

Charles O. Okafor (1), Imaga O. Uche (2,3)

and Leonard E. S. Akpanisi

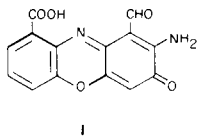
Department of Chemistry, University of Nigeria,  
Nsukka, Nigeria

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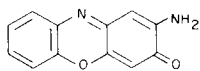
As a continuation of our search for new pharmaco-active phenothiazine compounds, the synthesis of 1,4,6,8-tetraazabenzobenzothiazine ring system is described. Derivatives of this new heterocycle were prepared by converting 4,5-diamino-6-hydroxypyrimidine to 4,5-diaminopyrimidine-6-(1*H*)thione followed by the action of 2,3-dichloroquinoxaline in refluxing DMF or DMAC. The reaction of mixed nitric and sulfuric acids with 9-amino-12-chloro-1,4,6,8-tetraazabenzobenzothiazine gave 9-amino-12-chloro-13-nitro-1,4,6,8-tetraazabenzobenzothiazine 5-oxide in satisfactory yields. Diazotization of 9-amino-1,4,6,8-tetraazabenzobenzothiazine led to 1,4,6,8-tetraazatriazolo[4,5,1-*k*]benzobenzothiazine which is a new heterocyclic compound and the parent compound of this ring system. The mechanistic pathways to these compounds are also proposed.

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Although many derivatives of phenoxazine are well-known dyes (4,5), considerable attention was still paid to them as a result of their antibacterial (6), antitubercular (7,8) and antitumor activities (9). Some naturally occurring phenoxazines were also studied in the hope of obtaining some active compounds in these series. Among the natural compounds of the phenoxazine class are tramesanguin (1) (10), a crystalline pigment that was isolated from the wood-rotting fungi, *Trametes cinnabarina* and *Coriulus sanguineus* and questiomycin A (2) (11,12), an extract from certain *Streptomyces* and *Waksmania* species.

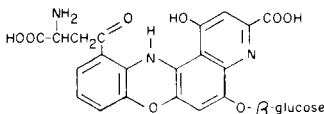


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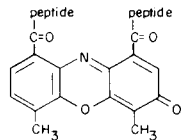


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Other representative examples are rhodommatin (3) (13) a pigment extracted from the wings of insects and larvae of *Hestina japonica* and *Sasakia charonda*, and actinomycin D (4) (14-16) which is a chromopeptide antibiotic with antitumor activities produced by certain species of *Streptomyces*.

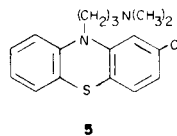


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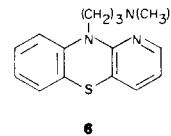


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The clinical effectiveness of chlorpromazine (5) (17,18) as a tranquilizing drug has however prompted greater focus on phenothiazine derivatives. Quandt (19) and Hift (20) discovered that prothipendyl (6), the 1-azaphenothiazine analog of promazine is even a superior drug to chlorpromazine in the treatment of mental disorders particularly in acute psychosis complicated with latent epilepsy.

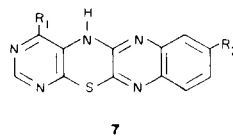


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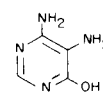


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These and other reports (21) led to redirection of attention once more to azaphenothiazine ring systems. So far, four monoaza- (22), ten diaza- (23,24), and four triaza-phenothiazine (25-27) ring systems have been prepared and characterized. Out of the thirty-five hypothetical structural isomers of the more complex tetraazaphenothiazine ring, only six of them have been reported (28,29); the rest of the twenty-nine isomeric structures remain unknown. Systems in which a benzo group is fused onto one of the side rings of the azaphenothiazine ring leading to tetracyclic azaphenothiazines (30) have also been prepared. As an extension of these studies we have successfully synthesized 1,4,6,8-tetraazabenzobenzothiazine (31) ring system (7) as a new ring in these series.



