SYNTHETIC STUDIES BASED ON NICOTINE

A Thesis for the Degree of Doctor of Philosophy submitted to the Board of the Faculty of Physical Sciences, Oxford University

by

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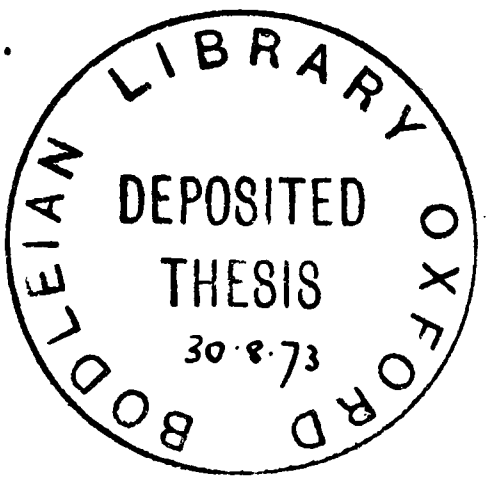
August 1972.



ACKNOWLEDGEMENTS

The author would like to extend his thanks and gratitude to the following:-

Dr. R. E. Acheson, who, never tiring, provided constant encouragement and enthusiasm throughout this investigation.

The Imperial Tobacco Group of Great Britain whose generous financial support allowed the author to pursue an enjoyable and interesting research project.

Imperial Chemical Industries Limited who tested my compounds for activity and offered useful discussion and opinions.

Dr. A. R. Hands, who accepted responsibility for my actions during my supervisor's absence.

Dr. R. Aplin, for allowing me to use his mass spectrometers and who provided interesting discussion.

Dr. G. M. Richards, for recording the 100 Mhz and spin decoupled spectra and offering advice on their interpretation.

Mrs. A. Collcutt whose nimble fingers typed this manuscript.

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INTRODUCTION

Since the middle of the eighteenth century L-nicotine (1), an alkaloid from tobacco leaves has been used as a broad spectrum insecticide. However, high mammalian toxicity has resulted in its substitution by other insecticidal types e.g. polychlorinated hydrocarbons, organo-phosphates.

Slight structural changes in biologically active compounds often cause large variations in physiological activity; thus modifications to L-nicotine might reduce harmful mammalian effects and retain or increase its useful properties. The preparation of potentially valuable new compounds from nicotine, for biological screening, is described in this thesis.

Occurrence

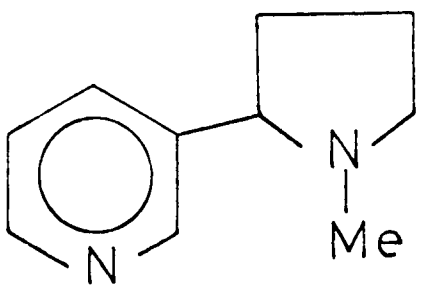
At least fifteen species of Nicotiana (family Solanaceae) produce appreciable quantities of nicotine and the cultivated varieties N. tabacum and N. rustica contain between 2-5% and 5-14% respectively by weight in the leaves from where it is obtained by steam distillation or solvent extraction.[98] Dawson[7,8,9] has shown that nicotine is formed in the roots and transmigrates to the leaves and the average nicotine distribution in Nicotiana to be, flowers (5%), stems (18%), roots (13%) and leaves (64%). Some related nicotinoids found in Nicotiana are shown in Scheme 1.

Structure and Synthesis of Nicotine

Nicotine (1) was first observed in 1809[1] and isolated in 1828.[2] The empirical formula was determined in 1843[3,4] and the molecular weight obtained in 1847.[5] Nicotine is a colourless oil, which discolours in air, it is very hygroscopic and has a boiling point of 246.1-246.2° at 760mm.; its physical properties have been listed.[6]

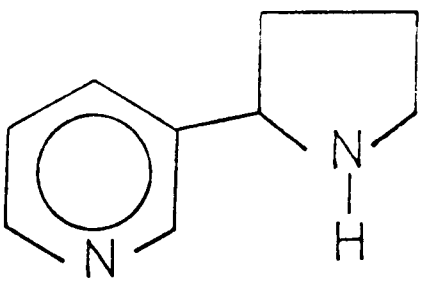
Nicotine gives nicotinic acid (10) by vigorous oxidation with chromic and sulphuric acid,[10,11,12,13] potassium permanganate,[12] hydrogen peroxide[15] nitric acid,[11,19,20] and also by anodic oxidation.[21]

Scheme 1



(1)

Nicotine



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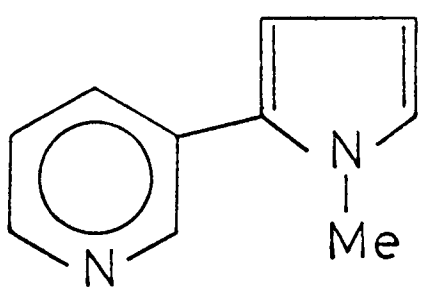
Nornicotine



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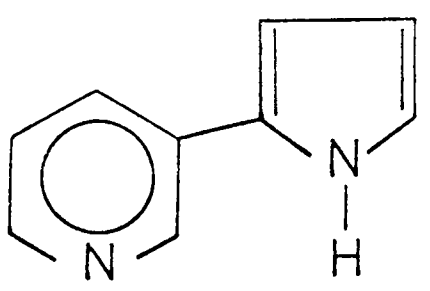
Nicotyrine



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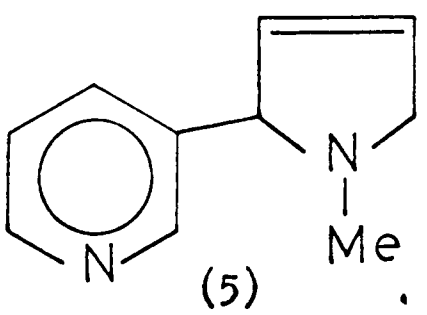
Nornicotyrine



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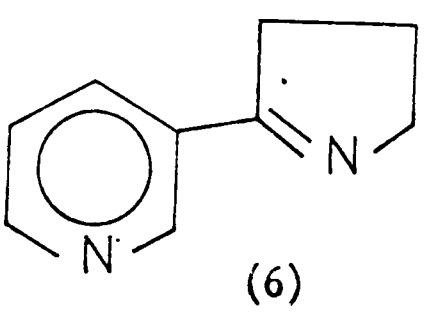
Dihydronicotyrine



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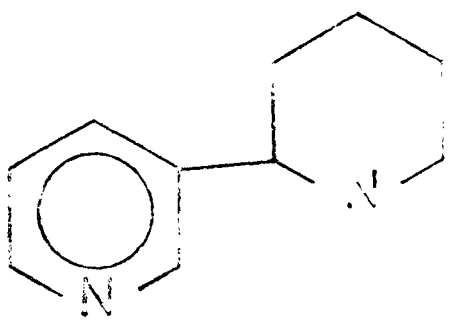
Myosmine



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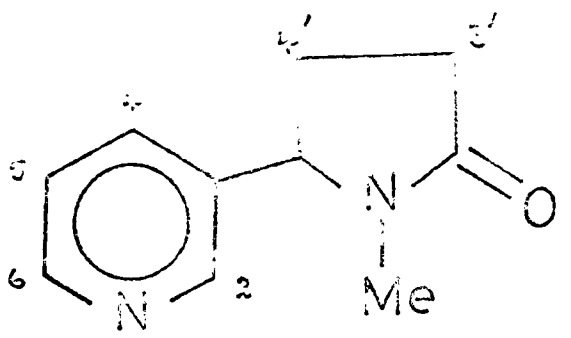
Anabasine



