Chemistry of Heterocyclic Compounds, Vol. 33, No. 1, 1997

PORPHYRINS. 34.* TRANSAMINATION IN *meso*-DIMETHYLAMINOMETHYL-PORPHYRINS. SYNTHESIS OF N-(*meso*-PORPHYRINYL-METHYL)AMINES AND AMINO ACIDS

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*Substituted N-(*meso*-porphyrinylmethyl)amines have been synthesized for the first time by the transamination of* meso*-dimethylaminomethylporphyrins with various amines, including derivatives of amino acids and dipeptides, in the presence of methyl (or ethyl) iodide.*

We showed previously that *meso*-dimethylaminomethyl derivatives of porphyrins [such as (I)] react readily by nucleophilic substitution with such reagents as alcohols [2], pyrroles [3], and also various C-nucleophiles (acetone, acetylacetone, dibenzoylmethane, benzoylacetone, cyanoacetic and nitroacetic esters, nitromethane) [4, 5] forming products with replacement of the dimethylamino group. The following are necessary to carry out the substitution reaction efficiently, a) electrophilic catalysis with zinc acetate [4] or b) quaternization of the dimethylamino group with an alkyl iodide (methyl or ethyl) [2, 3] or c) thermal activation (heating in a high-boiling alcohol such as ethyleneglycol) [2]. Dimerization with the formation of the corresponding 1,2-ethanebisporphyrins occurs on heating under the action of alkyl iodide in the absence of a foreign nucleophile [6].

The use of amines as nucleophiles [for example, the conversion of (I) into (IV)] on activation with alkyl iodide seemed to us extremely doubtful in view of the possibility of the ready conversion of the reaction product (IV) into the dimeric derivative (1,2-bisporphyrin) similarly to that described previously in [6]. At the same time the carrying out of such an approach might enable porphyrinyl derivatives to be obtained particularly from aminoacids and peptides, substances with unusual and promising spectral and pharmacological properties.

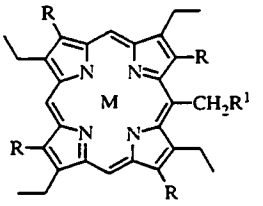
In the present work we report the possibility of the facile transmission of *meso*-dimethylaminoethyloctaalkylporphyrins (both free porphyrin bases and their metal complexes may be used in the reaction) under the action of various amines (aminoacids) using methyl (or ethyl) iodide as activator. The reactor proceeds on boiling a mixture of dimethylaminomethylporphyrin, alkyl iodide, and amine.

The yields of the porphyrin amino derivatives obtained were 79-98%. The reduction in the yield of the desired amine (VII) in the reaction of compound (I) with p-nitrobenzylamine to 75% is explained by the ready methylation of the latter under the reaction conditions which leads to the formation (up to 15%) of the nickel complex of *meso*-[N-methyl-N-(p-nitrobenzyl)]aminomethyletioporphyrin. Consequently, for highly reactive amines it is preferable to generate trimethyl(*meso*-porphyrinylmethyl)-ammonium iodide first by treating the initial porphyrin with an excess of methyl iodide, with subsequent evaporation of the reactant (together with the solvent) in vacuum at room temperature, and then treat with a chloroform solution of the appropriate amine. It is remarkable that no formation of even trace amounts of ethane-1,2-bisporphyrin was recorded in any reaction. The determination of the structures of the derivatives obtained was carried out by studying their PMR spectra, which indicated unambiguously the structure proposed for the reaction products. The possibility of using mass spectrometry to conform the structure of compounds was restricted by their high lability under the conditions of plotting mass spectra which led to the establishment of only the porphyrinylmethyl ion under all conditions.

*For Communication 33, see [1].

Institute of Biomedical Chemistry, Russian Academy of Medical Sciences, Moscow 119832. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 65-68, January, 1997. Original article submitted October 3, 1996.

0009-3122/97/3301-0056$18.00



I R = Me, R^1 = NMe_2, M = Ni; II R = Me, R^1 = NMe_2, M = 2H; III R = Et, R^1 = NMe_2, M = 2H; IV R = Me, R^1 = NPr_2-*i*; M = Ni; V R = Me, R^1 = NBn_2, M = Ni; VI R = Me, R^1 = N-morpholino, M = Ni; VII R = Me, R^1 = $NHCH_2C_6H_4NO_2$-*p*, M = Ni; VIII R = Me, R^1 = NHBu-*t*, M = Ni; IX R = Me, R^1 = $NHCH(CONH_2)CH_2CHMe_2$, M = Ni; X R = Me, R^1 = $NHCH(COOMe)CH_2CHMe_2$, M = Ni; XI R = Me, R^1 = N-(2-carbamoyl)syrrolidinyl, M = Ni; XII R = Me, R^1 = $NHCH(COOMe)CH_2C_6H_4OH$-*p*, M = Ni; XIII R = Me, R^1 = $NHCH(COOMe)CH_2SBzl$, M = Ni; XIV R = Me, R^1 = $NHCH(CH_2CHMe_2)CONHCH_2COOMe$, M = Ni; XV R = Me, R^1 = $NHCH(COOMe)CH_2CHMe_2$, M = 2H; XVI R = Et, R^1 = N-(2-carbamoylpyrrolidinyl, M = 2H; XVII R = Et, R^1 = $NHCH(CONH_2)CH_2CHMe_2$, M = 2H

