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Reactions at α-Pyridinium and α-Sulfonium Centres: Synthesis of Precursors to Hagedorn Oxime Analogs

Zhi Liu

A Thesis
in
The Department
of
Chemistry and Biochemistry

Presented in Partial Fulfillment of the Requirements
for the Degree of Master of Science at
Concordia University
Montreal, Quebec, Canada

March 1992

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ABSTRACT

Reactions of α-Pyridinium and α-Sulfonium Centres: Synthesis of Precursor to Hagedorn Oxime Analogs

Zhi Liu

Hagedorn oximes are a family of pyridinium-2-carboximes which are linked to the nitrogen atom of a second pyridinium ring by a dimethyl ether bridge.

The objective of this study was to develop, using unsubstituted pyridine and tetrahydrothiopyran as model compounds, synthetic methods for the alkylation of the heteroatom and the elaboration of an appropriately functionalized dimethyl ether chain (eg. **69**, Scheme 31).

Pyridine has been used as a model compound for reactions which were envisaged for the functionalization of an acetal derivative of 2-pyridinecarboxaldehyde. Reaction of pyridine with formaldehyde/thionyl chloride results in the corresponding *N*-chloromethyl derivatives, this can be converted into the *N*-alkoxymethyl compound by a simple substitution reaction.

We have investigated the applicability of the general synthetic route for the elaboration of a unsubstituted tetrahydrothiopyran, a model compound, into a Hagedorn oxime analog. Several sulfonium compounds have been made.

ACKNOWLEDGEMENTS

I wish to express my sincere appreciation to my thesis supervisor, Dr. F.J. Ablenas, for his guidance and direction throughout my work.

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Dr. T.J. Adley and Dr. S. Mikkelsen for serving on my research committee.

Dr. L.D. Colebrook and Dr. Q. Ning for help with the NMR spectra.

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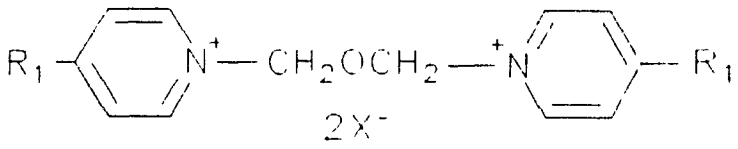
CHAPTER I. INTRODUCTION

Hagedorn oximes are a family of pyridinium-2-carboximes which are linked to the nitrogen atom of a second pyridinium ring by a dimethyl ether bridge. These compounds exhibit diverse biological activities such as antibacterial, antileukemic and, more significantly, acetylcholinesterase (AChE) reactivator activities. Mixed pyridinium salts **1** have been prepared because of their potential interest as antagonists for alkyl phosphate intoxication, as occurs with certain chemical warfare agents and insecticides [1].



R_1 = CH=NOH

1

In search of improved reactivators of organophosphate-inhibited AChE, we have studied the development of a reliable synthetic method for the preparation of unsymmetrical Hagedorn oximes and also analogs which contain sulfonium instead of pyridinium moieties.

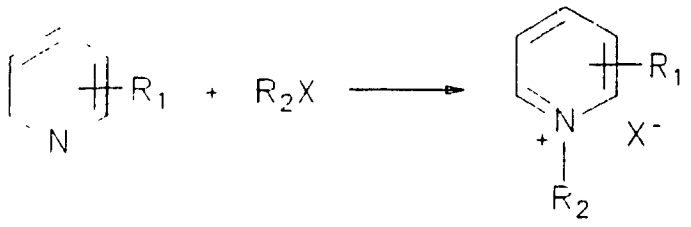
1. Pyridinium Compounds

1.1. Synthesis of Pyridinium Salts

1.1.1. Quaternization Reaction of Pyridines with Alkylating Agents

Perhaps the most common method to prepare quaternary pyridinium compounds 2 continues to be the Menschutkin reaction, the reaction of a pyridine derivative with an organic halide [2].

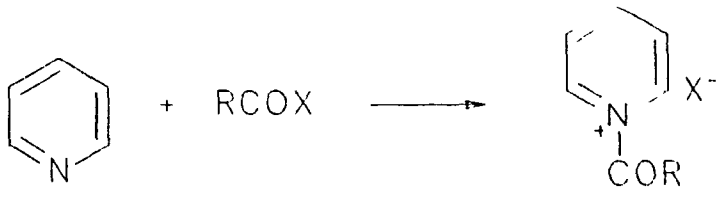
Scheme 1



2

Pyridine is a good nucleophile (the relative nucleophilicity: $RO^- > OH^- > NH_3 >$ pyridine $> F^- > H_2O$) and can be alkylated with alkyl halides, tosylates, and similar compounds. It also reacts readily, but reversibly, with acyl halides, anhydrides and similar acid derivatives and is often used as a catalyst in acylation reactions. The *N*-acylpyridinium salts 3 so formed are better acylating agents than acid anhydrides or acid chlorides [3].

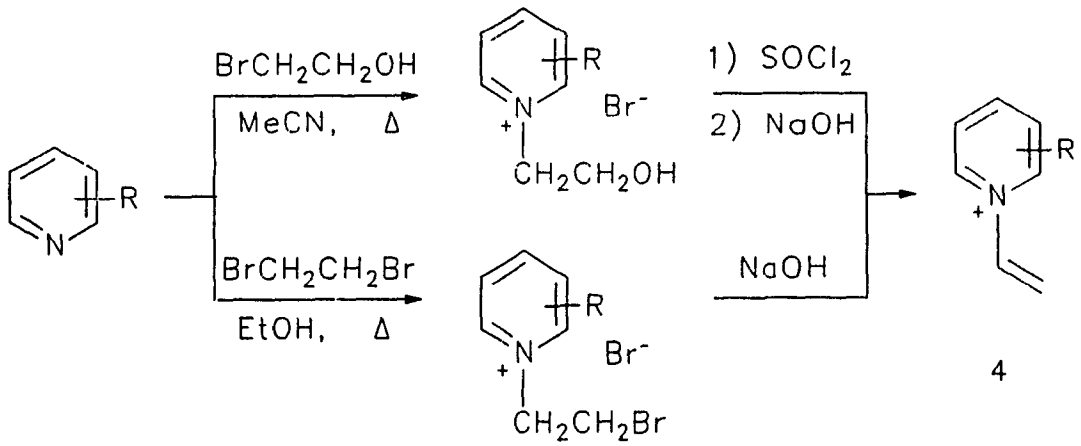
Scheme 2



3

N-Vinylpyridinium salts **4**, interesting as polymer components, can be obtained by two procedures [4,5].

Scheme 3

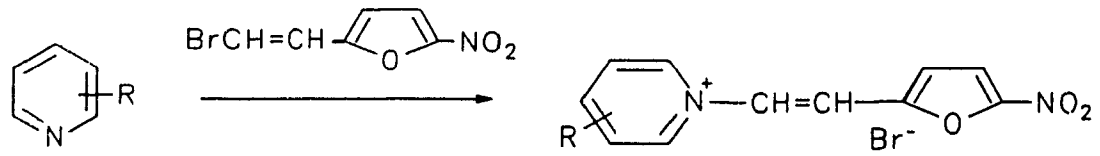


4

R = H, Me Ph, NMe_2

In the study of vinylpyridinium salts, their derivatives **5** have been prepared in the reaction proceeding *via* an addition-elimination mechanism (Scheme 4) [6].

Scheme 4

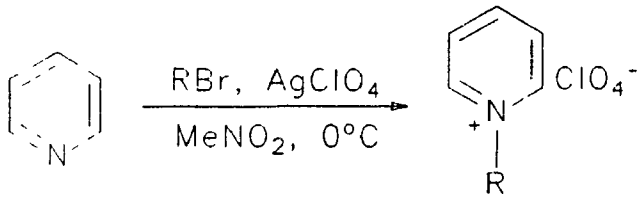


R = H, Me

5

So far, few *N-tert*-alkylpyridinium salts are known; examples of them are **6**, obtained from pyridine and corresponding alkyl bromide in the presence of silver perchlorate [7].

Scheme 5

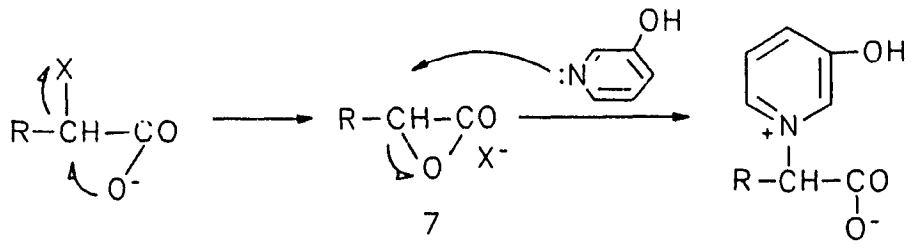


R = ^{t}Bu, $C(Me)_2Ph$ 6

Since neutral reactants form ionic products in the Menschutkin reaction, it provides a good opportunity for studying solvent effects on reaction rate.

The kinetics of reactions of substituted pyridines with phenacyl bromide have been reported. The reaction of 3-hydroxypyridine with α-bromo-acids is found to proceed with inversion of configuration unless there is branching at the ß carbon [8]. It is proposed that in the latter cases neighbouring group participation of the type **7** occurs.

Scheme 6

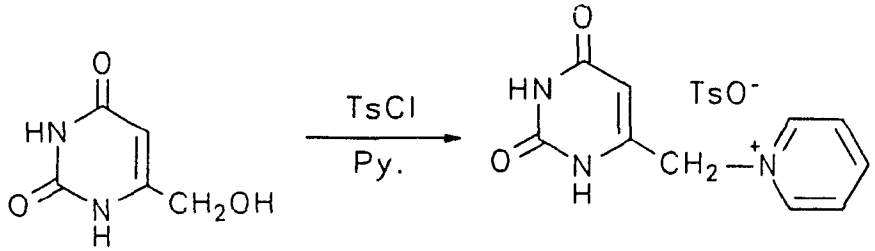


7

A general procedure for the synthesis of pyridinium compounds from alcohols, presumably *via* the corresponding alkyl chloride intermediate, has been reported. The method makes use of the dimethylformamide-thionyl chloride reagent which, in turn, has been investigated to determine the reactive species [9]. Pyridine has also been *N*-methylated using cyclic acyl phosphates [10].

Pyridinium compounds may also be prepared by displacement of the mesylate or tosylate group. For example, when the mesylation or tosylation of 6-hydroxy methyluracil was attempted, the pyridinium salt **8** was formed instead [11]. It was rationalized that the initially formed sulfonyl esters undergo facile ionization, yielding a resonance stabilized benzylic cation which can then undergo S_N1 attack by pyridine

Scheme 7



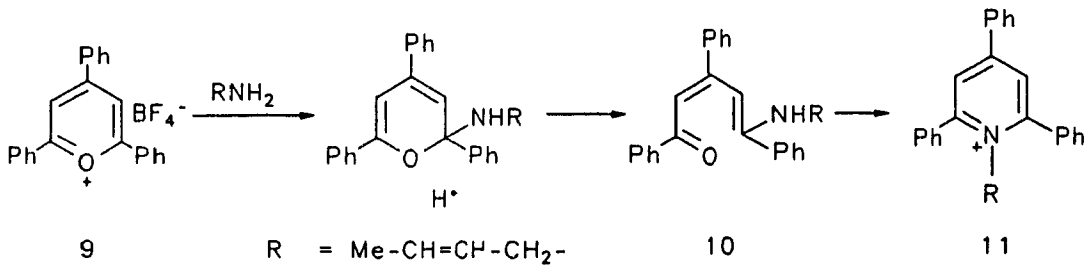
8

1.1.2. Reactions of Pyrylium Salts with Primary Amines

Pyrylium salts are important synthons of pyridinium compounds and a number of them have been obtained by this route.

Reaction of a pyrylium ion **9** with an amine initially forms a 2*H*-pyran, whose ring spontaneously opens to give the divinylogous amine **10**. Kinetic studies of pyridinium ion formation in organic solvents confirm the following reaction mechanism. For example, when 2,4,6-triphenylpyrylium undergoes reaction with γ-methylallylamine, the corresponding pyridinium salt **11** is formed [12].

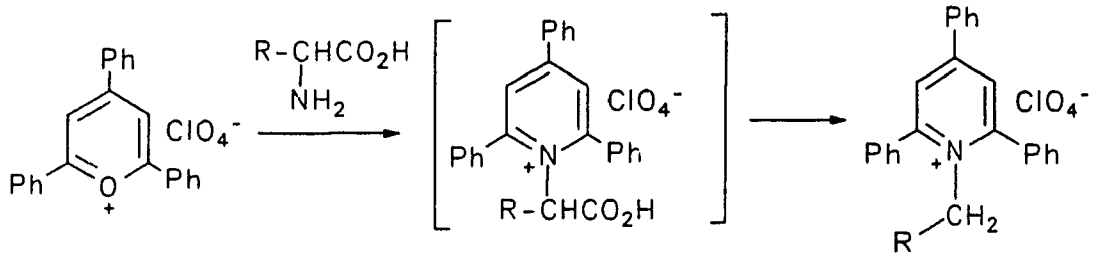
Scheme 8



9 10 11

Reaction of pyrylium salts with α-amino acids gives rise to alkyl-substituted *N*-methylpyridiniums *via* the spontaneous decarboxylation of initial products **12** [13].

Scheme 9



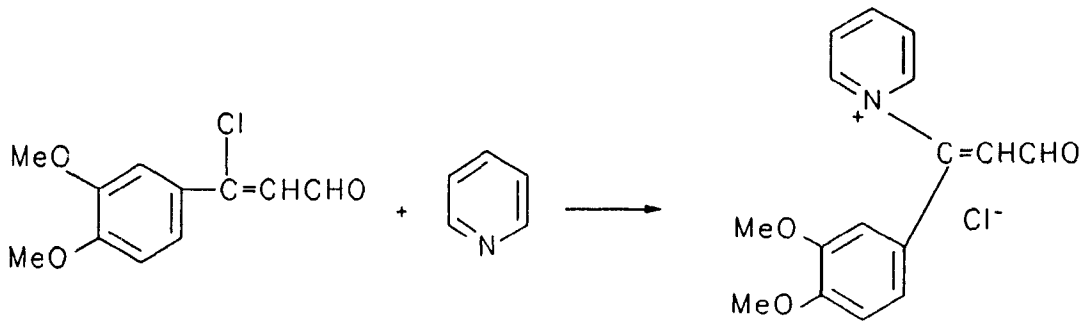
R = Me, Et, ^{i}Pr 12

1.1.3. Other Synthetic Reactions

A. By Addition of Pyridines to Unsaturated Systems [14]

Some unusual preparations of pyridinium compounds by the addition of the pyridine system to alkenes have been reported. The reported conversion of the chloroaldehyde **13** to the quaternary salt **14** probably involves the initial addition of pyridine to the double bond system, followed by the loss of chloride ion.

Scheme 10

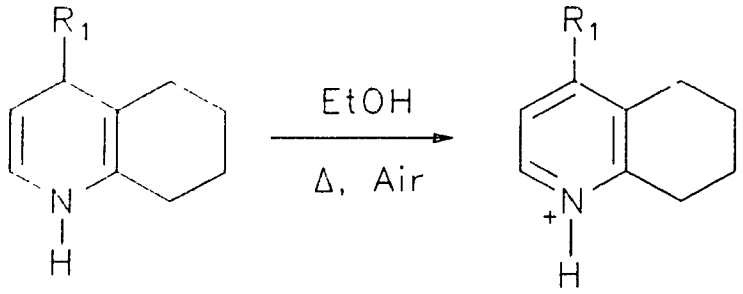


13 14

B. By Oxidation of 1-substituted dihydropyridines [15]

The facile nature of the oxidation of 1-substituted reduced pyridines to pyridinium salts is exemplified by the ready air oxidation of compounds of type **15** to the corresponding quaternary salts **16** in boiling ethanol.

Scheme 11

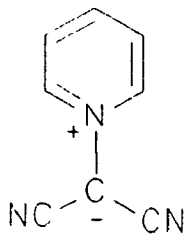


15 $R_1 = CH_3$, Ph. 16

1.2. Properties and Reactions of Pyridinium Salts

1.2.1. General Properties

Pyridinium salts have been used to measure $N(sp^2)$-$C(sp^2)$ bond distance by X-ray crystallographic methods to determine the importance of resonance contributions in the amide bond and other such structures [16]. An X-ray study of pyridinium dicyanomethylide **17** show that the two cyano group are inclined from the plane of the pyridine ring, even though a planar structure would be more highly favoured by resonance stabilization [17].



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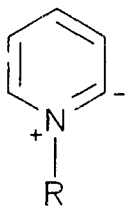
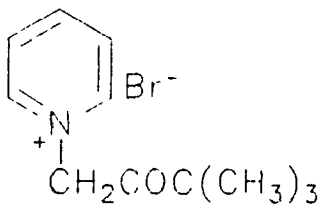


18

N-Alkylpyridinium salts undergo base-catalyzed α-hydrogen exchange by a simple deprotonation-protonation process *via* the intermediate ylide **18**, and the ability of substituents R to influence the rates of pyridinium ylide formation under buffer conditions has been studied [18]. The rates were found to correlate well with the Taft σ_I inductive parameter. These results indicate that substituents bonded to the positively charged annular nitrogen exert inductive effects in the same way as substituents bonded to the annular carbon of pyridine and that the substituent effects are large.

Pinacolylpyridinium bromide (**19**), readily prepared by the reaction of α-bromopinacolone with pyridine, has been reported as a colour reagent for amines. The intensity of the yellow colour obtained appears to be related to the basicity of the amine and is believed to be due to the formation of the resonance stabilized ylide **20** [19].



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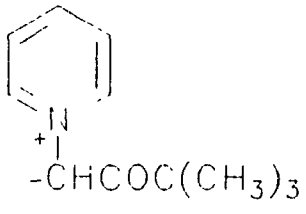
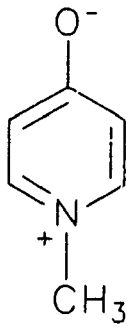


20

The distinguishing properties of pyridinium salts have prompted their use in certain kinetic studies. For example, the *N*-methyl-4-oxopyridinium iodide group (**21**) was used as a leaving group in a solvolytic investigation of the 2-bicyclo[3,1,0]hexyl cation **22** to avoid complications due to internal return, and *N*-alkylpyridinium cations

have been investigated extensively as model compounds in assessing the chemical properties of pyridine coenzymes such as nicotinamide adenine dinucleotide (NAD)[20].



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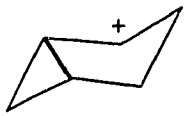
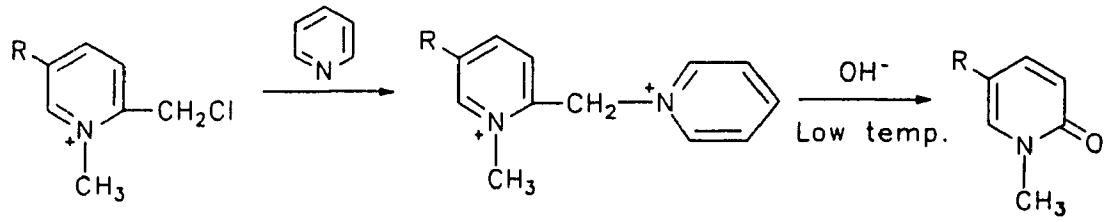


22

1.2.2. Pyridone Formation —— Anionic Attack on the Pyridinium Ring

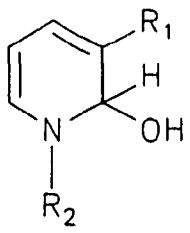
Matsumura et al. [21] reported a synthesis of 2-pyridone which consisted of treating 2-chloromethylpyridine derivative with pyridine and then dimethyl sulfate which yielded the bipyridinium salt **23**. Aqueous alkali treatment at low temperature gave the corresponding 2-pyridones **24**.

Scheme 12

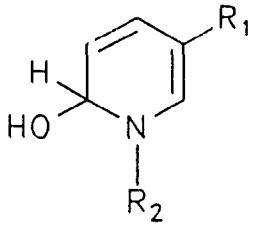


23 24

In aqueous base, *N*-alkylpyridinium salts can exist partly as the pseudobase (*cf.* **25** or **26**) which can be oxidized by selected agents to the corresponding pyridones; in these oxidations the 4-pyridone, expected from the pseudobase **27**, has been observed only when a 3-cyano substituent was present and then in very small amount[22].



25



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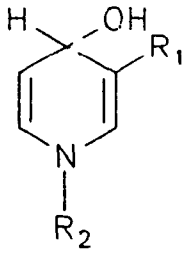


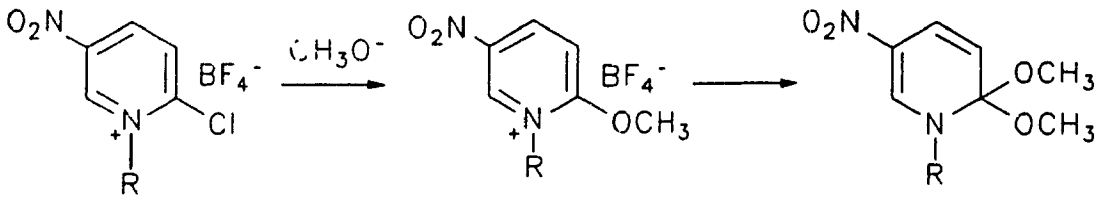
27

The studies of the mechanism of this oxidation show that both steric and electronic effects exert an influence on the position of oxidation, for example, 3-methyl and 3-cyano groups were found to activate the ring and direct an oxidative attack at C-2, while a 3-methoxycarbonyl group deactivates and directs exclusively to C-6. It was suggested that the rate determining step is the formation of a pseudobase-ferricyanide complex [23].

A nitro group in the C-3 or C-5 position of pyridinium salts activates the nucleophilic displacement of a C-2 halogen substituent, and these substances can in fact add a second mole of reagent to give dihydropyridine derivatives. Thus the 2-chloro-5-nitropyridinium salt **28** reacts with excess methoxide ion to give the substitution product **29** initially, which can react further to give the addition product

30. The dihydropyridine derivatives lose readily a molecule of dimethyl ether and are converted to the corresponding 2-pyridones; the 3-nitropyridinium salts behave similarly [24].

Scheme 13



28 29 30

1.2.3. Reduction

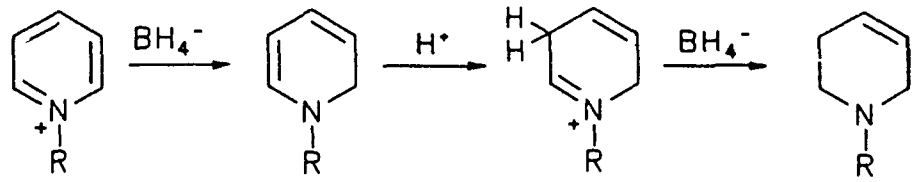
A. Reduction to Piperidines and Tetrahydropyridines

Ferles et al. [25] have studied the reduction of quaternary pyridinium salts using lithium aluminium hydride, sodium borohydride, and aluminum hydride. All of these reagents give predominantly 3-piperidines, with small amounts of hexahydro derivatives produced occasionally. In general, where several tetrahydro products are possible, one largely predominates. A useful comparison of the product ratios obtained from picolinium and lutidinium salts using the three metal hydride reagents has been made: 1-alkoxypyridinium salts yield pyridines, 3-piperidines, and piperidines on reduction with sodium in ethanol, metal hydrides, or by electrolysis.

Sodium borohydride reduction of pyridinium salts to tetrahydropyridines occurs *via* initial formation of the 1,2-dihydro intermediate, followed by protonation at the central position of the resulting dienamine and further reduction of the

immonium system to the tetrahydro product 31 [26].

Scheme 14

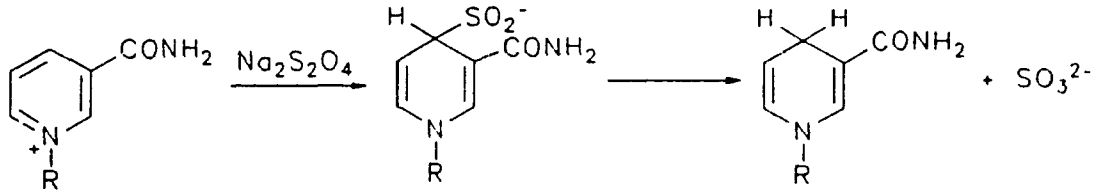


31

B. Nicotinamide Coenzymes

The reduction of nicotinamide quaternary salts and their analogs continues to harbour interest due to the great importance of this process in biological systems. Nicotinamide adenine dinucleotide (NAD) is the pyridinium salt **32** which acts as a coenzyme in biological hydrogen transfer reactions. When NAD is reduced with sodium dithionite a yellow intermediate is produced which decomposes readily to reduced nicotinamide adenine dinucleotide (NADH, **33**) and sulfite ion [27].

Scheme 15



32 R = ribose-P-P-ribose-adenine 33

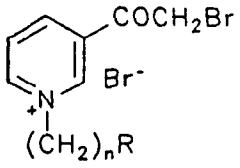
1.3. Biological Activity

1.3.1. Specific Enzyme Inhibitors and Reactivators

Certain styrylpyridinium salts are potent choline acetyltransferase inhibitors. The inhibitory potency was diminished by highly electronegative substituents on the styryl phenyl ring, but enhanced by chlorine and bromine [28].

The 3-(bromoacetyl)pyridinium bromides **34** slowly inactivate lactate dehydrogenase and a series of *N*-benzylpyridinium chlorides are inhibitors of the yeast alcohol dehydrogenase-catalyzed oxidation of ethanol [29].

