SYNTHESIS OF COPPER AND IRON COMPLEXES OF MESO-SUBSTITUTED ETIOPORPHYRIN DERIVATIVES

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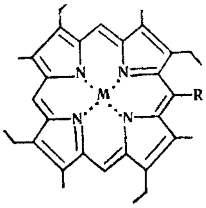
UDC 547.749'255.61'257.2.07:541.49

The synthesis of the copper complex of meso-cyanoetioporphyrin I has been effected from the corresponding meso-formyl derivative and meso-formyletiohemin. An intermediate compound of the copper complex of etioporphyrin I with the Vilsmeier complex (DMFA–$POCl_3$) has been isolated, and it has been reduced to the copper complex of dimethylaminomethyletioporphyrin I.

One of the promising methods of modifying simple octa-alkyl-substituted porphyrins is based on the initial introduction of a formyl group by the Vilsmeier reaction [1-5]. The yield of formylporphyrin depends on which metal complex is used for formylation. For example, in a brief communication [5] it was reported that in the formylation of the Cu^{II} and Ni^{II} complexes of etioporphyrin I in dichloroethane the yields were 74% and 57%, respectively, and etiohemin does not take part in the Vilsmeier reaction. Considerable difficulties arise in the demetallation of the copper complexes of meso-formylporphyrins [4], and in some cases it is quite impossible to obtain the free porphyrin [6]. Consequently, the aim of the present work was to investigate the possibility of modifying the formyl group without the previous demetallation of the meso-formylporphyrin complexes.

The copper complex of etioporphyrin I was treated with a mixture of DMFA and $POCl_3$ in chloroform with heating. The reaction was monitored by TLC on alumina until the initial complex had disappeared from the reaction mixture and the brown-green spot of the intermediate complex formed at the starting line had increased in size. After the treatment of the reaction mixture with aqueous alkali, the copper complex of meso-formyletioporphyrin I (I) was obtained with a yield of 94%, and its reduction with $NaBH_4$ in THF took place readily to the corresponding meso-hydroxymethyl derivative (II).

The preparation of the copper complex of meso-cyanoetioporphyrin I (III) is of special interest, since it is known [3] that free meso-cyanoetioporphyrin does not form metal complexes. We succeeded in converting the copper complex (IV) of the oxime (I), obtained from (I) with a yield of 99.5%,by heating it with acetic anhydride at 130-140°C with vigorous stirring for 3-4 h, into (III) with a yield of 66%.



I–X

I, IX, X $R{=}CHO$; II $R{=}CH_2OH$; III $R{=}CN$; IV $R{=}CH{=}NOH$; V $R{=}CH{=}\overset{+}{N}Me_2Cl^-$; VI $R{=}CH{=}\overset{+}{N}Me_2(OPOCl_2)^-$; VIII $R{=}CH_2NMe_2$; I—VI, VIII $M{=}Cu$; IX $M{=}\overset{III}{Fe}{-}OH$; X $M{=}\overset{III}{Fe}{-}Cl$

The next stage was an investigation of the possibility of isolating and establishing the structure of the intermediate phosphorus compound obtained as a result of the reaction of the Vilsmeier complex with the metalloporphyrin.

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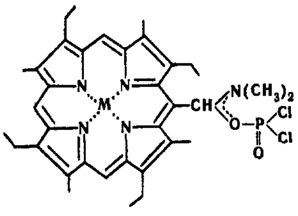
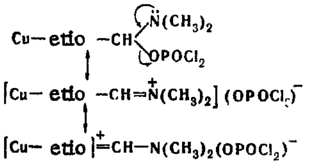
It was found that in the formylation of the copper complex of etioporphyrin, after the end of the reaction (chromatographic test),elimination of the solvent led to the crystallization of an intermediate compound. When the oily residue was carefully poured into water, this intermediate compound was not hydrolyzed to the immonium salt (V). The substance was stable in the air, crystallized well from chloroform–petroleum ether, and was completely insoluble in cold water. The IR spectrum of this compound clearly showed bands at 525 cm^{-1} (ν_{P-Cl}), 1300 cm^{-1} ($\nu_{P=O}$), and 1670 cm^{-1} ($\nu_{C=N}$), which should be characteristic for the structure of the immonium salt (VI). However, the lack of solubility in water, the presence of marked splitting of the Soret band, and the diffuse form of the α band in the electronic spectrum of this compound permit the assumption that this complex probably exists in a transitional form for which the ionic and covalent forms are limiting states. In this case, the structure of the compound under consideration can be expressed by formula (VII), in which the C–N bond is "essentially" double and the C–O bond "essentially" ionic.



