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Synthesis of Unsymmetrically Substituted Porphyrins*

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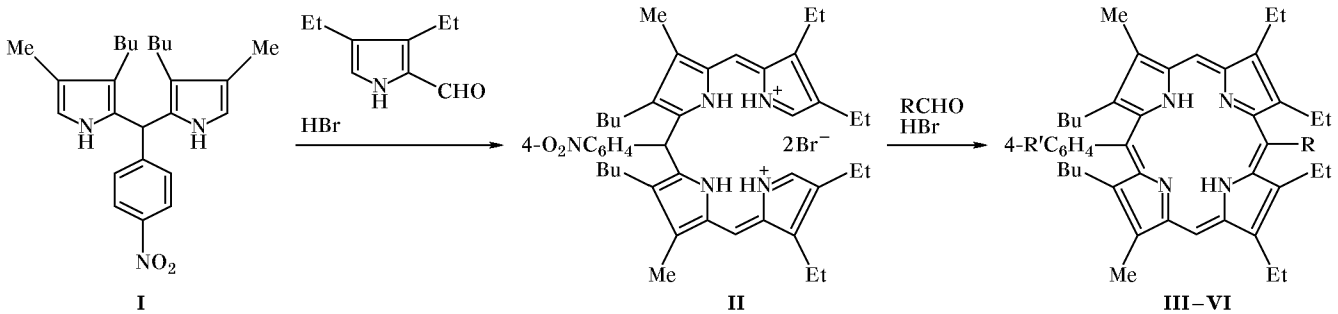
Abstract—Four new unsymmetrically substituted porphyrins have been synthesized using 10-aryl-*a*,*c*-biladiene dihydrobromide as key intermediate.

Various methods for synthesizing porphyrins are known. The choice of one or another procedure is determined by the desired substitution pattern in the final product. Methods suitable for preparation of relatively simple derivatives may be quite inapplicable to the synthesis of more complex structures. Porphyrins having more than three different substituents are usually synthesized through linear tetrapyrrole compounds which are subjected to ring closure in the final stage. Such intermediate products are *a*- and *b*-oxobilanes), *b*-bilenes, and *a*,*c*-biladienes [1–9]. The latter attract the greatest interest due to their accessibility. Hin *et al.* [3] described the synthesis of vinyl-substituted porphyrins through 1-bromo-19-methyl-*a*,*c*-biladienes. Lash and Roper [4] obtained porphyrins having two naphthyl groups in the macroring on the basis of *a*,*c*-biladienes. Lin *et al.* [5] synthesized the corresponding porphyrin derivative by cyclization of 1,19-arylmethyl-*a*,*c*-biladiene salts. In the present communication we report on the synthesis of porphyrins **III**–**VI** having various substituents in the opposite *meso*-positions with the use of 10-aryl-*a*,*c*-biladiene dihydrobromide as key intermediate (Scheme 1). The developed procedure is characterized by relative simplicity of the preparation of 10-nitrophenyloctaalkyl-*a*,*c*-biladiene dihydrobromide (which is a stable compound) and fairly high yields of the final products.

10-Aryl-substituted *a*,*c*-biladiene **II** was obtained by condensation of bis(3-butyl-4-methyl-2-pyrrolyl)-

Scheme 1.



I **II** **III**–**VI**

III, **V**, R = 4-$CH_3OC_6H_4$; **IV**, R = Et; **VI**, R = 4-HOC_6H_4; **III**, **IV**, **VI**, R′ = NO_2; **V**, R′ = NH_2.

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Table 1. Electron absorption spectra of compounds **II**–**VI** in chloroform

Comp. no.	λ_{max}, nm (log ε)				
	Soret	*IV*	*III*	*II*	*I*
II	373 (3.92)	452.4 (4.39)	521.7 (4.84)		
III	410.1 (5.14)	508.0 (4.01)	542.5 (3.61)	574.7 (3.71)	621.4 (3.49)
IV	405.3 (4.88)	509.4 (3.90)	539.0 (3.42)	572.4 (3.29)	626.3 (3.11)
V	409.3 (5.16)	508.2 (4.02)	543.6 (3.42)	574.9 (3.74)	625.8 (3.25)
VI	408.3 (5.11)	508.0 (4.00)	542.1 (3.38)	575.4 (3.69)	626.0 (3.16)

