SYNTHESIS OF 10H-PHENOTHIAZINE AND 4H-1,4-BENZOTHIAZINE SULFONES

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Abstract : Synthesis of phenothiazine and 4H-1,4-benzothiazine sulfones is reported by the oxidation of phenothiazines and 4H-1,4-benzothiazines respectively by 30% hydrogen peroxide in glacial acetic acid. The purity of the compounds has been checked by thin layer chromatography using various non-aqueous solvent systems. IR and NMR spectral studies have also been included.

Introduction

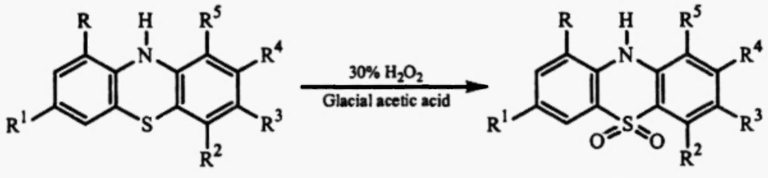
10H-Phenothiazine and 4H-1,4-benzothiazine sulfones constitute an important class of heterocyclic compounds which have been reported to find a number of applications in medicine **(1-13)** and industry **(14-15)**. Phenothiazine and 1,4-benzothiazine sulfones were obtained in quantitative yield by the oxidation of phenothiazines and benzothiazines respectively with hydrogen peroxide **(16)**.

Results and Discussion

The title sulfones have been synthesized by the oxidation of phenothiazines and 1,4-benzothiazines. Phenothiazines were prepared by the Smiles rearrangement of 2-amino-3-methyl / 5-methylbenzenethiols with o-halonitrobenzenes and 1,4-benzothiazines were prepared by the condensation and oxidative cyclization of 2-amino-3-methyl / 5-methyl benzenethiols with β-diketones / β-ketoesters in dimethylsulfoxide reported elsewhere **(17-19)**.

Phenothiazine-5,5-dioxides (Scheme 1, II a-j) and 4H-1,4-benzothiazine-1, 1-dioxides (Scheme 2, IV a-h) have been prepared by treating phenothiazines and 1,4-benzothiazines respectively with 30% hydrogen peroxide in glacial acetic acid.

The IR spectra of phenothiazine and 4H-1,4-benzothiazine sulfones have been recorded both in potassium bromide pellets and in chloroform solution. All the synthesized phenothiazine and 4H-1,4-benzothiazine sulfones exhibit a sharp intense peak in the region 1390-1300 cm^{-1} and 1390-1310 cm^{-1} respectively in chloroform which can be ascribed to the

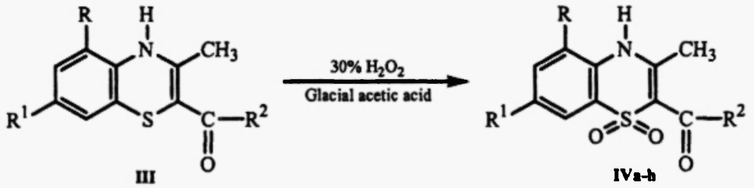


I

IIa-j

$R = H, CH_3$; $R^1 = H, CH_3$; $R^2 = H, Cl$
$R^3 = H, Cl, CF_3$; $R^4 = H, Cl$; $R^5 = H, Cl, NO_2$

Scheme 1



III

IVa-h

$R = H, CH_3$; $R^1 = H, CH_3$;
$R^2 = C_6H_6\text{-}Br$ (m), $C_6H_4\text{-}CH_3$(m), $C_6H_4\text{-}OC_2H_5$(p), $C_6H_4\text{-}C_2H_5$(p)

Scheme 2

asymmetric stretching (ν_3) mode of sulphonyl group which in the solid state splits into three bands in the region 1420-1330 cm^{-1}, 1355-1250 cm^{-1} and 1270-1200 cm^{-1} in phenothiazine sulfones and in benzothiazine sulfones it appears in the region 1420-1390 cm^{-1}, 1330-1300 cm^{-1} and 1270-1200 cm^{-1}. The symmetrical stretching vibrations ν_1 of phenothiazine and 4H-1,4-benzothiazine sulfones give rise to a doublet in potassium bromide pellets in the region 1180-1100 cm^{-1} and 1180-1050 cm^{-1} whereas in solution it appears in the region 1180-1080 cm^{-1} and 1180-1100 cm^{-1} respectively. The band appearing in the region 600-500 cm^{-1} and 590-510 cm^{-1} in phenothiazine and benzothiazine sulfones respectively can be attributed to bending vibrations (ν_2).

