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Title: A STUDY OF CERTAIN NOVEL REACTIONS OF 4, 6-DIMETHOXY-5-NITROPYRIMIDINE

Abstract approved: [redacted]
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Reaction of 4, 6-dimethoxy-5-nitropyrimidine [I], with refluxing pyridine, was discovered to yield the methylpyridinium salt of 1, 6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine [III]. Possible use of I as a general N-methylating agent was explored. No appreciable reaction occurred between I and refluxing excess n-butyl alcohol. Similar reaction involving quinoline failed to yield an isolable quinolinium salt although the reaction gave an oily product. Equimolar amounts of I and pyridine in refluxing ethanol solvent gave no evidence of a reaction. As a means of minimizing isolation problems, equimolar amounts of I and pyridine without solvent were reacted. Under these conditions a second product resulting from rearrangement of I, 1, 6-dihydro-4-methoxy-1-methyl-5-nitro-6-oxopyrimidine [V] was isolated in addition to III. Fusion of I with

equimolar amounts of piperidine, quinoline, and 4-methylpyrimidine, resulted in smaller amounts of V, and a black foamy solid, with no detectable methylation of the solvent.

A Study of Certain Novel Reactions of 4, 6-dimethoxy-5-nitropyrimidine

by

Richard Waltz Harper

A THESIS

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Typed by Clover Redfern for Richard Waltz Harper

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TABLE OF CONTENTS

LIST OF FIGURES

A STUDY OF CERTAIN NOVEL REACTIONS OF 4, 6-DIMETHOXY-5-NITROPYRIMIDINE

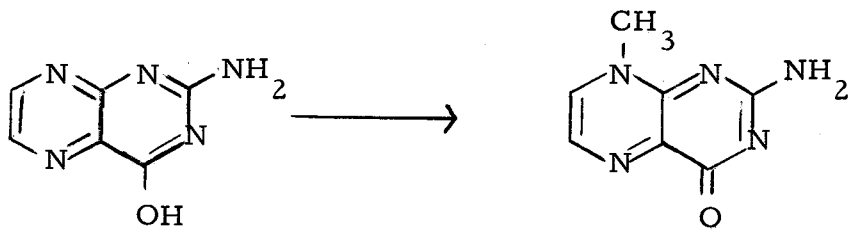
INTRODUCTION

Heterocyclic compounds containing annular nitrogen atoms, like other amines, readily undergo reaction with a variety of reagents to form N-methyl derivatives. Several general accounts of work in this area are available for reference (6, 13, 40, 47).

Methyl halides, and particularly methyl iodide, have been the most extensively used reagents for N-methylation of nitrogen heterocycles, especially in the formation of quaternary salts. The order of reactivity of methyl halides in this reaction, which is an example of the Menshutkin Reaction, is I $\rangle$ Br $\rangle\rangle$ Cl (30). While methyl fluoride has not been reported to undergo this reaction, methylations with methyl iodide proceed smoothly under a variety of conditions. Williams, in 1856, reported quaternization of quinoline by simply heating it with methyl iodide (52). Reactions of this type, with an excess of the methylating agent as the solvent are generally run in a sealed tube, due to the volatility of methyl iodide. In some instances, polar aprotic solvents have been used, since a high dielectric constant helps accomodate the charged products, while association with the product, as through hydrogen bonding, is minimized.

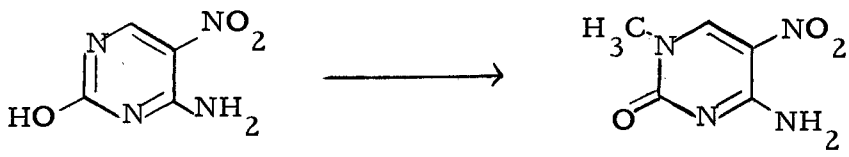
Aromatic nitrogen heterocycles with tautomeric groups in the

α-position, generally undergo base catalyzed N-methylation to yield the reduced N-methyl derivative. However, since these compounds are ambident in nature, methylation at the exocyclic site is often a competing side reaction, and in some cases becomes the principal reaction. Methyl iodide in alcoholic potassium hydroxide has been reported to convert 2-hydroxypyrimidine to 1, 2-dihydro-1-methyl-2-oxopyrimidine, plus a small amount of the 2-methoxy derivative (10). An unusual transannular methylation in the pteridine series was reported by Brown and Jacobsen (7). Heating 2-amino-4-hydroxypteridine with methyl iodide in methanol for 12 hours resulted in conversion to 2-amino-4, 8-dihydro-8-methyl-4-oxopteridine.



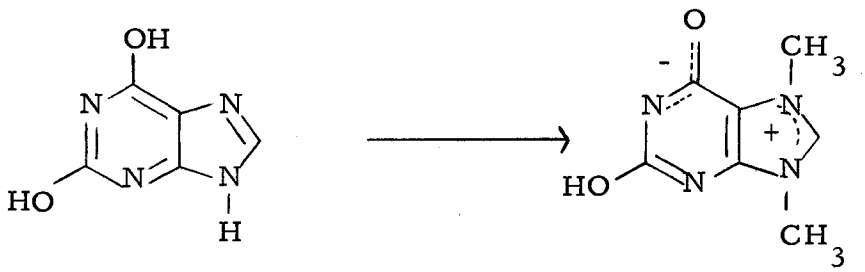
The general synthetic utility of various methyl alkyl sulfates, and aryl sulfonates in N-methylation of nitrogen heterocycles, has also been well established. Dimethyl sulfate, being less volatile than methyl iodide, and thus a more convenient reagent in many cases, has been particularly widely used. A mixture of the 1- and 3-methyl derivatives was obtained from 4-hydroxy-5-phenylpyrimidine on treatment with dimethyl sulfate and alkali (11). Reaction of 4-amino-5-nitro-2-hydroxypyrimidine with dimethyl sulfate yielded 1, 2-dihydro-

4-amino-1-methyl-5-nitro-2-oxopyrimidine, which is an important intermediate in purine and pteridine synthesis (20).



Many methylated purines have been identified in recent years in material from living organisms. Since these compounds are most likely methylated within the organism, the conditions in the laboratory preparations, most of which are carried out in basic medium, are quite different from those necessarily imposed on in vivo methylation. Jones and Robins, in an attempt to more closely duplicate physiological conditions, developed a method of methylation under near neutral conditions, without basic catalysis (21). Dimethylacetamide was chosen as the solvent, as most natural purines display at least some solubility in this polar solvent, and also because it acts as a buffer in the presence of dimethyl sulfate, and other methylating agents. Treatment of xanthine (2, 6-dihydroxypurine) with dimethyl sulfate in dimethylacetamide at 150°C led to 7, 9-dimethylxanthine in good yield. That later compound had been prepared previously, in lesser yield, by heating xanthine in a sealed tube with methyl iodide (5). Rate of reaction is dependent on both the alkylating agent and the

solvent system, as well as other conditions. The sterically hindered



compound 8-nitroquinoline, is unreactive with methyl iodide, but is converted to its quaternary salt by dimethyl sulfate (12).

Morley and Simpson attempted to quaternize 4-amino-6-nitroquinazoline with methyl iodide, but obtained no well defined product (35). Experiments with dimethyl sulfate in methanol also failed to give the desired product. Berg, however, found that fusion with methyl p-toluenesulfonate at 140°C, or heating with the same reagent in nitrobenzene at 170°C, produced the 4-amino-1-methyl-6-nitroquinazolinium salt in good yield (1). A vigorous reaction between piperidine and methyl p-toluenesulfonate, has been reported to give the 1-methyl derivative in 74% yield (45). Conversion of 6-aminouracil to its 3-methyl derivative through the action of methyl p-toluenesulfonate and sodium hydroxide in aqueous methanol, has also been observed (50). The unsubstituted methyl benzenesulfonate, with 3-methylxanthine, in alcoholic potassium hydroxide, produced a 75% yield of theobromine (38).

