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Synthesis Of A New And FirstTriazadibenzo[A,N]Triphenodithiazine

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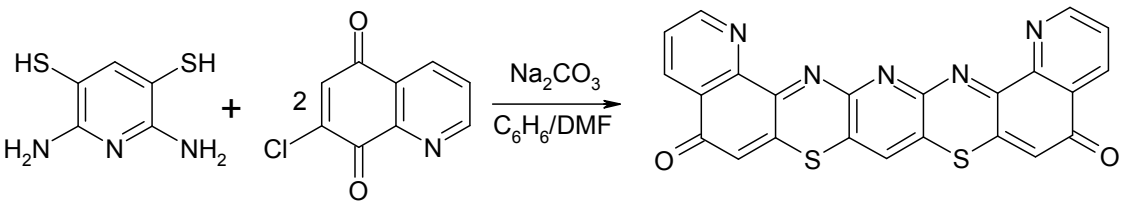
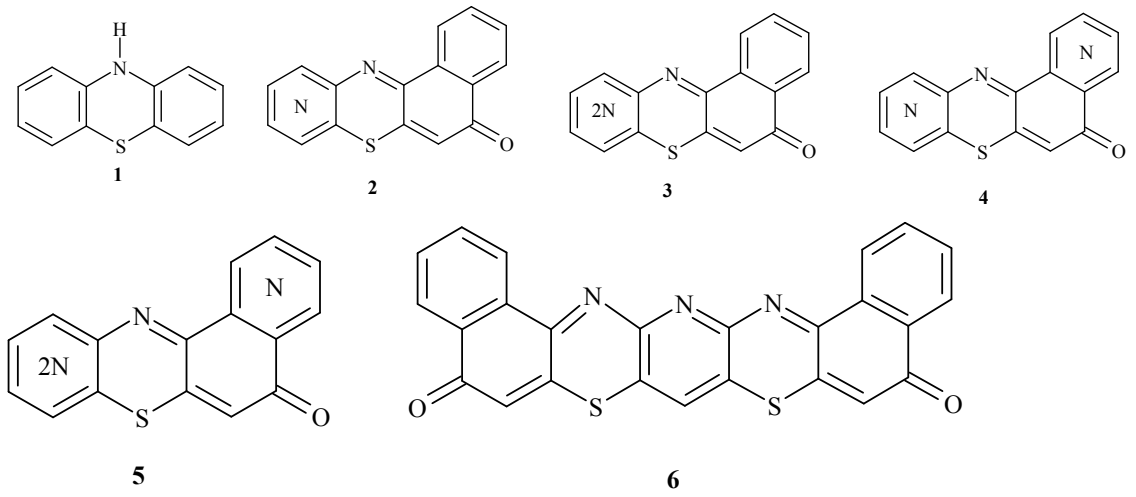
Abstract:
A new angular triazadibenzo[a,n]triphenodithiazine is synthesized and characterized by spectroscopic methods. The new compound 1,15,17-triazadibenzo[a,n]triphenodithiazine-5,11-dione was obtained by base catalyzed condensation reaction of 2,6-diaminopyridine-3,5-dithiol with 7-chloro-5,8-dioxoquinoline in anhydrous sodium carbonate. 2,6-diaminopyridine-3,5-dithiol was prepared by alkaline hydrolysis of 2,6-diamino-3,5-dithiacyanopyridine in 40% KOH solution while 7-chloro-5,8-dioxoquinoline was prepared by 4 reaction steps conversion of 8-hydroxyquinoline to 5-amino-7-chloro-8-hydroxyquinoline which was subsequently oxidized with acidified potassium dichromate.
Keywords: 2,6-Diaminopyridine-3,5-dithiol, 7-Chloro-5,8-dioxoquinoline, anhydrous sodium carbonate, alkaline hydrolysis, condensation reaction.

