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Conversion of 2-Amino-4-chloro-3-methylbenzenethiol into Bioactive Heterocycles Containing 1,4-Thiazine Nucleus: Phenothiazine Tranquillizers

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A convenient synthesis of some heterocycles containing 1,4-thiazine nucleus is reported. It involves the condensation and oxidative cyclization of 2-amino-4-chloro-3-methylbenzenethiol with 2-mono/2,6-dihalonitrobenzenes. The structures of the synthesised compounds have been characterised by the analytical and structural studies.

INTRODUCTION

Phenothiazine possesses a wide spectrum of pharmacological activities, and their several derivatives are in clinical use[1]. One of structural specificities considered responsible for such a wide spectrum of activities is a fold along nitrogen and sulphur axis. Our research programme concerns the development of suitable synthetic route for novel heterocyclic pharmaceuticals. In search of better medicinal agents we have investigated the reaction of 2-aminobenzenethiol with 2-mono/2,6-dihalonitrobenzenes to synthesize various substituted phenothiazines. The reaction of 2-amino-4-chloro-3-methylbenzenethiol (I) with 2-halo-nitrobenzenes in ethanol containing anhydrous sodium acetate yielded ring substituted 2-amino-2'-nitrodiphenylsulphides (II). The diphenylsulphide derivatives converted into formamido derivatives (III) by formylation with formic acid which on treatment with alc. KOH yielded substituted phenothiazines (IV). It involves the migration of an aromatic ring from one hetero atom to another by intramolecular nucleophilic aromatic substitution[2]. However, halonitrobenzenes containing a nitro group at both the *ortho* positions to the reactive halogen atom, on condensation with (I) yielded directly 1-nitrophenothiazines (V) (Scheme 1).

EXPERIMENTAL

Melting points are uncorrected and the purity of the compounds was checked by thin layer chromatography on silica gel in various non-aqueous solvents. The structure of the compounds has been characterised by their micro elemental analysis and spectral studies. The IR spectra were recorded on Perkin-Elmer 577 spectrophotometer using KBr discs. The ^{1}H-NMR spectra were recorded at 90 MHz on Jeol FX 90Q FT-NMR spectrometer in DMSO-d_6 solution using TMS as internal standard. Mass spectra were scanned on Jeol-300 mass spectrometer at 70 eV with 100 μ_{amp} ionising current.

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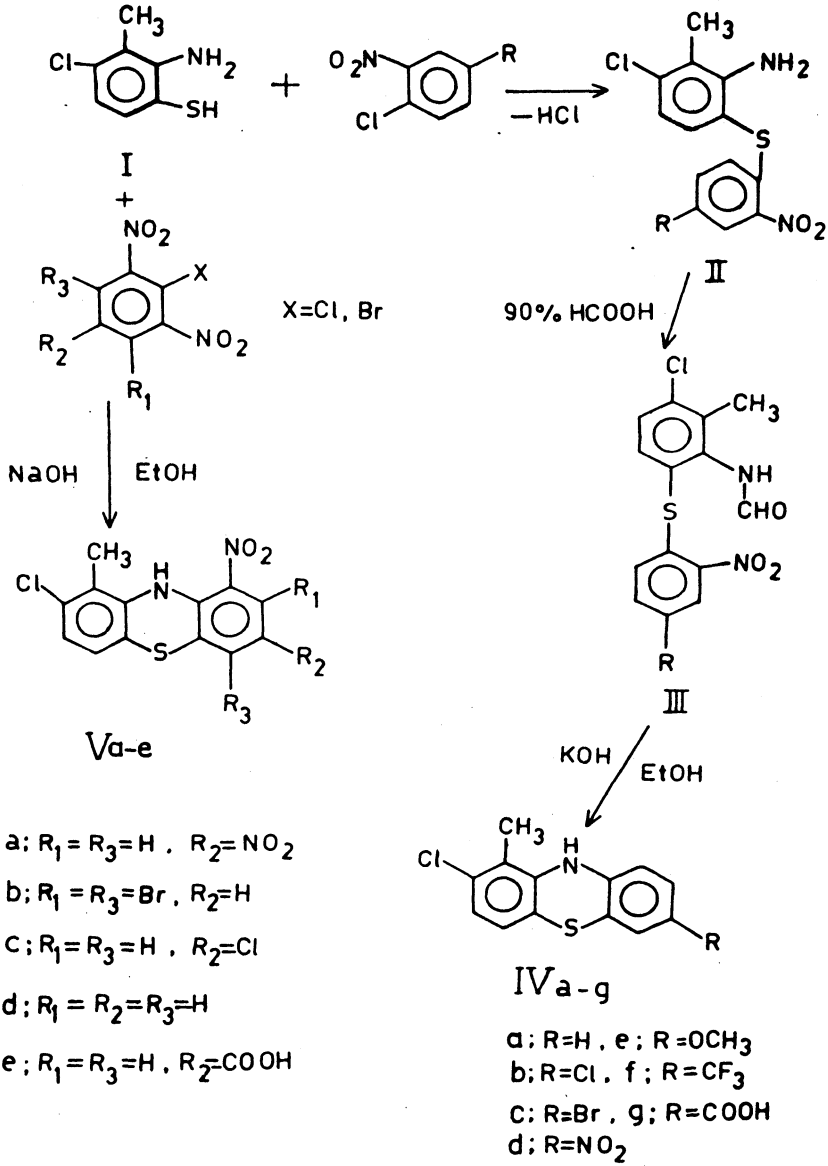