Bases which are difficult to quaternize with other reagents,

have been methylated in good yield by fusion with the methyl esters of o-nitrobenzenesulfonic acid, or 2, 4-dinitrobenzenesulfonic acid. While 2-methyl-6-nitrosobenzothiazole is unreactive with dimethyl sulfate or methyl p-toluenesulfonate, it is converted to the corresponding quaternary salt in 17% yield, by treatment with methyl o-nitrobenzenesulfonate for two hours at 65°C(25). The quaternary salt was obtained in 74% yield when the same compound was reacted with methyl 2, 4-dinitrobenzenesulfonate at ambient temperature for 24 hours. In addition to the above work, Kiprianov and co-workers also conducted rate studies with a number of methylating agents in various solvents. They found methyl o-nitrobenzenesulfonate to be six times faster than dimethyl sulfate, and the methyl 2, 3- and 2, 4-dinitrobenzenesulfonates to react 60 times as fast as dimethyl sulfate. Kinetic studies using 2-methylbenzothiazole substrate, were run in a toluene solvent. Values for rate constants agreed with a bimolecular mechanism.

Billman and Cash have reported the use of trimethyl phosphate in dimethylformamide, for the conversion of 4-nitrophthalidimide to its N-methyl derivative (3), although this reagent does not seem to have attracted too much general interest. Trimethyl phosphate gives the same product as methyl iodide, and like dimethyl sulfate, has the advantage of being less volatile.

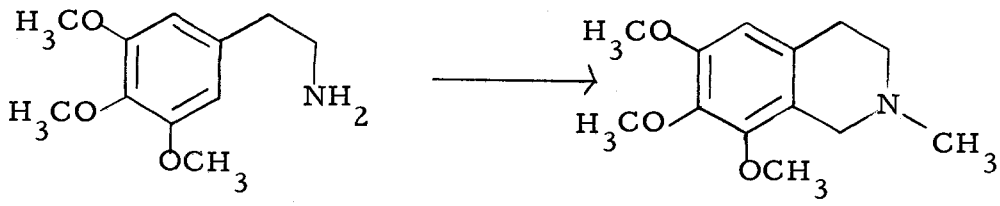
Diazomethane, which has been used largely for esterification of carboxylic acids, and generation of carbenes, is also known to produce N-methyl derivatives of nitrogen heterocycles. The products of alkylation with diazomethane, however, in some cases differ from those obtained with other methylating agents. Other methods are preferable if they give the desired result; since diazomethane, besides being toxic, is shock sensitive, and consequently prone to explosion. Diazomethane in ether, reacts with guanine in methanol to yield the 1-methyl derivative, plus the 6-methoxy derivative (16); whereas, treatment with dimethyl sulfate leads to the expected 7-methyl derivative. Prins, in an attempt to reproduce earlier work (34), found that 3-hydroxypyridine in an ice water slurry, forms a heterogeneous system, with diazomethane in ether, which reacted to give about a 10% yield of the 3-methoxypyridine, and about 30% of 1-methyl-3-hydroxypyridine which was isolated as the picrate (43). The desired 3-methoxy derivative was produced by the action of diazomethane in t-butyl alcohol, on a homogeneous system formed with an ethereal solution of 3-hydroxypyridine, in 68% yield. Among the pyrimidine

reactions, it has been reported that 6-methyl-4-hydroxypyrimidine, upon treatment with diazomethane yielded the 3-methyl derivative, plus a little of the 4-methoxy derivative (32).

Lewis acids such as boron trifluoride, and fluoroboric acid, have been found to catalyze the reaction of diazomethane with amines and alcohols. However, these Lewis acids also catalyze an unwanted side reaction involving polymerization of diazomethane (33), which is minimized through the use of an excess of the amine. Five parts of piperidine, with 1 part boron trifluoride, when reacted in ether with diazomethane, gave 1-methyl-piperidine in 30% yield, and 60% polymer. In contrast to this, reaction of 23 parts of piperidine and 1 part of boron trifluoride, with diazomethane, yielded 39% 1-methyl-piperidine, with no isolable polymer (36).

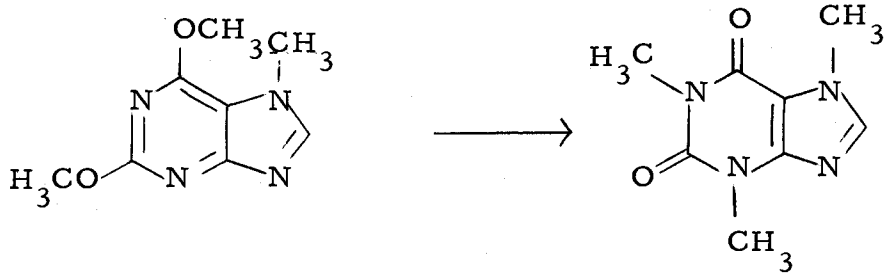
Reductive alkylation (14) employing formaldehyde and a hydrogen source has also been used in the preparation of N-methyl derivatives of nitrogen heterocycles. Piperazine, on treatment with formaldehyde, in the presence of zinc and hydrochloric acid, was converted to 1, 4-dimethylpiperazine in 88% yield (15). The Eschweiler-Clarke Modification of the Leuckart Reaction uses formic acid as the hydrogen source, in conjunction with formaldehyde. Clarke and coworkers reported the methylation of piperidine under these conditions, to produce the 1-methyl derivative in over 80% yield (9). Castrillion has reported cyclization in the course of methylation of a ring

substituted β-phenylethyl amine, with formaldehyde and formic acid, to yield a substituted 1, 2, 3, 4-tetrahydroisoquinoline as the only product (8). This occurrence is a special case of the Pictet-Spengler Synthesis.



Irreversible rearrangement of lactim ethers to their lactam forms, catalyzed thermally or chemically, also provides a useful synthetic route to N-methylated nitrogen heterocycles. Knorr found that certain 2- and 4-alkoxyquinolines formed unstable addition products with methyl iodide, which on heating, decomposed to yield the N-alkyloxoquinolines (27). On heating with methyl iodide, 2-ethoxyquinoline was found to be converted to 1-ethyl-2-oxoquinoline.. Rearrangements of a similar nature were noted by Lieben and Haitinger in the hydroxypyridines (31). Hilbert and Johnson established the synthetic utility of this rearrangement in the pyrimidine series (18). They found that 2, 4-dimethoxypyrimidine, on heating at 220°C for four hours, gave a quantitative yield of 1, 3-dimethyluracil. A mixture of five grams of 2, 4-dimethoxypyrimidine and ten grams of methyl iodine, yielded 1-methyl-4-methoxy-2-oxopyrimidine quantitatively, on standing at room temperature for two to three hours. In the same

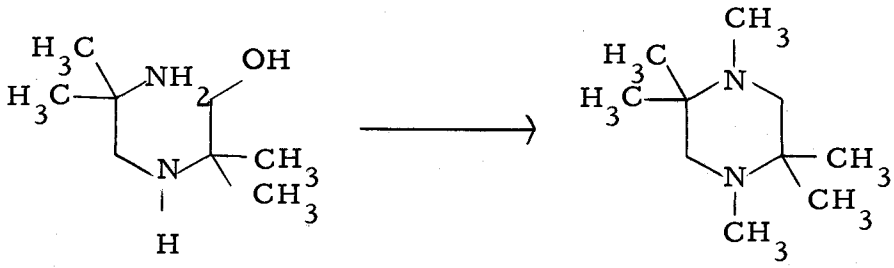
reaction mixture, diluted with benzene, discoloration was observed, and reaction was not complete for several weeks. Using five grams of the pyrimidine, and two drops of methyl iodide in a sealed tube, the reaction was complete in two days at ambient temperature. Addition of pyridine in catalytic or stoichiometric amounts, has been reported to improve the yield of this reaction, in cases where it was previously less than stoichiometric (44). This rearrangement has also found great synthetic utility in the Hilbert-Johnson Synthesis of nucleosides (42). Among the purine reactions, Bergman and Heimhold have noted that 2, 6-dimethoxy-7-methylpurine, on heating, or treatment with methyl iodide, was converted to 1, 3, 6-trimethyl-2,6-dioxopurine (2).



