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Synthesis of Bioactive Fluorinated 10*H*-Phenothiazines and their Sulfone Derivatives

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Abstract: The present communication deals with the synthesis of a series of fluorinated 10*H*-phenothiazines. 10*H*-phenothiazines is prepared by Smiles rearrangement of substituted 2-foramido-2'-nitrodiphenylsulfide. Substituted 2-foramido-2'-nitrodiphenylsulfide were obtained by the reaction of 2-amino-3-fluorobenzenethiol with *o*-halonitrobenzenes followed by formylation and 1-nitro/1-halo-10*H*-phenothiazines have been prepared by the reaction of substituted 2-aminobenzenethiols with reactive *o*-halonitrobenzene containing a nitro group or halogen atom at *o*-position to the reactive halogen atom directly yielded 1-nitro/1-halo-10*H*-phenothiazines in situ. 10*H*-phenothiazine sulfone derivatives have been synthesized by the oxidation of 10*H*-phenothiazines by 30% hydrogen peroxide in glacial acetic acid. The structure of the synthesized compounds has been characterized by spectroscopic data and elemental analysis. Antimicrobial studies of the synthesized compounds have also been included.

Keywords: Antimicrobial activity, Phenothiazines, Smiles rearrangement, Sulfones.

Introduction

Phenothiazines (heterocyclic ring system consisting of two benzene rings *ortho*-fused to 1,4-thiazine ring) and their analogues constituent an important class of bioactive heterocycles. They possess a wide spectrum of pharmacological/biological activities¹⁻¹³ and their several derivatives are in clinical use. Phenothiazines have been found to possess promising medicinal activities used as tranquilizers, antihistamines, diuretics, analgesics, neuroleptics,

sedatives, antipsychotics, antiinflammatories, anthelmintics, antiemetics, antivirals, anesthetic, tuberculostatic, CNS depressants, anticancer, antidepressants, antipyretics, antiparkinson drugs, antibacterial and antifungal *etc.*

A slight change in the substitution pattern of phenothiazine nucleus causes a marked difference in their biological activities. So it has been considered worthwhile to extend our efforts to synthesize phenothiazines and their sulfone derivatives to make them available for biological screening in order to study the effects of structural change with the biological activities and to obtain the drugs of improved therapeutic effects and with minimum undesirable side effects. Kerby Bauer procedure^{14,15} have been used for antimicrobial activity of newly synthesized 10H-phenothiazines and sulfone derivatives.

Experimental

All the melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on NICOLET-MEGNA FT-IR 550 spectrometer and the ¹H NMR spectra were recorded on JEOL AL-300 spectrometer (300 MHz) in CDCl₃/DMSO-d₆ using TMS, as an internal standard (chemical shifts are measured in δ ppm). Mass spectra were recorded on JEOL SX 102/DA 6000 using Argon/Xenon as FAB gas. The purity of the synthesized compounds were checked by TLC using silica gel "G" as adsorbent, visualizing these by UV light or Iodine chamber.

Synthesis of 2-amino-2'-nitrodiphenylsulfides (III_{a-b})

To the refluxing solution of 2-amino-3-fluorobenzenethiol I (0.01 mole in 20 mL ethanol) and anhydrous sodium acetate (0.01 mole in 5 mL ethanol) was added in alcoholic solution of halonitrobenzene II_{a,b} (0.01 mole in 20 mL of ethanol), refluxing was continued for four hours. The resultant solution was concentrated, cooled and kept overnight in an ice bath. The solid separated out was filtered, washed with 30% ethanol and recrystallized from methanol.

Synthesis of 2-formamido-2'-nitrodiphenylsulfides (IV_{a-b})

The diphenylsulfides III_{a-b} (0.01 mole) obtained was refluxed for 4h in 90% formic acid (20 mL). The contents were then poured into a beaker containing crushed ice, a solid separated out was filtered, washed with water until the filtrate was neutralized and crystallized from benzene.

Synthesis of 10H-phenothiazines (V_{a-b})

To a refluxing solution of formyl derivatives IV_{a-b} (0.01 mole) in acetone (15 mL) was added an alcoholic solution of potassium hydroxide (0.2 gm in 5 mL ethanol) was added. The contents were heated for 30 minutes. A second lot of potassium hydroxide (0.2 gm in 5 mL ethanol) was added to the reaction mixture and refluxed for 4h. The contents were poured into beaker containing crushed ice and filtered. The residue obtained was repeatedly washed with cold water and finally with 30% ethanol and then crystallized from benzene.

