2.63 (doublet, J = 9 Hz, 4-H), 1.70 (singlet, 1-NH); pmr (pyridine-d_5) τ 6.13 (singlet, 6-OH_3), 3.80 (doublet, J = 9 Hz, 5-H), 2.67 (doublet, J = 9 Hz, 4-H), 0.90 (broad singlet, 3-NH_2 and 1-NH); mass spectrum m/e (rel intensity) 52 (36), 53 (44), 54 (36), 80 (40), 97 (22), 114 (78), 141 (100), 156 (M^+, 94).

Anal. Calcd for $C_6H_8N_2OS$: C, 46.15; H, 5.13; N, 17.95; S, 20.51. Found: C, 46.26; H, 5.14; N, 17.84; S, 20.43.

3-Amino-6-chloropyridine-2[1*H*]-thione (10, R = Cl).—The base-catalyzed hydrolysis of 2-amino-5-chlorothiazolo[5,4-*b*]-pyridine (7, R = Cl) was carried out by the same method described for the preparation of the 6-methoxy analog.

From 18.55 g (0.10 mol) of this compound (7, R = Cl), 1 g of sodium sulfite, and 150 ml of 20% NaOH, 15.4 g (96%) of 3-amino-6-chloropyridine-2[1*H*]-thione[15] was obtained as glistening yellow needles melting at 210–211° dec: uv spectrum (MeOH) λ_{max} 355 mμ (log ϵ 3.5463), λ_{min} 292 (3.1362), λ_{max} 256 (3.8992), λ_{min} 237 (3.7832); ir spectrum (Nujol) ν_{max} 3480, 3311, 3180, 1600, 1550, 1545, 1300, 1250, 1136, 1108, 1088, 1030, 855, 815, 728 cm^{-1}; pmr spectrum (pyridine-d_5) τ 3.03 (singlet with broad base, 3-NH_2), 2.50 (doublet, J = 2 Hz, 4-H and5-H), 0.80 (singlet with broad base, 1-NH); pmr (DMSO-d_6) τ 3.53 (singlet with broad base, 3-NH_2), 2.33 (singlet, 4-H and 5-H); mass spectrum m/e (rel intensity) 44 (6), 64 (11), 81 (6), 98 (9), 115 (21), 116 (9), 125 (28), 132 (13), 133 (11), 159 (11), 160 (M^+, 100), 161 (13), 162 (39).

Anal. Calcd for $C_5H_5N_2SCl$: C, 37.38; H, 3.12; N, 17.45; S, 19.94; Cl, 22.12. Found: C, 37.76; H, 2.72; N, 17.46; S, 20.04; Cl, 22.35.

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Registry No.—7 (R = OCH_3), 13797-77-8; 7 (R = Cl), 31784-71-1; 10 (R = OCH_3), 42362-14-1; 10 (R = Cl), 42362-15-2; 11, 42449-30-9; 12, 42449-31-0; 2-methoxy-5-nitropyridine, 5446-92-4; 3-amino-6-methoxypyridine, 6628-77-9; 3-amino-6-methoxypyridine dipicrate, 42449-34-3; 2-chloro-5-nitropyridine, 4548-45-2; 3-amino-6-chloropyridine, 5350-93-6; 2-amino-6-picoline, 1824-81-3.

Studies in the Heterocyclic Series. VIII. The First Synthesis of a Triazaphenothiazine Ring

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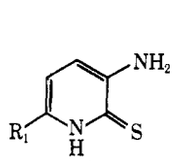
Compounds of 1,3,6-triazaphenothiazine, a new heterocyclic ring, are hereby described. Previously, no triazaphenothiazine compound was known. The synthesis of these compounds was achieved by acid-catalyzed reaction of suitably placed 3-aminopyridine-2[1*H*]-thiones with 5,6-dihalopyrimidines. Optimum yields were obtained in dilute sulfuric acid at concentrations between 0.12 and 0.50 *N*. Their uv, ir, pmr, and mass spectra were taken and used along with certain reactions to establish their structures. The related "open" 1,3,6-triazaphenothiazines were also synthesized and characterized and the abnormal appearance of their parent peaks in their mass spectra was rationalized. Many derivatives of these "open" and "closed" 1,3,6-triazaphenothiazines were also reported.

In continuation of our search for new azaphenothiazine drugs, a new azaphenothiazine ring was considered desirable, as previously reported azaphenothiazine rings are only the monoaza- and the diazaphenothiazine systems.[2] This work becomes even more important in the study of the mechanism of action of phenothiazine drugs where a correlation between tranquilizing activity and electron-donor property in charge-transfer complexes has been made. The stronger electron-donor property and hence the higher psychopharmacological activity have been associated with the heterocyclic ring, phenothiazine, and evidence for this conclusion has been provided.[3] More systematic studies in this direction will require a greater variety of phenothiazine rings. In an earlier paper[4] in this series, the synthesis of some 3,6-diazaphenothiazine compounds was described, and in continuation of this work, we present the first synthesis of a triazaphenothiazine system.

These compounds were obtained from 3-aminopyridine-2[1*H*]-thiones (**1**)[5] and 5-bromo-4-chloropyrimidines (**2**) prepared by an adaptation of Phillips' procedure.[6] The pmr spectra of the latter products showed no evidence for imino structures, contrary to the situation in related dihydroxypyrimidines.[7] In the crucial step involving the nucleophilic attack of the aminopyridinethione on the dihalopyrimidine followed by cyclization of the intermediate diarylamine **3**, several condensing agents were tried. Most promising results were obtained by acid-catalyzed procedures.[8] Using concentrated acid techniques, no reaction took place in concentrated hydrochloric and sulfuric acids, as all basic points were protonated. The insolubility of compound **1** in concentrated acids also posed a serious problem. However, upon dilution, it was possible to dissolve the compound and to protonate selectively the tertiary and secondary amino groups only, as these are more basic than the primary NH_2 group. The protona-



