PODAND-PORPHYRINS WITH PERIPHERAL CHELATES

V. I. Mel'nik, Z. I. Zhilina, S. A. Andronati, V. N. Ganevich, and M. V. Babchinskaya

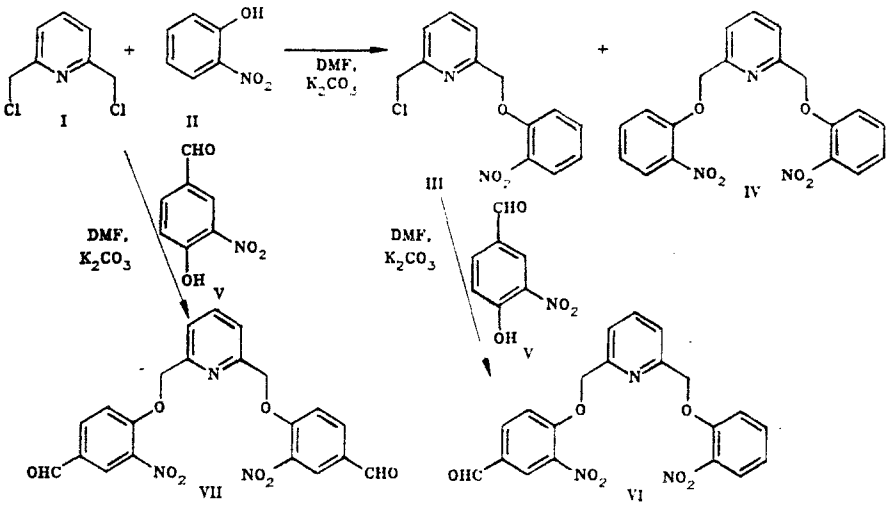
UDC 547.979.733.04

Alkylation of 5-(3'-nitro-4'-hydroxyphenyl)-10,15,20-triphenylporphyrin with chloropyridines[2,6-dichloromethyl- and 2-chloromethyl-6-(2'-nitrophenoxymethylpyridine)] as well as condensation by a mixed-aldehyde method starting with formylpyridines [2-(2'-nitro-4'-formylphenoxymethyl)-6-(2'-nitrophenoxy-methyl-) or 2,6-di(2'-nitro-4'-formylphenoxymethyl)pyridine], benzaldehyde, and pyrrole are used to synthesize previously unknown podand-porphyrins containing from one to four peripheral chelates.

Natural and synthetic porphyrins are known to localize in vivo in neoplastic cells. However, this affinity is lost for metalloporphyrins. If the porphyrin free base containing a radioactive or nonradioactive metal in the chelate could localize in tumors, then its value to cancer diagnosis and therapy would be inestimable. On the other hand, molecular ensembles containing a recognition center besides the porphyrin nucleus (prosthetic group) can be expected to be attractive enzyme models. Complexes of such polynuclear molecules are interesting as electron-transport systems [1-5].

In this respect, and in continuation of our studies of the properties of crown-porphyrins and porphyrin dimers [6-10], we synthesized new para-substituted podand-porphyrins containing from one to four 2,6-dinitrophenoxymethylpyridine fragments capable of complexing alkali, alkaline earth, and transition metals and neutral molecules. The affinity for guests can be changed by functionalizing this fragment [3].

The 2,6-disubstituted pyridines needed to synthesize such porphyrins were prepared in good yield by the scheme



The mono- and di(nitrophenoxymethyl)pyridines III and IV were prepared by reaction of a fourfold excess of dichloropyridine I with o-nitrophenol. The reaction was carried out in dry DMF in the presence of K_2CO_3 at 100°C for 10 h. Monoformyl- and diformylpyridines VI and VII were synthesized under analogous conditions by reacting monochloro- or dichloropyridines III and I with excess 3-nitro-4-hydroxybenzaldehyde. Pyridines III-V and VII were purified by column chromatography using silica gel and $CHCl_3$ eluent. The purity and identity of the previously unknown pyridines were monitored by TLC on Silufol plates. The composition was confirmed by elemental analysis and mass spectrometry; the structure, by PMR spectroscopy (see Tables 1 and 2).

