Monatshefte für Chemie 126, 983–991 (1995)

Monatshefte für Chemie
Chemical Monthly

1,2-*bis*-Dipyrrinon-9-yl-ethene – a Novel *b-homo*-Verdin Chromophore: the Reaction of 9-Methyl-10*H*-dipyrrin-1-ones with Bromine

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Summary. Upon treatment of 9-methyl-10*H*-dipyrrin-1-ones with bromine in dichloromethane, red bile pigment derivatives were obtained in moderate yields. They were structurally assigned as 1,2-*bis*-dipyrrinon-9-yl-ethenes, which are examples of the hitherto unknown *b-homo*-verdins. In addition, the corresponding *meso*-biliverdins-XIIIα could be isolated from the reaction mixture. The mechanistic aspects of the reaction are discussed.

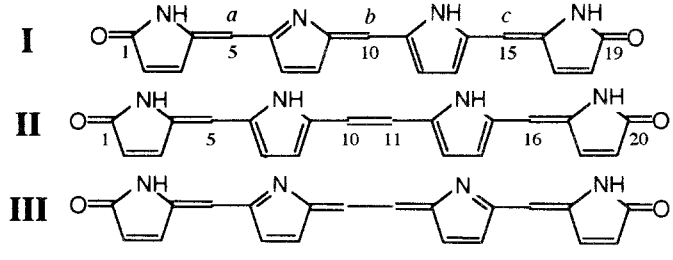
Keywords. 1,2-*bis*-Dipyrrinon-9-yl-ethene; *b-homo*-Verdin; Mesobiliverdin-XIIIα.

1,2-*bis*-Dipyrrinon-9-yl-ethen – ein neuer *b*-Homoverdinchromophor: Die Reaktion von 9-Methyl-10*H*-dipyrrin-1-onen mit Brom

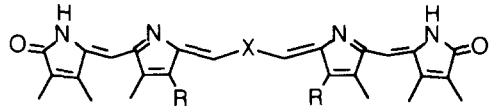
Zusammenfassung. Die Reaktion von 9-Methyl-10*H*-dipyrrin-1-onen mit Brom in Dichlormethan ergab in mäßigen Ausbeuten rotgefärbte Gallenfarbstoffderivate. Sie konnten strukturell als 1,2-*bis*-Dipyrrinon-ethene zugeordnet werden, die ein Beispiel für die bisher unbekannten *b*-Homoverdine darstellen. Darüber hinaus konnten aus der Reaktionsmischung die entsprechenden Mesobiliverdine-XIIIα isoliert werden. Die mechanistischen Aspekte dieser Reaktion werden diskutiert.

Introduction

The verdin chromophor **I** may be expanded at position 10 into homologues, as has been recently discussed [1]. Thereby two *b-homo*-verdin-chromophores **II** and **III**, differing in their oxidation states, are obtained.

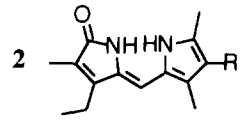


Although higher verdin *b*-homologues have been described, systems based on the chromophores of type **II** or **III** are still unknown to our knowledge. The first *b-homo*-verdin extended at C-10, the linear pentapyrrolic pigment **1a**, has been previously synthesized by one of our groups [2]. In this pentapyrrin system, a 3,4-dimethyl-pyrrole-2,5-diyl moiety has been inserted between two dipyrrinone chromophores to yield a system corresponding to the oxidation state of chromophore type **III**. Their analogs **1b**–**1d** have been recently prepared by *Lightner's* group [3] as intermediates on the way to the corresponding homologated rubin systems. Moreover, a *b-homo*-rubin derivative corresponding to the *meso*-hydrogenated system **II** has been advanced very recently by the latter group [4].



	X	*R*
1a	3,4-dimethyl-2,5-pyrrole-diyl	CH_3
1b	3,4-dimethyl-2,5-pyrrole-diyl	$CH_2CH_2CO_2CH_3$
1c	1,4-phenyl-diyl	$CH_2CH_2CO_2CH_3$
1d	1,3-phenyl-diyl	$CH_2CH_2CO_2CH_3$

About ten years ago, *Ribó's* group [5] has studied the bromination and nitration of dipyrrinones, amongst them **2c**. They mentioned that the bromination of **2c** in dichloromethane yielded an untractable *colored* mixture besides products corresponding to the bromination at the methyl group in the α-position of the pyrrole ring. Following this hint it turned out that fortunately this reaction provided an entry to the novel chromophoric system **II** of the *b-homo*-verdins **3** which will be described in the following.



