

# Synthesis of New Tetracyclic And Hexacyclic Non-linear Phenothiazine Derivatives

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## ABSTRACT:

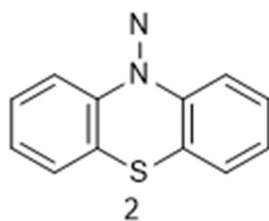
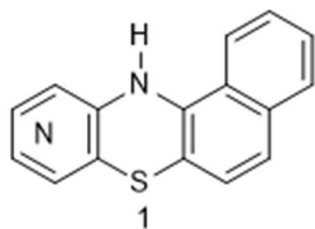
The synthesis of 6-chloro-11-azabenz[a]phenothiazine-5-one is described. This was achieved under anhydrous condition by alkaline catalyzed reaction of 2-aminopyridine-3-thiol and 2, 3-dichloro-1,4-naphthoquinone. Also described in this work is the synthesis of 6,15-diazabenz[a][1,4]benzothiazino[3,2-c]phenothiazine which was achieved by the condensation of 6-chloro-11-azabenz[a]phenothiazine-5-one with a second molecule of 2-aminopyridine-3-thiol in an alkaline medium. The ease of oxidation of these sodium dithionite ( $\text{Na}_2\text{S}_2\text{O}_3$ ) reduced compounds as well as the oxidation of these new compounds with hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) to sulphoxide make them suitable to be considered as a vat dyes and antioxidants in the textile and petroleum industries respectively.

**Keywords:** Aminopyridine-3-thiol, 6-Chloro-11-azabenz[a]phenothiazines-one 2,3-Chloro-1,4-naphthoquinone, 6,15-diazabenz[a][1,4]benzothiazino[3,2-c]phenothiazine, hydrolysis.

## 1 INTRODUCTION:

The biological and industrial importance of phenothiazines derivatives, especially the non-linear aza analogues of the types **1** as described in the literature revealed that these heterocyclic compounds are indispensable

due to their wide range of applications as drugs [1] [2] [3], dyes [4] [5] and pigment [6] [7], antioxidants in fuel and grease [8] pesticides [9], polymerization indicators [10] etc.



Although the chemistry of the linear phenothiazine of the type **2** has been known over a century ago, that of the non-linear analogue of the type **3** has remained poorly developed [11]. Recently attention has been focus on the synthesis of these non-linear azaphenothiazines and their derivation due to their superiority over the linear types. Owing to few reports on these types of compounds, we describe here the successful synthesis of 6-chloro-11-azabenz[a]phenothiazin-5-one, and 6,15-diazabenz[a][1,4]-benzothiazino[3,2-c]phenothiazine, new tetra and hexa cyclic non-linear azaphenothiazine derivatives of industrial importance.

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## 2 EXPERIMENTAL

Melting points were determined in open capillary tube and are uncorrected. IR spectra were recorded in KBr on a Fourier transform infrared spectrophotometer. UV-vis spectra in DMF on a Jenway 640 UV/Vis Spectrophotometer using 1cm quartz cell. <sup>1</sup>H-NMR and C-NMR were recorded on JEOL-AL-400 spectrophotometer (400MHz) in DMSO -d<sub>6</sub> (chemical shift are reported on the  $\sigma$  scale relative to tetramethylsilane (TMS) as internal standard. Analytical samples were obtained by column chromatography on aluminum oxide 90 (Merck, 70 – 230 Mesh ASTM) employing benzene-chloroform (1:1) as an eluent before recrystallization. Compound **6** was prepared as previously reported in the literature.

### 6-Chloro-11-azabenz[a]phenothiazin-5-one (**9**)

2-Aminopyridine-3(1H)-thione **6** (5.10, 0.04mole) was placed in a reaction flask containing DMF (5ml) and benzene (50ml). Sodium carbonate (7.10g, 0.06mole) was added and the mixture heated at 75°C with stirring for 45 minutes. 2,3-dichloro-1,4-naphthoquinone **8** (6.10g, 0.027mole) was added and the resulting mixture heated under reflux for 7hours. At the end of the

