Pergamon

Tetrahedron 55 (1999) 10871–10886

TETRAHEDRON

Stable 4*E*-Dipyrrinones

Stefan E. Boiadjiev and David A. Lightner*

Chemistry Department, University of Nevada, Reno, NV 89557 USA

Received 2 June 1999; accepted 12 July 1999

Abstract. Dipyrrinones formed by DBU and *n*-Bu_3P-promoted condensation of 5-*p*-toluenesulfonylpyrrolinones with pyrrole 2-aldehydes, gave high yields of product with predominantly the *E*-configuration when the aldehyde had a 5-carboethoxy group. The 4*E*-dipyrrinones were readily purified by chromatography and were stable in solutions shielded from light.

Keywords: Pyrroles; stereoselection; stereoisomerism; hydrogen bonding

Introduction

The dipyrrinone chromophore (Fig. 1) is the major structural unit of bilirubin, a cytotoxic tetrapyrrole which is produced copiously in normal human metabolism of hemes and is the yellow pigment of jaundice.[1-3] Dipyrrinones give bilirubin its color and stereochemistry. Through rotations about a central CH_2, to which two *syn-Z*-dipyrrinones are conjoined, bilirubin adopts preferentially a shape that allows for considerable intramolecular hydrogen bonding with opposing propionic acids.[4-7] Such intramolecular hydrogen bonding controls the conformation of bilirubin in the crystal and in solution and dominates its solution properties, *e.g.*, its considerable hydrophobicity.[5] Typical dipyrrinones are bright yellow compounds with an intense UV-vis absorption near 400 nm (ϵ ~35,000 L · mole^{-1} · cm^{-1}) associated with the long axis polarized $\pi \rightarrow \pi^*$ excitation of the 14π-electron conjugated chromophore.[8,9] The parent unsubstituted *Z*- and *E*-dipyrrinones (Fig. 1) are essentially equi-energetic, according to molecular mechanics calculations;[8] whereas, *ab initio* molecular orbital calculations place the *syn-Z* ~2.4 kcal/mole more stable than the *anti-E*.[10] In contrast, the more common C-alkylated dipyrrinones are known from X-ray crystallography, NMR nuclear Overhauser effect (NOE) studies and molecular mechanics calculations to prefer clearly the *Z*-configuration when positions 3 and 7 are occupied by alkyl groups (by

email: lightner@scs.unr.edu

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00617-1

~13 kcal/mole with 3-CH_3 and 7-CH_3).[8] The most stable conformation of these substituted *Z*-dipyrrinones is *syn* (*sc* or *sp*); whereas, the *E*-isomers are twisted out of planarity by steric repulsions between the C(3) and/or C(7) alkyl substituents and the opposing NH group. Such *E*-isomers are typically generated photochemically from the *Z*-isomers, and they are unstable, reverting rapidly back to (*Z*).[8,11] For the dipyrrinones of bilirubin, (*Z* → *E*) configurational inversion is the key event in phototherapy for neonatal jaundice, as it dissociates intramolecular hydrogen bonding, freeing the polar groups.[12] This renders the pigment less hydrophobic and readily excreted across the liver into bile without recourse to hepatic glucuronidation, an essential step in normal bilirubin clearance.[1,3,12a,d]

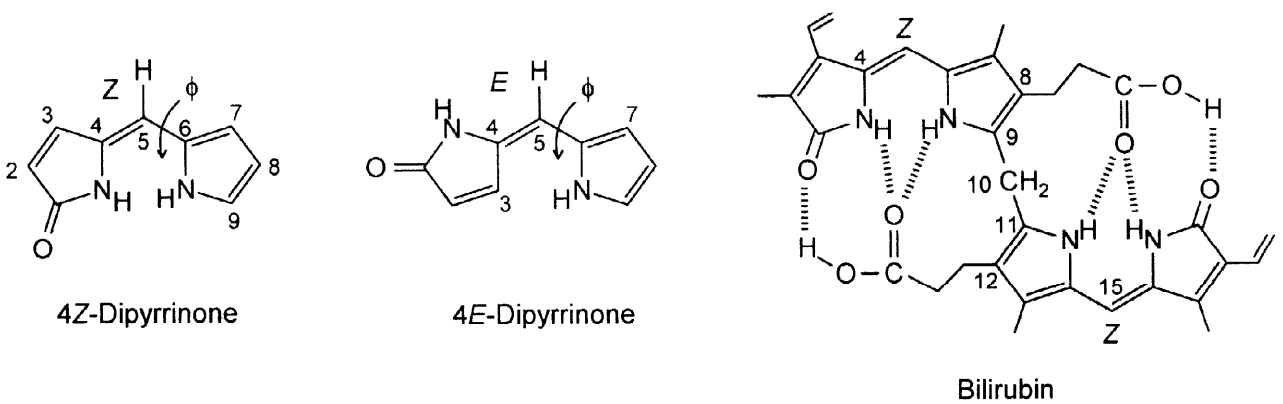
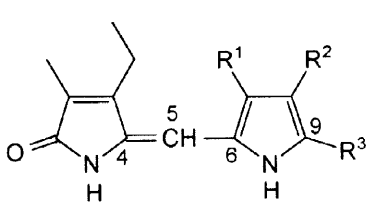


Figure 1. Naked unsubstituted dipyrrinones in their 4*Z*- and 4*E*- configurations. (4*Z*,15*Z*)-bilirubin-IXα (bilirubin), which is composed of two *Z*-dipyrrinones, each of which is intramolecularly hydrogen bonded to an opposing propionic acid. Hydrogen bonds are indicated by hatched lines.

While most C-substituted *E*-dipyrrinones are less stable than their *Z*-isomers and are thus usually not observed in the synthesis of dipyrrinones, recently Inomata and coworkers[13] detected, unexpectedly, what appeared to be mixtures of *Z*- and *E*-isomers in a Wittig-type synthesis of dipyrrinones. Purported *E*-isomers were not isolated but converted to (*Z*) by treating the crude mixture with iodine. Their synthesis tended to avoid conditions in which *E*-dipyrrinones might isomerize to (*Z*). Intrigued by the possibility of preparing *E*-dipyrrinones by synthesis (rather than photochemically), we investigated the preparation of dipyrrinones **1-5**.

