to melt between 202–203°; combined weight, 4.17 g. Recrystallization from methanol produced long yellow needles, m.p. 204.5–205°.

*Anal.* Calcd. for $C_{11}H_9N_3OS$: C, 57.12; H, 3.92; N, 18.17. Found: C, 57.46; H, 3.58; N, 17.80.

**2-(2-Methoxyethoxy)-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (LV).**—In efforts to convert 2-chloro-10*H*-pyrimido[5,4-*b*][1,4]-benzothiazine to the parent unsubstituted derivative, the method of Albert and Royer[22] was investigated. This involves reaction of a chloro heterocycle with *p*-toluenesulfonhydrazide, followed by treatment of the resultant unstable hydrazide derivative with alkali to produce the unsubstituted heterocycle. Since the 2-chloropyrimidobenzothiazine was virtually unsoluble in the chloroform medium used by these workers, the reaction was tried in 2-methoxyethanol. Most of the starting material was recovered; however, starting from 0.5 g. of 2-chloro-10*H*-pyrimido-[5,4-*b*][1,4]benzothiazine, 75 mg. of a more soluble derivative was obtained, which was isolated by adding water to the 2-methoxyethanol solution. Upon recrystallization from ethanol, this compound melted at 166–167°. It was pale yellow, and dissolved in acid to give a bright yellow solution. Its ultraviolet absorption spectrum was virtually identical with that of 2-methoxy-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine. It was concluded from the analysis that the compound was the 2-(2-methoxyethoxy) derivative.

*Anal.* Calcd. for $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26. Found: C, 56.31; H, 4.55; N, 15.20.

**10*H*-Pyrimido[5,4-*b*][1,4]benzothiazine[7] (LVI).**—A 13.4-g. sample (0.058 mole) of 2-hydrazino-10*H*-pyrimido[5,4-*b*][1,4]-benzothiazine was slurried in 750 ml. of water and dissolved by the addition of 60 ml. of 2 *N* hydrochloric acid. This was warmed to 80°, and 400 ml. of a 10% aqueous solution of copper sulfate pentahydrate was added dropwise over a 15-min. period, with stirring. Nitrogen was evolved vigorously. Heating at 80° was continued for another 15 min., followed by 5 min. at the boiling point. A brown precipitate was formed, which was separated, washed with water, and dried (19.7 g.) This copper-containing product was slurried in about 400 ml. of ethanol plus a small amount of hydrochloric acid, warmed, and hydrogen sulfide bubbled in until saturation was reached. The black precipitate was isolated, and found to contain some brown lumps. After grinding, the hydrogen sulfide treatment was repeated twice. The combined alcoholic filtrates were then evaporated to dryness, which yielded a yellow–orange residue weighing 11.7 g. This was warmed in dilute hydrochloric acid, which caused all but a small amount of reddish material to dissolve. After clarifying, the solution was made alkaline, which resulted in the separation of a yellow–gray precipitate, 9.2 g. (dry). This proved to be a mixture of the 10*H*-pyrimidobenzothiazine and the original 2-hydrazino derivative. It was extracted with hot benzene to remove the product. Upon concentration and chilling of the benzene extracts, the product crystallized as pale yellow needles weighing 4.3 g., m.p. 180–181°. Further recrystallization from benzene did not raise the melting point.

*Anal.* Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88. Found: C, 59.67; H, 3.40; N, 20.63.

**8-Chloro-10*H*-pyrimido[5,4-*b*][1,4]benzothiazine (LVII).**—To a solution of 4.8 g. of 2,8-dichloro-10*H*-pyrimido[5,4-*b*]-[1,4]benzothiazine in 180 ml. of hot 2-methoxyethanol, was added 10 ml. of water plus 10 ml. of glacial acetic acid. Ten grams of zinc dust was slowly added to the well-stirred solution over a 3-hr. period. The zinc was then filtered from the warm solution, and the filtrate chilled overnight. A yellow precipitate (1.38 g.) separated. This proved to be a mixture consisting mainly of the starting material with a little product. Several volumes of water were added to the filtrate, which precipitated light yellow crystals, 3.0 g. This product was recrystallized from ethanol, which yielded yellow needles, m.p. 220–221°.

*Anal.* Calcd. for $C_{10}H_6ClN_3S$: C, 50.96; H, 2.57; N, 17.83. Found: C, 51.28; H, 2.41; N, 17.60.

**Ultraviolet Absorption Spectra and p*Ka* Values.**—Ultraviolet spectral determinations were made with a Beckman DU spectrophotometer. Stock solutions of compounds to be tested were normally prepared at concentrations of 25 to 50 mg./100 ml. in ethanol or other suitable solvent, followed by 1:50 dilution into the test solution. Buffers which were used included phosphate, Walpole acetate, Sorensen's glycine–hydrochloric acid and glycene–sodium hydroxide, and borax, as well as hydrochloric acid and sodium hydroxide of varying normalities. pH determinations were made on a Beckman Model G pH meter. For determination of $pK_a$ values, the spectra were determined at seven or more pH values, to establish two points for each pure species and to obtain values clustering near the midpoints between. All optical density measurements when plotted against pH for a given wave length gave good sigmoid curves. Optical density values in the 250–300-mμ region only were used for $pK_a$ calculations. Slit widths below this region were considered too wide for accuracy. The $pK_a$ values were calculated from the formula

$$pK_a = pH - \log \frac{\epsilon a - \epsilon x}{\epsilon x - \epsilon b}$$[23]

where $\epsilon a$ is the extinction value of the protonated species, $\epsilon b$ is the value of the base, and $\epsilon x$ is the value at the measured pH. The reported $pK_a$ values represent averages from determinations at 3 wave lengths selected in the areas of greatest spectral differences. Individual $pK_a$ values obtained from the midpoints of the sigmoid curves were all within 0.1 pH unit of those calculated.

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(22) A. Albert and R. Royer, *J. Chem. Soc.*, 1148 (1949).

(23) J. C. Gage, *ibid.*, 221 (1949).

# Some New Syntheses of Amino- and Alkylaminopyrimidines and -pteridines

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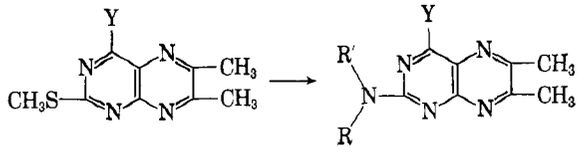
The fusion of ammonium acetate or alkylammonium acetates with certain 2-methylthiopyrimidines and -pteridines has been found to be a convenient method for the preparation of the corresponding 2-amino or 2-alkylamino derivatives. The utilization of these same reagents also has led to some interesting selective amine exchange reactions.