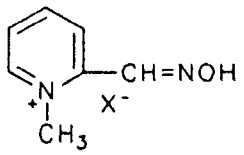
Substances containing the quaternary pyridinium system have been studied as reactivators of acetylcholinesterase inhibited by phosphorylation. Organophosphorus compounds which have the ability to rapidly and irreversibly inhibited this enzyme have gained importance as insecticides and nerve agents. These substances either phosphorylate or phosphonylate the enzyme, thus deactivating it, and reactivation can be effected by removing the phosphorous containing group with nucleophilic reagents such as oximes or hydroxamic acid. Three such compounds of high effectiveness are *N*-methylpyridinium-2-aldoxime chloride or iodide (2-PAM, **35**), the trimethylenebispyridinium oxime (TMB-4, **36**) [30]. However, many others have been studied as well.



n= 2-5

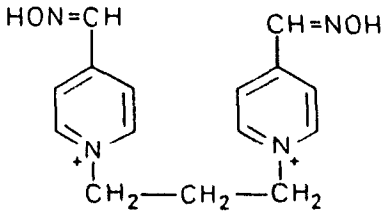
R= CH_3, COOH

34



2-PAM

35

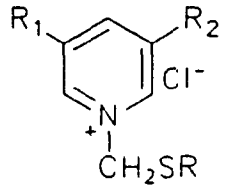


TMB-4

36

1.3.2. Other

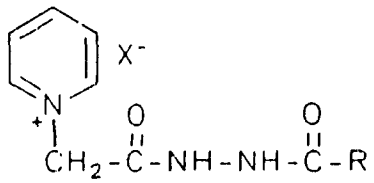
Compounds **37, 38, 39** have antibacterial antiviral and fungicidal properties, and **40** are used in treating skin disorders [31].



R= $Me(CH_2)_n$

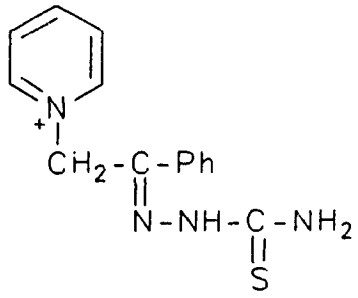
R_1=R_2= H, Cl, Br, Me

37



R= C_9-C_{19}

38



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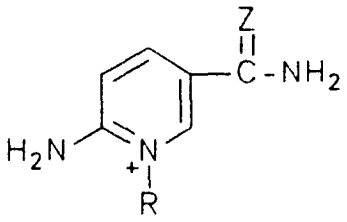
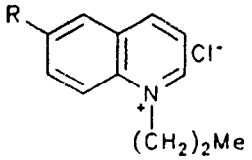


Z = O,S; R = alkyl, Ph.

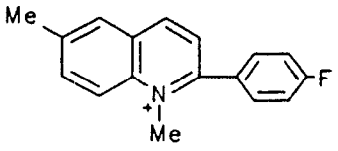
40

Among quinolinium salts one ought to mention **41** and **42** which show bactericidal, fungicidal and antiviral activities, as well as **43**, possessing antileukemic properties [32].



R= H, Me

41



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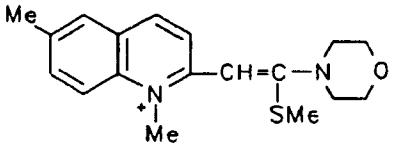


43

Many pyridinium salts can be applied as biological model systems. In the study of pyridinium salts structurally related to NAD, it was shown that they can serve as enolate transferring agents [33].

2. Sulfonium Compounds

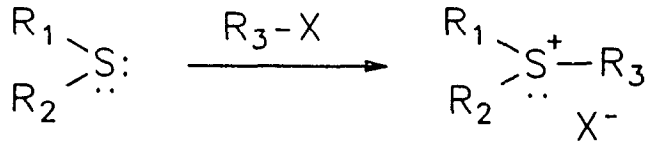
The term "sulfonium salt" is applied to compounds which contain a tricoordinate sulfur atom bearing a positive charge on sulfur. Sulfonium salts therefore have the general structure: $R_1R_2R_3S^+X^-$.

2.1. Synthesis of Sulfonium Salts

2.1.1. Alkylation of Sulfides

The sulfur atom in dialkyl sulfides is weakly nucleophilic and reaction with alkyl halides yields sulfonium salts directly.

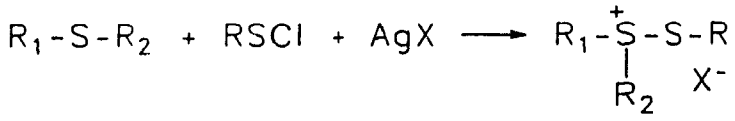
Scheme 16



This simple reaction is promoted by the use of a polar solvent such as methanol because the transition state for the reaction is more polar than the starting materials and the rate is in accordance with general experience in nucleophilic substitution at sp^3 carbon. Methyl halides are the most reactive of the simple alkyl halides. In general, iodides are most reactive; in simple alkylation reactions, sulfides are less reactive than amines [34].

The synthesis of thiasulfonium salts **45** *via* alkylthiolation of sulfides **44** has been carried out with sulfenyl chlorides in the presence of silver salts [35].

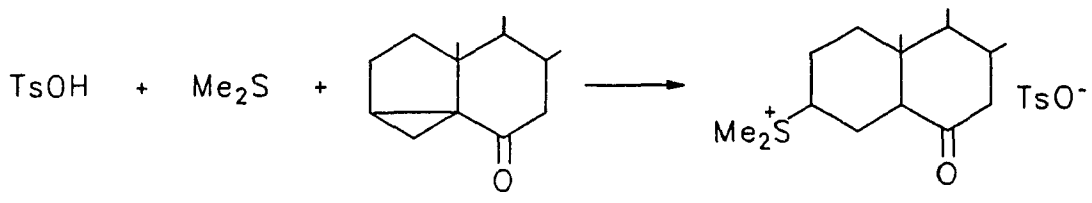
Scheme 17



44 45

Formation of sulfonium salts **46** can result from nucleophilic attack of dialkyl sulfides upon cyclopropanes [36].

Scheme 18

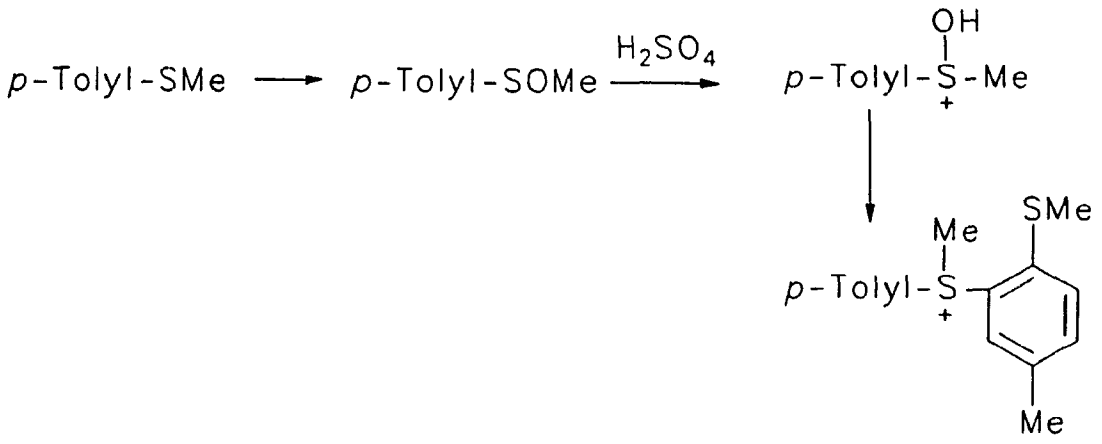


46

2.1.2. Aromatic Electrophilic Substitution

The poor nucleophilicity of aryl sulfides has been referred to and most arylsulfonium salts have been prepared by methods other than alkylation at sulfur. Formation of a sulfur electrophile is conveniently achieved by protonation of a sulfoxide in the presence of, for example, sulfuric acid, and attack by this electrophilic species on an activated nucleophile produces a sulfonium salt **47** [37].

Scheme 19



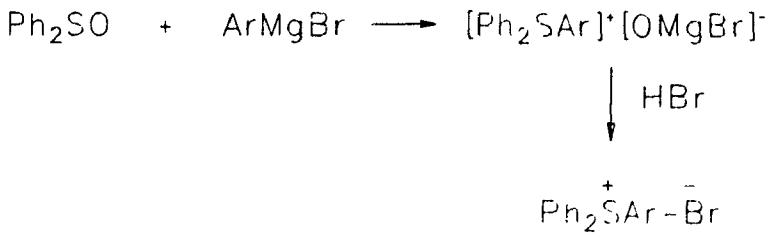
47

This type of electrophilic substitution requires nuclei activated by oxygen or sulfur atoms in this simple form.

2.1.3. Carbanion Addition to the Sulfinyl Group

This method has been mainly used for the rather inaccessible triaryl sulfonium salts. Treatment of diphenyl sulfoxide with phenylmagnesium bromide gives triphenylsulfonium bromide (**48**) in 50% yield [38].

Scheme 20

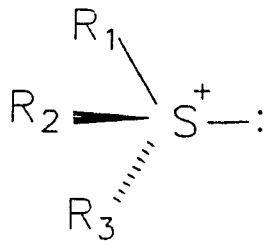


48

2.2. Properties and Reactions of Sulfonium Salts

2.2.1. General Properties

Sulfonium salts differ from ammonium ions by the presence of an unshared electron pair on the central atom and from phosphonium ions by the reluctance to give penta-coordinate compounds which can however, under some conditions, be obtained and which represents one of the most intriguing reaction intermediates along the reaction path of the sulfonium salts [39].



R_1, R_2, R_3 = alkyl, aryl, etc.

49

A wide variety of sulfonium salts crystallize well and do not show difficulties in characterization. It is often convenient, however, to change the common halide counter ion, for example, to picrate (or borate). This is simply achieved by treatment of the sulfonium halide with aqueous sodium picrate (or borate) and the sulfonium picrate (or borate) is precipitated.

Sulfonium salts are ionic and simple members of the series show high solubilities not only in water, but also in organic solvents such as chloroform.

These observations are consistent with the idea that in sulfonium salts $3p$ bonding orbitals are used producing pyramidal $3p$ geometry, the unshared electron pair on sulfur remaining in the $3s$ orbital.

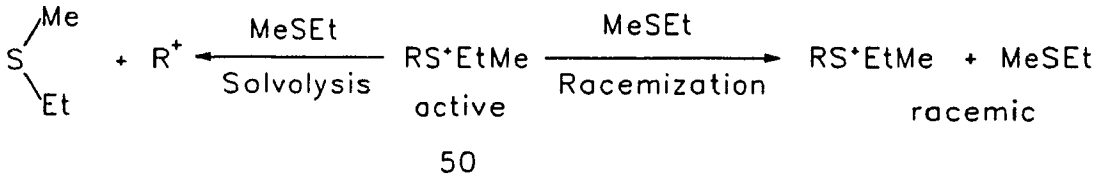
Sulfonium substituents cause marked bathochromic shifts on the spectra of aromatic compounds. This is in contrast to ammonium substituents where no such effect is observed. Further, when other conjugative substituents are present in the nucleus, further bathochromic shift are observed which can be attributed to the ability of the sulfonium group to conjugate with the nucleus and with electron-releasing conjugative substituents in the excited state. Conjugation with sulfonium substituents is not appreciably inhibited by large *ortho* groups which are known to inhibit $p\pi$ resonance sterically in compounds such as aromatic tertiary amines. It is concluded that overlap between the π orbital of the benzene nucleus and d orbitals on sulfur permits the sulfonium substituents to accept electrons conjugatively without stereoelectronic restriction.

2.2.2. The Sulfonium Group as Leaving Group in Displacement Reactions

The presence of the sulfonium pole causes strong polarization of the carbon-sulfur bond, and it may be expected that nucleophiles will be encouraged to attack at carbon with displacement of the sulfonium group. Further, under suitable circumstances, dissociation of sulfonium salts to sulfide and carbonium ion may be observed. Because of the presence of a positive charge, sulfonium salts are highly solvated, and their reactions in which they are involved are very solvent dependent.

Darwish et al.[40] have studied the racemization of benzylethylmethylsulfonium perchlorates (**50**) in methylethyl thioether (Table 1). Results for the first three sulfonium salts are consistent with a scheme in which racemization is independent of solvolysis and involves pyramidal inversion at sulfur. Electron-withdrawing groups such as *p*-nitro have a negligible effect on the inversion rate. For the *p*-methoxy substituted compound, however, solvolysis is very much more rapid, consistent with the formation of a stabilized *p*-methoxy-benzylcarbonium ion.

Table 1 Solvolysis and Racemization of Sulfonium Salts $RS^{+}EtMe \cdot ClO_4^{-}$ **50**



50

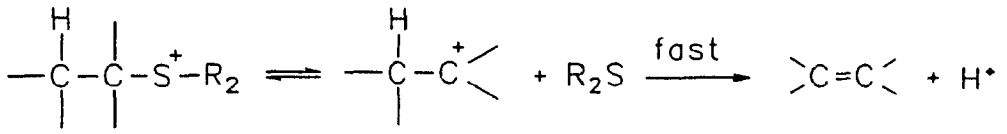
R	$k_{rel.}$ solvolysis	$k_{rel.}$ racemization
$PhCH_2$	1	1
p-$NO_2C_6H_4CH_2$	0.2	0.99
$PhCOCH_2$	0.03	0.6
p-$MeOC_6H_4CH_2$	10^3	15

2.2.3. Sulfonium Group in Elimination Reaction

A. As Leaving Group

The most familiar role is that in which the sulfonium group acts as a leaving group in 1,2-eliminations. Sulfonium compounds played an important part in defining the fundamental ideas on transition states in elimination reactions. Reference has already been made to heterolysis of sulfonium salts with formation of stabilized carbonium ions. This process occurs in 1,2-eliminations which have the unimolecular (E1) mechanism [41].

Scheme 21



More recent work on reactions in which the sulfonium group is the leaving group have concentrated on the interrelationship of the sulfonium and other leaving groups. Particular attention has been paid to the 2-phenylethyl system because of the possibility of examining transition states by the application of linear free energy treatments [42]. Data are given in Table 2.

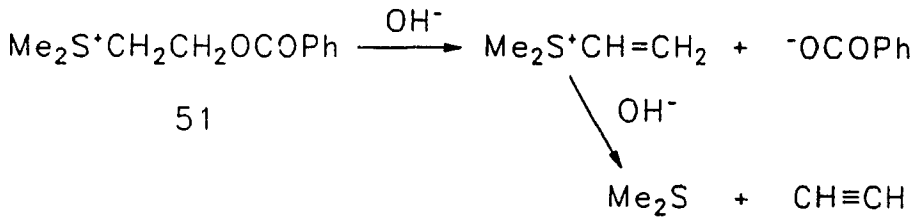
Table 2 E2 Reaction of ß-Arylethyl Compounds ($ArCH_2CH_2X$)

Leaving Group (X)	$k_{rel.}$	ρ	k_H/k_D	Leaving Group Isotope Effect
Br	530	+ 2.14	7.1	—
$^+SMe_2$	1	+ 2.75	5.1	~35% of theoretical maximum
$^+NMe_3$	0.02	+ 3.77	3.0	~30% of theoretical maximum

B. As Carbanion Stabilizing Group

In pioneering work, Rydon et al. [43] showed that the sulfonium group powerfully accelerated reactions in which a leaving group ß to the sulfonium group was eliminated under basic conditions. For example, esters **51** bearing a ß-sulfonium substituents in the alkoxy group decomposed readily to form carboxylate ion, acetylene, and dialkyl sulfide under very mildly basic conditions.

Scheme 22



The activating effect of the sulfonium group in eliminations has received quantitative study recently by Crosby and Stirling in the following system [44]:

Scheme 23

$$X\text{-}CH_2CH_2OPh \xrightarrow{EtO^-/EtOH} X\text{-}CH{=}CH_2 + OPh^-$$

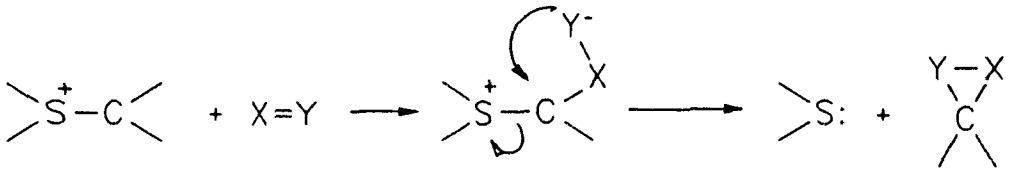
The dimethylsulfonio substituent ($X = Me_2S^+$) is found to cause very rapid elimination of phenoxide under basic condition.

2.2.4. Reactions of Sulfonium Ylides

Sulfonium ylides are zwitterionic species where an anionic carbon is bound to a positively charged sulfur atom. The H-atoms on a α-sulfonium carbon are relatively acidic and may be abstracted by base to form a ylide. For example, the pK_a of dimethylsulfonium (Me_2S^+-CH_2-H) is ca. 18.

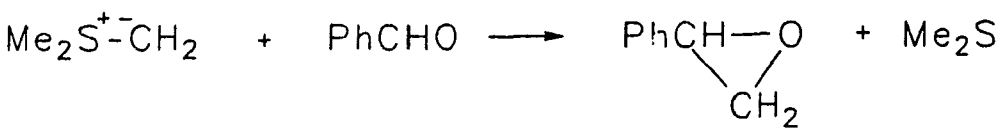
Sulfonium ylides show the reactivity typical of carbanions towards carbonyl groups and towards electrophilic alkenes. The key to the understanding of these reactions is the fact that the intermediate formed by addition is an anion bearing a γ-leaving group (the sulfonium group).

Scheme 24



Addition to ketones of a simple ylide, such as dimethylsulfonium methyl ylide, yields epoxide **52** in nearly quantitative yield [45].

Scheme 25

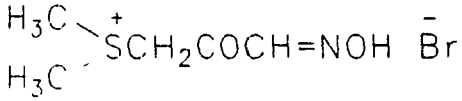


52

Note that this type of reaction differs from the reaction of the corresponding phosphonium ylides in which olefins are produced. The difference in reactivity may be ascribed to the fact that the sulfonium group is a much better leaving group than the phosphonium group in intramolecular displacement at sp^3 carbon.

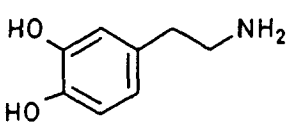
2.3. Biological Activity

Degorre et al. [46] have reported the ability of sulfonium oxime **53** to reactivate acetylcholinesterase (AChE) inhibited by organophosphates. *In vitro* experiments reveal a significant reactivation potency of **53** against paraoxon-inhibited immobilized eel AChE. Also, **53** has a low toxicity and it exhibited a significant antidotal effect at a relatively low dose against paraoxon in rats.



53

Hamada et al. [47] have investigated the biological activity of a series of methyl-, tetralinyl- and naphthalenylsulfonium analogues **55** and **56** of dopamine (**54**). These sulfonium analogues inhibited K^+-induced [^{3}H] ACh release from striatal slices. This inhibition seems to be due primarily to a direct agonist action, since their inhibitory effects on release were not blocked by reserpine-α-MPT treatment.



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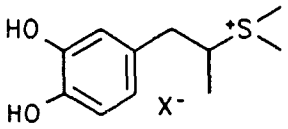

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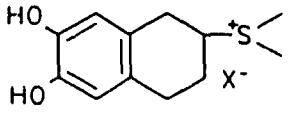
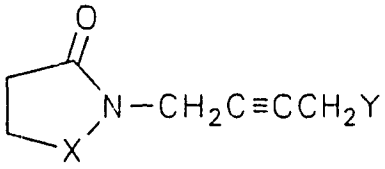


56

Ringdahl [48] reported that thiolanium analogues (**57** and **58**) of oxotremorine were synthesized and found to be potent muscarinic agonists having high affinity for central and peripheral muscarinic receptors.



X= CH_2, Y= ^+S 57

X= CO, Y= ^+S 58

3. Preparation of Mixed Hagedorn Oximes

3.1. The Reason for Preparing This Type of Compound

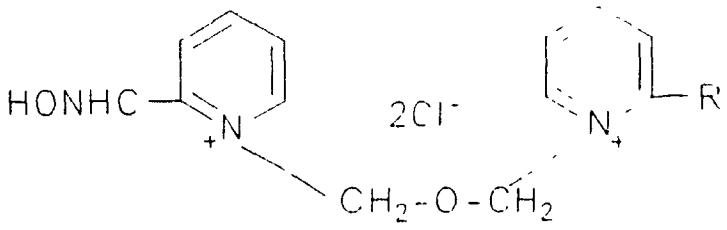
Acetylcholinesterase (AChE) functions in the central and peripheral nervous systems, along with the acetylcholine (ACh) receptor, in the transmission of action potentials across nerve-nerve and neuromuscular synapses. The enzyme's physiological task is the hydrolytic destruction of the cationic neurotransmitter ACh. AChE is an extrinsic membrane-bound enzyme that projects into the synapse.

Various organophosphorus compounds irreversibly inhibit AChE by phosphonylating a catalytic serine hydroxyl at the enzyme active site. Standard therapy for anti-AChE intoxication is based on coadministration of anticholinergics (eg. atropine) to antagonize the effects of accumulated ACh and of AChE "reactivators". AChE reactivators function as nucleophiles to displace the phosphate moieties from inhibited AChE and thereby restore activity to enzyme [49].

Currently, pyridinium aldoximes are the only clinically used reactivators. This conventional treatment is effective for general organophosphorus esters including the chemical warfare agents Sarin (isopropyl methylphosphonofluoridate, GB) and VX (ethyl-S-diisopropylaminoethyl methylthiophosphonate) but is unsuccessful in cases of Soman (pinacolyl methylphosphonofluoridate, GD) intoxication [50].

In 1970, Oldiges and Schoene [51] reported that certain unsymmetrically substituted bis(pyridinium)dimethyl ether derivatives constitute effective therapy for GD poisoning in mice. The findings of Oldiges and Schoene evoked considerable

interest in the synthesis and evaluation of bis(pyridinium)dimethyl ether derivatives. The reactivators that are effective against GD conform to the general structure **59**, where R = $C(O)NH_2$, $C(O)C_6H_5$, or $C(O)C_6H_{11}$ in the 2- or 4- position of the indicated pyridinium ring [52].



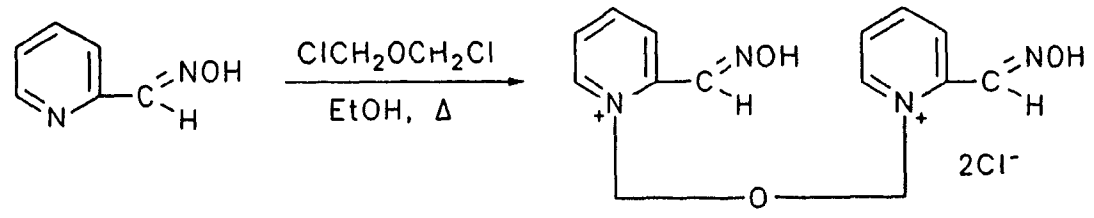
59

3.2. Classical Methods in the Preparation of Pyridinium Analogs of Hagedorn Oximes

3.2.1. Methods

Symmetrical substituted bis(pyridinium)dimethyl ether derivatives, such as **60**, have been prepared by heating an ethanolic solution of pyridine-2-carboxime **61** and bis(chloromethyl)ether.

Scheme 26



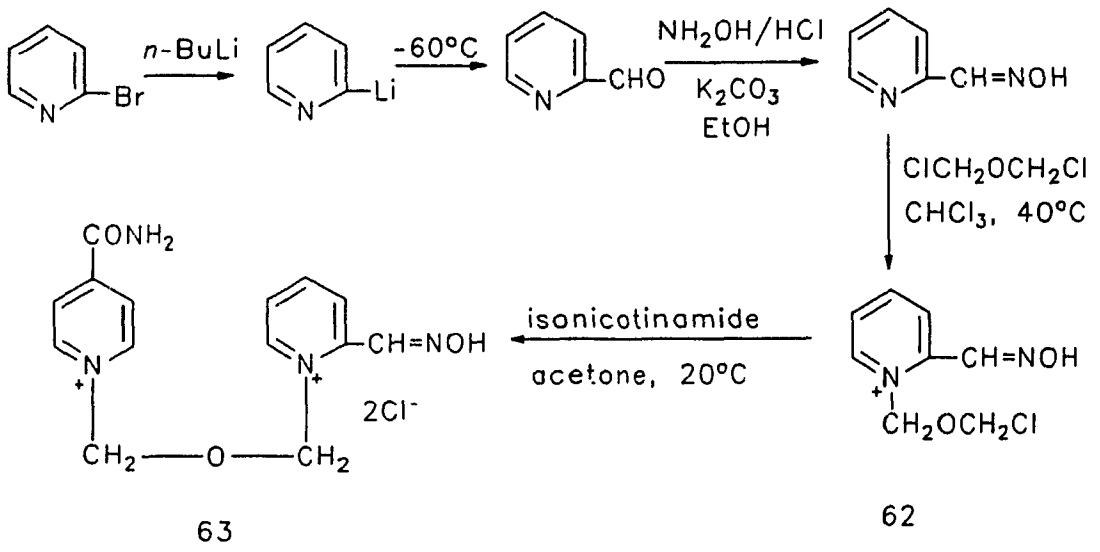
61

60

Unsymmetrical oximes can be prepared by using two different pyridines in the reaction, although a mixture of the possible products results and the desired oxime must be isolated.

