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PORPHYRINS.

21.* SYNTHESIS AND REACTIVITIES OF 13,17-DISUBSTITUTED DERIVATIVES OF 13,17-DESETHYLETIOPORPHYRIN III

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A method was developed for the preparation, from hemin, of a porphyrin with hydroxypropyl substituents in the 13 and 17 positions of the macroring and a number of its derivatives.

In the present research we solved the problem of the preparation, from hemin (I), of a porphyrin (IIa) with hydroxypropyl substituents in the 13 and 17 positions of the macroring and a number of its derivatives. In the synthesis of the substituted porphyrins special attention was directed to obtaining substances that contain tertiary amino groups, since it is known [2-4] that porphyrins that contain amino groups display diverse biological activity.

The preparation of porphyrin IIa from mesoporphyrin IX (IIIa) by reduction of its dimethyl ester (IIIb) with lithium aluminum hydride has been described in the literature [5]; the preparation of an aminoethylporphyrin from porphyrin IIIa by Curtius cleavage of the corresponding azide IIIc has also been described [6]. Porphyrin IIIa can be obtained in turn by treatment of hemin (I) with concentrated HI [7] or, more efficiently, by hydrogenation of it in formic acid on a palladium catalyst [8].

The process that we developed to obtain porphyrin IIa directly from hemin (I) [9] proceeds in up to 90% overall yield without isolation of intermediates; this made it possible to use this porphyrin for further chemical modification.

*See [1] for Communication 20.

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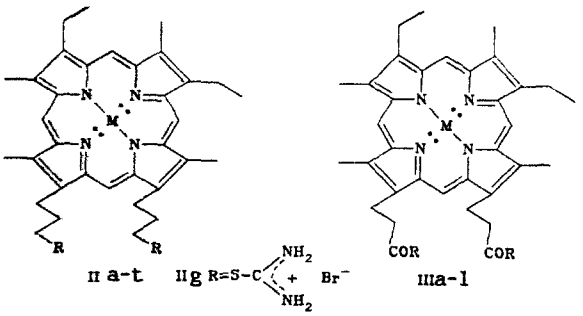

II a R=OH, b R=OCOCH$_3$, c,d R=OCOC$_9$H$_{19}$, e R=Br, f R=Cl, h R=CH(COOC$_2$H$_5$)$_2$, i R=piperazyl, j R=N(CH$_2$CH$_2$OH)$_2$, k R=N(CH$_2$COOCH$_3$)$_2$, l,p R=N(CH$_3$)$_2$, m,q R=N(C$_2$H$_5$)$_2$, n,r R=piperidyl, o,s R=morpholyl, t R=N(CH$_2$CH$_2$Cl)$_2$; a-c, e-o, t M=2H, d, p-s M=Zn; III a R=OH, b R=OCH$_3$, c R=N$_3$, d R=Cl, e,i R=N(CH$_3$)$_2$; f,j R=N(C$_2$H$_5$)$_2$, g,k R=piperidyl, h,l R=morpholyl, a-h M=2H, i—l M=Zn

The synthesis of porphyrin IIa was accomplished in the following way. Hemin (I) was allowed to stand in acetic acid saturated with HBr until it had dissolved completely. The solution was evaporated, and the residue was heated in acetyl bromide. The solvent was removed in vacuo, and the dry residue was treated with $LiBH_4$ in tetrahydrofuran (THF). The purification of porphyrin IIa after hydrolysis of the reaction mixture was restricted to removal of the polar impurities and inorganic salts. Hematoporphyrin can be used in place of hemin (I) as the starting compound.

Porphyrin IIa is readily acylated by acetic anhydride and decanoyl chloride to acyl derivatives IIb, c, respectively. The high solubilities of diester IIc and its zinc complex IId in organic solvents and oils make them convenient subjects for physicochemical experiments.

Replacement of the hydroxy group in porphyrin IIa by halogen is readily achieved by treatment with PBr_3 in dimethylformamide (DMF) or by dissolving in $SOCl_2$. The yield of dibromide IIe was 76%, and the yield of dichloride IIf was 80%. Dichloride IIf was isolated instead of the expected tosylate in the reaction of porphyrin IIa with toluenesulfonyl chloride in pyridine. Polar products, the structures of which could not be established, were simultaneously formed with it.

Bromo and chloro derivatives IIe, f undergo the nucleophilic substitution reactions that are typical for primary alkyl halides. Thus diisothiuronium salt IIg was obtained in the case of heating with thiourea, bis[(diethoxycarbonyl)butyl]porphyrin IIh was obtained in the case of heating with sodiomalonic ester, and aminopropylporphyrins IIi-l, to the synthesis of which primary attention was directed, were obtained in the case of heating with amines.

