SYNTHESIS OF TETRAPHENYLPORPHINES WITH ACTIVE GROUPS IN THE PHENYL RINGS.

5.* TETRA(CARBOXYMETHYLENOXYPHENYL)PORPHINES AND THEIR ETHYL ESTERS

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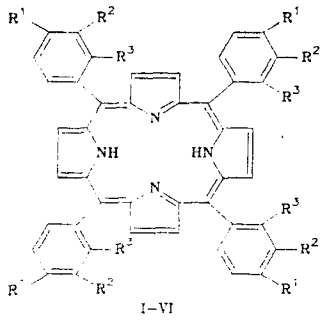
Tetra(carboxymethylenoxyphenyl)porphines which are soluble in bases are prepared by hydrolysis of the ethyl esters of tetra(carboxymethylenoxyphenyl)porphines. The starting ethyl esters of the tetra(carboxymethylenoxyphenyl)porphines were synthesized by alkylation of tetra(oxyphenyl)porphines with ethylchloroacetate, as well as by condensation of pyrrole with ethyl esters of formylphenoxyacetic acids.

Interest in the synthesis and study of water-soluble porphines is related to their contemplated uses as medicinal preparations [2], models of natural catalytically active systems [3], and homogeneous catalysts in aqueous media [4].

The purpose of the present work was to develop effective synthetic methods for the water-soluble tetra(carboxymethylenoxyphenyl)porphines I-III.

Attempts to prepare these porphines by alkylation of tetra(oxyphenyl)porphines with haloacetic acids ($ClCH_2COOH$, $BrCH_2COOH$, and ICH_2COOH) under various conditions had been unsuccessful. These facts contradicted the report that phenoxyacetic acid could be readily prepared by reaction of phenol with chloroacetic acid in aqueous bases [5].



I-VI

I $R^1=OCH_2COOH$; II $R^2=OCH_2COOH$; III $R^3=OCH_2COOH$; IV $R^1=OCH_2COOC_2H_5$; V $R^2=OCH_2COOC_2H_5$; VI $R^3=OCH_2COOC_2H_5$; unspecified R^1, R^2, $R^3=H$

The porphyrin fragment is known to act as a strong electron acceptor relative to the phenyl ring, about equal in strength to a nitro group [6]. Therefore, p-nitrophenol was chosen as a model during development of methods for methylcarboxylation of the oxyphenylporphines.

We found that alkylation of p-nitrophenol by haloacetic acids in the presence of bases does not proceed even under forcing conditions (boiling DMF). However, we succeeded in alkylating p-nitrophenol using ethylchloroacetate as the alkylating agent. Under the reaction conditions, the carbon atom of the methylene group in ethylchloroacetate acquires a larger positive charge than in the chloroacetate anion. Moreover, the alkylation becomes more probable. Nevertheless, it can only be carried out in boiling DMF with addition of potassium carbonate as the base. The reaction does not occur in such other nonaqueous solvents as 1-butanol or acetone.

*See [1] for Communication 4.

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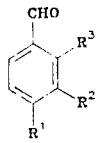
Using an analogous route, we succeeded in preparing the ethyl esters of the tetra(carboxymethylenoxyphenyl)porphines IV-VI (Table 1) and the ethyl esters of the formylphenoxyacetic acids VII-IX. Consendation of compounds VII-IX with pyrrole also leads to porphyrins IV-VI.

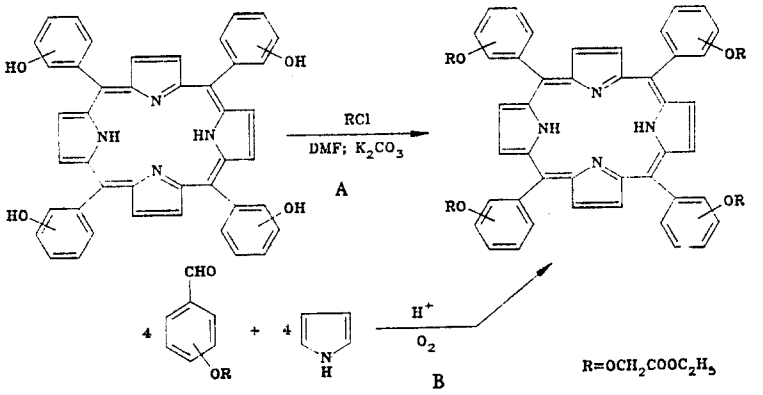


VII-IX

VII $R^1=OCH_2COOC_2H_5$; VIII $R^2=OCH_2COOC_2H_5$; IX $R^3=OCH_2COOC_2H_5$; unspecified R^1, R^2, $R^3=H$

Thus, compounds IV-VI are synthesized by two independent routes (Scheme 1).