VII



This hypothesis is also confirmed by the fact that on being heated in water the intermediate complex (VII) gradually dissolves and is converted into the true immonium salt (V).

The reduction of the complex (VII) with $NaBH_4$ in chloroform takes place exceptionally readily to the corresponding copper complex of dimethylaminomethyletioporphyrin I (VIII). At the same time, a small amount of another metal complex of unknown structure is obtained in the IR spectrum of which a series of bands is observed in the 2300-2400 cm^{-1} region that are characteristic for the stretching vibrations of P–H bonds. The reduction of (VII) in ethanol leads to partial demetallation and the splitting out of the meso substituent.

From the electronic spectra of the copper complexes of the compounds obtained it can be seen that (III) and (VIII) have the greatest bathochromic shifts. This effect can be explained by the high degree of conjugation of the nitrile group with the porphyrin ring in (III) and by the pronounced bending of the porphyrin ring as a result of the considerable steric effect of the meso-dimethylaminomethyl group in (VIII).

In the mass spectrum of (III), the main peak is the peak of the molecular ion M^+. Decomposition of the molecular ion takes place by the successive elimination of methyl radicals. The splitting out of the CN group from the molecular ion and from the intermediate demethylated fragments is not observed at all, which also indicates a high degree of conjugation of the nitrile group with the π system of the porphyrin ring, in contrast to the aryl cyanides, for which the formation of the $(M-HCN)^+$ ion is characteristic [7].

The use of the chromatographic method of monitoring the course of the reaction enabled us to perform the formylation of the iron complex of etioporphyrin (etiohemin), also, with high yield. Generally, during the formylation reaction a sharp change in the color of the solution from red to green takes place, which is one of the criteria for the completion of the reaction. However, in the formylation of the hemins no appreciable change in the color of the solution is observed. By means of TLC on alumina, we have found that practically none of the initial hemin remains in the reaction mixture after it has been heated for 6 h. After treatment with alkali, an intermediate meso-formyletiohematin (IX) was isolated, and this was then converted into the corresponding hemin (X) with a yield of about 85%. The low yield in the formylation of the dimethyl ether of meso-hemin (IX) obtained by Nichol [4] and the absence of the formylation of etiohemin reported by Grigg and Sweeney [5] can be explained by an insufficient time of heating of the hemins with the Vilsmeier complex in formylation.

In the mass spectrum of the hemin (X) the main peak is that of the molecular ion M^+, the decomposition of which leads to the ion $(M-CO)^+$ with a peak of approximately the same intensity. Fragmentation of a similar type has been observed in the mass spectrum of the dimethyl ether of β-formylmesoporphyrin IX [4].

In the mass spectrum of the hematin (IX) with the same type of fragmentation the intensity of the peak of the molecular ion M^+ is approximately half the intensity of the peak of the ion $(M-CO)^+$, which is probably due to the interaction of the formyl and hydroxy groups in the molecule concerned. It is possible that the additional band at 1665 cm^{-1} present in the IR spectrum of this compound is due to the formation of a hydrogen bond between the aldehyde and hydroxy groups.

