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Hydrogen-Bonded Dimers in Dipyrrinones and Acyldipyrrinones

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Summary. A crystal structure determination of the 9-acyl-dipyrrinone 9-butanoyl-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one indicates the presence of intermolecularly hydrogen-bonded dimers; however, in $CHCl_3$ solution the pigment is monomeric as determined by vapor pressure osmometry measurements. Lacking an alkyl group at C(8), the 9-acyl-dipyrrinone exhibits only a weak tendency to form dimers in $CHCl_3$ ($K_A \sim 60\,M^{-1}$) as determined by analysis of variable temperature ^1H NMR data. In contrast, when the 9-acyl group is replaced by formyl or when the acyl group is fixed in a *syn* orientation to the pyrrole NH, the dipyrrinone is strongly prone to dimerization in $CHCl_3$.

Keywords. Pyrrole; X-Ray structure; Hydrogen bonding; Vapor pressure osmometry.

Introduction

Dipyrrinones [1] are yellow chromophores found in nature as components of bilirubin (Fig. 1), the pigment of jaundice. They are known to be apprecatious participants in hydrogen bonding, both in the crystal [2–4] and in solution [4–8]. Using vapor pressure osmometry (VPO), *Falk et al.* [1, 6a] first showed that kryptopyrromethenone (Fig. 2A) is dimeric in $CHCl_3$. This conclusion was reaffirmed subsequently by analyzing the concentration dependence of the NH ^1H NMR chemical shifts of the dipyrrinone in $CDCl_3$ [8c]. The dimer, which is planar and intermolecularly hydrogen-bonded, exhibits lactam and pyrrole NH chemical shifts at 11.42 and 10.44 ppm at 22°C, whereas the monomer's NH chemical shifts appear at 7.75 and 8.10 ppm. The association constant of kryptopyrromethenone is rather large ($K_A \sim 23000$ at 22°C) [8c]. In contrast, in the polar, hydrogen-bonding solvent $(CD_3)_2SO$, dipyrrinones are apparently monomeric and hydrogen-bonded to solvent [8b], and the lactam and pyrrole NH chemical shifts again differ: 9.83 and 10.22 ppm, respectively. Dipyrrinone dimerization, with stabilization by hydrogen bonds, is thus apparently strongly preferred in nonpolar solvents. Even when the dipyrrinones are components of a larger molecule, such as bilirubin dimethyl ester or etiobilirubin-IVγ (Fig. 1A), the pigments are dimeric in chloroform [1, 6b, 8a]. However, the available evidence suggests that neither bilirubin dimethyl ester nor etiobilirubin-IVγ are dimeric in $(CD_3)_2SO$ [1, 8a, b].

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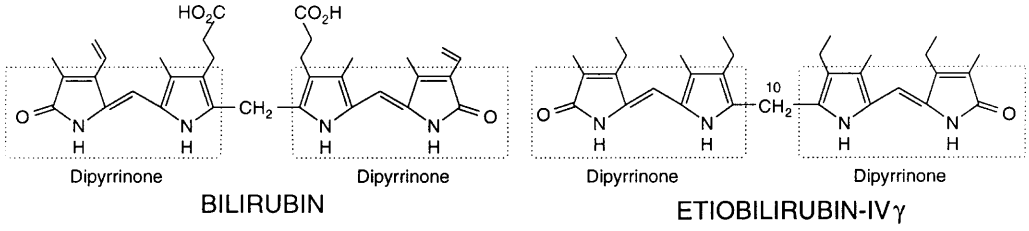


Fig. 1. Linear representations of bilirubin and etiobilirubin-IVγ, each with two dipyrrinone chromophores

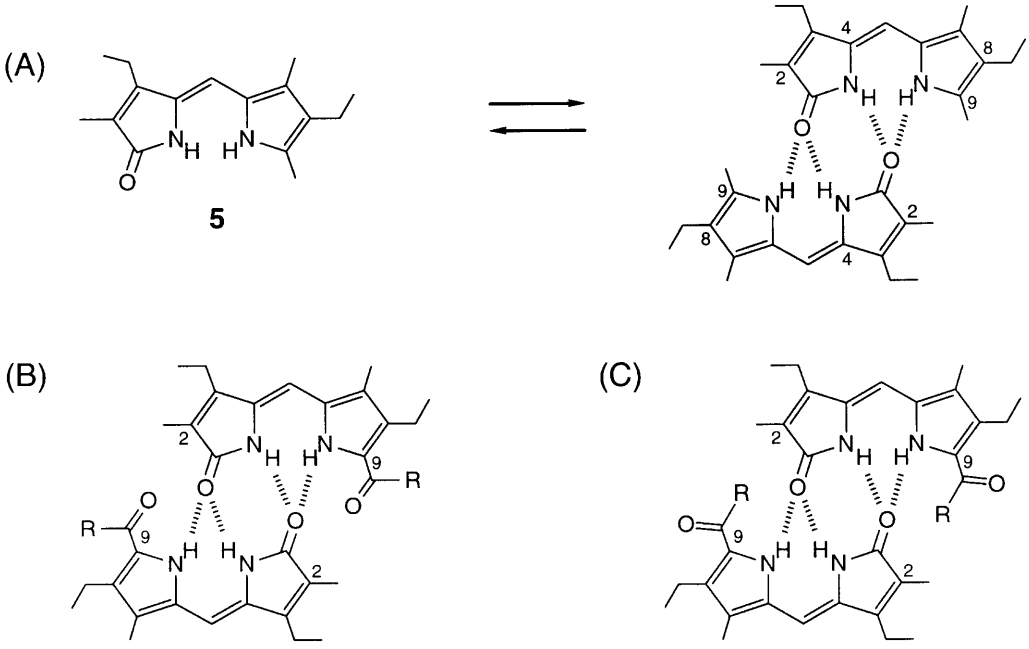
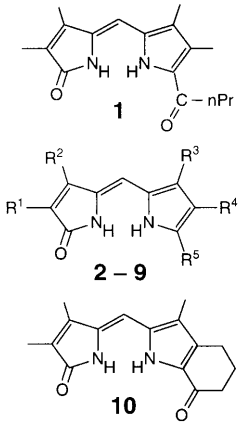


Fig. 2. (A) Kryptopyrromethenone (**5**) and its intermolecularly hydrogen-bonded planar dimer; (B) 9-acyl-dipyrrinone with the acyl group in a *syn*-orientation that might yield dimer-destabilizing nonbonded electronic repulsions between the lactam C=O and acyl C=O groups; (C) 9-acyl-dipyrrinone with the acyl group in an *anti*-orientation that might produce NOEs between the C(2) CH_3 and *R* groups

Intrigued by the apparently rather strong tendency of dipyrrinones to establish intermolecular hydrogen bonds in nonpolar solvents, we attempted to perturb the stability of the dimers by introducing an acyl group at C(9). If the acyl carbonyl of one dipyrrinone were oriented toward the lactam carbonyl of the companion dipyrrinone in the dimer, electrostatic repulsions might weaken the dimer. However, if the alkyl fragments of the acyl group in one dipyrrinone were oriented toward the C(2) methyl of the second dipyrrinone, this too might destabilize the dimer. Accordingly, in the following we explore the influence of an acyl group at C(9) on intermolecular association and hydrogen bonding in a set of dipyrrinones (**1**–**10**) using NMR spectroscopy and VPO (vapor pressure osmometry) measurements.



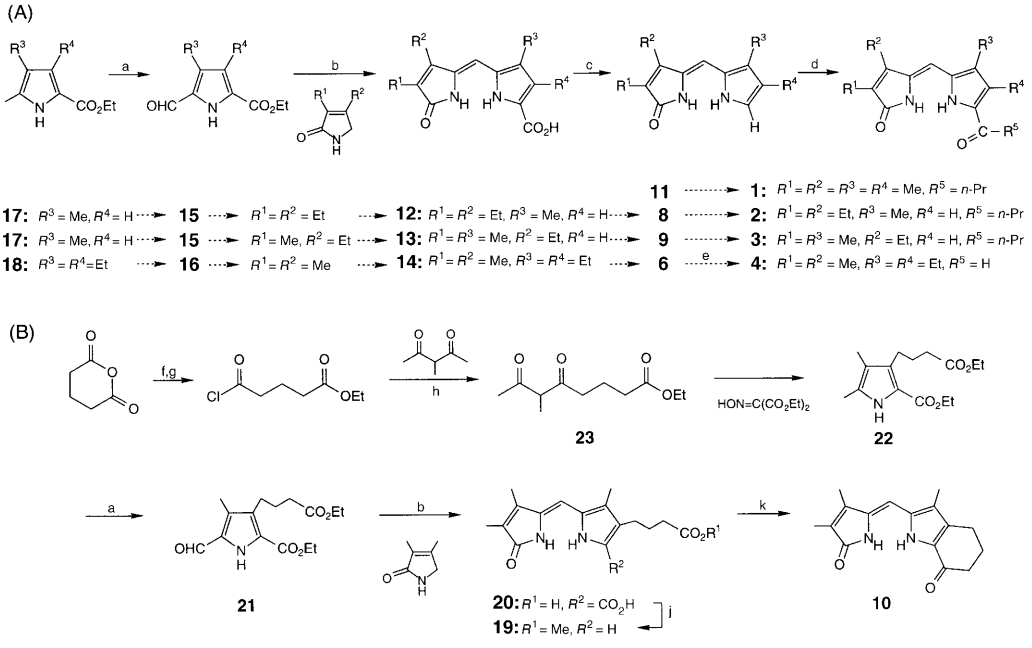
Dipyrrinone Structures

	R^1	R^2	R^3	R^4	R^5
2	Et	Et	Me	H	*n*-PrCO
3	Me	Et	Me	H	*n*-PrCO
4	Me	Me	Et	Et	CHO
5	Me	Et	Me	Et	Me
6	Me	Me	Et	Et	H
7	Et	Et	H	H	H
8	Et	Et	Me	H	H
9	Me	Et	Me	H	H

