3. Raju, N. R.,*Proceedings of the Annual Meetings of Association of Clinical Biochemists (India), Ahmedabad* 1986, B13.
4. Angyal, S. J.and Matheson, N. K., *J. Am. Chem. Soc.*, 1955, **77**, 4343.
5. Folin, O.and Wu, H., *J. Biol. Chem.*, 1920, **41**, 367.
6. Matin, M. A., Masih, A. H. and Kar, P. P., *J. Pharm. Pharmacol.*, 1982, **34**, 457.
7. Duncan, L. J. P. and Baird, J. D., *Pharm. Rev.*, 1960, **12**, 91.
8. Geigy, J. R., *Scientific tables*, Basle, Switzerland 1956, p. 39, 5th edn.
9. Benjamin Blank, In: *Burger's medicinal chemistry-Part II*, John Wiley, New York, 1979, p. 1045, 4th edn.
10. Frederick, A., Grunwald, In: *Burger's medicinal chemistry-Part II.*, 1970, p. 1172, 3rd edn.
11. Quirico Carta and Fransisco Pungliese, *Congr. Feder. Int., Diabetes*, 4th Geneva, Switzerland, 1961, **1**, 763, *Chem. Abstra.*, **57**, 15766d.
12. Kozo Okamoto, Tetsuro Taii, Hiromasa Koso, Norihisa Tekenaka, Teisuke Hayakawa, and Toshiniko Ibaraki, *Tohoku J. Exp. Med.*, 1955, **61**, 36, *Chem. Abstr.*, **49**, 16238a.
13. Cosgrove, D. J., *Inositol Phosphates*, Elsevier, New York, 1980, p. 173.
14. Clark, Wu. G. and Geissman, T. A., *J. Pharmacol. Exp. Therap.*, 1949, **95**, 362.
15. George, R. Herrmann, *Proc. Soc. Exp. Biol. Med.*, 1946, **63**, 436.

SYNTHESIS OF SOME NEW FLUORO-SUBSTITUTED NITROPHENOTHIAZINES

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THE zinc mercaptide of 2-amino benzene thiol and its substitutes have been used in the synthesis of a wide variety of phenothiazine compounds[1-3]. But little attention has been paid towards the synthesis of nitrophenothiazines especially by Smiles rearrangement[4]. With a view to explore the domain of such a reaction, we have studied the reaction of zinc mercaptide of 2-amino-4/5-fluorobenzenethiol with some reactive halonitrobenzenes in the presence of sodium hydroxide in absolute ethanol.

