THE CYCLIZATION REACTIONS OF CERTAIN
5-AMINO-4-CHLORO-6-HYDRAZINOPYRIMIDINES
WITH PHOSGENE

by

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THE CYCLIZATION REACTIONS OF CERTAIN
5-AMINO-4-CHLORO-6-HYDRAZINOPYRIMIDINES
WITH PHOSGENE

INTRODUCTION

In 1942 Hitchings, Elion, and coworkers began a study of the relationship between chemical structure and the ability of certain analogs of the naturally occurring pyrimidine and purine bases to serve as precursors for or to modify nucleic acid biosynthesis. The results of this study, published in 1950, led Hitchings to conclude that "pyrimidine derivatives can be found which do interfere with nuclear synthesis and metabolism in a variety of ways" (34, p. 1334).

Subsequent to these findings an ever-increasing amount of attention has been devoted to the synthesis of compounds which might support this conclusion and to the investigation of their effects upon biological systems. These efforts have led to the discovery of a number of antimetabolites, some of which are currently in clinical usage.

The biological activity of antimetabolites depends upon blocking a metabolic pathway in the cell. They may be considered to act by "fooling" the cell into accepting them as normal metabolites. The abnormal substances subsequently formed then interfere with
nucleic acid biosynthesis or other metabolic areas which affect cell growth.

Based upon an examination of the chemical structures of several hundred purine derivatives tested for possible effectiveness in cancer chemotherapy, Bendich and coworkers (5) have reported that the most active analogs possess the following characteristics: (a) the new group or atom introduced is not greatly different in size from the one replaced, and (b) the alteration occurs at a single site in the structure of the naturally occurring base. Bendich also noted that in adenine, hypoxanthine, and guanine, the replacement of carbons-2 or 8 by nitrogen, or substitution at carbons-2 or 6, has produced active analogs.

Thus 6-mercaptopurine (17), the sulfur analog of hypoxanthine, has proved to be an active drug in the treatment of acute leukemia in adults (30) and is also capable of rendering malignant tumors in mice non-viable (14).

Thioguanine and thioguanosine have also proven clinically active in the treatment of leukemia. In these compounds the atomic radius of the substituted atom, sulfur, is very similar to that of the oxygen which it is replacing, so that the analogs are essentially the same sterically. On the other hand, the electron distribution would be expected to be rather different, the carbon-sulfur double bond
being polarized to a greater extent than the carbon-oxygen double bond. It has been postulated (43) that the antimitotic activity observed with these compounds and also with certain selenium analogs (42, 43) may be attributed to the formation of a hydrogen bond of unusual strength between the highly polarized thiocarbamyl group and the amino group of the pyrimidine facing it in the double helix of deoxyribonucleic acid.

Switching the nitrogen at position 7 of the purine molecule to position 8 with formation of a pyrazolo[3,4-d]pyrimidine has produced a number of biologically interesting compounds (8, p. 62 and p. 68). In addition, the substitution of a nitrogen atom for one of the ring carbons has led to a number of compounds of experimental interest, including 6-azauracil (8, p. 62) and certain 2-aza- and 8-azapurines (56).

Studies indicate that folic acid, which takes part in intermediary metabolic reactions involving a one-carbon fragment, plays a vital role in biosynthesis of nucleic acids. An analog of folic acid, the 4-amino derivative (aminopterin), interferes with the action of folic acid (8, p. 59 and p. 62). Aminopterin, though very toxic, shows considerable temporary activity against leukemia in children. Other folic acid antagonists such as 4-aminopteroylaspartic acid and 4-amino-N₁₀-methylpteroylglutamic acid (66, p. 264) have also
been shown to produce considerable inhibition of growth in certain types of tumors. In light of these findings and of the demonstrated anti-tumor activity of some of the "aza" compounds such as the azapurines, it appeared worthwhile to investigate the preparation of a series of pyrimido-as-triazines. The parent compound, pyrimido[5,4-e]as-triazine (I), can be considered as an "azaapteridine". By virtue of the "aza" relationship to the pteridine moiety of folic acid and folinic acid, one might expect interference with metabolic processes involving one-carbon transfers.

![Chemical Structure](attachment:image.png)
DISCUSSION

At the time of the inception of this investigation, the pyrimido[5, 4-e]-as-triazine ring system was unknown. Two representatives of the system were first reported by Pfleiderer (48) in 1958. These compounds, 5, 6, 7, 8-tetrahydro-3, 6, 8-trimethyl-5, 7-dioxopyrimido[5, 4-e]-as-triazine (II) and 5, 6, 7, 8-tetrahydro-6, 8-dimethyl-5, 7-dioxopyrimido[5, 4-e]-as-triazine (III), were prepared by acylation of 1, 3-dimethyl-4-hydrazinouracil (see Figure 1). The acetyl and formyl derivatives formed, upon nitrosation of the 5-position and acidic reduction of the nitroso group, undergo cyclization and dehydrogenation to form the respective pyrimido[5, 4-e]-as-triazines II and III. It should, however, be noted that in each of these compounds the presence of methyl groups at positions 6 and 8 eliminates the possibility of aromatic resonance in the pyrimidine ring. Thus they cannot be classified as truly representative of this ring system.

Until quite recently, no other work in this area has been reported, although H.M. Taylor in a doctoral dissertation submitted to the University of North Carolina in 1959 (61) has discussed the investigation of possible routes for the synthesis of an isomeric ring system, the pyrimido[4, 5-e]-as-triazines (IV).
Figure 1. Synthesis of 5, 6, 7, 8-tetrahydro-5, 7-dioxopyrimido[5, 4-e]-as-triazines by Pfleiderer and Schuendehuette (48).
The general synthetic approach investigated in the work reported herein was to prepare 5-amino-6-hydrazino-pyrimidines and to cyclize these compounds by formylation of the hydrazino substituent and subsequent ring closure.

5-Amino-4-chloro-6-hydrazinopyrimidine (IX) was selected as a suitable pyrimidine for the initial cyclization studies because a relatively simple synthetic route to it could be devised. Furthermore, if the chloro substituent could be retained in the cyclized compound, a "handle" might be available for the preparation of other derivatives for purposes of characterization and testing.

A summary of the synthetic route to IX may be seen in Figure 2. It involved condensation of malonodiamide with ethyl formate by the method of Hull (35). The resulting pyrimidinediol was then nitrated using the procedure of Boon, Jones, and Ramage (7) to yield the corresponding nitropyrimidinediol (V) in excellent yields. Chlorination of V with phosphorus oxychloride and
Figure 2. Synthetic route to 5-amino-4-chloro-6-hydrazinopyrimidine (IX).
N, N-dimethylaniline is reported by Boon and coworkers (7) to yield 4, 6-dichloro-5-nitropyrimidine (VI) in yields of approximately 85 percent. However, repeated attempts in this laboratory yielded the desired product in yields of only 35 to 40 percent, a result in agreement with the findings of Lower (39, p. 4-5). It was subsequently discovered that substitution of N, N-diethylaniline for the dimethylaniline previously used markedly increases the yields in this reaction. With this modification, the crude product has been obtained in yields of 80-85 percent of theoretical.

Treatment of VI with an alcoholic solution of anhydrous hydrazine produced a vigorous reaction and resulted primarily in formation of a brown, water-insoluble, intractable material which is undoubtedly polymeric in nature, together with a small amount of the 4, 6-dihydrazino-5-nitropyrimidine (VII).

The high reactivity of the dichloronitropyrimidine (VI) suggested that synthesis of the hydrazino derivative might be accomplished with more success if the nitro group were first reduced. This reduction would be expected to decrease greatly the reactivity towards nucleophilic substitution of the chlorine substituents at positions 4 and 6, since the electron withdrawing effect of the nitro group would be replaced by the opposite effect of an amino substituent. Experimental evidence supporting this
hypothesis had previously been provided by Robins, Dille, and Christensen (55), who had noted that 5-amino-4,6-dichloropyrimidine (VIII) is completely unreactive with hot 15 percent aqueous ammonia. By catalytic reduction (55) of VI the aminodichloropyrimidine was obtained in good yield.

Upon refluxing VIII with anhydrous hydrazine in ethanol the desired product, 5-amino-4-chloro-6-hydrazinopyrimidine (IX), was obtained in yields of 85 to 90 percent. This material was recently described by Montgomery and Temple (45), who obtained yields of only 40 percent by treating the pyrimidine with pure hydrazine hydrate.

