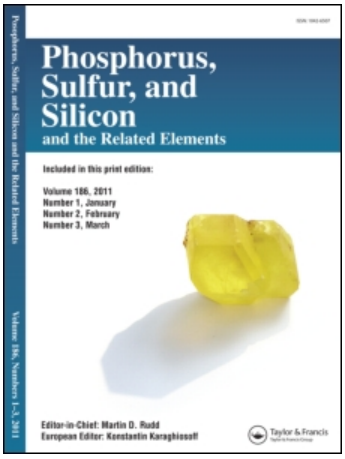

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SYNTHESIS OF SULFONES OF 4H-1,4-BENZOTHIAZINES AND PHENOTHIAZINES

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SYNTHESIS OF SULFONES OF 4H-1,4-BENZOTHIAZINES AND PHENOTHIAZINES

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Conversion of 5/7-chloro-4H-1,4-benzothiazines and 1/3-chlorophenothiazines into sulfones is reported. The 5/7-chloro-4H-1,4-benzothiazines were synthesized by the condensation and oxidative cyclization of 2-amino 3/5-chlorobenzenethiol with β diketones in DMSO. The phenothiazines have been synthesized via Smiles rearrangement by the reaction of 2-amino-3/5-chlorobenzenethiol with halonitrobenzenes. 4H-1,4-Benzothiazine and phenothiazine sulfones have been prepared by the oxidation of benzothiazines and phenothiazines with 30% hydrogen peroxide in glacial acetic acid. The structure of all the synthesized compounds has been confirmed by IR and NMR spectral studies.

Keywords: 2-Amino 3/5-chlorobenzenethiol; 4H-1,4-benzothiazines; 4H-1,4-Benzothiazine sulfones; β-diketones; phenothiazines; phenothiazine sulfones

4H-1,4-Benzothiazines and phenothiazines comprise an important class of heterocycles containing a 1,4-thiazine ring. Both benzothiazines and phenothiazines possess a wide range of pharmacological and biological activities.[1–10] The oxidation of sulfide linkage in both the compounds leads to an interesting class of heterocyclic sulfones. The synthesized sulfones possess useful medicinal[11–16] and industrial[17–20] applications. It has stimulated our interest to understand oxidation behavior of benzothiazines and phenothiazines and to investigate changes in infrared and nuclear magnetic resonance spectra by the conversion of sulfide linkage into sulfones.

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

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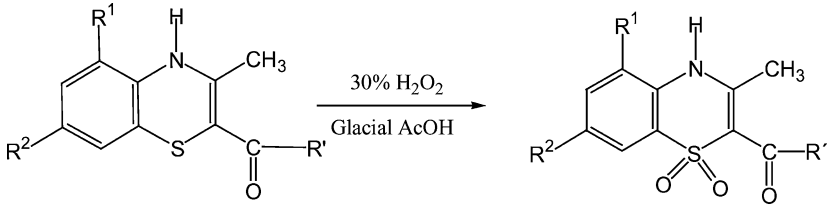
DISCUSSION

In the present work 4H-1,4-benzothiazines and phenothiazines have been converted to their corresponding S,S-dioxide by reacting them with 30% hydrogen peroxide in glacial acetic acid (Schemes 1 and 2). 4H-1,4-Benzothiazine[21,22] were prepared by the condensation and oxidative cyclization of 2-amino-3/5-chlorobenzenethiol with β diketones in dimethylsulfoxide. The phenothiazines were prepared by the Smiles rearrangement[23–25] of 2-amino-3/5-chlorobenzenethiols with o-halonitrobenzenes.

