Studies in the Heterocyclic Series. VII. The Use of Kaufmann's Reaction as a Route to o-Aminomercaptopyridines

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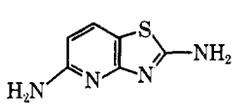
The Kaufmann's thiocyanation of 6-substituted 2-amino- and 3-aminopyridines has now been fully studied and analytically pure compounds obtained therefrom. A study of their uv, ir, pmr, and mass spectra establishes the products as 6-substituted 2-amino-3-thiocyanatopyridine and 5-substituted 2-aminothiazolo[5,4-*b*]pyridine, respectively. The action of 20% sodium hydroxide on the thiazolo[5,4-*b*]pyridines led to analytically pure 6-substituted 3-aminopyridin-2[1*H*]-thiones required for azaphenothiazine synthesis. Our modified procedures gave yields better than 90% overall. Isomerization and acetylation of 6-substituted 2-amino-3-thiocyanatopyridine to 5-substituted 2-acetamidothiazolo[4,5-*b*]pyridine was accomplished by prolonged heating in acetic anhydride.

The importance of phenothiazine compounds in medicine has prompted a lot of attention, not only on the aza- and thiaphenothiazines[2] themselves but also on their precursors.[3] A convenient method of synthesizing one of these precursors, *o*-aminomercaptopyridine, patterned after Kaufmann's reaction,[4] was developed, but contradictory results on both the structure[5,6] and purity[7] of the products were reported. Maggiolo's claim[5] that the thiocyanation of 2,6-diaminopyridine gave 2,5-diaminothiazolo[4,5-*b*]pyridine (**1**) was shown to be incorrect; the product is 3-thiocyanato-2,6-diaminopyridine (**2**).[6] Baker and Hill[6] therefore concluded that the reported base-catalyzed hydrolysis of thiazolopyridine could well be the hydrolysis of *o*-aminothiocyanatopyridine, since cleavage of the thiazole ring is unlikely owing to the aromatic stabilization of the ring. There is also a possibility that the thiocyanation of 3-aminopyridines should occur preferentially in the 4 position owing to greater reactivity of the 4 carbon center to nucleophiles such as thiocyanogen. All these reports and counterreports on the thiocyanation site, the purity and structure of the products, the isomerization of the thiocyanato derivative, and the cleavage of the thiazole ring led us to investigate these reactions, as they are crucial in our azaphenothiazine studies.



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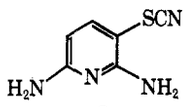

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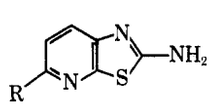
The action of potassium thiocyanate and bromine on 6-substituted 3-aminopyridine in glacial acetic acid led to a single product recrystallizable from methanol. From 3-amino-6-methoxy- (**3**) and 3-amino-6-chloropyridines (**4**), the products **5** and **6**, of molecular formulas $C_7H_7N_3OS$ and $C_6H_4N_3SCl$, respectively, were obtained. Their ultraviolet absorption spectra showed no maxima in the visible, but in the ultraviolet region, absorption maxima around 311 and 270 mμ were observed. The two spectra are nearly superimposable, indicating similarities in structure. There was no absorption in the 2000–2200-cm^{-1} region in their infrared spectra, thus showing the absence of the thiocyanato group. If, however, the thiocyanato derivatives were postulated as intermediates, isomerization of the 2- and 4-thiocyanato derivatives will lead to thiazolo[5,4-*b*]pyridine (**7**) and thiazolo[4,5-*c*]pyridine (**8**), respectively. Isomerization of the third possibility, 3-amino-5-thiocyanatopyridine, to a cyclic structure appears improbable owing to the rigidly planar structure of the pyridine ring. Spectral studies are in agreement with the structure **7** rather than **8**. In the proton magnetic resonance spectrum of the product **5**, taken in hexadeuteriodimethyl sulfoxide (DMSO-d_6), a large coupling constant is expected if the correct structure is **7** owing to strong coupling of the 6 and 7 protons, which are in close proximity. From structure **8**, a low coupling constant will be expected (0–3 Hz) owing to large separation between the protons at the 4 and 7 positions[8] and the planarity of the aromatic ring. As the observed coupling constant is quite large (J = 10 Hz), the alternative structure **8** was therefore ruled out and structure **7** (R = OCH_3) was assigned to this product. A similar effect was observed in the pmr spectrum of the product **6**. Here, the coupling constant is less (J = 8 Hz) than what was observed in the methoxy analog (J = 10 Hz) in agreement with the observation in the vinyl compounds that electronegative substituents tend to diminish the magnitude of J_{cis}.[9,10] The areas of the peaks are in agreement with the assigned structures **7** (R = OCH_3 and Cl). The absence of additional peaks in the spectrum led to the elimination of such imino tautomeric structures as **9**. The strong infrared absorption be-



