Synthesis of Porphyrinyl-Nucleosides

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Several porphyrinyl-nucleosides were prepared in the reaction of the OH group of one, two or four meso-*p*-hydroxyphenyl substituents of porphyrin with 5′-*O*-tosylates of 2′,3′-*O*-isopropylidene-adenosine or -uridine, or 5′-*O*-tosylthymidine; the remaining porphyrin meso-substituents were *p*-tolyl, *p*-hydroxyphenyl or 4-pyridyl. The following porphyrinyl-nucleosides were obtained with 8-17% yield: meso-di(*p*-tolyl)di(*p*-phenylene-5′-*O*-2′,3′-*O*-isopropylidene-adenosine) (or -uridine)porphyrins **1,2**, the respective meso-tetranucleoside-porphyrins **3,4**-meso-mono(*p*-phenylene-5′-*O*-thymidine)porphyrins **5-7**, meso-di(*p*-tolyl)di(*p*-phenylene-5′-*O*-thymidine)porphyrins **8,9** and the meso-di(*p*-hydroxyphenyl)di(*p*-phenylene-5′-*O*-thymidine)porphyrins **10**. Other compounds prepared belonged to the series: meso(4-pyridyl)$_{4-n}$(*p*-phenylene-5′-*O*-2′,3′-*O*-isopropylideneuridine)$_n$porphyrin, n = 1, 2 or 4, **11-13**. *N*-Methylation gave the water soluble iodide salts: (*N*-methyl-4-pyridinium)$_{4-n}$(*p*-phenylene-5′-*O*-2′,3′-isopropylideneuridine)$_n$porphyrins, n = 1, 2 or 4, **14-16**. The ms fab showed in most cases stepwise detachment of the CH_2(5′)-nucleoside fragments.

The porphyrins meso disubstituted by thymidine represent a convenient substrate for the build-up of both nucleoside units into the oligo/polynucleotide chains.

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Introduction.

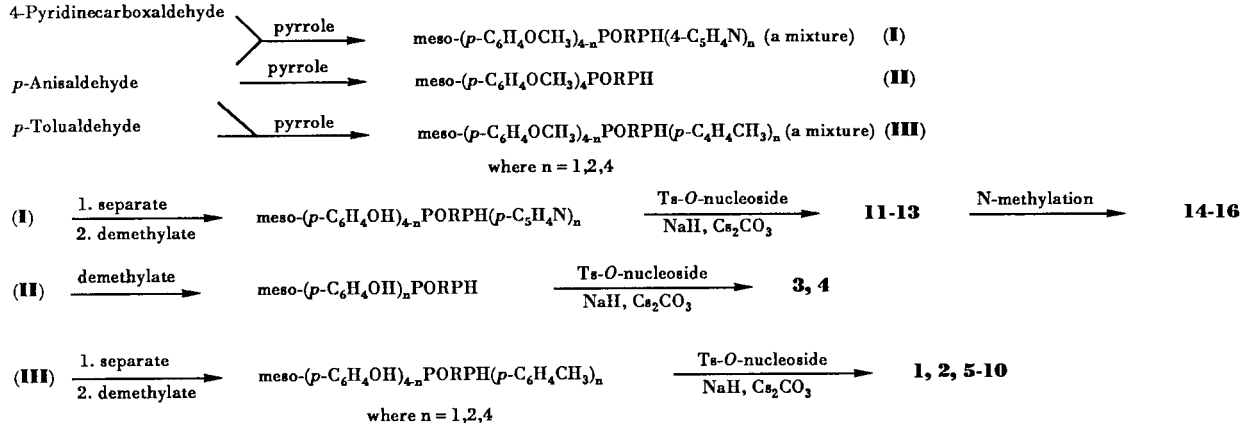
In spite of the enormous interest in the chemistry of meso-substituted derivatives of porphine, no porphyrins had yet been synthesized which contained covalently attached nucleoside substituents. The presence in one compound of the structural units of porphine, easily metallated by a number of different metals, and of a nucleoside, both having great chemical and biological importance, make the porphyrinyl-nucleosides a desired target for synthesis and structure elucidation.

As announced in our preliminary communication [1], we recently succeeded in obtaining the first representatives of this new class of compounds containing the *O*-glycoside bridge between the *p*-phenylene-porphyrin core and the C(5′) center of the nucleoside. We describe here detailed syntheses of new types of these compounds. They differ in the type of the nucleoside attached, the number of the nucleoside meso-substituents and the insolubility/solubility in water. The latter property which depends on the type of the meso-substituents other than the nucleoside present in the molecule, might be crucial for the *in vivo* behavior of these compounds and the respective *in vitro* simulations. Considering the interest paid in the last few years to the interactions of porphyrins and metallaoporphyrins with nucleic acids [2] one can also expect the importance of the (metallo)porphyrinyl-nucleosides in this regard. Also, the build-up of the two terminal nucleoside units of the dinucleoside-porphyrins (in particular at the 3′-OH centers of **8** and **9**) into the oligo- or polynucleotide will result [3] in the formation of two fragments of the biopolymer joined by covalent (metallo)porphyrin bridges, another interesting model for biochemical studies.

Results and Discussion.

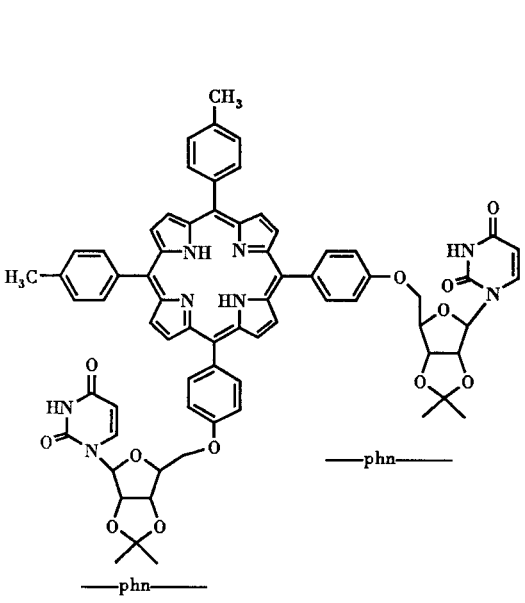
As shown in Figure 1, the synthesized porphyrinyl-nucleosides contain one or two (protected or unprotected)