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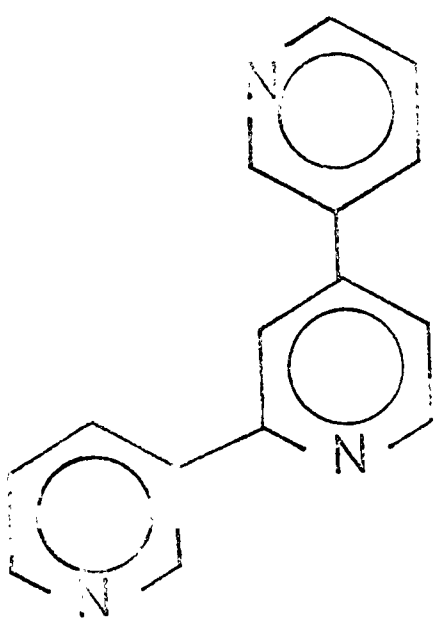
Cotinine



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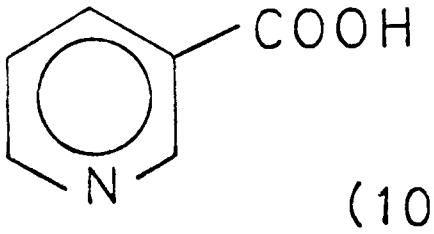
Nicotelline

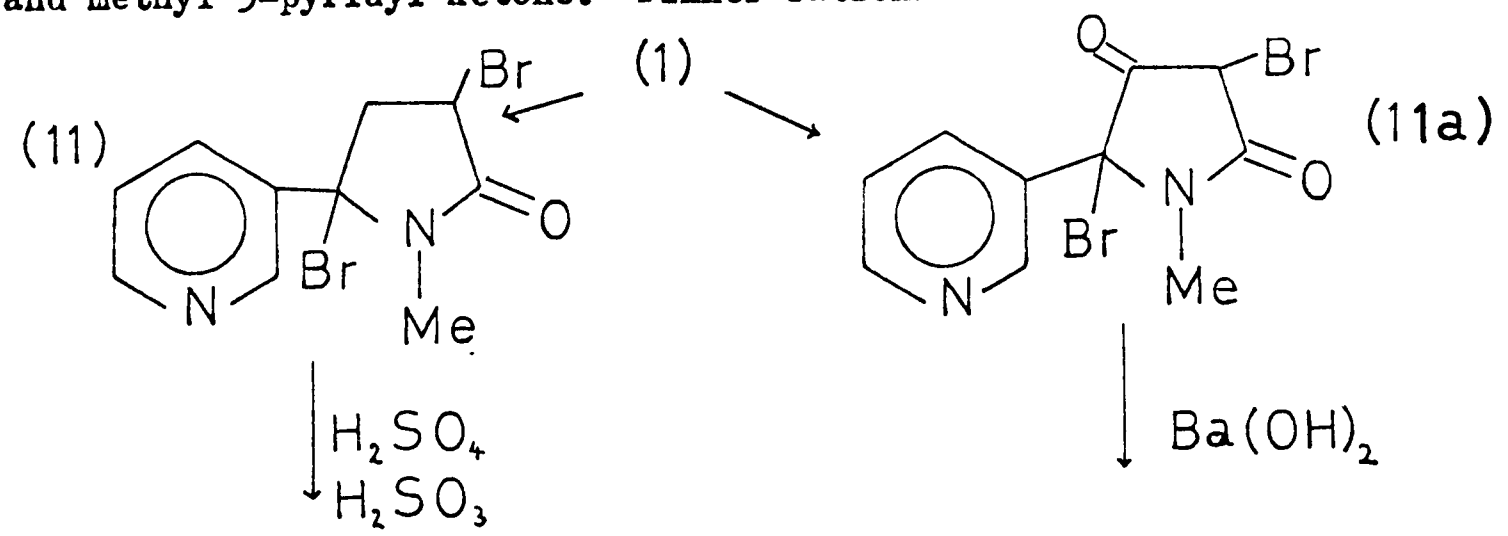
The pyrrolidone ring of cotinine (8) is numbered in the opposite sense to the pyrrolidine ring of nicotine (1). This convention, which is used throughout this thesis, is employed by Chemical Abstracts.

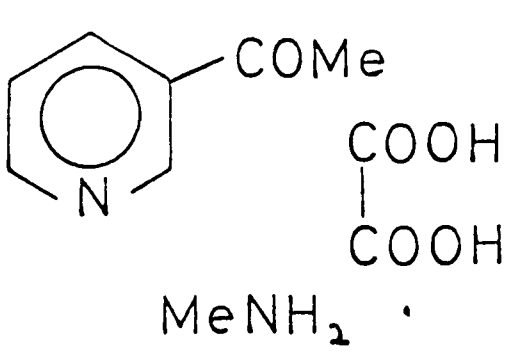


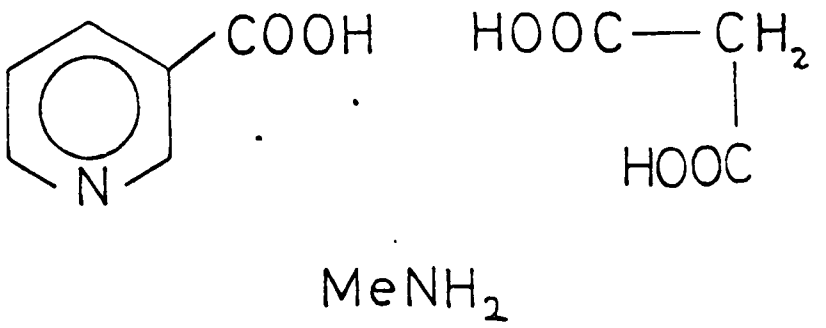
(10)

Distillation of nicotine with lime water gives pyrrole and methylamine[22] and with ethyl iodide nicotine behaves as a di-tertiary base.[23,84] These facts indicate an N-methylpyrrolidine ring although concentrated hydrochloric acid[24] or hydroiodic acid[25] fail to remove a methyl group.

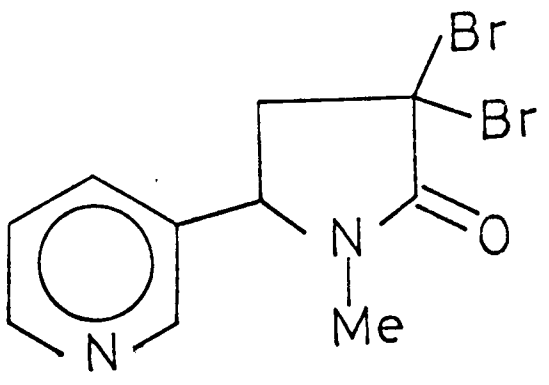
The nature of the $C_5H_{10}N$ residue was finally determined by Pinner[27] who oxidised nicotine with bromine in acetic acid and obtained dibromocotinine (11) and dibromoticonine (11a). The latter with hot barium hydroxide gave nicotinic acid, malonic acid and methylamine. The former with sulphurous and sulphuric acids gave methylamine, oxalic acid and methyl 3-pyridyl ketone. Pinner rationalised these reactions thus:







Djerassi [95] has shown (11) to have the 3,3-dibromo structure (12) the structure of (11a) has not been investigated.



(12)

Attempting to prove its structure Pictet[138] first synthesised nicotine, but two steps in his synthesis involve high temperatures and possible rearrangement. Späths synthesis[139] (Scheme 2) is a more satisfactory structure proof. Ethyl nicotinate was condensed with N-methylpyrrolidone and the product hydrolysed to the amino-ketone which reduced to the alcohol. The hydroxyl group was replaced by iodide, then alkali induced ring closure gave D,L-nicotine.

