On Corrole Chemistry. An Isomerization Study and Oxidative Cleavage of the Corrole Macroring to a Biliverdin Structure

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In the present paper, we report the synthesis of free 5- and 10-monophenylcorroles, **4** and **3** respectively as well as the first example of molecular oxygen oxidation of the corrole macrocycle identified as an open chain tetrapyrrole (biliverdin) structure **7**. Reaction of **1** and **2** in acetic acid leads to a mixture of two a,c-biladienes **3b** and **4b** and therefore to a mixture of two corrole isomers **3** and **4**. Reaction of **1** and **2** in trifluoroacetic acid leads only to the symmetrical corrole isomer **3** in 41% yield.

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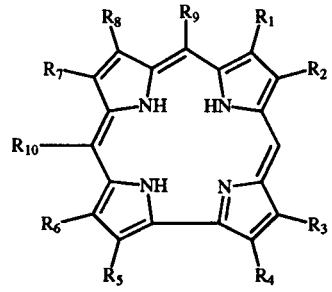
Introduction.

Recently, macrocyclic tetrapyrrole systems have gained considerable interest as they play an important role in various biological processes. Included among those compounds are the metal complexes of corroles, corrins and porphyrins, these ring systems being present in many natural products and synthetic derivatives [1,2]. Corroles can be considered as an intermediate between corrins and porphyrins as they present a direct link between two pyrroles and retain an 18 π-electron aromatic system [3,4]. Synthesis of these fundamental tetrapyrrole ring systems have attracted increasing interest during the last twenty years [3-9]. Indeed, novel macrocycles possessing the corrole nucleus present a particular challenge since the chemistry of corrole is far from developed.

In view of recent increasing attention to corroles, we wish to report the synthesis of free monophenyl-substituted corroles obtained by an isomerization reaction and the first example of molecular oxygen oxidation of the corrole macrocycle into an open chain tetrapyrrole structure, *i.e.* a biliverdin structure.

Results and Discussion.

Despite the absence of a C-20 meso carbon bridge, corroles are really attractive macrocycles as they possess a corrin like skeleton with double bonds involving porphyrin-like conjugation [3]. Johnson *et al.* showed in 1964 that oxidative intramolecular coupling of an a,c-biladiene led to the corresponding corrole macroring in yields higher than 60% [10]. Until the present, a,c-biladienes are the most important open-chain tetrapyrroles used in modern porphyrin and corrole syntheses and many methods have been developed since 1961 for their synthesis [11-15]. Condensation of a dipyrromethane-5,5'-dicarboxylic acid with an appropriately substituted 2-formylpyrrole provides high yields of the required a,c-biladienes. They are usually obtained in solution as a red dihydrobromide salt and thus it appears to be one of the best known methods to date. Interestingly, the chemistry of 1,19-dibromo-a,c-biladienes has been further extended by Smith *et al.* in 1994 [7]. They observed that an a,c-biladiene can be transformed into either or both corroles and biliverdins, under appropriate conditions. By refluxing the a,c-biladiene in acidic (*para*-toluenesulfonic acid) dimethyl sulfoxide, the corresponding biliverdin can be formed in yields as high as 70%. By refluxing in methanol, the corresponding corrole is formed in yields averaging 26% [7]. As the methods for the synthesis of a,c-biladienes and corroles steadily progresses [4,7,9], different functional groups have been appended to corroles. While not meant to be comprehensive, a few examples are instructive. Licoccia *et al.* have described the synthesis of cobalt(III) complexes of meso-phenyl-substituted corroles [5] and have also shown that even in the presence of steric groups at the periphery of the corrole macrocycle, a planar structure is finally obtained. Recently, Smith *et al.* have reported the first formylcorroles [6]. They have described the synthesis of biscorrole derivatives also [8]. Our group is also involved in the synthesis of free monoaryl-substituted corroles because the investigation of such a class of compounds might lead us to determine how variations in symmetry and the degree of conjugation affect the reactivity and the stability of tetrapyrroles. In order to prepare **3**, the proper precursor **3b** was first synthesized by dissolving 5,5'-dicarboxy-4,4'-diethyl-3,3'-dimethyldipyrryltoluene **1** with two equivalents of 3,4-diethyl-2-formylpyrrole **2** in acetic acid, followed by dropwise addition of 33% hydrobromic acid in the same solvent. The mixture was stirred at room temperature for two hours and the reaction monitored by spectrophotometry to determine complete conversion of the starting material to biladiene. Surprisingly, removing of the solvent *in vacuo* yielded a mixture of isomeric a,c-biladienes **3b** and **4b**. This reaction was further studied to find the origin of the isomerization step. Therefore, no attempts were made in order to separate the mixture of these two a,c-biladienes which were used in the following cyclization step.