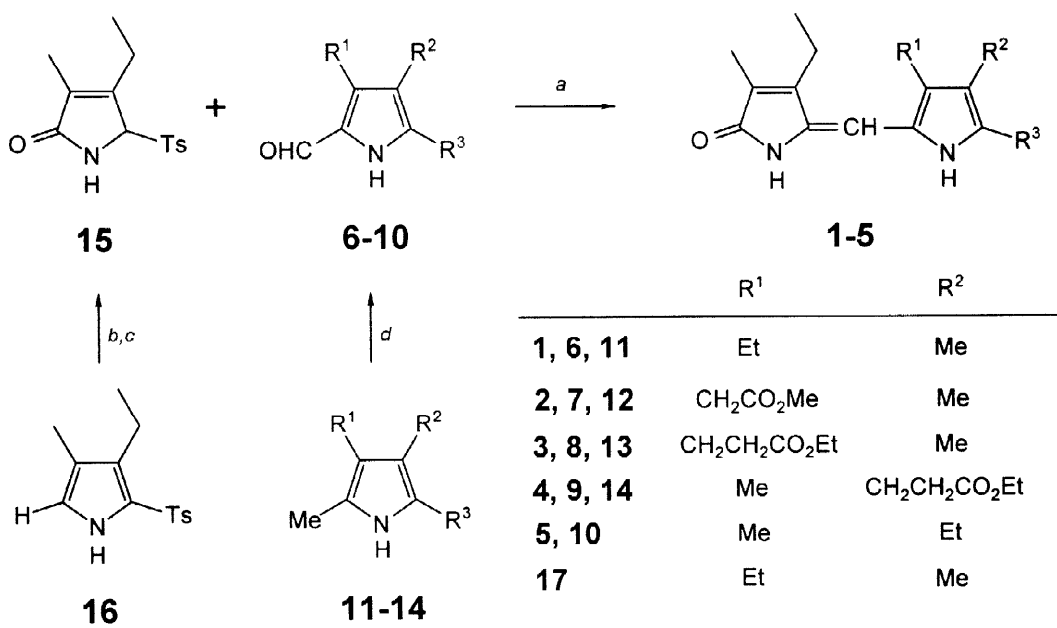


	R^1	R^2	R^3
1	Et	Me	CO_2Et
2	CH_2CO_2Me	Me	CO_2Et
3	$CH_2CH_2CO_2Et$	Me	CO_2Et
4	Me	$CH_2CH_2CO_2Et$	CO_2Et
5	Me	Et	Me

Results and Discussion

Synthesis. Dipyrrinones **1-5** were prepared by condensing tosyl-pyrrolinone **15** with pyrrole aldehydes **6-10** using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and tri-*n*-butylphosphine as catalysts[13] (Synthetic Scheme). The reaction proceeded smoothly and gave decent (57-75%) yields of dipyrrinone, except for **5**, which afforded only a 6% isolated yield. The precursors to **15** and **6-10** were tosylpyrrole **16** prepared by the Barton-Zard procedure using *p*-toluenesulfonylmethyl isocyanide (TosMIC)[14] and pyrroles **11-14**.[15-18] The latter were smoothly oxidized to aldehydes **6-9** in moderate yield (34-65%) using ceric ammonium nitrate (CAN) in acetic acid-water.[19] Pyrrole aldehyde **10** was prepared by Vilsmeier formylation of kryptopyrrole (**17**), as reported earlier.[20] Tosylpyrrole **16**[14] was brominated at the vacant α-position and the resultant bromo-tosylpyrrole was solvolyzed in aq. TFA to afford **15**.[21] Analysis of the initially-formed dipyrrinone products indicated a preponderance of *E*-isomer in **1-4**, ranging from 81-90% based on isolated yields using radial chromatography to effect the separation of *E*- and *Z*-isomers. Crude reaction product before separation showed barely traces of *Z*-isomer, indicating that the coupling reaction is highly stereoselective for (*E*). This is consistent with the suggestion of Inomata *et al.*[13] that the *E*-isomer is the kinetic product, as is known for phosphonium ylids.

Synthetic Scheme



	R^1	R^2	R^3
1, 6, 11	Et	Me	CO_2Et
2, 7, 12	CH_2CO_2Me	Me	CO_2Et
3, 8, 13	$CH_2CH_2CO_2Et$	Me	CO_2Et
4, 9, 14	Me	$CH_2CH_2CO_2Et$	CO_2Et
5, 10	Me	Et	Me
17	Et	Me	H

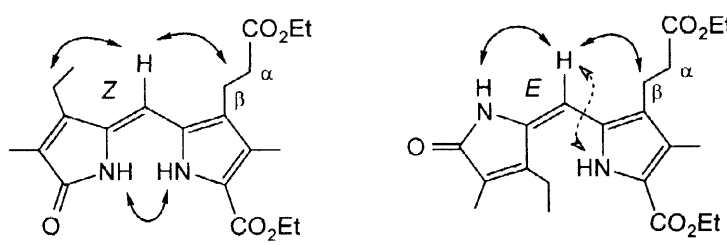
[a] DBU/*n*-Bu_3P. [b] $PhN^+Me_3Br^- \cdot Br_2$. [c] TFA / H_2O. [d] CAN / aq. HOAc.

In the case of kryptopyrromethenone (**5**), the low yield and absence of an *E*-isomer indicates that the reaction is promoted when the pyrrole α-aldehyde has an electron-withdrawing group at

the other α-position, and that the electron withdrawing carboethoxy group is much more effective than a methyl in stabilizing the *E*-configuration. In **1-4**, thermal (*E* → *Z*) isomerization is slow; in **5** it is rapid. Repeated recrystallization of mainly (*E*)-**1-4** at 70-75 °C led to an increasing presence of the *Z*-isomer, which crystallized more readily than (*E*).

Spectroscopic Characteristics. ^{13}C and ^{1}H-NMR chemical shift data of **1-4** and (**5***Z*) are reported in Tables 1 and 2 for both $CDCl_3$ and $(CD_3)_2SO$ solvents. The specific assignments and correlations were made on the basis of HMQC and HMBC correlation spectroscopy[22] using pulsed field gradient sequences. It will be shown in the following that there are characteristic differences in ^{13}C and ^{1}H-NMR chemical shifts that can be used to distinguish *E*- from *Z*- isomers of a given pair of diastereomers, but first we report on the use of $^{1}H\{^{1}H\}$-nuclear Overhauser effects (NOEs) for such identifications.

Distinguishing E and Z-Isomers. The diastereomeric pairs of dipyrrinones **1-4** differ structurally only in the configuration of the exocyclic C(4)=C(5) double bond, and the *E*- and *Z*-diastereomers of a given pair can easily be distinguished and assigned by NOE NMR spectroscopy. The dipyrrinone lactam and pyrrole NHs are easily distinguished from CHs as being more deshielded. Strong NOEs are found between the NHs in the minor diastereomers, as is characteristic of a *Z*-configuration, as illustrated in Figure 2 for (*Z*)-**3**. On the other hand, the major isomers found in the syntheses of **1-4** show no NOE between the NHs. Rather, one finds an NOE between the lactam NH and the C(5)H, and between the C(5)H and the C(7′) hydrogens, as shown for (*E*)-**3**. These NOEs are consistent with a nonplanar structure of the *E*-isomer, with considerable twisting about the C(5)-C(6) bond: an *ac*-*E*-conformation. In contrast, the *Z*-diastereomers show strong NOEs between the C(5)H and the C(3) ethyl as well as the C(7′) hydrogens (β-CH_2 in **3**), hence the *sp*-*Z*- or *sc*-*Z*-conformation. The only isomer isolated in the synthesis of **5** gave NOEs consistent with the *Z*-diastereomer.



(*Z*)-**3** (*E*)-**3**

Figure 2. Important $^{1}H\{^{1}H\}$-Homonuclear Overhauser effects found in (*Z*)-**3** and (*E*)-**3** are shown by curved, double-headed arrows.

