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SYNTHESIS OF SOME SUBSTITUTED 8-TRIFLUOROMETHYLNITROPHENOTHIAZINES

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SUMMARY

The syntheses of variedly ring substituted phenothiazines with two strong electron-withdrawing groups (trifluoromethyl and nitro) have been accomplished by the reactions of some reactive halonitrobenzenes with the zinc mercaptide of 2-amino-4-trifluoromethylbenzenethiol The products have been characterised by elemental analysis, IR, ^{1}H, ^{19}F NMR and mass spectral studies

INTRODUCTION

A number of trifluoromethyl phenothiazines are used as drugs [1-3] During the past few years an effort has been made to synthesise the possible metabolites [4-7] of the most important tranquilizers carrying trifluoromethyl groups trifluoperazine trifluopromazine fluophenazine etc The synthesis of analogous trifluoromethyl derivatives having different substituents at various positions in the phenothiazine moiety will be interesting and serve multifold purposes

In the present investigation, some ring substituted 8-trifluoromethylnitrophenothiazines were prepared via Smiles rearrangements [8,9], they had trifluoromethyl, nitro and halo groups at various positions in the peripheral rings of the phenothiazine nucleus Halo and nitro groups suited the best for such studies because they are relatively bulky and also change the nature of the phenothiazine moiety due to their strong electron-withdrawing tendencies Schemes 1 - 4 describe the syntheses of these substituted phenothiazines

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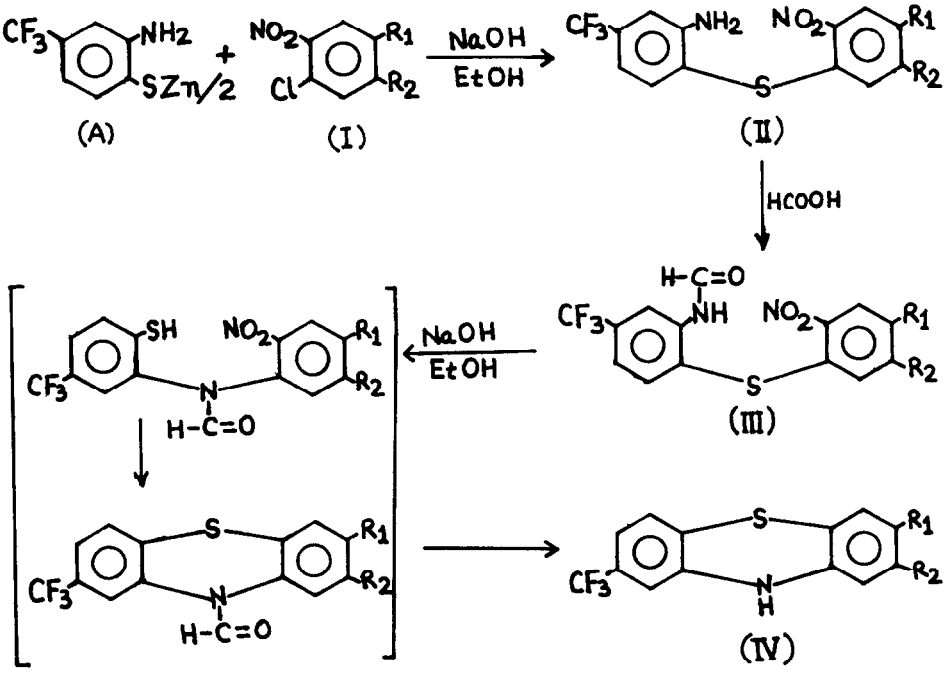
RESULTS AND DISCUSSION

1-Chloro-2,4-dinitrobenzene (Ia) and 1,3-dichloro-4,6-dinitrobenzene (Ib) which had only one nitro group ortho to the activated halogen atom, when reacted with the zinc mercaptide of 2-amino-4-trifluoromethylbenzenethiol(A) provided 2-amino-4-trifluoromethyl-2',4'-dinitrodiphenylsulphide (IIa) and 2-amino-4-trifluoromethyl-2',4', dinitro-5'-chlorodiphenylsulphide (IIb) respectively, but no phenothiazines were detected However, IIa and IIb when treated with formic acid gave corresponding formyl derivatives (IIIa and IIIb) which on Smiles rearrangement yielded the 3-nitro-8-trifluoromethyl (IVa) and 2-chloro-3-nitro-8-trifluoromethyl (IVb) phenothiazines respectively [Scheme 1]

