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Carboxylic acid to amide hydrogen bonding. 10-Oxo-semirubins

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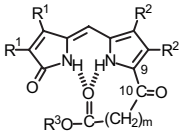
Abstract—Using their amide (and pyrrole) groups, dipyrrinones act as hydrogen bonding receptors for carboxylic acids, as found in a large number of 10-oxo-semirubins (**1**–**6**). The latter can be synthesized readily by Friedel–Crafts coupling of 9-*H* dipyrrinones with half-ester acid chlorides or diacid dichlorides of α,ω-dicarboxylic acids, ranging from C_2 to C_{10}. With ω-oxo-alkanoic acid chains of C_5 or $\geq C_5$, intramolecular hydrogen bonding is observed. With acid chains $<C_5$ hydrogen bonding is not observed. Uncharacteristically (for dipyrrinones), 10-oxo-dipyrrinone acids (**1**–**6**) and their corresponding esters (**1e**–**6e**) remain monomeric in hydrogen bond promoting solvents.

1. Introduction

Dipyrrinones[1] (Fig. 1A) are the component units and chromophores of bilirubin (Fig. 1B), the yellow-orange pigment of jaundice.[2] Previous studies showed that they tend to form intermolecularly hydrogen-bonded dimers (Fig. 1C) in the crystal[3,4] and in nonpolar solvents.[4,5] The association constant is surprisingly large (K_{assoc}~$3–4\times10^4$ at 23 °C) in $CDCl_3$,[5] given that simpler amide-to-amide hydrogen-bonded dimers have K_{assoc}~10^2 in $CHCl_3$.[6] In various dipyrrinones and their esters,[5] and in bilirubin dimethyl ester,[7] hydrogen-bonded dimers (Fig. 1C) prevail in nonpolar solvents. In bilirubin, however, the pigment is monomeric in solution[7] and in the crystal.[8] Its dipyrrinones are hydrogen-bonded intramolecularly to the opposing propionic CO_2H groups (Fig. 1D), and the resulting half-opened book, or ridge-tile-shaped conformation is greatly stabilized.[9] The requirements for intramolecular hydrogen bonding in bilirubin are: (1) a dipyrrinone and (2) a carboxylic acid with six carbons, as counted from dipyrrinone with nine carbons—as shown in [6]-semirubin (Fig. 1E),[10] the model for one-half bilirubin. [6]-Semirubin and its 10-oxo analog (a model for 10-oxo-bilirubin, a proposed bilirubin metabolite[11]) were shown to be monomeric in $CHCl_3$, which obeyed Beer's law and exhibited NOEs between the CO_2H and the lactam N*H*—all evidence for intramolecular hydrogen bonding.[10]

Later studies of [10]- and [20]-semirubins, and 10-oxo-[10]-semirubin showed even with very long carboxylic acid chains attached to C(9), the dipyrrinone chromophore is still strongly hydrogen-bonded intramolecularly to the CO_2H terminus.[12] Interestingly, the various [6]- and [10]-semirubin esters formed *intermolecularly* hydrogen-bonded dimers (as in Fig. 1C) in $CHCl_3$, but the corresponding 10-oxo-semirubin esters were monomers.[10,12] In the following, we report the syntheses of shorter chain 10-oxo-semirubins and their esters (see Structures below), along with their solution properties and hydrogen bonding.



10-Oxo-[n]-semirubins
(n=m+2)

Acid	[n]	m	R^1	R^2	R^3	R^3	Ester
1	2	0	Et	Et	H	Et	**1e**
2	4	2	Et	Et	H	Me	**2e**
3	5	3	Et	Et	H	Me	**3e**
4	6	4	Me	Me	H	Et	**4e**
5	7	5	Me	Me	H	Me	**5e**
6	10	8	Me	Me	H	Me	**6e**

Structures

2. Results and discussion

2.1. Synthesis

The syntheses of 10-oxo-semirubins **1**–**6** and their esters **1e**–**6e** are direct and short, assuming the availability of the required precursors 9-*H* dipyrrinones **7** and **8**.[13,14] The half-ester acid chloride (or diacid dichloride in the synthesis of **2**, **3**, and **6**) were obtained from the appropriate α,ω-dicarboxylic acid and reacted under Friedel–Crafts conditions (Scheme 1) with the relevant dipyrrinone: in cold CH_2Cl_2 and in the presence of anhydrous $AlCl_3$ (for **2**–**5e**) or $SnCl_4$ (for **1e** and **6**). Thus, **6** was obtained from **7** directly in 72% yield following aqueous acid work-up and purification by

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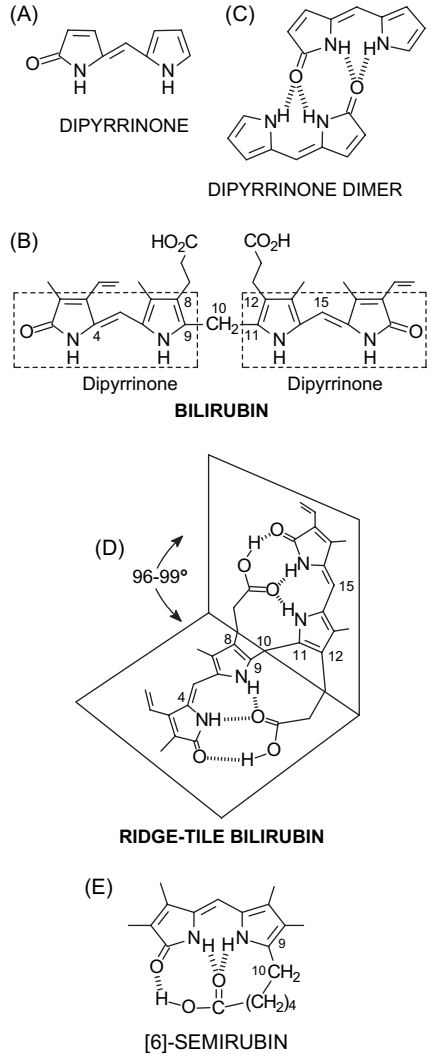


Figure 1. (A) Dipyrrinone chromophore. (B) Linear representation of bilirubin. (C) Dipyrrinone planar, hydrogen-bonded dimer. (D) The most stable conformation of bilirubin is not linear but it is shaped like a half-opened book, like a ridge-tile and stabilized by intramolecular hydrogen bonding. (E) Intramolecularly hydrogen-bonded dipyrrinone analog of bilirubin, called [6]-semirubin (where [6]=number of carbon atoms in the acid chain).

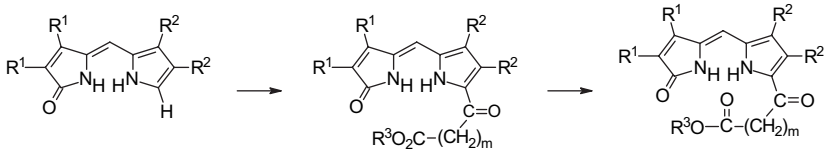
radial chromatography.[12] Its methyl ester (**6e**) was obtained in 93% yield following Fischer esterification.[12] Dipyrrinone **7** also served as precursor for **4e** and **5e′**, with yields of 64 and 40%, respectively. Saponification led to **4** and **6** in 81 and 88% yields.

