Studies in the Heterocyclic Series. X. 1,3,9-Triazaphenothiazine Ring System, a New Phenothiazine Ring

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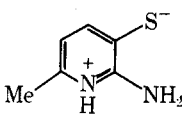
Functionally substituted novel triazaphenothiazines were sought for a study of their properties and reactions and for testing as antihypertensive and antipsychotic agents. The reaction of 2-amino-3-mercapto-6-picoline with 5,6-disubstituted pyrimidines under acid-catalyzed conditions produced good yields of the new 1,3,9-triazaphenothiazine ring system. This heterocyclic ring is now the second known phenothiazine with three annular nitrogen atoms; the remaining 22 structural isomers remain unknown. The aminomercaptopicoline precursor was obtained as the dipolar salt by base-catalyzed hydrolysis of 2-amino-3-thiocyano-6-picoline followed by acidification. A similar reaction with some 4-chloropyrimidines which are unsubstituted in the 5 position yielded 6-(3-mercapto-6-methyl-2-pyridyl)pyrimidinylamines as their dipolar salts. The structures of these products were established by chemical evidence and ultraviolet, infrared, NMR, and mass spectrometry.

Our interest in the chemistry of phenothiazine[1,2] and phenoxazine[3,4] with annular nitrogen atoms led us to investigate the related compounds, particularly those with isomeric azaphenothiazine rings. Some of the least explored group of compounds in these series are those bearing three ring nitrogen atoms. While four monoaza- and nine diazaphenothiazine systems are known,[1] the only known phenothiazine ring in this group is the 1,3,6-triazaphenothiazine;[5] the remaining 23 structural isomers of this ring have not been reported. In view of the remarkable psychopharmacological properties of the derivatives of azaphenothiazine heterocycles,[6,7] we became particularly interested in the synthesis of phenothiazines bearing annular nitrogen atoms in the active sites 1, 3, and 9 positions as these may combine the antihypertensive[8] and CNS depressant actions of 1-aza-[6,9] and 1,3-diazaphenothiazines.[10]

We have chosen the reaction path which utilizes 2-amino-3-mercaptopyridine precursor. Of all the possible routes at our disposal for the preparation of this compound, an adaptation of Kaufmann's electrophilic thiocyanation of aromatic amines with nascent thiocyanogen appears most convenient and attractive.[11] 2-Amino-6-picoline was converted to the 3-thiocyano derivative and hydrolyzed with 15% potassium hydroxide solution followed by acidification. The greenish-yellow solid obtained is soluble in sodium hydroxide, insoluble in mineral acids, and sparingly soluble in common organic solvents. The infrared spectrum shows strong absorption signals at 3340 d (2-NH_2), 3197 (ring NH), and 1667 cm^{-1} (C=NH).[12,13] The solubility in sodium hydroxide, insolubility in acid, and the absence of weak SH absorption at 2550 cm^{-1} even in concentrated solutions are strong evidence for zwitterionic character. The dipolar structure 1 was therefore assigned to this product.



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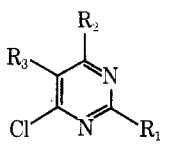
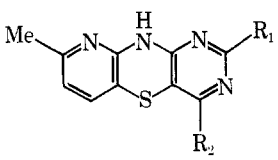
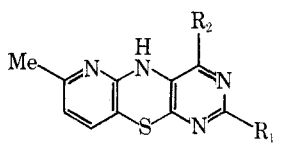
Upon refluxing an intimate mixture of this compound (1) with 5-bromo-4-chloro-2,6-dimethoxypyrimidine (2) in 0.20 *N* sulfuric acid, a white, high-melting solid was obtained in a good yield. The ultraviolet spectrum showed a maximum absorption band at 250 nm, characteristic of phenothiazine systems. While the NMR spectrum is in agreement with either the 1,3,9-triazaphenothiazine (3) or the 1,6,8-triazaphenothiazine (4) structures, it did not favor one over the other. Further experimentation was therefore necessary. If



