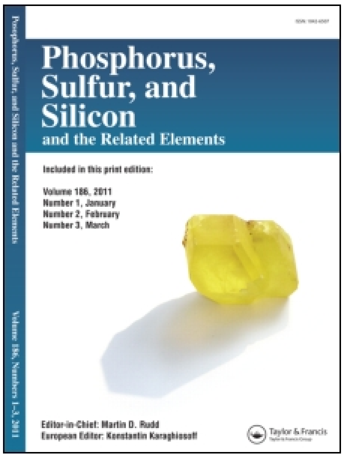

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ANGULAR HETEROCYCLES: STUDIES IN THESYNTHESIS OF BENZO[*a*][1,4]BENZOTHIAZINO-[3,2-C]PHENOTHIAZINES AND5H-BENZO[*a*]PHENOTHIAZIN-5-ONES

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ANGULAR HETEROCYCLES: STUDIES IN THE SYNTHESIS OF BENZO[*a*][1,4]BENZOTHIAZINO-[3,2-C]PHENOTHIAZINES AND 5H-BENZO[*a*]PHENOTHIAZIN-5-ONES

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The substituted benzo[*a*][1,4]benzothiazino[3,2-C]phenothiazines and 5H-benzo[*a*]phenothiazin-5-ones were prepared by the condensation of 2,3-dichloro-5-nitro-1,4-napthoquinones **1** with 2-amino-3,5-disubstituted benzenethiols **2a** and their zinc salts respectively. The resulting compounds were subjected to reduction, methylation and acetylation. Some of these compounds were screened for their antimicrobial activity against bacteria *S. aureus* and *E. coli* and fungi *Aspergillus niger*, *Aspergillus flavus*, *Fusarium moniliformae* and *Curvularia lunata*.

Key words: Angular phenothiazines; 5H-benzo[*a*]phenothiazin-5-ones; benzo[*a*][1,4]benzothiazino[3,2-C]phenothiazines; 12H-benzo[*a*]phenothiazin-5-ols; ^{1}H NMR data.

INTRODUCTION

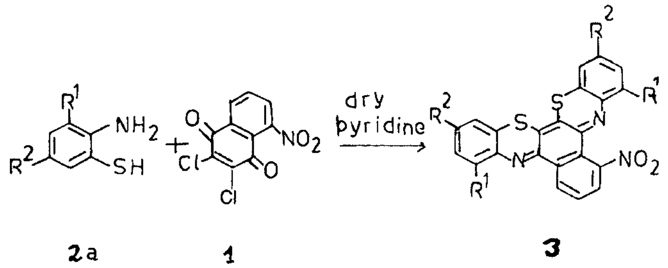
The biological and industrial applications of phenothiazines[1–5] and their derivatives have led to our interest in the synthesis of nuclear substituted benzo[*a*]phenothiazines and their derivatives. Besides this the benzophenothiazine[6] derivatives are of interest as potential carcinogenic agents. In the present paper we report the synthesis of substituted hydroxybenzo[*a*]phenothiazines and their derivatives.

It has been found that 2,3-dichloro-5-nitro-1,4-napthoquinone **1** reacts with 2-amino-3,5-disubstituted benzenethiols **2a** in dry pyridine to give the substituted benzo[*a*][1,4]benzothiazino[3,2-C]phenothiazines **3** (Scheme I).

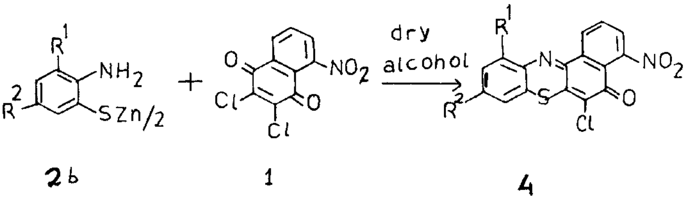
On the other hand when **1** was made to react with the zinc mercaptides of 2-amino-3,5-disubstituted benzenethiols **2b** in alcohol it gave the substituted 5H-benzo[*a*]phenothiazin-5-ones **4** (Scheme II). These 5H-benzo[*a*]phenothiazin-5-ones were further reduced to the corresponding substituted 12H-benzo[*a*]phenothiazin-5-ols **5** in very good yields with sodium dithionite in acetone (Scheme III).

The synthesis of esters of hydroxybenzo[*a*]phenothiazines **6** have been carried out in very good yields by following two methods: (A) acetylating hydroxybenzo-[*a*]phenothazines with acetic anhydride and pyridine and (b) by the reductive acetylation of substituted 5H-benzo[*a*]phenothiazin-5-ones.

