AN ABSTRACT OF THE THESIS OF

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Title: THE STUDY OF THE INFLUENCE OF THE NITRO SUBSTITUENT ON THE HYDRAZINOLYSIS OF CERTAIN SUBSTITUTED 5-NITROPYRIMIDINES

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The unique reaction between 4,6-dimethoxy-5-nitropyrimidine and methylhydrazine was investigated. The reaction product was identified as 4-hydrazino-6-hydroxypyrimidine from (a) spectral data, (b) by direct synthesis of the product via 4-chloro-6-hydroxypyrimidine and hydrazine, and (c) by conversion of the product to the known 4-amino-6-hydroxypyrimidine using Raney nickel. The product was not produced by the nucleophilic substitution of methylhydrazine with 4,6-dimethoxy-5-nitropyrimidine. The product was the result of an initial rearrangement of the methoxypyrimidine (presumably a methyl migration) to an intermediate which then reacted with the methylhydrazine. When the methoxypyrimidine was refluxed in pyridine, it was converted into at least two non-interconvertible products, one soluble and the other insoluble in cold

pyridine. The soluble product yielded 4-hydrazino-6-hydroxy-pyrimidine when treated with methylhydrazine at room temperature while the insoluble one did not. The insoluble product was tentatively identified from spectral data as an N-methylpyridinium N-methylpyrimidinate salt. The reason that 4,6-dimethoxy-5-nitropyrimidine does not respond to direct nucleophilic substitution with methylhydrazine (as in the case of hydrazine at both the 4- and 6-positions) apparently stems from steric hindrance imposed by the attacking methylhydrazine. Among the effects caused by the steric crowding is the forcing of the nitro substituent out of the plane of the pyrimidine ring thus losing the important resonance contribution of the nitro substituent in making the 4- and 6-positions more electrophilic.

Treatment of the 2-methyl- and 2-phenyl-derivatives of 4,6-dimethoxy-5-nitropyrimidine with methylhydrazine likewise does not yield products as a result of direct nucleophilic substitution but rather the corresponding 4-hydrazino-6-hydroxy-2-substituted pyrimidine.

Reaction of 4,6-dimethoxy-5-nitropyrimidine with either 1,1-dimethyl- or 1,2-dimethylhydrazine results in decomposition of the pyrimidine ring; with phenylhydrazine there is no apparent reactivity.

In the course of this investigation it was demonstrated that in most cases methoxy-nitropyrimidines are good intermediates for

the preparation of hydrazino-nitropyrimidines. The yields, when reaction occurred, were excellent and the product of analytical purity. This is important as most hydrazino-nitro compounds are thermally unstable and oxidized readily when heated in hot solvents. Some pyrimidine derivatives prepared by this method were: 4-amino-6-hydrazino-5-nitropyrimidine, and 2-R-4,6-dihydrazino-5-nitropyrimidine (where R = H, methyl or phenyl). Some pyrimidines which did not react with hydrazine are; 4-methoxy-6-(1-methylhydrazine)-5-nitropyrimidine and 4-dimethylamino-6-methoxy-5-nitropyrimidine. Thus a methoxy substituent in the 4-position can only be replaced by hydrazine if there is no large group (e.g. methylhydrazino) adjacent to the nitro substituent (6-position).

Also some substituted hydrazino-nitropyrimidines were prepared via displacement of chloro substituents. The reaction occurred under mild conditions (e.g. 0-20^{o}C in methanol) even with the less reactive hydrazines (e.g. phenylhydrazine). Generally the yields were good and occasionally the derivative needed no further purification. Some of the pyrimidine derivatives that were prepared by this method included: 2-R-4,6-di(1-methylhydrazino)-5-nitropyrimidine (where R = H, methyl or phenyl), 4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine, 4-dimethylamino-6-(1-methylhydrazino)-5-nitropyrimidine and 2-R-4,6-(2-phenylhydrazino)-5-nitropyrimidine (where R = H or phenyl).

The ir and uv spectral data are included for all previously unreported compounds which were prepared.

The Study of the Influence of the Nitro Substituent on the Hydrazinolysis of Certain Substituted 5-Nitropyrimidines

by

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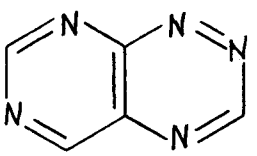
INTRODUCTION

A great deal of interest and a considerable amount of effort has been directed to the synthesis of "aza" homologs of naturally occurring compounds. These molecules which have been altered by inserting a nitrogen atom into a position normally occupied by a carbon atom are being rather intensively investigated because of the possible possession of biological properties of medicinal value. A number of biologically interesting "aza" compounds have been prepared which have attracted considerable attention due to their anti-carcinogenic properties. For example, certain 2-aza and 8-azapurine derivatives have demonstrated anti-tumor activity (55).

Inasmuch as this laboratory has been interested in the synthesis of compounds of biological interest for many years these developments have directed our attention to these areas. One ring system which appears attractive was the pyrimido [5,4-3]-as-triazine (I) which is actually an aza pteridine; the pteridine nucleus is a moiety of many important biological compounds such as folic and folinic acid.



I

Investigation into possible synthetic procedures for the synthesis of I was initiated by Krackov (44). One route that was investigated employed 4-hydrazino-5-nitropyrimidine derivatives as precusors. Thus by a 3-step procedure involving (a) reduction of the nitro group, (b) formylation of the hydrazino substituent and subsequent ring closure, and finally (c) dehydrogenation, one should obtain the desired product (I). At that time, no reports of the preparation of hydrazino-nitro-pyrimidines were to be found in the literature. Nonetheless their preparation appeared to be straight forward; a nucleophilic attack of hydrazine on a 5-nitropyrimidine having a good leaving group in the proper position. The most readily available compound for this purpose was 4,6-dichloro-5-nitropyrimidine (II). Not only did it have the desired substituent in the proper position but was known to be highly reactive toward nucleophilic reagents.

When II was dissolved in a refluxing solution of ethanolic hydrazine a vigorous reaction ensued which produced predominantly a brown intractable polymeric material and a small amount of 4,6-dihydrazino-5-nitropyrimidine (III) (see Figure 1).

Presuming a less reactive nitro-pyrimidine derivative might

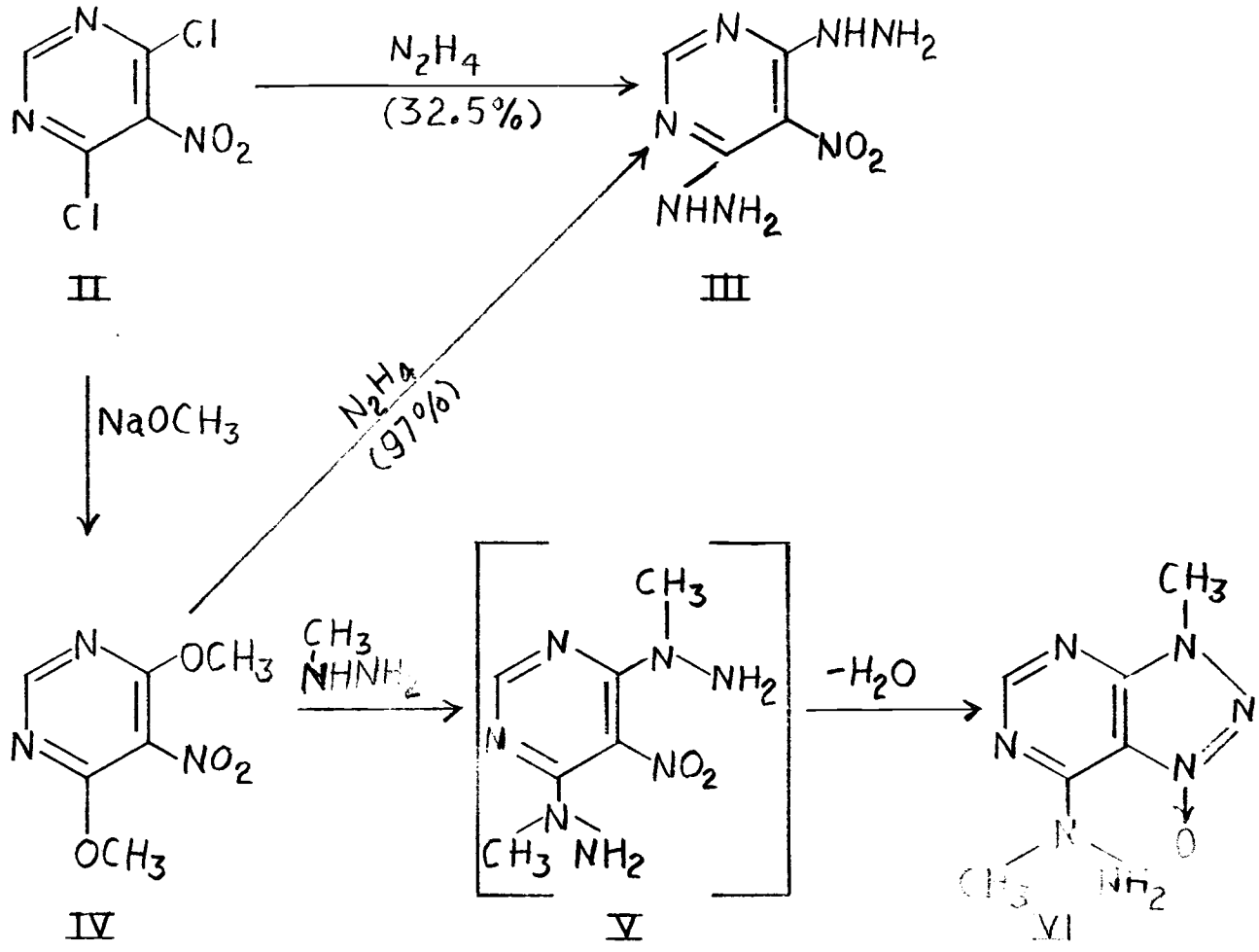


Figure 1. Hydrazinolysis of 5-nitropyrimidines as reported by Krackov.

give more favorable results, the 4,6-dichloro-5-nitropyrimidine was converted to the 4,6-dimethoxy derivative which is much more resistant to nucleophilic attack. The reaction of 4,6-dimethoxy-5-nitropyrimidine (IV) with a hot ethanolic solution of hydrazine proceeded smoothly to give III in excellent yield (probably quantitative) of analytical purity.

As a consequence of this experience, Krackov reacted the methoxy compound IV with methylhydrazine under identical conditions, anticipating the formation of an analogous product, 4,6-di-(1-methylhydrazino)-5-nitropyrimidine (V) in good yield. Instead, he recovered most of the starting material (IV) and only a trace amount of a new compound. The ethanol was replaced by n-butanol as a solvent to achieve a higher refluxing temperature; under these conditions the yield was increased. The product recrystallized from water melted with decomposition between 240-260°C. The carbon-hydrogen analysis however did not correspond to that of the expected product. The data suggested a compound which differed from the predicted product V by a loss of a molecule of water.

The product was thus thought to be the consequence of a two-step process. The first step was assumed to be the formation of the predicted product V. The second appeared to be a dehydrative ring closure between the free amino substituent of the hydrazino and

nitro group, leading to a product such as 3-methyl-7-(1-methyl-hydrazino)-3H-v-triazolo-[4, 5-d] pyrimidine-1-oxide (VI). However a nitrogen analysis disproved this proposed structure. On the basis of the carbon-hydrogen nitrogen analysis the empirical formula appeared to be $C_{10}H_{16}N_{10}O_3$.

Since no plausible structure could be written for this compound from the available data Krackov and Christensen (45) concluded that the reaction was not straightforward and hypothesized that the reaction led to a complex product or a mixture of products.

This was indeed a most unusual discovery. Numerous hydrazinopyrimidines have been successfully prepared by displacement of either a chloro or a methoxy group by the hydrazino, frequently in good yields (18, p. 199). However, none of these examples involved a pyrimidine with a nitro group in the 5-position.

A survey of the literature was made for other works pertaining to the reaction of nitropyrimidines with hydrazines. Only one other study that of Wiley, Lanet and Hussung (69) was found. These investigators described a procedure for the synthesis of 4, 6-dihydrazino-5-nitropyrimidine (III) via the 4, 6-dichloro-5-nitropyrimidine (II) under conditions which were quite different from the current work. Their method involved the slow addition of an ethereal solution of the chloropyrimidine to a very dilute ethereal solution of hydrazine. The yield was 16% of the crude product which does not

compare favorably with the procedure described by Krackov and Christensen (45).

The major part of their work was concerned with derivatives of the isomeric 2, 4-dichloro-5-nitropyrimidine (VII) (see Figure 2). The reaction of VII with hydrazine in dry ether produced the expected 2, 4-dihydrazino-5-nitropyrimidine (VIII) as a crude brown material in a 70% yield; no yield data was given for the purified compound. An estimated yield of pure material of less than 50% might be suggested on the basis of Krackov's results with the isomeric 4, 6-dichloro-5-nitropyrimidine (II).

When VII was converted into 4-amino-and 4-diethylamino-2-chloro-5-nitropyrimidine (IX a and b) by known reactions and then treated with hydrazine in an ether solution the expected products, 4-amino-2-hydrazino-5-nitropyrimidine (Xa) and 4-diethylamino-2-hydrazino-5-nitropyrimidine (Xb) were obtained in 80% and 90% yield respectively.

However, an unprecedented reaction did occur between certain 2, 4-disubstituted-5-nitropyrimidines and hydrazine. When 2, 4-bis-(dimethylamino)-5-nitropyrimidine (XIa) was refluxed in aqueous 85% hydrazine, a selective displacement of the dimethylamino substituent in the 4-position occurred thus producing 2-dimethylamino-4-hydrazino-5-nitropyrimidine (XIIa). The structure was confirmed by an independent synthesis of XIIa, which involved as the last step the

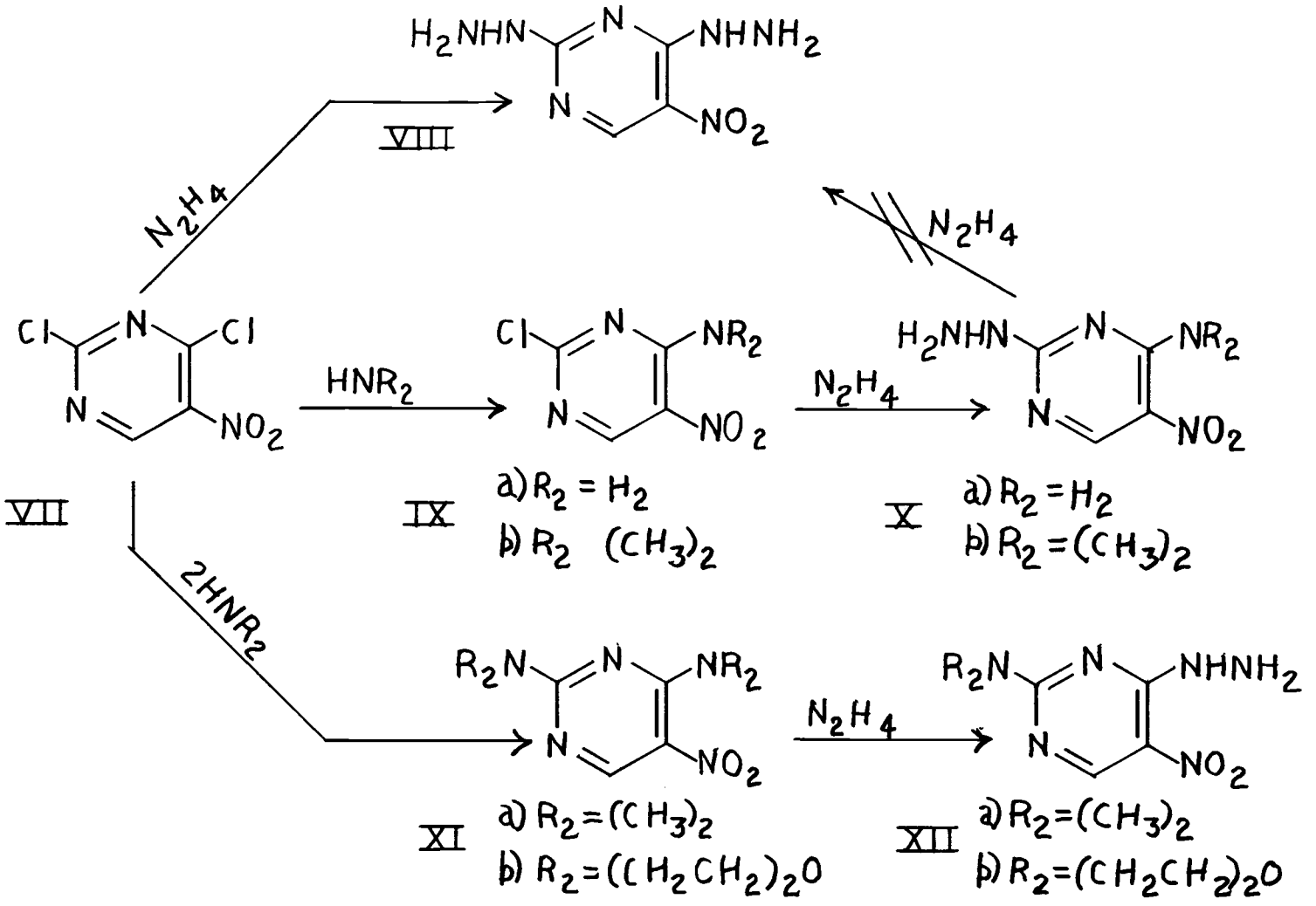


Figure 2. Hydrazinolysis of 5-nitropyrimidines as reported by Wiley, Lanet, and Hussung.

reaction of the known 4-chloro-2-dimethylamino-5-nitropyrimidine with hydrazine. Moreover, the 2,4-dimorpholino-5-nitropyrimidine (XIb) on treatment with hydrazine behaved in an identical manner i.e. the replacement only of one of the morpholino substituents by hydrazine. This product was assigned the structure 4-hydrazino-2-morpholino-5-nitropyrimidine (XIIb) on the assumption that the 4-position would be the more susceptible to nucleophilic attack as found with the former reaction. This reaction however had limited applicability; when two other compounds, the 2,4-dipiperidino- and the 2,4-bis-(diethylamino)-5-nitropyrimidine, were reacted under the identical conditions, only trace amounts (if any) of the intended products were obtained.

Another interesting observation was the inability of the hydrazine to displace the dimethylamino group of 4-dimethylamino-2-hydrazino-5-nitropyrimidine in view of the ease of formation of the isomeric XIIa by the hydrazinolysis of 2,4-bis-(dimethylamino) pyrimidine.

As a consequence of these discoveries it appeared that further exploration into the reaction of nitropyrimidines with hydrazines might prove to be most fruitful. This is a facet of pyrimidine chemistry which has received very little attention. Moreover, from the limited information available these reactions are so unusual as to make this area of the investigation extremely attractive.

In addition the hydrazino-nitropyrimidines have a definite utility as intermediates. For example, one could prepare many hereto unreported simple nitropyrimidines from the knowledge that hydrazino substituents can be removed by mild oxidizing agents such as copper (II) sulfate. Thus one could obtain 5-nitropyrimidine, itself, which has yet to be synthesized, by treating 4,6-dihydrazino-5-nitropyrimidine with copper (II) sulfate. Similarly, the unknown 4-alkyl-5-nitropyrimidines could be produced from 6-alkyluracils via nitration, chlorination, hydrazination and then mild oxidation. Moreover the hydrazino-nitropyrimidines have the potential of being influential intermediates in the formation of other ring systems as well. For instance, the intramolecular ring closure between the nitro and hydrazino groups would lead to 8-azapurine derivatives. Or, after reduction of the nitro group, one could have an intermolecular ring closure with carbon fragments to yield purines, 6-azapteridines, etc.

Furthermore, there are other important areas in which the hydrazino-nitropyrimidines could prove to be most useful e.g. medicinal chemistry. Encouragement along these lines came from the disclosure that the p-methoxybenzaldehyde derivative of 2,4-dihydrazino-5-nitropyrimidine exhibited slight activity in Sarcoma-180 tests (69).

For these reasons, it was decided to continue the study on the

hydrazinolysis of nitropyrimidines and to direct our interest to two main objectives. First, to investigate the unique reaction discovered by Krackov between 4, 6-dimethoxy-5-nitropyrimidine and methylhydrazine. This study was primarily concerned with the elucidation of structure of the product or products of the reaction. The second objective of this study was to determine whether this reaction is applicable to other related 5-nitropyrimidines and other hydrazines.

DISCUSSION

One of the puzzling aspects of this work was the problem of deducing the structure of the product(s) formed by the reaction of 4,6-dimethoxy-5-nitropyrimidine (IV) with methylhydrazine as first reported by Krackov and Christensen (45). To enable further studies of this reaction, it was necessary to prepare more of IV, the course of which led to further interesting developments.

This was accomplished by the following synthetic route. Malonodiamide was condensed with ethyl formate by the method of Hull (38) to yield crude 4,6-dihydroxypyrimidine, which was then nitrated in the 5-position using the directions of Boon, Jones and Ramage (14). The chlorination procedure of the latter workers, which was modified following the suggestion of Krackov (44), then afforded the 4,6-dichloro-5-nitropyrimidine in good yield. In scaling up this reaction it was discovered that it is important to slowly add the N,N-diethylaniline after the phosphorus oxychloride. If the addition is done in the reverse order, an uncontrollable exothermic reaction occurs producing copious amounts of foam which solidifies to a fluffy polymeric material.

Treatment of the chloropyrimidine with sodium methoxide, via directions of Rose and Brown (60), gave the desired 4,6-dimethoxy-5-nitropyrimidine (IV). This compound was purified by repeated

recrystallizations from n-butanol until it melted completely within one half a degree range.

Following the conditions given by Krackov and Christensen (45) methylhydrazine was refluxed with IV in freshly distilled n-butanol for three hours. As reported, a fine solid material precipitated in small amounts, which was removed by filtration after allowing the reaction mixture to stand overnight at refrigerated temperature. Both the ultraviolet and infrared spectra of the precipitate agreed quite well with that reported by Krackov (44). For clarity and conciseness this precipitate will be referred to as "2H-K". The "2H" is used to designate that the original pyrimidine reactant had a hydrogen substituent at the 2-position.

The filtrate from the reaction, which varied in color from a very deep yellow to red, was evaporated to dryness in vacuo at room temperature. The residue was a red viscous oil which could not be made to crystallize by the usual techniques. The infrared spectrum of the oil had very broad bands centered at 3250, 3000, 1600 and 1200 cm^{-1} as well as other small diffused peaks.

The ultraviolet spectrum of the filtrate exhibited mainly end absorption below 200 mμ. There was some adsorption with a broad maximum at 250 to 280 mμ. However, assuming an extinction coefficient of 5000 for pyrimidines absorbing in that region, the total amount of compound(s) is estimated to be less than 500 mg per liter

of filtrate. Since our concern was only with pyrimidine derivatives and not other possible degradation products, the filtrate was not subjected to further investigation.

The yellow-tan to light brown precipitate 2H-K was recrystallized from water m. p. 235-250°C (dec.). It was observed that prolonged heating in boiling water resulted in decomposition of 2H-K; for example, one hour of exposure to boiling water yielded a deep red product instead of the normal white to yellow-tan colored crystal. Analysis of the recrystallized 2H-K gave values ranging from C, 37.6-37.8%, H, 4.7-4.9%; N, 43.7-43.8%. Repeated recrystallization from water did not change these results. The analysis corresponded best to an empirical formula of $C_{11}H_{17}N_{11}O_3$ which suggested: (a) an impure compound, (b) a mixture of simple pyrimidines or (c) a polymeric product.

The infrared spectrum of a mull of 2H-K was complex (See Figure 3 and Table I). There were three bands in the N-H and O-H stretching region; 3320, 3260 and 3175 cm^{-1}. The sharp absorption peak at 3320 cm^{-1} was assigned to the free N-H of a secondary nitrogen. Though some amino-pyrimidines do exhibit absorption bands near 3300 cm^{-1}, usually they are broad bands due to the associated N-H stretching (20, 63); the free N-H stretching of aminopyrimidines generally occur in the 3500-3400 cm^{-1} region (20, 51) as one would predict for amino compounds. The N-alkylaminopyrimidines, such

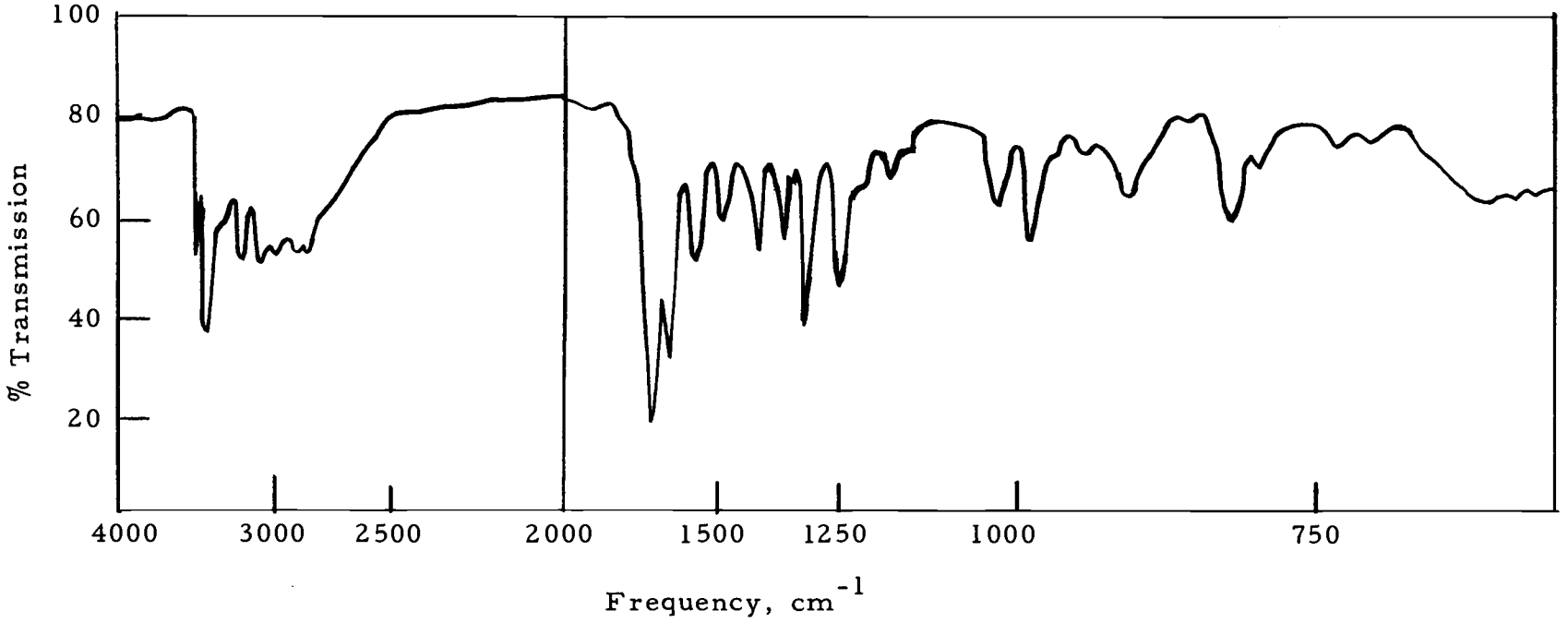


Figure 3. Infrared spectrum of 2H-K; composite of mulls in Kel-F-10 oil (4000-1300 cm^{-1}) and nujol oil (1300-625 cm^{-1}).

as 4-methylaminopyrimidine and the 4-aminopyrimidines, likewise do not appear as likely prospects for this band for they are hydrogen-bonded in the solid state; however the latter imines do exhibit sharp bands near 3300 cm^{-1} in a dilute solution (20, 49). The most satisfactory assignment appeared to be the N-H stretching vibration of a hydrazino group. Hydrazines normally absorb in this region. For instance, the N-H bond of methylhydrazine absorbs at 3317, 3245 and 3177 cm^{-1} (6) and 1,2-dimethylhydrazine absorbs at 3294 and 3223 cm^{-1} (64). Moreover, this assignment is further supported by the work of Kreutzberger (46) who investigated a series 2,2'-hydrazopyrimidines in which he observed that the N-H stretch of the hydrazino groups gave sharp absorption bands between 3270 and 3230 cm^{-1}.

The remaining broader 3260 and 3175 cm^{-1} bands are most reasonably interpreted as associated with N-H stretching. However this does not exclude when structurally feasible the possibility of "hydroxypyrimidines" which are found to exist in their tautomeric amido structures in the solid phase as well as in solution. These ketopyrimidines generally exhibit bands in the 3200-3100 cm^{-1} region (63) due to the N-H and not 3050 cm^{-1} region as formerly suggested by Brownlie (21). Moreover, the bands for a given ketopyrimidine have been found to vary, probably resulting from different crystalline structures. For instance, Short and Thompson

(63) found no band at a higher frequency than 3200 cm^{-1} for 4-hydroxypyrimidine in the solid phase while Mason (50) who also examined this compound in the solid phase reported finding bands at 3257 and 3200 cm^{-1}.

Aminopyrimidines also show a band near 3200 cm^{-1} but this band is normally accompanied by other strong bands in the 3300-3400 region. The alkylaminopyrimidines and iminopyrimidines, on the other hand, only exhibit absorption in the lower 3200-3100 cm^{-1} region (20). However, these two bands can also be explained as the N-H stretch of a hydrazino group.

Thus it is possible to assign the 3260 and 3175 cm^{-1} peaks to any of the following: (a) a ketopyrimidine, (b) a secondary amino-pyrimidine (c) an iminopyrimidine or (d) a hydrazino pyrimidine.

The 3050 cm^{-1} absorption peak is typical and can be assigned to the aromatic hydrogen of the pyrimidines. However, this is stronger than might be expected, especially if the pyrimidine is highly substituted (9, p. 282). Conceivably, this band may be due to the presence of a vinyl hydrogen.

In the double-bond stretching region, which includes the range of the N-H deformation mode, there are two strong absorption bands at 1666 and 1625 cm^{-1}, either of which could be assigned to a carbonyl or a primary nitrogen. Although absolute assignment of the peaks cannot be made, consideration of the possibilities poses some

interesting speculations. The 1666 cm^{-1} or the stronger absorption band is most likely due to a carbonyl group. The carbonyl stretching region for ketopyrimidines is 1720-1670 cm^{-1} (43, p. 268). This assignment is supported by the N-H stretch region and by a weak absorption band at 1548 cm^{-1} which can be attributed to the N-H deformation of the amide (43, p. 269). It is rather doubtful that the other strong band stems from the effect of a carbonyl function because dioxopyrimidines always show at least one absorption at a higher frequency than 1690 cm^{-1}; therefore, the 1625 cm^{-1} band is interpreted as an N-H deformation vibration of a primary nitrogen. An interesting observation is that the primary amine bending region for most compounds is given as 1640-1560 cm^{-1} (52, p. 38), in contrast to aminopyrimidines which are found to absorb at 1680-1660 cm^{-1} (20, 63). This implies that a primary nitrogen possibly (1625 cm^{-1}) may not be attached directly to a pyrimidine ring. Consequently, this suggests the presence of a ketopyrimidine with an aliphatic amino or hydrazino group. A hydrazino group is much more likely owing to the nature of the original reactants and the absorption in the 3000 cm^{-1} region which exhibits no peaks above 3320 cm^{-1}.

If, on the other hand, the 1666 cm^{-1} peak is assigned to a primary nitrogen absorption, then because of the high frequency of this band, one must also presume the presence of an

aminopyrimidine. However, an aminopyrimidine is not supported by spectral absorption in the N-H stretch region. A carbonyl structure in the pyrimidine ring is much less likely to absorb at the low frequency of 1625 cm^{-1}. This band is best assigned as before to a primary nitrogen not adjacent to a pyrimidine ring. Hence this suggests an aminopyrimidine with also an aliphatic amino or a hydrazino group.

Evidence for the existence of the pyrimidine ring is found in the bands at 990 and 810 cm^{-1} which are characteristic bands of most pyrimidines.

Important information was also deduced from the lack of certain bands. The usual strong absorption near 1100 cm^{-1} due to methoxy groups in the original pyrimidine had disappeared. Similarly the bands at 1540 and 1325 cm^{-1} associated with the nitro group were also absent.

In summary, it was concluded from the infrared spectrum that (a) the pyrimidine ring was still present (b) both methoxy groups and nitro group were absent (c) a hydrazino group was likely present and (d) that there was either a tautomeric hydroxy or amino group attached to the ring. Moreover, there might plausibly be an iminopyrimidine, an N-methyl group and also a vinyl hydrogen atom.

