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Hydrogen Bonding: $\text{HOC}=\text{O} \cdots \text{H}-\text{N}$ vs. $\text{HOC}=\text{O} \cdots \text{H}-\text{C}$

Sanjeev K. Dey,

Milliken & Company, PO Box 1926, Spartanburg, SC 29304

Suchitra Datta, and

Milliken & Company, PO Box 1926, Spartanburg, SC 29304

David A. Lightner

Department of Chemistry, University of Nevada, Reno, Nevada, 89557-0216 USA

Abstract

A chloroform-soluble dipyrnone, 8,9-bis-(5-carboxypentyl)-2,3-bis-(2-methoxyethoxy)-10*H*-dipyrin-1-one, with solubilizing 2-methoxyethoxy β -substituents on the lactam ring and two hexanoic acid groups (one at C(9), the other at C(8) of the pyrrole ring) was synthesized for its ability to form intramolecular hydrogen bonds to the lactam unit from either carboxylic acid, whether in the *syn*-(*Z*) or *anti*-(*Z*) conformation. In the *syn*-(*Z*) conformation, such intramolecular hydrogen bonds can also include the pyrrole N-H. In the *anti*-(*Z*), intramolecular hydrogen bonds can include the pyrrole C(7)-H. Evidence for both monomer conformations in equilibrium is provided by ^1H NMR analyses, which indicate that the *syn*-(*Z*) is favored over the *anti*-(*Z*) and predict an interconversion barrier of approximately 40 kJ mol $^{-1}$.

Keywords

Pyrroles; Conformation; NMR

Introduction

In connection with studies directed toward a better understanding of the importance of intramolecular hydrogen bonding in bilirubin (Fig. 1A) [1-4], the yellow pigment of jaundice and the end product of heme metabolism [5, 6], we previously identified a dipyrrole model, and synthesized 2,3,7,8-tetramethyl-9-(5-carboxypentyl)-10*H*-dipyrin-1-one, which for simplicity we named [6]-semirubin (Fig. 1B) [7]. Like bilirubin, [6]-semirubin exhibited intramolecular hydrogen bonding between its *syn*-(4*Z*)-configuration dipyrnone and carboxyl group at the terminus of the C(9)-hexanoic acid – a chain of six carbons mimicking the C(10)-C(11)-C(12)-C(12 1)-C(12 2)-CO $_2$ H and C(10)-C(9)-C(8)-C(8 1)-C(8 2)-CO $_2$ H covalent bonding pathways in bilirubin. The results from our study of [6]-semirubin thus clearly showed the considerable importance of dipyrnone to carboxylic acid to hydrogen intramolecular hydrogen bonding relative to any other type, such as the intermolecular type exhibited by the methyl ester of [6]-semirubin and shown in Fig. 1C [7].

Dipyrinone to dipyrinone intermolecular hydrogen bonding is a well-recognized phenomenon with a large equilibrium constant [8], e.g., $K_{\text{assoc}} \approx 30000$ at 298 K in CDCl_3 [9], and it appears to dominate the molecularity of dipyrinones in nonpolar solvents – unless an approximately situated carboxylic acid group is present.

Most of the known dipyrinones are β -substituted and favor the *syn*-(Z) conformation (Fig. 2) over the *anti*-(Z), unless the pyrrole nitrogens are also substituted [10]. This is especially true when C(7) of the pyrrole ring is substituted, for which the *anti*-(Z) is destabilized by steric buttressing, as illustrated in Fig. 2. Absent a substituent at C(7), the *syn* and *anti* conformations lie close in energy. Falk et al. [8, 10] predicted, using molecular mechanics calculations, that the “naked” dipyrinone ($R = H$) *syn*-(Z) is more stable than the *anti* by $\sim 5 \text{ kJ mol}^{-1}$, with an interconversion barrier of $\sim 20 \text{ kJ mol}^{-1}$. Using density functional ab initio calculations (DFT/B3LYP) on the “naked” dipyrinone ($R = H$), Lorb et al. [11] found the *syn*-(Z) to be more stable by 1.4 kJ mol^{-1} , and by 4.6 kJ mol^{-1} from semi-empirical studies. Molecular mechanics calculations using PCMODEL and the MMX force field predict the *syn*-(Z) to be more stable than the *anti*-(Z) by $\sim 1.7 \text{ kJ mol}^{-1}$ and to have a smaller dipole moment (2.8 vs. 3.6 Debye).

To explore the possibility of stabilizing the *anti*-(Z) conformer using intramolecular hydrogen bonds, in an earlier investigation [12] we prepared a new C(7)-H [6]-semirubin analog (Fig. 1D) with a hexanoic acid group at C(8), a dipyrinone designed to effect intramolecular hydrogen bonding between an *anti*-(Z) conformer dipyrinone and a CO_2H group. For this, the dipyrinone must adopt the less favored *anti*-(Z) conformation (Fig. 2) and apparently incorporate hydrogen bonding of the weak $\text{C}=\text{O}\cdots\text{H}-\text{C}$ type instead of the stronger $\text{C}=\text{O}\cdots\text{H}-\text{N}$ type. Indeed, here too, the former intramolecular hydrogen bonding was shown to preclude all other types. Taken collectively, these results [7, 12] and especially more recent studies [12] strengthen our belief that for the matrix of intramolecular hydrogen bonds the carboxylic acid to lactam is most important but that the pyrrole N-H, and to a lesser extent the C(7)-H contribute to the dominating capacity of a dipyrinone to sequester a carboxylic acid. Even when molecular structure precludes the possibility of engaging dipyrinone to CO_2H intramolecular hydrogen bonds, as in [3]- and [4]-semirubins, intermolecular dipyrinone to CO_2H hydrogen bonding dominates the dipyrinone to dipyrinone type [13].

In the current study, we investigate the relative ability of a C(8)-hexanoic acid chain and C(9)-hexanoic acid to displace the *syn*-(Z) $\rightleftharpoons$ *anti*-(Z) equilibrium (Fig. 3) of a new C(7)-H dipyrinone (**1**) designed for competitive intramolecular hydrogen bonding of the dipyrinone to CO_2H type (compare Figs. 1B and 1D). Such competition would thus be expected to serve for an evaluation of the relative importance of $\text{C}=\text{O}\cdots\text{H}-\text{N}$ and $\text{C}=\text{O}\cdots\text{H}-\text{C}$ hydrogen bonds.

Results and Discussion

Synthesis

Our approach (Scheme 1) to the synthesis of **1**, as well as analogs **10**, **11**, **16**, and **19**, followed an earlier procedure that was used to prepare [6]-semirubin (Fig. 1B) and its analog

(Fig. 1D). The key relay compound was dipyrinone **6**. Its analog with ethyl or methoxyl groups on the lactam ring afforded analogs of **1** that proved to be too insoluble in CDCl_3 for our studies. Dipyrinone **6** was prepared by condensing pyrrole α -aldehyde [14] with 3,4-bis-(2-methoxyethoxy)-3-pyrrolin-2-one, available from earlier work [15].

Thus, as outlined in Scheme 2, pyrrolinone **7** and pyrrole α -aldehyde were condensed in CH_3OH solvent in the presence of KOH to produce a separable 47% isolated yield of desired dipyrinone **6** plus a by-product (**8**) in a 4:1 ratio. The unanticipated formation of **8**, with the CH_3O replacing $\text{CH}_3\text{OCH}_2\text{CH}_2\text{O}$ at C(4) presumably arises from conjugate addition of methylate to the α,β -lactam followed by retro-addition with loss of 2-methoxyethylate.

