An Unusual Molecular Rearrangement of an N-Aminopyrimidine[1]

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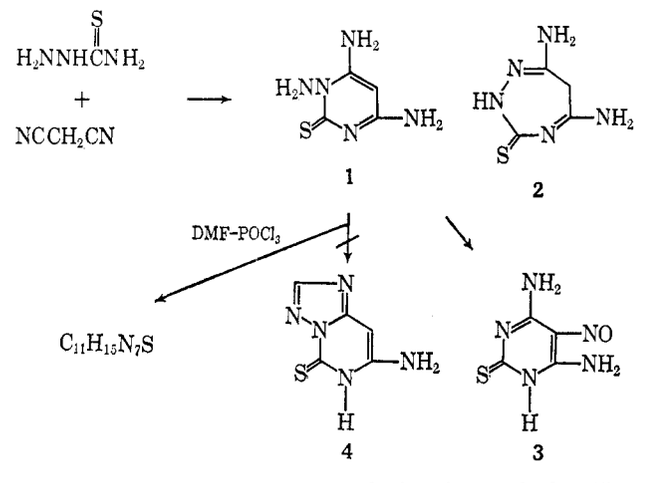
Condensation of malononitrile with thiosemicarbazide in ethanolic sodium ethoxide has been shown to give 1,4,6-triamino-2(1H)-pyrimidinethione (**1**). Treatment of **1** with dimethylformamide and phosphorus oxychloride results in an unusual molecular rearrangement involving the participation of doubly bonded sulfur as a neighboring group to give 2-thiocyanato-4,6-bis(dimethylaminomethylenamino)pyrimidine (**7**). The mechanism of the formation of **7** and its chemical and physical properties are discussed.

The condensation of thiourea with malononitrile in the presence of ethanolic sodium ethoxide to give 4,6-diamino-2(1H)-pyrimidinethione has for many years been the initial step in various purine syntheses.[3,4] We wish to describe in this paper the nature of the product formed by reaction of malononitrile with thiosemicarbazide and an unusual molecular rearrangement observed upon treatment of this product with dimethylformamide and phosphorus oxychloride (*i.e.*, Vilsmeier–Haack formylation conditions).

Addition of an ethanolic solution of malononitrile to a refluxing mixture of thiosemicarbazide and sodium ethoxide in ethanol[5] gave in fair yield 1,4,6-triamino-2(1H)-pyrimidinethione (**1**); the isomeric triazepine structure **2** was eliminated by the similarity of the ultraviolet absorption spectrum of **1** with the spectrum of 4,6-diamino-2(1H)-pyrimidinethione[3] and by nitrosation to 4,6-diamino-5-nitroso-2(1H)-pyrimidinethione (**3**),[4] identical with an authentic sample.[6] (See Scheme I).

SCHEME I



In an attempt to prepare derivatives of the "isopurine" system **4**, 1,4,6-triamino-2(1H)-pyrimidinethione (**1**) was treated with the dimethylformamide–phosphorus oxychloride complex,[7] which has been shown to be both a mild formylating agent[8] and an effective agent for converting 4,5-diaminopyrimidines into purines.[9] Instead of the expected cyclization product **4**, a compound $C_{11}H_{15}N_7S$ was isolated with unexpected physical characteristics. Its infrared spectrum showed the absence of N–H or S–H bands and a sharp band at 2172 cm^{-1}. In marked contrast to the starting N-aminopyrimidine **1**, this new product was soluble in relatively nonpolar solvents such as chloroform and acetone.

A product with the correct empirical formula ($C_{11}H_{15}N_7S$) may be derived from **1** by initial conversion to 1,4,6-tris(dimethylaminomethylenamino)-2(1H)-pyrimidinethione (**5**),[10] followed by loss of 1 mole of dimethylamine. Two possible pathways for the latter step are detailed in Scheme II; one leads to 1-isocyanato-4,6-bis(dimethylaminomethylenamino)-2(1H)-pyrimidinethione (**6**), while the other leads to its structural isomer, 2-thiocyanato-4,6-bis(dimethylaminomethylenamino)pyrimidine (**7**). The chemical and physical properties of this product which allow its unequivocal formulation as **7** are outlined below. To our knowledge, the conversion of **1** to **7** represents not only an unusual molecular rearrangement involving N–N bond cleavage, but a novel example of neighboring-group participation by doubly bonded sulfur.[11]

