THE ALKYLATION OF 4-PYRIDONE

by

Eugene A. Cioffi

Submitted in Partial Fulfillment of the Requirements

for the Degree of

Master of Science

in the

Chemistry

Program

James A. Peeler August 4, 1978

Adviser Date

Leon Knud August 10, 1978

Dean of the Graduate School Date

YOUNGSTOWN STATE UNIVERSITY

August, 1978

ABSTRACT

THE ALKYLATION OF 4-PYRIDONES

Eugene A. Cioffi

Master of Science

Youngstown State University, August 1978

2,6-dimethyl-4-pyridones have been prepared from the reaction of 3-acetyl-4-hydroxy-6-methyl-2-pyrone (dehydroacetic acid) with various aqueous amines. These pyridones further react with alkyl halides, producing the halide salts of the quaternary cation.

Preparation of alkyl derivatives from 2,6-dimethyl-4-pyridones as well as 2,6-dimethyl-4-methoxypyridine have conclusively established alkylation upon the carbonyl oxygen atom. Furthermore, coincidence of the relative chemical shifts of N-alkyl and O-alkyl substituents has been clearly demonstrated.

The 4-pyridones possess two strong sp^2 hybridized nucleophilic centers (i.e., the ring nitrogen and the carbonyl oxygen), and the alkylation may proceed upon either site. Previously, this reaction has not been investigated. Alkylation upon the nitrogen atom would result in quaternization via the Menschutkin reaction, whereas attack upon the carbonyl oxygen would proceed

analogous to the Williamson ether synthesis. Infrared studies alone of the compounds prepared were inconclusive in assignment of the alkylation site, since the complexity of the bands resulted in spectra remarkably similar to those of the non-alkylated initial reagents. Furthermore, the early results obtained from proton nmr spectra indicated the possibility of coincident relative chemical shifts (of N-alkyl vs. O-alkyl substituents) or rearrangement of the alkyl substituents to one specific nucleophilic site.

ACKNOWLEDGEMENTS

I take this opportunity to express my sincerest thanks and gratitude to Dr. James A. Reeder, for his suggestion of the problem, and for his valuable guidance and constant encouragement he afforded me throughout the course of this research.

Financial assistance from the Department of Chemistry is gratefully acknowledged. I also wish to thank Dr. Irwin Cohen and Dr. Stephen Schildcrout for their helpful suggestions in reviewing this manuscript. Further thanks are due to other faculty members and fellow graduate students for their helpful discussions and suggestions.

Finally, my grateful appreciation is extended to my family, whose encouragement and patience helped see this research through a successful completion.

TABLE OF CONTENTS

TABLE OF CONTENTS (CONT.)

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1

INTRODUCTION

It has long been known that 4-pyridones exist predominantly in the keto form in solution, are non-aromatic, and have large dipole moments. They are nucleophilic, and possess two strongly electronegative sp^2 hybridized heteroatoms (i.e., the ring nitrogen and the carbonyl oxygen). They may quarternize by either protonation or alkylation. Protonation had been the subject of much controversy, resulting in the establishment of carbonyl protonation in acidic media by infrared and proton nmr spectroscopy. However, the alkylation reactions of 4-pyridones, and conclusive establishment of the sites of alkylation, have not been previously reported.

The alkylation of 4-pyridones may proceed by two mechanisms, resulting in N-alkylation via the Menschutkin reaction, or O-alkylation analogous to the Williamson ether synthesis. Literature reports have suggested that N-methyl-4-pyridone undergoes methylation at the oxygen atom, resulting in the formation of the 1-methyl-4-methoxypyridinium cation, although this structural assignment has not been confirmed. Furthermore, steric considerations involving the accommodation of alkyl substituents, and

electronic interactions resulting in inductive charge stabilization by ring substituents, may alter the alkylation mechanism of both 2,6-dimethyl-4-pyridone and 1,2,6-trimethyl-4-pyridone.

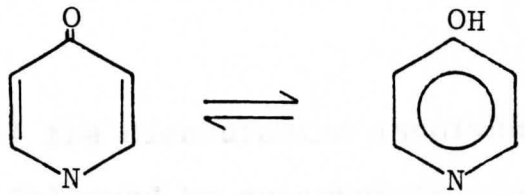
The preparation of alkylated products resulting from the reaction of 1,2,6-trimethyl-4-pyridone (I) and 2,6-dimethyl-4-methoxypyridine (III) with primary alkyl halides could result in formation of either the 1-alkyl-1,2,6-trimethyl-4-oxo-1,4-dihydropyridinium cation via N-alkylation of I (or by N-alkylation of III, followed by rearrangement), or formation of the 1,2,6-trimethyl-4-alkoxypyridinium cation via O-alkylation of I (or N-alkylation of III, followed by simultaneous exchange-rearrangement of the N- and O- substituents). In both reactions, spectral analyses by nmr and infrared spectroscopy should be able to identify the resultant products. However, these techniques individually may not yield the correct structural assignments, due to possible complexity of bands in the infrared spectra, or coincidental overlap of chemical shifts in the nmr spectra.

By complementary employment of infrared and proton nmr spectroscopy, combined with the syntheses of protonated and alkylated derivatives of various 4-pyridones, this research hopes to elucidate the structural configurations of these derivatives, and thus establish the site of alkylation.

CHAPTER II

HISTORICAL

The existence of 4-pyridones has been known for nearly a century, when Haitinger[1] first reported the synthesis. However, determination of the predominate tautomeric form, either keto or enolic (Eq.1) has been the subject of many investigations.

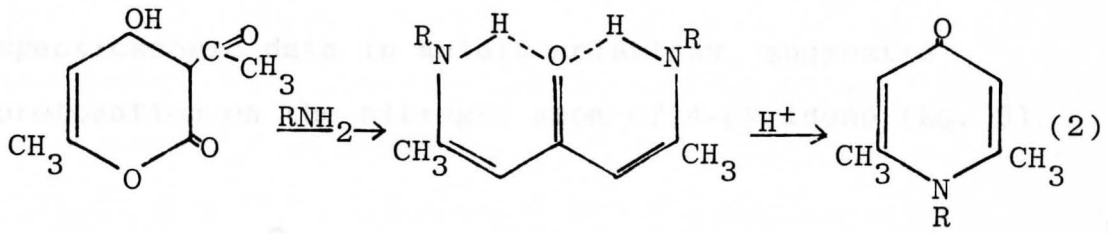


(1)

The enolic form has been found to predominate in the gas phase.[2] However, in solution, the keto tautomer predominates. This has been shown by titration,[3] ultraviolet,[4,9] infrared,[5] proton nmr,[6] ^{14}N nmr,[7] and esr spectroscopy (as anion radicals),[8] in water[3] and in other solvents.[4,7] The keto tautomer predominates in a ratio of 1.29 : 1 in chloroform,[4] 4.57 : 1 in acetonitrite,[4] 4.88 : 1 in acetone,[7] 9 : 1 in methanol, and 1950 : 1 in water.[3]

The synthesis of 4-pyridones has been performed by various means. The 2,6-dimethyl-4-pyridones have been prepared by the reaction of dehydroacetic acid

(3-acetyl-4-hydroxy-6-methyl-2-pyrone) with aqueous amines.[1] Cook[10] isolated stable open-chain compounds as reaction intermediates (2,6-bis [alkylamino] -2,5 heptadien-4-ones), and from this postulated the following reaction sequence for the preparation of 2,6-dimethyl-4-pyridones from dehydroacetic acid (Eq. 2):



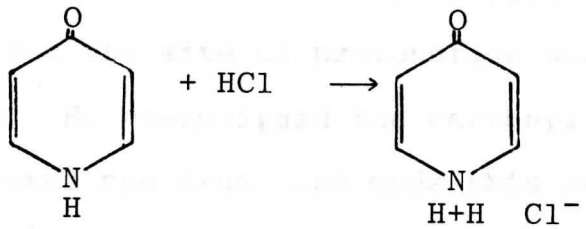
(2)

The formation of the dienediamine involves opening of the 2-pyrone ring, followed by decarboxylation. Other N-unsubstituted-4-pyridones have been prepared by the reaction of dehydroacetic acid and aqueous ammonia,[11,12] whereas the reaction with aliphatic amines yields N-substituted-4-pyridones.[13-16]

Pyridones are weakly basic substances, and may be protonated with strong acids. The pKa of the conjugate acid of 2,6-dimethyl-4-pyridone in water at 20°C has been estimated as 4.53 by titration,[17] and 4.13 by nmr exchange rates.[18] The corresponding values for 1,2,6-trimethyl-4-pyridone are 4.52[17] and 4.12[18] respectively. The pyridones are much weaker in basicity than the corresponding pyridines, as evidenced by the pKa of the

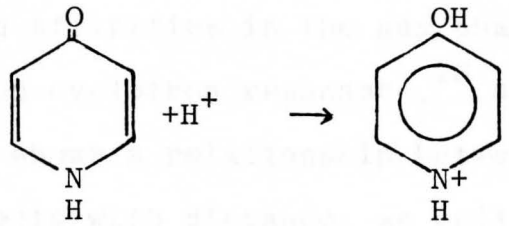
conjugate acid of 2,6-dimethyl-4-methoxypyridine (isomeric with 1,2,6-trimethyl-4-pyridone) being estimated as 8.26[17] and 7.86.[18]

Due to the presence of two strongly nucleophilic sites within the molecule, either nitrogen or carbonyl oxygen protonation may be considered as feasible. Early work by Spinner,[19] based upon infrared and Raman spectroscopic data in acidic solutions, suggested protonation on the nitrogen atom of 4-pyridone (Eq. 3).



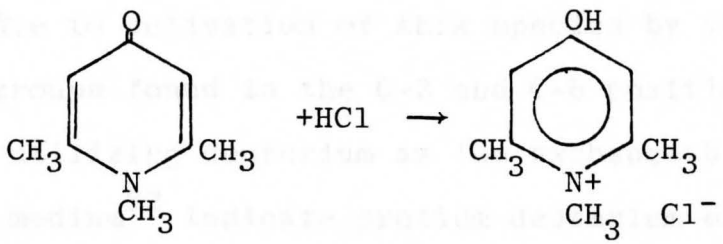
(3)

Spinner based his conclusions upon the existence of a strong infrared band at 1640 cm^{-1}, which he tentatively assigned as the ring carbonyl stretching frequency. Katritsky and Jones studied the ^1H nmr spectra of pyridone-hydrochloride in liquid SO_2, and from the C-H to N-H coupling, demonstrated protonation on the ring carbonyl oxygen.[20] Further ^1H nmr studies of 4-pyridone dissolved in sulfuric acid,[6,21] and deuterosulfuric acid[22] also corroborated protonation at the carbonyl oxygen atom (Eq. 4).



(4)

Based upon ^{13}C nmr chemical shifts compared with those shifts expected from studies in other systems, Sarneski and co-workers[23] also suggested carbonyl protonation. Later work by Cook[24] on 1,2,6-trimethyl-4-pyridone also suggested that the site of protonation was the carbonyl oxygen atom. He re-assigned the carbonyl band to 1560 cm^{-1} in the infrared spectrum, and made this assignment since the 1560 cm^{-1} band showed a gradual decrease in frequency when the compound was complexed with Lewis acids of increasing acid strength. The band reached a minimum frequency of 1480 cm^{-1} in the hydrochloride salt (Eq. 5).



(5)

He further observed that the band at 1640 cm^{-1} was not significantly shifted, and re-assigned this band to the C===N stretching mode. Further studies of protonation in

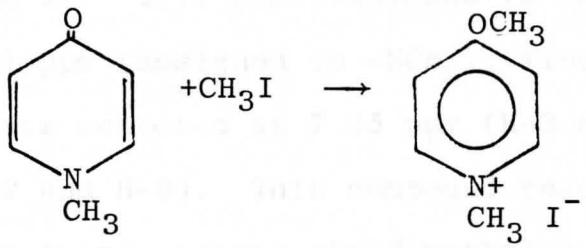
amino-substituted derivatives of pyridones have also been performed.[25]

Proton affinities in the gas phase have been measured by ion-cyclotron resonance,[26] and comparison of these results shows a relationship between attenuation of inductive effects with distance, as well as solvent effects. In addition, further work in this area has been done to determine the exact donor properties of the carbonyl oxygen atom.[27] However, the site of protonation in the gas phase may well be different than that found in solution phase. Thermodynamic studies of acid-base equilibria involving proton transfer have also been performed.[28-30]

Proton-exchange upon the non-nucleophilic sites of benzene and pyridine derivatives have been studied,[17,31] and the mechanism of this exchange at the C-3 and C-5 positions in 2,6-dimethyl-4-pyridone in acidic media[18] demonstrate that the reactant species undergoes exchange as the keto tautomer at low acidities, and behaves as the conjugate acid at higher acidic concentrations. This occurs due to activation of this species by the ring methyl groups found in the C-2 and C-6 positions. Further studies utilizing deuterium as the exchangeable species in a basic medium[32] indicate protium-deuterium exchange at the C-2 and C-6 positions in N-Methyl-4-pyridone. This base-catalyzed exchange is facilitated by the s-character of the

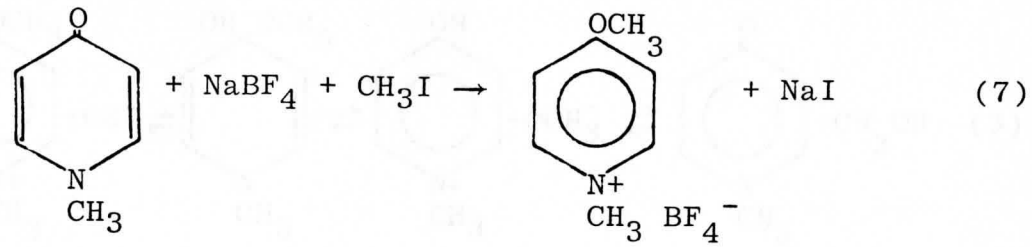
lone pair in the conjugate-base, resulting from removal of the H-2 or H-6 atoms. Further promotion of this exchange results from inductive stabilization of the negative charge. Other substituted derivatives as well as other heterocyclic systems have been analyzed by this technique.[33]

The nucleophilic substitution reactions of 4-pyridones leading to nitrogen quarternization via the Menschutkin reaction[34] or oxygen alkylation (as the Williamson ether synthesis)[35] have not been extensively studied. Analagous to protonation, the existence of two strongly nucleophilic centers suggest either N- or O-alkylation. The only alkylated derivative of 4-pyridones shown in the literature the 1-methyl-4-methoxypyridinium cation, the iodide salt of which was first prepared by Renshaw and Conn[36] in 1937 (Eq. 6).

