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A NEW TYPE OF ANGULAR PHENOTHIAZINE RING SYSTEM

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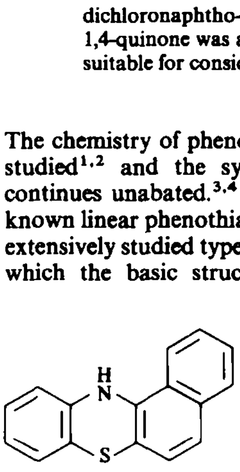
Abstract—The first synthesis of monoaza- and diaza-analogues of benzo[a]phenothiazine ring system is achieved under anhydrous conditions by base-catalysed reaction of *o*-aminoheterocyclic thiones with 2,3-dichloronaphtho-1,4-quinone. If the reactions were carried out in methanol, 2-chloro-3-methoxynaphtho-1,4-quinone was also isolated. The ease of air oxidation of the $Na_2S_2O_4$ reduced compounds makes them suitable for consideration as vat dyes.

The chemistry of phenothiazine has been extensively studied[1,2] and the synthesis of its aza-analogues continues unabated.[3,4] In addition to the now well-known linear phenothiazines, there is another but less extensively studied type of phenothiazine derivative in which the basic structure is angular. This is the benzo[a]phenothiazine structure (1).[5,6] Whereas all the four monoaza- and ten out of the fifteen isomeric linear diazaphenothiazines have been synthesized,[7,8] none of the angular azaphenothiazines of type 2 have been reported. We wish therefore to report our successful synthesis of the first monoaza- and diaza-phenothiazine ring systems of type 2.



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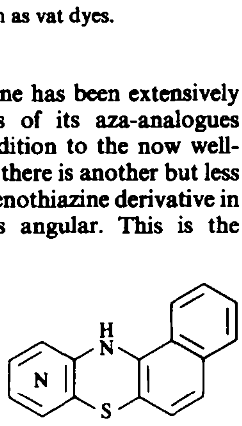

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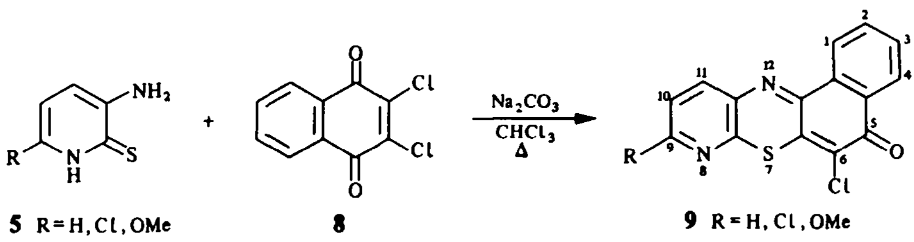
3-Amino-6-substitutedpyridines (3) were treated with sodium thiocyanate and bromine in glacial acetic acid at 0° followed by neutralization with concentrated ammonia. The resulting 2-aminothiazolo[5,4-b]pyridines (4) were converted to 3-amino-6-substituted-pyridine-2[1H]-thiones (5) in excellent yields. 3-Aminopyridine-2[1H]-thione, 5, R = H, which is not substituted with an *o,p*-director could not be prepared in this way. However, two modified procedures[7,11] gave satisfactory yields of this compound in small quantities. Unlike our method,[7] Rodig *et al.*'s procedure[11] is unsuitable for scale-up reactions because of the reported explosion that occurred during the conversion of nicotinamide to 3-amino-2-chloropyridine probably due to a high build-up of perchlorate ions in solution.

An equimolar mixture of the well-dried 3-aminopyridine-2[1H]-thione, 5, R = H and 2,3-dichloronaphtho-1,4-quinone (8) in chloroform was treated with anhydrous sodium carbonate and refluxed for 2–3 hr (Scheme 1). After workup, the product was recrystallized from aqueous acetone to give brown microneedles of 6-chlorobenzo[a]-8-azaphenothiazin-5-one, 9, R = H, in 88% yield. Microanalysis, NMR and mass spectroscopy agree with the assigned structure. The IR spectrum gave a CO band at 1658 cm^{-1}. In the same way, 6,9-dichloro- (9, R = Cl) and 6-chloro-9-methoxybenzo[a]-8-azaphenothiazin-5-ones (9, R = OMe) were obtained in 90 and 94% yields by the use of 5, R = Cl and OMe, respectively.