EXPERIMENTAL

The electronic spectra were taken on a Specord UV-vis spectrophotometer in $CHCl_3$, and the PMR spectra on a Bruker WM 250 instrument in $CDCl_3$ solution. Chromatographic purification of porphyrins was carried out on columns of silicagel 40 × 100 L.

General Procedure. A mixture of a chloroform solution (~ 10 mg/ml) of the dimethylaminomethylporphyrin (I)-(III), methyl (or ethyl) iodide (5 equiv.), and the appropriate amine (4-5 equiv.) (1.5 equiv. triethylamine was added in the case of aminoacid hydrochlorides) was boiled for 1-2 h. Amines (IV)-(XVII) were obtained and were purified by chromatography on silicagel.

Compound (IV) was obtained in 92% yield from compound (I) and diisopropylamine. UV spectrum, λ_{max} (relative intensity): 408 (1.0); 534 (0.20); 572 nm (0.24). PMR spectrum: 9.42 and 9.33 (2) (3H, s, *meso*-H); 5.61 (2H, br.s, *meso*-CH_2); 4.05-3.70 (8H, all q, Por$\underline{CH_2}CH_3$); 3.51, 3.39, 3.37, and 3.30 (12H, s, PorCH_3); 2.21 (2H, m, N$\underline{CH}Me_2$); 1.83, 1.80, 1.73, and 1.63 (12H, all t, J = 7.5 Hz, Por$CH_2\underline{CH_3}$); 0.32 ppm (12H, d, J = 7.5 Hz, NCH$\underline{Me_2}$).

Compound (V) was obtained in 92% yield from compound (I) and dibenzylamine. UV spectrum, λ_{max} (relative intensity): 407 (1.0); 535 (0.18), 570 nm (0.23). PMR spectrum: 9.42 and 9.41 (2) (3H, s, *meso*-H); 7.40-7.00 (10H, m, Ph); 6.23 and 6.16 (4H, d, J = 12 Hz, $\underline{CH_2}$Ph); 5.87 (2H, br.s, *meso*-CH_2); 3.90-3.70 (8H, all q, Por$\underline{CH_2}CH_3$); 3.39, 3.38, and 3.32 (12H, s, PorCH_3); 1.78, 1.76, 1.75, and 1.66 ppm (12H, all t, J = 17.5, Por$CH_2\underline{CH_3}$).

Compound (VI) was obtained in 93% yield from compound (I) and morpholine. UV spectrum, λ_{max} (relative intensity): 407 (1.0); 532 (0.19), 572 nm (0.25). PMR spectrum: 9.44 and 9.40 (2) (3H, s, *meso*-H); 5.60-5.05 (2H, m, *meso*-CH_2); 3.95-3.75 (8H, m, Por$\underline{CH_2}CH_3$); 3.49, 3.40, 3.39, and 3.34 (12 H, s, PorCH_3); 3.10 (4H, m, CH_2OCH_2); 1.90-1.60 ppm (16H, m, CH_2NCH_2 and Por$CH_2\underline{CH_3}$).

Compound (VII) was obtained in 75% yield from compound (I) and p-nitrobenzylamine hydrochloride. UV spectrum, λ_{max} (relative intensity): 410 (1.0); 529 (0.17); 575 (0.23). PMR spectrum: 9.43 and 0.38 (2) (3H, s, *meso*-H); 7.66 and 6.71 (4H, d, J = 9.0 Hz, Ph); 5.60 (2H, s, *meso*-CH_2); 3.90-3.75 (8H, m, Por$\underline{CH_2}CH_3$); 3.42 (2), 3.40, and 3.36 (12H, s, PorCH_3); 2.90 (2H, s, NH$\underline{CH_2}$Ar); 1.78, 1.77, 1.72, and 1.71 ppm (12H, all t, J = 7.5 Hz, Por$CH_2\underline{CH_3}$).