Introduction of the first hexanoic acid group onto **6** was expected to occur at C(9) [7, 12, 13], which was achieved using Friedel-Crafts acylation conditions with the half ester acid chloride of adipic acid [16] and SnCl_4 catalyst. Surprisingly, acylation produced a high yield of a separable mixture of two products, the 9-substituted (**5**) and the 8-substituted (**9**) dipyrinones in a 43:53 ratio. The formation of **9** was unexpected, as earlier acylation by the same acid chloride, as well as with butyryl chloride, of the 3,4-diethyl analog of **6** gave almost exclusively the 9-acylated product. The presence of 2-methoxyethoxyl groups of **6** does not seem to be the cause of acylation at C(8) because (as will be shown), acylation of **6** with butyryl chloride produced the expected 9-butanoyl product in >90% yield.

The keto group of the resulting oxo-ester **5** was reduced using $\text{NaBH}_4 + \text{BF}_3 \cdot \text{OEt}_2$ to give ester **4** (use of NaBH_4 alone produced a mixture of **4** and the corresponding acid). This, in turn was acylated as above to afford a 67% yield of keto-acid **3**, whose keto group was selectively reduced to methylene, again using $\text{NaBH}_4 + \text{BF}_3 \cdot \text{OEt}_2$, to afford a 64% yield of diester **2**. The last was saponified to afford the target compound, dihexanoic acid **1** in 81% yield.

For comparison purposes, we required analogs of **1** with but one hexanoic acid and with an adjacent butyl chain, e.g., **16** and **19** (Scheme 1). The butyl groups improved the CHCl_3 solubility of **16** and **19** relative to dipyrinones **10** and **11** and were approximately the size of the hexanoic acids they replaced. Their presence was important in comparing **16** and **19** to **1**. Thus, dipyrinone **4** was acylated with butyryl chloride in CH_2Cl_2 in the presence of SnCl_2 catalyst to afford **17** in 92% yield. Its keto group was reduced to CH_2 using $\text{NaBH}_4 - \text{BF}_3 \cdot \text{OEt}_2$ to give **18**, which was saponified to **19** in 88% yield. To prepare **16**, **6** was acylated at C(9) with butyryl chloride to give a 96% yield of **12**, which was reduced to **13** in 72% yield using $\text{NaBH}_4 + \text{BF}_3 \cdot \text{OEt}_2$. Further acylation (of **13**) using the Friedel-Crafts conditions with the half ester acid chloride of adipic acid afforded **14**, which was reduced and saponified to produce **16**.

Structures and ^{13}C NMR Spectra

The constitutional structures of **1**, **2**, **4**, **11**, **16**, **19**, and **6** follow from the method of synthesis and comparison of their ^{13}C NMR spectral data (Table 1). The $\text{CH}_3\text{OCH}_2\text{CH}_2\text{O}$ groups stand out recognizably between ~60-72 ppm, as do C(5) and the lactam and carboxyl

carbonyls. As expected, the acid carbonyl carbon is deshielded by ~5 ppm relative to its ester.

Monomers vs. Dimers

In order to establish that analysis of hydrogen bonding is related only to monomeric dipyrinones, and thus exclude dipyrinone to dipyrinone hydrogen bonded dimers [9] such as in Fig. 1C, or carboxylic acid to dipyrinone hydrogen bonded dimers or polymers, we determined the molecular weights of **1**, **11**, **16**, **19**, and (for comparison) ester **15** (Table 2) using vapor phase osmometry (VPO). The VPO data from CHCl₃ solvent over the concentration range 0.03-0.13 M show that **1** is monomeric, as are **11**, **16**, and **19**. As expected, ethyl ester **15** is dimeric.

Consistent with the conclusion that **1** is monomeric in chloroform, a Beer's Law plot over the ~ten-fold concentration range $\sim 7 \times 10^{-4}$ to $\sim 9.5 \times 10^{-5}$ M matched exactly the theoretical behavior for the presence of only one absorbing species (Fig. 4).

UV-Vis Spectroscopy

The UV-Vis spectral data of dipyrinones **1**, **5**, **6**, and **11** are shown in Table 3. In general, λ_{max} tends to increase with increasing substitution of the pyrrole β -substituents, thus explaining the longer wavelength λ_{max} of **1** vs. **11** and (especially) **6**. For semirubin **1** there is a small hypsochromic shift (~5 nm) going from less polar solvents to more polar solvents. There was no noticeable similar trend in the optical properties of other dipyrinones. As seen in earlier studies [7, 12], ketone **5** shows the expected enhancement of ϵ_{max} and hypsochromic shift of λ_{max} relative to **11**.

Conformational Analysis from ¹H NMR

The invariant ¹H NMR chemical shifts for the hydrogens at C(5) and C(7) (Fig. 5A) and the pyrrole and lactam N-H resonances (Fig. 5B) of **1** over the concentration range 10⁻³-10⁻¹ M suggest either a single monomer species or rapidly equilibrating species. In the case of the latter, the signals would reflect concentration-weighted averaged chemical shifts. Evidence to bear on this comes from analogs **16** and **19**, which were shown to be monomers by VPO measurements and confirmed to adopt the *syn*-(Z) and *anti*-(Z) intramolecularly hydrogen-bonded conformations by nuclear Overhauser effect (NOE) studies. Strong ¹H{¹H} NOEs were observed between the C(5)-H and both the pyrrole N-H and the pyrrole C(7)-H, between the lactam N-H and the pyrrole N-H as well as the pyrrole C(7)-H. These data, together with those from VPO (Table 2), define the presence in both **16** and **19** (Fig. 6) a (Z)-configuration dipyrinone with intramolecular hydrogen bonding.

Analog **16** and **19** provide useful variable temperature ¹H NMR data (Table 4) for interpreting the NMR chemical shifts of **1** in terms of the equilibrium shown in Fig. 3. Thus, the relative insensitivity of the C(5)-H and C(7)-H signals of **16** and **19** over the range of +25 to -35 °C correlate with the fixed conformations of Fig. 6, and the strong deshielding of the lactam N-H of **16** and **19** may be attributed to tightened intramolecular hydrogen bonding with temperature lowering. A similar deshielding trend for the pyrrole N-H is seen for **19**, as expected, and also for **16**, which was not expected – and may be due to solvation

effects. The insensitivity of the C(7)-H signal was expected for **19** but not for **16**. In considering the corresponding chemical shifts of **1** relative to **16** and **19**, one finds that the chemical shifts of the lactam N-H, pyrrole N-H, and C(7)-H of **1** lie between those of **16** and **19**. Actually close to the averaged values found for **16** and **19**, consistent with equilibrating *syn*-(Z) and *anti*-(Z) conformers. From a comparison of the sensitive lactam N-H chemical shifts of **1**, **16**, and **19**, one can make a qualitative assessment that the *syn* - *anti* equilibrium of **1** (Fig. 3) favors the *syn* as the temperature is lowered, consistent with (i) previous work [12] and (ii) the expectation that the pyrrole N-H (of the *syn* conformation) is more effective in hydrogen bonding to a CO₂H group than the pyrrole C(7)-H of the *anti* conformation. An attempt to obtain quantitative differences based on Table 3 were unsatisfactory. We estimate that the nearly 1:1 equilibrium at 25 °C drops to ~3:2 at -35 °C.

In an examination of the ¹H NMR chemical shift variation of **1** with temperature over the range +25 °C to -90 °C in Fig. 7, one may notice that the C(7)-H at ~6.3 ppm moves upfield and merges into the C(5)-H at ~6.2 ppm when the temperature reaches ~ -60 °C, then reappears at ~6.5 ppm at -65 °C. Likewise, at -57 °C the lactam N-H (~10.25 ppm) appears to split into two broad signals that are more clearly seen at 9.8 and 10.3 ppm at -80 °C. The pyrrole N-H signal at 8.7 ppm seen at 25 °C broadens without splitting and remains near 9.0 ppm down to -90 °C. These two sets of signals correlate with those (Table 3) from analogs locked into the *syn*-(Z) and *anti*-(Z) conformations of **19** and **16**, respectively. Quantifying these NMR results into G° was thwarted, however, by peak broadening as the temperature was lowered to -90 °C, rendering integration non-reproducible. Nonetheless, $G^\ddagger$, for interconversion of the two conformers could be estimated as ~40 kJ mol⁻¹ from the coalescence temperature of lactam N-H.