Graphical abstract



INTRODUCTION

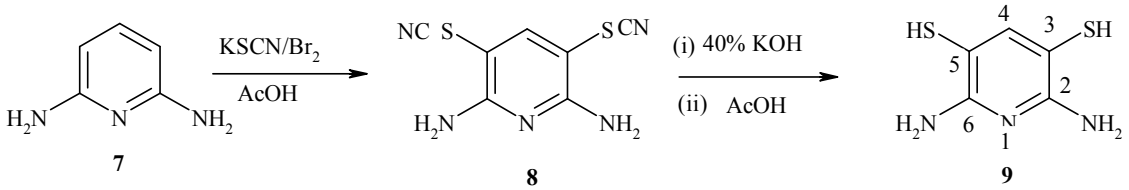
Phenothiazine compound and its derivatives are found useful as drugs, [1] industrial antioxidant, [2] thermal stabilizers, [3] pesticides, [4] polymeric indicators, [5] and as dyes [6] and pigments. [7] Structural modifications made on the parent structure **1** has resulted to the reports on the successful synthesis of many congeners both linear and angular phenothiazine compounds. Based on the fact that the pharmacological activities of phenothiazine is been attributed to the basic nitrogen of the ring which donates electrons to the biological receptors by charge transfer mechanism,[8] the synthesis of the aza analogues with improved pharmacological and biological activities has been of great interest to chemists in this present century. There have been reports the on the monoaza, [9] diaza[10, 11] and triaza[12] angular phenothiazine compounds of the types **2, 3, 4** and **5.** Although the mono-aza derivative of dibenzotriphenothiazine **6** which is our area of our interest has been reported, [13] there is practically no report on the triaza-analogues. Therefore the authors wish to report here the successful synthesis of the first triaza-analogues of the dibenzotriphenothiazine rings.



1 **2** **3** **4** **5** **6**

RESULTS AND DISCUSSION

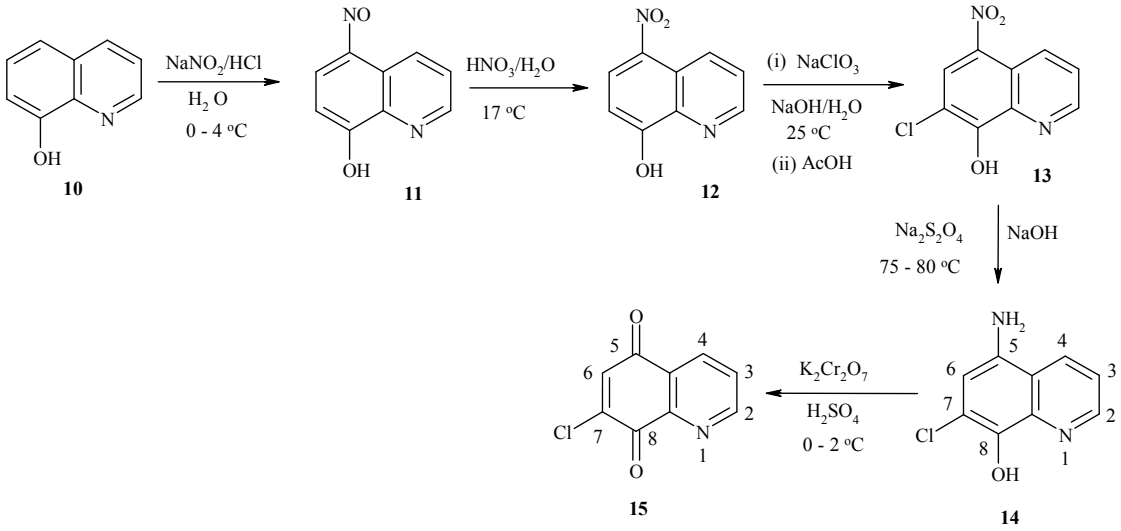
2,6-Diaminopyridine **7** was thiocyanated with potassium thiocyanate in glacial acetic in the presence of bromine to 2,6-Diamino-3,5-dithiacyanopyridine **8.** Hydrolysis of **8** with 40% aqueous potassium hydroxide in the presence of anti-oxidant (Na_2SO_3) followed by neutralization with acetic acid gave 2,6-diaminopyridine-3,5-dithiol **9.** Elemental analysis of **9** was in agreement with the molecular formular $C_5H_7N_3S_2$. The infrared spectrum showed absorption bands at 3410-3375cm^{-1} corresponding NH and 1595 cm^{-1} assigned to C=C of aromatic ring. ^{1}H-NMR exhibited signals at δ 7.20 (singlet) corresponding to pyridine ring proton, δ 3.95 (singlet) assigned to the (4H) of $2NH_2$ groups and δ 2.90 (singlet) corresponding to the (2H) of 2SH groups. ^{13}C-NMR provided further evidence by showing signals at ppm 147.024 assigned to (C-2, C-6), ppm 132.165 corresponding to (C-3, C-5) and ppm 120.105 assigned to (C-4) respectively (Scheme 1).