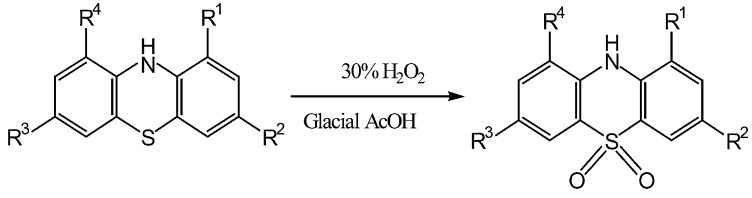


III **IVa-d**

$R' = C_6H_4$-Br(m), C_6H_4-CH_3(m), C_6H_4-C_2H_5(p)

R^1 = Cl, H; R^2 = Cl, H

SCHEME 1



I **IIa,b**

$R^1 = NO_2$; $R^2 = CF_3$; R^3 = Cl, H; R^4 = Cl, H

SCHEME 2

EXPERIMENTAL

All the melting points are uncorrected. The purity of all the compounds has been checked by thin layer chromatography using various nonaqueous solvent systems and characterized by spectral studies. The infrared

TABLE I Physical and Analytical Data of Phenothiazine Sulfones ($II_{a,b}$)

Compd.	R^1	R^2	R^3	R^4	M.p. (°C)	Yield (%)	Molecular formula	% (Calcd.) found C	H	N
I	II	III	IV	V	IX	X	XI	XII	XIII	XIV
II_a	NO_2	CF_3	H	Cl	176–178	55	$C_{13}H_6ClF_3N_2O_4S$	(41.23)	(1.60)	(7.40)
								41.22	1.62	7.41
II_b	NO_2	CF_3	Cl	H	220–222	65	$C_{13}H_6ClF_3N_2O_4S$	(41.23)	(1.60)	(7.40)
								41.21	1.61	7.42

(IR) spectra were recorded on Fourier transform infrared (FTIR) spectrometer, MAGNA IR 550, NICOLET in potassium bromide discs and in chloroform solution. ^1H NMR were scanned at 90 MHz on Jeol FX 90Q FT NMR spectrometer in using TMS as an internal standard.

Preparation of 4H-1,4-Benzothiazine and Phenothiazine Sulfones

To a solution of 0.01 mole of the compound (phenothiazine or 4H-1,4-benzothiazine) in 15 ml of glacial acetic acid, 5 ml of 30% hydrogen peroxide was added and refluxed at 50–60°C for 15 min. Heating was stopped and another lot of 5 ml of 30% hydrogen peroxide was added. The solution was refluxed for 4 h. The solution was poured into a beaker containing crushed ice. The yellow residue separated out was collected and crystallization from ethanol afforded the desired products. Analytical data of phenothiazine and 4H-1,4-benzothiazine sulfones are tabulated in Tables I and II, respectively.

IR and NMR are included, and changes caused in the spectra by oxidation of sulfide linkage to sulfones are discussed.

TABLE II Physical and Analytical Data of 4H-1,4-Benzothiazine Sulfones (IV_{a-d})

Compd.	R^1	R^2	R′	m.p. (°C)	Yield (%)	Molecular formula	% (Calcd.) found C	H	N
I	II	III	IV	V	VI	VII	VIII	IX	X
IV_a	Cl	H	C_6H_4-Br(m)	314–316	65	$C_{16}H_{11}BrClNO_3S$	(46.57)	(2.69)	(3.39)
							46.52	2.66	3.32
IV_b	H	Cl	C_6H_4-Br(m)	208–210	50	$C_{16}H_{11}BrClNO_3S$	(46.57)	(2.69)	(3.39)
							46.53	2.67	3.36
IV_c	Cl	H	C_6H_4-CH_3(m)	> 360	48	$C_{17}H_{14}ClNO_3S$	(58.70)	(4.06)	(4.03)
							58.69	4.02	4.01
IV_d	H	Cl	C_6H_4-C_2H_5(p)	222	55	$C_{18}H_{16}ClNO_3S$	(59.75)	(4.46)	(3.87)
							59.70	4.44	3.84

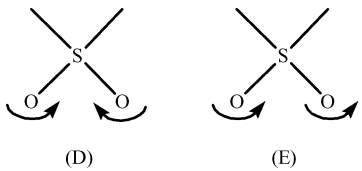
INFRARED SPECTRA

Sulfone group is of high polarity and strong bonding which causes vibrational localization and thereby exhibits well-defined group frequency in the IR region.

