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A C−H···O═C Hydrogen Bond? Intramolecular Hydrogen Bonding in a Novel Semirubin

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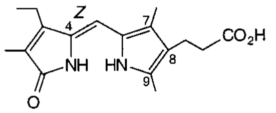
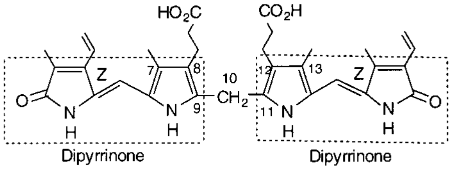
(4*Z*)-8-(5-Carboxypentyl)-9-butyl-2,3-diethyl-dipyrrin-1-one (**1**), a new analogue of xanthobilirubic acid, (4*Z*)-8-(carboxyethyl)-2,7,9-dimethyl-3-ethyl-dipyrrin-1-one, was synthesized in four steps from the known 2,3-diethyl-dipyrrin-1-one. Whereas xanthobilirubic acid (which is a model for one-half of bilirubin, the yellow pigment of jaundice) and its homologues with hexanoic and longer acid chains at C-8 engage only in *inter*molecular hydrogen bonding, **1** is found to engage in *intra*molecular hydrogen bonding. In $CDCl_3$ solution, dipyrrinone **1** adopts an *anti-Z* conformation, and its hexanoic acid COOH is hydrogen-bonded to the lactam H−N−C═O and to the pyrrole C(7)-H but not to the pyrrole NH. The latter constitutes an example of a hydrogen bond of the type C−H···O═C, weak and detected typically in crystals. Dipyrrinone **1** is found by vapor pressure osmometry to be monomeric in $CHCl_3$, but its methyl ester (**2**) tends toward being dimeric, like that of methyl xanthobilirubinate, which is dimeric.

Introduction

Xanthobilirubic acid (Figure 1) and related dipyrrinones[1,2] have long served as structurally simpler models for understanding the stereochemistry, chemical properties, and photobiology of bilirubin, the yellow neurotoxic pigment of jaundice.[3] Dipyrrinones are typically bright yellow compounds with an intense UV−visible absorption ($\epsilon^{max} \approx 30{,}000$ L mol^{-1} cm^{-1}) near 400 nm. They are known from spectroscopic measurements and molecular mechanics calculations to adopt the lactam tautomer and the *Z* configuration at C(4),[2] and they are avid participants in hydrogen bonding.[1e,2,4−8] Whether in the crystal[1a,2,8] or dissolved in nonpolar solvents,[1e,4−7] they are present as intermolecularly hydrogen-bonded planar dimers (Figure 2A) and adopt essentially planar conformations (~0° torsion angle, C(4)−C(5)−C(6)−N). For example, methyl xanthobilirubinate forms strongly associated dimers in $CHCl_3$, with $K_{assoc} \approx 25\,000$ M^{-1} at 22 °C, as measured by ^1H NMR spectroscopy.[4] The coplanar dipyrrinone-to-dipyrrinone motif with four hydrogen bonds shown in Figure 2A is probably the most common type of hydrogen bonding in dipyrrinone dimers[2,5−7] and is also found in bilirubin dimethyl ester.[2,9] However, if a carboxylic acid group is present, a different type of hydrogen bonding is often preferred, where the dipyrrinone embraces the COOH group through three hydrogen bonds (Figure 2B). This has been observed in [6]-semirubin (Figure 2C), a dipyrrinone acid that is monomeric and intramolecularly hydrogen-bonded in $CHCl_3$. This snug fit of carboxyl group and dipyrrinone was seen first in bilirubin,[2,11−13] where intramolecular hydrogen bonding stabilizes a ridge tile conformation (Figure 2D). Related dipyrrinone acids, such as xanthobilirubic acid (XBR, Figure 1), favor π-facial stacked



Xanthobilirubic Acid (XBR)



Bilirubin

Figure 1. (Top) A typical dipyrrinone, (4*Z*)-xanthobilirubic acid. (Bottom) Constitutional structure of bilirubin, which is composed of two dipyrrinone chromophores, each with a propionic acid, at C(8) and C(12).

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[1] (a) Cullen, D. L.; Black, P. S.; Meyer, E. F.; Lightner, D. A.; Quistad, G. B.; Pak, C.-S. *Tetrahedron* **1977**, *33*, 477−483. (b) Grunewald, J. O.; Walker, J. C.; Strope, E. R. *Photochem. Photobiol.* **1975**, *24*, 29−40. (c) Lightner, D. A.; Rodgers, S. L. *Experientia* **1981**, *37*, 1245−1246. (d) Lamola, A. A.; Braslavsky, S. E.; Schaffner, K.; Lightner, D. A. *Photochem. Photobiol.* **1983**, *37*, 263−270. (e) Trull, F. R.; Ma, J. S.; Landen, G. L.; Lightner, D. A. *Isr. J. Chem.* **1983**, *23*, 211−218. (f) McDonagh, A. F.; Lightner, D. A.; Agati, G. *Monatsh. Chem.* **1998**, *129*, 649−660.3.

[2] For leading references, see: Falk, H. *The Chemistry of Linear Oligopyrroles and Bile Pigments*; Springer-Verlag, New York, 1989.

[3] (a) McDonagh, A. F. Bile Pigments: Bilatrienes and 5,15-Biladienes. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1979; Vol. 6, pp 293−491. (b) Berk, P. D.; Noyer, C. *Seminars Liver Dis.* **1994**, *14*, 323−394.

[4] Nogales, D. F.; Ma, J.-S.; Lightner, D. A. *Tetrahedron* **1993**, *49*, 2361−2372.

[5] (a) Boiadjiev, S. E.; Anstine, D. T.; Lightner, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 8727−8736. (b) Boiadjiev, S. E.; Anstine, D. T.; Maverick, E.; Lightner, D. A. *Tetrahedron: Asymmetry* **1995**, *6*, 2253−2270.

[6] Huggins, M. T.; Lightner, D. A. *J. Org. Chem.* **2000**, *65*, 6001−6008.

[7] Huggins, M. T.; Lightner, D. A. *Monatsh. Chem.* **2000**, *132*, 203−221.

[8] For leading references, see: Sheldrick, W. S. *Isr. J. Chem.* **1983**, *23*, 155−166.

[9] Boiadjiev, S. E.; Lightner, D. A. *J. Heterocycl. Chem.* **2000**, *37*, 863−870.

[10] Person, R. V.; Peterson, B. R.; Lightner, D. A. *J. Am. Chem. Soc.* **1994**, *116*, 42−59.

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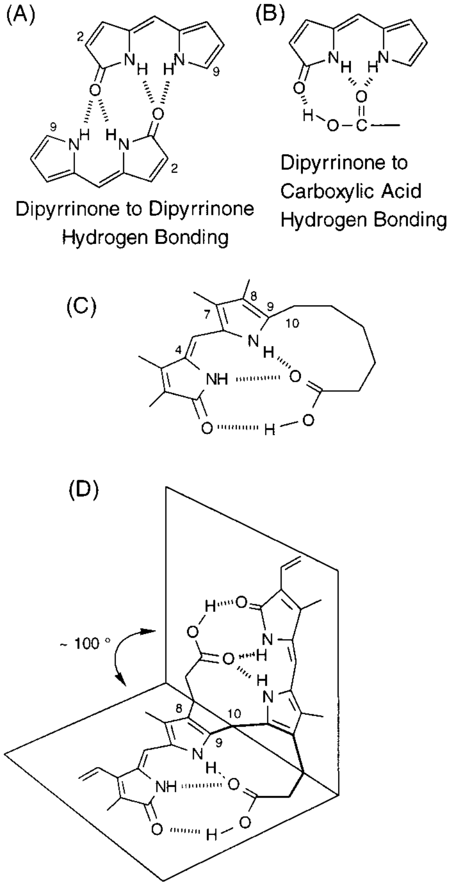

Figure 2. (A) Dipyrrinone-to-dipyrrinone hydrogen bonding affording a planar dimer with four intermolecular hydrogen bonds. In $CDCl_3$ ^{1}H NMR NOEs may be found between substituents (methyls) at C(2) and C(9) (ref 4). (B) Dipyrrinone-to-carboxylic acid hydrogen bonding. In $CDCl_3$ an ^{1}H NMR NOE is found between the lactam NH and carboxylic acid OH. (C) [6]-Semirubin in its favored intramolecularly hydrogen-bonded conformation with a shape similar to one-half of bilirubin. (D) The most stable bilirubin conformation, shaped like a ridge-tile with hydrogen bonds between the carboxylic acid groups and the opposing dipyrrinones. Hydrogen bonds are represented by dashed lines.

dimers in which each carboxylic acid group is engaged in hydrogen bonding to an opposing dipyrrinone.[5] Although xanthobilirubic acid has served as a convenient model for bilirubin, [6]-semirubin[6] is probably a better model because its dipyrrinone is engaged in intramolecular hydrogen bonding with the COOH. Xanthobilirubic acid cannot engage in intramolecular hydrogen bonding.

