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Novel Heterocyclic Intermediates for New Dyes and Pigments†

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SUMMARY

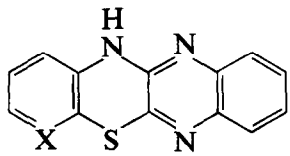
The synthesis of two new heterocyclic ring systems of the phenoxazine type is described. These are the 1,4,9-triazaphenoxazine and 1,4,6-triazabenzo[b]phenoxazine. The preparation of the parent ring of 1,4,9-triazaphenoxazine ring system is also reported. Spectroscopic data are in agreement with the assigned structures and the mechanistic pathway to these novel heterocycles is also presented. These ring systems provide a new framework for the development of novel dyes and pigments of the phenoxazine class.

1. INTRODUCTION

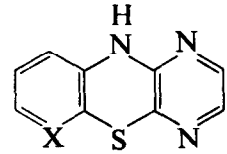
2-Aminothiophenol[1] has been shown to react readily with 2,3-dichloroquinoxaline (**1**) and 2,3-dichloropyrazine (**2**) to afford 1,4-diazabenzo[*b*]phenothiazine (**3**, X = CH) and 1,4-diazaphenothiazine (**4**, X = CH) respectively.‡ 3-Aminopyridine-2[1*H*]-thione also gives the corresponding triazaphenothiazines (**3** and **4**, X = N).[2,3]

† This paper is Part 26 of the author's Studies in the Heterocyclic Series.

‡ This compound was numbered as recommended by L. T. Capell and D. F. Walker, Jr, in *The ring index*, American Chemical Society, Washington, DC. The nomenclature is consistent with what is used in the current literature of phenothiazine and phenoxazine chemistry as it brings out more clearly the structural relationship with the parent phenothiazine and phenoxazine ring systems.

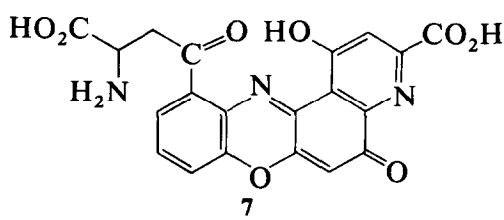


3, X = CH, N



4, X = CH, N

With the oxygen analogues of these *ortho*-aminothiols, disappointing results were obtained. In some cases no products are formed. Whereas 2-aminophenol[4] and 2-amino-3-pyridinol[5] (**5**) gave the cyclized products in reduced yields, 3-aminopyridin-2[1*H*]-one (**6**) failed to give the desired phenoxazines. The starting materials were recovered together with the hydrolysed dichlorodiazines. These results are consistent with the lower nucleophilic power of the hydroxyl ion compared to the mercaptide ion. Thus the synthesis of polyazaphenoxazines is expected to pose serious problems. So far, most of the known azaphenoxazine pigments are of natural origin, the most important of which is xanthommatin (**7**), an acidic pigment found in different arthropods and responsible for the coloration of moulting secretions of insects and coloration in the eyes of the blowflies *Calliphora erythrocephala* and *Musca domestica*.[6,7]



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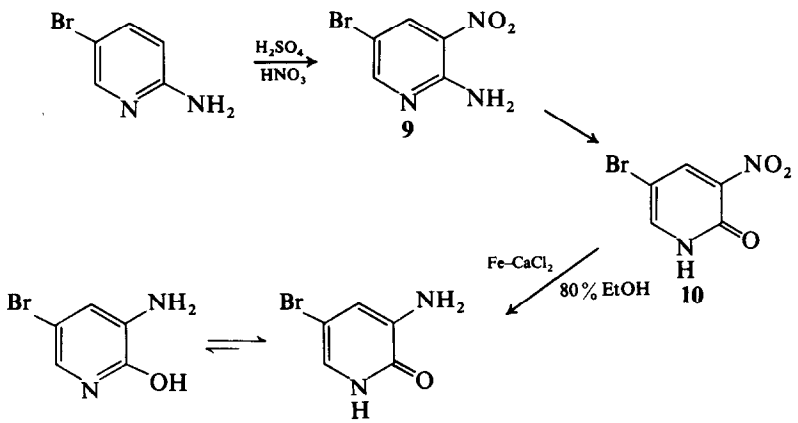
Because of the need for the isomeric triazaphenoxazines in our search for new phenoxazine dyes with strong fastness properties,[8] the synthesis of new triazaphenoxazines was carried out. Prior to this work only one triazaphenoxazine ring system[5] out of 35 possible isomeric forms was known to exist. (These 35 isomeric triazaphenoxazines do not include structural isomers with bridgehead nitrogen.) We now wish to describe our successful synthesis of three new triazaphenoxazine ring systems and the parent compound of one of them.

