96–96.5° (lit. m.p. ranged from 95 to 98°[4,10,16]); n.m.r. spectrum (CCl_4), a triplet (relative area 1.9) centered at −2.71, J = 6 c.p.s., and a quintuplet (relative area 1.0) centered at −2.06, J = 6 c.p.s. The infrared spectrum was identical with that given by Petrů and Galík.[10]

Anal. Calcd. for $C_{15}H_{16}$: C, 90.85; H, 9.15; Found: C, 90.62; H, 9.04.

Ozonolysis of 9.—Excess ozonized oxygen was passed through a solution of **9** (0.50 g., 0.0025 mole) in 50 ml. of methylene chloride at −78°. While the solution was still cold, 2 ml. of 30% aqueous hydrogen peroxide was added. The methylene chloride was evaporated leaving 0.71 g. (71%) of glutaric acid. Recrystallization from ether–hexane gave a material melting at 95–96°, which when mixed with an authentic sample melted at 95–96.5°. The infrared spectrum was identical with that of the authentic sample. According to the method of Shriner, Fuson, and Curtin,[17] the glutaric acid was converted to its di-*p*-bromophenacyl ester (81%) m.p. 137–138°, m.m.p. 137–138° with an authentic sample. The infrared spectra were identical.

(16) (a) O. Wallach, *Chem. Ber.*, **30**, 1094 (1897); (b) V. R. Skvarchenko, L. A. Chervoneva, J. I. Pastukhova, and R. Y. Levina, *Zh. Obshch. Khim.*, **29**, 2174 (1959); *Chem. Abstr.*, **54**, 10974 (1960); (c) W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, **127**, 1138 (1925); (d) S. C. S. Gupta and A. Bhattacharjee, *Sci. Cult.* (Calcutta), **19**, 157 (1953); (e) S. C. S. Gupta and A. Bhattacharjee, *J. Indian Chem. Soc.*, **31**, 897 (1954); (f) J. Plevek, *Chem. Listy*, **50**, 246 (1956); *Collection Czech. Chem. Commun.*, **21**, 368 (1956); (g) R. Mayer, *Chem. Ber.*, **89**, 1443 (1956).

Acknowledgment.—The financial assistance of the National Science Foundation and the Hooker Chemical Corporation is gratefully acknowledged.

(17) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 200.

8-Amino-7-chloro-s-triazolo[4,3-c]pyrimidine and Related Compounds[1]

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The third possible heterocyclic ring system derivable from 5-amino-4-chloro-6-hydrazinopyrimidine has now been prepared by a remarkably facile ring closure with diethoxymethyl acetate. The surprising specificity of this and previously described ring closure procedures is discussed.

Previous investigators have found that treatment of 4-hydrazinopyrimidines with formic acid gives rise to the *s*-triazolo[4,3-*c*]pyrimidine ring system, if the 4-hydrazinopyrimidines contain a tautomeric group at C-2.[2] Otherwise the product is the 4-(2-formylhydrazinopyrimidine). Shiho, *et al.*, found that one such 4-(2-formylhydrazino)pyrimidine could be cyclized under forcing conditions (*i.e.*, refluxing phosphorus oxychloride) to a *s*-triazolo[4,3-*c*]pyrimidine.[3]

We have found that treatment of 5-amino-4-chloro-6-hydrazinopyrimidine (II) with formic acid resulted in the formation of 9-formamidohypoxanthine (IXa)[4] *via* 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (VIa).[5] That no *s*-triazolo[4,3-*c*]pyrimidine was formed in this reaction is in keeping with the results described earlier, since this pyrimidine contains no tautomeric group at C-2 and the alternative ring closures take place relatively easily. We now wish to report a remarkably facile synthesis of 8-amino-7-chloro-*s*-triazolo[4,3-*c*]pyrimidine by the reaction of II with diethoxymethyl acetate and the synthesis of some related compounds by other ring closure procedures. The facility with which this ring closure with diethoxymethyl acetate occurs is emphasized by two facts: (1) II contains no tautomeric group at C-2 and (2) neither of the two products previously obtained from II were formed in this reaction.[6] Further, this procedure and those developed previously by us now permit the preparation in excellent yield of all three of the heterocyclic ring systems derivable from a 5-amino-4-hydrazinopyrimidine.

