Studies in the Heterocyclic Series XVII. A New Type of Triazaphenothiazine Heterocycle

Charles O. Okafor

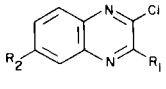
Department of Chemistry, University of Nigeria, Nsukka, Nigeria

Received July 13, 1979

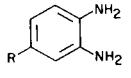
The synthesis of derivatives of 1,4,6-benzo[*b*]triazaphenothiazine, a novel aza-analog of phenothiazine, is described. The parent compound was obtained by base-catalysed condensation of 3-amino-2-mercaptopyridine with 2,3-dichloroquinoxaline in aqueous DMF. Several derivatives were also prepared by using the appropriately substituted aminomercaptopyridines and dichloroquinoxalines. Nitration with mixed nitric and sulfuric acids gave the corresponding 13-nitro-1,4,6-benzo[*b*]triazaphenothiazine derivatives. The structures were elucidated by chemical evidence and by a study of their infrared, ultraviolet, pmr and mass spectra.

J. Heterocyclic Chem., **17**, 149 (1980).

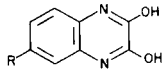
Phenothiazine derivatives have been recognised as an important class of compounds in the treatment of psychiatric disorders (1,2). As modifications of the parent ring, replacement of sulfur and the side ring carbon atoms with nitrogen (3,4), oxygen (5,6) and sulfur (7-9) has been undertaken by several workers. In the aza-analog series, four monoaza-, ten diaza-, three triaza- and four tetraaza-phenothiazine rings have been prepared (3,4). Such novel phenothiazine heterocycles can also be amino-alkylated at position 10 to afford congeners of tricyclic antipsychotics (10,11). Out of the anticipated twenty-four structural isomers of triazaphenothiazine, only three of them have so far been synthesized (12-16); the remaining twenty-one isomeric rings remain unknown. Our recent attempts at the synthesis of novel rings in these series have now led to a new heterocyclic ring system, its parent compound and its derivatives.



I

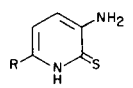


II

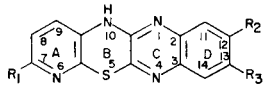


III

Our approach begins with the synthesis of quinoxaline derivatives having reactive groups in positions 2 and 3. Previously *o*-chloronitroaryl compounds were used in related syntheses but in view of the inherent reactivity of halogens in C-2 and C-3 of pyrazine towards nucleophilic reagents, 2,3-dichloroquinoxalines (I, R_1 = Cl, R_2 = H) were preferred. Essentially three methods were used to prepare these compounds from the appropriate *o*-phenylenediamines (II). With glyoxal sodium bisulfite (17), compounds II gave the corresponding quinoxalines which were converted to 2,3-dihydroxyquinoxalines (III) and quinoxaline-1,4-dioxides (IV) by the action of formic acid and hydrogen peroxide in 20% and 53% yields respectively. Both products were converted to the desired 2,3-dichloroquinoxalines by the action of phosphorus pentachloride and phosphorus oxychloride, respectively (18). In another method, hydroxylation of the quinoxalines formed in these reactions was also achieved in improved yields by a modified reaction with ammonium peroxodisulfate (19). A third and modified procedure leading to excellent yields of compounds I (R_1 = Cl, R_2 = H, Cl) involved the condensation of the *o*-phenylenediamine with ethyl oxalate (20) followed by heating the resulting 2,3-dihydroxyquinoxaline strongly in phosphorus pentachloride in the presence of catalytic amounts of phosphorus oxychloride in diethylamine.



V



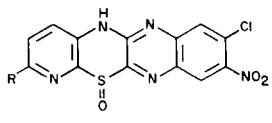
VI

When equimolar amounts of 2,3-dichloroquinoxaline (I, R_1 = Cl, R_2 = H) and 3-amino-6-methoxypyridin-2[1*H*]-thione (V, R = OCH_3) (21) were refluxed in an alkaline solution of aqueous *N,N*-dimethylformamide (DMF), an orange-yellow crystalline material melting at 287-288° was isolated after work-up. Elemental analysis and mass spectroscopy are in agreement with the molecular formula, $C_{14}H_{10}N_4SO$. A band at 241 nm characteristic of phenothiazinoid systems was observed in the uv spectrum. The infrared spectrum showed a medium band at 3280 cm^{-1} due to the presence of secondary aromatic NH group, a strong band at 820 cm^{-1} which was attributed to two adjacent hydrogens in the pyridine ring and a very strong peak at 758 cm^{-1} due to 1,2-disubstitution in the quinoxaline ring (22). These results are in perfect agreement with structure VI, R_1 = OCH_3, R_2 = R_3 = H which we have assigned to this product. Further evidence of structure was provided by the pmr spectrum in which the 10-NH proton appeared as a broad peak at 0.18 τ. A multiplet at 2.65 τ

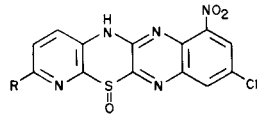
0022-152X/80/010149-05$02.25

was assigned to ring D protons while the C-8 and C-9 protons in ring A appeared as AB doublets at 3.60 and 2.97 τ, respectively (J_{89} = 9.0 Hz). The product of the reaction of compounds I, R_1 = Cl, R_2 = H and V, R = OCH_3 is therefore 7-methoxy-1,4,6-benzo[*b*]triazaphenothiazine (VI, R_1 = OCH_3, R_2 = R_3 = H) (23).

