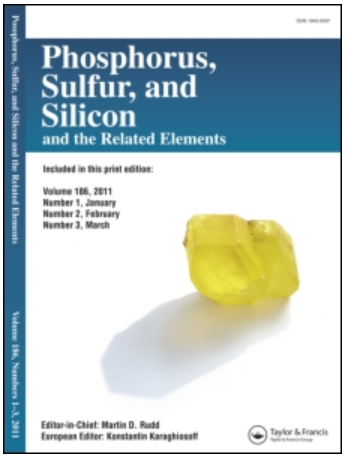

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SYNTHESIS OF SULPHONATED 4H-1,4-BENZOTHIAZINES

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SYNTHESIS OF SULPHONATED 4H-1,4-BENZOTHIAZINES

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Single step and convenient synthesis for 6-sulphonated 4H-1,4-benzothiazines is reported by the condensation and oxidative cyclization of 2-aminobenzenethiol-4-sulphonic acid with β-diketones. 2-Aminobenzenethiol-4-sulphonic acid has been synthesized directly by the reaction of sulphuric acid and 2-aminobenzenethiol. The structures of synthesized compounds were confirmed by spectral studies.

INTRODUCTION

Phenothiazines (dibenzothiazines) are of great importance because of their applications in medicines as tranquilisers[1-3] and antitumor agents.[4-7] The biological activities of phenothiazines have been ascribed to structural specificity due to a fold along N–S axis. Such structural specificity is also present in 4H-1,4-benzothiazines, but because of their limited availability significant research work on biological activities of 4H-1,4-benzothiazines could not be done. Therefore, it is considered worthwhile to report synthesis of 4H-1,4-benzothiazines by a single step and convenient method to make them available for screening their pharmacological activities.

DISCUSSION

In the present communication we wish to report synthesis of 6-sulphonated 4H-1,4-benzothiazines by a convenient method[8-13] involving the condensation and oxidative cyclization of 2-aminobenzenethiol-4-sulphonic acid with β-diketones in the presence of DMSO. Although a number of methods have been developed for the synthesis of substituted 2-aminobenzenethiols, none of them has been found convenient for the synthesis of 2-aminobenzenethiol-4-sulphonic acid. Substituted 2-aminobenzenethiols are generally prepared by alkaline hydrolysis of Herz compound,[14] but this reaction cannot be used to obtain 2-aminobenzenethiol-4-sulphonic acid because chlorination takes place at both 3- and 5-position during Herz reaction. Another widely used method[15] is by the hydrolytic fission of 2-aminobenzothiazoles which, in turn, are prepared by the thiocyanation of aryl amines. This process also does not provide 2-aminobenzenethiol-4-sulphonic acid, since thiocyanation occurs

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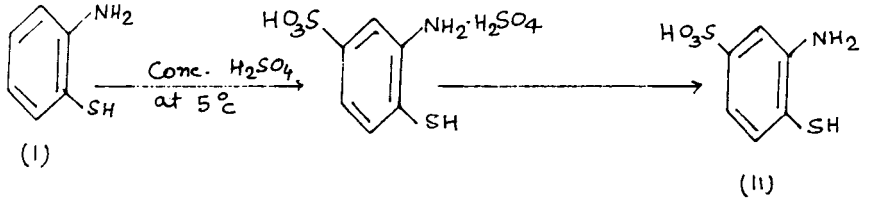
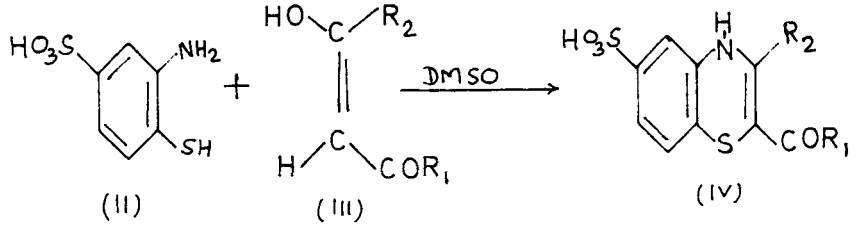
at both ortho and para positions. Most reported methods[16–18] used for the preparation of substituted 2-amino benzenethiol involved the formation of zinc thiolate as intermediate in which purification of zinc salt was found unsatisfactory and difficult.

In this communication 2-aminobenzenethiol-4-sulphonic acid (II) has been synthesized[19] directly from the 2-aminobenzenethiol (I) by the reaction of sulphuric acid at 5°C in quantitative yield (Scheme 1). Since thiol group is *o*, *p*-orienting and protonated amino group being electron withdrawing is meta orienting, the formation of para product would be most favoured. The formation of the ortho or ortho and para disulphonic acid product is less likely due to steric hinderance of the bulky sulphonic acid group.



SCHEME 1

6-Sulphonated 4H-1,4-benzothiazines (IV) have been synthesized by the condensation and oxidative cyclization of 2-aminobenzenethiol-4-sulphonic acid (II) with β-diketones (III) in DMSO (Scheme 2).



