Pyrimido[5,4-*e*]-*as*-triazines. I. The Preparation and Properties of 5-Chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine and Some of Its Methyl Derivatives[1]

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5-Chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (IIa) and five of its methyl derivatives have been synthesized from appropriate 5-amino-6-chloro-4-hydrazinopyrimidines. The preparation of 5-chloro-1,4-dihydro-4-methylpyrimido[5,4-*e*]-*as*-triazines (XII) from the corresponding 5-methylaminopyrimidines involved methylation of *N*-(4,6-dichloro-5-pyrimidinyl)trifluoroacetamide (IXc) in *N*,*N*-dimethylformamide.

In an earlier paper[3] we described the successful synthesis of 9-aminopurines from 5-amino-4-chloro-6-hydrazinopyrimidine and unsuccessful attempts to prepare a pyrimido[5,4-*e*]-*as*-triazine *unsubstituted* on the nitrogens of the triazine ring.[4] The present report describes two novel syntheses of such a compound, 5 - chloro - 1,2 - dihydropyrimido[5,4 - *e*] - *as* - triazine (IIa), and also the syntheses of some of its methyl derivatives. Two of these methyl compounds (XIIa and XIIb) were prepared *via* *N*-methyl-*N*-(4,6-dichloro-5-pyrimidinyl)trifluoroacetamide (Xb), which was easily deacylated to 4,6-dichloro-5-methylaminopyrimidine (VIIIb). The preparation of VIIIb exemplifies a new and versatile method for the preparation of 5-alkylaminopyrimidines. The value of this preparative procedure is exemplified by the paucity of methods for the preparation of 5-alkylaminopyrimidines in the literature and by the limitations of those methods that have appeared.[9]

Attempts to cyclize 5-amino-4-chloro-6-(2-formylhydrazino)pyrimidine (Ib), prepared from 5-amino-4-chloro-6-hydrazinopyrimidine (Ia)[3] and boiling butyl formate, to 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (IIa) by treatment with methanolic hydrogen chloride resulted instead in deformylation of Ib to Ia. Treatment of Ia with ethyl orthoformate at 115° also failed to provide the desired pyrimidotriazine (IIa). Addition of excess ethyl orthoformate at room temperature to an aqueous suspension of Ia containing a catalytic amount of hydrochloric acid, however, did result in the formation of IIa in 57% yield.

The structure of IIa was established by microanalysis, by a molecular weight determination, and by comparison of its ultraviolet spectrum to that of the known 1 - benzyl - 5 - chloro - 1,2 - dihydropyrimido[5,4 - *e*]-*as*-triazine (IIb).[3] Further support for the assigned structure of IIa was provided by an alternative synthesis. Reaction of 5 - amino - 4,6 - dichloropyrimidine (Va) with diethoxymethyl acetate yielded 4,6-dichloro-5-ethoxymethyleneaminopyrimidine (Vb), which on treatment with hydrazine in dioxane gave a 26% yield of IIa. The attempted oxidization of IIa to 5-chloropyrimido[5,4-*e*]-*as*-triazine with mercuric oxide, bromine in ethanol, or potassium permanganate in acetone yielded mainly unidentified solids and apparently none of the desired dehydrogenated product.

In addition to a 62% yield of the hydrochloride of IIa, treatment of an ethyl orthoformate suspension of Ia with concentrated hydrochloric acid at room temperature gave a 13% yield of 9-amino-6-chloropurine (IVb), identified by deamination with nitrous acid to 6-chloropurine.

After IIa was identified, the reaction of Ia with formic acid to give 9-formamidohypoxanthine (IVa)[3] was found to proceed by rearrangement of IIa. The ultraviolet spectrum of time aliquots from this reaction at 100° showed that 5-amino-4-chloro-6-(2-formylhydrazino)pyrimidine (Ib) was formed and cyclized to IIa within fifteen minutes. In a ring-opening reaction formic acid converted IIa to *N*-[4-chloro-6-(2-formylhydrazino)-5-pyrimidinyl]formamide (IIIa), which was present in the reaction mixture at the end of thirty minutes. After four hours IIIa had completely cyclized to IVa. In this conversion 6-chloro-9-formamidopurine (IVc) probably was formed first, but this intermediate was not detected. Also, the conversion of Ia to IVa occurred through the same intermediates when a formic acid solution of Ia was allowed to stand at room temperature for about ten days. The ultraviolet spectrum of a practically pure sample of IIIa, isolated from the reaction of Ia with formamide at 100°, was almost identical to that of an analytical sample of *N*-[4-(2-acetylhydrazino)-6-chloro-5-pyrimidinyl]acetamide (IIIb), obtained from the reaction of Ia with acetic anhydride. That the formyl group on the 2-nitrogen of the hydrazino group of IIIa prevents recyclization to IIa was demonstrated by ring closure of 4-(2-acetylhydrazino)-5-amino-6-chloropurine (Ic) with ethyl orthoformate in the presence of hydrochloric acid to yield the known 9-acetamido-6-chloropurine (IVd).[3]

Treatment of an ethyl orthoformate suspension of 5 - amino - 4 - chloro - 6 - (1 - methylhydrazino)pyrimidine (VIa)[3] with one equivalent of 12 *N* hydrochloric acid at room temperature yielded the hydrochloride of 5 - chloro - 1,2 - dihydro - 1 - methylpyrimido[5,4 - *e*]-

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(2) Affiliated with the Sloan–Kettering Institute.