A *syn*-*Z* configuration with preorganized lactam C═O and pyrrole and lactam NH groups appears to be essential for the ability of dipyrrinones to engage in the unusually strong hydrogen bonding in the motifs of Figure 2A and B. (4*Z*)-Dipyrrinones with a methyl (or other) substituent at C(7) of the pyrrole ring favor the *syn* conformation over the *anti*. The latter would be destabilized by a nonbonded steric repulsion between the lactam NH and the C(7) substituent (Figure 3A). Without a substituent group at C(7), however, 7-H (4*Z*)-dipyrrinones can adopt either the *anti* or the *syn* conformation with apparently equal facility.[2] Thus, a 7-H (4*Z*)-dipyrrinone bearing a hexanoic acid group at C(9) can be expected to be intramolecularly hydrogen-bonded in the *syn* conformation (Figure 3B), as found in [6]-semirubin (Figure 2). In contrast, when the hexanoic acid is attached to C(8), intramolecular hydrogen bonding is possible only in the *anti* conformation (Figure 3C), which would be a monomer. Two dimers are known with the *syn* conformation.[2,4,5] One involves dipyrrinone to dipyrrinone intermolecular hydrogen bonding (Figure 3D); the other (Figure 3E) involves carboxylic acid to dipyrrinone intermolecular hydrogen bonding. For *anti* dipyrrinones, there are also two types of dimer, as illustrated in Figure 3F and G. However, *anti* dimers would not be expected, except when the *syn* conformation is destabilized relative to the *anti*, for example, by a pyrrole N-alkyl group. Absent substituents at the pyrrole nitrogen and C-7, the *syn*-*syn* dimer (Figure 3D)[2,4] would still be expected to be more stable than the *anti*-*anti* (Figure 3F) because the pyrrole NH is a better H-bond donor. For the same reason, the *syn*-*syn* dimer of Figure 3E[5] can be expected to be more stable than the *anti*-*anti* of Figure 3G.

To explore the possibility that a hexanoic acid at C(8) might engage in intramolecular hydrogen bonding and stabilize the *anti*-*Z* conformation of a 7-H dipyrrinone, we synthesized **1** (Figure 3H), determined its molecular weight in $CHCl_3$ by vapor pressure osmometry (VPO), and investigated hydrogen bonding by ^{1}H NMR spectroscopy. An interesting consequence of the intramolecular hydrogen bonding shown in Figure 3C is that the C(7)-H lies in position to form a C−H···O═C hydrogen bond.[14]

Results and Discussion

Synthesis. We designed a synthesis of **1** starting from a dipyrrinone (**6**)[15] with a "naked" pyrrole ring. The plan involved first adding, regioselectively, an alkyl substituent at C(9) and then inserting the hexanoic acid chain regioselectively at C(8). Our previous studies[6,7] suggested that Friedel−Crafts acylation might be a convenient way to introduce the required substituents, and we expected that carbon-9 would be the most reactive site. However, it was unclear whether we could achieve the required regioselectivity for reaction at the desired pyrrole β-position. The synthesis of **1** thus required two regioselective acylations of the pyrrole ring. The first acylation involved reaction of dipyrrinone **6** with butyryl chloride (Scheme 1), and as expected, the reaction proceeded more rapidly at the pyrrole α-position, C(9), rather than at either of the β-positions, C(7) and C(8). A single crystallization of the reaction product gave a 65% yield of pure **5**. The butanoyl group was reduced to *n*-butyl by reaction of **5** with $NaBH_4$ in refluxing isopropyl alcohol to afford **4** in 95% yield. Regioselectivity was also achieved in the

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(11) (a) Bonnett, R.; Davies, J. E.; Hursthouse, M. B.; Sheldrick, G. M. *Proc. R. Soc. London, Ser. B* **1978**, *202*, 249−268. (b) LeBas, G.; Allegret, A.; Mauguen, Y.; DeRango, C.; Bailly, M. *Acta Crystallogr., Sect. B* **1980**, *B36*, 3007−3011. (c) Becker, W.; Sheldrick, W. S. *Acta Crystallogr., Sect. B* **1978**, *B34*, 1298−1304.

(12) (a) Dörner, T.; Knipp, B.; Lightner, D. A. *Tetrahedron* **1997**, *53*, 2697−2716. (b) Nogales, D.; Lightner, D. A. *J. Biol. Chem.* **1995**, *270*, 73−77.

(13) (a) Kaplan, D.; Navon, G. *Isr. J. Chem.* **1983**, *23*, 177−186. (b) Kaplan, D.; Navon, G. *Biochem. J.* **1982**, *201*, 605−613. (c) Navon, G.; Frank, S.; Kaplan, D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1145−1149.

(14) (a) Vargas, R.; Garza, J.; Dixon, D. A.; Hay, B. P. *J. Am. Chem. Soc.* **2000**, *122*, 4750−4755. (b) Baures, P. W.; Wiznycia, A.; Beatty, A. M. *Bioorg. Med. Chem.* **2000**, *8*, 1599−1605. (c) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond*; Oxford University Press: New York, 1999. (d) Desiraju, G. R. *Acc. Chem. Res.* **1996**, *29*, 441−449. (e) Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063−5070.

(15) Bonnett, R.; Buckley, D. G.; Hamzetesh, D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 322−325.