Excess diethoxymethyl acetate reacted with II at room temperature to give 7-chloro-8-ethoxymethyleneamino-*s*-triazolo[4,3-*c*]pyrimidine (IVa) in 91% yield. The structure of IVa was established by microanalysis and by acid hydrolysis to 8-amino-7-chloro-*s*-triazolo[4,3-*c*]pyrimidine (VIIa). This compound was identified by the dissimilarity of its ultraviolet spectrum with those of its previously reported isomers VIa[5] and 9-amino-6-chloropurine (VIIIb)[4] (see Table I), which were obtained by the hydrochloric acid-catalyzed reaction of II with ethyl orthoformate. It is surprising

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA[a]

Compound	λ_{max} in mμ (ε × 10⁻³) 0.1 *N* HCl	pH 7	0.1 *N* NaOH
VIIIb	263 (8.2)	264 (8.2)	262[b]
VIa	220[b]	222[b]	...
	335	330	
VIIa	221 (5.8)	222 (6.0)	276[b]
	278 (9.9)	277 (10.1)	303
	303 (8.4)	304 (7.9)	
VIIc	281 (9.85)	257 (8.7)	256[b]
	325 (8.30)	278 (10.1)	279
		319 (5.42)	320
VIIb	275 (11.0)	276 (10.9)	257 (10.1)
	320 (6.3)	320 (5.8)	281 (11.2)
			326 (4.04)

[a] The solutions used for these spectral determinations were prepared by dilution of aqueous VIIb, alcoholic VIIa, or *N*,*N*-dimethylformamide VIIc solutions with 0.1 *N* hydrochloric acid, 0.1 *N* sodium hydroxide, or pH 7 buffer. [b] Unstable.

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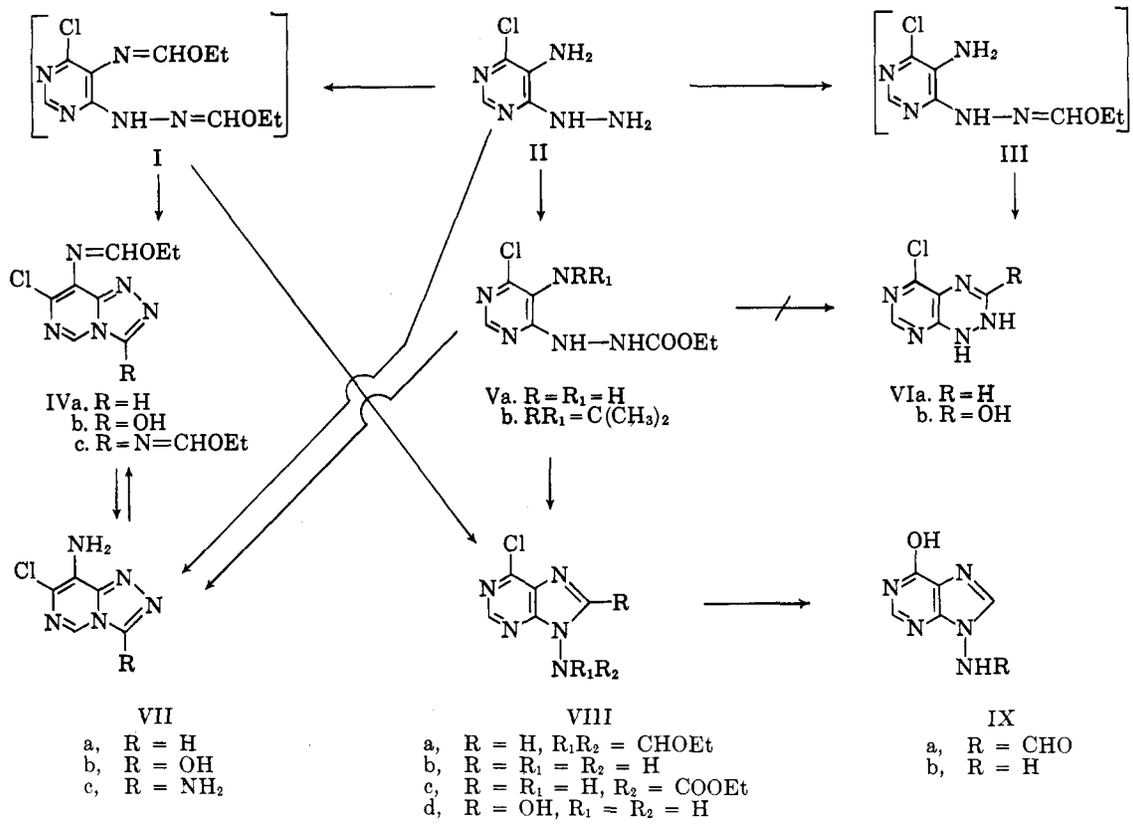
(2) B. Camerino, G. Palamidessi, and R. Sciaky, *Gazz. chim. ital.*, **90**, 1830 (1960).

