Studies on Phenothiazines. Part 7 (1). Synthesis of 3-Substituted 2-Aminobenzenethiols and their Conversion into Phenothiazines

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Synthesis of substituted 1-nitrophenothiazines is reported by the Smiles rearrangement *in situ*, which involves condensation of 3-chloro or methyl-2-aminobenzenethiol with *o*-halonitrobenzenes (2,4,6-trinitochlorobenzene, 1,4-dichloro-2,6-dinitrobenzene, 2,4,6-tribromo-1,3-dinitrobenzene) in the presence of ethanolic sodium hydroxide. Ir and mass spectral studies are included.

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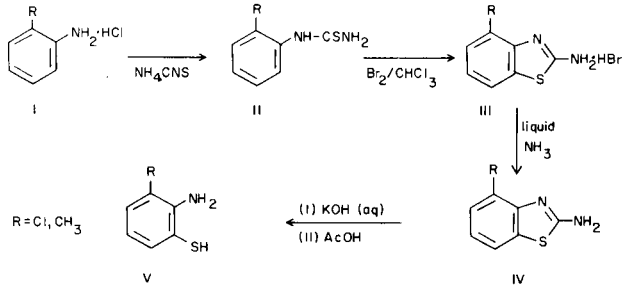
Phenothiazines find a number of uses in medicines such as tranquilisers (2), anticancer drugs (3), antiinflammatory agents (4), antihisteminics (5), anthelmintics (6), local anaesthetics (7), antiseptics (8), growth inhibitors (9) and in the treatment of neuropsychiatric disorders (10), in addition to their uses as insecticides (11) and in industry as antioxidants (12) and stabilisers (13). In continuation to our work (1) on phenothiazines it is considered worthwhile to extend studies on phenothiazine series to develop suitable methods for their synthesis. Substituted *o*-aminobenzenethiols required for the synthesis of phenothiazines are generally prepared by alkaline hydrolysis of the Herz compound (2-chloroisobenzo-1,2,3-dithiazole) or substituted 2-aminobenzothiazole. The Herz reaction (14) has been studied for the synthesis of 2-aminobenzenethiols from aromatic amines. However, the reaction cannot be used to prepare 2-aminobenzenethiols with a free 5-position. It has been reported that aryl amines that are unsubstituted at the *para* position undergo nuclear chlorination during the Herz reaction. Farrington and Warburton (15) failed to isolate 2-aminobenzenethiol from aniline by the Herz reaction, but obtained only 2-amino-5-chlorobenzenethiol. Similarly, the Herz reaction of *o*-chloroaniline and *o*-toluidine yielded (16) 2-amino-3,5-dichlorobenzenethiol and 2-amino-5-chloro-3-methylbenzenethiol, respectively.

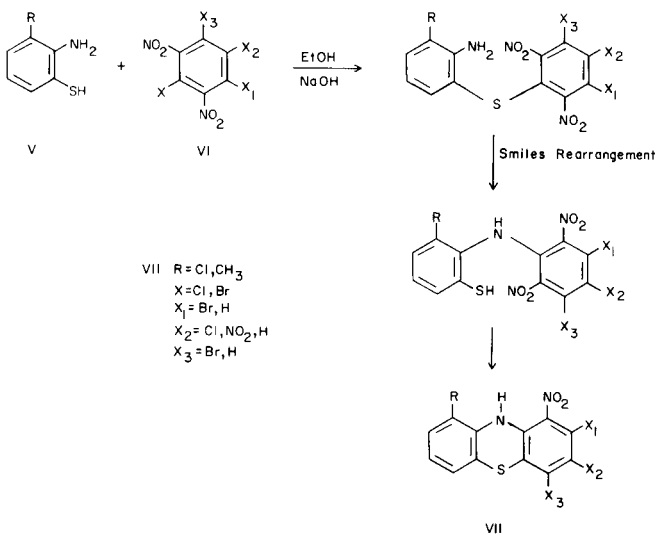
An alternative route for the synthesis of 2-aminobenzenethiols is by hydrolytic fission of 2-aminobenzothiazoles which are prepared by thiocyanogenation of arylamines (17). The reaction is, however, subjected to various limitations which proclude its wide application. When the *para* position in arylamines is free, thiocyanogenation occur in both the *ortho* and *para* positions. Therefore, this method cannot be used for the preparation of *o*-aminobenzenethiols with free 5-position. To overcome these limitations we are reporting a method for the preparation of 2-aminobenzenethiols unsubstituted at 5-position, and their subsequent conversion into 1-nitrophenothiazines. 4-Chloro or methyl-2-aminobenzothiazole has been prepared from the corresponding phenylthiourea by treating it with bromine in chloroform in order to affect cyclisation. The benzothiazoles on alkaline hydrolysis and subsequent neutralisation with acetic acid yielded 3-chloro or methyl-2-aminobenzenethiol as usual (Scheme 1).

Scheme 1



Substituted 2-aminobenzenethiols were condensed with reactive *o*-halonitrobenzenes (2,4,6-trinitrochlorobenzene, 1,4-dichloro-2,6-dinitrobenzene, 2,4,6-tribromo-1,3-dinitrobenzene) in ethanolic sodium hydroxide to give the corresponding phenothiazines *via* the Smiles rearrangement which occurs *in situ* (Scheme 2).

Scheme 2



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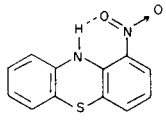
Ir.

