alcohol-hexane (2 : 8) to give a product with mp 318-319° (from acetone) in 1.4% yield. Found: C 74.0; H 5.3; N 12.2%. $C_{22}H_{19}N_3O_2$. Calculated: C 73.9; H 5.4; N 11.8%. IR spectrum: 3420, 3140, 1690 cm^{-1}. PMR spectrum, δ, ppm: 1.49 (2-$COOCH_2CH_3$, m); 2.51 (11-CH_3, s); 2.55 (6-CH_3, s); 4.51 (2-$COOCH_2CH_3$, q); 7.12-7.72 (aromatic protons, 4-H, 5-H, 9-H, 10-H, m); 8.07 (12-CH, s); 8.44 (7-CH, s); 11.6 (8-NH, s); 12.12 (3-NH, s).

1H,5H-2-Carbethoxy-4-oxo-8-methyl-1,4-dihydro-δ-carboline (IVc). The filtrate obtained after separation of VI was vacuum evaporated, and the residue was suspended in acetone. The resulting crystals were removed by filtration and recrystallized from 125 ml of acetone to give a product with mp 289-290° (from acetone) in 26.8% yield. Found: C 66.6; H 5.2; N 10.2%. $C_{15}H_{14}N_2O_3$. Calculated: C 66.6; H 5.2; N 10.4%. IR spectrum: 3480, 2700, 1710, 1680 cm^{-1}. PMR spectrum, δ, ppm: 1.36 (2-$COOCH_2CH_3$, m); 2.39 (8-CH_3, s); 4.42 (2-$COOCH_2CH_3$, q); 6.33 (3-CH, s); 7.11 and 7.20 (6-CH, d); 7.43 and 7.52 (7-CH, d); 7.76 (9-CH, s); 10.92 (5-NH, s); 11.75 (1-NH, s).

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PORPHYRINS

IV.* SYNTHESIS AND PROPERTIES OF SCHIFF BASES OF meso-FORMYLETIOPORPHYRIN I

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The reaction of salts of meso-dimethylformaldiminoetioporphyrin I and its copper complex with ammonia, hydrazine, aliphatic and alicyclic amines, and amino acids was investigated, and the corresponding azomethine derivatives were obtained.

It has recently been demonstrated [2] that meso-dimethylaminomethyletioporphyrin I, obtained from the phosphorus complex (I), facilitates the postradiation revivification of a culture of heart cells from the ape, cynomolgus. A number of compounds containing, in the meso position of the porphyrin ring, an effective, within a radiobiological framework, aminomethyl group with diverse substituents attached to the nitrogen atom, seem of interest for the study of the effect of porphyrins on the organs and tissues in the case of radiation sickness. Compounds of this type might have been synthesized by reduction of the corresponding Schiff bases.

Several examples of the preparation of Schiff bases of meso-formylporphyrins with aromatic amines [3], as well as a single communication regarding the synthesis of a Schiff base of meso-formyloctaethylporphyrin with β-alanine [4], are presently known. All of these reactions proceed at high temperatures because of the low reactivity of the meso-formyl group. This is probably why our attempts to obtain Schiff bases by the classical method [starting from meso-formyletioporphyrin I (II) with lower aliphatic amines] were unsuccessful.

* For Communication III, see [1].

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We have noted that I has increased activity in nucleophilic substitution reactions. However, prior demetallation of complex I was necessary for the synthesis of the Schiff bases of free porphyrins. The demetallation of complex I by the usual method – by treatment with concentrated sulfuric acid – proceeds very slowly because of its low solubility. We therefore used a method that consisted in treatment of the metal complex with phosphorus oxychloride in the presence of a small amount of water, in which both the starting material and the porphyrin dication (III), which was rapidly hydrolyzed by aqueous alkali under mild conditions to formylporphyrin II, were quite soluble.

