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Studies in the Synthesis of 1,2 and 9-substituted Phenothiazin-3 and 7-ols and their Derivatives

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1,2 and 9-substituted phenothiazin-3 and 7-ols have been synthesized by the condensation of chloro hydroquinone with various zinc salts of 2-amino-3-chloro/methyl benzenethiols and 2-amino-4-bromobenzenethiol in oxygen stream in ethanol *via* Mine's condensation. Their methoxy, isopropoxy, benzyloxy, acetate (esters) and benzoate (esters) have also been synthesized. The compounds synthesized are characterized by their spectral (IR, mass) and analytical data. Their R_f and relative R_f values by TLC have also been discussed.

INTRODUCTION

Phenothiazines were found to have urinary, antiseptic[1], antihistaminic[2], and antigastric secretary[3] activities. In the last few years phenothiazin-3-ol and its derivatives have also been used as antioxidant[4], lubricants and fuel[5], stabilizers for Vitamin-A, elastomers[6], vinyl pyridine and polymer with formaldehyde as heat resistant.

Hydroxy phenothiazines are potential metabolites[7–9] of tranquillising drugs having phenothiazine nucleus. Previously hydroxyphenothiazines[10, 11] were synthesized either by reduction of phenothiazines or by thionation of hydroxy diphenylamines or dealkylation of alkoxy phenothiazines[12] with some difficulties and in poor yields. Attempts have been made to synthesize hydroxyphenothiazines *via* condensation of zinc salt of *o*-amino benzenethiol and chlorohydroquinone in aqueous ethanolic NaOH with oxygen, which gave phenothiazones and reducing the phenothiazines so obtained by sodium dithionite[13] gave the required hydroxy phenothiazines in good yield.

Search for simpler synthesis of 2-bromo-phenothiazine-7-ol, 1-chloro-phenothiazin-7-ol and 9-methyl-phenothiazin-3-ol derivatives in good yields, prompted us to study Mine's[14] condensation. The condensation of chlorohydroquinone with various zinc salts of 2-amino-3-chloro/methyl-benzene thiols and 2-amino-4-bromo-benzene thiol in various condensing media has been studied in the presence of regular oxygen current and subseqent reduction to obtain 1,2 and 9-substituted phenothiazin-3 and 7-ols. (Scheme-I)

