Dyes and Pigments **6** (1985) 405–415

New Phenothiazine Dyes and Pigments*

Charles O. Okafor

Department of Pure and Industrial Chemistry,
University of Nigeria, Nsukka, Nigeria

(Received: 28 January, 1985)

SUMMARY

The synthesis of three new azaphenothiazine ring systems and an evaluation of their use as intermediates for new dyes and pigments is described. 2-Amino-5-bromopyrazine-3[4H]-thione (**11**) *was prepared and converted to the novel 1,4,6,9-tetraazaphenothiazine ring system. The reaction of 4,5-diaminopyrimidine-6[1H]-thione* (**15**) *with 2,3-dichloropyrazines gave the isomeric 1,4,6,8-tetraazaphenothiazine ring system, another new heterocycle in this series. With 2,3-dichloroquinoxaline a previously unknown tetracyclic tetraazaphenothiazine ring system was isolated in satisfactory yields. The properties and reactions of these new heterocyclic systems are presented. Mixed nitric and sulphuric acids convert them to their 5-sulphoxides. Structural assignments were based on chemical evidence and their UV, IR, NMR and mass spectra. Mechanistic pathways to these compounds are also proposed.*

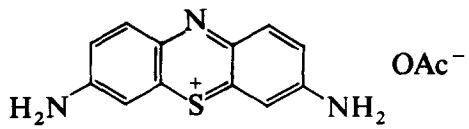
1. INTRODUCTION

About four decades ago practically all the known derivatives of phenothiazine[1–3] were the formal side-chain derivatives. A new variety[4] of phenothiazines was developed subsequently by incorporating nitrogen[5] and sulphur atoms[6,7] in the side-rings leading to aza- and thiaphenothiazine heterocycles, 3-azaphenothiazine being the first reported[5]

* This paper represents Part 27 in our 'Studies in the Heterocyclic Series'.

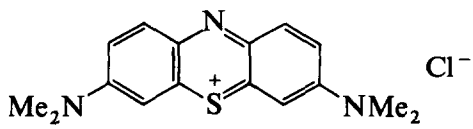
Dyes and Pigments 0143-7208/85/$03·30

aza analogue. Numerous reports have pointed out the usefulness of dyes and pigments derived from the phenothiazine framework.[1,3] The discovery of phenothiazine by Bernthsen[8] was made during his structural study of the purple dye, Lauth's Violet (Thionin; **1**). This work led to the recognition of phenothiazine derivatives as an important class of dyes.

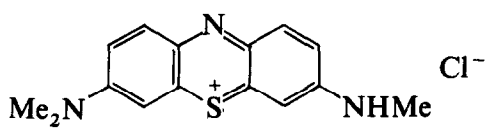


1

Notable among such dyes are Methylene Blue (**2**)[9] and Bernthsen's Azure B (C.I. 52010; **3**),[10] which are also important biological stains.

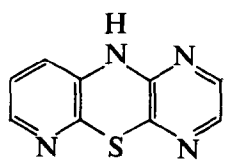


2

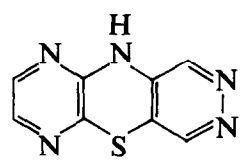


3

In order to investigate systematically the effect of the introduction of annular nitrogen atoms to the phenothiazine ring on the dyeing properties, we have studied the synthesis of isomeric azaphenothiazine ring systems and have reported the synthesis of some novel diaza-, triaza- and tetraaza-phenothiazines as typified by 1,4,6-triaza- (**4**)[14] and 2,3,6,9-tetraazaphenothiazine heterocycles (**5**).[15]

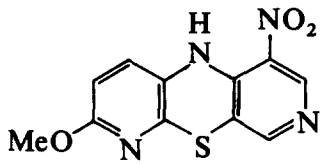


4

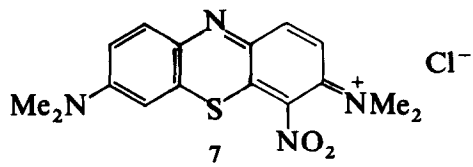


5

The differing dyeing properties of the bluish-purple 1-nitro-7-methoxy-3,6-diazaphenothiazine (**6**)[16] and the green-coloured Basic Green 5 (C.I. 52020; also called Methylene Green; **7**) demonstrate the variety of colorants based on this heterocyclic system.