R: **a** $CH_2CH_2COOCH_3$; **b** CH_2COOCH_3; **c** C_2H_5

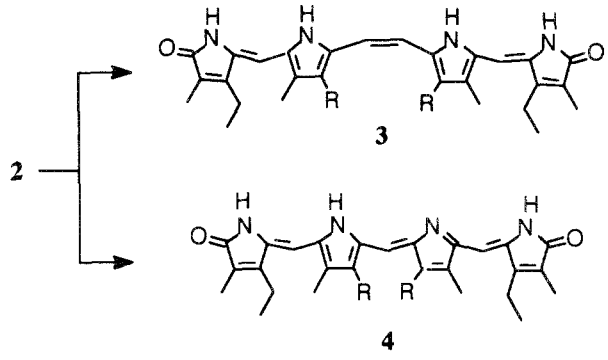
Results and Discussion

Synthetic Aspects

Bromine has been used in numerous reactions of pyrrole chemistry as an oxidative agent to investigate the reactivities of bile pigments [6–8] and to synthesize verdins from 1,19-*bis*-(*tert*-butoxycarbonyl)-biladienes-*ac* or 1,19-*bis*-(*tert*-butoxycarbonyl)-bilenes-*b* [9, 10]. Treatment of **2** with bromine in methanol is known to afford moderate yields of *meso*-biliverdin **4** [11]. This reaction represents the first useful synthetic method for the preparation of symmetrically substituted rubins as has been advanced by *Fischer* [11]. The mechanism of this reaction has been envisaged to be similar to the one of the formation of 4,5-dihydrodipyrrins by means of a thermal reaction of bromomethylpyrroles [12].

To synthesize 1,2-*bis*-dipyrrinone-ethenes as examples belonging to the *b-homo*-biliverdin chromophore **II**, the reaction of dipyrrinones **2** with bromine in dichloro-

methane was investigated in detail. Thus, following the route mentioned above, two different pigments could be isolated in reasonable yields upon reacting dipyrrinones **2** with bromine in dichloromethane under carefully controlled conditions. The first ones were colored red and, as discussed in the following chapter, they were structurally assigned as 1,2-*bis*-dipyrrinone-ethenes **3**. The second ones were of blue color and were spectroscopically identified as the known *meso*-biliverdins **4**.



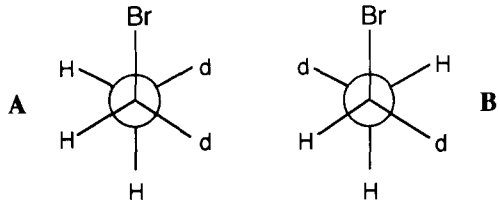
R: **a** $CH_2CH_2COOCH_3$; **b** CH_2COOCH_3; **c** C_2H_5

Structural Assignments

The constitutional, tautomeric, and configurational aspects [6] of **3** could be derived from their NMR, IR, and mass spectra. Thus, pigments **3** displayed nicely resolved ^{1}H NMR spectra in pyridine-d_5 solutions, whereas in deuteriochloroform solution the resolution was rather low, possibly due to traces of acid.

The CH_2CH_3 residues in positions 3, 18 of **3a**–**3c** and 8, 13 of **3c** could be assigned and correlated by ^{1}H–^{1}H COSY experiments (see Experimental) and shift considerations. The two methyl resonances were assigned on behalf of the slightly stronger long range coupling (larger line broadening, compare [13]) of the 2,19-methyl groups with their neighboring ethyl groups and methine protons as compared to the less broadened 7, 13 methyl group signals. The chemical shifts of the two –CH=CH– protons and the two –CH= protons of, *e.g.*, **3a** were significantly different (7.76 ppm in chloroform-d and 8.29 ppm in pyridine-d_5, and 5.68 ppm in chloroform-d and 6.04 ppm in pyridine-d_5). These resonances appeared as singlets of equal intensity. The chemical shifts of the methine protons corresponded to (*Z*) configurations at the two exocyclic double bonds [6].

