Studies in the Heterocyclic Series. XIX. Synthesis of 1,4-Diazaphenothiazine and its Benzo Derivatives

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1,4-Diazaphenothiazine, the parent compound of this heterocyclic ring has now been prepared from 2,3-dichloropyrazine and 2-aminothiophenol. Replacement of 2,3-dichloropyrazine with 2,3-dichloroquinoxaline and 2,3,6-trichloroquinoxaline led to the corresponding 1,4-diazabenzo[*b*]phenothiazine in good yields. Structural assignments were made by spectroscopic studies and by certain chemical transformations.

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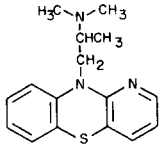
Many derivatives of monoaza- (1,2), diaza-(3,4), triaza-(5,6) and tetraazaphenothiazines (7) have been prepared and their biological properties evaluated (8). From these studies strong antipsychotic, anthelmintic, antihistaminic, CNS-depressant, antibacterial, antitumour, antiviral, antiemetic, sedative and antitussive activities (9-11) were observed. Notable among the azaphenothiazine derivatives are isothipendyl (**1**), (12) prothipendyl (13,14) pipazethate (15) and pervetral (16) which are presently used as drugs. In view of the medicinal importance of these compounds, much attention has been directed in the last two decades towards the synthesis of novel rings in these series.



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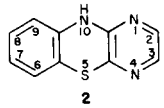
Although the number of azaphenothiazine ring systems (9,17) has grown tremendously, very little is still known about 1,4-diazaphenothiazine(**2**) which is one of the simplest members of these series. Some 2,3-disubstituted



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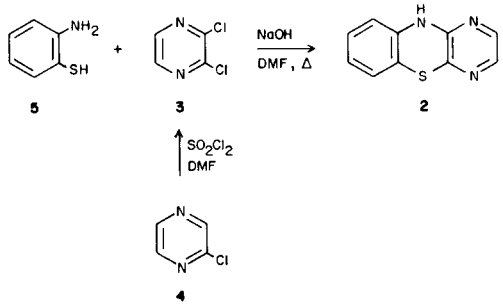
and 6-oxo-1,4-diazaphenothiazines were reported in patent literature in 1974 as having strong antibacterial effects (18-20). We have now succeeded in preparing the parent compound, 1,4-diazaphenothiazine (**2**), thereby



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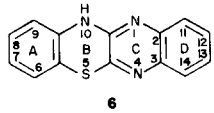
opening the way for a formal study of the reactions of this heterocyclic ring.

2,3-Dichloropyrazine (**3**) (21,22) was prepared from 2-chloropyrazine (**4**) and sulfuryl chloride in dimethylformamide and later treated with 2-aminothiophenol (**5**) in an alkaline medium. The resulting yellow crystalline product melted at 170°. Its molecular formula of $C_{10}H_7N_3S$ is in agreement with elemental analysis and mass spectroscopy. The product also had ultraviolet maximum band at 248 nm characteristic of phenothiazine-type of compounds (23-26). In the infrared region other diagnostic peaks include a medium band at 3400 cm^{-1} (10-NH), and very strong bands at 843 (2,3-disubstituted pyrazine) and 738 cm^{-1} (2,3-disubstituted benzene) (27). Confirmatory evidence for the assigned structure was provided by the pmr spectrum which had a broad peak at τ 1.73 (10-NH), a multiplet at τ 3.10 (benzene ring protons) and a singlet at τ 4.57 due to the two protons on the pyrazine ring.

