This paper describes the unequivocal synthesis of three new heterocycles: 2,3,6-triazaaphenothiazine (7) and 2,3,6,9-tetraazaaphenothiazine (10), both parents of the respective ring systems and the 6,8-dihydro-7,9-dioxo derivative of 2,3,6,8-tetrahydrophenothiazine (12). These compounds were obtained by base-catalysed condensation of 4,5-dichloropyridazine (8) with the appropriate N-amino-heterocyclic thiols 9, 11, 16. In contrast, reaction of 2,3,5-trichloropyridazine (20) with 4,6-diaminopyrimidine-5-thiol (21) and 2-aminoo-6-picolinol-3-thiol (28) gave 5-chloro-2,3-bis(diaminopyrimidinyl-5-thio)pyrazine (33) and 5-chloro-2,3-bis(2-aminoo-6-picolinyl-3-thio)pyrazine (29), respectively. Chloropyrazine (34) and 3-amino-opyridine-2(1H)-thione (9) followed the latter reaction path to 2(3-amino-2-pyridyl) pyrazinyl sulfide (35) in good yields. Structural assignments were based on their infrared, ultraviolet, nmr and mass spectra.

Previous reports have highlighted the importance of phenothiazine and its numerous derivatives in medicine, agriculture and industry [5,6]. New heterocyclic rings derived from phenothiazine were therefore sought in a search for improved agents in these areas. Among the major accomplishments is the replacement of one or more of the benzene rings in phenothiazine with heterocyclic systems, namely pyridine [7-10], pyridazine [12-16], pyrimidine [17-19], pyrazine [20-23], quinoxaline [24-25], 1,2,4-triazine [26], thiophene [27-28] and 1,4-thiazine [29]. These modifications have produced such interesting congeners of phenothiazine as 1-azaphenothiazine (1) [6], 1,4,6-triazaaphenothiazine (2) [23], 2,3,7,8-tetraazaaphenothiazine (3) [30], 9H-thieno[2,3-b][1,4]benzothiazine (4) [30], 4H-diethio[2,3-b:2',3'-e][1,4]thiazine (5) [31-32] and 1,4,6-triazabenzof[b]phenothiazine (6) [33].

Although all of the derivatives of these classes of phenothiazine have not been fully evaluated, interesting antipsychotic [34-37] and CNS-depressant activities [38-40] have been recorded for a number of them. Currently some derivatives of 1 are in use as neuroleptic [41], antihistaminic [42], antiemetic [43] and antiuvisse [44] agents. The observation of these effects in the aza congeners of phenothiazine has led to the synthesis of a great variety of aza-phenothiazines. In the more complex triaza-and tetraaza-phenothiazines, only four and seven [5,6] respectively, out of the possible 24 and 35 isomeric ring systems have been reported. In the preceeding paper [45] we described the preparation of some derivatives of the 2,3,6-triazaaphenothiazine ring system 7. We have now prepared 7, the parent heterocycle.

On heating a mixture of 4,5-dichloropyridazine (8) [30,46] and 3-amino-opyridine-2(1H)-thione (9) in ethanol in the presence of potassium hydroxide at 90° for 10 minutes, 2,3,6-triazaaphenothiazine (7) was isolated in 63% yield (Scheme 1). Microanalysis, infrared, ultraviolet and nmr spectroscopy agree with the assigned tricyclic structure. Since the condensation reaction was carried out in alkaline medium, the diaryl sulfide 10 was assumed to be
formed first in the reaction before the cyclization step. Cyclization of 10 then proceeds with or without Smiles rearrangement to yield the same product 7.

A similar reaction of 4,5-dichloropyridazine (8) with 5-aminouracil-6-thiol (11) [47] gave 2,3,6,8-tetraazaphenothiazine-7,9(6H,8H)dione (12), the first member of the 2,3,6,8-tetraazaphenothiazine system. As in compound 7, the same product is expected whether the reaction proceeds with or without Smiles rearrangement [5,48] of the intermediate pyrimidinylpyridazinyl sulfide 13 as shown in Scheme 2.

The reaction of a mixture of 4-aminopyridazine-5-thiol (16) [30,49] and 2,3-dichloropyrazine (17) [50-51] at room temperature in the presence of ethanolic potassium hydroxide led to 2,3,6,9-tetraazaphenothiazine (18) another new parent heterocycle in the tetraketio- series. Microanalysis, infrared and ultraviolet spectroscopy provide evidence for the assigned structure. Confirmatory proof of structure was obtained from the nmr spectrum which gave signals at δ 9.2 (broad, 10-NH), 9.26 (singlet, 1-H), 9.16 (singlet, 7-H and 8-H) and 9.01 (singlet, 4-H). As in compounds 7 and 12, the same product is expected whether or not the reaction proceeds by Smiles rearrangement of the sulfide 19.