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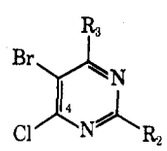

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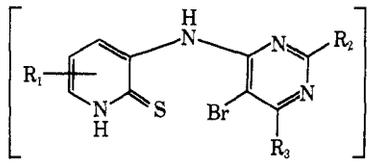
tion of the pyrimidine ring nitrogens enhances the positive characters of the 2,4 and 6 carbons both by inductive and conjugative mechanisms. The 5 carbon is relatively less reactive, as it is only affected by the inductive effect of the ring nitrogens, which are, even then, relatively more remote. Under these conditions, therefore, the 3-NH_2 group in structure **1** mounts a nucleophilic attack on the positive pyrimidine carbon bearing the active halogen (C-4) leading to the formation of the *o*-thioxopyridylpyrimidinylamine **3** as the intermediate. These diarylamines, bearing both ortho-halo and mercapto groups, are sufficiently reactive in the acid medium and spontaneously cyclize to the 1,3,6-triazaphenothiazines (**4**).



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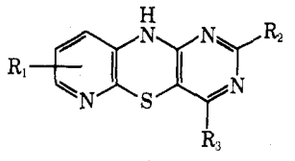

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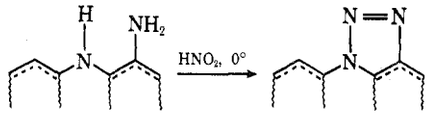
The conditions for optimum yields were also investigated. Best yields and purest products were obtained in aqueous solutions of 0.12 and 0.50 *N* H_2SO_4. Addition of a little amount of sodium sulfite helped to prevent the autoxidation of the aminopyridinethione which diverts the reaction to the undesirable disulfide. By refluxing for 3 hr, reproducible yields better than 70–95% were obtained in most cases.

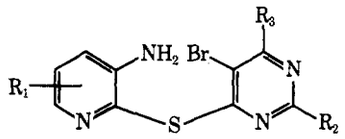
The reaction of 3-amino-6-methoxypyridine-2[1*H*]-thione (**1**, R_1 = 6-OCH_3) and 5-bromo-4-chloro-2,6-diaminopyrimidine (**2**, R_2 = R_3 = NH_2) under these conditions led to a triazaphenothiazine of molecular weight 262. Elemental analysis and molecular weight determination are consistent with the formula $C_{10}H_{10}N_6OS$. The uv spectrum gave three maximum absorptions at 335, 300, and 252 mμ; the strong band in the neighborhood of 252 mμ is consistent with similar observation in phenothiazinoid systems.[9] The infrared spectrum showed the NH_2 (doublet) and NH (singlet) stretching bands expected from structure **4**. The pmr and mass spectra of this compound were rationalized on the basis of the assigned structure **4** (R_1 = 7-OCH_3; R_2 = R_3 = NH_2).

Using 3-amino-6-chloropyridine-2[1*H*]-thione in place of **1** (R_1 = OCH_3), 7-chloro-2,4-diamino-1,3,6-triazaphenothiazine was obtained. These two triazaphenothiazines have similar uv spectra and the substitution of chlorine for the 7-methoxy group did not affect the characteristic phenothiazine band at 252 mμ. Owing to the stronger inductive effect of chlorine compared with the methoxy group, there was a general deshielding of all the proton absorptions found in the pmr spectrum. Diazotization of these diaminotriazaphenothiazines (**4**, R_2 = R_3 = NH_2) did not give the 1,10-diazoles (**5**) characteristic of *o*-aminodiarylamines (**6**).[10] 1-Amino-



6 **5**

3-azaphenothiazine[11] and 1-amino-3-azaphenoxazine,[12] structurally related to the alternative structure **8**, gave the corresponding 1,10-diazoles (**5**). It can be inferred from these reactions, therefore, that the *o*-thioxodiarylamine **3** does not undergo Smiles rearrangement to *o*-aminodiaryl sulfide **7**, which will lead to the alternative structure **8** expected to give the nitrous acid reaction. This is evidence for the assigned structures **4**.



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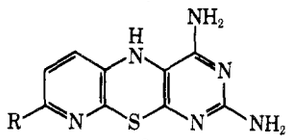
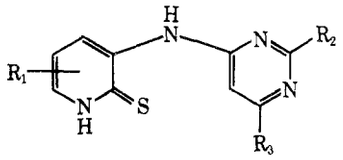


8

The synthesis of systems in which the central ring has been "opened" was also carried out, since many such systems are reported to be biologically active.[13] Furthermore, the determination of their structures as *o*-thioxodiarylamines will lend further support to the assigned structures of the "closed" systems, as this implies that Smiles rearrangement did not occur. These compounds were generally obtained by treating the 3-aminopyridine-2[1*H*]-thiones with 4-chloropyrimidines under the reaction conditions used for obtaining the "closed" systems. The uv spectra of these "open" products resemble those of the "closed" systems. In the ir spectrum, the absence of an SH band in the region of 2600–2550 cm^{-1} even in concentrated solutions and the appearance of NH bands as singlets rather than doublets show that these compounds exist as the thioxo form **9** rather than **10**. Examination of their pmr



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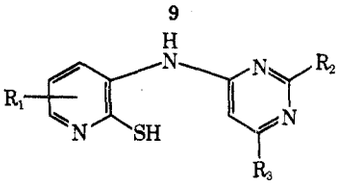

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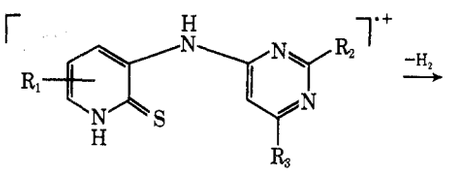
spectra confirmed the structures as **9**. The formation of these "open" nonrearranged structures, which are related to and formed by the same method used for the closed systems, is further evidence that the diaryl intermediate **3** did not rearrange to the diaryl sulfide **7**, which should yield 2,4,6-triazaphenothiazine **8** upon cyclization.