The infrared band at 2172 cm^{-1} suggests a thiocyanato[12] or perhaps a cyano substituent. The latter, however, which can only arise here by an isocyanide–nitrile rearrangement, appears unreasonable since there is no precedent for such a rearrangement under the mild conditions of this reaction (room temperature for 2 hr). Indeed, this type of rearrangement customarily requires heating for prolonged periods or under pressure.[13,14] The 2172-cm^{-1} band is too high to be compatible with structure **6**, for the only known examples of N-isocyanide groupings exhibit infrared bands at lower wavenumbers. For example, both

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(2) National Science Foundation Summer Fellow, 1961; National Institutes of Health Predoctoral Fellow, 1961–1964.

(3) W. Traube, *Ann. Chem.*, **331**, 64 (1904).

(4) A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **70**, 3109 (1948).

(5) These "inverse addition" conditions were chosen to minimize dimerization of malononitrile in the sodium ethoxide solution; see E. C. Taylor and K. S. Hartke, *ibid.*, **81**, 2452 (1959).

(6) Concurrent with the present work, an analogous condensation was effected [E. Carstens, H. G. Kazmirowski, and J. Donat, East German Patent 23,546 (1963); *Chem. Abstr.*, **58**, 9103 (1963)] by treatment of 1,1-dimethylthiosemicarbazide with ethyl cyanoacetate in ethanolic sodium ethoxide solution to give 1-dimethylamino-6-amino-4(3H)-oxo-2(1H)-pyrimidinethione.

(7) Z. Arnold and A. Holy, *Collection Czech. Chem. Commun.*, **27**, 2886 (1962).

(8) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(9) J. Clark and J. H. Lister, *ibid.*, 5048 (1961).

(10) Reaction of 4,5-diamino-6-fluoropyrimidine under these conditions has been shown to give 4,5-bis(dimethylaminomethylenamino)-6-fluoropyrimidine rather than 6-fluoropurine: A. C. Beaman and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 1067 (1962).

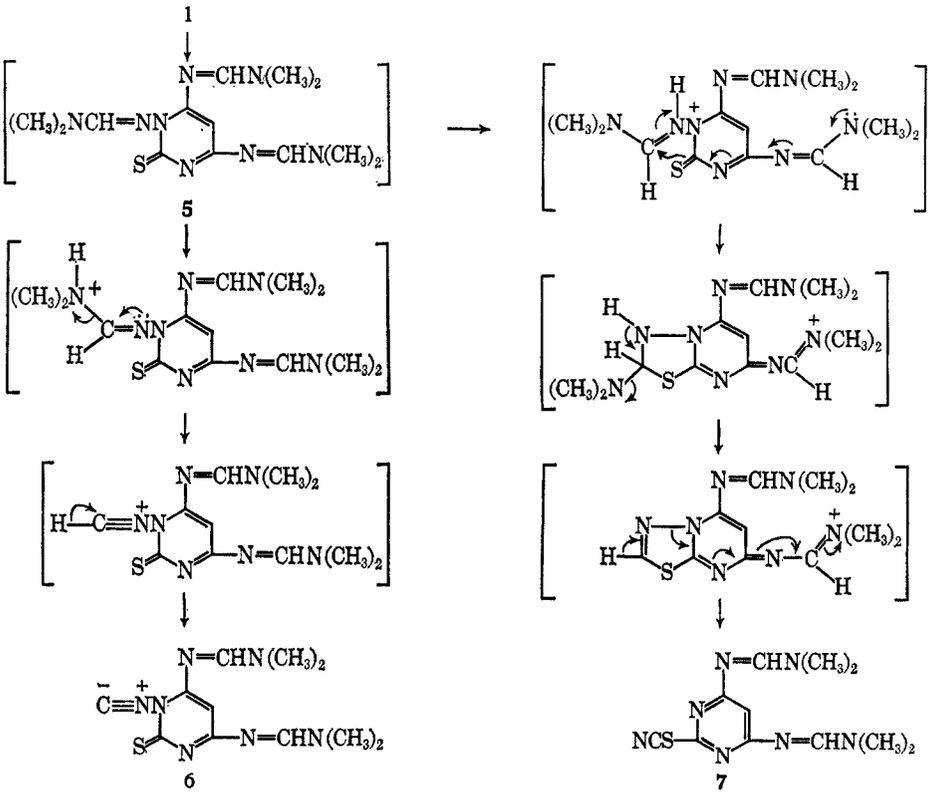
(11) For a preliminary account of this work, see E. C. Taylor and R. W. Morrison, Jr., *Angew. Chem.*, **77**, 859 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 868 (1965).

