# Studies on Phenothiazines. Part 16 [1]. Synthesis and Spectral Studies of Substituted 1,2-Dichlorophenothiazines



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Synthesis of the title compounds by the Smiles rearrangement has been reported. 1,2-Dichloro-7-substituted phenothiazines have been prepared by the Smiles rearrangement of 3,4-dichloro-2-formamido-2'-nitro-4'-substituted-diphenyl sulphides. The latter were obtained by the formylation of the diphenyl sulphides obtained by the condensation of 2-amino-3,4-dichlorobenzenethiol with *o*-halogenonitrobenzenes. 9-Nitrophenothiazines have been prepared by the reaction of 2-amino-3,4-dichlorobenzenethiol with substituted *o*-halonitrobenzenes containing a nitro group at both ortho positions to the halo atom in which Smiles rearrangement occurs *in situ*. The ir, nmr and mass spectral studies are also included.

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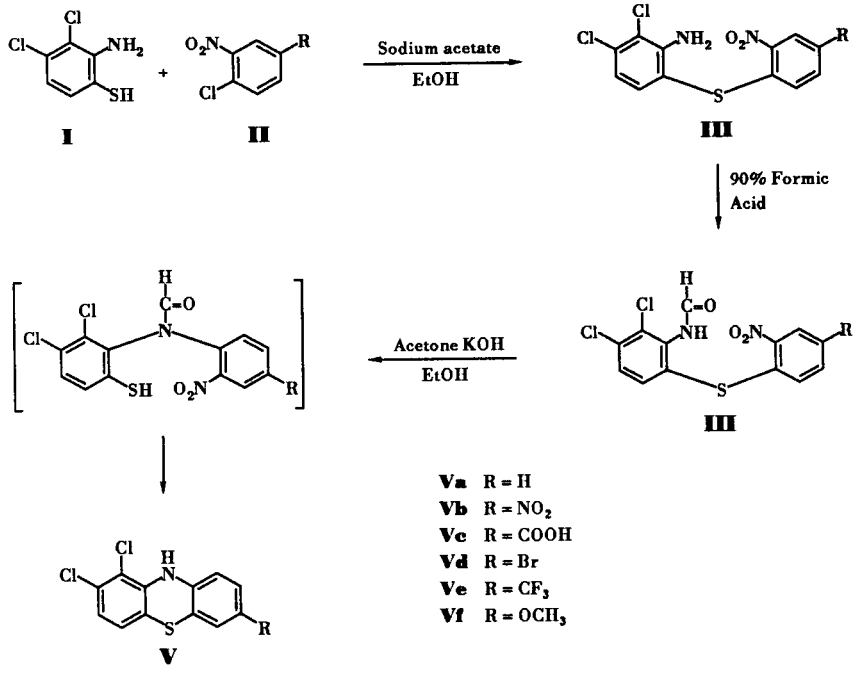
Phenothiazines possess a wide spectrum of pharmacological activities and its several derivatives are in clinical use [2] as tranquilizers [2], antiemetic [2], and antiinflammatory agents [2] *etc.* A slight variation in substitution pattern in phenothiazine nucleus causes a marked difference in activities and therefore phenothiazines with varied substituents are being synthesized and tested for activities in search of better medicinal agents [3-14]. Recently phenothiazines have been reported to exhibit significant anticancer activities [10-14] and a great interest has arisen to design and synthesize phenothiazines to explore their anticancer activities. It is considered worthwhile to synthesize hitherto unknown phenothiazines.

1,2-Dichloro-7-substituted-phenothiazines **Va-f** (Scheme 1) have been prepared by the Smiles rearrangement of 3,4-dichloro-2-formamido-2'-nitro-4'-substituted-diphenyl sulphides in alcoholic potassium hydroxide solution. The formyl derivatives were prepared by the formylation of resultant diphenyl sulphides obtained by the condensation of 2-amino-3,4-dichlorobenzenethiol with substituted *o*-halonitrobenzenes in ethanolic sodium acetate solution (Scheme 1).