A 10.0 mg sample of 2H-K in 1000 ml of aqueous acetic acid solution (pH 4.5) exhibited a smooth ultraviolet curve with a λ_{max}

at 260 mμ (absorbance, 0.79) and at 217 mμ (absorbance, 1.65). In a hydrochloric acid solution (pH 1.0), the same concentration of 2H-K showed a slight shift and broader peaks; λ_{max} 258 mμ (absorbance, 0.40) and 212 mμ (absorbance 1.70). Under basic conditions there was a notable change. A solution of 10.0 mg of 2H-K in 1000 ml of 0.1 N sodium hydroxide solution exhibited only one peak at about 214 mμ (absorbance greater than 1.8) with a shoulder at 251 mμ (absorbance 0.30). This behaviour is characteristic of the absorption of pyrimidine compounds in the uv range.

The ultraviolet spectrum indicated that 2H-K was a conjugated system, probably a pyrimidine or an aromatic system, which had groups adjacent to the ring that are pH dependent. Moreover the spectrum (of the solution at pH 4.5) is indicative of a fairly pure compound.

On the other hand the broad melting point and empirical formula are more suggestive of an impure compound. For this reason other methods of purification were applied to resolve the question of purity.

Use of a column packed with either silica gel or alumina led to decomposition of 2H-K as shown by a color change to deep red, as well as a decrease in the extinction coefficient, and broadening of maximum wavelength in the ultraviolet spectra of the fractions. This was confirmed by a time study of a slurry consisting of 2H-K, silica

gel and water; with increase in contact time the color changed from yellow-tan to a deep red while analysis of aliquots showed that the carbon content was increasing and nitrogen content decreasing with longer exposure time.

Attempts were made to separate 2H-K into other components with thin-layer chromatography. Two solvent systems were tried, n-butanol-acetic acid-water (4:1:5) and 95% ethanol-28% ammonium hydroxide (4:1). The plates were coated with Silica Gel G and then activated in an oven at 100°C for one hour. Only one spot could be detected on the developed plate when it was exposed to iodine vapors or short-wave (2590Å) ultraviolet light. When the developed plate was sprayed with concentrated sulfuric acid and charred in the oven, there appeared to be only one possible trace of an impurity.

Since the one spot found in the thin-layer chromatography is suggestive of purity but not conclusive proof, a further purification through recrystallization from another solvent was attempted. 2H-K was found to be insoluble in non-polar solvents. In acidic or basic solutions, 2H-K was very soluble--even at very low temperatures. A useful solvent was found in a mixture of 95% ethanol-water (1:1) mixture. Recrystallization twice from this solvent and treatment with charcoal yielded long white needles. Analysis of these crystals showed only a small increase in carbon content, 38.0 - 38.1% as compared to the original 37.6 - 37.8% and no difference in the

hydrogen and nitrogen content. A sample re-purified by this latter method exhibited no notable difference in its ultraviolet or infrared spectra.

A sample was also sublimed; the process was very slow, three days at 150°C and 0.02 Torr yielded only a small amount of sublimed material. The analysis and spectral data of the sublimed product was in agreement with the sample purified by recrystallization.

Although the 2H-K appeared to be pure, still the simplest empirical formula which would agree reasonably with the new analytical data was $C_{19}H_{29}N_{19}O_5$. It seemed unlikely that 2H-K was a mixture of two or more simple pyrimidines since repeated recrystallizations, sublimation and thin-layer chromatography could not resolve 2H-K into two or more components. Having satisfactorily demonstrated that 2H-K was a pure compound lead to the assumption that the reaction product was the consequence of not only the displacement of the reactive groups but polymerization as well.

It then became necessary to obtain a molecular weight of 2H-K to confirm the possible polymeric nature of the reaction product. Use of the common methods, such as cryoscopic, ebullioscopic or Signer methods, were not practical owing to the low solubility in non-polar solvents and the possible decomposition or dissociation in the protic solvents. Recourse to a spectroscopic method reported by Cunningham et al. (24) was employed. This method consisted of

observing the ultraviolet spectrum of a solution of the picrate of the unknown; the molecular weight could then be calculated from absorbance measurements. Values of 127 and 132 from such data were calculated from two picrate solutions of 2H-K. These low values being inconsistent with the analytical data were thought to be the result of more than one reactive basic site per molecule and hence represented an apparent sub-multiple of molecular weight. In correlating the empirical formula with this data a molecular formula $C_{38}H_{58}N_{38}O_{10}$ was calculated which requires nine reactive sites for picrate formation, a highly improbable hypothesis.

To verify this improbable molecular formula the decision was made to prepare another salt derivative with 2-nitro-1, 3-indandione. However, when 2H-K was refluxed with the 2-nitro-1, 3-indandione in alcohol a deep red precipitate formed which was insoluble in most solvents including water and only exhibited a decomposition point when heated. This particular indandione has previously been used with many other nitrogen bases including pyrimidines to yield nice yellow crystalline salts which were soluble in hot water and had characteristic melting or decomposition points.

It seemed therefore that a condensation between the carbonyl group of the indandione and the reactive primary nitrogen group on 2H-K had occurred instead of salt formation. Subsequent investigations with other amines and hydrazines revealed a selective

reactivity. With primary amines--including aliphatic, aromatic, and aminopyrimidines--an indandionate salt was produced. The hydrazines which possess at least one primary amino group, i.e, hydrazine, methylhydrazine, phenylhydrazine and hydrazinopyrimidines, when heated with an alcoholic solution of indandione yielded highly colored condensation products. Thus, this reagent, 2-nitro-1, 3-indandione, might be used to distinguish between amines and more reactive primary amino substituents such as occur in the hydrazines.

The observation that 2H-K appeared to have such a reactive primary amino substituent was confirmed by the treatment of 2H-K with an aqueous solution of sodium pentacyanoammineferroate. An intense red color was produced which is reported as a positive test for hydrazines of the type $RHN\text{-}NH_2$ and $R_2N\text{-}NH_2$ (29, p. 292; 30).

Another approach was taken to verify the molecular formula. Instead of making another type of salt with 2H-K for comparison, the initial pyrimidine or hydrazine reactant would be varied. Not only would this help confirm the molecular weight but also give information as to the ratio of hydrazino substituents to pyrimidine ring as well as the percentage of pyrimidine moiety in such a polymer.

The first to be varied was the reacting hydrazine. The following hydrazines were treated with 4, 6-dimethoxy-5-nitropyrimidine; 1, 1-dimethylhydrazine, 1, 2-dimethylhydrazine, phenylhydrazine, and 2, 4-dinitrophenylhydrazine. Under conditions which produced

2H-K with methylhydrazine none of the above yielded products with similar chemical and physical properties to 2H-K. The first two hydrazines resulted in decomposition of the pyrimidine to deep red oils which could not be made to crystallize and which exhibited mainly end absorption in their ultraviolet spectra. The latter two hydrazines showed no notable reactivity towards the pyrimidine and the starting pyrimidine was recovered in good yields.

Then 4, 6-dimethoxy-2-methyl-5-nitropyrimidine was prepared. The synthesis was straightforward; acetamidine having been prepared from acetonitrile was cyclized with diethyl malonate according to the directions of Henze, Clegg, and Smart (36). The 2-methyl-4, 6-pyrimidiol was nitrated easily in the 5-position and in good yields using the procedure of Albert, Brown, and Wood (5). Subsequent chlorination by a method reported by the latter workers yielded the 4, 6-dichloro-2-methyl-5-nitropyrimidine.

A modification of the procedure of Urban and Schnider (68) was used to replace the chloro substituents by methoxy substituents. A shorter reaction time was used and an improved isolation procedure resulted in a nearly quantitative yield of 4, 6-dimethoxy-2-methyl-5-nitropyrimidine (XIII) of high purity.

When XIII was treated with methylhydrazine under the conditions which formed 2H-K a precipitate was produced which had similar properties--chemical, physical and spectroscopic--to that of 2H-K.

For example, the precipitate, 2Me-K, could be recrystallized from an ethanol-water solvent, and had a reactive primary amino group as shown in its reaction with both 2-nitro-1, 3-indandione and sodium pentacyanoammineferroate. The ultraviolet spectrum in aqueous acetic acid (pH 4.5) showed strong absorption bands at 260 and 217 mμ. The infrared spectrum (see Figure 4) showed comparative absorption bands at 3320, 3265, 3170, 1660 and 1622 cm^{-1}.

The analysis of 2Me-K gave the values of C, 42.9%, H, 5.8%, N, 39.4% which corresponds to the empirical formula $C_{14}H_{23}N_{11}O_3$. Molecular weight determinations by the Cunningham procedure gave a value of 143. No reasonable formula could be determined for 2H-K and 2Me-K in which they differed by only an integral number of CH_2 units.

The use of nmr spectra to help solve this problem provided some surprising information. The nmr spectum of 2H-K in trifluoroacetic acid had only four peaks at 8.31, 8.11, 6.06 and 5.78 δ in an area ratio of about 1:2:2:1 respectively; for 2Me-K in the same solvent there were also only four peaks (5.75, 5.40, 2.37 and 2.17 δ) in a ratio of about 2:1:3:6 respectively. The first two peaks in the 2H-K spectrum and the latter two peaks in the 2Me-K spectrum can be attributed to their substituent in the 2-position because of the chemical shifts, and the absence of each doublet in the other spectrum.

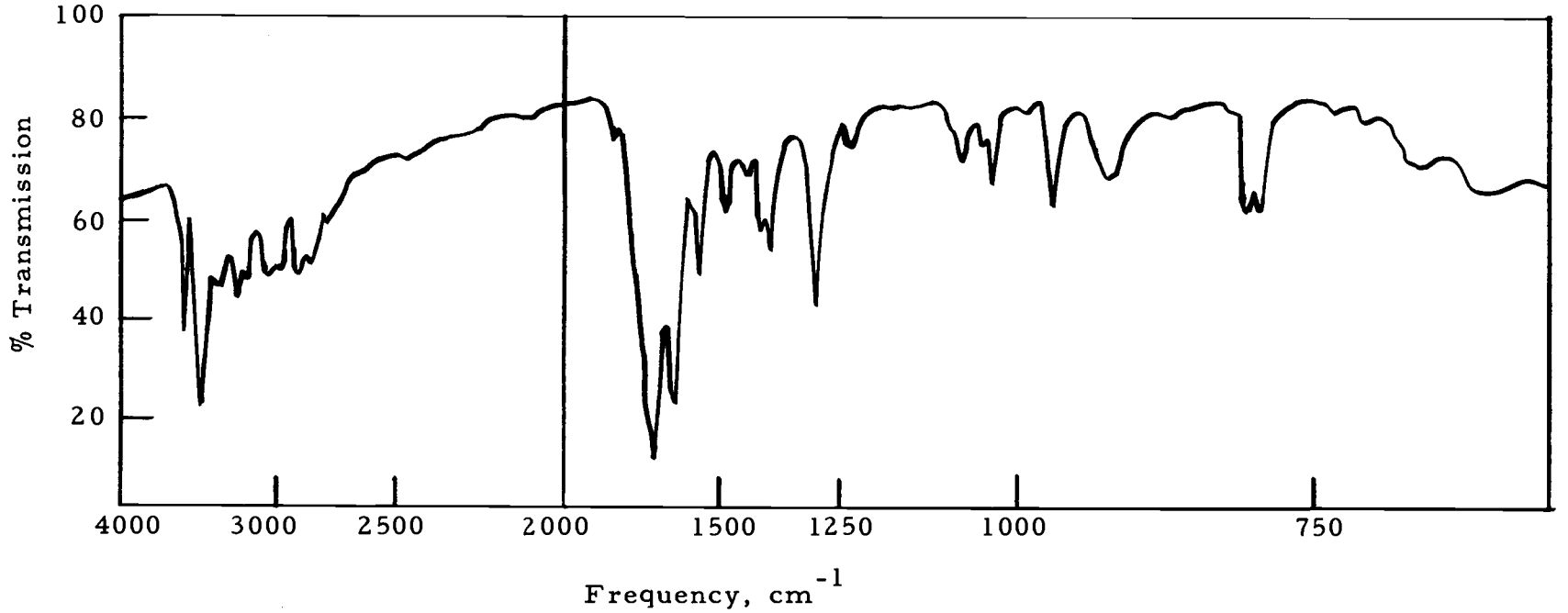


Figure 4. Infrared spectrum of 2Me-K; composite of mulls in Kel-F-10 oil (4000-1300 cm^{-1}) and nujol oil (1300-625 cm^{-1}).

The assignment of the two peaks near 6.0 δ was not as clear. Protons which absorb in this region are: (a) phenolic protons that are polymerically associated, (b) conjugated vinyl protons, (c) amide protons and (d) nonbenzenoid aromatic protons (26, p. 85). The phenolic and amide protons were rejected owing to the sharpness of the peaks and the fact that in our laboratory other pyrimidine derivatives did not exhibit peaks for these groups in trifluoroacetic acid.* This conclusion was confirmed by showing the chemical shifts of these peaks to be concentration independent.

Further interpretation of these peaks could not be made without more information. It was noted that a hydrogen substituent in the 5-position of most pyrimidine derivatives do appear in the 6.0-5.5 δ region (10, 11).

However, for this to be the case for 2H-K and 2Me-K, the reaction would have to result in the replacement of the nitro group by a hydrogen substituent. There are very few reactions with nitroaromatic compounds that will replace the nitro group with a hydrogen atom and in pyrimidine chemistry there are no examples of

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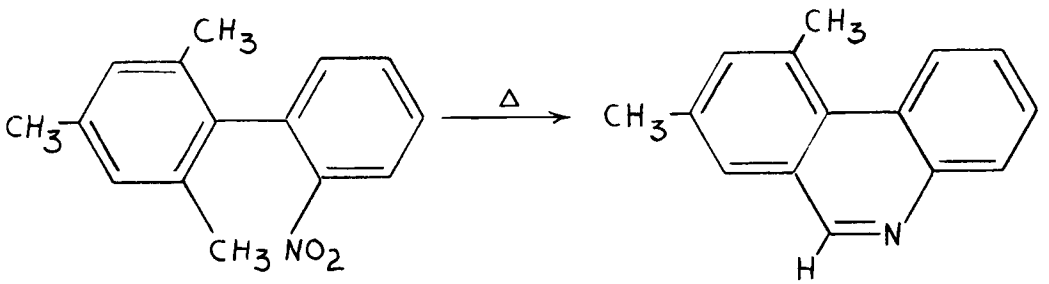
*Hydroxy - and aminopyrimidines (41) in trifluoroacetic acid in some cases do exhibit peaks for hydrogen atoms bound to nitrogen. However, if the solution is contaminated with a small amount of water, the exchange rate is increased to a point where the amino protons and solvent proton coalesce to one peak. Generally amido protons and sometimes other hydrogen atoms bonded to a nitrogen atom give extremely broad peaks which become nearly unobservable. In the spectrum of pure pyrrole, for example, the N-H band is so broad as not to be detectable (40, p. 73-74).

such behavior reported in the literature.

These two peaks (6.06, 5.78, or 5.75, 5.40 δ) may be due to vinyl protons as the consequence of the oxidative condensation reaction of the methyl group of either the methoxy substituent or methylhydrazine with the nitro group, a few examples of this can be found in the literature. One of the more recent examples is the formation of a phenanthredine by deoxygenative cyclization of 2, 4, 6-trimethyl-2'-nitrobiphenyl by heating in phenyl ether (65).



Even more puzzling was the fact there were two peaks in a 2:1 ratio for each particular functional group. Since both 2H-K and 2Me-K appeared pure, it seems unlikely that this observation was due to a mixture of two different pyrimidines. However it could involve equilibria among tautomeric forms of a single pyrimidine derivative. This spectrum also could arise from a trimer in which there were two equivalent pyrimidine moieties. Another explanation can be based on the possibility of a partial reaction with the solvent.

Later studies with 2H-K showed the latter case to be the correct hypothesis. Thus, immediately after 2H-K had dissolved in trifluoroacetic acid, the nmr spectrum was taken; only two peaks of equal area were found at 8.11 and 6.06 δ . On standing for three days, at room temperature, the same solution yielded a spectrum with two peaks of equal intensity at 8.31 and 5.78 δ with only traces of the two earlier peaks. The sample was recovered by evaporation of the solution to dryness and then placed in vacuo for 24 hours. The infrared spectrum of the residue (see Figure 5)showed a change from the 2H-K. The appearance of new peaks near 1700 cm^{-1}, and also near 1200 cm^{-1} as well as the change in the N-H stretch region suggested that acetylation of 2H-K by trifluroacetic acid was responsible for this shift and the double peaks for each type of proton in the earlier spectrum. Probably the most important property of the nmr spectra were their simplicity.

The nmr spectra of 2H-K and 2Me-K in a solution of 15% sodium deuteride in deuterium oxide exhibited only one peak due to the substituent in the 2-position. Dilution to a 1% solution which shifted the HOD peak 0.75 ppm to a lower frequency did not reveal a hidden peak.

In a 10% solution of deuterochloride in deuterium oxide, 2H-K and 2Me-K again showed only one major peak for the 2-positioned substituent. There was a trace peak in the 5.8-6.08 region in each

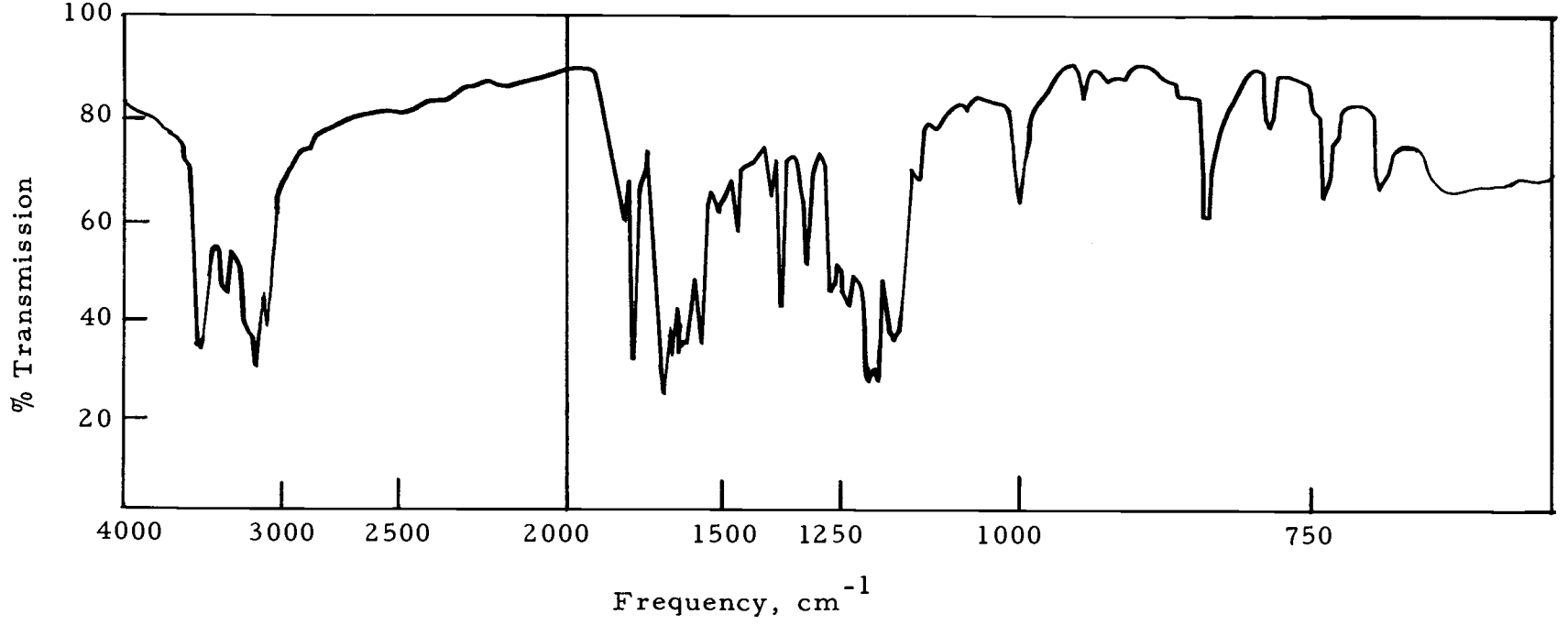


Figure 5. Infrared spectrum of residue from solution of 2H-K in trifluoroacetic acid.

spectrum which when integrated for the 2H-K spectrum was only in 5-10% of the substituent peak at 8.37 δ.

Thus the peak near 6.0 δ, which was common to both compounds, and which was observable in trifluoroacetic acid and appeared to be concentration independent, was found to exchange in both acidic and basic aqueous solutions. It seems questionable that a vinyl or primidyl hydrogen would be so labile and yet it seems just as doubtful that a phenolic or other labile hydrogen would not be exchanged rapidly in trifluoroacetic acid.

The simplicity of the nmr spectra made the concept of a polymeric structure doubtful. If polymeric, it must be made of equivalent pyrimidine units. Whereas the type and number of the other hydrogen atoms in the compound would provide useful information towards resolution of structure such data could not be ascertained from 2H-K or 2Me-K since they were insoluble in the non-polar solvents. A phenyl substituent in the reacting pyrimidine however might give rise to a product of more desirable solubility properties.

For this reason, 4,6-dimethoxy-5-nitro-2-phenylpyrimidine was synthesized. The benzamidine hydrochloride was prepared from benzonitrile. A modification suggested by Fanta and Hedman (28) was less time consuming and gave better yields than the usual procedure (32, p. 6). The benzamidine hydrochloride, which was made anhydrous by standing in vacuo over phosphorus pentoxide was cyclized

with diethyl malonate and the resulting pyrimidiol nitrated as described by Hendry and Homer (35). The chlorination procedure of the latter investigators was improved by the use of N, N-diethylaniline in place of N, N-dimethylaniline and a preheating to 90°C, for one hour prior to refluxing the solution for a period of one-half hour; under these conditions the yield was over 95%. This compound was converted to the unreported 4, 6-dimethoxy-5-nitro-2-phenylpyrimidine (XIV) by refluxing in an alcoholic solution of sodium methoxide.

Reaction of XIV with methylhydrazine yielded the expected precipitate in n-butanol. From infrared and ultraviolet data (see Figure 6 and Tables I and II), it was concluded that the product, 2Ph-K, was indeed similar in structure to 2H-K and 2Me-K, excepting of course, for the presence of a phenyl substituent.

The analysis of 2Ph-K gave C, 59.4%; H, 4.8%; N, 26.7%. Here again no reasonable molecular formula could be calculated for 2Ph-K that would correlate with those calculated for 2H-K and 2Me-K nor could a formula be calculated that would suggest a simple pyrimidine derivative.

The nmr spectrum of 2Ph-K in trifluoroacetic acid had two multiplets centered at about 7.70 and 7.24 δ and a singlet at 6.02 δ which integrated as 2:3:1 respectively. The two multiplets were similar to those found with phenyl substituents adjacent to a carbonyl group and were found to be typical of 2-phenylpyrimidines. The

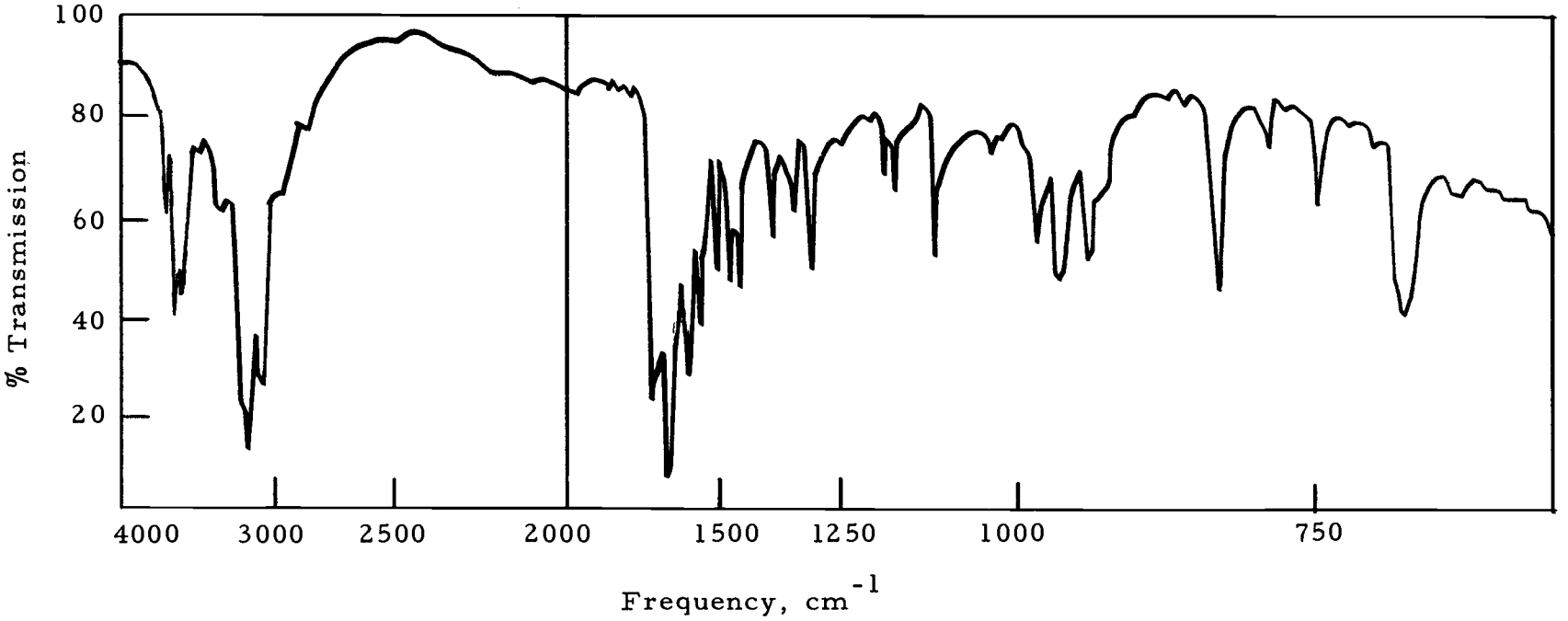


Figure 6. Infrared spectrum of 2Ph-K (nujol mull).

6.02 δ singlet did not appear in a basic aqueous solution, as was observed in the behavior of 2H-K and 2Me-K.

The 2Ph-K was soluble in deuterated dimethyl sulfoxide and gave the nmr spectrum; 8.39 (mult.), 7.80 (mult.), 5.66 (singlet) and 3.65 δ (broad) which roughly integrated as 3:3:1:2.7 respectively. The integration of 2.7 for the peak at 3.65 δ might be taken as evidence for a polymer or just an unsatisfactory integration caused by broadening of the peak. The latter reason seems more reasonable from experience in integrating other comparative broad peaks. Presuming then a relative area of 3 for the latter peak, there are ten total protons in the spectrum. The phenyl substituent accounts for five protons which are peculiar to 2Ph-K.

The other five protons should be common to all three compounds (2H-K, 2Me-K and 2Ph-K). The anomalous proton near 6.0 δ which has been discussed previously, is definitely observable in all three cases. The remaining four must be labile hydrogen substituents. The three at 3.65 δ appearing as one broad peak are undoubtedly nitrogen bonded hydrogen atoms. The last proton, though partially obscured by the multiplet from the two alpha protons of the phenyl substituent, can be distinguished as a sharp peak near 8.3 δ This can be assigned to either a phenolic or an amido hydrogen substituent.

The nmr data was suggestive of a pyrimidine from the chemical

shifts of each substituent as well as the pattern exhibited by the phenyl substituent. Also this data showed that for one pyrimidine ring there was present five other hydrogen substituents; four labile protons of which at least three were most likely bonded to nitrogen atoms and one proton that demonstrated unusual exchange properties. The spectrum was more like that of a single pyrimidine derivative than of a complex polymer implied from the carbon-hydrogen-nitrogen analysis. If indeed they are polymeric in nature, they must be made of equivalent or symmetrical pyrimidine units (not confirmed by analysis).

More precise and reliable molecular weight data was needed. Therefore, the mass spectra of 2H-K, 2Me-K and 2Ph-K were run at a probe temperature, 200° - 260°C, and an ionization voltage of (70 e.v.). Evidently these conditions were too harsh since there were enumerable peaks due to high-energy fragmentation processes or thermal decomposition; both possibilities are likely. These compounds are thermally unstable in that temperature range as judged by the behavior on the m.p. block. Furthermore, Rice, Dudek and Barber (54) have shown by their mass spectral investigations that 70 e.v. is too high an energy input for most pyrimidine compounds. They found at this voltage extensive high energy rearrangements giving rise to unpredictable and unexplainable fragments. For example pyrimidine itself at 70 e.v. was reported to

have a peak at m/e of 68 which corresponds to a loss of one carbon atom.

In each spectrum (2H-K, 2Me-K, and 2Ph-K) there were however a few peaks which did correspond with each other. There were four major peaks that were common to each that differed only by the substituent in the 2-position. With high resolution the exact masses were determined for each and these were calculated to be; $R - C_4H_5N_4O^+$, $R - C_4H_3N_3O^+$ and $R - C_3H_3N_2^+$ (R = H, Me, Ph). There were no peaks at higher mass that had this correlation. There were two major peaks in each spectrum that were common to all and independent of the different substituents at position-2; $C_3H_5N_3O^+$ and $C_7H_6N^+$. The former fragment can be explained by; $R - C_4H_5N_4O^+ \longrightarrow C_3H_5N_3O^+ + RCN$ which occurs commonly during pyrimidine fragmentations. The occurrence of the $C_7H_6N^+$ could not be explained.

Moreover the strongest peaks in the spectrum were of very low mass such as m/e of 18 or 28. Due to the excessive fragmentation and the unreliable high mass peaks, 2H-K and 2Me-K were sent to be rerun at lower temperatures and a lower ionization energy. Unfortunately (by mistake) they were again run at 70 e.v., however their spectra were superior to the early data (see Figures 7 and 8). The peaks which correlated before were all present with one exception, the unexplainable $C_7H_6N^+$. In both spectra the principal peak

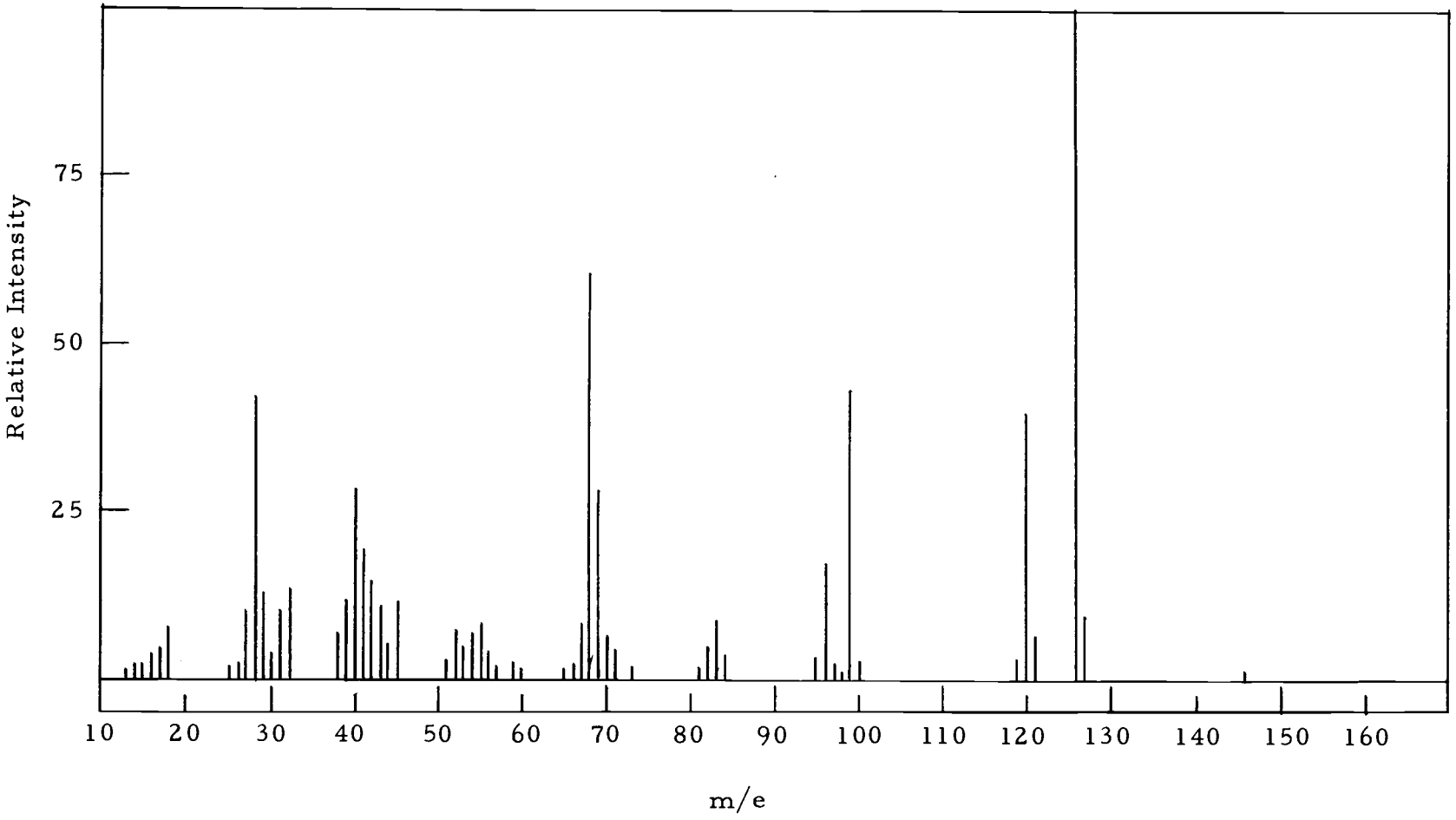


Figure 7. Mass spectrum of 2H-K.