Scheme 1



The yield of porphyrins IV-VI (Table 1) which were prepared by alkylation of tetra(oxyphenyl)porphine (route A) depends little on the position of the alkylated oxy group, in contrast to the reaction of pyrroles with aldehydes (Table 2). It is interesting that the yield of porphyrins IV-VI which are prepared by condensation of pyrrole with aldehydes (route B) depends little on the reaction medium which is used. This distinguished them from other porphyrins, for which the yield in xylene–chloroacetic acid averages about two times higher [7].

A hypsochromic shift of the absorption bands is observed in the electronic spectra of compounds IV-VI upon going from the para- to the ortho-isomer. This is probably associated with a distortion of the porphyrin macrocycle structure in the case of the ortho-isomer VI.

Comparison of the PMR spectra shows a substantial shift toward higher field for the signals of the substituent for the ortho-isomer VI in comparison with the para-(IV) and meta-(V) isomers. This is apparently related to effective shielding by the porphyrin macrocycle ring current.

Hydrolysis of the porphyrins IV-VI was carried out in aqueous-alcoholic base. Tetra(carboxymethylenoxyphenyl)porphines I-III, which are soluble in basic solutions, resulted (Table 2). Porphyrin I was also prepared for comparison by oxidation of tetra(4-allyloxyphenyl)porphine X (Scheme 2). This route is poorly suited for synthesis since the yield of I in this reaction is low (20%), apparently due to simultaneous oxidation of the porphyrin.

The yield of porphyrins I-III depends greatly on steric factors (Table 2). Thus, the most spatially hindered ortho-isomer is obtained in the lowest yield.

Comparison of the electronic absorption spectra of compounds I-III shows that, as in the case of compounds IV-VI, a hypsochromic shift of the absorption bands is observed upon going from the para- to the ortho-isomer. In our opinion, this is explained by a distortion of the porphyrin molecular structure in the case of the ortho-isomer I. An increase in the intensity of the electronic bands is observed in the spectrum of the para-isomer (in comparison with the ortho- and meta-isomers). The electronic bands I and III become larger than the vibrational bands II and IV (Fig. 1). Possibly, this is related to the formation of associates.

TABLE 1. Data for Ethyl Esters of Tetra(carboxymethylenoxyphenyl)porphines (IV-VI)

Compound	Electronic absorption spectra, λ, nm (log ε)					PMR, δ, ppm			IR spectrum, cm^{-1}	Yield, %	
	I	*II*	*III*	*IV*	Soret	OCH_2	CH_2	CH_3	$\nu_{C=O}$	A	B*
IV	650 (3,83)	593 (4,03)	594 (4,03)	518 (4,23)	422 (5,66)	4,84	4,34	1,34	1770	35	21 (20)
V	648 (3,92)	590 (4,04)	550 (4,12)	514 (4,46)	419 (5,79)	4,79	4,12	1,17	1740	32	10 (10)
VI	643 (3,73)	589 (4,04)	546 (4,00)	513 (4,48)	419 (5,78)	4,26	3,93	0,94	1760	33	3 (5)

*In propionic acid. Data from a xylene–chloroacetic acid mixture are given in parentheses.

TABLE 2. Data for Tetra(carboxymethylenoxyphenyl)porphines (I-III)

Compound	Empirical formula	Electronic absorption spectra, λ, nm (log ε)					IR spectrum, cm^{-1}		Yield, %
		I	*II*	*III*	*IV*	Soret	ν_{OH}	ν_{CO}	
I	$C_{52}H_{42}N_4O_{12}$	664 (3,99)		582 (4,23)	525 (4,10)	418 (5,24)	3210	1710	82
II	$C_{52}H_{42}N_4O_{12}$	630 (3,76)	603 (3,91)	562 (4,10)	518 (4,16)	416 (5,32)	3230	1740	64
III	$C_{52}H_{42}N_4O_{12}$	627 (3,52)	608 (3,79)	561 (4,03)	516 (4,11)	415 (5,60)	3220	1720	52