6

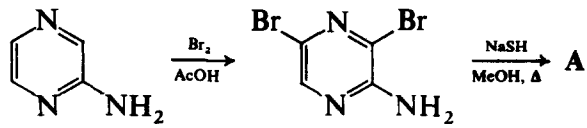


7

So far only nine out of the 35 tetraazaphenothiazine isomeric ring systems have been reported; the remaining 26 interesting isomers remain unknown. We now report the unambiguous synthesis of three new heterocyclic ring systems of this class.

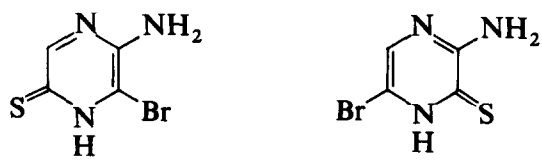
2. RESULTS AND DISCUSSION

2-Aminopyrazine (**8**) was converted to the 3,5-dibromo derivative (**9**) by the action of bromine in glacial acetic acid. Sato[17] has also reported this, and other products, using pyridine–chloroform mixture as solvent.



8 9

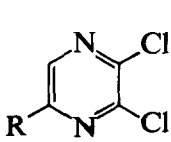
Compound **9** was converted to a monopyrazinethione **A** by refluxing with sodium hydrosulphide in methanol. Infrared, NMR and elemental analysis agreed with either **10** or **11** as the possible structure of product **A**.



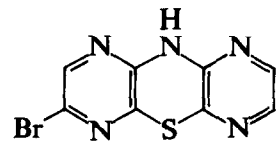
10 11

Further treatment of compound **A** with 2,3-dichloropyrazine (**12**, R = H) gave a yellowish brown solid which was formulated as 7-bromo-1,4,6,9-tetraazaphenothiazine (**13**) on the basis of its microanalysis and of its mass, infrared and NMR spectra. (This compound is numbered as recommended by L. T. Capell and D. F. Walker, Jr, in *The Ring Index*, Supplement 1, American Chemical Society, Washington, DC, 1963, p. 112. The nomenclature is consistent with that used in the current

literature of phenothiazine chemistry as it brings out the structural relationship with the parent phenothiazine. Compound **13** can also be named 10*H*-7-bromopyrazino[2,3-*b*]pyrazino[2′,3′-*e*][1,4]thiazine.)



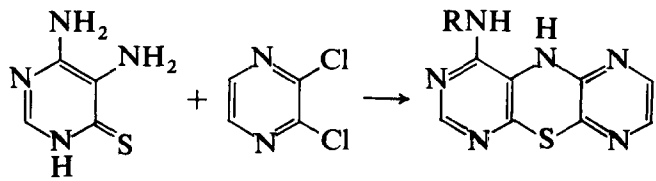
12, R = H
14, R = Cl



13

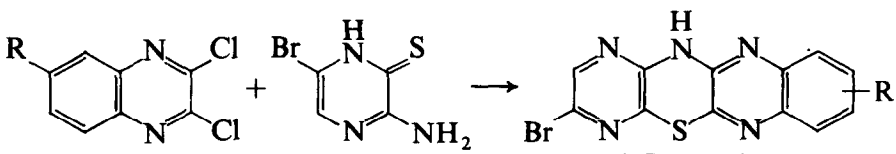
The formation of this tricyclic structure confirms that the precursor **A** is compound **11** and not **10**.

As a variation of this reaction, 4,5-diaminopyrimidine-6[1*H*]-thione (**15**) was prepared and condensed with 2,3-dichloropyrazine to form 9-amino-1,4,6,8-tetraazaphenothiazine (**16**, R = H), a derivative of the new tetraazaphenothiazine heterocycle. (Compound **17** (R = H) may also be named 10*H*-9-amino-pyrazino[2,3-*b*]pyrimidino[5′,6′-*e*][1,4]thiazine.) Acylation with acyl chlorides or acid anhydrides gave the appropriate 9-acylamido derivatives (**16**, R = acyl); 10-acylation did not occur.