An intermolecular rearrangement similar to the aforementioned intramolecular lactim-lactam rearrangement, has been patented (28). This reaction employes the 0-methyl ether of caprolactim as the methylating agent. Uric acid (2, 6, 8-trihydroxypurine), on heating for 18 hours with 100 parts of caprolactim 0-methyl ether, was converted to tetramethyl uric acid. A number of other aromatic nitrogen

heterocycles were found to react in a similar fashion.

Methanol in the presence of Raney Nickel, in a bomb at elevated temperature, has also been shown to give N-methylation. Plante and Clapp (41) have reported that 2, 2, 5, 5-tetramethyl piperazine, with methanol and Raney Nickel in a bomb at 200°C, was converted to 1, 2, 2, 4, 5, 5-hexamethylpiperazine in 46% yield. Under the same conditions 2, 3, 4, 5-tetrahydro-2, 2, 5, 5-tetramethylpyrazine, and 5-amino-3-aza-2, 2, 5-trimethyl-1-hexanol, were both also converted to the above product. Cyclization of this type of compound in the presence of Raney Nickel had been previously observed (26).

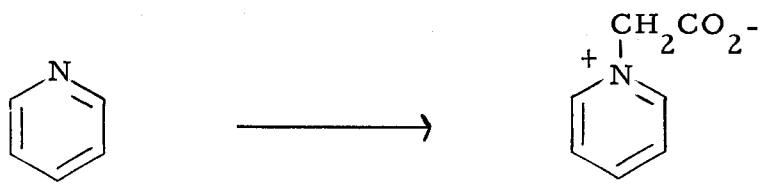


Methyl salicylate has been found to be synthetically useful in the quaternization of aromatic nitrogen heterocycles (23). Pyridine was converted to the corresponding quaternary salt by reaction with methyl salicylate at 120-30°C for five hours. The investigators hypothesized that this unexpected reaction proceeded because of the stabilization of the resulting salicylate ion through hydrogen bonding with the o-hydroxyl group. The reaction was unsuccessful using methyl benzoate as the methylating agent, lending credibility to the

above hypothesis. Methyl cyanoacetate was found to methylate pyridine, indicating that acid strength of the carboxylic acid involved is an important consideration. Subsequent work has shown that this reaction proceeds with a variety of methyl esters of carboxylic acids, and confirmed the idea that the yield of quaternary salt produced is proportional to the acid strength of the carboxylic acid from which the ester is derived (24).

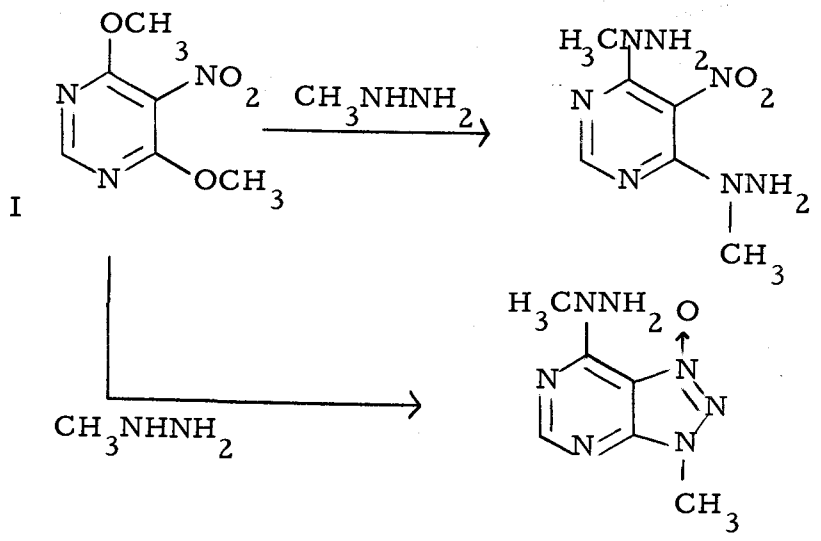
In some cases, methyl trichloroacetate has also been found to act as a methylating agent (39). The trifluoro- and tribromoacetates were also found to convert triethyl amine to the corresponding N-methyl triethylammonium acetate; however, in the case of the trifluoroacetic acid methyl ester, amide formation was a competing side reaction. These reagents appear to be of limited synthetic value, in view of the fact that with primary and secondary amines, only amides and urethanes are formed (22).

A novel N-methylation reaction of 2, 5-dimethylpyrazine, involving chloroacetic acid as the methyl precursor, has been reported (17). This reagent generally reacts with tertiary amines to form the betaine, as in the case of pyridine, which is a stable product. With

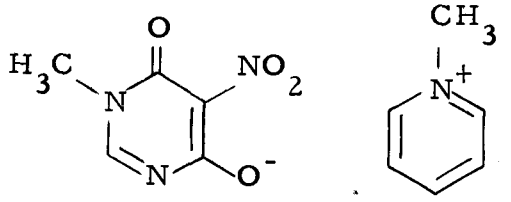


2, 5-dimethylpyrazine, however, bromo- or chloroacetic acid reacts with the evolution of carbon dioxide to form the N-methyl derivative. Unsubstituted pyrazine, and quinoxaline, react with some evolution of carbon dioxide, but the tarry product isolated was not the desired N-methyl quaternary salt. This isolated instance is possible due to mesomeric participation of the second ring nitrogen, which being in the para position, can help support the incipient negative charge.

The current investigation arose from work concerning an abnormal reaction of 4, 6-dimethoxy-5-nitropyrimidine [I], with methylhydrazine, which was first observed by Krakov, in normal butyl alcohol (29). Instead of the expected 4, 6-di(1-methylhydrazino)-5-nitropyrimidine, a few milligrams of an unknown crystalline solid, and a large amount of starting material were isolated. Krakov hypothesized that the unknown product was 3-methyl-7-(1-methylhydrazino)-3H-v-triazolo [4, 5-d] pyrimidine 1-oxide.



Stahl (49) investigated this reaction in several solvents, and found that the unknown material was produced in good yield using refluxing pyridine as the solvent, in about one hour. Subsequently, Stahl identified the unknown product as 4-hydrazino-6-hydroxypyrimidine [II], which he synthesized in an unambiguous manner. It was also found in the course of this investigation, that I reacted with refluxing pyridine to produce another compound [III], to which we assigned the following structure on the basis of its carbon and hydrogen analysis, proton magnetic resonance (PMR) spectrum, and infrared (IR) spectrum:



III

Upon dissolving III in fresh pyridine, and treating with methylhydrazine, II was not formed.

The subject of the current investigation is the unusual reaction resulting in III, and the possible general synthetic utility of I as an N-methylating agent.