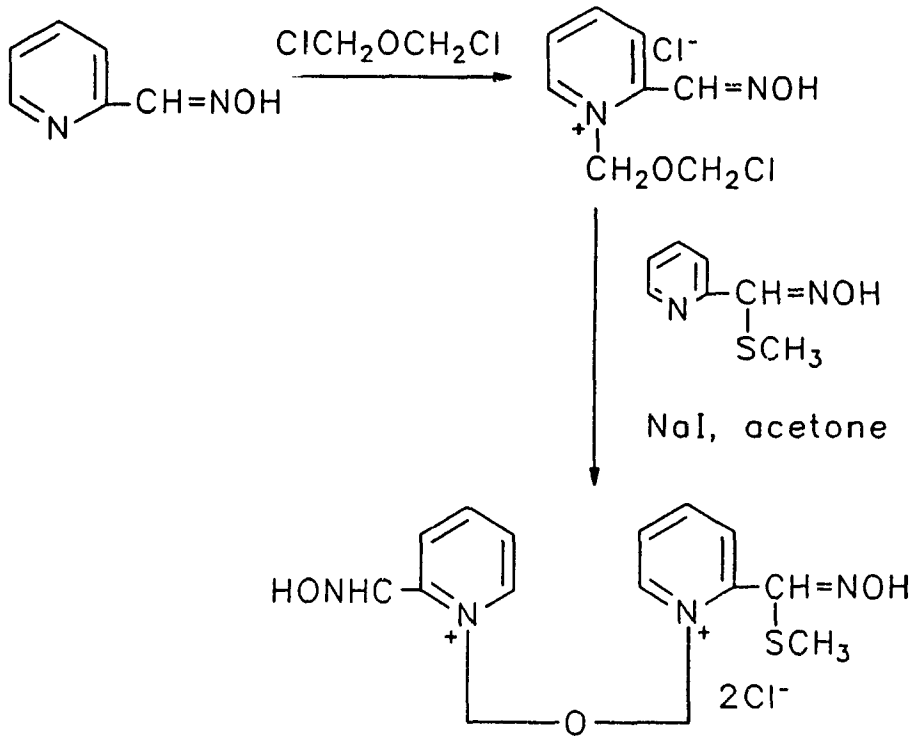
In 1989, Nicolas et al. [53] synthesized a mixed pyridinium salt **63** by the following procedure:

Scheme 27



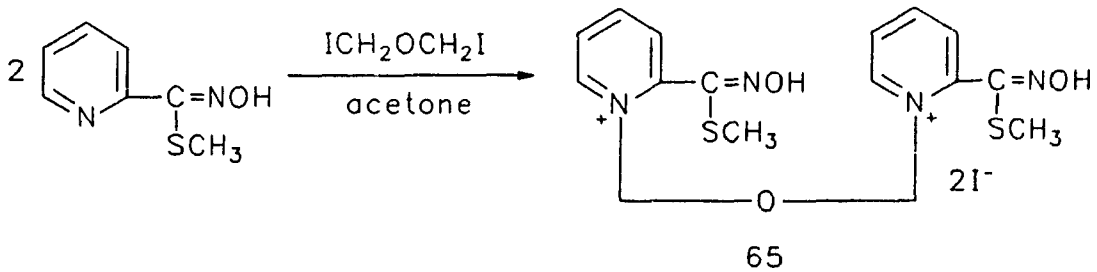
Bregovec et al. [54] prepared methylthio analogues of obidoxime **64** and **65** with the similar method.

Scheme 28



64

Scheme 29



65

3.2.2. Disadvantage of These Methods

The common and key point of these classical methods is the use of bis(chloromethyl)ether (**66**), which usually is prepared by saturation of formaldehyde with dry hydrogen chloride [55].

Scheme 30

$$2CH_2O + 2HCl \xrightarrow[-H_2O]{} ClCH_2\text{-}O\text{-}CH_2Cl$$

66

There are several disadvantages in the preparation of analogs of Hagedorn oximes by using bis(chloromethyl)ether.

1). Bis(chloromethyl)ether has a very high carcinogenic activity when administered to rats by inhalation and by subcutaneous injection [55] and it has been listed as a known carcinogen.

2). Reagent bis(chloromethyl)ether is not commercially available because of its high carcinogenic activity.

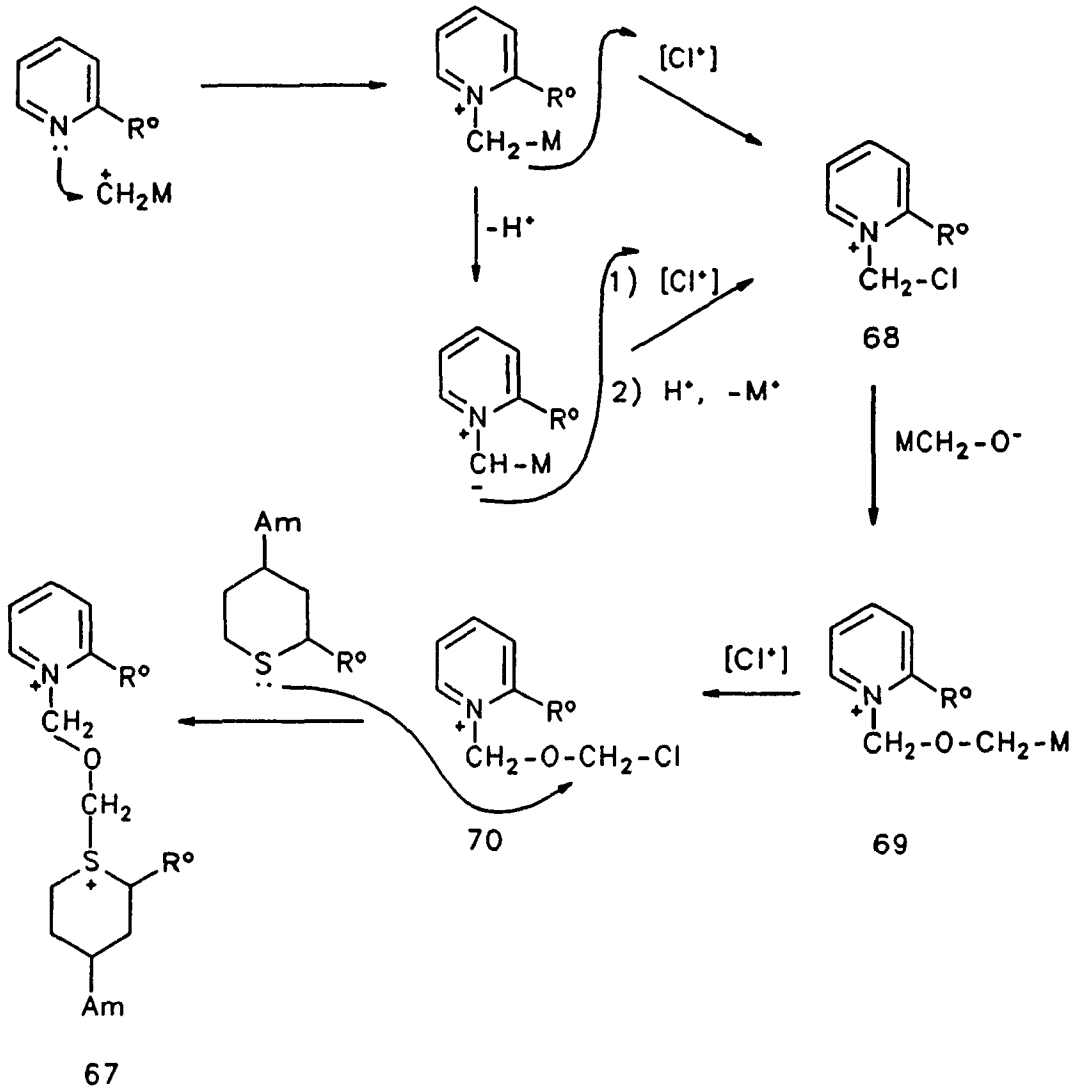
3). The reaction of oximes with bis(chloromethyl)ether can produce some by-products whose properties are similar to the product, so it is very difficult to isolate the desired product and the yield is low.

CHAPTER II. OBJECTIVES OF PRESENT STUDY

The original objective of the present study was to achieve a reliable synthetic method for the preparation of unsymmetrical Hagedorn oxime analogs including those which contain sulfonium instead of pyridinium moieties and avoids the use of the strong carcinogen bis(chloromethyl)ether.

In order to efficiently prepare unsymmetrical sulfonium analogs of Hagedorn oximes (eg. 67), it is desirable to build up the molecule from one heterocycle ring to the next. Furthermore, since the nucleophilicity of a sulfide is greater than that of pyridine, sulfonium analogs of Hagedorn oximes can only be prepared by such a controlled stepwise formation of the dimethyl ether bridge.

Scheme 31



R° = oxime or masked/precursor oxime group

M = boronyl or silyl group

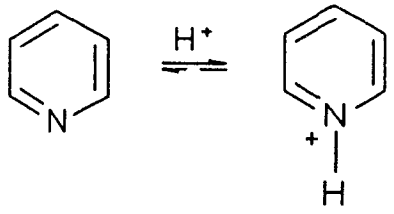
Am = amide group

CHAPTER III. RESULTS AND DISCUSSION

1. *N*-Alkylation

In reactions which involve bond formation with the lone pair of electrons on the ring nitrogen, such as protonation and quaternization, pyridine acts as a weak base because the lone electron pair on nitrogen is not tied up by conjugation.

Scheme 32

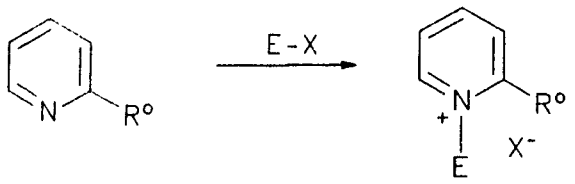


Pyridinium

$pK_a = 5.29$

The ring nitrogen of pyridine is modestly nucleophilic and requires a reactive species in order to effect *N*-alkylation. If the carbon bearing the leaving group has a second functionality which can be subjected to further reaction after the initial *N*-alkylation, this would allow elaboration to the desired dimethyl ether bridge (Scheme 31). Table 3 indicates the alkylating agents which were investigated.

Table 3 *N*-Alkylation of Pyridines



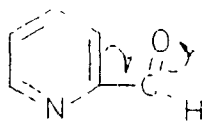
71

E^+X^-	R^0	Condition	Yield (%) (**Product**)
$(^iPrO)_2B\text{-}CHCl_2$	CHO	CH_2Cl_2, Δ,	No alkylation
		Toluene, Δ,	No alkylation
$(^iPrO)_2B\text{-}CHCl_2$	CH=NOH	Same as above	Same as above
$BrCH_2CO_2Et$	H	EtOH, Δ, 2 h	40 (**71a**)
Me_3SiCH_2I	H	Acetone, Δ, 12 h	32 (**71b**)
Me_3SiCH_2OTs	H	Neat, R.T.	26 (**71c**)
Me_3SiCH_2Cl	$CH(OMe)_2$	CH_2Cl_2, R.T., 2 h	No reaction
Me_3SiCH_2Cl	$CH(OMe)_2$	THF, $AgBF_4$, R.T., 2 h	No reaction
Me_3SiCH_2I	$CH(OMe)_2$	Dioxane, 200 °C [a], 20 h	No reaction
Me_3SiCH_2I	$CH(OMe)_2$	95% EtOH, 170 °C [a], 24 h	No reaction
Me_3SiCH_2OTs	$CH(OMe)_2$	Neat, 120 °C, 4 h	20 (**71e**)

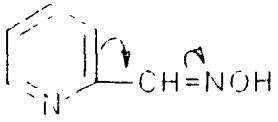
Note: a. Reaction performed in bomb above atmospheric pressure reflux temperature of solvent.

The *N*-alkylation reaction with the boron compound failed. The reaction of the diisopropoxy dichloromethyl boron compound with 2-pyridinecarboxaldehyde in toluene produced a solid that came out of solution once all the solvent was removed. Reaction of this solid with dilute HCl produced a compound whose ^{1}H NMR spectrum showed a loss of the two isopropoxy group and generation of signals that did not agree with the proposed structure of the desired *N*-alkylation material. It appeared that a Lewis acid-base adduct ($py \rightarrow B(O^iPr)_2CHCl_2$) was the only product. The reaction of the boron compound with 2-pyridinealdoxime led to a similar result.

Since the carbonyl- or oxime groups are strongly electron-withdrawing relative to hydrogen and have no capacity to donate electrons by a resonance effect, these groups will decrease the electron-density of the pyridine nitrogen (pK_a of oxime group is ca. 12). Therefore, the electron-withdrawing carbonyl- or oxime groups deactivated the ring nitrogen so as to preclude *N*-alkylation at temperatures below those used for Hagedorn oxime preparation.



72



A rough measure of the difference between carbonyl- or oxime- substituted and unsubstituted pyridines in nuclecphilicity is provided in the acidity of conjugate

acids. The oxime group causes a decrease in pK_a from that of protonated pyridine (5.25 to 3.59[56]). The carboxaldehyde group has the same effect.

Conversely, unsubstituted pyridine did undergo reaction with a variety of primary alkylating agents. Several *N*-alkylation reactions of pyridine were attempted with different alkylating agents under the conditions as described above. (*N*-Ethoxycarbonylmethyl)pyridinium bromide **71a** was obtained from ethyl bromoacetate in 40% yield and the reaction of pyridine with (iodomethyl)trimethylsilane gave *N*-trimethylsilylmethylpyridinium iodide **71b** in 32% yield.

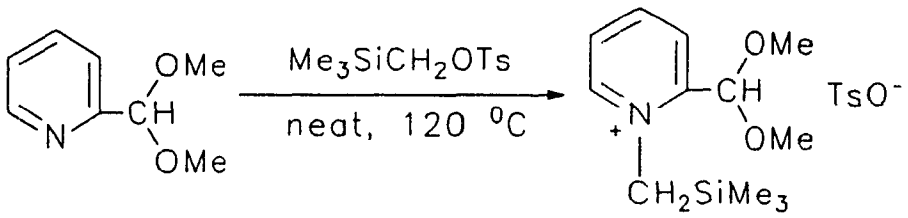
In order to avoid deactivation of the pyridine nitrogen and to facilitate alkylation, the 2-carbaldehyde group was converted into the corresponding acetal. This was done with trialkylsilylated alcohol derivatives and a catalytic amount of silylating agent.

Several reactions have been conducted by using different electrophiles and conditions in order to observe trends for the *N*-alkylation of the dimethyl acetal derivative **73b**. However, with chloromethyl trimethylsilane as the electrophile under a mild condition (CH_2Cl_2, room temperature for 2 h), the *N*-alkylation reaction could not work. The addition of silver tetrafluoborate ($AgBF_4$) is a less mild condition, which can shift the reaction equilibrium to the right side by precipitating silver chloride (AgCl) as precipitate forms, but the *N*-alkylation reaction still did not work. The attempt of reacting iodomethyl trimethylsilane with **73b** in a bomb at high temperature was also unsuccessful (lost trimethylsilyl group). These results suggested that the steric hindrance at the nitrogen required the use of more vigorous conditions

in order to force silylmethylation to occur. The conditions used appear to have promoted protodesilylation and the formation of the *N*-methyl compound.

With a much stronger electrophilic agent (trimethylsilylmethyl *p*-toluenesulfonate) and high temperature conditions, the *N*-alkylation of dimethyl acetal derivative **73b** seems to have worked but the yield under this specified condition was poor (~20%, from NMR spectra). Since the starting materials contained 2-pyridinecarboxaldehyde, the final mixture was too complicated to separate and purify the product **71e** easily. More detailed studies for this reaction have not been done yet.

Scheme 33

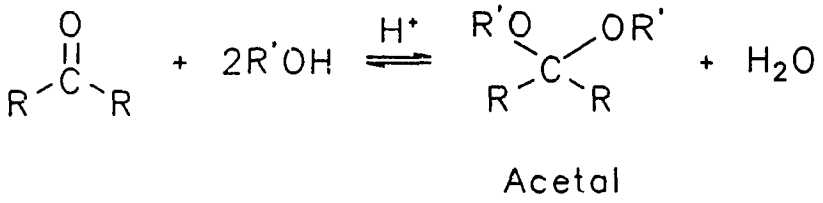


73b 71e

2. Acetal Formation

During a synthetic sequence, a carbonyl group may have to be protected against attack by various reagents such as strong or moderately strong nucleophiles. The protecting group is usually introduced by treating the carbonyl compound in the presence of acid with an alcohol, diol, thiol, or dithiol etc.. Acetals are stable under neutral and alkaline conditions and can, therefore, be used to protect carbonyl group during alkylation, acylation, oxidation, and reduction reactions.

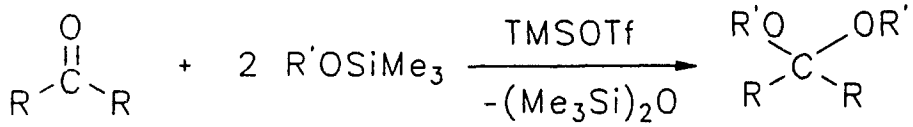
Scheme 34 General Acetal Synthesis



Acetal

The 1,3-dioxolane moiety is one of the most frequently used protecting groups for carbonyl compounds. Use of 1,2-bis(trimethylsilyloxy)ethane (BTSE) catalyzed by trimethylsilyl trifluoromethylsulfonate (TMSOTf) for 1,3-dioxolanation was first reported by Noyori [57].

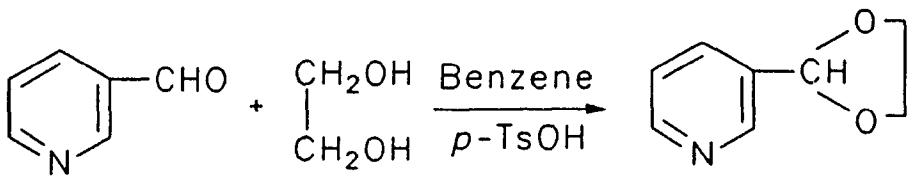
Scheme 35



This method has been shown to be useful for selective 1,3-dioxolanation of carbonyl groups in which one such group is less sterically hindered than another. It is also useful for dioxolanation of acid-sensitive α, ß-enals.

Aldehydes are also frequently protected as the acetals derived from ethylene glycol. Acetals are stable under neutral and alkaline conditions and can, therefore, be used to protect aldehydes during *N*-alkylation. Lounasma et al. [58] have reported that the acetalization of 3-pyridinecarboxaldehyde with ethylene glycol can yield the corresponding 3-pyridinecarboxaldehyde acetal, which was alkylated with methyl iodide to afford the corresponding methyl salt.

Scheme 36

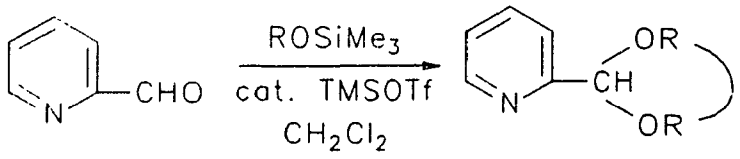


The treatment of a mixture of 2-pyridinecarboxaldehyde and ethylene glycol with *p*-TsOH as catalyst produced the desired acetal only in low yield. This suggested that acetal formation of 2-pyridinecarboxaldehyde (**72**) *via* standard Bronsted acid catalysis [58] was inefficient, probably because protonation of the ring nitrogen was competing with the desired catalysis. The efforts to obtain the acetal by the BTSE procedure at -78 °C did not succeed either.

The most efficient conversions resulted from the use of trialkylsilylated alcohol derivatives and a catalytic amount of silylating agent at higher temperature bomb

reaction. These results are summarized in Table 4.

Table 4 Preparation of acetals



72 73

$ROSiMe_3$	Condition	Yield (%)	Acetal
$Me_3SiOCH_2CH_2OSiMe_3$	- 78 °C	No reaction	**73a**
$MeOSiMe_3$	- 78 °C	No reaction	**73b**
$MeOSiMe_3$	150 °C (bomb)	20 - 40 [a]	**73b**
(MeOH)	TsOH, Δ	No reaction	

Note: a. Yield not optimized.

Trimethylsilyl trifluoromethylsulfonate ($Me_3SiO_3SCF_3$, TMSOTf) is a powerful silylating agent for organic compounds and acts as a catalyst for a variety of nucleophilic reactions in aprotic media [59]. In TMSOTf-catalysed nucleophilic reactions, carbonyl compounds smoothly give acetals and thio-acetals *via* the

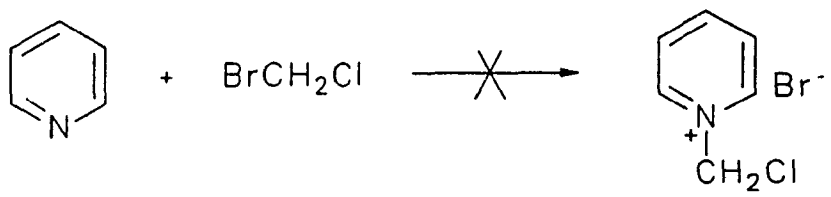
corresponding trimethylsilyl ether or thio ether. Acetalization of 2-pyridinecarboxalydehyde (**72**) with methoxytrimethylsilane in dichloromethane (TMSOTf as catalyst) gave a 3:1 mixture of 2-(bismethoxy)methylpyridine (**73b**) and 2-pyridinecarboxaldehyde (**72**) in 40% yield. The reaction was conducted in a bomb at 150 °C for 72 h. The proton NMR spectrum of this mixture exhibited a singlet at δ 3.3 ppm for the hydrogen of two methoxy groups and the hydrogen of methyl group on C_2 position of pyridine gave a singlet at δ 5.3 ppm. The reagent methoxytrimethylsilane ($MeOSiMe_3$) was synthesized by the reaction of methanol and trimethylsilyl chloride in the presence of pyridine at 0 °C, and the product was purified by fractional distillation.

3. Formation of *N*-Chloromethylpyridinium Chloride

N-halomethylpyridinium salts are very difficult to prepare by classical alkylation methods. To the best of our knowledge, *N*-halomethylpyridinium salts are unknown.

The treatment of pyridine with alkylating reagent bromochloromethane was investigated as a possible method for the synthesis of *N*-chloromethylpyridinium bromide, but the reaction failed (Scheme 37).

Scheme 37

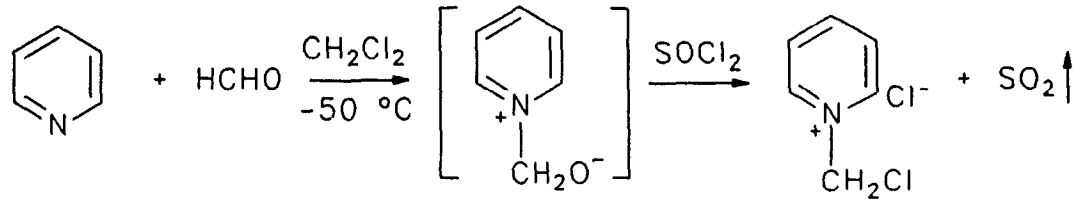


Unlike bromomethane (CH_3Br), bromochloromethane ($BrCH_2Cl$) has two halogens linked to the same carbon atom. Therefore, it is not an active alkylating agent because of the remarkable stability of the C-Br or C-Cl bonds to nucleophilic substitution.

An alternate strategy for the preparation of this kind of compound from a pyridine-formaldehyde-thionyl chloride three components system was more successful. We found that the *N*-chloromethylpyridinium chloride (**74a**) is formed at -50 °C in 70% yield from formaldehyde and thionyl chloride. It appears that pyridine adds to formaldehyde and the resultant pyridinium methoxide is sufficiently stable at -50 °C

to be trapped by reaction with thionyl chloride (Scheme 38).

Scheme 38

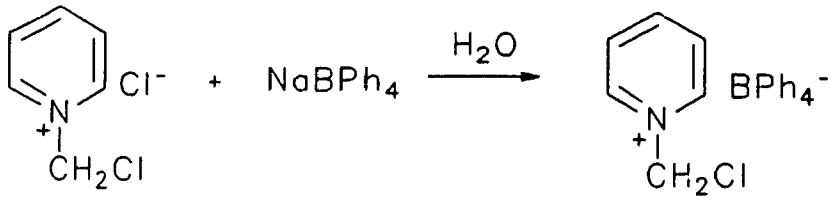


74a

Since the boiling point of formaldehyde is only -21 °C, this reaction was conducted at ca. -50 °C in dichloromethane in order to prevent the evaporation of reactant. Preformation of the formaldehyde is essential for the success of this reaction. The dry gaseous formaldehyde can be obtained by the thermal depolymerisation of paraformaldehyde. The formaldehyde vapour is carried into the stirred pyridine-thionyl chloride-dichloromethane solution at -50 °C by a slow stream of nitrogen through a wide glass tube fitted into the neck of the reaction flask. The reaction of the three components system at ca. -50 °C in dichloromethane gave the required *N*-chloromethyl pyridinium (**74a**) in good yield (70%). The ^{1}H NMR spectrum of **74a** clearly show that the -CH_2- bears a high degree of positive charge which significantly deshields the *N*-C**H**$_2$- protons, thereby shifting the signal downfield to δ 7.10 ppm. While *N*-C**H**$_2$-Cl signal of **74a** is shifted to lower field by the electron-withdrawing effect of both N and Cl atoms. The proton of C_4 position gave a doublet at δ 9.81 ppm (J = 6.8 Hz) while the proton from other positions gave both triplets at δ 8.10 and 8.55 ppm respectively.

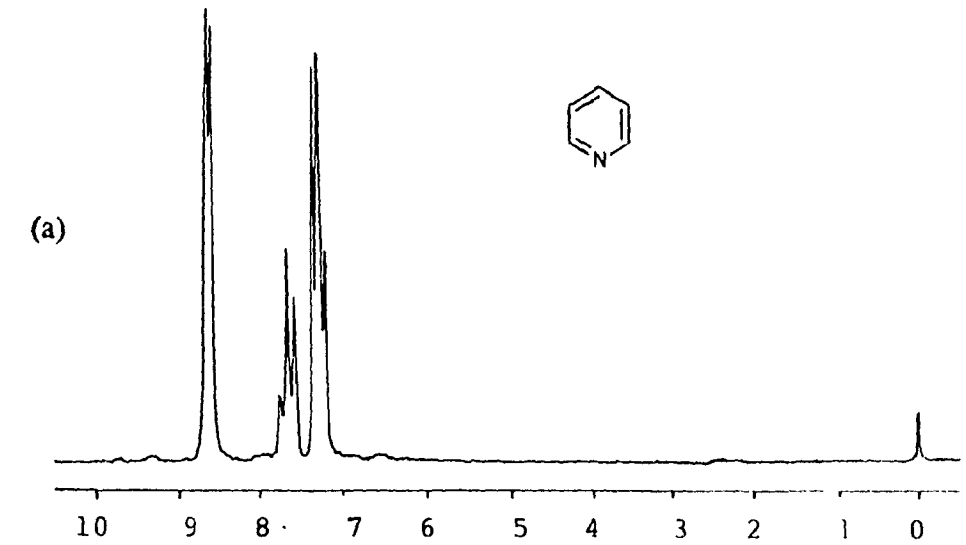
N-Chloromethylpyridinium chloride (**74a**) is hygroscopic. The salt of **74a** with tetraphenylborate instead of chloride, does not have this property, and can be readily prepared from the chloride **74a**. This is achieved by treatment of the **74a** with aqueous sodium tetraphenylborate and the pyridinium tetraphenylborate **74b** is precipitated.

