SYNTHESIS OF 9-SUBSTITUTED 1-NITRO AND 1,7-DISUBSTITUTED PHENOTHIAZINES VIA SMILES REARRANGEMENT

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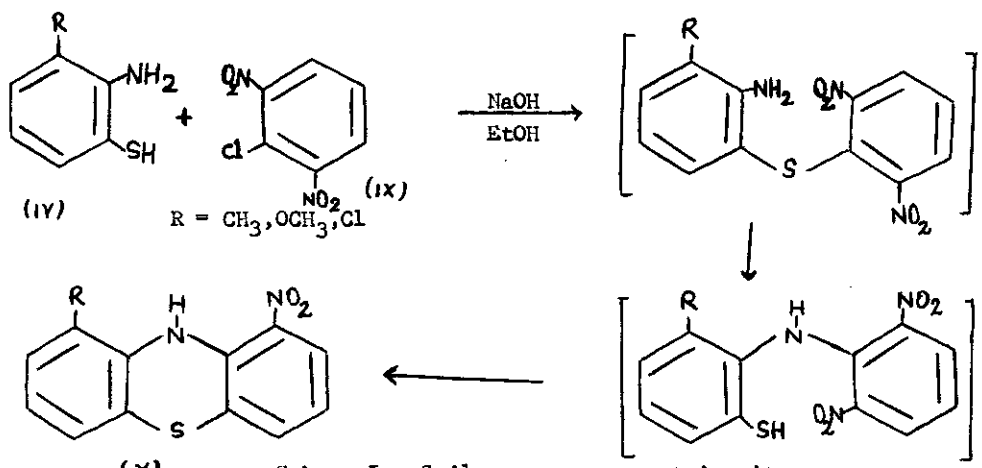
ABSTRACT - Substituted phenothiazines without nitro group at position-1 have been prepared via Smiles rearrangement of 2-formamido-2'-nitro-3,4'-disubstituted diphenyl sulphides. The latter were obtained by the action of formic acid on 2-amino-2'-nitro-3,4'-disubstituted diphenyl sulphides which have been prepared by condensing substituted o-aminothiophenol with o-halonitrobenzenes. 9-Substituted 1-nitrophenothiazines have also been synthesised by Smiles rearrangement in situ which involves condensation of 2-amino-3-chloro/methoxy thiophenols with 2,6-dinitrochlorobenzene in the presence of ethanolic sodium hydroxide. All the synthesised compounds have been characterised by IR, NMR and Mass spectral studies.

Phenothiazines of varying structural complicity have become well known in recent years. It has played an important role in pharmacology as tranquilisers[2], anticancer drugs[3], growth inhibitors[4], antihistaminics[5], local anaesthetics[6], antiseptics[7] and in treatment of CNS disorders[8] in psychiatric patients. In addition to pharmaceutical activities these have also been used in industry as antioxidants[9], stabilisers[10] and antiemetic[11] activities.

Keeping in view the wide spread pharmaceutical, physiological and industrial importance of phenothiazines series, it has been considered worthwhile to extend our previous work[1] on phenothiazines with an object to make available drugs of this series to develop a structural activity relationship to search tranquilisers with maximum activities and minimum side effects.

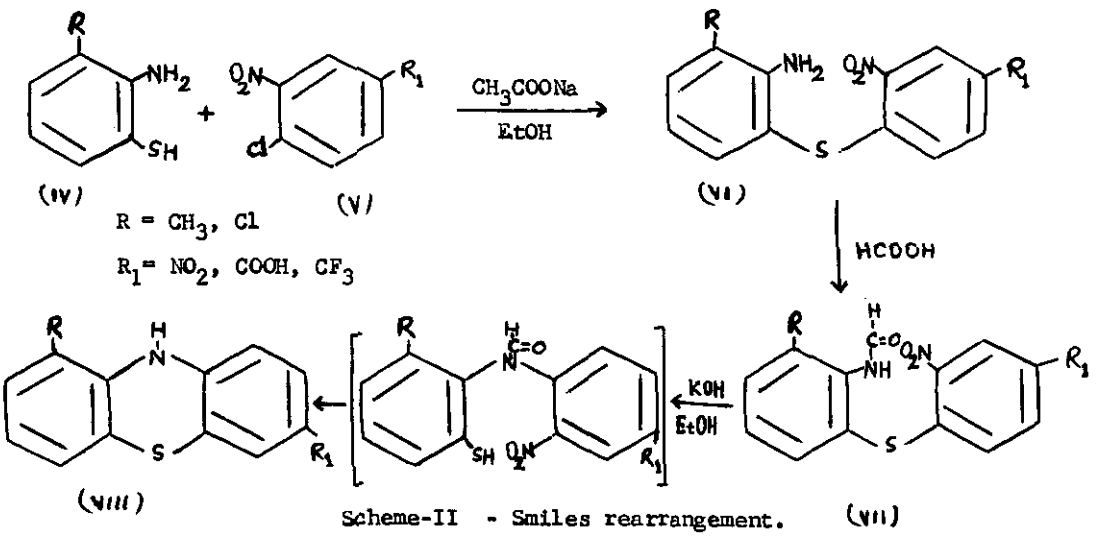
Our present communication is mainly concerned with synthesis of hitherto unknown