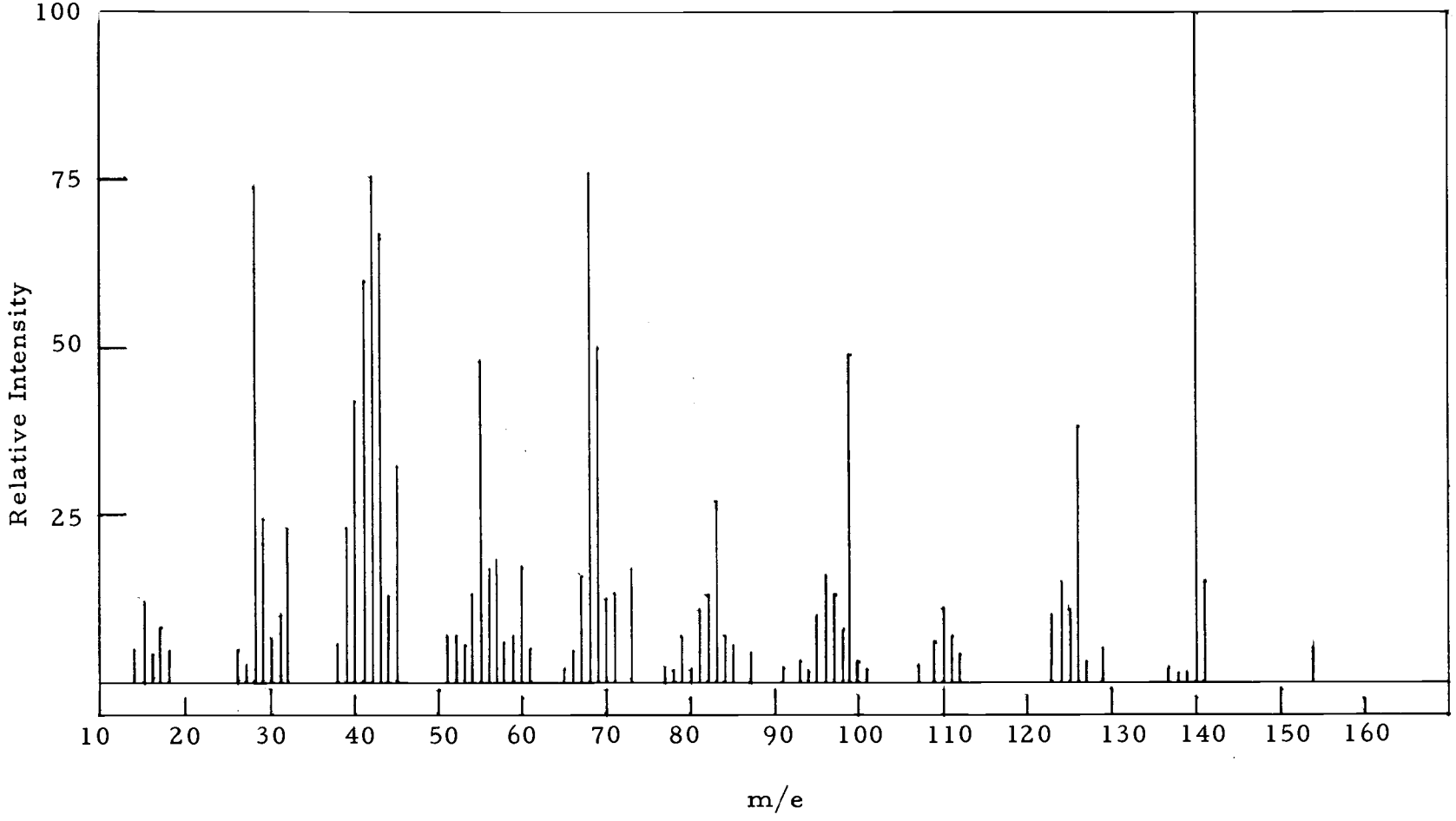


Figure 8. Mass spectrum of 2Me-K.

was R - $C_4H_5N_4O^+$ and only very weak peaks were found at higher mass numbers. Thus it appeared that the R - $C_4H_5N_4O^+$ was the molecular ion. On re-examination of the analytical data, it was noted, that the carbon-hydrogen analysis was in excellent agreement with the molecular formula proposed from the mass spectral data for all three compounds while the nitrogen analysis, on the contrary, disagreed with every compound. The nitrogen percentage was lower in each case than that calculated for R - $C_4H_5N_4O$.

Furthermore, the mass spectral data agreed with the nmr data on the number of hydrogen substituents. Also the earlier molecular weight determinations for 2H-K and 2 Me-K concurred with the proposed molecular weight. In fact, the only evidence that did not subscribe to this formula was the analytical nitrogen data.

In order to confirm the suspicion that the nitrogen analysis was incorrect and the true formula was indeed R - $C_4H_5N_4O$), acetylated derivatives of 2H-K and 2Ph-K were prepared. The compounds were treated with acetic anhydride using a moderate temperature (below 85°C) so as to avoid possible diacetylation of any amino substituent.

The carbon-hydrogen and nitrogen analysis of acetylated 2H-K and 2Ph-K corresponded to R - $C_4H_5N_4O \cdot 2C_2H_2O$ (R = H, Ph) or to diacetylation of the proposed formula R - $C_4H_5N_4O$. The infrared spectrum of the acetylated 2H-K (see Figure 9) confirms the diacylation with two carbonyl peaks at 1715 cm^{-1} and 1690 cm^{-1}. The

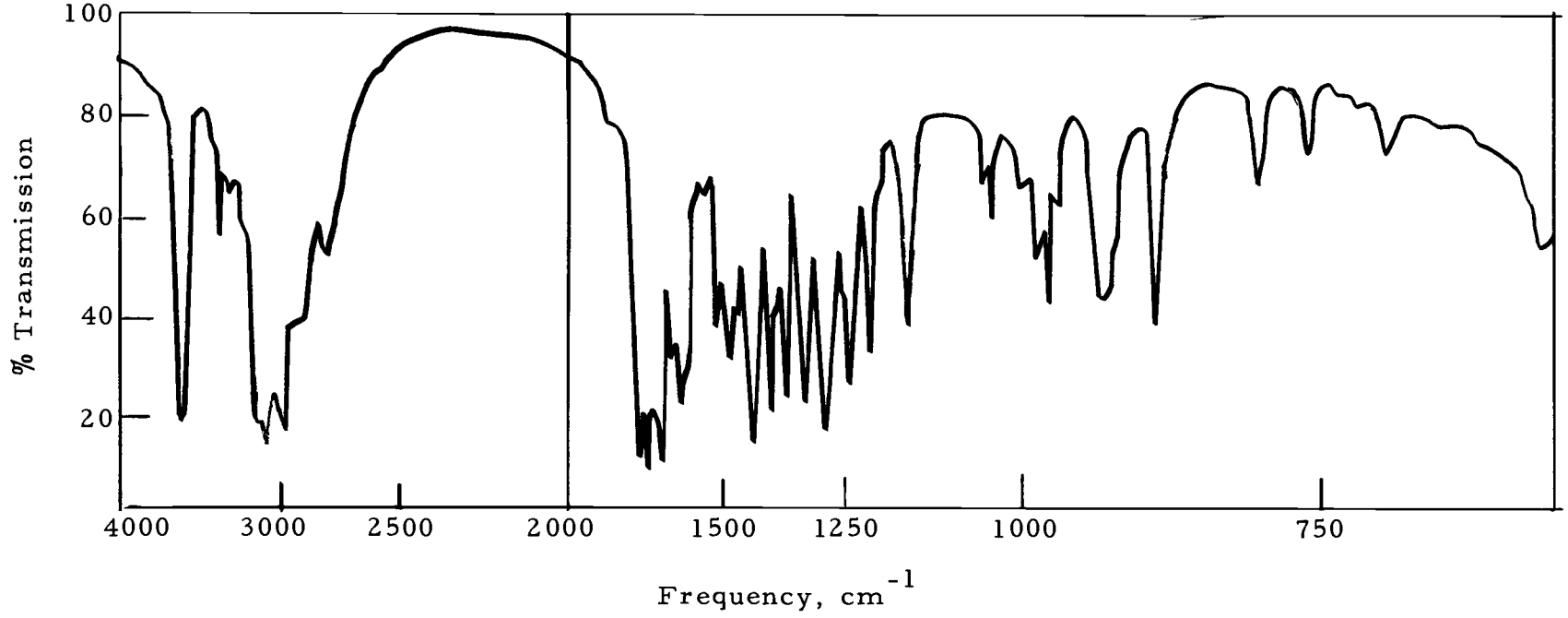


Figure 9. Infrared spectrum of acetylated 2H-K (nujol mull).

acetylated 2Ph-K (see Figure 10) however, had only one strong peak at 1690 cm^{-1} and a weak shoulder at 1700 cm^{-1}.

The nmr spectra showed definitely that diacetylation had occurred. The acetylated 2H-K in deutrated dimethyl sulfoxide gave peaks at 10.69, 8.23, 6.85, 2.21 and 2.02 δ with an area ratio of 1:1:1:3:3. There was one proton that was not observable which might be explained by an apparent broadness near 3.0 δ which could not be integrated. Acetylated 2Ph-K in the same solvent did exhibit all the expected peaks; 11.04, 8.49 (mult.), 7.78 (mult.), 7.15, 4.0 (broad), 2.32 and 2.15 δ that integrated 1:2:3:1:1:3:3 respectively.

Having demonstrated with reasonable certainty that the R - $C_4H_5N_4O$ was the real molecular formula, it now became the task to select the correct isomer. It was evident from the ultraviolet, infrared and nmr data that these three unknowns were pyrimidine derivatives which had preserved the original substituent in the 2-position of the initial pyrimidine reactant. Some of the more plausible pyrimidine isomers that fulfill the demands of the molecular formula for 2H-K are shown in Figure 11.

Of these only 4, 5-diamino-6-hydroxypyrimidine (XV) is a known compound. A sample of XV for comparison purposes was easily obtained by desulfurization of the 2-thio analog (3). The infrared and nmr spectra were fairly similar to 2H-K. The infrared

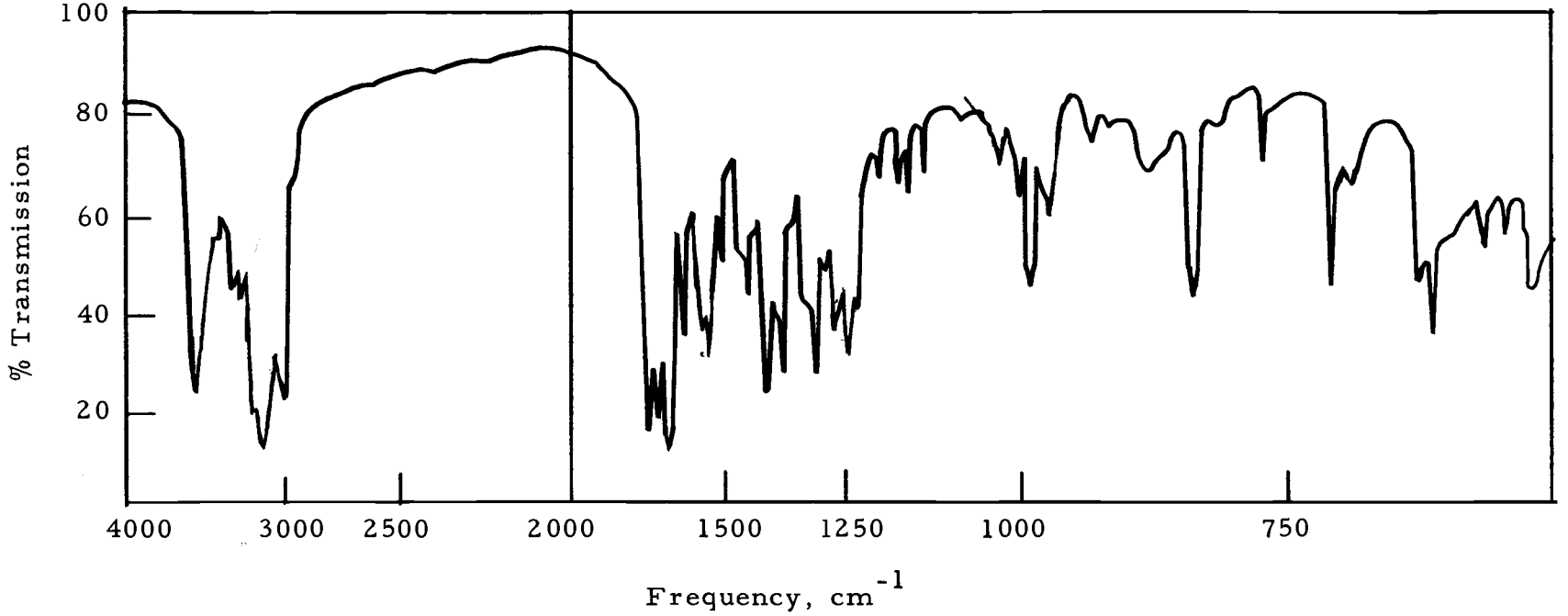


Figure 10. Infrared spectrum of acetylated 2Ph-K (nujol mull).

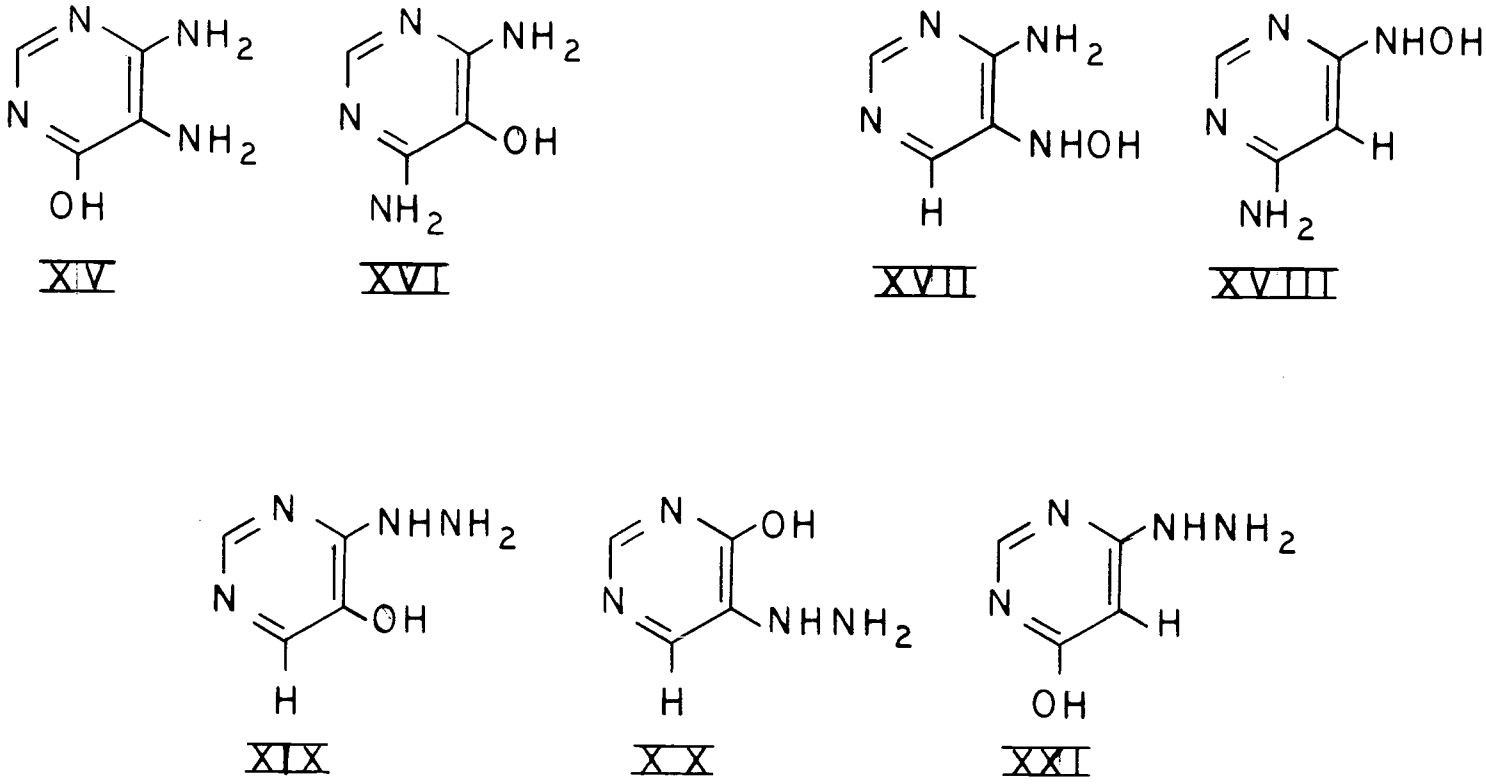


Figure 11. Some pyrimidine isomers that correspond to the empirical formula $C_4H_6N_4O$.

spectrum had the usual series of small peaks between 3000 and 2600 cm^{-1}, two strong peaks near 1650 cm^{-1} and a comparable N-H stretch region except for one band near 3450 cm^{-1}. The nmr spectrum of a trifluoroacetic acid solution showed only one peak at 8.25 δ which slowly decreased in size with the appearance of another increasing peak at 8.53 This was presumed to be due to acetylation of the compound by the solvent, which also had been observed with 2H-K and 2Me-K. The peak near 6.0 δ observed with 2H-K was absent.

Turning our attention to the remaining isomers, those having possible hydroxylamino substituents as for example (XVII and XVIII) were eliminated from further consideration on the basis of mass spectrographic data. As mentioned earlier the mass spectra exhibited ions for R - $C_4H_5N_4O$, R - $C_4H_3N_3O$ and R - $C_4H_3N_2O$. Since the oxygen moiety in XVII and XVIII is bonded to a nitrogen atom one would expect to find the presence of ions for R - $C_4H_5N_4$ and R - $C_4H_3N_3$, which were not observed. Also, the occurrence of R - $C_4H_3N_2O$ would require the rearrangement of the hydroxylamino group which is extremely unlikely.

In order to distinguish between the remaining isomers, a number of chemical tests were undertaken. There was only one other diamino-hydroxy isomer to be checked and the rest were hydrazino derivatives. Previously, the infrared and other chemical data had

strongly suggested a hydrazino derivative. Two further tests were run to verify the presence of the hydrazino group. A Tollen's test which is applicable to hydrazine gave a positive reaction for 2H-K. However, it was discovered that XV and other pyrimidines that have two easily oxidizable groups ortho to one another which would include XVI also give a positive Tollen's test. A second test, which is a test for Ar-NH-NH_2 groups (29, p. 214) involves oxidation of the hydrazine to a diazonium salt with selenious acid and coupling of the salt with 1-naphthylamine, thus producing a brightly red-violet colored aza compounds. This test gave only a yellow color with 2H-K. The same test with XV, on the other hand, produced an unexpected bright red color. Thus both tests gave inconclusive results.

The ferric chloride test is reported to be specific for 5-hydroxypyrimidines (39) which unlike the hydroxy isomers, exist truly in the hydroxyl form and hence are phenolic in character. The usual deep blue color that is considered a positive test for 5-hydroxypyrimidines was found with 2H-K, 2Me-K and weakly (due to solubility) with 2Ph-K.

On the basis of these results only two possibilities remain; the 4, 6-diamino-5-hydroxypyrimidine (XVI) and 4-hydrazino-5-hydroxypyrimidine (XIX). The spectral data showed conflicting evidence. The infrared spectra, lacking bands near 3400 cm^{-1}, supported the hydrazino derivative. The nmr spectra had a peak near

6.0 δ which exchanged in aqueous acidic and basic solutions. This peak, has to be attributed to the pyrimidyl hydrogen in the 6-position of XIX. This assignment appears unreasonable since the chemical shift is further up field than expected of a proton alpha to a ring nitrogen. Also, one would not predict an aromatic proton to be so labile in acidic or basic solutions.

The choice between the two isomers was made by further consideration of the reaction. Of all the possible isomers, none of them appeared to be reasonable products of the reaction of 4, 6-dimethoxy-5-nitropyrimidine with methylhydrazine. However, least probable of all was the replacement of the methoxy or nitro group with a proton considering the mild reaction conditions. Furthermore, it seemed just as plausible to cleave a methylhydrazino to an amino group as to cleave a methyl from a methylhydrazino group. Therefore, it was decided that the diamino derivative was most probable of the two choices.

The synthesis of the unreported XVI was based on the Elbs persulfate oxidation of hydroxybenzenes which was shown by Hull (39) to be successful with pyrimidines having at least one electron releasing group. The 4, 6-diamino-2-thiopyrimidine was converted to 4, 6-diaminopyrimidine via the desulfurization procedure of Brown (16). The diaminopyrimidine then treated with a basic solution of ammonium persulfate gave 4, 6-diamino-5-pyrimidyl hydrogen

sulfate in excellent yield, which on acid hydrolysis yielded the hydrochloride of XVI. The 4, 6-diamino-5-hydroxypyrimidine was obtained as the free base by neutralization with sodium bicarbonate.

The analytical data and nmr spectrum (only a singlet at 7.99 δ in trifluoroacetic acid) indicated that the product did have the expected structure of XVI. The spectral data also proved 2H-K did not have the structure of XVI. There was no doublet in the nmr spectrum, as with 2H-K and the infrared spectrum (see Figure 12)had two strong bands above 3400 cm^{-1} and only one strong peak near 1640 cm^{-1}.

Consequently, the product appeared to be, by process of elimination, a hydrazino-hydroxypyrimidine which meant that the nitro substituent had indeed been replaced by a hydrogen atom. The choice now was between three hydrazino isomers, XIX, XX and XXI.

There was disagreement between the chemical data and the spectral data as to the most plausible structure. From chemical data, XIX was preferred since it was the only structure that had a hydroxy group in the 5-position. However, from the spectral data, XXI was more strongly favored. The mysterious peak near 6.0 δ must be assigned to an aromatic hydrogen. The aromatic pyrimidine protons with a chemical shift near 6.0 δ are those at the 5-position. Also, from the infrared data, the absorption near 1670 cm^{-1} must be due to a ketopyrimidine since the NH deformation of hydrazine

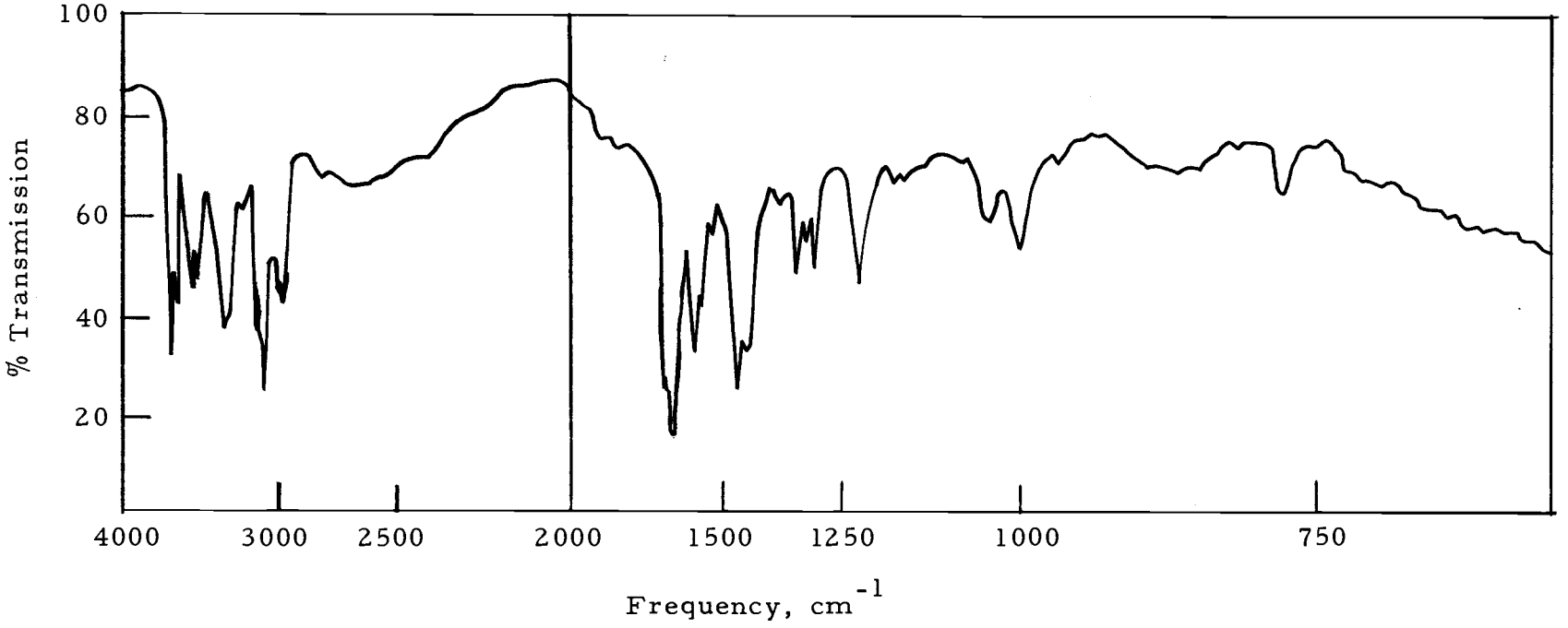


Figure 12. Infrared spectrum of 4, 6-diamino-6-hydroxypyrimidine (nujol mull).

occurs at a lower frequency.

Preferring the more reliable spectral data, XXI was synthesized. A sample of 4, 6-dihydroxypyrimidine was chlorinated by a modified procedure of Hull (38). The same reaction conditions were used except the N, N-diethylaniline replaced the dimethyl analog. The 4, 6-dichloropyrimidine was then isolated by vaccum distillation after removal of the phosphorus oxychloride. This method gives a better yield than via the laborious extraction procedure of the crude reaction mixture. Partial hydrolysis in aqueous acid, according to the procedure of Brown and Harper (19), gave 4-chloro-6-hydroxypyrimidine, which upon refluxing in absolute ethanolic solution of anhydrous hydrazine gave 4-hydrazino-6-hydroxypyrimidine (XXI). All of the spectral data of XXI was identical with that of 2H-K. It also gave the unique positive blue color with ferric chloride solution and the same low nitrogen value as obtained with 2H-K.

Due to the unusual spectral and chemical properties of unreported XXI and also the unprecedented reaction that had led to 2H-K it was decided to further confirm these results.

The 4-hydrazino-6-hydroxy-2-phenylpyrimidine, which should be identical to 2Ph-K was prepared. The 4, 6-dichloro-2-phenylpyrimidine was prepared by chlorination of the dihydroxy analog, via the usual manner with N, N-diethylaniline. This gave a slightly better yield than reported by Hendry and Homer (35). Although the

4-chloro-6-hydroxy-2-phenylpyrimidine is reported in the literature (22), experimental details are lacking; no m.p., yield or other data are given.

Another procedure for its preparation was developed which avoided the use of n-butanol. The starting dichloro compound was insoluble in both hot acid and base solutions. Basic hydrolysis was preferred since the reaction could be followed by disappearance of the dichloro and also in basic solution after one chloro group is replaced an anion will form protecting the ring from further nucleophilic attack. In acid solution, on the other hand, the monohydroxy pyrimidine would be protonated on the ring thus increasing its susceptibility to further hydrolysis. Refluxing the dichloro derivative in 3N sodium hydroxide gave the 4-chloro-6-hydroxy-2-phenylpyrimidine in excellent yield.

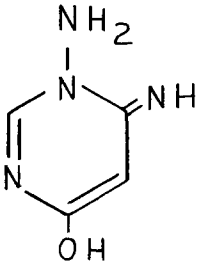
The reaction of this compound with hydrazine in ethanol gave the 4-hydrazino-6-hydroxy-2-phenylpyrimidine which was shown by its nmr and infrared spectra and chemical properties to be identical with 2Ph-K.

Since these hydrazino-hydroxy compounds were unreported, it seemed desirable to convert 2H-K (or XXI) to a known compound. Cleavage of the N-N bond of the hydrazino group with Raney nickel is a well known reaction that should yield the known 4-amino-6-hydroxypyrimidine if XXI is indeed the correct structure. An

authentic sample of the aminopyrimidine for comparison purposes was prepared from 4-amino-6-hydroxy-2-thiopyrimidine via the usual desulfurization procedure (16).

When the method of Ainsworth (1) for the cleavage of N-N bonds with Raney nickel was applied to 2H-K, the reaction resulted in a partial reduction of the ring as indicated by the analytical data and the low absorption in the ultraviolet. This procedure was modified by using less Raney nickel in an aqueous basic solution. Under these conditions a good yield of 4-amino-6-hydroxypyrimidine was obtained from both 2H-K and XXI.

There is still one other remote possibility that the structure for 2H-K (or XXI) might be the iminopyrimidine (XXII) which would satisfy the spectral data and also produce 4-amino-6-hydroxypyrimidine on mild treatment with Raney nickel.



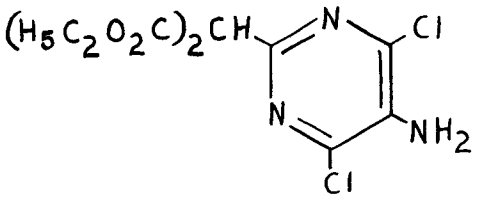
XXII

The nmr spectrum of XXII could very well be similar to that found for 2H-K having the required protons at the 2 and 5-positions as could the infrared spectrum by assigning the band at 1670 cm^{-1} to

the imino group instead of the carbonyl group. It has all the necessary substituents; the reactive amino group and a hydroxyl group, which would not likely tautomerize to a keto structure and should therefore give a positive ferric chloride test.

One might argue against it on mechanistic grounds, for to get to this structure would require (1) attack at the unsubstituted 2-position, (2) ring opening and (3) reclosure with the hydrazino substituent.

There are a few examples in the literature of the attack at an unsubstituted position in preference to displacement of a leaving group. A well known reaction of this type in pyrimidine chemistry is the nucleophilic attack of diethyl malonate ion at the free 2-position of 4, 6-dichloro-5-nitropyrimidine and synchronous reduction of the nitro group to give XXIV (60).

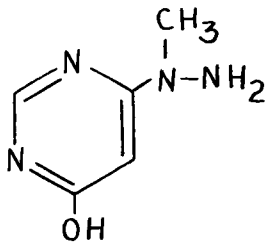


XXIV

The ring-opening and reclosing is encountered in many nucleophilic reactions of heterocyclic compounds (61). It is probably more

common than realized since in many cases the reclosure occurs with formation of the original ring thus appearing like a normal aromatic nucleophilic substitution (62, p. 155).

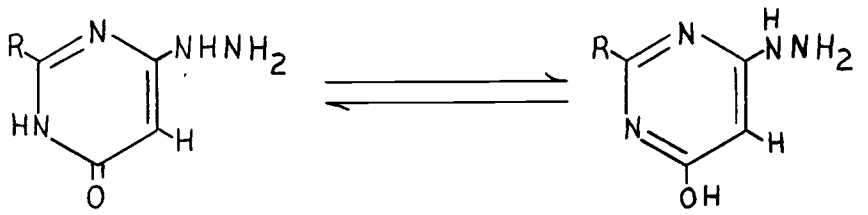
Hence a legitimate case can be made for the iminopyrimidine (XXIII) being the structure of 2H-K and XXII. To determine this point 4-chloro-6-hydroxypyrimidine was reacted with methylhydrazine in refluxing ethanol. Analysis indicated a product with an empirical formula $C_5H_8N_4O$. In a solution of trifluoroacetic acid the product exhibited three peaks in its nmr spectrum; 8.17, 5.73 and 3.10 δ which integrated as 1:1:3. These values can be assigned to the 2- and 5-position hydrogen substituents and an $N-CH_3$ group, respectively. The test for a free NH_2 group of a hydrazino substituent with sodium pentacyanoammineferroate (29, p. 212) was positive. On the basis of this data the product must be the expected 4-hydroxy-6-(1-methylhydrazino)-pyrimidine (XXV).