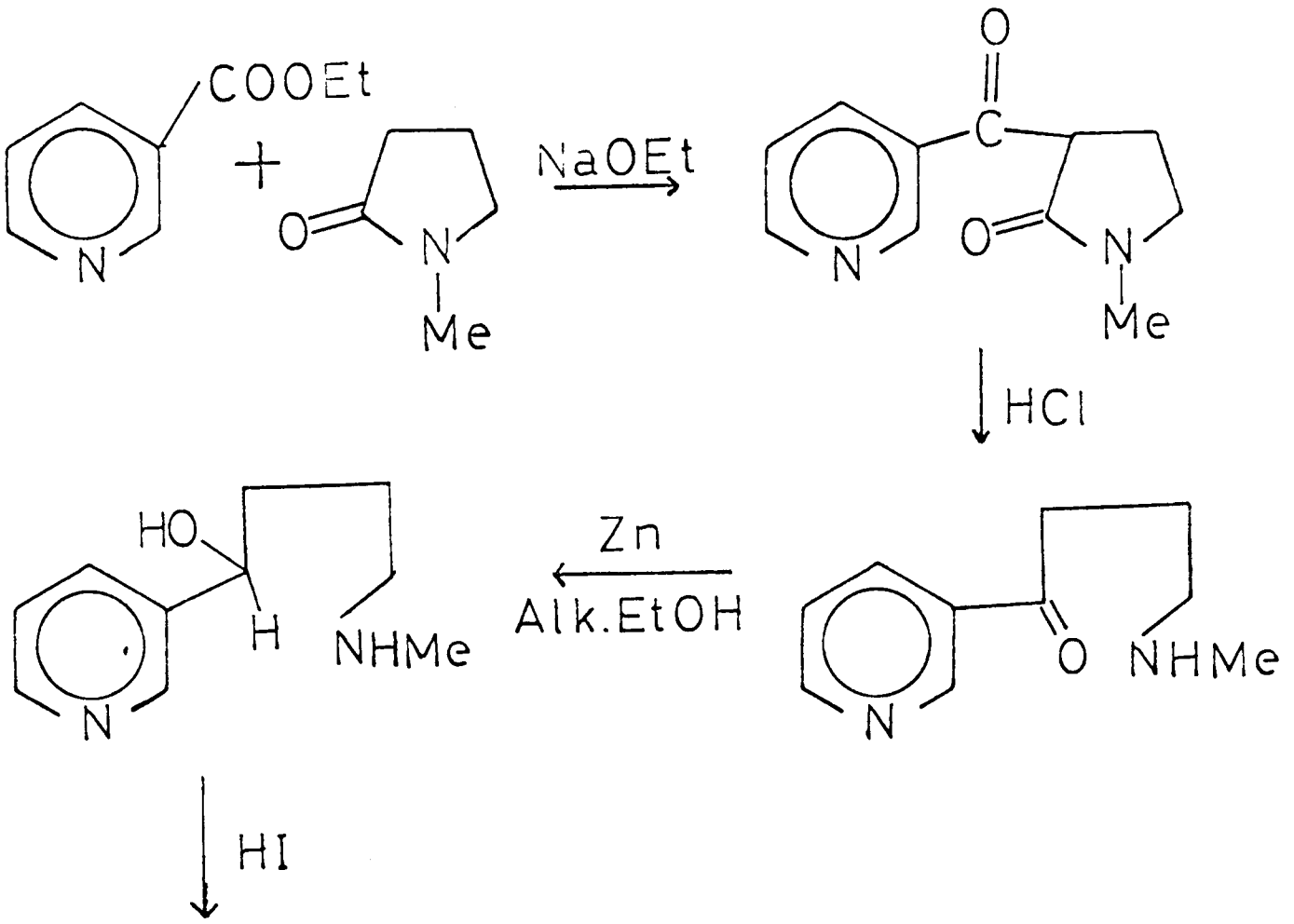
Craig[121,137] began by reacting 3-cyanopyridine with γ-ethoxypropylmagnesium bromide (Scheme 3). The oxime of the produced ketone was reduced to α-(3-pyridyl)-α-amino-δ-ethoxy-n-butane which cyclized in hydrobromic acid to D,L-nornicotine and methylation gave D,L-nicotine.

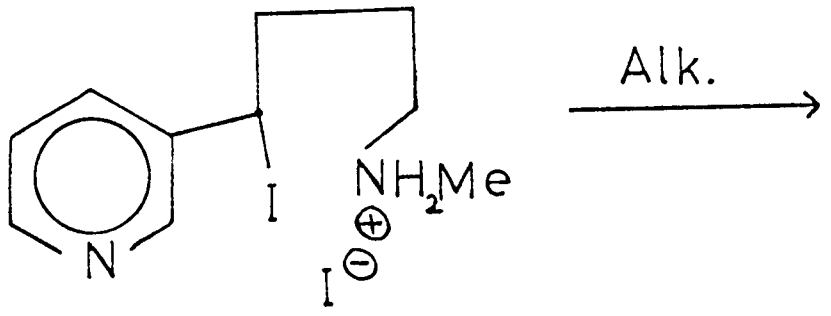
The preferred conformation has been deduced from n.m.r. and dipole moments,[29] and the n.m.r. spectrum has been fully documented.[14,36] Correlation with L-proline[99] has given the absolute configuration of natural nicotine.

More recent syntheses of nicotine have been reported.[101-104]

The biosynthesis of the pyrrolidine ring of nicotine has been studied by administering labelled acetate,[30] glutamate,[30] carbon dioxide,[31] ornithine[32] and α- and β-N-methylornithine[32] to N.rustica and N.tabacum.