(3) D. Shiho, S. Tagami, N. Takahayashi, and R. Honda, *J. Pharm. Soc. Japan*, **76**, 804 (1956).

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

(5) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *J. Org. Chem.*, **28**, 923 (1963).

(6) This statement is true although II is converted in high yield to 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (VIa) by treatment with ethyl orthoformate and mineral acid *at room temperature in less than an hour!*



that two such closely related reagents[7]—ethyl orthoformate with acid catalysis[9] and diethoxymethyl acetate[8]—converted II to entirely different ring systems.

In the ethyl orthoformate reaction the formation of VIa and VIIIb suggests that the carbonium ion[10] $(EtO)_2CH^+$ attacked both the hydrazino group and the amino group of II to give, after the elimination of ethanol, the intermediates I and III. In the presence of hydrochloric acid III cyclized to VIa and I to 6-chloro-9-ethoxymethyleneaminopurine (VIIIa) from which VIIIb was obtained. Treatment of II with the more reactive diethoxymethyl acetate probably gave I exclusively, which preferentially cyclized *in the absence of strong acid* to IVa rather than VIIIa.

The *s*-triazolo[4,3-*c*]pyrimidine ring system also was obtained in two other ring closures. Reaction of a dioxane suspension of II with ethyl chloroformate at room temperature gave 5-amino-4-(2-carbethoxyhydrazino)-6-chloropyrimidine (Va), which reacted with excess acetone to yield the monoisopropylidene derivative Vb and with diethoxymethyl acetate to provide ethyl *N*-(6-chloropurin-9-yl)carbamate (VIIIc). These reactions established that the carbethoxy group of Va is in fact on the terminal nitrogen of the hydrazino group. Basic hydrolysis of VIIIc cleaved the carbethoxy group and replaced the chloro group with hydroxy to give the known 9-aminohypoxanthine (IXb). Although Va failed to undergo cyclization when heated in dioxane, water, and aqueous hydrochloric acid, it did cyclize to 8-amino-7-chloro-3-hydroxy-*s*-triazolo[4,3-*c*]pyrimidine (VIIb) in hot 5% sodium bicarbonate solution. That VIIb, and not the isomeric pyrimidotriazine VIb, was the product of this reaction was shown by the conversion of VIIb to 7-chloro-3-hydroxy-8-ethoxymethyleneamino-*s*-triazolo[4,3-*c*]pyrimidine (IVb). 9-Amino-6-chloro-8-hydroxypurine (VIIId), which could result from the rearrangement of VIb, was eliminated by comparison of the ultraviolet spectrum of VIIb with that of 6-chloro-8-hydroxypurine.[11]

Treatment of a dioxane suspension of II with cyanogen bromide, then with sodium bicarbonate, directly formed VIIc. The ultraviolet spectrum of VIIc was similar to that of VIIb, and in addition VIIc reacted with diethoxymethyl acetate to yield the bisethoxymethyleneamino derivative (IVc).

Ultraviolet spectral studies showed that, although VIIb is reasonably stable in 0.1 *N* sodium hydroxide at room temperature, the other two *s*-triazolo[4,3-*c*]pyrimidines decompose to nonultraviolet-absorbing materials within an hour in this basic medium. All three compounds were more stable in 0.1 *N* hydrochloric acid, but after twelve days at room temperature a solution of VIIa showed only general absorption.

The three 8-amino-7-chloro-*s*-triazolo[4,3-*c*]pyrimidines (VIIa, b, c) exhibited in the 3500–3200-cm.$^{-1}$ region of the infrared three medium to strong bands that were not present in the spectra of the corresponding ethoxymethyleneamino derivatives (IVa, b, c). A medium to strong band at 1340–45 cm.$^{-1}$ also appears to be characteristic of the 8-amino-7-chloro-*s*-triazolo-[4,3-*c*]pyrimidines (see Experimental).