Assignments and Correlations. In addition to differing NOE behavior, *E*- and *Z*-dipyrrinones also show characteristic differences in their ^{13}C-NMR spectra run in $CDCl_3$ and $(CD_3)_2SO$ solvents. Since the type and position of the pyrrole ring β-substituents differ, data for those substituents are not included in Table 1. Although the chemical shifts show some selective sensitivity toward solvent, large differences in chemical shift in a given solvent are found to distinguish *E*- from *Z*-diastereomers. (*i*) The lactam C=O of an *E*-isomer is ~2 ppm more shielded than a (*Z*). (*ii*) Lactam ring atoms 2 and 4 are typically more deshielded in the *E*-isomer than the (*Z*): C(2) ~3-5 ppm more deshielded, C(4) an incredible ~5-8 ppm more deshielded. In contrast, C(3) is ~3 ppm more shielded in the *E*-isomer than the (*Z*). (*iii*) Bridging carbon 5 is found to be ~5 ppm more deshielded in the *E*-isomer than in the (*Z*). (*iv*) The pyrrole ring carbons are generally less sensitive to (*E/Z*) stereochemistry, especially C(6) and C(8), with C(7) and C(9) being ~2 ppm more shielded in the (*E*)-isomer than the (*Z*). (*v*) Differences in the C(9) substituent are relatively small; whereas, more substantial differences (~1 ppm) can be found in the C(3) ethyl group, with the CH_2 being generally more deshielded in the *E*-isomer and the CH_3 being more shielded. Whether such differences can be attributed to ineffective conjugation in the *E*-isomers due to severe twisting about the C(5)-C(6) bond is unclear, but likely.

The largest differences in the ^{1}H-NMR spectra are found for the lactam and pyrrole NH chemical shifts.[23] In the *E*-isomers, the lactam NH is ~0.9-1.6 ppm more shielded than the pyrrole in both $CDCl_3$ and $(CD_3)_2SO$ solvents. In the *Z*-isomers the lactam NH is also more shielded than the pyrrole NH (~0.5 ppm) in $(CD_3)_2SO$, but in $CDCl_3$ the pyrrole NH is more shielded. The difference in chemical shift between corresponding *E*- and *Z*-isomers in the same solvent is much greater for the lactam NH than pyrrole NH. Table 2 indicates that a lactam NH is typically 1.1-1.7 ppm more shielded in the *E*-isomer than in the (*Z*) in $CDCl_3$; in $(CD_3)_2SO$ it is 0.5-0.7 ppm more shielded. In contrast, the pyrrole NH is only ~0.2 ppm more deshielded in the *E*-isomer than in the (*Z*) in $(CD_3)_2SO$, and ~0.1 ppm more deshielded in $CDCl_3$.

There is also a strong concentration dependence on the NH chemical shifts (Fig. 3). In $CDCl_3$ the pyrrole NH (at ~8.6 ppm) of (*E*)-**3** changes only 0.24 ppm over the concentration range shown; whereas, that of the *Z*-isomer (9.4-7.4 ppm) is far more sensitive and changes by ~2 ppm. In contrast, the lactam NH chemical shift is about as sensitive to concentration in the *Z*-isomer (~9.6-8.6 ppm) as in the *E*-isomer (~8.0-7.1 ppm) with an ~1 ppm change. Similar shifts may be found for the other dipyrrinones of this study (Table 2). The sensitivity to concentration is thought to be due to a monomer-dimer equilibrium,[24] with the dimeric species held together by intermolecular hydrogen bonds, as illustrated in Figure 4. The *Z*-diastereomer can be expected to form a more stable dimer because of the greater number of hydrogen bonds than in the (*E*). Consistent with this thesis, only the lactam NH chemical shifts of the latter change significantly between 2.5×10^{-3} and 10^{-4} M concentration whereas, in the *Z*-isomer both the lactam and pyrrole NH chemical shifts show a large concentration-dependency. The data for the *E*-isomer are more consistent with lactam to lactam dimerization of Figure 4.

Table 1. Comparison of Selected ^{13}C-NMR Chemical Shifts of 4*E* and 4*Z*-Dipyrrinones.[a]

Position	1*E*	1*Z*	2*E*	2*Z*	3*E*	3*Z*	4*E*	4*Z*	5*Z*
1-CONH	170.41 *171.96*	172.72 *174.23*	170.49 *171.60*	172.74 *174.01*	170.44 *171.64*	172.74 *174.19*	170.42 *172.09*	172.67 *174.29*	171.84 *174.03*
2	130.95 *132.35*	127.25 *127.41*	131.15 *132.83*	126.64 *127.68*	131.06 *132.72*	125.92 *127.18*	131.08 *132.28*	128.08 *128.22*	127.04 *126.85*
2-CH_3	8.17 *8.60*	8.07 *8.27*	8.16 *8.60*	8.07 *8.29*	8.18 *8.61*	8.06 *8.29*	8.16 *8.50*	8.08 *8.27*	8.04 *8.49*
3	144.61 *144.69*	147.50 *147.91*	144.64 *144.72*	147.65 *147.77*	144.56 *144.59*	147.59 *148.11*	144.58 *144.79*	147.43 *147.90*	147.14 *148.22*
3^1-CH_2CH_3	17.23 *17.69*	16.81 *17.91*	18.33 *18.99*	17.06 *17.88*	18.44 *19.08*	17.09 *17.91*	18.29 *18.96*	17.08 *17.88*	17.14 *17.95*
3^2-CH_2CH_3	12.87 *13.40*	14.44 *14.60*	12.84 *13.35*	14.45 *14.49*	12.86 *13.38*	13.96 *14.17*	14.19 *14.30*	14.58 *14.60*	14.83 *15.05*
4	140.57 *139.15*	133.07 *133.99*	141.27 *140.22*	133.88 *135.64*	140.83 *139.64*	133.43 *134.59*	140.73 *139.78*	133.58 *134.21*	128.68 *131.12*
5-CH=	100.39 *102.16*	95.50 *97.37*	99.63 *100.80*	95.61 *96.68*	100.19 *101.40*	95.61 *97.18*	100.38 *101.99*	95.90 *97.42*	97.71 *101.22*
6	127.28 *128.05*	129.42 *130.28*	128.78 *127.78*	128.80 *128.83*	127.92 *126.98*	127.89 *128.06*	128.92 *129.89*	129.20 *129.96*	122.48 *124.59*
7	125.22 *126.35*	125.43 *126.74*	118.33 *119.54*	120.87 *121.61*	121.92 *124.02*	125.77 *126.21*	118.60 *120.84*	122.12 *123.09*	121.80 *122.20*
8	125.47 *126.73*	125.75 *126.95*	126.36 *127.61*	126.06 *127.59*	125.66 *126.94*	125.87 *127.05*	128.01 *127.26*	125.89 *127.09*	122.04 *122.90*
9	118.24 *119.39*	120.95 *121.78*	116.52 *117.88*	119.92 *119.41*	118.26 *119.52*	120.94 *121.81*	118.03 *119.11*	120.52 *121.53*	121.56 *122.16*
9^1-C=O	160.74 *161.58*	160.78 *161.44*	160.67 *161.42*	160.69 *161.35*	160.68 *161.43*	160.73 *161.36*	160.36 *161.15*	160.35 *160.96*	10.87[b] *11.48*[b]
9^2-CH_2	59.00 *60.01*	59.48 *60.10*	59.15 *60.18*	59.60 *60.27*	59.78 *60.44*	59.83 *60.50*	59.67 *60.21*	59.73 *60.29*	— —
9^3-CH_3	14.37 *14.48*	14.55 *14.46*	14.36 *14.47*	14.43 *14.44*	14.36 *14.47*	14.46 *14.55*	14.03 *14.18*	14.22 *14.31*	— —

