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Synthesis and Spectral Properties of [3-(Heptyloxy)phenoxy]acetic Acid and Its Derived *meso*-Sibstituted Tetrabenzoporphyrins

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Abstract—3-Heptyloxyphenol was obtained by reaction of resorcinol with 1-bromoheptane. Further alkylation with monochloroacetc acid resulted in the synthesis of [3-(heptyloxy)phenoxy]acetic acid. Heating of the latter with phthalimide in the presence of zinc acetate afforded zinc complexes of *meso*-[(3-heptyloxy)phenoxy] tetrabenzoporphyrins whose demetalization gave free porphyrin bases. Spectral properties of the synthesized compounds were studied.

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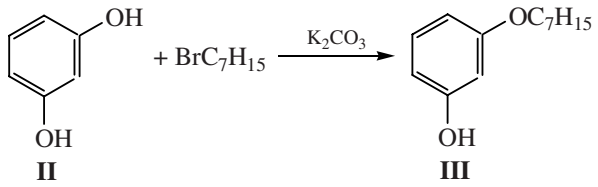
meso-Substituted tetrabenzoporphyrins are now intensively studied. The interest in them is defined by the fact that these compounds possess quite valuable physicochemical and spectral properties for application as materials for photodynamic cancer therapy [1–4] and nonlinear optics [5, 6]. Such properties of *meso*-substituted tetrabenzoporphyrins makes urgent synthesis of new compounds of this group for their further studies in various aspects.

In the recent time new methods of synthesis of a significant number of *meso*-arylsubstituted tetrabenzoporphyrins have been developed. However, the information concerning *meso*-aryloxy-substituted tetrabenzoporphyrins is scarce [7], even though such compounds can be fairly interesting for practical purposes. We failed to find in the literature any information on the synthesis and properties of *meso*-phenoxy-substituted tetrabenzoporphyrins containing bulky substituents in the phenoxy group, which is connected, in our opinion, with the absence of methods for preparation of substituted phenoxyacetic acids. Therefore, in the present work we set ourselves the task to develop a method for synthesis of [3-(heptyloxy)phenoxy]acetic acid (**I**) and its derived *meso*-substituted tetrabenzoporphyrins.

Acid **I** was obtained by a two-step procedure. In the first step, we reacted 1-bromoheptane with a fivefold excess of resorcinol (**II**) in the presence of K_2CO_3 in DMF under reflux for 7 h to obtain 3-(heptyloxy) phenol (**III**). Using a large excess of resorcinol (**II**) allowed us to avoid dialkylation forming 1,3-bis-(heptyloxy)benzene. Thus, compound **III** is formed by Scheme 1.

Scheme 1.



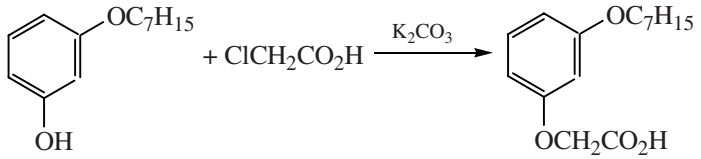
II **III**

Compound **III** is a viscous light yellow liquid readily soluble in most organic solvents. Its composition and structure were confirmed by elemental analysis and vibrational and ^1H NMR spectroscopy.

The IR spectrum of phenol **III** shows a broad band in the region of 3580 cm^{-1} due to hydroxyl O–H vibrations, a strong band in the region of 2987 cm^{-1} due to stretching vibrations of alkyl C–H bonds, and bands at 1221 and 1188 cm^{-1}, which correspond to C–O vibrations and thus confirm presence of an ether group.

The ^{1}H NMR spectrum of compound **III** contains a multiplet in the region of 6.98–6.71 ppm, corresponding to the resonance of four protons of the benzene ring. The singlet at 4.84 ppm belongs to the hydroxyl proton, the triplet in the region of 3.82–3.76 ppm, to two α-CH_2 protons, the multiplet in the region of 1.44–1.28 ppm, to 10 protons of the remaining five methylene groups, and the triplet at 0.89 ppm, to three protons of the terminal methyl group.

