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BILIRUBIN MONO AND BIS-DIMETHYLAMIDES. SYNTHESIS, SPECTROSCOPY AND SOLUTION STRUCTURES.

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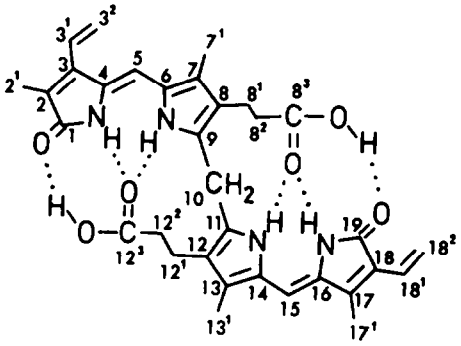
Abstract - Bilirubin-IXα bis-dimethylamide and 8- and 12-mono-dimethylamides, and bilirubin-IIIα and XIIIα bis-dimethylamides have been synthesized and characterized spectroscopically. In deuteriochloroform, as deduced from ^{1}H-nmr N-H resonances, the mono-dimethylamides prefer a folded, intramolecularly H-bonded conformation characteristic of the parent bilirubins. The possiblity of similar conformations for the bis-dimethylamides is discussed.

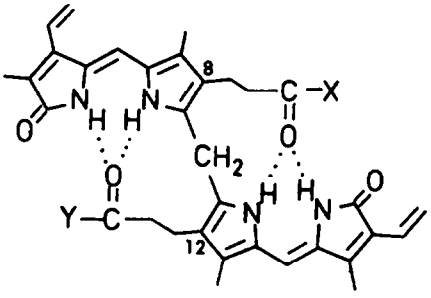
Considerable attention has been drawn to the properties of the potentially toxic biological waste product, bilirubin-IXα (BR) because of its central role in jaundice and phototherapy.[1,2] In particular, the three dimensional structure, as revealed by X-ray crystallography[3,4] and nuclear magnetic resonance studies[5] has proved to be of crucial importance in explaining its unexpected lipophilicity and the molecular mechanism of jaundice phototherapy.[2] One of the most interesting and important aspects of the structure of BR is its ability to exhibit intramolecular hydrogen-bonding (Figure 1).[1-5] The intramolecularly H-bonded conformation is probably the dominant species in non-H-bonding organic solvents, such as chloroform. Expectedly perhaps, the dimethyl ester of BR shows no strong tendency for intramolecular H-bonded conformations of the type shown in Figure 1.[6] Indeed, the available evidence supports intermolecularly H-bonded dimeric structures in chloroform.[3] The contrasting behavior raises the intriguing possibility that the amides of BR might exhibit conformations either like the ester or like the acid depending on the presence of an amide N-H. In the current work, we describe the preparation of and report and interpret the spectral data for BR bis-dimethylamide (1), the 8- and 12-mono-dimethylamides (2 and 3, respectively), and the bis-dimethylamides of the symmetrically substituted congeners of BR, bilirubin-IIIα and bilirubin-XIIIα.

Syntheses. The dimethylamides were prepared by reaction of BR with dimethylamine hydrochloride using diphenylphosphoryl azide as the coupling agent in dry dimethylformamide.[8] The reaction to give the bis-dimethylamide proceeded smoothly and in high yield but was also accompanied by constitutional isomerization[9] and

afforded consequently a separable mixture of the bis-dimethylamides of bilirubin-IIIα and XIIIα in addition to that of the expected IXα. With one equivalent of dimethylamine hydrochloride, the mono-dimethylamides could be prepared and isolated. Attempts to prepare and isolate the bis-methylamide and bis-amide of BR using methylamine hydrochloride and ammonium chloride were only partially sucessful. The reactions proceeded smoothly but the amide products exhibited such limited solubility that chromatographic separations were extremely difficult and the purity or homogeneity of material could not be ascertained.



