AN ABSTRACT OF THE THESIS OF

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(Name of student) (Degree)
in CHEMISTRY presented on Sept 15, 1976
(Major) (Date)

Title: THE REACTION OF METHYLHYDRAZINE WITH VARIOUS
2-SUBSTITUTED 4, 6-DIMETHOXY-5-NITROPYRIMIDINES

Abstract approved: Bert E. Christensen

The reaction between methylhydrazine and various 2-substituted
4, 6-dimethoxy-5-nitropyrimidines was investigated. It was discov-
ered that when the 2-substituent is a methoxyl or dimethylamino group,
the reaction, whether in pyridine or butanol solvent, proceeds in a
a straightforward manner to give the 4, 6-di(1-methylhydrazino)-5-
nitropyrimidines. However when an acetamido group was at the
2-position, the reaction in pyridine with methylhydrazine yielded 2-
amino-4-hydrazino-6-hydroxypyrimidines. This result was analogous
to the anomalous reactions that Stahl investigated. Stahl found that
when there was a hydrogen atom, methyl group or phenyl group at the
2 position the reaction proceeded to yield the correspondingly 2-sub-
stituted 4-hydrazino-6-hydroxypyrimidines.
The extremely good electron donating character of the methoxyl and dimethylamino groups explains the behavior of the 2-methoxy-and-2-dimethylamino-4,6-dimethoxy-5-nitropyrimidines towards methylhydrazine. Considering the transition state necessary for the "anomalous" 1,6-methyl shift to occur, as elucidated by Lehmkuhl, it is seen that a negative charge is developed on the ring. The electron rich character of the methoxyl and dimethylamino groups would tend to destabilize the transition state and thus allow insufficient time for the methyl migration from the hydrazino to the nitro group to occur.

Among some related studies that were done, there was discovered a threefold methylation reaction. 2-Thio-4,6-dihydroxy-pyrimidine was reacted with excess dimethylsulfate in aqueous
sodium hydroxide to yield 1, 6-dihydro-4-methoxy-1-methyl-2-
methylthio-6-oxopyrimidine.

A rearrangement occurred while nitrating 2-dimethylamino-
4, 6-dimethoxypyrimidine in sulfuric acid with fuming red nitric acid
to give 1, 6-dihydro-2-dimethylamino-4-methoxy-1-methyl-5-nitro-
6-oxopyrimidine. This rearrangement was not observed when acetic
acid was used as solvent for the nitration which yielded 2-dimethyl-
amino-4, 6-dimethoxy-5-nitropyrimidine in a straightforward manner.
The Reaction of Methylhydrazine with Various 2-Substituted 4, 6-Dimethoxy-5-Nitropyrimidines

by

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A THESIS
submitted to
Oregon State University

in partial fulfillment of the requirements for the degree of

Master of Science

June 1971
APPROVED:

Redacted for Privacy

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Date thesis is presented \textit{Sept. 18, 1970}

Typed by Opal Grossnicklaus for Björn Erik Landberg
ACKNOWLEDGMENT

I wish to extend my thanks to Dr. Bert E. Christensen for his aid in preparing this thesis. Dr. Frank Lehmkuhl is to be thanked for some of the n.m.r. and analytical data and I would also like to express my appreciation to Miss Sue Hutchinson and Miss Nancy Dahl for many hours of typing.

Lastly I wish to thank the Chemistry Department, Oregon State University, for support during my graduate studies.
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THEREACTIONOF METHYLHYDRAZINEWITHVARIOUS
2-SUBSTITUTED 4, 6-DIMETHOXY-5-NITROPYRIMIDINES

INTRODUCTION

This laboratory has long been investigating synthetic procedures
for aza homologs of naturally occurring compounds. Krackov (12)
was seeking a synthetic route for the preparation of pyrimido[5, 4-3]-
aza-triazine (I), (an aza homolog of pteridine).

One route that was investigated utilized 4-hydrazino-5-nitro-
pyrimidine intermediates. Formylation of the hydrazino group, ring
closure and dehydrogenation should yield the aza pteridine deriv-
atives.

The preparation of hydrazino-nitropyrimidines seemed straight-
forward. A readily available compound was 4, 6-dichloro-5-nitro-
pyrimidine (II) which was known to be highly reactive toward nucleo-
philic reagents. However, reaction of II with hydrazine in ethanol
was extremely vigorous and produced mainly intractable tars and
only a small amount of the desired product. A less reactive sub-
strate was desired, so the 4, 6 dichloro-5-nitropyrimidine was con-
verted to 4, 6-dimethoxy-5-nitropyrimidine (IV) which in turn gave
upon hydrazinolysis in ethanol a good yield of the hydrazine derivative (III).

Krackov, as a sidelight, reacted the methoxy compound (IV) with methylhydrazine, expecting a straightforward reaction to take place to give 4, 6-di(1-methylhydrazino)-5-nitropyrimidine (V). Instead, he recovered most of his starting material and a small amount of a new compound. When butanol was used as a solvent instead of ethanol, the yield of product was increased. This product melted with decomposition between 240-260° C. The elemental analysis, however, did not correspond to that of the predicted product, 4, 6-di(1-methylhydrazino)-5-nitropyrimidine (V) but to a compound which differed from V by the loss of a molecule of water. It was hypothesized that V was a reaction intermediate and that the product resulted from dehydrative ring closure to a compound such as 3-methyl-7-(1-methylhydrazino)-3H-v-triazolo-[4, 5-8] pyrimidine-1-oxide (VI). However, a nitrogen analysis disproved this structure.

Upon surveying the literature for other works pertaining to reactions of nitropyrimidine with hydrazines, only one study by Wiley, Lanet, and Hussing (22) was found. They prepared 2, 4-dihydrazino-5-nitropyrimidine from the corresponding dichloro compound. They also discovered an unprecedented selective displacement of the 4-dimethylamino substituent in 2, 4-bis (dimethylamino)-5-nitropyrimidine by hydrazine, to give 2-dimethylamino-4-hydrazino-5-nitropyrimidine.
Figure 1. Hydrazinolysis of 5-nitopyrimidines as reported by Krackov.
But interestingly, hydrazine did not displace the 4-dimethylamino substituent in 2-hydrazino-4-dimethylamino-5-nitropyrimidine.

Stahl (19) set out to elucidate the structure of the compound (VI) that Krackov had discovered. The compound was finally identified as 4-hydrazino-6-hydroxypyrimidine by spectra, by direct synthesis of VI from 4-chloro-6-hydroxypyrimidine and by conversion of VI to the known 4-amino-6-hydroxypyrimidine using Raney nickel.

![Structure of VI](image)

The product was obviously a result of a complex mechanism. The first stage was thought to be a methyl migration to an intermediate which was reactive to the methylhydrazine. This much was shown when the methoxypyrimidine (IV) was refluxed in pyridine alone, as a result of which, two products were obtained. One was soluble in cold pyridine and this yielded 4-hydrazino-6-hydroxypyrimidine (VI) when treated with methylhydrazine at room temperature. However, the insoluble product was tentatively identified as an N-methylpyridinium-N-methylpyrimidinate salt which was unreactive toward methylhydrazine.

Stahl reasoned that the 4,6-dimethoxy-5-nitropyrimidine did not react directly with the methylhydrazine via nucleophilic substitution, because 4 and 6 positions on the ring were sterically shielded
by the methoxyl groups and that the nitro group was forced out of the plane causing an increase in electrophilicity at the 4 and 6 positions.

Lehmkuhl (13) proposed the mechanism of the anomalous reaction between methylhydrazine and 4, 6-dimethoxypyrimidine (see Figure 2). The evidence was based on the isolation of the methylpyridinium salts of 1, 6-dihydro-4-methoxy-5-nitro-6-oxopyrimidine, detection of methyl nitrite and methanol as reaction products, the reaction of 4-hydroxy-6-methoxy-5-nitropyrimidine with methylhydrazine, the fact that 4-chloro-6-hydroxy-5-nitropyrimidine did not react in the same way as 4-hydroxy-6-methoxy-5-nitropyrimidine with methylhydrazine in ethanol and finally Kauffman's work (10) which predicts the reality of hydrazide ions in the solution which would be necessary for this mechanism to proceed.