In the second step, by the alkylation of phenol **III** with monochloroacetic acid in the presence of K_2CO_3 in DMF we obtained acid **I** (Scheme 2).



III **I**

Compound **I** is a wax-like yellow substance readily soluble in chloroform, benzene, and acetone, soluble in aqueous alkali, and practically insoluble in water. Its composition and structure were also confirmed by elemental analysis and vibrational and ^{1}H NMR spectroscopy.

The IR spectrum of acid **I** is similar to that of phenol **III**, except that the former spectrum contains a band at 1722 cm^{-1}, which attests presence of a carboxy group.

In the ^{1}H NMR spectrum of compound **I**, in the weakest field region (7.17–7.06 ppm) we observe a multiplet from the 5-H proton of the benzene ring and a multiplet in the region of 6.57–6.46 ppm from the 2-, 4-, and 6-H protons. In a stronger field region, there are a triplet at 3.94–3.88 ppm from two protons of the methylene group neighboring to carboxyl, a multiplet at 1.76–1.73 ppm from two protons of the alkoxyl α-methylene group, a multiplet at 1.43–1.28 ppm from 10 protons of the remaining five methylene groups, and, finally, a triplet at 0.89 ppm from three protons of the terminal methyl group.

We attempted to synthesize zinc *meso*-tetra[(3-heptyloxy)phenoxy]tetrabenzoporphyrinate by reaction of phthalimide **VI** with acid I in the presence of zinc oxide. However, upon heating of the reagents at 340°C for 2 h, a brown melt formed that did not contain even traces of the target compound. When zinc oxide was replaced by zinc acetate, the reaction mixture became green, which gave evidence for the formation of tetrabenzoporphyrin. In this case, the reaction proceeded at 320°C and was complete in 30–40 min. Chromatographic separation of the reaction mixture showed that, along with unsubstituted zinc tetrabenzoporphirinate, it contained only two porphyrin compounds, both readily soluble in organic solvents. These compounds were identified as zinc *meso*-mono[(3-heptyloxy)phenoxy]tetrabenzoporphirinate (**V**) and *meso-trans*-bis[(3-heptyloxy)phenoxy] tetrabenzoporphirinate (VI). The synthesis of metal complexes **V** and **VI** can be represenhed by the above Scheme 2.

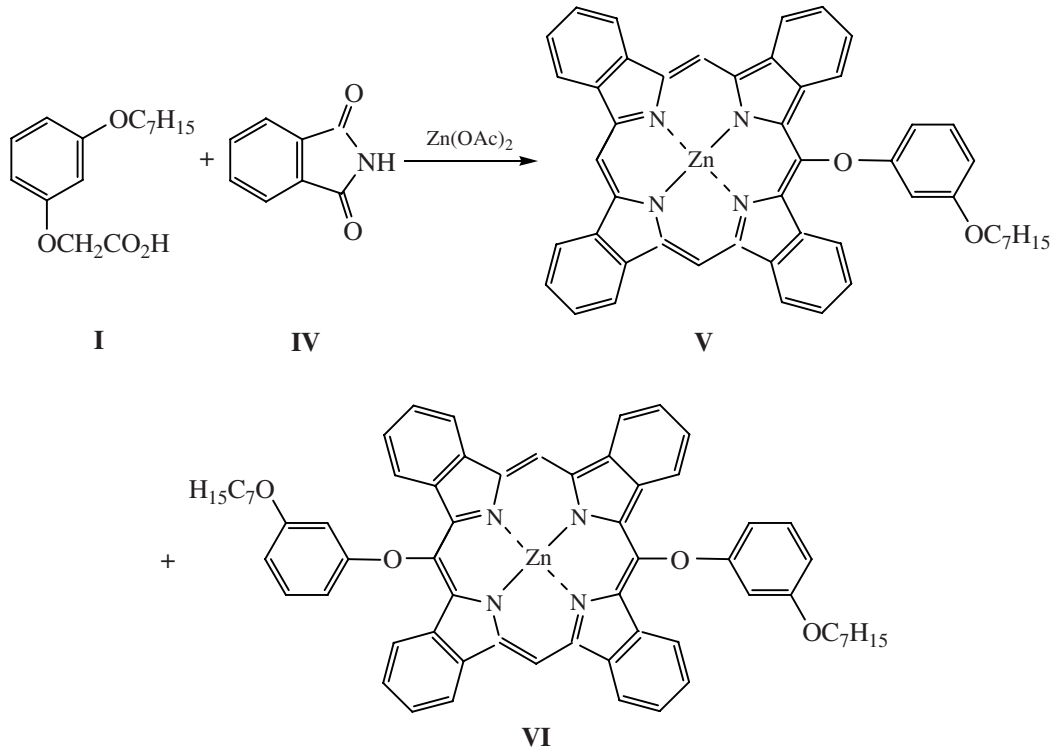
We suggest that in this case, due to weaker steric hindrances, specifically a *trans*-substituted tetrabenzoporphyrin **VI** is formed. Quantum-chemical calculations of compound **VI** and zinc *meso-cis*-bis[(3-heptyloxy)phenoxy]tetrabenzoporphirinate by the semiempirical AM1 method showed that the energy gain from the formation of compound **VI** as compared with the *cis* isomer is 28.88 kJ mol^{-1}. This is caused, as follows from the calculations, by a stronger planarity and, hence, aromaticity of the porphyrin **V** molecule.