Compound (VIII) was obtained in 79% yield from compound (I) and t-butylamine. UV spectrum, λ_{max} (relative intensity): 406 (1.0); 528 (0.12); 575 nm (0.15). PMR spectrum: 9.40 (3H, br.s, *meso*-H); 5.85 (2H, br.s, *meso*-CH_2); 4.00-3.75 (8H, m, Por$\underline{CH_2}CH_3$); 3.57, 3.36, 3.35, and 3.33 (12H, s, PorCH_3); 1.84, 1.72, and 1.65 (12H, all t, J = 7.5 Hz, Por$CH_2\underline{CH_3}$); 1.56 ppm (9H, br.s, NH$\underline{Bu}$-t).

Compound (IX) was obtained in 92% yield from compound (I) and L-leucinamide hydrochloride. UV spectrum, λ_{max} (relative intensity): 407 (1.0); 530 (0.19); 570 nm (0.23). PMR spectrum: 9.42 and 9.41 (2) (3H, s, *meso*-H); 6.33 and 5.00 (2H, d, J = 5.0 Hz, $CONH_2$); 5.59 (2H, m, *meso*-CH_2); 3.95-3.70 (8H, m, Por$\underline{CH_2}CH_3$); 3.48, 3.39, 3.38, and 3.36 (12H, s, PorCH_3); 2.81 (1H, m, $CH_2\underline{CH}NHCONH_2$); 1.81, 1.79, and 1.71 (12H, all t, J = 7.5 Hz, Por$CH_2\underline{CH_3}$); 1.40-0.80 (3H, m, $-\underline{CH_2}\underline{CH}Me_2$); 0.51 and 0.42 ppm (6H, d, J = 6.0 Hz, $-CH\underline{Me_2}$).

Compound (X) was obtained in 94% yield from compound (I) and L-leucine methyl ester hydrochloride. UV spectrum, λ_{max} (relative intensity): 406 (1.0); 532 (0.22); 572 nm (0.28). PMR spectrum: 9.42 and 9.40 (2) (3H, s, *meso*-H); 5.55 (2H, m, *meso*-CH_2); 3.95-3.75 (8H, m, Por$\underline{CH_2}CH_3$); 3.51, 3.40, 3.39, 3.36, and 3.35 (15H, s, COOMe and PorCH_3); 2.99 (1H, m, $CH_2\underline{CH}NHCOOMe$); 1.80, 1.76, and 1.70 (12H, all t, J = 7.5 Hz, Por$CH_2\underline{CH_3}$); 1.35-0.95 (3H, m, $-\underline{CH_2CH}Me_2$); 0.51 and 0.42 ppm (6H, d, J = 6.0 Hz, $-CH\underline{Me_2}$).

Compound (XI) was obtained in 98% yield from compound (I) and L-prolinamide trifluoroacetate. UV spectrum, λ_{max} (relative intensity): 412 (1.0); 536 (0.15); 576 nm (0.21). PMR spectrum: 9.42 and 9.36 (2) (3H, s, *meso*-H); 5.95 and 4.20 (2H, br.s, $CONH_2$); 5.65 (2H, m, *meso*-CH_2); 3.95-3.70 (8H, m, Por$\underline{CH_2}CH_3$); 3.50, 3.30, 3.37, and 3.33 (12H, s, PorCH_3); 2.45, 2.05, and 1.50-0.90 (7H, m, $\underline{CH_2CH_2CH_2CH}NCONH_2$); 1.90-1.65 ppm (12H, m, Por$CH_2\underline{CH_3}$).

Compound (XII) was obtained in 87% yield from compound (I) and L-tyrosine methyl ester hydrochloride. UV spectrum, λ_{max} (relative intensity): 406 (1.0); 532 (0.19); 570 nm (0.26). PMR spectrum: 9.46 and 9.40 (2) (3H, s, *meso*-H); 5.86 and 5.46 (4H, m, Ph); 5.90 and 5.30 (2H, m, *meso*-CH_2); 3.95-3.60 (8H, m, Por$\underline{CH_2}CH_3$); 3.43, 3.42, 3.39, 3.34, and 3.32 (15H, s, COOMe and PorCH_3); 2.30-2.05 (3H, m, $-\underline{CH_2CH}COOMe$); 1.90-1.60 (12H, m, Por$CH_2\underline{CH_3}$).

Compound (XIII) was obtained in 89% yield from compound (I) and S-benzyl-L-cysteine methyl ester hydrochloride. UV spectrum, λ_{max} (relative intensity): 406 (1.0); 532 (0.15); 576 nm (0.19). PMR spectrum: 9.41 and 9.39 (2) (3H, s, *meso*-H); 7.30-6.20 (9H, m, CH_2SCH_2Ph); 5.88 and 5.09 (2H, m, *meso*-CH_2); 3.95-3.75 (8H, m, Por$\underline{CH_2}CH_3$); 3.51, 3.36, 3.35, and 3.21 (15H, s, COOMe and PorCH_3); 1.98 (1H, d.d, J = 3.0. 5.0 Hz, $\underline{CH}CH_2SBn$); 1.78, 1.68, 1.67, and 1.64 ppm (12H, all t, J = 7.5 Hz, Por$CH_2\underline{CH_3}$).