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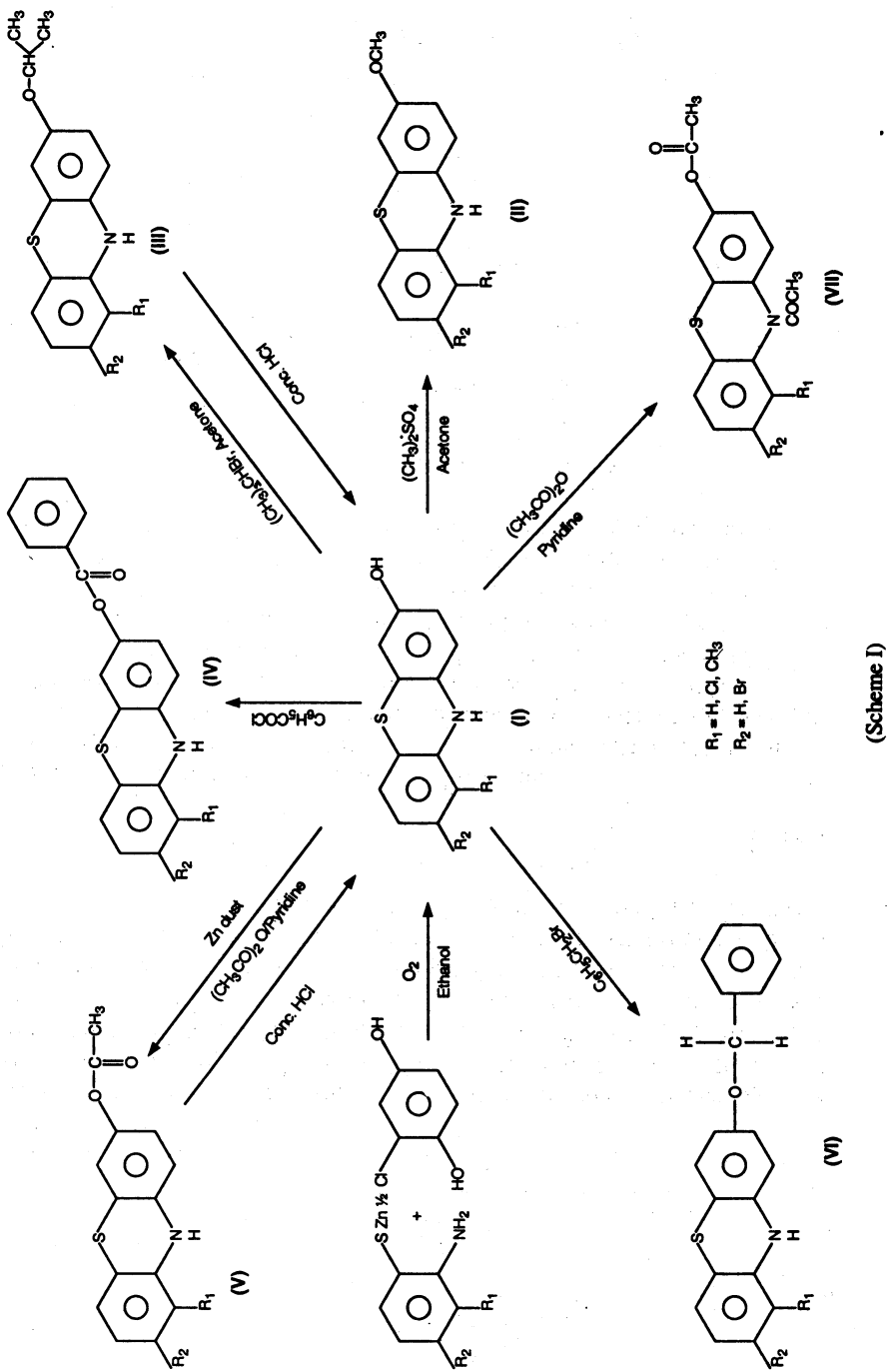
(CH3)2CHCH2OH, Acetone
Conc. HCl
(CH3)2SO4
Acetone
(CH3CO)2O
Pyridine
C6H5COCl
Zn dust
(CH3CO)2O/Pyridine
Conc. HCl
O2
Ethanol
C6H5CH2Br
R1 = H, Cl, CH3
R2 = H, Br
(I)
(II)
(III)
(IV)
(V)
(VI)
(VII)

(Scheme I)

Further, acetylation of 1 and 2-substituted phenothiazin-7-ols and 9-substituted phenothiazin-3-ol, under mild conditions, resulted in the formation of quantitative yield of 1 and 2-substituted phenothiazin-7-ol acetate (esters) and 9-substituted phenothiazin-3-acetate (ester). 10-Acetyl-1,2 and 9-substituted phenothiazin-3-ol acetate (esters) could be prepared only under vigorous reaction conditions. The synthesis of 3,7-isopropoxy phenothiazine derivatives were achieved by reacting the appropriate phenothiazine with 2-bromopropane in presence of 10% ethanolic KOH solution, while the reaction between 1,2 and 9-substituted phenothiazin-3 and 7-ols and dimethyl sulphate in 10% ethanolic KOH gave 3 and 7-methoxy phenothiazine derivatives. 1,2 and 9-Substituted 3 and 7-benzoyloxy phenothiazines have been synthesised by the reaction of benzoyl chloride with 1,2 and 9-substituted phenothiazin-3 and 7-ol, while the reaction of the latter with benzyl bromide led to the formation of 3 and 7-benzyloxy phenothiazine.

