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THE FIRST BRANCHED BENZOXAZINOPHENOTHIAZINE RING SYSTEM AND ITS AZA-ANALOGUES

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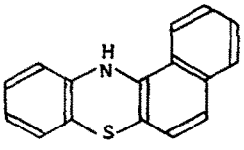
Abstract: The synthesis of a branched benzoxazinophenothiazine heterocycle is described. The parent compound benzo[a][1,4]-benzoxazino[3,2-c]phenothiazine (12), was obtained from 2,3-dichloro-1,4-naphthoquinone (6), 2-aminophenol and 2-amino-thiophenol. Monoaza-, diaza- and triaza- analogues of this novel heterocycle were also synthesized. The parent compounds, 16-oxa-15-thia-4,5,10-triazabenzo[h]pentaphene (18) and 16-oxa-15-thia-4,5,10,14-tetraazabenzo[h]pentaphene (22, R=H) were also synthesized as well as 4-amino-16-oxa-15-thia-4,5,10,12,14-pentaazabenzo[h]pentaphene (24). They are intensely coloured high-melting solids suitable for application as pigments. Their ease of reduction with $Na_2S_2O_4$ and the ready oxidation of the reduced compounds to the quinoid forms by atmospheric oxygen suggest their applicability also as vat dyes.

The chemistry of phenothiazine [1,2] and phenoxazine [3,4] has been of interest for over a century due to their wide range of applications and the natural occurrence of the latter. Angular systems exemplified by benzo[a]-phenothiazine (1)[5,6] and the blue dye, Meldola's Blue (2)[7,8], have been known for nearly a century. Although the "three-branched" fused phenothiazine ring, 3, is well-known, [9,11] there is practically no report of a mixed angular phenothiazine-phenoxazine system of type 4. We wish to report here the first synthesis of a three-branched benzoxazinophenothiazine ring system together with its monoaza-, diaza- and triaza-analogues.



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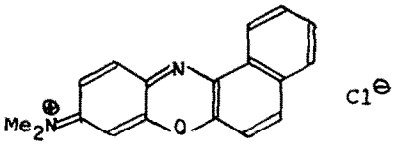

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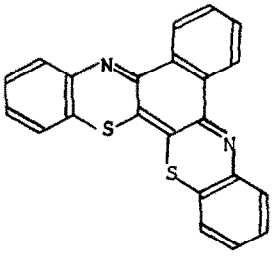

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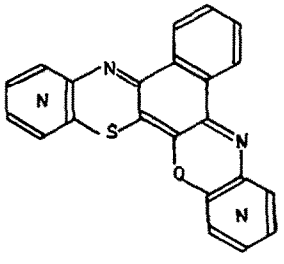
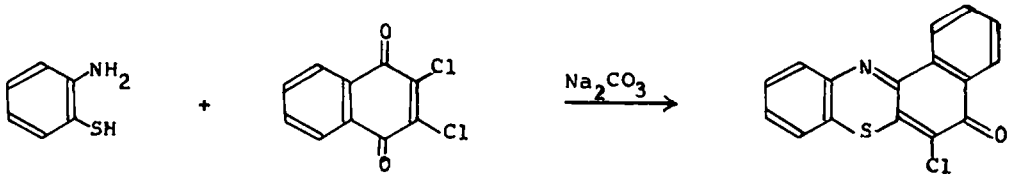


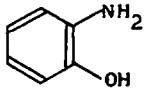
4

2,3-Dichloro-1,4-naphthoquinone (6) undergoes double condensation with 2-aminothiophenol (5) in the absence of a base to give excellent yields of the branched system 3.[11] However, in the presence of a base, monocondensation takes place resulting in the formation of the angular system, 6-chlorobenzo[a]phenothiazin-5-one (7), in satisfactory yield.



5 6 7

A similar reaction of compound 6 with 2-aminophenol (8) gave the phenoxazine analogue (9), also in good yield.[12] No "three-branched" systems were isolated in reactions carried out under alkaline conditions.