Experimental

The melting points reported were determined on a Kofler Heizbank and are corrected. The ultraviolet spectra were deter-

(7) These reagents have been used successfully for the preparation of purines from 4,5-diaminopyrimidines.[8,9]

(8) J. A. Montgomery and L. B. Holum, *J. Am. Chem. Soc.*, **80**, 404 (1958).

(9) J. A. Montgomery and C. Temple, Jr., *J. Org. Chem.*, **25**, 395 (1960); C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Med. Pharm. Chem.*, **5**, 866 (1962).

(10) H. W. Post, "The Chemistry of the Aliphatic Orthoesters," Reinhold Publishing Corp., New York, N. Y., 1943, p. 47.

(11) R. K. Robins, *J. Am. Chem. Soc.*, **80**, 6674 (1958).

mined in aqueous solution with a Cary Model 14 spectrophotometer. The infrared spectra were determined in pressed potassium bromide disks with a Perkin-Elmer Model 221 spectrophotometer.

7-Chloro-8-ethoxymethyleneamino-*s*-triazolo[4,3-*c*]pyrimidine (IVa).—A solution of 5-amino-6-chloro-4-hydrazinopyrimidine (II) (1.00 g., 6.27 mmoles) in diethoxymethyl acetate (15 ml.) was stirred at room temperature for 2 hr. The solid that precipitated was collected by filtration, washed with petroleum ether (85–105°) (20 ml.), and dried *in vacuo* over phosphorus pentoxide; yield, 700 mg. (49%); m.p. 159–161° dec. with premelting at 154°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), EtOH—275 (8.0), 308 (7.6); pH 7—263 (8.3), 304 (6.3); $\bar{\nu}_{max}$ in cm.$^{-1}$ 3070 and 3050 (aromatic CH), 2990 (aliphatic CH), 1620, 1595, 1520, and 1495 (C=C, C=N).

Anal. Calcd. for $C_8H_8ClN_5O$: C, 42.55; H, 3.55; Cl, 15.75; N, 31.00. Found: C, 42.58; H, 3.56; Cl, 15.53; N, 31.47.

An additional 590 mg. of product was obtained from the diethoxymethyl acetate filtrate; m.p. 153° dec. with presoftening. The total yield was 1.29 g. (91%).

7-Chloro-8-ethoxymethyleneamino-3-hydroxy-*s*-triazolo[4,3-*c*]-pyrimidine (IVb).—A solution of the hydrate of 8-amino-7-chloro-3-hydroxy-*s*-triazolo[4,3-*c*]pyrimidine (VIIb) (190 mg.) in diethoxymethyl acetate (5 ml.) was stirred at room temperature under anhydrous conditions for 30 hr. and evaporated to dryness *in vacuo*. The residue was washed with ether (4 ml.) and dried *in vacuo* over phosphorus pentoxide; yield, 50 mg. (22%); m.p. 182–184° dec.; λ_{max} in mμ ($\epsilon \times 10^{-3}$), EtOH—261 (13.31), 343 (4.50); pH 7—262 (10.4). 336 (3.28); $\bar{\nu}_{max}$ in cm.$^{-1}$, 3180 (NH), 1740 (C=O), 1610, 1595, 1540, and 1510 (C=C, C=N).

Anal. Calcd. for $C_8H_8ClN_5O_2$: C, 39.75; H, 3.31; Cl, 14.70; N, 28.95. Found: C, 39.68; H, 3.62; Cl, 14.70; N, 29.06.

From the ether wash 75 mg. of VIIb was recovered.

3,8-Bis(ethoxymethyleneamino)-7-chloro-*s*-triazolo[4,3-*c*]-pyrimidine (IVc).—A suspension of 7-chloro-3,8-diamino-*s*-triazolo[4,3-*c*]pyrimidine (VIIc) (150 mg.) in diethoxymethyl acetate (3.5 ml.) was stirred at room temperature for 22 hr.; the solid was collected by filtration, washed with petroleum ether (2 ml.), and dried *in vacuo* over phosphorus pentoxide; yield, 100 mg. (41.5%); m.p. 186–189° with sublimation and presoftening from 181°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), EtOH—286 (13.9), 320 (sh) (8.56); pH 7—246 (10.8), 281 (13.0), 317 (sh) (6.7); $\bar{\nu}_{max}$ in cm.$^{-1}$ 3080 (aromatic CH), 2985, 2940, 2900, and 2870 (aliphatic CH), 1630, 1615, 1580, 1515, and 1500 (C=C, C=N).

