Angular Heterocycles. A Convenient Synthesis of Azabenzophenothiazines

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The acid-catalysed reaction of substituted 1,4-naphthoquinones with *o*-aminoheterocyclic thiones in alcoholic solution afforded substituted monoazabenzo[*a*]phenothiazin-5-ones **4,5** and substituted benzo[*a*][1,4]diazabenzothiazino[3,2-*c*]phenothiazin-5-one (**6**). Some of the resulting compounds were subjected to dehalogenation. The structures of the products were assigned by elemental analysis, ^{1}H-nmr, and other spectral analysis.

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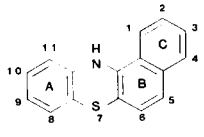
The phenothiazine and phenoxazine ring systems have been extensively studied and are widely used in medical practice and in dye industry [1-7]. Some of angular phenothiazine derivatives **1** have been synthesized [8-12] and



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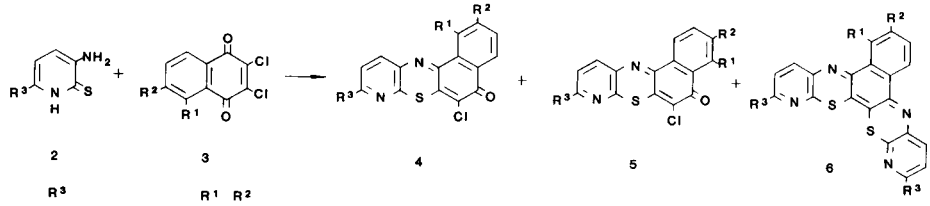
many of these compounds can be used as useful therapeutic agents for treating allergic conditions, cardiovascular disorders, inflammation and pain [13]. However, the angular azabenzo[*a*]phenothiazines have been less studied. We have reported the synthesis of monoazabenzo[*a*]phenothiazines with the N atom in ring C [14]. As a part of our studies [10-12,14] on the chemistry and spectroscopic properties of the new angular heterocycles here we report the synthesis of monoazabenzo[*a*]phenothiazine derivatives with the N atom in ring A.

In this work, substituted 8-azabenzo[*a*]phenothiazines **4** and **5** and substituted-benzo[*a*][1,4]diazabenzothiazino-[3,2-*c*]phenothiazine **6** were synthesized by the acid-catalyzed reaction of 2,3,5- or 2,3,6-trisubstituted-1,4-naphthoquinones **3** and 6-substituted-3-aminopyridine-2(1*H*)-thiones **2** [15] in ethanol (Scheme 1).

The mixture of 2,3-dichloro-5-nitro-1,4-naphthoquinone (**3a**, 1 mmole) and 5-amino-6-chloropyridine-2(1*H*)-thione (**2a**, 1.2 mmoles) in ethanol was treated with 15% hydrochloric acid and stirred for 1-6 hours (Scheme 1). The resulting precipitate was chromatographed on a silica gel column eluting with benzene-hexane to give 6,9-dichloro-1-nitro-5*H*-benzo[2,3-*a*]-8-azaphenothiazin-5-one (**4**, R^1 = NO_2, R^2 = H, R^3 = Cl) and 6,9-dichloro-4-nitro-5*H*-benzo-[3,2-*a*]-8-azaphenothiazin-5-one (**5**, R^1 = NO_2, R^2 = H, R^3 = Cl) in 85% yield. Trace amounts of 2,13-dichloro-6-nitro-1,14-diazabenzo[*a*][1,4]benzothiazino[3,2-*c*]phenothiazine (**6a**, R^1 = NO_2, R^2 = H, R^3 = Cl) were also isolated. When this reaction was carried out in ethanol in the presence of potassium acetate under refluxing, **6a**, **4a**, and **5a** were obtained as the main products together with 2-chloro-3-ethoxy-5-nitro-1,4-naphthoquinone and 3-chloro-2-ethoxy-5-nitro-1,4-naphthoquinone. These naphthoquinones were identified by comparing their spectroscopic data with the authentic samples prepared by the treatment of 2,3-dichloro-5-nitro-1,4-naphthoquinone with 5% sodium bicarbonate in ethanol [18].

