Synthesis and Reactions of the First Triazaphenoxazine Ring System

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1,4,9-Benzo[b]triazaphenoxazine, the first and parent compound of this new heterocyclic ring, as well as its derivatives were prepared essentially by cyclo-condensation of 2-amino-3-hydroxypyridine with the appropriate 2,3-dichloroquinoxaline in the presence of alkaline DMF or DMAC. Nitration of the product with mixed nitric and sulfuric acids gave the corresponding 13-nitro derivative. Structural assignments were made by chemical evidence and by a study of the ultraviolet, infrared, nmr and mass spectra.

Actinomycin (1), questiomycin (2,3), cinnabarin (4-6) and xanthommatinoprotein (7,8) are representative examples of naturally occurring compounds with the phenoxazine skeleton (9). In spite of the large number of these natural products, the chemistry of phenoxazine (I) (6,9,10,11) is less developed than its sulfur analogue, phenothiazine (II), which has no natural derivatives (12-15).
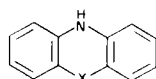
I, X = O
II, X = S

More recent papers, particularly those published after 1936 (16), include synthetic studies on heterocyclic analogues of these ring systems. While as many as four monoaza-(17), ten diaza- (18), three triaza- (19-20) and five tetraaza- (21) phenothiazine rings have been synthesized and characterised (22-23), only four monoaza- (24) and three diaza-analogues of phenoxazine (25,26) have been reported (9) despite the fact that the first azaphenoxazine was reported much earlier than the first azaphenothiazine. Furthermore, there is no report whatsoever of any of the twenty-four hypothetical structural isomers of the triazaphenoxazine ring system. This anomalous situation led to our present study on the synthesis of the first triazaphenoxazine system.

Starting with an *o*-phenylene diamine (III) and converting it to the corresponding 2,3-dihydroxyquinoxaline (IV) by reacting with diethyl oxalate (V) (27), 2,3-dichloroquinoxaline (VI) was obtained in excellent yields by refluxing with phosphorus pentachloride at 150° (27,28).

The cyclocondensation of 2-amino-3-hydroxypyridine (VII) with 2,3-dichloroquinoxaline (VI, R = H) in aqueous *N,N*-dimethylformamide (DMF) in the presence of a stoichiometric amount of potassium hydroxide led to a deep-green microcrystalline material. This product melted above 300° and had a greenish-blue fluorescence in aqueous DMF, toluene, benzene, methanolic and ethanolic solutions. Microanalysis and mass spectroscopy

Scheme I

III, R = H, Cl

X

VI, R = H, Cl

IV, R = H, Cl
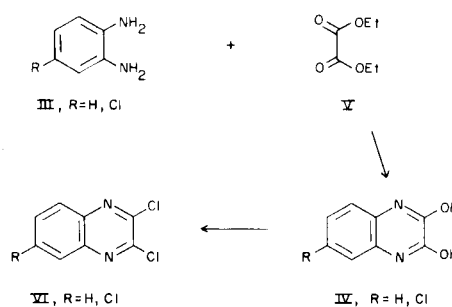
are in agreement with the molecular formula $C_{13}H_8N_4O$. The infrared spectrum showed a medium NH band at 3180 cm^{-1} and strong signals at 768 and 782 cm^{-1} due to CH out-of-plane deformation in the 1,2-di- and 1,2,3-trisubstituted aromatic rings, respectively. In the nmr spectrum, the 10-NH proton appeared as a very broad singlet between -1.7 and 0.7 τ, while the multiplet peaks between 2.00 and 3.30 τ were assigned to the aromatic protons. These results are in agreement with the cyclized structure VIII which is the parent compound of the 1,4,9-benzo[b]-triazaphenoxazine ring system (29) and the first triazaphenoxazine ring compound.
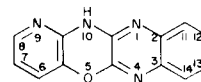

VIII

If 4-chloro-*o*-phenylenediamine (III, R = Cl) was used in these reactions, as shown in Scheme 1, the ultimate product that was obtained had two structural possibilities, IX and X, depending on whether the cyclization of the intermediate diaryl ether, XI, in the final step took place with or without Smiles rearrangement (22,30) (Scheme 2). This product is a greenish yellow solid melting above 300°. The molecular formula of $C_{13}H_7ClN_4O$ is in agreement with the elemental analysis and mass spectrum. The product had strong ultraviolet absorption maxima at 230,

