Angular Heterocycles. Utilization of Arylaminonaphthoquinones in the Synthesis of Benzophenothiazines

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Substituted 6-ethoxyanilino-5*H*-benzo[*a*]phenothiazin-5-ones (**3a-f**) were synthesized by the cyclocondensation of 2-chloro-3-ethoxyanilino-1,4-naphthoquinones with zinc mercaptides of 2-aminothiophenol in pyridine. The nmr, ir and mass spectral data are presented and discussed.

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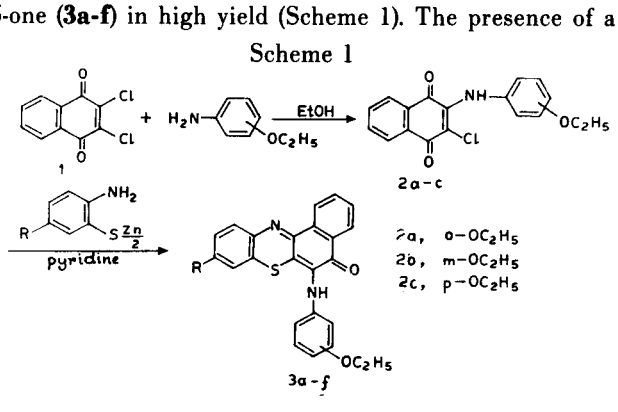
Benzophenothiazines are extensively used as potential carcinostatic agents [2], anthelmintics [3], anti-oxidants [4], lubricants [5], stabilizers [6] and in photography [7]. In spite of their wide applications, the reported synthesis [8,9] of benzophenothiazines involves lengthy procedures, is tedious, produces low yields and is limited to a few nuclear substituted derivatives. In continuation of our studies on naphthoquinone chemistry [1], it appeared reasonable to use them for the synthesis of benzophenothiazines. We also planned to attach the variously substituted ethoxyanilines to the benzophenothiazine moiety because their derivatives are widely used as drugs [10] and also are found to be a part of many compounds possessing biological activity [11]. Thus, the compounds which will result from the combination of these two widely used drugs may show promising biological activity. We report here a convenient, one pot, high yield synthesis of various ethoxyanilino-5*H*-benzophenothiazin-5-ones (**3a-f**).

2-Chloro-3-ethoxyanilino-1,4-naphthoquinones (**2a-c**) were prepared by the reaction of 2,3-dichloro-1,4-naphthoquinone with appropriately substituted ethoxyanilines in ethanol. In 2-chloro-3-arylamino-1,4-naphthoquinones the chlorine atom is not replaced by nucleophiles [12] because of hydrogen bonding of the arylamine with the quinonoid carbonyl group and the electron donating nature of the nitrogen atom. Since the mercapto group is highly nucleophilic, it was thought that a mercapto sulfur might replace the chlorine atom in **2**. Cyclocondensation reaction of zinc mercaptides of substituted 2-aminothiophenol with **2** in pyridine and dimethylformamide afforded the corresponding substituted ethoxyanilino-5*H*-benzo[*a*]phenothiazin-5-one (**3a-f**) in high yield (Scheme 1). The presence of a small amount of unidentified products in the reaction mixture was detected by thin layer chromatography. Further, the reaction of other bifunctional nucleophiles (*e.g.* *o*-aminophenols, *o*-phenylenediamines), with **2** in various solvents (*e.g.* pyridine, dimethylformamide, dimethylsulfoxide, triethylamine *etc*) yield no reaction products suggesting that the mercapto group is more nucleophilic than the amino group and the phenoxide anion [1c].