One interesting observation in the mass spectra of these "open" 1,3,6-triazaphenothiazines is the appearance of the parent peak (**11**) consistently at two mass units lower than the expected value. In all the four compounds whose mass spectra were examined, the parent peak appeared at two mass units lower than the expected charge to mass ratio. It appears therefore that the elimination of hydrogen occurs readily under the condition in which the mass spectra were run, thereby leading to the tricyclic ion **12**. This shows that,



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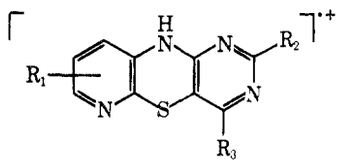

12

in the excited state, the diarylamine intermediate **3** is in a favorable steric arrangement within the molecule, which ensures cyclization in the acid medium. Many other derivatives of both the "closed" and "open" 1,3,6-triazaphenothiazines were also described.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus in open capillaries. Uv spectra were taken with a Cary Model 14 spectrophotometer in methanol solutions using matched 1-cm quartz cells. Ir spectra were determined on a Perkin-Elmer Model 137 spectrophotometer in Nujol (Kaydol) pastes. Nmr spectra were obtained with a Varian Associates A-60 spectrometer. Chemical shifts are reported on the τ scale relative to tetramethylsilane (TMS) used as an internal standard except in the case of compound **13**, where TMS was used as an external reference. The mass spectra were obtained on an AE1 MS-9 mass spectrometer at 70 eV.

3-Aminopyridine-2[1*H*]-thiones (1).—This class of compounds was obtained by the thiocyanation of substituted 3-aminopyridines with potassium thiocyanate and bromine in glacial acetic acid. The now formed 2-aminothiazolo[5,4-*b*]pyridine was treated with 20% sodium hydroxide solution to give excellent yields of 3-aminopyridine-2[1*H*]-thiones, fully described in the preceding paper.[5]

4-Chloro-2,6-diaminopyrimidine.—2,4-Diamino-6-hydroxypyrimidine (28.9 g, 0.2 mol) was treated with phosphoryl chloride (45 ml) and phosphorus pentachloride (40 g) and the mixture was refluxed in an oil bath maintained at 120–130° for a 3-hr period. Excess phosphorus halides were removed by distillation *in vacuo*. The gummy brown solid was poured *cautiously* into a few chips of ice in an ice bath. The solution was then partially neutralized with concentrated ammonia solution while cooling. The product was collected by filtration and recrystallized from methanol. White, glistening needles of 4-chloro-2,6-diaminopyrimidine (11.6 g, 80%) melting at 202–203° were obtained.

2-Amino-4-chloro-6-methylpyrimidine.—Dried and powdered 2-amino-4-hydroxy-6-methylpyrimidine (12.5 g, 0.1 mol) was refluxed with phosphoryl chloride (30 ml) and phosphorus pentachloride (40 g) as previously described. Long white needles of 2-amino-4-chloro-6-methylpyrimidine (11.7 g, 81.5%) melting at 182–183° were obtained after recrystallization from aqueous methanol (Norit).

5-Bromo-4-chloro-2,6-dimethoxypyrimidine (2, $R_2 = R_3 = OCH_3$).—4-Chloro-2,6-dimethoxypyrimidine (17.45 g, 0.1 mol) was slurried with 12 g of sodium bicarbonate in 300 ml of 50% methanol. Bromine (9 ml) was added with efficient stirring during a period of 1 hr. After 30 min of bromine addition, an additional 7 g of sodium bicarbonate was added and the mixture was stirred at room temperature for a total of 2 hr. The white precipitate obtained (mp 95–96°) was collected by filtration and recrystallized from aqueous methanol, yielding 24.1 g (95.1%) of white crystalline plates of 5-bromo-4-chloro-2,6-dimethoxypyrimidine melting at 97–98°. The analytical sample was purified by sublimation (sublimes at 98°): uv spectrum λ_{max} 273 mμ (log ϵ 3.84), λ_{min} 250 (3.40), λ_{max} 223 (3.97), λ_{min} 210 (3.84); ir spectrum (Kaydol) ν_{max} 1563, 1545, 1320, 1238, 1195, 1106, 1027, 1008, 937, 866, 772 cm^{-1}; pmr spectrum ($CDCl_3$) τ 5.73 (singlet, 6-OCH_3), 5.65 (singlet, 2-OCH_3).

Anal. Calcd for $C_6H_6N_2O_2BrCl$: C, 28.41; H, 2.37; N, 11.05; Cl, 14.01; Br, 31.53. Found: C, 28.45; H, 2.45; N, 10.97; Cl, 14.10; Br, 31.52.

5-Bromo-4-chloro-2,6-diaminopyrimidine (2, $R_2 = R_3 = NH_2$).—4-Chloro-2,6-diaminopyrimidine (14.45 g, 0.1 mol) was brominated with 16 ml of bromine in 750 ml of 50% methanol in the presence of a total of 20 g of sodium bicarbonate as described for 5-bromo-4-chloro-2,6-dimethoxypyrimidine. White needles of 5-bromo-4-chloro-2,6-diaminopyrimidine (15.87 g, 71%) melting at 217.5–218° were obtained: uv spectrum λ_{max} 294 mμ (log ϵ 3.78), λ_{min} 264 (2.79), λ_{max} 233 (4.05); ir spectrum (Kaydol) ν_{max} 3350 (doublet), 3200, 1670, 1645, 1605, 1530, 1328, 1270, 1063, 988, 886, 762 cm^{-1}.

Anal. Calcd for $C_4H_4N_4ClBr$: C, 21.48; H, 1.79; N, 25.07; Cl, 15.89; Br, 35.76. Found: C, 21.58; H, 1.68; N, 25.05; Cl, 15.92; Br, 35.68.