A similar reaction of compound V, R = OCH_3 with 2,3,6-trichloroquinoxaline (I, R_1 = R_2 = Cl) also gave a single product in a good yield. In this case there are two structural possibilities, VI, R_1 = OCH_3, R_2 = Cl, R_3 = H and VI, R_1 = OCH_3, R_2 = H, R_3 = Cl. Elemental analysis, infrared, ultraviolet, pmr and mass spectroscopy are in agreement with either of the structures. In order to establish the correct structure, the product of this reaction was treated with mixed concentrated nitric and sulfuric acids at room temperature. A mononitro sulfoxide (24) with strong infrared bands at 1052 cm^{-1} (S=O), 1343 cm^{-1} (Ar-NO_2) and 883 cm^{-1} (1,2,4,5-tetrasubstitution on

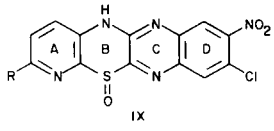


VII



VIII

ring D) was obtained. The above evidence fitted very well for structure VII, R = OCH_3. Structure VIII, R = OCH_3 was further eliminated on the ground that *o*-nitration at C-1 in phenothiazine (C-11 in this case) does not occur under the mild reaction conditions employed (25). The *m*-directing effect of C=N group in ring C leading to structure IX, R = OCH_3 is also eliminated for the same reason. The normal nitration site in phenothiazinoid



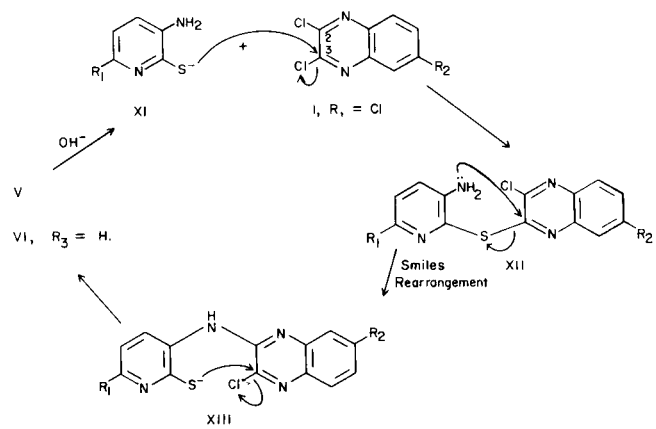
IX

systems is the position *para* to the amino group, that is, the 3-position which, in the case of structure VI, R_1 = OCH_3, R_2 = H, R_3 = Cl is blocked by chlorine in C-13. It follows therefore that the precursor of structure VII, R = OCH_3 is 12-chloro-7-methoxy-1,4,6-benzo[*b*]triazaphenothiazine VI, R_1 = OCH_3, R_2 = Cl, R_3 = H. Other derivatives of this ring structure with substituents in the 7- and 12- positions were similarly synthesized and characterized.

3-Amino-2-mercaptopyridine (X) required for the synthesis of the parent compound (VI, R_1 = R_2 = R_3 = H) was prepared by Hofmann rearrangement of nicotinamide (26) in the presence of chlorine and sodium hydroxide followed by sulfurization of the resulting 3-amino-2-chloropyridine with sodium hydrosulfide (27,28). It was found that if bromine which is more convenient to handle were used in the place of chlorine as the catalyst, the rearrangement however took place smoothly but without 2-halogenation (29) even on increasing the reaction time fivefold. Base catalysed condensation of compounds I, R_1 = Cl, R_2 = H and X in propylene glycol-aqueous DMF mixture gave a golden-yellow product, $C_{13}H_8N_4S$, m.p. >300°. The spectral data were in accord with the anticipated structure. Thus, the product of this reaction is therefore 1,4,6-benzo-[*b*]triazaphenothiazine VI, R_1 = R_2 = R_3 = H, the parent heterocyclic compound.

The formation of these 1,4,6-benzo[*b*]triazaphenothiazines was rationalised as proceeding by proton abstraction by the base from the 3-amino-2-mercaptopyridine leading to the mercaptide ion (XI) which now mounts a nucleophilic attack on C-3 of the quinoxaline ring. The resulting 2-chloro-3-(3-amino-2-pyridyl)quinoxalinyl sulfide (XII) underwent a Smiles rearrangement to the corresponding diarylamine XIII followed by an intramolecular mercaptide ion attack on C-2 of the quinoxaline ring (structure XIII) resulting in the loss of chloride ion and cyclization of the ring (Scheme 1). The nucleophile XI, attacks C-3 in

Scheme I



2,3,6-trichloroquinoxaline (I; R_1 = R_2 = Cl) because of the conjugative effect of the chlorine in C-6 position which, by release of electrons to the ring, will weaken the C_3-Cl bond thereby making the 2- position relatively more positive and hence susceptible to attack by the nucleophile. If Smiles rearrangement did not take place, the reaction of compound V (R = OCH_3) with 2,3,6-trichloroquinoxaline would have led to 13-chloro-7-methoxy-1,4,6-benzo[*b*]triazaphenothiazine VI, R_1 = OCH_3, R_2 = H, R_3 = Cl instead of compound VI, R_1 = OCH_3, R_2 = Cl, R_3 = H.

