HL **ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)**
http://heteroletters.org **Vol. 1: (4), 2011, 305-310**

SYNTHESIS AND BIOLOGICAL EVALUATION OF SUBSTITUTED 10H-1-AZAPHENOTHIAZINES AND THEIR 5-OXIDE DERIVATIVES

V. Khatri*, V. Sareen, K. Sharma, P. Singh & S. Sareen

Department of Chemistry, University of Rajasthan,
Jaipur-302055, India
Email: drkanti@gmail.com

Abstract

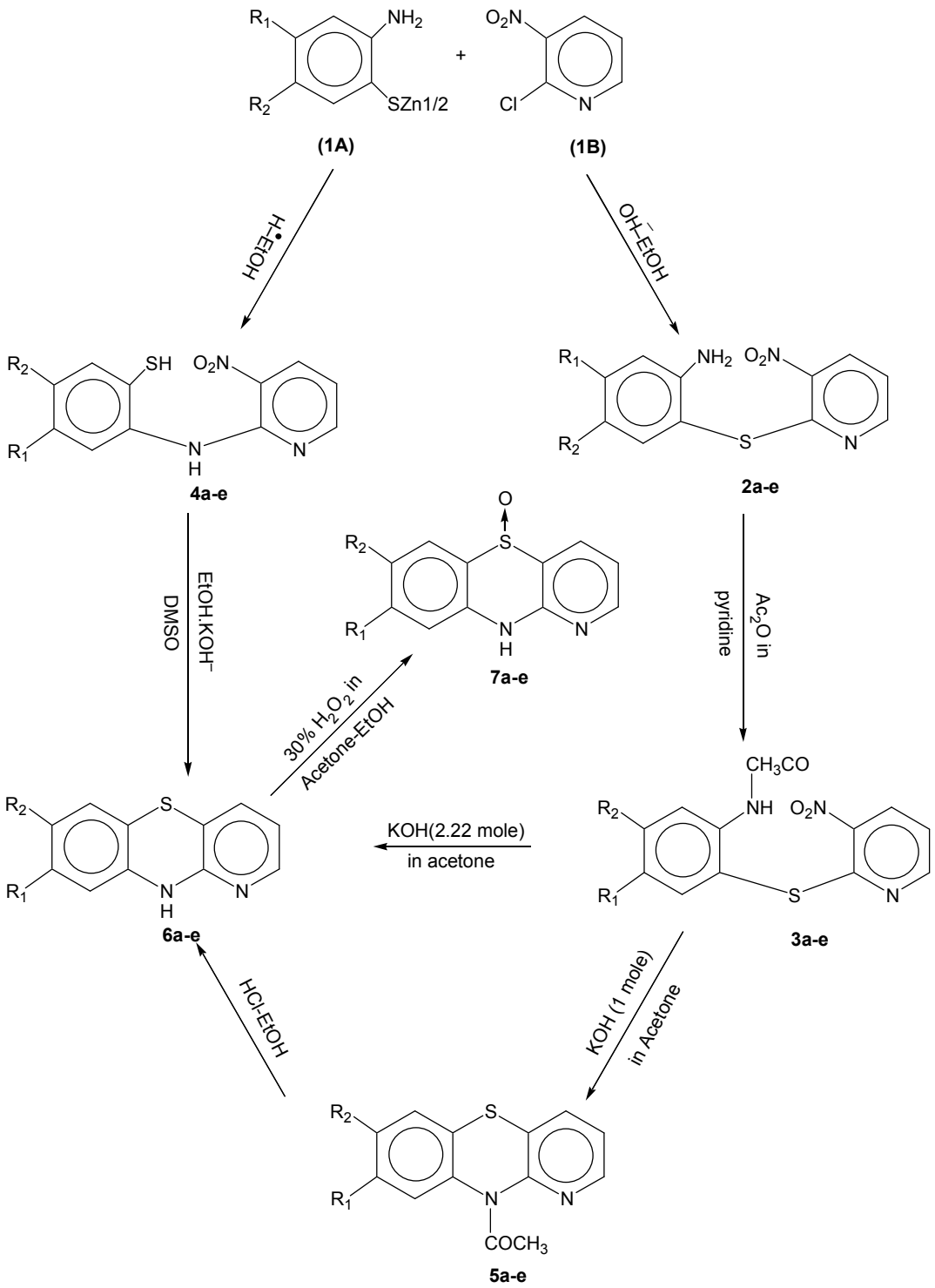
A series of substituted 10H-phenothiazines were synthesized via smiles rearrangement. Further 5-oxide derivatives are obtained by reacting the title compound with hydrogen peroxide. The structure assignments of compounds were made on the basis of spectroscopic data and elemental analysis. The synthesized compounds were evaluated for their antioxidative properties through in vitro and in vivo studies in Swiss albino mice.