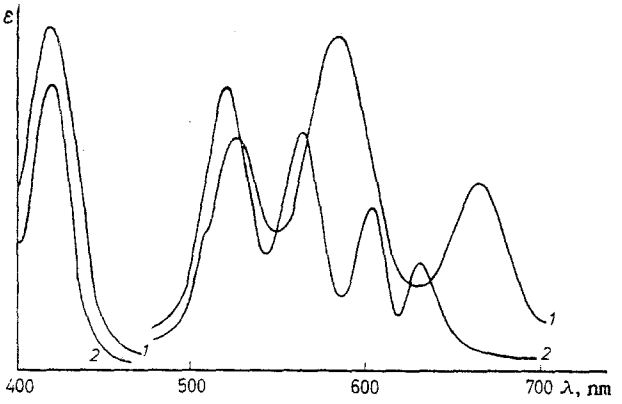
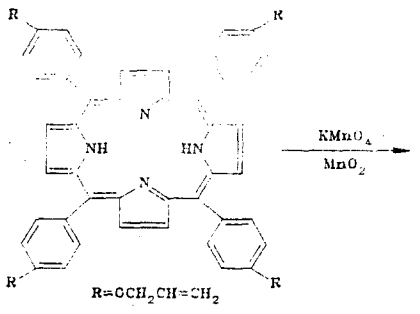


Fig. 1. Electronic absorption spectra of porphyrins in 5% KOH solution: 1) I and 2) II.

Scheme 2



EXPERIMENTAL

Electronic absorption spectra were taken on a Specord M-40 spectrophotometer in 5% aqueous KOH for porphyrins I-III and in $CHCl_3$ for porphyrins IV-VI.

PMR spectra of porphyrins IV-VI were recorded on a Tesla BS-497.0 (100 MHz) instrument in $CDCl_3$. The internal standard was HMDS.

IR spectra were taken on an IKS-29 spectrophotometer as mulls in mineral oil which were placed between KBr plates.

Elemental analyses of compounds I-III for C, H, and N corresponded to those calculated.

Ethyl Esters of Formylphenoxyacetic Acids (VII-IX). A mixture of 5 g (4.1 mmole) hydroxybenzaldehyde, 3 g (22 mmole) anhydrous K_2CO_3, 0.5 g (3 mmole) KI, and 9 ml (85 mmole) ethylchloroaceate in 60 ml DMF was boiled for 1 h with stirring. The cooled mixture was poured into 200 ml water and excess $ClCH_2COOC_2H_5$ was removed with water vapor. The residue was extracted with ether (3 × 100 ml). The ether extract was washed with 10% NaOH and then with water. The ether was evaporated. The product was dried over anhydrous $CaCl_2$.

Compound VII. Yield 6.1 g (71%); IR spectrum: 1760 ($\nu_{C=O(COO^-)}$), 1690 cm^{-1} ($\nu_{C=O(CHO)}$).

Compound VIII. Yield 3.6 g (42%); IR spectrum: 1760 ($\nu_{C=O(COO^-)}$), 1700 cm^{-1} ($\nu_{C=O(CHO)}$).

Compound IX. Yield 2.3 g (27%); IR spectrum: 1750 ($\nu_{C=O(COO^-)}$), 1680 cm^{-1} ($\nu_{C-O(CHO)}$).

Ethyl Esters of Tetra(carboxymethylenoxyphenyl)porphines (IV-VI). A. A mixture of 0.3 g (0.44 mmole) tetra(oxyphenyl)porphine, 0.93 ml (8.6 mmole) $ClCH_2COOC_2H_5$, 1.22 g (8.8 mmole) anhydrous K_2CO_3, and 0.32 g (1.9 mmole) KI in 30 ml DMF was boiled for 2 h with stirring. After cooling, the reaction mixture was poured into 150 ml water. The precipitate was filtered off, washed with water, and dried in air to constant mass. The precipitate which was dissolved in 50 ml chloroform was chromatographed on a silica gel (L 100/250) column and eluted with a mixture of chloroform-ether, 4:1. The solvent was evaporated to 5 ml and porphyrins IV-VI were precipitated with 100 ml hexane.

B-a. A mixture of 5.9 g (29 mmole) of the ethyl ester of formylphenoxyacetic acids VII-IX and 2 ml (29 mmole) of pyrrole were added to 100 ml of boiling propionic acid. The reaction mixture was boiled for 40 min, cooled, and extracted with chloroform (3 × 50 ml). The chloroform extract was washed with water, evaporated to 30 ml, and chromatographed on a silica gel (L 100/250) column, eluting with a mixture of chloroform–ether, 4:1. The solvent was evaporated to 5 ml and porphyrins IV-VI were precipitated with 100 ml hexane.