Upon examination of IX it can be readily observed that treatment with reagents such as anhydrous formic acid (17) or ethyl orthoformate-acetic anhydride (44, 51), normally used to prepare purines from 4,5-diaminopyrimidines, poses an interesting chemical problem, inasmuch as the reaction product may be a 9-aminopurine, a 1,2-dihydropyrimido[5,4-e]-as-triazine or a mixture of both. At that time neither type of compound had been synthesized, yet either product could be utilized in the preparation of potential anticarcenogenic agents.

A number of attempts to accomplish the cyclization of IX were made. Among the reagents employed were 90 percent formic
acid, formamide, 98-100 percent formic acid—acetic anhydride, and 98-100 percent formic acid. However it was not possible to isolate a product from any reaction mixture whose elemental analysis was in good agreement with any of the expected cyclized products or with any of their formyl derivatives. It was not until some time later that the work of Montgomery and Temple (45) showed that 5-amino-4-chloro-6-hydrazinopyrimidine (IX) can indeed be cyclized by formic acid to yield 9-N-formylamino-hypoxanthine (X).

\[
\begin{align*}
\text{O} & \\
\text{HN} & \\
\text{N} & \\
\text{N} & \\
\text{NHCHO} & \\
\text{O} & \\
\text{HN} & \\
\text{N} & \\
\text{N} & \\
\text{NH}_2 & \\
\end{align*}
\]

Difficulties in purification of the crude cyclized material obtained in this laboratory were probably the reason for the unsatisfactory analytical data obtained in our work. Montgomery apparently did not attempt isolation of X but proceeded to react the crude product further to yield 9-aminohypoxanthine (XI) as the ultimate product, which could be more readily isolated and purified.

Synthesis of a formylhydrazinopyrimidine was also
attempted, with a view to subsequent cyclization of the formylhydrazino compound. However, this also was unsuccessful; the aminodichloropyrimidine was found to be too unreactive to allow substitution of formylhydrazine (formhydrazide) while the nitrodichloropyrimidine formed with this reagent what appears to be a polymeric solid.

At this time it was decided to investigate the use of phosgene as a cyclizing agent. This reagent had been employed with some success previously in analogous syntheses, for example in the synthesis of 6-aminopurin-8-ol sulfate from 4, 5, 6-triaminopyrimidine sulfate (11).

Upon the introduction of phosgene gas into a slightly acidic solution of 5-amino-4-chloro-6-hydrazinopyrimidine (IX), a light tan solid material precipitated. Sublimation (210 °C., 0.02 mm.) or recrystallization from hot N,N-dimethylformamide yielded a white crystalline solid which decomposes at approximately 290 °C. Elemental analysis of this material indicated an empirical formula C₅H₄ClN₅O and suggested that the compound was either 9-amino-6-chloropurin-8-ol 1/ (XII) or 5-chloro-1, 2, 3, 4-tetrahydro-3-oxo-pyrimido[5, 4-e]-as-triazine (XIII).

1/ In conformity to the nomenclature system followed in the Chemical Abstracts Subject Index, all 8-oxo- (or 8-hydroxy-) purines are named herein as purin-8-ols, irrespective of the true tautomeric form in which they exist.
The infrared spectrum of the compound in question did not provide an unequivocal basis for structure assignment but indicated that structure XII was more likely, and on these grounds a tentative structure assignment was made. The most striking aspect of the spectrum (see Figure 3) is the presence of two very strong and well defined peaks (1745 and 1713 cm\(^{-1}\)) in what is normally considered as the C=O absorption region. The peak at 1745 cm\(^{-1}\) may be assigned to the amide-I absorption band. This is a considerably higher frequency than that normally assigned to amide-I absorptions but is in keeping with observations that the amide-I bands of cyclic amides in fused five-membered rings are often shifted upwards to frequencies in the neighborhood of 1700-1750 cm\(^{-1}\) (4, p. 214; 12, p. 390-391; 63). Furthermore, Mason has reported (41) that purin-8-ol and its 7-methyl and

\[\text{The reader is also referred to Table I, which provides a comparison of the major hydrogen stretching and double-bond absorptions in the infrared spectra of the condensed ring compounds discussed herein.}\]
Figure 3. Infrared spectrum of 9-amino-6-chloropurin-8-ol (XII).
Table 1. Summary of Infrared Data for Condensed Ring Compounds.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hydrogen Stretching Vibrations (3000-4000 cm^{-1})</th>
<th>Double-bond Vibrations (1500-1750 cm^{-1})</th>
</tr>
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<tr>
<td>XII</td>
<td>3460m* 3330m 3200s 3090m</td>
<td>1745s 1713s 1622s 1556s 1540m</td>
</tr>
<tr>
<td>XV</td>
<td>3460s** 3310m 3200m 3080m</td>
<td>1705vs 1647m 1611s 1556m 1529m</td>
</tr>
<tr>
<td>XVI</td>
<td>3455w 3365m</td>
<td>1745vs 1608vs 1558m 1537s</td>
</tr>
<tr>
<td>XXV</td>
<td>3125s 2995-3035m**</td>
<td>1707vs 1632s 1592s</td>
</tr>
<tr>
<td>XXVI</td>
<td>3450s 3305s 3200m 3095s</td>
<td>1622s 1551s 1520m</td>
</tr>
<tr>
<td>XIII</td>
<td>3370w 3315s 3175vs</td>
<td>1704m 1660m 1620vs 1585m 1550m</td>
</tr>
<tr>
<td>XXII</td>
<td>3190m 3100s</td>
<td>1715vs** 1590s 1579s 1538w</td>
</tr>
<tr>
<td>XXXII</td>
<td>3320w 3240m 3040m</td>
<td>1666vs 1625m 1547w</td>
</tr>
</tbody>
</table>

* w = weak; m = medium; s = strong
** broad
9-methyl derivatives all show carbonyl stretching frequencies in the region of 1740 to 1745 cm.\(^{-1}\) A six-membered cyclic amide such as in structure XIII would not be expected to absorb at this high frequency.

The strong absorption at 1713 cm.\(^{-1}\) still remains to be considered. Inasmuch as cyclic amides do not normally exhibit an amide-II band (4, p. 217-220; 12, p. 390; 26) and, in addition, the amide-II band is normally located at considerably lower frequencies, this does not appear to be a likely explanation. This absorption is also at a much higher frequency than that normally attributed to C=C and C=N vibrations in the pyrimidine ring, the strong band at 1622 cm.\(^{-1}\) being a more likely assignment for these vibrations. Perhaps the most satisfactory explanation of the 1713 cm.\(^{-1}\) band is that XII consists of a tautomeric mixture of XIIa and XIIb, the higher frequency absorption being supplied by

![Diagram of structures XII and XI]
the carbonyl group in XIIa and the lower band being a contribution of the enol form, XIIb. Gagnon and coworkers (24, p. 831-5; 25, p. 1031-3) have attributed absorptions in the range of 1670-1700 cm.\(^{-1}\) to cyclic C=N vibrations in certain pyrazolones, and the increase in frequency due to the five-membered ring of XIIb being fused could reasonably account for an absorption band at a frequency of 1713 cm.\(^{-1}\).

9-Amino-6-chloropurin-8-ol (XII) is insoluble in non-polar solvents and only slightly soluble in boiling water, dilute aqueous acids or ethanol but has a fair degree of solubility in N,N-dimethylformamide and in dimethylsulfoxide. It is also quite soluble in dilute alkali, probably forming a soluble salt involving the anionic species XIV. Aqueous solutions of XII have also been found to yield an insoluble white salt or complex with silver ion and a yellow product with mercurous ion.

Upon solution in dilute aqueous base, the material can be recovered as a monohydrate if the solution is immediately
re-acidified; if the basic solution is allowed to stand, decomposition rapidly ensues. The solution becomes yellow (after about fifteen minutes) and then brown. At this point acidification does not yield a precipitate. This instability in basic media is undoubtably related to the extreme ease with which hydrazino compounds are oxidized by air under alkaline conditions. In boiling water and in dilute aqueous acid XII is much more stable, although even under these conditions decomposition slowly proceeds, yielding ammonium chloride as one of the decomposition products.

The chlorine substituent appears to be surprisingly inert by comparison to 6-chloropurine, which can be readily aminated and can be quantitatively hydrolyzed to hypoxanthine by boiling either in 0.1N sodium hydroxide for four hours or in 0.1N hydrochloric acid for one hour (5). Thus 9-amino-6-chloropurin-8-ol (XII) failed to react when attempts were made to synthesize the morpholino derivative. This inertness of the 6-position towards nucleophilic reagents appears to be due to a stabilizing influence of the 8-hydroxy group; Robins (53) has reported a similar observation in the cases of 6-chloropurin-8-ol-2-sulfonic acid and purin-8-ol-2,6-disulfonic acid. Perhaps under the conditions of nucleophilic substitution, XII is converted into its enol form. As in the case of phenol (58, p. 435), the permanent inductive
effect of the -OH group, which is electron attractive, would be minor in comparison with the powerful mesomeric and electro-
meric effects of electron release. In basic solution the anion (XIV) produced has a negative charge on oxygen, which further facilitates electron release by this group. The net result would

\[
\begin{align*}
\text{Cl} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{NH}_2 &
\end{align*}
\]

XIV

be one of greatly increasing the electron density at the 6-position, thereby decreasing the ease of nucleophilic displacement.