Using PCMODEL calculations [14], a possible diastereoselective result of the elimination with respect to the *meso* ethene fragment (Scheme 1; compare *Mechanistic Aspects*) was considered. Although there were more unfavorable steric interactions between the two dipyrrinone moieties (d) for a *trans* elimination in the conformer **A** leading to the (*Z*) configuration, the difference to those in the case of the conformer **B** leading to an (*E*) configuration were not large enough (< 40 kJ/mol) to overrule the *Curtin-Hammett* principle. Thus, an unequivocal diastereomer configurational assignment of the *meso* ethene fragment based on mechanistic arguments could not be reached. However, the chemical shifts of the ethene protons of **3a**–**3c** around 7.8 ppm ($CDCl_3$) were significantly different from the 6.6 ppm observed in a series of dipyrrylethenes of (*E*) configuration [1]. Accordingly, the configuration of **3** at the *meso* ethene fragment was tentatively assigned to be (*Z*).



Scheme 1

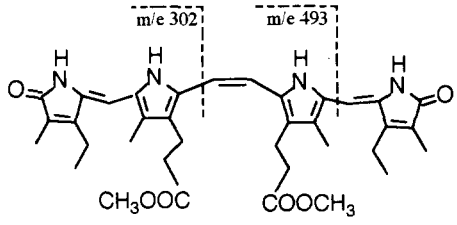


Fig. 1. Mass fragmentation of **3a** by CI and FAB methods

The ^{13}C NMR spectrum of **3a** displayed the appropriate number of carbon atom signals. Two peaks were observed at 172.16 and 172.71 ppm which were assigned to two ester carbonyl carbon atoms and two lactam carbonyl carbon atoms, respectively. The latter is in a region typical of lactam carbonyl tautomers [6]. Moreover, the IR spectra of **3** clearly revealed the typical lactam vibration at about 1700 cm^{-1} [6]. Thus, the *b-homo*-verdins **3** were assigned to be present predominantly as the *bis*-lactam tautomers.

The molecular ion peak of **3a** appeared in its mass spectrum at $m/e = 628$, and the peaks at m/e 493 and 302 corresponded the characteristic fragments shown in Fig. 1. The high resolution mass measurement of **3a** yielded its formula weight of 628.3265. This value compared favorably with the calculated one of 628.3260 for $C_{36}H_{44}N_4O_6$. Thus, the structural aspects of **3a** as evidenced from the NMR and IR spectra were well in accordance with the mass spectrum.

The absorption spectra of **4** contained the typical two band system of verdins at 630 and 360 nm. The constitutional assignment of compounds **4** followed easily from their ^1H NMR spectra. They exhibited besides the characteristic signals of the methyl, methylene, and methine signals also those of the corresponding side chains of the (*Z*,*Z*,*Z*)-mesobiliverdin-XIIIα derivatives **4** [12, 15, 16].

Concerning the Novel b-homo-Verdin Chromophore II

The electronic absorption spectra of the *b-homo*-verdins **3** were characterized by a two band system (Fig. 2). The long wavelength bands of **3a**–**3c** in chloroform solutions were observed at 540, 545, and 530 nm. In contrast to this rather strong variation, the short wavelength bands in this series were only slightly shifted to 290, 290, and 285 nm. The long wavelength band was found to be slightly more intensive than the short wavelength band. Compared to the verdin chromophore (Fig. 2), the absorption spectra of the *b-homo*-verdins were found to be strongly hypsochromically shifted. In contrast, the extension of a chromophore should lead to a bathochromic shift as has been experienced with an extension of the chromophoric system of mesobiliverdins by vinyl groups into biliverdins [6] or verdin homologs like **1** [2, 3].

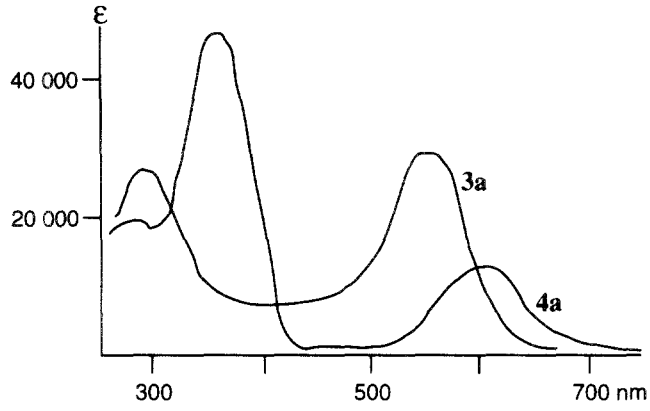


Fig. 2. Absorption spectra of **3a** and **4a** (chloroform)