To achieve improved solubility of 10-oxo-semirubins in $CHCl_3$, dipyrrinone **8**, with ethyl groups replacing methyls, was used as precursor. Thus, reaction of **8** with (i) monoethyl oxalyl chloride gave **1e** in 69% purified yield;[15] (ii) succinyl dichloride gave **2** in 22% purified yield; and (iii) glutaryl dichloride gave **3** in 35% purified yield. Ester **1e** was saponified easily and in high yield (70%) to the corresponding acid (**1**).[15]

2.2. Molecular structure

The constitutional structures of **1**–**6** and **1e**–**6e** (see Structures) follow from the structure of the well-known dipyrrinone starting materials (**7**[13] and **8**[14]) and from the method of synthesis. They were confirmed by their ^{13}C NMR spectra. Consistent with the postulated structures, 10-oxo-[2]-semirubin (**1**), 10-oxo-[4]-semirubin (**2**), 10-oxo-[5]-semirubin (**3**), 10-oxo-[6]-semirubin (**4**), 10-oxo-[7]-semirubin (**5**), and 10-oxo-[10]-semirubin (**6**) and their esters **1e**–**6e** show chemical shifts (Table 2) characteristic of the dipyrrinone core and the ω-oxo-alkanoic acid/ester fragment. The carbon resonances of acids **2**–**6** are scarcely distinguished from their corresponding esters in $(CD_3)_2SO$ (Table 1), except that the ester carbonyl is ∼1 ppm higher field than the acid, and an OCH_3 resonance is present.

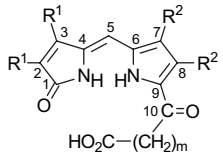
The carbon resonances of ring carbon at positions 2, 4, and 6 and the methyls or methylenes of **2**–**6** (Table 1) and **2e**–**6e** (Table 2) in $CDCl_3$ differ slightly from those in $(CD_3)_2SO$, while in $CDCl_3$ ring carbon at position 3 of **2**–**6** is more deshielded by ∼1 ppm. Ring carbon at position 9 of **4**–**6** and **3e**–**6e** is more shielded by ∼2 ppm in $CDCl_3$ than in $(CD_3)_2SO$. Larger differences appear at C(5), C(7), and C(8), which are ∼3–4 ppm more deshielded in $CDCl_3$. Of particular interest are the lactam C(1) and CO_2H carbonyl resonances of acids **2**–**6**, which are much more deshielded in $CDCl_3$ than in $(CD_3)_2SO$; yet the differences are only



	R^1	R^2			R^1	R^2	R^3	m			R^1	R^2	R^3	m
7	Me	Me	a	**4e,5e′**	Me	Me	Et	4,5	b	**4,5**	Me	Me	H	4,5
7	Me	Me	c	**6**	Me	Me	H	8	d	**6e**	Me	Me	Me	8
8	Et	Et	e	**1e**	Et	Et	Et	0	b	**1**	Et	Et	H	0
8	Et	Et	f	**2**	Et	Et	H	2	d	**2e**	Et	Et	Me	2
8	Et	Et	f	**3**	Et	Et	H	3	d	**3e**	Et	Et	Me	3

Scheme 1. Reagents and conditions: (a) $AlCl_3$+$EtO_2C(CH_2)_mCOCl$; (b) NaOH; (c) $SnCl_4$+$ClOC(CH_2)_8COCl$; (d) CH_3OH, H_2SO_4; (e) $SnCl_4$+EtO_2CCOCl; (f) $AlCl_3$+$ClOC(CH_2)_mCOCl$. [**5e′** is an ethyl ester, from which **5** is prepared by step (b). Compound **5e** is prepared from **5** by step (d).]

Table 1. ^{13}C NMR chemical shifts[a] of 10-oxo-semirubins **1–6**, in $CDCl_3$ and $(CD_3)_2SO$



	m	R^1	R^2
1	0	Et	Et
2	2	Et	Et
3	3	Et	Et
4	4	Me	Me
5	5	Me	Me
6	8	Me	Me

Carbon	Chemical shifts in $CDCl_3$						Chemical shifts in $(CD_3)_2SO$					
	1	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**
1	173.5	175.6	175.0	175.8	175.8	175.6	175.0	172.3	172.3	172.6	172.7	172.7
2	143.1	134.6	134.1	134.6	134.8	135.4	135.7	134.0	134.0	126.7	126.7	126.7
3	147.4	148.3	148.4	142.7	142.7	142.4	147.1	146.9	146.9	141.7	141.7	141.7
4	130.8	130.0	130.3	127.3	127.4	125.2	135.8	132.1	132.0	135.5	135.5	135.9
5	95.6	98.7	98.7	100.0	99.2	98.8	94.8	95.9	95.9	96.2	96.2	96.2
6	139.2	133.7	133.0	130.5	131.4	131.6	129.4	128.8	128.8	125.7	128.3	128.3
7	135.1	132.5	132.2	128.7	128.0	128.3	125.7	127.8	127.7	122.7	122.7	122.8
8	126.9	128.3	127.9	125.3	125.5	124.4	132.3	129.3	129.5	128.4	125.6	125.6
9	135.0	131.2	131.5	127.9	127.9	127.6	131.7	131.7	131.7	130.3	130.3	130.3
10	166.3	187.9	189.7	191.1	192.3	190.6	172.5	188.1	189.3	189.6	189.7	189.9
10^1	—	34.4	39.4	39.8	39.9	[b]	—	33.8	37.7	38.8		[c]
10^2	—	28.8	20.7	23.0	30.2	[b]	—	27.8	19.2	24.3	24.5	[c]
10^3	—	—	33.4	25.2	21.6	[b]	—	—	33.0	23.3	23.5	[c]
10^4	—	—	—	31.8	24.6	[b]	—	—	—	33.6	28.4	[c]
10^5	—	—	—	—	33.9	[b]	—	—	—	—	33.6	[c]
CO_2H	164.0	179.3	179.3	180.4	180.5	178.9	166.7	174.1	174.3	174.4	174.4	174.5
2^1-CH_2/CH_3	18.0	18.0	18.0	8.4	8.6	8.4	16.3	16.9	16.9	8.4	8.4	8.4
2^2-CH_3	15.5	15.7	15.8	—	—	—	16.2	15.6	15.6	—		—
3^1-CH_2/CH_3	17.3	17.3	17.4	9.8	10.1	9.9	16.8	16.5	16.5	9.5	9.5	9.6
3^2-CH_3	14.6	15.5	15.6	—	—	—	15.7	15.5	15.5	—		—
7^1-CH_2/CH_3	17.2	17.0	17.1	9.1	9.4	9.3	16.2	16.4	16.5	9.1	9.1	9.1
7^2-CH_3	13.8	14.0	14.0	—	—	—	15.3	13.7	13.7	—		—
8^1-CH_2/CH_3	19.2	18.6	18.7	11.0	11.4	11.5	17.7	17.9	17.9	11.2	11.2	11.3
8^2-CH_3	16.3	16.7	16.8	—		—	13.5	16.3	16.3	—		—

[a] δ, parts per million downfield from $(CH_3)_4Si$ for 10^{-2} M solution.
[b] Carbons 10^1–10^8, in order: 39.3, 33.9, 27.5, 27.3, 26.9, 23.43, 23.37 ppm.
[c] Carbons 10^1–10^8, in order: 33.7, 29.47, 28.9, 28.8, 28.7, 28.6, 28.55, 28.50 ppm.

small in their esters, **2e–6e**. As in earlier studies, the contrasting behavior of **2–6** (vs **2e–6e**) suggests intramolecular hydrogen bonding in the acids.

