chloride was separated by filtration. The solvent was removed from the filtrate under reduced pressure. Five milliliters of 10% hydrochloric acid was added to the remaining oil. Solvent was removed under reduced pressure. The residue was recrystallized from chloroform to give 2.70 g. of yellow solid.

Dimethyl 5-(4-amino-2-methylthiopyrimidyl)methyl phosphorothioate hydrochloride (XXVI). Dimethyl thionochlorophosphate (2.8 g., 0.018 mole) in 20 ml. of 1,4-dioxane was added dropwise to a stirred solution of I (3.0 g., 0.018 mole) and triethylamine (3.4 g., 0.034 mole) in 30 ml. of 1,4-dioxane. The mixture was refluxed for 2 hr. After cooling, solvent was removed under reduced pressure. The semisolid was treated with isopropyl alcohol. The residual triethylamine hydrochloride was separated by filtration. The solid formed on adding 5 ml. of 10% hydrochloric acid was separated by filtration and recrystallized from a methanol-ether mixture to give 1.52 g. of tan hygroscopic solid.

BUFFALO 14, N. Y.

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY, SOUTHERN RESEARCH INSTITUTE]

v-Triazolo[4,5-d]pyrimidines. I. Synthesis and Nucleophilic Substitution of 7-Chloro Derivatives of 3-Substituted v-Triazolo[4,5-d]pyrimidines[1]

Y. FULMER SHEALY, ROBERT F. STRUCK, JOE D. CLAYTON, AND JOHN A. MONTGOMERY

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3-Substituted 5-amino-7-chloro-v-triazolo[4,5-d]pyrimidines have been synthesized from the appropriate 2,5-diamino-4-chloro-6-alkyl(or aryl)aminopyrimidines. Retention of the chloro group until the v-triazolo[4,5-d]pyrimidine ring has been formed permits the introduction, by nucleophilic displacement, of a wide variety of substituents at position 7.

The synthesis of the v-triazolo[4,5-d]pyrimidine (8-azapurine) analogs of the principal purines of nucleic acids was reported[2] in 1945. Prior to that publication, only two derivatives of this ring system were known, but many have since been synthesized, chiefly as potential purine antagonists. The usual method of synthesis[3] depends on the preparation of a 4,5-diaminopyrimidine bearing the substituents at positions 2 and 6 desired in the v-triazolo[4,5-d]pyrimidine at positions 5 and 7, respectively; treatment of the pyrimidine with nitrite in acidic solution forms the triazole ring. v-Triazolo[4,5-d]pyrimidines have also been synthesized by cyclizing appropriately substituted v-triazoles[4,5c] and—for 2-substituted derivatives—by oxidizing 4-amino-5-arylazopyrimidines.[5,3q] The synthetic sequence described in this report was designed to produce the v-triazolo[4,5-d]pyrimidine ring with a replaceable chlorine atom at position 7 in order that a variety of derivatives might be synthesized by nucleophilic substitution.[6] The method, applied to the preparation of 3-substituted 3*H* - *v* - triazolo[4,5 - *d*]pyrimidines, is depicted in Chart I.

2-Amino-4-chloro-6-ethylaminopyrimidine (IIa) and the corresponding butylamino derivative (IIb) were obtained from 2-amino-4,6-dichloropyrimidine and an excess of the appropriate amine. The *p*-anisidino derivative (IIc) was prepared by the fusion method of Basford, Curd, Hoggarth, and Rose.[7] Disubstitution products (III) were ob-

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740, and by the C. F. Kettering Foundation.

(2) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole, and R. J. Vaughan, Jr., *J. Am. Chem. Soc.*, **67**, 290 (1945).

(3) For example: (a) L. F. Cavalieri, A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **70**, 3875 (1948); (b) P. Bitterli and H. Erlenmeyer, *Helv. Chim. Acta*, **34**, 835 (1951); (c) C. T. Bahner and D. E. Bilancio, *J. Am. Chem. Soc.*, **75**, 6038 (1953); (d) C. T. Bahner, D. E. Bilancio, E. B. Senter, S. Humphries, R. Nations, W. Porch, and J. Wilson, *J. Org. Chem.*, **22**, 558 (1957); (e) K. L. Dille and B. E. Christensen, *J. Am. Chem. Soc.*, **76**, 5087 (1954); (f) K. L. Dille, M. L. Sutherland, and B. E. Christensen, *J. Org. Chem.*, **20**, 171 (1955); (g) J. Davoll, *J. Chem. Soc.*, 1593 (1958); (h) J. Davoll and D. D. Evans, *J. Chem. Soc.*, 5041 (1960); (i) H. C. Koppel, D. E. O'Brien, and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 3046 (1959); (j) R. Weiss, R. K. Robins, and C. W. Noell, *J. Org. Chem.*, **25**, 765 (1960); (k) R. Hull, *J. Chem. Soc.*, 481, 2746 (1959); (l) S. Yamada, I. Chibata, and D. Kiguchi, *Tanabe Seiyaku Kenkyû Nempô*, **2**, 13 (1957) [*Chem. Abstr.*, **52**, 1177c (1958)]; (m) G. M. Timmis, I. Cooke, and R. J. W. Spickett, *The Chemistry and Biology of Purines*, G. E. W. Wolstenholme and C. M. O'Connor, eds., J. and A. Churchill, Ltd., 1957, p. 134; (n) C. L. Leese and G. M. Timmis, *J. Chem. Soc.*, 4107 (1958); (o) J. H. Lister and G. M. Timmis, *J. Chem. Soc.*, 327 (1960); (p) J. H. Lister, *J. Chem. Soc.*, 3394 (1960); (q) R. B. Angier and J. W. Marsico, *J. Org. Chem.*, **25**, 759 (1960).

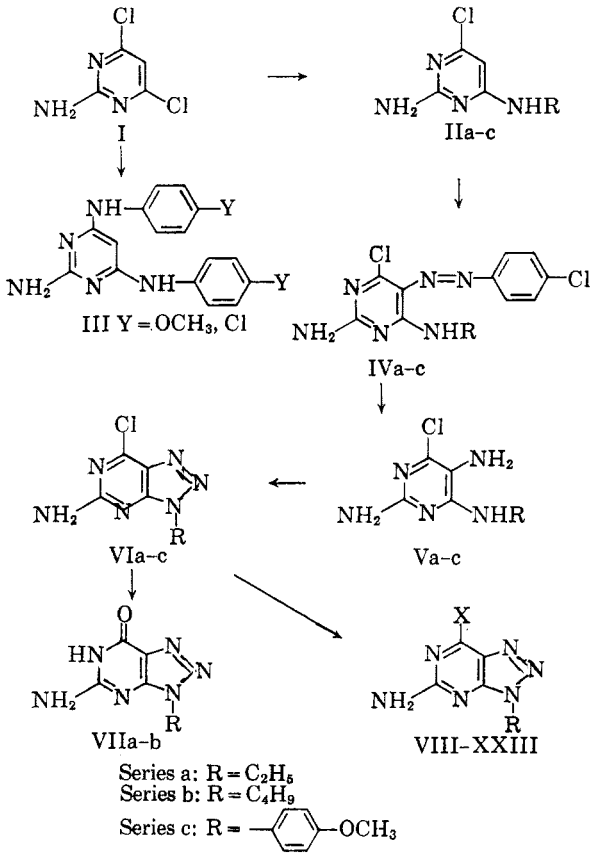
(4) J. Baddiley, J. G. Buchanan, and G. O. Osborne, *J. Chem. Soc.*, 1651, 3606 (1958); A. Dornow and J. Helberg, *Chem. Ber.*, **93**, 2001 (1960).