EXPERIMENTAL

Purity of all the compounds was checked on silica gel G plates using iodine vapour as the detecting agent. Melting points were determined in open capillary tubes using Gallenkamp melting point apparatus and are uncorrected. IR spectra (ν_{max} cm^{-1}) were recorded on a Perkin-Elmer 577 spectrophotometer in KBr pellets. The mass spectra were recorded on Kratos MS-30 and MS-50 spectrometer operating at an ionisation potential of 70 eV.

1-Chlorophenothiazin-7-ol (Ia): To a mixture of 9.939 g (0.026 mole) of zinc salt of 2-amino-3-chlorobenzene-thiol, 7.514 g (0.052 mole) of chlorohydroquinone and 100 mL of alcohol was added a solution of 2.1 g of sodium hydroxide in 5 mL of water. The reaction mixture was heated under reflux and a regular stream of oxygen was introduced for 1 h. The reaction mixture, which was converted from brown to blood red coloured during the reaction, was filtered hot and the filtrate was poured into 1 L of cold water containing 9 g sodium dithionite. It was then extracted with ether and the solvent layer was dried over anhydrous magnesium sulphate. The ether was evaporated under reduced pressure and the unreacted chlorohydroquinone was removed by distillation at 125–130°C (0–5 mm). Crystallization from benzene provides **Ia**.

In a similar way Ib and Ic were prepared.

1-Chloro-7-methoxy phenothiazine (IIa): 1-Chlorophenothiazin-7-ol (2.495 g; 0.01 mole) sodium dithionite (0.5 g) and 10% ethanolic KOH solution (110 mL) were reacted with dimethyl sulphate (1.76 g; 0.014 mole). The reaction mixture was refluxed for 5 h and the filtrate was pured into cold water. The brown solid separated was filtered, dried and crystallized from benzene to give **IIa**.

In a similar way IIb and IIc were prepared.

1-Chloro-7-isopropoxyphenothiazine (IIIa): To a mixture of 1-chlorophenothiazin-7-ol (1.996 g; 0.008 mole), sodium dithionite (0.7 g) and 70 mL of 10% ethanolic potassium hydroxide was added 2-bromo-propane (1.156 g; 0.0094 mole). The reaction mixture was refluxed for 4 h and poured into ice-cold water

and then extracted with ether. The removal of ether afforded a crude solid, which was crystallised from benzene to give the compound **IIIa.**

In a similar way compounds **IIIb** and **IIIc** were prepared.

1-Chloro-phenothiazin-7-ol-benzoate (ester) (IVa): A mixture of 1-chloro-phenothiazin-7-ol (2.495 g; 0.01 mole), sodium dithionite (0.5 g) and 10% ethanolic potassium hydroxide (100 mL) was added to benzoyl chloride (1.967 g; 0.014 mole). The reaction mixture was refluxed for 6 h and the resulting suspension was poured in one litre cold water. The solid was filtered and dried in vacuum. It was then crystallised with benzene to give the compound **IVa.**

In a similar way compounds **IVb** and **IVc** were prepared

1-Chloro-phenothiazin-7-ol-acetate (ester) (Va): A mixture of 1-chloro-phenothiazin-7-ol (0.948 g; 0.0038 mole), acetic anhydride (20 mL), pyridine (1 mL) and zinc dust (1 g) was stirred for 45 min and heated on a water bath for 3 min and the yellow suspension was decanted into 700 mL cold water which on being extracted with chloroform afforded a solid product which was crystallised from benzene to give compound **Va.**

In a similar way compounds **Vb** and **Vc** were prepared.

3-Benzyloxy-9-chlorophenothiazine (VIa): 1-Chloro-phenothiazin-7-ol (2.495 g; 0.01 mole), potassium carbonate (7 g; 0.05 mole), and acetone (50 mL) were heated under reflux for 1 h and then benzylbromide (2.223 g; 0.013 mole) was added and again refluxed for 8 h. The hot reaction mixture was poured into ice-cold water, extracted from ether and crystallised from benzene to give compound **VIa.**

In a similar way compounds **VIb** and **VIc** were prepared.