When high-boiling amines such as piperazine, diethanolamine, or iminediacetic ester were used, the corresponding derivatives IIi-k were obtained by heating porphyrin IIe in excess reagent. Since crystalline porphyrin IIe is only slightly soluble in the amines, it was first dissolved in chloroform, which was subsequently removed from the reaction mixture by distillation. In the case of the low-boiling dimethylamine product III was obtained by heating porphyrin IIf in a mixture of aqueous dimethylamine with DMF (1:9).

An alternative method for obtaining the amines consists in the reduction of the corresponding amides (IIIe-h) of mesoporphyrin IX. In accordance with this method mesoporphyrin IIIa was condensed, through the corresponding chloride IIId, with dimethylamine, diethylamine, piperidine, and morpholine. The reaction with an aqueous solution of dimethylamine proceeded under the conditions of the Schotten–Baumann reaction, whereas in the remaining cases an excess of the corresponding amine was added to a solution of acid chloride IIId in dry chloroform.

In the reduction of amides IIIe-h to amines III-o the starting amides were first converted to zinc complexes IIIi-l, since porphyrins that do not contain a metal decomposed upon contact with $LiAlH_4$ or formed aluminum complexes with unestablished structures.

Treatment of amino alcohol IIj with thionyl chloride gave "nitrogen mustard" IIt in high yield; IIt could be of interest as a potential cancerostatic susbtance, but aqueous solutions of its salts proved to be unstable.

All of the aminoporphyrins IIi-o, as well as zinc complexes IIp-s, formed water-soluble salts with two equivalents of acids. In contrast to this, the salt formed in the saponification of porphyrin IIk with sodium hydroxide in pyridine was virtually insoluble in water.

A molecular-ion peak of high intensity was present in the mass spectra of hydroxy- and aminopropylporphyrins IIa, i-o; however, the subsequent fragmentation of the molecules proceeded via different pathways. The fragmentation of the molecular ion of porphyrin IIa was accompanied by the appearance of an intense $[M - C_2H_5OH]^+$ ion; this is similar to the fragmentation of porphyrins that contain propionic acid residues [10]. Ions of $[M - CH_2N(R)_2]^+$, $[M - CH_2{=}CHN(R)_2]^+$, and $[M - CH_2CH_2CH_2N(R)_2]^+$ fragments are characteristic for the aminopropylporphyrins. It is interesting that the intensity of the molecular-ion peak is 100% in the mass spectrum of chloropropylporphyrin IIf, whereas the intensity of the $[M-2(H^{35}Cl)]^+$ ion peak does not reach 1%; in the case of its bromopropyl analog the molecular ion has an intensity of only 0.4%, whereas the $[M-2(H^{81}Br)]^+$ ion peak has an intensity of 100%.

Aminopropylporphyrin molecules associate with one another even indilute solutions. Zinc complexes IIp-s, which do not associate in a mixture of $CDCl_3$ with deuteropyridine, were therefore obtained to yield satisfactory PMR spectra from the porphyrins.

In conclusion, it should be noted that most of the synthesized aminopropylporphyrins had diverse biological activity [11], in view of which one might conclude that the further chemical study of aminoalkylporphyrins and related structures is a promising undertaking.

EXPERIMENTAL

The UV and visible spectra of solutions of the compounds in chloroform were recorded with an SF-18 spectrophotometer. The IR spectra of KBr pellets of the compounds were obtained with a Perkin-Elmer 398 spectrometer. The PMR spectra of solutions in $CDCl_3$ (with the addition of 5% d_5-pyridine in the case of the zinc complexes) were recorded with Bruker WM-360 and WM-250 spectrometers with tetramethylsilane (TMS) as the internal standard. The mass spectra were recorded with a Varian MAT-311 spectrometer. The R_f values were determined on Silufol plates in the following systems: chloroform (A), chloroform–methanol (8:2) (B), and chloroform–methanol–ammonium hydroxide (74:25:1) (C): except where specially indicated, activity II aluminum oxide was used for chromatography. Crystallization of the porphyrins from mixed solvents was carried out by the method in [12].