2-Amino-5-bromo-4-chloro-6-methylpyrimidine (2, $R_2 = NH_2$; $R_3 = CH_3$).—2-Amino-4-chloro-6-methylpyrimidine (10.76 g, 75 mmol) was treated with 15 g of sodium bicarbonate in 500 ml of 50% aqueous methanol. Bromine (14 ml) was added as described for 5-bromo-4-chloro-2,6-dimethoxypyrimidine. White needles of 2-amino-5-bromo-4-chloro-6-methylpyrimidine (16.9 g, 96.5%) melting at 206–207° were obtained after recrystallization from methanol (Norit): uv spectrum λ_{max} 310 mμ (log ϵ 3.57), λ_{min} 270 (2.88), λ_{max} 237 (4.22), λ_{min} 216 (3.68); ir spectrum (Kaydol) ν_{max} 3380, 3250, 1640, 1550, 1526, 1280, 1217, 1044, 1020, 888, 862, 771 cm^{-1}; pmr spectrum ($CDCl_3$) τ 7.33 (singlet, 6-CH_3), 2.22 (singlet, 2-NH_2).

Anal. Calcd for $C_5H_5N_3ClBr$: C, 26.98; H, 2.25; N, 18.88; Cl, 15.96; Br, 35.91. Found: C, 27.08; H, 2.21; N, 18.84; Cl, 15.83; Br, 36.02.

2-Amino-5-bromo-4,6-dichloropyrimidine (2, $R_2 = NH_2$; $R_3 = Cl$).—2-Amino-4,6-dichloropyrimidine (32.8 g, 0.2 mol) was mixed with 20 g of sodium bicarbonate and slurried in 600 ml of 50% methanol. Bromine (16 ml) was added as described for 5-bromo-4-chloro-2,6-dimethoxypyrimidine followed by addition of an additional 15 g of sodium bicarbonate. 2-Amino-5-bromo-4,6-dichloropyrimidine (46.2 g, 95%) was collected after recrystallization from methanol (Norit): mp 235–236°; uv spectrum λ_{max} 314 mμ (log ϵ 3.62), λ_{min} 277 (2.95), λ_{max} 238 (4.26), λ_{min} 217 (3.63); ir spectrum (Kaydol) ν_{max} 3290 (doublet), 1640, 1545, 1490, 1325, 1270, 1250, 1210 (doublet), 1050, 1023, 953, 815, 762 cm^{-1}; pmr spectrum ($CDCl_3$) τ 2.25 (singlet, 2-NH_2).

Anal. Calcd for $C_4H_2N_3Cl_2Br$: C, 19.76; H, 0.82; N, 17.29; Cl, 29.23; Br, 32.90. Found: C, 19.70; H, 0.87; N, 17.40; Cl, 29.11; Br, 33.08.

5-Bromo-2,4-diamino-6-hydroxypyrimidine.—2,4-Diamino-6-hydroxypyrimidine monohydrate (28.8 g, 0.2 mol) was dissolved in 5% aqueous sodium hydroxide (480 ml). The solution was cooled to 20° and 12.5 ml of bromine was added with efficient stirring during a 3-hr period. The temperature was maintained at 20° throughout the addition and for an additional 0.5 hr. The clear solution was stirred at room temperature for an additional 3 hr and allowed to stand overnight.

Upon acidification with concentrated hydrochloric acid while cooling, a massive white precipitate of 5-bromo-2,4-diamino-6-hydroxypyrimidine resulted. It was recrystallized from water after treating with activated charcoal, yielding glistening white

needles: mp 264–265°; ir spectrum ν_{max} 3300, 3190, 1650, 1600, 1550, 1430, 1160, 1088, 998, 875, 764, 683 cm^{-1}.

Anal. Calcd for $C_4H_5N_4OBr$: C, 23.43; H, 2.44; N, 27.32; Br, 38.99. Found: C, 23.44; H, 2.51; N, 27.21; Br, 39.06.

5-Bromo-6-chloro-2,4-diaminopyrimidine from 5-Bromo-2,4-diamino-6-hydroxypyrimidine.—To an intimate mixture of 5-bromo-2,4-diamino-6-hydroxypyrimidine (20.5 g, 0.1 mol) and phosphorus pentachloride (41.7 g, 0.2 mol) was added 60 ml of phosphoryl chloride and the mixture was refluxed in an oil bath maintained at 120–130° for 2.5 hr. The phosphorus halides were removed by vacuum distillation, leaving a yellow, gummy residue. It was then transferred to a beaker to which some ice chips were cautiously added. Upon neutralization with concentrated ammonia solution while cooling, a yellow precipitate was collected after filtration. Recrystallization from water after treating with activated charcoal (Norit) gave white, microcystalline plates of 5-bromo-6-chloro-2,4-diaminopyrimidine (15.2 g, 68%) melting at 217.5–218°. A mixture melting point with the product, obtained by the alternative method already described, did not show any depression. Furthermore, their spectra are superimposable.

2,4-Diamino-7-methoxy-1,3,6-triazaphenothiazine (4, R_1 = 7-OCH_3; R_2 = R_3 = NH_2).—3-Amino-6-methoxypyridine-2[1*H*]-thione (1.56 g, 10 mmol) was intimately mixed with 2.46 g (11 mmol) of 5-bromo-6-chloro-2,4-diaminopyrimidine in a mortar and placed in a 250-ml three-necked flask equipped with an efficient mechanical stirrer. Some 100 ml of water and 1 g of sodium sulfite were added and the mixture was refluxed with stirring for 2 hr in the presence of 1 ml. of concentrated sulfuric acid (*d* 1.84). Complete dissolution was achieved within 30 min followed by massive precipitation of a yellowish-green product.[14] The pH of the solution was checked from time to time to ensure that the solution remained acidic.[15]