2.3. Molecularity in solution

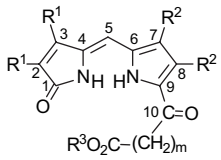
In order to assess whether **1–6** and **1e–6e** are monomeric in $CHCl_3$ solution, we determined their molecular weights by vapor pressure osmometry (VPO) over a molal concentration range $1.6–6.1\times10^{-3}$ mol/kg. The calibration standard was benzil (fw=210, $MW_{obs}=220\pm15$ g/mol), and the molecular weights determined for the compounds of this work are summarized in Table 3. The data indicate that all of the 10-oxo-semirubins, as well as their esters, are monomeric in $CHCl_3$ solution, and all obey Beer's law. In contrast, ordinary dipyrrinones and semirubin esters tend strongly toward dimerization. The differing behavior is apparently due to the presence and orientation of the oxo group: the C=O is probably oriented *anti* to the pyrrole NH,[4] leaving the alkyl chain oriented *syn* to the pyrrole NH and thus preventing intermolecular hydrogen bonding.

2.4. ^1H NMR and hydrogen bonding

syn-Z-Dipyrrinone N–H ^1H NMR chemical shifts in $(CD_3)_2SO$ all are typically very similar.[1,10,12] The 10-oxo-semirubins and their esters are no exception, as the data in Table 4 show. Thus the lactam and pyrrole NHs have similar chemical shifts, with the pyrrole NH being slightly more deshielded due to the presence of the nearby 10-oxo group.[4] In $CDCl_3$ solvent, however, where both intra- and intermolecular bonding is promoted, major differences in the NH chemical shifts are seen.

Dipyrrinones are avid participants in hydrogen bonding.[1,4,5,10,12,16–18] Diagnostic behavior and typical hydrogen bonding of this pattern are found in the planar dimer motif (Fig. 1C); the intrinsic N–H ^1H NMR chemical shifts of the lactam and pyrrole hydrogens of the monomer (δ ~8 ppm) become strongly deshielded to, approximately, 11 and 10 ppm, respectively, in nonpolar solvents such as $CDCl_3$.[4,5,17,19] However, when the dipyrrinones engage in hydrogen bonding with CO_2H groups, whether intermolecularly (Fig. 1C)[18] or intramolecularly[10,12] (Fig. 1E), the NH chemical shifts are relatively more shielded, especially the pyrrole NH (~9 ppm), and to a lesser degree the lactam NH (~10.5).[10,12,18] Similar chemical shifts are also found in tetrapyrroles such as bilirubin.[9,18,20] Consistent with these data for NH chemical shifts where the dipyrrinone is hydrogen-bonded to a CO_2H group, we observe lactam NH chemical shifts of 10.4–10.7 ppm and pyrrole NH chemical shifts of ~9.2 ppm for 10-oxo-semirubins **3–6** in $CDCl_3$. Though, we cannot strictly rule out the possibility that one or more H_2O molecules might intervene between the dipyrrinone moiety and the remote carboxylic acid group, special care was taken to exclude traces of water from the samples and

Table 2. ^{13}C NMR chemical shifts[a] of 10-oxo-semirubin esters **1e–6e** in $CDCl_3$ and $(CD_3)_2SO$



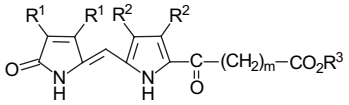
	m	R^1	R^2	R^3
1e	0	Et	Et	Et
2e	2	Et	Et	Me
3e	3	Et	Et	Me
4e	4	Me	Me	Et
5e	5	Me	Me	Me
6e	8	Me	Me	Me

Carbon	Dipyrrinone chemical shifts in $CDCl_3$						Dipyrrinone chemical shifts in $(CD_3)_2SO$					
	1e	**2e**	**3e**	**4e**	**5e**	**6e**	**1e**	**2e**	**3e**	**4e**	**5e**	**6e**
1	173.1	173.5	173.2	173.1	174.1	172.7	173.3	172.3	172.3	172.6	172.7	172.7
2	140.7	135.4	134.5	136.8	136.7	135.4	136.2	134.2	134.0	135.5	135.5	126.7
3	147.4	147.6	147.7	141.8	142.1	141.7	147.2	146.9	146.9	141.7	141.4	141.7
4	132.4	133.4	130.4	128.4	131.4	130.3	136.3	129.1	129.5	126.7	126.7	135.5
5	95.9	96.9	96.5	96.8	97.2	96.2	94.7	95.9	95.9	96.2	96.2	96.2
6	137.8	133.6	134.4	130.9	128.5	126.7	129.6	128.8	127.8	122.7	128.3	128.3
7	134.5	130.1	132.9	129.1	123.9	122.8	125.6	128.0	128.8	125.7	122.8	122.8
8	128.1	129.3	128.9	123.5	129.3	128.3	132.6	131.8	131.7	128.3	125.6	125.6
9	130.1	130.1	129.8	126.3	126.3	125.6	132.6	132.3	132.1	130.3	130.3	130.3
10	168.6	188.0	189.5	189.7	190.3	189.8	172.5	187.8	189.1	189.5	189.7	189.8
10^1	—	34.3	39.1	39.7	40.1	[b]	—	33.7	37.5	38.7	38.9	[c]
10^2	—	28.6	20.9	23.9	29.2	[b]	—	27.6	19.1	24.2	28.3	[c]
10^3	—	—	33.0	24.7	24.3	[b]	—	—	32.7	23.2	23.4	[c]
10^4	—	—	—	34.2	25.1	[b]	—	—	—	33.4	24.4	[c]
10^5	—	—	—	—	34.1	[b]	—	—	—	—	33.2	[c]
CO_2R	164.1	174.1	175.7	175.6	174.3	173.3	165.0	173.1	173.2	172.8	173.3	173.3
OCH_2/CH_3	62.9	52.2	53.0	60.3	51.6	51.1	62.0	51.3	51.2	59.6	51.1	51.2
CH_2CH_3	13.8	—	—	14.2		—	13.6	—	—	14.1	—	—
2^1-CH_2/CH_3	14.9	18.0	18.0	8.6	8.8	8.4	16.9	16.9	16.9	8.3	8.4	8.4
2^2-CH_3	17.3	16.1	15.8	—		—	16.2	15.6	15.6	—	—	—
3^1-CH_2/CH_3	18.0	17.5	17.4	9.9	10.0	9.6	16.4	16.4	16.5	9.5	9.6	9.6
3^2-CH_3	15.4	15.6	15.6	—		—	15.8	13.7	13.7	—	—	—
7^1-CH_2/CH_3	17.2	17.1	17.5	9.5	9.6	9.1	16.3	16.5	16.5	9.1	9.1	9.1
7^2-CH_3	14.2	14.0	14.0	—		—	15.3	15.5	15.5	—	—	—
8^1-CH_2/CH_3	18.9	18.9	18.7	11.7	11.9	11.2	17.4	17.9	17.9	11.2	11.2	11.2
8^2-CH_3	16.4	16.6	16.7	—		—	13.7	16.3	16.3	—	—	—

[a] δ, parts per million downfield from $(CH_3)_4Si$ for 10^{-2} M solutions.
[b] Carbons 10^1–10^8, in order: 40.2, 34.1, 29.4, 29.3, 29.1, 24.9, 24.5 ppm.
[c] Carbons 10^1–10^8, in order: 39.4, 23.8, 28.8, 28.7, 28.6, 28.4, 28.4, 33.3 ppm.