Previous estimates of the barrier to interconversion of the nearly equi-energetic *syn*-(Z) and *anti*-(Z) conformers of Fig. 2, where R = CH₃, are 16.6 and 18.0 kJ mol⁻¹, respectively, by DFT computations [11] and ~20 kJ mol⁻¹ by molecular mechanics calculations [8, 10]. In **1**, the interconversion barrier is raised above these values by ~20-23 kJ mol⁻¹ because here the barrier also includes the breaking of three hydrogen bonds. Given an interconversion barrier in **1** of ~40 kJ mol⁻¹, and a difference of 20-23 kJ mol⁻¹ above that computed for the “naked” dipyrinones of Fig. 2, one can estimate the two or three hydrogen bonds of **1** are worth 7-12 kJ mol⁻¹ each. Unfortunately, it is difficult to estimate the energy difference between the C=O...H-N and C=O...H-C bond, though it is probably less than the ~6 kJ mol⁻¹ previously estimated [12].

Concluding Comments

With the knowledge of effective intramolecular hydrogen bonding in [6]-semirubin (Fig. 1B), a novel dipyrinone (**1**) was synthesized with hexanoic acids located at C(8) and C(9) for an investigation into the relative importance of two types of intramolecular hydrogen bonding: (i) CO₂H to lactam + pyrrole NH and (ii) to lactam + pyrrole CH. Both types were found, with (i) being favored over (ii) by ~6 kJ mol⁻¹ and an interconversion barrier of ~40 kJ mol⁻¹.

Experimental

All nuclear magnetic resonance (NMR) spectra were obtained in deuteriochloroform on a Varian unity plus at 11.75 T magnetic strength operating at 500 MHz (^1H) and 125 MHz (^{13}C). Chemical shifts were reported in ppm referenced to the residual chloroform proton signal at 7.26 ppm and ^{13}C signal at 77.23 ppm unless otherwise noted. A combination of heteronuclear multiple bond correlation (HMBC) spectra, heteronuclear single bond correlation (HSQC) spectra, two-dimensional correlation spectroscopy (COSY), and $^1\text{H}\{^1\text{H}\}$ NOE data were used to assign ^1H and ^{13}C NMR spectra. All UV-Vis spectra were recorded on a Perkin-Elmer λ -12 spectrophotometer. Melting points were taken on a Mel-Temp capillary apparatus and are corrected. Analytical samples were dried under vacuum in a drying pistol (Abderhalden) at refluxing ethanol or toluene temperature using P_2O_5 as desiccant. Combustion analyses were performed by Desert Analytics, Tucson, AZ and gave results within $\pm 0.4\%$ of theoretical values. For some compounds, FAB HRMS mass determinations of the molecular ion were obtained from the Nebraska Center for Mass Spectrometry. UV-Visible spectra were recorded on a Perkin-Elmer Lambda-12 spectrometer. Vapor pressure osmometry (VPO) measurements were performed on an OSMOMAT 070-SA instrument (Gonotech GmbH, Germany) in HPLC grade CHCl_3 (Fisher) at 45 °C with benzil used for calibration in CHCl_3 . For final purification, radial chromatography was carried out on Merck silica gel PF₂₅₄ with gypsum binder, preparative layer grade, using a Chromatotron (Harrison Research, Palo Alto, CA). All reagents and solvents used in the syntheses were obtained from Fisher-Acros, Aldrich, and Alfa Aesar. Deuterated chloroform was from Cambridge Isotope Laboratories. The half ester-acid chloride of adipic acid was prepared as described [16]. Pyrrolinone **7** and pyrrole-2-aldehyde were prepared previously, Refs [14] and [15], respectively.

Solution Preparation for Beer's Law Study

As in earlier studies [7, 17], a solution ($\sim 1 \times 10^{-3}$ M) was prepared in chloroform, and the UV-Vis spectrum was measured using a cell path length of 0.5 mm (using a 9.5 mm quartz spacer inside a 1 cm quartz cuvette). The initial solution was diluted by half using a volumetric flask. The UV-Vis spectrum was measured for this new solution with a cell path length of 0.5 mm. The new solution was then diluted in half and the UV-Vis spectrum was measured this time with a cell path length of 1.0 mm. The new solution was then diluted by a fifth and the UV-Vis spectrum was measured now with a path length of 1.0 cm. The new solution was then diluted by a tenth and the UV-Vis spectrum was measured again with a cell path length of 1.0 cm.

The first three measurements using 0.5 mm cell path length were normalized to a path length of 1.0 cm. A graph of normalized absorbances (at λ_{max}) vs. concentration was plotted for these experimental points. Molar absorptivity (ϵ) was calculated from a separate UV-Vis spectrum of the compound at 10^{-5} M concentration. Theoretical absorbances were calculated at known concentrations (used to determine experimental values) using Lambert-Beer's Law ($A = \epsilon \times c \times l$) (where ϵ is known and $l = 1$ cm). A graph of theoretically calculated absorbances and the experimental normalized absorbances were plotted against concentrations. Any deviation of experimental absorbances from theoretical absorbances is a

violation of Beer's Law and suggests aggregation in solution with increase of concentration [7].

5-[[1,5-Dihydro-3,4-bis(2-methoxyethoxy)-5-oxo-2H-pyrrole-2-ylidene]methyl]-1H-pyrrole-2,3-dihexanoic acid (1, C₂₇H₄₀N₂O₉)

To a solution of 30 mg of diester **2** (0.051 mmol) in 10 cm³ dry tetrahydrofuran (THF) was added 0.07 g NaOH. The solution was heated at reflux for 1.5 h under N₂, then quenched by pouring it into 100 cm³ ice-water, acidified to pH ~4, extracted into CH₂Cl₂, dried over anhyd. MgSO₄, and evaporated in vacuo. Purification by radial chromatography (eluent: CH₂Cl₂-CH₃OH, 98:2 by vol.) gave pure diacid **1**. Yield: ~20 mg (81%); m.p.: 86-89 °C; ¹H NMR: δ = 10.03 (1H, brs), 8.84 (1H, brs), 6.27 (1H, s), 6.22 (1H, s), 4.58 (2H, m), 4.28 (2H, m), 4.10 (4H, m), 3.70 (2H, m), 3.63 (2H, m), 3.43 (3H, s), 3.38 (3H, s), 2.63 (2H, t, J = 7.2 Hz), 2.41 (2H, t, J = 7.2 Hz), 2.35 (4H, m), 1.68-1.53 (8H, m), 1.40 (4H, m) ppm; ¹³C NMR data in Table 1.

Diethyl 5-[[1,5-dihydro-3,4-bis(2-methoxyethoxy)-5-oxo-2H-pyrrole-2-ylidene]methyl]-1H-pyrrole-2,3-dihexanoate (2, C₃₁H₄₈N₂O₉)

To a solution of 70 mg **3** (0.012 mmol) in ~10 cm³ dry THF cooled to 0-5 °C in an ice-water bath was added ~25 mg NaBH₄ followed by addition of 0.8 cm³ BF₃·Et₂O in ~2 cm³ dry THF. After the reaction mixture was stirred at 0-5 °C for 25 min, it was quenched by dropwise addition of CH₃OH (1-2 cm³) and then carefully with 100 cm³ H₂O. The entire solution was extracted into CH₂Cl₂, dried over anhyd. MgSO₄, and evaporated in vacuo. The crude product was purified by radial chromatography using CH₂Cl₂-CH₃OH as eluent (98:2 by vol.) to give **2**. Yield: 44 mg (64%); ¹H NMR: δ = 10.01 (1H, brs), 9.54 (1H, brs), 6.23 (1H, s), 6.21 (1H, s), 4.60 (2H, m), 4.26 (2H, m), 4.10 (4H, m), 3.70 (2H, m), 3.60 (2H, m), 3.43 (3H, s), 3.36 (3H, s), 2.65 (2H, t, J = 7.2 Hz), 2.36 (2H, t, J = 7.2 Hz), 2.27 (4H, m), 1.66-1.52 (8H, m), 1.36 (4H, m), 1.24 (6H, m) ppm; ¹³C NMR data in Table 1.

