ISSN 1070-3632, Russian Journal of General Chemistry, 2007, Vol. 77, No. 7, pp. 1300–1307. © Pleiades Publishing, Ltd., 2007.
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Nickel Complexes of Chlorophyll Derivatives

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Received December 21, 2006

Abstract — Nickel complexes of certain phorbine and amide derivatives of chlorophyll *a* were synthesized. Most of the chlorophyll *a* derivatives studied form nickel complexes when boiled in toluene with an equimolar amount of nickel acetylacetonate in high yield. The yields of the nickel complexes of the chlorophyll derivatives are determined by the stability of the starting ligand under the reaction conditions.
DOI: 10.1134/S1070363207070249

Natural porphyrins and their modified analogs find wide application in medicine for diagnostics and treatment of oncological diseases [1, 2]. It was fairly recently found that nickel and zinc complexes of some chlorophyll *a* derivatives act as photo-independent cytotoxic agents with respect to malignant cells [3]. In this work we synthesized a series of nickel complexes by reactions of natural chlorins with nickel acetate and acetylacetonate under various conditions.

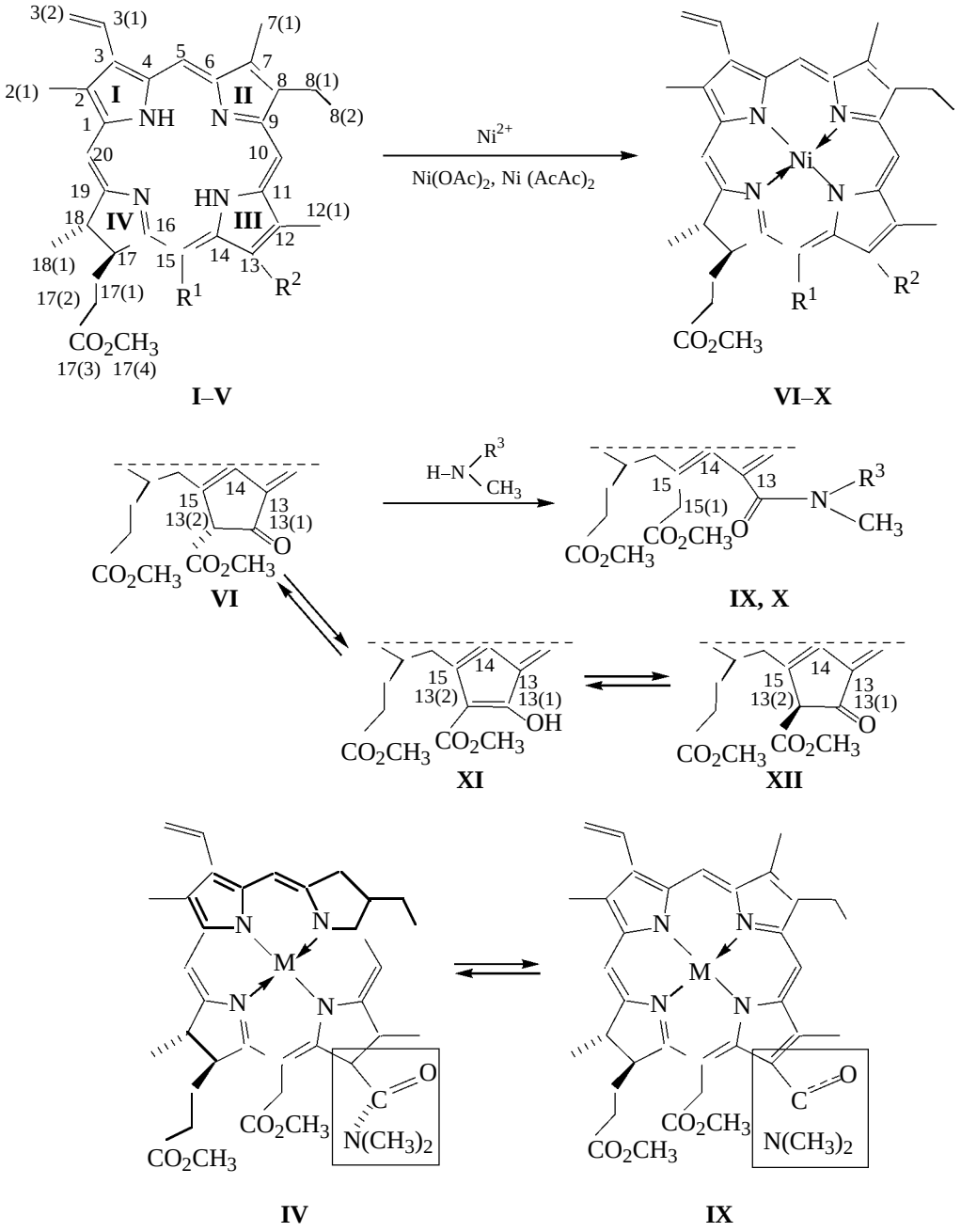
To synthesize nickel complexes, we used chlorophyll *a* phorbine and amide derivatives **I**–**V** obtained by published procedures [4–6]. To synthesize nickel complexes **VI**–**X**, we studied the reaction of these chlorins with nickel acetate and acetylacetonate under various conditions (see scheme and table).