EXPERIMENTAL

General.

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Ultraviolet and visible spectra were recorded on Pye

Unicam SP 8000 spectrophotometer using matched 1 cm quartz cells. The solvent in all cases is methanol and the absorption maxima are always given in nanometers; the figures in parenthesis are log ϵ values. Infrared spectra were obtained on a Perkin Elmer Model 257 spectrophotometer using potassium bromide discs. Pmr spectra were determined on a Varian Associates T-60 instrument. Chemical shifts are reported on the τ scale relative to TMS used as an internal standard. The mass spectra were obtained on an AE1 MS-9 double-focusing mass spectrometer at 70 eV.

6-Chloroquinoxaline (I, $R_1 = R_2 = H$).

This compound was prepared by a modification of the previously described procedure (17,30). 4-Chloro-*o*-phenylenediamine (II, R = Cl) (2.85 g., 20 mmoles) was suspended in 50 ml. of 3 *M* acetic acid containing 25 ml. of 5 *M* sodium acetate. It was warmed to 50° and poured into a second solution of glyoxal sodium bisulfite monohydrate (8.52 g., 30 mmoles) in 250 ml. of water. The mixture was stirred on a water bath for 2 hours at 60° and cooled in an ice bath. It was then neutralized with concentrated ammonia to *p*H 10. The dark oily material which separated out was chilled and filtered. The residue was redissolved in benzene, treated with Norit and filtered. On cooling the filtrate, 6-chloroquinoxaline (3.03 g., 92% yield), was obtained as creamy long needles, m.p. 65°, lit. (30), 79% yield, m.p. 63.8-64.3°.

2,3-Dihydroxyquinoxaline (III, R = H).

A mixture of quinoxaline (3.25 g., 25 mmoles) and ammonium peroxodisulfate (45.6 g., 200 mmoles) in 150 ml. of water was relfuxed for 1 hour. It was later cooled in a refrigerator and filtered. The filtrate was concentrated to near dryness and neutralized with concentrated ammonia to *p*H 8 while cooling. After filtration and recrystallization of the residue from water (Norit), 1.70 g. (42% yield) of 2,3-dihydroxyquinoxaline (III, R = H) was obtained, m.p. >350°; (Bergmann and Ogg (19) reported a yield of 30%).

Conversion of *o*-Phenylenediamine to 2,3-Dichloroquinoxaline.

This compound was prepared from *o*-phenylenediamine by a modification of the previously described method.

To a mixture of *o*-phenylenediamine (14 g., 100 mmoles) and diethyl oxalate (29.20 g., 200 mmoles) was added 200 ml. of ethanol. The mixture was refluxed on a heating mantle for 8 hours, cooled and filtered. The residue was crystallized twice from ethanol after treatmenet with Norit. 2,3-Dihydroxyquinoxaline (14.58 g., 90% yield) was collected as colourless needles, m.p. >300°.

A portion of this product (4.05 g., 25 mmoles) was placed in the reaction flask to which was added 20.85 g. (100 mmoles) of phosphorus pentachloride, 10 ml. of phosphorus oxychloride and 3 ml. of diethylaniline. The mixture was refluxed for 2.5 hours in an oil bath maintained at 140-150°. The excess phosphorus halides were removed by distillation to near dryness. The gummy brown product was poured into ice and neutralized with concentrated ammonia while cooling. The resulting light brown precipitate was crystallized from benzene (Norit) to give glistening white crystalline plates of 2,3-dichloroquinoxaline (4.78 g., 96% yield), m.p. 148-149° (Stevens, Pfister and Wolf (20) reported a yield of 75%, m.p. 147-150°).

7-Methoxy-1,4,6-benzo[*b*]triazaphenothiazine (VI, $R_1 = OCH_3$, $R_2 = R_3 = H$).