$CDCl_3$ solvent. In the absence of such procedures, the OH and NH resonances were somewhat broadened. We can rule out intermolecular hydrogen bonding between dipyrrinones and CO_2H groups of 10-oxo-semirubins **3–6**, as it has been reported for xanthobilirubic acid[18] because VPO studies indicate that they are monomeric in $CHCl_3$.

Table 3. Molecular weights determined by vapor pressure osmometry[a] and Beer's law behavior in chloroform solution for 10-oxo-dipyrrinones **1–6** and their esters **1e–6e**



Compound	*m*	R^1	R^2	R^3	FW[b]	MW[c]	Conc. range[d]	Beer's law[e]
1	0	Et	Et	H	344	386±11	$2.0–5.8\times10^{-3}$	✓
2	2	Et	Et	H	372	403±13	$1.8–5.6\times10^{-3}$	✓
3	3	Et	Et	H	386	398±5	$1.7–5.2\times10^{-3}$	✓
4	4	Me	Me	H	344	364±30	$2.2–6.1\times10^{-3}$	✓
5′	5	Me	Et[f]	H	386	381±11	$1.6–5.1\times10^{-3}$	✓
6	8	Me	Me	H	400	411±10	$1.6–5.7\times10^{-3}$	✓
1e	0	Et	Et	Et	372	374±7	$1.9–5.4\times10^{-3}$	✓
2e	2	Et	Et	Me	386	396±9	$1.9–5.6\times10^{-3}$	✓
3e	3	Et	Et	Me	400	384±36	$1.8–5.6\times10^{-3}$	✓
4e	4	Me	Me	Et	372	373±10	$1.7–5.5\times10^{-3}$	✓
5e	5	Me	Me	Et	386	385±4	$1.9–5.4\times10^{-3}$	✓
6e	8	Me	Me	Me	414	455±25	$2.0–5.0\times10^{-3}$	✓

[a] Calibrated with benzil (FW=210, measured MW=220±15) at 45 °C.
[b] Formula weight.
[c] Molecular weight in g/mol.
[d] mol/kg.
[e] Obeys Beer's Law (✓).
[f] Semirubin **5** was replaced in the VPO study with the more soluble analog **5′**.

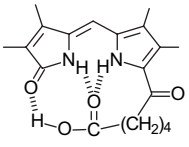
Table 4. Comparison of the dipyrrinone NH and CO_2H ^1H NMR chemical shifts[a] in $CDCl_3$ and $(CD_3)_2SO$ solvents[b]

10-Oxo-semirubin	δ (ppm) in $CDCl_3$			δ (ppm) in $(CD_3)_2SO$		
	Lactam	Pyrrole	CO_2H	Lactam	Pyrrole	CO_2H
1	11.83	10.01	14.34	11.14	10.52	[c]
2	10.4	9.2	[c]	10.4	10.7	12.1
3	10.57	9.39	13.16	10.36	10.77	12.04
4	10.66	9.21	12.80	10.33	10.75	11.99
5	10.74	9.10	13.09	10.34	10.75	11.97
6	10.40	9.22	12.03	10.35	10.74	11.95
1e	10.54	7.55	—	11.24	10.44	—
2e	9.37	8.24	—	10.3	10.73	—
3e	9.72	8.59	—	10.33	10.75	—
4e	9.14	8.05	—	10.32	10.74	—
5e	9.52	9.17	—	10.33	10.73	—
6e	9.28	8.48	—	10.34	10.73	—

[a] δ, Downfield from Me_4Si.
[b] Run as 10^{-2} M solutions in $(CD_3)_2SO$ and ~3×10^{-3} M solutions in $CDCl_3$.
[c] Not observed.

Although, the presence of C(10) carbonyl group might be expected to cause some differences in the NH chemical shifts in **3–6** relative to those of dipyrrinones with alkyl groups at C(9), the shielding of the pyrrole NH is typical of a dipyrrinone hydrogen-bonded to a carboxylic acid, as it is the chemical shift of the lactam NH. Thus, on the basis of the ^1H NMR NH chemical shifts it seems probable that the 10-oxo-semirubins **3–6** are strapped into a conformation shown in Figure 2 for **4**. Although the lactam, pyrrole, and carboxylic acid proton chemical shifts of **1** (and **1e**) differ greatly from **2–6** (and **2e–6e**), this is apparently a consequence of the acid group being directly conjugated with the dipyrrinone chromophore in **1** (and **1e**). Intramolecular hydrogen bonding is impossible in **1** (and **1e**), and intermolecular hydrogen bonding apparently does not occur, since VPO indicates only monomers in $CHCl_3$ solution.

The pyrrole and lactam NH chemical shifts of the 10-oxo-semirubin esters (**2e** and **6e**) in $CDCl_3$ are unusually shielded to 9.2 and 8.5 ppm, respectively. In contrast, monomeric dipyrrinones have corresponding NH chemical shifts at 7.7 and 8.1 ppm,[5] and intermolecularly hydrogen-bonded dipyrrinones exhibit corresponding chemical shifts more deshielded to ~11.2 and ~10.2 ppm,[4] and intramolecular hydrogen bonding also causes deshielding NH resonances.[7,10,12] VPO studies of **1e–6e** indicate that the monomers in $CHCl_3$ solution (Table 3), unusual for dipyrrinone esters, and their ^1H NMR NH chemical shifts in $CDCl_3$ do not correlate with either *intra* or *inter*molecular hydrogen bonding, e.g., the observed lactam NH chemical shift of **4e** (9.14 ppm) lies between that of a typical nonhydrogen-bonded dipyrrinone monomer (~7.7 ppm) and a hydrogen-bonded dimer (~11.2 ppm). One might expect the presence of the ester group to weaken any intramolecular hydrogen bonding of the ester carbonyls to the dipyrrinone NHs, thereby causing them to move upfield, thus explaining the atypical NH chemical shifts of **3e–6e**. The 8.5 ppm chemical shift of the pyrrole NH is indicative of an *anti* orientation of the C(10) carbonyl relative to the pyrrole NH,[4] suggesting that the ω-oxo-ester chain interferes with intermolecular hydrogen bonding but orients the ester chain for limited intramolecular hydrogen bonding. One may find a parallel for the dependence of the NH chemical shift on the orientation of the ketone carbonyl group in certain pyrryl ketones. For example, when the carbonyl is *anti* to the pyrrole NH, as in *tert*-butyl 2-(3,4-dimethylpyrryl) ketone, the NH chemical shift is 8.6 ppm, but when the carbonyl group is *syn*, as in *tert*-butyl 2-pyrryl ketone, it lies at 9.5 ppm.[21]



4

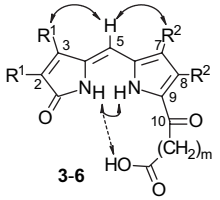
Figure 2. Intramolecularly hydrogen-bonded 10-oxo-[6]-semirubin (**4**).