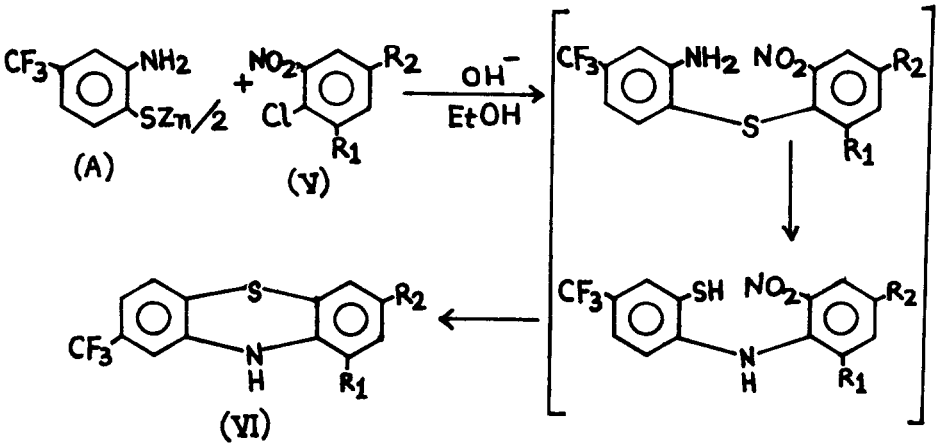


Where I-IVa R_1=NO_2 R_2=H
b R_1=NO_2 R_2=Cl

SCHEME 1

On the other hand, 1-chloro-2,6-dinitrobenzene(Va), 1-chloro-2,4,6-trinitrobenzene(Vb) and 1,4-dichloro-2,6-dinitrobenzene(Vc) which possessed two nitro groups ortho to the reactive halogen atom when reacted with zinc salt(A), afforded 1-nitro-8-trifluoromethyl(VIa), 1,3-dinitro-8-trifluoromethyl(VIb) and 3-chloro-1-nitro-8-trifluoromethyl(VIc) phenothiazine respectively, under the similar reaction conditions [Scheme 2]

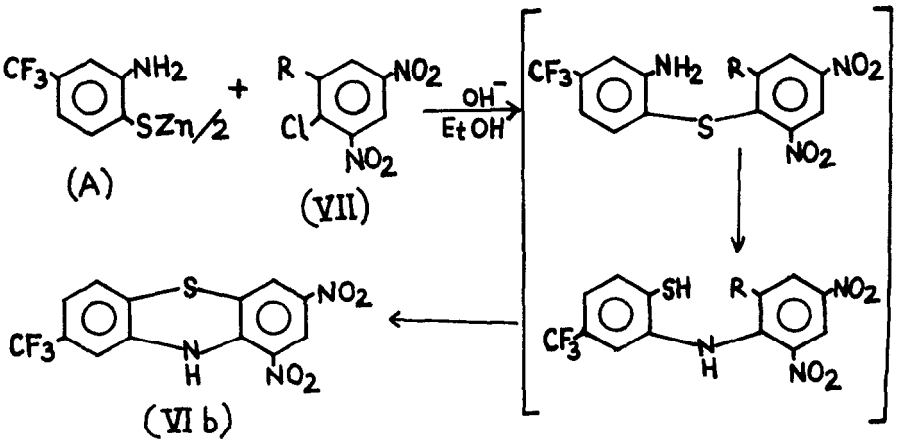
1,2-Dichloro-4,6-dinitrobenzene(VIIa) and 2-bromo-1-chloro-4,6-dinitrobenzene(VIIb), in which the activated halogen atom had a nitro group as well as a halogen atom at its ortho positions, when treated with the zinc mercaptide of 2-amino-4-trifluoromethylbenzenethiol(A) furnished 1,3-dinitro-8-trifluoromethylphenothiazine(VIb) identical to that obtained from 1-chloro-2,4,6-trinitrobenzene(Vb) This showed that cyclisation had involved the replacement of the ortho halogen atom in preference to the ortho nitro group [Scheme 3]



