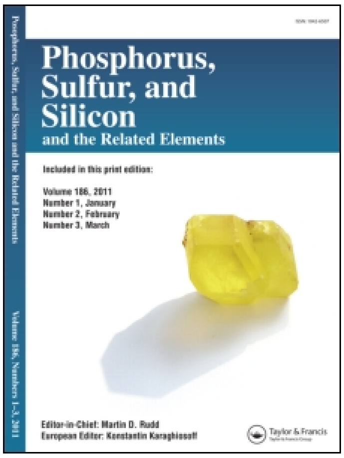

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SYNTHESIS OF 5,8-DICHLORO-3-METHYL-4H-1,4- BENZOTHIAZINES AND THEIR CONVERSION INTO SULFONES

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SYNTHESIS OF 5,8-DICHLORO-3-METHYL-4H-1,4-BENZOTHIAZINES AND THEIR CONVERSION INTO SULFONES

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The present work consists of the one pot synthesis of 5,8-dichloro-3-methyl-4H-1,4-benzothiazines by the condensation and oxidative cyclization of 2-amino-3,6-dichlorobenzenethiol with β-diketones/β-ketoesters in dimethyl sulfoxide and oxidation behaviour of 4H-1,4-benzothiazines by 30% hydrogen peroxide in glacial acetic acid to 1,4-benzothiazine sulfones. The structure of all the newly synthesized compounds has been confirmed by elemental analysis and spectral studies.

Key words: 4H-1,4-Benzothiazines, 1,4-benzothiazine sulfones, 3,6-dichloro-2-aminobenzenethiol, β-diketones; β-ketoesters.

INTRODUCTION

4H-1,4-Benzothiazines constitute an important class of heterocycles containing 1,4-thiazine ring fused to benzene. 4H-1,4-Benzothiazines possess a wide spectrum of pharmacological/biological activities similar to phenothiazines[1-3] due to the presence of a fold along the nitrogen-sulfur axis which is one of the structural factors needed to impart similar pharmaceutical/biological activities.[4-9] The oxidation of sulfide linkage in 4H-1,4-benzothiazines to dioxide leads to an interesting class of heterocyclic sulfones not only from the medicinal[10-13] and industrial[14] point of view, but also from structural aspects. It has stimulated our interest to convert benzothiazines to sulfones to understand oxidation behaviour of 4H-1,4-benzothiazines and to investigate changes in infrared and nuclear magnetic resonance spectra caused by the conversion of sulfide linkage to sulfones.

DISCUSSION

The title compounds have been synthesized by a one pot reaction involving the condensation and oxidative cyclisation of 2-amino-3,6-dichlorobenzenethiol with dicarbonyl compounds in dimethyl sulfoxide. The reaction is believed to proceed through the formation of an intermediate enaminoketone (**III**).[15,16] Under the experimental conditions substituted 2-aminobenzenethiols (**I**) are readily oxidized to bis(2-aminophenyl) disulfides (**Ia**)[16,17] which cyclise to substituted 4H-1,4-benzothiazines (**IV**) by scission of sulfur-sulfur bond due to high reactivity of α-position of enaminoketone system (**III**) towards nucleophilic attack (Scheme 1).