Podand-porphyrins X-XII were prepared by two paths: condensation of podand-aldehydes with pyrrole and alkylation of hydroxyporphyrin VIII with chloropyridines I or III.

Porphyrin X, which contains one chelate, was condensed using a mixture of aldehydes (podand-aldehyde VI and benzaldehyde, 1:5) and an equivalent amount of pyrrole. The reaction was carried out in boiling propanoic acid for 1.5 h. Dimeric porphyrin XI was prepared using a mixture of aldehydes (dialdehyde VII and benzaldehyde, 1:6). It was not expected that dimeric porphyrin XI would form using such an approach. However, direct synthesis of this dimer and PMR spectroscopic data left no doubt. The proposed method offers wide possibilities for synthesizing dimeric porphyrins with very different substituents. Porphyrin XII, which contains four chelates, was prepared by

I. I. Mechnikov Odessa State University, Odessa. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 475-481, April, 1991. Original article submitted May 12, 1989; revision submitted March 12, 1990.

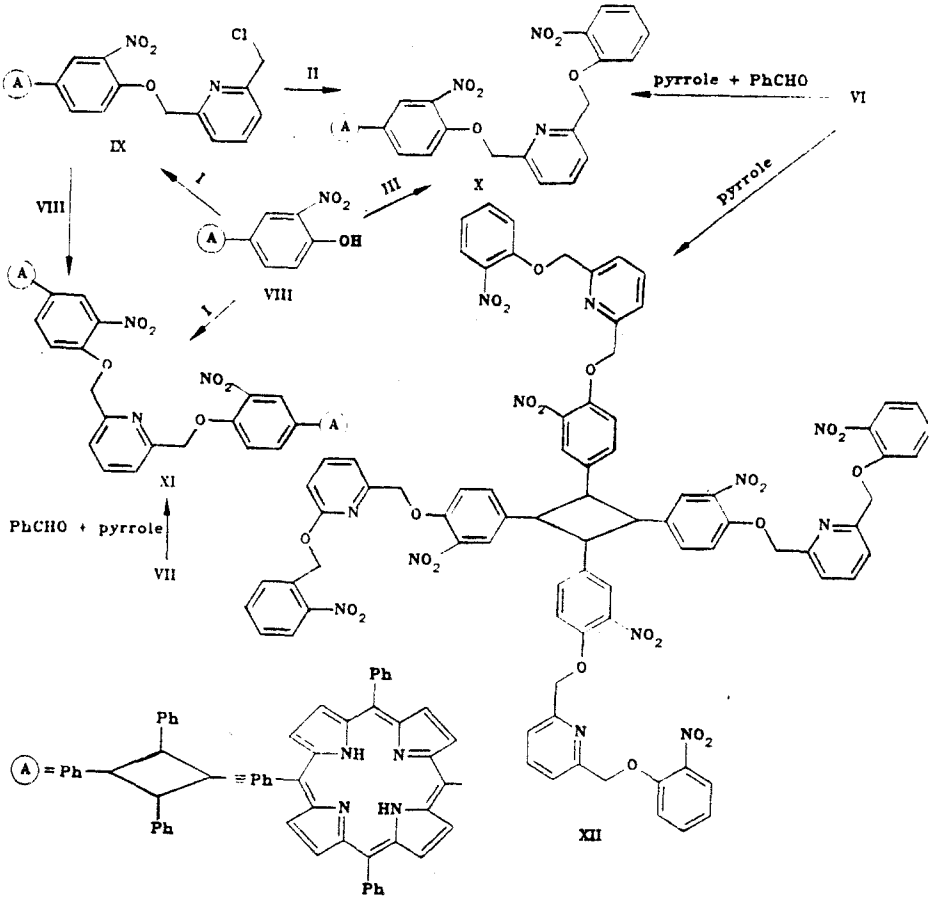
0009-3122/91/2704-0376$12.50 •1991 Plenum Publishing Corporation