7 **8** **9**

Scheme 1

On the other hand, treatment of solution of 8-hydroxyquinoline **10** in concentrated hydrochloric and water with solution of sodium nitrite in water which was added in portions with continuous stirring for over 1 hr gave 8-hydroxy-5-nitrosoquinoline **11**. Oxidation of compound **11**with concentrate nitric acid furnished 8-hydroxy-5-nitroquinoline **[12]** which was converted to 7-chloro-8-hydroxy-5-nitroquinoline **13** with solution of sodium hypochlorite. Compound **13** was later treated with sodium dithionite at 75-80^{o}C in aqueous sodium hydroxide solution to give 5-amino-7-chloro-8-hydroxyquinoline **14.** Elemental analysis of **14** agrees the molecular formular $C_9H_7ClN_2O$. The infrared spectrum showed NH absorption band at 3400-3350 cm^{-1}, C=C absorption band at 1605 cm^{-1}. ^{1}H-NMR gave signals at δ 7.30-8.90 (m, 3H) corresponding to the pyridine ring protons, δ 7.10 (s, 1H) assigned to the phenolic ring and δ 5.10 and δ 3.95 (s, 1H; s, 2H) corresponding the OH and NH_2 groups respectively. Oxidation of 5-amino-7-chloro-8-hydroxyquinoline **14** with acidified potassium dichromate furnished 7-chloro-5,8-dioxoquinoline **15.** Elemental analysis of **15** agrees with the molecular formular $C_9H_4ClNO_2$. Infrared spectrum showed C=O strong absorption band at 1660 cm^{-1}. ^{1}H-NMR exhibited signals at δ 8.50-9.20 (m, 3H) corresponding to pyridine ring protons, δ 7.15 (s, 1H) assigned to the quinoid ring protons. ^{13}C-NMR provided further evidence by exhibiting signals at ppm 185.015 assigned to the equivalent 2C=O group (Scheme 2).

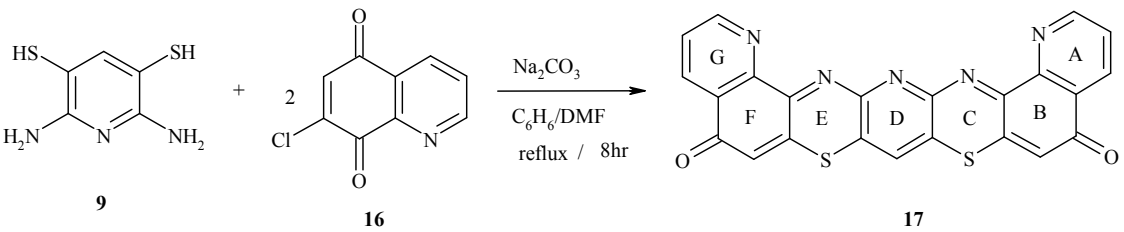


Scheme 2

Base catalyzed condensation of 2,6-diminopyridine-3,5-dithiol **9** with 2 moles of 7-chloro-5,8-dioxoquinoline **16** in the presence of anhydrous sodium carbonate gave the new compound characterized as 1,15,17-triazadibenzo[a,n]triphenodithiazine-5,11-dione **17** as pale red powder in good yield. Elemental analysis of the new compound agrees with the molecular formular $C_{23}H_9N_5O_2S_2$. The IR spectrum showed bands at 1670 cm^{-1} corresponding to C=O group and 1560 cm^{-1} assigned to aromatic C=C.