Scheme 1



The structures of **3a-f** were fully confirmed by microanalytical results and spectral data. The ir spectra of benzophenothiazones exhibited characteristic weak hydrogen bonded bands at 3190-3295 cm^{-1} due to N-H stretching and at 1610-1620 cm^{-1} attributed to a hydrogen bonded C=O stretching vibration. The pmr spectral data are listed in Table 2. All compounds showed a triplet centered in the region δ 1.2-1.52, J = 7 Hz due to methyl protons of the ethoxy group and a quartet centered in the region δ 3.96-4.22, J = 7 Hz assigned to O-CH_2- protons. The aromatic protons occurred between δ 6.02-8.62 as a complex multiplet, totally supported by integration but individual proton assignments could not be made.

Mass Spectra.

Mass spectral fragmentation of **3a-f** is shown in Scheme 2 and data are collected in Table 3. The molecular ion is the base peak suggesting a high stability of the anilinobenzophenothiazone ring system due to a higher degree of conjugation. The principal fragmentation is governed by the ethoxy group attached to the anilino ring of the molecule. The prominent peak at $M^+ - 29$, indicates a loss of $C_2H_5^{\cdot}$ to give **F**, which further loses a CO molecule to afford **G**, and this fragmentation is characteristic of alkoxybenzenes [13]. The other very intense ion **B** is probably formed from the molecular ion as shown in path a. Similar electron impact behaviour has been observed in the case of other analogous heterocycles [1c]. Elimination of $H_2CN^{\cdot}$ from **B** gives **C**, which further gave an ion **D** due to loss of S. The other interesting fragmentation of the heterocycles of **3a-f** are depicted in Scheme 2 and are in complete accord with anticipated fragmentation [13]. It is remarkable to note that in **3d-f**, the principal ions are not formed by the loss of a chlorine radical as in the case of chlorophenothiazines [15]. It can be concluded from the inspection of

Scheme 2

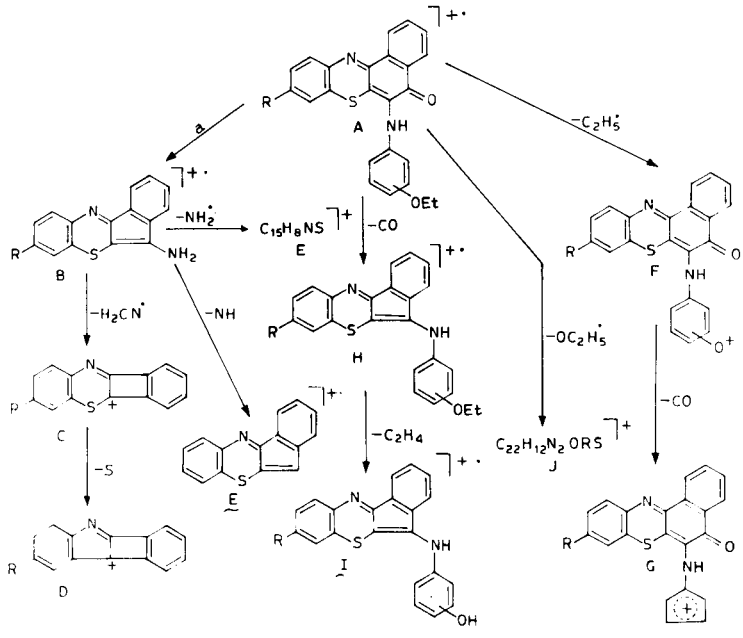


Table 1

Synthesis of Substituted 6-Ethoxyanilino-5*H*-benzo[*a*]phenothiazin-5-ones (**3a-f**)