Diethyl 5-[[1,5-dihydro-3,4-bis(2-methoxyethoxy)-5-oxo-2H-pyrrole-2-ylidene]methyl]-e³-oxo-1H-pyrrole-2,3-dihexanoate (3, C₃₁H₄₆N₂O₁₀)

To a pre-cooled mixture of 308 mg of the half ethyl ester-acid chloride of adipic acid (1.6 mmol) and 4.1 cm³ 1 M SnCl₄ (4.0 mmol) in 150 cm³ CH₂Cl₂, 360 mg dipyrinone **4** (0.8 mmol) dissolved in 250 cm³ CH₂Cl₂ was added dropwise using a cannula over 1.5 h at 0-5 °C. When the addition was complete, the reaction was stirred for another 30 min in an ice-water bath. The reaction was quenched by pouring the solution into 500 cm³ ice-water and stirring for 2 h. The aqueous layer was discarded. The organic layer was washed with 10% HCl (2 × 100 cm³) then with saturated aq. NaHCO₃. The organic layer was dried, evaporated in vacuo, purified first on a chromatography column of silica gel to remove polar impurities, then by radial chromatography using CH₂Cl₂-CH₃OH (98:2 by vol.) to give **3**. Yield: 278 mg (67%); ¹H NMR: δ = 10.03 (1H, brs), 9.84 (1H, brs), 6.69 (1H, brs), 6.23 (1H, s), 4.60 (2H, m), 4.25 (2H, m), 4.12 (4H, m), 3.71 (2H, m), 3.60 (2H, m), 3.43 (3H, s), 3.36 (3H, s), 3.06 (2H, t, J = 7.2 Hz), 2.76 (2H, t, J = 7.2 Hz), 2.34 (2H, t, J = 7.2 Hz), 2.26 (2H, t, J = 7.2 Hz), 1.69-1.62 (8H, m), 1.33 (2H, m), 1.24 (6H, m) ppm; ¹³C NMR: δ = 196.6, 174.2, 173.8, 171.4, 168.8, 147.6, 144.5, 122.7, 125.2, 123.7, 121.5, 115.8, 101.2,

72.2, 71.5, 71.4, 71.3, 60.6, 60.5, 59.3, 59.0, 40.2, 34.5, 34.3, 28.9, 28.6, 27.6, 26.7, 25.0, 24.7, 24.2, 21.3, 14.5, 14.4 ppm.

Ethyl 5-[[1,5-dihydro-3,4-bis(2-methoxyethoxy)-5-oxo-2H-pyrrole-2-ylidene]methyl]-1H-pyrrole-2-hexanoate (4, C₂₃H₃₄N₂O₇)

To a solution of 500 mg **5** (1.07 mmol) in ~30 cm³ dry THF cooled to 0-5 °C in an ice-water bath was added ~160 mg of NaBH₄ followed by addition of 5 cm³ BF₃·Et₂O in ~8 cm³ dry THF. After the reaction mixture was stirred in the cold (0-5 °C) for 25 min, the reaction was quenched by dropwise addition of CH₃OH (1-2 cm³), then with 100 cm³ of water (carefully). The entire solution was extracted into CH₂Cl₂, dried over anhyd. Na₂SO₄, and evaporated in vacuo. The crude product was purified using radial chromatography (eluent: CH₂Cl₂-CH₃OH, 98:2 by vol.) to obtain **4**. Yield: 398 mg (82%); m.p.: 44-46 °C; ¹H NMR: δ = 10.37 (1H, brs), 9.95 (1H, brs), 6.34 (1H, brs), 6.29 (1H, s), 5.94 (1H, brs), 4.60 (2H, m), 4.25 (2H, m), 4.26 (2H, q, *J* = 7.5 Hz), 3.71 (2H, m), 3.65 (2H, m), 3.43 (3H, s), 3.39 (3H, s), 2.70 (2H, t, *J* = 7.2 Hz), 1.60-1.40 (8H, m), 1.24 (3H, t, *J* = 7.5 Hz) ppm; ¹³C NMR: δ = 174.0, 168.5, 148.2, 139.6, 126.1, 125.0, 120.8, 116.8, 107.8, 103.2, 72.0, 71.6, 71.3, 71.2, 60.4, 59.3, 59.0, 34.4, 31.1, 29.2, 28.8, 27.8, 24.9, 14.4 ppm.

Ethyl 5-[[1,5-dihydro-3,4-bis(2-methoxyethoxy)-5-oxo-2H-pyrrole-2-ylidene]methyl]-ε-oxo-1H-pyrrole-2-hexanoate (5, C₂₃H₃₂N₂O₈) and ethyl 5-[[1,5-dihydro-3,4-bis(2-methoxyethoxy)-5-oxo-2H-pyrrole-2-ylidene]methyl]-ε-oxo-1H-pyrrole-3-hexanoate (9, C₂₃H₃₂N₂O₈)

To a pre-cooled mixture of 406 mg of the half ethyl ester-acid chloride of adipic acid (2.11 mmol) and 5.4 cm³ 1 M SnCl₄ (5.28 mmol) in 150 cm³ CH₂Cl₂, 325 mg dipyrinone **6** (1.06 mmol) dissolved in 250 cm³ CH₂Cl₂ was added dropwise using a cannula over 1.5 h at 0-5 °C. After the addition was complete, the reaction was stirred for another 30 min in an ice-water bath. The reaction was quenched by pouring the solution into 500 cm³ ice-water and stirring for 2 h. The aqueous layer was discarded. The organic layer was washed with 10% HCl (2 × 100 cm³) then with saturated aq. NaHCO₃, dried, and evaporated in vacuo. It was purified first by column chromatography on silica gel (eluent: CH₂Cl₂-CH₃OH) to remove polar impurities, then by radial chromatography (eluent: CH₂Cl₂-CH₃OH, 98:2 by vol.) to obtain a mixture of both regioisomers. Yield: **5** (260 mg, 43%) and **9** (320 mg, 53%); m.p. of **5**: 155-157°C; ¹H NMR of **5**: δ = 9.69 (1H, brs), 7.85 (1H, brs), 6.94 (1H, s), 6.40 (1H, brs), 6.15 (1H, s), 4.61 (2H, m), 4.36 (2H, m), 4.12 (2H, q, *J* = 7.5 Hz), 3.71 (2H, m), 3.65 (2H, m), 3.43 (3H, s), 3.39 (3H, s), 2.80 (2H, t, *J* = 7.2 Hz), 2.33 (2H, t, *J* = 7.2 Hz), 1.70 (4H, m), 1.24 (3H, t, *J* = 7.5 Hz) ppm; ¹³C NMR of **5**: δ = 190.4, 173.6, 167.9, 145.8, 133.4, 132.8, 129.8, 126.6, 118.5, 112.7, 97.9, 71.7, 71.6, 71.5, 71.2, 60.6, 59.3, 59.0, 37.8, 34.3, 24.9, 24.8, 14.5 ppm; ¹H NMR of **9**: δ = 10.55 (1H, brs), 10.22 (1H, brs), 7.64 (1H, t, *J* = 1.5 Hz), 6.78 (1H, t, *J* = 1.5 Hz), 6.29 (1H, s), 4.62 (2H, m), 4.34 (2H, m), 4.10 (2H, q, *J* = 7.5 Hz), 3.72 (2H, m), 3.67 (2H, m), 3.42 (3H, s), 3.40 (3H, s), 2.78 (2H, t, *J* = 7.5 Hz), 2.34 (2H, t, *J* = 7.5 Hz), 1.70 (2H, m), 1.24 (3H, t, *J* = 7.5 Hz) ppm; ¹³C NMR of **9**: δ = 195.7, 173.7, 168.9, 147.0, 128.5, 127.1, 126.9, 125.5, 124.5, 113.9, 101.1, 71.9, 71.7, 71.5, 71.1, 60.5, 59.2, 59.1, 39.3, 34.4, 24.9, 24.3, 19.4 ppm.