2, $R_1 = R_2 = OMe$; $R_3 = Br$
7, $R_1 = R_2 = OMe$; $R_3 = H$
11, $R_1 = H$; $R_2 = NH_2$; $R_3 = NO_2$
14, $R_1 = NH_2$; $R_2 = OH$; $R_3 = H$
15, $R_1 = NH_2$; $R_2 = OH$; $R_3 = Br$

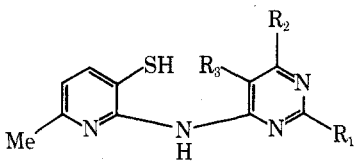


3, $R_1 = R_2 = OMe$
12, $R_1 = H$; $R_2 = NH_2$
16, $R_1 = NH_2$; $R_2 = OH$

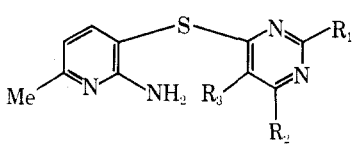


4, $R_1 = R_2 = OMe$
13, $R_1 = H$; $R_2 = NH_2$

the initial reaction is the acid-catalyzed condensation of the amine 1 with the chloropyrimidine 2, a diarylamine intermediate, 5, will be formed followed by cyclization and loss of hydrogen bromide leading to the 1,3,9-triazaphenothiazine compound 3. Compound 4, on the other hand, will be formed from 5 by Smiles rearrangement leading to the diaryl sulfide 6, which can then cyclize by loss of hydrogen bromide. The initial reaction could also involve a



5, $R_1 = R_2 = OMe$; $R_3 = Br$

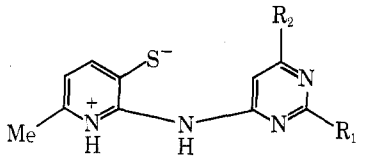


6, $R_1 = R_2 = OMe$; $R_3 = Br$

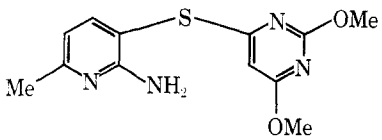
nucleophilic attack of the mercaptide ion on the four-carbon center of the pyrimidine ring; however, this reaction is untenable owing to protonation of the mercaptide ion in the acid medium employed. Furthermore, the same reactions, carried out in basic media, where the concentration of the mercaptide ion is extremely high, yielded no prod-

ucts; the starting materials were quantitatively recovered. These results favor an initial formation of an *o*-mercaptodiarylamine intermediate, **5**, and in agreement with our results, such acid-catalyzed reactions are known to be retarded by increasing the pH of the solution.[14]

In order to decide conclusively whether the reactions took place with or without rearrangement, the dipolar compound **1** was treated with compound **7**, which lacked a reactive group at the five-carbon center and hence would prevent cyclization. Under similar reaction conditions used for the preparation of the tricyclic structures, a 62% yield of a white, crystalline material of molecular formula $C_{12}H_{14}N_4O_2S$ was obtained. The compound is soluble in sodium hydroxide and insoluble in mineral acids; the infrared spectrum showed the absence of a mercapto group even in concentrated solutions. The dipolar nonrearranged structure, **8**, was therefore assigned to this product. This result rules out the diaryl sulfide structure **9** and thus shows that

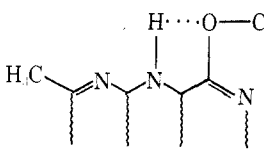


8, $R_1 = R_2 = OCH_3$
17, $R_1 = NH_2$; $R_2 = OH$



9

after the initial acid-catalyzed condensation of compound **1** with the bromochloropyrimidine **2**, the diarylamine intermediate, **5**, cyclizes without rearrangement to yield the tricyclic compound which we have now identified as a derivative of the 1,3,9-triazaphenothiazine ring (compound **3**). Structure **4** was further rejected on the premise that the 10-NH proton should have a more diffuse NMR signal[15] and should show a stronger intramolecular hydrogen bonding with the methoxy group oxygen leading to the chelate structure **10**. The *o*-aminomercaptopyridine **1** also reacts



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with an acidic solution of 4-amino-6-chloro-5-nitropyrimidine (**11**) and gave 4-amino-8-methyl-1,3,9-triazaphenothiazine (**12**). Further evidence of structure was provided by diazotization of compound **12**, which failed to give the 1,10-diazole structure characteristic of *o*-aminodiaryl amines.[5,16] It therefore confirms that the amino group in the product is not in an ortho position with regard to the central ring NH as one would expect from structure **13**. Other derivatives of this novel triazaphenothiazine ring[17] as well as the "open" systems were also prepared and characterized.