15 **12** **16**, R = H, acyl

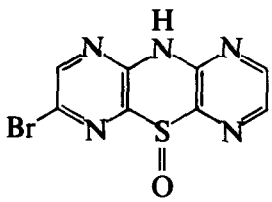
The reaction of 2-amino-5-bromopyrazine-3[4*H*]-thione (**11**) with 2,3-dichloroquinoxaline (**18**) in alkaline dimethyl sulphoxide gave a new tetraazaphenothiazine ring system identified as 7-bromo-1,4,6,9-tetraazabenzo[*b*]phenothiazine (**19**). (This compound can also be named 10*H*-7-bromoquinoxalino[2,3-*b*]pyrazino[2′,3′-*e*][1,4]thiazine.)



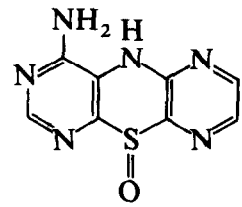
17, R = Cl, H **11** **18**, R = 12-Cl or B-Cl
19, R = H

With the exception of compound **16** (R = H), where 9-acylation took place, acetylation of these azaphenothiazines was not possible because of the weakly basic character of the 10-NH group due to the electron-withdrawing effects of the ring nitrogens. Treatment of compounds **13**

and **16** (R = H) with mixed nitric and sulphuric acids at room temperature gave good yields of their 5-sulphoxides. Nitration could not take place because of ring deactivation by the four annular nitrogen atoms. In all cases, oxidation of the ring sulphur to the sulphoxide rather than the sulphone was, however, achieved.

