slowly over the weekend leaving a tan gummy solid. This material was stirred vigorously with a mixture of 400 ml. of absolute ethanol and 400 ml. of benzene. The inorganic material was filtered and the filtrate taken to dryness *in vacuo* in a 45–50° water bath leaving 6.7 g. of a pinkish solid (80% yield) which gave an analysis corresponding to the monohydrate of the Mannich base. The amorphous form turned yellow at 250° and decomposed with gas evolved between 260° and 300°.

Anal. Calcd. for $C_9H_{12}N_4O + H_2O$: C, 51.3; H, 6.6; N, 26.7. Found: C, 51.3; H, 6.2; N, 27.0.

The anhydrous base was obtained by recrystallization from acetone with no change in melting properties.

Anal. Calcd. for $C_9H_{12}N_4O$: C, 56.3; H, 6.3. Found: C, 56.3; H, 6.1.

A quantitative yield of the methiodide was obtained using a slight excess of methyl iodide with the above Mannich base in methanol. This yellowish product melted at 228–229° dec.

Anal. Calcd. for $C_{10}H_{15}N_4OI$: C, 35.8; H, 4.5; N, 16.8. Found: C, 35.5; H, 4.8; N, 17.0.

4-Hydroxy-5-acetamide and 5-acetic acid pyrrolo[2,3-d]-pyrimidines. Five grams of the Mannich base and 5.7 g. of sodium cyanide were refluxed for 80 hr. in 60 ml. of ethanol and 15 ml. of water during which a volatile amine was liberated. Seventy milliliters of water and a small amount of Darco were added to the warm brown solution and filtered after shaking well. The solution was concentrated to one-third volume and chilled. Filtration yielded 0.9 g. of the amide. The filtrate was acidified with dilute hydrochloric acid to *p*H 1.0–2.0 and chilled overnight, yielding 3.3 g. of the acid after filtering and drying.

The amide was recrystallized from hot water yielding a white amorphous solid which turned yellow at 250–260°, then decomposed from 303–310°.

Anal. Calcd. for $C_9H_9N_4O_2$: C, 50.0; H, 4.2; N, 29.2. Found: C, 50.2; H, 4.2; N, 29.4.

The acid recrystallized from water as a pinkish solid decomposing between 225–235° (gas evolved).

Anal. Calcd. for $C_8H_7N_3O_2$: C, 49.8; H, 3.6; N, 21.7. Found: C, 49.9; H, 3.4; N, 21.5.

Reduction of the Mannich base. Into 200 ml. of absolute ethanol containing 15 g. of Raney nickel was added 6.9 g. of the Mannich base in a high pressure hydrogenator equipped for heating. The temperature was raised slowly to 140–145° over 4 hr. at 1000 p.s.i. initial pressure and held there for 15 hr. longer. The warm solution smelled of a volatile amine and was charcoal treated and filtered. The solvent was driven off over steam and the resulting residue was recrystallized from water, yielding 5.3 g. of white product which had an analysis corresponding to 4-hydroxy-5-methylpyrrolo[2,3-d]pyrimidine. The compound was similar to the preparation III by paper chromatography, infrared and ultraviolet spectra, melting properties and elemental analysis.

Anal. Calcd. for $C_7H_7N_3O$: C, 56.4; H, 4.7. Found: C, 56.2; H, 4.7.

Chloro compound derived from the above preparation. One gram of the above hydroxy compound derived by reduction of the Mannich base was treated with 20 ml. of phosphorus oxychloride by the exact procedure above yielding 0.75 g. of a chloro compound which after recrystallizing from benzene had the same melting point, infrared and ultraviolet spectra, nitrogen analysis, and R_f value as that of the 4-chloro-5-methylpyrrolo[2,3-d]pyrimidine prepared above. No melting point depression resulted with a mixture of both chloro compounds.

Anal. Calcd. for $C_7H_5N_3Cl$: N, 25.1. Found: N, 25.1.

Acknowledgment. Our thanks go to Mr. Charles Marr, Dr. Samuel Blackman, and Mrs. R. Purdy for their microanalytical contributions and to Miss L. Beauchamp for technical assistance.

TUCKAHOE, N. Y.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Studies in Purine Chemistry. X. Some Derivatives of 9-Aminopurines[1,2]

EDWARD C. TAYLOR, JOHN W. BARTON, AND WILLIAM W. PAUDLER

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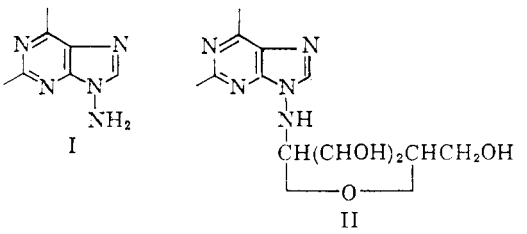
The synthesis of a number of derivatives of 6-methyl- and 6-methylmercapto-9-aminopurine has been carried out. Attempts to obtain 6-methyl-9-aminopurine itself by acid hydrolysis of 6-methyl-9-formylaminopurine or 6-methyl-9-(*p* aminobenzal)aminopurine led to ring expansion with the formation of 5-methyl-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine. Further treatment with acid then resulted in ring contraction of the latter compound to 6-methyl-9-aminopurine, which could not, however, be isolated because of its subsequent rapid hydrolysis to 4-hydrazino-5-amino-6-methylpyrimidine.

As a part of the intensive current effort to find more effective antitumor agents, considerable attention has been given to the field of purine chemistry in a search for potential antagonists of the naturally-occurring purines involved in nucleic acid biosynthesis. We wish to describe in this paper our preliminary efforts to prepare some representative 9-aminopurines (I) as examples of a class of derivative potentially capable of transformation into an interesting type of 'pseudo' nucleoside (II).



I II

2 - Mercapto - 4 - hydroxy - 5 - phenylazo - 6-methylpyrimidine (III), prepared from ethyl phenylazoacetoacetate and thiourea by a modifi-

(1) For the previous paper in this series, see E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960).