(12) Aromatic thiocyanates exhibit infrared absorption bands in the approximate region between 2175 and 2160 cm^{-1}: K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 28.

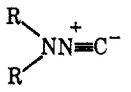
(13) F. W. Schneider and B. S. Rabinovitch, *J. Am. Chem. Soc.*, **85**, 2365 (1963).

(14) J. Casonova, Jr., N. D. Werner, and R. E. Schuster, *J. Org. Chem.*, **31**, 4373 (1966).

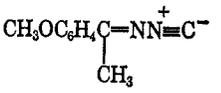
SCHEME II



diethylamino isocyanide (**8a**) and di-*n*-butylamino isocyanide (**8b**) give a characteristic infrared band at



8a, R = C_2H_5
b, R = *n*-C_4H_9



9

2100 cm^{-1},[15] while the α,β-unsaturated compound **9** absorbs at 2080 cm^{-1}.[16] There was no report that these N-isocyanides showed any tendency to rearrange to the corresponding nitriles.

The compound under study also showed hydrolysis behavior in conflict with that expected for an N-isocyanopyrimidine (**6**),[17] but consistent with the thiocyanatopyrimidine (**7**) formulation.[18] Reaction with hot benzylamine, dilute sodium hydroxide at room temperature, or refluxing ethanolic ammonia, or fusion with urea, produced 4,6-diamino-2(1H)-pyrimidinethione (**10**).[19] Dilute hydrochloric acid (0.5 *N*) at room temperature effected hydrolysis of **7** to 2-thiocyanato-4-dimethylaminomethylenamino-6-aminopyrimidine (**11**). This partial conversion was apparently a basic hydrolysis, with water acting as the base, since no hydrolysis occurred with 6 *N* hydrochloric acid under the same conditions. This product showed an infrared absorption band at 2170 cm^{-1} and also reacted with hot benzylamine to give 4,6-diamino-2(1H)-pyrimidinethione (**10**). Refluxing 6 *N* hydrochloric acid, however, effected hydrolysis to barbituric acid which was isolated as its ammonium salt (**12**). Finally, treatment of **7** with glacial acetic acid, aqueous acetic acid, or formic acid in ethyl acetate gave in each case 2-thiocyanato-4,6-bis(formylamino)pyrimidine (**13**). This product exhibited an infrared absorption band at 2190 cm^{-1} and was also converted into **10** with benzylamine. (See Scheme III.)

Further evidence against the N-isocyanide (**6**) formulation but in accord with the thiocyanate (**7**) structure was revealed by reaction behavior with halogens. Isocyanides have been shown to add bromine and chlorine at the terminal carbon to give 1,1-dihalo compounds.[13,20] However, treatment of the reaction product **7** with bromine in chloroform gave a compound containing only one bromine atom and which still exhibited the characteristic infrared absorption band at 2163 cm^{-1}. The product thus appears to be 2-thiocyanato-4,6-bis(dimethylaminomethyleneamino)-5-bromopyrimidine (**14**).

Treatment of **7** with chlorine in acetic acid followed by hydrolysis of the crude product with dilute hydrochloric acid gave 2,5-dichloro-4,6-diaminopyrimidine (**15**).[21,22] Displacement of the 2-thiocyanato group in

(15) H. Bredereck, B. Folisch, and K. Walz, *Angew. Chem.*, **74**, 388 (1962).

(16) I. Hagedorn and U. Eholzer, *ibid.*, **74**, 499 (1962).

(17) Isocyanides are known to be inert to hot, aqueous alkali, although they hydrolyze with aqueous mineral acids to give formic acid and the corresponding amines [A. Gautier, *Ann. Chim.* (Paris), **17** (4), 217 (1869)]. Carboxylic acids hydrate isocyanides to give formamides, becoming themselves converted to anhydrides (CO in the case of formic acid) [J. U. Nef, *Ann. Chem.*, **270**, 267 (1892)]. Thus, compounds **8a** and **8b** hydrolyze with formic acid in ethyl acetate to give the corresponding formylhydrazines and CO.[15]

(18) Thiocyanates, as contrasted with isonitriles, are hydrolyzed more readily by bases than by acids [D. S. Tarbell and D. P. Harnisch, *Chem. Rev.*, **49**, 1 (1951)]. Several pyrimidinethiones have been isolated as basic hydrolysis products of the corresponding thiocyanatopyrimidines [T. Naito and S. Inoue, *Chem. Pharm. Bull.* (Tokyo), **6**, 338 (1958); W. Trzcinski, *Ber.*, **16**, 1057 (1883)].