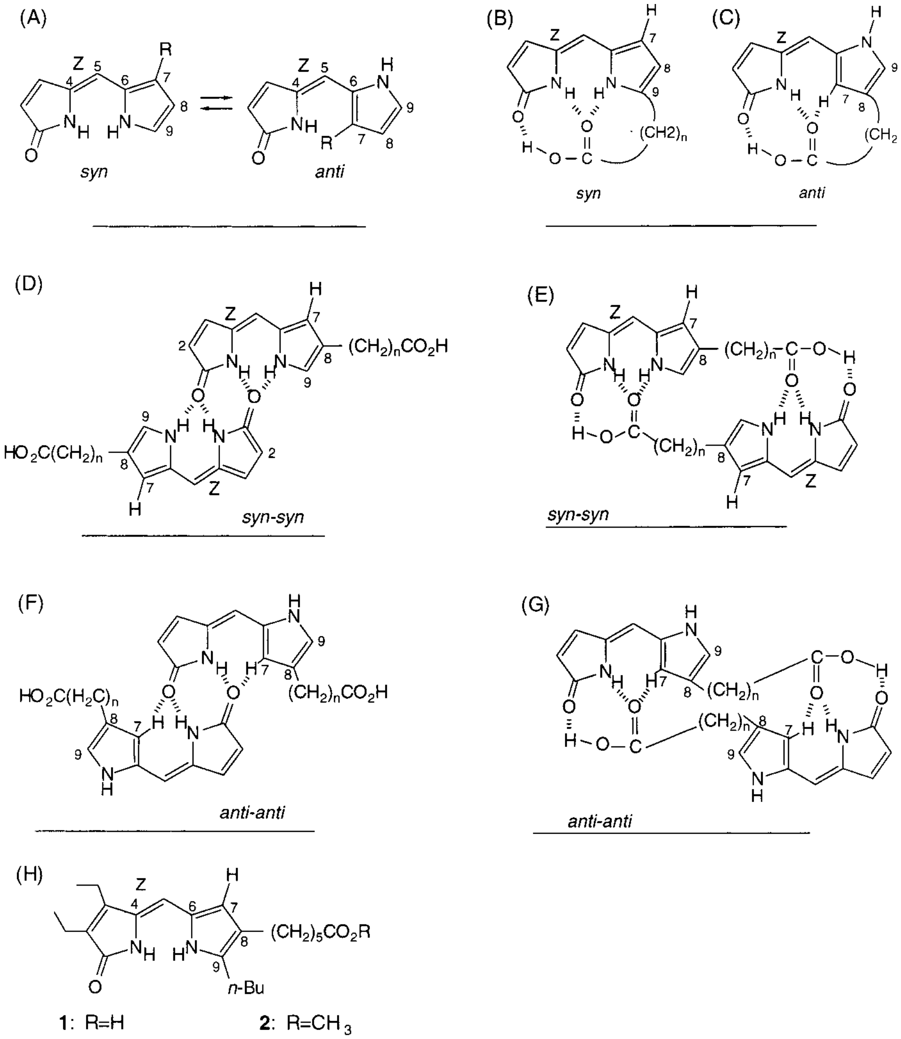


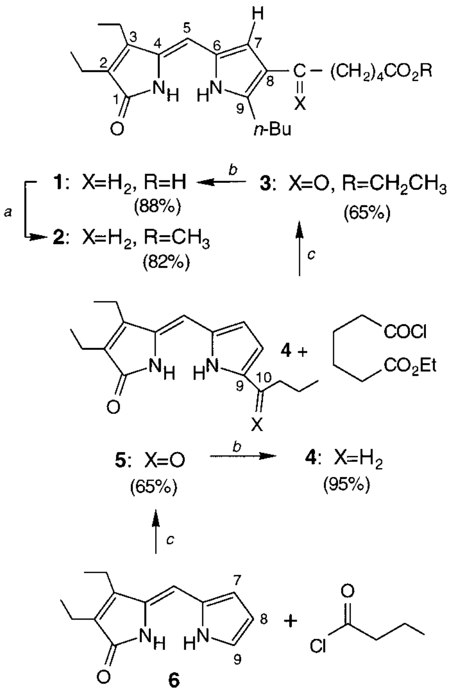
Figure 3. (A) Equilibrating *syn* ⇄ *anti* conformations of (4*Z*)-dipyrrinones. When R > H (as in R = CH_3), the *anti* conformer is destabilized relative to the *syn* by nonbonded steric repulsion between the R-group and the lactam NH. When R = H, the serious steric interaction is removed and the *syn* and *anti* conformers are nearly equal energy (ΔH_f (*syn*) ≈ 74.9 kcal/mol; (ΔH_f (*anti*) ≈ 75.4 kcal/mol, as determined by MM3 molecular mechanics calculations). (B and C) Intramolecularly hydrogen-bonded dipyrrinones stabilizing the C(7)-H *syn* conformation when a hexanoic acid group (*n* = 5) is attached to C(9), and the C(7)-H *anti* conformation when attached to C(8). (D) Planar dipyrrinone-to-dipyrrinone hydrogen-bonded dimer of the *syn* conformer of the dipyrrinone of (C). (E) Dipyrrinone dimer with intermolecular hydrogen bonding between a CO_2H group and a *syn* dipyrrinone. (F) Planar dipyrrinone-to-dipyrrinone hydrogen-bonded dimer of the *anti* conformer of the dipyrrinone of (C). (G) Dipyrrinone dimer with intermolecular hydrogen bonding between a CO_2H group and an *anti* dipyrrinone. (H) Target C(7)-H dipyrrinone (**1**) and its methyl ester (**2**).

second acylation step. Thus, Friedel−Crafts reaction of **5** with the half-ester acid chloride of adipic acid afforded a 65% yield of pure **3**. Subsequent reduction of **3** with $NaBH_4$ in refluxing isopropyl alcohol afforded an 82% yield of the desired acid **1**. Esterification of **1** in methanol/H_2SO_4 gave the corresponding methyl ester (**2**) in 88% yield.

Molecular Structure. The constitutional structures of dipyrrinones **1**−**4** (Scheme 1) follow from the structure of the well-known dipyrrinone (**6**),[15] which is common to their syntheses, and from the reagents used. The structures were confirmed by their ^{13}C NMR spectra run in $CDCl_3$, and all assignments were made by HMQC and HMBC experiments. Thus, dipyrrinone **4** shows chemical shifts (Table 1) characteristic of both the dipyrrinone unit (**6**) and the *n*-butyl group at C(9). Dipyrrinones **1**−**3** show the signals of **4**, mutatis mutandis, plus those of the hexanoic acid (ester) or (5-carboethoxy)pentanoyl fragment. The presence of the *n*-butyl group in **4** causes a deshielding at C(9), the origin of which is unclear. However, the C_6 chain attached to C(8) in **1**−**3** shifts the C(9) resonance back up to approximately that seen in **6**. The presence of the *n*-butyl in **1**−**4** causes C(6) to become 3−4 ppm more shielded than in **6**. Other dipyrrinone carbons are not as strongly perturbed.

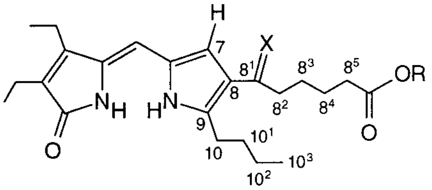
Molecularity in Solution. To assess whether dipyrrinone **1** is monomeric or dimeric in $CHCl_3$ solution, we determined its molecular weight by vapor pressure osmometry (VPO). The calibration standard was benzil (MW_{calc}= 210, MW_{obs}= 220 ± 15), and the molecular weight determined for **1** clearly indicates that the compound is monomeric in $CHCl_3$ solution, as is [6]-semirubin.[6] In contrast, VPO of the methyl ester (**2**) showed a molecular weight 1.5 times the molecular weight of the monomer, a clear indication that **2** tends toward dimer formation. Dimer formation in **2** is not surprising, but self-association is clearly not as favored as in methyl xanthobilirubinate, which is constrained to the *syn*-Z

Scheme 1[a]



[a] (a) CH_3OH/H_2SO_4, 82%; (b) $NaBH_4/(CH_3)_2CHOH$ reflux; (c) $AlCl_3/CH_2Cl_2$.

Table 1. ^{13}C NMR Chemical Shifts[a] **of 1 ($X = H_2$, $R = H$), Its Methyl Ester 2 ($X = H_2$, $R = CH_3$), 3 ($X = O$, $R = CH_2CH_3$), and Dipyrrinones 4 (H at C-8) and 6 (H at C-8 and C-9)**



carbon position	chemical shifts				
	1	**2**	**3**	**4**	**6**
1	174.24	174.29	174.16	173.82	174.10
2	129.98	129.18	130.51	129.23	129.97
3	147.38	147.79	148.33	148.02	148.12
4	130.09	128.16	129.99	127.99	127.48
5	102.54	103.09	102.41	103.65	103.19
6	124.89	125.22	125.30	126.25	129.41
7	114.93	116.69	117.31	117.16	115.88
8	134.11	136.11	145.89	107.33	109.91
9	122.67	121.99	120.15	140.47	123.34
10	24.19	24.89	27.83	27.76	
10^1	30.06	30.69	31.87	31.60	
10^2	22.42	22.40	22.55	22.41	
10^3	13.85	14.03	14.02	13.96	
8^1	24.50	25.35	198.17		
8^2	32.19	32.70	40.04		
8^3	27.82	28.98	24.78		
8^4	25.70	25.99	24.00		
8^5	33.84	34.09	34.27		
CO_2R	178.67	173.58	173.62		
$R = CH_3$		51.45	14.24		
$R = CH_2CH_3$			60.5		
2^1	16.75	16.77	16.79	16.81	17.00
2^2	13.95	14.33	14.24	14.35	13.81
3^1	17.65	17.73	17.74	17.74	17.72
3^2	15.67	15.75	15.67	15.77	15.71

[a] Chemical shifts in δ (ppm, 125.75 MHz) downfield from the residual solvent resonances. All measurements in $CDCl_3$ in $\sim 5 \times 10^{-3}$ M solutions.

Table 2. Molecular Weights of Dipyrrinones 1−4 and 6 Determined by Vapor Pressure Osmometry[a] **at 45 °C in $CHCl_3$ Solution**

dipyrrinone	molecular weight (g/mol)		concn range (mol/kg)
	calcd	measured by VPO	
1	386	388 ± 25	$2.1-6.6 \times 10^{-3}$
2	400	613 ± 25	$1.7-6.1 \times 10^{-3}$
3	428	686 ± 15	$2.2-6.1 \times 10^{-3}$
4	272	463 ± 30	$1.7-5.5 \times 10^{-3}$
6	216	378 ± 20	$2.1-6.6 \times 10^{-3}$
methyl xanthobilirubinate	316	579 ± 20[b]	$2.3-8.4 \times 10^{-3}$
[6]-semirubin	330	337 ± 20[c]	$2.1-6.6 \times 10^{-3}$
[6]-semirubin methyl ester	344	584 ± 30[c]	$1.7-6.1 \times 10^{-3}$

[a] Calibrated with benzil (FW = 210, measured MW = 220 ± 15. [b] From ref 9. [c] From ref 6.

conformation. Also, it is not as favored as in the parent dipyrrinone **6** or its 9-*n*-butyl derivative, both of which can easily adopt either the *syn* or *anti* conformation. The weakened tendency toward dimerization seen in **2** is also found in its 8^1-oxo analogue (**3**) but is not as pronounced in [6]-semirubin methyl ester, which favors the *syn* conformation. The data suggest that it is the added presence of the C_6 ester chain at C(8), and not the 9-*n*-butyl alone, that influences the weaker dimerization in **2** and **3** than in **4** and **6**. The C(8) substituent probably prevents the large *n*-butyl from completely vacating the hydrogen bonding region of the dipyrrinone-to-dipyrrinone dimer in **2** and **3**, which would destabilize the dimer, but destabilization may also arise from steric interaction between the 9-*n*-butyl of one dipyrrinone and the 2-ethyl of the second dipyrrinone of the dimer.