The dehalogenation of the compounds **4a** and **5a** in pyridine-dioxane-water in the presence of sodium hydrosulfite under an argon atmosphere gave 1-amino-9-chloro-5*H*-benzo[2,3-*a*]-8-azaphenothiazin-5-one (**7**) and 4-amino-9-chloro-5*H*-benzo[3,2-*a*]-8-azaphenothiazin-5-one (**8**) respectively.



2 3 4 5 6

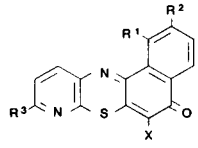
	R^3
2a	Cl
2b	OCH_3

	R^1	R^2
3a	NO_2	H
3b	H	NO_2
3c	Cl	H
3d	H	Cl
3e	H	H

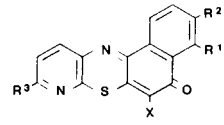
Scheme 1

Table 1

Physical and Analytical Data of Compounds **4**, **5**, **6**, **7**, and **8**



4, 7



5, 8

Compound	R^1	R^2	R^3	X	MP (°C)	Molecular formula	Mass (M^+) (relative intensity %)	Elemental Analysis (%) Found (Calcd.) C	H	N
4a	NO_2	H	Cl	Cl	297-300 [a]	$C_{15}H_5Cl_2N_3O_3S$ 378.2	377/379/381 (100) (62) (13)	47.90 (47.64)	1.23 (1.33)	10.84 (11.11)
5a	NO_2	H	Cl	Cl	339-342 [a]	$C_{15}H_5Cl_2N_3O_3S$ 378.2	377/379/381 (100) (60) (15)	48.01 (47.64)	1.19 (1.33)	10.82 (11.11)
6a	NO_2	H	Cl	—	386-388 [b]	$C_{20}H_7Cl_2N_5O_2S_2$ 484.3	483/485/487 (100) (71) (17)	49.93 (49.60)	1.62 (1.46)	14.21 (14.46)
4b	NO_2	H	OCH_3	Cl	268-270 [b]	$C_{16}H_8ClN_3O_4S$ 373.5	373/374/376 (100) (42) (25)	51.59 (51.42)	1.93 (2.16)	11.26 (11.24)
5b	NO_2	H	OCH_3	Cl	334-336 [c]	$C_{16}H_8ClN_3O_4S$ 373.5	373/374/375 (100) (19) (39)	51.55 (51.42)	2.02 (2.16)	10.95 (11.24)
4c	H	NO_2	Cl	Cl	359-361 [a]	$C_{15}H_5Cl_2N_3O_3S$ 378.2	377/379/381 (100) (64) (14)	47.62 (47.64)	1.25 (1.33)	10.91 (11.11)
5c	H	NO_2	Cl	Cl	300-303 [d]	$C_{15}H_5Cl_2N_3O_3S$ 378.2	377/379/381 (100) (63) (10)	47.44 (47.64)	1.31 (1.33)	10.84 (11.11)
4d	H	NO_2	OCH_3	Cl	310 dec [b]	$C_{16}H_8ClN_3O_4S$ 373.7	373/374/375 (100) (19) (37)	51.24 (51.42)	2.06 (2.16)	11.00 (11.24)
5d	H	NO_2	OCH_3	Cl	300 dec [c]	$C_{16}H_8ClN_3O_4S$ 373.7	373/374/375 (100) (18) (36)	51.80 (51.42)	2.53 (2.16)	10.87 (11.24)
4e	Cl	H	Cl	Cl	268-270 [e]	$C_{15}H_5Cl_3N_2OS$ 367.5	366/368/370 (97) (100) (37)	49.22 (49.01)	1.48 (1.37)	7.43 (7.62)
4f	Cl	H	OCH_3	Cl	327-329 [b]	$C_{16}H_8Cl_2N_2O_2S$ 363.2	362/364/366 (100) (73) (16)	52.87 (52.91)	2.05 (2.22)	7.87 (7.71)
5f	Cl	H	OCH_3	Cl	277-279 [c]	$C_{16}H_8Cl_2N_2O_2S$ 363.2	363/364/366 (100) (75) (16)	53.20 (52.91)	2.55 (2.22)	7.41 (7.71)
4g	H	Cl	Cl	Cl	288-290 [b]	$C_{15}H_5Cl_3N_2OS$ 367.6	366/368/370/372 (96) (100) (44) (6)	49.14 (49.01)	1.31 (1.37)	7.66 (7.62)
5g	H	Cl	Cl	Cl	315-316 [b]	$C_{15}H_5Cl_3N_2OS$ 367.6	366/368/370/372 (96) (100) (34) (6)	48.91 (49.01)	1.28 (1.37)	7.73 (7.62)
4h	H	Cl	OCH_3	Cl	336-338 [b]	$C_{16}H_8Cl_2N_2O_2S$ 363.2	362/364/368 (100) (71) (16)	53.17 (52.91)	2.16 (2.22)	7.55 (7.71)
5h	H	Cl	OCH_3	Cl	342-343.5 [b]	$C_{16}H_8Cl_2N_2O_2S$ 363.2	362/364/368 (100) (78) (17)	52.74 (52.91)	2.12 (2.22)	7.50 (7.71)
4i	H	H	Cl	Cl	250-252 [e]	$C_{15}H_6Cl_2N_2OS$ 333.2	332/334/336 (100) (87) (23)	53.91 (54.07)	1.63 (1.82)	8.38 (8.41)
4j	H	H	OCH_3	Cl	311-312 [b]	$C_{15}H_6Cl_2N_2OS$ 333.2	328/330 (100) (37)	58.56 (58.45)	2.47 (2.76)	8.42 (8.52)
7	NH_2	H	Cl	H	293-296 [b]	$C_{15}H_8ClN_3OS$ 313.8	313/315 (100) (47)	57.55 (57.42)	2.42 (2.57)	13.16 (13.39)
8	NH_2	H	Cl	H	265-267 [b]	$C_{15}H_8ClN_3OS$ 313.8	313/315 (100) (35)	57.27 (57.42)	2.31 (2.57)	13.20 (13.39)