By treatment of solutions of compounds **V** and **VI** in chloroform with concentrated hydrochloric acid we synthesized *meso*-mono[(3-heptyloxy)phenoxy]tetrabenzoporphyrin (**VII**) and *meso-trans*-bis[(3-heptyloxy)phenoxy]tetrabenzoporphyrin (**VIII**), respectively. They were also purified by column chromatography.

Porphyrins **V–VIII** are dark red crystalline substances readily soluble in a wide series of organic solvents. Their compositions and structures were confirmed by elemental analysis and vibrational, ^{1}H NMR, and electronic spectroscopy.

The IR spectra of porphyrins **V–VIII** contain a series of similar absorption bands formed by vibrations of alkyl C–H bonds (2990–2973 cm^{-1}), C–O bonds (1228, 1186 cm^{-1}), and C–C and C–N bonds (1494 and 1464 cm^{-1}). The ^{1}H NMR spectrum of complex **VI** contains in a weak-field region a multiplet at 8.33–

Scheme 2.



8.14 ppm form three *meso*-protons of the macrocycle, a multiplet at 7.98–7.65 ppm from 16 protons of the benzene rings in the isoindole fragments, a multiplet at 6.62–6.32 ppm from four protons of the benzene ring of the *meso*-substituent. In a stronger field, a multiplet at 1.78–1.76 ppm from two alkoxyl α-methylene protons, a multiplet at 1.41–1.25 ppm from 10 protons of the remaining five methylene groups, and, finally, a triplet at 0.88 ppm from three protons of the terminal methyl group. The ^{1}H NMR spectrum of complex **VI** is similar to that of compound **V**, but the signals of protons of the *meso*-substituent are enhanced, while those of *meso*-protons are weaker. In the strongest field region of the ^{1}H NMR spectra of metal-free porphyrins **VII** and **VIII** we observe signals of endocyclic imino groups (–2.22 and –2.15 ppm, respectively).

The electronic absorption spectra of porphyrins **V–VIII** (Figs. 1 and 2) are quite similar to the spectra of unsubstituted tetrabenzoporphyrin and its zinc complex in terms of the positions of band maxima [8]. This fact suggests that the alkoxy-substituted phenoxy groups in the *meso* positions of porphyrins **V–VIII** only slightly affect the molecular geometry. However, in the spectrum of compound **V** (Fig. 1, spectrum *1*), we observe, in the Soret region, a weak diffuse band (446 nm) that is absent from the spectrum of zinc tetrabenzoporphirinate. This band is assignable to charge transfer from the electron-donor substituent onto the macrocycle. In the spectrum of metal-free prophyrin **VII** (Fig. 1, spectrum *2*), the respective band at 443 nm is much stronger, and an additional band at 677 nm appears, which, too, is assignable to charge transfer. The presence in the electronic absorption spectra of charge transfer bands is also characteristic of other unsymmetrical tetrabenzoporphyrins [9].