(2) This work was supported by grants to Princeton University from the American Cancer Society and the National Cancer Institute, National Institutes of Health, Public Health Service (Grant No. CY-2551).

cation of the method of Polonovski and Pesson,[3] was reduced with sodium hydrosulfite in dilute sodium hydroxide to give 2-mercapto-4-hydroxy-5-amino-6-methylpyrimidine (IV), which was then desulfurized with Raney nickel to 4-hydroxy-5-amino-6-methylpyrimidine (V). V could be converted in very low yield to 4-chloro-5-amino-6-methylpyrimidine (VI) with a mixture of phosphorus oxychloride and dimethylaniline, and to 4-mercapto - 5 - amino - 6 - methylpyrimidine (VII) in much better yield by treatment with phosphorus pentasulfide in pyridine. Methylation of VII in dilute sodium hydroxide yielded 4-methylmercapto - 5 - amino - 6 - methylpyrimidine (VIII). Treatment of either VI or VIII with hydrazine gave 4 - hydrazino - 5 - amino - 6 - methylpyrimidine (IX). Attempts to prepare IX from VII by replacement of the mercapto group with hydrazine were unsuccessful.

Reaction of 4-hydrazino-5-amino-6-methylpyrimidine (IX) with formic acid yielded two products which were separated by extraction with ethanol. The ethanol-soluble fraction was shown to be 6-methyl - 9 - *N* - formylaminopurine (X) by microanalysis and by comparison of its ultraviolet spectrum ($\lambda_{max}^{0.1N\ HCl}$ 263 mμ) with the spectrum of 9-aminopurine ($\lambda_{max}^{0.1N\ HCl}$ 262.5 mμ).[4] The ethanol-insoluble fraction was shown to be the formic acid salt of 5-methyl-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (XI) on the basis of microanalysis and comparison of its ultraviolet spectrum ($\lambda_{max}^{0.1N\ HCl}$ 245(sh), 330 mμ; ε 10,500, 9300) with the spectrum of 1-methyl-1,2-dihydropyrimido(5,4-*e*)-*as*-triazine ($\lambda_{max}^{0.1N\ HCl}$ 239 (sh), 331 mμ; ε 12,500, 3550).[4]

Mild acid hydrolysis of 6-methyl-9-*N*-formylaminopurine (X) did not give 6-methyl-9-aminopurine (XIII) as expected, but the hydrochloride of 5-methyl-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (XII). XII turned out to be unstable upon standing in acid solution. The initial spectrum changed rapidly so that after fourteen minutes at room temperature, the 245-mμ shoulder and the maximum at 330 mμ had disappeared, while a new maximum at 262 mμ and an inflection at 300 mμ appeared. The 262-mμ maximum slowly disappeared and was replaced by a broad peak at 275 mμ, while the 300-mμ inflection changed to a sharp maximum. This remaining spectrum was identical with that given by an authentic sample of 4-hydrazino-5-amino-6-methylpyrimidine (IX) in 0.1*N* hydrochloric acid, while the intermediate spectrum (exhibiting a maximum at 262 mμ) closely resembled that of 6-methyl-9-*N*-formylaminopurine (X). It thus appears that hydrolysis of XII results in initial *ring contraction* to give 6-methyl-9-aminopurine (XIII), followed by rapid cleavage of the imidazole ring to give IX. The acid-lability of XIII as contrasted with the considerable acid-stability of 9-aminohypoxanthine[4] is noteworthy.

Reaction of IX with benzaldehyde in ethanol solution gave a mixture of products from which a dibenzal derivative was obtained. However, substitution of *p*-nitrobenzaldehyde for benzaldehyde yielded a mono(*p*-nitrobenzal) derivative (XIV) in high yield, probably because the low solubility of the latter resulted in its immediate separation and thus prevented further reaction from taking place. Cyclization of XIV was effected with a mixture of ethyl orthoformate and acetic anhydride to give 6-methyl-9-(*p*-nitrobenzal)aminopurine (XV. R = H). The use of ethyl orthoacetate in this reaction afforded 6,8-dimethyl-9-(*p*-nitrobenzal)aminopurine (XV. R = CH_3), which was also formed in lower yields by the action of acetic anhydride alone on XIV. The structure of XV (R = H) was confirmed by its ultraviolet spectrum ($\lambda_{max}^{0.1N\ HCl}$ 267 mμ, ε 20,000). 6-Methyl-8-hydroxy-9-(*p*-nitrobenzal)aminopurine (XV. R = OH) was prepared from 4-(*p*-nitrobenzal)hydrazino - 5 - amino - 6 - methylpyrimidine (XIV) by treatment with ethyl chloroformate in anhydrous pyridine to give an intermediate urethane, followed by cyclization to XV (R = OH) with dilute alkali. A one-step conversion of XIV to XV (R = OH) was achieved by the use of the phosgene-pyridine complex described by Scholtissek.[5]

Attempts to hydrolyze XV (R = H) with dilute hydrochloric acid did not yield 6-methyl-9-aminopurine (XIII), as might have been expected, but rather led to rapid ring cleavage to give the hydrochloride of 4-(*p*-nitrobenzal)hydrazino-5-amino-6-methylpyrimidine (XIV). The rate of formation of *p*-nitrobenzaldehyde upon further refluxing indicated that hydrolysis of the benzal grouping was taking place much more slowly than cleavage. The presence of an 8-alkyl substituent slowed down the rate of ring cleavage but did not alter the course of the hydrolysis. Thus, 6,8-dimethyl-9-(*p*-nitrobenzal)aminopurine (XV. R = CH_3) was also cleaved to the hydrochloride of XIV with dilute hydrochloric acid, although the reaction required a somewhat longer time. The presence of an 8-hydroxyl group helped to stabilize the imidazole ring, but once again cleavage proceeded faster than hydrolysis of the *p*-nitrobenzal group. Some 6-methyl-8-hydroxy-9-(*p*-nitrobenzal)-aminopurine (XV. R = OH) could be recovered unchanged after four hours of refluxing with 6*N* hydrochloric acid, and the only other compounds isolated from the reaction mixture were *p*-nitrobenzaldehyde, *p*-nitrobenzalazine, and a trace of a material which appeared to be a pyrimidine derivative. The formation of *p*-nitrobenzalazine