The structure of the resulting complexes was proved by means of electronic and ^{1}H NMR spectroscopy. Comparison of the electronic absorption spectra of the ligands and their nickel complexes shows that the maximum of band I in the spectrum of the complex is shifted by 10–30 nm to the short-wave region, implying that nickel enters in the chlorin coordination sphere. The ^{1}H NMR spectra of the complexes contain signals of the same groups as the spectra of the starting ligands, except for the NH proton signals of the porphyrin cycle. As follows from the ^{1}H NMR spectrum of complex **VI** (Fig. 1), the reaction of compound I with nickel acetylacetonate involves, along with complex formation, isomerization of the ligand in the 13(2) position, leading to enol **XI** as intermediate. As a result, a mixture of diastereoisomeric Ni-methylpheophorbid *a* (**VI**) and Ni-methylpheophorbid *a*' (**XII**) was obtained. The fact that the product of the reaction between nickel acetylacetonate and compound **I** is a mixture of diastereoisomers is confirmed by the ^{1}H NMR data and by its reaction with methyl- and dimethylamine. The ^{1}H NMR spectrum of the product can be interpreted as a superposition of the spectra of two compounds, and, therewith, the superimposed spectra are identical by the number and multiplicity of signals and differ by the chemical shifts of the signals. The greatest difference is in the chemical shifts of the signals of the protons in position 13(2). Under the action of dimethyl- and methylamine, the product gives complexes **IX** and **X**, respectively. The formation of amide complexes as single reaction products provides evidence for the conclusion based on the ^{1}H NMR data.

Tertiary 13-amides of chlorin e_6 are known to exist in the form of two atropoisomers (see scheme) in equilibrium with each other [5]. The same is true of complex **IX**. Compared to starting ligand **IV**, the ratio of atropoisomers in the complex is different (Fig. 2). The change in the isomeric ratio in the equilibrium mixture seems to be connected with a change in the macrocycle conformation on introduction of the metal into the chlorin coordination sphere. The change of the macrocycle conformation changes the relative stability of the atropoisomers and, as a result, their contents in the equilibrium mixture.

Nickel complexes are most commnly synthesized using nickel acetate taken in a great excess. The reaction with nickel acetate is carried out either in a mixture of chloroform with methanol or in glacial acetic acid. When the reaction is carried out in glacial acetic acid, nickel complexes are formed only on boiling.

As seen from the table, high yields of nickel complexes are obtained only with fairly stable ligands **II** and **III**. With amides **IV** and **V**, the yields are much

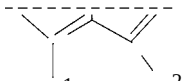
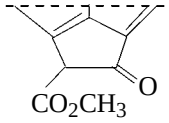
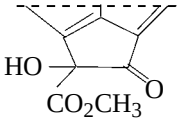
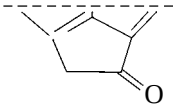
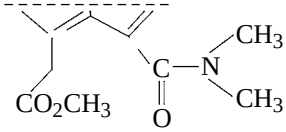
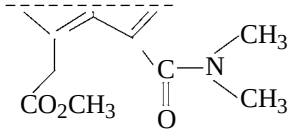


M = H_2 (**IV**), Ni (**IX**). For R^1 and R^2, see table, R^3 = CH_3 (**IX**), H (**X**).

lower. With compound **I**, no nickel complex forms under these conditions. Complex **VI** could be obtained with 10% yield by boiling compound **I** in toluene with an equimolar amount of nickel acetylacetonate. Under these conditions, the yields of other complexes also increase, especially strongly with relatively labile ligands **II** and **III**.

The preparative yields of the complexes are most affected by the reactivity of the ligands and metal salt in the complex-formation reaction and also by the stability of the ligands under the reaction conditions. The stability of a ligand is determined by its reactivity in all reactions except for complex formation (undesirable side reactions). The tendency for various undesirable reactions can be predicted on the basis of available information on the chemistry of chlorophyll derivatives. Compound **I** containing a reactive exo cycle is known to be most labile of all the ligands used, whereas compounds **II** and **III** are the most

Yields of nickel complexes (**VI**–**X**), %

Starting ligand	Complex		CH_3COOH, $Ni(CH_3COO)_2$	Toluene, $Ni(AcAc)_2$
I	**VI**		0	10
II	**VII**		60	65
III	**VIII**		45	78
IV	**IX**		25	69
V	**X**		21	70

stable. In their stability, chlorins **IV** and **V** occupy an intermediate position between methylpheophorbid **I** and phorbine derivatives **II** and **III**. The activated methylene group in position 15(1) of molecules **IV** and **V** can take part in many reactions similar to reactions of the 13(2)-methine group in compound **I**, but the reactivity of the 15(1)-methylene groups in chlorins **IV** and **V** is essentially lower. Summarizing the data in the table, we note that the preparative yield of natural chlorin complexes is most affected by the stability of the ligands under the reaction conditions. The highest yields of complexes were obtained with compounds **II** and **III** and the lowest, with compound **I**.

The fact that higher yields of complexes are attained on boiling in toluene is explained by the use of a more inert (compared to acetic acid) solvent. Replacement of toluene by benzene that has a lower boiling point provides a higher yield (30%) of complex **VI**. However, with benzene, we failed to achieve complete conversion of the starting ligand, which essentially complicated isolation of the complex. Therefore, with more stable ligands, with which the yields of complexes are sufficiently high, such replacement is inexpedient. Complexes **IX** and **X** can also be obtained by the action of amines on complex **VI**. However, this synthetic approach is less effective because of the difficulties in preparation of complex **VI**. Similar difficulties also arise when complex **VI** is converted to complex **VIII**.

EXPERIMENTAL

The ^1H NMR spectra were recorded in deuterochloroform on Bruker AMX-400 (400 MHz) and TESLA BS 587A (80 MHz) instruments. The IR spectra were recorded on a Specord M-80 device in KBr. The electronic absorption spectra were recorded on a Shimadzu UV-1700 spectrometer (PharmaSpec) at 200–1100 nm in quartz cells 10 mm in thickness with chloroform as reference. Thin-layer chromatography was performed on Silufol plates, eluent CCl_4–acetone (4 : 1 v/v). Silica gel of 100/400 grade (Silica gel L, wet packing) was used for column chromatography.