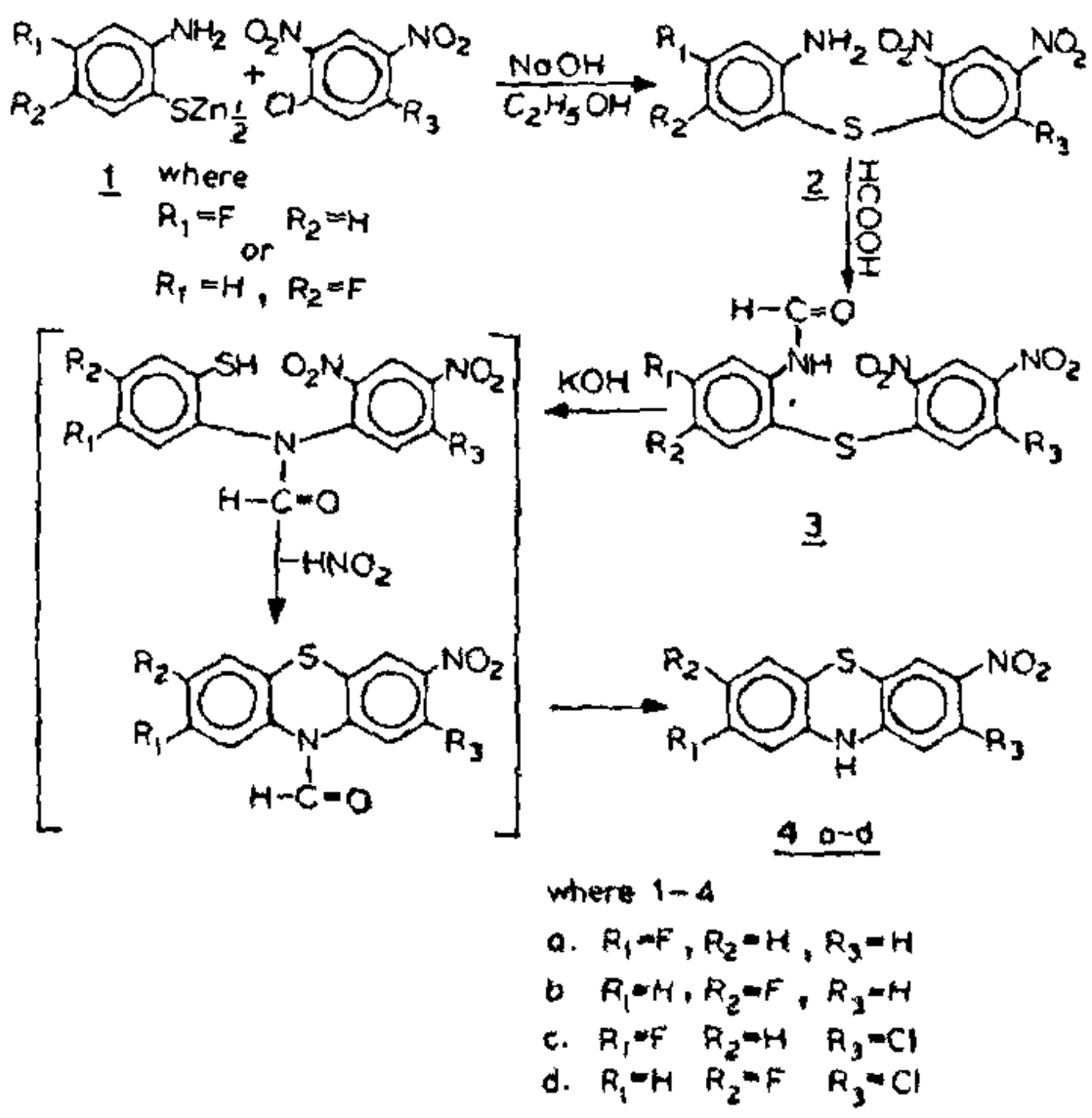
The experimental techniques were the same as reported earlier for 1-chloro-2,4-dinitrobenzene[5], 1,3-dichloro-4,6-dinitrobenzene[6], 1,2,3-trichloro-4,6-dinitrobenzene[7]. Zinc mercaptide of 2-amino-4/5-fluorobenzenethiol[8,9] were prepared by adopting the procedure already reported.

Preparation of nitrophenothiazines (4a-d, 5a-b, 6a-b, 7a-b)

To a refluxing mixture of zinc mercaptide of 2-amino-4/5-fluorobenzenethiol (1) (0.005 mol), sodiumhydroxide (0.01 mol) in absolute ethanol (20 ml) was added hot solution of reactive halonitrobenzene (0.01 mol) in ethanol (5 ml). The colour of the reaction mixture darkened immediately on the addition reactive halonitrobenzene. The refluxing was continued for 5–7 hr. After refluxing, the reaction mixture was cooled, filtered, washed well with hot water and finally with ice-cold dilute ethanol to obtain nitrophenothiazine.

Purification was effected by recrystallization from benzene to get a better sample of the title compound. The IR and mass spectral data of nitrophenothiazines (4a-d, 5a-b, 6a-b, 7a-b) are given in table 1. The R_f values of the compound (5a-b, 6a-b, 7a-b) are also reported and discussed. All the compounds synthesized are new and gave satisfactory elemental analysis (table 2).

We observed that 1-chloro-2,4-dinitrobenzene and 1,3-dichloro-4,6-dinitrobenzene reacts with zinc