Thus, the hypsochromic shift of the *b-homo*-verdins pointed to a considerable twisting of the chromophore at the two single bonds joining the ethene moiety to the two dipyrrinones which prevent extensive conjugation. Indeed, a PCMODEL [14] force field calculation of (*Z*,*Z*,*Z*)-**3c** suggested a torsion of about 25° at both ethene single bonds. It should be mentioned that for (*Z*,*E*,*Z*)-**3c** such calculations resulted in a more or less coplanar conformation at the central ethene fragment. It is interesting to note that this situation is comparable to the one for the (*Z*) and (*E*) diastereomers of stilbene [17]. This result also corroborated the tentative configurational assignment of (*Z*,*Z*,*Z*)-**3** as deduced above from NMR arguments. The delicate conformational situation at the *meso* double bond of **3** was also stressed by the pronounced shifts of the long wavelength band on changing the residues in positions 8, 13 on proceeding from **3a** to **3c**. These shifts indicated slightly different torsions at the ethene single bonds. In conclusion, the *b-homo*-verdin chromophore **II** was found to be more similar to a rubin than to a verdin.

Upon addition of acid, the long wavelength absorptions of **3** were strongly shifted bathochromically and hyperchromically to about 740 nm (Fig. 3). This dramatic change could be reversed by addition of base. This behavior could be rationalized by the unique possibility of the chromophore **II** to stabilize the positive

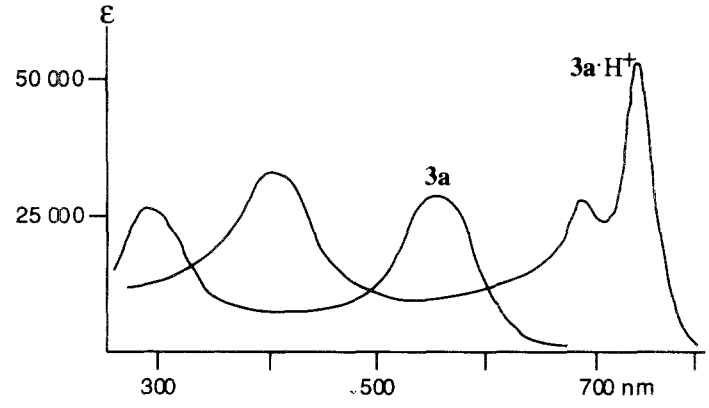
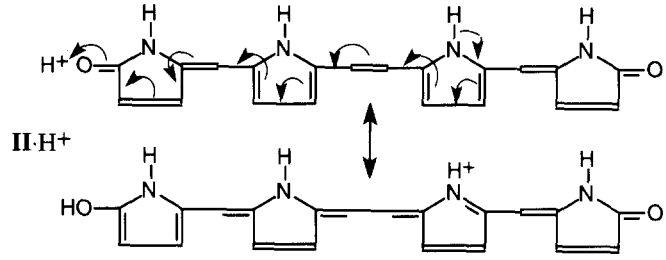


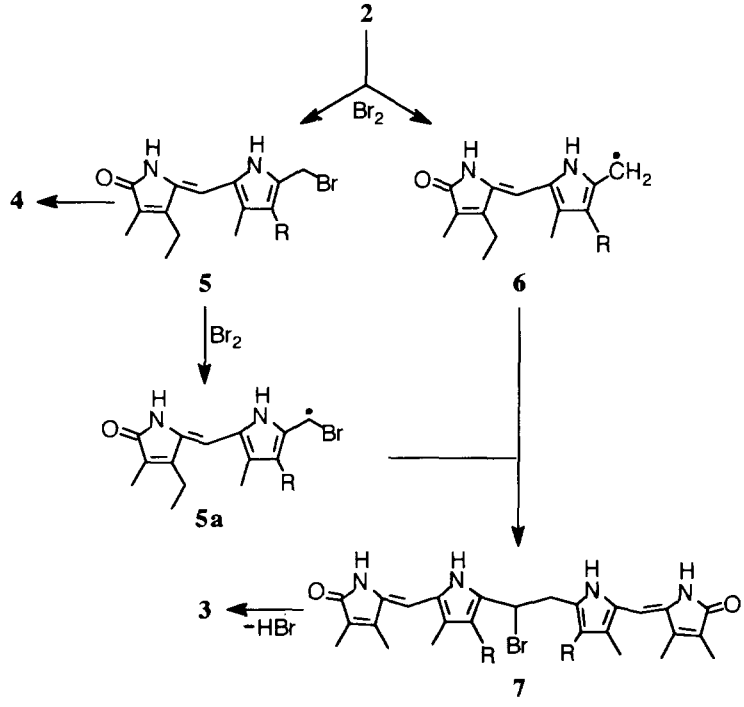
Fig. 3. Absorption spectra of **3a** and **3a**·H^+ (chloroform)