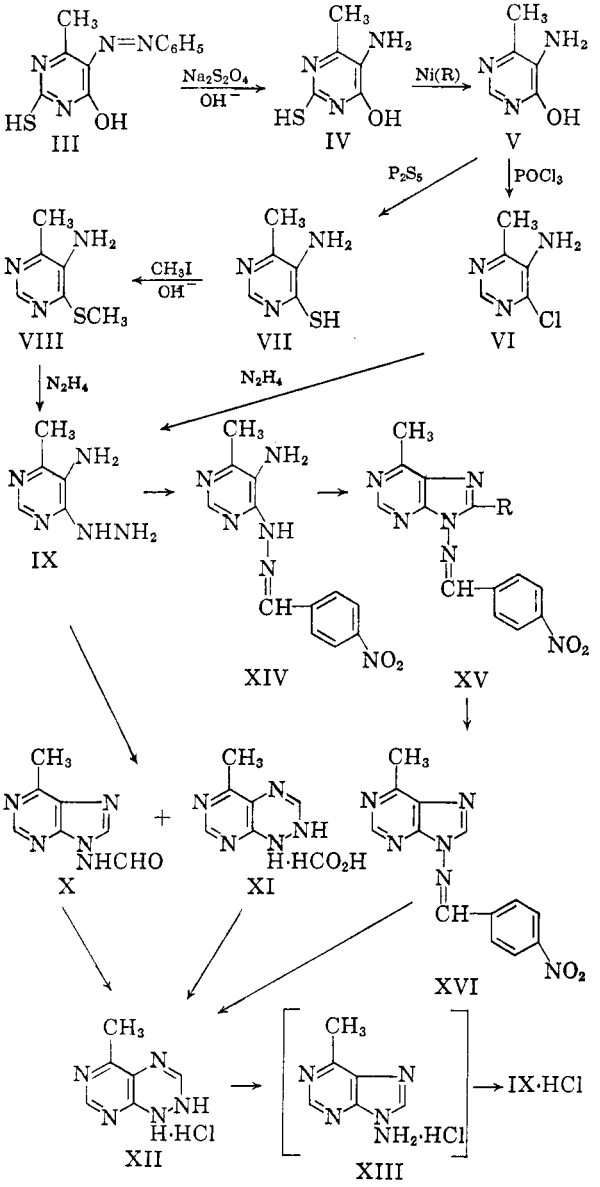
(3) M. Polonovski and M. Pesson, *Bull. soc. chim. Fr.*, 15, 688 (1948).

(4) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, 82, 4592 (1960).

(5) C. Scholtissek, *Ber.*, 89, 2562 (1956).

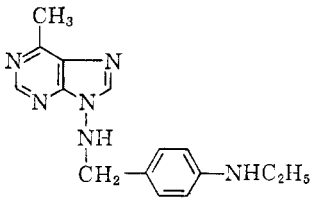
indicated that some hydrolytic displacement of the hydrazino group had taken place.

Catalytic reduction of XV (R = H) gave 6-methyl - 9 - (*p* - aminobenzal)aminopurine (XVI), which underwent rapid hydrolysis with dilute hydrochloric acid. The product was not the expected 6-methyl-9-aminopurine (XIII), however, but the hydrochloride of 5-methyl-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (XII).



Hydrolysis had thus involved the same ring expansion as the previously described conversion of X to XII. Further reduction of XVI was not observed.

Since 6 - methyl - 8 - hydroxy - 9 - (*p* - nitrobenzal)aminopurine (XV. R = OH) is a cyclic hydrazide, it was thought that the use of excess Raney nickel might result in cleavage of the N—N bond[6-8] to give 6-methyl-8-hydroxypurine and thus provide independent support for the assigned structure. However, microanalysis of the product indicated that both the nitro and the benzal groups had been reduced, and that an ethyl group had been added to the molecule. Since alkylation of primary aromatic amines with ethanol (employed as the solvent in the Raney nickel reduction) is well known,[9] the product is assigned the structure 6-methyl-8-hydroxy - 9 - (*p* - ethylaminobenzyl)aminopurine (XVII). The observed failure to remove the benzylamino group by reduction is not unusual in this



XVII

series. Thus, 1-benzyl-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine could not be debenzylated,[4] and all attempts to debenzylate 4,6-diamino-2-dibenzylaminopyrimidine or 2-dibenzylaminoadenine were reported to be unsuccessful.[10]

Some analogous derivatives of 6-methylmercapto-9-aminopurine were prepared from 4,6-dichloro-5-nitropyrimidine (XVIII). Treatment with one mole of sodium methoxide gave 4-methoxy-5-nitro-6-chloropyrimidine (XIX), which was converted in high yield with methanolic potassium hydrosulfide to 4-methoxy-5-nitro-6-mercaptopyrimidine (XX), along with a small amount of the dipyrimidyl sulfide XXI. Reduction of XX with sodium hydrosulfite in alkaline solution to XXII, followed by reaction of XXII with hydrazine, gave 4-hydrazino-5-amino-6-mercaptopyrimidine (XXIII).

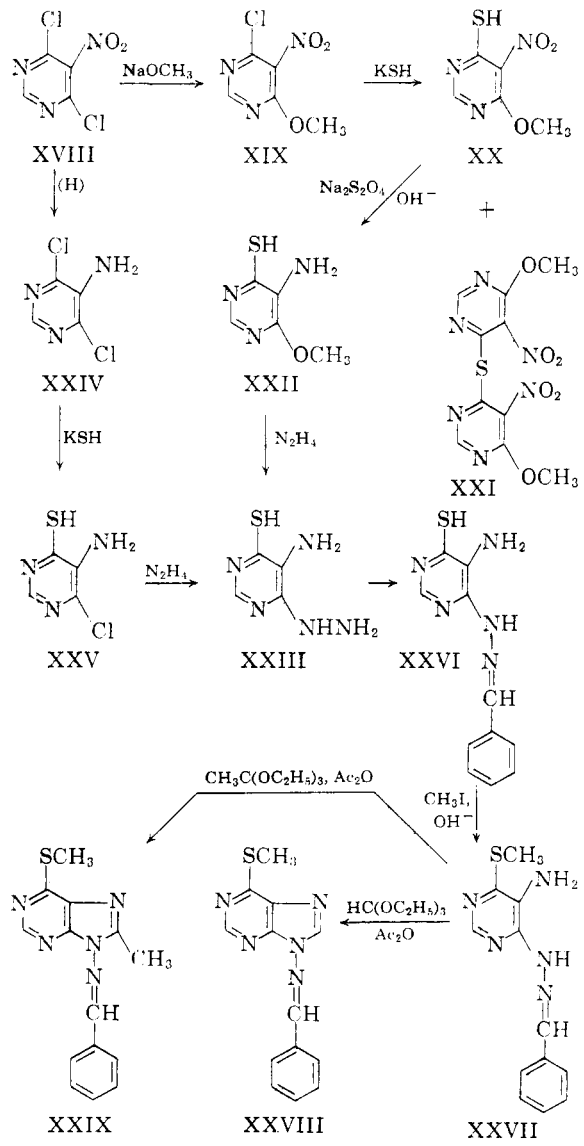
At this stage of the synthesis, work by Marchal and co-workers[11,12] suggested an alternative route to XXIII which proved to be more satisfactory. 4,6-Dichloro-5-nitropyrimidine (XVIII) was reduced to 4,6-dichloro-5-aminopyrimidine (XXIV) by a modification of the method of Christensen *et al.*[13] Treatment of XXIV with potassium hydrosulfide gave 4-mercapto-5-amino-6-chloropyrimidine (XXV) which with hydrazine yielded XXIII in good yield.