BR: Bilirubin-IXα



2: BR-8-dimethylamide
(X = $N(CH_3)_2$, Y = OH)

3: BR-12-dimethylamide
(X = OH, Y = $N(CH_3)_2$)

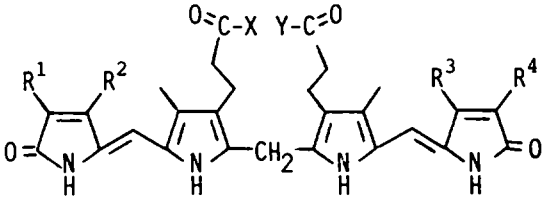
FIGURE 1. Intramolecularly H-bonded conformations of (4Z,15Z)-bilirubin-IXα (BR) and its isomeric mono-dimethylamide derivatives (2 and 3).

Spectral Properties and Solution Conformation. Symmetric bilirubins (IIIα and XIIIα) and their dimethyl esters typically exhibit two N-H resonances, one assigned to the lactam and one to the pyrrole (Table 1).[6] The non-symmetric IXα isomer and its dimethyl ester have long been known to exhibit two sets of N-H resonances.[5-7] All of the N-H signals are sensitive to solvent H-bonding characteristics. Thus, comparison of the lactam and pyrrole N-H signals of the acids and esters (Table 1) in d_6-dimethylsulfoxide shows only small differences, with the lactam N-H resonances falling near 10.0 ppm and the pyrrole N-H near 10.5 ppm. The various bis-dimethylamide derivatives behave very much the same, and since dimethylsulfoxide is known to form H-bonds with amide[10] and pyrrole[11] N-H groups, we assume that all compounds of Table 1 are similarly H-bonded to dimethylsulfoxide and possess similar conformations.[5-8].

In deuteriochloroform, which H-bonds less well than dimethylsulfoxide, the N-H resonances are shifted. With comparisons being made between d_6-dimethylsulfoxide and deuteriochloroform, in the latter solvent and for bilirubin acids, the lactam N-H signals become relatively more deshielded ($\Delta\delta \sim +0.8$ ppm), an indicator of intensified H-bonding,[6] and the pyrrole N-H signals become relatively more strongly

TABLE 1

TABLE 1. Assignments and Comparisons of Lactam and Pyrrole N-H ^{1}H-NMR Resonances (δ, ppm) of Bilirubins,[a] their Bis-dimethylamides[b] and Dimethyl Esters.[a] Assignments are indicated under the appropriate N-H.



$CDCl_3$	10.44	9.79	9.79	10.44	Bilirubin-IIIα Bis-dimethylamide $R^1=R^4=CH=CH_2$, $R^2=R^3=CH_3$, $X=N(CH_3)_2$.
d_6-DMSO	9.79	10.55	10.55	9.79	
$CDCl_3$	10.68	9.27	9.27	10.68	Bilirubin-IIIα $R^1=R^4=CH=CH_2$, $R^2=R^3=CH_3$, $X=OH$
d_6-DMSO	9.87	10.46	10.46	9.87	
$CDCl_3$	10.43	10.22	10.22	10.43	Bilirubin-IIIα dimethyl ester $R^1=R^4=CH=CH_2$, $R^2=R^3=CH_3$, $X=OCH_3$
d_6-DMSO	9.85	10.52	10.52	9.85	
$CDCl_3$	10.39	10.01	10.01	10.39	Bilirubin-XIIIα Bis-dimethylamide $R^1=R^4=CH_3$, $R^2=R^3=CH=CH_2$, $X=N(CH_3)_2$
d_6-DMSO	9.95	10.54	10.54	9.95	
$CDCl_3$	10.75	9.25	9.25	10.75	Bilirubin-XIIIα $R^1=R^4=CH_3$, $R^2=R^3=CH=CH_2$, $X=OH$
d_6-DMSO	10.06	10.46	10.46	10.06	
$CDCl_3$	10.80	10.31	10.31	10.80	Bilirubin-XIIIα dimethyl ester $R^1=R^4=CH_3$, $R^2=R^3=CH=CH_2$, $X=OCH_3$
d_6-DMSO	9.97	10.48	10.48	9.97	
$CDCl_3$	10.43	10.32	9.78	10.43	Bilirubin-IXα Bis-dimethylamide $R^1=R^3=CH_3$, $R^2=R^4=CH=CH_2$, $X=N(CH_3)_2$
d_6-DMSO	9.93	10.53	10.53	9.80	
$CDCl_3$	10.80	9.27	9.30	10.70	Bilirubin-IXα $R^1=R^3=CH_3$, $R^2=R^4=CH=CH_2$, $X=OH$
d_6-DMSO	10.07	10.48	10.48	9.93	
$CDCl_3$	11.23	10.49	10.18	10.10	Bilirubin-IXα dimethyl ester $R^1=R^3=CH_3$, $R^2=R^4=CH=CH_2$, $X=OCH_3$
d_6-DMSO	10.00	10.57	10.55	9.89	

[a] Data from reference 6.

