

## SYNTHESIS OF 7-BROMO/8,9-DIMETHYLPHENOTHIAZINE SULFONES

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### ABSTRACT

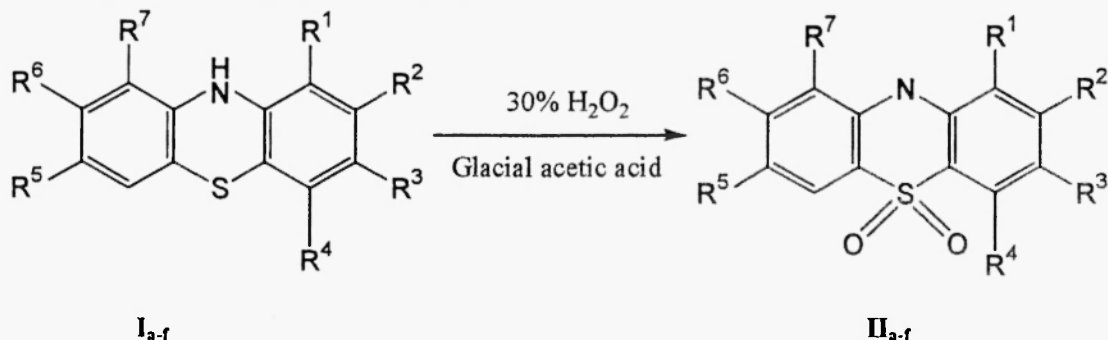
The synthesis of 7-bromo/8,9-dimethylphenothiazine sulfones is reported. 7-Bromo/8,9-dimethylphenothiazine sulfones were prepared by the oxidation of their corresponding phenothiazines by 30% hydrogen peroxide in glacial acetic acid. The structure of newly synthesized compounds has been confirmed by the elemental analysis, IR and  $^1\text{H}$  NMR spectral studies.

### INTRODUCTION

Phenothiazine sulfones constitute an important class of heterocycles possess a wide spectrum of pharmacological / biological activities.<sup>1-11</sup> The oxidation of sulfide linkage in phenothiazines to dioxide leads to an interesting class of heterocyclic sulfones not only the medicinal and industrial point of view, but also from structural aspects. It has stimulated our interest to understand oxidation behaviour of phenothiazines and to investigate changes in infrared and nuclear magnetic spectra caused by the conversion of sulfide linkage to sulfones<sup>12-16</sup>.

### RESULTS AND DISCUSSION

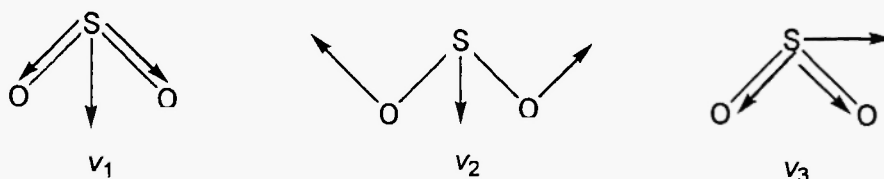
The title compounds have been synthesized by corresponding phenothiazines. Phenothiazines were prepared by the Smiles rearrangement of 2-amino-5-bromo/3,4-dimethylbenzenethiols with a halonitrobenzenes. 7-Bromo/8,9-dimethyl-10H-phenothiazines-5,5-dioxides (**II<sub>a-f</sub>**) have been prepared by treating phenothiazine with 30% hydrogen peroxide in glacial acetic acid (Scheme I).



Compound	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	R <sup>7</sup>
II <sub>a</sub>	Cl	H	H	H	Br	H	H
II <sub>b</sub>	H	H	Cl	H	Br	H	H
II <sub>c</sub>	NO <sub>2</sub>	H	Cl	Cl	Br	H	H
II <sub>d</sub>	NO <sub>2</sub>	H	CF <sub>3</sub>	H	Br	H	H
II <sub>e</sub>	H	H	Cl	H	H	CH <sub>3</sub>	CH <sub>3</sub>
II <sub>f</sub>	H	Cl	Cl	H	H	CH <sub>3</sub>	CH <sub>3</sub>