Although 4-hydrazino-5-amino-6-mercaptopyrimidine (XXIII) was fairly stable in the solid state, it rapidly underwent oxidation in alkaline solution to give a deep blue material of unknown constitu-

(6) C. Ainsworth, *J. Am. Chem. Soc.*, **76**, 5774 (1954).
(7) E. C. Taylor, J. W. Barton, and T. S. Osdene, *J. Am. Chem. Soc.*, **80**, 421 (1958).
(8) R. L. Hinman, *J. Org. Chem.*, **22**, 148 (1957).
(9) C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 1635 (1956).
(10) K. J. M. Andrews, N. Anand, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 2490 (1949).
(11) L. Marchal and R. Promel, *Bull. soc. chim. Belg.*, **66**, 406 (1957).
(12) L. Marchal, R. Promel, R. H. Martin, and A. Cardon, *Bull. soc. chim. Belg.*, **69**, 177 (1960).
(13) R. K. Robins, K. L. Dille, and B. E. Christensen, *J. Org. Chem.*, **19**, 930 (1954).

tion. It was therefore condensed with benzaldehyde to give 4-benzalhydrazino-5-amino-6-mercaptopyrimidine (XXVI), which proved to be sufficiently stable to alkali so that methylation with methyl iodide in sodium hydroxide solution in the presence of a small amount of sodium hydrosulfite proceeded satisfactorily to give 4-benzalhydrazino-5-amino-6-methylmercaptopyrimidine (XXVII). Treatment of XXVII with a mixture of ethyl orthoformate and acetic anhydride then gave 6-methylmercapto-9-benzalaminopurine (XXVIII). The use of ethyl orthoacetate, as in the analogous reaction with XIV, yielded 6-methylmercapto-8-methyl-9-benzalaminopurine (XXIX).

Treatment of the pyrimidines XIV and XXVII with nitrous acid yielded 1-(*p*-nitrobenzal)amino-4-methyl-*v*-triazolo[*d*]pyrimidine (XXX) and 1-benzalamino - 4 - methylmercapto - *v* - triazolo-[*d*]pyrimidine (XXXI) respectively. Once again, however, destruction of the ring system took precedence over hydrolysis of the benzal groupings, and all hydrolysis attempts to prepare debenzalated derivatives failed.



EXPERIMENTAL[14]

2-Mercapto-4-hydroxy-5-phenylazo-6-methylpyrimidine (III). This material was prepared essentially by the method of Polonovski and Pesson[3] except that sodium methoxide in methanol rather than sodium ethoxide in ethanol was used as the condensing agent. A much cleaner product resulted, probably as a result of the lower reaction temperature.

2-Mercapto-4-hydroxy-5-amino-6-methylpyrimidine (IV) was prepared in 79% yield by reduction of 2-mercapto-4-hydroxy-5-phenylazo-6-methylpyrimidine in dilute sodium hydroxide solution with sodium hydrosulfite. Recrystallization of the product from water yielded small yellow needles, m.p. 320–322° dec., with darkening above 300°.

Anal. Calcd. for $C_5H_7N_3OS$: C, 38.2; H, 4.45; N, 26.8; S, 20.4. Found: C, 38.4; H, 4.35; N, 26.2; S, 20.3.

4-Hydroxy-5-amino-6-methylpyrimidine (V). A solution of 24 g. of 2-mercapto-4-hydroxy-5-amino-6-methylpyrimidine in 300 ml. of water containing 36 ml. of concd. ammonium hydroxide was heated to boiling and treated in small portions with 75 g. of Raney nickel. The reaction mixture was stirred and heated under reflux for 1.5 hr., filtered while hot and the Raney nickel extracted with boiling water. The filtrate and extract were combined and evaporated to dryness under reduced pressure. Recrystallization of the residue from ethanol gave 13.9 g. (73%) of colorless, fluffy needles, m.p. 221–222.5°.

Anal. Calcd. for $C_5H_7N_3O$: C, 48.0; H, 5.6; N, 33.6. Found: C, 48.0; H, 5.6; N. 33.7.

4-Chloro-5-amino-6-methylpyrimidine (VI). Chlorination of 4-hydroxy-5-amino-6-methylpyrimidine with a mixture of phosphorus oxychloride and dimethylaniline in the usual manner, followed by extraction of the product with methylene chloride, evaporation to dryness, and sublimation of the residue at 70°/0.05 mm., yielded colorless needles, m.p. 98–99°, in 13% yield.

Anal. Calcd. for $C_5H_6N_3Cl$: C, 41.8; H, 4.2. Found: C, 41.6; H, 4.3.

4-Mercapto-5-amino-6-methylpyrimidine (VII). A mixture of 5 g. of 4-hydroxy-5-amino-6-methylpyrimidine, 75 ml. of dry pyridine and 10 g. of phosphorus pentasulfide was heated under reflux for 1 hr. and then poured over 200 g. of crushed ice. After 2 hr., the orange solution was made alkaline with sodium hydroxide, treated with charcoal, and filtered. Acidification of the filtrate with glacial acetic acid followed by evaporation to a small volume yielded 3.5 g. of a pale yellow microcrystalline solid, m.p. 300–301° dec. Recrystallization from a large volume of ethanol gave 2.9 g. (51%) of straw-yellow needles, m.p. 305–306° dec.

Anal. Calcd. for $C_5H_7N_3S$: C, 42.5; H, 5.0; N, 29.8; S, 22.7. Found: C, 42.5; H, 5.0; N, 29.6; S, 22.7.

4-Methylmercapto-5-amino-6-methylpyrimidine (VIII) was prepared in 72% yield by methylation of 4-mercapto-5 amino-6-methylpyrimidine in dilute sodium hydroxide solution with methyl iodide. Recrystallization of the crude product from petroleum ether (b.p. 60–70°) yielded pale yellow needles, m.p. 85–86°.

Anal. Calcd. for $C_6H_9N_3S$: C, 46.5; H, 5.8; N, 27.1. Found: C, 46.6; H, 5.9; H, 27.1.