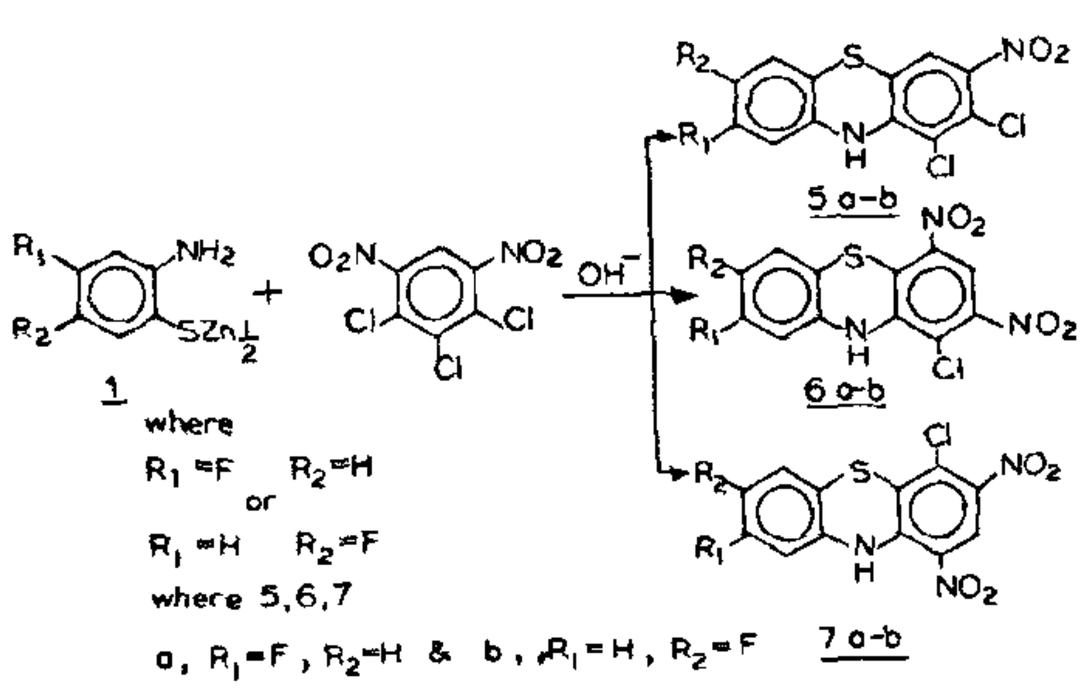
Scheme-1

Table 1 *Distinctive infrared absorption bands* (cm^{-1})

Compound	A	B	C	D	E	Other peaks
4a	3325	1570 1330	1120	815	–	1550w, 1440m, 1000m, 810m, 610w
4b	3330	1580 1335	1125	822	–	1590w, 1510w, 1410w, 1330b, 1140m, 900m, 710w
4c	3320	1580 1325	1128	817	745	3130w, 1610w, 1390m, 1410m, 760m, 630m, 470w
4d	3310	1560 1335	1130	820	725	3100b, 1560w, 1370m, 630w, 470m
5a	3330	1565 1330	1129	820	740	1600s, 1530w, 1440m, 1390w, 1175w, 1000s, 920m, 770w
5b	3350	1570 1335	1125	815	725	1630s, 1520w, 1442m, 1235m, 890m, 762w
6a	3315	1560 1328	1120	815	745	1600s, 1520m, 1450m, 1375m, 1280m, 1070w, 945m, 830w
6b	3318	1562 1330	1130	816	738	1630s, 1515m, 1452w, 940m, 838w
7a	3280	1555 1328	1128	815	740	1628s, 1430m, 1380w, 1345w, 1200m, 945m, 720w
7b	3395	1558 1330	1125	809	738	1630m, 1428m, 1370w, 1342w, 1185w, 940m, 742m

A = NH– stretching aromatic; B = asymmetry and symmetry nitro group; C = C–F;
D = 1,2,4-trisubstitution; E = C–Cl stetching vibration; s = strong, m = medium, w = weak.

mercaptide of 2-amino-4/5-fluorobenzenethiol (1) to yield 4a, b, c, and d respectively (scheme 1), whereas 1,2,3,-trichloro-4,6-dinitrobenzene reacts with zinc mercaptide of 2-amino-4/5-fluorobenzenethiol (1) to yield 5a–b, 6a-b, 7a and b respectively (scheme 2). It appears that nitrophenothiazines were formed only when the position ortho to the activated halogen atom in halonitrobenzenes is substituted either by nitro group or by a nitro group and a halogen atom. Also in latter case, the halogen atom was eliminated in preference to the nitro group during cyclization (scheme 2).



Scheme-2

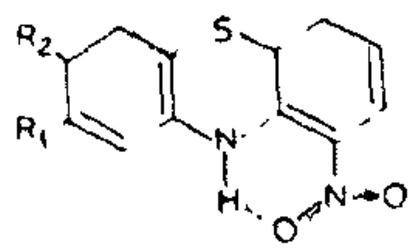
It was noticed that three isomeric nitrophenothiazines were formed 1,2-dichloro-7/8-fluoro-3-nitrophenothiazine (5a-b), 1-chloro-7/8-fluoro-2,4-dinitro phenothiazine (6a-b) and 4-chloro-7/8-fluoro-1,3-dinitrophenothiazine (7a-b), when 1,2,3-trichloro-2,4-dinitrobenzene was condensed with zinc mercaptide of 2-amino-4/5-fluorobenzenethiol (scheme 2). No appreciable difference was found in the IR spectra of these isomers. The finding was checked by TLC. Although several TLC techniques are reported for the analysis of 10-substituted phenothiazines[10], those for 10-unsubstituted one have not been established. The methods reported by Hashimoto[11] and modified by Sugita and Tsujino[12] were successfully applied to the present study using benzene: hexane (1 : 3) as a solvent system. Each developed zone could be easily located because of its red-violet-purple colour. The crude product containing the mixture of three isomers separated into zones (R_f 0.60, 0.55 and 0.62 for 5a, 6a and 7a and R_f 0.62, 0.57 and 0.63 for 5b, 6b and 7b respectively) and at the origin there was a black spot which must be due to obstinate impurity.

