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Phthalocyanines and Related Compounds: XXXVII.[1] Synthesis of Covalent Conjugates of Carboxy-substituted Phthalocyanines with α-Amino Acids

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Abstract—Methods of synthesis of covalent conjugates of metal complexes of octa-4,5-carboxy- and tetra-4-carboxyphthalocyanine, as well as of octa-6,7-carboxy-2,3-naphthalocyanine with α-amino acids, glycine and sarcosine, were developed and certain properties of the products were studied. The prepared conjugates are soluble in organic solvents and water.

In recent years water-soluble derivatives of phthalocyanine (Pc) have found wide practical use, specifically, as catalysts for generation of active oxygen species whose cytotoxic activity is exploited in photodynamic and catalytic (dark) cancer therapy [2–5].

Structural modification of porphyrins, specifically chlorins, by introduction in their molecules of α-amino acid fragments by way of covalent linking by methods of peptide synthesis [2] or even as counter ions [6] enhances their efficiency as photosensitizers for generation of singlet oxygen.

The aim of the present study was to develop convenient methods of synthesis of an almost unknown group of phthalocyanine derivatives, i.e. covalent conjugates with α-amino acids. Among other possible base structures for preparing such compounds we chose the presently fairly well-studied tetra-4- and octa-4,5-carboxy-substituted phthalocyanines. As an example, sodium salt of cobalt octa-4,5-carboxyphthalocyanine can be mentioned, which is now under clinical tests as a remedy for catalytic therapy [5].

Introduction into carboxy-substituted phthalocyanines of α-amino acid fragments can be achieved by two approaches: either starting from phthalic acid derivatives, primarily *o*-dinitriles, that already contain desired fragments, or by structural modification of carboxy groups in the existing macroring via their activation by transformation, for instance, into anhydrides or acyl halides.

In the course of the present study we have synthesized a new series of conjugates of metal complexes of octa-4,5-carboxyphthalocyanine with glycine (**I**, **II**) and sarcosine (**III**, **IV**) and studied their properties. α-Amino acids with primary amino groups, specifically glycine, react with *o*-phthaloyl group to form cyclic amides thus giving a series of tetracarboxy-substituted tetraimides of octa-4,5-carboxyphthalocyanines, while α-amino acids with secondary amino groups (sarcosine) give their octacarboxy-substituted octaamides. It is important that in both cases the high symmetry of the starting octa-4,5-carboxyphthalocyanine (the same as in unsubstituted Pc), i.e. D_{4h} for M(II) metal complexes and C_{4v} for M(III)X complexes with an axially coordinated ligand X.

The starting dinitriles, *N*-(ethoxycarbonylmethyl)-4,5-dicyanophthalimide (**VI**) and *N*,*N*'-bis(ethoxycarbonylmethyl)-*N*,*N*'-dimethyl-4,5-dicyanophthalamide (**VII**), were prepared by reactions of 4,5-dibromophthaloyl dichloride (**V**) with ethyl esters of aminoacetic and methylaminoacetic acids and subsequent substitution of the bromine atoms in the resulting *N*-(ethoxycarbonylmethyl)-4,5-dibromophthalimide (**VIII**) and *N*,*N*'-bis(ethoxycarbonylmethyl)-*N*,*N*'-dimethyl-4,5-dibromophthalamide (**IX**) by cyano groups by the Rosenmund–Brown reaction.

By reacting dinitriles **VI** and **VII** with metal salts in a solvent or without it and ammonium molybdate as catalyst and subsequent hydrolysis of esters **Ia**–**Ic**, **Ie**, **IIIa**, and **IIIb** to free acids we obtained copper, zinc, cobalt, and aluminum complexes of tetra(*N*-carboxymethyl)imides of octa-4,5-carboxyphthalocyanines (**IIa**–**IIc**, **IIe**) and copper and zinc complexes of octakis-4,5-(*N*-carboxymethyl-*N*-methyl)carbamoylphthalocyanines (**IVa**, **IVb**).

For communication XXXVI, see [1].

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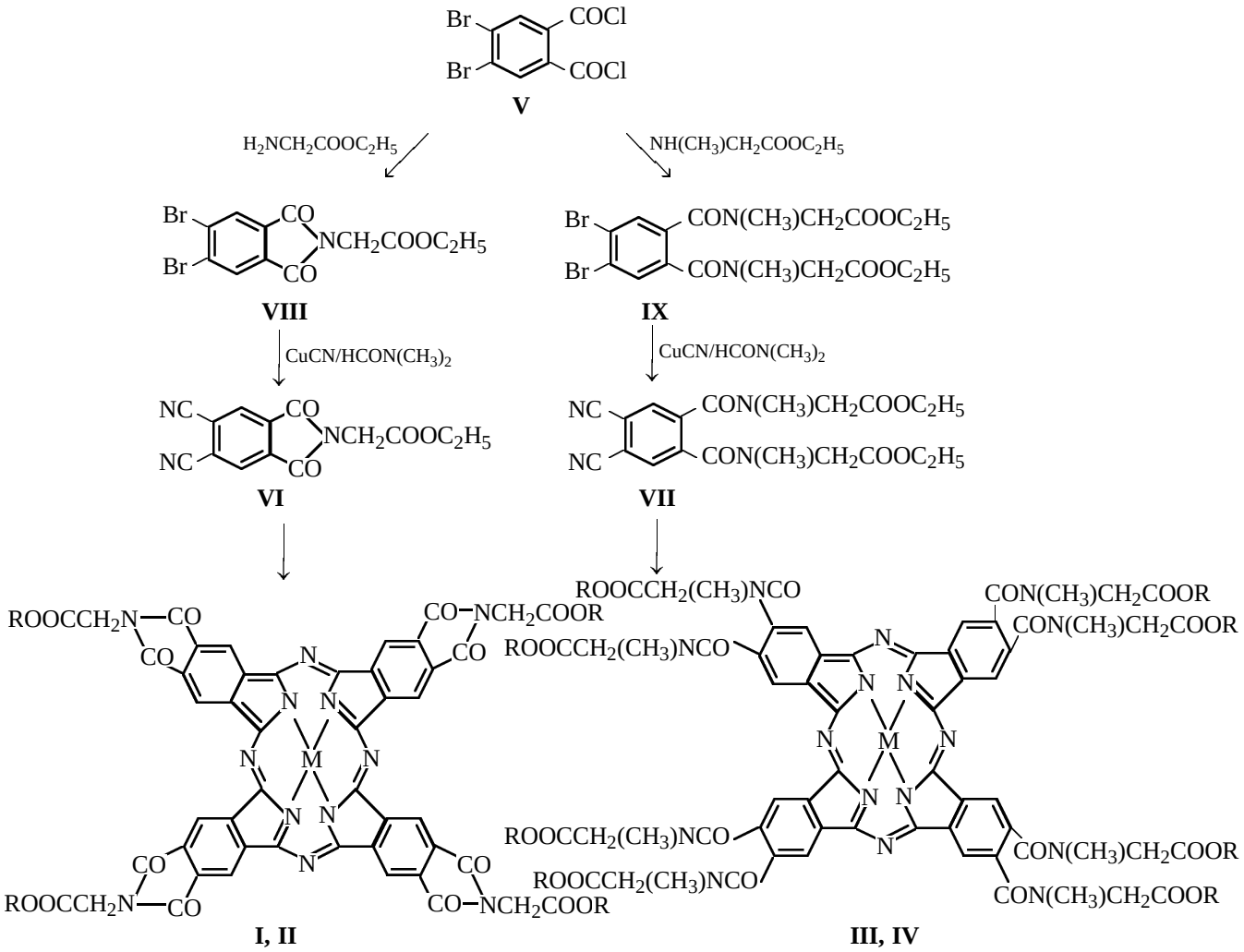
The obtained compounds are rather readily soluble not only in organic solvents, but in water, too, even at room temperature. The best soluble in water, much better than the starting octa-4,5-carboxyphthalocyanines, are metal octakis-4,5-[(*N*-carboxymethyl-*N*-methyl)carbamoyl]phthalocyanines (**IV**). As the above-described method of synthesis of these compounds is rather elaborate, we tried a new synthetic approach, starting from zinc and cobalt octakis-4,5-(chlorocarbonyl)phthalocyanines (**Xb**, **Xc**). The latter were prepared in quantitative yields by reactions of the corresponding tetraanhydrides of octa-4,5-carboxyphthalocyanines (**XIb**, **XIc**) with equimolar amount of phthaloyl chloride in the presence of anhydrous zinc chloride at 210–215°C. By refluxing octaacyl chlorides **Xb**, **Xc** with ethyl *N*-methylaminoacetate in chloroform followed by hydrolysis of the ester groups we obtained zinc and cobalt octakis-4,5-[(*N*-methyl-*N*-carboxymethyl)carbamoyl]phthalocyanines (**IVb**, **IVc**). As judged from the elemental analyses and IR and UV spectra, complexes **IVb**, **IVc** prepared by this method are identical to those obtained from dinitrile **VII**.



