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Studies in the Synthesis of 10 H-8-Bromo and 9-Methyl-1-Azaphenothiazine and Their 5-Oxide Derivatives via Smiles Rearrangement

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The condensation of zinc salt of 2-amino-4-bromo/3-methyl benzene thiols and 2-chloro-3-nitropyridine yielded an amine and a sulfide. The sulfide was acetylated with acetic anhydride. The acetylated sulfide undergoes Smiles rearrangement in acetone and KOH (2.22 mole) to give the title compound. The amine also gave the same compound when treated with dimethyl sulfoxide and ethanolic potassium hydroxide. The acetylated sulfide rearranges to 10-acetyl derivative of the title compound when treated with one mole of potassium hydroxide in acetone. Further, 5-oxide derivatives can be obtained by reacting the title compound with hydrogen peroxide. The structures of all the compounds are confirmed by their IR and mass spectral data and elemental analysis.

INTRODUCTION

Azaphenothiazines have marked pharmaceutical properties as neuroleptics[1], antitussives[2], antihistaminics[3], antihypertensives[4], etc. Little work has been reported on 1-azaphenothiazine and its derivatives[5, 6]. In continuation with our work[7–10] on phenothiazines, we have synthesized 10H-8-bromo and 10H-9-methyl-1-azaphenothiazine and its 10-acetyl derivatives *via* Smiles rearrangement. The condensation of zinc salt of 2-amino-4-bromo/3-methyl benzene thiol ($\mathbf{I_A}$) and 2-chloro-3-nitro pyridine ($\mathbf{I_B}$) in anhydrous sodium acetate and absolute ethanol yielded 2-amino-4-bromo/3-methyl phenyl 2′-(3′-nitro) pyridyl sulfide **(II)**, which on acetylation with acetic anhydride in pyridine gave 2-acetyl amino-4-bromo/3-methyl phenyl 2′-(3′-nitro) pyridyl sulfide **(III)**. The acetylated sulfide **(III)** rearranged in potassum hydroxide (2.22 mole) and acetone to give 10 H-8-bromo/9-methyl-1-azaphenothiazine. Compounds ($\mathbf{I_A}$) and ($\mathbf{I_B}$) were condensed in concentrated hydrochloric acid and ethanol to yield 2-mercapto-5-bromo/6-methyl phenyl 2′-(3′-nitro) pyridyl amine **(IV)**, which on treatment with dimethyl-sulfoxide and ethanolic potassium hydroxide gave the title compound **(VI)**.

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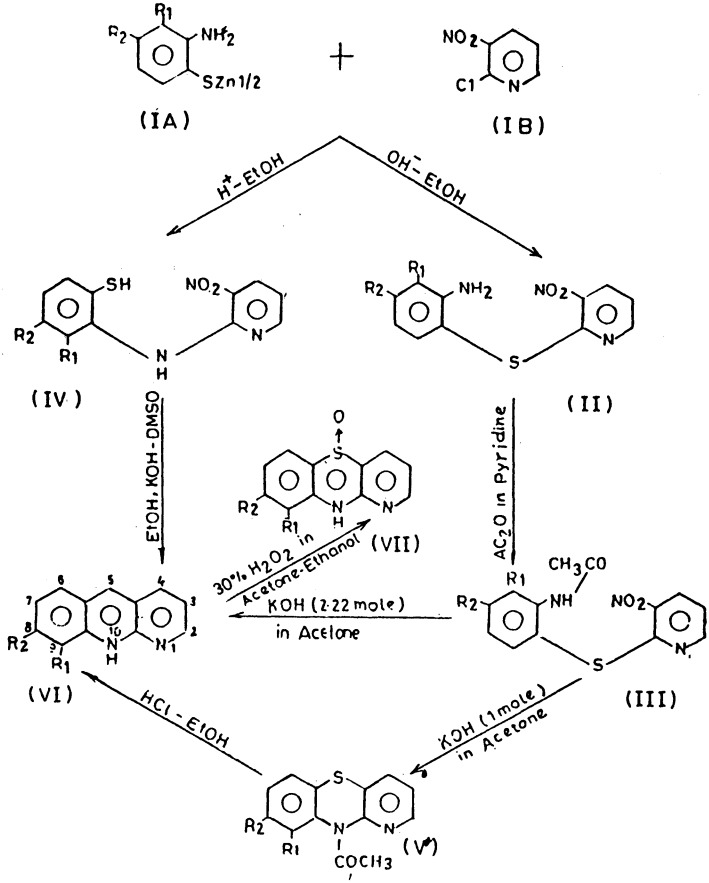
10-Acetyl-8-bromo/9-methyl-1-azaphenothiazine (V) could be obtained when (III) was reacted with one mole of potassium hydroxide in acetone. Compound (V) on hydrolysis with concentrated hydrochloric acid and ethanol yielded (IV).