Where V-VIa R_1=NO_2 R_2=H
b R_1=NO_2 R_2=NO_2
c R_1=NO_2 R_2=Cl

SCHEME 2

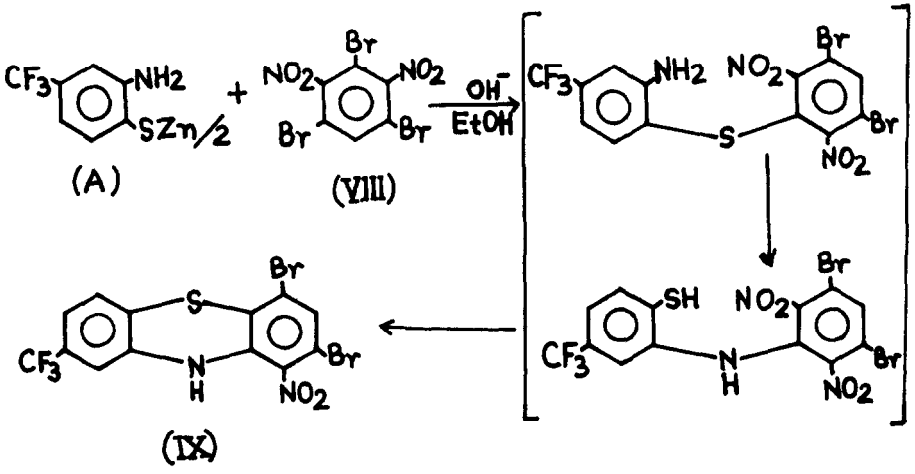
As was expected, the condensation of symmetrical 1,3-dinitro-2,4,6-tribromobenzene(VIII) and zinc salt(A) yielded only one phenothiazine i e 2,4-dibromo-1-nitro-8-trifluoromethyl phenothiazine(IX) [Scheme 4]



Where VII a R=Cl

b R=Br

SCHEME 3



SCHEME 4

SPECTROSCOPIC ANALYSIS

The IR spectra of substituted 8-trifluoromethylnitrophenothiazines IVa and IVb showed a single stretching-NH frequency between 3350-3320 cm^{-1} On the other hand 1-nitrophenothiazines VIa, VIb, VIc and IX exhibited -NH stretching frequencies between 3300-3280 cm^{-1} This shift to a lower frequency suggests the possibility of a six-membered chelate of high stability formed through a strong N-H------O-N bonding [10-13] due to the proximity of the N atom to the nitro group at position 1

Evidence of such a chelation was found in the IR spectra of these 8-trifluoromethylnitrophenothiazines because of the single N-H stretching frequency which appeared at 3450 cm^{-1} in phenothiazine (used as the reference compound), was shifted to a lower frequency All these phenothiazines exhibited two strong and sharp bands at 1580-1550 cm^{-1} and 1335-1320 cm^{-1} due to the asymmetric and symmetric stretching vibrations of the nitro group respectively

Nakanishi [12] reported the bands in the range 825-805 cm^{-1} and 885-870 cm^{-1} for 1,2,4-trisubstitution All these compounds exhibited this absorption as a sharp, medium intensity band at 820-810 cm^{-1}

A sharp band at 745-730 cm^{-1} exhibited by the chloro derivatives could be attributed to C-Cl stretching vibrations and a sharp band at 540 cm^{-1} exhibited by the compound IX could be assigned to C-Br stretching vibrations All the compounds exhibited three intense and sharp bands at 1335-1320 cm^{-1} and 1175-1150 cm^{-1}, 1135-1120 cm^{-1} due to the trifluoromethyl group

The ^{1}H NMR spectrum of the phenothiazine (used as the reference compound) showed a complex multiplet between δ 6 58-7 20 ppm, in which it was not possible to isolate the signals of any one of the protons In substituted 8-trifluoromethylnitrophenothiazines IVa and IVb in which the nitro group is at position 3 showed a multiplet in the range of δ 6 77-7 56 ppm for aromatic and -NH protons In substituted phenothiazines having a nitro group at position 1

