AN ABSTRACT OF THE THESIS OF

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in CHEMISTRY (Organic) (Major) presented on June 9, 1970 (Date)

Title: A STUDY OF CERTAIN REACTIONS OF 4-CHLORO-6-METHYLHYDRAZINO-5-NITROPYRIMIDINE AND THE 4-METHOXY AND 6-DIMETHYLAMINO ANALOGS

Abstract approved: Redacted for privacy

Dr. Bert E. Christensen

The reaction between 4-chloro-6-methoxy-5-nitropyrimidine and methylamine was investigated. The reaction product was identified as 4-methoxy-6-methylamino-5-nitropyrimidine from synthesis of the product via 4-chloro-6-methylamino-5-nitropyrimidine. The product was the result of displacement of chloro substituent with methylamine. The reaction occured under mild condition (e.g. 15-20° C. in dioxane). Reaction of 4-chloro-6-methoxy-5-nitropyrimidine with methylhydrazine does yield product as a result of direct nucleophilic substitution.

When the 4-methoxy-6-methylamino-5-nitropyrimidine was refluxed with methylhydrazine in absolute methanol to yield a product, carbon-hydrogen-nitrogen analysis of this substance indicated that the compound was 4-methylamino-6-(1-methylhydrazino)-5-nitropyrimidine.

During the course of a study involving the preparation of certain derivatives, 4-dimethylamino-6-methoxy-5-nitropyrimidine or 4-methylhydrazino analog was refluxed with methylhydrazine in pyridine there was no evidence of nucleophilic substitution of methoxy group; approximately 40% of starting material was recovered. The reason that 4-dimethylamino-6-methoxy-5-nitropyrimidine does not respond to direct nucleophilic substitution with methylhydrazine apparently stems from steric hindrance imposed by the methylhydrazine substituent. 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.

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

A Study of Certain Reactions of 4-Chloro-6-methylhydrazino-5-nitropyrimidine and the 4-Methoxy and 6-Dimethylamino Analogs

by

Amnard Tantivanich

A THESIS

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APPROVED:

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Typed by Carolyn Irving for Amnard Tantivanich

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I would also like to thank Mr. F. A. Lehmkuhl for obtaining the analytical data and encouragement during some of the most difficult times.

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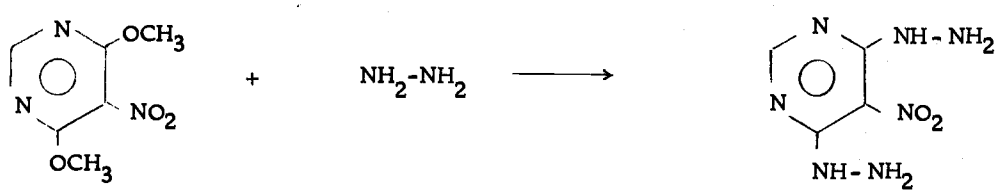
A STUDY OF CERTAIN REACTIONS OF 4-CHLORO-6-METHYLHYDRAZINO-5-NITROPYRIMIDINE AND THE 4-METHOXY AND 6-DIMETHYLAMINO ANALOGS

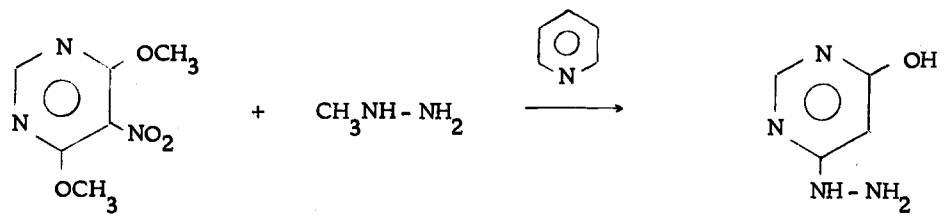
INTRODUCTION AND DISCUSSION

In 1963 Krackov and Christensen (12) were investigating the reactions of 4,6-dichloro-5-nitropyrimidine with various amines. The reactions of this compound with hydrazine gave a partially polymerized product in addition to low yields of 4,6-dihydrazino-5-nitropyrimidine. The reaction of 4,6-dimethoxy-5-nitropyrimidine, on the other hand with hydrazine was far less vigorous and led to formation of the desired product in excellent yields.

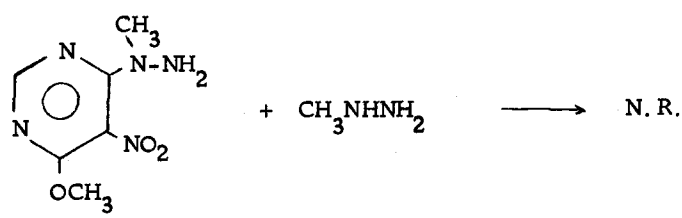


When this study was extended to reactions with methylhydrazine these investigators discovered that the reaction instead of being straightforward was very complex leading to a product in which the nitro substituent appeared to be absent.

Stahl and Christensen (18) investigated this unknown reaction product and found that the nitro substituent had indeed been lost in this very complicated reaction in which the final product was eventually identified as 4-hydrazino-6-hydroxypyrimidine.