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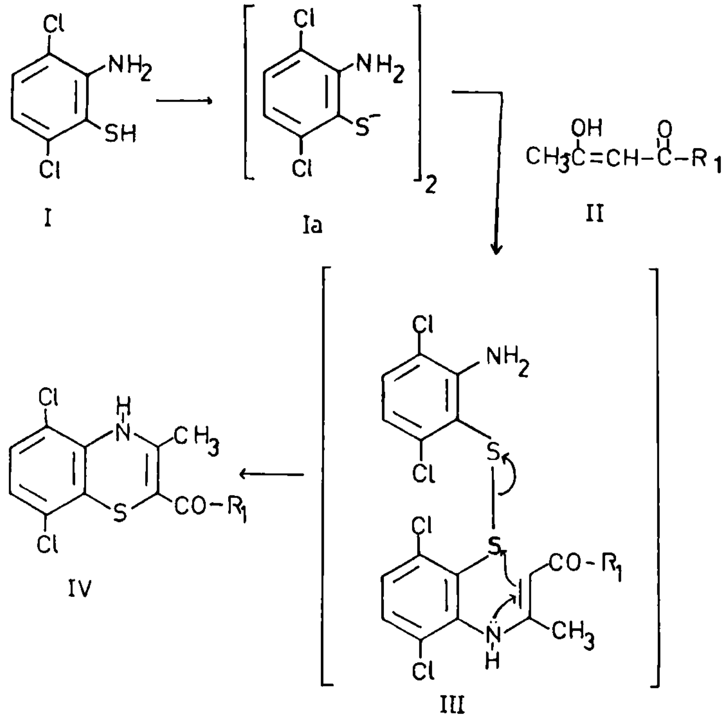
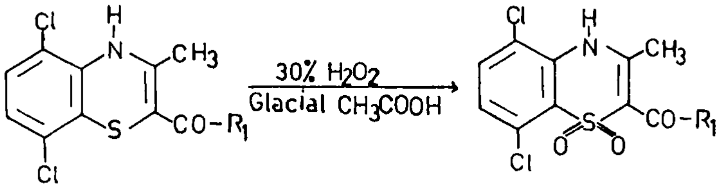


R_1=CH_3, OCH_3, OC_2H_5, —$C_6H_4CH_3$(p), —$C_6H_4OCH_3$(p), —C_6H_5, —C_6H_4Cl(p), —C_6H_4Br(p), —C_6H_4F(p), —$C_6H_3(OCH_3)_2$(o,p) —$C_6H_3(OCH_3)_2$(m,p)

Scheme-1



Scheme-2

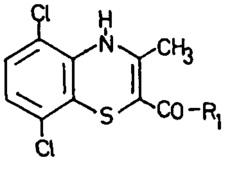
4H-1,4-Benzothiazines sulfones (V) have been prepared by the oxidation of 4H-1,4-benzothiazines with 30% hydrogen peroxide in glacial acetic acid (Scheme 2).

EXPERIMENTAL

All the melting points are uncorrected. The purity of synthesized compounds was tested by thin layer chromatography using various non-aqueous solvents. Infra-red 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 in DMSO-d_6 containing TMS as internal standard and their mass spectra were recorded on Jeol JMSD-300 mass spectrometer at 70 eV with 100 μamp ionising current.

Preparation of substituted-5,8-dichloro-3-methyl-4H-1,4-benzothiazines. To the stirred suspension of β-diketones/β-ketoesters (**II**; 0.01 M) in dimethyl sulfoxide (5 ml) was added in 3,6-dichloro-2-amino-

TABLE I
Physical data of 4H-1,4-benzothiazines (**IVa–k**)