Methylpheophorbid *a* (I) was prepared from nettle [4]. Electronic absorption spectrum ($CHCl_3$), λ, nm: 668, 610, 541, 514, and 416 (Soret band). IR spectrum (KBr), cm^{-1}: 1624 (chlorin band), 1746 ($\nu_{C=O}$, ester), 1706 ($\nu_{C=O}$, keto group in the exo cycle). ^1H NMR spectrum ($CDCl_3$, 80 MHz), δ, ppm: 9.42 s

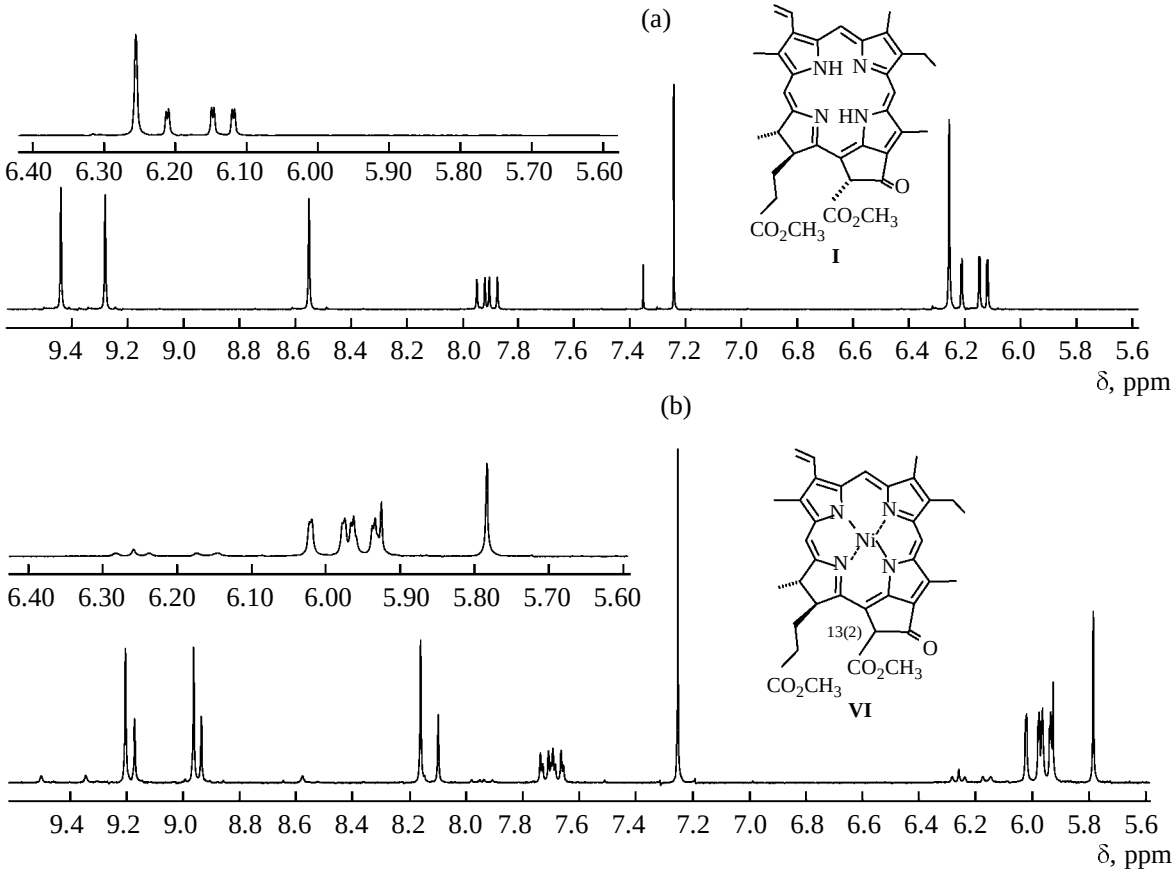


Fig. 1. ^{1}H NMR spectrum of (a) methylpheophorbid *a* (**I**) and (b) its nickel complex **VI** ($CDCl_3$, 400 MHz).

(1H, H^{10}), 9.30 s (1H, H^5), 8.55 s (1H, H^{20}), 7.92 d.d [1H, 3-(C*H*=CH_2), *J* 17.0 and 12.0 Hz], 6.27 s [1H, $H^{13(2)}$], 6.20 br.d [1H, 3-(CH=CHH_{trans}), *J* 16.0 Hz], 6.12 br.d [1H, 3-(CH=CHH_{cis}) *J* 12.0 Hz], 4.1–4.5 m (2H, H^{17}, H^{18}), 3.91 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.61 s (3H, 12-CH_3), 3.32 s (3H, 2-CH_3), 3.00 s (3H, 7-CH_3), 3.8–3.4 m [2H, 8-(CH_2CH_3)], 2.2–2.8 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.84 d (3H, 18-CH_3, *J* 10 Hz), 1.58 t (3H, 8-CH_2CH_3, *J* 12 Hz), 0.51 br.s (1H, I-NH), –1.8 br.s (1H, III-NHNH).