DISCUSSION

In order to obtain more III for purposes of confirmation of the structure suggested by Stahl, it was first necessary to synthesize some 4, 6-dimethoxy-5-nitropyrimidine. This was done according to the scheme depicted in Figure 1. Malondiamide was made to undergo base catalyzed cyclization with ethyl formate and sodium ethoxide in ethanol, according to the method of Hull (19), to yield 4, 6-dihydroxy-pyrimidine. The later compound was nitrated in the 5-position by the procedure of Boon, Jones and Ramage (4), using glacial acetic acid and red fuming nitric acid. Chlorination of the 4, 6-dihydroxy-5-nitropyrimidine was accomplished employing phosphorus oxychloride, as reported by the same workers (4). However, N, N-diethylaniline was used in place of N, N-dimethylaniline as the catalyst, a modification which was reported by Krakov (29) to result in increased yield. It may be noted here for later reference, that addition of the N, N-diethylaniline to the 4, 6-dihydroxy-5-nitropyrimidine previous to addition of the phosphorus oxychloride, was reported by Stahl (49), to result in a highly exothermic polymerization reaction, accompanied in large scale preparations by uncontrollable foaming. Treatment of 4, 6-dichloro-5-nitropyrimidine with a cold solution of sodium methoxide in methanol, resulted in conversion to 4, 6-dimethoxy-5-nitropyrimidine [I], as described by Rose and Brown (46).

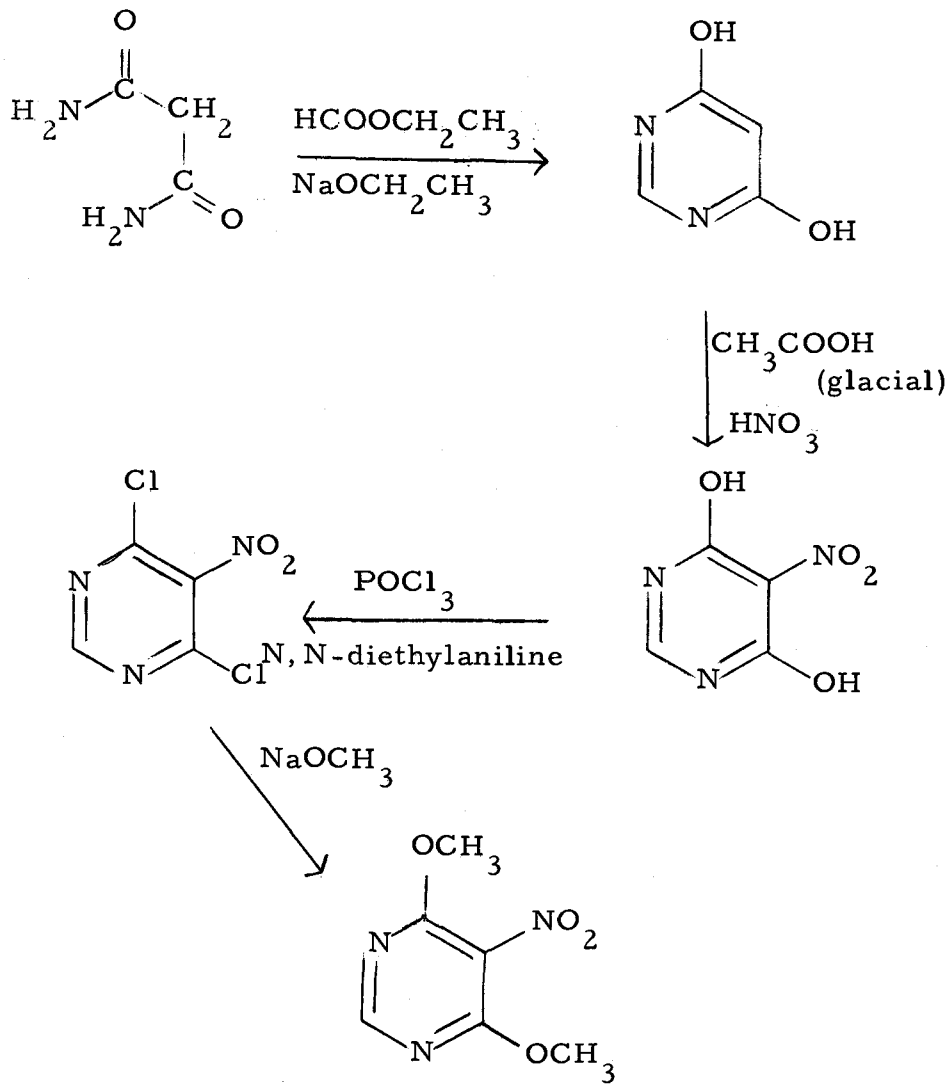


Figure 1. Synthetic route to 4, 6-dimethoxy-5-nitropyrimidine.

Upon refluxing I in excess pyridine it was converted to a compound having the properties of III in about 25% yield, melting point 155-7°C. Evaporation of the pyridine yielded only a red oil, which was found by Stahl to be converted to II, upon dissolving in fresh pyridine followed by treatment with methylhydrazine. No attempt was made to elucidate the structure of the oil.

The PMR spectrum of III showed that the two equivalent methoxy methyl groups of I, absorbing at 4.12δ, had split into a three proton singlet of 3.42δ and another at 4.42δ. The spectrum of III was observed in deuterium oxide, in which it is very soluble, while the spectrum of I, which is very insoluble in water, was taken in deuterochloroform. The difference in shift between the two solvents is not significant. This change was accompanied by disappearance of the strong absorption band in the 1125 cm^{-1} region of the IR spectrum, which had been attributed to the methoxy groups in I. An N-methyl group is suggested by the band at 3.42δ in the PMR spectrum, as would result from a lactim-lactam rearrangement analogous to that reported by Hilbert and Johnson in the 2, 4-dihydroxypyrimidines (18), which has been shown to be catalyzed by pyridine (44). Absorption bands due to the N-methyl groups of 1, 3-dimethyluracil, shown in spectrum number 461 of the Varian NMR spectra catalogues, appear at 3.30δ and 3.43δ (51). Further evidence is provided by the appearance of an absorption band at about 1650 cm^{-1} in the IR

spectrum of III, which is indicative of a conjugated amide carbonyl group (37), such as is present in the proposed structure. Methylation of the pyridine annular nitrogen to form the methylpyridinium portion of III, could be responsible for the three proton singlet at 4.42δ. Synthesis of methylpyridinium iodide, by mixing pyridine with methyl iodide at ambient temperature, provided further evidence inasmuch as a three proton singlet for the N-methyl group of the methylpyridinium iodide appeared at 4.46δ. The absorption pattern of methyl pyridinium iodide in deuterium oxide between 8 and 9δ were also found to be identical to that observed for III, except for apparent enhancement by one proton in the spectrum of III, in the region of 8.10δ, due to the overlap with the 2-proton of the pyrimidine ring. This methylation of the solvent may be analogous to the previously cited work of Kametani and co-workers (23, 24), involving N-methylation of nitrogen heterocycles with the methyl esters of certain organic acids as the methyl precursors. Later in the discussion this possibility will be dealt with in greater depth.

