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Methoxyl-induced fluorescence quenching in *N,N′*-bridged 9*H*-dipyrrinones and an X-ray crystal structure

Sanjeev K. Dey, David A. Lightner

Department of Chemistry, University of Nevada, Reno, Nevada, USA

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Abstract Strongly fluorescent dipyrrinones can be prepared by bridging the pyrrole and lactam nitrogens with a carbonyl group, from reaction with *N,N′*-carbonyldiimidazole in the presence of a strong, non-nucleophilic base. The yellow, *N,N′*-carbonyl-bridged dipyrrinones typically have fluorescent quantum yields (ϕ_F) approaching 1.0. Thus, in chloroform, *N,N′*-bridged 9*H*-dipyrrinones with β-alkyl substituents: 2,3-diethyl-7,8-dimethyl has $\phi_F = 0.90$ ($\lambda_{em} =$ 465 nm) and 2,3-dimethyl-7,8-dimethoxy has $\phi_F =$ 0.84 ($\lambda_{em} = 482$ nm). In contrast, 2,3-dimethoxy-7,8-dimethyl and 2,3,7,8-tetramethoxy show red-shifted λ_{em} but with strongly reduced ϕ_F: $\phi_F = 0.10$ ($\lambda_{em} =$ 511 nm) and 0.08 ($\lambda_{em} = 511$ nm), respectively. Methoxy substituents on the lactam, but not the pyrrole ring act to quench the fluorescence and shift the emission and excitation wavelengths bathochromically. The first X-ray crystal structure of an *N,N′*-carbonyl-bridged dipyrrinone was obtained from 7,8-dimethoxy-2,3-dimethyl-10*H*-dipyrrin-1-one.

Keywords Pyrrole; Synthesis; Fluorescence; X-Ray.

Introduction

In contrast to the parent dipyrrinones, *N,N′*-carbonyl-bridged dipyrrinones are typically intensely fluorescent [1, 2], with fluorescence quantum yields (ϕ_F) approaching unity in organic solvents. The chromophore has been used to probe chirality in circular dichroism (*CD*) spectroscopy [2a, 2b] and in fluorescence-detected *CD* [2c]. Recently analogs for assessing Ca^{2+} concentrations [3], for incorporation into biomolecules [4], and with potential medical applications in detecting cholestasis [5] and use in fluorescence imaging were prepared [5]. In only a few instances we have found markedly reduced fluorescence in this chromophore: analogs with –CH=$C(CN)CO_2CH_2CH_3$ and –CH=$C(CO_2CH_2CH_3)_2$ substituents at the pyrrole β-position, where ϕ_F dropped to ~0.1 in cyclohexane and $\sim 10^{-3}$ in *DMSO* [1d], and those with substituents at the pyrrole α-position, –CH=$CHCO_2CH_3$, $C(=O)CH_3$, and CHO, also with large decreases in ϕ_F [1g].

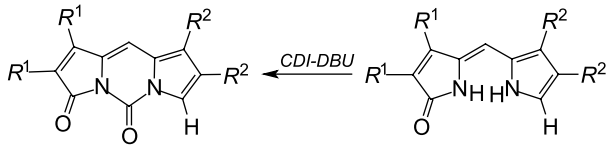
In order to explore the influence of heteroatoms on the fluorescence of dipyrrinones, we prepared four 9*H*-dipyrrinones with a combination of β-methoxyls and alkyls (**5**–**8′**) and converted them to the carbonyl-bridged analogs **1**–**4′** (Fig. 1). In the following, we describe their syntheses and characterization, including the X-ray structure determination, first and we report on the surprising fluorescence quenching effect of the β-methoxyls located on the lactam ring.

Correspondence: David A. Lightner, Department of Chemistry, University of Nevada, Reno, Nevada 89557-0020, USA. E-mail: lightner@scs.unr.edu

Results and discussion

Synthesis aspects

For the preparation of **5**–**7** (Scheme 1) and **1**–**3** (Fig. 1), 3,4-dimethoxy-1*H*-pyrrole was the required



	R^1	R^2	
1	OCH_3	OCH_3	**5**
2	OCH_3	CH_3	**6**
3	CH_3	OCH_3	**7**
4	CH_2CH_3	CH_3	**8**
4′	CH_3	CH_3	**8′**

Fig. 1 The target *N*,*N*′-carbonyl-bridged 9*H*-dipyrrinones of this work (**1**–**4**′) and their dipyrrinone precursors (**5**–**8**′)

synthetic relay compound. It was known from published work [6], and previously we had shown how to convert it to the corresponding pyrrolin-2-one (**9**) [7], which serves as the precursor to **5** and **6**, and **1** and **2**. Conversion of **9** to dipyrrinones **5** and **6** with methoxy groups on the lactam ring required either 3,4-dimethoxy-2-formyl-1*H*-pyrrole (**12**) or 3,4-dimethyl-2-formyl-1*H*-pyrrole (**13**). The former was prepared in 52% yield by a *Vilsmeier* reaction [8] on **9**; the latter was prepared by treatment of the known ethyl 3,4-dimethyl-1*H*-pyrrole-2-carboxylate first with KOH to saponify, then with trifluoroacetic acid and ethyl orthoformate. Base-catalyzed condensation of **9** and **12** yielded the tetramethoxydipyrrinone **5** in 40% yield, from which the carbonyl-bridged analog **1** was prepared in 91% yield by reaction of 1,1′-carbonyldiimidazole (*CDI*) and 1,8-diazabicyclo[5.4.0]undec-7-ene (*DBU*). Similarly, **6** was prepared from **9** and **13** in 55% yield and converted to **2** in 92% yield, and **7** was prepared from **10** and **12** in 87% yield and converted to **3** in 91% yield.