Results and Discussion

Synthesis

9-Acyl-dipyrrinones **1–3** were prepared (Scheme 1A) in acceptable yields (35–60%) by *Friedel-Crafts* acylation of the appropriate parent 9-H-dipyrrinone with butanoyl chloride in CH_2Cl_2 using anhydrous $AlCl_3$ as catalyst. 9-Formyl-dipyrrinone (**4**) was prepared in 82% yield from the parent dipyrrinone-9-carboxylic acid (**6**) by reaction first with *TFA* to decarboxylate, then with triethyl orthoformate. All of the precursor 9-H-dipyrrinones (**6**, **8**, **9**) were prepared by decarboxylation of the



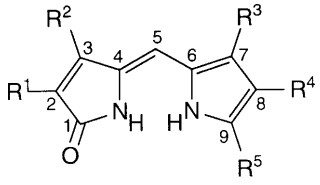
Scheme 1.[a]$Ce(NH_4)_2(NO_3)_6$; [b]4 *M* aq. KOH, MeOH, refl.; [c]molten KOAc/NaOAc/Δ; [d]butanoyl chloride/$AlCl_3$, CH_2Cl_2; [e]$(EtO)_3CH$, CH_2Cl_2/*TFA*; [f]EtOH refl.; [g]$SOCl_2$; [h]$Mg(OEt)_2$; [i]Zn/HOAc; [j]MeOH-H_2SO_4; [k]*TFA*

corresponding dipyrrinone-9-carboxylic acids (**12**–**14**) that had been prepared by a standard base-catalyzed dipyrrinone-forming condensation reaction of either 3,4-dimethyl-, 3,4-diethyl-, or 3-methyl-4-ethyl-pyrrolinone and a pyrrole α-aldehyde. The acyl-dipyrrinone with a fused cyclohexanone ring (**10**) was prepared in 60% yield by treatment of the methyl ester of the 9-H-dipyrrinone with a C(8) butanoic acid chain (**19**) with *TFA*. Dipyrrinone **19** was prepared from glutaric anhydride as outlined in Scheme 1B.

Constitution

The structures of the various dipyrrinones discussed in this paper follow from the method of synthesis (Scheme 1) and are confirmed by their ^{13}C NMR spectra (Table 1). Kryptopyrromethenone (**5**) [6a] 9-H-dipyrrinones **7** [9] and **11** [10] are known from previous work. Allowing for differences in substituents and substitution

Table 1. Dipyrrinone ^{13}C NMR chemical shifts and assignments; all measurements were made in $CDCl_3$ at $\sim 10^{-2}\,M$ chemical shifts (δ) reported in ppm downfield from $(CH_3)_4Si$ and referenced to the residual $CHCl_3$ located at 77.00 ppm; carbon assignments are made from HMBC and HMQC experiments; superscripts denote carbon atoms in sequence (see Ref. [1])



	1	**11**	**2**	**8**	**3**	**9**	**4**	**6**	**7**	**10**
1	173.66	172.3	173.65	174.14	174.00	174.34	174.12	174.46	174.10	173.82
2	136.25	118.5	134.81	129.32	134.96	123.45	138.71	130.41	129.97	136.56
3	141.92	141.5	147.29	148.08	147.72	148.53	141.99	142.63	148.12	141.82
4	128.12	131.6	132.99	128.40	127.61	128.40	136.82	129.90	127.48	128.24
5	97.14	98.14	96.79	101.19	96.66	101.08	95.65	101.36	103.19	95.84
6	131.18	124.5	131.08	124.32	130.85	124.22	130.57	126.00	129.41	137.82
7	128.94	124.1	123.92	125.09	123.92	125.16	130.19	123.83	115.88	133.00
8	123.73	122.0	118.62	111.20	118.45	111.20	128.42	124.49	109.91	129.29
9	126.04	120.1	133.07	122.57	132.99	122.60	132.72	120.54	123.34	121.06
9^1	190.41	–	190.51	–	190.44	–	177.23	–	–	188.76
9^2	42.09	–	40.11	–	40.09	–	–	–	–	21.75
9^3	17.93	–	19.19	–	19.16	–	–	–	–	24.68
9^4	13.98	–	13.80	–	13.99	–	–	–	–	30.93
2^1	8.59	8.57	16.87	16.99	8.38	8.06	8.66	10.18	17.00	8.64
2^2	–	–	13.99	13.83	–	–	–	–	13.81	–
3^1	9.88	9.36	17.74	17.80	17.90	17.99	9.93	8.52	17.72	9.27
3^2	–	–	15.47	15.85	14.57	14.94	–	–	15.71	–
7^1	9.44	9.83	11.53	11.54	11.53	11.57	17.36	18.47	–	9.94
7^2	–	–	–	–	–	–	17.11	17.94	–	–
8^1	11.66	10.26	–	–	–	–	17.11	16.78	–	–
8^2	–	–	–	–	–	–	16.27	15.10	–	–

pattern, 9-H-dipyrrinones **6**–**9** show the expected ^{13}C NMR chemical shifts. Conversion of the 9-H-dipyrrinones **6**, **8**, **9**, and **11** to the corresponding 9-butanoyl or 9-formyl derivatives leads to new carbon signals characteristic of the butanoyl group and to interesting shifts in the dipyrrinone ring carbons. Thus, as expected, C(9) shifts downfield in **1**–**4** relative to C(9) in **11**, **8**, **9**, and **6**; however, C(8) is not much affected. Interestingly, the chemical shift of remote C(2) is also strongly deshielded by a carbonyl group on C(9), whereas C(3) is scarcely affected. Ring carbons 6 and 8 are relatively more deshielded in **1**–**4** than in **11**, **8**, **9**, and **6**, but bridging carbon 5 is more shielded.

Curiously, C(4) is more deshielded in **2** and **4** than in **8** and **6**, but it is more shielded in **1** and **3** than in **11** and **9**. This is particularly odd because **2** and **3** (and **8** and **9**) differ only in a methyl or ethyl substituent at C(2).

Constraining the acyl carbonyl into a 6-membered ring, where it is forced to be *syn* to the pyrrole NH, has a strong effect on the dipyrrinone pyrrole ring carbon chemical shifts. Carbon-9 is more shielded by $\sim$5–12 ppm in **10** relative to C(9) in **1**–**4**, but carbons 6–8 are more deshielded.

Molecular geometry and hydrogen bonding in the crystal

The only reported dipyrrinone crystal structures reported so far [1, 2] had been obtained from three different dipyrroles, none of which had a 9-acyl group. All three exhibited intermolecular hydrogen bonding and dipyrrinone pairing in the crystal as in the example of Figure 2A. Triclinic 9-butanoyldipyrrinone (**1**) is no exception, and it too appears as a planar hydrogen-bonded dimer in the crystal (Fig. 3A). The individual dipyrrinone units are planar, with a *syn*-(*Z*) configuration at C(4)=C(5) and a C(4)=C(5)–C(6)–N(2) torsion angle of 3.5°. Distances between molecules **A** and **B** of the dimer are best represented by nonbonded distances in the hydrogen bonding region: N(2A) to O(1B) = 3.044 Å and N(1A) to O(1B) = 2.765 Å. These nonbonded distances are close to the sum (2.90 Å) of the van der Waals radii of N (1.50 Å) and O (1.40 Å). The acyl group also adopts the *sp* stereochemistry relative to the dipyrrinone moiety, with an N(2)–C(9)–C(10)=O(2) torsion angle of 3.8°. Layers of dimers stack in the crystal with interplanar distances of $\sim$3.5 Å (Fig. 3B). Interestingly, whereas **1** prevails in the *syn*-acyl conformation illustrated in Fig. 2B, it still prefers to be a dimer in the crystal.

Molecular geometry and hydrogen bonding in solution

Dipyrrinones alkylated at the β-positions generally adopt a *syn*-(*Z*) stereochemistry as the most stable conformation [1]. As revealed by $^1H\{^1H\}$ NOE experiments in $CDCl_3$, the 9-acylated dipyrrinones (**1**–**3**, **10**) and 9-formyl dipyrrinone (**4**) are no exception. Thus, as indicated in Fig. 4, NOEs are observed between the lactam and pyrrole NHs in **1**–**4** and **10**, and between the C(5)–H and the C(4) and C(7) alkyls. Similar sorts of NOEs have been reported previously for **5** [8c]. Most interestingly, an NOE is observed between the pyrrole NH and the α-CH_2 of the butanoyl chain of **1**, suggesting differing conformations of the acyl group in solution and in the crystal. Curiously, the same NOE was absent in **2** and **3**, but an NOE was detected between the C(8)–H and the α-CH_2 of the butanoyl chain of **2** and **3**. No equivalent