2.5. Conformation and NOE

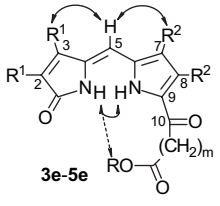
The structural assignment, particularly the *syn-Z*-configuration of the C(4) exocyclic double bond of the dipyrrinone moiety in **1–6** and **1e–6e** was confirmed by the observation of strong nuclear Overhauser effects (NOEs) in $CDCl_3$ between the lactam and pyrrole NHs, and moderate NOEs between the C(5)–H and the C(3) and C(7) methyls (or methylenes of the ethyls) (Fig. 3). Since we were interested in evidence for hydrogen bonding, the relative orientation of the alkanoic acid group and the dipyrrinone terminus was of considerable interest. Their close proximity in **3–6** and **3e–5e** was confirmed by NOEs observed between the carboxylic acid hydrogens and the lactam NHs. The data indicate a proximal spatial relationship between the carboxylic acid and lactam groups in **3–6** that is consistent with the intramolecular hydrogen bonding motif shown in the structural representation of Figures 1E and 2. Taken collectively, the NOE data are consistent with the VPO data, which show that **1–6** (and **1e–6e**) are monomeric in $CDCl_3$.

2.6. Molecular dynamics calculations

In support of the conclusions reached (above) by NMR spectroscopic analysis, molecular dynamics calculations[22] of 10-oxo-[5]-semirubin (**3**) and 10-oxo-[10]-semirubin (**6**) show that these compounds prefer intramolecularly hydrogen-bonded conformations (Fig. 4), which are computed to lie



3-6



3e-5e

Figure 3. Selected $^1H\{^1H\}$-NOEs found in 10-oxo-semirubins **3–6** and their esters (**3e–5e**) in $CDCl_3$ solvent are indicated by curved double-headed arrows. The dotted arrows signify weak NOEs.

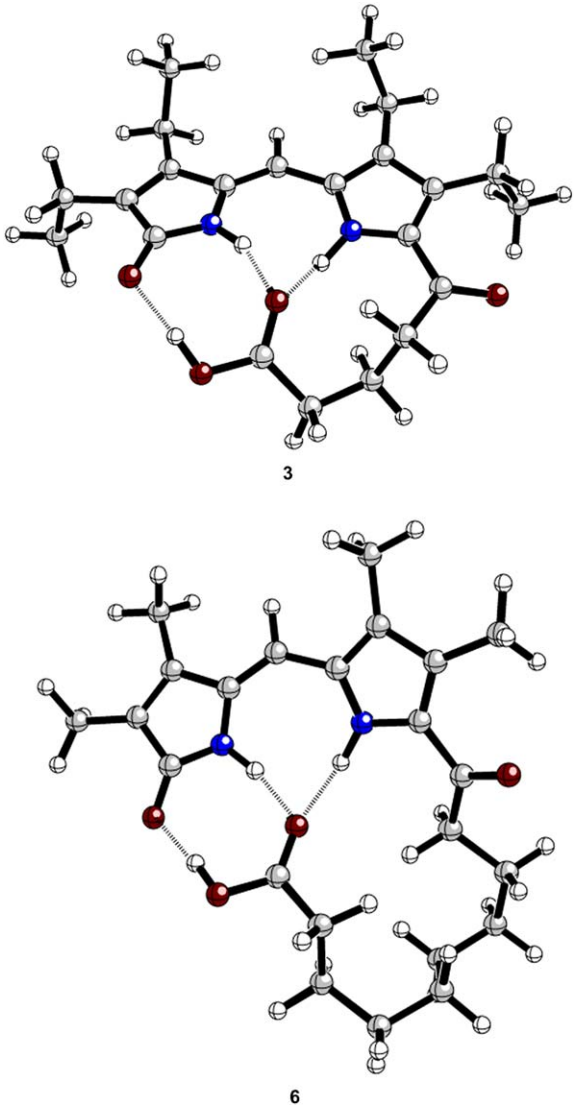


Figure 4. Energy-minimum structures of **3** and **6** from molecular dynamics calculations using Sybyl, Ref. 22.

some 12–13 kcal/mol lower in energy than the nonhydrogen-bonded forms. The intramolecularly hydrogen-bonded conformations have computed molecular parameters similar to those found in the dipyrrinones of bilirubin and mesobilirubin.[9,23,24] The dipyrrinone moieties of **3** and **6** are only slightly twisted, with C(4)–C(5)–C(6)–N torsion angles of ~15° and 22°, respectively.

2.7. Optical spectra

The UV–vis spectral data for **1**–**6** and **1e**–**6e** in solvents with a wide range of polarity are given in Table 5. The long wavelength bands of 10-oxo-semirubins (**1**–**6**) and their esters (**1e**–**6e**) have nearly the same λ_{max} in polar solvents, except λ_{max} of the acids that is shifted bathochromically by 10–15 nm in nonpolar solvents, solvents likely to promote hydrogen bonding. Smaller wavelength shifts attend the spectra of the esters over the range of solvents used. While the spectral shifts do not unambiguously confirm an intramolecularly hydrogen-bonded structure for **1**–**9**, they lend support to this conclusion, based on NMR spectral analysis and VPO studies, and they are consistent with the ability of the 10-oxo-semirubin acids of this study to adopt a unique conformational structure in nonpolar solvents.

3. Concluding comments

The presence of an oxo group in **1**–**6** and **1e**–**6e** does little to inhibit intramolecular hydrogen bonding and appears to inhibit dimer formation. From VPO measurements, it was found that 10-oxo-semirubins and their esters are monomeric in $CHCl_3$, a solvent that promotes hydrogen bonding. The preferred *anti* orientation of the oxo group[4] of 10-oxo-semirubins directs the alkanoic chain toward the dipyrrinone NHs, thereby promoting intramolecular hydrogen bonding in the case of acids (but probably to a lesser extent in the esters). The *anti* orientation of the oxo group effectively inhibits the formation of dipyrrinone dimers of the type shown in Figure 1C.