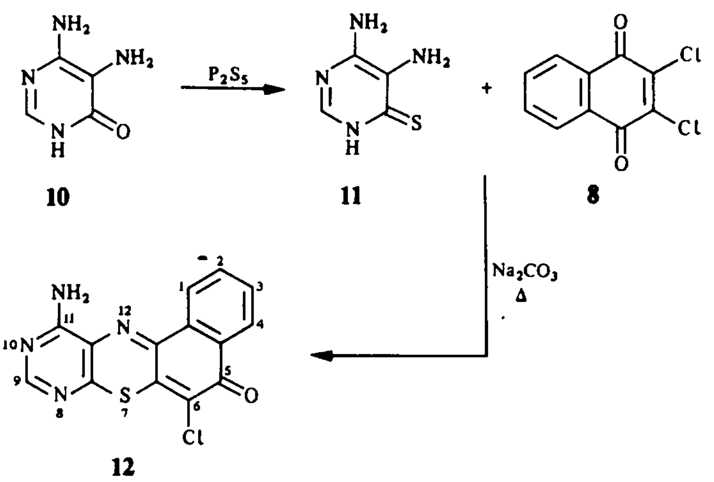
Conversion of 4,5-diaminopyrimidin-6[1H]-one (10) to the corresponding thione (11) by refluxing with P_2S_5 in dried pyridine followed by treatment with a stoichiometric amount of 2,3-dichloronaphtho-1,4-quinone (8) in the presence of anhydrous sodium carbonate gave 98% yield of 11-amino-6-chlorobenzo[9]-8,10-diazaphenothiazin-5-one (12) as purple–red microneedles (Scheme 2). Again, spectroscopic data are in perfect agreement with the assigned structure.

Treatment of these angular monoaza- and diaza-phenothiazin-5-ones (9, R = H, Cl, OMe and 12) with near 1:1 molar ratio of 30% hydrogen peroxide converted them to their sulfoxides, 13 and 14. The reagent is probably not strong enough to oxidize the ring N atoms.[12] The ease of oxidation of these compounds to the sulfoxides suggests their applicability as antioxidants in grease.

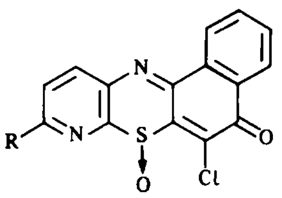
Reduction of these angular azaphenothiazin-5-ones to the corresponding azaphenothiazin-5-ols, 15 and 16, was achieved by the use of sodium dithionite. However,



Scheme 1.



Scheme 2.



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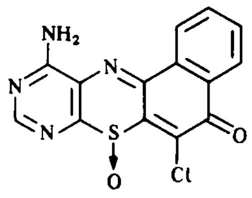

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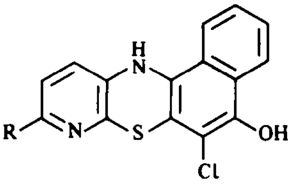

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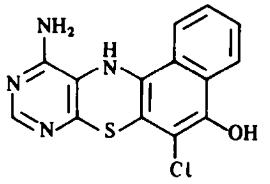