XXV

This being the structure precludes any ring opening and reclosure on the hydrazino substituent which would have had to either expel the methyl group or it would have had to react with the unsubstituted end of methylhydrazine. This would have produced a product that had no free amino group.

Without a doubt then the structure for 2H-K, 2Me-K and 2Ph-K is (where R = H, Me and Ph respectively);



It is still perplexing why the hydrogen in the 5-position is so labile to aqueous acids and bases. To have the hydrogen substituent exchange at the 5-position in aqueous basic solutions means that the pyrimidine anion formed must have a sufficient amount of the negative charge delocalized at the 5-position. The most reasonable hydrogen substituent to be abstractable by a base is either the 2-hydrazino hydrogen or the ring nitrogen hydrogen (if in keto form) or the hydroxyl hydrogen (if in hydroxyl form). Any of the structures resulting from the abstraction of these particular protons (see Figure 13) would give rise to resonance anion structures which fulfill the requirement for hydrogen exchange, i.e. the negative charge is

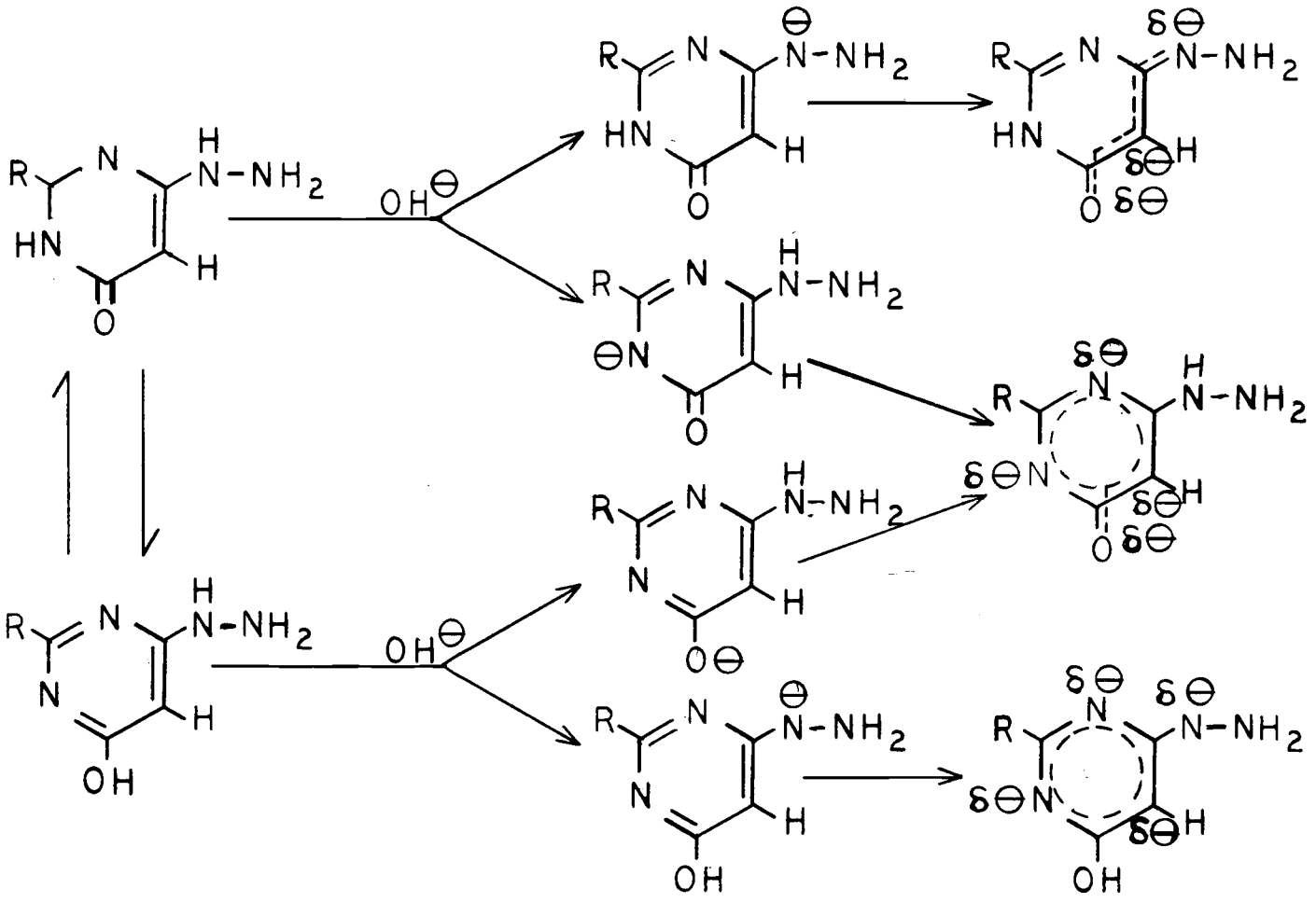


Figure 13. Possible anions of 4-hydrazino-6-hydroxypyrimidine.

partially delocalized at the 5-position. For hydrogen exchange at the 5-position in aqueous acid means the pyrimidine must be protonated in the 5-position. Although protonation of the 5-position does result in a resonance stabilized pyrimidine cation (especially for the pyrimidine hydroxyl structure (see Figure 14)) it appears from the consideration of other cationic structures that the protonation of oxygen (for keto structure) should be favored as they can give aromatized resonance structures which are impossible for protonation of the 5-position.

The other misleading data--the low nitrogen analysis and positive ferric chloride test--are not unique to this compound. There are numerous examples to be found in the literature of other hydrazino compounds that give low nitrogen values. Some of the more recent examples are 5-amino-4-chloro-3-hydrazinopyridazine (47) and 2, 4-dihydrazino-5-nitropyrimidine (69).

Likewise, it is a common misconception that α and γ-hydroxy N-hereroaromatic compounds give no color with ferric chloride. Albert (2, p. 55) points out that there are many exceptions to this rule and he cites the example of 2-hydroxypyridine which gives the identical red color as its 3-hydroxy isomer. In our laboratories, 4, 6-dihydroxypyrimidine and its 2-methyl homolog produced a red color with ferric chloride. This is not surprising, since both hydroxy groups are unable to tautomerize simultaneously to amido

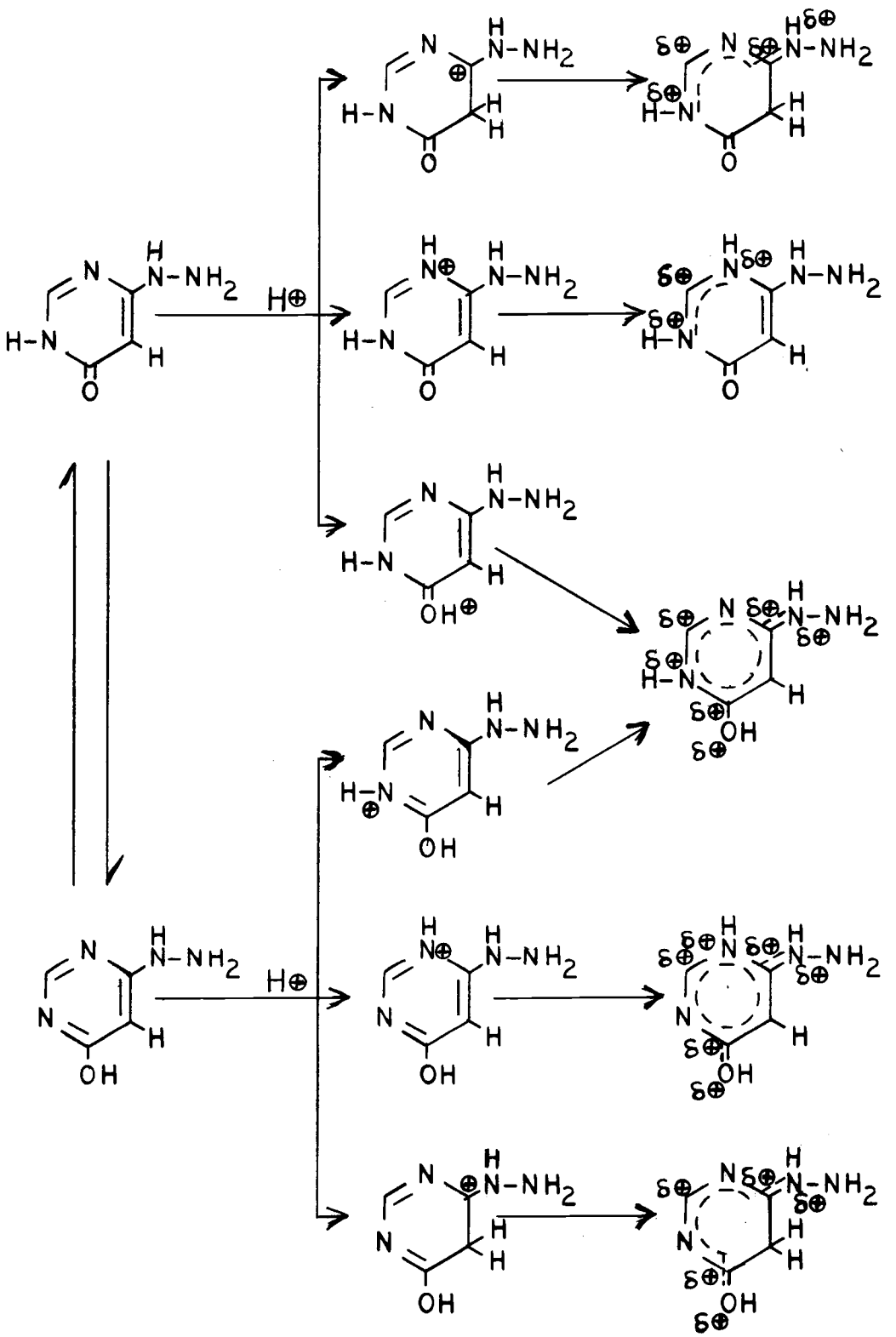


Figure 14. Possible cations of 4-hydrazino-6-hydroxypyrimidine.

groups. However, it is interesting that Hull (38) claimed the synthesis of 2-methyl-4, 5, 6-trihydroxypyrimidine via persulfate oxidation of the 4, 6-dihydroxy-2-methylpyrimidine. He did not isolate the product, but gave as evidence the red color produced when the hydrolyzed reaction mixture was treated with ferric chloride. From our results and the fact that most 5-hydroxypyrimidines give a deep blue color, it is rather doubtful that Hull did actually obtain the trihydroxyl derivative but instead recovered the starting material.

Another interesting result obtained with ferric chloride was the negative test with the diacetyl derivatives of 2H-K and 2Ph-K. From this it might be presumed that the hydroxyl group was involved in the acylation. If one considers both tautomeric forms of 2H-K there are four nitrogen sites and one oxygen site in which acylation could occur. Tautomeric hydroxypyrimidines do not form O-acetyl derivatives but rather acylate only on the ring nitrogen. Thus, uracil (66), thymine (66), and 4-hydroxypyrimidine (15) give only the N-acetyl derivatives with acetic anhydride. A test suggested by Carson (23) for diacetylated nitrogens which is also applicable to ring nitrogen acetylated pyrimidines was negative for both the acetylated derivatives of 2H-K and 2Ph-K. The negative test would also disprove diacetylation of the β-position of the hydrazino substituent.

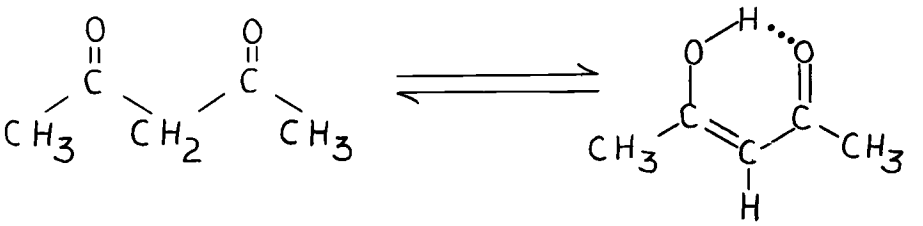
From this it can only be concluded that the acylations took

place at the α- and β-positions of the hydrazine substituent. This is what would be predicted from the reactivity of the different sites. Acylation should take place first at the more nucleophilic β-position of the hydrazino, which would deactivate this position from further attack, as it is now like an acetamido group. This leaves the α-position of the hydrazino substituent as the next most reactive site.

One might wonder why such similar acetyl groups have such a large difference in their chemical shifts in the nmr spectrum; for instance, for the 2Ph-K acetyl derivative the two methyl peaks were found at 2.32 and 2.15 δ in deuterated dimethylsulfoxide. This could be explained by the peak near 11.0 δ which was not observable in the non-acetylated derivatives and disappeared on addition of deuterium oxide. An absorption so far down field suggests that there is intramolecular hydrogen bonding between one of the carbonyl groups and one of the labile hydrogen substituents.

This hydrogen bonding should result in a lowering of the deshielding properties of the carbonyl group which in turn would give rise to a greater shielding of the adjacent methyl group.

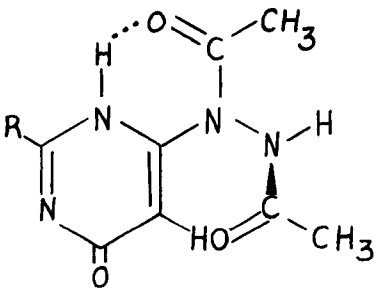
A similar situation is found with acetylacetone which exists in equilibrium with both its keto (XXVIa) and enol (XXVIb) forms (26, p. 921). The methyl peak for the keto structure is found at 2.14 while in the hydrogen-bonded enol form it is at 1.97 δ.



XXVI a XXVI b

The difference in chemical shift of the methyl groups for the two forms of acetylacetone is 0.17 ppm and for the two methyl groups in diacetylated 2Ph-K is also 0.17 ppm.

Therefore a reasonable conformation of the diacetylated derivative could be:



This conformation would also explain the large change in chemical shift of the proton in the 5-position; for example for 2Ph-K the 5-position proton which gave a peak at 5.66 δ changed on acetylation to 7.15 δ. Furthermore this conformation would also explain why the acetylated derivatives did not give a positive ferric chloride test

when only the hydrazino group was acetylated.

Early in this investigation it was noted that 2H-K definitely was not a predictable product. For this reason studies were undertaken which might give some insight as to some possible intermediate or mechanistic pathway. Since the yield in the original reaction was rather low (23%), a study was initiated in an effort to improve the yield.

The stoichometry of the reaction was studied by varying the concentration of methylhydrazine reacting with a fixed amount of the pyrimidine over a three hour period at reflux temperatures. The yield of 2H-K was determined from the weight of the precipitate obtained after allowing the reaction mixture to stand overnight at approximately $0^{o}C$. The yield was found to be maximized when there was three to four moles of the hydrazine per mole of the pyrimidine; when the mole ratio became greater than 6: 1 the yield declined rapidly.

Using the 4: 1 mole ratio of hydrazine to pyrimidine, the reaction time was varied from one hour to 24 hours. The yield was determined as before and was found to be the greatest at a reaction time of around two and one-half hours. Considerable decomposition was observed if the reaction mixture was allowed to reflux for six hours. In neither study was there a significant improvement in the yield. Under the best of conditions the yield was raised to

approximately 29% compared to the original yield of 23%.

A series of different solvents were then tested. In non-polar solvents, such as toluene and heptane, the reaction proceeded very slowly with recovery of starting material and a small amount of a deep red oil with no trace of 2H-K. A slight increase in yield was found when higher boiling alcohols were used as the solvents. There was a notable increase in the yield using solvents which were aprotic. Thus, dioxane and pyridine gave yields of 44% and 55% respectively. Not only was the yield better but the reaction was much more rapid, precipitation occurring after refluxing for five minutes yielding a crude product which was of a higher purity than that obtained with alcoholic solvents.

As a consequence of these studies a pyridine solvent was selected to determine the effects of concentration and time. It was discovered that a shorter reflux time of one hour at a higher concentration of the reactants increased the yield to 65%; also it was noted that under identical conditions the yield would vary from 56 to 65%.

When the solvent was changed to alkylpyridines, such as 2- and 3- picoline, thus enabling one to attain a higher reflux temperature, there was a slight increase in yield to about 70%. When the reflux temperature was much greater than 150°C, e.g. by using 2, 4, 6-trimethylpyridine (b.p. 172°C), then the yield was decreased due to excessive decomposition giving a red oily by-product.

Thus it was demonstrated that under certain conditions the reaction between the 4, 6-dimethoxy-5-nitropyrimidine and methylhydrazine gave 4-hydrazino-6-hydroxypyrimidine as the major product.

Our attention was now directed towards obtaining a better understanding of this very unusual reaction. For example, what are the necessary steric requirements for this reaction to occur? It was noted earlier that the reaction seemed specific to methylhydrazine since hydrazine, phenylhydrazine, 1, 2-dimethyl- and 1, 1-dimethylhydrazine did not yield 2H-K or related products when reacted with 4, 6-dimethoxy-5-nitropyrimidine. Moreover, the replacement of the 2-position of the original pyrimidine reactant with either a methyl or phenyl group did result in the formation of 2-substituted-4-hydrazino-6-hydroxypyrimidines.

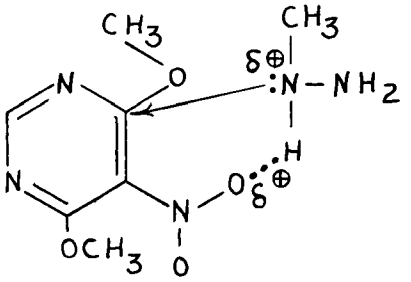
In all these cases the methoxy groups in the pyrimidine reactant were both adjacent to the nitro group. As a consequence one wonders if this is a necessary structural condition for the reaction. To answer this question, 2, 4-dimethoxy-6-methyl-5-nitropyrimidine was prepared. 2, 4-Dihydroxy-6-methylpyrimidine was nitrated and then converted to the dichloro derivative by the procedure of Albert, Brown and Wood (5). Subsequent treatment of the chloro-nitro derivative with sodium methoxide as described by Backer and Grevenstock (7) yielded the desired 2, 4-dimethoxy-6-methyl-5-nitropyrimidine (XXVII). No attempt was made to increase the yield (57%),

although as judged from the experiments with the 2-methyl isomer a shorter reaction period and better isolation procedure should give a much higher yield of XXVII.

When XXVII was treated with methylhydrazine using a pyridine solvent there was no evidence to indicate that the course of the reaction was identical to that of the isomeric 2-methyl-4, 6-dimethoxy-5-nitropyrimidine. Evaporation of the solvent yielded an oil which could not be made to crystallize nor could any of the XXVII be recovered; similar results were obtained when n-butanol was used as the solvent. Since one would predict that an isomeric hydrazinohydroxypyrimidine would have similar solubility properties to 2Me-K a product should have precipitated from both solvents. The fact that no precipitation was observed was taken as an indication that the reaction did not form a product isomeric to 2Me-K. The red oil was believed to be a result of degradation of the pyrimidine ring analogous to the red oils obtained with the isomeric pyrimidine under the same reaction conditions. Therefore, it appears as though both of the methoxy groups have to be adjacent to the nitro group for the reaction to proceed to a product such as 2Me-K.

Another question was the role which the nitro group played in this reaction. The presence of the nitro substituent at the 5-position of a pyrimidine renders the 4- and 6-positions highly reactive with respect to nucleophilic attack. This is attributed to a marked decrease

in electron density at these positions arising from the inductive and resonance effects of the strongly electron-attracting nitro substituent. There is another accelerating effect that can occur with these reactants arising from the interaction of the reacting hydrazine and the nitro group, sometimes referred to as the "ortho effects" or "built-in solvation" (12). This is best described as the result of the electrostatic attraction and hydrogen bonding between the nitro and hydrazino groups which in both instances helps stabilize the transition state (see below).



If the effect of the nitro group with respect to the reaction occurring at the 4- and 6-positions of 4, 6-dimethoxy-5-nitropyrimidine (IV) upon treatment with methylhydrazine was only to accelerate the nucleophilic attack, then the 2, 4-dimethoxy analog should have also given rise to an analogous reaction. Considering the transformations necessary to yield the hydrazino-hydroxypyrimidine from IV and methylhydrazine, particularly the loss of the nitro group, it is apparent that the reaction is based on an unconventional participation

of the nitro substituent.

This brings up an important point, e.g. to what degree does the reaction progress in a predictable manner before these abnormal (at least in pyrimidine chemistry) transformations occur? Hydrazines are very reactive nucleophiles. Edward (27, p. 58) gives the following order of reactivity of nucleophiles towards 2, 4-dinitrochlorobenzene;

$$CH_3O^- > N_2H_4 > OH^- > C_6H_5NH_2 > NH_3$$

He suggests that the polarizability of hydrazine accounts for its high reactivity. Another important factor which would also contribute to hydrazines high reactivity is the accelerative ortho effect of the adjacent nitro group which is not operative with attacking anions.

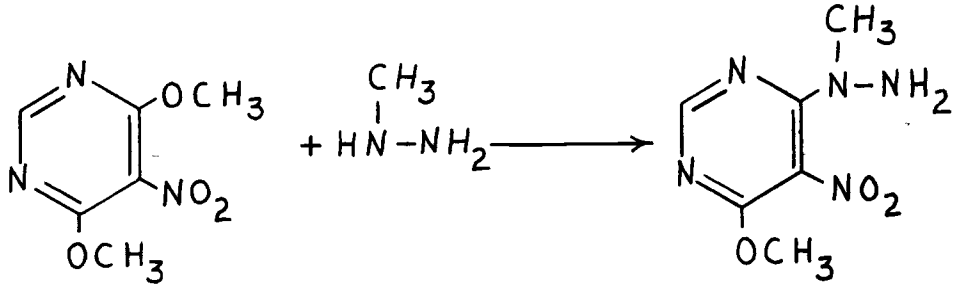
Furthermore, as previously mentioned, Krackov and Christensen (45) reported that if 4, 6-dimethoxy-5-nitropyrimidine was refluxed with hydrazine in ethanolic solvent the product was 4, 6-dihydrazino-5-nitropyrimidine in which both methoxyl groups had been displaced. On the basis of this result one would reasonably predict that the treatment of the same pyrimidine with methylhydrazine (a more reactive nucleophile) in refluxing n-butanol or pyridine (more favorable conditions) would produce the analogous 4, 6-di-(1-methylhydrazino)-5-nitropyrimidine (V) as an intermediate in the formation of 2H-K.

The synthesis of V was approached via the intermediate 4, 6-dichloro-5-nitropyrimidine (II). Krackov and Christensen (45) found that II upon reacting with hydrazine yielded a significant amount of an unidentified brown insoluble material and only a 33% yield of dihydrazino derivative. From the analytical and chemical data it was concluded that this brown material was probably polymeric in nature. Consequently reaction conditions were changed to avoid this occurrence with methylhydrazine. A very dilute solution of II in methanol was cooled to -10°C and to this was added the methylhydrazine to give V in 85% yield. A 100% mole excess (four to one ratio) of the hydrazine was used since the hydrochloric acid formed as a by-product will selectively protonate a reacting hydrazine thus rendering it inactive towards further nucleophilic substitution.

The refluxing of V in either pyridine or n-butanol did not yield the precipitate 2H-K. Evaporation of the solvent at room temperature yielded the usual uncrystallizable red oil; no V could be recovered. The heating of V in the presence of methylhydrazine or IV likewise did not result in formation of 2H-K. In the latter case, IV could almost be totally recovered from the residual oil by the addition of water. The apparent thermal instability of V was also observed in attempting to recrystallize V from various solvents. In fact, care must be taken to avoid air oxidation through long periods

of heating when working with V.

Having established that V was not an intermediate to 2H-K, the other possibility, 4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine (XXVIII), was prepared. Considering the reactants (IV and methylhydrazine) the most logical first step of the reaction would be the nucleophilic substitution of methylhydrazino for a methoxy group to give XXVIII.



IV XXVIII

It would not be advantageous to try to attempt the preparation of XXVIII via an initial reaction between 4, 6-dichloro-5-nitropyrimidine (II) and methylhydrazino. The high reactivity of II, would make it difficult to stop the reaction at the mono-substituted stage since disubstitution results very rapidly even at -10°C with hydrazines. Thus even carefully controlled addition of an equivalent of the hydrazine would no doubt yield a mixture. Furthermore the hydrazino group of the 4-chloro-(1-methylhydrazino)-5-nitropyrimidine, if

obtained, would likely be unstable in the presence of the strong basic sodium methoxide which is needed to complete the synthesis of XXVIII.

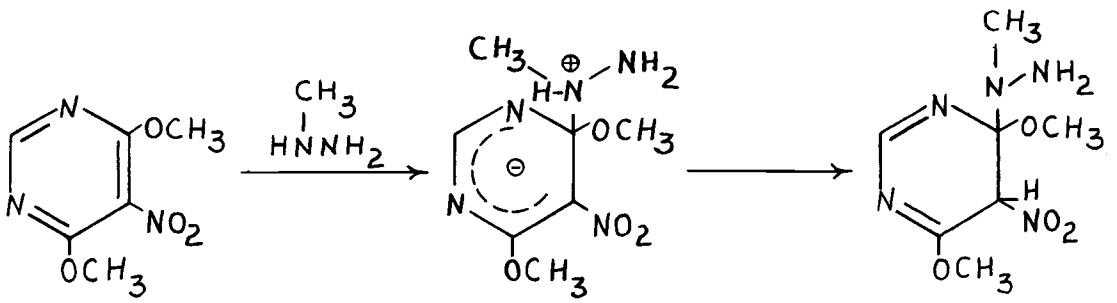
Therefore, the synthesis was approached in the reverse order. The dichloro derivative II was carefully treated with one equivalent of sodium methoxide according to the procedure of Taylor, Barton and Pauler (67) yielding the 4-chloro-6-methoxy-5-nitropyrimidine (XXIX). A dilute methanolic solution of XXIX after precooling below $0^{o}C$ was treated with methylhydrazine giving the desired XXVIII.

The heating of XXVIII alone or in the presence of methylhydrazine in either pyridine or n-butanol did not give an observable precipitation of 2H-K. Moreover, most of XXVIII was successfully recovered from the residual red oil. It appeared that XXVIII was much more unreactive than would have been predicted under these conditions.

It is indeed surprising that 4-methoxy-6-methylhydrazino-5-nitropyrimidine was not converted to 2H-K. This indicates that the reaction is proceeding in an unusual manner in the early stages of the process. There were three possible explanations for this unexpected behavior. First, the methylhydrazine was not attacking at the expected 4- or 6-position. To have the attack at the 2-position would not be expected to result in 2H-K but rather give rise to

something more like XXVII, an N-aminopyrimidine derivative (see page 63). The other alternative reactive site in this case would be at the nitrogen atom of the nitro substituent. It is presumed that the stronger electrophilic 4-position would supercede the nitro group in reactions with a nucleophile. Also any attack of the nitro group by hydrazine would probably give rise to reduction of the nitro group to a nitroso or amino group which would deactivate the ring to any further nucleophilic attacks, thus yielding an entirely different product.

The second explanation stems from the possibility of an initial attack at the 4-position to give the transition state XXX but with the retention of the methoxy group instead of its displacement. It seems plausible that the formation of XXX could be followed by a rapid proton transfer to one of the strongly negative sites such as adjacent to the nitro group to give XXXI. If XXXI is an intermediate



XXX XXXI

it could explain the appearance of the hydrogen substituent in the 5-position of 2H-K. The plausible mechanisms for the conversion of XXXI or the other reasonable proton-transfer products to 2H-K are too numerous to discuss here in view of the limited information.

The final possible explanation is based on a rearrangement or interaction with the solvent with IV prior to the reaction with the methylhydrazine. This latter suggestion was most easily tested; IV was refluxed in pyridine for 20-30 minutes in the absence of methylhydrazine. On cooling the solution, a yellow-tan material (XXXII) precipitated which had a lower melting point (m.p. 150 - 151.5°C) than IV (m.p. 175 - 176°C). The infrared spectrum of XXXII (see Figure 15) was quite different from IV; the strong absorption band near 1125 cm^{-1} for the methoxy groups was absent and new strong bands at 1655, 1610, 793 and 678 cm^{-1} were present. The latter two bands suggested the presence of another aromatic ring besides pyrimidine and is further supported by an unusually strong aromatic C-H stretch band at 3067 cm^{-1}. The broad bands above 3400 cm^{-1} were attributed to water as the compound is very hygroscopic.

The nmr spectrum of XXXII was very informative; in deutrium oxide, in which the compound was extremely soluble, there were a series of peaks between 8.0 and 9.0 δ. These appeared as two doublets (centered at 8.88 and 8.54 δ) and a triplet (8.07 δ) which

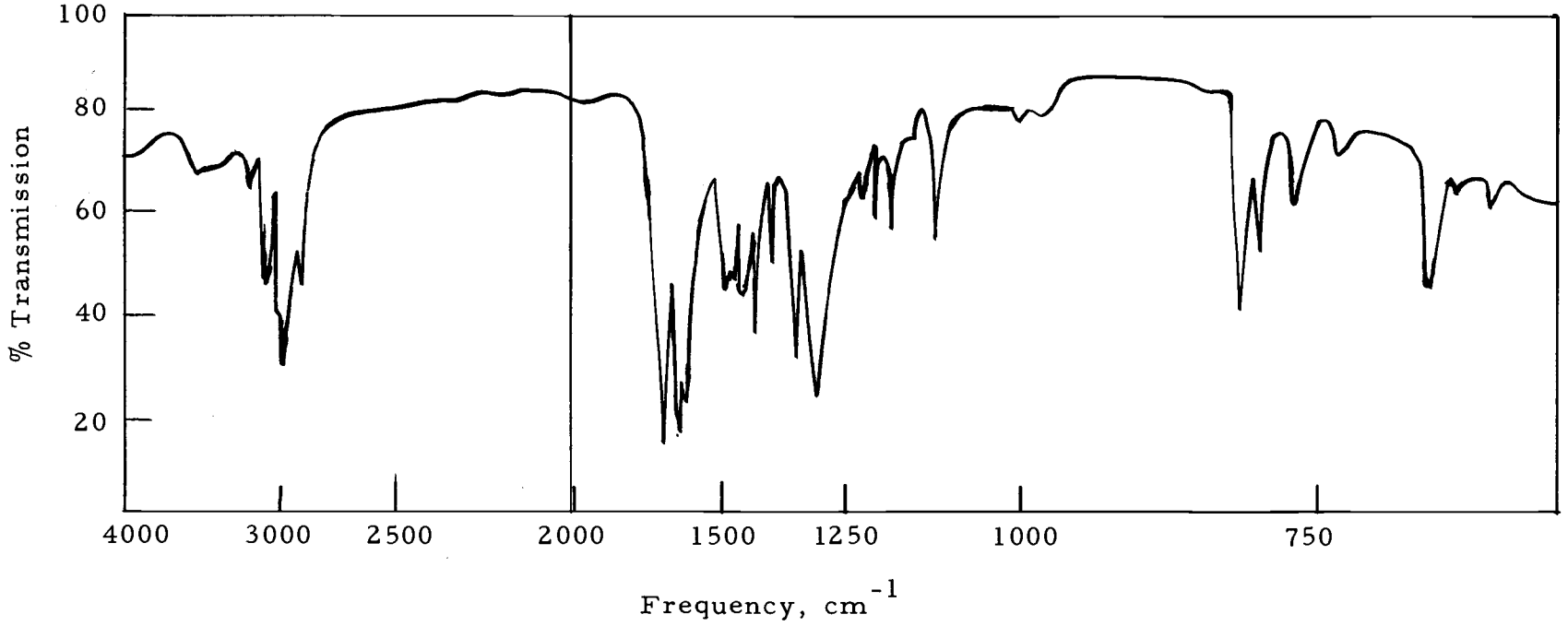


Figure 15. Infrared spectrum of N-methylpyridium pyrimidinate salt (XXXII).

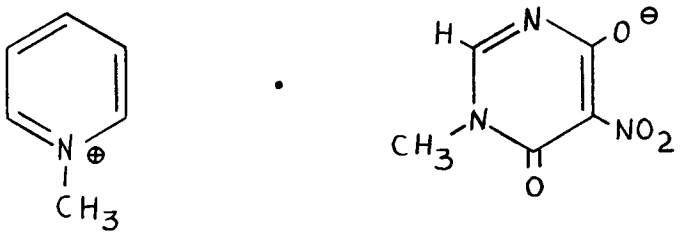
integrated 2:1:3 and two singlets at 4.51 and 3.45 δ each of which integrated as 3. The pattern above 8.0 δ is that expected for pyridine except that it is at a much higher δ value than normal. Cationization of the ring nitrogen would produce a shift in this direction. A sample of pyridine in water showed a small shift but only when acid had been added to the solution were the aromatic protons to be found above 8.0 δ. The pattern must then be due to the presence of a real pyridinium ion and not just hydrogen bonding with the water.