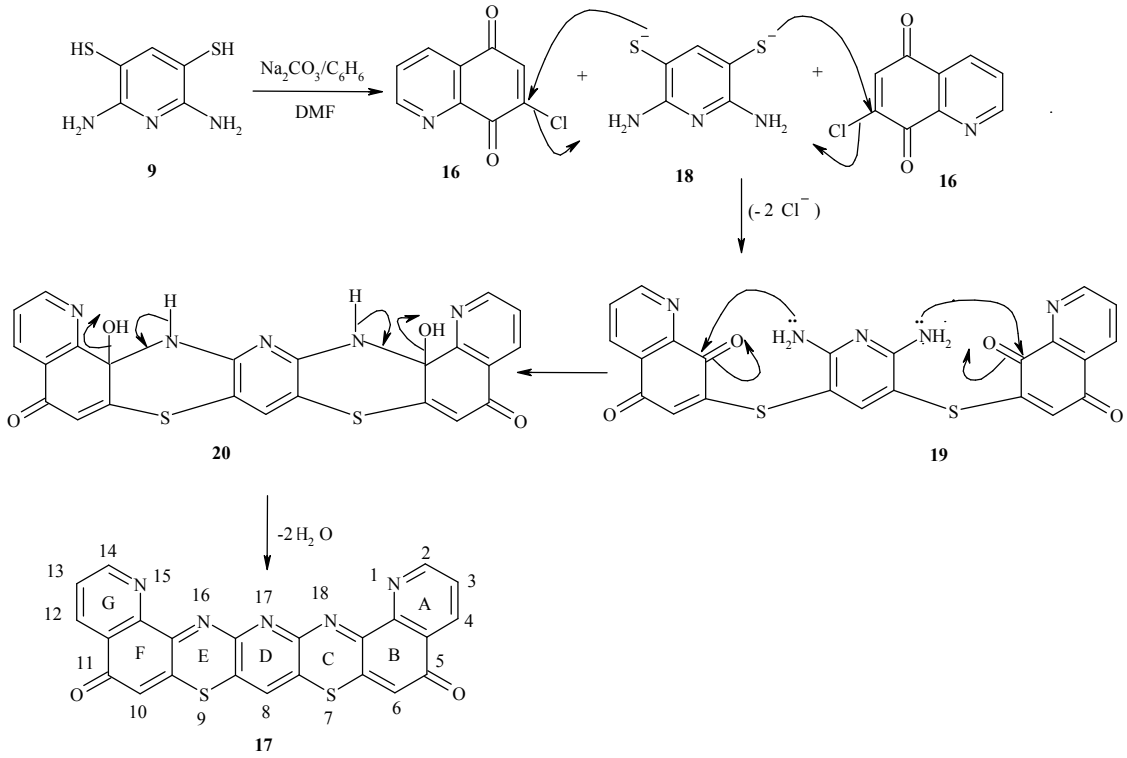
^{1}H-NMR provided further evidence for the structure. The singlet at δ 7.50 (1H) was assigned to the aromatic proton in ring D. The multiplet at δ 7.75-9.10 (6H) was assigned to protons in rings A and G as a result of symmetry of the compound while the singlet at δ 6.10 (2H) was assigned to the protons in the quinoid rings B and F.

^{13}C-NMR spectrum exhibited signal at 178.502 ppm corresponding to the two C=O groups and signals at ppm 115.8-165.0 corresponding to 21C-atoms as a result of many overlaps (scheme 3).



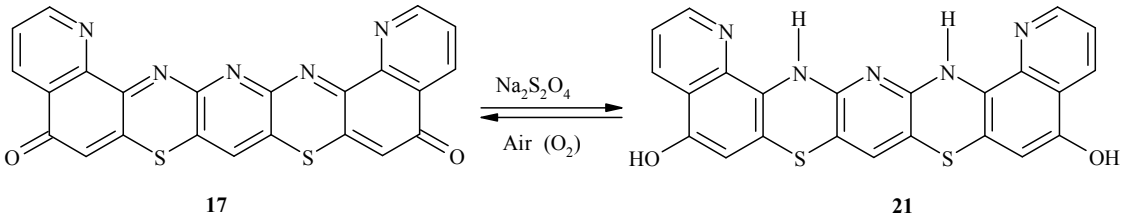
Scheme3

The formation of the product probably proceeded by nucleophilic attack by 2,6-diminopyridine-3,5-dithio ion **18** on the 7-chlorodioxquinoline **16** and the displacement of chloride ions thereby generating the diaryl disulphide **19.** Cyclization was achieved by internal nucleophilic attack by the amino group on the carbonyl of the diaryl **19** to give the unstable intermediate **20.** Structure **20** by subsequent lose of water molecules gave the parent compound 1,15,17-triazadibenzo[a,n]triphenodithiazine-5,11-dione **17** (Scheme 4).



