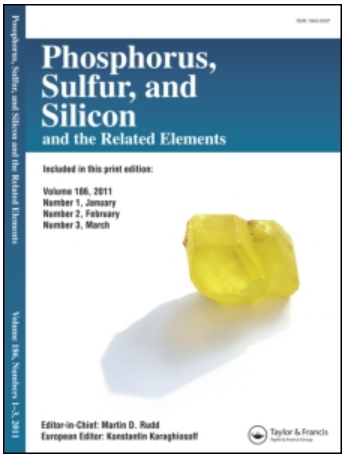

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SYNTHESIS OF 7-BROMO/5,6-DIMETHYL-4*H*-1,4-BENZOTHIAZINES AND THEIR CONVERSION INTO SULFONES

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*The synthesis of 7-bromo/5,6-dimethyl-4*H*-1,4-benzothiazines and their conversion into sulfones is reported. The 7-bromo/5,6-dimethyl-4*H*-1,4-benzothiazines were synthesized by the condensation and oxidative cyclization of 2-amino-5-bromo/3,4-dimethylbenzenethiol with β-diketones in dimethyl sulfoxide. The reaction is believed to proceed via an enaminoketone system. 4*H*-1,4-Benzothiazine sulfones have been synthesized by the oxidation of 4*H*-1,4-benzothiazines using 30% H_2O_2 in glacial acetic acid. The structures of all newly synthesized compounds have been confirmed by elemental analysis and spectral studies.*

Keywords: 2-Amino-5-bromo/3,4-dimethylbenzenethiol; 4*H*-1,4-benzothiazines; 1,4-benzothiazine sulfones; β-diketones

4*H*-1,4-Benzothiazines constitute an important class of heterocycles containing a 1,4-thiazine ring fused to benzene. 4*H*-1,4-Benzothiazines possess a wide spectrum of pharmacological/biological activities.[1–9] The oxidation of sulfide linkage in 4*H*-1,4-benzothiazines to dioxide leads to an interesting class of heterocyclic sulfones not only from the medicinal[10–13] and industrial[14] points of view, but also from structural aspects. It has stimulated our interest to convert benzothiazines to sulfones to understand oxidation behaviour of 4*H*-1,4-benzothiazines and to investigate changes in infrared and nuclear magentic resonance spactra caused by the conversion of sulfide linkage to sulfones.

Thanks to RSIC, Lucknow for providing NMR and mass spectra.

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DISCUSSION

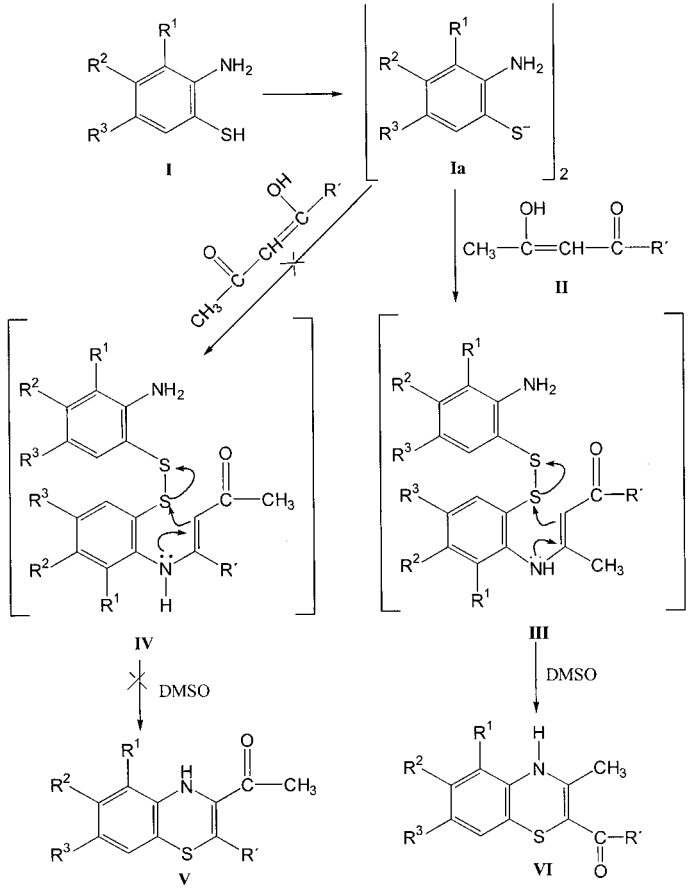
2-Amino-5-bromo/3,4-dimethylbenzenthiol **I** required in the synthesis of title compounds has been prepared by the hydrolytic cleavage of 2-amino-6-bromo/1,5-dimethylbenzothiazole which in turn was prepared by the cyclization of 4-bromo/2,3-dimethyl phenylthiourea by bromine in chloroform. Phenylthiourea was obtained by the action of ammonium thiocyanate on 4-bromo/2,3-dimethylaniline.

