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Synthesis of 4H-1,4-Benzothiazine-1,1-dioxides (Sulfones) and Phenothiazine-5,5-dioxides (Sulfones)

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The study of the oxidation behavior of 4H-1,4-benzothiazines and phenothiazines by 30% hydrogen peroxide in acetic acid results in the formation of 4H-1,4-benzothiazine-1,1-dioxides (sulfones) and 10H-phenothiazine-5,5-dioxides (sulfones) respectively. The purity of all the synthesized compounds has been checked by thin layer chromatography using silica "G" as an adsorbent in various nonaqueous solvent systems. Infra-red and proton-magnetic resonance spectral studies are also included.

INTRODUCTION

The oxidation of sulfide linkage in 4H-1,4-benzothiazines and 1-/9-nitro-10H-phenothiazines leads to formation of their sulfones. Sulfones constitute an important class of heterocyclic compounds which have been reported to find a number of applications in medicine^{1–13} and industry.^{14,15} 4H-1,4-Benzothiazine-1,1-dioxides (sulfones) and phenothiazine-5,5-dioxides (sulfones) were obtained in quantitative yield by the oxidation of 4H-1,4-benzothiazines and phenothiazines, respectively, with hydrogen peroxide.¹⁶

RESULTS AND DISCUSSION

The sulfones have been synthesized by the oxidation of 4H-1,4-benzothiazines and phenothiazines. 4H-1,4-benzothiazines were prepared by the condensation and oxidative cyclization of 2-amino-5-fluoro-3-methyl/5-ethoxy benzenethiols with β -diketones in dimethylsulfoxide

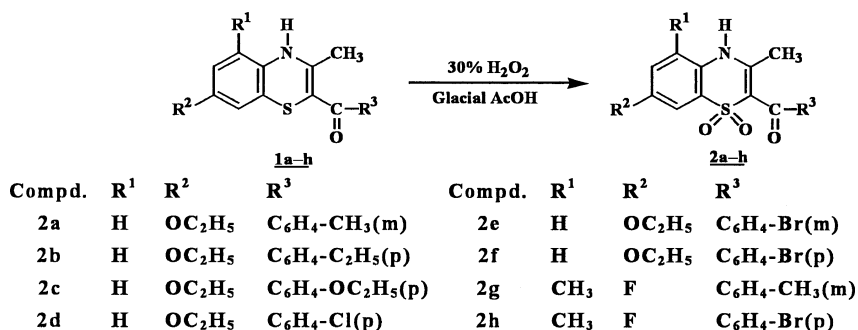
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RSIC and Lucknow are thanked for providing proton magnetic resonance spectra.

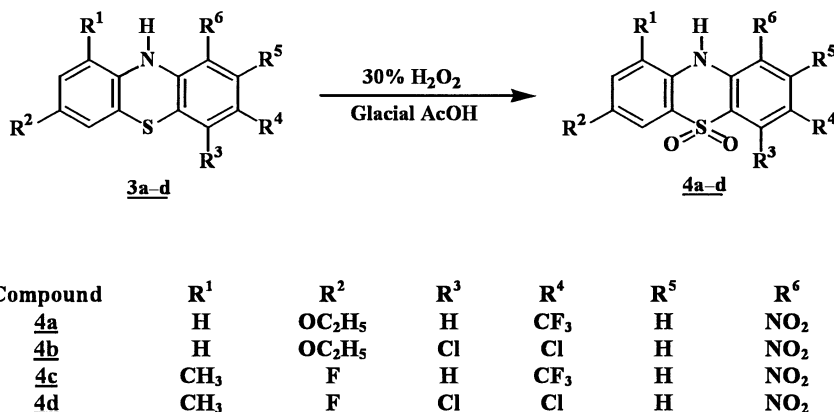
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reported elsewhere.^{17–19} Phenothiazines were prepared by the Smiles rearrangement of 2-amino-5-fluoro-3-methyl/5-ethoxybenzenethiols with o-halonitrobenzenes containing nitro groups at both ortho positions to the halogeno atom.

4H-1,4-Benzothiazine-1,1-dioxides (Scheme-1, IIa–h) and 1-/9-nitro-10H-phenothiazine-5,5-dioxides (Scheme 2, IVa–d) have been prepared by treating 4H-1,4-benzothiazines and 1-/9-nitro-10H-phenothiazines, respectively, with 30% hydrogen peroxide in glacial acetic acid.