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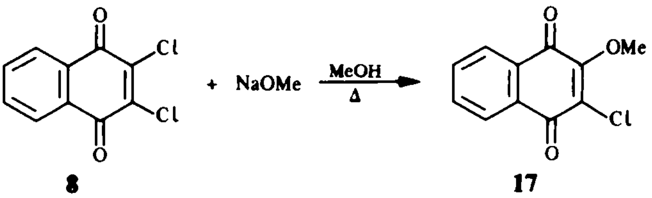
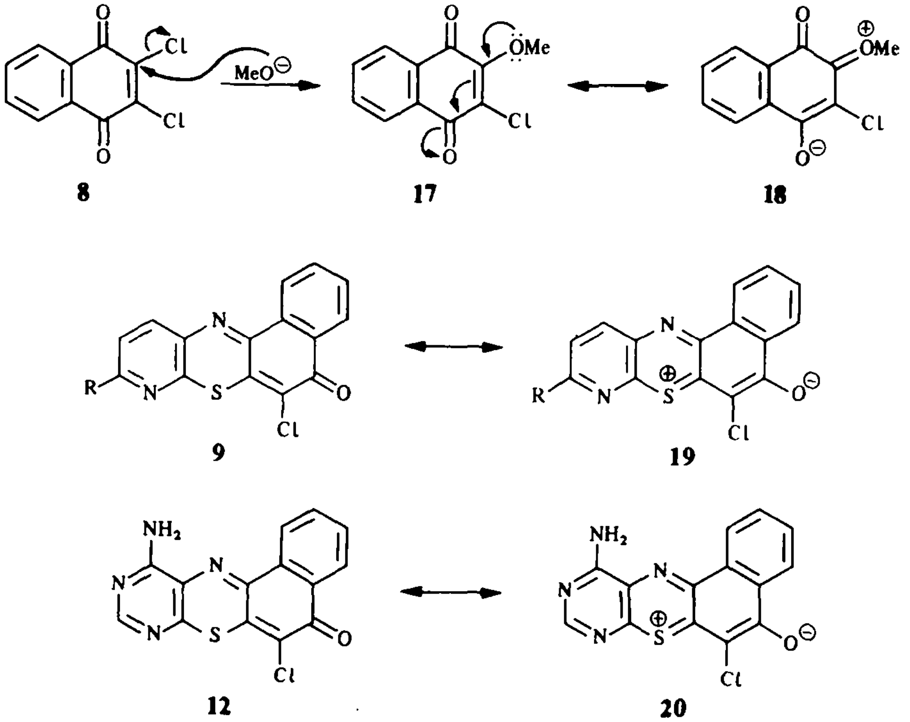
the products are too unstable to be isolated in the pure state as they revert back, under the atmospheric conditions, to the oxidized and intensely coloured quinoid compounds, 9, R = H, Cl, OMe and 12. Owing to this property, these angular monoaza- and diazaphenothiazin-5-ones may be applied in textile industries as vat dyes for textile materials if they satisfy such other conditions as fastness to light, solvent and soap.

If the reactions of 5, R = H, Cl, OMe and 11 with 2,3-dichloronaphtho-1,4-quinone (8) were carried out in methanol, two products, A and B, were isolated in each case. Product A was the expected angular azaphenothiazin-5-one (9, R = H, Cl, OMe; 12). Product B was later identified as 2-chloro-3-methoxynaphtho-1,4-quinone (17) from its microanalysis, IR, UV, NMR and mass spectra. An authentic material was prepared by refluxing 2,3-dichloronaphtho-1,4-quinone with methanol in the presence of sodium methoxide, thereby establishing its structure as 17. Use of excess sodium methoxide did not lead to the displacement of the second Cl atom. This shows that the reactivity of the halogen is considerably reduced by the replacement of one of them with an electron releasing group. It therefore means that the resonance structure 18 makes an appreciable contribution to the overall structure of the compound. The structure of product B is therefore a mixture of structures 17 and 18. Similarly such resonance forms as 19 and 20 are responsible for the low reactivity of the C-6 halogen atom of 9 and 12. Such resonance structures as 19 and 20 are expected to increase the C=O bond lengths. This will result in the reduction of the CO frequency as was observed in the IR spectra of these compounds. As





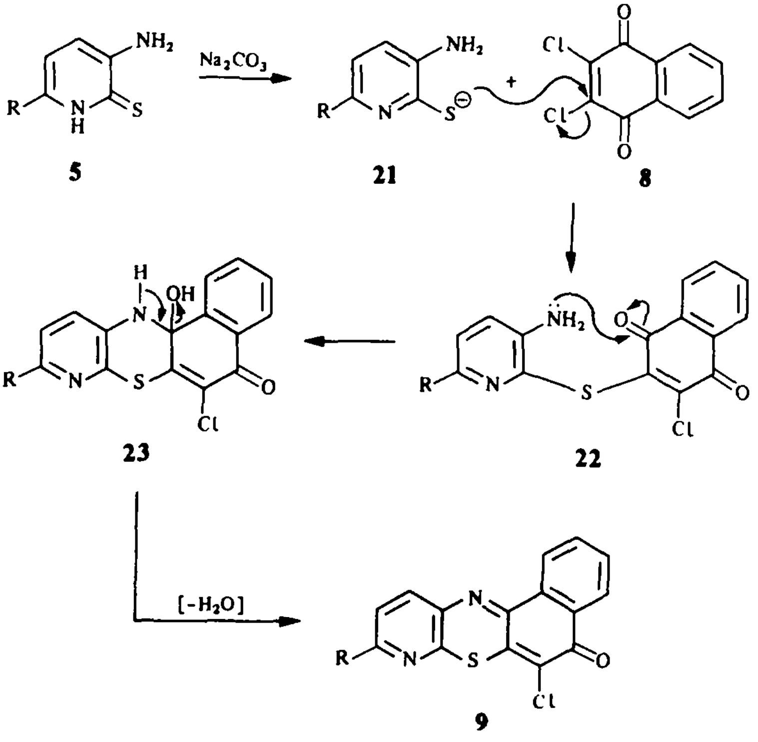
8 **17** **18**

9 **19**

12 **20**

further support for this model, condensation of **9**, **12** and **17** with a second mole of the *o*-aminoheterocyclic thione under the same conditions was unsuccessful; the starting materials were recovered.