[b] Run at 20-25°C on 2 x 10^{-3} M solutions.

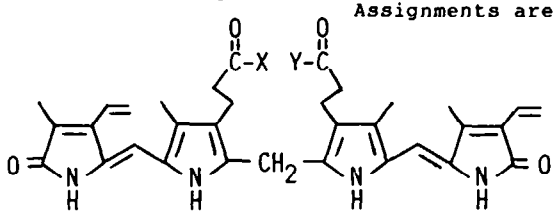
shielded ($\Delta\delta$ ~ -1.2 ppm). The data (Table 1) are consistent with an intramolecularly H-bonded conformation (Figure 1) in deuteriochloroform. As with the bilirubin acid behavior, the dimethyl ester lactam N-H signals become more deshielded ($\Delta\delta$ ~ +0.8 ppm); however, the pyrrole N-H signals are less strongly shielded ($\Delta\delta$ ~ -0.3 ppm). The data here are consistent with intermolecularly H-bonded dimers in chloroform, as described earlier.[5-7] The N-H resonances of the bis-dimethylamides (Table 1) show a qualitatively similar solvent dependence: the lactam N-H signal is more deshielded in deuteriochloroform than in d_6-dimethylsulfoxide ($\Delta\delta$ ~ +0.5) and the pyrrole N-H is relatively more shielded ($\Delta\delta$ ~ -0.7). By way of comparison, xanthobilirubic acid, its methyl ester and dimethylamide, all pyrromethenone models that are incapable of intramolecular H-bonding and prefer intermolecularly H-bonded (pyrromethenone-to-pyrromethenone) dimeric conformation in chloroform, show a larger deshielding of the lactam N-H resonance in deuteriochloroform than in d_6-dimethylsulfoxide ($\Delta\delta$ ~ +1.5) and essentially no change in the pyrrole N-H resonances ($\Delta\delta$ ~ 0).[8] With a large pyrrole N-H shielding ($\Delta\delta$) taken as an indicator of intramolecular H-bonding, one is tempted to conclude that intramolecularly H-bonded conformations in chloroform may play a more important role in the structures of bilirubin bis-dimethylamides than of the dimethyl esters. In any event, the data (Table 1) show that the propionamide group plays a conformation-determining role, a role that might not be expected in an intermolecularly H-bonded dimeric structure.

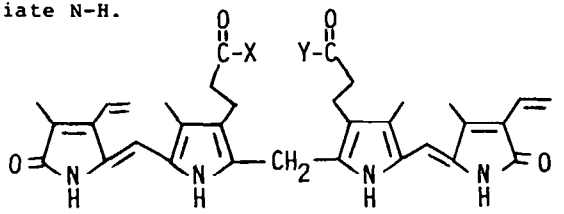
Unlike the dimethyl esters and bis-dimethylamides, however, partial intramolecular H-bonding is still possible between the remaining propionic acid and opposing pyrromethenone groups (Figure 1) of the mono-dimethylamides, as with the monomethyl esters. Since an earlier analysis of the N-H chemical shifts of the monomethyl esters of bilirubins-IXα, IIIα and XIIIα concluded in favor of such intramolecular H-bonding,[14] it seemed likely that similar conformations might obtain with the mono-dimethylamides as well. Thus, if one assumes that the propionic acid groups of mono-amides 2 and 3 (and mono-esters (5 and 6) might participate in intramolecular H-bonding, the resulting conformation (Figure 1) should be expected to show one set of pyrromethenone N-H resonances at approximately the deshieldings observed in the parent BR (Table 1). This expectation is in fact borne out in the NMR data of Table 2 in which very good agreement is found between the experimental and predicted values for the mono-amides, cf. 2: I and I', 3: II and II', and also for the mono-esters, cf. 4: I and I', 5: II and II'. We conclude, therefore, that the conformation in deuteriochloroform is at least "half" intramolecularly H-bonded (cf. Figure 1).