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

(4) Three such compounds have been reported[5,6] but two of these were prepared from 5-amino-4-(2-acylhydrazino)pyrimidines substituted on N-3 of the pyrimidine ring.[5] Similar pyrimidines *unsubstituted* on N-3 of the pyrimidine ring cyclize preferentially to *s*-triazolo[4,3-*c*]pyrimidines.[7] In other reported syntheses of this ring system,[3,8] the pyrimidine precursors, being substituted on N-1 of the hydrazino group, cannot cyclize to the isomeric 9-aminopurines.[3]

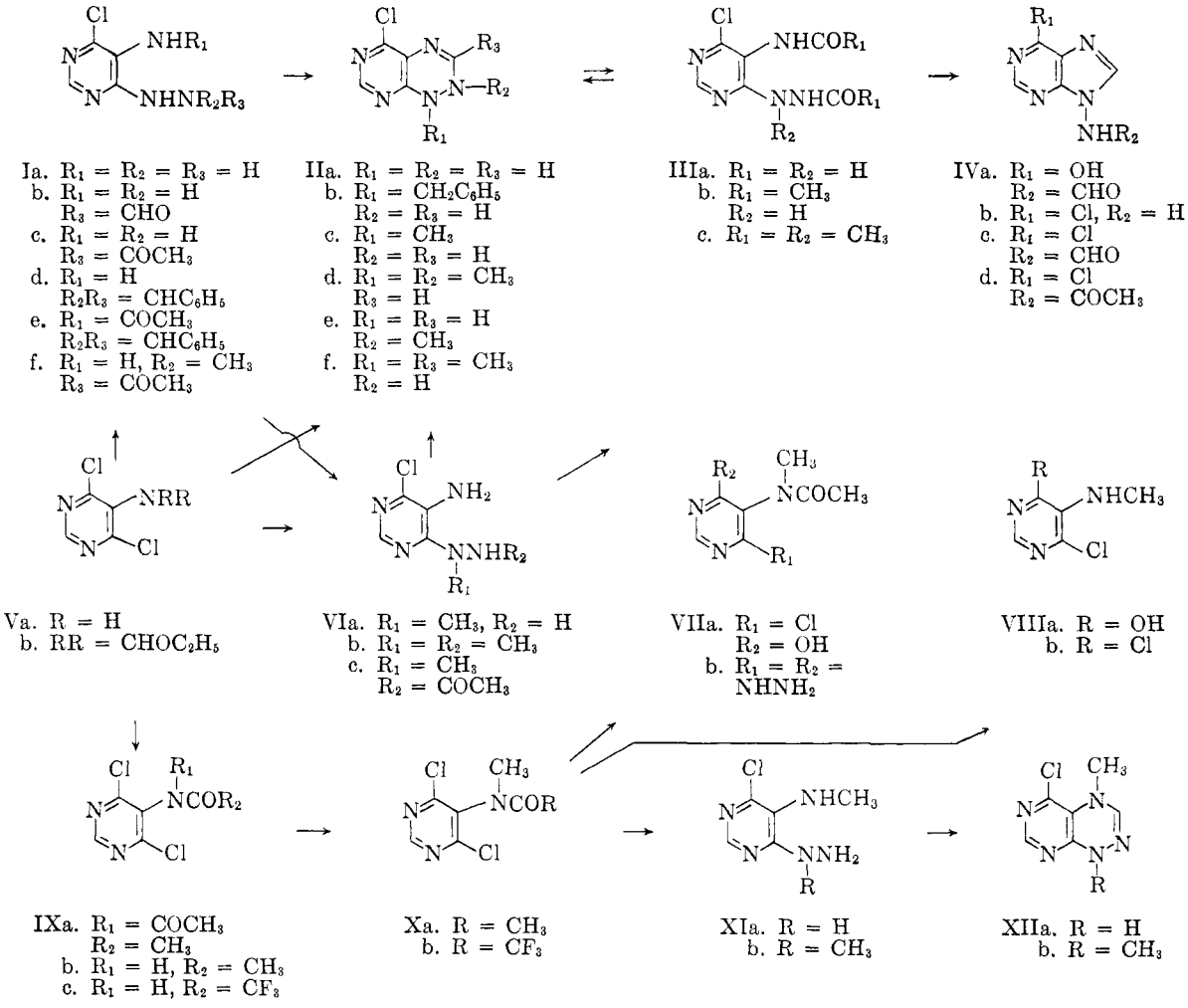
(5) W. Pfleiderer and K. H. Schundehutte, *Ann.*, **615**, 42 (1958).

(6) E. C. Taylor, J. W. Barton, and W. W. Paudler, *J. Org. Chem.*, **26**, 4961 (1961).

(7) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, unpublished data.

(8) G. D. Daves, Jr., R. K. Robins, and C. C. Cheng, *J. Am. Chem. Soc.*, **84**, 1724 (1962).

(9) D. J. Brown in A. Weissberger, "The Chemistry of Heterocyclic Compounds—The Pyrimidines," Interscience Publishers, London, 1962, p. 315.



as-triazine (IIc). Similarly, 5-amino-4-chloro-6-(1,2-dimethylhydrazino)pyrimidine (VIb), prepared from Va and 1,2-dimethylhydrazine, yielded the hydrochloride of 5-chloro-1,2-dihydro-1,2-dimethylpyrimido(5,4-*e*]-*as*-triazine (IId).