Scheme 2
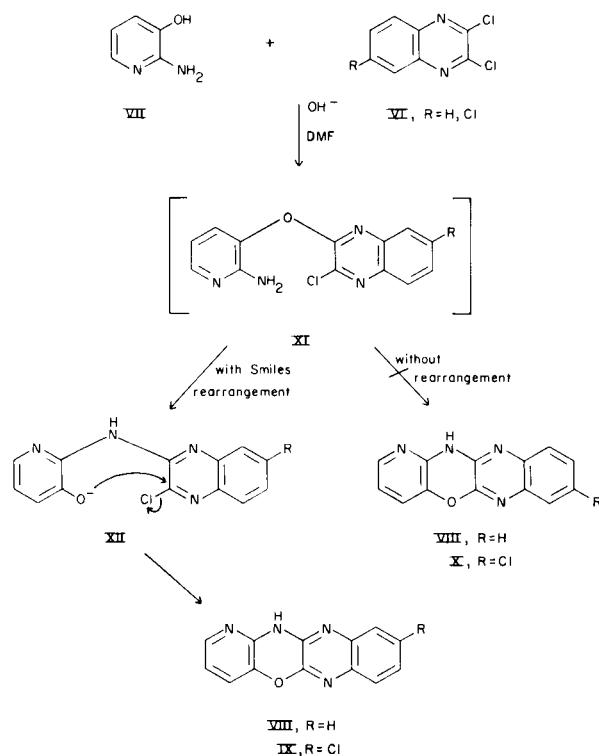
272 and 378 nm. The infrared spectrum showed a medium peak at 3176 cm^{-1} (10-NH stretching frequency), and strong bands at 815 cm^{-1} (CH out-of-plane deformation in 1,2,4-trisubstituted benzenes) and 788 cm^{-1} (2,3-disubstituted pyridine).

Confirmatory evidence for structure IX, R = Cl, was obtained by nitration of this product with mixed nitric and sulfuric acids at room temperature. Only a single product was isolated from this reaction and the yield was excellent. Infrared analysis of this derivative showed a strong band at 1340 cm^{-1} which was attributed to the nitro group. Two other strong bands at 786 and 882 cm^{-1}, which were due to 1,2,3-trisubstitution and 1,2,4,5-tetrasubstitution (31) on rings A and D, respectively, were also observed. These
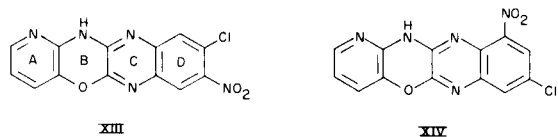
results show that the nitration product is 12-chloro-13-nitro-1,4,9-benzo[b]triazaphenoxazine, XIII, and not structure XIV.

Structure XIV is further eliminated by the fact that mild nitration of phenothiazine and related compounds takes place preferentially at the position *para* to the activating group (24,32). If that position is blocked by another substituent as in the case of structure X, R = Cl,

substitution will not take place under the mild conditions employed, or at best it will give an extremely low yield of compound XIV.

Having established the structure of the nitro-compound as XIII, its precursor is therefore 12-chloro-1,4,9-benzo[b]-triazaphenoxazine IX, R = Cl, which is the rearranged structure. The parent compound VIII is also a rearranged product but in this case both the rearranged and non-rearranged structures are identical.

EXPERIMENTAL

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Ultraviolet 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 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 which was used as an internal standard. The letters b, s and m are used to indicate, broad, singlet and multiplet, respectively. The mass spectra were obtained on an AE1 MS-9 double focusing mass spectrometer at 70 eV. Microanalyses were done partly by the department of Pure and Applied Chemistry, University of Strathclyde, Glasgow, Scotland and partly by the Department of Chemistry, University of Ibadan, Ibadan, Nigeria.

2,3-Dihydroxyquinoxalines (IV).

These compounds were obtained by refluxing 2:1 molar ratios of diethyl oxalate (V) and the appropriate o-phenylenediamine (III) in ethanol for 8 hours as described previously, except that dissolution in dilute sodium hydroxide and reprecipitation with dilute acid was found unnecessary. Crystallization from ethanol (twice) afforded excellent yields of the corresponding 2,3-dihydroxyquinoxalines after treatment with activated charcoal, m.p. > 350° (IV, R = Cl) (27,28).

Chlorination of 2,3-Dihydroxyquinoxalines.

The appropriate 2,3-dihydroxyquinoxaline was treated at 140-150° with phosphorus pentachloride containing 10 ml. of phosphorus oxychloride and 10 ml. of aniline in an oil bath as described by Stevens, Pfister and Wolf (27), except that the reaction time was doubled and 10 ml. of diethylaniline were also added. Very good yields of 2,3-dichloroquinoxalines (VI) were obtained.

1,4,9-Benzo[b]triazaphenoxazine (VIII).

2-Amino-3-hydroxypyridine (VII, 2.42 g., 22 mmoles) was placed in the reaction flask to which was added 2.24 g. (40 mmoles) of potassium hydroxide and 50 ml. of water. The mixture was warmed on a steam bath with constant swirling until there was complete dissolution. To this solution was then added 3.98 g. (20 mmoles) of 2,3-dichloroquinoxaline and 20 ml. of dimethylformamide (DMF). The entire mixture was then refluxed on a heating mantle for 2 hours.