### Scheme I : Synthesis of 7-bromo/8,9-dimethylphenothiazine sulfones

The IR spectra of phenothiazines sulfones have been recorded both in potassium bromide pellets and in chloroform solution. All the synthesized phenothiazine sulfones exhibit a sharp intense peak in the region 1390-1300  $\text{cm}^{-1}$  which can be ascribed to the asymmetric stretching ( $\nu_3$ ) mode of sulfonyl group which in the solid state splits into three bands in the region 1420-1330  $\text{cm}^{-1}$ , 1355-1250  $\text{cm}^{-1}$  and 1270-1200  $\text{cm}^{-1}$ . The asymmetric stretching vibrations in sulfones is strongly affected on passing from solution to the crystalline state. The symmetric stretching vibrations ( $\nu_1$ ) of phenothiazines sulfones give rise to a doublet in potassium bromide pellets in the region 1180-1100  $\text{cm}^{-1}$  whereas in solution it appears in the region 1180-1080  $\text{cm}^{-1}$ . These frequencies are slightly affected by the state of aggregation. The bond appearing in the region 600-500 in phenothiazine sulfones can be attributed to bending vibrations ( $\nu_2$ ) on passing from solution to the crystalline state.



In all the phenothiazines sharp peaks in KBr discs are observed in region (3380-3215  $\text{cm}^{-1}$ ) due to N-H stretching vibrations and shifted to slightly higher frequency (3420-3370  $\text{cm}^{-1}$ ) in corresponding sulfones.

NMR spectra of each synthesized phenothiazine sulfones (II<sub>a-f</sub>) exhibit a singlet in the region  $\delta$  8.91-9.98 ppm due the N-H proton. All compound (II<sub>a-f</sub>) exhibit a multiplet in the region  $\delta$  5.78-8.62 ppm due to aromatic protons. In compound (II<sub>e,f</sub>) two singlets are observed in the region  $\delta$  3.16-3.24 ppm and  $\delta$  1.16-1.27 ppm assigned to CH<sub>3</sub> protons at C<sub>8</sub> and C<sub>9</sub>, respectively.

### EXPERIMENTAL

All the melting points are uncorrected. The purity was checked by thin layer chromatography using various non-aqueous solvents and characterized by their spectral studies. The infrared spectra have been recorded on FTIR spectrometer MAGNA IR 550

NICOLET using both of KBr discs as well as chloroform. The NMR spectra were recorded on 90MHz on Jeol FX 90 Q FT NMR spectrometer in  $\text{CDCl}_3$  using TMS as an internal standard. Physical and analytical data of synthesized compounds are summarized in Table 1.

**Table I : Physical and analytical data of phenothiazine sulfones ( $\text{II}_{a-f}$ )**

Compound	$\text{R}^1$	$\text{R}^2$	$\text{R}^3$	$\text{R}^4$	$\text{R}^5$	$\text{R}^6$	$\text{R}^7$	M.P. °C	% yield	Molecular Formula	Found (Calculated)		
											C	H	N
I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
$\text{II}_a$	Cl	H	H	H	Br	H	H	178	46	$\text{C}_{12}\text{H}_7\text{O}_2\text{NSBrCl}$	(41.81) 41.77	(2.03) 2.00	(4.07) 4.05
$\text{II}_b$	H	H	Cl	H	H	Br	H	198	39	$\text{C}_{12}\text{H}_7\text{O}_2\text{BrNSCl}$	(41.81) 41.80	(2.03) 2.01	(4.07) 4.05
$\text{II}_c$	$\text{NO}_2$	H	Cl	Cl	H	Br	H	199	64	$\text{C}_{12}\text{H}_5\text{O}_4\text{N}_2\text{SBrCl}_2$	(41.81) 41.81	(1.18) 1.15	(6.60) 6.61
$\text{II}_d$	$\text{NO}_2$	H	$\text{CF}_3$	H	H	Br	H	219	78	$\text{C}_{12}\text{H}_6\text{O}_4\text{N}_2\text{SF}_3\text{Br}$	(41.81) 41.45	(1.48) 1.51	(6.91) 6.66
$\text{II}_e$	H	H	Cl	H	H	$\text{CH}_3$	$\text{CH}_3$	120	42	$\text{C}_{14}\text{H}_{12}\text{SO}_2\text{NCl}$	(57.24) 57.20	(4.09) 4.05	(4.77) 4.77
$\text{II}_f$	H	Cl	Cl	H	H	$\text{CH}_3$	$\text{CH}_3$	164	50	$\text{C}_{14}\text{H}_{11}\text{SO}_2\text{NCl}_2$	(51.22) 51.20	(3.35) 3.35	(4.26) 4.25