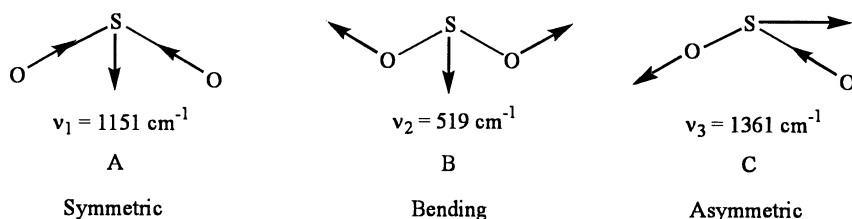
SCHEME 1 Synthesis of 4H-1,4-benzothiazine-1,1-dioxides (sulfones).



SCHEME 2 Synthesis of 1-/9-nitro-10H-phenothiazine-5,5-dioxides (sulfones).

INFRARED SPECTRA

Infrared spectra have been recorded both in potassium bromide pellets and in chloroform solution. In the solid state as well as in chloroform,

**FIGURE 1**

all 4H-1,4-benzothiazine sulfones and 10H-phenothiazine sulfones exhibit three characteristic absorption bands viz. 1151 cm^{-1} , 519 m^{-1} , and 1361 cm^{-1} , which can be attributed to the three strong fundamental absorption bands in the molecule of sulfur dioxide and can be assigned to the three normal modes of vibrations^{20,21} shown in (Figure 1).

All synthesized 4H-1,4-benzothiazine-1,1-dioxides (sulfones) and phenothiazine-5,5-dioxides (sulfones) exhibit a sharp intense peak in the region $1390\text{--}1310 \text{ cm}^{-1}$ and $1375\text{--}1348 \text{ cm}^{-1}$ in chloroform solution, respectively, which can be assigned to the asymmetric stretching mode ν_3 of the sulfonyl group. While in a solid state, this absorption band ν_3 split into three bands and appears in the region $1410\text{--}1325 \text{ cm}^{-1}$, $1320\text{--}1285 \text{ cm}^{-1}$, and $1290\text{--}1240 \text{ cm}^{-1}$ for the 4H-1,4-benzothiazine-1,1-dioxides (sulfones) and in the 1-/9-nitro-10H-phenothiazine-5,5-dioxides (sulfones) its appears in the region $1380\text{--}1345 \text{ cm}^{-1}$, $1330\text{--}1280 \text{ cm}^{-1}$, and $1285\text{--}1260 \text{ cm}^{-1}$. The asymmetric stretching vibrations in the sulfones are strongly affected on passing from the solution to the crystalline state. The symmetrical stretching vibrations ν_1 of 4H-1,4-benzothiazine-1,1-dioxides (sulfones) and 1-/9-nitro-10H-phenothiazine-5,5-dioxides (sulfones) give rise to high intensity doublet and in some cases a broad signal obtained in the KBr disc in the region $1190\text{--}1100 \text{ cm}^{-1}$ and $1185\text{--}1110 \text{ cm}^{-1}$, whereas in solution it appears at $1205\text{--}1105 \text{ cm}^{-1}$ and $1180\text{--}1110 \text{ cm}^{-1}$, respectively. Hence, these frequencies are slightly affected by the state of aggregation. The bending vibration ν_2 in sulfur dioxide exhibits medium absorption bands in low frequency region, $590\text{--}510 \text{ cm}^{-1}$ and $585\text{--}522 \text{ cm}^{-1}$. These absorption bands appear either as a doublet or singlet band with an inflection, which have been compared with fundamental vibrations^{22,23} in sulfonyl chloride appearing below 600 cm^{-1} . Analogously, the band in the region $590\text{--}510 \text{ cm}^{-1}$ and $585\text{--}522 \text{ cm}^{-1}$ in 4H-1,4-benzothiazine-1,1-dioxides (sulfones) and 1-/9-nitro-10H-phenothiazine-5,5-dioxides (sulfones) can be ascribed to sulfur-dioxide scissoring (D) and rocking (E) vibrations (Figure 2).

