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Synthetic Porphyrins. I. Synthesis and Spectra of Some *para*-Substituted *meso*-Tetraphenylporphines (1)

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A series of derivatives of *meso*-tetraphenylporphine, with neutral, acidic and basic functional groups, has been prepared. Several of these compounds were synthesized directly via the Rothemund reaction, under a variety of conditions to obtain optimal yields; others were prepared by interconversions of various functional groups. Drastic reaction conditions employed for hydrolysis, alcoholysis, or lithium aluminum hydride reduction did not affect the porphine ring system. The two amino derivatives showed anomalous spectra in the visible range.

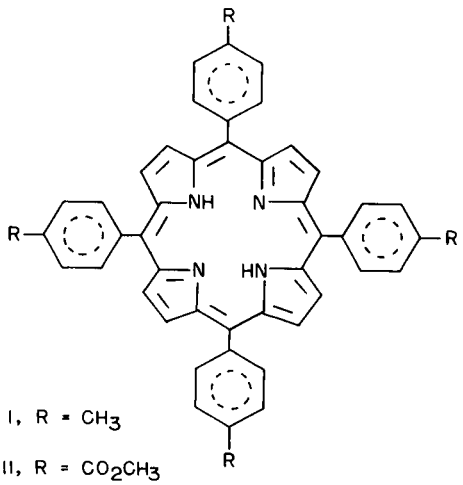
Synthetic porphyrins are of potential interest in medicinal chemistry for a variety of reasons: (1) they are structurally related to important biological substances (heme, vitamin B_{12}); (2) they are powerful metal chelating agents; (3) they absorb radiation energy at certain wavelengths, including the visible spectral range, and may act either as radiation sensitizers or protecting agents against radiation; (4) they show selective tissue distribution properties. Hematoporphyrin reportedly accumulates in tumors and other rapidly growing tissues (3-5) and was used as a fluorescent indicator for the delineation of neoplastic tissue in cancer patients (6). A sulfonated derivative of *meso*-tetraphenylporphine was recently reported to be even more selective and to attain a 50-100 times greater tumor concentration than hematoporphyrin (7-9). It would seem, therefore, that such compounds may be used as tumor-selective radiation sensitizers, and in the form of their chelates either with a toxic metal (*e.g.*, Hg) (10) or, with a gamma-ray emitting radioistope (*e.g.*, Co^{57}) (9), as potential chemotherapeutic agents.

In order to establish the effects of various functional groups in the porphyrin molecule on the solubility, tissue distribution and specificity of binding to certain cell-constituents, a series of new *meso*-tetraphenylporphine derivatives, substituted in the *para* positions with acidic, basic or neutral groups (II-VIII), were synthesized and studied. The previously known *meso*-tetra-*p*-tolylporphine (I) was prepared in serial experiments designed to study the optimal methods and conditions for the synthesis of these compounds.

Compounds I to V were prepared directly by various applications of the Rothemund reaction, *i.e.*, by condensation of the appropriately substituted benzaldehyde with pyrrole. Compounds VI to VIII were prepared by chemical conversion from II and III.

Two major variations of the Rothemund reaction as applied to the synthesis of *meso*-tetraphenylporphine and some of its derivatives were found in the literature:

(A) Heating a mixture of pyrrole with the appropriate aldehyde in a sealed bomb at high pressure and temperature, usually with pyridine as a solvent. This method originally used by Rothemund (11,12) gave extremely low yields (<1%). When the reaction was conducted in the presence of metal salts (Calvin,



I, R = CH_3

II, R = CO_2CH_3

III, R = CN

IV, R = $N(CH_3)_2$

V, R = $N(C_2H_5)_2$

VI, R = $CO_2C_2H_5$

VII, R = COOH

VIII, R = CH_2OH

TABLE I

Yields of *meso*-tetra-*p*-tolyporphine (I) by Method (A) Under Various Reaction Conditions