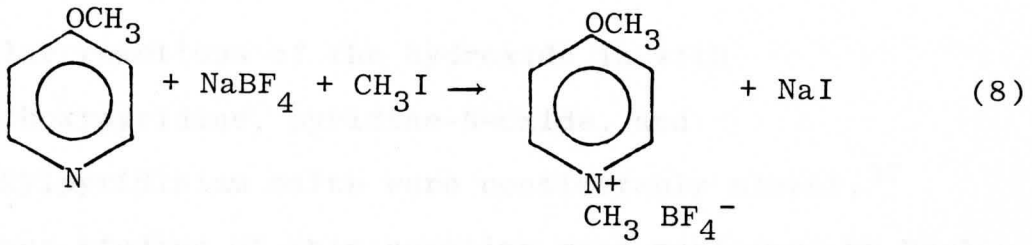


(6)

The fluoroborate salt derivative was prepared by two routes (equations 7 and 8) by Beak and Bonham.[32]

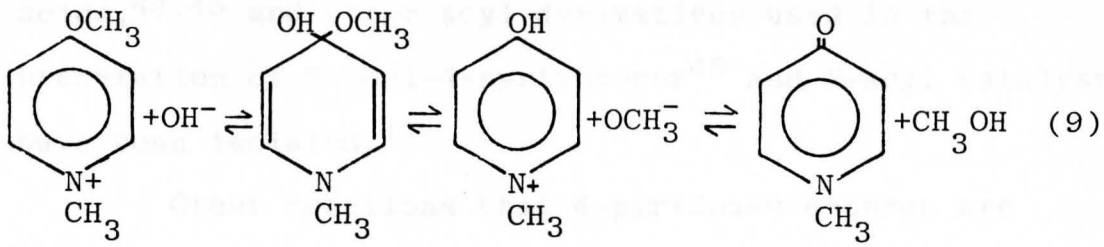


(7)



(8)

These authors apparently assumed methylation on oxygen of 1-methyl-4-pyridone, because the same compound was formed by methylation of either N-methyl-4-pyridone (Eq. 7) or 4-methoxypyridine (Eq. 8). The nmr spectra of the fluoroborate salt (in acetone, $-d_6$) consisted of 2 singlets, one at 4.17 ppm (assigned to $-OCH_3$), and the other at 4.31 ppm (assigned to $-NCH_3$), along with a pair of A_2B_2 multiplets centered at 7.55 ppm (H-3 and H-5) and 8.70 ppm (H-2 and H-6). This compound reacted with hydroxide ion to regenerate the N-methyl-4-pyridone. A kinetic study of this reaction [37] indicates a mechanism similar to the nucleophilic substitution of halogenated nitrobenzenes. The mechanism of this reaction could be written as follows (Eq. 9):



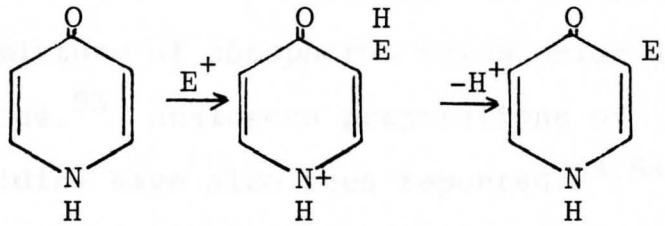
(9)

Similar reactions of the hydroxide in with 4-methoxypyridine, pyridine-N-oxide, and N-alkylpyridinium salts were considerably slower.[37] Further studies of this reaction were performed by Barlin and Benbow[38,39] using the iodides, and compared with similar studies on 2- and 3- substituted pyridinium salts.[37,40]

Investigations of acylation reactions have shown that similar to protonation reactions, attack upon either nucleophilic center is plausible. The earliest examinations, performed by Tschitschibabin and Szokow,[41] resulted in isolation of only O-acylated derivatives of 2-pyridones. When the reactions of 4-pyridones with acylating agents were studied, it was believed that O-acylation had occurred, analogous to the reactions of 2-pyridones (and 4-pyrones).[42] However, later research[43] demonstrated an equilibrium mixture of the two isomers in solution, with predominance of the N-acylated isomer in solid state, however. Further work isolated 4-acyloxypyridines by reaction of 4-chloropyridines and

4-bromopyridines with the silver salts of carboxylic-acids,[44,45] and other acyl derivatives used in the preparation of N-acyl-4-pyrithiones[46] and N-acyl catalysts have been isolated.[47]

Other reactions that 4-pyridones undergo are dependent upon the nature of attacking reagents, resulting in either an electrophilic attack upon the carbonyl oxygen, or nucleophilic attack upon the carbon atom (C-4) of the carbonyl group, yielding substitution (as opposed to ring-opening). Electrophilic reagents (E^+) may attack ring

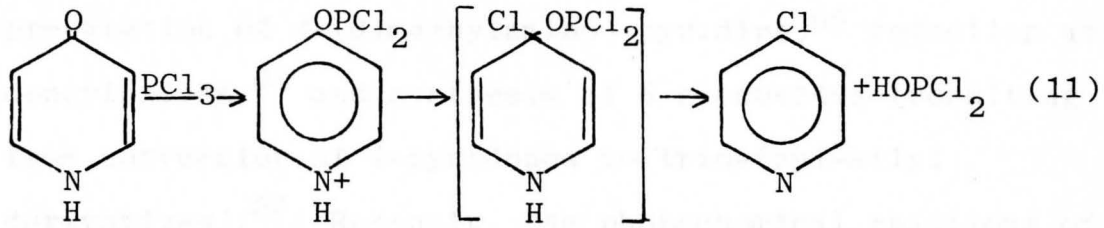


(10)

carbon atoms to the nitrogen atom, yielding substituted products after loss of a proton (Eq. 10).
In this manner, 3-halo- or 3,5-dihalo- compounds are readily synthesized. These compounds have shown interesting bacteriostatic activities.[44,48,49]

Reactions of the carbonyl group in nucleophilic displacements have led to the preparation of 4-halogenated derivatives, with the yields depending upon the reagent employed. Haitinger and Lieben[50] converted 2- and 4-pyridones to their corresponding chloropyridines with

phosphorus trichloride, and the reaction is believed to proceed with the mechanism suggested in Equation 11.



(11)

It was found that product yields increased using phosphorus pentachloride,[51] increased again using phosphorus oxychloride,[52] and the maximum yields resulting from an equimolar mixture of phosphorus oxychloride and phorphorus pentachloride.[53] Analogous preparations of 4-bromopyridine have also been reported.[53,54] An early synthesis of 4-chloropyridine from N-methyl-4-pyridone and phosgene was achieved by Fischer and Demeler.[55] The 4-halogenated derivatives and 4-nitropyridines have also been isolated from their respective N-oxides.[56,57] Chlorinated products resulting from reaction of 4-pyridones with thionyl chloride[57] and benzenesulfonyl chloride[58] have also been synthesized. The 4-halopyridines as free bases are unstable to storage, but they are stable as the conjugate acids in acidic media.[59]

The 4-chloropyridine derivatives have been utilized as starting materials in preparation of other compounds, especially 4-methoxypyridines.[45,60-62] These

compounds exhibit interesting properties, such as novel pharmacological activity[63] and donor ability in charge-transfer complexes.[64]

Other reactions involving 4-pyridones include preparation of 4-(dimethylamino) pyridine,[65] reduction and deacylations,[66] and synthesis of N-glycosides (resulting from conversion of 4-pyridones to trimethyl-silyl derivatives).[67] Recently, the photochemical reactions of 4-pyridones have been investigated.[68,69]

The 4-pyrones behave essentially as their nitrogenous analogs, i.e., they will undergo the same reactions as the 4-pyridones. However, they will not react electrophilic reagents at the heterocyclic oxygen atom, which may indeed be expected. The 4-pyrones react readily with nucleophilic reagents at the C-2 ring carbon atom, and may then undergo ring-opening, which may upon ring-closure yield a new heterocycle. For example, 2,6-dimethyl-4-pyrone reacts readily with methylamine to form 1,2,6-trimethyl-4-pyridone.[10] A common pyrone, 2,6-dimethyl-4-pyrone may be prepared in aqueous solution from dehydroacetic acid and hydrochloric acid in this manner.[70] Reactions involving the carbonyl oxygen atom include alkylation, acylation, and protonation.[71,72] Based upon molecular magnetic susceptibility anisotropies,[73] microwave spectra,[74] and dipole-moment results,[75-77] the

pyrones have been classified as non-aromatic. The pyrones readily form pyrillium salts,[74,78-80] undergo condensation reactions at the carbonyl oxygen atom,[16,81,82] form pyrathiones and selenium analogs,[83] form metal complexes,[84] and undergo photodimerization.[85]

CHAPTER III

EXPERIMENTAL

Materials

The materials used in synthetic procedures and spectral determinations, their grades, and manufacturers are as follows:

Material	Grade*	Manufacturer
Chloroform	N.F.	J.T. Baker
Methyl iodide	A.R.	J.T. Baker
Phosphorus pentoxide	A.R.	J.T. Baker
Sodium bicarbonate	A.R.	J.T. Baker
Ethyl bromide	A.R.	J.T. Baker
n-Butyl bromide	A.R.	J.T. Baker
n-Octyl bromide	A.R.	J.T. Baker
Sulfur dioxide (anhy)	A.R.	J.T. Baker
t-Butyl bromide	A.R.	Eastman Kodak
Dehydroacetic acid	A.R.	Eastman Kodak
Phosphorus pentachloride	A.R.	Eastman Kodak
Phosphorus oxychloride	A.R.	Eastman Kodak
Methyl amine (40% aq.)	A.R.	Matheson, Coleman, Bell
Sodium metal	A.R.	Matheson, Coleman, Bell
Thionyl chloride	A.R.	Matheson, Coleman, Bell
Diethyl ether	A.R.	Fisher Scientific

Ammonium hydroxide	A.R.	Matheson Scientific
Ammonia (anhy.)		Airco, Inc.
Deuterium oxide	A.R.	Merck, Sharp, and Dohme
Deuterochloroform	A.R.	Norell Chemical
Deuterated dimethyl sulfoxide	A.R.	Stohler Isotope Chemicals
Trifluoroacetic acid	A.R.	Aldrich Chemical
Methyl alcohol	A.R.	Burdick & Jackson Laboratories
Tetramethylsilane (TMS)	A.R.	Thompson Packard Inc.
3(Trimethylsilyl)-1-propane sulfonic acid (DSS)	A.R.	Aldrich Chemical

* Based upon: N.F. = National Formulary

A.R. = Analytical Reagent

All elemental analysis were performed by M-H-W Laboratories, Garden City, Michigan 48135. Samples dried in vacuo in an Abderhalden apparatus had phosphorus pentoxide as the dessicant, and benzene was used to maintain a constant temperature of 80°. The pressure within the drying chamber was maintained at about 1 mm using a vacuum pump, manometer, and bleeder valve.

All melting points were taken using a Thomas-Hoover Melting-point apparatus supplied by the Arthur Thomas Co., Philadelphia, Pa., and are uncorrected.

1,2,6-Trimethyl-4-pyridone (I)

This compound was prepared by modification of the procedure of Cook.[10] In a 250 ml Erlenmeyer flask, 33.6 g (0.2 mole) of dehydroacetic acid was mixed with 150 ml (1.46 mole) of methyl amine (40% aq.). The mixture was gently heated over steam for 1 hour, and copious effervesence was observed. The product was filtered and recrystallized five times from water. The purified material was then dried in vacuo for 24 hours in an Abderhalden apparatus, yielding 30.0 g (79.2%) of product, m.p. = 246°, (lit = 244-246°)[86]; nmr ($CDCl_3$) δ 6.07 (s,2,c-H), 3.46 (s,3,N-CH_3), 2.27 (s,6,C-CH_3). The nmr spectra in other solvents are found in Table 1, and the infrared spectra in Table 2.

2,6-Dimethyl-4-pyridone (VII)

This compound was prepared from a modification of the procedure of Hraby.[11] To a 250 ml 3-neck flask equipped with a mechanical stirrer and reflux condenser, 16.8 g (0.1 mole) of dehydroacetic acid was reacted with 119 g (2.0 mole) of ammonium hydroxide (28.8% NH_3). A yellowish solution resulted which thickened considerably with continued stirring, gassing vigorously as the reaction proceeded. Another 50 ml of ammonium hydroxide was added, and the mixture was gently refluxed for 30 hours. The resulting yellowish solution was allowed to cool, and

ammonia gas was slowly bubbled through the solution for another 6 hours with continued stirring. The solution was reduced to 1/3 the original volume under reduced pressure, and chilled. The pale-brown crude product was removed by filtration while cold, and recrystallized twice from water. The purified material, slightly off-white in color was then dried in vacuo in an Abderhalden apparatus for 24 hours, mp = 225-227°d, (lit = 227-229°); nmr ($CDCl_3$) δ 12.5 (s(broad),1,N-H), 6.14 (s,2,C-H), 2.37 (s,6,C-CH_3). The infrared spectra are found in Table 2.

1,2,6-Trimethyl-4-methoxypyridinium iodide (II)

A. From 1,2,6-Trimethyl-4-pyridone

To a 100 ml round-bottom flask equipped with reflux condenser and drying tube was added 1.3709 g (0.01000 mole) of 1,2,6-Trimethyl-4-pyridone (I),3.1 ml methyl iodide, (0.05 mole), and 30 ml chloroform. The mixture was refluxed for 48 hours, and upon cooling a small amount of white crystals were removed by filtration, yielding 0.5559 g (19.9%). The chloroform solution remaining was evaporated to dryness, and the yellowish crystals resulting were purified by recrystallization from chloroform, yielding 1.1046 g (39.6%) of white crystals. The two samples were dried in vacuo in an Abderhalden apparatus for 24 hours, their melting points identical, mp = 195-205°d, nmr ($CDCl_3$) δ 7.21 (s,2,C-H), 4.10 (s,6,-N-CH_3 & O-CH_3);

2.88 (s,6,C-CH_3). Additional nmr spectra in various solvents are found in Table 1, and the infrared spectra in Table 2.

Anal. Calcd for $C_9H_{14}NOI$; C,38.73; H,5.06; I,45.47. Found: C,38.66; H,5.28; I,45.63.

B. From 2,6-Dimethyl-4-methoxypyridine

To a 25 ml flask equipped with reflux condenser and drying tube, was added 0.5974 g (0.0044 mole) of 2,6-Dimethyl-4-methoxypyridine (III), 1.4 ml (0.0219 mole) of methyl iodide, and 15 ml chloroform. A small amount of crystal immediately formed. The mixture was refluxed for 24 hours, and the chloroform removed in vacuo. The yellowish crystals were purified by recrystallization form chloroform and hexane and dried in an Abderhalden apparatus in vacuo for 24 hours, yielding 0.6102 g (50.2%) of white crystals, mp = 195-205°d. The nmr and infrared spectra were identical to those obtained from procedure A.

1,2,6-Trimethyl-4-ethoxypyridinium bromide (IV)

To a 100 ml round-bottom equipped with reflux condenser and drying tube, was added 0.8968 g (0.0036 mole) of 1,2,6-trimethyl-4-pyridone (I), 2.4 ml (0.0327 mole) ethyl bromide, and 25 ml chloroform. The mixture was refluxed for 48 hours and the chloroform removed in vacuo. The white crystalline product was recrystallized twice from chloroform and hexane, and dried in vacuo in an Abderhalden

apparatus for 24 hours, yielding 1.0350 g (64.3%) of white crystals mp = 195-200°; nmr ($CDCl_3$) δ 7.40 (s,2,C-H); 4.42 (q,2,OC_2H_5); 4.14(s,3,N-CH_3); 2.88 (s,6,C-CH_3); 1.46 (t,3,OC_2H_5). The infrared spectra are found in Table 2.

Anal Calcd. for $C_{10}H_{16}NOBr$: C,48.74; H,6.56; Br,32.46.

Found: C,48.76; H,6.66; Br,32.41.

1,2,6-Trimethyl-4-butoxypyridinium bromide (XIV)

To a 100 ml round-bottom flask equipped with reflux condenser and drying tube, was added 1.3707 g (0.01000 mole) of 1,2,6-trimethyl-4-pyridone (I), 5.37 ml (0.05 mole) of n-bromobutane, and 20 ml chloroform. The mixture was refluxed for 72 hours, and the chloroform removed in vacuo. The white product was recrystallized twice from chloroform and hexane, and dried in vacuo in an Abderhalden apparatus for 24 hours, yielding a white crystalline product; nmr ($CDCl_3$) δ 7.23 (s,2,C-H); 4.25 (m,2,O-C_4H_9); 4.05 (s,3,N-CH_3); 2.80 (s,6,C-CH_3); 1.63 (m,4,O-C_4H_9); 0.93 (m,3,O-C_4H_9). The infrared spectra are found in Table 2.

1,2,6-Trimethyl-4-octyloxypyridinium bromide

To a 100 ml round-bottom flask equipped with reflux condenser and drying tube, was added 1.3702 g (0.05 mole) of 1,2,6-trimethyl-4-pyridone (I), 8.6 ml (0.05 mole) of n-bromooctane, and 20 ml chloroform. The mixture was

refluxed for 48 hours, and the chloroform removed *in vacuo*, yielding a white product, mp = 131-133°.