The salt-like nature of the hypothetical III suggested that examination of the hydrolysis products might provide further support for this structure. Hydrolysis of III in dilute hydrochloric acid yielded a tan crystalline compound IV, which melted with decomposition in the range 265-9°C., to which was assigned the structure 1, 6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine. Carbon and hydrogen

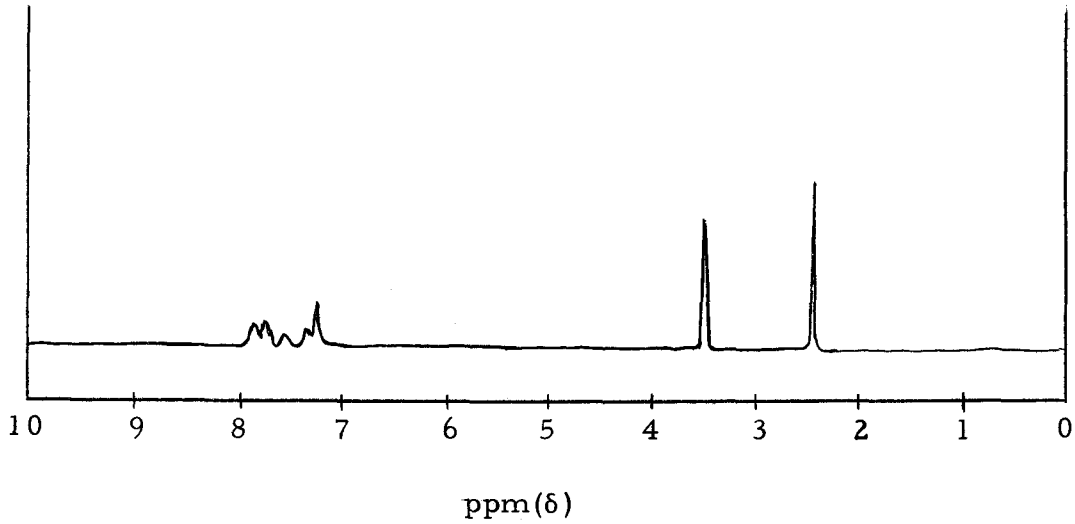


Figure 2. The PMR spectrum of the methylpyridinium salt of 1, 6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine [III].

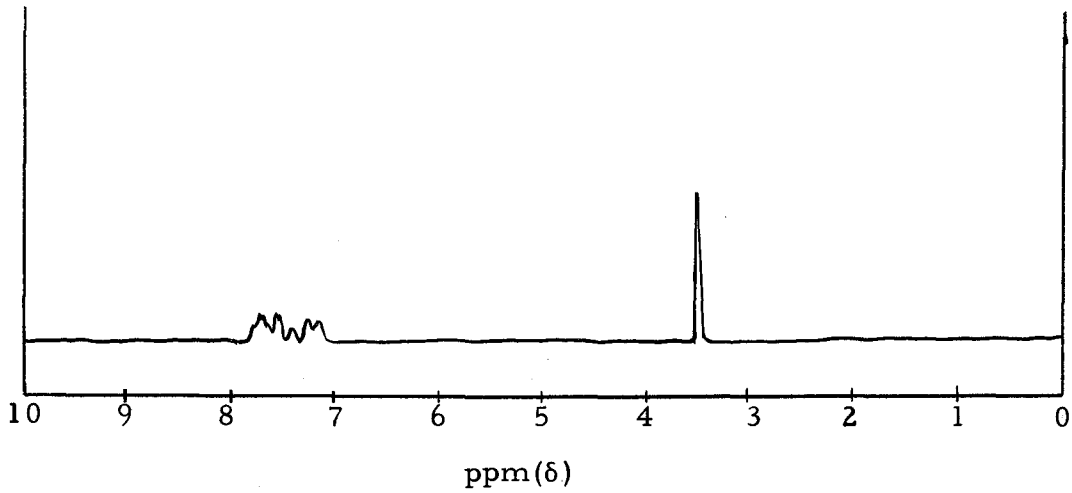
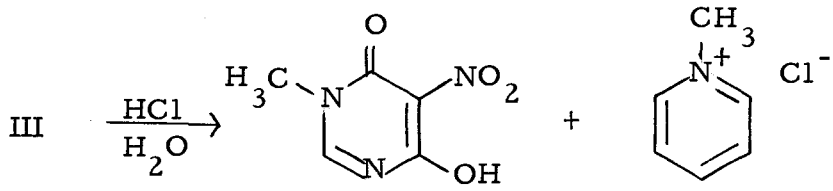


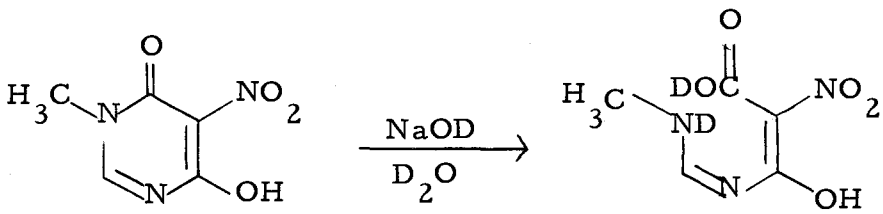
Figure 3. The PMR spectrum of methylpyridinium iodide.

analysis supported an empirical formula of $C_5H_5N_3O_4$, which is consistent with the proposed structure.



IV

In deuterium oxide-deuterated sodium hydroxide, the PMR spectrum of IV appeared as two singlets at 8.47δ, and 2.83δ, present in a ratio of one to three. While the integration data is consistent with the proposed structure of IV, the N-methyl absorption would be expected to occur at lower, rather than higher field with respect to the N-methyl group on the pyrimidine portion of III, due to the inductive effect of the negative charge in III. The possibility of base catalyzed ring cleavage, to which 4, 6-dihydroxypyrimidines appear to be particularly disposed, was considered as a likely explanation for



the observed spectrum. Subsequently, deuterated sodium hydroxide, which was thought to be essential to increase the solubility of IV in

deuterium oxide, was found to be unnecessary. In deuterium oxide, the PMR spectrum of IV showed a singlet of 9.07δ, and another at 3.62δ, again integrating one to three, which is more consistent with the proposed structure.

An attempt was made to examine the PMR spectrum of 4, 6-dihydroxy-5-nitropyrimidine, in deuterium oxide, as a possible model for the absorption of the 2-proton of IV, which seemed further downfield than might be expected. However, no absorption was observed, indicating that the proton had exchanged with the solvent deuterons rather readily. This suggests that the 2-proton is indeed reasonably acidic, and should appear considerably shifted downfield.

With the structures of III and IV reasonably established, extension of the reaction to other solvent systems was attempted. The abnormal reaction of I with methylhydrazine was first observed by Krakov in normal butyl alcohol solvent, so the possibility of reaction between I and that solvent was explored. Refluxing I in normal butyl alcohol for three hours resulted in recovery of 94% of the starting material as identified by its melting point and IR spectrum. After refluxing for 36 hours, 84% of the starting material was recovered. Upon evaporation of the solvent from the later reaction under reduced pressure, a small amount of another white crystalline material was isolated, melting point greater than 300°C.; although, it began to decompose about 230°C. Examination of the infrared spectrum of this

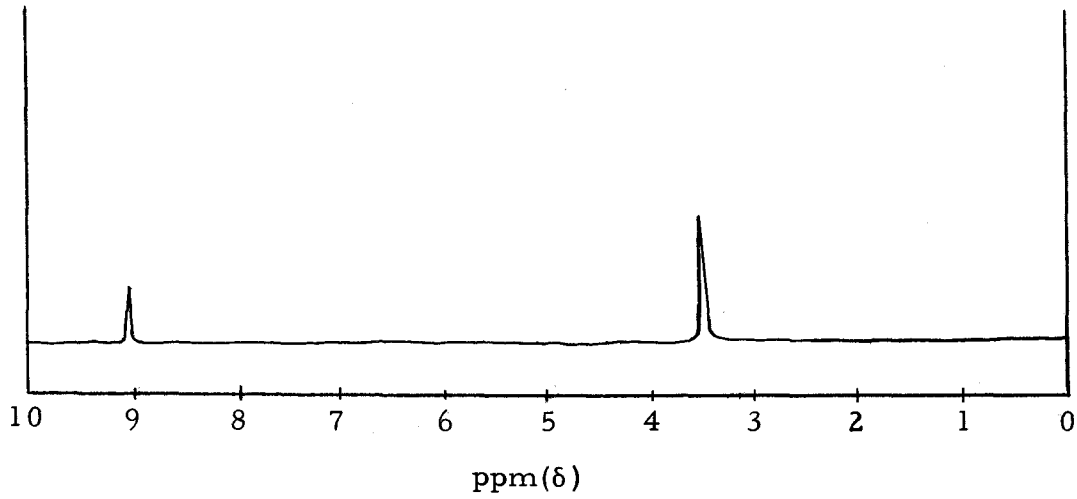


Figure 4. The PMR spectrum of 1, 6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine [IV].