R_2 = CH_3, C_6H_5; R_1 = CH_3, OC_2H_5, C_6H_5, C_6H_4Cl-p

SCHEME 2

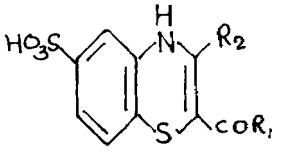
EXPERIMENTAL

All the melting points have been recorded on IEC (India) melting point apparatus calibrated with oxalic acid. The purity of synthesized compounds was tested by thin layer chromatography on silica gel in various non-aqueous solvents. The IR spectra of all the synthesized 4H-1,4-benzothiazines exhibit a single intense peak in the region 3260–3350 cm^{-1} which corresponds to NH-stretching vibrations. The sharp band in the region 1575–1620 cm^{-1} is due to C=O stretching vibrations. All the compounds, except compound (c), exhibit sharp bands in the region 1370–1480 cm^{-1} due to C—H deformation vibrations of CH_3 group. The absorption bands in the region 1250–1350 cm^{-1} are attributed to—SO_3H group vibrations. 2-Aminobenzenethiol-4-sulphonic acid exhibited a peak at 2570 cm^{-1}, characteristic of the SH group and two peaks in the region 3350–3475 cm^{-1}, characteristic of NH_2 group.

The NMR spectra of all the 4H-1,4-benzothiazines having allylic linkage (C=C–CH_3) exhibit resonance signals in the region δ 2.3–2.0. A singlet peak in the region δ 8.7–8.35 is ascribed to NH proton in all compounds. A triplet signal centered at δ 1.0 is due to CH_3 protons and quartet centered at δ 3.9 is

TABLE I

6-Sulphonated 4H-1,4-benzothiazines (IVa–e)



Compound No.	Compound		Melting point	Colour	Molecular formula	Found (%)			Calcd. (%)		
	R_1	R_2				C	H	N	C	H	N
a	CH_3	CH_3	176°	Orange	$C_{11}H_{11}NS_2O_4$	46.40	3.88	4.93	46.31	3.85	4.91
b	OC_2H_5	CH_3	119°	Yellow	$C_{12}H_{13}NS_2O_5$	45.79	4.14	4.45	45.71	4.12	4.44
c	C_6H_5	C_6H_5	170°	Red	$C_{21}H_{15}NS_2O_4$	61.68	3.69	3.43	61.61	3.66	3.42
d	C_6H_5	CH_3	165°	Red	$C_{16}H_{13}NS_2O_4$	55.40	3.76	4.04	55.33	3.74	4.03
e	C_6H_4Cl-p	CH_3	190°	Red	$C_{16}H_{12}NS_2O_4Cl$	50.45	3.16	3.69	50.32	3.14	3.66

assigned to CH_2 protons of ethyl group in compound (b) having ester group. The multiplets in the region of δ 7.6–6.2 are due to aromatic ring protons. A singlet centered at δ 7.9 arising due to SO_3H group in all 4H-1,4-benzothiazines was also observed.

The mass spectrum showed molecular ion peaks corresponding to their molecular weights. The fragment M^+-81, although weak (about 20% of the base peak) is always present which is suggesting the loss of SO_3H radical from the nucleus. The peak M^+-17, although of variable intensity, is present in the case of all these 4H-1,4-benzothiazines by the loss of OH radical from sulphonic group at position-6 in their second fragmentation path. McLafferty rearrangement[20] appears to exist in compound (b) and gave peaks at $M^+-C_2H_5$, $M^+-C_2H_4$ and $M^+-OC_2H_5$.

Synthesis of 2-Aminobenzenethiol-4-sulphonic acid (II). To sulphuric acid (sp. gr. 1.84) (100 ml) distilled 2-aminobenzenethiol (I; 50 ml) was added dropwise and then the yellowish-white mass obtained was dissolved immediately by mechanical stirring. The stirring was continued for 30 min and the thick white mass obtained was poured into a beaker containing ice cold water and stirred till the effervescences ceased. The precipitate was filtered, washed with ice cold water and recrystallized from water and the colourless shining crystals (38 gm) obtained were dried over calcium chloride (m.p. 190°C, Calcd. : C, 35.12; H, 3.41; N, 6.82; S, 31.21. Found C, 35.20; H, 3.44 : N, 6,87; S, 31.24%).

Synthesis of 6-Sulphonated 4H-1,4-Benzothiazines (IVa–e). β-Diketone (III; 0.01 mol) (acetylacetone, ethyl acetoacetate, dibenzoylmethane, benzoylacetone or *p*-chlorobenzoylacetone) was added to the stirred suspension of 2-aminobenzenethiol-4-sulphonic acid (II; 0.01 mol) in DMSO (5 ml) and heated for only 15 min at 80°C. The reaction mixture was cooled down to room temperature and solid substance separated was filtered and crystallized from methanol. The physical data are summarized in Table I.

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