Introduction

Azaphenothiazines (10H-pyrido[3,2-b][1,4] benzothiazines) exhibit wide spectrum of biological activity.[1,2] The parent compound has interested us due to its antischizophrenic[3] anthelmintic[4], antimicrobial[5] and anticancer[6] properties. Little work has been reported on 1-azaphenothiazine and its derivatives. In continuation with our work on synthesis of bioactive heterocycles[7,8], the synthesis of some new 10H-7,8 substituted 1-azaphenothiazine and its derivatives were undertaken via smiles rearrangement (Scheme-1).

Experimental

Melting points were determined in open capillary tubes and are uncorrected. Purity of these compounds were checked by TLC on silica gel plate. IR spectra were recorded in KBr on a NICOLET-MEGNA FT IR 500 spectrometer and the ^{1}H NMR spectra were recorded on a JEOL spectrometer (300 MHz) in DMSO-d_6 using TMS as an internal standard (chemical shifts are measured in δ ppm). Mass spectra were scanned on a JEOL SX 102/DA-6000 using Argon / Xenon as FAB gas.



a, $R_1 = H$, $R_2 = Br$
b, $R_1 = H$, $R_2 = F$
c, $R_1 = H$, $R_2 = CH_3$
d, $R_1 = OC_2H_5$, $R_2 = CH_3$
e, $R_1 = F$ $R_2 = H$

Scheme 1

2-Amino-5-bromo/fluoro/methyl-4-ethoxy/fluorophenyl-2'-(3-nitropyridyl sulfide) 2

A mixture of zinc mercaptide of 2-amino-5-bromo/fluoro/methyl/4-ethoxy/fluorobenzenethiol / A (0.5 m mol), 2-chloro-3-nitropyridine / B (1.58 g, 0.01 mol), anhydrous sodium acetate (2.0 g, 0.025 mol) and absolute ethanol (15 ml) was refluxed for 2 hr over a water bath. the reaction mixture was cooled, solid was washed with water and recrystallised from ethanol to give yellow shinning needles of **2**.

2-Acetylamino-5-bromo/fluoro/methyl-4-ethoxy/fluorophenyl-2'-(3'-nitropyridyl sulfide 3

The phenyl pyridyl sulfide (**2** 5.12 m mole) was added to pyridine (0.4 ml; 0.005 mole) and acetic anhydride (4.8 ml, 0.04 mole) and the mixture was heated over a steam bath for 2 hr. The mixture was cooled to give yellow shinning crystals of **3**. The solution was filtered and the solid was washed with water and recrystalized from ethanol.

2-Mercapto-4-bromo/fluoro/methyl-5-ethoxy/fluorophenyl-2'-(3'-nitropyridyl) amine 4

To a mixture of 1A and 1B (2.46 m mole each) 20 ml ethanol, water (10 ml) conc. HCl (1.5 ml) were added and the mixture was heated and evaporated over a steam bath of half the volume of the contents. After cooling, the separated solid was filtered, washed with hot water and dried, recrystallised from benzene gave light orange crystals of **4**.

10-Acetyl-7-bromo/fluoro/methyl 8-ethoxy/fluoro-1-azaphenathiazine 5

To a stirred mixture of KOH (0.01 mole) and ethanol (3.5 ml), acetone (120 ml) was added under nitrogen, then **3** (6.6 m mole) 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. Recrystallization of the solid from isopropanol gave yellow crystals of **5**.

10H-7-Bromo/fluoro/methyl 8-ethoxy/fluoro-1-azaphenothiazine 6

A. From smiles rearrangement of acetylated sulfide 3

To a stirred refluxing solution of **3** (4 m mole) in acetone (50 ml) was added powdered KOH (250 mg, 8.88 m mole) in small portions and the mixture was refluxed for 3 hr. After refluxing, the acetone was distilled out and water (50 ml) was added to the residue, stirred and filtered. The solid was washed well with water and dried. Recrystallization of the solid from benzene gave shining light yellow crystals of **6**.

Hydrolysis of 5

A mixture of **5** (4 mol), ethanol (4.2 ml) concentration HCl (0.7 ml) was refluxed for 2 hr and concentrated. The residue was treated with excess ammonia. The solid thus formed was filtered. The solid was dried by azeotropic distillation with benzene and the solvent was evaporated in vacuum. Recrystallization from dry benzene yielded crystals of **6**.

