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The synthesis of tetramethyl-tetraphthalimidomethyl-phthalocyaninato zinc(II) (**6**) and tetramethyl-tetraaminomethyl-phthalocyaninato zinc(II) (**7**) is described.

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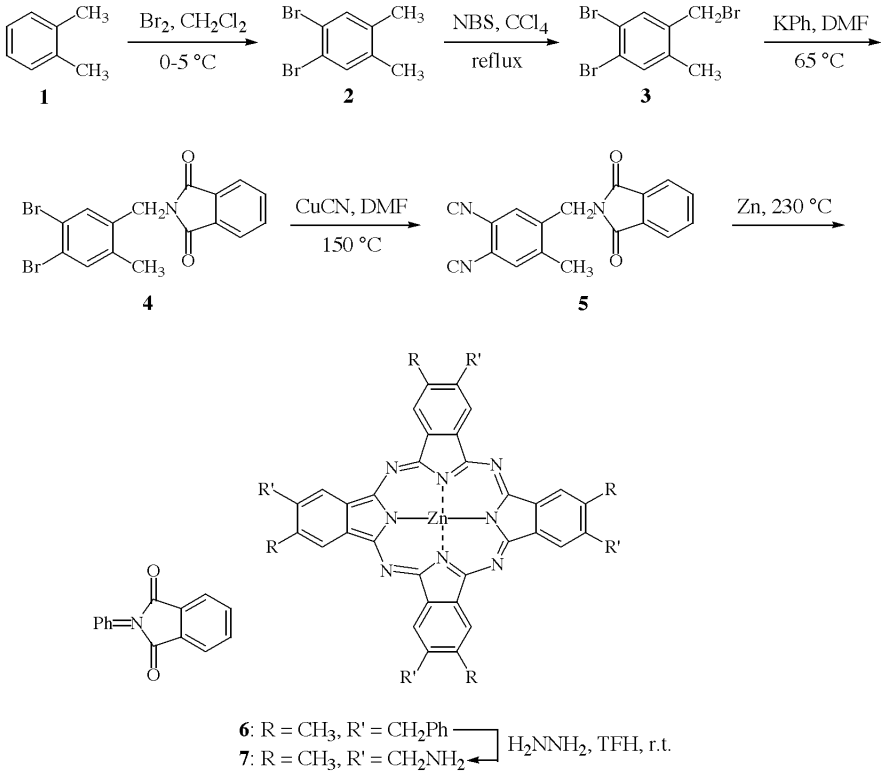
Photodynamic therapy (PDT) is a treatment based on the ability of certain photosensitizers to absorb light and, *via* an excited state, cause damage to the neoplastic area. If the photosensitizer concentrates selectively in the tumor, activation with light of appropriate wavelength induces its destruction [1,2].

In the last few years several photosensitizers have been studied for application in PDT [3]. Among them, phthalocyanines have been found to be promising dyes [4] with high molar extinction coefficients, red-shifted absorption and generation of singlet oxygen, the active species being responsible for the cytotoxic effect [5]. Zinc and aluminium phthalocyanines have been extensively studied due to their high fluorescence and triplet quantum yield, and their efficiency of singlet oxygen photoproduction [6,7].

As unsubstituted phthalocyanines are extremely insoluble in most common solvents, improving the water solubility of the dye has been the main reason for the synthesis of sulphonated derivatives [6,8]. However, a correlation has been found between amphiphilicity of the dye and its uptake in cells. The amphiphilic character is accentuated through the addition of sulphonated groups and alkyl groups [9,10], alkylamino groups and quaternary alkylammonium salts [11] as well as alkylhydroxy substituents [12].

Scheme 1



We regulated the amphiphilic character of zinc(II) phthalocyaninates by introducing alkyl and amino groups [13,14] to the macrocycle. We also reported their phototoxic properties, which showed the importance of the amphiphilicity of the dye, improving its cell association and photodynamic activity [15]. On the basis of the above results, we investigated the synthesis of two novel octasubstituted zinc(II) phthalocyanines whose amphiphilic properties were regulated by the introduction of alkylamino groups.

As shown in Scheme 1, the sequence begins with the reaction of *o*-xylene (**1**) with bromine to give 1,2-dibromo-4,5-dimethylbenzene (**2**). There are several reports for aryl bromination of *o*-xylene [16-22]. The synthesis reported by Y. Orihashi *et al.* [21] has been employed herein with minor modifications.

The reaction of compound **2** with *N*-bromosuccinimide in carbon tetrachloride afforded the tribromo derivative **3**. The reaction of **3** with potassium phthalimide in *N*,*N*-dimethylformamide gave compound **4**, that was subsequently reacted with copper (I) cyanide in the same solvent, to yield the required phthalonitrile **5**. A mixture in the order of 2% yield of 1-bromo-2-cyano-4-phthalimidomethyl-5-methylbenzene and 1-bromo-2-cyano-4-methyl-5-phthalimidomethylbenzene were obtained as side products. Phthalocyanine **6** was readily prepared by the cyclotetramisation of phthalonitrile **5** with powdered zinc at 230° [13,23]. Attempts to obtain **6** by employing 1,8-diazabicyclo[5,4,0]undec-7-ene in butanol and zinc acetate yielded only traces of compound **6** [7].

