

AN ABSTRACT OF THE THESIS OF

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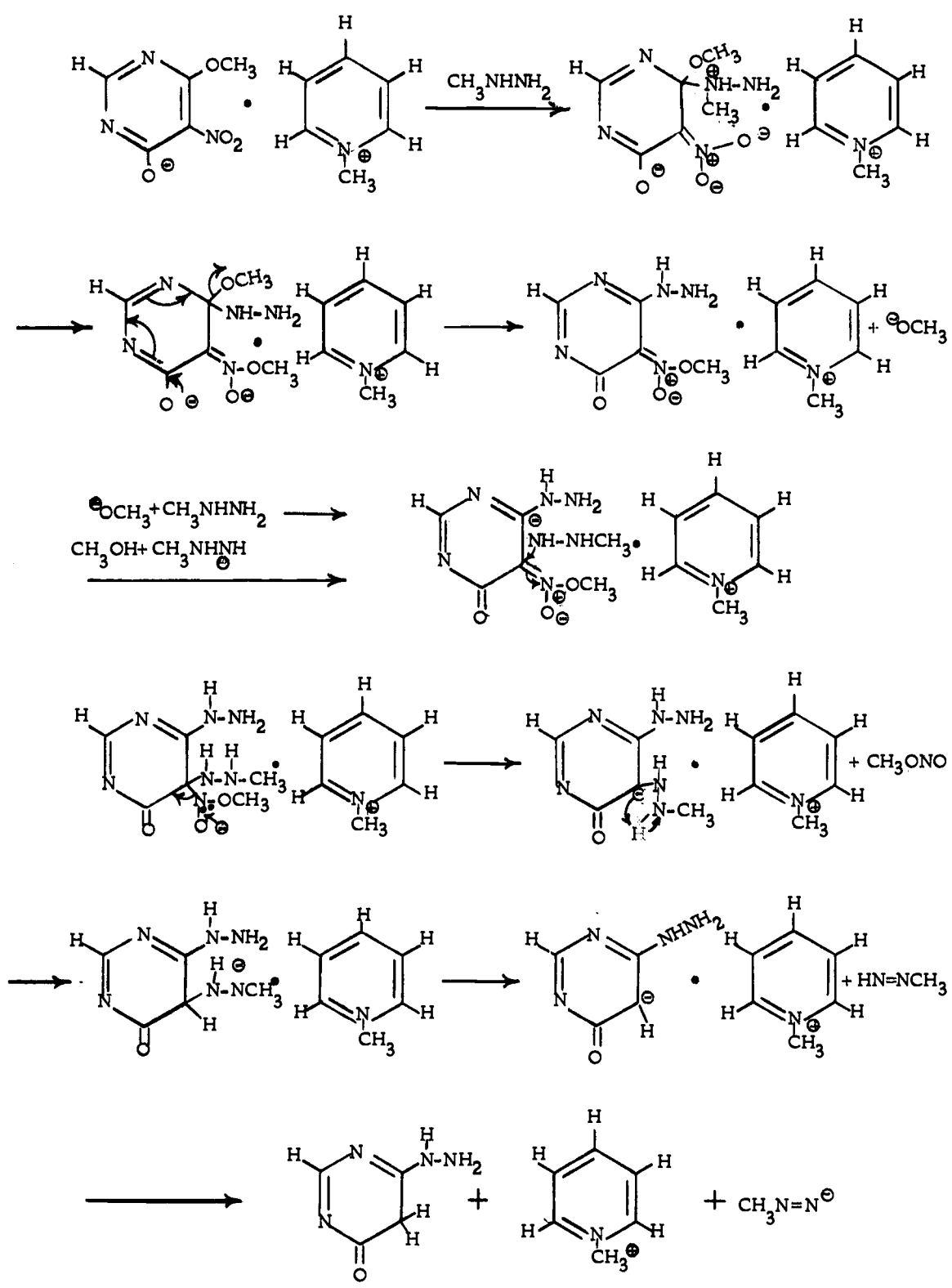
Title: A STUDY OF THE ANOMALOUS REACTION OF 4, 6-  
DIMETHOXY-5-NITROPYRIMIDINE WITH METHYL-  
HYDRAZINE

Abstract approved: \_\_\_\_\_

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Bert E. Christensen

The anomalous reaction of 4, 6-dimethoxy-5-nitropyrimidine with methylhydrazine in a pyridine solvent to yield 4-hydrazino-6-hydroxypyrimidine was investigated. When 4, 6-dimethoxy-5-nitropyrimidine was refluxed in pyridine in the absence of methylhydrazine two non-interconvertible salts were formed. The salt insoluble in cold pyridine had been previously identified as the methylpyridinium salt of 1, 6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine. The soluble salt which reacts with methylhydrazine to yield 4-hydrazino-6-hydroxypyrimidine has been identified as the methylpyridinium salt of 4-hydroxy-6-methoxy-5-nitropyrimidine. This salt reacts with the methylhydrazine as follows:



The tautomeric form resulting from the reaction pathway explains why the 5-proton does not appear in the nmr spectra of the compound when using either (a) sodium deuterioxide in deuterium oxide or (b) deuterium chloride in deuterium oxide solvents.

The following supporting evidence is provided for the mechanism:

- 1) Isolation and characterization of the methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine.
- 2) Synthesis of the methylpyridinium salt of 4-hydroxy-6-methoxy-5-nitropyrimidine and the recovery of 4-hydroxy-6-methoxy-5-nitropyrimidine by acid hydrolysis.
- 3) Detection of by-products methyl nitrite and methanol in the reaction mixture.
- 4) The behavior of 4-hydroxy-6-methoxy-5-nitropyrimidine in the presence of methylhydrazine which yields 4-hydrazino-6-hydroxypyrimidine in pyridine, benzene, and alcohol solvents.
- 5) The failure of 4-chloro-6-hydroxy-5-nitropyrimidine to behave in the same manner as 4-hydroxy-6-methoxy-5-nitropyrimidine in the presence of methylhydrazine and ethanol.
- 6) The work of Kauffman which predicts the presence of hydrazine ions in basic solutions of hydrazine which are essential for this mechanism to proceed.

Also reported is the reaction of 4,6-dimethoxy-5-nitropyrimidine in pyridine with hydrazine to yield 6-hydrazino-7-hydroxy-8-azapurine monohydrate. When 4,6-dihydrazino-5-nitropyrimidine in pyridine was treated with two equivalents of hydrazine, 6-hydrazino-7-hydroxy-8-azapurine monohydrate was again isolated.

A Study of the Anomalous Reaction of 4, 6-  
Dimethoxy-5-Nitropyrimidine with Methylhydrazine

by

Frank Arvid Lehmkuhl

A THESIS

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Professor of Chemistry  
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Date thesis is presented

Sept. 14, 1970

Typed by Mary Jo Stratton for Frank Arvid Lehmkuhl

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My wife, Kathy, is also to be thanked for her long hours of typing and for her understanding and encouragement.

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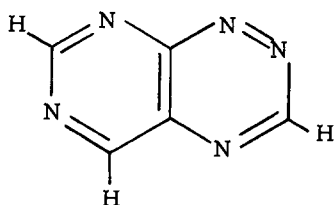
A STUDY OF THE ANOMALOUS REACTION OF  
4,6-DIMETHOXY-5-NITROPYRIMIDINE  
WITH METHYLHYDRAZINE

INTRODUCTION

Hitchings, Elion, and coworkers in 1942, began a study correlating the chemical structure of certain analogs of pyrimidine and purine bases with their ability to serve as precursors for or to modify nucleic acid synthesis. The consequences of these studies published in 1950 led Hitchings (20) to conclude that certain pyrimidines in fact do interfere with the nucleic acid synthesis and metabolism.

This initial study stimulated much interest in the synthesis of the analogs of naturally occurring nucleic acids and their component parts. One group of compounds of particular interest were the "aza" homologs and analogs of the purine and pyrimidine moieties of the nucleic acid molecule due to their possible value as medicinal agents; for example certain 2-aza and 8-aza purines were known to demonstrate anti-tumor activity (31).

Since this laboratory, for several years, had been interested in the synthesis of compounds of biological interest, work was initiated on the synthesis of the pyrimido-[5,4-3]-as-triazine ring system which in actuality is an aza pteridine.



Krackov (25) in seeking possible methods for the synthesis of the parent ring investigated the preparation of a 4-hydrazino-5-nitropyrimidine intermediate. The procedure which he devised was based on the following sequence of reactions using 4,6-dichloro-5-nitropyrimidine as the starting materials: a) hydrazinolysis of the chloropyrimidine, b) reduction of the nitro group, c) formylation of the hydrazino substituent followed by ring closure, and finally d) dehydrogenation to yield the desired product.

Since no other methods for the synthesis of hydrazino-nitropyrimidines had been previously reported in the literature, new procedures had to be devised for their preparation. The obvious starting material was 4,6-dichloro-5-nitropyrimidine, it was readily available, had a good leaving group in the proper position, and was known to be very reactive toward nucleophilic reagents. However, when 4,6-dichloro-5-nitropyrimidine was dissolved in a refluxing solution of ethanolic hydrazine a vigorous reaction occurred which led primarily to brown polymeric material together with an exceedingly small yield of 4,6-dihydrazino-5-nitropyrimidine (see Figure 1).

In view of this behavior it was evident that a less reactive nitropyrimidine would be needed to give a more controllable reaction. For this reason attention shifted to the 4,6-dimethoxy derivative which could be prepared from 4,6-dichloro-5-nitropyrimidine. The

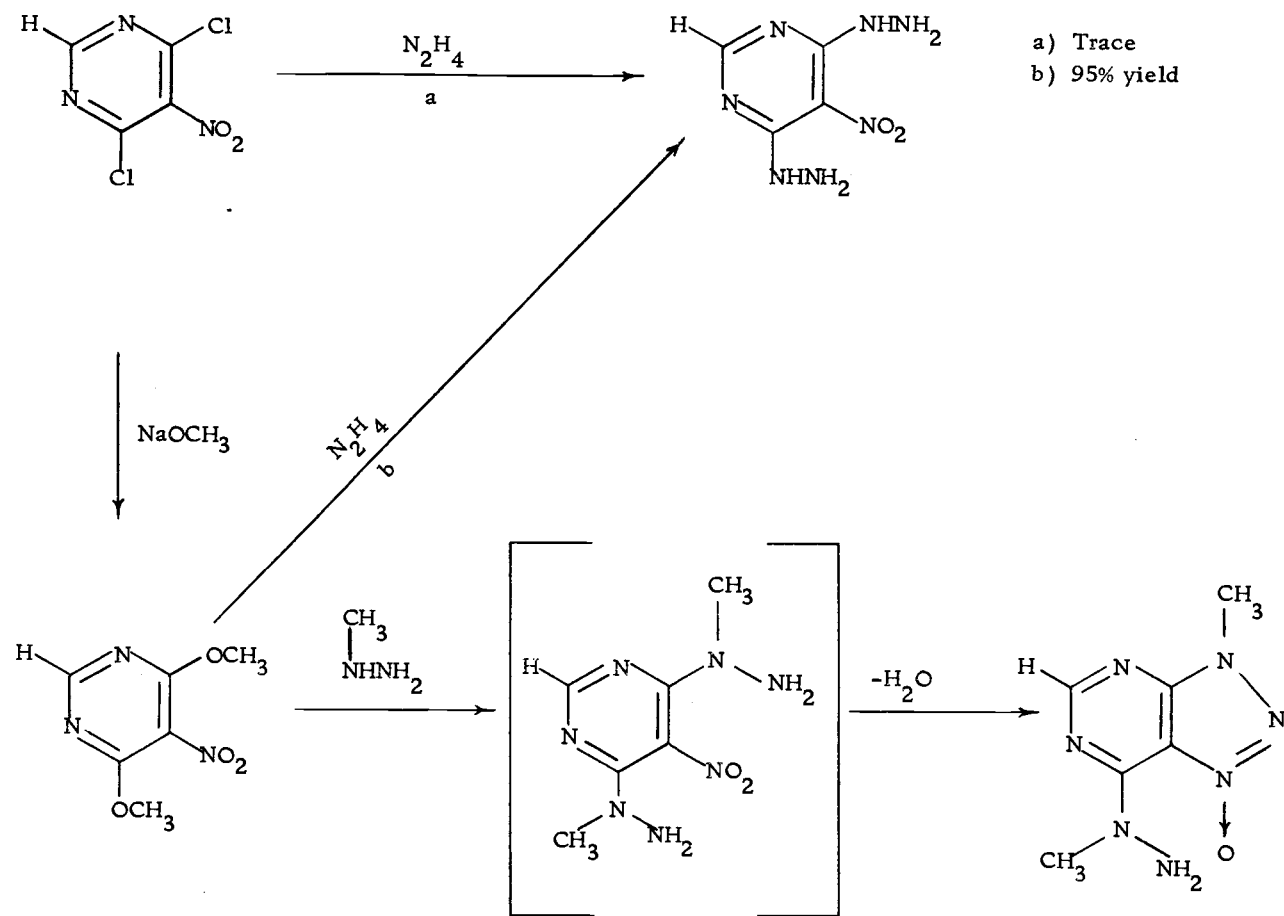
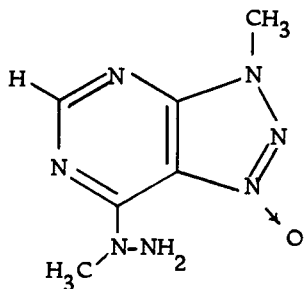


Figure 1. Hydrazinolysis of 5-nitropyrimidines as reported by Krackov.

4, 6-dimethoxy-5-nitropyrimidine was readily converted to the corresponding 4, 6-dihydrazino derivative by refluxing in a solution of ethanolic hydrazine; this led to an analytically pure product in 97% yield.

In an attempt to prepare the corresponding 4, 6-di-(1-methylhydrazino)-5-nitropyrimidine, Krackov reacted 4, 6-dimethoxy-5-nitropyrimidine with methylhydrazine under identical conditions. Unlike the hydrazine reaction the methylhydrazine was unreactive and he recovered most of the starting material together with a trace of an unknown compound. Krackov found that the small yield could be increased considerably by shifting to a butanol solvent thereby increasing the refluxing temperature over that of an ethanolic medium.

The product from the butanol medium recrystallized from water, melted with decomposition between 240-260°C, and gave a carbon-hydrogen analysis which suggested a compound that differed from the expected product, 4, 6-di-(1-methylhydrazino)-5-nitropyrimidine, by loss of a molecule of water. Krackov proposed a tentative structure for the product, 3-methyl-7-(1-methylhydrazino)-3H-v-triazolo-[4, 5, d]pyrimidine-1-oxide



which was later discarded on the basis of a nitrogen analysis. The carbon-hydrogen and nitrogen analyses suggested a compound with an empirical formula of  $C_{10}H_{16}N_{10}O_3$ .

As a probable structure could not be determined for the compound from the available data, Krackov and Christensen (26) came to the conclusion that the reaction was not straightforward and that either a complex product or a mixture of products had resulted from this unusual reaction.

Hydrazinopyrimidines have been successfully prepared from chloro- and methoxypyrimidines in good yields (9). However, in these investigations the pyrimidine derivative did not have a 5-nitro substituent. The relatively easy conversion of 4,6-dimethoxy-5-nitropyrimidine to the corresponding dihydrazino derivative together with the preparation of other hydrazinopyrimidines from corresponding methoxypyrimidines made the behavior of methylhydrazine with 4,6-dimethoxy-5-nitropyrimidine even more puzzling.