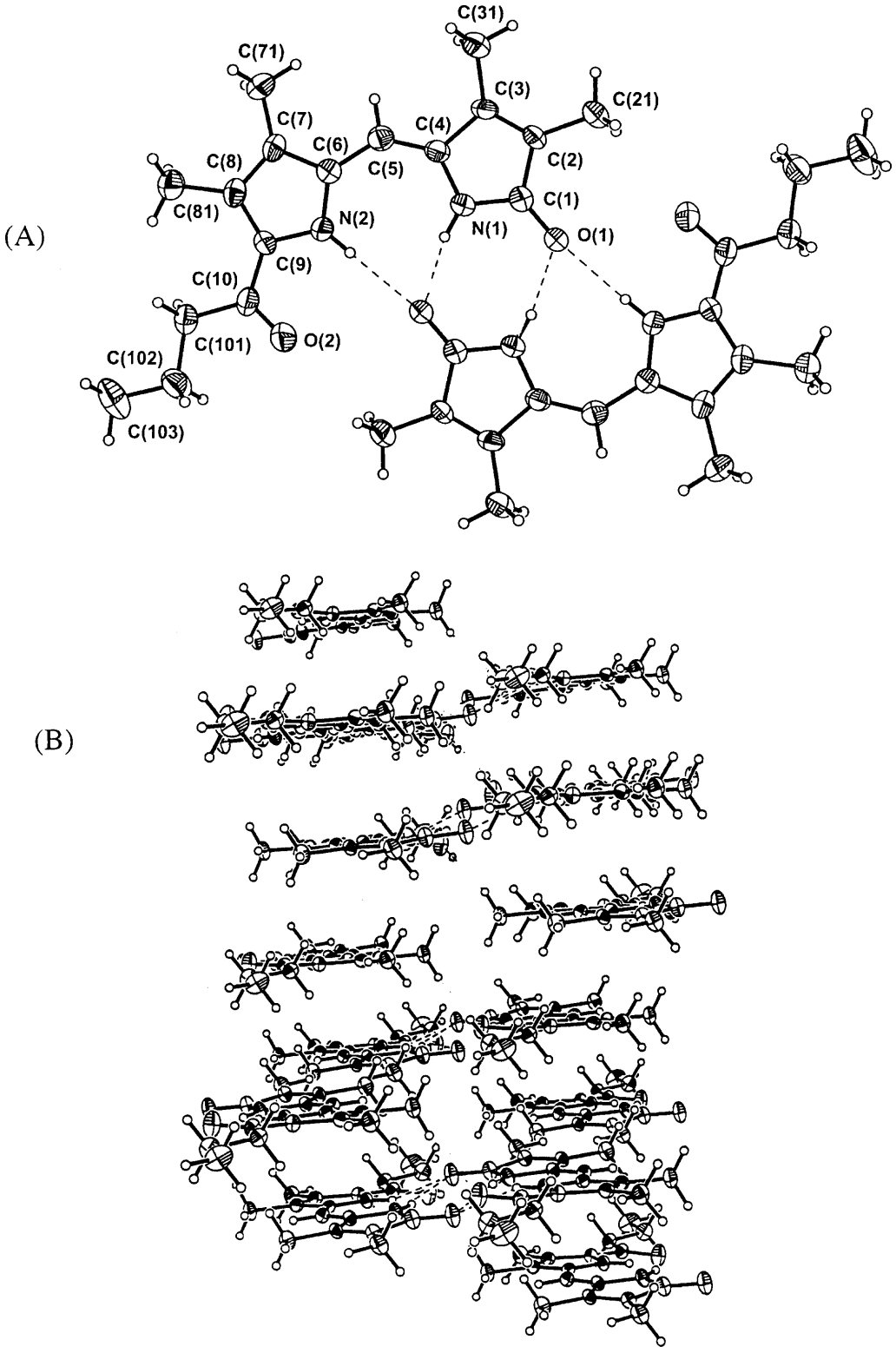


Fig. 3. (A) Structural drawing of **1** showing the atom numbering scheme (50% probability ellipsoids) as observed in its crystal structure; hydrogens are added and have an arbitrary radius of 0.1 Å; (B) packing arrangement of **1** in the crystal

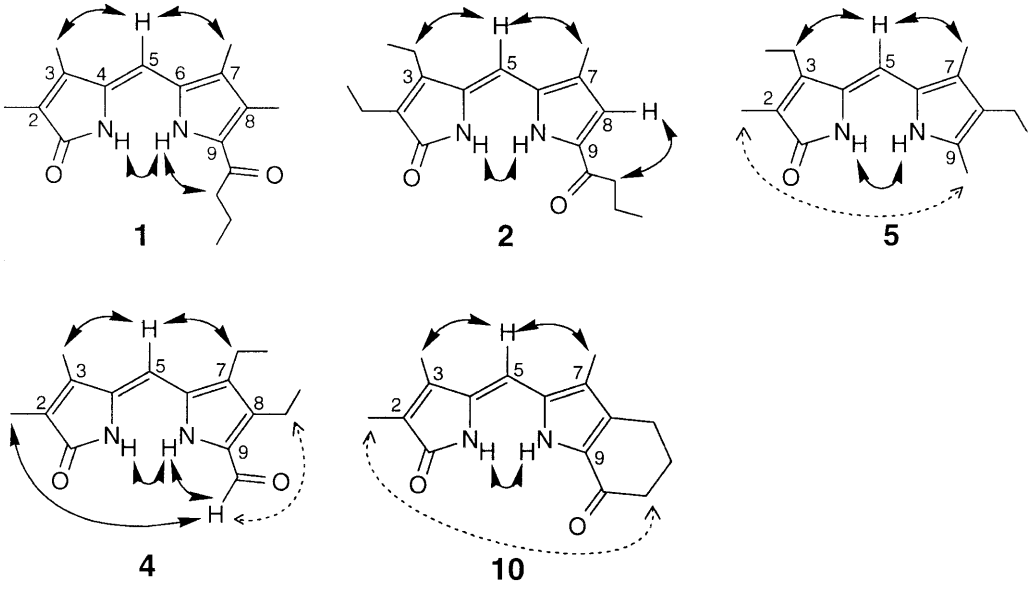
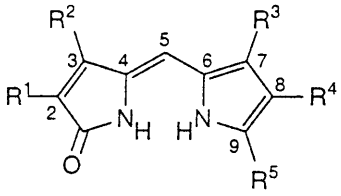


Fig. 4. Selected $^1H\{^1H\}$ NOEs observed in dipyrrinones in $CDCl_3$; strong NOEs are indicated by curved double headed arrows, weak NOEs by dashed double headed arrows

NOE was seen between the C(8)–CH_3 and the α-CH_2 of the butanoyl chain of **1**. In **4**, an NOE was measured between the formyl hydrogen and the pyrrole NH. These data suggest a conformational preference for the 9-ketone or aldehyde carbonyl group *anti* to the pyrrole NH in **1** and **4** and *syn* to the pyrrole NH in **2** and **3**. Evidence for dimer formation can be found in the weak NOEs between the C(2) methyl group and remote hydrogens, as reported previously in 9-H- and 9-CH_3-dipyrrinones such as **5** [8c]. An NOE between the C(2) methyl and the α-CH_2 of the fused cyclohexanone ring also confirms dimer formation for **10** in $CDCl_3$. Similarly, the NOE seen between the C(2)-methyl and the formyl proton of **4** is compatible with the presence of planar, intermolecularly hydrogen-bonded dimers. In summary, the NOE data are consistent with an intramolecularly hydrogen-bonded dimer in $CDCl_3$ for **4** and **10** analogously to **5** (Fig. 2A), but we could find no NOE evidence for dimers in **1**–**3**.

Dipyrrinone dimers may also be detected from an examination of their NH chemical shifts. Typical dipyrrinones exhibit rather different NH ^1H NMR chemical shifts in $(CD_3)_2SO$ and $CDCl_3$. Thus, kryptopyrromethenone (**5**) shows lactam and pyrrole NH chemical shifts of 9.83 and 10.22 ppm in $(CD_3)_2SO$, probably due to hydrogen bonding to the solvent [1, 8b]. In contrast, the NH chemical shift of the lactam NH is strongly deshielded by $\sim$2 ppm (to $\sim$11.42 ppm) in $CDCl_3$, a solvent in which **5** is known to be an intermolecularly hydrogen-bonded dimer (Fig. 2A) [1, 6a]. Similar sets of lactam and pyrrole NH chemical shifts are found in the ^1H NMR spectra of the simple dipyrrinones **6**–**9** and **11** (Table 2), suggesting a similar behavior: hydrogen-bonded dimers in $CDCl_3$, monomers hydrogen-bonded to the solvent in $(CD_3)_2SO$. In further distinction, and consistent with dipyrrinone monomers hydrogen-bonded to the solvent in $(CD_3)_2SO$, the monomer of **5** in $CDCl_3$ exhibits strongly shielded pyrrole (8.10 ppm) and lactam (7.75 ppm) NH chemical shifts [8c].

Table 2. Solvent dependence of lactam and pyrrole NH chemical shifts in the ^{1}H NMR spectra of dipyrrinones[a]



						^{1}H NMR chemical shifts (δ/ppm)			
						DMSO-d_6		$CDCl_3$	
	R^1	R^2	R^3	R^4	R^5	Lactam	Pyrrole	Lactam	Pyrrole
1	Me	Me	Me	Me	*n*-PrCO	10.36	10.74	8.65	9.33
2	Et	Et	Me	H	*n*-PrCO	10.49	11.31	9.28	10.05
3	Me	Et	Me	H	*n*-PrCO	10.50	11.31	9.65	10.09
4	Me	Me	Et	Et	CHO	10.57	10.96	10.69	10.91
5	Me	Et	Me	Et	Me	9.83	10.22	11.42	10.44
6	Me	Me	Et	Et	H	9.72	10.48	11.05	10.41
7	Et	Et	H	H	H	9.59	10.99	10.71	10.54
8	Et	Et	Me	H	H	9.76	10.74	11.13	10.67
9	Me	Et	Me	H	H	9.76	10.72	11.09	10.63
10	Me	Me	Me	$(CH_2)_3$	CO[b]	10.41	11.35	10.52	11.09
11	Me	Me	Me	Me	H	9.71	10.45	10.90	10.23

[a] For $\sim 10^{-2}$ *M* solutions at 25°C; chemical shifts (δ) are reported in ppm downfield from $(CH_3)_4Si$ and referenced to residual non-deuterated solvent: 7.26 ppm, $CHCl_3$ and 2.49 ppm, *DMSO*; assignments are derived from HMBC, $^1H\{^1H\}$ NOE, or homonuclear decoupling experiments; [b] bridged from C(8) to C(9)

There is remarkable consistency in the NH chemical shifts of dipyrrinones **5–9** and **11** in $CDCl_3$: a lactam NH signal near 11 ppm and a pyrrole NH signal near 10.5 ppm. The data are consistent with a dimer. In contrast, the lactam NH chemical shifts in $(CD_3)_2SO$ are shielded to $\sim$9.7 ppm, whereas the pyrrole NH signals remain near 10.5 ppm. The data are consistent with monomeric dipyrrinones hydrogen-bonded to the solvent.