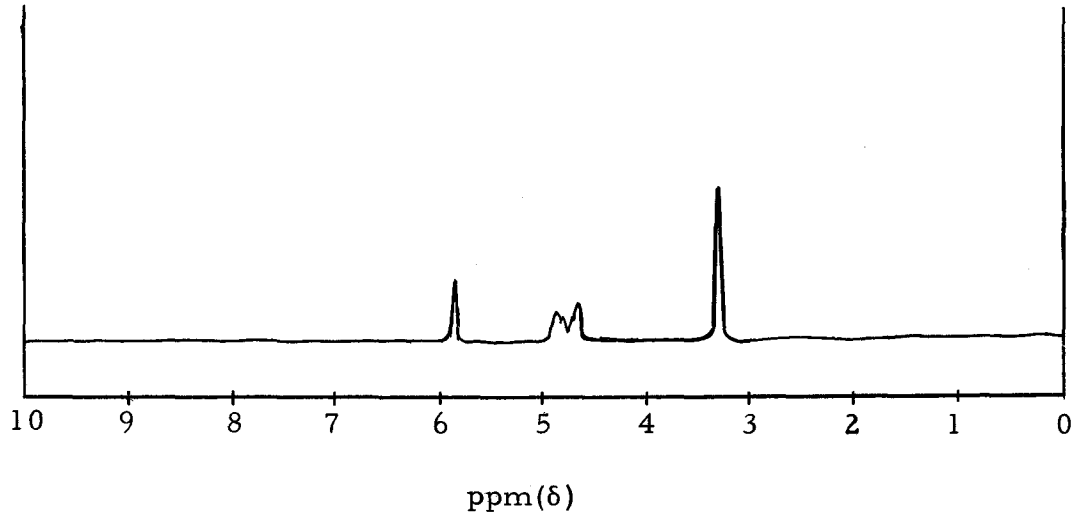


Figure 5. The PMR spectrum of 4-methoxy-1-methyl-4-nitro-6-oxo-1, 4, 5, 6-tetrahydropyrimidine [VI].

material showed it to be different from any of the other compounds involved in this study, and possibly a mixture. Since insufficient material was isolated for analysis, and this solvent showed little promise, the reaction was not pursued further. This did show, however, that no reaction between I and the solvent is necessary in the formation of II from I and methylhydrazine in the original reaction described by Stahl.

To ascertain if the basicity of the solvent might be an important factor, the reaction of I with quinoline was examined. A flask fitted with a reflux condensor, and magnetic stirrer bar, containing 1 g of I and 50 ml of quinoline, was placed in an oil bath maintained at 135-40°C. Although the mixture turned dark very quickly, the heating was continued for 45 minutes. The dark solution was then refrigerated for several hours, at which time a trace of black precipitate, melting point greater than 300°C., was isolated. Due to the difficulty involved in removal of this high boiling solvent, the reaction was run in the same fashion, using only 25 ml of quinoline. Still no significant amount of precipitation occurred.

An effort to run the reaction in some solvent inert to the reaction conditions was made at this time, as a possible way of minimizing the isolation problem. Absolute ethanol was chosen as a reasonably volatile, polar solvent, which would not be acidic enough to react with the expected salt, nor basic enough to react with I. A mixture

of 1 g of I, plus 0.45 ml, an equimolar quantity of pyridine, in 25 ml of absolute ethanol was refluxed with stirring for three hours. Cooling the reaction mixture in a refrigerator for several hours, then filtering with suction, resulted in recovery of 95% of the starting material as identified by its melting point and IR spectrum.

The apparent unsuitability of solvents other than excess substrate, led to experiments with a limiting amount of substrate. Reactions of I with pyridine, in a one to two molar ratio was first attempted. Heating 1 g of I, and 0.85 ml of pyridine in an oil bath maintained at 110-5°C., for 30 minutes, resulted in a dark yellow oil, which crystallized upon cooling and agitation. The IR spectrum of the product was similar to that of III, but indicated contamination, as was confirmed by its melting range of 128-34°C. Treatment with water, and suction filtration of the resulting mixture, yielded a white, water insoluble, crystalline solid [V] which decomposed slowly starting about 220°C., but melted above 300°C. The infrared spectrum of V showed bands at about 1412, 1497, 1600, and 1635 cm^{-1}, which indicate that the pyrimidine nucleus is still intact (48). A strong band at 1682 cm^{-1} supports the presence of an amide type carbonyl function (37). While being somewhat reminicent of the spectrum of IV, the decided difference in the fingerprint region of the spectrum led to the hypothesis that V is the 1, 6-dihydro-4-methoxy-5-nitro-6-oxopyrimidine, since 1, 3-dimethylation of this compound is prohibited by its

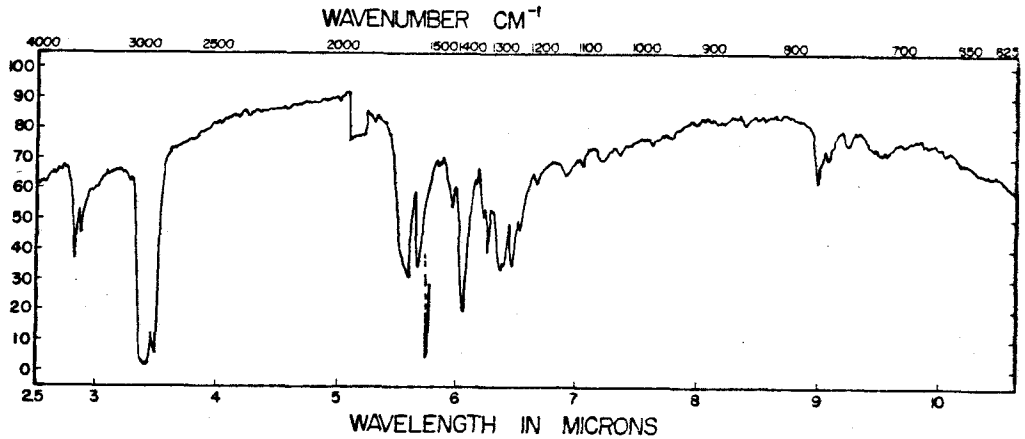


Figure 6. The IR spectrum of 1, 6-dihydro-4-methoxy-1-methyl-5-nitro-6-oxopyrimidine [V].