Experimental Section

General. Melting points were determined with a Fisher-Johns apparatus. Uv spectra were taken with a Pye Unicam SP 8000 spectrophotometer using matched 1-cm quartz cells. The solvent is methanol; absorptions are given in nanometers; the figures in parentheses are ϵ values. Ir spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer using KBr disks unless otherwise stated. NMR spectra were determined on a Varian Associates A-60 instrument. Chemical shifts are reported on the τ scale relative to Me_4Si used as an internal standard. The letters br, s, sh, and d are used to indicate broad, singlet, shoulder, and doublet, respectively. The mass spectra were obtained on an AEI MS-9 double-focusing mass spectrometer at 70 eV.

2-Amino-3-mercapto-6-picoline (1). 2-Amino-6-picoline (5.4 g, 50 mmol) was converted to 2-amino-3-thiocyano-6-picoline by the action of 45 g of potassium thiocyanate in 60 ml of glacial acetic acid and 8 ml of bromine as was previously described.[11]

The product, 2-amino-3-thiocyano-6-picoline (3.30 g, 20 mmol), was treated with 2 g of sodium sulfite and refluxed in 30 ml of 15% potassium hydroxide solution on a steam bath for 4 hr. The dark brown solution was treated with activated charcoal, boiled for an additional 15 min, and filtered. The yellowish-brown solution was cooled, neutralized with glacial acetic acid, and chilled. The yellowish precipitate obtained was collected by filtration and recrystallized from aqueous methanol–acetone mixture (Norit) to yield greenish-yellow crystals of the dipolar salt of 2-amino-3-mercapto-6-picoline (**1**, 1.29 g, 92%): mp 245°; uv spectrum λ_{min} 226 nm (2030), λ_{max} 256 (6998), λ_{min} 290 (3220), λ_{max} 302 (3639); ir spectrum ν_{max} 3340 d, 3197, 1667, 1645, 1600, 1325, 1229, 1206, 1087, 1019, 943, 841 cm^{-1}; NMR spectrum (Me_2SO-d_6) τ 7.47 s (6-CH_3), 3.22 d (J = 9.2 Hz, 5-CH), 2.20 br (2-NH_2), 2.06 d (J = 9.2 Hz, 4-CH). 1.73 s, br (1-NH).

Anal. Calcd for $C_6H_8N_2S$: C, 51.42; H, 5.72; N, 20.00; S, 22.86. Found: C, 51.61; H, 5.88; N, 19.76; S, 22.89.

2-Amino-5-bromo-4-chloro-6-hydroxypyrimidine (15). To a suspension of 2-amino-4-chloro-6-hydroxypyrimidine (**14**, 7.28 g, 50 mmol) in 150 ml of 50% aqueous methanol was added sodium bicarbonate (6.0 g) with constant stirring. Bromine (7.0 ml) was added to the stirred mixture in drops during a period of 80 min. After 40 min of constant stirring at room temperature, the solution became acidic. An additional 4 g of sodium bicarbonate was then added. The mixture was stirred at room temperature for an additional 1 hr. The crude product was collected by vacuum filtration and recrystallized twice from aqueous acetone after treatment with activated charcoal. White crystals of 2-amino-5-bromo-4-chloro-6-hydroxypyrimidine (10.55 g, 94%) were collected: mp >300°; uv spectrum λ_{min} 211 nm (9313), λ_{max} 229 (14,170), λ_{min} 258 (3367), λ_{max} 297 (14,310); ir spectrum (Nujol) ν_{max} 3290, 3010, 1650, 1567, 1500, 1314, 1208, 1070, 1014, 970, 911, 804, 750 cm^{-1}; NMR spectrum (Me_2SO-d_6) τ 2.82 br (area 2, 2-NH_2), −0.30 br (area 1, 6-OH).