Scheme I

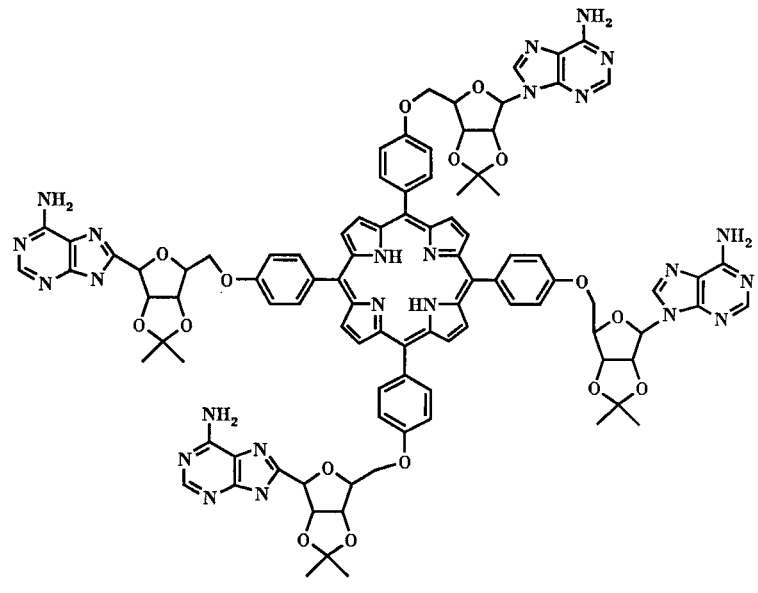


5′-*O*-adenosine or 5′-*O*-uridine substituents **1, 2** and [1a]; four 2′,3′-*O*-protected-adenosine or -uridine units **3, 4**; one or two 5′-*O*-thymidine substituents, **5-10**. The meso-positions in **1,2** and **5-10** that are not taken by the nucleoside contain the *p*-tolyl and/or *p*-hydroxyphenyl substituents. Also the porphyrinyl-(protected)uridines were obtained with one, two or three 5′-*O*-uridine units, the remaining substituents being 4-pyridyls, **11-13**. All these compounds are insoluble in water. The water soluble porphyrinyl-nucleosides are represented by the analogs of the compounds **11-13** containing the *N*-methyl-4-pyridinium substituents, **14-16**. In the case of the porphyrins having two identical meso-substituents, either only the 5,10-isomer or both 5,10- and 5,15-isomers were obtained.

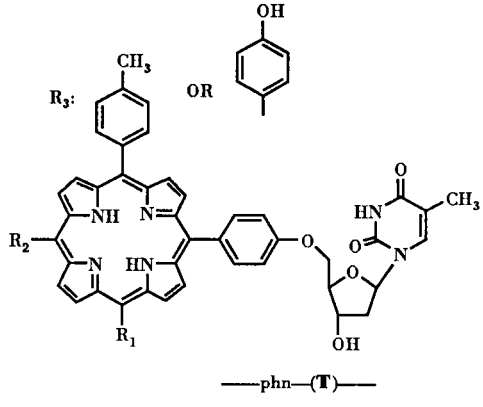
In the crucial step of the formation of the glycoside link between the porphyrin and the nucleoside, the solution in DMF of the proper *p*-hydroxyphenylporphyrin (see Scheme I) and 5′-*O*-tosylnucleoside (2′,3′-*O*-isopropylidene



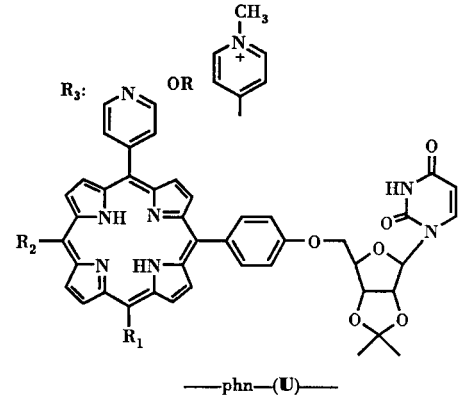
1 phn contain A, not U
2



3
4 U present, instead of A



5 $R_1 = R_2 = R_3 =$ tol
6 $R_1 = R_3 =$ tol; $R_2 =$ hp
7 $R_1 =$ hp; $R_2 = R_3 =$ tol
8 $R_1 = R_3 =$ tol; $R_2 =$ phn(T)
9 $R_1 =$ phn(T); $R_2 = R_3 =$ tol
$R_1 = R_3 =$ hp; $R_2 =$ phn(T)
10 $R_1 =$ phn(T); $R_2 = R_3 =$ hp



11 $R_1 = R_2 = R_3 =$ py
12 $R_1 =$ phn(U); $R_2 = R_3 =$ py
13 $R_1 = R_2 =$ phn(U); $R_3 =$ py
14 $R_1 = R_2 = R_3 =$ Mpy
15 $R_1 =$ phn(U); $R_2 = R_3 =$ Mpy
16 $R_1 = R_2 =$ phn(U); $R_3 =$ Mpy

Figure 1. Synthesized porphyrinyl-nucleosides. The following abbreviations are used: A - adenine, U - uracil, T - thymine, tol - *p*-tolyl, hp - *p*-hydroxyphenyl, py - 4-pyridyl, Mpy - *N*-methyl-4-pyridinium.

protected in the case of adenosine and uridine and unprotected for thymidine) was added to the DMF solution of sodium hydride and cesium carbonate. The reaction carried at 65° for 24-48 hours was followed by column chromatographic separation of the product. Until now our attempts to obtain the tetrathymidine-porphyrin, the analog of the synthesized tetraadenosine- and tetraudidine-porphyrins, were unsuccessful; only the dithymidine-derivatives were formed, the two *p*-hydroxyphenyl units in the starting tetra-*p*-hydroxyphenylporphyrin being left unreacted **10**. In most cases at least one additional product was also formed, characterized by a greater number and complexity of the signals in the 6-3 ppm region of the ^{1}H nmr spectra, and the ms-fab spectra which did not show detachment of nucleoside structural units.

The ms-fab of the porphyrinyl-nucleosides containing adenosine or uridine, **1-4**, **11-13**, clearly showed stepwise detachment of all CH_2(5′)-nucleoside fragments (see Experimental) which were also visible in the spectra of some (**8,9**) porphyrinyl-thymidines, see Figure 2. The ^{1}H nmr spectra of porphyrinyl-nucleosides, see Figure 3, when compared among themselves and with the *p*-hydroxyphenyl-porphyrin substrates, showed constant values of the chemical shift of β-pyrrole protons, 8.88-8.80 ppm, with the exception of tetraadenosine-porphyrin **3**, for which the shift took place to 8.33 ppm. The porphyrin NH protons appeared in a rather narrow region of −2.85 to −2.94 ppm. Also fairly stable were three regions of the signals of aromatic protons, 8.16-7.99, 7.61-7.38 and 7.21-7.14. The "doublet of doublets" characteristics typical for the starting *p*-hydroxyphenylporphyrins, appeared only in the spectra of porphyrinylmononucleosides and porphyrinyldithymidines **8,9**. *N*-Methylation of 4-pyridyl substitutents in **14-16** resulted not only in the down-field shifts of the signals of the pyridyl protons from 9.04-9.01 and 8.15-8.14 to 9.48-9.43 and 9.16-8.85 ppm, respectively, but also made the signals of the latter range very complex, especially in the case of the respective porphyrin-diuridine and -triuridine, **15,16**. The signals of protons in nucleobases appeared at ppm rather characteristic for the spectra of the respective differently modified nucleobases [4] with no porphyrin attached. However, the chemical shifts of the ribose or 2-deoxyribose protons showed much greater variability. In particular, for the adenosine-porphyrins **1,3** the signals were shifted toward the lower fields; this especially concerned the H-1′, H-2′, H-3′ and H-5′ protons: H-1′ 6.32-6.24 (6.10-5.90), H-2′, 3′ 5.61-5.06 (4.40-4.00), H-5′ 4.52-3.81 (4.00-3.50), the values in brackets referring to the ranges typical for non-porphyrinyl nucleosides [4]. Some of these shifts were also characteristic for the thymidine-porphyrins, H-3′ 5.61-4.36 (4.20-3.39), H-5′ 4.55-4.28 (3.75-3.00). Limited to H-5′, they also appeared in the spectra of uridine-porphyrins, H-5′ 4.50-4.13 (3.95-3.80) with the exception of those containing the *N*-methyl-4-pyridinium substituents.