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-hydroxypropyl)porphyrin (IIa). A) A suspension of 10 g (15.34 mmole) of protohemin (I) in 100 ml of acetic acid saturated with HBr (d = 1.42-1.47) was maintained at 20°C for 48 h, after which the solvent was removed at reduced pressure [2-5 mm (mercury column)], 75 ml of acetyl bromide was added to the residue, and the mixture was heated at 70°C for 3 h to completely dissolve the solid material. After this, the acetyl bromide was evaporated at reduced pressure, the residue was dissolved in 200 ml of dry tetrahydrofuran (THF), and the solution was cooled to −5°C and treated with a solution of 2.5 g (114.7 mmole) of lithium borohydride in 150 ml of THF. The mixture was stirred at 5°C for 2 h and at 20°C for 12 h, after which it was poured into 2 liters of cold 5% hydrochloric acid solution, and the mixture was made alkaline to pH 8-9 by the addition of ammonium hydroxide. The resulting precipitate was removed by filtration, air dried, and dissolved in 0.5 liter of chloroform–methanol (8:2). The solution was passed through a column (d = 20 cm, h = 1 cm) packed with activity IV aluminum oxide and evaporated to dryness. The residue was crystallized from chloroform–methanol to give 6.7 g of porphyrin IIa. An additional 0.95 g of porphyrin IIa was obtained from the mother liquor after chromatographic purification with a column (d = 5 cm, h = 50 cm) packed with silica gel in a chloroform–methanol (95:5) system and crystallization from chloroform–hexane. The overall yield of porphyrin IIa was 7.65 g (9.3%). The product had R_f 0.74 (B). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 399 (117), 498 (11.6), 534 (8.25), 567 (5.66), 621 nm (4.22). IR spectrum: 3360 cm^{-1} (OH). PMR spectrum: 10.35, 10.11, 10.10 (1H, 1H, 2H, all s, meso-H); 4.21, t, $CH_2CH_2CH_2OH$); 4.12 (4H, q, CH_2CH_3); 3.97 (4H, t, $CH_2CH_2CH_2OH$); 3.66 (12H, s, ring CH_3); 2.53 (4H, m, $CH_2CH_2CH_2OH$) 1.89 (6H, t, CH_2CH_3); −3.76 ppm (2H, s, NH). Mass spectrum, m/z (%): 538 (M^+, 100), 492 (33) Found: C 75.9; H 7.7; N 10.6%. $C_{34}H_{42}N_4O_2$. Calculated: C 75.8; H 7.9; H 10.4%.