In order to gain a better understanding of this reaction, Stahl (33) set out to identify the anomalous product. Using the method of Krackov and Christensen, he prepared more of the compound and confirmed the infrared and ultraviolet data reported earlier by Krackov. His analytical data however indicated that the empirical formula was  $C_{11}H_{17}N_{11}O_3$ , suggesting an impure product, a mixture of simple pyrimidines, or a polymeric product.

The purity of the product was finally established by thin layer chromatography, which gave only one spot, suggesting it was a reasonably pure compound and not a mixture. Since this is not conclusive, further purification was attempted; the product was recrystallized from 95% ethanol-water (1:1) and a second sample was subjected to a sublimation procedure. Both methods of purification gave identical analyses. However, the carbon analysis showed an increase from 37.6-37.8% to 38.0-38.1% while the nitrogen and hydrogen content agreed with that found previously. The empirical formula calculated from the new data was  $C_{19}H_{29}N_{19}O_5$ . As it seemed fairly certain that the product was pure it appeared that the compound was polymeric in nature.

A molecular weight of the product was determined by the spectroscopic method reported by Cunningham *et al.* (11); molecular weights of 127 and 132 were obtained from two separate trials. Cunningham's procedure is based on the amount of absorption at  $3800 \overset{O}{\text{Å}}$  contributed by the picric acid moiety (which does not shift) in salt formation with nitrogenous bases. For these values (127 and 132) to be consistent with the empirical formula required that more than one basic reactive site be present. This led to a molecular formula of  $C_{38}H_{58}N_{38}O_{10}$  which required nine such reactive sites, a highly unlikely possibility.

To confirm the molecular weight determination an attempt was

made to use the 2-nitro-1,3-indandionate procedure (12) which is based on the same principle as the Cunningham method (11). Unfortunately, instead of obtaining the indandionate salt a condensation product formed, thereby changing the usable absorption band and making this procedure inoperative. This behavior suggested a primary amino group on a hydrazino substituent may have caused this unpredicted reaction. This assumption was confirmed by a test with an aqueous solution of sodium pentacyanoammineferroate.

Since the confirmation of the molecular weight failed, the 4,6-dimethoxy-2-methyl-5-nitropyrimidine was treated with methylhydrazine and the molecular weight of this product determined by the Cunningham procedure. Methylhydrazine reacted with 4,6-dimethoxy-2-methyl-5-nitropyrimidine using identical procedure giving a product which appeared to be  $C_{14}H_{23}N_{11}O_3$  as judged by analytical data. This product was chemically and spectrally similar to that obtained with 4,6-dimethoxy-5-nitropyrimidine. A molecular weight determination using the same spectral techniques (11) gave a value of 143 which was approximately 14 units more than that obtained by using the lower homolog of the reactant. The two compounds would be expected to differ by an integral number of  $CH_2$  units but no reasonable formula relating this assumption could be determined. In view of these results and the discrepancy between molecular weight and elemental analytical data, the compounds obtained from 4,6-dimethoxy-5-nitropyrimidine



and the 2-methyl homolog as well as the 2-phenyl analog (which also had been prepared) were subjected to mass spectral analysis. The highest significant mass peak in each of these spectra corresponded to  $R-C_4H_5N_4O^+$  in which R was H,  $CH_3$ , or phenyl. Since there were traces of higher mass peaks, the two lower analogs were rerun using a different mass spectrometer. The highest mass peak in each of these spectra was 126 and 140 respectively, with mere traces of peaks at higher mass numbers. These extraneous peaks were thought to be due to residual material present in the spectrometer. Thus the compounds from both analogs differed by 14 mass units which confirmed the results using the Cunningham method. The molecular formula from mass spectral data were calculated and found for the product from the 4,6-dimethoxy-5-nitropyrimidine reaction to be  $HC_4H_5N_4O$  and the other two were  $CH_3C_4H_5N_4O$  and  $C_6H_5C_4H_5N_4O$ . The molecular weight for the first two compounds agreed closely with the previous molecular weight determinations obtained from ultraviolet spectral data. The molecular formulas also agreed with the carbon-hydrogen data but required a higher nitrogen value than was actually found.

As combustion problems were suspected as the cause of the low nitrogen values (27, 36) the compounds derived from 4,6-dimethoxy-5-nitropyrimidine and the 2-phenyl analog were acetylated. Acetylation as expected gave a derivative which had much better combustion

characteristics and indeed analysis of the compounds gave values confirming  $R-C_4H_5N_4O \cdot 2C_2H_3O$  for diacetylation of  $R-C_4H_5N_4O$ .

Once the certainty of the molecular weights were established and the molecular formula determined, the major obstacle to identification was overcome. The remaining spectral information along with the chemical properties of the compounds led to the elucidation of the structures of the compounds.

From the infrared spectrum (see Figure 2) of the product derived from 4,6-dimethoxy-5-nitropyrimidine it was concluded that the pyrimidine ring was still present, that both the methoxy and the nitro group were absent, that a hydrazino group was most likely present, and that there was a tautomeric hydroxy or amino group attached to the ring.

The ultraviolet spectrum was characteristic of those found among pyrimidine derivatives; moreover the spectrum was pH dependent as is the case with pyrimidines.

The nmr spectrum of the compound taken immediately after it was dissolved in trifluoroacetic acid gave two peaks of equal area at 8.11 $\delta$  and 6.06 $\delta$ . In comparing the spectrum to that of the 2-methyl compound it appeared that the 8.11 $\delta$  peak was due to the proton at the 2-position. Moreover it has generally been observed that the peak due to the hydrogen substituent at the 5-position of most pyrimidines occurs in the 6.0-5.5 $\delta$  region (3, 4). The assignment of this peak to a

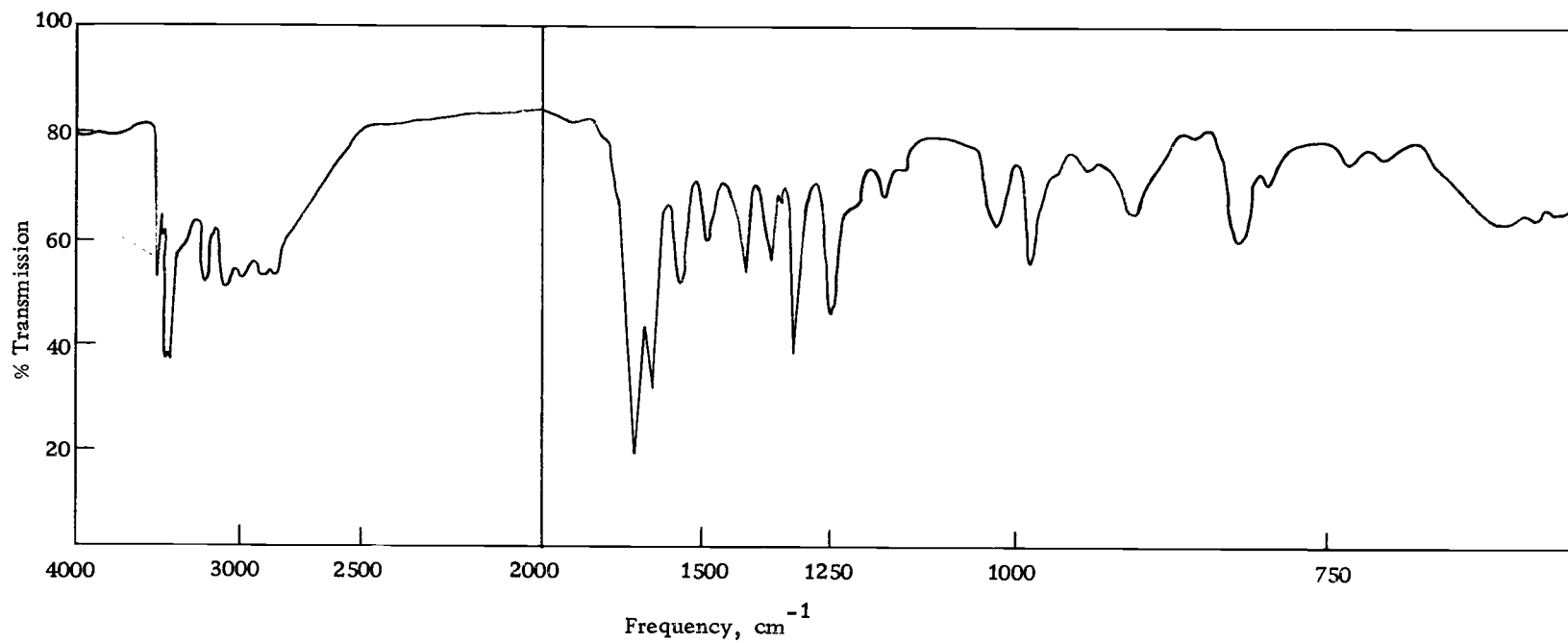


Figure 2. Infrared spectrum of the product from the reaction of 4,6-dimethoxy-5-nitropyrimidine and methylhydrazine; composite of mulls in Kel-F-10 oil (4000-1300  $\text{cm}^{-1}$ ) and nujol oil (1300-625  $\text{cm}^{-1}$ ).

hydrogen substituent in the 5-position was questioned in that the nmr spectrum in both sodium deuterioxide in deuterium oxide or in deuterium chloride in deuterium oxide gave a peak for the 2-proton while the 6.06  $\delta$  peak was absent.

To gain further insight about the type and number of protons in the compound the decision was made to take an nmr spectrum in a non-polar solvent. The 2-phenyl compound proved to be soluble in deuterated dimethyl sulfoxide. The nmr spectrum in this solvent gave peaks at 8.39 (mult.), 7.80 (mult.), 5.66 (singlet), and 3.65 $\delta$  (broad) and integrated as 3:3:1:2.7. Assuming that the 2.7 integration was due to broadening of the 3.65 $\delta$  peak, this peak was assigned a relative area of 3. Thus the compound integrated for ten protons; five of which were due to the phenyl substituent and the remaining five which were common to all three compounds. The 5.66  $\delta$  peak was assumed to correspond to the 6.06 $\delta$  peak in trifluoroacetic acid. The four remaining protons were assumed to be labile; the three at the broad 3.65 $\delta$  peak were thought to be due to nitrogen bonded hydrogen atoms. The other proton gave a sharp peak near 8.30 $\delta$  which was somewhat obscured by the multiplet from the two alpha protons of the phenyl substituent. This peak was assigned to either a phenolic or amino hydrogen substituent.

The information concerning the compound led to several structures being postulated. Assuming a hydrazino group was present

as previously indicated from the indandionate experiments and that the anomalous peak in the nmr was due to a hydrogen substituent in the 5-position suggested that the compound might be 4-hydrazino-6-hydroxypyrimidine.

Thus the anomalous reaction product of methylhydrazine and 4,6-dimethoxy-5-nitropyrimidine was eventually found to be identical in spectral and chemical properties to 4-hydrazino-6-hydroxypyrimidine prepared from 4-chloro-6-hydroxypyrimidine and hydrazine. The 4-hydrazino-6-hydroxy-2-phenylpyrimidine was also prepared and was found to be identical to the product obtained from the reaction of 4,6-dimethoxy-5-nitro-2-phenylpyrimidine with methylhydrazine. As additional proof the compound derived from the methylhydrazine reaction with 4,6-dimethoxy-5-nitropyrimidine was converted to the 4-amino derivative with Raney nickel. This product was found to be identical to an authentic sample of 4-amino-6-hydroxypyrimidine.

Once the structure of the product was determined it was evident that the reaction producing it was far from being straightforward. The methyl group of the methylhydrazine had been lost, the 5-nitro substituent had been replaced by a hydrogen substituent and the methyl group of a methoxy substituent had disappeared.

The remaining problem in this study is the determination of the sequence of reactions which would account for these unusual changes which must occur when 4,6-dimethoxy-5-nitropyrimidine is converted

to 4-hydrazino-6-hydroxypyrimidine by treatment with methylhydrazine.

## DISCUSSION

Knowing that 4,6-dimethoxy-5-nitropyrimidine reacts with methylhydrazine in pyridine to give 4-hydrazino-6-hydroxypyrimidine, the behavior of other 4,6-dialkoxy-5-nitropyrimidines was investigated under identical reaction conditions. The starting material in this sequence of reactions was 4,6-dichloro-5-nitropyrimidine. This compound was synthesized by the following method. Diethylmalonate and formamide in sodium ethoxide-ethanol solution were reacted to give 4,6-dihydroxypyrimidine according to the procedure of Fujimoto and Ono (15). This compound in turn was nitrated at the five position by the method of Boon, Jones and Ramage (6) using red fuming nitric acid and glacial acetic acid. Chlorination of the 4,6-dihydroxy-5-nitropyrimidine was carried out by the use of phosphorus oxychloride as reported by the above authors (6) with N,N-diethylaniline replacing N,N-dimethylaniline as the catalyst as recommended by Krackov (25). The 4,6-dichloro-5-nitropyrimidine was converted to 4,6-dimethoxy-5-nitropyrimidine by treatment with a cold solution of sodium methoxide in methanol as reported by Rose and Brown (32). The 4,6-diethoxy-5-nitropyrimidine was prepared by a method used by Boon and Jones (5) to prepare 4,6-diethoxy-2-methyl-5-nitropyrimidine. To a solution of 4,6-dichloro-5-nitropyrimidine in ethanol was added an ethanolic solution of sodium ethoxide from which 4,6-diethoxy-5-

nitropyrimidine was isolated after two hours of stirring in 73% yield.

The preparation of the diisopropyl derivative proved to be somewhat more difficult. The addition of 4,6-dichloro-5-nitropyrimidine to a cold isopropyl alcohol solution of sodium isopropoxide resulted in a very exothermic reaction which led to a high melting charred product. Since alkoxy-pyrimidines have previously been prepared from methoxy-pyrimidines (7, p. 248), this approach was attempted. 4,6-Dimethoxy-5-nitropyrimidine was added to a cold isopropyl alcohol solution of sodium isopropoxide. The mixture was stirred and then allowed to warm to room temperature and finally the entire solution was brought to a gentle reflux. Under these conditions the solution turned dark and no product was obtained. However, if the heat treatment was omitted and instead the solution was stirred for three hours at room temperature following addition of the dimethoxy compound, 4,6-diisopropoxy-5-nitropyrimidine was obtained in 55% yield.

Using the procedure of Stahl (33), a pyridine solution of 4,6-dimethoxy-5-nitropyrimidine was reacted with methylhydrazine. This gave a product, 4-hydrazino-6-hydroxypyrimidine which had spectral properties identical to those reported by Stahl. When 4,6-diethoxy-5-nitropyrimidine was used instead of the 4,6-dimethoxy derivative, 4-hydrazino-6-hydroxypyrimidine was obtained in only 20.6% yield compared to 55-65% yield from 4,6-dimethoxy-5-nitropyrimidine as originally discovered by Stahl. Using the diisopropoxy derivative



resulted in recovery of 27.5% of the starting material; there was no evidence of 4-hydrazino-6-hydroxypyrimidine formation.

The reaction of 4,6-dimethoxy-5-nitropyrimidine with methylhydrazine in pyridine to give 4-hydrazino-6-hydroxypyrimidine was observed to be accompanied by evolution of an amine, possibly ammonia. An experiment was designed in which the volatile products which separated were first passed through a trap cooled in a salt-ice bath and then bubbled into 0.1N hydrochloric acid. The acid was then back titrated with 0.1N sodium hydroxide which indicated that 0.006 equivalents of acid had been neutralized by the volatile bases given off from reaction of 0.01 equivalents of 4,6-dimethoxy-5-nitropyrimidine. This suggested that perhaps the nitro group was first reduced to an amino group and then lost as ammonia. To check this hypothesis, 5-amino-4,6-dimethoxypyrimidine was prepared by a method described by Krackov (25). Reaction of this compound with methylhydrazine in pyridine resulted in decomposition of the starting material and no evidence of 4-hydrazino-6-hydroxypyrimidine formation. This experiment left no doubt that 5-amino-4,6-dimethoxypyrimidine was not the intermediate in formation of 4-hydrazino-6-hydroxypyrimidine.