4-Hydrazino-5-amino-6-methylpyrimidine (IX). *Method A.* A solution of 0.2 g. of 4-chloro-5-amino-6-methylpyrimidine in 1 ml. of 100% hydrazine hydrate and 3 ml. of absolute ethanol was heated under reflux for 2 hr. and then evaporated to dryness. The residual mass of needles was sublimed at 160–170°/17 mm. to give 0.165 g. (85%) of a colorless solid, m.p. 206–208°. Recrystallization from ethanol yielded

(14) We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J., and to Drs. G. Weiler and F. B. Strauss, Oxford, England. All melting points are corrected.

shining needles, m.p. 214–215° which became opaque on drying. $\lambda_{max}^{C_2H_5OH}$ 273, 314 mμ; ε = 5900, 8000. $\lambda_{max}^{0.1N\ HCl}$ 275,300 mμ; ε 6100, 6700.

Anal. Calcd. for $C_5H_9N_5$: C, 43.2; H, 6.5; N, 50.4. Found: C, 43.2; H, 6.5; N, 50.4.

Method B. The same product was obtained in 74% yield by heating 4-methylmercapto-5-amino-6-methylpyrimidine with hydrazine hydrate for 3 hr., followed by evaporation of of the reaction mixture to dryness and recrystallization of the residue from ethanol.

4-(p-Nitrobenzal)hydrazino-5-amino-6-methylpyrimidine (XIV). A concentrated ethanolic solution of 7.0 g. of *p*-nitrobenzaldehyde was added cautiously to a solution of 5.8 g. of 4-hydrazino-5-amino-6-methylpyrimidine in 100 ml. of boiling ethanol. The product separated immediately as a thick red paste. After heating on a water bath for 20 min. to ensure completion of the reaction, the mixture was cooled to 0° and filtered to give 10.8 g. (95%) of small, deep red needles, m.p. 242–243° dec. Recrystallization of a small sample from ethanol raised the decomposition point to 243–244°. $\lambda_{max}^{C_2H_5OH}$ 291 mμ; ε 10,000. $\lambda_{max}^{0.1N\ HCl}$ 269 mμ; ε 15,000.

Anal. Calcd. for $C_{12}H_{12}N_6O_2$: C, 53.0; H, 4.4; N, 30.9. Found: C,53.2; H,4.2; N,30.6.

6-Methyl-9-(p-nitrobenzal)aminopurine (XV, R = H). A mixture of 5 g. of 4-(*p*-nitrobenzal)hydrazino-5-amino-6-methylpyrimidine, 50 ml. of ethyl orthoformate, and 50 ml. of acetic anhydride was heated under reflux for 1 hr. The starting material became pale yellow in color and slowly dissolved. The solution was cooled, diluted with an equal volume of ether, chilled to 0° for 1 hr., and filtered. The collected needles were sublimed at 190–200°/0.05 mm. to give 3.5 g. (68%) of almost colorless needles, m.p. 241–242°. Recrystallization from ethanol raised the m.p. to 243–244°. $\lambda_{max}^{C_2H_5OH}$ 262, 313 mμ, ε = 8,900, 14,500. $\lambda_{max}^{0.1N\ HCl}$ 267 mμ; ε = 20,000.

Anal. Calcd. for $C_{13}H_{10}N_6O_2$: C, 55.3; H, 3.55; N, 29.8. Found: C, 55.5; H, 3.7; N, 29.2.

6,8-Dimethyl-9-(p-nitrobenzal)aminopurine (XV, R = CH_3). *Method A.* A mixture of 1 g. of 4-(*p*-nitrobenzal)-hydrazino-5-amino-6-methylpyrimidine and 20 ml. of acetic anhydride was heated under reflux for 1 hr. and then evaporated to dryness. The residue was dissolved in ethanol and the solution again evaporated to dryness. Repetition of this process three times followed by recrystallization of the residue from ethanol yielded 0.38 g. (35%) of colorless needles, m.p. 224–225°. $\lambda_{max}^{C_2H_5OH}$ 265,315 mμ; ε 15,600, 24,000. $\lambda_{max}^{0.1N\ HCl}$ 267 mμ; ε 22,800.

Anal. Calcd. for $C_{14}H_{12}N_6O_2$: C, 56.8; H, 4.05; N, 28.4. Found: C, 56.9; H, 4.1; N, 28.3.

Method B. The use of ethyl orthoacetate instead of ethyl orthoformate in the reaction with 4-(*p*-nitrobenzal)hydrazino-5-amino-6-methylpyrimidine, as described above in the preparation of XV (R = H), yielded a product identical with that given by *Method A*, but in greatly increased yield (90.5%).

6-Methyl-9-(p-aminobenzal)aminopurine (XVI, R = H). A solution of 1.0 g. of 6-methyl-9-(*p*-nitrobenzal)aminopurine in 150 ml. of ethyl acetate was hydrogenated in the presence of 0.5 g. of 10% palladium-on-charcoal catalyst at 45 p.s.i. and at 40° for 12 hr. The reduction mixture was filtered and the collected catalyst extracted with 100 ml. of hot ethyl acetate. The combined filtrate and extract was evaporated to dryness under reduced pressure and the residue sublimed at 200°/0.05 mm. to give 0.77 g. (86%) of pale yellow needles, m.p. 258–260°.

Anal. Calcd. for $C_{13}H_{12}N_6$: C, 61.9; H, 4.8; N, 33.3. Found: C, 61.9; H, 5.1; N, 32.9.

6,8-Dimethyl-9-(p-aminobenzal)aminopurine (XVI, R = CH_3). *Method A.* Reduction of 1.0 g. of 6,8-dimethyl-9-(*p*-nitrobenzal)aminopurine as described above yielded 0.73 g. (81%) of yellow flakes, m.p. 271–273°.

Anal. Calcd. for $C_{14}H_{14}N_6$: C, 63.2; H, 5.3; N, 31.6. Found: C, 62.9; H, 5.2; N, 31.7.

Method B. A mixture of 2.0 g. of 6,8-dimethyl-9-(*p*-nitrobenzal)aminopurine and 20 g. of Raney nickel in 200 ml. of absolute ethanol was stirred and heated under reflux for 4 hr. The hot reaction mixture was filtered, the collected catalyst extracted with boiling ethanol, and the combined filtrate and extract evaporated to dryness. The residue crystallized upon trituration with benzene to give 1.6 g. (89%) of small yellow needles, m.p. 268–270°. Two sublimations at 230°/0.1 mm. yielded yellow flakes, m.p. 271–273°, identical with the material prepared by *Method A* above.

