Studies on the Oxidation of Phenothiazine Derivatives

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The sulfoxides of pharmacologically active phenothiazine derivatives have been widely studied as biological transformation products in body fluids and tissue (1,2). The majority of the work has been devoted to the development of analytical techniques for detection of these products (2,3,4).

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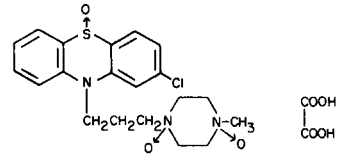
The synthesis of sulfoxides is usually effected by oxidation with equimolar quantities of aqueous hydrogen peroxide in alcoholic solution (5,6). Oxidation with two moles of peroxide in alcoholic solution produces the *N,S*-dioxide; whereas, in glacial acetic acid containing sulfuric acid, the sulfone is obtained (7).

We were interested in preparing additional quantities of 4-[3-(2-chloro-10-phenothiazinyl)propyl]-1-methylpiperazine 5-oxide. The compound has been prepared (8) by alkylation of 2-chlorophenothiazine 5-oxide with 1-methyl-4-(3′-hydroxypropyl)piperazine but we did not feel this to be a suitable procedure. We had prepared the compound previously as the dihydrochloride salt (5) but the procedure proceeded in low yield and the product was difficult to crystallize. We have now developed a simple modification of this procedure which provided us with the stable crystalline free base.

The acetate salt, prepared *in situ*, of 4-[3-(2-chloro-10-phenothiazinyl)propyl]-1-methylpiperazine, prochlorperazine, in methanol was heated with aqueous 30% hydrogen peroxide for 18 hours. Concentration of the reaction mixture, neutralization with excess ammonium hydroxide and cooling afforded a 37% yield of 4-[3-(2-chloro-10-phenothiazinyl)propyl]-1-methylpiperazine 5-oxide as a crystalline solid.

Studies were initiated to determine whether the yield could be improved and to evaluate the effect of additional hydrogen peroxide. A thin layer chromatographic system was used to follow the course of the reaction. It was noted that as additional peroxide was added the amount of starting material decreased and the amount of 5-oxide was simultaneously reduced. The concentration of an unknown compound at the origin also increased and we undertook an investigation to establish the identity of this material.

An alcohol solution of prochlorperazine acetate was heated at the reflux temperature while aqueous hydrogen peroxide was added in portions. After six hours the starting material had essentially disappeared. The reaction mixture was concentrated under reduced pressure and treated with oxalic acid. The solids which were isolated were further purified by heating with boiling methanol to provide a 65% yield of material which was shown to be the oxalate salt of 2-chloro-10[3-(1-methyl-*N,N′*-bisoxido-4-piperazinyl)propyl]phenothiazine 5-oxide (I).



The structure of I was established from its ^{13}C-nmr spectrum. Unequivocable assignments were made when the spectrum was compared to models of sulfoxide, sulfone, and their respective dechlorinated analogs containing the 3-dimethylamino-*n*-propyl side chain in place of the 3-(1-methyl-*N,N′*-bisoxido-4-piperazinyl)-*n*-propyl side chain. A summary of the ^{13}C aromatic assignments of I and the sulfoxide model is shown in Table I.

Infrared analysis also showed the presence of the sulfoxide moiety, γ max at 1030 cm^{-1}. This is in agreement with data reported by Warren, *et al.* (9). However, the analysis of the infrared spectrum did not allow for the differentiation of the structure of I from the sulfoxide mono *N*-oxide model.

A proton magnetic resonance evaluation was shown to be inapplicable in distinguishing I from the model sulfone analog.

Further confirmation for the structure of I was obtained from its CHN analysis. Although, the reported CHN analysis would agree with structure for a sulfone mono *N*-oxide, oxalate, salt, this was precluded from its ^{13}C-nmr spectral assignments. In addition, the CHN analysis also did not allow for the presence of the sulfone di-*N*-oxide, oxalate salt (Calcd.: C, 47.36; H, 4.33; N, 7.53.).

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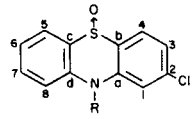
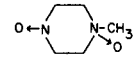
Table I



C#	R (a) $-CH_2CH_2CH_2N(CH_3)_2$	R (b) $-CH_2CH_2CH_2$		△
a	139.1	140.2		1.08
d	137.9	139.7		1.76
2	137.4	138.1		0.77
7	133.1	135.3		2.14
4	132.4	133.1		0.68
5	130.7	131.8		1.15
c	125.1	123.3		2.2
b	123.6	121.6		2.0
3	122.5	124.3		1.8
6	121.9	123.4		1.5
1	117.2	118.0		0.8
8	116.5	117.5		1.0

(a) Carbon-13 obtained in DMSO-d_6. (b) Carbon-13 obtained in deuterium oxide/dioxane.

EXPERIMENTAL

2-Chloro-10[3-(1-methyl-4-piperazinyl)-propyl]phenothiazine 5-Oxide.

A solution of 102 g. (0.27 mole) of prochlorperazine and 35.4 g. (0.59 mole) of acetic acid in 1250 ml. of methanol was treated with 36.3 g. (0.32 mole) of 30% hydrogen peroxide and heated at the reflux temperature for 17 hours. The solution was concentrated under reduced pressure to give 154 g. of oil which was dissolved in 150 ml. of water and treated with 350 ml. of concentrated ammonium hydroxide. The mixture was extracted with ether (5 x 200 ml.) and the combined extractions evaporated to 400 ml. to give 21 g. of white solid, m.p. 160-162°. The aqueous solution upon standing overnight deposited an additional 27 g., m.p. 163-164°. The solids were combined and recrystallized from ethyl acetate to give 38.4 g. (37%), m.p. 164-165°; ir (Nujol): 1033 (S → O) cm^{-1}; nmr (deuteriochloroform), δ = 7.1-8.0 (m, 2H); 2.0-2.6 (m, 15H) ppm.

Anal. Calcd. for $C_{20}H_{24}ClN_3O_3S$: C, 61.60; H, 6.20; N, 10.78; Cl, 9.09; S, 8.22. Found: C, 61.62; H, 6.36; N, 11.00; Cl, 9.10; S, 8.38.

2-Chloro-10[3-methyl-4-piperazinyl-*N*,*N'*-bisoxido)propyl]phenothiazine 5-Oxide (I).

A solution of 37.4 g. (0.1 mole) of prochlorperazine and 18.0 g. (0.3 mole) of acetic acid in 750 ml. of methanol was heated to reflux and 22.8 g. (0.2 mole) of 30% hydrogen peroxide was added. After two hours of reflux an additional 11.4 g. (0.1 mole) of peroxide solution was added and reflux continued for two hours when an additional 11.4 g. of peroxide was added. After an additional two hours, the solution was concentrated to an oil which was dissolved in 200 ml. of methanol and 18.0 g. (0.2 mole) of oxalic acid was added. Cooling gave 34 g. of solid, m.p. 184-190° and a second crop of 11 g., m.p. 187-189°. The solids were combined and treated twice with 500 ml. of boiling methanol to give 33.4 g. (65%) of I, m.p. 195-196°; ir (Nujol): 1030 (S → O) cm^{-1}.

Anal. Calcd. for $C_{20}H_{24}ClN_3O_3S{\cdot}(COOH)_2$: C, 51.61; H, 5.12; N, 8.21. Found: C, 51.41; H, 5.11; N, 8.20.

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