A new porphyrin, in the IR spectrum of which we observed an intense band at 1625 cm^{-1} corresponding to vibrations of the C=N group and bands at 3290 and 3230 cm^{-1} characteristic for the N–H vibrations of pyrrole rings in porphyrin and N–H vibrations in imines, respectively, was obtained when ammonium hydroxide was used to neutralize the solution of porphyrin III. A signal from the proton of a CH group in the meso position and close to the signal of the methylidyne proton in the spectrum of the oxime of porphyrin II [4] was observed in the PMR spectrum of this porphyrin. These data unambiguously indicate that the isolated compound is meso-aldiminoetioporphyrin I (IVa) [5]. It was subsequently established that complex I is converted to the copper complex of the aldimine (Va) in 89% yield when a chloroform solution of it is stored for 3-4 h. However, if complex I is first treated with any protic acid (for example, acetic, trifluoroacetic, or hydrochloric), the subsequent reaction with ammonium hydroxide proceeds rapidly in the cold, and the reaction to form complex Va is complete after a few seconds.

The considerable increase in the rate of reaction of I with ammonia after prior treatment with acid constitutes evidence that complex VI, with a meso-immonium group capable of conjugation and resonance with the porphyrin ring, is formed in this case.

A characteristic feature of aldimine IVa is its exceptionally high lability in acidic media. Even a weak acid such as silicic acid catalyzed the conversion of IVa to a formylporphyrin. Porphyrin II was obtained in quantitative yield when a solution of IVa in chloroform was passed slowly through a column filled with silica gel. At the same time, copper complex Va was found to be resistant to the action of both organic acids and alkali.

As expected, we were unable to synthesize aldimines IVa and Va by condensation of formylporphyrin II or its copper complex with ammonia.

The preparation of aldimines IV and V exclusively from the immonium salts can be represented by the general scheme

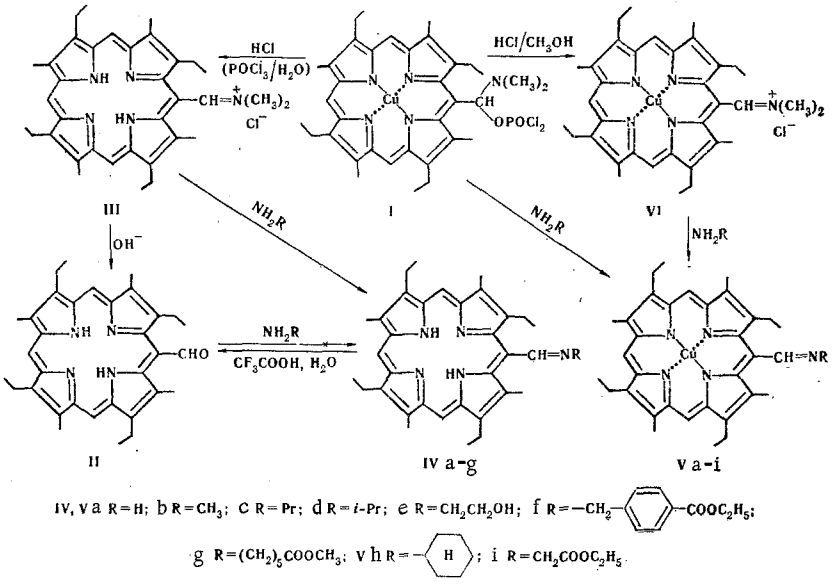
$$R{-}CH{=}\overset{+}{N}(CH_3)_2\,Cl^- + NH_2R' \longrightarrow R{-}CH\begin{matrix}N(CH_3)_2\\ NHR'\end{matrix} \longrightarrow R{-}CH{=}N{-}R' + HN(CH_3)_2$$

where R is a porphyrin residue or a residue of its metal complex, and R'=H, OH, NH_2, alkyl, aryl, etc.

Proceeding from this representation of the reaction mechanism, we extended it for the synthesis not only of Schiff bases with aliphatic, alicyclic, and aromatic amines but also of Schiff bases with hydroxylamine, hydrazines, thiosemicarbazide, and amino acids.