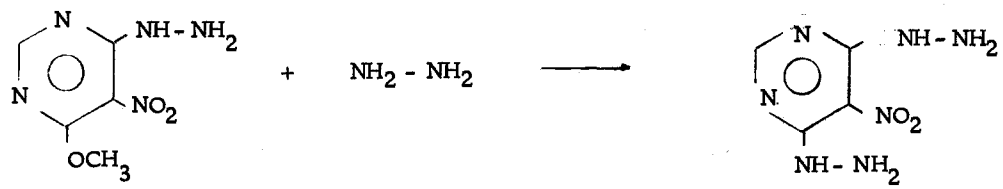


In order to determine whether the reaction of 4, 6-dimethoxy-5-nitropyrimidine (16) had general applicability, other methoxy-nitropyrimidine derivatives were treated with hydrazine. In the course of this investigation it was discovered that neither the yield nor the purity of the product was affected by the addition of anhydrous hydrazine to a hot solution of the 4, 6-dimethoxy-5-nitropyrimidine; it was also extablished that the yield was almost quantitative in most cases. The treatment of 2-substituted-4, 6-dimethoxy-5-nitropyrimidines (the 2-methyl- and 2-phenyl-) with hydrazine gave the same results as found with the 4, 6-dimethoxy-5-nitropyrimidine leading to excellent yields of high purity dihydrazino derivatives. Strangely enough 4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine made from 4-chloro-6-methoxy-5-nitropyrimidine (19) showed no observable reactivity when refluxed with methylhydrazine in an ethanolic solution; the starting material was recovered in good yield.



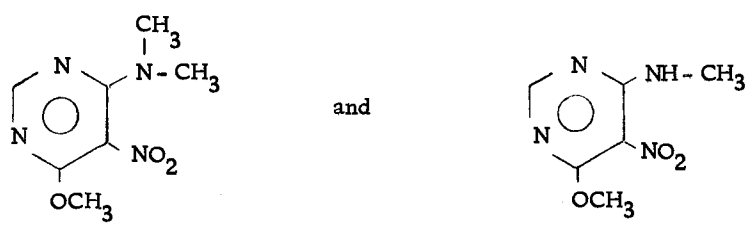
This lack of reactivity suggested that the methyl group of the 1-methylhydrazino substituent must be responsible, inasmuch as the 4-hydrazino-6-methoxy-5-nitropyrimidine would be expected to be an intermediate product in the conversion of the 4, 6-dimethoxy-5-nitropyrimidine to the 4, 6-dihydrazino-derivative. This hypothesis was

confirmed by synthesizing the 4-hydrazino-6-methoxy-5-nitropyrimidine (20) and reacting it with hydrazine. The 4, 6-dihydrazino-5-nitropyrimidine was prepared in good yield in a two step operation.



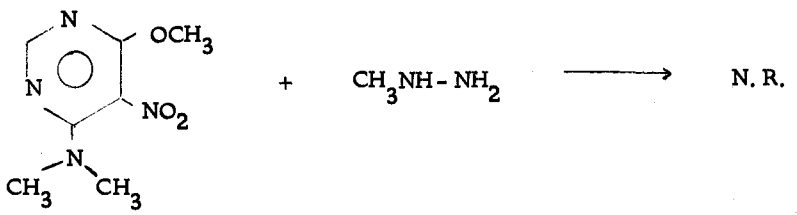
From these results it appeared that the type of substituent adjacent to the nitro group could influence the outcome of the interchange of methoxy substituent with the methylhydrazine. The most logical explanation for this behavior appears to be the steric hindrance offered by the group flanking the nitro substituent.

To confirm this hypothesis, two other derivatives were prepared, one with as large as and one with a smaller group than $-NCH_3-NH_2$ group adjacent to the nitro substituent, e. g. 4-dimethylamino-6-methoxy-5-nitropyrimidine was synthesized inasmuch as the dimethylamino substituent should be comparable in size to the methylhydrazino substituent.

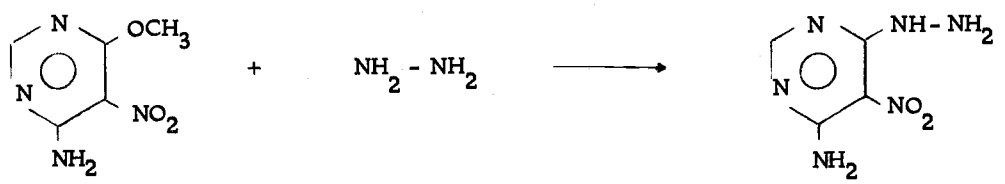


When 4-dimethylamino-6-methoxy-5-nitropyrimidine (15) was refluxed with methylhydrazine for three hours, only unreacted

starting material was recovered together with decomposition products.



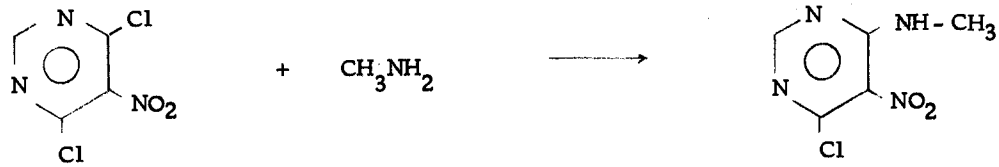
4-Amino-6-methoxypyrimidine (10) on the other hand was also prepared and then treated with hydrazine in refluxing alcohol to yield 4-amino-6-hydrazino-5-nitropyrimidine.



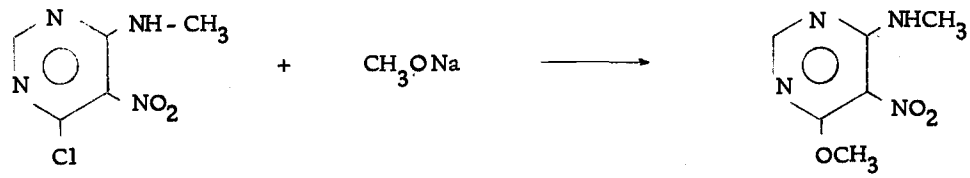
These results indicated that the failure of the 4-dimethylamino-derivative to react was indeed steric.