Having established a plausible mechanism, it seemed that the only part of the ring that remains unaffected in this reaction is the 2-position. The fact that the reaction proceeds when there are methyl or phenyl substituents in the 2-positions, had been established by Stahl. It seemed that these substituents have little effect on the reaction. However, is this also true for other 2-substituents? If not, the problem would be to determine how the 2-substituent's electron donating character correlates with the compound's reactivity. This study is concerned with the effect of the 2-substituent on the
unique reaction with methylhydrazine, as well as with some other related studies of reactions with hydrazine.
Figure 2. Reaction mechanism elucidated by Lehmkuhl.
DISCUSSION

In preparing a series of different 2-substituted 4, 6-dimethoxy-5-nitropyrimidines, it was decided that the 2-acetamido, 2-methylthio, 2-amino, 2-dimethylamino, 2-thio, 2-hydroxy and 2-methoxy compounds would be logical choices for a study of the 2 substituent's effect on the hydrazinolysis of 4, 6-dimethoxy-5-nitropyrimidines. Moreover, the reagents were readily available and synthetic procedures had been developed for the condensation of diethylmalonate with the various amidines to give various 2-substituted 4, 6-dihydroxy-pyrimidines, which were the necessary starting materials (6).

Furthermore, the choice of these substituents offered a range of electron donating ability at the 2 position, with acetamido being the least electron donating group and methylthio being the best.

For practical synthetic reasons, however, not all of the desired compounds could be made. The 2-substituted 4, 6-dimethoxy-5-nitropyrimidines that were finally synthesized were the 2-acetamido, 2-methylthio, 2-dimethylamino and 2-methoxy compounds.
The first series that was investigated was the group of 2-amino-substituted pyrimidines, with the main object being to make 2-amino-4, 6-dimethoxy-5-nitropyrimidine (IVa). Diethylmalonate and guanidine hydrochloride were condensed in a methanolic solution of sodium methoxide according to the directions of Brown (6). A good yield (85% or more) of the 2-amino-4, 6-dihydroxypyrimidine (Ia) was obtained. Chlorination was effected by refluxing Ia in phosphorus oxychloride for several hours. Although Brown (6) reported only a 25% yield of product, more (35%) could be obtained by careful extraction of the powder (which results from hydrolysing the chlorination mixture), with ether. Despite the relatively low yield, the starting material is easily made on a large scale so that fair amounts of 2 amino-4, 6-dichloropyrimidine (IIa) could be obtained. An alternative route to 2 amino-4, 6-dichloropyrimidine (IIa) was the amination of trichloropyrimidine, as reported by Büttner (7). Trichloropyrimidine, obtained by chlorinating barbituric acid (7) was treated with 15% alcoholic ammonia, and the product mixture, (consisting of isomeric 2- and 4-amino dichloropyrimidines) was extracted by benzene in a Soxhelet extractor. The first method is actually preferable despite the lower yield of desired product, since fair amounts could easily be

1 The small letter designation after a Roman numeral refers to the series in which the compound belongs. Thus a refers to 2-amino- or acetamido-substituted compounds, b to 2-methylthio derivatives and c to 2-dimethylamino derivatives.
obtained and the procedure did not involve an isomeric separation. The method of Büttner utilized the extremely irritating trichloropyrimidine which was not pleasant to work with, either when isolating it from the chlorination reaction or when reacting it with ammonia; trichloropyrimidine causes severe blistering if it comes in contact with the skin.

In order to synthesize 2-amino-4,6-dimethoxypyrimidine (IIIA) it was necessary to have a sufficiently high reflux temperature for the reaction to occur (8). When the 2-amino-4,6-dichloropyrimidine (IIa) was refluxed in methanolic sodium methoxide, only monosubstitution occurred to give 2-amino-4-chloro-6-methoxyprprimidine. However, by using a xylene medium, the increased reflux temperature allowed the disubstitution to occur in a reasonable length of time.

Although the nitration of the dimethoxy compound so as to obtain the desired 2-amino-4,6-dimethoxy-5-nitropyrimidine appeared to be straightforward, this turned out not to be the case. This was attempted using both glacial acetic acid and sulfuric acid as solvents at various temperatures. Fuming red nitric acid was dripped into acetic acid solutions at 10°C. and at 25°C but only starting material was recovered in either case. Use of sulfuric acid as solvent caused considerable decomposition to occur, especially above 15°C., and the recovered material (in poor yield) contained starting material and what may have been a rearranged compound. Melting points and
infrared spectra were not consistent. But no nitration had occurred in the recovered material, as judged by the negative ferrous hydroxide tests for nitro groups (9).

In view of the failure of 2-amino-4,6-dimethoxypyrimidine to be nitrated, it was decided to try a different route to the desired nitro compound (IVa). It seemed feasible that 2-amino-4,6-dihydroxy-pyrimidine might be nitrated, giving the dihydroxy 5-nitro compound (Va). This could then be followed by chlorination of the hydroxy groups and further reaction with sodium methoxide to yield 2-amino-4,6-dimethoxy-5-nitropyrimidine. Nitration of 2-amino-4,6-dihydroxypyrimidine was reported by Büttner (7). This was effected by slowly adding the powdered dihydroxy compound (Ia) to fuming red nitric acid directly with stirring. An interesting gaseous change was observed when the 2-amino-4,6-dihydroxypyrimidine was added to the nitric acid at a too rapid rate. The brown nitrogen dioxide vapors above the solution changed in character to a yellowish billowy smoke, whereupon the vapors became incandescent, lighting the flask with a bright orange glare. More ice water was applied to the flask and the incandescence disappeared in a short time.

No procedure was reported in the literature for chlorination of the 2-amino-4,6-dihydroxy-5-nitropyrimidine (Va). Several sets of conditions were tried in an attempt to chlorinate the compound: reflux in phosphorus oxychloride, and reflux in phosphorus
oxychloride with added diethylaniline or dimethylaniline as catalyst. None of these methods yielded anything except starting material.

At this point the decision was made to change the character of the amino substituent by a blocking reaction prior to nitration. The group that was chosen was the obvious acetyl group. Upon refluxing 2-amino-4,6-dimethoxypyrimidine in acetic anhydride for two hours, a product was obtained which proved to be 2-acetamido-4,6-dimethoxypyrimidine (VIIa). This was confirmed by elemental analysis and the carbonyl group showed up well in the infrared spectrum at 5.89 μ.

Nitration of 2-acetamido-4,6-dimethoxypyrimidine (VIIa) in sulfuric acid afforded 2-acetamido-4,6-dimethoxy-5-nitropyrimidine (VIIIa) in the form of a yellow precipitate which recrystallized from ethanol to give nice yellow prisms.

Instead of hydrolysing the acetamido group at the 2 position of VIIa it was decided to leave it there and directly react the compound with methylhydrazine in pyridine according to the method that Krackov had used. Upon refluxing the 2-acetamido-4,6-dimethoxy-5-nitropyrimidine in pyridine with the addition of methylhydrazine, a small amount of light yellowish powder was obtained with a decomposition point at 325-327°C. The elemental analysis showed a carbon value of 34.0%, a hydrogen value of 5.0%, and a nitrogen value of 48.9%. An n.m.r. spectrum of a sample dissolved in sodium deuteroxide failed to show any peaks. It appeared that all the protons were
exchanging with the solvent. An infrared spectrum was not very informative. A qualitative test for nitro groups with ferrous hydroxide (9) was negative. On the basis of these data then, the compound's structure was assigned as 2-amino-4-hydrazino-6-hydroxypyrimidine (IXa).

This structure agreed well with all the data except for the nitrogen analysis which was slightly low, but this was also the case with other similar compounds being analyzed on the instrument. So the slight discrepancy was likely due to instrumental error. The calculated values for IXa ($C_4H_7N_5O$) were: C, 34.0%, H, 5.0% N, 49.5%. Thus this reaction is exactly analogous to that discovered by Krackov and elucidated by Stahl for the 2-hydrogen, 2-methyl, and 2-phenyl substituted compounds, although the yield is very poor.

