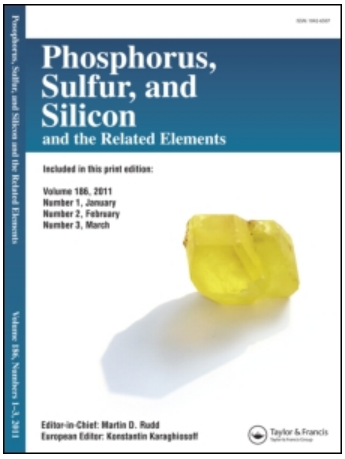

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CHEMICAL SYNTHESIS AND BIO-SCREENING OF BENZO-PHENOTHIAZINES, BEARING SIDE CHAIN AT THE 6-POSITION

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CHEMICAL SYNTHESIS AND BIO-SCREENING OF BENZO-PHENOTHIAZINES, BEARING SIDE CHAIN AT THE 6-POSITION

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Some new anilino-5H-benzo[a]phenothiazin-5-ones (**III**) were synthesized by the condensation of 2-(4-bromoanilino)-3-chloro-1,4-naphthoquinone (**II**) with corresponding zinc mercaptide (**I**). Derivatives of compound (**III**) were prepared by its reduction, methylation and acetylation and were screened for antimicrobial evaluation. Structural assignments were done on the basis of elemental analyses, IR and ^{1}H NMR.

Key words: Angular phenothiazines and their derivatives, IR, ^{1}H NMR, bioscreening.

INTRODUCTION

A thorough survey of the literature revealed the synthesis[1,2] and properties[3,4] of angular phenothiazines. The growing importance[5–10] of phenothiazines has been signified by the research papers and the patents[11,12] appearing in the last few decades. The importance of this class of compounds was further strengthened when N-alkyl, aryl derivatives exhibited carcinogenic activity.[13] Sensing that little work has been done and under the influence of the above prospects some new substituted angular phenothiazines have been synthesized and their physical (Table I), chemical and biological (Table II) properties have been studied.

RESULTS AND DISCUSSION

2-(4-Bromoanilino)-3-chloro-1,4-naphthoquinone (**II**) was synthesized by the reaction of 2,3-dichloro-1,4-naphthoquinone with bromoaniline (**II**) which on treatment with substituted zinc mercaptide (**I**) gave substituted-5H-benzo[a]phenothiazin-5-ones (**III**). Compound (**III**) were easily reduced to corresponding 5-ols (**IV**) by sodiumdithionite. Reductive acetylation of (**III**) and acetylation of (**IV**) in pyridine gave the O-acetylated product (**V**). Methylated product (**VI**) was obtained by chemical transformation of (**IV**) with dimethylsulfate (Scheme I).

Compounds (**III**) and (**V**) were screened for their biocidal activity against the bacteria E. coli & S. Aureus and fungi Aspergillus flavus, Aspergillus niger, Fusarium moniliformae & Curvularia lunata.

SPECTRAL STUDIES

The structure of the synthesized compounds was confirmed by IR and ^{1}H NMR spectral studies.

TABLE I

Characterization data of compounds (III_a–VI_c)