The spectra of the 5,10- and 5,15-isomers of meso-di(*p*-tolyl)di(*p*-hydroxyphenyl)porphyrin serving as a substrate for some isomeric nucleoside-porphyrins differed only slightly in the coupling constants of their aromatic protons, ΔJ = 0.05 Hz and 0.7 Hz for the 8.08/7.53 and

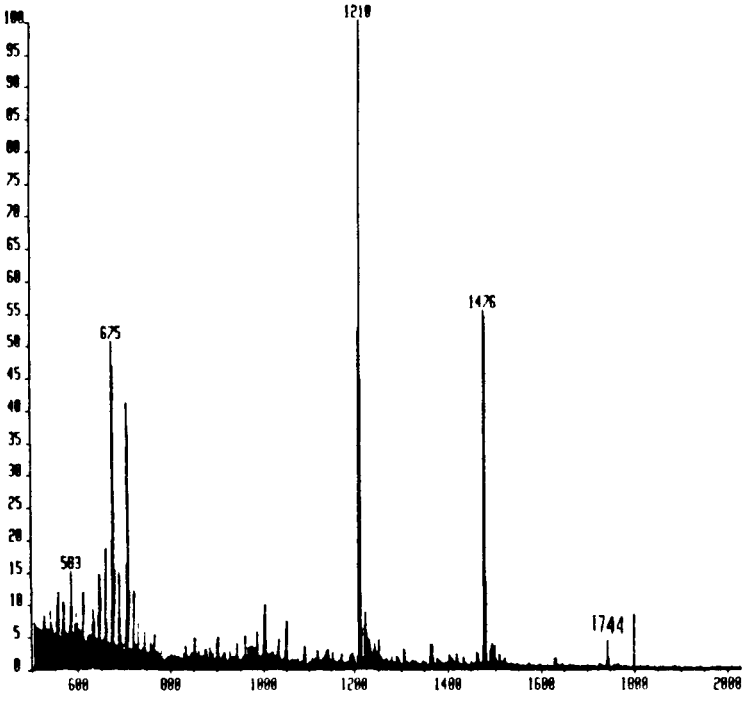


Figure 2. Fab mass spectrum of **4**.

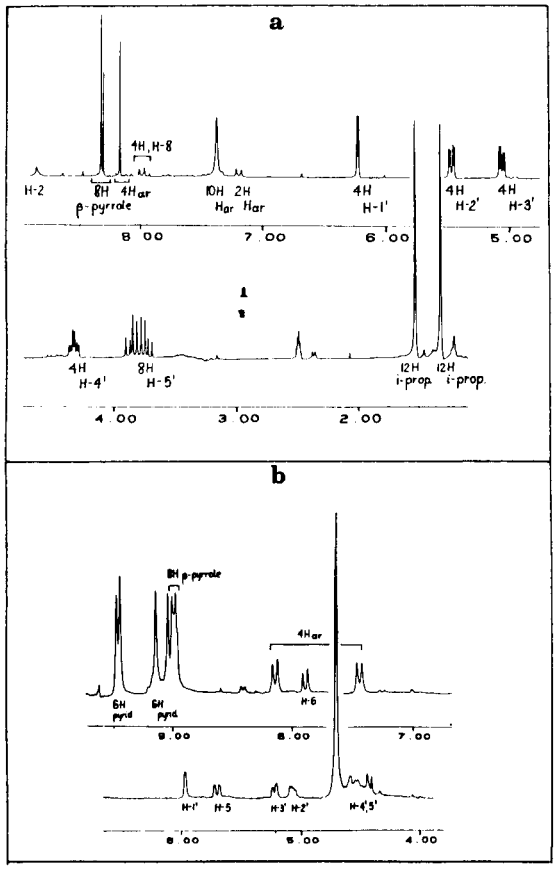


Figure 3. 1H nmr spectra in DMSO of **3** (a) and **14** (b).

8.04/7.16 doublets of doublets, respectively. Such close similarity of the spectra characterized also the nucleoside-derivatives of the mentioned isomers which were considered in our investigation, *i.e.*, the porphyrinyl-thymidine pairs **6, 7** and **8, 9**. This happened inspite of the fact that in the latter there appeared new regions of the signals originating from protons of the nucleobase and 2-deoxyribose. Our particular attention was attracted by the isomeric meso-ditolyldithymidine-porphyrins **8, 9** which represent the convenient substrate for the build-up of the oligo/polynucleotide chains on the 3'-OH groups of both terminal thymidine units [3]. The ^{1}H nmr spectra of the 5,10- and 5,15-isomers are identical in shape, the differences between the coupling constant values of the corresponding doublets of doublets in **8** and **9** (see Experimental) being very small, ΔJ = 0.10-0.45 Hz. The discussed spectra reveal, however, a feature which is unique for all porphyrinyl-nucleosides under consideration: the two H-1' protons, like the H-3' and H-4' protons, appear as the pairs of complex multiplets separated, respectively, by 0.24, 0.19 and 0.26 ppm, giving the whole spectrum in the 6-4 ppm region the character of a "double-spectrum", see Figure 4. This might be do to the diastereomeric nature of these protons or/and the existence of the barrier to interconversion of the conformers of each isomer which is high enough to create different environments for the formally corresponding protons of two sugar units of the thymidine substituents, see Figure 5.

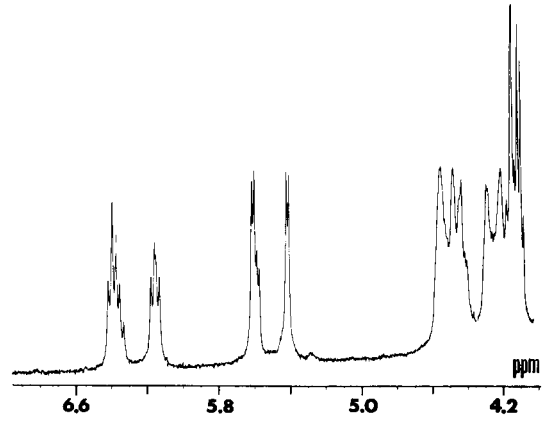


Figure 4. Fragment of ^{1}H nmr spectrum in DMSO of **9**.