Phthalocyanine **6** was purified by chromatography, followed by recrystallization to attain 25% of the desired tetramethyl-tetraphthalimidomethyl-phthalocyaninato zinc (II). Treatment of **6** with hydrazine in tetrahydrofuran at room temperature [13,24] gave phthalocyanine **7** in quantitative yields.

With regard to the solubility of the new phthalocyanines, though tetrakis(1,1-dimethyl-2-phthalimido)-ethylphthalocyaninato zinc (II) [13] is soluble in almost all organic solvents, **6** shows the influence of a minor lipophilicity owing to the presence of both a methyl and a methylene chain. On the other hand, phthalocyanine **7** is insoluble in tetrahydrofuran and soluble in dimethyl sulfoxide, *N*,*N*-dimethylformamide and pyridine.

Phthalocyanine **6** and **7** were characterized by their uv-visible spectra. Both compounds **6** and **7** showed the Soret band at λ_{max} 347 nm and the Q band at 676 nm in tetrahydrofuran $\varepsilon = 134{,}000\ M^{-1}\ cm^{-1}$ ($c = 1 \times 10^{-7}\ M$) and 686 nm in dimethyl sulfoxide $\varepsilon = 40{,}000\ M^{-1}\ cm^{-1}$ ($c = 8 \times 10^{-8}\ M$) respectively. The low extinction coefficient and the non-linearity of the Lambert-Beer law obtained is evidence that **7** remains aggregated even at low concentrations (*i.e.* $8 \times 10^{-8}\ M$). Photophysical and photobiological studies of compounds **6** and **7** are in progress.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. The ^{1}H nmr and ^{13}C nmr were recorded on a Bruker MSL 300 spectrometer. The ^{1}H nmr of phthalocyanine **7** was recorded on a Bruker AM 500. Mass Spectra were obtained with a TRIO 2 (electronic ionization 70 eV) spectrometer. Phthalocyanines FAB-ms were measured using 3-nitrobenzylalcohol as a matrix for **6** and glycerol for **7**, with a ZAB SEQ (VG, Fisons) spectrometer. Electronic absorption spectra were determined using a Shimadzu UV-160A spectrophotometer. Infrared spectra were performed with an FT-IR Nicolet 510P spectrometer. Microanalyses were performed using a Carlo Erba EA 1108 elemental analyzer.

The silica gel used in column chromatography was tlc Kiesegel (Merck). *N*,*N*-Dimethylformamide was dried over 3 Å molecular sieves during 72 hours, filtered and freshly distilled [25] before using.

1,2-Dibromo-4-bromomethyl-5-methylbenzene (**3**).

To a solution of 1.18 g (4.47 mmol) of 1,2-dibromo-4,5-dimethylbenzene in 17 mL of carbon tetrachloride, 0.816 g (4.58 mmol) of *N*-bromosuccinimide was added. The mixture was stirred under reflux during 16 hours. After cooling, the precipitate was filtered, washed with carbon tetrachloride and the filtrate evaporated *in vacuo* to eliminate the solvent. The residue was dissolved in a small volume of hexane and filtered through a tlc silica gel column packed and pre-washed with the same solvent. The elution fractions containing **3** were monitored using tlc. The solvent was evaporated to dryness affording a thick oil 0.540 g (35%); ms: m/z 343 (M^+, 2.47%), 345 ($M^+ + 2$, 1.47%), 341 ($M^+ - 2$, 1.90%), 263 (100%); ^{1}H nmr (deuteriochloroform): δ 2.34 (s, 3H, CH_3), 4.38 (s, 2H, CH_2), 7.45, 7.54 (s, s, 2H, Ar); ir (film CCl_4): 2359, 1723, 1466, 1350, 1212, 1123, 905, 721, 652, 565 cm^{-1}.

Anal. Calcd for $C_8H_7Br_3$: C, 28.02; H, 2.06. Found: C, 28.10, H, 2.20.

1,2-Dibromo-4-phthalimidomethyl-5-methylbenzene (**4**).

A mixture of 1.08 g (3.15 mmol) of **3**, 0.582 g (3.16 mmol) of potassium phthalimide and 30 mL of *N*,*N*-dimethylformamide was stirred at 65° during 7 hours. The mixture was poured over ice-water, the precipitate was filtered, dried and crystallized from methylene chloride-hexane, 1.140 g (89% yield), mp 172-173°; ms: m/z 409 (M^+, 26.57%), 411 ($M^+ + 2$, 11.66%), 407 ($M^+ - 2$, 13.07%), 160 (100%); ^{1}H nmr (deuteriochloroform): δ 2.42 (s, 3H, CH_3), 4.76 (s, 2H, CH_2), 7.43, 7.48 (s, s, 2H, Ar), 7.82 (m, 4H, phthalimide); ir (potassium bromide): 1713, 1479, 1420; 1395, 1364, 1113, 951, 725, 713 cm^{-1}.