(VIa, VIc, IX) a broad signal appearing in the range of δ9 82-9 94 ppm was assigned to -NH proton and aromatic protons were found in the range of δ6 85-7 76 ppm as a complex multiplet In the phenothiazine having nitro groups at position 1 and 3 (VIb) a broad signal found at δ10 72 ppm corresponded to -NH proton and the aromatic protons were found at δ 6 86-9 67 ppm The downfield shift of -NH proton in ^{1}H NMR also supports the chelation noticed in IR studies

In the ^{19}F NMR spectra, a characteristic signal was observed in the range of δ -57 918 to -58 763 ppm assigned to the trifluoromethyl group carried on the phenyl ring

The mass spectra of all the 8-trifluoromethylnitrophenothiazines showed a most abundant peak corresponding to the molecular ion M^+ (100%) which also represented the base peak

The fragments M^+-1 (loss of hydrogen from position 10) and M^+-32 (loss of sulphur) were always present with variable intensity in all the 8-trifluoromethylnitrophenothiazines synthesised All the compounds with a NO_2 group at C-1 gave an OH loss, this M^+-17 specific of 1-NO_2 position is in agreement with the space coplanar situation of the atoms compatible with McLafferty rearrangement

The fragments M^+-30 and M^+-46 were always present with variable intensity in all the nitrophenothiazines present under investigation The fragments M^+-30 and M^+-46 were prominent and originated due to the loss of NO radical and the entire NO_2 group respectively The fragment M^+-47 was also present in some cases with variable intensity due to the loss of HNO_2, which involved an isomerisation of the molecule

The expulsion of CO followed by the elimination of NO radical took place in all the 8-trifluoromethylnitrophenothiazines The fragment M^+-92 originated in the mass spectra of all the dinitrophenothiazines The loss of both the nitro groups took place by two step process The detailed information about the fragmentation pattern has been reported earlier [14] The spectroscopic data of all the 8-trifluoromethylnitrophenothiazines are given in Table 4

In the classical Smiles rearrangement of diphenylsulphides to diphenylamines, the activation was usually

provided by the resonance effect of an ortho or a para nitro group However the condensation of halonitrobenzenes (Ia and Ib) with the zinc mercaptide of 2-amino-4-trifluoromethylbenzenethiol(A) did not provide the expected diphenylamine but only the diphenylsulphides, i e Smiles rearrangement of the products IIa and IIb did not occur On the other hand, the increased resonance effects due to the presence of two nitro groups at both the ortho positions as in the halonitrobenzenes like Va, Vb and Vc and the combined resonance and the inductive effects enforced by the one nitro and one halogen atom as in halonitrobenzenes VIIa, VIIb and VIII, activated the Smiles rearrangement followed by ring closure to such an extent that both the processes were virtually instantaneous Therefore, it was rather difficult to isolate the intermediate diphenylsulphides and diphenylamines The possibility of the formation of the substituted nitrophenothiazines by the direct ring closure of the respective diphenylsulphide instead via Smiles rearrangement is ruled out on the grounds of the experimental results

The phenomenon has been explained by our school [15] by taking steric factors into consideration Our observation is further supported by taking into account the findings of Okamoto and Bunnett [16] who have reported that methyl, chlorine or bromine in the 6-position of 2-hydroxy-2'-nitrodiphenylsulphones, accelerates the rearrangement about 500,000 fold They have also interpreted this enormous accelerative effect by steric considerations

EXPERIMENTAL

All melting points were uncorrected The IR spectra were recorded in KBr pellets and as nujol nulls on a Perkin-Elmer 577 grating infrared spectrophotometer The ^{1}H and ^{19}F NMR spectra were recorded in $CDCl_3$ and in DMSO-d_6 on a FX90Q JEOL spectrometer (at 90 MHz)and chemical shifts were reported in ppm (δ) relative to Me_4Si as an internal standard for ^{1}H and to C_6F_6 as an external standard for ^{19}F NMR Mass spectra were determined on an A E I MS9 mass

spectrometer. Samples were vaporised in the ionisation chamber under different electronic accelerations (70eV and 12eV).

Synthesis of Zinc mercaptide of 2-Amino-4-trifluoromethyl-benzenethiol(A)

Zinc mercaptide of 2-amino-4-trifluoromethylbenzene-thiol(A) has been prepared by the method reported earlier in the literature [17] : m.p. >300°C; yield 70%.