IR spectra have been recorded both in potassium bromide pellets and chloroform solution. In the crystalline state as well as in chloroform all the phenothiazines (IIIa, b) and 4H-1,4-benzothiazine sulfones (IVa–d) exhibit three characteristic intense absorption bands viz 1151, 519, and 1361 cm^{-1}, which can be attributed to the three strong fundamental absorption bands in the molecule of sulfur dioxide. All the synthesized 4H-1,4-benzothiazine sulfones (IVa–d) and phenothiazine sulfones (IIa, b) give asymmetric stretching mode of the sulfonyl group as sharp peaks in the regions 1350–1310 cm^{-1} and 1370–1320 cm^{-1} in chloroform. This peak in the solid state splits into three bands in the regions 1430–1380 cm^{-1}, 1370–1290 cm^{-1}, and 1280–1200 cm^{-1} in benzothiazine sulfones and at 1350 cm^{-1}, 1310 cm^{-1}, and 1290–1210 cm^{-1} in phenothiazine sulfones (IIa, b). The asymmetric stretching vibrations in the sulfones are strongly affected on passing from solution to the crystalline state.

The symmetrical stretching vibrations give rise to a doublet and in same cases a broad signal in potassium bromide in the region 1190–1070 cm^{-1} and 1190–1120 cm^{-1} for benzothiazine and phenothiazine sulfones, whereas in solution they appear in the region 1180–1070 cm^{-1} and 1160–1100 cm^{-1}, respectively. These frequencies are slightly affected by the state of aggregation.

The bending vibrations in sulfur dioxide exhibit medium absorption band in the low frequency region 595–510 cm^{-1}. Thus the bands appearing in the region 580–500 cm^{-1} in 4H-1,4-benzothiazine sulfones (IVa–d) and in the region 590–500 cm^{-1} in phenothiazine sulfones (IIa, b) can be ascribed to sulfur dioxide scissoring (D) and rocking vibrations (E). The infrared spectral data of benzothiazine sulfones and phenothiazine sulfones are summarized in Tables III and IV.



(D) (E)

FIGURE 1

TABLE III Infrared Spectral Data of Substituted 4H-1,4-Benzothiazines and Their Sulfones (IVa–d) (in KBr in cm^{-1})

	Compounds					
	R^1	R^2	R^3	A	B	C
IIa	Cl	H	C_6H_4-Br(m)	(3410)	(1610)	(1070)
				3375	1605	1060
IIb	H	Cl	C_6H_4-Br(m)	(3410)	(1670)	(1090)
				3260	1610	1030
IIc	Cl	H	C_6H_4-CH_3(m)	(3300)	(1690)	(1050)
				3260	1670	1010
IId	H	Cl	C_6H_4-C_2H_5(m)	(3400)	(1680)	(1080)
				3270	1610	1040

*The bonds in brackets corresponds to sulfones.

A, N—H streching vibrations; B, C═O streching vibrations; C, v (C—S) streching vibrations.

The substituted vibrations can provide information about the electron donor and electron acceptor abilities of the heteroaromatic rings. In the present investigation substituted vibrations both in sulfones and in their parent phenothiazines and benzothiazines have been examined (Tables III and IV). The vibrational frequency corresponding to each substitutuent is shifted to higher frequency in both types of sulfones.

In phenothiazines N—H stretching frequency appears in the region 3280–3260 cm^{-1}, and in their sulfones (IIa, b) they appear in the region 3310–3280 cm^{-1}. A sharp intense peak observed for 4H-1,4-benzothiazines in the region 3375–3260 cm^{-1} due to free N—H stretching vibrations shifts to higher frequency region 3410–3400 cm^{-1} in the corresponding sulfones (IVa–d).