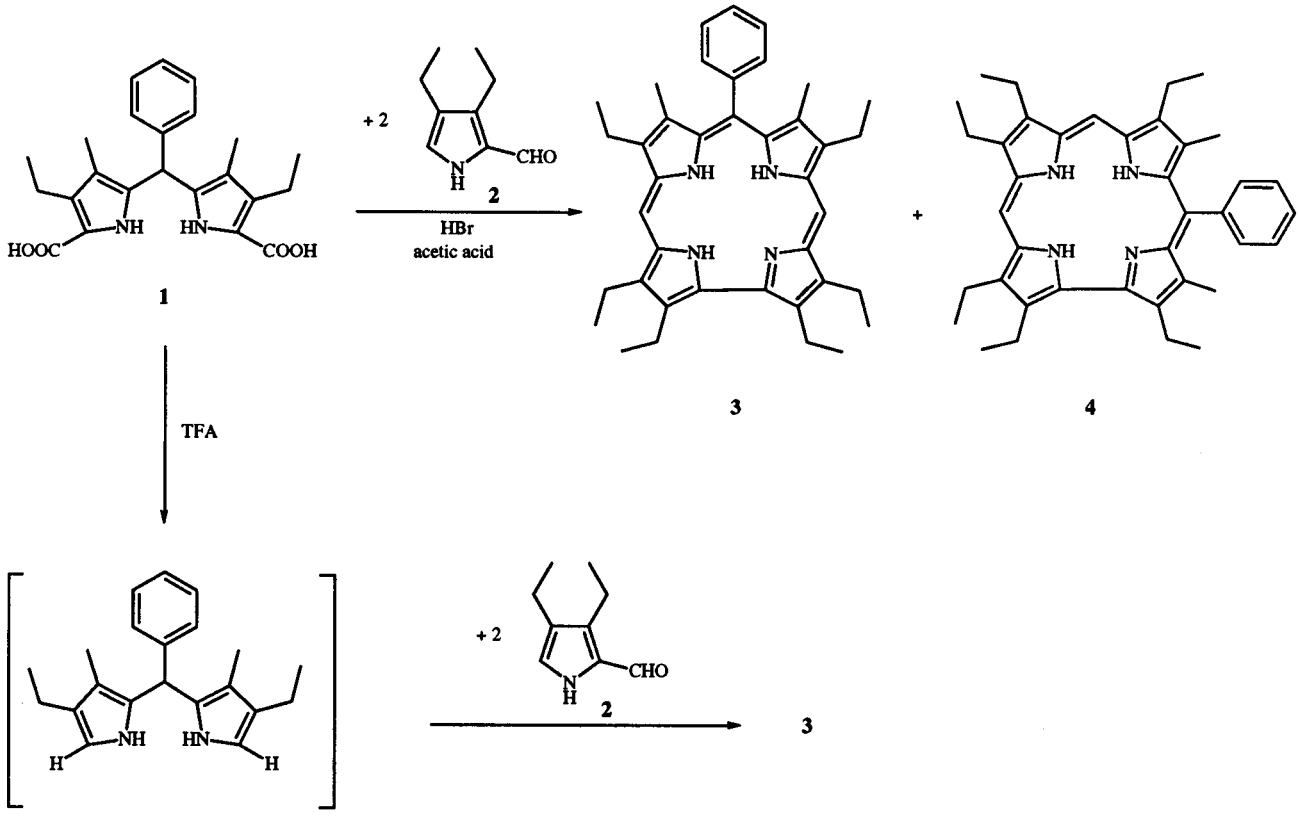
3: R_1, R_8 = Me ; $R_2, R_3, R_4, R_5, R_6, R_7$ = Et ; R_9 = Ph ; R_{10} = H
4: R_6, R_7 = Me ; $R_1, R_2, R_3, R_4, R_5, R_8$ = Et ; R_9 = H ; R_{10} = Ph
5: R_1, R_2, R_7, R_8 = Me ; R_3, R_4, R_5, R_6 = Et ; R_9 = Ph ; R_{10} = H

The mixture of **3b** and **4b** was dissolved in methanol saturated with sodium hydrogencarbonate and stirred for 5 minutes at room temperature. Addition of *p*-chloranil followed by addition of 50% hydrazine in water led, after removing the solvent, to a crude mixture of **3** and **4** in 34% yield (Scheme 1). Final purification was accomplished by means of preparative scale thin layer chromatography on glass plates. The less polar band (blue when protonated) was shown to correspond to the asymmetrical corrole **4** and the most polar band (green when protonated) corresponded to the symmetrical corrole **3**.