Base-catalysed reaction of 2,3,5-trichloropyrazine (20) [52] with 4,6-diaminopyrimidine-5-thiol (21) on the other hand gave, contrary to expectation, an 87% yield of 5-chloro-2,3-bis(4,6-diaminopyrimidinyl-5-thio)pyrazine (22, R = H). Structural assignment was based on microanalysis, infrared, ultraviolet and nmr spectra. Acetylation with acetic anhydride gave the tetaacetyl derivative 23, R = Ac (Scheme 3).

The reaction of a mixture of 4-aminopyridazine-5-thiol (16) [30,49] and 2,3-dichloropyrazine (17) [50-51] at room temperature in the presence of ethanolic potassium hydroxide led to 2,3,6,9-tetraazaphenothiazine (18) another new parent heterocycle in the tetraketio- series. Microanalysis, infrared and ultraviolet spectroscopy provide evidence for the assigned structure. Confirmatory proof of structure was obtained from the nmr spectrum which gave signals at δ 9.2 (broad, 10-NH), 9.26 (singlet, 1-H), 9.16 (singlet, 7-H and 8-H) and 9.01 (singlet, 4-H). As in compounds 7 and 12, the same product is expected whether or not the reaction proceeds by Smiles rearrangement of the sulfide 19.

Base-catalysed reaction of 2,3,5-trichloropyrazine (20) [52] with 4,6-diaminopyrimidine-5-thiol (21) on the other hand gave, contrary to expectation, an 87% yield of 5-chloro-2,3-bis(4,6-diaminopyrimidinyl-5-thio)pyrazine (22, R = H). Structural assignment was based on microanalysis, infrared, ultraviolet and nmr spectra. Acetylation with acetic anhydride gave the tetaacetyl derivative 23, R = Ac (Scheme 3).

Confirmatory evidence of structure was obtained by mass spectroscopy which showed two prominent fragments at m/e 253 (97%) and m/e 141 (69%) due respectively to the pyrazinylpyrimidinyl sulfide ion 25 and 4,6-diaminopyrimidinyl-5-thiol diradical 26 which probably rearranges to give the radical ion 27.

2,3,5-Trichloropyrazine (20) was also reacted with 2-amino-6-picoline-3-thiol (28) [53] under alkaline conditions to yield 5-chloro-2,3-bis(2-amino-6-picolinyl-3-thio)pyrazine
The assigned structure was in agreement with microanalytical and spectroscopic data. The fragmentation pattern in the mass spectrum of compound 29 was similar to that of compound 22, R = H except that in the latter case the fragment ion 31, formed by loss of one of the 2-amino-6-picolyln-3-thiol radicals was the base peak in the spectrum. As a matter of fact, recognition of a major peak at m/e 139 has been used satisfactorily in this work in deciding whether phenothiazinoid or diaryl sulfides are formed by the reaction of compound 28 with o-dichloro heterocyclic compounds.

Such reactions leading to sulfides of types 24 and 29 are not limited to 2,3-dichloropyrazines. 2-Chloropyrazine has sufficient reactivity to condense with o-amino-heterocyclic thiols. Thus when a mixture of 2-chloropyrazine 34 [51,54] and 3-aminopyridine-2(1H)-thione (9) was refluxed for three hours in the presence of sodium hydroxide, 2-(3-amino-2-pyridyl)pyrazinyl sulfide (35) was obtained in good yield.

The assigned structure was in good agreement with analytical and spectroscopic data. This reaction confirms the ease of condensation of o-amino-heterocyclic thiols with halogenopyrazines.

**EXPERIMENTAL**

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 337 grating infrared spectrophotometer using potassium bromide discs. The ultraviolet spectra were obtained in a Bausch and Lomb Spectronic 505 spectrometer using matched 1 cm quartz cells. The absorption maxima are reported in nanometers. The 'H nmr spectra were obtained in the solvent indicated using a Varian A-60 or EM-360 spectrometer. Chemical shifts are reported in ppm from TMS used as an internal standard and are given in δ units. The following abbreviations were used to designate the multiplicity of individual signals: s = singlet, d = doublet and m = multiplet. Mass spectral data were recorded on a Hewlett Packard Model 5980 mass spectrometer at 70 eV. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona and Istituto Superiore di Sanita, Rome, Italy.

2,3,6-Triazaphenothiazine (7).