Anal. Calcd. for $C_{11}H_{13}ClN_6O_2$: C, 44.50; H, 4.38; Cl, 11.95; N, 28.30. Found: C, 44.36; H, 4.11; Cl, 11.99; N, 28.62.

5-Amino-4-(2-carbethoxyhydrazino)-6-chloropyrimidine (Va).—A suspension of 5-amino-6-chloro-4-hydrazinopyrimidine (II) (4.60 g., 28.9 mmoles) and ethyl chloroformate (2.8 ml.) in purified dioxane (90 ml.) was stirred at room temperature for 20 hr. The solid (8.03 g.) was collected by filtration, suspended in fresh dioxane (200 ml.), and sodium bicarbonate (2.64 g.) was added. This mixture was stirred for 18 hr., the residue was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The resulting gum was extracted with ether (three 250-ml. portions), the combined extracts were evaporated to dryness, and the solid was dried *in vacuo* over phosphorus pentoxide; yield, 5.05 g. (70%); m.p. 144–145° [recrystallization of this solid from ethyl acetate–petroleum ether (85–105°) did not raise the melting point]; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—271 (sh) (6.7), 304 (8.5); pH 7—255 (6.8), 290 (8.05); $\bar{\nu}_{max}$ in cm.$^{-1}$, 3415, 3320, and 3240 (NH); 2980 (aliphatic CH); 1735 (COOEt); 1640 (NH); 1600 and 1575 (C=C, C=N).

Anal. Calcd. for $C_7H_{10}ClN_5O_2$: C, 36.60; H, 4.32; Cl, 15.33; N, 30.23. Found: C, 36.50; H, 4.29; Cl, 15.29; N, 30.44.

4-(2-Carbethoxyhydrazino)-6-chloro-5-isopropylideneamino-pyrimidine (Vb).—A suspension of the hydrochloride of 5-amino-4-(2-carbethoxyhydrazino)-6-chloropyrimidine (Va) (2.0 g.) in acetone (200 ml.) containing sodium hydrogen carbonate (630 mg.) was stirred at room temperature for 4 hr. The residue was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure to yield a hygroscopic glass. An ether solution of the glass was filtered and allowed to evaporate to dryness in a hood at room temperature. The resulting solid was washed with ether (50 ml.), collected by filtration, and dried *in vacuo* over phosphorus pentoxide; yield, 1.2 g. (59%); m.p. 172–173°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 7—301 (9.46); $\bar{\nu}_{max}$ in cm.$^{-1}$, 3230 (NH), 3065 (aromatic CH), 2980 and 2935 (aliphatic CH), 1710 (COOEt), 1615, 1585, 1530, and 1505 (C=C, C=N).

Anal. Calcd. for $C_{10}H_{14}ClN_5O_2$: C, 44.20; H, 5.16; Cl, 13.08; N, 25.80. Found: C, 44.22; H, 5.36; Cl, 12.98; N, 25.56.

8-Amino-7-chloro-*s*-triazolo[4,3-*c*]pyrimidine (VIIa).—A suspension of 7-chloro-8-ethoxymethyleneamino-*s*-triazolo[4,3-*c*]pyrimidine (IVa) (300 mg., 1.33 mmoles) in 0.1 *N* hydrochloric acid (10 ml.) was stirred at room temperature for 1 hr. The solid was collected by filtration, washed with water (3 ml.), and dried *in vacuo* over phosphorus pentoxide; yield, 160 mg. (71%); m.p. 266–268° dec. with sublimation. This solid was recrystallized from methanol; $\bar{\nu}_{max}$ in cm.$^{-1}$, 3480, 3315, 3200, and 3160 (NH), 3075 and 3010 (aromatic CH), 1620 (NH), 1605, 1550, and 1505 (C=C, C=N); 1345 (unassigned).

Anal. Calcd. for $C_5H_4ClN_5$: C, 35.40; H, 2.36; Cl, 20.92; N, 41.30. Found: C, 35.50; H, 2.63; Cl, 20.97; N, 41.39.