(13^2-Hydroxy)methylpheophorbid *a* (II) was isolated by column chromatography on silica gel (with subsequent crystallization from chloroform–methanol) from the fraction of polar chlorophyll derivatives obtained on isolation of compound **I**. The mixture contained diastereoisomers differing in the configuration of the asymmetric carbon atom in position 13(2). Electronic absorption spectrum ($CHCl_3$), λ, nm: 669, 609, 535, 505, 414 (Soret band). ^{1}H NMR spectrum ($CDCl_3$, 400 MHz), δ, ppm: major isomer, 9.37 s (1H, H^{10}), 9.15 s (1H, H^5), 8.60 s (1H, H^{20}), 7.79 d.d [1H, 3-(C*H*=CH_2), *J* 20.0 and 12.0 Hz], 6.14 d [1H, 3-(CH=CHH_{trans}), *J* 20.0 Hz], 6.05 d [1H, 3-(CH=CHH_{cis}) *J* 12.0 Hz], 5.43 s (1H, 13^2-OH), 4.50 q (1H, H^{18}, *J* 8.0 Hz), 4.16 br.d (1H, H^{17}, *J* 8.1 Hz), 3.68 s (3H, 13^2-$COOCH_3$), 3.67 s (3H, 12-CH_3), 3.63 s [1H, 17-($CH_2CH_2COOCH_3$)], 3.57 s (3H, 2-CH_3), 3.32 s (3H, 7-CH_3), 3.40 q [2H, 8-(CH_2CH_3), *J* 8.0 Hz], 2.23–2.65 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.56 t [3H, 8-(CH_2CH_3), *J* 8.0 Hz)], 1.61 d (3H, 18-CH_3, *J* 8.0 Hz), 0.20 br.s (1H, I-NH), –1.98 (br.s 1H, III-NHNH); minor isomer, 9.30 s (1H, H^{10}), 9.13 s (1H, H^5), 8.58 s (1H, H^{20}), 7.79 d.d [1H, 3-(C*H*=CH_2), *J* 16.0 and 12.0 Hz], 6.14 d [1H, 3-(CH=CHH_{trans}), *J* 16.0 Hz], 6.05 [1H, 3-(CH=CHH_{cis}) *J* 12.0 Hz], 5.27 s (1H, 13^2-OH), 4.50 q (1H, H^{18}, *J* 8.0 Hz), 4.16 br.d (1H, H^{17}, *J* 8.1 Hz), 3.68 s (3H, 13^2-$COOCH_3$), 3.66 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.62 s (3H, 12-CH_3), 3.56 s (3H, 2-CH_3), 3.32 s (3H, 7-CH_3), 3.40 q [2H, 8-(CH_2CH_3), *J* 8.0 Hz], 2.23–2.65 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.56 t [3H, 8-(CH_2CH_3), *J* 8.0 Hz)], 1.71 d (3H, 18-CH_3, *J* 8.0 Hz), 0.24 br.s (1H, I-NH), –1.98 br.s (1H, III-NHNH).

Methylpyropheophorbid *a* (III). A solution of 200 mg of compound **I** in 6 ml of pyridine was boiled