To a stirred solution of 4,5-dichloropyrazidine (8, 0.15 g, 1 mmole) [30,46] in 15 ml of ethanol was added slowly a solution of 3-aminopyridine-2(1H)-thione (9, 0.127 g, 1 mmole) [33] and potassium hydroxide (0.15 g) in ethanol (25 ml). The reaction mixture was heated on a steam bath at 90° (bath temperature) for 10 minutes and then allowed to stand at room temperature for an additional 14 hour period. During this time a precipitate was formed. The crude product was collected by filtration, washed with water and air-dried. Recrystallization of the precipitate from methanol-water (10:1) yielded cream-colored crystals of 2,3,6-triazaphenothiazine (7) (0.95 g, 63%), mp 214-215°; ir: ν max 3390-3345 cm⁻¹ (C=N); uv (95% ethanol): λ max (ε) 254 (16,300), 283 (14,600); 'H nmr (DMSO-d₆): δ 9.26 (s, 1-H), 9.06 (s, 4-H).

Analytical: C₅H₃N₂S; C, 53.47; H, 2.99; N, 27.71. Found: C, 53.24; H, 3.16; N, 27.38.

2,3,6,8-Tetraazaphenothiazine-7,9(6H,8H)-dione (12).

To a stirred solution of 4,5-dichloropyrazidine (8, 0.15 g, 1 mmole) in ethanol (15 ml) at room temperature was added slowly 5-aminoacrnil-6-thiol (11, 0.15 g, 1 mmole) [47] and potassium hydroxide in 25 ml of 50% ethanol. The reaction mixture was stirred for 24 hours at room temperature. The precipitate which formed was collected by filtration and washed with water. Recrystallization of the crude product from water furnished compound 12 (0.13 g, 50% yield), mp 263-265°; uv (water, saturated solution): λ max 258, 276 nm; ir: ν max 3340-2290 (broad, C≡N), 1680 cm⁻¹ (C=O); 'H nmr (DMSO-d₆): δ 9.78 (s, 1-H), 9.03 (s, 4-H).

Analytical: C₇H₅N₅O₂S; C, 40.86; H, 2.14; N, 29.78. Found: C, 41.06; H, 2.28; N, 30.17.

2,3,6,9-Tetraazaphenothiazine (18).

To a mixture of 4-aminopyrazidine-5-thiol (16) (0.127 g, 1 mmole) and potassium hydroxide (0.25 g) in ethanol (25 ml) was added 2,3-dichloropyrazine (17, 0.15 g, 1 mmole) [50,51] in ethanol (10 ml) at room temperature. The mixture was allowed to react for 8 hours during which a precipitate formed. The crude product was collected and washed with cold water (20 ml) and air dried. Recrystallization from an ethanol-water mixture furnished 2,3,6,9-tetraazaphenothiazine (18) (0.07 g, 30% yield), mp
5-Chloro-2,3-bis(4,6-diaminopyrimidin-5-yl)thiopyrazine (22, R = H).

4,6-Diamino-5-pyrimidinethiol (21, 2.84 g, 20 mmoles) was placed in the reaction flask to which was added 4 g of potassium hydroxide in water (15 ml) and N,N-dimethylethacacetate (DMAC) (30 ml). The mixture was warmed to dissolve compound 21 completely and then 2,3,5-trichloropyrazine (20, 4.58 g, 25 mmoles) was added. The reaction mixture was heated under reflux for 4 hours. A yellow precipitate was formed as soon as refluxing started and it persisted throughout the reflux period. The mixture was then poured onto crushed ice (500 g), cooled further and filtered. The impure product was recrystallized from aqueous DMAC after treatment with activated charcoal to afford 5-chloro-2,3-bis(4,6-diaminopyrimidin-5-yl)thiopyrazine (22, R = H) (7.34 g, 93% yield) as yellow-green plates, mp > 300°; uv (methanol): λ max (ε) 251 (81,87), 323 (60,56); ir: ν = 3340, 3330, 3336, 1650, 1650, 1515, 1430, 1474, 1366, 1310, 1290, 1202, 1184, 1160, 1130, 1090, 1038, 1010, 990, 962, 890, 867, 843, 777, 735, 694, 640 cm⁻¹; 1H nmr (DMSO-d₆): δ 8.30 (s, 2'H), 7.50 (s, 6-H), 6.57 (s, 4'-NH₂, 4''-NH₂, 6'-NH₂, 6''-NH₂) ppm (relative intensity) 77 (12), 83 (12), 83 (12), 80 (36), 88 (47), 89 (88), 89 (17), 91 (15), 93 (30), 97 (26), 114 (30), 141 (69), 147 (16), 149 (11), 219 (20), 221 (10), 252 (11), 253 (97), 254 (20), 255 (35), 288 (38), 290 (26), 309 (M⁺, 100%), 395 (M⁺ + 1, 14), 396 (M⁺ + 2, 36).