To further confirm this hypothesis another derivative of 6-methoxy-5-nitropyrimidine, namely 4-methylamino-6-methoxy-5-nitropyrimidine was prepared. 4-Methylamino-5-nitropyrimidine was prepared in two different ways from 4, 6-dichloro-5-nitropyrimidine (5, 6). This starting material was converted to 4-chloro-6-methylamino-5-nitropyrimidine by treatment with methylamine in dioxane at 15-20° C. The 4-chloro 6-methylamino-5-nitropyrimidine was then treated with sodium methoxide in methanol to yield the desired product. The sequence of reactions was then reversed

to give the identical product.

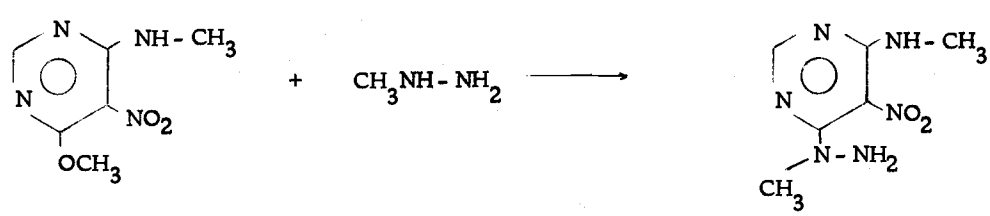


and

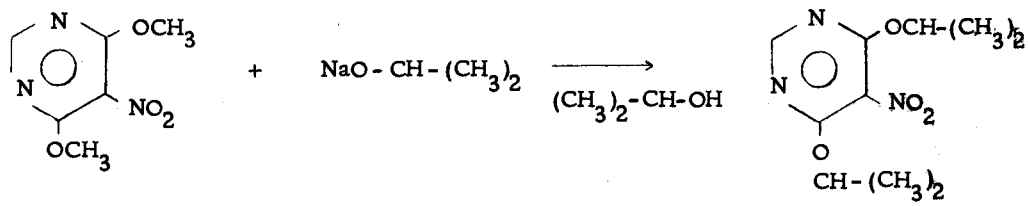


4-Methoxy-6-methylamino-5-nitropyrimidine was treated with hydrazine in an effort to determine the validity of the original hypothesis that steric factors were responsible for the failure of certain of these reactions to take place.

The 4-methoxy-6-methylamino-5-nitropyrimidine was treated with methylhydrazine at room temperature in a methanolic media yielding 4-methylamino-6-(1-methylhydrazino)-5-nitropyrimidine. Thus the presence of methylamino substituent in 4 or 6 position allows the reaction of methylhydrazine to proceed in contrast to either dimethylamino or methylhydrazino.



When 4, 6-dimethoxy-5-nitropyrimidine was allowed to react with isopropyl alcohol in the presence of sodium isopropoxide one obtains the 4, 6-diisopropoxy-5-nitropyrimidine as the product (16).



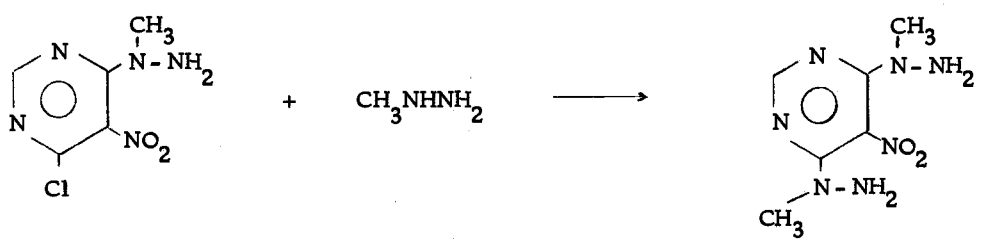
For this reaction to occur the intermediate product 4-isopropoxy-6-methoxy-5-nitropyrimidine must have been formed in the course of the reaction. If such is the case we have an example in which a large bulky group (isopropoxy) flanking the nitro group did not prevent the other substituent (methoxy) flanking the nitro substituent from reacting.

In an attempt to prepare 4-isopropoxy-6-methoxy-5-nitropyrimidine, 4, 6-dichloro-5-nitropyrimidine was prepared and reacted with equimolar amounts of sodium methoxide. The 4-chloro-6-methoxy-5-nitropyrimidine was isolated without much difficulty. This derivative was then reacted with sodium isopropoxide in (a) isopropyl alcohol, (b) heptane and (c) t-butyl alcoholic solvent in a one to one molar ratio. In no case were we able to isolate the desired product.

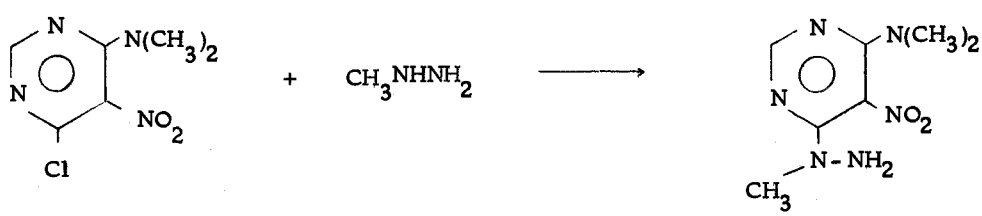
Inasmuch as the 4-methoxy substituent of 6-dimethylamino and 6-(1-methylhydrazino)-5-nitropyrimidine was unreactive in

nucleophilic substitution reactions with hydrazine or methylhydrazine the reactions of the 4-chloro-analog of these compounds were investigated.