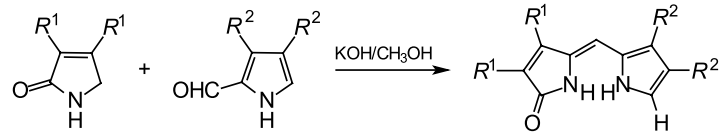
Dipyrrinone **8** was prepared in 60% yield from 3,4-diethyl-3-pyrrolin-2-one (**11**) and 3,4-dimethyl-2-formyl-1*H*-pyrrole (**13**), and **8**′ [9] was prepared from **10** and **13** in 52% yield. As above, these dipyrrinones were converted in excellent yields to their *N*,*N*′-carbonyl-bridged analogs using *CDI* and *DBU* to give **4** from **8** in 92% yield, and **4**′ from **8**′ in 80% yield.

Structural aspects

The dipyrrinone structures **5**–**8**′ and their derivatives **1**–**4**′ follow from the method of synthesis and the known structures of their monopyrrole precursors **9**–**13**. The structures were confirmed by their ^{13}C NMR spectra (Table 1). Characteristic of *N*,*N*′-carbonyl-bridged dipyrrinones, the new C=O group appears near 140 ppm and the lactam carbonyl is more shielded (by ~5–10 ppm) than that in the parent dipyrrinone. Other carbon signals remain close to those observed for the parent dipyrrinones. Clearly, the location of the methoxy groups plays a role in shifting the carbon resonances. Thus, when on the pyrrole β-positions, C(7) and C(8) are deshielded by ~20 ppm, and C(6) and C(9) are shielded by ~15 ppm. Substituting the lactam β-positions with methoxyls imparts no similar strong shifts to the lactam ring carbons: C(1) becomes more shielded by ~5 ppm.

Molecularity in solution from vapor pressure osmometry

As determined in chloroform solution, and consistent with the behavior of other dipyrrinones [10, 11], the parent 9*H*-dipyrrinones **5**–**8**′ are dimeric in solution (Table 2). The dimers are held together by intermolecular hydrogen bonds [10, 11]. However, when the dipyrrinone nitrogens are connected *via* a carbonyl bridge (**1**–**4**′), intermolecular hydrogen bonding is no longer possible, and compounds **1**–**4**′ all are monomers over the concentration range studied. This is understandable in terms of **5**–**8**′ being intermolecularly hydrogen-bonded dimers involving the NHs

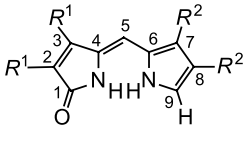


9: $R^1 = OCH_3$ **12**: $R^2 = OCH_3$
10: $R^1 = CH_3$ **13**: $R^2 = CH_3$
11: $R^1 = CH_2CH_3$

5 (from **9** + **12**)
6 (from **9** + **13**)
7 (from **10** + **12**)
8 (from **11** + **13**)
8′ (from **10** + **13**)

Scheme 1

Table 1 Assignments and comparison of the ^{13}C NMR chemical shifts of **1**–**8′** in $(CD_3)_2SO$ at 23°C



