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Synthesis and Characterization of New Complex Heterocyclic Ring Systems of Industrial Importance

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Abstract: The synthesis and characterization of new complex monoaza and pentaaza angular phenothiazine derivatives is reported. The first derivative, 6,10-dichloro-17-azadibenzo[a,n]triphenodithiazin-5,11-dione 10 was obtained by a base-catalyzed reaction of 2,6-diaminopyridine-3,5-dithiol 5 and 2,3-dichloro-1,4-naphthaquinone 9, while the second derivative, 7,9,15,17-tetraamino-6,8,16,18,25-pentazadibenzo[a,n]di([1,4]benzothaizino[3,2-c,l])triphenodiathizine 11 was obtained by the reaction of two moles of 2, 4, 6-triaminopyrimidine-3-thiol 8 and one mole of compound 10 under the same reaction conditions. The assigned structures to the above synthesized compounds were done on the basis of spectroscopic analysis.

Keywords: Monoaza, Pentaaza, Triphenodiathiazine, Triaminopyrimidine-3-Thiol, Phenothiazine

1. Introduction

The search for active chemical compounds that can be used for the production of drugs to combat many of the diseases plaguing mankind is ongoing. Most of these compounds are heterocyclic compounds of which phenothiazine and its numerous derivatives are not left out. The study of phenothiazine and its derivatives has remained unabated due a wide range of applications they have. Apart from their medicinal and biological importance [1] [2] [3], these group of heterocyclic organic compounds are very useful in agricultural, textile, paint, petroleum, pharmaceutical industries etc. [4], for the production of pesticides, dyes and pigments, antioxidants, drugs and many other pharmaceutical products [4] [5] [6] [7]. A good number of them have been synthesized and reported. However, there are few reports on the synthesis and chemistry of phenothiazine derivatives of the type 1. Although Ezema and co-workers [8] have reported on the synthesis of the type 1, at the moment, there is no report on the synthesis and chemistry of phenothiazine derivatives of the type 2. Therefore, to contribute a little to the study and chemistry of these derivatives, we present the synthesis and characterization of phenothiazine derivative of the type 2.

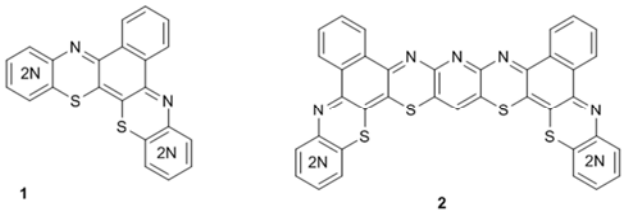


Figure 1. *Structures of triazabenzo[a][1,4]-benzothiazino-[3,2-c]phenothiazine and pentaazadibenzo[a,n]di-([1,4]-benzothiazino-[3,2])-[c,l]triphenodithiazine.*

2. Experimental Procedure

The melting points of all the synthesized compounds were determined with a Fisher John apparatus and are uncorrected. UV/Visible spectra were recorded on a Pye-Unicam SP 800 spectrophotometer using matched 1cm quartz cells; IR spectra in KBr on a Perkin Elmer 137 spectrophotometer; ^{1}HMNR spectra on a Varian Associates T – 60 instrument (chemical shiftare reported on the δ scale relative to tetramethylsilane (TMS) as internal standard). Analytical samples were obtained by column chromatography on

aluminum oxide 90(Merck, 70–230 mesh ASTM) using acetone and benzene (1:1) as an eluent before recrystallization.

2.1. 2, 6-Diaminopyridine-3, 5-dithiocyanatopyridine (4)

Compound 4 was prepared as previously reported in the literature [9, 10].