As has been noted above, when an alkaline solution of XII is acidified, the material is recovered as a monohydrate. This hydrated material was also obtained upon recrystallization of XII from both pH 5 and pH 7 buffer solutions. The hydrate can be quantitatively reconverted to XII by sublimation and also by removal of water via distillation as a toluene-water azeotrope.

The infrared spectrum of the hydrated material (see Figure 4) is similar to that of XII but shows some major differences. Among these are the strengthening and broadening of the band at 3460 cm.\(^{-1}\)
Figure 4. Infrared spectrum of 9-amino-6-chloropurin-8-ol monohydrate (XV).
and the complete elimination of the strong absorption which the anhydrous compound exhibits at 1745 cm.$^{-1}$ Based upon the hypothesis that XII is a tautomeric mixture of XIIa and XIIb, these spectral changes suggest that the structure of XII·H$_2$O involves complete conversion of the heterocycle into its enol form, possibly with the water molecule bonded to the heterocycle as in structure XVa. The strengthening and broadening of the band at 3460 cm.$^{-1}$ can be attributed to superimposition of O-H stretching frequencies contributed by the bound water. The C=O absorption at 1745 cm.$^{-1}$ would, of course, be eliminated.

One can write an alternate, but less likely, structure for the hydrate, XVb. This involves formation of a gem-diol at the carbonyl carbon to yield a structure similar to that of the monohydrated form of ninhydrin. This structure, too, explains the elimination of the carbonyl peak at 1745 cm.$^{-1}$, but one would also expect loss of the band at 1713 cm.$^{-1}$ if the assignment of that band
to the enol C=N vibration is correct. In order for structure XVb to be valid, one would be forced to assign the 1713 cm$^{-1}$ band to pyrimidine ring vibrations; and, as has been suggested earlier, these vibrations are normally found at a considerably lower frequency.

Efforts to chlorinate the oxygen function at the 8-position of 9-amino-6-chloropurin-8-ol (XII) by the usual chlorination procedures (refluxing in phosphorus oxychloride with N, N-diethylaniline) led, apparently, to destruction of the ring system and did not yield any isolable products. Subsequent investigation showed that XII was inert to boiling phosphorus oxychloride and that no reaction occurred until a few milliliters of diethylaniline were added, whereupon the mixture rapidly darkened as the solid material dissolved in the hot solution. If this solution was immediately allowed to cool, a yellow microcrystalline solid, XVI, was obtained.

XVI is a highly acidic and very reactive material. Its elemental analysis suggests an empirical formula $\text{C}_5\text{H}_4\text{Cl}_4\text{N}_5\text{O}_2\text{P}$. This empirical formula corresponds to the addition of a molecule of phosphorus oxychloride to XII ($\text{C}_5\text{H}_4\text{ClN}_5\text{O} \cdot \text{POCl}_3$), but should not lead one to consider XVI as simply a complex in which equimolar quantities of phosphorus oxychloride and XII crystallize.
together in a manner analogous to the formation of solids containing water of crystallization. If this were the case, one would not expect the formation of XVI to require the presence of a tertiary amine. Furthermore, such a complex should not produce the major changes observed in the infrared spectrum (see Figure 5). Here, it will be noted, the band at 1713 cm.\(^{-1}\) has disappeared and the band at 1745 cm.\(^{-1}\) has remained. In the hydrogen stretching region, the peak at 3200 cm.\(^{-1}\) has disappeared. In addition, two strong absorption bands have been added at 1295 cm.\(^{-1}\) and 1210 cm.\(^{-1}\)

This spectral data provides only a very shaky basis for assigning a structure to XVI but suggests that XVIa, phosphoryl 7-(9-amino-6-chloro-7,8-dihydro-8-oxopurinamide) dichloride hydrochloride, \(1/\) is the most likely assignment. The disappearance  

\(1/\) The current confusion in the chemical literature with regard to the nomenclature of phosphorus compounds is compounded in the case of an organophosphorus molecule such as XVI, especially since there is considerable divergence of the organic and inorganic rules of nomenclature. The name assigned above appears to fit most closely within the framework of the IUPAC system of terminology (16, p. 5531-5532 and p. 5535-5536) and is also in agreement with Van Wazer's suggested name (62, p. 333) for compounds of the type R-NH-POCl\(_2\) (phosphoryl alkylamide dichloride). XVI also might well be named 7-(9-amino-6-chloropurin-8(7H)-one) phosphoryl chloride hydrochloride by analogy to the naming of HOOCCH(NH\(_2\))CH\(_2\)CH\(_2\)CH\(_2\)NHC(-NH)NHPO(OH)\(_2\) (arginine phosphoric acid (62, p. 836). Another name which merits
of the peak at 1713 cm\(^{-1}\) gives rather conclusive proof that this band is not due to C=C or C=N vibrations in the pyrimidine ring and lends credence to its previous assignment to the enol C=N of XIIb. This also means that XVa is a preferable structure for the monohydrate. In addition, XVI must be completely in the amide form, thus eliminating from consideration structure XVIc, which might appear chemically to be the most reasonable structure. The disappearance of the N-H stretching band at the lowest frequency, consideration follows the organic nomenclature system more closely; here XVI is named as a purine derivative: 9-amino-6-chloro-7-dichlorophosphorylpurin-8(7H)-one hydrochloride.
Figure 5. Infrared spectrum of phosphoryl 7-(9-amino-6-chloro-7,8-dihydro-8-oxopurinamide) dichloride hydrochloride (XVI).
accompanied by only minor changes in the two highest bands, would indicate that substitution has occurred at the 7-position (XVIa) rather than on the 9-amino group (XVIb). Structure XVIa would also best explain the absence of any of the enol tautomer. The strong band at 1295 cm\(^{-1}\) may safely be assigned to the P=O stretching vibration; it coincides precisely with the frequency of the P=O vibration in phosphorus oxychloride (4, p. 312). The band at 1210 cm\(^{-1}\) can not be assigned with any certainty, although it could conceivably result from P-N stretching vibrations. As Bellamy points out (4, p. 323), "Any correlation for the P-N link must be expected to be mass sensitive, and therefore liable to considerable frequency shifts with minor alterations in structure. The correlation is not therefore a particularly useful one, and in a number of cases it has not proved possible to identify the band in question."

When XVI was titrated potentiometrically with 0.02N sodium hydroxide solution, the titration curve reproduced in Figure 6 was obtained. This curve shows that not all of the potential hydrogen ions can be titrated and also indicates that two of them are neutralized above the major inflection point. If XVI does indeed have a structure in which the phosphoryl chloride is covalently bound to the heterocycle in some manner such as is
Figure 6. Potentiometric titration of XVI.

Wt of XVI = 5.852 mg
NEUTRALIZATION EQUIVALENT (TO INFLECTION POINT) = 113.7
MOLECULAR WT = 341.1
indicated in structures XVIa, b, c, then one would expect the molecule to produce three equivalents of strong acid and two of weak acid (see Figure 7). Two molecules of hydrochloric acid would be produced upon hydrolysis of the phosphoryl chloride and these plus the hydrochloric acid directly bound to the heterocycle would, of course, titrate as strong acids. The two hydrogen atoms of the phosphoramide would both titrate as weak acids.

On the other hand, if the phosphorus oxychloride were present merely as "solvent of crystallization", each molecule would produce four equivalents of strong acid and two of weak:

\[ \text{POCl}_3 + 3 \text{H}_2\text{O} \rightarrow \text{H}_3\text{PO}_4 + 3 \text{HCl} \]

\[ \text{H}_3\text{PO}_4 + 3 \text{HCl} + 4 \text{OH}^- \rightarrow \text{H}_2\text{PO}_4^- + 3 \text{Cl}^- + 4 \text{H}_2\text{O} \]

\[ + 2 \text{OH}^- \rightarrow \text{PO}_4^{3-} + 2 \text{H}_2\text{O} \]

From the data in Figure 6, the neutralization equivalent up to the major inflection point (i.e., the milligrams of XVI per milli-equivalent of base to arrive at the major inflection point) can be calculated to be 113.7. Based on three equivalents of acid neutralized at this point, the calculated molecular weight of XVI is 341.1, which is well within experimental error of the theoretical value of 338.9. This, then, gives further proof that the
Figure 7. Neutralization of XVI, showing the formation of three equivalents of strong acid and two of weak acid.
phosphoryl chloride is bound to the heterocycle by covalent bonding.

