Synthesis and Properties of Thiolactam Analogs of Pyrromethenones

Meiqiang Xie and David A. Lightner*

Department of Chemistry, University of Nevada,
Reno, Nevada 89557-0020

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Thiolactam analogs of kryptopyrromethenone and xanthobilirubic acid methyl ester were prepared from the parent pyrromethenone using Lawesson's reagent and are shown to form dimeric association complexes through intermolecular hydrogen bonding.

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Introduction.

Normal human metabolism produces and excretes ~300 mg/individual/day of the yellow-orange cytotoxic pigment of jaundice, (4*Z*,15*Z*)-bilirubin-IXα, which has a remarkable tendency to form intramolecular hydrogen bonds and thereby control its shape, polarity, solution properties and, apparently, its metabolism [1-4]. Consequently, investigations into the nature of hydrogen bonding in bile pigments and their analogs is of considerable importance to providing an understanding of pigment three-dimensional stereochemistry and the relationship between conformation and amphiphilicity, between bilirubin conformation and bilirubin transport and hepatic excretion.

The three features that together have a dominating effect on the shape of bilirubin include: (i) two pyrromethenone chromophores, each in a *syn*-periplanar conformation with *Z*-configuration C=C bonds (at C-4 and C-15); and (ii) an sp^3 carbon at C-10, which constrains the molecule to bend in the middle and allows the two pyrromethenone chromophores to rotate independently about the C-9,10 and C-10,11 single bonds; and (iii) two propionic acid groups, located at C-8 and C-12, which can form intramolecular hydrogen bonds with the pyrrole and lactam functions in the opposite half of the molecule. The preference for intramolecularly hydrogen-bonded conformers in which polar groups are neutralized internally explains why bilirubin exhibits lipophilic behavior and requires glucuronidation for excretion. It also explains why analogs with vinyl groups reduced to ethyl, *e.g.*, mesobilirubin, or with methyl and vinyl groups interchanged at C-2/C-3 or C-17/C-18, *e.g.*, the symmetrical bilirubins [5] and mesobilirubins IIIα and XIIIα, all exhibit similar solubility properties, *e.g.* soluble in chloroform, insoluble in methanol; insoluble in dilute aqueous bicarbonate. However, isomers that do not have their propionic acid groups located at C-8 and C-12 have been shown to have very different solubility properties, *viz.* insoluble in chloroform, soluble in methanol; soluble in dilute aqueous bicarbonate [6].

As part of a program to prepare bilirubin analogs with perturbations on the intramolecular hydrogen bonding network, we began to synthesize the thiolactam derivatives of bilirubin. One route involves a total synthesis proceeding through pyrromethenethiones to the thiobili-

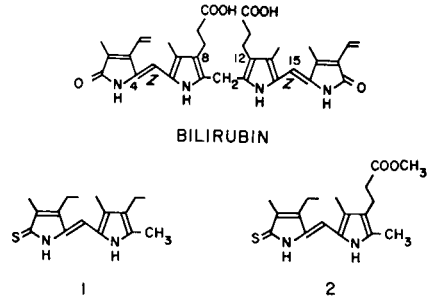


Figure 1. (Upper) Linear representation of (4*Z*,15*Z*)-bilirubin-IXα (BR-IX). (Lower) Kryptopyrromethenethione (1) and Thioxanthobilirubic Acid Methyl Ester (2).

Table 1

Ultraviolet-Visible Spectra of Pyrromethenethiones and Pyrromethenones [a]

	Methanol		Chloroform		Dimethyl sulfoxide	
	[b] λ max	ε ($cm^{-1}M^{-1}$)	λ max	ε ($cm^{-1}M^{-1}$)	[b] λ max	ε ($cm^{-1}M^{-1}$)
Kryptopyrromethenethione (**1**)	485	34,500	493	32,200	484	33,700
Kryptopyrromethenone	416	39,400	409	33,900	415	35,600
Thioxanthobilirubic Acid Methyl Ester (**2**)	481	32,000	489	32,500	482	31,100
Xanthobilirubic Acid Methyl Ester	411	37,700	408	34,000	410	34,000

[a] Spectra run on 1 x 10^{-5} *M* solutions at 20°. [b] In nanometers.

rubin. Another route involves direct conversion of bilirubins to their thiolactam analogs. In the current work we present our syntheses and properties of the first pyrromethenones with thiolactam groups, kryptopyrromethenethione (**1**) and thioxanthobilirubic acid methyl ester (**2**).

Synthesis and Spectroscopic Properties.

In order to provide a model compound for comparative studies of the influence of a thiocarbonyl on the lactam N-*H* chemical shifts and to calibrate the experimental method for converting lactams to thiolactams, ε-caprolactam was converted to ε-caprothiolactam in 81% yields using Lawesson's reagent. Conversion of kryptopyrromethenone [7] and xanthobilirubic acid methyl ester [7,8] to **1** and **2**, respectively, proceeded smoothly in 82% and 83% isolated yields.