To obtain the necessary 5-methylaminopyrimidines XIa and XIb for the preparation of XIIa and XIIb, a procedure similar to that recently employed for the synthesis of *N*-alkyl-*N*-(5-pyrimidinyl)formamides[10] by alkylation of *N*-(5-pyrimidinyl)formamides was investigated. Reaction of 5-amino-4-benzylidenehydrazino-6-chloropyrimidine (Id)[3] with acetic anhydride gave a mixture from which *N*-(4-benzylidenehydrazino-6-chloro-5-pyrimidinyl)acetamide (Ie) was obtained in 42% yield. Because of the difficulties encountered this approach to the *N*-methylpyrimido[5,4-*e*]-*as*-triazines was abandoned in favor of a more general route that involved acylation of 5-amino-4,6-dichloropyrimidine (Va). Treatment of Va with acetic anhydride in the presence of a catalytic amount of pyridine resulted in diacetylation but gave only a 21% crude yield of *N*-acetyl-*N*-(4,6-dichloro-5-pyrimidinyl)acetamide (IXa). The acid-catalyzed reaction of Va with isopropenyl acetate, however, provided a 79% yield of practically pure IXa. Reaction of IXa with one equivalent of sodium hydroxide gave *N*-(4,6-dichloro-5-pyrimidinyl)acetamide (IXb), which was then methylated with methyl iodide in *N*,*N*-dimethylformamide containing sodium hydride to yield *N*-methyl-*N*-(4,6-dichloro-5-pyrimidinyl)acetamide (Xa). Spectral data indicated that an attempt to remove the acetyl group of Xa with methanolic hydrogen chloride produced *N*-(4-chloro-6-hydroxy-5-pyrimidinyl)acetamide (VIIa). Reaction of Xa with anhydrous hydrazine formed *N*-methyl - *N* - (4,6 - dihydrazino - 5 - pyrimidinyl)-acetamide (VIIb) and gave further indication that the acetyl group would be difficult to remove in the presence of the chloro groups. For this reason *N*-(4,6-dichloro-5-pyrimidinyl)trifluoroacetamide (IXc) was prepared by the reaction of Va with trifluoroacetic anhydride. Methylation of IXc with methyl iodide in *N*,*N*-dimethylformamide containing potassium carbonate proceeded smoothly and gave a good yield of *N*-methyl - *N* - (4,6 - dichloro - 5 - pyrimidinyl)trifluoroacetamide (Xb). Reaction of Xb with methanolic hydrogen chloride removed the trifluoroacetyl group as well as one chloro group to give the hydrochloride of 4-chloro - 6 - hydroxy - 5 - methylaminopyrimidine (VIIIa), but reaction of Xb with aqueous triethylamine formed 4,6-dichloro-5-methylaminopyrimidine (VIIIb). Furthermore, treatment of Xb with aqueous hydrazine or methyl hydrazine removed the trifluoroacetyl group and also introduced one hydrazino group to give the desired 4-hydrazinopyrimidines XIa and XIb. Reaction of XIa and XIb with the ethyl orthoformate-hydrochloric acid reagent formed the hydrochlorides of 5-chloro-1,4-dihydro-4-methylpyrimido[5,4-*e*]-*as*-tri-

(10) J. A. Montgomery and K. Hewson, *J. Org. Chem.*, **26**, 4469 (1961).

TABLE I

5-CHLORODIHYDROPYRIMIDO[5,4-*e*]-*as*-TRIAZINE HYDROCHLORIDES

Compound	Reaction time, hr.	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
IIa	1	62	...[a]	29.10	29.59	2.43	2.53	34.45	34.21	34.00	33.89
		48[b]	...[a]	35.40[c]	35.28	2.36[c]	2.37	20.92[c]	20.78	41.30[c]	40.82
IIc	18	90.5	191–195 dec.	32.70	33.07	3.18	3.37	32.25	32.46	31.80	31.80
IId	20	93	...[a]	35.90	35.98	3.85	3.84	30.30	30.30	29.90	29.83
IIf	..	81[b]	180–182 dec.	42.50[c]	42.40	4.05[c]	4.01	17.95[c]	17.70	35.40[c]	35.19
XIIa	22	52[b]	199–200	39.20[c]	39.26	3.27[c]	3.42	19.35[c]	19.50	38.10[c]	38.28
XIIb	20	70	...[a]	35.90	35.76	3.85	3.94	30.30	30.10	29.90	30.16

[a] Indefinite. [b] Isolated as hydrochloride but converted to free base for analyses. See Experimental. [c] Calcd. for free base.

azine (XIIa) and 5-chloro-1,4-dihydro-1,4-dimethylpyrimido[5,4-*e*]-*as*-triazine (XIIb).

An attempt to prepare 5-chloro-1,2-dihydro-2-methylpyrimido[5,4-*e*]-*as*-triazine (IIe) resulted in the synthesis of 5-chloro-1,2-dihydro-1,3-dimethylpyrimido-[5,4-*e*]-*as*-triazine (IIf). Alkylation of 4-(2-acetylhydrazino) - 5 - amino - 6 - chloropyrimidine (Ic) with methyl iodide in dimethylformamide containing potassium carbonate gave 4-(2-acetyl-1-methylhydrazino)-5-amino-6-chloropyrimidine (VIc) rather than the expected product 4 - (2 - acetyl - 2 - methylhydrazino)-5-amino-6-chloropyrimidine (If). VIc was not isolated pure but was converted to the hydrochloride of IIf by treatment with 2 *N* hydrochloric acid. The position of alkylation was established by acetylation of VIa with acetic anhydride to yield *N*-[4-(2-acetyl-1-methylhydrazino) - 6 - chloro - 5 - pyrimidinyl]acetamide (IIIc), which provided IIf on treatment with hot 2 *N* hydrochloric acid.