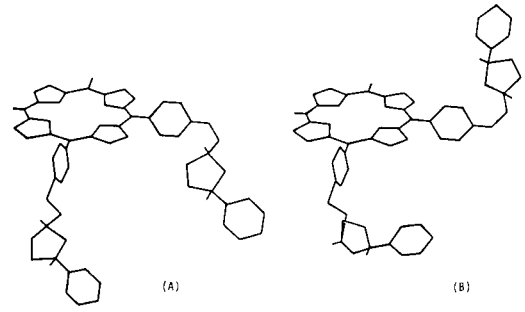


Figure 5. Two examples of possible conformers of **9** obtained using molecular modeling program (the tolyl meso-substituents are omitted).

The uv-vis absorption spectra of the porphyrinyl-nucleosides, see Figure 6, showed typical for porphyrins four absorption bands in the 514-650 nm region, and the predominating Soret band, 418-426 nm. The energy of bands differed for the individual compounds by no more than 2-3 nm, greater differences appearing only after *N*-methylation of the pyridyl substituents, *e.g.*, **13** *vs* **16**. The bands in the uv region originating from the nucleobases were much more differentiated both in number (one to four) and in shape. The usefulness of these spectra in theoretical elucidation of the electronic structure was seriously impaired by the difficulty in obtaining suitable crystals, and in consequence by the lack of the data concerning the 3-D structure. The application of theoretical optimization of geometry in the above mentioned elucidation, although very useful for the [2.2] paracyclophanyl-porphyrins syn-

thesized in this laboratory [5], encountered serious limitations in the case of porphyrinyl-nucleosides. They arose from the doubts concerning the porphine core *vs* furanose ring *vs* nucleobase positions in the numerous expected conformers.

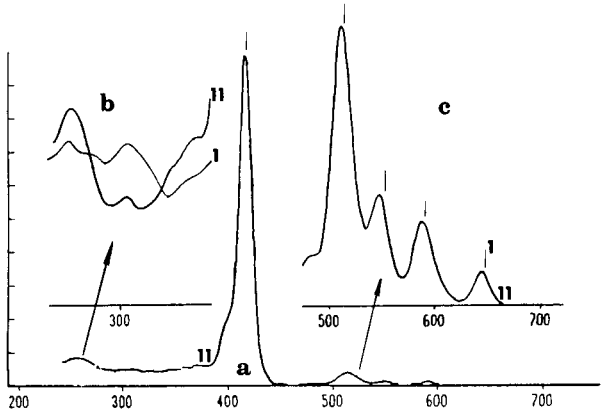


Figure 6. Electronic spectra in chloroform of **I** and **II**. (a) Uv visible spectrum showing the Soret band; (b) uv region, and (c) visible region, both expanded on the arbitrary absorption axis. The positions of the maxima concerning **I** are marked in (c) by vertical lines.

EXPERIMENTAL

The following commercially available chemicals from Aldrich (unless otherwise stated) were used without further purification: 2',3'-*O*-isopropylideneadenosine, thymidine, 2',3'-*O*-isopropylideneuridine (US Biochemical), sodium hydride as 60% suspension in mineral oil, cesium carbonate, *p*-toluenesulfonyl chloride, *p*-hydroxybenzaldehyde (Baker), *p*-anisaldehyde, 4-pyridinecarboxaldehyde, pyrrole, propionic acid, iodomethane, nitromethane, pyridine, *N,N*-dimethylformamide, absolute ethanol (Quantum Chemical), chloroform (Baker), methanol (Baker), dichloromethane (Baker), silica gel 70-230 mesh 60 A, and tlc sheets with silica gel 60 F254 (EM Reagents). Fast atom bombardment mass spectrometry for the compounds of m/z up to 1400 was performed on a V6 Micromass 70/70 mass spectrometer with an 11/250 data system, 3-nitrobenzyl alcohol applied as a matrix. For other compounds a 70 E HFVG mass spectrometer was used. The ^{1}H nmr spectra were recorded on a Bruker IBM AF 300 MHz Fourier transform spectrometer and, for the routine measurements, on Bruker AC 200 MHz Fourier transform spectrometer. In a few cases the spectra were obtained on a Bruker 500 MHz Fourier transform spectrometer. Electronic absorption spectra were recorded on a Perkin-Elmer Lambda 4C uv-vis spectrometer model C 688-0002.

General Procedures for the Synthesis of the Porphyrin Substrates.

Meso-(*p*-tolyl)$_{4-n}$(*p*-hydroxyphenyl)$_n$porphyrins [6], n = 1, 2 or 4, used for preparation of compounds **1-10** were obtained by demethylation [7] of the respective meso-(*p*-tolyl)$_{4-n}$(*p*-methoxyphenyl)$_n$porphyrins, n = 1, 2 or 4. The latter were obtained by standard procedure of Adler *et al.* [8] by cross-condensation of *p*-anisaldehyde and *p*-tolualdehyde with pyrrole in propionic acid (when n = 1 or 2) or in the respective reaction in which *p*-anisaldehyde was the only aldehyde used (when n = 4). The desired porphyrin derivatives formed in each condensation in addition to a number of other differently substituted prophyrins and polymers, were separated by column chromatography (compare [9]) on silica gel column with chloroform/methanol 20:1 as an eluent. The two isomers of di(*p*-tolyl)di(*p*-methoxyphenyl)porphyrin were collected in one fraction and after demethylation they were separated into the 5,10- and 5,15-isomers of meso-di(*p*-tolyl)di(*p*-hydroxyphenyl)porphyrin. The 5,15-isomer being less polar was eluted first; ^{1}H nmr, 500 MHz (DMSO), the 5,10-isomer: 8.84 (s, 8H, β-pyr), 8.08 and 7.53 (dd, 7.6 Hz, 8H ar), 8.03 and 7.15 (dd, 7.15 Hz, 8H ar), −2.78 (s, 2H por); 5,15-isomer: 8.84 (s, 8H, β-pyr), 8.07 and 7.53 (dd, 7.7 Hz, 8H ar), 8.04 and 7.17 (dd, 8.2 Hz, 8H ar), −2.77 (s, 2H por).

Meso-(4-pyridyl)$_{4-n}$(*p*-hydroxyphenyl)$_n$porphyrins, n = 1, 2 or 4, used to obtain the compounds **11-16** were separated after demethylation of the mixture of the respective meso-(4-pyridyl)$_{4-n}$(*p*-methoxyphenyl)$_n$porphyrins, n = 1, 2 or 4. The mixture of the latter was obtained in one condensation step in which 4-pyridinecarboxaldehyde (16.05 g, 0.15 mole), *p*-anisaldehyde (6.81 g, 0.05 mole) and pyrrole (3.42 g, 0.20 mole) were refluxed in propionic acid (800 ml) for 3 hours. After cooling overnight to 0-5°, the obtained crystals were filtered off, washed with water, 5% aqueous potassium carbonate, and again with water. Chromatographic separation on a silica gel column with chloroform/methanol 30:1 as an eluent, changed gradually to 20:1, yielded the meso-tetra-*p*-methoxyphenylporphyrin as the first fraction, the next ones representing, respectively, meso-4-pyridyltri-*p*-methoxyphenylporphyrin, 5,15- and then 5,10-isomers of di(4-pyridyl)di-*p*-methoxyphenylporphyrin, tri(4-pyridyl)-*p*-methoxyphenylporphyrin and finally tetra(4-pyridyl)porphyrin. The separated fractions were refluxed with pyridine hydrochloride for 2.5 hours, poured into water, treated with 5% aqueous ammonia and the precipitate obtained chromatographed on a silica gel column, chloroform/methanol 20:1 as an eluent. The first fraction was always the unreacted porphyrin, the second contained the hydroxyporphyrin product, yields 75-81%.