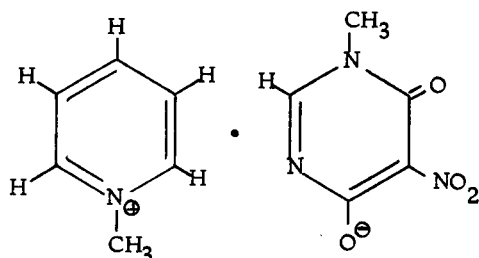
Since reaction of 4,6-dimethoxy-5-nitropyrimidine with hydrazine is straightforward, but with methylhydrazine abnormal, there was considerable interest in the behavior of both 1,1-dimethylhydrazine and 1,2-dimethylhydrazine. When these experiments with

4, 6-dimethoxy-5-nitropyrimidine were repeated with 1, 1-dimethylhydrazine only decomposition products were observed; with 1, 2-dimethylhydrazine 14% of the starting material was recovered, the remainder decomposed.

Because of the unusual replacement of the methoxy substituent by a hydrazino group using a methylhydrazine reagent, the purity of the methylhydrazine has always been suspect. For this reason the conditions for separating hydrazine and methylhydrazine using gas chromatographic procedures were established. The methylhydrazine reagent was then checked with gas chromatographic techniques and found to be absolutely hydrazine free.

Knowing that the anomalous reaction occurred with either solutions of 4,6-dimethoxy-5-nitro- or 4,6-diethoxy-5-nitropyrimidine and methylhydrazine the next step was to determine probable intermediates and a possible reaction pathway.

Stahl had refluxed 4, 6-dimethoxy-5-nitropyrimidine with pyridine (in the absence of methylhydrazine) and obtained a salt that he tentatively identified and Harper (18) confirmed to be the methylpyridinium salt of 1, 6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine.



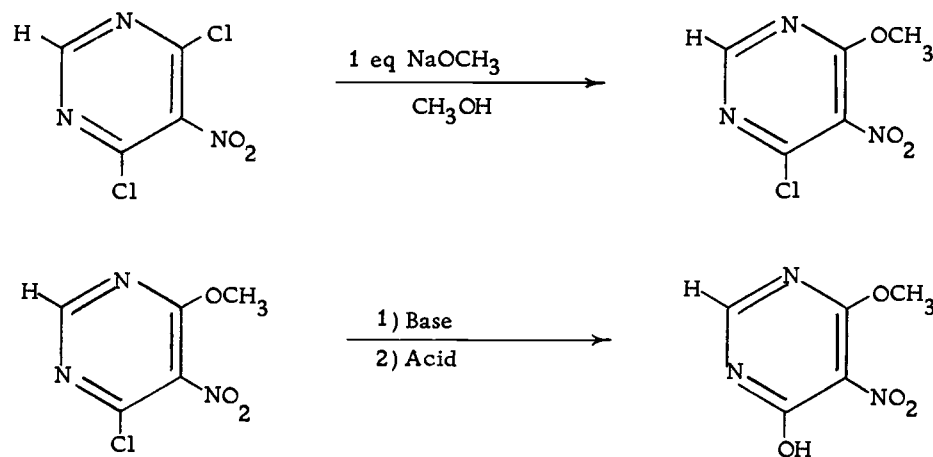
Stahl also found that this salt was not an intermediate in the formation of 4-hydrazino-6-hydroxypyrimidine. When this salt was treated with methylhydrazine in refluxing pyridine it did not yield 4-hydrazino-6-hydroxypyrimidine but resulted in recovery of only 20% of the salt. He also reported that the salt was somewhat thermally unstable in refluxing pyridine but that the decomposition was accelerated by methylhydrazine.

On the other hand, the filtrate from the salt formation, when refluxed with methylhydrazine, gave 4-hydrazino-6-hydroxypyrimidine 65% yield based on the amount of pyrimidine not accounted for in the salt formation. A portion of the original filtrate was evaporated at room temperature and the resultant red oil placed in a vacuum desiccator over phosphorus pentoxide. An infrared spectrum of this sample gave peaks showing that a pyridine ring was present and that a methoxyl group was also present but this band was much weaker than that found in 4,6-dimethoxy-5-nitropyrimidine.

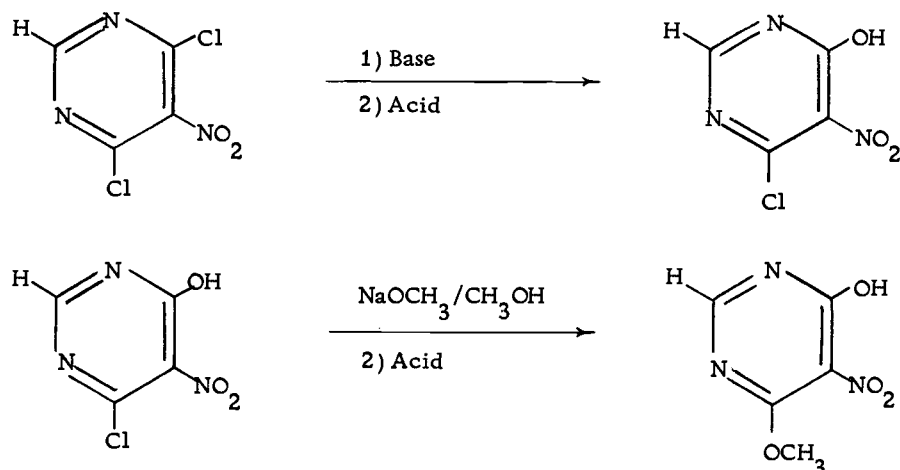
This together with the structure of the pyrimidine moiety of the pyridine insoluble salt suggested that perhaps one methyl group had been lost from the 4,6-dimethoxy-5-nitropyrimidine and that 4-hydroxy-6-methoxy-5-nitropyrimidine should be investigated as a possible precursor to 4-hydrazino-6-hydroxypyrimidine.

Two methods for the synthesis of 4-hydroxy-6-methoxy-5-nitropyrimidine immediately suggest themselves; both appear to be

promising. The first method involved preparation of 4-chloro-6-methoxy-5-nitropyrimidine from 4,6-dichloro-5-nitropyrimidine and then treatment of this compound with base followed by acidification to give the desired product.



The second method reversed the sequence of reactions by first preparing 4-chloro-6-hydroxy-5-nitropyrimidine and then treatment of this compound with sodium methoxide in methanol followed by acidification to give the desired product. The first procedure was selected since the second method requires nucleophilic attack on an anion.

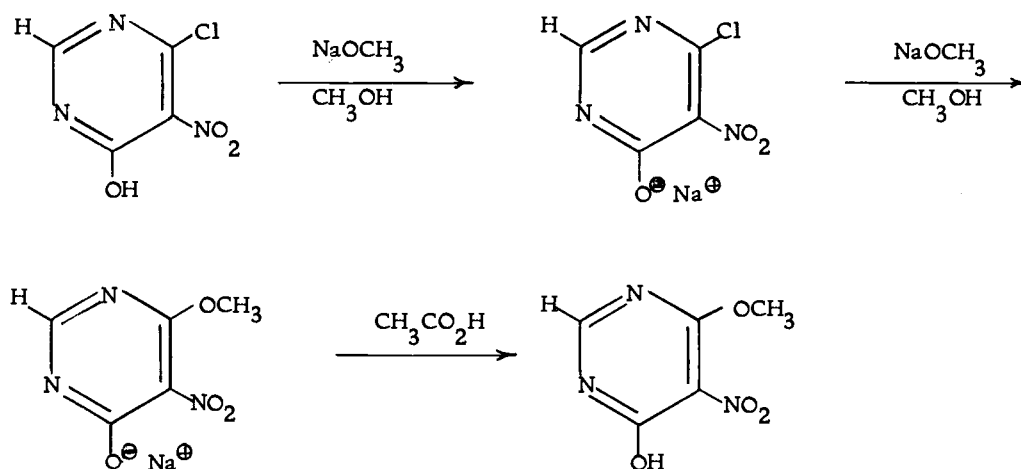


The hydrolysis of 4-chloro-6-methoxy-5-nitropyrimidine to the desired hydroxypyrimidine in the second step of this synthetic operation proved to be unsuccessful. Two equivalents of sodium hydroxide or sodium carbonate in aqueous solution at room temperature were used. The reaction after acidification gave a small amount of material that was something other than 4-hydroxy-6-methoxy-5-nitropyrimidine, as judged by the analytical data.

A search of the literature revealed an earlier reported synthesis of 4-chloro-6-hydroxy-5-nitropyrimidine by Khromov-Borisov and Kheifets (24). A later article by the same authors described the synthesis of the desired 4-hydroxy-6-methoxy-5-nitropyrimidine (23). In this laboratory the first step in the preparation of 4-chloro-6-hydroxy-5-nitropyrimidine by partial hydrolysis of 4,6-dichloro-5-nitropyrimidine following the directions of Khromov-Borisov was not successful; only starting material was recovered. A slight modification of the procedure did produce some of the desired product but only in very low yield. Since the concentration of sodium carbonate in the original directions appeared to be excessive (6:1 molar ratio) the reaction was repeated using a 2:1 ratio of sodium carbonate. This did give the desired product in a much lower yield than reported by Khromov-Borisov and Kheifets. Moreover, most of the starting material not accounted for by 4-chloro-6-hydroxy-5-nitropyrimidine formation was recovered. Since the reaction mixture was not a

homogeneous solution, it was found that the yield could be improved significantly by first grinding the 4,6-dichloro-5-nitropyrimidine in a mortar and then stirring the fine suspension of the aqueous pyrimidine-carbonate mixture at room temperature for 24 hours; the yield under these conditions was 61% compared to the reported 56%.

The conversion of 4-chloro-6-hydroxy-5-nitropyrimidine to 4-hydroxy-6-methoxy-5-nitropyrimidine is interesting in that the reaction proceeds by nucleophilic attack by the methoxide anion upon the sodium salt of 4-chloro-6-hydroxy-5-nitropyrimidine.



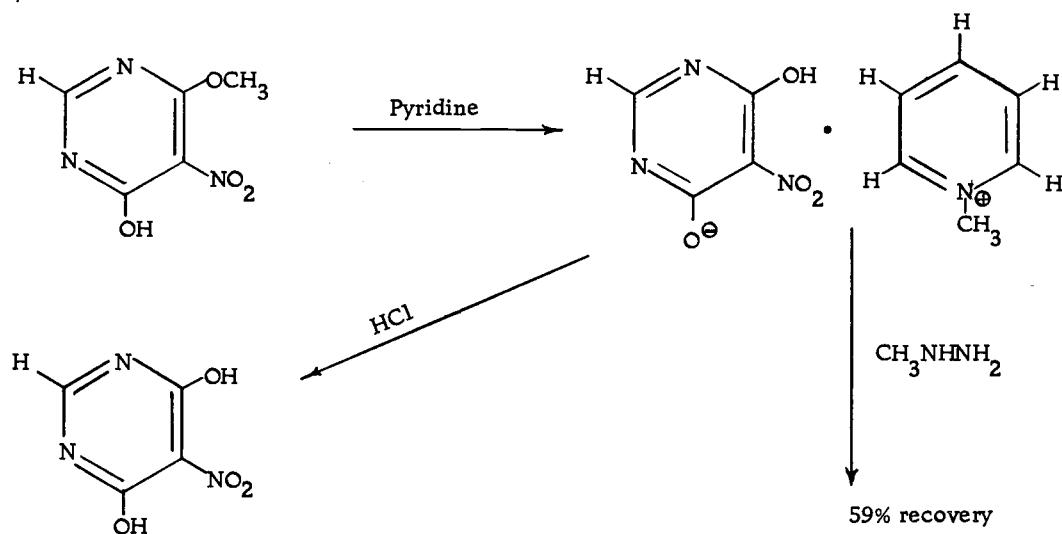
Having obtained the desired 4-hydroxy-6-methoxy-5-nitropyrimidine, the behavior of this compound toward a pyridine solution of methylhydrazine was investigated. The reaction was found to give 4-hydrazino-6-hydroxypyrimidine in 87% yield compared to 56% yield with 4,6-dimethoxy-5-nitropyrimidine. This suggested that 4-hydroxy-6-methoxy-5-nitropyrimidine or a compound closely related

to it may be an intermediate in the sequence of reactions leading to 4-hydrazino-6-hydroxypyrimidine. When ethanol was used as the solvent the yield was 56%, with butanol as a solvent the yield rose to 66.5%. The corresponding yields for the 4,6-dimethoxy-5-nitropyrimidine were only in trace quantities and 22.1% respectively (25).

The fact that 4-hydroxy-6-methoxy-5-nitropyrimidine also yields 4-hydrazino-6-hydroxypyrimidine in reactions with methylhydrazine lends strong support that initial methylation of the solvent takes place prior to denitrogenation. In those experiments in which n-butanol was used as the solvent the product of such a methylation step would yield methyl n-butyl ether. Indeed, when the reaction was undertaken with a butanol solution of 4,6-dimethoxy-5-nitropyrimidine, methyl n-butyl ether was isolated as one of the by-products. Also detected was methanol, an expected product from the nucleophilic displacement of a methoxy group. Assuming that an initial methylation of the solvent is necessary for the reaction to proceed, it is not surprising that the yield of 4-hydrazino-6-hydroxypyrimidine is higher when pyridine is used in place of the alcohols as the solvent for the reaction.

To determine whether 4-hydroxy-6-methoxy-5-nitropyrimidine or a pyridine derivative was the intermediate in the reaction which led to the formation of 4-hydrazino-6-hydroxypyrimidine, a pyridine solution of 4-hydroxy-6-methoxy-5-nitropyrimidine (in the absence of

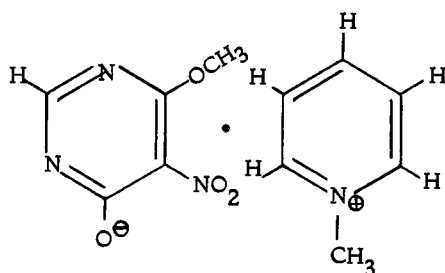
methyl hydrazine) was refluxed for one hour. In the ensuing reaction, two phases separated. The lower liquid layer which formed, crystallized upon agitation. The material was removed by filtration, washed with fresh pyridine, and dried. The infrared and nmr spectra suggested that the material was the methylpyridinium salt of 4-hydroxy-6-methoxy-5-nitropyrimidine, and carbon-hydrogen and nitrogen analyses confirmed this hypothesis. The salt, when dissolved in water and acidified with dilute hydrochloric acid, precipitated 4,6-dihydroxy-5-nitropyrimidine in 86.3% yield; the salt had been produced in 65% yield. It seemed unlikely that this salt would react with methylhydrazine to give 4-hydrazino-6-hydroxypyrimidine and this was verified. The salt in fresh pyridine was treated with four equivalents of methylhydrazine and the mixture was refluxed for one hour. No 4-hydrazino-6-hydroxypyrimidine was formed yet only 59% of the salt was recovered. This salt apparently is more stable than the salt formed when 4,6-dimethoxy-5-nitropyrimidine was refluxed with pyridine. In a similar experiment only 20% of the salt was recovered (33).