In the 1700–1500-cm.$^{-1}$ region of the infrared spectra the pyrimido[5,4-*e*]-*as*-triazine hydrochlorides exhibit four medium-to-strong bands, which are listed in Table II. The highest band in each set was attributed to

TABLE II

5-CHLORO-DIHYDROPYRIMIDO[5,4-*e*]-*as*-TRIAZINES

Compound	Ultraviolet absorption spectra,[a] λ_{max} in mμ ($\epsilon \times 10^{-3}$) 0.1 *N* HCl	pH 7	0.1 *N* NaOH	Infrared absorption spectra, strong bands in the 1700–1500-cm.$^{-1}$ region			
IIa	220[b]	222[b]	...[b]	1660	1610	1570	1530
	335	330					
IIc	225[b]	223 (19.0)	...[b]	1660	1600	1560	1510
	335	337 (5.51)					
IId	...[b]	228 (12.8)	...[b]	1675	1580	1565	1510
		334 (5.35)					
IIf	226[b]	224 (18.7)	...[b]	1665	1575	1555	1510
	336	338 (5.35)					
XIIa	225 (11.6)	224 (14.8)	223[b]	1645	1585	1565	1515
	338 (4.50)	337 (4.45)	349				
XIIb	228 (14.2)	226 (18.4)	226 (18.6)	1650	1575	1545	1510
	342 (5.71)	345 (5.43)	345 (5.43)				

[a] These spectra were determined by dilution of a neutral solution with the appropriate solvent. [b] Unstable.

the carbon–nitrogen double bond between the 2,3 or 3,4 positions of the triazine ring. The absorption due to this double bond occurs at a higher wave number when its conjugation with the pyrimidine ring through N-4 is fixed by methyl groups (*i.e.*, IId), and it occurs at a lower wave number when the double bond is fixed in an unconjugated position (*i.e.*, XIIa and XIIb). The absorption due to this double bond occurs at intermediate wave numbers when tautomerization between the conjugated and unconjugated positions can occur (*i.e.*, IIa, IIc, and IIf).

Measurement of the ultraviolet absorbances of 0.1 *N* sodium hydroxide solutions of the pyrimido[5,4-*e*]-*as*-triazine hydrochlorides over a ten-minute period at room temperature indicated that only XIIb was stable in this medium. When 0.1 *N* hydrochloric acid solutions of the pyrimido[5,4-*e*]-*as*-triazines were examined under similar conditions, both XIIa and XIIb appeared to be stable. Further studies revealed that the triazine ring of IIa was slowly cleaved in 0.1 *N* hydrochloric acid to the pyrimidine Ia, and the triazine ring of IId was immediately opened in either 0.1 *N* hydrochloric acid or 0.1 *N* sodium hydroxide to the pyrimidine VIb. A similar cleavage of 1,2-dihydro-5-methylpyrimido[5,4-*e*]-*as*-triazine to 5-amino-4-hydrazino-6-methylpyrimidine in an acidic medium was recently reported.[6] Only the parent dihydropyrimido-[5,4-*e*]-*as*-triazine (IIa) appeared to be unstable in a pH 7 buffered solution.

Experimental

The melting points reported were determined on a Kofler Heizbank and are corrected. The ultraviolet spectra were determined in aqueous solution with a Cary Model 14 or with a Beckman DK-2 (optical densities at the maxima with a Beckman DU). The infrared spectra were determined in pressed potassium bromide disks with a Perkin–Elmer, Model 221, spectrophotometer.

5-Amino-6-chloro-4-(2-formylhydrazino)pyrimidine (Ib).—A mixture of 5-amino-6-chloro-4-hydrazinopyrimidine (Ia; 2.16 g., 13.5 mmoles) and butyl formate (60 ml.) was heated at reflux for 2.5 hr., the solid removed from the hot mixture, and the filtrate allowed to stand overnight. The solid that deposited was collected by filtration, washed with ether (25 ml.), and dried *in vacuo* over phosphorus pentoxide; yield 1.26 g. The sample did not melt but decomposed at 150–155°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1,260 (sh) (5.5); 296 (6.8). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3500–3200 (broad) (NH); 1680 (C=O); 1640 (NH); 1580 and 1500 (C=C, C=N).

Anal. Calcd. for $C_5H_6ClN_5O$: C, 32.00; H, 3.20; Cl, 18.92; N, 37.30. Found: C, 31.86; H, 3.45; Cl, 18.94; N, 37.46.

An additional 180 mg. of product was obtained from the butyl formate filtrate. The total yield was 1.44 g. (57%).

4-(2-Acetylhydrazino)-5-amino-6-chloropyrimidine (Ic).—A mixture of 5-amino-6-chloro-4-hydrazinopyrimidine (Ia; 3.00 g., 18.8 mmoles) and acetic anhydride (60 ml.) was stirred at room temperature for 2.5 hr.; the solid was collected by filtration, stirred with water (50 ml.), and dried *in vacuo* over phosphorus pentoxide at 78°; yield, 1.82 g. (48%); m.p. 177–179° dec. 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 7, 255 (6.97), 289 (8.00). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3440 and 3230 (NH); 3025 (aromatic CH); 1680 (C=O); 1630 (NH); 1565 and 1525 (C=C, C=N).

Anal. Calcd. for $C_6H_8ClN_5O$: C, 35.70; H, 3.97; Cl, 17.60; N, 34.75. Found: C, 35.86; H, 4.04; Cl, 17.60; N, 35.05.