5,10-Di-*p*-tolyl-15,20-di(*p*-phenylene-5'-*O*-2',3'-*O*-isopropylideneadenosine)porphyrin **1**.

The 5,10-di-*p*-tolyl-15,20-di-*p*-hydroxyphenylporphyrin (37.1 mg, 0.055 mmole) and 5'-tosyl-2',3'-*O*-isopropylideneadenosine [10a] (101 mg, 0.22 mole) were dissolved in DMF (30 ml), added dropwise to the DMF (60 ml) solution of cesium carbonate (36 mg, 0.11 mole) and sodium hydride (26.4 mg, 0.66 mmole) at 65° and the mixture stirred at that temperature for 36 hours. After filtration the filtrate was poured into water (150 ml) and extracted with chloroform (3 x 60 ml). The combined extracts were washed with 5% aqueous ammonia, then with water and dried over anhydrous sodium sulfate. After evaporating to dryness and dissolving in chloroform the residue was chromatographed on silica gel column, dichloromethane/methanol first 50:1 then 50:2, used as an eluent. The first and the second fractions contained the unreacted porphyrin and its monoadenosine derivative (compare [1a]) respectively, the third fraction representing the product **1**, yield 16%; fab ms: (m/z) $(M+1)^+$ 1254; ^{1}H nmr (deuteriochloroform): δ 8.80 (m, 8H, β-pyr), 8.46 (s, 2H, H-2), 8.21 (m, 2H, H-8), 8.02 (m, 8H ar), 7.48 (m, 4H ar), 7.18 (m, 4H ar), 6.32 (m, 2H, H-1'), 5.61 (m, 2H, H-2'), 5.37 (m, 2H, H-3'), 4.86 (m, 2H, H-4'), 4.52 (m, 4H, H-5'),

2.65 (s, 6H, CH_3 tol), 1.72 (s, 6H ip), 1.49 (s, 6H ip), −2.83 (s, 2H por); uv (chloroform): λ (nm) 240, 260 (sh), 306, 378 (sh), 430 (S) 517, 554, 592, 648.

Anal. Calcd. for $C_{72}H_{64}N_{14}O_8$: C, 68.99; H, 5.15; N, 15.65. Found: C, 69.20; H, 5.19; N, 15.82.

5,10-Di-*p*-tolyl-15,20-di(*p*-phenylene-5′-*O*-2′,3′-*O*-isopropylideneuridine)porphyrin **2**.

The procedure described for **1** was followed, the applied reagents being 5,10-di-*p*-tolyl-15,20-di(*p*-hydroxyphenyl)porphyrin (37 mg, 0.055 mmole), 5′-*O*-tosyl-2′,3′-*O*-isopropylideneuridine [10a] (96 mg, 0.22 mmole), cesium carbonate (36 mg, 0.11 mmole) and sodium hydride (26.4 mg, 0.66 mmole), the volume of solvents remaining unchanged, yield 11%; fab ms: m/z 1208 $(M+1)^+$; ^1H nmr (deuteriochloroform): δ 8.83 (m, 8H β-pyr), 8.05 (m, 8H ar), 7.63 (d, 8.2 Hz, 1H, H-6), 7.52 (d, 7.9 Hz, 4H ar), 7.19 (m, 4H ar), 5.95 (d, 2.3 Hz, 2H, H-1′), 5.78 (m, 2H, H-5), 5.16-5.04 (m, 4H, H-2′, H-3′), 4.72 (m, 2H, H-4′), 4.46 (m, 4H, H-5′), 2.68 (s, 6H, CH_3 tol), 1.67 (s, 6H ip), 1.44 (s, 6H ip), −2.81 (s, 2H por); uv (chloroform): λ (nm) 239, 257, 297, 305 (sh), 375 (sh), 420 (S), 517, 554, 593, 649.

Anal. Calcd. for $C_{70}H_{62}N_8O_{12}$: C, 69.64; H, 5.18; N, 9.28. Found: C, 69.81, H, 5.23; N, 9.46.

5,10,15,20-Tetra(*p*-phenylene-5′-*O*-2′,3′-*O*-isopropylideneadenosine)porphyrin **3**.

The meso-tetra-*p*-hydroxyphenylporphyrin (136 mg, 0.2 mmole) and 5′-*O*-tosyl-2′,3′-*O*-isopropylideneadenosine (738 mg, 1.6 mmoles) dissolved in DMF (100 ml) were added dropwise to the solution in DMF (150 ml) of cesium carbonate (260 mg, 0.8 mmole) and sodium hydride (192 mg, 4.8 mmoles) at 65° and the mixture stirred at that temperature for 48 hours. The filtrate was added to water (200 ml) with methanol (50 ml) and extracted with chloroform (4 x 100 ml). The combined extracts were washed with 5% aqueous ammonia (50 ml) then with water, dried over anhydrous sodium sulfate and chromatographed on a silica gel column with chloroform/methanol as an eluent, its composition gradually changed from 50:1 to 15:1. The product **3** was eluted in the first fraction, the second fraction containing the starting porphyrin, yield 7%; fab ms: mz 1837 $(M+1)^+$; ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.86 (br s, 4H, H-2), 8.33 (m, 8H, β-pyr), 8.16 (s, 4H ar), 7.99 (d, 8.0 Hz, 4H, H-8), 7.38 (m, 10H ar), 7.21 (d, 8.4 Hz, 2H ar), 6.24 (d, 2.4 Hz, 4H, H-1′), 5.47 (dd, 2.4 Hz, 4H, H-2′), 5.06 (dd, 2.9 Hz, 4H, H-3′), 4.34 (reg m, 4H, H-4′), 3.81 (m, 8H, H-5′), 1.55 (s, 12H ip), 1.34 (s, 12H ip), −2.84 (br s, 2H por); uv (dimethyl sulfoxide): λ (nm) 263, 424 (S), 519, 558, 595, 652.

Anal. Calcd. for $C_{96}H_{90}N_{24}O_{16}$: C, 62.80; H, 4.94; N, 18.31. Found: C, 62.75; H, 5.01; N, 18.43.

5,10,15,20-Tetra(*p*-phenylene-5′-*O*-2′,3′-*O*-isopropylideneuridine)-porphyrin **4**.