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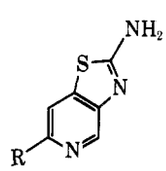

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(2) C. O. Okafor, *Int. J. Sulfur Chem., B*, **6**, 237 (1971); **7**, 109 (1972).

(3) O. R. Rodig, R. E. Collier, and R. K. Schlatzer, *J. Org. Chem.*, **29**, 2652 (1964).

(4) H. P. Kaufmann and P. Schulz, *Arch. Pharm. (Weinheim)*, **273**, 31 (1935); H. P. Kaufmann, *Ber.*, **62B**, 390 (1929); H. P. Kaufmann and M. Schubert, German Patent 493,025 (1927) [*Chem. Abstr.*, **24**, 2754 (1930)].

(5) A. Maggiolo, *J. Amer. Chem. Soc.*, **73**, 5815 (1951).

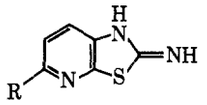
(6) J. A. Baker and S. A. Hill, *J. Chem. Soc.*, 3464 (1962).

(7) T. Takahashi and Y. Maki, *Chem. Pharm. Bull.*, **3**, 92 (1955).

(8) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, London, 1969, pp 305–311.

(9) P. Laszlo and P. R. Schleyer, *Bull. Soc. Chim. Fr.*, 87 (1964).

(10) T. Schaefer, *Can. J. Chem.*, **40**, 1 (1962).



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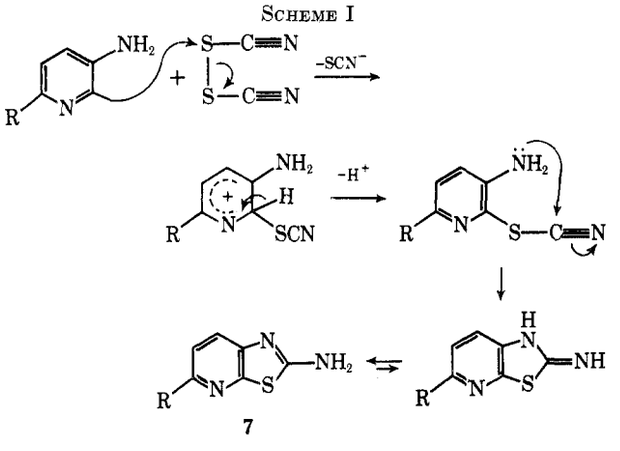
tween 810 and 820 cm^{-1} is consistent with structure **7**, in which two aromatic protons are in adjacent carbons.[11] The mass spectra of these compounds were also taken and the observed fragmentation patterns were rationalized with the assigned structures **7** (R = OCH_3 and Cl).

From the molecular orbital calculations of the π-electron densities in 3-amino-6-chloropyridine,[12] the 4 position is the most positive center. As the attack, however, was on the 2 position, which is the electrophilic center, it is probable that thiocyanogen, being a pseudohalogen, behaves as an electrophile by attacking this electrophilic center (the 2 position). It is equally plausible to consider the 2 position as mounting a nucleophilic attack on thiocyanogen as the substrate. Thus the reactions which led to the structures **7** can be formulated according to Scheme I.