Before refluxing began, there was no immediate dissolution, but as refluxing progressed, a greenish brown coloration which later gave way to a brown color was observed. After 12 minutes of refluxing, heavy yellow-brown precipitation occurred, which persisted throughout the reflux period. The mixture was transferred to a beaker, cooled and filtered. The filtrate was discarded while the residue was crystallized from a water-DMF-methanol (4:4:1) mixture after treatment twice with activated charcoal. Deep green glistening microneedles of 1,4,9-benzo-[b]triazaphenoxazine (VIII) (3.35 g., 72% yield) were collected, m.p. > 300°; uv: λ max 255 (45,548), 300 (17,700), 348 (28,320); ir: ν max 3180, 2940 (d), 1642, 1600, 1585, 1554, 1512, 1467, 1460, 1420, 1408, 1383, 1355, 1320, 1280, 1255, 1225, 1178, 1145, 1060, 1034, 970, 940, 920, 890, 865, 840, 782, 768, 760, 725, 674 cm^{-1}; nmr (DMSO-d_6): τ -1.7 to 0.7 (v.b., 10-NH) and 2.00 to 3.30 (m, aromatic protons); ms: m/e (relative intensi-

ty) 90 (16), 107 (25), 108 (6), 118 (11), 128 (3), 129 (56), 131 (32), 146 (4), 157 (8), 172 (14), 236 (M$^+$, 100%), 237 (65).

Anal. Calcd. for $C_{13}H_8N_4O$: C, 66.10; H, 3.39; N, 23.73. Found: C, 66.16; H, 3.49; N, 23.53.

12-Chloro-1,4,9-benzo[b]triazaphenoxazine (IX, R = Cl).

2-Amino-3-hydroxypyridine (VII) (5.50 g., 50 mmoles) was added to a solution of 5.6 g. (100 mmoles) of potassium hydroxide in 75 ml. of water. The mixture was warmed to dissolve followed by the addition of 11.68 g. (50 mmoles) of 2,3,6-trichloroquinoxaline (VI, R = Cl) and 50 ml. of dimethylacetamide (DMAC). The entire mixture was refluxed on a heating mantle for 3 hours during which period a yellow precipitate formed.

At the end of the reflux period, 200 ml. of water was added to the hot solution and it was cooled overnight. On filtering, the yellow product was collected and recrystallized from an ethanol-p-dioxane mixture after treatment with activated charcoal. 12-Chloro-1,4,9-benzo[b]triazaphenoxazine (IX, R = Cl, 12.58 g., 93% yield) was collected as greenish yellow microcrystals, m.p. > 300°; uv: λ max 230 (28,403), 272 (3,381), 378 (8,115); ir: ν max 3176, 3040, 2920, 1630, 1610, 1578, 1557, 1525, 1480, 1455, 1433, 1385, 1324, 1300, 1277, 1263, 1245, 1220, 1190, 1120, 1110, 1070, 956, 895, 870, 815, 788, 770, 745, 700 cm^{-1}; nmr (DMF-d$_7$): τ -0.95 to -0.23 (b, 10-NH), 1.97 to 2.75 (m, aromatic protons); ms: m/e (relative intensity) 106 (32), 109 (25), 149 (7), 165 (24), 206 (6), 211 (6), 270 (M$^+$, 100%), 271 (28), 272 (34).

Anal. Calcd. for $C_{13}H_7ClN_4O$: C, 57.67; H, 2.59; N, 20.70; C, 13.12. Found: C, 57.54; H, 2.64; N, 20.49; Cl, 13.26.

12-Chloro-13-nitro-1,4,9-benzo[b]triazaphenoxazine (XIII).

Concentrated sulfuric acid (30 ml.) was precooled to 0° in the reaction flask. 12-Chloro-1,4,9-benzo[b]triazaphenoxazine (IX, 2.71 g., 10 mmoles) was then added giving a deep yellow suspension. Concentrated nitric acid (25 ml.), also procooled to 0°, was added in drops with cooling and stirring. During this period the mixture turned deep yellowish-red with massive heat evolution. The reaction was brought under control by using an ice-isopropanol bath. Nitric acid addition was completed during thirty minutes. The deep yellowish-red mixture was stirred in the freezing mixture for additional hour. The bath was removed and the mixture left to stand for 16 hours at room temperature. Ice cubes were added and the solution neutralized with concentrated ammonia with cooling. On filtering and recrystallizing from methanol (Norit), 12-chloro-13-nitro-1,4,9-benzo[b]triazaphenoxazine (XIII) (1.96 g., 62% yield) was obtained as a creamy yellow powder, m.p. > 300°; uv: λ max 275 (20,508), 335 (11,305); ir: ν max 3200, 3063, 2930, 1620, 1600, 1560, 1540, 1495, 1455, 1394, 1340, 1320, 1287, 1260, 1225, 1135, 1010, 882, 848, 805, 786, 685 cm^{-1}.

Anal. Calcd. for $C_{13}H_6ClN_5O_3$: C, 49.45; H, 1.90; N, 22.19; Cl, 11.25. Found: C, 49.29; H, 2.01; N, 22.08; C, 11.24.

Acknowledgement.

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