Exp. No.	Aldehyde	Pyrrole	Pyridine	Time/Temp	Yield g.	Yield percent
(1)	22.6 ml. (0.185 mole)	10 ml. (0.157 mole)	20 ml.	24 hrs./157°	1.0	3.81
(2)	22.6 ml. (0.185 mole)	15 ml. (0.236 mole)	14 ml.	24 hrs./156°	0.9	2.90
(3)	22.6 ml. (0.185 mole)	10 ml. (0.157 mole)	20 ml.	48 hrs./157°	1.0	3.81
(4)	22.6 ml. (0.185 mole)	10 ml. (0.157 mole)	20 ml.	24 hrs./190°	1.5	5.70
(5)	34 ml. (0.273 mole)	23 ml. (0.362 mole)	21 ml.	24 hrs./190-200°	2.5	5.47
(6)	34 ml. (0.273 mole)	23 ml. (0.362 mole)	21 ml.	24 hrs./190-200°	2.55	5.60
(7)	34 ml. (0.273 mole)	23 ml. (0.362 mole)	21 ml.	24 hrs./200°	4.0	8.77

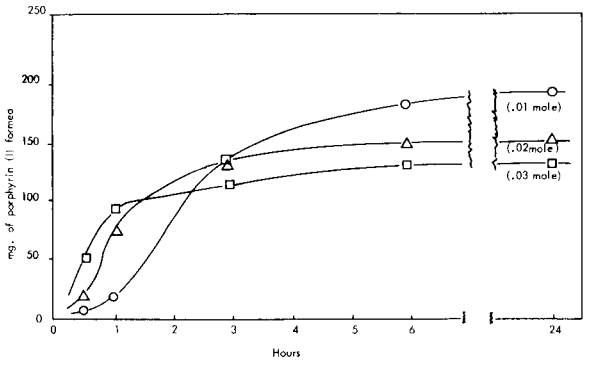


Fig. 1. Time course of condensation (in 99.7% acetic acid solution) between pyrrole and (0.01 mole) and *p*-tolualdehyde (0.01, 0.02 and 0.03 mole) to porphyrin I, at 118°.

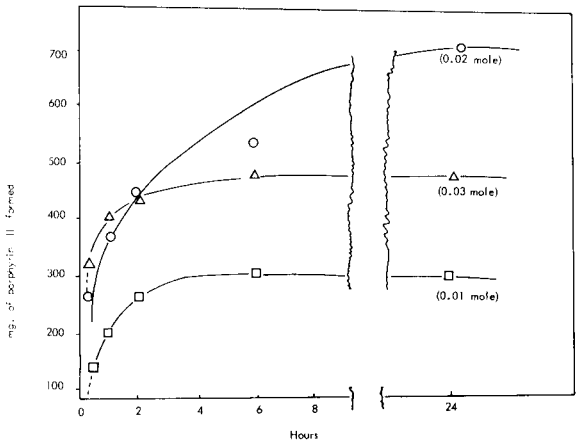


Fig. 2. Time course of condensation (in 99.7% acetic acid solution) between pyrrole (0.01 mole) and *p*-carbomethoxybenzaldehyde (0.01, 0.02 and 0.03 mole) to porphyrin II, at 118°.

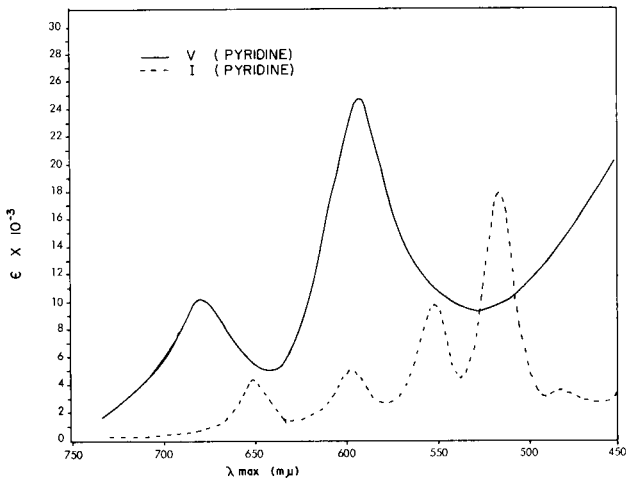


Fig. 3. Visible spectra of compounds I and V.

et al. (13), Badger *et al.* (14)), the yield improved considerably (10-11%); however, still a considerable amount of the corresponding chlorin was obtained, which had to be separated by chromatography. Besides *meso*-tetraphenylporphine, a few of its *ortho* and *para* substituted derivatives (R = CH_3, OCH_3, Cl) (15) and their zinc complexes (14) were prepared by this method.