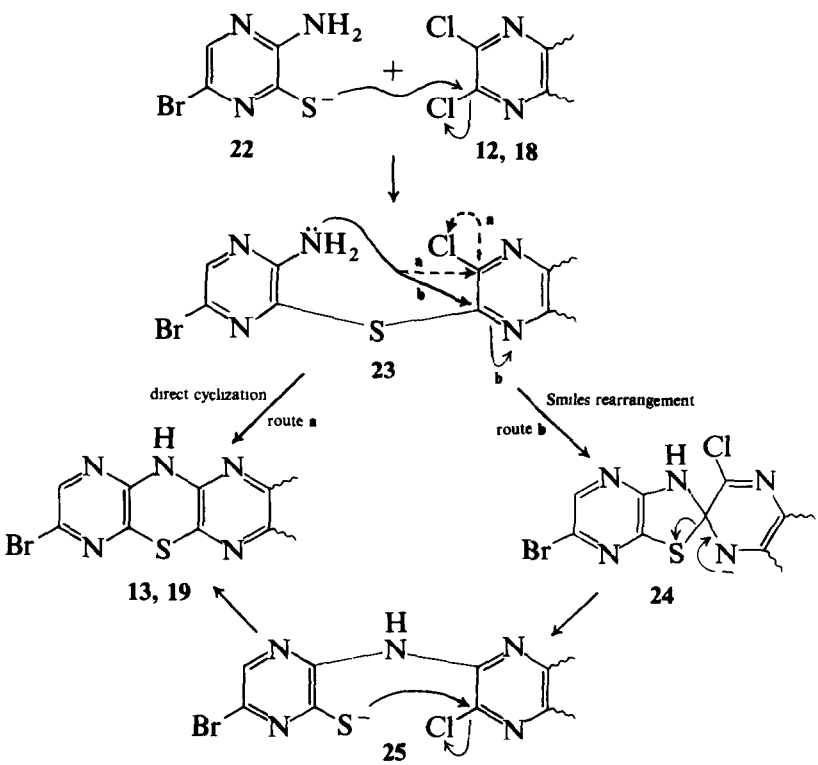


20



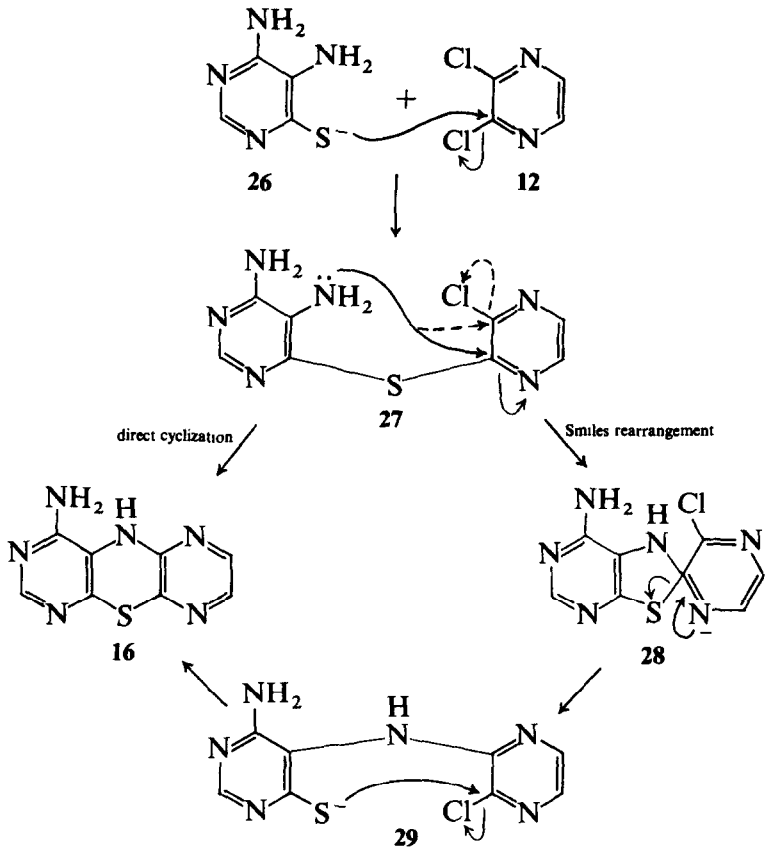
21

Two possible routes have been proposed for the formation of these tetraazaphenothiazine ring systems, **13** and **19**. One of them involves direct cyclization of the initially formed diaryl sulphide, **23**, while the other proceeds via Smiles rearrangement of the sulphide to the diarylamine before cyclization (Scheme 1).



Scheme 1

The formation of the 1,4,6,8-tetraazaphenothiazine ring system, **16**, can be rationalized in the way illustrated in Scheme 2.



Scheme 2

3. EXPERIMENTAL

3.1. General methods

Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Ultraviolet and visible spectra were recorded on a Pye Unicam SP 8000 spectrophotometer using matched 1 cm quartz cells and methanol as solvent; the absorption maxima are given in nanometres (nm); the figures in parentheses are ε values. Infrared spectra were

obtained on a Perkin–Elmer Model 137 spectrophotometer using potassium bromide 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 Me_4Si used as an internal standard. The letters br, s, d and m are used to indicate broad, singlet, doublet and multiplet, respectively. The mass spectra were determined on an AE1 MS-9 double-focusing mass spectrometer at 70 eV.

3.2. Syntheses

2-Amino-3,5-dibromopyrazine (**9**)

2-Aminopyrazine (9·5 g, 100 mmol) was placed in a reaction flask containing 70 ml of glacial acetic acid and warmed on a steam bath until it dissolved. Sodium acetate trihydrate (33 g, 243 mmol) was added with constant swirling. The slurry was stirred in an ice–salt bath maintained at −5 °C and bromine (16 ml) was added dropwise over a 4 h period (if the bromine addition was speeded up the reaction became turbulent and potentially hazardous).

The mixture was stirred in the ice bath for 2 h and then at room temperature for 24 h. It was then poured into 50 g of ice and neutralized to pH 8 with concentrated ammonia. The crude product was collected and recrystallized from methanol (Norit) to give colourless needles of 2-amino-3,5-dibromopyrazine (**9**, 20·49 g, 81 % yield), m.p. 114–115 °C; ^{1}H-NMR (Me_2SO-d_6), δ 6·87 (2H, s, br, 2-NH_2), 8·08 (1H, s, 6-H).