The preparation of 2- and 4-aminopyrimidines and condensed pyrimidines by the reaction of amines with the corresponding mercapto and alkylthio derivatives has long been utilized in heterocyclic chemistry.[1] Many of these reactions require rather strenuous conditions and are usually carried out in a bomb except when high boiling amines are used. We have found that in many instances the same results can be obtained by utilizing the acetate salt of the appropriate amine in a

(1) For a recent discussion of these reactions in the pyrimidine series, see D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., a division of John Wiley and Sons, Inc., New York, N. Y., pp. 284 and 289.

simple fusion reaction. As an extension of this work a very useful preparation of some 4-alkylaminopyrimidines by an amine exchange reaction has also been developed.

The preparation of 2-amino and 2-alkylaminopteridines (II) by nucleophilic displacement reactions of 2-mercapto- and 2-methylthiopteridines has been amply demonstrated by the work of Taylor and Cain.[2-4] The usual procedure employed for these reactions was to treat a 2-methylthiopteridine (such as I) with an excess of alcoholic amine at 180° in a bomb for ten to twelve hours. By heating for longer periods (eighteen to twenty hours) the 2,4-bisalkylaminopteridines are usually obtained. Replacement of the 2-methylthio group has now been accomplished by fusing compound I with ammonium or methylammonium acetate at 150–160° for one to three hours. For example, 2,4-diamino-6,7-dimethylpteridine (II, R and R′ = H) was obtained in fair yield by heating compound I with ammonium acetate at 165° for three hours. Similarly, 2-dimethyl-



I, Y = $NH_2$
III, Y = OH

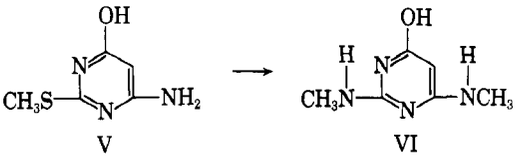
II, Y = $NH_2$
IV, Y = OH

amino-4-amino-6,7-dimethylpteridine (II, R and R′ = $CH_3$) was obtained from compound I and dimethylammonium acetate.

In the same manner 2-amino-, 2-alkylamino-, and 2-dialkylamino-4-hydroxy-6,7-dimethylpteridines (IV) have been prepared by treating 2-methylthio-4-hydroxy-6,7-dimethylpteridine (III) with the appropriate ammonium acetate. With *n*-butylammonium acetate, compound III gave a 5% yield of 2,4-bis-*n*-butylamino-6,7-dimethylpteridine along with 72% of IV (R = H, R′ = $CH_3CH_2CH_2CH_2$). In addition the 2-anilino compound (IV, R = H, R′ = $C_6H_5$) was synthesized from anilinium acetate and compound III. However, refluxing in aniline affords the same product in good yield. The 2-mercapto group was more difficult to replace than the 2-methylthio group since the conversion of 2-mercapto-4-hydroxy-6,7-dimethylpteridine to the 2-amino compound IV (R and R′ = H) with ammonium acetate required a longer time and resulted in a lower yield of product than compound III.

The replacement of the 2-methylthio function in the pyrimidine series with amino groups by this same fusion reaction has also been partially successful. 2-Methylthio-4-hydroxypyrimidine, its 6-amino, and 5-methoxy derivatives were converted to the 2-amino compounds in fair yield but 2-methylthio-4-dimethylaminopyrimidine and the corresponding 6-amino compound were unreactive. 2-Mercapto-4-hydroxypyrimidine was also recovered unchanged after heating in ammonium acetate for three and one-half hours at 165°.

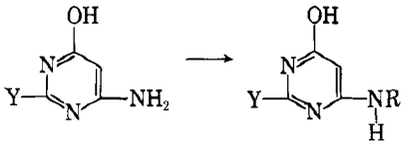
Roth, *et al.*,[5] have reported that 2-methylthio-4-hydroxy-6-aminopyrimidine (V) did not react with alcoholic methylamine at 200°. By using aqueous conditions at 120° a mixture resulted from which they isolated a product which was believed to have resulted from displacement of both the 2-methylthio and the 6-amino groups. We have found that the fusion of



V VI

compound V with methylammonium acetate at 155° does, in fact, replace both groups with the formation of 2,6-bismethylamino-4-hydroxypyrimidine (VI).

This finding prompted us to investigate other amine exchange reactions. Thus 2,4-dihydroxy-6-aminopyrimidine (VII) and 2,6-diamino-4-hydroxypyrimidine (IX) with methylammonium acetate under the usual conditions afforded good yields of the corresponding 6-methylamino derivatives VIII (R = $CH_3$) and X (R = $CH_3$).



VII, Y = OH
IX, Y = $NH_2$

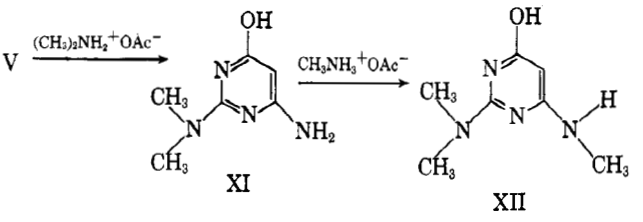
VIII, Y = OH
X, Y = $NH_2$

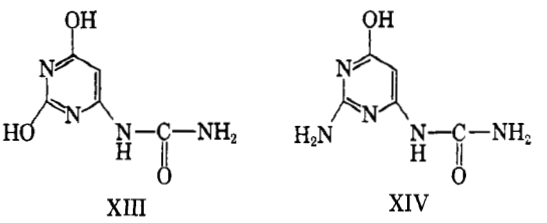
Structure of each compound was rigorously proved by conversion to a known pteridine derivative.[6] Previous syntheses of the pyrimidines VIII and X required at least four steps from a preformed pyrimidine.[7,8] Several other derivatives of VIII (R = $C_6H_5CH_2$, furfuryl, and $HOCH_2CH_2$) and X (R = $C_6H_5CH_2$ and furfuryl) were prepared by the same procedure. No reaction took place with 2,4,6-triaminopyrimidine and methylammonium acetate.

Several attempts to replace the 6-amino function of VII with a dimethylamino group by heating with dimethylammonium acetate did not meet with success. Similarly, treating the same pyrimidine with benzylmethylammonium acetate gave only starting material. The fact that 6-alkylaminopyrimidines are readily prepared by this method, whereas the 6-dialkylamino analogs are not, tends to implicate steric factors. This view is supported by the fact that reaction of VII with isopropylammonium acetate also was unsuccessful.