The mixture was allowed to cool in an ice bath and neutralized with dilute ammonia and the residue was collected by filtration. Upon recrystallization from acetone after addition of activated charcoal (Norit), light, yellowish-green plates of 2,4-diamino-7-methoxy-1,3,6-triazaphenothiazine (2.38 g, 91%) melting at 255–256° were obtained: uv spectrum λ_{max} 335 mμ (log ϵ 3.79), λ_{min} 307 (3.65), λ_{max} 300 (3.65), λ_{min} 283 (3.55), λ_{max} 252 (4.36), λ_{min} 234 (4.22); ir spectrum ν_{max} 3390 (doublet), 3200, 1630, 1602, 1565, 1500, 1478, 1417, 1332, 1300, 1280, 1260, 1220, 1173, 1155, 1105, 1088, 1057, 1028, 980, 903, 818, 810, 740 cm^{-1}; pmr spectrum (DMSO-d_6) τ 6.00 (singlet, 7-OCH_3), 3.78 (broad peak, 4-NH_2), 3.50 (broad peak, 2-NH_2), 3.12 (doublet, J = 8.4 Hz, 9-H), 2.40 (doublet, J = 8.4 Hz, 8-H), 0.82 (broad peak, 10-NH); mass spectrum *m/e* (rel intensity) 150 (5), 177 (6), 178 (8), 219 (18), 220 (8), 247 (24), 262 (M^+, 100).

Anal. Calcd for $C_{10}H_{10}N_6OS$: C, 45.78; H, 3.84; N, 32.04; S, 12.22. Found: C, 45.95; H, 4.01; N, 31.97; S, 12.22.

7-Chloro-2,4-diamino-1,3,6-triazaphenothiazine (4, R_1 = 7-Cl; R_2 = R_3 = NH_2).—This compound was prepared from 3-amino-6-chloropyridine-2[1*H*]-thione (1.61 g, 10 mmol) and 5-bromo-4-chloro-2,6-diaminopyrimidine (2.46 g, 11 mmol) as described for 2,4-diamino-7-methoxy-1,3,6-triazaphenothiazine. Yellow microcrystals of 7-chloro-2,4-diamino-1,3,6-triazaphenothiazine (2.35, g, 88%) melting at 309–310° were collected: uv spectrum λ_{max} 353 mμ (log ϵ 3.64), λ_{min} 313 (3.11), λ_{infl} 290 (3.61), λ_{max} 254 (4.47), λ_{min} 230 (4.12); ir spectrum ν_{max} 3395, 3240, 1640, 1588, 1555, 1500, 1440, 1400, 1340, 1285, 1260, 1224, 1173, 1140, 1110, 1092, 1060, 992, 934, 877, 814, 790, 760, 730 cm^{-1}; pmr spectrum (DMSO-d_6) τ 3.63 (broad peak 4-NH_2), 3.32 (broad peak, 2-NH_2), 2.48 (singlet, 8-H and 9-H), 0.40 (broad peak, 10-NH); mass spectrum *m/e* (rel intensity) 192 (6), 199 (8), 234 (23), 266 (M^+, 100), 268 (37).

Anal. Calcd for $C_9H_7N_6SCl$: C, 40.53; H, 2.65; N, 31.51; S, 12.00; Cl, 13.29. Found: C, 40.59; H, 2.80; N, 31.30; S, 11.92; Cl, 13.48.

2,4,7-Trimethoxy-1,3,6-triazaphenothiazine (4, R_1 = 7-OCH_3; R_2 = R_3 = OCH_3).—To a mixture of 1.56 g (10 mmol) of 3-amino-6-methoxypyridine-2[1*H*]-thione (**5**, R_1 = 6-OCH_3) and 5.07 g (20 mmol) of 5-bromo-4-chloro-2,6-dimethoxypyrimidine **7** (**6**, R_2 = R_3 = OCH_3) in 100 ml of water was added 1 ml of concentrated sulfuric acid and 1 g of sodium sulfite. The mixture was refluxed with efficient stirring for 6 hr. There was complete dissolution after 5 min followed by extensive sublimation of **7**. It was washed down with water followed by reduction in heating to reduce its reappearance at 96°. At the end of the reaction, a tarry, greenish product, which solidified upon cooling, was formed. It was collected by decanting off the hot supernatant liquid, neutralized with concentrated ammonia, and filtered. The bulk of this product was the unreacted pyrimidine compound **7**, which was removed by extraction with boiling methanol. The greenish residue was recrystallized from ethanol to give 0.32 g (11%) of 2,4,7-trimethoxy-1,3,6-triazaphenothiazine (**10**, R_1 = 7-OCH_3; R_2 = R_3 = OCH_3) as green plates melting at 187–188°: uv spectrum λ_{max} 308 mμ (log ϵ 4.21), λ_{max} 250 (4.00); ir spectrum ν_{max} 3250 (singlet), 1600, 1535, 1280, 1219, 1192, 1178, 1141, 1111, 1103, 1077, 1030, 1021, 939, 926, 901, 840, 826, 786, 771, 690 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}N_4O_3S$: C, 49.32; H, 4.11; N, 19.18; S, 10.96. Found: C, 49.49; H, 4.30; N, 19.01; S, 11.05.

7-Chloro-2,4-dimethoxy-1,3,6-triazaphenothiazine (4, R_1 = 7-Cl; R_2 = R_3 = OCH_3).—A mixture of 1.61 g (10 mmol) of 3-amino-6-chloropyridine-2[1*H*]-thione and 3.80 g (15 mmol) of 5-bromo-4-chloro-2,6-dimethoxypyrimidine in 200 ml of water was refluxed for 4 hr in the presence of 1 g of sodium sulfite and 1 ml of concentrated sulfuric acid as was described for compound **4** (R_1 = 7-OCH_3; R_2 = R_3 = NH_2). Recrystallization from ethanol after treatment with activated charcoal afforded 2.82 g (95%) of 7-chloro-2,4-dimethoxy-1,3,6-triazaphenothiazine as green plates: mp 202–203°; uv spectrum λ_{max} 343 mμ (log ϵ 3.89), λ_{min} 333 (3.87), λ_{max} 308 (4.19), λ_{min} 281 (3.90), λ_{max} 261 (4.05), λ_{min} 247 (4.03), λ_{infl} 224 (4.14); ir spectrum ν_{max} 3200 (singlet), 1600, 1570, 1525, 1476, 1350, 1309, 1281, 1270, 1223, 1189, 1174, 1153, 1101, 1070, 1022, 1004, 930, 870, 845, 820, 808, 770, 689 cm^{-1}.