2-Amino-5-bromopyrazine-3[*4H*]-*thione* (**11**)

A mixture of 2-amino-3,5-dibromopyrazine (**9**, 7·59 g, 30 mmol) and sodium hydrosulphide (13·33 g, 238 mmol) was added to methanol (60 ml) and the mixture was refluxed for 4·5 h.

Methanol was then removed by distillation and the residual dark moist solid was dissolved in 150 ml of water, treated with Norit, boiled and filtered. The filtrate was cooled and acidified with glacial acetic acid. The product was filtered and recrystallized from DMF (Norit) to yield pure 2-amino-5-bromopyrazine-3[*4H*]-thione (**11**, 3·96 g, 64 % yield) as a yellow solid, m.p. 208–210 °C (dec.); UV (MeOH), λ_{max} 256 (5600), 355 nm (5081); IR, ν_{max} 3300(d) (2-NH_2), 1450 (N—C=S), 882 cm^{-1} (6-CH); ^{1}H-NMR (Me_2SO-d_6), δ 6·63 (2H, s, 2-NH_2), 7·70 (1H, s, 6-H), 9·40 (1H, s, br, 4-H); mass spectrum, *m/e* (relative intensity) 163 (21 %, M − H_2NCN), 205 (100 %, M^+), 207 (98 %, M + 2).

Analysis: Calc. for $C_4H_4N_3BrS$: C, 23·31; H, 1·94; N, 20·40; Br, 38·81; S, 15·54. Found: C, 23·17; H, 2·03; N, 20·44; Br, 39·00; S, 15·53%.

7-Bromo-1,4,6,9-tetraazaphenothiazine (**13**)

Freshly prepared 2,3-dichloropyrazine (**12**, R = H) (3·3 g, 22 mmol) was added to a mixture of 4·12 g (20 mmol) of 2-amino-5-bromopyrazine-3[4*H*]-thione (**11**), anhydrous sodium carbonate (10·6 g, 100 mmol) and 50 ml of dimethylsulphoxide and the slurry was refluxed for 2 h.

The dark blood-red mixture was poured on to 500 ml of water, stirred and cooled, and the crude product collected by filtration and recrystallized from aqueous dimethylacetamide (DMAC) (Norit) to give 7-bromo-1,4,6,9-tetraazaphenothiazine (**13**, 3·33 g, 59% yield) as a yellowish brown solid; m.p. >300 °C (dec.); UV (MeOH), λ_{max} 273 (7619), 384 nm (5956); UV (MeOH + 1·0M NaOH), λ_{max} 278 (7420), 408 nm (8304); UV (MeOH + 1·0M HCl), no change; IR, ν_{max} 3305 (10-NH), 893 (8-CH), 790 cm^{-1} (2-CH and 3-CH); ^{1}H-NMR (MeSO-d_6), δ 7·64 (2H, s, 2-H, 3-H), 7·70 (1H, s, 8-H), 9·63 (1H, s, br, 10-NH); mass spectrum, *m/e* (relative intensity) 222 (18%, M − HCN − S), 249 (31%, M − S), 281 (100%, M^+), 283 (97%, M + 2).

Analysis: Calc. for $C_8H_4N_5BrS$: C, 34·05; H, 1·42; N, 24·83; Br, 28·34; S, 11·35. Found: C, 33·89; H, 1·50; N, 25·02; Br, 28·17; S, 11·34%.

9-Amino-1,4,6,8-tetraazaphenothiazine (**16**, *R = H*)