The 5-oxide derivative (VII) can be obtained by refluxing 10 H-8-bromo/9-methyl-1-azaphenothiazine (VI) with 30% hydrogen peroxide in a mixture of acetone and ethanol for 3 h. The overall reaction is shown in Scheme-1.



SCHEME-1

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 ionization potential of 70 eV.

2-Amino-4-bromo/3-methyl phenyl 2′-(3′-nitro)-pyridyl sulfide (II)

A mixture of zinc mercaptide of 2-amino-4-bromo/3-methyl benzene thiol (I_A, 5 mmole), 2-chloro-3-nitropyridine (I_B, 1.58 g, 0.01 mole), anhydrous sodium acetate (2.0 g, 0.025 mole) and 15.0 mL of absolute ethanol was refluxed for 2 h over a water bath. The reaction mixture was cooled, filtered, washed with water and dried. It was further recrystallized from ethanol to give yellow shining needles of **(II)**.

2-Acetyl amino-4-bromo/3-methyl phenyl 2′-(3′-nitro)-pyridyl sulfide (III)

The phenyl pyridyl sulfide (**II**, 5.12 mmole) was added to pyridine (0.4 mL; 0.005 mole) and acetic anhydride (4.8 mL, 0.047 mole) and the mixture was heated over a steam bath for 2 h. The mixture was cooled to give yellow shining crystals of **(III)**. The solution was filtered, washed with water and recrystallized from ethanol.

2-Mercapto-5-bromo/6-methyl phenyl 2′-(3′-nitro)-pyridyl amine (IV)

To a mixture of (I_A) and (I_B) (2.46 mmole each), 20 mL ethanol, 10 mL water and 1.5 mL conc. HCl were added and the mixture was heated and evaporated over a steam bath to half the volume of contents. After cooling, the separated solid was filtered, washed with hot water and dried. Crystallisation from benzene gave light orange crystals of **(IV)**.

10-Acetyl-8-bromo/9-methyl-1-azaphenothiazine (V)

To a stirred mixture of KOH (0.01 mole) and ethanol (3.5 mL), acetone (120 mL) was added under nitrogen, then **(III)** (6.6 mmole) was added to the mixture and acetone distilled out rapidly to a volume of 10 mL. Equal volume of water (10 mL) was added, filtered and dried. Crystallization from isopropanol gave yellow crystals of **(V)**.

10 H-8-Bromo/9-Methyl-1-azaphenothiazine (VI)

1. *From smiles rearrangement of acetylated sulfide* **(III)**: To a stirred, refluxing solution of (IV, 4 m mole) in 50 mL acetone was added 250 mg (8.88 mmole) of powdered KOH in small portions and the mixture was refluxed for 3 h. After refluxing the acetone was distilled out and 50 mL water were added to the residue. Crystallisation from benzene gave shining light yellow crystals of **(VI)**.

2. *Hydrolysis of* **(V)**: A mixture of (**V**, 4 mole), 4.2 mL of ethanol and 0.7 mL conc. HCl was refluxed for 2 h and concentrated. The residue was treated with excess NH_3. The solid thus formed was filtered. The solid was dried by azeotropic distillation with benzene and the solvent was evaporated in vacuum. Crystallization from dry benzene yielded crystals of **(VI)**.

3. *From ring closure of* **(IV)**: To a stirred mixture of (**IV**, 2 mmole) and 10 mL of DMSO was added a hot mixture of DMSO (15 mL), KOH (170 mg, 3.0 mmole) and 10 mL ethanol was added and refluxed for 7 h. After refluxing,

ethanol was distilled off and 100 mL water was added to the residue. This mixture was three times extracted, washed with water, then dried (Na_2SO_4). The solvent was removed in vacuum. Crystallisation from benzene gave crystals of **(VI).**

The compound **(VI)**, prepared by three different ways, has the same m.pt., analytical and spectral data.