The stability of the 6-amino function toward dimethylammonium acetate suggested the possibility of selectively replacing the 2-methylthio group of 2-methylthio-4-hydroxy-6-aminopyrimidine (V) with a dialkylamino group. By heating compound V with dimethylammonium acetate it was readily converted to the known 2-dimethylamino derivative XI.[5] This was in turn transformed to 2-dimethylamino-4-hydroxy-6-methylaminopyrimidine (XII) by heating with methylammonium acetate.

(2) E. C. Taylor and C. K. Cain, *J. Am. Chem. Soc.*, **73**, 4384 (1951).
(3) E. C. Taylor and C. K. Cain, *ibid.*, **74**, 1644 (1952).
(4) E. C. Taylor and C. K. Cain, *ibid.*, **74**, 1688 (1952).
(5) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *ibid.*, **73**, 2864 (1951).
(6) 2,4-Dihydroxy-6-methylaminopyrimidine (VIII, R = $CH_3$) was converted to 6,7,8-trimethyl-2,4(1*H*,8*H*)-pteridinedione as described by Pfleiderer and Nübel.[7] 2-Amino-4-hydroxy-6-methylaminopyrimidine (X, R = $CH_3$) was converted to 2-amino-6,7,8-trimethyl-4(8*H*)-pteridinone by the method of Fidler and Wood.[8]
(7) W. Pfleiderer and G. Nübel, *Ann.*, **631**, 168 (1960).
(8) W. E. Fidler and H. C. S. Wood, *J. Chem. Soc.*, 4157 (1960).




Treatment of compound VI with *n*-butylammonium acetate in an attempt to prepare 2-methylamino-4-hydroxy-6-*n*-butylaminopyrimidine was not successful. However, by heating VI with ammonium acetate, 2-methylamino-4-hydroxy-6-aminopyrimidine was obtained in low yield.[9a] These results again point up the possibility of steric factors as being important in this type reaction.

The success encountered in these amine exchange reactions with amine salts suggested that higher boiling amines also might be effective amine exchange reagents. Hence 2,4-dihydroxy-6-aminopyrimidine (VII) was refluxed for twenty-four hours with benzylamine resulting in a 52% yield of the desired 2,4-dihydroxy-6-benzylaminopyrimidine (VIII, R = $C_6H_5CH_2$). Similar treatment with methylbenzylamine gave unchanged starting material. When ethanolamine was used, a poor yield (15%) of the desired compound VIII (R = $CH_2CH_2OH$) was obtained and in this case the ethanolammonium acetate fusion gave a much better yield (50%). 2,6-Diamino-4-hydroxypyrimidine (IX) in refluxing benzylamine gave a compound which, in all probability, resulted from a ring opening to produce an intermediate which reacted with a second mole of benzylamine and the ring closed back to a pyrimidine. The product had analysis agreeing with $C_{18}H_{18}N_4O$ while its ultraviolet absorption spectra more closely resembled 1-methylisocytosine than the corresponding 3-methyl isomer.[9b] This evidence suggests that the structure could be 2-amino-1-benzyl-6-benzylamino-4-(1*H*)-pyrimidinone. The 6-benzylamino compound X (R = $C_6H_5CH_2$) was successfully synthesized by fusing IX with benzylammonium acetate.

Recently Whitehead and Traverso[12] have described similar exchange amination reactions by treating 2,4-dimethyl-6-amino-, 4-amino-6-hydroxy-, 2-hydroxy-4-amino-, and 2-methyl-4-amino-6-hydroxypyrimidine with a molar equivalent of an amine hydrochloride in the presence of excess free amine at temperatures of 145–170° for periods varying from one to twenty hours. These workers also found that treating 4-amino-6-hydroxypyrimidine with benzylamine in absence of acid gave a product which they suggest is best represented by the structure 1-benzyl-6-benzylamino-4-(1*H*)-pyrimidinone or 3-benzyl-6-benzylamino-4(3*H*)-pyrimidinone.

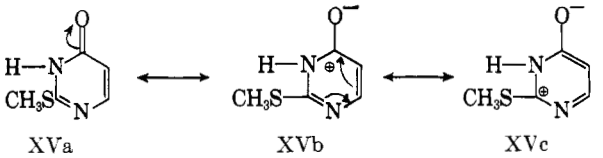
Both 2,4-dihydroxy-6-amino-(VII) and 2,6-diamino-4-hydroxypyrimidine (IX) also were readily converted to the corresponding 6-ureido compounds XIII and XIV by fusion with urea. These previously unreported compounds are quite insoluble in common solvents and do not melt below 400°. An attempt to extend this reaction to substituted ureido derivatives by heating 2,4-dihydroxy-6-aminopyrimidine with N-benzylurea resulted in a complex mixture of products.

The fusion of amine salts of carboxylic acids is an equilibrium process as shown and is, in fact, a preparative procedure for amides.[13]

$$RNH_2 + R'COOH \rightleftharpoons R'COO^-RNH_3^+ + \underset{\rightleftharpoons}{\rightarrow} R'CONHR + H_2O$$

Amides are usually prepared by employing an excess of one of the reactants and distilling the water during the heating period, thereby driving the equilibrium to the right. In using these amine salts for the replacement of methylthio groups and amino groups, the reaction has been carried out using a reflux condenser which keeps the water in contact with the reaction mixture. This serves to maintain the equilibrium and ensures the presence of the ammonium salt which can also hydrolyze to give some free amine and acetic acid. The efficacy of this reagent in nucleophilic substitution reactions can therefore be explained by assuming that the amine is the active nucleophile.

The ability of pteridines and pyrimidines to undergo nucleophilic substitution reactions on the carbons adjacent to ring nitrogens is well authenticated and readily explicable in view of the $\pi$ electron deficient nature of these systems.[14] The difference in reactivity of the 2-methylthiopyrimidines containing hydroxyl groups in the 4- and 6-position and those containing only amino groups in these positions also can be rationalized since $\pi$ electron deficient heterocycles containing hydroxyl groups in positions alpha or gamma to ring nitrogens are known to actually exist as cyclic lactams[15] (such as XVa) under neutral and acidic conditions. Hence they are capable of electron-attracting properties which are apparent from canonical structures such as XVb and c.