These angular monoaza- and diazaphenothiazines are probably formed by the initial nucleophilic attack of the mercaptide ion, **21**, on C-2 of the 2,3-dichloronaphtho-1,4-quinone (**8**) leading to loss of sodium chloride (Scheme 3). Condensation of a naphthoquinone carbonyl with the 3-amino group in the pyridine moiety (**22**) would lead to the isolated 6-chlorobenzo[a]-8-azaphenothiazin-5-ones, **9**, R = H, Cl, OMe. In a similar way the formation of **12** can be rationalized.



5 **21** **8**

23 **22**

9

Scheme 3.

EXPERIMENTAL

General. M.ps were determined with a Fisher–Johns apparatus and are uncorrected. UV and visible spectra were recorded on a Pye Unicam SP 8000 spectrophotometer using matched 1 cm quartz cells. The solvent was MeOH, and the absorption maxima are given in nanometers; the figures in parentheses are ε values. IR spectra were obtained on a Perkin–Elmer 137 spectrophotometer using KBr discs unless otherwise stated. ^{1}H-NMR spectra were determined on a Varian Associates T-60 instrument. Chemical shifts are reported on the δ scale relative to tetramethylsilane (TMS) used as an internal standard. The letters br, s, d, t, q, sh and m are used to indicate, broad, singlet, doublet, triplet, quartet, shoulder and multiplet, respectively. The mass spectra were obtained on an AE1 MS-9 double-focusing mass spectrometer at 70eV.

3-*Amino-6-substitutedpyridine*-2[1H]-*thiones* (**5**, R = Cl, OMe). These compounds were prepared as previously reported[9] except that purification was done by crystallization from chloroform. The crystalline product was oven dried and preserved in a desiccator until it was ready for use.

3-*Aminopyridine*-2[1H]-*thione* (**5**, R = H). Two methods are available for the preparation of this compound. Rodig *et al.*'s modified method,[11] although successful in small quantities, suffers from a major handicap due to a violent explosion which occurred when the reaction was scaled up. This was probably due to a heavy buildup of the explosive perchlorate ions. The three-step method,[7] starting from 2-amino-3-nitropyridine, is therefore preferable.

2,3-*Dichloronaphtho*-1,4-*quinone* (**8**). 2,3-Dichloronaphtho-1,4-quinone used for these reactions was recrystallized from ethanol (Norit) and dried both in the oven and desiccator.

6-*Chlorobenzo*[a]-8-*azaphenothiazin-5-one* (**9**, R = H). To a suspension of 3-aminopyridine-2[1H]-thione (2.52 g, 20 mmol) in 80 ml of chloroform was added anhyd Na_2CO_3 (2.12 g, 20 mmol) in the reaction flask. The mixture was warmed to boiling temp. 2,3-Dichloronaphtho-1,4-quinone (4.54 g, 20 mmol) was added and the mixture refluxed on a water bath with magnetic stirring for 3 hr.

The solvent was distilled off *in vacuo*. The dark solid was taken up in water, warmed and filtered to remove the inorganic salts. The dark residue was crystallized twice from aqueous dimethylacetamide after treatment with activated charcoal. Compound **9** (R = H) (5.25 g, 88% yield) was obtained as glistening brown needles; m.p. 136–137°; UV λ_{max} (MeOH) 245 nm (ε 16,617), 250 (16,636), 325 (4338), 498 (2388); IR (KBr) ν_{max} 1658 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) δ 7.87 (m, aromatic-H's); MS *m/e* (relative intensity) 298 (100%, M^+), 300 (38.8%) (M + 2). (Found: C, 60.22; H, 2.39; N, 9.50; S, 10.70; Cl, 12.02. Calc for $C_{15}H_7N_2ClOS$: C, 60.30; H, 2.35; N, 9.38; S, 10.72; Cl, 11.89%.)

