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Synthesis and Evaluation of Phenothiazine Singlet Oxygen Sensitising Dyes for Application in Cancer Phototherapy

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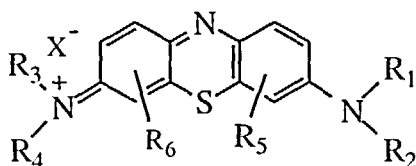
The synthesis of phenothiazine carboxylic dyes for PDT treatment of cancer is discussed.

The photodynamic therapeutic treatment of cancer (PDT) is now a well established clinical treatment for certain 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 method¹. Oxidation of phenothiazine by iodine in chloroform gave phenothiazin-5-ium periodide. Subsequent treatment with an *N,N*-dialkylamine in methanol gave the

All R₁=H and X=Cl, except stated otherwise



- a) R₁=R₂=R₃=Me
- b) R₁=R₂=Et, R₃=Me
- c) R₁=R₂=R₃=Me, R₄=CH₂CO₂Et, R₅ or R₆=I
- d) R₁=R₂=Et, R₃=Me, R₄=CH₂CO₂Et, R₅ or R₆=I
- e) R₁=R₃=Me, R₂=R₄=(CH₂)₃CO₂H
- f) R₁=R₂=R₃=Me, R₄=(CH₂)₃CO₂H
- g) R₁=R₂=Et, R₃=Me, R₄=(CH₂)₃CO₂H
- h) R₁=Et, R₃=R₄=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 occurred when another method was followed². Compound (h) was obtained from *N*-methyl-*N*-phenylglycine in 66% yield and showed no C=O (IR, ¹³C NMR) and a correct elemental analysis for C₁₆H₁₈N₃SCl₃Zn.2H₂O. 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 used¹ and compounds (e, f, g) were obtained in low yields.

Another approach³ which is now in course, is based on a *N*-propionyl side chain.

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