10-Acetyl-1-chlorophenothiazin-7-ol-acetate (ester) (VIIa): 1-Chloro-phenothiazin-7-ol (0.948 g; 0.0038 mole) was stirred with acetic anhydride (20 mL), pyridine (2 mL) and excess of zinc dust for 45 min. The reaction mixture was refluxed for 1 h and after decantation the yellow suspension was poured into 500 mL ice-cold water. It was extracted with chloroform and removal of chloroform layer afforded a solid product, which was crystallised from benzene to give compound **VIIa.**

In a similar way compounds **VIIb** and **VIIc** were prepared.

The analytical and spectral data of compounds synthesised are given in Table-1 and Table-2, respectively.

RESULTS AND DISCUSSION

Formation of 1,2 and 9-substituted phenothiazin-7 and 3-ols and their derivatives are confirmed and characterised by their IR, mass spectral data and elemental analysis, as given in Table-1 and Table-2.

Further R_f and relative R_f values byTLC have also been recorded. Combinations of many solvents were examined for developing the chromatograms on silica gel G. The best of these were found to be:

(A) Benzene : Acetone : : 70 : 30 v/v

(B) Toluene : Acetone : : 80 : 20 v/v

(C) Carbon tetrachloride : Acetone : : 60 : 40 v/v

TABLE-1: ANALYTICAL DATA OF 1,2 AND 9-SUBSTITUTED PHENOTHIAZIN-3- AND 7-OLS AND THEIR DERIVATIVES

Compd. (yield, %)	R^1	R^2	Position of OH 3/7 or derivative	m.p. (°C)	m.f.	Analysis %, found (calcd)			
						C	H	N	S
Ia (55)	Cl	H	7	115	$C_{12}H_8ClNOS$	57.77 (57.73)	3.25 (3.20)	5.68 (5.60)	12.90 (12.84)
Ib (70)	H	Br	7	200	$C_{12}H_8BrNOS$	49.02 (49.00)	2.75 (2.72)	4.79 (4.76)	10.94 (10.90)
Ic (60)	CH_3	H	3	243	$C_{13}H_{11}NOS$	68.16 (68.12)	4.74 (4.79)	6.14 (6.10)	14.01 (13.98)
IIa (65)	Cl	H	7	165	$C_{13}H_{10}ClNOS$	59.20 (59.22)	3.69 (3.73)	5.35 (5.31)	12.19 (12.16)
IIb (65)	H	Br	7	174	$C_{13}H_{10}BrNOS$	50.60 (50.67)	3.27 (3.24)	4.59 (4.54)	10.45 (10.40)
IIc (58)	CH_3	H	3	212	$C_{14}H_{13}NOS$	69.17 (69.13)	5.40 (5.34)	5.78 (5.75)	13.12 (13.18)
IIIa (66)	Cl	H	7	160	$C_{15}H_{14}ClNOS$	61.79 (61.76)	4.84 (4.80)	4.85 (4.80)	11.02 (10.99)
IIIb (60)	H	Br	7	248	$C_{15}H_{14}BrNOS$	53.64 (53.60)	4.20 (4.16)	4.19 (4.16)	9.56 (9.53)
IIIc (60)	CH_3	H	3	68	$C_{16}H_{17}NOS$	70.89 (70.85)	6.21 (6.26)	5.11 (5.16)	11.86 (11.82)
IVa (58)	Cl	H	7	>300	$C_{19}H_{12}ClNO_2S$	64.55 (64.51)	3.41 (3.39)	3.92 (3.95)	9.11 (9.08)
IVb (50)	H	Br	7	>300	$C_{19}H_{12}BrNO_2S$	57.34 (57.31)	3.05 (3.01)	3.55 (3.51)	0.09 (0.03)
IVc (50)	CH_3	H	3	110	$C_{20}H_{15}NO_2S$	72.04 (72.08)	4.55 (4.50)	4.24 (4.20)	9.68 (9.62)
Va (68)	Cl	H	7	66	$C_{14}H_{10}ClNO_2S$	57.69 (57.65)	3.47 (3.42)	4.86 (4.80)	10.93 (10.99)
Vb (60)	H	Br	7	50	$C_{14}H_{10}BrNO_2S$	50.06 (50.02)	2.94 (2.97)	4.19 (4.16)	9.57 (9.53)
Vc (55)	CH_3	H	3	80	$C_{15}H_{13}NO_2S$	66.48 (66.42)	4.75 (4.79)	5.12 (5.16)	11.88 (11.82)
VIa (58)	Cl	H	7	75	$C_{19}H_{14}ClNOS$	67.12 (67.17)	4.18 (4.12)	4.10 (4.12)	9.46 (9.43)
VIb (52)	H	Br	7	>300	$C_{19}H_{14}BrNOS$	53.45 (53.40)	3.60 (3.64)	3.67 (3.64)	0.37 (0.34)
VIc (60)	CH_3	H	3	140	$C_{20}H_{17}NOS$	75.28 (75.23)	5.36 (5.32)	4.35 (4.38)	10.09 (10.04)
VIIa (60)	Cl	H	7	60	$C_{16}H_{12}ClNO_3S$	57.55 (57.59)	3.61 (3.59)	4.17 (4.19)	9.62 (9.60)
VIIb (55)	H	Br	7	63	$C_{16}H_{12}BrNO_3S$	51.85 (50.82)	3.20 (3.17)	3.76 (3.70)	8.49 (8.47)
VIIc (65)	CH_3	H	3	137	$C_{17}H_{15}NO_3S$	65.21 (65.18)	4.81 (4.78)	4.42 (4.46)	10.25 (10.23)