Scheme -I

2-Amino-4-chloro-3-methylbenzenethiol was prepared[3] by the hydrolytic fission of 2-amino-5-chloro-4-methylbenzothiazole which in turn was prepared by the reaction of 3-chloro-2-methyl aniline with ammonium thiocyanate followed by cyclisation with bromine and chloroform.

Preparation of 2-Amino-2′-nitrodiphenylsulphides (II)

2-Amino-4-chloro-3-methylbenzenethiol (I, 0.01 mol) was dissolved in etha-

nol (20 mL) containing anhydrous sodium acetate (0.01 mol) and substituted 2-halonitrobenzenes (0.01 mol) in ethanol (10 mL) was added. The reaction mixture was refluxed for 4 h, concentrated and cooled in ice- bath overnight. The solid separated out was filtered and recrystallized from methanol.

2-Formamido-2′-nitrodiphenyl sulphides (III)

Corresponding diphenyl sulphides (II, 0.01 mol) was refluxed for 4 h in 90% formic acid (20 mL). The contents were then poured into a beaker containing crushed ice. The solid separated out was filtered, washed with water until the filtrate was neutral, dried and recrystallised from benzene.

Substituted Phenothiazines (IV)

Corresponding formamido derivatives (I, 0.01 mol) in acetone (15 mL) was added to alcoholic solution of KOH (0.2 g in 5 mL ethanol). The contents were heated for about 30 min. A second lot of alc. KOH solution was added to the reaction mixture and refluxed for 2 h. The contents were poured into a beaker containing crushed ice and filtered. The residue obtained was washed with cold water, finally with 30% ethanol and recrystallised from benzene. The physical and analytical data are given in Table-1.

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF PHENOTHIAZINES

Compound	Formula (m.w.)	m.p. (°C) Yield (%)	% Analysis (calcd/found)		
			C	H	N
IVa	$C_{13}H_{10}ClNS$	163	63.03	4.04	5.65
	(247.5)	55	62.95	4.00	5.62
IVb	$C_{13}H_9Cl_2NS$	147	55.31	3.19	4.96
	(282.0)	40	55.24	3.15	4.92
IVc	$C_{13}H_9BrClNS$	159	47.77	2.75	4.28
	(326.5)	43	47.71	2.71	4.25
IVd	$C_{13}H_9ClN_2O_2S$	217	53.33	3.07	9.57
	(292.5)	48	53.29	3.02	9.51
IVe	$C_{14}H_{12}ClNOS$	172	60.54	4.32	5.04
	(277.5)	54	60.49	4.28	5.00
IVf	$C_{14}H_9ClF_3NS$	146	53.24	2.85	4.43
	(315.5)	65	53.15	2.80	4.38
IVg	$C_{14}H_{10}ClNO_2S$	195	57.63	3.43	4.80
	(291.5)	51	57.50	3.40	4.72
Va	$C_{13}H_8ClN_3O_4S$	126	46.22	2.37	12.44
	(337.5)	78	46.11	2.30	12.39
Vb	$C_{13}H_7Br_2ClN_2O_2S$	130	34.62	1.55	6.21
	(450.5)	65	34.51	1.51	6.18
Vc	$C_{13}H_8Cl_2N_2O_2S$	128	47.70	2.44	8.56
	(327.0)	75	47.61	2.39	8.52
Vd	$C_{13}H_9ClN_2O_4S$	115	53.33	3.07	9.57
	(292.5)	56	53.15	3.05	9.54
Ve	$C_{14}H_9ClN_2O_4S$	153	49.92	2.67	8.32
	(336.5)	48	49.81	2.63	8.29

1-Nitrophenothizines(V)

A mixture of 2.6-dihalonitrobenzenes (0.01 mol), 2-amino-4-choloro-3-methylbenzenethiol (I, 0.01 mol), sodium hydroxide (0.01 mol), absolute ethanol (25 mL) was refluxed for 2 h. The reaction mixture was cooled down and filtered. The mass obtained was washed with hot water, finally with 30% ethanol, dried and recrystallised from acetone. The characterisation data are given in Table-1.

