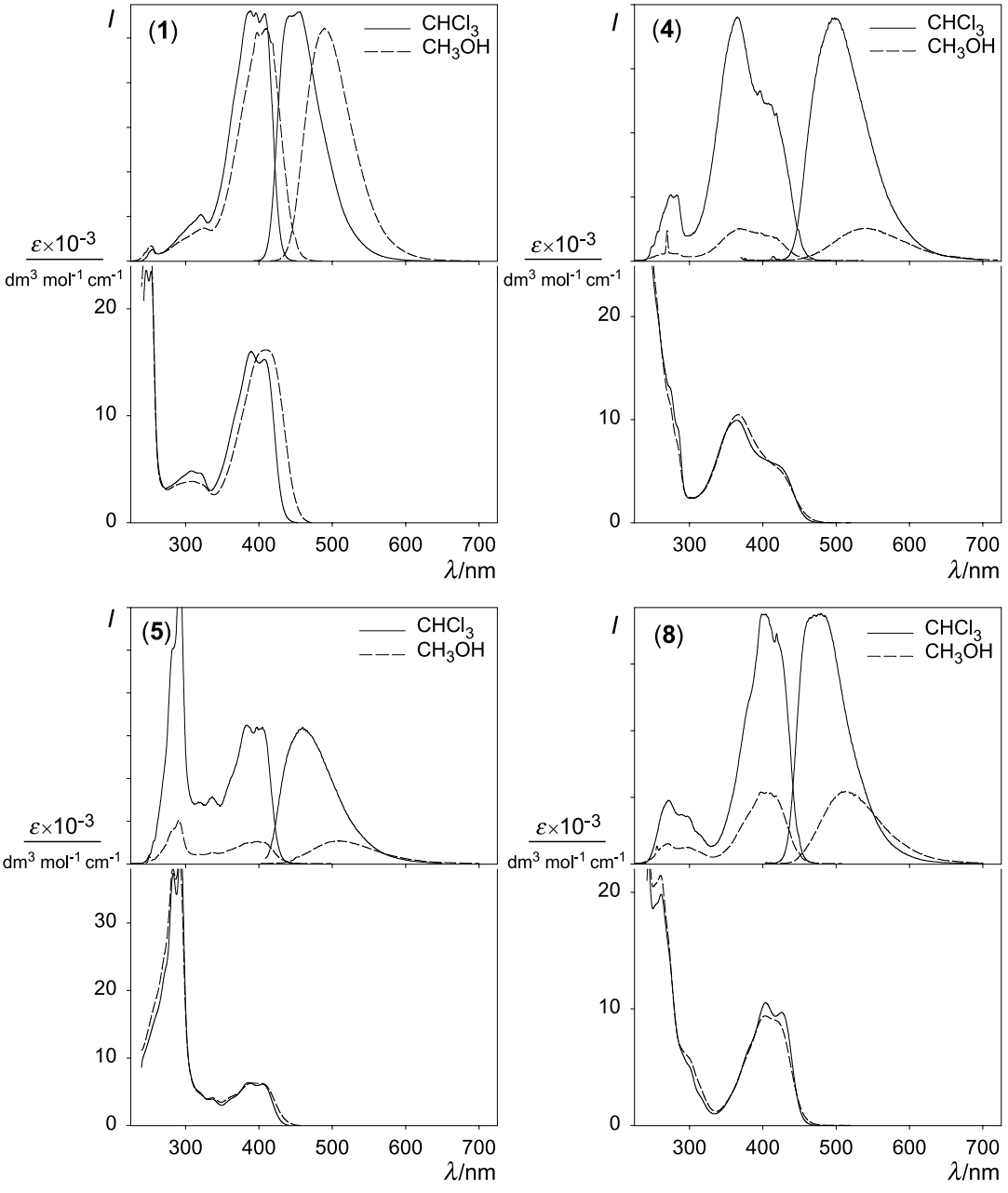

Fig. 4. Comparison of the fluorescence emission and excitation spectra (upper) and *UV*-visible absorption spectra (lower) of dipyrrinones **1**, **4**, **5**, and **8** in $CHCl_3$ and CH_3OH

in which they exhibit good solubility ($CHCl_3$, $(CH_3)_2SO$), but only weak fluorescence ($\phi_F \sim 0.01$–0.1, $\lambda_{em} \sim 450$–550 nm) in solvents such as cyclohexane. Similar results are found with new members (**7** and **8**) of the $\alpha\alpha\beta$ skeletal type based on bridged (4*Z*)-dipyrrinones in the *anti* conformation.