The same procedure as for **3** was followed, the applied reagents being: meso-tetra-*p*-hydroxyphenylporphyrin (102 mg, 0.15 mmole) and 5′-*O*-tosyl-2′,3′-*O*-isopropylideneuridine (526 mg, 1.20 mmoles) dissolved in DMF (100 ml), sodium hydride (144 mg, 3.6 mmoles) and cesium carbonate (196 mg, 0.60 mmole) dissolved in DMF (150 ml). The product **4** was obtained in the first fraction, yield 9%; fab ms: m/z 1744 $(M+1)^+$ (3% base), also 1743 (4.3%); ions resulting from the detachment of the first CH_3 (5′)-nucleoside unit: 1477 (54%), 1476 (55%); detachment of the second and the fourth units: 1210 (100%), 676 (51%); ^1H nmr (dimethyl-d_6) sulfoxide): δ 10.00 (s, 4H, H-3), 8.86 (m, 8H, β-pyr), 8.11 and 7.39 (dd, 8.2 Hz, 4H ar); 7.99 and 7.20 (dd, 8.2 Hz, 12H ar), 7.83 (d, 7.7 Hz, 4H, H-6), 5.98-5.80 (m, 8H, H-1′, H-5), 4.93, 4.90 (dd, 2.6 Hz) and 4.76, 4.73 (dd, 3.2 Hz) (8H, H-2′, H-3′), 4.39-4.13 (m, 12H, H-4′, H-5′), 1.50 (s, 12H ip), 1.31 (s, 12H ip), −2.88 (s, 2H por); uv (etanol): λ (nm) 230, 250, 418 (S), 516, 554, 593, 650.

Anal. Calcd. for $C_{92}H_{86}N_{12}O_{24}$: C, 63.37; H, 4.97; N, 9.64. Found: C, 63.23; H, 4.96; N, 9.81.

5,10,15-Tri-*p*-tolyl-20-(*p*-phenylene-5′-*O*-thymidine)porphyrin **5**.

The meso-tri-*p*-tolyl-*p*-hydroxyphenylporphyrin (134 mg, 0.2 mmole) and 5′-*O*-tosylthymidine [10b] (159 mg, 0.4 mmole) dissolved in DMF (50 ml) were added dropwise to the DMF (100 ml) solution of cesium carbonate (65 mg, 0.2 mmole) and sodium hydride (48 mg, 1.2 mmoles) at 65°, and the stirring was continued at that temperature for 48 hours. After the usual procedure (see above) the final chromatographic separation was carried on silica gel column using chloroform/methanol 20:1 as an eluent. The first fraction contained the porphyrin reagent, the second one the product **5**, yield 18%; fab ms: m/z 898 $(M+1)^+$; ^1H nmr (deuteriochloroform): δ 8.83 (m, 8H, β-pyr), 8.15 (m, 2H ar), 8.07 and 7.53 (dd, 7.9 Hz, 12H ar tol), 7.72 (s, 1H, H-6), 7.26 (m, 2H ar), 6.52 (tr, 1H, H-1′), 4.83 (m, 1H, H-3′), 4.51 (m, 1H, H-4′), 4.43 (m, 2H, H-5′), 2.68 (s, 9H, CH_3 tol), 2.45 (m, 2H, H-2′), 1.96 (s, 3H, C_5-CH_3), −2.82 (s, 2H por); uv (chloroform): λ (nm) 267, 305 (sh), 370 (br), 420 (S), 517, 553, 592 and 647.

Anal. Calcd. for $C_{57}H_{48}N_6O_5$: C, 76.32; H, 5.39; N, 9.37. Found: C, 76.58; H, 5.59; N, 9.42.

Meso-di-*p*-tolyl-(*p*-hydroxyphenyl)-(*p*-phenylene-5′-*O*-thymidine)-porphyrin, Isomer 5,15 **6**, Isomer 5,10 **7**, and meso-di-*p*-tolyl-di-(*p*-phenylene-5′-*O*-thymidine)porphyrin, Isomer 5,15 **8**, Isomer 5,10 **9**.

All these compounds were the products of one reaction, separated on a silica gel column. The mixture of two isomeric di-*p*-tolyl-di-*p*-hydroxyphenylporphyrins (400 mg, 0.59 mmole) and 5′-*O*-tosylthymidine (940 mg, 2.4 mmoles) dissolved in DMF (150 ml) was added dropwise to the DMF (150 ml) solution of cesium carbonate (390 mg, 1.2 mmoles) and sodium hydride (288 mg, 7.2 mmoles) at 65° and the mixture stirred at that temperature for 48 hours. After cooling to room temperature it was filtered, and after adding water (200 ml) to the filtrate it was extracted with chloroform (4 x 100 ml). The combined extracts were washed with 5% aqueous ammonia then water (4 x 5 ml) and dried over anhydrous sodium sulfate. After evaporation of the solvent the chromatographic separation was performed on silica gel column, chloroform/methanol 30:1 used as an eluent. The 5,15- and 5,10-isomers of the unreacted starting porphyrin appeared, respectively, in fractions 1 and 2. The third and fourth fractions contained, respectively, the 5,15- and 5,10-isomers **6** and **7**, while the respective isomers **8** and **9** were separated as the fifth and the sixth fraction; yields: **6** 4.7%, **7** 8.5%, **8** 2.7%, **9** 5%.

Compound **6**.

This compound had fab ms: m/z 900 $(M+1)^+$; ^1H nmr (deuteriochloroform): δ 8.86 (m, 8H, β-pyr), 8.05 (m, 10H ar), 7.72 (s, 1H, H-6), 7.53 (d, 7.9 Hz, 4H ar), 7.20 (m, 2H ar), 6.51 (tr, 1H, H-1′), 4.80 (m, 1H, H-3′), 4.49-4.37 (c, 3H, H-4′, H-5′), 2.68 (s, 6H, CH_3 tol), 2.47 (m, 2H, H-2′), 1.97 (s, 3H, C_5-CH_3, −2.78 (br s, 2H por);

uv (chloroform): λ (nm) 268, 305 (sh), 328, 420 (S), 518, 551, 594, 648.

Anal. Calcd. for $C_{56}H_{36}N_6O_6$: C, 74.81; H, 5.16; N, 9.35. Found: C, 74.92; H, 5.34; N, 9.44.

Compound **7**.

This compound had fab ms: m/z 900 $(M+1)^+$; ^1H nmr (deuteriochloroform): δ 8.82 (m, 8H, β-pyr), 8.03 (m, 8H ar), 7.62 (s, 1H, H-6), 7.47 (m, 4H ar), 7.07 (m, 4H ar), 6.44 (s, 1H, H-1'), 4.60 (m, 1H, H-3'), 4.32-4.10 (c, 3H, H-4', H-5'), 2.63 (s, 6H, CH_3 tol), 2.37 (m, 2H, H-2'), 1.92 (s, 3H, C_5-CH_3), −2.77 (s, 2H por); uv (chloroform): λ (nm) 268, 328, 420 (S), 518, 555, 592, 650.