In the course of devising and perfecting these procedures, some related studies were made. 2-Amino-4-chloro-6-hydroxypyrimidine (XIIa) was synthesized from the dichloro compound by refluxing it in sodium hydroxide solution (8). The possibility that the 2-amino-4-chloro-6-hydroxypyrimidine would react with hydrazine to give 2-amino-4-hydrazino-6-hydroxypyrimidine (IXa) was investigated. Thus the structure of the compound obtained from
2-amino-4, 6-dimethoxy-5-nitropyrimidine would be proven by independent synthesis. However when this reaction was run in ethanolic hydrazine, only a small amount of product was obtained. This product was not able to be purified by recrystallization and seemed to contain traces of starting material. It had a wide melting range around 200 °C. But this melting point did not agree with that for IXa synthesized from the dimethoxy-5-nitro compound (VIIa), which melted at 325-327 °C. The infrared spectra of the compounds did not correspond. Since the compound could not be obtained pure, no elemental analyses were run, but judging from the differences in melting points and spectra, the compounds obtained from VIIa and 2-amino-4-chloro-6-hydroxypyrimidine (XIIa) are not the same.

2-Acetamido-4, 6-dimethoxy-5-nitropyrimidine (VIIIa) was refluxed with methanolic methylhydrazine in order to compare its reaction with that in pyridine. Interestingly, the only reaction that occurred was between the methyl-hydrazine and the acetamido group. The acetyl substituent was removed, leaving 2-amino-4, 6-dimethoxy-5-nitro-pyrimidine (IVA). Apparently the low reflux temperature of methanol inhibited any substitution of the methoxyl groups. The presence of the free 2-amino substituent was shown in the infrared spectrum by bands at 2.90 μ, 2.95 μ, and 3.05 μ. The presence of the methoxyl group was indicated by a band at 3.36 μ. Elemental analyses corresponded with the calculated values for
Figure 3. Reaction scheme of 2-amino substituted compounds. Series a.
Figure 4. Infrared spectrum of 2-amino-4,6-dimethoxy-5-nitopyrimidine (IVa)
2-amino-4,6-dimethoxy-5-nitropyrimidine.

A further study of the behavior of 2-acetamido-4,6-dimethoxy-5-nitropyrimidine with hydrazines was desired. This compound was reacted with hydrazine in methanol, whereupon a flakey yellow precipitate formed which could not be recrystallized from ethanol or other common recrystallizing solvents.

The second series of 2-substituted pyrimidines that was investigated was the 2-thio- and 2-methylthio- substituted series. 2-Thio-4,6-dihydroxypyrimidine (Ib) (14) was easily made by condensing thiourea with diethylmalonate. Chlorination of 2-thio-4,6-dihydroxypyrimidine in phosphorus oxychloride would have been desirable, but it failed, yielding only an extremely vile-smelling yellow slime upon hydrolysis of the reaction mixture. A protecting group was sought for the 2-thio group and the choice was the methylated derivative. Methylation of 2-thio-4,6-dihydroxypyrimidine with one mole of dimethylsulfate in sodium hydroxide at room temperature yielded the desired 2-methylthio-4,6-dihydroxypyrimidine (IIb). Chlorination of the methylthio compound was effected by refluxing it in phosphorus oxychloride. The resulting 2-methylthio-4,6-dichloropyrimidine (IIIb) was recrystallized from ethanol. Chlorination of 2-methylthio-4,6-dihydroxypyrimidine with phosphorus pentachloride has been reported by Wheeler (21). However, this was not a desirable method due to its lengthy extractions and vacuum distillation procedures.
2-Methylthio-4,6-dimethoxypyrimidine (IV) was easily obtained by refluxing the corresponding dichloro derivative ((IIIb) in methanolic sodium methoxide. Elemental analysis confirmed that the dimethoxy compound had, indeed, been obtained and the infrared spectrum showed the methoxyl C-H stretching wave length of 3.36 μ.

Nitration of 2-methylthio-4,6-dimethoxy-5-nitropyrimidine with fuming red nitric acid in sulfuric acid at room temperature afforded 2-methylthio-4,6-dimethoxy-5-nitropyrimidine (Vb) which recrystallized nicely from ethanol to give fine yellow prisms. The calculated carbon and hydrogen values agreed with those found.

Unfortunately, none of the reactions in this series went in more than fair yield, and the methylation reaction and the chlorination were especially odorous. But the synthesis of 2-methylthio-4,6-dimethoxy-5-nitropyrimidine (Vb) had thus been achieved and this compound was subjected to hydrazinolysis by methylhydrazine in refluxing pyridine solvent according to the directions that Stahl and Krackov used with their compounds. That is, a four molar excess of methylhydrazine was used. Soon after the addition of the methylhydrazine, the solution turned dark and after distilling away most of the pyridine, only a murky intractable residue remained. Decomposition apparently occurred, yielding methylmercaptan. This could be detected both nasally and with lead acetate paper. The decomposition that occurred was somewhat puzzling. Normally, the methylthio group in the
2 position is quite stable to nucleophilic attack, although some examples of acid hydrolysis are cited by Brown (6).

An interesting sidelight in these studies was the reaction that was discovered when attempting to methylate 2-thio-4,6-dihydroxy-pyrimidine (Ib) with dimethyl sulfate in aqueous sodium hydroxide. In one run an excess of dimethylsulfate was used and the temperature was inadvertently allowed to rise to about 80°C. The expected product, 2-methylthio-4,6-dihydroxypyrimidine (IIb) would normally have been precipitated with acetic acid in the isolation. However, the solution was already acidic due to the insufficient base and no precipitate had formed and none formed upon addition of acetic acid to a small portion of the mixture. Addition of sodium hydroxide to the mixture, however, resulted in immediate precipitation of a fluffy white material. This precipitate was obviously not the expected compound, since that is soluble in base. Recrystallization of this unexpected product in benzene afforded fragrant white needles. The elemental analysis gave a carbon value of 45.2% and a hydrogen value of 5.37%. This analysis corresponded to the formula C₇H₁₀N₂O₂ which is the same as that of 2-methylthio-4,6-dimethoxyprimididine (IVb). But its melting point (108-110°C) was far different from that of 2-methylthio-4,6-dimethoxypyrimidine (m.p. 48-50°C). An n.m.r. spectrum revealed four singlet peaks at 2.58 δ, 3.30 δ, 3.69 δ, 5.32 δ which were respectively integrated in a ratio of 3:3:3:1. Assuming
then that there were ten protons (corresponding to the elemental analysis), the assumption was that there were three methyl groups, each in a different environment and one lone hydrogen on the ring's 5-position. The most likely structure one could draw for such a compound was 1,6-dihydro-4-methoxy-1-methyl-2-methylthio-6-oxopyrimidine (VIb), which was consistent with the n.m.r. data.

![VIb]

Methylation of the ring nitrogen in pyrimidine is a well known reaction (6). The only problem was in assigning some of the δ values to the correct methyl groups. The 5.32 δ value was unambiguously ascribed to the ring hydrogen (position d). The 2.58 δ was ascribed to the methylthio protons (a) since they would logically be the least deshielded; sulfur is less electronegative than oxygen or ring nitrogen. There was some ambiguity in how to assign the 3.30 δ and 3.69 δ values between the methoxyl (c) and the ring N-methyl (b) protons but this problem was solved when the compound was nitrated and the resulting product's n.m.r. spectrum was studied. Nitration of 1,6-dihydro-4-methoxy-1-methyl-2-methylthio-6-oxopyrimidine would logically yield the 1,6-dihydro-4-methoxy-1-methyl-2-methylthio-5-nitro-6-oxopyrimidine (VIIb). This was carried out in sulfuric acid with fuming red nitric acid and the product was recrystallized from
benzene yielding five long yellow needles. Carbon and hydrogen analyses agreed with the theoretical values.

\[
\begin{align*}
(b) & \quad \text{CH}_3 \quad \text{O} \\
& \quad \text{NO}_2 \\
(a) & \quad \text{CH}_3 \text{S} \\
& \quad \text{OCH}_3 \\
(c) & \\
\end{align*}
\]

\(\text{VIIb}\)

The n.m.r. spectrum of this compound showed singlet peaks at 2.57 \(\delta\), 3.52 \(\delta\) and 4.09 \(\delta\). These values, when compared with those of its precursor (VIb) show a definite downfield shift as a result of the nitro group's deshielding effect. However, not all the shifts were equal in magnitude. The peak at 3.30 \(\delta\) in VIb shifted to 3.52 \(\delta\) in VIIb (a shift of +.22 \(\delta\)) and the peak at 3.69 \(\delta\) in VIb shifted to 4.09 \(\delta\) in VIIb (a shift of +.40 \(\delta\)). Due to their proximity to the nitro group, the methoxyl group (c) protons would be expected to show the greatest deshielding effect. Thus the value of 3.69 \(\delta\) in VIb could be assigned to the methyl (c) protons and 3.30 \(\delta\) to the N-methyl protons (b).