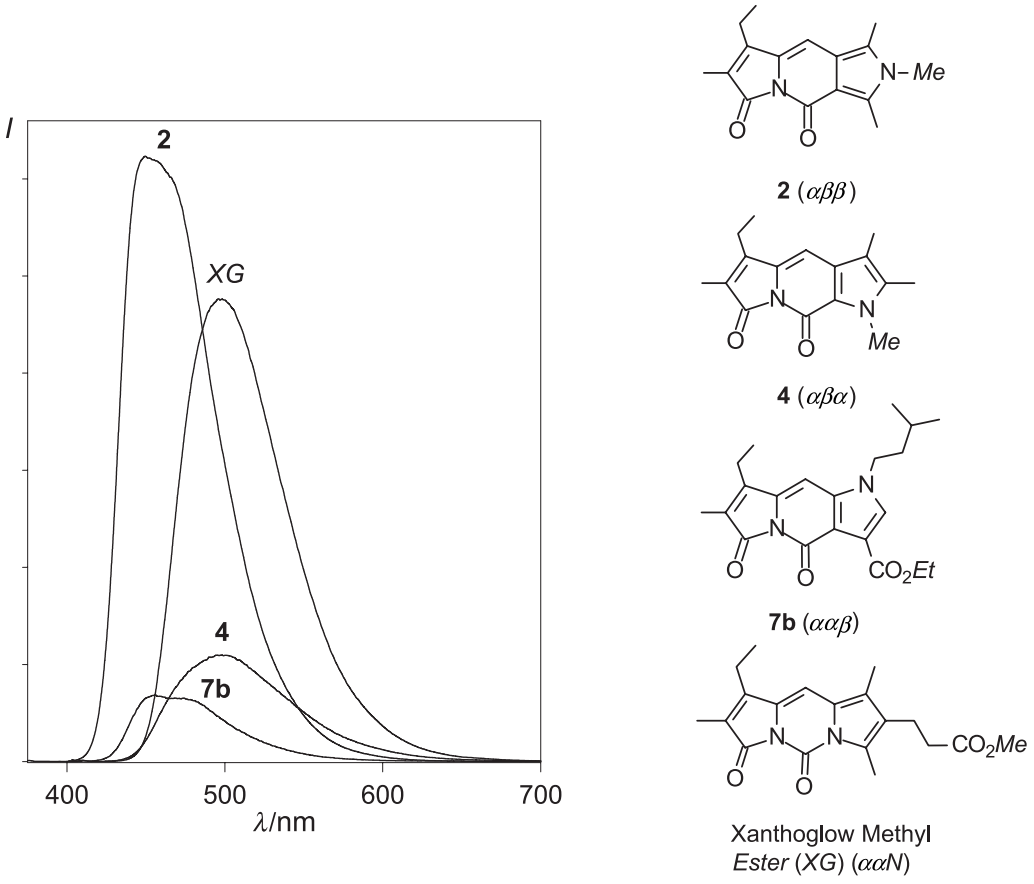

Fig. 5. Normalized relative fluorescence of **2**, **4**, **7b**, and xanthoglow (*XG*) in $CHCl_3$

Experimental

All fluorescence spectra were measured on a Jobin Yvon Fluorolog 3 model FL 3-22 instrument by using constant spectral parameters: step resolution (increment) of 1 nm, both excitation and emission slits of 2 nm and integration time of 0.5 sec and were uncorrected. The *UV*-visible spectra were recorded on a Perkin-Elmer Lambda 12 spectrophotometer. NMR spectra were acquired on a Varian Unity Plus spectrometer at 11.75 T magnetic field strength operating at ^1H frequency of 500 MHz and ^{13}C frequency of 125 MHz in solutions of $CDCl_3$ (referenced at 7.26 ppm for ^1H and 77.00 ppm for ^{13}C) or $(CD_3)_2SO$ (referenced at 2.49 ppm for ^1H and 39.50 ppm for ^{13}C). *J*-Modulated spin-echo (*A*ttached *P*roton *T*est) and gHMBC experiments were used to assign the ^{13}C NMR spectra. Gas chromatography-mass spectrometry analyses were carried out on a Hewlett-Packard 5890A gas chromatograph (30 m DB-1 column) equipped with a Hewlett-Packard 5970 mass selective detector. Radial chromatography was carried out on Merck silica gel PF_{254} with $CaSO_4$ binder preparative layer grade, using a Chromatotron (Harrison Research, Inc., Palo Alto, CA) with 1, 2, or 4 mm thick rotors and analytical thin-layer chromatography was carried out on J. T. Baker silica gel IB-F plates (125 μm layer). Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. The combustion analyses were carried out by Desert Analytics, Tucson, AZ; their results agreed favourably with the calculated values.