1,5-Dihydro-3,4-bis(2-methoxyethoxy)-5-(1H-pyrrol-2-ylmethylene)-2H-pyrrol-2-one (6, C₁₅H₂₀N₂O₅) and 1,5-dihydro-4-methoxy-3-(2-methoxyethoxy)-5-(1H-pyrrol-2-ylmethylene)-2H-pyrrol-2-one (8, C₁₃H₁₆N₂O₄)

To a mixture of 2.2 g pyrrole-2-carbaldehyde (25 mmol) and 5.76 g MEG pyrrolinone **7** (27 mmol) in 100 cm³ of CH₃OH was added 6.9 g solid KOH. The entire reaction mixture was then heated at reflux under N₂ for 36 h. The reaction was quenched by addition of H₂O. The aqueous solution was extracted into CH₂Cl₂, dried over anhyd. Na₂SO₄, and evaporated in vacuo. The resulting solid was purified first on a column (eluent: 5% CH₃OH in CH₂Cl₂) to remove very polar impurities, then by radial chromatography using ethyl acetate-hexane (1:1 by vol.) to obtain 80% pure bis-ethylene glycol dipyrrolinones **6** and 20% of **8**. Yield of **6**: 2.59 g (80%); **8**: 0.55g (20%); m.p. of **6**: 126-128 °C; ¹H NMR of **6**: δ = 10.26 (1H, brs), 10.18 (1H, brs), 7.02 (1H, brs), 6.42 (1H, brs), 6.35 (1H, s), 4.62 (2H, m), 4.35 (2H, m), 3.73 (2H, m), 3.68 (2H, m), 3.44 (3H, s), 3.42 (3H, s) ppm; ¹³C NMR: δ = 168.8, 147.4, 27.3, 125.1, 123.3, 122.1, 115.9, 110.2, 102.9, 71.9, 71.6, 71.5, 71.1, 59.4, 59.2 ppm.

5-[[1,5-Dihydro-3,4-bis(2-methoxyethoxy)-5-oxo-2H-pyrrole-2-ylidene]methyl]-1H-pyrrole-3-hexanoic acid (10, C₂₃H₃₄N₂O₇)

To a solution of 130 mg dipyrrolinone **9** (0.28 mmol) dissolved in 2-isopropanol was added 73 mg NaBH₄, and the entire mixture was heated at reflux for 1.5 h. The reaction was quenched by pouring the solution into ice-water acidified to pH ~4, extracted into CH₂Cl₂, dried over anhyd. Na₂SO₄, and evaporated in vacuo. The crude solid was dissolved in 15 cm³ THF and 2 cm³ CH₃OH. To it was added 0.1 g NaOH, and the mixture was heated at reflux for 1 h. The reaction was quenched by pouring the solution into ice-water, acidified to pH ~4 using HCl, extracted into CH₂Cl₂, and dried over anhyd. Na₂SO₄. The crude material was purified by radial chromatography (eluent: CH₂Cl₂-CH₃OH, 98:2 by vol.) to obtain a trace amount of **10**. ¹H NMR: δ = 11.86 (1H, brs), 9.67 (1H, brs), 8.81 (1H, brs), 6.68 (1H, brs), 6.41 (1H, brs), 6.20 (1H, s), 4.59 (2H, m), 4.30 (2H, m), 3.70 (2H, m), 3.64 (2H, m), 3.43 (3H, s), 3.39 (3H, s), 2.49 (2H, t, *J* = 7.2 Hz), 2.39 (2H, t, *J* = 7.2 Hz), 1.68-1.62 (4H, m), 1.43 (2H, m) ppm; ¹³C NMR: δ = 178.9, 169.2, 146.9, 139.8, 127.0, 125.2, 123.6, 119.4, 113.9, 108.3, 102.0, 71.8, 71.59, 71.57, 71.0, 59.3, 59.0, 33.9, 30.8, 28.5, 26.5, 24.5, 14.2 ppm.

5-[[1,5-Dihydro-3,4-bis(2-methoxyethoxy)-5-oxo-2H-pyrrole-2-ylidene]methyl]-1H-pyrrole-2-hexanoic acid (11, C₂₁H₃₀N₂O₇)

To a solution of 100 mg of ester **4** (0.022 mmol) in 10 cm³ dry THF was added 0.02 g NaOH. The mixture was heated at reflux for 1.5 h under N₂, then quenched by pouring it into 100 cm³ ice-water acidified to pH ~4. The crude product was extracted in CH₂Cl₂, dried, evaporated in vacuo, and purified by radial chromatography (eluent: CH₂Cl₂-CH₃OH, 98:2 by vol.) to give pure acid **11**. Yield: 89 mg (96%); ¹H NMR: δ = 12.91 (1H, brs), 10.22 (1H, brs), 9.17 (1H, brs), 6.31 (1H, t, *J* = 2.3 Hz), 6.27 (1H, s), 5.94 (1H, t, *J* = 2.3 Hz), 4.60 (2H, m), 4.29 (2H, m), 3.69 (2H, m), 3.64 (2H, m), 3.43 (3H, s), 3.39 (3H, s), 2.75 (2H, t, *J* = 7.2 Hz), 2.47 (2H, t, *J* = 7.2 Hz), 1.68-1.53 (4H, m), 1.42 (2H, m) ppm; ¹³C NMR data in Table 1.

1,5-Dihydro-3,4-bis(2-methoxyethoxy)-5-(5-butanoyl-1H-pyrrol-2-ylmethylene)-2H-pyrrol-2-one (12, C₁₉H₂₆N₂O₆)

To a pre-cooled mixture of 208 mg butyryl chloride (1.95 mmol) and 6.7 cm³ 1 M SnCl₄ in CH₂Cl₂ (6.5 mmol) in 150 cm³ CH₂Cl₂, 400 mg dipyrinone **6** (1.29 mmol) dissolved in 250 cm³ CH₂Cl₂ was added dropwise using a cannula over 1.5 h at 0-5 °C. When the addition was complete, the reaction was stirred for another 30 min in an ice-water bath. The reaction was quenched by pouring the solution into 500 cm³ ice-water and stirring for 2 h. The aqueous layer was discarded. The organic layer was washed with 10% HCl (2 × 100 cm³), then with saturated aq. NaHCO₃, dried, and evaporated in vacuo to obtain pure **12**. Yield: 470 mg (96%); ¹H NMR: δ = 9.99 (1H, brs), 8.09 (1H, brs), 6.93 (1H, brm), 6.40 (1H, brm), 6.12 (1H, s), 4.60 (2H, m), 4.38 (2H, m), 3.70 (2H, m), 3.65 (2H, m), 3.43 (3H, s), 3.39 (3H, s), 2.76 (2H, t, *J* = 7.2 Hz), 1.76 (2H, q, *J* = 7.2 Hz), 0.99 (3H, t, *J* = 7.2 Hz) ppm; ¹³C NMR: δ = 199.1, 167.6, 145.7, 133.4, 133.1, 129.8, 126.6, 118.4, 112.6, 97.6, 71.6, 71.6, 71.5, 71.2, 59.3, 59.0, 40.1, 19.1, 14.2 ppm.