TABLE 1. Properties of Synthesized Compounds

Compound	Empirical formula	mp, °C	R_f*	M^+ found	M calc.	Yield, %
III	$C_{13}H_{11}ClN_2O_3$	91,0	0,42	278	278,69	40,0
IV	$C_{19}H_{15}N_3O_6$	134,0	0,30	381	381,34	31,0
VI	$C_{20}H_{15}N_3O_7$	160,0	0,27	409	409,35	71,5
VII	$C_{21}H_{15}N_3O_8$	191,0	0,11	437	437,36	70,5
VIII	$C_{44}H_{29}N_5O_3$	<300	0,54	675	675,75	6,3
IX	$C_{51}H_{35}ClN_6O_3$	285,0	0,38	815	815,33	55,2
X	$C_{57}H_{39}N_7O_6$	193,0	0,49	917	917,98	87,6 (A); 91,0 (B); 6,4 (C)
XI	$C_{95}H_{63}N_{11}O_6$	<300	0,78	1454	1454,62	81,0 (A); 83,4 (B); 3,0 (C)
XII	$C_{96}H_{65}N_{16}O_{24}$	225,0	0,12	1827	1827,67	14,7

*R_f of III, IV and VI-VIII were determined in toluene:acetone 10:1; IX in toluene; X-XII in toluene:acetone 20:1.

condensing aldehyde VI with pyrrole. The podand-porphyrins were isolated and purified by column chromatography on silica gel.



The starting compound for synthesizing X and XI was mono(m-nitro-p-hydroxyphenyl)triphenylporphyrin VIII, prepared by condensation of a mixture of aldehydes (m-nitro-p-hydroxybenzaldehyde and benzaldehyde, 1:6) with pyrrole in xylene in the presence of monochloroacetic acid [11]. Porphyrin VIII was isolated by column chromatography on silica gel using toluene eluent. The hydroxyporphyrin VIII was alkylated by heating in DMF in the presence of K_2CO_3. Dimer XI was obtained in 81% yield by reacting VIII with an equivalent amount of 2,6-dichloromethylpyridine. The two porphyrins are covalently bound to the podand. This dimer is identical to XI, prepared by condensation and by reaction of VIII and IX. If a large excess of I is used during alkylation of VIII, a small amount of XI is formed along with IX. Then, treating IX with excess o-nitrophenol gives X, synthesized also from VIII and monochloropyridine III. The porphyrins prepared this way are soluble in most organic solvents and crystallize well.

TABLE 2. Spectral Characteristics

Compound	λ_{max}, nm (log ε)					Chemical shift, δ, ppm ($CDCl_3$)
	I	II	III	IV	Soret band	
III						4,43s (2H, CH_2Cl); 5,10s (2H, CH_2O); 6,70...7,32m (7H, arom.)
IV						5,12 s (4H, CH_2O); 6,80...7,80m (11H, arom.)
VI						5,10 s, 5,20 s (4H, CH_2O); 6,85...8,20m (10H, arom.); 9,74s (1H, CHO)
VII						5,23 s (4H, CH_2O); 6,90...8,20 m (9H, arom.); 9,75 s (2H, CHO)
VIII	647 (3,12)	591 (3,46)	552 (3,63)	516 (4,08)	420 (5,21)	−2,86 s (2H, NH); 7,50...8,30 m (18H, arom.); AB 8,83, 8,69, 8,76 s (8H, β-CH pyrrole); 10,86 s (1H, OH)
IX	647 (3,65)	591 (3,79)	552 (3,95)	516 (4,32)	420 (5,52)	−2,87s (2H, NH); 4,65 s (2H, CH_2Cl); 5,53 s (2H, CH_2O); 7,41...8,31m (21H, arom.); AB 8,82, 871, 8,78 s (8H, β-CH pyrrole)
X	646 (3,08)	591 (3,49)	552 (3,74)	516 (4,16)	421 (5,47)	−2,86 s (2H, NH); 5,42 s, 5,55 s (4H, CH_2O); 7,35...8,30 m (25H, arom.); AB 8,85, 8,73, 8,80s (8H, β-CH pyrrole)
XI	647 (3,87)	591 (3,97)	552 (4,13)	516 (4,51)	421 (5,65)	−2,86 s (4H, NH); 5,58 s (4H, CH_2O); 7,47...8,33 m (39H, arom.); AB 8,83, 8,72; 8,78s (16H, β-CH pyrrole)
XII	649 (3,26)	592 (3,35)	554 (3,58)	518 (4,05)	424 (5,36)	−2,87 s (2H, NH); 5,46, 5,54 s (16H, CH_2O); 7,40...8,27 m (40H, arom); 8,78 s (8H, β-CH pyrrole)