Anal. Calcd for $C_{11}H_9N_4SOCl$: C, 44.52; H, 3.04; N, 18.89; S, 10.79; Cl, 11.98. Found: C, 44.66; H, 2.89; N, 18.69; S, 10.76; Cl, 12.08.

2-Amino-7-chloro-4-methyl-1,3,6-triazaphenothiazine (4, R_1 = 7-Cl; R_2 = NH_2; R_3 = CH_3).—A mixture of 1.61 g (10 mmol) of 3-amino-6-chloropyridine-2[1*H*]-thione and 2.45 g (11 mmol) of 2-amino-5-bromo-4-chloro-6-methylpyrimidine was treated as described earlier except that the reflux period was increased to 3.5 hr. Green plates of 2-amino-7-chloro-4-methyl-1,3,6-triazaphenothiazine (1.94 g, 73%) were collected after recrystallization from aqueous acetone (Norit): mp 247–249°; uv spectrum λ_{max} 321 mμ (log ϵ 3.47), λ_{max} 245 (3.45); ir spectrum ν_{max} 3420, 1660, 1608, 1565, 1525, 1500, 1320, 1270, 1200, 1150, 1116, 1066, 1050, 853, 813, 803, 772, 736 cm^{-1}.

Anal. Calcd for $C_{10}H_8N_5SCl$: C, 45.21; H, 3.01; N, 26.37; S, 12.05; Cl, 13.38. Found: C, 44.99; H, 2.89; N, 26.41; S, 12.11; Cl, 13.47.

2-Amino-7-methoxy-4-methyl-1,3,6-triazaphenothiazine (4, R_1 = 7-OCH_3; R_2 = NH_2; R_3 = CH_3).—3-Amino-6-methoxypyridine-2[1*H*]-thione (3.12 g, 20 mmol) was treated with 2.45 g (11 mmol) of 2-amino-5-bromo-4-chloro-6-methylpyrimidine in the presence of sodium sulfite and sulfuric acid as was described for 2,4-diamino-7-methoxy-1,3,6-triazaphenothiazine. This time the reflux period was extended to 5 hr. White plates of 2-amino-7-methoxy-4-methyl-1,3,6-triazaphenothiazine were obtained after recrystallization from aqueous acetone: mp 243–244°; uv spectrum λ_{max} 308 mμ (log ϵ 3.91), λ_{min} 278 (3.57), λ_{max} 232 (4.07), λ_{min} 217 (4.05); ir spectrum ν_{max} 3340, 3200, 1640, 1600, 1570, 1540, 1500, 1400, 1327, 1280, 1270, 1260, 1238, 1220, 1058, 1042, 1020, 984, 973, 884, 858, 825, 806, 776, 770 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}N_5SO$: C, 50.58; H, 4.21; N, 26.82; S, 12.26. Found: C, 50.25; H, 3.37; N, 26.90; S, 12.25.

2-Amino-4,7-dichloro-1,3,6-triazaphenothiazine (4, R_1 = 7-Cl; R_2 = NH_2; R_3 = Cl).—2-Amino-5-bromo-4,6-dichloropyrimidine (1.34 g, 5.5 mmol) and 3-amino-6-methoxypyridine-2[1*H*]-thione (0.78 g, 5 mmol) were refluxed in 0.43 *N* H_2SO_4 as described for the 4-amino analog. Yellow microplates of 2-amino-4,7-dichloro-1,3,6-triazaphenothiazine (1 g, 70%) were collected; mp >300°; uv spectrum λ_{max} 318 mμ (log ϵ 4.07), λ_{min} 287 (3.77), λ_{max} 234 (4.21), λ_{min} 222 (4.19); ir spectrum ν_{max} 3380, 3230, 1606, 1550, 1530, 1410, 1342, 1261, 1220, 1138, 1065, 1050, 1003, 913, 838, 827, 770 cm^{-1}.

Anal. Calcd for $C_9H_5N_5SCl_2$: C, 37.76; H, 1.75; N, 24.47; S, 11.19; Cl, 24.82. Found: C, 37.70; H, 1.96; N, 24.22; S, 11.28; Cl, 24.65.

2,4-Diamino-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (9, R_1 = 6-OCH_3; R_2 = R_3 = NH_2).—This "open" 1,3,6-triazaphenothiazine was prepared as described for the corresponding closed system. From 1.56 g (10 mmol) of 3-

(14) There was excessive frothing and foaming if an efficient stirrer was not used.

(15) Alternatively, a 0.22 *N* H_2SO_4 solution was used satisfactorily.

amino-6-methoxypyridine-2[1*H*]-thione (1, R_1 = 6-OCH_3) and 4-chloro-2,6-diaminopyrimidine in 0.50 *N* H_2SO_4, 1.36 g (94% yield) of 2,4-diamino-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine was obtained as yellow plates: mp 270–272°; uv spectrum λ_{max} 384 mμ (log ε 3.54), λ_{min} 342 (3.36), λ_{max} 311 (3.88), λ_{min} 280 (3.62), λ_{max} 249 (3.87), λ_{min} 242 (3.85); ir spectrum ν_{max} 3200, 1675, 1595, 1404, 1290, 1260, 1225, 1200, 1163, 1130, 1080, 1060, 1030, 1012, 980, 900, 865, 796, 774 cm^{-1}; mass spectrum *m/e* (rel intensity) 147 (16), 178 (10), 218 (8), 220 (14), 231 (30), 262 (M^+, 100).