4,5-Diaminopyrimidine-6[1*H*]-thione (**15**) (1·42 g, 10 mmol) was added to 1 g of sodium hydroxide dissolved in 30 ml of water and the mixture was then warmed until a solution was obtained. Dimethylformamide (25 ml) was then added, followed by freshly prepared 2,3-dichloropyrazine (1·79 g, 12 mmol). The solution was then refluxed for 5 h and the mixture poured on to 500 ml of ice-cold water, stirred and cooled overnight. The solid product was filtered and recrystallized from ethanolic dimethylformamide (Norit) to give 9-amino-1,4,6,8-tetraazaphenothiazine (**16**, R = H) (1·35 g, 62% yield) as a yellow solid; m.p. 230–231 °C (dec.); UV (MeOH), λ_{max} 264 (5213), 306 (2180), 396 nm (21 800); UV (MeOH + 1·0M NaOH), λ_{max} 285 (6917), 334 (2890), 425 nm (26 230); IR (KBr disc), ν_{max} 3400 (10-NH), 887 cm^{-1} (7-CH); ^{1}H-NMR (Me_2SO-d_6), δ 6·88 (2H, s, 9-NH_2), 7·80 (2H, s, 2-H, 3-H), 8·35 (1H, s, 7-H), 8·90 (1H, s, br, 10-NH); mass spectrum, *m/e* (relative intensity) 149 (12%, M − HCN − H_2NCN), 191 (15%, M − HCN), 218 (100%, M^+).

Analysis: Calc. for $C_8H_6N_6S$: C, 44·04; H, 2·75; N, 38·53; S, 14·68. Found: C, 43·87; H, 2·76; N, 38·70; S, 14·61 %.

7-Bromo-1,4,6,9-tetraazabenzo[b]*phenothiazine* (**19**)
A suspension of 2-amino-5-bromopyrazine-3[4*H*]-thione (**11**) (4·12 g, 20 mmol) in 45 ml of dimethyl sulphoxide was added to sodium hydroxide (4 g) and the mixture was warmed. 2,3-Dichloroquinoxaline (3·98 g, 20 mmol) was then added and the slurry was refluxed for 4 h.

It was then poured into about 500 g of ice, chilled and filtered. The crude residue was recrystallized from aqueous DMF to give 7-bromo-1,4,6,9-tetraazabenzo[*b*]phenothiazine (**19**) (2·29 g, 69 % yield) as an orange-yellow solid; m.p. > 300 °C (dec.); UV (MeOH), λ_{max} 252 (31 530), 312 (31 199), 326 (31 398), 343 nm (26 552); UV (MeOH + 1·0M NaOH), λ_{max} 256 (30 980), 3333 (32 890), 350 (32 970), 388 nm (29 760); IR (KBr disc), ν_{max} 333 (10-NH); ^{1}H-NMR (Me_2SO-d_6), δ 7·03 (4H, s, 11-H, 12-H, 13-H, 14-H), 7·90 (1H, s, 8-H), 11·78 (1H, s, br, 10-NH); mass spectrum, *m/e* (relative intensity) 252 (28 %, M − Br), 331 (100 %, M^+), 333 (97 %, M + 2).

Analysis: Calc. for $C_{12}H_6N_5BrS$: C, 43·39; H, 1·81; N, 21·09; Br, 24·07; S, 9·64. Found: C, 43·38; H, 2·00; N, 20·82; Br, 24·21; S, 9·68 %.

9-Acetamido-1,4,6,8-tetraazaphenothiazine (**16**, *R = Ac*)
Acetyl chloride (30 ml) was added to 9-amino-1,4,6,8-tetraazaphenothiazine (**16**, R = H) (1·09 g, 5 mmol). About 1·0 ml of pyridine was then added and the solution refluxed for 3 h. Acetyl chloride was then distilled off and the brown residue cooled. After addition of ice the solid product was collected and recrystallized from aqueous dimethylacetamide (Norit) to afford yellowish green crystals of 9-acetamido-1,4,6,8-tetraazaphenothiazine (**16**, R = Ac) (1·03 g, 79 % yield); m.p. > 300 °C (dec.); IR (Nujol), ν_{max} 3280 (NH), 1665 cm^{-1} (N—C=O); mass spectrum, *m/e* (relative intensity) 260 (100 %, M^+).

Analysis: Calc. for $C_{10}H_8N_6OS$: C, 46·15, H, 3·08; N, 32·31; S, 12·31. Found: C, 46·29; H, 3·00; N, 32·54; S, 12·33 %.

7-Bromo-1,4,6,9-tetraazaphenothiazine 5-oxide (**20**)
Sulphuric acid (*d* 1·84, 10 ml) was cooled to 0 °C and added to 2·82 g (10 mmol) of 7-bromo-1,4,6,9-tetraazaphenothiazine. Concentrated nitric acid (*d* 1·42, 20 ml) precooled to 0 °C was then added dropwise with cooling over a period of 20 min.