2,6-Diaminopyridine 3 (5.50g, 0.0413mole), potassium thiocyanate (5.0g,0.526mole) and precooled acetic acid (100ml) were placed in a two neck flask equipped with a mechanical stirrer, and the mixture was stirred for 30 minutes. Bromine (5ml) in a precooled acetic acid was then added intermittently using thistle funnel. The addition of bromine took about 2hours. After the addition of bromine, the mixture was stirred for another two hours while maintaining a temperature between -5°C and 0°C. Thereafter, the mixture was stirred for additional 10 hours at room temperature and the slurry was left to stand overnight. Boiled water (50ml) was later added to the mixture and then filtered hot. The residue was washed with acetic acid (50ml) and water (50ml) respectively and added to the filtrate and neutralized with concentrated ammonia to a pH of 9 without allowing the temperature to exceed 20°C. A yellow precipitate was formed, filtered, dried and recrystallized with acetone to yield compound 4 (8.50g, 70%), melting at about 150°C.

2.2. 2,6-Diaminopyridine-3-thiol (5)

2,6-Diamino-3,5-dithiocyanatpyridine 4 (9.0g, 0.0672mole) was placed in a 250ml two-necked flask equipped with refluxing apparatus. 20% potassium hydroxide (15.50g, 0.2768mole) in distilled water (80ml) was added to above and the content of the flask was refluxed for 30h in a sand bath until evolution of ammonia gas stopped. At the end of the reaction, the mixture was allowed to cool and neutralized with acetic acid in an ice-saltbath, while maintaining a temperature below 20°C during the process to give a massive yellow precipitate. The precipitate was filtered, dried and recrystallized from acetone to give compound 5 in good yield as a crystalline product (6.8g 60%), melting at 240°C as described previously [10].

2.3.2, 4, 6-Triamino-3-Thiocyanatopyrimidine (7)

2,4,6-Triaminopyrimidine 6 (5.50g, 0.0413mole), potassium thiocyanate (5.0g,0.526mole) and precooled acetic acid (100ml) were placed in a two neck flask equipped with a mechanical stirrer, and the mixture was stirred for 30 minutes. Bromine (5ml) in a precooled acetic acid was the added intermittently using thistle funnel. The addition of bromine took about 2hours. Thereafter, the mixture was stirred for another two hours always maintaining a temperature between -5°C and 0°C. After this, the mixture was stirred for additional 10 hours at room temperature and theslurrywas formed and left to stand overnight. Boiled water (50ml) was later added to the mixture and then filtered hot. The residue was washed with acetic acid (50ml) and water (50ml) respectively and added to the filtrate and neutralized with concentrated ammonia to a pH of 9 without allowing the temperature to exceed 20°C. A yellow precipitate was obtained, filtered, dried and recrystallized with acetone to yield compound **7** (8.50g, 70%), melting at 200°C,as described previously [10].

2.4. 2,4,6-Triaminopyrimidine-3-thiol (8)

2,4,6-Triamino-3-thiocyanatpyrimidine 7 (9.0g, 0.0672mole) was placed in a 250ml two-necked flask equipped with refluxing apparatus. 20% potassium hydroxide (15.50g, 0.2768mole) in water was added and the content of the refluxed for 30h in a sand bath until the production of ammonia gas was completed. At the end of the reaction, the mixture was allowed to cool and neutralized with acetic acid in an ice-salt bath, while maintaining a temperature below 20°C during the process. A massive yellow precipitate was formed and was filtered, dried and recrystallized from acetone to give compound 8 in good yield as a crystalline product (6.8g 60%), m.p. > 260°C. UV-Vis (EtOH) λ_{max}(nm) (ε): 248 (2.7499), 325(3.6037), 390(4.3244); IR (KBr): ν_{max}3385cm^{-1}(3NH), 1532CM^{-1} (C=C, C=N), 779, 740,660cm^{-1}. ^{1}HNMR (DMSO-d_6): δ 9.40 (s,3NH_2) and δ 6.13 (s,SH); ^{13}CNMR(DMSO-d_6) (ppm): 163.142 (3C-NH_2),and 125.121(C-SH).