The ^{1}H nmr spectra of the 5- and 10-phenyl derivatives were easily identified by the number and the integration of the meso methylene bridge (Figure 1). The assignment of the resonances was made on the basis of symmetry properties. Only one signal (2H) due to the meso hydrogens was present in the ^{1}H nmr spectrum of the symmetrical 10-phenyl derivative **3** whereas two signals (each 1H) were observed in the low field region of the spectrum of **4**. The isomer which shows two signals (each 3H) due to the methyl groups has been identified as being **4**. The ^{1}H nmr spectrum for the second isomer indicated that the methyl groups were equivalent (one signal, 6H), these data were in good agreement with the structure **3**. It has to be noted that some similar isomerization reactions have been recently described by Paolesse *et al.* [16] and by Smith *et al.* [8]. In one case, separation of the two isomers isolated as Co(III) complexes has been accomplished by careful fractional crystallization from *n*-pentane at -30° but no further investigation was done [16].

To obtain a better understanding of such intriguing isomerization, we decided to carry out the same reaction with a prior *in situ* decarboxylation of the tetraalkyldipyrromethane-5,5'-dicarboxylic acid **1** before addition of the dialkyl-2-formylpyrrole **2**. Only the required a,c-biladiene

Scheme 1



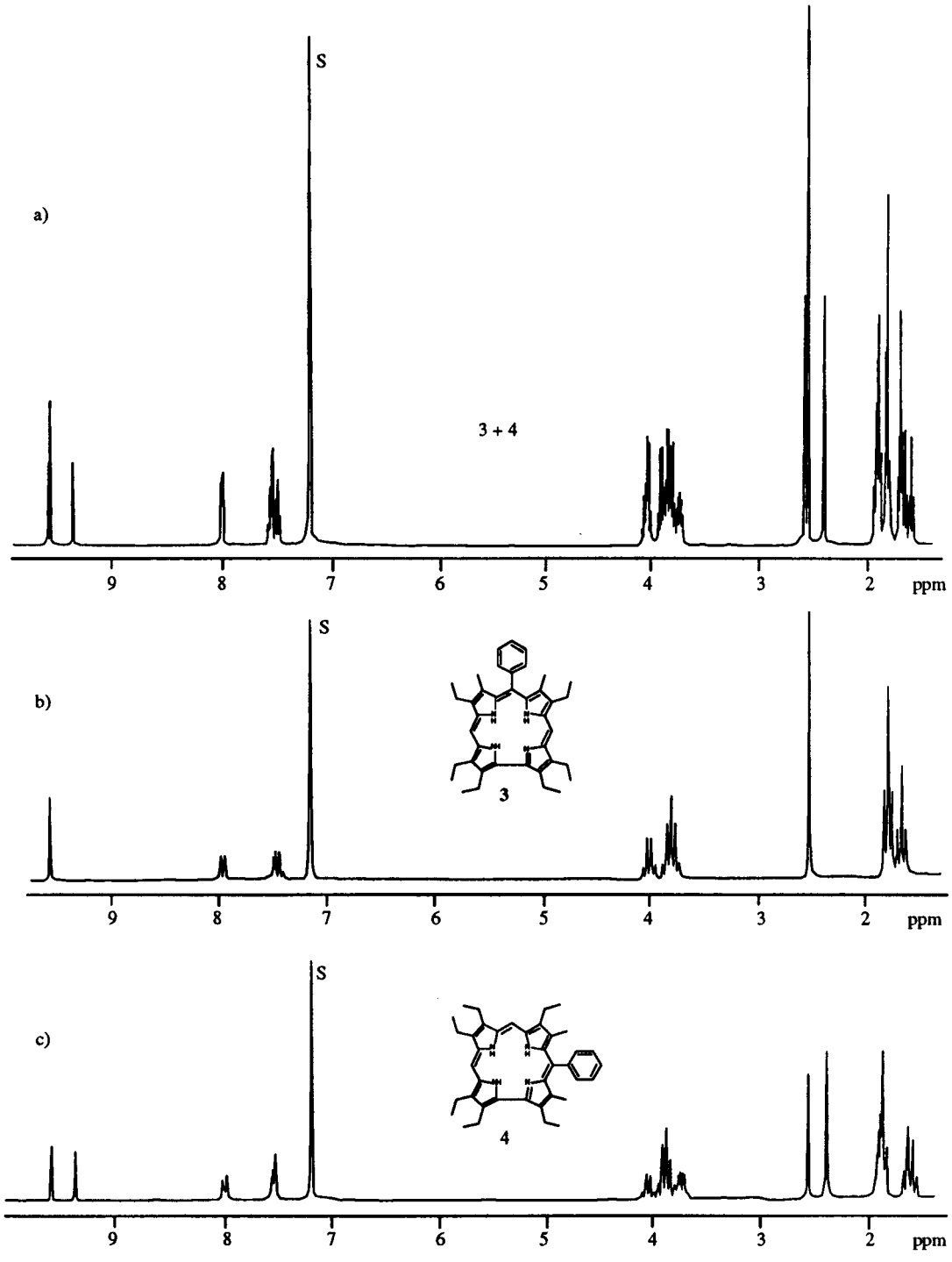
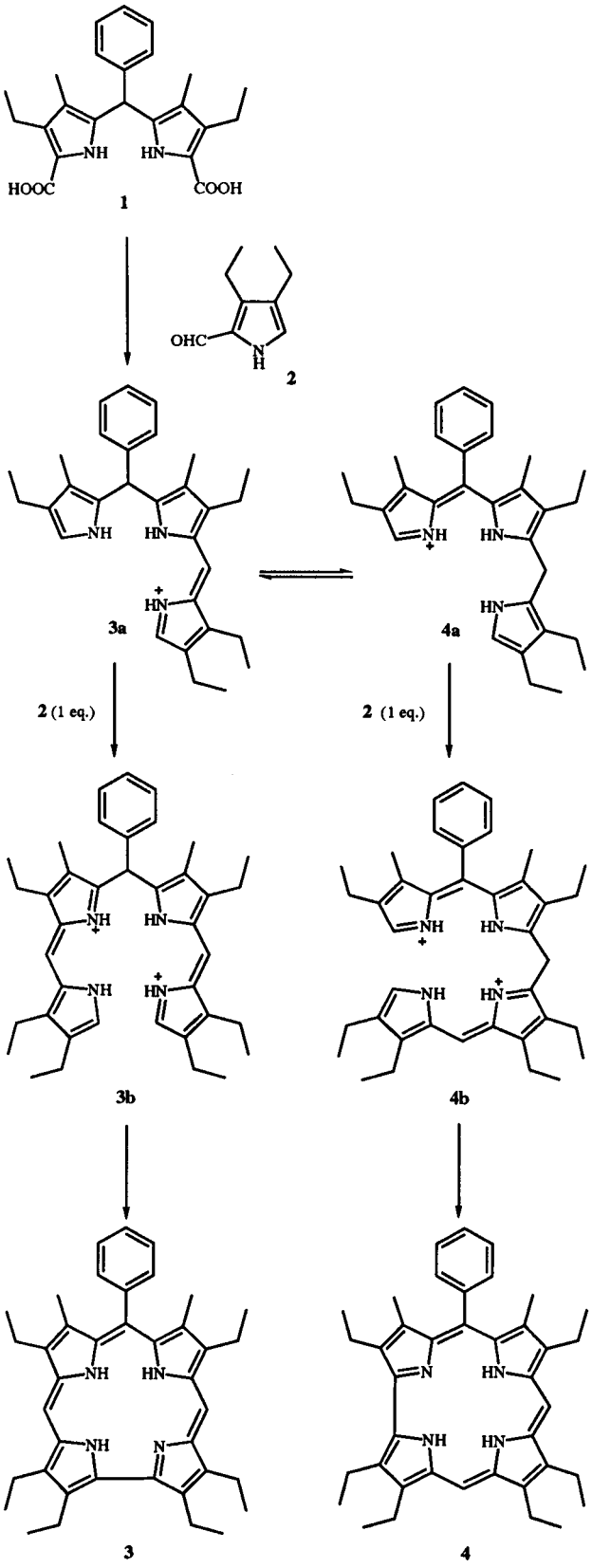


Figure 1.

salt **3b** was observed and isolated as a green solid. Oxidative cyclization was then carried out and this later led only to the symmetrical corrole **3** in 41% yield (Scheme 1). Similarly, only compound **5b** was obtained when **6** with **2** were allowed to react, and then in the next cyclization step, corrole **5** was isolated in 37% yield. It appears that the electron-withdrawing character of the meso-phenyl substituent slows down the decarboxylation reaction rate by making the α-pyrrolecarboxylic position less reactive to proton attack. A possible pathway leading to the formation of the two isomers **3** and **4** is shown in Scheme 2. Indeed, the condensation reaction can proceed