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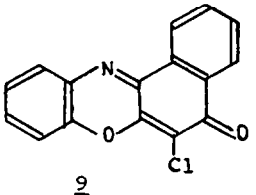
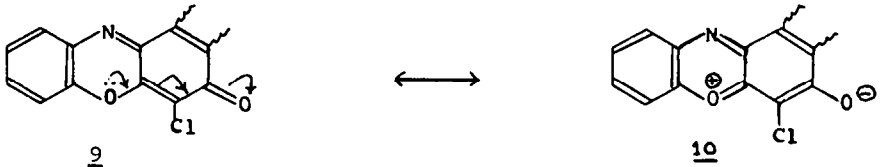
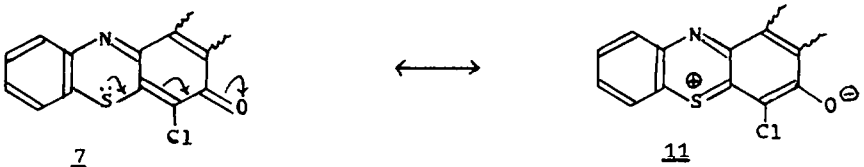


9

Further condensation of product 7 or 9 with sodium 2-aminophenoxide did not give the expected branched system, 4. Instead, the starting materials were recovered. It was shown in an earlier paper[13] that although the nucleophilic displacement of one of the halogens in compound 6 proceeds with ease, the displacement of the second halogen is difficult due to the existence of the covalent and ionic forms in which the ionic form predominates. In the particular cases, the zwitterionic enol forms 10 and 11 predominate.



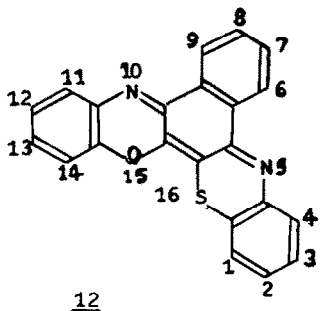
9 10



7 11

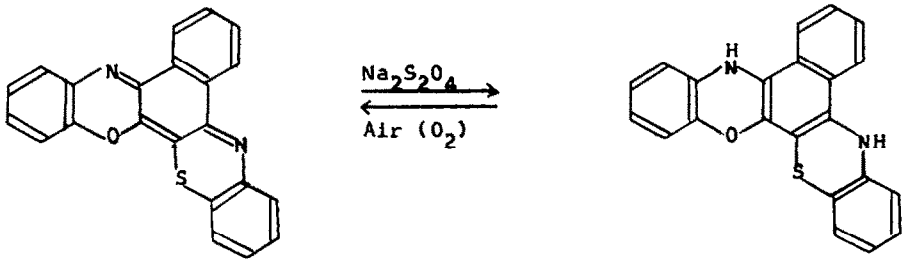
The predominance of forms 10 and 11 will therefore reduce the ease of nucleophilic displacement of the halogen by the nucleophile. Sodium 2-aminophenoxide, being a weaker nucleophile than sodium 2-aminothiophenoxide, will not successfully displace the halogen. In the circumstances, the starting materials were recovered.

If, however, compound 9 is first obtained and later treated with the more powerful sodium 2-aminothiophenoxide, the displacement of the halogen should occur. This, in fact, is the case. The treatment of compound 9 with o-aminothiophenol in the presence of anhydrous sodium carbonate gave an intensely coloured solid A. Microanalysis and spectroscopy are in agreement with the branched hexacyclic structure 12. This compound, benzo[a][1,4]benzoxazino-[3,2-c]phenothiazine (12), is a new heterocyclic compound and the parent compound of this new ring system.