Stahl prepared 4, 6-di(1-methylhydrazino)-5-nitropyrimidine from 4, 6-dichloro-5-nitropyrimidine. In the course of this reaction the intermediate 4-chloro-6-(1-methylhydrazino-5-nitropyrimidine) must have been formed. In this instance we have again a large bulky group flanking the 5-nitro substituent which did not prevent the nucleophilic substitution of the second methylhydrazine substituent in the other flanking position.



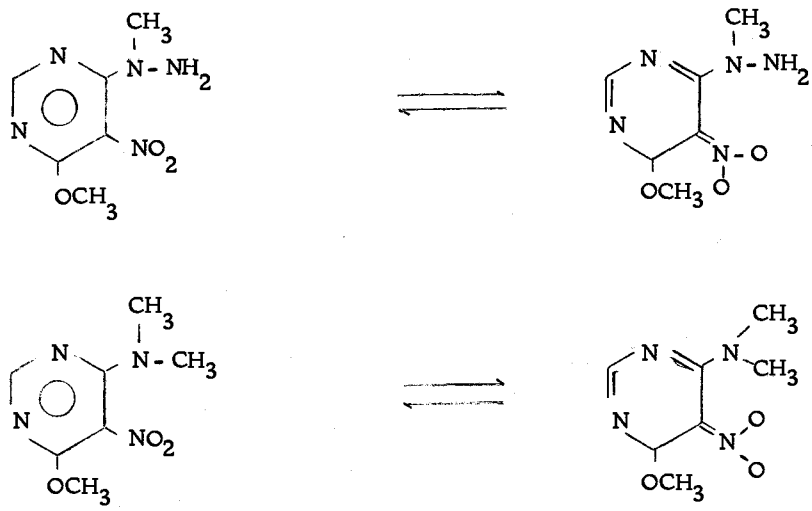
Moreover 4-dimethylamino-6-(1-methylhydrazino-5-nitropyrimidine can be prepared by the reaction of methylhydrazine with 4-chloro-6-dimethylamino-5-nitropyrimidine.



These reactions indicate that the failure of 4-methylhydrazino-6-methoxy-5-nitropyrimidine and its 4-dimethylamino-analog to undergo further nucleophilic substitutions with large nucleophilic

reagents may stem from other reasons than steric hindrance. Methoxy substituents on pyrimidine ring do not readily undergo nucleophilic substitution unless activated by another substituent such as a nitro group.

The most reasonable explanation for this behavior is still that of steric hindrance. In order for the nitro substituent to activate the methoxy group it must accept electrons via a resonance effect; e. g.,



Sterically it may not be possible for the nitro substituent to become planar with the ring and in so doing exert its activating influence on the adjacent methoxyl group.

The chloro substituents on quinazoline (8) and pyrimidine ring systems (3) are sufficiently reactive as to require no additional activation in nucleophilic substitution reactions.

Thus the 4-chloro analogs of 4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine and 6-dimethylamino-5-nitropyrimidine are

reactive under the same conditions and are not influenced by the steric hindrance of the 6-position substituents.

EXPERIMENTAL

All melting points are uncorrected and were taken on a Fish-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 approximately 1460 and 1375 cm^{-1}. 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 (9, 13). The homogeneity analysed substances was checked by thin-layer chromatography.

4, 6-Dihydroxypyrimidine

Malondiamide 10.2 g was added to alcoholic sodium ethoxide (4.6 g of sodium in 150 ml of alcohol), followed by ethyl formate 11.0 g, and the mixture heated under reflux for two hours. Next morning the solid was collected, washed with alcohol, and dissolved in 50 ml water. The solution was acidified with glacial acetic acid, and the solid 4.5 g collected. Crystallization from water gave the product as microprisms, which on being dried became yellow, m. p. > 300°C. (11).

4, 6-Dihydroxy-5-nitropyrimidine

4, 6-Dihydroxypyrimidine 1 mole was added, with stirring, at 15-20°C to a mixture of 93% nitric acid and glacial acetic acid (3: 6 moles). Stirring was continued for a further half hour and the mixture then poured on ice. After filtration, washing with water, and drying, the product (90% yield) was pure enough for further use. The nitro compound crystallized from water in colorless leaflets, m. p. > 300°C.

4, 6-Dichloro-5-nitropyrimidine

Diethylaniline 93 g was added to a suspension of 4, 6-dihydroxy-5-nitropyrimidine 78. 5 g in phosphorus oxychloride 505 g and heated in an oil-bath at 125-130°C for one hour. After removal of the excess of phosphorus oxychloride under reduced pressure, the reaction mixture was poured on ice 800 g and filtered. The filtrate was extracted with ether (3 x 350 ml), each extract being also used to extract the filter cake. The combined extracts were washed with water (5 00 ml) and dried (Na_2SO_4) and the ether was removed. The residual dichloro-compound crystallized from light petroleum (b. p. 80-100°), m. p. 101-102°C (4, 14).

4-Chloro-6-methoxy-5-nitropyrimidine

Alcoholic sodium methoxide (1.2 g of sodium in 50 ml of cool absolute methanol) was added with stirring, at 0°C to alcoholic dichloro compound 10 g of 4, 6-dichloro-5-nitropyrimidine (4) in 50 ml of methanol. Stirring was continued for a further half hour and then the mixture was poured into an equal volume of water, and the solid collected and washed with water. Recrystallization from water gave pale yellow crystals, m.p. 64-65°C.

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

A. Into 140 ml of an absolute ethanolic solution containing 9.48 g (0.05 mole) of 4-chloro-6-methoxy-5-nitropyrimidine was pipetted, with stirring, 6.4 ml (0.13 mole) of methylhydrazine. After refluxing for two hours, the pale yellow solution was cooled, whereupon needle-like crystals appeared. These were filtered, washed with a little ethanol, and recrystallized from approximately 500 ml of boiling water. After two to three hours of refrigeration, 7.2 g (83%) of well formed, yellow crystals were collected and air dried, m.p. 200-201°C.