2. RESULTS AND DISCUSSION

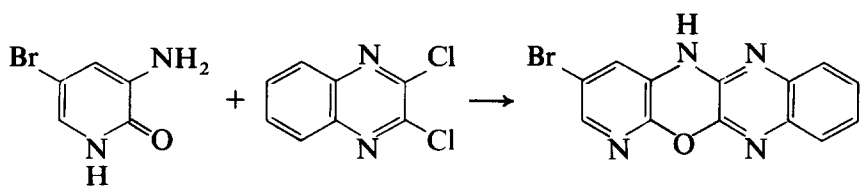
Owing to the failure of compound **6** to react with 2,3-dichloroquinoxaline or 2,3-dichloropyrazine in alkaline media to yield the desired triaza-

phenoxazines, an electron releasing group such as bromine which would enhance the nucleophilicity of the hydroxyl group was introduced at the 5-position of compound **6**. This compound, 3-amino-5-bromopyridin-2-[1*H*]-one (**8**), was obtained by converting 2-amino-5-bromopyridine to the 3-nitro derivative (**9**). Although diazotization[9] of compound **9** gave 5-bromo-3-nitropyridin-2[1*H*]-one (**10**), an improved yield was obtained by nucleophilic displacement of the more labile 2-amino group by the hydroxyl group. Catalytic hydrogenation with palladized charcoal or by the newly developed Fe–$CaCl_2$ reagent[3] gave the desired precursor (**8**) in satisfactory yields as shown in Scheme 1. Microanalysis, infrared and NMR spectroscopy are in agreement with the assigned amido tautomer **8**.



Scheme 1

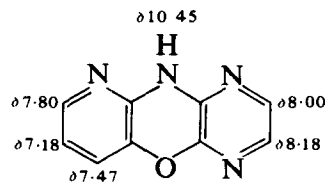
By refluxing an equimolar mixture of the dichloroquinoxaline (**1**) and the aminopyridone **8** in dried dimethyl sulphoxide in the presence of anhydrous sodium carbonate, a light grey microcrystalline material was obtained. Microanalysis and mass spectroscopy are in good agreement with the formula, $C_{13}H_7N_4BrO$. The infrared band at 3370 (10-NH) and the NMR signals at δ 12·38 (broad, 10-NH), 9·24 (singlet, 7-H), 8·75 (singlet, 9-H) and the aromatic multiplet at 7·30 are consistent with the tetracyclic structure **11** which we have assigned to this product. As



8 **1** **11**

expected, the product 1,4,6-triazabenzo[*b*]phenoxazine (**11**) is quite stable; it is not oxidized by long exposure to air and it is not acylated by reaction with acyl chlorides due mainly to the -*M* and -*I* effects of ring nitrogen at the 1-position. (1,4,6-Triazabenzo[*b*]phenoxazine can also be named 10*H*-quinoxalino[2,3-*b*]pyrido[3′,2′-*e*][1,4]oxazine.)

By similarly reacting 2-amino-3-pyridinol (**5**) with 2,3-dichloropyrazine (**2**),† another new triazaphenoxazine ring system was obtained in good yield. This compound, 1,4,9-triazaphenoxazine (**12**) (which can also be named 10*H*-pyrazino[2,3-*b*]pyrido[2′,3′-*e*][1,4]oxazine) is the parent compound of this heterocyclic ring system. Elemental analysis, ultraviolet, infrared, NMR and mass spectroscopy are in agreement with the assigned structure (**12**).