The uv-visible spectra of **1** and **2** (Table 1) show an expected bathochromic shift of the long wavelength excitation, from near 415 in the oxo analogs to near 480 in the thio; however, the molar extinction coefficient, ε, of the oxo and thio pyrromethenones are essentially the same in the range of solvents studied. Interestingly, in chloroform solvent, where dimeric association might be anticipated [9], the thiones show a clear bathochromic shift in their long wavelength λ max; whereas, the corresponding oxo analogs show a slight hypsochromic shift in going from the more polar, hydrogen-bonding methanol and dimethyl sulfoxide. This is currently unexplained but may be related to differing tendencies to form dimers.

The N-H chemical shifts in the proton-nmr spectra of ε-thiocaprolactam show a strong deshielding relative to the corresponding lactam. The influence of solvent hydrogen bonding (dimethyl sulfoxide) is qualitatively similar for both compounds, but the deshielding due to hydrogen bonding is more pronounced in the case of lactam. No comparably large deshielding of the thio lactam N-H (relative to the lactam) is seen with the pyrromethenones. The strong N-H deshielding, due mainly to intermolecular hydrogen bonding [9] (Figure 2), accounts for the approximately 11.2 ppm signals of kryptopyrromethenone and

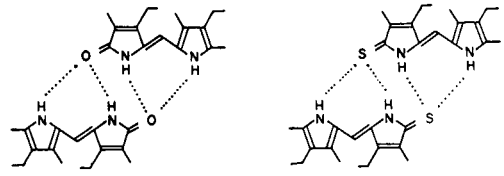


Figure 2. Intermolecularly hydrogen-bonded dimers of kryptopyrromethenone (left) and kryptopyrromethenethione (right)

xanthobilirubic acid methyl ester in deuteriochloroform. One might have expected thiolactam N-H deshielding some 3 ppm greater based on the caprolactam/caprothiolactam models. The thiolactam N-H shielding of 11.3-11.4 may reflect a reduced tendency toward forming the hydrogen-bonded dimeric structure of Figure 2.

The carbon-13 nmr data of Table 3 show the expected deshielding of the C=S *vs* C=O resonances [10]. The ring carbons of the pyrromethenethiones, as well as those carbons directly attached to the rings, are all deshielded relative to the pyrrinone analogs. Substitution of C=O by C=S has a powerful long range effect. It is only the more remote carbons (3^2, 8^2, 8^3, 8^4) that are essentially uneffected by the sulfur substitution.

EXPERIMENTAL

General.

All nmr spectra were run on a GE QE-300 spectrometer in either deuteriochloroform (99.9% d_1) of dimethyl sulfoxide-d_6 (99.5% d_6), both from Aldrich. All uv-visible absorption spectra were run on a Perkin-Elmer 3840 diode array spectrophotometer. All infrared (ir) spectra were run on a Perkin-Elmer 1610 FT instrument. High resolution mass spectra were run at the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln. Analytical thin layer chromatography (tlc) was carried out on J. T. Baker silica gel 1B-F plates (125 μ layer). Preparative layer chromatography (plc) was accomplished on 1000 μ layers of Woelm silica gel F. Column chromatography was carried out on 32-63 μ activated silica gel for medium pressure chromatography (M.

Table 2

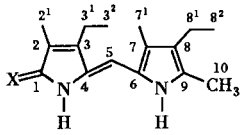
Comparison of Lactam and Pyrrole N-H Chemical Shifts [a] in the ^{1}H NMR Spectra of ε-Caprothiolactam, Kryptopyrromethenethione, Thioxanthobilirubic Acid Methyl Ester and Their Parent Lactams in Deuteriochloroform and Dimethyl sulfoxide-d_6

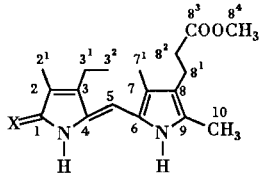
Compound	Deuteriochloroform		Dimethyl sulfoxide-d_6	
	Lactam	Pyrrole	Lactam	Pyrrole
ε-Caprothiolactam	9.45	–	10.06	–
ε-Caprolactam	6.68	–	7.90	–
Kryptopyrromethenethione	11.41	9.94	11.43	10.91
Kryptopyrromethenone	11.10	10.05	9.83	10.33
Thioxanthobilirubic Acid Methyl Ester	11.47	9.95	11.44	10.94
Xanthobilirubic Acid Methyl Ester	11.15	10.25	9.72	10.26

[a] Spectra run on 4×10^{-2} *M* solutions at 23°.