The spectral data were obtained in spectral grade solvents (Aldrich or Fisher) which were distilled under Ar stream just prior to use. Before the distillation $CHCl_3$ was passed through a basic alumina column. Distillation of $(CH_3)_2SO$ was carried out at 0.5 mm Hg vacuum collecting the solvent at 0°C and thawing it under Ar. The starting compounds, 4-ethyl-3-methyl-3-pyrrolin-2-one (**9**) [12], ethyl 2,5-dimethyl-1*H*-pyrrole-3-carboxylate [13], benzyl 4,5-dimethyl-1*H*-pyrrole-2-carboxylate [14], dimethyl 3-formyl-4-methyl-1*H*-pyrrole-2,5-dicarboxylate (**14**) [15], and diethyl 1*H*-pyrrole-3,4-dicarboxylate [16], were synthesized according to literature methods.

Ethyl 2,5-dimethyl-4-formyl-1H-pyrrole-3-carboxylate (**10**, $C_{10}H_{13}NO_3$)

To N_2-protected anhydrous *DMF* (1.55 cm^3, 20 mmol) were added 1.49 cm^3 (16 mmol) of phosphorus oxychloride during 8 min at 0°C, and the mixture was stirred at the same temperature for 30 min. 1,2-Dichloroethane (8 cm^3) was added, followed by a solution of ethyl 2,5-dimethyl-1*H*-pyrrole-3-carboxylate [13] (1.67 g, 10 mmol) in 15 cm^3 of 1,2-dichloroethane and the mixture was heated at reflux for 45 min. After slight cooling, a solution of 7.00 g (50 mmol) of sodium acetate trihydrate in 15 cm^3 of H_2O was added and the mixture was reheated at reflux for 30 min. After cooling, the product was extracted with CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), filtered through a short silica pad, and the solvent was evaporated under vacuum. The residue was recrystallized from ethyl acetate-hexane to afford **10**. Yield 1.70 g (87%); mp 151–152°C (Ref. [17] 151–152°C); ^{1}H NMR ($CDCl_3$): $\delta = 1.36$ (3H, t, $J = 7.2$ Hz), 2.49 (3H, s), 2.52 (3H, s), 4.32 (2H, q, $J = 7.2$ Hz), 9.35 (1H, br.s), 10.41 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.20$, 13.44, 14.39, 60.06, 111.88, 120.15, 135.39, 135.72, 165.18, 190.30 ppm.

Ethyl 4-formyl-1,2,5-trimethyl-1H-pyrrole-3-carboxylate (**11**, $C_{11}H_{15}NO_3$)

To a solution of 1.95 g (10 mmol) of pyrrole **10** in 25 cm^3 of anh. *DMSO*, protected under N_2, was added 1.23 g (11 mmol) of potassium *t*-butoxide, and the mixture was stirred for 1 h. Methyl iodide (0.92 cm^3, 15 mmol) was then added, and stirring was continued at 60°C for 2 h. After cooling, the mixture was diluted with 100 cm^3 of $CHCl_3$ and washed with 2% aq. HCl (50 cm^3) and H_2O (4×50 cm^3). The solution was dried ($MgSO_4$) and filtered, and the solvent was evaporated under vacuum. Recrystallization of the residue from ethyl acetate-hexane afforded **11**. Yield 1.67 g (80%); mp 89–90°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.35$ (3H, t, $J = 7.2$ Hz), 2.50 (3H, s), 2.53 (3H, s), 3.42 (3H, s), 4.30 (2H, q, $J = 7.2$ Hz), 10.39 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.46$, 11.56, 14.39, 30.01, 59.92, 111.76, 119.66, 136.34, 136.56, 164.99, 189.93 ppm.

