SYNTHESIS OF SUBSTITUTED 3-CHLORO-1-METHYLPHENOTHIAZINES VIA SMILES REARRANGEMENT

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Abstract : Synthesis of title compounds by the Smiles rearrangement has been reported. 3-Chloro-1-methyl-7-substituted phenothiazines have been prepared by the Smiles rearrangement of 5-chloro-3-methyl-2-formamido-2'-nitro-4'-substituted-diphenyl sulphides. The latter were obtained by the formylation of diphenyl sulphides which were prepared by the condensation of 2-amino-5-chloro-3-methylbenzenethiol with o-halonitrobenzenes. 9-Nitrophenothiazines have been prepared by the reaction of 2-amino-5-chloro-3-methylbenzenethiol with substituted halonitrobenzenes containing a nitro group at both ortho positions to halo atom in which Smiles rearrangement occurs in situ. The IR, NMR and mass spectral studies are also reported.

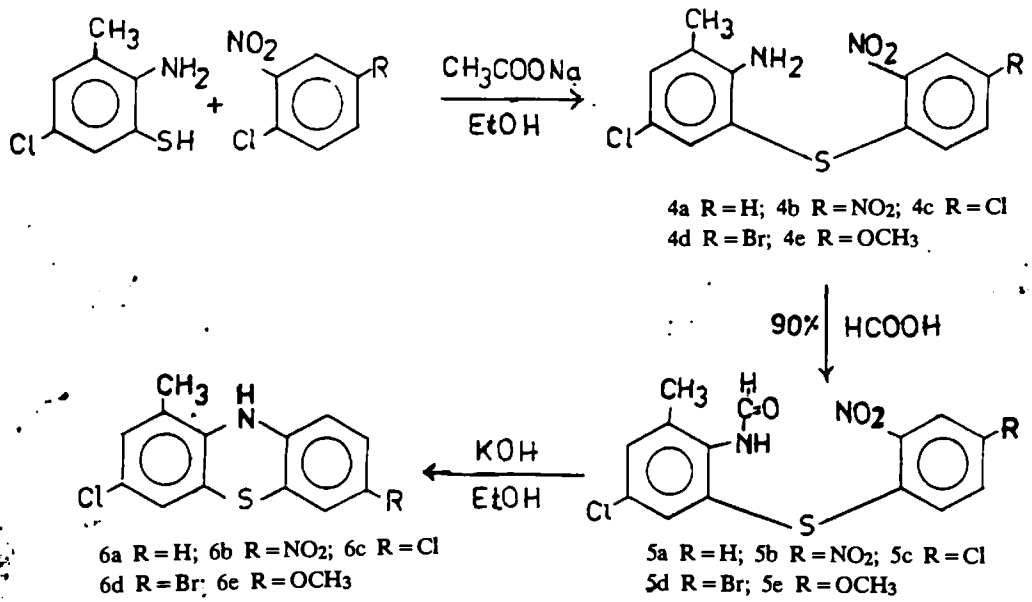
Introduction

Phenothiazines possess a wide spectrum of pharmacological activities and its several derivatives are in clinical use (1,2). Recently phenothiazines have been reported to exhibit significant anticancer activities (3-8) and a great interest has arisen to design and synthesize hitherto unknown phenothiazines to explore their anticancer activities. A slight modification in nuclear substitution causes a marked difference in the biological activities. Therefore it has been considered worth while to synthesize title phenothiazines to make them available for biological screening.

Results and Discussion

2-Amino-5-chloro-3-methylbenzenethiol 1 required in the synthesis of title compounds has been prepared by the alkaline hydrolytic cleavage of 2-amino-6-chloro-4-methylbenzothiazole adopting the method reported elsewhere (9,10).