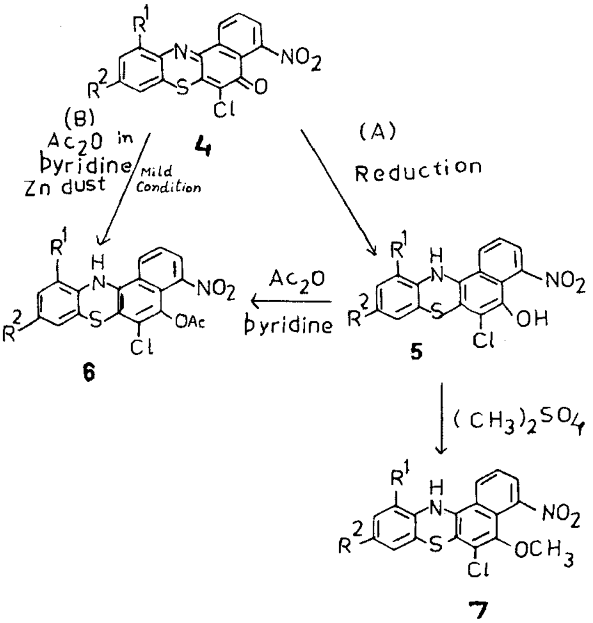
The compound **5** was converted into the substituted 5-methoxy-12H-benzo[*a*]phenothiazine **7** with dimethyl sulphate and sodium dithionite in ethanolic KOH (Scheme III).



SCHEME I



SCHEME II



SCHEME III

RESULTS AND DISCUSSION

The structure of the above synthesized compounds were confirmed by their IR and ^{1}H NMR spectral studies. In the IR spectra some characteristic peaks were found which indicated the presence of particular functional groups. In the IR spectra of

4 a sharp peak was found at 1685–1660 cm^{-1} instead of 1720–1690 cm^{-1} due to the presence of the C=O group. This lowering in the frequency is attributed to ionic resonance effect. In all the compounds two sharp bands in the region 1585–1560 cm^{-1} and 1320–1300 cm^{-1} were found which could be attributed to NO_2 group. In the compound **6** and **7** the bands in the region 1240–1220 cm^{-1} and 1040–1025 cm^{-1} were due to C—O—C stretching of the acetoxy and acetyl group. In the compound **5**, **6** and **7** a band in the region 3300–3280 cm^{-1} could be assigned to NH stretching vibrations. In the compound **3** characteristic ring vibrations were observed in the region 1600–1190 cm^{-1}.

In the ^1H NMR spectra the multiplet of the phenyl protons appeared in the region δ 6.55–8.90 ppm. The methyl and methoxy derivatives made their appearance by giving signals at δ 2.08–2.30 ppm and δ 3.85–4.20 ppm, respectively.

In the compound **5** the —OH signal appeared at δ 8.20–10.95 ppm as a broad singlet. The —NH protons were found at δ 8.65–9.40 ppm.

EXPERIMENTAL

Melting points determined on a Toshniwal melting point apparatus (capillary method) are uncorrected. The purity of the synthesized compounds was checked by tlc on silica gel in various nonaqueous solvents. IR spectra were recorded in KBr on a Perkin Elmer 577 grating spectrophotometer. The ^1H NMR spectra were scanned on FX 900 JEOL spectrometer (90 MHz) using TMS as internal standard.

(i) *2,3-Dichloro-5-nitro-1,4-napthoquinone* (**1**) *was synthesized by the nitration of 2,3-dichloro-1,4-napthoquinone.*

(ii) *Substituted benzo[a][1,4]benzothiazino[3,2-C]phenothiazines* (**3**). A mixture of 2,3-dichloro-5-nitro-1,4-napthoquinone (**1**; 0.01 mole) and 2-amino-3,5-disubstitutedbenzenethiol (**2**; 0.025 mole) in dry pyridine (50 ml) was stirred for 30 min at room temperature, then heated to reflux for 2 hr; an equal volume of methanol was added and the mixture chilled, the product was collected by filtration, washed with hot water and methanol and recrystallized from benzene.

(iii) *Substituted 5H-benzo(a)phenothiazin-5-ones* (**4**). A mixture of 2,3-dichloro-5-nitro-1,4-napthoquinone (**1**; 0.01 mole) and the zinc thiolate of 2-amino-3,5-disubstituted benzenethiol (0.005 mole) in dry ethanol (100 ml) was stirred for 1 hr at room temperature. In most cases the color of the solution changed to orange-red; it was then refluxed for 2 hr. The solid which deposited on cooling was collected by filtration, washed with 5% hydrochloric acid and water. The product was recrystallized from benzene.