***N*-(4-Benzylidenehydrazino-6-chloro-5-pyrimidinyl)acetamide (Ie).**—A solution of 5-amino-4-benzylidenehydrazino-6-chloropyrimidine[3] (Id; 1.67 g., 6.75 mmoles) in acetic anhydride (20 ml.) was heated at 100–105° for 30 min., a trace of insoluble

material removed by filtration, and the filtrate evaporated to a small volume *in vacuo*. The oil was triturated with ether (80 ml.) and the solid was collected by filtration and dried *in vacuo* over phosphorus pentoxide; yield, 810 mg. (42%); m.p. 205–207° dec. with melting and sublimation from 200°. This solid was recrystallized from ethyl acetate. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 7, 323 (28.8). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3180 (NH); 3020 (aromatic CH); 2925 and 2890 (aliphatic CH); 1665 (C=O); 1600, 1575, 1565, 1520 and 1490 (sh) (C=C, C=N); 750 and 685 (monosubstituted phenyl).

Anal. Calcd. for $C_{13}H_{12}ClN_5O$: C, 53.90; H, 4.15; Cl, 12.27; N, 24.20. Found: C, 53.66; H, 4.40; Cl, 12.10; N, 23.94.

5-Chlorodihydropyrimido[5,4-*e*]-*as*-triazine Hydrochlorides (IIa, IIc, IId, XIIa, and XIIb). **A.**—The 4-hydrazinopyrimidine was suspended in ethyl orthoformate (11 ml./g. of 4-hydrazinopyrimidine) followed by the addition of about one equivalent of concentrated hydrochloric acid (0.5 ml./g. of 4-hydrazinopyrimidine). After stirring the mixture at room temperature (see Table I for reaction time), the solid was collected by filtration and washed with acetone with the exception of IId, which was washed with ether. To obtain pure IIa the hydrochloride was washed with hot acetone. The colored hydrochloride then was dried *in vacuo* over phosphorus pentoxide (see Table I for microanalysis and Table II for spectral data).

To obtain consistent microanalysis for XIIa an aqueous suspension of the hydrochloride (1.35 g.) was neutralized with sodium bicarbonate; the solid was recrystallized from benzene–petroleum ether (85–105°); yield, 240 mg. (21%). Similarly, the hydrochloride (5.0 g.) of IIa yielded 3.1 g. of solid, which was extracted with acetone (600 ml.) to give 2.6 g. of the free base. The molecular weight of IIa was determined by the isothermal distillation method.[11] Calcd. for $C_5H_4ClN_5$, 169.5. Found, 171. Recrystallization of IIa from dioxane–petroleum ether (85–105°) deposited the one-half dioxanate in 70% yield.

Anal. Calcd. for $C_7H_8ClN_5O$: C, 39.35; H, 3.75; Cl, 16.60; N, 32.80. Found: C, 39.56; H, 3.92; Cl, 16.70; N, 32.79.

B.—A dioxane solution (10 ml.) of anhydrous hydrazine (0.16 ml.) was added with stirring to a dioxane solution (10 ml.) of 4,6-dichloro-5-ethoxymethyleneaminopyrimidine (Vb; 1.00 g., 4.54 mmoles), and the mixture was stirred at room temperature for 70 hr. The solid was collected by filtration and washed first with methanol (5 ml.) and then acetone (500 ml.). Evaporation of the acetone wash gave 200 mg. (26%) of 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (IIa).

5-Chloro-1,2-dihydro-1,3-dimethylpyrimido[5,4-*e*]-*as*-triazine (IIf). **A.**—A solution of *N*-[4-(2-acetyl-1-methylhydrazino)-6-chloro-5-pyrimidinyl]acetamide (IIIc; 500 mg., 1.94 mmoles) in 2 *N* hydrochloric acid (10 ml.) was refluxed for 2 hr., evaporated to dryness, and the residue washed with acetone (30 ml.); yield, 370 mg. The hygroscopic hydrochloride and sodium bicarbonate (150 mg.) were suspended in acetone (25 ml.) and stirred overnight. The solid was removed by filtration, the filtrate was evaporated to dryness, and the residue was recrystallized from petroleum ether (85–105°); yield, 150 mg. (39%). For analyses see Table I.

B.—To a solution of 4-(2-acetylhydrazino)-5-amino-6-chloropyrimidine (Ic; 2.00 g., 9.94 mmoles) in anhydrous dimethylformamide (20 ml.) containing potassium carbonate (1.4 g.) was added methyl iodide (0.7 ml.). The mixture was stirred at room temperature for 60 hr., diluted with water (80 ml.) and extracted with chloroform (2 × 100 ml.). Evaporation of the combined extracts yielded 810 mg. of 4-(2-acetyl-1-methylhydrazino)-5-amino-6-chloropyrimidine (VIc), which could not be purified. A solution of this residue (760 mg.) in 2 *N* hydrochloric acid (10 ml.) was stirred at room temperature for 6 hr., evaporated to dryness *in vacuo*, and the hydrochloride of 5-chloro-1,2-dihydro-1,3-dimethylpyrimido[5,4-*e*]-*as*-triazine (IIf) was washed with dioxane (30 ml.); yield, 760 mg. (33%).

***N*-[4-(2-Acetylhydrazino)-6-chloro-5-pyrimidinyl]acetamide (IIIb).**—The acetic anhydride filtrate from Ic (see above) was evaporated to dryness and the residue was washed with acetone (100 ml.); yield, 260 mg. (5.5%); m.p. 261–264° taken fast from 200°. This solid was recrystallized from dioxane–petroleum ether (85–105°). λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1, 238 (11.0), 270 (sh), (5.2); pH 7, 238 (11.0); 270 (sh) (5.2). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3290 and 3260 (NH); 2990 (aliphatic CH); 1680 and 1670 (sh) (C=O); 1570 and 1510 (C=C, C=N).