B) The process was carried out as in the synthesis by method A using hematoporphyrin IX (Koch-Light) as the starting substance. Porphyrin IIa, which was identical to the product obtained via method A with respect to TLC and IR spectroscopic data, was isolated in 74% yield.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17 bis(3-acetoxypropyl)porphyrin (IIb). A 1-g (1.86 mmole) sample of porphyrin IIa was dissolved in a mixture of 50 ml of pyridine and 3 ml (31.74 mmole) of acetic anhydride. After 3 h, 0.5 liter of water was added, and the precipitate was separated and dissolved in 250 ml of chloroform. The solution was passed through a column (d = 10 cm, h = 3 cm) packed with aluminum oxide and evaporated to dryness, and the residue was crystallized from chloroform–methanol to give 0.89 g (76%) of porphyrin IIb with R_f 0.67 (A). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 400 (116), 499 (13.0), 534 (9.53), 568 (6.29), 622 nm (4.87). IR spectrum: 1733 cm^{-1} (C=O). PMR spectrum: 10.07, 9.99 (3H and 1H, two s, meso-H); 4.398, 4.392 (2H, 2H, two t, $CH_2CH_2CH_2OCOCH_3$); 4.14 (4H, q, CH_2CH_3); 4.07 (4H, m, $CH_2CH_2CH_2OCOCH_3$); 3.61, 3.63 (6H, 6H, two s, ring CH_3); 2.63 (4H, m, $CH_2CH_2CH_2OCOCH_3$); 2.15, 2.14 (3H, 3H, two s, OCH_3); 1.86 (6H, t, CH_2CH_3); −3.79 ppm (2H, s, NH). Found: C 73.0; H 7.5; N 9.0%. $C_{38}H_{46}N_4O_4$. Calculated: C 73.3; H 7.4; N 9.0%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-nonylcarbonyloxypropyl)porphyrin (IIc). A 1-g (1.86 mmole) sample of porphyrin IIa was dissolved in 50 ml of pyridine, and the mixture was cooled to 0°C and treated with 1.54 g (8.07 mmole) of capryl chloride. The mixture was stirred at 5°C for 1 h and at 20°C for 4 h, after which 0.5 liter of water was added, and the mixture was stirred for 30 min and extracted with chloroform (three 150 ml portions). The combined extracts wre dried with Na_2SO_4 and evaporated to dryness in vacuo. The residue was treated with 3 ml of triethylamine and chromatographed with a column (d = 5 cm, h = 50 cm) packed with aluminum oxide in a chloroform–carbon tetrachloride (2:3) system. The principal fraction was separated and evaporated, and the residue was crystallized from chloroform–ethanol to give 1.37 g (87%) of porphyrin IIc with R_f 0.83 (A). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 400 (134), 500 (12.6), 534 (9.19), 568 (6.23), 622 nm (4.68). IR spectrum: 1730 cm^{-1} (C=O). Found: C 76.5; H 9.2; N 6.6%. $C_{54}H_{78}N_4O_4$. Calculated: C 76.6; H 9.3; N 6.6%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-nonylcarbonyloxypropyl)porphyrin Zinc Complex (IId). This complex was obtained in 79% yield from porphyrin IIc by heating it in chloroform–methanol (9:1) in the presence of zinc acetate. The product had R_f 0.84 (A). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 405 (286), 539 (16.1), 576 nm (21.3). IR spectrum: 1733 cm^{-1} (C=O). Found: C 71.2; H 8.4; N 7.2%. $C_{54}H_{76}N_4O_4Zn$. Calculated: C 71.2; H 8.4; N 6.2%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-bromopropyl)porphyrin (IIe). A 1-ml (10.53 mmole) sample of PBr_3 was added to a cooled (to 0°C) solution of 0.87 g (1.61 mmole) of prophyrin IIa in a mixture of 50 ml of DMF and 150 ml of dichloroethane, after which the mixture was stirred at 20°C for 2 h and heated to 70°C. AFter 15 min, a solution of 50 g of sodium acetate in 0.5 liter of water was added, and the organic layer was separated, washed with water (two 150-ml portions), and evaporated to dryness. The residue was dissolved in 50 ml of chloroform, and the solution was passed through a column (d = 10 cm, h = 3 cm) packed with aluminum oxide and evaporated to dryness. The residue was crystallized from chloroform–methanol to give 0.72 g (76%) of porphyrin IIe with R_f 0.86 (A). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 400 (155), 498 (13.5), 533 (9.53), 567 (6.43), 620 nm (4.77). PMR spectrum: 10.18, 10.10, 10.09 (1H, 1H, 2H, all s, meso-H); 4.28 (4H, t, $CH_2CH_2CH_2Br$); 4.10 (4H, q, CH_2CH_3); 3.740, 3.741 (2H, 2H, two t, $CH_2CH_2CH_2Br$); 3.63, 3.64, 3.66, 3.67 (all s, ring CH_3); 2.86 (4H, m, $CH_2CH_2CH_2Br$); 1.87 (6H, t, CH_2CH_3); −3.75 ppm (2H, s, NH). Mass spectrum for $C_{34}H_{40}{}^{81}Br_2N_4$, m/z (%): 666 ($M^+$, 0.4), 584 (4.7), 502 (100), 487 (23), 475 (9). Found: C 6.15; H 6.0; Br 24.1; N 8.4%. $C_{34}H_{40}Br_2N_4$. Calculated 61.5; H 6.1; Br 24.1; N 8.4%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-chloropropyl)porphyrin (IIf). A) A 1-g (1.86 mmole) sample of porphyrin IIa was dissolved in 25 ml (350 mmole) of thionyl chloride. After 18 h, the solution was evaporated to dryness in vacuo, and the residue was dissolved in 200 ml of chloroform. The solution was washed with 100 ml of 10% sodium bicarbonate solution and 100 ml of water, passed through a column (d = 10 cm, h = 3 cm) packed with aluminum oxide, and evaporated to dryness. The residue was crystallized from chloroform–methanol to give 0.86 g (80%) of porphyrin IIf with R_f 0.82 (A). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 401 (108), 500 (13.3), 534 (9.61), 568 (6.56), 621 nm (4.96). PMR spectrum: 10.11, 10.05 (3H, 1H, two s, meso-H); 4.233, 4.222 (2H, 2H, two t, $CH_2CH_2CH_2Cl$); 4.07 (4H, q, CH_2CH_3); 3.831, 3.825 (2H, 2H, two t, $CH_2CH_2CH_2Cl$); 3.63, 3.62, 3.61 (3H, 6H, 3H, all s, ring CH_3); 2.73 (4H, m, $CH_2CH_2CH_2Cl$); 1.86 (6H, t, CH_2CH_3); −3.795 ppm (2H, s, NH). Mass spectrum for $C_{34}H_{40}{}^{35}Cl_2N_4$, m/z (%): 574 ($M^+$, 100), 559 (10), 538 (7), 512 (38), 502 (1). Found: C 70.9; H 7.0; Cl 12.8; N 9.6%. $C_{34}H_{40}Cl_2N_4$. Calculated: C 70.9; H 7.0; Cl 12.3; N 9.7%.