This electron-attracting ability tends to favor nucleophilic substitution reactions.[16] Addition of electron-

(9) (a) The conventional synthesis of 2-methylamino-4-hydroxy-6-aminopyrimidine using methylguanidine and ethyl cyanoacetate affords a mixture of the 2-methylamino compound and 2,6-diamino-1-methyl-4(1*H*)-pyrimidinone.[10,11] (b) R. B. Angier and W. V. Curran, *J. Org. Chem.*, **26**, 1891 (1961).

(10) W. V. Curran and R. B. Angier, *J. Am. Chem. Soc.*, **80**, 6095 (1958).

(11) W. R. Boon and G. Bratt, *J. Chem. Soc.*, 2159 (1957).

(12) C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **82**, 3971 (1960).

(13) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 567.

(14) For a comprehensive discussion of $\pi$ electron deficient heterocyclic systems see A. Albert, "Heterocyclic Chemistry," The Athlone Press, London, England, 1959.

(15) D. J. Brown and L. N. Short, *J. Chem. Soc.*, 331 (1953); D. J. Brown, E. Hoerger, and S. F. Mason, *ibid.*, 211 (1955).

(16) This explanation is supported by a recent publication of A. Albert [*J. Chem. Soc.*, 1020 (1960)], who has shown that the hydroxyl group of 2-hydroxypyridine is acid strengthening on a further substituent (*e.g.*, 6-hydroxypyridine-3-carboxylic acid is a stronger acid than pyridine-3-carboxylic acid).

releasing groups to the 5-position would be expected to retard the reaction and this was found to be true in the case of 2-methylthio-4-hydroxy-5-methoxypyrimidine which required a longer time to react with methylammonium acetate than compound XVa (six hours *vs.* one hour) as revealed by paper chromatography. The unreactive nature of those 2-methylthiopyrimidines containing only amino or substituted amino groups in the 4- and 6- positions can be attributed in part to the electron-releasing ability of these groups which would tend to inhibit nucleophilic substitution.[17] Similar explanations may be invoked to explain the amine exchange reactions since 2,4,6-triaminopyrimidine did not react with methylammonium acetate, whereas those compounds containing a hydroxyl group in the 4- position reacted readily.

## Experimental

All of the fusion reactions described in this section were carried out using a round-bottom flask provided with a reflux condenser in an oil bath at the specified temperatures. Paper chromatography was utilized to follow the course of the reactions and $R_f$ values are recorded for the following solvent systems: solvent A, isopropyl alcohol–1 *N* ammonium hydroxide (7:3); solvent B, 0.5% aqueous sodium carbonate; solvent C, butanol-5 *N* acetic acid (7:3); solvent D, 0.1 *N* hydrochloric acid. The spots were detected using an ultraviolet lamp provided with a filter to give mainly light of 254 mμ.

**2-Amino-4-hydroxy-6,7-dimethylpteridine (IV, R and R′ = H). A.**—One gram (4.5 mmoles) of 2-methylthio-4-hydroxy-6,7-dimethylpteridine[18] (III) and 10 g. of ammonium acetate were heated for 1 hr. at 160–165°. The reaction mixture was cooled, diluted with 15 ml. of water, and filtered to give 0.80 g. (93%) of product. Paper chromatographic patterns (solvents A and B) and ultraviolet spectra were identical to an authentic specimen.[10]

**B.**—One gram of 2-mercapto-4-hydroxy-6,7-dimethylpteridine[19] gave 0.50 g. of the 2-amino compound by heating for 4.0 hr. at 165°.

**2-*n*-Butylamino-4-hydroxy-6,7-dimethylpteridine (IV, R = H, R′ = $CH_3CH_2CH_2CH_2$).**—*n*-Butylammonium acetate was prepared by slowly adding 6.8 ml. (0.069 mole) of glacial acetic acid to 6.8 ml. (0.069 mole) of *n*-butylamine in an ice bath. Compound III (1 g., 4.5 mmoles) was added and fused for 2 hr. at 140°. Sixty milliliters of water was added to give a turbid solution which was evaporated to a sirup *in vacuo*. This was dissolved in 20 ml. of hot water and brought to pH 8 with sodium bicarbonate to give a crystalline solid; yield, 1.15 g. Paper chromatography in solvent A revealed a major spot at $R_f$ 0.61 (purple) together with a minor green-fluorescing spot, $R_f$ 0.07. The product was extracted with 15 ml. of 0.33 *N* sodium hydroxide leaving a solid; yield, 90 mg.; m.p. 168–172°. Recrystallization of the material from 4 ml. of 50% ethanol gave 40 mg. of 2,4-bis-*n*-butylamino-6,7-dimethylpteridine, m.p. 169–170°, $R_f$ 0.92 (blue-green in ammonia vapor) in solvent C; $\lambda_{max}^{0.1\ N\ HCl}$ 214 (26,500), 253 (13,500), 295–313 (7250), 343 mμ (ε 14,100); $\lambda_{max}^{CH_3OH}$ 237 (15,700), 271 (20,800), 380 mμ (ε 8700).

*Anal.* Calcd. for $C_{16}H_{26}N_6$(302): C, 63.5; H, 8.7; N, 27.8. Found: C, 63.5; H, 8.4; N, 27.9.

The basic filtrate was heated on a steam bath, treated with charcoal, then acidified to pH 6.5 with glacial acetic acid to give crystals of 2-*n*-butylamino-4-hydroxy-6,7-dimethylpteridine; yield, 0.65 g.; m.p. 234–240°, with previous wetting. An additional 0.15 g., m.p. 242–243°, was obtained by further acidification, $R_f$ 0.61 (solvent B). For analyses a portion of the first crop of this material was dissoved in dilute base, reprecipitated with acetic acid, and then recrystallized from 50% ethanol, m.p. 238–241.5°; $\lambda_{max}^{0.1\ N\ NaOH}$ 259 (18,000), 367 mμ (ε 7060); $\lambda_{max}^{0.1\ N\ HCl}$ 217 (17,600), 240–250 (10,400), 322 mμ (ε 7900).

*Anal.* Calcd. for $C_{12}H_{17}N_5O$ (247): C, 58.3; H, 6.9; N, 28.3. Found: C, 58.2; H, 7.0; N, 28.4.