Reaction of 1,2,6-Trimethyl-4-pyridone with Thionyl chloride: 1,2,6-Trimethyl-4-chloropyridinium chloride (XII)

To a 100 ml 3-neck flask equipped with reflux condenser, drying tube, and addition funnel, was added 0.4411 g (0.0032 mole) of 1,2,6-trimethyl-4-pyridone (I) and 30 ml chloroform. From the additional funnel, 2.3 ml (0.032 mole) of thionyl chloride was slowly added to the solution. The flask rapidly warmed upon addition of the thionyl chloride, and crystals immediately formed. The mixture was refluxed for 36 hours, and the crystals removed by filtration and washed three times with chloroform. The product was dried for 24 hours *in vacuo* in an Abdenhalden apparatus, yielding white crystals, mp = 277-279°; nmr (SO_2) δ 7.13 (s,2,C-H); 3.89 (s,3,-N-CH_3); 2.68 (s,6,C-CH_3). The infrared spectrum is found in Table 2.

Reaction of 1,2,6-Trimethyl-4-pyridone with t-butyl bromide: 1,2,6-Trimethyl-4-hydroxypyridinium bromide (X)

To a 25 ml round-bottom flask equipped with reflux condenser and drying tube, was added 0.6874 g (0.005 mole) of 1,2,6-trimethyl-4-pyridone (I), 2.8 ml (0.025 mole) of t-butyl bromide, and 12 ml chloroform. After refluxing for 1½ hours, a considerable amount of long needle-like crystals, pale white in color, had formed in the flask.

These were removed by filtration, washed three times with chloroform, and dried in vacuo in an Abderhalden apparatus for 24 hours, a pale white crystalline product resulted, mp = 280-282°d; nmr (SO_2) δ 7.19(s,2,C-H); 5.42 (s,1,O-H); 3.95 (s,3,N-CH_3); 2.73 (s,6,C-CH_3). An additional nmr spectrum is found in Table 1.

Anal Calcd for $C_8H_{12}NOBr$: C,44.06; H,5.55; Br,36.64.

Found: C,44.03; H,5.53; Br,36.39

2,6-Dimethyl-4-chloropyridine (VI)

This compound was prepared by modification of the synthesis developed by Wilbaut and Brockman.[53] To a 100 ml flask equipped with reflux condenser and drying tube was added 15.0 g (0.0719 mole) phosphorus pentachloride and 9.0 ml (0.0977 mole) of phosphorus oxychloride. The mixture was heated until all the phosphorus pentachloride dissolved, and the solution allowed to cool to room temperature. After removal of the drying tube from the top of the reflux condenser, 13.5 g (0.1090 mole) of 1,2,6-trimethyl-4-pyridone (I) was slowly added through the condenser. The pyridone reacted vigorously, warming the flask considerably. The drying tube was replaced, and the mixture was then allowed to cool and chilled in ice. After slow addition of 25 ml of water, a dark-brown solution resulted.

The flask was removed and 45.5 g (0.542 mole) of sodium bicarbonate was slowly added with stirring for neutralization. The mixture bubbled vigorously, and a heavy brown oil formed in the flask as the sodium bicarbonate was added. After cessation of gassing, the 2-layered mixture was transferred to a liquid-liquid extractor, and the crude product extracted with diethyl ether in 48 hours. The dark-brown ether layer was dried over anhydrous magnesium sulphate, followed by removal of the ether *in vacuo*. Fraction distillation under reduced pressure yielded 10.04 g (72%) of clear product, bp = 85-86° at 40 mm (lit. bp = 69-70° at 20 mm), n_D=1.5180; nmr: ($CDCl_3$) δ 6.89 (s,2,C-H), 2.48 (s,6,C-CH_3). The infrared spectrum is found in Table 2.

Reaction of 2,6-Dimethyl-4-chloropyridine (VI) with t-butyl bromide: 2,6-Dimethyl-4-chloropyridinium bromide

To a 25 ml round-bottom flask equipped with reflux condenser, was added 0.7148 g (0.005 mole) of 2,6-dimethyl-4-chloropyridine (VI), 2.8 ml (0.025 mole) of t-butyl bromide, and 12 ml chloroform. The mixture was refluxed for 18 hours, during which time small white crystals slowly formed. The crystals were removed by filtration and washed with cold chloroform. The white crystalline product was dried *in vacuo* in an Abderhalden apparatus,

mp = 286-288°d.; nmr ($CDCl_3$) δ 7.46 (s,2,C-H); 3.04 (s,6,C-CH_3). Additional product slowly crystallized out of solution over 72 hours at 0. The spectra were identical to those of the first crystals. The nmr spectra in other solvents are found in Table 1, and the infrared spectra in Table 2.

2,6-Dimethyl-4-methoxypyridine (III)

By modification of the synthesis procedure used by Kato and Hamaguchi,[45] this compound was prepared by reacting 8.0 g (0.0565 mole) of 2,6-dimethyl-4-chloropyridine (VI), and 1.4 g sodium metal dissolved in 40 ml anhydrous methanol. The mixture was refluxed for 72 hours in a 100 ml round-bottom flask equipped with reflux condenser and drying tube. The methanol was removed by flash-distillation, and the crude product extracted with diethyl ether from the oil and salt mixture remaining. The ether was removed by fractional distillation under reduced pressure. Three fractions were isolated, the first at 84-88° (20 mm) (unreacted 2,6-dimethyl-4-chloropyridine), the second fraction at 96-99° (mixture of product and reactants), and the third fraction at 112-115° (20 mm), yielding 1.2696 g (16.7%) clear viscous oil, n_D=1.5125; nmr ($CDCl_3$) δ 6.45 (s,2,C-H); 3.81 (s,3,O-CH_3); 2.48 (s,6,C-CH_3). The infrared spectrum is found in Table 2.

2,6-Dimethyl-4-methoxypyridinium bromide

To a 50 ml round-bottom flask equipped with reflux condenser and drying tube, was added 0.5693 g (0.0042 mole) of 2,6-dimethyl-4-methoxypyridine (III), 2.4 ml (0.0208 mole) of t-butyl bromide, and 15 ml chloroform. The mixture was refluxed for 24 hours, and the crude pale-yellow product recovered by evaporation of the chloroform under reduced pressure. The product was recrystallized from a mixture of chloroform and hexane and dried in vacuo in an Abderhalden apparatus, yielding white crystals, mp = 201-203°; nmr ($CDCl_3$) δ 6.92 (s,2,C-H); 4.04 (s,3,O-CH_3); 2.9 (s,6,C-CH_3); the N-H peak was unobservable. Additional nmr spectra are found in Table 1, and infrared spectra in Table 2.

1-Ethyl-2,6-dimethyl-4-methoxypyridinium bromide

To a 10 ml round-bottom flask equipped with a reflux condenser, was added 0.2 ml of 2,6-dimethyl-4-methoxypyridine (III), and 5.0 ml (0.067 mole) ethyl bromide. The mixture was refluxed for 72 hours, and the product slowly crystallized out. The very small amount of product was dried in vacuo for 24 hours. Due to the small amount of product, only an nmr spectrum was obtained; nmr ($CDCl_3$) δ 7.52 (s,2,C-H), 4.62 (q,2,N-CH_2-); 4.16 (s,3,O-CH_3), 2.95 (s,6,C-CH_3); 1.48 (t,3,N-CH_2-CH_3).

Reaction of 2,6-Dimethyl-4-pyridone with methyl iodide

In an nmr tube containing about 0.05 g (4.06×10^{-4} mole) of 2,6-dimethyl-4-pyridone was added 0.05 ml (8.03×10^{-4} mole) of methyl iodide and 1.0 ml deuterochloroform. The nmr tube was sealed, and the mixture reacted in a constant temperature bath, constructed from a 250 ml 3-neck flask equipped with a reflux condenser in one neck, a thermometer adapter (Teflon) in another neck, and a glass plug in the third neck. The flask was filled about 75% full of chloroform, and the nmr tube placed within the adapter. The chloroform refluxed, and the nmr tube removed every 24 hours for an nmr spectral determination (after cooling to room temperature), however, a slow reaction occurred while under reflux, equilibrating after 96 hours. The nmr shifts of the product are: nmr ($CDCl_3$) δ 13.4 (s,(broad), 1,N-H); 6.95 (s,2,C-H); 4.09 (s,3,O-CH_3); 2.85 (s,6,C-CH_3).

Reaction of 1,2,6-Trimethyl-4-pyridone with methyl bromide: 1,2,6-Trimethyl-4-methoxypyridinium bromide (XI)

To a 10 ml Erlenmeyer flask was added 0.25 ml of 2,6-dimethyl-4-methoxypyridine (III). Methyl bromide, generated by the reaction of methyl alcohol, phosphoric acid, and sodium bromide in another flask, was bubbled through (III) for 2 hours. The resulting product was recrystallized from chloroform, yielding white crystals,

mp = 185°d.; nmr ($CDCl_3$) δ 7.38 (s,2,C-H); 4.11 (s,6,N-CH_3 & O-CH_3); 2.86 (s,3,C-CH_3). The infrared spectrum is found in Table 2.

Spectral Determinations

All nmr spectra were obtained on a Varian EM-360 spectrometer, using 5% TMS as an internal reference in all organic solvents, and 5% w/v DSS as an internal standard when deuterium oxide was used. All samples were prepared in a concentration of about 5% w/v. The instrumental settings used were: Amplitude, 100x; filter, 0.1 sec.; RF gain, 0.05 mG; sweep time, 5 min.; end of sweep, 0.0 ppm; sweep width, 10.0 ppm (sweep width expanded when necessary). The nmr tubes were supplied by the Wilmad Glass Co., Buena, N.J. 08310.

The infrared spectra were obtained on a Beckman IR-12 spectrophotomer in the double-beam mode with speed suppression. The instrumental settings were: gain, 10.60; period, 2; SB/DB ratio, 1 : 1; chart speed, 40 cm^{-1}/sec. Samples as solids were prepared as duplicate mulls, in Nujol and hexachlorobutadiene respectively, and placed upon sodium chloride plates supplied by International Crystal, Irvington, N.J. 07111. Samples in solution were prepared 30% w/v as aqueous samples, and 5% w/v in organic

solvents. The liquid cells were supplied by Perkin-Elmer Corp., Norwalk, Conn., trade name "Irtran," 0.1 mm pathlength. All elemental analysis were performed by M-H-W Laboratories, Garden City, Michigan 48135.

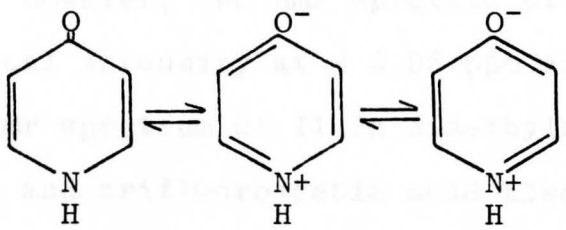
CHAPTER IV

RESULTS AND DISCUSSION

The alkylation of 4-pyridones has not previously been investigated, although protonation and acylation studies have been conducted. The reaction of alkyl halides with 4-pyridones may involve either alkylation on the nitrogen atom via the Menschutkin reaction,[34] or alkylation of the oxygen atom as in the Williamson ether synthesis.[35] Either reaction leads to quaternization of the nitrogen atom, and proceeds as a bimolecular nucleophilic substitution (S_N2 mechanism) as in equation 12.

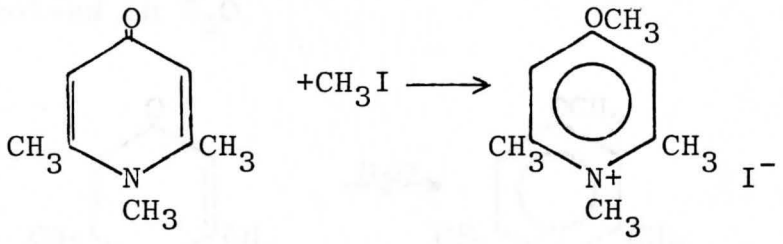
$$\underset{\text{N=nucleophile}}{N:} + RX \quad \overset{\delta+ \quad \delta+ \quad \delta-}{N\text{---}R\text{---}X} \quad N^{+}\text{—}R + X^{-} \qquad (12)$$

In the 4-pyridone molecule, the existence of two strongly electronegative centers suggests possible alkylation of either the ring nitrogen or the carbonyl oxygen, since three important canonical forms may be written (Eq. 13).

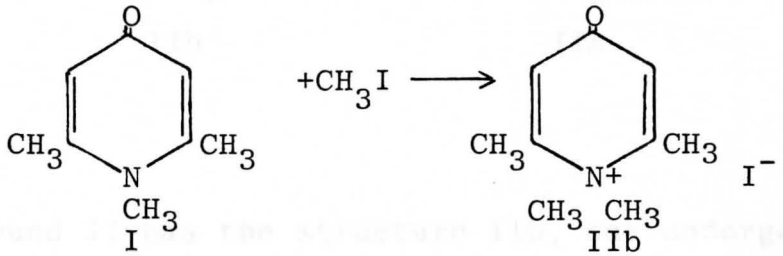


(13)

The reaction of methyl iodide with 1,2,6-trimethyl-4-pyridone (I) would thus be expected to give the O-methylated product (IIa) by equation 14, or the N-methylated product (IIb) by equation 15.



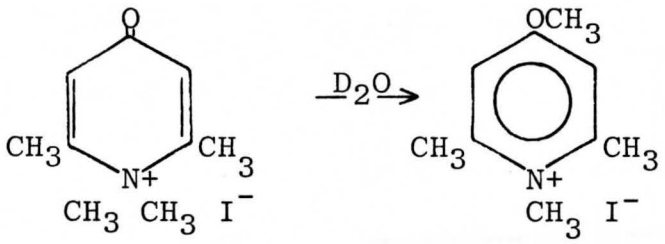
I IIa (14)



I IIb (15)

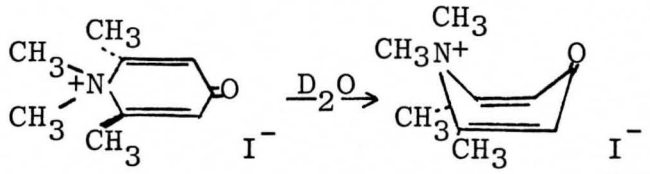
In the present research, methyl iodide reacted with I in chloroform over a period of 48 hours to produce a sparingly soluble salt (iodide), II. The nmr spectrum of this salt had a sharp singlet peak at 4.10 ppm in deuterochloroform, with an integration of 6 protons (Fig.1). This led initially to the assumption that II has the structure IIb. Such an assumption would not be unreasonable, in view of the steric crowding of methyl groups in structure IIa. However, the nmr spectrum of II in D_2O gave two peaks of equal intensity at δ 3.95 ppm and 4.07 ppm. (Fig.2). The nmr spectrum of II in dimethylsulfoxide (d-6), sulfur dioxide, and trifluoroacetic acid also showed two methyl peaks.

There are three possibilities for the difference in spectra between chloroform and other solvents. These are: 1) The methyl iodide reacts initially by equation 15 to form IIb, but rapidly rearranges as shown in equation 16 when dissolved in D_2O.



IIb IIa (16)

2) Compound II has the structure IIb, but undergoes ring-puckering in solvents other than chloroform (Eq. 17), resulting in non-equivalence of the N-CH_3 protons.



