Synthesis of 6-Halogenated 4*H*-1,4-Benzothiazines

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The synthesis of 6-halogenated 4*H*-1,4-benzothiazines is reported by the condensation and oxidative cyclization of 4-substituted 2-aminobenzenethiols (I, R = Cl, Br) with β-diketones in presence of DMSO. The ir, nmr and mass spectral studies are included. 4-Substituted 2-aminobenzenethiols were also prepared by an improved and direct method.

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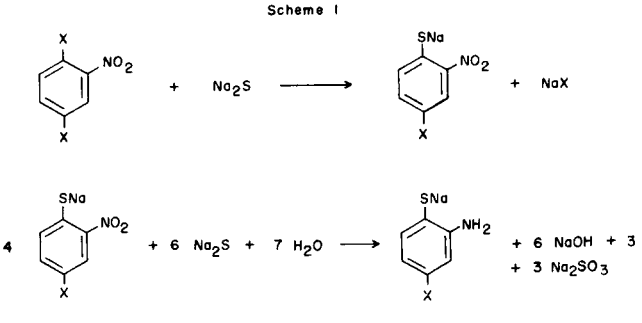
Phenothiazine derivatives are well known for their CNS activity [1] and antitumor effects [2-5]. These types of activities have been ascribed to a structural specificity, *i.e.* a fold along N-S axis which is present in phenothiazines. Similar structural specificity is also present in 4*H*-1,4-benzothiazines and benzothiazines are, therefore, also supposed to have similar types of biological activities. Therefore, with this in mind we have been prompted to synthesize 6-halogenated 4*H*-1,4-benzothiazines by a convenient method to make them available for biological screening and to search out potential drugs of 4*H*-1,4-benzothiazine series.

Substituted 2-aminobenzenethiols are generally prepared by alkaline hydrolysis of the Herz compound [6], but 4-substituted 2-aminobenzenethiols cannot be prepared by the Herz reaction because chlorination takes place at the 3- and 5-positions during the Herz reaction. Most of the methods reported for the preparation of substituted 2-aminobenzenethiols involve the formation of zinc mercaptide as an intermediate [7-10]. While preparing these compounds we found that a large amount of zinc hydroxide was precipitated along with the formation of zinc mercaptide.

Decomposition of the zinc salt with concentrated hydrochloric acid gave the hydrochloride of the amine, but because of the low solubility of the zinc salt prolonged heating was required and thus led to extensive loss of product. The purification of the zinc salt was found unsatisfactory and difficult and resulted in low yields and impure samples.

Scheme 1



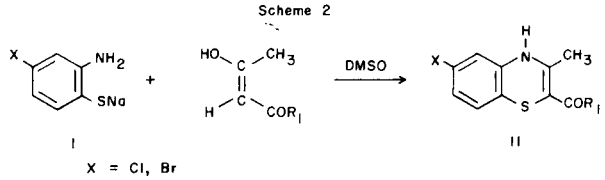
A survey of the literature revealed that the 4-substituted 2-aminobenzenethiols have been prepared mostly by the reduction of the appropriate dinitrodiphenyl sulphides, however in the present manuscript we describe the formation of the sodium salts of 4-chloro- and 4-bromo-2-aminobenzenethiols directly from the respective 2,5-dihalonitrobenzenes (Scheme 1).

The identity of the two different samples of the sodium salts (one obtained by the conversion of zinc salt into the sodium salt and other obtained directly) was established by the formation of the same diphenyl sulphides with 2,4-dinitrochlorobenzene.

This method provided an excellent route for the preparation of 4-substituted 2-aminobenzenethiols without the necessity of isolating the zinc mercaptides.

4-Substituted 2-aminobenzenethiols (I, Cl, Br) were condensed with β-diketones (acetylacetone, ethyl acetoacetate, benzoylacetone, *p*-chlorobenzoylacetone, *p*-methoxybenzoylacetone and *p*-methylbenzoylacetone) in DMSO which in turn by oxidative cyclization gave the corresponding 4*H*-1,4-benzothiazines (Scheme 2).

Scheme 2



I II

X = Cl, Br

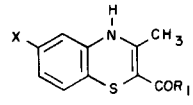
R_1 = CH_3, C_6H_5, C_6H_4Cl-p, $C_6H_4CH_3$-p, $C_6H_4OCH_3$-p, OC_2H_5

Infrared Spectra.

The substituted 2-aminobenzenethiols exhibited two peaks in the region 3350-3475 cm^{-1}; characteristic of the primary amino group. All of the 6-halogenated 4*H*-1,4-benzothiazines showed an NH absorption in the region of 3250-3350 cm^{-1} and carbonyl absorption in the region of 1570-1635 cm^{-1}. The bands in the region of 1600-1510 cm^{-1} are attributed to C=C stretching vibrations. The sharp absorption bands in the region 1355-1480 cm^{-1} are attributed to C-CH_3 vibrations in all 6-halogenated 4*H*-1,4-benzothiazines.