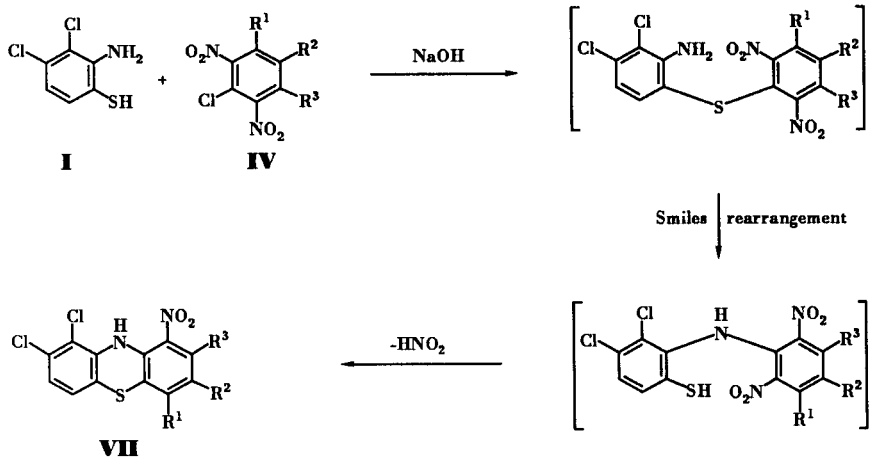
9-Nitrophenothiazines **VIIa-c** have been prepared by the condensation of 2-amino-3,4-dichlorobenzenethiol with appropriately substituted *o*-halonitrobenzenes containing a nitro group at both *ortho* positions to the halogen atom in ethanolic sodium hydroxide solution where the Smiles rearrangement occurs *in situ* (Scheme 2) due to the nitro groups (Scheme 2).

2-Amino-3,4-dichlorobenzenethiol required in the synthesis of phenothiazines has been prepared by the alkaline hydrolytic cleavage of 2-amino-4,5-dichlorobenzothiazole adopting the method reported by us earlier [15,16].

Scheme 1



Scheme 2




I IV VII

**VIIa** $R^1 = R^3 = H$, $R^2 = NO_2$
**VIIb** $R^1 = R^3 = H$, $R^2 = Cl$
**VIIc** $R^1 = R^3 = Br$, $R^2 = H$

## EXPERIMENTAL

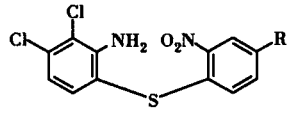
All the melting points are uncorrected. The purity of the compounds synthesized has been checked by tlc and the structures have been assigned by elemental analysis and spectral data. The infrared spectra were recorded on a Perkin-Elmer spectrophotometer model 577. The nmr spectra have been recorded at 90 MHz on a Jeol FX 90Q FT NMR using TMS as an internal standard in DMSO-$d_6$. Mass spectra were recorded on a Jeol JMSD-300 mass spectrometer at 70 eV with 100 $\mu$amp ionising current.

Preparation of 2-Amino-3,4-dichloro-2'-nitro-4'-substituted Diphenyl Sulphides.

To a refluxing solution of 2-amino-3,4-dichlorobenzenethiol (0.01 mole) in ethanol (20 ml) and anhydrous sodium acetate (0.01 mole in 5 ml of ethanol) was added an alcoholic solution of halonitrobenzene (0.01 mole) in ethanol (12 ml) and refluxed for three hours. The reaction mixture was concentrated and cooled overnight in an ice chamber. The solid which separated was filtered and washed with 30% ethanol. Crystallization from methanol afforded the desired products. Physical data are tabulated in Table 1.

Table 1

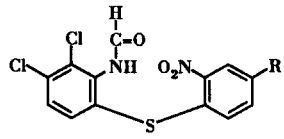
Physical Data of Substituted 2-Amino-2'-nitrodiphenyl Sulphides



| Compound | R | Yield % | Mp (°C) | Molecular Formula | Analysis % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|
| **a** | H | 38.49 | 144 | $C_{12}H_8Cl_2N_2SO_2$ | 45.71 | 2.53 | 8.88 |
| | | | | | 45.52 | 2.54 | 8.92 |
| **b** | $NO_2$ | 45.42 | 112 | $C_{12}H_7Cl_2N_3SO_4$ | 40.00 | 1.94 | 11.66 |
| | | | | | 40.21 | 1.95 | 11.71 |
| **c** | COOH | 48.86 | 98 | $C_{13}H_8Cl_2N_2SO_4$ | 43.45 | 2.22 | 7.79 |
| | | | | | 43.63 | 2.21 | 7.82 |
| **d** | Br | 50.54 | 80 | $C_{12}H_7BrCl_2N_2SO_2$ | 36.54 | 1.77 | 7.10 |
| | | | | | 36.39 | 1.78 | 7.06 |
| **e** | $CF_3$ | 36.90 | 132 | $C_{13}H_7F_3Cl_2N_2SO_2$ | 40.73 | 1.82 | 7.31 |
| | | | | | 40.89 | 1.81 | 7.28 |
| **f** | $OCH_3$ | 22.47 | 139 | $C_{13}H_{10}Cl_2N_2SO_3$ | 45.21 | 2.89 | 8.11 |
| | | | | | 45.02 | 2.88 | 8.14 |