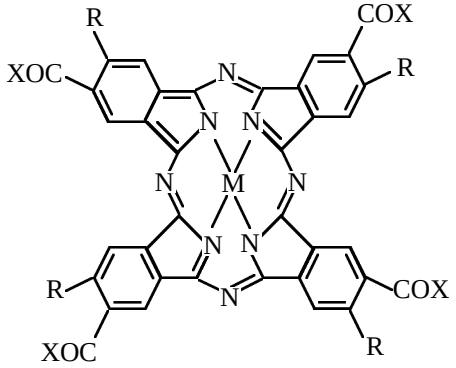
R = C_2H_5 (**I, III**), H (**II, IV**); M = Cu (**a**), Zn (**b**), Co (**c**), Fe (**d**), AlOH (**e**).

To simplify the route to conjugates like glycine derivatives **II**, by reactions of zinc, cobalt, iron, and hydroxyaluminum octa-4,5-carboxyphthalocyanine tetraanhydrides (**XIb**–**XIe**) with ethyl glycinate in methylpyrrolidone under an inert gas followed by hydrolysis of the ester groups in the resulting tetra(*N*-ethoxycarbonylmethyl)imides **Ib**–**Ie** we prepared zinc, cobalt, iron, and hydroxyaluminum octa-4,5-carboxyphthalocyanine tetra(*N*-carboxymethyl)imides (**IIb**–**IIe**) in yields of 15–60%. The moderate yields of

Absorption maxima in the UV spectra of aqueous solutions of sodium salts of octa-4,5-carboxyphthalocyanines $PcM(COONa)_8$, octakis-4,5-[(*N*-carboxymethyl-*N*-methyl)carbamoyl]phthalocyanines $PcM[CON(CH_3)CH_2COONa]_8$, and octa-4,5-carboxyphthalocyanine tetra(*N*-carboxymethyl)imides $PcM[(CO)_2NCH_2COONa]_4$

Comp. no.	Compound	λ_{max}, nm	Relative intensity
IVa	$PcCu(COONa)_8$	685, 655 sh, 615, 348	2.25 : 0 45 : 0.45 : 1
	$PcCu[CON(CH_3)CH_2COONa]_8$	685, 650 sh, 617, 349	2.34 : 0.40 : 0.45 : 1
IIa	$PcCu[(CO)_2NCH_2COONa]_4$	674, 650 sh, 356	1.05 : 1.03 : 1
	$PcZn(COONa)_8$	686, 656 sh, 618, 354	2.20 : 0 45 : 0.40 : 1
IVb	$PcZn[CON(CH_3)CH_2COONa]_8$	686, 655 sh, 619, 354	1.95 : 0.45 : 0.40 : 1
IIb	$PcZn[(CO)_2NCH_2COONa]_4$	657, 654, 358	1.10 : 1.08 : 1
	$PcCo(COONa)_8$	675, 608, 333	1.40 : 0.40 : 1
IVc	$PcCo[CON(CH_3)CH_2COONa]_8$	675, 619, 331	1.50 : 0.45 : 1
IIc	$PcCo[(CO)_2NCH_2COONa]_4$	674, 600 sh, 328	0.85 : 0.45 : 1
	$PcFe(COONa)_8$	682, 612, 340	1.50 : 0.35 : 1
IId	$PcFe[(CO)_2NCH_2COONa]_4$	678, 610, 335	1.25 : 0.30 : 1
	$PcAlOH(COONa)_8$	690, 650 sh, 614, 361	2.22 : 0.45 : 0.40 : 1
IIe	$PcAlOH[(CO)_2NCH_2COONa]_4$	688, 650 sh, 618, 360	1.42 : 0.48 : 0.55 : 1

certain conjugates can be explained by rather rigid conditions of their synthesis.