phenothiazines with and without nitro group at position-1 via two different routes of Smiles rearrangement viz: Smiles rearrangement in situ and Smiles rearrangement of 2-formamido-3'-nitro-substituted diphenyl sulphide derivatives. 9-Substituted 1-nitrophenothiazines were prepared by Smiles rearrangement in situ which involves the condensation of 2-amino-3-chloro/methyl/methoxythiophenols with 2,6-dinitrochlorobenzene in presence of alcoholic sodium hydroxide. The pathway of reactions is shown in scheme-I. The reaction may be adopted to provide phenothiazines with novel type of substitution which is otherwise accessible with difficulties.



Scheme-I - Smiles rearrangement in situ.

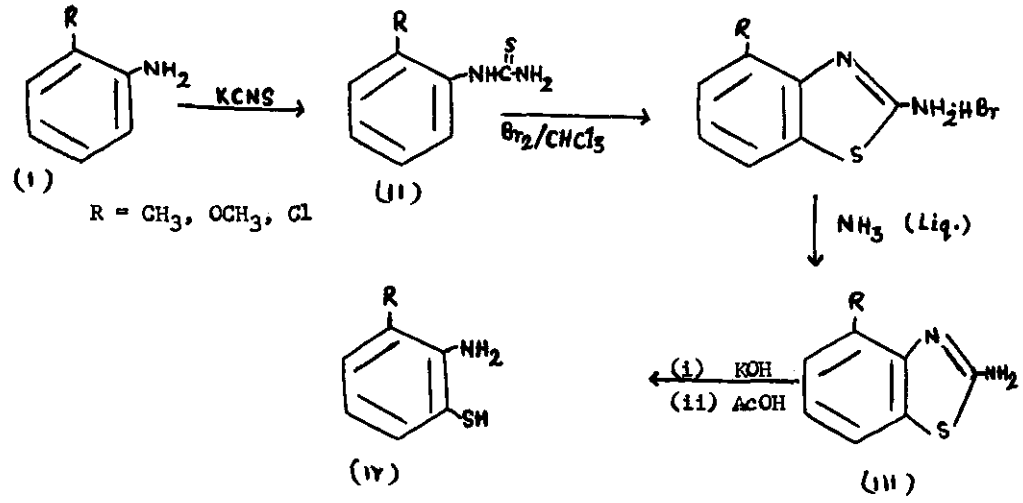
Phenothiazines without nitro group at position-1, i.e. 1,7-disubstituted phenothiazines were prepared by Smiles rearrangement of 2-formamido-2'-nitro-3,4'-disubstituted diphenyl sulphides with alcoholic potassium hydroxide. The formyl derivatives were prepared by action of 90% formic acid on 2-amino-2'-nitro-3,4'-disubstituted diphenyl sulphides which are condensation products of 2-amino-3-chloro/methylthiophenol and substituted o-halonitrobenzenes in the presence of anhydrous sodium acetate. The pathway of reactions is shown in scheme-II.



(IV) R = CH_3, Cl; R_1 = NO_2, COOH, CF_3 (V) (VI) (VII) (VIII)

Scheme-II - Smiles rearrangement.

2-Amino-3-chloro/methyl/methoxythiophenols used in synthesis of phenothiazines have been prepared by hydrolytic cleavage of 2-amino-4-chloro/methyl/methoxy-benzothiazoles which were synthesised by treating ice cold suspension of 2-chloro/methyl/methoxyphenylthiourea in chloroform with bromine in order to effect cyclisation. The details were reported by us elsewhere[12]. The pathway of reactions is shown in scheme-III.



(I) R = CH_3, OCH_3, Cl (II) (III) (IV)

Scheme - III

EXPERIMENTAL

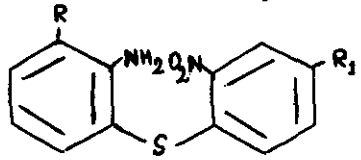
All the melting points are uncorrected. The purity of the compounds was checked by TLC in various non-aqueous solvents.

Preparation of Diphenyl Sulphides(VIa-c)

To a refluxing solution of 2-amino-3-chloro/methyl/methoxythiophenol (IV; 0.012 mole) in ethanol (20 ml), a solution of anhydrous sodium acetate (0.01 mole) in alcohol (5 ml) was added. To this refluxing solution, an alcoholic solution of halonitrobenzene (V, 0.01 mole in 10 ml ethanol) was added and refluxed for four hours. The resulted solution was concentrated and cooled over night in ice and the solid which separated was collected and washed with water and finally with 30% alcohol. Recrystallization from methanol afforded the desired diphenyl sulphides which were summarised in Table-1.