2.5. 6,10-Dichloro-17-Azadibenzo [a,n]Triphenodithiazin-5,11-Dione(10)

Compound 10 was prepared as previously reported in the literature [9, 10]. A mixture of 2,6-diaminopyridine-3,5-dithiol 5 (5.0g, 0.0472mole) and anhydrous sodium carbonate(2.50g, 0.0236mole) was place in a 250ml 3-necked reaction flask equipped with a magnetic stirrer, thermometer, and reflux condenser. A mixed solution of DMF (5ml) and benzene (50ml) was added and the mixture reflux for 30minutes. Thereafter, 2,3-dichloro-1,4-naphthoquinone 9 (2.50g, 0.00483mole) was added and the content of the flask was refluxed in a water bath with continuous stirring for 8h. At the end of the reaction, benzene was distilled and water was added to the slurry and heated to boil for about 2minutes, filtered, dried and subjected to column chromatography on aluminum oxide employing benzene and acetone as eluent. The product was later recrystallized from acetone to obtain the above compound 10 a reddish crystalline substance (3.65g, 60%), melting at 200°C.

2.6. 7,9,15,17-Tetraamino-6,8,16,18,25-Pentaazadibenzo[a,n]di-([1,4]-Benzothiazino-[3,2])-[c,l]Triphenodithiazine(11)

A mixture of 2,4,6-tiaminopyrimidine-3-thiol 8 (5.0g, 0.0472mole) and anhydrous sodium carbonate (2.50g, 0.0236mole) was place in a 250ml 3- necked reaction flask equipped with a magnetic stirrer, thermometer, and reflux condenser. A mixed solution of DMF (5ml) and benzene (50ml) was added and the mixture was

refluxedfor 30 minutes. Thereafter, 6, 10-dichhloro-17-azadibenzo [a,n]triphenodithiazin-5,11-dione 10 (2.50g, 0.00483mole) was added and content of the flask was refluxed in a water bath with continuous stirring for 8h. At the end of the reaction, benzene was distilled and water was added to the slurry and heated boil for 2minutes, filtered, dried and subjected to column chromatography on aluminum oxide employing benzene and acetone as eluent. The product was later recrystallized from acetone to obtain the above compound 11 a reddish crystalline substance (3.65g, 60%), melting at 300^{o}C. UV-Vis:(nm)(ε) 420(4.6571), 525(5.8214), 600(6.6530); IR: 3402cm^{-1} (>N-H), 2951cm^{1},1525cm^{-1}, 790cm^{-1},724cm^{-1}; ^{1}HNMR(DMSO-d_6) δ: 9.89(8H,m,4NH_2), 8.76(8H,m,Ar-H), 7.00(s,12-H); ^{13}CNMR(DMSO-d_6): (ppm) 160.10(4C), 150.12(1C). 145.25(8C), 142.20(5C), 14021(4C), 139.32(3C), 138.10(3C), 137.6094C)

3. Results and Discussion

The first key intermediate 2,6-diaminopyridine-3,5-dithiol 5 was obtained by the thiocyanation of 2,6-diaminopyridine 3 to give 2,6-diamino-3,5-dithiocyanatopyridine 4 which underwent hydrolysis with potassium hydroxide to furnish compound 5 [9] [10].

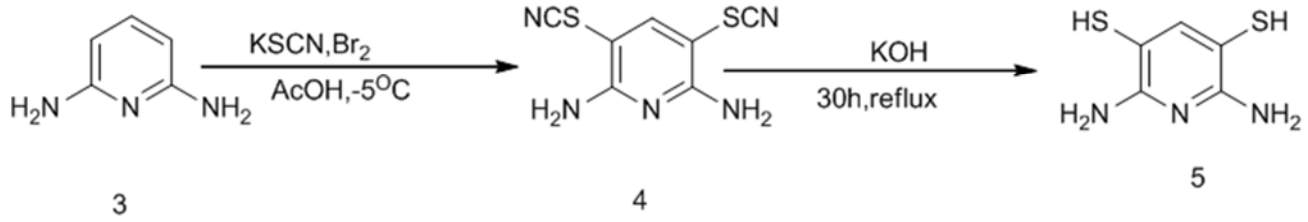


Figure 2. *Synthesis of 2, 6-diaminopyridine-3, 5-dithiol.*

The second key intermediate, 2,4,6-triaminopyrimidine-3-thiol 8 was also obtained using a similar method as described above. Here, 2,4,6-triaminopyrimidine 6 was subjected to thiocyanation to give 2,4,6-triamino-3,5-dithiocyanatopyrimidine 7 which was later hydrolyzed using potassium hydroxide to furnish the product 8 in good yield. [10].