Benzyl 4,5-dimethyl-3-formyl-1H-pyrrole-2-carboxylate (**12**, $C_{15}H_{15}NO_3$)

Aldehyde **12** was obtained following the same procedure for *Vilsmeier* formylation as for **10**. Yield 69% (after recrystallization from CH_3OH–H_2O); mp 146–147°C; ^{1}H NMR ($CDCl_3$): $\delta = 2.21$ (3H, s), 2.24 (3H, s), 5.35 (2H, s), 7.34–7.44 (5H, m), 9.20 (1H, br.s), 10.55 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 10.41$, 10.45, 66.74, 119.52, 123.68, 126.59, 128.18, 128.40, 128.56, 130.98, 135.17, 160.00, 189.50 ppm.

Benzyl 3-formyl-1,4,5-trimethyl-1H-pyrrole-2-carboxylate (**13**, $C_{16}H_{17}NO_3$)

Following the same procedure as above for **11**, formylpyrrole **12** was N-methylated to afford **13**. Yield 86%; mp 71–72°C; ^{1}H NMR ($CDCl_3$): $\delta = 2.17$ (3H, s), 2.25 (3H, s), 3.83 (3H, s), 5.36 (2H, s), 7.32–7.42 (5H, m), 10.47 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 9.66$, 10.70, 33.25, 66.56, 118.60, 124.98, 127.01, 128.35, 128.40, 128.65, 133.98, 135.48, 160.39, 189.86 ppm.

Dimethyl 1,4-dimethyl-3-formyl-1H-pyrrole-2,5-dicarboxylate (**15**, $C_{11}H_{13}NO_5$)

Formylpyrrole **14** [15] (1.13 g, 5 mmol) was dissolved in a solution of 0.28 g (5 mmol) of KOH in 5 cm^3 of CH_3OH at ~55°C. Dimethylsulfate (0.65 cm^3, 6.5 mmol) was added during 2 min, and the mixture was stirred for 45 min while cooling slowly from 55°C to ambient temperature. The separated product was collected by filtration, purified by radial chromatography, and recrystallized from ethyl acetate-hexane to give **15**. Yield 0.91 g (76%); mp 110–111°C; ^{1}H NMR ($CDCl_3$): $\delta = 2.54$ (3H, s), 3.91 (3H, s), 3.96 (3H, s), 4.11 (3H, s), 10.32 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.80$, 35.59, 51.69, 52.45, 125.67, 125.82, 129.56, 131.21, 160.59, 161.80, 188.53 ppm.

Diethyl 2-formyl-1H-pyrrole-3,4-dicarboxylate (**16**, $C_{11}H_{13}NO_5$)

Aldehyde **16** was synthesized following the same procedure for *Vilsmeier* formylation as above for **10**, except the reaction time was 1.5 h. Yield 73% (after recrystallization from ethyl acetate-hexane); mp 70–71°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.34$ (3H, t, $J = 7.2$ Hz), 1.39 (3H, t, $J = 7.2$ Hz), 4.31 (2H, q, $J = 7.2$ Hz), 4.41 (2H, q, $J = 7.2$ Hz), 7.59 (1H, dd, $^3J = 3.3$ Hz, $^5J = 0.9$ Hz), 9.88 (1H, d, $^5J = 0.9$ Hz), 10.53 (1H, br.s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.05$, 14.10, 60.74, 61.69, 118.07, 124.32, 129.02, 132.34, 162.74, 163.23, 180.97 ppm.

Diethyl 2-formyl-1-(3-methylbutyl)-1H-pyrrole-3,4-dicarboxylate (**17**, $C_{16}H_{23}NO_5$)

Following the same procedure as above for **11**, the formylpyrrole **16** was N-alkylated using *iso*-amyl iodide to afford **17** as a colorless oil. Yield 90%; ^{1}H NMR ($CDCl_3$): $\delta = 0.95$ (6H, d, $J = 6.2$ Hz), 1.32 (3H, t, $J = 7.2$ Hz), 1.38 (3H, t, $J = 7.2$ Hz), 1.56–1.65 (3H, m), 4.28 (2H, q, $J = 7.2$ Hz), 4.32 (2H, t, $J = 7.4$ Hz), 4.40 (2H, q, $J = 7.2$ Hz), 7.38 (1H, s), 9.82 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.04$, 14.15, 22.22, 25.51, 39.82, 48.54, 60.52, 61.75, 115.51, 128.43, 129.66, 132.37, 162.29, 163.80, 180.16 ppm.