In the case of *meso*-disubstituted porphyrins **VI** and **VIII** (Fig. 2), again, there are two charge-transfer bands in the Soret region. However, while in the spectrum of zinc complex **VI** (Fig. 2, spectrum *1*) these bands have maxima at 441 and 460 nm, in the spectrum of metal-free compound **VIII** (Fig. 2, *2*) these bands are slightly stronger, and their maxima are shifted red by 6 and 9 nm, respectively. The long-wave charge-transfer band has a maximum at 709 nm, that is, red shifted from that of *meso*-mono-substituted tetrabenzoporphyrin **VI** by 32 nm.

To confirm the above assumption that *meso*-substitution only slightly affects the geometry of

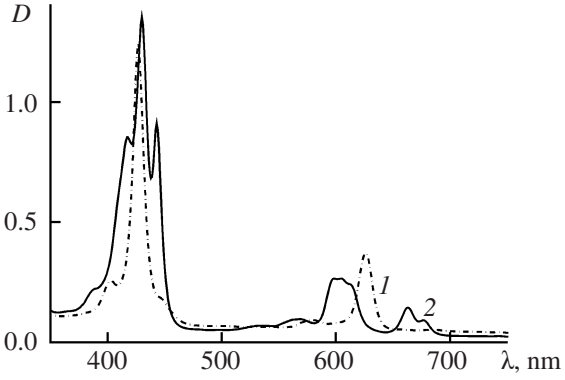


Fig. 1. Electronic absorption spectra of benzene solutions of (*1*) **V** and (*2*) **VII**.

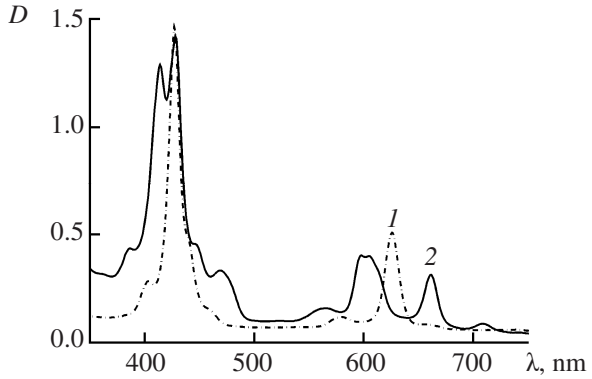


Fig. 2. Electronic absorption spectra of benzene solutions of (*1*) **VI** and (*2*) **VIII**.

compounds **VII** and **VIII**, we carried out quantum-chemical calculations of the respective molecules by the AM1 method. The calculation results are depicted in Fig. 3. As seen, molecule **VII** (Fig. 3a) is planar, while molecule **VIII** (Fig. 3b) is slightly saddle-distorted, but the isoindole fragments deviates from the conventional plane defined by nitrogen atoms by no more than 8°.

Thus, the electronic optical properties of tetrabenzoporphyrins with alkoxy-substituted phenoxyacetic acid residues in the *meso* positions are defined by electronic effects of the substituents only, unlike *meso*-phenyltetrabenzoporphyrins [10–12] whose spectral properties mostly controlled by the degree of planarity distortion of the macrocycle.

EXPERIMENTAL

The electronic absorption spectra were registered on a Hitachi UV-2001 spectrophotometer. The ^{1}H NMR spectra were taken on a Bruker WM-250 instrument (250 MHz) in $CDCl_3$, internal reference TMS. The IR spectra were recorded on an Avatar 360 FT-IR spectrophotometer in the region 400–4000 cm^{-1} in films on TlI glass. Elemental analysis was carried out on a FlashEA 1112 CHNS–O Analyzer.