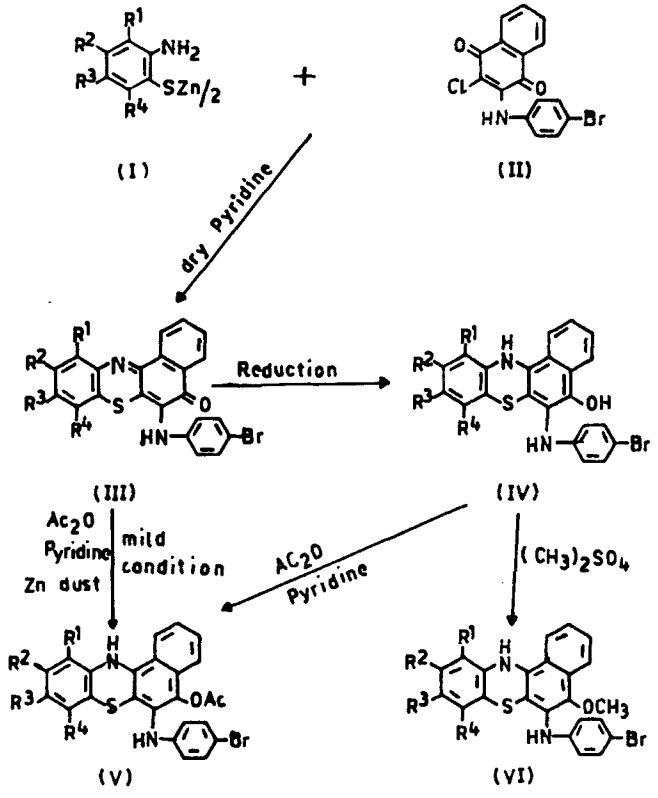
Compound No	R^1	R^2	R^3	R^4	M.P. °C	Yield (%)	Molecular formula	Elemental Analyses (%) Found (Calcd.) C	H	N	S
III_a	H	H	OC_6H_5	H	291-93	45	$C_{28}H_{17}BrN_2O_2S$	64.06 (64.00)	3.27 (3.24)	5.30 (5.33)	6.08 (6.10)
III_b	H	Cl	CH_3	H	272-74	46	$C_{23}H_{14}BrClN_2OS$	57.36 (57.32)	2.94 (2.91)	5.80 (5.82)	6.63 (6.65)
III_c	OCH_3	H	H	Cl	259-62	46	$C_{23}H_{14}BrClN_2O_2S$	55.50 (55.48)	2.84 (2.81)	5.60 (5.63)	6.41 (6.43)
IV_a	H	H	OC_6H_5	H	265-67	49	$C_{28}H_{19}BrN_2O_2S$	63.79 (63.76)	3.64 (3.61)	5.29 (5.31)	6.06 (6.07)
IV_b	H	Cl	CH_3	H	284-86	50	$C_{23}H_{16}BrClN_2OS$	57.10 (57.08)	3.34 (3.31)	5.76 (5.79)	6.61 (6.62)
IV_c	OCH_3	H	H	Cl	235-37	50	$C_{23}H_{16}BrClN_2O_2S$	55.40 (55.26)	3.24 (3.20)	5.60 (5.61)	6.40 (6.41)
V_a	H	H	OC_6H_5	H	287-89	58	$C_{30}H_{21}BrN_2O_3S$	63.29 (63.27)	3.70 (3.69)	4.90 (4.92)	5.60 (5.62)
V_b	H	Cl	CH_3	H	301-03	52	$C_{25}H_{18}BrClN_2O_2S$	57.11 (57.09)	3.45 (3.43)	5.30 (5.33)	6.08 (6.09)
V_c	OCH_3	H	H	Cl	211-13	49	$C_{25}H_{18}BrClN_2O_3S$	55.43 (55.40)	3.35 (3.32)	5.15 (5.17)	5.89 (5.91)
VI_a	H	H	OC_6H_5	H	240-42	45	$C_{29}H_{21}BrN_2O_2S$	64.35 (64.33)	3.90 (3.88)	5.15 (5.18)	5.90 (5.91)
VI_b	H	Cl	CH_3	H	272-74	44	$C_{24}H_{18}BrClN_2OS$	57.91 (57.89)	3.65 (3.62)	5.61 (5.63)	6.41 (6.43)
VI_c	OCH_3	H	H	Cl	249-51	48	$C_{24}H_{18}BrClN_2O_2S$	56.11 (56.09)	3.53 (3.51)	5.42 (5.45)	6.22 (6.23)

TABLE II

Antimicrobial activity of the compounds (**III** & **V**)

Test organisms	Inhibition zone (mm)					
	III_a	III_b	III_c	V_a	V_b	V_c
Bacteria	16.5	11.9	12.5	15.5	12.2	12.0
S. aureus	(1.50)	(1.08)	(1.13)	(1.40)	(1.10)	(1.09)
	12.5	10.8	12.0	12.4	12.0	12.2
E. Coli	(1.13)	(0.98)	(1.09)	(1.12)	(1.09)	(1.10)
Fungi	8.9	8.2	6.8	9.2	8.2	8.2
A. niger	(1.10)	(1.02)	(0.85)	(1.15)	(1.02)	(1.02)
	8.5	7.9	7.5	8.9	6.7	7.9
A. flavus	(1.06)	(0.98)	(0.93)	(1.11)	(0.83)	(0.98)
	9.9	7.7	6.9	8.2	7.0	8.2
F. moniliformac	(1.23)	(0.96)	(0.85)	(1.02)	(0.87)	(1.02)
	7.5	8.4	8.0	8.5	7.0	6.7
C. lunata	(0.93)	(1.05)	(1.00)	(1.06)	(0.87)	(0.83)

Values in parentheses represent activity index : Activity index = $\frac{\text{inhibition area of the sample}}{\text{inhibition area of the standard}}$



SCHEME I

IR Spectra

Certain functional groups were identified with the help of IR spectra. The N—H stretching frequency which generally appears at 3350–3310 cm^{-1} is shifted to lower frequency viz. 3120–3090 cm^{-1} (**III**, **IV**, **V**). In compound (**VI**) the N—H band occurred at 3300–3280 cm^{-1}. Carbonyl stretching vibrations of compounds (**III**) and (**V**) are also shifted to lower frequency range, 1630–1620 cm^{-1}, instead of 1720–1690 cm^{-1}. The shift in C=O and N—H stretching vibrations towards lower frequency indicates the possibility of intramolecular hydrogen bonding through NH . . . . . O=C. In compound (**IV**) a downward shift of the hydroxy stretching vibration from its normal value 3600 cm^{-1} to 3980–3070 cm^{-1} is another evidence in the favor of hydrogen bonding. In compounds ($\mathbf{III}_c$), ($\mathbf{IV}_c$), (**V**) and (**VI**), C—O—C stretching vibrations of acetoxy and acetyl groups appeared in the region 1240–1230 cm^{-1} and 1040–1030 cm^{-1}.