7



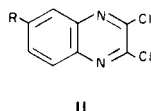
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As we pointed out in one of our earlier papers (29), a serious limitation in azaphenothiazine synthesis is the difficulty in preparing *o*-amino heterocyclic thiols (32). This problem was largely overcome in some cases by the application of Kaufmann's thiocyanation (33) of aromatic amines, intramolecular Schonberg rearrangement of *O*-aryl thiocarbonates (34,35), the Chugaev reaction (36) and the condensation of heterocyclic phenols with phosphorus pentasulfide (37,38) among others. For the synthesis of 1,4,6,8-tetraazabenzophenothiazine, we found 4,5-diamino-6-hydroxypyrimidine (8) a more suitable star-

ting material. Thiation with phosphorus pentasulfide converted it to a product thought to be 4,5-diaminopyrimidine-6-thiol (**9**). The infrared spectrum showed the absence of the weak but diagnostic SH band at  $2555\text{ cm}^{-1}$  and the presence of N=C=S band at  $1485\text{ cm}^{-1}$  suggesting that the cyclothioamido tautomer (**10**) is the isolated product. This structure is also confirmed by the  $^1\text{H}$  nmr spectrum and should be described as such as was pointed out by Katritzky (39).



Thus the product of the reaction is 4,5-diaminopyrimidin-6-(1H)thione (**10**) and not the thiol tautomer as was reported earlier (40,41).



The reaction of compound **10** with 2,3-dichloroquinoxaline (**11**, R = H) in *N,N*-dimethylformamide in the presence of near stoichiometric amounts of sodium hydroxide gave an orange microcrystalline material melting above  $300^\circ$ . Microanalysis and mass spectral studies agree with the formula  $\text{C}_{12}\text{H}_8\text{N}_6\text{S}$ . The ultraviolet spectrum gave a strong maximum absorption band at 258 nm characteristic of phenothiazine systems. The tentative structure **7**,  $\text{R}_1 = \text{NH}_2$ ,  $\text{R}_2 = \text{H}$  was assigned to this product. In the infrared spectrum, two medium bands at 3390 and 3300 (d) were assigned to the 10-NH and 9-NH<sub>2</sub> groups respectively while two strong bands at 765 (1,2-disubstitution in ring D) and  $870\text{ cm}^{-1}$  (4,5,6-trisubstituted pyrimidine) were also observed. Confirmatory evidence for the structure was obtained from the  $^1\text{H}$  nmr spectrum shown in Figure 1. The broad peak at  $\delta$  7.08 was at-

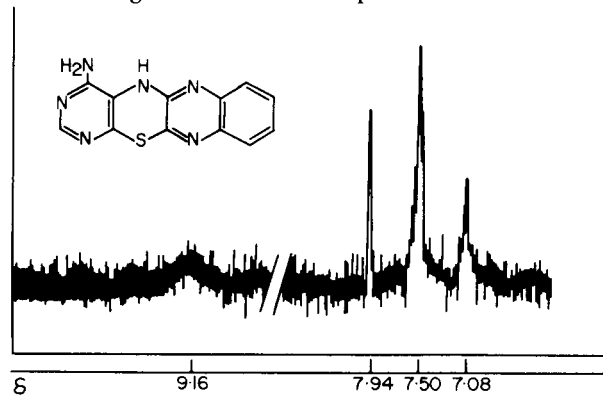
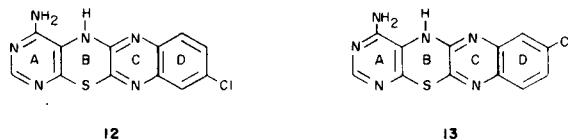


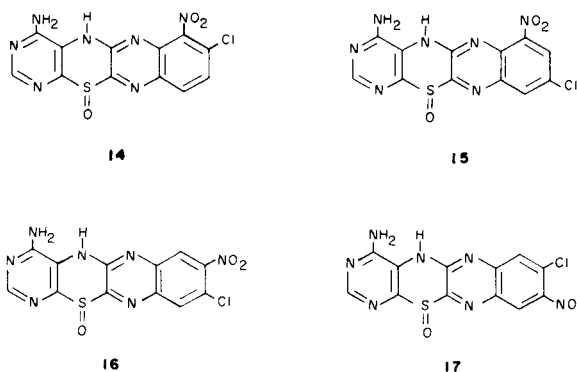
Figure 1. PMR Spectrum of 9-Amino-1,4,6,8-tetraaza-benzo[*b*]phenothiazine (**7**,  $\text{R}_1 = \text{NH}_2$ ,  $\text{R}_2 = \text{H}$ ).