B) A 2-g (10.49 mmole) sample of toluenesulfonyl chloride was added to a solution of 2 g (3.71 mmole) of porphyrin IIa in 100 ml of pyridine, after which the mixture was stirred at 20°C for 3 days. It was then poured into 1 liter of water, and the precipitate was removed by filtration, dried, and dissolved in 250 ml of chloroform. The solution was passed through a column (d = 10 cm, h =3 cm) packed with aluminum oxide and evaporated to dryness. The residue was crystallized from chloroform–methanol to give 0.56 g (26%) of porphyrin IIf, which, according to the TLC and IR spectroscopic data, was identical to the product obtained by method A.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-S-isothiuroniapropyl)porphyrin Dihydrobromide (IIg). A solution of 0.5 g (0.75 mmole) of porphyrin IIe and 0.17 g (2.23 mmole) of thiourea in 50 ml of dioxane was refluxed for 3 h, after which the resulting precipitate was removed by filtration and recrystallized from DMF–ether (1:9) to give 0.52 g (85% of porphyrin IIg with R_f 0.01 (C). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 398 (129), 496 (12.5), 530 (8.87), 566 (5.83), 618 nm (4.38). IR spectrum: 1635 cm^{-1} (NH_2–C–NH_2). Found: Br 19.0; N 13.7; S 7.9%. $C_{36}H_{48}Br_2N_8S_2$. Calculated: Br 19.6; N 13.7; S 7.6%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(4,4-diethoxycarbonylbutyl)porphyrin (IIh). A 3.84-g (23.97 mmole) sample of malonic esters was added to a solution of 0.55 g (23.9 mmole) of sodium in 50 ml of ethanol, after which the mixture was evaporated to dryness, 50 ml of benzene was added, and the mixture was again evaporated to dryness. The residue was dissolved in 50 ml of THF, 0.65 g (0.98 mmole) of porphyrin IIe was added, and the mixture was refluxed for 5 h. It was then cooled to 20°C and treated with 0.5 liter of water, and the resulting precipitate was removed by filtration, dried, and dissolved in 100 ml of chloroform. The solution was chromatographed with a column (d = 5 cm, h = 50 cm) packed with silica gel by elution with chloroform. The principal fraction was evaporated to dryness, and the residue was crystallized from chloroform–methanol to give 0.69 g (85%) of porphyrin IIh with R_f 0.76 (A). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 399 (123), 499 (14.0), 534 (10.2), 568 (6.76), 621 nm (5.18). IR spectrum: 1740 cm^{-1} (C=O). PMR spectrum: 10.05, 9.99 (3H, 1H, two s, meso-H); 4.17-4.05 (16H, m, CH_2CH_3, $CH_2CH_2CH_2CH$, OCH_2CH_3); 3.61 (12H, s, ring CH_3); 3.52 (2H, t, $CH_2CH_2CH_2CH$); 2.35 (8H, m, $CH_2CH_2CH_2CH$); 1.86 (6H, t, CH_2CH_3); 1.14 (12H, t, OCH_2CH_3); –3.81 ppm (2H, s, NH). Found: C 70.1; H 7.4; N 6.8%. $C_{48}H_{62}N_4O_8$. Calculated: C 70.1; H 7.6; N 6.8%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-piperazino-propyl)porphyrin (IIi). A 25-g (290 mmole) sample of anhydrous piperazine was added to a solution of 2 g (3.01 mmole) of porphyrin IIe in 100 ml of chloroform, after which the mixture was heated to 130°C with removal of the chloroform by distillation. After 1 h, the solution was cooled to 20°C, 0.5 liter was added, and the resulting precipitate was removed by filtration, air dried, and dissolved in 150 ml of chloroform. The solution was passed through a column (d = 10 cm, h = 3 cm) packed with activity IV aluminum oxide and evaporated to dryness. The residue was crystallized from chloroform–heptane to give 1.64 g (81%) of porphyrin IIi with R_f 0.04 (C). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 400 (148), 499 (12.8), 534 (9.37), 567 (6.25), 621 nm (4.84). Mass spectrum, m/z (%): 674 (M^+, 100), 575 (63), 562 (25), 549 (40), 547 (36). Found: C 74.4; H 8.5; N 16.3%. $C_{42}H_{58}N_8$. Calculated: C 74.4; H 8.7; N 16.6%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis[3-N,N-bis(2-hydroxyethyl)aminopropyl] porphyrin (IIj). This compound was obtained as in the preparation of porphyrin IIi by the reaction of 2 g (3.01 mmole) of porphyrin IIe with 25 g (240 mmole) of diethanolamine. The product was obtained in 92% yield and had R_f 0.51 (C). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 400 (141), 499 (12.7), 534 (9.25), 567 (6.21), 620 nm (4.87). IR spectrum: 3370 cm^{-1} (OH). Mass spectrum, m/z (%): 712 (M^+, 24), 594 (100). Found: C 69.0; H 8.4; N 11.6%. $C_{42}H_{60}N_6O_4 \cdot H_2O$. Calculated: C 69.0; H 8.5; N 11.5%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis[3-N,N-bis(methoxymethyl)aminopropyl] porphyri (IIk). This compound was obtained as in the preparation of porphyrin IIi by the reaction of 2 g (3.01 mmole) of porphyrin IIe with 25 g (160 mmole) of iminediacetic ester for 40 h. The product was obtained in 78% yield and had R_f 0.84 (B). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 400 (181), 498 (14.7), 534 (10.7), 567 (7.17), 620 nm (5.57). IR spectrum: 1730 cm^{-1} (C=O). PMR spectrum: 10.11, 10.10, 10.087, 10.083 (all s, meso-H); 4.15 (4H, t, $CH_2CH_2CH_2N$); 4.10 (4H, q, CH_2CH_3); 3.66 (8H, m, CH_2OCH_3); 3.65, 3.64, 3.59, 3.585 (all s, ring CH_3); 3.12 (4H, t, $CH_2CH_2CH_2N$); 2.48 (4H, m, $CH_2CH_2CH_2N$); 1.872, 1.868 (3H, 3H, two t, CH_2CH_3); –3.77 ppm (2H, s, NH). Mass spectrum, m/z (%): 824 (M^+, 79), 750 (100), 650 (92), 637 (43). Found: C 76.0; H 7.4; N 10.4%. $C_{46}H_{60}N_6O_8$ Calculated: C 67.0; H 7.3; N 10.2%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-N,N-di-methylaminopropyl)porphyrin (III). A) A solution of 0.3 g (0.52 mmole) of porphyrin IIf in a mixture of 27 ml of DMF and 3 ml of 33% aqueous dimethylamine (~23 mmole) was refluxed for 4 h, after which it was cooled and treated with 60 ml of water. The resulting precipitate was removed by filtration, dried, and dissolved in 50 ml of chloroform. The solution was passed through a column (d = 5 cm, h = 3 cm) packed with silica gel by dilution with chromatographic system C. The principal fraction was evaporated to dryness, and the residue was crystallized from chloroform–heptane to give 0.26 g (84%) of porphyrin III1 with R_f 0.34 (C). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 400 (156), 500 (12.7), 534 (9.73), 567 (6.55), 620 nm (5.02). IR spectrum: 2750 cm^{-1} (N–CH_3). PMR spectrum: 10.13, 10.081, 10.065 (1H, 2H, 1H, all s, meso-H); 4.0-4.18 (8H, m, $CH_2CH_2CH_2N$, CH_2CH_3); 3.642, 3.618, 3.602 (3H, 6H, 3H, all s, ring CH_3); 2.675, 2.626 (2H, 2H, two t, $CH_2CH_2CH_2N$); 2.453 (4H, m, $CH_2CH_2CH_2N$); 2.333, 2.317 (6H, 6H, two s, N–CH_3); 1.846, 1.862 (3H, 3H, two t, CH_2CH_3); –3.76 ppm (2H, s, NH). Mass spectrum, m/z (%): 592 (M^+, 59), 577 (10), 534 (100), 521 (29), 506 (15), 463 (85). Found: C 77.0; H 8.8; N 14.0%. $C_{38}H_{52}N_6$. Calculated: C 77.0; H 8.8; N 14.2%.