The remaining pyrromethenone "half", the one not obviously involved in intramolecular H-bonding might become involved in intermolecular H-bonding of the pyrromethenone-to-pyrromethenone type characteristic of bilirubin dimethyl esters.[6,7] Or, given the already partially folded conformation dictated by the propionic acid and opposing pyrromethenone groups (vide ante), some type of intramolecular H-bonding between the remaining propionamide and opposing pyrromethenone groups might obtain. The experimental data (Table 2) indicate a preference for the same type of conformation in this part of the mono-dimethylamide as that exhibited by the bis-dimethylamide, cf. 2: II and II', and 3: I and I'. The net preferred conformation of 2 and 3 in deuteriochloroform would appear to be something akin to the intramolecularly H-bonded structures of Figure 1. Consistent with this picture, the data of Table 2 for the monomethylesters are incompatible with the dimethyl ester[6,7] or xanthobilirubic acid ester[8] type of dimeric pyrromethenone-pyromethenone H-bonding, cf. 5: II vs II', and 6: I vs I'. Here, too, an even weaker intramolecular H-bonding between the propionic ester and opposing pyrromethenone groups seems likely (Figure 1).

TABLE 2

Lactam and Pyrrole N-H Assignments in the ^{1}H-NMR Spectra[a] of Bilirubin Mono-dimethylamides and Monomethyl Esters.[b] Assignments are indicated under the appropriate N-H.





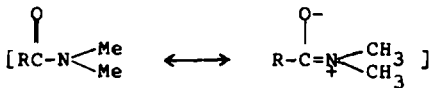
	Experimental Data					Calculated[c]			
	I		II			I'		II'	
$CDCl_3$	10.72	9.18	9.42	10.48	(2)Bilirubin-IXα 8-Dimethylamide	10.80	9.27	9.78	10.43
d_6-DMSO	10.02	10.50	10.50	9.82	X=N$(CH_3)_2$, Y=OH	10.07	10.48	10.53	9.80
$CDCl_3$	10.45	9.46	9.18	10.72	(3)Bilirubin-IXα 12-Dimethylamide	10.43	10.32	9.30	10.70
d_6-DMSO	10.06	10.51	10.51	9.84	X=OH, Y=N$(CH_3)_2$	9.93	10.53	10.48	9.93
$CDCl_3$	10.83	9.29	8.48	9.17	(5)Bilirubin-IXα 8-Methyl Ester	10.80	9.27	10.18	10.10
d_6-DMSO	10.04	10.50	10.50	9.90	X=OCH_3, Y=OH	10.07	10.48	10.55	9.89
$CDCl_3$	9.24	8.45	9.28	10.74	(6)Bilirubin-IXα 12-Methyl Ester	11.23	10.49	9.30	10.70
d_6-DMSO	10.03	10.52	10.52	9.88	X=OH, Y=OCH_3	10.00	10.57	10.48	9.93

[a] Reported in ppm downfield from TMS for 10^{-3} M solutions in $CDCl_3$ and 10^{-2} M solutions in d_6-DMSO at 25°C.

[b] Data for monomethyl esters from reference 14.

[c] Derived from data reported in Table 1, assuming one pyrromethenone behaves like the bilirubin and the other pyrromethenone behaves like the bilirubin bis-dimethylamide or dimethyl ester.

The ^{13}C-nmr data for the bis-dimethylamides of bilirubin-IXα, IIIα and XIIIα are assigned and summarized in Table 3. The carbon resonances do not vary significantly, and here, but not with xanthobilirubic acid dimethylamide,[8] the amide methyl groups are non-equivalent. Non-equivalence is to be expected as the charge-separated resonance structure assumes greater importance.[8,15] These data



thus offer further evidence for involvement of the propionamide groups in a conformationally restricted way (with neighboring pyrromethenone groups) as in an intramolecularly H-bonded structure (Figure 1). Presumably, the enhanced basicity of the propionamide oxygen strengthens intramolecular H-bonding in amides relative to esters, where the importance of the charge separated resonance structure is not as great.