It is thus not difficult to imagine a monomeric structure for **1** that looks similar to that shown in Figure 3C. The VPO data do not support the presence of dimers, thus excluding those similar to the representations of Figure 3D and E. The VPO data do, however, point to the presence of dimers in **2**−**4** and **6**, which probably take forms similar to those of Figure 3D, the form common to dipyrrinone esters and dipyrrinones with only alkyl substituents.[4,7] Although VPO studies cannot exclude a dimer of the *anti-anti* type (Figure 3F and G), evidence for the *syn-syn* dimer (Figure 3D) can be obtained from NOE measurements. In **2** and **3**, where dimer formation is not as complete as in **4** and **6**, structures of the monomers are unclear, but here too, ^1H NMR offers insights.

^1H NMR and Hydrogen Bonding. Dipyrrinones are known to be strong participants in hydrogen bonding,[2,4−6] which is typically detected by the ^1H NMR chemical shifts in $CDCl_3$ solvent. Thus, in the planar *dimer* motif (Figure 2A), the intrinsic NH chemical shifts of the lactam and pyrrole hydrogens found in the non-hydrogen bonded *monomer* (~8 ppm)[3] are shifted downfield to approximately 11 and 10 ppm,[1e,4,5] respectively. Other types of hydrogen bonding also cause a deshielding of the NHs, but when the dipyrrinones engage in hydrogen bonding to CO_2H groups (Figure 2B), whether intermolecularly or intramolecularly,[1e,5−7] the NH chemical shifts are relatively more shielded, especially the pyrrole NH (~9 ppm), and to a lesser degree the lactam NH (~10.5 ppm). Dipyrrinones **2**−**4** and **6**, which are shown to be dimeric by VPO, do not have CO_2H groups, and exhibit ^1H NMR NH chemical shifts (Table 3) that are in accord with a predominance of intermolecularly hydrogen-bonded dimers of the general type shown in Figures 2A and 3D. Dimers

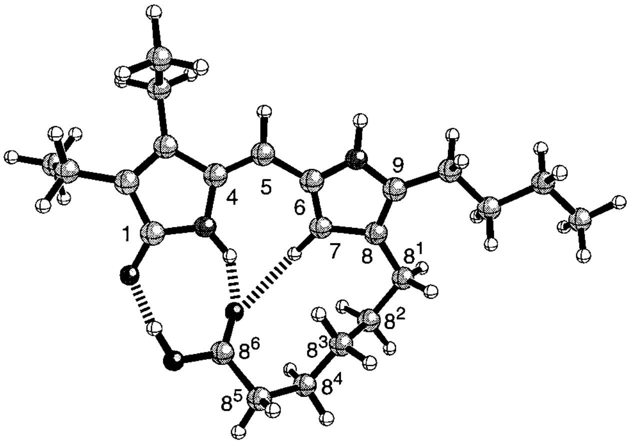


Figure 4. Ball and stick models of the energy-minimized intramolecularly hydrogen-bonded conformations of **1**. Hydrogen bonds are shown by dashed lines, and the hydrogen bond distances are 1.6 (N−H···O), 1.5 (O−H···O), and 2.3 Å (C−H···O) in **1**. The corresponding distances in [6]-semirubin are 1.6, 1.5, and 1.6 Å, respectively. The main atom nonbonded distances are 2.4 (lactam N to carbonyl O), 2.5 (lactam O to carboxylic O), and 3.2 Å (C(7) to carbonyl O), while the corresponding distances in [6]-semirubin are 2.5, 2.5, and 2.6 Å (pyrrole N to carbonyl O). The X−H···Y angles are computed to be 145° (N−H···O), 174° (O−H···O), and 142° (C−H···O) in **1**. In [6]-semirubin they are 147°, 169°, and 155° (pyrrole N−H···O), respectively.

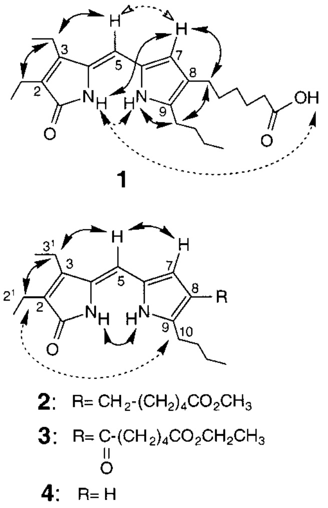


Figure 5. $^1H\{^1H\}$-NOEs found in **1**−**4** in $CDCl_3$ solvent are indicated by curved double-headed arrows. The dotted arrows signify weak NOEs. In **2**, additional NOEs are seen between the C(7)-H and 8^1-CH_2. In **4**, additional NOEs are seen between the 8-H and both the C(7)-H and the 10-CH_2.

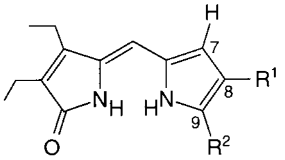
of the type found in Figure 3F and G would be expected to show a pyrrole NH shielding near 8 ppm,[4] which is not observed. In contrast, dipyrrinone **1** is a monomer by VPO. It has a CO_2H group, and its NH chemical shifts do not correspond to a dipyrrinone-to-dipyrrinone dimer. Nor do they correspond to those of [6]-semirubin or bilirubin (which are intramolecularly hydrogen-bonded) or to xanthobilirubic acid, which favors a CO_2H to dipyrrinone hydrogen-bonded dimer (as in Figure 3E) that is π-stacked.[5] Rather, they are indicative of hydrogen bonding between the hexanoic acid CO_2H and the dipyrrinone lactam, but not the pyrrole NH, as would be required by the structures shown in Figures 3C and 4. Its pyrrole NH is clearly not involved in hydrogen bonding because the observed chemical shift is similar to that observed for the pyrrole NH of monomeric non-hydrogen-bonded *syn*-(4*Z*) dipyrrinones at high dilution (~7.8 ppm).[4] In contrast, as seen in xanthobilirubic acid (XBR, Figure 1), intermolecular hydrogen bonding between the *syn* conformation of dipyrrinone **1** and a carboxylic acid in **1** (Figure 3E) would presumably involve the pyrrole NH and cause it to be deshielded to ~9 ppm.[5]

Unlike the ^1H NMR data in $CDCl_3$, those in $(CD_3)_2SO$ solvent show pyrrole NH chemical shifts from **1**−**4**, **6**, [6]-semirubin, and xanthobilirubic acid that are all very similar, indicative of dipyrrinone hydrogen bonding to the solvent.[2] The large deshielding of the pyrrole NH and 7-H of **3** can be attributed to the presence of the keto group attached directly to (C-8) of the pyrrole ring. In contrast, the large shielding of these signals in $CDCl_3$ (relative to $(CD_3)_2SO$ is consistent with a dimer in $CDCl_3$ of the type shown in Figure 2A, for **3** as well as for **2**, **4**, and **6**.

Conformation and NOE. The geometric structural assignments were supported by nuclear Overhauser effects (NOEs). Thus, the *syn*-*Z* configuration of the C(4) exocyclic double bond of the dipyrrinone moiety in **1**−**4** was confirmed by the observation of a strong NOE in $CDCl_3$, between the C(5)-H and the 3^1-CH_2. The *syn* conformation of **2**−**4** was confirmed by strong NOEs between the C(5)-H and the C(7)-H as well as between the lactam and pyrrole NHs (Figure 5). However, in **1** these NOEs are only very weak. In **2**−**4** (but not in **1**) we also observed NOEs between the 10-CH_2 of the butyl chain and the 2^1-CH_2 of the C(2) ethyl group, data that are consistent with the presence of a planar, intermolecularly hydrogen-bonded dimer of the type shown in Figures 2A and 3D. Significant for **1** (but absent in **2**−**4**), a strong NOE was found between the C(7)-H and the lactam NH, which indicates the presence of the *anti*-*Z* conformer. In addition, weak NOEs were detected between the lactam NH and the carboxylic acid hydrogen of **1**, signifying, as it did in [6]-semirubin[6] and in bilirubin,[13] a proximal spatial relationship between the COOH and lactam group consistent with the intramolecular hydrogen bonding motif shown in the ball and stick[2] structural representation (Figure 4). Taken collectively, the NOE data are also in accord with a mainly monomeric structure for **1** in $CDCl_3$ solvent and dimeric structures for **2**−**4**.