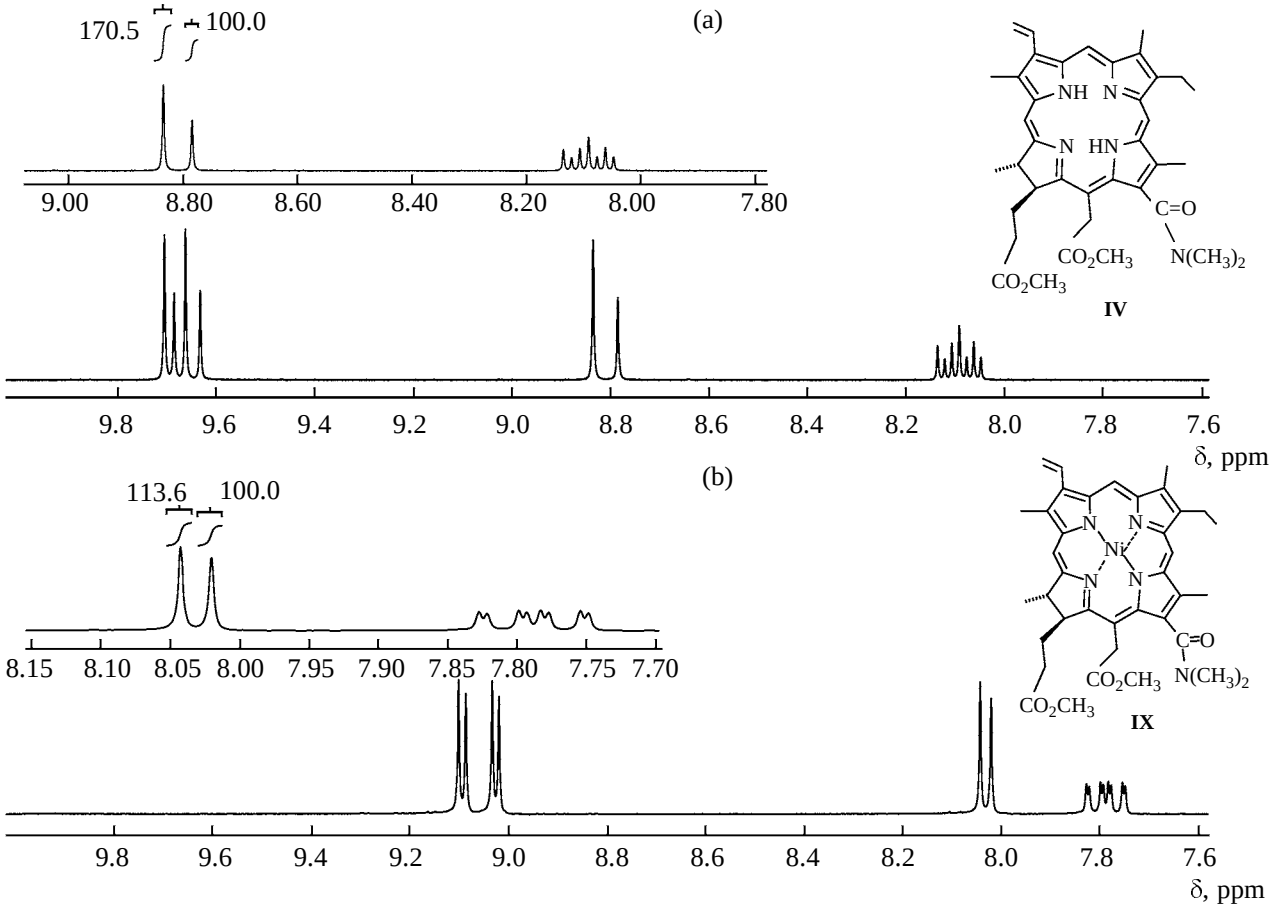


Fig. 2. ^{1}H NMR spectrum of (a) 13-*N,N*-dimethylamide-15,17-dimethyl ester of chlorin e_6 (**IV**) and (b) its nickel complex **IX** ($CDCl_3$, 400 MHz).

for 5 h, the mixture was cooled, mixed with 150 ml of chloroform, pyridine was removed with 5–7% HCl, and excess acid was removed with water. The chloroform solution was dried with anhydrous sodium sulfate and evaporated. The residue was subjected to column chromatography on (eluent CCl_4–acetone, 60 : 1). Yield 175 mg (97%). Electronic absorption spectrum ($CHCl_3$), λ, nm: 668, 611, 535, 506, 417 (Soret band). IR spectrum (KBr), cm^{-1}: 1745 ($\nu_{C=O}$, ester, the intensity of the band is much lower than that of the same band of compound I), 1702 ($\nu_{C=O}$, keto group in the exo cycle), 1610 (chlorin band). ^{1}H NMR spectrum ($CDCl_3$, 80 MHz), δ, ppm: 9.37 s (1H, H^{10}), 9.27 s (1H, H^5), 8.52 s (1H, H^{20}), 7.95 d.d [1H, 3-(C*H*=CH_2), *J* 19.0 and 11.0 Hz], 6.23 d [1H, 3-(CH=CHH_{trans}), *J* 18.0 Hz], 6.13 d [1H, 3-(CH=CHH_{cis}) *J* 10.0 Hz], 5.30 d (1H, $H^{13(2),A}$, *J* 22.0 Hz), 5.05 d [1H, $H^{13(2),B}$, *J* 21.0 Hz], 4.1–4.6 m (2H, H^{18}, H^{17}), 3.7 m [2H, 8-(CH_2CH_3)], 3.61 s [6H, 12-CH_3, 17-($CH_2CH_2COOCH_3$)], 3.37 s (3H, 2-CH_3), 3.14 s (3H, 7-CH_3), 2.10–2.80 m [4H, 17-(CH_2CH_2·$COOCH_3$)], 1.80 d (3H, 18-CH_3, *J* 7.0 Hz), 1.64 (3H, 8-CH_2CH_3, *J* 12.0 Hz), 0.80 br.s (1H, I-NH), –1.78 br.s (1H, III-NHNH).

13-(*N,N*-Dimethylamide)-15,17-dimethyl ester of chlorin e_6 (IV). Dimethylamine, 1 ml of a 33% aqueous solution, was added to a solution of 120 mg of compound **I** in 3 ml of chloroform. The reaction mixture was stirred for 1 h, diluted with chloroform, transferred to a separatory funnel, and the residual dimethylamine was washed off with distilled water to neutral washings. The resulting solution was dried with anhydrous sodium sulfate, the solvent was distilled off, and the residue was subjected to column chromatography. Yield 70 mg (55%). Electronic absorption spectrum ($CHCl_3$), λ, nm: 663, 607, 557, 529, 501, 402. IR spectrum (KBr), cm^{-1}: 1630 (chlorin band, 1732 ($\nu_{C=O}$, ester), 1653 (amide I band). ^{1}H NMR spectrum ($CDCl_3$, 80 MHz), δ, ppm: major isomer, 9.69 s (1H, H^{10}), 9.66 s (1H, H^5), 8.88 s (1H, H^{20}), 8.21 d.d [1H, 3-(C*H*=CH_2), *J* 17.9 and 11.5 Hz], 6.33 d.d [1H, 3-(CH=CHH_{trans}), *J* 19.6 and 1.8 Hz],

6.05 d.d [1H, 3-(CH=CHH_{cis}) *J* 11.5 and 1.6 Hz], 5.73 d (1H, $H^{15(1),A}$, *J* 19.0 Hz), 5.04 d (1H, $H^{15(1),B}$, *J* 19.0 Hz), 4.40–4.60 m (2H, H^{17}, H^{18}), 3.97 s [3H, 15-(CH_2COOCH_3)], 3.75 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.62 s (3H, 12-CH_3), 3.48 s (3H, 2-CH_3), 3.31 s (3H, 7-CH_3), 3.49 s [3H, 13-C(O)N(CH_3)(CH_3)], 2.72 s [3H, 13-(O)N(CH_3)(CH_3)], 3.68–3.85 m [2H, 8-(CH_2CH_3)], 2.10–2.70 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.60–1.75 m (6H, 18-CH_3, 8-CH_2CH_3), –1.75 br.s (I-NH), –1.91 br.s (III-NHNH); minor isomer, 9.67 s (1H, H^{10}), 9.63 s (1H, H^5), 8.77 s (1H, H^{20}), 7.99 d.d [1H, 3-($CH=CH_2$), *J* 17.7 and 11.5 Hz], 6.33 d.d [1H, 3-(CH=CHH_{trans}), *J* 19.6 and 1.8 Hz], 6.05 d.d [1H, 3-(CH=CHH_{cis}) *J* 11.5 and 1.6 Hz], 5.57 d (1H, $H^{15(1),A}$, *J* 19.0 Hz), 5.13 d (1H, $H^{15(1),B}$, *J* 19.0 Hz), 4.40–4.60 m (2H, H^{17}, H^{18}), 3.97 s [3H, 15-(CH_2COOCH_3)], 3.74 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.59 s (3H, 12-CH_3), 3.45 s (3H, 2-CH_3), 3.31 s (3H, 7-CH_3), 3.49 [3H, C(O)N(CH_3)(CH_3)], 3.08 s [3H, C(O)N(CH_3)(CH_3)], 3.68–3.85 m [2H, 8-(CH_2CH_3)], 2.10–2.70 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.60–1.75 m (6H, 18-CH_3, 8-CH_2CH_3), –1.65 br.s (I-NH), –1.73 br.s (III-NHNH).