As an extension of the chemistry of 1,4-diazaphenothiazine, the preparation of the monobenzo-derivative was also carried out. On refluxing 2-aminothiophenol with 2,3-dichloroquinoxaline in the presence of dilute base, a bright yellow microcrystalline solid melting at 279° to 280° was obtained. In benzene or toluene it gave greenish fluorescence. Elemental analysis and mass spectroscopy agree with the formula $C_{14}H_9N_3S$. This product also showed the usual phenothiazinoid ultraviolet absorption maximum at 251 nm. It was therefore formulated as 1,4-diazabenzo[*b*]phenothiazine **6** (28). Confirmatory evidence



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for the assigned structure was obtained from the infrared and pmr spectral analysis. The infrared band at 755 (d) was attributed to the 1,2-disubstitution in the two benzene rings. The pmr spectrum gave a broad peak at τ 0.07 (10-NH), 2.73 (ring D protons) and 3.18 (ring A protons). Thus contrary to the report of Walter and his co-workers, a pure tetracyclic phenothiazine was obtained in the basic medium (29).

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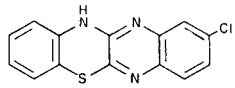
If 2-aminothiophenol were however made to react with 2,3,6-trichloroquinoxaline two isomeric products **7** and **8** are anticipated. When this reaction was carried out, only a



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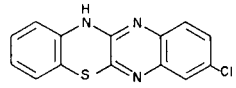

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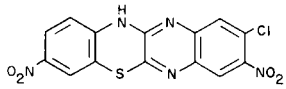
single product was realised and in a good yield. The molecular formula determination by mass spectroscopy and the ultraviolet, infrared and proton magnetic resonance spectra are in agreement with either of the two structures.

In order to determine the correct structure, this product was treated with mixed nitric and sulfuric acids at room temperature. Analysis of the single product showed that it is a dinitro sulfoxide. By considering the directive influence of the functional groups in the starting compound (30,31) the possible structures are **9** and **10**. Structure **9** is the expected product if structure **7** were the product of the initial reaction while structure **10** follows from **8**.



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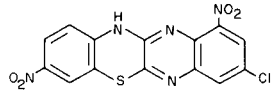

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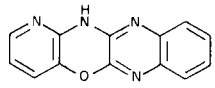
The infrared spectrum of this compound showed a strong band at 1036 cm^{-1} attributed to the S=O group while the nitro groups appeared as a very strong broad peak at 1344 cm^{-1}. The band at 752 cm^{-1} which was present in the unnitrated material disappeared showed that ring A is no longer disubstituted and that nitration had in fact also occurred in that ring. Two other strong bands at 795 and 888 cm^{-1} characteristic of 1,2,4-trisubstituted and 1,2,4,5-tetrasubstituted benzene rings were also observed (32). These results show that the product of the nitration reaction is 12-chloro-7,13-dinitro-1,4-diaza-benzo[*b*]phenothiazin-5-oxide (**9**) rather than structure **10**. It follows therefore that the starting material is 12-chloro-1,4-diazabenzo[*b*]phenothiazine (**7**) and not the alternative compound **8**. These results also show that the nitration of 1,4-diazabenzo[*b*]-phenothiazine follows a similar pattern as the nitration of 1,4,9-triazaphenoxazine (**11**) (33) and 1,4,6-triazabenzo-[*b*]phenothiazine (**12**) (34) reported



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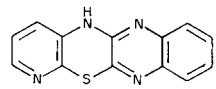

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earlier. The main difference however is that dinitration occurred in view of the higher reactivity of the second benzene ring in structure **6** towards electrophilic reagents compared to the pyridine ring in structures **11** and **12**.

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 external standard. The letters b, s, d and m are used to indicate broad, singlet, doublet and multiplet respectively. The mass spectra were obtained on an AE1 MS-9 double focusing mass spectrometer at 70 eV. Microanalyses were carried out 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-Dichloropyrazine (**3**).

2,3-Dichloropyrazine was prepared by chlorination of 2-chloropyrazine with sulfuryl chloride in dimethylformamide as was described previously (21). Starting with 8 ml. (10.26 g., 90 mmoles) of 2-chloropyrazine in 7 ml. of DMF and 40 ml. of sulfuryl chloride, 2,3-dichloropyrazine (10.86 g., 81% yield) was obtained in a sufficiently pure form for the next stage of the reaction.

1,4-Diazaphenothiazine (**2**).