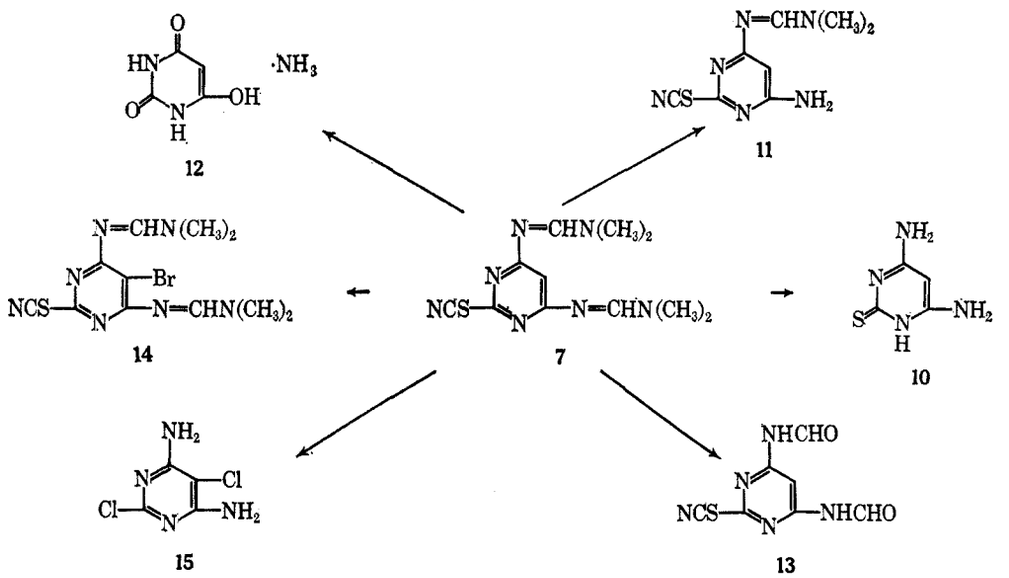
(19) These conversions of **7** into **10** eliminate the possibility, albeit remote, that the thiocyanato group had rearranged to an isothiocyanato group.

(20) J. U. Nef, *Ann. Chem.*, **280**, 297 (1894).

(21) E. C. Taylor and P. Drenchko, *J. Am. Chem. Soc.*, **74**, 1101 (1952).

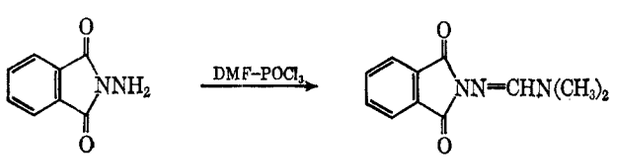
(22) S. J. Childress and R. L. McKee, *ibid.*, **72**, 4271 (1950).

SCHEME III



7 by chlorine is reasonable, since mercapto and alkylmercapto groups attached to pyrimidine and purine rings are known to undergo analogous displacement reactions with chlorine.[23-26] This conversion is likewise incompatible with the isocyanide (6) formulation, since its conversion into **15** with chlorine would require N–N bond cleavage. Treatment of the N-amino compound **1** with chlorine under similar conditions, followed by acid hydrolysis, did not give **15**.

It is interesting to note that reaction of N-aminophthalimide (**16**) with the dimethylformamide–phosphorus oxychloride complex gave only N-(dimethylaminomethyleneamino)phthalimide (**17**). Since **17** does not contain suitably situated thioxo and amino groups for participation in the elimination of dimethylamine, reaction stops at the amidine stage.