3-Amino-6-methoxypyridin-2[1*H*]thione (6.86 g., 44 mmoles) was placed in a reaction flask containing 5.04 g. (90 mmoles) of potassium hydroxide and 50 ml. of water. The mixture was warmed to dissolve the contents. 2,3-Dichloroquinoxaline (7.96 g., 40 mmoles) and 30 ml. of *N,N*-dimethylformamide (DMF) were added. The solution was then refluxed on a heating mantle for three hours. After about five minutes of refluxing, massive yellowish precipitation took place but towards the end of the reflux period much of the precipitate went into solution. The contents of the flask were poured into a beaker. The flask was rinsed with water and the washings added to the beaker containing the products and cooled for 14 hours. On filtering, brown sperically-shaped materials were collected as the product. The entire product was recrystallized from DMF-methanol (2:1) mixture after treatment with Norit A. 7-Methoxy-1,4,6-benzo[*b*]triazaphenothiazine (VI, $R_1 = OCH_3$, $R_2 = R_3 = H$) was collected as an orange yellow powder (10.38 g., 92% yield), m.p. 287-288°; uv spectrum: λ max 241 nm (log ϵ 4.6544), 231 (3.8762), 426 (3.9274); ir spectrum (potassium bromide): ν max 3280, 2940, 1610, 1580, 1570, 1544, 1508, 1475, 1445, 1407, 1355, 1345, 1313, 1288, 1270, 1314, 1177, 1142, 1127, 1073, 1027, 978, 954, 932, 895, 847, 820, 800, 758, 735, 718, 680, cm^{-1}; pmr spectrum (DMSO-d_6): τ 0.18 (broad, 10-NH), 2.65 (multiplet, 11-H, 12-H, 13-H and 14-H), 2.97 (doublet, J = 9.0 Hz; 9-H), 3.60 (doublet, J = 9.0 Hz; 8-H), 6.40 (singlet, 7-OCH_3); ms: m/e (relative intensity) 141 (7), 212 (3), 213 (3), 239 (16), 267 (7), 289 (4), 282 (M^+; 100%), 283 (19), 284 (6).

Anal. Calcd. for $C_{14}H_{10}N_4OS$: C, 59.57; H, 3.55; N, 19.86; S, 11.35. Found: C, 59.67; H, 3.49; N, 19.88; S, 11.30.

7-Chloro-1,4,6-benzo[*b*]triazaphenothiazine (VI, $R_1 = Cl$, $R_2 = R_3 = H$).

An intimate mixture of 1.93 g. (12 mmoles) of 3-amino-6-chloropyridin-2[1*H*]thione and 1.99 g. (10 mmoles) of 2,3-dichloroquinoxaline was placed in a reaction flask containing 1.12 g. (20 mmoles) of potassium hydroxide dissolved in 20 ml. of water followed immediately by the addition of 12 ml. of DMF. The mixture turned yellowish-red in colour. It was then heated under reflux on a heating mantle for 2.5 hours. A massive yellowish brown precipitate which formed after 15 minutes persisted until the end of the reaction period. The mixture was then poured into a beaker, cooled and filtered. The product separated as yellow balls of various sizes ranging from 0.3 mm to 3.00 mm in diameter. It was collected and recrystallized from DMF-methanol-water (5:1:5) mixture. 7-Chloro-1,4,6-benzo[*b*]triazaphenothiazine (VI, $R_1 = Cl$, $R_2 = R_3 = H$) separated as yellowish-brown powder (2.06 g., 72% yield), m.p. 244-245°; uv spectrum: λ max 243 nm (log ϵ 4.3991), λ infl. 285 (3.8093), 337 (3.8762), λ infl. 390 (3.7582); ir spectrum (potassium bromide): ν max 3320, 1640, 1620, 1573, 1545, 1510, 1480, 1450, 1440, 1407, 1373, 1346, 1310, 1290, 1275, 1254, 1238, 1222, 1130, 1073, 1050, 1018, 994, 952, 1930, 874, 863, 831, 758, 730, 715, 673 cm^{-1}; pmr spectrum (DMSO-d_6): τ 2.45 (multiplet, aromatic protons); ms: m/e (relative intensity) 113 (77), 133 (29), 251 (3), 254 (5), 285 (5), 286 [M^+, 100%], 287 (17), 288 (35).

Anal. Calcd. for $C_{13}H_7ClN_4S$: C, 54.45; H, 2.44; N, 19.55; S, 11.17; Cl, 12.39. Found: C, 54.73; H, 2.24; N, 19.60; S, 11.02; Cl, 12.10.

12-Chloro-7-methoxy-1,4,6-benzo[*b*]triazaphenothiazine (VI, $R_1 = OCH_3$, $R_2 = Cl$, $R_3 = H$).

A mixture of 3-amino-6-methoxypyridin-2[1*H*]thione (3.43 g., 22 mmoles) and 4.67 g. (20 mmoles) of 2,3,6-trichloroquinoxaline was placed in an three-necked flask containing 2.24 g. (40 mmoles) of potassium hydroxide in 25 ml. of water and 30 ml. of DMF. The mixture was refluxed on a heating mantle for 3 hours. A massive yellow precipitation took place after about 5 minutes. The product was nearly lost from the condenser as a yellow foam. This problem was overcome by using a long condenser or two condensers joined at the ground joint. The original yellow colour of the precipitate changed to brown and the colour persisted throughout the reflux period. It was poured into a beaker, cooled over night and the product collected by filtration. The brown residue was crystallized from *N,N*-dimethylacetamide (DMAC)-ethanol (1:3) mixture after treatment with activated charcoal to give glistening brownish-orange plates (4.30 g., 68% yield) of 12-chloro-7-methoxy-1,4,6-benzo[*b*]-triazaphenothiazine (VI, $R_1 = OCH_3$, $R_2 = Cl$, $R_3 = H$) melting at 277-278°; uv spectrum: λ max 244 nm (log ϵ 4.5704), 326 (3.7734), 430 (3.8759); ir spectrum (potassium bromide): ν max 3300, 3050, 1606, 1560, 1542, 1503, 1478, 1464, 1420, 1400, 1343, 1314, 1264, 1236, 1205, 1183, 1140, 1092, 1076, 1029, 950, 910, 880, 850, 834, 820, 778, 737, 714, 692, 682, 638 cm^{-1}; pmr spectrum (DMSO-d_6): τ −0.02 (broad, 10-NH), 2.70 (singlet; 11-H), 2.83 (singlet; 13-H and 14-H), 2.97 (doublet; J = 9.0 Hz; 9-H), 3.60 (doublet, J = 9.0 Hz, 8-H), 6.42 (singlet; 7-OCH_3); ms: m/e (relative intensity) 113 (14), 162 (9), 246 (3), 273 (21), 301 (7), 316 [M^+; 100%], 317 (20), 318 (36).