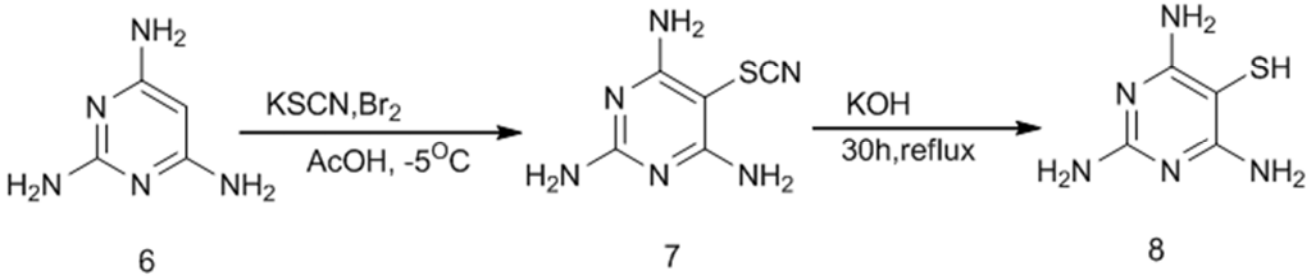


Figure 3. *Synthesis of 2, 4, 6-triaminopyrimidine-3, 5-dithiol.*

The condensation of equimolar amounts of compound 5 with 2,3-dichloro-1,4-naphthoquinone 9 in an alkaline medium yielded 6, 10-dichloro-17-azadibenzo[a,n]triphenodithiazin-5,11-dione 10, in good yield [10] [11].

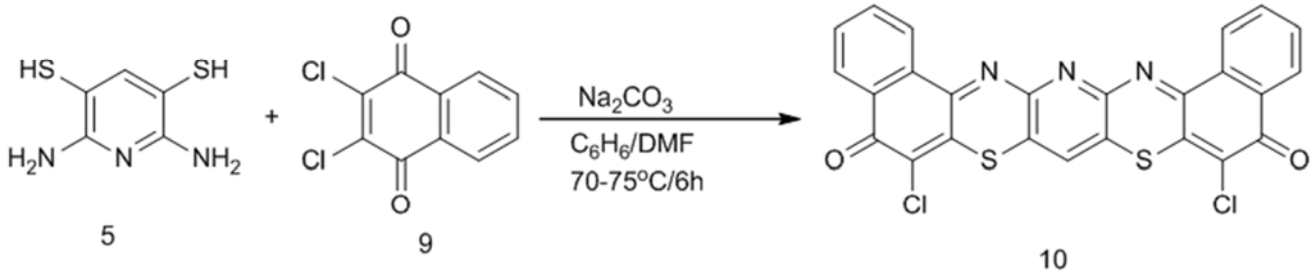


Figure 4. *Synthesis of 6, 10-dichloro-17-azadibenzo[a,n]triphenodithiazin-5,11-dione.*

The presence of the active halide atoms at 6th and10th positions as well as the carbonyl groups at the 5thand 11th positions of compound 10 above, provided reaction sites for the second reaction with two moles of 2,4,6-triaminopyrimidine-3-thiol 8 to give 7,9,15,17-tetraamino-6,8,16,18,25-pentaazadibenzo[a,n]di([1,4]benzothiazino[3,2])-[c,l]triphenodithiazine.