Scheme 4

Reduction of compound **17** to the corresponding triazadibenzotriphenodithiazine-5,11-diol **21** was achieved by the use of $Na_2S_2O_4$. Compound **21** was unstable and difficult to be isolated in the pure state as it quickly reverted back to the oxidized quinonoid compound **17** by the atmospheric oxygen (scheme 5).



Scheme 5

EXPERIMENTAL

The product was purified by column chromatography on alumina eluting with methanol-benzene. Melting points were determined with Fisher-Johns apparatus and are not corrected. UV and visible spectra were recorded on Cecil CE 9050 spectrophotometer using matched 1 cm quartz cells. The solvent is dimethylformamide. The absorption maxima are given in nanometer. Infrared spectra were recorded on Buck 504 spectrophotometer using KBr discs. Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) are determined using Varian mercury 200 MHz spectrophotometer: chemical shifts are reported in (δ) scale. Elemental analysis is obtained using Heraous CHN-O rapid analyzer.

2,6-Diamino-3,5-dithiacyanopyridine (8)

2,6-Diaminopyridine **7** (20 g, 12 mmole) was placed in a litre three-necked flask with reflux condenser, a dropping funnel and mechanical glass stirrer, glacial acetic acid (250 ml) precooled at 18^{o}C was added and the mixture cooled in ice-salt bath. After 15 min potassium thiocyanate dehydrate (36 g) was added while maintaining the temperature between -5^{o} and 0^{o}. Bromine (15 ml) was added in droplets from the dropping funnel to the stirred ice cooled mixture during a period of 1.30 hr. The slurry turned from its initial brilliant yellow colour to deep orange after 2 hr with continuous stirring. Stirring was continued at 0^{o} for a total period of 5 hr. the slurry was left to stand over night. Water was added and the mixture warmed to 80^{o}C and filtered hot. The filtrate was preserved and the residue was extracted thrice with glacial acetic acid and combined with the original filtrate and neutralized to pH 6.5 with concentrated ammonia by maintaining the temperature below 10^{o}. The orange product was collected by filtration and recrystallized from methanol after treatment with activated charcoal.

2,6-Diaminopyridine-3,5-dithiol (9)

2,6-Diamino-3,5-dithiacyanopyridine **3** (10 g, 45 mmole) was weighed into a 500 ml reaction flask equipped with reflux condenser. Potassium hydroxide (40 g in 100 ml of water) was added and the entire mixture was refluxed for 14 hr. on a sand bath. At the end of reflux period, little amount of activated carbon was added to the solution and heated for further 30 min, it was filtered and cooled. The filtrate was neutralized in salt ice bath with ethanoic acid by maintaining the temperature below 10^{o}C. It was filtered and recrystallized from minimum amount of methanol and dried in a desicator to give 2,6-diaminopyridine-3,5-dithiol as pale yellow crystals m. p. > 250^{o}C. (dec); Uv (MeOH) λ_{max} (ε): 217nm (12015), 245nm (14105), 293nm (9470), 345nm (8655). IR (KBr): ν cm^{-1}: 3450-3360 (NH), 1620, 1565, 1470 (C=C), 1415, 1345, 1315, 1150, 870, 790. ^{1}H-NMR exhibited signals at δ 7.20 (1H, s, pyridine ring), δ 3.95 (4H, s, 2NH$_2$), δ 2.90 (2H, s, 2SH). ^{13}C-NMR provided further evidence by showing signals at ppm 147.024 (C-2, C-6), 132.165 (C-3, C-5), 120.105 (C-4).

Elemental analysis calculated for $C_5H_7N_3S_2$. %: C-34.64; H-4.07; N-24.25; S-37.01; Found: C-34.86; H-4.02; N-24.23; S-37.03

5-Nitroso-8-hydroxyquinoline hydrochloride (11)

8-hydroxyquinoline **10** (29 g, 22 mmole) was dissolved in a solution of water (100 ml) and concentrated hydrochloric acid (37.5 ml) in a 500 ml beaker immersed in salt-ice bath. 100 g of ice was added and the temperature allowed dropping down to 0^{o}. A solution of sodium nitrite (15 g) in 50 ml of ice-cold water was later added in portions with vigorous stirring over 1hr and maintaining the temperature at 0-4°C. At the of reaction period, the mixture was allowed to stand overnight at 0°C. It was filtered, washed with cold water and air dried to give 5-nitroso-8-hydroxyquinoline hydrochloride **11** as bright yellow solid which melted at 178^{o}C (dec) (lit. 180^{o}C (dec)).[14]