Synthesis of substituted diphenylsulphides (IIa, IIb) and 8-trifluoromethylnitrophenothiazines (VIa-VIc,VIb,IX)

To a refluxing solution of the zinc mercaptide of 2-amino-4-trifluoromethylbenzenethiol(A) (0.005 mol) and sodium hydroxide (0.01 mol) in absolute ethanol (20 ml) was added a hot solution of the halonitrobenzene (0.01 mol) in ethanol (5 ml). The colour of the reaction mixture darkened immediately on the addition of halonitrobenzene. The refluxing was continued for 5-7 hours. After cooling, the reaction mixture was filtered, washed well with hot water and finally with ice-cold dilute ethanol. The products were crystallised from benzene and recrystallised from glacial acetic acid. The characterisation and analytical data of substituted diphenylsulphides (IIa,IIb) and 8-trifluoromethylnitrophenothiazines (VIa-VIc,VIb,IX) are given in Tables 1 and 3 respectively. The spectroscopic data of substituted diphenylsulphides (IIa,IIb) are given in Table 2.

Formylation of substituted diphenylsulphides (IIIa, IIIb)

To the diphenylsulphide (IIa or IIb) (0.005 mol) was added 15-20 ml of 95% formic acid and the mixture was heated under reflux for 6 hours. The contents of the flask were poured into crushed ice. The solid so obtained was filtered, washed with water and crystallised from ethanol to give the formyl derivatives (IIIa, IIIb) of the substituted diphenylsulphides (Table 1). The spectroscopic data of these compounds (IIIa, IIIb) are given in Table 2.

TABLE 1

Characterisation and analytical data of substituted diphenylsulphides (IIa and IIb) and their formyl derivatives (IIIa and IIIb) (New Compounds)

Comp No	Name of the compound	Molecular Formula	m p [a] °C	Yield %	Analysis % Calcd (Found) C	H	N
IIa	2-Amino-4-trifluoromethyl-2',4'-dinitrodiphenyl-sulphide	$C_{13}H_8F_3N_3O_4S$	154	80	43 45 (43 01)	2 23 (2 15)	11 69 (11 82)
IIb	2-Amino-4-trifluoromethyl-2',4'-dinitro-5'-chloro-diphenylsulphide	$C_{13}H_7ClF_3N_3O_4S$	180	83	39 64 (39 90)	1 78 (1 82)	10 67 (10 91)
IIIa	2-Formamido-4-trifluoro-methyl-2',4'-dinitro-diphenylsulphide	$C_{14}H_8F_3N_3O_5S$	178	70	43 41 (43 25)	2 07 (2 05)	10 85 (10 69)
IIIb	2-Formamido-4-trifluoro methyl-2',4'-dinitro-5-chlorodiphenylsulphide	$C_{14}H_7ClF_3N_3O_5S$	205	82	39 86 (39 96)	1 66 (1 59)	9 96 (9 65)

[a] Melting points are uncorrected

TABLE 2

The IR, ^{1}H and ^{19}F NMR spectral data of substituted diphenylsulphides (IIa, IIb) and their formyl derivatives(IIIa, IIIb)

Comp No	IR (KBr ν max cm^{-1})							^{1}H NMR (ppm from TMS)[a]				^{19}F NMR(ppm)[a]
	$-NH_2$(str)	>NH(str)	C=O(str)	C-H(str) (aldehyde)	NO_2(str)	CF_3(str)	C-Cl (str)	$-NH_2$	>NH	-CHO	Ar-H	A_1-CF_3
IIa	3460,3400	-	-	-	1570 1345	1125,1165 1330	-	7 56(bs)	-	-	6 70-7 78(m)	-57 234(s)
IIb	3460,3390	-	-	-	1580 1345	1130,1170 1330	740	7 57(bs)	-	-	6 74-7 87(m)	-57 223(s)
IIIa	-	3350	1680	2720	1575 1340	1125,1165 1330	-	-	7 60(bs)	9 72(s)	6 73-7 78(m)	-57 221(s)
IIIb	-	3340	1675	2710	1575 1340	1125,1170 1340	745	-	7 64(bs)	9 74(s)	6 75-7 85(m)	-57 230(s)