tributed to the 9-NH<sub>2</sub> protons while the four aromatic protons in ring D appeared as a multiplet at  $\delta$  7.50. The isolated proton on C-7 gave a sharp singlet at  $\delta$  7.94. A broad peak at  $\delta$  9.16 was assigned to the 10-NH proton. Thus, the proton nmr spectrum is in good agreement with structure **7**,  $\text{R}_1 = \text{NH}_2$ ,  $\text{R}_2 = \text{H}$ . The product of this reaction is therefore 9-amino-1,4,6,8-tetraazabenz[*b*]phenothiazine.

A similar reaction of compound **10** with 2,3,6-trichloroquinoxaline (**11**, R = Cl) gave a high yield of a single product of molecular formula  $\text{C}_{12}\text{H}_7\text{ClN}_6\text{S}$ . Spectroscopic data are in agreement with the structures **12** and **13**.



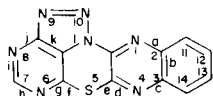
In order to determine the correct structure, the product was treated with mixed concentrated nitric and sulfuric acids at room temperature. Under this condition, mononitration and 5-sulfoxide formation took place. Elemental analysis and molecular weight determination by mass spectroscopy agree with the formula  $\text{C}_{12}\text{H}_6\text{ClN}_7\text{O}_3\text{S}$ . By considering the directive influence of the functional groups in the starting material, the possible structures of the nitro-product are **14**, **15**, **16** and **17**.



The infrared spectrum of the product was also studied. A strong band at  $1014\text{ cm}^{-1}$  was attributed to the S=O group (42,43) while a strong peak at  $882\text{ cm}^{-1}$  was associated with C-H out-of-plane deformation in 1,2,4,5-tetrasubstituted benzenes. Structure **14** was therefore ruled out on the basis of this evidence. Structure **15** was eliminated on the ground that *ortho*-nitration at C-1 in phenothiazine (C-11 in this case) does not occur under the mild reaction conditions that were employed (8,29). Although the *meta*-directing effect of C=N group in ring C of structure **12** would cause 12-nitration to take place leading to structure **16**, this product was also ruled out partly because of the mild reaction condition and partly because only a single product was isolated in excellent

yields. Furthermore, the normal site now established for nitration of phenothiazinoid systems is the position *para* to the 10-NH group (44,45) which in this case is C-13. The above evidence fitted very well for structure **17** which we have assigned to the product of the nitration reaction. It therefore follows that the precursor is 9-amino-12-chloro-1,4,6,8-tetraazabenzobenzothiazine (**13**).

To confirm the presence of a proton in C-10, compound **7**,  $R_1 = \text{NH}_2$ ,  $R_2 = \text{H}$  was diazotized and later heated to boiling. A product of molecular formula,  $\text{C}_{12}\text{H}_5\text{N}_7\text{S}$  and melting above  $300^\circ$  was obtained in a good yield. The  $^1\text{H}$  nmr spectrum and the absence of  $\text{NH}_2$  and  $\text{NH}$  absorption peaks in the infrared spectrum show that the product is 1,4,6,8-tetraazatriazolo[4,5,1-*kl*]benzo[*b*]phenothiazine (**18**) (46).

**18**

*ortho*-Aminodiarylamines and related compounds (47-49) are also known to give similar reactions. The formation of the triazolophenothiazine derivatives can be used to confirm the presence of  $\text{NH}_2$  and  $\text{NH}$  groups on *ortho*-carbon atoms in structure **7**,  $R_1 = \text{NH}_2$ ,  $R_2 = \text{H}$ . Compound **18** is a new heterocyclic compound as well as

the parent compound of this new ring structure.

The mechanism for the formation of 1,4,6,8-tetraazabenzobenzothiazine ring system was also rationalized. The pathways shown in Scheme 1 were proposed.