	R^1	R^2	
1	OCH_3	OCH_3	**5**
2	OCH_3	CH_3	**6**
3	CH_3	OCH_3	**7**
4	CH_2CH_3	CH_3	**8**
4′	CH_3	CH_3	**8′**

Carbon		Chemical Shifts (δ/ppm) for									
		1	**2**	**3**	**4**	**4′**	**5**	**6**	**7**	**8**	**8′**
1	C=O	161.4	161.6	166.8	166.6	166.8	165.9	166.0	171.6	171.6	171.8
2	=C–	126.8	126.8	125.9	130.8	125.9	127.0	126.1	125.7	129.1	124.1
3	=C–	147.0	147.3	142.5	147.8	142.5	146.6	146.4	141.5	146.9	141.5
4	=C–	123.4	126.1	131.6	130.6	131.9	122.5	121.6	131.5	128.4	129.7
5	=C–	95.9	97.4	96.6	98.3	97.9	96.3	96.7	97.5	97.9	97.8
6	=C–	114.7	123.7	115.7	126.9	126.8	114.6	123.2	115.1	123.7	123.6
7	=C–	135.8	121.9	135.8	122.0	121.8	135.2	118.2	134.9	118.2	118.1
8	=C–	144.7	125.8	145.0	126.0	125.8	140.6	121.0	140.7	121.8	121.7
9	=CH	99.5	116.9	99.2	116.8	116.6	104.3	120.1	104.1	120.0	119.8
10	C=O	139.8	140.0	140.6	140.9	140.7	–	–	–	–	–
2^1	CH_2/CH_3	–	–	8.2	16.3	8.2	–	–	9.1	16.3	8.3
2^2	CH_3	60.6	60.9	–	13.3	–	61.0	60.3	–	13.8	–
3^1	CH_2/CH_3	–	–	9.6	17.1	9.6	–	–	10.2	17.0	9.5
3^2	CH_3	59.6	59.6	–	14.5	–	59.7	59.1	–	15.7	–
7^1	CH_3	–	8.6	–	8.7	8.6	–	9.1	–	9.1	9.1
7^2	CH_3	60.9	–	60.7	–	–	61.8	–	61.9	–	–
8^1	CH_3	–	9.9	–	10.0	10.0	–	10.0	–	10.0	10.0
8^2	CH_3	58.1	–	58.1	–	–	58.6	–	58.6	–	–

and lactam carbonyl [10, 11]. When the NHs are no longer available, as in **1**–**4′**, hydrogen bonding is no longer possible, and monomers prevail.

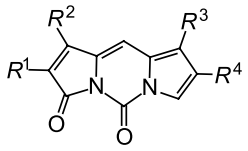
UV-visible spectra

Consistent with measurements from other dipyrrinones, the UV-visible spectra (Table 3) of 9*H*-dipyrrinones **5**–**8′** show a long wavelength maximum absorption of 30,000–40,000 near 400 nm. Absent an alkyl substituent at C(9), the 9*H*-dipyrrinones **8** and **8′** exhibit a small (~10 nm) hypsochromic shift. Methoxyl substituents on the lactam ring of **5** and **6** cause a 10–15 nm hypsochromic shift in λ_{max} relative to **8** and **8′**; when the methoxyl substituents are located at the pyrrole β-positions, the shift is much less: ~5 nm. Locating methoxy groups on the lactam ring apparently has a much greater influence on the UV-visible λ_{max} than locating them on the pyrrole ring. The trends seen for the parent dipyrrinones generally carry over to the bridged analogs **1**–**4′**. In addition, the long wavelength UV-visible absorbance coefficients of **1**–**4′** are greatly reduced compared with the parent dipyrrinones.

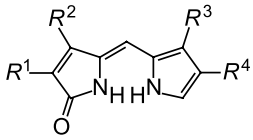
Fluorescence

We noticed immediately that to the eye bridged dipyrrinone **1** seemed to be less fluorescent than is typical of other bridged dipyrrinones. And, in fact, when the fluorescence quantum yield (ϕ_F) was determined (Table 4), it became clear that severe fluorescence

Table 2 Molecular weights (MWs) of carbonyl-bridged 9*H*-dipyrrinones **1**–**4′** and parent 9*H*-dipyrrinones **5**–**8′** determined by vapor pressure osmometry[a] at 45°C in $CHCl_3$ solution[b]



1–4′



5–8′

	R^1	R^2	R^3	R^4	Formula weight (FW/g mol^{-1})	Measured MW/g mol^{-1}
1	OCH_3	OCH_3	OCH_3	OCH_3	306	305 ± 3
2	OCH_3	OCH_3	CH_3	CH_3	274	277 ± 6
3	CH_3	CH_3	OCH_3	OCH_3	274	281 ± 11
4	CH_2CH_3	CH_2CH_3	CH_3	CH_3	270	275 ± 7
4′	CH_3	CH_3	CH_3	CH_3	242	235 ± 13
5	OCH_3	OCH_3	OCH_3	OCH_3	280	570 ± 15
6	OCH_3	OCH_3	CH_3	CH_3	248	490 ± 12
7	CH_3	CH_3	OCH_3	OCH_3	248	496 ± 8
8	CH_2CH_3	CH_2CH_3	CH_3	CH_3	244	485 ± 4
8′	CH_3	CH_3	CH_3	CH_3	216	430 ± 7

[a] Calibrated with benzil (FW = 210 g mol^{-1}, MW = 220 ± 15 g mol^{-1}); [b] Conc. range $0.5–2.0 \times 10^{-3}$ mol kg^{-1}

Table 3 Solvent dependence of the UV-visible spectra of **1**–**8′**

Compound	λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1})				
	Cyclohexane	C_6H_6	$CHCl_3$	CH_3OH	$(CH_3)_2SO$
1	398 (12700)	398 (14900)	402 (15300)	398 (14500)	400 (14900)
2	393 (12700)	398 (14900)	402 (14700)	398 (14100)	399 (15600)
3	419 (7400)^{sh} 396 (8200)	417 (12100)^{sh} 398 (12900)	401 (11800)	406 (12500)	394 (11800)
4	421 (15700)^{sh} 398 (15900)	419 (16000)^{sh} 404 (16500)	412 (14800)	412 (14800)	412 (12700)
4′	419 (17500)^{sh} 397 (18000)	416 (16500)^{sh} 402 (16800)	411 (15500)	410 (16000)	411 (17000)
5	380 (37200)	382 (22800) 367 (22500)^{sh}	379 (23300)	382 (26000)	382 (24500)
6	381 (37000)	383 (32000)	381 (29400)	386 (34200)	385 (32700)
7	412 (21400)^{sh} 390 (35800)	392 (27000) 377 (26000)^{sh}	391 (28700)^{sh} 377 (30100)	395 (32900)	396 (31900) 384 (31000)^{sh}
8	415 (24700)^{sh} 394 (42500)	395 (33900)	392 (29300)	400 (33900)	400 (32400)
8′	395 (41000)	394 (33600)	393 (30000)	400 (32600)	400 (32000)