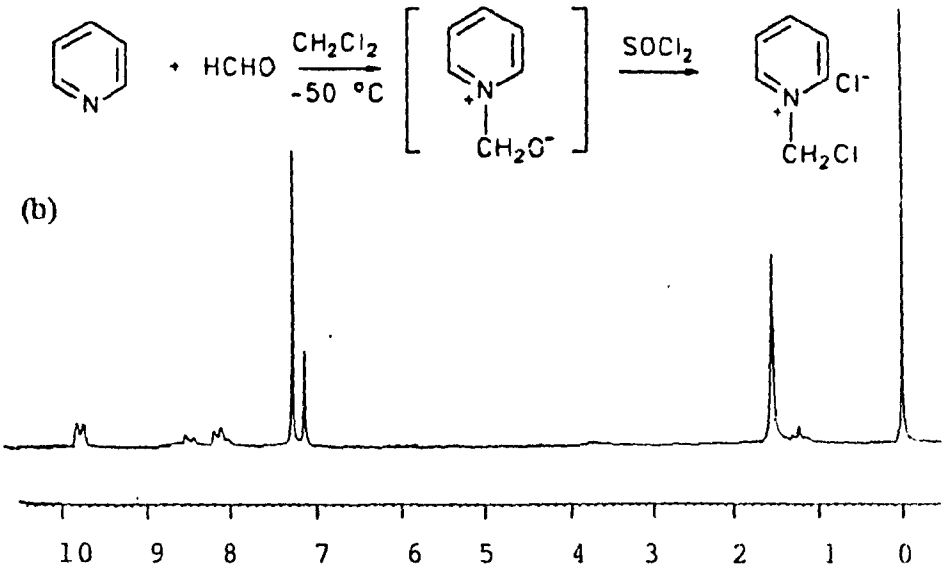
Scheme 39



74a 74b

Figure 1. (a). Reference spectrum of pyridine. (b). ^1H NMR spectrum taken during reaction among pyridine, formaldehyde and thionyl chloride.

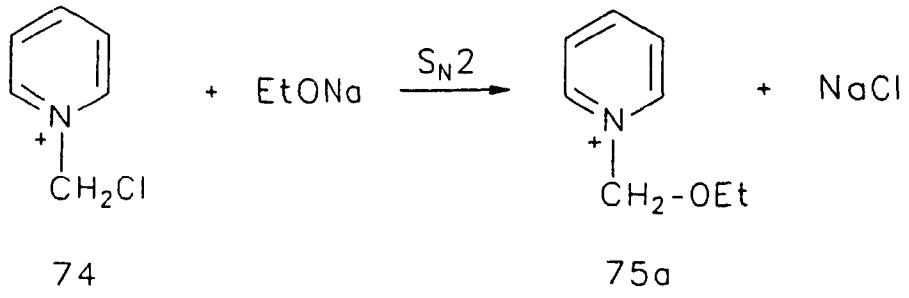




4. Ether Formation

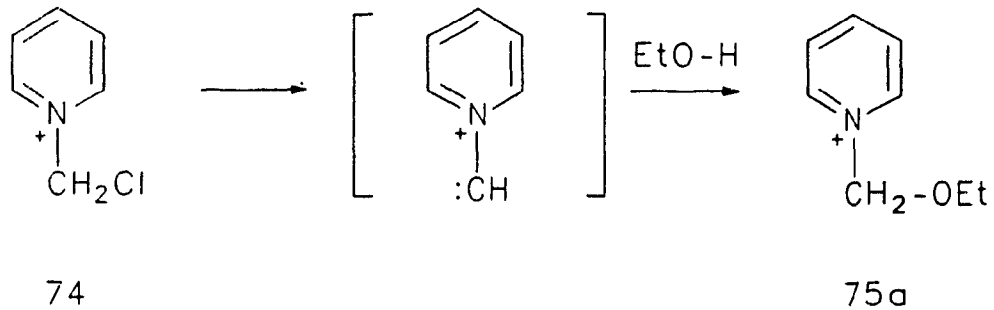
The original synthetic strategy was validated by the formation of the ethyl ether **75a** in the reaction of ethoxide ion with the *N*-chloromethyl compound. This reaction proceeded only at elevated temperature, raising the mechanistic question of whether product formation occurs by a simple S_N2 displacement of chloride ion (Scheme 40) or generation of a carbene which then inserts into the hydroxyl group of the alcohol (Scheme 41).

Scheme 40



74 75a

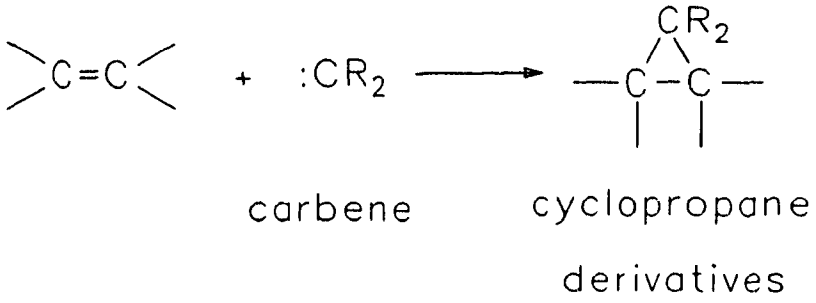
Scheme 41



74 75a

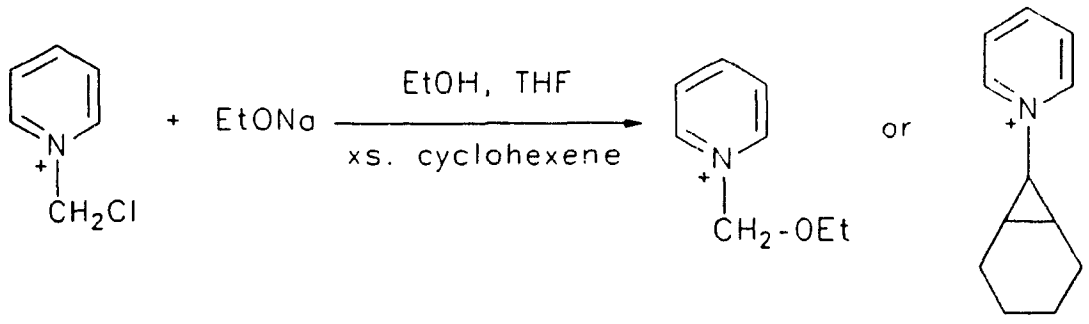
Carbenes, in general, are reactive electrophilic species in which a divalent carbon atom has only six valence electrons. Carbenes have very high reactivity toward many classes of organic compounds. For example, in the cycloaddition reaction, cyclopropane derivatives can be formed by addition of carbenes to the double bond of olefins (Scheme 42).

Scheme 42



To confirm the reaction mechanism, the reaction of **74a** and sodium ethoxide with excess amount of cyclohexene was carried out (Scheme 43).

Scheme 43



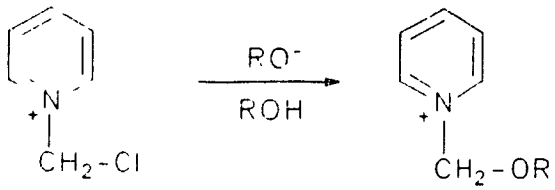
74 75a 75c

If a cyclohexene addition product **75c** is obtained, that means the mechanism

is probably *via* carbene because a carbene intermediate should react with the double bond of excess cyclohexene to form cyclopropane derivative **75c**.

However, since there was no cyclopropane derivatives **75c** by ^1H NMR (last entry in Table **5**), it appears that this is, in fact, a simple S_N2 displacement reaction. It was also gratifying that displacement of chloride ion and not pyridine was occurring in alcoholic solution because no chloromethylethyl ether was found in this kind of reaction. The latter would be attributed to the cleavage of N-CH_2Cl bond and displacement of pyridine by ethoxide.

Table **5** Preparation of Ethers



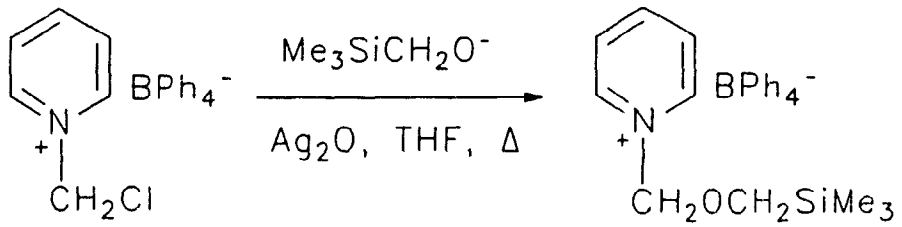
74 75

RO	Condition	Product	Yield (%)
EtO	xs. EtOH, R.T., 30 min.	**75a**	78
Me_3SiCH_2O	THF, Δ	No reaction	0
Me_3SiCH_2O	Ag_2O, THF, Δ	**75b**	Not optimized
EtO	xs. cyclohexene, EtOH, Δ, 24 h	**75a**	50

The product *N*-(ethoxymethyl)pyridinium chloride (**75a**) was confirmed by ^{1}H NMR spectroscopy. There is a singlet at δ 6.4 ppm for the hydrogen of *N*-C**H**$_2$-OEt. The *N*-C**H**$_2$- signal of **75a** is shifted to higher field than that of *N*-Chloromethyl group of **74a** (**75a**, δ = 6,4; **74a**, δ = 7.10 ppm), which may be attributed to the opposite effects of electronegativity of nitrogen atom and electron-donating effect of -OEt group. The reason is that ethoxide group has less electronegative activity than that of chlorine atom.

The reaction of the *N*-chloromethyl compound with trimethylsilylmethoxide ion is of greater interest because this product would allow further elaboration to the desired mixed oxime according to Scheme 31. In this case, ^{1}H NMR spectrum showed that the trimethylsilylmethoxymethyl product **75b** appeared to have formed as expected (Scheme 44).

Scheme 44



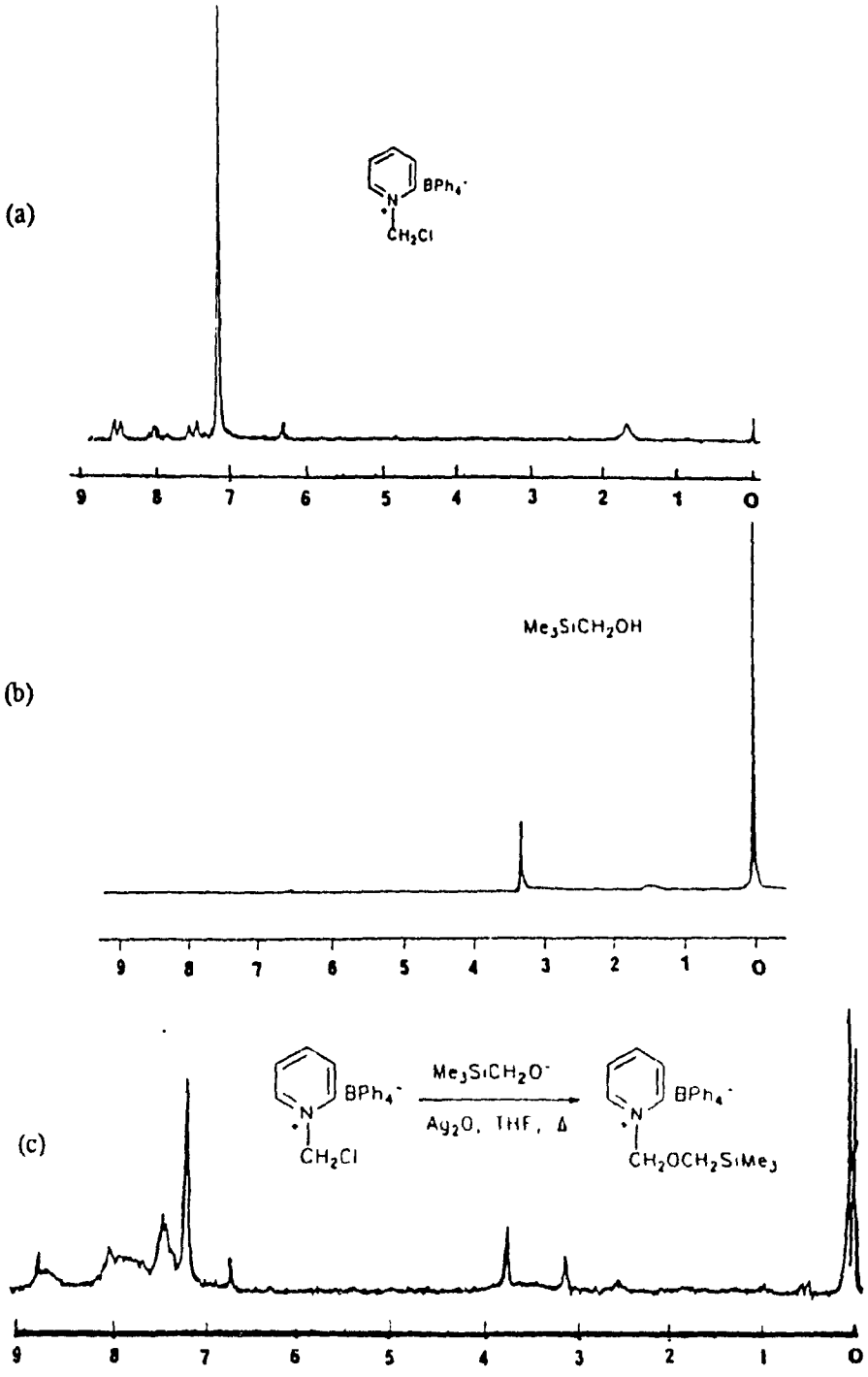
74b 75b

The reaction procedure is that to the solution of pyridinium salt **74b** and trimethylsilylmethanol in THF was added silver oxide and then the solution was heated at reflux for 24 h. In order to let the reaction equilibrium shift to the right

side as soon as possible and get a relatively high yield, the addition of silver oxide is necessary. The end products were detected by NMR. The proton NMR spectra (d_6-DMSO) showed that there were a singlet at δ 0.1 ppm (the hydrogen of trimethylsilyl group) and the signal of hydrogen of -OC**H**$_2$SiMe$_3$ group turn to δ 3.70 ppm from δ 3.15 ppm (Me$_3$SiC**H**$_2$OH). In order to separate the final product from the reaction mixture, the purification process was performed by using column chromatography.

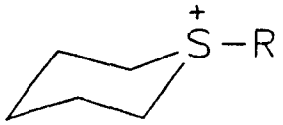
Unfortunately, the desired product **75b** underwent a desilylation during chromatographic purification to lose the trimethylsilyl group. It appeared that the reaction of trimethylsilyl group with silica gel resulted in the C-Si bond cleavage and a *N*-methoxymethylpyridinium salt seem to be obtained after the desilylation of the product **75b**. A product isolation procedure that can effectively avoid the desilylation need be optimized.

Figure 2. (a). Reference spectrum of *N*-chloromethylpyridinium tetraphenylborate. (b). Reference spectrum of trimethylsilylmethanol. (c). ^{1}H NMR spectrum taken during reaction between *N*-chloromethyl tetraphenylborate and trimethylsilylmethanol.

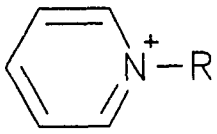


5. *S*-Alkylation of Tetrahydrothiopyran

Some fundamental differences exist in the behaviour of pyridinium and sulfonium compounds. For example, there is more charge localization on the heteroatom in the tetrahydrothiopyran series and the sulfonium compounds have a non-planar structure (eg. **76** versus **71**).

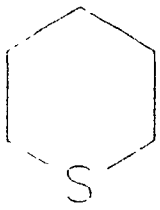


76



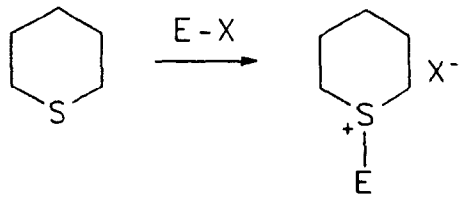
71

Since the sulfur atom of tetrahydrothiopyran (***77***) is more nucleophilic than the nitrogen atom of pyridine, the preparation of sulfonium derivatives of **77** could be accomplished using milder reaction condition (Table **6**).



77

Table 6 *S*-Alkylation of Tetrahydrothiopyran



77 78

E-X	Condition	Product	Yield (%)
$BrCH_2CO_2Et$	EtOH, Δ, 2 h	**78a**	66
Me_3SiCH_2I	Acetone, Δ, 12 h	**78b**	35
CH_3I	EtOH, Δ, 4 h	**78c**	88

All of the sulfonium salts could be obtained as well-behaved crystalline materials. These sulfonium compounds were also stable in polar solvents (eg., acetone, ethanol) but underwent reversion to the parent compound **77** and alkyl halide in non-polar solvents such as deuteriochloroform.

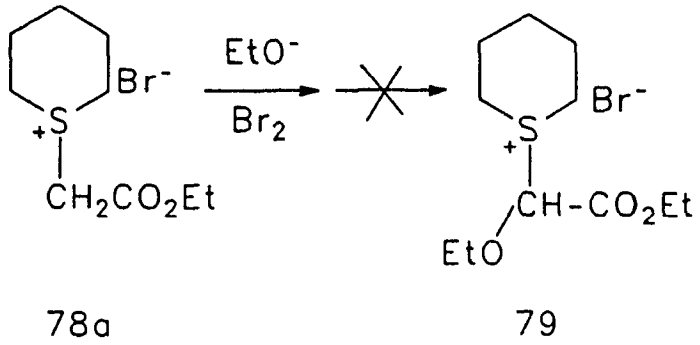
The preparation of **78a** is noteworthy, since the new alkyl group contains one more carbon than is required in the methyl ether linkage of the ultimate product. Unlike the pyridinium compounds, the sulfonium compounds **78a-c** have two different sites at which deprotonation can generate a carbanion. Fluorodesilylation of **78b**

would effectively generate a carbanion regiospecifically at the methyl position of **78c**. The presence of the carbonyl group further increases the acidity of the exocyclic methylene position from the estimated pK_a value of 18 for the ring α-positions. Furthermore, iododemethylation and decarboxylation of related sulfonium acetates has been demonstrated [60], suggesting that once the ester group has been used to control carbanion reactions at the future methoxy group, this ester group can be mildly and selectively removed.

The poor solubility of **78b** in common polar aprotic solvents precluded any attempt to fluorodesilylate the alkyl group and trap the resultant sulfonium-stabilized carbanion with bromine or iodine. When deprotonation of the methylene group of **78b** was attempted using aqueous hydroxide ion in the presence of iodine, only the *S*-methyl compound **78c** was obtained. This suggests that desilylation generated a carbanion which underwent protonation.

Bromination of **78a** was attempted by generating an enolate with ethoxide ion in ethanol (using ethanol as a model for the analogous reaction with trimethylsilylmethoxide ion). Instead of the anticipated α-ethoxy product **79** resulting from halogenation and substitution (Scheme 45), this reaction gave ethyl α-ethoxyacetate. The final crystallized product, detected by ^1H NMR, lacks both the ester and ether group, suggesting the reaction underwent a S^+-C bond cleavage to form α-ethoxyacetate. This product corresponds to the displacement of **77** by ethoxide ion and not enolate formation and bromination. This reaction was not pursued further.

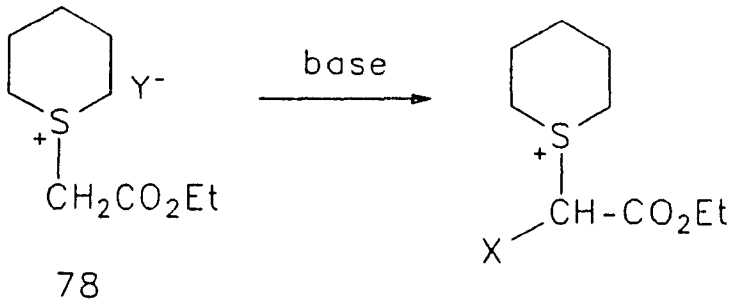
Scheme 45



78a 79

Similar halogenations were attempted using a variety of reagents. The results are summarized in Table 7.

Table 7 Reactions of 78a with Base and Halogen



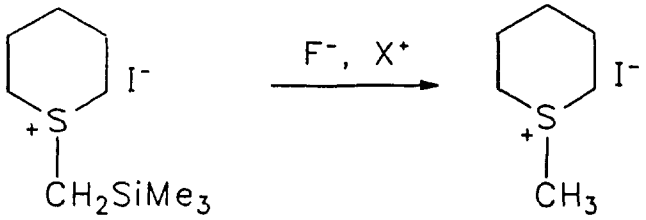
78

Y⁻	Condition	X	Yield (%)
Br^-	EtO^-, Br_2, Δ, 1 h	EtO	56 (**78c**)
Br^-	AcOH, Br_2	-	Ring cleavage
BPh_4^-	NaH, THF, I_2, R.T. 15 h	I	45 (**78c**)

It is mildly surprising that acid-catalysed enolization and attempted halogenation led to only eliminative cleavage of the tetrahydrothiopyran ring.

Table 8 presents the results of attempted replacement of the silyl group by bromine. When fluorodesilylation was attempted with commercial tetra-*n*-butylammonium fluoride solution, only **78c** was obtained. Suspecting that protonation was the result of adventitious water in the fluoride solution, the same reaction was attempted with anhydrous fluoride ion and a phase transfer reagent. This resulted in no reaction of the silylmethyl compound under similar temperature conditions, suggesting that further investigation of more vigorous reaction conditions is required.

Table 8 Attempted Conversion of **78b** to Bromomethyl Derivative

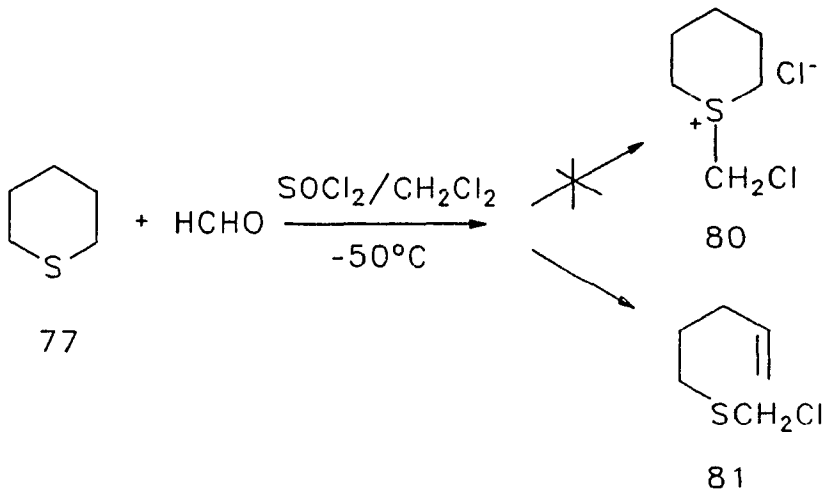


78b **78c**

Condition	Yield (%)
Br_2, Bu_4NF (THF solution), CH_2Cl_2, 0 °C, 1 h	39 (**78c**)
Br_2, anh. NaF/Bu_4NBr, CH_2Cl_2, 0 °C, 1 h	No reaction

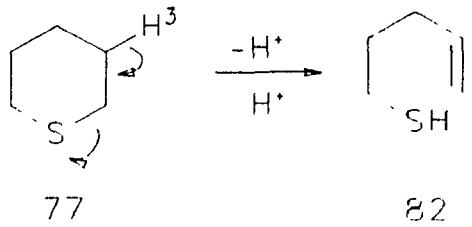
Attempts to prepare the *S*-chloromethyl sulfonium compound **80** by the reaction of **77** with formaldehyde in the presence of thionyl chloride (Scheme 46) were unsuccessful. Instead of formation of *S*-chloromethyltetrahydrothiopyranium **(80)**, it appeared that a thiopyran ring cleavage product as 5-chlorothiomethoxy pentene **(81)** was obtained.

Scheme 46



The reason for ring opening was probably that tetrahydrothiopyran **(77)** can undergo a eliminative ring cleavage reaction if the acidity of the proton at C-3 or the leaving group ability of the sulfur atom has been enhanced (Scheme 47).

Scheme 47



CHAPTER IV. SUMMARY

Using unsubstituted pyridine and tetrahydrothiopyran, synthetic methods have been developed for the alkylation of the heteroatom and the partial elaboration of functionalized dimethyl ether chain (eg. **69**, Scheme 31). The complete elaboration of this dimethyl ether chain into a species which will alkylate a second heterocycle has not been completed.

Pyridine has been used as a model compound in reactions which were envisaged for the functionalization of an acetal derivative of 2-pyridinecarboxaldehyde. The general proposed synthetic strategy has been validated as far as intermediate **70** in Scheme 31.

N-Chloromethylpyridinium derivatives were prepared in good yield by the reaction of pyridine with formaldehyde/thionyl chloride at -50 °C in dichloromethane.

Investigation into ether formation suggests that *N*-chloromethylpyridinium salts can easily be converted into the corresponding *N*-alkoxymethyl compounds by a simple S_N2 reaction.

The following new compounds were obtained in this investigation:

(*N*-Ethoxycarbonylmethyl)pyridinium bromide **71a**

N-Trimethylsilylmethylpyridinium iodide **71b**

N-Trimethylsilylmethylpyridinium *p*-toluenesulfonate **71c**

N-Chloromethylpyridinium chloride **74a**

N-Chloromethylpyridinium tetraphenylborate **74b**

N-(Ethoxymethyl)pyridinium chloride **75a**

(*S*-Ethoxycarbonylmethyl)tetrahydrothiopyranium bromide **78a**

S-(Trimethylsilylmethyl)tetrahydrothiopyranium iodide **78b**

S-Methyltetrahydrothiopyranium iodide **78c**

The preparation of a general series of sulfonium analogs of Hagedorn oximes has not yet been accomplished. The development of satisfactory reaction conditions for the conversion of the silylmethoxymethyl group into a halomethoxymethyl group and a determination of the suitability of the dimethyl acetal group on the pyridine ring for the various reactions, before it is converted into the desired oxime, remain to be completed.

CHAPTER V. EXPERIMENTAL

Chemicals were purchased from the Aldrich Chemical Co.. Technical grade solvents (J.T. Baker) were distilled prior to use. Anhydrous dichloromethane (CH_2Cl_2) was distilled from P_2O_5, anhydrous ethanol (EtOH) was prepared by distillation after reacting with magnesium and stored over 4Å molecular sieves, anhydrous tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl.

All reaction were carried out under an inert atmosphere of dry, oxygen free nitrogen and reaction vessels were flame- or oven-dried prior to use. The reactions were usually monitored by thin-layer chromatography (TLC) on plates precoated with silica-gel 60 F_{254}. Dichloromethane was used as the solvent.

Flash chromatography was performed using silica gel 60 (230-400 mesh, Merck) and a mixture of dichloromethane and petroleum ether (30 : 70) eluent was used unless otherwise specified.