12

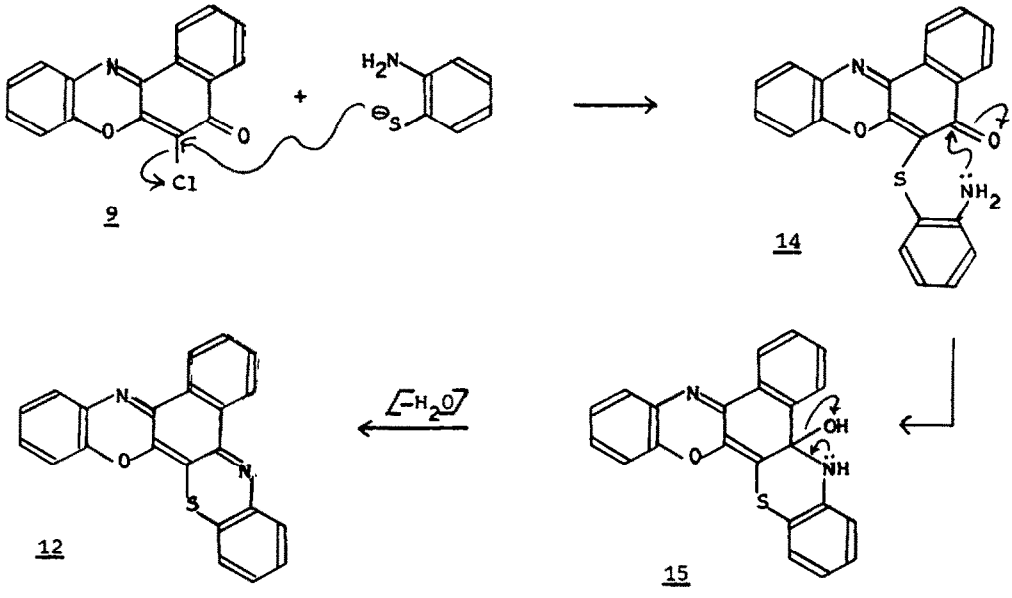
It is a stable purple-blue compound and is easily reduced by sodium hydrosulphite to give a discoloured unstable compound 13 which reverted to the quinoid and more stable structure (12) by air oxidation during work-up.



12 13

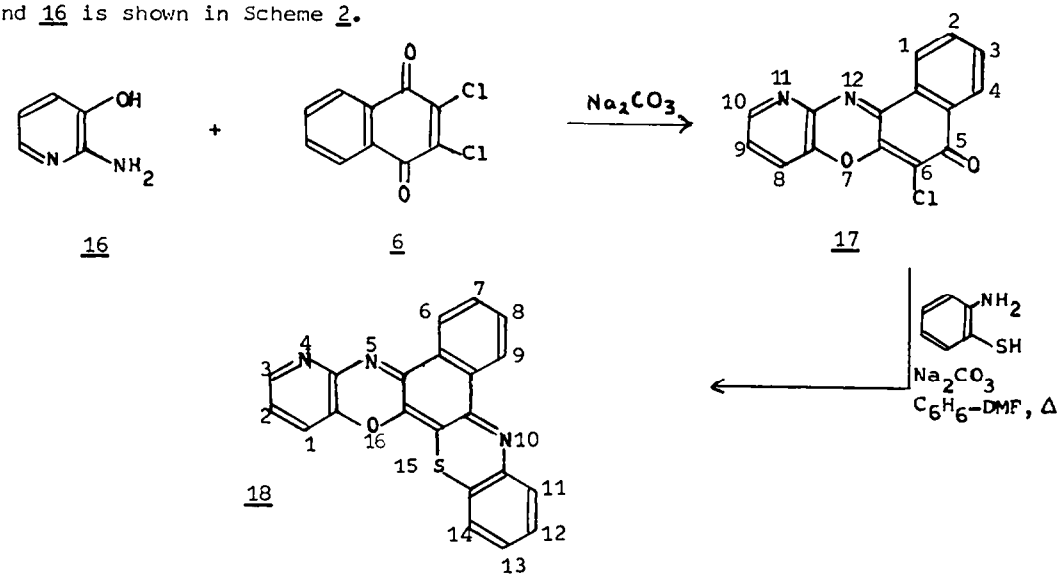
Reaction of compound 7 with sodium 2-aminothiophenoxide gave benzo[a]-[1,4]benzothiazino[3,2-c]phenothiazine (3) identical in all respects with an authentic sample prepared by the previously reported methods.[9-11]

Product 12 was probably formed by an initial nucleophilic displacement of the halogen by the thiophenoxide ion fcllowed by condensation and cyclization of the resulting diaryl sulphide 14 (Scheme 1).