Compound No.	R	OC_2H_5	Solvent of Crystallisation	Mp (°C)	Yield %	Molecular Formula	Analysis (Calcd.) C	H	N
3a	H	o-OC_2H_5	Dichloromethane	242	70	$C_{24}H_{18}N_2O_2S$	72.50 (72.11)	4.86 (4.86)	7.32 (7.0)
3b	H	*m*-OC_2H_5	Dichloromethane [a]	191-193	87	$C_{24}H_{18}N_2O_2S$	72.32 (72.11)	4.80 (4.86)	6.89 (7.0)
3c	H	*p*-OC_2H_5	Dichloroethane	216	80	$C_{24}H_{18}N_2O_2S$	72.08 (72.11)	4.50 (4.86)	7.08 (7.0)
3d	Cl	*o*-OC_2H_5	Dichloromethane	205	75	$C_{24}H_{17}ClN_2O_2S$	66.01 (66.39)	4.08 (4.22)	6.08 (6.45)
3e	Cl	*m*-OC_2H_5	Benzene [a]	198	68	$C_{24}H_{17}ClN_2O_2S$	66.58 (66.39)	4.30 (4.22)	6.50 (6.45)
3f	Cl	*p*-OC_2H_5	Toluene [a]	212	62	$C_{24}H_{17}ClN_2O_2S$	66.75 (66.39)	4.50 (4.22)	6.55 (6.45)

[a] Purified by column chromatography and crystallization.

Table 2

PMR and Infrared Spectral Data of Substituted 6-Ethoxyanilino-5*H*-benzo[*a*]phenothiazin-5-ones (**3a-f**)

Compound No.	IR Data (cm^{-1})	PMR Data (δ, Deuteriochloroform) OCH_2CH_3	OCH_2CH_3	aromatic protons
3a	3190 w [b], 1620 vs (C=O), 1570 m, 1530 m	1.52 (t) [a]	4.22 (q) [a]	6.02-8.62 (m, 12H)
3b	3295 m, 1610 vs (C=O), 1590 vs, 1510 w	1.36 (t)	3.96 (q)	6.2-8.60 (m, 12H)
3c	3280 w, 1620 vs (C=O), 1580 m, 1520 w	1.29 (t)	4.01 (q)	6.8-8.6 (m, 12H)
3d	3260 w, 1620 s (C=O), 1590 m, 1520 m	1.50 (t)	4.20 (q)	6.6-8.60 (m, 11H)
3e	3280 w, 1620 vs (C=O), 1590 vs, 1512 w	1.2 (t)	4.0 (q)	6.2-8.6 (m, 11H)
3f	3270 w, 1620 m, (C=O), 1590 m, 1575 w	1.48 (t)	4.06 (q)	6.7-8.6 (m, 11H)

[a] J = 7 Hz. [b] w, weak; m, medium; vs, very strong.

Table 3

Principal Ions in Mass Spectra of **3a-f**

m/e (Fragment)	Relative Intensity (%) 3a	3b	3c	m/e (Fragment)	Relative Intensity (%) 3d	3e	3f
398 (**A**)	M^+, 100	M^+, 100	M^+, 100	432 (**A**)	M^+, 100	M^+, 100	M^+, 100
370 (**H**)	2.0	4.0	22.5	404 (**H**)	10.6	4.5	21.6
369 (**F**)	18.5	16.7	68.3	403 (**F**)	36.3	3.6	66.0
353 (**J**)	4.7	6.0	0.5	387 (**J**)	7.8	5.3	7.3
342 (**I**)	2.0	4.0	1.2	376 (**I**)	—	3.7	1.3
341 (**G**)	3.0	12.6	40.0	375 (**G**)	2.3	3.7	3.7
250 (**B**)	27.3	19.9	29.3	284 (**B**)	58.4	10.6	27.4
235 (**E**)	6.6	4.0	11.3	—	—	—	—
234 (**K**)	4.8	7.3	3.1	—	—	—	—
222 (**C**)	16.7	13.4	3.8	256 (**C**)	19.1	4.5	6.2
190 (**D**)	11.5	21.5	8.4	224 (**D**)	3.8	3.3	3.8

Table 3 that the relative abundance of the ions of *p*-ethoxy derivatives (**3c** and **f**) is higher than other isomeric ethoxy compounds (**3a,b,d,e**).