Attempts to form the diethyl ester of XVI by refluxing the compound in absolute ethanol led to an unexpected result. Besides a substantial amount of brown amorphous material, the only major product was a solid which could be sublimed with difficulty to yield a white, crystalline, phosphorus-free substance.

Carbon-hydrogen analysis of this substance indicated that it is isomeric with 9-amino-6-chloropurin-8-ol (XII), but its infrared and ultraviolet spectra are markedly different. While the general physical properties of the two compounds are similar, this second material is far less soluble in the same solvents and has a considerably higher decomposition point (above 320 °C.). The structure tentatively assigned to it was 5-chloro-1, 2, 3, 4-tetrahydro-3-oxopyrimido[5, 4-e]-as-triazine (XIII). This had been previously considered as an alternate possibility for the product of the original cyclization, and its formation from XVI would have to involve a ring expansion.
When XII was refluxed in an approximately 0.33M alcoholic solution of anhydrous hydrogen chloride, under the same conditions, XIII was again obtained (in about 55 percent yield). In the absence of hydrogen chloride no reaction occurs, indicating that acid catalysis is required for this isomerization to occur. Apparently the only function of the phosphoryl chloride in XVI is to provide the necessary acid catalysis.

Although unexpected at the time, the ring expansion here postulated is not at all unreasonable. Several possible mechanisms for the acid catalyzed transformation can be written, one of which is presented in Figure 8. Just recently Taylor and coworkers (60) have reported another instance of this type of ring expansion. They found that mild acid hydrolysis of 6-methyl-9-N-formylaminopurine (XVII) yielded 5-methyl-1, 2-dihydropyrimido[5, 4-e]-as-triazine (XVIII).

\[ \text{XVII} \quad \xrightarrow{H^+} \quad \text{XVIII} \]
Figure 8. A proposed mechanism for the formation of XIII from XII via an acid catalyzed ring expansion.
The absorption band at 1704 cm$^{-1}$ in the infrared spectrum of XIII (see Figure 9) can be reasonably assigned to the C=O stretching vibrations of an amide in a six-membered ring. This frequency is ordinarily rather high for such an assignment, but it has been reported (50, p. 1250-1252) that in a series of anilides in which the aromatic ring has substituents that will increase the ring's electron attracting properties, values as high as 1715 cm$^{-1}$ have been observed. The relative weakness of the 1704 cm$^{-1}$ band is surprising; it may perhaps be due to the compound existing partly as the enol tautomer XIIIb.

![XIIIb](image)

The absorption at 1660 cm$^{-1}$ might very well be caused by C=N vibrations of the enol. The strong band at 1620 cm$^{-1}$ can, as in the spectra discussed previously, be assigned to C=C and C=N stretching in the fused pyrimidine ring.

Both the aminopurinol (XII) and the tetrahydro-oxo-pyrimido-as-triazine (XIII) can be considered as cyclic
Figure 9. Infrared spectrum of 5-chloro-1, 2, 3, 4-tetrahydro-3-oxopyrimido[5, 4-e]-astriazine (XIII).
derivatives of semicarbazide (XIX), with structure XII involving substitution at positions 2 and 4, and structure XIII being a 1,4-disubstituted derivative. Attempts were therefore made to prepare semicarbazone derivatives of benzaldehyde using the two isomers in the hope that this might contribute further proof of the assigned structures. XII would be expected to yield the benzylidene derivative XX, while XIII should be unreactive. It was found, however, that neither isomer exhibits semicarbazide-like activity.

Under the usual conditions of semicarbazide formation (59, p. 170-171) no reaction at all was detected, XII being recovered as its
monohydrate and XIII, which does not form a hydrate, being recovered unchanged. Attempts to form an isopropylidene derivative by a method successfully employed by Grovenstein and coworkers (27) with a cyclic hydrazide of cyclohexane-1, 2-dicarboxylic acid were also fruitless with both isomers. The failure to obtain these derivatives does not, of course, invalidate the proposed structures; it merely fails to support them.

Figure 10 is a summary of the fused ring compounds which have been discussed thus far. The structures shown therein are considered the most likely structures based upon the evidence presented above.

The synthesis and cyclization with phosgene of 5-amino-4-chloro-6-(1-methylhydrazino)-pyrimidine (XXI) were also investigated. The procedure for preparing XXI consisted of treating 5-amino-4, 6-dichloropyrimidine (VIII) with an alcoholic solution of methylhydrazine. This method is very straightforward, and yields of the order of 80-85 percent can be readily obtained. The substituted nitrogen of methylhydrazine, being more basic due to electron release from the alkyl substituent, is the more reactive of the two nitrogens, and only the (1-methylhydrazino)-pyrimidine is formed. For verification of this, the methylhydrazinopyrimidine was treated with an aqueous solution of sodium
Figure 10. Some fused ring compounds derived from 5-amino-4-chloro-6-hydrazinopyrimidine.
pentacyanoaminoferroate. A very intense red to violet color was produced. Hydrazines of the type RNH-NH₂ and R₂N-NH₂ are reported to give a red to violet color with this reagent (18, p. 292; 19).

Shortly after this work was accomplished, Montgomery and Temple (45) also reported synthesis of XXI, by a slightly different procedure. Using pure methylhydrazine these workers obtained the hydrazinopyrimidine in yields of only 40 percent; however, by using an aqueous suspension of methylhydrazine, yields comparable to those obtained in this laboratory were achieved.

The cyclization of XXI with phosgene was best accomplished by employing a procedure very similar to that used in the synthesis of 9-amino-6-chloropurin-8-ol (XII). Ethanol and pyridine were also investigated as possible reaction media, but although some of the desired product was obtained in each experiment, the best yields were achieved by use of an aqueous medium.

The structure of the cyclized product, 5-chloro-1, 2, 3, 4-tetrahydro-1-methyl-3-oxopyrimido[5, 4-e]-as-triazine (XXII), can be presumed to be unequivocal. It is quite similar in its physical properties to XIII, the non-methylated compound, having the same solubility characteristics and exhibiting a similar high melting point with decomposition. Like XII and XIII, the compound demonstrates an extreme lability when dissolved in
Figure 11. Synthesis of 5-chloro-1, 2, 3, 4-tetrahydro 1-methyl 3-oxo-pyrimido[5, 4-e]-as-triazine (XXII).
dilute alkali. The solution rapidly darkens, and unless it is immediately re-acidified, none of the material can be recovered upon subsequent acidification. This instability is rather surprising inasmuch as the methylhydrazinopyrimidine precursor does exhibit considerable stability in a basic medium. These observations indicate that decomposition is not simply a matter of initial hydrolysis of the semicarbazide followed by air oxidation of the precursor pyrimidine.

The infrared and ultraviolet spectra of XXII (see Figure 12 and Table II) are surprisingly different from those of XIII. To be sure, many points of similarity can be detected, but the spectra are far more different than one would expect solely as a result of the substitution of a methyl group at the 1-position. A similar unexpectedly large variation can be noted between the infrared spectra of 5-amino-4-chloro-6-hydrazinopyrimidine and 5-amino-4-chloro-6-(1-methylhydrazino)-pyrimidine (see Figures 13 and 14). It would appear that such spectral variations are not unusual with pyrimidines and purines. Bellamy, in reference to these heterocycles, has written, "It has not yet proved possible to develop satisfactory correlations for the recognition of this particular class of compounds." (4, p. 282).

At first glance, nuclear magnetic resonance (NMR)
Figure 12. Infrared spectrum of 5-chloro-1, 2, 3, 4-tetrahydro-1-methyl-3-oxopyrimido[5, 4-e]-as-triazine (XXII).
Figure 13. Infrared spectrum of 5-amino-4-chloro-6-hydrazinopyrimidine (IX).
Figure 14. Infrared spectrum of 5-amino-4-chloro-6-(1-methylhydrazino)-pyrimidine (XXI).
spectroscopy would seem to provide an easily obtained and unequivocal means of assigning the structures of XII and its isomer XIII. The major technical problem with the use of this tool for such determinations is the insolubility of these compounds in all of the solvents best suited for nuclear magnetic resonance work. Nevertheless, at our request D.P. Hollis of Varian Associates recently attempted to obtain the nuclear magnetic resonance spectra of XII, XIII, and XXII. The solvent selected was dimethylsulfoxide, which has previously been used successfully with certain nitrogen heterocycles (38).