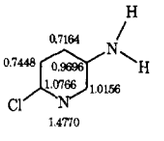
SCHEME I



The structures of the products of the base-catalyzed reactions were also investigated. When these thiazolo[5,4-*b*]pyridines were refluxed in 20% sodium hydroxide followed by acidification, massive yellowish precipitates were formed. Upon recrystallization from methanol, yellow, glistening needles of the product of each reaction were collected in near-quantitative yields. Analyses of these products are in agreement with the formulas $C_6H_8N_2OS$ and $C_5H_5N_2SCl$, which were confirmed by an examination of their mass spectra. A study of their uv, ir, and particularly pmr spectra confirmed that these products are 3-aminopyridine-2[1*H*]-thiones **10**.

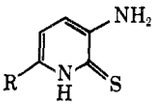
(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Methuen and Co., London, 1964, pp 65, 277.

(12) The π-electron densities given were calculated by the LCAO–MO method. The figures in the structure show a higher electron density in the 2 position compared to the 4 and 5 positions.



A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1967, pp 97–135; J. Ridd in "Physical Methods in Heterocyclic Chemistry," A. R. Katritzky, Ed., Vol. I, Academic Press, New York, N. Y., 1963, pp 27–43, 109–160.

The ready solubility in dilute base and the absence of the SH group in the ir spectra are further evidence of the structures **10** (R = OCH_3, Cl).



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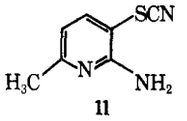
The thiocyanation of the isomeric 2-aminopyridine was also investigated for comparison with the 3-amino isomer. In the 2-aminopyridine series, the 4-methyl and 5-methyl derivatives failed to react and in both cases nearly 50% of the starting amines was recovered. When 2-amino-6-picoline was, however, thiocyanated, a single product of molecular weight 165 and molecular formula $C_7H_7N_3S$ was isolated in 35% yield. The infrared spectrum of this compound showed a strong SCN peak at 2145 cm^{-1}. The large spin–spin coupling constant in the pmr spectrum (J = 9 Hz) and the ready conversion of the product to thiazolo[4,5-*b*]pyridine prove that this compound is 2-amino-3-thiocyanato-6-picoline (**11**) rather than 2-amino-5-thiocyanato-6-picoline or 2-amino-4-thiocyanato-6-picoline. This structure is also in conformity with the mass spectrum.

Although the acetylation of 2-amino-3-thiocyanato-6-picoline (**11**) is expected to give the 2-acetamido derivative, the product obtained showed no thiocyanate peak between 2000 and 2200 cm^{-1} in the ir spectrum but gave the expected single NH peak at 3290 cm^{-1} and the amide II band at 1665 cm^{-1}. This product was therefore formulated as 2-acetamido-5-methylthiazolo[4,5-*b*]pyridine (**12**), which is formed by isomerization and acetylation of compound **11**.



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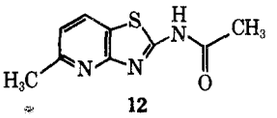

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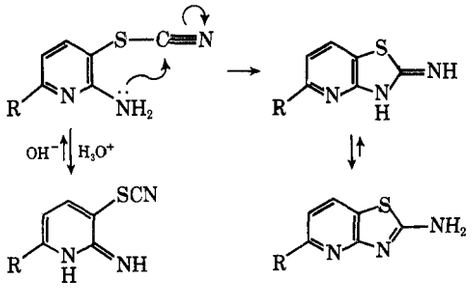
These results therefore show that, although the thiocyanation of 2- and 3-aminopyridines gives the thiocyanato derivatives, isomerization of the 3-amino-2-thiocyanatopyridine takes place with much ease, leading to the isolated 2-aminothiazolo[5,4-*b*]pyridines, while the 2-amino-3-thiocyanatopyridine does so only on prolonged heating. The difficulty in the isomeriza-



tion of 2-amino-3-thiocyanato-6-picoline is probably a result of amino–imino tautomerism in which the imino form hinders the intramolecular nucleophilic attack on the positive carbon of the thiocyanate group. In the isomeric 3-amino-2-thiocyanatopyridine, no such tautomerism can be formulated, as the amino group is

meta and remote from the ring nitrogen, and therefore the isomerization to the 2-aminothiazolo[5,4-*b*]pyridine will proceed with ease.