6,9-*Dichlorobenzo*[a]-8-*azaphenothiazin-5-one* (**9**, R = Cl). This compound is prepared from **5** (R = Cl) (1.61 g, 10 mmol), **8** (2.2 g, 10 mmol) and anhyd Na_2CO_3 (1.06 g, 10 mmol) in chloroform as reported for **9**, R = H. Red microcrystals of **9** (R = Cl) (3.00 g, 90% yield) were obtained; m.p. > 250°; UV λ_{max} (MeOH) 245 nm (ε 17,982), 251 (18,049), 328 (5994), 462 (5594); IR ν_{max} 1645 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) δ 8.05 (m, aromatic-H's). (Found: C, 53.90; H, 1.85; N, 8.58; S, 9.44; Cl, 21.30. Calc for $C_{15}H_6N_2SClO$: C, 54.05; H, 1.80; N, 8.41; S, 9.61; Cl, 21.32%.)

6-*Chloro*-9-*methoxybenzo*[a]-8-*azaphenothiazin*-5-*one* (**9**, R = OMe). From 30 mmol of each of **5** (R = OMe), **8** and Na_2CO_3 in chloroform was obtained **9** (R = OMe) as described for **9** (R = H). This compound was isolated in 94% yield as bluish-purple microneedles; m.p. 273–274° (dec); UV λ_{max} (MeOH) 256 nm (ε 9357), 335 (3662), 480 (5655); IR ν_{max} 1634 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) δ 4.00 (s, 9-OMe), 8.69 (s, 11-H), 8.00 (m, 1-H, 2-H, 3-H, 4-H, 10-H); MS *m/e* (relative intensity), 328 (100%, M^+), 330 (39%) (M + 2). (Found: C, 58.64; H, 2.71; N, 8.68; S, 9.55; Cl, 10.78. Calc for $C_{16}H_9N_2SClO_2$: C, 58.45; H, 2.74; N, 8.52; S, 9.74; Cl, 10.81%.)

4,5-*Diaminopyrimidine*-6[1H]-*thione* (**11**). This compound was prepared from **10** as previously described[13] except that the pyridine used was dried over NaOH pellets.

11-*Amino*-6-*chlorobenzo*[a]-8,10-*diazaphenothiazin*-5-*one* (**12**). Anhyd Na_2CO_3 (2.12 g, 20 mmol) was added to a suspension of **11** (2.84 g, 20 mmol) in 100 ml of chloroform. The mixture was warmed to dissolve. Compound **8** (4.54 g, 20 mmol) was added and the entire slurry refluxed on a water bath with stirring for 3.5 hr.

Chloroform was distilled off and the solid product taken up in warm water (100 ml). The mixture was filtered and the filtrate discarded. The residue was crystallized from aqueous dimethylformamide after treatment with activated charcoal to yield purple–red microneedles of **12** (6.16 g, 98% yield); m.p. > 310° (dec); UV λ_{max} (MeOH) 234 nm (ε 16,249), 279 (17,298), 329 (9524), 476 (9763); IR (KBr) ν_{max} 1633 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) δ 9.03 (s, 9-H), 8.12 (m, 1-H, 2-H, 3-H, 4-H), 7.71 (br, 11-NH_2); MS *m/e* (relative intensity) 314 (100%, M^+), 316 (38) (M + 2). (Found: C, 53.26; H, 2.30; N, 17.60; S, 10.28; Cl, 11.17. Calc for $C_{14}H_7N_4SClO$: C, 53.42; H, 2.22; N, 17.81; S, 10.17; Cl, 11.29%.)

6-*Chlorobenzo*[a]-8-*azaphenothiazin-5-one 7-oxide* (**13**, R = H). A suspension of 6-chlorobenzo[a]-8-azaphenothiazin-5-one (2.99 g, 10 mmol) and 10 ml of glacial AcOH in 100 ml of MeOH was treated with 1.4 ml of 30% H_2O_2. The mixture was refluxed for 10 hr. The soln was concentrated *in vacuo* leaving a dark yellow oil. Water was added and the mixture neutralized with concentrated ammonia. Five successive extractions with petroleum ether gave a dull yellow solid. Recrystallization from aqueous acetone yielded **13**, R = H (1.83 g, 58% yield) as a yellow powder, m.p. > 300° (dec); IR (KBr) ν_{max} 1650 (C=O), 1042 cm^{-1} (S=O). (Found: C, 57.03; H, 2.30; N, 8.75; S, 10.19; Cl, 11.33. Calc for $C_{15}H_7N_2SClO_2$: C, 57.23; H, 2.23; N, 8.90; S, 10.18; Cl, 11.29%.)