8-Amino-7-chloro-3-hydroxy-*s*-triazolo[4,3-*c*]pyrimidine (VIIb).—A solution of the hydrochloride of 5-amino-4-(2-carbethoxyhydrazino)-6-chloropyrimidine (Va) (7.0 g.) in 5% aqueous sodium bicarbonate (200 ml.) was gently refluxed for 3 hr. The hot solution was filtered, and the filtrate was acidified with 12 *N* hydrochloric acid (10 ml.). The solid (1.15 g.) that deposited was collected by filtration and recrystallized from water to give the monohydrate; yield, 790 mg. (16%); m.p. >264°; $\bar{\nu}_{max}$ in cm.$^{-1}$, 3420, 3310, 3205, and 3090 (NH), 3050 (aromatic CH), 1705 (C=O), 1625 (sh) (NH), 1610, 1550, and 1530 (C=C, C=N), 1345 (unassigned).

Anal. Calcd. for $C_5H_4ClN_5O \cdot H_2O$: C, 29.50; H, 2.95; Cl, 17.40; N, 34.40. Found: C, 29.53; H, 2.85; Cl, 17.20; N, 34.37.

A small sample of the hydrate was dried overnight *in vacuo* over phosphorus pentoxide at 110° to yield the anhydrous material, m.p. >264°.

Anal. Calcd. for $C_5H_4ClN_5O$: C, 32.33; H, 2.16; Cl, 19.12; N, 37.70. Found: C, 32.30; H, 2.35; Cl, 19.03; N, 37.42.

From the combined filtrates 1.4 g. of Va was recovered.

7-Chloro-3,8-diamino-*s*-triazolo[4,3-*c*]pyrimidine (VIIc).—Solid cyanogen bromide (1.33 g., 12.5 mmoles) was added to a suspension of 5-amino-6-chloro-4-hydrazinopyrimidine (II) (2.00 g., 12.5 mmoles) in purified dioxane (40 ml.), and the mixture was stirred at room temperature for 18 hr. The solid (2.8 g.) was collected by filtration, suspended in water (60 ml.), and treated with sodium bicarbonate (840 mg., 10.0 mmoles). The basic mixture was stirred at room temperature for 15 min., and the solid was collected by filtration, washed with water (20 ml.), and dried *in vacuo* over phosphorus pentoxide; yield, 1.18 g. (51%); m.p. >264°. The analytical sample was obtained by recrystallization of a small sample from a mixture of benzene–*N*,*N*-dimethylformamide; $\bar{\nu}_{max}$ in cm.$^{-1}$, 3460, 3360, 3240, and 3090 (NH), 3070 (aromatic CH), 1665 and 1610 (NH), 1590, 1540, and 1500 (C=C, C=N), 1340 (unassigned).

Anal. Calcd. for $C_5H_5ClN_6$: C, 32.50; H, 2.71; Cl, 19.25; N, 45.50. Found: C, 32.31; H, 2.83; Cl, 19.34; N, 45.52.

Ethyl *N*-(6-chloropurin-9-yl)carbamate (VIIc).—A solution of the hydrochloride of 5-amino-4-(2-carbethoxyhydrazino)-6-chloropyrimidine (Va) (1.0 g.) in diethoxymethyl acetate (10 ml.) was stirred at room temperature for 18 hr. and evaporated to a small volume *in vacuo*. A solution of this residue in ether was filtered and after the removal of ether, the resulting gum was suspended in 0.1 *N* hydrochloric acid (10 ml.) and stirred at room temperature for 2 hr. The solid was collected by filtration, washed with water (10 ml.), and dried *in vacuo* over phosphorus pentoxide; yield, 330 mg. (37%); m.p. 137–138°. This solid was recrystallized from petroleum ether (85–105°); λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—262 (8.90); pH 7—263 (8.68); pH 13—266 (7.42); $\bar{\nu}_{max}$ in cm.$^{-3}$, 3130 (NH or OH), 2950 and 2920 (aliphatic CH); 1745 (COOEt), 1600, 1570, and 1520 (C=C, C=N).

Anal. Calcd. for $C_8H_8ClN_5O_2$: C, 39.70; H, 3.31; Cl, 14.70; N, 28.95. Found: C, 39.96; H, 3.70; Cl, 14.57; N, 28.53.

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