1,5-Dihydro-3,4-bis(2-methoxyethoxy)-5-(5-butyl-1H-pyrrol-2-ylmethylene)-2H-pyrrol-2-one (13, C₁₉H₂₈N₂O₅)

To a solution of 230 mg **12** (0.61 mmol) in ~30 cm³ dry THF cooled to 0-5 °C in an ice-water bath was added ~85 mg of NaBH₄, followed by the addition of 3 cm³ BF₃·Et₂O in ~8 cm³ dry THF. After the reaction mixture was stirred in the cold (0-5 °C) for 25 min, it was quenched by dropwise addition of CH₃OH (1-2 cm³) and then with 100 cm³ H₂O (carefully). The solution was extracted by CH₂Cl₂, dried over anhyd. Na₂SO₄, and evaporated in vacuo. The crude product was purified by radial chromatography using CH₂Cl₂-CH₃OH (98:2 by vol.) as eluent to obtain **13**. Yield: 160 mg (72%); ¹H NMR: δ = 10.07 (1H, brs), 9.70 (1H, brs), 6.33 (1H, brt, *J* = 2.5 Hz), 6.28 (1H, s), 5.97 (1H, brt), 4.61 (2H, m), 4.28 (2H, m), 3.71 (2H, m), 3.59 (2H, m), 3.43 (3H, s), 3.39 (3H, s), 2.72 (2H, t, *J* = 7.2 Hz), 1.76 (2H, m), 1.43 (2H, m), 0.99 (3H, t, *J* = 7.2 Hz) ppm; ¹³C NMR: δ = 168.5, 148.0, 139.8, 126.0, 125.2, 121.1, 116.4, 107.8, 103.0, 72.0, 71.6, 71.4, 71.2, 59.3, 59.0, 31.7, 27.8, 22.6, 14.2 ppm.

Ethyl 2-butyl-5-[[1,5-dihydro-3,4-bis(2-methoxyethoxy)-5-oxo-2H-pyrrole-2-ylidene]methyl]-e-oxo-1H-pyrrole-3-hexanoate (14, C₂₇H₄₀N₂O₈)

To a pre-cooled mixture of 212 mg of half ethyl ester-acid chloride of adipic acid (1.1 mmol) and 2.8 cm³ 1 M SnCl₄ (2.8 mmol) in 150 cm³ CH₂Cl₂, 200 mg dipyrinone **13** (0.55 mmol) dissolved in 100 cm³ CH₂Cl₂ was added dropwise using a cannula over 1.0 h at 0-5 °C. After the addition was complete, the reaction mixture was stirred for another 30 min in an ice-water bath. The reaction was quenched by pouring the solution into 200 cm³ ice-water and stirring for 2 h. The aqueous layer was discarded. The organic layer was washed with 10% HCl (2 × 100 cm³) then with aq. saturated NaHCO₃. The organic layer was dried, evaporated in vacuo, purified first on a column of silica gel to remove polar impurities, then by radial chromatography using CH₂Cl₂-CH₃OH (98:2 by vol.) to give **14**. Yield: 220 mg (78%); ¹H NMR: δ = 10.23 (1H, brs), 10.04 (1H, brs), 6.70 (1H, brs), 6.25 (1H, s), 4.60 (2H, m), 4.25 (2H, m), 4.13 (4H, q, *J* = 7.2 Hz), 3.71 (2H, m), 3.60 (2H, m), 3.43 (3H, s), 3.36 (3H, s), 3.08 (2H, t, *J* = 7.2 Hz), 2.76 (2H, t, *J* = 7.2 Hz), 2.34 (2H, t, *J* = 7.2 Hz), 1.69-1.62

(4H, m), 1.33 (4H, m), 1.24 (3H, t, $J = 7.2$ Hz), 0.99 (3H, t, $J = 7.2$ Hz) ppm; ^{13}C NMR: $\delta = 196.5, 173.8, 169.0, 147.9, 145.5, 125.5, 125.0, 123.2, 121.4, 116.6, 101.8, 72.2, 71.5, 71.3, 71.3, 60.5, 59.3, 59.1, 40.2, 34.5, 31.7, 26.7, 25.0, 24.2, 22.6, 14.5, 14.2$ ppm.

2-Butyl-5-[[1,5-dihydro-3,4-bis(2-methoxyethoxy)-5-oxo-2H-pyrrole-2-ylidene]methyl]-1H-pyrrole-3-hexanoic acid (16, C₂₅H₃₈N₂O₇)

To a solution of 100 mg **14** (0.19 mmol) in ~30 cm³ dry THF cooled to 0–5 °C in an ice-water bath was added ~60 mg NaBH₄ followed by the addition of 2 cm³ BF₃·Et₂O in ~8 cm³ dry THF. After the reaction mixture was stirred in the cold (0–5 °C) for 25 min, it was quenched by dropwise addition of CH₃OH (1–2 cm³), then with 100 cm³ H₂O (carefully). The solution was extracted using CH₂Cl₂, dried over anhyd. Na₂SO₄, and evaporated in vacuo. The crude product was purified by radial chromatography using CH₂Cl₂–CH₃OH (98:2 by vol.) as eluent to obtain reduced product **15**. Yield: 40 mg (41%); ^1H NMR: $\delta = 9.47$ (1H, brs), 9.04 (1H, brs), 6.20 (2H, brs), 4.60 (2H, m, 2H), 4.25 (2H, m), 4.13 (4H, q, $J = 7.2$ Hz), 3.71 (2H, m), 3.60 (2H, m), 3.43 (3H, s), 3.36 (3H, s), 2.62 (2H, t, $J = 7.2$ Hz), 2.37 (2H, t, $J = 7.2$ Hz), 2.34 (4H, t, $J = 7.2$ Hz), 1.69–1.62 (4H, m), 1.33 (4H, m), 1.24 (3H, t, $J = 7.2$ Hz), 0.99 (3H, t, $J = 7.2$ Hz, 3H).

The crude product (40 mg, 0.08 mmol) from above was dissolved in 10 cm³ dry THF in a 50 cm³ round bottom flask, and to it was added 0.02 g NaOH. The mixture was heated at reflux for 1 h under N₂, and then quenched by pouring the solution into 100 cm³ ice-water acidified to pH ~4. It was extracted in CH₂Cl₂, dried over anhyd. Na₂SO₄, evaporated in vacuo, and purified by radial chromatography, eluting with CH₂Cl₂–CH₃OH (98:2 by vol.) to give pure acid **16**. Yield: 20 mg (54%); ^1H NMR: $\delta = 9.71$ (1H, brs), 8.54 (1H, brs), 6.37 (1H, s), 6.18 (1H, s), 4.58 (2H, m), 4.28 (2H, m), 3.69 (2H, m), 3.63 (2H, m), 3.43 (3H, s), 3.38 (3H, s), 2.56 (2H, t, $J = 7.2$ Hz), 2.37 (4H, m), 1.68–1.53 (6H, m), 1.40 (2H, m), 1.32 (2H, m), 0.99 (3H, t, $J = 7.2$ Hz) ppm; ^{13}C NMR data in Table 1.