[a] Values in δ, ppm downfield from $(CH_3)_4Si$ in $(CD_3)_2SO$ and *$CDCl_3$ (values in italics)* at 25 °C. Assignments are made from a combination of HMBC and HMQC correlation experiments. [b] 9-CH_3

Table 2. Comparison of Selected ^{1}H-NMR Chemical Shifts of 4*E* and 4*Z*-Dipyrrinones.[a]

Position	1*E*	1*Z*	2*E*	2*Z*	3*E*	3*Z*	4*E*	4*Z*	5*Z*
Lactam NH	9.80 *7.33*	10.53 *9.04*	9.84 *8.27*	10.48 *9.41*	9.83 *7.51*	10.49 *9.23*	9.84 *7.55*	10.38 *9.24*	9.73 *11.31*
Pyrrole NH	11.23 *8.62*	11.01 *8.41*	11.46 *9.13*	11.17 *9.08*	11.31 *8.71*	11.05 *8.70*	11.37 *8.72*	11.12 *8.66*	10.22 *10.35*
2-CH_3	1.76 *1.93*	1.79 *1.95*	1.76 *1.90*	1.79 *1.93*	1.76 *1.93*	1.80 *1.94*	1.76 *1.93*	1.79 *1.95*	1.77 *1.95*
3-CH_2CH_3	2.31 *2.43*	2.51 *2.52*	2.10 *2.24*	2.51 *2.52*	2.10 *2.27*	2.52 *2.54*	2.14 *2.28*	2.51 *2.53*	2.49 *2.55*
3-CH_2CH_3	0.95 *1.05*	1.09 *1.18*	0.68 *0.89*	1.08 *1.18*	0.69 *0.94*	1.10 *1.19*	0.64 *0.91*	1.09 *1.18*	1.07 *1.17*
5-CH=	6.07 *6.14*	5.92 *5.97*	6.02 *6.17*	5.97 *5.99*	6.08 *6.19*	5.98 *6.06*	6.02 *6.10*	5.93 *5.96*	5.92 *6.15*
9-$CO_2CH_2CH_3$	4.18 *4.32*	4.26 *4.32*	4.19 *4.30*	4.27 *4.31*	4.18 *4.31*	4.26 *4.31*	4.18 *4.32*	4.25 *4.32*	2.16[b] *2.41*[b]
9-$CO_2CH_2CH_3$	1.26 *1.36*	1.30 *1.35*	1.26 *1.35*	1.30 *1.34*	1.25 *1.36*	1.30 *1.34*	1.26 *1.36*	1.29 *1.35*	— —

[a] Values in δ, ppm downfield from $(CH_3)_4Si$ in $(CD_3)_2SO$ and *$CDCl_3$ (values in italics)* at 25°C. [b] 9-CH_3.

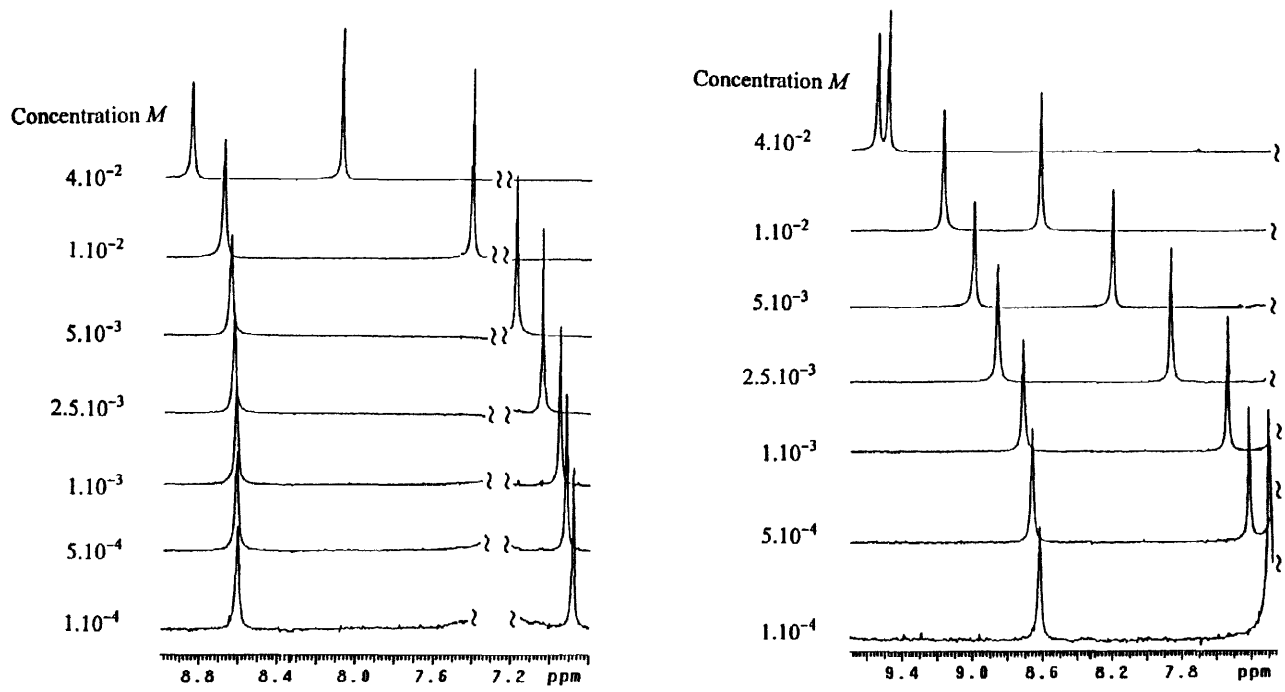


Figure 3. Partial ^{1}H-NMR spectra showing concentration dependence in $CDCl_3$ solvent of the dipyrrinone lactam and pyrrole NH chemical shifts of (*E*)-**3** (left) and (*Z*)-**3** (right). The lactam NH is more shielded in (*E*)-**3**, but more deshielded in (*Z*)-**3**.