Table 2. Yields and elemental analyses of compounds **II**–**VI**

Comp. no.	Yield, %	Found, %			Formula	Calculated, %		
		C	H	N		C	H	N
II	64	61.74	6.79	8.35	$C_{43}H_{57}Br_2N_5O_2$	61.79	6.83	8.38
III	60	77.51	7.42	8.83	$C_{51}H_{59}N_5O_3$	77.57	7.48	8.87
IV	65	77.81	7.73	9.82	$C_{46}H_{55}N_5O_2$	77.86	7.76	9.87
V	87	80.59	7.98	9.18	$C_{51}H_{61}N_5O$	80.63	8.04	9.22
VI	97	77.37	7.30	8.98	$C_{50}H_{57}N_5O_3$	77.42	7.35	9.03

p-nitrophenylmethane (**I**) with 2 equiv of 3,4-diethylpyrrole-2-carbaldehyde in methanol. The use of hydrobromic acid as catalyst ensured a good yield (64%) of crystalline 1,19-unsubstituted 10-nitrophenyl-*a*,*c*-biladiene **II**. The latter was brought into reaction with aldehydes in methanol to obtain the corresponding 5,15-unsymmetrically substituted porphyrins **III** and **IV**. Here, we used as catalyst organic (trifluoroacetic, chloroacetic, and acetic) and inorganic acids (hydrochloric and hydrobromic). The greatest yield of the products (55–60%) was obtained in the presence of hydrobromic acid.

Porphyrin derivatives **V** and **VI** with active peripheric functional groups were obtained by chemical modification of the substituents in the phenyl rings of 5,15-diarylporphyrin **III**. Reduction of the nitro group in **III** with tin(II) chloride dihydrate gave 87% of aminophenyl derivative **V**. The reaction of **III** with boron trifluoride resulted in cleavage of the carbon–oxygen bond in the methoxy group with formation of 97% of hydroxyphenyl derivative **VI**.

The electron absorption and ^{1}H NMR spectra of porphyrins **III**–**VI** and *a*,*c*-biladiene **II** are fully consistent with the assumed structures. In the ^{1}H NMR spectrum of linear tetrapyrrole derivative **II** we observed two kinds of signals from the NH and *meso*-CH protons. Presumably, the presence of a nitrophenyl group in position *10* of *a*,*c*-biladiene **II** reduces the molecular symmetry, so that the above protons become nonequivalent and give separate signals in the spectrum.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker 200 instrument operating at 200 MHz. Tetramethylsilane was used as internal reference, and chloroform-*d*, as solvent. The electron absorption spectra (Table 1) were measured on a Specord M-400 spectrophotometer. The IR spectrum of porphyrin **VI** in KBr was obtained on a Specord M80 spectrometer.

Bis(3-butyl-4-methyl-2-pyrrolyl)-4-nitrophenylmethane (**I**) and 3,4-diethylpyrrole-2-carbaldehyde were synthesized by the procedures described in [10]. Organic solvents were purified by standard methods [11]. The purity of the products was checked by TLC on Silufol UV-254 plates. The yields and analytical data of compounds **II**–**VI** are given in Table 2.

8,12-Dibutyl-2,3,17,18-tetraethyl-7,13-dimethyl-10-(4-nitrophenyl)-*a*,*c*-biladiene dihydrobromide

(**II**). 3,4-Diethylpyrrole-2-carbaldehyde [12], 0.45 g (3 mmol), and aryldipyrrolylmethane **I**, 0.61 g (1.5 mmol), were dissolved in 300 ml of methanol under stirring, 1 ml of 46% hydrobromic acid was added, and the mixture was stirred for 1 h at room temperature. The precipitate of *a*,*c*-biladiene dihydrobromide **II** was filtered off, washed in succession with methanol and diethyl ether, and dried. Yield 0.80 g. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 13.42 s (2H, NH), 13.30 s (2H, NH), 7.12 s (2H, =CH), 6.88 d (2H, *o*-H), 6.36 d (2H, *m*-H), 5.27 s (1H, CH), 3.30 m and 3.12 m (12H, β-C**H**$_2$CH$_3$, β-C**H**$_2$CH$_2$CH$_2$CH$_3$), 2.71 s (3H, β-CH$_3$), 2.41 s (3H, β-CH$_3$), 2.17 quint (4H, β-CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.68 m (4H, β-CH$_2$CH$_2$-C**H**$_2$CH$_3$), 1.01 m and 0.87 m (18H, β-CH$_2$C**H**$_3$, β-CH$_2$CH$_2$CH$_2$C**H**$_3$).

3,7-Dibutyl-12,13,17,18-tetraethyl-15-(4-methoxyphenyl)-2,8-dimethyl-5-(4-nitrophenyl)porphine (III). A solution of 0.50 g (0.6 mmol) of *a*,*c*-biladiene **II**, 0.10 ml (1 mmol) of 4-methoxybenzaldehyde, and 1 ml of 46% hydrobromic acid in 50 ml of methanol was heated for 4 h under reflux. Iodine, 0.10 g, was added, and the mixture was refluxed for an additional 15 min. It was then cooled, and the precipitate was filtered off, washed with methanol, and dried. The product was dissolved in benzene and subjected to chromatography on aluminum oxide (Brockmann activity grade II). The eluate was evaporated, and compound **III** was precipitated with methanol. Yield 0.28 g. R_f 0.52 (eluent benzene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 10.12 s (2H, *meso*-H), 7.80 d (4H, *o*-H), 7.12 d (4H, *m*-H), 3.94 s (3H, OCH$_3$), 3.87 m (12H, β-C**H**$_2$CH$_3$, β-C**H**$_2$CH$_2$-CH$_2$CH$_3$), 3.42 s (6H, β-CH$_3$), 2.12 quint (4H, β-CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.52 sext (4H, β-CH$_2$CH$_2$C**H**$_2$-CH$_3$), 0.97 m (18H, β-CH$_2$C**H**$_3$, β-CH$_2$CH$_2$CH$_2$C**H**$_3$), –2.42 s (2H, NH).