(17)

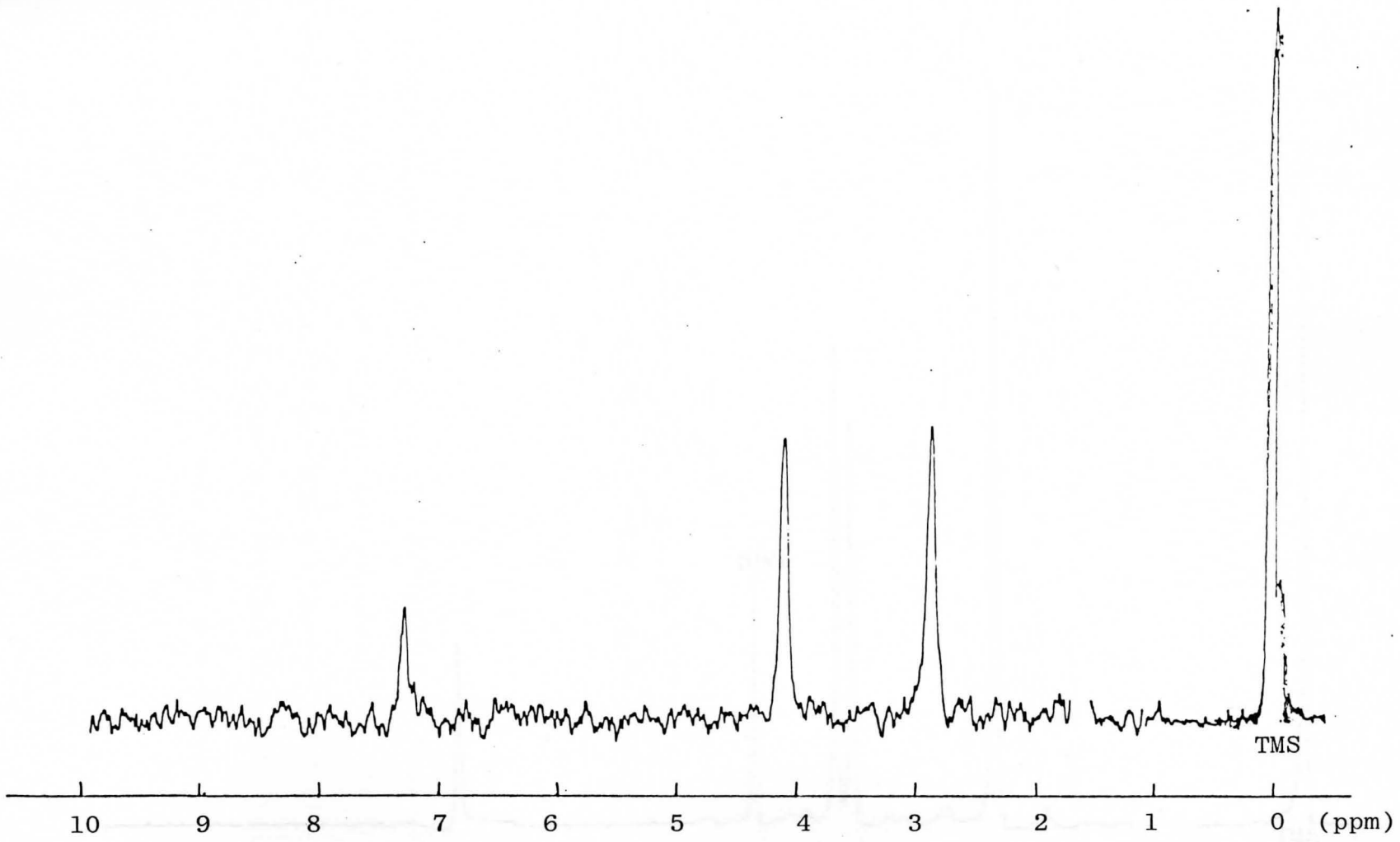


Fig. 1 1,2,6-Trimethyl-4-methoxypyridinium iodide in $CDCl_3$

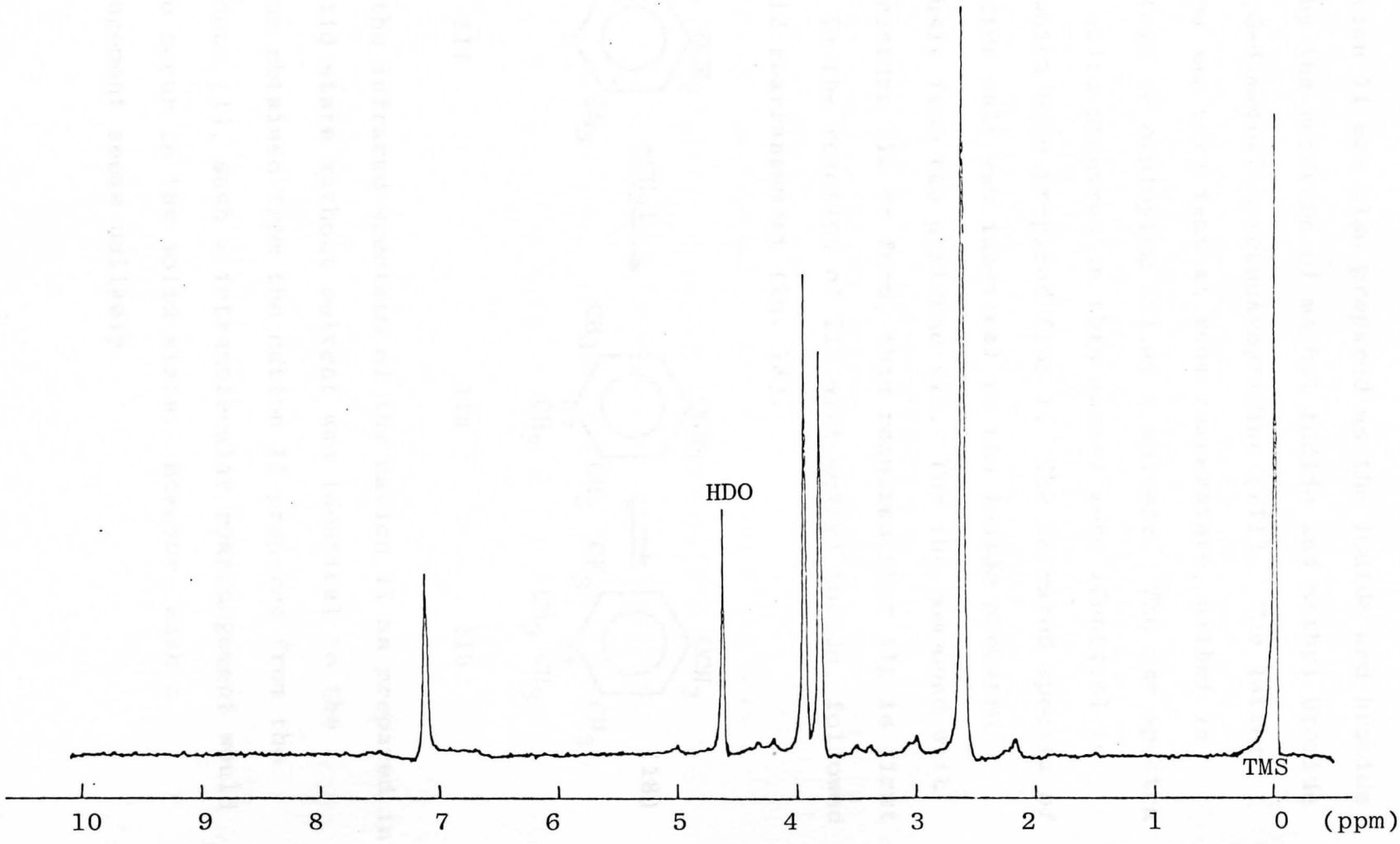
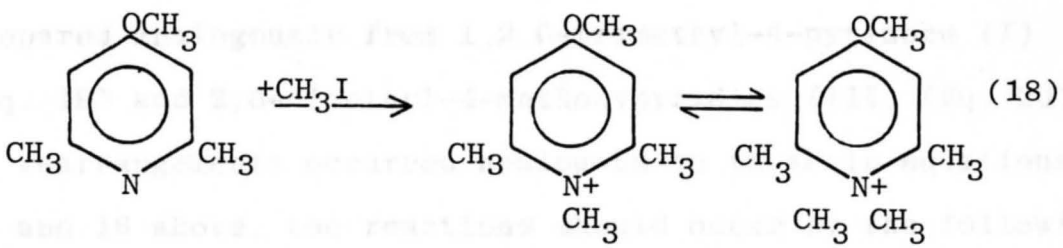


Fig. 2 1,2,6-Trimethyl-4-methoxypyridinium iodide in D_2O

The cation II was also prepared as the iodide and bromide salts by the reaction of methyl iodide and methyl bromide with 2,6-dimethyl-4-methoxypyridine (III). The latter reaction was very fast at room temperature, either in chloroform or employing III as a solvent. The nmr spectra of the salts prepared in this manner were identical to those which were prepared from I. The infrared spectra of the iodide salt was identical to the iodide prepared previously from the pyridone (I). For the compound with the structure IIb to form, this requires that IIa is first formed in the reaction of III with methyl iodide, followed by rapid rearrangement (Eq. 18).



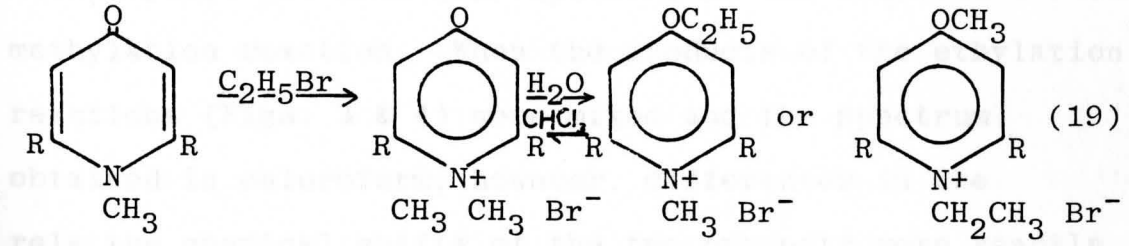
(18)

III IIa IIb

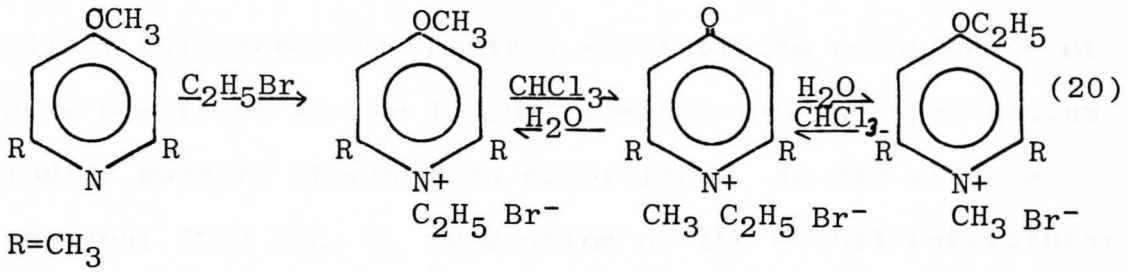
Since the infrared spectrum of the cation II as prepared in the solid state without solvent was identical to the spectrum obtained from the cation II prepared from the 4-pyridone (I), such a intramolecular rearrangement would need to occur in the solid state. However, such a rearrangement seems unlikely.

3) The chemical shifts of N-CH_3 and O-CH_3 protons are identical in chloroform, and the peaks are superimposed; however, non-superimposition occurs in other solvents. The rearrangement discussed in equations 14 and 16, and the ring-puckering in equation 15 appear unlikely, since we have shown that the infrared spectrum of II in the solid state, $CHCl_3$, $CDCl_3$, H_2O and D_2O are essentially identical. (Table 1). Conversely, the exact coincidence of chemical shifts of the N-CH_3 and O-CH_3 peaks seems unlikely. Thus there is a dilemma, and spectroscopic evidence alone does not afford reasonable differentiation between IIa and IIb.

To ascertain whether indeed intramolecular rearrangement had occurred, the ethylated salts were prepared analogously from 1,2,6-trimethyl-4-pyridone (I) (Eq. 19) and 2,6-dimethyl-4-methoxypyridine (III) (Eq. 20). If rearrangements occurred analogous to those in equations 14 and 16 above, the reactions should occur by the following schemes:



R=CH_3 I IVa IVb Va



In equation 19, it is seen that alkylation may proceed with the ethyl group attacking the ring nitrogen, with retention of the N-CH_3 moiety, or possibly rearrangement of both the methyl and ethyl groups. Equation 20 suggests alkylation of the carbonyl oxygen with simultaneous rearrangement again of both the methyl and ethyl substituents. In both equations, the postulated rearrangement in chloroform should yield the identical spectra, as was observed for the methylation reaction. When the products of the ethylation reactions (Figs. 3 & 4) were mixed and the spectrum obtained in chloroform, however, differences in the relative chemical shifts of the two products were readily apparent (Fig. 5). From this, it may be concluded that alkylation proceeds without rearrangement, and the alkylation of 4-pyridones and their N-methyl derivatives should proceed with alkyl attack upon the carbonyl oxygen

atom, and the actual products of equations 19 and 20 are IVb and Va, respectively. Furthermore, the spectrum (Fig.5) indicates an N-CH_3 and O-CH_3 peak separation of only 1 Hz., which corresponds to 0.017 ppm in chloroform. Thus this slight difference in chemical shift proves coincidence of peak positions in the 1,2,6-trimethyl-4-methoxypyridinium iodide spectra observed in chloroform. As may also be apparent from Fig. 5, separation of the methyl substituent on C-2 and C-6 is only 4 Hz., which corresponds to 0.07 ppm, and the methyl groups on the ethyl moieties in both compounds differ by 1 Hz., again corresponding to only 0.017 ppm (analogous to the difference in chemical shifts of the coincidental N-CH_3 and O-CH_3 substituents). In all alkylated compounds, the chemical shifts of the O-CH_3 groups were assigned downfield of the N-CH_3 groups. Although the chemical shifts of Barlin and Benbow[38] for N-methyl-4-methoxypyridinium iodide were tentative (assigning the N-CH_3 group downfield of the O-CH_3 group), it appears that the absence of ring methyl substituents may allow the N-CH_3 group to appear downfield of the O-CH_3 substituent. This may occur, since the ring methyl groups at C-2 and C-6 would minimize a downfield shift of the N-CH_3 moiety due to electron contribution through the ring to the N^+CH_3 group.