3-Chloro-1-methyl-7-substituted-phenothiazines 6a-e have been prepared by the Smiles rearrangement of 5-chloro-3-methyl-2-formamido-2-nitro-4-substituted diphenyl sulphides 5 in alcoholic potassiam hydroxide solution. The formyl derivatives were prepared by the formylation of resultant diphenylsulphides 4 obtained by the condensation of 2-amino-5-chloro-3-methylbenzenethiol 1 with substituted o-halonitrobenzenes 2 in ethanolic sodium acetate solution (Scheme 1)



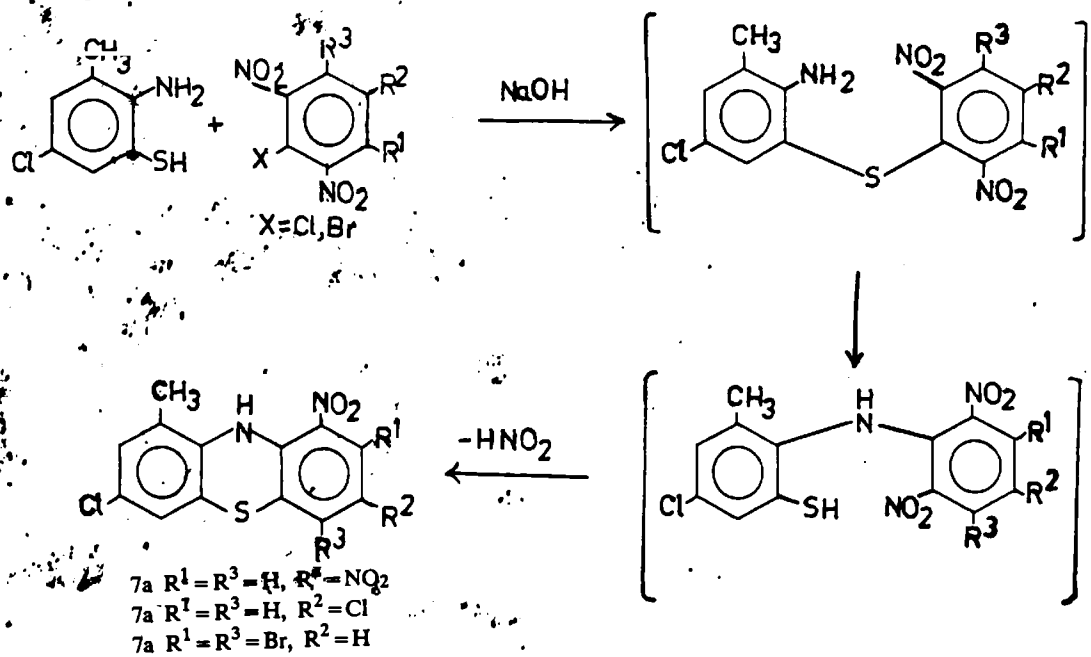
4a R = H; 4b R = NO_2; 4c R = Cl
4d R = Br; 4e R = OCH_3

5a R = H; 5b R = NO_2; 5c R = Cl
5d R = Br; 5e R = OCH_3

6a R = H; 6b R = NO_2; 6c R = Cl
6d R = Br; 6e R = OCH_3

Scheme 1

9-Nitrophenothiazines 7a-c have been prepared by the condensation of 2-amino-5-chloro-3-methylbenzenethiol 1 with appropriately substituted o-halonitrobenzenes 3 contatining a nitro group at both ortho positions to the halogen atom in ethanolic sodium hydroxide solution where the Smiles rearrangement occurs in situ due to nitro group (Scheme 2)



7a $R^1 = R^3 = H$, $R^2 = NO_2$
7a $R^1 = R^3 = H$, $R^2 = Cl$
7a $R^1 = R^3 = Br$, $R^2 = H$

Scheme 2

The IR spectra of all the phenothiazines except 9-nitro, exhibit a sharp peak in the region 3180-3380 cm^{-1} due to NH stretching vibrations, but 9-nitrophenothiazines show a large shift in the secondary NH vibrational frequency. This shifting to lower frequency suggests a six-membered chelate through NH---O-N bonding (Fig. 1).