The N-H stretching frequency appears in the region 3430-3305 cm^{-1} and 3420-3315 cm^{-1} in phenothiazine and 4H-1,4-benzothiazine sulfones respectively. A sharp band in the region 1700-1600 cm^{-1} appears due to C=O stretching vibrations in 4H-1,4-benzothiazine sulfones. The asymmetric and symmetric stretching vibrations of methyl group in phenothiazine sulfones occur in the region 2960-2920 cm^{-1} and 2890-2850 cm^{-1} which in 4H-1,4-benzothiazine sulfones occur in the region 2980-2930 cm^{-1} and2950-2860 cm^{-1}. All the phenothiazine and benzothiazine sulfones exhibit a medium intensity band in the region 1080-1040 cm^{-1} and 1070-1030 cm^{-1} respectively due to C-S stretching vibrations.

The ^1H NMR spectra of phenothiazine sulfones **II a-j** and 4H-1,4-benzothiazine sulfones **IV a-d** exhibit a sharp peak in the region δ 9.926-9.352 ppm and δ 10.30-9.70 ppm respectively due to N-H proton. The multiplets observed in the region δ 8.89-6.48 ppm and δ 8.781-6.61 ppm respectively are attributed to the aromatic protons. Compounds **II a,g,h** exhibits a singlet in the region δ 3.663-2.663 ppm due to CH_3 protons at C_9. Compounds **II b** and **II c** exhibit a singlet at δ 2.61 ppm and δ 2.168 ppm respectively due to CH_3 protons at C_1. A singlet in the region δ 3.402-1.934 ppm is observed in compounds **IV d-f, i, j** due to three protons of CH_3 group at C_7. Compounds **IV a-d** show resonance signal in the region δ 2.49-1.81 ppm due to allylic protons at C_3 and another singlet in the region δ 2.38-1.744 ppm due to CH_3 protons at C_7. Compound **IV b** exhibits a singlet at δ 2.40 ppm due to CH_3 protons at meta position of benzoyl side chain at C_2. Compound **IV c** exhibits a quartet and a triplet in the region δ 4.35-3.39 ppm and δ 1.75-1.22 ppm due to CH_2 and CH_3 protons of OC_2H_5 group at para position of benzoyl side chain at C_2. The quartet and triplet observed in the region δ 3.202-2.63 ppm and δ 1.24-1.01 ppm in the compound **IV d** can be assigned to C_2H_5 group at para position of benzoyl side chain at C_2.

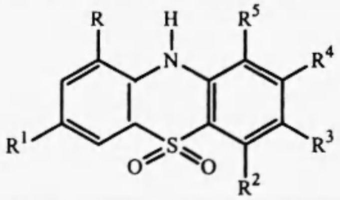
Experimental

All the melting points are uncorrected. The purity of the compounds has been checked by thin layer chromatography using various non-aqueous solvents and characterized by spectral studies. The infrared spectra were recorded on FT IR spectrometer, MAGNA IR 550, NICOLET using potassium bromide discs and in chloroform solution. NMR spectra were recorded on FT NMR Bruker DRX-300 MHz in DMSO-d_6 or $CDCl_3$ containing TMS as an internal standard. Analytical data of newly synthesized compounds are summarized in Tables 1 and 2.

Preparation of phenothiazine sulfones (II a-j) and 4H-1,4-benzothiazine sulfones (IV a-h)

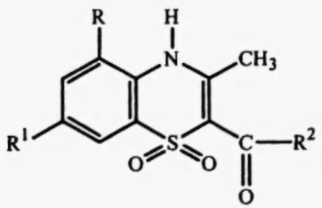
To a solution of 0.01 mole of phenothiazines or 4H-1,4-benzothiazines in 15 ml of glacial acetic acid, 5ml of 30% hydrogen peroxide was added and refluxed at 50-60°C for fifteen minutes. Heating was stopped and another lot of 5 ml of 30% hydrogen peroxide was added. The solution was refluxed for four hours. A major portion of the solvent was then removed by distillation under reduced pressure and then the solution was poured into a beaker

Table 1 : Analytical data of phenothiazine sulfones (IIa-j)