10 H-8-bromo/9-methyl-1-azaphenothiazine-5-oxide (VII)

10 H-8-bromo/9-methyl-1-azaphenothiazine **(VI)** 0.021 mole was dissolved in a hot mixture of dry ethanol (75 mL) and acetone (150 mL). To this solution was added 0.021 mole of 30% H_2O_2 and the solution was heated under reflux for 3 h. The colour of the solution darkened during refluxing. The solvent was then removed by distillation and the residue was crystallised from ethanol to get **(VII).**

The analytical and spectral data of compounds synthesised are given in Tables 1 and 2, resepectively.

TABLE-1
ANALYTICAL DATA OF 1-AZAPHENOTHIAZINES AND THEIR DERIVATIVES

Comp.	R_1	R_2	Yield (%)	m.p. (°C)	m.f.	emental analysis, Found (Calcd) %			
						C	H	N	S
IIa	H	Br	70	95	$C_{11}H_8N_3O_2SBr$	40.41 (40.49)	2.40 (2.45)	12.92 (12.88)	9.78 (9.81)
IIb	CH_3	H	75	103	$C_{12}H_{11}N_3O_2S$	55.06 (55.17)	4.12 (4.21)	16.23 (16.09)	12.18 (12.26)
IIIa	H	Br	75	85	$C_{13}H_{10}N_3O_3SBr$	42.31 (42.39)	2.65 (2.71)	11.48 (11.41)	8.72 (8.69)
IIIb	CH_3	H	80	83	$C_{14}H_{13}N_3O_3S$	55.40 (55.44)	4.19 (4.29)	13.80 (13.86)	10.59 (10.56)
IVa	H	Br	72	100	$C_{11}H_8N_3O_2SBr$	40.40 (40.49)	2.39 (2.45)	12.91 (12.88)	9.78 (9.81)
IVb	CH_3	H	75	85	$C_{12}H_{11}N_3O_2S$	55.10 (55.17)	4.24 (4.21)	16.12 (16.09)	12.30 (12.26)
Va	H	Br	65	102	$C_{13}H_9N_2OSBr$	48.62 (48.59)	2.84 (2.80)	8.79 (8.72)	10.02 (9.96)
Vb	CH_3	H	55	96	$C_{14}H_{12}N_2OS$	65.68 (65.62)	4.71 (4.68)	10.98 (10.93)	12.47 (12.50)
VIa	H	Br	48	110	$C_{11}H_7N_2SBr$	47.28 (47.31)	2.61 (2.50)	10.09 (10.03)	11.51 (11.46)
VIb	CH_3	H	50	126	$C_{12}H_{10}N_2S$	67.20 (67.28)	4.71 (4.67)	13.12 (13.08)	14.89 (14.95)
VIIa	H	Br	67	124	$C_{10}H_7N_2OSBr$	42.35 (42.40)	2.14 (2.47)	9.81 (9.89)	11.37 (11.30)
VIIb	CH_3	H	65	168	$C_{11}H_{10}N_2OS$	60.51 (60.55)	4.54 (4.58)	12.88 (12.84)	14.71 (14.67)