refluxing period, the resulting reddish liquor was poured onto crushed ice (200g) stirring and the solid was collected by filtration. It was then treated with water, filtered and the residue allowed to dry. The dried residue was subjected to column chromatography on aluminum oxide using benzene chloroform (1:1) as eluent. The first yellow band eluted was the unreacted 2, 3-chloro 1,4-naphthoquinone **8**. The second and reddish band was collected give **9** (5.50g, 53%) as a reddish crystalline product m.p >190°C. UV-vis max 327nm ( $\epsilon=1.844$ ), 343nm ( $\epsilon=1.934$ ). IR(KBr): 3097 $\text{cm}^{-1}$  (C-H, Aromatic), 1672 $\text{cm}^{-1}$  (C=O), 1559 (C=N), 1263 $\text{cm}^{-1}$  (C-N, C=C), 1124 $\text{cm}^{-1}$ , 811 $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  8.27 (d, 9-H, 10-H),  $\delta$ 8.05 (d, 4-H, 8-H),  $\delta$ 7.9 (d, 1-H, 2-H, 3-H).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ):  $\delta$ 176.43 (C=O),  $\delta$ 135.21 (1C, s),  $\delta$ 131.48 (1C, s), 127.6 (1C, s),  $\delta$  40.27(6C, m),  $\delta$  39.86(5C, m).

#### **6-Chloro-11-azabenz[a]phenothiazin-5-one-7-oxide (15)**

A solution of 6-chloro-11-azabenz[a]phenothiazin-5-one (3.0g, 0.020mole) and glacial acetic acid (10ml) in methanol (90ml) was treated with 30%  $\text{H}_2\text{O}_2$  (2ml). The mixture was refluxed for 6hours. The solution was concentrated using a water bath leaving a dark yellow oily substance. Water was added and the mixture

neutralized with concentrated ammonia and extracted thrice with petroleum ether to give a yellow solid. This was crystallized from acetone to give **15**(1.50g, 50%) as a bright yellow powder m.p > 250°C. IR = 1650 $\text{cm}^{-1}$  (C=O), 1056 $\text{cm}^{-1}$  (S=O).

#### **Reduction of 6-Chloro-11-azabenz[a]phenothiazin-5-one (9)**

Compound **9**(0.010mole) was placed in a reaction flask containing water (10ml) and acetone (40ml). Sodium dithionite (2.5g) was added and the mixture refluxed on a water bath for 3hours. During the refluxing period, the color changed from red to light yellow. The content of the flask was poured onto a solution of  $\text{Na}_2\text{S}_2\text{O}_3$  (2.5ml) in ice-cold water (300ml) and stirred. The mixture was quickly filtered under suction; however, before the product could be obtained from the filter paper, it had reverted to the original reddish color of the iminoquinoid compound **9**. This is due to autoxidation in the presence of atmospheric oxygen, which was facilitated by the addition of hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) [12].

#### **6,15-diazabenz[a][1,4]benzothiazino[3,2-c]phenothiazine 16**

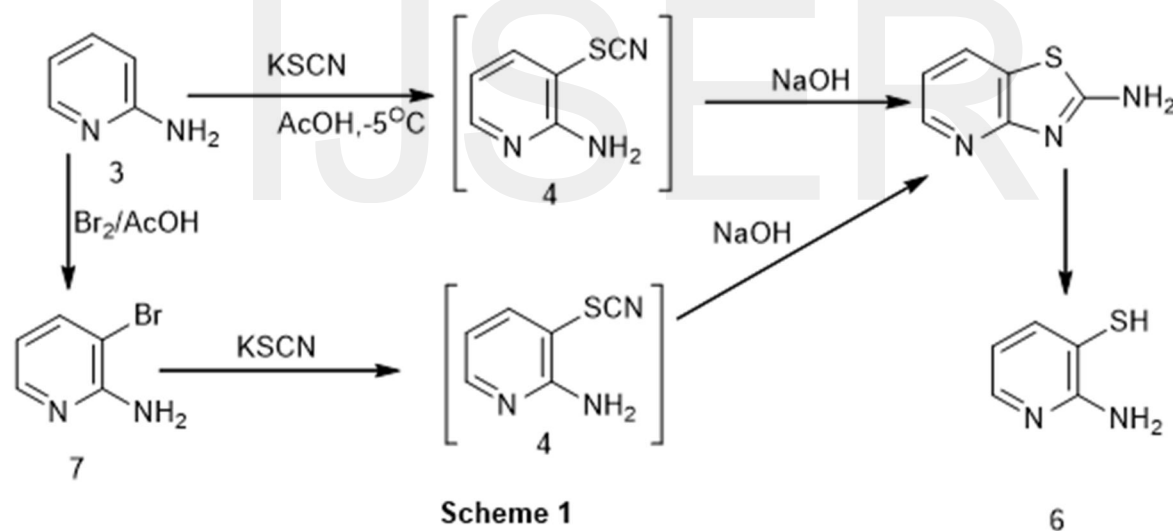
2-Aminopyridine-3-thiol (0.04mole) was placed in a reaction flask containing DMF (5ml) and benzene (50ml). Sodium carbonate (0.065mole) was added and the mixture