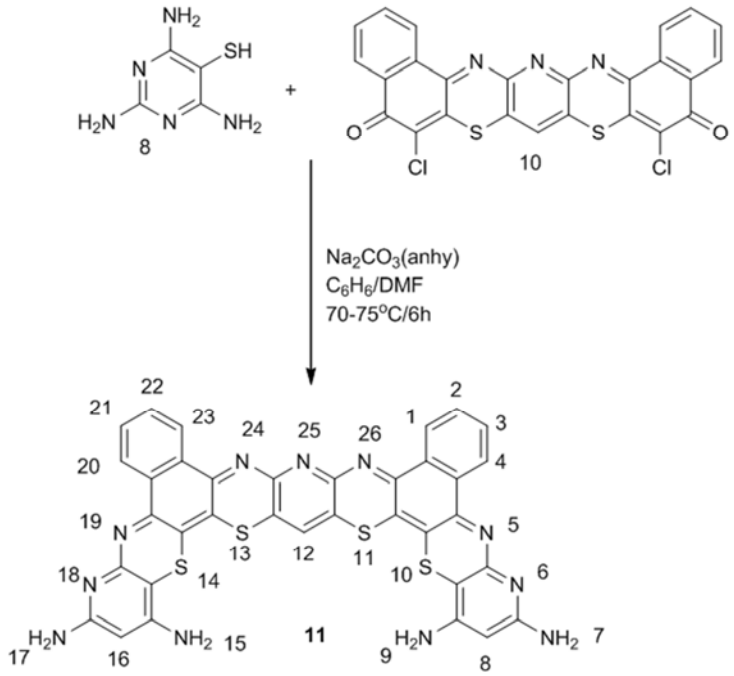


Figure 5. *Synthesis of 7,9,15,17-tetraamino-6,8,16,18,25-pentaazadibenzo[a,n]di([1,4]benzothiazino[3,2])-[c,l]triphenodithiazine.*

The structures of the above synthesized compounds agreed with the microanalyses of both ^{1}HNMR and ^{13}CNMR thus: The ^{1}HNMR of compound 10 showed peaks at δ7.06 (singlet, 8-H) and 8.90 (multiplets for benzenoid protons). However, in the ^{13}CNMR spectrum of compound 10, the band at 190.52ppm (singlet) represents the two carbonyl carbons, while the band at 160.15ppm(singlet) represents the carbon atoms at the 6th and 10th positions of the above compound, the absorption band at 151.61ppm(singlet) stands for C-8 while those at 141.34-139.43ppm (multiplets) stand for all other benzenoid carbons. The UV-Vis spectrum of compound 10 revealed signals at 370nm (ε = 3.9919), 500nm (ε = 4.1582) and 593nm (ε = 4.9233), while the IR spectrum showed peaks at 2950cm^{-1} (C-CH stretching), 1680cm^{-1} due to the carbonyl (C=O) stretching, 1540cm^{-1} (C=C, C=N stretching), 780cm^{-1} (for a 1,2-disubstituted benzene rings). However, a lowering in the carbonyl absorption band was observed, from the expected 1730cm^{-1} to 1680cm^{-1} as a result of the contribution of the ionic structure 12 to the resonance stability of the compound 10 as shown below [10] [11].

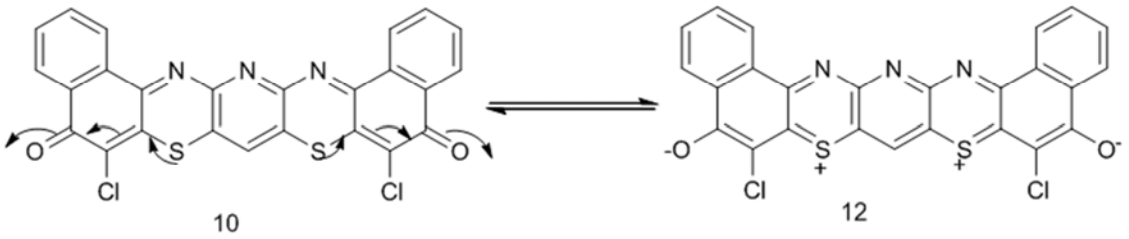


Figure 6. *The contribution of the ionic resonance structure to the stability of compound 10.*

The^{1}HNMR spectrum of compound 11 showed signals at δ9.89 (multiplets) representing the eight N-H protons, 8.76 (multiplets), for all the eight benzenoid (C-1, 2, 3, 4, 20, 21, 22 and23) protons, 7.00(singlet) for the proton at C–12. The ^{13}CNMR spectrum gave no signal at 170-200ppm which explains the absence of the carbonyl carbons. This is consistent with the assigned structure. However, signals were observed at 160.10ppm (multiplets) for C-7, 9, 15 and 17, while the signal at 150.02(a singlet) is assigned to C-12, where as those at 145.25-137.60 (multiplets) are for the remaining carbon atoms of the above compound. The absence of absorption at 1970-1650cm^{-1} for the carbonyl(C=O) group in the IR spectrum of compound 11 further supported the assigned structure. The absorption bands at 420nm, 525nm and 680nm in the visible region showed that there is extension in conjugation, hence the violet color of the compound.