Anal. Calcd for $C_4H_3N_3OClBr$: C, 21.38; H, 1.34; N, 18.71; Cl, 15.81; Br, 35.63. Found: C, 21.54; H, 1.18; N, 18.60; Cl, 15.95; Br, 35.69.

5-Bromo-4-chloro-2,6-dimethoxypyrimidine (2). This compound was prepared from 4-chloro-2,6-dimethoxypyrimidine (**7**) as described in the literature.[5]

4-Amino-6-chloro-5-nitropyrimidine (11). This compound was partly prepared and partly purchased from Aldrich Chemical Co.[18] and recrystallized from boiling methanol, NMR spectrum τ 2.37 s (2-H), 1.90 br (4-NH_2).

2,4-Dimethoxy-8-methyl-1,3,9-triazaphenothiazine (3). A mixture of 2-amino-3-mercapto-6-picoline (1.40 g, 10 mmol) and 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**2**, 2.79 g, 11 mmol) was ground in a mortar and placed in the reaction flask containing 200 ml of 0.20 N sulfuric acid. Sodium sulfite[19] (1.0 g) was then added and the mixture was refluxed with constant mechanical agitation for 5 hr on a steam bath.[20] Extensive sublimation of the pyrimidine compound, **2**, was observed and the sublimate settled on the condenser and upper half of the reaction flask. This light crystalline compound was periodically washed down into the reaction solution with minimal amount of water from a wash bottle. At the end of the reflux period, the solution was cooled, when a slimy white product formed. Vacuum filtration proved difficult as the product blocked the fine holes in the filter paper. However, by ordinary filtration, it was possible to isolate the product. It was then washed with boiling methanol and recrystallized from aqueous acetone (Norit) to yield 2,4-dimethoxy-8-methyl-1,3,9-triazaphenothiazine (**3**, 1.88 g, 68%) as white powder:[21] mp >300°; uv spectrum λ_{min} 213 nm (6112), λ_{max} 221 (7244), λ_{min} 235 (5409), λ_{max} 250 (5864), λ_{min} 266 (5036), λ_{max} 283 (7174); ir spectrum ν_{max} 3480, 3418, 3360 d, 3180, 1650, 1630, 1616, 1560, 1550, 1456, 1428, 1402, 1374, 1365, 1340, 1274, 1260, 1190, 1150, 1143, 1090, 1050, 1020, 984, 893, 815, 785, 746 cm^{-1}; NMR spectrum (Me_2SO-d_6) τ 7.67 s (8-CH_3), 6.37 s (4-OCH_3), 6.02 s (2-OCH_3), 3.63 d (J = 8.2 Hz, 7-CH), 3.70 s, br (10-NH), 2.60 d (J = 8.2 Hz) (6-CH); mass

spectrum *m/e* (rel intensity) 94 (100), 112 (29), 180 (5), 261 (5), 262 (20), 276 (M^+, 9).

Anal. Calcd for $C_{12}H_{12}N_4O_2S$: C, 52.18; H, 4.35; N, 20.29; S, 11.60. Found: C, 51.79; H, 4.19; N, 20.46; S, 11.51.