4-(p-Nitrobenzal)hydrazino-6-methyl-5-pyrimidylurethane. To a stirred solution of 1.0 g. of 4-(*p*-nitrobenzal)hydrazino-5-amino-6-methylpyrimidine in 10 ml. of dry pyridine was added 0.3 ml. of ethyl chloroformate. The red solution became lighter in color and some solid separated. The reaction mixture was allowed to stand at room temperature for 10 min. and was then treated dropwise with 20 ml. of water and cooled to 0°. Filtration yielded 1.22 g. (79%) of a yellow solid. When heated, it softened at 200–203°, resolidified and finally decomposed at 318–319°.

Anal. Calcd. for $C_{15}H_{16}N_6O_4 \cdot C_5H_5N$: N, 23.2. Found: N, 23.0.

6-Methyl-8-hydroxy-9-(p-nitrobenzal)aminopurine (XV, R = OH). *Method A.* Four grams of powdered 4-(*p*-nitrobenzal)hydrazino-6-methyl-5-pyrimidylurethane was added with stirring to 20 ml. of 5% sodium hydroxide at 50–60°. After 20 min., the red solution was filtered and the filtrate acidified with acetic acid. The cream colored solid which had separated was collected by filtration, washed with water, and recrystallized from ethanol to give 2.8 g. (99%) of almost colorless needles, m.p. 319–321° dec.

Anal. Calcd. for $C_{13}H_{10}N_6O_3$: C, 52.4; H, 3.35; N, 28.2. Found: C, 52.4; H, 3.4; N, 28.0.

Method B. A solution of 0.8 ml. of dry pyridine in 20 ml. of dry benzene was treated with phosgene until no more solid separated (approximately 30 min.). Excess phosgene was removed by boiling the solution under reflux for 10 min. To this suspension was added 1.0 g. of finely powdered 4-(*p*-nitrobenzal)hydrazino-5-amino-6-methylpyrimidine and the mixture was heated under reflux for 3 hr. Water was added to the cooled reaction mixture and the *p*H was adjusted to 7–8 with ammonium hydroxide and then to *p*H 6 with acetic acid. Filtration yielded a tan solid which was washed thoroughly with water and dissolved in dilute sodium hydroxide. Decolorization with charcoal followed by acidification of the filtrate with acetic acid yielded 0.79 g. (72%) of a light tan powder, m.p. 285–290° dec. Recrystallization of this material from ethanol gave almost colorless needles, m.p. 319–321° dec., identical with the material obtained by *Method A* above.

6-Methyl-9-N-formylaminopurine (X). A solution of 10.0 g. of 4-hydrazino-5-amino-6-methylpyrimidine in 20 ml. of formic acid was heated at 90–95° for 90 min. and then evaporated to dryness under reduced pressure. The residual orange solid was extracted with boiling ethanol, and the mixture filtered. Evaporation of the ethanol filtrate yielded a grey solid which was recrystallized from ethanol to give 2.85 g. (22%) of a colorless solid, m.p. 199–200°. $\lambda_{max}^{C_2H_5OH}$ 260 mμ; ε 7200. $\lambda_{max}^{0.1N\ HCl}$ 263 mμ; ε 6800.

Anal. Calcd. for $C_7H_7N_5O$: C, 47.45; H, 4.0; N, 39.5. Found: C, 47.3; H, 3.9; N, 39.8.

5-Methyl-1,2-dihydropyrimido(5,4-e)-as-triazine (XI). *Method A.* The ethanol-insoluble material (5.80 g., 44%) from the above reaction was recrystallized from 50% aqueous ethanol to give orange cubes, m.p. 185–187° dec. $\lambda_{max}^{0.1N\ HCl}$ 245(sh), 330 mμ; ε 10,500, 8300.

Anal. Calcd. for $C_6H_7N_5 \cdot HCO_2H$: C, 43.1; H, 4.65; N, 35.9. Found: C, 42.8; H, 4.6; N, 35.8.

Addition of sodium carbonate solution to a solution of 0.2 g. of the above material in 1 ml. of water yielded 0.125 g. of a yellow solid, m.p. 153–154.5°, which was collected by filtration, washed with ice water, and dried *in vacuo*. Exposure to moisture caused rapid discoloration of this material.

Anal. Calcd. for $C_6H_7N_5 \cdot 1/2H_2O$: C, 45.8; H, 5.1; N, 44.55. Found: C, 46.1; H, 4.7; N, 44.5.

Acidification of a solution of 0.1 g. of the formic acid salt of 5-methyl-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine in 1 ml. of water resulted in the separation of 0.105 g. of the corresponding hydrochloride as a dark orange solid, m.p. 304–306° dec. Recrystallization from 50% aqueous ethanol raised the decomposition point to 308–309°.

Anal. Calcd. for $C_6H_7N_5 \cdot HCl$: C, 38.8; H, 4.35; N, 37.8. Found: C, 38.8; H, 4.5; N, 37.7.

Method B. A suspension of 1.0 g. of 6-methyl-9-*N*-formylaminopurine in 15 ml. of 10% aqueous hydrochloric acid was heated at 80° for 1 hr., and the resulting clear orange solution evaporated to dryness under reduced pressure. Recrystallization of the residual solid from 50% aqueous ethanol gave 0.7 g. of orange crystals, m.p. 308–309° dec. identical with the hydrochloride of 5-methyl-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine as prepared by *Method A* above.

Method C. A solution of 0.1 g. of 6-methyl-9-(*p*-aminobenzal)aminopurine, 5 ml. of ethanol and 1 ml. of concd. hydrochloric acid was allowed to stand at room temperature for 3 days and then filtered. The collected dark orange solid (46 mg.) was recrystallized from 50% aqueous ethanol to give orange crystals, m.p. 308–309° dec., identical with the material prepared by *Methods A* and *B* above.

4-Methoxy-5-nitro-6-chloropyrimidine (XIX). To a rapidly stirred solution of 48.5 g. of 4,6-dichloro-5-nitropyrimidine in 500 ml. of absolute methanol maintained at 0° was added dropwise a solution of sodium methoxide prepared from 400 ml. of methanol and 5.75 g. of sodium. After addition was complete, the reaction mixture was stirred for an additional hour, filtered, and the filtrate evaporated to dryness. Recrystallization of the residue from petroleum ether (b.p. 60–70°) yielded 44.0 g. (93%) of pale yellow, stout needles, m.p. 65–66°.

Anal. Calcd. for $C_5H_4N_3O_3Cl$: C, 31.65; H, 2.1; N, 22.2. Found: C, 31.8; H, 2.1; N, 22.0.