The structure of the compound (4a-d, 5a-b, 6a-b, 7a-b) was confirmed on the basis of IR and mass

Table 2 *Fluoro-substituted nitrophenothiazines (4a-d, 5a-b, 6a-b, and 7a-b)*

Compound	M. P. (°C)	Yield (%)	Colour of spot on TLC plate	Molecular formula	% Analysis	Calculated	Found
4a	281	48	Dark-red	$C_{12}H_7FN_2O_2S$	C	54.96	54.88
					H	2.69	2.61
					N	10.68	10.59
4b	275	52	Maroon-red	$C_{12}H_7FN_2O_2S$	C	54.96	54.84
					H	2.69	2.59
					N	10.68	10.61
4c	225	59	Darkened	$C_{12}H_6ClFN_2O_2S$	C	48.58	48.52
					H	2.04	2.00
					N	9.44	9.39
4d	285	55	Red	$C_{12}H_6ClFN_2O_2S$	C	48.58	48.59
					H	2.04	1.98
					N	9.44	9.33
5a	> 300	30	Orange-red	$C_{12}H_6Cl_2FN_2O_2S$	C	46.03	45.99
					H	1.61	1.59
					N	8.94	8.91
5b	> 300	28	Orange	$C_{12}H_6Cl_2FN_2O_2S$	C	46.03	45.99
					H	1.61	1.59
					N	8.94	8.91
6a	265	15	Maroon	$C_{12}H_6ClFN_3O_4S$	C	42.17	42.15
					H	1.46	1.41
					N	12.30	12.27
6b	253	18	Maroon-red	$C_{12}H_6ClFN_3O_4S$	C	42.17	42.13
					H	1.46	1.40
					N	12.30	12.22
7a	289	16	Dark-red	$C_{12}H_6ClFN_3O_4S$	C	42.17	42.12
					H	1.46	1.39
					N	12.30	12.21
7b	281	14	Red	$C_{12}H_6ClFN_3O_4S$	C	42.17	42.13
					H	1.46	1.38
					N	12.30	12.24

spectral data. The IR spectra of nitrophenothiazines 4a, 4b, 4c, 4d, 5a and 5b having a nitro group at position 3 exhibited a single stretching NH-frequency between 3310 and 3350 cm^{-1}. On the other hand, nitrophenothiazines 7a and 7b having a nitro group at positions 1 and 3 exhibited NH- stretching frequency between 3280 and 3300 cm^{-1}. This shift to a lower frequency suggests the possibility of a six-membered chelate of high stability, formed through a strong NH--- O-N bonding[13-18] due to the proximity of the N proton to the nitro group at position-1.



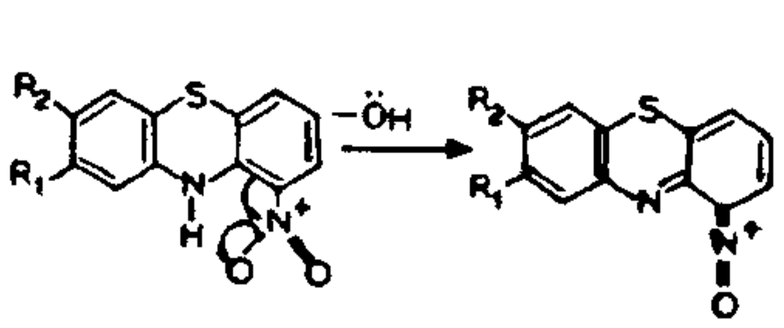
where $R_1 = F$, $R_2 = H$,

$R_1 = H$, $R_2 = F$.

Evidences for such a chelation was found in the IR spectra of 7a and 7b because the single N-H stretching frequency which generally appears at 3450 cm^{-1} in unsubstituted phenothiazines was shifted to a lower frequency. All these phe-

nothiazines exhibited two strong and sharp bands at 1550–1580 cm^{-1} and 1325–1330 cm^{-1} due to the asymmetric and symmetric stretching vibrations of the nitro group. The absorption due to C–F linkage was observed in the region 1120–1130 cm^{-1}. Koji Nakanishi[17] suggested the range 820–805 cm^{-1} and 885–870 cm^{-1} for 1,2,4-trisubstitution. All these exhibited this absorption as a sharp, medium intensity band at 815–820 cm^{-1}. A sharp peak at 730–745 cm^{-1} exhibited by 4c, 4d, 5a, 5b, 6a, 6b, 7a and 7b could be attributed to C–Cl stretching vibration.