4-Amino-8-methyl-1,3,9-triazaphenothiazine (12). To a mixture of 2-amino-3-mercapto-6-picoline (0.7 g, 5 mmol) and 0.96 g (5.5 mmol) of 4-amino-6-chloro-5-nitropyrimidine (11) in 100 ml of water was added 2 ml of concentrated sulfuric acid and 1.0 g of sodium sulfite. The solution was then refluxed on a steam bath at 92° with vigorous mechanical agitation. The pH of the solution was checked and maintained at 1.0 throughout the reflux period. After 1 hr, a yellowish material started to form. At the end of the reflux period (6 hr), the product was collected by filtration, washed with hot methanol, and recrystallized twice from water after treatment with activated charcoal. Yellowish-white crystals of 4-amino-8-methyl-1,3,9-triazaphenothiazine (**12**, 1.05 g, 91%) were collected: mp >300°; uv spectrum λ_{max} 270 nm (6900), λ_{min} 290 (5558), λ_{max} 314 (6640); ir spectrum (Nujol) ν_{max} 3390, 3100, 1650, 1603, 1250, 1180, 1136, 1019, 980, 895, 794 cm^{-1}; NMR spectrum (Me_2SO) τ −0.46 (10-NH),[22] 1.80 br (4-NH_2), 2.40 d (J = 9.0 Hz, 6-H), 2.42 s (2-H), 3.31 d (J = 9.0 Hz, 7-H), 2.37 s (8-CH_3).

Anal. Calcd for $C_{10}H_9N_5S$: C, 51.95; H, 3.89; N, 30.31; S, 13.86. Found: C, 52.08; H, 3.70; N, 30.14; S, 14.00.

2-Amino-4-hydroxy-8-methyl-1,3,9-triazaphenothiazine (16). A mixture of 2-amino-5-bromo-4-chloro-6-hydroxypyrimidine (**15**, 1.24 g, 5.5 mmol) and 2-amino-3-mercapto-6-picoline (0.7 g, 5 mmol) was pulverized by grinding and placed in the reaction flask containing 150 ml of water. The aqueous suspension was acidified with 1.0 ml of concentrated sulfuric acid. Sodium sulfite (0.5 g) was then added and the acidic mixture was refluxed on a steam bath for 4.5 hr. The solution was cooled and the white precipitate was collected by filtration. The crude powdery material was recrystallized twice from water (800 ml) after treatment with activated charcoal. 2-Amino-4-hydroxy-8-methyl-1,3,9-triazaphenothiazine (**16**, 1.14 g, 92%) was collected as a white microcrystalline powder: mp >300°; uv spectrum λ_{min} 215 nm (6528), λ_{max} 230 (8412), λ_{min} 251 (5757), λ_{max} 300 (11,110); ir spectrum (Nujol) ν_{max} 3340, 3100, 1675, 1585, 1543, 1478, 1327, 1220, 1084, 1020, 918, 840, 811, 755 cm^{-1};

Anal. Calcd for $C_{10}H_9N_5OS$: C, 48.59; H, 3.64; N, 28.34; S, 12.95. Found: C, 48.70; H, 3.55; N, 28.19; S, 13.00.

3′-Mercapto-6′-methyl-2′-pyridyl-2,4-dimethoxy-6-pyrimidinylamine (8). 2-Amino-3-mercapto-6-picoline (1.40 g, 10 mmol) and 4-chloro-2,6-dimethoxypyrimidine (**7**, 1.92 g, 11 mmol) were mixed and refluxed in 200 ml of water containing 2 ml of concentrated sulfuric acid and 1.0 g of sodium sulfite. Considerable sublimation of the chlorodimethoxypyrimidine **7** was observed. It was washed down to the reaction flask from time to time with a small amount of water.

At the end of the reflux period (4 hr), the mixture was cooled and filtered. The impure product was washed with warm methanol to remove the unreacted chlorodimethoxypyrimidine. The white residue was then recrystallized from dilute acetic acid after treatment with activated charcoal to yield glistening white plates of 3′-mercapto-6′-methyl-2′-pyridyl-2, 4-dimethoxy-6-pyrimidinylamine (**8**, 1.72 g, 62%): mp 260°; uv spectrum λ_{max} 206 nm (19,110), λ_{min} 227 (5572), λ_{max} 257 (23,280), λ_{min} 281 (10,630), λ_{max} 305 (11,470); ir spectrum ν_{max} 3300 (6-NH), 3194 (C=NH^+), 1650, 1590, 1530, 1344, 1235, 1202, 1150, 1020, 980, 900, 841 cm^{-1}; NMR spectrum (Me_2SO-d_6) τ 6.10 (6′-CH_3, 2-OCH_3, 4-OCH_3), 3.26 d (J = 5.9 Hz, 5′-CH), 2.53 br (5-CH, 6-NH, 1′-NH), 2.45 d (J = 5.9 Hz, 4′-CH); mass spectrum *m/e* (rel intensity) 64 (80), 106 (12), 139 (100), 140 (33), 278 (M^+, 21), 279 (3), 280 (1).