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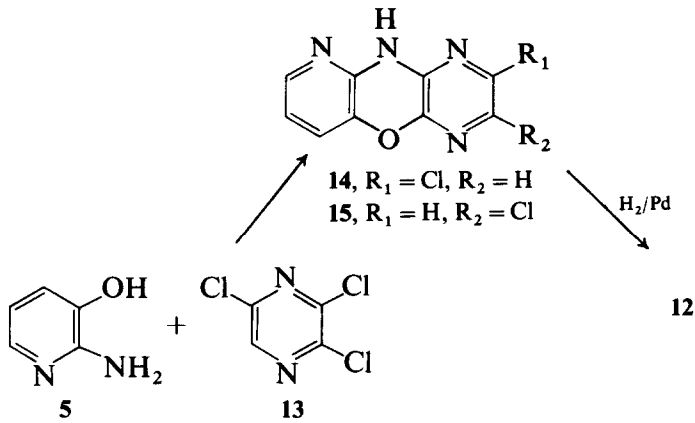
As in compound **11**, 1,4,9-triazaphenoxazine is stable to air and is not readily acylated with acyl halides due to the combined -*M* and -*I* effects of the ring nitrogens in the 1- and 9-positions.

2-Amino-3-pyridinol also condenses with 2,3,5-trichloropyrazine (**13**)[12] to give product **A**, a single chlorine-containing derivative of compound **12**, in 85% yield.

Compound **A** analysed well for $C_9H_5N_4ClO$ and mass spectroscopic work is in agreement with this formula. This product has an infrared band at 3390 cm^{-1} (NH group in the 10-position) and NMR absorptions at δ 10·82 (broad, 10-NH), 7·50 (2-H or 3-H) and the aromatic protons of the pyridine moiety appeared as a multiplet at δ 7·35. These spectral characteristics are in agreement with either of the structures **14** and **15**.

Comparison of the ultraviolet spectra of the parent compound **12** and the monochloro derivative (**A**) obtained reveals that the introduction of a halogen in the pyrazine moiety did not appreciably alter the wavelength and intensity of maximum absorption even upon ion formation arising

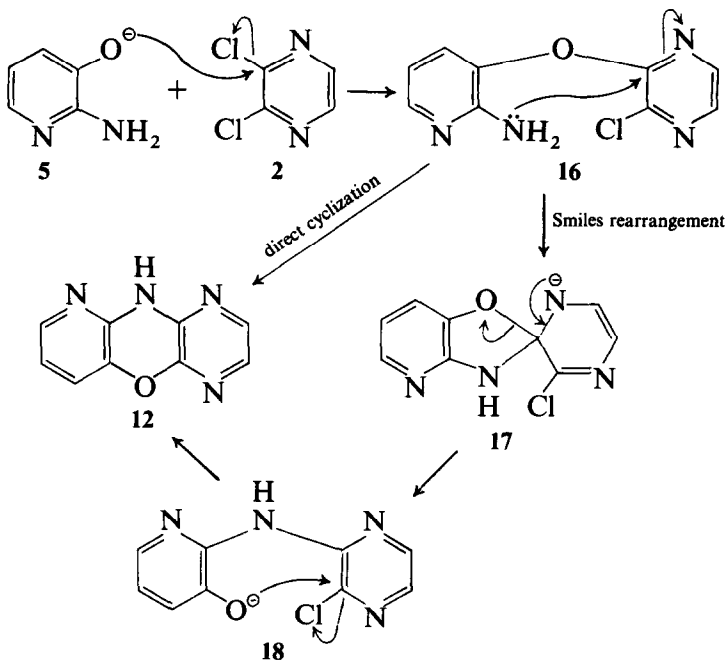
† 2,3-Dichloropyrazine prepared according to Bernardi's procedure is found to be contaminated by 2,3,5-trichloropyrazine which is the major product.[10] 2,3-Dichloropyrazine free from trichloropyrazine impurity is reported in Ref. 11.