In summary, we have prepared the bis-amides of bilirubin-IXα, IIIα and XIIIα, and the 8- and 12-mono-dimethylamides of bilirubin-IXα. These have been characterized spectroscopically and have been found to exhibit a tendency toward intramolecular H-binding in chloroform solution.

EXPERIMENTAL

General: All nmr spectra were run on a JEOL FX-100 FT spectrophotometer in either d_6-dimethylsulfoxide (d_6-DMSO) (99.5% d_6) from Merck or deuteriochloroform (99.8% d_1), from Stohler. All ir spectra were obtained on a Perkin-Elmer model 599 instrument, and all uv-visible absorption spectra were run on a Cary 219 instrument. Melting points were determined on a Mel-Temp capillary unit. Combustion microanalyses were obtained from MICANAL, Tucson, AZ. Thin layer chromatography (tlc) was carried out using silica gel F (M. Woelm) on analytical plates (125μ) prepared from ethanol slurries with the plates being activated at 110-120° following ethanol evaporation. Preparative layer chromatography (plc) was carried out with 20 x20 cm plates having a 1 mm thick layer of silica gel F. Bilirubin was from Sigma. Dimethyl formamide, triethylamine (dried by distillation from calcium hydride) and dimethylamine hydrochloride were from Matheson, and diphenylphosphorylazide was from Aldrich.

Bilirubin-IIIα, IXα, and XIIIα Bis-dimethylamides: Bilirubin-IXα, previously crystallized from chloroform-methanol (150.8 mg, 0.258 mmoles), freshly sublimed dimethylamine hydrochloride (118 mg, 2.24 mmole), diphenylphosphoryl azide (0.454 ml, 0.575 mmoles) and triethylamine (0.35 ml, 0.25 g, 2.5 mmoles) were stirred in 50 ml of dried dimethylformamide in a glass pressure bottle at 60° under Ar for 2.5 hours. The solvents were removed under vacuum (rotary evaporator) to afford a solid. Which was dissolved in chloroform. The chloroform solution was washed with 1 N sodium bicarbonate (2 x 25 ml) then water (50 ml) and dried (sodium sulfate) and evaporated. The resulting residue was applied to two 20 x 20 cm plc plates (1 mm, silica gel) and developed with benzene-ethanol, 25:3 v/v. Three faint, fast moving bands (unreacted bilirubin and mono amides) were separated from the major three bands (R_f 0.47-0.41, 0.41-0.31 and 0.31-0.21), which were themselves separated and collected to give fractions totalling 61.9 mg, 95.7 mg and 32.9 mg of the IIIα, IXα and XIIIα isomers, respectively. The isomers were each further purified by preparative tlc on silica gel to give 31.6 mg (19%), 64.8 mg (39%) and 11.3 mg (7%) of the pure IIIα, IXα and XIIIα isomers, respectively. The IIIα and IXα isomers could be crystallized from methanol: 29.8 mg of IIIα gave 19.7 mg of dark red crystals, mp 127-132° dec. and 49.8 mg of IXα gave 42.1 mg of dark red crystals, mp 125-130°, dec. The IXα isomer had uv-vis (chloroform): λ max 441 nm, ε, 61,200, (dimethylsulfoxide): λ max 460 nm, ε, 61.899; ir (chloroform): ν 3300, 3005, 1678, 1634, 1619, 1205, 1013, 925 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ ppm 1.77 (s, CH_3), 2.01 (s, 2 x CH_3), 2.3-2.8 (m, 8H), 2.88 (s, 6H), 4.00 (s, 2H), 4.96 (q, 1H, J(AB) = ~1.5 Hz, J(AX) = ~12 Hz), 5.41 (q, 1H, J(AB) = ~1.5 Hz, J(BX)= ~11.6 Hz), 5.44 (q, 1H, J(AB) ~1.5 Hz, J(BX) = ~18 Hz), 5.89 (s, 1H), 6.07 (s, 1H), 6.23 (q, 1H, J(AX) = ~12 Hz, J(BX) = ~18 Hz), 6.52 (q, 1H, J(BX) = ~18 Hz, J(AX) = ~12 Hz), 9.78 (s, 1H), 10.32 (s, 1H), 10.43 (s, 2H); ^{13}C-nmr in Table 3; field desorption mass spectral molecular weight = 630.