In the presence of a base, compound **10** exists predominantly as the salt of the tautomer **9** which condenses with compound **11** leading to the pyridylquin-oxalanyl sulfide **19** (50). Cyclization of the diaryl sulfide **19** could proceed through two routes. In route *a*, cyclization of compound **19** takes place directly without rearrangement leading to structure **20**. However in route *b* the sulfide undergoes Smiles rearrangement through the formation of the spiro intermediate **21** and the diarylamine **22** followed by cyclization to compound **23**. If  $R = \text{H}$ , the product obtained through either of the two routes, *a* and *b*, will be the same. However, different products are expected if  $R \neq \text{H}$ .

It has been shown that when  $R = \text{Cl}$ , the product of the reaction was 9-amino-12-chloro-1,4,6,8-tetraazabenzobenzothiazine **13**. It therefore follows that these reactions proceed through route *b* rather than *a*. In other words, the formation of these 1,4,6,8-tetraazabenzobenzothiazines proceeds by formation of the diaryl sulfide **19** followed by Smiles rearrangement and cyclization of the diarylamine intermediate leading to the isolated products.

## 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 is methanol and the absorption maxima are always given in nanometers; the figures in parenthesis are  $\log \epsilon$  values. Ir spectra were obtained on a Perkin Elmer Model 137 spectrophotometer using potassium bromide discs unless otherwise stated.  $^1\text{H}$  nmr spectra were determined on a Varian Associates T-60 instrument. Chemical shifts are reported on the  $\delta$  scale relative to TMS used as an internal standard. The letters b, 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 AE1 MS-9 double-focusing mass spectrometer at 70 eV.

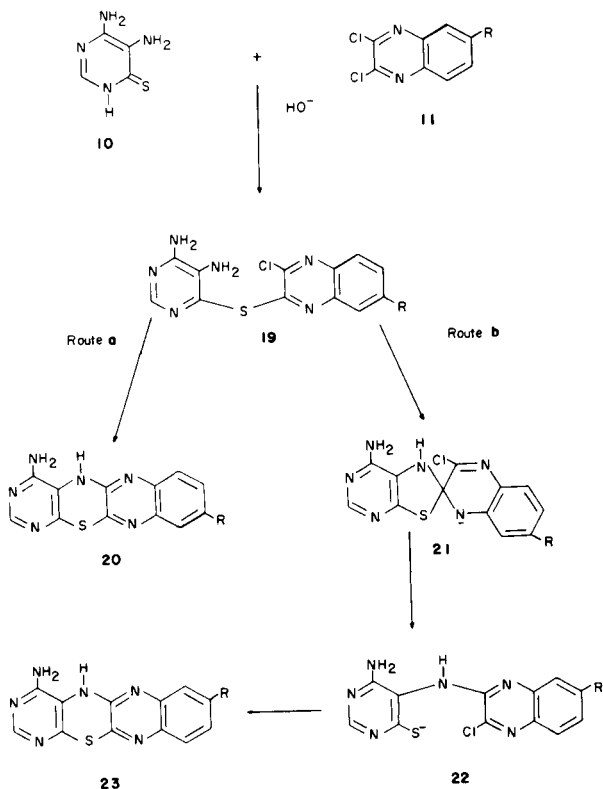
### 4,5-Diamino-6-hydroxypyrimidine (**8**).

Commercially available 4,5-Diamino-6-hydroxypyrimidine sulfate was placed in ethanol and then neutralized with concentrated ammonia to pH 7. It was filtered, dried and used for the next stage of the reaction without further purification.

### 4,5-Diaminopyrimidine-6-(1*H*)thione (**10**).

A mixture of 12.6 g (100 mmoles) of 4,5-diamino-6-hydroxypyrimidine (**8**), 88.8 g of phosphorus pentasulfide and 250 ml of pyridine (dried over sodium hydroxide) was refluxed on a heating mantle for 15 hours. The solvent was removed by vacuum distillation. About 400 g of crushed ice were added to the residue. The mixture was heated on a steam bath to remove hydrogen sulfide. When the evolution of hydrogen sulfide ceased the dark solution was treated with Norit and filtered. The filtrate was acidified with concentrated hydrochloric acid to pH 1 with cooling. The solution was chilled in a refrigerator for 2 days, filtered and the residue collected and dried in a dessicator. The brown solid product was recrystallized from aqueous ethanol to yield 10.02 g (71% yield) of 4,5-diaminopyrimidine-6-(1*H*)thione (**10**) as glistening yellow plates, mp