5-Nitro-8-hydroxyquinoline (12)

Grounded powder of 5-nitroso-8-hydroxyquinoline hydrochloride **11** (36.0 g, 22 mmole) was added in portion to a solution of concentrated nitric acid (108 ml) and water (72 ml) at 17°C in a 500 ml beaker with vigorous stirring for a period 45 min. At the end of addition, the mixture was stirred occasionally at 10 min interval for over 1 hr 15 min at 17°C in cold water bath. It was diluted with water, cooled to 0^{o} and made alkaline with potassium hydroxide solution and later neutralized with acetic acid. The mixture was filtered, washed with water, dried and recrystallized from ethanol to give 5-nitro-8-hydroxyquinoline **12** as yellow powder which melted at 180-181^{0}C (lit.181-183^{0}C).[14]

7-Chloro-5-nitro-8-hydroxyquinoline (13)

5-Nitro-8-hydroxyquinoline **12** (10.0 g, 0.05mol) was suspended in water (1000 ml). 1M potassium hydroxide solution (50 ml) also was added, 5% sodium hypochlorite (72 ml) was later added in portions with vigorous stirring at room temperature for over a period of 1.5 hr. The mixture was stirred for further 2 hr, neutralized with acetic acid, and stirred to for further 30 min to permit complete conversion of the precipitate to the free quinoline. It was filtered and washed with water; the solid product was recrystallized from aqueous ethyl acetate to give 7-chloro-5-nitro-8-hydroxyquinoline **13** as a bright orange solid which melted at 238-239^{0}C (lit. 239-240.5^{o}C). [14]

7-Chloro-5-amino-8-hydroxyquinoline (14)

7-Chloro-5-nitro-8-hydroxyquinoline **13** (7.0 g, 33 mmole) was grounded in a mortar with 1 M potassium hydroxide solution (33 ml) to ensure complete reduction of the insoluble potassium salt. The suspension was transferred with water (100 ml) into 250 ml round bottom flask equipped with a long magnetic stirring bar; it was heated in a water bath with vigorous stirring. 8M potassium hydroxide solution (22 ml) was added while the stirring and heating continued. At 50° the mixture was treated with sodium dithionite (22.0 g) and re-heated to a temperature of 80°C and maintained for 10 min. More sodium dithionite (10 g) was added and the reaction continued for further 10 min. The resulting suspension was cooled in ice and the precipitate was filtered, washed with cold water containing a trace of dithionite to avoid auto-oxidation and dried quickly in an oven to give 7-chloro-5-amino-8-hydroxyquinoline **14** (4.3 g), a golden yellow solid, which melted at 170-171^{o}C (lit. 172-173^{o}C).[14]
FT-IR spectrum (DMF) cm^{-}1:3400-3350 (NH), 1605, 1560, 1480 (C=). ^{1}H-NMR (DMSO-d_6) δ: 7.30-8.90 (3H, m, pyridine protons), 7.10 (1H, s, phenolic proton), 5.10 (1H, s, OH) and 3.95 (1H, s, NH_2). ^{13}C-NMR ($CDCl_3$) ppm: 152.2 (C-2), 144.1 (C-8), 142.3 (1C), 137.6(C-5), 128.7 (C-7), 121.2 (1C), 118.4 (1C), 115.6 (1C), 112.5 (1C).
Elemental analysis calculated for $C_9H_7ClN_2O$, %: C, 55.54; H, 3.63; Cl, 18.22; N, 14.39; Found; C, 55.62; H, 3.65; Cl, 18.17; N, 14.40.

7-Chloro-5,8-dioxoquinoline (15).