Anal. Calcd. for $C_{14}H_9ClN_4SO$: C, 53.08; H, 2.84; N, 17.69; S, 10.11; Cl, 11.22. Found: C, 52.91; H, 2.89; N, 17.89; S, 10.10; Cl, 11.03.

12-Chloro-7-methoxy-13-nitro-1,4,6-benzo[*b*]triazaphenothiazine 5-Oxide (VII, R = OCH_3).

Ice-cooled concentrated sulfuric acid (30 ml., d. 1.84) was poured gradually, with stirring and cooling, into a conical flask containing 3.17 g. (10 mmoles) of 12-chloro-7-methoxy-1,4,6-benzo[*b*]triazaphenothiazine (VI, R_1 = OCH_3, R_2 = Cl, R_3 = H). The deep pink solution that resulted was chilled in an ice-acetone bath. Nitric acid (25 ml., d. 1.42) which was precooled at 0° was added in drops during a period of fifteen minutes while cooling and stirring. The solution turned dark brown. Stirring was continued for an hour at 0° and for 2 hours at room temperature. The dark solution was left to stand in a fume cupboard for 18 hours and later poured into ice. The *p*H of the mixture was raised to 8 by the addition of concentrated ammonia while cooling. A little glacial acetic acid was later added to bring the *p*H down to 5. The flask was chilled further and filtered. The residue was crystallized from methanol after treatment with activated charcoal (Norit A) to give 12-chloro-7-methoxy-13-nitro-1,4,6-benzo[*b*]triazaphenothiazin-5-oxide (VII, R = OCH_3) (3.32 g., 88% yield) as yellowish brown powder decomposing above 200°; uv spectrum: λ infl. 260 nm (log ε 4.2014), λ max 364 (3.9748); ir spectrum (potassium bromide): ν max 3240, 3080, 1625, 1580, 1560, 1545, 1506, 1465, 1410, 1382, 1343, 1280, 1225, 1184, 1052, 1011, 883, 833, 821 cm^{-1}.

Anal. Calcd. for $C_{14}H_8ClN_5SO_4$: C, 44.50; H, 2.12; N, 18.55; S, 8.48; Cl, 9.40. Found: C, 44.73; H, 2.19; N, 18.46; S, 8.41; Cl, 9.47.

7,12-Dichloro-1,4,6-benzo[*b*]triazaphenothiazine (VI, R_1 = R_2 = Cl, R_3 = H).

Freshly prepared 3-amino-6-chloropyridin-2-[1*H*]thione (4.82 g., 30 mmoles) was dissolved in 50 ml. of water containing 3.36 g. (60 mmoles) of potassium hydroxide. 2,3,6-Trichloroquinoxaline (7.01 g., 30 mmoles) and 50 ml. of DMAC were later added and the mixture refluxed on a steam bath for 3.5 hours. There was an initial blood-red coloration followed by the formation of a yellowish product which turned yellowish-brown at the end of the reaction period. The mixture was poured into a beaker and an equal volume of water added. Upon cooling and filtering the yellowish-brown solid that separated was collected and recrystallized from DMAC-ethanol mixture after treatment with Norit. 7,12-Dichloro-1,4,6-benzo[*b*]triazaphenothiazine (VI, R_1 = R_2 = Cl, R_3 = H; 7.0 g., 75% yield) was obtained as a light greenish yellow powder, m.p. >300°; uv spectrum: λ max 245 nm (4.6314), 285 (3.5735), 332 (3.4273), 410 (3.9187); ir spectrum (potassium bromide): ν max 3380, 3066, 1630, 1570, 1540, 1482, 1474, 1443, 1410, 1372, 1345, 1277, 1270, 1260, 1234, 1210, 1138, 1103, 1078, 1063, 946, 882, 820, 770, 752, 730, 710, 685, 670 cm^{-1}; pmr spectrum (DMSO-d_6): τ 1.97 (singlet, 11-H), 2.18 (singlet, 8-H and 9-H), 2.43 (singlet, 13-H and 14-H); mass spectrum m/e (relative intensity) 69 (100), 113 (29), 133 (12), 151 (28), 162 (31), 163 (21), 251 (33), 286 (17), 320 [M^+, 84%], 321 (12), and 322 (37).