Compound		M.P.	Yield	Molecular	% Found/(Calcd.)		
	R_1	°C	%	Formula	C	H	N
I	II	III	IV	V	VI	VII	VIII
IVa	$-OCH_3$	105-107	56.59	$C_{11}H_9Cl_2NO_2S$	45.66 (45.51)	3.12 (3.10)	4.71 (4.82)
IVb	$-C_6H_4Br(p)$	125-127	63.17	$C_{16}H_{10}BrCl_2NOS$	46.44 (46.26)	2.41 (2.40)	3.36 (3.37)
IVc	$-OC_2H_5$	106-108	72.74	$C_{12}H_{11}Cl_2NO_2S$	47.58 (47.36)	3.59 (3.61)	4.57 (4.60)
IVd	$-CH_3$	119-121	63.97	$C_{11}H_9Cl_2NOS$	48.36 (48.17)	3.26 (3.28)	5.07 (5.10)
IVe	$-C_6H_5$	125-129	60.46	$C_{16}H_{11}Cl_2NOS$	57.35 (57.14)	3.29 (3.27)	4.19 (4.16)
IVf	$-C_6H_4Cl(p)$	139-141	70.65	$C_{16}H_{10}Cl_3NOS$	51.94 (51.82)	2.70 (2.69)	3.75 (3.77)
IVg	$-C_6H_4OCH_3(p)$	152-154	49.90	$C_{17}H_{13}Cl_2NO_2S$	55.94 (55.73)	3.57 (3.55)	3.80 (3.82)
IVh	$-C_6H_4CH_3(p)$	114-116	40.42	$C_{17}H_{13}Cl_2NOS$	58.49 (58.28)	3.73 (3.71)	3.97 (4.00)
IVi	$-C_6H_3(OCH_3)_2(o,p)$	167-169	71.62	$C_{18}H_{15}Cl_2NO_3S$	54.78 (54.54)	3.80 (3.78)	3.51 (3.53)
IVj	$-C_6H_4F(p)$	163-166	40.03	$C_{16}H_{10}FCl_2NOS$	54.45 (54.23)	2.83 (2.82)	3.96 (3.95)
IVk	$-C_6H_3(OCH_3)_2(m,p)$	144-146	68.71	$C_{18}H_{15}Cl_2NO_3S$	54.77 (54.54)	3.80 (3.78)	3.52 (3.53)

benzenethiol (**I**; 0.01 M) and the resulting mixture was refluxed for 30–40 minutes. The reaction mixture was concentrated and cooled down to room temperature and filtered. The product obtained was washed with petroleum ether and crystallised from methanol. The physical and analytical data of 4H-1,4-benzothiazines are given in Table I.

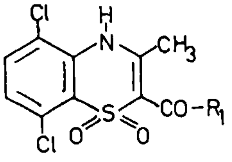
Preparation of substituted-5,8-dichloro-3-methyl-4H-1,4-benzothiazine sulfones. 30% Hydrogen peroxide (5 ml) was added to a solution of substituted 4H-1,4-benzothiazines (IV; 0.01 M) in glacial acetic acid (20 ml) and refluxed for fifteen minutes. Heating was stopped and another lot of hydrogen peroxide (5 ml) was added. The reaction mixture was again refluxed for 3–4 hours. 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 crystallised from ethanol. Physical data of 4H-1,4-benzothiazine sulfones synthesized are tabulated in Table II.

INFRARED SPECTRA

In all the 4H-1,4-benzothiazines, sharp peaks in KBr discs are observed in the region 3260–3480 cm^{-1} due to N—H stretching vibrations and are shifted to slightly

TABLE II

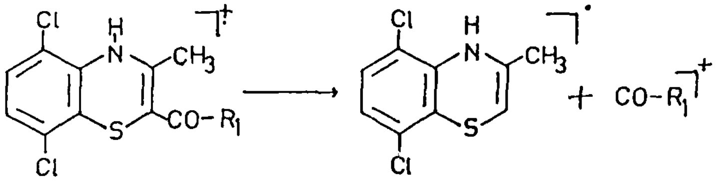
Physical data of 4H-1,4-benzothiazines sulfones (Va–k)