Anal. Calcd for $C_{10}H_{12}N_6OS$: C, 45,45; H, 4.55; N, 31.82; S, 12.12. Found: C, 45.20; H, 4.49; N, 32.00; S, 12.19.

2,4-Diamino-6-(6-chloro-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (9, R_1 = 6-Cl; R_2 = R_3 = NH_2).—This compound was again prepared as described for the closed analog **4**. From 0.80 g (5 mmol) of 3-amino-6-chloropyridine-2[1*H*]-thione (1, R_1 = 6-Cl) and 0.80 g (5.5 mmol) of 4-chloro-2,6-diaminopyrimidine, 1.22 g (91% yield) of yellow plates of 2,4-diamino-6-(6-chloro-2[1*H*]-thion-3-pyridyl)pyrimidinylamine was collected: mp >300°; uv spectrum λ_{max} 345 mμ (log ε 3.72), λ_{min} 333 (3.67), λ_{max} 306 (3.96), λ_{min} 283 (3.79), λ_{max} 251 (4.15), λ_{min} 232 (4.10); ir spectrum ν_{max} 3400, 3250, 1675, 1600, 1575, 1525, 1273, 1232, 1240, 975, 885, 870, 832, 786, 776, 745 cm^{-1}; mass spectrum *m/e* (rel intensity) 199 (10), 224 (9), 231 (8), 234 (25), 266 (M^+ 100), 268 (40).

Anal. Calcd for $C_9H_9N_6SCl$: C, 40.23; H, 3.35; N, 31.29; S, 11.92; Cl, 13.22. Found: C, 40.32; H, 3.11; N, 31.50; S. 12.03; Cl, 13.19.

6′-Methoxy-2′[1′*H*]-thion-3′-pyridyl-2,4-dimethoxy-6-pyrimidinylamine 13 (9, R_1 = 6-OMe; R_2 = R_3 = OCH_3).—The reaction of 1.56 g (10 mmol) of 3-amino-6-methoxypyridine-2[1*H*]-thione and 1.59 g (11 mmol) of 4-chloro-2,6-dimethoxypyrimidine was carried out as described for "closed" 1,3,6-triazaphenothiazine compounds. A 2.56-g (87%) yield of 2,4-dimethoxy-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine was obtained as white plates: mp 163–164°; uv spectrum λ_{max} 272 μ (log ε 4.16); ir spectrum ν_{max} 3440, 1608, 1580, 1520, 1418, 1340, 1284, 1257, 1202, 1193, 1162, 1132, 1120, 1105, 1094, 1073, 1048, 1026, 1000, 984, 976, 940, 888, 868, 834, 810, 802, 772, 733, 701 cm^{-1}; pmr spectrum [$(CD_3)_2SO$] τ 5.93 (singlet, 2-OMe, 4-OMe, 6′-OMe), 4.02 (singlet, 5-H), 3.27 (singlet, 1′-NH), 2.58 (doublet, *J* = 9.6 Hz, 4′-H), 1.53 (doublet, *J* = 9.6 Hz, 5′-H), 0.45 (singlet, 6-NH); mass spectrum *m/e* (rel intensity) 247 (3), 260 (12), 261 (58), 262 (10), 277 (35), 292 (100).

Anal. Calcd for $C_{12}H_{14}N_4O_3S$: C, 48.98; H, 4.76; N, 19.05; S, 10.88. Found: C, 49.15; H, 4.63; N, 19.22 S, 11.00.

6′-Chloro-2′[1′*H*]-thion-3′-pyridyl-2,4-dimethoxy-6-pyrimidinylamine (9, R_1 = 6-Cl; R_2 = R_3 = OCH_3).—This compound was obtained by the reaction of 3-amino-6-chloropyridine-2[1*H*]-thione (1.6 g, 10 mmol) and 4-chloro-2,6-dimethoxypyrimidine (1.59 g, 11 mmol) as described for the closed triazaphenothiazines. White plates of 6′-chloro-2′[1′*H*]-thion-3′-pyridyl-2,4-dimethoxy-6-pyrimidinylamine (2.39 g, 80%) were obtained: mp 270–271°; uv spectrum λ_{max} 348 mμ (log ε 3.67), λ_{min} 320 (3.47), λ_{max} 295 (3.72), λ_{min} 270 (3.47), λ_{max} 244 (4.39), λ_{min} 225 (4.19), λ_{max} 209 (4.37); ir spectrum ν_{max} 3320, 3250, 1620, 1590, 1570, 1530, 1440, 1420, 1337, 1290, 1272, 1238, 1196, 1173, 1148, 1133, 1110, 1048, 978, 960, 938, 886, 816, 809, 774 cm^{-1}; pmr spectrum (DMSO-d_6) τ 5.95 (singlet, 4-OCH_3), 5.90 (singlet, 2-OCH_3), 2.60 (singlet, 4-H and 5-H), −0.25 (singlet, 3-NH); mass spectrum *m/e* (rel intensity) 252 (3), 261 (4), 265 (53), 266 (8), 281 (28), 296 (M^+ 100), 298 (61).

Anal. Calcd for $C_{11}H_{11}N_4O_2SCl$: C, 44.23; H, 3.68; N, 18.76; S, 10.72; Cl, 11.90. Found: C, 44.51; H, 3.36; N, 18.81; S, 10.70.

2-Amino-4-methyl-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (9, R_1 = 6-OCH_3; R_2 = NH_2; R_3 = CH_3).—This compound was prepared by acid-catalyzed condensation of 3-amino-6-methoxypyridin-2[1*H*]-thione (4.68 g, 30 mmol) and 2-amino-4-chloro-6-methylpyrimidine (4.74 g, 33 mmol) as described for the closed systems. A 90% (7.10 g) yield of white 2-amino-4-methyl-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine was obtained: mp >300; ir spectrum ν_{max} 3400, 3230, 1650, 1595, 1550, 1412, 1290, 1262, 1058, 1020, 969, 890, 866, 810, 788 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}N_5OS$: C, 50.19 H, 4.94; N, 26.62; S, 12.16. Found: C, 49.97; H, 5.09; N, 26.71; S, 12.10.