The peak at 4.51 δ for a methyl proton was likewise unusually high for a methyl group bound to oxygen. This suggested the possibility of a methylpyridinium ion. The nmr spectrum of 1-methylpyridinium iodide in deutrium oxide did exhibit a peak at 4.50 δ for the methyl group and an almost identical pattern for the five pyridinium protons. The major difference was in the spectrum of XXXII, the center peak of the pattern for the triplet for the α protons was much larger. This is due to overlapping of this pattern with the peak for the proton at the 2-position of the pyrimidine moiety as confirmed by an integration of 3 for the triplet.

This furthermore establishes the ratio of one pyrimidinium ion per methylpyridinium ion. There remains only one methyl peak that absorbs at 3.45 δ. This is best assigned to an $N-CH_3$ group which suggests that a pyrimidine nitrogen ring atom has been methylated. This conclusion is supported by the carbonyl band in the

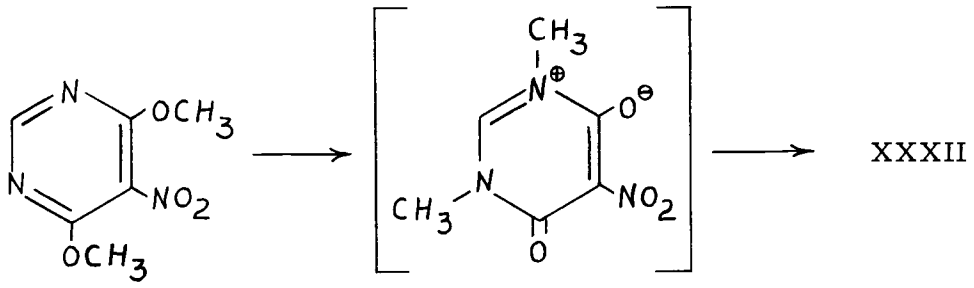
ir spectrum near 1655 cm^{-1} indicative of an amide structure for the substituted pyrimidine ring.

From the spectral data the structure of XXXII is tentatively assigned as:



XXXII

The rearrangement of an alkoxypyrimidine to the isomeric N-alkyloxopyrimidine has been known since 1929 (57). The trans-alkylation can occur thermally at a reasonable rate at 150 - 250°C. The reaction is also known to be accelerated in the presence of pyridine or methyl iodide (18, p. 371). The fact that the methoxy groups are in the 4- and 6-positions might explain the formation of 1-methylpyridinium ion. Thus, under conditions of refluxing pyridine might cause both methyl groups of IV to migrate to ring nitrogens producing XXXIII which would be a strong alkylating agent and result in the alkylation of pyridine.



IV XXXIII

Thus it appears that IV can undergo a rearrangement and even methylate the pyridine solvent. The next question is XXXII a by-product or an intermediate to 2H-K.

When XXXII was refluxed for one-half hour with methylhydrazine in pyridine no formation of 2H-K was observed. This was not too surprising since the pyrimidine moiety of XXXII, if, even it is not the structure given, must have some kind of anionic structure. This would definitely lower its response to a possible nucleophilic attack by the hydrazine. It did seem that XXXII was unstable because it was only recovered in about 20% yield. The heating of XXXII in refluxing pyridine (and other solvents) demonstrated that it was somewhat thermally unstable in solution. The decomposition seems to be accelerated by the presence of methylhydrazine or other protic molecules.

A portion of the remaining filtrate, XXXIV, from the treatment of IV in refluxing pyridine was refluxed together with methylhydrazine

which did give 2H-K. A calculation of the yield, corrected for the loss of reacting pyrimidine due to formation of XXXII, was approximately 65%.

The filtrate from the reaction of IV with pyridine might contain unreacted IV although doubtful considering the solubility of IV in cold pyridine. To check this possibility a portion of the filtrate XXXIV was evaporated at room temperature yielding a red oil and then placed in vacuo at 0.02 Torr over phosphorus pentoxide for two days. A portion of the residual red oil was added to water which yielded only trace amounts of the very water insoluble IV (approximately 1%). The remainder of the red oil was dissolved in n-butanol and refluxed with additional methylhydrazine which reacted to yield 2H-K in about 46% yield (based on expected amount of pyrimidine left after removal of XXXII and IV). This suggests that there is another reactive intermediate in XXXIV that is neither IV nor XXXII which will yield 2H-K upon reaction with methylhydrazine.

This was confirmed by adding some methylhydrazine to an aliquot of XXXIV and allowing this solution to stand at room temperature for two days. The 2H-K that precipitated was in about 65-70% yield. This same experiment was repeated with a pyridine solution of IV and methylhydrazine and gave only trace amounts of 2H-K (less than 1% yield).

An infrared spectrum was obtained of the red oil from

evaporation of XXXIV that yielded 2H-K (see Figure 16). Here again the presence of a pyridine ring can be seen by the stronger bands in the 850-650 cm^{-1} region as well as the strong aromatic hydrogen band near 3050 cm^{-1}. Unlike the spectrum of XXXII though, it has only two weak bands above 1650 cm^{-1} and a strong methoxyl band at 1116 cm^{-1}. This methoxyl band was however weaker than that found for IV.

To determine whether the salt XXXII was actually a derivative from IV or the compound in XXXIV, a sample of XXXIV was again refluxed for one-half hour. On cooling, no more XXXII precipitated; addition of methylhydrazine to this solution and further refluxing did produce 2H-K.

In light of this behavior, it is evident that IV and pyridine react rapidly upon refluxing and in doing so produce at least two independent compounds. One is insoluble in cold pyridine and is a yellow-tan pyridinium salt with the possible structure of XXXII resulting from two methyl migrations; it is not an intermediate to 2H-K. The other compound is very soluble in cold pyridine and is definitely a more reactive intermediate toward methylhydrazine than IV, since it yields 2H-K under much milder conditions. Although its structure is not known, the spectral data suggests that it too may be a pyridinium salt and that the pyrimidine moiety probably possesses at least one methoxy group.

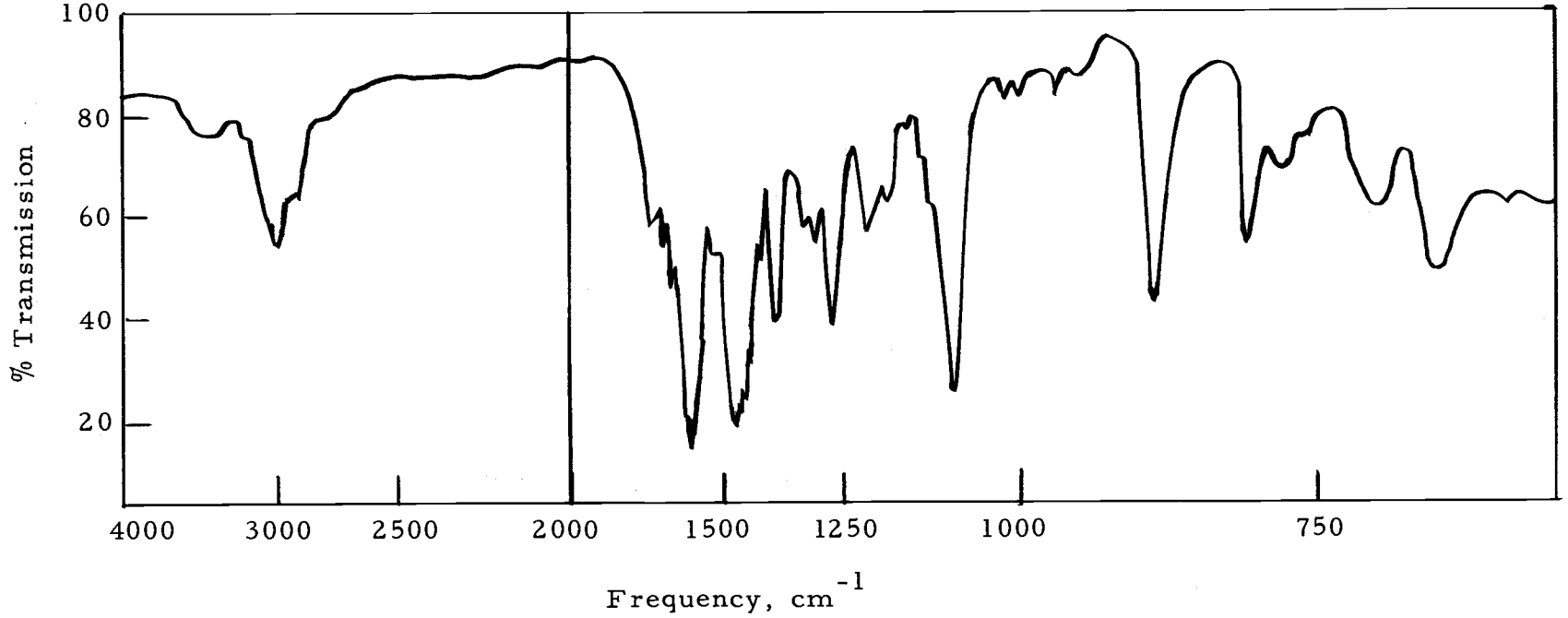


Figure 16. Infrared spectrum of residue from evaporation of XXXIV filtrate.

It is strange that IV, a compound that was so reactive towards nucleophilic substitution with hydrazine, is apparently unreactive in this respect with methylhydrazine, or for that matter, with other hydrazine derivatives. The fact that in IV there is steric crowding of the substituents can be seen with models. If the non-bonded electrons of the oxygen of the methoxy substituent and those of the oxygen atoms of the nitro group are placed as far apart as possible then the methyl groups interfere with the planarity of the nitro substituent with the ring. It has been demonstrated that two methyl substituents ortho to a nitro group is sufficient to hinder the nitro group from lying in the plane of the aromatic ring (37, p. 64).

The steric hindrance would explain the unusually facile methyl migration that is apparent with IV in pyridine which would relieve most of the steric crowding. It also might explain the unreactivity of IV to methylhydrazine. The nucleophilic substitution would have to go through a transition state as shown by Figure XXX (page 70) where the substituted (more nucleophilic) end of the hydrazine molecule would attack. A model of this transition state shows the planarity of the nitro group with the ring is virtually impossible. Thus, when the methylhydrazine approaches the 4-position the nitro group is forced out of the plane of the ring. This in turn deactivates the electrophilicity of the 4-position by loss of the important resonance effect of the nitro group. The added steric crowding caused by the attacking hydrazine molecule coupled with further deactivation through loss of

resonance stabilization of the nitro group results in an energy barrier which is too great to permit the substitution to take place.

This leads to the conclusion that the steric effects and related contributing factors (e.g. loss of resonance of the nitro group with the ring) makes substitution of 4, 6-dimethoxy-5-nitropyrimidine and related derivatives by methylhydrazine or other attacking nucleophiles with similar bulkiness virtually impossible. Thus 2H-K is not a product from the interaction of methylhydrazine and IV, but rather arises after IV has rearranged to another compound with less steric crowding which can then be attacked by the methylhydrazine.

If the approaching nucleophile is not as large as methylhydrazine, this would decrease the steric crowding, making the attack easier and also allowing the nitro group to assist (by resonance effect) to a greater extent. Thus hydrazine having no restricting methyl substituent can react rapidly with IV at both the 4- and 6-position.

These results stimulated further interest in this most unique facet of pyrimidine chemistry. Investigations were undertaken to obtain a better understanding of the reactivity of 5-nitropyrimidines (particularly those substituted in the 4- and 6-positions) with the hydrazines.

Of special interest was the reaction of methoxy-nitropyrimidines with hydrazine. The results of Krackov and Christensen (45)

showed that the reaction of hydrazine with 4, 6-dimethoxy-5-nitropyrimidine not only gave a nearly quantitative yield but the dihydrazino product obtained from the reaction needed no further purification. This is in contrast to their results found with the 4, 6-dichloro derivative which under the same reaction conditions with hydrazine gave a low yield of the very crude 4, 6-dihydrazino derivative and a large amount of polymeric by-product. Thus the methoxy derivatives appeared to be useful intermediates for preparing good yields of very high purity hydrazino derivatives. This is indeed important as most hydrazino-nitro derivatives are thermally unstable and oxidize readily when heated in solvents.

In order to determine whether this reaction has general applicability, other methoxy-nitropyrimidine derivatives were treated with hydrazine. In the course of this investigation it was discovered that neither the yield nor purity of the product was affected by the addition of anhydrous hydrazine to a hot solution (almost refluxing) of the pyrimidine. Also it was found that evaporation of the reaction liquor at room temperature in vacuo resulted in a quantitative yield of product in most cases.

The treatment of 2-substituted-4, 6-dimethoxy-5-nitropyrimidines, (the 2-methyl and 2-phenyl derivatives) with hydrazine did produce the same results as found with IV; excellent yield of a very pure 4, 6-dihydrazino derivatives.

However, it was found that 4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine showed no observable reactivity when refluxed with hydrazine in an ethanol solution. The pyrimidine reactant was recovered in good yield.

This result suggested that the α methyl group on the hydrazine substituent must be responsible for lack of reactivity, inasmuch as the conversion of the other 4, 6-dimethoxy derivatives to the dihydrazino product would be expected to go via the hydrazinomethoxy derivative.

To confirm the hypothesis that the 4-hydrazino-6-methoxy-5-nitropyrimidine (XXXV) was an intermediate to the dihydrazino derivative or at least would be reactive, it was prepared. The dropwise addition of methanolic solution of hydrazine to a methanolic solution of 4-chloro-6-methoxy-5-nitropyrimidine maintained below $0^{o}C$ yielded XXXV. The treatment of an alcoholic solution of XXXV with hydrazine did result as predicted in a good yield of the dihydrazino derivative.

Therefore it appeared that the type of substituent adjacent to the nitro group could influence the outcome of the reaction of the methoxy substituent with hydrazine. The most logical explanation seemed that the size of an adjacent substituent was the determining factor. To confirm this hypothesis, two other derivatives were prepared, one with and one without a large group adjacent to the

nitro group.

The 4-dimethylamino-6-methoxy-5-nitropyrimidine (XXXVI) was selected since the dimethylamino substituent is comparable in size to a methylhydrazino substituent. XXXVI was obtained in the following manner; 4, 6-dichloro-5-nitropyrimidine (II) was treated with the dimethylamine acetate at room temperature (17) to yield the mono methylamino derivative which when refluxed with sodium methoxide gave the unreported XXXVI in 91% yield.

As expected, when an ethanolic solution of XXXVI was refluxed with hydrazine for three hours, only the unreacted XXXVI was recovered in good yield.

The second compound, 4-amino-6-methoxy-5-nitropyrimidine (XXXVII) was prepared in a similar manner; II was treated with ammonium acetate (33) to give the mono-amino derivative which was converted to the desired product XXXVII with sodium methoxide (4).

The reaction of XXXVII with hydrazine in refluxing ethanol was successful giving 4-amino-6-hydrazino-5-nitropyrimidine (XXXVIII) in 97% yield, m.p. 248 - 249°C (dec.). Ladwig (48) reported the synthesis of XXXVIII from 4-amino-6-chloro-5-nitropyrimidine in 82% yield, m.p. 245 - 250°C (dec.). It should be noted that the hydrazino compound was obtained in better yield and higher purity from the methoxy derivative than from the chloro

derivative.

These results confirmed the hypothesis that if there is a large group ortho to the nitro group then this inhibits the displacement of the other ortho substituent (methoxy group) by methylhydrazine. An explanation of this phenomenon might be that a large ortho substituent (similar in size to methylhydrazine) increases the steric hindrance in the molecule to the point that in the ground state the nitro group is prohibited from lying in the plane of the ring. And without the strongly contributing resonance effect of the nitro group, the 4- (or 6-) position does not have the necessary electrophilic character; even a strong nucleophile like hydrazine cannot replace the methoxy group.

This also focused attention to the early hypothesis that large groups, such as methylhydrazine, do not react with methoxy groups that are ortho to nitro groups since the steric hindrance produced by the large incoming group forces the nitro group out of the plane of the pyrimidine ring. This also results in a loss of the necessary resonance effect of the nitro group and gives rise to an unobtainable activation energy.

If this theory is correct, then 4-amino-6-methoxy-5-nitropyrimidine (XXIX), which exhibited high reactivity with hydrazine, should not react with the larger methylhydrazine, even though the latter is a better nucleophile than hydrazine. Also the amino substituent should not impose steric requirements on the nitro group but

rather assist, to some degree with stabilizing the resonance of the nitro group with the ring by hydrogen bonding.

Upon refluxing an ethanolic solution of the 4-amino-6-methoxy-5-nitropyrimidine (XXXVII) and methylhydrazine for three hours (more than 15 times longer than needed to form the hydrazino derivatives) no methylhydrazino derivative was observed and XXXVII was recovered in good yield. This behavior lends strong support for the above theory.

In nucleophilic substitutions of nitropyrimidines the difference in reactivity of a pyrimidine possessing a full resonating nitro group (from non-nitro) is considerable. Although this effect has not been studied with heterocyclic compounds, in nitrofluorobenzenes the inductive activation is less than the resonance activation by a rate factor of about 10,000 (53, p. 326).

Realizing that the resonance effect of a nitro group is by far the most important contributing factor in these substitutions, one can get a qualitative idea of the influence of a nitro group in nucleophilic substitutions with pyrimidines from the following examples. The amination of 4,6-dichloropyrimidine requires a sealed tube reaction at 100°C for monoamination to occur and 180°C for complete amination which occurs along with a large amount of decomposition of pyrimidine ring (18, p. 190). The nitro analog, 4,6-dichloro-5-nitropyrimidine, however, undergoes monamination rapidly at 20°C (33)

and at 60°C forms the diaminated product in 95% yield in five minutes (33).

Whatever the reason, the hydrazinolysis of the 4-methoxy-5-nitropyrimidines appears to be successful only with hydrazine and only in this case if there is no large substituent adjacent to the nitro group. Therefore, if one desires to synthesize other hydrazino-nitro derivatives a more reactive leaving group is necessary. One of the most reactive and the easiest to obtain leaving groups in pyrimidine chemistry is the chloro substituent. The high reactivity of this substituent is partly due to its inductive effect which unlike methoxy groups imparts greater electrophilicity at the adjacent carbon. Also, due to its greater stability as an anion and its lower basicity and lower nucleophilicity the chloro group produces a lower rate of reverse reaction with the product.

This increase in reactivity of the chloro group appeared to be sufficient to allow displacement of it by methylhydrazine, as shown earlier by the synthesis of 4-methoxy-6-(1-methlhydrazino)- and 4, 6-di(1-methylhydrazino)-5-nitropyrimidine from their corresponding chloro derivatives. They required only very mild reaction conditions which are necessary to avoid the side reactions of the highly reactive chloronitropyrimidines.

Under similar conditions the 4, 6-di(1-methylhydrazino)-2-methyl-5-nitropyrimidine as well as the 2-phenyl derivative were

also successfully prepared from their chloro derivatives and methylhydrazine. Undoubtedly this reaction proceeds via monosubstitution or the 4-chloro-6-(1-methylhydrazino)-5-nitropyrimidine intermediate. Thus, it appears that the presence of the large methylhydrazino substituent in the intermediate does not stop the reaction, as found with the methoxy derivatives.

To prove that the reaction does proceed in fact via the proposed intermediate, attempts were made to prepare these compounds. However, when the 4, 6-dichloro derivative was treated with one mole of methylhydrazine a mixture of mono and disubstituted products resulted which could not be separated without decomposition of the desired product.

The question of the importance of the size of the group ortho to the nitro group was resolved by another route. The following compounds were prepared from 4, 6-dichloro-5-nitropyrimidine; 4-amino-6-chloro- (14), 4-chloro-6-methylamino- (17) and the 4-chloro-6-dimethylamino-5-nitropyrimidine (59). In each case on treatment with methylhydrazine, they gave the corresponding methylhydrazino derivative with no apparent difficulty even under mild conditions.

This can be explained on the basis that the more reactive chloro leaving group is not as strongly dependent on the contributing resonance of the nitro substituent. The result of this greater

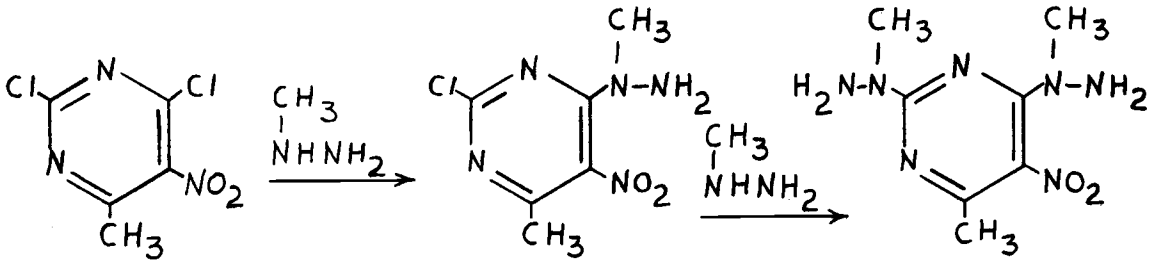
reactivity of a chloro group in comparison with a methoxy group can be seen in the results of Krackov and Christensen (45). They reported that 4, 6-dimethoxy-5-aminopyrimidine exhibited no activity with hydrazines, while 4, 6-dichloro-5-aminopyrimidine successfully react with both hydrazine and methylhydrazine to displace one of the chloro substituents. Incidentally, a good comparison of the greater reactivity of hydrazines over ammonia can be illustrated by this experiment. If 4, 6-dichloro-5-aminopyrimidine is suspended in refluxing 15% aqueous ammonia for thirty minutes the starting material can be recovered almost quantitatively (56).

This high reactivity of chloro-nitropyrimidines is also observed with hydrazines having the deactivating electron-withdrawing substituents. Thus, the 4, 6-dichloro-5-aminopyrimidine did not react with phenylhydrazine while both 4, 6-dichloro-5-nitropyrimidine and its 2-phenyl analog yielded the di-(phenylhydrazino) derivatives at room temperature.

In order to get a better understanding of the importance of the resonance effects of the nitro group, 2, 4-dichloro-6-methyl-5-nitropyrimidine (XXXIX) was prepared. 6-Methyluracil was first nitrated (57) then chlorinated (13) to yield XXXIX. The treatment of XXXIX with methylhydrazine gave the 2, 4-di (1-methylhydrazino)-6-methyl-5-nitropyrimidine (XXXXI)).

It is expected that the reaction proceeds first by the substitution

of the more electrophilic 4-position to give 2-chloro-4-(1-methylhydrazino)-6-methyl-5-nitropyrimidine (XXXIX) and then substitution at the 2-position to yield XXXXI.



XXXX XXXXI

This conclusion is supported by the studies of Shepherd and Fedrick (62, p. 281). By comparing the reaction rates of 2-chloropyrimidine and 2-chloro-3-nitropyridine with piperidine, they concluded that an ortho nitro group was more effective in nucleophilic substitutions than an ortho ring nitrogen atom by a factor of six. Furthermore, with other pyrimidines, they found a para ring nitrogen atom to be a better activator than a para nitro group by a factor of approximately two.

If these correlations are valid for XXXIX then the 4-position should be more reactive than the 2-position by a factor of twelve. Therefore, assuming XXXX as an intermediate then the combined steric hindrance of the methyl and the methylhydrazino as substituents should greatly hinder the planarity of the nitro group with the

ring. This means that the inductive effect of the nitro group, although not as important as the resonance effects, is still very significant in imparting greater reactivity, especially, if one considers that reactions at the 2-position (in contrast to 4- and 6-) are not accelerated by the ortho effects of the nitro group.

One further experiment was carried out to measure the reactivity of hydrazine in replacing methoxy substituents. One wonders whether three methoxy groups could be displaced by hydrazine, as each hydrazino substituent tends to deactivate a pyrimidine ring toward nucleophilic substitution. Barbituric acid was first chlorinated according to the directions of Baddiley and Topham (8) to give the 2, 4, 6-trichloropyrimidine, which upon treatment with refluxing sodium methoxide yielded the 2, 4, 6-trimethoxy derivative (31). The slow addition of trimethoxypyrimidine to a sulfuric acid-red fuming nitric acid mixture maintained below $0^{o}C$ gave a 97% yield of the unreported 5-nitro-2, 4, 6-trimethoxypyrimidine (XXXXII). When XXXXII was refluxed with 6 mole excess of hydrazine in ethanol only a dihydrazino-methoxy-nitropyrimidine (XXXXIII) could be obtained.

In summary, the following conclusions can be made about hydrazinolysis of 4, 6-disubstituted-5-nitropyrimidines:

(1) A chloro substituent in the 4-position can be replaced by hydrazines (including less reactive types, i.e. phenylhydrazine) under very mild conditions even when a large group (e.g. dimethylamino or

1-methylhydrazino) is occupying the 6-position (adjacent to the nitro group). In the case of 4, 6-dichloro pyrimidine derivatives, the reactivity with hydrazines even under very mild conditions makes monosubstitution impractical.

(2) A methoxy substituent in the 4-position can only be replaced by a hydrazino and this is true only, if there is no large group (e.g. 1-methylhydrazino) in the 6-position. However, if these conditions are fulfilled the yields of the hydrazino derivative is excellent and of high purity. The unreactivity of certain methoxyl derivatives is attributed to steric effects caused either by a large attaching nucleophile or the presence of a large substituent adjacent to the nitro group.

Under certain conditions the methyl groups of 4, 6-dimethoxy-5-nitropyrimidines can migrate and even cause methylation of the solvents. At least one of these presumed methyl migration products can react with methylhydrazine to result in unexpected products, 4-hydrazino-6-hydroxypyrimidines in good yield.

EXPERIMENTAL

All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus. The infrared spectra were obtained with a Beckman Model IR-8 spectrophotometer with the samples in the form of nujol mulls, which produces two strong absorption bands at approximately 2920 and 2860 cm^{-1} and two weaker bands at about 1460 and 1375 cm^{-1}. Occasionally, when it was necessary to see these regions, the sample was mulled with Kel-F-10 oil which has no absorptions in the 4000 to 1300 cm^{-1} region. The ultraviolet spectra were measured with a Cary Model 15 spectrophotometer (using 1.0 cm quartz cells). The nuclear magnetic resonance (nmr) spectra were recorded on a Varian Model A-60 spectrometer. For the nmr spectra, an internal standard of sodium 3-trimethylsilyl-1-propane sulfonate was used for samples run in aqueous or dimethylsulfoxide solutions; for trifluoracetic acid solutions, an external standard of 10% tetramethylsilane in chloroform was employed.

All the hydrazine reagents were stored in tightly sealed containers in a refrigerator to avoid decomposition. All possible precautions were taken to avoid exposure to either hydrazine vapors or through physical contact with the liquid. All reactions were carried out in well ventilated hoods employing closed systems whenever

possible. The very rapid absorption of hydrazine through the skin presents a dangerous hazard to workers in hydrazine chemistry.

4-Hydrazino-6-hydroxypyrimidine (2H-K or XXI)

A. Two and six-tenths (0.02 mole) of 4-chloro-6-hydroxypyrimidine (19) was dissolved in 100 ml of absolute ethanol and heated to approximately 70°C. To this solution was added 1.35 ml (0.04 mole) of 95% anhydrous hydrazine and the resultant mixture was refluxed for 30 minutes; within five minutes crystals were observed. Upon cooling, the solution was diluted with 50 ml of water and then allowed to stir for an additional five minutes. The precipitate was collected, washed with cold water; yield 1.26 (50%) of the white product, m.p. 235 - 245° C (dec.)

Concentration of the mother liquor to about 10 ml gave another 1.0 g (40%) of crude product. Recrystallization of a small portion from ethanol-water (1/1) solvent gave long white needles. The product had a decomposition point at approximately 237°C; it exhibited a melting point at approximately 310°C when the sample was placed on a block that has been preheated close to the melting point.

This compound gives a positive Tollen's test, a positive reaction with sodium pentacyanoammineferroate (29), and (unexpected) positive test (a deep blue color) with ferric chloride solution.

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, 43.7.

B. Into a refluxing solution containing 1.85 g (0.01 mole) of 4, 6-dimethoxy-5-nitropyrimidine (60) in 50 ml of reagent grade pyridine was pipetted 1.84 ml of methylhydrazine which caused an instant yellow coloration; the solution was allowed to reflux for one hour. During the first five minutes of the reflux period, a fine white material began to precipitate. After cooling in the refrigerator the solution was filtered; the filter cake was washed with cold methanol, yielding 0.71 - 0.82 g (56-65%) of crude cream colored product m.p. 245 - 255°C (dec.). Evaporation of the filtrate yielded only unidentified decomposition products which exhibited mainly end absorption in its ultraviolet spectrum. Recrystallization of the solid product twice from an ethanol-water solvent (1/1) produced fine long white crystals which decomposed on heating at 237°C.

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

Found C, 38.1; H, 4.7; N, 43.8.

Samples obtained from methods A and B gave identical ultraviolet, infrared and nmr spectra as well as giving the same results with the chemical classification tests.

4-Hydrazino-6-hydroxy-2-methylpyrimidine (2Me-K)

To a gently refluxing solution containing 2.0 g (0.01 mole) of

4, 6-dimethoxy-2-methyl-5-nitropyrimidine in 50 ml of reagent grade pyridine was added 1.84 ml (0.04 mole) of methylhydrazine; the solution was allowed to reflux for 30 minutes. During the first five minutes of the refluxing period a fine solid material precipitated. After standing in a refrigerator overnight, a crude cream colored material (0.80 g) deposited which was collected by filtration. Recrystallization twice from an ethanol-water (1/2) solvent yielded 0.72 g (51%) of long white crystals m.p. 155 - 156°C (dec.).

This compound also gave the unexpected positive test (blue color) with ferric chloride solution.

Anal. Calc'd for $C_5H_8N_4O$: C, 42.9; H. 5.7; N, 40.0.

Found: C, 42.9; H, 5.8; N, 39.4.

4-Hydrazino-6-hydroxy-2-phenylpyrimidine (2Ph-K)

A. The addition of 0.67 ml (0.02 mole) of 95% anhydrous hydrazine to a gently refluxing suspension of 2.1 g (0.01 mole) of 4-chloro-6-hydroxy-2-phenylpyrimidine in 50 ml of absolute ethanol gave a clear colorless solution. This solution was refluxed for 30 minutes before the product began to precipitate. After refluxing for an additional 30 minutes, the mixture was cooled and diluted with 25 ml of cold water. The product was isolated by filtration; yield 1.2 g (59%) of the white product, m.p. 239 - 241°C (dec.). Concentration of the mother liquor to 10 ml, gave 0.7 g (35%) more of the

crude product. A small portion was recrystallized for analysis from n-butanol as fine white crystals, m.p. 239 - 240° C (dec.).

The compound gave a weakly positive test (blue color) with ferric chloride solution. The compound also gave a positive reaction with Tollen's reagent and with sodium pentacyanoammineferroate solution.

Anal. Calc'd for $C_{10}H_{10}N_4O$: C, 59.5; H, 5.0; N, 27.7.

Found: C, 59.6; H, 4.9; N, 27.1.

B. The 4, 6-dimethoxy-5-nitro-2-phenylpyrimidine in hot pyridine did not react with methylhydrazine to give 2Ph-K in an isolatable yield but instead yielded other products most likely from the cleavage of the pyrimidine ring. By the use of n-butanol (dried with calcium sulfate and freshly distilled) as solvent a small amount of 2Ph-K was formed.

A solution 10.4 g consisting of (0.04 mole) 4, 6-dimethoxy-5-nitro-2-phenylpyrimidine and 600 ml of refluxing n-butanol was added dropwise to a solution of 7.4 ml (0.16 mole) of methylhydrazine in 100 ml of n-butanol over a period of 45 minutes. The deep yellow solution was refluxed for two hours becoming orange (no precipitation). On cooling in a deep freeze overnight, 2.5 g (31%) of the crude yellow-tan crystals were obtained, m.p. 210 - 230°C (dec.). Recrystallization from n-butanol gave pale yellow crystals m.p. 227 - 228°C (dec.).

Anal. Calc'd for $C_{10}H_{10}N_4O$: C, 59.5; H, 5.0; N, 27.7.

Found: C, 59.4; H, 4.8; N, 26.7.

The infrared and nmr spectra of the samples prepared from methods A and B were identical.