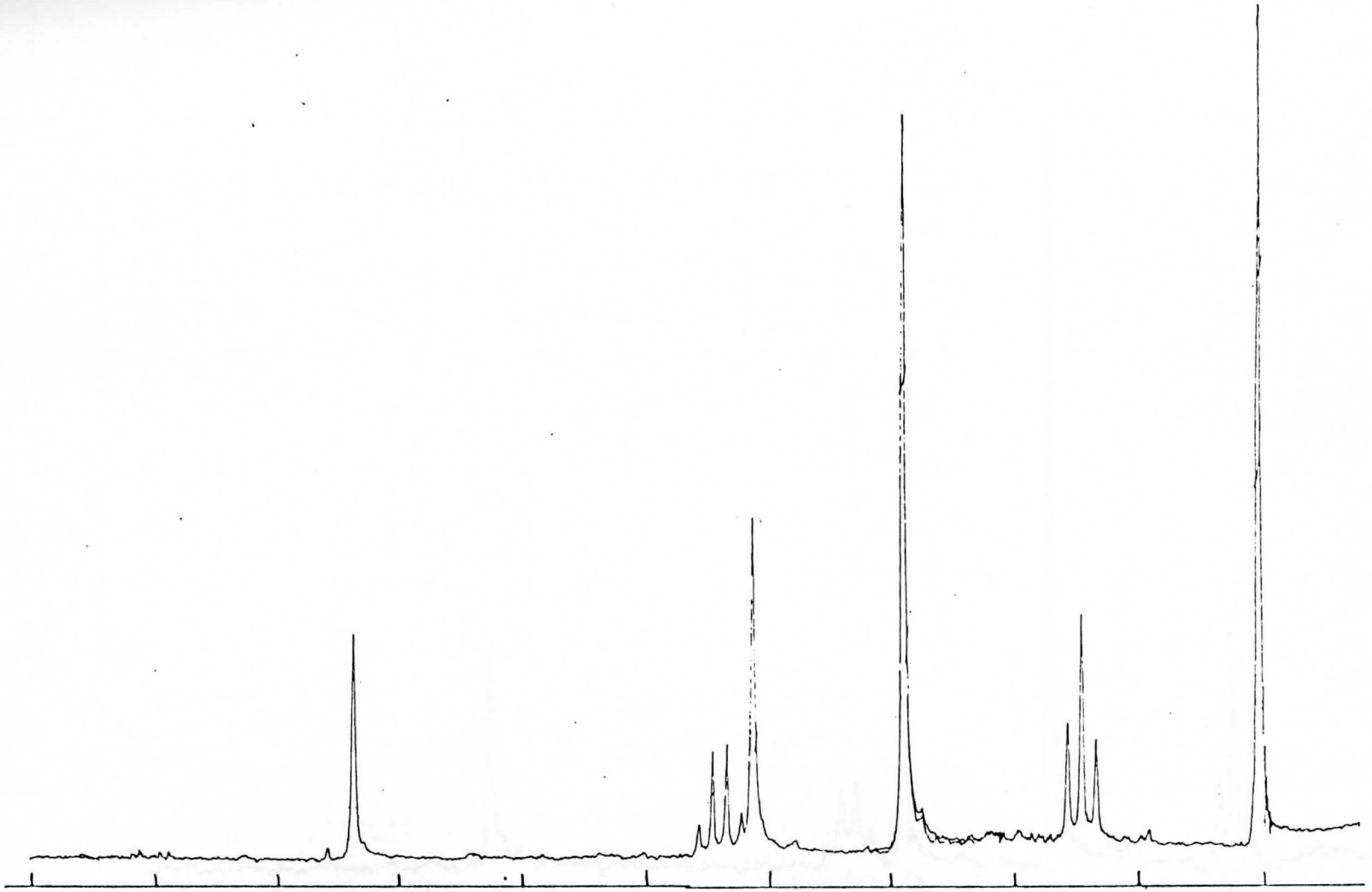


Fig. 3 1,2,6-Trimethyl-4-ethoxypyridinium bromide in $CDCl_3$

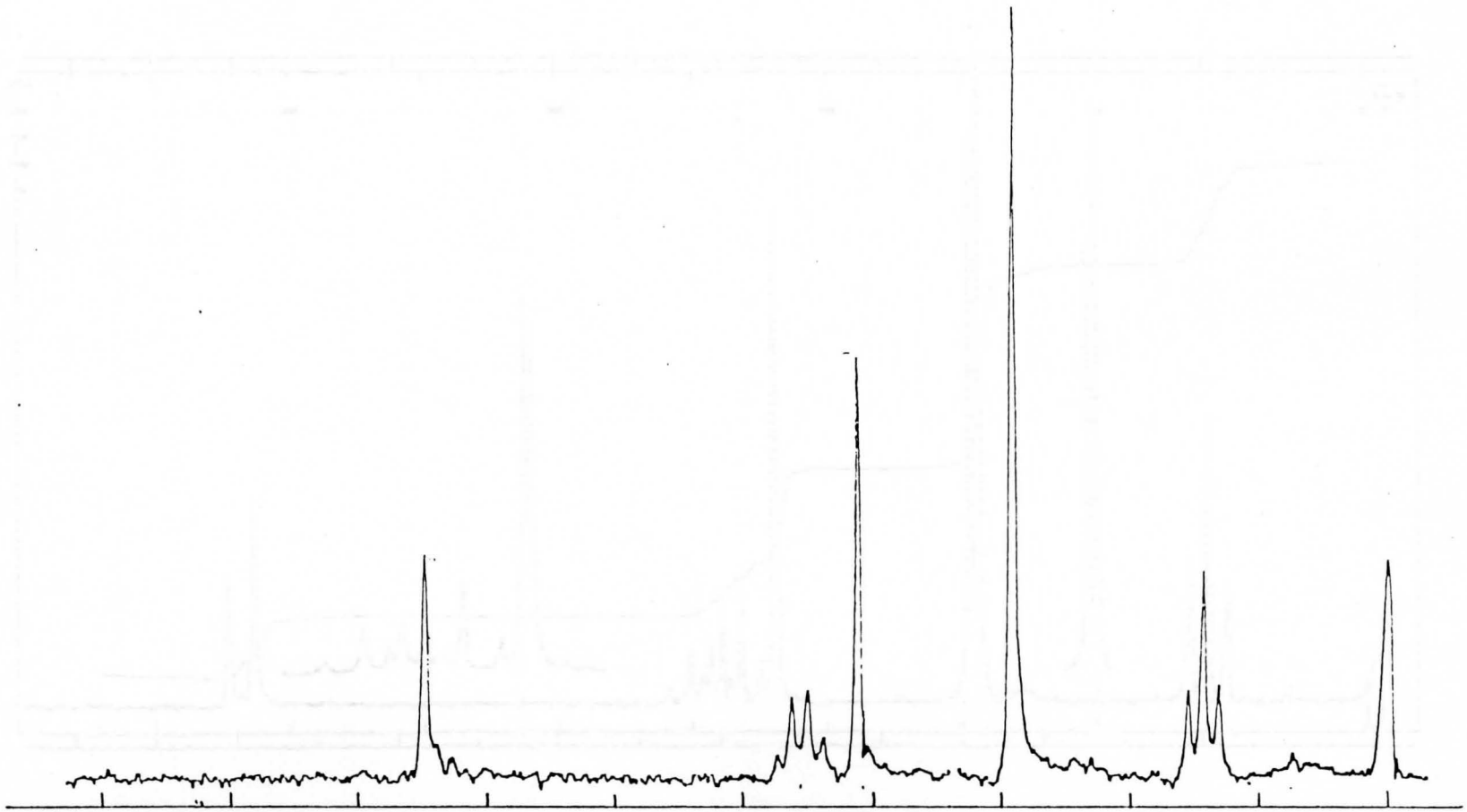


Fig. 4 1-Ethyl-2,6-dimethyl-4-methoxypyridinium bromide in $CDCl_3$

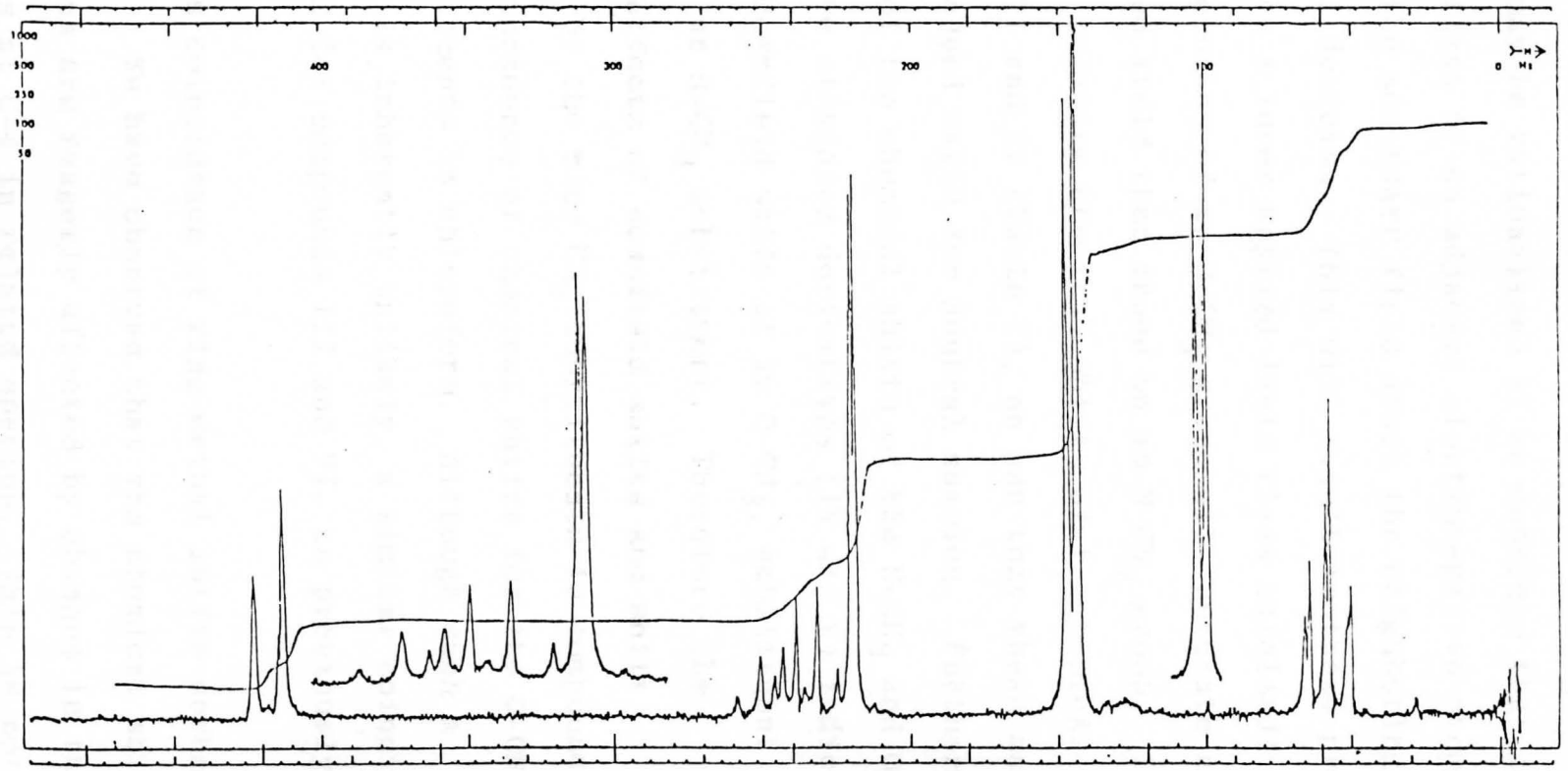


Fig. 5 Mixed Ethylated Compounds

The present tentative assignments ($N-CH_3$ downfield of ($O-CH_3$) may be rationalized if we consider that as the inductive effect of an adjacent electronegative atom increases, the secondary field about the neighboring protons will decrease. This will result in these protons resonating at a lower applied field (less shielded). Thus the methyl protons of an $O-CH_3$ group will resonate at a lower applied field than those on an $N-CH_3$ group. If we observe the relative chemical shifts of the protons in compounds III and VI (Table 1), we see that these assignments are indeed valid for neutral species. Furthermore, inspection of the chemical shifts of the $N-CH_3$ and $O-CH_3$ groups in the ethylated derivatives (IV and V) indicates a relative downfield shift of an $O-CH_3$, substituent relative to an $N-CH_3$ substituent. Therefore the cumulative effects of downfield shifts and shift attenuation by the ring CH_3 substituents in compound II leads to coincidence of chemical shifts for the $O-CH_3$ and $N-CH_3$ substituents in chloroform. Although such a coincidence is inherently unlikely, a similar coincidence has occurred for compounds III and VI, as previously indicated.

This coincidence of ring-methyl shifts perhaps needs explanation. We have observed that the chemical shifts of these protons are meagerly affected by changes in the substituents at C-4 in related species. This is not unexpected, in that changes in the C-4 moieties will

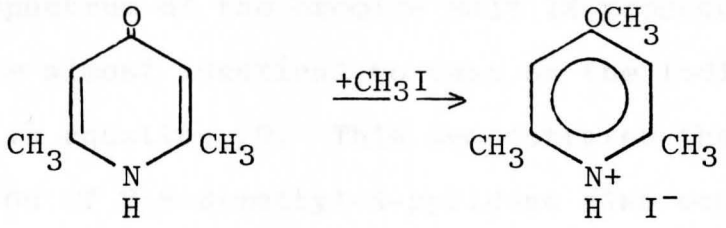
indeed affect the electron density of the molecule, although Wu and Dailey[87] have shown that this effect is not exclusive. Nonetheless, the effect upon the ring methyl groups by π-electron density modification is minimal. However, if the ring currents within related molecular species are varied, this will result in a relative chemical shift in methyl ring substituents due to inductive and mesomeric effects. If we reflect upon the extent of aromaticity of the various neutral species in Table 1, and note their relative chemical shifts in identical solvents, we observe a downfield shift of the ring methyl protons in III or VI, relative to I. This indicates less electron delocalization in I, hence a decreased ring current. This order of aromaticity (III, VI>I) is in agreement with predictions of Stewart and Siddall,[88] and corroborated by dipole-moment information.[75]

If we now examine the relative shifts of the ring protons at C-3 and C-5, it is observed that the ring protons shift downfield as the electronegativities of C-4 substituents increase. This effect correlates well with the relative shifts predicted from σ values (Cl = +0.23, H = 0.00, OCH_3 = -0.27, OH = -0.37);[89] and is also in agreement with shift-correlation predictions calculated from shielding parameters (for compounds without a ring-nitrogen substituent).[90] Analogous to the protonation of pyridine, protonation[91] of III and IV resulted also in the

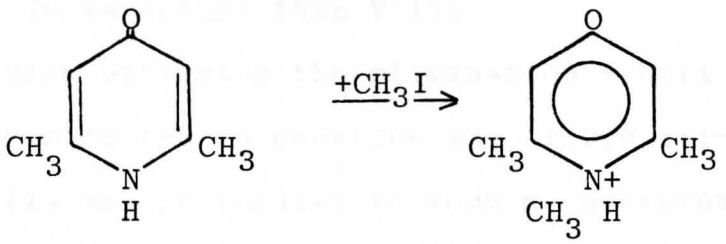
downfield, shift of the ring protons. Thus, the chemical shifts of the compounds studied are in agreement with those of the literature, and show a decrease to a lower field when the order of C-4 substituents are $OH < OCH_3 < H < Cl$. Interestingly enough, however, this trend is reversed for compounds solvated in liquid sulfur dioxide.

If the chemical shifts of the $N-CH_3$ and $O-CH_3$ groups are observed, it is apparent that the relative shift of the $O-CH_3$ substituents are small, not exceeding 0.05 ppm in various solvents (see Table I, compound II). Furthermore, this compound shows that the $N-CH_3$ protons may experience a shift as large as 0.18 ppm. This observation is at variance with a method of identification for $N-CH_3$ protons developed by Ma and Warnhoff,[92] who predicted a downfield shift of only $O-CH_3$ substituents, and no significant shift of $N-CH_3$ substituents when solvents of varying acidities were used.

The reaction of methyl iodide with 2,6-dimethyl-4-pyridone (VII) could give methylation upon the ring carbonyl (Eq. 21) to produce the cation VIIIa as the iodide salt, or on the nitrogen atom (Eq. 22) to produce the cation VIIIb as the iodide salt.

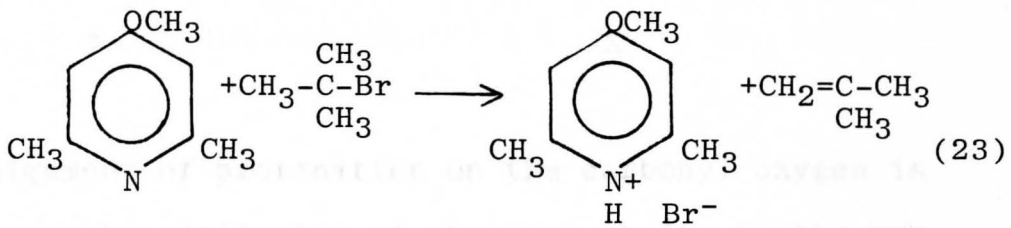


VII VIIa (21)



VII VIIb (22)

The cation IX was prepared (as the bromide salt) by the protonation of 2,6-dimethyl-4-methoxypyridine (III), utilizing an elimination reaction of t-butyl bromide (Eq. 23).

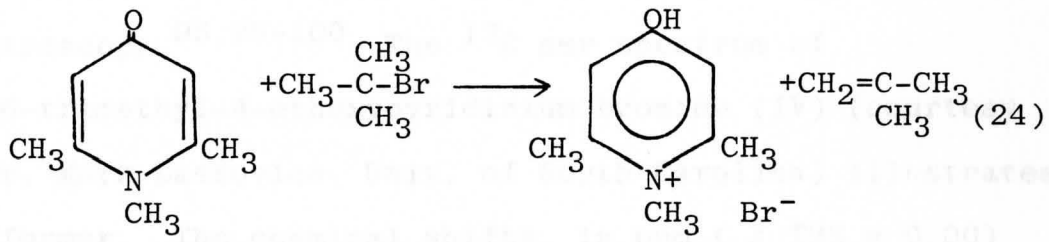


III IX (23)

This reaction provides an exceptionally facile source of anhydrous amine hydrobromides in relatively non-polar media, and avoids possible complications due to excessive HBr.