Experimental Section

General.—Melting points were determined with a Thomas-Hoover apparatus in open capillaries and are corrected. Uv absorption spectra were measured 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. Pmr spectra were recorded at 60 MHz on a Varian Associates A-60 spectrometer. Chemical shifts were reported on the τ scale relative to tetramethylsilane (TMS) used as an internal standard. The mass spectra of these compounds were obtained on an AEI MS-9 (ion source temperature 190°, 70 eV) mass spectrometer.

2-Amino-5-methoxythiazolo[5,4-*b*]pyridine (7, R = OCH_3).—This compound was prepared by a modification of the previously described methods.[13,14]

2-Methoxy-5-nitropyridine was prepared by the condensation of 2-chloro-5-nitropyridine with sodium methoxide in methanol. Reduction of the nitrogroup was accomplished by slow addition of 15.4 g (0.1 mol) of 2-methoxy-5-nitropyridine to a well-stirred and ice-cooled solution of 113 g (0.5 mol) of stannous chloride dihydrate and 150 ml of concentrated hydrochloric acid (*d* 1.42). The addition of the nitro compound was carried out in small quantities and at such a rate that the temperature never exceeded 85°. The reduction was highly exothermic and a cooling bath was therefore used.

After all the nitro compound had been added, the mixture was stirred for 4 hr and allowed to stand overnight. Neutralization with sodium carbonate followed by the use of concentrated ammonia solution gave 3-amino-6-methoxypyridine, which was isolated by successive extraction with four 200-ml portions of ether. After removal of the solvent by distillation followed by purification by fractional distillation *in vacuo*, 11.6 g (94%) of the red liquid was isolated, $n^{20}D$ 1.5729, dipicrate mp 128–129°.

To glacial acetic acid (100 ml) precooled to 5° were added 40 g (0.41 mol) of potassium thiocyanate and 6.2 g (0.05 mol) of 3-amino-6-methoxypyridine. The mixture was placed in a freezing mixture of ice and salt and mechanically stirred while 8 ml of bromine in 30 ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature never rose beyond 0°. After all the bromine has been added (105 min), the solution was stirred for an additional 2 hr at 0° and at room temperature for 10 hr. It was then allowed to stand overnight, during which period an orange precipitate settled at the bottom. Water (30 ml) was added quickly and the slurry was heated to 85° on a steam bath and filtered hot. The orange residue was placed in the reaction flask and treated with 50 ml of glacial acetic acid, heated again to 85°, and filtered hot. The combined filtrates were cooled and neutralized with concentrated ammonia solution to pH 6, when a dark yellow precipitate was collected. Recrystallization from methanol (twice) after treatment with activated charcoal gave colorless plates of 2-amino-5-methoxythiazolo[5,4-*b*]pyridine after drying in a vacuum oven at 50° (0.02 mm). The dry material (8.7 g, 96%) melted at 192–193°: uv spectrum (MeOH) λ_{max} 314 mμ (log ϵ 3.8603), λ_{min} 293 (3.6033), λ_{max} 267 (4.1037), λ_{min} 240 (3.5102); uv (HCl) λ_{max} 302 (4.0378), λ_{min} 285 (3.8902), λ_{max} 270 (3.9535); uv (NaOH) λ_{max} 314 (3.8202), λ_{min} 293 (3.5398), λ_{max} 267 (4.1170); ir spectrum (Nujol) ν_{max} 3330, 3100, 1640, 1580, 1565, 1544, 1403, 1290, 1280, 1247, 1170, 1122, 1108, 1078, 1020, 949, 907, 845, 815, 743, 700 cm^{-1}; pmr spectrum (DMSO-d_6) τ 5.87 (singlet, 5-OCH_3), 2.04 (broad peak, 2-NH_2), 2.87 (doublet, J = 10 Hz, 6-H), 1.85 (doublet, J = 10 Hz, 7-H); mass spectrum *m/e* (rel intensity) 52 (13), 80 (33), 107 (33), 111 (5), 122(4), 138 (10), 151 (11), 152 (42), 154 (4), 166 (21), 181 (M^+, 100).