It should be noted that the dimer free base or the complex of the dimer with certain metals is obtained in high yield by method A. The dimer free base is formed in lower yield by method B. However, the complex of the dimer with different metals or the metal-free base can be obtained.

EXPERIMENTAL

PMR spectra were obtained on a Bruker AM-250 (250 MHz) instrument in $CDCl_3$ with TMS internal standard. Absorption spectra were recorded on a Specord M-40 spectrophotometer in dry $CHCl_3$ ($c = 10^{-6}$-10^{-4} M). Mass spectra were taken on a Varian MAT-112 instrument using a direct probe. The ionizing electron energy was 40 eV. The temperature was 100-200°C. The course of the reaction and the purity of the compounds obtained were monitored using TLC on Silufol plates. Activated Al_2O_3 and L5/40 silica gel were used for column chromatography.

Elemental analyses for C, H, and N agreed with those calculated.

2,6-Dichloromethylpyridine (I) was prepared as before [12] in 68% yield, mp 96°C; 3-nitro-4-hydroxybenzaldehyde (V) [13], in 55% yield, mp 145°C.

2-Chloromethyl-6-(2′-nitrophenoxymethyl)pyridine (III). A solution of 38.2 g (200 mmole) 2,6-dichloromethylpyridine (I), 6.95 g (50 mmole) o-nitrophenol, and 39.6 g (400 mmole) K_2CO_3 in 200 ml dry DMF was stirred at 100°C for 10 h. The course of the reaction was monitored by TLC in toluene:acetone 10:1. After o-nitrophenol was used up, the mixture was cooled to room temperature and 200 ml of water were added. The precipitate was filtered off, washed with water, dried, dissolved in the minimal amount of $CHCl_3$, and transferred to a chromatography column filled with silica gel. The column was eluted with $CHCl_3$. Unreacted 2,6-dichloromethylpyridine was eluted first. The second fraction contained monochloromethylpyridine III. The solution was evaporated to a small volume. The product was precipitated with heptane. The precipitated was filtered off and dried. Yield 5.57 g. Pyridine IV was eluted third. The effluent was evaporated. The solid was recrystallized from acetone:heptane 1:2. Yield 5.91 g.

2-(2′-Nitro-4′-formylphenoxymethyl)-6-(2′-nitrophenoxymethyl)pyridine (VI). A solution of 1.5 g (5 mmole) III, 1.7 g (10 mmole) benzaldehyde V, and 10.0 g (70 mmole) K_2CO_3 in 50 ml dry DMF was stirred at 90-95°C for 12 h. After cooling the reaction mixture to room temperature, 60 ml water were added. The precipitate was filtered off, washed with water, dried, dissolved in the minimal amount of $CHCl_3$, and transferred to a chromatography column filled with silica gel. The column was eluted with $CHCl_3$. The effluent containing aldehyde VI was evaporated. The solid was recrystallized from $CHCl_3$:heptane 1:1. Yield 1.52 g.

2,6-Di-(2′-nitro-4′-formylphenoxymethyl)pyridine (VII). Compound VII was prepared analogously to VI from 1.76 g (10 mmole) I and 5.1 g (30 mmole) V. Yield 3.08 g.