In the mass spectra of all the compounds, the molecular ion peak is the base peak and suggests a high stability of the phenothiazine ring due to a high degree of conjugation. The fragment M^+–32 although weak is always present and suggested the loss of the sulphur nucleus. The peak M^+–17, although of variable intensity, is present in the case of 7a and 7b which contain a nitro group at position-1. This provides evidence that the nitro group takes part in McLafferty rearrangement[19], which may be postulated in the following way:



where R_1 = F, R_2 = H;
R_1 = H, R_2 = F

The McLafferty rearrangment which involves a six-membered cyclic transition state has been reported by other workers in the case of *o*-nitro derivatives of benzene[19,20]. The peak M^+–19, although of variable intensity, is present in the case of all the nitrophenothiazines due to the loss of fluorine radical. The fragments M^+–46 and M^+–47 are present with variable intensity of 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[20].

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1. Sharma, H. L., Banerjee, S. P., Sharma, V. N. and Mital, R. L., *Jpn. J. Pharmacol.*, 1969, **19,** 211.
2. Gordon, M., Craig, P. N. and Zirkle, C. L., *Adv. Chem. Ser.*, 1964, **45,** 140.
3. Kehrman, F. and Zybs, P., *Ber. Dt. Chem. Ges.*, 1919, **B52,** 130; Kehrman, F. and Ringer, E., *Ber. Dt. Chem. Ges.*, 1913, **46,** 3014; Schmalz, A. C. and Burger, A., *J. Am. Chem. Soc.*, 1954, **76,** 5455; Michels, J. G. and Amstutz, E. D., *J. Am. Chem. Soc.*, 1950, **72,** 888.
4. Wight, C. F. and Smiles, S., *J. Chem. Soc.*, 1935, 340; Baltzly, R., Harjenist, H. and Webb, F. J., *J. Am. Chem. Soc.*, 1946, **68,** 2673.
5. Hoffman, E. F. and Dame, P. A., *J. Am. Chem. Soc.*, 1919, **41,** 1013.
6. *Beilsteins Handbuch der Organischen Chemie*, Vol. 5, p. 265, 1942 Verlag Von Julius Spring, Berlin, 1939, Reproduction, 1942.
7. Huffer, R. J. E., *Rec. Trav. Chim.*, 1921, **40,** 451; *Chem. Abstr.*, 1921, **15,** 3636.
8. Khatri, V., Gupta, C. L. and Mital, R. L., *Chem. Ind.*, 1984, **189.**
9. Tambi, S. B. Anand, M. Taneja, V., Gupta, C. L. and Mital, R. L., *J. Heterocycl. Chem.*, 1983, **20,** 803.
10. Mellinger, T. J., *J. Pharm. Sci.*, 1962, **51,** 1169; Noirfalse, A., *J. Chromatogr.*, 1964, **16,** 236; Baumler, J., *J. Pharm. Acta-Helv.*, 1961, **36,** 382.
11. Hashimoto, Y., *Hakuso (thin layer) chromatography*, Hirokawa Publishing Co., Tokyo, 1963. p. 30.
12. Sugita, J. and Tsujino, Y., *J. Chromatogr.*, 1966, **21,** 341.
13. Brady, O. L. and Waller, C., *J. Chem. Soc.*, 1930, 1218.
14. Roberts, K. C. and Clark, H. B., *J. Chem. Soc.*, 1935, 1312.
15. Rodig, O. R., Collier, R. E. and Schlatzer, R. K., *J. Med. Chem.*, 1966, **9,** 116.
16. Bellamy, L. J., (ed.) *The infrared spectra of complex molecules*, Metheun and Company Ltd., London, 1964, p. 254.
17. Nakanishi, K., (ed.) *Infrared absorption spectroscopy practical*, Nankodo Company Ltd., Tokyo, 1964, 2nd edn.
18. Shukla, A. P. Ph.D. thesis, University of Rajasthan, Jaipur, 1975.
19. McLafferty, F. W., *Anal. Chem.*, 1959, **31,** 82.
20. Harley Mason, J., Toube, T. P. and Williams, D. M., *J. Chem. Soc.*, 1966, 396.