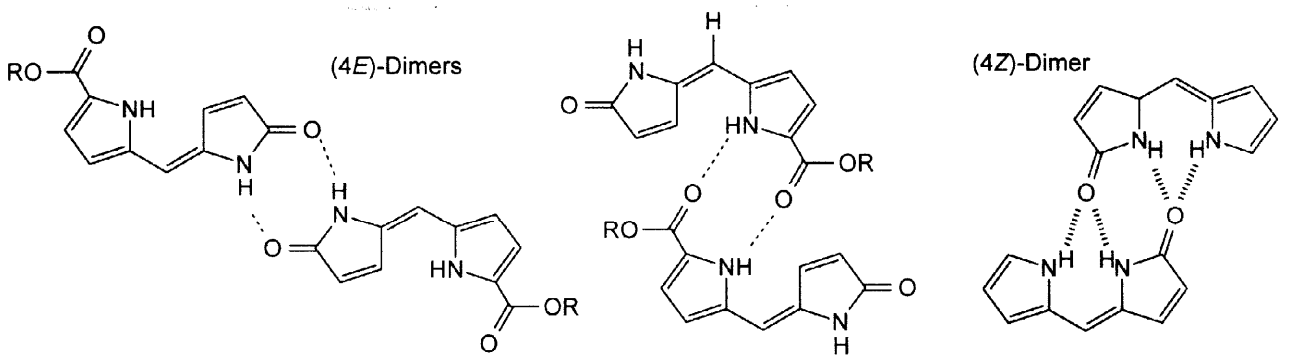


Figure 4. Intermolecularly hydrogen-bonded dipyrrinone dimers.

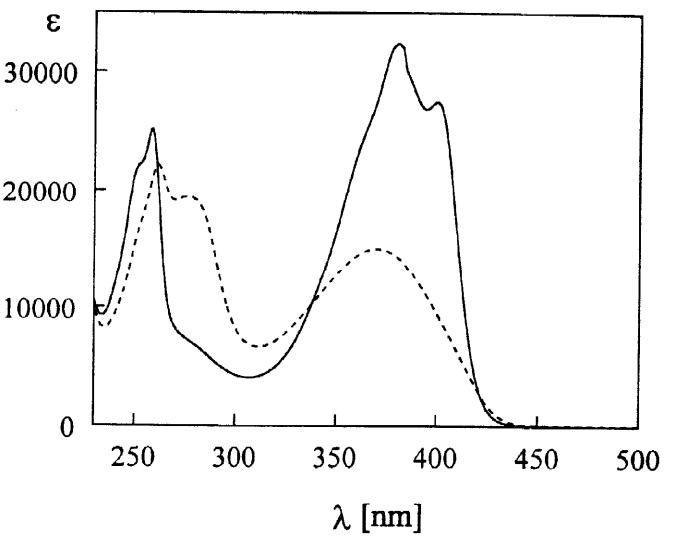
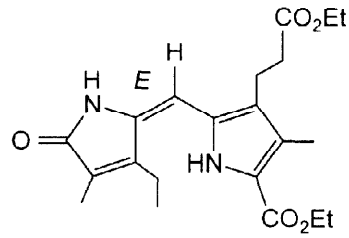
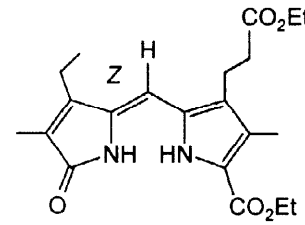


Figure 5. Comparison of UV-vis spectra from 6.3×10^{-5} M solutions of (*Z*)-**3** (——) and (*E*)-**3** (- - - -) in methanol.

UV-Visible Spectra. *Z*-Dipyrrinones are typically bright yellow compounds with an intense absorption near 400 nm.[8,16,17] The corresponding excitation of *E*-dipyrrinones is roughly half as intense (see Fig. 5) and crystals of the *E*-isomers of this work are not as strongly yellow as the corresponding *Z*-diastereomers. The *E*-isomer long wavelength λ_{max} is hypsochromically shifted from that of the (*Z*) by ~20 nm, while the shorter wavelength λ_{max} is bathochromically shifted. Only small solvent shifts in the UV-vis spectra are detected over a wide range of solvent polarity (Table 3). Interestingly, the long wavelength band in (*Z*)-**3** (or **1-4**) is split, suggesting two transitions not seen in the UV-vis spectra of (*Z*)-**5**, or (*E*)-**3**. In both the *Z*- and *E*-isomers of **1-4**, the shorter wavelength band near 260-280 nm is also split, but that was not detected in **5**.

Slow ($E \leftrightharpoons Z$) photoisomerization of (*E*)-**2** was observed upon low intensity light irradiation (370 nm monochromatic light from a 500 W tungsten-halogen lamp), as detected by ^{1}H-NMR for the appearance of a second set of signals corresponding to *Z*-isomer. With unfiltered light from a 100 W mercury lamp, $E \leftrightharpoons Z$ photoisomerization was rapid, to a photoequilibrium, $E{:}Z \leq 1{:}3$.

Table 3. UV-vis Data for Dipyrrinones (*E*)-**3** and (*Z*)-**3**.

				
Solvent	ϵ^{max} (λ, nm)	ϵ^{max} (λ, nm)	ϵ^{max} (λ, nm)	ϵ^{max} (λ, nm)
$CHCl_3$	17,000 (377)	16,200 (278)^{sh} 20,600 (262)	24,200 (402) 30,300 (382)	23,700 (259) 22,900 (254)^{sh}
THF	13,800 (364)	18,600 (273) 21,600 (261)	23,500 (399) 30,000 (378)	23,600 (258) 21,200 (252)^{sh}
CH_3CO_2Et	14,400 (362)	18,000 (273)^{sh} 21,300 (260)	24,500 (396) 31,100 (376)	23,900 (258)
CH_3CN	14,500 (362)	17,900 (273) 21,100 (260)	21,900 (392)^{sh} 28,400 (374)	23,400 (257) 21,200 (251)^{sh}
CH_3OH	15,000 (370)	19,500 (276) 22,100 (262)	27,500 (400) 32,400 (380)	25,000 (258) 22,200 (251)^{sh}
$(CH_3)_2SO$	14,200 (367)	18,600 (276) 21,000 (263)	29,300 (405) 33,500 (383)	22,600 (261)

Concluding Comments

E-Dipyrrinones are typically unstable with respect to their *Z*-isomers; yet, synthesis of dipyrrinones with electron-withdrawing groups at C(9), *e.g.*, carboethoxy, appear to afford unusual stability to the *E*-diastereomers. The dipyrrinone-forming Wittig-type condensation reactions of this work give the *E*-diastereomer as the isolable kinetic product, which only slowly converts to (*Z*). On the other hand, when the electron-withdrawing C(9)-carboethoxy group is replaced by methyl or hydrogen, only *Z*-isomers are isolated in dipyrrinone-forming reactions. The current studies suggest that *E*-isomers of 10-oxo-bilirubin, a proposed metabolite formed in alternate pathways of bilirubin elimination, should be more stable than *E*-isomers of bilirubin. Bilirubin, which is composed of two dipyrrinones connected to a 10-CH_2, forms *E*-isomers photochemically and during neonatal phototherapy, but they are known to be unstable and readily revert to *Z*.