heated at 75°C with stirring for 45 minutes. 6-Chloro-11-azabenz[*a*]-phenothiazin-5-one (0.065 mole) was added and the resulting mixture heated under reflux for 7 hr. At the end of the refluxing period, the reddish-brown liquor was poured onto crushed ice (200g), stirred and filtered and the residue allowed to dry. The dried residue was subjected to column chromatography on aluminum oxide using benzene-chloroform (1:1) as eluent. A reddish crystalline product was obtained, melting >250°C. Uv-vis:  $\lambda_{\max}$  (nm) ( $\epsilon$ ): 327(1.844), 343(1.934); IR (KBr): 3087 $\text{cm}^{-1}$ , 2805 $\text{cm}^{-1}$ , 1643 $\text{cm}^{-1}$ , 1550 $\text{cm}^{-1}$ ;

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 8.23 (s, 7-H and 14-H), 8.05 (m, 8-H, 9-H, 12 and 13H), 7.90 (m, 4Hs, Aromatic);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ) (ppm): 160.46 (2C), 136.31 (3C), 130.48 (2C), 125.67 (3C), 41.27(5C), 37.79(5C).

### 3 RESULTS AND DISCUSSION

2-Aminopyridine **3** was converted to 2-aminothiozole [5,4b] pyridine **5** using sodium thiocyanate and bromine in glacial acetic acid at -5°C, alkaline hydrolysis of compound **5** yielded 2-aminopyridine-3-thiol **6** in good yield.



Although the intermediate **6** has been previously prepared [13] by the conversion of compound **3** to the 3-bromo derivative **7** followed by its thiocyanation with KSCN to give **5**, which subsequently underwent alkaline hydrolysis to give compound **6**, this route was avoided because it is time

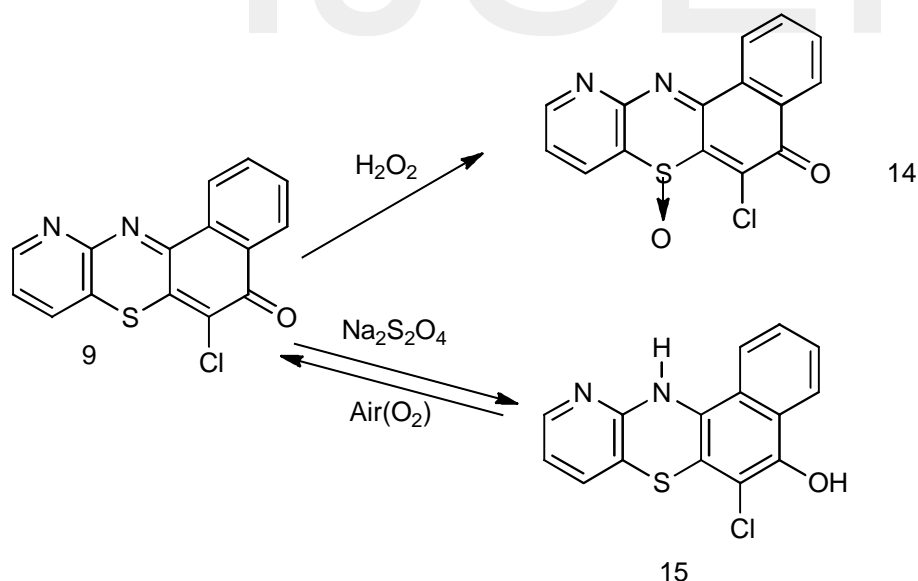
consuming and leads to poor yield of the product **6**. The former route was preferred because it is straight forward and gives higher yield [13], [14]