Anal. Calcd. for $C_{16}H_{11}NBr_2O_2$: C, 46.97; H, 2.71; N, 3.42. Found: C, 47.00; H, 2.85; N, 3.22.

1,2-Dicyano-4-phthalimidomethyl-5-methylbenzene (**5**).

A solution of 1.07 g (2.62 mmol) of **4** and 1.00 g cuprous cyanide in *N*,*N*-dimethylformamide (35 mL) was heated at 150° during 9 hours under nitrogen. The solution adquired a light brown color. After cooling, it was poured into a concentrated ammonia solution (35 mL) and stirred during 4 hours. The solid residue obtained was separed by centrifugation, washed twice with cold water and then dried. The residue was dissolved in methylene chloride and filtered through a tlc silica gel column.

After evaporation of the solvent the solid residue R_f 0.3 was recrystallized from methylene chloride-hexane, 0.197 g (25%), mp 225-226°; ms: m/z 301 (M^+, 100%), 160 (22.77%); ^{1}H nmr (deuteriochloroform): δ 2.60 (s, 3H, CH_3), 4.88 (s, 2H, CH_2), 7.63, 7.64 (s, s, 2H, Ar), 7.80 (m, 4H, phthalimide); ir (potassium bromide): 2238, 1773, 1715, 1420, 1397, 1384, 1356, 1335, 1111, 953, 727, 715, 635, 534 cm^{-1}.

Anal. Calcd. for $C_{18}H_{11}N_3O_2$: C, 71.75; H, 3.68; N, 13.95. Found: C, 71.68; H, 3.81; N, 13.74.

The ^{13}C nmr spectrum of **5** shows four new signals at δ 113.65, 113.65, 114.85, 115.18 corresponding to the two nitriles and the two adjacent aromatic carbons, instead of the signals at δ 121.89 and 123.58 observed in **4**.

2,9,16,23-Tetramethyl-3,10,17,24-tetraphthalimidomethyl-phthalocyaninato Zinc (II) (**6**).

A mixture of 0.100 g (0.33 mmol) of **5** and 0.050 g of powdered zinc was heated at 230° in a closed vessel during 16 hours. It was allowed to cool, methylene chloride (500 mL) was added and the remaining zinc filtered under suction. The solution was evaporated *in vacuo*, leaving a green solid. This residue was dissolved in methylene chloride and filtered through a tlc silica gel column packed and pre-washed with the same solvent. The band eluted corresponded to compound **5**. The title dye was eluted with methylene chloride-acetone-methanol (5:0.5:0.25). After evaporation, the deep green solid was recrystallized from methylene chloride-hexane, 0.026 g (25%); FAB-ms: m/z 1269 (M^+); ^{1}H nmr (deuteriochloroform): δ 2.63 (s, 12H, CH_3), 4.91 (s, 8H, CH_2), 7.61, 7.68 (s, s, 8H, Ar), 7.86 (m, 16H, phthalimide); ir (potassium bromide): 1771, 1716 (phthalimide CO), 1395, 1343, 1110, 951, 716 cm^{-1}.

Anal. Calcd. for $C_{72}H_{44}N_{12}O_8Zn$: C, 68.06; H, 3.49; N, 13.23. Found: C, 68.38; H, 3.61; N, 13.39.

2,9,16,23-Tetraaminomethyl-3,10,17,24-tetramethylphthalo-cyaninato Zinc (II) (**7**).

A solution of 0.056 g of **6** and 0.4 mL of hydrazine in 20 mL of tetrahydrofuran was stirred during 17 hours at room temperature. After evaporation of the solvent, the residue was sublimated at 140° and 50 microns to eliminate the phthalhydrazide obtained. The residue was dissolved in a 0.1 *M* hydrochloric acid solution and then adjusted to pH 7 with a 0.1 *M* sodium hydroxide solution. After 18 hours the fine green powder was centrifuged and dried to give 0.033 g of the titled compound (quantitative yield) . FAB-ms: m/z 841(M^++ glycerol); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.55 (br, 12H, CH_3), 4.85 (br, 8H, CH_2), 7.82, 8.03 (brs, brs, 8H, Ar), 9.23 (br, 8H, NH_2); ir (potassium bromide): 3419, 3421 (NH_2), 2924, 1646, 1496, 1081, 793 cm^{-1}.

Anal. Calcd. for $C_{40}H_{36}N_{12}Zn$: C, 64.04; H, 4.84; N, 22.41. Found: C, 63.78; H, 4.86; N, 22.50.

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