Table 4 Solvent dependence of the fluorescence excitation (λ_{ex}/nm) and emission (λ_{em}/nm) wavelengths and quantum yields (ϕ_F) of **1**–**4′**

Pigment	Cyclohexane		C_6H_6		$CHCl_3$		CH_3OH		$(CH_3)_2SO$	
	λ_{em}	ϕ_F	λ_{em}	ϕ_F	λ_{em}	ϕ_F	λ_{em}	ϕ_F	λ_{em}	ϕ_F
1[a]	479	0.27	491	0.30	511	0.08	545	0.03	516	0.13
2[a]	480	0.37	493	0.42	511	0.10	540	0.02	511	0.11
3[a]	470	1.0	468	0.92	482	0.84	512	0.39	503	0.90
4[a]	454	1.0	482	1.0	465	0.90	514	0.44	494	1.0
4′[a]	456	1.0	468	0.95	482	0.99	519	0.52	494	0.94

[a] $\lambda_{exc} = 398$ nm; reference standard: 9,10-diphenylanthracene

quenching had occurred. The behavior may be compared with carbonyl-bridged all-alkyl-substituted 9*H*-dipyrrinones **4** and **4′** where ϕ_F approaches unity over the range of solvents studied. In order to probe the cause of the fluorescence quenching found in **1**, we synthesized and measured ϕ_F values for analogs **2** and **3** each with two methoxy groups and two methyl groups. In **2** the methoxy groups are located on the lactam ring; in **3** they are located on the pyrrole ring. And the fluorescence data clearly show (Table 4) that β-methoxy groups on the pyrrole ring have only a minor effect in quenching fluorescence, while methoxy groups on the lactam ring exert the major effect. The reason for the strong fluorescence quenching is unclear. Methoxy groups are not known to quench fluorescence in fluorogenic substances, such as in stilbenes [12a], coumarins [12b, 12c], quinolinones [12c], and fluoranthenes [12d]. Dipole–dipole effects between the methoxy groups and the lactam chromophore may play a role.

All bridged dipyrrinones show a clear solvatochromic effect in their fluorescence spectra, with λ_{em} shifting strongly toward the red with increasing solvent dielectric. For **1** and **2**, the shift is accompanied by a strongly reduced ϕ_F. For **3** and **4**, ϕ_F remains near unity, except in CH_3OH solvent, where contact between solvent and pigment probably involves hydrogen bonding to the pigment carbonyl group(s). In the most polar solvent ($(CH_3)_2SO$), ϕ_F remains high for **3**, **4**, and **4′** but subdued for **1** and **2**. The presence of methoxy groups on the lactam ring (as in **1** and **2**) causes λ_{em} to shift toward the red by ~25 nm relative to **4** and **4′**, but with methoxy groups only on the pyrrole ring (**3**), the shift is less pronounced (~10–15 nm relative to **4** and **4′**).

X-Ray crystal structure of 3

As might be anticipated from its drawn structure (Fig. 1), **3** (and we assume other *N,N*-carbonyl-bridged dipyrrinones) has a planar polycyclic skeleton. Molecules of **3** in the crystal stack in pairs (Fig. 2A) that lie in layers of parallel sheets some 3.5 Å apart (Fig. 2B, C). The molecules stack one above each other such that the relative orientation of molecules in each stack is orientated by 180° in plane. The new C=O group is slightly longer (1.214 Å) than the lactam C=O (1.212 Å), and the associated N–C=O single bonds of the former (1.380 Å) are much shorter than that in the lactam (1.436 Å). Carbon–carbon double bond alternation C(2)=C(3): 1.349 Å; C(3)–C(4): 1.452 Å; C(4)=C(5): 1.345 Å; C(5)–C(6): 1.422 Å; C(6)=C(7): 1.379 Å; C(7)–C(8): 1.427 Å; C(8)=C(9): 1.356 Å is well established. Curiously, only in the pyrrole ring do the double bonds differ much in length, with the long C(6)=C(7) bond. The other C=C double bonds are remarkably similar in length. And in this sense they differ from those found in dipyrrinones, *e.g.*, 2,3,8-tetraethyl-7,9-dimethyl-10*H*-dipyrrin-2-one, C(2)=