Anal. Calcd for $C_{37}H_{46}N_6O_4$ (638): C, 69.59; H, 7.21; N, 13.17.
Found: C, 69.40; H, 6.85; N, 12.79.

IIIα bis-dimethylamide had mp 127-132° (dec.) uv-vis (chloroform): λ max 446 nm, ε, 69.000, (dimethylsulfoxide): λ max 464 nm, ε, 70,100; ir (chloroform): ν 3300, 3005, 1678, 1634, 1619, 1205, 1013, 925 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ ppm 2.02 (s, 2 x CH_3), 2.09 (s, 2 x CH_3), 2.3-2.8 (m, 8H), 2.90 (s, 2 x syn CH_3-N), 2.96 (s, 2 x anti CH_3-N), 3.91 (s, 2H), 5.14 (q, 2H, J(AB) = ~2.5 Hz, J(AX)= ~11 Hz), 5.93 (q, 2H, J(AB) = ~2.4 Hz, J(BX) = ~18 Hz), 5.95 (s, 2H), 6.38 (q, 2H, J(AX) = ~11 Hz, J(BX) = ~18 Hz), 9.79 (s, 2H), 10.44 (s, 2H); ^{13}C-nmr in Table 3.

Anal. Calcd for $C_{37}H_{46}N_6O_4$ (638): C, 69.59; H, 7.21; N, 13.17.
Found: C, 69.42; H, 6.86; N, 12.80.

XIIIα bis-dimethylamide had 129-135° (dec.), uv-vis (chloroform): λ max 435 nm, ε, 52,900, (dimethylsulfoxide): λ max 456 nm, ε, 55,900; ^{1}H-nmr (deuteriochloroform): δ ppm 1.75 (s, 2 x CH_3), 2.01 (s, 2 x CH_3), 2.4-2.8 (m, 8H), 2.88 (s, 2 x syn CH_3-N), 2.91 (s, 2 x anti CH_3-N), 3.98 (s, 2H), 5.42 (q, 2H, J(AB) = ~2.0 Hz, J(AX) = ~12 Hz), 5.46 (q, 2H, J(AB) = ~2.0 Hz, J(BX) = ~17 Hz), 6.02 (s, 2H) 6.56 (q, 2H, J(AX) = ~12 Hz, J(BX) = ~17 Hz), 10.01 (s, 2H), 10.39 (s, 2H); ^{13}C-nmr in Table 3.

Anal. Calcd for $C_{37}H_{46}N_6O_4$ (638): C, 69.59; H, 7.21; N, 13.17.
Found: C, 69.43; H, 6.83; N, 12.89.

Bilirubin-IXα 8-Dimethylamide and 12-Dimethylamide. Bilirubin-IXα, previously crystallized form chloroform-methanol (201.5 mg, 0.345 mmoles), freshly sublimed dimethylamine hydrochloride (28 mg, 0.345 mmoles), diphenylphosphoryl azide (0.224 ml, 284.6 mg, 1.035 mmoles) and triethylamine (0.144 ml, 104.5 mg, 1.035 mmoles) were combined and stirred in 50 ml of dried dimethylformamide under argon in a pressure bottle at ca 60°C for 1.5 hours. The solvents were then removed at reduced pressure (rotary evaporator), and the residue was dissolved in chloroform, washed with 1 N aq. sodium bicarbonate (2 x 30 ml), water (1 x 50 ml) and dried (sodium sulfate). After evaporation of the chloroform, the resulting solid was chromatographed by plc (2 plates) using chloroform-methanol-acetic acid (97:2:1, v/v/v) as eluent. The mono-amides migrated as compact bands (R_f > 0.5) that were preceded slightly by bilirubin. The yield of crude mono-amides was 43.6 mg (20%) of 8-dimethylamide and 65.7 mg (30%) of 12-dimethylamide. These partially purified monoamides were further chromatographed twice by plc using chloroform-acetic acid 99:1 v/v) to afford 14.7 mg 97%) of pure 8-dimethyl amide (R_f 0.2) and 31.0 mg (15%) 12-dimethylamide (R_f 0.05). The 8-dimethylamide isomer had mp 205-210° dec. (chloroform): λ max 444 nm, ε, 51,800, (dimethylsulfoxide): λ max 460 nm, ε, 45,400; ^{1}H-nmr (deuteriochloroform): δ ppm 1.92 (s, CH_3), 2.03 (s, CH_3), 2.07 (s, CH_3), 2.09 (s, CH_3), 2.4-2.8 (m, 8H), 2.90 (s, syn CH_3-N), 3.07 (s anti CH_3-N), 3.92 (s, 2H), 5.1-5.7 (m, 3H), 6.15 (s, 1H), 6.0-6.6 (m, 3H), 9.18 (s, 1H), 9.42 (s, 1H), 10.48 (s, 1H), 10.72 (s, 1H).