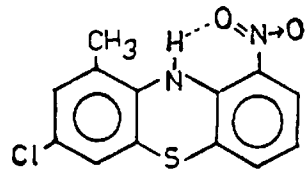


Fig. 1

9-Nitro 7a-c and 7-nitrophenothiazines 6b exhibit two peaks of medium intensity in the region 1530-1570 cm^{-1} and 1310-1370 cm^{-1} due to asymmetric and symmetric vibrations of the aromatic nitro group. The peak in the region 1425-1460 cm^{-1} and 1310-1355 cm^{-1} are due to C-H asymmetric and symmetric deformation vibrations of CH_3 group. Peaks corresponding to the chlorine atom have been observed in all the phenothiazines in the range 700-785 cm^{-1}. In phenothiazine 6e two peaks at 1020 cm^{-1} and 1235 cm^{-1} are due to C-O-C symmetric and asymmetric vibrations.

The ^1H NMR spectra of all the phenothiazines exhibit a multiplet in the region δ 56.43-8.55 due to aromatic protons. All the phenothiazines 6a-e except those having a nitro group at 9-position exhibit a siglet at δ 8.13-9.06 due to N-H proton. In the 9-nitrophenothiazines 7a-c the N-H proton gives rise to a singlet at δ 8.59-10.17 and this down field shift suggests hydrogen bonding between the nitro and a secondary amino groups as -NH..O=N which has been also indicated by the IR spectral data. All the phenothiazines exhibit a singlet in the regions δ 1.74- 2.30 due to CH_3 proton at C-1. Compound 6e exhibit a singlet at δ 3.99 due to OCH_3 protons at C-7.

The mass spectra of phenothiazines have the most abundant peaks corresponding to their molecular ions. All the phenothiazines show very similar behaviour on electron impact fragmentation and nitrophenothiazines have exhibited the characteristics of an aromatic nitro group in the fragmentation besides the other fragmentations caused by different substituents. Moieties M^+-30, M^+-46 and M^+-47 are obsered with variable intensity in nitrophenothiazines and are ascribed to loss of NO, NO_2 and HNO_2 respectively. All 9-nitrophenothiazines 7a-c exhibit a peak at M^+-17 which is assigned to the loss of the OH radical by a McLafferty rearrangement (11) (Fig. 2).

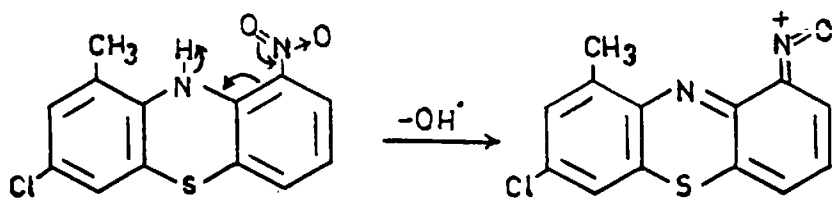


Fig. 2

Experimental

All the melting points are uncorrected. The purity of the compounds synthesized has been checked by TLC. The IR spectra were recorded on a perkin-Elmer spectrophotometer model 577. The NMR spectra have been recorded at 90 MHz on a Jeol FX 90Q FT NMR using TMS as an internal standered in DMSO-d_6. Mass spectra were recorded on a Jeol JMSD-300 mass spectrometer at 70 ev with 100 μamp ionising current.

Preparation of 2-anuno-5-chloro-3-methyl-2'-nitro-4-substituted-diphenyl sulphides 4a-e

To a refluxing solution of 2-amino-5-chloro-3-methylbenzenethiol (1, 0.01 mol) in ethanol (20 ml) and anhydrous sodium acetate (0.01 mol in 5 ml alcohol) was added an alcoholic solution of halonitrobenzene (2, 0.01 mol) in ethanol (12 ml) and refluxed for three hours. The reaction mixture was concentrated and cooled overnight in an ice chamber. The solid separated out was filtered and washed with 30% ethanol. Crystallization from methanol afforded the desired products. Physical data are recorded in Table 1.