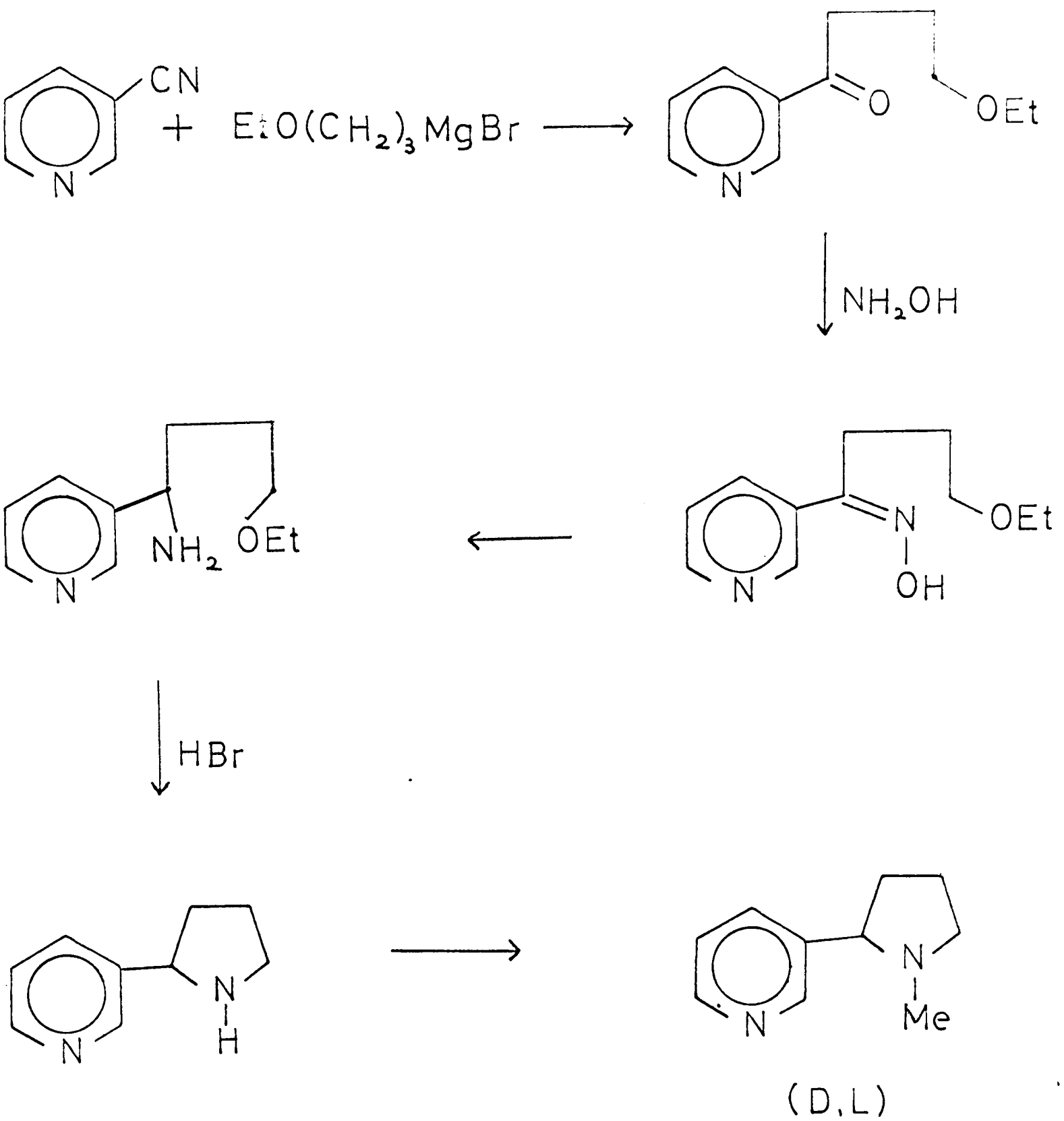
Scheme 2





(1) (D,L)

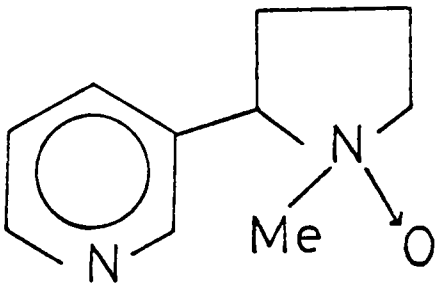
Scheme 3



D-glyceraldehyde[33,34] is incorporated into the pyridine ring of nicotine, as is quinolinic acid,[35] nicotinic acid,[35] nicotinamide adenine dinucleotide,[35] aspartic acid[36] and malic acid.[36]

Chemical Reactions of Nicotine

Catalytic dehydrogenation of nicotine with palladium charcoal or palladium asbestos gives nicotyrine (3),[17] reduction of which gives dihydronicotyrine (5).[85,86,131] Oxidation by bromine in acetic acid gives dibromocotinine (12)[18,27,48,127-130] and bromine in hydrobromic acid gives dibromoticonine (11a).[127-130] Hydrogen peroxide[131] or m-chloroperbenzoic acid[132] oxidises nicotine to nicotine mono-N-oxide (13) or nicotine di-N-oxide (14) depending on conditions.



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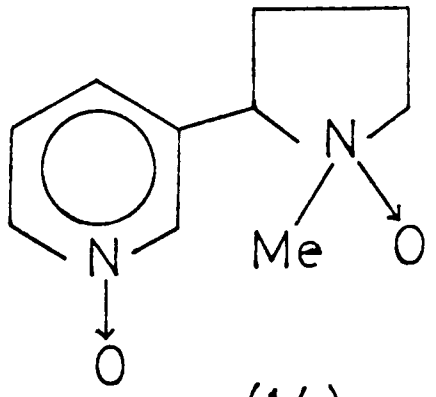

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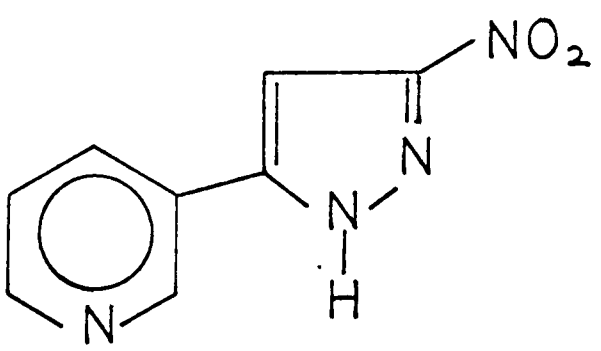
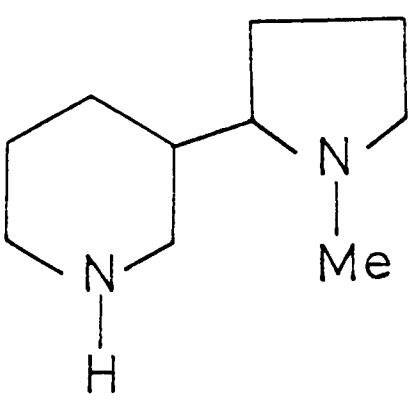


(15)

Nitric acid oxidation gives nicotinic acid and a 7% yield of 5-(3-pyridyl)-3-nitropyrazole (15).[63-66] Potassium ferricyanide has no action on nicotine,[67] but calcium ferricyanide,[69] silver acetate,[70] silver oxide[26,72] or electrolysis[73] all give small quantities of nicotyrine (3).

Pyrolysis of nicotine at 450° gives myosmine (6),[71] which can be hydrogenated to nornicotine (2).[74,75] The latter is also obtained in low yield by reaction of nicotine with hydrocinnamic acid,[76] potassium permanganate,[77] silver oxide[76] or selenium dioxide.[78]

Reduction with sodium in alcohol or hydrogenation with Adams catalyst gives a mixture of hexahydronicotine (16) and octahydronicotine (17).[28,80-83]



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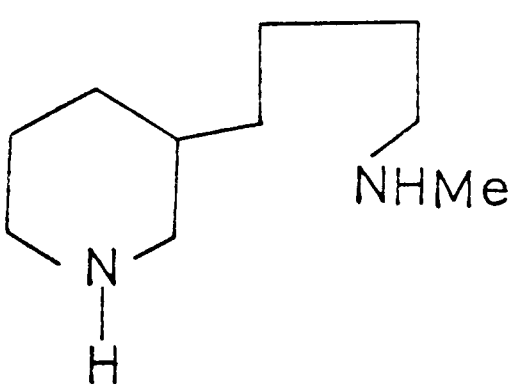

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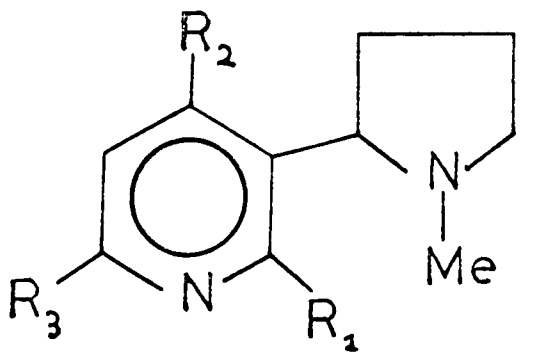
Amination with sodamide in xylene yields a mixture of 2- (18) and 6-aminonicotine (19).[87,88]