(5) For example: (a) F. R. Benson, L. W. Hartzel, and W. L. Savell, *J. Am. Chem. Soc.*, **72**, 1816 (1950); (b) R. P. Parker and J. S. Webb, U. S. Pat. **2,543,333**, Feb. 27, 1951; (c) E. Richter and E. C. Taylor, *J. Am. Chem. Soc.*, **78**, 5848 (1956); (d) G. M. Timmis, D. G. I. Felton, H. O. J. Collier, and P. L. Huskinson, *J. Pharm. Pharmacol.*, **9**, 46 (1957); (e) E. J. Modest, H. N. Schlein, and G. E. Foley, *J. Pharm. Pharmacol.*, **9**, 68 (1957).

(6) Amino derivatives have been converted to oxo derivatives with nitrous acid and oxo derivatives to thiones with phosphorus pentasulfide (ref. 3). Recently, Weiss, Robins, and Noell have prepared amino derivatives from 7-alkylthio-v-triazolo[4,5-d]pyrimidines (ref. 3j).

(7) F. R. Basford, F. H. S. Curd, E. Hoggarth, and F. L. Rose, *J. Chem. Soc.*, 1354 (1947).

CHART I



tained when an excess of *p*-anisidine or of *p*-chloroaniline was employed in the procedure used for the alkylamino derivatives.

Coupling of the alkylaminopyrimidines (IIa–b) with *p*-chlorobenzenediazonium chloride was conducted, in aqueous acetic acid buffered with sodium acetate, by a procedure similar to that used by Boon[8] with related pyrimidines. The coupling reaction with 2-amino-4-(*p*-anisidino)-6-chloropyrimidine (IIc) proved to be more difficult to effect. Although yields of 70–92% of the *p*-chlorophenylazo derivatives IVa and IVb were obtained, 2-amino-4-(*p*-anisidino)-6-chloro-5-(*p*-chlorophenylazo)pyrimidine (IVc) was isolated only in low yield. An improved yield (64%) was obtained by conducting the reaction in aqueous ethanol containing pyridine to stabilize the diazonium salt, employing an excess of diazonium salt, and adding the pyrimidine to the diazonium salt solution.

Reductive removal of halogen from halopyrimidines is a well-known synthetic tool in the pyrimidine field.[9] For this reason it was anticipated that reduction of the 5-arylazopyrimidines to the 5-amino derivatives (Va–c), without reductive dehalogenation, might be the crucial step in the projected synthetic scheme. An investigation of several methods of chemical reduction of the ethylamino derivative resulted in the isolation of 2,5-diamino-6-chloro-4-ethylaminopyrimidine (Va) in yields of 70–75%. Because of the ease of isolation of the product, reduction with zinc and acetic acid was the most convenient of the methods tried, although the stannous chloride–hydrochloric acid and iron–hydrochloric acid reagents also afforded good yields of Va. 2,5-Diamino-4-butylamino-6-chloropyrimidine (Vb) was more difficult to isolate and to free of colored impurities, which, if not removed at this stage, gave colored products in the subsequent cyclization and substitution reactions. Removal of the colored by-products was achieved by a process of selective precipitation depending on *p*H. No attempt was made to prepare a pure specimen of the *p*-anisidino derivative (Vc) after trial recrystallizations caused further discoloration.

Treatment of the 4,5-diaminopyrimidines with sodium nitrite in aqueous acetic acid afforded good yields of the 3-alkyl-7-chloro-3*H*-*v*-triazolo[4,5-*d*]-pyrimidines (VIa,b). The *p*-anisidino derivative (VIc) was prepared without isolating the 4,5-diaminopyrimidine Vc.

The 7-chloro substituent was readily displaced by nucleophilic reagents of considerable variety. In alkaline solution, the 7-chloro derivatives were converted to 5-amino-3-alkyl-3*H*-*v*-triazolo[4,5-*d*]-pyrimidin-7(6*H*)-ones (VIIa,b), desired for comparative biochemical studies.[10] Other reagents that easily effected displacement were hydrosulfide, ethoxide, hydrazine, diisopropyl phosphite, ammonia, simple alkyl and aryl amines, substituted amines, and histamine. No attempt was made to define the optimum conditions for the displacement reactions; in general, they were conducted at the reflux temperature of the reaction mixture during arbitrarily fixed reaction periods. With several reagents—for example, ethoxide, ethanolamine, hydrazine, and hydrosulfide—reaction appeared to occur rapidly. These observations are in accord with the expectation that substituents on the *v*-triazolo[4,5-*d*]pyrimidine ring would undergo nucleophilic displacement with greater ease than the corresponding substituents on the purine ring.

The 7-benzylthio-3-ethyl derivative (XI) was prepared by alkylating the 7[6*H*]thione[11] by the method of Johnston, Holum, and Montgomery,[12] and a 7-phosphonic acid (XIV) was obtained by hydrolyzing the corresponding diisopropyl phos-

(8) W. R. Boon, *J. Chem. Soc.*, 2146 (1957).

(9) G. W. Kenner and A. Todd, Chap. 7, *Heterocyclic Compounds*, Vol. 6, R. C. Elderfield, ed., John Wiley and Sons, Inc., N. Y., 1957.

(10) R. W. Brockman, C. Sparks, D. J. Hutchison, and H. E. Skipper, *Cancer Res.*, 19, 177 (1959).

(11) Although compounds IX and X are written (Table I) as 7-thiols, they are probably 7(6*H*)-thiones. See, for example, E. Spinner, *J. Chem. Soc.*, 1237 (1960); A. Albert and G. B. Barlin, *J. Chem. Soc.*, 2384 (1959); and R. A. Jones and A. R. Katritzky, *J. Chem. Soc.*, 3610 (1958), for investigations of other heterocyclic thiones.

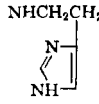
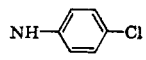
(12) T. P. Johnston, L. B. Holum, and J. A. Montgomery, *J. Am. Chem. Soc.*, 80, 6265 (1958).

TABLE I

3*H*-*v*-TRIAZOLO[4,5-*d*]PYRIMIDINES. ULTRAVIOLET ABSORPTION DATA[a]