Table 3

Carbon-13 Nuclear Magnetic Resonance Spectral Assignments and Comparisons between Pyrromethenethiones and Pyrromethenones [a]





	$CDCl_3$		DMSO-d_6		$CDCl_3$		DMSO-d_6	
	X = S	X = O	X = S	X = O	X = S	X = O	X = S	X = O
1	185.9	174.1	187.9	171.8	186.7	174.1	187.6	171.9
2	131.0	122.2	130.8	122.0	131.5	122.4	131.1	122.2
2^1	10.4	9.5	11.4	9.1	10.4	9.6	10.5	9.1
3	146.0	148.2	146.1	147.1	146.1	148.4	145.3	147.2
3^1	18.4	15.4	18.1	15.4	18.4	18.0	18.0	17.1
3^2	17.3	17.5	16.6	10.8	15.1	15.0	15.5	14.8
4	132.0	127.0	131.1	127.0	132.3	127.2	131.3	127.4
5	104.2	101.2	102.8	97.7	103.9	101.4	101.5	97.6
6	129.8	122.9	127.8	121.8	129.3	122.4	128.0	121.8
7	125.2	122.2	124.2	121.5	121.3	119.1	120.6	118.4
7^1	11.9	11.5	14.9	14.8	11.9	11.5	11.7	10.9
8	123.5	124.6	123.1	122.5	123.6	124.6	123.2	122.7
8^1	18.0	18.0	17.3	17.1	19.7	19.9	19.7	19.4
8^2	15.1	15.1	16.6	16.9	34.7	35.2	34.8	34.6
8^3	–	–	–	–	173.5	174.1	172.6	172.8
8^4	–	–	–	–	51.7	51.2	51.7	51.1
9	136.0	131.1	134.0	128.6	136.1	131.6	134.4	129.4
10	9.7	8.5	10.6	8.0	9.8	8.5	9.8	8.0

[a] Chemical shifts in ppm downfield from tetramethylsilane for 3 x 10^{-2} *M* solutions at 23°.

Woelm). High performance liquid chromatographic (hplc) analyses used a detector set at 420 nm and a Beckman-Altex Ultrasphere-IP 5 μm C-18 ODS column (25 x 0.46 cm), with a Beckman ODS precolumn (4.5 x 0.46 cm) and a flow of 0.75 ml/minute of 0.1 *M* di-*n*-octylamine acetate in 5% aqueous methanol as the eluent. Tetrahydrofuran (Fisher) was distilled from lithium aluminum hydride, stored over sodium wire and filtered through activity 0 basic alumina (M. Woelm) before use. Lawesson's reagent and ϵ-caprolactam triethylamine and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), sodium borohydride, trifluoroacetic acid and dimethyl sulfoxide were form Aldrich. Chloroform and methanol (hplc grade) were from Fisher. Ascorbic acid and glycine were from Matheson, Coleman and Bell. Disodium EDTA, glacial acetic acid and benzene were from Mallinckrodt. All solvents and solutions used were rendered oxygen-free, argon-saturated by bringing to brief reflux under a stream of argon, cooling and storing under argon. Reactions were typically carried out under argon.

ϵ-Caprothiolactam.

ϵ-Caprolactam (34 mg, 0.30 mmole) and Lawesson's reagent (65 mg, 0.16 mmole) in 1.5 ml of dry tetrahydrofuran was blanketed with nitrogen and heated in a sealed glass tube at 80° for 12 hours, during which the emergence of a new, less polar thiolactam product was observed by tlc. The reaction was cooled, and the solvent was evaporated. The residue was chromatographed on a short column of silica gel, using chloroform as eluent, to give 31 mg of colorless product (81% yield) of pure thiolactam. The product showed only one spot on analytical tlc (chloroform) and had mp 98-100° (lit [21] mp 106-109°) and ir (potassium bromide): ν 3365 (N-H) and 1122 (C=S) cm^{-1}. It had uv-visible (chloroform): λ max 279 nm, ϵ, 9,000 and (methanol) λ max 276, ϵ, 7,800; ^{13}C-nmr (deuteriochloroform): δ 209.6 (s), 46.9 (t), 45.0 (t), 27.9 (t), 26.1 (t), 24.3 (t) ppm and (dimethyl sulfoxide-d_6): 208.2 (s), 46.1 (t), 45.2 (t), 30.0 (t), 28.2 (t), 24.4 (t) ppm; and ^{1}H-nmr (deuteriochloroform): δ 1.64 (2H, J = 7 Hz), 1.72 (2H, J = 7 Hz), 2.93 (2H, J = 7 Hz), 3.31 (2H, J = 7 Hz), 3.77 (2H, J = 7 Hz), 9.45 (1H, NH) ppm and (dimethyl sulfoxide-d_6): δ 1.47 (2H, J = 7 Hz), 1.63 (2H, J = 7 Hz), 2.82 (2H, J = 7 Hz), 3.25 (2H, J = 7 Hz), 3.77 (2H, J = 7 Hz), 10.06 (1H, NH) ppm.