The nmr spectrum of the bromide salt IX produced in this manner was almost identical to that of the iodide VIII obtained in equation 19. This demonstrates that methylation of 2,6-dimethyl-4-pyridone also occurs on the carbonyl oxygen atom (analogous to previous alkylations), and VIIIa forms rather than VIIIb.

Again utilizing the elimination reaction of t-butyl bromide (as in equation 23), 1,2,6-trimethyl-4-pyridone (I) was protonated to form a quaternary salt (Eq. 24).

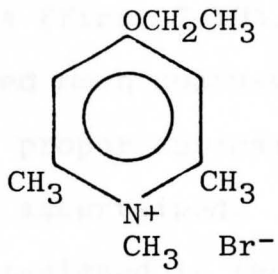


I X

The assignment of protonation on the carbonyl oxygen is based upon the similarity of chemical shifts in the nmr spectra to those of previously prepared compounds, and the similarity in the infrared spectra to that of the hydrochloride salt recorded by Cook.[24] The chemical shift of the OH group is at high field, as would be expected by an enolic proton.[93] A curious feature of the protonated compounds prepared are the insolubilities of the O-protonated species in $CDCl_3$, whereas the N-protonated

species (Ex. VIII) are quite soluble in $CDCl_3$. It appears that protonation occurs only on oxygen both in aqueous solution,[24] and in relatively non-polar solvents as found by the present research.

The nmr spectra of nuclei other than ^1H have been utilized in the study of 4-pyridone and its derivatives. Determination of the molar ratios of the equilibrium tautomers of 4-pyridones,[94-95] as well as relative shifts and coupling constants[94-97] resulted from ^{14}N nmr. Further corroboration of structural determinations and equilibrium constants have been achieved by employing ^{13}C nmr spectroscopy.[95,98-100] The ^{13}C nmr spectrum of 1,2,6-trimethyl-4-ethoxypyridinium bromide (IV) (courtesy of Dr. Mark Laskovics, Univ. of South Carolina) illustrates the former. The chemical shifts, in ppm (δ, TMS = 0.00) and their tentative assignments are as follows (Fig.6):



IV

$CDCl_3$: 14.25, $CH_2\underline{C}H_3$; 22.64, ring CH_3; 39.96, N-$\underline{C}H_3$; 67.25, $\underline{C}H_2CH_3$; 113.50, C-3 & C-5; 155.66, C-2 & C-6; 168.94, C-4.

D_2O: 20.20, $CH_2\underline{C}H_3$; 28.01, ring CH_3; 45.05, N-$\underline{C}H_3$; 73.24, $\underline{C}H_2CH_3$; 119.26, C-3 & C-5; 163.34, C-2 & C-6; 175.41, C-4.

Fig.6 ^{13}C nmr shifts in ppm.(δ,TMS=0.00) of 1,2,6,-trimethyl-4-ethoxy-pyridinium bromide in $CDCl_3$ and D_2O.

In view of the assignments of the chemical shifts of substituted pyridine and pyridinium compounds found in the literature,[95,101] these assignments are not unreasonable.

The infrared spectra of substituted 4-pyridone and its derivatives show a remarkable similarity to the spectra of substituted pyridines (Figs. 7-10). At first inspection, these resemblances caused much confusion, in that from the infrared spectra alone, proper assignment of the site of alkylation could not be ascertained. If a carbonyl band could be unambiguously assigned in the alkylated salts, then definite proof of nitrogen alkylation would be established. Furthermore, the absence of the carbonyl in polar solvents would indicate possible alkyl migration in the solution phase, and thus conveniently resolve the unexplained early nmr results. At best, conclusive assignment of the major infrared bands in the alkylated derivatives of 4-pyridone appeared tenuous.

The proper assignment of the carbonyl band in 4-pyridone and N-methyl-4-pyridone was controversial for years. Analogous to 4-pyrones, two bands existed in the 1650-1550 cm^{-1} region which were not clearly assigned. The higher-frequency band at 1640 cm^{-1} had been assigned to a carbonyl stretching mode (ν CO), and the lower frequency band at 1560 cm^{-1} assigned to a ring-mode stretch (ν CC), similar to that found in benzene.[102] Due to possible coplanarity of the N-R moiety with the ring a lower bond order, and hence lower frequency of the carbonyl group in pyridones (compared with pyrones) was suggested by Cook.[24] He explained this effect by proposing p-π-type orbital

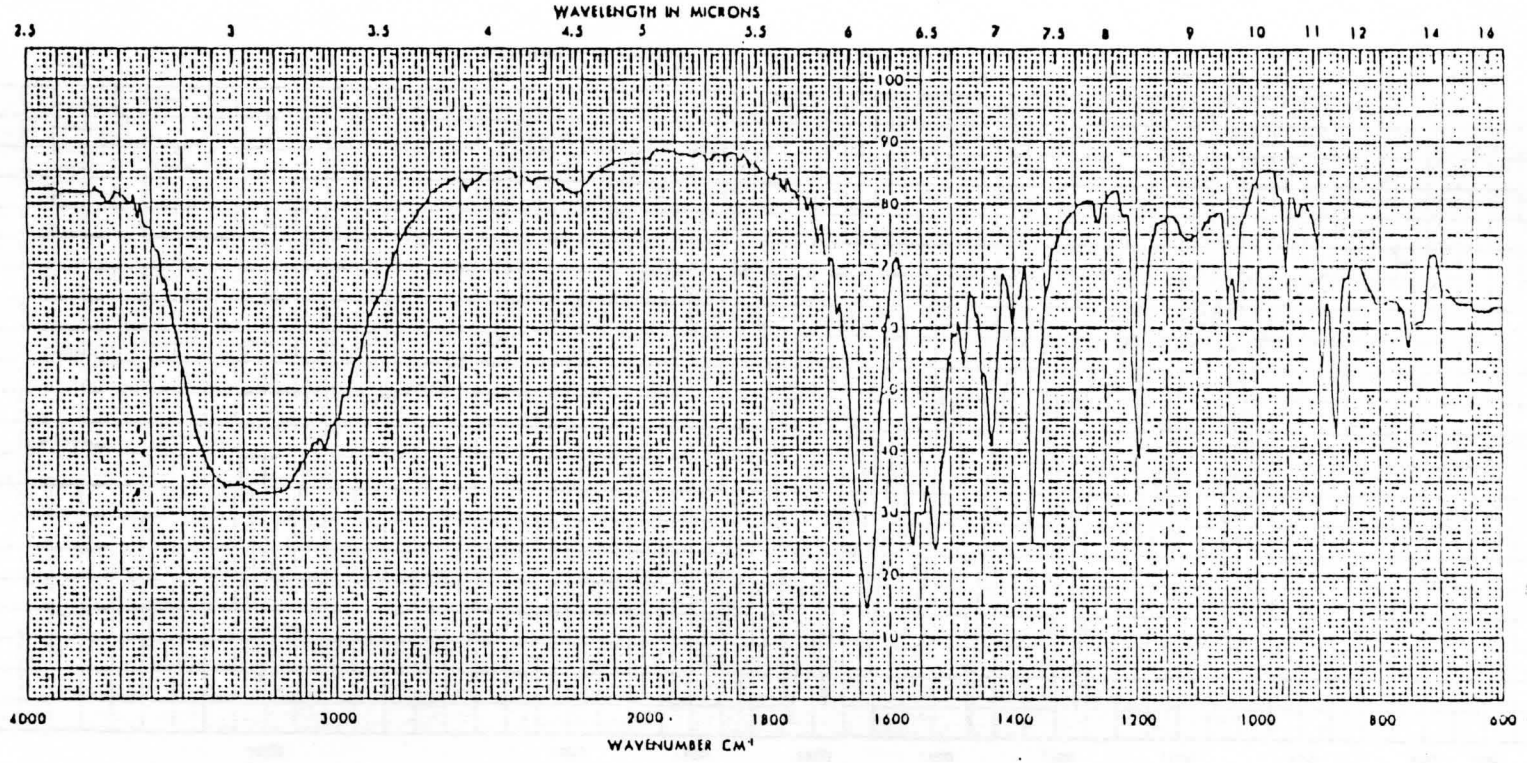


Fig. 7 1,2,6-Trimethyl-4-pyridone (KBr)

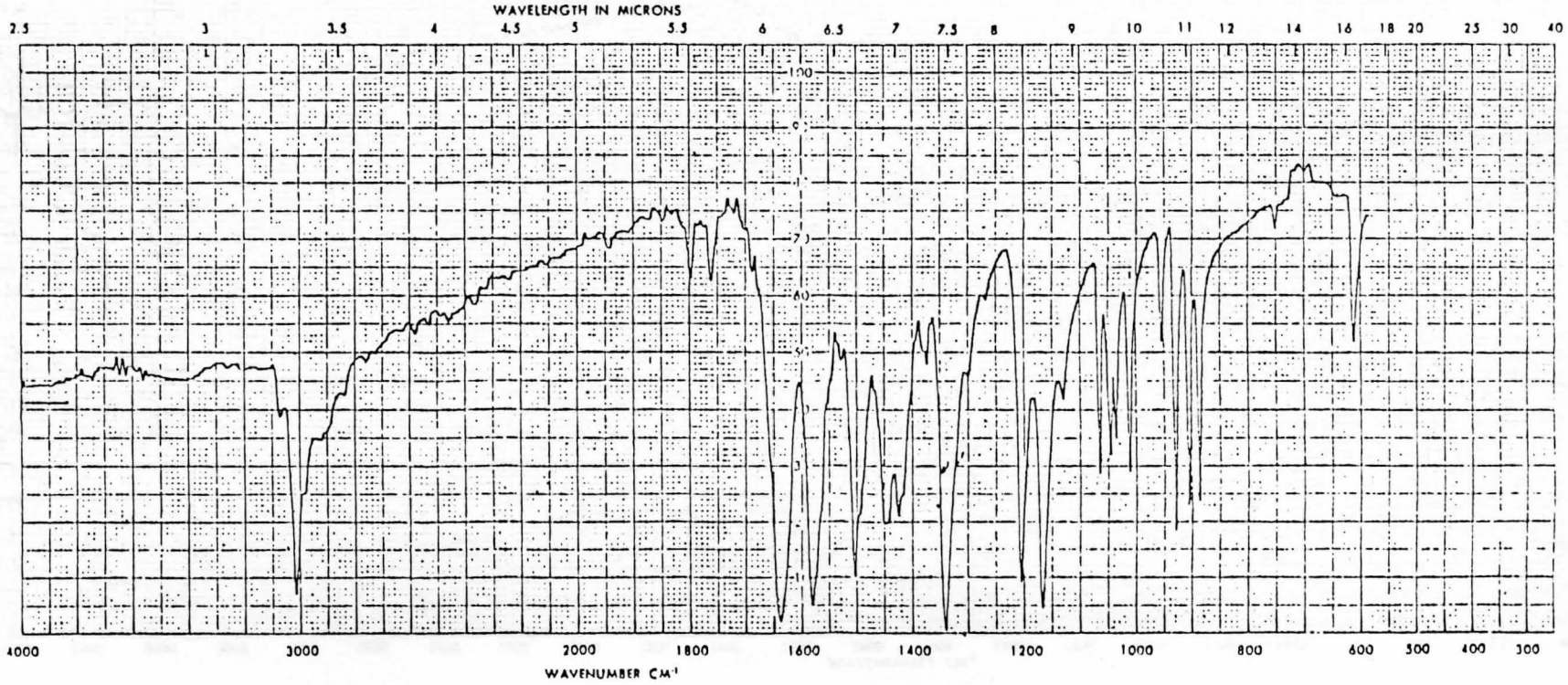


Fig. 8 1,2,6-Trimethyl-4-methoxypyridinium iodide (KBr)

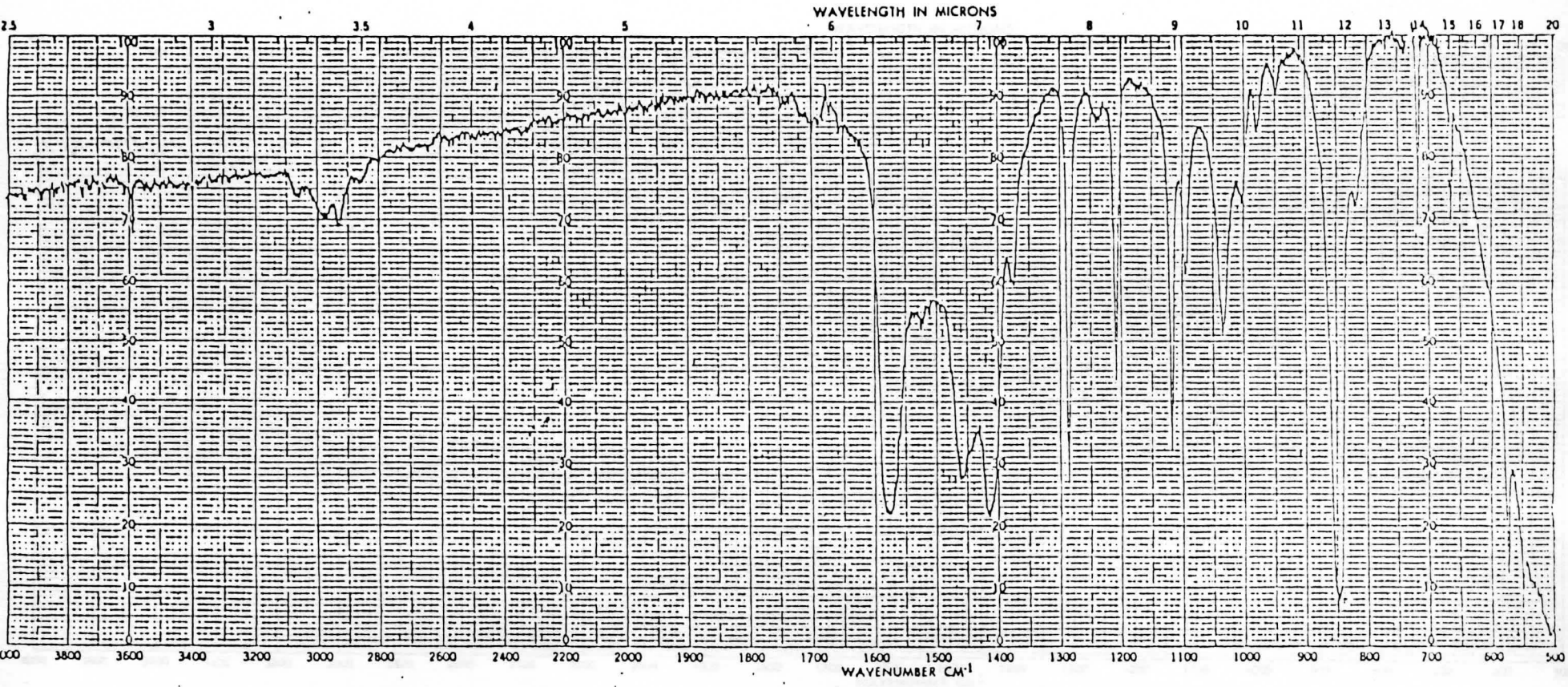


Fig. 9 2,6-Dimethyl-4-chloropyridine (NaCl)