3-(Heptyloxy)phenol (III). A mixture of 11.0 g of resorcinol (II), 3.5 g of 1-bromoheptane, 5.5 g of K_2CO_3 and 30 ml of DMF was stirred under reflux for 6 h, cooled, diluted with 50 ml of water, acidified with HCl to pH 2, and extracted with two 30-ml portion of CCl_4. The combined extracts were washed consecutively with 10% NaOH, water, 10% HCl, and water, and the organic solvent was then distilled off. Yield 3.2 g (78%), viscous light yellow liquid, readily soluble in benzene, acetone, chloroform, CCl_4. IR spectrum , ν, cm^{-1}: 3580, 2987, 1221, 1188. ^{1}H NMR spectrum, δ, ppm: 6.98–6.71 m (4H), 4.84 s (1H), 3.82–3.76 t (2H), 1.44–1.28 m (10H), 0.89 t (3H). Found, %: C 75.01; H 10.12. $C_{13}H_{20}O_2$. Calculated, %: C 74.96; H 9.68.

[3-(Heptyloxy)phenoxy]acetic acid (I). A mixture of 3.0 g of phenol **III**, 2.0 g of monochloroacetic acid, 4.5 g of K_2CO_3, and 20 ml of DMF was stirred under reflux for 6 h, cooled, diluted with 30 ml of water, and acidified with HCl to pH 2. The precipitate dropped was filtered off, washed with water, and dried. Yield

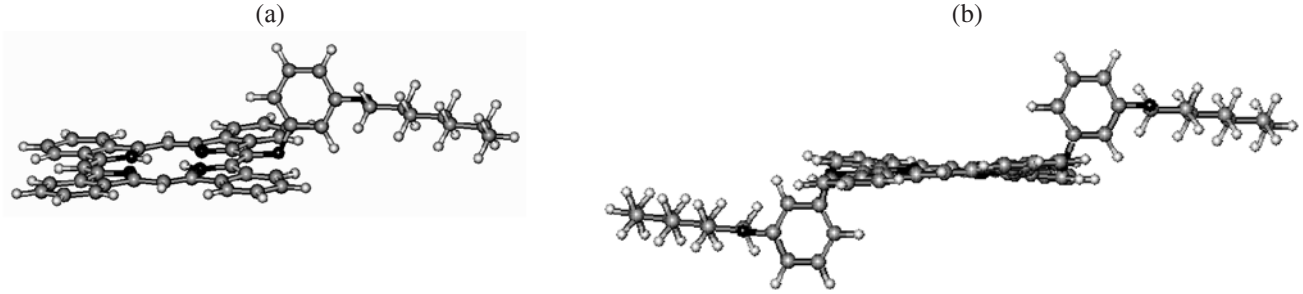


Fig. 3. Geometry of compounds (a) **VII** and (b) **VIII**, as given by AM1 calculations.

3.2 g (83%), wax-like yellow substance readily soluble in chloroform, benzene, acetone, soluble in aqeous alkali, and insoluble in water. IR spectrum , ν, cm^{-1}: 3582, 2983, 1722, 1220, 1181. ^1H NMR spectrum, δ, ppm: 7.17–7.06 m (1H), 6.57–6.46 m (3H), 3.94–3.88 t (2H), 1.76–1.73 m (2H), 1.43–1.28 m (10H), 0.89 t (3H). Found, %: C 67.89; H 8.63. $C_{15}H_{22}O_4$. Calculated, %: C 67.65; H 8.33.

Condensation of acid I c phthalimide in the presence of zinc acetate. A mixture of 2.0 g of acid **I**, 1.1 g of phthalimide **IV** and 2.0 g of zinc acetate dihydrate was heated for 40 min at 320°C, cooled, dissolved in chloroform, and passed through a column of activity grade II alumina (eluent chloroform–acetone, 5:1 w/w), and a green zone was collected. The solvent was removed, and the residue was dissolved in benzene and passed again through an alumina column (eluent benzene). The mixture separated into two green zones containing, respectively, compounds **VI** and **V**.

