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Photodecomposition of some substituted phenothiazines

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Phototoxicity has been noted as a side effect in chlorpromazine therapy for a number of years (Stewart et al 1974) and the photochemical breakdown of chlorpromazine has been studied extensively. Early investigators noted that phenothiazines were oxidized in u.v. light to yield the sulphoxide (Felmeister & Discher 1964). More recently Grant (1974) observed that chlorpromazine was reduced to promazine and also underwent substitution to the hydroxy compound upon illumination in aqueous solution. Huang & Sands (1964, 1967) isolated and identified a number of photodecomposition products of chlorpromazine including the *N*-oxide, the sulphoxide, promazine, 2-hydroxypromazine, and a dimer and polymer of chlorpromazine.

Ljunggren & Möller (1977a) have investigated the relative phototoxicities of a series of phenothiazines and related tricyclic drugs in an attempt to illucidate the molecular characteristics attributable to phototoxic activity. They found that the phenothiazine ring system was essential for phototoxic activity and that chloro-substituted compounds displayed by far the greatest activity. Thin layer chromatography of the products of chlorpromazine irradiation indicated the presence of the dechlorinated derivative promazine and the oxidation product chlorpromazine sulphoxide (Ljunggren & Möller 1977b). This communication reports the effects of substituent alteration on the photodecomposition of phenothiazines in order to explain the observed differences in phototoxicity found in phenothiazines.

Phenothiazine, 2-chlorophenothiazine and 2-trifluoromethylphenothiazine were purchased from the Aldrich Chemical Company Inc. 2-Bromo, 2,3-dichloro, 2-methoxy, 2-methyl and 2-nitrophenothiazines were prepared by synthesis.

Solutions of the phenothiazines in methanol (10 mg ml^{-1}) were photo-irradiated for 3 h by exposure to u.v. light using an Allen type A409 fixed wavelength (365 nm) u.v. lamp. The solutions were examined by t.l.c. on silica gel using ether–light petroleum (b.p. 40–60 °C) (1:1) as developing solvent. The spots were visualized by exposure to iodine vapour.

As can be seen from Table 1, only the 2-chloro, 2-methyl and 2-methoxyl compounds photodecompose to any great extent under these conditions. Methanolic solutions (100 mg ml^{-1}) of these three compounds were photo-irradiated for 16 h and the decomposition products separated by preparative t.l.c. on silica gel plates (20 × 20 cm). The different bands were scraped off the plates, eluted from the silica with acetone, the acetone solutions evaporated to dryness in a stream of nitrogen, and the different fractions analysed by mass spectroscopy (Table 2).

Mass spectral analysis of the photodecomposition products of 2-chloro-, 2-methyl- and 2-methoxyphenothiazines showed that the 2-chloro-compound gave rise to the dechlorinated product, phenothiazine, a dimeric product and 2-chlorophenothiazine sulphoxide. 2-Methylphenothiazine gave rise to a dimeric product and 2-methylphenothiazine sulphoxide while 2-methoxyphenothiazine gave 2-methoxyphenothiazine sulphoxide as sole degradation product. The production of the three sulphoxides was further confirmed by comparison with authentic samples of the three sulphoxides on t.l.c. and u.v. spectroscopy (Table 3).

In general, 2-substituted phenothiazines photodecompose to yield the corresponding sulphoxide. The 2-chloro-derivative, however, can also lose the 2 substituent via free radical formation (Sames 1973)

$$ArCl \xrightarrow{\text{u.v.}} Ar\cdot + Cl\cdot \longrightarrow ArH + HCl$$

Such free radicals are believed to be responsible for phototoxic reactions (Harber et al 1967) explaining the high phototoxicity of the 2-chlorophenothiazines as

Table 1. R_F values for phenothiazines before and after u.v. irradiation.

Compound		R_F before irradiation	R_F after irradiation
	phenothiazine	0·72	0·72
2-Chloro	,,	0·786	0·786, 0·714, 0·528 (pink), 0·243
2,3-Dichloro	,,	0·629	0·629
2-Bromo	,,	0·672	0·672
2-Nitro	,,	0·175	0·175
2-Trifluoromethyl	,,	0·286	0·286, 0·70 (trace), 0·30 (trace)
2-Methyl	,,	0·70	0·70, 0·528 (pink), 0·22
2-Methoxy	,,	0·636	0·66, 0·218

Table 2. Mass spectral analysis of phenothiazine photodecomposition products.

Fraction	Peaks m/z (Relative abundance)
2-Chlorophenothiazine (Fraction 1. R_F 0·786)	235 (36%), 233 (100%), 201 (36%), 198 (76%), 166 (24%)
2-Chlorophenothiazine (authentic)	235 (82%), 233 (75%), 201 (19%), 198 (66%), 166 (9%)
2-Chlorophenothiazine (Fraction 2. R_F 0·714)	198 (58%), 166 (10·6%)
Phenothiazine (authentic)	198 (100%), 166 (52%)
2-Chlorophenothiazine (Fraction 3. R_F 0·528)	464 (15%), 460 (68%), 448 (20%), 446 (43%), 430 (23%), 424 (46%), 235 (41%), 233 (100%), 198 (73·5%)
2-Chlorophenothiazine (Fraction 4. R_F 0·243)	249 (17%), 235 (39%), 233 (100%), 198 (53%)
2-Chlorophenothiazine sulphoxide (authentic)	249 (57%), 235 (29%), 233 (68%), 198 (31%)
2-Methylphenothiazine (Fraction 1. R_F 0·70)	213 (100%), 212 (28·5), 181 (29%), 180 (86%), 167 (20%)
2-Methylphenothiazine (authentic)	213 (100%), 212 (75·5%), 181 (18·5%), 180 (48%), 167 (12%)
2-Methylphenothiazine (Fraction 2. R_F 0·528)	424 (60%), 213 (100%), 212 (41%), 181 (22%), 180 (52%), 167 (13%)
2-Methylphenothiazine (Fraction 3. R_F 0·22)	229 (63%), 227 (72%), 213 (48%), 212 (19%), 199 (79%), 198 (41%)
2-Methylphenothiazine sulphoxide (authentic)	229 (100%), 213 (55%), 198 (32%)
2-Methoxyphenothiazine (Fraction 1. R_F 0·66)	229 (62%), 214 (35%), 186 (34%)
2-Methoxyphenothiazine (authentic)	229 (100%), 214 (42%), 186 (57%)
2-Methoxyphenothiazine (Fraction 2. R_F 0·218)	245 (70%), 229 (100%), 214 (15%), 186 (10%)
2-Methoxyphenothiazine sulphoxide (authentic)	245 (100%), 229 (52%), 214 (20%), 186 (19%)

Table 3. T.l.c. and u.v. spectral data for phenothiazine sulphoxides.

Compound	R_F (solvent as Table 1)	u.v. peaks (nm)
2-Chlorophenothiazine (Fraction 4)	0·243	208, 235, 248, 275, 308
2-Chlorophenothiazine sulphoxide	0·283	208, 235, 248, 275, 308
2-Methylphenothiazine (Fraction 3)	0·22	205, 230, 243, 270, 300
2-Methylphenothiazine sulphoxide	0·21	215, 240, 270, 300
2-Methoxyphenothiazine (Fraction 2)	0·218	240, 250, 280, 320
2-Methoxyphenothiazine sulphoxide	0·22	240, 260, 302, 333

opposed to other variously substituted phenothiazines found by Ljunggren & Moller (1977a).

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