The mother liquor from the salt formation reaction with 4-hydroxy-6-methoxy-5-nitropyrimidine was treated with methylhydrazine, thus repeating the earlier experiments with the mother liquor from the 4,6-dimethoxy-5-nitropyrimidine-pyridine reaction. 4-Hydrazino-6-hydroxypyrimidine was produced in 6.06% yield (17.3% based on pyrimidine not accounted for by salt) as compared to 65% (based on the pyrimidine not accounted for by the salt) in the prior experiment. In no experiments in which the methylhydrazine is added prior to the reflux period is any salt isolated. This is probably due to the instability of the insoluble salt in the presence of methylhydrazine or due to the removal of the soluble methylpyridinium salt which could alter reaction rates.

At this point it was strongly suspected that the methylpyridinium salt of 4-hydroxy-6-methoxy-5-nitropyrimidine was the soluble compound in the mother liquor from the treatment of 4,6-dimethoxy-5-nitropyrimidine that reacts with methylhydrazine which gave 4-hydrazino-6-hydroxypyrimidine.



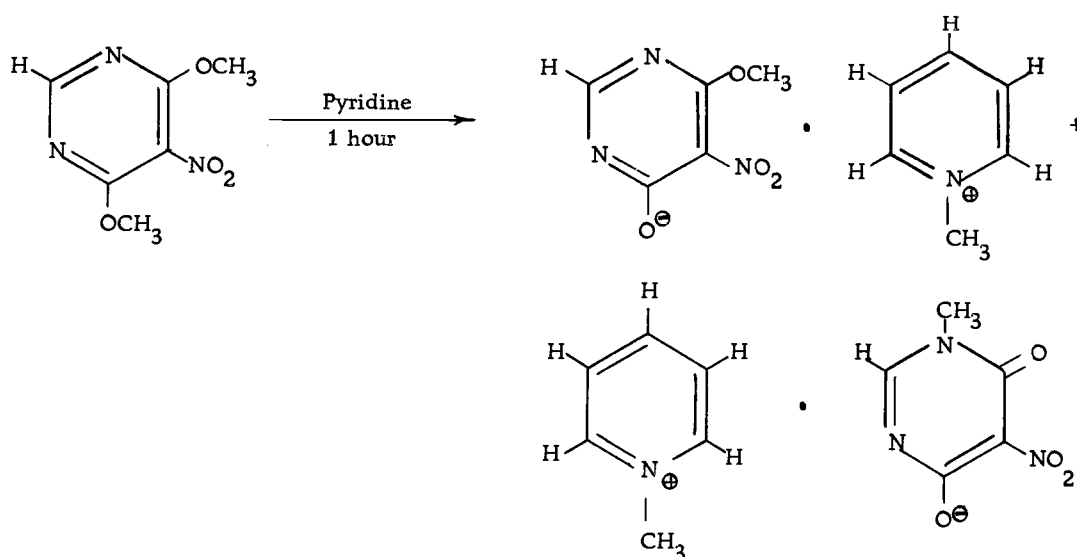
For this reason the methylpyridinium salt of 4-hydroxy-6-methoxy-5-nitropyrimidine was synthesized. The 4-hydroxy-6-methoxy-5-nitropyrimidine was converted to its sodium salt by use of sodium methoxide in methanol. After removal of the methanol this salt was added to a pyridine solution of methylpyridinium iodide which had been prepared by reaction of methyl iodide with pyridine. The preparation was carried out so that there was one equivalent of the methylpyridinium cation to one equivalent of the pyrimidine anion.

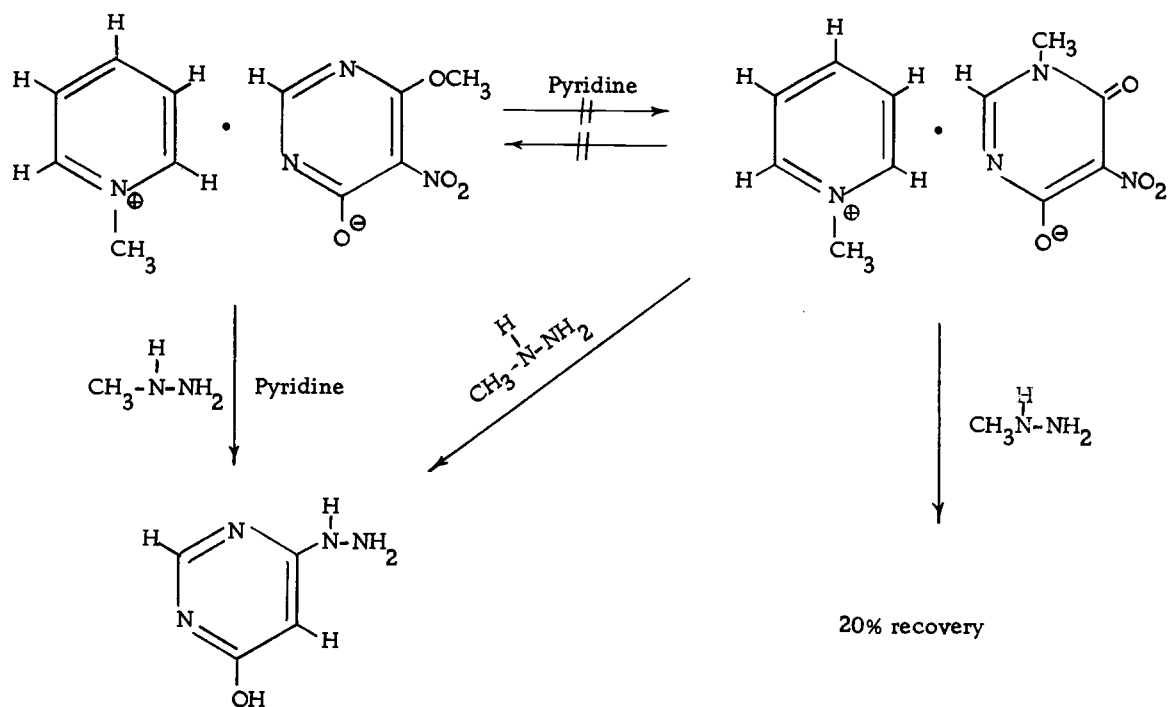
When a pyridine solution of the desired salt containing sodium iodide was refluxed for one hour, there was no formation of the methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine which was described by Stahl (33) and Harper (18). Removal of the pyridine and acidification with glacial acetic acid gave a 38% yield of 4-hydroxy-6-methoxy-5-nitropyrimidine and thus accounted for 38% of the salt. This salt when refluxed in pyridine for one hour followed by addition of four equivalents of methylhydrazine and a second one hour reflux gives a 36.5% yield of 4-hydrazino-6-hydroxypyrimidine. Omitting the initial pyridine reflux gave a 72.7% yield of 4-hydrazino-6-hydroxypyrimidine.

To show that the soluble salt from the treatment of 4,6-dimethoxy-5-nitropyrimidine with methylhydrazine was in fact the

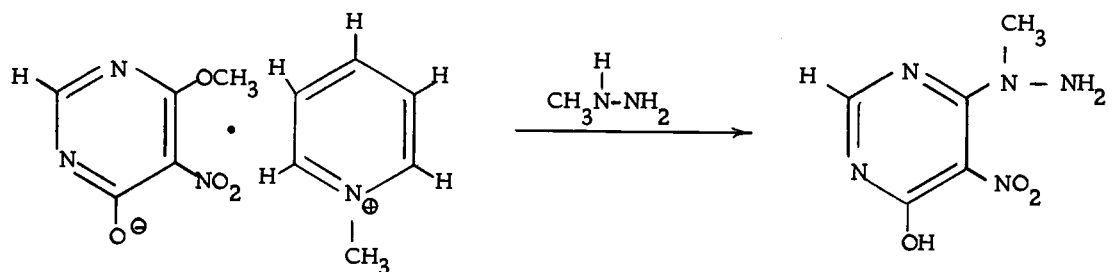
methylpyridinium salt of 4-hydroxy-6-methoxy-5-nitropyrimidine the reaction was repeated. The methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine was removed by filtration and then the pyridine was removed by vacuum distillation. The residue was dissolved in a small amount of ice water and then acidified with glacial acetic acid. The precipitate was dried and was found by means of its infrared spectra to be identical to 4-hydroxy-6-methoxy-5-nitropyrimidine. This compound accounted for 27.4% of the starting 4,6-dimethoxy-5-nitropyrimidine and the two salts thus account for 66.2% of the starting material.

Thus 4,6-dimethoxy-5-nitropyrimidine in refluxing pyridine undergoes two competing reactions yielding two non-interconvertible salts; one which is soluble and the other insoluble in pyridine. The insoluble salt decomposes in its reaction with methylhydrazine; the soluble salt on the other hand yields 4-hydrazino-6-hydroxypyrimidine.





Based on previous information regarding the reactions of hydrazines with methoxy-nitropyrimidines, the formation of the methylpyridinium salt of 4-hydroxy-6-methoxy-5-nitropyrimidine could explain the isolation of the expected 4-hydroxy-6-(1-methylhydrazino)-5-nitropyrimidine instead of the product which was actually isolated. Thus the loss of the nitro group as well as the methyl group of the methylhydrazine remain to be explained.



At this point the most logical explanation appears to be one which involves a 1,6-methylation followed by subsequent loss of methyl nitrite (see Figure 3). The methanol formed in the proposed reaction pathway had been previously detected. It is reported that hydrazines in the presence of a stronger base react to give a hydrazide anion which is unstable (10, p. 2). The methyl nitrite had not been previously identified so a method was devised for its detection.

In the preparation of nitromethane from methanol and nitric acid some methyl nitrite is formed. The amount of methyl nitrite can be determined by acidifying a methanol solution of the mixture, adding potassium iodide, and determining the amount of iodine released (13). This is also similar to the procedure used to check for the presence of excess nitrous acid to determine if a nitrosation reaction has gone to completion (30). This method employs the use of starch-iodide test paper. The iodide is oxidized to iodine by the nitrous acid which then gives a blue complex with the starch.

The starch-iodide test paper was used to detect the methyl nitrite. It was observed that known methyl nitrite would not affect starch-iodide test paper that had been wetted with distilled water.



However, if the paper had been wetted with dilute hydrochloric acid, the blue complex would form. Apparently the methyl nitrite was easily hydrolyzed to nitrous acid by the dilute acid on the test paper. It was also observed that both nitric oxide and nitrogen dioxide would produce the blue complex on the test paper whether the paper was wetted with aqueous ammonia, distilled water, or dilute hydrochloric acid.

Following these initial experiments for the detection of methyl nitrite, these procedures were applied to the detection of this ester as a possible by-product by the reaction of methyl hydrazine and 4,6-dimethoxypyrimidine in refluxing pyridine.

The volatile products in the reaction leading to the formation of 4-hydrazino-6-hydroxypyrimidine were passed through two U-tubes. In the first U-tube was placed a strip of starch-iodide test paper wetted with distilled water, in the second, a strip of test paper wetted with dilute hydrochloric acid. If methyl nitrite were being given off, the first strip of test paper would remain unchanged while the second would give the blue complex. If an oxide of nitrogen were evolved both strips of test paper would give the blue complex. When the reaction was run the first strip of test paper remained unchanged while the second turned dark blue. This is a fairly good indication that methyl nitrite was evolved but additional confirmation would be desirable.

In order to confirm the evidence that methyl nitrite was produced by the reaction instead of something that behaved like methyl nitrite, the volatile products from the reaction were then trapped and an infra-red spectrum taken of this volatile material. This was compared with the spectrum of methyl nitrite which had been reported in the literature (34). The reaction apparatus (see Figure 4) was set up so that the gaseous products given off would first pass through an ice-salt cold trap to remove any volatile solvents and then through a Dry Ice-acetone trap to condense the gases. At the exit end of the trap cooled in the Dry Ice-acetone was attached a drying tube containing soda lime and then a drying tube containing Drierite. The system was then flushed with nitrogen for five minutes to insure that all carbon dioxide or water was removed. The reactants were then added to the reaction vessel and the reflux period started. After the one hour reflux period the Schwartz tube trap cooled in the Dry Ice-acetone bath was removed from the system. This trap was then cooled in liquid nitrogen and was evacuated to about  $10^{-4}$  mm on a vacuum system. The material in the trap was then transferred to a gas infrared cell which had previously been evacuated to about  $10^{-4}$  mm pressure. The spectrum taken with a Beckman IR-7 spectrophotometer revealed the presence of ammonia and methyl amine but did not indicate the presence of methyl nitrite.

It had been determined earlier that volatile amines were given



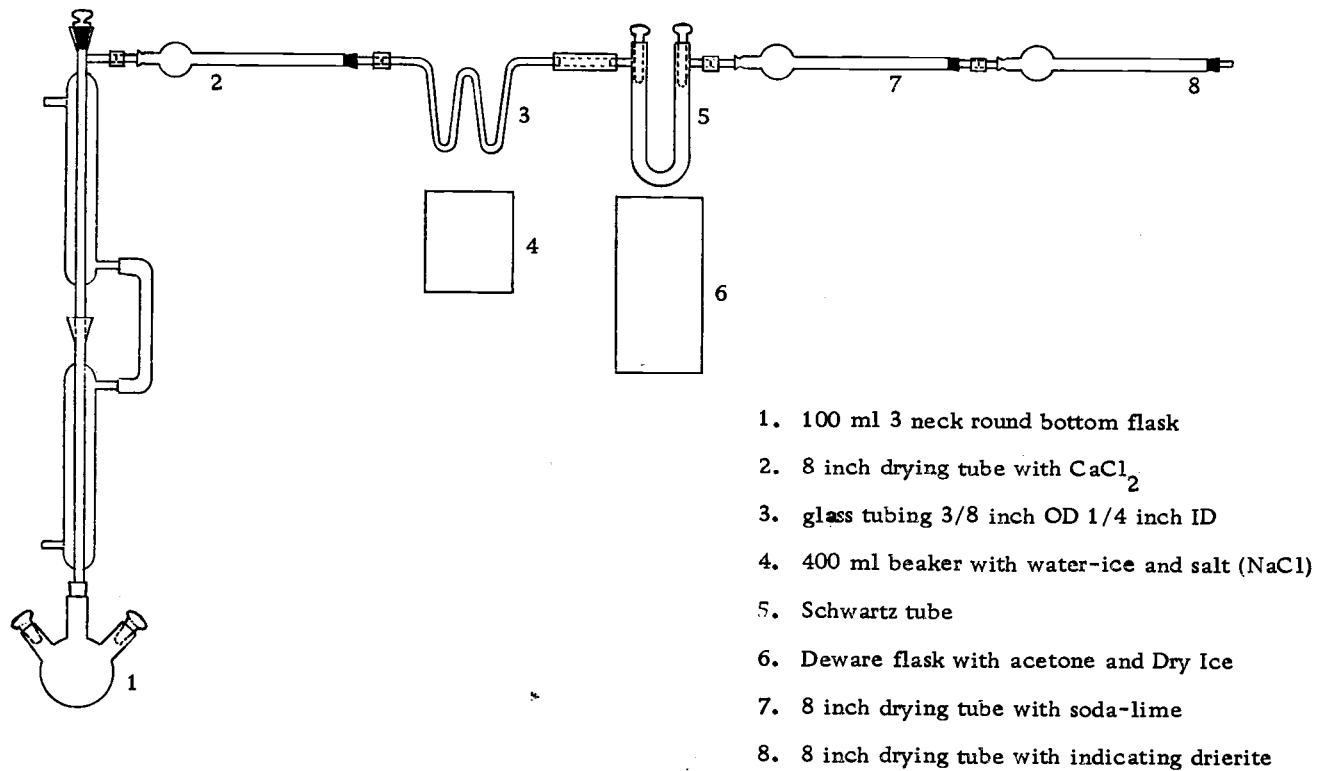


Figure 4. Reaction apparatus used for trapping the volatile by-products from the reaction of 4,6-dimethoxy-5-nitropyrimidine with methylhydrazine in pyridine.

off in the reaction. It was quite possible that the methyl nitrite could have reacted with the liquid ammonia cooled and concentrated in the Schwartz tube in the Dry Ice-acetone bath to give methylamine and ammonium nitrite. Since calcium chloride will absorb amines as well as ammonia, experiments were conducted to determine the effect of calcium chloride on methyl nitrite. These tests revealed that methyl nitrite would pass through a calcium chloride tube intact. Therefore, the reaction apparatus was modified by placing a calcium chloride drying tube before the cold traps. After the system was cleaned up, reassembled, and swept with nitrogen the reaction was again repeated. The trapped gas was then transferred to the gas infrared cell and the spectrum taken. This time the spectrum was void of any bands. However it was noted that the stopcock grease on the ground glass joints in the vacuum system used for transfer of the gas had changed color, turning white which indicated some kind of chemical action. The vacuum system was then carefully cleaned to remove the Apiazon grease that had been used and was then reassembled using Silica Gel based grease. To insure that everything was now in order and that methyl nitrite could be detected, a known sample of methyl nitrite was prepared and tested with the analytical train. The test was made on a 0.006 molar scale so that the amount of methyl nitrite would be approximately equal to that evolved from an experimental run of the reaction being studied. The gas was trapped and a perfect spectrum

of methyl nitrite was obtained (see Figure 5). With the perfection of the experimental technique for obtaining infrared spectra of gaseous by-products, the next step was to examine the actual gaseous by-products of reaction yielding 4-hydrazino-6-hydroxypyrimidine to determine if methyl nitrite was produced. This determination gave an infrared spectrum which confirmed the fact that methyl nitrite was produced in the reaction; it also showed that another gas or other gases evolved (see Figure 6).