Concentration Dependence. In $CDCl_3$, dipyrrinone **1** exhibits an interesting concentration dependence of its NH chemical shifts. At ~9×10^{-4} M, the chemical shift of the pyrrole is ~7.85 ppm whereas that of the lactam is ~9.35 ppm (Figure 6, top). At even lower concentrations of **1**, the chemical shifts are essentially invariant (Figure 6, lower), but at higher concentrations, e.g., ~1.5×10^{-2} M, the pyrrole NH shifts to ~8.55 ppm whereas that of the lactam shifts to ~10.15 ppm. The deshielding grows with increasing concentration and approaches the chemical shift values observed for the hexanoic acid analogue of xanthobilirubic acid (Table 3), which is present in $CDCl_3$ as a π-stacked dimer, with intermolecular hydrogen bonding between the CO_2H and dipyrrinone. Since this type of intermolecular hydrogen bonding requires the *syn*-*Z* dipyrrinone conformation, whereas intramolecular hydrogen bonding requires the *anti*-*Z* conformation, we examined changes in NOEs between the C(7)-H and the C(5)-H and lactam NH in order to assess dipyrrinone conformations (Figure 3A and B). With decreasing concentration of **1**, a relatively decreased

Table 3. Comparison of ^{1}H NMR NH and CO_2H Chemical Shifts[a] of Dipyrrinones in $CDCl_3$ and $(CD_3)_2SO$ Solvents



			δ (ppm) in $CDCl_3$[b]				δ (ppm) in $(CD_3)_2SO$[b]			
dipyrrinone	R^1	R^2	lactam	pyrrole	7-H	CO_2H	lactam	pyrrole	7-H	CO_2H
1	$(CH_2)_5CO_2H$	*n*-Bu	9.62	8.05	6.55	12.52	9.55	10.44	6.48	11.92
2	$(CH_2)_5CO_2Me$	*n*-Bu	10.85	10.01	6.23		9.45	10.35	6.48	
3	$C(O)(CH_2)_4CO_2Et$	*n*-Bu	11.11	10.67	6.73		9.85	11.37	7.21	
4	H	*n*-Bu	11.24	10.52	6.37		9.57	10.68	6.52	
6	H	H	10.71	10.54	6.44		9.59	10.99	6.69	
[6]-semirubin			10.48	8.98		13.22	9.81	10.12		11.95
xanthobilirubic acid[c]			10.58	9.15		13.64	9.74	10.27		11.98
bilirubin			10.80	9.27		13.69	10.07	10.48		11.89

[a] As δ, downfield from Me_4Si. [b] Run as 10^{-2} M $(CD_3)_2SO$ and 10^{-3} M $CDCl_3$ solutions at 25 °C. [c] Approximately 5×10^{-4} M in $CDCl_3$. [d] Taken from ref 13a.

NOE was found between the C(7)-H and the C(5)-H, and a relative increased NOE was found between the C(7)-H and the lactam NH (Figure 7). This is what one would expect for an increasing concentration of *anti* conformer relative to *syn*. Consistent with these observations, with increasing concentration of **1**, a relatively larger NOE at the C(7)-H is found when irradiating the C(5)-H.

The data thus indicate two inter-related equilibria: (i) the *syn* ⇄ *anti* conformational equilibrium and (ii) a monomer ⇄ dimer equilibrium. Hydrogen bonding between the dipyrrinone and carboxylic acid dominates both equilibria. In the monomer, the dipyrrinone is intramolecularly hydrogen-bonded in the *anti-Z* conformation; in the dimer it is intermolecularly hydrogen-bonded in the *syn-Z* conformation. The dimer is detected only at very high concentrations of **1** ($\geq 1.45 \times 10^{-2}$ M, Figure 6), and the VPO study clearly shows that solutions of **1** in $CHCl_3$ at 45 °C are mainly monomeric at $\sim 0.3-1.0 \times 10^{-2}$ M concentration (Table 2). Consequently, K_{assoc} is small, apparently as a result of favorable intramolecular hydrogen bonding. Such hydrogen bonding (Figure 3C) includes not only the lactam O=C−N−H but also the C(7)-H, and thus **1** may serve as a good example of a system with the unusual C−H···O=C hydrogen bond, which has been observed mainly in crystal structures.[14]

Molecular Dynamics Calculations. In support of the conclusions reached (above) by NMR spectroscopic analysis, molecular dynamics calculations[16] of dipyrrinone **1** indicate that it prefers the intramolecularly hydrogen-bonded conformation (Figure 4) to either dimer of Figure 3D and E. The computations show that two intramolecularly hydrogen-bonded molecules of **1** lie some 11.4−12.6 kcal/mol lower in energy than the intermolecularly hydrogen-bonded π-stacked dimer (Figure 3E) of **1**. The intramolecularly hydrogen-bonded conformation shown in Figure 4 has computed molecular parameters similar to those found in the dipyrrinone of [6]-semirubin.[6] The dipyrrinone moiety in **1** and in [6]-semirubin is not planar. In the latter it is twisted (about the C(5)−C(6) bond) approximately 11° out of planarity; whereas in **1** it is twisted ~24°. Such twisting is not unusual in dipyrrinones.[2]

The C−H···O=C Hydrogen Bond. The hydrogen bonding pattern found in [6]-semirubin (Figure 2C) consists of strong hydrogen bonds of the N−H···O=C and O−H···O=C types.[2,5,6,11,14] In **1** (Figure 4) there is a combination of strong hydrogen bonds as well as the possibility for an unusual C−H···O=C hydrogen bond, which is classified as weak.[14c] The strong hydrogen bonds in the computed minimum energy conformers of **1** and [6]-semirubin exhibit the typical main atom nonbonded distances: ~2.5 Å for N to O and O to O, or less than the sums (2.8 and 2.9 Å) of their van der Waals radii. The 3.2 Å nonbonded C(7) to O distance in **1** is close to the sum (3.1 Å) of the van der Waals radii and falls within the conservative threshold for weak C−H···O hydrogen bonds (3.25−3.3 Å).[14c] Similarly the "nonbonded" H to main atom distances in the strong hydrogen bonds of **1** and [6]-semirubin are ordinary (~1.5−1.6 Å), while the C−H···O=C hydrogen bond distance is computed to be longer (2.3 Å) and within the normal range of weak hydrogen bonds (2.0−2.8 Å) when accompanied by large C−H···O angles. In **1** the C(7)−H···O angle is computed to be 142°. The comparable pyrrole N−H···O angle of [6]-semirubin is computed to be 155°. The corresponding angles about the lactam are comparable in **1** and [6]-semirubin: O−H···O, 174° and 169°, respectively; and N−H···O, 145° and 147°, respectively.

The ^{1}H NMR chemical shift of the C(7) hydrogen was examined in order to gain insight into the C(7)−H···O=C interaction. In DMSO-d_6, the chemical shift of the C(7) hydrogen of acid **1** and its methyl ester **2** were found at 6.48 ppm (Table 3), indicating that both adopt very similar conformations: a *syn* conformation of the dipyrrinone with the pyrrole and lactam NHs being hydrogen-bonded to the solvent. In contrast, in $CDCl_3$ at 25 °C the C(7) hydrogen of 10^{-2} M **1** was found to be deshielded by ~0.3 ppm compared with the C(7) hydrogen of its methyl ester **2**. This deshielding is consistent with the C(7) hydrogen lying in the deshielding cone of the carboxylic acid carbonyl and thus within distance for a C(7)−H···O=C interaction in the dipyrrinone *anti* conformation. Further evidence for the interaction comes from the concentration dependence of the C(7) hydrogen chemical shift (Figure 6, lower). At high concentrations, where NOE data show the presence of some *syn* dipyrrinone

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(16) Molecular Mechanics calculations and molecular modelling was carried out on an SGI Octane workstation using version 6.6 of Sybyl (Tripos Assoc., St. Louis, MO) as described in ref 10. The ball and stick drawings were created from the atomic coordinates of the molecular dynamics structures using Müller and Falk's "Ball and Stick" program for the Macintosh.