Scheme 2

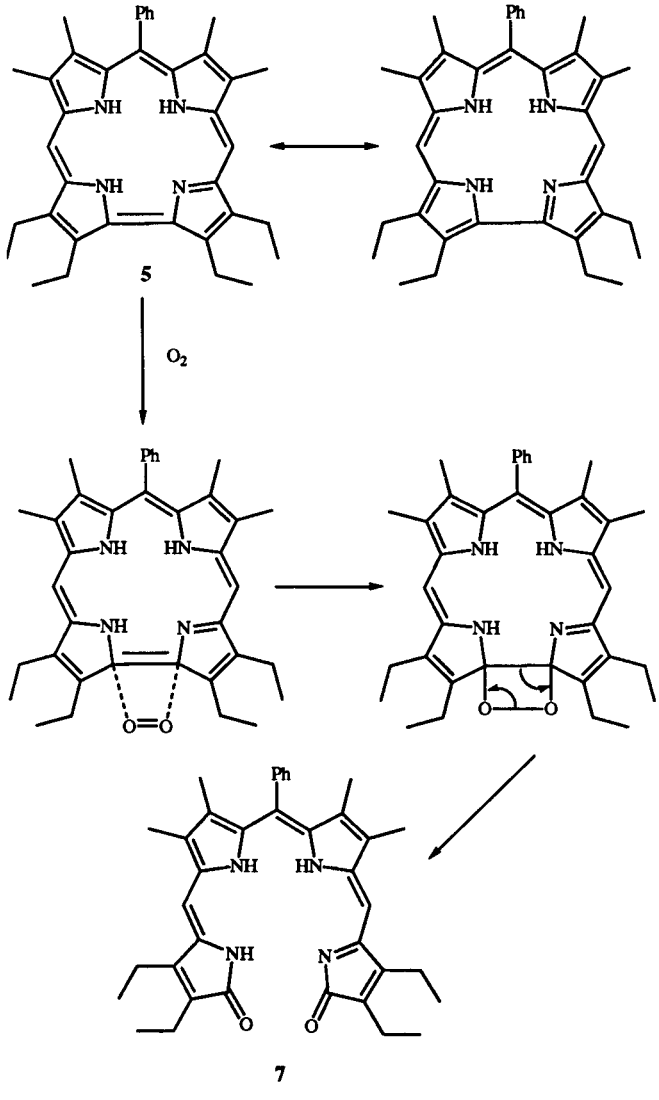


via the two tripyrryl-like intermediates **3a** and **4a**. Two possible isomeric forms can further react with monoformylpyrrole **2** yielding first, two different substituted-a,c-biladienes **3b** and **4b** followed by a mixture of the two corrole isomers **3** and **4**.

Compounds **3**, **4** and **5** were found to be air-sensitive when left in solution. In order to identify the decomposition products, ^{1}H nmr studies were carried out on compound **5** as this later presents a ^{1}H nmr spectrum easier to assign in the methyl and ethyl regions than compounds **3** or **4**. In the presence of air and light, **5** in solution slowly transformed over a few hours into a more polar compound **7** and a large amount of base-line material as well as less polar materials. The mass spectra of **7** reveals a molecular peak at m/z = 574 corresponding to the parent peak of **5** plus 32. This can be explained by the gain of two oxygen atoms in the molecule. The nmr and ir studies revealed that the isolated product from the degradation reaction of **5** is a ring-opened compound possessing two amide functions. The ^{1}H nmr spectrum of **7** shows that the NH resonance has moved considerably downfield when compared to the spectrum of **5**. The shielding of the CH bridges linking the pyrrole rings observed at around 6 ppm for **7** has also to be noted since these resonances appear around 10 ppm in the case of the corrole macrocycle. This is consistent with the loss of the macrocyclic aromaticity and the presence of an open-chain tetrapyrrole derivative. This hypothesis was further confirmed by an ir spectroscopic study. Indeed, the ir spectra of **7** shows a characteristic absorption band at 1660 cm^{-1} (strong) owing to the presence of two amide functions.