4-(1, 2 Diacetohydrazino)-6-hydroxypyrimidine

A mixture of 0.50 g (0.004 mole) of 4-hydrazino-6-hydroxypyrimidine and 150 ml of acetic anhydride was stirred at a bath temperature of 80°C until a clear solution was produced. After a continual heat for additional 15 minutes, the clear solution was evaporated to dryness at 50°C. Recrystallization of the crude residue from ethyl acetate-isopropyl alcohol (3/1, v/v) and decolorized with charcoal yielded 0.42 g (63.5%) of tiny white crystals, m.p. 216.0° - 216.5°C. Evaporation of the mother liquor yielded another 0.23 g (34%) of less pure product, m.p. 215 - 216°C.

This diacelylated compound did not give a positive test on addition of ferric chloride. Furthermore, the color test for the identification of diacetylated amino nitrogens was negative. The procedure used for this latter test is a modification proposed by Carson (23) for a method described by Davidson (25).

Anal. Calc'd for $C_8H_{10}N_4O_3$: C, 45.7; H, 4.8; N, 26.7.

Found: C, 45.8; H, 5.0; N, 26.5.

4-(1,2-Diacetohydrazino)-6-hydroxy-2-phenylpyrimidine

A solution of 0.50 g (0.0025 mole) of 4-hydrazino-6-hydroxy-2-phenylpyrimidine in 100 ml of acetic anhydride was stirred for two hours at 75°C. The residue, obtained by evaporation of the solution to dryness at 50°C, was recrystallized and decolorized with charcoal twice from an ethanol-water solvent (4/1); yield 0.49 g (68%) of white crystals, m.p. 278 - 279°C.

Anal. Calc'd for $C_{14}H_{14}N_4O_3$: C, 58.7; H, 4.9; N, 19.6.

Found: C, 58.8; H, 4.8; N, 19.5.

4-Amino-6-hydroxypyrimidine

A. The method described by Brown (16) was used to obtain a sample of 4-amino-6-hydroxypyrimidine for comparison purposes. 4-Amino-6-hydroxy-2 thiopyrimidine was dethionated with Raney nickel to the desired product, m.p. 264 - 265°C.

B. The general procedure suggested by Ainsworth (1) for cleavage of N-N bonds was followed. A mixture of 1 g (0.008 mole) of 4-hydrazino-6-hydroxypyrimidine, 10 g of Raney nickel (prepared according to the directions of Brown (16)) and 50 ml of 95% ethanol was refluxed for three hours. Upon filtration of the hot mixture and washing the precipitate with two portions of 2 ml of water, the solution was evaporated to dryness yielding approximately 400 mg of a

white solid. Sublimation of the solid at 150°C and 0.02 Torr gave about 100 mg of crude product, m.p. 253 - 261°C (dec.). From the analysis and the very low yield it appears that some reduction of the ring takes place.

Anal. Cal'd for $C_4H_5N_3O$: C, 43.2; H, 4.5; N, 37.8.

Found: C, 43.0; H, 5.1; N, 35.8.

C. The procedure of Ainsworth (1) was modified in an effort to prevent the reduction of the pyrimidine ring. To a gently boiling solution of 0.50 g (0.004 mole) of 4-hydrazino-6-hydroxypyrimidine in 10 ml of water and 3 ml of 28% aqueous ammonium hydroxide was added in small portions 2 g of Raney nickel, prepared according to the directions of Brown (16). After completing the addition, the mixture was gently refluxed, with stirring for 30 minutes; upon evaporation to dryness 400 mg of crude product was obtained. Recrystallization from water or sublimation yielded 350 mg (79%), m.p. 264 - 265°C.

Anal. Calc'd for $C_4H_5N_3O$: C, 43.2; H, 4.5; N, 37.8.

Found: C, 43.1; H, 4.6; N, 37.6.

4-Chloro-6-hydroxy-2-phenylpyrimidine

A mixture of 5 g (0.22 mole) of 4,6-dichloro-2-phenylpyrimidine (35) and 50 ml of 3N sodium hydroxide was refluxed vigorously until only a clear solution remained (approximately eight hours).

The solution was carefully acidified to pH 2-4 with concentrated hydrochloric acid.

After filtering and thoroughly washing with water, the product was pressed dry and finally dried in vacuo over phosphorus pentoxide; yield 4.5 g (98%) of a white product, m.p. 227 - 229°C. Recrystallization from isopropyl alcohol yielded fine white needles (over 90% recovery), m.p. 226 - 227°C.

Anal. Calc'd for $C_{10}H_7ClN_2O$: C, 58.1; H, 3.49; N, 13.1.

Found: C, 58.0; H, 3.5; N, 13.3.

4, 6-Diamino-5-pyrimidyl hydrogen sulfate

A solution of 34.2 g (0.15 mole) of ammonium persulfate in 70 ml of water was added dropwise during a period of one hour to a stirred fine suspension of 11.0 g (0.10 mole) of 4, 6-diaminopyrimidine (16) in 220 ml of 3N sodium hydroxide which was maintained at 10°C. After the addition was complete, the ice bath was removed, and the mixture stirred at room temperature for eight hours. The resulting deep yellow solution was cooled in an ice bath and acidified to pH 1 with concentrated hydrochloric acid. After 30 minutes the product was collected and washed with cold water to yield 20.1 g (97.6%) of a yellow-tan powder. The compound gave a negative ferric chloride test and was soluble in sodium hydrogen sulfate. A small portion was recrystallized for analysis from water (90%

recovery) to yield clear pale yellow needles. The compound started to decompose at 260°C but did not melt by 350°C.

Anal. Calc'd for $C_4H_6N_4O_4S$: C, 23.3; H, 2.9; N, 27.2.

Found: C, 23.3; H, 2.8; N, 27.2.

4, 6-Diamino-5-hydroxypyrimidine (XVI)

To 10.3 g (0.05 mole) of 4, 6-diamino-5-pyrimidyl hydrogen sulfate was added 25 ml of 6N hydrochloric acid. The mixture was refluxed for one half hour. The pale yellow solution was cooled in the refrigerator and the pale yellow hydrochloride (pyrimidine hydrochloride) of the pyrimidine which precipitated was collected and washed with ice water. The crystals were suspended in 30 ml of water and while stirring powdered bicarbonate was slowly added until the effervescence abated. After stirring for one hour the precipitate was collected yielding 4.9 g (78%) of white microcrystals of the free base. Recrystallization from water gives white needles, if care is taken to avoid air oxidation of the compound. The purified pyrimidine when slowly heated on the melting point block began darkening at 220°C and slowly turned completely black with no apparent melting. However, the compound did exhibit a melting point of 240-1°C (dec.) if the block was first preheated to a temperature within two degrees of m.p. before placing the sample on the block.

The 4, 6-diamino-5-hydroxypyrimidine gave a positive ferric chloride test (red brown color); pale green color if an excess ferric chloride solution is used.

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

Found. C, 38.1; H, 4.7; N, 44.3.

4-(1-Methylhydrazino-6-hydroxypyrimidine (XXV)

Into a solution containing 1.3 g (0.01 mole) of 4-chloro-6-hydroxypyrimidine (19) in 50 ml of absolute ethanol heated to about 70°C, was pipetted 0.92 ml (0.02 mole) of methylhydrazine. After refluxing for five minutes a white precipitate appeared. The reflux period was continued for an additional 25 minutes; on cooling, 25 ml of water was added which dissolved the precipitate. Concentration of the solution to 20 ml yielded 1.15 g (82%) of the methylhydrazinopyrimidine which was isolated by filtration, m.p. 199 - 221°C (dec.). A small amount was recrystallized from ethanol-water (1/1) solvent for analysis; m.p. 220 - 221°C (dec.).

Anal. Calc'd for $C_5H_8N_4O$: C, 42.9; H, 5.7; N, 40.0.

Found: C, 42.9; H, 5.8; N, 39.9.

4, 6-Di-(1-methylhydrazino-5-nitropyrimidine (V)

A 250 ml standard taper Erlenmeyer flask containing a solution of 1.94 g (0.01 mole) of 4, 6-dichloro-5-nitropyrimidine (35) in 200

ml of absolute methanol was cooled to -10°C. On addition of 1.85 ml (0.04 mole) of methylhydrazine the solution turned to a yellow color. The solution in the stoppered flask was stirred for one hour while allowing the temperature to rise to room temperature. During this period the product precipitated as a yellow powder. After removing the product by filtration and drying the yield was 1.85 g (84.5%), m.p. 175 - 177°C (dec.). Recrystallization from dioxane gave fine yellow crystals, m.p. 183.5 - 184.5°C (dec.).

Anal. Calc'd for $C_6H_{11}N_7O_2$: C, 33.8; H, 5.2; N, 46.0.

Found: C, 33.9; H, 5.2; N, 45.8.

4,6-Di-(1-methylhydrazino)-2-methyl-5-nitropyrimidine

Under similar conditions, 2.08 g (0.01 mole) of 4,6-dichloro-2-methyl-5-nitropyrimidine (5) in 200 ml of absolute methanol reacted with 1.85 ml (0.04 mole) of methylhydrazine to give 2.15 g (94.7%) of fine yellow crystals; m.p. 155 - 156°C (dec.).

Anal. Calc'd for $C_7H_{13}N_7O_2$: C, 37.0; H, 5.7; N, 43.2.

Found: C, 37.2; H, 5.7; N, 43.0.

4,6-Di-(1-methylhydrazino)-5-nitro-2-phenylpyrimidine

Into a fine suspension of 2.70 g (0.01 mole) of 4,6-dichloro-5-nitro-2-phenylpyrimidine in 200 ml of absolute methanol at room temperature was pipetted 1.85 ml (0.04 mole) of methylhydrazine.

Almost immediately a clear yellow solution formed. After one hour of stirring at room temperature during which time crystals appeared, the yellow mixture was cooled in the refrigerator. The product was collected; yield 2.57 g (89%) of yellow crystals, m.p. 159 - 161°C (dec.). Recrystallization from water-dimethylforamide (7/3 v/v) gave small yellow needles, m.p. 160 - 161°C.

Anal. Calc'd for $C_{12}H_{15}N_7O_2$: C, 49.8; H, 5.2; N, 34.2.

Found: C, 49.6; H, 4.9; N, 34.0.

2,4-Di-(1-methylhydrazino)-6-methyl-5-nitropyrimidine (XXXXII)

When 0.46 ml (0.01 mole) of methylhydrazine was introduced into a solution containing 10 g (0.0048 mole) of 2,4-dichloro-6-methyl-5-nitropyrimidine (13) in 100 ml of absolute methanol the solution became yellow. No precipitation occurred after stirring at room temperature for one hour. Concentration of the yellow solution to approximately 20 ml at 50°C was effected by means of a rotary evaporator. The mixture was cooled in the refrigerator overnight and filtered; yield 0.4 g (37%) of the bright yellow product, m.p. 124 - 125°C.

Anal. Calc'd for $C_7H_{13}N_7O_2$: C, 37.0; H, 5.7; N, 43.2.

Found: C, 37.1; H, 5.9; N, 42.8.

4-Dimethylamino-6-(1-methylhydrazino)-5-nitropyrimidine

Methylhydrazine (0.46 g, 0.01 mole) was introduced into a solution of 1.0 g (0.005 mole) of 4-chloro-6-dimethylamino-5-nitropyrimidine (59) in 50 ml of absolute methanol. After stirring the solution for four hours at room temperature, the precipitate was collected; yield, 0.32 g (30%), m.p. 199 - 200°C.

Anal. Calc'd for $C_7H_{12}N_6O_2$: C, 39.6; H, 5.7; N, 39.6.

Found: C, 39.3; H, 5.3; N, 40.5.

General Procedure for the Preparation of Hydrazino-nitropyrimidines from Methyoxy-nitropyrimidines

This procedure is a modification of the one suggested by Krackov and Christensen (45). Approximately 0.005 mole of methoxy-nitropyrimidine was dissolved in 75 ml of boiling absolute ethanol. Two equivalents of absolute hydrazine per equivalent of methoxy group were then pipetted directly into the rapidly stirred, refluxing solution. In the case of very reactive pyrimidines, such as 4, 6 dichloro-5-nitropyrimidine, the hydrazine was first dissolved in 10 ml of absolute ethanol before its addition to the pyrimidine solution. The solution was maintained at a gentle reflux, whereupon (usually within 0-5 minutes) the hydrazino derivative settled out of solution in the form of long yellow crystals. The thick

suspension was refluxed for an additional five minutes. The less reactive pyrimidines take a longer time to crystallize; a final reflux period of 10 minutes is preferable. After cooling in a refrigerator the crystals are collected by filtration, washed thoroughly with cold ethanol and then dried in vacuo over phosphorus pentoxide. One should obtain at least 95% of the theoretical yield. Since the reaction is usually almost quantitative the remaining hydrazinopyrimidine can be recovered by concentration of the mother liquor; however the evaporating temperature must be maintained below 30°C to avoid decomposition. The purity of the product is dependent on the purity of the starting material and complete removal of the excess hydrazine.

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

A. To a refluxing solution of 1.0 g (0.0055 mole) of 4, 6-dimethoxy-5-nitropyrimidine (60) in 75 ml of absolute ethanol was added portionwise a solution consisting of 0.74 ml (0.022 mole) of 95% anhydrous hydrazine in 10 ml of absolute ethanol. The reaction proceeds rapidly with almost immediate precipitation of the product (III). After five to ten minutes of additional reflux time, the pyrimidine was isolated as mentioned above, yielding 0.98 g (98%) of a bright yellow needles, m.p. 200 - 201°C, dec. (3), m.p. 202 - 203 dec.,(5), m.p. 206.

Anal. Calc'd for $C_4H_7N_7O_2$: C, 30.0; H, 3.8; N, 53.0.

Found: C, 29.9; H, 3.9; N, 53.1.

B. A solution consisting of 4-hydrazino-6-methoxy-5-nitropyrimidine (0.50 g, 0.0027 mole) in 35 ml of absolute ethanol and a solution of hydrazine (0.2 ml, 0.054 mole) in 10 ml absolute ethanol reacted similarly to yield 0.49 g (98%) of III, m.p. 200 - 201°C (dec.).

4, 6-Dihydrazino-2-methyl-5-nitropyrimidine

Following the same procedure a solution consisting of 1.99 g (0.01 mole) of 4, 6-dimethoxy-5-nitropyrimidine in 150 ml absolute ethanol and a solution prepared by dissolving 95% anhydrous hydrazine (1.35 ml, 0.04 mole) in 10 ml of absolute ethanol were reacted; yield 1.91 g (96%) of yellow needles, m.p. 201 - 202°C (dec.).

Anal. Calc'd for $C_5H_9N_7O_2$: C, 30.2; H, 4.5; N, 49.3.

Found: C, 30.3; H, 4.5; N, 49.1.

4, 6-Dihydrazino-5-nitro-2-phenylpyrimidine

Into a refluxing solution containing 2.61 g (0.01 mole) of 4, 6-dimethoxy-5-nitro-2-phenylpyrimidine in 150 ml of absolute ethanol was pipetted 1.35 g (0.04 mole) of 95% anhydrous hydrazine. The solution was refluxed about 35 minutes before the appearance of the crystalline product in the hot solution; consequently the final reflux

period was extended to 10 minutes. Yield 2.54 g (97%) of the dihydrazinopyrimidine was obtained as fluffy long yellow needles, m.p. 225 - 226°C with decomposition.

Anal. Calc'd for $C_{10}H_{11}N_7O_2$: C, 46.0; H, 4.2; N, 37.6.

Found: C, 46.2; H, 4.0; N, 37.4.

4-Amino-6-hydrazino-5-nitropyrimidine (XXXVIII)

A solution of 0.67 ml (0.02 mole) of 95% anhydrous hydrazine in 10 ml absolute ethanol was added portionwise to a rapidly stirred, refluxing solution containing 1.70 g (0.01 mole) of 4-amino-6-methoxy-5-nitropyrimidine (4) in 150 ml of absolute ethanol. Upon precipitation of the pyrimidine the mixture was refluxed for an additional five minutes; yield, 1.65 g (97%) of tiny yellow needles. When a sample was placed on the melting point block, it started to darken at 230°C. If the block was preheated, it melted at 248-249°C (dec.); Ladwig (48, p. 30) reported 82% yield, m.p. 245-250°C (dec.).

Anal. Calc'd for $C_4H_6N_6O_2$: C, 28.2; H, 3.5; N, 49.4.

Found: C, 28.4; H, 3.5; N, 49.3.

4-Methoxy-6-(1-methylhydrazino)-5-nitropyrimidine (XXVIII)

A solution containing 9.48 g (0.05 mole) of 4-chloro-6-methoxy-5-nitropyrimidine (67) in 400 ml of absolute methanol was

cooled below 0°C. Then 4.6 ml (0.1 mole) of methylhydrazine was pipetted into the solution, producing a yellow color. The solution in a stoppered flask, was stirred for 30 minutes while allowing it to warm to room temperature. Evaporation of the solution to approximately 150 ml, followed by filtration and washing of the filter cake with cold water yielded 8.3 g (83.5%) of yellow product, m.p. 196 - 198°C. Purification by either crystallization from absolute ethanol or by sublimation gives yield of 6.8 g (68%), m.p. 201 - 202°C.

Anal. Calc'd for $C_6H_9N_5O_3$: C, 36.2; H, 4.5; N, 35.2.

Found: C, 36.1; H, 4.6; N, 35.1.

4-Hydrazino-6-methoxy-5-nitropyrimidine (XXXV)

A solution of 1.9 g (0.01 mole) of 4-chloro-6-methoxy-5-nitropyrimidine (67) in 100 ml of absolute methanol was cooled below 0°C. Then during a period of 30 minutes a solution consisting of 0.67 ml (0.02 mole) of 95% anhydrous hydrazine in 10 ml of methanol was introduced dropwise into the pyrimidine solution. When slightly over half of the hydrazine solution had been added crystallization of XXXV as long fluffy yellow needles was observed. Isolation of the product by filtration yielded 1.6 g (86.5%), m.p. 160 - 161°C (dec.).

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

Found: C, 32.6; H, 3.6; N, 37.6.

4, 6-Dimethoxy-2-methyl-5-nitropyrimidine (XIII)

Using a modification of the procedure of Urban and Schnider (68) a nearly quantitative yield of high purity product was obtained in much shorter time.

To a rapidly stirred solution of sodium methoxide, prepared by adding 4.8 g (0.21 mole) of sodium to 150 ml of reagent grade methanol, was added dropwise a solution containing 11.0 g (0.053 mole) of 4, 6-dichloro-2-methyl-5-nitropyrimidine (5) dissolved in 100 ml of methanol; addition was made over a period of 30 minutes. The pale red mixture was allowed to reflux for one hour and then the methanol was removed by distillation until a thick paste remained. An ice-water slurry (approximately 400 ml) was added, followed by dilute hydrochloric acid until the mixture was neutral to litmus paper. The precipitate was collected, washed well with cold water and dried to yield 10.2 g (97%) of the cream colored product, m.p. 123 - 124°C. Urban and Schnider (68) reported an 86% yield, m.p. 116 - 117°C. A small amount was recrystallized from methanol (m.p. 124.0 - 124.5°C).

4, 6-Dimethoxy-5-nitro-2-phenylpyrimidine (XIV)

4, 6-Dichloro-5-nitro-2-phenylpyrimidine (40.5 g, 0.15 mole) (35) was suspended in 200 ml of anhydrous methanol and the mixture

then cooled in an ice bath. A solution of sodium methoxide, prepared by adding 13.8 g (0.60 mole) of sodium to 300 ml of anhydrous methanol, was introduced dropwise into the stirred suspension at a rate which did not allow the temperature to rise above 20°C. After the addition was complete, the mixture was refluxed for one hour, whereupon on cooling it was poured into 400 ml of ice cold water. The precipitate was collected, washed well with cold water and dried, yield 36.9 g (94.4%) of a yellow product. Recrystallization from ligroin (b.p. 90 - 120°C) gave pale yellow needles, m.p. 122.5 - 123°C.

Anal. Calc'd for $C_{12}H_{11}N_3O_4$: C, 55.2; H, 4.2; N. 16.1.

Found: C, 55.3; H, 4.2; N, 15.8.

4-Dimethylamino-6-methoxy-5-nitropyrimidine (XXXVI)

To a vigorously stirred solution of sodium methoxide, prepared by reacting 0.9 g (0.4 mole) of sodium with 100 ml of methanol (17), was added 7.1 g (0.35 mole) of finely powdered 4-chloro-6-dimethyl-amino-5-nitropyrimidine in small portions. The mixture was then refluxed for one hour with subsequent evaporation of the solvent until only a thick residue remained. The residue was stirred with approximately 100 ml of cold water, collected by filtration and dried, giving 6.3 g (91%) of the white methoxypyrimidine, m.p. 101.5 - 102.5°C. A small portion was recrystallized from absolute

ethanol for analysis, m.p. 102 - 102.5°C.

Anal. Calc'd for $C_7H_{10}ClN_4O$: C, 42.4; H, 5.1; N, 28.2.

Found: C, 42.6; H, 5.0; N, 28.0.

5-Nitro-2, 4, 6-trimethoxypyrimidine (XXXXII)

A nitrating solution was prepared by slowly adding 25 ml of concentrated sulfuric acid (d. 1.86) to 25 ml of red fuming nitric acid (d. 1.59 - .60) kept cold with an ice-salt bath. To this rapidly stirred solution, maintained below 0°C was added 20.4 g (0.12 mole) of 2, 4, 6-trimethoxypyrimidine (31) in small portions over a period of 20 minutes. The ice-salt bath was removed and the temperature of the solution allowed to rise to 20°C. After one-half hour at room temperature, the solution was carefully poured over 900 g of cracked ice with constant stirring. The nitropyrimidine was filtered and washed thoroughly with cold water; yield 25.0 g (97%) of the fluffy pale yellow compound, m.p. 123 - 124°C.

For analysis a small portion was recrystallized from 95% ethanol to give pale yellow needles, m.p. 123.5 - 124°C.

Anal. Calc'd for $C_7H_9N_3O_5$: C, 39.1; H, 4.2; N, 19.5.

Found: C, 39.3; H, 4.4; N, 19.2.

4, 6-Di-(2-phenylhydrazino)-5-nitropyrimidine

Following the solution of 1.94 g (0.01 mole) of

4, 6-dichloro-5-nitropyrimidine (35) in 100 ml of absolute methanol, 4.3 g (0.04 mole) of phenyl hydrazine was added, producing a yellow solution. This solution, upon sitting for one hour at room temperature, was poured slowly into 250 ml of ice cold water which was constantly stirred. The yellow precipitate that formed was collected and dried in vacuo to give 2.75 g (82%) of crude product. The compound appeared to be easily oxidized by air.

Anal. Calc'd for $C_{16}H_{15}N_7O_2$: C, 57.0; H, 4.5; N, 29.1.

Found: C, 56.7; H, 4.5, N, –

4, 6-Di(2-phenylhydrazino)-5-nitro-2-phenylpyrimidine

In a similar manner as described above, 1.35 g (0.005 mole) of 4, 6-dichloro-5-nitro-2-phenylpyrimidine (as a fine suspension) and 2.2 g (0.02 mole) of phenylhydrazine in 50 ml of methanol yielded 1.9 g (92%) of the yellow product. Using a mixed solvent procedure with acetone and water, recrystallization yielded fine yellow needles. This product also appeared susceptible to air oxidation.

Anal. Calc'd for $C_{22}H_{19}N_7O_2$: C, 63.9; H, 4.6; N, 23.7.

Found: C, 63.7; H, 4.7; N, 23.3.

Dihydrazino-methoxy-5-nitropyrimidine (XXXXIII)

A solution of 2.0 g (0.01 mole) of 5-nitro-2,4,6-trimethoxy-pyrimidine in 50 ml of absolute ethanol was heated to a gentle reflux. With vigorous stirring 1.9 g (0.06 mole) of anhydrous hydrazine was added to the solution whereupon a yellow solid precipitated. After an additional 30 minutes of refluxing the mixture was cooled to 0°C and filtered. The precipitate was thoroughly washed with cold absolute ethanol yielding 1.9 g (95%) of bright yellow crystals, m.p. 198 - 200°C.

Anal. Calc'd for $C_5H_9N_7O_2$: C, 30.2; H, 4.5; N, 49.2.

Found: C, 30.4; H, 4.6; N, 49.0.

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APPENDIX

Table I. Summary of Infrared Data

Name of Compounds	Hydrogen Stretching Vibrations (3000 - 4000 cm^{-1})*	Double Bond - N-H Bending Vibrations (1500 - 1750 cm^{-1})*
4-amino-6-(1-methylhydrazino)-5-nitropyrimidine	3635 (vs) 3333 (s) 3125 (m) 3470 (vs) 3235 (w) 3085 (m)	1647 (vs) 1669 (s) 1628 (m) 1574 (vs) 1521 (s)
4-chloro-6-hydroxy-2-phenylpyrimidine	3069 (w) 3048 (w)	1650 (s) 1672 (vs) 1602 (w) 1550 (m) 1536 (m)
4-(1,2-diacetohydrazino)-6-hydroxy-2-phenylpyrimidine	3280 (s) 3175 (w) 3090 (2) 3030 (2)	1710 (s) 1658 (vs) 1605 (m) 1564 (m) 1689 (s) 1645 (vs) 1595 (m) 1545 (m)
4-(1,2-diacetohydrazino)-6-hydroxypyrimidine	3400 (s) 3145 (w) 3100 (w) 3030 (w)	1724 (vs) 1667 (vs) 1595 (s) 1500 (m) 1698 (vs) 1625 (m)
4,6-diamino-5-hydroxypyrimidine (XVI)	3483(s) 3350 (m) 3430 (m) 3311 (m)	1636 (s) 1590 (m) 1568 (w)
4,6-diamino-5-pyrimidyl hydrogen sulfate	3430 (m) 3345 (s) 3156 (s) 3021 (vw) 3390 (s)	1661 (vs) 1605 (vs) 1570 (m)
dihydrazino-methoxy-5-nitropyrimidine (XXXXIV)	3380(m) 3289(s) 3180 (m)	1617 (s) 1562 (s) 1929 (s) 1500 (s)
4,6-dihydrazino-2-methyl-5-nitropyrimidine	3356 (m) 3279 (s) 3205 (m)	1613 (s) 1572 (s) 1550 (s) 1525 (vs)
4,6-dihydrazino-5-nitro-2-phenylpyrimidine	3390 (m) 3330 (m) 3067 (vw)	1616 (w) 1585 (m) 1540 (vs)

Continued on next page

Table I Continued.

Name of Compounds	Hydrogen Stretching Vibrations (3000 - 4000 cm^{-1})*	Double Bond - N-H Bending Vibrations (1500 - 1750 cm^{-1})*
4,6-dimethoxy-5-nitro-2-phenylpyrimidine (XIV)	3058 (w)	1592 (s) 1562 (vs) 1522 (s)
4-dimethylamino-6-methoxy-5-nitropyrimidine (XXXVI)		1591 (vs) 1524 (s)
4-dimethylamino-6-(1-methylhydrazino)-5-nitropyrimidine	3378 (m) 3356 (s) 3075 (vs)	1603 (s) 1531 (s)
2,4-di(1-methylhydrazino)-6-methyl-5-nitropyrimidine (XXXXI)	3340 (w) 3247 (vs) 3210 (vs)	1647 (m) 1562 (vs) 1550 (vs)
4,6-di(1-methylhydrazino)-2-methyl-5-nitropyrimidine	3344 (s) 3252 (m)	1647 (s) 1570 (vs) 1520 (vs)
4,6-di-(1-methylhydrazino)-5-nitro-2-phenylpyrimidine	3356 (m) 3268 (w) 3095 (vs) 3040 (vs)	1645 (m) 1548 (vs) 1515 (s)
4,6-di-(1-methylhydrazino)-5-nitropyrimidine (V)	3356 (m) 3322 (w) 3257 (vs) 3049 (vw)	1636 (s) 1570 (s) 1526 (s) 1512 (m)
4,6-di-(2-phenylhydrazino)-5-nitro-2-phenylpyrimidine	3413 (m) 3333 (w) 3077 (w)	1631 (w) 1587 (m) 1548 (s) 1515 (m)
4,6-di-(2-phenylhydrazino)-5-nitropyrimidine	3335 (w) 3215 (w) 3070 (w)	1642 (m) 1600 (m) 1565 (vs) 1536 (m)

Continued on next page

Table I Continued.

Name of Compounds	Hydrogen Stretching Vibrations (3000 - 4000 cm^{-1})*	Double Bond - N-H Bending Vibrations (1500 - 1750 cm^{-1})*
4-hydrazino-6-hydroxy-2-methylpyrimidine (2 Me-K)	3335 (w) 3265 (m) 3142 (vs) 3058 (w)	1671 (vs) 1621 (s) 1550 (w)
4-hydrazino-6-hydroxy-2-phenylpyrimidine (2 Ph-K)	3367 (w) 3289 (m) 3252 (m) 3050 (w)	1668 (s) 1618 (vs) 1568 (s) 1538 (m)
4-hydrazino-6-hydroxy pyrimidine (2H-K and XXI)	3320 (w) 3257 (m) 3186 (w) 3068 (w)	1667 (vs) 1626 (s) 1550 (w)
4-hydrazino-6-methoxy-5-nitropyrimidine (XXXV)	3356 (s) 3280 (s) 3030 (w)	1598 (vs) 1530 (vs)
6-hydroxy-4-(1-methylhydrazino) pyrimidine (XXV)	3322 (w) 3195 (w) 3110 (vs) 3040 (vw)	1669 (s) 1653 (s) 1630 (m) 1551 (w)
4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine	3355 (s) 3278 (w) 3067 (vw) 3020 (vw) 3320 (w)	1658 (s) 1642 (vs) 1587 (vs) 1529 (vs)
4-methylamino-6-(1-methylhydrazino)-5-nitropyrimidine	3465 (s) 3340 (s) 3065 (vw) 3435 (s)	1642 (s) 1595 (vs) 1570 (s) 1520 (s)
N-methylpyridinium pyriminate salt (XXXII)	3550 (vw) 3410 (vw) 3150 (vw) 3067 (vs)	1655 (vs) 1610 (vs) 1595 (s) 1502 (w)
5-nitro-2, 4, 6-trimethoxy-pyrimidine (XXXXII)		1598 (s) 1587 (s) / 1572 (s) 1516 (w)

* See other sheet for names of compounds
s = strong; m = medium; w = weak; v = very

Table II. Summary of Ultraviolet Spectral Data

Name of Compounds	max (mμ)*	E X 10^3
4-amino-6-(1-methylhydrazino)-5-nitropyrimidine	357, 250	4.46, 15.8
4-chloro-6-hydroxy-2-phenylpyrimidine	289, 242	9.76, 11.5
4-(1,2-diacetohydrazino)-6-hydroxy-2-phenylpyrimidine	285, 241	7.15, 21,5
4-(1,2-diacetohydrazino)-6-hydroxypyrimidine	275, 222	5.34, 20.4
4,6-diamino-5-hydroxypyrimidine (XVI)	276, 214	11.8, 16.8
4,6-diamino-5-pyrimidyl hydrogen sulfate	269, 217	9.40, 19.5
dihydrazino-methoxy-5-nitropyrimidine (XXXXIII)	327, 232.5, 202	10.5, 16.6, 21.8
4,6-dihydrazino-2-methyl-5-nitropyrimidine	325, 242sh, 230, 202	4.98, 13.5, 16.5, 21.2
4,6-dihydrazino-5-nitro-2-phenylpyrimidine	339, 290sh, 202	20.9, 12.7, 41.8

Continued on next page

Table II Continued

Name of Compound	max (mμ)*	E X 10^3
4,6-dimethoxy-5-nitro-2-phenylpyrimidine (XIV)	200	7.38
4-dimethylamino-6-methoxy-5-nitropyrimidine (XXXVI)	314, 212	14.9, 15.1
4-dimethylamino-6-(1-methylhydrazino)-5-nitropyrimidine	309, 207	14.2, 25.2
2,4-di-(1-methylhydrazino)-6-methyl-5-nitropyrimidine (XXXXI)	255, 223	11.9, 18.5
4,6-di-(1-methylhydrazino)-2-methyl-5-nitropyrimidine	367, 263, 237.5	5.40, 11.3, 12.8
4,6-di-(1-methylhydrazino)-5-nitro-2-phenylpyrimidine	244	15.9
4,6-di(1-methylhydrazino)-5-nitropyrimidine (V)	311, 207	7.38, 15.5
4,6-di-(2-phenylhydrazino)-5-nitro-2-phenylpyrimidine	273, 229	2.71, 4.20
4,6-di-(2-phenylhydrazino)-5-nitropyrimidine	329, 241	4.91, 8.63
4-hydrazino-6-hydroxy-2-methylpyrimidine (2 Me-K)	261, 210	6.81, 29.3

Continued on next page

Table II Continued

Name of Compound	max (mμ)*	E X 10^3
4-hydrazino-6-hydroxy-2-phenylpyrimidine (2 Ph-K)	287.5, 239, 206	8.08, 16.4, 34.0
4-hydrazino-6-hydroxy-pyrimidine (2H-K & XXI)	258, 212	5.04, 21.4
4-hydrazino-6-methoxy-5-nitropyrimidine (XXXV)	323, 284, 223	3.93, 2.37, 13.4
6-hydroxy-4-(1-methylhydrazino) pyrimidine (XXV)	262, 218	6.38, 22.8
4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine	311, 228	8.51, 8.26
4-methylamino-6-(1-methylhydrazino)-5-nitropyrimidine	352, 301, 241	10.3, 6.47, 27.4
N-methylpyridinium pyrimidinate salt (XXXII)	322, 266sh, 258, 215	4.10, 4.48, 6.42, 31.1
5-nitro-2, 4, 6-trimethoxy-pyrimidine (XXXXII)	284, 246, 218	2.28, 1.82, 8.04

* Solvent for all compounds was aqueous HCl (pH 1.0)

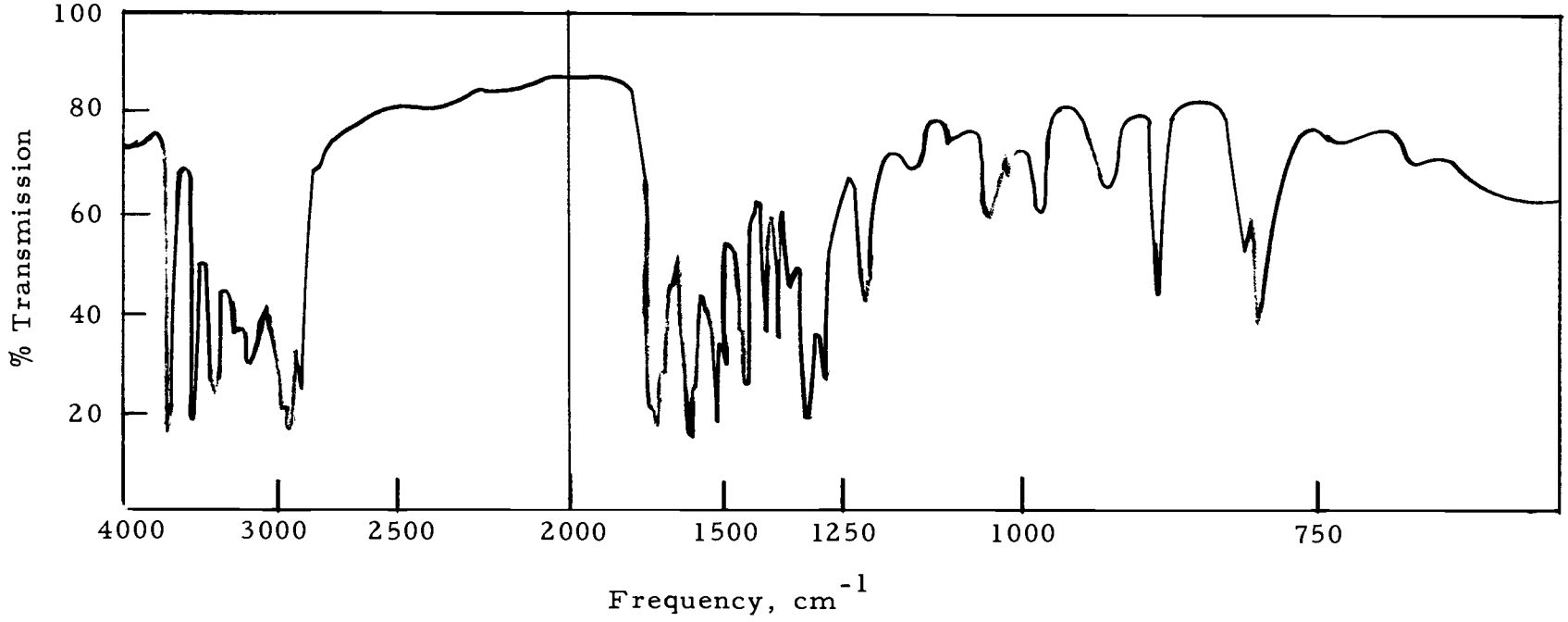

Figure 17. Infrared spectrum of 4-amino-6-(1-methylhydrazino)-5-nitropyrimidine.