Experimental

General Methods. Nuclear magnetic resonance spectra were obtained on a GE GN-300 or Varian Unity Plus spectrometers operating at ^1H frequency of 300 MHz or 500 MHz, respectively. Unless otherwise specified, $CDCl_3$ solvent was used throughout and chemical shifts were reported in δ ppm referenced to the residual $CHCl_3$ ^1H signal at 7.26 ppm and $CDCl_3$ ^{13}C signal at 77.00 ppm. A J-modulated spin-echo experiment (*A*ttached *P*roton *T*est) was used to obtain the ^{13}C-NMR assignments. A double pulsed field gradients spin echo experiment was used for $^1H\{^1H\}$-NOE measurements.[25] All ultraviolet-visible spectra were recorded on a Perkin-Elmer Lambda-12 spectrophotometer. Gas chromatography-mass spectrometry analyses were carried out on Hewlett-Packard 5890A capillary gas chromatograph (30 m DB-1 column) equipped with Hewlett-Packard 5970 mass selective detector. Analytical thin layer chromatography was carried out on J.T. Baker silica gel IB-F plates (125 μm layer). Radial chromatography was carried out on preparative layer grade Merck silica gel PF_{254} with $CaSO_4$ binder using a Chromatotron (Harrison Research, Inc., Palo Alto, CA) with 1, 2, or 4 mm thick rotors. Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ.

The spectral data were obtained in spectral grade solvents (Aldrich or Fischer). HPLC grade solvents were dried and purified following standard procedures.[26]

The starting compounds, **ethyl 3,5-dimethyl-4-ethyl-1*H*-pyrrole-2-carboxylate (11)**,[15] **ethyl 3,5-dimethyl-4-(methoxycarbonyl)methyl-1*H*-pyrrole-2-carboxylate (12)**,[16] **ethyl 3,5-dimethyl-4-(2-ethoxycarbonyl)ethyl-1*H*-pyrrole-2-carboxylate (13)**,[17] **ethyl 4,5-dimethyl-3-(2-ethoxycarbonyl)ethyl-1*H*-pyrrole-2-carboxylate (14)**,[18] **4-ethyl-3-methyl-5-tosyl-1,5-dihydro-2*H*-pyrrol-2-one (15)**,[21] **3-ethyl-4-methyl-2-tosyl-1*H*-pyrrole (16)**,[14] **2,4-dimethyl-3-ethyl-1*H*-pyrrole (17)**,[17c,27] were synthesized as previously described. The α-methyl groups of **11-14** were oxidized to formyl groups using ceric ammonium nitrate as indicated below.

General procedure for synthesis of aldehydes 6-9. To a solution of 10 mmol α-methylpyrrole (**11-14**) in 60 mL of THF cooled to 0 °C, 60 mL of acetic acid, and 60 mL of H_2O was added at once ceric (IV) ammonium nitrate (22.5 g, 41 mmol), and the mixture was stirred at 0 °C for 1 h. Water (300 mL) was added, and the product was extracted with CH_2Cl_2 (4 × 70 mL). The combined organic extracts were washed with H_2O (3 × 100 mL), dried (anh. $MgSO_4$), and filtered. The solvent was evaporated under vacuum to afford the crude product, which was purified by radial chromatography on silica gel and recrystallized (from EtOAc / hexane) to afford pure α-formyl pyrrole.

Ethyl 4-ethyl-5-formyl-3-methyl-1*H*-pyrrole-2-carboxylate (6). Obtained in 58% yield. It had mp 92-93 °C (Lit. mp 87-89 °C;[28] lit. mp 90 °C[29]); ^1H-NMR: δ 1.20 (3H, t, J=7.6 Hz), 1.38 (3H,

t, J=7.1 Hz), 2.29 (3H, s), 2.74 (2H, q, J=7.6 Hz), 4.35 (2H, q, J=7.1 Hz), 9.42 (1H, br.s), 9.77 (1H, s) ppm; ^{13}C-NMR: δ 9.48, 14.23, 16.32, 16.70, 60.77, 124.56, 126.12, 129.33, 136.67, 160.92, 179.14 ppm; MS, *m/z* (rel abund.): 209 ($M^{+\cdot}$, 74%), 180 (24%), 162 (45%), 148 (37%), 135 (100%) amu.

Ethyl 5-formyl-4-(methoxycarbonyl)methyl-3-methyl-1*H*-pyrrole-2-carboxylate (7). Obtained in 59% yield. It had mp 91-92 °C; ^{1}H-NMR: δ 1.38 (3H, t, J=7.1 Hz), 2.31 (3H, s), 3.71 (3H, s), 4.36 (2H, q, J=7.1 Hz), 9.63 (1H, br.s), 9.78 (1H, s) ppm; ^{13}C-NMR: δ 9.76, 14.29, 29.32, 52.33, 61.02, 124.42, 125.28, 127.37, 130.30, 160.76, 170.81, 179.49 ppm; MS, *m/z* (rel. abund.): 253 ($M^{+\cdot}$, 31%), 225 (40%), 194 (19%), 175 (19%), 166 (48%), 148 (100%), 120 (34%), 92 (19%) amu.

Anal. Calcd. for $C_{12}H_{15}NO_5$: (253.2): C, 56.91; H, 5.97; N, 5.53.
Found: C, 56.79; H, 5.87, N, 5.51.

Ethyl 5-formyl-4-(2-ethoxycarbonyl)ethyl-3-methyl-1*H*-pyrrole-2-carboxylate (8). Obtained in 65% yield. It had mp 61-62 °C (lit. mp 62-63 °C[30]); ^{1}H-NMR: δ 1.22 (3H, t, J=7.1 Hz), 1.37 (3H, t, J=7.1 Hz), 2.30 (3H, s), 2.55 (2H, t, J=7.4 Hz), 3.05 (2H, t, J=7.4 Hz), 4.10 (2H, q, J=7.1 Hz), 4.35 (2H, q, J=7.1 Hz), 9.51 (1H, br.s), 9.81 (1H, s) ppm; ^{13}C-NMR: δ 9.63, 13.99, 14.18, 18.67, 35.04, 60.46, 60.81, 124.44, 126.40, 129.86, 131.93, 160.82, 172.17, 179.69 ppm; MS, *m/z* (rel. abund.): 281 ($M^{+\cdot}$, 47%), 253 (55%), 236 (40%), 207 (56%), 179 (61%), 162 (90%), 148 (100%), 134 (73%), 120 (50%) amu.

Ethyl 5-formyl-3-(2-ethoxycarbonyl)ethyl-4-methyl-1*H*-pyrrole-2-carboxylate (9). Obtained in 34% yield. It had mp 85-86 °C; ^{1}H-NMR: δ 1.23 (3H, t, J=7.1 Hz), 1.37 (3H, t, J=7.1 Hz), 2.33 (3H, s), 2.54 (2H, t, J=7.5, 8.1 Hz), 3.03 (2H, t, J=8.1, 7.5 Hz), 4.11 (2H, q, J=7.1 Hz), 4.35 (2H, q, J=7.1 Hz), 9.54 (1H, br.s), 9.77 (1H, s) ppm; ^{13}C-NMR: δ 8.29, 14.06, 14.10, 19.69, 34.52, 60.25, 60.99, 124.38, 129.53, 129.69, 130.02, 160.43, 172.78, 179.20 ppm; MS, *m/z* (rel. abund.): 281 ($M^{+\cdot}$, 34%), 236 (17%), 207 (100%), 194 (41%), 178 (34%), 167 (37%), 148 (41%) amu.

Anal. Calcd. for $C_{14}H_{19}NO_5$: (281.3): C, 59.77; H, 6.81; N, 4.98.
Found: C, 59.71; H, 6.88; N, 5.20.