Anal. Calcd for $C_{37}H_{46}N_6O_4$ (611): C, 68.72; H, 6.76; N, 11.45.
Found: C, 68.52; H, 7.18; N, 11.05.

The 12-dimethylamide had mp 208-214° dec., uv-vis (chloroform): λ max 443 nm, ε, 49,800, (dimethylsulfoxide): λ max 456 nm, ε, 51,100; ^{1}H-nmr (deuteriochloroform): δ ppm 1.89 (s, CH_3), 1.99 (s, CH_3), 2.06 (s, CH_3), 2.08 (s, CH_3), 2.3-2.8 (m, 8H), 2.89 (s, syn CH_3-N), 3.06 (s, anti CH_3-N), 3.92 (s, 2H), 5.2-5.7 (m, 3H), 5.01 (s, 1H), 6.14 (s, 1H), 6.0-6.8 (m, 3H), 9.18 (s, 1H), 9.46 (s, 1H), 10.46 (s, 1H), 10.72 (s, 1H).

Anal. Calcd for $C_{35}H_{41}N_5O_5$ (611): C, 68.72; H, 6.76; N, 11.45.
Found: C, 68.52; H, 7.18; N, 11.05.

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TABLE 3

^{13}C-NMR Assignments[a] for Bilirubin Bis-Dimethylamides.[b]

Carbon	Bilirubin-IIIα Bis-Dimethylamide	Bilirubin-IXα Bis-Dimethylamide	Bilirubin-XIIIα Bis-Dimethylamide
1		171.25	171.19
2		123.10	123.16
3		140.24	140.24
4		127.31	127.37
5		98.76 (d)	98.82 (d)
6		121.93	121.87
7		120.23	120.18
8		123.45	123.45
9		131.00	131.12
10	23.70 (t)	23.76 (t)	23.70 (d)
11	131.64	131.76	
12	124.15	124.15	
13	120.47	120.41	
14	121.93	121.93	
15	99.70 (d)	99.70 (d)	
16	127.08	127.08	
17	141.76	141.70	
18	122.28	122.28	
19_1	170.25	170.25	
2^1		9.49 (q)	9.43 (q)
3_2^1		127.31 (d)	127.37 (d)
3^2		121.75 (t)	121.76 (t)
7^1		9.02 (q)	9.02 (q)
8^1		19.43 (t)	19.43 (t)
8^2		32.54	32.66 (t)
8^3		171.25	171.31
syn-NCH_3		36.11 (q)	36.11 (q)
anti-NCH_3		34.41 (q)	34.47 (q)
12^1	19.38 (t)	19.43 (t)	
12^2	32.54 (t)	32.54 (t)	
12^3	171.25	171.25	
syn-NCH_3	36.11 (q)	36.11 (q)	
anti-NCH_3	34.41 (q)	34.41 (q)	
13^1	9.02 (q)	9.02 (q)	
17^1	128.07 (d)	128.07 (d)	
18^2	117.07 (t)	117.02 (t)	

[a] For numbering, see Figure 1; for structures, see Table 1.

[b] Run in d_6-dimethylsulfoxide.