The title compounds have been synthesized by a one-pot reaction involving the condensation and oxidative cyclization of 2-amino-5-bromo/3,4-dimethylbenzenethiol with β-diketones in dimethyl sulfoxide. The reaction is believed to proceed through the reaction of enol **II** with formation of an intermediate enaminoketone **III**.[15,16] Under the experimental conditions 2-aminobenzenethiols **I** are readily oxidized to bis(2-aminophenyl) disulfides **Ia**[16,17] which cyclize to 4*H*-1,4-benzothiazines **VI** by scission of sulfur-sulfur bond due to high reactivity of α-position of enaminoketone system **III** toward nucleophilic attack (Scheme-1). 4*H*-1,4-Benzothiazines sulfones **V** have been prepared by the oxidation of 4*H*-1,4-benzothiazines with 30% hydrogen peroxide in glacial acetic acid (Scheme 2).

EXPERIMENTAL

All the melting points are uncorrected. The purity of synthesized compounds was tested by thin layer chromatography using various non-aqueous solvents. Infrared spectra of benzothiazines and their sulfones have been recorded on a Perkin-Elmer spectrophotometer model 577 in KBr discs as well as in chloroform. ^{1}H NMR spectra were scanned on 90 MHz Jeol FX 90Q FT NMR spectrometer and FT NMR Bruker DRX-300 MHz in DMSO-d_6 and $CDCl_3$ containing TMS as internal standard. Their mass spectra were recorded on Jeol SX 102/DA 600 mass spectrometer/data system using argon/xenon as FAB gas at 6KV with 10 mA ionizing current.

*Preparation of 4*H*-1,4-Benzothiazines*: To the stirred supension of β-diketones (**II**; 0.01 *M*) in dimethyl sulfoxide (5 ml) was added 2-amino-5-bromo/3,4-dimethylbenzenethiol (**I**; 0.01 *M*) and the resulting mixture was refluxed for 30–40 minutes. The reaction mixture was concentrated and cooled to room temperature and filtered. The product obtained was washed with petroleum ether and crystallized from methanol. The physical and analytical data of 4*H*-1,4-benzothiazines are given in Table I.

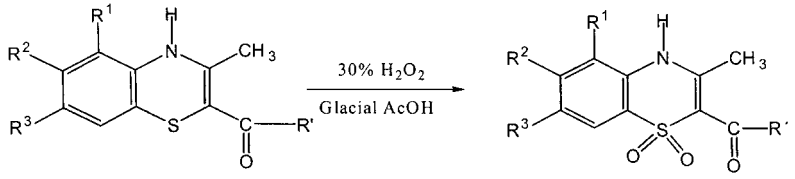


Where

	R^1	R^2	R^3	R′		R^1	R^2	R^3	R′
VI$_a$	CH_3	CH_3	H	C_6H_4-Br(m)	**VI$_e$**	H	H	Br	C_6H_4-Br(m)
VI$_b$	CH_3	CH_3	H	C_6H_4-OC_2H_5(p)	**VI$_f$**	H	H	Br	C_6H_4-CH_3(m)
VI$_c$	CH_3	CH_3	H	C_6H_4-C_2H_5(p)	**VI$_g$**	H	H	Br	C_6H_4-C_2H_5(p)
VI$_d$	CH_3	CH_3	H	C_6H_4-CH_3(m)	**VI$_h$**	H	H	Br	C_6H_4-OC_2H_5(p)

SCHEME 1

*Preparation of 4*H*-1,4-Benzothiazine Sulfones*: 30% hydrogen peroxide (5 ml) was added to a solution of substituted 4*H*-1,4-benzothiazines, (**VI**, 0.01 *M*) in glacial acetic acid (20 ml) and refluxed for 15 min. Heating was stopped and another lot of hydrogen peroxide (5 ml) was added. The reaction mixture was again refluxed for 3–4 h. The excess of solvent was removed by distillation under reduced pressure and poured into a beaker containing crushed ice. The yellow residue obtained was filtered off, washed with water successively, and crystallized from ethanol.



VI VII

SCHEME 2

Physical data of 4*H*-1,4-benzothiazine sulfones synthesized are shown in Table II.