Anal. Calcd. see **6**. Found: C, 74.98; H, 5.30; N, 9.50.

Compound **8**.

This compound had fab ms: m/z 1124 $(M+1)^+$; ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.82 (m, 8H, β-pyr), 8.12 and 7.99 (dd, 8.4 Hz, 4H ar), 8.07 and 7.61 (dd, 8.0 Hz, 8H ar), 7.41 and 7.19 (dd, 8.46 Hz, 4H ar), 7.79 (s) and 7.70 (s) (2H, H-6), 6.42-6.35 (c) and 6.17-6.13 (c) (2H, H-1'), 5.61-5.57 (c) and 5.41 (d, 3.94 Hz) (2H, H-3'), 4.55-3.95 (c, 6H, H-4', H-5'), 2.66 (s, 6H, CH_3 tol), 2.27 (m) and 2.11 (m) (4H, H-2'), 1.86 (tr, 6H, C_5-CH_3), −2.93 (s, 2H por); uv (dimethyl sulfoxide): λ (nm) 257, 270 (sh), 421 (S), 518, 555, 593, 649.

Anal. Calcd. for $C_{66}H_{58}N_8O_{10}$: C, 70.57; H, 5.21; N, 9.98. Found; C, 70.79; H, 5.22; N, 10.13.

Compound **9**.

This compound had fab ms: m/z 1124 $(M+1)^+$; ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.82 (m, 8H, β-pyr), 8.12 and 7.99 (dd, 8.3 Hz, 4H ar), 8.07 and 7.60 (dd, 7.55 Hz, 8H ar), 7.41 and 7.20 (dd, 8.24 Hz, 4H ar), 7.79 (s) and 7.70 (s) (2H, H-6), 6.42-6.36 (c) and 6.18-6.13 (c) (2H, H-1'), 5.62-5.58 (c) and 5.41 (d, 3.76 Hz), (2H, H-3'), 4.56-3.95 (c, 6H, H-4', H-5'), 2.65 (s, 6H, CH_3 tol), 2.27 (m) and 2.09 (m) (4H, H-2'), 1.86 (m, 6H, C_5-CH_3), −2.93 (s, 2H por); uv (dimethyl sulfoxide): λ (nm) 256, 270 (sh), 421 (S), 518, 555, 593, 651.

Anal. Calcd. see **8**. Found: C, 70.72; H, 5.18; N, 10.03.

5,10- and 5,15-Di-*p*-tolyl-di(*p*-phenylene-5'-*O*-thymidine)porphyrin **10**.

Meso-tetra-*p*-hydroxyphenylporphyrin (200 mg, 29 mmoles) and 5'-*O*-tosylthymidine (919 mg, 2.3 mmoles) dissolved in DMF (60 ml) were added dropwise into DMF (120 ml) solution of cesium carbonate (378 mg, 1.16 mmoles) and sodium hydride (278 mg, 6.96 mmoles), and stirred at 65° for 48 hours. The mixture was poured into water (200 ml) with methanol (50 ml) and the procedure described for **3** was followed, yield 6% of the mixture of both isomers which did not separate under the applied conditions; fab ms: m/z 1128 $(M+1)^+$; ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.88 (m, 8H, β-pyr), 8.14 and 7.43 (dd, 8.5 Hz, 4H ar), 8.02 and 7.22 (dd, 8.4 Hz, 12H ar), 7.72 (m, 2H, H-6), 6.35 (tr) and 6.06 (tr) (2H, H-1'), 5.58 (d, 4.2 Hz, 2H, H-5), 4.56-4.46 (m, 2H, H-3'), 4.27-3.92 (c, 6H, H-4', H-5'), 2.28 (m, 2H, H-2'), 1.84 (s, 3H, C_5-CH_3), −2.90 (s, 2H por); uv (dimethyl sulfoxide): λ (nm) 262, 308, 356 (sh), 373 (sh), 424 (S), 520, 558, 596, 653.

Anal. Calcd. for $C_{64}H_{54}N_8O_{12}$: C, 68.15; H, 4.83; N, 9.94. Found: C, 68.35; H, 4.86; N, 10.08.

5,10,15-Tri-4-pyridyl-20-(*p*-phenylene-5',2',3'-*O*-isopropylideneuridine)porphyrin **11**.

The 5,10,15-tri-4-pyridyl-20-*p*-hydroxyphenylporphyrin (90 mg, 0.14 mmole), 5'-*O*-tosyl-2',3'-*O*-isopropylideneuridine (123 mg, 0.28 mmole) dissolved in DMF (50 ml) were added dropwise to DMF (100 ml) solution of cesium carbonate (46 mg, 0.14 mmole) and sodium hydride (34 mg, 0.84 mmole) and the mixture stirred at that temperature for 48 hours. After filtration, the filtrate was poured into water (150 ml) with methanol (50 ml), extracted with chloroform (3 x 100 ml), the combined extracts washed with 5% aqueous ammonia, then with water and dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the residue chromatographed on silica gel column with dichloromethane/methanol eluent, its composition being gradualy changed from 30:1 to 20:1. The product **11** appeared in the first fraction, the second one contained the unreacted porphyrin, yield 17%; fab ms: m/z 901 $(M+1)^+$; ^1H nmr (deuteriochloroform): δ 9.04 (s, 4H py), 8.83 (s, 8H, β-pyr), 8.14 (m, 8H py), 8.06 (m, 2H ar), 7.60 (d, 8.1 Hz, 1H, H-6), 7.27 (m, 2H ar), 5.93 (s, 1H, H-1'), 5.79 (m, 1H, H-5), 5.14 (m, 2H, H-2', H-3'), 4.75 (m, 1H, H-4'), 4.50 (m, 2H, H-5'), 1.68 (s, 3H ip), 1.45 (s, 3H ip), −2.91 (s, 2H por); uv (chloroform): λ (nm) 255, 307, 418 (S), 514, 548, 589, 645.

Anal. Calcd. for $C_{53}H_{41}N_9O_6$: C, 70.73; H, 4.59; N, 14.01. Found: C, 70.61; H, 4.74; N, 14.19.

5,10-Di-4-pyridyl-15,20-di(*p*-phenylene-5'-*O*-2',3'-*O*-isopropylideneuridine)porphyrin **12**, and 5-(4-Pyridyl)-10,15,20-tri(*p*-phenylene-5'-*O*-2',3'-*O*-isopropylideneuridine)porphyrin **13**.

They were both obtained in the same way as compound **11**. The amounts of reagents applied were as follows, **12**: 5,10-di-4-pyridyl-di-*p*-hydroxyphenylporphyrin (70 mg, 0.11 mmole), 5'-*O*-tosyl-2',3'-*O*-isopropylideneuridine (189 mg, 0.43 mmole) in DMF (50 ml), cesium carbonate (71 mg, 0.22 mmole), sodium hydride (52 mg, 1.3 mmoles) in DMF (100 ml); **13**: 5-(4-pyridyl)-10,15,20-tri(*p*-hydroxyphenyl)porphyrin (180 mg, 0.27 mmole) and 5'-*O*-tosyl-2',3'-*O*-isopropylideneuridine (710 mg, 1.6 mmoles) in DMF (50 ml), cesium carbonate (264 mg, 0.81 mmole), and sodium hydride (194 mg, 4.9 mmoles) in DMF (100 ml), yields, **12** 11%, **13** 4.5%.