Scheme 1



260-262°; uv spectrum  $\lambda$  max 338 (3.9041), 245 (3.9181), 235 (3.8970); ir:  $\nu$  max 3335 (d), 3160, 2980, 2881, 1665, 1610, 1584, 1556, 1511, 1480, 1364, 1348, 1225, 1154, 1140, 1097, 940, 837, 750, 672  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  7.77 s, b (4-NH<sub>2</sub>, 5-NH<sub>2</sub>), 8.14 s (2-H).

9-Amino-1,4,6,8-tetraazabenzob[*b*]phenothiazine (7, R<sub>1</sub> = NH<sub>2</sub>, R<sub>2</sub> = H).

To 2.84 g (20 mmoles) of 4,5-diaminopyrimidin-6-(1*H*)thione (10) placed in a 250 ml three-necked flask was added 30 ml of water and 3 g of sodium hydroxide pellets. The mixture was swirled until all the solids dissolved. *N,N*-Dimethylformamide (70 ml) was then added followed by the addition of 3.98 g (20 mmoles) of 2,3-dichloroquinoxaline.

The mixture turned immediately blood-red followed by massive evolution of heat. The reaction flask with the contents was then refluxed on a heating mantle for 3 hours. When refluxing started the solution became orange yellow in colour followed by the formation of massive orange precipitate that persisted throughout the reflux period. It was poured into a beaker containing 500 ml of water, cooled and filtered.

The residue was crystallized from DMF after treatment with activated charcoal to yield 4.93 g (92% yield) of 9-amino-1,4,6,8-tetraazabenzob[*b*]phenothiazine (7, R<sub>1</sub> = NH<sub>2</sub>, R<sub>2</sub> = H) as glistening orange-yellow microneedles, mp >300°; uv:  $\lambda$  max 415 (3.8260), 292 (3.9007), 258 (4.2130); ir:  $\nu$  max 3390, 3300, 3130, 2940, 1674, 1584, 1557, 1502, 1487, 1464, 1430, 1415, 1367, 1345, 1330, 1295, 1266, 1248, 1224, 1193, 1136, 1080, 971, 950 (d), 930, 870, 862, 823, 767, 716  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO- $d_6$ ): 7.08 s, b (area 2, 9-NH<sub>2</sub>), 7.50 m (area 4, 11-H, 12-H, 13-H, 14-H), 7.94 s (area 1, 7-H), 9.16 s, b (area 1, 10-NH); ms: *m/e* (relative intensity) 73 (6), 75 (5), 76 (4), 90 (7), 102 (11), 103 (4), 113 (2), 118 (2), 122 (3), 128 (6), 129 (5), 134 (10), 144 (3), 154 (2), 155 (3), 160 (3), 161 (4), 171 (3), 172 (3), 187 (4), 208 (4), 209 (2), 213 (10), 214 (5), 215 (2), 241 (8), 242 (2), 267 (4), 268 [*M*<sup>+</sup>, 100%], 269 (17).

*Anal.* Calcd. for C<sub>12</sub>H<sub>8</sub>N<sub>6</sub>S: C, 53.73; H, 2.99; N, 31.34; S, 11.94. Found: C, 53.58; H, 3.01; N, 31.39; S, 11.92.

9-Amino-12-chloro-1,4,6,8-tetraazabenzob[*b*]phenothiazine (7, R<sub>1</sub> = NH<sub>2</sub>, R<sub>2</sub> = Cl).

A mixture of 1.42 g (10 mmoles) of 4,5-diaminopyrimidine-6-(1*H*)thione (10) and 3 g of sodium hydroxide was dissolved in 25 ml of water by warming on a steam bath. To this solution was added 2.57 g (11 mmoles) of 2,3,6-trichloroquinoxaline (11, R = Cl) and 40 ml of DMF. The blood-red mixture was refluxed on a heating mantle for 3½ hours.