INFRARED SPECTRA

In all the 4*H*-1,4-benzothiazines sharp peaks in KBr discs are observed in the region (3260–3280 cm^{-1}) due to N—H stretching vibrations and shifted to slightly higher frequency (3350–3410 cm^{-1}) in corresponding sulfones. A sharp band appears in the region 1600–1620 cm^{-1} due to C=O stretching vibrations in 4*H*-1,4-benzothiazines and shifts toward higher frequency region of (1620–1660 cm^{-1}) in the corresponding sulfones. All the 4*H*-1,4-benzothiazine sulfones exhibit an intense peak in the region (1340–1355 cm^{-1}) in chloroform which can be ascribed to the asymmetric stretching mode of the sulfonyl group which in solid

TABLE I Physical and Analytical Data of 4*H*-1,4-Benzothiazines (**VI_{a-h}**)

								% (Calcd.) found		
Compd.	R_1	R_2	R_3	R^1	m.p. °C	Molecular formula	% Yield	C	H	N
VI_a	CH_3	CH_3	H	C_6H_4Br(m)	93	$C_{18}H_{16}BrNOS$	24.54	(57.75) 57.73	(4.27) 4.28	(3.74) 3.73
VI_b	CH_3	CH_3	H	$C_6H_4OC_2H_5$(p)	125	$C_{20}H_{21}NO_2S$	18.08	(70.79) 70.77	(6.19) 6.18	(4.12) 4.12
VI_c	CH_3	CH_3	H	$C_6H_4C_2H_5$(p)	105	$C_{20}H_{21}NOS$	55.06	(74.30) 74.30	(6.50) 6.51	(4.33) 4.31
VI_d	CH_3	CH_3	H	$C_6H_4CH_3$(m)	120	$C_{19}H_{19}NOS$	21.82	(73.78) 73.78	(6.14) 6.13	(4.53) 4.52
VI_e	H	H	Br	C_6H_4Br(m)	104	$C_{16}H_{11}Br_2NOS$	90.24	(45.20) 45.16	(2.58) 2.59	(3.29) 3.27
VI_f	H	H	Br	$C_6H_4CH_3$(m)	110	$C_{17}H_{14}BrNOS$	19.83	(56.68) 56.67	(3.89) 3.86	(3.88) 3.89
VI_g	H	H	Br	$C_6H_4OC_2H_5$(p)	105	$C_{18}H_{16}BrNOS$	54.54	(57.75) 57.74	(4.27) 4.25	(3.74) 3.75
VI_h	H	H	Br	$C_6H_4OC_2H_5$(p)	75	$C_{18}H_{16}BrO_2NS$	28.77	(55.39) 55.39	(4.10) 4.08	(3.59) 3.57

TABLE II Physical and Analytical Data of Benzothiazine Sulfones (**VII$_{a–d}$**)

	R_1	R_2	R_3	R^1	m.p. °C	% yield	Molecular formula	% (Calcd.) found C	H	N
VII$_a$	H	H	Br	C_6H_4-Br(m)	149	54	$C_{16}H_{11}NSO_3Br_2$	(42.02)	(2.41)	(3.06)
								42.01	2.41	3.07
VII$_b$	H	H	Br	C_6H_4-CH_3(m)	122	43	$C_{17}H_{14}NSO_3Br$	(52.05)	(3.57)	(3.57)
								52.05	3.55	3.57
VII$_c$	H	H	Br	C_6H_4-C_2H_5(p)	224	32	$C_{18}H_{16}NSO_3Br$	(53.21)	(3.94)	(3.45)
								53.21	3.92	3.44
VII$_d$	CH_3	CH_3	H	C_6H_4-CH_3(m)	138	48	$C_{19}H_{19}NSO_3$	(66.86)	(5.57)	(4.11)
								66.80	5.57	4.12

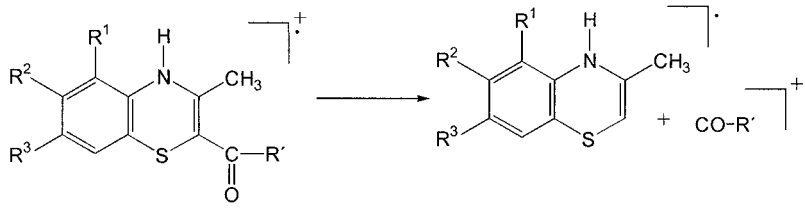
state splits into three bands in the region (1350–1360,1300–1320, 1220–1230 cm^{-1}). The asymmetric stretching vibration in sulfones is strongly affected on passing from solution to the crystalline state. The symmetrical stretching vibrations v_1 gives rise to a doublet and in some cases a broad signal is obtained in potassium bromide pellets in the region (1115–1180 cm^{-1}) whereas in solution it appears at (1116–1182 cm^{-1}). These frequencies are slightly affected by the state of aggregation. In 4*H*-1, 4-benzothiazines a medium intensity band appears at (1010–1070 cm^{-1}) due to C—S stretching vibrations[18] and shifts to higher frequency region (1020–1095 cm^{-1}) in corresponding sulfones.