4. Experimental

4.1. General procedures

All UV–vis spectra were recorded on a Perkin–Elmer λ-12 spectrophotometer, and vapor pressure osmometry (VPO) measurements were performed using an Osmomat 070 (Gonotec, Berlin, Germany) in $CHCl_3$ at 45 °C with benzil as calibration standard. Nuclear magnetic resonance (NMR) spectra were obtained on a GE QE-300 spectrometer operating at 300 MHz, or on a Varian Unity Plus 500 MHz spectrometer in $CDCl_3$ solvent (unless otherwise specified). Chemical shifts δ were reported in parts per million referenced to the residual $CHCl_3$; ^1H signal at 7.26 ppm and ^{13}C signal at 77.0 ppm. To ensure anhydrous samples and solvent in the ^1H NMR experiments, the samples were dried under vacuum in a drying pistol at refluxing ethanol or toluene temperature and using P_2O_5 desiccant. The $CDCl_3$ solvent was stored over CaH_2 after having been passed through a column of Woelm basic Al_2O_3 (super Act 1). Heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond correlation (HMBC) spectra were used to assign ^{13}C NMR spectra. Melting points were taken on a Mel Temp capillary apparatus and are uncorrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ. Analytical thin layer chromatography was carried out on J.T. Baker silica gel IB-F plates (125 μm layers). Flash chromatography was carried out using Woelm silica gel F, thin layer chromatography grade. Radial chromatography was carried out on Merck silica gel PF_{254} with gypsum preparative layer grade, using a Chromatotron (Harrison Research, Palo Alto, CA). Spectral data were obtained in spectral grade solvents (Aldrich or Fisher). Dichloromethane, methanol, tetrahydrofuran, hexane, and 2-propanol were obtained from Fisher, and anhydrous stannic chloride, aluminum chloride, diacid chloride of succinic acid, and the half ethyl ester acid chloride of oxalic acid were obtained from Acros.

Deuterated chloroform and dimethyl sulfoxide were obtained from Cambridge Isotope Laboratories. Mono-ester acid chlorides of adipic and pimelic acids were synthesized

Table 5. Solvent dependence of UV–vis data for 10-oxo-semirubins **1–6** and esters **1e–6e**

	λ_{max} (ε_{max})[a]				
	C_6H_6	$CHCl_3$	CH_3OH	CH_3CN	$(CH_3)_2SO$
1	420 (19,450) 440 (19,450)	436 (18,000)	403 (23,300) 421 (21,400)	425 (17,500)	407 (24,800) 427 (23,800)
2	423 (31,750) 402 (32,700)	420 (29,000) 399 (31,750)	417 (29,000) 396 (32,700)	410 (23,950) 389 (29,950)	420 (32,250) 398 (34,550)
3	423 (44,050) 401 (38,250)	422 (42,000) 400 (38,250)	418 (31,700) 396 (34,550)	411 (26,350) 390 (30,050)	420 (32,500) 398 (34,550)
4	421 (19,200) 400 (20,600)	421 (27,500) 400 (28,600)	411 (22,200) 393 (27,200)	408 (16,300) 386 (21,700)	413 (17,800) 400 (20,600)
5	400 (29,150) 422 (29,150)	400 (29,150) 421 (27,950)	394 (28,550) —	388 (25,850) —	396 (28,250) 416 (24,300)
6	422 (19,800) 399 (21,600)	422 (26,300) 399 (28,500)	416 (24,300) 393 (28,400)	409 (18,300) 387 (23,400)	412 (19,800) 400 (21,700)
1e	424 (23,250)	427 (25,150)	424 (27,500) 410 (27,100)	412 (24,650)	432 (30,350) 411 (27,050)
2e	396 (27,800) 417 (23,400)	397 (28,250) 418 (23,400) sh	395 (32,650) 416 (28,250)	388 (29,750) 410 (23,400) sh	397 (32,150 419 (29,750)
3e	395 (34,850) 419 (35,900)	397 (33,750) 420 (32,100)	396 (32,100) 416 (28,300)	389 (29,950) 409 (24,500)	397 (32,650) 419 (29,950)
4e	415 (16,700) 395 (22,900)	415 (19,100) 394 (24,200)	412 (22,100) 393 (26,600)	406 (18,300) 384 (24,000)	414 (16,700) 395 (22,900)
5e	393 (23,300) 416 (16,000)	393 (23,650) 414 (17,850)	394 (29,500) 413 (24,050)	386 (27,850) 406 (21,500)	395 (30,200) 416 (25,500)
6e	419 (17,500) 397 (22,600)	419 (21,600) 398 (24,200)	418 (25,100) 393 (27,900)	409 (19,800) 386 (25,600)	414 (17,700) 396 (23,900)

[a] λ_{max} in nanometer, ε_{max} in L mol^{-1} cm^{-1}.

from the corresponding diacids (m=4 and 5) by standard literature procedures.[25] Eicosanedioyl dichloride was prepared by standard methods from eicosanedioic acid. (4*Z*)-2,3,7,8-Tetramethyl-10*H*-dipyrrin-1-one (**7**)[13] and (4*Z*)-2,3,7,8-tetraethyl-10*H*-dipyrrin-1-one (**8**)[14] were prepared as described in the literature. The syntheses of **1/1e**,[15] **4/4e**,[10] and **6/6e**[12] were reported previously.

4.1.1. (4*Z*)-9-(Carboethoxymethanoyl)-2,3,7,8-tetraethyl-(10*H*)-dipyrrin-1-one (1e). Prepared as described in the literature.[15] Mp 152–153 °C [lit.[15] mp 152–153 °C]; IR (NaCl, thin film) ν: 3310, 2477, 2933, 2873, 1737, 1702, 1682, 1638, 1213 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.16 (m, 9H), 1.22 (t, J=7.69 Hz, 3H), 1.43 (t, J=6.95 Hz, 3H), 2.4 (q, J=7.69 Hz, 2H), 2.54 (m, 4H), 2.81 (q, J=7.69 Hz, 2H), 4.39 (q, J=6.69 Hz, 2H), 5.94 (s, 1H), 7.56 (br s, 1H), 10.54 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) and UV–vis data are given in Table 2 and Table 5, respectively.

4.1.2. (4*Z*)-9-(3-Carbomethoxypropanoyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one (2e). Acid **2** (40 mg, 0.11 mmol) was dissolved in CH_3OH (25 mL), then 10% sulfuric acid (5 mL) was added slowly, and the solution was heated to reflux for 1 h. The solution was cooled to room temperature and taken up in CH_2Cl_2 and washed with satd aq $NaHCO_3$ (2×50 mL). The organic layer was separated and dried with Na_2SO_4 and the solvent was removed. The residue was crystallized with hexane–CH_2Cl_2 to give 35 mg (85%) of pure **2**. Mp 148 °C; IR (NaCl, film) ν: 3325, 2968, 1742, 1673, 1651, 1225, 1164, 946 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.13 (t, J=7.76 Hz, 3H), 1.14 (t, J=7.76 Hz, 3H), 1.21 (m, 6H), 2.39 (q, J=7.76 Hz, 2H), 2.52 (q, J=7.76 Hz, 2H), 2.54 (q, J=7.3 Hz, 2H), 2.77 (q, J=6.85 Hz, 2H), 2.78 (q, J=6.85 Hz, 2H), 3.14 (t, J=6.85 Hz, 2H), 3.73 (s, 3H), 5.94 (s, 1H), 8.24 (br, 1H), 9.37 (br, 1H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) and UV–vis data are given in Table 2 and Table 5, respectively.

Anal. Calcd for $C_{22}H_{30}O_4N_2$ (386): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.15; H, 7.64; N, 7.02.