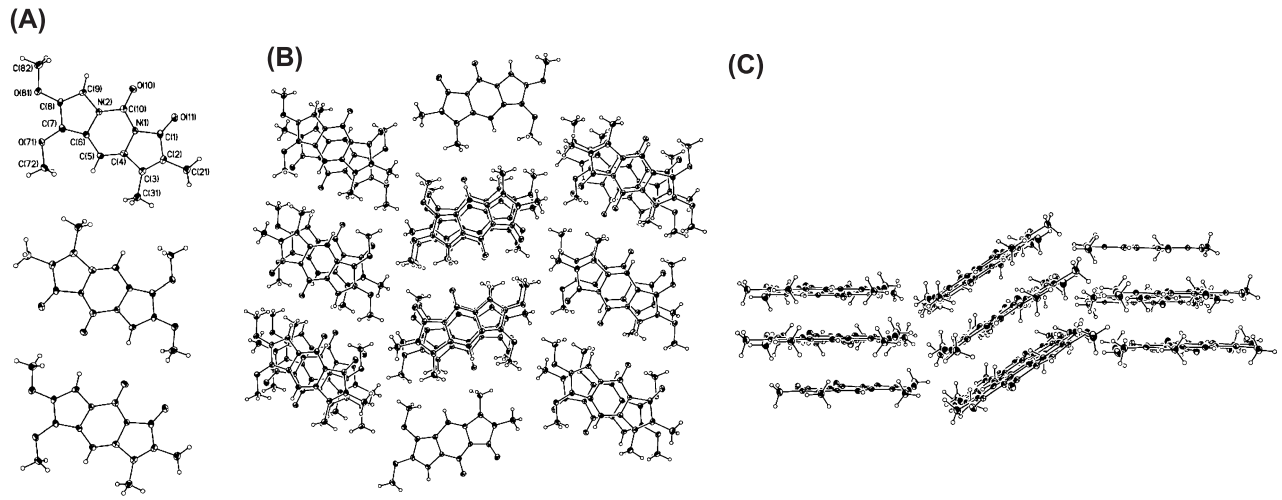


Fig. 2 Crystal structure drawings of **3** showing (A) the numbering system used and orientation of molecules lying in a common plane and the stacking pattern in face (B) and edge (C) views. The three molecules of (A), as viewed from top to bottom, may be located in the left column of structures in (B) as the topside structures in the upper and middle pairs and the structure sandwiched in the middle of the bottom set of three

C(3): 1.303 Å; C(3)–C(4): 1.443 Å; C(4)=C(5): 1.347 Å; C(5)–C(6): 1.405 Å; C(6)=C(7): 1.399 Å; C(7)–C(8): 1.376 Å, and C(8)=C(9): 1.367 Å, where bond alternation was previously noted [13], and where it can be seen that the C(2)=C(3), C(5)–C(6), and C(7)–C(8) are shorter than in **3**, whereas C(6)=C(7) is longer. These differences are presumably due to the β-methoxy substituents on the pyrrole ring of **3**.

The internal bond angle at C(5) in **3** (119°) is much smaller than that in the dipyrrinone (133°) [12], indicating that strain is imposed here in forming the third ring of **3**. The adjacent internal bond angles, at C(6) and C(4), 117 and 121°, respectively, of **3** are also more compressed than those of the dipyrrinone, 126 and 127°, respectively [13], all apparently due to steric compression in forming the *N*,*N*′-carbonyl bridge.

Concluding comments

In our attempts to prepare strongly-fluorescent *N*,*N*′-carbonyl-bridged dipyrrinones with $\lambda_{em} > 500$ nm, from methoxy-substituted dipyrrinones **5**–**7** we prepared analogs (**1**–**3**) whose UV-visible long wavelength absorption was shifted ~10–15 nm hypsochromically relative to the all-alkyl substituted analogs (**4**, **4**′). Yet the fluorescent emission wavelength (λ_{em}) of **1** and **2** is bathochromically shifted relative to **4** and **4**′ by ~25 nm. Unexpectedly, the derivatives with methoxy groups on the lactam ring (**1** and **2**) were only poorly-fluorescent, whereas, with methoxy groups on the pyrrole ring no such quenching is observed. It is unclear why **1** and **2** are such weak fluorophores, while **3** remains strongly fluorescent. An X-ray crystal structure of **3** indicates a planar polycyclic framework with the molecules paired up and lying in parallel sheets.

Experimental

All fluorescence spectra were measured as reported previously [14] using 9,10-diphenylanthracene as reference standard 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 ^{1}H frequency of 500 MHz and ^{13}C frequency of 125 MHz in solutions of $CDCl_3$ (referenced at 7.26 ppm for ^{1}H and 77.00 ppm for ^{13}C or $(CD_3)_2SO$ (referenced at 2.49 ppm for ^{1}H 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. Vapor-pressure osmometry (VPO) experiments were run on an OSMOMAT 070 instrument (Gonotek, Berlin). 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 corrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ, and found to be within ±0.3% of theoretical values.