Acylation at C(9) causes the dipyrrinone NH chemical shifts (in $(CD_3)_2SO$) to become somewhat more deshielded than those of the 9-H-dipyrrinones: down to $\sim$11 ppm for the pyrrole NH and to $\sim$10.5 ppm for the lactam. The deshielding can be attributed to the carbonyl attached to C(9), since the presence of an alkyl group (as in **5**) has little effect. A wider spread of chemical shift values is seen $CDCl_3$ where dimers tend to be favored. Thus, both the pyrrole and lactam NHs are found to fall in wide ranges: between 9.3 and 11.1 ppm for the pyrrole NHs and between 8.7 and 10.7 ppm for the lactams. The wide range of pyrrole chemical shifts might be attributed to the orientation of the carbonyl at C(9) relative to the pyrrole NH. The influence of carbonyl group orientation has been reported earlier for α-acylated monopyrroles [11], where the *anti*-orientation led to a more shielded pyrrole NH than the *syn*-orientation. In **10**, the carbonyl group attached to C(9) is fixed in *syn*-orientation. In **1**, the carbonyl also appears to be *anti*, based on the NOE data, and thus indicates that it is perhaps the *syn*-orientation of the ketone α-CH_2 that shields the pyrrole NH. On the basis of the monopyrrole studies, one is tempted to conclude

that the 9.33 ppm chemical shift of the pyrrole NH of **1** can be attributed to the acyl group oriented *anti* to the pyrrole NH, whereas in **2–4** it is *syn*.

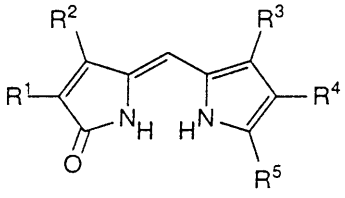
Homoassociation measured by vapor pressure osmometry

Given the fact that **1** is present in the crystal as an intermolecularly hydrogen bonded dimer, but apparently as a monomer in chloroform (a solvent where dipyrrinones are known to be dimeric [1, 6]), we investigated possible dimer formation in chloroform solutions of **1–11** by vapor pressure osmometry (VPO). Previously it had been shown by VPO [1, 6] and by ^{1}H NMR analysis [8b,c] that kryptopyrromethonone (**5**) is present largely as an intermolecularly hydrogen-bonded dimer in chloroform. The simple 9-H-dipyrrinones **6–9** are no exception and give molecular weights corresponding to dimers (Table 3). Similarly and consistent with the NOE data (Fig. 4), **4** and **10** also show molecular weights pointing to dimers. In contrast, however, VPO measurements of **1–3** clearly indicate mainly monomers in chloroform. Thus, whereas **1** is a dimer in the crystal, it is monomeric in solution, and the latter explains its unusually shielded NH chemical shifts observed in $CDCl_3$.

Homoassociation constants from ^{1}H NMR measurements

The VPO studies (Table 3) indicated a slight extent of dimer formation in 9-acyldipyrrinone **2**. An examination of concentration dependence of the dipyrrinone NH chemical shifts in $CDCl_3$ over the temperature range from -60 to $+60$°C shows considerable variation (Fig. 5, left). The sets of curves for the pyrrole NH show a clear plateau (at 10.87 ppm) at -60°C in the high concentration region and a second

Table 3. Molecular weights of dipyrrinones in $CHCl_3$[a]



	R^1	R^2	R^3	R^4	R^5	Formula weight (g/mol)	Measured molecular weight (g/mol)
1:	Me	Me	Me	Me	*n*-PrCO	286	301±10
2:	Et	Et	Me	H	*n*-PrCO	300	370±15
3:	Me	Et	Me	H	*n*-PrCO	286	379±15
4:	Me	Me	Et	Et	CHO	272	550±15
5:	Me	Et	Me	Et	Me	258	509±20
6:	Me	Me	Et	Et	H	244	448±25
7:	Et	Et	H	H	H	216	378±20
8:	Et	Et	Me	H	H	230	453±20
9:	Me	Et	Me	H	H	216	428±25
10:	Me	Me	Me	$(CH_2)_3$	CO[b]	270	504±25

[a] At 45°C, dipyrrinone concentration range from 2.0 to 12.8 $\times$ 10^{-3} mol/kg, calibrated using benzil (formula wt. 210, measured molecular wt. 220 $\pm$ 15 g/mol; [b] bridged from C(8) to (9)

Table 4. Dipyrrinone NH chemical shifts and thermodynamic parameters[a] for homoassociation of **2**

Parameter	Lactam-NH	Pyrrole-NH
δ_M (ppm)	7.17	8.89
δ_D (ppm)	10.58	10.87
K_a (−25°C, M^{-1})	638	625
K_a (0°C, M^{-1})	228	196
K_a (25°C, M^{-1})	63.0	63.7
ΔH° (kJ/mol)	−28.0	−28.4
ΔS° (e.u.)	−14.2	−14.3
ΔG° (kJ/mol)	−10.5	−10.5

[a] ΔH° and ΔG°: ±2.1 kJ/mol, ΔS°: ±1.0 e.u.; all plots (Fig. 6) have *R*-values above 0.99

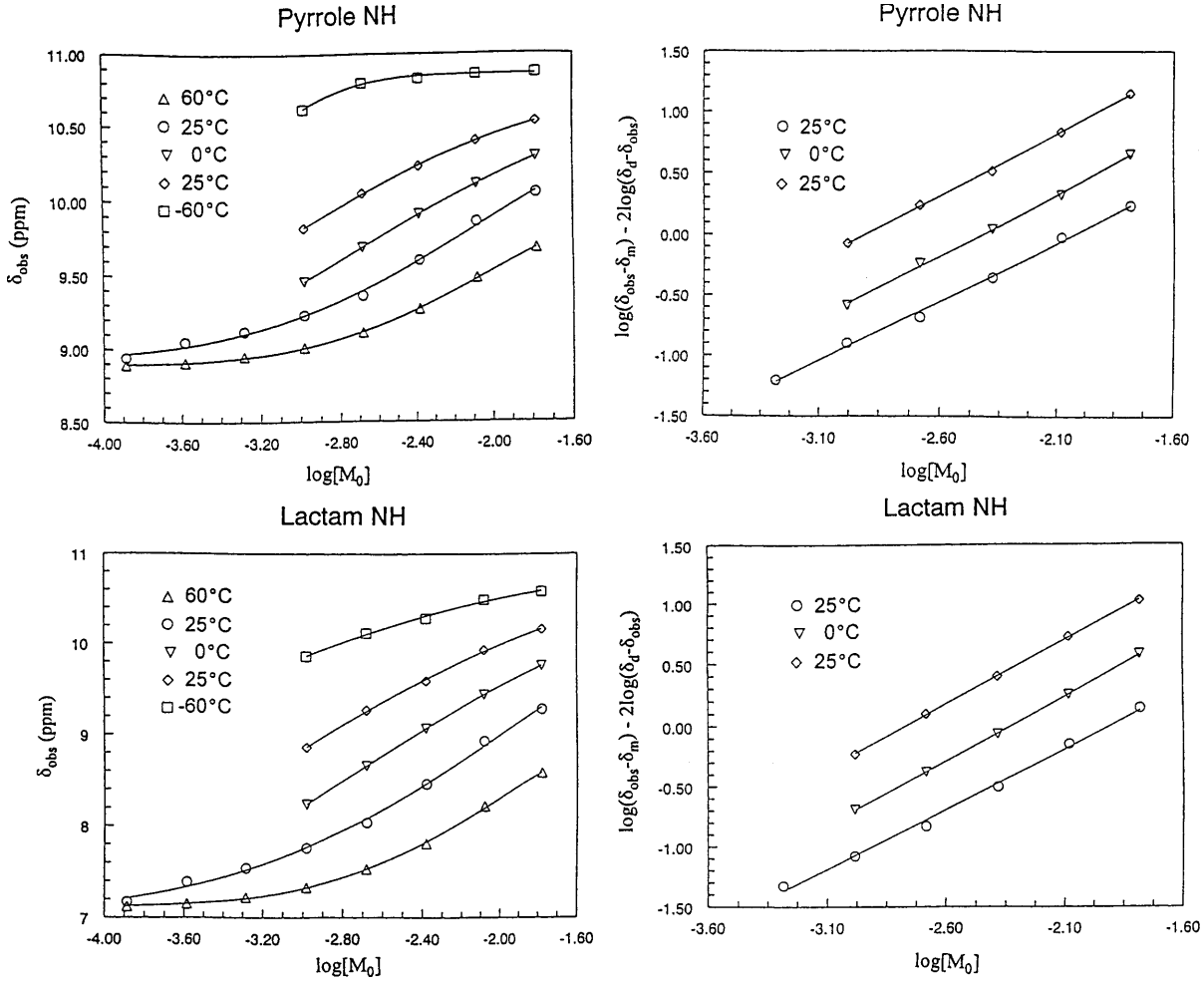


Fig. 5. Behavior of the pyrrole (upper) and lactam (lower) NH ^{1}H NMR chemical shifts between −60°C and +60°C over a concentration range from 1.66×10^{-2} *M* to 1.30×10^{-4} *M*; left: δ_{NH} *vs.* logarithm of initial concentration of monomeric dipyrrinone; right: $\log(\delta_{obs} - \delta_{Mo}) - 2\log(\delta_D - \delta_{obs})$ *vs.* logarithm of initial concentration of monomeric dipyrrinone from −25°C to +25°C