General Procedure for Condensation-Cyclization

A mixture of 6.0 mmol of pyrrolinone **9** [12], 4.0 mmol of the corresponding pyrrolealdehyde, 15 cm^3 of abs. ethanol and 2.25 cm^3 (15.0 mmol) of *DBU* was heated in a thick walled sealed tube under Ar at 85–90°C for 72 h. After cooling, about 7 cm^3 of ethanol were evaporated under a stream of N_2, and the residue was diluted with 2 cm^3 of acetic acid and 6 cm^3 of H_2O. The mixture was cooled at 0°C to −10°C, and the precipitated product was collected by filtration (or in cases of incomplete crystallization – extracted with $CHCl_3$). Purification by recrystallization or radial chromatography afforded pure bright yellow tricyclics.

8-Ethyl-1,3,7-trimethylpyrrolo[3,4-f]indolizine-4,6-dione (**1**, $C_{15}H_{16}N_2O_2$)

Yield 62%; mp 353–355°C (dec.); ^{1}H NMR ($(CD_3)_2SO$ at 60°C): $\delta = 1.14$ (3H, t, $J = 7.6$ Hz), 1.81 (3H, s), 2.30 (3H, s), 2.48 (3H, s), 2.54 (2H, q, $J = 7.6$ Hz), 6.78 (1H, s), 11.59 (1H, br.s) ppm; ^{13}C NMR ($(CD_3)_2SO$ at 60°C): $\delta = 7.63$, 10.08, 11.75, 13.55, 17.00, 101.38, 109.87, 117.53, 123.34, 124.41, 133.30, 133.57, 146.63, 157.48, 167.77 ppm.

8-Ethyl-1,2,3,7-tetramethylpyrrolo[3,4-f]indolizine-4,6-dione (**2**, $C_{16}H_{18}N_2O_2$)

Yield 73%; mp 252–254°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.19$ (3H, t, $J = 7.7$ Hz), 1.91 (3H, s), 2.30 (3H, s), 2.50 (2H, q, $J = 7.7$ Hz), 2.63 (3H, s), 3.46 (3H, s), 6.32 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 8.21$, 10.15, 11.06, 13.90, 17.89, 30.43, 99.77, 110.49, 117.88, 124.21, 126.09, 134.63, 135.44, 146.38, 158.37, 169.04 ppm.

5-Ethyl-2,3,6-trimethylpyrrolo[2,3-f]indolizine-7,9-dione (**3**, $C_{15}H_{16}N_2O_2$)

Yield 75%; mp 337–339°C (dec); ^{1}H NMR ($(CD_3)_2SO$ at 60°C): $\delta = 1.15$ (3H, t, $J = 7.6$ Hz), 1.82 (3H, s), 2.06 (3H, s), 2.20 (3H, s), 2.55 (2H, q, $J = 7.6$ Hz), 6.75 (1H, s), 11.90 (1H, br.s) ppm; ^{13}C NMR ($(CD_3)_2SO$ at 60°C): $\delta = 7.44$, 7.80, 10.59, 13.14, 17.00, 100.29, 111.35, 121.52, 124.34, 128.18, 134.80, 135.52, 148.03, 150.94, 168.20 ppm.

5-Ethyl-1,2,3,6-tetramethylpyrrolo[2,3-f]indolizine-7,9-dione (**4**, $C_{16}H_{18}N_2O_2$)

Yield 47%; mp 211–213°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.20$ (3H, t, $J = 7.7$ Hz), 1.91 (3H, s), 2.08 (3H, s), 2.19 (3H, s), 2.50 (2H, q, $J = 7.7$ Hz), 4.00 (3H, s), 6.37 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 8.15$, 8.69, 9.90, 13.66, 17.92, 32.21, 99.42, 111.40, 121.78, 125.92, 128.29, 135.45, 137.37, 147.48, 153.08, 169.35 ppm.

