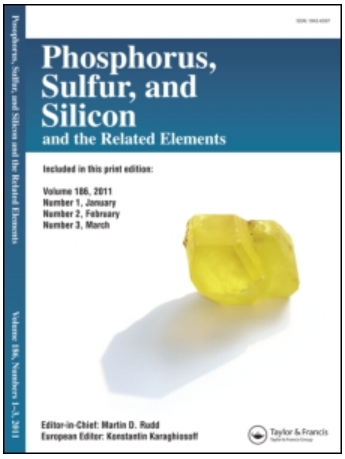

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Moura, João C. V. P. , Oliveira-Campos, Ana M. F. and Griffiths, John(1997) 'Synthesis and Evaluation of Phenothiazine Singlet Oxygen Sensitising Dyes for Application in Cancer Phototherapy', Phosphorus, Sulfur, and Silicon and the Related Elements, 120: 1, 459 — 460
To link to this Article: DOI: 10.1080/10426509708545597
URL: http://dx.doi.org/10.1080/10426509708545597

Phosphorus, Sulfur, and Silicon, 1997, Vol. 120 & 121, pp. 459–460
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Synthesis and Evaluation of Phenothiazine Singlet Oxygen Sensitising Dyes for Application in Cancer Phototherapy

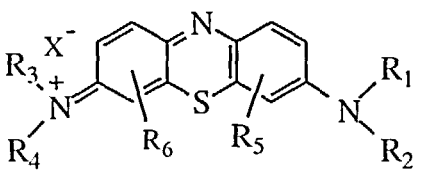
JOÃO C.V.P MOURA[a], ANA M.F. OLIVEIRA-CAMPOS[a] and JOHN GRIFFITHS[b]
[a]*Departamento de Química, Universidade do Minho, 4710 Braga, Portugal*
[b]*Department of Colour Chemistry, University of Leeds, Leeds, UK*

The synthesis of phenothiazine carboxylic dyes for PDT treatment of cancer is discussed.

The photodynamic therapeutic treatment of cancer (PDT) is now a well established clinical treatment for certains kinds of cancer, using a photosensitizing dye administered by injection together with laser light. Selective accumulation of the dye in the tumour cells can occur, and on exposure of the tumour area to light the dye generates singlet oxygen which results in destruction of the host cell.

The technique of PDT is developing rapidly, and there is a need for improved photosensitising dyes to enable a wider range of tumour types to be treated. Research in this area is intense, but is mainly directed towards porphyrin-type molecules and phthalocyanines. The thiazine dyes are also promising candidates but they have received relatively little attention, possibly because the simpler dyes (eg. Methylene Blue) do not penetrate cells readily. However derivatives of the same type containing carboxylic acid groups, such as (e, f, g) may be reacted with proteins which are known to have excellent penetrating properties.

All of the compounds were obtained by a known method[1]. Oxidation of phenothiazine by iodine in chloroform gave phenothiazin-5-ium periodide. Subsequent treatment with an *N,N*-dialkylamine in methanol gave the



All R_i=H and X=Cl, except stated otherwise

a) R_1=R_2=R_3=Me
b) R_1=R_2=Et; R_3=Me
c) R_1=R_2=R_3=Me, R_4=CH_2CO_2Et, R_5 or R_6=I
d) R_1=R_2=Et, R_3=Me, R_4=CH_2CO_2Et, R_5 or R_6=I
e) R_1=R_3=Me, R_2=R_4=$(CH_2)_3CO_2H$
f) R_1=R_2=R_3=Me, R_4=$(CH_2)_3CO_2H$
g) R_1=R_2=Et, R_3=Me, R_4=$(CH_2)_3CO_2H$
h) R_1=Et, R_3=R_4=Me, X=I

3-(dialkylamino)phenothiazin-5-ium triiodide. This was followed by treatment with sarcosine or sarcosine ethyl ester. When sarcosine was used, decarboxymethylation occurred (a, b). When it was replaced by its ethyl ester one iodine atom entered the ring (c, d). But the carbonyl group was present as shown by IR absorption and mass spectrometry.

Decarboxymethylation also occured when another method was followed[2]. Compound (h) was obtained from *N*-methyl-*N*-phenylglycine in 66% yield and showed no C=O (IR, ^{13}C NMR) and a correct elemental analysis for $C_{16}H_{18}N_3SCl_3Zn.2H_2O$. However it showed a M^+ ion at 343 probably due to contamination with the carboxylated product.

Dye	Yield(%)	$\bar{\nu}$ (cm^{-1}) (KBr disc)	M^+(%) (CI)	λ_{max}(nm) (MeOH)	δ_C/ppm
a	50	no C=O	271 (66)	635	–
b	49	no C=O	299 (64)	638	no C=O
c	61	1740	483 (4)	631	–
d	60	1741	511 (10)	622	–
e	58	1718	428 (15)	654.8	–
f	50	1714	356 (55)*	650	–
g	58	1713	-	646.4	174 (C=O), 155 and 149 (C-NR_2)

* mass spectrum determined by ES

To prevent decarboxymethylation 4-(methylamino)butyric acid was used[1] and compounds (e, f, g) were obtained in low yields.

Another approach[3] which is now in course, is based on a *N*-propionyl side chain.

We thank JNICT (IBQF-UM) and PRAXIS XXI for a grant (BPD-4159-94) to J. Moura.

REFERENCES

1. L. Strekowski *et.al.*, *J. Heterocycl. Chem.*, **30**, 1693 (1993).
2. H. E. Fierz-David and L. Blangey, "Fundamental Processes of Dye Chemistry", Intersc. Pub. Inc., NY, 1949, 311.
3. H. Masuya *et.al.*, EP 0510668 A2 (1992).