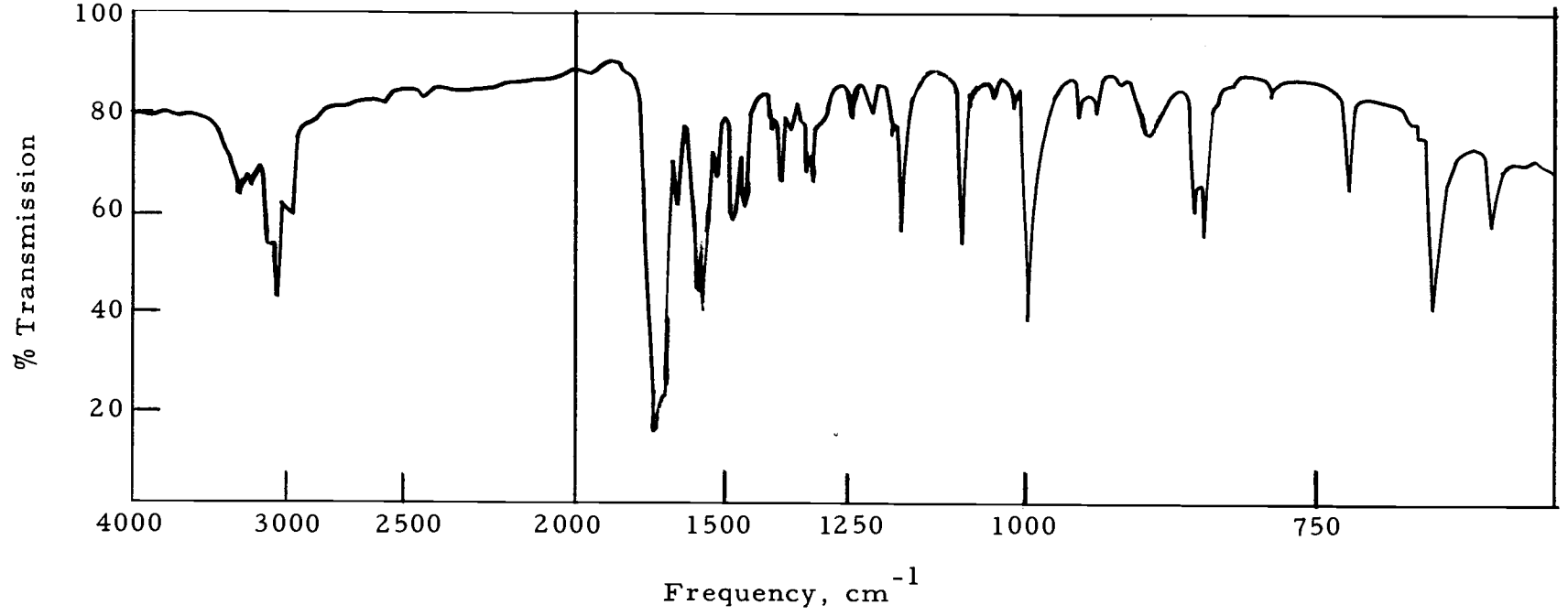

Figure 18. Infrared spectrum of 4-chloro-6-hydroxy-2-phenylpyrimidine.

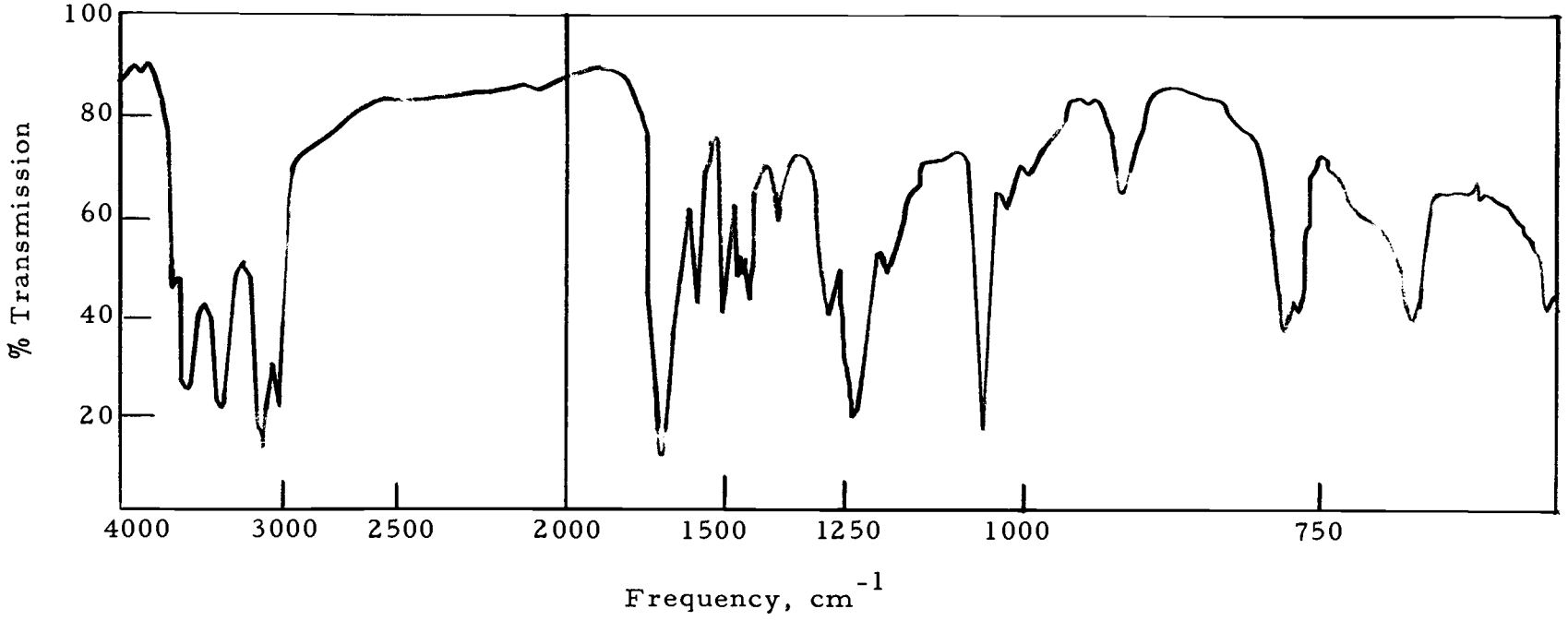

Figure 19. Infrared spectrum of 4,6-diamino-5-pyrimidyl hydrogen sulfate.

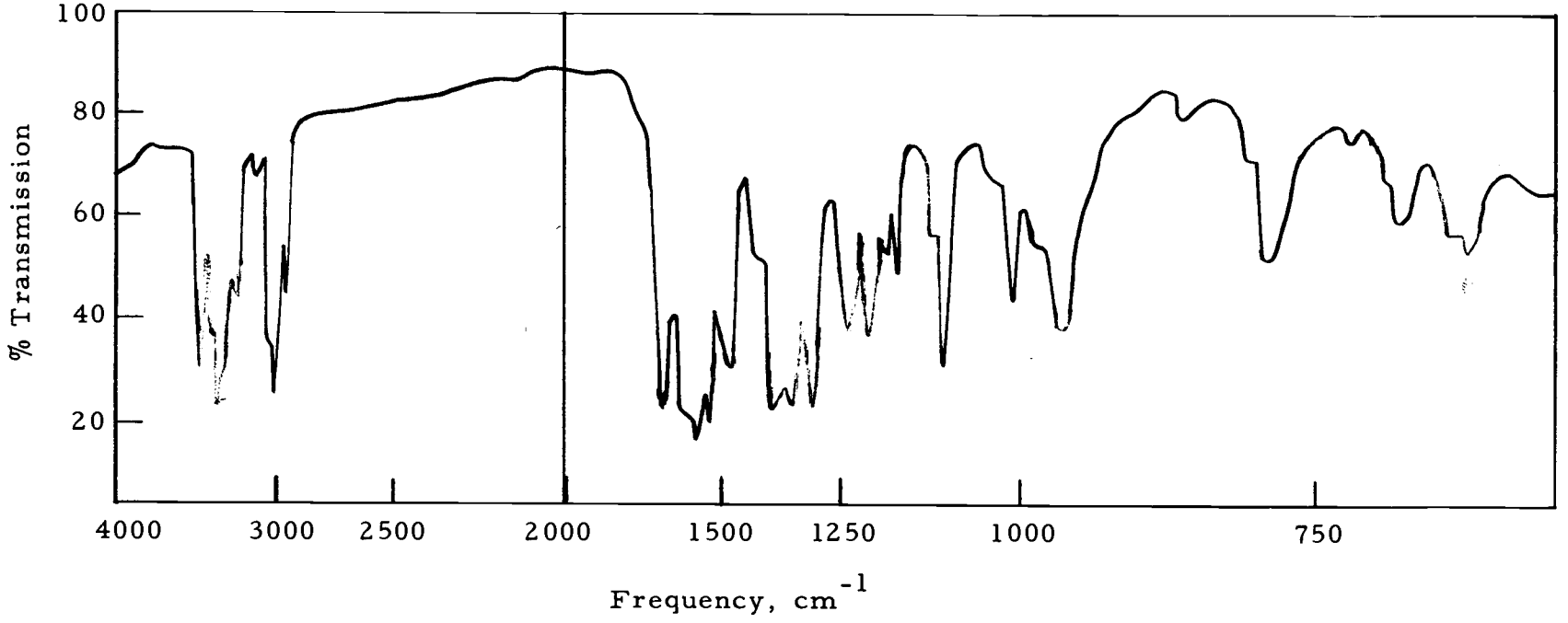

Figure 20. Infrared spectrum of dihydrazino-methoxy-5-nitropyrimidine.

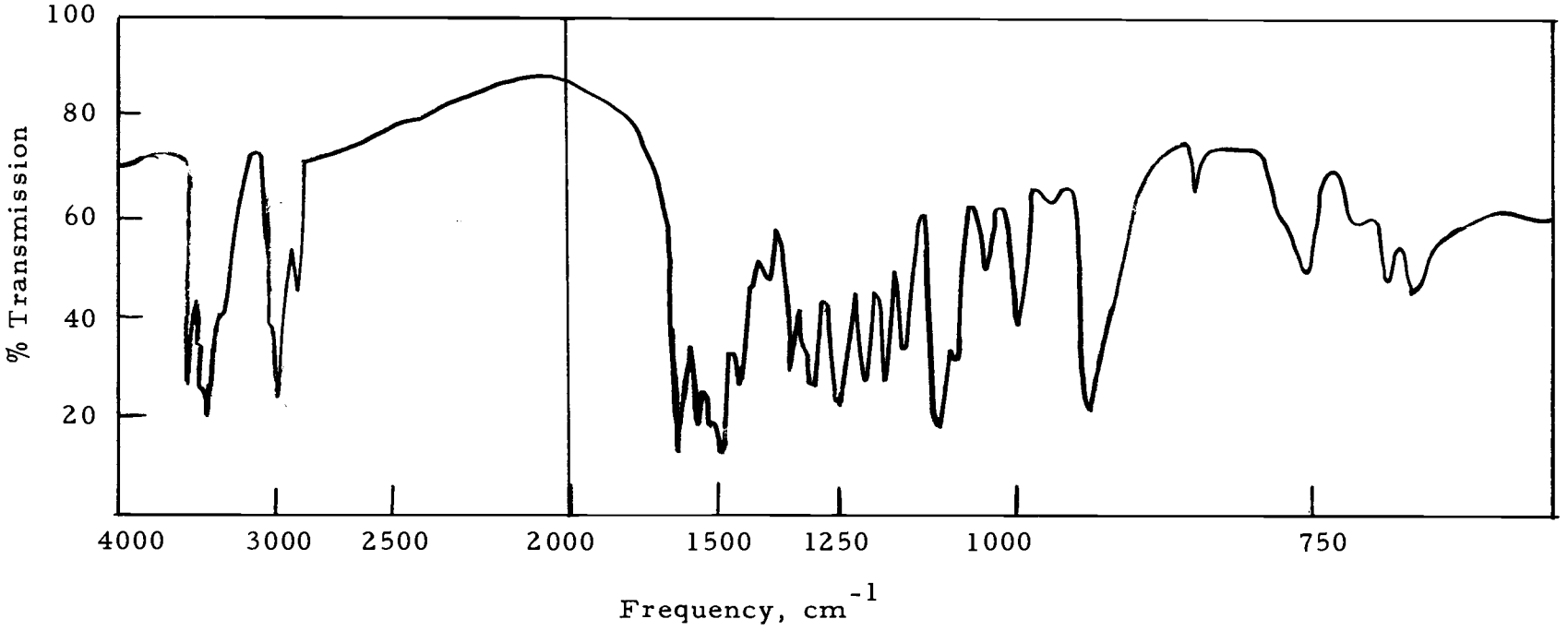

Figure 21. Infrared spectrum of 4, 6-dihydrazino-2-methyl-5-nitropyrimidine.

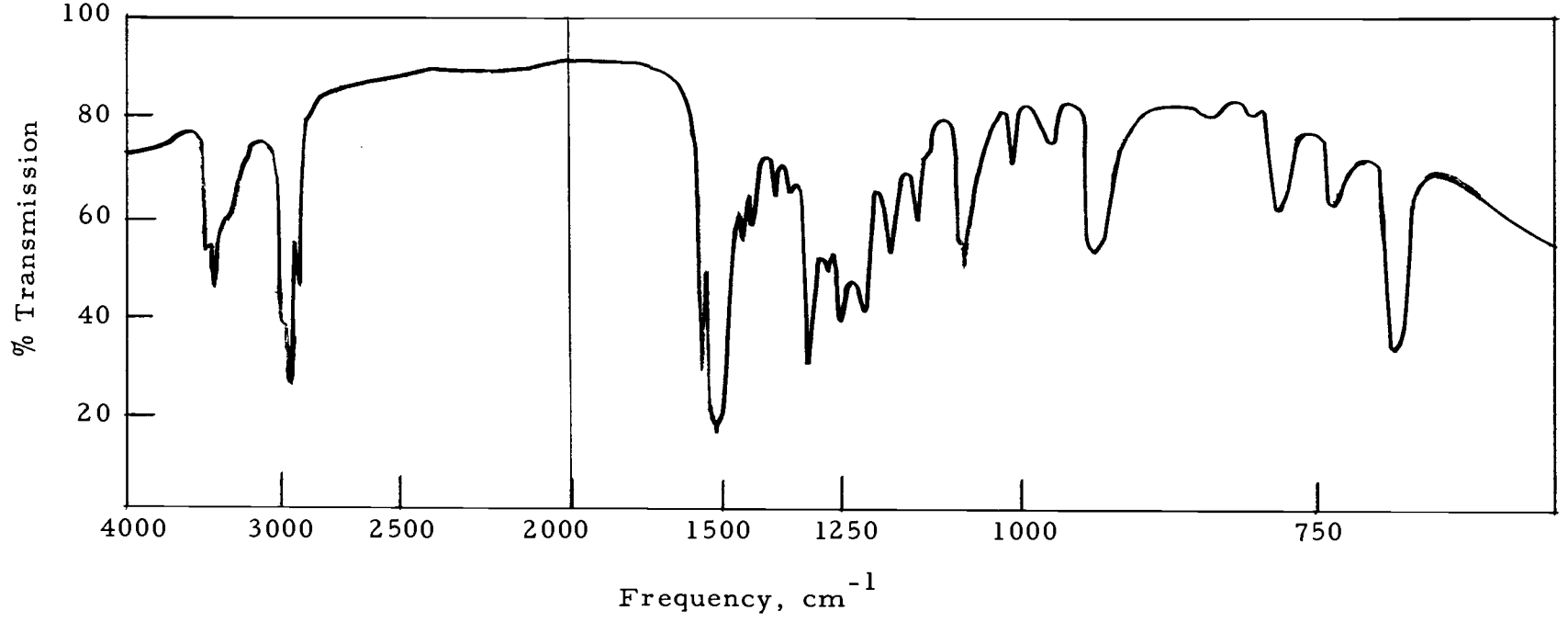

Figure 22. Infrared spectrum of 4,6-dihydrazino-5-nitro-2-phenylpyrimidine.

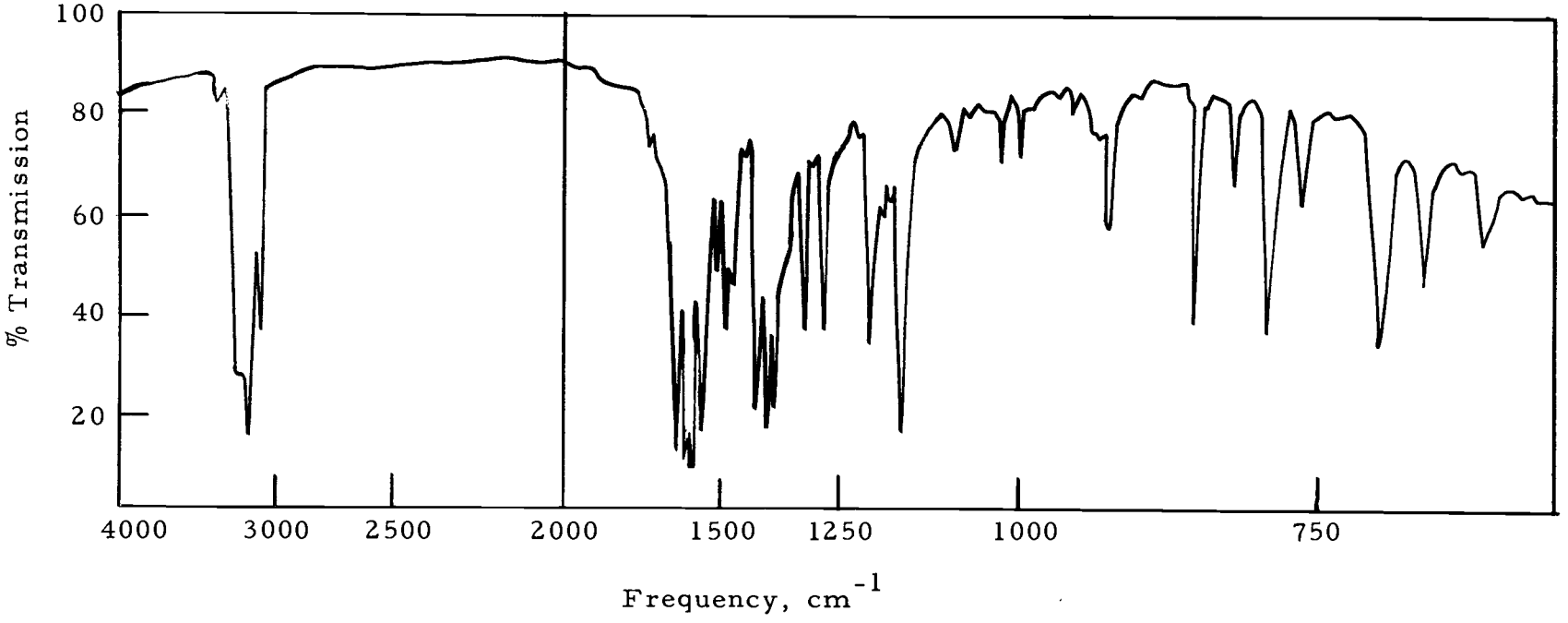

Figure 23. Infrared spectrum of 4, 6-dimethoxy-5-nitro-2-phenylpyrimidine.

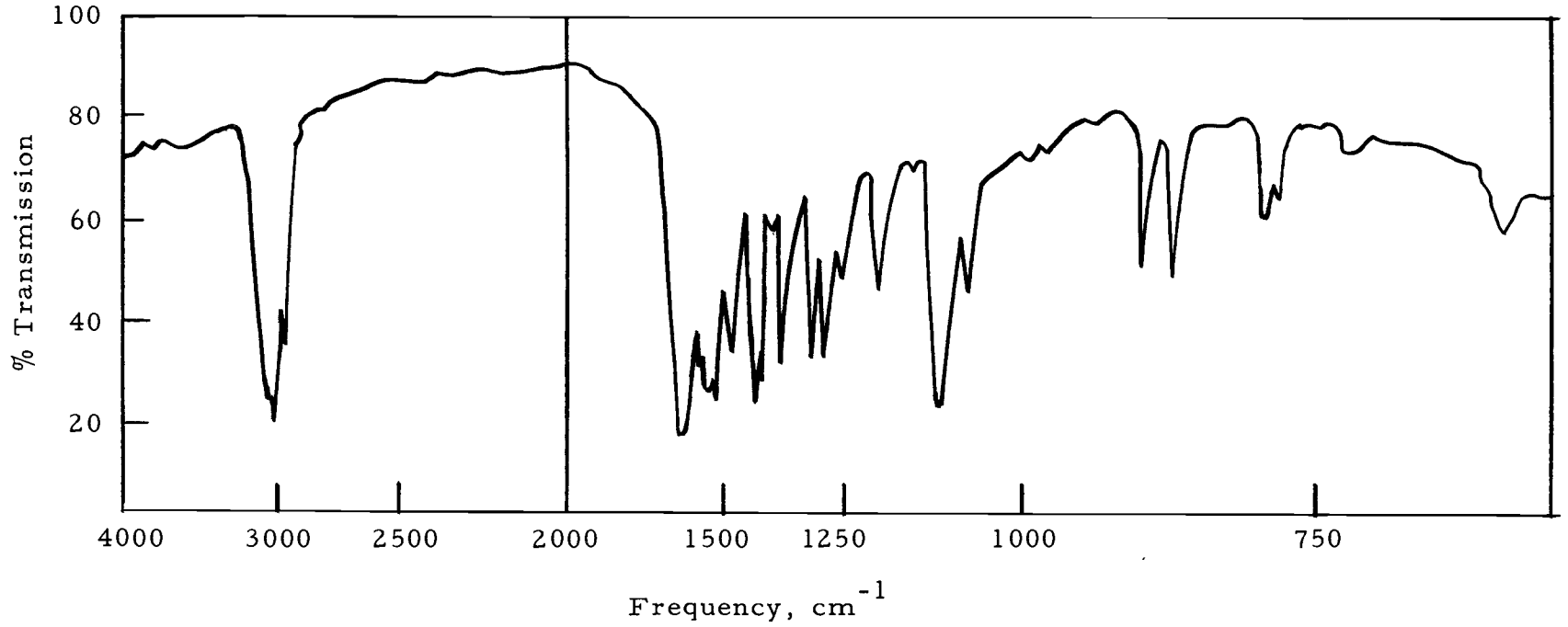

Figure 24. Infrared spectrum of 4-dimethylamino-6-methoxy-5-nitropyrimidine.

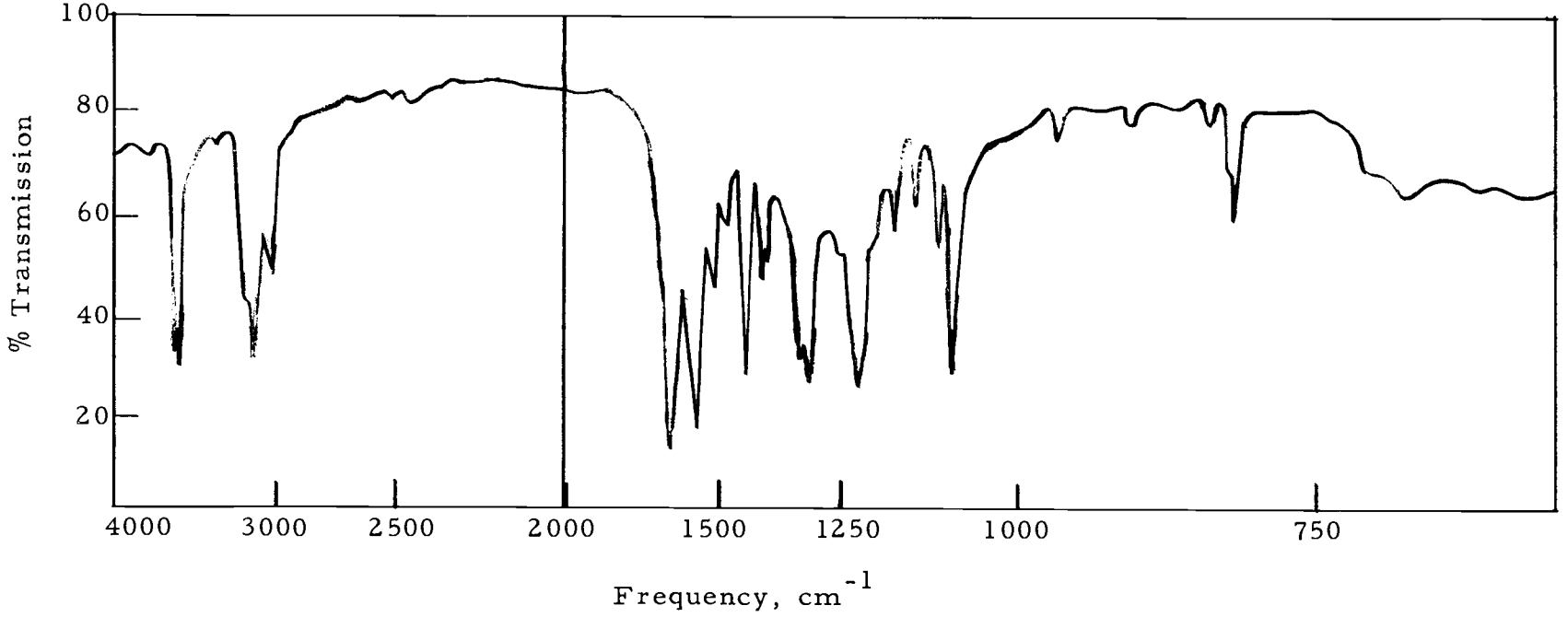

Figure 25. Infrared spectrum of 4-dimethylamino-6-(1-methylhydrazino)-5-nitropyrimidine.

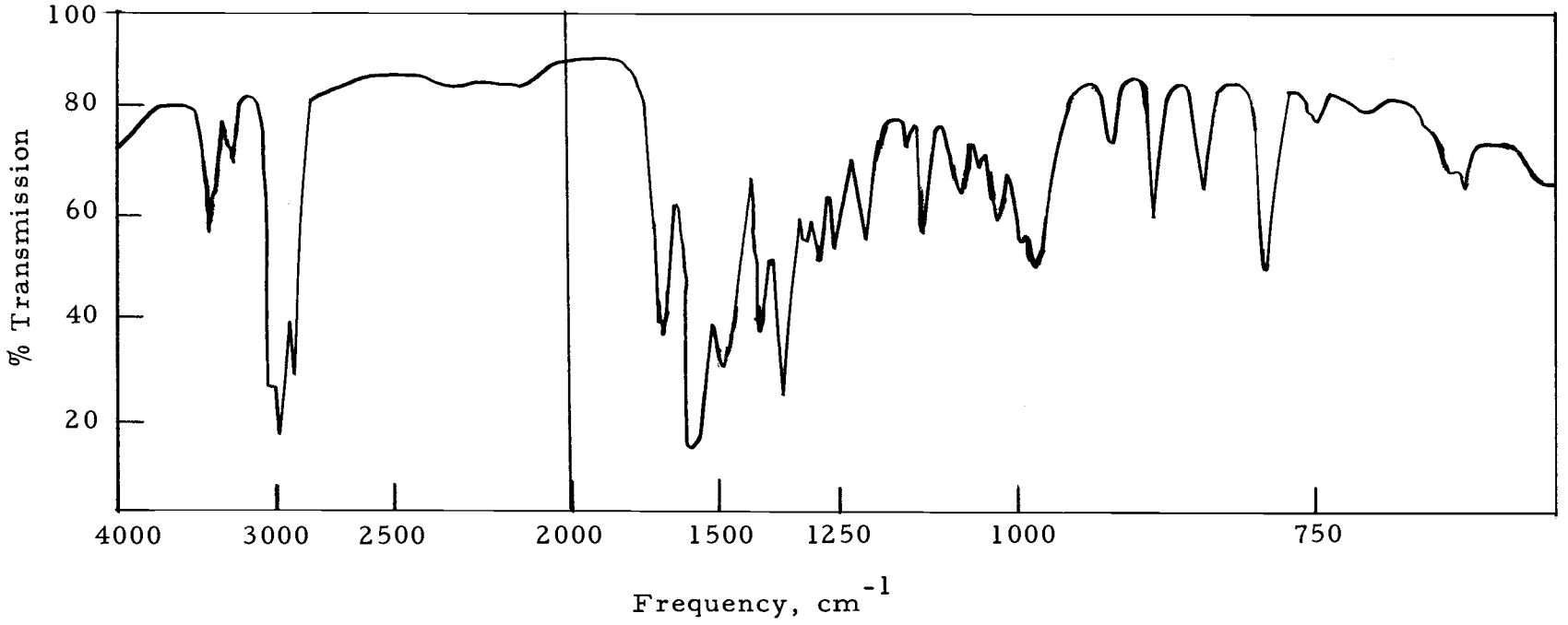

Figure 26. Infrared spectrum of 2,4-di-(1-methylhydrazino)-6-methyl-5-nitropyrimidine.