[a] From benzene. [b] From benzene-hexane. [c] From acetone. [d] From benzene-acetyl acetate. [e] From methanol.

The reaction of 2,3,6-trichloro-1,4-naphthoquinone (**3c**) and **2** (R^3 = Cl) produced 1,6,9-trichloro-5*H*-benzo[2,3-*a*]-8-azaphenothiazin-5-one (**4**, R^1 = R^3 = Cl, R^2 = H) selectively.

The structures of all these compounds were supported by their spectra. Thus the ν (C=O) occurred characteristically for the benzophenothiazinones **4** and **5** near 1640 cm^{-1}. The proton at the 10 position absorbed as a doublet (J = 8-8.5 Hz) at 7.0-7.2 ppm for **4** and **5** (R^3 = OCH_3) and 7.7-7.9 ppm for **4** and **5** (R^3 = Cl) respectively. The proton signals at the 11 position usually appeared as a doublet ($J_{10,11}$ = 8-8.5 Hz) at 8.3-8.5 ppm for **4** and **5** except **4** (R^1 = NO_2, R^2 = H, R^3 = Cl, 7.96 ppm) and **4** (R^1 = NO_2, R^2 = H, R^3 = OCH_3, 7.90 ppm). The proton at 1 position absorbed at lower field (8.80-9.50 ppm) than the proton at 4 position (8.25-8.80 ppm). The protons at the 2 and 3 positions showed a doublet or a triplet in the region 7.80-8.80 ppm. Some of the physical and analytical data of the compounds are summarized in Table 1.