B. A solution containing 0.9 g (0.005 mole) of 4-chloro-6-methoxy-5-nitropyrimidine in 40 ml of absolute methanol was cooled below 0°C. Then 0.46 ml (0.01 mole) of methylhydrazine was

pipetted into the solution, producing a yellow color. After stirring the solution for one hour at room temperature, the precipitate was collected. The carbon and hydrogen analysis of the samples by methods A and B were identical.

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

Found: C, 36.4; H, 4.3; N, 35.1

4-Methoxy-6-methylamino-5-nitropyrimidine

Aqueous methylamine (25% w/v 26 ml) was brought to pH 8 with acetic acid (15 ml). This solution was added over 20 minutes with stirring to 4:6-dichloro-5-nitropyrimidine (10.5 g) in 40 ml dioxane at 15-20°C. After stirring for two hours, iced water 120 ml was added and after two hours at 0°C, the solid was filtered off, washed with cold water and dried. The precipitate was recrystallized twice from water giving colorless 4-methoxy-6-methylamino-5-nitropyrimidine, m.p. 150-152°C.

4-Dimethylamino-6-methoxy-5-nitropyrimidine

Three grams (0.16 mole) of 4-chloro-6-methoxy-5-nitropyrimidine was dissolved in 12 ml dioxane at 15-20°C. Aqueous dimethylamine 11.25 ml was added slowly, with stirring. The mixture was stirred for four hours, during which time it changed from colorless to yellowish-green color. Iced water (35 ml) was added and after

2-3 hours of refrigeration, the precipitate was filtered off, washed with cold water and dried. Two recrystallizations from ethanol gave white crystals, m.p. 100-101°C.

Anal. Calc'd for $C_7H_{10}N_4O_2$: C, 42.4; H, 5.1; N, 28.2.

Found: C, 42.6; H, 5.03; N, 28,1.

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

A solution of 4-methoxy-6-methylamino-5-nitropyrimidine 1 g (0.005 mole) in 45 ml of methanol was added dropwise, with stirring, to a solution of 0.5 ml (0.01 mole) of methylhydrazine in 5 ml of methanol. The mixture was then refluxed with stirring for three hours, during which time it turned to a bright yellow color. After refluxing, the mixture was cooled and the precipitate collected. Recrystallization from approximately 100 parts of water yield 0.72 g (74%) of yellow-orange crystals, m.p. 210-211°C.

Anal. Calc'd for $C_6H_{10}N_6O_2$: C, 36.4; H, 5.05; N, 42.4.

Found: C, 36.3; H, 5.1; N, 42.0.

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 in 50 ml of absolute methanol. After stirring the solution for four hours at room temperature, the precipitate was

collected; yield, 0.45 g (41%) m.p. 198-200°C.

4-Dimethylamino-6-hydrazino-5-nitropyrimidine

A solution of 0.35 ml (0.01 mole) of 95% anhydrous hydrazine in 5 ml absolute ethanol was added to a rapidly stirred, refluxing solution containing 1.0 g (0.005 mole) or 4-chloro-6-dimethylamino-5-nitropyrimidine (5) in 50 ml of absolute ethanol. Upon precipitation of the pyrimidine the mixture was refluxed for an additional five minutes; yield, 0.88 g of product. Recrystallization from water yield 9.70 g (72%) of yellow-orange, needle-like crystals, m.p. 207-211° C (dec).

Anal. Calc'd for $C_6H_{10}N_6O_2$: C, 36.4; H, 5.6; N, 42.4

Found: C, 36.3; H, 5.8; N, 42.7

The reaction of methylhydrazine with 4-dimethylamino-6-methoxy-5-nitropyrimidine

Methylhydrazine (0.4 g, 0.01 mole) was pipetted into a hot solution of 1.0 g (0.005 mole) of 4-dimethylamino-6-methoxy-5-nitropyrimidine in 50 ml pyridine. The mixture was stirred for three hours under gentle reflux. Toward the end of the reflux period, the solution color turned to a dark red color. Evaporation of the solvent yielded unreacted starting material together with decomposition products.