Melting points were determined on a Gallenkamp melting point apparatus. The reported melting points are uncorrected.

Chemical analyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario.

Infrared spectra were recorded as nujol mulls (sodium chloride disk) on a BOMEM Michelson 102 FT-IR spectrometer. Band positions are reported in reciprocal centimetres (cm^{-1}).

Proton magnetic resonance (^1H NMR) and Carbon-13 NMR spectra were recorded on a Bruker WP80 instrument in deuteriochloroform (for ^1H NMR) and dimethyl-d_6-sulfoxide (for ^{13}C NMR) with tetramethylsilane (TMS) as internal standard unless otherwise indicated. Chemical shifts are expressed in parts per million downfield from TMS and NMR coupling constants are reported in Hertz. NMR multiplicities as recorded by using the following abbreviations : s, singlet; d, doublet; t, triplet; q, quarter; m, multiplet.

Mass spectra were measured with a LKB 9000 spectrometer at 70 eV of ionization energy. Signals are reported as *m/z*.

(*N*-Ethoxycarbonylmethyl)pyridinium bromide **71a**

A mixture of pyridine (0.8 g, 10 mmol) and ethyl bromoacetate (1.67 g, 10.00 mmol) in ethanol (5 ml) was refluxed in a round bottom flask under nitrogen atmosphere for 2 h, then stirred under N_2 for an additional 12 h. The crude precipitate was collected by vacuum filtration, washed with petroleum ether and dried.

Recrystallization (EtOH) gave colourless crystals (0.92 g, 40%). Mp 131-132 °C. **IR** ν: 1732; 1629; 1027; 781; 722; 667 cm^{-1} . ^1H **NMR**(D_2O) δ: 1.3, t (J=7.7), 3H; 4.3, q (J = 7.7), 2H; 5.6, s, 2H; 8.3, t (J = 5.6), 2H; 8.7, t (J = 7.7), 1H; 8.9, d (J = 7.0), 2H ppm. ^{13}C **NMR** δ: 15, 62 (OCH_2), 65 (NCH_2), 130, 147, 148, 168 (CO_2) ppm.

Anal. Calcd. for $C_9H_{12}BrNO_2$: C, 43.72; H, 4.86; N, 5.67; Br, 32.79.

Found: C, 42.65; H, 5.11; N, 6.10; Br, 32.64.

N-Trimethylsilylmethylpyridinium iodide **71b**

To a solution of (iodomethyl)trimethylsilane (2.14 g, 10.00 mmol) in acetone (10 ml) was added pyridine (0.79 g, 10.00 mmol), then the solution was heated at reflux for 12 h under N_2. After cooling, the solvent was concentrated under vacuum to give a light yellow solid.

Recrystallization (EtOH) gave colourless crystals (2.14 g, 32%). Mp 110-112 °C. **IR** ν: 1620; 1158; 1037; 723 cm^{-1}. **^{1}H NMR** δ: 0.2, s, 9H; 4.8, s, 2H, (CH_2); 8.0, t (J = 5.0), 2H; 8.4, t (J = 6.6), 1H; 9.1, d (J = 7.0), 2H ppm.

N-Trimethylsilylmethylpyridinium *p*-toluenesulfonate **71c**

A slurry of trimethylsilylmethyl *p*-toluenesulfonate (Me_3SiCH_2OTs, 0.5 g, 1.9 mmol) and pyridine (0.15 g, 1.9 mmol) was stirred for 10 h at room temperature under N_2. The precipitate was collected on a Büchner funnel and dried.

Recrystallization (MeOH) gave colourless crystals (0.18 g, 25.8%). Mp 125-128 °C. **^{1}H NMR** δ: 0.1, s, 9H; 2.3, s, 3H (Ar-C**H**$_3$); 4.6, s, 2H (C**H**$_2$); 7.1, d (J = 6.8), 2H; 7.8, d (J = 6.8), 2H; 8.0, t, 2H; 8.3. t, 1H; 9.05, d (J = 5.1), 2H ppm.

N-(Trimethylsilylmethyl)-2-(bismethoxymethyl)pyridinium tosylate **71e**

A neat mixture of trimethylsilylmethyl *p*-toluenosulfonate (0.40 g, 1.55 mmol) and the partially purified acetal **73b** (0.20 g, 0.88 mmol acetal mixed with the aldehyde) was heated at 120 °C for 4 h. The oil was cooled and triturated with diethyl ether and the precipitate filtered and washed with cold ether.

Recrystallization (methanol) gave off-white crystal (0.36 g, 20%). **^{1}H NMR** δ: 0.2, s, 9H; 2.6, s, CH_3; 3.7, s, $(OMe)_2$; 4.5, s, *N*-CH_2; 6.15, s, $CH(OMe)_2$; 7.5, d (J = 7.8), 2H; 7.9, d (J = 7.80), 2H; 8.1, t, 1H; 8.8, t, 1H; 9.45, d, 2H ppm.

2-(Bismethoxy)methylpyridine 73b

To a solution of trimethylsilyl trifluoromethanesulfonate (TMSOTf , 0.10 mmol) in CH_2Cl_2 (50 ml) was added methoxytrimethylsilane (13.76 g, 130.00 mmol) and 2-pyridecarboxaldehyde (5.04 g, 47.00 mmol). The mixture was heated in a bomb for 72 h at 150 °C. After cooling to room temperature, triethylamine (1 ml) and methanol (1 ml) were added to quench the reaction and the solution was concentrated. Vacuum distillation gave a light green-brown liquid bp 165-168 °C (4.72 g, containing ca. 30% aldehyde). ^{1}H NMR δ: 3.3,s, 6H, (OMe); 5.3,s, 1H; 7.2, t, 2H; 7.6, t, 1H; 8.6, d (J = 6.2), 2H ppm.

Preparation of methoxytrimethylsilane

To a solution of methanol (0.96 g, 30.00 mmol) and trimethylsilyl chloride (3.29 g, 30.00 mmol) was added pyridine (2.44 ml, 30.00 mmol) at 0 °C under N_2. The solution was stirred for 2 h in an ice bath followed by 2 h at room temperature. The siloxy compound was purified by fractional distillation (bp 56 to 58 °C) and was identical to the authentic compound (Aldrich) (^{1}H NMR δ: 0.1, s, 9H; 3.35, s, 3H ppm).

N-Chloromethylpyridinium chloride **74a**

Paraformaldehyde (3 g, 100 mmol) was cracked by heating and the monomer carried with a stream of nitrogen gas onto the surface of a cold (- 50 °C) solution of thionyl chloride (18 ml, 90 mmol) and pyridine (15.0 ml, 90 mmol) in dry dichloromethane (75 ml). The solution was stirred for 2 h at - 50 °C then allowed to warm to room temperature and stirred for an additional 3 h. The volatiles were removed and the crude product triturated by the addition of tetrahydrofuran.

Recrystallization (EtOH-THF) gave colourless hygroscopic crystals (9.79 g, 70%). Mp unavailable because of deliquescence. **IR** ν: 1623; 1534; 1039; 751; 681 cm^{-1}. **^{1}H NMR** δ: 7.10, s, 2H (CH_2Cl); 8.10, t (J = 6.9), 2H; 8.55, t (J = 6.9), 1H; 9.81, d (J = 6.8), 2H ppm. **^{13}C NMR** δ: 65 (CH_2Cl); 128; 146; 149 ppm. **MS** *m/z*: 79; 50; 38.

Anal. Calcd. for $C_6H_7Cl_2N$: C, 43.90; H, 4.27; N, 8.54; Cl, 43.29.

Found: C, 43.83; H, 4.32; N, 8.86; Cl, 42.85.

N-Chloromethylpyridinium tetraphenylborate **74b**

To a stirred solution of **74a** (0.45 g, 3.05 mmol) in H_2O (20 ml) was added sodium tetraphenylborate (0.95 g, 3.05 mmol) with continually stirring. After 1 h at room temperature, the crude product precipitated was collected by vacuum filtration, washed with distilled water and vacuum-dried.

Recrystallization (EtOH-THF) gave colourless crystals quantitatively. Mp 194-196 °C. **IR** ν: 1614; 1160; 1073; 864; 732; 700 cm^{-1}. ^1H **NMR** δ: 7.25, s, 20H; 7.35, s, 2H, (CH_2Cl); 7.7-7.9,t, 2H; 8.1-8.3,t, 1H; 8.7-8.9,d, 2H ppm.

N-(Ethoxymethyl)pyridinium chloride **75a**

Sodium ethoxide was prepared by dissolving sodium metal (0.1 g, 4.0 mmol) in anhydrous ethanol (10 ml). To this solution was added a solution of the pyridinium salt **74a** (0.7 g, 14.0 mmol) in ethanol (10 ml) and the solution stirred for 30 min. Precipitated sodium chloride was removed by filtration and the mother liquor evaporated to dryness.

Recrystallization of residue (THF-EtOH) gave light yellow crystals (0.56 g, 78%). ^{1}H NMR δ: 1.25, t (J = 6.7), 3H; 3.8, q (J = 6.8), 2H; 6.4, s, 2H,(*N*-C**H**$_2$); 8.3, t (J = 7.5), 2H; 8.65, t (J = 6.8), 1H; 9.55, d (J = 7.0), 2H ppm.

Anal. Calcd. for $C_8H_{12}ClNO$: C, 55.17; H, 6.90; N, 8.04; Cl, 20.46.

Found: C, 48.26; H, 6.39; N, 8.14; Cl, 21.54.

N-(Trimethylsilylmethoxy)pyridinium tetraphenylborate **75b**

To a solution of pyridinium salt **74b** (0.45 g, 1.00 mmol) and trimethylsilylmethanol (0.16 g, 1.50 mmol) in THF (40 ml) was added silver oxide (0.17 g, 0.75 mmol) and the solution was heated at reflux for 24 h. After cooling, the solvent THF and excess alcohol were removed by vacuum. to give a light yellow solid (0.12 g, 47%). ^{1}H NMR δ: 0.1, s, 9H; 3.7, s, SiC**H**$_2$; 6.75, s, *N*C**H**$_2$O; 7.2, m, 20H; 7.45, t, 2H; 8.05, t, 1H; 8.7, d, 2H ppm.

(*S*-Ethoxycarbonylmethyl)tetrahydrothiopyranium bromide **78a**

This preparation was similar to the procedure used for **71a**.

Recrystallization (EtOH) gave crystals (66 %). Mp 137-137.5 °C. **IR** ν: 1712; 1317; 1194; 1009; 724 cm^{-1}. ^{1}H **NMR** δ: 1.3, t (J = 6.7), 3H; 1.8-2.3, m, 6H (ring H_{3-5}); 3.8-4.0, m, 4H (ring $H_{2,6}$); 4.35, q (J = 6.1), 2H; 5.5, s, (CH_2CO_2) ppm. ^{13}C **NMR** δ: 14 (CH_3), 21 (ring $C_{2,6}$), 22 (ring C_4), 37 (OCH_2CH_3), 41 (ring $C_{3,5}$), 64 (SCH_2), 165 (CO_2) ppm.

S-(Trimethylsilylmethyl)tetrahydrothiopyranium iodide **78b**

This preparation was similar to the procedure used for **71b**.

Recrystallization (EtOH) gave colourless crystals (35 %). Mp 190-192 °C. **IR** ν: 1646; 1245; 1158; 964; 848; 723 cm^{1}. ^{1}H **NMR** δ: 0.2, s, 9H; 1.7-2.2, m, 6H (ring H_{3-5}); 3.25, s, 2H (SCH_2Si); 3.7-3.9, m, 4H (ring $H_{2,6}$) ppm. ^{13}C **NMR** ($CDCl_3$) δ: 0 (d, $-SiMe_3$); 21 (ring $C_{2,6}$); 22 (ring C_4); 37 (ring $C_{3,5}$); 39 (SCH_2) ppm.

S-Methyltetrahydrothiopyranium iodide **78c**

To a solution of tetrahydrothiopyran (1.0 g, 9.8 mmol) in ethanol (5 ml) was added iodomethane (1.62 g, 11.40 mmol). The solution was heated at reflux for 3 h under N_2, then cooled and the white precipitate was collected by filtration and washed with cold ethanol.

Recrystallization (EtOH) gave colourless crystals (2.1 g, 87.8%). Mp 181-184 °C. **IR** ν: 1643; 1154; 953; 725 cm^{-1}. ^{1}**H NMR** δ: 1.9-2.2,m, 6H; 3.4,s, 3H (S-C**H**$_3$); 3.9-4.1,m, 4H (ring $H_{2,6}$) ppm. **MS** *m/z*: 142; 128; 102; 88.

Anal. Calcd. for $C_6H_{13}IS$: C, 29.51; H, 5.32; S, 13.11; I, 52.05.

Found: C, 32.61; H, 5.10; S, 14.00; I, 48.50.

Preparation of trimethylsilylmethyl *p*-toluenesulfonate

To a solution of trimethylsilyl methanol (Me_3SiCH_2OH, 1.08 g, 10.00 mmol) and pyridine (1.59 g, 20.00 mmol) in chloroform (10 ml) was added *p*-toluenesulfonyl chloride (TSCl, 2.90 g, 15.00 mmol) at 0 °C under N_2. The solution was stirred for 3 h at 0 °C. Ether (30 ml) and distilled water (7 ml) were added and organic layer separated and washed successively with 2N HCl; 5% $NaHCO_3$; and water. The organic layer was separated and dried over anhydrous sodium sulfate and solvent removed. The residue was chromatographed to afford trimethylsilylmethyl *p*-toluenesulfonate as a colourless liquid (1.32 g, 53%). ^{1}H NMR δ: 0.1, s, 9H; 2.4, s, 3H (Ar-C**H**$_3$); 3.55, s, 2H (C**H**$_2$O); 7.23, d (J = 8.1), 2H; 7.7, d (J = 8.1), 2H ppm.

CHAPTER VI. REFERENCES

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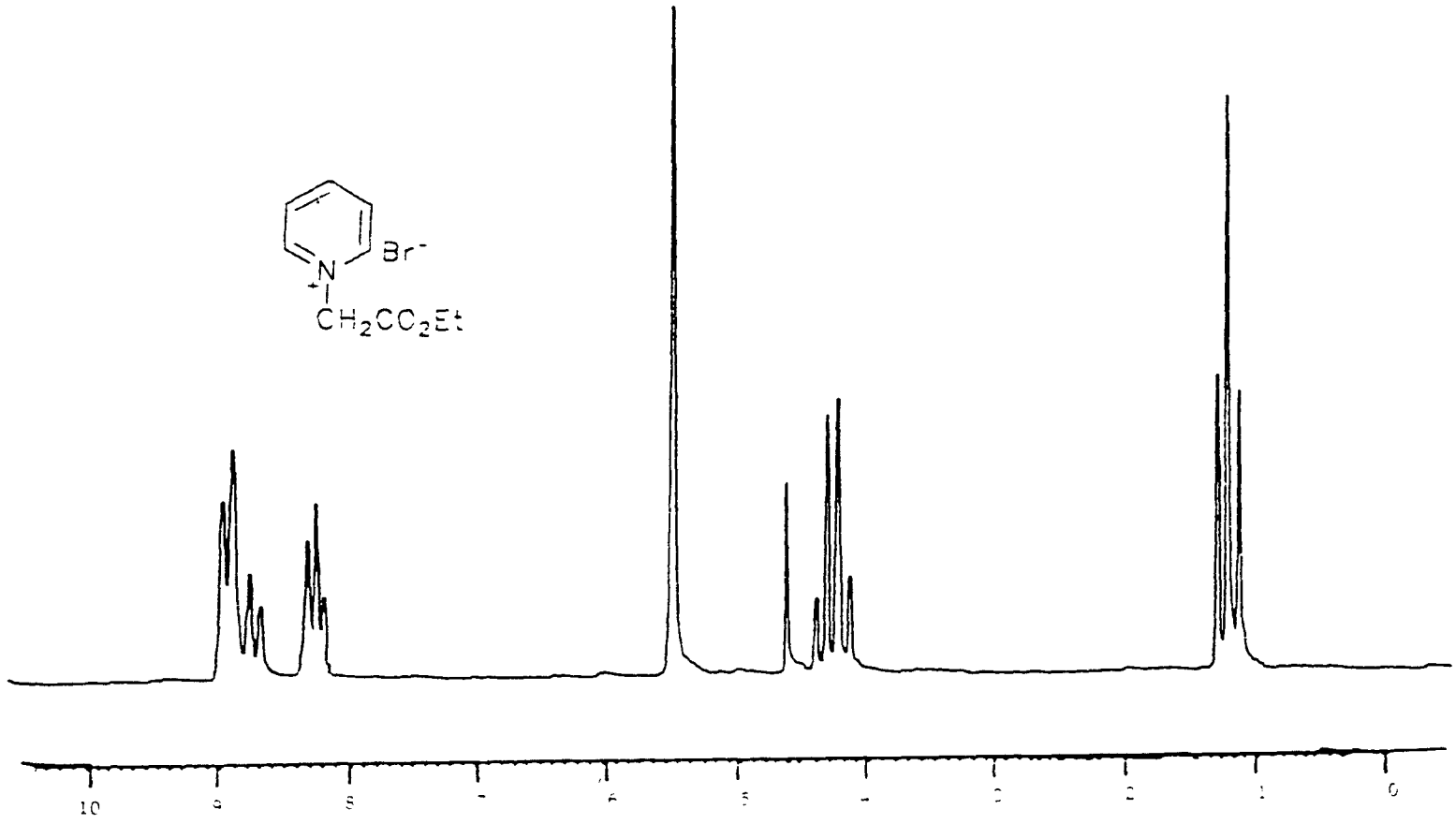
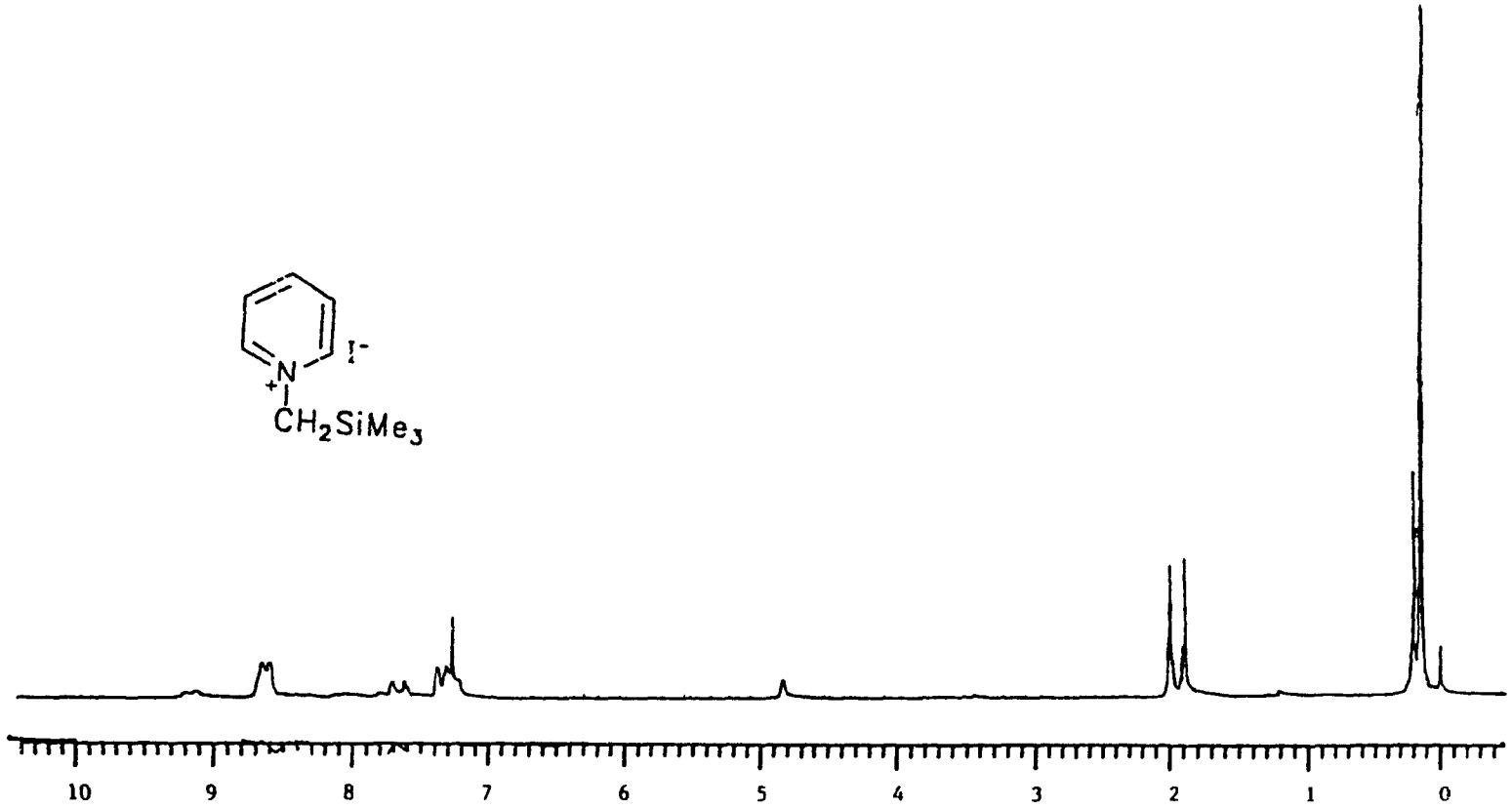
Appendix I. ^{1}H NMR Spectra

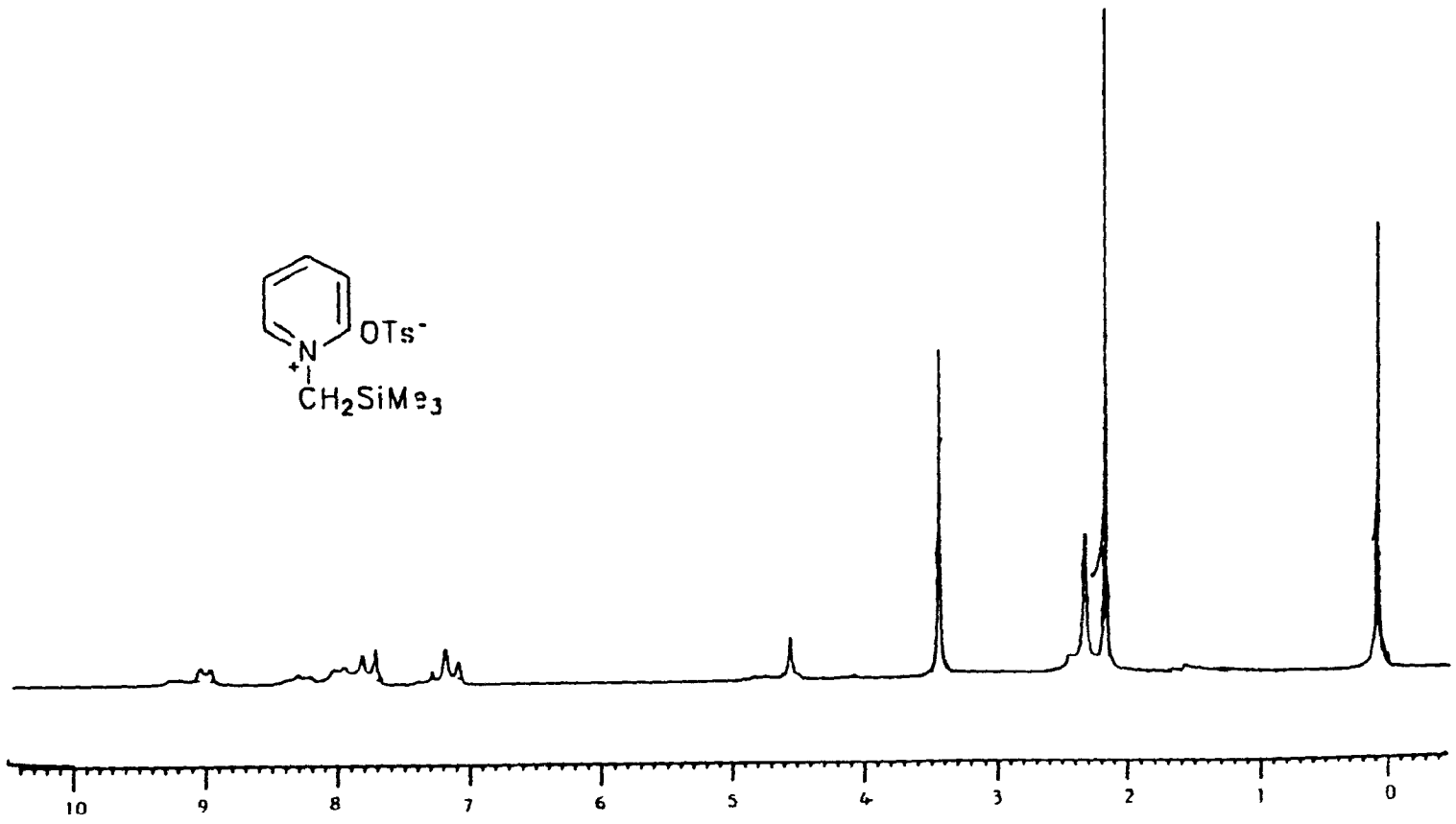
I-1. (*N*-Ethoxycarbonylmethyl)pyridinium bromide **71a**