2-Amino-4-methyl-6-(6-chloro-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (9, R_1 = 7-Cl; R_2 = NH_2; R_3 = CH_3).—The preparation of this compound from 3-amino-6-chloropyridine-2[1*H*]-thione (0.80 g, 5 mmol) and 2-amino-4-chloro-6-methylpyrimidine (0.79 g, 5.5 mmol) was carried out as described for the closed 1,3,6-triazaphenothiazine analog. White plates of 2-amino-4-methyl-6-(6-chloro-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (1.19 g, 89%) were obtained: mp 275–276°; uv spectrum λ_{max} 315 mμ (log ε 4.06), λ_{min} 286 (3.65), λ_{infl} 280 (3.66), λ_{max} 245 (3.89), λ_{min} 240 (3.89), λ_{max} 220 (3.96), λ_{min} 210 (3.96); ir spectrum ν_{max} 3390, 3240, 1647, 1590, 1550, 1515, 1420, 1292, 1271, 1248, 1211, 1148, 1120, 1070, 1028, 974, 965, 874, 856, 827, 794, 784, 768 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_5SCl$: C, 44.86; H, 3.74; N, 26.17; S, 11.96; Cl, 13.27. Found: C, 44.67; H, 3.92; N, 26.15; S, 12.11.

2-Amino-4-chloro-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (9, R_1 = 6-OCH_3; R_2 = NH_2; R_3 = Cl).—This compound was prepared in the usual way, starting with 1.56 g (10 mmol) of 3-amino-6-methoxypyridine-2[1*H*]-thione and 1.80 g (11 mmol) of 2-amino-4,6-dichloropyridmidine. Yellow platelets of 2-amino-4-chloro-6-(6-methoxy-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (2.04 g, 72%) were obtained: mp 270–272°; ir spectrum ν_{max} 3400, 3290, 1660, 1625, 1520, 1420, 1350, 1309, 1263, 1020, 974, 888, 815 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_5OSCl$: C, 42.33; H, 3.53; N, 24.69; S, 11.29; Cl, 12.52. Found: C, 42.51; H, 3.33; N, 24.59; S, 11.42; Cl, 12.44.

2-Amino-4-chloro-6-(6-chloro-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (9, R_1 = 6-Cl; R_2 = NH_2; R_3 = Cl).—By acid-catalyzed condensation of 1.60 g (10 mmol) of 3-amino-6-chloropyridine-2[1*H*]-thione and 1.80 g (11 mmol) of 2-amino-4,6-dichloropyrimidine, yellow plates of 2-amino-4-chloro-6-(6-chloro-2[1*H*]-thion-3-pyridyl)pyrimidinylamine (2.65 g, 92%) were obtained as described for the closed system: mp >300°; ir spectrum ν_{max} 3400, 3280, 1625, 1575, 1550, 1405, 1267, 1220, 1138, 975, 910, 835, 790 cm^{-1}.

Anal. Calcd for $C_9H_7N_5SCl_2$: C, 37.50; H, 2.43; N, 24.31; S, 11.11; Cl, 24.65. Found: C, 37.74; H, 2.30; N, 24.19; S, 11.25; Cl, 24.61.

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Registry No.—1 (R_1 = 6-OCH_3), 42362-14-1; 1 (R_1 = 6-Cl), 42362-15-2; 2 (R_2 = R_3 = OCH_3), 42362-16-3; 2 (R_2 = R_3 = NH_2), 7150-68-7; 2 (R_2 = NH_2; R_3 = CH_3), 6314-12-1; 2 (R_2 = NH_2; R_3 = Cl), 7781-26-2; 4 (R_1 = 7-OCH_3; R_2 = R_3 = NH_2), 42362-20-9; 4 (R_1 = 7-Cl; R_2 = R_3 = NH_2), 42362-21-0; 4 (R_1 = 7-OCH_3; R_2 = R_3 = OCH_3), 42362-22-1; 4 (R_1 = 7-Cl; R_2 = R_3 = OCH_3), 42362-23-2; 4 (R_1 = 7-Cl; R_2 = NH_2; R_3 = CH_3), 42362-24-3; 4 (R_1 = 7-OCH_3; R_2 = NH_2; R_3 = CH_3), 42362-25-4; 4 (R_1 = 7-Cl; R_2 = NH_2; R_3 = Cl), 42362-24-3; 9 (R_1 = 6-OCH_3; R_2 = R_3 = NH_2), 42362-27-6; 9 (R_1 = 6-Cl; R_2 = R_3 = NH_2), 42362-28-7; 9 (R_1 = 6-OCH_3; R_2 = R_3 = OCH_3), 42362-29-8; 9 (R_1 = 6-Cl; R_2 = R_3 = OCH_3), 42362-30-1; 9 (R_1 = 6-OCH_3; R_2 = NH_2; R_3 = CH_3), 42362-31-2; 9 (R_1 = 7-Cl; R_2 = NH_2; R_3 = CH_3), 42362-32-3; 9 (R_1 = 6-OCH_3; R_2 = NH_2; R_3 = Cl), 42362-33-4; 9 (R_1 = 6-Cl; R_2 = NH_2; R_3 = Cl), 42362-34-5; 4-chloro-2,6-diaminopyrimidine, 156-83-2; 2,4-diamino-6-hydroxypyrimidine, 56-06-4; 2-amino-4-chloro-6-methylpyrimidine, 5600-21-5; 2-amino-4-hydroxy-6-methylpyrimidine, 3977-29-5; 4-chloro-2,6-dimethoxypyrimidine, 6320-15-6; 2-amino-4,6-dichloropyrimidine, 56-05-3; 5-bromo-2,4-diamino-6-hydroxypyrimidine 6312-72-7.