A possible mechanism of this oxidation reaction would proceed *via* the cleavage of the pyrrole-pyrrole bond after the attack of dioxygen as proposed in Scheme 3. It is interesting to note that in the case of *meso*-unsubstituted corrole, and to the best of our knowledge, a similar degradation reaction has never been reported. In contrast, such oxidative cleavage is usually observed in heme series [17,18]. Indeed, heme compounds are particularly sensitive to oxidative attack at the meso positions leading to the rupture or elimination of the carbon bridge. This results in the cleavage of the porphyrin macrocycle and the formation of an open chain tetrapyrrole (bilin) structure. Moreover, Hanack *et al.* have shown very recently that photolysis of the silicium complex of the substituted α, β, γ-triazabenzcorrole results in an open chain triazatetrapyrrole structure [19], the cleavage of the 1,2-double bond of the corrole derivative giving two amide groups as terminal functions. It is also important to note that up to now no product has ever been isolated from the degradation reaction of the corrole ring. Compound **7** is therefore the first example of molecular oxygen oxidation of the corrole macrocycle.

Scheme 3



EXPERIMENTAL

The uv-visible spectra were recorded on a Varian Cary 1 spectrophotometer. Mass spectra were obtained with a Kratos Concept 32 S spectrometer in the eims mode or the hrms mode. Data were collected and processed using a Sun 3/80 workstation. The ^1H nmr spectra were recorded on a Bruker AC 200 Fourier transform spectrometer at the Centre de Spectrométrie Moléculaire de l'Université de Bourgogne. All chemical shifts are given downfield from internal tetramethylsilane. The nmr data are presented in the following order: chemical shift, integration, peak multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Preparative scale thin layer chromatography was carried out on 20 cm x 20 cm glass plates coated with Merck G 254 silica gel (2 mm thick). 5,5'-Dicarboxy-4,4'-diethyl-3,3'-dimethyldipyrryltoluene **1** [20], 5,5'-dicarboxy-3,3',4,4'-tetramethyldipyrryltoluene **6** [20] and 3,4-diethyl-2-formylpyrrole **2** [21] have been synthesized as already described.

1,19-Dideoxy-2,3,7,13,17,18-hexaethyl-8,12-dimethyl-10-phenyl-a,c-biladiene Dihydrobromide (**3b**).

5,5'-Dicarboxy-4,4'-diethyl-3,3'-dimethyldipyrryltoluene **1** (325 mg, 0.8 mmole) was dissolved in trifluoroacetic acid (25 ml) and the resulting orange solution was stirred for 5 minutes at room temperature. 3,4-Diethyl-2-formylpyrrole **2** (250 mg, 1.6 mmoles) in methanol (30 ml) was added dropwise, and the red solution was stirred for 15 minutes, before addition of 33% hydrobromic acid in acetic acid (5 ml). After dropwise addition of diethyl ether (50 ml), the title a,c-biladiene salt did not precipitate and was further isolated by evaporation of the solvent as a green solid. Compound **3b** was not further purified but used as a crude compound in the next reaction.

2,3,7,13,17,18-Hexaethyl-8,12-dimethyl-10-phenylcorrole (**3**).

a,c-Biladiene dihydrobromide **3b** was dissolved in methanol (200 ml) saturated with sodium hydrogencarbonate and stirred for 5 minutes. *p*-Chloranil (300 mg) was then added. The solution was again stirred for 15 minutes, and then 3 ml of 50% hydrazine in water was added. After 1 hour, the solvent was evaporated under vacuum to give a crude solid which was redissolved in methylene chloride, washed with water and dried over magnesium sulfate. Chromatography on basic alumina (methylene chloride elution), afforded product **3** (m = 193 mg, 41%) which corresponds to the first purple eluted compound.

Compound **3** had uv-vis (methylene chloride, λ_{max}, nm, (ε x 10^{-3}, $mol^{-1}1\ cm^{-1}$)): 401 (72.8), 413 (69.7), 546 (10.3), 555 (10.0), 598 (10.1); ^1H nmr (deuteriochloroform): δ 1.63 (t, 6H, CH_2CH_3), 1.76 (m, 12H, CH_2CH_3), 2.31 (s, 6H, Me), 3.84 (m, 8H, CH_2CH_3), 4.00 (q, 4H, CH_2CH_3), 7.69 (m, 3H, Ph), 7.98 (m, 2H, Ph), 9.45 (s, 2H, meso 5,15); ms: (ei) m/z 570 (M^+) (100), 285 (M^{2+}); hrms: Calcd. for $C_{39}H_{46}N_4$: 570.3722 (M^+). Found: 570.3727.

Anal. Calcd. for $C_{39}H_{46}N_4$: C, 82.05; H, 8.13; N, 9.82. Found: C, 82.33; H, 7.94; N, 9.43.