**FIGURE 2**

The substituent vibrations can provide information about the electron donor and electron acceptor abilities of heteroaromatic rings.²⁴ The present work deals with the vibrational frequencies of substituents in IR spectra, both in dioxides (sulfones) and in their parent 4H-1,4-benzothiazines and 1-/9-nitro-10H-phenothiazines. The vibrational frequency corresponding to each substituent is shifted to higher frequency in both types of dioxides (sulfones).

In the spectra of 1-/9-nitro-10H-phenothiazine-5,5-dioxides (sulfones), the absorption band due to >N–H stretching vibrations (frequency) appears at nearly the same frequency region. In 1-/9-nitro-10H-phenothiazines >N–H stretching vibrations (frequency) appears in the region 3400–3360 cm^{-1} and in 1-/9-nitro-10H-phenothiazine-5,5-dioxides (sulfones) it appears in the region 3410–3360 cm^{-1} . A sharp intense peak observed in the region 3380–3260 cm^{-1} in 4H-1,4-benzothiazines that was assigned to free >N–H stretching vibrations shifted to higher frequency region 3430–3380 cm^{-1} in the corresponding dioxides (sulfones).

A sharp band observed in the region 1710–1590 cm^{-1} due to >C=O stretching vibrations in 4H-1,4-benzothiazine shifts to higher frequencies 1730–1630 cm^{-1} in the corresponding dioxides (sulfones). This shifting to higher frequency is assigned to the increased electron acceptor ability of heteroaromatic nucleus in the sulfones as compared to the parent nucleus. The lone pair of electrons at nitrogen is withdrawn more effectively towards the ring; it conjugates less effectively with the carbonyl group and results in higher carbonyl group frequencies. The –I effect of the SO₂ group combines with the mesomeric effect operating in the same direction and also hinders the conjugation of the lone pair of electrons at nitrogen with the carbonyl group.

The asymmetric and symmetric stretching vibrations of methyl, which occur in the region 2950–2890 cm^{-1} (asymm.) and 2925–2840 cm^{-1} (symm.) in 4H-1,4-benzothiazines, is shifted to the higher frequency region 2980–2900 cm^{-1} (asymm.) and 2950–2850 cm^{-1}

(symm.) in the corresponding sulfones. Similarly, the same vibrations which occur in the region 2930–2910 cm^{-1} (asymm.) and 2860–2830 cm^{-1} (symm.) in 1-/9-nitro-10H-phenothiazines is shifted to a higher frequency region 2960–2930 cm^{-1} (asymm.) and 2870–2860 cm^{-1} (symm.) in the corresponding sulfones.

A medium intensity band appearing in the region 1060–1010 cm^{-1} in 4H-1,4-benzothiazines and exhibits in the region 1045–1020 in 1-/9-nitro-10H-phenothiazine due to $>\text{C}-\text{S}-\text{C}<$ stretching vibrations is shifted to a higher frequency region 1070–1040 cm^{-1} and 1070–1045 cm^{-1} in the corresponding sulfones.

It can be concluded that the oxidation of 4H-1,4-benzothiazines and 1-/9-nitro-10H-phenothiazines to their corresponding sulfones causes the appearance of specific absorption peaks with the change in the vibrational modes. These changes in the vibrational modes could be elaborated by the strong electron-withdrawing oxygen atoms at the oxidized sulfide linkage. The oxidation behavior of 4H-1,4-benzothiazines and 1-/9-nitro-10H-phenothiazines explain the similarities in their core nuclear structure and conformations, which are responsible for pharmaceutical activities.

NUCLEAR MAGNETIC RESONANCE SPECTRA

NMR spectral data of synthesized 4H-1,4-benzothiazine-1,1-dioxides (sulfones) and 1-/9-nitro-10H-phenothiazine-5,5-dioxides (sulfones) are discussed in detail below.

Each 1-/9-nitro-10H-phenothiazine-5,5-dioxide (sulfone) exhibits a sharp peak in the region δ 9.686–9.38 ppm due to $>\text{N}-\text{H}$ proton. Compounds **4c** and **4d** exhibit a singlet in the region δ 2.72 and δ 2.64 ppm due to three protons of $-\text{CH}_3$ group at C_1 , respectively. The multiplet in the region δ 8.38–6.72 ppm is observed due to the aromatic ring protons. Compounds **4a** and **4b** exhibit a quartet and triplet in the region δ 2.61–2.26 ppm and δ 1.68–1.08 ppm due to $>\text{CH}_2$ and $-\text{CH}_3$ protons of $-\text{OC}_2\text{H}_5$ group at C_7 .