No.	Compound R	Compound X	λ_{max} in mμ (ε × 10^{-3})[b] Ethanol	0.1*N*HCl	*p*H 7	0.1*N*NaOH
VIa	C_2H_5		224 (26.3) 242 (sh.) 316 (7.0)			
VIb	C_4H_9		225 (28.2) 243 (sh.) 316 (7.2)	224 (24.2) 242 (sh.) 316 (7.0)	224 (25.8) 242 (sh.) 316 (7.6)	 244 (5.4) 285 (9.7)
VIc	*p*-$CH_3OC_6H_4$		250 (23.7) 316 (8.4)			
VIIa	C_2H_5		254 (13.4) 270 (sh.)	252 (11.6) 267 (sh.)	252 (11.2) 270 (7.8)	255 (sh.) 277 (10.2)
VIIb	C_4H_9		256 (13.6) 270 (sh.)	253 (11.7) 267 (7.9)	253 (11.2) 270 (7.9)	255 (sh.) 278 (10.5)
VIII	C_2H_5	OC_2H_5	243 (5.8) 288 (9.1)	242 (4.6) 282 (10.2)	243 (5.0) 288 (9.3)	243 (4.9) 288 (9.4)
IX	C_2H_5	SH	232 (13.3) 263 (7.0) 338 (19.2)	233 (16.4) 263 (7.0) 338 (19.2)	231 (15.5) 256 (7.2) 336 (17.6) 282 (4.6)	252 (8.1) 289 (8.2) 328 (16.3)
X	C_4H_9	SH	232 (13.3) 263 (6.8) 338 (19.6)	233 (16.6) 263 (6.8) 338 (19.1)	232 (14.7) 256 (6.9) 280 (4.6) 336 (17.0)	252 (8.0) 288 (8.2) 328 (16.6)
XI	C_2H_5	$SCH_2C_6H_5$	222[c] (23.4) 247 (9.3) 272 (9.7) 317 (11.5)	220[c] (21.4) 245 (sh.) 279 (9.6) 316 (12.9)	222[c] (21.7) 245 (sh.) 276 (8.9) 318 (12.4)	 245 (sh.) 276 (8.9) 317 (11.5)
XII	C_4H_9	$NHNH_2$	219[c] (18.7) 291 (11.5)	255 (9.9) 286 (10.0)	218[c] (18.9) 291 (11.3)	 245 (sh.) 315 (6.3)
XIII	C_2H_5	$PO[O(CH_3)_2]_2$	226 (21.8) 272 (1.7) 338 (6.4)	224 (21.5) 273 (2.0) 340 (6.6)	224 (20.6) 272 (1.4) 340 (6.1)	 277 (9.8)
XIV	C_2H_5	$PO(OH)_2$	223 (21.8) 323 (6.7)			
XV	C_2H_5	NH_2	224[c] (25.2) 258 (5.6) 286 (9.2)	214[c] (25.6) 253 (9.6) 282 (7.0)	223[c] (24.6) 257 (5.5) 287 (9.6)	222 (25.2) 257 (5.5) 287 (9.6)
XVI	C_4H_9	NH_2	224[c] (25.7) 258 (5.9) 287 (9.7)	214[c] (25.6) 254 (9.6) 283 (7.1)	223[c] (25.1) 257 (5.5) 287 (9.7)	223 (24.5) 258 (5.5) 287 (9.7)
XVII	C_4H_9	NHC_4H_9	220[c] (sh.) 229 (21.1) 265 (sh.) 289 (12.6)	214[c] (24.3) 230 (sh.) 259 (13.0) 277 (10.3) 283 (sh.) 295 (sh.)	221[c] (18.7) 230 (18.7) 265 (sh.) 291 (12.8)	 231 (19.0) 265 (sh.) 291 (13.0)
XVIII	C_2H_5	$NHCH_2CH_2OH$		216[c] (20.3) 230 (sh.) 258 (13.9) 274 (10.9) 283 (sh.) 295 (sh.)	219[c] (19.4) 228 (19.4) 265 (sh.) 289 (11.9)	 229 (19.1) 265 (sh.) 290 (11.9)
XIX	C_2H_5	$N(CH_3)_2$	216[c] (sh.) 233 (20.1) 237 (sh.) 270 (sh.) 290 (12.8)	216[c] (18.1) 227 (sh.) 233 (sh.) 262 (15.0) 275 (sh.) 285 (sh.) 300 (sh.)	216[c] (15.8) 233 (18.1) 238 (sh.) 270 (sh.) 292 (13.4)	 233 (18.7) 238 (sh.) 270 (sh.) 292 (13.4)
XX	C_4H_9	$N(CH_2CH_2OH)_2$	235 (18.7) 239 (sh.) 273 (sh.) 293 (13.6)	227 (sh.) 234 (sh.) 267 (18.9) 280 (sh.) 290 (sh.) 305 (sh.)	235 (16.8) 240 (sh.) 273 (sh.) 294 (14.1)	235 (17.0) 240 (sh.) 273 (sh.) 295 (14.4)

TABLE I (*Continued*)

No.	Compound R	Compound X	λ_{max} in mμ (ε × 10^{-3})[b] Ethanol	0.1*N*HCl	*p*H 7	0.1*N*NaOH
XXI	C_2H_5	$NHCH_2CH_2$ | $(C_2H_5)_2N$	229 (20.4) 266 (sh.) 289 (12.3)	222 (15.3) 230 (sl. sh.) 256 (15.7) 272 (13.3) 300 (sh.)	224 (19.9) 260 (6.3) 290 (11.3)	 265 (sh.) 291 (12.3)
XXII	C_4H_9		218[c] (22.8) 227 (sh.) 265 (sh.) 290 (12.8)	214[c] (23.4) 230 (sl. sh.) 258 (15.5) 274 (sh.) 285 (sl. sh.) 298 (sh.)	217[c] (22.2) 227 (sh.) 265 (sh.) 291 (12.2)	 228 (sh.) 265 (sh.) 291 (12.8)
XXIII	C_4H_9		256 (11.5) 280 (sh.) 314 (24.7)	 302 (18.3)		

[a] Spectra were determined in the region 220–400 mμ unless indicated otherwise (footnote *c*). [b] sh. = shoulder or inflection (wave length estimated). [c] Spectrum determined in the region 210–400 mμ.

phonate (XIII). The *v*-triazolo[4,5-*d*]pyrimidines prepared are listed in Table I with ultraviolet absorption data. The ethanolic spectrum of 5-amino - 3 - ethyl - 7 - ethoxy - 3*H* - *v* - triazolo-[4,5-*d*]pyrimidine (VIII) shows absorption at 243 mμ and 288 mμ, whereas the 3-alkyl-8-azaguanines (VIIa,b) have a maximum at 254 mμ with a slight inflection near 270 mμ. This difference indicates that VIIa and VIIb are predominantly in the amide form as written, and this structure in the solid state is supported by the presence of a carbonyl band above 1700 $cm.^{-1}$ in the infrared spectra.

The chemotherapeutic incentive for this investigation derives from the fact that 3-alkyl-3*H*-*v*-triazolo[4,5-*d*]pyrimidines are purine analogs that are blocked at the position corresponding to the point of attachment of the ribofuranoside moiety of purine ribonucleotides. Such derivatives of 5-amino - *v* - triazolo[4,5 - *d*]pyrimidin - 7(6*H*) - one (8-azaguanine) may be of interest because they are derivatives of a compound having widespread biological activity.[13] Biochemical studies, however, indicate that the activity of 8-azaguanine in bacterial and neoplastic systems is due primarily to enzymatic conversion to its ribonucleotide[10,14]; preventing ribotidation by blocking position 3 should result in loss of this mechanism of action. 5 - Amino - 3 - ethyl - 3*H* - *v* - triazolo[4,5 - *d*]-pyrimidine (9-ethyl-8-azaguanine) (VIIa) was, indeed, without effect on an organism, *Streptococcus faecalis*, sensitive to 8-azaguanine.[10] Subsequently, the synthesis of several 3-substituted 5-amino-3*H*-*v*-triazolo[4,5-*d*]pyrimidin-7(6*H*)-ones by the conventional method has been reported.[3i] The method of synthesis described here permitted the preparation from a common intermediate (VI) of a variety of blocked purine analogs in addition to the 9-substituted 8-azaguanines. Mechanisms of action other than ribotidation are possible, and the importance of having a variety of *v*-triazolo[4,5-*d*]-pyrimidines blocked at position 3 is attested by recent findings with derivatives of purine-6(1*H*)-thione (6-mercaptopurine). Wheeler, Kelley, and Montgomery[15] have shown that sublines of neoplastic cells (Human Epidermoid Carcinoma No. 2) resistant to purine-6(1*H*)-thione are highly sensitive to certain of its 9-substituted derivatives. Preliminary tests indicate that compounds XII, XVII, and XXII have moderate activity against Sarcoma 180 in mice and that compounds VIb and XVI are active against Adenocarcinoma 755.[16]

EXPERIMENTAL

Melting points followed by the designation "cap." were determined in a capillary tube heated in an oil bath; those designated "Al block" were determined in a capillary tube heated in an aluminum block; and all others were determined on a Kofler Heizbank and are corrected. Ultraviolet spectra were determined either with a Beckman Model DK-2 spectrophotometer (with optical densities at the maxima measured with a Beckman Model DU) or with a Cary Model 14 spectrophotometer. Infrared spectra of all the compounds reported were determined with a Perkin-Elmer Model 21 spectrophotometer and the potassium bromide disk technique.