SCHEME 1

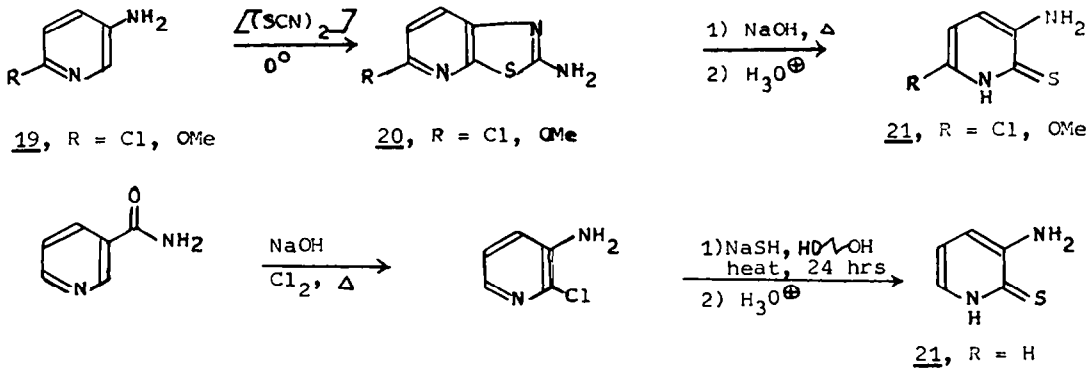
As an extension of this chemistry, the synthesis of some monoaza-, diaza- and triaza-analogues of the benzoxazinophenothiazine system 12 was undertaken. 2,3-Dichloro-1,4-naphthoquinone (6) was condensed with 2-amino-3-pyridinol (16) in an alkaline medium to yield 6-chloro-7-oxa-11,12-diazabenz[a]antharen-5-one (17). Further treatment with an equimolar amount of alkaline 2-aminothiophenol gave a purple-red product of molecular formula $C_{21}H_{11}N_3OS$. Mass spectroscopy, infrared, ultraviolet and visible spectra of the solid are in agreement with structure 18. Thus this product is 16-oxa-15-thia-4,5,10-triazabenzo[h]pentaphene (18). It is a new heterocyclic ring system as well as the parent compound of this new heterocycle. Its preparation from compounds 6 and 16 is shown in Scheme 2.



16 6 17 18

SCHEME 2

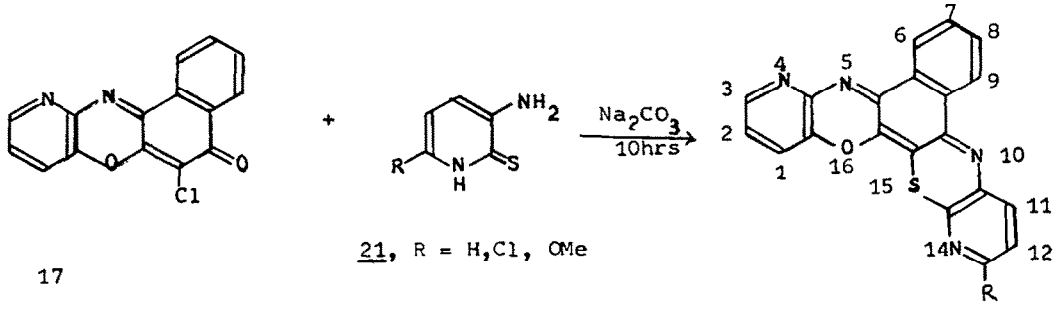
For the synthesis of the diaza-analogues, 2-aminopyridine thiols replaced o-aminothiophenol. These compounds were obtained by treating 3-amino-6-substituted pyridines (19) with potassium thiocyanate in the presence of bromine.[14] The resulting 2-amino-5-substituted-thiazolo[5,4-b]pyridines (20) were hydrolysed to yield 3-amino-6-substituted pyridine-2(1H)-thiones (21) in good yields. This reaction works well if the aminopyridine is substituted with an electron-releasing group para-to the amino group. 3-Aminopyridine-2(1H)-thione (21, R=H) was therefore not obtained in this way. A successful procedure for the synthesis of compound 21, R=H, involves the conversion of nicotinamide to 3-amino-2-chloropyridine followed by heating this product strongly in admixture with sodium hydrosulphide[15] in ethylene glycol for 24 hours.