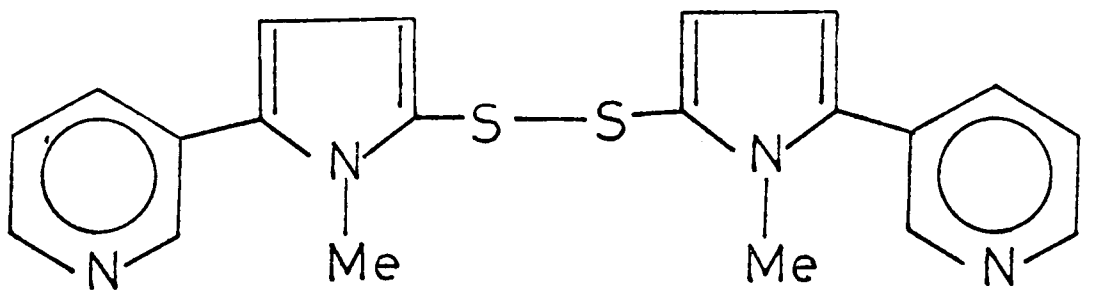


(for key see over page)

	R_1	R_2	R_3
(18)	NH_2	H	H
(19)	H	H	NH_2
(20)	H	H	Me
(21)	H	Me	H
(22)	Ph	H	H
(23)	H	H	Ph

Alkylation [90,94] with methyl lithium gives 6-methylnicotine (20) and a little 4-methylnicotine (21), arylation[91,92,93] with phenyl lithium gives a mixture of equal quantities of 2-phenyl- (22) and 6-phenylnicotine (23).

Nicotine is oxidised by and couples with sulphur in refluxing toluene to give dithiodinicotyrine (24).[97] (see discussion)



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Biological Properties of Nicotine

Numerous reports on nicotine toxicity to mammals and insects show large discrepancies, Negherbon,[37] provides a comprehensive review and Metcalfe[105] and O'Brien[106] short discussions.

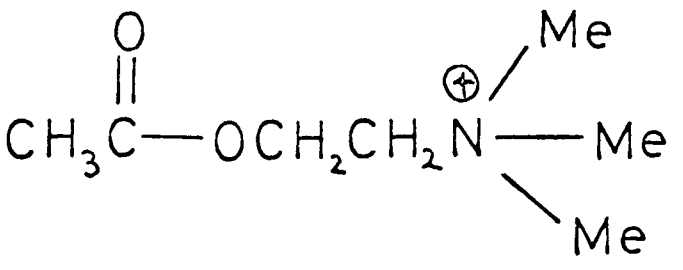
Nicotine shows large species variations in toxicity (Table 1), the median lethal concentration (MLC) in mg./kg. for aphids, thrips and silkworms is 0.003 to 0.008 but 0.28 for the Japanese beetle and 0.145 for the Mexican bean beetle.[106] Nicotine kills insects rapidly, tremors are followed by convulsions, paralysis and death.

Table 1. Toxicity of Nicotine to some Insects.[106] LD_{50} mg./kg. when base applied topically.

American cockroach	650
Squash bug	350
Milkweed bug	190
Japanese beetle	650
Yellow mealworm	3200
Bombyx silkworm	4
Honey bee	315

It is agreed that nicotine acts primarily on insect ganglia (central nervous system)[38,39,40] but at very high concentrations it can also stimulate neuro-muscular junctions.[41] Attack of an insect's central nervous system (CNS) is in contrast to mammalian attack, where the primary target is the peripheral nervous system.

The synapses of an insect's CNS and a mammal's peripheral nervous system are both cholinergic, acetylcholine (25) being the chemical transmitter conveying a nerve impulse from the axon across the synaptic cleft to the receptor, which may be another axon or muscle.



(25)

Histochemical,[42] enzymological[43] and physiological[44] evidence show that the peripheral nervous system in insects is not cholinergic (the identity of the transmitter is not known) and thus appears to be unaffected by nicotine.

After exciting the receptor, acetylcholine is removed quickly by cholinesterase, freeing the receptor for the next impulse. Removal of cholinesterase from the CNS causes death.[107,108]

In 1939 Gause and Smaragdova[109] proposed that nicotine mimics acetylcholine at the receptor site, causing initially acute nervous excitement and then (because nicotine is not removed by cholinesterase from the receptor) blockage of the nerve, paralysis and death. This inability of cholinergic receptors to distinguish between acetylcholine and nicotine is now recognised as the cause of nicotine poisoning.[110]

It is surprising that only recently has this knowledge been utilised as a basis for the synthesis of new nicotine analogues. Von Euler[54] and Yamamoto[55-61] have synthesised and quantified the activity of some analogues and Yamamoto[45] has reviewed the electronic and stereochemical parameters which appear necessary for production of cholinergic effects on insect ganglia. He concludes that:

(i) A pyridine ring must be present and

(ii) must be substituted in the 3 position.

(iii) The other nitrogen atom must have a pKa between 8 and 9 and

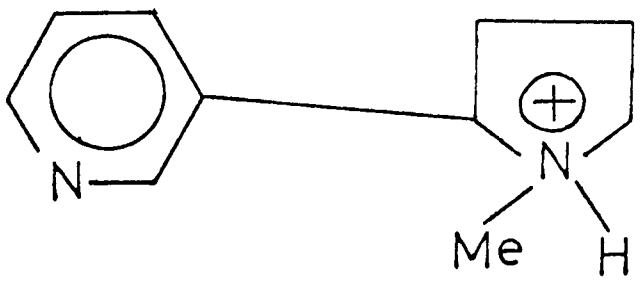
(iv) should be about 4.2 Å from the pyridine nitrogen.

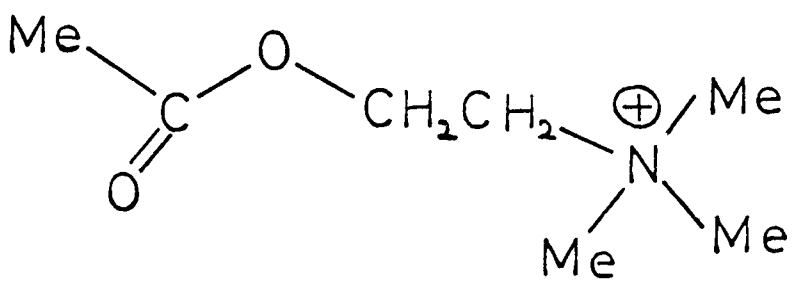
(v) The basic nitrogen must not possess a hydrogen atom.

(vi) If either nitrogen atom is quaternised, activity ceases.

