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Novel photosensitizers of mitochondrial localization

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Introduction

Photodynamic therapy (PDT) has been developed in recent years as a strategy for tumor treatment (Mody and Pandey, 2001). This technique uses a photosensitizer that is not toxic until it is irradiated with light of appropriate wavelength (Henderson and Dougherty, 1992; Foultier *et al.*, 1994), and consequently, the photosensitizer generates a toxic species usually singlet oxygen, thus resulting in tumor death.

The subcellular localization of many photosensitizers and their response to light activation indicates that mitochondria plays an important role in photodynamic cell death (Morgan and Oseroff, 2001).

It has been postulated that cationic photosensitizers are located in mitochondria, depending on the extent of lipophilicity and on charge delocalization (Chen, 1988). Some cationic photosensitizers (Huglin *et al.*, 1995), *e.g.*, cationic porphyrins (Cernay and Zimmermann, 1996), revealed their localization in other cell compartments. Besides, addition they showed the disadvantage of a low molar extinction coefficient in the area of light absorption by skin (about 630 nm), which is unfavorable for the photodynamic effect.

Consequently, higher photosensitizer concentrations should be used, which increases dye toxicity, limiting its use besides producing low values (< 10%) of quantum yield of singlet oxygen. Little attention has been paid so far to obtaining cationic-lipophilic zinc (II) phthalocyaninates (Dummin *et al.*, 1997) as a structural photosensitizer improvement for its incorporation and localization in strategic cell centers.

The synthesis of cationic-lipophilic zinc (II)-chelated phthalocyaninates is aimed to obtain a photosensitizer with a long life time of the triplet state, and tehrefore, an effective generation of singlet oxygen, responsible for the PDT effect (Fernández *et al.*, 1996, 1997). Cationic colourants with short aliphatic chains have a low lipophilicity and are located in the lysosomes, moreover cationic dyes with aliphatic chains of high lipophilicity are accumulated in the mitochondria.

Methodology

Obtaining phthalocyanines from *o*-dinitriles has proved to be the most efficient synthesis, despite the difficulties of the nucleophilic substitution involved in obtaining the intermediate *o*-dinitriles (Fernández *et al.*, 1995; Hu *et al.*, 1998; Rodríguez *et al.*, 2001). The synthetic strategy shown in Scheme 1 was the most convenient for obtaining *o*-dinitrile, whose tetramerization will lead to zinc (II) phthalocyaninate. Subsequent reduction with diboranes and quaternization with methyl iodide will allow to obtain the desired quaternary amine (Strassert *et al.*, 2006).

To obtain the target compounds classical laboratory techniques of organic synthesis were used. The intermediates were purified by medium pressure chromatography. All compounds were characterized by spectroscopic methods: ^{1}H-NMR and ^{1}H-NMR, mass spectrometry, IR spectroscopy.

Results

With the aim of obtaining a phthalonitrile, a key intermediary for the synthesis of these colourants a synthetic strategy has been designed, which is outlined as: 1,2-dibromo - 4-aminomethyl-5-methylbenzene (**2**) was obtained from 1,2-dibromo-4-phthalimidomethyl-5-methylbenzene (**1**), whose treatment with butyroyl chloride gave the amide **3**. The reduction of **3** with diborane led to the amine **4**, which treated with butyroyl chloride gave the tertiary amide **5**. The treatment of **5** with cuprous cyanide allowed to obtain the dinitrile **6** key intermediary for the synthesis of the proposed phthalocyanine.

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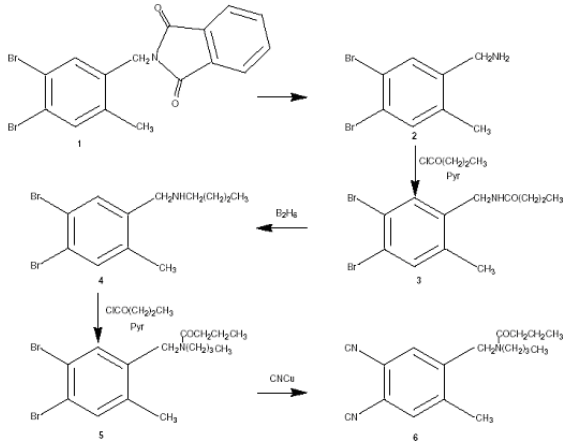

Conclusions

The intermediate **6**, which is precursor of zinc (II) phthalocyaninate, was obtained with a 60% total yield.

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