EXPERIMENTAL

Melting points were determined with a Yanaco micromelting point apparatus and uncorrected. The ir spectra were recorded on a JASCO A-102 spectrometer using potassium bromide pellets. The uv spectra were obtained with a JASCO UV1DEC-505 spectrometer using 1 cm quartz cells. The absorption maxima are reported in nanometers. The ^{1}H-nmr spectra were obtained in dimethyl sulfoxide-d_6 using a Varian XL-200 spectrometer operating in an FT mode. Chemical shifts are reported in ppm from TMS used as internal standard and are given in δ units. The following abbreviations were used to designate the multiplicity of individual signals: s = singlet, d = doublet and m = multiplet. The ms spectra were recorded on a ESCO EMD-05B spectrometer. For column chromatography, silica gel (Kieselgel 60, Merck, 70-230 mesh) was used.

General Procedure for the Preparation of Substituted 8-aza-6-chloro-5*H*-benzo[*a*]phenothiazin-5-ones, **4a-j** and **5a-h**.

To a suspension of 1 mmole of substituted 2,3-dichloro-1,4-naphthoquinone (**3**) [16] in 60 ml of ethanol were added 1.2 mmoles of thione **2** and 5 ml of 15% hydrochloric acid. The mixture was stirred for 1-6 hours at different temperature from 20° to refluxing. The resulting precipitate was filtered and the filtrate was extracted with benzene. The benzene layer was evaporated *in vacuo*. Then the residue and the precipitate were chromatographed on silica gel eluting with benzene-hexane (3:1), giving **4** and **5** in 70-90% yields.

The Condensation of 5-Nitro-2,3-dichloro-1,4-naphthoquinone (**3a**) with 5-amino-6-chloropyridine-2(1*H*)-thione (**2a**, R = Cl).

Route A.

By the procedure described above, **3a** and **2a** were stirred for 4 hours at 60°. 6,9-Dichloro-1-nitro-5*H*-benzo[2,3-*a*]-8-azaphenothiazin-5-one (**4a**) and 6,9-dichloro-4-nitro-5*H*-benzo[3,2-*a*]-8-azaphenothiazin-5-one (**5a**) were obtained in the yield of 85% in the ratio of 3:1. A small amount of 2,13-dichloro-6-nitro-1,14-diazaphenothiazin-5-one (**6a**) was also obtained.

Route B.

To a suspension of **3a** (816 mg, 3 mmoles) and **2a** (482 mg, 3 mmoles) in ethanol (60 ml) was added 882 mg (9 mmoles) of potassium acetate. The mixture was stirred for 1 hour under refluxing. After workup the resulting residue was chromatographed in the same way described in Route A. From the first and the second fractions 2-chloro-3-ethoxy-5-nitro-1,4-naphthoquinone and 3-chloro-2-ethoxy-5-nitro-1,4-naphthoquinone were obtained. Then from the third blue fraction 347 mg of **6a** (24%), from the fourth red fraction 215 mg of **4a** (19%), and from the fifth fraction 192 mg of **5a** (17%) were obtained respectively.

Compound **4a**.

This compound had ir: 1646 (C=O), 1588 (C=N) cm^{-1}; ^{1}H-nmr (DMSO-d_6): 80°, 8.53 (dd, H-4), 8.18 (dd, H-2), 8.07 (t, H-3), 7.96 (d, H-11), 7.74 (d, H-10); uv (chloroform): λ max, nm (log ϵ), 257 (4.33), 274 (4.24), 288 (sh, 4.13), 332 (4.19), 480 (4.13).

Compound **5a**.