The non-linear azaphenothiazine-5,11-dione 10 is formed by the nucleophilic attack of the mercaptide diions 12 on C-3 of the 2,3-dichloro-1,4-naphthoquinone molecules 9 leading to the loss of two moles of Hydrogen chloride [10] [11 [12]. Condensation of the appropriate naphthoquinone carbonyl groups with amino groups in the pyridine moiety led to the isolation of 10.

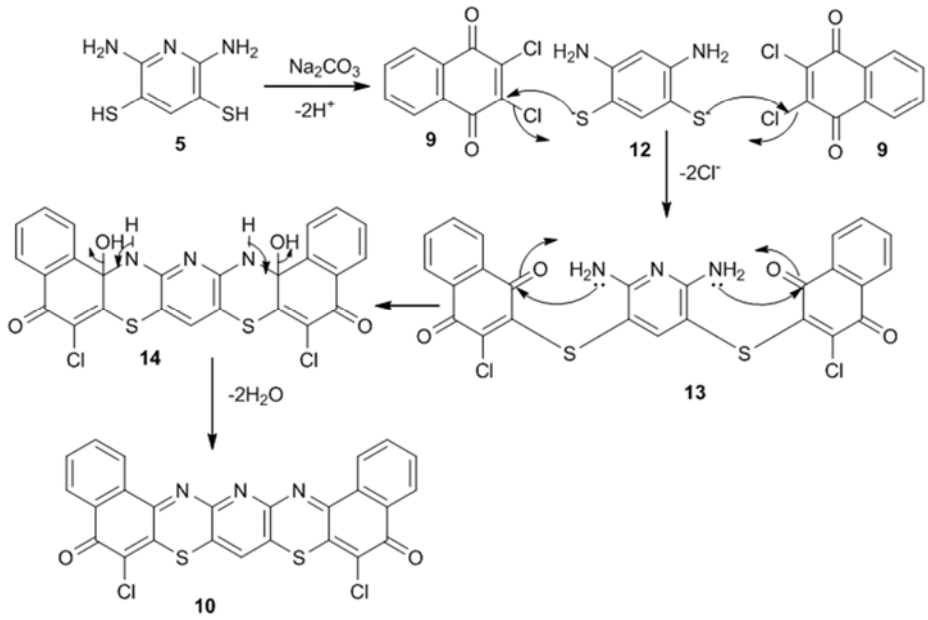


Figure 7. *The reaction mechanism for the formation of7,9,15,17-tetraamino-6,8,16,18,25-pentaazadibenzo[a,n]di([1,4]benzothiazino[3,2])-[c,l]triphenodithiazine.*

The mechanism for the formation of compound 11 is similar to that of compound 10, thus: Compound 11 isprobably formed by initial nucleophilic attack by the dithiopyrimidine ions 15 on compound 10 by displacing the reactive halogen groups to form a diaryl sulphide intermediate 16 [13], [14]. Condensation of the amino and the carbonyl groups of 16 followed by the loss of two water molecules gave, 9,15,17-tetraamino-6,8,16,18,25-pentaazadibenzo[a,n]di([1,4]benzothiazino[3,2])-[c,l]triphenodithiazine 11 as shown below;