Table 2

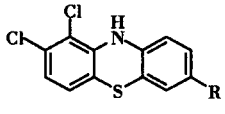
Physical Data of Substituted 2-Formamido-2'-nitrodiphenyl Sulphides



| Compound | R | Yield % | Mp (°C) | Molecular Formula | Analysis % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|
| **a** | H | 98.25 | 220 | $C_{13}H_8Cl_2N_2SO_3$ | 45.48 | 2.33 | 8.16 |
| | | | | | 45.21 | 2.32 | 8.12 |
| **b** | $NO_2$ | 68.46 | 132 | $C_{13}H_7Cl_2N_3SO_5$ | 40.20 | 1.80 | 10.82 |
| | | | | | 39.93 | 1.81 | 10.77 |
| **c** | COOH | 90.40 | 152 | $C_{14}H_8Cl_2N_2SO_5$ | 43.41 | 2.06 | 7.23 |
| | | | | | 43.63 | 2.05 | 7.19 |
| **d** | Br | 77.64 | 212 | $C_{13}H_7BrCl_2N_2SO_3$ | 36.96 | 1.65 | 6.63 |
| | | | | | 36.77 | 1.64 | 6.60 |
| **e** | $CF_3$ | 78.32 | 198 | $C_{14}H_7F_3Cl_2N_2SO_3$ | 40.87 | 1.70 | 6.81 |
| | | | | | 41.09 | 1.69 | 6.82 |
| **f** | $OCH_3$ | 87.94 | 216 | $C_{14}H_{10}Cl_2N_2SO_4$ | 45.04 | 2.68 | 7.50 |
| | | | | | 45.28 | 2.66 | 7.47 |

Table 3

Physical Data of 1,2-Dichloro-7-substituted Phenothiazines



| Compound | R | Yield % | Mp (°C) | Molecular Formula | Analysis % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|
| **a** | H | 35.89 | 137 | $C_{12}H_7Cl_2NS$ | 53.73 | 2.61 | 5.22 |
| | | | | | 53.51 | 2.60 | 5.24 |
| **b** | $NO_2$ | 43.03 | 158 | $C_{12}H_6Cl_2N_2SO_2$ | 46.00 | 1.91 | 8.94 |
| | | | | | 45.78 | 1.90 | 8.90 |
| **c** | COOH | 23.44 | 172 | $C_{13}H_7Cl_2N_2SO_2$ | 50.00 | 2.24 | 4.48 |
| | | | | | 50.23 | 2.25 | 4.46 |
| **d** | Br | 42.34 | 149 | $C_{12}H_6BrCl_2NS$ | 41.49 | 1.72 | 4.03 |
| | | | | | 41.71 | 1.73 | 4.05 |
| **e** | $CF_3$ | 17.02 | 151 | $C_{13}H_6F_3Cl_2NS$ | 46.42 | 1.78 | 4.16 |
| | | | | | 46.21 | 1.77 | 4.14 |
| **f** | $OCH_3$ | 51.03 | 163 | $C_{13}H_9Cl_2NSO$ | 52.34 | 3.02 | 4.69 |
| | | | | | 52.56 | 3.04 | 4.72 |

Preparation of 3,4-Dichloro-2-formamido-2'-nitro-4'-substituted Diphenyl Sulphide.

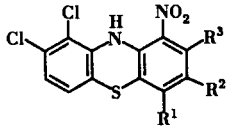
The diphenyl sulphide (0.01 mole) in 90% formic acid (20 ml) was refluxed for three hours. The contents of the reaction flask were poured into crushed ice. The solid which separated out was collected, washed until free from acid and crystallized from methanol. The physical data are tabulated in Table 2.

Preparation of 1,2-Dichloro-7-substituted Phenothiazines.

To a refluxing solution of formyl derivatives (0.01 mole) in acetone (5 ml) was added an alcoholic solution of potassium hydroxide (0.2 g 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 g in 5 ml of ethanol) 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 which separated was filtered, washed with cold water and finally with 30% ethanol. Crystallization from methanol/benzene afforded the desired phenothiazines. The physical data are tabulated in Table 3.