2-Amino-4-butylamino-6-chloropyrimidine (IIb). A mixture composed of 6.14 g. (84 mmoles) of butylamine, 6.56 g. (40 mmoles) of 2-amino-4,6-dichloropyrimidine,[17] and 120 ml. of absolute ethanol was heated, with stirring, at the reflux temperature for 6 hr. and was then concentrated *in vacuo* to about 40 ml. Water (40 ml.) was added slowly to the stirred ethanol solution until saturation was attained,

(13) H. G. Mandel, *Pharmacol. Revs.*, 11, 743 (1959); R. E. F. Matthews, p. 270 of ref. 3m.

(14) R. W. Brockman, L. L. Bennett, Jr., M. S. Simpson, A. K. Wilson, J. R. Thomson, and H. E. Skipper, *Cancer Res.* 19, 856 (1959); R. W. Brockman, C. Sparks, M. S. Simpson, and H. E. Skipper, *Biochem. Pharmacol.*, 2, 77 (1959).

(15) G. P. Wheeler, G. G. Kelley, and J. A. Montgomery, *Proc. Am. Assoc. Cancer Res.*, 3, 277 (1961).

(16) Biological data were furnished by Dr. F. M. Schabel, Jr., Dr. W. R. Laster, Jr., and associates of the Chemotherapy Division, Southern Research Institute.

(17) E. Büttner, *Ber.*, 36, 2227 (1903).

seed crystals from an earlier experiment were introduced, and the dropwise addition of water to the stirred suspension was continued until a total of 80 ml. had been added. The crystalline product was collected on a filter, washed with 35% aqueous ethanol and with water, and dried *in vacuo* at 40°; yield, 7.3 g. (91.5%); m.p. 95–97°. Two recrystallizations from cyclohexane gave colorless needles of 2-amino-4-butylamino-6-chloropyrimidine having a m.p. of 97–98°; λ_{max} in mμ ($\epsilon \times 10^{-3}$) in ethanol: 240 (10.9) and 284 (8.6).

Anal. Calcd. for $C_8H_{13}N_4Cl$: C, 47.88; H, 6.53; N, 27.92. Found: C, 47.90; H, 6.64; N, 27.72.

2-Amino-4-chloro-6-ethylaminopyrimidine (IIa). The use of an autoclave reaction for the preparation of this compound is reported to leave some starting material unchanged.[18] The compound is conveniently prepared under atmospheric pressure and in high yield by the following method. A solution of 56.1 g. (0.34 mole) of 2-amino-4,6-dichloropyrimidine, 250 ml. of absolute ethanol, and 250 ml. of ethanolic ethylamine—prepared from 148 g. (3.28 moles) of anhydrous ethylamine and 830 ml. of absolute ethanol—was heated at the reflux temperature for 2 hr. The reaction was carried out in a flask equipped with a water-cooled condenser surmounted by a Dewar-type condenser containing solid carbon dioxide, and the reaction mixture was protected from atmospheric moisture with a tube of calcium chloride. The remainder of the ethylamine solution was added, refluxing was continued for 4 hr., and the reaction solution was then concentrated *in vacuo* to about 175 ml. and chilled. The crystalline product was collected on a filter, washed with three 30-ml. portions of water, and dried *in vacuo* over phosphorus pentoxide; wt., 43.6 g. (74%); m.p. 147–148°. After molten material had been allowed to cool and resolidify, it remelted at 153–154°. Additional product was obtained by diluting the filtrate with water: wt., 10.1 g. (total yield, 91%); m.p. 144–146°. A specimen of 2-amino-4-chloro-6-ethylaminopyrimidine that had been recrystallized from 2-propanol and then sublimed had melting points of 149° and 154° (lit.[18] m.p. 152.5°); λ_{max} in mμ ($\epsilon \times 10^{-3}$) in ethanol: 239 (10.8) and 284 (8.5).

Anal. Calcd. for $C_6H_9N_4Cl$: C, 41.74; H, 5.26; N, 32.46; Cl, 20.56. Found: C, 41.71; H, 5.09; N, 32.45; Cl, 20.74.

2-Amino-4-(p-anisidino)-6-chloropyrimidine (IIc) was obtained by fusing equimolar quantities of 2-amino-4,6-dichloropyrimidine, *p*-anisidine, and acetic acid[7]; yield, 53%; m.p. 223–224°; λ_{max} in mμ ($\epsilon \times 10^{-3}$) in ethanol: 242 (sh.), 272 (11.5), 300 (18.4). A procedure similar to that used to prepare the alkylamino derivatives gave the disubstitution product (below); the use of equimolar amounts of *p*-anisidine and potassium carbonate in refluxing ethanol gave a 15% yield of the desired monosubstitution product.

2-Amino-4,6-bis(p-anisidino)pyrimidine (III. Y = OCH_3). A solution of 10 g. (61 mmoles) of 2-amino-4,6-dichloropyrimidine, 30 g. (244 mmoles) of *p*-anisidine, and 200 ml. of ethanol was heated at the reflux temperature for 5.5 hr. A crystalline precipitate was removed by filtration from the chilled mixture. In order to remove any *p*-anisidine or its hydrochloride, the product was washed several times with 1*N* hydrochloric acid and then heated briefly to boiling with 150 ml. of 1*N* hydrochloric acid. After having been dried *in vacuo* over phosphorus pentoxide, the pale lavender crystals weighed 12.3 g. (m.p. 250–255°). A second crop of purple solid, which remained after the residue from the filtrate had been leached with 1*N* hydrochloric acid, amounted to 7.2 g. (m.p. 250–255°). The crude product (total yield, 85%) was recrystallized twice, with the aid of decolorizing carbon, from ethanol. The hydrochloride, a white crystalline solid with a lavender cast, melted at 257–261° (Al block).

Anal. Calcd. for $C_{18}H_{18}N_6O_2 \cdot HCl$: C, 57.87; H, 5.40; N, 18.74. Found: C, 57.81; H, 6.07; N, 18.79.

(18) H. S. Forrest, R. Hull, H. J. Rodda, and A. R. Todd, *J. Chem. Soc.*, 3 (1951).

An ethanolic solution of crude hydrochloride was made basic with aqueous sodium hydroxide and concentrated. The faintly lavender precipitate was leached with hot ethyl acetate and then was recrystallized twice from ethyl acetate. The white needles melted at 195–196° and, after cooling, remelted at 203–204°; λ_{max} in mμ ($\epsilon \times 10^{-3}$) in ethanol: 253 (22.9) and 300 (31.5).

Anal. Calcd. for $C_{18}H_{18}N_6O_2$: C, 64.21; H, 5.68; N, 20.79. Found: C, 64.29; H, 5.45; N, 20.72.

2-Amino-4,6-bis(p-chloroanilino)pyrimidine (III. Y = Cl) was obtained as a monohydrochloride monoethanolate by using a ten-fold excess of *p*-chloroaniline, in a procedure patterned after that for the preparation of the bis(*p*-anisidino) derivative, and by recrystallizing the crude product from ethanol; m.p. 298–301° (Al block).

Anal. Calcd. for $C_{16}H_{12}N_5Cl_2 \cdot HCl \cdot C_2H_5OH$: C, 50.42; H, 4.70; N, 16.34; Cl, 24.81. Found: C, 50.19; H, 4.64; N, 16.55; Cl, 25.06.