All synthesized 4H-1,4-benzothiazine sulfones **2a–h** exhibit a single sharp peak in the region δ 9.984–8.88 ppm due to $>\text{N}-\text{H}$ -proton. The multiplet observed in the region δ 8.51–5.96 ppm is attributed to the aromatic protons. Compounds **2a–h** show resonance signal in the region δ 2.54–2.28 ppm due to allylic protons ($>\text{C}=\text{C}-\text{CH}_3$) at C_3 . Compounds **2g** and **2h** exhibit a singlet at δ 2.09 ppm and 2.16 ppm due to $-\text{CH}_3$ protons at C_5 . Compounds **2a** and **2g** exhibit a singlet at 2.22 ppm and 1.96 ppm due to $-\text{CH}_3$ protons at the 3-position of the benzoyl side chain at C_2 respectively. Compounds **2a–f** exhibit quartet and triplet in region δ 4.56–3.16 ppm and 2.08–1.28 ppm due to $>\text{CH}_2$ and $-\text{CH}_3$

protons of $-\text{OC}_2\text{H}_5$ group at C_7 . Compound **2c** exhibits quartet and triplet in region 4.22–3.99 ppm and 1.75–1.42 ppm due to $>\text{CH}_2$ and $-\text{CH}_3$ protons of $-\text{OC}_2\text{H}_5$ group at 4-position of benzoyl side chain at C_2 . The quartet and triplet observed in the region δ 3.32–3.12 ppm and 1.36–1.24 ppm in the compound **2b** can be assigned to $-\text{C}_2\text{H}_5$ group at para-position of benzoyl side chain at C_2 .

EXPERIMENTAL

The melting points of all synthesized compounds are uncorrected. The purity of all synthesized compounds has been checked by thin layer chromatography using silica “G” as an adsorbent in various nonaqueous solvent systems. The infrared spectra have been recorded on a NICOLET-MAGNA FTIR spectrophotometer model 550 in potassium bromide discs and in chloroform solution. Proton magnetic resonance (^1H NMR) spectra were recorded at 90 MHz on Jeol Fx 90Q FT NMR spectrometer in $\text{DMSO}-d_6$ containing TMS as an internal standard.

SYNTHESIS OF 4H-1,4-BENZOTHAZINES **1a–h**

To a stirred suspension of 0.01 mole of β -diketone **2** in 5 mL of dimethylsulfoxide was added 0.01 mL of 2-aminobenzenethiols **1** and the resulting mixture was refluxed for 40–60 min and cooled down to room temperature. The solid that was separated out was filtered and washed with petroleum ether and crystallized from methanol/solvent ether.

SYNTHESIS OF 1-/9-NITRO-10H-PHENOTHAZINES **3a–h**

To a stirred suspension of 0.01 mole of 2-amino-5-fluoro-3-methyl- and 5-ethoxybenzenethiols **1**, 0.01 mole of sodium hydroxide and 20 mL of absolute ethanol were taken in a 50 mL R.B. flask fitted with a reflux condensor and heated for 5 min. To this solution, 0.01 mole of substituted reactive halonitrobenzene **2** in 10 mL of ethanol was added with stirring. The color of the reaction mixture immediately darkened to brown. The contents were refluxed for 4 h, concentrated, cooled, and filtered. The solid separated out was washed with hot water followed by 30 % ethanol. The crystallization from methanol/acetone afforded a pure compound.

SYNTHESIS OF 4H-1,4-BENZOTHAZINE-1,1-DIOXIDES (SULFONES) **2a–h** AND 1-/9-NITRO-10H-PHENOTHAZINE-5,5-DIOXIDES (SULFONES) **4a–d**

30% Hydrogen peroxide (5 mL) was added to a solution of 0.01 mole of 4H-1,4-benzothiazine or 0.01 mole of 1-/9-nitro-10H-phenothiazine in