Chloro-2,3-bis(4,6-diaminopyrimidin-5-yl)thiopyrazine (22, R = Ac) (3.95 g, 10 mmoles) was placed in a reaction flask containing acetic anhydride (50 ml) and pyridine (1 ml). The mixture was heated at reflux temperature for 2 hours in an oil bath. The clear solution was treated with activated charcoal, filtered, and cooled to ice-bath temperature. Crushed ice was then added and the mixture gently warmed until a homogenous solution was achieved. The yellow solution was made alkaline with concentrated ammonia while cooling. The greenish yellow solid that precipitated out was collected by filtration and recrystallized from N,N-dimethylethacetate to yield 5-chloro-2,3-bis(4,6-diaminopyrimidin-5-yl)thiopyrazine (23, R = Ac) (4.95 g, 88% yield) as yellow-green-yellow plates, mp > 300°; uv (methanol): λ max (ε) 235 (35,100), 275 (5,850), 372 (11,700); ir: ν = 3200, 3000, 2920, 2840, 1702, 1600, 1595, 1557, 1520, 1484, 1407, 1360, 1300, 1250, 1232, 1191, 1165, 1097, 1055, 1000, 953, 904, 865, 820, 770, 733, 672 and 642 cm⁻¹; 1H nmr (DMSO-d₆): δ 10.72 (s, 2'H), 8.49 (s, 4''-NH₂, 6'-NH₂, 6''-NH₂); 8.17 (m, 2'H, 2-′H, 6-′H); 2.10 (s, 14 CH₃ protons).

Analog. Calcd. for C₄₀H₂₄N₄O₂S₄: C, 42.67; H, 3.38; N, 24.89; Cl, 6.31; S, 11.38. Found: C, 42.88; H, 3.20; N, 25.00; Cl, 6.29; S, 11.24.

5-Chloro-2,3-bis(2-amino-6-picolyl-3-thiopyrazine (29).

2-Amino-6-picolyl-3-thiol (28) (5.6 g, 40 mmoles) was placed in a 250 ml three-necked flask equipped with a dropping funnel, a mechanical stirrer and a reflux condenser. Sodium hydroxide (6 g) in water (50 ml) was added and the mixture was heated to dissolve. N,N-Dimethylethacacetate (30 ml) was then added followed by the addition of 2,3,5-trichloropyrazine (20, 9.18 g, 50 mmole). The mixture was heated under reflux for 5 hours. At the end of the reflux period, the mixture was cooled and poured into a beaker containing ice-cold water (500 ml), stirred and cooled overnight in a refrigerator. The crude product was collected by filtration and recrystallized from a methanol-N,N-dimethylethacacetate mixture after treating with activated charcoal to afford 2-amino-6-picolyl-3-thiopyrazine (29) (12.81 g, 82% yield), mp 185-186°; uv (methanol): λ max (ε) 310 (5,940), 260 (14,850); ir: ν = 3455, 3290, 1660, 1530, 1505, 1470, 1430, 1380, 1365, 1344, 1333, 1299, 1205, 1190, 1120, 1080, 1042, 1006, 954, 930, 842, 820, 745, 720 and 665 cm⁻¹; 1H nmr (DMSO-d₆): δ 8.30 (s, 2′-NH₃, 2'"-NH₃), 7.40 (d, J = 8.2 Hz, 4"-H, 4"'-H), 6.38 (m, 5"-H, 5"'-H, 6-H); 2.27 (s, 6'C-H₂, 6''C-H₂) ppm (relative intensity) 95 (18), 139 (52), 218 (15), 237 (20), 251 (100), 252 (21), 253 (34), 271 (27), 273 (9), 286 (49), 288 (34), 309 (M⁺, 79%), 392 (M⁺ + 2, 36).

Analog. Calcd. for C₃₀H₂₄N₄O₂S₄: C, 49.17; H, 3.84; N, 21.51; Cl, 8.84; S, 16.41.

5-Chloro-2,3-bis(2-amino-6-picolyl-3-thiopyrazine (29).

5-Chloro-2,3-bis(2-amino-6-picolyl-3-thiopyrazine (29).

Acknowledgement.

The authors wish to thank the University of South Florida Biomedical Research Support Grant Committee for research funds making this investigation possible. We express our appreciation to Dr. M. L. Lee, Department of Chemistry, Brigham Young University for the mass spectra and Professor C. Galletti, Istituto Superiore di Sanita, Rome, Italy for some of the microanalyses.

REFERENCES AND NOTES

[1] This paper is part 24 in the "Studies in the Heterocyclic Series".
[3] To whom inquiries regarding this manuscript should be directed at the Department of Chemistry, University of South Florida, Tampa, Florida 33620 USA.
[4] Present address: College of Pharmacy, University of Michigan, Ann Arbor, Michigan 48109.
2,3,6-Triazaphenothiazine and Two New Tetraazaphenothiazine Heterocycles

1051

Japan Kokai, 74, 48,698 (1974); Chem. Abstr., 82, 43471q (1975);