4-Methoxy-5-nitro-6-mercaptopyrimidine (XX). To a rapidly stirred solution of potassium hydrosulfide (prepared by saturation of a solution of 4.2 g. of potassium hydroxide in 140 ml. of methanol with hydrogen sulfide) was added 13.5 g. of finely powdered 4-methoxy-5-nitro-6-chloropyrimidine. After 20 min. the orange solution was filtered and the filtrate evaporated to dryness under reduced pressure. Treatment of the residue with a little dilute acetic acid, followed by addition of 10% sodium hydroxide to *p*H 9 and filtration yielded a small amount (0.15 g.) of a pale solid. The filtrate was immediately neutralized with glacial acetic acid and cooled to 0°. Filtration then yielded 12.55 g. (95%) of a bright yellow microcrystalline solid, m.p. 164–166°. Recrystallization from water gave yellow leaflets, m.p. 165–166°.

Anal. Calcd. for $C_5H_5N_3O_3S$: C, 32.1; H, 2.7; N, 22.5. Found: C, 32.5; H, 2.7; N, 22.1.

Di(4-methoxy-5-nitro-6-pyrimidyl) sulfide (XXI). The pale, alkali-insoluble solid obtained as described above was recrystallized from ethanol to give pale yellow needles, m.p. 189–190°.

Anal. Calcd. for $C_{10}H_8N_6O_6S$: C, 35.3; H, 2.35; N, 24.7. Found: C, 35.5; H, 2.5; N, 24.1.

4-Methoxy-5-amino-6-mercaptopyrimidine (XXII) was prepared in 76% yield by reduction of 4-methoxy-5-nitro-6-mercaptopyrimidine with sodium hydrosulfite in dilute sodium hydroxide solution. Recrystallization of the pale yellow crude product (m.p. 211–213°) from ethanol yielded long needles or leaflets with a greenish luster, m.p. 214–215°.

Anal. Calcd. for $C_5H_7N_3OS$: C, 38.2; H, 4.45. Found: C, 37.8; H, 4.6.

4,6-Dichloro-5-aminopyrimidine (XXIV). A solution of 10 g. of 4,6-dichloro-5-nitropyrimidine in 150 ml. of ethanol was hydrogenated at 35 p.s.i. at room temperature in the presence of 5 g. of Raney nickel. Uptake of hydrogen was complete within 90 min. The reduction mixture was filtered through Celite, the filtrate evaporated to dryness, and the residue recrystallized from cyclohexane to give 7.3 g. (87%) of colorless needles, m.p. 146–147°. The reported melting point for this compound is 147–148°.[13]

4-Chloro-5-amino-6-mercaptopyrimidine (XXV). A solution of 3.3 g. of 4,6-dichloro-5-aminopyrimidine in methanolic potassium hydrosulfide (prepared by saturation of a solution of 1.5 g. of potassium hydroxide in 50 ml. of absolute methanol with hydrogen sulfide) was heated under reflux for 2.5 hr. and then evaporated to dryness under reduced pressure. The residue was dissolved in dilute sodium hydroxide and the solution was then treated with charcoal and filtered. Neutralization of the filtrate with acetic acid yielded 2.4 g. (74%) of a tan solid, m.p. 196–200°. The reported[11] melting point for this compound is 190–200° dec.

4-Hydrazino-5-amino-6-mercaptopyrimidine (XXIII). *Method A.* A mixture of 7.0 g. of 4-methoxy-5-amino-6-mercaptopyrimidine and 60 ml. of 95% hydrazine hydrate was heated under reflux for 1 hr. and then evaporated to dryness. The residue was triturated with very dilute acetic acid and the tan solid collected by filtration to give 6.25 g. (89%), m.p. 220–224° dec. Recrystallization from a large volume of water yielded greenish metallic needles, m. p. 222–224° dec.

Anal. Calcd. for $C_4H_7N_5S$: C, 30.6; H, 4.5; N, 45.0. Found: C, 30.3; H, 4.3; N, 45.0.

Method B. A mixture of 2.0 g. of 4-chloro-5-amino-6-mercaptopyrimidine and 50 ml. of 85% hydrazine hydrate was treated as described above to give 1.5 g. (77%), m.p. 214–217° dec., identical with the product obtained by Method A.

4-Benzalhydrazino-5-amino-6-mercaptopyrimidine (XXVI). A suspension of 1.6 g. of 4-hydrazino-5-amino-6-mercaptopyrimidine in 20 ml. of ethanol was treated with 1.2 g. of benzaldehyde followed by 3 drops of acetic acid, and the mixture was heated on a water bath for 1 hr. Cooling and filtering yielded 2.3 g. (92%) of a yellow solid, m.p. 239–241° dec. Recrystallization from a large volume of ethanol narrowed the decomposition point to 240–241°.

Anal. Calcd. for $C_{11}H_{11}N_5S$: C, 53.9; H, 4.5; N, 28.6. Found: C, 53.6; H, 4.5; N, 28.3.

4-Benzalhydrazino-5-amino-6-methylmercaptopyrimidine (XXVII). To a stirred solution of 2.5 g. of 4-benzalhydrazino-5-amino-6-mercaptopyrimidine in 20 ml.of water containing 0.6 g. of sodium hydroxide and 0.1 g. of sodium hydrosulfite was added 0.7 ml. of methyl iodide, and the mixture was stirred for 15 min. Filtration yielded a green solid which was washed well with water and recrystallized from ethanol to give 2.4 g. (91%) of fluffy yellow needles, m.p. 181–182°.

Anal. Calcd. for $C_{12}H_{13}N_5S$: C, 55.6; H, 5.0; N, 27.0. Found: C, 55.5; H, 4.9; N, 26.5.

6-Methylmercapto-9-benzalaminopurine, (XXVIII). A mixture of 1.0 g. of 4-benzalhydrazino-5-amino-6-methylmercaptopyrimidine, 10 ml. of ethyl orthoformate, and 10 ml. of acetic anhydride was heated under reflux for 1 hr. and then cooled, diluted with an equal volume of ether, and chilled to 0°. After 1 hr., the mixture was filtered to give 0.85 g. (82%) of a colorless solid, m.p. 201–203°. Recrystallization from ethanol yielded colorless needles, m.p. 202–203°. $\lambda_{max}^{C_2H_5OH}$ 289 mμ; ε 28,800.

Anal. Calcd. for $C_{13}H_{11}N_5S$: C, 58.0; H, 4.1; N, 26.0. Found: C, 58.2; H, 4.2; N, 25.7.