The free base was recrystallized from ethyl acetate: m.p. 193°.

Anal. Calcd. for $C_{16}H_{12}N_5Cl_2$: C, 55.52; H, 3.78; N, 20.22; Cl, 20.46. Found: C, 55.83; H, 3.96; N, 20.06; Cl, 20.23.

2-Amino-4-chloro-5-(p-chlorophenylazo)-6-ethylaminopyrimidine (IVa). A cold (0–5°) solution of *p*-chlorobenzenediazonium chloride that had been prepared from 39.4 g. (0.31 mole) of *p*-chloroaniline, 23.8 g. (0.345 mole) of sodium nitrite, 86 ml. of concd. hydrochloric acid, and 245 ml. of water was added dropwise during 6.5 hr. to a stirred solution of 48.7 g. (0.282 mole) of 2-amino-4-chloro-6-ethylaminopyrimidine, 424 g. of sodium acetate, 1410 ml. of glacial acetic acid, and 1175 ml. of water. Stirring was continued for 11.5 hr. at room temperature. By using a jacketed addition funnel through which cold water was circulated, the diazonium salt solution was maintained at 0–5° during the addition period; a nitrogen atmosphere was employed during the addition and subsequent stirring. The yellow crystalline precipitate was collected by filtration, washed five times with 300-ml. portions of water, and dried *in vacuo* over phosphorus pentoxide; yield, 73.2 g. (83%); m.p. 257–258°, dec.(cap.). This material could be reduced in good yield without further purification. Recrystallization of a specimen from ethyl acetate–acetone–benzene and then from a large volume of ethyl acetate gave yellow needles with a melting temperature of 263–264°, dec. (cap., inserted at 250°).

Anal. Calcd. for $C_{12}H_{12}N_6Cl_2$: C, 46.31; H, 3.89; N, 27.01; Cl, 22.79. Found: C, 46.46; H, 4.06; N, 27.14; Cl, 22.83.

2-Amino-4-butylamino-6-chloro-5-(p-chlorophenylazo)pyrimidine (IVb). A procedure similar to that described for the preparation of the ethylamino derivative (IVa) furnished 2-amino-4-butylamino-6-chloro-5-(*p*-chlorophenylazo)pyrimidine in yields of 70–92% (m.p. 195–197°). Two recrystallizations of a specimen from 2-propanol furnished golden needles that melted at 197–198° (cap.).

Anal. Calcd. for $C_{14}H_{16}N_6Cl_2$: C, 49.56; H, 4.75; N, 24.77; Cl, 20.90. Found: C, 49.45; H, 4.80; N, 24.81; Cl, 21.10.

2-Amino-4-(p-anisidino)-6-chloro-5-(p-chlorophenylazo)-pyrimidine (IVc). A cold solution composed of 7.0 g. of 2-amino-4-(*p*-anisidino)-6-chloropyrimidine (28 mmoles), 700 ml. of ethanol, and 140 ml. of pyridine was added dropwise to a stirred solution of *p*-chlorobenzenediazonium chloride maintained at 0–5°. The diazonium salt solution had been prepared from 14.3 g. (112 mmoles) of *p*-chloroaniline, 50 ml. of concd. hydrochloric acid, 200 ml. of ethanol, 80 ml. of water, and 9.52 g. (138 mmoles) of sodium nitrite. The pyrimidine solution was added over a period of 3 hr.; the mixture was stirred for 3 more hr. and then stored at 5° overnight. The orange, crystalline precipitate was removed by filtration, washed twice with 50-ml. portions of water, and dried *in vacuo* over phosphorus pentoxide at 80° for 5 hr.; yield, 7.0 g. (64%); m.p. 271–274° (Al block, inserted at 250°). Two recrystallizations of a crude specimen from mixtures of ethanol and 2-methoxyethanol gave yellow needles that melted at 282–283° (Al block, inserted at 255°).

Anal. Calcd. for $C_{17}H_{14}N_6OCl_2$: C, 52.45; H, 3.63; N, 21.59; Cl, 18.22. Found: C, 52.41; H, 3.90; N, 21.68; Cl, 18.06.

Reduction of 2-amino-4-chloro-5-(p-chlorophenylazo)-6-ethylaminopyrimidine with zinc and acetic acid. A suspension consisting of 25.2 g. (0.081 mole) of 2-amino-4-chloro-5-(*p*-chlorophenylazo)-6-ethylaminopyrimidine, 625 ml. of ethanol, 625 ml. of water, and 62.5 ml. of glacial acetic acid was heated to 70° with vigorous stirring in a nitrogen atmosphere. Sixty grams (0.83 mole) of zinc dust was added in small portions during 1 hr., and the mixture was heated at 70° for an additional hr. Excess zinc was then removed from the hot mixture by filtration and was washed three times with 20-ml. portions of ethanol. The filtrate, combined with the ethanol washings, was concentrated under reduced pressure in an atmosphere of nitrogen to about 350 ml. After the mixture had cooled to room temperature, the precipitate was collected on a filter and washed three times with 50-ml. portions of ether. The red crystals obtained were dried *in vacuo* over phosphorus pentoxide; yield, 11.3 g. (74%); m.p. 210–213° (Kofler); λ_{max} in ethanol = 306 mμ (ϵ = 7510). This material was used without further purification for the preparation of 5-amino-7-chloro-3-ethyl-3*H*-*v*-triazolo[4,5-*d*]pyrimidine. A specimen of 2,5-diamino-4-chloro-6-ethylaminopyrimidine (Va) was obtained as beige crystals by recrystallizing the crude product from ethanol; m.p. 207–208° (cap., inserted at 190°); λ_{max} in mμ ($\epsilon \times 10^{-3}$) in ethanol: 240 mμ (sh.) and 306 (7.55).

Anal. Calcd. for $C_6H_{10}ClN_5$: C, 38.43; H, 5.35; Cl, 18.91. Found: C, 38.58; H, 5.42; Cl, 18.72.

With stannous chloride. A mixture of 1.0 g. of the *p*-chlorophenylazo derivative and 20 ml. of ethanol, under an atmosphere of nitrogen, was stirred while a solution of 2.75 g. of stannous chloride dihydrate in 20 ml. of concd. hydrochloric acid was added dropwise over a period of 15 min. The mixture was heated at 55–60° for 45 min., during which time complete dissolution occurred. The reaction solution was cooled to room temperature, treated with a solution of 16 g. of sodium hydroxide in 40 ml. of water, allowed to stand for 1 hr., and filtered to remove a precipitate, which was washed with two 5-ml. portions of water and dried *in vacuo* over phosphorus pentoxide. Treatment of a portion of the precipitate with hydrogen sulfide gave a black precipitate of stannous sulfide. Sublimation of a 200-mg. sample of the crude product (710 mg.) gave 130 mg. (corresponding to a yield of 76%) of the 5-amino derivative: m.p. 208–209° (cap.), 213–214° (Kofler). The sublimate was recrystallized from ethanol.

Anal. Found: C, 38.47; H, 5.37.

With iron and hydrochloric acid. 2,5-Diamino-4-chloro-6-ethylaminopyrimidine was obtained as red crystals by reduction of the 5-*p*-chlorophenylazo derivative with iron powder and hydrochloric acid in an ethanol–acetic acid–water medium; yield, 71%; m.p. 209–212°; infrared spectrum identical with the products of the reduction with zinc and with stannous chloride.