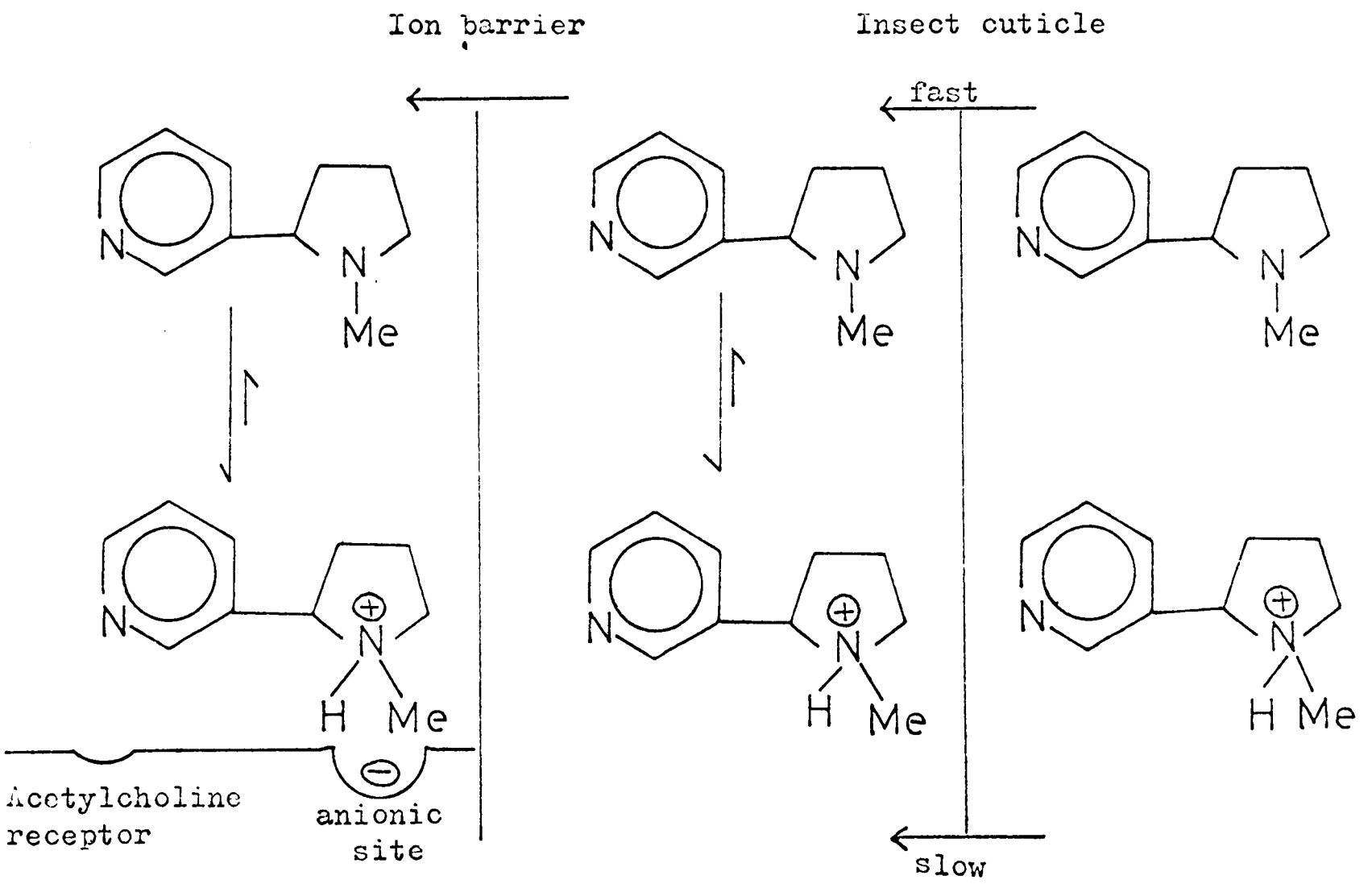
Points (iii) and (vi) merit further discussion. Cationic species such as quaternised nitrogen compounds only slowly penetrate insect cuticles and are totally unable to pass through the ion barrier into the synaptic region. However, acetylcholine (produced inside the ion barrier) possesses a cationic head which reacts with the anionic receptor. Hence the need for the basic nitrogen which is protonated when nicotine arrives in the synaptic medium which has a pH of about 7.

The similarity between acetylcholine and nicotine has been represented[45] as:-





and total penetration of nicotine to the receptor as[45]:-



It is not yet clear why the receptor appears to find the 3-pyridyl and the acetoxy groups so similar.

Metabolism of Nicotine in Insects

The majority of insects quickly metabolise nicotine to the non-toxic cotinine,[51] but many which are insensitive to nicotine, e.g. tobacco bud worms or cabbage loopers, do not metabolise nicotine but have extremely rapid excretory mechanisms. Tobacco hornworms can excrete 83% of a nicotine dose only fifteen minutes after ingestion.[53]

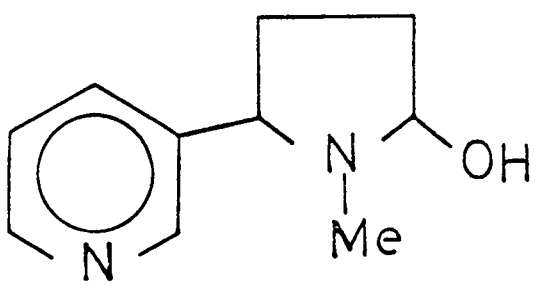
Thus chemical modifications could also increase toxicity by interfering with the metabolic process or reducing the excretory rate.

Metabolism and Effects of Nicotine in Mammals

Nicotine is metabolised in the liver by mammals to 5'-hydroxynicotine (26) which is rapidly oxidised to cotinine (8), and in turn partially hydrolysed to γ-(3-pyridyl)-γ-methylaminobutyric acid (27).[48,49] Nornicotine (2), demethylcotinine (28), 3-pyridylacetic acid (29) and nicotine mono-N-oxide (13) have been isolated from rabbit liver microsomes.[50]

Reviews on the action of nicotine in mammals have appeared,[117,118,119,120] experimental results are conflicting in many cases and much further work is required.

Generally small doses stimulate the central nervous system and large doses cause suppression but correlations between the produced actions and the central levels have not been established. Mammalian studies indicate conditioned reflexes may be inhibited, it seems nicotine abolishes the relationship between stimulus strength and response. In acute and chronic experiments nicotine appears to reduce performance of rats in a labyrinth,[120] however these effects can be explained simply in terms of the ill health of the animals, there is no conclusive evidence that nicotine inhibits learning



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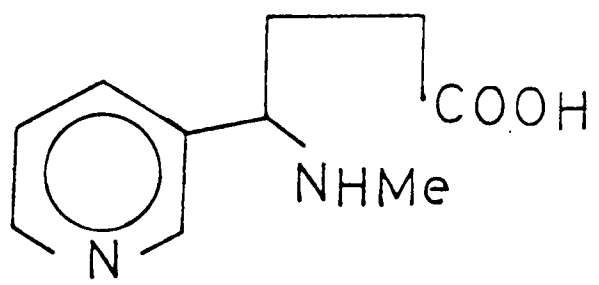

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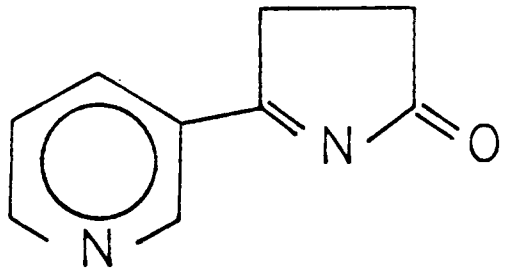

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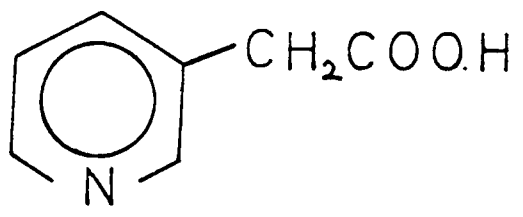


(29)

in man or animals.

Studies on brain potentials have shown that nicotine abolishes visual action potentials in the optic lobes. Very large nicotine doses cause 'grand mal' seizure patterns in electroencephalograms, smaller doses give rise to prolonged desynchronization, tonic and clonic contractions and muscular fibrillation.

No reliable data exist concerning nicotine action on the brain stem, cerebellum or spinal chord, it is believed[120] that the spinal depressant action of nicotine has been considerably overestimated.

Acute nicotine poisoning in man (forty mg./kg or more) can cause death, symptoms reported include extreme nausea, vomiting, evacuation of bowel and bladder, mental confusion, convulsions and finally death due to respiratory paralysis. Experiments[122] in mammals have shown small nicotine doses to be emetic but larger doses suppress vomiting and may be anti-emetic, central and peripheral factors are involved, the former being the central medullary mechanism.[122]

Nicotine stimulates the chemoreceptors of the carotid and aortic bodies causing an increase in the rate and depth of breathing, vasoconstriction mingled with vasodilation, cardiac acceleration and increase of blood pressure. Low nicotine concentrations activate sensory receptors in the pulmonary and coronary circulation.