The spectral data were obtained in spectral grade solvents (Aldrich or Fischer) which were distilled under Ar stream just prior to use. Before the distillation $CHCl_3$ was passed through a basic alumina column. Distillation of $(CH_3)_2SO$ solvent was carried out at 0.5 mm Hg vacuum collecting the solvent at 0°C and thawing it under Ar. The starting compounds 3,4-dimethoxy-3-pyrrolin-2-one (**9**) [7], 3,4-dimethyl-3-pyrrolin-2-one (**10**) [9], 3,4-diethyl-3-pyrrolin-2-one (**11**) [7], and 3,4-dimethyl-2-formyl-1*H*-pyrrole (**13**) [9] were prepared as described previously.

1,2,8,9-Tetramethoxy-3H,5H-dipyrrolo[1,2-c:2′,1′-f]-pyrimidine-3,5-dione (**1**, $C_{14}H_{14}N_2O_6$)
To a solution of 280 g (1.00 mmol) dipyrrinone **5** was added 0.81 (5.0 mmol) *CDI*, 80 cm^3 anhydrous CH_2Cl_2 and 0.75 cm^3 (0.20 mmol) *DBU*, and the mixture was heated at reflux under nitrogen for 16 h. After cooling, the mixture was washed with 100 cm^3 of 1% aqueous HCl, then with H_2O (1×100 cm^3), and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under vacuum, the residue was purified by radial chromatography (eluent: 2% CH_3OH in CH_2Cl_2, vol/vol) and recrystallized from *n*-hexane-ethyl acetate to give pure **1**. Yield: 270 mg (90%); mp 188–190°C; ^{1}H NMR ($CDCl_3$): $\delta = 3.82$ (3H, s), 3.96 (3H, s), 3.98 (3H, s), 4.18 (3H, s), 6.62 (1H, s), 7.12 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 58.4$, 59.8, 61.7, 61.18, 96.2, 99.5, 115.7, 123.9, 127.4, 136.5, 145.6, 147.1, 162.3 ppm.

1,2-Dimethoxy-8,9-dimethyl-3H,5H-dipyrrolo[1,2-c:2′,1′-f]-pyrimidine-3,5-dione (**2**, $C_{14}H_{14}N_2O_4$)
Following the procedure for **1**, 248 mg (1.00 mmol) dipyrrinone **6**, (0.81 g, 5.0 mmol) *CDI*, and 0.75 cm^3 (0.20 mmol) *DBU* gave pure **2** after crystallization from ethyl acetate-*n*-hexane. Yield: 255 mg (93%); mp 159–160°C; ^{1}H NMR ($CDCl_3$): $\delta = 2.05$ (3H, s), 2.08 (3H, s), 3.96 (3H, 2), 4.19 (3H, s), 6.52 (1H, s), 7.43 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 9.2$, 10.5, 59.8, 61.2, 97.2, 117.8, 122.3, 126.3, 126.5, 127.4, 141.0, 147.3, 162.4 ppm.

1,2-Dimethyl-8,9-dimethoxy-3H,5H-dipyrrolo[1,2-c:2′,1′-f[pyrimidine-3,5-dione (**3**, $C_{14}H_{14}N_2O_4$)
As in the procedure for **1**, a mixture of 248 mg (1.00 mmol) dipyrrinone **7**, 0.81 g (5.0 mmol) of *CDI*, and 0.75 cm^3 (2.0 mmol) *DBU* in 80 cm^3 anhydrous CH_2Cl_2 was heated at reflux under nitrogen for 16 h. Work-up afforded pure **3**, after purification by radial chromatography (eluent: 2% CH_3OH in CH_2Cl_2, vol/vol) and recrystallization from *n*-hexane-ethyl

acetate. Yield: 240 mg (91%); mp 245–247°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.93$ (3H, s), 2.11 (3H, s), 3.82 (3H, s), 3.97 (3H, s), 6.49 (1H, s), 7.11 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 8.8$, 10.0, 58.4, 61.2, 95.8, 99.3, 116.5, 127.5, 132.3, 136.4, 141.5, 145.8, 167.6 ppm.

1,2-Diethyl-8,9-dimethyl-3H,5H-dipyrrolo[1,2-c:2′,1′]-pyrimidine-3,5-dione (**4**, $C_{16}H_{18}N_2O_2$)

Following the synthesis procedure for **1**, to a solution of 260 mg (1.00 mmol) dipyrrinone **8** in 80 cm^3 anhydrous CH_2Cl_2 was added 0.81 mg (5.0 mmol) *CDI* and 0.75 cm^3 (0.50 mmol) *DBU*, and the mixture was heated at reflux under nitrogen for 16 h. Work-up and purification as before gave pure **4**. Yield 240 mg (92%); mp 198–199°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.13$ (3H, t, $J = 7.5$ Hz), 1.24 (3H, t, $J = 7.5$ Hz), 2.05 (3H, s), 2.11 (3H, s), 2.40 (2H, q, $J = 7.5$ Hz), 2.55 (2H, q, $J = 7.5$ Hz), 6.42 (1H, s), 7.44 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 9.3$, 10.5, 13.7, 14.8, 17.1, 18.1, 97.2, 117.6, 122.2, 126.5, 126.9, 131.4, 132.3, 141.9, 147.0, 167.5 ppm.