2,5-Diamino-4-butylamino-6-chloropyrimidine (Vb). A reduction of 50.4 g. of 2-amino-4-butylamino-6-chloro-5-(*p*-chlorophenylazo)pyrimidine with 120 g. of zinc dust in 1260 ml. of ethanol, 1260 ml. of water, and 126 ml. of glacial acetic acid was performed according to the procedure for the ethylamino derivative (IVa). The red solution obtained by removal of the excess zinc by filtration (under nitrogen) was cooled in an ice bath and made alkaline to *p*H 9–10 with 6*N* sodium hydroxide solution (approximately 420 ml.). Activated carbon and diatomaceous silica (Celite) were added to the mixture to facilitate removal of the finely-divided precipitate, and the mixture of solids was then removed by filtration (under nitrogen) through a layer of Celite. The orange-red filtrate was neutralized to *p*H 7 with acetic acid (32 ml.), concentrated under diminished pressure at temperatures below 40° to about 1.5 l., and cooled at 5°. The red, crystalline precipitate was collected on a filter, washed with two 30-ml. portions of water, stirred twice with 100-ml. portions of cyclohexane–isopropyl ether (1:1), and dried *in vacuo* over phosphorus pentoxide; yield 29.2 g. (92%); m.p.[19] 106–107°; λ_{max} in ethanol = 305 mμ (ϵ = 6,940).

A solution of 10.6 g. of the crude product in 120 ml. of 1*N* hydrochloric acid was filtered to remove insoluble material, and the *p*H of the filtrate was raised to 5. Colored impurities precipitated. After the resulting mixture had been treated with activated carbon and filtered, the filtrate was made basic to *p*H 9 with 6*N* sodium hydroxide solution and chilled. The pale pink crystals were removed by filtration, washed four times with 50-ml. portions of water, and dried *in vacuo* over phosphorus pentoxide at 45°; yield, 6.7 g.; m.p. 125°. Sublimation under reduced pressure gave white crystals; m.p.[19] 125–126°.

Spectral data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): 236(14.8), 297 (7.35) in 0.1*N* hydrochloric acid; 240 (sh.), 303 (8.65) at *p*H 7; 240 (sh.), 302 (8.3) in 0.1*N* sodium hydroxide; 240 (sh.), 306 (8.0) in ethanol.

Anal. Calcd. for $C_8H_{14}ClN_5$: C, 44.52; H, 6.54; Cl, 16.44; N, 32.47. Found: C, 44.35; H, 6.52; Cl, 16.46; N, 32.62.

2,5-Diamino-4-(p-anisidino)-6-chloropyrimidine (Vc). A reduction of 2-amino-4-(*p*-anisidino)-6-chloro-5-(*p*-chlorophenylazo)pyrimidine with zinc, by the procedure used for the 4-ethylamino derivative, gave a rust-brown crystalline product (25% yield) that melted at 158–160° dec. A second crop (m.p. 154–156° dec.) raised the yield of crude product to 75%. After initial efforts to recrystallize this material resulted in extensive darkening, no further attempts were made to obtain a pure specimen.

5-Amino-7-chloro-3-ethyl-3H-v-triazolo[4,5-d]pyrimidine (VIa). A solution of 11.3 g. (60.3 mmoles) of 2,5-diamino-4-chloro-6-ethylaminopyrimidine in 900 ml. of water and 180 ml. of glacial acetic acid was cooled to 0–5°, and a solution of 4.45 g. (64.5 mmoles) of sodium nitrite in 20 ml. of water was added dropwise, during a period of 1 hr., to the stirred pyrimidine solution. The product began to precipitate during the addition of the nitrite solution. The reaction mixture was stirred at 0–5° for an additional hour; and the crystalline precipitate was then collected by filtration, washed three times with 75-ml. portions of water, and dried *in vacuo* over phosphorus pentoxide; yield, 9.4 g. (79%); m.p. 159–160°. Recrystallization of a specimen from ethanol gave white crystals with the same melting temperature and ultraviolet spectrum.

Anal. Calcd. for $C_6H_7ClN_6$: C, 36.28; H, 3.55; N, 42.32; Cl, 17.85. Found: C, 36.34; H, 3.47; N, 42.31; Cl, 18.04.

5-Amino-3-butyl-7-chloro-3H-v-triazolo[4,5-d]pyrimidine (VIb). The procedure used for the preparation of the 3-ethyl derivative gave an 82% yield of 5-amino-3-butyl-7-chloro-3*H*-*v*-triazolo[4,5-*d*]pyrimidine. White needles obtained by recrystallization of the reaction product from isopropyl ether–cyclohexane melted at 88–89°.

Anal. Calcd. for $C_8H_{11}ClN_6$: C, 42.38; H, 4.89; Cl, 15.64; N, 37.08. Found: C, 42.47; H, 5.07; Cl, 15.42; N, 37.10.

Reduction of 2-amino-4-butylamino-6-chloro-5-(*p*-chlorophenylazo)pyrimidine with zinc and treatment (at 0–5°) of the reaction mixture, after removal of the excess zinc, with 2.05 equivalents of sodium nitrite gave an amorphous red product from which some VIb was obtained after laborious purification. A small amount of 5-amino-3-butyl-7-(*p*-chloroanilino)-3*H*-*v*-triazolo[4,5-*d*]pyrimidine (XXIII) was also isolated, although sufficient nitrite was present to diazotize both the *p*-chloroaniline and the 5-aminopyrimidine from the reduction reaction. The infrared and ultraviolet spectra of the 7-*p*-chloroanilino derivative showed it to be identical with a specimen prepared by treating VIb with *p*-chloroaniline (below).

5-Amino-3-(p-anisyl)-7-chloro-3H-v-triazolo[4,5-d]pyrimidine (VIc). A solution of 2,5-diamino-4-(*p*-anisidino)-6-chloropyrimidine, prepared by reducing 2.5 g. (6.4 mmoles) of the 5-(*p*-chlorophenylazo) derivative and removing the

(19) Polymorphic forms, both analytically pure, had melting points of 107° and 125–126°.

excess zinc by filtration under nitrogen, was treated with 945 mg. (13.7 mmoles) of sodium nitrite and additional acetic acid (6.5 ml.). The reaction was conducted at 0–5° for 1 hr. under an atmosphere of nitrogen. The dark, crystalline product was removed by filtration and dried; weight, 1.21 g. (68%); λ_{max} in mμ ($\epsilon \times 10^{-3}$) in ethanol, 248 (20.4) and 318 (8.5). White needles were obtained by recrystallizing the crude product twice, with the aid of decolorizing carbon, from ethyl acetate: m.p. 267–269° dec. (Al block, inserted at 250°).

Anal. Calcd. for $C_{11}H_9N_6ClO$: C, 47.74; H, 3.28; N, 30.38; Cl, 12.81. Found: C, 47.37; H, 3.58; N, 30.10; Cl, 12.70.

5-Amino-3-ethyl-3H-v-triazolo[4,5-d]pyrimidin-7(6H)-one-(9-ethyl-8-azaguanine) (VIIa). A solution of 3.1 g. of 5-amino-7-chloro-3-ethyl-3*H*-*v*-triazolo[4,5-*d*]pyrimidine, 250 ml. of ethanol, and 75 ml. of 1*N* aqueous sodium hydroxide was stirred at the reflux temperature for 7 hr. The reaction solution was concentrated to approximately 100 ml., acidified (*p*H 4.8) with concentrated hydrochloric acid, and filtered to remove the white crystalline product, which was washed twice with 10-ml. portions of water and dried *in vacuo* over phosphorus pentoxide; yield, 2.3 g. (82%); m.p. 295–296° dec. (cap.). The product could be recrystallized from ethanol or from 2-methoxyethanol–ethanol: m.p. 296–297° dec. (cap.); $\tilde{\nu}$ (potassium bromide), 1705 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_6H_8N_6O$: C, 40.00; H, 4.48; N, 46.65. Found: C, 40.09; H, 4.55; N, 46.70.