Anal. Calcd. for $C_7H_7N_3SO$: C, 46.41; H, 3.87; N, 23.21; S, 17.68. Found: C, 46.28; H, 3.96; N, 22.84; S, 17.70.

2-Amino-5-chlorothiazolo[5,4-*b*]pyridine (7, R = Cl).—The synthesis of this compound from 2-chloro-5-nitropyridine is similar to what was reported for the 5-methoxy analog. From 31.7 g (0.2 mol) of 2-chloro-5-nitropyridine, 225 g (1.0 mol) of stannous chloride dihydrate, and 300 ml of concentrated hydrochloric acid, 25.0 g (97%) of white needles of 3-amino-6-chloropyridine was obtained, mp 82–83°.

This product (12.85 g, 0.1 mol) was treated with 80 g (0.82 mol) of potassium thiocyanate in 200 ml of glacial acetic acid and 6 ml of bromine to yield 15.2 g (95%) of 2-amino-5-chlorothiazolo-[5,4-*b*]pyridine as glistening, light-yellow needles melting at 243–244° dec: uv spectrum (MeOH) λ_{max} 310 mμ (log ϵ 3.9164), λ_{min} 292 (3.7029), λ_{max} 272 (4.1606), λ_{min} 246 (3.6101); uv (HCl) λ_{max} 297 (4.0803), λ_{min} 277 (3.8801), λ_{max} 260 (4.0661), λ_{min} 233 (3.7503); uv (NaOH) λ_{max} 310 (3.9507), λ_{min} 292 (3.7765), λ_{max} 272 (4.1910), λ_{min} 246 (3.7366); ir spectrum (Nujol) ν_{max} 3310, 1640, 1577, 1525, 1400, 1316, 1300, 1280, 1240, 1138, 1120, 1082, 940, 895, 813, 769, 736, 690 cm^{-1}; pmr spectrum (DMSO-d_6) τ 1.48 (broad peak, 2-NH_2), 1.77 (doublet, J = 8 Hz, 6-H), 2.20 (doublet, J = 8 Hz, 7-H); mass spectrum *m/e* (rel intensity) 96 (7), 108 (7), 123 (15), 150 (13), 158 (15), 185 (M^+, 100), 187 (39).

Anal. Calcd for $C_6H_4N_3SCl$: C, 38.81; H, 2.16; N, 22.64; S, 17.25; Cl, 19.14. Found: C, 38.90; H, 2.28; N, 22.62; S, 17.46; Cl, 19.18.

2-Amino-3-thiocyanato-6-picoline (11).—This compound was prepared by the same procedure used for the 2-aminothiazolo-[5,4-*b*]pyridines 7.

From 10.8 g (0.1 mol) of 2-amino-6-picoline, 80 g (0.82 mol) of potassium thiocyanate in 100 ml of glacial acetic acid, and 16 ml of bromine in 60 ml of glacial acetic acid, 5.8 g (35%) of white needles of 2-amino-3-thiocyanato-6-picoline (11), melting at 161–162°, were obtained after recystallization twice from methanol (more products were collected by keeping the volume of the partially neutralized solution to a minimum and for several days at 0–3°): uv spectrum (MeOH) λ_{max} 302 mμ (log ϵ 3.7462), λ_{min} 282 (3.6309), λ_{max} 256 (4.2015), λ_{min} 220 (3.4883); ir spectrum ν_{max} 3330, 3150, 2145, 1640, 1572, 1547, 1390, 1339, 1292, 1186, 1134, 1020, 960, 928, 822, 750 cm^{-1}; pmr spectrum (DMSO-d_6) τ 7.37 (singlet, 6-CH_3), 2.95 (broad based singlet, 2-NH_2), 3.17 (doublet, J = 9 Hz, 5-H), 1.91 (doublet, J = 9 Hz, 4-H); mass spectrum *m/e* (rel intensity) 53 (12), 70 (12), 97 (26), 106 (8), 124 (20), 138 (15), 165 (M^+, 100).