<table>
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<th>Functionality</th>
<th>VIIb</th>
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<tr>
<td>(\text{CH}_3\text{S}) (a)</td>
<td>2.58 (\delta)</td>
<td>2.67 (\delta)</td>
</tr>
<tr>
<td>ring N-(\text{CH}_3) (b)</td>
<td>3.30 (\delta)</td>
<td>3.52 (\delta)</td>
</tr>
<tr>
<td>(\text{CH}_3\text{O}) (c)</td>
<td>3.69 (\delta)</td>
<td>4.09 (\delta) (greatest deshielding shift)</td>
</tr>
<tr>
<td>5-H (d)</td>
<td>5.32 (\delta)</td>
<td></td>
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Figure 5. Reaction scheme of 2-methylthio- and 2-hydroxypyrimidines. Series b.
It was decided to try to run the reaction on the nitrated compound with methylhydrazine in pyridine. However, when this was tried the same sort of decomposition occurred as was observed in the reaction of 2-methylthio-4,6-dimethoxy-5-nitropyrimidine (Vb) under similar conditions with methylhydrazine in pyridine.

This line of investigation, then, did not yield any concrete results as far as hydrazinolysis studies were concerned, but this was compensated for by the accidental discovery of a threefold methylation reaction.

The third, and most fruitful series of compounds that was investigated contained a dimethylamino substituent in the 2-position (see Figure 6). The synthesis of 2-dimethylamino-4,6-dihydroxy-pyrimidine (Ic) involved the condensation of 1,1-dimethylguanidine sulfate with diethylmalonate in methanolic sodium methoxide. However, the procedure reported by Boon (4) failed to yield any product on the two occasions it was tried. The failure in that procedure was found to be due to insufficient equivalents of sodium methoxide being used. It was found that approximately a twofold excess of the base was needed to effect the condensation in good yield.

From the dihydroxy compound (Ic), two routes to the 2-dimethylamino-4,6-dimethoxy-5-nitropyrimidine became immediately apparent. In following one route, 2-dimethylamino-4,6-dihydroxypyrinidine, it was chlorinated according to the method of Boon (5) to yield
the dichloro compound. It was discovered that if the reflux period in phosphorus oxychloride was less than 30 minutes, partial recovery of monochlorinated product was effected. The yield of 2-dimethylamino-4-chloro-6-hydroxypyrimidine (VIIc) could be increased by refluxing for only 10 minutes instead of 30 minutes. The 2-dimethylamino-4, 6-dichloropyrimidine (IIc) was separated from the monochlorinated compound (VIIc) by fractional crystallization from benzene, or by extraction of VIIc with sodium hydroxide solution.

The next step was to treat 2-dimethylamino-4, 6-dichloropyrimidine in refluxing methanolic sodium methoxide to yield 2-dimethylamino-4, 6-dimethoxypyrimidine (IIIc) in 80% yield. Nitration of IIIc with fuming red nitric acid in acetic acid below 10° yielded the desired 2-dimethylamino-4, 6-dimethoxy-5-nitropyrimidine (IVc) in 60% yield. The greenish precipitate was separated from the blue mother liquor and recrystallized from ethanol. An n.m.r. spectrum of this compound revealed two singlet peaks, one at 3.16 δ, the second at 3.96 δ, which were integrated at a ratio of 1:1. The peak at 3.96 δ was assigned to the methoxyl protons while that at 3.16 δ belonged to the N-methyl protons. Carbon and hydrogen analyses confirmed the molecular formula.

Since there was some problem with the acetic acid freezing out at the low temperature (5-10° C) required for the nitration, it was decided to try using sulfuric acid as the solvent. Sulfuric acid had
been used in some earlier analagous nitrations (i.e. of 2-acetamido-
4, 6-dimethoxypyrimidine and 2-methylthio-4, 6-dimethoxypyrimidine)
so it was reasonable to expect that it would work as well with 2-di-
methylamino-4, 6-dimethoxypyrimidine (IIIc). However, when this
was carried out, again at temperatures below 5°C, a light green
powder separated out when the reaction mixture was poured onto ice.
This precipitate could not be recrystallized from ethanol. However,
it was soluble in sodium hydroxide. Carbon and hydrogen analyses
were not possible, however, since the compound was exploding at
about 130°C, before the combustion column could be placed and
purged. An n.m.r. spectrum in deuterium oxide-sodium deuterox-
ide solution proved most helpful; peaks were observed at 3.14 δ,
3.67 δ and 4.10 δ with an integration ratio of 2:1:1. Considering
the integration and comparison of these values with the n.m.r. spec-
tra of 2-dimethylamino-4, 6-dimethoxy-5-nitropyrimidine (IVc) and
1, 6-dihydro-4-methoxy-1-methyl-2-methylthio-5-nitro-6-oxopyr-
imidine (VIIb), it was concluded that there was one ring N-methyl
group (3.67δ), one methoxyl group (4.10 δ) and of course the two
methyl groups due to the 2-dimethylamino substituent (3.14 δ). A
brief tabular comparison of δ values for the compounds was illus-
trative in elucidating the structure of this compound (XIIIc).
Thus the compound XIIIc was deduced to be 1, 6-dihydro-2-dimethylamino-4-methoxy-1-methyl-5-nitro-6-oxopyrimidine:

It had been shown by Stahl that the 4-methoxy group in 4, 6-dimethoxy-5-nitropyrimidine is a methylating agent (19). It is reasonable to theorize that the methyl group migrates to the sulfuric acid to form some sort of methyl bisulfate intermediate which immediately methylates the ring. Bisulfate ion, in equilibrium with sulfuric acid would serve as the most likely catalyst.
Another possibility would be the direct intermolecular methylation of one molecule of IVc by another, similar to the methylation of pyridine reported by Stahl.

![Chemical structure](image)

The first scheme is the more attractive, since (a) the rearrangement occurs only in sulfuric, not acetic acid and the proposed mechanism requires a methylating intermediate and (b) the positive charge that would be developed on the ring in the second scheme would be destabilized by the nitro group. Internal rearrangements of this sort in alkoxypyrimidines have been effected by heating the compounds. The alkyl group migrates only to the α- and never to the γ nitrogen atom (6).

2-Dimethylamino-4,6-dimethoxy, 5-nitropyrimidine (IVc) was also synthesized via another route. The chlorination step was preceded by the nitration step. Nitration of the 2-dimethylamino-4,6-dihydroxy pyrimidine with fuming red nitric acid in acetic acid according to the procedure of Boon (5) yielded 2-dimethylamino-4,6-dihydroxy-5-nitropyrimidine (Vc). Chlorination of Vc with phosphorus oxychloride, using dimethylaniline as a catalyst, afforded a
15% yield of 2-dimethylamino-4, 6-dichloro-5-nitropyrimidine (VIc),
(5). Refluxing VIc in methanolic sodium methoxide for fifteen minutes
gave a good yield (80%) of the desired 2-dimethylamino-4, 6-dimethoxy-
5-nitropyrimidine (IVc), which had an identical melting point (183-
185°C) and an identical infrared spectrum as a sample of IVc pre-
pared by the first method. This second method was somewhat unde-
sirable especially due to the low yield from the chlorination step.