Zinc *meso*-mono[(3-heptyloxy)phenoxy]tetrabenzoporphyrinate (V), yield 0.14 g (10%), dark green powder readily soluble in benzene, chloroform, acetone, and DMF. Electronic absorption spectrum (benzene), λ_{max}, nm (log ε): 626 (4.66), 579 (4.05), 446 (4.34), 427 (5.18), 403 (4.49). IR spectrum , ν, cm^{-1}: 2990, 1494, 1464, 1228, 1186. ^1H NMR spectrum, δ, ppm: 8.33–8.14 m (3H), 7.98–7.65 m (16H), 6.62–6.32 m (4H), 1.78–1.76 m (2H), 1.41–1.25 m (10H), 0.88 t (3H). Found, %: C 75.88; H 5.02; N 6.88. $C_{49}H_{38}N_4O_2Zn$. Calculated, %: C 75.43; H 4.91; N 7.18.

Zinc *meso-trans*-bis[(3-heptyloxy)phenoxy]tetrabenzoporphirinate (VI), yield 0.11 g (6%), dark green powder, readily soluble in benzene, chloroform, acetone, and DMF. Electronic absorption spectrum (benzene), λ_{max}, nm (log ε): 627 (4.76), 580 (4.13), 460 (4.22), 441 (4.72), 427 (5.22), 403 (4.51). IR spectrum , ν, cm^{-1}: 2993, 1499, 1460, 1225, 1181. ^1H NMR spectrum, δ, ppm: 8.34–8.20 m (2H), 7.94–7.68 m (16H), 6.63–6.30 m (8H), 1.79–1.76 m (4H), 1.43–1.28 m (20H), 0.89 t (6H). Found, %: C 75.99; H 5.96; N 5.01. $C_{62}H_{56}N_4O_4Zn$. Calculated, %: C 75.48; H 5.72; N 5.68.

Synthesis of metal-free porphyrins VII–VIII (*general procedure*). Complex **V–VI**, 0.1 g, was dissolved in 20 ml of chloroform, 10 ml of conc. HCl was added, and the mixture was stirred for 24 h at 20°C. The organic layer was washed with water, then with 10% NH_3, and again with water to pH 7. The solvent was removed, and the residue was dissolved in chloroform and passed through a column of activity grade II alumina (eluent chloroform), collecting the main green zone.

***meso*-Mono[(3-heptyloxy)phenoxy]tetrabenzoporphyrin (VII)**, yield 0.07 g (76%), dark green powder, mp 167°C, readily soluble in benzene, chloroform, acetone, and DMF. Electronic absorption spectrum (benzene), λ_{max}, nm (log ε): 677 (3.97), 663 (4.16), 614 (4.37), 603 (4.42), 567 (3.98), 443 (4.96), 430 (5.13), 417 (4.93), 389 (4.35). IR spectrum , ν, cm^{-1}: 3232, 2991, 1492, 1477, 1233, 1180. ^1H NMR spectrum, δ, ppm: 8.31–8.19 m (3H), 7.88–7.62 m (16H), 6.61–6.38 m (4H), 1.78–1.77 m (2H), 1.42–1.28 m (10H), 0.89 t (3H), –2.22 s (2H). Found, %: C 83.13; H 5.88; N 6.94. $C_{49}H_{40}N_4O_2$. Calculated, %: C 82.10; H 5.62; N 7.82.

***meso-trans*-Bis[(3-heptyloxy)phenoxy]tetrabenzoporphyrin (VIII)**, yield 0.06 g (65%), dark green powder, mp 153°C, readily soluble in benzene, chloroform, acetone, and DMF. Electronic absorption spectrum (benzene), λ_{max}, nm (log ε): 709 (3.74), 662 (4.30), 605 (4.41), 598 (4.41), 565 (4.00), 469 (4.33), 447 (4.46), 428 (4.96), 414 (4.92), 386 (4.44). IR spectrum , ν, cm^{-1}: 3239, 2999, 1487, 1455, 1275, 1177. ^1H NMR spectrum, δ, ppm: 8.35–8.28 m (2H), 7.90–7.71 m (16H), 6.68–6.25 m (8H), 1.73–1.71 m (4H), 1.45–1.28 m (20H), 0.89 t (6H), –2.15 s (2H). Found, %: C 80.91; H 6.48; N 5.89. $C_{62}H_{58}N_4O_4$. Calculated, %: C 80.67; H 6.33; N 6.07.

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