An equimolar mixture of 2,3-dichloronaphthoquinone **8** and properly dried 2-aminopyridine-3-thiol **6** in a mixture

of DMF and benzene (1:10) was treated with anhydrous sodium carbonate for this to furnish 6-chloro-11-azabenzothiazin-5-one **9** as a reddish crystalline product in good yield. Microanalyses agree with the assigned structure. In the IR spectrum, there was a decrease in the carbonyl(C=O) absorption from the expected  $1700\text{cm}^{-1}$  to  $1672\text{cm}^{-1}$ . This was due to ionic resonance effect in which the ionic resonance form **13** contributed appreciably to the ground state. This however, led to increase in the carbonyl bond length in **9** which eventually decreased the frequency of (C=O) absorption [14]. Treatment of this new tetra cyclic non-linear azaphenothiazin-5-one **9** with (1:1) molar

ratio of 3%  $\text{H}_2\text{O}_2$  converted them to sulphoxide **14** while the nitrogen atoms were not affected<sup>15</sup>. The ease of the oxidation of **9** to the corresponding sulphoxide **14** suggests its applicability as antioxidant in fuel and grease [14].

Again when compound **9** was treated with sodium dithionite ( $\text{Na}_2\text{S}_2\text{O}_3$ ), the carbonyl functionality was converted to hydroxyl functionality in **15**. This led to a discharge of the reddish color of **9** which reverted on exposure to air. This property also suggests that compound **9** can be used as a vat dye in the textile industry [15].



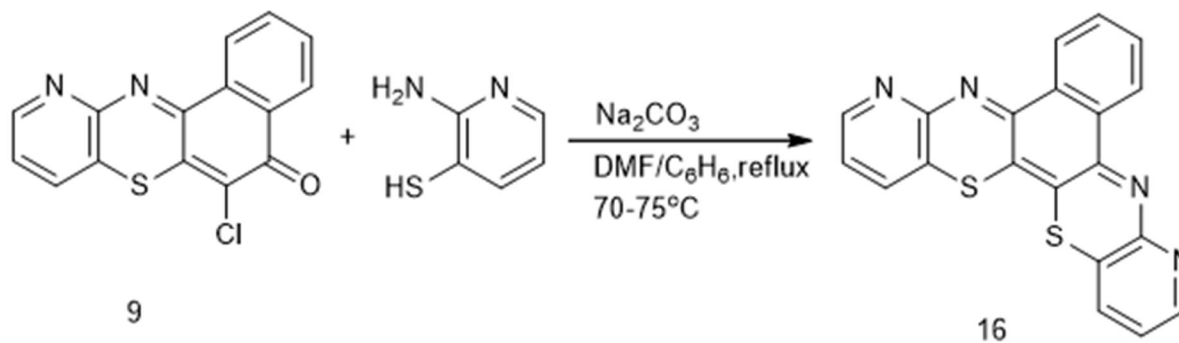
The presence of a reactive halogen atom and a carbonyl group at positions 5 and 6 of compound **9** brought about further

condensation with another molecule of 2-aminopyridine-3-thiol to furnish a new diaza heterocyclic system known as 6,15-

diazabenz[*a*]-[1,4]-benzothiazino-[3,2,*c*]-phenothiazine **16** a reddish crystalline solid melting  $> 260^{\circ}\text{C}$ .

The H-NMR spectrum gave a signal at 8.27-8.05 multiplet corresponding to aromatic protons, while C-NMR spectrum gave on signal which confirmed the absence of the

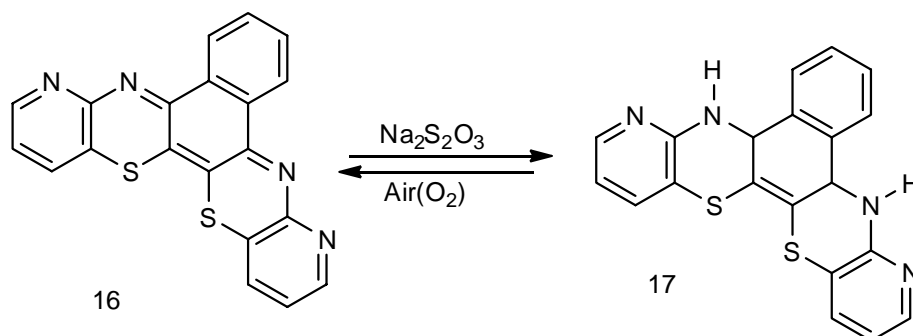
carbonyl(C=O) carbon. This is consistent with the assigned structure. The UV-Vis spectrum showed absorption at 340nm to 400nm in **16**. This revealed that there is extension in conjugation. The IR spectrum gave signals at  $3087\text{cm}^{-1}$ , (C=C-H),  $1670\text{cm}^{-1}$ ,  $1550\text{cm}^{-1}$ (Aromatic C=C, C=N).