^1H NMR Spectra

In all the synthesized compounds a complex multiplet appeared at δ 8.52–6.77 ppm which could be assigned to the phenyl protons. Methyl and methoxy derivatives appeared, showing sharp singlets at δ 2.31–2.24 ppm and δ 4.25–4.21 ppm re-

spectively. Compound ($\mathbf{VI}_c$) gave a broad singlet centered at δ 4.25 ppm indicating the presence of methoxy protons situated in a different environment. The hydroxyl proton in compound (**IV**) occurred at δ 10.95–10.41 ppm. The protons of the secondary amines appeared at δ 6.52–6.48 ppm and δ 9.09–8.82 ppm. The latter being due to the proton on the N incorporated in the phenothiazine nucleus.

BIOCIDAL ACTIVITY

Compounds (**III**) and (**V**) of the series were screened for their biocidal activity following the methods of Gould *et al.*[14] Streptomycin and Mycostatin were used as reference compounds in antibacterial and antifungal activity respectively.

It was observed that these compounds possess considerable antimicrobial activity especially in the case of compounds (**IIIa**) and (**Va**) where the maximum activity index was found, ranging from 0.92 mm to 1.50 mm. These compounds were found to be more potent, against the tested micro-organisms in comparison to those other types of substituted angular phenothiazines synthesized by our research colleagues.[15] In this aspect these compounds merit further research.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR (KBr; max cm^{-1}) spectra were recorded on a Perking-Elmer 577 grating spectrophotometer and ^1H NMR spectra in DMSO-d_6 or $CDCl_3$ on a Jeol Fx 90Q (90 MHz) using TMS as internal standard.

Synthesis of 2-(4-bromoanilino)-3-chloro-1,4-naphthoquinone (**II**)

Compound (**II**) was prepared by reported method.[16]

Synthesis of 6-(4-bromoanilino)-9-phenoxy/-10-chloro-9-methyl/-8-chloro-11-methoxy-5H-benzo[a]phenothiazine-5-ones (**III**)

A mixture of zinc mercaptide of substituted 2-aminobenzothiol (1; 0.005 mole) and (2-4-bromoanilino)-3-chloro-1,4-naphthoquinone (**II**; 0.01 mole) in 50 ml of dry pyridine was heated under reflux for 3 hr. An equal volume of methanol was added and the solution was chilled. The precipitate was filtered washed with ethanol and 5% hydrochloric acid, dried and recrystallized from benzene.

Synthesis of 6-(4-bromoanilino)-9-phenoxy/-10-chloro-9-methyl/-8-chloro-11-methoxy-12H-benzo[a]phenothiazine-5-ol (**IV**)

A mixture of **III** (0.005 mole) and sodium dithionite (0.01 mole) in 5 ml of water and 50 ml of acetone was heated under reflux for 2 hr. The mixture, which became colorless, was allowed to cool and poured into a solution of sodiumdithionite (0.02 mole) in ice cold water (1 lit). The resulting solid was extracted with ether.

Synthesis of 6-(4-bromoanilino)-9-phenoxy/10-chloro-9-methyl/-8-chloro-11-methoxy-5-acetoxy-12H-benzo[a]phenothiazine (**V**)

Method A: By reductive acetylation of **III**. A mixture of **III** (0.005 mole) and zinc dust (0.03 mole) in acetic anhydride (35 ml) and prydine (2 ml) was stirred for 15 minutes at room temperature and warmed on a water bath for 15 minutes. Excess zinc dust was removed by filtration and the filtrate was poured into the crushed ice to get a yellow precipitate. The solid was extracted from chloroform and the solution was washed with saturated aqueous sodium-bicarbonate and water and then dried by anhydrous Na_2SO_4. The desired product was obtained by evaporation of solvent and recrystallized from benzene-petroleum ether (b.p. 60–80°C).

Method B: By acetylation of **IV**. To a solution of **IV** (0.005 mole) in pyridine (0.005 mole), acetic anhydride (0.047 mole) was added and the mixture was refluxed over a steam-bath for 6 hr. The reaction mixture was cooled, filtered, dried and recrystallized from benzenepetroleum ether (b.p. 60–80°C).

Synthesis of 6-(4-bromoanilino)-9-phenoxy/-10-chloro-9-methyl/-8-chloro-11-methoxy-5-methoxy-12H-benzo[a]phenothiazine (**VI**)

A mixture of **IV** (0.01 mole) and sodiumdithionite (0.002 mole) in 10% ethanolic potassium hydroxide (110 ml) solution was heated under reflux for 15 minutes. Dimethyl sulfate (0.15 mole) was added to the above mixture and refluxed for 6 hr. Resulting solution was poured into the crushed ice. The precipitate was filtered, dried and recrystallized from benzene.

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