4-ethyl-2-formyl-3,5-dimethyl-1*H*-pyrrole (10). Phosphorous oxychloride (18.6 mL, 0.2 mol) was added to cooled, nitrogen-blanketed anhydrous dimethylformamide (15.5 mL, 0.2 mol) over 10 min. After stirring for 10 min at 0 °C, to the solidified Vilsmeier complex was added 60 mL of dry 1,2-dichloroethane followed by a solution of 12.5 g (0.1 mol) kryptopyrrole **17** in 70 mL of 1,2-dichloroethane over 10 min. The mixture was warmed slowly (30 min) and then heated at reflux for 1 h. After cooling a solution of 62.5 g of sodium acetate trihydrate in 100 mL of H_2O was added, and the mixture was heated at reflux for 30 min. After cooling, the aqueous layer was

separated and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with H_2O (3 × 100 mL), dried (Na_2SO_4) and filtered through a silica gel pad. The solvent was evaporated under vacuum, and the resulting solid was recrystallized from ethanol/water to afford 11.84 g (78%) of aldehyde **10**. It had mp 103-104°C (lit. mp 105-106°C,[31,32] lit. mp 108-109°C[33]); ^{1}H-NMR: δ 1.05 (3H, t, J=7.6 Hz), 2.25 (3H, s), 2.26 (3H, s), 2.38 (2H, q, J=7.6 Hz), 9.45 (1H, s), 9.74 (1H, br.s) ppm; ^{13}C-NMR: δ 8.65, 11.36, 15.00, 16.87, 124.76, 127.70, 132.44, 136.43 175.38 ppm; MS, *m/z* (rel. abund.): 151 ($M^{+\cdot}$, 42%), 136 (100%), 107 (8%) amu.

General procedure for the syntheses of dipyrrinones 1-5. To a mixture of 2 mmol of tosyl lactam (**15**), 2 mmol of the corresponding aldehyde (**6-10**), 1.10 mL (4.4 mmol) of tri-*n*-butylphosphine and 20 mL of anhydrous THF under N_2 was slowly added a solution of 0.33 mL (2.2 mmol) of DBU in 5 mL of THF. The mixture was stirred and protected from light for 6 h. It was diluted with 150 mL of CH_2Cl_2, washed with 1% aq. HCl (70 mL), H_2O (3 × 70 mL), dried (anh. $MgSO_4$) and filtered. The solvent was evaporated under vacuum, and the crude mixture was separated by radial chromatography on silica gel, eluting with 1-3% of a gradient CH_3OH in CH_2Cl_2. After evaporation of the pure fractions, the polar *E*-isomer was recrystallized from ethyl acetate-hexane, and the nonpolar *Z*-isomer, from methanol.

(*E*)-3,7-Diethyl-2,8-dimethyl-9-ethoxycarbonyl-1,10-dihydro-11*H*-dipyrrin-1-one[(*E*)-**1**]. The polar isomer was obtained in 56% yield. It had mp 209-211°C; ^{1}H-NMR: δ 0.96 (3H, t, J=7.6 Hz), 1.05 (3H, t, J=7.6 Hz), 1.36 (3H, t, J=7.1 Hz), 1.93 (3H, s), 2.31 (3H, s), 2.32 (2H, q, J=7.6 Hz), 2.43 (2H, q, J=7.6 Hz), 4.32 (2H, q, J=7.1 Hz), 6.14 (1H, s), 7.33 (1H, br.s), 8.62 (1H, br.s) ppm; ^{13}C-NMR: δ 8.60, 10.36, 13.40, 14.48, 15.23, 17.69, 19.10, 60.01, 102.16, 119.39, 126.35, 126.73, 128.05, 132.35, 139.15, 144.69, 161.58, 171.96 ppm.

Anal. Calcd. for $C_{18}H_{24}N_2O_3$: (316.4): C, 68.33; H, 7.65; N, 8.85.
Found: C, 68.11; H, 7.76; N, 8.80.

(*Z*)-3,7-Diethyl-2,8-dimethyl-9-ethoxycarbonyl-1,10-dihydro-11*H*-dipyrrin-1-one[(*Z*)-**1**]. The nonpolar isomer was obtained in 6% yield. It had mp 185-186°C; ^{1}H-NMR: δ 1.10 (3H, t, J=7.6 Hz), 1.18 (3H, t, J=7.6 Hz), 1.35 (3H, t, J=7.1 Hz), 1.95 (3H, s), 2.30 (3H, s), 2.51 (2H, q, J=7.6 Hz), 2.52 (2H, q, J=7.6 Hz), 4.32 (2H, q, J=7.1 Hz), 5.97 (1H, s), 8.41 (1H, br.s), 9.04 (1H, br.s) ppm; ^{13}C-NMR: δ 8.27, 10.29, 14.46, 14.60, 15.73, 17.53, 17.91, 60.10, 97.37, 121.78, 126.74, 126.95, 127.41, 130.28, 133.99, 147.91, 161.44, 174.23 ppm.

Anal. Calcd. for $C_{18}H_{24}N_2O_3$: (316.4): C, 68.33; H, 7.65; N, 8.85.
Found: C, 67.98; H, 7.62; N, 8.79.

(*E*)-3-Ethyl-2,8-dimethyl-9-ethoxycarbonyl-7-(methoxycarbonyl)methyl-1,10-dihydro-11*H*-dipyrrin-1-one [(*E*)-**2**]. The polar isomer was obtained in 47% yield. It had mp 159-160°C; ^{1}H-

NMR: δ 0.89 (3H, t, J=7.6 Hz), 1.35 (3H, t, J=7.1 Hz), 1.90 (3H, s), 2.23 (2H, q, J=7.6 Hz), 2.29 (3H, s), 3.43 (2H, s), 3.65 (3H, s), 4.30 (2H, q, J=7.1 Hz), 6.17 (1H, s), 8.27 (1H, br.s), 9.13 (1H, br.s) ppm; ^{13}C-NMR: δ 8.60, 10.55, 13.35, 14.47, 18.99, 30.19, 52.01, 60.18, 100.80, 117.88, 119.54, 127.61, 127.78, 132.83, 140.22, 144.72, 161.42, 171.60, 171.69 ppm.

Anal. Calcd. for $C_{19}H_{24}N_2O_5$: (360.4): C, 63.32; H, 6.71; N, 7.77.
Found: C, 63.05; H, 6.86; N, 7.69.

(*Z*)-3-Ethyl-2,8-dimethyl-9-ethoxycarbonyl-7-(methoxycarbonyl)methyl-1,10-dihydro-11*H*-dipyrrin-1-one [(*Z*)-**2**]. The nonpolar isomer was obtained in 11% yield. It had mp 183-184°C; ^{1}H-NMR: δ 1.18 (3H, t, J=7.6 Hz), 1.34 (3H, t, J=7.1 Hz), 1.93 (3H, s), 2.30 (3H, s), 2.51 (2H, q, J=7.6 Hz), 3.51 (2H, s), 3.70 (3H, s), 4.31 (2H, q, J=7.1 Hz), 5.99 (1H, s), 9.08 (1H, br.s), 9.41 (1H, br.s) ppm; ^{13}C-NMR: δ 8.29, 10.50, 14.44, 14.49, 17.88, 30.37, 52.23, 60.27, 96.68, 119.41, 121.61, 127.59, 127.68, 128.83, 135.64, 147.77, 161.35, 171.92, 174.01 ppm.