Hydrazinolysis studies on 2-dimethylamino-4, 6-dimethoxy-5-
nitropyrimidine (IVc) were then undertaken to determine if Krackov's
anomalous reactions would occur when there was a dimethylamino
substituent in the 2-position. Methylhydrazine was reacted with IVc
in refluxing pyridine or butanol. When refluxed for about ten minutes
and cooled, the product that was collected had a melting point of 145-
147°C and had an elemental analysis that corresponded closely to
a compound in which one methoxyl group had been replaced by a
methylhydrazino group; i.e. 2-dimethylamino-4(1-methylhydrazino)
6-methoxypyrindine. The calculated values for this compound, C,
39.7% H, 5.7% N, 34.7% corresponded closely to those that were
found: C, 39.9% H, 5.5% N, 32.4%.

Upon refluxing the reaction mixture somewhat longer (about
one hour) the disubstituted product was obtained which was 2-dimethyl-
amino-4, 6-di(methylhydrazino)-5-nitropyrimidine (XIIc). The struc-
ture of XIIc was proven by elemental analysis (Calc'd for
C_{18}H_{16}N_{8}O_{2}: C, 37.5\% H, 6.3\% found: C, 37.7\% H, 6.0\%) and by an n.m.r. spectrum which revealed two equal peaks at 3.20 $\delta$ and 2.68 $\delta$. Those were resolved on the H.A. 100 spectometer. The primary amino protons were seen at .58 $\delta$.

Interestingly, the melting point of the disubstituted compound (XIIc) was found to be exactly the same as that of the starting material (IVc) (183-184°C) while that of the assymmetric monosubstituted compound (2-dimethylamine-4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine) was 145-147°C. Stahl found that a methoxysubstituent in the 4-position could only be replaced by hydrazine if there is no large group (i.e. methylhydrazine) adjacent to the nitro substituent (6 position). Also he concluded that the reason that 4,6-dimethoxy-5-nitropyrimidine did not react with methylhydrazine via nucleophilic substitution was due to steric crowding by the methylhydrazine in forcing the nitro group out of the plane and thus, by loss of resonance, making the 4 and 6 positions less electrophilic. This rationale does not explain the formation of IVc, especially since the dimethylamino group is electron donating with respect to the ring and
would tend to deactivate the 4 and 6 positions to nuclear attack.

Hydrazinolysis of 2-dimethylamino-4,6-dimethoxy-5-nitropyrimidine (IVc) with hydrazine in refluxing methanol gave a compound (XIVc) whose elemental analysis (C, 36.1%, H, 5.5%, 4.97%) did not correspond with that of the expected 2-dimethylamino-4,6-dihydrazino-5-nitropyrimidine (calc'd for C$_6$H$_{12}$N$_8$O$_2$, MW 228: C, 31.6%, H, 5.27%). Lehmkühl (13) reported that 4,6-dimethoxy-5-nitropyrimidine in pyrimidine with hydrazine yielded 6-hydrazino-7-hydroxy-8-azapurine monohydrate, which was also obtained when 4,6-dihydrazino-5-nitropyrimidine was treated with two equivalents of hydrazine.

This type of ring closure has been long known. Arndt discovered such a reaction in 1913 (1). He reported the base catalyzed cyclization of o-nitrophenylguanidine to form 3-amino-1,2,4-benzotriazine-1-oxide. Reasoning along these lines, a structure for XIVc such as 4-dimethylamino-6-hydrazino-7-hydroxy-8-azapurine monohydrate was postulated (calc'd for C$_6$H$_{12}$N$_8$O$_2$, MW 228: C, 31.6%
H, 5.27% which is the same as that of 2-dimethylamino-4,6-dihydrazino-5-nitropyrimidine). Unfortunately the compound could not be purified by crystallization since it did not dissolve in any common recrystallizing solvents. The infrared spectrum (see Figure 8) indicated that a primary amino or free hydroxyl function was present by a strong sharp band at 3.03 μ.

Lehmkuhl (13) investigated some reactions of 4,6-dihydroxy-5-nitropyrimidine with hydrazine and methylhydrazine in pyridine. With hydrazine, a product was obtained that seemed to be 4-hydrazino-6-hydroxy-5-nitropyrimidine monohydrate. Methylhydrazine in an analogous fashion afforded 4-hydroxy-6-(1-methylhydrazino)-5-nitropyrimidine monohydrate. This displacement of a hydroxyl group on the pyrimidine ring was most unusual and 2-dimethylamino-4,6-dihydroxy-5-nitropyrimidine (Vc) was treated with hydrazine and methylhydrazine in this manner, but no reaction occurred.

However, partially chlorinated compounds in this series were available and it was decided to try some hydrazinolyses on 4-chloro-2-dimethylamino-6-hydroxy-5-nitropyrimidine (VIIIc). Pfeiderer and Nübel (15) reported the preparation of this compound from 4-chloro-2-dimethylamino-6-hydroxypyrimidine (VIIc) which was prepared by refluxing 2-dimethylamino-4,6-dichloropyrimidine (IIc) in sodium hydroxide.
Reaction of 4-chloro-2-dimethylamino-6-hydroxy-5-nitropyrimidine (VIIIc) with fourfold excess of methylhydrazine in butanol resulted in a small amount of a compound which melted at 325-350°C with decomposition. This mysterious compound (IXc) did not dissolve in any common recrystallizing agents so that it could not be purified by the usual procedures, but it was washed with water and ethanol. A negative ferrous hydroxide test (18) indicated the absence of a nitro group and elemental analyses were puzzling: C, 44.9%, 44.7% H, 6.10% 6.43%. These did not correspond to any values that could be calculated for expected compounds. The infrared spectrum of IXc was not particularly helpful. A very wide absorption in the region 3.05-3.50 μ was observed (see Figure 9).

The same reaction carried out in methanolic methylhydrazine afforded 2-dimethylamino-4-hydroxy-6-(1-methylhydrazino)-5-nitropyrimidine (Xc) which decomposes sharply at 228-230°C.

\[ \text{Xc} \]

The n.m.r. spectrum of a solution of Xc in deuterium oxide-deuterium chloride taken on the H.A. 100 spectrometer revealed two singlet peaks, one at 3.26 δ, the other at 3.25 δ, with an integration ratio of 2:1. Elemental analysis proved the postulated molecular
formula \((C_{7}H_{12}N_{6}O_{3})\) to be correct.

A similar reaction with 4-chloro-2-dimethylamino-6-hydroxy-5-nitopyrimidine (VIIIc) was carried out in methanolic hydrazine. This yielded 2-dimethylamino-4-hydrazino-6-hydroxy-5-nitopyrimidine (XIc) with a sharp decomposition point at 210°C. The elemental analysis of XIc corresponded with the postulated formula, \(C_{6}H_{10}N_{6}O_{3}\). The infrared spectrum of XIc showed a strong peak at 3.03 \(\mu\) and a broad absorption in the region 3.1-3.4 \(\mu\) typical of hydrazinosubstituted pyrimidines. The spectra of Xc and XIc are virtually identical in the region below 10 \(\mu\), but the spectrum of Xc shows more absorptions in the 11-14 \(\mu\) region.