In all cases we were able to obtain the corresponding azomethines by simple treatment of solutions of III and VI with excess reagent. Chloroform was used as the solvent, since the yields of final products were lower in other solvents. In the case of the formation of aldimines IVa and Va and N-methylaldimines IVb and Vb, the use of ammonium hydroxide and aqueous methylamine solutions practically does not lead to the hydrolysis of III and VI to formylporphyrin II and its copper complex.

Since the reactivities of amino acids are considerably lower than the activities of aliphatic amines, a twofold to threefold excess of the hydrochloride of the ester of the corresponding amino acid, absolute solvents, and prolonged refluxing of the reaction mixture must be used for the preparation of the Schiff bases. Because of the low solubilities of the hydrochlorides of the amino acids in chloroform, they were first dissolved in a small amount of methanol containing excess triethylamine. This method was used to obtain Schiff bases with the ethyl esters of p-aminomethylbenzoic acid, glycine, and ε-aminocaproic acid. Ethyl ε-aminocaproate underwent saponification during the reaction. The reaction products were therefore esterified with 5% sulfuric acid in methanol at room temperature for 12 h. In this case hydrolysis of the Schiff bases and demetallation of the copper complex were not observed, and the corresponding methyl esters IVg and Vg were isolated in high yields.



IV, V a R=H; b R=CH_3; c R=Pr; d R=*i*-Pr; e R=CH_2CH_2OH; f R=—CH_2—C$_6$H$_4$—$COOC_2H_5$;

g R=$(CH_2)_5COOCH_3$; v h R=—C$_6$H$_5$; i R=$CH_2COOC_2H_5$

The formation of oximes IV and V, anilide V, and a hydrazone takes place in the cold, and the products were obtained in quantitative yields. Their structures were proved by comparison with samples obtained from porphyrin III by known methods [3, 6].

A slight bathochromic shift (4-5 nm) of all of the bands as compared with the unsubstituted etioporphyrin and its copper complex is characteristic for the electronic spectra (Table 1) of the Schiff bases of both the free porphyrins and their copper complexes; this indicates the practically complete absence of conjugation of the azomethine group with the porphyrin macrocycle. Substituents attached to the nitrogen atom also have little effect on the shape and form of the bands in the electronic spectra. At the same time, protonation of the azomethine group, which occurs exceptionally easily for most of the compounds in the series of Schiff bases obtained, leads to significant changes in the electronic spectra. This is particularly true of the spectra of the copper complexes, in which the two bands in the visible portion of the spectrum vanish, and an intense broad band appears at 720 nm. Only one compound — the copper complex of the Schiff base with glycine ethyl ester (Vi) — was protonated with difficulty; this is probably associated with the effect of the adjacent ester group. As seen from the data presented in Table 1, bands of the protonated and unprotonated forms are observed in the electronic spectrum even in the presence of a considerable amount of trifluoroacetic acid.

An intense band of stretching vibrations of a C=N group appears distinctly at 1620-1660 cm^{-1} in the IR spectra of all of the azomethines; this band is easily interpreted and can serve for the identification of Schiff bases of the porphyrin series.

The synthesis of a large number of azomethines (Table 2) makes it possible to conclude that their preparation from meso-formylporphyrins by utilization of immonium salts of the III and VI types is extremely promising and in many cases is an as yet unique method.

EXPERIMENTAL

The electronic spectra of solutions of the compounds in chloroform were recorded with Hitachi EPS-3T and Shimadzu MPS-50L spectrophotometers; the electronic spectra of chloroform solutions of the cations of the copper complexes of the porphyrins containing 1% trifluoroacetic acid were also recorded. The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. Chromatographic purification of the compounds was accomplished with columns filled with silica gel; thin-layer chromatography (TLC) data are presented for Silufol in chloroform (A) and chloroform + 1% diethylamine (B) systems.