16 **17**

Experimental Section

1,4,6-Triamino-2(1H)-pyrimidinethione (1).—Into a three-necked round-bottomed flask fitted with a mechanical stirrer, dropping funnel, and reflux condenser with drying tube was placed 100 ml of absolute ethanol and 4.60 g (0.20 mole) of sodium. After the sodium had reacted, 18.22 g (0.20 mole) of thiosemicarbazide was added and the mixture was refluxed on the steam bath for 1 hr. Then a solution of 13.21 g (0.20 mole) of malononitrile in 20 ml of absolute ethanol was added dropwise over a period of 2 hr to the refluxing mixture. Refluxing was continued for 18 hr and the mixture was filtered while hot to give 10.62 g (34%) of a pale ivory solid, mp 261° dec (rapid heating). Recrystallization from water (charcoal) gave colorless needles: mp 265° dec (rapid heating); $\lambda_{max}^{H_2O}$ 212, 244, 291 mμ; ε 26,200, 18,700, 14,600.

Anal. Calcd for $C_4H_7N_5S$: C, 30.56; H, 4.49; N, 44.55. Found: C, 30.40; H, 4.48; N, 44.28.

4,6-Diamino-5-nitroso-2(1H)-pyrimidinethione (3).—A solution of 0.2 g of 1,4,6-triamino-2(1H)-pyrimidinethione in 20 ml of 0.5 *N* acetic acid was treated with 0.5 g of sodium nitrite and the mixture was warmed slightly. A heavy green precipitate formed which was collected and washed with water and acetone. Comparison of the infrared and ultraviolet spectra of this material with those of a freshly prepared authentic sample of 4,6-diamino-5-nitroso-2(1H)-pyrimidinethione (prepared by treatment of 4,6-diamino-2(1H)-pyrimidinethione with nitrous acid)[4] indicated that the two compounds were identical.

2-Thiocyanato-4,6-bis(dimethylaminomethylenamino)pyrimidine (7).—A 250-ml erlenmeyer flask, with an attached drying tube, containing 150 ml of dimethylformamide was placed in an ice bath. Into this chilled flask was introduced 18.0 ml (0.195 mole) of phosphorus oxychloride in small portions. After 10 min, 5.00 g (0.0318 mole) of 1,4,6-triamino-2(1H)-pyrimidinethione was added with vigorous swirling until all of the solid had dissolved and the mixture was allowed to stand at room temperature for 2 hr. After chilling in an ice–water bath for 15 min, the reaction mixture was filtered through a sintered-glass funnel and sucked as dry as possible. A piece of aluminum foil was fastened over the top of the funnel during the filtration to prevent excess exposure to atmospheric moisture. The precipitate was then added to 300 ml of crushed ice with vigorous stirring in order to dissolve the precipitate as rapidly as possible. As soon as dissolution had been effected, the pH of the mixture was adjusted to 9–10 with 6 *N* sodium hydroxide. The white precipitate was filtered and washed well with ice water. It must be noted that both speed and low temperature were essential in this work-up. As much water as possible was removed by filtration and then the white product was dried overnight in the vacuum desiccator over phosphorus pentoxide to give 5.72 g (65%), mp 129–130°. Recrystallization from 1:2 acetone–petroleum ether (bp 60–70°) gave colorless needles: mp 130–131.5°; λ_{max}^{EtOH} 261, 332 mμ; ε 26,000, 35,900.

Anal. Calcd for $C_{11}H_{15}N_7S$: C, 47.62; H, 5.46; N, 35.35. Found: C, 47.96; H, 5.64; N, 35.32.

The infrared spectrum of this product showed the absence of absorption in the N–H and S–H stretching region, but a sharp band at 2172 cm^{-1}.

4,6-Diamino-2(1H)-pyrimidinethione (10) **from 7.**—2-Thiocyanato-4,6-bis(dimethylaminomethyleneamino)pyrimidine (0.1 g) was added to a few drops of benzylamine in a test tube. The mixture was warmed on a steam bath for about 15 min. During this time the solid dissolved and after a few minutes colorless crystals appeared. The product was collected and washed well with ethanol. Both a mixture melting point determination with an authentic sample and a comparison of infrared and ultraviolet spectra indicated that this product was 4,6-diamino-2(1H)-pyrimidinethione (**3**). Similar results were obtained upon treat-