**Scheme 4**

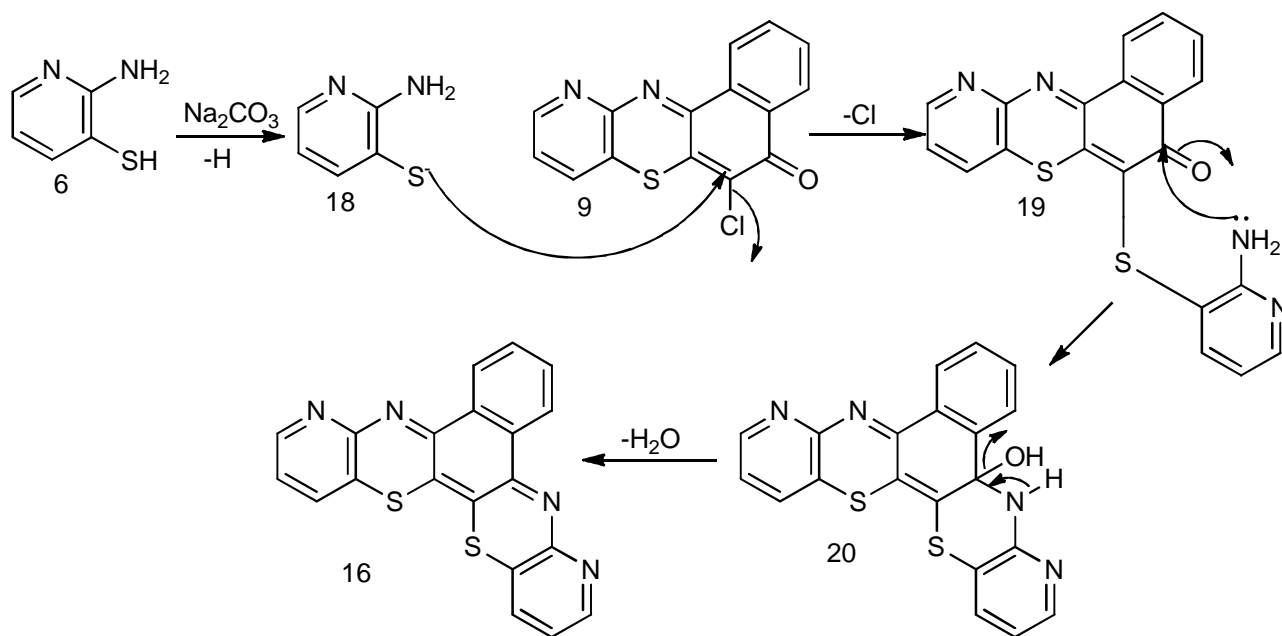
When compound **16** was treated with sodium dithionite, it gave color discharged unstable leuco-base **17** which reverted in the

presence of atmospheric oxygen to dehydro compound **16**. This property makes compound **16** applicable as a vat dye [16].



Compound **16** above was probably formed by the initial nucleophilic attack by the thio-pyridine ion **18** on compound **9** by displacing the reactive halogen group to form a diarylsuphide intermediate **19**.

Condensation of the new amino and the carbonyl groups of **19** and the loss of water [15] gave the new heterocyclic compound **16**.



#### 4 CONCLUSION:

These newly synthesized compounds were characterized on the basis of UV-Vis, IR,  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectroscopic analysis and all the assigned structures are in agreement with the spectroscopic data. The molecular formulae of the compounds are  $\text{C}_{12}\text{H}_7\text{ONSCl}$  and  $\text{C}_{19}\text{H}_{11}\text{N}_4\text{S}_2$ . These compounds are novel and will very useful in petroleum, pharmaceutical, agricultural, textile, paint industries etc.

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