Methyl 3,6-dimethyl-5-ethylpyrrolo[2,3-f]indolizine-7,9-dione-2-carboxylate (**5**, $C_{16}H_{16}N_2O_4$)

Yield 65%; mp 298–300°C (dec); ^{1}H NMR ($(CD_3)_2SO$ at 60°C): $\delta = 1.16$ (3H, t, $J = 7.6$ Hz), 1.84 (3H, s), 2.39 (3H, s), 2.58 (2H, q, $J = 7.6$ Hz), 3.82 (3H, s), 6.88 (1H, s), 12.73 (1H, br.s) ppm; ^{13}C NMR ($(CD_3)_2SO$ at 60°C): $\delta = 7.50$, 9.41, 13.03, 17.02, 51.16, 99.63, 121.71, 125.06, 125.65, 126.09, 127.65, 135.35, 148.31, 151.21, 160.55, 167.85 ppm.

Methyl 5-ethyl-1,3,6-trimethylpyrrolo[2,3-f]indolizine-7,9-dione-2-carboxylate (**6**, $C_{17}H_{18}N_2O_4$)

Yield 35%; mp 219–220°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.22$ (3H, t, $J = 7.7$ Hz), 1.93 (3H, s), 2.37 (3H, s), 2.53 (2H, q, $J = 7.7$ Hz), 3.91 (3H, s), 4.38 (3H, s), 6.44 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 8.22$, 10.85, 13.59, 17.98, 35.04, 51.66, 98.78, 122.45, 125.85, 126.64, 127.49, 128.24, 135.82, 147.74, 153.49, 161.81, 168.83 ppm.

Ethyl 8-ethyl-7-methylpyrrolo[3,2-f]indolizine-4,6-dione-3-carboxylate (**7a**, $C_{16}H_{16}N_2O_4$)

Yield 88% (crude product); mp 363–367°C (dec); ^{1}H NMR ($(CD_3)_2SO$ at 90°C): $\delta = 1.18$ (3H, t, $J = 7.6$ Hz), 1.30 (3H, t, $J = 7.1$ Hz), 1.87 (3H, s), 2.57 (2H, q, $J = 7.6$ Hz), 4.23 (2H, q, $J = 7.1$ Hz), 6.69 (1H, s), 7.62 (1H, d, $J = 2.7$ Hz), 12.00 (1H, br.s) ppm; ^{13}C NMR ($(CD_3)_2SO$ at 90°C): $\delta = 7.35$, 12.59, 13.66, 16.77, 59.08, 94.92, 113.67, 115.14, 126.33, 128.69, 137.54, 138.48, 146.21, 153.50, 162.22, 167.84 ppm; HRMS (FAB, 3-*NBA* + Li): calcd for $C_{16}H_{16}N_2O_4 \cdot {}^7$Li 307.1270; found 307.1275.

Ethyl 8-ethyl-7-methyl-1-(3-methylbutyl)pyrrolo[3,2-f]indolizine-4,6-dione-3-carboxylate (**7b**, $C_{21}H_{26}N_2O_4$)

To a mixture of 300 mg (1.0 mmol) of **7a** and 8 cm^3 of anh. *DMF* under Ar was added Cs_2CO_3 (652 mg, 2.0 mmol) followed by 1.3 cm^3 (10.0 mmol) of *iso*-amyl iodide, and the mixture was stirred at 85–90°C for 16 h. After cooling, the product was partitioned between 100 cm^3 of $CHCl_3$ and 100 cm^3 of H_2O. The organic layer was washed with 1% aq. HCl (100 cm^3) and H_2O (4 × 50 cm^3), and then dried (anh. Na_2SO_4). After filtration and removal of solvent, the residue was purified by radial chromatography and recrystallization from ethyl acetate–hexane to give 318 mg (86%) of **7b**. Yield 86%; mp 158–159°C; ^{1}H NMR ($CDCl_3$): $\delta = 0.96$ (6H, d, $J = 6.6$ Hz), 1.19 (3H, t, $J = 7.7$ Hz), 1.38 (3H, t, $J = 7.2$ Hz), 1.54–1.64 (1H, m), 1.66–1.70 (2H, m), 1.91 (3H, s), 2.51 (2H, q, $J = 7.7$ Hz), 4.00 (2H, t, $J = 7.5$ Hz), 4.35 (2H, q, $J = 7.2$ Hz), 6.26 (1H, s), 7.38 (1H, s) ppm; ^{13}C NMR ($CDCl_3$):

$\delta = 8.30$, 13.53, 14.36, 17.85, 22.25, 25.44, 39.29, 45.54, 60.65, 92.21, 115.14, 116.28, 128.03, 131.32, 137.92, 139.54, 146.15, 154.61, 163.41, 168.68 ppm.