X, XIII–XVI

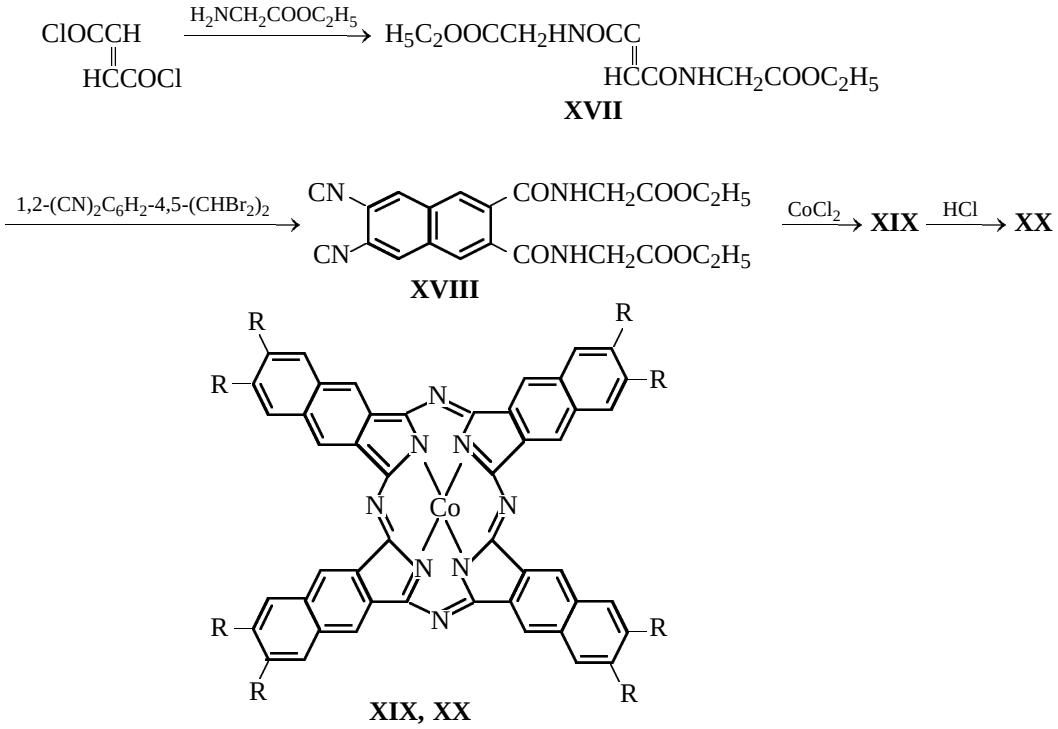
X = Cl, R = COCl (**X**); R = H, X = OH (**XIV**), Cl (**XV**), $N(CH_3)CH_2COOH$ (**XIII**), $N(CH_3)CH_2COOC_2H_5$ (**XVI**); M = Zn (**b**), Co (**c**), Fe (**d**), AlOH (**e**).

In a similar way, by a one-step reaction of cobalt octa-4,5-carboxyphthalocyanine tetraanhydride (**XIc**) with *tert*-butyl α-aminopropanoate (*L*-alanine) hydrochloride in an aprotic solvent in the presence of triethylamine we obtained cobalt octa-4,5-carboxyphthalocyanine tetra(*N*-carboxyethyl)imide (**XIIc**). By reactions of acyl chlorides **XVb**, **XVc** of zinc and cobalt tetra-4-carboxyphthalocyanines (**XIVb**, **XIVc**) with ethyl ester of sarcosine, followed by hydrolysis of the ester groups in the resulting tetrakis-4-[*N*-(ethoxycarbonylmethyl)-*N*-methylcarbamoyl]phthalocyanines (**XVIb**, **XVIc**) we obtained zinc and cobalt complexes **XIIIb**, **XIIIc**.

The position of the long-wave absorption band (*Q* band) in the UV spectra of aqueous solutions of complexes **IV** containing eight sarcosine moieties is almost the same as in the spectra of octa-4,5-carboxyphthalocyanines (see table). The long-wave absorption maxima in the spectra of complexes **II** containing cyclic imide groups are shifted hypsochromically (by about 10 nm) and have lower intensities, which is explained by aggregation like that observed with tetra-4-carboxyphthalocyanine complexes [7]. Thus, considering published and our present data on the effect of carboxy groups on the UV spectra of phthalocyanines we can conclude that the number of carboxy groups in the molecule is a key factor controlling its aggregation in solutions.

We also tried to synthesize similar conjugates of 2,3-naphthalocyanines.

By condensation of fumaroyl chloride with ethyl glycinate we prepared *N*,*N*'-bis(ethoxycarbonylmethyl)-fumaramide (**XVII**). The latter was reacted with bis-4,5-(dibromomethyl)phthalonitrile [8] to obtain *N*,*N*'-bis(ethoxycarbonylmethyl)-6,7-dicyanonaphthalene-2,3-dicarboxamide (**XVIII**). Condensation of the latter with anhydrous cobaltous chloride in 1-bromonaphthalene followed by hydrolysis of the ester groups in the resulting cobalt octakis-6,7-(ethoxycarbonylmethylaminocarbonyl)-2,3-naphthalocyanine (**XIXc**) by refluxing with dilute hydrochloric acid gave cobalt octakis-6,7-(carboxymethylaminocarbonyl)]-2,3-naphthalocyanine (**XXc**) soluble in aqueous alkali and aprotic solvents. The UV spectra of complex **XXc** in both cases show a broad band with its maximum near



R = $CONHCH_2COOC_2H_5$ (**XIX**), $CONHCH_2COOH$ (**XX**).

740 nm, which is evidence for aggregation of the complex.

The compounds obtained in the present work extend the range of water-soluble phthalocyanines containing in the macroring active functional groups capable of forming stable covalent bonds with proteins and oligonucleotides [9].

EXPERIMENTAL

The UV spectra were measured on an HP-8453 instrument. The IR spectra were taken on an FSM-1201 instrument.

4,5-Dibromophthaloyl dichloride (V) was prepared in 91% yield, mp 48–50°C, by fusing 4,5-dibromophthalic anhydride with phosphorus pentachloride at a temperature gradually raised from 150 to 250°C and simultaneous distillation of the phosphorus oxychloride formed. The starting 4,5-dibromophthalic anhydride was prepared by bromination of *o*-xylene with molecular bromine [10] to 4,5-dibromo-*o*-xylene, its subsequent oxidation with potassium permanganate in aqueous pyridine [11] to 4,5-dibromophthalic acid, and refluxing the latter with acetic anhydride.

***N*-(Ethoxycarbonylmethyl)-4,5-dibromophthalimide (VIII).** To a solution of 0.56 g of diacyl chloride **VII** in 7 ml of dry ethyl ether, a solution of 0.8 g of ethyl glycinate in 3 ml of absolute ethanol was added dropwise at –8 to –10°C. The mixture was stirred for 3 h at this temperature, then for 2 h at –5 to –7°C and then heated to room temperature. The solvent was removed, and the residue was subjected to chromatography on silica gel (eluent benzene) to isolate 0.54 g (89%) of compound **VIII**, mp 120–121°C. Found, %: C 36.85, 36.67; H 2.23, 2.27; Br 39.95, 39.79; N 3.35, 3.65. $C_{12}H_{10}Br_2NO_4$. Calculated, %: C 36.76; H 2.58; Br 40.76; N 3.57.