	Compound R_1	M.P. °C	Yield %	Molecular Formula	% Found/(Calcd.)		
					C	H	N
I	II	III	IV	V	VI	VII	VIII
Va	$-OCH_3$	99-101	41.12	$C_{11}H_9Cl_2NO_4S$	41.15 (40.99)	2.80 (2.79)	4.31 (4.34)
Vb	$-C_6H_4Br(p)$	87-89	60.85	$C_{16}H_{10}BrCl_2NO_3S$	42.17 (42.95)	2.24 (2.23)	3.12 (3.13)
Vc	$-OC_2H_5$	116-118	70.55	$C_{12}H_{11}Cl_2NO_4S$	42.97 (42.85)	3.29 (3.27)	4.14 (4.16)
Vd	$-CH_3$	119-121	40.30	$C_{11}H_9Cl_2NO_3S$	43.36 (43.13)	2.95 (2.94)	4.60 (4.57)
Ve	$-C_6H_5$	81-83	58.71	$C_{16}H_{11}Cl_2NO_3S$	52.38 (52.17)	3.00 (2.98)	3.81 (3.80)
Vf	$-C_6H_4Cl(p)$	149-151	64.87	$C_{16}H_{10}Cl_3NO_3S$	47.90 (47.70)	2.50 (2.48)	3.48 (3.47)
Vg	$-C_6H_4OCH_3(p)$	79-81	48.28	$C_{17}H_{13}Cl_2NO_4S$	51.36 (51.25)	3.28 (3.26)	3.52 (3.51)
Vh	$-C_6H_4CH_3(p)$	84-86	38.09	$C_{17}H_{13}Cl_2NO_3S$	53.81 (53.40)	3.42 (3.40)	3.64 (3.66)
Vi	$-C_6H_3(OCH_3)_2(o,p)$	75-77	70.62	$C_{18}H_{15}Cl_2NO_5S$	50.65 (50.46)	3.52 (3.50)	3.29 (3.27)
Vj	$-C_6H_4F(p)$	69-71	37.26	$C_{16}H_{10}FCl_2NO_3S$	49.56 (49.74)	2.60 (2.59)	3.61 (3.62)
Vk	$-C_6H_3(OCH_3)_2(m,p)$	89-91	65.30	$C_{18}H_{15}Cl_2NO_5S$	50.17 (50.46)	3.52 (3.50)	3.29 (3.27)

higher frequency, 3320–3485 cm^{-1}, in the corresponding sulfones. A sharp band appears in the region 1550–1625 cm^{-1} due to C=O stretching vibrations in 4H-1,4-benzothiazines and shifts towards the higher frequency region of 1670–1695 cm^{-1} in the corresponding sulfones.

All the 4H-1,4-benzothiazine sulfones exhibit an intense peak in the region 1340–1390 cm^{-1} in chloroform which can be ascribed to the asymmetric stretching mode of the sulfonyl group, which in solid state splits into three bands in the region 1340–1395, 1305–1345 and 1235–1280 cm^{-1}. The asymmetric stretching vibration in the sulfone 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 4H-1,4-benzothiazines a medium intensity band appears at 1010–1070 cm^{-1} due to C—S stretching vibration[18] and shifts to higher frequency region 1020–1095 cm^{-1} in corresponding sulfones. Peaks



Scheme-3

corresponding to C—Cl stretching vibrations appear at 750–770 cm^{-1} in benzothiazines as well as in sulfones.

NMR

A resonance signal due to a N—H proton in benzothiazines appears at δ 7.95–8.62 and is shifted to downfield (δ 8.36–8.84 ppm) in corresponding sulfones. The NMR spectra of 4H-1,4-benzothiazine (**IVa–k**) exhibit resonance signals in the region δ 1.93–2.65 ppm due to allylic protons ($C{=}C{-}CH_3$) and is also shifted downfield (δ 2.12–2.91 ppm) in sulfones. A singlet due to CH_3 protons of the $COOCH_3$ group (**IVa**) at C_2, observed at δ 3.51 ppm, is shifted to downfield (δ 3.86 ppm) in corresponding sulfones (**Va**). Quartets and triplets due to the carboethoxy group at C_2 in benzothiazine (**IVc**) are centered in the region δ 4.02–4.40 ppm and δ 4.10–4.45 ppm respectively in sulfones (**Vc**). The singlet observed at δ 3.51 ppm due to OCH_3 protons at the para position of the benzoyl side chain at C_2 in benzothiazines (**IVg**) is also shifted downfield (δ 3.62 ppm) in the corresponding sulfone. Two signals obtained at δ 4.00 ppm and δ 4.09 ppm in benzothiazine (**IVi**), due to the two methoxy groups at ortho and para positions in benzoyl side chain at C_2, are shifted downfield (δ 4.15 ppm) and (δ 4.37 ppm) respectively in the corresponding sulfone (**Vi**).

MASS SPECTRA

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

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