The cells of the supraopticnucleus are stimulated by nicotine, causing impulses to pass to the posterior lobe of the pituitary and a discharge of vasopressin results, producing a reduction of coronary flow.[111] Nicotine also causes release of catecholamines, notably adrenalin (ephinephrine) and noradrenalin (norephinephrine) by stimulation of the stellate ganglia. Vasopressin produces a reduction in coronary circulation whilst catecholamine causes a dilation of the coronary vessels thus increasing blood circulation.

Nicotine has been shown to produce release of 5-hydroxytryptamine from rabbit-blood platelets,[115] probably by increasing the permeability of the platelet membrane, the mechanism of action is not known.

It is still uncertain as to whether inhalation of tobacco smoke causes gastric acid secretion, divergent effects have been obtained in fasting human beings and tobacco smoke has never initiated acid secretion in fasting dogs.[116] However, mucosal application of acetylcholine in the antrum has produced gastric acid secretion in dogs, caused , in all probability, by the release from the antrum of the secretory hormone gastrin. Recently[166] it has been definitely established that nicotine applied to the antrum also produces gastric secretion, almost certainly by stimulating gastrin release. Very high nicotine concentrations prevent gastric acid release, probably by blocking the ganglia responsible for gastrin release.

Nicotine is "biologically soft", being rapidly degraded in the soil and leaves no harmful residues. Insects develop resistance to nicotine very slowly. These are important advantages, both commercially and socially, thus a nicotinoid which is more toxic than nicotine but has similar biodegradable properties would have considerable potential as an insecticide. Much scope exists for further research in nicotine chemistry.

D I S C U S S I O N

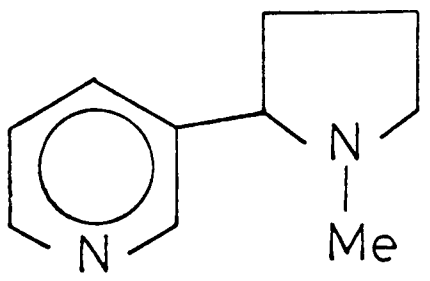
Section 1. Alkyl Derivatives of Nicotine

Biological Implications

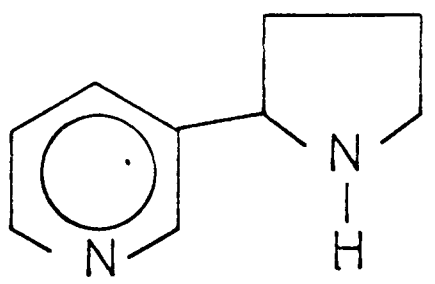
Papers[55-61] and a review[45] by Yamamoto have attempted to show the electronic and stereochemical requirements for toxicity in the nicotine molecule. By correlating toxicity studies from many workers he has obtained an indication of the parameters necessary to produce biological activity similar in character and strength to nicotine.

The term "toxicity" is not defined by Yamamoto; as no attempts have been made to standardise activity testing, precise correlations are not possible and the term is best considered as a general indication of the effectiveness of a compound against a representative number of insects.

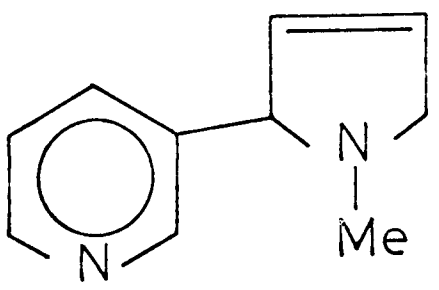
Metcalf[105] has reviewed the nicotine analogues studied to 1954 and in no case has nicotine like activity been observed. Only anabasine (7), nornicotine (2) and dihydronicotyrine (5) had activity comparable to nicotine.



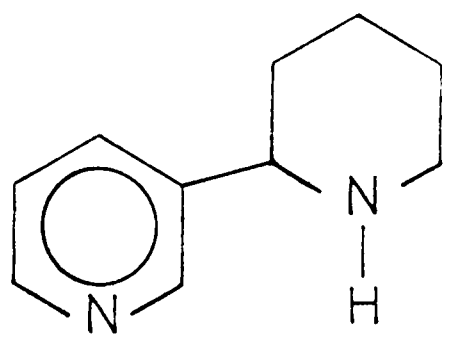
(1)



(2)



(5)



(7)

Yamamoto assumed that all nicotinoids would affect the same receptor site and because no direct way exists of obtaining structure-activity relationships directly at the receptor, he used insecticidal toxicity as an approximate value of target effectiveness.

Because (1), (2), (5) and (7) were all highly toxic Yamamoto decided that the presence or absence of an N-methyl group on the pyrrolidine ring and the presence of four or five carbon atoms in the ring connected to the 3 position of the pyridine ring had no significance.

A combination of two rings seems necessary for toxicity as the separate ring systems all show very low activity. (Table 2)

The relative toxicities shown in Tables 2,3,4,5 and 6 are weight ratios. The compounds were applied as a spray, usually in dilute aqueous solution.

The tables were compiled by Yamamoto from data published by various authors.

Table 2. Relative Toxicities of Simple Ring Systems[45]

Compound	Insect	
	Aphis rumicis	Tribolium confusum
L-nicotine	1.00	1.00
Pyridine	0.008	0.0009
Pyrrolidine	0.05	0.028
N-Methylpyrrolidine	-	0.003
Piperidine	0.04	-
Pyrrole	0.04	-
α-Picoline	0.015	
Lutidine	0.04	
Quinoline	0.1	
Isoquinoline	0.067	

Table 3. Relative Toxicities of 2-Substituted N-Methylpyrrolidines[45]

Substituent	Aphis rumicis
3-Pyridyl (L-nicotine)	1.00
Phenyl	0.03
n-Butyl	0.02
n-Propyl	0.01
Ethyl	0.008
Methyl	0.006

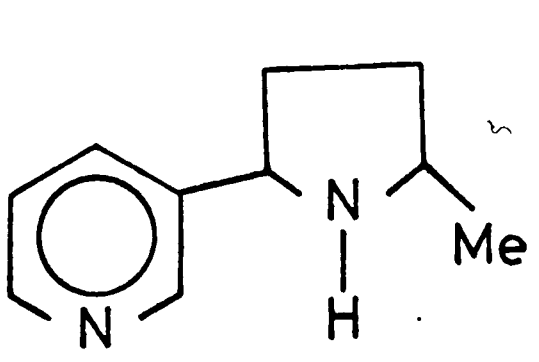
Table 4. Relative Toxicities of Pyridylpyrrolidines and Pyridylpiperidines[45]

Compound	Aphis rumicis
L-nicotine	1.00
1-Methyl-2-(2-pyridyl)pyrrolidine	0.03
2-(2-Pyridyl)pyrrolidine	0.03
3-(3-Pyridyl)piperidine	0.02
3-(2-Pyridyl)piperidine	0.02
2-(2-Pyridyl)piperidine	0.01

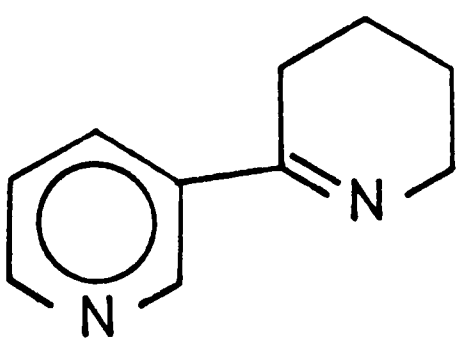
Table 5. Relative Toxicity and Basicity of some Nicotinoids

Compound	Basicity[45]		Basicity*		Toxicity[45]
	pK_a1	pK_a2	pK_a1	pK_a2	
Nornicotine (2)	3.3	9.0			2.0
Dihydronicotyrine (5)	2.9	7.4		7.07	2.0
5'-Methylnornicotine (30)	3.4	8.9			1.0
L-Nicotine (1)	3.1	7.9	3.12	8.02	1.00
Anabaseine (31)	2.8	6.7			0.3
Cotinine (8)	2.7	4.5			0.1
Nicotyrine (3)	2.2	4.7		4.35	0.1
Myosmine (6)	2.8	5.5		5.26	0.03

* "Dissociation Constants of Organic Bases", published by The International Union of Pure and Applied Chemistry, (1965).