Synthesis of phenothiazines (V_{c-e}) by one step process

A mixture of reactive o-halonitrobenzene II_{c-e} (0.01 mole), 2-amino-3-fluoro/2-amino-3-isopropyl and 2-amino-5-isopropylbenzenethiols I (0.01 mole), sodium hydroxide (0.01 mole) and absolute alcohol (25 mL) was refluxed for two hours. The reaction mixture was concentrated on water bath, cooled and filtered. The precipitate was washed with hot water and ethanol and crystallized from acetone.

Synthesis of 10H-phenothiazine sulfones (VI_{a-e})

To a solution of substituted 10H-phenothiazines V_{a-e} (0.01 mole) in 20 mL of glacial acetic acid, 5 mL of 30% hydrogen peroxide was added and refluxed for fifteen minute. Heating was stopped and another lot of hydrogen peroxide (5 mL) was added. The reaction mixture was again refluxed for 3-4h. The contents were poured in a beaker containing crushed ice. The yellowish residue obtained was filtered and washed with water and recrystallized with ethanol.

Scheme 1. Synthesis of 10H – Phenothiazines and their sulfones

Antimicrobial activity

Newly synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus* and *Pseudomonas fluorescense* bacterial strain by Kerby Bauer procedure using Streptomycin as standard drugs. Compounds are also screened for their antifungal activity against *Aspergillus flavus* and *Aspergillus niger*. The activity of each compound was compared with that of flukanazole as a standard drug. The results of such studies are given in Table 2. Antimicrobial activities are given in term of activity index.

Table 1. Characterization data of phenothiazines and sulfones.

Comd No.	Compound					Mol wt	Yield %	m.p. °C	Molecular formula	% found (calcd.)		
	R ₁	R ₂	R ₃	R ₄	R ₅					C	H	N
V _a	F	H	H	H	H	217	65	126	C ₁₂ H ₈ NSF	66.16(66.35)	3.65(3.68)	6.42(6.45)
V _b	F	H	NO ₂	H	H	262	69	93	C ₁₂ H ₇ N ₂ O ₂ SF	54.79(54.96)	2.67(2.67)	10.65(10.68)
V _c	F	H	H	F	F	253	69	280	C ₁₂ H ₆ NSF ₃	56.74(56.91)	2.37(2.37)	5.50(5.53)
V _d	H	(CH ₃) ₂ CH	H	F	F	277	74	240	C ₁₅ H ₁₃ NSF ₂	64.72(64.98)	4.67(4.69)	5.03(5.05)
V _e	(CH ₃) ₂ CH	H	H	F	F	277	65	245	C ₁₅ H ₁₃ NSF ₂	64.74(64.98)	4.66(4.69)	5.04(5.05)
VI _a	F	H	H	H	H	249	67	170	C ₁₂ H ₈ NSO ₂ F	57.70(57.83)	2.70(2.72)	9.49(9.52)
VI _b	F	H	NO ₂	H	H	294	55	140	C ₁₂ H ₇ N ₂ O ₄ SF	48.85(48.97)	2.36(2.38)	9.50(9.52)
VI _c	F	H	H	F	F	285	68	184	C ₁₂ H ₆ NSO ₂ F ₃	50.35(50.52)	2.09(2.10)	4.89(4.91)
VI _d	H	(CH ₃) ₂ CH	H	F	F	309	54	210	C ₁₅ H ₁₃ NSO ₂ F ₂	58.09(58.25)	4.17(4.20)	4.51(4.53)
VI _e	(CH ₃) ₂ CH	H	H	F	F	309	61	199	C ₁₅ H ₁₃ NSO ₂ F ₂	58.06(58.25)	4.18(4.20)	4.50(4.53)

Table 2. R and ¹H NMR spectral data and antimicrobial activity of synthesized compounds.