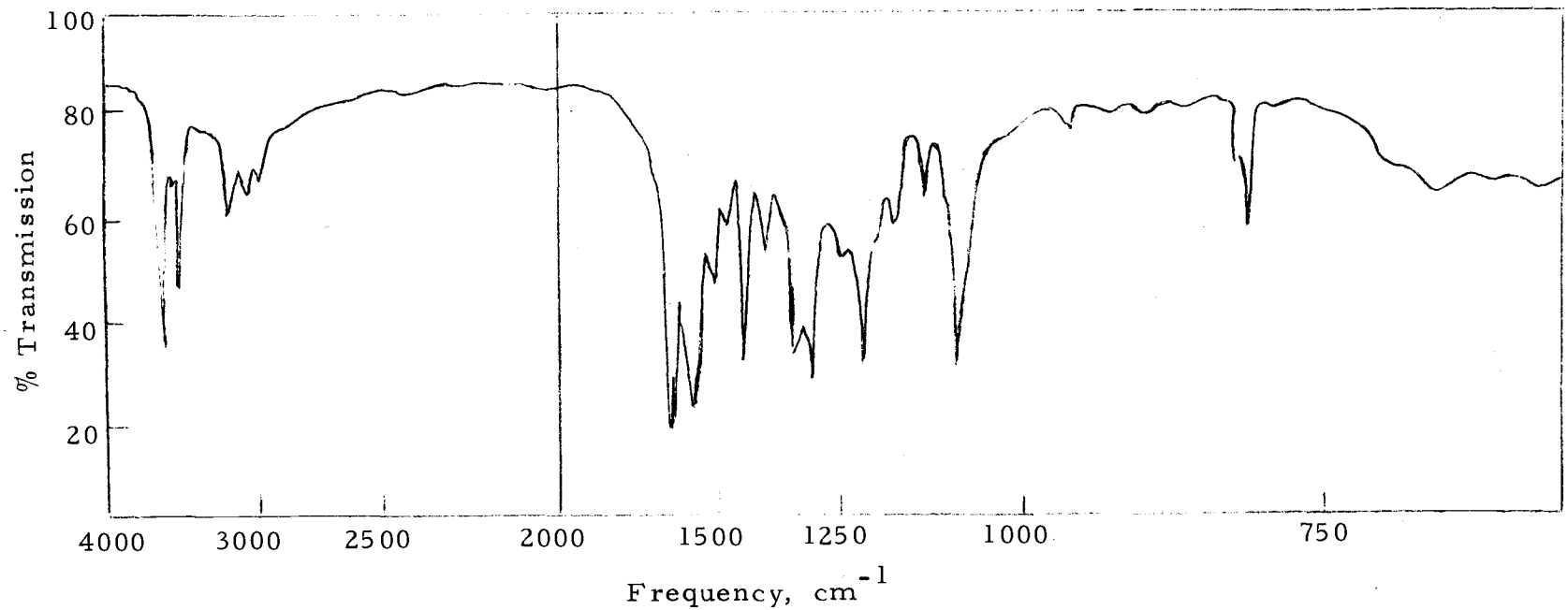


Figure 1. Infrared spectrum of 4-methylamino-6-(1-methylhydrazino)-5-nitropyrimidine