13-(*N*-Methylamide)-15,17-dimethyl ester of chlorin e_6 (V). Methylamine, 0.8 ml of a 33% aqueous solution, was added to a solution of 146 mg of compound **I** in 8 ml of THF. The reaction mixture was stirred for 30 min, diluted with chloroform, the residual methylamine was washed off with distilled water to neutral washings. The resulting solution was dried with anhydrous sodium sulfate, and the solvent was distilled off. The residue was subkected to column chromarography. Yield 110 mg (72%). Electronic absorption spectrum ($CHCl_3$), λ, nm: 663, 607, 557, 529, 500, 402. IR spectrum (KBr), cm^{-1}: 1608 (chlorin band), 1744 ($\nu_{C=O}$, ester), 1636 (amide I band). ^1H NMR spectrum ($CDCl_3$, 400 MHz), δ, ppm: 9.70 s (1H, H^{10}), 9.64 s (1H, H^5), 8.81 s (1H, H^{20}), 8.10 d.d [1H, 3-($CH=CH_2$), *J* 23.8 and 15.4 Hz], 6.37 d.d [1H, 3- (CH=CHH_{trans}), *J* 23.8 and 1.8 Hz], 6.15 d.d [1H, 3-(CH=CHH_{cis}), *J* 15.8 and 1.8 Hz], 6.40 m (1H, 13-CONHCH$_3$), 5.54 d (1H, $H^{15(1),A}$, *J* 25.0 Hz), 5.26 d (1H, $H^{15(1),B}$, *J* 25.0 Hz), 4.36–4.49 m (2H, H^{17}, H^{18}), 3.84 s (3H, 13^2-$COOCH_3$), 3.62 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.56 s (3H, 12-CH_3), 3.50 s (3H, 2-CH_3), 3.33 s (3H, 7-CH_3), 3.81 q [2H, 8-(CH_2CH_3) *J* 10.0 Hz], 3.24 d (3H, 13-CONHCH_3, *J* 5.6 Hz), 1.90–2.60 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.73 m (6H, 18-CH_3, 8-CH_2CH_3), –1.60 br.s (I-NH), –1.80 br.s (III-NHNH).

Nickel acetylacetonate was obtained by precipitation from aqueous solution [7]. Distilled (137°C) acetylacetone, 6.5 ml, was added to a solution of 8.77 g of $Ni(NO_3)_2 \cdot 6\ H_2O$ in 70 ml of distilled water. The mixture was stirred at room temperature until the reagents dissolved completely. Ammonium solution was then added dropwise with stirring to pH 7.5. The light green precipitate that formed was filtered off, dried in vacuum (yield 9.54 g), and recrystallized from alcohol (light green crystals). The crystals are suitable for X-ray diffraction analysis. IR spectrum (KBr), cm^{-1}: 3353 (ν_{O-H}), 3276, 2992, 1620 ($\nu_{C=O}$), 1522 (ν_{C-O}), 1464, 1406, 1256, 1213, 1017, 928, 764, 660, 569 (ν_{M-O}). Found after decomposition with nitric acid, %: Ni 20.68. $C_5H_8NiO_2 \cdot H_2O$. Calculated, %: Ni 21.27.

Nickel complexes of chlorophyll derivatives. *a*. Starting ligand was boiled for 30 min with an equimolar amount of nickel acetate in glacial acetic acid. The formation of the reaction product was controlled by TLC on Silufol plates (CCl_4–acetone, 4 : 1). When the reaction was complete, the mixture was diluted with chloroform, and the acid and excess nickel acetate were washed off with distilled water to neutral washings. The resulting solution was dried with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting complex was isolated by column chromatography.

b. Starting ligand was boiled for 3 h with an equimolar amount of nickel acetylacetonate in toluene. The formation of the reaction product was controlled by TLC. The resulting complex was isolated by column chromatography. The mixture to be separated was applied on the column directly from the reaction mixture without its pretreatment. The reaction of compound **I** with nickel acetylacetonate in benzene was carried out similarly.