Table 4

Physical Data of Substituted 9-Nitrophenothiazines



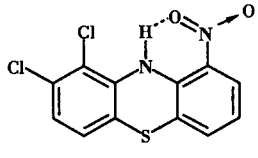
| Compound | $R^1$ | $R^2$ | $R^3$ | Yield % | Mp (°C) | Molecular Formula | Analysis % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **a** | H | $NO_2$ | H | 58.54 | 216 | $C_{12}H_5Cl_2N_3SO_4$ | 40.22 | 1.39 | 11.73 |
| | | | | | | | 40.02 | 1.40 | 11.78 |
| **b** | H | Cl | H | 46.32 | 210 | $C_{12}H_5Cl_3N_2SO_2$ | 41.43 | 1.43 | 8.05 |
| | | | | | | | 41.21 | 1.44 | 8.09 |
| **c** | Br | H | Br | 51.42 | 195 | $C_{12}H_4Br_2Cl_2N_2SO_2$ | 30.57 | 0.84 | 5.94 |
| | | | | | | | 30.70 | 0.84 | 5.91 |

Preparation of Substituted 9-Nitrophenothiazines.

To a stirred suspension of 2-amino-3,4-dichlorobenzenethiol (0.01 mole) and a reactive *o*-halonitrobenzene (0.01 mole in 20 ml of ethanol) was added an alcoholic solution of sodium hydroxide (0.01 mole) and the contents were refluxed for two hours. The contents were cooled, filtered, washed with hot water, and finally with 20% ethanol. Crystallization from methanol/acetone afforded the phenothiazines. The physical data are tabulated in Table 4.

Infrared Spectra.

The ir spectra of all the phenothiazines except the 9-nitro, exhibit a sharp peak in the region 3300-3350 $cm^{-1}$ due to NH stretching vibrations, but the 9-nitrophenothiazines show a large shift in the secondary NH vibrational frequency. This shifting to lower frequency suggests a six-membered chelate through N-H...O-N bonding.



9-Nitro **VIIa-c** and 7-nitrophenothiazines **Vb** exhibit two peaks of medium intensity in the region 1570-1575 $cm^{-1}$ and 1310-1365 $cm^{-1}$ due to asymmetric and symmetric valance vibrations of the aromatic nitro group. Peaks corresponding to the chlorine atom have been observed in all the phenothiazines in the range 720-780 $cm^{-1}$. In phenothiazine **Ve** two peaks have been observed at 1165 $cm^{-1}$ and 1320 $cm^{-1}$ due to C-F bond stretching vibrations. In phenothiazine **Vf** two peaks appear at 1025 $cm^{-1}$ and 1275 $cm^{-1}$ due to asymmetric and symmetric vibrations of C-O-C linkage.

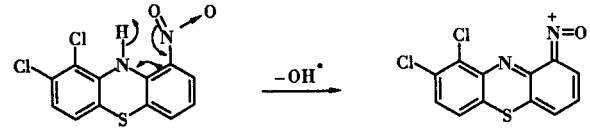
NMR Spectra.

The $^1H$ nmr spectra of all the phenothiazines exhibit a multiplet in the region $\delta$ 6.38-7.30 due to aromatic protons. All the phenothiazines **Va-f** except those having a nitro group at the 9-position exhibit a singlet at $\delta$ 8.18-9.85 due to the N-H proton. In the 9-nitrophenothiazines **VIIa-c** the N-H proton gives rise to a singlet at $\delta$ 10.12-10.42 and this downfield shift suggests hydrogen bonding between the nitro and a secondary amino group as -NH....O=N which has been also indicated by the ir spectral data. A singlet was observed at $\delta$ 11.4 due to the carboxyl group in compound **Vc** and at $\delta$ 4.00 due to the methoxy group in compound **Vf**.

Mass Spectra.

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 [17] in the fragmentation besides the other fragmentations caused by different substituents. Moieties $M^+$-30, $M^+$-46 and $M^+$-47 are observed with variable intensity in nitrophenothiazines and are ascribed to the loss of NO, $NO_2$ and $HNO_2$ respectively. All 9-nitrophenothiazines **VIIa-c** exhibit a peak at $M^+$-17 which is assigned to the loss of the OH radical by a McLafferty rearrangement [18] (Scheme 3).

Scheme 3



Trifluoromethyl derivative **Ve** exhibits a peak at $M^+$-50 which may be assigned to the loss of $-CF_3$ moiety. Phenothiazine **Vc** containing a carboxyl group suffers the simultaneous loss of fragments having a mass of 17 and 28. These are assigned to the loss of OH and CO respectively.

Acknowledgement.

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## REFERENCES AND NOTES

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