2-Aminothiophenol (3.13 g., 25 mmoles) was placed in the reaction flask containing 3.3 g. of potassium hydroxide in 15 ml. of water. The mixture was warmed to dissolve. DMF (15 ml.) was then added followed by the addition of 2.98 g. (20 mmoles) of 2,3-dichloropyrazine (**3**).

The entire mixture was refluxed on a heating mantle with efficient stirring for 4 hours. At the end of the reflux period the mixture was poured while hot into a beaker containing 200 ml. of cold water. It was swirled and later cooled overnight in a refrigerator. The impure product was collected by filtration and recrystallized twice from dimethylacetamide (DMAC)-methanol mixture after treatment with activated charcoal.

Bright yellow microcrystals of 1,4-diazaphenothiazine (**2**) (3.78 g., 94% yield) were collected, m.p. 170°; uv: λ max (ϵ) 321 (6415), 248 (10905); ir (potassium bromide): ν max 3400, 3328, 3080, 1640, 1595, 1573, 1530, 1490, 1450, 1370, 1330, 1305, 1288, 1250, 1190, 1160, 1134, 1083, 1040, 930, 880, 843, 738 cm^{-1}; pmr (DMSO-d_6): τ 1.73 (s, b) (10-NH, area 1), 3.10 (m) (6-H, 7-H, 8-H, 9-H; area 4) and 4.57 (s) (2-H, 3-H; area 2); ms: m/e (relative intensity) 124 (60), 125 (6), 134 (6), 135 (10), 136 (6), 115 (1), 142 (5), 146 (20), 147 (6), 148 (23), 157 (20), 161 (6), 169 (24), 173 (17), 174 (19), 175 (15), 200 (44), 201 [M^+; 100%]; 202 (30), 203 (16).

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.70; H, 3.48; N, 20.90; S, 15.92. Found: C, 59.92; H, 3.44; N, 21.03; S, 16.02.

1,4-Diazabenzo[*b*]phenothiazine (**6**).

2,3-Dichloroquinoxaline (19.9 g., 100 mmoles) was dissolved by warming in 80 ml. of DMF. Another solution of 13.75 g. (110 mmoles) of 2-aminothiophenol and 13.2 g. of potassium hydroxide in 75 ml. of water was also prepared.

The two solutions were then mixed and refluxed on a heating mantle for 3 hours. It was later poured into 600 g. of crushed ice, stirred and further cooled in a refrigerator for 20 hours.

The crude product was isolated by filtration and crystallized from methanol-DMF mixture after treatment with activated charcoal. Pure 1,4-diazabenzo[*b*]phenothiazine (**6**) (22.84 g., 91% yield) was collected as yellow microcrystalline powder, m.p. 279-280° dec.; uv: λ max (ϵ) 408 (10040), 251 (107,930), λ infl 217 (32630); ir (potassium bromide): ν max 3246, 1610, 1588, 1567, 1540, 1505, 1477, 1405, 1366, 1344, 1292, 1263, 1255, 1220, 1146, 1127, 1083, 1074, 1035, 1020, 970, 945, 930, 862, 814, 755 (d), 720, 686, 660 cm^{-1}; pmr (DMSO-d_6): τ 0.07 (s,b) (10-NH, area 1), 2.73 (s) (11-H, 12-H, 13-H, 14-H; area 4), 3.18 (s) (6-H, 7-H, 8-H, 9-H; area 4); ms: m/e (relative intensity) 75 (2), 76 (1), 78 (1), 90 (6), 91 (1), 102 (3),

112 (2), 125 (3), 126 (3), 206 (1), 207 (4), 218 (2), 219 (14), 220 (2), 250 (12), 251 [M⁺, 100%], 252 (17), 253 (6).

Anal. Calcd. for $C_{14}H_9N_3S$: C, 66.93; H, 3.59; N, 16.73; S, 12.75. Found: C, 66.79; H, 3.75; N, 16.59; S, 12.66.

12-Chloro-1,4-Diazabenzo[*b*]phenothiazine (**7**).