TABLE-2: SPECTRAL DATA OF 1,2 AND 9-SUBSTITUTED PHENOTHIAZIN-3- AND 7-OLS AND THEIR DERIVATIVES

Compd.	R^1	R^2	Position of OH 3/7 of derivative	IR (KBr) ν_{max} cm^{-1}	Mass spectrum (M^+) = m/e
Ia	Cl	H	7	3350 s (>NH), 3200 (—OH), 1420 m, 1620 b (C—C and C—N vibrations), 925 m, 840 m (C—H), 650 m (C—S—C), 730 s (C—Cl)	249.6
Ib	H	Br	7	3350 s (>NH), 3200 m (—OH), 1620 m, 1420 m (C—C and C—N), 920 m, 840 m (C—H), 680 m (C—S—C),	294
Ic	CH_3	H	3	3380 s (>NH), 3200 b (—OH), 1620 m, 1430 b (C—C and C—N), 925 m, 830 s (C—H), 680 m (C—S—C),	229.2
IIa	Cl	H	7	3390 s (>NH), 1640 m, 1420 s (C—C and C—N), 1230 m, 1050 m (C—O—C), 870 s 810 b (C—H), 610 m (C—S—C), 755 s (C—Cl)	263.6
IIb	H	Br	7	3380 b (>NH), 1620 s, 1420 m (C—C and C—N), 1235 s, 1045 m (C—O—C), 920 s, 810 s (C—H), 620 w (C—S—C)	308
IIc	CH_3	H	3	3350 s (>NH), 1620 m, 1410 w (C—C and C—N), 1265 s, 1040 m (C—O—C), 860 m, 810 m (C—H), 640 m (C—S—C)	243
IIIa	Cl	H	7	3350 s 1620 s, 1420 s (C—C and C—N), 1240 m, 1045 m (C—O—C), 930 b, 820 w (C—H), 660 m (C—S—C), 770 s (S—Cl)	291.7
IIIb	H	Br	7	3430 m (>NH), 1630 s, 1380 m (C—C and C—N), 1250 s, 1030 m (C—O—C), 930 m 840 m (C—H), 655 (C—S—C)	336
IIIc	CH_3	H	3	3400 b (>NH), 1620 s, 1340 m (C—C and C—N), 1250 s, 1035 m (C—O—C), 940 m, 830 m (C—H), 650 w (C—S—C)	271.2
IVa	Cl	H	7	3400 b (>NH), 1750 b (>C=O), 1600 s, 1440 m (C—C and C—N), 1260 m, 1020 w, (C—O—C), 940 s, 845 m (C—H), 690 w (C—S—C), 730 w (C—Cl)	353.7
IVb	H	Br	7	3400 s (>NH), 1755 s (>C=O), 1630 m, 1465 b (C—C and C—N), 1265 b, 1085 m, (C—O—C), 920 m, 850 b (C—H), 680 m (C—S—C)	398
IVc	CH_3	H	3	3400 b (>NH), 1750 s (>C=O), 1640 m, 1460 m (C—C and C—N), 1260 b, 1080 m, (C—O—C), 920 m, 850 b (C—H), 680 m (C—S—C)	333
Va	Cl	H	7	3375 (>NH), 1755 s (C=O), 1625 w, 1440 s (C—C and C—N), 1240 m, 1040 s, (C—O—C), 920 m, 840 m (C—H), 640 w (C—S—C), 735 w (C—Cl)	291.6