Compound No.	IR (KBr : ν _{max} cm ⁻¹)			¹ H NMR (δ ppm from TMS)		Antibacterial activity		Antifungal activity	
	>NH	$\begin{array}{c} \text{O} \\ \parallel \\ \text{N} \rightarrow \text{O} \end{array}$	C–F	>NH Singlet	Ar-H Multiplet	<i>S. aurivis</i>	<i>P. fluorescense</i>	<i>A. niger</i>	<i>A. flavus</i>
V _a	3380	-	1260	9.31	7.52-6.80	0.94	0.89	0.99	0.91
V _b	3410	15851380	1270	9.18	8.15-7.15	0.95	1.00	0.87	0.82
V _c	3220	-	1295	9.22	7.70-6.35	0.81	0.78	0.98	0.94
V _d	3280	-	1290	9.65	8.10-6.72	0.94	0.96	0.81	0.76
V _e	3290	-	1285	9.70	8.30-6.70	0.96	0.98	0.80	0.74
VI _a	3380	-	1260	9.30	7.62-6.82	0.94	0.90	0.91	0.85
VI _b	3405	15801385	1295	9.21	8.20-7.22	0.96	0.98	0.86	0.85
VI _c	3215	-	1270	9.23	7.72-6.32	0.84	0.80	0.94	0.96
VI _d	3275	-	1275	9.71	8.10-6.80	0.92	0.83	0.73	0.74
VI _e	3290	-	1275	9.72	8.40-6.80	0.93	0.95	0.78	0.71

Antimicrobial activities are given in term of activity index

$$\text{Activity index} = \frac{\text{Inhibition diameter of test compound}}{\text{Inhibition diameter of standard}}$$

Results and Discussion

2-Amino-3-fluorobenzenethiol **I** was condensed with *o*-halonitrobenzenes **II**_{a,b} (2-chloronitrobenzene and 2,4-dinitrochlorobenzene) to give substituted 2-amino-2'-nitrodiphenyl sulfides **III**_{a,b}, which on formylation with 90% formic acid and substituent treatment with alcoholic KOH underwent smiles rearrangement yielding fluorinated 10*H*-phenothiazines. When reactive *o*-halonitrobenzene (containing a nitro group as well as halogen atom at *ortho* position to the reactive halogen atom) condensed with 2-aminobenzenethiols, yielded 10*H*-phenothiazines in a single step. Here cyclisation take place with the preference of halogen elimination and Smiles rearrangement as well as ring closure occurs simultaneously and in situ. Fluorinated 10*H*-phenothiazines **5**_{c-e} have been prepared by condensation of 2-amino-3-fluoro/2-amino-3-isopropyl and 2-amino-5-isopropylbenzenethiols with reactive halonitrobenzene **II**_{c-e}.

Substituted 10*H*-phenothiazine (**V**_{a-e}) converted into corresponding sulfones (**VI**_{a-e}) by oxidation with 30% hydrogenperoxide in glacial acetic acid (Scheme 1). The structures of all the synthesized compounds are characterized by spectroscopic data and elemental analysis. Kerby-Bauer procedure (Filter paper disc method) has been used for study of antimicrobial activity of newly synthesized compound.

The structure assignment of these compounds was made on basis of elemental analysis (Table 1) and spectral data (Table 2). The characteristic IR bands and ¹H NMR data of compounds (**V**_{a-e}) and (**VI**_{a-e}) are presented in Table 2.

IR spectra

Compounds (**V**_{a-e}) and (**VI**_{a-e}) exhibit a single sharp peak in the region 3410-3275 cm⁻¹ due to N-H stretching vibration. Compound **V**_b and **VI**_b exhibit peaks 1585-1580 cm⁻¹ and 1385-1380 cm⁻¹ due to assymetric and symmetric stretching vibrations of -NO₂ group. Compounds (**V**_{a-e}) and (**VI**_{a-e}) also exhibit a single peak in the region 1295-1260 cm⁻¹ due to C-F stretching vibrations. Sulfones derivatives of these 10*H*-Phenothiazines exhibit three characteristic absorption peaks as symmetric stretching ν_1 (1195-1140 cm⁻¹), Asymmetric stretching ν_3 (1380-1370 cm⁻¹) and banding vibration ν_2 (575-520 cm⁻¹) in chloroform solution.

NMR Spectra

All the synthesized compounds show a singlet in the region δ 9.72-9.18 ppm is due to N-H protons. Multiplet due to aromatic protons appeared in the region δ 8.40-6.32 ppm. (Table 2).

Mass spectra

In mass spectra molecular ion peak are in accordance with their molecular weight.

Conclusion

The structure proposed to the synthesized compound is well supported by spectroscopic data and elemental analysis. From the antimicrobial activity data (Table 2), it may be concluded that all the synthesized compounds showed good and moderate activity against the antimicrobes.

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