19, R = Cl, OMe 20, R = Cl, OMe 21, R = Cl, OMe

21, R = H

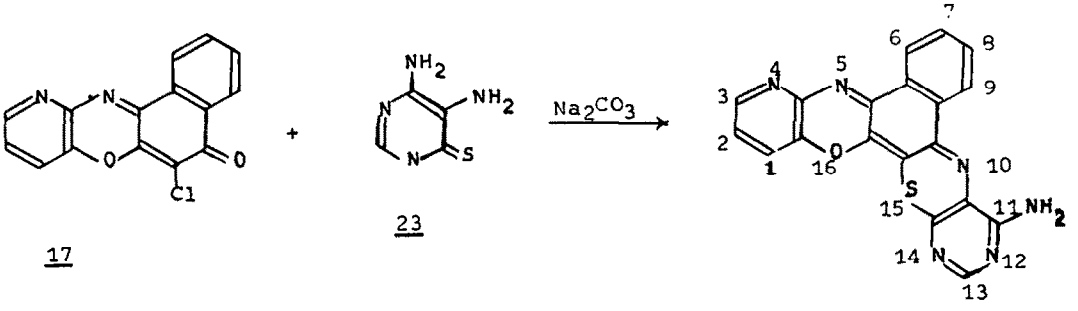
Reaction of these 3-aminopyridine-2(1H)-thiones (21, R = H, Cl, OMe) with product 17 in the presence of anhydrous sodium carbonate gave 16-oxa-15-thia-4,5,-10, 14-tetraazabenzo[h]pentaphene (22, R = H, Cl, OMe) whose structures were confirmed by analysis and spectroscopy. These are derivatives of a new branched hexacyclic heterocycle while product 22, R=H is the parent heterocycle (Scheme 3).



17 21, R = H,Cl, OMe 22, R = H,Cl, OMe

SCHEME 3

An alkaline solution of 4,5-diaminopyrimidine-6(1H)-thione (23) also reacts with compound 17 to give the first triaza-analogue (24) of this 'three-branched' phenoxazinophenothiazine ring system. Product 24 is a purple red solid melting above 300°. It is the only product isolated from this reaction. Microanalysis and mass spectroscopy agree the molecular formula $C_{19}H_{10}N_6OS$. Infrared, ultraviolet and visible spectroscopy are also in agreement with the assigned structure in Scheme 4.



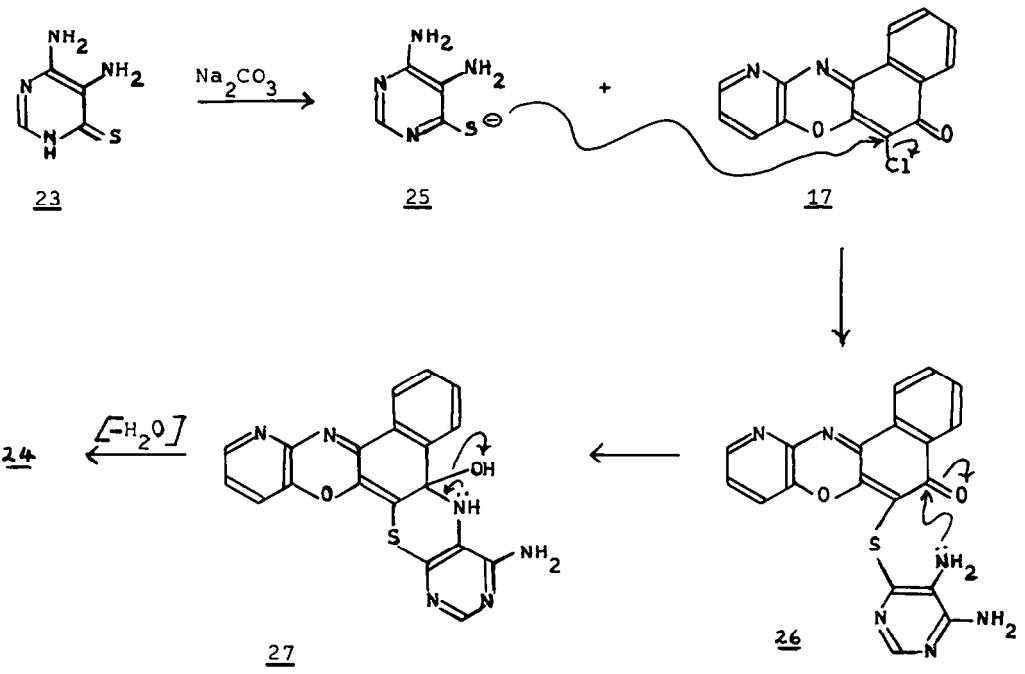
17 23 24

SCHEME 4

Thus compound 24 is 11-amino-16-oxa-15-thia-4,5,10,12,14-pentaazabenzo[h]pentaphene.