B-b. A solution of 15 g (72 mmole) of the ethyl ester of formylphenoyxacetic acids VII-IX and 5 ml pyrrole (72 mmole) in 50 ml xylene was added over a period of 15 min to a boiling solution of 14 g chloroacetic acid in 300 ml xylene with passage of air. The reaction mixture was boiled for 1.5 h more. After cooling, it was neutralized with a 25% ammonia solution until changing color from green to reddish-brown. The xylene solution was chromatographed on a silica gel (100/250) column, eluting with a mixture of chloroform–ether, 4:1. The solvent was evaporated to 5 ml and porphyrins IV-VI were precipitated with 100 ml hexane.

Tetra(carboxymethylenoxyphenyl)porphines (I-III). A. The porphines IV-VI (0.6 g, 0.58 mmole) were boiled for 1 h in 50 ml of 10% aqueous-ethanolic, 1:1, KOH solution. The solvent was evaporated and the residue was dissolved in 30 ml water. Porphyrins I-III were precipitated with conc. HCl.

B. A solution of $KMnO_4$ (0.24 g, 1.5 mmole) in 25 ml of a pyridine–water, 1:1, mixture was added dropwise with stirring to a solution of 0.3 g (0.36 mmole) tetra(4-allyloxyphenyl)-porphine in 25 ml pyridine. The mixture was stirred for 2 h. The precipitate of MnO_2 was filtered off and washed with 50 ml hot water. The filtrate and washings were evaporated to 20 ml and porphyrin I was precipitated with 10 ml conc. HCl. Porphyrin I was filtered off and dried in air to constant mass.

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PORPHYRINS.

25.* USE OF THE NUCLEAR OVERHAUSER EFFECT FOR ESTABLISHMENT OF THE STRUCTURE OF ISOMERIC meso-SUBSTITUTED METALLOPORPHYRINS

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Nickel complexes of the dimethyl esters of meso-dimethylaminomethyl derivatives of mesoporphyrin-II and mesoporphyrin-IX are synthesized. The structure of the prepared isomeric compounds is determined by analysis of their chromatographic properties, visible spectra, as well as of their PMR spectra using the nuclear Overhauser effect.

Porphyrins which contain a dimethylaminomethyl (DMAM) group in the meso-position hold great interest as starting materials for synthesis of widely differing compounds, e.g., meso-hydroxy(alkoxy)methylporphyrins [2] and meso-methylporphyrins [3]. Besides this, certain of the DMAM porphyrins are biologically active substances [4].

We demonstrated that formation of DMAM porphyrins can be used successfully for proving the structure of formylation products in the case of simple symmetrically substituted octaalkylporphyrins, for example, etioporphyrin-II [5].

Recently, PMR spectroscopy using the nuclear Overhauser effect (NOE) has been used to establish the structure of complicated natural porphyrins of unknown structure.

The purpose of the present work is to expand the possibilities for using DMAM porphyrins for establishment of the structure of formylation products in the case of complicated unsymmetrically substituted porphyrins and to confirm independently the structures of these compounds using the NOE.

We chose mesoporphyrin-II (Ia) and mesoporphyrin-IX (IIa) for the study. Earlier it was shown that formation of all four possible meso-substituted products occurs during formylation of the copper complex of mesoporphyrin-IX. However, unambiguous and correct establishment of the structure for each of these has not been carried out [6].

The PMR spectra of porphyrins Ia and IIa were simplified by preparation of the trideuteromethyl esters of the Ni complexes Ic and IIc. The Ni complexes of the DMAM porphyrins were synthesized by a method which was developed earlier [5]. The individual isomers Id, Ie, and IVa-d were separated by preparative thin-layer chromatography on silica gel.

Initial data on the proposed structure of the isomers were obtained based on analysis of chromatographic mobility data. The chromatographic mobility of DMAM porphyrins is known to depend to a large extent on the screening effect of the β-pyrrole substituents next to the DMAM group [5]. Therefore, the more mobile isomer in the case of the Ni complexes of the DMAM isomers of mesoporphyrin-II was assigned structure Id. In this structure, the meso-substituent is located between the methyl and methoxycarbonylethyl group. This is in contrast to the less mobile isomer Ie, in which the DMAM group is located between the less bulky substituents.

A small bathochromic shift in comparison with compound Id is characteristic for the electronic spectrum of porphyrin Ie. This agrees with the electronic spectral data for derivatives of etioporphyrin-II [5].

*See [1] for Communication 24.

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