At the end of the reflux period, the mixture was poured while hot into 500 ml of water, stirred and cooled overnight. On filtering, the crude product was recrystallized from aqueous DMF solution after treatment with activated charcoal. Yellowish orange microcrystals of 9-amino-12-chloro-1,4,6,8-tetraazabenzob[*b*]phenothiazine (7, R<sub>1</sub> = NH<sub>2</sub>, R<sub>2</sub> = H) (2.57 g, 85% yield) were formed, mp >300°; uv:  $\lambda$  max 313 (4.3837), 267 (5.0216); ir:  $\nu$  max 3135, 3080, 2965, 1625, 1600, 1520, 1500, 1485, 1437, 1392, 1370, 1336, 1300, 1280, 1260, 1230, 1145, 1087, 750, 900, 860, 833, 807, 793, 768, 674  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  6.57 s, b (9-NH<sub>2</sub>, 13-H, 14-H), 7.64 s (7-H, 11-H), 9.33 s, b (10-NH); ms: *m/e* (relative intensity) 69 (17), 73 (4), 78 (14), 105 (89), 106 (6), 113 (15), 115 (4), 140 (13), 142 (4), 168 (55), 169 (8), 170 (18), 196 (100%), 197 (10), 198 (31), 302 [*M*<sup>+</sup>, 30%], 303 [*M*<sup>+</sup> + 1, 5], 304 [*M*<sup>+</sup> + 2, 9].

*Anal.* Calcd. for C<sub>12</sub>H<sub>7</sub>ClN<sub>6</sub>S: C, 47.60; H, 2.31; Cl, 11.74; N, 27.77; S, 10.58. Found: C, 47.45; H, 2.39; Cl, 11.75; N, 27.95; S, 10.51.

9-Amino-12-chloro-13-nitro-1,4,6,8-tetraazabenzob[*b*]phenothiazine 5-Oxide (15).

To 8 ml of concentrated sulfuric acid (d, 1.84) in an ice-bath was added 1.51 g (5 mmoles) of 9-amino-12-chloro-1,4,6,8-tetraazabenzob[*b*]phenothiazine (7, R<sub>1</sub> = NH<sub>2</sub>, R<sub>2</sub> = Cl). The resulting yellowish-red solution was further cooled while stirring. Concentrated nitric acid (d, 1.42) (8 ml) was added in drops during a period of 15 minutes. There was vigorous evolution of heat during the addition. The dark reddish yellow solution was stirred and cooled for an additional hour and allowed to stand overnight

(16 hours).

The clear solution was poured into three ice cubes and while cooling, the pH of the solution was adjusted to 4 with concentrated ammonia. The solid product was collected by filtration and recrystallized from aqueous ethanol after treatment with activated charcoal to yield 1.64 g (90% yield) of 9-amino-12-chloro-13-nitro-1,4,6,8-tetraazabenzob[*b*]phenothiazine 5-oxide (15) as greenish yellow microcrystalline powder, mp >300°; uv:  $\lambda$  max 346 (3.9584), 275 (4.2461), 241 (4.1723); ir:  $\nu$  max 3250, 3178, 3085, 2940, 1650, 1624, 1607, 1545, 1510, 1395, 1340, 1320, 1284, 1260, 1230, 1140, 1116, 1013, 882, 846, 805, 790, 775, 724, 688, 655  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  7.24 s (11-H, 9-NH<sub>2</sub>), 7.80 s (7-H, 14-H), 9.90 (10-NH).

*Anal.* Calcd. for C<sub>12</sub>H<sub>6</sub>ClN<sub>7</sub>O<sub>3</sub>S: C, 39.62; H, 1.65; Cl, 9.77; N, 26.96; S, 8.80. Found: C, 39.80; H, 1.55; Cl, 9.75; N, 27.08, S, 8.72.

1,4,6,8-Tetraazatriazol[4,5,1-*k*]benzob[*b*]phenothiazine (18).