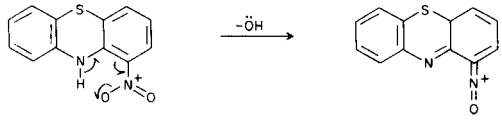
The substituted 2-aminobenzenethiols exhibited a peak at 2570 cm^{-1}, characteristic of the SH group and two peaks in the regions 3350-3475 cm^{-1}, characteristic of NH_2 group. All the phenothiazines exhibited a single sharp peak at 3350-3320 cm^{-1} which is attributed to -NH stretching vibrations. This large shift to a lower frequency suggested a six membered chelate of high stability through strong NH ------ O-N bonding. All the phenothiazines



exhibited sharp and intense bands at 1500-1495 cm^{-1} and 1230-1350 cm^{-1}, which are attributed to aromatic nitro group as usual.

Mass Spectra.

In the compounds studied, the molecular ion in the base peak suggests a high stability of the phenothiazine ring due to a high degree of conjugation. The fragment M^+-32, although weak, is always present, suggesting the lose of the sulphur nucleus. The peak M^+-17, although of variable intensity, is present in the case of all these phenothiazines which contain a nitro group at position-1. This provides evidence that the nitro group takes part in the McLafferty rearrangement (18), which may be postulated in the following way. The McLafferty rearrangement



which involves a six membered cyclic transition state, has been reported by other workers in the case of *o*-nitro derivatives of benzene (18,19). The fragments M^+-46 and M^+-47 are present with variable intensity in all the phenothiazines due to the loss of NO_2 and HNO_2. The fragment M^+-30 arises due to loss of NO radical. These fragments are characteristic of the aromatic nitro derivatives (19).

EXPERIMENTAL

Substituted Phenylthiourea (II).

2-Chloro or methylphenylthiourea was prepared by refluxing 2-chloro or methylaniline hydrochloride (0.1 mole) with ammonium thiocyanate (0.1 mole) in 100 ml. of water for 4 hours. The solid which separated on cooling was filtered, washed with water and recrystallized from ethanol.

2-Chlorophenylthiourea.

This compound had m.p. 121°.

2-Methylphenylthiourea.

This compound had m.p. 160°.

4-Chloro or Methyl-2-aminobenzothiazole (IV).

Substituted phenylthiourea (II) (0.1 mole) and chloroform (100 ml.) were placed in a three necked round bottomed flask. Bromine (0.1 mole) in chloroform (20 ml.) was then added dropwise, and the temperature of the reaction mixture was kept below 5° by immersing the flask in crushed ice. After complete addition of bromine, the contents of the flask were refluxed for 4 hours on a water bath until the evolution of bromine ceased. The contents were heated on a water bath to remove the chloroform and the resulting solid was treated with sulphurous acid and filtered. The clear filtrate was neutralised with aqueous ammonia. The precipitate was filtered, washed with water and crystallised from ethanol.

4-Chloro-2-aminobenzothiazole.

This compound had m.p. 183°.

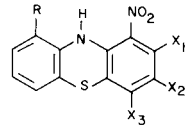
4-Methyl-2-aminobenzothiazole.

This compound had m.p. 190°.

3-Chloro or Methyl-2-aminobenzenethiol (V).

Table I

Substituted 1-Nitrophenothiazines



Compound No.	R	X_1	X_2	X_3	M.p. °C	Yield %	%C Found	%H Found	%N	Molecular Formula	%C Calcd.	%H Calcd.	%N
1	Cl	H	NO_2	H	217	60	44.90	1.83	12.80	$C_{12}H_6ClN_3O_4S$	44.51	1.85	12.98
2	Cl	H	Cl	H	240	75	45.58	1.93	8.88	$C_{12}H_6Cl_2N_2O_2S$	46.00	1.91	8.94
3	Cl	Br	H	Br	127	65	32.70	1.15	6.34	$C_{12}H_5ClBr_2N_2O_2S$	32.98	1.14	6.41
4	CH_3	H	NO_2	H	173	65	51.98	3.00	13.82	$C_{13}H_9N_3O_4S$	51.48	2.97	13.86
5	CH_3	H	Cl	H	206	70	52.87	3.04	9.50	$C_{13}H_9ClN_2O_2S$	53.33	3.07	9.57
6	CH_3	Br	H	Br	251	75	37.85	1.91	6.64	$C_{13}H_8Br_2N_2O_2S$	37.50	1.92	6.73

Substituted aminobenzothiazole was refluxed with sodium hydroxide (5 times by weight of benzothiazole) and water (10 times by weight of benzothiazole) until evolution of ammonia gas ceased (about 24 hours). The contents were filtered and the clear solution on neutralisation with acetic acid afforded the desired thiol.

3-Chloro-2-aminobenzenethiol.

This compound had m.p. 78°.

Anal. Calcd. for C_6H_6ClNS: C, 45.40; N, 8.70; H, 3.73. Found: C, 45.14; N, 8.77; H, 3.76.

3-Methyl-2-aminobenzenethiol.

This compound had m.p. 48°.

Anal. Calcd. for C_7H_9NS: C, 60.05; N, 10.16; H, 6.53. Found: C, 60.43; N, 10.07; H, 6.47.

Preparation of Phenothiazines (VII).

To substituted *o*-aminobenzenethiol (0.011 mole) in ethanol (20 ml.), a solution of sodium hydroxide (0.01 mole) in ethanol (5 ml.) was added. An ethanolic solution of the reactive halogenonitrobenzene was added and refluxed for 4 hours. The contents were filtered, and washed with water followed by 50% ethanol. Crystallization from acetone afforded the pure sample of phenothiazines summarised in Table I.

The purity of all the compounds was checked by tlc in various non-aqueous solvent systems.

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