Table 1

6-Halogenated 4*H*-1,4-Benzothiazines



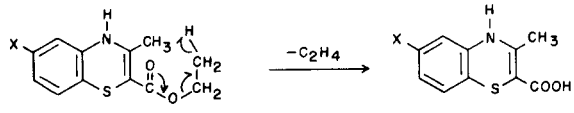
Compound No.	X	Compound R_1	Mp °C	Colour	Yield %	Molecular formula	Analysis, % Found C	Found H	Found N	Calcd. C	Calcd. H	Calcd. N
1	Cl	CH_3	221	Orange	56	$C_{11}H_{10}ClNSO$	55.20	4.19	5.86	55.11	4.17	5.84
2	Cl	OC_2H_5	154	Yellow	61	$C_{12}H_{12}ClNSO_2$	53.51	4.50	5.13	53.43	4.45	5.19
3	Cl	C_6H_5	199	Red	68	$C_{16}H_{12}ClNSO$	63.76	4.01	4.66	63.68	3.98	4.64
4	Cl	C_6H_4Cl-*p*-	209	Red	64	$C_{16}H_{11}Cl_2NSO$	57.20	3.30	4.17	57.14	3.27	4.16
5	Cl	C_6H_4-OCH_3-p	182	Red	70	$C_{17}H_{14}ClNSO_2$	61.42	4.20	4.25	61.53	4.22	4.22
6	Cl	$C_6H_4CH_3$-*p*	190	Red	68	$C_{17}H_{14}ClNSO$	64.56	4.41	4.47	64.65	4.43	4.43
7	Br	CH_3	234	Orange	54	$C_{11}H_{10}BrNSO$	46.56	3.54	4.93	46.47	3.52	4.92
8	Br	OC_2H_5	150	Yellow	56	$C_{12}H_{12}BrNSO_2$	45.96	3.88	4.50	45.85	3.82	4.45
9	Br	C_6H_5	183	Red	63	$C_{16}H_{12}BrNSO$	55.58	3.49	4.09	55.49	3.46	4.04
10	Br	C_6H_4Cl-*p*	193	Red	69	$C_{16}H_{11}BrClNSO$	50.52	2.91	3.70	50.45	2.89	3.68
11	Br	$C_6H_4OCH_3$-*p*	168	Red	68	$C_{17}H_{14}BrNSO_2$	54.18	3.70	3.75	54.25	3.72	3.72
12	Br	$C_6H_4CH_3$-*p*	176	Red	53	$C_{17}H_{14}BrNSO$	56.58	3.87	3.90	56.66	3.88	3.88

Nuclear Magnetic Resonance Spectra.

For all of the 6-halogenated 4*H*-1,4-benzothiazines resonance signals in the region τ 7.8-8.3 show the presence of a methyl group in the allylic form. A single sharp peak in the region τ 1.05-1.65 was observed for all the compounds which is due to the NH proton. A triplet centered in the region τ 8.7-9.1 and a quartet in the region τ 5.8-6.4 was observed in compounds **2** and **8** and are due to methyl and methylene of the ethyl group. The multiplets in the region of τ 2.0-3.8 are due to aromatic ring protons. A singlet in the region τ 6.2-6.0 in compounds **5** and **11**, arising due to presence of a methoxy group, was observed.

Mass Spectra.

Mass spectra of all the 6-halogenated 4*H*-1,4-benzothiazines have their abundant peak corresponding to their molecular ion and also display a comparatively intense doubly charged molecular ion peak which indicates the overall stability of the benzothiazine ring system to electron impact. The fragment M^+-32, although weak, suggests the loss of the sulphur nucleus. The peak M^+-105 with high intensity is present in compound **3** and **9** due to the loss of benzoyl free radical. Compounds **2** and **8** with an ethoxyl group of the ester linkage at the 2-position eliminates ethylene (CH_2=CH_2). The elimination of ethylene in the mass spectra of these compounds can be explained by a McLafferty rearrangement [11] which suggests the formation of a 4-membered intermediate in the following way.



EXPERIMENTAL

All of the melting points are uncorrected and the purity of all the compounds synthesized has been checked by thin layer chromatography on silica gel in various non-aqueous solvents. The infrared spectra of all compounds have been scanned in potassium bromide on a Perkin-Elmer 577 grating spectrophotometer and their nmr spectra were recorded on a Perkin Elmer R12B spectrometer using tetramethylsilane as an internal standard. The mass spectra were recorded on a Jeol, JMSD-300 mass spectrometer at 70 eV with 100 μ amp ionizing current.

Preparation of 4-Substituted-2-aminobenzenethiols I.

In a 500 ml round bottom flask equipped with a reflux condenser and a mechanical stirrer, 2,5-dihalonitrobenzene (0.15 mole) and crystalline sodium sulphide (1.41 mole) in water (250 ml) were placed with stirring and heated slowly to a reflux temperature and continued for 24 hours. The reaction mixture was cooled to 15° and filtered to remove insoluble material such as sulphur. The filtrate on concentration and drying provided a light yellow solid and the extraction of the solid with refluxing alcohol gave the sodium salt of 2-amino-4-substituted benzenethiol as a white solid in 50% yield.

Preparation of 6-Halogenated-4*H*-1,4-benzothiazines II.

4-Substituted-2-aminobenzenethiol (I, 0.01 mole) was added to the stirred suspension of β-diketone (0.01 mole) (acetylacetone, ethyl acetoacetate, benzoylacetone, *p*-chlorobenzoylacetone, *p*-methylbenzoylacetone, or *p*-methoxybenzoylacetone) in DMSO (5 ml) and the resulting mixture was refluxed for one hour. The mixture was cooled to room temperature and a solid substance which separated was filtered and crystallised from methanol. The physical data are given in Table 1.

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