TABLE-2
SPECTRAL DATA OF 1-AZAPHENOTHIAZINE AND THEIR DERIVATIVES

Comp	R_1	R_2	IR (KBr) ν_{max} cm^{-1}	Mass spectrum (M+) M/e
IIa	H	Br	3400 m, 3355 m (—NH_2); 1550 m, 1270 m (—NO_2); 1490 m, 1450 s, 1460 m, 1340 s, 1170 m, 1140 w, 1070 m, 960 m, 770 m, 740 m, 650 s	326
IIb	CH_3	H	3390 m, 3348 m (—NH_2); 1550 m, 1260m (—NO_2); 1480 m, 1360s, 1300 m, 1230 s, 1150 m, 1040 s, 990 m, 820 s, 780 m, 690 s	261
IIIa	H	Br	1550 m, 1320 m (—NO_2); 1680m (> $NHCOCH_3$); 3330 s, 3120 m, 3030 s, 1720 w, 1580 w, 1480 m, 1410 s, 1380 m, 1340 s, 1250 s, 1150 m, 1040 m, 850 m, 800 m, 730 vs.	368
IIIb	CH_3	H	1540 s, 1350 m (—NO_2); 1690m (> $NHCOCH_3$); 3330 m, 3100 w, 1600 m, 1240 m, 1140 s, 1030 s, 950 m, 800 s, 750 s, 680 s, 670 w	303
IVa	H	Br	3100 m (> NH); 2545 s (—SH); 1540 m, 1285 m (—NO_2); 2920 s, 2710 w, 1930 w, 1890 w, 1490 m, 1450 m, 1340 s, 1180 m, 1130 m 1090 m, 990 m, 930 m, 770 m, 750 m, 660 s	326
IVb	CH_3	H	3200 m (> NH); 2560; 1540, 1290m (—NO_2); 2980 m, 2900 vs, 1480 m, 1450 s, 1410 s, 1330 m, 1180 s, 1080 m, 980 m, 800 vs, 770 vs, 730 s, 680 m, 660 vs, 630 w, 261	261
Va	H	Br	1680 m (> $NCOCH_3$); 3140 m, 1650 s, 1580 s, 1560 m, 1540 w, 1480 m, 1460 w, 1430 s, 1400 w, 1350 m, 1320 w, 1260 w, 1050 m, 730 m	321
Vb	CH_3	H	1685 m (> $NCOCH_3$); 3350 m, 3000 w, 1620 s, 1550 s, 1440 m, 1390 m, 1335 s, 1260 m, 1170 s, 780 vs, 730 m, 650 s	256
VIa	H	Br	3230 m (> NH); 3130 m, 1680 s, 1580 s, 1560 m, 1530 w, 1480 m, 1450 w, 1420 s, 1400 w, 1350 m, 1320 w, 1240 s, 1060 m, 770 m	279
VIb	CH_3	H	3200 m (> NH); 3300 m, 3000 w, 1600 s, 1540 s, 1440 m, 1380 m, 1330 s, 1250 m, 1170 s, 780 vs, 730 m, 680 s	214
VIIa	H	Br	3150 m (> NH); 1045 s (S → O), 3190 m, 1660 s, 1590 m, 1540 w, 1480 m, 1458 w, 1425 s, 1405 w, 1335 m, 1315 w, 1250 s, 770 m	283
VIIB	CH_3	H	3200 m (> NH); 1030 s (S → O), 3325 m, 3005 w, 1620 s, 1548 s, 1435 m, 1370 m, 1320 s, 1255 m, 1160 s, 790 vs, 740 m, 675 s	218

RESULTS AND DISCUSSION

During various attempts for synthesising the substituted-1-azaphenothiazine, it was observed that 2-acetyl amino-4-bromo/3-methyl phenyl-2′-(3′-nitro) pyridyl sulfide **(III)** could rearrange smoothly to 10-acetyl-8-bromo/9-methyl-1-azaphenothiazine **(V)** in KOH (1 mole) and acetone. But it was also observed that if 2-acetylamino-4-bromo/3-methyl phenyl-2′-(3′-nitro) pyridyl sulfide **(III)** was refluxed with 2.22 mole of powdered KOH in dry acetone for 3 h or more, the Smiles rearrangement, ring closure and hydrolysis took place *in situ*.

It was found that 2-mercapto-5-bromo/6-methyl phenyl 2′-(3′-nitro) pyridyl amine **(IV)** could be prepared in good yield, involving one step synthesis directly from condensation of ($\mathbf{I_A}$) and ($\mathbf{I_B}$) Scheme 1. It became intriguing to attempt the synthesis of substituted-1-azaphenothiazine directly by the ring closure of compound **(IV)**. However, when the compound **(IV)** was refluxed even for several hours in ethanolic KOH no ring closure occurred. The IR spectrum of compound **(IV)** also clearly indicates the possibility of the intramolecular hydrogen bonding of the secondary amino group with the *o*-nitro group. It seems to us remarkable that this bonding is indeed of such a magnitude as to preclude the formation of substituted-1-azaphenothiazine under the conditions investigated. The N—H stretching frequencies were studied both in solid and liquid phases.

The N—H stretching frequency phase of compound ($\mathbf{IV_A}$) are stated below:

1.	Solid phase KBr	3310 cm^{-1}
2.	Liquid phase CCl_4	3270 cm^{-1}
3.	Liquid phase CCl_4-DMSO	3090 cm^{-1}

From the IR data of the phenyl pyridyl amine in the solid and liquid phase it is clear that the secondary amino group is intramolecularly hydrogen bonded.

A prominent shift to a lower frequency in DMSO/CCl_4 system clearly indicates that in DMSO hydrogen gets bonded with amino group more strongly than nitro group thus the nitro group is free to assure the success of the cyclic process. Therefore, this reaction was carried out in the presence of DMSO-ethanol.

The characterisations of the compounds synthesized are done on the basis of IR, mass spectra and elemental analyses.

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