The synthesis of 2-dimethylamino-4-hydroxy-6-(1-methylhydrazino)pyrimidine (XVc) from 4-chloro-2-dimethylamino-6-hydroxy pyrimidine (VIIc) in refluxing ethanolic methylhydrazine was carried out to test the reactivity of VIIc. The resulting compound (XVc) decomposes between 228 and 235°C and its elemental analysis corresponds with the postulated molecular formula: \(C_{7}H_{13}N_{5}O\).

\[\text{XVc}\]
Figure 6. Reaction scheme c: Reactions of 2-dimethylaminosubstituted pyrimidines.
Figure 7. Infrared spectrum of 2-dimethylamino-4-hydroxy-6-(1-methylhydrazino)-5-nitropyrimidine (Xc).
Figure 8. Infrared spectrum of XIVc, reaction product from reaction between IVc and hydrazine.
Figure 9. Infrared spectrum of IXc, reaction product of VIIIc with methylhydrazine in butanol.
Another series of compounds that would have been desirable to have was the 2-hydroxysubstituted series. 2-Hydroxy-4,6-dichloropyrimidine was prepared in a rather roundabout fashion (see Figure 5) by the method of Koppel (11), using 2-methylthio-4,6-dichloropyrimidine (IIIb) as the precursor. The methylthio substituent was oxidized with chlorine gas in methanol, by passing a stream of the gas through a methanolic solution of the compound to yield the methyl sulfonate derivative. The methylsulfonate group was easily displaced by a hydroxyl group by treating the methylsulfonate compound with aqueous sodium hydroxide at room temperature to give the 4,6-dichloro-2-hydroxypyrimidine. The reason that this circuitous route had to be taken was the low susceptibility of the 2-position to nucleophilic substitution when compared to the more reactive 4 and 6 positions. For example, 2,4,6-trichloropyrimidine, when treated with sodium hydroxide, given successive substitution at the 4 and then the 2-position, to yield 2,4-dichloro-6-hydroxypyrimidine and 6-chloro-2,4-dihydroxypyrimidine. But an extremely good leaving group at the 2-position such as methylsulfonate, affords substitution at that position in preference to the 4- and 6-positions.

The sodium salt of 4,6-dichloro-2-hydroxypyrimidine was then refluxed in methanolic sodium methoxide. Upon acidification of the mixture, a 25% yield of 4-chloro-2-hydroxy-6-methoxypyrimidine was obtained. This compound melted at 195-197°C and the elemental
analyses corresponded well with the calculated values (Calc'd for C₅H₅N₂O₂Cl: C, 36.6% H, 3.13% Found: C, 36.8% H, 3.26%). The infrared spectrum revealed the presence of the methoxyl group by a band at 3.36 μ.

The monosubstitution observed in this last reaction is exactly analogous to the case where 2-amino-4, 6-dichloro-pyrimidine (IIa) was refluxed in methanolic sodium methoxide to yield 2-amino-4-chloro-6-methoxypyrimidine. The 2-hydroxysubstituted series was not further investigated.

The last group of compounds that was studied was a group leading to 2-methoxysubstituted compounds. Barbituric acid was the starting material in two separate routes leading to the synthesis of 5-nitro-2, 4, 6-trimethoxypyrimidine. One method involved the chlorination of barbituric acid in phosphorus oxychloride and dimethyl-aniline according to the directions of Baddiley (2) to yield 2, 4, 6-trichloropyrimidine. Treatment of the chlorinated compound with sodium methoxide in methanol yielded 2, 4, 6-trimethoxypyrimidine(7)
which was nitrated according to the procedure of Stahl (19) to give 5-nitro-2, 4, 6-trimethoxypyrimidine. Alternatively, barbituric acid was nitrated in fuming red nitric acid by the method of Hartman (9). The 5-nitrobarbituric acid was then chlorinated according to the directions given by Robins (16) and treatment of the 5-nitro-2, 4, 6-trichloropyrimidine with methanolic sodium methoxide afforded the 5-nitro-2, 4, 6-trimethoxypyrimidine. This latter route was less desirable than the first due to the low yield (15%) from the chlorination step and the tedious extraction procedures involved in the isolation of the compound.

5-Nitro-2, 4, 6-trimethoxypyrimidine was treated with methylhydrazine (two moles of methylhydrazine per 4- or 6-methoxyl group) in refluxing pyridine. The resultant product, recrystallized from ethanol, had carbon and hydrogen analyses corresponding well with
those calculated for 4, 6-di(1-methylhydrazino)-2-methoxy-5-nitropyrimidine. The infrared spectrum showed a strong absorption in the 3.05 \( \mu \) region, typical of primary amines (see Figure 10). The ferrous hydroxide test for nitro groups was positive. It is assumed that the substitution occurs at the 4- and 6-positions and that the 2-position is unreactive. The enhanced reactivity of the 4- and 6-positions over that of the 2-position when there is a nitro group in the 5-position was shown by amination studies of trichloro-5-nitropyrimidine, by Bitterli and Erlenmeyer (3).

\[
\begin{array}{cc}
\text{OCH}_3 & \text{CH}_3\text{NNH}_2 \\
\text{CH}_3\text{NHNH}_2 & \text{OCH}_3 \\
\text{N} & \text{NO}_2 \\
\text{CH}_3 & \text{O} \\
\end{array}
\]

Stahl (19) reported that the hydrazinolysis of 5-nitro-2, 4, 6-trimethoxypyrimidine in refluxing ethanolic hydrazine yielded dihydrazino-methoxy-5-nitropyrimidine with a melting point of 198-200\(^\circ\)C. Stahl also reported the infrared spectrum of this compound. However, when the reaction was carried out in this laboratory using either pyridine or methanol as solvent, a compound was obtained whose melting point was 225-227\(^\circ\)C and whose infrared spectrum was similar to but not identical to that of Stahl's compound.

In conclusion, the studies of the hydrazinolyses with methylhydrazine of the various 2-substituted, 4, 6-dimethoxy-5-nitropyrimidines showed a definite pattern. The "anomalous" reaction
proceeded when the 2-substituent was a hydrogen atom, a methyl or phenyl group, as shown by Stahl, and when it was an acetamido group. The reaction failed in the case of the 2-dimethylamino and 2-methoxy-substituted compounds, giving only direct nucleophilic substitution products, while the thio compounds decomposed. These observations are easily explained when one considers the mechanism elucidated by Lehmkuhl (13) see Figure 2). Negative charge is developed on the oxyanion of the pyrimidinate salt and is instrumental in displacing the methoxyl group.

If the negatively charged species is destabilized by an electron-releasing group in the 2-position, this species will not survive sufficiently long to permit the methyl migration from the hydrazino to the nitro group. The dimethylamino and methoxy substituents are examples of highly electron releasing groups, whereas the alkyl groups etc. show relatively little electron releasing character. It would be interesting to carry out some studies on a whole series of variously substituted phenyl groups as substituents on the 2-position. Stahl showed that 4,6-dimethoxy-5-nitro-2-phenylpyrimidine reacts in this "anomalous" fashion. A para methoxyl group on the phenyl
substituent should inhibit the reaction while a para nitrosubstituted phenyl compound should facilitate the reaction.
Figure 10. Infrared spectrum of 4, 6-di(1-methylhydrazino)-2-methoxy-5-nitopyrimidine.
EXPERIMENTAL

All melting points below 250 °C. are uncorrected and were taken on a Büchi melting point apparatus in capillary tubes. The infrared spectra were obtained with a Beckman Model IR-8 spectrophotometer with the samples in the form of potassium bromide pressed pellets or in carbon tetrachloride solution together with a reference cell. The nuclear magnetic resonance spectra were recorded on a Varian Model A-60 spectrometer or on a model HA-100 instrument. Most of the nmr spectra were run in carbon tetrachloride or deuterochloroform solutions with tetramethylsilane as an internal standard, but sodium-3-trimethylsilyl-1-propane sulfonate was used as an internal standard with aqueous solutions.

Hydrazines, being both hazardous to the skin and noxious to inhale, were stored in a refrigerator and used only in a hood with adequate ventilation.

2-Amino-4, 6-dimethoxypyrimidine (IIa)

This procedure is a modification of the one suggested by Rose (17). To a solution of sodium methoxide made by dissolving 9.6 gm sodium in 160 ml methanol, was added 33.0 gm 2-amino-4, 6-dichloropyrimidine (IIa), being careful to let the exothermic reaction proceed slowly. Xylene (160 ml) was then added and the mixture was refluxed
with stirring for one hour. The methanol was then removed by distillation, with occasional addition of more xylene to the mixture. After all the methanol was removed, the mixture was refluxed one additional hour with rapid stirring to minimize bumping. The solution was cooled and benzene (100 ml) and water (200 ml) were added to the mixture. After washing with two additional 100 ml portions of water, the organic layer was dried with anhydrous calcium chloride, filtered and distilled off. The solid, recrystallized from ethanol, weighed 15.4 gm (49%), m.p. 91-92°C. (lit. 92-93°C.).