***N*,*N*'-Bis(ethoxycarbonylmethyl)-*N*,*N*'-dimethyl-4,5-dibromophthalamide (IX)** was obtained similarly to compound **VIII** by the reaction of 4.03 g of diacyl chloride **V** in 50 ml of dry ethyl ether with a solution of 6.58 g ethyl ester of sarcosine in 20 ml of anhydrous ethanol followed by purification by chromatography on alumina (eluent benzene). Yield 4.89 g (85%), oily eventually crystallizing material, mp 98–99°C. Found, %: C 41.78, 41.65; H 4.22, 4.24; Br 30.38, 30.48; N 5.13, 5.01. $C_{18}H_{22} \cdot Br_2N_2O_6$. Calculated, %: C 41.37; H 4.25; Br 30.60; N 5.36.

***N*-(Ethoxycarbonylmethyl)-4,5-dicyanophthalimide (VI).** A mixture of 1.18 g of dibromide **VIII** and 0.81 g of CuCN in 30 ml of DMF was refluxed for 4 h with stirring, cooled, and a solution of 2.8 g of $FeCl_3 \cdot 6H_2O$ in 20 ml of 5% hydrochloric acid

were added. The mixture was stirred for 10 min at 45°C, cooled, diluted with water, and extracted with ether. The ether extracts were washed with water to neutral reaction, the solvent was removed, and the residue was subjected to chromatography on silica gel (eluent chloroform) to isolate 0.33 g (39%) of dinitrile **VI**, mp 164–165°C. IR spectrum (Vaseline oil), ν, cm^{-1}: 1715, 1730, 1778 (C=O), 2225 (C≡N). Found, %: C 59.76, 59.79; H 3.35, 3.35; N 14.12, 14.29. $C_{14}H_{10}N_3O_3$. Calculated, %: C 59.14; H 3.55; N 14.78.

Further elution with a chloroform–methanol (10 : 1) mixture gave 0.14 g (15.5%) of copper octa-4,5-carboxyphthalocyanine tetra(*N*-ethoxycarbonylmethyl)-imide (**Ia**).

***N*,*N*'-Bis(ethoxycarbonylmethyl)-*N*,*N*'-dimethyl-4,5-dicyanophthalamide (VII)** was prepared similarly to compound **VI** by the reaction of 2.4 g of dibromide **IX** with 1.26 g of CuCN in 72 ml of DMF. Yield 0.59 g (31%), mp 93–94°C. IR spectrum (Vaseline oil), ν, cm^{-1}: 1635–1645, 1728 (C=O), 2225 (C≡N). Found, %: C 57.24, 57.32; H 5.27, 5.18; N 13.07, 13.21. $C_{20}H_{22}N_4O_6$. Calculated, %: C 57.95; H 5.36; N 13.52.

Along with dinitrile **VII**, further elution with a chloroform–methanol (10 : 1) mixture gave 0.43 g of the dinitrile with partly hydrolyzed ester groups. IR spectrum (Vaseline oil), ν, cm^{-1}: 1630–1640, 1730 (C=O), 2230 (C≡N), 3610 (OH).

Copper octa-4,5-carboxyphthalocyanine tetra(*N*-ethoxycarbonylmethyl)imide (Ia). A mixture of 0.25 g of dinitrile **VI**, 0.05 g of CuCl, and 0.01 g of ammonium molybdate in 1 ml of anhydrous trichlorobenzene was stirred for 3 h at 200–205°C, cooled, and subjected to repeated chromatography on silica gel (eluent methanol–chloroform, 1 : 10) to isolate 0.05 g (ca. 20%) of complex **Ia**. IR spectrum (Vaseline oil), ν, cm^{-1}: 1700–1715, 1730, 1765 (C=O). UV spectrum (chloroform), λ_{max}, nm: 360.5, 694.5 (relative intensity 1 : 1.95).

Further elution with pyridine gave 0.02 g of a partly hydrolyzed complex. Found, %: C 56.46, 56.42; H 3.05, 3.14; N 14.02,14.12. $C_{56}H_{36}CuN_{12}O_{16}$. Calculated, %: C 56.21; H 3.04; N 14.05.

Zinc octa-4,5-carboxyphthalocyanine tetra(*N*-ethoxycarbonylmethyl)imide (Ib). A mixture of 0.29 g of dinitrile **VI**, 0.09 g of anhydrous zinc acetate, and 0.01 g of ammonium molybdate in 0.9 ml of 1-bromonaphthalene was stirred for 3 h under helium at 210–215°C, cooled, and diluted with methanol. The resulting suspension was filtered, and the solid material was washed successively with benzene, methanol, and water, squeezed, and dried. Repeated chromatography on silica gel (eluent chloroform–methanol, 30 : 1) gave 0.6 g (ca. 20%) of complex **Ib**. UV spectrum (chloroform), λ_{max}, nm: 357, 699 (relative intensity 1 : 1.85). Further elution with pyridine gave 0.03 g of the complex with partly hydrolyzed ester groups. IR spectrum (Vaseline oil), ν, cm^{-1}: 1695, 1715, 1740, 1765 (C=O).

Cobalt octa-4,5-carboxyphthalocyanine tetra(*N*-ethoxycarbonylmethyl)imide (Ic). A mixture of 0.29 g of dinitrile **VI**, 0.09 g of anhydrous cobalt acetate, and 0.01 g of ammonium molybdate were heated for 2 h under helium at 205–210°C, cooled, and subjected to chromatography on silica gel (eluent chloroform–methanol, 10 : 1) to isolate 0.04 g (ca. 13%) of complex **Ic**. UV spectrum (chloroform), λ_{max}, nm: 339, 689 (relative intensity 1 : 1.15). IR spectrum (Vaseline oil), ν, cm^{-1}: 1700, 1728, 1765 (C=O).