Ethyl 3-butanoyl-5-[[1,5-dihydro-3,4-bis(2-methoxyethoxy)-5-oxo-2H-pyrrole-2-ylidene]methyl]-1H-pyrrole-2-hexanoate (17, C₂₇H₄₀N₂O₈)

To a pre-cooled mixture of 0.08 cm³ butyryl chloride (0.62 mmol) and 2.6 cm³ 1 M SnCl₄ in CH₂Cl₂ (2.5 mmol) in 100 cm³ CH₂Cl₂, 230 mg dipyrinone **4** (0.51 mmol) dissolved in 150 cm³ CH₂Cl₂ was added dropwise using a cannula over 1.5 h at 0–5 °C. When the addition was complete, the reaction mixture was stirred for another 30 min in an ice-water bath. The reaction was quenched by pouring the solution into 300 cm³ ice-water and stirring for 2 h. The aqueous layer was discarded. The organic layer was washed with 10% HCl (2 × 100 cm³), then with saturated aq. NaHCO₃, dried over anhyd. Na₂SO₄, and evaporated in vacuo to obtain pure **17**. Yield: 260 (95%); ^1H NMR: $\delta = 10.03$ (1H, brs), 9.90 (1H, brs), 6.70 (1H, brs), 6.25 (1H, s), 4.62 (2H, m), 4.25 (2H, m), 4.08 (4H, q, $J = 7.2$ Hz), 3.71 (2H, m), 3.60 (2H, m), 3.43 (3H, s), 3.36 (3H, s), 3.08 (2H, t, $J = 7.2$ Hz), 2.72 (2H, t, $J = 7.2$ Hz), 2.26 (2H, t, $J = 7.2$ Hz), 1.73–1.62 (6H, m), 1.34 (2H, m), 1.24 (3H, t, $J = 7.2$ Hz), 0.99 (3H, t, $J = 7.2$ Hz) ppm; ^{13}C NMR: $\delta = 197.2, 174.2, 168.8, 147.8, 144.6, 125.6, 125.0, 123.4, 121.7, 116.2, 101.5, 72.2, 71.5, 71.4, 71.3, 60.5, 59.3, 59.1, 42.3, 34.3, 29.0, 28.6, 26.7, 24.7, 18.2, 14.4, 14.2$ ppm.

Ethyl 3-butyl-5-[[1,5-dihydro-3,4-bis(2-methoxyethoxy)-5-oxo-2H-pyrrole-2-ylidene]methyl]-1H-pyrrole-2-hexanoate (18, C₂₇H₄₂N₂O₇)

To a solution of 260 mg **17** (0.50 mmol) in ~30 cm³ dry THF cooled to 0-5 °C in an ice-water bath was added ~92 mg NaBH₄ followed by the addition of 3 cm³ BF₃·Et₂O in ~8 cm³ dry THF. After the reaction mixture was stirred in the cold (0-5 °C) for 35 min, it was quenched by dropwise addition of CH₃OH (1-2 cm³) and then with 100 cm³ H₂O (carefully). The resulting solution was extracted into CH₂Cl₂, dried over anhyd. Na₂SO₄, and evaporated in vacuo. The crude product was purified by radial chromatography using CH₂Cl₂-CH₃OH as eluent (98:2 by vol.) to obtain **18**. Yield: 105 mg (42%); ¹H NMR: δ = 9.97 (1H, brs), 9.51 (1H, brs), 6.24 (1H, s), 6.21 (1H, s), 4.60 (2H, m, 2H), 4.27 (2H, m), 4.09 (4H, q, *J* = 7.2 Hz), 3.70 (2H, m), 3.60 (2H, m), 3.43 (3H, s), 3.36 (3H, s), 2.66 (2H, t, *J* = 7.2 Hz), 2.36 (2H, t, *J* = 7.2 Hz), 2.27 (2H, t, *J* = 7.2 Hz), 1.62 (4H, m), 1.50 (2H, m), 1.33 (4H, m), 1.24 (3H, t, *J* = 7.2 Hz), 0.92 (3H, t, *J* = 7.2 Hz); ¹³C NMR: δ = 174.1, 168.2, 148.0, 135.4, 125.1, 125.0, 122.7, 120.8, 116.5, 102.9, 71.9, 71.5, 71.2, 70.8, 60.4, 59.3, 59.0, 34.4, 33.2, 29.9, 28.7, 26.7, 25.9, 25.5, 24.9, 22.7, 14.4, 14.2 ppm.

3-Butyl-5-[[1,5-dihydro-3,4-bis(2-methoxyethoxy)-5-oxo-2H-pyrrole-2-ylidene]methyl]-1H-pyrrole-2-hexanoic acid (19, C₂₅H₃₈N₂O₇)

A solution of 105 mg **18** (0.21 mmol) was dissolved in 20 cm³ dry THF and 2 cm³ CH₃OH in a 50 cm³ round bottom flask, and to it was added 0.02 g NaOH. The mixture was heated at reflux for 1.5 h under N₂, then quenched by pouring it into 100 cm³ ice-water acidified to pH ~4. It was extracted in CH₂Cl₂, dried, evaporated in vacuo, and purified by radial chromatography eluting with CH₂Cl₂-CH₃OH (98:2 by vol.) to give pure acid **19**. Yield: 88 mg (89%); ¹H NMR: δ = 13.12 (2H, brs), 10.18 (1H, brs), 8.97 (1H, brs), 6.23 (1H, s), 6.21 (1H, s), 4.58 (2H, m), 4.28 (2H, m), 3.69 (2H, m), 3.63 (2H, m), 3.43 (3H, s), 3.38 (3H, s), 2.68 (2H, t, *J* = 7.2 Hz), 2.47 (2H, t, *J* = 7.2 Hz), 2.35 (2H, t, *J* = 7.2 Hz), 1.71 (2H, m), 1.68-1.41 (6H, m), 1.34 (2H, m), 0.99 (3H, t, *J* = 7.2 Hz) ppm; ¹³C NMR data in Table 1.

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Fig. 1. Structures of (A) intramolecularly hydrogen bonded bilirubin, (B) [6]-semirubin, (C) intermolecularly hydrogen bonded [6]-semirubin methyl ester, and (D) "H"-confused analog of [6]-semirubin with C-H hydrogen bonding

Fig. 2.

Equilibrating conformations of (4Z)-dipyrinone. Molecular mechanics calculations (PCMODEL, MMX forcefield) predict the *syn*-(Z) to be more stable than the *anti*-(Z) by 1.7 kJ mol⁻¹ when R = H and by 4 kJ mol⁻¹ when R = CH₃. When R = H the C(4)-C(5)-C(6)-N torsion angles are predicted by molecular mechanics calculations to be 25° and 42° in the *syn* and *anti* conformers, respectively; when R = CH₃, they are predicted to be 28° and 55°, respectively

Fig. 3.

The (4*Z*)-configuration target dipyrinone **1** in *syn* and *anti* conformations (upper) stabilized by intramolecular hydrogen bonding, lactam to carboxylic acid (lower). In the *syn*-(*Z*) conformation, additional stabilization comes from the pyrrole N-H; in the *anti*-(*Z*) additional stabilization might come from the C(7)-H. R = R' = CH₃OCH₂CH₂O-

Fig. 4.