(B) Refluxing of a mixture of pyrrole with benzaldehyde in a solvent or solvent mixture. This method has been applied only in a rate study of the formation of *meso*-tetraphenylporphine itself (16), and the product was not isolated. Spectrophotometric determinations indicated that under certain conditions as much as 50% of the theoretical yield of porphyrin was formed in the reaction mixture.

In order to obtain the maximum yields of compounds I, II and III, using method (A), serial experiments were run with variations of reaction temperatures and reaction times, the relative concentrations of pyrroles and aldehydes and the amount of solvent (pyridine). All preparations of I were successful, with a maximum yield of 8.8% (see Table I) when the conditions given for experiment No. 7 were used. Compound I was previously synthesized by Thomas and Martell (15) with a maximum yield of 3%. The improved yield obtained in the present work appears to be due to the higher molar ratio of pyrrole to *p*-tolualdehyde and to the employment of higher reaction temperature. Applications of this method to the synthesis of II and III gave variable results with maximum yields of 4.6 and 7.3% respectively; however, the reproducibility of these yields was poor.

Application of method (B) using 99.7% acetic acid as the solvent and varying the aldehyde to pyrrole ratios, solvent dilutions and reaction times, resulted in somewhat higher maximal yields of I, and in much higher and reproducible yields for II and III (see Table II). Interestingly, in the case of I and III,

TABLE II

Optimal Yields of Purified Products

Porphyrins	Method (A)	Method (B)
I	8.8%	11.7%
II	4.6%	33.1%
III	7.3%	36.4%
IV	2.4%	No reaction
V	8.9%	No reaction

equimolar ratios of the reactants gave the highest final yields (see Fig. 1), while 2:1 molar ratio of aldehyde to pyrrole resulted in the highest final yield of II (see Fig. 2). It should be noted, however, that in either case the initial rate of porphyrin formation (*i.e.* the yield obtained in the first half hour of reaction time) increased with the concentration of the aldehyde in the reaction mixture.

The amino derivatives, IV and V could not be prepared by method (B), even when a variety of other solvents (dimethylformamide, dimethylformamide-boric acid and dimethylsulfoxide) were substituted for glacial acetic acid. These compounds could be made only by a rather drastic modification of method (A) in which no solvent, a reaction temperature of 220°, and 48 hours of reaction time were employed. Even so the yields obtained were low (see Table II).

The *p*-carbethoxy derivative (VI) was prepared by alcoholysis of the cyano derivative (III) with absolute ethanol and concentrated sulfuric acid. The tetracarboxylic acid (VII) was obtained by the hydrolysis of II with 10% aqueous potassium hydroxide in tetrahydrofuran as solvent. The hydroxymethyl derivative (VIII) was prepared by lithium aluminum hydride reduction of II in dry tetrahydrofuran solution. All three compounds were obtained in satisfactory yields. The fact, that these relatively drastic reactions did not affect the porphine nucleus, shows the remarkable stability of this ring system.

The ultraviolet and visible absorption spectra of these compounds were studied in several solvents (see Table III). Among the new porphyrins the spectra of II, III, VI, VII and VIII show the intense Soret band and the five characteristic visible absorption bands of previously described *para*-substituted *meso*-tetraphenylporphin derivatives (14), with only minor individual differences in the exact positions and intensities when compared to each other or to I. In contrast, the spectra of the basic porphyrins, IV and V, while similar to each other, are both vastly different in comparison to those of other tetraphenylporphine derivatives. Their Soret bands are less intense and significantly displaced to longer wavelength, and only two other visible absorption bands appear in the "red region" of the spectrum. This general bathochromic shift of the ultraviolet and visible spectrum (which is particularly apparent when V in pyridine is compared with the other compounds in the same solvent (see Table and Fig. 3) seems to indicate an increase in the resonance interaction between the benzene ring and the porphine system and thus a higher degree of coplanarity. X-Ray diffraction studies are currently in progress in order to explain this anomaly. It should be noted that the copper (II) complex of IV was found to have similar visible spectrum to those of the copper (II) complexes of the other tetraphenylporphine derivatives.

The infrared spectra of compounds I to VIII are shown in Table IV. The characteristic band frequencies previously assigned to the tetraphenylporphine structure (15) are found to be present in all new compounds although some of them are slightly shifted in the case of IV and V.

