Syntheses of 1,3-Diazaphenothiazines.[1] I.

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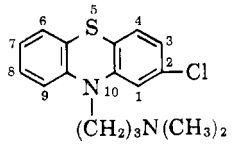
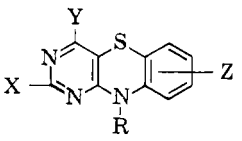
Excellent yields of 2,4-diamino-1,3-diazaphenothiazine have been obtained by the reaction of 2,4-disubstituted 5-bromo-6-chloropyrimidines with *o*-mercaptoaniline under either acidic or basic conditions. Using basic conditions, it was possible to isolate a stable intermediate, the 6-*o*-aminophenylmercaptopyrimidine, which subsequently could be made to rearrange and cyclize. Under acid conditions the identical diazaphenothiazine was obtained directly from the reactants.

The chemical structure of the well known tranquillizer drug, chlorpromazine, I, has been modified extensively by numerous workers. Most of the earlier variations



I

involved changes in the structure of the side chain at position 10 and in the substituent at position 2. More recently a number of investigators have modified the chlorpromazine structure by the introduction of another heteroatom, nitrogen, in the positions 1,[2] 2,[3] 3,[4] and 4[5] of the phenothiazine ring to give monoazaphenothiazines. It seemed worthwhile to attempt to prepare some analogous diazaphenothiazines,[6] such as II.



II

X and/or Y = H, alkyl, OH, NH_2, $N(R_1)(R_2)$, halogen, etc.
Z = H, halogen, etc.
R = H, alkyl, ω-aminoalkyl, etc.

Of several routes considered by us for the syntheses of diazaphenothiazines, those described in this paper are the first successfully completed. These syntheses were accomplished by the reaction of *o*-mercaptoaniline with suitably substituted 5-bromo-6-chloropyrimidines.[7]

Figure 1 shows two alternative routes used for the preparation of 2,4-diamino-5-bromo-6-chloropyrimidine VI. Replacement of the hydroxy group of 2,4-diamino-6-hydroxypyrimidine, III, by chlorine with phosphorus oxychloride gave 2,4-diamino-6-chloropyrimidine, IV, which was then brominated in the 5 position to give VI. This bromination was done in aqueous methanol keeping the solution near neutrality by the addition of sodium bicarbonate, in order to neutralize the hydrobromic acid liberated in the reaction, which otherwise might promote hydrolysis of the 6-chlorine. Compound VI was also obtained by bromination of III in the 5-position, to give V, in which the 6-hydroxy group was then replaced by chlorine using phosphorus oxychloride. Employing essentially the same procedure, except bubbling chlorine gas into the solution, 2,4-diamino-5,6-dichloropyrimidine was also prepared.

As shown in Fig 2, the chlorobromopyrimidine (VI) reacted with *o*-mercaptoaniline under two different sets of conditions to give the desired 1,3-diazaphenothiazine, IX.

The success of these syntheses, as planned, depended on several features of reactivity peculiar to pyrimidine derivatives. The reactivity for nucleophilic replacement reactions of halogens in the 2-, 4-, or 6-positions of pyrimidines is well known, while halogen in the 5-position is relatively inert.[8] Furthermore, Banks[9] showed that the reaction of aromatic amines with such chloropyrimidines was greatly accelerated by the use of acid catalysts.

While the mercapto group of *o*-mercaptoaniline is more nucleophilic than the amino group, it was hoped that use of the acid-catalyzed procedure of Banks[9] (see upper route of Fig. 2) would both favor the replacement of the 6-chlorine of the pyrimidine, VI, by the anilino nitrogen, and also possibly minimize attack by the sulfur. If the 6-(*o*-mercaptoanilino)pyrimidine intermediate, VII (shown in brackets in Fig. 2), were formed, it seemed almost certain that it could be cyclized readily to the diazaphenothiazine IX (Fig. 2). The cyclization perhaps would require the use of a weak base catalyst to generate the even more nucleophilic mercaptide anion to react with the relatively inert 5-bromo group. In the intermediate shown, VII, it seemed that the combination of the high nucleophilicity of the sulfur and the favorable steric arrangement within the molecule, should ensure the success of the reaction. Interestingly, under the Banks-type reaction conditions, the diazaphenothiazine, IX, was obtained directly from the acid

(1) Presented at the Metropolitan Regional Meeting, American Chemical Society, New York, N. Y., January, 1962.