The results of this study were not very informative. Solvent lines, plus side-bands, plus impurities in the solvent completely obscure the region from about 1 to 4.2 ppm, and essentially no information could be derived from the spectra of XIII and XXII. In the case of XII, three regions of resonance were observed outside the region of solvent interference: a sharp line at approximately 8.1 ppm, which can be assigned to the aromatic proton; a broad band at approximately 12.6 ppm with an intensity equal to that of the 8.1 ppm line (assigned to the amidic proton on the five-membered ring); and a broad band at about 6 ppm, assigned to the two amino protons. The intensity of the latter peak was difficult to measure because of a rapid drift on the up-field side of
this resonance, but was approximately correct for two protons. 
At any rate, this spectrum seems to be in reasonable accord with 
the proposed structure for XII.

Dr. Hollis also attempted to obtain the spectra of XII 
and XIII by dissolving these compounds in deuterium oxide to which 
a small piece of sodium had been added to furnish the necessary 
basic solution. In both cases he was able to obtain only single line 
spectra which appeared to correspond to the aromatic protons. No 
other protons could be observed in either case, presumably due to 
rapid exchange between the deuterium oxide solvent and the protons 
on the nitrogen atoms.

Because of its structural similarity to XII, the synthesis 
of 6-chloropurin-8-ol (XXV) was also investigated. This material 
had been synthesized earlier by Robins (52), who had obtained it in 
25 percent yield by acid hydrolysis of 6,8-dichloropurine, but 
who had reported no infrared data for the compound.

The synthetic route employed in this laboratory for the 
preparation of XXV is outlined in Figure 15. It involved mono-
amination of 4,6-dichloro-5-nitropyrimidine (VI) by the method of 
Boon, Jones, and Ramage (7) to yield 4-amino-6-chloro-5-nitro-
pyrimidine (XXIII), which on reduction with zinc dust (54) yielded 
the diaminochloropyrimidine (XXIV). This material was then
Figure 15. Synthesis of 6-chloropurin-8-ol (XXV).
cyclized by reaction with phosgene. It was found that the conditions employed for the previously discussed cyclizations yielded only very small amounts of the desired product, most of the diaminochloro-pyrimidine remaining unreacted. Fortunately, the N-N linkage is absent in both the pyrimidine and the cyclized product, and therefore these compounds do not exhibit instability under basic conditions. Using an aqueous alkaline medium, the cyclization proceeded well; XXV was obtained in yields of 30-35 percent, and a large portion of the unreacted starting material could be recovered for recyclization in a subsequent preparation.

XXV has the expected high decomposition point (318-322 °C.), and its ultraviolet spectrum agrees very well with that reported by Robins (52). The infrared spectrum (see Figure 16) is, however, rather surprising. On the basis of Mason's reported values for several 8-hydroxypurines (41), a C=O absorption in the region of 1740-1745 cm$^{-1}$ was expected. Instead a strong band was found at 1707 cm$^{-1}$. At this time it is impossible to offer a good explanation for this observation. This might indicate that XXV exists completely in the enol form (XXVb), but if such is the case, this is in complete disagreement with Mason's conclusions for 8-hydroxypurine and its derivatives and
Figure 16. Infrared spectrum of 6-chloropurin-8-ol (XXV).
with our previously discussed findings for 9-amino-6-chloropurin-8-ol (XII).

The inertness of the chlorine substituent in XII, XIII, and XXII can, for reasons presented earlier, be attributed to the presence of the oxygen function on the ring. This has led us to make a determined effort to chlorinate these ring systems, thereby accomplishing removal of the oxygen. The results obtained in attempts to chlorinate XII have previously been discussed. With the other compounds, chlorinations using phosphorus oxychloride were investigated under a variety of conditions. In all cases, under vigorous reaction conditions in the presence of diethylaniline neither starting material nor product could be isolated. Under milder conditions only starting material could be obtained from the reaction mixture. In the absence of a tertiary amine there was no evidence whatsoever of any reaction, even when the material was heated for six hours in a sealed tube at 140 °C. (By this method Tieckelmann
and coworkers (33) report chlorination of pyrazolono[3, 4-d]pyrimidines in yields of up to eighty percent.

Early in 1961, Robins (53) published a new method for the synthesis of chloropurines. He reported that 2, 6, 8-trichloropurine had been obtained in nearly quantitative yield by passing chlorine gas through a cooled mixture of 2, 6, 8-purinetrithiol (47) suspended in a reaction medium consisting of methanol and concentrated hydrochloric acid saturated with gaseous hydrogen chloride. This procedure is far superior to those methods previously used, which involved chlorination of uric acid with phosphorus oxychloride, either in a sealed tube (21, 28) or in the presence of N, N-dimethylaniline (15), and at best achieved yields of only 16-25 percent. The success of Robins' method suggested a possible solution to the chlorination problems discussed above, and work was soon undertaken to synthesize the thio analog of XII.

This synthesis was achieved by the use of thiophosgene in a procedure analogous to that employed in the preparation of XII. The resultant product (XXVI) was very difficult to obtain in a purified condition, the purest material being obtained by triple sublimations at approximately 210 °C. and 0.03 mm. pressure.

XXVI is a pale yellow solid which melts with
decomposition at 280-290 °C. It is even less soluble in water than its oxo analog; its maximum solubility is approximately 300 mg/l. in boiling water and 6-7 mg/l. at room temperature. It possesses a slightly higher solubility in ethanol and, like XII, is quite soluble in N, N-dimethylformamide and dimethylsulfoxide. It may be reprecipitated by the addition of water to its solutions in the latter two solvents, but this procedure will not successfully purify the crude material. Like its oxygen analog, XXVI is labile in alkaline solutions. It does not, however, form a hydrate on crystallization from water.

Based upon our previous findings, and those of Montgomery and Temple (45), with regard to the cyclization reactions of 5-amino-4-chloro-6-hydrazinopyrimidine (IX), it is probably safe to assume that cyclization occurred at the inside nitrogen atom of the hydrazino group. XXVI is therefore assigned the
the structure 9-amino-6-chloropurine-8-thiol.

The C=S frequency in thioamides, thioureas and related compounds is extremely variable and may fall anywhere in the range 1400-1150 cm$^{-1}$ (4, p. 356; 29; 37). It is thus impossible to assign this vibration to a specific band in the infrared spectrum of XXVI (see Figure 17). It is interesting to note, however, the striking similarity of the hydrogen stretching regions in the spectra of XII and XXVI. This gives further support to the hypothesis that both compounds contain the same ring system.

In comparing the ultraviolet spectra of the two analogs (see Table II), one can also see a similarity with regard to the number of absorption maxima and their relative intensities. A pronounced bathochromic shift of 20 to 30 millimicrons is evident for all three peaks, an effect predicted by Pullman (49) for thio group substitutions in purines.

Several attempts to chlorinate XXVI by the method used so successfully by Robins (53) proved fruitless. The formation of large quantities of ammonium chloride indicates that oxidative degradation of the purine nucleus occurred. A further indication of this phenomenon is the absence of any absorption maxima in ultraviolet spectra of solutions of the reaction mixture. This effect is not unknown. Biltz (6) has reported that alloxan may be
Figure 17. Infrared spectrum of 9-amino-6-chloropurine-8-thiol (XXVI).
prepared by oxidation of uric acid with chlorine. In addition, Fischer records oxidation of 2,6-dihydroxypurine-8-thiol (23, p. 494) and xanthine with chlorine water, the latter degradation producing alloxan and urea (22, p. 2236 and 20, p. 310-11). Robins (53) also reports oxidative degradation when this chlorination procedure is used on 8-hydroxy-2,6-purinedithiol. It would appear, however, that alloxan was not a product of the degradation of XXVI; the residual material from the reaction mixture gave negative tests for alloxan when tested by both the violuric acid test (32, p. 1798) and the murexide test (31).

In the course of the work described thus far, the syntheses and reactions of a number of 4,5,6-trisubstituted pyrimidines were investigated. A summary of certain of these reactions is presented in Figure 18, and the more interesting aspects of a few of them will now be discussed.