**2,4-Diamino-6,7-dimethylpteridine (II, R and R′ = H).**—One gram (4.5 mmoles) of the 2-methylthio compound I was fused for 3.0 hr. at 165° with 10 g. of ammonium acetate. After having been cooled, the reaction mixture was diluted with 30 ml. of water, warmed on a steam bath, and then filtered; yield, 0.15 g. Paper chromatography in solvent A showed several spots; hence, this crop was discarded. The filtrate was treated with charcoal, filtered, and brought to pH 5.5 with sodium bicarbonate to give crystals; yield, 0.55 g. Paper chromatography in solvent A indicated this was mainly the desired product with minor impurities, one of which was almost certainly 2-amino-4-hydroxy-6,7-dimethylpteridine. This product was extracted with a solution of 15 ml. of water containing 2 ml. of 1 *N* sodium hydroxide to give 0.50 g. of product, $R_f$ 0.59 (yellow-green which turns blue on fuming with ammonia) in solvent D. This product was identical to an authentic specimen ($R_f$ in solvent D and ultraviolet spectra[20]).

**2-Dimethylamino-4-amino-6,7-dimethylpteridine (II, R and R′ = $CH_3$).**—Dimethylammonium acetate was prepared from 15 ml. of anhydrous dimethylamine and 7 ml. of glacial acetic acid. The excess amine was allowed to evaporate at room temperature. One gram of 2-methylthio-4-amino-6,7-dimethylpteridine (I)[4] was added and the mixture was heated at 165–170° for 2.5 hr. Fifty milliliters of water was added and evaporated *in vacuo*. The residue was slurried in water, filtered, and dried; yield, 0.90 g.; $R_f$ 0.68 (purple) with small amount of $R_f$ 0.83 (yellow-green) in solvent C; ultraviolet spectra same as previously reported.[4]

**2-Di-*n*-butylamino-4-hydroxy-6,7-dimethylpteridine (IV, R and R′ = $CH_3CH_2CH_2CH_2$).**—Acetic acid (2.85 ml., 0.05 mole) was added slowly to 8.4 ml. (0.05 mole) of di-*n*-butylamine in an ice bath. One gram (4.5 mmoles) of the 2-methylthiopteridine (III) was added and the mixture was heated for 1 hr. at 165°. Twenty millliliters of water was added, chilled, and filtered to yield 0.40 g. of product; m.p. 242–243° dec.; $R_f$ 0.66 (yellow-green) with a trace of lower $R_f$ compound in solvent B. For analyses a portion was recrystallized from 50% ethanol, m.p. 243–245° dec.; $\lambda_{max}^{0.1\ N\ NaOH}$ 273 (21,800), 383 mμ (ε 8500); $\lambda_{max}^{0.1\ N\ HCl}$ 222 (16,800), 246 (13,700), 293 (8340), 326 mμ (ε 7270).

*Anal.* Calcd. for $C_{16}H_{25}N_5O$ (303): C, 63.3; H, 8.3; N, 23.1. Found: C, 63.1; H, 8.5; N, 22.9.

**2-Dimethylamino-4-hydroxy-6,7-dimethylpteridine (IV, R and R′ = $CH_3$).**—Glacial acetic acid (7 ml.) was added cautiously to 20 ml. of 25% aqueous dimethylamine with cooling, after which the solution was evaporated to an oily liquid *in vacuo*. This was dissolved in 40 ml. of absolute ethanol and again evaporated to an oil *in vacuo*. After this procedure had been repeated, 1 g. of compound III was added and heated at 160° for 1 hr. The reaction mixture was cooled, diluted with 40 ml. of water, and evaporated to dryness *in vacuo*. The resulting solid was dissolved in 20 ml. of hot water, treated with charcoal, and filtered. The filtrate was reheated on a steam bath and brought to pH 7 with sodium bicarbonate to afford 0.70 g. of a product (needles); $R_f$ 0.64 (green fluorescence) in solvent B. Ultraviolet absorption data agreed with the literature.[5]

**2-Anilino-4-hydroxy-6,7-dimethylpteridine (IV, R = H, R′ = $C_6H_5$). A.**—Compound III (1 g., 4.5 mmoles) was refluxed for 8 hr. in 20 ml. of aniline. Paper chromatography in solvent B showed $R_f$ 0.25 (yellow-green elongated spot) with some starting compound $R_f$ 0.56 (blue) also present. Ten milliliters of aniline was added and refluxed for an additional 4 hr. A trace of starting material was still present. Ethanol (25 ml.) was added and heated on a steam bath until solution was complete. The solution was treated with charcoal and filtered to give 0.65 g. of product, m.p. 315–320° dec. An additional 0.15 g. was obtained by adding an equal volume of ether to the filtrate. These two crops were combined and recrystallized from ethanol to yield 0.65 g. of product; m.p. 317–320° dec.; $R_f$ 0.23 (yellow-green elongated spot) in solvent B; $\lambda_{max}^{0.1\ N\ NaOH}$ 281 (24,400), 366 mμ (ε 8900); $\lambda_{max}^{0.1\ N\ HCl}$ 255 (12,800), 295 (9,900), 324 mμ (ε 8,100).

*Anal.* Calcd. for $C_{14}H_{13}N_5O$ (267): C, 62.9; H, 4.9; N, 26.2. Found: C, 62.9; H, 5.4; N, 26.3.

**B.**—Five milliliters (0.055 mole) of aniline was cooled in an ice bath and 3.3 ml. (0.055 mole) of glacial acetic acid was added slowly. One gram (4.5 mmoles) of compound III was added and heated at 150° for 1 hr. After having been cooled, the crystalline

(17) All evidence regarding the tautomerism of α- and γ-aminopyrimidines suggests that they exist as amino groups rather than the isomeric imines (see ref. 14, p. 52).

(18) R. B. Angier and W. V. Curran, *J. Am. Chem. Soc.*, **81**, 5650 (1959).

(19) E. M. Gal, *ibid.*, **72**, 3532 (1950).

(20) M. F. Mallette, E. C. Taylor, and C. K. Cain, *ibid.*, **69**, 1814 (1947).

mass was slurried in 20 ml. of water, filtered, and dried to yield 3.25 g. of crude product; $R_f$ 0.24 (yellow-green) and $R_f$ 0.81 (absorption). This product was extracted with 100 ml. of boiling water. The insoluble portion (1.0 g.) was the desired pteridine, identical to the material prepared by method A (mixture melting point and $R_f$). The filtrate deposited 1.0 g. of acetanilide on standing overnight, m.p. 111–113°.

**2-Amino-4-hydroxypyrimidine (Isocytosine).**—One gram (6.4 mmoles) of 2-methylthio-4-hydroxypyrimidine[21] was heated for 1 hr. with 6.5 g. of ammonium acetate at 160°. Seven milliliters of water was added, and the mixture was chilled and filtered to give 0.90 g. of product. This was dissolved in 8 ml. of water, warmed on a steam bath, and brought to pH 8 with sodium carbonate, then chilled and filtered to give 0.40 g. of isocytosine ($R_f$ in solvent A and infrared absorption spectrum).