These compounds and their various metal chelates are currently being studied in various biochemical and biological systems for the following properties: (1) binding to proteins and nucleic acids, (2) inhibition of various cell-free enzyme systems, (3) distribution in various organs and tissues, (4) selective sensitization of tissues and of cellular macromolecules to radiation, and (5) effect on experimental animal tumors. The results of these studies will be presented elsewhere.

EXPERIMENTAL (17)

meso-Tetratolylporphine (I).

(a) Using method (A).

Mixtures of *p*-tolualdehyde and pyrrole, in dry pyridine, were allowed to react in a sealed bomb, at various temperatures and for various lengths of time. The reaction mixture was cooled to room temperature and diluted with a large excess of acetone. The deeply

TABLE III

Ultraviolet and Visible Absorption Spectra of New Porphyrins

Compound (solvent)	λ max (mμ) (ε x 10^{-3}) Soret	IV* (d)	III* (d)	II* (d)	Ia* (d)	I* (d)
I (a)	420 (483)	485 (4.2)	516 (19.0)	550 (9.7)	592 (5.4)	650 (4.4)
I (b)	422 (454)	485 (4.1)	517 (17.8)	552 (10)	594 (5.1)	651 (4.7)
III (b)	423 (351)	488 (3.8)	521 (19.7)	556 (8.1)	597 (5.88)	655 (3.4)
II (b)	423 (403)	485 (3.7)	516 (17.8)	551 (8.3)	592 (5.3)	650 (3.2)
VII (b)	422 (161)	486 (3.1)	517 (14.4)	552 (7.0)	591 (4.3)	649 (2.9)
VIII (b)	422 (392)	485 (3.4)	517 (15.3)	553 (8.9)	594 (4.6)	651 (4.4)
VI (b)	424 (455)	486 (4.2)	517 (19.7)	551 (8.8)	591 (6.1)	649 (3.4)
VII (c)	412 (365)		527 (8.0)	566 (7.9)	593 (3.7)	654 (3.9)
IV (6*N* HCl)	438 (298)				597 (8.31)	649 (28.0)
V (6*N* HCl)	439 (320)				599 (8.8)	652 (32.8)
V (b)	449 (122)				592 (25)	682 (9.8)

(a) Benzene. (b) Pyridine. (c) 5% Sodium carbonate. (d) Numbering of visible spectral bands according to Falk (18).

purple crystals were filtered and washed with acetone. Table I summarizes the results obtained from seven sets of experiments.

(b) Using method (B).

A number of small-scale reactions were carried out in the following manner: *p*-tolualdehyde and pyrrole, in various proportions, were dissolved in 500 ml. of glacial acetic acid and refluxed for various lengths of time. The acetic acid was evaporated *in vacuo*. A few milliliters of pyridine were added to the dark viscous liquid, and to this mixture 500 ml. of acetone was added. Purple crystals separated, which were filtered, washed with 50 ml. of acetone, dried and weighed. Some of these studies are represented in Fig. 1 which shows that equimolar aldehyde-to-pyrrole ratio gave the highest yield (11.7%) of I with 24 hours refluxing time.

Chromatographic fractionation of a sample of this material, using a column of talc, and trichloroethylene as the eluent, gave essentially quantitative recovery of the starting material in a large number of eluate fractions which all showed identical spectra, corresponding to pure I (15). Therefore, the conclusion was reached that the reflux method (B) produced only TTP (I) without any chlorin by-product.

An analytical sample of I was prepared by recrystallization from pyridine.

Anal. Calcd. for $C_{48}H_{38}N_4$: C, 85.97; H, 5.67; N, 8.36. Found: C, 85.70; H, 5.78; N, 8.52.

meso-Tetra-(*p*-carbomethoxyphenyl)porphine (II).

(a) Using method (A).

A series of reactions were carried out under pressure at high temperature in sealed tubes, in a similar manner as described for I, under (a). Of ten sets of reactions, showing rather erratic results, five did not lead to any isolatable products. The best yield (4.5%) was obtained by heating a mixture of *p*-carbomethoxybenzaldehyde (16.4 g., 0.1 mole), pyrrole, 12 ml. (0.17 mole), and dry pyridine, 32 ml., to 180-190° for 24 hours.

An analytical sample of the compound was prepared by crystallization from pyridine followed by drying over phosphorous pentoxide *in vacuo*.

Anal. Calcd. for $C_{52}H_{38}N_4O_8$: C, 73.74; H, 4.52; N, 6.62. Found: C, 74.20; H, 4.81; N, 6.93.