charge introduced by protonation according to Scheme 2. Thereby, the protonated system **II**·H^+ would become a stretched and more or less coplanar chromophore which should absorb at rather long wavelengths and with high intensity at the long wavelength band as was found experimentally.



Scheme 2

Mechanistic Aspects



With respect to the reaction mechanism, we suggest that the treatment of dipyrrinone **2** with bromine in dichloromethane first yields the bromomethyl derivative **5** together with the radical intermediate **6**. The intermediate **5** could then undergo acid catalyzed self condensation in the common way of bile pigment synthesis [6] to yield the corresponding mesobilirubin-XIIIα **4** on the one hand. On the other hand, upon further reaction with bromine **5** could yield the radical intermediate **5a**. Recombination of **5a** with **6** would result in the bromo intermediate **7**. The latter could then easily eliminate HBr (see Scheme 1) to yield the *b-homo*-verdins **3**.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz instrument with *TMS* as internal standard. UV/Vis spectra were recorded on a HP-8451A instrument, and IR spectra on a Perkin-Elmer 983 G spectrophotometer. Mass spectra were measured on a Finnigan MS-90 instrument, and melting points were determined with a micro melting point apparatus. Silica GF_{254} was used for column chromatography.

Dimerization procedure

1 mmol dipyrrinone **2** [18] was dissolved in 100 ml argon saturated dichloromethane. The mixture was stirred at room temperature for 15 min under an argon atmosphere. Then bromine (320 mg, 2 mmol, 2.0 mole equivalents) dissolved in 100 ml dichloromethane was added dropwise during 1 h. The color of the solution changed from yellow *via* light yellow to green. The mixture was stirred for another 30 min after all bromine was added. TLC (eluent: dichloromethane / ethyl acetate / tetrachloromethane = 2/1/1, v/v/v) showed that the reaction was complete. The reaction mixture was treated with 50 ml saturated aqueous $NaHCO_3$ and 150 ml dichloromethane. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 30 ml). The combined extracts were washed successively with water (2 × 50 ml), saturated aqueous $NaHCO_3$ (2 × 50 ml), water (2 × 50 ml), brine (50 ml), and then dried over anhydrous sodium sulfate. After removing the solvent, the residue was dissolved in the minimum amount of dichloromethane, then chromatographed on a silica GF_{254} column with dichloromethane / ethyl acetate / tetrachloromethane = 2/1/1 (v/v/v) as the eluent. This resulted in two fractions: a red compound (**3**, first fraction) and a blue compound (**4**, second fraction).

(Z,Z,Z)-1,2-bis-(2,7-Dimethyl-3-ethyl-8-methoxycarbonylethyl-dipyrrinone-9-yl)-ethene (**3a**; $C_{36}H_{44}N_4O_6$)