A suspension of 5.36 g (20 mmoles) of 9-amino-1,4,6,8-tetraazabenzob[*b*]phenothiazine in 25 ml of concentrated hydrochloric acid was placed in the reaction flask and cooled to 0°. An ice-cooled aqueous solution of 1.5 g (22 mmoles) of sodium nitrite was prepared and added slowly, with mechanical agitation, to the reaction mixture. The temperature was maintained at 0° for about 2 hours. The freezing mixture was removed and the solution refluxed on a heating mantle for 1 hour.

The mixture was cooled, neutralized to pH 8 with concentrated ammonia and cooled overnight in a refrigerator. The solid product was crystallized from aqueous ethanol after treatment with activated charcoal to yield 4.52 g (81% yield) of 1,4,6,8-tetraazatriazol[4,5,1-*k*]benzob[*b*]phenothiazine (18) as yellow powder, mp >300°; uv:  $\lambda$  max 348 (3.7270), 250 (3.7434); ir:  $\nu$  max 3160, 1670, 1617, 1600, 1560, 1510, 1445, 1405, 1354, 1290, 1267, 1220, 1183, 1140, 1094, 1063, 1030, 965, 930, 893, 852, 750, 674  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  7.58 m (4-H, 8-H, 9-H, 10-H, 11-H).

*Anal.* Calcd. for C<sub>12</sub>H<sub>5</sub>N<sub>7</sub>S: C, 51.62; H, 1.79; N, 35.13; S, 11.47. Found: C, 51.50; H, 1.97; N, 35.33; S, 11.34.

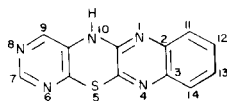
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## REFERENCES AND NOTES

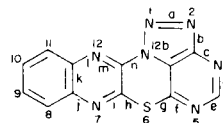
- (1) To whom all correspondence should be addressed. Present address: Department of Chemistry, University of South Florida, Tampa, Florida 33620.
- (2) Abstracted in part from the thesis submitted by I. O. Uche to the School of Postgraduate Studies of the University of Nigeria in partial fulfillment of the requirements for the M. Sc. degree in Chemistry.
- (3) Present address: Department of Chemistry, Alvan Ikoku College of Education, Owerri, Imo State, Nigeria.
- (4) P. Rys and H. Zollinger, "Fundamentals of the Chemistry and Application of Dyes", Wiley-Interscience Publishers, London, 1972, pp. 99-109.
- (5) C. O. Okafor, *Int. J. Sulfur Chem., B*, **6**, 345 (1971).
- (6) T. Yuasa, *Ann. Rep. Res. Inst. Tuberc. Kanazawa Univ.*, **11**, 265 (1953).
- (7) B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, 1499 (1953).
- (8) H. Fuhrer, P. Sutter and C. D. Weis, *J. Heterocyclic Chem.*, **16**, 1121 (1979).
- (9) M. R. Lewis, P. P. Golland and H. A. Sloviter, *Cancer Res.*, **9**, 736 (1949).