Compound (XIV) was obtained in 97% yield from compound (I) and L-leucylglycine methyl ester trifluoroacetate. UV spectrum, λ_{max} (relative intensity): 4.6 (1.0); 531 (0.21); 572 nm (0.27). PMR spectrum: 9.45 and 9.44 (2) (3H, s, *meso*-H); 7.02 (1H, br.s, CONH); 5.71 and 5.52 (AB, J = 13.0 Hz, *meso*-CH_2); 3.95-3.75 (8H, m, Por$\underline{CH_2}CH_3$); 3.67 (2H, br.s, $\underline{CH_2}COOMe$); 3.58, 3.51, 3.41, 3.40, and 3.37 (15H, s, COOMe and PorCH_3); 2.66 (1H, m, NHCO$\underline{CH}NH$); 1.80, 1.75, and 1.71 (12H, all t, J = 7.5 Hz, Por$CH_2\underline{CH_3}$); 1.10-0.70 (3H, m, $-\underline{CH_2CH}Me_2$); 0.40 and 0.00 ppm (6H, d, J = 6.0 Hz, $-CH\underline{Me_2}$).

Compound (XV) was obtained in 98% yield from compound (II) and L-leucine methyl ester hydrochloride. UV spectrum, λ_{max} (relative intensity): 406 (1.0); 507 (0.14); 542 (0.07); 576 (0.06); 626 nm (0.05). PMR spectrum: 10.18, 10.16, and 9.93 (3H, s, *meso*-H); 6.22 and 6.05 (AB, J = 12.0 Hz, *meso*-CH_2); 4.35-4.00 (8H, m, Por$\underline{CH_2}CH_3$); 3.77, 3.73, 3.68, and 3.62 (15H, s, COOMe and PorCH_3); 2.70 (1H, m, $CH_2\underline{CH}NHCOOMe$); 2.00, 1.98, and 1.97 (12H, all t, J = 7.5 Hz, Por$CH_2\underline{CH_3}$); 1.75-1.10 (3H, m, $-CH_2\underline{CH}Me_2$); 1.02 and 0.89 (6H, d, J = 6.0 Hz, $-CH\underline{Me_2}$); 2.90 ppm (2H, m, NH).

Compound (XVI) was obtained in 94% yield from compound (III) and L-prolinamide trifluoroacetate. UV spectrum, λ_{max} (relative intensity): 407 (1.0); 506 (0.15); 542 (0.08); 576 (0.07); 625 nm (0.06). PMR spectrum: 10.08 and 9.92 (3H, s, *meso*-H); 6.39 and 4.29 (2H, m, $CONH_2$); 6.28 and 6.20 (AB, J = 13.0 Hz, *meso*-CH_2); 4.10 (16H, m, Por$\underline{CH_2}CH_3$); 3.05 (1H, d.d, J = 3.0, 10.0 Hz, $\underline{CH}CONH_2$); 2.55-2.40 and 1.60-1.20 (6H, m, $\underline{CH_2CH_2CH_2CH}NCONH_2$); 2.00-1.70 (24H, m, Por$CH_2\underline{CH_3}$); −2.80 ppm (2H, m, NH).

Compound (XVII) was obtained in 92% yield from compound (III) and L-leucinamide hydrochloride. UV spectrum, λ_{max} (relative intensity): 408 (1.0); 506 (0.16); 540 (0.08); 575 (0.07); 624 nm (0.05). PMR spectrum: 10.09 and 9.93 (3H, s, *meso*-H); 6.64 and 5.14 (2H, m, $CONH_2$); 6.22 and 6.07 (AB, J = 9.0 Hz, *meso*-CH_2); 4.20-3.95 (16H, m, Por$\underline{CH_2}CH_3$); 3.02 (1H, m, $CH_2\underline{CH}NHCONH_2$); 1.95, 1.90, and 1.82 (12H, all t, J = 7.5 Hz, Por$CH_2\underline{CH_3}$); 1.40-0.90 (3H, m, $-\underline{CH_2CH}Me_2$); 0.56 and 0.10 (6H, d, J = 6.0 Hz, $-CH\underline{Me_2}$); −2.75 ppm (2H, m, NH).

The authors are grateful to their scientific coworker, Candidate of Chemical Sciences V. S. Borodkin of the N. D. Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, for help in plotting the PMR spectra.

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