**2,6-Diamino-4-hydroxypyrimidine (IX).**—One gram (7.9 mmoles) of 2-methylthio-4-hydroxy-6-aminopyrimidine[22] (V) was treated in the same manner as for isocytosine to give 0.50 g. of product ($R_f$ 0.41 in solvent A).

**2-Amino-4-hydroxy-5-methoxypyrimidine.**—2-Methylthio-4-hydroxy-5-methoxypyrimidine[23] (1.0 g., 5.3 mmoles), was heated for 4.0 hr. at 160° with 10 g. of ammonium acetate. Paper chromatography in solvent A revealed $R_f$ 0.47 and a small amount of starting material, $R_f$ 0.59. Five grams of ammonium acetate was added and heated for an additional 2.0 hr. at 160°. Paper chromatography showed that reaction was complete. The reaction mixture was diluted with 150 ml. of water which was then evaporated *in vacuo*. After this procedure had been repeated twice, the oily residue was taken up in 20 ml. of hot water, treated with charcoal, and allowed to stand overnight. The solid was collected and dried; yield, 0.29 g. The filtrate was added to 200 ml. of water and evaporated to an oil *in vacuo*. This was taken up in 15 ml. of ethanol and chilled overnight. The product was collected and dried; yield, 0.25 g. Both crops were homogeneous by paper chromatography ($R_f$ 0.47 in solvent A); therefore, they were combined and recrystallized from 15 ml. of ethanol to yield 0.26 g. of product, m.p. 254–259° dec.[24]

*Anal.* Calcd. for $C_5H_7N_3O_2$ (141): C, 42.5; H, 5.0; N, 29.8. Found: C, 42.5; H, 5.0; N, 30.1.

**2,6-Bismethylamino-4-hydroxypyrimidine (VI).**—Methylamine (75 ml. of 40% aqueous solution) was chilled in an ice bath and 75 ml. of glacial acetic acid was added slowly with swirling. The resulting solution was evaporated to an oil *in vacuo*, dissolved in 100 ml. of absolute ethanol, and again evaporated *in vacuo*. The alcohol procedure was repeated. To 60 ml. of the oily methylammonium acetate was added 10 g. (0.08 mole) of 2-methylthio-4-hydroxy-6-aminopyrimidine (V). This was heated at 160° for 2 hr. Two hundred milliliters of water was added and evaporated *in vacuo*. After this procedure had been repeated the oily residue was taken up in 75 ml. of hot water and treated with charcoal. The solution was chilled for several days to afford 4.65 g. of the 2,6-bismethylamino compound, m.p. 238–244°. For analyses a small portion of this product was recrystallized from water; m.p. 241–244°; $R_f$ 0.69 in solvent A.

*Anal.* Calcd. for $C_6H_{10}N_4O$ (154): C, 46.7; H, 6.5; N, 36.3. Found: C, 46.6; H, 6.9; N, 36.8.

**2-Amino-4-hydroxy-6-methylaminopyrimidine (X, R=CH$_3$).**—2,6-Diamino-4-hydroxypyrimidine (IX) (15 g.) was heated for 2 hr. at 145° in 50 ml. of methylammonium acetate (preparation given previously). The reaction mixture was diluted with 100 ml. of water and the product was collected after standing at room temperature overnight; yield, 10.2 g. Recrystallization from ethanol using charcoal afforded 7.4 g. of product, m.p. 254.5–256.5° (lit.[8] m.p. 255–257°); $R_f$ 0.50 (solvent A).

*Anal.* Calcd. for $C_5H_8N_4O$ (140): C, 42.9; H, 5.8; N, 40.0. Found: C, 43.0; H, 5.8; N, 40.1.

**2,4-Dihydroxy-6-methylaminopyrimidine (VIII, R = CH$_3$).**—2,4-Dihydroxy-6-aminopyrimidine (VII) (2.0 g.) was heated for 2 hr. at 160° in methylammonium acetate (prepared from 20 ml. of 40% aqueous methylamine and 20 ml. of glacial acetic acid). Water (25 ml.) was added to the reaction mixture which was then chilled for several days. The product was collected and dried; yield, 1.6 g.; m.p. 302–305° dec. (lit.[7] m.p. 300–301°); $R_f$ 0.46 in solvent A and 0.52 in solvent C.

**2,4-Dihydroxy-6-benzylaminopyrimidine (VIII, R = C$_6$H$_5$CH$_2$).**—2,4-Dihydroxy-6-aminopyrimidine (2.5 g., 19.7 mmoles) was refluxed for 24 hr. in 100 ml. of benzylamine and filtered hot to give 1.8 g. of product. The filtrate deposited an additional 1.1 g. on standing in the cold. These two crops were combined and dissolved in 250 ml. of hot water by adding 10 ml. of 10 *N* sodium hydroxide, treated with charcoal, and filtered. The filtrate was acidified hot with 7 ml. of glacial acetic acid to give a white crystalline product; yield, 2.2 g. (52%); m.p. 293–294° dec. (lit.[7] m.p. 298–299°); $R_f$ 0.76 (solvent A).

*Anal.* Calcd. for $C_{11}H_{11}N_3O_2$ (217): C, 60.8; H, 5.1; N, 19.4. Found: C, 61.0; H, 5.1; N, 19.2.

**2-Amino-4-hydroxy-6-benzylaminopyrimidine (X, R = C$_6$H$_5$CH$_2$).**—Two grams of 2,6-diamino-4-hydroxypyrimidine was heated at 155° for 2 hr. in 0.15 mole of benzylammonium acetate, then diluted with 25 ml. of ethanol and allowed to crystallize; yield 0.95 g., m.p. 173–198°. The filtrate was chilled for several days to give a second crop of 0.65 g., m.p. 163–200°. These two crops were combined and recrystallized from water using charcoal; yield, 0.80 g. (23.4%); m.p. 220–223°; $R_f$ 0.76 in solvent A; $\lambda_{max}^{0.1\ N\ NaOH}$ 265 mμ (ε 13,000); $\lambda_{max}^{0.1\ N\ HCl}$ 270 mμ (ε 22,800).

*Anal.* Calcd. for $C_{11}H_{12}N_4O$ (216): C, 61.1; H 5.6; N, 25.9. Found: C, 61.2; H, 5.5; N, 26.0.