- (10) J. Gripenberg, *Acta Chem. Scand.*, **17**, 703 (1963).  
 (11) M. Matsuoka, *J. Antibiotics (Tokyo), Ser.*, **A13**, 121 (1960).  
 (12) N. N. Gerber and M. P. Lechevalier, *Biochemistry*, **3**, 598 (1964).  
 (13) A. Butenandt, E. Biekert, H. Kuebler, B. Linzen and P. Traub, *Hoppe-Seyler's Z. Physiol. Chem.*, **334**, 71 (1963).  
 (14) S. K. Sengupta and S. K. Tinter, *J. Heterocyclic Chem.*, **17**, 17 (1980).  
 (15) E. Frei III, *Cancer Chemother. Rep.*, **58**, 49 (1966).  
 (16) J. L. Lewis, Jr., *Cancer*, **30**, 1517 (1972).  
 (17) "New Drugs Evaluated by the American Medical Association Council on Drugs", American Medical Association, Chicago, 1965, Chapter 12, pp. 121-150.  
 (18) "Developments in Neuroscience", Vol. 7, "Phenothiazines and Structurally Related Drugs", E. Usdin, H. Eckert and I. S. Forrest, eds., Elsevier North Holland, Inc., New York, 1980, pp. 3-60.  
 (19) J. Quandt, L. von Horn and H. Schliep, *Psychiat. Neurol.*, **135**, 197 (1958).  
 (20) St. Hift and K. Kryspin-Exner, *Med. Wochenschr.* **108**, 664 (1958).  
 (21) E. von Schenker and H. Herbst in "Progress in Drug Research", Vol. 5, E. Jucker, ed., Birkhauser Verlag, Basel, Switzerland, 1963, pp. 269-627.  
 (22) C. O. Okafor, *Int. J. Sulfur Chem.*, **B**, 6, 237 (1971).  
 (23) Y. C. Tong, Dow Chem. Co., U. S. Patent 3,821,213 (20 June 1974); *Chem. Abstr.*, **81**, 136180p (1974).  
 (24) C. O. Okafor, *Phosphorus Sulfur*, **4**, 79 (1978).  
 (25) C. O. Okafor, *J. Org. Chem.*, **38**, 4386 (1973).  
 (26) K. Kaji, H. Nagashima, Y. Masaki, M. Yoshida and K. Kamiya, Japan Kokai 74, 48,699 (1974); *Chem. Abstr.*, **82**, 43475u (1975).  
 (27) C. O. Okafor, *J. Org. Chem.*, **40**, 2753 (1975).  
 (28) D. S. Wise, Jr. and R. N. Castle, *J. Heterocyclic Chem.*, **11**, 1001 (1974).  
 (29) C. O. Okafor, *ibid.*, **17**, 1587 (1980).  
 (30) C. O. Okafor, *ibid.*, **17**, 149 (1980).  
 (31) The compound was numbered as recommended by L. T. Capell and D. F. Walker, Jr., in the "Ring Index, Supplement I", published by the American Chemical Society, Washington, D. C., 1963. p. 112.



The nomenclature is consistent with that which is used in the current literature of phenothiazine chemistry as it brings out the structural relationship with the parent phenothiazine ring. 1,4,6,8-Tetraazabenzob[*b*]phenothiazine may also be named quinoxalino[2,3-*b*][1,4]pyrimido[5,6-*e*]thiazine.

- (32) C. O. Okafor, *Phosphorus Sulfur*, **1**, 323 (1976).  
 (33) H. P. Kaufmann and P. Schulz, *Arch. Pharm.*, **273**, 31 (1935).  
 (34) M. S. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).  
 (35) E. J. Blanz, Jr., F. A. French, J. R. Deamaral and D. A. French, *J. Med. Chem.*, **13**, 1124 (1970).  
 (36) L. Katz, W. Schroeder and M. Cohen, *J. Org. Chem.*, **19**, 710 (1954).  
 (37) H. King and L. L. Ware, *J. Chem. Soc.*, **873** (1939).  
 (38) R. N. Castle, H. Ward, N. White and K. Adachi, *J. Org. Chem.*, **25**, 570 (1960).  
 (39) A. R. Katritzky, *Chem. Ind., (London)*, 331 (1965).  
 (40) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **76**, 4027 (1954).  
 (41) F. Bergmann and A. Kalmus, *J. Chem. Soc.*, 860 (1962).  
 (42) L. J. Bellamy, "The Infrared Spectra of Complex Molecules", Methuen and Co., Ltd., London, 1964, pp. 350-374.  
 (43) Peracids are required for *N*-oxide formation in *N*-heterocyclic systems.  
 (44) F. Kehrman and P. Zybs, *Ber.*, **52**, 132 (1919).  
 (45) C. Bodea and I. Silberg in "Advances in Heterocyclic Chemistry", A. R. Katritzky and A. J. Boulton, eds., Vol. 9, Academic Press Inc., New York, N. Y., 1968, pp. 321-460.  
 (46) An alternative name for this compound is 6-thia-1,2,3,5,7,12,12b-heptaazabenzob[*k*]aceanthrylene and numbered as shown below:



- (47) F. Kehrman and J. Steinberg, *Ber.*, **44**, 3011 (1911).  
 (48) G. R. Clemo, W. H. Perkin, Jr. and R. Robinson, *J. Chem. Soc.*, **125**, 1751 (1924).  
 (49) V. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 313 (1945).  
 (50) C. O. Okafor, *J. Heterocyclic Chem.*, **18**, 1445 (1981).