2-Aminothiophenol (6.88 g., 55 mmoles) was dissolved in 50 ml. of water containing 14 g. of potassium hydroxide. To the stirred mixture was added a solution of 2,3,6-trichloroquinoxaline (11.68 g., 50 mmoles) in 50 ml. of DMAC.

The mixture was refluxed on a heating mantle for about 3.5 hours. The hot solution was poured into a beaker containing 600 ml. of water, stirred and cooled. On filtration, the crude product was collected and crystallized from aqueous DMAC after treatment with activated charcoal to give 12.42 g. (87% yield) of 12-chloro-1,4-diazabenzo[*b*]phenothiazine (**7**) as orange yellow microcrystalline powder, m.p. 241-242° dec.; uv: λ max (ε) 420 (9993), 252 (79940), λ infl 218 (19985); ir (potassium bromide): ν max 3240, 3030, 1605, 1590, 1564, 1545, 1530, 1475, 1460, 1440, 1403, 1370, 1356, 1328, 1302, 1284, 1265, 1253, 1243, 1230, 1203, 1156, 1130, 1095, 1085, 1078, 1035, 952, 938, 897, 880, 855, 820, 780, 752, 740, 720, 710, 692, 680, 650 cm^{-1}; pmr (DMSO-d_6): τ 0.23 (s,b) (10-NH, area 1), 2.40 (m) 11-H, 13-H, 14-H; area 3), 2.85 (s) (6-H, 7-H, 8-H, 9-H; area 4); ms: m/e (relative intensity) 70 (31), 75 (5), 82 (11), 95 (13), 101 (30), 113 (61), 125 (1), 133 (26), 137 (2), 145 (7), 165 (2), 183 (14), 233 (9), 245 (3), 250 (2), 253 (12), 255 (3), 284 (6), 285 [M⁺, 100%], 286 (24), 287 (41).

Anal. Calcd. for $C_{14}H_8ClN_3S$: C, 58.84; H, 2.80; Cl, 12.43; N, 14.71; S, 11.21. Found: C, 58.93; H, 2.72; Cl, 12.10; N, 14.69; S, 11.29.

12-Chloro-7,13-dinitro-1,4-diazabenzo[*b*]phenothiazin 5-oxide (**9**).

To 30 ml. of ice-cooled concentrated sulfuric acid (d, 1.84) placed in a 250 ml. three-necked flask equipped with a stirrer, a reflux condenser and a dropping funnel was added 14.28 g. (50 mmoles) of 12-chloro-1,4-diazabenzo[*b*]phenothiazine (**7**). Concentrated nitric acid (d. 1.42) (30 ml.) was also pre-cooled and added in drops during a period of 20 minutes while maintaining the temperature of the reaction flask at around 0°. The entire reddish brown solution was stirred at 0° for 1 hour.

The ice-bath was then removed and the mixture stirred at room temperature for 3 hours. The solution which remained reddish brown was poured into crushed ice and neutralized with concentrated ammonia while cooling in an ice bath. The deep yellow product was collected by filtration and crystallized from aqeous DMF after treatment with activated charcoal. 12-Chloro-7,13-dinitro-1,4-diazabenzo[*b*]phenothiazin 5-oxide (**9**) (12.14 g) was collected in 62% yield as yellow powder; m.p. > 240° dec.; uv: λ max (ε) 394 (12920), 265 (15660); ir (potassium bromide): ν max 3090, 1625, 1590, 1560, 1544, 1505, 1466, 1440, 1400, 1383, 1344(b), 1210, 1170, 1115, 1074, 1055, 1037, 986, 888, 835, 795, 765, 740 cm^{-1}; ms: m/e (relative intensity) 263 (12), 313 (15), 343 (5), 359 (3), 391 [M⁺, 100%], 392 (21), 393 (38).

Anal. Calcd. for $C_{14}H_6ClN_5O_5S$: C, 42.91; H, 1.53; Cl, 9.07; N, 17.88; S, 8.17. Found: C, 43.08; H, 1.26; Cl, 8.88; N, 18.12; S, 8.14.

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