6,9-*Dichlorobenzo*[a]-8-*azaphenothiazin*-5-*one* 7-*oxide* (**13**, R = Cl). This compound was prepared in 45% yield as was reported for **13**, R = H; m.p. > 250° (dec); IR ν_{max} 1645 (C=O), 1028 cm^{-1} (S=O). (Found: C, 51.71; H, 1.70; N, 7.88; S, 9.02; Cl, 20.50. Calc for $C_{15}H_6N_2SCl_2O_2$: C, 51.58; H, 1.72; N, 8.02; S, 9.17; Cl, 20.34%.)

6-*Chloro*-9-*methoxybenzo*[a]-8-*azaphenothiazin*-5-*one* 7-*oxide* (**13**, R = OMe). This compound was obtained in 62% yield as described for **13**, R = H; m.p. > 300° (dec); IR ν_{max} 1630 (C=O), 1035 cm^{-1} (S=O). (Found: C, 55.90; H, 2.55; N, 8.02; S, 9.28; Cl, 10.44. Calc for $C_{16}H_9N_2SClO_3$: C, 55.73; H, 2.61; N, 8.13; S, 9.29; Cl, 10.31%.)

11-*Amino*-6-*chlorobenzo*[a]-8,10-*diazaphenothiazin*-5-*one* 7-*oxide* (**14**). This compound was prepared in 42% yield using the procedure described earlier for **13**, R = H; m.p. > 300° (dec); IR ν_{max} 1645 (C=O), 1048 cm^{-1} (S=O). (Found: C, 51.01; H, 2.08; N, 17.00; S, 9.49; Cl, 10.62. Calc for $C_{14}H_7N_4SClO_2$: C, 50.83; H, 2.12; N, 16.95; S, 9.68; Cl, 10.74%.)

Reduction of compounds **9**, R = H, Cl, OMe *and* **12** *with sodium dithionite.* In a typical experiment, 6-chloro-9-methoxybenzo[a]-8-azaphenothiazin-5-one (**9**, R = OMe) (3.29 g, 10 mmol) was placed in the reaction flask containing 5 ml of water and 100 ml of acetone. Sodium dithionite (5 g) was then added and the mixture refluxed on a water bath for 3 hr. During the reflux period, the colour changed from brown to yellow.

The entire mixture was poured into a soln of 5 g of sodium dithionite in 800 ml of ice-cold water and stirred. It was quickly filtered by suction but before the product could be collected from the filter paper, it had turned bluish-purple. Analysis of this purple solid confirmed that the reduced product had been oxidized to the starting compound by atmospheric oxygen.

Reaction of 2,3-*dichloronaphtho*-1,4-*quinone* (**8**), *with* 3-*aminopyridine*-2[1H]-*ones*, **5**, R = H, Cl, OMe *in methanol.* The procedure for these reactions is similar to the method described for **9**, R = H, Cl, OMe except that the solvent for the reaction is methanol instead of chloroform.

At the work up stage, the first product is the expected angular phenothiazin-5-ones, **9**, R = H, Cl, OMe. The next crop was recrystallized twice from ethanol after treatment with activated charcoal to yield 2-chloro-3-methoxynaphtho-1,4-

quinone, **17**, as greenish yellow plates, m.p. 147–148°; UV λ_{max} (MeOH) 245 nm (ε 23,363), 250 (22,621), 326 (7343), 500 (1113); IR (Nujol) ν_{max} 1670 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) δ 4.21 (s, 3-OMe), 7.90 (m, 5-H, 6-H, 7-H, 8-H); MS *m/e* (relative intensity) 222 (100%, M$^+$), 224 (38). (Found: C, 59.38; H, 3.07; Cl, 16.10. Calc for $C_{11}H_7ClO_3$: C, 59.32; H, 15, Cl, 15.96%.)

2 - *Chloro* - 3 - *methoxynaphtho* - 1,4 - *quinone*, **17**. Methanol (200 ml) was added to a mixture of 2,3-dichloronaphtho-1,4-quinone (**8**) (2.27 g, 10 mmol) and sodium methoxide (0.81 g, 15 mmol). The mixture was refluxed for 4 hr. It was then poured into 1 l of ice-cold water and chilled. The yellow solid was collected by filtration and crystallized from aqueous dimethylformamide after treatment with activated charcoal to give **17** as greenish yellow plates, m.p. 147–148°. This product is identical to the side product from the reaction of **8** with **5** in methanol.

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