This compound had ir: 1642 (C=O), 1594 (C=N) cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 9.08 (dd, H-1), 8.45 (d, H-11), 8.16 (m, 2H, H-2, H-3), 7.82 (d, H-10); uv (chloroform): λ max, nm (log ϵ), 251 (4.35), 257 (sh, 4.38), 276 (sh, 4.24), 335 (sh, 4.12), 353 (sh, 4.05), 481 (4.17).

Compound **6a**.

This compound had ir: 1569, 1535 cm^{-1}; ^{1}H-nmr [17]; uv (chloroform): λ max (nm), 274, 346, 552, 585 sh.

The Condensation of 5-Nitro-2,3-dichloro-1,4-naphthoquinone (**3a**) with 3-Amino-6-methoxypyridine-2(1*H*)-thione (**2b**, R = OCH_3).

Compounds **3a** and **2b** were stirred for 2 hours at 60° by the general procedure. From the first and the second fraction 6-chloro-9-methoxy-1-nitro-5*H*-benzo[2,3-*a*]-8-azaphenothiazin-5-one (**4b**) and 6-chloro-9-methoxy-4-nitro-5*H*-benzo[3,2-*a*]-8-azaphenothiazin-5-one (**5b**) were obtained respectively in the ratio of 2:1 in 80% yield.

Compound **4b**.

This compound had ir: 1641 (C=O), 1594 (C=N) cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90° 8.51 (dd, H-4), 8.15 (dd, H-2), 8.05 (t, H-3), 7.90 (d, H-11), 7.13 (d, H-10), 4.07 (s, 3H, OCH_3); uv (chloroform): λ max, nm (log ϵ), 260 (4.49), 330 (4.11), 347 (4.11), 363 (4.08), 502 (4.32).

Compound **5b**.

This compound had ir: 1640 (C=O), 1594 (C=N) cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°; 9.09 (d, H-1), 8.35 (d, H-11), 8.11 (d, 2H, H-2, H-3), 7.18 (d, H-10), 4.08 (s, 3H, OCH_3); uv (chloroform): λ max, nm (log ϵ), 260 (4.42), 285 (4.13), 330 (3.95), 346 (4.00), 362 (4.01), 503 (4.28).

The Condensation of 2,3-Dichloro-6-nitro-1,4-naphthoquinone (**3b**) with **2a**.

The suspension of **3b** and **2a** in ethanol was stirred under refluxing for 1 hour to give 6,9-dichloro-2-nitro-5*H*-benzo[3,4-*a*]-8-azaphenothiazin-5-one (**4c**, the first fraction) and 6,9-dichloro-3-nitro-5*H*-benzo[4,3-*a*]-8-azaphenothiazin-5-one (**5c**, the second red fraction) in the ratio of 1:1 in 87% yield.

Compound **4c**.

This compound had ir: 1642 (C=O), 1602 (C=N) cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 9.49 (dd, H-1), 8.64 (d, H-2), 8.54 (d, H-11), 8.48 (d, H-3), 7.79 (d, H-10); uv (chloroform): λ max, nm (log ϵ), 243 (4.49), 273 (4.47), 318 (4.10), 329 (4.11), 352 (4.04), 484 (4.22).

Compound **5c**.

This compound had ir: 1640 (C=O), 1604 (C=N) cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 9.02 (d, H-1), 8.87 (d, H-4), 8.67 (dd, H-2), 8.43 (d, H-11), 7.78 (d, H-10); uv (chloroform): λ max, nm (log ϵ), 274 (4.45), 336 (4.29), 489 (4.14).

The Condensation of **3b** with **2b**.

The mixture of **3b** and **2b** was stirred for 6 hours at room temperature by the general procedure. The reaction mixture was chromatographed on silica gel eluting with benzene-hexane (3:1). From the first red fraction 6-chloro-9-methoxy-2-nitro-5*H*-benzo[3,4-*a*]-8-azaphenothiazin-5-one (**4d**) and from the second fraction 6-chloro-9-methoxy-3-nitro-5*H*-benzo[4,3-*a*]-8-azaphenothiazin-5-one (**5d**) were obtained in the ratio of 1:1.2 (70%).