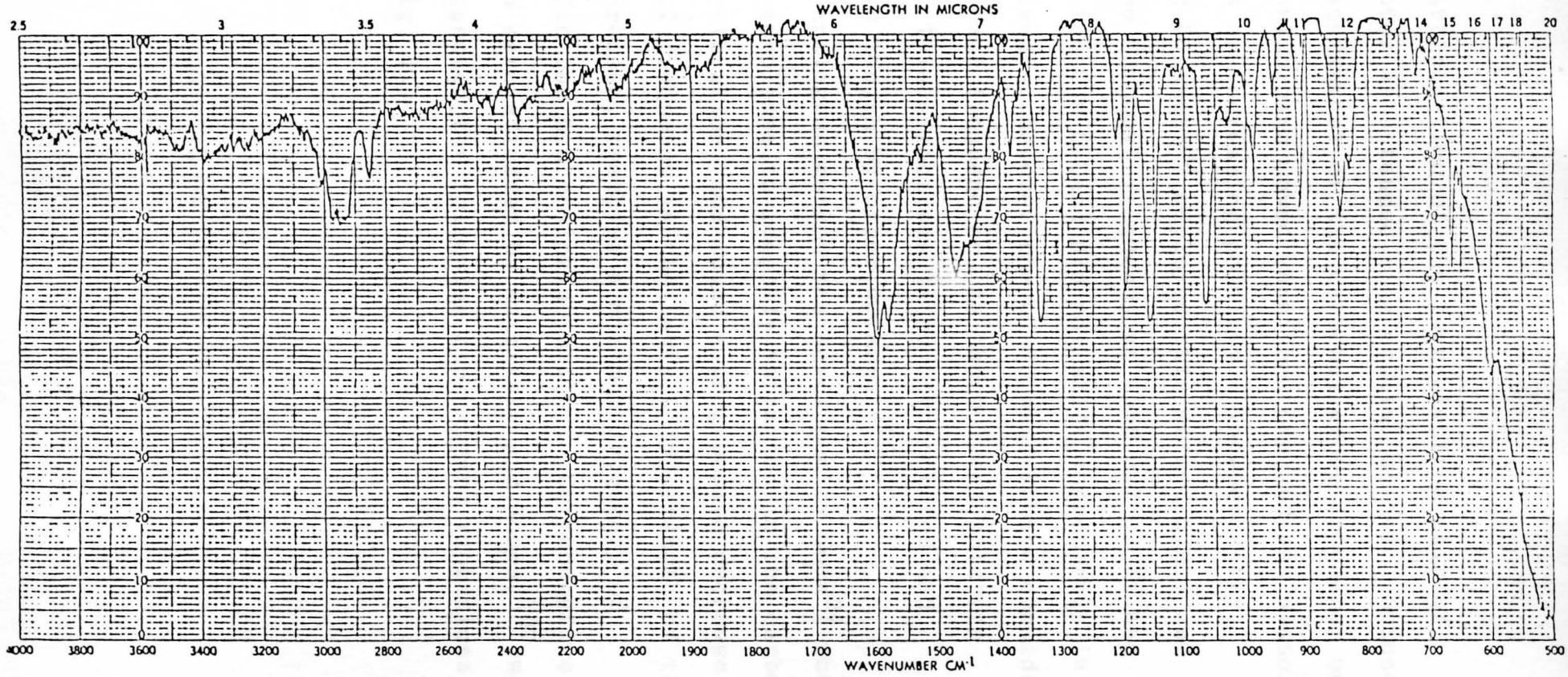


Fig. 10 2,6-Dimethyl-4-methoxypyridine (NaCl)

electron participation of the lone electron pair of nitrogen, over an extended ring orbital system. Spinner[103] suggested assignment of the carbonyl group frequency by observing which band moved when the compound was dissolved in solvents of increasing polarity. Independently, Bellamy and Rogasch[104] employed this method also, and assigned the carbonyl frequency at 1590 cm^{-1}. It was found that the C = C band did not shift appreciably in various solvents, however the C = O band showed considerable shifts to lower frequencies, as the solvent polarity increased. This effect was later corroborated and discussed in length by other workers.[105,106]

An analogous method was developed by Cook[24] who used Lewis acid complexes to identify variation in the carbonyl stretching vibration, and found a progressive decrease in the carbonyl frequency as the Lewis acid strength of the complex increased, reaching a minimum frequency of 1480 cm^{-1} (in the hydrochloride salts). Corroborative assignments were afforded by Katritsky and Jones,[107] who further suggested the following approximate vibrational modes[46] (Fig. 11):

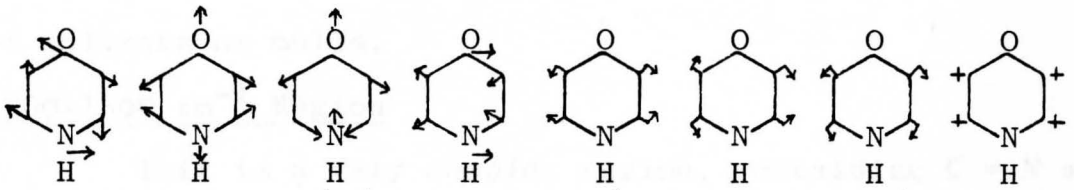


Fig.11 Approximate vibrational modes of 4-pyridones.

In figure 11, the first four vibrations are assigned to ring stretches (ν CC), the next three modes are assigned to in-plane bends (β CH), and the last vibration assigned to in phase, out-of-plane wagging (γ CH).

The complete tabulation of all infrared peaks, of each compound studied with the associated relative peak appearances and intensities (in various solvents where applicable) are found in Table 2. Assignment of the predominant diagnostic peaks are found in Table 3.
A brief synopsis of the regions of interest is as follows:

NH and OH Stretching Frequencies

Free N-H bands are found in the region of 3200-2300 cm^{-1}, [108] and where strong intermolecular hydrogen bonding may occur, the region for O-H stretching has been assigned at 3200-2650 cm^{-1}. [46]

330-2600 cm^{-1} Region

This region contains peaks assigned to C-H and $N-CH_3$ symmetric stretches, $C-CH_3$ symmetric and asymmetric stretches, and N^+H stretches for amine salts.[109] Bands in this region may be obscured due to contributory peaks of solvents or mulls.

1700-1300 cm^{-1} Region

This is a very complex region, containing C = N and C = C skeletal ring mode stretches, as well as C-H, N-H, N^+H, and $N-CH_3$ bends.[109] Four bands, at 1630, 1601, 1528, and 1480 cm^{-1} respectively have been assigned to ring vibrations by Greenwood and Wade[110] for pyridinium ions. Bands at 1640 cm^{-1} and 1550 cm^{-1} have been assigned as "coupled" C = C and C = O modes.[106]

1450-800 cm^{-1} Region

In this region are found O-H bending vibrations, C-C, C-O, C-N, and $C-CH_3$ stretching vibrations, as well as aryl-Cl stretching modes. A band near 1050 cm^{-1} has been assigned to CH_3 rocking,[109] although this band is tentatively assigned at 1028 cm^{-1} for lutidines (dimethyl-substituted pyridines).[111]

900-600 cm^{-1} Region

This region contains C-H and N-H rocking, C-H bends, and planar ring bends of substituents on the ring at C-4.[109]

CHAPTER V

CONCLUSIONS

As seen from previous literature reports, neither the exact site of alkylation of the 4-pyridones had been established, nor the structural assignments of the methylated derivatives had been confirmed. However, interpretations of infrared and proton nmr spectra indicated protonation upon the carbonyl oxygen atom.

This research has conclusively demonstrated that the site of alkylation of the 4-pyridones is also upon the carbonyl oxygen atom. Furthermore, results obtained from proton nmr and infrared spectroscopy combined have elucidated the exact structures of these compounds.

TABLE 1

^1H, NMR SHIFTS

All values in PPM. (δ(TMS) = 0.00)

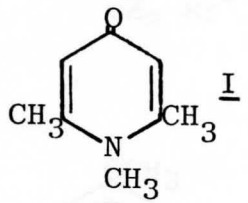
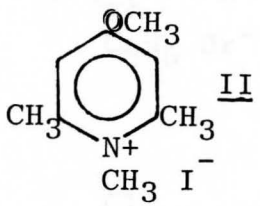
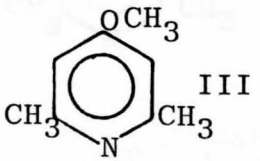
Compound	Solvent	N-H	Ring (3,5)	O-CH_3	N-CH_3	Ring (CH_3(2,6)	Other
 I	$CDCl_3$		6.07		3.46	2.27	
	D_2O		6.32		3.57	2.39	
	CF_3COOH		7.05		3.95	2.73	
 II	$CDCl_3$		7.21	4.10	4.10	2.88	
	D_2O		7.25	4.07	3.95	2.75	
	DMSO		7.51	4.05	3.92	2.75	
	SO_2		7.15	4.10	4.00	2.85	
	CF_3COOH		7.12	4.09	4.00	2.79	
 III	$CDCl_3$		6.45	3.81		2.48	

TABLE 1 (Cont.)

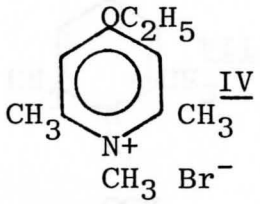
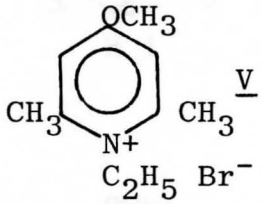
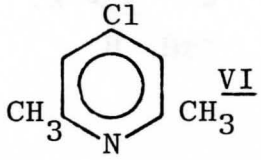
Compound	Solvent	N-H	Ring (3,5)	O-CH_3	N-CH_3	Ring (CH_3(2,6)	Other
 IV	$CDCl_3$		7.40		4.14	2.88	O-CH_2CH_3 = 4.42 O-CH_2CH_3 = 1.46
 V	$CDCl_3$		7.52	4.16		2.95	N-CH_2CH_3 = 4.62 N-CH_2CH_3 = 1.48
 VI	$CDCl_3$		6.89			2.48	

TABLE 1 (Cont.)

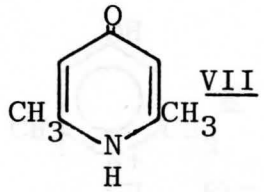
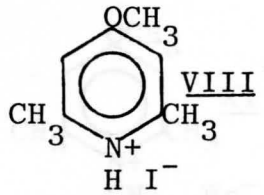
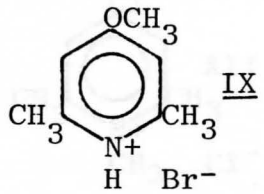
Compound	Solvent	N-H	Ring (3,5)	$O-CH_3$	$N-CH_3$	Ring (CH_3(2,6)	Other
 VII	$CDCl_3$	13.0	6.14			2.37	
 VIII	$CDCl_3$	13.4	6.95	4.09		2.85	
 IX	$CDCl_3$	unobserved	6.92	5.05		2.90	
	CF_3COOH		7.01	4.09		2.71	

TABLE 1 (Cont.)

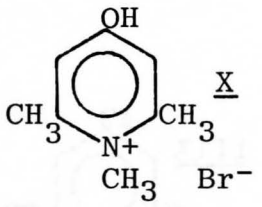
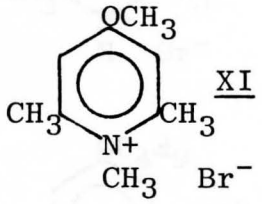
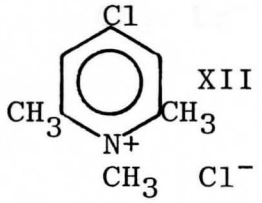
Compound	Solvent	N-H	Ring (3,5)	O-CH_3	N-CH_3	Ring (CH_3(2,6)	Other
 X	SO_2		7.19	3.95		2.73	OH=5.42
	CF_3COOH		7.01	4.09		2.71	
 XI	$CDCl_3$		7.38	4.11	4.11	2.86	
 XII	SO_2		7.13		3.89	2.68	

TABLE 1 (Cont.)

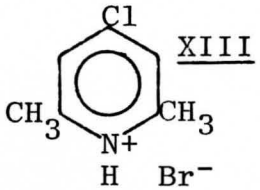
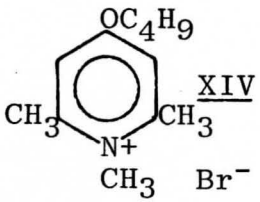
Compound	Solvent	N-H	Ring (3,5)	O-CH_3	N-CH_3	Ring (CH_3(2,6)	Other
	$CDCl_3$	unobserved	7.46			3.04	
 XIII	SO_2	unobserved	7.48			2.82	
	CF_3COOH		7.65			2.81	
 XIV	$CDCl_3$		7.23		4.05		O-C_4H_9=4.25 O-C_4H_9=1.63 O-C_4H_9=0.93

TABLE 2

ALL INFRARED BANDS

(Phase)[a]:	Frequency[b](Appearance,[c] indensity[d])
I	(KBr & Nujol): 2862(m,s): 2850(m,s); 1640(b,vs); 1567(s,vs); 1550(sh,vs); 1452(sh,s); 1428(s,s); 1393(s,m); 1367(s,ms); 1195(mb,ms); 1051(s,m,): 952(s,ms); 895(s,s).
II	(KBr): 3020(mb,s); 1800(s,w); 1762(s,w); 1640(mb,s); 1580(mb,s); 1505(mb,s); 1450(mb,ms); 1425(mb,ms); 1375(mb,w); 1340(mb,s); 1205(ms,s); 1168(mb,vs); 1130(sh,m), 1065(s,ms); 1045(s,m); 1035(s,m); 1012(s,ms); 955(s,w); 930(s,ms); 905(s,ms); 887(s,ms); 752(s,vs); 607(s,w).
	(H_2O): 1505(mb,vs); 1448(mb,m); 1430(mb,m); 1345(mb,vs); 1205(ms,s); 1165(mb,ms); 1058(s,m); 1035(s,w); 1003(ms,m).
	(D_2O): 1645(mb,vs); 1581(mb,s); 1550(mb,m); 1505(mb,s); 1455(mb,m); 1449(mb,m); 1430(mb,m); 1380(b,w); 1340(mb,vs); 1058(s,ms); 1035(s,ms); 1005(s,ms); 928(s,ms); 870(mb,ms).
	($CHCl_3$): 1646(mb,vs); 1584(mb,s); 1465(s,m); 1446(mb,ms); 1342(mb,vs); 929(s,ms); 867(s,ms).
	($CDCl_3$): 2207(ms,vs); 1582(mb,vs); 1340(mb,vs); 1205(s,vs); 1061(s,m); 1037(s,m).

TABLE 2 (Cont.)

III	(between NaCl plates): 3280(mb,w); 2960(ms,m); 1600(ms,vs); 1580(sh,vs); 1470(b,s); 1450(sh,s); 1382(s,m); 1337(s,vs); 1312(sh,m); 1196(s,s); 1158(s,vs); 1065(s,vs); 988(s,m); 958(s,w); 914(s,ms); 850(b,ms); 832(sh,m); 724(s,w); 665(vs,w); 605(s,vs).
IV	(Nujol & hexa.): 3490(mb,ms); 3415(mb,ms); 3035(mb,ms); 2988(ms,ms); 2962(mb,m); 1900(b,w); 1635(sh,s); 1611(ms,vs); 1593(ms,ms); 1575(mb,s); 1495(sh,ms); 1467(ms,m); 1440(s,m); 1430(s,m); 1399(ms,m); 1387(s,w); 1379(s,w); 1365(s,w); 1340(ms,vs); 1333(ms,s); 1199(s,m); 1174(ms,vs); 1144(sh,w); 1108(ms,m); 1060(s,ms); 1042(ms,m); 1027(ms,ms); 902(s,w); 888(s,m); 878(s,w); 720(mb,w).
	(D_2O): 1648(mb,vs); 1585(ms,s); 1510(ms,s); 1478(ms,ms); 1451(mb,ms); 1395(ms,m); 1343(ms,vs).
VI	(between NaCl plates): 2970(mb,w); 2915(ms,w); 1575(mb,vs); 1525(b,ms); 1460(mb,s); 1415(mb,vs); 1375(sh,m); 1287(s,s); 1250(b,vw); 1209(s,ms); 1118(s,s); 1095(s,m); 1034(mb,ms); 1003(mb,w); 980(s,w); 949(s,vw); 846(ms,vs); 820(sh,w); 718(s,m); 665(s,w); 582(s,w); 550(s,w).

TABLE 2 (Cont.)