(23) C. W. Noell and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 5997 (1959).
(24) E. Ballard and T. B. Johnson, *ibid.*, **64**, 794 (1942).
(25) J. M. Sprague and T. B. Johnson, *ibid.*, **57**, 2252 (1935).
(26) R. O. Roblin, Jr., and J. W. Clapp, *ibid.*, **72**, 4890 (1950).
(27) All melting points were determined on a Thomas–Hoover silicone oil bath and are uncorrected. Microanalyses were performed by the Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.; Spang Microanalytical Laboratories, Ann Arbor, Mich.; and Dr. G. Robertson, Florham Park, N. J. Ultraviolet spectra were determined on a Cary Model 11 recording ultraviolet spectrophotometer. Infrared spectra were determined on a Perkin-Elmer Model 237 B Infracord by the normal Nujol mull technique.

ment of **7** with 1 *N* sodium hydroxide for 10 hr at room temperature, with ethanolic ammonia under reflux for 7 hr, or upon fusion with urea.

2-Thiocyanato-4-amino-6-(dimethylaminomethylenamino)-pyrimidine (11).—A solution of 2.00 g of 2-thiocyanato-4,6-bis-(dimethylaminomethylenamino)pyrimidine in 0.5 *N* hydrochloric acid was allowed to stand at room temperature for 21 hr. The pH was then adjusted to 8 with 3 *N* sodium hydroxide and the precipitate was collected and washed with water to give 1.09 g (68%) of a white solid, mp 195°. Recrystallization from methanol gave colorless needles: mp 198.5–199°; λ_{max}^{EtOH} 212, 233, 264, 303 mμ; ε 14,800, 17,000, 19,600, 24,700.

Anal. Calcd for $C_8H_{10}N_6S$: C, 43.22; H, 4.54; N, 37.81. Found: C, 43.57; H, 4.75; N, 37.55.

This product exhibited an infrared band at 2170 cm^{-1} and reacted immediately with hot benzylamine to give 4,6-diamino-2(1H)-pyrimidinethione.[3]

Hydrolysis of 7 to Ammonium Barbiturate (12).—A solution of 15.00 g of 2-thiocyanato-4,6-bis(dimethylaminomethylenamino)-pyrimidine in 150 ml of 6 *N* hydrochloric acid was heated under reflux for 1 hr. The solution was cooled, adjusted to pH 4 with 28% ammonium hydroxide, and chilled. The precipitate was collected and washed with a small amount of cold water and then with acetone to give 4.74 g (60%) of a pale yellow solid, mp >350°. The analytical sample, mp >350°, was prepared by recrystallization from water. Both microanalysis and comparison of infrared spectra indicated that this compound was ammonium barbiturate (an authentic sample of the latter was prepared by dissolving barbituric acid in hot 1 *N* hydrochloric acid and neutralizing to pH 7 with 28% ammonium hydroxide).

Anal. Calcd for $C_4H_7N_3O_3$: C, 33.11; H, 4.87; N, 28.96. Found: C, 33.51; H, 4.71; N, 28.68.

2-Thiocyanato-4,6-bis(formylamino)pyrimidine (13). Method A.—A suspension of 2.00 g of 2-thiocyanato-4,6-bis(dimethylaminomethylenamino)pyrimidine in 35 ml of water was stirred while glacial acetic acid was added dropwise until all of the solid had dissolved. Stirring was continued for 22 hr at room temperature. The white gelatinous precipitate was then collected and washed with cold water until the filtrates were no longer acidic, yield 1.60 g (100%), mp 243–244° dec. Recrystallization from acetone gave a white amorphous solid: mp 249° dec; λ_{max}^{EtOH} 230, 284 (sh), 290 mμ; ε 53,200, 13,900, 15,000. This product showed a sharp infrared band at 2190 cm^{-1} and a broad band centered at 1710 cm^{-1}.

Anal. Calcd for $C_7H_5N_5O_2S$: C, 37.67; H, 2.26; S, 14.37. Found: C, 37.67; H, 2.46; S, 14.61.

Method B.—A solution of 1.0 g of 2-thiocyanato-4,6-bis(dimethylaminomethylenamino)pyrimidine in a mixture of 2 ml of 98% formic acid and 20 ml of ethyl acetate was allowed to stand overnight at room temperature. The solution was evaporated to dryness *in vacuo* and the residue was taken up and washed with ethanol. Both a mixture melting point determination and a comparison of infrared spectra indicated that this product was identical with that prepared above by method A.