3,7-Dibutyl-12,13,15,17,18-pentaethyl-2,8-dimethyl-5-(4-nitrophenyl)porphine (IV) was synthesized in a similar way, by condensation of 0.50 g (0.6 mmol) of *a*,*c*-biladiene **II** with 0.07 ml (1 mmol) of propionaldehyde. Yield 0.27 g. R_f 0.64 (eluent benzene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 10.16 s (2H, *meso*-H), 7.85 d (2H, *o*-H), 7.19 d (2H, *m*-H), 4.08 q (4H, *meso*-C**H**$_2$CH$_3$), 3.87 m (12H, β-C**H**$_2$CH$_3$, β-C**H**$_2$CH$_2$CH$_2$CH$_3$), 3.49 s (6H, β-CH$_3$), 2.24 t (6H, *meso*-CH$_2$C**H**$_3$), 2.12 quint (4H, β-CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.52 sext (4H, β-CH$_2$CH$_2$C**H**$_2$CH$_3$), 0.97 m (18H, β-CH$_2$C**H**$_3$, β-CH$_2$CH$_2$CH$_2$C**H**$_3$), –2.26 s (2H, NH).

5-(4-Aminophenyl)-3,7-dibutyl-12,13,17,18-tetraethyl-15-(4-methoxyphenyl)-2,8-dimethylporphine (V). A mixture of 0.25 g (0.3 mmol) of porphyrin **III**, 0.67 g (3.0 mmol) of tin(II) chloride dihydrate, and 50 ml of hydrochloric acid was stirred for 30 min at 90–100°C. The mixture was cooled, filtered, and diluted with an equal volume of water. The precipitate of porphyrin **V** hydrochloride was filtered off, washed in succession with dilute (1:2) hydrochloric acid, aqueous ammonia, and hot water, and dried. The product was dissolved in benzene and subjected to chromatographic purification on aluminum oxide (Brockmann activity grade II). The eluate was evaporated, and porphyrin **V** was precipitated with hexane. Yield 0.21 g. R_f 0.56 (eluent pyridine–chloroform, 1:4). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 10.15 s (2H, *meso*-H), 7.41 d (4H, *o*-H), 7.27 d (4H, *m*-H), 3.92 s (3H, OCH$_3$), 3.82 m (12H, β-C**H**$_2$CH$_3$, β-C**H**$_2$CH$_2$CH$_2$CH$_3$), 3.38 s (6H, β-CH$_3$), 2.07 quint (4H, β-CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.48 sext (4H, β-CH$_2$CH$_2$-C**H**$_2$CH$_3$), 0.81 m (18H, β-CH$_2$C**H**$_3$, β-CH$_2$CH$_2$-CH$_2$C**H**$_3$).

3,7-Dibutyl-15-(4-hydroxyphenyl)-12,13,17,18-tetraethyl-2,8-dimethyl-5-(4-nitrophenyl)porphine (VI). A solution of 0.15 ml (1.50 mol) of boron tribromide in 5 ml of chloroform was added to a solution of 0.25 g (0.3 mmol) of porphyrin **III** in 10 ml of chloroform, and the mixture was stirred for 1 h at room temperature. Methanol, 5 ml, was added, and the mixture was stirred for 30 min, neutralized with an ammonia solution, and evaporated to a minimal volume. The residue was subjected to chromatography on aluminum oxide (Brockmann activity grade II) with chloroform as eluent. The eluate was evaporated, and porphyrin **VI** was precipitated with hexane. Yield 0.24 g. R_f 0.76 (eluent ethyl acetate–heptane, 3:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 10.01 s (2H, *meso*-H), 7.86 d (4H, *o*-H), 7.19 d (4H, *m*-H), 4.94 s (1H, OH), 3.81 m (12H, β-C**H**$_2$CH$_3$, β-C**H**$_2$CH$_2$CH$_2$-CH$_3$), 3.38 s (6H, β-CH$_3$), 2.04 quint (4H, β-CH$_2$-C**H**$_2$CH$_2$CH$_3$), 1.59 sext (4H, β-CH$_2$CH$_2$C**H**$_2$CH$_3$), 0.91 m (18H, β-CH$_2$C**H**$_3$, β-CH$_2$CH$_2$CH$_2$C**H**$_3$), –2.31 s (2H, NH). IR spectrum, ν, cm^{-1}: 3300 (O–H), 1345 (δO–H), 1275 (C–O).

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