The present report offers a facile method for the synthesis of ethoxyanilino-5*H*-benzo[*a*]phenothiazin-5-ones from easily available starting materials. The biological studies are under investigation and will be reported elsewhere.

EXPERIMENTAL

Melting points were determined in open capillary tubes using a Toshniwal melting point apparatus and are uncorrected. The infrared spectra were obtained in potassium bromide pellets using a Perkin-Elmer 377 grating spectrophotometer, and pmr spectra were taken on a T-60A Varian spectrometer using tetramethylsilane as the internal reference. Low resolution mass spectra were recorded on JEOL JMS-D300 equipped with a Model JMS-2000 data system at an ionizing energy of 70 eV and an ion source temperature of 250°. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The purity of all the compounds was checked on thin layer chromatography [18] using silica gel and various non-aqueous solvent systems. Zinc mercaptides of substituted 2-aminothiophenols were prepared by the procedure described in the literature [1d].

General Procedure for the Preparation of 2-Chloro-3-ethoxyanilino-1,4-naphthoquinones (**2a-c**).

A mixture of 2,3-dichloro-1,4-naphthoquinone (2.27 g, 0.01 mole) and the appropriately substituted ethoxyaniline (2.46 g, 0.02 mole) in 50 ml dry ethanol was heated under reflux with stirring for 2 hours. It was then cooled to room temperature and chilled. The product was collected, dried and crystallized from dichloroethane-hexane to afford analytically pure 2-chloro-3-ethoxyanilino-1,4-naphthoquinones.

Compound **2a** was isolated as orange violet crystals, yield 2.63 g (81%), mp 185° [16]; ir (potassium bromide): 3240 m (NH), 1670 s (C=O), 1595 m, 1555 m cm^{-1}; pmr (deuteriochloroform): δ 1.43 (t, 3H, J = 7 Hz, $-OCH_2CH_3$), 4.06 (q, 2H, J = 7 Hz, OCH_2CH_3), 6.76-8.35 (m, 9H, NH and aromatic protons).

Compound **2b** was isolated as a crimson red precipitate, yield 3.0 g (92%), mp 138°; ir (potassium bromide): 3210 s (NH), 1670 s (C=O), 1630 m, 1595 m, 1550 s cm^{-1}; pmr (deuteriochloroform): δ 1.33 (t, 3H, J = 7 Hz, OCH_2CH_3), 4.11 (q, 2H, J = 7 Hz, OCH_2CH_3), 6.35-8.40 (m, 9H, NH and aromatic protons).

Anal. Calcd. for $C_{18}H_{14}ClNO_2$: C, 66.55; H, 4.30; N, 4.30. Found: C, 66.24; H, 4.08; N, 4.47.

Compound **2c** was isolated as red violet crystals, yield 2.83 g (87%), mp 126° [17], ir (potassium bromide): 3280 m (NH), 1675 s (C=O), 1580 m, 1550 s, 1500 cm^{-1}; pmr (deuteriochloroform): δ 1.33 (t, 3H, J = 7 Hz, OCH_2CH_3), 4.08 (q, 2H, J = 7 Hz, OCH_2CH_3), 6.75-8.35 (m, 9H, NH and aromatic protons).

General Procedure for the Synthesis of Substituted 6-Ethoxyanilino-5*H*-benzo[*a*]phenothiazin-5-ones (**3a-f**).

A mixture of the corresponding 2-chloro-3-ethoxyanilino-1,4-naphthoquinone (**2a-c**) (0.01 mole, 3.25 g), and zinc mercaptide of substituted 2-aminothiophenol (0.005 mole) in 25-40 ml of dry pyridine was heated to reflux with stirring for 4 hours. It was brought to room temperature, chilled and an equal volume of ethanol was added. The precipitate was collected and dried over phosphorus pentoxide. Pure samples were obtained by column chromatography (silica gel) or recrystallization with suitable solvents. Analytical and other data are summarised in Table 1.

Acknowledgement.

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