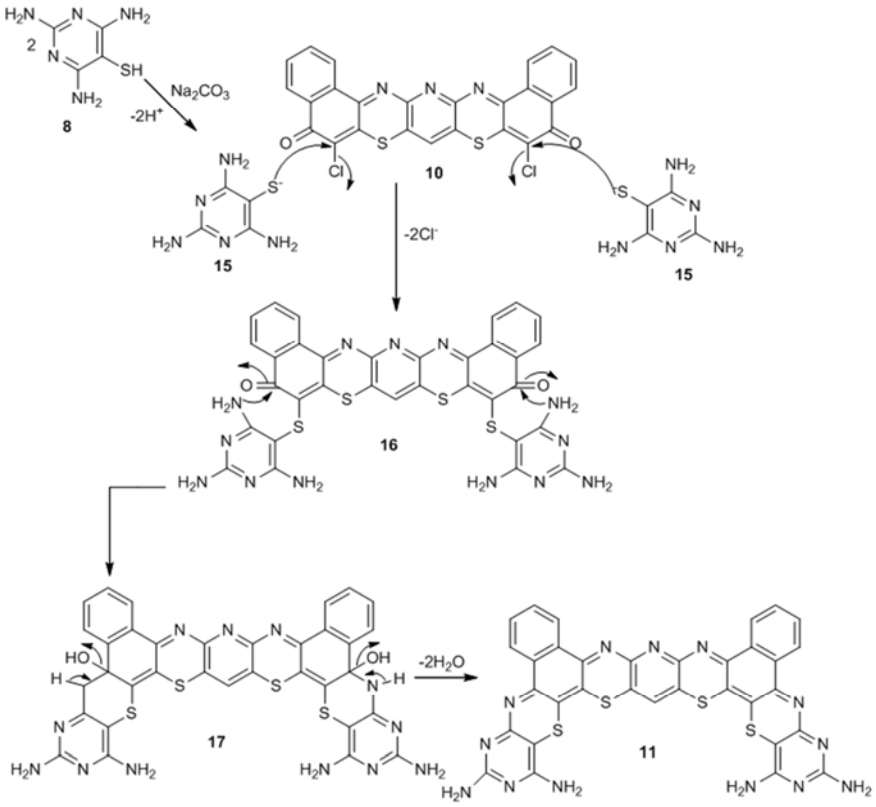
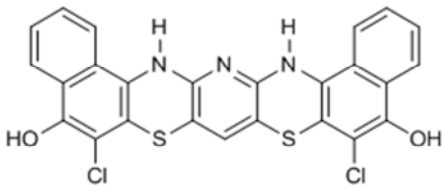


Figure 8. *The reaction mechanism for the formation of 7,9,15,17-tetraamino-6,8,16,18,25-pentaazadibenzo[a,n]di([1,4]benzothiazino[3,2])-[c,l]triphenodithiazine.*

Reduction of compounds 10 and 11to their corresponding leuco-bases forms of 18 and 19 using sodium hydrogen sulphite was also achieved; nevertheless, these derivatives were unstable and could not be isolated. They reverted to the dehydro forms which are highly colored quinonoid compounds 10 and 11, when exposed to air. The oxidation was however, facilitated by the use of hydrogen peroxide. This property as well as their high melting points makes them applicable as vat dyes and pigments [12] [13] [14].



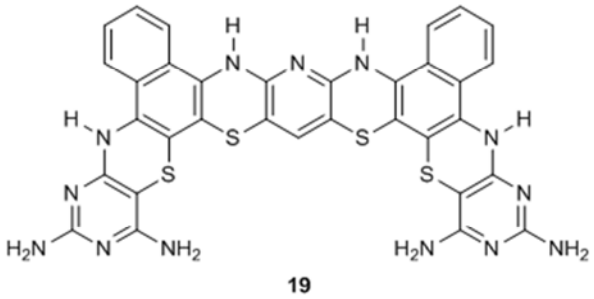


Figure 9: *Structures of the reduced forms of compounds 10 and 11.*

4. Conclusion

The synthesis of phenothiazine derivatives discussed above was carried out using simple commercially available starting materials. The methods employed are straight forward and stereo-selective products were obtained. These newly synthesized compounds have promising and interesting applicability in pharmaceutical, textile, petroleum, agricultural industries etc.

The intense colors of these compounds suggest that they could be used as dyes. Studies on their dyeing and antimicrobial potentials are ongoing in our laboratory.

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