As has been previously noted, the presence of a strongly electron attracting nitro group at the 5-position imparts very high reactivity with respect to nucleophilic substitution of potential anions at positions 4 and 6. This effect is readily understandable when one considers that in 5-nitro-4,6-dichloropyrimidine (VI), the electronic effect of the nitro group is reinforced by a like effect due to the ring nitrogens so that a situation similar to that
Figure 18. Some reactions of 4, 5, 6-trisubstituted pyrimidines.
found in picryl chloride is obtained. The extremely low electron
density on the carbon atoms bonded to the chlorine atoms facilitates
an SN$_2$ displacement of these substituents. It is for this reason that
the substitution of hydrazine for the methoxyl groups in 4-chloro-6-
methoxy-5-nitropyrimidine (XXVII) and 4, 6-dimethoxy-5-nitro-
pyrimidine (XXVIII) can not be considered unusual. The methoxyl
groups of these compounds should resemble closely in chemical
behavior the alkoxy group of a simple ester. Thus, the formation
of 4, 6-dihydrazino-5-nitropyrimidine (VII) by nucleophilic substitu-
tion of hydrazine can, in a sense, be considered as the formation of
a hydrazide from an ester. Synthesis of VII from the dimethoxy-nitropyrimidine provides the best yields (over 95 percent) of the three routes investigated, the two major reasons for this being (a) the decreased tendency for reaction at both reactive sites of the hydrazine molecule, with formation of a polymeric material, and (b) the ease with which the product can be isolated and purified (the only by-product formed is methanol).

The marked deactivation of the 4 and 6 positions upon reduction of the 5-nitro group to the corresponding amine has been mentioned earlier. The electron releasing effect of the amine is such that 5-amino-4, 6-dichloropyrimidine (VIII) is inert to all but the most powerful nucleophiles and the aminodimethoxy compound (XXIX) will not react with even so strong a nucleophile as ethanolic hydrazine. In the aminochlorohydrazinopyrimidines IX and XXI, the presence of the hydrazino substituent provides additional electron release and reinforces the deactivating effect of the amino group. The 4-chloro substituent in IX is so inert that this compound underwent no reaction even with sodium methoxide. (In this last instance, it was necessary to conduct the experiment in an atmosphere of carefully scrubbed nitrogen; even traces of oxygen will cause considerable oxidation of the hydrazino moiety under these highly basic conditions.)
Hydrazines carrying electron attracting substituents, which decrease the nucleophilicity of the hydrazino group, (e.g., formylhydrazine and phenylhydrazine) undergo no reaction with VIII. Maggiolo and Phillips (40) have reported that amines of low basic strength can often be made to react with halogenated pyrimidines in the presence of a mineral acid. This acid catalysis is explained by Banks (3) as involving the protonation of a hetero-nitrogen atom, thus increasing its electron withdrawing power (see Figure 19). However, even in the presence of a mineral acid no reaction of VIII with phenylhydrazine was observed.

The reaction of VIII with 1,1-dimethylhydrazine was found to yield 5-amino-4-chloro-6-(1-methylhydrazino)-pyrimidine (XXI) instead of the expected product, 5-amino-4-chloro-6-(2,2-dimethylhydrazino)-pyrimidine (XXX). The identity of this

\[
\begin{align*}
\text{XXI} & : \quad \begin{array}{c}
\text{Cl} \\
\begin{array}{c}
\text{N} \\
\hline
\text{NH}_2 \\
\text{N} \\
\hline
\text{NH}_2 \\
\text{CH}_3 \\
\end{array}
\end{array} \\
\text{XXX} & : \quad \begin{array}{c}
\text{Cl} \\
\begin{array}{c}
\text{N} \\
\hline
\text{NH}_2 \\
\text{N} \\
\hline
\text{N} \\
\text{H} \\
\text{CH}_3 \\
\end{array}
\end{array}
\end{align*}
\]
Figure 19. Banks' proposed mechanism (3) for acid catalysis of nucleophilic substitution in nitrogen heterocycles.
product was established by elemental analysis, by a positive reaction with sodium pentacyanoaminoferroate, and by a comparison of the infrared spectrum of this material with that of XXI which had been prepared from methylhydrazine. It is known that with low molecular weight alkyl hydrazines, further alkylation leads to azinium salts, $\text{NH}_2\text{NR}_3\text{X}$, as end products (13, p. 30; 64, p. 759; 65), and this is probably the process by which the demethylation proceeded (see Figure 20).

One other reaction which deserves some discussion is the reaction of 4, 6-dimethoxy-5-nitropyrimidine (XXVIII) with methylhydrazine. By analogy to its reaction with hydrazine, one would expect XXVIII to yield 4, 6-di-(1-methylhydrazino)-5-nitropyrimidine (XXXI) in good yield. Instead, after two hours

![XXXI](image)

refluxing with methylhydrazine in ethanol, there was isolated from the reaction mixture a large amount of starting material and a few milligrams of an unknown crystalline product (XXXII) which melted
Figure 20. Proposed mechanism for the formation of 5-amino-4-chloro-6-(1-methylhydrazino)-pyrimidine (XXI) by the reaction of 1,1-di-<br>dimethylhydrazine with 5-amino-4,6-dichloropyrimidine (VIII).
with decomposition at 240-260 °C. This reaction was repeated using n-butanol as a solvent in order to obtain a higher reflux temperature. Under these conditions the yield of XXXII was increased considerably.

Carbon-hydrogen analysis of XXXII indicates an empirical formula corresponding to the removal of a molecule of water from the expected product XXXI. The only structure which can reasonably be written to fit this analytical data is the following:

![XXXII](image)

The reaction presumably involves a slow initial formation of XXXI, followed by a rapid dehydrative cyclization involving the nitro group and the terminal nitrogen atom of the hydrazino substituent.

Ring closure between an -NH$_2$ and an ortho nitro group has been long known. In 1913 Arndt (1) reported the base catalyzed cyclization of o-nitrophenylguanidine (XXXIII) to form 3-amino-1, 2, 4-benzotriazine 1-oxide (XXXIV). Similar cyclizations were shown to occur with o-nitrophenylurea and o-nitrophenylthiourea (2).
Since then a number of workers have extended this reaction to the synthesis of a variety of 1, 2, 4-benzotriazines (36, 10), although attempts to prepare pyrimido-as-triazines by this method have been reported to be unsuccessful (9). Nietzki (46) observed in 1894 the formation of a hydroxybenzotriazole (XXXVI) by the action of dilute alkali on o-nitrophénylhydrazine. In this instance there occurs simultaneously with the dehydration an intramolecular oxidation-reduction so that a cyclic hydroxylamine is the product rather than an azoxy compound. The presence of the methyl group would, of course, prevent this
oxidation-reduction in XXXII.

Admittedly, analytical data alone is not a sufficient basis for unequivocally assigning the triazolopyrimidine 1-oxide structure to XXXII. However, in view of the established occurrence of the similar reactions cited above, this structure appears to be a valid tentative assignment. To our knowledge, this is the first example reported of a triazolopyrimidine 1-oxide. It is possible that further investigation of this reaction might yield a useful new synthetic route to this ring system.
Table II. Ultraviolet Spectral Data for Condensed Ring Compounds.

<table>
<thead>
<tr>
<th>Ring System</th>
<th>X</th>
<th>Y</th>
<th>pH</th>
<th>$\lambda_{\text{max}}$ (m$\mu$)</th>
<th>$\epsilon \times 10^{-3}$</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>O H</td>
<td>4.5</td>
<td></td>
<td></td>
<td>277, 241</td>
<td>13.7, 4.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td></td>
<td></td>
<td>279, 243</td>
<td>13.3, 3.8</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>11.0</td>
<td></td>
<td></td>
<td>289</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>O NH$_2$</td>
<td>4.5</td>
<td>ethanol</td>
<td></td>
<td>320, 274, 210</td>
<td>6.1, 10.9, 2.7</td>
<td></td>
</tr>
<tr>
<td>S NH$_2$</td>
<td>4.5</td>
<td>ethanol</td>
<td></td>
<td>340, 291, 243</td>
<td>&gt;7.4 &gt;10.5 &gt;6.7*</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>4.5</td>
<td></td>
<td></td>
<td>305,** 275, 242</td>
<td>4.0, 8.3</td>
<td>31.6</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>4.5</td>
<td></td>
<td></td>
<td>322, 218</td>
<td>5.5,</td>
<td>19.1</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td></td>
<td></td>
<td>260, 217</td>
<td>14.5, 27.2</td>
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* A portion of the sample remained undissolved.
**A very slight shoulder.
Table III. Ultraviolet Data for Some 4, 5, 6-Trisubstituted Pyrimidines.