The infrared spectrum of the volatiles from the reaction (see Figure 6) had all the peaks present in the spectrum of a known sample of methyl nitrite (see Figure 5). The peaks of special interest in confirming the presence of methyl nitrite are those between 800 and 900  $\text{cm}^{-1}$  and between 1550 and 1750  $\text{cm}^{-1}$ . The peaks in these regions have the shape characteristic of methyl nitrite. However the sharp peak at 1033  $\text{cm}^{-1}$  as well as the strong peaks at 1277  $\text{cm}^{-1}$  and 1305  $\text{cm}^{-1}$  are not found in the spectrum of this ester. Other peaks not accounted for by methyl nitrite are at 2580, 2936, 3012, and 3488  $\text{cm}^{-1}$ .

The peak at 1458  $\text{cm}^{-1}$  when compared to the peak at 1441  $\text{cm}^{-1}$  is stronger than the corresponding peaks due to the ester. Moreover the peaks at 2232  $\text{cm}^{-1}$  and 2212  $\text{cm}^{-1}$  are much stronger than those for methyl nitrite.

The peaks above 3400  $\text{cm}^{-1}$  are in the N-H or O-H stretch region

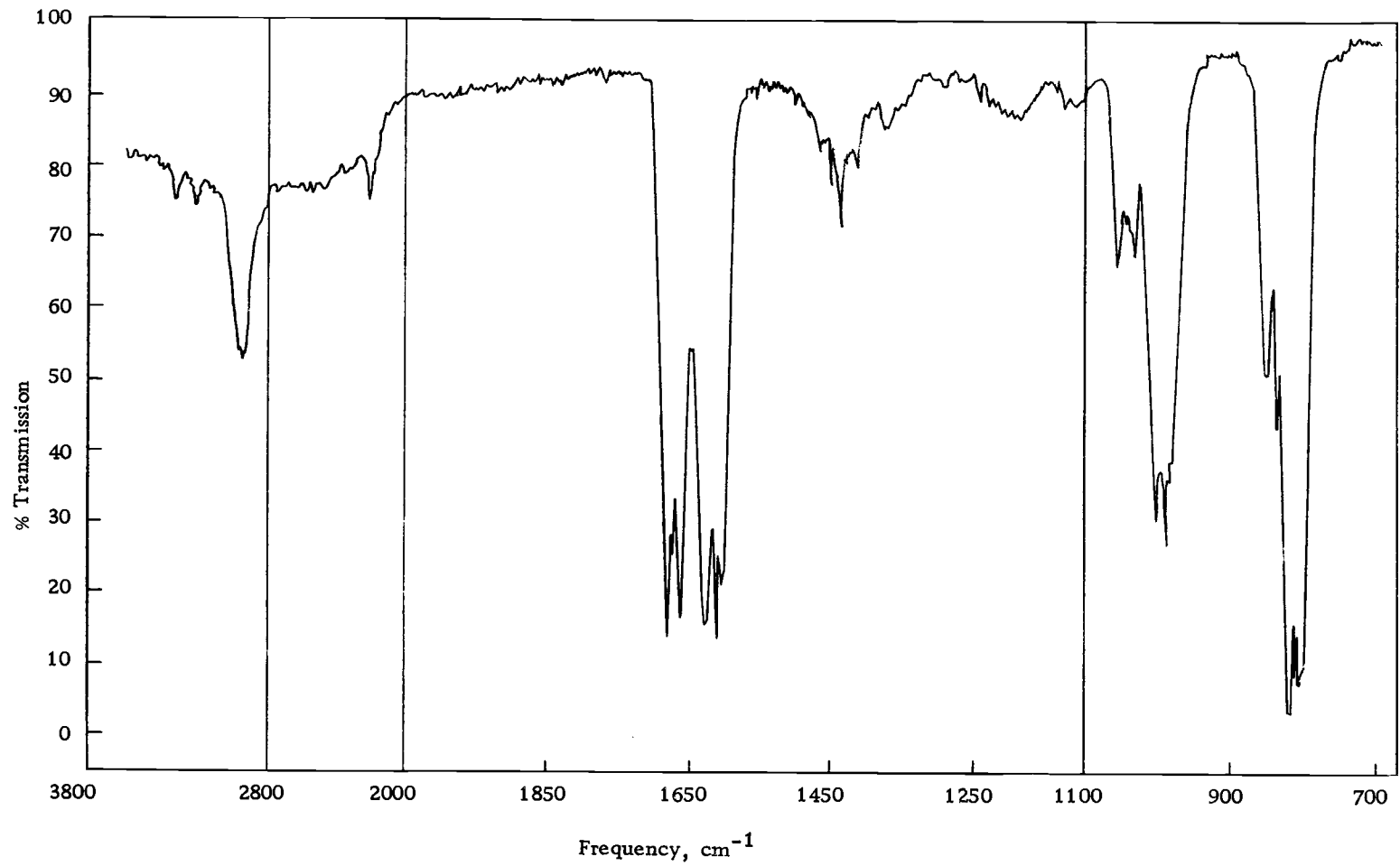


Figure 5. Infrared spectrum of authentic methyl nitrite.

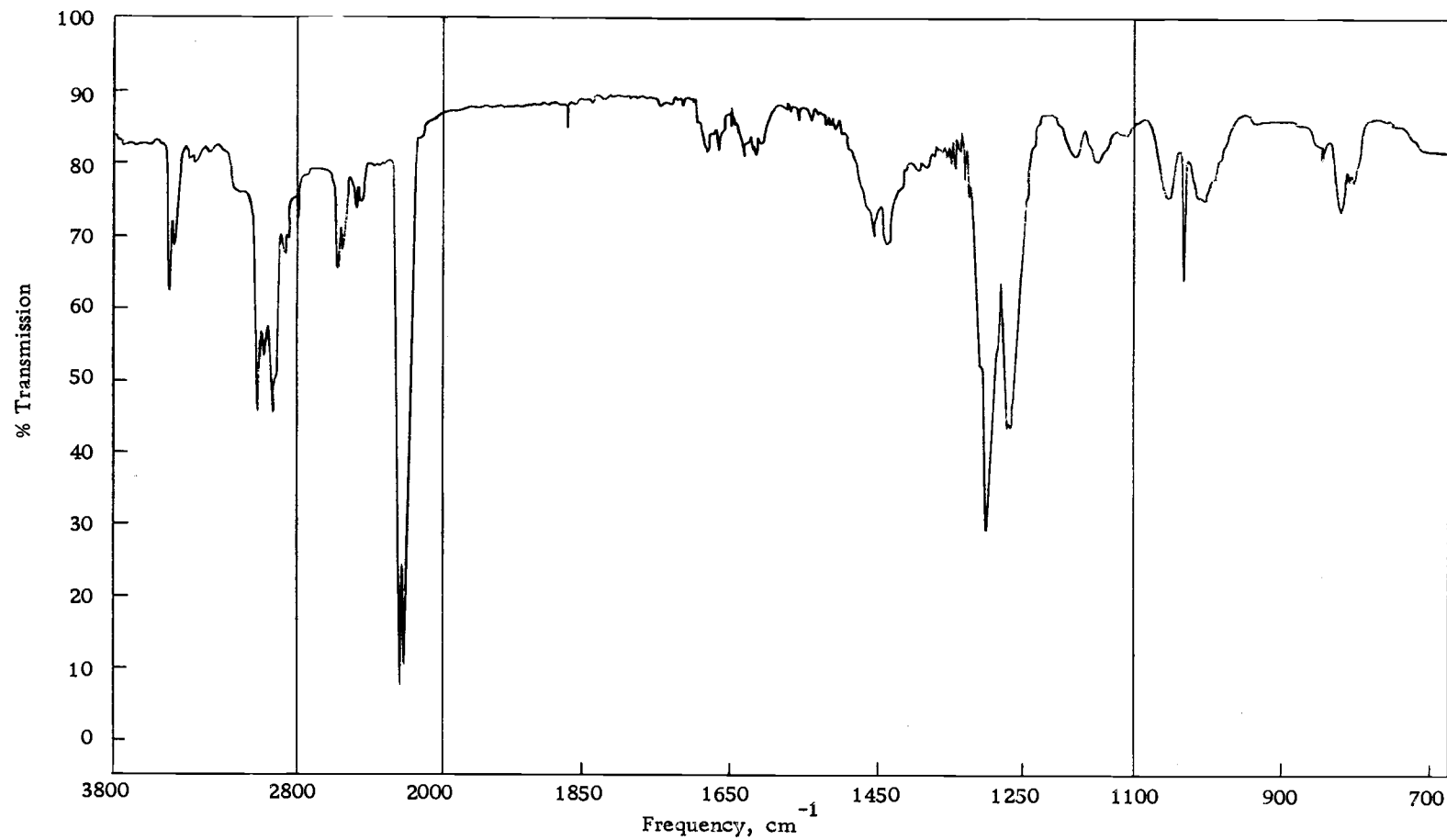


Figure 6. Infrared spectrum of the volatiles from the reaction of 4,6-dimethoxy-5-nitropyrimidine with methylhydrazine in pyridine.

and the peaks at 2232 and 2212  $\text{cm}^{-1}$  are in the  $\text{C}\equiv\text{N}$  stretch region. The peaks between 1250 and 1350  $\text{cm}^{-1}$  are in the C-O stretch region. A careful study of the DMS Infrared Card File did not disclose any compound that would give an infrared spectrum which would explain the extra peaks. It seemed very likely that the unidentified volatile material resulted from decomposition of the 4,6-dimethoxy-5-nitropyrimidine by way of the methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine.

Two possible compounds from such a decomposition having low enough boiling points to be carried over into the cold trap and having the structural features suggested by the infrared data are cyanic and isocyanic acid. The infrared spectrum of isocyanic acid (19) had peaks in approximately the same region as those reported above but all the peaks were shifted.

A survey of the literature did not disclose a spectrum of cyanic acid for comparative purposes but did reveal one article which provided evidence for the existence of cyanic acid (17); although another article gave the infrared spectrum of methyl cyanate (16). Groving and Holm prepared "cyanic acid" by treating sodium cyanate with gaseous hydrogen chloride (17). An infrared spectrum of the material did not allow them to draw any conclusions regarding the existence of cyanic acid. However, when the material was treated with diazoisobutane (a method used to produce isobutyl isocyanate) in solution or in the vapor

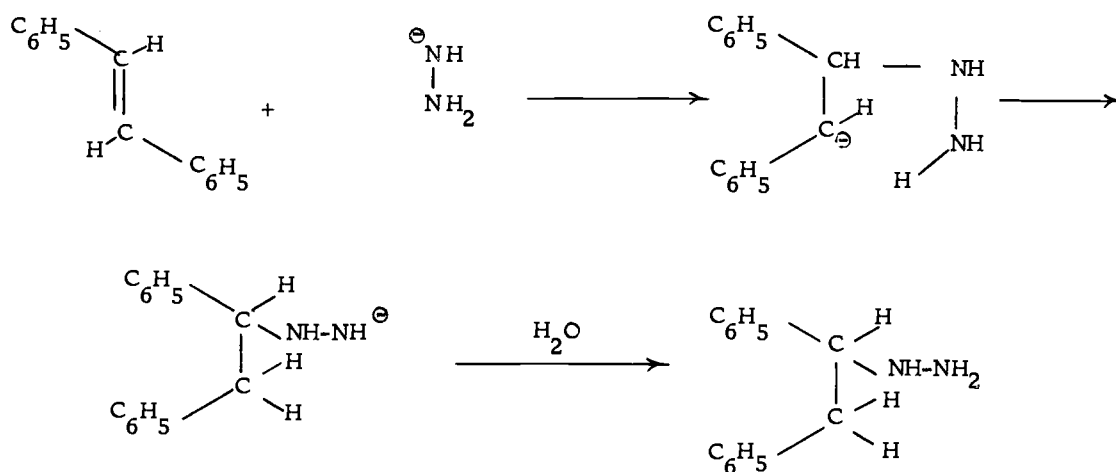
phase, they obtained isobutyl isocyanate and isobutyl cyanate in a 100:3 ratio. These investigators concluded that this suggests the existence of cyanic acid.

Until the actual spectrum of cyanic acid is known, one can only hypothesize that the extra peaks in the infrared spectrum of the volatiles from the reaction are due to cyanic acid.

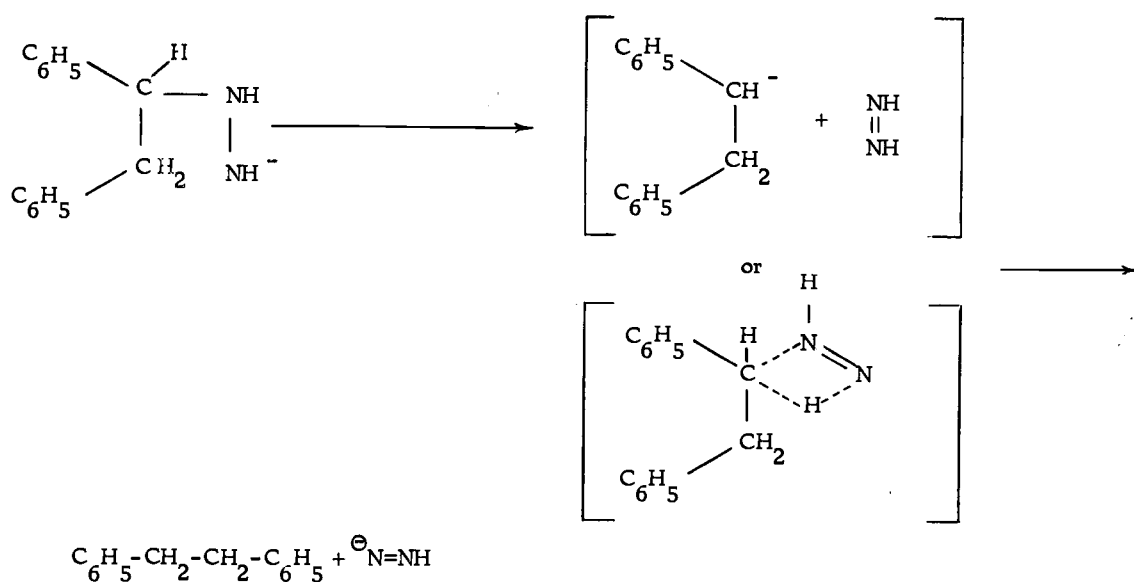
An examination of the proposed reaction sequence discloses that the evolution of ammonia and methylamine has not been explained. Also good evidence for the decomposition of the methylhydrazide ion to yield a hydride ion is not available.