3-Carboxy-8-ethyl-7-methyl-1-(3-methylbutyl)pyrrolo[3,2-f]indolizine-4,6-dione (**8**, $C_{19}H_{22}N_2O_4$)

Yield 7%; mp 255–256°C; ^{1}H NMR ($CDCl_3$): $\delta = 0.97$ (6H, d, $J = 6.5$ Hz), 1.24 (3H, t, $J = 7.7$ Hz), 1.55–1.63 (1H, m), 1.70 (2H, dt, $J = 7.5$, 7.2 Hz), 1.96 (3H, s), 2.60 (2H, q, $J = 7.7$ Hz), 4.07 (2H, t, $J = 7.5$ Hz), 6.45 (1H, s), 7.51 (1H, s), 14.07 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 8.33$, 13.19, 18.15, 22.21, 25.43, 38.95, 45.94, 93.61, 113.19, 116.22, 127.89, 133.52, 138.44, 139.16, 148.96, 158.71, 162.79, 167.73 ppm.

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References

[1] Falk H (1989) The Chemistry of Linear Oligopyrroles and Bile Pigments, Springer, Vienna
[2] Brower JO, Lightner DA (2002) J Org Chem **67**: 2713
[3] van Es JJGS, Koek JH, Erkelens C, Lugtenburg J (1986) Recl Trav Chim Pays-Bas **105**: 360
[4] Ma JS, Lightner DA (1991) Tetrahedron **47**: 3719
[5] Hwang KO, Lightner DA (1994) Tetrahedron **50**: 1955
[6] Boiadjiev SE, Lightner DA (2004) J Phys Org Chem **17**: 675
[7] Boiadjiev SE, Lightner DA (2004) J Org Chem (in press)
[8] Clezy PS, Liepa AJ (1971) Aust J Chem **24**: 1933
[9] Mironov AF, Ivanova LA, Abramenko TV, Evstigneeva RP (1979) Zhur Org Chem **15**: 1082, and references therein
[10] a) Corwin AH, Ellingson RC (1944) J Am Chem Soc **66**: 1146; b) Corwin AH, Buc SR (1944) J Am Chem Soc **66**: 1151
[11] Weidel X, Ciamician G (1880) Monatsh Chem **1**: 279. See also Fischer H, Orth H (1934) Die Chemie des Pyrrols, vol I. Akademische Verlagsgesellschaft, Leipzig, pp 236
[12] a) Chen Q, Huggins MT, Lightner DA, Norona W, McDonagh AF (1999) J Am Chem Soc **121**: 9253; b) Kinoshita H, Hayashi Y, Murata Y, Inomata K (1993) Chem Lett 1437
[13] a) Fischer H, Orth H (1934) Die Chemie des Pyrrols, vol 1, Akademische Verlagsgesellschaft, Leipzig, pp 247–248; b) Hantzsch A (1890) Chem Ber **23**: 1474
[14] Budzikiewicz H, Djerassi C, Jackson AH, Kenner GW, Newman DJ, Wilson JM (1964) J Chem Soc 1949
[15] Woodward RB, Ayer WA, Beaton JM, Bickelhaupt F, Bonnett R, Buchschacher P, Closs GL, Dutler H, Hannah J, Hauck FP, Ito S, Langemann A, Le Goff E, Leimgruber W, Lwowski W, Sauer J, Valenta Z, Volz H (1990) Tetrahedron **46**: 7599
[16] a) Arnold DP, Nitschinsk LJ, Kennard CHL, Smith G (1991) Aust J Chem **44**: 323; b) Kaesler RW, Le Goff E (1983) J Org Chem **48**: 4399; c) van Leusen AM, Siderius H, Hoogenboom BE, van Leusen D (1972) Tetrahedron Lett 5337
[17] Dezelic M, Grom-Dursun K (1960) Glasnik Drustva Hemicana Technol, NR Bosne Hercegovine **9**: 49; Chem Abstr (1963) **58**: 2423h