(b) Using method (B).

In order to establish the best conditions for the synthesis of *meso*-tetra-(*p*-carbomethoxyphenyl)porphine (II), which was to be used as the starting material for the preparation of other derivatives (VII, VIII), a series of experiments were carried out similar to those described for I, under (b). Some of these experiments are represented in Fig. 2, which shows that a 2:1 aldehyde-to-pyrrole ratio and 24 hours refluxing time gave the highest yield of II (33.1%). A further increase of the relative aldehyde concentration caused a decrease in final yield.

TABLE IV

Infrared Absorption Spectral Data of the New *para*-Substituted *meso*-Tetraphenylporphines

I	II	III	IV	V	VII	VIII	VI	Assignments
3350 (w)	3370 (vw)	3800-3600 (broad)	3470 (m)	3450 (w) 3330 (wsh)	3550-2400 (broad)	3350 (s)	3370 (vw)	N-H···N (stretch)
	3030 (w)	3000 (wsh)	2885 (m) 2800 (w)	3000 (w)		2940 (vw) 2860 (vw)	2995 (w)	C-H (stretch)
		2300 (w) 2220 (s)						-C≡N
	1725 (s)				1690 (s)		1720 (s)	-C=O
			1660 (m)			1650 (wsh)		
1600 (w)	1610 (s)	1595 (s)	1600 (s)	1600 (s)	1600 (s)	1600 (w)	1605 (m)	-C=C- (phenyl)
1550 (w)	1560 (w)	1540 (vw)	1545 (w)	1540 (vw)	1560 (w) 1520 (vw)	1550 (w)	1560 (w)	-C=C- (pyrrole)
1500 (w)		1495 (w)	1500 (s)	1505 (s)	1510 (vw)	1495 (w)		-C=C-; -C=N- (phenyl)
	1475 (wsh)				1490 (vw)			
1465 (m)	1460 (w)	1460 (w)	1460 (w)		1467 (w)	1465 (w)	1460 (m)	
1446 (wsh)	1440 (wsh)		1435 (w)	1435 (s)			1440 (wsh)	-C-H (bend)
1430 (wsh)								
1395 (w)	1400 (m)	1390 (m)	1396 (wsh)	1386 (s)	1398 (s)	1400 (m)	1400 (m)	
1370 (vw)				1361 (w)				
1345 (m)	1365 (w)	1340 (m)	1345 (s)	1343 (s)	1340 (w)	1345 (m)	1362 (w)	=C-N- ; Ø-N (stretch)
	1350 (wsh)						1350 (vw)	
	1305 (vw)		1310 (wsh)		1310 (w)		1305 (vw)	
1270 (wsh)	1270 (s)			1260 (s)	1280-1208 (broad)	1285 (wsh)	1263 (s)	
1250 (w)	1250 (wsh)		1240 (wsh)	1242 (m)		1247 (vw)		
1215 (m)	1222 (vw)							
	1212 (vw)	1210 (w)	1215 (s)	1212 (w)		1220 (wsh)	1220 (wsh)	
							1200 (m)	
	1185 (wsh)	1180 (w)	1190 (s)	1185 (s)	1185 (wsh)	1180 (m)	1185 (wsh)	C-N (stretch)

TABLE IV (continued)