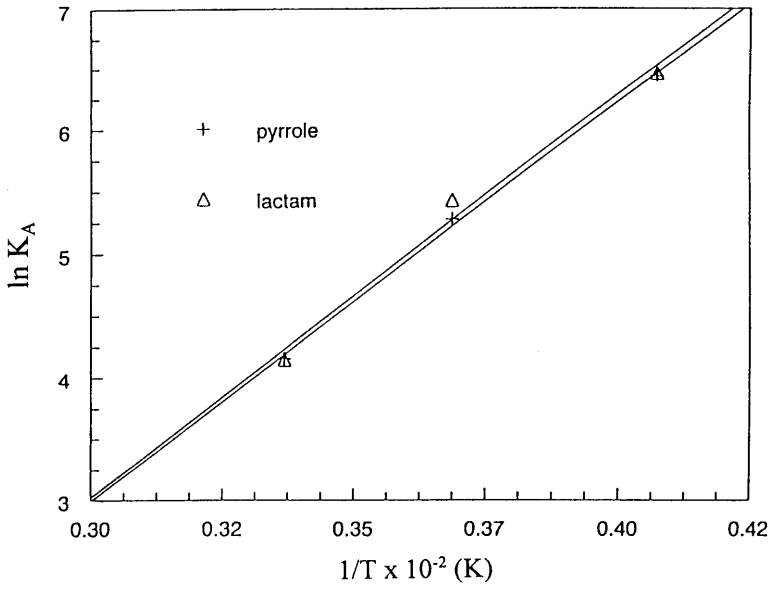


Fig. 6. *van't Hoff* plot for 9-acyl-dipyrrinone **2**, with K_{assoc} determined from the temperature and concentration dependence of the pyrrole and lactam NH chemical shifts

plateau at 8.89 ppm at +60°C in the dilute concentration range. These data are consistent with $\delta_{monomer} = 8.89$ and $\delta_{dimer} = 10.87$ ppm. Observing the curves for the lactam NHs gives a plateau at 7.17 ppm (monomer) at +60°C, and we assume a second one at 10.58 ppm and −60°C for the dimer. From these data, and assuming a simple monomer-dimer equilibrium ($K = [\text{Dimer}]/[\text{Monomer}]^2$), by plotting $\log(\delta_{obs} - \delta_{monomer}) - 2\log(\delta_{dimer})$ *vs.* log[sample] [8c] we obtain straight-line plots for three temperatures (Fig. 5, right). From such plots, one obtains K at each temperature. Plots of ln$K$ *vs.* $1/T$ for the pyrrole and the lactam NH data give straight-line plots (Fig. 6) from which various thermodynamic parameters (Table 4) may be attained. As expected, the dimerization constant is small ($K \sim 60\,M^{-1}$) at room temperature, and ΔS is negative. In contrast, K is $\sim 23000\,M^{-1}$ for kryptopyrromethenone [8c], and thus we assumed similarly large K values for dipyrrinones **4**–**11**.

Unless the acyl carbonyl group is constrained to adopt a *syn*-orientation with respect to the dipyrrinone's pyrrole NH, as in **10**, it prefers the *anti*-orientation when a C(8)-alkyl is present. This apparently alleviates an unfavorable nonbonded steric buttressing between the ketone α-CH_2 and the C(8)-alkyl when the acyl carbonyl is oriented *syn*, as in **1**. In the *anti*-orientation, the ketone α-CH_2 is oriented in such a way as to inhibit intermolecular hydrogen bonding. Only the special circumstances of crystal packing cause **1** to adopt the *anti*-conformation and thereby achieve intermolecular hydrogen bonding. In **2**, which has no C(8)-alkyl group, the NOE data of Fig. 4 indicate a preference for the *syn*-orientation, and from a K of *ca.* $60\,M^{-1}$ for the dimerization of **2** one can anticipate about 20% of dimer (and, thus, mainly monomer) from an initial concentration of $10^{-2}\,M$ **2** at 25°C. Here, strong dimerization may be prevented by a modest steric repulsion between the C(2)-alkyl and the C(10)-carbonyl.

Table 5. Comparison of dipyrrinone UV/Vis spectroscopic data[a]

Compound[b]					Solvent				
R^1	R^2	R^3	R^4	R^5	C_6H_6	$CHCl_3$	CH_3OH	CH_3CN	$(CH_3)_2SO$
M	*M*	*M*	*M*	*B*	412 (14800)[s]	412 (18200)[s]	411 (22400)	404 (19400)[s]	415 (21800)
		1			392 (20500)	392 (23700)	392 (28000)	384 (26000)	394 (26200)
E	*E*	*M*	H	*B*	415 (15400)[s]	410 (17900)[s]	415 (25500)	406 (19000)[s]	420 (24500)
		2			393 (22400)	391 (24100)	393 (30600)	385 (26200)	396 (28500)
M	*E*	*M*	H	*B*	418 (20500)	415 (20400)[s]	414 (22900)	403 (18500)[s]	418 (26800)
		3			395 (25900)	395 (26700)	392 (27700)	384 (25200)	395 (30500)
M	*M*	*E*	*E*	*F*	423 (26300)	416 (19400)[s]	415 (28200)	408 (22300)[s]	420 (29000)
		4			400 (30900)	397 (25700)	395 (31900)	389 (27700)	398 (31500)
M	*E*	*M*	*E*	*M*	411 (36200)	407 (33500)	416 (33700)	403 (30000)	413 (25800)
		5							
M	*M*	*E*	*E*	H	394 (29400)	389 (25400)	398 (22000)	384 (29700)	395 (28600)
		6							
E	*E*	*M*	H	H	387 (30600)	384 (29800)	390 (32700)	376 (28900)	384 (31200)
		8							
M	*E*	*M*	H	H	387 (30200)	381 (29400)	389 (32400)	374 (28300)	385 (29900)
		9							
M	*M*	*M*	$(CH_2)_3$	CO	420 (22200)	413 (16400)[s]	415 (24200)	405 (19200)[s]	419 (25600)
		10			397 (27500)	393 (22700)	393 (28000)	386 (24800)	396 (27400)
M	*M*	*M*	*M*	H	392 (23500)	394 (25300)	396 (27200)	395 (26700)	395 (26300)
		11							

[a] λ nm (ϵ/dm$^3 \cdot$ mol^{-1}); [b] *M* = Me, *E* = Et, *B* = butanoyl, *F* = formyl; [s] shoulder

UV/Vis comparisons

(4*Z*)-Dipyrrinones typically show UV/Vis maxima in the region of 380–420 nm, depending on the location, type, and number of substituents. The absorption band is typically intense ($\varepsilon \sim 30000$) as might be expected for a π–π^* type excitation. With fewer alkyl substituents (as in **8** and **9**), λ_{max} is hypsochromically shifted; with more alkyl substituents (as in **5**, **6**, and **11**), a bathochromic shift is observed. Peralkylated (4*Z*)-dipyrrinones, *e.g.* **5**, tend to have λ_{max} near 410 nm and larger ϵ values. With an acyl or formyl substituent at C(9), as in **1**–**4** and **10**, two distinct maxima of roughly equal intensity appear between 390 and 425 nm in all solvents studied. The two bands are not due to an exciton, as there is little evidence for dimer formation. It is also apparently not due to rotational isomers about the acyl or formyl group, since **10** also exhibits two λ_{max}, and its acyl group is constrained to the *syn*-orientation. The data suggest the emergence of a second long-wavelength electronic transition to complement that seen in simpler dipyrrinones [1], but the spectroscopic characterization of the new transition is currently unknown. In view of its intensity, the corresponding transition dipole presumably lies along the length of the molecule.

Experimental

All UV/Vis spectra were recorded on a Perkin-Elmer λ-12 spectrophotometer. Vapor pressure osmometry (VPO) measurements were performed using an Osmomat 070 (Gonotec, Berlin,

Germany) in $CHCl_3$ (from Allied, with amylene stabilizer) at 45°C; benzil was used for calibration. NMR spectra were obtained on GE QE-300 or GE GN-300 spectrometers operating at 300 MHz, or on a Varian Unity Plus 500 MHz spectrometer in $CDCl_3$ unless otherwise specified. Chemical shifts are reported in ppm and referenced to the residual $CHCl_3$ ^1H signal at 7.26 ppm and the ^{13}C signal at 77.0 ppm. HMQC and HMBC spectra were used to assign ^{13}C NMR chemical shifts. Melting points were taken on a Mel Temp capillary apparatus and are uncorrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ; their results agreed with the calculated values within experimental error. Analytical thin layer chromatography was carried out on J.T. Baker silica gel IB-F plates (125 μ layer), flash column chromatography on Woelm silica gel F, thin layer chromatography grade. Radial chromatography was performed on Merck Silica Gel PF_{254} with gypsum preparative layer grade using a Chromatotron (Harrison Research, Inc., Palo Alto, CA). Spectroscopic data were obtained in spectral grade solvents. Deuterated solvents were purchased from Cambridge Isotope Labs, ceric ammonium nitrate from Alfa Aesar. CH_2Cl_2, MeOH, acetic acid, *THF*, hexane, $AlCl_3$, and 2-propanol were from Fisher, butanoyl chloride was obtained from Acros.

2,3,7,8-Tetramethyl-(10*H*)-dipyrrin-1-one (**11**) [10], 2,3-dimethyl-7,8-diethyl-(10*H*)-dipyrrin-1-one (**6**) [12], 2,3-dimethyl-7,8-diethyl-(10*H*)-dipyrrin-1-one-9-carboxylic acid (**14**) [12], and 2,3-diethyl-(10*H*)-dipyrrin-1-one (**7**) [9] were prepared by literature methods. 4-Carboethoxy butanoyl chloride was readily prepared from the reaction of ethyl hydrogen glutarate with $SOCl_2$ as a modified procedure from Ref. [13].