In 4H-1,4-benzothiaines a sharp band that appears in the region 1670–1605 cm^{-1} due to C═O stretching vibrations is shifted to higher

TABLE IV Infrared Spectral Data of Phenothiazines and Their Sulfones (IIa, b) (in KBr in cm^{-1})

	Compounds					
	R^1	R^2	R^3	R^4	A	B
IVa	Cl	H	NO_2	CF_3	(3280)	(1050)
					3260	1030
IVb	H	Cl	NO_2	CF_3	(3310)	(1060)
					3280	1020

*The bonds in brackets corresponds to sulfones.

A, N—H streching vibrations; B, C═O streching vibrations.

TABLE V ^{1}H NMR Spectral Data of Benzothiazines and Benzothiazine Sulfones (IVa–d) in ppm

	Compounds					
	R^1	R^2	R^3	A (NH)	B (Aromatic)	C (CH_3 at C_3)
IVa	Cl	H	C_6H_4-Br(m)	(8.9)	(8.33–7.44)	(2.3)
				9.22	8.24–7.00	1.61
IVb	H	Cl	C_6H_4-Br(m)	(9.57)	(8.55–7.67)	(1.80)
				9.33	8.33–6.69	2.07
IVc	Cl	H	C_6H_4-CH_3(m)	(9.03)	(8.24–7.32)	(2.63)
				8.6	8.05–7.140	2.53
IVd	H	Cl	C_6H_4-C_2H_5(p)	(10.5)	(8.62–7.16)	(2.28)
				8.97	8.08–6.49	2.21

*The bands in bracket corresponds to sulfones.

frequency region 1690–1610 cm^{-1} in the corresponding sulfones (IVa–d). The mesomeric and −1 effects of SO_2 group, both operating in the same direction, hinder the conjugation of a lone pair of electrons at nitrogen with the carbonyl group. The lone pair of electrons at nitrogen are withdrawn more effectively towards the ring due to SO_2 group, and it conjugates less effectively with carbonyl group and results in higher frequency of carbonyl group.

The C–S stretching vibrations appearing in the region 1060–1010 cm^{-1} and 1030–1020 cm^{-1} in benzothiazines and phenothiazines are shifted to higher frequency region 1090–1050 cm^{-1} and 1060–1050 cm^{-1}, respectively, in the corresponding sulfones.

PROTON MAGNETIC RESONANCE SPECTRA

The signals are normally observed in low fields in both phenothiazines and benzothiazines sulfones as compared to their parent

TABLE VI ^{1}H NMR Spectral Data of Phenothiazines and Phenothiazines Sulfones (IIa, b) in ppm

	Compounds					
	R1	R2	R3	R4	A (NH)	B (Aromatic)
IIa	Cl	H	NO_2	CF_3	(10.3)	(8.93–7.16)
					10.30	8.15–6.97
IIb	H	Cl	NO_2	CF_3	(11.2)	(8.87–7.60)
					9.85	8.01–6.93

*The bands in bracket corresponds to sulfones.

phenothiazines and benzothiazines. The nuclear magnetic resonance spectral data for benzothiazines and their sulfones and for phenothiazines and their sulfones have been described in Tables V and VI, respectively.

All the synthesized benzothiazine sulfones (IVa–d) exhibit a single sharp peak in the region δ 10.5–8.9 ppm due to N—H proton. All compounds show multiplet in the region δ 8.62–7.16 ppm due to aromatic protons. That compounds (IVa–d) show resonance signal in the region δ 2.63–1.80 ppm is attributed to allylic protons (C=C—CH_3) at C_3. Compounds IVc exhibit a singlet at δ 1.74 ppm due to CH_3 protons at 3-position of benzoyl side chain at C_2. The synthesized compound IVd exhibits quartet and triplet in the region δ 3.36–2.72 ppm and δ 1.83–1.20 ppm due to CH_2 and CH_3 protons of C_2H_5 group at p-position to benzoyl side chain at C_2.

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