Anal. Calcd. for $C_{13}H_6Cl_2N_4S$: C, 48.60; H, 1.87; N, 17.45; S, 9.97; Cl, 22.12. Found: C, 48.91; H, 1.96; N, 17.20; S, 9.92; Cl, 21.95.

7,12-Dichloro-13-nitro-1,4,6-benzo[*b*]triazaphenothiazine 5-Oxide (VII, R = Cl).

7,12-Dichloro-1,4,6-benzo[*b*]triazaphenothiazine (VI, R_1 = R_2 = Cl, R_3 = H) (3.21 g., 10 mmoles) was added gradually to 30 ml. of concentrated sulfuric acid (d, 1.84) on a freezing mixture of ice and 2-propanol. To the deep pink mixture was added in droplets and with constant stirring 25 ml. of concentrated nitric acid also precooled to 0°. The nitric acid addition was completed within 15 minutes. Since much heat was evolved during the addition, an efficient freezing mixture was used. The mixture which now turned deep yellowish red was stirred at 0° for 2 hours and at room temperature for another 2 hour period. It was then left to stand overnight (16 hours) and later poured into ice. The *p*H of the solution was raised to 8 by the addition of concentrated ammonia with cooling. Filtration and crystallization of the residue from methanol-DMSO (20:1) mixture afforded greenish yellow crystals of 7,12-dichloro-13-nitro-1,4,6-benzo[*b*]triazaphenothiazine 5-oxide (VII, R = Cl) (2.29 g., 60% yield) decomposing above 185°; uv spectrum: λ max 310 nm (log ε 4.2105), 382 (4.1840); ir spectrum (potassium bromide): ν max 3270, 3090, 1618, 1580, 1560, 1550, 1508, 1466, 1432, 1382, 1340, 1285, 1150, 1056, 1030, 890, 867, 842, 830, 800, 770, 660 cm^{-1}.

Anal. Calcd. for $C_{13}H_5Cl_2N_5SO_3$: C, 40.84; H, 1.31; N, 18.32; S, 8.38; Cl, 18.59. Found: C, 40.80; H, 1.45; N, 18.39; S, 8.55; Cl, 18.50.

Reaction of Nicotinamide with Chlorine and Sodium Hydroxide.

In our modified procedure chlorine, which was generated by the action of concentrated hydrochloric acid on potassium permanganate at room temperature, was passed through water to remove hydrogen chloride fumes and dried by passing it through concentrated sulfuric acid. It was then bubbled into a weighed flask containing 200 ml. of 10% sodium hydroxide at 0°. When the increase in weight came to 13 g., finely powdered nicotinamide (12.2 g., 100 mmoles) was added gradually with vigorous mechanical agitation. The mixture which was stirred in a fume cupboard at room temperature for about 30 minutes became clear after about 20 minutes. It was heated with constant stirring to 70°. The temperature was maintained constant between 65° and 75° for 2 hours. The product was later acidified with about 140 ml. of concentrated hydrochloric acid followed by the addition of 100-volume hydrogen peroxide (20 ml.) in droplets such that the temperature remained at 70° ± 5°. The reaction solution was then concentrated under reduced pressure and treated with concentrated ammonia solution until the *p*H came to 8. The dark brown mixture was extracted with ten 1 litre portions of ether. The ethereal extracts were combined and dried with anhydrous sodium sulfate followed by removal of the ether by distillation on a steam bath. The brown residue was taken up in benzene, treated with activated charcoal and filtered. On cooling at −10°, 3-amino-2-chloropyridine (10.10 g., 78.6% yield) separated as long white needles; m.p. 79-80°, lit (26) 57% yield, m.p. 79-80°.

Reaction of Nicotinamide with Bromine and Sodium Hydroxide.

The above procedure was repeated using bromine in the place of chlorine. 3-Aminopyridine (m.p. 63-64°) only was isolated in 62% yield even when the reaction time was increased five-fold.

3-Amino-2-mercaptopyridine (X).

This compound was prepared by a modification of Thirtle's procedure for 2-mercaptopyridine (27). A solution of 4 kg. of potassium hydroxide in 1 litre of water was saturated with hydrogen sulfide. The dark ferrous sulfide impurity which formed was removed by filtration and the filtrate evaporated to dryness by vacuum distillation on a steam bath. The white crystalline potassium hydrosulfide thus obtained was quickly bottled and stored in a desiccator as it is highly hygroscopic.

To a mixture of 3-amino-2-chloropyridine (25.70 g., 200 mmoles) and 36 g. of the dried potassium hydrosulfide was added 100 ml. of propylene glycol (b.p. 186-189°). The mixture was refluxed on a heating mantle with vigorous mechanical agitation for 27 hours. When boiling started, it was observed that the solution changed from yellow to deep green coloration which persisted throughout the reflux period. At the end of the reaction, potassium chloride by-product (13 g.) was removed by filtration.

The filtrate which is a heavy brown oil was concentrated to dryness on a steam bath. The residue was taken up in 60 ml. of water, treated with Norit, boiled and filtered. The filtrate was acidified with glacial acetic acid when yellow crystals of 3-amino-2-mercaptopyridine separated out after crystallization from benzene (Norit) (20.66 g., 82% yield) m.p. 133-134°; Rodig and co-workers (28) reported a yield of 65%, m.p. 131-133°.

