

Dye-Sensitized Photooxidation of Chlorpromazine

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Chlorpromazine efficiently quenches singlet oxygen ($^1\text{O}_2$) with a $k_q = 3.5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.The major result of the chemical interaction between these two species is the cleavage of the *N*-side chain.*J. Heterocyclic Chem.*, 14, 355 (1977).

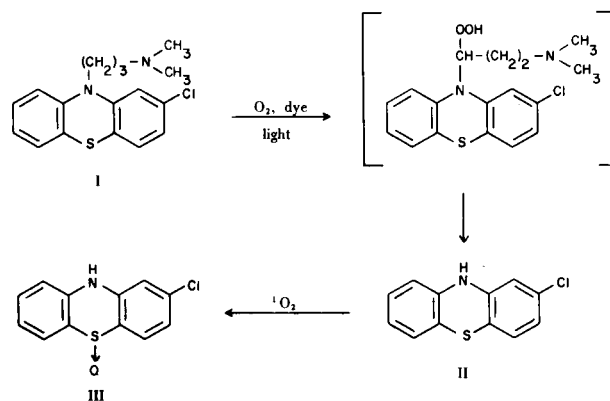
Sir:

Substituted phenothiazines exhibit an extremely broad spectrum of pharmacological properties, but are primarily employed in psychopharmacology (1). Allergic skin reactions and ocular opacity are known to occur during phenothiazine treatment, which suggest a photochemical-induced modification *in vivo*. In this respect the photooxidation reaction could shed some light on the chemical process at the molecular level responsible for this effect.

Herein we report the results of the reaction between chlorpromazine (I) and singlet molecular oxygen. A solution of I (500 mg.) in methanol (500 ml.) containing 500 mg. of insoluble dye sensitizer (Rose Bengal attached to Amberlite IRA-400 (2)) was irradiated (3) under continuous oxygen flushing and magnetically stirred for 5 hours. The sensitizer was filtered off and the solvent was removed under reduced pressure. The residue was separated by preparative layer chromatography (Merck PSC-Fertig-platten Kieselgel 60F 254, eluted by a mixture of benzene, methanol, ammonium hydroxide, 6:14:0.1) to yield 2-chlorophenothiazine 5-oxide (III) (80 mg., 20% yield, m.p. 260° dec. (4)) in addition to unreacted I and minute amounts of unidentified materials. Shorter irradiation times permitted the isolation of 2-chlorophenothiazine (II) (m.p. $194\text{--}195^\circ$ (5)) as well. This observation suggests that the first reaction step entails *N*-side chain cleavage followed by the photooxidation at the sulfur atom. It was noted that chlorpromazine *S*-oxide and *N*-oxide were formed only in very small amounts if at all. Spots of the corresponding R_f value could be discerned by

the analyses of the reaction mixture, but since the amounts actually formed were minute, isolation and identification were precluded. Similar results were obtained when methylene blue or rose bengal served as the sensitizer in a homogeneous solution, but the chromatographic separation was complicated by the presence of the dye in the reaction mixture. Interestingly, a chain cleavage similar to that observed in the photooxidation of I occurs during the *in vivo* metabolism of phenothiazine drugs (6).

Control experiments showed that the simultaneous presence of sensitizer, light and oxygen were required for reaction. In addition, a singlet oxygen mechanism for this reaction was indicated by the fact that when a degassed methanolic solution of methylene blue or rose bengal ($1.1 \times 10^{-5} \text{ M}$) was flashed (7) in the presence of I ($5 \times 10^{-4} \text{ M}$) the decay curves were practically superimposable on those obtained in its absence, which



excluded an excited sensitizer-chlorpromazine interaction.

The dealkylation of tertiary amines during photo-oxidation has a few precedents. There is, however, no unanimity of opinion regarding the mechanistic details of this reaction (8-11). The reaction may proceed by the prior formation of an α -hydroperoxy amine which subsequently dissociates to 2-chlorophenothiazine.

Under reaction conditions similar to that described for I, 10-methylphenothiazine was exclusively converted to the corresponding 10-methylphenothiazine *s*-oxide (m.p. 189-190° (12) 46% yield). No demethylated product could be detected.

The ability of a few phenothiazines to quench singlet oxygen was calculated from the extent of the inhibition of singlet oxygen (Δ_p) peroxidation of rubrene by a technique previously described (13). The results of the quenching experiments are summarized in Table I.

Table I

Quenching Rates of Singlet Oxygen by Phenothiazines

	k_q ($M^{-1} s^{-1}$) (a)
Phenothiazine	4.2×10^7
10-Methylphenothiazine	$\leq 1.2 \times 10^6$
Chlorpromazine	3.5×10^7
Phenoxazine	1.0×10^7

(a) The measurements were performed in a mixture of bromobenzene-methanol (2:1). The values employed for calculations have been previously compiled (I. Rosenthal and A. Frimer, *Photochem. Photobiol.*, **23**, 209 (1976)). Under identical photo-lyses conditions k_q was virtually independent on $[R_o]$ (2; 1.5; $1 \times 10^{-4} M$) or $[Q]$ (1; 1.5; $2 \times 10^{-3} M$).

These values represent the sum of physical and chemical quenching (14) of singlet oxygen.

The inhibition observed is most probably due to quenching of singlet oxygen rather than that of the rubrene excited states. Thus, fluorescence intensities of rubrene solutions (λ emission = 560 nm) remained unchanged when phenothiazines were added (rubrene $10^{-4} M$, phenothiazine $10^{-3} M$). Since the location of the triplet level of rubrene is not known from spectroscopic measurements, emission studies cannot exclude the possibility that the rubrene triplet might be quenched. However, rubrene with an energy of the excited singlet state of 51 Kcal/mole, cannot transfer its excitation energy from the triplet state to acceptors whose triplets lie around 60 Kcal/mole (I, 57.2 (15); phenothiazine 61 (16)).

It was noted that the quenching rate of 10-methylphenothiazine is much lower than the unsubstituted analog. This is despite the fact that the quenching ability

of amines has been reported to increase with substitution at the nitrogen (17). Nevertheless, our results can be readily understood in terms of the steric effect resulting from the substitution at position 10 in phenothiazine. In *N*-substituted phenothiazines the participation of the nonbonding electron pair of nitrogen in the extended π system of the molecule is diminished due to the change from an "intra" to an "extra" configuration. Thus the energy of the highest filled molecular orbital is lowered and the susceptibility to electrophilic attack decreases (18). The higher quenching rate obtained for chlorpromazine can be attributed to the influence of the second nitrogen atom in the side chain. The ability of tertiary amines to efficiently quench singlet oxygen is well documented (19).

Acknowledgement.

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thiazine in methanol yielded phenothiazine 5-oxide and phenothiazone-3 in ratio 8:1. Similarly, phenoxazine was converted to phenoxazone-3. Neither reaction could be performed to high conversions since prolonged irradiation yields several minor unidentified products which turn the mixture black and inhibit further reaction.

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