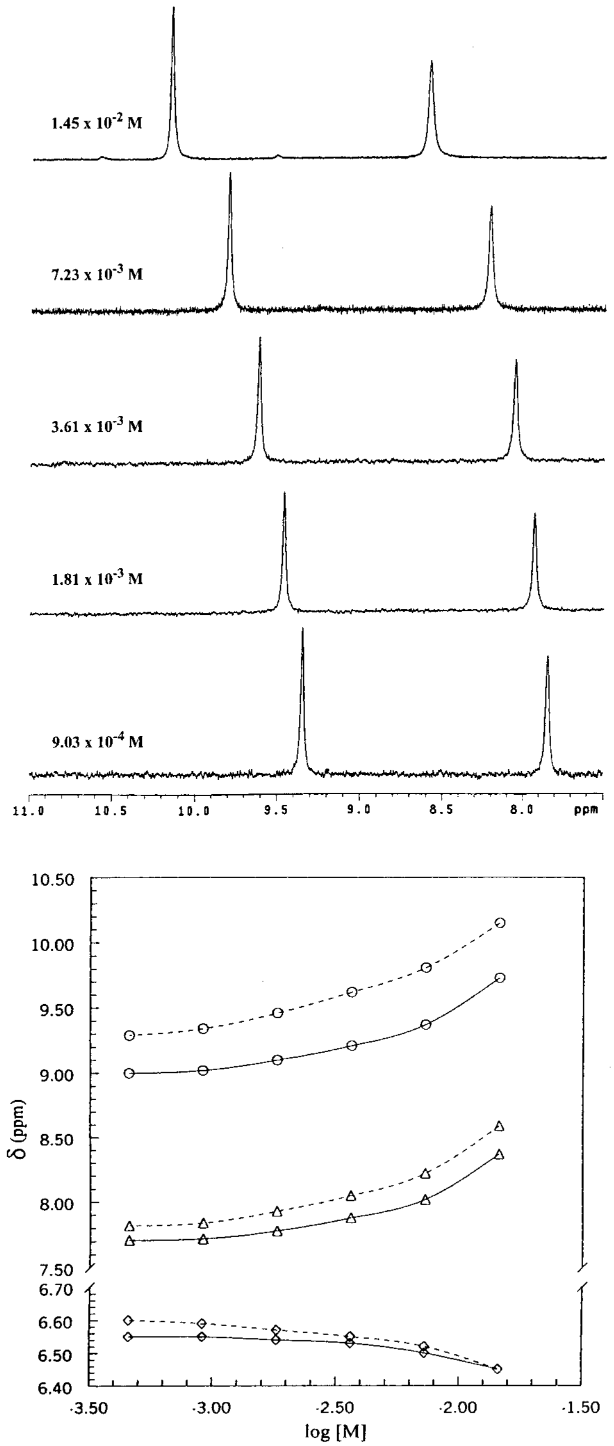

Figure 6. (Upper) Variation of the dipyrrinone NH chemical shifts of **1** with concentration in $CDCl_3$. (Lower) Plot of NH chemical shifts of **1** vs log molar concentration of **1**.

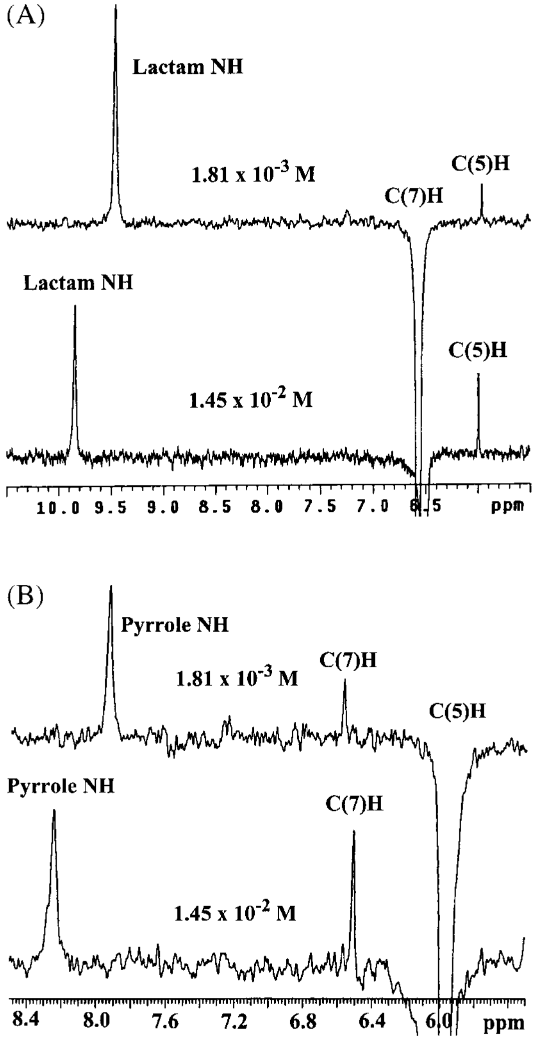

Figure 7. Variation of $^1H\{^1H\}$-NOEs with concentration of **1**. (A) NOEs of the C(5)-H and pyrrole NH from irradiation of the C(7)-H. (B) NOEs of the C(7)-H and pyrrole NH from irradiating the C(5)-H.

conformer and reveal the existence of a monomer ⇄ dimer equilibrium, the C(7)-H resonance of **1** is shifted upfield to ~6.4 ppm, or within 0.2 ppm of that found for the C(7)-H of **2**. A lower concentration, where ^1H NMR concentration studies of the NH chemical shifts show that the monomer dominates, the C(7) hydrogen of **1** is deshielded substantially to ~6.6 ppm, or some 0.4 ppm downfield of the chemical shift found in the ester. Thus, the C(7)−H···O=C interaction must help stabilize the monomer conformation, otherwise **1** would adopt a dimeric conformation similar to that found in XBR (Figure 1) and its homologues (Figure 3E).[5a] The favorable interaction may be looked upon as a weak hydrogen bond.[14]

The temperature dependence of the C(7) hydrogen and the lactam and pyrrole NH chemical shifts is also shown in Figure 6 (lower). The lactam and pyrrole NH resonances are shifted upfield by 0.2−0.4 ppm at 60 °C as compared to the spectra at 25 °C, but the C(7) hydrogen shifts by <0.1 ppm. In contrast, the carboxylic acid OH resonance is shifted more dramatically upfield to ~11.7 ppm at 60 °C from ~12.5 ppm at 25 °C (not shown in Figure 6, lower). When considering a monomer ⇄ dimer equilibrium, there is an additional conformer that must be considered. At the elevated temperature, the non-hydrogen-bonded monomer conformation becomes more prevalent; thus, the chemical shifts move toward those associated with such a conformation (~7.8 for pyrrole and lactam NHs[4] and ~6.2 for the C(7) hydrogen). With the knowledge that [6]-semirubin shows no temperature dependence of the NH chemical shifts, the temperature variations found for **1** suggest that the binding of the CO_2H to the dipyrrinone of **1** is weaker than its binding to the dipyrrinone in [6]-semirubin. These data indicate that the C−H···O interation is weaker than the N−H···O interaction but is still an important interaction helping to determine the preferred conformation of **1**.

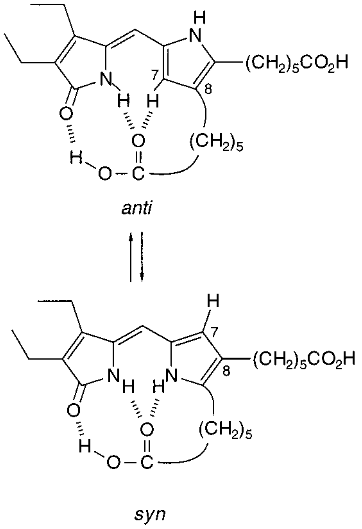

Figure 8. A proposed intramolecularly hydrogen-bonded semirubin analogue that combines the hydrogen bonding potential of **1** (Figures 3B, 4) and semirubin (Figure 2C) and presents a choice for hydrogen bonding. The *anti* shown is computed (Sybyl, ref 16) to lie some 9.3 kcal/mol below the non-hydrogen-bonded *anti* conformation. The *syn* is computed to lie ∼11.6 kcal/mol below the *syn* geometry devoid of hydrogen bonds. Hydrogen bonds are indicated by hatched lines.

Clearly, any possible C(7)−H···O=C hydrogen bond of **1** is not as stabilizing as is the comparable pyrrole N−H···O=C hydrogen bond in [6]-semirubin. Molecular dynamics calculations[16] of the model equilibrium shown in Figure 8 indicate a stabilization of ∼9.3 kcal/mol from hydrogen bonding in the *anti* conformer and ∼11.6 kcal/mol in the *syn*. If one assumes an average value of ∼3.9 kcal/mol per hydrogen bond in the latter, then one might estimate a value of $\sim 1.5 = (9.3 - 2 \times 3.9)$ kcal/mole stabilization from the C−H···O=C hydrogen bond in the anti. This analysis suggests that the stabilization from the weak hydrogen bond in **1** is 35−40% of the strong hydrogen bonds, consistent with the indications of other work.[14c] Work currently underway on the synthesis of the dipyrrinone of Figure 8 may provide a quantitative measure of the relative stabilization of C−H···O=C and N−H···O=C hydrogen bonds.