Ni-(13^2-Hydroxy)methylpheophorbid *a* (VII). *a*. From 222 mg of compound **II** and 64 mg of nickel acetate, 145 mg (60%) of complex **VII** was obtained. Electronic absorption spectrum ($CHCl_3$), λ, nm: 652, 610, 542, 495, 422, 394. ^1H NMR spectrum ($CDCl_3$, 400 MHz), δ, ppm: major isomer, 9.26 s (1H, H^{10}), 9.01 s (1H, H^5), 8.22 s (1H, H^{20}), 7.72 d.d [1H, 3-($CH=CH_2$), *J* 18.0 and 12.0 Hz], 6.00 d [1H, 3-(CH=CHH_{trans}), *J* 18.0 Hz], 5.97 d [1H, 3-(CH=CHH_{cis}), *J* 12.0 Hz], 5.10 s (1H, 13^2-OH), 4.26–4.32 m (2H, H^{17}, H^{18}), 3.78 s (3H, 13^2-$COOCH_3$), 3.64 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.50 s (3H, 12-CH_3), 3.15 s (3H, 2-CH_3), 3.00 s (3H, 7-CH_3), 3.42–3.58 m [2H, 8-(CH_2CH_3)], 2.19–2.46 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.53 t (3H, 8-CH_2CH_3, *J* 8.0 Hz), 1.42 d (3H, 18-CH_3, *J* 10.0 Hz); minor isomer, 9.22 s (1H, H^{10}), 8.98 s (1H, H^5), 8.18 s (1H, H^{20}), 7.72 d.d [1H, 3-($CH=CH_2$), *J* 18.0 and 12.0 Hz], 6.00 d. [1H, 3-(CH=CHH_{trans}), *J* 18.0 Hz], 5.97 d

[1H, 3-(CH=CHH_{cis}), *J* 12.0 Hz], 5.16 s (1H, 13^2-OH), 4.26–4.32 m (2H, H^{17}, H^{18}), 3.78 s (1H, 13^2-CO_2CH_3), 3.64 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.48 s (3H, 12-CH_3), 3.14 s (3H, 2-CH_3), 3.00 s (3H, 7-CH_3), 3.42–3.58 m [2H, 8-(CH_2CH_3)], 2.19–2.46 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.53 t (3H, 8-CH_2CH_3, *J* 8.0 Hz), 1.42 d (3H, 18-CH_3, *J* 8.0 Hz).

b. From 19 mg of compound **II** and 9 mg of nickel acetylacetonate, 14 mg (65%) of complex **VII** was obtained. The complexes obtained by procedures *a* and *b* coincide in chromatographic mobility (TLC) and spectral characteristics.

Ni-methylpyropheophorbid *a* (VIII). *a*. From 34 mg of compound **III** and 12 mg of nickel acetate, 17 mg (45%) of complex **VIII** identical to the sample prepared by procedure *b* was obtained.

b. From 29 mg of compound **III** and 15 mg of nickel acetylacetonate, 25 mg (78%) of complex **VIII** was obtained. Electronic absorption spectrum ($CHCl_3$), λ, nm: 652, 607, 543, 501, 422, 397. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz), δ, ppm: 9.30 s (1H, H^{10}), 9.06 s (1H, H^5), 8.16 s (1H, H^{20}), 7.77 d.d [1H, 3-(C*H*=CH_2), *J* 16.0 and 8.0 Hz], 6.03 d.d [1H, 3-(CH=CHH_{trans}), *J* 16.0 and 2.0 Hz], 5.97 d.d [1H, 3-(CH=CHH_{cis}) *J* 12.0 and 2.0 Hz], 4.87 d (1H, $H^{13(2),A}$, *J* 22.0 Hz), 4.79 d (1H, $H^{13(2),B}$, *J* 21.0 Hz), 3.97–4.01 m 18, (1H, H^{17}), 4.28 q (1H, *J* 8.0 Hz), 3.60 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.48 s (3H, 12-CH_3), 3.15 s (3H, 2-CH_3), 3.12 s (3H, 7-CH_3), 3.58–3.61 m [2H, 8-(CH_2CH_3)], 2.06–2.48 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.53–1.62 m (6H, 18-CH_3, 8-CH_2CH_3).

Ni-(13-*N*,*N*-dimethylamide)-15,17-dimethyl ester of chlorin e_6 (IX). *a*. From 34 mg of compound **IV** and 10 mg of nickel acetate, 9 mg (25%) of complex **IX** identical to the sample prepared by procedure *b* was obtained.

b. From 20 mg of compound **IV** and 9 mg of nickel acetylacetonate, 15 mg (69%) of complex **IX** was obtained. Electronic absorption spectrum ($CHCl_3$), λ, nm: 642, 495, 402. ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: major isomer, 9.11 s (1H, H^{10}), 9.04 s (1H, H^5), 8.06 s (1H, H^{20}), 7.80 d.d [1H, 3-(C*H*=CH_2), *J* 18.8 and 8.0 Hz], 6.03 m [1H, 3-(CH=CHH_{trans})], 5.90 br.d [1H, 3-(CH=CHH_{cis}) *J* 12.0 Hz], 5.26 d (1H, $H^{15(1),A}$, *J* 19.0 Hz), 4.48 d (1H, $H^{15(1),B}$, *J* 19.0 Hz), 4.06–4.09 m (1H, H^{18}), 3.89–3.92 m (1H, H^{17}), 3.90 s [3H, 15-(CH_2COOCH_3)], 3.63 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.34 s (3H, 12-CH_3), 3.13, 3.11 both br.s [both 6H, 2-CH_3, 12-CH_3, 7-CH_3, 13-C(O)N(CH_3)(CH_3)], 2.94 s [3H, 13-C(O)N(CH_3)·(CH_3)], 3.47–3.60 m [2H, 8-(CH_2CH_3)], 2.03–2.50 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.53–1.70 m (3H, 8-CH_2CH_3), 1.48 d (3H 18-CH_3, *J* 8.0 Hz); minor isomer: 9.09 s (1H, H^{10}), 9.02 s (1H, H^5), 8.02 s (1H, H^{20}), 7.78 d.d [1H, 3-(CH=CH_2), *J* 18.8 and 8.0 Hz], 6.03 m [1H, 3-(CH=CHH_{trans})], 5.90 br.d [1H, 3-(CH=CHH_{cis}) *J* 12.0 Hz], 4.15–4.08 m [2H, 15-($CH_2CO_2CH_3$)], 4.09 m (1H, H^{18}), 3.89–3.92 m (1H, H^{17}), 3.69 s [3H, 15-(CH_2COOCH_3)], 3.65 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.37 s (3H, 12-CH_3), 3.13, 3.11 both br.s [both 6H, 2-CH_3, 12-CH_3, 7-CH_3, 13-C(O)N(CH_3)(CH_3)], 2.96 s [3H, 13-C(O)N(CH_3)·(CH_3)], 3.47–3.60 m [2H, 8-(CH_2CH_3)], 2.03–2.50 m [2H, 17-($CH_2CH_2COOCH_3$)], 1.53–1.70 m (3H, 8-CH_2CH_3), 1.44 d (3H, 18-CH_3, *J* 8.0 Hz).