1,19-Dideoxy-2,3,7,13,17,18-hexaethyl-8,12-dimethyl-10-phenyl-a,c-biladiene Dihydrobromide (**3b**) and 1,19-Dideoxy-2,8,12,13,17,18-hexaethyl-3,7-dimethyl-5-phenyl-a,c-biladiene Dihydrobromide (**4b**).

A mixture of compounds **3b** and **4b** was obtained by dissolving **1** (325 mg, 0.8 mmole) and **2** (250 mg, 1.6 mmoles) in 50 ml of acetic acid followed by addition of 33% hydrobromic acid in acetic acid (5 ml). The mixture was stirred at room temperature for two hours with monitoring by spectrophotometry until the complete conversion of the starting material to biladienes was accomplished. The solvent was removed *in vacuo* to yield a mixture of isomeric biladienes **3b** and **4b**.

2,8,12,13,17,18-Hexaethyl-3,7-dimethyl-5-phenylcorrole (**4**) and 2,3,7,13,17,18-Hexaethyl-8,12-dimethyl-10-phenylcorrole (**3**).

These compounds were prepared as described above from a,c-biladienes **3b** and **4b**. The solution was evaporated to dryness and the residue was dissolved in methylene chloride, washed with water until neutral pH and dried (magnesium sulfate). The residue was dissolved in methylene chloride and filtered through a column of tlc alumina gel eluted and packed with the same solvent. This first purification affords the title compounds as a mixture of the two isomers **3** and **4** (m = 158 mg, 34%). Final purification was accomplished by preparative scale thin layer chromatography glass plates using methylene

chloride/methanol (98:2) and few drops of triethylamine. This purification step was shielded from light. The less polar band (blue) corresponds to the asymmetrical corrole **4** and the most polar band (green) corresponds to the symmetrical corroles **3**. The yields were: symmetrical isomer **3** (m = 77 mg, 17%): see above and the asymmetrical isomer **4** (m = 77 mg, 17%); uv-vis (methylene chloride, λ_{max}, nm,(ε x 10^{-3}, $mol^{-1}l\ cm^{-1}$)): 402 (88.4), 412 (77.1), 560 (17.5), 596 (12.2); ^{1}H nmr (deuteriochloroform): δ 1.57 (m, 6H, CH_2CH_3), 1.78 (m, 12H, CH_2CH_3), 2.28 (s, 3H, Me), 2.46 (s, 3H, Me), 3.86 (m, 12H, CH_2CH_3), 7.70 (m, 3H, Ph), 8.05 (m, 2H, Ph), 9.13 (s, 1H, meso), 9.30 (s, 1H, meso); ir (potassium bromide): ν 3350 (NH), 2962 (CH), 2928 (CH), 2868 cm^{-1} (CH); ms: (ei) m/z 570 ($M^{+\bullet}$) (100), 285 ($M^{2+\bullet}$); hrms: Calcd. for $C_{39}H_{46}N_4$: 570.3722 (M^+). Found: 570.3724.

Anal. Calcd. for $C_{39}H_{46}N_4$: C, 82.05; H, 8.13; N, 9.82. Found: C, 82.26; H, 7.74; N, 9.43.

1,19-Dideoxy-2,3,17,18-tetraethyl-7,8,12,13-tetramethyl-10-phenyl-a,c-biladiene Dihydrobromide (**5b**).

The title compound was prepared as reported for **3b** from 182 mg (0.5 mmole) of 5,5'-dicarboxy-3,3',4,4'-tetramethyldipyrryltoluene **6** and 150 mg (1 mmole) of **2**. This biladiene **5b** was used without further purification.

2,3,17,18-Tetraethyl-7,8,12,13-tetramethyl-10-phenylcorrole (**5**).

The title compound was prepared from **5b** as described for **3** (m = 100 mg, 37%); ^{1}H nmr (deuteriochloroform): δ 1.77 (m, 12H, CH_2CH_3), 2.29 (s, 6H, Me 8,12), 3.31 (s, 6H, Me 7,13), 3.88 (q, 4H, CH_2CH_3), 4.00 (q, 4H, CH_2CH_3), 7.69 (m, 3H, Ph), 7.94 (m, 2H, Ph), 9.40 (s, 2H, meso 5,15); ms: (ei) m/z 542 ($M^{+\bullet}$) (100).

2,3,17,18-Tetraethyl-7,8,12,13-tetramethyl-10-phenyl-a,b,c-bilatriene (**7**).