Preparation of 5-chloro-3-methyl-2-formamido-2-nitro-4 substituted-dipheyl sulphide 5a-e

The diphenyl sulphide (4; 0.01 mol) in 90% formic acid (20 ml) was refluxed for three hours. The contents of the reaction flask were poured into crushed ice. The solid separated out was collected, washed until free from acid and crystallised from methonol. The physical data are summarised in Table 1.

Preparation of 3-chloro-1-methyl-7-substituted phenothiazines 6a-e

To a refluxing solution of formyl derivatives (5, 0.01 mol) in acetone (5 ml) was added an alcoholic solution of potassium hydroxide (0.2 gm in 5 ml of ethanol). The colour of the solution darkened immediately on addition of the alkaline alcoholic solution. The contents were heated for half an hour. To this solution a second lot of potassium hydroxide (0.2 gm in 5 ml of ethannol) was added and refluxing was continued for two hours and the contents were cooled down and poured into a beaker containing crushed ice. The solid separated out was filtered, washed with cold water and finally with 30% ethanol. Crystallisation from methanol/benzene affords the desired phenothiazines. The physical data are summarised in Table 1.

Preparation of substituted phenothiazines 7a-c

To a stirred suspension of 2-amino-5-chloro-3-methylbenzenethiol (1; 0.01 mol) and a reactive o-halonitrobenzene (3; 0.01 mol in 20 ml of ethanol) was added and alcoholic solution of sodium hydrooxide (0.01 mol) and the contents were refluxed for two hours. The contents were cooled down, filtred, washed with hot water and finally with 20% ethanol. Crystallisation from methnol/acetone affords the phenothiazine. The physical data are summarised in Table 1.

Table 1 : Physical data of compound 4-7

Compd.	M.P. (°C)	Yield (%)	Molecular Formula	% Found / Cald. C	H	N
4a	128	42	$C_{13}H_{11}ClN_2O_2S$	52.80 52.97	3.72 3.73	9.44 9.50
4b	156	48	$C_{13}H_{10}ClN_3O_4S$	46.09 45.94	2.94 2.94	12.39 12.37
4c	154	61	$C_{13}H_{10}Cl_2N_2O_2S$	47.29 47.41	3.02 3.03	8.48 8.51
4d	188	58	$C_{13}H_{10}BrClN_2O_2S$	41.52 41.76	2.66 2.67	7.54 7.49
4e	159	52	$C_{14}H_{13}ClN_2O_3S$	51.93 51.77	4.01 4.00	8.59 8.62
5a	171	38	$C_{14}H_{11}ClN_2O_3S$	43.56 43.41	3.40 3.41	8.73 8.68
5b	166	44	$C_{14}H_{10}ClN_3O_5S$	45.49 45.71	2.99 2.99	11.41 11.42
5c	204	54	$C_{14}H_{10}Cl_2N_2O_3S$	39.02 39.21	2.81 2.80	7.86 7.84
5d	164	51	$C_{14}H_{10}BrClN_2O_3S$	42.02 41.84	2.48 2.49	6.93 6.97
5e	182	36	$C_{15}H_{13}ClN_2O_4S$	51.32 51.06	3.67 3.68	7.89 7.94
6a	144	24	$C_{13}H_{10}ClNS$	63.29 63.03	4.03 4.04	5.62 5.65
6b	122	36	$C_{13}H_9ClN_2O_2S$	53.04 53.33	3.06 3.07	9.53 9.57
6c	188	52	$C_{13}H_9Cl_2NS$	55.59 55.31	3.18 3.19	4.94 4.96
6d	153	48	$C_{13}H_9BrClNS$	48.04 47.77	2.73 2.75	4.27 4.28
6e	138	29	$C_{14}H_{12}ClNOS$	60.21 60.54	4.31 4.32	5.06 5.04
7a	90	32	$C_{13}H_8ClN_3O_4S$	46.46 46.22	2.38 2.37	12.52 12.44
7b	110	42	$C_{13}H_8Cl_2N_2O_2S$	47.98 47.70	2.45 2.44	8.61 8.56
7c	112	46	$C_{13}H_7Br_2ClN_2O_2S$	34.40 34.62	1.54 1.55	6.18 6.21

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