Method C.—A solution of 0.40 g of 2-thiocyanato-4,6-bis(dimethylaminomethylenamino)pyrimidine in 5 ml of glacial acetic acid was allowed to stand overnight at room temperature. The solution was then concentrated *in vacuo* to an oil which was allowed to stand for 24 hr at room temperature. Water was then added to precipitate a white solid which was shown by comparison of infrared spectra to be identical with the product prepared above by method A. Reaction of this compound with benzylamine for a few minutes converted it to 4,6-diamino-2(1H)-pyrimidinethione in 70% yield.

2-Thiocyanato-4,6-bis(dimethylaminomethylenamino)-5-bromopyrimidine (14).—A dilute solution of bromine in chloroform (2:95) was added dropwise with stirring to a solution of 5.00 g of 2-thiocyanato-4,6-bis(dimethylaminomethylenamino)-pyrimidine in 50 ml of chloroform until a pale yellow color persisted. Stirring was continued for 0.5 hr and the white precipitate was collected, washed well with chloroform, and then with chloroform containing a little cyclohexene to remove traces of bromine, yield 2.39 g, mp 277° dec. This by-product was shown by independent synthesis (by passing hydrogen bromide into a chloroform solution of 2-thiocyanato-4,6-bis(dimethylaminomethylenamino)pyrimidine) to be a hydrobromide salt of the starting material (which can be regenerated by neutralization of the salt with ammonium hydroxide).

The filtrate (excluding the cyclohexene washings) was refiltered and shaken with a little water containing a few drops of 28% ammonium hydroxide to remove the excess bromine. The organic layer was washed several times with water, dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. The residue consisted of an off-white powder, yield 3.19 g (50%), mp 179–181°. Recrystallization from acetone gave pale yellow crystals: mp 180.5–181.5°; λ_{max}^{EtOH} 217, 267, 347 mμ; ε 12,000, 38,000, 43,000; ν_{max}^{Nujol} 2163 cm^{-1}. No further reaction was observed when this compound was allowed to stand overnight in a solution of chloroform containing excess bromine.

Anal. Calcd for $C_{11}H_{14}N_7BrS$: C, 37.08; H, 3.96; N, 27.52. Found: C, 37.30; H, 4.13; N, 27.39.

2,5-Dichloro-4,6-diaminopyrimidine (15).—Chlorine was bubbled for 1 hr into a solution of 1.00 g of 2-thiocyanato-4,6-bis-(dimethylaminomethylenamino)pyrimidine in 15 ml of glacial acetic acid. The excess chlorine was flushed out with a stream of dry nitrogen and the solution was concentrated *in vacuo*. The residual oil was treated with 30 ml of 0.5 *N* hydrochloric acid and the solution was allowed to stand overnight at room temperature. During this time, off-white crystals formed, yield 0.46 g (71%), mp 295–297°. Recrystallization from water (charcoal) gave colorless, fine needles on slow cooling: mp 300.5–301.5° (lit. mp 303–305°,[21] 302–304°[22]); λ_{max}^{EtOH} 218, 268 mμ; ε 38,600, 7200.

Anal. Calcd for $C_4H_4N_4Cl_2$: C, 26.84; H, 2.25; N, 31.30; Cl, 39.62. Found: C, 27.06; H, 2.32; N, 31.21; Cl, 39.48.

N-(Dimethylaminomethylenamino)phthalimide (17).—Slow addition of 20 ml of phosphorus oxychloride to 100 ml of chilled dimethylformamide was carried out with external cooling to keep the temperature of the reaction mixture below 10°. After the solution had warmed up to room temperature, 5.00 g of N-aminophthalimide[28] was added and the mixture was stirred overnight at room temperature. After chilling in an ice bath, the reaction mixture was filtered through a sintered-glass funnel. The precipitate was dissolved in a small amount of ice water and the solution was then adjusted to pH 7 with 6 *N* sodium hydroxide. The yellow product was collected and washed with water, yield 4.45 g (66%), mp 189–190°. Recrystallization from acetone gave yellow crystals: mp 189–190.5°; λ_{max}^{EtOH} 236, 292 mμ; ε 29,100, 2200.

Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.11; N, 19.35. Found: C, 61.01; H, 4.95; N, 19.62.

Registry No.—**1**, 4765-63-3; **7**, 4765-64-4; **11**, 4765-65-5; **12**, 13117-12-9; **13**, 4765-66-6; **14**, 13135-45-0; **15**, 13117-14-1; **17**, 13117-15-2.

(28) H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, 16 (1937).