From ring closure of 4

To a stirred mixture of **4** (2 m mole) and DMSO (10 ml) was added a hot mixture of DMSO (15 ml), KOH (170 mg, 3 m mole) and ethanol (10 ml) was then added. The mixture was refluxed for 7 hr. After refluxing, ethanol was distilled off and water (100 ml) was added to the residue. The mixture was extracted three times with ether washed with water, then dried over sodium sulphate. The solvent was removed in vacuum, crystalization from benzene gave crystal of **6**.

10H-7-Bromo/fluoro/methyl 8-ethoxy/fluoro-1-azaphenothiazine-5-oxide 7

10H-7/8 substituted-1-azaphenothiazine **6** (0.021 mole) was dissolved in a hot mixture of dry ethanol (75 ml) and acetone (150 ml) to this solution was added 30% H_2O_2 (0.021 mole) and the solution was heated under reflux for 3 hr. The colour of the solution darkened during refluxing. The solvent was then removed by distillation and the residue was crystallised from ethanol to give **7**.

Antioxidant activity

All the synthesized compounds were screened for their antioxidant activity by 1,1-diphenyl-2-picryl hydrazyl (DPPH) radial scavenging assay and 2,2-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^+$) radical cation decolonization assay. the present study demonstrated that synthesized compounds showed mixed radical scavenging activity in both DPPH and $ABTS^+$ assays.

The compounds were further treated for evaluation of antioxidative properties on Swiss albino mice. Result showed significant increase in sulfhydryl group assay (GSH). Some compounds showed significant decrease in lipid peroxidation (LPO) content showing potent antioxidant activities in Swiss albino mice.

Result and Discussion

During various attempts for synthesising the substituted 1-azaphenothiazines it was observed that 2-acetylamino-5/4-substituted phenyl-2'-(3'-nitropyridyl) sulfide **3** could rearrange smoothly to 10 acetyl-7/8 substituted 1-azaphenothiazine **5** with KOH (1 mole) in acetone. But it was also observed that if 2-acetylamino-5/4-substituted phenyl-2'(3'-nitropyridyl) sulfide **3** was refluxed with 2.22 mole of powdered KOH in dry acetone for 3 hr or more, the smiles rearrangement, ring closure and hydrolysis took place in situ.

It was found that 2-mercapto-4/5 substituted phenyl-2'-(3'-nitropyridyl) amine **4** could be prepared in good yields involving one step synthesis by the condensation of 1A and 1B Scheme 1. It became intriguing to attempt the synthesis of substituted 10H-1-azaphenothiazine directly by the ring closure of compound **4**. However when the compound **4** was refluxed even for several hours in ethanolic KOH no ring closure occurred.

IR spectra of compound 2 show peak at 3300-3400 cm^{-1} for $–NH_2$ group and 1540, 1290 for $–NO_2$ group attached in pyridyl ring. Mass spectrum shows M^+ at m/z 326 (2a).

Formation of compound 3 was confirmed by IR, peak at 1680 shows acetylation of NH_2 group. In ^1H NMR peak at δ 3.2 confirms $–COCH_3$ group mass spectrum shows M^+ at m/z 368 (3a).

Formation of compound **4** was confirmed by IR spectra peak appeared at 3100 cm^{-1} due to secondary amino >NH group 2650 (SH), 1550, 1295 ($–NO_2$). IR spectrum shown possibility of intramolecular H-bonding of the secondary amino group with O nitro group. Further mass spectrum shown M^+ at m/z 326 (4a).

Formation of compound **5** was confirmed by IR spectra which shows peak at 1670-1680 cm^{-1} due to $COCH_3$ group with disappearance of peak due to >NH of compound 3. In ^1H NMR $CO\underline{C}H_3$ group appears at δ 3.5 ppm. Mass spectrum shows M^+ at m/z 321 (5a).

Compound **6** phenothiazines shows >NH at 3210 cm^{-1} in IR spectrum, ^1H NMR shows >NH at δ 8.78 ppm. Mass spectrum shows M^+ at m/z 279 (6a).

Formation of 5-oxides derivatives **7** was confirmed by IR having peak at 3190 and 1050 cm^{-1} due to (>NH) and S→O. Mass spectra also shows M^+ at m/z 295 (7a).