Anal. Calcd. for $C_{19}H_{24}N_2O_5$: (360.4): C, 63.32; H, 6.71; N, 7.77.
Found: C, 63.24; H, 6.69; N, 7.83.

(*E*)-3-Ethyl-2,8-dimethyl-9-ethoxycarbonyl-7-(2-ethoxycarbonyl)ethyl-1,10-dihydro-11*H*-dipyrrin-1-one [(*E*)-**3**]. The polar isomer was obtained in 50% yield. It had mp 160-162°C; ^{1}H-NMR: δ 0.94 (3H, t, J=7.6 Hz), 1.22 (3H, t, J=7.1 Hz), 1.36 (3H, t, J=7.1 Hz), 1.93 (3H, s), 2.27 (2H, q, J=7.6 Hz), 2.31 (3H, s), 2.43 (2H, t, J=7.5, 8.0 Hz), 2.75 (2H, t, J=8.0, 7.5 Hz), 4.09 (2H, q, J=7.1 Hz), 4.31 (2H, q, J=7.1 Hz), 6.19 (1H, s), 7.51 (1H, br.s), 8.71 (1H, br.s) ppm; ^{13}C-NMR: δ 8.61, 10.43, 13.38, 14.16, 14.47, 19.08, 19.90, 34.89, 60.09, 60.44, 101.40, 119.52, 124.02, 126.94, 126.98, 132.72, 139.64, 144.59, 161.43, 171.64, 172.82 ppm.

Anal. Calcd. for $C_{21}H_{28}N_2O_5$: (388.4): C, 64.93; H, 7.27; N, 7.21.
Found: C, 64.75; H, 7.17; N, 7.19.

(*Z*)-3-Ethyl-2,8-dimethyl-9-ethoxycarbonyl-7-(2-ethoxycarbonyl)ethyl-1,10-dihydro-11*H*-dipyrrin-1-one [(*Z*)-**3**]. The nonpolar isomer was obtained in 7% yield. It had mp 147-148°C; ^{1}H-NMR: δ 1.19 (3H, t, J=7.6 Hz), 1.22 (3H, t, J=7.1 Hz), 1.34 (3H, t, J=7.1 Hz), 1.94 (3H, s), 2.30 (3H, s), 2.46 (2H, t, J=7.4, 7.8 Hz), 2.53 (2H, q, J=7.6 Hz), 2.84 (2H, t, J=7.8, 7.4 Hz), 4.10 (2H, q, J=7.1 Hz), 4.31 (2H, q, J=7.1 Hz), 6.06 (1H, s), 8.70 (1H, br.s), 9.23 (1H, br.s) ppm; ^{13}C-NMR: δ 8.29, 10.42, 14.17 14.46, 14.55, 17.91, 19.71, 35.26, 60.20, 60.50, 97.18, 121.81, 126.21, 127.05, 127.18, 128.06, 134.59, 148.11, 161.36, 172.91, 174.19 ppm.

Anal. Calcd. for $C_{21}H_{28}N_2O_5$: (388.4): C, 64.93; H, 7.27; N, 7.21.
Found: C, 64.79; H, 7.27; N, 7.20.

(*E*)-3-Ethyl-2,7-dimethyl-9-ethoxycarbonyl-8-(2-ethoxycarbonyl)ethyl-1,10-dihydro-11*H*-dipyrrin-1-one [(*E*)-**4**]. The polar isomer was obtained in 59% yield. It had mp 152-153°C; ^{1}H-

NMR: δ 0.91 (3H, t, J=7.6 Hz), 1.25 (3H, t, J=7.1 Hz), 1.36 (3H, t, J=7.1 Hz), 1.93 (3H, s), 2.00 (3H, s), 2.28 (2H, q, J=7.6 Hz), 2.53 (2H, t, J=7.6, 8.3 Hz), 3.04 (2H, t, J=8.3, 7.6 Hz), 4.12 (2H, q, J=7.1 Hz), 4.32 (2H, q, J=7.1 Hz), 6.10 (1H, s), 7.58 (1H, br.s), 8.72 (1H, br.s) ppm; ^{13}C-NMR: δ 8.50, 9.31, 13.29, 14.18, 14.30, 18.96, 20.72, 35.03, 60.17, 60.21, 101.99, 119.11, 120.84, 127.26, 129.89, 132.28, 139.78 144.79, 161.15, 172.09, 173.10 ppm.

Anal. Calcd. for $C_{21}H_{28}N_2O_5$: (388.4): C, 64.93; H, 7.27; N, 7.21.
Found: C, 64.68; H, 7.42; N, 7.17.

(*Z*)-3-Ethyl-2,7-dimethyl-9-ethoxycarbonyl-8-(2-ethoxycarbonyl)ethyl-1,10-dihydro-11*H*-dipyrrin-1-one [(*Z*)-**4**]. The nonpolar isomer was obtained in 9% yield. It had mp 190-191 °C; ^{1}H-NMR: δ 1.18 (3H, t, J=7.6 Hz), 1.25 (3H, t, J=7.1 Hz), 1.35 (3H, t, J=7.1 Hz), 1.95 (3H, s), 2.10 (3H, s), 2.52 (2H, q, J=7.6 Hz), 2.53 (2H, t, J=7.7, 8.3 Hz), 3.04 (2H, t, J=8.3, 7.7 Hz), 4.13 (2H, q, J=7.1 Hz), 4.32 (2H, q, J=7.1 Hz), 5.96 (1H, s), 8.66 (1H, br.s), 9.24 (1H, br.s) ppm; ^{13}C-NMR: δ 8.27, 9.22, 14.23, 14.31, 14.60, 17.88, 20.66, 34.96, 60.27, 60.29, 97.42, 121.53, 123.09, 127.09, 128.22, 129.96, 134.21, 147.90, 160.96, 173.23, 174.29 ppm.

Anal. Calcd. for $C_{21}H_{28}N_2O_5$: (388.4): C, 64.93; H, 7.27; N, 7.21.
Found: C, 65.19; H, 7.18; N, 7.23.

(*Z*)-3,8-Diethyl-2,7,9-trimethyl-1,10-dihydro-11*H*-dipyrrin-1-one [(*Z*)-5, kryptopyrromethenone]. This isomer was obtained in 6% yield. It had mp 252-253 °C (lit. mp 248-250 °C,[17b,34] lit. mp 250-251 °C[18b]); ^{1}H-NMR: δ 1.07 (3H, t, J=7.6 Hz), 1.17 (3H, t, J=7.6 Hz), 1.95 (3H, s), 2.14 (3H, s), 2.41 (2H, q, J=7.6 Hz), 2.42 (3H, s), 2.55 (2H, q, J=7.6 Hz), 6.15 (1H, s), 10.35 (1H, br.s), 11.31 (1H, br.s) ppm; ^{13}C-NMR: δ 8.49, 9.50, 11.48, 15.05, 15.42, 17.44, 17.95, 101.22, 122.16, 122.20, 122.90, 124.59, 126.85, 131.12, 148.22, 174.03 ppm.

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

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