Ni-(13-*N*-methylamide)-15,17-dimethyl ester of chlorin e_6 (Ni–V). *a*. From 28 mg of compound **V** and 8 mg of nickel acetate, 6 mg (21%) of complex **X** identical to the sample prepared by procedure *b* was obtained.

b. From 29 mg of compound **V** and 13 mg of nickel acetylacetonate, 22 mg (70%) of complex **X** was obtained. Electronic absorption spectrum ($CHCl_3$), λ, nm: 634, 497, 409. ^{1}H NMR ($CDCl_3$, 400 MHz), λ, ppm: 9.09 s (1H, H^{10}), 9.03 s (1H, H^5), 8.03 s (1H, H^{20}), 7.79 d.d [1H, 3-(C*H*=CH_2), *J* 17.0 and 12.0 Hz], 6.02 d.d [1H, 3-(CH=CHH_{trans}), *J* 17.0 and 2.0 Hz], 5.93 d.d [1H, 3-(CH=CHH_{cis}), *J* 12.0 and 2.0 Hz], 6.22 br.q (1H, 13-CON*H*CH_3, *J* 4.8 Hz), 4.91 d (1H, $H^{15(1),A}$, *J* 20.0 Hz), 4.50 d (1H, $H^{15(1),B}$, *J* 20.0 Hz), 4.11 q (1H, H^{18}, *J* 7.2 Hz), 3.94–3.97 m (1H, H^{17}), 3.82 s [3H, 15-(CH_2COOCH_3)], 3.64 s [1H, 17-($CH_2CH_2COOCH_3$)], 3.20 s (3H, 12-CH_3), 3.18 d (3H, 13-CONHCH_3, *J* 5.2 Hz), 3.12 s (3H, 2-CH_3), 3.11 s (3H, 7-CH_3), 3.25–3.50 m [2H, 8-(CH_2CH_3)], 2.27–2.50 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.54–1.58 m (3H, 8-CH_2CH_3), 1.46 d (3H, 18-CH_3, *J* 7.2 Hz).

Mixture of diastereoisomeric Ni-methylpheophorbid *a* (VI) and Ni-methylpheophorbid *a*′ (XII). From 78 mg of compound **I** and 33 mg of nickel acetylacetonate, 9 mg (10%) of a mixture of stereoisomeric complexes **VI** and **XII** was obtained. Electronic absorption spectrum ($CHCl_3$), λ, nm: 652, 539, 496, 416. ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: complex **VI**: 9.31 s (1H, H^{10}), 9.07 s (1H, H^5), 8.17 s (1H, H^{20}), 7.75 d.d [1H, 3-(C*H*=CH_2), *J* 17.5 and 12.0 Hz], 6.02 d.d [1H, 3-(CH=CHH_{trans}), *J* 17.6 and 1.6 Hz], 5.98 d.d [1H, 3-(CH=CHH_{cis}), *J* 12.0 and 2.0 Hz], 5.79 s (1H, $H^{13(2)}$), 4.20–4.28 m (2H, H^{17}, H^{18}), 3.91 s (3H, 13^2-CO_2CH_3), 3.58 s [3H,

17-($CH_2CH_2COOCH_3$)], 3.48 s (3H, 12-CH_3), 3.15 s (3H, 2-CH_3), 3.12 s (3H, 7-CH_3), 3.54–3.65 m [2H, 8-(CH_2CH_3)], 2.06–2.42 m [4H, 17-($CH_2CH_2COO\cdot CH_3$)], 1.45–1.62 m (6H, 18-CH_3, 8-CH_2CH_3); complex **XII**: 9.27 s (1H, H^{10}), 9.04 s (1H, H^5), 8.10 s (1H, H^{20}), 7.75 d.d [1H, 3-($CH=CH_2$), *J* 17.5 and 12.0 Hz], 6.02 d [1H, 3-($CH=CH_{trans}$), *J* 17.6 and 1.6 Hz], 5.98 br.d [1H, 3-($CH=CH_{cis}$), *J* 11.6 Hz], 5.93 s (1H, $H^{13(2)}$), 4.20–4.28 m (1H, H^{18}), 1.44 d (1H, H^{17}, *J* 9.2 and 2.4 Hz), 3.70 s (3H, 13^2-CO_2CH_3), 3.59 s [3H, 17-($CH_2CH_2COOCH_3$)], 3.47 s (3H, 12-CH_3), 3.13 s (3H, 2-CH_3), 3.10 s (3H, 7-CH_3), 3.54–3.65 m [2H, 8-(CH_2CH_3)], 2.06–2.42 m [4H, 17-($CH_2CH_2COOCH_3$)], 1.45–1.62 m (3H, 8-$CH_2\cdot CH_3$); 1.44 d (3H, 18-CH_3, *J* 7.2 Hz).

ACKNOWLEDGMENTS

The work was performed under the Program of Support for Leading Scientific Schools of the Presudent of the Russian Federation (project no. NSh1206.2006.3).

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