B) A 1.76-g (3.18 mmole) sample of porphyrin IIIa was dissolved in 25 ml (350 mmole) of thionyl chloride. After 1 h, the solution was evaporated to dryness, and the residue was dissolved in 200 ml of chloroform. The solution was cooled to –5°C, and 50 ml of a 33% aqueous solution of dimethylamine (~380 mmole) was added with vigorous stirring. After 10 min, the organic layer was separated, dried with Na_2SO_4, and treated with a solution of 2 g (9.11 mmole) of zinc acetate in 50 ml of methanol. The mixture was then refluxed for 0.5 h, after which it was cooled and passed through a column (d = 10 cm, h = 2 cm) packed with aluminum oxide and evaporated to dryness. The residue was dissolved in 150 ml of THF, 0.26 g (6.85 mmole) of $LiAlH_4$ was added, and the mixture was maintained at 60°C for 3 h. Water (5 ml) was added to the solution, the precipitate was removed by filtration, the filtrate was evaporated to dryness, and the residue was dissolved in 200 ml of chloroform and treated with 50 ml of concentrated HCl. The mixture was made alkaline to pH 7-8 with ammonium hydroxide, and the organic layer was separated, dried with Na_2SO_4, and passed through a column (d = 10 cm, h = 3 cm) packed with aluminum oxide. The solution was evaporated to dryness, and the residue was crystallized from chloroform–heptane to give 1.29 g (71%) of porphyrin III1, which, according to the TLC and IR spectroscopic data, was identical to the product obtained by method A.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-N,N-diethylaminopropyl)porphyrin (IIm). This compound was obtained as in the preparation of porphyrin III1 by condensation of acid chloride IIId with diethylamine by method B. The product was obtained in 81% yield and had R_f 0.41 (C). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 400 (144), 498 (13.3), 534 (9.85), 567 (6.45), 619 nm (4.98). Mass spectrum, m/z (%): 648 (M^+, 85), 562 (100), 545 (30), 534 (35). Found: C 77.4; H 9.6; N 13.0%. $C_{42}H_{60}N_6$. Calculated C 77.7; H 9.3; N 13.0%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-piperidinopropyl)porphyrin (IIn). This compound was obtained as in the preparation of porphyrin III1 from acid chloride IIId and piperidine by method B. The product was obtained in 60% yield and has R_f 0.73 (C). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 403 (126), 501 (12.4), 537 (8.84), 571 (5.47), 626 nm (3.67). Mass spectrum m/z (%): 672 (M^+, 100), 574 (70), 561 (17), 547 (18), 546 (19). Found: C 78.4, H 8.9, N 12.4%. $C_{44}H_{60}N_6$. Calculated: C 78.5, H 9.0, N 12.5%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-morpholinopropyl)porphyrin (IIo). This compound was obtained as in the preparation of porphyrin III1 from acid chloride IIId and morpholine by method B. The product was obtained in 62% yield and had R_f 0.63 (B). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 405 (151), 502 (11.8), 537 (8.40), 572 (5.14), 626 nm (3.68). Mass spectrum, m/z (%): 676 (M^+, 100), 576 (75), 563 (29), 550 (38), 548 (38). Found: C 74.4; H 8.3; N 12.4%. $C_{42}H_{56}N_6O_2$. Calculated: C 74.5; H 8.3; N 12.4%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-N,N-dimethylaminopropyl)porphyrin Zinc Complex (IIp). This compound was obtained by heating porphyrin III1 with zinc acetate in chloroform–methanol (19:1). The product was obtained in 84% yield and has R_f 0.29 (C). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 403 (270), 533 (16.4), 569 nm (17.3). IR spectrum: 2760, 2780 cm^{-1} (N–CH_3). PMR spectrum: 10.07, 10.056, 10.048 (1H, 2H, 1H, all s, meso-H); 4.12 (4H, t, $CH_2CH_2CH_2N$); 4.09 (4H, q, CH_2CH_3); 3.64, 3.636, 3.63, 3.62 (all s, ring CH_3); 2.648, 2.651 (2H, 2H, two t, $CH_2CH_2CH_2N$); 2.46 (4H, m, $CH_2CH_2CH_2N$); 2.30, 2.28 (6H, 6H, two s, N–CH_3); 1.86 ppm (6H, t, CH_2CH_3). Found: C 69.5; H 7.7; N 12.7%. $C_{38}H_{50}N_6Zn$. Calculated: C 69.6; H 7.7; N 12.8%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-N,N-diethylaminopropyl)porphyrin Zinc Complex (IIq). This compound was obtained by a procedure similar to that used to obtain zinc complex IIp. The complex was obtained in 86% yield and had R_f 0.34 (C). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 405 (193), 536 (14.3), 572 nm (16.8). PMR spectrum: 10.09, 10.07 (1H, 3H, two s, meso-H); 4.09 (4H, t, $CH_2CH_2CH_2N$); 4.10 (4H, q, CH_2CH_3); 3.64, 3.63 (9H, 3H, two s, ring CH_3); 2.88, 2.94 (2H, 2H, two t, $CH_2CH_2CH_2N$); 2.60; 2.58 (4H, 4H, two q, NCH_2CH_3); 2.48 (4H, m, $CH_2CH_2CH_2N$); 1.86 (6H, t, CH_2CH_3); 1.01, 0.99 ppm (6H, 6H, two t, NCH_2CH_3). Found: C 67.4; H 8.6; N 11.2%. $C_{42}H_{58}N_6Zn \cdot 2H_2O$. Calculated: C 67.4; H 8.4; N 11.2%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-piperidinopropyl)porphyrin Zinc Complex (IIr). This compound was obtained by a procedure similar to that used to obtain zinc complex IIp. The product was obtained in 88% yield and had R_f 0.71 (C). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 403 (302), 533 (15.4), 570 nm (21.0). PMR spectrum: 9.87, 9.83, 9.80, 9.76 (all s, meso-H); 4.03, 3.99 (2H, 2H, two q, CH_2CH_3); 3.92 (4H, t, $CH_2CH_2CH_2N$); 3.58, 3.53, 3.52, 3.49 (all s, ring CH_3); 2.71 (4H, t, $CH_2CH_2CH_2N$); 2.43 [12H, m, $CH_2CH_2CH_2N$, $-N(CH_2)_2-$]; 1.82, 1.78 (3H, 3H, two t, CH_2CH_3); 1.60 [8H, m, $CH_2(CH_2)_2-$]; 1.42 ppm (4H, m, $\diagdown CH_2\diagup$). Found: C 71.7; H 7.9; N 11.3%. $C_{44}H_{58}N_6Zn$. Calculated: C 71.8; H 7.9; N 11.4%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis(3-morpholinopropyl)porphyrin Zinc Complex (IIs). This compound was obtained by a procedure similar to that used to obtain zinc complex IIp. The product was obtained in 85% yield and had R_f 0.6 (B). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 402 (316), 534 (15.6), 570 nm (21.2). PMR spectrum: 9.87, 9.80, 9.72 (1H, 2H, 1H, all s, meso-H); 4.00 (4H, q, CH_2CH_3); 3.94 (4H, t, $CH_2CH_2CH_2N$); 3.55, 3.53, 3.51, 3.50 (all s, ring CH_3); 3.33 [8H, m, $O(CH_2)_2-$]; 2.56 (4H, t, $CH_2CH_2CH_2N$); 2.33 (4H, m, $CH_2CH_2CH_2N$); 2.21 [8H, m, $-N(CH_2)_2-$]; 1.82, 1.79 ppm (3H, 3H, two t, CH_2CH_3). Found: C 67.8; H 7.2; N 11.2%. $C_{42}H_{54}N_6O_2Zn$. Calculated: C 68.1; H 7.4; N 11.4%.