Optical Spectra. The UV−visible spectral data for **1**−**4** and **6** in solvents with a wide range of polarity are shown in Table 4. The long wavelength bands of semirubin (**1**) and its methyl ester (**2**) have nearly the same λ_{max} in polar solvents, but λ_{max} of **1** is strongly bathochromically shifted from that of **2** in nonpolar solvents, solvents likely to promote hydrogen bonding. Smaller wavelength shifts attend the spectra of oxo-semirubin **3** and its ethyl ester (**4**) over the range of solvents used. While the spectral shifts do not unambiguously confirm an intramolecularly hydrogen-bonded structure for **1** and **3**, they lend support to this conclusion, on the basis of NMR spectral analysis and VPO studies, and they are consistent with the ability of **1** and **3** to adopt a unique conformational structure in nonpolar solvents. The UV−visible spectral data for ester **4** are less solvent dependent than those of ester **2**, consistent with the indications that **2** tends toward dimeric in nonpolar solvents and **4** does not. Beer's Law plots of **1** show the same linearity reported earlier for [6]-semirubin.

Conclusions

Dipyrrinone **1**, which has the core chromophore of one-half bilirubin, has been synthesized and, like bilirubin, is found to be monomeric in $CHCl_3$ solvent and to adopt an intramolecularly hydrogen-bonded conformation as its energy-minimum structure. As such, it is less polar than its methyl ester and much less polar than related dipyrrinone analogues, e.g., xanthobilirubic acid, that are incapable of intramolecular hydrogen bonding. In $CDCl_3$ solution, and unlike xanthobilirubic acid, bilirubin, or [6]-semirubin, **1** adopts the unusual *anti* conformation around the C(5)−C(6) bond, a conformation stabilized by intramolecular hydrogen bonds. Included among the three hydrogen bonds is a C−H···O=C hydrogen bond (typically classified as weak and found elsewhere mainly in the solid state),[14] which we estimate to contribute ∼35−40% of the stabilization as the result of a strong hydrogen bond of the N−H···O=C or O−H···O=C type. Whether **1** behaves similarly to bilirubin in hepatic metabolism, requiring glucuronidation of its hydrogen-bonded carboxylic acid in order to be excreted into bile, remains to be investigated.

Experimental Section

General Procedures. All nuclear magnetic resonance (NMR), infrared (IR), and ultraviolet−visible spectra were determined as reported previously.[4−7] HMQC, HMBC, and NOE NMR measurements were obtained at 500 MHz. Vapor pressure osmometry (VPO) measurements were performed in $CHCl_3$ at 45 °C with benzil used for calibration.[7] To ensure anhydrous solvents and samples for the ^1H NMR experiments, the samples were dried under vacuum in a drying pistol at refluxing toluene temperature and with P_2O_5 desiccant. The $CDCl_3$ solvent used was stored over CaH_2 after having been passed through a column of Woelm Super I activity basic alumina. Combustion analyses were carried out by Desert Analytics, Tucson, AZ. The fast atom bombardment high-resolution mass spectrum (FAB-HRMS) of **1** was run at the University of Minnesota Mass Spectrometry Facility. Melting points were taken on a MelTemp capillary apparatus and are uncorrected. Analytical thin-layer chromatography was on J. T. Baker silica gel IB-F plates (125 μm layers). Flash column chromatography used Woelm silica gel F, thin-layer chromatography grade. Radial chromatography was carried out on Merck silica gel PF_{254} with gypsum, preparative layer grade. Spectral data were obtained in spectral grade solvents (Aldrich or Fisher). Dichloromethane, methanol, tetrahydrofuran, hexane, aluminum chloride, and 2-propanol were from Fisher, and sodium borohydride and thionyl chloride were from Acros. 5-Carboethoxypentanoyl chloride was prepared from 5-carboethoxypentanoic acid[1717] by standard methods, and 2,3-diethyl-dipyrrin-1-one[15] (**6**) was prepared according to the literature.

9-Butyl-2,3-diethyl-dipyrrin-1-one (4). To a 500 mL round-bottom flask equipped with magnetic stirring were added 0.400 g (1.8 mmol) of dipyrrinone (**6**) and 200 mL of dichloromethane. The solution was stirred in an ice bath for 20 min. Butanoyl chloride (1.2 g, 11.3 mmol) and anhydrous $AlCl_3$ (4.4 g, 33 mmol) in 100 mL of dichloromethane was added all at once, and the reaction mixture stirred for 2 h at room temperature. The reaction mixture was then poured onto (HCl(conc)/ice (200 mL/100 g) and stirred for 2 h. The biphasic suspension was filtered (vacuum), washed with cold CH_2Cl_2, and air-dried.

The crude product (**5**) was suspended in 100 mL of 2-propanol in a 250 mL round-bottom flask equipped for magnetic stirring. Sodium borohydride (200 mg, 3.4 mmol) was added, and the reaction mixture was heated at reflux for 2 h. The hot reaction mixture was poured into 100 mL of ice water, and

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[17] Swann, S.; Oehler, R.; Boswell, R. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, pp 276−277.

Table 4. Solvent Dependence of UV−Visible Data for Dipyrrinones

		λ_{max} (ϵ_{max})[b]				
solvent	ϵ[c]	**1**	**2**	**3**	**4**	[6]-semirubin
C_6H_6	2.3	422 (27 900)	411 (33 200)	415 (16 700) 395 (22 900)	411 (33 200)	426 (27 300)
$CHCl_3$	4.7	415 (31 200)	407 (28 800)	415 (19 100) 394 (24 200)	407 (28 800)	421 (28 400)
CH_3OH	32.6	414 (34 200)	415 (33 500)	412 (22 100) 393 (26 600)	415 (33 500)	416 (38 000)
$(CD_3)_2SO$	49.0	411 (31 700)	411 (33 200)	414 (16 700) 395 (22 900)	411 (33 200)	413 (28 000)

[a] Data obtained at 22 °C on 2−4 × 10^{-5} M solutions. [b] λ_{max} in nm, ϵ_{max} in $M^{-1}\,cm^{-1}$. [c] Dielectric constants from Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley: New York, 1972; pp 4−8.

the solution was acidified with 10% aqueous HCl. The suspension was extracted with dichloromethane, and the combined organic extracts were washed with water and dried over Na_2SO_4 (anhydrous). The solvent was removed (rotovap), and the crude product was purified by radial chromatography (97:3 vol/vol CH_2Cl_2/MeOH) and recrystallized from CH_2Cl_2/hexane to give **4** (450 mg, 63% yield): mp 153−154 °C; IR (KBr) ν 3350, 3189, 2962, 2930, 2877, 1667 cm^{-1}; ^1H NMR δ (DMSO-d_6, 500 MHz) 0.89 (t, 7.5 Hz, 3H), 1.01 (t, 7.5 Hz, 3H), 1.10 (t, 7.5 Hz, 3H), 1.30 (sextet, 7.5 Hz, 2H), 1.55 (pentet, 7.5 Hz, 2H), 2.23 (q, 7.5 Hz, 2H), 2.44 (q, 7.5 Hz, 2H), 2.53 (t, 7.5 Hz, 2H), 5.86 (t, 3.0 Hz, 1H), 6.00 (s, 1H), 6.52 (t, 3.0 Hz, 1H), 9.57 (s, 1H), 10.68 (s, 1H) ppm; ^1H NMR δ ($CDCl_3$, 500 MHz) 0.95 (t, 7.5 Hz, 3H), 1.14 (t, 7.5 Hz, 3H), 1.20 (t, 7.5 Hz, 3H), 1.41 (sextet, 7.5 Hz, 2H), 1.71 (pentet, 7.5 Hz, 2H), 2.42 (q, 7.5 Hz, 2H), 2.54 (q, 7.5 Hz, 2H), 2.82 (t, 7.5 Hz, 2H), 6.00 (dd, 1.5 Hz, 2.0 Hz, 1H), 6.11 (s, 1H), 6.34 (dd, 1.5 Hz, 2.0 Hz, 1H), 10.52 (s, 1H), 11.24 (s, 1H) ppm; ^{13}C NMR data are in Table 1 and UV−vis data are in Table 4. Anal. Calcd for $C_{17}H_{24}N_2O$ (272.4): C, 74.96; H, 8.88; N, 10.28. Found: C, 74.66; H, 8.64; N, 10.11.