Prepared from **2a** [18] according to the procedure given above to yield 29%; m.p.: 260 °C (dec.); ^1H NMR (chloroform-d, δ, 500 MHz): 1.18 (t, J = 7.65 Hz, $2CH_2\mathbf{CH_3}$-3,18), 1.95 (br s, $2CH_3$-2,19), 2.10 (br s, $2CH_3$-7,13), 2.60 (br s, $2\mathbf{CH_2}CH_3$3,18), 2.96 (br s, $2\mathbf{CH_2}CH_2COO$), 3.08 (br s, $2CH_2\mathbf{CH_2}COO$), 3.64 (s, $2OCH_3$), 5.68 (s, 2-CH=), 7.76 (s, –CH=CH–) ppm; ^1H–^1H COSY (chloroform-d): 1.18↔2.60 ppm (J = 7.65 Hz; CH_2CH_3-3,18); 2.96↔3.08 ppm (CH_2CH_2-8,13); ^1H NMR (pyridine-d_5, δ, 500 MHz): 1.05 (t, J = 7.65 Hz, $2CH_2\mathbf{CH_3}$-3,18), 1.90 (s, $2CH_3$-2,19), 2.00 (s, $2CH_3$-7,13), 2.40 (q, J = 7.65 Hz, $2\mathbf{CH_2}CH_3$-3,18), 2.65 (t, J = 6.51 Hz, $2\mathbf{CH_2}CH_2COO$), 2.90 (t, J = 6.51 Hz, $2CH_2\mathbf{CH_2}COO$), 3.73 (s, $2OCH_3$), 6.04 (s, 2-CH=), 8.29 (s, –CH=CH–) ppm; ^1H–^1H COSY (pyridine-d_5): 1.05↔2.40 ppm (J = 7.65 Hz; CH_2CH_3-3,18); 2.65↔2.90 ppm (J = 6.51 Hz; CH_2CH_2-8,13); ^{13}C NMR (pyridine-d_5, δ 125 MHz): 8.48 ($\mathbf{CH_2}CH_3$), 9.79 (CH_3), 14.21 (CH_3), 17.76 ($\mathbf{CH_2}CH_3$), 20.14 ($CH_2\mathbf{CH_2}COO$), 35.27 ($CH_2\mathbf{CH_2}COO$), 51.66 (OCH_3), 95.49 (–CH=CH–), 125.77, 130.70, 138.81, 142.61, 146.74, 148.00, 160.36, 170.95, 172.16 (C=O), 172.71 ($\mathbf{COOCH_3}$) ppm; UV/Vis ($CHCl_3$): $\lambda_{max.}$ = 290 (25300), 540 (27000) nm (ε); UV/Vis ($CHCl_3$ + $Zn(OAc)_2$): $\lambda_{max.}$ = 302 (700), 400 (1000), 644 (26500) nm (ε); UV/Vis ($CHCl_3$ + $Zn(OAc)_2$ + *TFA*): $\lambda_{max.}$ = 400 (55200), 674 (17200), 744 (111500) nm (ε); UV/Vis ($CHCl_3$ + *TFA*): $\lambda_{max.}$ = 400 (33400), 690 (27600), 744 (50600) nm (ε); IR (KBr): ν = 3434, 2967, 2890, 1733, 1707, 1625, 1601, 1141, 1382, 1358, 1285, 1210, 1090 cm^{-1}; MS (CI): *m/e* (%) = 628 (30; M^+), 493 (10), 386 (15), 350 (20), 302 (100), 125 (55), 96 (37); MS (FAB): *m/e* (%) = 628 (20; M^+), 493 (10), 413 (50), 176 (55), 149 (60); *m/e*; (M^+) for $C_{36}H_{44}N_4O_6$: calcd.: 628.3260, obsd.: 628.3265. The elemental analysis (C, H, N) was in accordance with the calculated values.

(Z,Z,Z)-1,2-bis-(2,7-Dimethyl-3-ethyl-8-methoxycarbonylmethylene-dipyrrinone-9-yl)-ethene (**3b**: $C_{34}H_{40}N_4O_6$)

Prepared from **2b** [19] according to the procedure given above to yield 28%; m.p.: 270 °C (dec.); ^1H NMR (pyridine-d_5, δ, 500 MHz): 0.98 (t, J = 7.65 Hz, $2CH_2\mathbf{CH_3}$-3,18), 1.85 (s, $2CH_3$-2,19), 2.00 (s,

$2CH_3$-7,13), 2.32 (q, $J = 7.65$ Hz, $2CH_2CH_3$-3,18), 3.50 (s, $2OCH_3$), 4.20 (s, $2CH_2COOCH_3$), 5.92 (s, 2-CH=), 8.80 (s, –CH=CH–) ppm; UV/Vis ($CHCl_3$): $\lambda_{max.} = 290$ (17500), 545 (18300) nm (ε); UV/Vis ($CHCl_3 + Zn(OAc)_2$): $\lambda_{max.} = 300$ (12900), 400 (20800), 628 (19300) nm (ε); UV/Vis ($CHCl_3 + Zn(OAc)_2 + TFA$): $\lambda_{max.} = 300$ (800), 400 (25800), 744 (49700) nm (ε); UV/Vis ($CHCl_3 + TFA$): $\lambda_{max.} = 300$ (13000), 400 (20200), 744 (27600) nm (ε); IR (KBr): $\nu = 3434$, 2951, 1739, 1694, 1604, 1448, 1382, 1359, 1287, 1213, 1134, 1091 cm^{-1}; MS (FAB): *m/e* (%) = 600 (M^+, 15), 490 (10), 413 (20), 329 (25), 176 (100), 136 (98); MS (EI, 70 eV): *m/e* (%) = 600.3 (100), 574.3 (89), 542.3 (33), 524.2 (32), 465.2 (22), 300.1 (21), 267 (26), 236 (16), 207 (27), 162 (47); *m/e* (M^+) for $C_{34}H_{40}N_4O_6$: calcd.: 600.2948, obsd.: 600.2922.