from an addition of a few drops of sodium hydroxide. This observation agrees with the results of Simov[13] who worked with the parent phenothiazine and its derivatives. It thus shows that the halogen is probably substituted at the 2-position of compound **12**. This conclusion is also in accord with Saari's[14] major products of the reactions of 2-aminophenol with 2,3,5-trichloropyrazine and 2,3-dichloro-5-methylpyrazine. It therefore suggests that 2-chloro-1,4,9-triazaphenoxazine (**14**, $R_1 = Cl$, $R_2 = H$) is the product of this reaction. Only X-ray crystallographic analysis will however decide the correct structure as either **14** or **15**. (Crystals with well-defined structures required for X-ray crystallographic work could not be grown in the crystallization solvent, dimethylacetamide–ethanol mixture, and hence the exact structure could not be ascertained.) Catalytic hydrogenation of this product converts it to the parent compound **12** which gave identical properties to an authentic sample.

Compound **12** is probably formed by initial base-catalysed condensation of compounds **2** and **5** to produce the pyridyl pyrazinyl ether **16**. Direct cyclization without rearrangement will lead to the product **12** (Scheme 2).

Alternatively the amino group could mount an intramolecular nucleophilic attack on C-3 of the pyrazine ring leading to the diarylamine **18** (Smiles rearrangement).[8a] Cyclization and formation of product **14** will be achieved by loss of chloride ion through aryloxide attack on C-2. Further evidence for the proposed intermediate **16** was provided by *O*-methylation of 2-amino-3-pyridinol with dimethyl sulphate. The resulting 2-amino-3-methoxypyridine could not react with 2,3-dichloropyrazine under the conditions used for the formation of the diaryl ether, **16**. The



Scheme 2

starting compounds were recovered. This shows that the reaction of compounds **2** and **5** in an alkaline medium first forms a diaryl ether **17** instead of the diarylamine **18**.

3. EXPERIMENTAL

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. The solvent was methanol and the absorption maxima are always 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.

5-Bromo-3-nitropyridin-2[1*H*]-one, 10

2-Amino-5-bromo-5-nitropyridine[15,16] (10·9 g, 50 mmol) was refluxed in 100 ml of 10% sodium hydroxide solution for 6 h. The clear solution was treated with Norit, filtered and cooled. Upon acidification with glacial acetic acid a nearly quantitative yield of 5-bromo-3-nitropyridin-2[1*H*]-one (10·2 g, 93% yield) was obtained after crystallization from ethanol (Norit), m.p. 239–240 °C.

Alternatively this compound can be obtained by diazotiazation[9] with sodium nitrite and dilute hydrochloric acid but in reduced yields.

3-Amino-5-bromopyridin-2[1*H*]-one, 8

5-Bromo-3-nitropyridine-2[1*H*]-one (6·57 g; 30 mmol) in 100 ml of ethanol was hydrogenated over 10% palladium on charcoal (1 g). After the theoretical volume of hydrogen was absorbed (*ca* 6 h), the catalyst was filtered off. The ethanolic filtrate was concentrated *in vacuo* to afford the crude product. Recrystallization from ethanol (Norit) gave 5·1 g (90% yield) of 3-amino-5-bromopyridin-2[1*H*]-one as creamy white powder, m.p. 182–183 °C; λ_{max} 262 (6398), 319 nm (9597); ν_{max} 3375 (m, 3-NH_2), 3270 (m, 1-NH), 1660 (s, C=O), 1340 (s, Ar-NH_2), 1182 (w, 3,5,6-trisubstituted pyridine), 860 cm^{-1} (s, lone C—H); δ (DMSO-d_6) 5·31 (2H, br, 3-NH_2), 6·43 (1H, d, $J = 2{\cdot}5$ Hz, 4-H), 6·74 (1H, d, $J = 2{\cdot}5$ Hz, 6-H), 11·40 (1H, br, 1-NH); *m/e* 160 (29·8%, M − CO), 162 (29·6%, M + 2 − CO), 188 (100%, M^+), 190 (97·3%, M + 2). (Found: C, 31·79; H, 2·53; N, 15·00; Br, 42·21. $C_5H_5N_2BrO$ requires: C, 31·76; H, 2·65; N, 14·82; Br, 42·30%.)