The formation of compounds 18, 22 (R=H, Cl, OMe) and 24 proceeds by a mechanism similar to that formulated for benzo[a][1,4]benzoxazino[3,2-c]phenothiazine (12). The isolation of only compound 24 in the reaction of compound 17 with 4,5-diaminopyrimidine-6(1H)-thione (23) which has an additional nucleophilic (amino) group is another evidence for the proposed mechanism (Scheme 5).

The mercaptide ion (25) being more nucleophilic than any of the two amino groups preferentially mounts a nucleophilic attack on the chlorophenoxazone 17 leading to the formation of the diaryl sulphide 26. Cyclization was achieved by the internal condensation of the carbonyl and amino groups leading to the isolated branched triazabenzoxazinophenothiazine heterocycle.



SCHEME 5

The parent compounds and the derivatives of these novel hexacyclic ring systems are intensely coloured compounds applicable as dyes and pigments. Their ease of preparation and reduction with sodium hydrosulphite coupled with the ease of autoxidation of the reduced forms in atmospheric oxygen to the quinoid systems make them applicable as vat dyes.

Experimental

Melting points 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 (nm); 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 AEI MS-9 double-focussing mass spectrometer at 70 eV. All products were purified by column chromatography on aluminium oxide 90 (Merck, 70-230 mesh ASTM) eluting with benzene-ethyl acetate mixture before recrystallization.

6-Chlorobenzo[a]phenoxazin-5-one (9): This compound was prepared as previously[12] reported except that benzene/N,N-dimethylformamide (DMF) (25:1) mixture was used as the solvent and anhydrous sodium carbonate used in the place of anhydrous sodium acetate; m.p. 202-203°, yield 95% (lit.[12] m.p. 203°C, yield 89%).

Benzo[a][1,4]benzoxazino[3,2-c]phenothiazine (12): 2-Aminothiophenol (5) (1.25 g, 10 mmol) was placed in the reaction flask containing 30 ml of benzene and 20 ml of DMF. Anhydrous sodium carbonate (2.12 g, 20 mmol) was added and the mixture heated on a water bath until refluxing commenced. 6-Chlorobenzo[a]phenoxazin-5-one (9) (2.82 g, 10 mmol) was then added and the entire mixture refluxed on the water bath with stirring for 9 hours. It was then poured into 500 g of crushed ice and filtered. The dark residue was dissolved in a large volume of boiling acetone, boiled and filtered hot. The filtrate was allowed to cool in the refrigerator. The solid that separated was collected by filtration and repurified by chromatography. Unreacted 6-chlorobenzo[a]phenoxazin-5-one (9) (0.59 g, 2.1 mmol) was recovered during chromatographic separation of the products. The second component was collected and recrystallized from aqueous acetone after treatment with activated charcoal. Purple-

blue plates of benzo[a][1,4]benzoxazino[3,2-c]phenothiazine (12) which separated were collected by filtration to yield 2.15 g (61% yield); m.p. 275-276°C (dec); UV-V λ_{max} (MeOH) 271 nm (ε 22,250), 366 (18,800), 380 (18,700), 529 (5,670), 558 (5,820); IR (KBr) ν_{max} 746 cm^{-1} (four adjacent aromatic hydrogen atoms; ^{1}H-NMR (DMSO-d_6) δ 8.03 (m, aromatic protons); MS m/e (relative intensity) 320 (21%, M^+-S), 352 (100%, M^+). [Found: C, 75.15; H, 3.24; N, 8.01; S, 8.92. Calc. for $C_{22}H_{12}N_2OS$: C, 75.00; H, 3.41; N, 7.95; S, 9.09].

Sodium hydrosulphite reduction of Benzo[a][1,4]benzoxazino[3,2-c]phenothiazine (12): Benzo[a][1,4]-benzoxazino[3,2-c]phenothiazine (12) (1.76 g, 5 mmol) was dissolved in 200 ml of acetone to which was added 2 ml of water. Sodium hydrosulphite (4.0 g) was added and the mixture refluxed on a water bath for 3 hr.

At the end of the reflux period, the yellowish brown mixture was poured into 500 ml of ice-cold water containing 5 g of sodium hydrosulphite. It was quickly filtered but in the process the residue changed colour to that of the starting quinoid system 12. It was purified however in the usual way. Mixed melting point, infrared and ultraviolet-visible spectra show that the isolated product is 12 confirming air oxidation of product 13 to the starting compound 12.