The impure product in propylene glycol could be used in the next stage of the reaction without an appreciable effect on the yield.

1,4,6-Benzo[*b*]triazaphenothiazine (VI, R_1 = R_2 = R_3 = H).

3-Amino-2-mercaptopyridine (6.93 g., 55 mmoles) was dissolved in a mixture of propylene glycol (10 ml.) and water (50 ml.) containing 5.6 g. (100 mmoles) of potassium hydroxide. 2,3-Dichloroquinoxaline (I, R_1 = Cl, R_2 = H) (9.95 g., 50 mmoles) and 20 ml. of DMF were then added. The mixture was refluxed for 2.5 hours. The entire mixture dissolved

after 15 minutes followed by the appearance of a brown oil which solidified towards the end of the reflux period. The entire solution was poured while hot into a beaker and cooled overnight. The supernatant liquid was decanted and discarded leaving a dark oily solid which was crystallized from DMF-methanol mixture after treatment with activated charcoal. Golden yellow microcrystals of 1,4,6-benzo[*b*]triazaphenothiazine (VI, $R_1 = R_2 = R_3 = H$) (11.67 g., 93% yield) were collected; m.p. >300°; uv spectrum: λ max 240 nm (log ε 4.2274), 280 (3.4428), 322 (3.3556), 405 (3.6318); ir spectrum (potassium bromide): ν max 3220, 3060, 1617, 1595, 1585, 1574, 1546, 1488, 1450, 1416, 1370, 1297, 1275, 1255, 1217, 1130, 1110, 1077, 1060, 1020, 945, 870, 820, 800, 754, 730, 705, 665 cm^{-1}; pmr spectrum (DMSO-d_6): τ −0.17 (broad, 10-NH), 2.13 (multiplet, 7-H and 9-H), 2.60 (multiplet, 8-H, 11-H and 14-H), 2.95 (multiplet, 12-H and 13-H); ms: m/e (relative intensity) 90 (5), 92 (7), 102 (9), 126 (16), 128 (1), 204 (7), 219 (2), 220 (6), 251 (8), 252 [M^+, 100%], 253 (17), 254 (6).

Anal. Calcd. for $C_{13}H_8N_4S$: C, 61.90; H, 3.18; N, 22.22; S, 12.70. Found: C, 61.83; H, 3.26; N, 22.24; S, 12.59.

12-Chloro-1,4,6-benzo[*b*]triazaphenothiazine (VI, $R_1 = R_3 = H$, $R_2 = Cl$).

To a mixture of 1.26 g. (10 mmoles) of 3-amino-2-mercaptopyridine and 1.23 g. (22 mmoles) of potassium hydroxide was added 10 ml. of propylene glycol and 25 ml. of water and heated until dissolved. 2,3,6-Trichloroquinoxaline (2.34 g., 10 mmoles) and 20 ml. of DMF were later added. The entire mixture was refluxed on a heating mantle for 4.5 hours. Before refluxing started, it was observed that the mixture turned deep red followed by intensification of the colour as refluxing proceeded. Later, the mixture turned greenish brown followed by the formation of a dark brown oily product.

At the end of the reflux period, the mixture which again turned bright red was poured into a beaker, cooled overnight and filtered. The residue was collected by filtration and crystallized from DMF-methanol-water mixture after treatment with Norit. 12-Chloro-1,4,6-benzo[*b*]triazaphenothiazine (VI, $R_1 = R_3 = H$, $R_2 = Cl$) (2.41 g., 84% yield) was obtained as a bright yellow powder; m.p. 298-299°; uv spectrum: λ max 242 nm (log ε 4.2790); 355 (4.0229); ir spectrum (potassium bromide): ν max 3250, 2946, 1608, 1590, 1570, 1545, 1484, 1450, 1436, 1409, 1385, 1366, 1300, 1246, 1208, 1193, 1142, 1085, 1070, 1053, 944, 915, 867, 820, 800, 782, 760, 734, 710 cm^{-1}; pmr spectrum (DMSO-d_6): τ 0.02 (broad, 10-NH), 2.10 (singlet 11-H), 2.81 (multiplet, 7-H, 8-H, 9-H, 13-H and 14-H); ms: m/e (relative intensity) 113 (48), 141 (52), 162 (58), 194 (100), 251 (4), 286 [M^+; 9], 287 (1), 288 (3).

Anal. Calcd. for $C_{13}H_7ClN_4S$: C, 54.45; H, 2.44; N, 19.55; S, 11.17; Cl, 12.39. Found: C, 54.03; H, 2.68; N, 19.45; S, 11.00; Cl, 12.52.

Acknowledgement.

The author wishes to express his appreciation for the financial support of this work through a grant from the Senate Research Grants Committee of the University of Nigeria. We also wish to thank (i) Dr. E. N. Okafo of the Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow, for parts of the microanalyses and mass spectra and (ii) the Chairman, Department of Pure and Applied Chemistry, University of Strathclyde for permitting the use of the facilities of his Department. Grateful acknowledgement is also extended to Messrs. F. I. Ozoh, F. U. Ekezie, O. O. Ibe, N. Igwe, D. O. Nwankwo and A. E. Umo of the Department of Chemistry, University of Nigeria, Nsukka, for their technical assistance.