Compound **12**.

This compound had fab ms: m/z 1182 $(M+1)^+$; ^1H nmr (deuteriochloroform): δ 9.01 (d, 6.0 Hz, 4H py), 8.80 (m, 8H, β-pyr), 8.14 (m, 4H py), 8.05 (m, 4H ar), 7.62 (d, 8 Hz, 2H, H-6), 7.34-7.19 (m, 4H ar), 5.91 (d, 1.5 Hz, 2H, H-1'), 5.79 (m, 2H, H-5), 5.12 (m, 4H, H-2', H-3'), 4.70 (br s, 2H, H-4'), 4.47 (m, 4H, H-5'), 1.67 (s, 6H ip), 1.44 (s, 6H ip), −2.87 (s, 2H por); uv (chloroform): λ (nm) 256, 306, 420 (S), 516, 552, 590, 647.

Anal. Calcd. for $C_{66}H_{56}N_{10}O_{12}$: C, 67.11; H, 4.78; N, 11.86. Found: C, 66.97; H, 4.87; N, 12.00.

Compound **13**.

This compound had fab ms: m/z 1463 $(M+1)^+$; ^1H nmr (deuteriochloroform): δ 9.01 (d, 4 Hz, 2H py), 8.87 (m, 8H, β-pyr), 8.15 (m, 2H py), 8.05 (m, 4H ar), 7.59 (d, 8 Hz, 3H, H-6), 7.32-7.19 (m, 8H ar), 5.77 (d, 8.1 Hz, 3H, H-1'), 5.51 (d, 2.8 Hz, 3H, H-5), 5.11-4.88 (c, 6H, H-2', H-3'), 4.30 (m, 3H, H-4'), 3.85 (m, 6H, H-5'), 1.67 (s, 9H ip), 1.44 (s, 9H ip), −2.82 (s, 2H por); uv (chloroform): λ (nm) 257, 306 (sh), 419 (S), 517, 553, 591, 648.

Anal. Calcd. for $C_{79}H_{71}N_{11}O_{18}$: C, 64.88; H, 4.89; N, 10.54. Found: C, 65.07; H, 5.00; N, 10.62.

5,10,15-Tri(*N*-methyl-4-pyridinium)-20-(5′-*O*-2′,3′-*O*-isopropylideneuridine)porphyrin, Iodide Salt **14**.

The compound **11** (4 mg, 0.004 mmole) was refluxed overnight with the mixture of iodomethane (4 ml) and nitromethane (3 ml). The reaction was checked for the disappearance of the unreacted substrates by tlc using chloroform/methanol 30:1 as an eluent. The solvent and the excess of methylating agent were evaporated in vacuum, yield 94%; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.48 (d, 6.4 Hz, 6H py), 9.16 (s, 5H py), 9.05 (s, 1H py), 8.99 (m, 8H, β-pyr), 8.14 and 7.44 (dd, 8 Hz, 4H ar), 7.88 (d, 8 Hz, 1H, H-6), 5.96 (s, 1H, H-1′), 5.70 (d, 8 Hz, 1H, H-5), 5.21 (d, 7.8 Hz, 1H, H-3′), 5.09 (m, 1H, H-2′), 4.72 (s, 9H, N-CH_3), 4.50-4.40 (m) and 3.87 (m) (3H, H-4′, H-5′), 1.61 (s, 3H ip), 1.41 (s, 3H ip), −3.02 (s, 2H por); uv, (water): λ (nm) 259, 425 (S), 522, 559, 585, 643; (dimethyl sulfoxide): 259, 427 (S), 520, 554, 590, 646.

Anal. Calcd. for $C_{56}H_{50}N_9O_6I_3$: C, 50.73; H, 3.80; N, 9.51. Found: C, 51.01; H, 4.02; N, 9.79.

5,10-Di(*N*-methyl-4-pyridinium)-15,20-di(*p*-phenylene-5′-*O*-2′,3′-*O*-isopropylideneuridine)porphyrin, Iodide Salt **15**, and 5-(*N*-Methyl-4-pyridinium)-10,15,20-tri(5′-*O*-2′,3′-*O*-isopropylideneuridine)-porphyrin, Iodide Salt **16**.

They were both obtained in the same way as **14**, the substrates for *N*-methylation being, respectively, the compounds **12** and **13**, yields, 93%.

Compound **15**.

This compound had ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.47 (d, 6.5 Hz, 4H py), 9.02 (m, 12H, 4H py, 8H, β-pyr), 8.16 and 7.44 (dd, 8.5 Hz, 6H ar), 8.03 and 7.26 (dd, 8.2 Hz, 2H ar), 7.91 (d, 8.1 Hz, 2H, H-6), 5.99 (d, 1.9 Hz, 2H, H-1′), 5.73 (d, 7.9 Hz, 2H, H-5), 5.25 (m, 2H, H-3′), 5.11 (m, 2H, H-2′), 4.72 (s, 6H, N-CH_3), 4.60-4.43 (m) and 3.87 (m) (6H, H-4′, H-5′), 1.61 (s, 6H ip), 1.41 (s, 6H ip), −2.90 (s, 2H por); uv (water): λ (nm) 225, 258, 432 (S), 524, 564, 590, 650; (dimethyl sulfoxide): 259, 428 (S), 520, 558, 592, 648.

Anal. Calcd. for $C_{68}H_{62}N_{10}O_{12}I_2$: C, 55.74; H, 4.27; N, 9.56. Found: C, 56.00; H, 4.46; N, 9.76.

Compound **16**.

This compound had ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.43 (d, 6.6 Hz, 2H py), 9.06-8.85 (c, 10H, 2H py, 8H, β-pyr), 8.12 and 7.40 (dd, 8 Hz, 4H ar), 8.02 (d, 8.3 Hz, 2H ar), 7.95-7.73 (c, 4H ar), 7.85 (d, 8.1 Hz, 3H, H-6), 7.23 (d, 8.3 Hz, 2H ar), 5.98 (m, 3H, H-1′), 5.85-5.70 (c, 3H, H-5), 5.25-5.08 (m, 6H, H-2′, H-3′), 4.92-4.70 (m) and 4.08 (m) (9H, H-4′, H-5′), 1.61 (s, 9H ip), 1.40 (s, 9H ip), −2.81 (s, 2H por); uv (water): λ (nm) 219, 258, 425 (S), other bands not visible because of low solubility; (dimethyl sulfoxide): 259, 427 (S), 520, 560, 593, 651.

Anal. Calcd. for $C_{80}H_{74}N_{11}O_{18}I$: C, 59.88; H, 4.65; N, 9.61. Found: C, 60.10; H, 4.73; N, 9.83.

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