[a] The ^{1}H and ^{19}F NMR spectra were recorded in DMSO-d_6

s = singlet, bs= broad singlet, m = multiplet

TABLE 3

Characterisation and analytical data of substituted trifluoromethylnitrophenothiazines (IVa-IVb,VIa-VIc,IX) (New compounds)

Comp. No.	Name of the compound	Molecular Formula	m.p.[a] °C	Yield %	Analysis % Calcd.(Found) C	H	N
IVa	3-Nitro-8-trifluoro-methyl phenothiazine	$C_{13}H_7F_3N_2O_2S$	216	32	50.00 (49.60)	2.24 (2.04)	8.97 (8.90)
IVb	2-Chloro-3-nitro-8-trifluoromethyl phe-nothiazine	$C_{13}H_6ClF_3N_2O_2S$	240	35	45.02 (45.05)	1.73 (1.79)	8.08 (7.95)
VIa	1-Nitro-8-trifluoro-methyl phenothiazine	$C_{13}H_7F_3N_2O_2S$	210	80	50.00 (50.05)	2.24 (2.14)	8.97 (8.95)
VIb	1,3-Dinitro-8-trifluoro-methyl phenothiazine	$C_{13}H_6F_3N_3O_4S$	205	90	43.69 (43.82)	1.68 (1.69)	11.76 (12.05)
VIc	3-Chloro-1-Nitro-8-tri-fluoromethyl phenothia-zine	$C_{13}H_6ClF_3N_2O_2S$	195	82	45.02 (45.18)	1.73 (1.70)	8.08 (8.01)
IX	2,4-Dibromo-1-nitro-8-trifluoromethyl phenothiazine	$C_{13}H_5Br_2F_3N_2O_2S$	178	90	33.19 (33.05)	1.06 (1.05)	5.96 (5.72)

[a] Melting points are uncorrected.

TABLE 4

The IR, ^{1}H, ^{19}F NMR and mass spectral data of substituted 8-trifluoromethylnitrophenothiazines

Comp No	IR (νmax cm^{-1})					^{1}H NMR(ppm from TMS)[a]		^{19}F NMR(ppm)[a]	MS(m/e)[b]
	>NH(str)	NO_2(str)	1,2,4-substitution	CF_3(str)	C-Cl(str.) C-Br(str)	>NH	Ar-H	Ar-CF_3	M^+
IVa	3350	1580 1335	820	1170,1135 1330	-	-	6 77-7 47(m) (Ar-H + >NH)	-57 918(s)	312
IVb	3320	1570 1330	820	1160,1130 1325	745	-	6 84-7 56(m) (Ar-H + >NH)	-57 942(s)	346
VIa	3300	1560 1328	815	1175,1120 1335	-	9 82(bs)	6 85-7 71(m)	-58 266(s)	312
VIb	3280	1550 1320	810	1165,1125 1320	-	10 72(bs)	6 86-9 67(m)	-58 763(s)	357
VIc	3300	1555 1325	815	1150,1125 1325	730	9 94(bs)	6 92-7 76(m)	-58 453(s)	346
IX	3300	1555 1328	820	1155,1125 1330	540	9 87(bs)	6 88-7 74(m)	-58 356(s)	468

[a] The ^{1}H and ^{19}F NMR spectra of the compounds IVa and IVb were recorded in $CDCl_3$ and rest in DMSO-d_6

[b] M^+ = Molecular ion peak

s = singlet, bs = broad singlet, m = multiplet

Smiles rearrangement of the formyl derivatives (IIIa,IIIb) to the corresponding phenothiazines (IVa,IVb)

The formyl derivative (IIIa or IIIb) (0 005 mol) was dissolved in absolute ethanol (20 ml) To this, a solution of sodium hydroxide (0 2 g in absolute ethanol 10 ml) was added The colour of the reaction mixture darkened immediately on the addition of alkali solution The contents of the flask were refluxed After 30 minutes, a second portion of 0 2 g of sodium hydroxide in absolute ethanol (10 ml) was added and refluxing was continued for two hours The mixture was poured into crushed ice, filtered and the product was washed well with cold water and finally with dilute ethanol Crystallisation from benzene yielded the corresponding phenothiazines(IVa and IVb) (Table 3)

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