The same product[17,18] was obtained in 84% yield by reduction of 4·38 g (20 mmol) sample with 5 g of iron powder, 2 g of calcium chloride in 80% aqueous ethanol as by the recently developed process.[3]

8-Bromo-1,4,6-triazabenzo[*b*]phenoxazine, 11

3-Amino-5-bromopyridin-2-[1*H*]-one (3·78 g, 20 mmol) was dissolved in 40 ml of dimethyl sulphoxide and sodium carbonate (5·3 g, 50 mmol) was then added. The mixture was slurried for about 10 min at room temperature. To this mixture was then added 4·38 g (22 mmol) of 2,3-dichloroquinoxaline and the entire slurry refluxed with stirring for 15 h. At the end of the reflux period, the reaction mixture was cooled and

poured into about 500 g of crushed ice and stirred. The alkaline solution was filtered. The residue was collected by filtration and recrystallized from aqueous DMF after treatment with Norit to give 8-bromo-1,4,6-triazabenzo[*b*]phenoxazine (**11**, 2·82 g, 45% yield) as light green microplates; m.p. > 300 °C; λ_{max} 362 (37 593), 379 nm (35 035); ν_{max} 3220 (m, 10-NH), 878 (s, lone CH), 740 cm^{-1} (s, four adjacent CH); δ 7·40 (4H, m, 11-H, 12-H, 13-H, 14-H), 8·72 (1H, s, 9-H), 9·20 (1H, s, 7-H); *m/e* 314 (100%, M^+), 316 (98%, M + 2). (Found: C, 49·72; H, 2·23; N, 17·80; Br, 25·19. $C_{13}H_7N_4BrO$ requires: C, 49·54; H, 2·22; N, 17·78; Br, 25·38%.)

2,3,5-Trichloropyrazine, 13

The preparation of 2,3,5-trichloropyrazine from 2,6-dichloropyrazine via its 4-oxide[12] has been reported. Its preparation from 2-chloropyrazine is now described by a modification of Bernardi's procedure for 2,3-dichloropyrazine synthesis.[10]

To 8 ml (10·24 g, 89 mmol) of 2-chloropyrazine in 6 ml of DMF or DMAC in an ice-bath was added 40 ml of sulphuryl chloride with stirring during 20 min. After the addition of sulphuryl chloride the mixture was stirred for an additional 10 min; the ice-bath was then removed and the mixture refluxed for 3 h at 75 °C.

The sulphuryl chloride was removed by distillation and the yellow slurry poured into crushed ice and neutralized with concentrated ammonia while cooling. The heavy yellow liquid was separated from the upper aqueous layer and steam-distilled to afford 2,3,5-trichloropyrazine (10·9 g, 67% yield); m.p. 30–31 °C; literature[12] m.p. 31·5 °C; δ 8·63 (1H, s, 6-H).

1,4,9-Triazaphenoxazine, 12

To a solution of 2·2 g (20 mmol) of 2-amino-3-pyridinol in 25 ml of dimethyl sulphoxide was added 5·3 g (50 mmol) of anhydrous sodium carbonate and 3·29 g (22 mmol) of freshly prepared 2,3-dichloropyrazine. The mixture was refluxed on an oil bath for 3 h. It was poured into 500 ml of crushed ice and filtered. The dark green residue was recrystallized from DMF after treatment with Norit to afford 1,4,9-triazaphenoxazine (2·72 g, 73% yield) as glistening green plates, m.p. > 300 °C (dec); λ_{max} 359 (6559); UV (+0·1 M NaOH) 395 (8811); UV (+1·0 M NaOH), 395 nm