6-Methylmercapto-8-methyl-9-benzalaminopurine (XXIX). Repetition of the previous experiment using ethyl orthoacetate rather than ethyl orthoformate yielded a colorless solid, m.p. 183–184°, in 48% yield. Recrystallization of this material from ethanol gave colorless needles with no change in the melting point.

Anal. Calcd. for $C_{14}H_{13}N_5S$: C, 59.4; H, 4.6; N, 24.75. Found: C, 59.2; H, 4.9; N, 24.45.

Hydrolysis of 9-benzalaminopurines. The following experiments are illustrative of the attempts made to remove the protecting benzal groupings by hydrolysis.

A. A solution of 0.5 g. of 6-methylmercapto-9-benzal-

aminopurine in 4 ml. of concd. hydrochloric acid and 12 ml. of water was heated under reflux for 10 min. During this time a flocculent yellow solid separated from the hot reaction mixture. After cooling to 0°, the mixture was filtered to give 0.46 g. (96%), m.p. 237–239° dec. Recrystallization from ethanol yielded small yellow needles, m.p. 243–245° dec., which were shown to be identical with an authentic sample of the hydrochloride of 4-benzalhydrazino-5-amino-6-methylmercaptopyrimidine by comparison of infrared spectra and by a mixture melting point determination.

Anal. Calcd. for $C_{12}H_{14}N_5SCl \cdot H_2O$: C, 46.0; H, 5.1; N, 22.4. Found: C, 45.8; H, 5.1; N, 22.9.

B. A mixture of 1.5 g. of 6-methyl-8-hydroxy-9-(*p*-nitrobenzal)aminopurine, 15 ml. of concd. hydrochloric acid and 15 ml. of water was heated under reflux for 4 hr. During this time *p*-nitrobenzaldehyde collected in the condenser and was recovered by recrystallization from ethanol. The reaction mixture was evaporated to dryness under reduced pressure and the residue triturated with cold 5% sodium hydroxide. Filtration removed 0.12 g. of brownish plates which were sublimed at 210°/0.05 mm. and then recrystallized from cellosolve to give golden plates, m.p. 307–308°, identical with an authentic sample of *p*-nitrobenzalazine prepared by the method of Curtius and Lublin.[15]

Anal. Calcd. for $C_{14}H_{10}N_4O_4$: C, 56.4; H, 3.4; N, 18.8. Found: C, 56.4; H, 3.4; N, 18.4.

Acidification of the alkaline filtrate above yielded 0.85 g. of unchanged starting material.

6-Methyl-8-hydroxy-9-(p-ethylaminobenzyl)aminopurine (XVII). A mixture of 1.5 g. of 6-methyl-8-hydroxy-9-(p-nitrobenzal)aminopurine and 15 g. of Raney nickel in 150 ml. of absolute ethanol was stirred and heated under reflux for 4 hr. The hot reaction mixture was filtered, the collected catalyst extracted with boiling ethanol, and the combined filtrate and extract evaporated to dryness. Recrystallization of the residue from dilute ethanol yielded 1.1 g. (73%) of pale yellow needles, m.p. 225–226°.

(15) T. Curtius and A. Lublin, *Ber.*, **33**, 2460 (1900).

Anal. Calcd. for $C_{15}H_{18}N_6O$: C, 60.4; H, 6.0; N, 28.2. Found: C, 59.8; H, 5.7; N, 28.0.

1-(p-Nitrobenzal)amino-4-methyl-v-triazolo[d]pyrimidine. (XXX). To a rapidly stirred suspension of 2.0 g. of 4-(p-nitrobenzal)hydrazino-5-amino-6-methylpyrimidine in 20 ml. of water containing 2 ml. of concd. hydrochloric acid at room temperature was added, over the course of 20 min., a solution of 0.75 g. of sodium nitrite in 5 ml. of water. Stirring was continued for 1 hr. following addition of the sodium nitrite, and the reaction mixture was warmed to 60° for 15 min., cooled to 0°, and filtered. The collected solid was washed well with 5% sodium acetate solution followed by water and recrystallized from ethanol to give 1.1 g. (53%) of a yellow microcrystalline solid, m.p. 231–233° dec.

Anal. Calcd. for $C_{12}H_9N_7O_2$: C, 50.9; H, 3.2; N, 34.6. Found: C, 50.9; H, 3.3; N, 34.75.

1-Benzalamino-4-methylmercapto-v-triazolo[d]pyrimidine (XXXI). Nitrosation of 2.0 g. of 4-benzalhydrazino-5-amino-6-methylmercaptopyrimidine as described above yielded, after recrystallization of the crude product from ethanol, 1.65 g. (79%) of colorless needles, m.p. 176–177° dec. $\lambda_{max}^{C_2H_5OH}$ 269, 317 mμ; ε 18,000, 18,500.

Anal. Calcd. for $C_{12}H_{10}N_6S$: C, 53.3; H, 3.7; N, 31.1. Found: C, 53.5; H, 3.6; N, 31.6.

The following experiment is representative of hydrolysis attempts made with XXX and XXXI: A suspension of 10. g. of 1-benzalamino-4-methylmercapto-*v*-triazolo[d]pyrimidine (XXXI) in 40 ml. of 6*N* hydrochloric acid was steam distilled until no more benzaldehyde passed over (approximately 30 min). The reaction mixture was evaporated to dryness under reduced pressure, the residue treated with 5% sodium acetate solution and again evaporated to dryness. A cold-finger assembly was inserted into the reaction flask and the residue was sublimed at 0.05 mm. up to 180° (bath temperature) to give 0.24 g. of ammonium chloride contaminated with a trace of organic material of unknown composition. No identifiable material could be found in the sublimation residue.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Reaction of Nitriles with *o*-Aminonitriles: A Convenient Synthesis of Fused 4-Aminopyrimidines[1a,b]

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The base-catalyzed condensation of various aromatic and heterocyclic *o*-aminonitriles with nitriles to give 4-aminoquinazolines, 4-aminopyrazolo(3,4)pyrimidines, 4-aminopyrido(2,3-d)pyrimidines, and 6-aminopurines (adenines) is described. The scope, limitations, mechanism, and synthetic utility of this reaction are discussed.

A number of examples of the base-catalyzed dimerization of *o*-aminonitriles, leading to fused 4-aminopyrimidine heterocycles, have been reported recently from this Laboratory.[3–5] The reaction may be illustrated by the dimerization of 2-amino-5-nitrobenzonitrile (I) in methanolic ammonia to give 2-(2-amino-5-nitrophenyl)-4-amino-6-nitroquinazoline (II). It was suggested[3] that this reaction proceeds by initial condensation of the amino group of one molecule of the *o*-aminonitrile

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