Anal. Calcd. for $C_8H_{10}ClN_5O_2$: C, 39.40; H, 4.10; Cl, 14.58; N, 28.75. Found: C, 39.10; H, 4.10; Cl, 14.80; N, 28.97.

***N*-[4-(2-Acetyl-1-methylhydrazino)-6-chloro-5-pyrimidinyl]-acetamide (IIIc).**—A mixture of 5-amino-6-chloro-4-(1-methylhydrazino)pyrimidine[3] (VIa; 1.00 g., 5.76 mmoles) and acetic anhydride (20 ml.) was stirred at room temperature for 2 hr.; the solid was collected by filtration, washed with ether (20 ml.), and dried *in vacuo* over phosphorus pentoxide; yield, 980 mg. (79%); m.p. 251–252° dec. Recrystallization of this solid from ethanol–petroleum ether (85–105°) did not raise the melting point. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1, 249 (12.0), 277 (sh), (5.72); pH 7, 248 (12.2), 277 (sh) (5.82). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3280 (NH); 1675 and 1665 (C=O); 1580 and 1515 (C=C, C=N).

Anal. Calcd. for $C_9H_{12}ClN_5O_2$: C, 41.90; H, 4.66; Cl, 13.80; N, 27.15. Found: C, 41.90; H, 4.87; Cl, 13.76; N, 27.08.

9-Formamidohypoxanthine (IVa).—A solution of 9-aminohypoxanthine[3] (1.00 g., 6.62 mmoles) in 98% formic acid (20 ml.) was refluxed for 4 hr., evaporated to dryness *in vacuo*, and the residue was recrystallized from methanol; yield, 480 mg. (40.5%); m.p. > 264°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1, 247 (11.8); pH 7, 247 (11.2); pH 13, 256 (11.7). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3275 and 3155 (NH); 2900–2500 (acidic H); 1720, 1700, and 1680 (C=O); 1595, 1560, 1530, and 1500 (C=C, C=N).

Anal. Calcd. for $C_6H_5N_5O_2$: C, 40.20; H, 2.79; N, 39.10. Found: C, 40.34; H, 2.94; N, 39.44.

9-Amino-6-chloropurine (IVb).—The ethyl orthoformate filtrate from preparation of the hydrochloride of IIa (method A) was evaporated to dryness *in vacuo* and the solid (1.43 g.) recrystallized from benzene–ethyl acetate; yield, 620 mg. (6%); m.p. 173–176° dec. when taken from 150°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1, 263 (8.2); pH 7, 264 (8.2). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3330, 3270, and 3180 (NH); 3080 and 3055 (aromatic CH); 1618 (NH); 1585 and 1560 (C=C, C=N).

Anal. Calcd. for $C_5H_4ClN_5$: C, 35.40; H, 2.36; Cl, 20.92; N, 41.30. Found: C, 35.41; H, 2.51; Cl, 20.86; N, 40.83.

4,6-Dichloro-5-ethoxymethyleneaminopyrimidine (Vb).—A solution of 5-amino-4,6-dichloropyrimidine (Va; 5.00 g., 30.5 mmoles) in diethoxymethyl acetate (30 ml.) was stirred at room temperature for 24 hr., evaporated to a small volume under reduced pressure, and the residue was distilled at 94–96°/0.7 mm. to give a colorless liquid; yield, 5.4 g. (81%). λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 7, 240 (5.96), 274 (6.24). $\bar{\nu}_{max}$ in cm.$^{-1}$: 2985, 2940, and 2905 (aliphatic CH); 1650, 1540, and 1505 (C=C, C=N).

Anal. Calcd. for $C_7H_7Cl_2N_3O$: C, 38.20; H, 3.18; Cl, 32.35; N, 19.10. Found: C, 38.55; H, 3.32; Cl, 32.36; N, 19.20.

5-Amino-6-chloro-4-(1,2-dimethylhydrazino)pyrimidine (VIb).—A suspension of 5-amino-4,6-dichloropyrimidine (Va; 2.00 g., 12.2 mmoles) in water (80 ml.) containing 1,2-dimethylhydrazine (2.0 ml.) was heated with stirring at 65–70° for 2 hr. The resulting solution was filtered hot, evaporated to a small volume, and the oil was dissolved in ethanol (20 ml.). This solution was evaporated to dryness and the residue extracted with ether (50 ml.). Removal of the ether and recrystallization of the resulting solid from petroleum ether (85–105°) yielded 860 mg. (37.5%) of product; m.p. 79–81°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1, 249 (7.92), 307 (7.17); pH 7, 274 (7.27), 307 (10.2); pH 13, 274 (7.27), 307 (10.2). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3395 and 3275 (NH); 2925 (aliphatic CH); 1630 (sh) (NH); 1560 and 1510 (sh) (C=C, C=N).

Anal. Calcd. for $C_6H_{10}ClN_5$: C, 38.40; H, 5.33; Cl, 18.90; N, 37.30. Found: C, 38.10; H, 5.24; Cl, 19.20; N, 37.03.

An additional 620 mg. of impure product, m.p. 60–75°, was obtained by evaporation of the pet ether filtrate.

***N*-Methyl-*N*-(4,6-dihydrazino-5-pyrimidinyl)acetamide (VIIb).**—A mixture of *N*-methyl-*N*-(4,6-dichloro-5-pyrimidinyl)acetamide (Xa; 500 mg., 2.27 mmoles) and anhydrous hydrazine (5 ml.) was stirred at room temperature for 1 hr., evaporated to dryness *in vacuo*, and the residue was dissolved in hot water (10 ml.). The solid that precipitated was collected by filtration and dried *in vacuo* over phosphorus pentoxide; yield, 80 mg. This sample melted and exploded at 240–245°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1, 217 (23.1), 265 (6.31). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3310, 3250, and

(11) J. E. Morton, A. D. Campbell, and T. S. Ma, *Analyst*, **78**, 722 (1953).