Compound **4d**.

This compound had ir: 1636 (C=O), 1600 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 9.51 (s, 1H), 8.53 (d, 1H), 8.43 (d, 1H), 7.67 (m, 1H), 7.16 (d, 1H), 4.09 (s, 3H, OCH_3); uv (chloroform): λ max, nm 248, 274, 323 (sh), 333, 358, 506.

Compound **5d**.

This compound had ir: 1641 (C=O), 1599, 1580 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 9.04 (d, 1H), 8.91 (s, 1H), 8.5 (m, 2H), 7.18 (d, 1H), 4.09 (s, 3H, OCH_3); uv (chloroform), λ max, nm: 278, 335 (sh), 355, 510.

Reaction of 2,3,5-Trichloro-1,4-naphthoquinone (**3c**) and **2a**.

The mixture of **3c** and **2a** in ethanol was refluxed for 1 hour to give exclusively 1,6,9-trichloro-5*H*-benzo[2,3-*a*]-8-azaphenothiazin-5-one (**4e**) in 72% yield.

Compound **4e**

This compound had ir: 1648 (C=O), 1575 (C=N); cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 8.31 (d, 2H, H-4, H-11), 8.02 (d, H-2), 7.84 (t, H-3), 7.74 (d, H-10); uv (chloroform): λ max, nm (log ε): 249 (sh, 4.33), 257 (4.36), 273 (4.33), 331 (4.18), 466 (4.17).

Condensation of **3c** and **2b**.

By the general procedure **3c** and **2b** were stirred for 4.5 hours at 40°. After workup the resulting residue was chromatographed on a silica gel column eluting with benzene-hexane (1:1). From the first red fraction 9-methoxy-4,6-dichloro-5*H*-benzo[3,2-*a*]-8-azaphenothiazin-5-one (**5f**) and from the second 9-methoxy-1,6-dichloro-5*H*-benzo[2,3-*a*]-8-azaphenothiazin-5-one (**4f**) were obtained in the ratio of 2:1 in 78% yield.

Compound **4f**.

This compound had ir: 1633 (C=O), 1591 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 8.30 (d, 1H), 8.23 (d, 1H), 7.99 (d, 1H), 7.78 (t, 1H), 7.11 (d, 1H), 4.03 (s, 3H, OCH_3); uv (chloroform): λ max, nm 260, 338, 486.

Compound **5f**.

This compound had ir: 1635 (C=O), 1592 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 8.86 (d, 1H), 8.29 (d, 1H), 8.21 (d, 1H), 7.81 (t, 1H), 7.08 (d, 1H), 4.04 (s, 3H, OCH_3); uv (chloroform): λ max, nm: 259, 339, 355 (sh), 488.

Reaction of 2,3,6-Trichloro-1,4-naphthoquinone (**3d**) and Thione **2a**.

The suspension of **3d** (55 mg, 0.21 mmole) and thione **2a** (51 mg, 0.32 mmole) in 10 ml of ethanol and 2 ml of 15% hydrochloric acid was refluxed for 2 hours with stirring. After workup the reaction mixture was column chromatographed. From the first red fraction 48 mg of 3,6,9-trichloro-5*H*-benzo[4,3-*a*]-8-azaphenothiazin-5-one (**5g**) and from the second 23 mg of 2,6,9-trichloro-5*H*-benzo[3,4-*a*]-8-azaphenothiazin-5-one (**4g**) were obtained in 94% yield.

Compound **4g**.

This compound had ir: 1641 (C=O), 1589 (C=N) cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 8.78 (s, H-1), 8.45 (d, H-11), 8.26 (d, H-4), 7.95 (d, H-3), 7.77 (d, H-10); uv (chloroform): λ max, nm (log ε) 250 (4.10), 271 (4.35), 279 (4.41), 335 (4.19), 475 (4.17).

Compound **5g**.