A search of the literature for information concerning the methylhydrazide ion provided several publications dealing with the reduction of unsaturated or polycyclic aromatic hydrocarbons with sodium hydrazide in the presence of excess hydrazine. Kauffmann (22) reported that the reduction was accompanied by the evolution of nitrogen and ammonia in a 1:2 molar ratio, together with the observation that the reaction mixture became darkly colored.

In a study of the reduction of trans-stilbene to 1,2-diphenylethane, Kauffmann was able to isolate 1,2-diphenyl-1-hydrazinoethane which resulted when the trans-stilbene was treated with a cold solution of sodium hydrazide in hydrazine followed by water (21).



If the water was not added, 1,2-diphenylethane could be isolated in 92% yield. The observation that diisopropylidenehydrazide was formed when acridine was reduced with sodium N, N'-diisopropylhydrazide suggested that the second stage of the reaction involved loss of diimide.

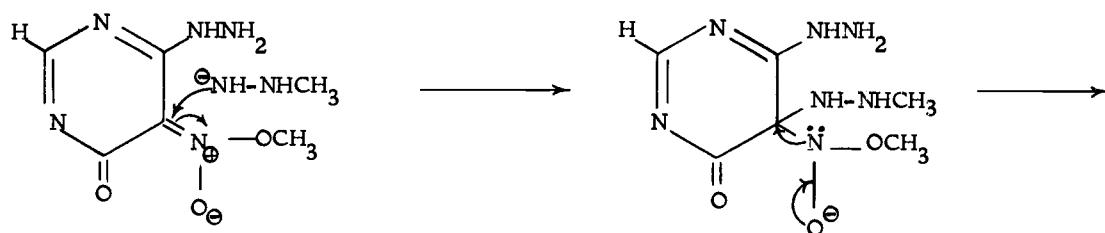
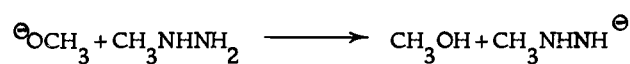
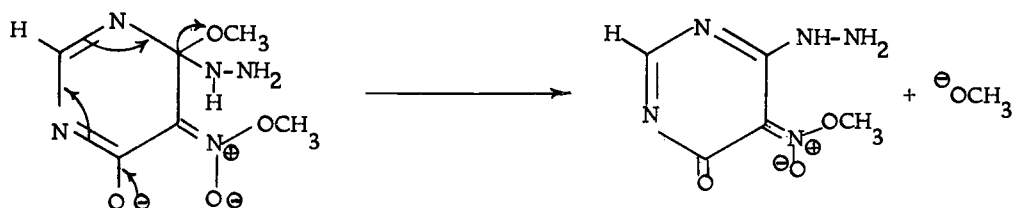


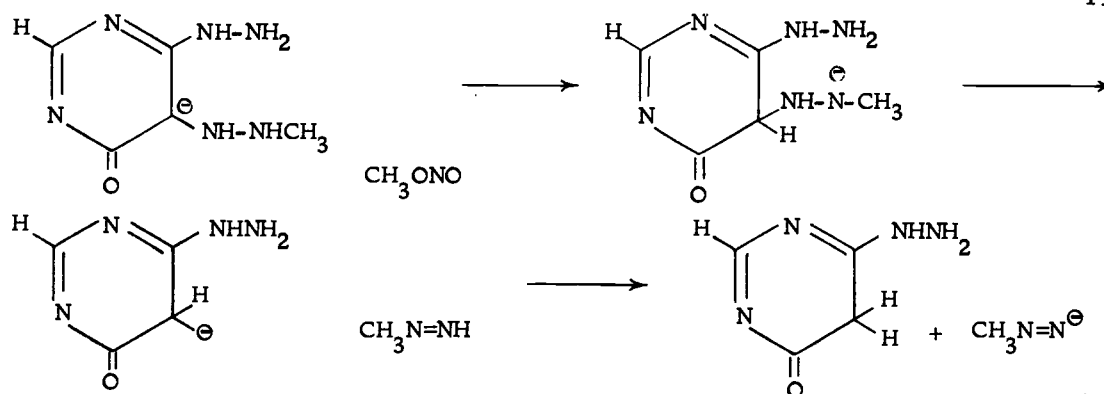
Kauffmann does not indicate whether the diimide occurs free or as part of a transition complex. However he does report that compounds containing isolated C=C double bonds are not reduced when added to



the mixture. Also he was of the opinion that if free diimide were produced, being more strongly "acidic" than hydrazine, it would lose a proton immediately to the carbanion or to excess hydrazide present in the mixture.

A sequence similar to that proposed by Kauffmann can be used to explain steps leading up to loss of methyl nitrite in the reaction of 4,6-dimethoxy-5-nitropyrimidine with methylhydrazine.

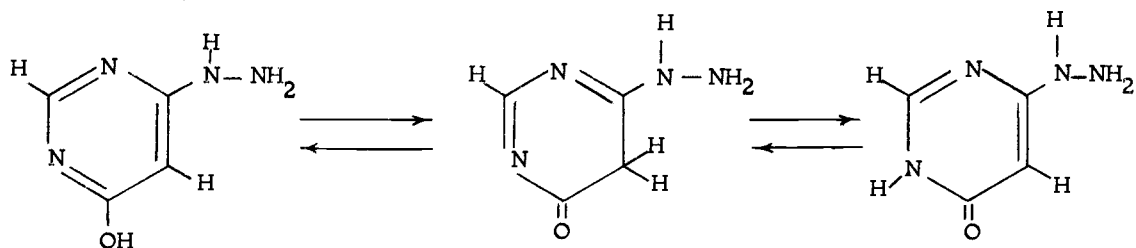




The ammonia detected in the reaction would have to come from decomposition of the methyl diimide anion. Supporting evidence for the above hydrazide mechanism is the observations by Stahl (33) that the yield of 4-hydrazino-6-hydroxypyrimidine is greatest when there are three or four moles of methylhydrazine to one mole of the pyrimidine. This excess methylhydrazine would be necessary for the above sequence of reactions to take place.

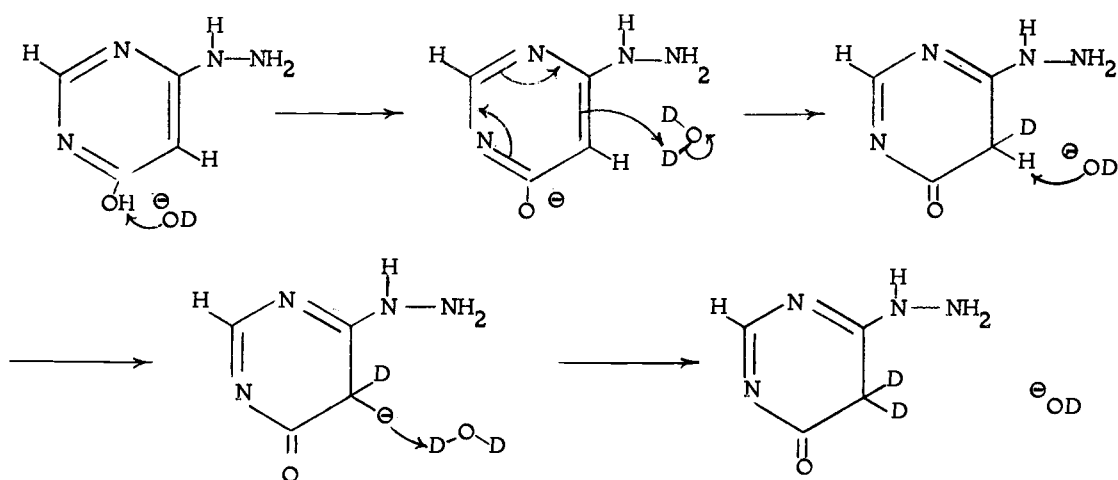
The fact that the soluble salt produced when 4,6-dimethoxy-5-nitropyrimidine is refluxed with pyridine yields 4-hydroxy-6-methoxy-5-nitropyrimidine upon acidification fairly well substantiates that methylation is the initial step in the reaction. The detection of methanol and methyl nitrite is good evidence for supporting the remainder of the suggested mechanism. The tautomeric form that results from the reaction pathway explains why the 5-proton does not show up when the nmr spectrum of the compound is run in deuterium chloride in deuterium oxide or sodium deuterioxide in deuterium oxide. This form would explain the deuterium exchange at the 5 position while the hydroxyl form or the amide form alone would not explain

this exchange.

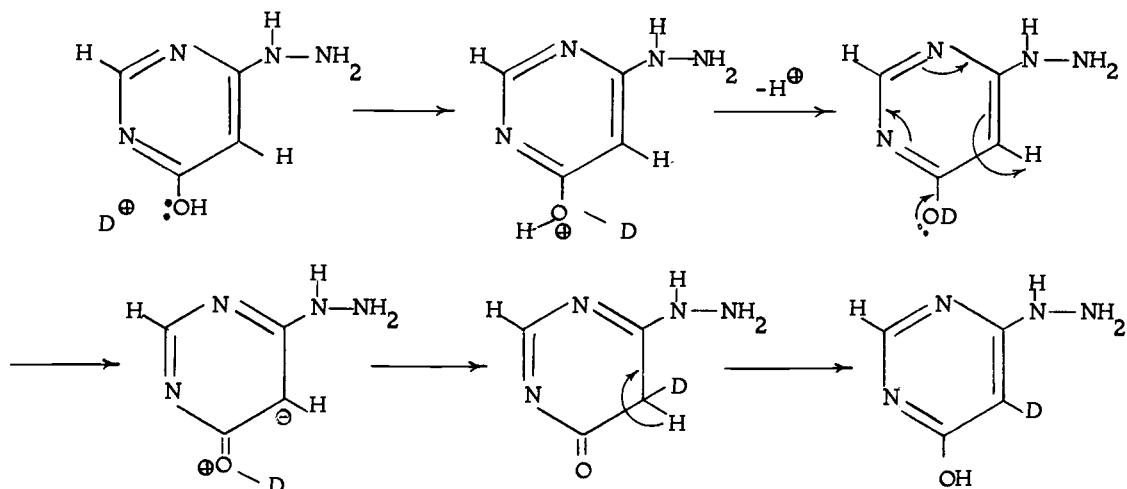


In each of these cases the 5-proton is bonded to a doubly bonded carbon atom.

The exchange in base can be explained by the following steps:



The exchange in acid can be explained by the following sequence:



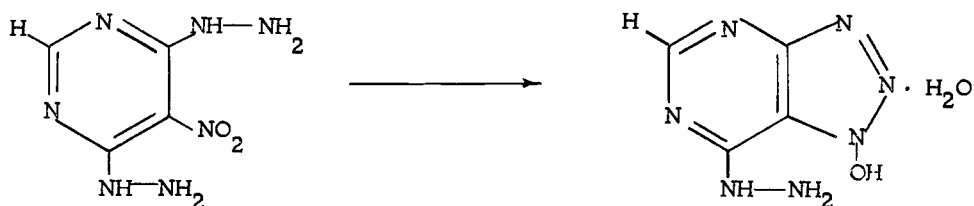
Thus based on direct and indirect evidence, the scheme proposed explains the course the reaction must be taking in going from 4,6-dimethoxy-5-nitropyrimidine to the unexpected product, 4-hydrazino-6-hydroxypyrimidine.

As stated earlier, the anomalous reaction when first discovered by Krackov had been run in ethanol and butanol. Stahl later reported that when pyridine was used as the solvent the yield of 4-hydrazino-6-hydroxypyrimidine increased significantly. Krackov had shown that in ethanol, hydrazine when used in place of methylhydrazine gave the expected product; 4,6-dihydrazino-5-nitropyrimidine. However, the reaction had never been run in pyridine. To determine if pyridine would markedly alter the course of the reaction with hydrazine, the reaction was repeated under conditions identical to the original methylhydrazine reaction. When the hydrazine was added to 1.85 g of 4,6-dimethoxy-5-nitropyrimidine in 50 ml of pyridine a precipitate formed immediately. After five minutes of reflux, the precipitate dissolved and after an additional 20 minutes started coming out of solution again. After the one hour reflux period the reaction mixture was cooled, filtered, and the precipitate was washed with cold methanol. If the reaction proceeded as it had in ethanol approximately 1.85 g of 4,6-dihydrazino-5-nitropyrimidine melting at  $202-203.5^{\circ}\text{C}$  (25) should have been produced. Instead, 1.09 g of a material which slowly decomposed on the melting point block between  $235-240^{\circ}$  was

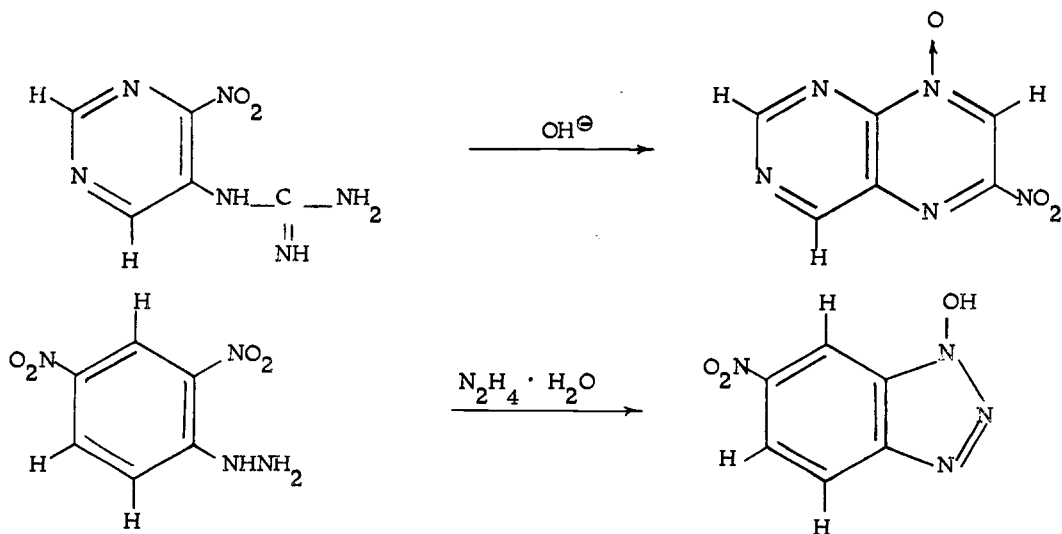
obtained. Elemental analysis gave results consistent with the expected 4,6-dihydrazino-5-nitropyrimidine although the material burned smoothly instead of with the violent explosion reported for 4,6-dihydrazino-5-nitropyrimidine (25).