1,2,8,9-Tetramethyl-3H,5H-dipyrrolo[1,2-c:2′,1′-f]-pyrimidine-3,5-dione (**4′**, $C_{14}H_{14}N_2O_2$)

Following the procedure outlined for **1**, to a solution of 216 mg (1.00 mmol) dipyrrinone **8′** in 80 cm^3 anhydrous CH_2Cl_2 was added 81 mg (5.0 mmol) *CDI* and 0.75 cm^3 (0.50 mmol) *DBU* and the mixture was heated at reflux under nitrogen for 16 h. Work-up and purification as before gave pure **4′**. Yield: 193 mg (80%); mp 240–242°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.93$ (3H, s), 2.05 (3H, s), 2.10 (3H, s), 2.1 (3H, s), 6.93 (1H, s), 7.42 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 8.8$, 9.3, 10.0, 10.6, 97.0, 117.5, 126.5, 126.9, 127.4, 132.4, 141.7, 141.7, 167.7 ppm.

2,3,7,8-Tetramethoxy-10H-dipyrrin-1-one (**5**, $C_{13}H_{16}N_2O_5$)

To a mixture of 0.50 g (3.2 mmol) 3,4-dimethoxy-2-formyl-1*H*-pyrrole (**12**), 1.0 mg (7.0 mmol) 3,4-dimethoxy-1,5-dihydro-2*H*-pyrrol-2-one (**9**) in 80 cm^3 of methanol was added a solution of 5.6 g (0.10 mmol) KOH, and the mixture was heated at vigorous reflux for 48 h. After 24 h cooling, an additional equivalent of **9** was added. After cooling, the solvent was evaporated under vacuum, the residue was diluted with 10 cm^3 H_2O, cooled in an ice bath, and extracted with CH_2Cl_2 (5×100 cm^3). The organic layer was evaporated (rotovap) and purified by flash chromatography to give dipyrrinone **5**, which was pure enough for use in the next step. Yield: 0.36 g (40%); mp 150–152°C; ^{1}H NMR ($CDCl_3$): $\delta = 3.79$ (3H, s), 3.89 (3H, s), 3.92 (3H, s), 4.1 (3H, s) 5.85 (1H, s), 6.35 (1H, dd, $J = 2.0$ Hz), 8.10 (1H, br.s), 9.30 (1H, br.s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 58.4$, 59.2, 60.8, 61.7, 97.8, 102.8, 115.2, 123.6, 127.1, 135.0, 141.1, 146.4, 166.6 ppm.

2,3-Dimethoxy-2,8-dimethyl-10H-dipyrrin-1-one (**6**, $C_{13}H_{16}N_2O_4$)

Following the preparation of **5**, to a solution of 100 mg (0.80 mmol) pyrrole aldehyde **13** and pyrrolinone **9** (120 mg, 0.80 mmol) in 30 cm^3 methanol was added 2.5 cm^3 5 *N* methanolic KOH, and the mixture was heated at reflux under nitrogen for 12 h. Work-up as before gave pure **6**. Yield: 0.11 g (55%); mp 240–242°C; ^{1}H NMR ($CDCl_3$): $\delta = 2.03$ (3H, s), 2.12 (3H, s), 3.93 (3H, s), 4.17 (3H, s), 6.30 (1H, s), 6.77 (1H, d, $J = 2.5$ Hz), 9.98 (1H, br.s), 18.43 (1H, br.s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 9.6$, 10.3, 59.4, 60.9, 101.1, 119.6, 120.6, 121.3, 124.3, 124.6, 126.3, 148.2, 168.7 ppm.

7,8-Dimethoxy-2,3-dimethyl-10H-dipyrrin-1-one (**7**, $C_{13}H_{16}N_2O_3$)

Following the same procedure for synthesis of **5**, 500 mg (3.23 mmol) of pyrrole aldehyde **12** and 0.716 g (6.45 mmol) pyrrolinone **10** were dissolved in 60 cm^3 methanol to which ~2.8 g solid KOH were added. Reflux for 30 h under nitrogen was followed by cooling and quenching by the addition of 50 cm^3 water. After extraction with 600 cm^3 CH_2Cl_2 (6×100 cm^3), the organic phases were combined, dried over anhydrous Na_2SO_4, and evaporated. The residue was dissolved in a little ethyl acetate, and after addition of *n*-hexane, pure product **7** precipitated. Yield: 700 mg (87%); mp 220–222°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.90$ (3H, s), 2.10 (3H, s), 3.89 (3H, s), 4.02 (3H, s), 6.50 (1H, s), 6.9 (1H, s), 9.48 (1H, br.s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 8.6$, 10.1, 58.7, 61.8, 99.21, 104.3, 115.6, 125.3, 131.3, 137.0, 140.9, 142.1, 173.6 ppm.