(2) (a) W. A. Schuler and H. Klebe, German Patent 964,050 (1957); U. S. Patent 2,974,139 (1961); *Ann.*, **653**, 172 (1962); (b) H. L. Yale and F. Sowinski, *J. Am. Chem. Soc.*, **80**, 1651 (1958); (c) A. v. Schlichtegroll, *Arzeneimittel Forsch.*, **7**, 237 (1957); **8**, 489 (1958).

(3) (a) A. J. Saggiomo, P. N. Craig, and M. Gordon, *J. Org. Chem.*, **23**, 1906 (1958); (b) P. N. Craig, M. Gordon, J. J. Lafferty, B. Lester, M. Pavloff, and L. Zirkle, *ibid.*, **25**, 944 (1960).

(4) V. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 591 (1945).

(5) T. Takahashi and E. Yoshii, *Pharm. Bull.* (Tokyo), **2**, 382 (1954); *Chem. Abstr.*, **50**, 13032e (1956).

(6) Independent syntheses of compounds containing this ring system have also been reported: (a) A. Westermann, O. Bub, and L. Suranyi, D.R. Patent 1,110,651 (1961); *Chem. Abstr.*, **56**, 2461*a* (1962); (b) B. Roth, L. Schloemer, and G. H. Hitchings, 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

(7) Several such bromochloropyrimidines had been made and used in an earlier investigation from these laboratories: A. P. Phillips and A. Maggiolo, *J. Am. Chem. Soc.*, **74**, 3922 (1952); *cf.* also C. C. Price, N. J. Leonard, and R. H. Reitsema; *ibid.*, **68**, 766 (1946); E. Ochiai and Y. Ito, *J. Pharm. Soc. Japan*, **57**, 579 (1937); *Chem. Abstr.*, **31**, 6238[6] (1937).

(8) Although 5-halogenopyrimidines have usually been found to be inert in displacement reactions, when activated by the presence of one or more C=O groups in the 4- and 2-position as in 5-bromouracil [A. P. Phillips, *J. Am. Chem. Soc.*, **73**, 1061 (1951)] and 5-bromoisocytosine [A. P. Phillips, *ibid.*, **75**, 4092 (1953)], replacement of the bromo by amines has been accomplished.

(9) C. K. Banks, *ibid.*, **66**, 1131 (1944).

reaction mixture in yields of 70–90% after about two hours of warming.

Similarly, 2,4-diamino-5,6-dichloropyrimidine reacted with *o*-mercaptoaniline under acid-catalyzed conditions to give IX in excellent yield. Under identical conditions of acid catalysis 2,4-diamino-5-bromo-6-chloropyrimidine reacted with aniline to give 2,4-diamino-5-bromo-6-anilinopyrimidine in excellent yield.

When the chlorobromopyrimidine, VI, and *o*-mercaptoaniline were combined in ethanol solution containing an excess of triethylamine, a nearly quantitative yield of the sulfide intermediate, VIII, 2,4-diamino-5-bromo-6-*o*-aminophenylmercaptopyrimidine, was obtained rapidly after a brief period of heating. The basic reaction conditions were used in this case in order to favor the displacement of the 6-chloro by the mercaptide anion. In the intermediate, VIII, presumably the same steric relationship, favorable for cyclization, exists as in the postulated isomeric intermediate, VII. Because of the lower nucleophilicity of the anilino nitrogen *no easy displacement* of the inert 5-bromo by it should be anticipated. As expected, VIII was easily isolable, and was stable to handling, to recrystallization, and to heating to its melting point.

The ultraviolet spectrum obtained from VIII was substantially in agreement with that of 2,4-diamino-5-bromo-6-phenylmercaptopyrimidine. This was prepared from 2,4-diamino-5-bromo-6-chloropyrimidine and thiophenol in a solution of ethanol containing triethylamine. The ultraviolet spectrum of VIII differed significantly from that of the diazophenothiazine product IX, and from that of 2,4-diamino-5-bromo-6-anilinopyrimidine (see Experimental).

Using triethylamine as a solvent 2,4-diamino-6-chloropyrimidine reacted with *o*-mercaptoaniline to form 2,4-diamino-6-(*o*-aminophenylmercapto)pyrimidine as expected.

The stable sulfide intermediate, VIII, was transformed rapidly, cleanly, and nearly quantitatively, by warming for a short period (ten to twenty minutes) in alcoholic hydrogen chloride, into the same diazaphenothiazine, IX, obtained previously. This transformation most probably involves a Smiles-type[10,11] rearrangement. A reasonable but tentative representation of the mode of acid-catalyzed Smiles-type rearrangement involved here is outlined in Fig. 3.