**Reaction of 2,6-Diamino-4-hydroxypyrimidine with Benzylamine.**—Two grams of 2,6-diamino-4-hydroxypyrimidine was refluxed for 2 hr. in 100 ml. of benzylamine, diluted with 200 ml. of water, and chilled overnight. The resulting yellow crystals were collected; yield, 1.25 g.; m.p. 186–191°. This product was recrystallized from ethyl acetate using charcoal; yield, 0.60 g.; m.p. 195–197°; $\lambda_{max}^{0.1\ N\ NaOH}$ 270 mμ (ε 13,150); $\lambda_{max}^{0.1\ N\ HCl}$ 228 (18,100), 271 mμ (ε 21,000). Comparison of these spectra with those of 1- and 3-methylisocytosine[9b] revealed similarity to the 1-methyl derivative indicating that this product could be 2-amino-1-benzyl-6-benzylamino-4(1*H*)-pyrimidinone.

*Anal.* Calcd. for $C_{18}H_{18}N_4O$ (306): C, 70.6; H, 5.9; N, 18.3. Found: C, 70.0; H, 6.0; N, 18.5.

**2,4-Dihydroxy-6-furfurylaminopyrimidine (VIII, R = Furfuryl).**—One gram of 2,4-dihydroxy-6-aminopyrimidine was fused for 2 hr. in furfurylammonium acetate prepared from 10 ml. (0.103 mole) of furfurylamine and 5.7 ml. (0.103 mole) of acetic acid. After the reaction mixture had been cooled, 20 ml. of water was added to give crystals; yield, 1.2 g. (55%); m.p. 267–274°. This product was recrystallized from 50% ethanol; yield, 0.90 g.; m.p. 275–278°; $R_f$ 0.67 in solvent A.

*Anal.* Calcd. for $C_9H_9N_3O_3$ (207): C, 52.2; H, 4.4; N, 20.3. Found: C, 52.2; H, 4.4; N, 20.2.

**2,4-Dihydroxy-6-(2-hydroxyethylamino)pyrimidine (VIII, R = CH$_2$CH$_2$OH). A.**—Two grams of pyrimidine compound VII was heated for 1.5 hr. in 0.10 mole of ethanolammonium acetate, then diluted with 15 ml. of water. The crystals were collected and recrystallized from water; yield, 1.35 g. (50%); m.p. 243–246°, gas evolution (lit.[7] m.p. 249°).

**B.**—A low yield (15%) of this same compound was obtained by refluxing the pyrimidine (2.0 g.) in ethanolamine (100 ml.) for 2 hr. Paper chromatography of the reaction mixture in solvent A showed at least two compounds present.

**2-Amino-4-hydroxy-6-furfurylaminopyrimidine (X, R = Furfuryl).**—Furfurylammonium acetate (0.21 mole), prepared from 20 ml. of furfurylamine and 11.8 ml. of acetic acid, was added to 12.6 g. (0.10 mole) of 2,6-diamino-4-hydroxypyrimidine and heated in an oil bath at 155–160° for 2 hr. After the reaction mixture had been cooled it was dissolved in 100 ml. of boiling ethanol and chilled; yield, 12.75 g.; m.p. 190–200°. Recrystallization of this material from water using charcoal gave 6.2 g. (30%) of product, m.p. 204–206°. For analyses a portion of this product was again recrystallized from water; melting point was raised to 206–208.5°; $R_f$ 0.67 in solvent A; $\lambda_{max}^{0.1\ N\ NaOH}$ 264 mμ (ε 13,000); $\lambda_{max}^{0.1\ N\ CHl}$ 267 mμ (ε 22,800).

*Anal.* Calcd. for $C_9H_{10}N_4O_2$ (206); C, 52.4; H, 4.9; N, 27.2. Found: C, 52.0; H, 4.8; N, 27.6.

**2-Dimethylamino-4-hydroxy-6-aminopyrimidine (XI).**—Two grams (12.7 mmoles) of 2-methylthio-4-hydroxy-6-aminopyrimidine was heated for 1 hr. at 155–160° with 20 ml. of dimethylammonium acetate. The reaction mixture was allowed to crystallize at room temperature over night, then diluted with 20 ml. of water, and the product collected and dried; yield, 1.2 g. (62%); m.p. 285–294°. Recrystallization from water gave 1.15

(21) H. W. Barrett, I. Goodman, and K. Dittmer, *J. Am. Chem. Soc.*, **70**, 1753 (1948).

(22) B. R. Baker, J. P. Joseph, and R. E. Schaub, *J. Org. Chem.*, **19**, 631 (1954).

(23) We wish to thank Dr. J. L. Fedrick for a sample of this compound. Details of its preparation will appear at a later date.

(24) E. A. Falco, P. B. Russell, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3753 (1951), give m.p. 266–267° dec. for the hemihydrate of this compound.

g.; m.p. 286–291° (lit.[5] m.p. 290.5–292.5°); $R_f$ 0.65 in solvent A; $\lambda_{max}^{0.1\ N\ NaOH}$ 243 (9100), 269 mμ (ε 9700); $\lambda_{max}^{0.1\ N\ HCl}$ 268 mμ (ε 17,500); $\lambda_{max}^{CH_3OH}$ 221 (30,600), 274 mμ (ε 14,600).

*Anal.* Calcd. for $C_6H_{10}N_4O$ (154): C, 46.7; H, 6.54; N, 36.3. Found: C, 46.8; H, 6.59; N, 36.5.

**2-Dimethylamino-4-hydroxy-6-methylaminopyrimidine (XII).**—2-Dimethylamino-4-hydroxy-6-aminopyrimidine (10.0 g., 0.065 mole) was refluxed in 120 ml. of methylammonium acetate in an oil bath for 2 hr. (internal temperature, 130–135°). The reaction mixture was chilled overnight, whereupon some crystals had come out. Additional crystals separated after agitation and further cooling; yield 6.5 g. (44%) of the acetate salt, m.p. 120–125°. A portion of this product was recrystallized from ethyl acetate for analytical purposes; melting point was raised to 128–130°; $R_f$ 0.83 with trace of lower $R_f$ spot in solvent A; dried at room temperature *in vacuo*.

*Anal.* Calcd. for $C_9H_{16}N_4O_3$(228): C, 47.4; H, 7.07; N, 24.6. Found: C, 47.3; H, 7.28; N, 25.2.