TABLE I Physical Data of 4H-1,4-Benzothiazine-1,1-dioxides (Sulfones) **2a-h**

I	Compound			M.P. °C	Yield %	Molecular formula	Molecular weight	% Found (calcd.)				
	R ¹	R ²	R ³					C	H	N	S	
	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	
2a	H	OC ₂ H ₅	C ₆ H ₄ -CH ₃ (m)	116	78.16	C ₁₉ H ₁₉ NSO ₄	357.36	63.72 (63.85)	5.40 (5.35)	3.84 (3.92)	8.86 (8.97)	
2b	H	OC ₂ H ₅	C ₆ H ₄ -C ₂ H ₅ (m)	161	54.25	C ₂₀ H ₂₁ NSO ₄	371.39	64.45 (64.67)	5.90 (5.69)	3.72 (3.77)	8.72 (8.63)	
2c	H	OC ₂ H ₅	C ₆ H ₄ -OC ₂ H ₅ (p)	206	86.19	C ₂₀ H ₂₁ NSO ₅	387.38	62.52 (62.00)	5.31 (5.45)	3.68 (3.61)	8.18 (8.27)	
2d	H	OC ₂ H ₅	C ₆ H ₄ -Cl (p)	98	76	C ₁₈ H ₁₆ NSO ₄ Cl	377.78	57.16 (57.22)	4.36 (4.26)	3.72 (3.70)	8.42 (8.48)	
2e	H	OC ₂ H ₅	C ₆ H ₄ -Br (m)	137	80.20	C ₁₈ H ₁₆ NSO ₄ Br	421.33	51.26 (51.31)	3.68 (3.82)	3.19 (3.32)	7.54 (7.61)	
2f	H	OC ₂ H ₅	C ₆ H ₄ -Br (p)	226	69.19	C ₁₈ H ₁₆ NSO ₄ Br	421.33	51.24 (51.31)	3.71 (3.82)	3.38 (3.32)	7.38 (7.61)	
2g	CH ₃	F	C ₆ H ₄ -CH ₃ (m)	26	82.15	C ₁₈ H ₁₆ NSO ₃ F	345.34	62.38 (62.59)	4.48 (4.66)	4.01 (4.05)	9.10 (9.28)	
2h	CH ₃	F	C ₆ H ₄ -Br (p)	86	65.17	C ₁₇ H ₁₃ NSO ₃ BrF	409.31	49.78 (49.88)	3.08 (3.20)	3.32 (3.42)	7.66 (7.83)	

TABLE II Physical Data of 1-/9-Nitro-10H-phenothiazine-5,5-dioxides (Sulfones) 4a-d

Compound										% Found (calcd.)				
R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	M.P. °C	Yield %	Molecular formula	Molecular weight	C	H	N	S	
0 I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV
4a	H	OC ₂ H ₅	H	CF ₃	H	NO ₂	214	89	C ₁₅ H ₁₁ N ₂ O ₅ SF ₃	388.28	46.37 (46.39)	2.78 (2.85)	7.25 (7.21)	8.21 (8.25)
4b	H	OC ₂ H ₅	Cl	Cl	H	NO ₂	226	76	C ₁₄ H ₁₀ N ₂ O ₅ SCl ₂	389.16	43.12 (43.20)	2.54 (2.59)	7.29 (7.20)	8.19 (8.23)
4c	CH ₃	F	H	CF ₃	H	NO ₂	165	86	C ₁₄ H ₈ N ₂ O ₄ SF ₄	376.25	44.62 (44.68)	2.08 (2.14)	7.32 (7.44)	8.44 (8.52)
4d	CH ₃	F	Cl	Cl	H	NO ₂	178	81	C ₁₃ H ₇ N ₂ O ₄ SCl ₂ F	377.14	41.36 (41.39)	1.82 (1.87)	7.40 (7.43)	8.46 (8.50)

20 mL of glacial acetic acid and refluxed for 15 min at 50–60°C. Heating was stopped and another lot of 5 mL of 30% hydrogen peroxide was added. The reaction mixture was again refluxed for 3–4 h. The excess of solvent was removed by distillation under reduced pressure and the solution was poured into a beaker containing crushed ice. The yellow residue that separated out was collected, filtered, and crystallized from ethanol. Physical data of 4H-1,4-benzothiazine-1,1-dioxides (sulfones) and 1/9-nitro-10H-phenothiazine-5,5-dioxides (sulfones) are tabulated in Tables I and II respectively.

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