In acid solution, protonization of the pyrimidine ring at the 1-nitrogen should activate the 6-position for an initial intramolecular attack of the sulfide bond by the anilino nitrogen. Subsequently, a nearly synchronous rupture of sulfide bond at the 6-position of the pyrimidine should place the newly formed and highly nucleophilic sulfide anion in a favorable steric position such that rotation, around the newly formed carbon–nitrogen bond, would allow the mercaptide ion to attack the carbon–bromine bond at the adjacent 5-position. In the cyclic five-membered transition state hypothesized the two rings would appear in a spiro-type arrangement of two planes at right angles.

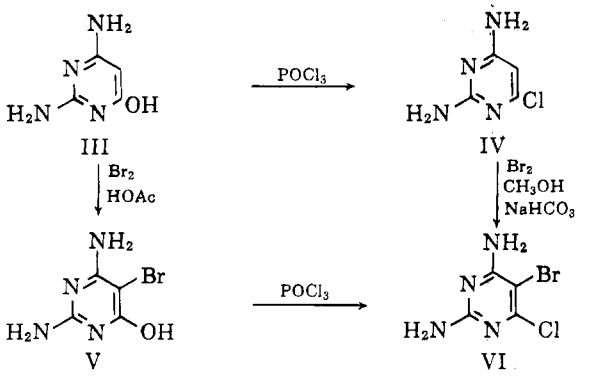


Figure 1

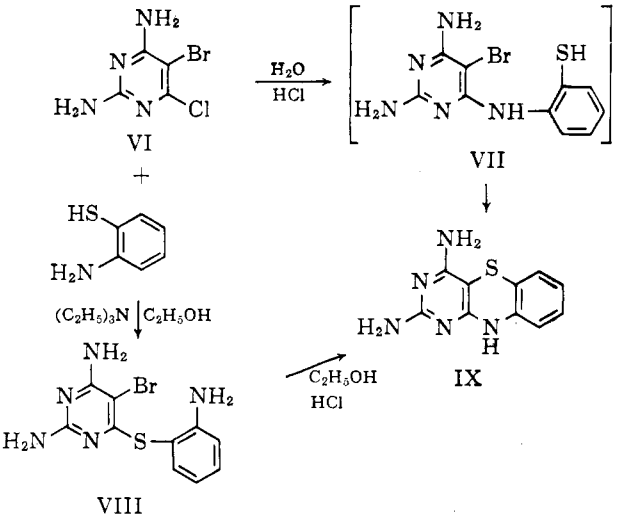


Figure 2

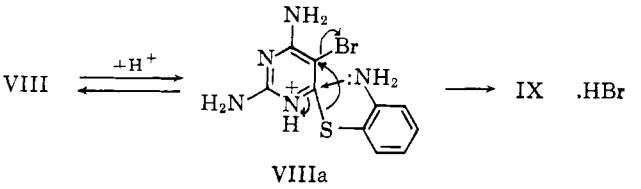


Figure 3

Experimental[12]

2,4-Diamino-5-bromo-6-chloropyrimidine (Compound VI).—To a rapidly stirred solution of a mixture of 15 g. (0.1 mole) of 2,4-diamino-6-chloropyrimidine (m.p. 202°) and 10 g. of sodium bicarbonate in 300 ml. of 50% aqueous methanol, was added dropwise a solution of 16 g. of bromine in 50 ml. of methanol over 30 min. After half the amount of bromine had been added, 5 g. of additional solid sodium bicarbonate was added to the reaction mixture. It was stirred for a total of 1.5 hr. The flocculent precipitate which separated was filtered off and washed with water. The product, 14 g. (62% yield), was crystallized from boiling water, m.p. 217°.

Anal. Calcd. for $C_4H_4BrClN_4$: C, 21.5; H, 1.8; N, 25.0. Found: C, 21.3; H, 1.6; N, 25.3.

Ultraviolet spectra: at pH 1: λ_{max} 300, ϵ 5480, λ_{min} 270, ϵ 1400; at pH 11: λ_{max} 296, ϵ 6750, λ_{min} 265, ϵ 1170.