Copper octa-4,5-carboxyphthalocyanine tetra(*N*-carboxymethyl)imide (IIa). A mixture of 0.05 g of compound **Ia** and 1 ml of 10% HCl was refluxed for 4 h, cooled to 4–5°C, and filtered. The solid material was washed with 10% HCl, squeezed, and dried at 100–105°C to obtain 0.04 g (95%) of water-soluble complex **IIa**. UV spectrum, λ_{max}, nm: (H_2O + 1% NH_4OH) 347, 611, 681 (relative intensity 1 : 0.85 : 1.41); (H_2O): 350, 633 (relative intensity 1 : 1.08); (H_2O + 0.5% NaOH): 355, 633, 674 (relative intensity 1 : 1 : 1.06). IR spectrum (Vaseline oil), ν, cm^{-1}: 1695, 1765 (C=O), 3350 (OH). Found, %: C 54.16, 54.03; H 2.24, 1.99. $C_{48}H_{20}CuN_{12}O_{16}$. Calculated, %: C 53.16; H 1.86.

Zinc octa-4,5-carboxyphthalocyanine tetra(*N*-carboxymethyl)imide (IIb) was prepared similarly to compound **IIa** from compound **Ib**. UV spectrum, λ_{max}, nm: (H_2O) 352, 646 (relative intensity 1 : 0.90); (H_2O + 1% NH_4OH): 352, 620.5, 689 (relative intensity 1 : 0.41 : 2.23). IR spectrum (KBr), ν, cm^{-1}: 1695, 1760 (C=O), 3390 (OH).

Metal complexes of octa-4,5-carboxyphthalocyanine tetraanhydride XIb–XIe. A mixture of 0.3 mmol of metal octa-4,5-carboxyphthalocyanine and 6 ml of acetic anhydride was refluxed for 6 h. The resulting suspension was cooled and filtered. The solid material was washed with a little acetic anhydride, squeezed, and dried in a vacuum at 115–120°C. Yield > 90%. IR spectrum (Vaseline oil), ν, cm^{-1}: 1760, 1830 (C=O).

Conjugates of octa-4,5-carboxyphthalocyanines with glycine IIb–IIe. To a solution of 0.15 mmol of tetraanhydride **XIb–XIe** in 8 ml of anhydrous *N*-methyl-2-pyrrolidone, 0.8 mmol of ethyl glycinate

was added, and the mixture was stirred for 6 h under an inert gas at 180–185°C, 0.5 mmol more ethyl glycinate was added,[2] and stirring was continued for an additional 8 h at the same temperature. The reaction mixture was cooled, diluted with 5% HCl to pH 1, and stirred for 15–20 min. The resulting suspension was filtered, and the solid material was washed successively with dilute HCl and water, squeezed, and dried to obtain tetra(ethoxycarbonylmethyl)imide **Ib**–**Ie**.

Compound Ib. UV spectrum (chloroform), λ_{max}, nm: 357, 646, 699 (relative intensity 1 : 0.60 : 1.80). IR spectrum (Vaseline oil), ν, cm^{-1}: 1695, 1715, 1735, 1768 (C=O). **Compound Ic.** UV spectrum (chloroform), λ_{max}, nm: 334, 689 (relative intensity 1 : 1.10). IR spectrum (Vaseline oil), ν, cm^{-1}: 1700, 1715, 1730, 1760 (C=O). **Compound Id.** UV spectrum (chloroform–methanol, 20 : 1), λ_{max}, nm: 335, 628, 695 (relative intensity 1 : 0.90 : 1.55). IR spectrum (Vaseline oil), ν, cm^{-1}: 1705, 1735, 1768 (C=O). **Compound Ie.** UV spectrum (chloroform), λ_{max}, nm: 353, 611, 704 (relative intensity 1 : 0.50 : 1.80). IR spectrum (Vaseline oil), ν, cm^{-1}: 1710, 1740, 1770 (C=O).

Compounds **Ib**–**Ie** were refluxed in 10% HCl for 4 h, the hot suspension was filtered, the solid material was washed with hot water to neutral reaction, squeezed, and treated with 0.1% aqueous NaOH to pH 8.5. The resulting solution was subjected to chromatography on alumina [eluent phosphate buffer (pH 6.75)]. The eluate (blue band) was acidified with dilute HCl, the resulting suspension was filtered, and the precipitate of tetra(carboxymethyl)imide **IIb**–**IIe** was washed with 5% HCl and cold water to neutral reaction, squeezed, and dried.

Compound IIb. Yield 25%. UV spectrum (H_2O + NaOH), λ_{max}, nm: 358, 657, 680 sh (relative intensity 1 : 0.95 : 1.15). IR spectrum (Vaseline oil), ν, cm^{-1}: 1695, 1765 (C=O), 3380 (OH). **Compound IIc.** Yield 61%. UV spectrum (H_2O + NaOH), λ_{max}, nm: 330, 674 (relative intensity 1 : 0.95). IR spectrum (Vaseline oil), ν, cm^{-1}: 1695, 1755 (C=O), 3380 (OH). Found N, %: 14.14, 14.40. $C_{48}H_{20}CrN_{12}O_{16}$. Calculated N, %: 15.57. **Compound IId.** Yield 15%. UV spectrum (H_2O + NaOH), λ_{max}, nm: 335, 678 (relative intensity 1 : 1.25). IR spectrum (Vaseline oil), ν, cm^{-1}: 1690, 1755 (C=O), 3400 (OH). **Compound IIe.** Yield 27%. UV spectrum (H_2O + NaOH), λ_{max}, nm: 360, 618, 688 (relative intensity 1 : 0.55 : 1.45). IR spectrum (Vaseline oil), ν, cm^{-1}: 1695, 1760 (C=O), 3370 (OH).

[2] Excess ethyl glycinate is taken in view of the possible formation of diketopiperazine.

Cobalt octa-4,5-carboxyphthalocyanine tetra(*N*-α-carboxyethyl)imide (XIIc). To a solution of 0.1 mmol of tetraanhydride **XIc** in 10 ml of anhydrous *N*-methyl-2-pyrrolidone, 1.1 mmol of L-alanine *tert*-butyl ester hydrochloride and 1.1 mmol of triethylamine were added. The mixture was stirred for 6 h under an inert gas at 175–185°C, an additional ester and triethylamine, 3.7 mmol each, were added, the mixture was heated for 5 h at this temperature and then cooled and diluted with 5% HCl to pH 1. The suspension was filtered, the solid material was successively washed with water and chloroform, squeezed, and dried. The product was purified by reprecipitation from 0.1% aqueous NaOH with HCl. Yield 0.08 g (71%). The complex is soluble in water, especially when heated. IR spectrum (KBr), ν, cm^{-1}: 1695 (carboxyl C=O), 1755 (C=O), 2900 (C–H). UV spectrum, λ_{max}, nm (relative intensity): (DMSO) 348, 610, 684 (1 : 0.45 : 1.66); (0.1 NaOH): 332, 610, 674 (1 : 0.43 : 1.34). Found, %: C 54.27, 54.35; H 2.63, 2.78; N 14.62, 14.58. $C_{52}H_{28}CoN_{12}O_{16}$. Calculated, %: C 54.98; H 2.49; 14.80.