2-Amino-4-chloro-6-methoxypyrimidine

This compound resulted when the xylene was not added in the procedure to make 2-amino-4,6-dimethoxypyrimidine (17).

2-Amino-4,6-dichloropyrimidine (17) (4.0 gm) was added to a methanolic solution of sodium methoxide (1.2 gm sodium in 50 ml methanol). The mixture was refluxed one hour, cooled and poured into 100 ml water, whereupon the product separated. It was collected and recrystallized from ethanol-water; yield, (2.8 gm (70%), m.p. 165-166°C).

Anal. Calc'd for C₅H₆ClN₃O (M.W. 159, 5): C, 37.60% H, 3.76%

C 37.52% H, 3.58%
2-Acetamido-4, 6-dimethoxypyrimidine (VIIa)

2-Amino-4, 6-dimethoxypyrimidine (IIIa) (5.3 gm) was dissolved in 30 ml acetic anhydride and refluxed for two hours with stirring. The solution was allowed to stand overnight in the refrigerator, whereupon the solid acetylated product precipitated; yield, 2.4 gm, (36%), m.p. 130-132°C. More product was recovered upon further cooling and addition of a little water, but this was contaminated with starting material. The crude product was dried but not recrystallized.

Anal. Calc'd for C_8H_11N_3O_3 (M.W. 197): C, 48.70% H, 5.58%

Found: C, 48.40% H, 5.45%

2-Acetamido-4, 6-dimethoxy-5-nitropyrimidine (VIIla)

2-Acetamido-4, 6-dimethoxypyrimidine (VIIa), (3.3 gm), was dissolved in 20 ml con sulfuric acid. Fuming red nitric acid (3 ml) was added dropwise with stirring, while keeping the flask in a cool water bath. Care was taken not to permit the temperature to rise above 30°C. After the addition was completed, the solution was let stand for an additional twenty minutes and then poured onto 100 gm ice, whereupon a precipitate formed. The filtered precipitate was recrystallized from absolute ethanol; yield, 2.4 gm fine yellow needles (60%), m.p. 212-214°C (dec).
Anal. Calc'd for $C_8H_{10}N_4O_5$ (M.W. 242): C, 39.70% H, 4.13%

Found: C, 39.70% H, 4.32%

2-Amino-4-hydrazino-6-hydroxy pyrimidine (IXa)

2 Acetamido-4,6-dimethoxy-5-nitropyrimidine (VIIa), (1.0 gm) was dissolved in 20 ml of pyridine. Methylhydrazine (.50 ml) was added and the solution was refluxed 30 minutes. The mixture was then placed in the refrigerator overnight. The precipitate which was collected was a fine powder, it was washed with ethanol and weighed .1 gm (17%) and it was insoluble in all common recrystallizing solvents, m.p. 325-327°C (dec).

Anal. Calc'd for $C_4H_7N_5O$ (M.W. 141): C, 34.00% H, 4.98% N, 49.60%

Found: C, 34.05% H, 5.00% N, 48.95%

4,6-Dimethoxy-2-methylthiopyrimidine (IVb)

4, 6-Dichloro-2-methylthiopyrimidine (IIIb) (7), (6.9 gm) was dissolved in 20 ml of methanol. A methanolic solution of sodium methoxide (3.5 gm sodium in 50 ml methanol) was added slowly with stirring. The mixture was refluxed 20 minutes, cooled and poured into 100 ml of cold water, whereupon the product separated. The solid was recrystallized from ethanol-water; yield, 4.8 gm (70%), m.p. 48-50°C.
49

Anal. Calc'd for C$_7$H$_{10}$N$_2$O$_2$S (M. W. 186): C, 45.15% H, 5.38%

Found: C, 45.21% H, 5.35%

4,6-Dimethoxy-2-methylthio-5-nitropyrimidine (Vb)

4,6-Dimethoxy-2-methylthiopyrimidine (IVb), (5.0 gm) was dissolved in 15 ml concentrated sulfuric acid. Fuming red nitric acid (2.5 ml.) was added dropwise with stirring while the flask was kept on a cold water bath. After the addition had been completed, the solution was allowed to stand twenty more minutes and then it was poured onto 100 gm of ice. The precipitate was recrystallized from ethanol; yield 3.5 gm (57%) fine yellow needles, m.p. 115-117° C.

Anal. Calc'd for C$_7$H$_9$N$_3$O$_4$S (M. W. 231) C, 36.35% H, 3.90%

Found: C, 36.28% H, 4.05%

1,6 Dihydro-2-Methylthio-1-methyl-4-methoxy-6-oxopyrimidine (VIb)

2-Thio-4,6-dihydroxypyrimidine (Ib) (14) (14.4 gm) was dissolved in a solution of sodium hydroxide (4.0 gm) in 30 ml water. To this solution was added 40 gm dimethylsulfate with vigorous stirring. The temperature was allowed to rise to approximately 80° C, whereupon the flask was cooled to room temperature with a water bath and stirred further for one more hour. The solid that forms was soluble in acid but insoluble in base, and was recrystallized from benzene; yield 10.6 gm (57%) long fragrant white needles, m.p. 108-110° C.
Anal. Calc'd for C$_7$H$_{10}$N$_2$O$_2$S (M. W. 186): C, 45.15% H, 5.38%

Found: C, 45.20% H, 5.37%

1,6-Dihydro-1-methyl-2-methylthio-4-methoxy-5-nitro-6-oxopyrimidine

1,6-Dihydro-1-methyl-2-methylthio-4-methoxy-5-nitro-6-oxopyrimidine (VIb), (5.0 gm) was dissolved in 10 ml con sulfuric acid. Fuming red nitric acid (2.5 ml) was added dropwise with stirring, while the flask was cooled in a cold water bath. The solution was let stand another half hour after the addition was complete and then poured on ice (50 gm). The precipitate was recrystallized from benzene; yield, 3.6 gms (58%) (fine yellow needles, m.p. 186-188° C.

Anal. Calc'd for C$_7$H$_{10}$N$_2$O$_2$S (M. W. 231): C, 36.35% H, 3.90%

Found: C, 36.40% H, 3.92%

2-Dimethylamino-4,6-dimethoxypyrimidine (IIIc)

A methanolic solution of sodium methoxide (5 gm sodium in 100 ml methanol) was slowly added with stirring to a solution of 15 gm 2-dimethylamino-4,6-dichloropyrimidine (IIc) (5) in 25 ml CH$_3$OH. After the vigorous reaction had died down, the mixture was refluxed for one hour with stirring to minimize bumping, cooled and poured into 100 ml of cold water. The precipitate was collected and recrystallized from ethanol-water; yield, 12.8 gm (90%) m.p. 55-56° C.
Anal. Calc'd for $C_{8}H_{13}N_{3}O_{2}$ (M. W. 183): C, 52.50% H, 7.10%

Found: C, 52.38% H, 7.06%

2-Dimethylamino-4,6-dimethoxy-5-nitropyridine (IVc)

This compound was prepared by two procedures:

(A). 2-Dimethylamino-4,6-dimethoxypyrimidine (IIIc) (4.6 gm), was added slowly with stirring to a solution of 4.5 ml fuming red nitric acid in 18 ml glacial acetic acid, taking care not to let the reaction temperature exceed room temperature. The dark blue mixture was poured onto 100 gm of ice and the precipitate was collected and washed with water. Recrystallization from ethanol afforded light green needles; yield, 3.2 gm (54%) m.p. 183-184°C. The importance of keeping the reaction mixture at room temperature was illustrated when during one run, the temperature rose to 40°C whereupon the blue solution changed in color to purple and no product could be recovered from this latter solution.

Anal. Calc'd for $C_{8}H_{12}N_{4}O_{4}$ (M. W. 228): C, 42.12% H, 5.27%

Found: C, 42.02% H, 5.24%

(B). 4,6-Dichloro-2-dimethylamino-5-nitropyridine (VIc) (5), (28.0 gm), was added to a methanolic solution of sodium methoxide (15 gm sodium in 200 ml methanol). The mixture was refluxed with stirring for 15 minutes, cooled and poured onto 200 ml of cold water. Recrystallization of the precipitate from ethanol afforded
yellow needles; yield, 26.0 gm (75%), m.p. 183-184°C. The melting point and infrared spectrum of this compound were identical to those of the compound obtained by method A.