#### Preparation of 7-bromo-8/9-dimethylphenothiazine sulfones( $\text{II}_{a-f}$ )

30% Hydrogen peroxide (5ml) was added to the solution of phenothiazine (**I**, 0.01 mole) in glacial acetic acid (20 ml) and refluxed for fifteen minutes. Heating was stopped and another lot of hydrogen peroxide (5 ml) was added. The reaction mixture was refluxed for 3-4 hrs. The contents were poured in a beaker containing crushed ice. The yellow residue obtained was filtered off, washed with water and crystallized from ethanol.

#### ACKNOWLEDGEMENT

Thanks are due to RSIC, Lucknow for providing NMR spectra.

#### REFERENCES

1. R.R. Gupta (Ed.), "Phenothiazines and 1,4-Benzothiazines-Chemical and Biomedical Aspects", Elsevier, Amsterdam (1988).
2. H. Keyzer, G.M. Eckert, I.S. Forrest, R.R. Gupta, F. Gutmann, J. Molnar (Eds.), "Thiazines and Structurally Related Compounds" (Proceedings of Sixth International Conference on Phenothiazines and Structurally Related Psychotropic Compounds, Pasadena, California Sept. 11-14 (1990), Krieger Publishing Co. Molabar, Florida, U.S.A. (1992).
3. C.R. Rasmussen, U.S. Pat., 3,476,749 (1969); Chem. Abstr., **72**, 217227 (1970).

4. H. Zenno and T. Mizutani, Jap. Pat., 7,006,262 (1970); Chem. Abstr., **72**, 132759 (1970).
5. H. Zinnes, M. Schwartz and J. Shavel, Jr., Ger. Offen, 2,208,351 (1972); Chem. Abstr., **77**, 164722 (1972).
6. G. Fengler, D. Arlt, K. Grohe, H.J. Zeiler and K. Metzger, Ger. Offen, 3,229,125 (1984); Chem. Abstr., **101**, 7176 (1984).
7. G. Filacchioni, V. Nacci and G. Stfancich, Farmaco. Ed. Sci., **31**(7), 478 (1976); Chem. Abstr., **85**, 143048 (1976).
8. K.H. Mayer and A. Haberkorn, Ger. Offen, 2,020,298 (1971); Chem. Abstr., **76**, 72533 (1972).
9. G. Frengler, D. Arlt and K. Grohe, Ger. Offen, 3,329,124 (1984); Chem. Abstr., **101**, 90953 (1984).
10. R.N. Prasad, J. Med. Chem., **12**(2), 290 (1969); Chem. Abstr., **70**, 106447 (1969).
11. R.R. Gupta, Rakesh Kumar, G.S. Kalwania and R.K. Gautam, Ann. Soc. Sic. Bruxelles, **98**(4), 195 (1984).
12. W. Ried and W. Ochs in R.R. Gupta (Ed.), "Physical methods in heterocyclic chemistry", John & Sons, Inc., pp. 58 (1984).
13. R. Kumar, Ph.D. Thesis, University of Rajasthan, Jaipur, India (1984).
14. G.S. Kalwania, Ph.D. Thesis, University of Rajasthan, Jaipur, India (1983).
15. R.R. Gupta, R.K. Rathore, V. Gupta and R.S. Rathore, Pharmazie, **46**, 602 (1991).
16. R.K. Rathore, V. Gupta, M. Jain and R.R. Gupta, Ind. J. Chem. Sect. **B**, **32**, 370 (1993).

**Received on July 12, 2002**