5-Amino-3-butyl-3H-v-triazolo[4,5-d]pyrimidin-7(6H)-one (VIIb) was prepared in 86% yield by the method described for the 3-ethyl derivative. The analytical sample was prepared by recrystallizing the reaction product from aqueous ethanol. Material obtained by acidification of the reaction mixture melted at 290–292° dec. (cap.) and showed carbonyl absorption at 1705 cm.$^{-1}$ (potassum bromide disk). The analytical sample had a m.p. of 284–285° dec. (cap.) and carbonyl absorption near 1740 cm.$^{-1}$ (potassium bromide disk). The two forms were shown to be identical by paper chromatography (in four solvent systems) and by identical ultraviolet spectra in ethanol.

Anal. Calcd. for $C_9H_{12}N_6O$: C, 46.15; H, 5.81; N, 40.37. Found: C, 46.15; H, 6.08; N, 40.49.

5-Amino-7-ethoxy-3-ethyl-3H-v-triazolo[4,5-d]pyrimidine (VIII). A solution of 7.0 g. of VIa in 400 ml. of dry ethanol was added to a solution of sodium ethoxide prepared from 1.214 g. of sodium and 80 ml. of dry ethanol. Sodium chloride began to separate within 1 min. The reaction mixture was successively heated to 70°, maintained at 70° for 10 min., cooled, acidified (*p*H 4–5) with concentrated hydrochloric acid, and evaporated to dryness under reduced pressure. Leaching the residue with two 500-ml. portions of hot benzene and evaporation of the benzene furnished 4.9 g. (68%) of crystals that melted at 120°. A specimen was recrystallized twice from benzene-cyclohexane (1:1); m.p. 120°.

Anal. Calcd. for $C_8H_{12}N_6O$: C, 46.15; H, 5.81; N, 40.37. Found: C, 45.89; H, 5.80; N, 40.59.

5-Amino-3-ethyl-3H-v-triazolo[4,5-d]pyrimidine-7(6H)-thione[11] (IX). A reagent solution saturated with hydrogen sulfide was prepared by introducing gaseous hydrogen sulfide into a solution of 5.75 g. of sodium in 300 ml. of absolute ethanol during 1.5 hr. The reaction mixture resulting from the addition of 6.5 g. of VIa was heated at the reflux temperature. The mixture became homogeneous momentarily and then clouded as sodium chloride formed; it was kept at reflux for 2 hr. The preparation of the reagent solution and the subsequent reaction were conducted in a flask equipped with a water-cooled condenser surmounted by a Dewar-type condenser containing solid carbon dioxide to condense hydrogen sulfide. The reaction mixture was protected from atmospheric moisture with a calcium chloride drying tube attached to the Dewar-type condenser. At the end of the heating period the reaction mixture was diluted with 100 ml. of water, treated with decolorizing carbon, and filtered. The yellow crystalline precipitate obtained by acidifying the filtrate to *p*H 2 was separated by filtration, washed thoroughly with water, and dried *in vacuo* at 50° over phosphorus pentoxide and sodium hydroxide pellets: weight, 4.1 g.; m.p. 200–202° dec. (cap.). Crude material, obtained in yields of 64–89%, could be purified by dissolving it in 0.5*N* sodium hydroxide solution, filtering, and re-precipitating the product by acidifying the filtrate to *p*H 2. An analytical sample was prepared by recrystallizing a specimen from ethanol. The melting temperature (dec.) varied with the method of determination: 210° (Kofler, specimen moved slowly up the scale); 199–201° (cap., inserted at 188°, temp. increased 2–3°/min.).

Anal. Calcd. for $C_6H_8N_6S$: C, 36.72; H, 4.11; N, 42.83; S, 16.34. Found: C, 36.65; H, 4.08; N, 42.59; S, 16.62.

5-Amino-3-butyl-3H-v-triazolo[4,5-d]pyrimidine-7(6H)-thione[11] (X) was prepared (82% yield) by a procedure similar to that employed in the preparation of the corresponding 3-ethyl derivative (IX). The thione was purified by acidification of a 0.5*N* sodium hydroxide solution to *p*H 2 or by recrystallization from 2-methoxyethanol-ethanol: m.p. 193–194°.

Anal. Calcd. for $C_8H_{12}N_6S$: C, 42.84; H, 5.39; N, 37.47; S, 14.30. Found: C, 42.84; H, 5.27; N, 37.43; S, 14.28.

5-Amino-7-benzylthio-3-ethyl-3H-v-triazolo[4,5-d]pyrimidine (XI). To a mixture of 5.67 g. of 5-amino-3-ethyl-3*H*-*v*-triazolo[4,5-*d*]pyrimidine-7-(6*H*)-thione, 4.39 g. of potassium carbonate, and 100 ml. of dimethylformamide was added 3.65 ml. of benzyl chloride in three portions. An increase in temperature of a few degrees (to 30°) occurred. The temperature of the reaction mixture was raised to 50° and maintained at 50–55° for 1 hr. The reaction mixture was cooled and poured into 600 ml. of water. The oil that separated was induced to crystallize to a tan-white solid, which was dried at 56° *in vacuo*. The crude solid (7.8 g.) appeared to be solvated; it softened at 65°, melted at 71–74°, resolidified, and remelted at 102°. This material was dissolved in 60 ml. of hot ethanol, the solution was treated with decolorizing carbon and filtered, and the hot filtrate was diluted with 40 ml. of water and allowed to cool. The solution deposited 5.25 g. (63%) of crystals that melted at 102°. The analytical sample (m.p. 102°) was prepared by recrystallizing a specimen from ethanol-water and was dried at 55° *in vacuo*.

Anal. Calcd. for $C_{13}H_{14}N_6S$: C, 54.52; H, 4.93; N, 29.35; S, 11.20. Found: C, 54.49; H, 5.09; N, 28.68; S, 11.16.

This compound appears to form moderately stable hydrates. Specimens giving analytical results in agreement with values calculated for a monohydrate and for a one-quarter hydrate were sometimes obtained.

5-Amino-3-butyl-7-hydrazino-3H-v-triazolo[4,5-d]pyrimidine (XII). To a stirred solution of 6.00 g. of VIb in 400 ml. of anhydrous ethanol was added 2.80 g. of hydrazine hydrate. A white solid separated after 2–3 min. After the mixture had been stirred at room temperature for 1 hr. and then chilled in an ice bath, the product was removed by filtration, washed with water, and dried *in vacuo* at 56°; yield, 5.10 g. (85.5%); m.p. 194–195° (cap.). A specimen that had been recrystallized from ethanol melted at 195° (cap., inserted at 185°).

Anal. Calcd. for $C_8H_{14}N_8$: C, 43.05; H, 6.32; N, 50.21. Found: C, 43.05; H, 6.30; N, 50.15.

Diisopropyl 5-amino-3-ethyl-3H-v-triazolo[4,5-d]pyrimidine-7-phosphonate (XIII). A mixture of 400 mg. of VIa and 8 ml. of triisopropyl phosphite was heated at 168° for 7 hr. The mixture was allowed to stand at 0–5° for 3 days. The crystalline precipitate was removed by filtration, slurried twice with 25-ml. portions of hexane, and dried *in vacuo* at 55°; weight, 507 mg.; m.p. 119°. Recrystallization from benzene-cyclohexane (1:1) gave 423 mg. (64% yield) of the diisopropyl phosphonate; m.p. 119°. A specimen (m.p. 119–120°) that had been recrystallized twice from benzene-cyclohexane was submitted for analysis.