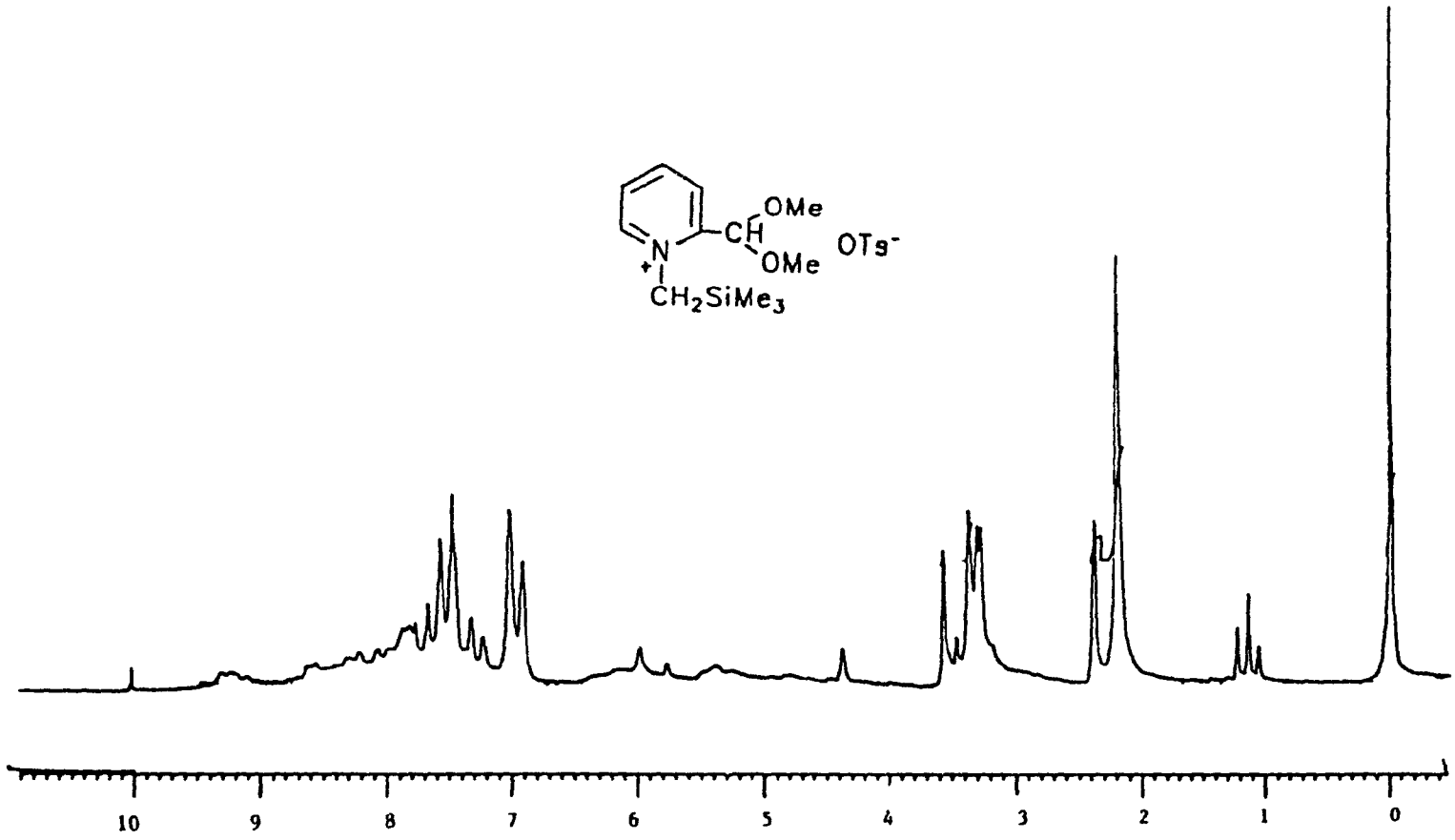
I-2. *N*-Trimethylsilylmethylpyridinium iodide **71b**



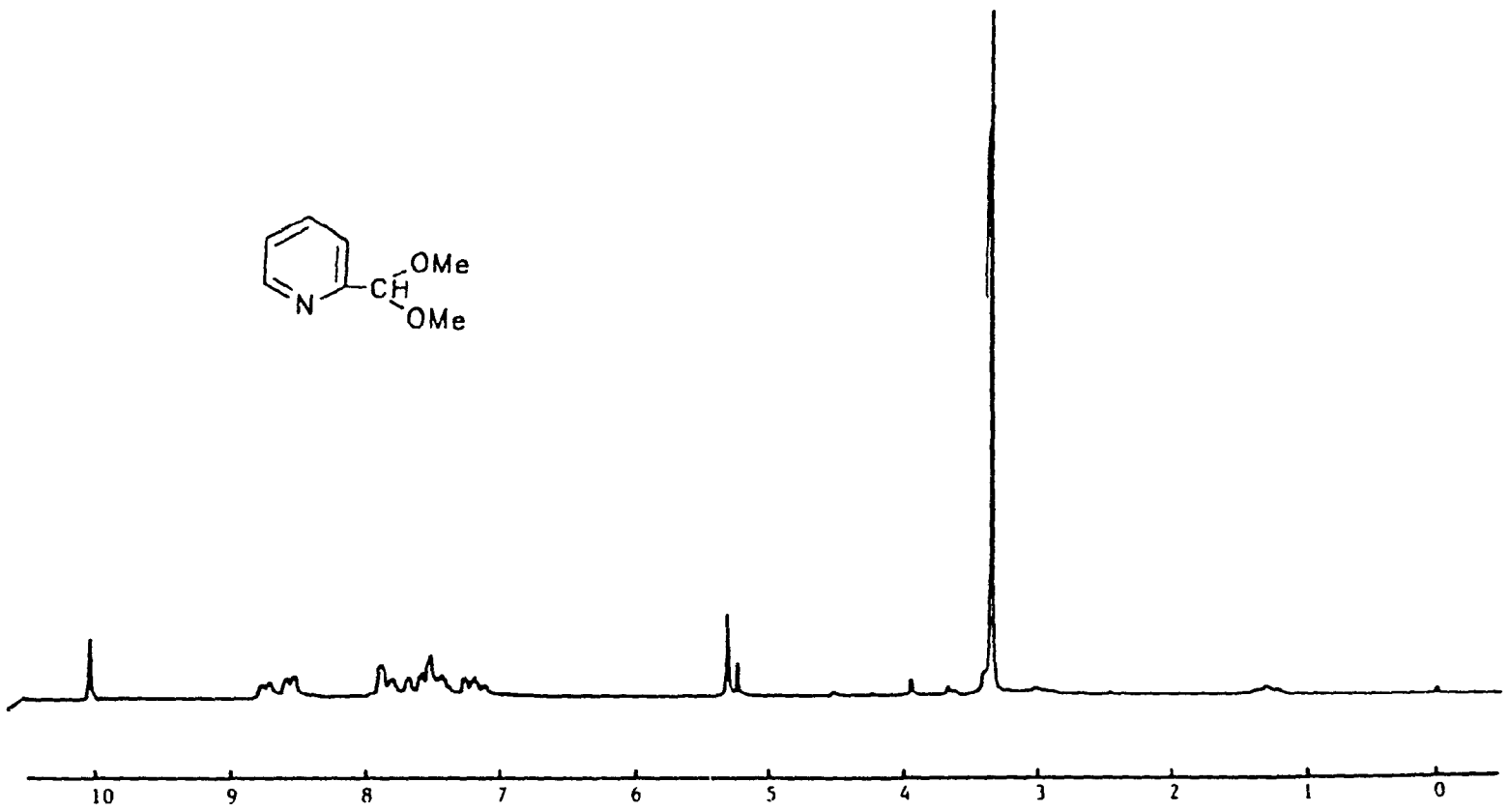
I-3. *N*-Trimethylsilylmethylpyridinium *p*-toluenesulfonate **71c**



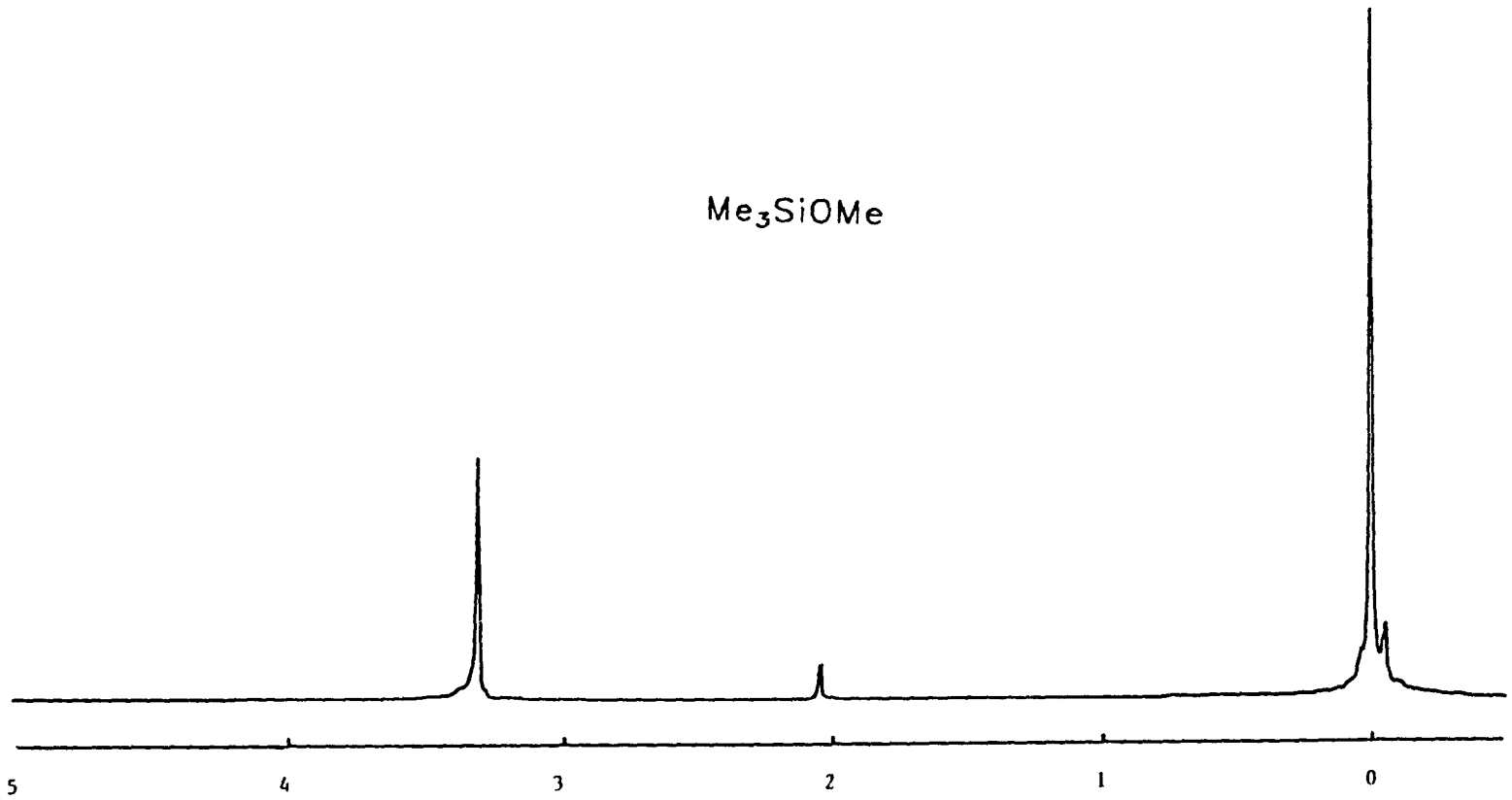
1-4. *N*-(Trimethylsilylmethyl)-2-(bismethoxymethyl)pyridinium tosylate **71e**



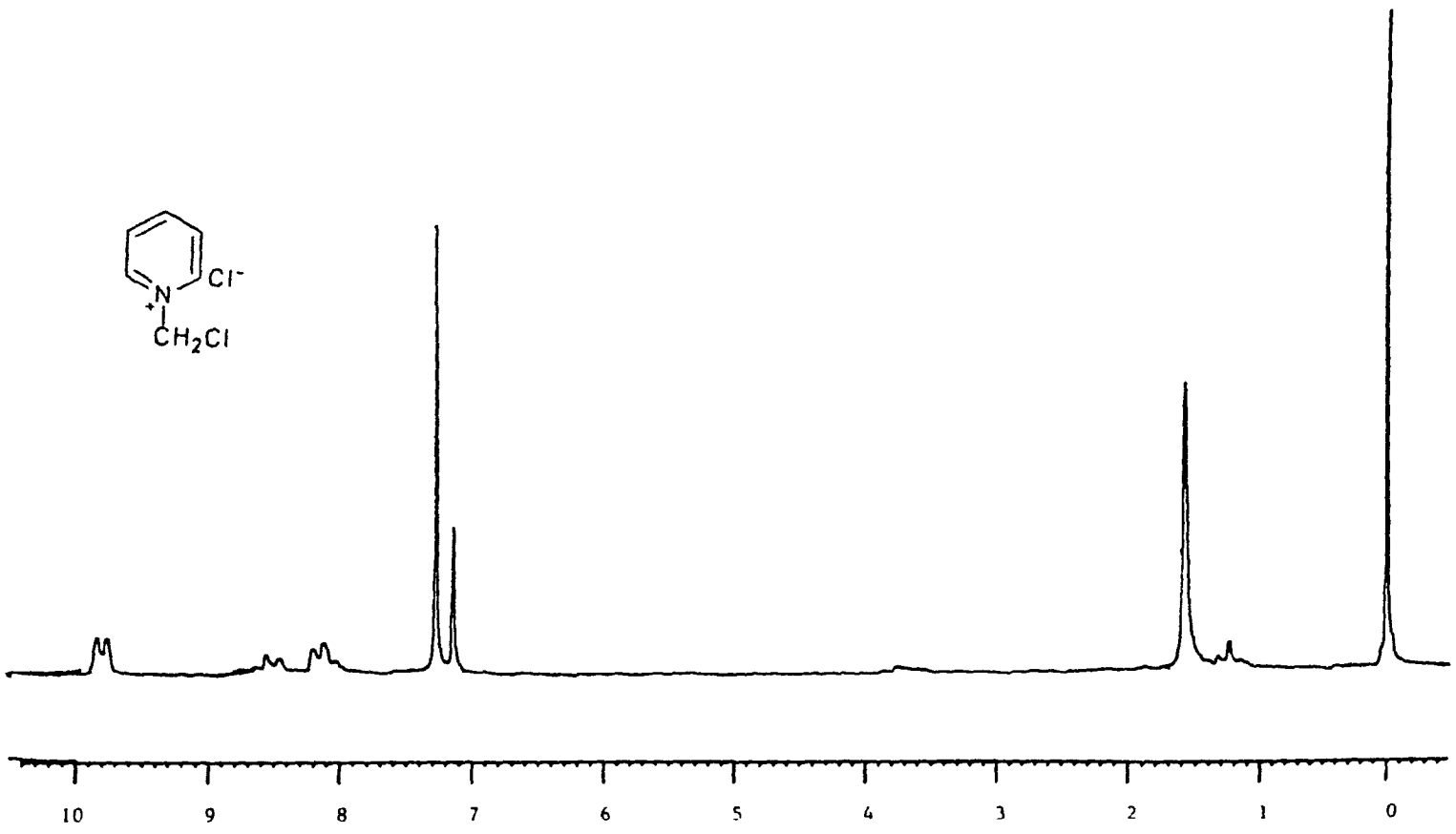
I-5. 2-(Bismethoxy)methylpyridine **73b**



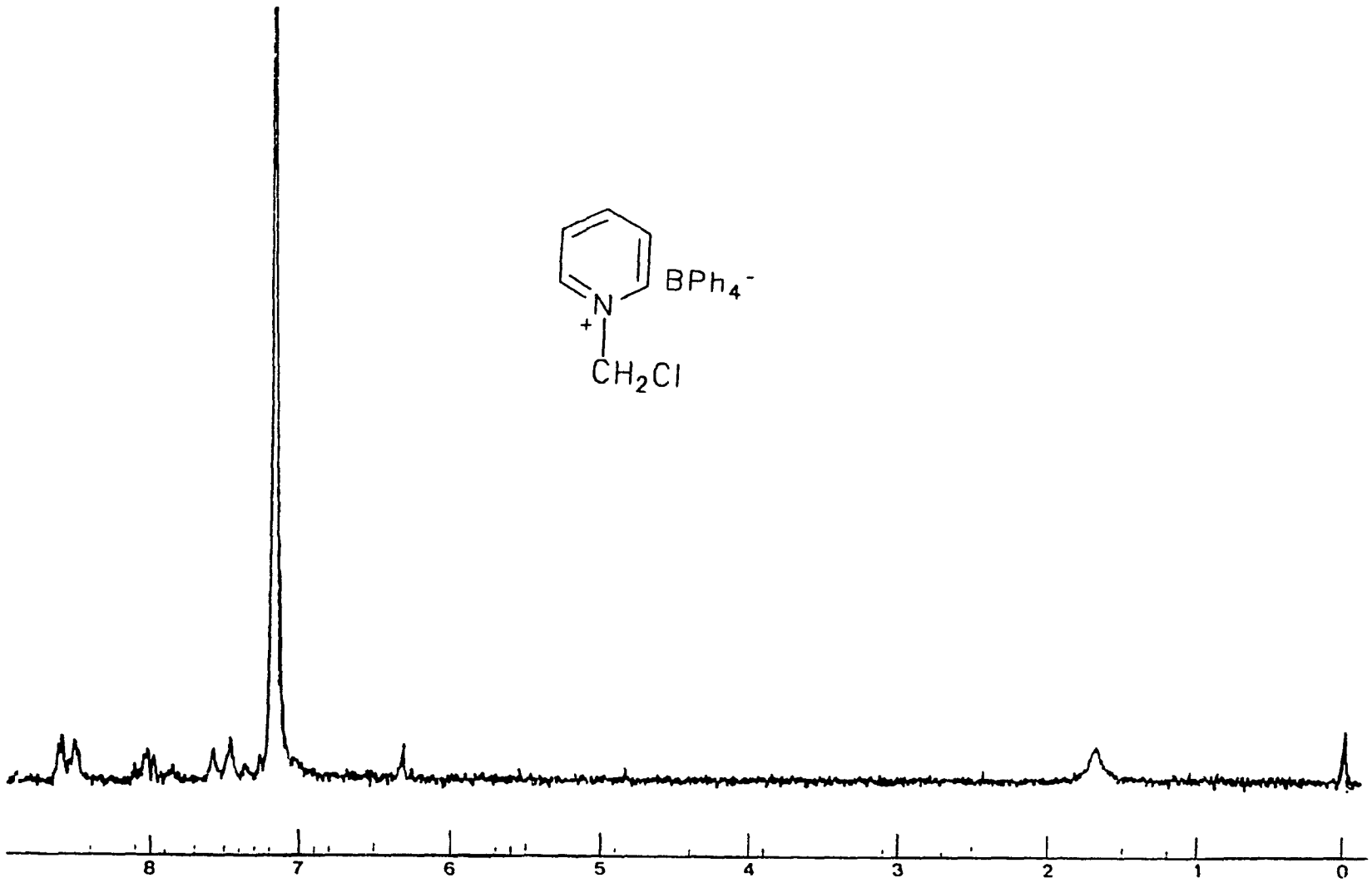
I-6. Methoxytrimethylsilane



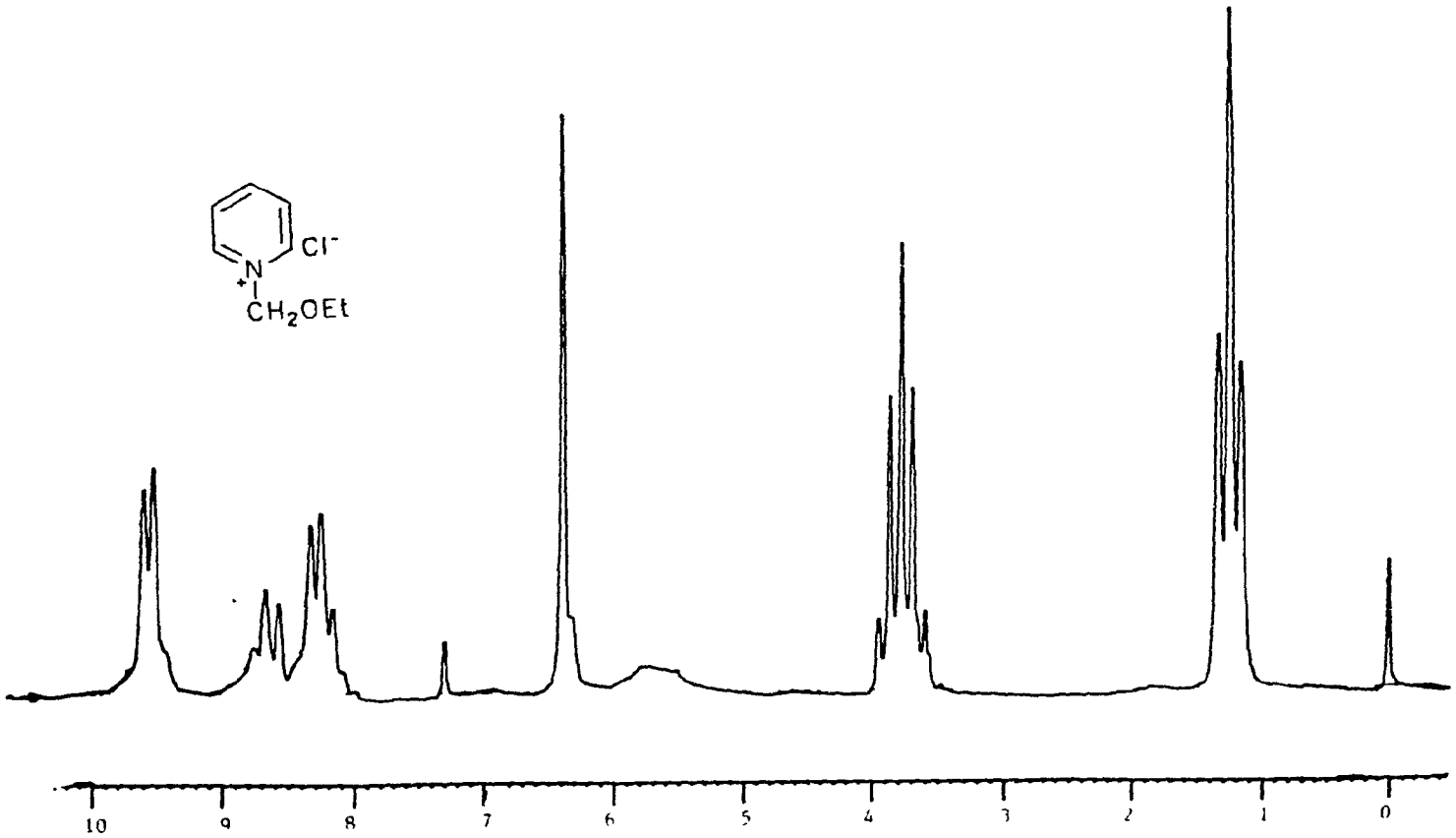
I-7. *N*-Chloromethylpyridinium chloride **74a**



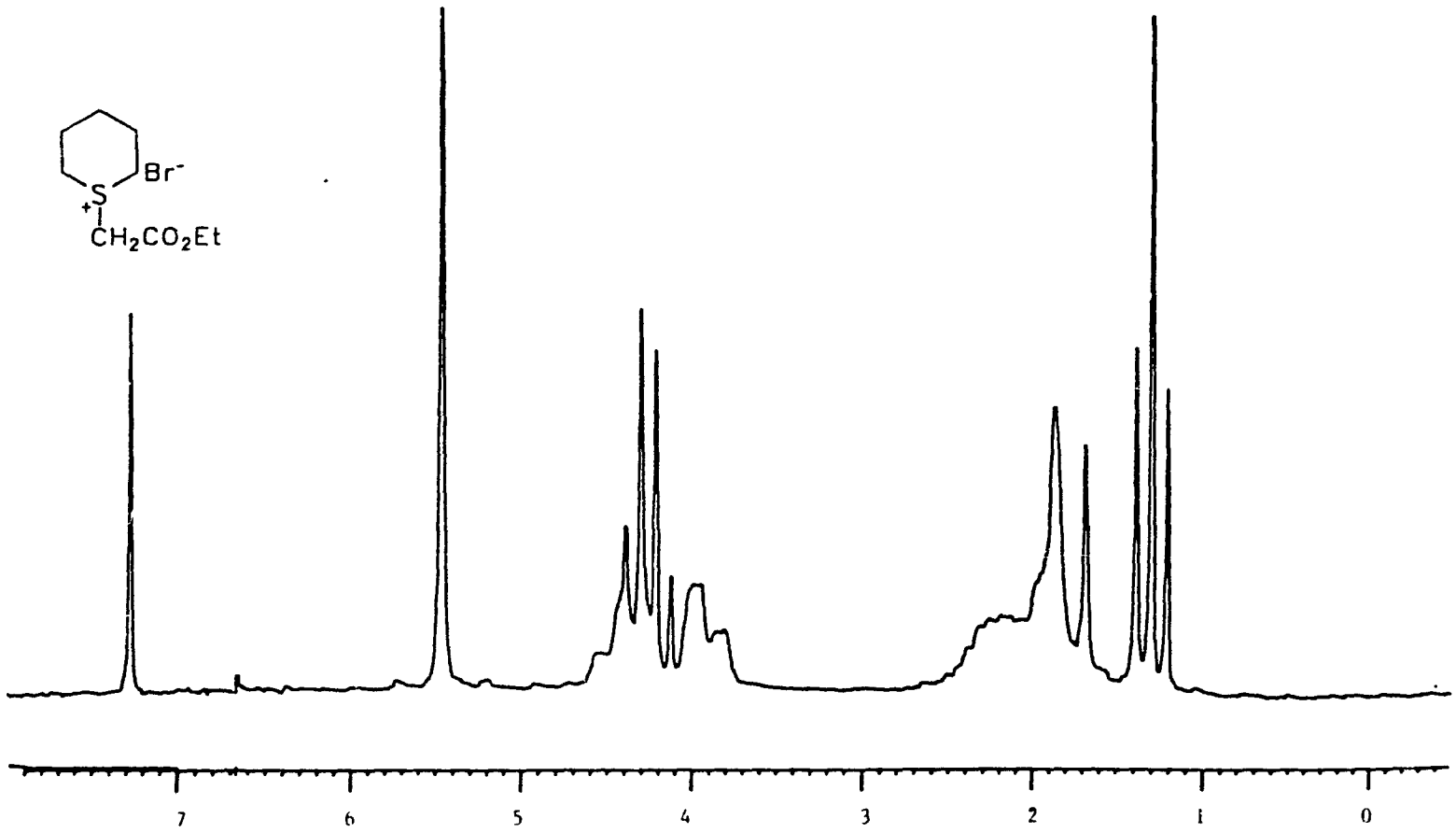
I-8. *N*-Chloromethylpyridinium tetraphenylborate **74b**