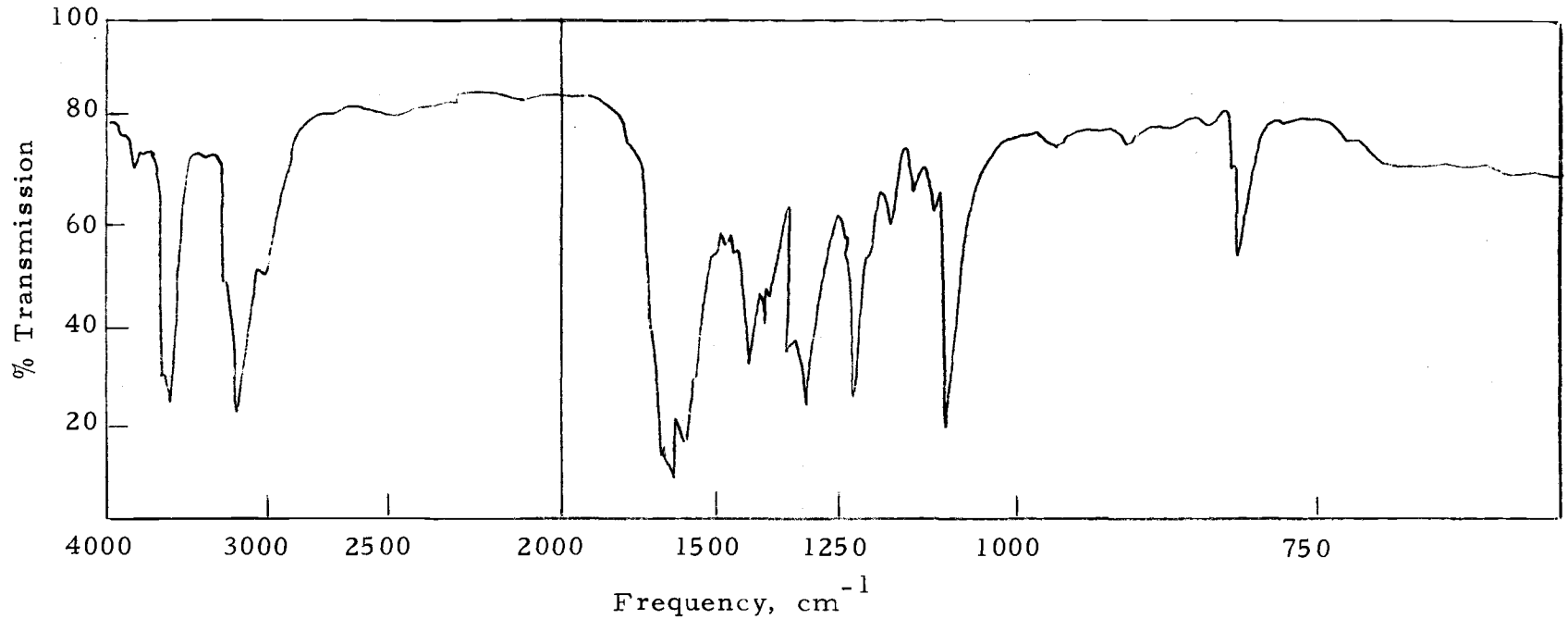


Figure 2. Infrared spectrum of 4-dimethylamino-6-hydrazino-5-nitropyrimidine

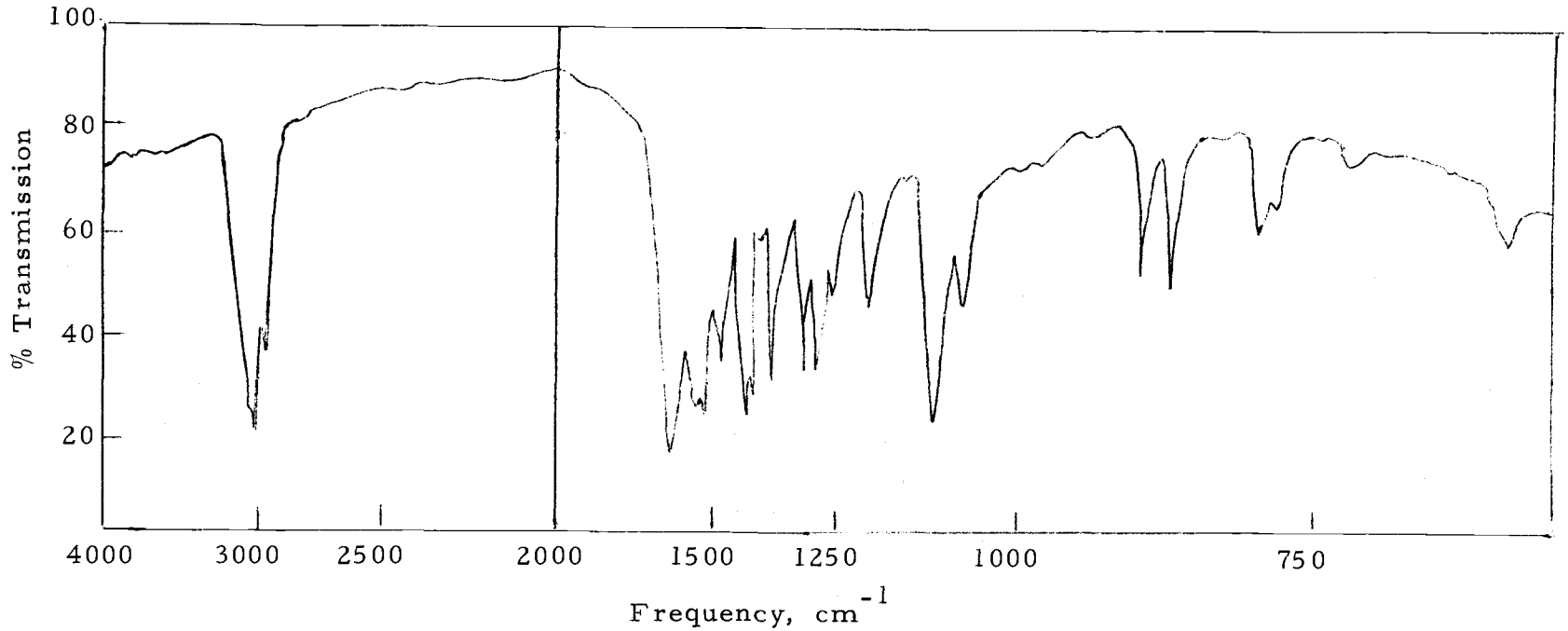


Figure 3. Infrared spectrum of 4-dimethylamino-6-methoxy-5-nitropyrimidine

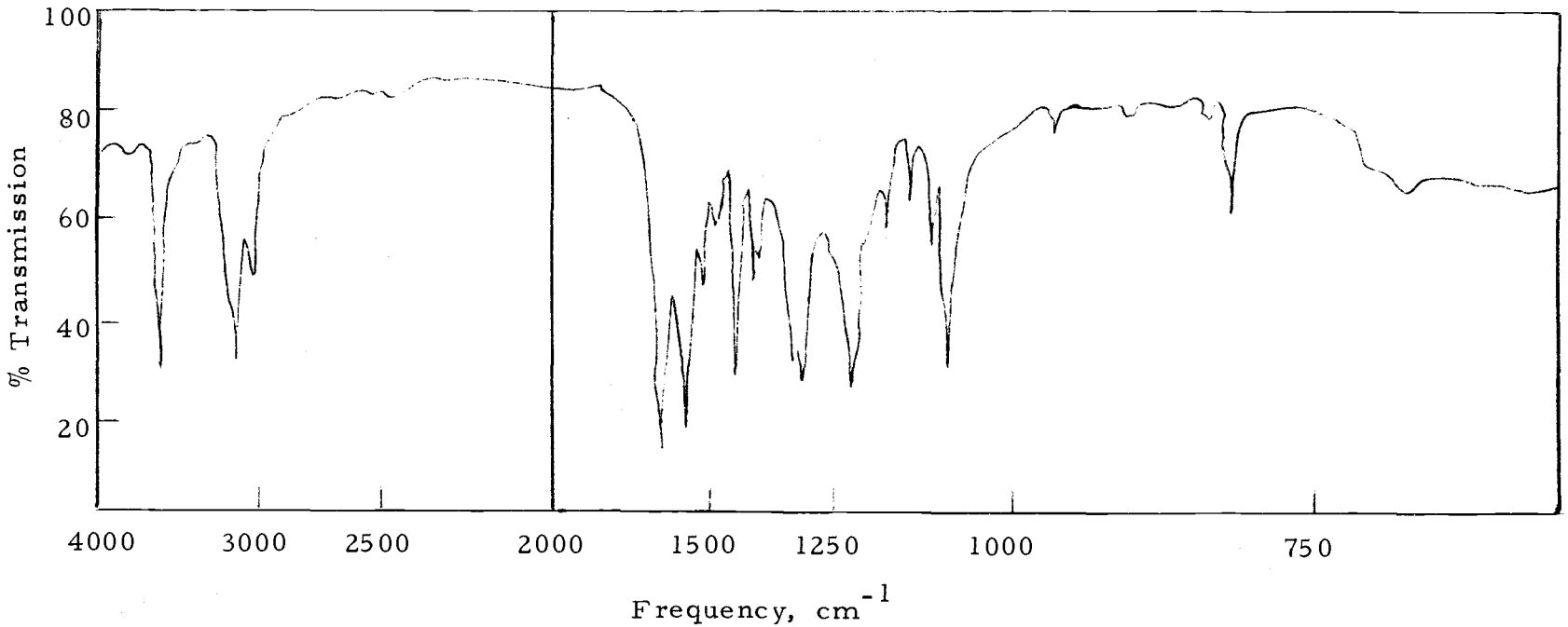


Figure 4. Infrared spectrum of 4-dimethylamino-6-(1-methylhydrazino)-5-nitropyrimidine