1, 6-Dihydro-2-dimethylamino-4-methoxy-1-methyl-5-nitro-6-oxopyrimidine (XIIIc)

The procedure for the preparation of IVc by method A was followed in all respects except that concentrated sulfuric acid was used as the solvent and an icebath was used to keep the reaction temperature below 5°C. 2-Dimethylamino-4, 6-dimethoxypyrimidine (IIIC), (1.3 gm) was added to a nitrating solution of 1.2 ml fuming red nitric acid in 15 ml concentrated sulfuric acid, a little at a time. The precipitate that was collected after workup in icewater was a light green powder which was not soluble in any common recrystallizing solvent but it did dissolve in aqueous sodium hydroxide; yield, 0.7 gm (43%), m.p. 130-131°C (explodes). Due to its explosive nature, consistent elemental analyses could not be obtained but the compound was identified by its n.m.r. spectrum.

2-Dimethylamino-4-hydroxy-6-(1-methylhydrazino)pyrimidine (XVc)

To a solution of 1.0 gm 4 chloro-2-dimethylamino-6-hydroxy-pyrimidine (VIIc), (5) in 20 ml absolute ethanol was added 3.0 ml of methylhydrazine. The mixture was refluxed with stirring for one hour and the precipitate that formed upon cooling was recrystallized
from ethanol; yield, .5 gm, (45%) m.p. 228-235°C (dec).

Anal. Calc'd for C\textsubscript{7}H\textsubscript{13}N\textsubscript{5}O (M.W. 183): C, 45.82% H, 7.10%

Found: C, 45.91% H, 7.10%

2-Dimethylamino-4-hydroxy-6-hydrazino-5-nitropyrimidine (XIc)

To a suspension of 1.0 gm 4-chloro-2-dimethylamino-6-hydroxy-5-nitropyrimidine (VIIIc) (5) in 20 ml methanol was added .75 ml of 95% hydrazine. The mixture was brought to reflux. whereupon the starting material dissolved. A yellow precipitate formed within one minute and this mixture was refluxed further for one hour. The yellow precipitate was collected and washed with cold anhydrous methanol; yield, 1.05 gm, (100%) m.p. 210°C (decomposes sharply).

Anal. Calc'd for C\textsubscript{6}H\textsubscript{10}N\textsubscript{6}O\textsubscript{3} (M.W. 214): C, 33.61% H, 4.67%

Found: C, 33.50% H, 4.50%

2-Dimethylamino-4-hydroxy-6-(1-methylhydrazino)-5-nitropyrimidine (Xc)

The procedure for the synthesis of XIc was followed, using 1.0 gm of VIIIc and 1.0 ml methylhydrazine. The yield of yellow precipitate was .9 gm (84%) m.p. 228-230°C (dec).

Anal. Calc'd for C\textsubscript{7}H\textsubscript{12}N\textsubscript{6}O\textsubscript{3} (M.W. 228): C, 36.80% H, 5.26%

Found: C, 36.75% H, 5.15%
2-Dimethylamino-4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine

To a solution of 2.2 gm 2-dimethylamino-4,6-dimethoxy-5-nitropyrimidine (IVc) in 25 ml of pyridine or n-butyl alcohol was added 1.7 ml of methylhydrazine. The solution was refluxed with stirring for 20 minutes and cooled in a refrigerator overnight. The resulting yellow crystals were recrystallized from ethanol; yield from reaction in butanol, 1.6 gm, (69%) yield from reaction in pyridine, .4 gm, (17%) m.p. 145-147°C.

Anal. Calc'd for C₈H₁₄N₆O₃ (M. W. 242); C, 39.69% H, 5.78% N, 34.71%

Found: C, 39.85% H, 5.67% N, 32.4%

It should be mentioned with regard to the low nitrogen analysis that the instrument was giving consistently low values with other analyses being run, as well as with the standards. Compounds of this type often give low nitrogen values when analyzed on the Coleman Model 29 Analyser.

2-Dimethylamino-4,6-di(1-methylhydrazino)-5-nitropyrimidine (XIIc)

To a solution of 2.0 gm 2-dimethylamino-4,6-dimethoxy-5-nitropyrimidine (IVc) in 20 ml of pyridine or butanol, was added 1.5 ml methylhydrazine. The solution was refluxed for one hour. When pyridine was used it was necessary to distill away most of the solvent in order to obtain the product. The precipitate recrystallized well
from ethanol giving fine yellow needles; yield, 1.5 gm, (67%) m.p. 183-185°C (dec).

Anal. Calc'd for C₂₂H₂₆N₆O₂ (M. W. 256): C, 37.52% H, 6.26%

Found: C, 37.68% H, 6.09%

IXc, The reaction of methylhydrazine with 4-chloro-2-dimethylamino-6-hydroxy-5-nitropyrimidine

To a solution of 1.0 gm 4-chloro-2-dimethylamino-6-hydroxy-5-nitropyrimidine (VIIIc) (5) in 30 ml butanol was pipetted 5 ml methylhydrazine and the solution was refluxed for one hour and let to stand in the refrigerator overnight. The cream-colored precipitate was washed with water and with methanol; yield, .2 gm, m.p. 325-330°C (dec), (IXc).

Anal. Found: C, 44.9%, 44.7% H, 6.1%, 6.4%

XIVc, The reaction of hydrazine with 2-dimethylamino-4, 6-dimethoxy-5-nitropyrimidine

To a solution of 1.4 gm 2-dimethylamino-4, 6-dimethoxy-5-nitropyrimidine (IVc) (.006 mol) in 40 ml methanol, was added .75 ml (0.24 mol) of 95% hydrazine. Upon heating to reflux, a precipitate soon formed and the mixture was further refluxed for 30 minutes. The precipitate was collected and washed with methanol; yield, 1.4 gm, m.p. 205-212°C (dec).

Anal. Found: C, 36.1%, 36.0% H, 5.15%, 4.97%.
5-Nitro-2, 4, 6-trimethoxypyrimidine

This compound was prepared by (A) a method developed by Stahl, by reacting 2, 4, 6-trichloropyrimidine with fuming red nitric acid and (B) by reacting 5-nitro-2, 4, 6-trichloropyrimidine with sodium methoxide.

(A). 2, 4, 6-Trimethoxypyrimidine (7), (20.4 gm), was added to a solution of 25 ml of red fuming nitric acid in 25 ml concentrated sulfuric acid over a period of 20 minutes, keeping the flask on a salt-ice bath and never allowing the solution's temperature to rise above 1 °C. After the addition was complete, the solution was let to stand at room temperature 30 minutes and then poured onto 900 gm ice. The crude compound weighed 24 gm (95%) and this was recrystallized from ethanol, m.p. 123-125 °C.

(B). 5-Nitro-2, 4, 6-trichloropyrimidine (16) (3.5 gm) was dissolved in 20 ml methanol. To this solution was added methanolic sodium methoxide (1.2 gm sodium dissolved in 25 ml methanol), slowly with stirring. When the reaction had slowed sufficiently, the mixture was refluxed for 30 minutes, cooled and poured into 100 ml of water. Yield after recrystallization from methanol-water was 1.9 gm (43%), m.p. 120-121 °C.
2-Methoxy-4,6-di(1-methylhydrazino)-5-nitropyrimidine

To a solution of 1.3 gm (.006 mol) 5-nitro-2,4,6-trimethoxy-pyrimidine in 20 ml pyridine, was added 1.1 ml (.024 mol) methyl-hydrazine. The solution was refluxed 30 minutes, refrigerated and the resulting precipitate was collected. Recrystallization from ethanol afforded fine yellow needles; yield, .3 gm, (21%) m.p. 180-181 °C (dec).

Anal. Calc'd for C$_7$H$_{13}$N$_7$O$_3$ (M.W. 243): C, 34.50% H, 5.34%

Found: C, 34.38% H, 5.16%