5-Amino-7-chloro-8-hydroxyquinoline **14** (3.0 g, 17 mmole) was weighed into a 500 ml round bottom flask equipped with long magnetic bar immersed in an ice-salt bath. Water (100 ml) was added with vigorous stirring, 6 M sulphuric acid (3 ml) was later added to dissolve the amine. The entire mixture was cooled to 2^{o}C with continuous stirring while ice cold solution of 2 M potassium dichromate (17 ml) and 6 M sulphuric acid (12 ml) was added at once and the stirring continued for further 20 min. At the end of the reaction period, the mixture was filtered in a Buckner funnel containing trace amount of ice, it is washed with cold water and air dried. It is recrystallized from dimethylformamide to give 7-chloro-5,8-dioxoquinolne (6) as fine orange solid, m. p. 171-172^{o}C (dec.).[14] FT-IR (KBr): cm^{-1}: 3162 (C=C-H), 1670 (C=O), 1600, 1572, 1465 (C=C), 1370, 703. ^{1}H-NMR (DMSO-d_6) δ: 8.50-9.20 (3H, m, pyridine protons), 7.15 (1H,s, quinoid ring proton). ^{13}C-NMR ($CDCl_3$) ppm: 185.0 (2C=O), 153.8 (C-2), 151.4 (1C), 147.6 (C-7), 138.2 (C-4), 135.6 (C-6), 130.8 (1C), 128.7 (1C).
Elemental analysis calculated for $C_9H_4ClNO_2$ %: C, 55.84; H, 2.08; Cl, 18.31; N, 7.24; Found C, 55.96; H, 2.08; Cl, 18.20; N, 7.28.

1,15,17-Triazadibenzo[a,n]triphenodithiazine-5,11-dione (17)

2,6-Diminopyridine-3,5-dithiol **9 (**2.0 g, 10 mmole) was weighed into a 250 ml 3-necked reaction flask equipped with reflux condenser, magnetic bar and thermometer. A solution of benzene (100 ml) and DMF (20 ml) was added, anhydrous sodium carbonate (3.0 g, 28 mmole) was also added and the entire mixture warmed for 45 minutes for dissolution. 7-Chloro-5,8-dioxoquinolne **(6)** (3.8 g, 20 mmole) was later added and the entire mixture refluxed for 7 hr on a water bath. At the end of the reflux period, the benzene solvent was distilled of and water added to the slurry and warmed to dissolve the inorganic material. It was filtered and dried. It was later chromatographed on alumina column eluting with methanol-benzene and recrystallized twice from acetone/DMF after treatment with activated carbon to give the parent new heterocycle characterized as 1,15,17-triazadibenzo[a,n]triphenodithiazine-5,11-dione **(17)** as a pale red powder, m. p. > 300^{o}C.
Uv-visible: (DMF); λ max (ε) 236nm (13505), 287nm (15107), 337nm (16035), 441nm (12650), 499nm (11670), 620nm (10755). FT-IR (KBr) v cm^{-1}: 3130 (C=C-H), 1680 (C=O), 1558, 1460 (C=C), 1377, 1273, 1138, 881, 791, 708, 661.
^{1}H-NMR (DMSO), δ 7.10 (s, H-8), δ7.85-8.35 (m, H-2, H-3, H-4, H-12, H-13, H-14), δ 8.95 (s, H-6, H-10), ^{13}C-NMR: ($CDCl_3$) (ppm); 178.5 (2C=O), 163.6 (2C), 157.4 (2C), 154.7 (2C), 153.5 (2C), 150.2 (2C), 147.0 (2C), 135.6 (2C), 133.1 (2C), 127.6 (2C), 118.2 (2C), 115.3 (1C).
Elemental analysis calculated for $C_{23}H_9N_5O_2S_2$ %: C, 61.19; H, 2.01; N, 15.51; S, 14.20, Found %: C, 61.23; H, 1.97; N, 15.50; S, 14.23.

1,15,17-Triazadibenzo[a,n]triphenodithiazine-5,11-diol (21)

1,15,17-Triazadibenzo[a,n]triphenodithiazine-5,11-dione (1.0 g, 22 mmole) is placed into a 250 ml reaction flask containing 150 ml of methanol and equipped with reflux condenser. Sodium dithionite (4.0 g, 22 mmole) was added and the entire mixture refluxed for 2 hr on a water bath. During the time of reflux, the colour of mixture changed from pale red to bright yellow. At the time of workup, the reduced dye became re-oxidized resulting in the regeneration of the original colour of the dye which made it difficulty to isolate the pure leuco-base and characterize.

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