EXPERIMENTAL

The electronic spectra in chloroform were obtained on a Shimadzu MPS-50L instrument. The IR spectra were taken on a UR-10 instrument in tablets with KBr. The mass spectra were obtained on an LKB-900 instrument at a temperature of the ionization chamber of 270-290°C and an energy of the ionizing electrons of 70 eV. The TLC figures are given for alumina of activity grade 2.5 in chloroform.

Vilsmeier Salt with the Copper Complex of Etioporphyrin I (VII). At 0°C, 6 ml of phosphorus oxychloride was added to 5 ml of dimethylformamide. After 15 min, the crystalline Vilsmeier complex was dissolved in 60 ml of dry chloroform, 200 mg of the copper complex of etioporphyrin I was added, and the mixture was heated at the boil for 15 min. Then the chloroform was driven off in vacuum and the residual oil with the porphyrin complex that had crystallized out in it was added dropwise with stirring to 150 ml of cold water. The resulting precipitate was filtered off, washed with cold water, dried in the air, and recrystallized from chloroform–petroleum ether to give 120 mg (44.5%) of the Vilsmeier salt with mp > 250°C. R_f 0. λ_{max}, nm ($E \cdot 10^{-3}$); 401 (139); 440 (75); 535 (7.5); 575 (10.9). Found, %: C 57.7; H 5.5; Cl 9.5; N 9.6. $C_{35}H_{42}Cl_2CuN_5PO_2$. Calculated, %: C 57.6; H 5.8; Cl 9.7; N 9.6.

Copper Complex of Meso-dimethylaminomethyletioporphyrin I (VIII). A solution of 60 mg of the Vilsmeier salt (VII) in 10 ml of chloroform was treated with 200 mg of $NaBH_4$ and the mixture was stirred for 5 min. The color of the solution rapidly changed from green to red. The resulting solution was chromatographed on a column of silica. Chloroform eluted a small amount of a metal complex of unknown structure. The fraction containing the main substance was eluted with chloroform containing 1% of methanol, the eluate was evaporated and the residue was recrystallized from chloroform–methanol to give 39 mg (79%) of the copper complex of meso-dimethylaminomethyletioporphyrin I (VIII) in the form of long prismatic crystals with mp 332-333°C. R_f 0.7. λ_{max}, nm ($E \cdot 10^{-3}$): 408 (130), 542 (10.0), 585 (12.6). Found, %: C 70.3; H 7.6; N 11.9. $C_{35}H_{43}N_5Cu$. Calculated, %: C 70.4; H 7.3; N 11.7.

Copper Complex of Meso-formyletioporphyrin I (I). A mixture of 200 mg of the copper complex of etioporphyrin I and the complex obtained from 2 ml of $POCl_3$ and 3 ml of dimethylformamide was heated at the boil in chloroform until the initial copper complex was absent from a sample (1 h 30 min). Then the reaction mixture was poured into 200 ml of water, the aqueous layer was brought to pH 9-10 with alkali, the mixture was stirred for 4 h, and then the organic layer was separated off, dried with magnesium sulfate, and evaporated. The residue was recrystallized from dichloroethane–ethanol to give 198 mg (94%) of the copper complex of meso-formyletioporphyrin I with decomp. p. above 300°C. R_f 0.5. ν_{max} 1700 cm^{-1} (C=O), λ_{max}, nm ($E \cdot 10^{-3}$): 406 (192), 530 (8.8), 566 (13.2), 640 (4.0). Found, %: C 69.4; H 6.4. $C_{33}H_{36}CuN_4O$. Calculated, %: C 69.6; H 6.4.