Compd.	R^1	R^2	Position of OH 3/7 of derivative	IR (KBr) ν_{max} cm^{-1}	Mass spectrum (M^+) = m/e
Vb	H	Br	7	3460 s (>NH), 1755 b (C=O), 1590 b, 1380 m (C—C and C—N), 1240 s, 1030 m (C—O—C), 920 m, 840 s (C—H), 640 m (C—S—C)	336
Vc	CH_3	H	3	3400 b (>NH), 1775 s (C=O), 1590 m, 1340 s (C—C and C—N), 1240 b, 1020 b, (C—O—C), 930 m, 820 m (C—H), 670 m (C—S—C)	271.2
VIa	Cl	H	7	3390 b (>NH), 1600 m, 1450 s (C—C and C—N), 1265 m, 1020 w (C—O—C), 945 s, 820 w (C—H), 690 w (C—S—C), 740 b (C—Cl)	339.7
VIb	H	Br	7	3390 s (>NH), 1650 s, 1450 m (C—C and C—N), 1240 m, 1030 m (C—O—C), 945 m, 835 m (C—H), 680 m (C—S—C)	384
VIc	CH_3	H	3	3390 s (>NH), 1660 s, 1460 m (C—C and C—N), 1250 m, 1020 m (C—O—C), 950 m, 840 m (C—H), 680 m (C—S—C)	319.2
VIIa	Cl	H	7	1650 m, 1750 s (>C=O), 1655 b, 1360 m (C—C and C—N), 1190 m, 1130 w, (C—O—C), 920 s, 830 b (C—H), 640 m (C—S—C), 720 m (C—Cl)	333.6
VIIb	H	Br	7	1630 m, 1750 s (>C=O), 1660 s, 1390 b (C—C and C—N), 1600 w, 1375 s, (C—O—C), 935 m, 820 w (C—H), 650 m (C—S—C)	378
VIIc	CH_3	H	3	1630 m, 1750 s (>C=O), 1660 s, 1350 m (C—C and C—N), 1190 m, 1130 m, (C—O—C), 935 s, 820 m (C—H), 640 m (C—S—C)	313.2

It was observed that 1,2-halo-7-substituted phenothiazines have higher values than the corresponding 9-methyl-3-substituted analogs in almost all the solvent systems. It was noticed that a substituent at position 1 or 2 also affects the R_f values, *i.e.*, a halogen (—Cl, —Br) derivative has higher R_f values than the —CH_3 substituted derivative. But the correlation could not be made among acetylated derivatives. The relative R_f values were also calculated using 1,2 and 9-substituted phenothiazin-3 and 7-ol in each case as a standard.

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