After the addition of nitric acid, the mixture was stirred at room temperature for 3 h and left to stand overnight. The clear yellowish-brown solution was poured into ice and neutralized with concentrated ammonia while cooling. The solid product was filtered and recrystallized from aqueous DMAC (Norit) to give 7-bromo-1,4,6,9-tetraazaphenothiazine 5-oxide (**20**) (2·50 g, 84 % yield) as a yellow solid, m.p. > 250 °C (dec.); IR (Nujol), ν_{max} 1048 cm^{-1} (S=O).

Analysis: Calc. for $C_8H_4N_5BrOS$: C, 32·23; H, 1·34; N, 23·50; Br, 26·82; S, 10·74. Found: C, 32·46; H, 1·32; N, 23·29; Br, 27·00; S, 10·75 %.

9-Amino-1,4,6,8-tetrazaphenothiazine 5-oxide (**21**)

This compound was obtained in 80 % yield using the procedure described for 7-bromo-1,4,6,9-tetraazaphenothiazine 5-oxide (**20**); m.p. > 250 °C (dec.); IR (Nujol), ν_{max} 1042 cm^{-1} (S=O).

Analysis: Calc. for $C_8H_6N_6OS$: C, 41·03; H, 2·56; N, 35·90; S, 13·68. Found: C, 40·99; H, 2·47; N, 36·11; S, 13·56 %.

ACKNOWLEDGEMENTS

We express our appreciation to the Senate Research Grants Committee of the University of Nigeria for its financial support of this work through Research Grant No. 00134/76. Grateful acknowledgement is extended to Professor C. Galeffi of Istituto Superiore di Sanita, Rome, Italy, for some of the microanalysis and mass spectra. We also thank Professor Z. T. Fomum of the Department of Organic Chemistry, University of Yaounde, Yaounde, Cameroun, for some of the infrared and ultraviolet spectra. The technical assistance of Messrs O. O. Ibe, N. Igwe and F. U. Ekezie and Mrs P. Agwuna of these laboratories is deeply appreciated.

REFERENCES

1. S. P. Massie, *Chem. Rev.*, **54**, 791 (1954).
2. D. E. Pearson, in *Heterocyclic compounds*, Volume 6, ed. R. C. Elderfield, Chapter 14, pp. 624–726. New York, Wiley (1957).
3. K. Venkataraman, *The chemistry of synthetic dyes*, Volume 2, p. 791. New York, Academic Press (1952).

4. V. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 591 (1945).
5. C. O. Okafor, *J. Org. Chem.*, **38**, 4386 (1973).
6. C. O. Okafor, *Int. J. Sulfur Chem.*, **7B**, 109 (1972).
7. C. J. Grol and J. S. Faber, *Rec. Trav. Chim., Pays-Bas*, **89**, 68 (1970).
8. A. Bernthsen, *Ber. Deut. Chem. Ges.*, **16**, 2896 (1883).
9. H. E. Fierz-David, *Fundamental processes of dye chemistry*, p. 311. New York, Interscience (1949).
10. A. Bernthsen, *Ann.*, **230**, 169 (1885); H. J. Conn, *Biological stains*, 7th edn (1961), pp. 98–9, 103, 255–8, 289–90; 8th edn (1969), pp. 296–7. Baltimore, Maryland, Waverly Press.
11. C. O. Okafor, *Int. J. Sulfur Chem.*, **6B**, 237 (1971).
12. C. O. Okafor, *Phosphorus and Sulfur*, **4**, 79 (1978).
13. C. O. Okafor, *J. Org. Chem.*, **40**, 2753 (1975).
14. C. O. Okafor, *J. Org. Chem.*, **47**, 592 (1982).
15. C. O. Okafor, R. N. Castle and D. S. Wise, Jr, *J. Heterocyclic Chem.*, **20**, 1047 (1983).
16. C. O. Okafor, *J. Org. Chem.*, **32**, 2006 (1967).
17. N. J. Sato, *Heterocyclic Chem.*, **19**, 673 (1982).