To determine what was happening 4,6-dihydrazino-5-nitropyrimidine was prepared as reported by Stahl. This material was then refluxed in pyridine for one hour and when isolated, 80% of the starting material was recovered. Since the original reaction mixture starting from 4,6-dimethoxy-5-nitropyrimidine contained four to one molar ratio of pyrimidine to hydrazine, a second reaction was run with 4,6-dihydrazino-5-nitropyrimidine in the presence of excess hydrazine. This time the material dissolved after 5 minutes and started coming out of solution after 20 minutes; upon isolation the product was found to be identical with that obtained starting with the treatment of 4,6-dimethoxy-5-nitropyrimidine in refluxing pyridine solution of hydrazine. It is obvious that the initial product in the dimethoxy reaction was the expected 4,6-dihydrazino-5-nitropyrimidine which then underwent further reaction in the presence of excess hydrazine to yield an isomeric product.

The only likely further reaction yielding an isomeric product could be a condensation between a hydrazino group and the nitro group to give 6-hydrazino-7-hydroxy-8-azapurine-mono-hydrate.



This type of ring closure has been known for a long time. Arndt in 1913 reported the base catalyzed cyclization of *o*-nitrophenyl guanidine to form 3-amino-1,2,4-benzotriazine-1-oxide (1). Similar cyclizations have been reported (2); for example, cyclization of 2,4-dinitrophenylhydrazine has been studied which closely resembles this reaction (29).



Thus Krackov in 1962 postulated a triazolopyrimidine 1-oxide structure for the product from the reaction of methylhydrazine and 4,6-dimethoxy-5-nitropyrimidine. Stahl in 1968 identified the product as being 4-hydrazino-6-hydroxypyrimidine. We have now explained the reaction and have synthesized the first example of a

hydroxypyrimidotriazole.

In these studies, methylation of the solvent (alcohols and pyridine) appears to be the first step in the reaction. To determine if such is the case, the reaction of methylhydrazine with 4, 6-dimethoxy-5-nitropyrimidine was attempted using a benzene medium. Normally one would have predicted the product to be either 4-hydrazino-6-methoxypyrimidine, 4-(1-methylhydrazino)-6-methoxy-5-nitropyrimidine, or 4, 6-di(1-methylhydrazino)-5-nitropyrimidine. When the reaction was run, evolution of methyl nitrite was detected by use of starch-iodide test paper. After one hour of reflux and cooling, a black oil was present at the bottom of the round bottom flask; this oil could not be crystallized. The solvent from the reaction was separated from the oil and then removed by vacuum distillation. This left a residue which when washed with cold ethanol gave a yellow powder. An infrared spectrum of this material gave sharp bands. When the material was recrystallized from a mixture of ethanol and water and the infrared spectrum of this material was compared to that of the ethanol washed material, it was noted that only a few bands were absent for the recrystallized product. Although the product was not characterized, elemental analysis indicated that the material did not correspond to any of the expected products.

It was expected that the reaction of a benzene solution of 4, 6-dimethoxy-5-nitropyrimidine with methylhydrazine would not give

4-hydrazino-6-hydroxypyrimidine, but possibly 4-hydrazino-6-methoxypyrimidine since the solvent could not be methylated under these reaction conditions. However using 4-hydroxy-6-methoxy-5-nitropyrimidine this initial methylation step should not be necessary. Thus if the proposed mechanism was valid this reaction should follow the same course as it did in a pyridine medium. When this compound was reacted with methylhydrazine in benzene medium, methyl nitrite evolution was again detected; moreover a product precipitated during the reflux period. This material proved to be the predicted 4-hydrazino-6-hydroxypyrimidine in 50.8% yield.

Another compound investigated for its behavior with methylhydrazine was 4-chloro-6-hydroxy-5-nitropyrimidine. The chloro group is a better leaving group and also is less basic than the methoxy group. Because of this difference in basicity one would not expect 4-hydrazino-6-hydroxypyrimidine to be formed in a reaction with methylhydrazine. Since the chloropyrimidine reacts with pyridine, ethanol was used as the solvent for the reaction with methylhydrazine. An ethanol solution of methylhydrazine was added to 4-chloro-6-hydroxy-5-nitropyrimidine in ethanol. After one hour of reflux the reaction mixture was cooled. Isolation of the product gave a material that gave a carbon-hydrogen analysis that suggested that the compound was 4-hydroxy-6-(1-methylhydrazino)-5-nitropyrimidine. The nitrogen analysis gave a value that was 0.6% low for the above compound,



but low nitrogen values are very common with these type of compounds (27, 36). Stahl found that the nitrogen analysis for 4-hydrazino-6-hydroxypyrimidine was consistently 0.7% low.

Out of curiosity, the behavior of 4,6-dihydroxy-5-nitropyrimidine was investigated with respect to its reactions with hydrazine and methylhydrazine. In each case 0.01 moles of the pyrimidine in 50 ml of pyridine was heated with 0.04 moles of the hydrazine. The mixtures were refluxed for 30 minutes. With hydrazine a product was obtained which gave carbon-hydrogen and nitrogen analysis which indicated that the compound may have been 4-hydrazino-6-hydroxy-5-nitropyrimidine monohydrate.

With methylhydrazine the recrystallized product gave a different infrared spectrum than the initial product direct from the reaction indicating another change in the process of recrystallization. The initial product, direct from the reaction, gave an elemental analysis which was consistent with that of 4-hydroxy-6-(1-methylhydrazino)-5-nitropyrimidine monohydrate.

During the course of this study attempts were made to synthesize 4,6-dibenzyloxy-5-nitropyrimidine and 4,6-dimethoxy-5-nitrosopyrimidine. Obviously it would have been interesting to see how these compounds would behave when reacted with methylhydrazine in pyridine. In the case of the nitroso compound, 4,6-dihydroxy-5-nitrosopyrimidine would have to be synthesized. It had been

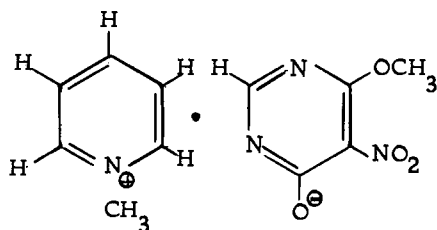
reported that 4, 6-dihydroxypyrimidine does nitrosate but the evidence given was a color change and not the isolation of the nitroso product (28). Several methods for nitrosation of pyrimidines (14, 30, 35) were attempted in this laboratory but in each case the product was not 4, 6-dihydroxy-5-nitrosopyrimidine.

The preparation of the dibenzyloxy compound was attempted using both the dichloro and the dimethoxy compounds as starting materials. With the dichloro derivative a very exothermic reaction occurred which did not yield the desired product and with the dimethoxy derivative no 4, 6-dibenzyloxy-5-nitropyrimidine was ever detected.

In summary, the work reported herein indicates that the first stage of the reaction of 4, 6-dimethoxy-5-nitropyrimidine in the presence of pyridine and methylhydrazine involves the methylation of the solvent for example, pyridine.

The demethylated 4, 6-dimethoxy-5-nitropyrimidine then reacts with the methylpyridinium ion to form two non-interconvertible salts, one which is soluble and the second which is insoluble in pyridine.

The soluble methylpyridinium salt is the precursor of





Support for this mechanism stems from the following considerations:

- (1) Isolation and characterization of the methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine.
- (2) Synthesis of the methylpyridinium salt of 4-hydroxy-6-methoxy-5-nitropyrimidine and recovery of 4-hydroxy-6-methoxy-5-nitropyrimidine by acid hydrolysis.
- (3) Detection of by-products methyl nitrite and methanol in the reaction mixture.
- (4) Behavior of 4-hydroxy-6-methoxy-5-nitropyrimidine in the presence of methylhydrazine which yields 4-hydrazino-6-hydroxypyrimidine both in pyridine as well as benzene solvent.
- (5) The failure of 4-chloro-6-hydroxy-5-nitropyrimidine to behave in the same manner as 4-hydroxy-6-methoxy-5-nitropyrimidine in the presence of methyl hydrazine and ethanol.
- (6) The work of Kauffmann which predicts the presence of hydrazide ions in basic solution of hydrazine which are essential for this mechanism to proceed.

## EXPERIMENTAL

All melting points were taken on a Fischer Johns melting point apparatus and are uncorrected. The infrared spectra with the exception of the methyl nitrite spectra were obtained with a Beckman Model IR-8 spectrophotometer with the samples in the form of potassium bromide pellets. The methyl nitrite spectra were obtained through the use of a Beckman Model IR-7 spectrophotometer using a gas cell with sodium chloride windows. The nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer. An external standard of 10% tetramethylsilane in deuteriochloroform was used for the samples run in deuterium oxide solutions. The carbon-hydrogen analyses were obtained through the use of a Coleman Model 33 carbon-hydrogen analyzer. A Coleman Model 29 nitrogen analyzer was used to obtain the nitrogen analyses.

4, 6-Diethoxy-5-Nitropyrimidine

A solution consisting of sodium ethoxide (4.6 g sodium (0.2 mole) in 100 ml ethanol) was added to 19.4 g (0.1 mole) 4, 6-dichloro-5-nitropyrimidine in 160 ml absolute ethanol. The sodium ethoxide solution was added slowly so as to keep the temperature between 28-32°C. After addition of the sodium ethoxide, the mixture was stirred two hours and then poured over ice. The precipitate was filtered, dried, and recrystallized from petroleum ether. Fifteen and

five-tenths g (73% yield) of long needle like crystals, m. p. 62-63°C, 61.5-62°C (8), were obtained.

Anal calc'd for  $C_8H_{11}N_3O_4$ : C, 45.1; H, 5.2

Found: C, 45.0; H, 5.3

#### 4, 6-Diisopropoxy-5-Nitropyrimidine

To a cold solution of sodium isopropoxide prepared by addition of 1.84 g (0.08 mole) of sodium to 75 ml isopropyl alcohol was added 7.40 g (0.04 mole) of 4, 6-dimethoxy-5-nitropyrimidine. The solution was stirred while allowing it to warm to room temperature and was then stirred for an additional three hours at room temperature. The solution was poured onto ice and filtered yielding 5.3 g (55%) of compound, m. p. 42-43°C. Attempts at recrystallization from water resulted in oiling out of the product. For this reason the compound was dissolved in ethanol and precipitated out with cold water. Analysis on the crude product and purified product gave the same results.

Anal. calc'd for  $C_{10}H_{15}N_3O_4$ : C, 49.8; H, 6.2; N, 17.4

Found: C, 49.6; H, 6.2; N, 17.2

#### 4-Chloro-6-Hydroxy-5-Nitropyrimidine

To 75 g (0.39 mole) of finely ground 4, 6-dichloro-5-nitropyrimidine suspended in 450 ml water was added 82.5 g (0.78

mole) sodium carbonate. The suspension was stirred with a mechanical stirrer for 24 hours at room temperature. The sodium salt was then removed by filtration and washed with ethyl ether. The salt was then suspended in a minimum amount of ice water and the suspension was carefully acidified with concentrated hydrochloric acid to the acid range of Congo Red. The precipitate was removed, washed with a small amount of ice water, and dried in a desiccator over phosphorus pentoxide; yield 41.5 g (61%) of the pale yellow product, m. p. 199-200°C (dec), m. p. 198-199°C (dec) (24).

Anal. calc'd for  $C_4H_2ClN_3O_3$ : C, 27.4; H, 1.4; N, 23.9

Found: C, 27.3; H, 1.5; N, 23.8

#### 4-Hydroxy-6-(1-Methylhydrazino)-5-Nitropyrimidine

A solution consisting of 1.84 ml (0.04 mole) of methylhydrazine in 5 ml of absolute ethanol was added dropwise to 1.76 g (0.01 mole) of 4-chloro-6-hydroxy-5-nitropyrimidine in 50 ml of absolute ethanol. After addition of the ethanolic methylhydrazine, the mixture was refluxed for one hour. The reaction mixture was cooled, filtered and the product washed with cold ethanol. The product 0.84 g (45.4% yield) decomposed between 168-172°C.

Anal calc'd for  $C_5H_7N_5O_3$ : C, 32.4; H, 3.8; N, 37.8

Found: C, 32.5; H, 4.0; N, 37.2

6-Hydrazino-7-Hydroxy-8-Azapurine

A. To 1.85 g 4,6-dimethoxy-5-nitropyrimidine in 50 ml of reagent pyridine was added 1.28 ml (0.04 mole) of 95% anhydrous hydrazine. The mixture was refluxed for one hour. After five minutes the initial precipitate dissolved and later reprecipitated during the remainder of the reflux period. The mixture was cooled, filtered, and the precipitate was washed with cold methanol. A 59.0% yield of the compound, 1.09 g, was obtained, m. p. 235-240°C, (dec.).

Anal calc'd for  $C_4H_7N_7O_2$ :            C, 25.9; H, 3.8; N, 53.0

Found:                                    C, 25.8; H, 3.7; N, 52.9

B. To 0.20 g (0.00108 mole) 4,6-dihydrazino-5-nitropyrimidine in 5.4 ml reagent pyridine was added 0.07 ml (0.00216 mole) 95% anhydrous hydrazine. The mixture was refluxed for one hour. After five minutes the 4,6-dihydrazino-5-nitropyrimidine dissolved and the product precipitated out during the remainder of the reflux period. The product was isolated as described above, yielding 0.094 g (47.0%). The infrared spectra of the product obtained by both methods were identical and were different than the infrared spectrum of 4,6-dihydrazino-5-nitropyrimidine.

4-Hydroxy-6-Methoxy-5-Nitropyrimidine

A solution of 1.85 g (0.01 moles) of 4,6-dimethoxy-5-



nitropyrimidine in 50 ml of pyridine was refluxed for 30 minutes. After filtration of the insoluble salt (the methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine) 1.03 g (38.8%), the pyridine was removed by vacuum distillation. The resulting dark oil was dissolved in 15 ml of cold water and acidified with glacial acetic acid. The light yellow precipitate was isolated by filtration, washed with cold water, and dried; yield 0.47 g, (27.4% yield based on the 4,6-dimethoxy-5-nitropyrimidine not accounted for by the insoluble salt), m. p. 242-243°C. An infrared spectrum of the material was identical to the infrared spectrum of an authentic sample of 4-hydroxy-6-methoxy-5-nitropyrimidine. The two compounds accounted for 66.2% of the starting material.

Anal calc'd for  $C_5H_5N_3O_4$ : C, 35.1; H, 2.9

Found: C, 35.0; H, 2.9

#### 4-Hydrazino-6-Hydroxy-5-Nitropyrimidine Monohydrate

To a mixture of 1.57 g (0.01 mole) of 4,6-dihydroxy-5-nitropyrimidine were added 1.28 ml (0.04 mole) of 95% anhydrous hydrazine. An exothermic reaction occurred. The mixture was then refluxed for 30 minutes. After the reaction mixture was cooled, it was filtered yielding 1.45 g of product, m. p. (dec.) 210-212°C. A portion was recrystallized from ethanol/water. The product direct from the reaction and the recrystallized produce gave identical

analysis. The analysis gave an empirical formula of  $C_4H_7N_5O_4$  which corresponds to 4-hydrazino-6-hydroxy-5-nitropyrimidine monohydrate.

Anal cal'd for  $C_4H_7N_5O_4$ :           C, 25.4; H, 3.7; N, 37.0

Found:                                   C, 25.3; H, 3.7; N, 36.8

4-Hydroxy-6-(1-Methylhydrazino)-5-Nitropyrimidine Monohydrate

To a mixture of 1.57 g (0.01 mole) of 4,6-dihydroxy-5-nitropyrimidine in 50 ml of pyridine was added 1.84 ml (0.04 mole) of methylhydrazine. An exothermic reaction ensued. The mixture was refluxed for 30 minutes. The reaction mixture was cooled, filtered, and the product washed with cold methanol. The product, 1.77 g (87.2% yield) decomposed between 205-210°C. The analysis of the product direct from the reaction gave an empirical formula of  $C_5H_9N_5O_4$  which corresponds to 4-hydroxy-6-(1-methylhydrazino)-5-nitropyrimidine monohydrate. The product recrystallized from ethanol and water gave a different analysis and a different infrared spectrum.