I	II	III	IV	V	VII	VIII	VI	Assignments
1177 (m)	1170 (m)		1160 (m)		1172 (m) 1160 (wsh)		1170 (m)	
1150 (w)	1155 (wsh)						1156 (wsh)	
				1140 (s)	1140 (wsh)			
1130 (wsh)	1122 (wsh)				1120 (wsh)			
1105 (w)	1105 (wsh)				1100 (m)	1105 (w)	1100 (s)	*p*-substituted phenyl
	1096 (s)			1089 (wsh)	1085 (w)			
	1080 (wsh)			1073 (s)		1070 (wsh)		
	1060 (wsh)		1060 (m)				1056 (wsh)	
1050 (vw)	1040 (wsh)					1040 (m)		
1020 (w)	1024 (s)	1020 (s)	1010 (w)		1020 (m) 1005 (w)	1010 (m)	1023 (s)	-C-H rock (pyrrole)
990 (w)	993 (w)	990 (vw)		1000 (m)	994 (w)	993 (vw)	993 (w)	
980 (w)	982 (w)	980 (vw)	977 (m)	978 (m)	980 (m)	981 (vw)	980 (w)	-C-H rock (pyrrole)
966 (s)	965 (m)	965 (s)	963 (s)	962 (s)	965 (s)	967 (s)	963 (m)	
945 (vw)		950 (wsh)	941 (s)	940 (wsh)		947 (wsh)		
	915 (wsh)				904 (wsh)		915 (wsh)	
878 (w)	883 (wsh)	877 (vw)	875 (m)	875 (w)	883 (wsh)	880 (w)	880 (wsh)	
	865 (m)	862 (wsh)			867 (s)		863 (m)	
847 (m)	847 (m)	850 (m)	855 (vw)		845 (wsh)	847 (m)	846 (wsh)	
836 (w)	840 (vw)	835 (vw)	829 (m)	827 (m)				
			815 (wsh)		820 (vw)		819 (wsh)	
		805 (wsh)	808 (wsh)					
800 (s)	807 (s)	800 (s)	802 (s)	800 (s)	795 (s)	800 (s)	805 (s)	*p*-substituted phenyl and pyrrole rings
			790 (s)					
787 (wsh)	792 (wsh)	790 (wsh)	787 (wsh)	790 (wsh)				
777 (w)	780 (wsh)				780 (wsh)		780 (wsh)	
	765				765		765	

TABLE IV (continued)

I	II	III	IV	V	VII	VIII	VI	Assignments
	(wsh)				(w)		(wsh)	
	758						756	
	(m)						(m)	
743	738		740	737			736	
(wsh)	(m)		(m)	(s)			(m)	
734								
(s)								
	727	732	726	725	725	730		
	(wsh)	(s)	(w)	(w)	(m)	(s)		
	713	710	710			708		
	(wsh)	(wsh)	(w)			(wsh)		
705	703			705	700		705	
(vw)	(w)			(w)	(m)		(m)	
	690							
	(wsh)							

meso-Tetra-(*p*-cyanophenyl)porphine (III).

(a) Using method (A).

A mixture of *p*-cyanobenzaldehyde, 5 g. (0.038 mole), pyrrole, 3 ml. (0.043 mole) and pyridine, 10 ml., was heated for 22 hours at 180-210°, in a sealed tube. The sealed tube was cooled, opened and the dark brown liquid filtered. The purple crystals were washed with 100 ml. of acetone and dried *in vacuo*, yield, 0.5 g. (7.3%). An analytical sample was prepared by recrystallization from pyridine.

Anal. Calcd. for $C_{48}H_{26}N_8$: C, 80.69; H, 3.66; N, 15.68. Found: C, 80.70; H, 3.70; N, 15.66.

(b) Using method (B).

Different mixtures of *p*-cyanobenzaldehyde and pyrrole in 99.7% acetic acid (250 ml.) were refluxed for 6 hours. The results are shown in Table V.

TABLE V

Aldehyde (mole)	Pyrrole (mole)	Yield mg.	Yield %
0.1	0.2	330	(18.5)
0.1	0.1	550	(36.4)
0.2	0.1	400	(22.4)

The products obtained by methods (A) and (B) had identical spectral data.

meso-Tetra-(*p*-dimethylaminophenyl)porphine (IV).

Using method (A).

A mixture of *p*-dimethylaminobenzaldehyde, 20 g. (0.134 mole) and pyrrole, 8.3 g. (0.124 mole) was heated in a sealed tube to 210-220° for 12 hours. The reaction mixture was very slowly cooled to room temperature, diluted with 500 ml. of acetone and filtered. The crystals were washed with acetone and dried, yield, 600 mg. (2.44%). Since the compound was insoluble in all organic solvents, a sample was dried *in vacuo* for analysis.

Anal. Calcd. for $C_{52}H_{50}N_8$: C, 79.35; H, 6.40; N, 14.24. Found: C, 78.93; H, 6.74; N, 14.10.

Method (B) was not tried for the synthesis of IV because of its failure in the case of the analogous porphyrin, V.

meso-Tetra-(*p*-diethylaminophenyl)porphine (V).

(a) Using method (A).