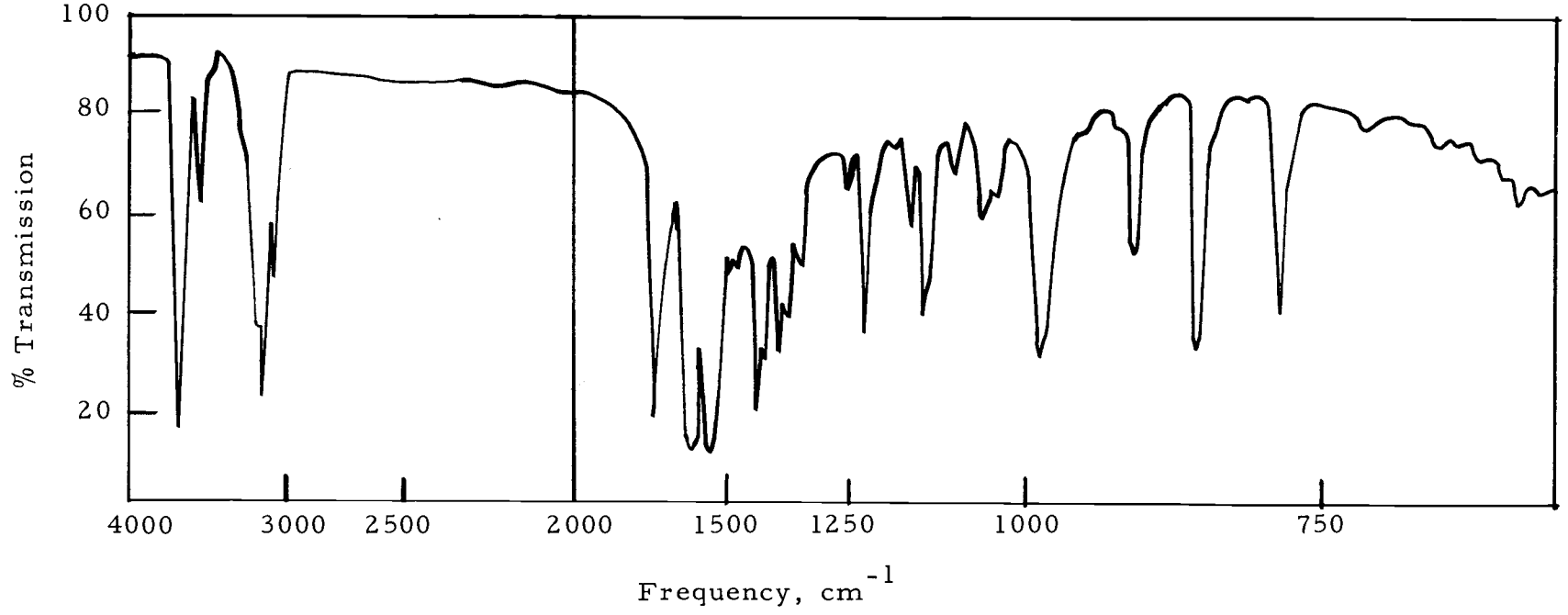

Figure 27. Infrared spectrum of 4,6-di-(1-methylhydrazino)-2-methyl-5-nitropyrimidine.

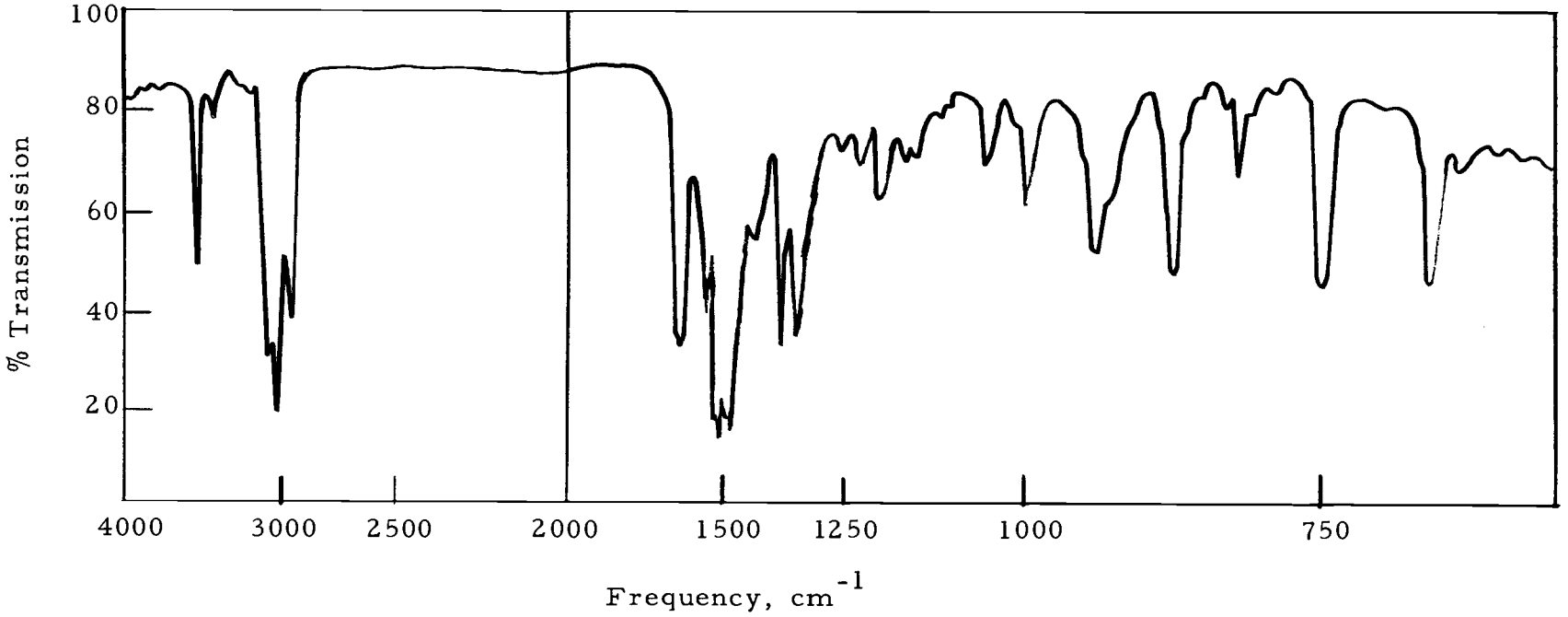

Figure 28. Infrared spectrum of 4,6-di-(1-methylhydrazino)-5-nitro-2-phenylpyrimidine.

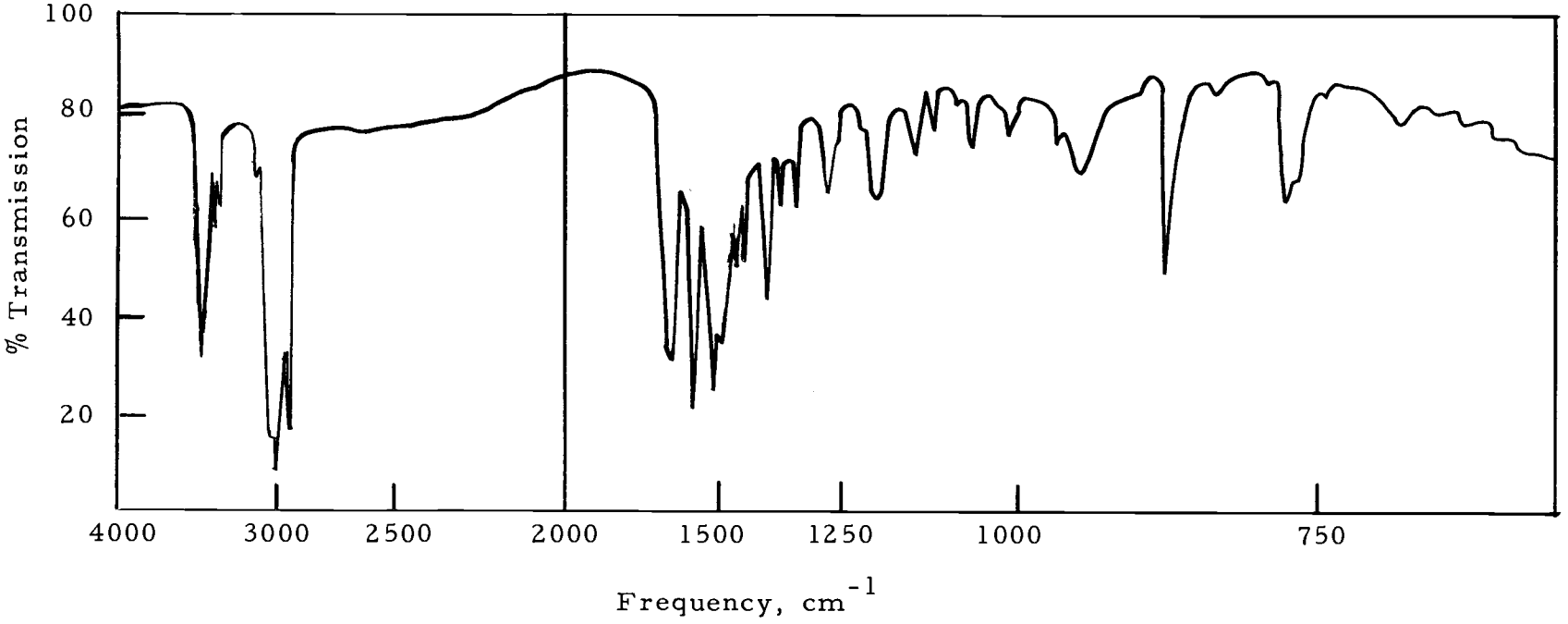

Figure 29. Infrared spectrum of 4,6-di-(1-methylhydrazino)-5-nitropyrimidine.

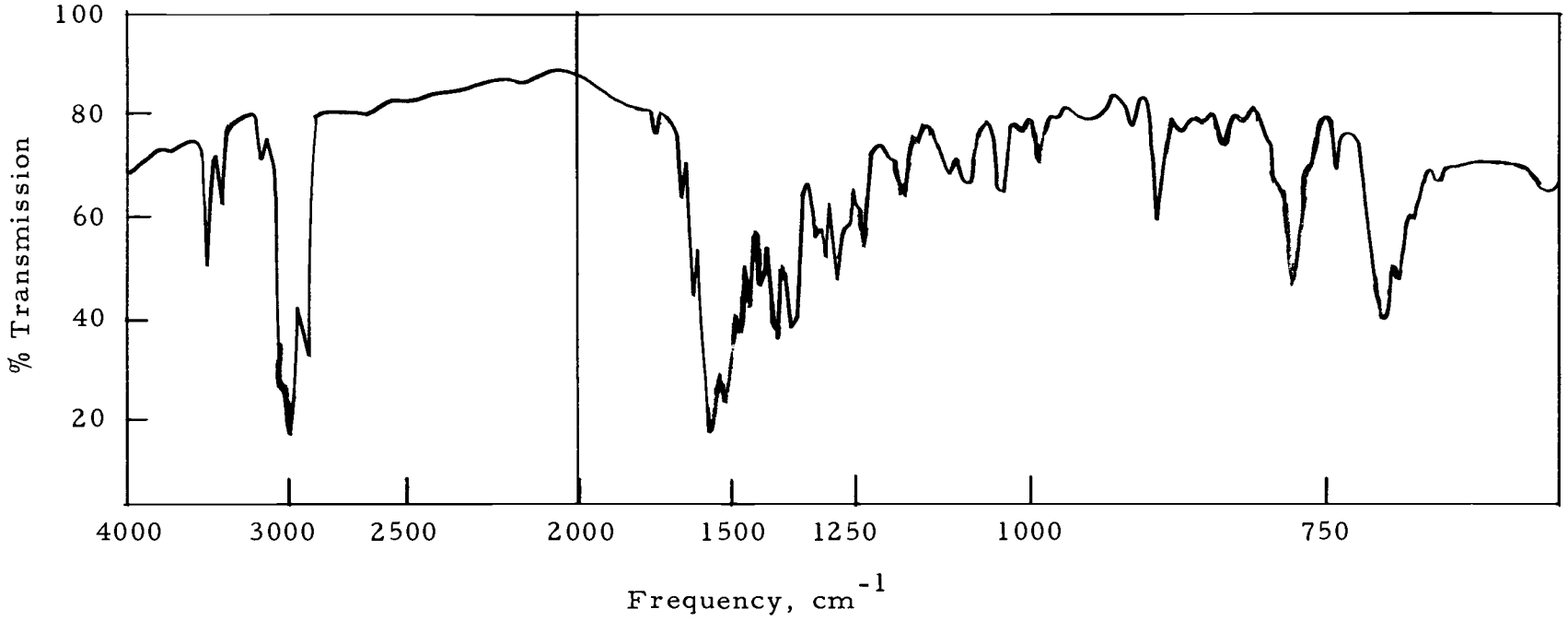

Figure 30. Infrared spectrum of 4,6-di-(2-phenylhydrazino)-5-nitro-2-phenylpyrimidine.

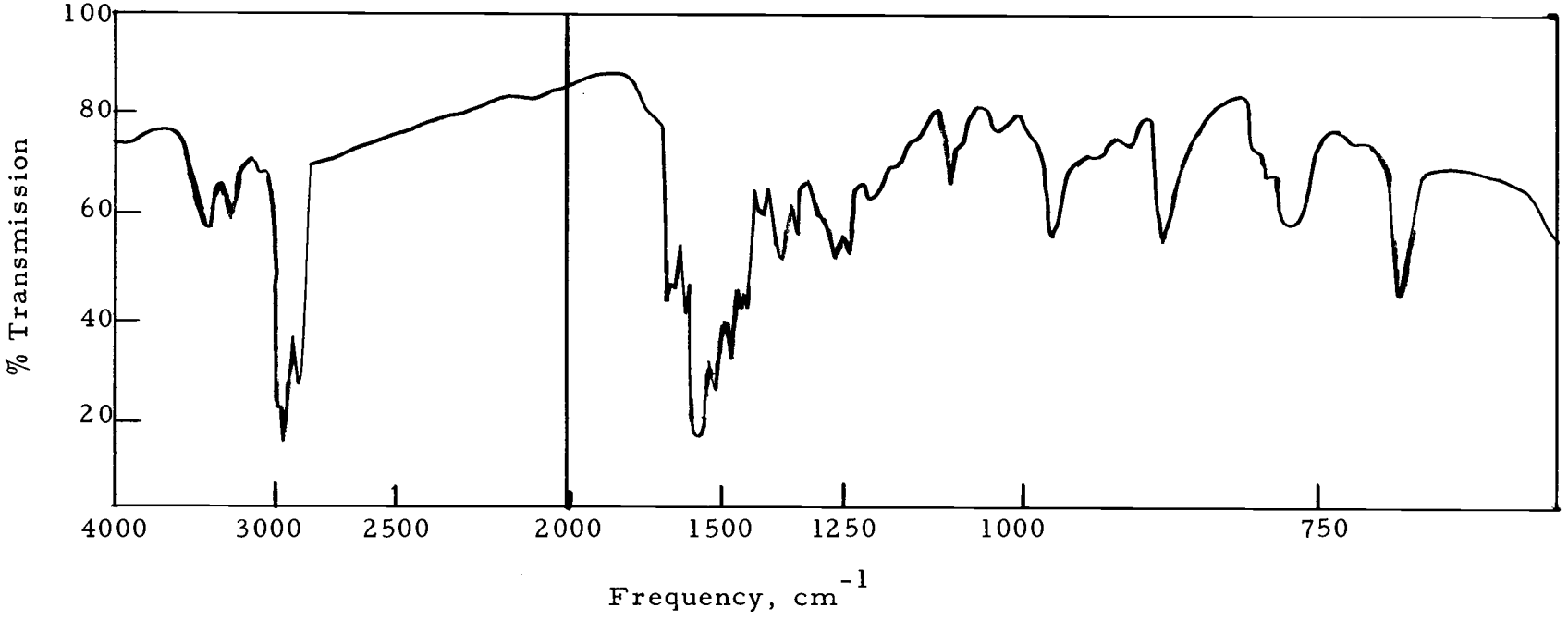

Figure 31. Infrared spectrum of 4,6-di-(2-phenylhydrazino)-5-nitropyrimidine.

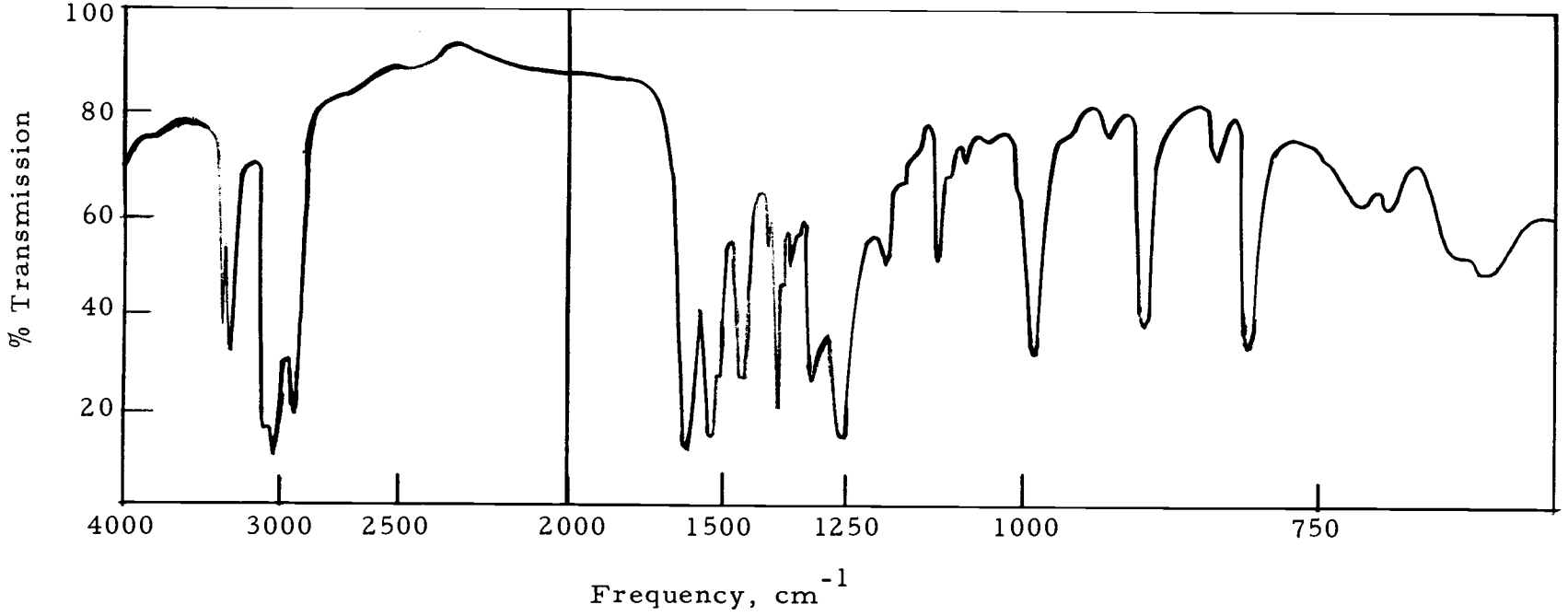

Figure 32. Infrared spectrum of 4-hydrazino-6-methoxy-5-nitropyrimidine.

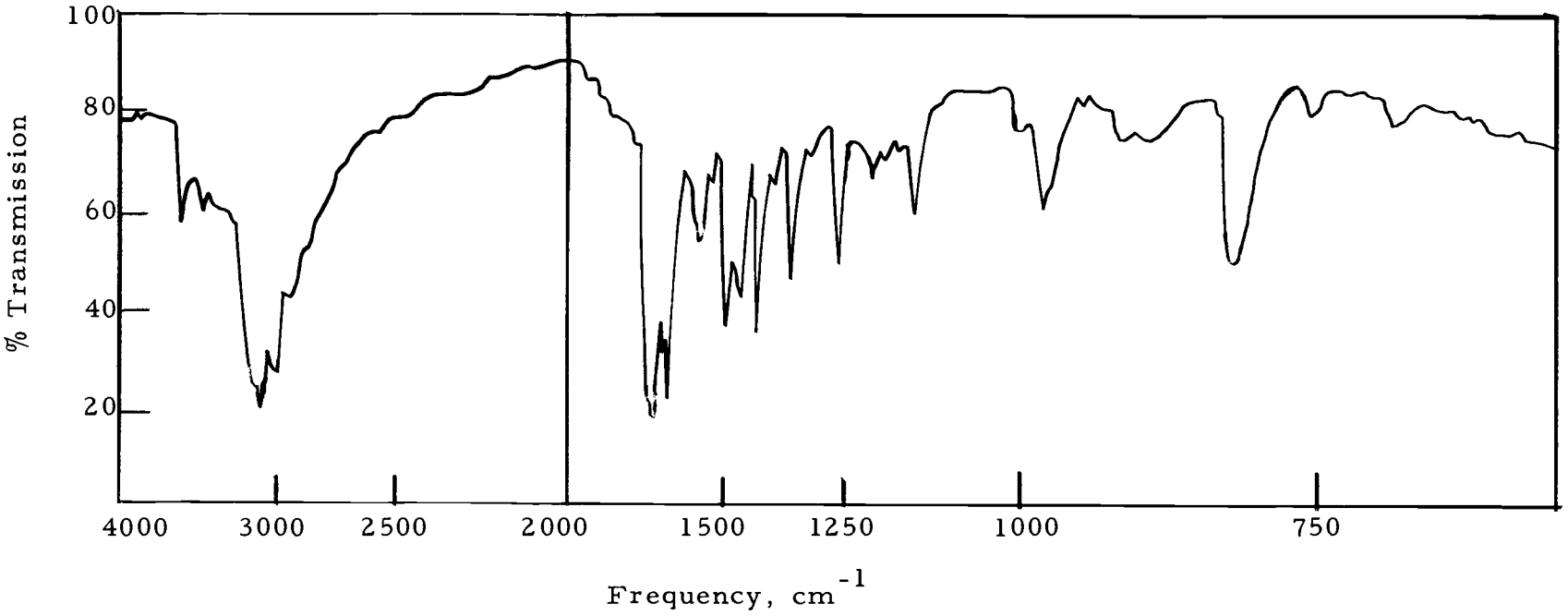

Figure 33. Infrared spectrum of 4-hydroxy-6-(1-methylhydrazino) pyrimidine.

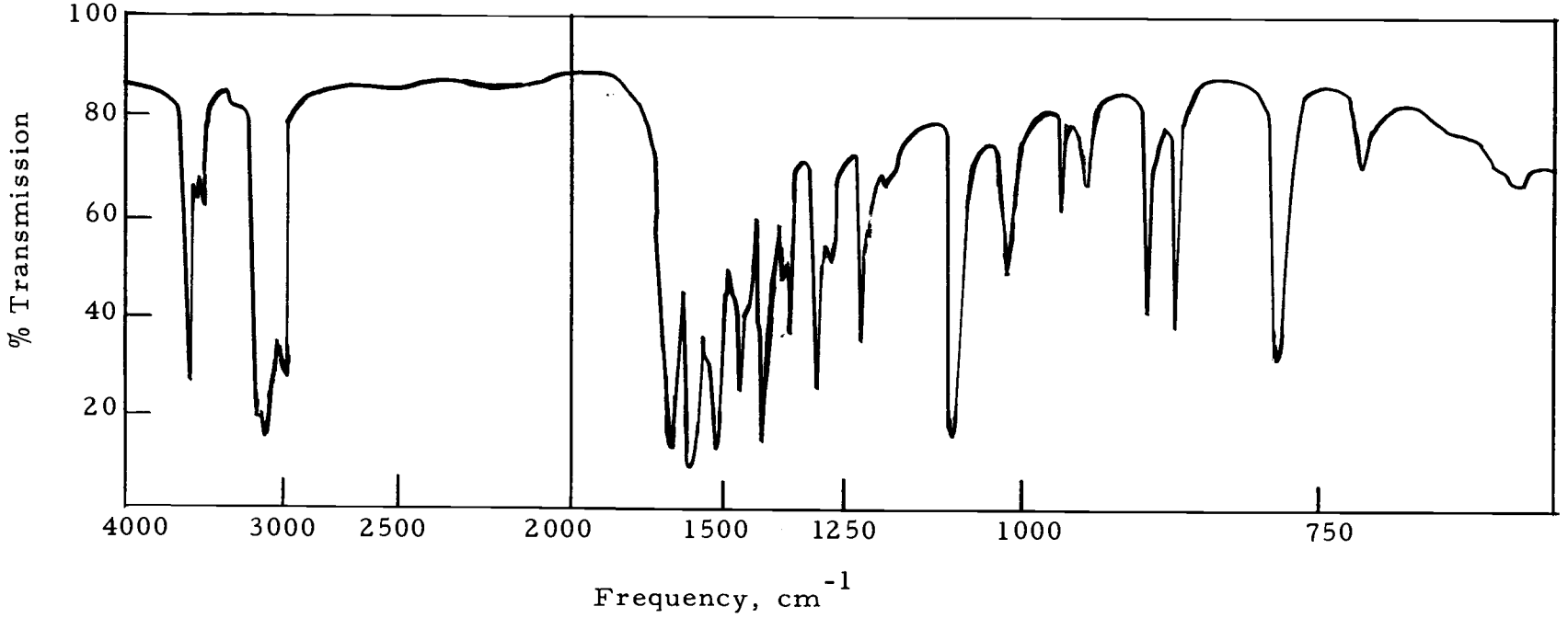

Figure 34. Infrared spectrum of 4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine.

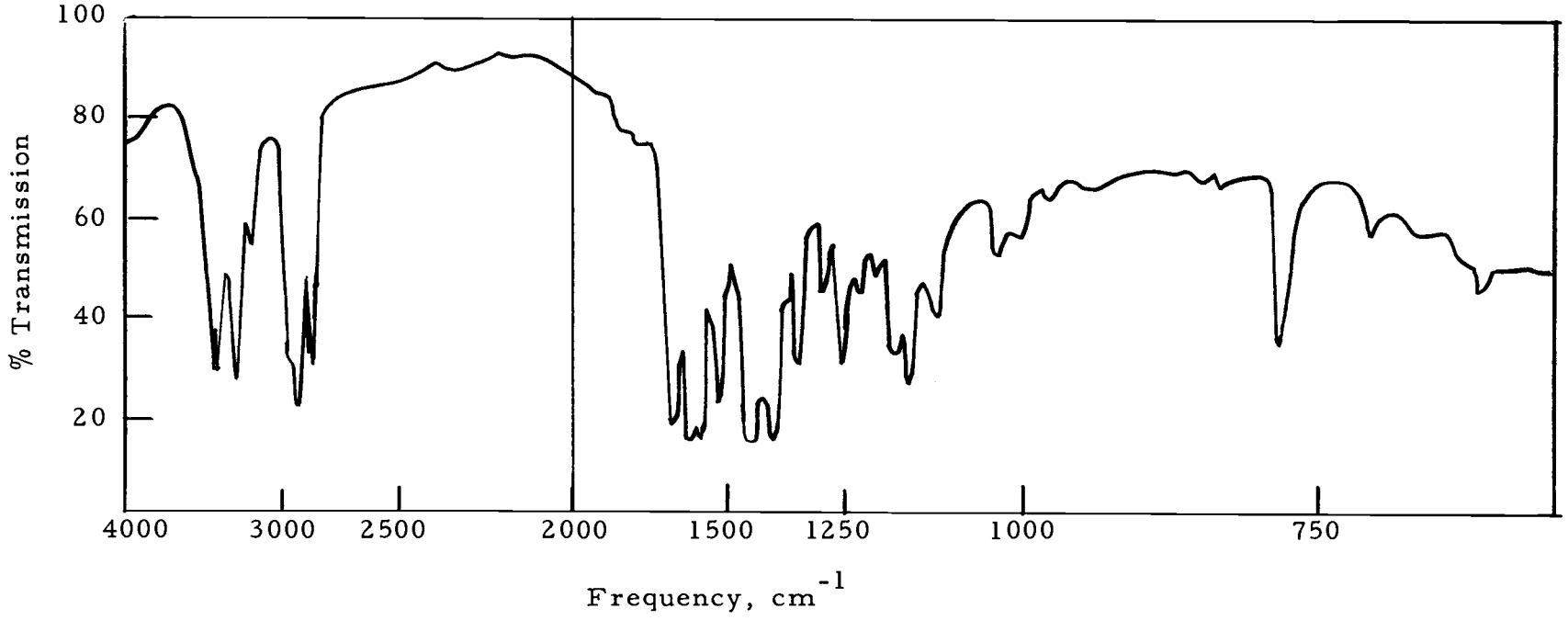

Figure 35. Infrared spectrum of 4-methylamino-6-(1-methylhydrazino)-5-nitropyrimidine.

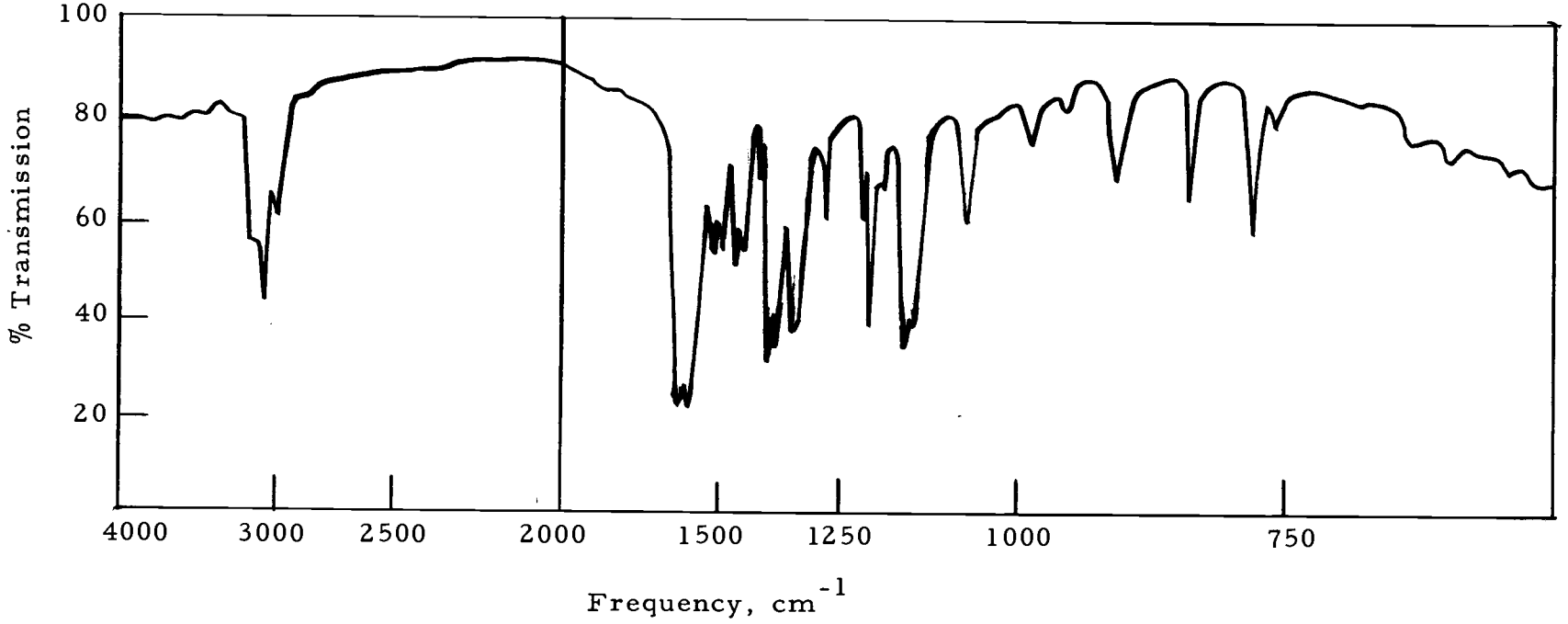

Figure 36. Infrared spectrum of 5-nitro-2,4,6-trimethoxypyrimidine.