5-(3′-Nitro-4′-hydroxyphenyl)-10,15,20-triphenylporphyrin (VIII). A solution of 6.36 g (60 mmole) benzaldehyde, 1.81 g (12 mmole) V, and 4.82 g (72 mmole) pyrrole in 50 ml xylene was added dropwise over 30 min to a boiling solution of 16 g monochloroacetic acid in 300 ml xylene. The reaction mixture was boiled for 1.5 h with air passing

through. It was then cooled and neutralized with aqueous ammonia. The solvent was evaporated in a rotary evaporator. The solid was dissolved in toluene and transferred to a chromatography column filled with Al_2O_3. The column was eluted with toluene. The first fraction contained tetraphenylporphyrin; the second, traces of tetraphenylporphyrin and monosubstituted porphyrin VIII. The effluent was evaporated. The solid was dissolved and transferred to a chromatography column filled with silica gel. The column was eluted with toluene. The fraction containing VIII was collected. The solvent was evaporated. The solid was recrystallized from toluene:heptane 1:1. Yield 0.51 g.

5-[3′-Nitro-4′(6"-chloromethyl-2"-methyleneoxypyridyl)phenyl]-10,15,20-triphenylporphyrin (IX). A solution of 0.338 g (0.5 mmole) VIII, 0.440 g (2.5 mmole) I, and 3.50 g (25.4 mmole) K_2CO_3 in 70 ml freshly distilled DMF was stirred at 100°C under N_2 flow for 8 h. After cooling, 40 ml water were added. The precipitate was filtered off, washed with water, dried, dissolved in toluene, and transferred to a chromatography column filled with silica gel. The column was eluted with toluene. Unreacted VIII was eluted first. The fraction containing IX was then collected. The solvent was evaporated. The solid was recrystallized from toluene:heptane 1:1. Yield 0.225 g.

The third fraction contained a small amount of dimeric porphyrin XI.

5-{3′-Nitro-4′-[6"-methyleneoxy(2‴-nitrophenyl)-2"-methyleneoxypyridyl)]phenyl}-10,15,20-triphenylporphyrin (X). A. Compound X was synthesized from 0.338 g (0.5 mmole) VIII and 0.279 g (1 mmole) monochloropyridine III by the method given above. Yield 0.402 g.

B. Compound X was prepared analogously from 0.407 g (5 mmole) IX and 0.139 g (1 mmole) o-nitrophenol. Yield 0.417 g.

C. Benzaldehyde (5.30 g, 50 mmole) and aldehyde VI (4.09 g, 10 mmole) were added to 200 ml boiling propanoic acid. Pyrrole (4.02 g, 60 mmole) was added over 5 min. The reaction mixture was boiled with stirring for 1 h, cooled, diluted with water, and neutralized with aqueous ammonia. The oily precipitate was filtered off, washed with water, and dried. The mixture of porphyrins was separated from the oily products by dissolving the dried solid in $CHCl_3$ and transferring to a chromatography column filled with Al_2O_3. The column was eluted with $CHCl_3$. The effluent was evaporated. The solid was dissolved in toluene and transferred to a column filled with silica gel. The column was eluted with toluene. The fraction containing porphyrin X was collected. Toluene was removed in a rotary evaporator. The solid was crystallized from toluene:heptane 1:1 Yield 0.587 g.

2,5-Di[2′-nitro-4′-(10,15,20-triphenyl-5-porphyrinyl)phenyl]oxymethylpyridine (XI). A. Compound XI was prepared analogously to IX from 0.338 g (0.5 mmole) VIII and 0.044 g (2.5 mmole) 2,6-dichloromethylpyridine I. Yield 0.294 g.

B. Compound XI was prepared analogously to IX from 0.338 g (0.5 mmole) VIII and 0.408 g (0.5 mmole) IX. Yield 0.606 g.

C. Compound XI was prepared analogously to X by method B from 6.36 g (60 mmole) benzaldehyde, 4.37 g (10 mmole) dialdehyde VII, and 5.36 g (80 mmole) pyrrole. Yield 0.436 g.

5,10,15,20-Tetra{3′-nitro-4′-[6"-methyleneoxy(2‴-nitrophenyl)-2"-methyleneoxypyridyl]phenyl}porphyrin (XII). Aldehyde VI (12.69 g, 30 mmole) was added to 170 ml boiling propanoic acid. Pyrrole (2.01 g, 30 mmole) was added dropwise over 5 min. The reaction mixture was boiled with stirring for 1.5 h, cooled, diluted with water, and neutralized with aqueous ammonia. The oily precipitate was filtered off, washed with water, dissolved in $CHCl_3$, and transferred to a chromatography column filled with silica gel. The column was eluted with $CHCl_3$. The effluent containing XII was evaporated. The solid was recrystallized from $CHCl_3$:heptane 1:1. Yield 2.08 g.