TABLE - I

Physical Data of Substituted Diphenyl Sulphides(VIa-c).



S.No.	Compounds R	Compounds R_1	M.P. (°C)	Yield (%)	Molecular formula	% N Calcd. (Found)
a	CH_3	COOH	114	69	$C_{14}H_{12}N_2SO_4$	9.21 (9.25)
b	CH_3	NO_2	110	63	$C_{13}H_{11}N_3SO_4$	13.77 (13.78)
c	Cl	CF_3	91	64	$C_{13}H_8N_2SClF_3O_2$	8.03 (8.00)

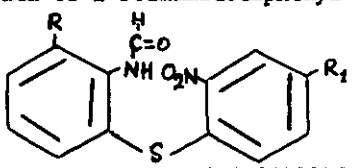
Preparation of 2-Formamidodiphenyl Sulphides (VIIa-c)

The diphenyl sulphide (VIIa-c; 0.01 mole) was added in 90% formic acid (20 ml) and refluxed for four hours. The contents of the refluxion flask were then poured into beaker containing crushed ice. The solid which separated was collected and washed with cold water till the filtrate was neutral. The crude product was crystallised from benzene/methanol. The physical data of the

compounds were summarised in Table-II.

TABLE - II

Physical Data of 2-Formamidodiphenyl Sulphides (VIIa-c).



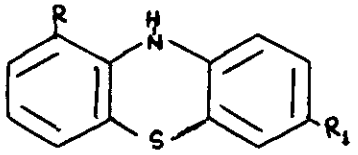
S.No.	Compounds R	Compounds R_1	M.P. (°C)	Yield (%)	Molecular formula	% N Calcd. (Found)
a	CH_3	COOH	130	59	$C_{15}H_{12}N_2SO_5$	8.43 (8.45)
b	CH_3	NO_2	118	64	$C_{14}H_{11}N_3SO_5$	12.61 (12.59)
c	Cl	CF_3	135	61	$C_{14}H_8N_2SClF_3O_3$	7.43 (7.44)

Preparation of 1,7-Disubstituted Phenothiazines via Smiles Rearrangement(VIIIa-c)

To a solution of formyl derivative (VIIa-c; 0.01 mole) in acetone (15 ml) was added a first lot of alcoholic solution of potassium hydroxide (0.2 gm. in 5 ml ethanol). The colour of the solution darkned immediately on addition of alkaline alcoholic solution. The contents were heated for half an hour. To this refluxing solution, a second lot of alcoholic potassium hydroxide (0.2 gm. in 5 ml ethanol) was added and refluxed continuously for two hours. The contents were then poured into crushed ice contained in a beaker and the solid separated out was collected and washed with cold water followed by 30% ethanol. Recrystallization from benzene/methanol afforded the desired phenothiazines which were summarised in Table-III.

TABLE - III

Physical Data of 1,7-Disubstituted Phenothiazines (VIIIa-c)



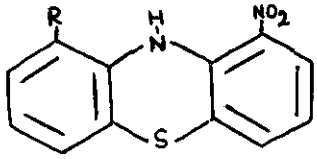
S.No.	Compounds R	Compounds R_1	M.P. (°C)	Yield (%)	Molecular formula	% C Calcd. (Found)	% H Calcd. (Found)	% N Calcd. (Found)
a	CH_3	COOH	153	62	$C_{14}H_{11}NSO_2$	65.36 (65.45)	4.28 (4.30)	5.44 (5.46)
b	CH_3	NO_2	172	58	$C_{13}H_{10}N_2SO_2$	66.46 (66.20)	3.87 (3.88)	10.85 (10.82)
c	Cl	CF_3	159	56	$C_{13}H_7NSClF_3$	51.74 (51.93)	2.32 (2.31)	4.64 (4.65)

Preparation of 9-Substituted 1-Nitrophenothiazines via Smiles Rearrangement in situ (Xa-c).

To a solution of 2-amino-3-methyl/methoxy/chlorothiophenol (IV; 0.012 mole) in ethanol (15 ml), an alcoholic solution of sodium hydroxide (0.1 mole in 5 ml ethanol) was added and contents were heated. Later on an ethanolic solution of 2,6-dinitrochlorobenzene (0.01 mole) was added to the boiling solution and refluxed for four hours. The contents were filtered and washed with water followed by 50% ethanol. Recrystallisation from methanol/benzene afforded the pure sample of phenothiazines which were summarised in Table-IV.