8-(5-Ethoxycarbonoylpentanoyl)-9-butyl-2,3-diethyl-dipyrrin-1-one (3). 9-Butyl-2,3-diethyl-dipyrrin-1-one (**4**) (0.195 g, 0.7 mmol) and 100 mL of dichloromethane were added to a 500 mL round-bottom flask equipped for magnetic stirring. The solution was cooled in an ice bath for 20 min with stirring, and then a solution of ethyl adipoyl chloride (0.9 g, 4.7 mmol) and $AlCl_3$ (4.5 g, 31.7 mmol) in 100 mL of dichloromethane was added in one portion. The reaction mixture was stirred for 1.5 h at room temperature, poured into a mixture of concentrated HCl (200 mL) and 100 g of ice, and stirred for 2 h. The organic layer was separated, and the aqueous layer extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and then with water and dried over anhydr. Na_2SO_4. The solvent was removed (rotovap), and the crude product was purified by radial chromatography (97:3 vol/vol CH_2Cl_2/MeOH) and recrystallized from CH_2Cl_2/hexane to afford pure **3** (0.198 g, 65% yield): mp 123−130 °C; IR (KBr) ν 3324, 2964, 2943, 2874, 1736, 1693, 1678 cm^{-1}; ^1H NMR δ (DMSO-d_6, 500 MHz) 0.87 (t, 7.5 Hz, 3H), 1.04 (t, 7.5 Hz, 3H), 1.11 (t, 7.5 Hz, 3H), 1.16 (t, 7.5 Hz, 3H), 1.27 (sextet, 7.5 Hz, 2H), 1.52 (pentet, 7.5 Hz, 2H), 1.56 (m, 4H), 2.25 (q, 7.5 Hz, 2H), 2.31 (m, 4H), 2.45 (q, 7.5 Hz, 2H), 2.76 (t, 7.5 Hz, 2H), 2.85 (t, 7.5 Hz, 2H), 4.03 (q, 7.5 Hz, 2H), 5.99 (s, 1H), 7.21 (d, 2.5 Hz, 1H), 9.75 (s, 1H), 11.37 (s, 1H) ppm; ^1H NMR δ ($CDCl_3$, 500 MHz) 0.91 (t, 7.5 Hz, 3H), 1.14 (t, 7.5 Hz, 3H), 1.21 (t, 7.5 Hz, 3H), 1.25 (t, 7.5 Hz, 3H), 1.37 (sextet, 7.5 Hz, 2H), 1.67 (pentet, 7.5 Hz, 2H), 1.73 (m, 4H), 2.36 (t, 7.0 Hz, 2H), 2.42 (q, 7.5 Hz, 2H), 2.55 (q, 7.5 Hz, 2H), 2.79 (t, 7.0 Hz, 2H), 3.13 (t, 7.5 Hz, 2H), 4.13 (q, 7.0 Hz, 2H), 6.07 (s, 1H), 6.73 (d, 2.5 Hz, 1H), 10.67 (s, 1H), 11.11 (s, 1H) ppm; ^{13}C NMR data are in Table 1 and UV−vis data in Table 4. Anal. Calcd for $C_{25}H_{36}N_2O_4$ (428.6): C, 70.06; H, 8.47; N, 6.54. Found: C, 69.89; H, 8.55; N, 6.38.

8-(5-Carboxypentyl)-9-butyl-2,3-diethyl-dipyrrin-1-one (1). Dipyrrinone **3** (198 mg, 0.46 mmol) and 100 mL of 2-propanol were placed in a 250 mL round-bottom flask equipped for magnetic stirring. Sodium borohydride (100 mg, 1.7 mmol) was added, and the reaction mixture was heated at reflux for 2 h. The hot reaction mixture was poured into ice water, and the solution was acidified with 10% aq. HCl. The suspension was extracted with dichloromethane, and the combined organic extracts were washed with water and dried over Na_2SO_4 (anhydrous). The solvent was removed (rotovap), and the crude product was purified by radial chromatography (97:3 vol/vol CH_2Cl_2/MeOH) and recrystallized from CH_2Cl_2/hexane to give 0.143 g (88% yield) of pure acid **1**: mp 122−124 °C; IR (KBr) ν 3431, 2965, 2932, 2868, 1747, 1663 cm^{-1}; ^1H NMR δ (DMSO-d_6, 500 MHz) 0.88 (t, 7.5 Hz, 3H), 1.01 (t, 7.5 Hz, 3H), 1.09 (t, 7.5 Hz, 3H), 1.29 (m, 4H), 1.50 (m, 6H), 2.19 (t, 7.5 Hz, 2H), 2.23 (q, 7.5 Hz, 2H), 2.28 (t, 7.5 Hz, 2H), 2.43 (q, 7.5 Hz, 2H), 2.49 (m, 6H), 5.97 (s, 1H), 6.48 (d, 2.5 Hz, 1H), 9.55 (s, 1H), 10.44 (s, 1H), 11.92 (s, 1H) ppm; ^1H NMR δ ($CDCl_3$, 500 MHz) 0.89 (t, 7.5 Hz, 3H), 1.12 (t, 7.5 Hz, 3H), 1.16 (t, 7.5 Hz, 3H), 1.31 (sextet, 7.5 Hz, 2H), 1.44 (pentet, 7.5 Hz, 2H), 1.54 (pentet, 7.5 Hz, 2H), 1.60 (pentet, 7.5 Hz, 2H), 1.73 (pentet, 7.5 Hz, 2H), 2.35 (q, 7.5 Hz, 2H), 2.41 (t, 6.5 Hz, 2H), 2.45 (t, 6.5 Hz, 2H), 2.48 (q, 7.5 Hz, 2H), 2.55 (t, 7.5 Hz, 2H), 5.99 (s, 1H), 6.55 (d, 2.5 Hz, 1H), 8.05 (s, 1H), 9.62 (s, 1H), 12.52 (bs, 1H) ppm; ^{13}C NMR data are in Table 1 and UV−vis data are in Table 4; FAB-HRMS (3-NBA + PEG400) calcd for $C_{23}H_{34}N_2O_3$ [$M^{+\bullet}$] 386.2569, found 386.2561, error 2.2 ppm, Δ 0.8 mDa. Anal. Calcd for $C_{23}H_{34}N_2O_3$ (386.5): C, 71.47; H, 8.87; N, 7.25. Found: C, 71.12; H, 8.79; N, 7.50.

8-(5-Carbomethoxypentyl)-9-butyl-2,3-diethyl-dipyrrin-1-one (2). To a 100 mL round-bottom flask equipped for magnetic stirring was added 65 mg of acid **1** and 50 mL of methanol. To this solution was added 10 mL of 10% H_2SO_4, and the solution was heated at reflux for 1 h. The reaction mixture was cooled to room temperature, taken up in 100 mL of dichloromethane, washed with water and saturated sodium bicarbonate solution, and dried over Na_2SO_4 (anhydrous). The solvent was removed (rotovap), and the residue was purified by radial chromatography (97:3 vol/vol CH_2Cl_2/MeOH) and recrystallized from absolute ethanol overnight at −20 °C to give pure target **2** (55 mg, 82%): mp 95−97 °C; IR (KBr) ν 3432, 3350, 2963, 2933, 1739, 1674 cm^{-1}; ^1H NMR δ (DMSO-d_6, 500 MHz) 0.88 (t, 7.5 Hz, 3H), 1.01 (t, 7.5 Hz, 3H), 1.09 (t, 7.5 Hz, 3H), 1.27 (m, 4H), 1.51 (m, 6H), 2.23 (q, 7.5 Hz, 2H), 2.28 (t, 7.5 Hz, 2H), 2.43 (m, 6H), 3.56 (s, 3H), 5.97 (s, 1H), 6.48 (d, 2.5 Hz, 1H), 9.54 (s, 1H), 10.44 (s, 1H) ppm; ^1H NMR δ ($CDCl_3$, 500 MHz) 0.91 (t, 7.5 Hz, 3H), 1.13 (t, 7.5 Hz, 3H), 1.18 (t, 7.5 Hz, 3H), 1.34 (sextet, 7.5 Hz, 2H), 1.39 (pentet, 7.5 Hz, 2H), 1.57 (m, 4H), 2.32 (t, 7.5 Hz, 2H), 2.39 (m, 4H), 2.52 (q, 7.5 Hz, 2H), 2.71 (t, 7.5 Hz, 2H), 3.67 (s, 3H), 6.04 (s, 1H), 6.23 (d, 2.5 Hz, 1H), 10.01 (s, 1H), 10.85 (s, 1H) ppm; ^{13}C NMR data are in Table 1 and UV−vis data are in Table 4. Anal. Calcd for $C_{24}H_{36}N_2O_3$ (400.6): C, 71.96; H, 9.06; N, 6.99. Found: C, 71.77; H, 8.95; N, 6.90.

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