3200 (NH); 3060 (aromatic CH); 2920 (aliphatic CH); 1660 and 1620 (NH); 1580 and 1500 (C=C, C=N).

Anal. Calcd. for $C_7H_{13}N_7O$: C, 39.80; H, 6.16; N, 46.40. Found: C, 39.76; H, 6.08; N, 46.18.

From the aqueous filtrate an additional 270 mg. of impure product was obtained.

4-Chloro-6-hydroxy-5-methylaminopyrimidine Hydrochloride (VIIIa).—A solution of *N*-methyl-*N*-(4,6-dichloro-5-pyrimidinyl)-trifluoroacetamide (Xb; 1.00 g., 3.65 mmoles) in methanolic hydrogen chloride (saturated at 10°) was stirred at room temperature for 20 hr. and was evaporated to a small volume *in vacuo*. The residue was washed with ethyl acetate (20 ml.), and the solid was collected by filtration and dried *in vacuo* over phosphorus pentoxide; yield, 570 mg. (75.5%); m.p. 247–248° dec. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1, 276 (4,60); pH 7, 293 (7.40); pH 13, 262 (sh) (5.73), 282 (7.40). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3040 (aromatic CH); 2940 and 2890 (aliphatic CH); 2800–2400 (acidic H); 1685 (C=O); 1600 and 1550 (C=C, C=N).

Anal. Calcd. for $C_5H_6ClN_3O \cdot HCl$: C, 30.60; H, 3.57; Cl, 36.20; N, 21.40. Found: C, 30.72; H, 3.58; Cl, 36.00; N, 21.30.

Recrystallization of the hydrochoride from methanol yielded the face base; m.p. 247–248° dec.

Anal. Calcd. for $C_5H_6ClN_3O$: C, 37.60; H, 3.76; N, 26.30. Found: C, 37.61; H, 3.73; N, 26.38.

4,6-Dichloro-5-methylaminopyrimidine (VIIIb).—A suspension of *N*-methyl-*N*-(4,6-dichloro-5-pyrimidinyl)-trifluoroacetamide (Xb; 1.00 g., 3.65 mmoles) in water (10 ml.) containing triethylamine (1.0 ml.) was stirred at room temperature for 16 hr. The solid was collected by filtration, washed with water (5 ml.), and dried *in vacuo* over phosphorus pentoxide; yield, 490 mg. (75%); m.p. 78–79°. Recrystallization of this solid from water did not raise the melting point. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1,264 (8.4), 316 (3.23); pH 7, 264 (8.4), 316 (3.23); pH 13, 264 (8.4), 316 (3.23). $\bar{\nu}_{max}$ in cm.$^{-1}$: 2970, 2940, and 2875 (aliphatic CH); 1560, 1520 and 1500 (C=C, C=N).

Anal. Calcd. for $C_5H_5Cl_2N_3$: C, 33.70; H, 2.81; Cl, 39.90; N, 23.60. Found: C, 33.75; H, 2.83; Cl, 39.70; N, 23.36.

***N*-(4,6-Dichloro-5-pyrimidinyl)acetamide (IXb).**—A solution of 5-amino-4,6-dichloropyrimidine (Va; 3.00 g., 18.3 mmoles) in isopropenyl acetate (30 ml.) containing 1 drop of concentrated sulfuric acid was heated at 75–80° for 1 hr., evaporated to a small volume *in vacuo*, and the residue was dissolved in petroleum ether (85–105°) (60 ml.). This solution was evaporated to dryness *in vacuo*, and the residue was washed with water (5 ml.) to give practically pure *N*-acetyl-*N*-(4,6-dichloro-5-pyrimidinyl)acetamide (IXa); yield, 3.60 g. (79%); m.p. 73–75°. Without further purification IXa was stirred in 1.07 *N* sodium hydroxide (13.6 ml., 14.5 mmoles) for 4 hr. at room temperature; the solid was collected by filtration and recrystallized from 1:1 benzene–petroleum ether (85–105°); yield, 1.65 g. (44%); m.p. 149–150° sub. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1, 255 (4.45) (broad); ph 7, 255 (4.55) (broad); ph 13, 245 (5.7), 276 (6.35). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3240 (NH); 1670 (C=O); 1550, 1535, and 1500 (C=C, C=N); 1410 and 810 (strong unassigned peaks).

Anal. Calcd. for $C_6H_5Cl_2N_3O$: C, 34.95; H, 2.43; Cl, 34.45; N, 20.40. Found: C, 34.99; H, 2.67; Cl, 34.54; N, 20.64.

***N*-(4,6-Dichloro-5-pyrimidinyl)trifluoroacetamide (IXc).**—A suspension of 5-amino-4,6-dichloropyrimidine (Va; 10 g., 61 mmoles) in trifluoroacetic anhydride (50 ml.) was stirred at room temperature for 3 hr., the resulting solution was evaporated to dryness *in vacuo*, and the residue was dissolved in methanol (100 ml.). Evaporation of the methanol gave 16.7 g. (105%) of impure product, m.p. 117–120°. Microanalysis indicated that recrystallization lowered the chloro content of this material. A portion of this solid was redissolved in methanol, and the solution was evaporated to dryness to give material that melted at 120–122°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1, 253 (4.42); pH 7, 243 (5.77); 273 (6.34); pH 13, 243 (5.84), 273 (6.39). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3220 (NH); 1730 (C=O); 1540 and 1515 (C=C, C=N).