This compound had ir: 1645 (C=O), 1589 (C=N) cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 8.83 (d, H-1), 8.39 (d, H-11), 8.20 (s, H-4), 8.00 (d, H-2), 7.77 (d, H-10); uv (chloroform): λ max, nm (log ε) 252 (4.51), 272 (sh, 4.48), 2.80 (4.52), 332 (4.16), 352 (sh, 4.09), 378 (4.11), 471 (4.28).

9-Methoxy-2,6-dichloro-5*H*-benzo[3,4-*a*]-8-azaphenothiazin-5-one (**4h**) and 9-methoxy-3,6-dichloro-5*H*-benzo[4,3-*a*]-8-azaphenothiazin-5-one (**5h**).

To a stirred suspension of 2,3,6-trichloro-1,4-naphthoquinone (**3d**) (130 mg, 0.5 mmole) was added 110 mg (0.7 mmole) of thione **2b** and then the mixture was stirred for 2 hours at 60°. After the workup in the same way as the general procedure 71 mg of **5h** and 96 mg of **4h** were obtained from the first red fraction and the second fraction respectively in the ratio of 1:1.5 in 92% yield.

Compound **4h**.

This compound had ir: 1638 (C=O), 1589 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 8.77 (s, 1H), 8.33 (d, 1H), 8.25 (d, 1H), 7.88 (d, 1H), 7.12 (d, 1H), 4.06 (s, 3H, OCH_3); uv (chloroform): λ max, nm (log ε) 254 (sh, 4.49), 262 (4.53), 284 (sh, 4.27), 339 (4.22), 356 (sh, 4.13), 491 (4.33).

Compound **5h**.

This compound had ir: 1649 (C=O), 1600, 1590 cm^{-1}; ^{1}H-nmr [17]; uv (chloroform): λ max, nm (log ε) 263 (4.50), 326 (3.99), 340 (sh, 3.98), 358 (3.97), 383 (3.83), 490 (4.29).

6,9-Dichloro-5*H*-benzo[*a*]-8-azaphenothiazin-5-one (**4i**).

This compound was prepared from the reaction of 2,3-dichloro-1,4-naphthoquinone (**3e**, 182 mg, 0.8 mmole) and thione **2a** (154 mg, 0.96 mmole) in the same way as the procedure described above. From the reaction mixture 200 mg of **4i** was isolated in 75% yield.

Compound **4i**.

This compound had ir: 1653 (C=O), 1580 (C=N) cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 8.83 (dd, H-1), 8.48 (d, H-11), 8.28 (dd, H-4), 7.95 (m, 2H, H-2, H-3), 7.76 (d, H-10); uv (chloroform): λ max, nm (log ε): 248 (4.36), 266 (4.31), 274 (4.36), 285 (4.17), 333 (4.11), 370 (sh, 3.91), 466 (4.14).

9-Methoxy-6-chloro-5*H*-benzo[*a*]-8-azaphenothiazin-5-one (**4j**).

The mixture of 2,3-dichloro-1,4-naphthoquinone (0.5 mmole) and 0.6 mmole of thione **2b** in 20 ml of ethanol and 3 ml of 15% hydrochloric acid was stirred for 1 hour at 60°. After workup 131 mg of **4j** was obtained in 80% yield.

Compound **4j**.

This compound had ir: 1638 (C=O), 1588 (C=N) cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 8.84 (m, H-1), 8.30 (d, 2H, H-4, H-11), 7.91 (m, 2H, H-2, H-3), 7.12 (d, H-10), 4.06 (s, 3H, OCH_3); uv (chloroform): λ max, nm (log ε) 257 (4.52), 336 (4.16), 353 (4.06), 375 (sh, 3.85), 484 (4.34).

1-Amino-9-chloro-5*H*-benzo[2,3-*a*]-8-azaphenothiazin-5-one (**7**).