The Copper Complex of Meso-hydroxymethyletioporphyrin I (II). A few drops of water and 300 mg of $NaBH_4$ were added to a solution of 150 mg of the copper complex of meso-formyletioporphyrin I in 50 ml of THF. The solution was stirred at 45°C for 15 min and was poured into 100 ml of water, the substance was extracted with chloroform, the extract was dried with magnesium sulfate and evaporated to 10 ml, 30 ml of dichloroethane was added, the mixture was heated until the solid matter had dissolved completely, and the solution was then allowed to cool slowly. The precipitate that deposited was filtered off to give 130 mg (86%) of the copper complex of meso-hydroxymethyletioporphyrin I in the form of long, very thin bright-red crystals with mp 275-278°C (decomp.). R_f 0.25. λ_{max}, nm ($E \cdot 10^{-3}$): 405 (132), 533 (11.0), 570 (15.8). Found, %: C 69.7; H 7.0; N 9.6. $C_{33}H_{38}CuN_4O$. Calculated, %: C 69.5; H 6.7; N 9.8.

Copper Complex of the Oxime of Meso-formyletioporphyrin I (IV). A mixture of 150 mg of the copper complex of meso-formyletioporphyrin I and 550 mg of hydroxylamine hydrochloride in 25 ml of pyridine was heated at 120°C for 20 min. Then the solution was cooled to 100°C and 10 ml of water was added slowly in drops. The bright red microcrystalline precipitate that deposited was filtered off and washed with water, methanol, and ether to give 153 mg (99%) of the copper complex of the oxime of meso-formyletioporphyrin I. After crystallization from dichloroethane it formed threadlike crystals with decomp. p. above 300°C. R_f 0.26. λ_{max}, nm ($E \cdot 10^{-3}$): 405 (294), 530 (11.8), 566 (18.6). Found, %: C 67.7; H 6.6; N 11.9. $C_{33}H_{37}CuN_5O$. Calculated, %: C 68.0; H 6.4; N 12.0.

Copper Complex of Meso-cyanoetioporphyrin I (III). A suspension of 100 mg of the copper complex of the oxime of meso-formyletioporphyrin I in 100 ml of acetic anhydride was stirred at 130-140°C until the initial complex had dissolved completely (3-4 h). After cooling, the dark-red precipitate that deposited was filtered off, washed with water and methanol, and dried to give 64 mg (66%) of the copper complex of meso-cyanoetioporphyrin I with mp greater than 300°C. R_f 0.7. $\nu_{C\equiv N}$ 2208 (cm^{-1}): λ_{max}, nm (E · 10^{-3}): 409 (152), 547 (4.5), 588 (12.1). Mass spectrum, m/e (%): 566 (62), 564 (100), 551 (14), 549 (2.8), 534 (11), 519 (10), 504 (5.5). Found, %: N 12.7. $C_{33}H_{35}CuN_5$. Calculated, %: N 12.4.

Meso-formyletiohemin I (X). A mixture of 250 mg of etiohemin and the complex obtained from 5 ml of dimethylformamide and 5 ml of phosphorus oxychloride was heated in 50 ml of dry chloroform for 6 h. Then the reaction mixture was poured into 200 ml of water, alkali was added to pH 9-10, and the mixture was stirred at 60°C until a sample contained no immonium salt (TLC) (1 h). The green chloroform layer was separated off, dried with sodium sulfate, and evaporated to dryness. The residue, which consisted of meso-formylhematin (IX) was dissolved in 10 ml of glacial acetic acid, and 0.5 ml of concentrated hydrochloric acid was added. The microcrystalline precipitate that deposited was filtered off, washed with water, and dried to give 210 mg (80%) of meso-formyletiohemin I. It did not melt below 300°C. R_f 0. ν_{max} 1702 cm^{-1} (C=O). Mass spectrum, m/e (%): 561 (40), 560 (100), 546 (7), 545 (8), 533 (35), 532 (95), 517 (17), 502 (13), 487 (9), 472 (6.5), 457 (3.5). Found, %: C 66.7; H 6.2; N 9.6. $C_{33}H_{36}ClFeN_4O$. Calculated,%: C 66.5; H 6.1; N 9.4.

The meso-formyletiohematin I (IX) prepared in a similar manner to that described above from [^{57}Fe]etiohemin had R_f 0.4 and the mass spectrum, m/e (%): 561 (50), 546 (5), 518 (20), 533 (100), 503 (15), 488 (10), 473 (5).

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