(Z,Z,Z)-1,2-bis-(3,8-Diethyl-2,7-dimethyl-dipyrrinone-9-yl)-ethene (**3c**; $C_{32}H_{40}N_4O_2$)

Prepared from **2c** [20] according to the procedure given above to yield 25%; m.p.: 300 °C (dec.); ^1H NMR (pyridine-d_5, δ, 500 MHz): 0.91 (t, $J = 7.65$ Hz, $2CH_2CH_3$-8,13), 0.98 (t, $J = 7.65$ Hz, $2CH_2CH_3$-3,18), 1.85 (s, $2CH_3$-2,19), 2.00 (s, $2CH_3$-7,13), 2.32 (q, $J = 7.65$ Hz, $2CH_2CH_3$-8,13), 2.40 (q, $J = 7.65$ Hz, $2CH_2CH_3$), 6.00 (s, 2-CH=), 8.20 (s, –CH=CH–) ppm; UV/Vis ($CHCl_3$): $\lambda_{max.} = 285$ (41600), 530 (39100) nm (ε); UV/Vis ($CHCl_3 + Zn(OAc)_2$): $\lambda_{max.} = 390$ (29500), 670 (36500), 710 (38500) nm (ε); UV/Vis ($CHCl_3 + Zn(OAc)_2 + TFA$): $\lambda_{max.} = 240$ (41200), 310 (26800), 390 (28500), 670 (25800), 750 (29200) nm (ε); UV/Vis ($CHCl_3 + TFA$): $\lambda_{max.} = 240$ (40400), 310 (24320), 390 (29200), 750 (131700) nm (ε); IR (KBr): $\nu = 3444$, 2962, 2962, 1697, 1622, 1599, 1443, 1382, 1362, 1283, 1205, 1093 cm^{-1}; MS (FAB): *m/e* (%) = 512 (100; M^+), 413 (30), 255 (33), 149 (48), 136 (98); MS (EI, 70 eV): *m/e* (%) = 512.2 (8), 266.1 (16), 255 (8), 238 (26), 221 (100), 210 (38), 165 (15); *m/e* (M^+) for $C_{32}H_{40}N_4O_2$: calcd.: 512.3151, obsd.: 512.3153.

Mesobiliverdin-XIIIα dimethyl ester (**4a**)

4a was obtained in 23% yield besides **3a**; m.p.: 233–235 °C (Ref. [12]: 230–232 °C); IR, UV/Vis, and ^1H NMR spectra agreed with literature data [13, 14].

3,17-Diethyl-8,12-di-(methoxycarbonylmethyl)-1,19,21,24-tetrahydro-2,7,13,18-tetramethyl-1,19-dioxo-22H-bilin (**4b**)

4b was obtained in 24% yield besides **3b**; m.p.: 200–202 °C (dec.) (Ref. [14]: 202–203 °C); IR, UV/Vis, and ^1H NMR spectra agreed with literature data [12].

3,17,8,12-Tetraethyl-1,19,21,24-tetrahydro-2,7,13,18-tetramethyl-1,19-dioxo-22H-bilin (**4c**)

4c was obtained in 23% yield besides **3c**; m.p.: 200–202 °C (Ref. [13]: 202–203 °C); IR, UV/Vis, and ^1H NMR spectra agreed with literature data [13].

Acknowledgments

Financial support from the *China National Science Foundation* is greatly appreciated. Q.C. thanks the *Austrian Founds zur Förderung der Wissenschaftlichen Forschung* for a *Lise-Meitner* postdoctoral reaseach fellowship in order to continue his research on bile pigments at the Institute of Chemistry, Johannes Kepler University, Linz. We are grateful to Prof. Dr. *D. A. Lightner* for providing us with a preprint of [4].

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Received January 13, 1995, Accepted January 17, 1995