4.1.3. (4*Z*)-9-(4-Carboethoxybutanoyl)-2,3,7,8-tetraethyl-(10*H*)-dipyrrin-1-one (3e). As in the preparation of **2e** (above), **3** (40 mg, 0.1 mmol) was converted to its methyl ester to give 31 mg (76%) of pure **3e**. Mp 96–98 °C; IR (NaCl, film) ν: 3275, 2968, 2935, 1739, 1674, 1645, 1462, 1436, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.13 (t, J=7.52 Hz, 3H), 1.15 (t, J=7.52 Hz, 3H), 1.17 (t, J=7.26 Hz, 3H), 1.22 (t, J=7.52 Hz, 3H), 2.04 (m, 2H), 2.39 (q, J=7.78 Hz, 2H), 2.53 (m, 6H), 2.8 (m, 4H), 3.87 (s, 3H), 5.96 (s, 1H), 8.59 (br, 1H), 9.72 (br, 1H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) and UV–vis data are given in Table 2 and Table 5, respectively.

Anal. Calcd for $C_{23}H_{32}O_4N_2$ (400): C, 68.97; H, 8.05; N, 6.99. Found: C, 68.99; H, 7.95; N, 6.99.

4.1.4. (4*Z*)-9-(6-Carboethoxyhexanoyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one (5e). As in **2e** and **3e**, **5** (83 mg, 0.22 mmol) was converted to its methyl ester to give 59 mg (68%) of pure **5e**. Mp 147–149 °C; IR (NaCl,

film) ν: 3339, 2949, 1739, 1656, 1436, 1170, 760, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.4 (m, 2H), 1.68 (m, 4H), 1.93 (s, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 2.3 (s, 3H), 2.31 (t, J=7.69 Hz, 2H), 2.79 (t, J=7.32 Hz, 2H), 3.66 (s, 3H), 5.94 (s, 1H), 8.71 (br, 1H), 9.36 (br, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) and UV–vis data are given in Table 2 and Table 5, respectively.

Anal. Calcd for $C_{21}H_{28}O_4N_2$ (372): C, 67.72; H, 7.58; N, 7.52. Found: C, 67.44; H, 7.41; N, 7.39.

4.1.5. (4*Z*)-9-(6-Carboethoxyhexanoyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one (5e′). In a 1 L round bottom flask equipped with a magnetic stir bar and drying tube, anhyd $AlCl_3$ (3.0 g, 22.5 mmol) was dissolved in CH_2Cl_2 (300 mL). The solution was cooled in an ice bath for 30 min at which time monoethyl pimeloyl chloride (3.04 g, 14.7 mmol) was added in one portion to the solution. The solution was stirred and cooled for 5 min, then a solution of **7** (1.0 g, 4.6 mmol) in CH_2Cl_2 (200 mL) was added, and cooling was continued for 30 min (ice bath) followed by stirring overnight at room temperature. The solution was poured into a 2 L beaker filled with 400 mL of ice-water, and the mixture was stirred for 30 min. The organic layer was removed, and the aq layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with H_2O (3×200 mL), dried over anhyd Na_2SO_4, and the solvent was removed (roto-vap). The residue was purified by radial chromatography (2% MeOH in CH_2Cl_2) and then crystallized to give 0.67 g (40%) of yellow crystals. Mp 129–130 °C; IR (NaCl, thin film) ν: 3341, 2939, 1735, 1656, 1436, 1248, 1171, 759, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.24 (t, J=7.32 Hz, 3H), 1.42 (m, 2H), 1.69 (m, 4H), 1.74 (s, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 2.3 (m, 5H), 2.79 (t, J=7.33 Hz, 2H), 4.11 (q, J=6.96 Hz, 2H), 5.94 (s, 1H), 8.8 (br s, 1H), 9.39 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 8.8, 9.7, 10.1, 11.9, 14.5, 24.3, 25.1, 29.2, 34.4, 40.1, 60.4, 97.4, 124.1, 126.3, 128.3, 129.3, 131.3, 136.4, 142.2, 174, 174.2, 190.3 ppm.

Anal. Calcd for $C_{22}H_{30}O_4N_2$ (386): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.16; H, 7.73; N, 7.22.

4.1.6. (4*Z*)-9-(Carboxymethyl)-2,3,7,8-tetraethyl-(10*H*)-dipyrrin-1-one (1). Prepared in 70% yield as described in the literature.[15] Mp 154–158 °C (dec [lit.[15] mp 154–158 °C]); IR (NaCl, thin film) ν: 3165, 3162, 2962, 1682, 1686, 1650, 1272 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.17 (m, 12H), 2.41 (q, J=7.33 Hz, 2H), 2.59 (m, 4H), 2.82 (q, J=7.33 Hz, 2H), 6.13 (s, 1H), 10 (br s, 1H), 11.83 (br s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) and UV–vis data are given in Table 1 and Table 5, respectively.

4.1.7. (4*Z*)-9-(2-Carboxyethyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one (2). In a 250 mL round bottom flask equipped with a stir bar and drying tube, anhyd $AlCl_3$ (1.0 g, 7.5 mmol) was dissolved in CH_2Cl_2 (50 mL). The mixture was cooled in an ice bath for 30 min. To the mixture was added succinyl dichloride (0.5 mL, 0.1 mmol) and the mixture was cooled for an additional 10 min. A solution of **8** (40 mg, 0.15 mmol) in 20 mL of CH_2Cl_2 was added in one portion to the reaction mixture. The reaction mixture was stirred in the ice bath for 10 min and stirred for 72 h at room temperature. The reaction mixture was poured into 100 mL of 10% aq HCl and ice. The mixture was stirred for 1 h and the organic layer was removed from the aqueous layer. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were washed with water (4×100 mL) and dried (Na_2SO_4). The solvent was removed (roto-vap), and the residue was purified by radial chromatography (eluting with 3% MeOH in CH_2Cl_2) and crystallized from hexane–CH_2Cl_2 to give 13 mg (22%) of yellow crystals of pure **2**. Mp 148–150 °C; IR (NaCl, thin film) ν: 3267, 2968, 2932, 1684, 1653, 1463, 1434, 1262, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.09 (t, J=7.3 Hz, 3H), 1.12 (t, J=7.3 Hz, 3H), 1.14 (t, J=7.3 Hz, 3H), 1.2 (t, J=7.76 Hz, 3H), 2.37 (q, J=7.76 Hz, 2H), 2.52 (q, J=7.76 Hz, 2H), 2.54 (q, J=7.76 Hz, 2H), 2.72 (t, J=5.93 Hz, 2H), 2.74 (q, J=7.76 Hz, 2H), 3.32 (t, J=6.39 Hz, 2H), 6.04 (s, 1H), 9.25 (br s, 1H), 10.36 (br s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) and UV–vis data are given in Table 1 and Table 5, respectively.

Anal. Calcd for $C_{21}H_{28}O_4N_2$ (372): C, 67.72; H, 7.58; N, 7.52. $C_{21}H_{28}O_4N_2 \cdot \frac{1}{4}\ H_2O$ (377): C, 66.91; H, 7.62; N, 7.43. Found: C, 67.29; H, 7.50; N, 7.41.