A mixture of *p*-diethylaminobenzaldehyde, 20 g. (0.113 mole) and pyrrole, 7 ml. (0.101 mole) was heated in a sealed tube to 220°, for 48 hours. The reaction mixture was cooled to room temperature, diluted with a liter of acetone, and filtered. The crystals were washed with more acetone and dried under suction, yield, 2 g. (8.9%). A sample of this compound was recrystallized from chloroform and dried *in vacuo* at 100° for 8 hours.

Anal. Calcd. for $C_{60}H_{66}N_8$: C, 80.13; H, 7.39; N, 12.46. Found: C, 80.46; H, 7.29; N, 12.07.

Several unsuccessful attempts were made to synthesize V by method (B), using as solvents 99.7% acetic acid, dimethylformamide, dimethylformamide containing some boric acid, and dimethylsulfoxide, at reflux temperatures.

meso-Tetra-(*p*-carbethoxyphenyl)porphine (VI).

A mixture of *meso*-tetra-(*p*-cyanophenyl)porphin (III), 100 mg., anhydrous alcohol, 50 ml., and concentrated sulfuric acid, 3 ml., was refluxed for 72 hours. After distilling the alcohol, the residue was taken up in water and neutralized with sodium bicarbonate solution. The precipitate was filtered and washed with water to free it from inorganic materials. The dried material was purple in color and its infrared spectrum did not show any -C≡N absorption at 2100 cm^{-1} but, instead, a very strong ester-carbonyl peak appeared, yield, 75.4 mg. (65.0%). After five recrystallizations from pyridine, the sample was dried over phosphorus pentoxide *in vacuo*, at room temperature, for 8 hours.

Anal. Calcd. for $C_{56}H_{46}N_4O_8$: C, 74.5; H, 5.1; N, 6.22. Found: C, 74.68; H, 5.01; N, 6.42.

meso-Tetra-(*p*-carboxyphenyl)porphine (VII).

meso-Tetra-(*p*-carbomethoxyphenyl)porphine (II), 100 mg., was refluxed with a mixture of tetrahydrofuran (25 ml.) and 4% aqueous potassium hydroxide (5 ml.) for twenty four hours. The solvents were removed by distillation. The residue was dissolved in 5 ml. of water and acidified with hydrochloric acid to *p*H 1-2. The purple precipitate was centrifuged and repeatedly washed with water to free it from traces of mineral acid. The yield was quantitative. An analytical sample of this compound was prepared by crystallization from a mixture of pyridine and alcohol. The sample was dried over phosphorus pentoxide at room temperature for 8 hours.

Anal. Calcd. for $C_{48}H_{30}N_4O_8$: C, 72.90; H, 3.80; N, 7.09. Found: C, 72.65; H, 4.01; N, 7.14.

meso-Tetra-(*p*-hydroxymethylphenyl)porphine (VIII).

To a suspension of 0.28 g. of lithium aluminum hydride in 15 ml. of tetrahydrofuran (dried and distilled over lithium aluminum hydride) was added slowly 200 mg. of *meso*-tetra-(*p*-carbomethoxyphenyl)-porphine (II), dissolved in 85 ml. of dry tetrahydrofuran and refluxed for an hour. Another 50 ml. portion of dry tetrahydrofuran was added to the reaction mixture and refluxing was continued for an additional 30 minutes. The unreacted lithium aluminum hydride was decomposed with moist ether at 0° and filtered through a celite bed. Since the filtrate was almost colorless (indicating that the celite bed absorbed all of the porphyrin), the celite was repeatedly extracted with pyridine. The combined pyridine extracts were distilled under reduced pressure, and the residue was triturated with acetone and filtered. The purple solid was dried *in vacuo*, yield, 60 mg. (34.5%).

This material did not show the characteristic ester-carbonyl peak but had a strong peak in the 3400 cm^{-1} region (O-H). An analytical sample was prepared by recrystallization from a mixture of pyridine and acetone. The sample was dried over phosphorus pentoxide *in vacuo* for 8 hours at room temperature.

Anal. Calcd. for $C_{48}H_{38}N_4O_4$: C, 78.45; H, 5.21; N, 7.63. Found: C, 78.03; H, 5.51; N, 8.00.

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(2) Abstracted from a portion of the thesis submitted in partial fulfillment of the requirements for the Ph.D. degree in Medicinal Chemistry at the State University of New York at Buffalo, Feb. 1966. Present Address: Springville Laboratories, Roswell Park Memorial Institute, Springville, New York.

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