2,3,4,8-Tetramethyl-9-butanoyl-(10H)-dipyrrin-1-one (**1**; $C_{17}H_{22}N_2O_2$)

To a 500 cm^3 round bottomed flask equipped with magnetic stirring, 0.200 g (0.9 mmol) of 3,4,7,8-tetramethyl-(10*H*)-dipyrrinone (**11**) [10] and 150 cm^3 of CH_2Cl_2 were added. The solution was stirred in an ice bath for 20 min. A solution of 2 cm^3 of acid chloride and 4.0 g of $AlCl_3$ in 100 cm^3 of CH_2Cl_2 was added all at once, the reaction mixture was stirred for 2 h at room temperature, poured onto concentrated HCl/ice (200 cm^3/100 g), and stirred for further 2 h. The organic layer was separated, and the aqueous layer was extracted twice with 100 cm^3 CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ solution (2×200 cm^3), water (400 cm^3), and dried over anhydrous Na_2SO_4. The solvent was removed, and the crude product was purified by radial chromatography ($MeOH:CH_2Cl_2 = 97:3$) and recrystallized from CH_2Cl_2/hexane to give pure **1**.

Yield: 92 mg (35%); m.p.: 225–226°C; IR (KBr): $\nu = 3341, 2956, 2920, 1668, 1640, 1436, 1385, 1297, 1234, 1169, 943, 728, 695\ cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 500 MHz): 0.99 (t, 7.5 Hz, 3 H), 1,70 (p, 7.5 Hz, 2 H), 1.93 (s, 3 H), 2.07 (s, 3 H), 2.11 (s, 3 H), 2.31 (s, 3 H), 2.78 (t, 7.5 Hz, 2 H), 5.94 (s, 1 H), 8.65 (s, 1 H), 9.33 (s, 1 H) ppm; ^1H NMR (*DMSO*-d_6, δ, 300 MHz): 0.93 (t, 7.5 Hz, 3 H), 1.60 (p, 7.5 Hz, 2 H), 1.78 (s, 3 H), 2.01 (s, 3 H), 2.07 (s, 3 H), 2.22 (s, 3 H), 2.79 (t, 7.5 Hz, 2 H), 5.95 (s, 1 H), 10.36 (s, 1 H), 10.74 (s, 1 H) ppm; ^{13}C NMR: Table 1; UV/Vis: Table 4.

2,3-Diethyl-7-methyl-9-butanoyl-(10H)-dipyrrin-1-one (**2**; $C_{18}H_{24}N_2O_2$)

2 was prepared from 0.30 g (1.3 mmol) of 2,3-diethyl-7-methyl-(10*H*)-dipyrrin-1-one (**8**) following the same procedure as for **1**.

Yield: 194 mg (50%); m.p.: 149–150°C; IR (KBr(: $\nu = 3337, 2967, 2927, 1700, 1673, 1652, 1458, 1416, 1297, 1250, 1163, 1057, 1023\ cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 500 MHz): 0.96 (t, 7.0 Hz, 3 H), 1.13 (t, 7.5 Hz, 3 H), 1.22 (t, 7.0 Hz, 3 H), 1.71 (m, 2 H), 2.19 (s, 3 H), 2.45 (q, 7.5 Hz, 2 H), 2.55 (q, 7.0 Hz, 2 H), 2.76 (t, 4.0 Hz, 2 H), 5.97 (s, 1 H), 6.77 (d, 1.5 Hz, 1 H), 9.88 (s, 1 H), 10.36 (s, 1 H) ppm; ^1H NMR (*DMSO*-d_6, δ, 300 MHz): 0.90 (t, 7.0 Hz, 3 H), 1.02 (t, 7.5 Hz, 3 H), 1.11 (t, 7.5 Hz, 3 H), 1.60 (p, 7.0 Hz, 2 H), 2.12 (s, 3 H), 2.27 (q, 7.5 Hz, 2 H), 2.51 (q, 7.5 Hz, 2 H), 2.69 (t, 7.0 Hz, 2 H), 5.91 (s, 1 H), 2.88 (d, 3.0 Hz, 1 H), 10.49 (s, 1 H), 11.31 (s, 1 H) ppm; ^{13}C NMR: Table 1; UV/Vis: Table 4.

2,7-Dimethyl-3-ethyl-9-butanoyl-(10H)-dipyrrin-1-one (**3**; $C_{16}H_{20}N_2O_2$)

3 was prepared from 0.15 g (0.69 mmol) of 2,7-dimethyl-3-ethyl-(10*H*)-dipyrrin-1-one (**9**) following the same procedures as for **1**.

Yield: 0.104 g (53%); m.p.: 249–250°C; IR (KBr): $\nu = 3331$, 2961, 2867, 1654, 1454, 1378, 1292, 1248, 1165, 1053, 981, 818, 766, 669 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 0.96 (t, 75 Hz, 3 H), 1.19 (t, 7.5 Hz, 3 H), 1.71 (sextet, 7.5 Hz, 2 H), 1.99 (s, 3 H), 2.18 (s, 3 H), 2.54 (q, 7.5 Hz, 2 H), 2.74 (t, 7.5 Hz, 2 H), 5.97 (s, 1 H), 6.77 (d, 2 Hz, 1 H), 9.65 (s, 1 H), 10.85 (s, 1 H) ppm; ^1H NMR (*DMSO*-d_6, δ, 300 MHz): 0.90 (t, 7.5 Hz, 3 H), 1.09 (t, 7.0 Hz, 3 H), 1.79 (s, 3 H), 2.12 (s, 3 H), 2.51 (q, 7.5 Hz, 2 H), 2.69 (t, 7.0 Hz, 2 H), 5.92 (s, 1 H), 6.89 (d, 2.5 Hz, 1 H), 10.50 (s, 1 H), 11.31 (s, 1 H) ppm; ^{13}C NMR: Table 1; UV/Vis: Table 4.

2,3-Dimethyl-7,8-diethyl-(10H)-dipyrrinone-9-aldehyde (**4**; $C_{16}H_{20}N_2O_2$)

To a 200 cm^3 round bottomed flask equipped with magnetic stirring, 1.8 g (6.3 mmol) of dipyrrinone carboxylic acid (**14**) and 40 cm^3 of *TFA* were added. The reaction mixture was stirred for 30 min at room temperature followed by cooling to 0°C in an ice/salt bath. 5 cm^3 triethyl orthoformate were added dropwise followed by stirring for 10 min. The reaction mixture was then poured onto 100 g ice/water and stirred for 30 min. The crude product was collected by vacuum filtration and purified by trituration with cold CH_2Cl_2 to give pure **4**.

Yield: 1.4 g (82%); m.p.: 256–257°C; IR (KBr): $\nu = 3338$, 2970, 2903, 1708, 1687, 1658, 1601, 1558, 1463, 1252, 1175, 756, 696 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 300 MHz): 1.17 (t, 7.5 Hz, 3 H), 1.26 (t, 7.5 Hz, 3 H), 2.00 (s, 3 H), 2.13 (s, 3 H), 2.57 (q, 7.5 Hz, 2 H), 2.78 (q, 7.5 Hz, 2 H), 5.96 (s, 1 H), 9.70 (s, 1 H), 10.69 (s, 1 H), 10.91 (s, 1 H) ppm; ^1H NMR (*DMSO*-d_6, δ, 300 MHz): 1.05 (t, 7.5 Hz, 3 H), 1.07 (t, 7.5 Hz, 3 H), 1.79 (s, 3 H), 2.07 (s, 3 H), 2.50 (q, 7.5 Hz, 2 H), 2.67 (q, 7.5 Hz, 2 H), 5.90 (s, 1 H), 10.57 (s, 1 H), 10.96 (s, 1 H), 12.36 (s, 1 H) ppm; ^{13}C NMR: Table 1; UV/Vis: Table 4.

2,3-Diethyl-7-methyl-(10H)-dipyrrin-1-one (**8**; $C_{14}H_{18}N_2O$)

3-Methyl-2-formyl-5-carboethoxy-(1*H*)-pyrrole (**15**, 4.2 g, 23 mmol), 3,4-ethyl-1*H*-pyrrol-2-one [14] (3.2 g, 23 mmol), and 50 cm^3 of methanol were placed in a 500 cm round bottomed flask equipped with magnetic stirring. 200 cm^3 of 4 *M* aqueous KOH were added, and the reaction mixture was heated at reflux for 6 h and then chilled in an ice bath for 30 min. After acidification with concentrated HCl to *pH* ~3, the resultant solid product (**12**) was collect by filtration (vacuum), washed with 100 cm^3 of water, and dried *in vacuo*. The resulting powder was placed in a 500 cm^3 round bottomed flask and mixed with 5.0 g of potassium acetate and 5.0 g of sodium acetate trihydrate which had been ground with mortar and pestle until intimately mixed. The solid mixture was heated to *ca.* 160°C at which time it melted with the evolution of CO_2. The temperature was maintained at 160°C until the evolution of CO_2 ceased (*ca.* 10 min). The reaction mixture was cooled to room temperature, and 400 cm^3 of water were added followed by vigorous stirring for 1 h. The product was collect by filtration (vacuum) and triturated with 50 cm^3 cold acetone to give pure **8**.