2,4-Diamino-5,6-dichloropyrimidine.—The previous procedure was used except the pH was maintained at 6–6.5 by the addition of an aqueous methanolic solution of sodium bicarbonate and the chlorine gas was bubbled through the solution. The product, obtained in 50% yield, was crystallized twice from 20% methanol–water solution, m.p. 218°.[13]

(10) While the Smiles rearrangement of benzenoid compounds is usually accomplished in basic media, it is quite reasonable that this sort of migration in the pyrimidine series should be facilitated by acid catalysis, just as is the bimolecular displacement of the 6-chlorine by aniline.

(11) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 181 (1935).

(12) All melting points are uncorrected. All ultraviolet spectra in 50% aqueous methanol.

(13) S. J. Childress and R. L. McKee, *J. Am. Chem. Soc.*, **72**, 4271 (1950), reported m.p. 218°. This was a by-product in 11% yield.

Anal. Calcd. for $C_4H_4Cl_2N_4$: C, 26.8; H, 2.2; N, 31.3. Found: C, 26.8; H, 2.2; N, 30.8.

Ultraviolet spectra: at pH 1: λ_{max} 297, ϵ 6440, λ_{min} 265, ϵ 2480; at pH 11: λ_{max} 295, ϵ 7700, λ_{min} 265, ϵ 2200.

2,4-Diamino-5-bromo-6-phenylmercaptopyrimidine.—This was a model compound prepared to compare its spectral data with those of compound VIII.

A mixture of 2.3 g. (0.01 mole) of 2,4-diamino-5-bromo-6-chloropyrimidine and 1.1 g. (0.01 mole) of thiophenol in 50 ml. of ethanol containing 4 ml. of triethylamine was refluxed for 2 hr. The product was recrystallized successively from aqueous ethanol, aqueous methanol, and finally from an ethyl acetate–hexane mixture whereupon 1.5 g., m.p. 183–185°, was obtained.

Anal. Calcd. for $C_{10}H_9BrN_4S \cdot H_2O$: C, 38.1; H, 3.5. Found: C, 38.3; H, 3.3.

Ultraviolet spectra: at pH 1: λ_{max} 312, ϵ 15,300, λ_{min} 270, ϵ 5680; at pH 11: λ_{max} 301, ϵ 13,510, λ_{min} 270, ϵ 5620.

2,4-Diamino-5-bromo-6-anilinopyrimidine.—This was a model compound prepared to contrast with the spectral data of compounds VIII and IX.

A mixture of 0.01 mole of 2,4-diamino-5-bromo-6-chloropyrimidine and 1.5 g. of aniline hydrochloride in 50 ml. of water was heated at 100° for 3 hr. It was left at room temperature overnight when 1.5 g. of water-insoluble material separated. The aqueous filtrate was made basic with ammonia to pH 10. The basic product, after repeated crystallization from acetone, weighed 1 g., m.p. 208–209°.

Anal. Calcd. for $C_{10}H_{10}BrN_5$: C, 42.9; H, 3.6; N, 25.0. Found: C, 42.8; H, 3.6; N, 25.2.

Ultraviolet spectra: at pH 1: λ_{max} 295, ϵ 21,400, λ_{min} 270, ϵ 7800; at pH 11: λ_{max} 292, ϵ 21,700, λ_{min} 270, ϵ 9800.

2,4-Diamino-5-bromo-6-(*o*-aminophenylmercapto)pyrimidine (Compound VIII).—To a solution of 1.5 g. (0.012 mole) of *o*-mercaptoaniline in 80 ml. of ethanol containing 4 ml. of triethylamine was added 2.3 g. (0.01 mole) of 2,4-diamino-5-bromo-6-chloropyrimidine. The mixture was heated for 2 hr. on the water bath. Ethanol and excess triethylamine were removed by evaporation *in vacuo*. The residue was washed successively with ether and water to remove any triethylamine hydrochloride. The product, 2.7 g. (90%), crystallized as fluffy white crystals from methanol, m.p. 175–176°.

Anal. Calcd. for $C_{10}H_{10}BrN_5S$: C, 38.4; H, 3.2; N, 22.4. Found: C, 38.6; H, 3.0; N, 22.5.

Ultraviolet spectra: at pH 1: λ_{max} 312, ϵ 14,350, λ_{min} 275, ϵ 4140; at pH 11: λ_{max} 303, ϵ 14,200, λ_{min} 270, ϵ 3,280.