Anal. Calcd for $C_{12}H_{14}N_4O_2S$: C, 51.81; H, 5.03; N, 20.14; S, 11.51. Found: C, 51.94; H, 5.10; N, 20.11; S, 11.50.

3′-Mercapto-6′-methyl-2′-pyridyl-2-amino-4-hydroxy-6-pyrimidinylamine (17). A mixture of 2-amino-4-chloro-6-hydroxypyrimidine (**14**, 1.455 g, 10 mmol) and 2-amino-3-mercapto-6-picoline (1.40 g, 10 mmol) was ground in a mortar and refluxed for 3 hr in 100 ml of 0.20 *N* sulfuric acid containing 1.0 g of sodium sulfite. The product was collected by filtration and recrystallized from aqueous ethanol–acetone mixture after treatment with activated charcoal. Glistening white crystals of 3′-mercapto-6′-methyl-2′-pyridyl-2-amino-4-hydroxy-6-pyrimidinylamine (**17**, 2.17 g, 87%) separated out: mp 263°; uv spectrum λ_{max} 203 nm (14,010), λ_{sh} 230 (7158), λ_{min} 238 (6691), λ_{max} 268 (11,520); ir spectrum (Nujol) ν_{max} 1650, 1575, 1531, 1275, 1210, 1197, 1146, 1010, 971, 793 cm^{-1}; NMR spectrum (Me_2SO-d_6) τ 6.57 s (6′-CH_3), 3.80 s (5-CH), 2.90 d (J = 5.8 Hz, 5′-CH), 2.82 br (2-NH_2), 2.20 br (4-OH, 6-NH, and 1′-NH), 2.07 d (J = 5.8 Hz, 4′-CH).

Anal. Calcd for $C_{10}H_{11}N_5OS$: C, 48.19; H, 4.42; N, 28.11; S, 12.85. Found: C, 48.17; H, 4.25; N, 28.20; S, 12.78.

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Registry No.—**1**, 33761-31-8; **2**, 42362-16-3; **3**, 55740-61-9; **7**, 6320-15-6; **8**, 55740-62-0; **11**, 4316-94-3; **12**, 55740-63-1; **14**, 1194-21-4; **15**, 55740-64-2; **16**, 55740-65-3; **17**, 55740-66-4; 2-amino-3-thiocyano-6-picoline, 42449-30-9, bromine, 7726-95-6.

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(17) Preliminary psychopharmacological studies carried out by M. L. Steenberg and J. P. Buckley of the College of Pharmacy, University of Houston, Texas, show that these 1,3,9-triazaphenothiazine compounds have appreciable tranquilizing activity when compared to chlorpromazine. A detailed report will be published later.
(18) Aldrich Chemical Co., Milwaukee, Wis. W. R. Boon, W. G. M. Jones, and G. R. Ramage *J. Chem. Soc*, 96 (1951).
(19) Sodium sulfite was added to minimize autoxidation which would convert the *o*-aminomercaptopicoline **1** to the corresponding dipyridyl disulfide.
(20) The bath temperature is 92°.
(21) This compound is highly hydroscopic and retains a lot of solvent after recrystallization, chromatography, and on exposure to air. It is quite stable to heat and was oven dried at 100° for 48 hr and preserved in a vacuum desiccator. In spite of these precautions, the drying procedure was repeated each time before any spectrum is taken and before analysis.
(22) When the NMR spectrum was run in hexadeuteriodimethyl sulfoxide the 10-NH proton was not observed owing to proton exchange with deuterium from the solvent. The 4-NH_2 protons, however, did not exchange with deuterium.