Kryptopyrromethenethione.

This thiolactam was prepared as above, using 20 mg (0.078 mmole) of kryptopyrromethenone [7] and 17 mg (0.04 mmole) of Lawesson's reagent. The two reactants were dissolved together in 1 ml of dry tetrahydrofuran, blanketed with nitrogen and stirred for 2 hours at room temperature, during which time the solution turned from red to yellow. Work-up was accomplished first by evaporation of the solvent under reduced pressure followed by chromatography on a short column of neutral alumina (activity 1). Elution with chloroform gave 17.6 mg (82% yield) of pure product. It had mp 200-202°; ir (potassium bromide): ν 3448, 1618, 1269, 1235, 1120 (C=S) cm^{-1}; uv-visible (chloroform): λ max 485 nm, ϵ, 32,200, and (methanol): λ max 485, ϵ, 34,500, λ max 269, ϵ, 8,500; ^{1}H-nmr (deuteriochloroform): δ 1.05 (3H, t, J =

7 Hz), 1.15 (3H, t, J = 7 Hz), 2.11 (3H, s), 2.13 (3H, s), 2.17 (3H, s), 2.40 (2H, q, J = 7 Hz), 2.56 (2H, q, J = 7 Hz), 6.28 (1H, s), 9.94 (1H, s), 11.41 (1H, s) (dimethyl sulfoxide-d_6): 0.96 (3H, t, J = 7 Hz), δ 1.06 (t, 3H, J = 8 Hz), 1.91 (s, 3H), 2.04 (s, 3H), 2.18 (s, 3H), 2.28 (q, 2H, J = 7 Hz), 2.49 (q, 2H, J = 8 Hz), 6.12 (1H, s), 10.91 (1H, s), 11.43 (1H, s) ppm; hrms: 274.1502 [$M^{+\cdot}$] (100%), 259.1257 [$C_{15}H_{19}N_2S$] (40%), 226.1603 [$C_{16}H_{20}N$] (51%), 212.1314 [$C_{14}H_{16}N_2$] (45%), 197.1080 [$C_{13}H_{13}N_2$] (12%).

Anal. Calcd. for $C_{16}H_{22}N_2S$: 274.1504. Found: 274.1502.

Anal. Calcd. for $C_{16}H_{22}N_2S$ (274.4): C, 70.03; H, 8.08; N, 10.21; S, 11.68. Found: C, 70.02; H, 8.30; N, 10.11; S, 11.06.

Thioxanthobilirubic Acid Methyl Ester.

Xanthobilirubic acid methyl ester [7,8] (16 mg, 0.05 mmole) was converted to its thiolactam analog using the same procedures (above) for kryptopyrromethione to give 13.5 mg (83% yield) of product, mp 163-165°. It was pure by tlc on silica gel using chloroform-methanol-acetic acic (100:1:1, vol/vol/vol) or chloroform-ethanol (10:1) as eluent, and by hplc. It had ir (potassium bromide): ν 3449, 1735, 1618, 1265, 1240, 1115 cm^{-1} (C=S); uv-visible (chloroform): λ max 489, ε, 32,500 and (methanol): λ max 481, ε, 32,000, λ max 270, ε, 8,200; ^{1}H-nmr (deuteriochloroform): δ 1.15 (3H, t, J = 7 Hz), 2.10 (3H, s), 2.13 (3H, s), 2.42 (3H, s), 2.46-2.74 (6H, m), 3.67 (3H, s), 6.25 (1H, s), 9.95 (1H, s), 11.47 (1H, d) and (dimethyl sulfoxide-d_6): δ 1.05 (6H, t, J = 8 Hz), 1.91 (3H, s), 2.04 (3H, s), 2.18 (3H, s), 2.35-2.63 (6H, m), 3.54 (3H, s), 6.08 (1H, s), 10.94 (1H, s), 11.44 (1H, s); hrms: 332.1545 [$M^{+\cdot}$] (100%), 284.1527 [$C_{17}H_{20}N_2O_2$] (21%), 270.1367 [$C_{16}H_{18}N_2O_2$] (16%), 259.1268 [$C_{15}H_{19}N_2S$] (20%), 229.0869 [$C_{17}H_{11}N$] (19%), 211.1234 [$C_{14}H_{15}N_2$] (8%), 197.1078 ($C_{13}H_{13}N_2$] (7%).

Anal. Calcd. for $C_{18}H_{24}O_2N_2S$: 332.1558. Found: 332.1545.

Anal. Calcd. for $C_{18}H_{24}N_2O_2S\cdot\frac{1}{2}CH_3OH$ (348.5): C, 63.76; H, 7.52; N, 8.04; S, 9.20. Found: C, 64.34; H, 7.39; N, 8.23; S, 8.83.

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