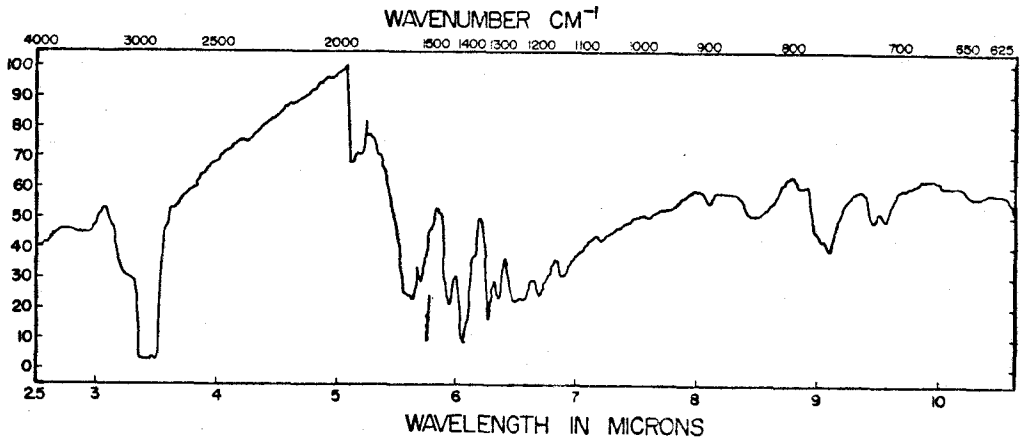
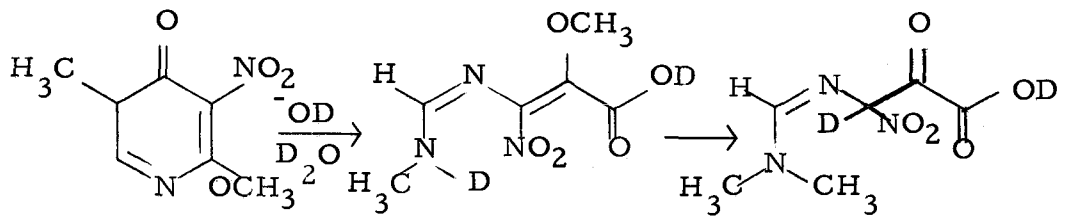


Figure 7. The IR spectrum of 1, 6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine [IV].

valence requirements.

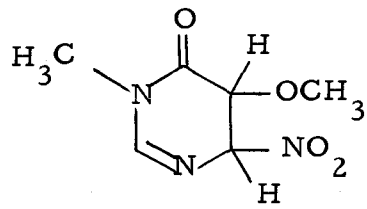
The solubility behavior of V is such that its PMR spectrum could only be taken in deuterium oxide-deuterated sodium hydroxide, which as was previously noted, reacts with this type of compound, resulting in ring cleavage. The PMR spectrum showed two singlets, at 2.93δ and 8.57δ, present in a ratio of six to one. Equivalence of the two methyl groups suggests that the ring cleavage reaction was followed by an intermolecular reaction to yield the N,N-dimethyl compound. This follows from the fact that the spectrum is essentially identical to that of IV in deuterium oxide-deuterated sodium hydroxide, except that the N-methyl peak, at 2.93δ, was doubled in size.



Elemental analysis revealed a hydrogen and nitrogen content consistent with the formula $C_6H_7N_3O_4$; whereas, the carbon was low and variable, indicating poor combustion of the compound.

In view of the low carbon analysis, it seemed advisable to attempt reduction of the compound to its amino derivative, which should combust more easily, and be more soluble for PMR analysis, to provide a confirmation for the structure of V. A Parr low pressure

hydrogenation apparatus was used, employing 10% palladium on charcoal as the catalyst, and methanol as the solvent. Removal of the solvent under reduced pressure, revealed a red oil, which gave a yellow crystalline solid VI when dissolved in water. Recrystallization from water resulted in isolation of VI as a white crystalline material, m.p. 138-9°C., which was supposed to be the 5-amino-1, 6-dihydro-1-methyl-6-oxopyrimidine, in relatively poor yield. Elemental analysis, however, indicated an empirical formula of $C_6H_9N_3O_4$, supporting reduction of a double bond rather than reduction of the nitro group, to give 4-methoxy-1-methyl-5-nitro-6-oxo-1, 4, 5, 6-tetrahydropyrimidine.



VI

This later structure is also supported by the PMR spectrum of VI. In deuterochloroform, the spectrum appeared as a broad singlet at 3.27; a mutliplet centered at about 4.80δ, and a singlet at 5.80δ, integrating six to two to one. The 3.27δ band can be assigned as due to the overlap of the N- and O-methyl groups, the 4.80δ band to the 4- and 5-protons, which split each other, and the 5.80δ band to the 2-proton. If the other double bond had been reduced, the methoxy

methyl group should appear further downfield, and the 4.80δ band should appear as a singlet.

With the structure of V reasonably established, the other products of the reaction were examined. The aqueous solution from which V was taken, when evaporated to dryness under reduced pressure, yielded again yellow oily crystals. Extraction of these crystals with cold pyridine removed the oil, yielding 0.56 g of dry yellow crystals. This later material was identified as pure III, in 40% yield, by melting point, infrared spectrum, and by hydrolysis in dilute hydrochloric acid to IV, as identified by its melting point and infrared spectrum.

Evaporation of the pyridine used in the extraction noted above, revealed a dark, thick oil, which did not crystallize upon heating in vacuo for several hours, then cooling. This oil was dissolved in fresh pyridine, and treated with methylhydrazine, to determine whether it would lead to 4-hydrazino-6-hydroxypyrimidine, as did the oil isolated from the reaction of I with excess pyridine. This reaction led to no isolable product except oil, upon evaporation under reduced pressure.

Reaction of I with pyridine was then tried on an equimolar basis, and subjected to the same work-up procedure as the previous reaction. This led to isolation of V in 48% yield, III in 32% yield, and a small amount of oil which did not lead to II when treated with methylhydrazine.

Thus, the reaction of I with pyridine is found to change course as the amount of pyridine present is varied. When excess pyridine is present as a solvent, no V is isolated; and the amount of V isolated is found to increase as the amount of pyridine decreases. This could be at least in part, due to the viscosity of the fusion type reaction medium involved in reaction of I with a small amount of pyridine. In the very viscous oil formed, the ions formed by initial attack of pyridine on I, would be very slow to diffuse apart, providing ample time for the methyl group to be transferred from the pyridinium ion back to the ring nitrogen of the pyrimidine to form V. It was also found that upon refluxing V in fresh pyridine, no isolable III was formed. The unreactivity of V towards pyridine would then explain why V accumulates more rapidly as the amount of solvent is decreased.

Experiments involving reaction of I with other nitrogen heterocycles on an equimolar basis were then performed. Heating I with one equivalent of piperidine, led to isolation of V in 19.6% yield, plus a thick, dark oil, which was unaffected by acid. Upon refluxing this oil with fresh piperidine, and methylhydrazine, no II could be isolated.

In the course of this reaction, it was found that heating the reaction mixture too rapidly, or too hot, results in a violently exothermic reaction, which sprays material out the top of the condensor. This leads to a black, insoluble material as the only isolable product.

Apparent decomposition of a similar nature was also noted in other equimolar reactions, but was minimized by heating the bath slowly, to a temperature not over about 120°C. There seems to be an analogy between this observation, and the exothermic, foaming reaction between 2, 4-dihydroxy-5-nitropyrimidine, and N, N-diethylaniline observed by Stahl, as previously noted.

Quinoline was then reacted with I in an equimolar ratio. The resulting dark oil was heated in vacuo to produce a black, foamy mass, which broke up into an apparently crystalline material, which could be recrystallized from water to give V in about 15% yield. The black material, recovered from water, and dissolved in fresh quinoline, was heated with methylhydrazine at about 120-5°C. No II could be isolated from this reaction, or from similar reactions involving the black decomposition products from equimolar experiments.

Reaction of I with 4-methylpyrimidine, run and worked up in the same manner as the reaction with quinoline, yielded about the same results. A 10% yield of V was isolated, plus the black, decomposition products previously noted. No further investigation of the later material was undertaken.

Thus, 4, 6-dimethoxy-5-nitropyrimidine does not seem promising as a general reagent for the N-methylation of nitrogen heterocycles. Reactions involving I, with excess substrate as the solvent lead in some cases to problems in separating the products from the

reaction mixture, and in any case, do not lead to high yields of isolable N-methylated product. Side reactions, apparently involving decomposition, or polymerization, become major reactions when I is fused with an equimolar amount of substrate, and the only isolable product is the rearranged pyrimidine, 1, 6-dihydro-4-methoxy-1-methyl-5-nitro-6-oxopyrimidine.