Anal calc'd for  $C_5H_9N_5O_4$ :           C, 29.6; H, 4.4; N, 34.5

Found:                                   C, 29.4; H, 4.2; N, 34.3

Reaction of 5-Amino-4,6-Dimethoxypyrimidine  
With Methylhydrazine in Pyridine

To 1.43 g (0.01 mole) of 4,6-dimethoxy-5-aminopyrimidine in 50 ml of pyridine was added 1.84 ml (0.04 mole) of methylhydrazine. The

solution was heated to reflux for one hour. The reaction mixture turned very dark and no precipitate occurred on cooling. The pyridine was removed by vacuum distillation and a black tar was obtained. No starting material was recovered.

Reaction of 4, 6-Diisopropoxy-5-Nitropyrimidine  
With Methylhydrazine

To a refluxing solution of 2.41 g (0.01 mole) of 4, 6-diisopropoxy-5-nitropyrimidine in 50 ml of pyridine was added 1.84 ml (0.04 mole) of methylhydrazine. The mixture was refluxed for one hour. Upon cooling no precipitation occurred from the dark solution. The pyridine was removed by vacuum distillation and the black tar was dissolved in ethanol. Addition of water to the ethanol solution precipitated 0.66 g (27.5% recovery) of the original 4, 6-diisopropoxy-5-nitropyrimidine. This material was identical to an authentic sample of 4, 6-diisopropoxy-5-nitropyrimidine.

Reaction of 1, 2-Dimethylhydrazine with  
4, 6-Dimethoxy-5-Nitropyrimidine

To 1.85 g (0.01 mole) of 4, 6-dimethoxy-5-nitropyrimidine in 50 ml of pyridine was added 2.90 ml (0.04 mole) of 1, 2-dimethylhydrazine. The solution was refluxed for 30 minutes during which time the solution turned very dark. After cooling the solution, the pyridine was removed by vacuum distillation leaving a black tar.

Twenty-six-hundredths g (14%) of the original 4,6-dimethoxy-5-nitropyrimidine was recovered. This material was identical to an authentic sample of 4,6-dimethoxy-5-nitropyrimidine. No other isolable product could be recovered from the tar.

Reaction of 4,6-Dimethoxy-5-Nitropyrimidine  
with 1,1-Dimethylhydrazine

Five and thirty-two-hundredths g (0.04 mole) of 1,1-dimethylhydrazine dihydrochloride in 10 ml of ethanol was treated with sodium ethoxide resulting from the reaction of 1.84 g (0.08 mole) of sodium with 15 ml ethanol. The solution of the hydrazine free base in ethanol was filtered and added to 1.85 g (0.01 mole) of 4,6-dimethoxy-5-nitropyrimidine in 50 ml pyridine. The reaction mixture was heated under reflux for 30 minutes and cooled. No precipitate occurred. Upon removal of the pyridine only a black tar remained. No starting material was recovered nor could any other product be isolated.

The Preparation of the Methylpyridinium Salt of  
4-Hydroxy-6-Methoxy-5-Nitropyrimidine and  
Its Reactions with Methylhydrazine

To 1.71 g (0.01 mole) of 4-hydroxy-6-methoxy-5-nitropyrimidine in 10 ml of methanol was added 0.54 g (0.01 mole) of sodium methoxide. The suspension was stirred for five minutes to insure that all the hydroxypyrimidine had been converted to its sodium salt; the

methanol was then removed by evaporation under reduced pressure. The sodium salt was then added to 50 ml of reagent pyridine that had previously been methylated by treatment with 0.62 ml (0.01 mole) of methyl iodide. This gave a pyridine solution containing 0.01 mole of methyl pyridinium salt of 4-methoxy-5-nitro-6-hydroxypyrimidine.

One-hundredth mole of the methylpyridinium salt of 4-hydroxy-6-methoxy-5-nitropyrimidine was prepared as described. The mixture was refluxed for one hour, cooled and filtered. The precipitate, 0.31 g, was found by infrared analysis to be different from the insoluble methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxypyrimidine obtained in the original experiments with 4,6-dimethoxy-5-nitropyrimidine and pyridine. This material was dissolved in water and the solution was acidified with glacial acetic acid which precipitated 0.19 g of 4-hydroxy-6-methoxy-5-nitropyrimidine. The mother liquor was distilled in vacuo to remove the pyridine. The residue was dissolved in water and acidified with glacial acetic acid which again precipitated 0.65 g of 4-hydroxy-6-methoxy-5-nitropyrimidine.

#### Methylhydrazine Reactions

(1) To this mixture was added 1.84 ml (0.04 mole) of methylhydrazine. The mixture was refluxed for one hour and the product isolated as described before. The 4-hydrazino-6-hydroxypyrimidine

(as determined by infrared analysis) was obtained in 72.7% yield (0.92 g).

(2) The preparation of the salt was repeated and the mixture refluxed for one hour prior to the addition of 1.84 ml (0.04 mole) of methylhydrazine followed by a second one hour reflux period. The mixture was then cooled, filtered, and the precipitate washed with cold water to remove the sodium iodide. The product, 0.46 g, (36.5% yield), was determined to be 4-hydrazino-6-hydroxypyrimidine by comparison with an authentic sample by infrared analysis.

#### 4-Hydrazino-6-Hydroxypyrimidine

A. One and seven-tenths g (0.01 mole) of 4-hydroxy-6-methoxy-5-nitropyrimidine (23) was dissolved in 50 ml of absolute ethanol. To this solution was added 1.84 ml (0.04 mole) of methylhydrazine. The solution was refluxed for one hour; within five minutes of the start of reflux a precipitate was observed. After cooling in an ice bath the reaction mixture was filtered; the precipitate was washed with cold methanol, yielding 0.71 g (56%) of cream colored product, m. p. (dec.) 245-255°C. An infrared spectrum of the compound was identical to that obtained from an authentic sample.

Anal calc'd for  $C_4H_6N_4O$ : C, 38.1; H, 4.8; N, 44.4

Found: C, 38.1; H, 4.9; N, 44.0

B. One and seventy-one hundredths g (0.01 mole) of 4-hydroxy-6-methoxy-5-nitropyrimidine in refluxing pyridine was treated with 1.84 ml (0.04 mole) of methylhydrazine. The mixture was refluxed for 30 minutes, cooled and filtered. The product was washed with cold methanol and dried. The yield was 1.10 g (87%), m. p. (dec.) 235-255°C. The product was shown by infrared spectral analysis to be identical to the product obtained from the similar reaction with 4,6-dimethoxy-5-nitropyrimidine.

Anal calc'd for  $C_4H_6N_4O$ : C, 38.1; H, 4.8; N, 44.4

Found: C, 38.0; H, 4.7; N, 44.1

C. To a refluxing solution of 2.13 g (0.01 mole) 4,6-diethoxy-5-nitropyrimidine in 50 ml of pyridine was added 1.84 ml (0.04 mole) of methylhydrazine. The mixture was refluxed for one hour, cooled, and filtered. The product was washed with cold methanol and dried. The yield was 0.259 g (20.6%), m. p. 235-255°C (with dec.). The product was shown by infrared spectral analysis to be identical to the product obtained from the similar reaction with 4,6-dimethoxy-5-nitropyrimidine.

D. To a refluxing solution of 0.925 g (0.0073 mole) 4-hydroxy-6-methoxy-5-nitropyrimidine in 50 ml n-butanol was added 1.34 ml (0.0292 mole) of methylhydrazine. The mixture was refluxed for 30 minutes, cooled, and filtered. The product was washed with cold

methanol and dried. The yield was 0.453 g (66.5%), m. p. (dec.) 235-255°C. The product was shown to be identical with an authentic sample of 4-hydrazino-6-hydroxypyrimidine.

E. To 1.71 g (0.01 mole) of 4-hydroxy-6-methoxy-5-nitropyrimidine in 50 ml of dry benzene was added 1.84 ml (0.04 mole) of methylhydrazine. The mixture was refluxed for 30 minutes. The product was isolated by filtration, washed with cold methanol and dried; yield 0.64 g (50.8%), m. p. (dec.) 235-255°C. An infrared spectrum of the compound was identical to that obtained for an authentic sample of 4-hydrazino-6-hydroxypyrimidine.

The Methylpyridinium Salt of  
4, 6-Dihydroxy-5-Nitropyrimidine

To 50 ml of refluxing pyridine was added 1.71 g (0.01 mole) of 4-hydroxy-6-methoxy-5-nitropyrimidine. After one hour two immiscible layers separated which were then cooled in an ice bath. Upon stirring the lower layer crystallized, yielding light brown crystals. The mixture was separated by filtration and the crystalline product was washed with fresh pyridine, yielding 1.62 g (65%) of the light brown salt, m. p. 147-148°C.

Anal calc'd for  $C_{10}H_{10}N_4O_4$ : C, 48.0; H, 4.0; N, 22.4

Found: C, 47.8; H, 3.9; N, 22.2

One gram of the methylpyridinium salt of 4, 6-dihydroxy-5-



nitropyrimidine in 15 ml cold water was acidified with dilute hydrochloric acid until the solution was acidic to litmus paper, whereupon a white precipitate formed. Isolation of the precipitate yielded 0.54 g (86.3%) which was identified from infrared spectra and C, H, and N analysis as 4,6-dihydroxy-5-nitropyrimidine, m. p. > 300°C.

Anal calc'd for  $C_4H_3N_3O_4$ : C, 30.6; H, 1.9; N, 26.8

Found: C, 30.5; H, 1.9; N, 26.7

To the mother liquor from the preparation of the methylpyridinium salt of 4,6-dihydroxy-5-nitropyrimidine was added 0.64 ml (0.04 mole) of methylhydrazine. The solution was refluxed for 30 minutes and isolation yielded 0.076 g (17.3% based on the 4-hydroxy-6-methoxy-5-nitropyrimidine not accounted for by the salt) of 4-hydrazino-6-hydroxypyrimidine as judged by comparison of infrared spectra.

Reaction of the Methylpyridinium Salt of  
4,6-Dihydroxy-5-Nitropyrimidine  
With Methylhydrazine in Pyridine

To 2.50 g (0.01 mole) of the methylpyridinium salt of 4,6-dihydroxy-5-nitropyrimidine in 50 ml of pyridine was added 1.84 ml (0.04 mole) of methylhydrazine. The mixture was heated under reflux for one hour. The solution was cooled with stirring and the resulting precipitate removed by filtration and washed with pyridine. This precipitate consisted entirely of starting material which was recovered

in 59% yield (1.47 g). There was no evidence indicating any formation of 4-hydrazino-6-hydroxypyrimidine.

Volatile By-products Evolved from Reaction of  
Methylhydrazine, 4, 6-Dimethoxy-5-Nitropyrimidine  
and Pyridine and Butanol Solvents

A. Amines

To 1.85 g (0.01 mole) of 4, 6-dimethoxy-5-nitropyrimidine in 50 ml of pyridine heated under reflux was added 1.84 ml (0.04 mole) of methylhydrazine. The system was flushed with nitrogen gas. The volatiles from the reaction system were first passed through a salt-ice cold trap and then into 100 ml of standard 0.1 Normal hydrochloric acid. The acid was back titrated with standard 0.1 Normal sodium hydroxide; 33.60 ml of sodium hydroxide were required. This accounts for 0.00664 moles of amine vapors. The yield of 4-hydrazino-6-hydroxypyrimidine was 0.708 g (56.2%).

B. Methyl Nitrite

(1) The 4, 6-dimethoxy-5-nitropyrimidine-methylhydrazine reaction in pyridine was carried out as described previously. The volatiles from the reaction were passed through a double U-tube. In the first U-tube was placed a strip of starch-iodide test paper wetted with distilled water, in the second was placed a strip of starch-iodide test paper wetted with dilute hydrochloric acid. During the

reaction the first strip of test paper remained white while the second strip started turning dark purple after about five minutes of reflux (simultaneous with the first appearance of precipitation in the reaction vessel).

(2) A reaction was carried out with methylhydrazine and 4,6-dimethoxy-5-nitropyrimidine in pyridine using the apparatus illustrated in Figure 4.

The system was first flushed with nitrogen gas and then the reactants were added. The usual scale of 0.01 mole of 4,6-dimethoxy-5-nitropyrimidine was used. The purpose of the calcium chloride tube was to remove amine vapors, the double U-tube cooled in the salt-ice bath was to insure that no pyridine carried over into the Schwartz tube which was used to trap the very low boiling volatiles from the reaction. The soda-lime tube and drierite tube were used to prevent carbon dioxide or water from condensing into the Schwartz tube. After the reflux period the Schwartz tube was sealed off and attached to a vacuum line. The material in the tube was then transferred by normal techniques to a gas infrared cell. The spectrum was then obtained using a Beckman IR-7 spectrophotometer. This spectrum accounted for the presence of methyl nitrite as well as another extremely volatile compound, possibly cyanic acid.

### C. Methanol and Methyl-n-Butyl Ether

To 1.85 g (0.01 mole) of 4,6-dimethoxy-5-nitropyrimidine in 100 ml n-butanol was added 1.84 ml (0.04 mole) of methylhydrazine. The solution was refluxed for three hours and then cooled in an ice bath. The 4-hydrazino-6-hydroxypyrimidine, 0.24 g (19% yield) was removed by filtration. The mother liquor was analyzed by gas chromatographic techniques which revealed the presence of methanol, methyl n-butyl ether, methylhydrazine and n-butanol.

#### Reaction of 4,6-Dimethoxy-5-Nitropyrimidine With Methylhydrazine in Benzene Solvent

To 1.85 g (0.01 mole) of 4,6-dimethoxy-5-nitropyrimidine in 50 ml of anhydrous benzene was added 1.84 ml (0.04 mole) of methylhydrazine. Addition of the methylhydrazine initiated a very slow evolution of vapor from the benzene solution; methyl nitrite was detected in these vapors by use of starch-iodide test paper. The solution was refluxed for one hour, after 30 minutes of the reflux period, a small amount of dark oil formed. Upon cooling the reaction mixture the benzene solution was removed from the insoluble oil. Attempts to crystallize the oil failed. The benzene was then removed by vacuum distillation and the residue was washed with cold ethanol. The residue, 0.48 g, m. p. 177-178°C, as judged by elemental analysis was not one of the predicted products; 4-hydrazino-6-

methoxypyrimidine (I), 4,6-di-(1-methylhydrazino)-5-nitropyrimidine (II), or 4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine (III).

Anal calc'd for  $C_5H_8N_4O$  (I): C, 42.9; H, 5.7; N, 40.0

$C_6H_{11}N_7O_2$  (II): C, 33.8; H, 5.2; N, 46.0

$C_6H_9N_5O_3$  (III): C, 36.2; H, 4.5; N, 35.2

Found crude: C, 36.5; H, 4.84; N, 32.2

Recrystallized: C, 37.1; H, 4.47; N, 32.0

This analysis is consistent with that of a mixture containing three parts of 4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine to one part of starting material. This mixture gives an analysis of C, 39.9; H, 4.3; N, 32.1. However, thin layer chromatography indicated that there was no 4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine or 4,6-di-(1-methylhydrazino)-5-nitropyrimidine present in the reaction product although it did show the presence (10-20%) of unreacted starting material.

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