Yield: 1.75 g (50%); m.p.: 206–208°C; IR(KBr): $\nu = 3356$, 2969, 2920, 1657, 1557, 1464, 1372, 1265, 1178, 1102, 1057, 1017, 946, 739, 675 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 1.18 (t, 7.50 Hz, 3 H), 1.20 (t, 7.50 Hz, 3 H), 2.23 (s, 3 H), 2.41 (q, 7.5 Hz, 2 H), 2.56 (q, 7.5 Hz, 2 H), 6.11 (dd, 1.5 Hz, 3.0 Hz, 1 H), 6.17 (s, 1 H), 6.97 (dd, 3.0 Hz, 3.0 Hz, 1 H), 10.67 (s, 1 H), 11.13 (s, 1 H) ppm; ^1H NMR (*DMSO*-d_6, δ, 300 MHz): 1.10 (t, 7.5 Hz, 3 H), 1.10 (t, 7.5 Hz, 3 H), 2.11 (s, 3 H), 2.23 (q, 7.5 Hz, 2 H), 2.50 (q, 7.5 Hz, 2 H), 5.96 (s, 1 H), 5.99 (dd, 1.5 Hz, 3.0 Hz, 1 H), 6.99 (t, 3.0 Hz, 1 H), 9.76 (s, 1 H), 10.74 (s, 1 H) ppm; ^{13}C NMR: Table 1; UV/Vis data: Table 4.

2,7-Dimethyl-3-ethyl-(10H)-dipyrrin-1-one (**9**; $C_{14}H_{18}N_2O$)

9 was prepared from 1.6 g (8.9 mmol) of 3-methyl-2-formyl-5-carboethoxy-(1*H*)-pyrrole (**15**) and 0.91 g (0.93 mmol) of 3-methyl-4-ethylpyrrolin-2-one [15] following the same procedure as for **8**.

Yield: 0.58 g (53%); m.p.: 201–202°C; IR (KBr): $\nu = 3354, 3167, 3092, 2970, 2922, 1668, 1632, 1470, 1377, 1264, 1177, 1059, 747, 672\,cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 300 MHz): 1.19 (t, 7.5 Hz, 3 H), 1.95 (s, 3 H), 2.23 (s, 3 H), 2.55 (q, 7.5 Hz, 2 H), 6.12 (dd, 2.5 Hz, 1.5 Hz, 1 H), 6.17 (s, 1 H), 7.00 (t, 2.5 Hz, 1 H), 10.63 (s, 1 H), 11.02 (s, 1 H) ppm; ^1H NMR (*DMSO*-d_6, δ, 300 MHz): 1.08 (t, 7.5 Hz, 3 H), 1.78 (s, 3 H), 2.11 (s, 3 H), 2.51 (q, 7.5 Hz, 2 H), 5.97 (s, 1 H), 6.00 (dd, 2.5 Hz, 1.5 Hz, 1 H), 6.89 (t, 2.5 Hz, 1 H), 9.76 (s, 1 H), 10.72 (s, 1 H) ppm; ^{13}C NMR: Table 1; UV/Vis: Table 4.

3,4-Dimethyl-5-(3-methyl-4,5,6,7-tetrahydro-7-oxo-indolinyl-2-methylidene)-3-pyrrolin-2-one (**10**; $C_{16}H_{22}N_2O_3$)

To a 25 cm^3 round bottomed flask equipped with magnetic stirring, 50 mg of 2,3,7-trimethyl-8-(4-carbomethoxypropyl)-(10*H*)-dipyrrin-1-one (**19**) and 10 cm^3 of trifluoroacetic acid were added and the mixture was heated at reflux for 1 h. It was then cooled in an ice bath to 0°C, and 25 cm^3 of cold water were added to yield a yellow-green precipitate. The solid was collected by filtration and purified by radial chromatography (CH_2Cl_2:MeOH = 97:3) to give the desired product after removal of the solvent.

Yield: 27 mg (60%); m.p.: 247–248°C (dec); IR (film): $\nu = 3273, 2917, 1698, 1659, 1590, 1461\,cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 500 MHz): 1.98 (s, 3 H), 2.13 (m, 5 H), 2.17 (s, 3 H), 2.66 (t, 6.0 Hz, 2 H), 2.76 (t, 6.0 Hz, 2 H), 5.96 (s, 1 H), 10.52 (s, 1 H), 11.09 (s, 1 H) ppm; ^1H NMR (*DMSO*-d_6, δ, 300 MHz): 1.78 (s, 3 H), 2.00 (p, 6.0 Hz, 2 H), 2.04 (s, 3 H), 2.07 (s, 3 H), 2.38 (t, 6.0 Hz, 2 H), 2.57 (t, 6.0 Hz, 2 H), 5.92 (s, 1 H), 10.41 (s, 1 H), 11.35 (s, 1 H) ppm; ESI-MS:$m/z = 271.2$ [M^+] (calcd.: 272.2); ^{13}C NMR: Table 1; UV/Vis: Table 4.

2,3-Dimethyl-5-(ethoxycarbonyl)-(1H)-pyrrole-4-butyric acid ethyl ester (**22**; $C_{15}H_{23}NO_4$)

To a 1 dm^3 round bottomed flask equipped for magnetic stirring, 15.34 g of magnesium shavings, 3.2 cm^3 of CCl_4, and 166 cm^3 of absolute ethanol were added. The mixture was heated at reflux for 4 h to form magnesium ethoxide. The excess ethanol was removed (rotovap), and 370 cm^3 of anhydrous diethyl ether were added and the reaction mixture was cooled to 15°C. 3-Methyl-2,4-pentanedione [16] (70.07 g (0.614 mol)) was added with magnetic stirring, and the mixture was stirred at room temperature for 3 h followed by 1 h of heating at reflux. The reaction mixture was transferred to a 2 dm^3 3-neck round bottomed flask equipped with a mechanical stirrer, an addition funnel, and a thermometer. A solution of 123.3 g (0.69 mol) of 4-carboethoxy butanoyl chloride and 125 cm^3 of anhydrous diethyl ether were placed in the addition funnel, and the reaction mixture was cooled to −10°C. The solution was added dropwise to the reaction mixture with continued cooling. After the addition was complete, the mixture was slowly warmed to room temperature and stirred for 4 h. The reaction mixture was cooled in ice bath and acidified with 50 cm^3 of 25% aqueous H_2SO_4. The biphasic reaction mixture was then decanted from the magnesium salts which were washed with 150 cm^3 of diethyl ether. Both the ether wash and the reaction mixture were combined, and the organic layer was separated. The ether solution was washed with 10% aqueous NaOH (2 × 200 cm^3) and saturated aqueous NaCl (2 × 100 cm^3) and dried over anhydrous $MgSO_4$. The ether was then removed by rotary evaporation to afford **23**.

The residual oil and 500 cm^3 of glacial acetic acid were transferred to a 2 dm^3 3-neck round bottomed flask equipped with a mechanical stirrer, addition funnel, and thermometer. The solution was heated to ∼80°C, and 125 g of anhydrous sodium acetate and 106 g of zinc dust were added all at once. The reaction mixture was then heated to ∼95°C, and a solution of 95 g (0.5 mol) diethyl oximinomalonate [17], 150 cm^3 acetic acid, and 50 cm^3 H_2O was placed in the addition funnel and added to the reaction mixture such that the temperature was maintained between 100–110°C. After the addition was complete, the reaction mixture was heated at reflux for 2.5 h. The hot reaction mixture was poured into 2 dm^3 of ice water with stirring. The solution was placed in a cold room for 24 h, and the solid product was collected by filtration and recrystallized from EtOH/H_2O.

Yield: 25.8 g (20%); m.p.: 64–65°C; IR (thin film): $\nu = 3310$, 2979, 2934, 1736, 1663, 1501, 1438, 1268, 1172, 1111, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 1.24 (t, 7.0 Hz, 3 H), 1.34 (t, 7.0 Hz, 3 H), 1.84 (p, 7.5 Hz, 2 H), 1.92 (s, 3 H), 2.17 (s, 3 H), 2.32 (t, 7.5 Hz, 2 H), 2.75 (t, 7.5 Hz, 2 H), 4.11 (q, 7.0 Hz, 2 H), 4.28 (q, 7.0 Hz, 2 H), 8.61 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 8.70, 11.42, 14.23, 14.51, 24.48, 25.75, 33.94, 59.60, 60.17, 116.50, 116.75, 129.63, 131.02, 161.42, 173.81 ppm.

2-Formyl-3-methyl-5-(ethoxycarbonyl)-1H-pyrrole-4-butyric acid ethyl ester (**21**; $C_{15}H_{23}NO_5$)

To a 1 dm^3 round bottomed flask equipped with magnetic stirring, 2.1 g (7.5 mmol) of 2,3-dimethyl-5-(ethoxycarbonyl)-(1*H*)-pyrrole-4-butyric acid ethyl ester (**22**), 60 cm^3 of *THF*, 120 cm^3 of acetic acid, and 100 cm^3 of H_2O were added. The reaction mixture was placed in an ice bath for 30 min, 16.6 g ceric ammonium nitrate (30.0 mmol) were added all at once, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2 (3×150 cm^3), and the combined extracts were washed with H_2O (3×400 cm^3), saturated aqueous $NaHCO_3$ (2×300 cm^3), and dried over anhydrous Na_2SO_4. The solvent was removed (rotovap), and the oily product was recrystallized from MeOH/H_2O.

Yield: 1.6 g (74%); m.p.: 56–57°C; IR (thin film): $\nu = 3278$, 2984, 2940, 2875, 1728, 1710, 1672, 1462, 1447, 1370, 1253, 1173, 1020, 775, 732 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 300 MHz): 1.25 (t, 7.0 Hz, 3 H), 1.38 (t, 7.0 Hz, 3 H), 1.85 (p, 7.0 Hz, 2 H), 2.32 (s, 3 H), 2.34 (t, 7.0 Hz, 2 H), 2.79 (t, 7.0 Hz, 2 H), 4.12 (q, 7.0 Hz, 2 H), 4.35 (q, 7.0 Hz, 2 H), 9.47 (bs, 1 H), 9.78 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 8.36, 14.16, 14.24, 23.47, 25.36, 33.70, 60.22, 60.92, 124.35, 129.79, 130.04, 130.69, 160.52, 173.37, 179.15 ppm.