4.1.8. (4*Z*)-9-(3-Carboxypropyl)-2,3,7,8-tetraethyl-(10*H*)-dipyrrin-1-one (3). In a 250 mL round bottom flask equipped with a magnetic stir bar and drying tube, anhyd $AlCl_3$ (1.0 g, 7.5 mmol) was dissolved in CH_2Cl_2 (50 mL). The mixture was cooled (ice bath) while the diacid chloride of glutaric acid was added. The solution was cooled for an additional 10 min and a solution of **8** (200 mg, 0.73 mmol) in CH_2Cl_2 (50 mL) was added in one portion. The solution was stirred at room temperature for 23 h. The mixture was then poured into ice-water (300 mL) and stirred for 1 h. The organic layer was separated from the aqueous layer and the aqueous layer was extracted with CH_2Cl_2 (3×75 mL). The organic layers were combined and washed with H_2O (3×100 mL) and dried over anhyd Na_2SO_4. The solvent was removed (roto-vap), and the residue was purified by radial chromatography (3% MeOH–CH_2Cl_2). The purified residue was crystallized from hexane–CH_2Cl_2 to give 100 mg (35%) of pure **3**. Mp 212–213 °C; IR (NaCl, thin film) ν: 3295, 2968, 2935, 1719, 1654, 1462, 1273, 1196 cm^{-1}; ^1H-NMR ($CDCl_3$, 500 MHz) δ: 1.14 (m, 9H), 1.21 (t, J=7.76 Hz, 3H), 2.13 (p, J=7.3 Hz, 2H), 2.55 (m, 6H), 2.75 (q, J=7.3 Hz, 2H), 2.92 (t, J=7.76 Hz, 2H), 6.06 (s, 1H), 9.39 (br s, 1H), 10.57 (br s, 1H), 13.16 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) and UV–vis data are given in Table 1 and Table 5, respectively.

Anal. Calcd for $C_{22}H_{30}O_4N_2$ (386): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.33; H, 7.74; N, 7.52.

4.1.9. (4*Z*)-9-(6-Carboxyhexyl)-2,3,7,8-tetramethyl-(10*H*)-dipyrrin-1-one (5). In a 250 mL round bottom flask equipped with a magnetic stir bar was dissolved 10-oxo-semirubin ethyl ester **5e′** (200 mg, 0.52 mmol) in THF (100 mL). To the mixture was added 2 M aq NaOH (20 mL) and the mixture was held at reflux for 3 h. The warm solution was poured into ice-water (100 mL) and stirred while 10% aq HCl was slowly added until the pH of the mixture was ~1. The acidic solution was extracted with CH_2Cl_2 (3×50 mL), and the combined organic extracts

were washed with H_2O (200 mL) and dried over Na_2SO_4 (anhyd). The solvent was removed (roto-vap). The crude product was washed with cold CH_2Cl_2 to give 150 mg (81%) of pure **5**. Mp 215–216 °C; IR (NaCl, film) ν: 3272, 2967, 1698, 1683, 1652, 1458, 1267, 1164, 434 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.17 (m, 12H), 1.8 (m, 2H), 1.94 (m, 2H), 2.4 (q, J=7.69 Hz, 2H), 2.55 (m, 4H), 2.8 (q, J=7.69 Hz, 2H), 2.86 (m, 4H), 6.1 (s, 1H), 9.2 (br s, 1H), 10.8 (br s, 1H), 12.9 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) and UV–vis data are given in Table 1 and Table 5, respectively.

Anal. Calcd for $C_{20}H_{26}O_4N_2$ (358): C, 67.02; H, 7.31; N, 7.82. Found: C, 66.78; H, 7.22; N, 7.66.

4.1.10. (4*Z*)-9-(6-Carboxyhexyl)-7,8-diethyl-2,3-dimethyl-(10*H*)-dipyrrin-1-one (5′). In a 300 mL round bottom flask equipped with a magnetic stir bar and drying tube anhyd $AlCl_3$ (1.0 g, mmol) was dissolved in CH_2Cl_2 (100 mL). The solution was cooled in an ice bath for 30 min at which time monoethyl pimeloyl chloride (1.00 g, 4.85 mmol) was added in one portion to the solution. The solution was stirred and cooled for 5 min, then a solution of (4*Z*)-7,8-diethyl-2,3-dimethyl-(10*H*)-dipyrrin-1-one (0.50 g, 2.1 mmol) in CH_2Cl_2 (100 mL) was added, and cooling was continued for 30 min (ice bath) followed by stirring overnight at room temperature. The solution was poured into a 1 L beaker filled with 200 mL of ice-water, and the mixture was stirred for 30 min. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3×75 mL). The combined organic layers were washed with brine (3×200 mL), dried over anhyd Na_2SO_4, and the solvent was removed (roto-vap). The residue was purified by radial chromatography (2% MeOH in CH_2Cl_2) and then crystallized to give 0.30 g (35%) of yellow crystals that were used directly in the next step. Mp 118–120 °C; IR (NaCl, film) ν: 2965, 2931, 2870, 1735, 1670, 1654, 1457, 1437, 1257, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.14 (t, J=7.3 Hz, 3H), 1.2 (t, J=7.3 Hz, 3H), 1.24 (t, J=7.3 Hz, 3H), 1.39 (p, J=7.3 Hz, 2H), 1.65 (p, J=7.3 Hz, 2H), 1.73 (m, 2H), 1.92 (s, 1H), 2.11 (s, 1H), 2.29 (t, J=7.76 Hz, 2H), 2.53 (q, J=7.3 Hz, 2H), 2.75 (q, J=7.3 Hz, 2H), 2.85 (t, J=7.3 Hz, 2H), 4.11 (q, J=6.85 Hz, 2H), 5.96 (s, 1H), 9.26 (br s, 1H), 9.48 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 8.9, 10.1, 14.5, 16.3, 16.7, 17.5, 18.9, 24.3, 25.1, 29.1, 34.4, 39.3, 60.4, 97.2, 128.3, 128.8, 130.4, 130.6, 132.7, 136.3, 142.4, 174, 174.1, 190.3 ppm.

The above compound (100 mg, 0.24 mmol) was saponified for 3 h as for **5**. The residue was crystallized from CH_2Cl_2 to give 55 mg (59%) of pure **5′**. Mp 210–212 °C; IR (NaCl, film) ν: 2964, 1718, 1659, 1622, 1435, 1406, 1267, 1251, 1200, 1172, 995 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.15 (t, J=7.3 Hz, 3H), 1.16 (t, J=7.3 Hz, 3H), 1.57 (m, 2H), 1.7 (p, J=6.85 Hz, 2H), 1.85 (p, J=7.3 Hz, 2H), 1.93 (s, 1H), 2.14 (s, 1H), 2.48 (t, J=5.48 Hz, 2H), 2.55 (q, J=7.76 Hz, 2H), 2.79 (q, J=7.3 Hz, 2H), 2.9 (t, J=7.3 Hz, 2H), 6.09 (s, 1H), 9.09 (br s, 1H), 10.78 (br s, 1H), 13.2 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 8.6, 10.1, 15.6, 16.7, 17.4, 18.6, 21.3, 24.6, 30.3, 33.9, 39.7, 99.1, 127.2, 127.3, 130.9, 131.6, 134.2, 134.4, 142.8, 175.8, 180.8, 192 ppm.

Anal. Calcd for $C_{22}H_{27}O_4N_2$ (383): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.29; H, 7.89; N, 7.28.

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