NMR

A resonance signal due to a N—H proton in benzothiazines appears at (δ 9.51–8.62) and is shifted to downfield (δ 9.32–9.18) in corresponding sulfones. The NMR spectra of 4*H*-1,4-benzothiazines (**VI$_{a–h}$**) exhibit resonance signals in the region (δ 2.31–3.32) due to allylic protons (C=C—CH_3) and are also shifted to downfield (δ 2.32–3.33) in sulfones. A singlet due to CH_3 protons of benzoyl side in compound (**VI$_{d,f}$**) observed at (δ 1.60–1.75) is shifted to downfield (δ 1.87–2.16) in corresponding sulfones (**VII$_{b,d}$**). Quartet and triplet due to ethyl group of benzoyl side in compound (**VI$_{b,c,g,h}$**) are centered in the region (δ2.24–4.27) and (δ 1.08–1.65) are shifted to slightly downfield (δ 2.40–2.80) and (δ 1.49–1.55) in corresponding sulfones. Two signals obtained at (δ 2.28) and (δ1.90) in benzothiazines (**VI$_{a–d}$**) due to two methyl groups at C_5 and C_6 are shifted downfield (δ 2.47) and (δ 1.92) respectively in corresponding sulfone (**VII$_d$**).

MASS SPECTRA

The mass spectrum of each benzothiazine shows molecular ion peak in accordance with their molecular weight and in all cases the side chain at C_2 appears as base peak (Scheme 3).



SCHEME 3

REFERENCES

[1] R. R. Gupta (ed.), *Phenothiazines and 1,4-Benzothiazines: Chemical and Biomedical Aspects* (Elsevier, Amsterdam, 1988).
[2] M. Gordon, *Psychopharmacological Agents Medicinal Chemistry*, edited by M. Gordon (Academic Press, New York, 1967), vol. H, p. 119.
[3] H. Keyzer, G. M. Eckert, I. S. Forrest, et al., Proceedings of the Sixth International Conference on Phenothiazines and Structurally Related Psychotropic Compounds, Pasadena, California, Septermber 11–14, 1990 (Kriger Publishing Company, Malabar, Florida, 1992).
[4] R. R. Gupta, R. S. Rathore, M. Jain, and V. Saraswat, *Pharmazie*, **47,** 229 (1992).
[5] J. Iwao, T. Iso, and M. Oya, Eur. Pat. 166, 386 (1984); *Chem. Abstr.*, **102**, 24637 (1985).
[6] C. Sastry, V. Reddy, B. Ram., et al., *Ind. J. Chem.*, **28,** 52 (1989).
[7] V. Gupta and R. R. Gupta, *J. Prakt. Chem.*, **333,** 153 (1989).
[8] R. R. Gupta, S. K. Jain, V. Gupta, and R. K. Rathore, *Pharmazie*, **44,** 572 (1989).
[9] R. R. Gupta, R. K. Gautam, and R. Kumar, *Heterocycles*, **22,** 1143 (1984).
[10] G. Filacchioni, V. Nacci, and G. Stefancich, *Farmaco. Ed. Sic.*, **31,** 478 (1976); *Chem. Abstr.*, **85,** 143048 (1976).
[11] G. Fengler, D. Arlt, and K. Groche, Ger. Offen., 3, 329, 124 (1984); *Chem. Abstr.*, **101,** 90953 (1984).
[12] R. N. Prasad, *J. Med. Chem.*, **12,** 290 (1969); *Chem. Abstr.*, **70,** 106447 (1969).
[13] H. Zinnes, M. Schwtrz, and J. Shavel, Jr. Ger. Offen., 2, 208, 351 (1972); *Chem. Abstr.*, **77,** 164722 (1972).
[14] C. R., Rasmussen, U.S. Pat., 3, 476, 749 (1969); *Chem. Abstr.*, **72,** 217227 (1970).
[15] D. D. Bhatnager, K. K. Gupta, V. Gupta, and R. R. Gupta, *Curr. Sci.*, **58**, 1091 (1989).
[16] R. R. Gupta, R. K. Rathore, V. Gupta, and R. S. Rathore, *Pharmazie*, **46,** 602 (1991).
[17] R. R. Gupta and Rakesh Kumar, *J. Fluor. Chem.*, **31,** 19 (1986).
[18] M. Marziano, G. Montavdo, and R. Passerini, *Ann. Chim.*, **52,** 121 (1962).