2,4-Diamino-5-chloro-6-(*o*-aminophenylmercapto)pyrimidine.—A solution of 1.8 g. of 2,4-diamino-5,6-dichloropyrimidine and 1.3 g. of *o*-mercaptoaniline in 70 ml. of triethylamine was refluxed for 45 min. An oily layer separated. The solvent was decanted and the oily product solidified on scratching to a waxy mass. It was washed successively with additional triethylamine and water. Recrystallization from acetone gave 2.8 g., m.p. 175–176°.

Anal. Calcd. for $C_{10}H_{10}ClN_5S$: C, 44.9; H, 3.7; N, 26.2. Found: C, 45.0; H, 3.6; N, 25.8.

2,4-Diamino-6-(*o*-aminophenylmercapto)pyrimidine.—This was prepared by the same procedure as that used for compound VIII from 10 g. of 2,4-diamino-6-chloropyrimidine and 9 g. of *o*-mercaptoaniline in 100 ml. of triethylamine solution containing 15 ml. of ethanol. On repeated crystallization from methanol there was obtained 7.5 g. of needles, m.p. 221–222°.

Anal. Calcd. for $C_{10}H_{11}N_5S$: C, 51.5; H, 4.7; N, 30.0. Found: C, 51.7; H, 4.9; N, 29.9.

Ultraviolet spectra: at pH 1: λ_{max} 287, ϵ 12,000, λ_{min} 265, ϵ 7240; at pH 11: λ_{max} 287, ϵ 11,300, λ_{min} 265, ϵ 5500.

2,4-Diamino-1,3-diazaphenothiazine (Compound IX). Method A.—A solution of 2.3 g. (0.01 mole) of 2,4-diamino-5-bromo-6-chloropyrimidine and 1.5 g. (0.012 mole) of *o*-mercaptoaniline in 100 ml. of water containing a few drops of concentrated hydrochloric acid[14] was heated for 2 hr. on a water bath. A clear yellow solution resulted within 15–20 min. On cooling a turbidity (disulfide) appeared. The solution was filtered and the product was precipitated from the clear filtrate by the addition of ammonia to pH 8–10. Recrystallization from acetone gave 2.1 g. (90%) of yellow crystals, m.p. 255–256°.

Anal. Calcd. for $C_{10}H_9N_5S$: C, 52.0; H, 3.9; N, 30.3; S, 13.8. Found: C, 52.2; H, 4.3; N, 30.3; S, 13.8.

Ultraviolet spectra: at pH 1: λ_{max} 268, ϵ 29,940, λ_{max} 295, ϵ 6600, λ_{min} 291, ϵ 6580; at pH 11: λ_{max} 255, ϵ 30,000, λ_{max} 293, ϵ 5940, λ_{min} 277, ϵ 4130.

The **hydrochloride** salt of the base was obtained by the addition of ethanolic hydrogen chloride to the acetone solution of 1 g. of this base. After recrystallization from methanol–ether mixtures, it melted at 336–337° dec.

Anal. for $C_{10}H_9N_5S \cdot HCl$: C, 44.8; H, 3.6; N, 26.2. Found: C, 45.0; H, 3.8; N, 25.6.

Compound IX was also obtained readily using 2,4-diamino-5,6-dichloropyrimidine with *o*-mercaptoaniline under the conditions of method A. When liberated as the base and recrystallized from acetone it melted at 255–256°.

Method B.—To a suspension of 7 g. (0.023 mole) of 2,4-diamino-5-bromo-6-(*o*-aminophenylmercapto)pyrimidine in 100 ml. of ethanol was added excess ethanolic hydrogen chloride to pH 1–2. After heating on a water bath for 10–20 min. the original white precipitate dissolved to give first a clear deep yellow solution after which a deep yellow precipitate separated. The product, m.p. 335–337° dec., was obtained in 95% yield. The mixture melting point with the hydrochloride, obtained by method A, was undepressed. The spectral and analytical data were identical.

This hydrochloride when neutralized afforded a base identical with that described previously.

Alternatively, when a clear solution of 1 g. of 2,4-diamino-5-chloro-6-(*o*-aminophenylmercapto)pyrimidine in 20 ml. of methanolic hydrogen chloride was warmed in a water bath for 1 hr., a precipitate appeared. It was worked up as before whereupon recrystallization from methanol–ether mixtures gave the product, m.p. 335–337°. The mixture melting point with the product from method B above was undepressed.

Acknowledgment.—The authors wish to thank Ronald E. Brooks for his assistance in the early part of this project.

(14) Alternatively, the hydrochloride salt of *o*-mercaptoaniline could be used without any additional acid.