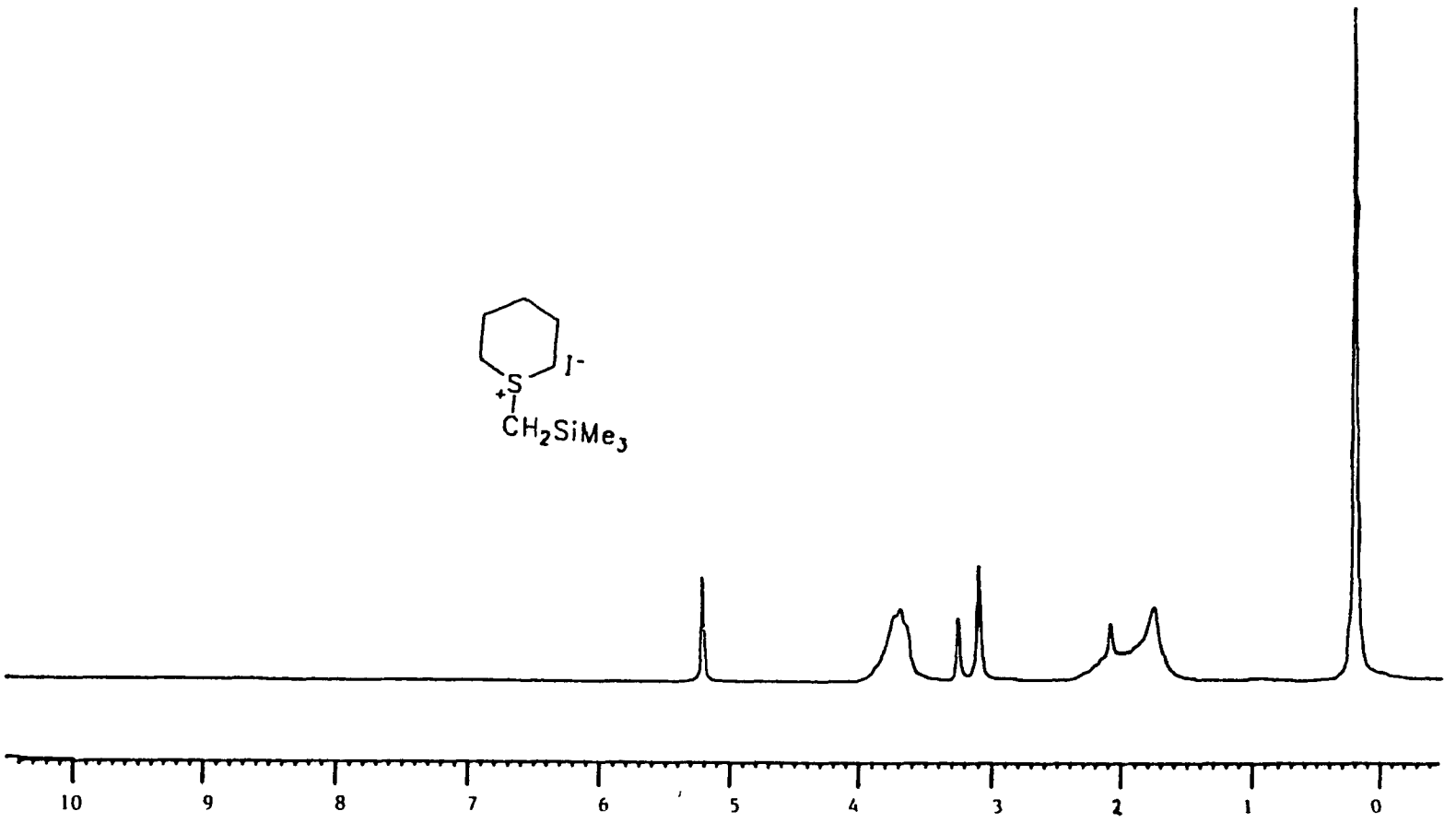
I-9. *N*-(Ethoxymethyl)pyridinium chloride **75a**



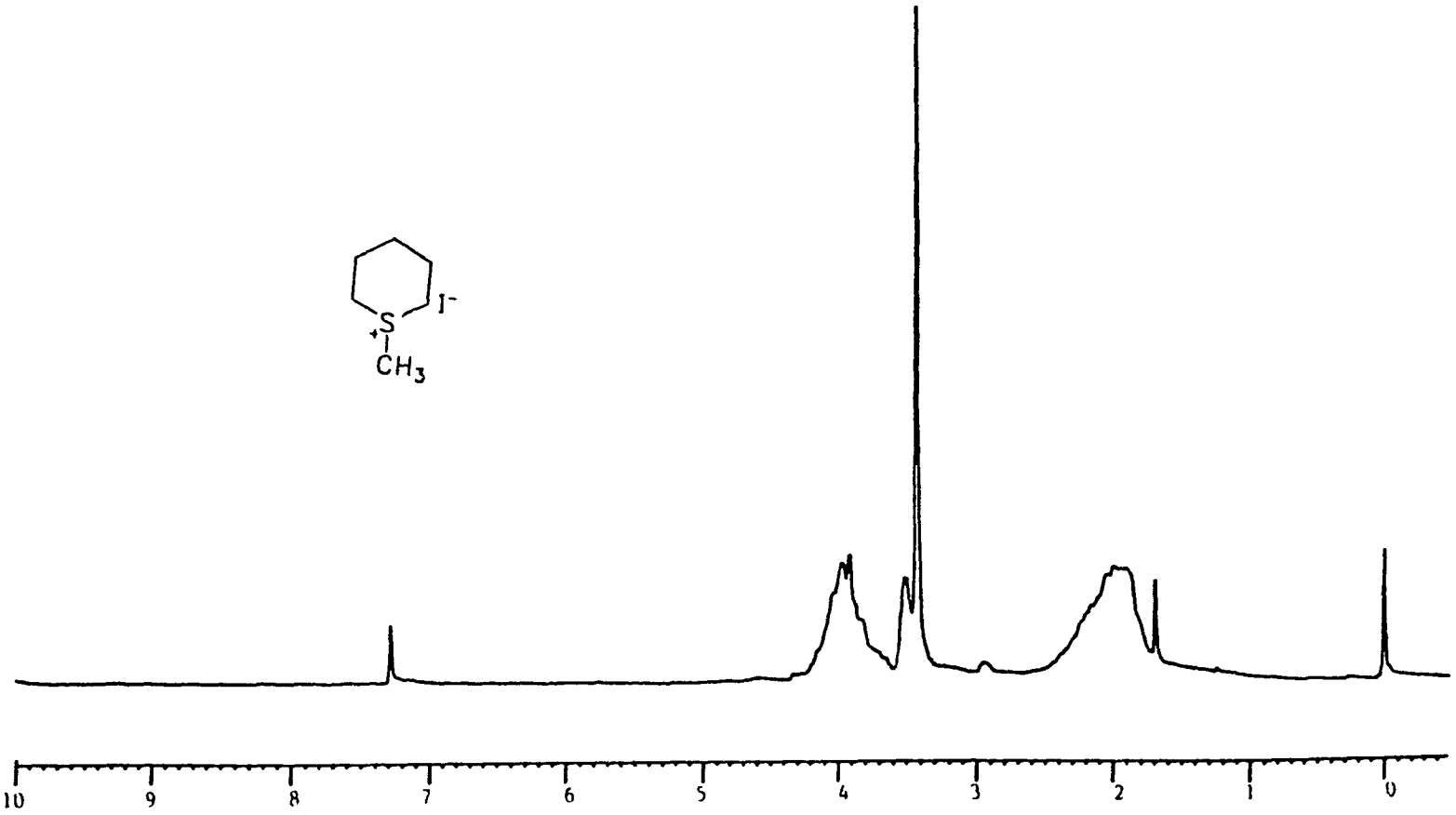
I-10. (*S*-Ethoxycarbonylmethyl)tetrahydrothiopyranium bromide **78a**



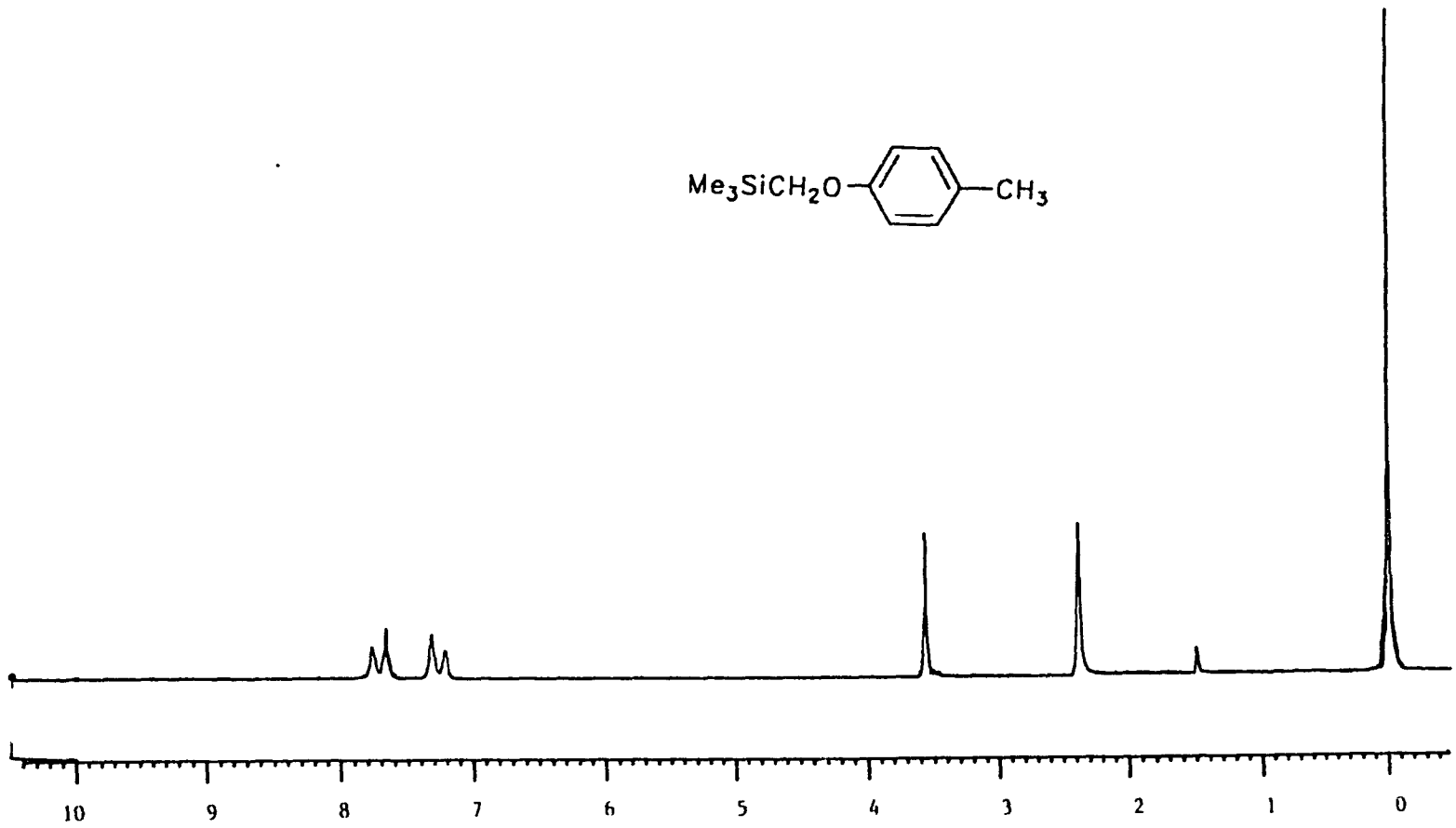
I-11. *S*-(Trimethylsilylmethyl)tetrahydrothiopyranium iodide **78b**



I-12. *S*-Methyltetrahydrothiopyranium iodide **78c**

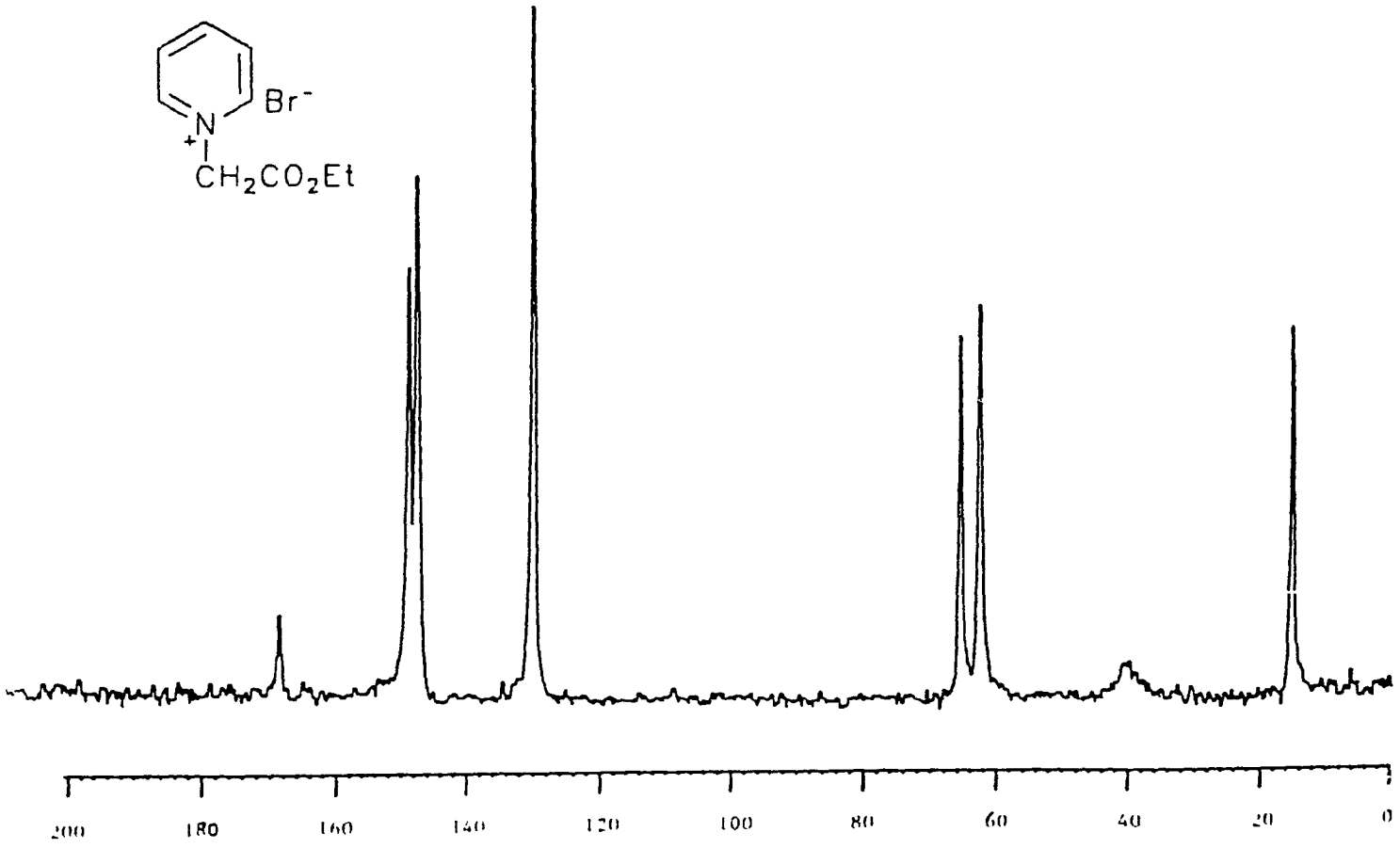


I-13. Trimethylsilylmethyl *p*-toluenesulfonate **81**

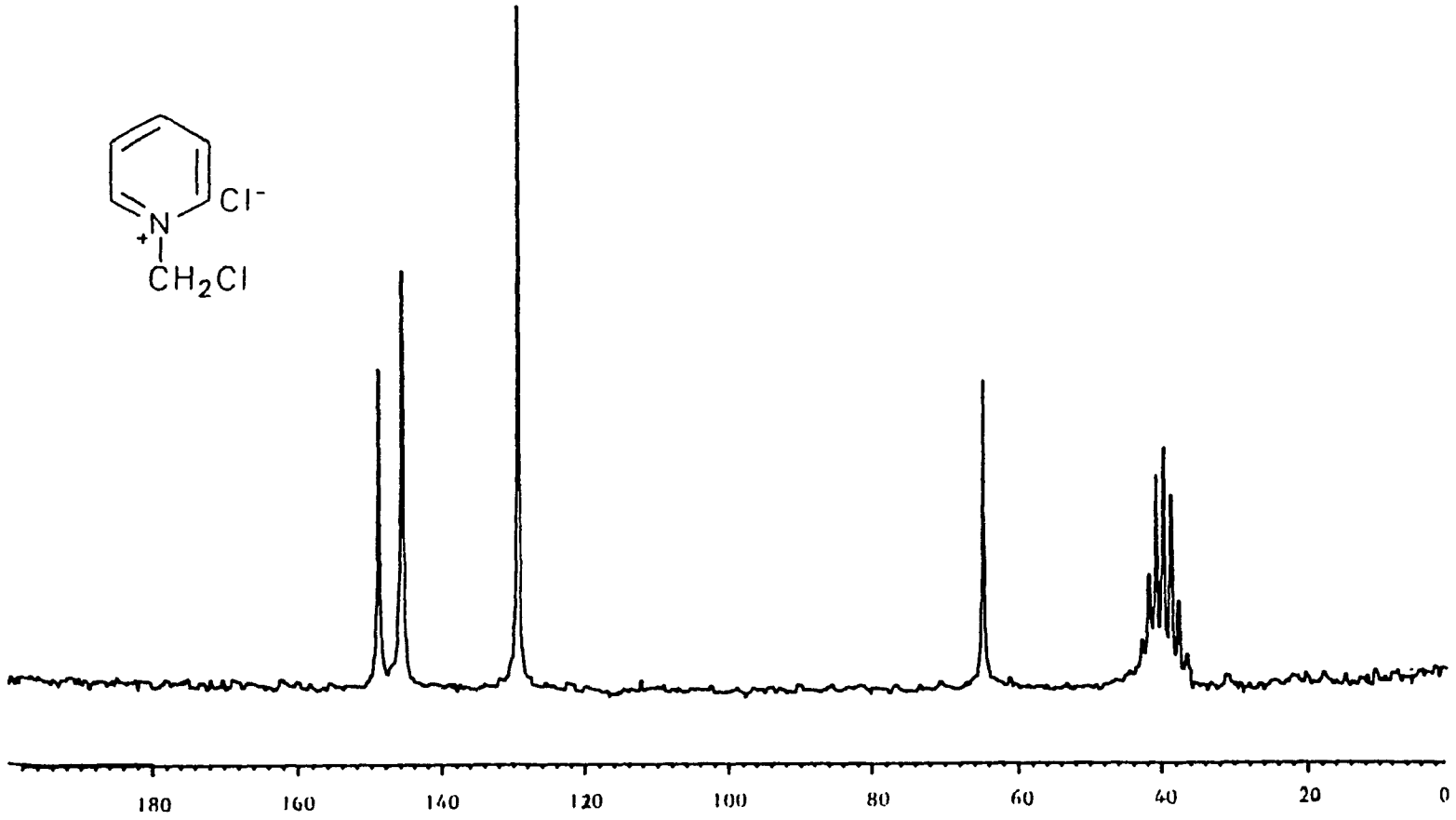


Appendix II. ^{13}C NMR Spectra

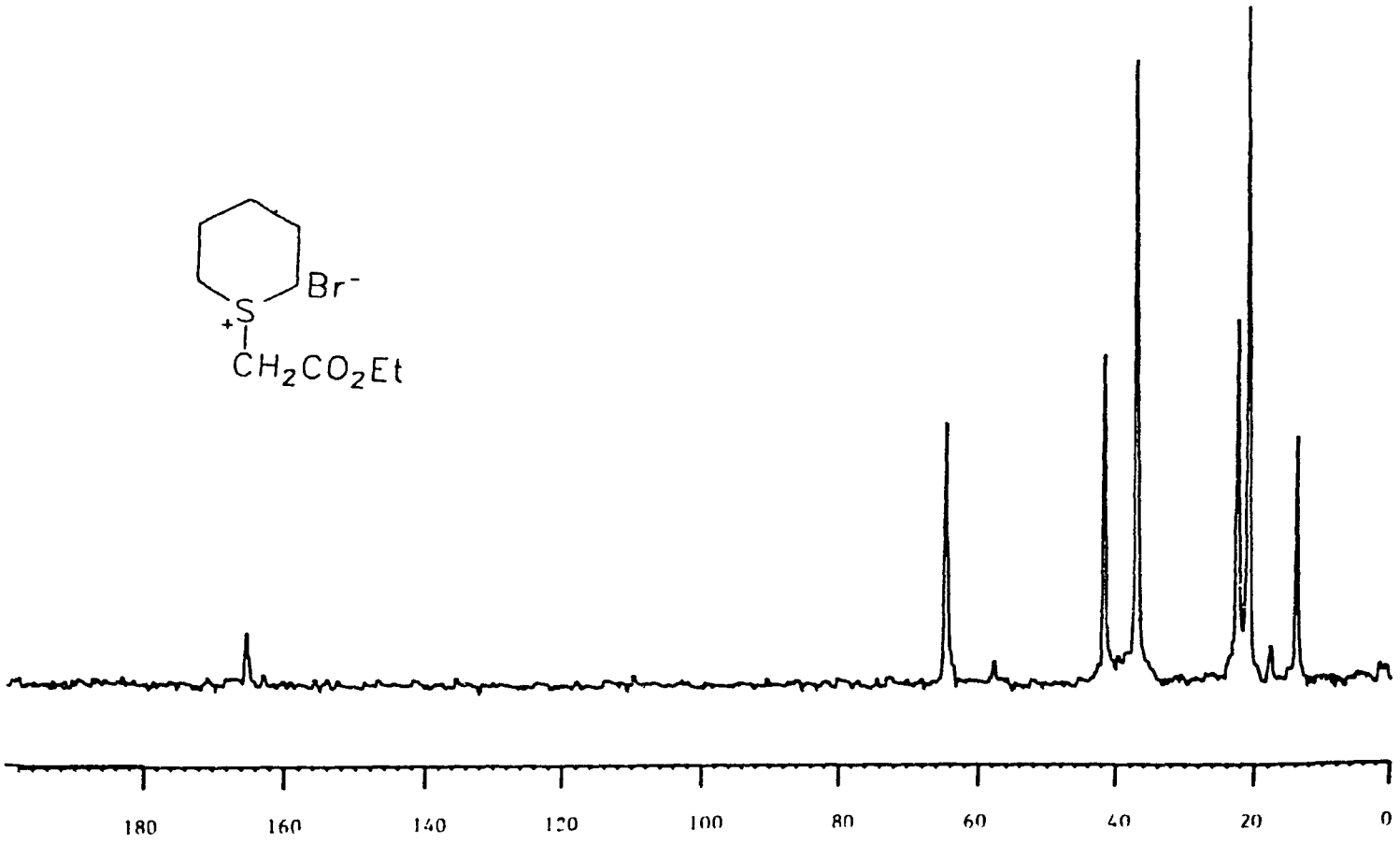
II-1. (*N*-Ethoxycarbonylmethyl)pyridinium bromide **71a**



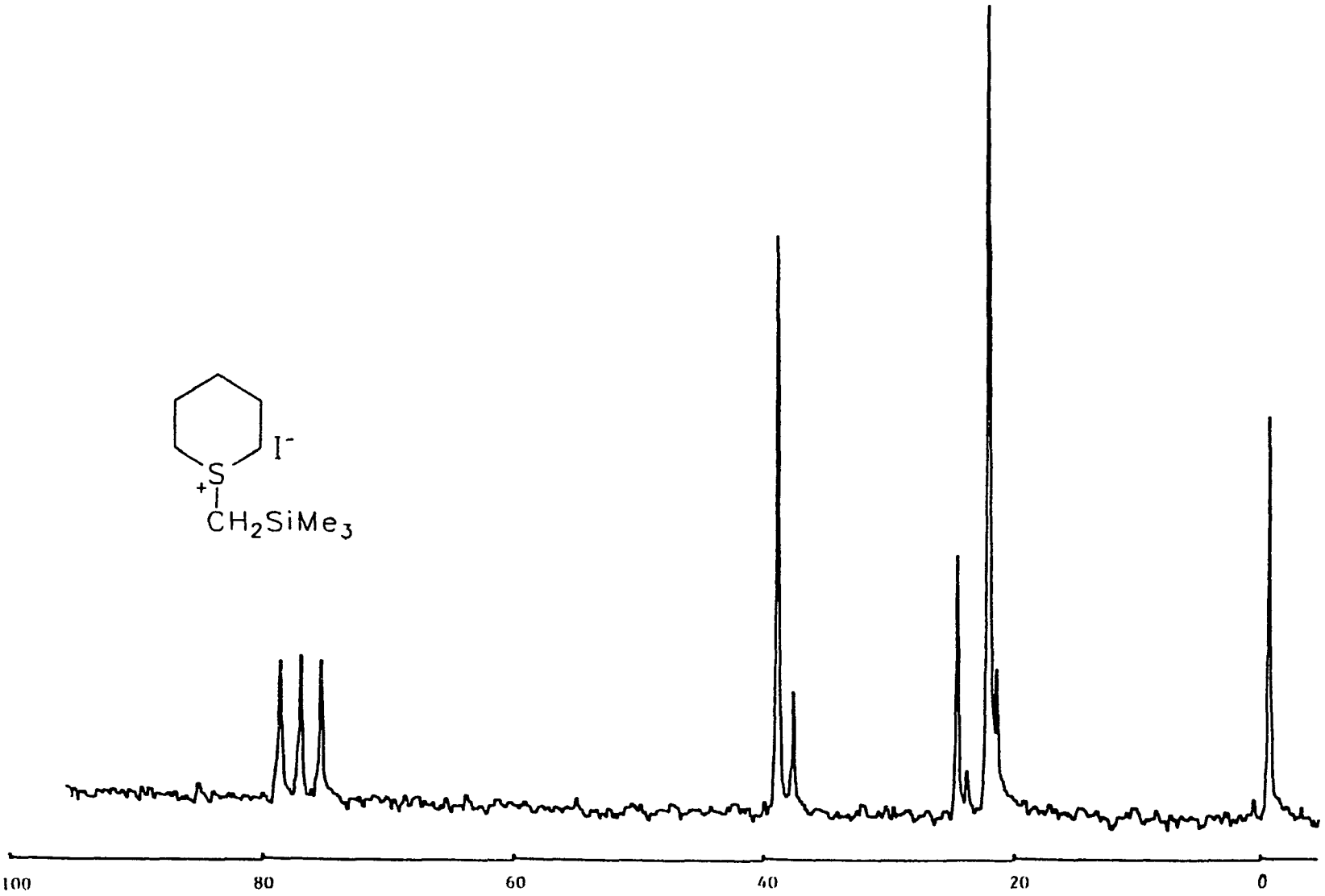
II-2. *N*-Chloromethylpyridinium chloride **74a**