2,3,7-Trimethyl-8-(4-carboxypropyl)-(10H)-dipyrrin-1-one-9-carboxylic acid (**20**; $C_{17}H_{20}N_2O_5$)

To a 125 cm^3 round bottom flask equipped with magnetic stirring, 0.52 g (1.7 mmol) of 2-formyl-3-methyl-5-(ethoxycarbonyl)-(1H)-pyrrole-4-butyric acid ethyl ester (**21**), 0.20 g of 3,4-dimethylpyrrolin-2-one [9], and 10 cm^3 of MeOH were added. A solution of 5 g of sodium hydroxide in 50 cm^3 of water was added, and the reaction mixture was stirred at room temperature for 14 h. The solution was acidified with 10% aqueous HCl, and the precipitate was collected by centrifugation and triturated with MeOH.

Yield: 0.40 g (69%); m.p.: 200–201°C (dec); IR (KBr): $\nu = 3374$, 1672, 1460, 1260, 964, 796 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 1.65 (p, 7.5 Hz, 2 H), 1.75 (s, 3 H), 2.12 (s, 3 H), 2.15 (t, 7.5 Hz, 2 H), 2.46 (s, 3 H), 2.65 (t, 7.5 Hz, 2 H), 5.89 (s, 1 H), 10.42 (s, 1 H), 10.96 (s, 1 H), 12.15 (s, 2 H) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 125 MHz): 8.36, 9.01, 9.56, 23.65, 25.55, 33.26, 96.17, 121.31, 122.34, 126.30, 127.49, 130.04, 134.28, 141.85, 161.99, 172.68, 174.39 ppm.

2,3,7-Trimethyl-8-(4-carbomethoxypropyl)-(10H)-dipyrrin-1-one (**19**; $C_{17}H_{22}N_2O_3$)

To a 125 cm^3 round bottom flask equipped with magnetic stirring, 0.99 g of 2,3,7-trimethyl-8-(4-carboxypropyl)-(10*H*)-dipyrrin-1-one-9-carboxylic acid (**20**) and 50 cm^3 of MeOH were added. To this solution, 10 cm^3 of 10% H_2SO_4 were added, and the mixture was heated at reflux for 2 h. The reaction mixture was cooled to room temperature, taken up in 150 cm^3 of CH_2Cl_2, washed with H_2O (2×100 cm^3), saturated aqueous $NaHCO_3$ (2×100 cm^3) and dried over anhydrous Na_2SO_4. The solvent was removed (rotovap), and the residue was purified by radial chromatography (CH_2Cl_2:MeOH = 97:3) to give the desired ester.

Yield: 0.66 g (73%); m.p.: 194–195°C (dec); IR (film): $\nu = 3353$, 1733, 1656 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 1.88 (p, 7.5 Hz, 2 H), 1.94 (s, 3 H), 2.13 (s, 6 H), 2.37 (t, 7.5 Hz, 2 H), 2.47 (t, 7.5 Hz, 2 H), 3.70 (s, 3 H), 6.12 (s, 1 H), 6.85 (d, 1.5 Hz, 1 H), 10.44 (s, 1 H), 11.04 (s, 1 H) ppm;

^{13}C NMR ($CDCl_3$, δ, 125 MHz): 8.26, 9.44, 9.96, 9.96, 24.62, 25.49, 33.58, 51.47, 102.24, 121.56, 126.59, 123.82, 124.30, 124.37, 129.48, 142.78, 173.72, 174.16 ppm.

2-Formyl-3-methyl-5-(ethoxycarbonyl)-(1H)-pyrrole (**15**; $C_9H_{11}NO_3$)

To a 500 cm^3 round bottom flask equipped with magnetic stirring, 7.1 g of 2,3-dimethyl-5-carboethoxypyrrole (**17**) [18], 250 cm^3 of methanol, and 20 cm^3 H_2O were added. The reaction mixture was placed in a ice bath for 30 min, 93.8 g of ceric ammonium nitrate were added all at once, and stirring was continued at room temperature for 3 h. The reaction mixture was taken up in CH_2Cl_2 (500 cm^3), washed with water (3 × 400 cm^3) and saturated sodium bicarbonate (2 × 300 cm^3), and dried over anhydrous Na_2SO_4. The solvent was removed (rotovap) to yield an oily product which was recrystallized from methanol to give the desired pyrrole aldehyde.

Yield: 4.45 g (55%); m.p.: 243–244°C (Ref. [18]: 245–247°C) ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.37 (t, 7.5 Hz, 3 H), 2.39 (s, 3 H), 4.35 (q, 7.5 Hz, 2 H), 6.72 (d, 2.0 Hz, 1 H), 9.59 (bs, 1 H), 9.78 (s, 1 H) ppm; GC-MS: $m/z = 253$ [M^+], 224 (100%), 192, 174, 148, 104, 77, 65.

Table 6. Crystallographic data for dipyrrinone **1**

Formula Weight	286.37
Crystallized from	$CDCl_3$
Temperature (K)	298(2) K
Crystal Size (mm)	0.20 × 0.40 × 0.24
Formula	$C_{17}H_{22}N_2O_2$
Space group	$P\overline{1}$
Z	2
Cell dimensions	$a = 7.7765\ (8)$ Å
	$b = 10.2949\ (10)$ Å
	$c = 11.0329\ (10)$ Å
	$\alpha = 66.155\ (7)^\circ$
	$\beta = 76.741\ (10)^\circ$
	$\gamma = 87.947\ (10)^\circ$
	$V = 784.74\ (13)$ Å^3
Nr/ν range of Refs. used for cell refinements	$40/10.08 > \theta > 24.81$
Calc. density d_x (g/cm^3)	1.212
Data collection range	$2.08 < \theta < 24.99^\circ$
Scan type/scan range	$\omega/1.2^\circ$
No. of total data recorded	3336
No. of unique data	2679
Weighting Scheme[a]	$a = 0.0681$
No. obs / no. parameters	2679/191
R_1^b, wR_2^c ($I > 2\sigma(I)$)	$R_1 = 0.0798,\ R_2 = 0.1456$
e.s.d. of C–C bond length	0.007
Highest peak in final ΔF map (e · Å^{-3})	0.245
Anisotropic non-H atoms	all
Isotropic non-H atoms	none
μ (MoK_α) (mm^{-1})	0.081
Radiation (λ (Å))	0.71073
Transmittance factors	0.78–0.99

[a] $w^{-1} = \sigma^2(F^2) + (aP)^2$ where $P = (F_o^2 + wF_c^2)/3$; Goodness of Fit (GOOF): $(\Sigma(w(F_o^2 - F_c^2)^2)/(M - N))^{0.5}$ where M is the number of reflections and N is the number of parameters refined; [b] $R_1 = \Sigma \parallel F_o \mid - \mid F_c \parallel / \Sigma \mid F_o \mid$; $wR_2 = (\Sigma(w(F_o^2 + wF_c^2)^2)/\sigma(w(F^2)^2))^{0.5}$

Table 7. Atomic cordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **1**; U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
O(1)	5051(5)	11894(4)	−368(4)	67(1)
O(2)	3986(5)	4800(4)	2642(5)	78(2)
N(1)	2775(6)	10145(4)	784(4)	52(1)
N(2)	1455(6)	6721(4)	2366(4)	46(1)
C(1)	3464(8)	11519(6)	185(6)	55(2)
C(2)	2019(7)	12427(5)	348(5)	44(2)
C(3)	534(7)	11591(5)	974(5)	45(2)
C(4)	963(7)	10107(5)	1295(5)	43(2)
C(5)	−196(7)	8955(6)	1991(5)	47(2)
C(6)	−50(7)	7449(5)	2460(5)	40(1)
C(7)	−1475(7)	6437(6)	3164(5)	46(2)
C(8)	−793(8)	5096(6)	3481(5)	47(2)
C(9)	1024(7)	5287(5)	2972(5)	43(2)
C(10)	2440(8)	4322(6)	3051(6)	52(2)
C(21)	2305(8)	14009(5)	−174(6)	62(2)
C(31)	−1312(7)	12021(5)	1344(6)	61(2)
C(71)	−3387(7)	6731(6)	3508(6)	63(2)
C(81)	−1931(7)	3716(5)	4266(6)	66(2)
C(101)	2018(7)	2727(5)	3624(6)	54(2)
C(102)	3645(8)	1880(5)	3456(6)	69(2)
C(103)	3123(10)	290(6)	4072(7)	94(3)

X-Ray structure determination

Crystals of dipyrrinone **1** were grown by slow evaporation of $CDCl_3$. Suitable crystals were coated with epoxy cement, mounted on a glass fiber, and placed on a Siemens P4 diffractomer. Unit cell parameters were determined by least squares analysis of 25 reflections with $22.8 < \theta < 25.0$ using graphite monochromatized MoK_α radiation ($\lambda = 0.71073$ Å). 3336 reflections were collected in the range $2.08 < 2\theta < 24.99°$ yielding 2679 unique reflections ($R_{int} = 0.0417$). The data were corrected for *Lorentz* and polarization effects and absorption using an empirical model derived from azimuthal data collections. Crystal data are given in Table 6. Scattering factors and corrections for anomalous dispersion were taken from a standard source [19].

Calculations were performed using the Siemens SHELXTL PLUS, version 5.03, system of programs refining on F^2. The structure was solved by direct methods in the space group $P\bar{1}$. The unit cell contains an ordered array of the molecule with no unusual contacts.

All non-hydrogen atoms (Table 7) were refined with anisotropic thermal parameters. Hydrogen atom positions were calculated using a riding model with a C–H distance fixed at 0.96 Å and a thermal parameter of 1.2 times of that of the host carbon atom. The largest peak in the final difference map corresponded to $0.245\,e^-/Å^3$ was located 1.178 Å from C(81). Tables of bond lengths, bond angles, and anisotropic and isotropic displacement parameters have been deposited at the Cambridge Structural Data File (CDC No. 149741).

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