Anal. Calcd. for $C_6H_2Cl_2F_3N_3O$: C, 27.70; H, 0.77; Cl, 27.30; N, 16.15. Found: C, 27.79; H, 0.95; Cl, 27.00; N, 16.01.

***N*-Methyl-*N*-(4,6-dichloro-5-pyrimidinyl)acetamide (Xa).**—Sodium hydride (1.25 g.), 51.5% dispersed in mineral oil, was added in portions with stirring to an externally cooled solution of *N*-(4,6-dichloro-5-pyrimidinyl)acetamide (IXb; 5.00 g., 24.3 mmoles) in anhydrous *N*,*N*-dimethylformamide (25 ml.). Methyl iodide (2.0 ml.) then was added slowly to the mixture and the reaction temperature was maintained below 40° by intermittent cooling with an ice bath. After stirring the mixture for 2.5 hr., the whole was evaporated to dryness under reduced pressure; the residue was washed with water (30 ml.) and dried *in vacuo* over phosphorus pentoxide; yield, 4.1 g. (77%); m.p. 122–124°. Recrystallization of this solid from water did not raise the melting point. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1, 256 (4.30); pH 7, 256 (4.25); pH 13, 261 (5.50), 272 (sh) (5.10). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3090 (aromatic CH); 2930 (aliphatic CH); 1685 (C=O); 1545 and 1515 (C=C, C=N).

Anal. Calcd. for $C_7H_7Cl_2N_3O$: C, 38.20; H, 3.18; Cl, 32.25; N, 19.10. Found: C, 38.45; H, 3.40; Cl, 32.04; N, 19.22.

***N*-Methyl-*N*-(4,6-dichloro-5-pyrimidinyl)trifluoroacetamide (Xb).**—Methyl iodide (2.0 ml.) was added to a solution of *N*-(4,6-dichloro-5-pyrimidinyl)trifluoroacetamide (IXc; 7.10 g., 27.3 mmoles) in *N*,*N*-dimethylformamide (50 ml.) containing anhydrous potassium carbonate (4 g.). The mixture was stirred at room temperature for 18 hr., diluted with water (150 ml.), and the oil that separated was extracted with ether (3 × 100 ml.). The combined extracts were evaporated under reduced pressure over a room-temperature water bath to a small volume, and the residue was washed with water (10 ml.). The white solid that formed was collected by filtration and dried *in vacuo* over phosphorus pentoxide; yield, 5.83 g. (78%); m.p. 60–63°. This solid cannot be recrystallized satisfactorily but can be sublimed at 55–60°/1 mm. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1, 254 (3.72); pH 7, 254 (3.76); pH 13, 262 (7.96), 300 (broad sh) (3.19). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3100 (aromatic CH); 2940 (aliphatic CH); 1720 (C=O); 1550 and 1520 (C=C, C=N).

Anal. Calcd. for $C_7H_4Cl_2F_3N_3O$: C, 30.65; H, 1.46; Cl, 25.90; N, 15.32. Found: C, 30.79; H, 1.67; Cl, 25.60; N, 15.46.

6-Chloro-4-hydrazino-5-methylaminopyrimidine (XIa).—A suspension of *N*-methyl-*N*-(4,6-dichloro-5-pyrimidinyl)trifluoroacetamide (Xb; 2.0 g., 7.3 mmoles) in water (20 ml.) containing 95% hydrazine (1.6 ml.) was stirred at room temperature for 66 hr. The solid was collected by filtration, washed with water (10 ml.) and ether (5 ml.), and dried *in vacuo* over phosphorus pentoxide; yield, 380 mg.; m.p. 160–161° dec. The analytical sample was obtained by recrystallization of a portion of this solid from petroleum ether (85–105°); m.p. 158–159° dec. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1, 277 (broad) (5.88); pH 7, 256 (7.2), 285 (sh) (4.96). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3370, 3320, and 3260 (NH); 2935 (aliphatic CH); 1635 (NH); 1570 and 1495 (C=C, C=N).

Anal. Calcd. for $C_5H_8ClN_5$: C, 34.60; H, 4.61; Cl, 20.45; N, 40.30. Found: C, 34.85; H, 4.83; Cl, 20.50; N, 40.47.

The aqueous filtrate yielded an additional 620 mg. of product; m.p. 159–160° dec. The total yield was 1.00 g. (79%).

6-Chloro-5-methylamino-4-(1-methylhydrazino)pyrimidine (XIb).—A suspension of *N*-methyl-*N*-(4,6-dichloro-5-pyrimidinyl)trifluoroacetamide (Xb; 1.00 g., 3.65 mmoles) in water (10 ml.) containing methylhydrazine (1.0 ml.) was stirred at room temperature for 4 days. The resulting solution was concentrated to one-half volume *in vacuo;* the solid that precipitated was collected by filtration, washed with water (1 ml.) and dried *in vacuo* over phosphorus pentoxide; yield, 400 mg. (58%); m.p. 119–121°. The analytical sample was obtained by recrystallization of a portion of this solid from water; m.p. 122–123°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1, 250 (14.4), 283 (sh) (3.54); 7, 274 (7.52), 298 (7.11); pH 13, 274 (7.52), 298 (7.11). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3250 and 3160 (NH); 2960, 2915, and 2870 (aliphatic CH); 1655 (NH); 1560, 1520, and 1490 (C=C, C=N).

Anal. Calcd. for $C_6H_{10}ClN_5$: C, 38.40; H, 5.34; Cl, 18.90; N, 37.30. Found: C, 38.34; H, 5.28; Cl, 18.70; N, 37.01.

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