16-Oxa-15-thia-4,5,10-triazabenzo[h]pentaphene (18): A mixture of 2-amino-3-pyridinol (16) and 2,3-dichloro-1,4-naphthoquinone (6) in chloroform in the presence of anhydrous sodium carbonate was converted to 6-chloro-7-oxa-11,12-diazabenz[a]anthracen-5-one (17) as was previously described[16]. 2-Aminothiophenol (5) (0.625 g, 5 mmol) was placed in the reaction flask containing 60 ml of benzene-DMF (10:1) mixture and anhydrous sodium carbonate (1.06 g, 10 mmol). The mixture was heated on the water bath until boiling commenced. 6-Chloro-7-oxa-11,12-diazabenz[a]anthracen-5-one (17) (1.41 g, 5 mmol) was then added and the mixture refluxed on a water bath for 8 hr.

At the end of the reflux period, the slurry was poured into 800 ml of water, stirred and filtered. The residue, which is very insoluble in most organic solvents, was separated into its components by column chromatography on alumina (Merck, 70-230 mesh ASTM) eluting with (1 : 10 : 10) DMF-benzene-acetone mixture. Unreacted 6-chloro-7-oxa-11,12-diazabenz[a]anthracen-5-one (17) (0.25 g, 0.9 mmol) was recovered. 16-Oxa-15-thia-4,5,10-triazabenzo[a]pentaphene (18)(1.20 g, 68% yield) was isolated from the column as a purple-red powder, m.p. 284-285°C (dec); UV-V λ_{max} (MeOH) 263 nm (ε 20,900), 316 (14,700), 366 (16,700), 527 (12,800); IR (KBr) ν_{max} 770 (2,3-disubstituted pyridine), 764 cm^{-1} (four adjacent aromatic hydrogen atoms); ^{1}H-NMR (DMSO-d_6) δ 8.07 (m, aromatic protons); MS m/e (relative intensity) 321 (M-S, 100%), 353 (95%m M^+) [Found: C, 71.41; H, 3.00; N, 12.06; S, 8.94. Calc for $C_{21}H_{11}N_3OS$: C, 71.39; H, 3.12; N, 11.90; S, 9.06].

16-Oxa-15-thia-4,5,10,14-tetraazabenzo[h]pentaphene (22, R = H): 3-Amino pyridine-2(1H)-thione (21, R=H) required for this synthesis was prepared by the Hofmann rearrangement of nicotinamide followed by the reaction of the 3-amino-2-chloropyridine[15] with sodium hydrosulphide in ethylene glycol for 24 hr.

3-Aminopyridine-2(1H)-thione (21, R=H) (0.63 g, 5 mmol) was placed in the reaction flask containing anhydrous sodium carbonate (1.06 g, 10 mmol) in benzene (50 ml)-DMF (5 ml) mixture. The mixture was heated to reflux temperature. 6-Chloro-7-oxa-11,12-diazabenz[a]anthracen-5-one (17) (1.41 g, 5 mmol) was then added. The entire mixture was then refluxed for 10 hr. At the end of the reflux period, the solvent was removed by distillation. The dark residue was taken up in 600 ml of water and heated to near boiling and filtered. The residue was crystallized from acetone after treatment with activated charcoal to yield 16-oxa-15-thia-4,5,10,14-tetraazabenzo[h]pentaphene (22, R=H) (1.03 g, 58% yield) as purple-brown microplataes, m.p. > 300°C, UV-V λ_{max} (MeOH) 280nm (ε 20,500), 342, (18,900), 457 (7,080); IR (KBr) ν_{max} 800 (2,3-disubstituted-pyridine), 742 cm^{-1} (four adjacent aromatic hydrogen atoms); ^{1}H-NMR (DMSO-d_6) δ 7.80 (m, aromatic protons); MS m/e (relative intensity) 352 (92%, M^+). [Found: C, 67.77; H, 3.01; N, 15.89; S, 8.95. Calc for $C_{20}H_{10}N_4OS$: C, 67.80; H, 2.82; N, 15.82; S, 9.04].