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>pH</th>
<th>( \lambda_{\text{max}} ) (m(\mu))</th>
<th>( \varepsilon \times 10^{-3} )</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Cl</td>
<td>NH(_2)</td>
<td>NH(_2)</td>
<td>4.5</td>
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<td>7.5, 6.2</td>
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<tr>
<td>Cl</td>
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<td>NHNH(_2)</td>
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<td>8.9, 7.5</td>
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<td>N(CH(_3))NH(_2)</td>
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<td>N(CH(_3))NH(_2)</td>
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<td>5.3, 5.7</td>
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<tr>
<td>Cl</td>
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<td>303, 272</td>
<td>9.7, 7.0</td>
<td>17</td>
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<tr>
<td>Cl</td>
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<td>304, 273.5</td>
<td>9.1, 7.1</td>
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<td>NH(_2)</td>
<td>OCH(_3)</td>
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<td>268, 215</td>
<td>&gt;2.3, &gt;10.3 *</td>
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<td>NH(_2)NH(_2)</td>
<td>NO(_2)</td>
<td>NH(_2)NH(_2)</td>
<td>4.5</td>
<td>266</td>
<td>11.5</td>
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</tbody>
</table>

* A portion of the sample remained undissolved.
EXPERIMENTAL

All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus. The infrared spectra were taken with a Perkin-Elmer model 21 infrared spectrophotometer using a sodium chloride prism, with samples in the form of nujol mulls. (The two strong absorptions at approximately 2920 and 2860 cm$^{-1}$ and the weaker ones at about 1460 and 1375 cm$^{-1}$ are produced by nujol.) The ultraviolet absorption spectra were determined with a Beckman model DB spectrophotometer.

5-Amino-4-chloro-6-hydrazinopyrimidine (IX)

To 25.6 g. (0.8 mole) of anhydrous hydrazine in 60 ml. of absolute ethanol was added dropwise with stirring 50 g. (0.3 mole) of 5-amino-4,6-dichloropyrimidine (55) dissolved in 900 ml. of absolute ethanol. The mixture was refluxed for 5 hours. Upon cooling, large, spar-like crystals formed. Recrystallization from 875 ml. of water yielded 43.1 g. (88.7%) of product, m.p. (dec.) 183.5-185.5 °C. (Montgomery and Temple (45) report m.p. 184 °C.)
9-Amino-6-chloropurin-8-ol (XII)

The apparatus employed for the phosgene cyclization reactions consisted of a three-necked flask fitted with a magnetic stirrer and gas inlet and outlet tubes. A series of trap bottles containing 20 percent sodium hydroxide solution was connected to the outlet tube in order to absorb excess phosgene. When used with a good hood, this arrangement permitted the reactions to be carried out conveniently and without danger.

5-Amino-4-chloro-6-hydrazinopyrimidine (12.8 g., 0.08 mole) was dissolved in 200 ml. of water containing 8 ml. of concentrated hydrochloric acid. Phosgene gas was then introduced into this solution with stirring for 50 minutes; a light tan solid material precipitated. After flushing the unreacted phosgene out of the system, the precipitate was filtered, washed well with water, and dried; yield 10.1 g.

This crude material was most easily purified by two recrystallizations from approximately 10 percent hot N, N-dimethylformamide. However, the purest samples were obtained by sublimation (210 °C., 0.02 mm.), the sublimate being a white crystalline material, decomposing at 285-295 °C. Sublimation must be performed by use of a long sublimation tube because the brown residual material is
extremely light and fluffy and tends to fly upwards onto the sublimate.

Anal. Calc'd for C₅H₄ClN₅O: C, 32.4; H, 2.17; N, 37.8; Cl, 19.1.

   Found: C, 32.4; H, 2.20; N, 39.7; Cl, 19.2.

XII crystallized from aqueous solutions buffered at pH 5 and pH 7 in the form of a monohydrate (XV). The monohydrate was also obtained by acidification of a basic solution of XII.

Anal. Calc'd for C₅H₄ClN₅O·H₂O: C, 29.5; H, 2.97.

   Found: C, 29.6; H, 3.04.

Dehydration of XV to give the original anhydrous material was accomplished by both (a) sublimation and (b) azeotropic distillation using toluene. A comparison of the infrared spectra demonstrated that the products obtained by these procedures were both identical to the original anhydrous compound, XII.

Phosphoryl 7-(9-amino-6-chloro-7,8-dihydro-8-oxopurinamide) dichloride hydrochloride (XVI)

One g. (0.0054 mole) of 9-amino-6-chloropurin-8-ol (XII) was suspended in 22 ml. of redistilled phosphorus oxychloride, and the mixture was placed in a flask equipped with a reflux condenser. No observable reaction or solution occurred at boiling temperature until a few ml. of N,N-diethylaniline was introduced, whereupon XII dissolved with formation of a dark solution. As soon as the suspended
material was completely dissolved, the solution was allowed to cool, whereupon XVI, a yellow microcrystalline solid, precipitated. XVI was removed by filtration, washed well with ether, and dried in vacuo over phosphorus pentoxide and flaked sodium hydroxide; yield 1.28 g. (70%).

Anal. Calc'd for C$_5$H$_4$Cl$_4$N$_5$O$_2$P: C, 17.7; H, 1.19; N, 20.7; P, 9.15. Found: C, 18.2; H, 1.32; N, 21.5; P, 8.69.

Neutralization equivalent. Calc'd (based on formation of three equivalents of strong acid): 113.0. Found: 113.7.

5-Chloro-1, 2, 3, 4-tetrahydro-3-oxopyrimido[5,4-e]-1,2,3-triazine (XIII)

A. Two g. (0.0108 mole) of 9-amino-6-chloropurin-8-ol was suspended in 90 ml. of an approximately 0.33M solution of anhydrous hydrogen chloride in absolute ethanol. The mixture was refluxed on a steam bath for one hour, during which time the suspended material turned to a bright yellow color. After filtration from the cooled solution and drying, the crude product weighed 1.4 g. This material was then dissolved in 50-60 ml. of hot N,N-dimethylformamide, and the hot solution was filtered to remove a small amount of insoluble material. Upon addition of an equal volume of water to the cooled solution, XIII precipitated as an almost white solid, dry weight 1.1 g.
(55%), m.p. (dec.) >320 °C.

A 150 mg. portion of the crude product was purified for analysis by sublimation at 210 °C. and 0.03 mm. pressure; yield 91 mg.

Anal. Calc'd for C₅H₄ClN₅O: C, 32.4; H, 2.17.

Found: C, 32.2; H, 2.22.

B. XVI (385 mg., 0.00113 mole) was refluxed in 10 ml. of absolute ethanol for 1.5 hours on a steam bath. The tan material darkened slowly on heating and slowly dissolved with formation of a dark solution. At the completion of the reflux period the reaction mixture was placed in a deep-freeze overnight. From the cold liquid mixture a brown solid (106 mg.) was collected. Addition of ether to the ethanolic filtrate precipitated an additional 30 mg. of material. The combined crops were sublimed twice to yield 43.4 mg. (21%) of XIII as a white, crystalline solid. Both ultraviolet and infrared absorption spectra demonstrated that the material obtained in this manner was identical to that obtained by method A.

Anal. Calc'd for C₅H₄ClN₅O: C, 32.4; H, 2.17.

Found: C, 32.1; H, 2.42.
5-Amino-4-chloro-6-(1-methylhydrazino)-pyrimidine (XXI)

A. Into 140 ml. of an absolute ethanolic solution containing 8 g. (0.049 mole) of 5-amino-4,6-dichloropyrimidine was pipetted, with stirring, 6.4 ml. (0.13 mole) of methylhydrazine. After refluxing for two hours, the pale yellow solution was cooled, whereupon needle-like crystals appeared. These were filtered, washed with a little ethanol, and recrystallized from approximately 500 ml. of boiling water. After 2 to 3 hours of refrigeration, 7.5 g. (89%) of well-formed, white needles was collected and air-dried; m.p. 206-208 °C. (Montgomery and Temple (45) report m.p. 203-204 °C.)

B. One g. (0.0061 mole) of 5-amino-4,6-dichloropyrimidine was dissolved in 18 ml. of absolute ethanol contained in a flask fitted with a reflux condenser and magnetic stirrer. A solution of 1.2 ml. of 1,1-dimethylhydrazine in an equal volume, of absolute ethanol was added, with stirring, to the refluxing solution. The mixture was maintained at reflux for five hours, during which time it changed from a yellow to a red color. Upon cooling, crystallization occurred. Recrystallization of the product from water yielded 400 mg. (38%) of 5-amino-4-chloro-6-(1-methylhydrazino)-pyrimidine. The infrared spectra of the samples prepared by methods A and B were identical.
5-Chloro-1, 2, 3, 4-tetrahydro-1-methyl-3-oxopyrimido[5, 4-e]-as-
triazine (XXII)

To a solution of 1.2 ml. of concentrated hydrochloric acid in 4.5
ml. of water was added 2 g. (0.011 mole) of 5-amino-4-chloro-6-
(1-methylhydrazino)-pyrimidine. Phosgene gas was then bubbled
through the solution; a heavy white precipitate soon began to form.
After approximately 25 minutes the unreacted phosgene was flushed
out of the system with nitrogen gas, and the precipitate was collected,
washed well with water, and dried. The dry material (1.1 g.) was
recrystallized from 50 ml. of hot N,N-dimethylformamide. The
yield of the light gray material, which appears to be a very fluffy
mat of tiny needles, was 0.9 g. (39.4%). A sample was purified for
analysis by the sublimation technique described for XII, yielding a
white sublimate. On the melting point block, darkening commenced
at about 295 °C. and slowly progressed until the temperature
reached 320 °C.
Anal. Calc'd for C_{6}H_{6}ClN_{5}O: C, 36.1; H, 3.03; N, 35.1.
    Found:       C, 36.1; H, 3.18; N, 35.2.