meso-N-Methylformaldiminoetioporphyrin I (IVb). A 200-mg (2.75 mmole) sample of complex I was dissolved by stirring in 10 ml of phosphorus oxychloride, to which 0.5 ml of water had been added. After 1.5 h, the solution was carefully poured into 100 ml of cold water. After complete decomposition of the phosphorus oxychloride, the solution was neutralized with a saturated sodium acetate solution to pH 5-6. The resulting precipitate was removed by filtration and dissolved in 50 ml of chloroform. The solution was treated with 5 ml of a 25% aqueous solution of methylamine, and, 1-2 min after complete disappearance of the starting material in the solution [determined by chromatographic monitoring on Silufol in a chloroform—triethylamine system

TABLE 1. Electronic Spectra of the Schiff Bases

Compound	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)
IVa	408 (80,5); 508 (13,1); 540 (7,75); 577 (6,12); 629 (3,68)
Va	407 (313); 534 (11,4); 572 (16,1)
Va*	405 (61) sh, 448 (142); 608 (5,34); 650 (7,10)sh, 710 (11,7)
IVb	403 (78,1); 505 (13,1); 538 (8,1); 572 (6,90); 625 (3,26)
Vb	405 (286); 533 (12,1); 571 (17,4)
IVc	404 (170.5); 505 (14.9); 538 (8,77); 572 (7,23); 625 (4,16)
Vc	404 (330); 533 (13,2); 571 (19,0)
Vc*	450 (140); 728 (12,1)
IVd	405 (198); 506 (13,96); 539 (8,1); 573 (6,52); 626,5 (3,65)
Vd	404 (402); 543 (17,4); 571 (24,3)
IVe	404 (190,4); 505 (14,71); 539 (9,24); 572 (7,54); 625 (3,96)
Ve	404 (288); 533 (10,0); 571 (14,0)
IVf	405 (183); 506 (13,29); 539 (7,75); 573 (6,28); 626,5 (3,56)
Vf	404 (383); 533 (14,4); 571 (20,5)
IVg	404 (172); 505 (14,3); 538 (8,61); 572 (6,84); 625 (3,75)
Vg	404 (327); 533 (13,1); 571 (18,9)
Vg*	450 (137); 718 (11,6)
Vh	404,5 (370); 535 (14,1); 573 (17,4)
Vh*	450 (162); 718 (9,4)
Vi	404 (462); 533 (17,6); 571 (23,2)
Vi*	405 (162); 450 (242); 736 (13,6)

*These spectra were recorded from solutions in chloroform containing 1% CF_3COOH.

TABLE 2. Characteristics of the Compounds Obtained

Compound	Empirical formula	Found, %			Calc., %			R_f (system)*	Yield, %†
		C	H	N	C	H	N		
IVa	$C_{33}H_{39}N_5$	78,4	7,65	13,8	78,4	7,8	13,8	0,53 (B)	72,3
Va	$C_{33}H_{37}CuN_5$	69,9	6,6	12,9	69,9	6,6	12,9	0,38 (A)	77,5
IVb	$C_{34}H_{41}N_5$	78,8	7,8	13,4	78,9	7,6	13,5	0,52 (B)	63,5
Vb	$C_{34}H_{39}CuN_5$	70,3	6,8	11,8	70,3	6,8	12,0	0,58 (A)	79,0
IVc	$C_{36}H_{45}N_5$	78,8	8,1	12,8	78,9	8,4	12,8	0,73 (B)	74,6
Vc	$C_{36}H_{43}CuN_5$	71,1	7,0	11,5	70,9	7,1	11,5	0,67 (A)	87,0
IVd	$C_{36}H_{45}N_5$	78,8	8,1	12,8	78,9	8,4	12,8	0,67 (B)	73,5
Vd	$C_{36}H_{43}CuN_5$	70,7	7,2	11,5	70,9	7,1	11,5	0,66 (A)	82,0
IVe	$C_{35}H_{43}N_5O$	76,6	7,7	12,5	76,8	7,6	12,8	0,06 (B)	62,0
Ve	$C_{35}H_{41}CuN_5O$	68,5	6,7	11,1	68,7	6,8	11,5	0,05 (A)	89,5
IVf	$C_{43}H_{49}N_5O_2$	77,3	7,3	10,5	77,3	7,4	10,5	0,75 (B)	37,0
Vf	$C_{43}H_{47}CuN_5O_2$	70,5	6,6	9,6	70,8	6,5	9,6	0,63 (A)	77,0
IVg	$C_{40}H_{51}N_5O_2$	75,8	8,0	11,0	75,8	8,1	11,1	0,62 (B)	48,0
Vg	$C_{40}H_{49}CuN_5O_2$	69,0	7,0	10,0	69,1	7,1	10,1	0,44 (A)	40,0
Vh	$C_{39}H_{47}CuN_5$	72,1	7,5	10,7	72,1	7,3	10,8	0,71 (A)	80,0
Vi	$C_{37}H_{43}CuN_5O_2$	67,7	6,6	10,6	68,0	6,6	10,7	0,49 (A)	80,0