Copper octakis-4,5-[*N*-(ethoxycarbonylmethyl)-*N*-methylcarbamoyl]phthalocyanine (IIIa). A mixture of 0.37 g of dinitrile **VII**, 0.05 g of CuCl, and 0.01 g of ammonium chloride in 1 ml of anhydrous trichlorobenzene was stirred for 3 h at 200–205°C and cooled. Repeated chromatography on silica gel (eluent methanol–chloroform, 1 : 10) gave 0.08 g (ca. 20%) of complex **IIIa**. UV spectrum (chloroform), λ_{max}, nm: 348.5, 613.5, 631.5, 679.5 (relative intensity 1 : 0.43 : 0.32 : 2.08). IR spectrum (KBr), ν, cm^{-1}: 1635, 1730 (C=O), 2815–2930 (C–H).

Further elution with pyridine gave 0.03 g of partly hydrolyzed complex **IIIa**, whose IR spectrum (KBr) shows an additinal band at 3400 cm^{-1} (OH).

Copper octakis-4,5-[*N*-(carboxymethyl)-*N*-methylcarbamoyl]phthalocyanine (IVa) was prepared by refluxing compound **IIIa** in 10% HCl (reagent ratio 1 : 10), yield 90%. It is soluble in water, alkali solutions, and aprotic solvents. IR spectrum (KBr), ν, cm^{-1}: 1610–1640, 1690 (C=O), 2815–2920 (C–H), 3400 (OH). UV spectrum (H_2O), λ_{max}, nm: 340.5, 616.0 (relative intensity 1 : 1.10). UV spectrum, λ_{max}, nm: (H2O + NOH) 349, 617.5, 685 (relative intensity 1 : 0.40 : 2.34); (DMSO): 351, 614, 683 (relative intensity 1 : 0.80 : 3.45)

Complex **IVb** was prepared similarly to complex **IIIa** by the reaction of dinitrile **VII** with anhydrous zinc acetate. Yield 22%. UV spectrum (chloroform), λ_{max}, nm: 360.5, 695 (relative intensity 1 : 1.95). IR spectrum (KBr), ν, cm^{-1}: 1640, 1730 (C=O), 2815–2925 (C–H). The product is readily soluble in aro-

matic (benzene) and aliphatic solvents, alcohols, and ketones (acetone).

Hydrolysis of compound **IIIb**, as described above for compound **IIIa**, gave 90% of compound **IVb**. IR spectrum (KBr), ν, cm^{-1}: 1610–1640, 1690 (C=O), 2815–2920 (C–H), 3400 (OH). UV spectrum, λ_{max}, nm: (H_2O) 344, 636 (relative intensity 1 : 0.95); (H_2O + N OH): 353.5, 618, 635, 687 (relative intensity 1 : 0.40 : 0.35 : 1.85); (DMSO): 354, 618, 683 (relative intensity 1 : 0.63 : 2.09).

Cobalt octakis-4,5-[(*N*-carboxymethyl-*N*-methylcarbamoyl]phthalocyanine (IVc). A mixture of 0.41 g of dinitrile **VII**, 0.09 g of anhydrous cobalt acetate, 0.06 g of ammonium molybdate, and 1 ml of anhydrous nitrobenzene was heated for 4.5 h at 190°C with stirring under an inert gas. Purification by chromatography on silica gel (eluent chloroform–methanol, 5 : 1) gave 0.12 g of octaester **IIIc**. IR spectrum (KBr), ν, cm^{-1}: 1630, 1750 (C=O), 2845, 2922, 2945 (C–H). UV spectrum (chloroform), λ_{max}, nm: 338, 614, 673 (relative intensity 1 : 0.60 : 1.55).

Refluxing of compound **IVc** with 10 ml of 10% HCl for 4 h gave 24% of acid **IVc**. IR spectrum (KBr), ν, cm^{-1}: 1627, 1698 (C=O), 2852, 2923, 2957 (C–H). UV spectrum (H_2O), λ_{max}, nm: 319, 632, 675 (relative intensity 1 : 0.65 : 1.05).

A suspension of acid **IVc** in water was diluted with 0.1% aqueous NaOH to pH 8.5, filtered, the filtrate was evaporated to dryness in a vacuum (20 mm), and further dried at 110°C to constant weight. The yield of the sodium salt is quantitative. UV spectrum (0.01 M NaOH), λ_{max}, nm: 331, 619, 675 (relative intensity 1 : 0.40 : 1.35). Found, %: C 45.89, 45.96; H 2.67, 2.72; N 12.84, 12.88. $C_{64}H_{48}CoN_{16}Na_8O_{24}$. Calculated, %: C 46.07; H 2.91; N 13.44.

Zinc octakis-4,5-(chlorocarbonyl)phthalocyanine (Xb). A mixture of 0.86 g of tetraanhydride **XIb**, 0.812 g of phthaloyl chloride, and 0.19 g of anhydrous zinc chloride was stirred for 24 h at 210–215°C to obtain 1.06 g (95%) of compound **Xb**.

Cobalt octakis-4,5-(chlorocarbonyl)phthalocyanine (Xc). A mixture of 0.78 g of tetraanhydride **XIc**, 0.82 g of phthaloyl chloride, and 0.16 g of anhydrous zinc chloride was stirred for 24 h at 210–215°C to obtain 1.06 g (98%) of crude octachloride **Xc** as a running friable powder.

Zinc octakis-4,5-[(*N*-carboxymethyl-*N*-methylcarbamoyl]phthalocyanine (IVb). To a solution of 3.11 g of sarcosine ethyl ester in 70 ml of absolute chloroform, 1.42 g of octaacyl chloride **Xb** was added in portions over a period of 15 min. The mixture was refluxed with stirring for 25 h, the solvent was then removed in a vacuum, the residue was agitated in a chloroform–methanol (5 : 1) mixture, the precipitate was filtered off and washed on the filter with the same solvent mixture to a colorless filtrate. The filtrate was evaporated to dryness, and the reside was subjected to chromatography on silica gel first in methanol–chloroform, 1 : 10, and then in methanol–chloroform, 1 : 5, to obtain 0.69 g of octaester **IIIb**. IR spectrum (KBr), ν, cm^{-1}: 1616, 1721 (C=O), 2854, 2925 (C–H).