6-Chloropurin-8-ol (XXV)

4, 5-Diamino-6-chloropyrimidine (4.0 g., 0.028 mole),
prepared by the method of Robins et al. (54), was added to 240 ml.
of 6 percent sodium hydroxide solution contained in a 500 ml. three-
necked flask fitted with inlet and outlet tubes for delivery of phosgene
gas, a magnetic stirrer, and a pressure-equalizing separatory funnel. Phosgene was then bubbled through the mixture. After about two hours, an additional 100 ml. of 6 percent sodium hydroxide solution was added through the separatory funnel. At the end of another hour, the flow of phosgene was interrupted and the pale yellow precipitate which had formed during the reaction was separated by filtration from the acidic filtrate. After refrigeration a small second crop of crystals was obtained from the filtrate. The combined crops, weighing 2.8 g., were triturated with approximately 30 ml. of dilute sodium hydroxide solution, and the insoluble starting material was removed by filtration. Acidification of the filtrate reprecipitated the 6-chloropurin-8-ol. This procedure was repeated again to insure that all of the starting material was removed from the product. The yield of XXV was 1.5 g. (31.8%), m.p. 322 °C. (with dec.). A small portion of XXV was sublimed for analysis. The total recovery of starting material (from purification of the crude product and neutralization of the acidic filtrate from the reaction mixture) was 1.7 g. (42.5%).

Anal. Calc'd for C₅H₃ClN₄O: C, 35.2; H, 1.77.

Found: C, 35.0; H, 1.80.
9-Amino-6-chloropurine-8-thiol (XXVI)

5-Amino-4-chloro-6-hydrazinopyrimidine (4 g., 0.025 mole) was partially dissolved in 60 ml. of water containing 2.2 ml. of concentrated hydrochloric acid. To this mixture 4 ml. (0.0525 mole) of thiophosgene was added dropwise, with stirring, over a period of 35-40 minutes. After an additional 10 minutes of stirring, the brown precipitate which formed was collected, washed well with ether to remove unreacted thiophosgene, and dried. Sublimation of the crude product at 210 °C. and 0.03 mm. pressure was a very slow process, requiring two days. A very light and fluffy residue, which tended to fly up onto the sublimate, probably as a result of de-gassing, necessitated the use of a 3-foot sublimation tube. Increasing the vacuum very gradually helped to reduce the de-gassing problem. The yield of sublimed product was 1.12 g. (22.2%). 9-Amino-6-chloropurine-8-thiol is a pale yellow, crystalline material, m.p. (dec.) 280-290 °C.

Anal. Calc'd for C₅H₄ClN₅S: C, 29.8; H, 2.00.

Found: C, 29.7; H, 2.14.

4,6-Dihydrazino-5-nitropyrimidine (VII)

A. 4,6-Dimethoxy-5-nitropyrimidine (XXVIII) was prepared by the method of Rose and Brown (57). A warm solution of 2 g. (0.011 mole) of XXVIII in approximately 130 ml. of absolute ethanol
was added portionwise to approximately 5 ml. of an ethanolic solution containing 1.4 g. (0.044 mole) of anhydrous hydrazine; a bright yellow solid immediately precipitated. The mixture was stirred for one hour under gentle reflux, cooled, and filtered to yield 1.94 g. (97%) of VII, m.p. (dec.) 202-203.5 °C.

Anal. Calc'd for C₄H₇N₃O₂: C, 26.0; H, 3.81; N, 53.0.

Found: C, 25.7; H, 3.87; N, 54.5.

This material exploded violently in the combustion tube during carbon-hydrogen analyses. In order to obtain valid analytical results it was necessary to mix the sample with an inert diluent (ignited Celite was used) and to use an oversized combustion boat.

B. A solution of 2 g. (0.0106 mole) of 4-chloro-6-methoxy-5-nitropyrimidine (60) in 60 ml. of absolute ethanol was added dropwise, with stirring, to 5 ml. of an ethanolic solution containing 1.36 g. (0.042 mole) of anhydrous hydrazine; a heavy, orange precipitate formed immediately. After refluxing for one hour, the mixture was cooled and the precipitate collected. Recrystallization from approximately 200 parts of water yielded 1.48 g. (76%) of yellow-orange, needle-like crystals. The product was shown by infrared spectral analysis to be identical to that obtained by procedure A.

C. One g. (0.0052 mole) of 4,6-dichloro-5-nitropyrimidine (VI),
prepared by the method of Boon et al. (7), was dissolved in 65 ml. of absolute ethanol. This solution was then added dropwise, with stirring, to a solution of 0.72 g. (0.022 mole) of hydrazine in 1 ml. of ethanol. After refluxing for one hour the mixture was cooled, and the orange solid which formed was collected by filtration. This solid was suspended in approximately 150 parts of boiling water, and the brown, insoluble portion was removed by filtration from the hot solution. The clear filtrate was found to have a pH of 4.1. The solution was brought to pH 6 by the addition of 0.02N sodium hydroxide solution, whereupon the formation of tiny, needle-like crystals was observed. At this point the solution was again brought to an incipient boil, and a small amount of undissolved material was removed by filtration. Upon cooling, the filtrate yielded 0.31 g. (32.5%) of long, red, needle-like crystals of 4,6-dihydrazino-5-nitropyrimidine. The identity of the compound was confirmed by elemental analysis and by its infrared spectrum.

The brown, insoluble material obtained above was very intractable. Carbon-hydrogen analysis showed it to contain 29.9% C and 2.77% H. The infrared spectrum exhibited only very diffuse peaks. This material is probably polymeric in nature.
5-Amino-4, 6-dimethoxypyrimidine (XXIX)

Three g. (0.016 mole) of 4, 6-dimethoxypyrimidine (57) was dissolved in approximately 180 ml. of hot absolute ethanol, and to this solution was added approximately 2 g. (wet weight) of Raney nickel catalyst. The mixture was then shaken under an initial pressure of 20 p.s.i. of hydrogen for two hours. During this period the mixture was kept warm by directing the rays from an infrared lamp on the reaction bottle. At the conclusion of the shaking period a theoretical quantity of hydrogen had been absorbed. The hydrogenation mixture was heated to an incipient boil and the catalyst removed by filtration from the hot solution. Evaporation of the clear, colorless filtrate with the aid of a hot air fan yielded 2.4 g. of crude material. This was recrystallized from 25 ml. of heptane to yield 1.9 g. (76%) of thick, off-white, needle-like crystals, m.p. 95-96 °C. (accompanied by sublimation). The product has a pronounced odor resembling that of licorice. A small amount of the material was sublimed for analysis.

Anal: Calc'd for \( \text{C}_6\text{H}_9\text{N}_3\text{O}_2 \): C, 46.4; H, 5.85; N, 27.1.

Found: C, 46.6; H, 6.03; N, 27.0.
Product of the reaction of methylhydrazine with 4, 6-dimethoxy-5-
nitropyrimidine (3-methyl-7-(1-methylhydrazino)-3H-v-tri-
azolo[4, 5-d]pyrimidine 1-oxide) (XXXII)

A hot solution of 4, 6-dimethoxy-5-nitropyrimidine (1 g.,
0.0054 mole) in 65 ml. of n-butanol was added, with stirring, to a
solution of 1.1 ml. (0.021 mole) of methylhydrazine in 5 ml. of
n-butanol. The mixture was then refluxed with stirring for three
hours, during which time it turned to a bright yellow color.
Toward the end of the reflux period a fine, solid material began to
precipitate. After a night in the deep-freeze, crude XXXII (150 mg.)
was removed by filtration from the cold reaction mixture and re-
 crystallized from water. The product consists of very tiny, yellow-
tan, needle-like crystals, m.p. 240-260 °C. (with dec.).
Found: C, 37.0; H, 4.95.
BIBLIOGRAPHY


32. The absorption spectra of uric acid, murexide, and the ureides in relation to colour and to their chemical structure. Journal of the Chemical Society 87:1796-1822. 1905.