EXPERIMENTAL

All melting points were taken on a Fischer-Johns melting point apparatus, and are uncorrected. Infrared spectra were obtained through the use of a Beckman Model IR-8 spectrometer, using sodium chloride plates. These spectra were calibrated with the 6.246 μ band of polystyrene. The infrared samples were run as mulls in nujol oil (nujol itself absorbs strongly at about 2920 cm^{-1}, and 2860 cm^{-1}, and less intensly at about 1460 cm^{-1}, and 1375 cm^{-1}). A Varian A-60 spectrometer produced the proton magnetic resonance spectra. Tetramethylsilane was used as an internal standard for samples run in deuterochloroform. An external standard composed of 10% tetramethylsilane in deuterochloroform was used for samples dissolved in deuterium oxide, unless otherwise noted.

The Methylpyridinium Salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine [III]

In a 100 ml round-bottom flask, were placed 1.027 g (0.0056 mole) of 4,6-dimethoxy-5-nitropyrimidine, prepared by the method of Rose and Brown (46) and 50 ml of anhydrous pyridine. The flask was fitted with a reflux condensor, and heated in an oil bath maintained at 135-40°C., for about 40 minutes, with stirring. On cooling overnight in a refrigerator, the salt precipitated as a brown crystalline solid. The mixture was filtered with suction, and the solid

washed with fresh pyridine, and dried in vacuo at about 80°C., for 24 hours, yielding 0.379 g (25.8%) of the light brown salt, m.p. 155-7°C.

Anal. Calc'd for $C_{11}H_{12}N_4O_4$: C, 49.99; H, 4.59.

Found: C, 49.81; H, 4.56.

1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine [IV]

To 0.379 g of the methylpyridinium salt of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine, was added five ml of dilute hydrochloric acid, whereupon, a tan precipitate formed immediately. The mixture was refrigerated for several hours, then filtered with suction. Recrystallization of the solid from water, yielded 0.118 g (43.3%) of 1,6-dihydro-4-hydroxy-1-methyl-5-nitro-6-oxopyrimidine, m.p. (dec.) 265-9°C.

Anal. Calc'd for $C_5H_5N_3O_4$: C, 35.09; H, 2.95.

Found: C, 34.83; H, 2.89.

Reaction of 4,6-dimethoxy-5-nitropyrimidine with pyridine in ethanol

A mixture of 1.035 g (0.0056 mole) of 4,6-dimethoxy-5-nitropyrimidine, 0.45 ml (0.0056 mole) of pyridine, and 25 ml of absolute ethanol, in a 50 ml round-bottom flask, fitted with reflux condensor, and magnetic stirrer bar, was heated at reflux for three hours with stirring. Cooling the mixture, and filtering with suction,

resulted in recovery of 0.978 g (94.5%) of the starting material, as identified by its IR spectrum and melting point.

1,6-dihydro-4-methoxy-1-methyl-5-nitro-6-oxopyrimidine [V]

A. In a ten ml round-bottom flask, were placed 0.978 g (0.0053 mole) of I, and two equivalents of pyridine, 0.834 g (0.85 ml). The flask was fitted with a reflux condensor, and placed in an oil bath, which was heated to 110-5°C., and maintained at that temperature for about 30 minutes. A dark viscous oil resulted, which upon cooling and agitation, formed yellow, hygroscopic crystals. When these crystals were extracted with water, a relatively water insoluble crystalline compound was obtained. This later compound recrystallized from water as 0.194 g (19.5%) of pale yellow crystals of V, which, dried in vacuo, melted above 300°C., although gradual decomposition was observed above about 230°C.

Anal. Calc'd for $C_6H_7N_3O_4$: C, 38.92; H, 3.82; N, 22.70.

Found: C, 37.65; H, 3.85; N, 22.67.

The water with which the crystals were extracted above, was evaporated under reduced pressure to again yield oily yellow crystals. These crystals were extracted with pyridine, which removed the oil, to yield 0.556 g of III, m.p. 155-7°C. This compound was further identified by its IR spectrum, and by hydrolysis to IV, which was recognized by its melting point and IR spectrum.

Under reduced pressure, the pyridine used in the extraction above was evaporated to yield a yellow oil. This oil was dissolved in 15 ml of fresh pyridine, and combined with one ml of methylhydrazine. After standing for three days no isolable 4-hydrazino-6-hyroxypyrimidine had formed.

B. A mixture of 1.047 g (0.0056 mole), of I, and 0.54 ml (0.0056 mole), of pyridine, equimolar amounts, was reacted, and worked up as described above. A 48% yield of V, 0.500 g, was obtained. The salt III was isolated in 32% yield, 0.474 g. The oil which was isolated, again did not lead to II.

C. In a ten ml round-bottom flask, fitted with reflux condensor, were placed 1.004 g of I (0.0054 mole), and 0.54 ml (0.0054 mole) of piperidine. The flask was placed in an oil bath, which was heated slowly to 110°C., and maintained at 110-5°C., for about 45 minutes, at which time a thick, dark oil had formed. On cooling, the oil solidified, but did not crystallize. With addition of about five ml of water, a white precipitate formed. Recrystallization from water yielded 0.197 g (19.6%) of V, m.p. greater than 300°C.

Evaporation under reduced pressure, as previously described, of the aqueous solution failed to give any solid material yielding only the oil. This oil was unaffected by acid, and upon dissolving in 25 ml of fresh piperidine, and treatment with methylhydrazine at room

temperature for two days, yielded no isolable II.

D. 4, 6-dimethoxy-5-nitropyrimidine, 1.026 g (0.0055 mole) and 0.66 ml (0.0055 mole) of quinoline, in a ten ml round-bottom flask equipped with reflux condensor, were placed in an oil bath, which was heated to 108°C., then maintained at 108-12°C., for about one hour. The resultant oil was heated in vacuo, in an oil bath maintained at 80-90°C., for two days. A black foam formed, which broke up into fine crystals. Treatment of this black material with water resulted in 0.137 g (13.4%) of V, after recrystallization from water.

E. 4-methylpyrimidine, 0.488 g (0.0054 mole), and 1.012 g of 4, 6-dimethoxy-5-nitropyrimidine (0.0054 mole), were reacted and worked up as described in the previous procedure. After recrystallization from water, 0.128 g (12.7%) of V, m.p. greater than 300°C.

The product isolated from each of the previous procedures, showed identical infrared absorption spectra, and elemental analysis. The carbon was found to be low and slightly variable presumably due to incomplete combustion.

4-Methoxy-1-methyl-5-nitro-6-oxo-1, 4, 5, 6-tetrahydropyrimidine [VI]

In a Parr low pressure hydrogenation apparatus, were placed 1.124 g (0.0061 moles) of V, suspended in 150 ml of anhydrous methanol, and 0.057 g of 10% palladium on charcoal catalyst, under an initial pressure of 15 psi. The flask was then agitated for about ten hours, at which time all of the starting material had gone into solution, and the pressure had dropped indicating a reaction had taken place. The pressure drop was not significant enough to calculate moles of hydrogen absorbed. The solution was then heated to an incipient boil, and the catalyst removed, and washed with fresh methanol. The combined methanol solution was evaporated under reduced pressure, yielding a reddish-brown oil. Addition of a small amount of water to the oil resulted in a white, crystalline material. Recrystallization from water gave VI, 0.169 g (14.8%), m.p. 138-9°C.

Anal. Calc'd for $C_6H_9N_3O_4$:	C, 38.50;	H, 4.86; N, 22.45.
Found:	C, 38.66;	H, 4.94; N, 22.18.

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