(iv) *Substituted 12H-benzo(a)phenothiazin-5-ols* (**5**). A mixture of the substituted 5H-benzo(*a*)phenothiazin-5-one (**4**; 0.005 mole), sodium dithionite (0.01 mole), water (5 ml) and acetone (50 ml) was refluxed for 80 min. The mixture, which had turned from orange-red to colorless, was allowed to cool and poured into a solution of sodium dithionite (0.02 mole) in cold water (1000 ml). The resulting solid was washed with water, dried in vacuum and recrystallized from toluene.

(v) *Substituted 5-acetone-12H-benzo[a]phenothiazines* (**6**). First method: Acetylation of the substituted 12H-benzo[*a*]phenothiazin-5-ols (**5**). A mixture of the substituted 12H-benzo[*a*]phenothiazin-5-ol (0.005 mole), pyridine (40 ml), sodium dithionite (3 g) and acetic anhydride (1.58 ml) was stirred for 2.5 hr at room temperature, concentrated to 30 ml and poured into 500 ml of cold water. The resulting solid was collected, washed with water, dried and recrystallized from benzene petroleum ether (b.p. 60–80°C) to obtain (**6**).

Second method: Reduction acetylation of the substituted 5H-benzo[*a*]phenothiazin-5-one (**4**). A mixture of the substituted 5H-benzo[*a*]phenothiazin-5-one (0.005 mole), acetic anhydride (35 ml) and pyridine (2 ml) was shaken with zinc dust (2 g), stirred at room temperature for 15 min and then warmed on a water bath at 100°C for 15 min. The pale yellow solution was separated from the excess of zinc dust by filtration and poured on ice to obtain a light yellow precipitate. The solid was extracted in chloroform and the solution washed with saturated aqueous sodium hydrogen carbonate and water, and then dried (Na_2SO_4). Evaporation of the solvent gave a crystalline residue, which after recrystallization from benzene-petroleum ether (b.p. 60–80°C) provided the substituted-5-acetoxy-12H-benzo[*a*]phenothiazine.

TABLE I
Physical and analytical data of the compounds

Compd.	R^1	R^2	Yield (%)	M.P. (°C)	M.F.	Anals. % Cal. (Found) C	H	S
1	2	3	4	5	6	7	8	9
3a	F	F	50	278–81	$C_{22}H_7F_4N_3O_2S_2$	54.43 (54.57)	1.44 (1.49)	13.19 (13.20)
3b	Cl	Cl	54	260–61	$C_{22}H_7Cl_4N_3O_2S_2$	47.91 (47.10)	1.27 (1.31)	11.61 (11.69)
3c	OCH_3	OCH_3	52	265–66	$C_{26}H_{19}N_3O_6S_2$	58.54 (58.63)	3.56 (3.51)	12.01 (12.12)
3d	Br	CH_3	55	250–52	$C_{24}H_{13}Br_2N_3O_2S_2$	48.08 (48.10)	4.86 (4.80)	10.68 (10.72)
4a	F	F	46	259–262	$C_{16}H_5ClF_2N_2O_3S$	50.73 (50.86)	1.32 (1.40)	8.45 (8.56)
4b	Cl	Cl	50	220–22	$C_{16}H_5Cl_3N_2O_3S$	46.66 (46.78)	1.21 (1.28)	7.78 (7.62)
4c	OCH_3	OCH_3	47	253–55	$C_{18}H_{11}ClN_2O_5S$	53.66 (53.74)	2.73 (2.80)	7.95 (7.89)
4d	Br	CH_3	48	260–61	$C_{17}H_8BrClN_2O_3S$	46.84 (46.94)	1.84 (1.80)	7.35 (7.40)