VII	(KBr, Nujol & Hexa.): 2800(vb,vs); 1650(mb,vs); 1595(ms,s); 1558(mb,s); 1490(mb,vs); 1450(ms,s); 1430(ms,s); 1392(s,m); 1378(s,m); 1330(mb,s); 1281(ms,ms); 1235(ms,ms); 1176(mb,vs); 1040(s,ms); 1028(s,s); 993(s,ms); 965(s,s); 788(mb,s); 721(ms,ms).
XIII	(Nujol): 2660(b,vs); 1902(mb,m); 1855(mb,m); 1805(mb,m); 1649(ms,vs); 1629(mb,vs); 1305(s,s); 1270(s,ms); 1130(vs,vs); 1098(s,w); 1073(s,w); 1049(ms,m); 995(mb,m); 967(vs,w); 900(s,ms); 890(ms,m); 860(vs,m); 725(ms,w); 702(s,w).
IX	(Nujol): 1642(s,vs); 1624(s,vs); 1355(s,vs); 1208(s,s); 1176(s,s); 1070(b,m); 908(s,ms); 882(s,s).
X	(KBr, Nujol & Hexa.): 1638(mb,vs); 1588(mb,vs); 1530(s,s); 1489(s,vs); 1448(s,vs); 1423(s,vs); 1328(b,s); 1280(ms,s); 1235(ms,vs); 1175(m,vs); 1118(b,vs); 1045(s,s); 1028(s,s); 955(b,s); 900(b,s); 882(sh,s); 865(ms,s); 790(mb,s).

TABLE 2 (Cont.)

XI	(KBr): 3010(mb,ms); 1640(mb,vs); 1582(mb,s); 1505(mb,ms); 1465(ms,m); 1435(mb,m); 1385(ms,w); 1342(mb,vs); 1270(mb,vw); 1208(ms,s); 1168(mb,vs); 1068(s,m); 1050(mb,w); 1038(sh,w); 1013(s,m); 958(s,vw); 933(s,m); 910(s,w); 895(mb,m); 887(s,m); 612(mb,vw).
XII	(Nujol): 2400(b,ms); 1640(mb,s); 1590(mb,m); 1484(mb,m); 1450(ms,w); 1415(mb,w); 1340(ms,vs); 1178(ms,s); 880(ms,m).
XIV	(Nujol): 3420(b,m); 1640(mb,vs); 1588(ms,s); 1500(ms,ms); 1332(ms,vs); 1273(ms,w); 1170(s,vs); 1128(s,w); 1058(s,m); 1048(s,w); 1035(ms,w); 1021(s,m); 1003(s,w); 975(ms,w); 945(ms,w); 898(ms,m); 853(s,m).

---

[a]Solid phase as KBr pellet or mulls (Nujol, hexachlorobutadiene); liquid phase in indicated solvent or between NaCl plates.

[b]Wavenumber in cm^{-1}.

[c]Physical appearance; b = band, mb = moderately broad, s = sharp, vs = very sharp, sh = shoulder.

[d]Relative band intensity; vs = very strong, s = strong, ms = moderately strong, m = moderate, w = weak, vw = very weak.

TABLE 3

TENTATIVE BAND ASSIGNMENTS
(Wave numbers in cm^{-1})

	I	II	III	XI	IV	XIV
ν N-H						
ν C-H	2862, 2850	3020	3280, 2960	3010		3420
ν C=N	1550, 1452	1580		1582		
ν C=C	1640	1639		1640	1635	1640
ν C=O	1567					
δ N-H						
δ C-H	1367, 1195		724	1465, 1342		
δ O-H						
ν C-C	1428, 1393	1425, 1375		1435, 1385		
ν C-N	1428, 1393	1205		1208		
ν C-O		1450	1465	1465	1450	1500

TABLE 3 (Cont.)

	I	II	III	XI	IV	XIV
r CH_3	1051	1065	1065	1068	1061	1058
γ C-H	895	905,887		895,887	888	898
	X	**VII**	**IX**	**VI**	**XII**	**XIII**
ν N-H		2800				2660
ν C-H		2800		2970,2915	2400	2660
ν C=N				1575		
ν C=C	1638	1650	1642		1640	1649
ν C=O	1448					
δ N-H						

TABLE 3 (Cont.)

	X	VII	IX	VI	XII	XIII
δ C-H						
δ O-H	1280,1235					
ν C-C						
ν C-N				1209		
ν C-O	1448					
r CH_3	1045	1040	1048	1035		1049
γ C-H	790	713		820		
ν (ring Cl)				1095		1098

BIBLIOGRAPHY

1. L. Haitinger, Chem. Ber., 18, 452 (1885).

2. A. Maquestian, Y. Van Haverbecke, C. DeMeyer, A. R. Katritzky, M. J. Cook, A. D. Page, Can J. Chem., 53, 490 (1975).

3. A. Albert and J. N. Phillips, J. Chem. Soc., 1294 (1956).

4. J. Frank and A. R. Katritzky, J. Chem. Soc., Perkin Trans. II, 12, 1428 (1976).

5. P. Sensi and G. G. Gallo, Ann. Chim., 44, 232 (1954) CA 49, 14757 (1955) .

6. A. R. Katritzky, R. A. Jones, J. M. Lagowski, Chem. Ind., 870 (1960.

7. L. Stefaniak, Tetrahedron Letters, 32, 1065 (1975).

8. P. H. Kasai, D. McLeod, J. Am. Chem. Soc., 96, 2342 (1974).

9. P. Beak, and F. S. Fry, J. Am. Chem. Soc., 95, 1700 (1973).

10. D. Cook, Can. J. Chem., 41, 1435 (1963).

11. M. Hraby, Czech., 142, 903 (1971).

12. C. F. Rassweiler and R. Adams. J. Am. Chem. Soc.,46, 2758 (1924).

13. J. Van Allan, G. Reynolds, J. Alessi, S. Chang, R. Joines, J. Hetero. Chem., 8, 919 (1971).

14. P. Beak and J. Bonham, J. Am. Chem. Soc., 87, 3368 (1965).

15. C. S. Wang, J. P. Easterly, N. E. Skelly, Tetrahedron Letters, 27, 2581 (1971).

16. I. Belsky, H. Dodiuk, Y. Shvo, J. Org. Chem., 39, 989 (1974).

17. A. El-Anani, J. Banger, G. Bianchi, S. Clementi, C. Johnson, A. R. Katritzky, J. Chem. Soc., Perkin Trans. II, 7, 1065 (1973).

18. P. Bellingham, C. D. Johnson, A. R. Katritzky, J. Chem. Soc. (B), 1226 (1967).

19. E. Spinner, J. Chem. Soc., 1226 (1960).

20. A. R. Katritzky and R. A. Jones, Proc. Chem. Soc., 313 (1960).

21. R. A. Jones and A. R. Katritzky, Chem. Ind., 722 (1961).

22. P. J. van der Haak and T. J. de Boer, Rec. Trav. Chim., 83, 186 (1964).

23. J. E. Sarneski, H. L. Suprenant, C. N. Reilley, Spect. Letters, 9, 885 (1976).

24. D. Cook, Can. J. Chem., 41, 515 (1963).

25. G. Barlin and W. Pfleiderer, J. Chem. Soc. (B), 7, 1425 (1971).

26. M. Taagepera, W. G. Henderson, R. T. Brownlee, J. L. Beauchamp, D. Holtz, R. W. Taft, J. Am. Chem. Soc., 94, 1369 (1972).

27. M. L. Tosato, L. Socorsi, M. Cignitti, L. Paoloni, Tetrahedron Letters, 29, 1339 (1973).

28. T. Groneberg and K. Undheim, Org. Mass. Spec., 6, 823 (1972).

29. J. Christensen, D. Smith, M. Slades, R. Izatt, Thermochimica Acta, 5, 35 (1972).

30. C. L. Liotta, E. Perdue, H. P. Hopkins, J. Am. Chem. Soc., 96, 7308 (1974).

31. S. Clementi, C. D. Johnson, A. R. Katritzky, J. Chem. Soc., Perkin Trans. II, 11, 1294 (1974).

32. P. Beak and J. Bonham, J. Am. Chem. Soc., 87, 3365 (1965).

33. P. Beak and R. Watson, Tetrahedron Letters, 27, 953 (1971).

34. G. Hornke, H. Krauch, W. Kunz, Chemiker Ztg., 89, 440 (1965). [CA 63, 17813C]

35. J. March, Advanced Organic Chemistry, McGraw-Hill Inc., 1977, p. 357.

36. R. R. Renshaw and R. C. Conn, J. Am. Chem. Soc., 59, 297 (1937).

37. M. H. O'Leary and R. W. Stach, J. Org. Chem., 37, 1491 (1972).

38. G. B. Barlin and J. A. Benbow, J. Chem. Soc., Perkin Trans. II, 790 (1974).

39. G. B. Barlin and J. A. Benbow, J. Chem. Soc., Perkin Trans. 2, 1267 (1975).

40. H. Gilow and J. Ridd, J. Org. Chem., 39, 3481 (1974).

41. A. E. Tschitschibabin and P. G. Szokow, Chem. Ber., 58, 2650 (1925).

42. J. Cadogan, J. Chem. Soc., 2844 (1959).

43. I. Fleming and D. Philipides, J. Chem. Soc. (C), 2426 (1970).

44. E. Ochaii and M. Fujimoto, Pharm. Bull. (Tokyo), 2, 131 (1954).

45. T. Kato and F. Hamaguchi, Pharm. Bull. (Tokyo), 4, 174 (1956).

46. A. R. Katritzky and R. A. Jones, J. Chem. Soc., 2947 (1960).

47. G. D. Titskii and L. M. Litvinenko, Zh. Obsch. Khim., 40, 2680 (1970).

48. P. P. Ibanez, Brit., 1, 542 (1973).

49. V. Janata and A. Svab, Czech., 149, 731 (1973).

50. L. Haitinger and A. Lieben, Monatsh., 6, 279 (1885).

51. E. Koenigs and G. Kinne, Chem. Ber., 54, 1357 (1921).

52. M. V. Rubtsov and A. F. Klimkova, Zh. Obsch. Khim., 16, 1860 (1946).

53. J. P. Wilbaut and F. W. Broekmann, Rec. Trav. Chim., 58, 885 (1939).

54. J. P. Wilbaut, J. Overhoff, H. Geldof, Rec. Trav. Chim., 54, 807 (1935).

55. O. Fischer and K. Demeler, Chem. Ber., 32, 1307 (1899).

56. T. Kato and M. Ohta, J. Pharm. Soc. Japan, 71, 217 (1951) [CA 46, 4541 (1952)].

57. D. Vorlander, Chem. Ber., 58, 1908 (1925).

58. S. Hunig and G. Kobrich, Ann. Chem., 617, 181 (1958).

59. F. E. Cislak, Ind. Eng. Chem., 47, 800 (1955).

60. P. Billingham, C. D. Johnson, A. R. Katritzky, J. Chem. Soc. (B), 866 (1968).

61. T. Kato and F. Hamaguchi, J. Pharm. Soc. Japan, 77, 222 (1957), CA 51, 11342 (1957).

62. H. N. Borjarska-Dahlig, Rec. Trav. Chim., 78, 981 (1959).

63. D. E. Butler, J. Med. Chem., 14, 575 (1971).

64. A. H. Ewald and J. A. Scudder, J. Phys. Chem., 76, 249 (1972).

65. H. Vorbruegger, Synthesis, 5, 301 (1973).

66. A. Harder, G. Cornuz, H. Wyler, Helv. Chim. Acta., 58, 1287 (1975).

67. W. J. Woodford, J. Med. Chem., 17, 1027 (1974).

68. S. C. Shim and G. S. Hammond, Hanguk Saenghwa Hakhoe Chi, 9, 181 (1976).

69. S. C. Shim, M. H. Hyun, S. H. Lee, Taehan Hwahak Hoechi, 20, 520 (1976), [CA 86, 139082 (1977)].

70. A. Svab, Czech., 144, 978 (1973).

71. R. W. Taft and H. B. Yang, J. Am. Chem. Soc., 93, 1310 (1971).

72. J. W. Pavlik and E. Clennan, J. Am. Chem. Soc., 95, 1697 (1973).

73. R. C. Benson, C. L. Norris, W. H. Flygare, P. Beak, J. Am. Chem. Soc., 93, 5591 (1971).

74. C. L. Norris, R. C. Benson, P. Beak, J. Am. Chem. Soc., 95, 2766 (1973).

75. I. Belsky, Tetrahedron Letters, 28, 1001 (1972).

76. E. C. Hunter and J. R. Partington, J. Chem. Soc., 87, (1933).

77. C. G. LeFevre and R. J. Le Febre, J. Chem. Soc., , 1088 (1937).

78. G. N. Dorofeenko, A. V. Koblik, B. A. Tertov, T. I. Polyakova, Khim. Geterotsikl. Soedin., 11, 1580 (1972) [CA 78, 58189].

79. H. Khedija, H. Strzelecka, M. Simalty, Bull. Soc. Chem. France, 8, 3173 (1972).

80. J. Wilt, G. A. Reynolds, J. A. Van Allan, Tetrahedron Letters, 29, 795 (1973).

81. G. A. Reynolds and J. A. Van Allan, J. Hetero. Chem., 11, 405 (1974).

82. G. Seitz and H. Moenninghoff, Arch. Pharm., 306, 389 (1973).

83. D. Reid and R. Webster, J. Chem. Soc., Perkin Trans. I, 8, 775 (1975).

84. F. Kutek and V. Dusek, Zh. Neorg. Khim., 19, 2360 (1974).

85. D. Yates and D. J. MacGregor, Can. J. Chem., 51, 1267 (1973).

86. M. A. Elkaschef and M. H. Nosseir, J. Am. Chem. Soc., 82, 4344 (1960).

87. T. K. Wu and B. P. Dailey, J. Chem. Phys., 41, 2796 (1964).

88. W. E. Stewart and T. H. Siddall, J. Chem. Phys., 74, 2027 (1970).

89. T. H. Lowry and K. S. Richardson, Mechanism and Theory in Organic Chemistry, Harper and Row, 1976, p. 62.

90. M. Zanger and W. W. Simons, Anal. Chem., 46, 2042 (1974).

91. I. Smith and W. Schneider, Can J. Chem., 39, 1158 (1961).

92. J. C. Ma and E. W. Warnhoff, Can. J. Chem., 43, 1849 (1965).

93. R. M. Silverstein, G. C. Bassler, T. C. Morrill, Spectrometric Identification of Organic Compounds, John Wiley and Sons, 1974, p. 175.

94. M. Witanowski, L. Stefaniak, H. Januszenski, Nitrogen NMR, Plenum Press, London, 1973, p. 163.

95. L. Stefaniak, Tetrahedron Letters, 32, 1065 (1976).

96. M. Witanowski, L. Stefaniak, H. Januszenski, T. Slauvere, G. Webb, Adv. Mol. Relax. Proc., 5, 169 (1973).

97. M. Witanowski, L. Stefaniak, H. Januszenski, T. Slauvere, G. Webb, Mol. Phys., 23, 1071 (1972).

98. C. J. Turner and G. W. Chessman, Org. Mag. Res., 6, 663 (1974).

99. Y. Takeuchi and N. Dennis, Org. Mag. Res., 7, 244 (1975).

100. U. Vogeli and W. Von Phillipsborn, Org. Mag. Res., 5, 551 (1974).

101. A. J. Gordon and R. A. Ford, The Chemist's Companion, J. Wiley and Sons, 1972, p. 280.

102. N. J. Leonard and D. M. Locke, J. Am. Chem. Soc., 77, 1852 (1955).

103. E. Spinner, J. Chem. Soc., 1237 (1960).

104. L. J. Bellamy and P. E. Rogasch, Spectrochim. Acta., 16, 30 (1960).

105. D. Smith and P. Taylor, Spectrochim. Acta., 32A, 1477 (1976).

106. B. Batts and E. Spinner, Aust. J. Chem., 22, 2581 (1969).

107. A. R. Katritzky and R. A. Jones, J. Chem. Soc., 2942 (1960).

108. L. J. Bellamy and P. E. Rogasch, Proc. Roy. Soc., A257, 98 (1960).

109. A. R. Katritzky, Physical Methods in Heterocyclic Chemistry, II, Academic Press, 1963.

110. N. Greenwood and K. Wade, J. Chem. Soc., 1130 (1960).

111. J. H. Green, D. J. Harrison, W. Kyaston, H. M. Paisley, Spectrochim. Acta., 26A, 2139 (1970).