This compound was prepared from the dehalogenation of **4a**. Then to the suspension of **4a** (57 mg, 0.15 mmole) in benzene (10 ml), water (10 ml), and dioxane (5 ml) were added 10 ml of pyridine and 450 mg of sodium hydrosulfite under argon atmosphere. The mixture was refluxed for 4 hours and poured into 100 ml of water and extracted with benzene. After removing the solvent the residue was chromatographed on a silica gel column eluting with benzene. 32 mg of **7** was obtained in 69% yield.

Compound **7**.

This compound had ir: 3390 (NH_2), 1619 (C=O), 1595 (C=N); cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 8.30 (m, 3H), 7.56 (m, 1H), 7.48 (m, 2H), 7.28 (m, 1H), 6.96 (s, 1H, iminoquinone H); uv (chloroform): λ max, nm (log ε) 249 (4.53), 277 (4.16), 335 (3.94), 457 (4.03), 514 (4.02).

4-Amino-9-chloro-5*H*-benzo[3,2-*a*]-8-azaphenothiazin-5-one (**8**).

This compound was prepared from **5a** in 65% yield as the method was reported for **7** (refluxed for 1 hour).

Compound **8**.

This compound had ir: 3470 and 3313 (NH_2), 1615, 1600, 1578, 1540 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 90°, 8.12 (m, 2H), 7.98 (m, 1H), 7.56 (m, 3H), 7.14 (d, 1H), 6.82 (s, 1H, iminoquinone H); uv (chloroform): λ max, nm (log ε) 249 (4.55), 276 (4.21), 335 (4.07), 435 (3.79), 461 (3.78), 538 (4.01).

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REFERENCES AND NOTES

[1] S. P. Massie, *Chem. Rev.*, **54**, 797 (1954).

[2] D. E. Pearson, in "Heterocyclic Compounds", by R. C. Elderfield, ed, Vol. **6**, John Wiley and Sons, NY, 1957, p 624.

[3] C. R. Thompson, *Ind. Eng. Chem.*, **42**, 922 (1950).

[4] E. Schenker and H. Herbest, *Progr. Drug Res.*, **5**, 269 (1963).

[5] F. Mietzsch, *Angew. Chem.*, **66**, 363 (1954).

[6] H. B. Collier and S. C. Mcrae, *Can. J. Med. Sci.*, **31**, 195 (1953).

[7] M. Ashikaga, *Okayama Igakkai Zasshi*, **66**, 977 (1954).

[8] M. Akatsuka and S. Yoshinaga, *Yakugaku Zasshi*, **90**, 154 (1970).

[9] N. L. Agarwal, S. Ghosh, A. K. Tripathi and C. K. Atal, *J. Heterocyclic Chem.*, **21**, 509 (1984).

[10] S. Nan'ya, E. Maekawa, W. B. Kang and Y. Ueno, *J. Heterocyclic Chem.*, **23**, 589 (1986).

[11] W. B. Kang, S. Nan'ya, Y. Yamaguchi, E. Maekawa, and Y. Ueno, *ibid.*, **24**, 91 (1987).

[12] Y. Ueno, S. Nan'ya, H. Hayakawa, W. B. Kang and E. Maekawa, *Monatsh. Chem.*, **118**, 318 (1987).

[13] Y. Guindon, *et al.*, U. S. US 4,611,056 (1986); *Chem. Abstr.*, **106**, 33082p (1987).

[14] Y. Ueno, *Pharmazie*, **41**, 144 (1986).

[15] C. O. Okafor, *J. Org. Chem.*, **47**, 592 (1982).

[16] T. Kasai and R. Kurabayashi, *Yuki Gosei Kagaku Kyokai Shi*, **28**, 70 (1970).

[17] No ^{1}H nmr data were recorded because of its insolubility even in dimethyl sulfoxide-d_6 solution at 90° in the FT mode.

[18] W. B. Kang, S. Nan'ya, E. Maekawa, and Y. Ueno, unpublished work.