2,7,12,18-Tetramethyl-3,8-diethyl-13,17-bis[3-N,N-bis(2-chloroethyl)aminopropyl] porphyrin (IIt). A 0.5-g (0.7 mmole) sample of porphyrin IIj was dissolved in 25 ml (350 mmole) of thionyl chloride, and the solution was allowed to stand at room temperature for 18 h. It was then evaporated in vacuo, and the residue was dissolved in 150 ml of chloroform. The chloroform solution was washed with 100 ml of 10% $NaHCO_3$ solution and 100 ml of water and passed through a column (d = 10 cm, h = 3 cm) packed with aluminum oxide. The solution was then evaporated to dryness in vacuo, and the residue was crystallized from CCl_4–heptane to give 0.52 g (94%) of prophyrin IIt with R_f 0.78 (A). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 400 (176), 498 (14.4), 534 (10.6), 567 (7.05), 620 nm (5.57). PMR spectrum: 10.10, 10.09, 10.85, 10.03 (all s, meso-H); 4.11 (8H, m, CH_2CH_3, $CH_2CH_2CH_2N$); 3.65, 3.64 (3H, 9H, two s, ring CH_3); 3.54 (8H, t, NCH_2CH_2Cl); 2.96 (12H, m, NCH_2CH_2Cl, $CH_2CH_2CH_2N$); 2.44 (4H, m, $CH_2CH_2CH_2N$); 1.87, 1.866 (3H, 3H, two t, CH_2CH_3); −3.76 ppm (2H, s, NH). Found: C 64.1; H 7.2; N 10.5%. $C_{42}H_{56}Cl_4N_6$. Calculated: C 64.1; H 7.2; N 10.7%.

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