Anal. Calcd for $C_7H_7N_3S$: C, 50.91; H, 4.21; N, 25.46; S, 19.39. Found: C, 50.81; H, 4.28; N, 25.19; S, 19.48.

2-Acetamido-5-methylthiazolo[4,5-*b*]pyridine (12).—2-Amino-3-thiocyanato-6-picoline (1.65 g, 0.01 mol) was refluxed in 40 ml of acetic anhydride for 7 hr, during which period there was complete dissolution.

After cooling in an ice bath, a few ice cubes were added and the mixture was stirred with constant cooling until a precipitate was formed. Upon filtration and recrystallization of the material from aqueous acetone after treatment with activated charcoal, 1.95 g (94%) of glistening white needles of 2-acetamido-5-methylthiazolo[4,5-*b*]pyridine melting at 193–194° was obtained: uv spectrum (MeOH) λ_{max} 292 mμ (log ϵ 4.1516), λ_{min} 277 (3.9664), λ_{max} 255 (4.1361), λ_{min} 223 (3.8493); ir spectrum (Nujol) ν_{max} 3290, 1665, 1576, 1540, 1420, 1292, 1268, 1235, 1139, 1038, 1003, 956, 912 (doublet), 826, 775, 742, 677 cm^{-1}; mass spectrum *m/e* (rel intensity) 41 (8), 42 (9), 97 (9), 111 (3), 124 (14), 138 (9), 165 (100), 207 (M^+, 30), 208 (4), 209 (3).

Anal. Calcd. for $C_9H_9N_3OS$: C, 52.17; H, 4.35; N, 20.29; S, 15.46. Found: C, 52.02; H, 4.47; N, 20.00; S, 15.70.

3-Amino-6-methoxypyridine-2[1*H*]-thione (10, R = OCH_3).—2-Amino-5-methoxythiazolo[5,4-*b*]pyridine (7, R = OCH_3) (18.1 g, 0.1 mol) containing 1 g of sodium sulfite was refluxed in 20% sodium hydroxide (150 ml) for 3 hr. Complete dissolution was achieved after 1 hr. The clear, yellowish brown solution was treated with activated charcoal, boiled, and filtered. Upon cooling and neutralizing with glacial acetic acid, a massive yellowish precipitate was obtained. It was purified quickly[15] by recrystallization from methanol after treating with charcoal again. Long, yellowish needles of 3-amino-6-methoxypyridine-2[1*H*]-thione (15.2 g, 97%) melting at 178–179° dec were obtained after drying in a vacuum oven at 5-mm pressure for 24 hr: uv spectrum (MeOH) λ_{max} 388 mμ (log ϵ 4.0947), λ_{min} 297 (2.4282), λ_{max} 270 (3.8102), λ_{min} 235 (3.5743); ir spectrum (Nujol) ν_{max} 3400, 3300, 1600, 1560, 1400, 1360, 1283, 1272, 1260, 1120, 1103, 1056, 1028, 1020, 890, 875, 778, 765 cm^{-1}; pmr spectrum (DMSO-d_6) τ 6.0 (singlet, 6-OCH_3), 3.50 (doublet, J = 9 Hz, 5-H),

(13) T. Takahashi and E. Yoshii, *Chem. Pharm. Bull.*, **2**, 382 (1954).

(14) C. O. Okafor, *J. Org. Chem.*, **32**, 2006 (1967); C. O. Okafor, *J. Med. Chem.*, **10**, 126 (1967).

(15) These 3-aminopyridine-2-thiones are unstable to heat and light. They are best recrystallized from methanol and oven dried at 50° (10 mm) and preserved in brown bottles wrapped with aluminium foil.

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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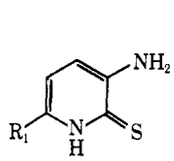
Compounds of 1,3,6-triazaphenothiazine, a new heterocyclic ring, are hereby described. Previously, no triazaphenothiazine compound was known. The synthesis of these compounds was achieved by acid-catalyzed reaction of suitably placed 3-aminopyridine-2[1*H*]-thiones with 5,6-dihalopyrimidines. Optimum 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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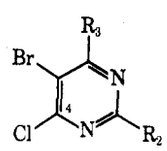

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