References

1. N. Gautam, M.K. Sharma and D.C. Gautam, *Indian J. Heterocyclic Chem*., **19**, 401 (2010).
2. A.R. Trivedi, A.B. Siddiqui and V.H. Shah, *ARKIVOC*, **(ii)**, 210 (2008).
3. A.P. Feinberg and S.H. Shyder, *Proc. Nat. Acad. Sci. U.S.A.,* **72(5)**, 1899 (1975).
4. J.C. Craig, M.E. Tate, G.P. Warwick and W.P. Rogers, *J. Med. Chem.,* **2(6)**, 659 (1959).
5. M.M. Kristian, C. Leandro C, D. Ordway, M. Martins, M. Viveiros, T. Pacheco, J.E. Kristiansen and L. Amaral, *Int. J. Antimicrob Abents,* **22(3)**, 250 (2003).
6. N. Motohashi, M. Kawase, T. Karihara, A. Hever, S. Nagy, I. Olsocvszki, M. Tanaka and J. Molnar, *Anticancer Research,* **16 (5A)**, 2525 (1996).
7. V. Khatri, U. Gupta, V. Sareen and K. Sharma, *Asian J. Chem*., **12(4)**, 1273 (2000).
8. V. Sareen, V. Khatri, K. Sharma, D. Shinde and S. Sareen, *Heterocyclic Communications,* **1**, 39 (2010).

Received on July 26, 2011.

Table 1. Physical and Analytical Data of the Compounds

Compound	M.P. °C	Yield %	Mol Formula	Elemental Analysis %		Mass (M^+) m/z
				N	S	
2a	98	68	$C_{11}H_8BrN_3O_2S$	12.88 (12.92)	9.87 (9.81)	326
2b	103	60	$C_{11}H_8FNN_3O_2S$	15.78 (15.82)	12.02 (12.07)	265
2c	113	61	$C_{12}H_{11}N_3O_2S$	16.08 (16.06)	12.29 (12.26)	261
2d	198	62	$C_{13}H_{13}N_3O_3S$	14.40 (14.44)	11.02 (10.99)	291
2e	100	64	$C_{11}H_8FN_3O_2S$	15.80 (15.82)	12.01 (12.07)	265
3a	97	70	$C_{13}H_{10}BrN_3O_3S$	11.45 (11.42)	8.65 (8.69)	368
3b	185	72	$C_{13}H_{10}FN_3O_3S$	13.64 (13.69)	10.48 (10.42)	307
3c	171	71	$C_{14}H_{13}N_3O_3S$	13.82	10.59	303

				(13.86)	(10.56)	
3d	202	68	$C_{15}H_{15}N_3O_4S$	12.56	9.68	333
				(12.61)	(9.60)	
3e	99	69	$C_{13}H_{10}FN_3O_3S$	13.61	10.49	307
				(13.66)	(10.42)	
4a	190	65	$C_{11}H_8BrN_3O_2S$	12.88	9.87	326
				(12.89)	(9.81)	
4b	113	62	$C_{11}H_8FN_3O_2S$	15.84	12.02	265
				(15.85)	(12.07)	
4c	118	68	$C_{12}H_{11}N_3O_2S$	16.08	12.21	261
				(16.06)	(12.26)	
4d	145	65	$C_{13}H_{13}N_3O_3S$	14.42	11.02	291
				(14.42)	(10.99	
4e	215	66	$C_{11}H_8FN_3O_2S$	15.72	12.02	265
				(15.85)	(12.07)	
5a	192	70	$C_{13}H_9BrN_2OS$	8.77	9.95	321
				(8.72)	(9.96	
5b	104	61	$C_{13}H_9FN_3OS$	10.72	10.36	260
				(10.76)	(10.30	
5c	98	64	$C_{14}H_{12}N_2OS$	10.99	12.58	256
				(10.93)	(12.52)	
5d	120	66	$C_{15}H_{14}N_2O_2S$	9.81	11.21	286
				(9.79)	(11.18)	
5e	187	69	$C_{13}H_9FN_2OS$	10.78	12.34	260
				(10.76)	(12.30)	
6a	>300	62	$C_{11}H_7BrN_2S$	10.01	14.67	279
				(10.04)	(14.67)	
6b	>300	64	$C_{11}H_7FN_2S$	12.79	11.42	218
				(12.84)	(11.46)	
6c	274	66	$C_{12}H_{10}N_2S$	13.02	15.01	214
				(13.09)	(14.95)	
6d	>300	67	$C_{13}H_{12}N_2OS$	11.41	13.17	244
				(11.47)	(13.11)	
6e	292	68	$C_{11}H_7FN_2S$	12.81	14.71	218
				(12.88)	(14.67)	
7a	>300	60	$C_{11}H_7BrN_2OS$	9.45	10.90	295
				(9.49)	(10.84)	
7b	240	62	$C_{11}H_{17}FN_2OS$	11.99	13.69	234
				(11.97)	(13.67)	
7c	>300	66	$C_{12}H_{10}N_2OS$	12.77	13.97	230
				(12.72)	(13.94)	
7d	260	68	$C_{13}H_{12}N_2O_2S$	10.87	12.36	260
				(10.80)	(12.30)	
7e	>300	67	$C_{11}H_7FN_2OS$	11.92	13.71	234
				(11.97)	(13.61)	