Compound **5** (30 mg) was dissolved in methylene chloride (150 ml) in the presence of air and light and stirred at room temperature for two hours (until monitoring by spectrophotometry indicated the complete degradation of the corrole). Compound **7** was obtained as a purple solid after purification by chromatography (tlc basic alumina gel eluted with methylene chloride), (m = 7.6 mg, 24%); ^{1}H nmr (deuteriochloroform): δ 1.01 (t, 3H, CH_2CH_3), 1.20 (m, 9H, CH_2CH_3), 1.54 (s, 3H, Me), 1.60 (s, 3H, Me), 1.99 (s, 3H, Me), 2.24 (s, 3H, Me), 2.53 (m, 4H, CH_2CH_3), 2.80 (m, 4H, CH_2CH_3), 6.10 (s, 1H, CH), 6.84 (s, 1H, CH), [7.09 (m, 3H), 7.87 (m, 2H)] Ph, 10.61 (s, 1H, NH), 11.49 (s, 2H, NH); ir (potassium bromide): ν 3350 (NH), 2963 (CH), 2926 (CH), 2853 (CH), 1656 cm^{-1} (C=O); ms: (ei) m/z 574 ($M^{+\bullet}$) (100).

Anal. Calcd. for $C_{37}H_{42}N_4O_2$: C, 76.32; H, 7.69; N, 10.18. Found: C, 75.98; H, 7.49; N, 10.34.

REFERENCES AND NOTES

[1] K. M. Smith, in Porphyrins and Metalloporphyrins, Vol I, 1st Ed, K. M. Smith, ed, Elsevier Scientific, Amsterdam, 1975, p 3.

[2] Y. Murakami, J. Kikuchi, Y. Hisaeda and O. Hayashida, *Chem. Rev.*, **96**, 721 (1996).

[3] R. Grigg, in The Porphyrins, Vol **2**, 1st ed, D. Dolphin, ed, Academic, New York, 1978, p 327.

[4] N. S. Genokhova, T. A. Melent'eva and V. M. Berezovskii, *Russ. Chem. Rev.*, **49**, 1056 (1980).

[5] S. Licoccia and R. Paolesse, in Metal Complexes with Tetrapyrrole Ligands III, J. W. Buchler, ed, Springer-Verlag, Berlin and Heidelger, 1995, p 71.

[6] R. Paolesse, L. Jaquinod, M. O. Senge and K. M. Smith, *J. Org. Chem.*, **62**, 6193 (1997).

[7] R. K. Pandey, K. R. Gerzevske, H. Zhou and K. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, 971 (1994).

[8] R. Paolesse, R. K. Pandey, T. P. Forsyth, L. Jaquinod, K. R. Gerzevske, D. J. Nurco, M. O. Senge, S. Licoccia, T. Boschi and K. M. Smith, *J. Am. Chem. Soc.*, **118**, 3869 (1996).

[9] S. Neya, K. Ohyama and N. Funasaki, *Tetrahedron Letters*, **38**, 4113 (1997).

[10] A. W. Johnson and I. T. Kay, *Proc. Chem. Soc.*, 89 (1964).

[11] A. W. Johnson and I. T. Kay, *J. Chem. Soc.*, 2418 (1961).

[12] A. W. Johnson and D. Oldfield, *J. Chem. Soc. (C)*, 794 (1966).

[13] R. Grigg, A. W. Johnson, R. Kenyon, V. B. Math and K. Richardson, *J. Chem. Soc. (C)*, 176 (1969).

[14] Y. Murakami, K. Sakata, Y. Tanaka and T. Matsuo, *Bull. Chem. Soc. Japan.*, **48**, 3622 (1975).

[15] I. D. Dicker, R. Grigg, A. W. Johnson, H. Pinnock, K. Richardson and P. Van den Broek, *J. Chem. Soc.*, 536 (1971).

[16] R. Paolesse, S. Licoccia, G. Bandoli, A. Dolmella and T. Boschi, *Inorg. Chem.*, **33**, 1171 (1994).

[17] P. O'Carra, in Porphyrins and Metalloporphyrins, Vol. I, 1st Ed, K. M. Smith, Elsevier Scientific, Amsterdam, 1975, p 123.

[18] R. Bonnett and A. F. McDonagh, *J. Chem. Soc., Chem. Commun.*, 237 (1970).

[19] J. Li, L. R. Subramanian and M. Hanack, *Chem. Commun.*, 679 (1997).

[20] C. K. Chang and I. Abdalmuhdi, *J. Org. Chem.*, **48**, 5388 (1983).

[21] Y. Murakami, Y. Kohno and Y. Matsuda, *Inorg. Chim. Acta*, **3**, 671 (1969).