II-3. (*S*-Ethoxycarbonylmethyl)tetrahydrothiopyranium bromide **78a**

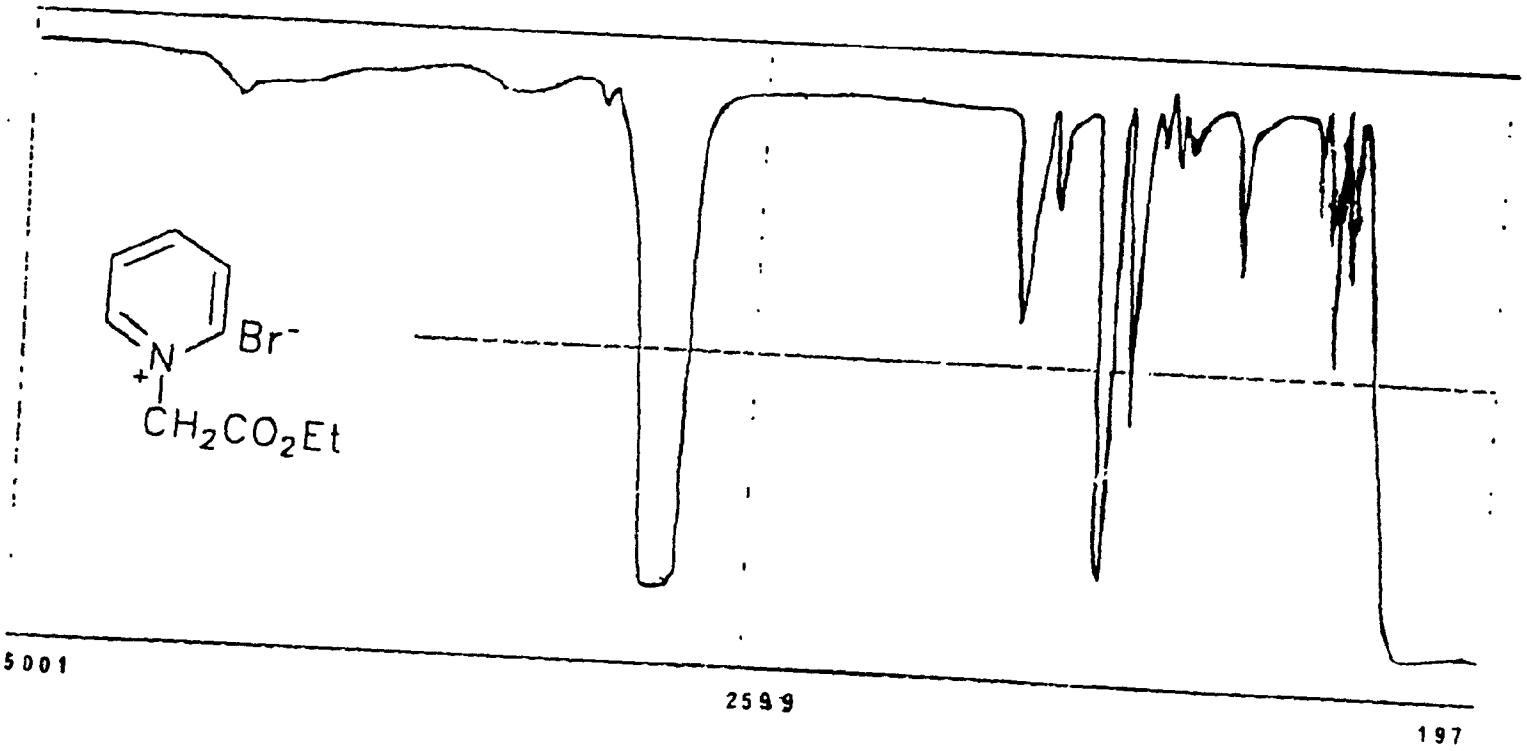


II-4. *S*-(Trimethylsilylmethyl)tetrahydrothiopyranium iodide **78b** ($CDCl_3$)

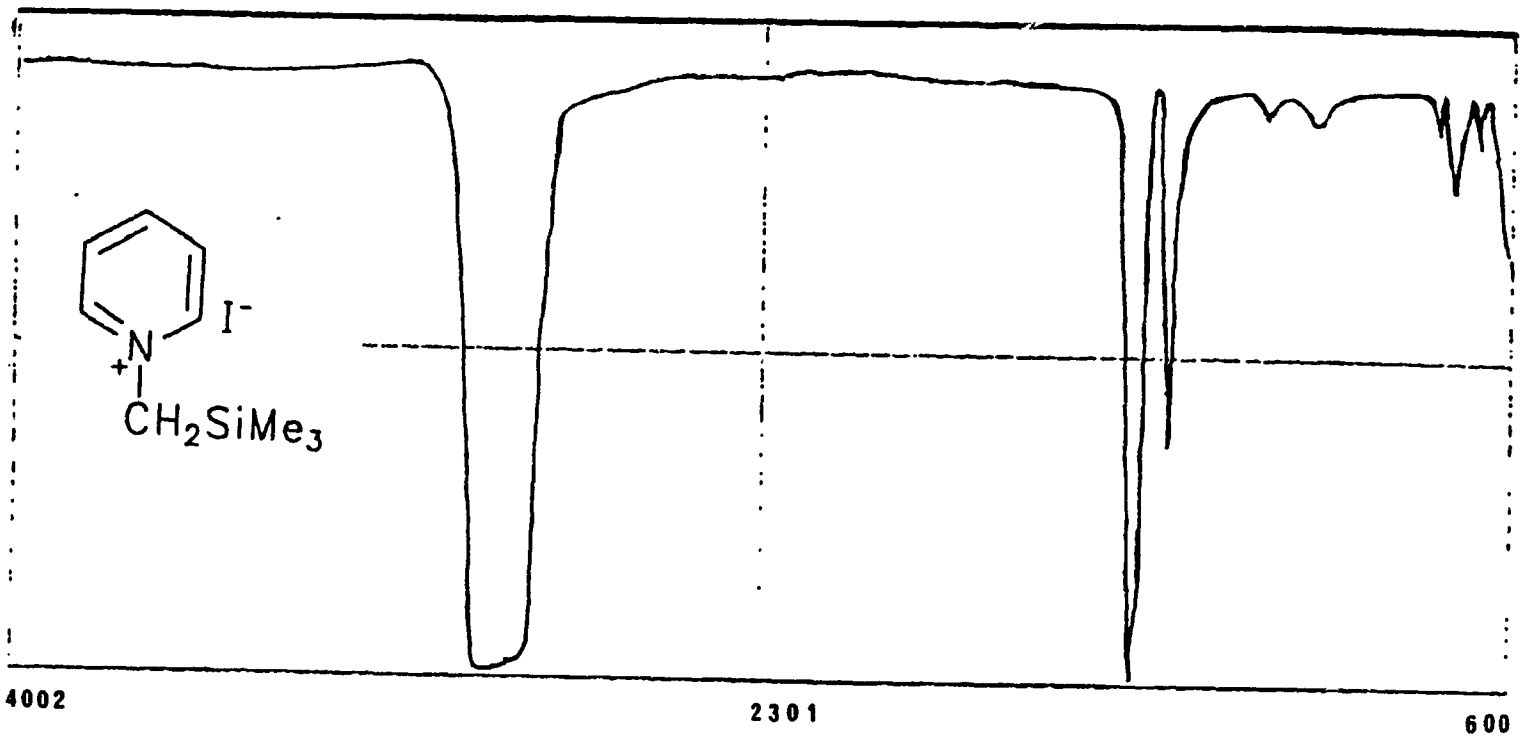


Appendix III. FT-IR Spectra

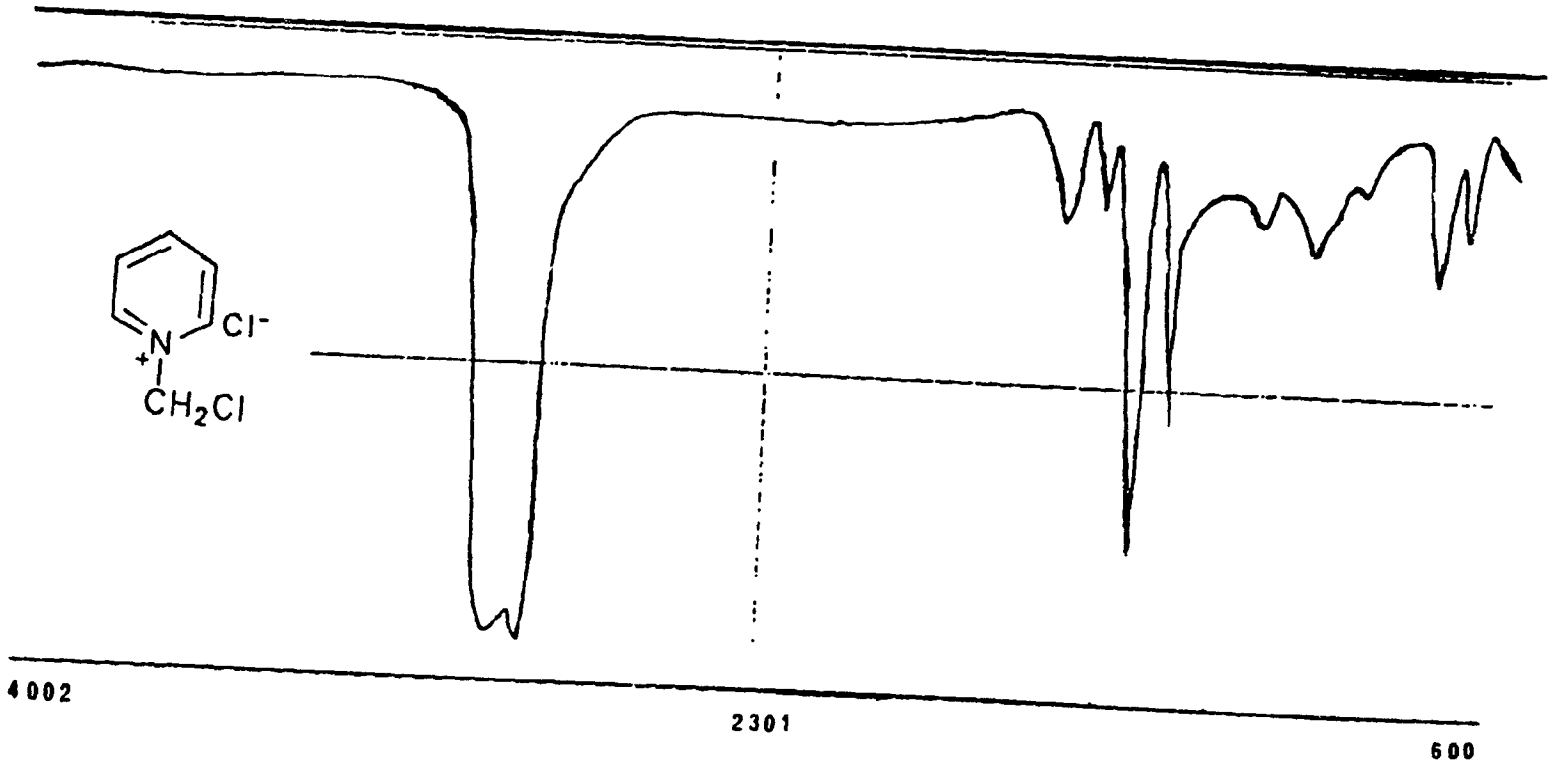
III-1. (*N*-Ethoxycarbonylmethyl)pyridinium bromide **71a**



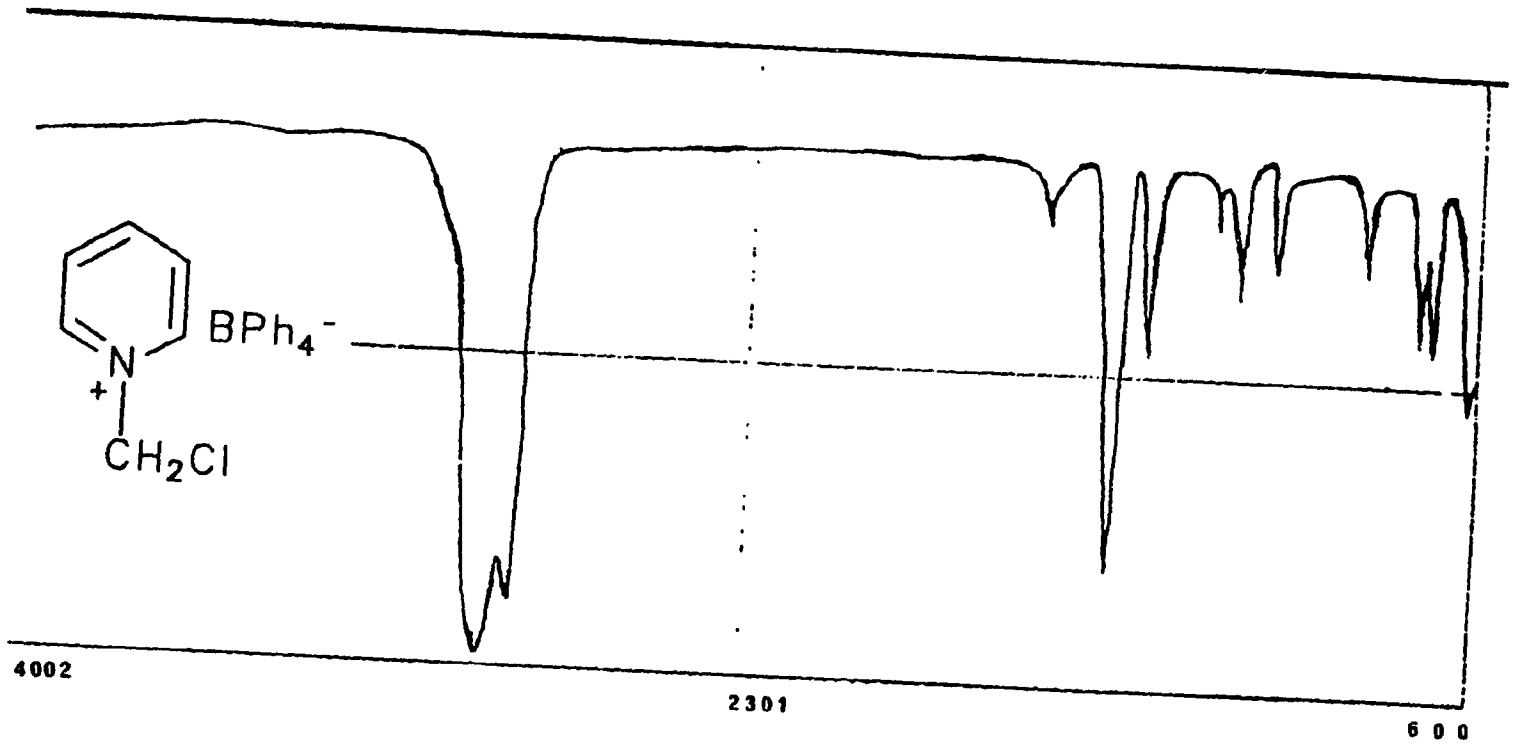
III-2. *N*-Trimethylsilylmethylpyridinium iodide **71b**



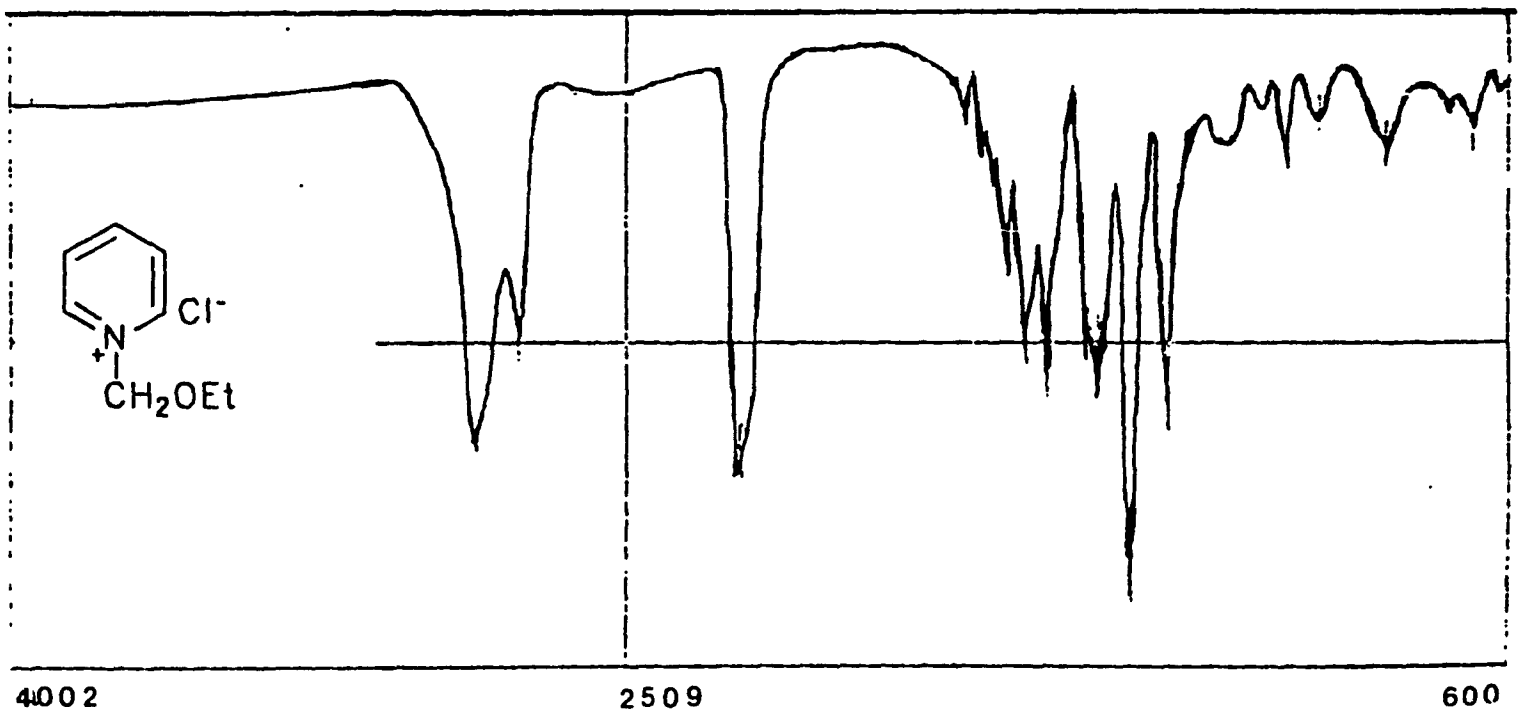
III-3. *N*-Chloromethylpyridinium chloride **74a**



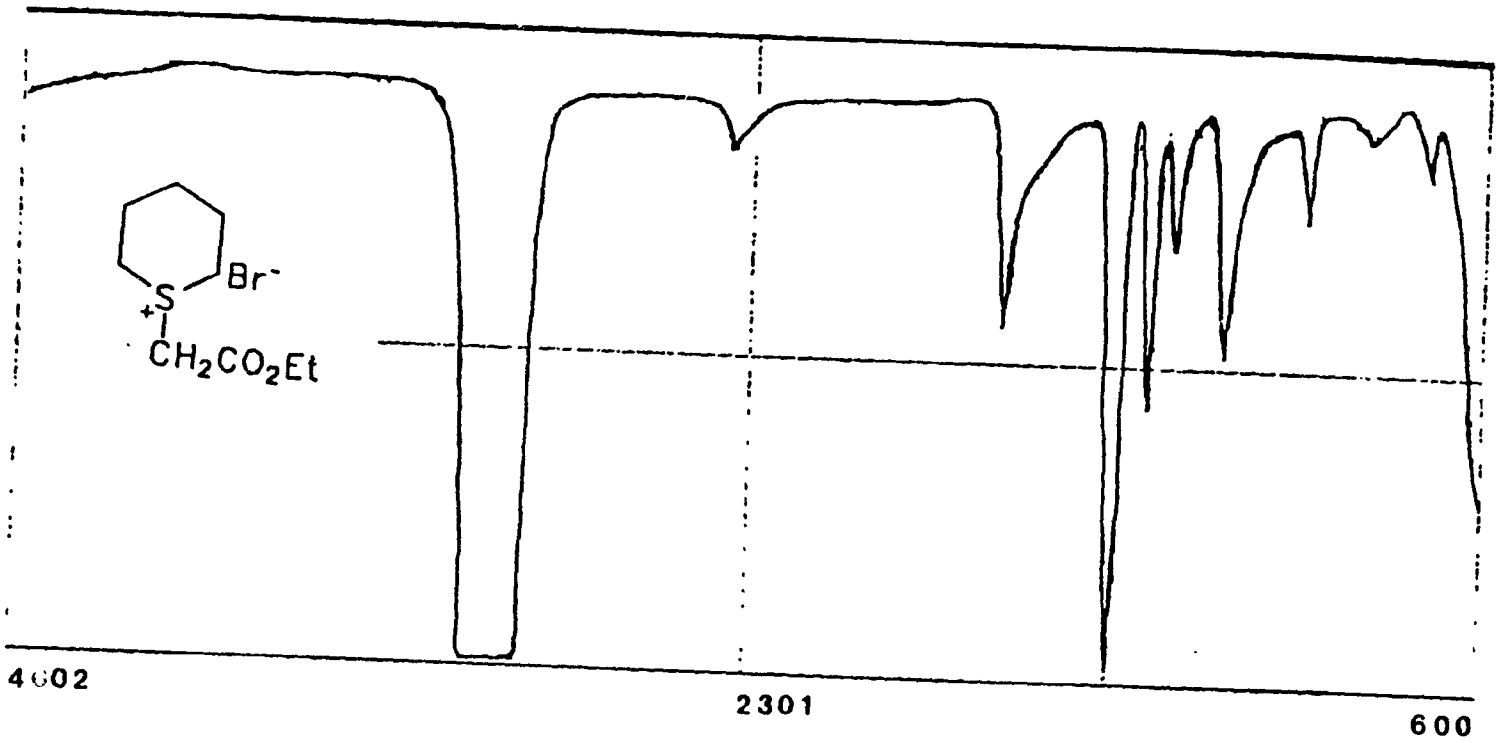
III-4. *N*-Chloromethylpyridinium tetraphenylborate **74b**



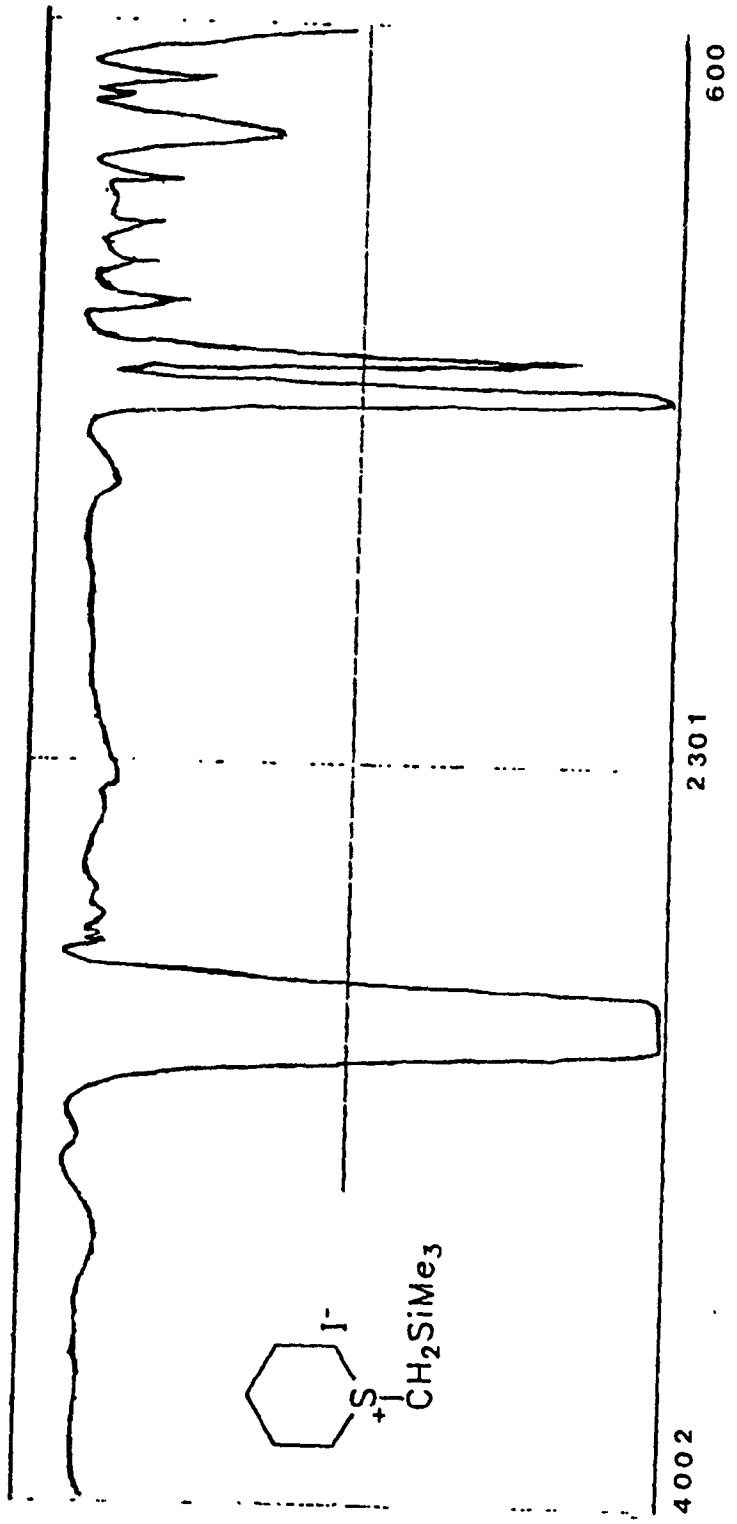
III-5. *N*-(Ethoxymethyl)pyridinium chloride **75a**



III-6. (*S*-Ethoxycarbonylmethyl)tetrahydrothiopyranium bromide **78a**



III-7. *S*-(Trimethylsilylmethyl)tetrahydrothiopyranium iodide **78b**



III-8. *S*-Methyltetrahydrothiopyranium iodide **78c**