REFERENCES AND NOTES

(1) Von E. Schenker and H. Herbst in "Progress in Drug Research", Vol. 5, E. Jucker, Ed., Birkhauser Verlag, Basel, Switzerland, 1963, pp. 269-627.

(2) M. Gordon, P. N. Craig and C. L. Zirkle, "Molecular Modification in Drug Design", R. F. Gould, Ed., American Chemical Society, Washington D. C., 1964, pp. 140-147.

(3) C. O. Okafor, *Int. J. Sulfur Chem.*, **6, B,** 237 (1971).

(4) C. O. Okafor, *Phosphorus and Sulfur,* **4,** 79 (1978).

(5) C. O. Okafor, *Int. J. Sulfur Chem.*, **6, B,** 345 (1971).

(6) C. O. Okafor, *Heterocycles,* **7,** 391 (1977).

(7) C. O. Okafor, *Int. J. Sulfur Chem.*, **7, B,** 109 (1972).

(8) V. Carelli, P. Marchini, G. Liso, F. Micheletti-Moracci, M. Cardellini, F. Liberatore and M. G. Lucarelli, *Int. J. Sulfur Chem.*, **A, 1,** 251 (1971).

(9) C. J. Grol and H. Rollema, *J. Med. Chem.*, **18,** 857 (1975); C. J. Grol, *J. Chem. Soc., Perkin Trans. I,* 1234 (1975); C. J. Grol, *J. Heterocyclic Chem.*, **11,** 953 (1974).

(10) St. Hift and K. Kryspin-Exner, *Wien. Med. Wochenschr.* **108,** 664 (1958).

(11) J. Quandt, L. von Horn and H. Schliep, *Psychiatr. Neurol.*, **135,** 197 (1958).

(12) C. O. Okafor, *J. Org. Chem.*, **38,** 4386 (1973).

(13) K. Kaji, M. Nagashima, Y. Masaki, M. Yoshida, and K. Kamiya, Japan Kokai 1974, 48,697, 48,698, 48,699 (11th May 1974) [*Chem. Abstr.*, **82,** 43470p, 43471q and 43475u (1975)].

(14) C. O. Okafor, M. L. Steenberg and J. P. Buckley, *J. Heterocyclic Chem.*, **12,** 813 (1975); C. O. Okafor, *J. Chem. Soc., Chem. Commun.*, 868 (1974).

(15) C. O. Okafor, *J. Org. Chem.*, **40,** 2753 (1975); C. O. Okafor, *Int. J. Sulfur Chem.*, **7, B,** 121 (1972).

(16) C. O. Okafor, M. L. Steenberg and J. P. Buckley, *Eur. J. Med. Chem.*, **12,** 249 (1977).

(17) J. K. Landquist, *J. Chem. Soc.*, 2816 (1953); H. McIlwain, *ibid.*, 322 (1943).

(18) F. Kehrmann and C. Bener, *Helv. Chim. Acta,* **8,** 20 (1925); R. D. Haworth and S. Robinson, *J. Chem. Soc.*, 777 (1948).

(19) F. W. Bergstrom and R. A. Ogg, *J. Am. Chem. Soc.*, **53,** 245 (1931).

(20) J. R. Stevens, K. Pfister, 3rd and F. J. Wolf, *J. Am. Chem. Soc.*, **68,** 1035 (1946).

(21) C. O. Okafor, *J. Org. Chem.*, **38,** 4383 (1973).

(22) S. F. Dyke, A. J. Floyd, M. Sainsbury and R. S. Theobald, "Organic Spectroscopy: An Introduction", Penguin Books Ltd., Harmondsworth, Middlesex, England, 1971, pp. 48-100.

(23) The numbering used is that recommended by L. T. Capell and D. F. Walker, Jr., in "The Ring Index, Supplement 1", American Chemical Society, Washington D. C., 1963, p. 112. The nomenclature used is consistent with that used in the current literature as it brings out the structural relationship with phenothiazine. The ring can also be named quinoxalino[2,3-*b*][1,4]pyrido[3′,2′-*e*]thiazine and numbered as stated earlier.

(24) Peracids are required for *N*-oxide formation in *N*-heterocyclic systems.

(25) V. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 591 (1945).

(26) Y. Ahmad and D. H. Hey, *ibid.*, 4516 (1954).

(27) J. R. Thirtle, *J. Am. Chem. Soc.*, **68,** 342 (1946).

(28) O. R. Rodig, R. E. Collier and R. K. Schlatzer, *J. Org. Chem.*, **29,** 2652 (1964).

(29) C. F. H. Allen and C. N. Wolf in "Organic Synthesis", Coll. Vol. IV, N. Rabjohn, Ed., J. Wiley and Sons, Inc., New York, N.Y., 1963, pp. 45-47.

(30) J. C. Cavagnol and F. Y. Wiselogle, *J. Am. Chem. Soc.*, **69,** 795 (1947).