Octaester **IIIb** was refluxed with 0.5 h in 5% HCl. The subsequent reprecipitation from 0.1% NaOH gave ca. 30% of complex **IVb** identical to that prepared from dinitrile **VII**. IR spectrum (KBr), ν, cm^{-1}: 1615, 1712 (C=O), 2850, 2930 (C–H). UV spectrum, λ_{max}, nm: (H_2O) 643, 680 sh (aggregated); (0.1% NaOH): 354, 615, 683. Found, %: C 50.91, 50.93; H 3.86, 3.82; N 14.49, 14.47. $C_{64}H_{56}N_{16}O_{24}Zn$. Calculated, %: C 51.28; H 3.72; N 14.96.

Cobalt octakis-4,5-[(*N*-carboxymethyl-*N*-methylcarbamoyl]phthalocyanine (IVc). Octaester **IIIc** was prepared similarly compound **IVb** by the reaction of 1.06 g of octaacyl chloride **Xc** with 2.34 g of sarcosine ethyl ester in 50 ml of absolute chloroform. Yield 0.15 g. IR spectrum (KBr), ν, cm^{-1}: 1616, 1721 (C=O), 2854, 2925 (C–H).

Octaester **IIIc** was hydrolyzed with 5% HCl, as described for compound (**IIIb**), to obtain complex **IVc** identical to that prepared from dinitrile **VII**. IR spectrum (KBr), ν, cm^{-1}: 1620, 1703 (C=O), 2850, 2925 (C–H). UV spectrum, λ_{max}, nm: (H_2O) 630, 675 sh (0.1% NaOH): 330, 618 : 675 (relative intensity 1 : 0.45 : 1.30). Found, %: C 51.84, 51.86; H 3.24, 3.31; N 14.17, 14.19. $C_{64}H_{56}CoN_{16}O_{24}$. Calculated, %: C 51.50; H 3.73; N 15.02.

Zinc tetra-4-carboxyphthalocyanine (XIVb). A mixture of 4.75 g of trimellitic acid (or its anhydride), 2.52 g of zinc acetate dihydrate, 0.3 g of ammonium molybdate, 0.5 g of anhydrous sodium sulfate, and 13.5 g of urea in 5 ml of 1-bromonaphthalene was stirred for 4 h at 200–205°C, cooled, diluted with methanol, and the resulting suspension was filtered. The solid material was successively washed with methanol, chloroform, and acetone, thoroughly squeezed, and ground, and refluxed for 1 h with 5% HCl, after which it was filtered off, washed with water, and dried. The reaction product was reprecipitated from conc. H_2SO_4 (35 ml) to obtain 1.95 g of a complex which was then treated for 2 h at 130–135°C with a 15% solution of KOH in triethylene glycol (9.2 g of KOH in 54 ml of triethylene glycol). Acidification with dilute HCl to pH 1 gave 0.76 g (ca.

18%) of complex **XIVb**. Found N, %: 14.74, 15.02. $C_{36}H_{16}N_8O_8Zn$. Calculated N, %: 14.86.

Cobalt tetra-4-carboxyphthalocyanine (XIVc). A mixture of 2.6 g of trimellitic anhydride, 0.88 of anhydrous $CoCl_2$, 8.2 g of urea, 5.2 g of anhydrous sodium sulfate, 0.3 g of ammonium molybdate, and 2.6 g of 1-bromonaphthalene was stirred for 4 h at 210–215°C, cooled, diluted with methanol, and the resulting suspension was filtered. The solid material was successively washed with methanol, chloroform, and water, squeezed, and dried. The crude product was purified by successive refluxing with 10 NaOH (6 h) and 10 HCl (1 h). Yield 1.9 g (75%). Found, %: C 57.64, 57.35; H 2.90, 2.63; N 15.11, 15.15. $C_{36}H_{16}\cdot CoN_8O_8$. Calculated, %: C 57.83; H 2.16; N 14.99.

Zinc and cobalt tetra-4-(chlorocarbonyl)phthalocyanines (XVb, XVc). A mixture of 0.002 mmol of zinc or cobalt tetra-4-carboxyphthalocyanine (**XIVb** or **XIVc**), 30 ml of dry benzene, and 2 ml of thionyl chloride was refluxed for 7 h, and the suspension was cooled and filtered. The solid material was washed with dry benzene and dried in a vacuum at room temperature. The yields of complexes **XVb** and **XVc** were 95 and 98%, respectively.

Zinc tetrakis-4-[*N*-(ethoxycarbonylmethyl)-*N*-methylcarbamoyl]phthalocyanine (XVIb). A suspension of 0.62 g of acyl chloride **XVb** and 0.88 g of sarcosine ethyl ester in 30 ml of dry chloroform was refluxed with stirring for 16 h. The solvent was then removed in a vacuum, and the residue was subjected to chromatography on alumina. Impurities were eluted with bezene and chloroform, and zinc complex **XVIb**, with chloroform–methanol, 10:1. Yield 25%. IR spectrum (KBr), ν, cm^{-1}: 1643, 1742 (C=O), 2930, 2975 (C–H). Found, %: C 58.61, 58.49; H 4.75, 4.52; N 14.45, 14.52. $C_{56}H_{52}N_{12}O_{12}Zn$. Calculated, %: C 58.45; H 4.56; N 1 4.61.

Zinc tetrakis-4-[*N*-(carboxymethyl)-*N*-methylcarbamoyl]phthalocyanine (XIIIb). A mixture of 0.23 g of ester **XVIb** and 5 ml of 10% HCl was refluxed for 2 h, the precipitate that formed was filtered off, washed with 10% HCl and water, squeezed, and dried to obtain 0.21 g (93%) of complex **XIIIb**. IR spectrum (KBr), ν, cm^{-1}: 1616, 1720 (C=O), 2900, 2950 (C–H). Found N, %: N 15.79, 15.88. $C_{48}H_{36}\cdot N_{12}O_{12}Zn$. Calculated N, %: 16.19.

Cobalt tetrakis-4-[*N*-(ethoxycarbonylmethyl)-*N*-methylcarbamoyl]phthalocyanine (XVIc). A mixture of 0.62 g of acyl chloride **XIVc** and 0.88 g of sarcosine ethyl ester in 30 ml of dry chloroform was refluxed for 16 h with stirring. The solvent was then removed in a vacuum, and the residue was subjected to chromatography on alumina. Impurities were eluted with benzene and chloroform, and acid **XVIc**, with chloroform–methanol, 10:1. Yield 0.31 (35%). IR spectrum (KBr), ν, cm^{-1}: 1641, 1743 (C=O), 2932, 2977 (C–H). UV spectrum (chloroform), λ_{max}, nm: 619, 670. Found, %: C 58.70, 58.52; H 4.88, 4.78; N 14.73, 14.71; ash 7.00, 6.73. $C_{56}H_{52}CoN_{12}O_{12}$. Calculated, %: C 58.78; H 4.59; N 14.69; ash 7.02.