*Chromatographic systems A and B are presented in the experimental section.

†Compounds IVa-g and Vi were recrystallized from chloroform–methanol, and Vc, d, g, h were recrystallized from chloroform–ether–methanol. The remaining compounds were recrystallized from chloroform–ether.

(99 : 1)], the organic layer was separated, washed with water, and dried with sodium sulfate. The solvent was removed in vacuo, and the residue was chromatographed with a column filled with 40/100 L silica gel in a chloroform–ether system (95 : 5). The main fraction was concentrated, and the substance was crystallized by the addition of methanol to give 90 mg of large prismatic needles of porphyrin IVb with mp > 300°.

The Schiff bases with propylamine, isopropylamine, ethanolamine, and cyclohexylamine were similarly obtained by adding 0.5-1 ml of the amine, and the Schiff base with ammonia was obtained by adding 10 ml of concentrated ammonium hydroxide.

meso-N-Propylformaldiminoetioporphyrin I Copper Complex (Vc). A 73-mg (0.1 mmole) sample of complex I was dissolved in 5 ml of methanol saturated with hydrogen chloride, after which the solution was vacuum evaporated to dryness, and the residue was dissolved in 10 ml of chloroform. Excess (0.5 ml) propylamine was added, and the mixture was stirred for 2-3 min until the reaction was complete. The mixture was then vacuum evaporated to dryness, and the residue was dissolved in a small amount of chloroform. The chloroform solution

was chromatographed with a column filled with 100/250 L silica gel with elution by chloroform. The main fraction was evaporated, and the residue was crystallized from chloroform–ether–methanol to give 53 mg of bright-red prismatic needles of complex Vc with mp > 300°.

The copper complexes of the Schiff bases with other amines and ammonia were similarly obtained.

meso-N-(p-Ethoxycarbonylbenzyl)formaldiminoetioporphyrin I (IVf). A 146-mg (0.2 mmole) sample of complex I was dissolved in 10 ml of phosphorus oxychloride treated with 0.5 ml of water. After 2.5 h, the solution was poured carefully into 250 ml of cold water, and the mixture was neutralized with sodium acetate. The resulting flocculent precipitate was removed by filtration and dissolved in 100 ml of chloroform. The chloroform solution was added to a solution of 107 mg (0.5 mmole) of the hydrochloride of ethyl p-aminomethylbenzoate [7] in a mixture of 1 ml of methanol, 5 ml of chloroform, and 0.1 ml of triethylamine. The reaction mixture was refluxed for 1 h until the starting porphyrin was absent in a sample, after which the solvent was vacuum evaporated, and the dry residue was washed with methanol and chromatographed with a column filled with 100/250 L silica gel in a chloroform–ether system (95 : 5). The main fraction was crystallized from chloroform–methanol to give 50 mg of porphyrin IVf with mp > 300°.

The Schiff base with glycine ethyl ester was similarly obtained. In the case of condensation with ethyl ε-aminocaproate, the dry residue was esterified for 12 h in 20 ml of a 5% solution of sulfuric acid in methanol prior to chromatographic purification. The synthesis of the copper complexes of the Schiff bases with amino acids was carried out similarly using the product of treatment of I with hydrogen chloride in methanol.

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