5a	F	F	52	255–56	$C_{16}H_7F_2ClN_2O_3S$	50.46 (50.58)	1.84 (1.99)	8.41 (8.46)
5b	Cl	Cl	56	233–35	$C_{16}H_7Cl_3N_3O_3S$	44.91 (44.98)	1.64 (1.70)	7.48 (7.52)
5c	OCH_3	OCH_3	49	268–70	$C_{18}H_{13}ClN_2O_5S$	53.40 (53.58)	3.21 (3.26)	7.91 (7.92)
5d	Br	CH_3	54	240–42	$C_{17}H_{10}BrClN_2O_3S$	46.63 (46.69)	2.28 (2.30)	7.31 (7.44)
6a	F	F	50	273–75	$C_{18}H_9F_2Cl_2N_2O_4S$	51.12 (51.26)	2.13 (2.20)	7.57 (7.62)
6b	Cl	Cl	48	280–81	$C_{18}H_9Cl_3N_2O_4S$	47.42 (47.50)	1.97 (1.20)	7.02 (7.17)
6c	OCH_3	OCH_3	42	256	$C_{20}H_{15}ClN_2O_6S$	53.75 (53.82)	3.36 (3.41)	7.17 (7.22)
6d	Br	CH_3	52	262–63	$C_{19}H_{12}BrClN_2O_4S$	47.55 (47.66)	2.50 (2.58)	6.67 (6.60)
7a	F	F	49	280	$C_{17}H_9ClF_2N_2O_3S$	51.71 (51.86)	2.28 (2.35)	8.11 (8.25)
7b	Cl	Cl	56	265–67	$C_{17}H_9Cl_3N_2O_3S$	47.72 (47.84)	2.10 (2.20)	7.48 (7.50)
7c	OCH_3	OCH_3	50	286	$C_{19}H_{15}ClN_2O_5S$	54.48 (54.53)	3.58 (3.63)	7.65 (7.69)
7d	Br	CH_3	51	284–85	$C_{18}H_{12}BrClN_2O_3S$	47.84 (47.95)	2.66 (2.61)	7.09 (7.16)

TABLE II

Antimicrobial activity of 5,7-disubstituted pyrido[2,3-*d*]pyrimidine derivatives

	Zone of inhibition (mm)							
Compd. no.	**6a**	**6b**	**6c**	**6d**	**7a**	**7b**	**7c**	**7d**
Gram positive bacteria *S. aureus*	10.2	12.0	11.6	9.6	9.8	11.2	10.8	11.0
	(0.93)	(1.09)	(1.05)	(0.87)	(0.89)	(1.02)	(0.98)	(1.00)
Gram negative bacteria *E. coli*	12.4	10.6	12.0	9.8	8.6	9.0	8.6	9.7
	(1.11)	(0.95)	(1.07)	(0.87)	(0.7)	(0.80)	(0.77)	(0.87)
Fungi:								
Aspergillus flavus	6.3	8.5	9.2	10.4	7.9	6.8	6.6	9.0
	(0.79)	(1.06)	(1.15)	(1.3)	(0.99)	(0.85)	(0.82)	(1.12)
Aspergillus niger	6.8	6.6	7.6	6.9	6.9	6.8	8.2	9.0
	(0.80)	(0.78)	(0.89)	(0.81)	(0.81)	(0.80)	(0.96)	(1.06)
Curvularia lunata	7.1	7.4	6.4	7.0	6.4	8.4	10.2	8.5
	(0.86)	(0.90)	(0.78)	(0.85)	(0.78)	(1.02)	(1.24)	(1.04)
Fusarium moniliformae	7.6	6.9	8.2	9.0	8.4	6.1	7.9	6.8
	(0.95)	(0.86)	(1.02)	(1.12)	(1.05)	(0.76)	(0.99)	(0.85)

Values in parentheses represent activity index defined as:

$$\frac{\text{Inhibition area of the sample}}{\text{Inhibition area of the standard.}}$$

(vi) *Substituted 5-methoxy-12H-benzo[a]phenothiazines* (**7**). A mixture of the substituted 12H-benzo[*a*]phenothiazin-5-ol (**5**; 0.01 mole) and dimethyl sulphate (0.015 mole) was refluxed over a steam bath for 5 hrs and the filtrate was poured into cold water. The product was collected by filtration, dried and recrystallized from benzene.

The characterization data of the synthesized compounds are given in Table I.

ANTIMICROBIAL ACTIVITY

Some of the compounds prepared were screened for their antimicrobial activity at concentration 100 μg/disc in agar media following the method of Gould *et al.*[7] using streptomycin in antibacterial and mycostatin in antifungal activity as reference compounds. All the compounds showed activity against gram positive bacteria *Staphyloccus aureus* and gram negative bacteria *Escherichia coli*. The compound **6a** showed maximum zone of inhibition (12.4 mm) against *Escherichia coli*, while the compound **6b** showed maximum zone of inhibition (12.0 mm) against *Staphyloccus aureus*. The compounds showed moderate activity against the fungi used. The results are recorded in Table II.

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