2,3-Diethyl-7,8-dimethyl-10H-dipyrrin-1-one (**8**, $C_{15}H_{22}N_2O$)

Following the procedure for the synthesis of **5**, the residue was purified by radial chromatography (eluent: 1–3% CH_3OH in CH_2Cl_2, vol/vol) and then recrystallized from CH_3OH in CH_2Cl_2 to give pure dipyrrinone **8**. Yield: 1.1 gm (60%); mp 118–120°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.13$ (3H, t, $J = 7.6$ Hz), 1.20 (3H, t, $J = 7.6$ Hz), 2.00 (3H, s), 2.34 (3H, s), 2.55 (2H, q, $J = 7.6$ Hz), 2.56 (2H, q, $J = 7.6$ Hz), 6.16 (1H, s), 6.80 (1H, d, $J = 2.5$ Hz), 10.49 (1H, br.s), 11.17 (1H, br.s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 9.7$, 10.4, 14.1, 16.1, 17.2, 18.0, 101.7, 119.6, 121.5, 124.5, 124.6, 128.4, 129.2, 148.2, 174.3 ppm.

3,4-Dimethoxy-2-formyl-1H-pyrrole (**12**, $C_7H_9NO_3$)

3,4-Dimethoxy-1*H*-pyrrole (500 mg, 4.00 mmol) was dissolved in 50 cm^3 anhydrous ether in a 250 cm^3 r.b. flask. To it was added 0.36 cm^3 dry *DMF* and 0.43 cm^3 $POCl_3$. A yellow solid precipitated, and the reaction was allowed to stir at 0°C for 6 h, then kept at 5°C overnight. The organic layer was evaporated (rotovap) and to the solid residue was added ~2 g KOH in minimal amount of water while cooling in an ice bath. The resulting solution was allowed to stir for 30 min, then it was extracted with 6×100 cm^3 CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated (rotovap) to obtain crude pyrrole aldehyde **9**, which was purified using column chromatography. Yield: 320 mg (52%); mp 47–48°C; ^{1}H NMR ($CDCl_3$): $\delta = 3.68$ (3H, s), 3.98 (3H, s), 6.58 (1H, dd, $J = 2.0$ Hz), 8.4 (1H, br.s), 9.52 (1H, s) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 59.3$, 61.5, 111.7, 119.6, 139.1, 144.4, 176.9 ppm.

X-Ray structure and solution

Crystals of **3** were grown by slow diffusion of *n*-hexane into a solution of CH_2Cl_2. A crystal was placed into the tip of a

0.1 mm diameter glass capillary and mounted on a Bruker SMART Apex system for data collection at 100(2) K. A preliminary set of cell constants was calculated from reflections harvested from 3 sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed (final orientation matrices determined from global least-squares refinement of 4984 reflections). The data collection was carried out using MoKα radiation (0.71073 Å graphite monochromator) with a frame time of 20 s and a detector distance of 4.94 cm. A randomly oriented region of reciprocal space was surveyed to the extent of 2 hemispheres and to a resolution of 0.66 Å. Four major sections of frames were collected with 0.5° steps in ω at 600 different ϕ settings and a detector position of 27° in 2θ. The intensity data were corrected for absorption and decay (SADABS) [15]. Final cell constants were calculated from the *xyz* centroids of strong reflections from the actual data collection after integration (SAINT 6.45, 2003) [16]. Crystal data and refinement information given in Table 5.

Table 5 Crystal data and structure refinement for **3**

Compound	**3**
Empirical formula	$C_{14}H_{14}N_2O_4$
Formula weight	274.28
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/*c*
Unit cell dimensions	$a = 6.9495(6)$ Å $\alpha = 90°$ $b = 21.2529(19)$ Å $\beta = 106.366(5)°$ $c = 8.5671(6)$ Å $\gamma = 90°$
Volume	1214.07(17) Å^3
Z	4
Density (calculated)	1.358 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F(000)	528
Crystal size	$0.24 \times 0.10 \times 0.05$ mm^3
Theta range for data collection	1.92 to 22.50°
Index ranges	$-8 \le h \le 5$, $-17 \le k \le 24$, $-10 \le l \le 10$
Reflections collected	6259
Independent reflections	2104 [R(int) = 0.0406]
Completeness to Theta = 25.00°	98.2%
Absorption correction	None
Max. and min. Transmission	0.9951 and 0.9770
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2104/0/186
Goodness-of-fit on F^2	1.048
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0393$, w$R2 = 0.0915$
R indices (all data)	$R1 = 0.0591$, w$R2 = 0.0981$
Extinction coefficient	0.0109(18)
Largest diff. peak and hole	0.236 and −0.223 eÅ^{-3}

The structure was solved and refined using SHELXL-L [17]. The monoclinic space group P2(1)/*c* was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the *E*-map. Full-matrix least squares/difference *Fourier* cycles were performed for structure refinement. All non-hydrogen atoms were refined with anisotropic displacement parameters unless stated otherwise. Hydrogen atom positions were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters (a C–H distance fixed at 0.96 Å and a thermal parameter 1.2 times the host carbon atom). Tables of atomic coordinates, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates, and isotropic displacement parameters have been deposited at the Cambridge Crystallographic Data Centre, CCDC No. 677268 (Table 5).

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