13-Chloro-16-oxa-15-thia-4,5,10,14-tetraazabenzo[h]pentaphene (22, R=Cl): Thiocyanation of 3-amino-6-chloropyridine followed by base-catalysed hydrolysis of the resulting 2-amino-5-chloro[thiazolo][5,4-b]pyridine (20, R=Cl) gave 3-amino-6-chloropyridine-2(1H)-thione (21, R=Cl) after acidification. A mixture of 3-amino-6-chloropyridine-2(1H)-thione (1.61 g, 10 mmol), 6-chloro-7-oxa-11,12-diazabenz[a]anthracen-5-one (17) (2.82 g, 10 mmol) and anhydrous sodium carbonate (2.12 g, 20 mmol) was converted to 13-chloro-16-oxa-15-thia-4,5,10,14-tetraazabenzo[h]pentaphene (22, R=Cl) as was described for compound 22, R=H. The product, 22, R=Cl, is a red-brown powder, m.p > 300°C, UV-V λ_{max} (MeOH) 285 nm (ε 18,800), 346 (14,200), 460 (21,400); IR (KBr) ν_{max} 825 (two adjacent aromatic hydrogen atoms), 772 cm^{-1} (2,3-disubstituted-pyridine); ^{1}H-NMR (DMS)-d_6) δ 8.17 (m, aromatic protons); MS m/e (relative intensity) 388 (100%, M^+), 390 (34%, M + 2). [Found: C, 61.90; H, 2.36; N, 14.25. S, 8.11; Cl, 8.98.

Calc for $C_{20}H_9N_4OSCl$: C, 61.78; H, 2.32; N, 14.41; S, 8.24; Cl, 9.14%.

13-Methoxy-16-oxa-15-thia-4,5,10,14-tetraazabenzo[h]pentaphene (22, R=OMe): This compound was prepared from 3-amino-6-methoxypyridine-2(1H)-thione (21, R=OMe) and 6-chloro-7-oxa-11,12-diazabenz[a]anthracen-5-one (17) in alkaline medium as was described for compound 22, R=H. Glistening red plates of 13-methoxy-16-oxa-15-thia-4,5,10,14-tetraazabenzo[h]pentaphene (22, R=OMe) were obtained in 73% yield; m.p. > 300°; UV-V λ_{max} (MeOH) 251 nm (ε 21,800); 278 (14,200), 350 (12,000), 480 (13,700); IR (KBr) ν_{max} 824 (two adjacent aromatic hydrogen atoms), 770 cm^{-1} (2,3-disubstituted pyridine); ^{1}H-NMR (DMSO-d_6) δ 7.57-8.00 (m,aromatic protons), 4.03 (s, 2-OCH_3); MS m/e (relative intensity) 384 (100%, M^+). [Found: C, 65.60; H, 3.25; N, 14.76; S, 8.21. Calc for $C_{21}H_{12}N_4O_2S$: C, 65.63; H, 3.13; N, 14.58; S, 8.33%.

11-Amino-16-oxa-15-thia-4,5,10,12,14-pentaazabenzo[h]pentaphene (24): 4,5-Diaminopyridine-6(1H)-thione (23) was obtained by the action of phosphorus pentasulphide on 4,5-diaminopyrimidin-6(1H)-one as was earlier reported[16]. Compound 23 (0.71 g, 5 mmol) was placed in a 60 ml solution of benzene and DMF (10 : 1). Anhydrous sodium carbonate (1.06 g, 10 mmol) was then added. The mixture was refluxed on a water bath for 15 minutes. 6-Chloro-7-oxa-11,12-diazabenz[a]anthracen-5-one (17) (1.41 g, 5 mmol) was added to the boiling mixture and the entire solution refluxed with stirring for 9 hr.

It was then poured into 700 ml of water and stirred for half an hour, cooled and filtered. The purple residue was collected and recrystallized from aqueous acetone after treatment with activated charcoal to give 11-amino-16-oxa-15-thia-4,5,10,12,14-pentaazabenzo[h]pentaphene (24) (1.2 g, 65% yield) as purple-red microncedles, m.p. > 300°C; UV-V λ_{max} (MeOH) 255 nm (ε 20,900), 353 (14,000), 443 (18,200); IR (KBr) ν_{max} 3420 (NH_2), 870 (one lone aromatic hydrogen atom), 784 (2,3-disubstituted pyridine), 765 cm^{-1} (four adjacent aromatic hydrogen atoms); MS m/e (relative intensity) 370 (97%, M^+). [Found: C, 61.45; H, 2.64; N, 22.88; S, 8.62. Calc for $C_{19}H_{10}N_6OS$: C, 61.62; H, 2.70; N, 22.70; S, 8.65%.

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