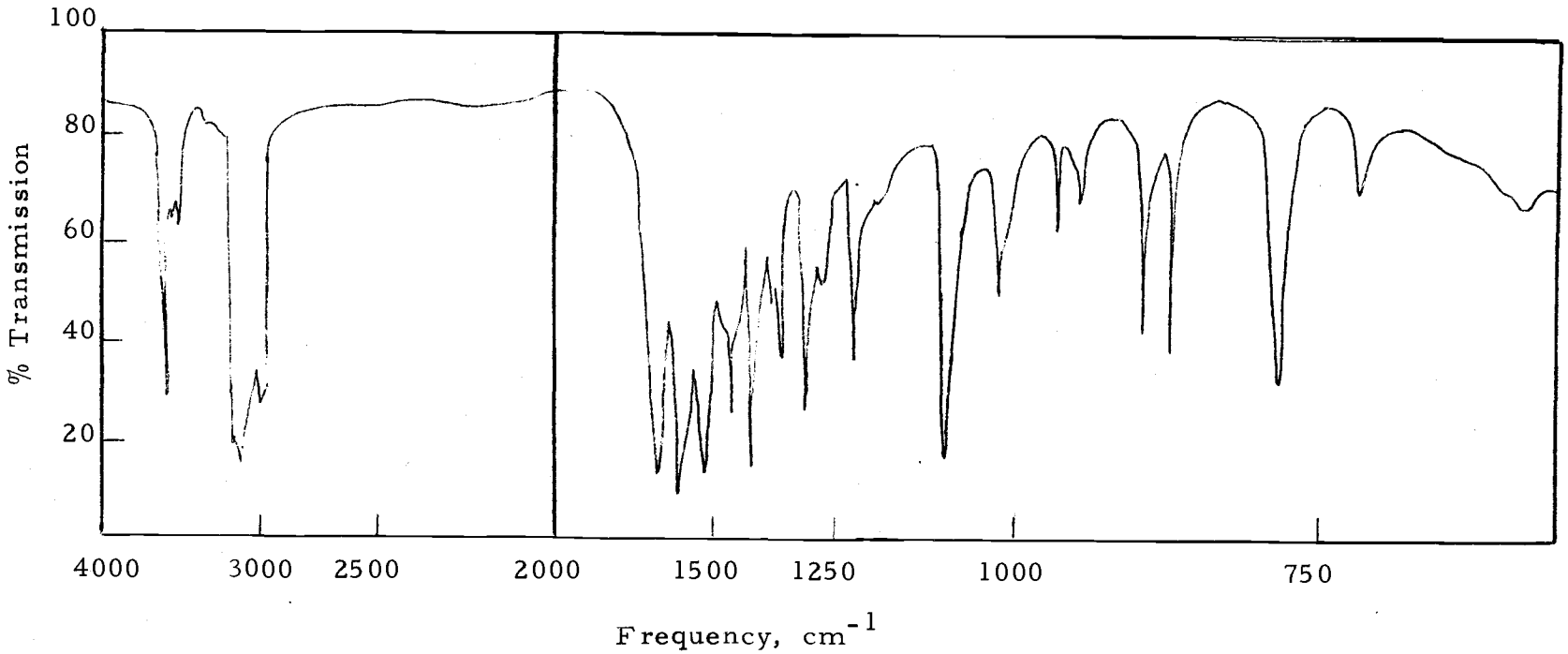


Figure 5. Infrared spectrum of 4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine

Table 1. Summary of Infrared Data*

Name of Compounds	Hydrogen Stretching Vibrations (3000 - 4000 cm^{-1})	Double Bond -N-H Bending Vibrations (1500 - 1700 cm^{-1})
4-dimethylamino-6-hydrazino-5-nitropyrimidine	3356(s) 3054(w)	1667(s) 1623(vs) 1572(s)
4-dimethylamino-6-methoxy-5-nitropyrimidine		1591(vs) 1524(s)
4-dimethylamino-6-(1-methylhydrazino)-5-nitropyrimidine	3378(m) 3356(s) 3075(vs)	1603(s) 1531(s)
4-methoxy-6-(1-methylhydrazino)-5-nitropyrimidine	3355(s) 3320(w) 3278(w)	1658(s) 1642(s) 1587(s) 1529(vs)
4-methylamino-6-(1-methylhydrazino)-5-nitropyrimidine	3465(s) 3340(s) 3065(w)	1642(s) 1595(vs) 1570(s)

s = strong; m = medium; w = weak; v = very

* Names of reference (1), (2), (7), (17).

SUMMARY

In summary, the following conclusion can be made about reactivity of 4(-6) chloro substituted-5-nitropyrimidines.

(a) A chloro substituent in the 4(-6-) position of 4, 6-dichloro-5-nitropyrimidine can be replaced by methylhydrazine under mild conditions even when a large group (e. g. dimethylamino) is occupying the 4-position.

(b) The unreactivity of certain methoxy derivatives is attributed to steric effects caused by the presence of a large substituent adjacent to the nitrogroup. The presence of methylamino substituent in 4 or 6 position did allow the reaction of methylhydrazine to proceed in contrast to either dimethylamino or methylhydrazino.

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