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FREE RADICALS IN ELECTROCHEMICAL REDUCTION OF 3,5-DICARBETHOXY-1,4-DIHYDROPYRIDINES WITH NITROPHENYL GROUPS IN POSITIONS 2, 4, AND 6

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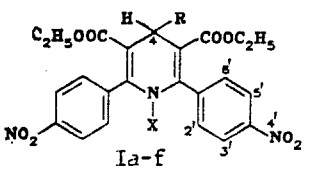
UDC 547.822.1:541.138.3:543.422.27

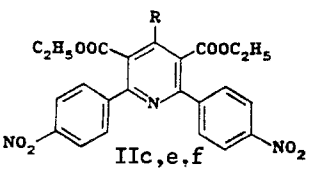
In the electrochemical reduction of 2,6-bis- and 2,4,6-tris(nitrophenyl) derivatives of 3,5-dicarbethoxy-1,4-dihydropyridine, in the first stage, one of the para-nitrophenyl groups in position 2 or 6 of the heterocycle is reduced. Free radicals have been obtained and identified, the primary species being ion radicals of the nitrophenyl type. The presence of the heterocycle in the molecule of the 1,4-dihydropyridine derivative stabilizes secondary free radicals of the nitrosophenyl type. In the process of electrochemical reduction, no evidence has been found of any intramolecular transfer of electrons or protons from the dihydropyridine part of the molecule to the nitrophenyl groups. Derivatives of 2,6-bis(p-nitrophenyl)-3,5-dicarbethoxy-1,4-dihydropyridine have been synthesized, and the oxidation and methylation of these derivatives have been studied.

Among the derivatives of 1,4-dihydropyridine (1,4-DHP) with a nitrophenyl fragment in position 4, certain compounds have been found to have very definite cardiovascular activity, for example the preparation nifedipine (Corinfar), which is 4-(o-nitrophenyl)-3,5-dicarbethoxy-2,6-dimethyl-1,4-DHP. In the course of searching for compounds that offer promise in medical applications, derivatives of 1,4-DHP with nitrophenyl fragments in various positions of the heterocycle have been synthesized and studied.

The mechanism of electrochemical reduction of 3,5-dicarbethoxy- and 3,5-dicyano-1,4-DHP with a nitrophenyl substituent in position 4 has been examined in detail [1-3]. If p-nitrophenyl substituents are introduced into positions 2 and 6 of the 1,4-DHP, while either retaining or removing the nitrophenyl substituent in position 4, certain special features of the electroreduction mechanism are observed, related to the introduction of the second nitrophenyl fragment and to the shift of the reaction center from the 4-nitrophenyl group to the 2-nitrophenyl group. In all cases, the primary electroreduction involves, first of all, the nitrophenyl fragment, and anion radicals or dianion radicals of the nitrobenzene type are formed. Here we are reporting on a more detailed study of the formation and structure of these anion radicals.

We have investigated the course of electrochemical reduction, in DMFA, of 3,5-dicarbethoxy derivatives of 1,4-DHP containing nitrophenyl groups in positions 2 and 6 (compounds Ia-c, f) or in positions 2, 4, and 6 (compounds Id, e). Certain data are presented on the electrochemical reduction of the model compounds IIc, e, f, which are the oxidized forms of the corresponding 1,4-DHPs.





I a X=CH_3, b –f) X=H; I, II a, c) R=4-ClC_6H_4, b) R=C_6H_5, d) R=4-$NO_2C_6H_4$, e) R=3-$NO_2C_6H_4$, f) R=CH_3

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 481-487, April, 1991. Original article submitted May 29, 1990; revision submitted September 4, 1990.

 0009-3122/91/2704-0380$12.50 •1991 Plenum Publishing Corporation