	Compound						M.P. °C	Yield %	Molecular formula	% Found (Calcd.)			
	R	R^1	R^2	R^3	R^4	R^5				C	H	N	S
I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
a	CH_3	H	H	H	H	Cl	160	90	$C_{13}H_{10}NO_2SCl$	55.70 (55.82)	3.62 (3.60)	4.97 (5.01)	11.49 (11.46)
b	CH_3	H	H	Cl	Cl	H	189	94	$C_{13}H_9NO_2SCl_2$	49.78 (49.70)	2.84 (2.89)	4.43 (4.46)	10.26 (10.21)
c	CH_3	H	H	Cl	H	H	159	47	$C_{13}H_{10}NO_2SCl$	55.93 (55.82)	3.59 (3.60)	5.05 (5.01)	11.43 (11.46)
d	H	CH_3	H	H	H	Cl	280	81	$C_{13}H_{10}NO_2SCl$	55.75 (55.82)	3.61 (3.60)	4.96 (5.01)	11.42 (11.46)
e	H	CH_3	H	Cl	Cl	H	260	99	$C_{13}H_9NO_2SCl_2$	49.75 (49.70)	2.93 (2.89)	4.49 (4.46)	10.24 (10.21)
f	H	CH_3	H	Cl	H	H	168	53	$C_{13}H_{10}NO_2SCl$	55.76 (55.82)	3.57 (3.60)	5.06 (5.01)	11.41 (11.46)
g	CH_3	H	H	CF_3	H	NO_2	209	77	$C_{14}H_9N_2O_4SF_3$	46.97 (46.93)	2.57 (2.53)	7.79 (7.82)	8.99 (8.95)
h	CH_3	H	Cl	Cl	H	NO_2	275	91	$C_{13}H_8N_2O_4SCl_2$	43.42 (43.47)	2.25 (2.24)	7.83 (7.80)	8.95 (8.93)
i	H	CH_3	H	CF_3	H	NO_2	260	87	$C_{14}H_9N_2O_4SF_3$	47.01 (46.93)	2.51 (2.53)	7.84 (7.82)	8.97 (8.95)
j	H	CH_3	Cl	Cl	H	NO_2	178	85	$C_{13}H_8N_2O_2SCl_2$	43.59 (43.47)	2.21 (2.24)	7.85 (7.80)	8.94 (8.93)

Table 2 : Analytical data of 4H-1,4-benzothiazine sulfones (IVa-h)



	Compound			M.P. °C	Yield %	Molecular Formula	% Found (Calcd.)			
	R	R¹	R²				C	H	N	S
I	II	III	IV	V	VI	VII	VIII	IX	X	XI
a	H	CH_3	C_6H_4-Br (m)	157	79	$C_{17}H_{14}NO_3SBr$	52.10 (52.05)	3.62 (3.60)	3.60 (3.57)	8.15 (8.17)
b	H	CH_3	C_6H_4-CH_3 (m)	192	82	$C_{18}H_{17}NO_3S$	66.01 (66.03)	5.26 (5.23)	4.33 (4.28)	9.83 (9.79)
c	H	CH_3	C_6H_4-OC_2H_5 (p)	135	89	$C_{19}H_{19}NO_4S$	63.96 (63.85)	5.33 (5.36)	3.89 (3.92)	9.02 (8.97)
d	H	CH_3	C_6H_4·C_2H_5 (p)	163	46	$C_{19}H_{19}NO_3S$	66.69 (66.84)	5.66 (5.61)	4.11 (4.10)	9.32 (9.39)
e	CH_3	H	C_6H_4-Br (m)	239	88	$C_{17}H_{14}NO_3SBr$	52.03 (52.05)	3.62 (3.60)	3.55 (3.57)	8.21 (8.17)
f	CH_3	H	C_6H_4-CH_3 (m)	256	85	$C_{18}H_{17}NO_3S$	65.97 (66.03)	5.21 (5.23)	4.32 (4.28)	9.84 (9.79)
g	CH_3	H	C_6H_4-OC_2H_5 (p)	112	82	$C_{19}H_{19}NO_4S$	63.72 (63.85)	5.40 (5.36)	3.90 (3.92)	8.91 (8.97)
h	CH_3	H	C_6H_4-C_2H_5 (p)	207	44	$C_{19}H_{19}NO_3S$	66.76 (66.84)	5.59 (5.61)	4.12 (4.10)	9.36 (9.39)

containing crushed ice. The residue separated out was collected and crystallization from ethanol afforded the desired product.

Acknowledgement

Head of the Chemistry Department, University of Rajasthan, Jaipur is thanked for providing necessary facilities. Thanks are also due to RSIC, Lucknow for providing NMR spectra.

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