Anal. Calcd. for $C_{12}H_{21}N_6O_3P$: C, 43.90; H, 6.45; N, 25.60; P, 9.44. Found: C, 44.04; H, 6.49; N, 25.51; P, 9.07.

5-Amino-3-ethyl-3H-v-triazolo[4,5-d]pyrimidine-7-phosphonic acid (XIV). A mixture of 100 mg. of the diisopropyl phosphonate (XIII) and 5 ml. of 1*N* hydrochloric acid was heated at the reflux temperature for 1 hr., and the reaction mixture was then freeze-dried. Addition of 3 ml. of ethanol to the residue caused the formation of a white solid. The product was removed by filtration, washed with ethanol, and dried *in vacuo* at 55°; weight, 20 mg. (27% yield); m.p. 271–273° dec. (cap.). The crude material was recrystallized from ethanol–water (3:1); m.p. 284–285° (Al block).

Anal. Calcd. for $C_6H_9N_6O_3P$: C, 29.51; H, 3.72; N, 34.42; P, 12.69. Found: C, 29.59; H, 3.71; N, 34.03; P, 12.57.

5,7-Diamino-3-ethyl-3H-v-triazolo[4,5-d]pyrimidine (XV). A mixture of 500 mg. of VIa and 25 ml. of ethanol saturated with ammonia was kept for 4 hr. at 95–100° in a 40-ml. stainless-steel bomb. The precipitated solid was separated by filtration, washed twice with 5-ml. portions of water, and dried *in vacuo* over phosphorus pentoxide; yield, 330 mg. (73%); m.p. 260–264°. Recrystallization from ethanol gave white crystals that had a m.p. of 263–264° (cap.).

Anal. Calcd. for $C_5H_9N_7$: C, 40.21; H, 5.07; N, 54.72. Found: C, 40.22; H, 4.89; N, 54.75.

5-Amino-7-dimethylamino-3-ethyl-3H-v-triazolo[4,5-d]pyrimidine (XIX). A solution consisting of 500 mg. of VIa, 40 g. of 25% aqueous dimethylamine, and 50 ml. of ethanol was heated at the reflux temperature for 2.5 hr. The reaction was conducted in a flask fitted with a water-cooled condenser surmounted by a Dewar-type condenser containing solid carbon dioxide. At the end of the heating period the solution was concentrated to a volume of approximately 20 ml. A white crystalline precipitate was separated by filtration, washed with 5-ml. portions of water, and dried *in vacuo* over phosphorus pentoxide; yield, 470 mg. (90%); m.p. 195–197°. Two recrystallizations from ethanol afforded the 7-dimethylamino derivative as white needles with a m.p. of 198–199°.

Anal. Calcd. for $C_8H_{13}N_7$: C, 46.36; H, 6.32; N, 47.32. Found: C, 46.12; H, 6.28; N, 47.63.

5,7-Diamino-3-butyl-3H-v-triazolo[4,5-d]pyrimidine (XVI) was obtained in 88% yield (m.p. 256–258°) by the procedure used to prepare the 7-dimethylamino-3-ethyl derivative (XIX) and in 91% yield by the method used to prepare XV. Recrystallization of a specimen from 2-methoxyethanol–ethanol gave white crystals; m.p. 256–258° (cap.).

Anal. Calcd. for $C_8H_{12}N_7$: C, 46.37; H, 6.32; N, 47.33. Found: C, 46.41; H, 6.41; N, 47.44.

5-Amino-3-butyl-7-[bis(2-hydroxyethyl)amino]-3H-v-triazolo[4,5-d]pyrimidine (XX). A solution of 300 mg. (1.32 mmoles) of VIb, 300 mg. (2.85 mmoles) of diethanolamine, and 15 ml. of anhydrous ethanol was heated at the reflux temperature for 4 hr. The reaction solution was then treated with decolorizing carbon and filtered. The filtrate, in combination with the ethanol (5 ml.) used to wash the carbon, was freed of the solvent by evaporation *in vacuo*. To the residual sirup, ethanol (10 ml.) was added and evaporated, and this operation was repeated. The solidified residue was triturated with 10 ml. of water, separated by filtration, washed with 5 ml. of water, and dried *in vacuo* over phosphorus pentoxide at 100°; yield, 325 mg. (98%); m.p. 124° (cap.). An analytical sample (m.p. 124–125°) was prepared by recrystallizing the product from ethyl acetate.

Anal. Calcd. for $C_{12}H_{21}N_7O_2$: C, 48.80; H, 7.17; N, 33.20. Found: C, 48.89; H, 7.16; N, 33.06.

5-Amino-3-ethyl-7-(2-hydroxyethylamino)-3H-v-triazolo[4,5-d]pyrimidine (XVIII) was prepared (96% yield) by the method used for XX. The reaction time was 45 min.; a precipitate began to form after 3 min. of heating. An analytical sample was prepared by recrystallizing the product twice from dimethylformamide–ethanol; m.p. 210°.

Anal. Calcd. for $C_8H_{13}N_7O$: C, 43.05; H, 5.87; N, 43.93. Found: C, 42.90; H, 6.12; N, 44.12.

5-Amino-7-(2-diethylaminoethylamino)-3-ethyl-3H-v-triazolo[4,5-d]pyrimidine (XXI) was obtained by the method employed for XX except that excess *N,N*-diethylethylenediamine was used. The product (78% yield) was recrystallized from ethanol; m.p. 168–169°.

Anal. Calcd. for $C_{12}H_{22}N_8$: C, 51.77; H, 7.97; N, 40.26. Found: C, 51.66; H, 7.58; N, 40.08.

5-Amino-3-butyl-7-butylamino-3H-v-triazolo[4,5-d]pyrimidine (XVII) was obtained (89% yield) by the method used for XX (reaction time, 1.75 hr.). The m.p., 160°, was unchanged after the product had been recrystallized from 50% aqueous ethanol.

Anal. Calcd. for $C_{12}H_{21}N_7$: C, 54.72; H, 8.04; N, 37.24. Found: C, 54.45; H, 8.06; N, 37.31.

5-Amino-3-butyl-7-[2-(4-imidazoyl)ethylamino]-3H-v-triazolo[4,5-d]pyrimidine (XXII). A solution of 6.0 g. (26.6 mmoles) of VIb, 5.08 g. (27.6 mmoles) of histamine dihydrochloride, 8.4 g. (83 mmoles) of triethylamine, and 250 ml. of anhydrous ethanol was heated under anhydrous conditions at the reflux temperature for 4 hr. The reaction mixture was diluted with 50 ml. of water, chilled, and filtered in order to remove a small amount (0.66 g.) of a high-melting solid. Concentrating the filtrate to approximately 40 ml. afforded 6.65 g. (83.5%) of the 7-histaminyl derivative; m.p. 190–193° dec. (cap.). Recrystallization of the crude product from 50% aqueous ethanol gave a 94% recovery of material having a m.p. of 193–194°.

Anal. Calcd. for $C_{13}H_{19}N_9$: C, 51.80; H, 6.35; N, 41.83. Found: C, 51.85; H, 6.42; N, 41.59.

5-Amino-3-butyl-7-(p-chloroanilino)-3H-v-triazolo[4,5-d]pyrimidine (XXIII) was prepared in 84% yield by the method used for XXII. A sample for analysis was prepared by recrystallizing the product from ethanol; m.p. 233°.

Anal. Calcd. for $C_{14}H_{16}N_7Cl$: C, 52.90; H, 5.07; N, 30.86; Cl, 11.16. Found: C, 52.86; H, 5.09; N, 30.69; Cl, 11.07.

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