RESULTS AND DISCUSSION

The IR spectra (Table 2) of the compounds IV and V show N—H and C—Cl stretching vibration in the region 3350–3180 cm^{-1} and 740–715 cm^{-1} respectively. The N—H band positions in 1-nitrophenothiazines appear in lower frequency region than phenothiazines due to hydrogen bonding in former cases. Compounds Va–e exhibited two bands in the region 1570–1530 cm^{-1} and 1370–1340 cm^{-1} due to asymmetirc and symmetric vibration of nitro group. Each phenothiazine exhibited two bands in the region 1475–1430 cm^{-1} and 1385–1320 cm^{-1} due to C—H deformation vibration of methyl group. Phenothiazine (IVe) exhibited two bands at 1280 and 1060 cm^{-1} due to C—O—C asymmetric and symmetic vibrations respectively. The bands were observed at 1310 and 1170 cm^{-1} in compound IV_f due to C—F vibration of CF_3 group.

TABEL-2
IR SPECTRAL DATA (Cm^{-1}) OF PHENOTHIAZINES

Compound	ν(N—H)	ν(NO_2)	ν(C—H)	ν(C—O—C)		ν(C—Cl)
IVa	3330	—	1430, 1340	—	—	715
IVb	3200	—	1475, 1320	—	—	730
IVc	3300	—	1465, 1385	—	—	730
IVd	3350	1570, 1345	1435, 1325	—	—	720
IVe	3290	—	1440, 1350	1280, 1060	—	735
IVf	3300	—	1460, 1355	—	1370, 1170	720
IVg	3310	—	1470, 1365	—	—	740
Va	3210	1540, 1370	1475, 1380	—	—	740
Vb	3250	1550, 1340	1445, 1350	—	—	740
Vc	3180	1530, 1360	1445, 1330	—	—	725
Vd	3260	1535, 1355	1475, 1385	—	—	735
Ve	3215	1555, 1345	1460, 1350	—	—	725

The ^{1}NMR (Table-3) of each phenothiazine exhibited a single peak in the region 10.40–8.70 ppm due to NH proton. Phenothiazine without a nitro group at C_1 exhibited NH signal in high field as compared to 1-nitrophenothiazines as hydrogen bonding exist in later cases. Each compound exhibited a multiplet in the region 9.12–6.34 ppm due to aromatic ring protons. A singlet is observed in all phenothiazines in the region 2.66–2.15 ppm due to methyl protons at C_1 (C_9 in case of 1-nitrophenothiazines). Phenothiazine (IVe) exhibited singlet at 4.24 ppm due to methoxy protons at C_7.

TABLE-3
^{1}H NMR SPECTRAL DATA (δ, ppm) OF PHENOTHIAZINES

Compound	N—H[a]	Arom[b]	1-CH_3	9-CH_3	Other protons	
IVa	9.33	8.62–7.86	2.28	—	—	
IVb	8.87	8.05–7.54	2.66	—	—	
IVc	9.12	8.62–7.35	2.15	—	—	
IVd	8.96	8.68–7.54	2.53	—	—	
IVe	8.70	8.11–7.54	2.63	—	4.24[a]	(OCH_3)
IVf	8.92	8.68–7.51	2.37	—	—	
IVg	9.24	8.49–7.44	2.31	—	10.53[a]	(COOH)
Va	10.04	9.12–7.38	—	2.51	—	
Vb	10.40	7.06–6.34	—	2.53	—	
Vc	10.25	8.49–7.63	—	2.47	—	
Vd	9.87	7.35–6.34	—	2.43	—	
Ve	10.03	9.08–7.83	—	2.35	10.15[a]	(COOH)

[a]singlet, [b]multiplet

The mass spectra of all the phenothiazines showed molecular ion peaks corresponding to their molecular weights. 1-Nitrophenothiazines undergo fragmentation yielding M^+—17 due to loss of —OH moiety according to McLafferty rearrangement.

REFERENCES

1. R.R. Gupta (Ed.), Phenothiazines and 1,4-Benzothiazines—Chemical and Biomedical Aspects, Elsevier, Amsterdam (1988) and references therein.
2. W.J. Evans and S. Smiles, *J. Chem. Soc.*, 181, 1263 (1935).
3. R.K. Rathore and R.R. Gupta, *Collect. Czech. Chem. Commun.*, **60**, 2209 (1995).

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