A small crop of the yellow, crystalline acetate salt was dried at 80° *in vacuo* over phosphorus pentoxide to give the free base; m.p. 201–203° (lit.[25] m.p. 198–200°); $\lambda_{max}^{0.1\ N\ HCl}$ 222 (13,000), 270 mμ (ε 22,500); $\lambda_{max}^{0.1\ N\ NaOH}$ 270 mμ (ε 10,800).

*Anal.* Calcd. for $C_7H_{12}N_4O$ (168): C, 50.0; H, 7.19; N, 33.3. Found: C, 50.0; H, 7.20; N, 33.6.

**2-Methylamino-4-hydroxy-6-aminopyrimidine.**—Two grams (13 mmoles) of 2,6-bis(methylamino)-4-hydroxypyrimidine was added to 15.0 g. of ammonium acetate and refluxed for 2 hr. The reaction mixture was diluted with 250 ml. of water and evaporated to an oily liquid *in vacuo*. After repeating this procedure the resulting oil was crystallized from 10 ml. of water; yield, 0.60 g., m.p. 219–221°, with previous wetting. The crude product was boiled in 12 ml. of ethanol, treated with charcoal, and filtered. The filtrate was cooled and the product was collected; yield, 0.44 g. (24%); m.p. 221–223°, after drying *in vacuo* over phosphorus pentoxide at 105° (lit.[5] m.p. 227–229°); $R_f$ 0.63 in solvent A; $\lambda_{max}^{0.1\ N\ NaOH}$ 239 (6000), 267 mμ (ε 9900); $\lambda_{max}^{0.1\ N\ HCl}$ 265 mμ (ε 21,700).

*Anal.* Calcd. for $C_5H_8N_4O$ (140): C, 42.9; H, 5.8; N, 40.0. Found: C, 43.1; H, 5.8; N, 39.9.

**2,4-Dihydroxy-6-ureidopyrimidine (XIII).**—One gram (7.9 mmoles) of 2,4-dihydroxy-6-aminopyrimidine was added to 10 g. of urea and placed in an oil bath at 150°. The bath temperature increased to 160° over the first 15 min. and to 170° over the next 15 min. during which time complete solution took place. The reaction mixture was kept at 170° for an additional 15 min. during which time crystals appeared. The mixture was diluted with 20 ml. of water while still warm, then allowed to stand at room temperature overnight before collecting the crystals; yield, 1.4 g.; unmelted at 400°. The material was recrystallized from 200 ml. of 50% aqueous ethanol; yield, 1.0 g. (75%); $R_f$ 0.50 with trace of lower $R_f$ spot in solvent B; $\lambda_{max}^{0.1\ N\ NaOH}$ 262 mμ (ε 19,000); $\lambda_{max}^{0.1\ N\ HCl}$ 257 mμ (ε 20,700); $\lambda_{max}^{CH_3OH}$ 259 mμ (ε 19,200).

*Anal.* Calcd. for $C_5H_6N_4O_3$(170): C, 35.3; H, 3.6; N, 32.9. Found: C, 35.5; H, 3.7; N, 32.9.

**2-Amino-4-hydroxy-6-ureidopyrimidine (XIV).**—One gram (8.0 mmoles) of 2,6-diamino-4-hydroxypyrimidine was added to 10 g. of urea and heated in an oil bath for 1 hr. at 165°. The mixture was diluted with 20 ml. of water, then allowed to stand at room temperature overnight. The product was collected and dried; yield, 0.75 g. Recrystallization from aqueous ethanol gave 0.65 g. (43%), unmelted at 400°. For analytical purposes, a portion of this product was dried over phosphorus pentoxide for several hours, then allowed to equilibrate in air; $\lambda_{max}^{0.1\ N\ NaOH}$ 223 (28,000), 272 mμ (ε 16,800); $\lambda_{max}^{0.1\ N\ HCl}$ 260 mμ (ε 18,700); $\lambda_{max}^{CH_3OH}$ 222 (39,000), 269 mμ (ε 17,600).

*Anal.* Calcd. for $C_5H_7N_5O_2 \cdot H_2O$ (187): C, 32.1; H, 4.9; N, 37.4. Found: C, 32.3; H, 4.9; N, 37.4.

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# The Cyclization Reactions of Certain 5-Amino-4-chloro-6-hydrazinopyrimidines with Phosgene[1]

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The synthesis of 5-amino-4-chloro-6-hydrazinopyrimidine and its cyclization with phosgene gas is described. The initial product of the cyclization is shown to be the 9-aminopurin-8-ol III. Upon refluxing in ethanolic hydrogen chloride, 9-amino-6-chloropurin-8-ol (III) undergoes an acid-catalyzed ring expansion to yield the isomeric 5-chloro-1,2,3,4-tetrahydro-3-oxopyrimido[5,4-*e*]-*as*-triazine. Other phosgene cyclizations investigated include the preparation of 6-chloropurin-8-ol from 4,5-diamino-6-chloropyrimidine and the synthesis of 5-chloro-1,2,3,4-tetrahydro-1-methyl-3-oxopyrimido[5,4-*e*]-*as*-triazine from 5-amino-4-chloro-6-(1-methylhydrazino)pyrimidine. In addition, the preparation of the 8-thio analog of 9-amino-6-chloropurin-8-ol by the use of thiophosgene as the cyclizing reagent is described. In the course of the work described herein, the syntheses and reactions of a number of 4,5,6-trisubstituted pyrimidines were investigated. 4,6-Dimethoxy-5-nitropyrimidine was found to react readily with hydrazine to form 4,6-dihydrazino-5-nitropyrimidine in excellent yield; yet it was surprisingly unreactive with methylhydrazine yielding as the only isolable material an unknown product containing a degraded nitro substituent.

4,6-Dichloro-5-nitropyrimidine (I), first described by Boon and co-workers,[2] has been found to be a very useful intermediate due to the marked activity of the chloro substituents toward nucleophilic reagents.

During the course of a study involving the preparation of certain derivatives of this intermediate for screening purposes, I was found to yield an intractable material, undoubtedly polymeric in nature, when treated with an anhydrous alcoholic solution of hydrazine. Upon substituting the amino analog for I, 5-amino-4-chloro-6-hydrazinopyrimidine (II) was obtained in excellent yields. Attempts to cyclize II led to the discovery of some very interesting reactions which are the subject of this manuscript. The usual cyclization procedures[3] for the preparation of purines did not yield in isolable product, although Montgomery and Temple[4] recently did, indeed, effect the cyclization of 5-amino-4-chloro-6-hydrazinopyrimidine with formic acid to yield a crude product from which they obtained 9-aminohypoxanthine.

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