Theoretical and experimental plots of Beer's Law for **1**, constructed as described in the Experimental section

Fig. 5. Concentration dependent ^1H NMR of (A) C(5)-H at $\delta = 6.22$ ppm and C(7)-H at $\delta = 6.27$, and (B) pyrrole NH at $\delta = 8.98$ ppm and lactam NH $\delta = 10.0$ ppm of semirubin **1** in CDCl_3 solvent at 25°C

Fig. 6. Selected $^1\text{H}\{^1\text{H}\}$ NOEs observed in model [6]-semirubins **16** and **19** in CDCl_3 are indicated by curved double headed arrows (solid for strong NOEs and dotted for weak NOEs)

Fig. 7. Variable temperature ^1H NMR chemical shift of semirubin **1** in CDCl_3 solvent at 1×10^{-2} M pigment concentration over the range of $+25^\circ\text{C}$ to -90°C

Scheme 2.

i, KOH/CH₃OH, reflux 36 h, 47%; ii, EtO₂C(CH₂)₄COCl, SnCl₄/CH₂Cl₂, 0-5 °C, 2 h; iii, NaBH₄-BF₃·Et₂O, 0-5 °C, 25 min; iv, NaOH/CH₃OH-THF (1:5), reflux 1.5 h; v, NaBH₄/i-PrOH, reflux 1.5 h, NaOH/CH₃OH, reflux 1 h

Scheme 3.

i, CH₃CH₂CH₂COCl, SnCl₄/CH₂Cl₂, 0-5 °C, stir 1 h; ii, NaBH₄-BF₃·Et₂O, 0-5 °C, 45 min; iii, EtO₂(CH₂), COCl, SnCl₄, CH₂Cl₂, 0-5 °C, stir 2 h; iv NaOH/THF-CH₃OH, reflux 1 h

Table 1¹³C NMR^a of semirubin acids **1**, **19**, **16**, and **11**, esters **2** and **4**, and dipyrinone **6**

Position	Carbon ^b	1	19	16	11	2	4	6
1	C=O	169.2	169.2	168.9	169.4	168.3	168.6	168.8
2	–C=	125.2	125.2	124.7	126.5	125.1	126.0	125.1
3	–C=	147.4	147.6	147.2	147.6	148.0	148.1	147.4
5	–CH=	103.1	103.3	102.5	103.2	102.2	103.3	102.9
6	–C=	121.1	120.5	122.0	120.9	120.9	120.7	122.1
4	–C=	125.2	125.1	125.2	125.2	125.1	125.0	123.3
7	–C=	116.4	117.5	114.8	117.1	116.5	117.0	115.9
8	–C=	122.5	122.6	122.9	108.3	122.3	107.8	110.2
9	–C=	135.2	136.0	134.2	139.8	135.4	139.7	127.3
2 ²	CH ₂	71.6	71.6	71.6	71.6	70.9	71.6	71.6
2 ³	CH ₂	71.0	71.1	71.1	71.2	71.4	71.2	71.1
2 ⁵	CH ₃	59.2	59.3	59.2	59.3	59.1	59.3	59.4
3 ²	CH ₂	71.8	71.8	71.8	71.9	71.6	72.0	71.9
3 ³	CH ₂	71.6	71.6	71.6	71.6	71.3	71.4	71.5
3 ⁵	CH ₃	59.0	59.0	59.0	59.1	59.1	59.1	59.2
8 ¹	CH ₂	24.5	24.5	24.7	–	25.6	–	–
8 ²	CH ₂	23.2	27.8	22.6	–	24.9	–	–
8 ³	CH ₂	27.8	25.3	28.7	–	28.7	–	–
8 ⁴	CH ₂ (CH ₃)	29.5	14.2	30.6	–	30.8	–	–
8 ⁵	CH ₂	33.7	–	34.3	–	34.5	–	–
8 ⁶	C=O	179.2	–	178.8	–	174.0	–	–
8 ⁷	CH ₂	–	–	–	–	60.4	–	–
8 ⁸	CH ₃	–	–	–	–	14.4	–	–
9 ¹	CH ₂	25.4	25.3	26.7	27.9	25.9	27.9	–
9 ²	CH ₂	24.8	22.7	30.6	26.8	25.1	26.3	–
9 ³	CH ₂	29.0	26.7	22.6	23.4	29.2	25.0	–
9 ⁴	CH ₂ (CH ₃)	30.8	29.5	14.7	29.7	29.9	29.0	–
9 ⁵	CH ₂	34.3	34.1	–	34.2	34.5	34.6	–
9 ⁶	C=O	180.0	180.7	–	180.4	174.1	174.0	–
9 ⁷	CH ₂	–	–	–	–	60.4	60.5	–
9 ⁸	CH ₃	–	–	–	–	14.5	14.5	–

^aDetermined for $\sim 1 \times 10^{-3}$ M concentrations in CDCl₃. For position numbering see Scheme 1.

Table 2Molecular weight determination of semirubins at 45 °C in CHCl₃ solution^a by vapor pressure osmometry^b

Compound	Formula weight /g mol ⁻¹	Experimental molecular weight in CHCl ₃ /g mol ⁻¹
1	536.6	598 ± 34
11	422.5	473 ± 27
16	478.6	503 ± 27
19	478.6	490 ± 23
15	506.6	894 ± 18

^a Conc. range: 3.1-12.8 × 10⁻³ mol kg⁻¹.^b Calibrated with benzil (FW = 210 g mol⁻¹, MW = 220 ± 15 g mol⁻¹).

Table 3

Solvent-dependence of the UV-Vis spectral data^a of dipyrinones **1**, **5**, **6**, and **11**

Dipyrinone	Solvent					
	C ₆ H ₆	CHCl ₃	(CH ₃) ₂ CO	CH ₃ OH	CH ₃ CN	(CH ₃) ₂ SO
1	405 (29500)	404 (27600)	395 (31000)	401 (30900)	395 (31000)	399 (30800)
11	392 (25000)	393 (24800)	383 (27000)	390 (27200)	382 (26800)	389 (26700)
6	365 (29200)	366 (27500)	362 (28950)	370 (30000)	361 (28900)	371 (31000)
5	370 (32600)	370 (36500)	368 (40400)	372 (40900)	366 (40400)	375 (49300)
			386 (37600) ^b	390 (38700) ^b	383 (37000) ^b	394 (37600) ^b

^a Data shown as molar absorption coefficients ($\epsilon_{\text{max}}/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$) in parentheses following $\lambda_{\text{max}}/\text{nm}$ for $\sim 1.4 \times 10^{-5}$ M concentrations at 22 °C with 2% (vol.) CHCl₃ present in the non-CHCl₃ solutions;

^b Shoulders (or) inflections were determined from first and second derivative spectra.

Table 4

Chemical shifts /ppm of lactam NH (^LNH), pyrrole NH (^PNH), C(5)-H, and C(7)-H in ¹H NMR of model semirubins and their esters in CDCl₃^a

		25 °C	10 °C	0 °C	-10 °C	-25 °C	-35 °C
1	^L NH	9.896	9.93	10.014	10.042	10.082	10.171
		9.875	9.97	10.042	10.102	10.174	10.216
	^P NH	8.813	8.85	8.888	8.932	8.998	9.001
		8.749	8.784	8.812	8.837	8.886	8.925
	C(5)-H	6.193	6.190	6.186	6.183	6.169	6.125
		6.209	6.194	6.177	6.166	6.155	6.147
16	^L NH	9.541	9.691	9.784	9.864	9.947	9.975
	^P NH	8.500	8.572	8.628	8.685	8.780	8.836
	C(7)-H	6.410	6.416	6.421	6.428	6.431	6.435
	C(5)-H	6.159	6.157	6.155	6.152	6.140	6.127
15	^L NH	9.330	9.490	9.60	9.673	9.729	9.810
	^P NH	8.980	9.115	9.214	9.360	9.490	9.530
	C(7)-H	6.198	6.190	6.193	6.193	6.199	6.198
	C(5)-H	6.170	6.160	6.172	6.174	6.180	6.179
19	^L NH	10.208	10.25	10.30	10.341	10.401	10.457
	^P NH	8.998	8.993	8.995	8.989	8.992	9.014
	C(7)-H	6.235	6.225	6.220	6.214	6.214	6.214
	C(5)-H	6.259	6.230	6.199	6.180	6.170	6.166
b	^L NH	9.603	9.821	9.917	9.969	10.051	10.241
	^P NH	8.230	8.369	8.410	8.434	8.457	8.501
	C(7)-H	6.504	6.506	6.504	6.501	6.495	6.490
	C(5)-H	6.024	6.028	6.028	6.026	6.023	6.030

^aConcentration range of 9-10 × 10⁻² M.

^bData from Ref. [12].