(12 974); the UV spectrum is unchanged by the addition of 1·0 M HCl; ν_{max} 3200 (m, 10-NH), 822 (s, two adjacent C-H), 780 cm^{-1} (s, three adjacent C-H); δ (DMSO-d_6) 7·18 (1H, 7-H), 7·47 (1H, 6-H), (1H, 8-H), 8·00 (1H, 2-H), 8·18 (1H, 3-H), 10·45 (1H, br, 10-NH); *m/e* 186 (100%, M^+). (Found: C, 58·14; H, 3·24; N, 30·14. $C_9H_6N_4O$ requires C, 58·06; H, 3·23; N, 30·11%.)

Condensation of 2,3,5-trichloropyrazine with 2-amino-3-pyridinol

2-Amino-3-pyridinol (3·3 g, 30 mmol) was added to a solution of 4 g (100 mmol) of sodium hydroxide in 20 ml of water. Dimethylacetamide (40 ml) was then added. The mixture was warmed to dissolve.

2,3,5-Trichloropyrazine (6·1 g, 33 mmol) was then added and the entire reaction mixture refluxed for 9 h. The hot solution was poured into 600 ml of crushed ice and filtered. The green residue was collected by filtration and recrystallized from ethanol–DMAC mixture (1:2) after treatment with Norit. A product, **A**, formulated as 2-chloro- or 3-chloro-1,4,9-triazaphenoxazine (5·6 g, 85% yield), was obtained as light green crystalline plates; m.p. 289–290 °C (dec); λ_{max} 359 (5586); UV (+0·1 M NaOH), 408 (7350); UV (+1·0 M NaOH), 403 (9555); UV (+1·0 M HCl), no change in spectrum; ν_{max} 3180 (m, 10-NH), 863 (s, lone C-H), 780 cm^{-1} (s, three adjacent C-H); δ 6·92 (3H, m), 7·60 (1H, s), 10·52 (1H, s, br); *m/e* 130 (27%, M − Cl, HCN, CO), 158 (18%, M − Cl, HCN), 185 (21%, M − Cl), 220 (100%, M^+), 222 (37%, M + 2). Found: C, 48·89; H, 2·13; N, 25·48; Cl, 16·02. $C_9H_5N_4ClO$ requires C, 48·98; H, 2·27; N, 25·40; Cl, 16·10%.)

Dechlorination of product A

To a solution of 50 ml of ethanol was added 0·221 g (1 mmol) of product **A**, 0·21 ml of concentrated ammonia and about 0·25 g of 10% palladium on charcoal. Hydrogen was passed at room temperature into this solution under atmospheric pressure until the theoretical amount of hydrogen had been absorbed (about 6 h).

The solution was filtered to remove the spent catalyst and charcoal. The filtrate was evaporated to dryness and the yellowish green solid was recrystallized from acetone–ethanol mixture to give greenish plates of 1,4,9-triazaphenoxazine, **12** (0·151 g, 81%).

The action of 3-aminopyridin-2[1*H*]-one (6) on 2,3-dichloroquinoxaline and 2,3-dichloropyrazine

To 3-aminopyridin-2[1*H*]-one (1·1 g, 10 mmol) in 40 ml of dimethyl sulphoxide containing anhydrous sodium carbonate (2·12 g, 20 mmol) was added 2,3-dichloroquinoxaline (1·99 g, 10 mmol). The mixture was refluxed on an oil bath for 12 h. The dark solution was poured into ice, stirred and filtered. The grey solid, m.p. > 300 °C, is insoluble in ethanol–DMF mixture but readily soluble in water to give an alkaline solution. NMR spectroscopy shows that this product is the disodium salt of 2,3-dihydroxyquinoxaline.

No crystalline product was obtained from a similar reaction of 3-aminopyridin-2[1*H*]-one with 2,3-dichloropyrazine; the starting compound **6** was recovered after chromatographic separation of the resulting mixture.

ACKNOWLEDGEMENTS

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