TABLE - IV

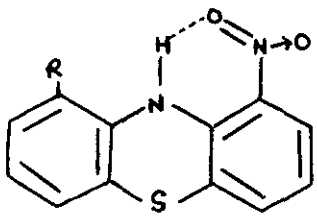
Physical Data of 9-Substituted 1-Nitrophenothiazines(Xa-c).



S.No.	Compounds R	M.P. (°C)	Yield (%)	Molecular formula	% C Calcd. (Found)	% H Calcd. (Found)	% N Calcd. (Found)
a	CH_3	225	65	$C_{13}H_{10}N_2SO_2$	60.46 (60.35)	3.87 (3.88)	10.85 (10.83)
b	OCH_3	193	59	$C_{13}H_{10}N_2SO_3$	56.93 (56.80)	3.64 (3.65)	10.21 (10.23)
c	Cl	208	61	$C_{12}H_7N_2SClO_2$	51.70 (51.61)	2.51 (2.50)	10.05 (10.04)

Infrared

Infrared spectra of phenothiazines which are included in this communication have been studied. Spectra of these compounds have been scaned in KBr/Nujol on Perkin-Elmer 577 spectrophotometer. All the 9-substituted 1-nitrophenothiazines exhibited a peak in the region 3350-3320 cm^{-1} which is assigned to -NH group. The shift to lower frequency suggested a highly stable six membered chelate through strong NH----O=N bonding. Spectra of these phenothiazines have sharp bands at 1500-1495 cm^{-1} and 1230-1350 cm^{-1} which are attributed to aromatic nitro group.



Other phenothiazines without nitro group at position-1 exhibit a sharp peak in the region 3350-3370 cm^{-1} which is assigned to -NH group. All the 2-amino-2'-nitro-3,4'-disubstituted diphenyl sulphides exhibit two peaks in the region 3340-3475 cm^{-1} which is characteristic of primary amino group, whereas in

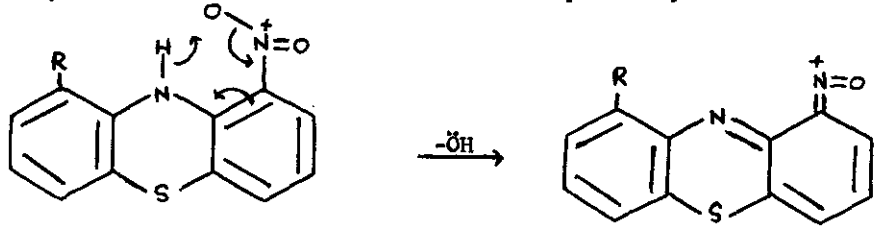
2-formamido-2'-nitro-3,4'-disubstituted diphenyl sulphides, only one peak is obtained in the region 3360-3375 cm^{-1} which is assigned to -NH group. A band in region 1605-1630 cm^{-1} is attributed to aldehyde group.

N.M.R.

NMR spectral studies have also been made for all phenothiazines. These studies reveal that the structures of these phenothiazines are in accordance with their NMR spectra. In all 1-nitro-substituted phenothiazines, the signal of the proton attached to nitrogen significantly shifted to downfield due to the hydrogen bonding between N-O --- H-N and peak spread over a large range. This peak is observed in the region 0.85-0.95 τ . In spectra of other phenothiazines having no nitro group at position-1, a singlet peak is observed for -NH proton at 1.35-1.45τ A singlet in the region 7.8-7.85τ is observed in compound VIIIa, VIIIb and Xa arising due to CH_3 group at position-9 in VIIIa, VIIIb and position-1 in Xa. A singlet peak centered at 6.2τ in spectra of compound Xb arising due to -O-CH_3 group at position-1. In compound VIIIa, a singlet peak is observed in extremely low field at -1.5τ which is assigned to -COOH group at position-7. The multiplets in the region 2.1-3.35τ are due to aromatic ring protons.

Mass

High stability of phenothiazine nucleus due to a greater degree of conjugation is suggested by molecular ion base peak. From detailed study it has been shown that all the phenothiazines gave exactly similar behaviour in mass fragmentation pattern. The fragment M-32, although weak, is always found in all phenothiazines suggesting the loss of sulphur nucleus. The peak M-17 of variable intensity is present in all the 9-substituted 1-nitrophenothiazines. This suggests that nitro group at position-1 takes part in the McLafferty rearrangement[13], which may be shown in the following way. The McLafferty rearrangement which involves a six membered cyclic transition state has been also reported by other workers in case



of o-nitrobenzene derivatives[13,14]. Moieties M-46 and M-47 are exist with variable intensity in nitrophenothiazines due to loss of NO_2 group and HNO_2. The fragment M-30 also present due to loss of NO radical. All these fragments are characteristics of aromatic nitro derivatives. In compound VIIIc a peak M-50 is assigned to loss of $-CF_2$ moiety.

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