Cobalt tetrakis-4-[*N*-(carboxymethyl)-*N*-methylcarbamoyl]phthalocyanin (XIIIc). A mixture of 0.23 g of ester **XVIc** and 5 ml of 10% HCl was refluxed for 2 h, the precipitate was filtered off, washed with 10% HCl and water, squeezed, and dried to obtain 0.19 g (90%) of acid **XIIIc**. IR spectrum (KBr), ν, cm^{-1}: 1616, 1727 (C=O), 2900–2960 (C–H). UV spectrum (0.1% NaOH), λ_{max}, nm: 630, 670 (aggregated). Found, %: C 56.12, 55.96; H 3.68, 3.73; N 15.98, 15.87, ash 7.08, 7.26. $C_{48}H_{36}CoN_{12}O_{12}$. Calculated, %: C 55.87; H 3.52; N 16.29, ash 7.78.

***N*,*N*'-Bis(ethoxycarbonylmethyl)fumaramide (XVII).** To a cooled (–12°C) solution of 3.24 g of fumaroyl chloride in absolute ether, 10.4 g of ethyl glycinate was added dropwise with stirring over a period of 2.5 h. Stirring was continued for 1 h at the same temperature, and then the temperature was raised to 20°C. The solvent was removed, the residue was mixed with water, the resulting suspension was filtered, the solid material was washed with water, dried, and subjected to chromatography on alumina (eluent chloroform–methanol, 10:1) to obtain 3.15 g (32.4%) of diamide **XVII**, mp 202–203°C. IR spectrum (Vaseline oil), ν, cm^{-1}: 1615, 1725 (C=O). Found, %: C 50.22, 50.33; H 6.33, 6.34; N 9.86, 9.98. $C_{12}H_{18}N_2O_6$. Calculated, %: C 50.34; H 6.35; N 9.79.

***N*,*N*'-Bis(ethoxycarbonylmethyl)-6,7-dicyanonaphthalene-2,3-dicarboxamide (XVIII).** A mixture of 0.95 g of 4,5-bis(dibromomethyl)phthalonitrile [8], 0.63 g of diamide **XVII**, and 1.7 g of anhydrous sodium iodide in 40 ml of dry DMF was stirred for 7 h at 85–87°C, cooled, poured into ice-cold water and treated with sodium hydrosulfite. The precipitate that formed was filtered off, dried, and subjected to chromatography on silica gel (eluent chloroform–methanol, 5:1) to obtain 0.16 g (18.5%) of compound **XVIII**, mp 220–222°C. IR spectrum (Vaseline oil), ν, cm^{-1}: 1610, 1650, 1720, 1735 (C=O), 2230 (C≡N).

Cobalt octakis-6,7-[*N*,*N*-(carboxymethyl)carbamoyl]-2,3-naphthocyanine (XXc). A mixture of 0.13 g of dinitrile **XVIII**, 0.12 g of anhydrous $CoCl_2$, and 0.01 g of ammonium molybdate in 0.7 ml of 1-bromonaphthalene, and 0.02 ml of *N*-methyl-2-pyrrolidone was stirred for 4.5 h under helium at 225–240°C, cooled, and diluted with methanol. The

resulting suspension was filtered, the solid material was successively washed with chloroform, acetone, water, and again with acetone, squeezed, and dried to obtain 0.07 g of crude compound **XIXc**. IR spectrum (Vaseline oil), ν, cm^{-1}: 1590, 1645, 1695, 1745 (C=O). UV spectrum (DMSO), λ_{max}, nm: ~750.

By refluxing octaester **XIXc** in 10% HCl for 4 h, followed by isolation of the reaction product by the procedure described for conjugates **II** and **IV**, 63% of complex **XXc** was obtained. The product is soluble in aqueous alkali and aprotic solvents (DMSO, quinoline, etc). IR spectrum (Vaseline oil), ν, cm^{-1}: 1600 (NH), 1695 (C=O), 3360 (OH). UV spectrum, λ_{max}, nm: (H_2O + NaOH) 735; (DMSO): 743; (quinoline): 744 (always aggregated).

REFERENCES

1. Makarova, E.A., Koroleva, G.V., and Lukyanets, E.A., *Zh. Obshch. Khim.*, 1999, vol. 69, no. 8, p. 1356.
2. Bonnett, R., *Chem. Soc. Rev.*, 1995, vol. 24, p. 19.
3. Verle, D., Girt, A., Bogdan-Rai, T., and Shnurpfail, G., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 1998, no. 4, p. 836.
4. Lukyanets, E.A., *Ross. Khim. Zh.*, 1998, vol. 42, no. 5, p. 9.
5. Syrkin, A.B., Zhukova, O.S., Kikot', B.S., Gatinskaya, L.G., Treshchalina, E.M., Yakubovskaya, R.I., Pankratov, A.A., Mikhailova, L.M., Kolesnikova, E.Yu., Oborotova, N.A., Polozkova, A.P., Gerasimova, G.K., Kuz'min, S.G., Lukyanets, E.A., Kaliya, O.L., Vorozhtsov, G.N., and Trapeznikov, N.N., *Ross. Khim. Zh.*, 1998, vol. 42, no. 5, p. 140.
6. Ponomarev, G.V., Reshetnikov, A.V., Guseva-Donskaya, T.N., Shvets, V.I., Baum, R.F., and Ashmarova, V.V., RU Patent no. 2 144 538, 2000, *Byull. Izobret.*, 2000, no. 2.
7. Solov'eva, L.I., Lukyanets, E.A., *Zh. Obshch. Khim.*, 1980, vol. 50, no. 5, p. 1122.
8. Kovshev, E.I., Puchnova, V.A., and Lukyanets, E.A., *Zh. Obshch. Khim.*, 1971, vol. 7, no. 2, p. 369.
9. Koval, V.V., Chernonosov, A.A., Abramova, T.V., Ivanova, T.M., Fedorova, O.S., Derkacheva, V.M., and Lukyanets, E.A., *Nucleosides, Nucleotides Nucleic Acids*, 2001, vol. 20, nos. 4–7, p. 1259.
10. Jacobsen, O., *Chem. Ber.*, 1884, vol. 17, p. 2732.
11. Solov'eva, L.I. and Lukyanets, E.A., *Anilinokras. Prom-st*, Moscow: NIITEKhim, 1976, no. 9, p. 1.