(30)



(31)

[The pK_a values for compounds (1), (2), (5) and (30) are in general agreement with those of 1-methylpyrrolidine (10.4) and pyridine (5.2).

The first proton added will attack the more basic centre and the addition of the second proton to the charged species will be inhibited as compared with the protonation of pyridine itself.

The more basic centres of nicotyrine (3) and cotinine (8) will be the pyridine rings, so a pK_a of about 5 is expected. Addition of a second proton as suggested by Yamamoto[45] seems very unlikely as pyrrole and N-methylpyrrolid-2-one have pK_a values of about +0.4* and +0.2* respectively. Professor A. H. Beckett has confirmed this idea by showing (personal communication) that nicotyrine and cotinine in water form only mono-cations with pK_a values of 4.9 and 4.2 respectively.

The pK_a values given by Yamamoto[45] for myosmine (6) and anabaseine (31) may also be incorrect.

* "Dissociation Constants of Organic Bases", published by The International Union of Pure and Applied Chemistry, (1965).

* R.L.Aldeman, J. Org. Chem. , 25, 551 (1960).]

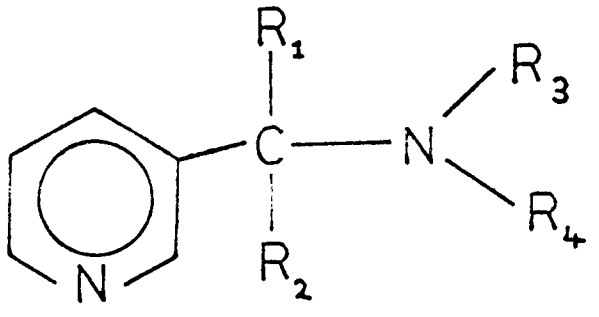
A pyridine ring must be at the 2 position of the pyrrolidine ring, other substituents cause low activity (Table 3).

Only those compounds containing a 3-2' linkage show high toxicity, similar ring systems connected by 2-3' , 2-2' or 3-3' linkages have low toxicity (Table 4).

The minimum distance between the nitrogen atoms in nicotine and other 3-2' systems is approximately 4.2 Å, if this is changed activity falls.

However, if this distance is held constant, but the basicities of the two nitrogens are changed, activity again falls (Table 5). The pyridine nitrogen should have a pK_a of between 2.5 and 3.0 and the pyrrolidine nitrogen should have a pK_a of about 8.5 for maximum activity.

Yamamoto reasoned from the above requirements that the essential moiety for activity could be reduced to (32).



(32)

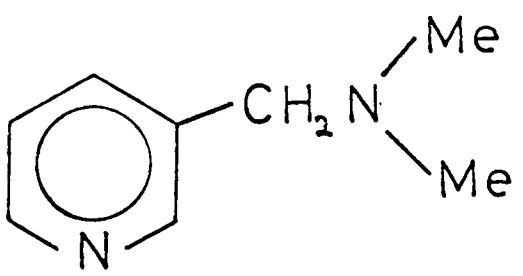
He found that if $R_1 = R_2 = H$ and $R_3 = R_4 = Me$ then activity comparable to nicotine results and that increasing the size of the alkyl groups R_3 and R_4 increased activity still further (Table 6).

Table 6. Relative Toxicities of Pyridylmethylamines[45]

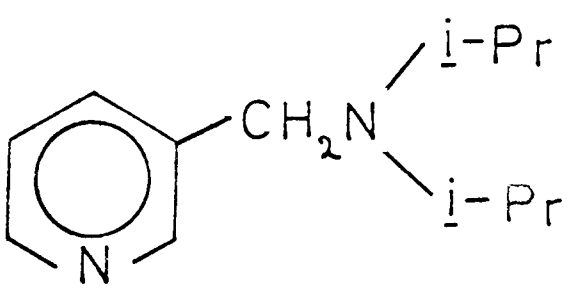
Compound ($R_1 = R_2 = H$)	Musca domestica
$R_3 = R_4 = Me$	1.1
$R_3 = R_4 = Et$	2.0
$R_3 = R_4 = n\text{-}Pr$	3.2
$R_3 = R_4 = i\text{-}Pr$	4.3
$R_3 = R_4 = n\text{-}Bu$	4.0
L-nicotine	1.0

However if either R_3 and R_4 are hydrogens activity falls. Yamamoto does not record the consequences of having either R_1 = alkyl, R_2 = hydrogen or $R_1 = R_2$ = alkyl.

Von Euler[54] investigated a similar series of compounds and obtained a conflicting set of results. However Yamamoto determined activity by using relative insect toxicities i.e. <u>in vivo</u> ganglionic attack, von Euler has recorded that activity induced in isolated biological preparations (Table 7).



(32; $R_1 = R_2 = H$, $R_3 = R_4 = Me$)



(32 ; $R_1 = R_2 = H$, $R_3 = R_4 = \underline{i}$-Pr)

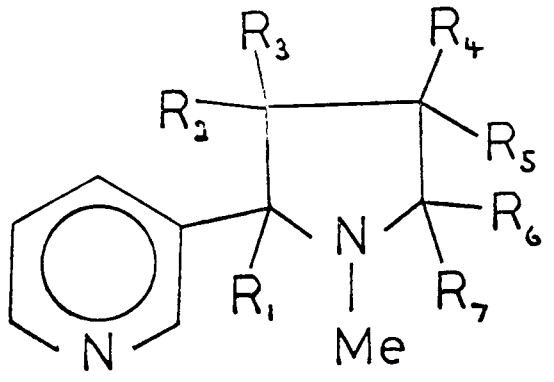
For the above compound (32; $R_1 = R_2 = H$, $R_3 = R_4 = Me$) Yamamoto reported activity similar to nicotine, von Euler however obtained only 0.1 the activity of nicotine. For (32; $R_1 = R_2 = H$, $R_3 = R_4 = \underline{i}$-Pr) Yamamoto obtained four times the activity of nicotine but von Euler states that when $R_1 = R_2 = H$, $R_3 = Me$, $R_4 = \underline{i}$-Pr activity has dropped to only 0.001 of that of nicotine.

The pyridylalkylamines may possess insecticidal properties other than those shown by nicotine, thus causing the high toxicities observed by Yamamoto. The divergent results obtained by von Euler and Yamamoto serve to emphasise the impossibility of attempting to correlate biological activity results obtained by different methods.

Table 7. Physiological Activity of Pyridylmethylamines[54]

Compound	Rabbit jejunum	Guinea Pig ileum	Cat blood pressure	Frog muscle
(1) L-nicotine	1	1	1	1
(32) R_1,R_2,R_3,R_4=H	0.004	0.001	-	0
(32) R_1,R_2,R_3=H; R_4=Me	0	0	-	0
(32) R_1,R_2=H; R_3,R_4=Me	0.11	0.10	0.08	0.02
(32) R_1,R_2=H; R_3=Me; R_4=Et	0.06	0.02	-	0.03
(32) R_1,R_2=H; R_3,R_4=Et	0.002	0	0.004	0
(32) R_1,R_2=H; R_3=Me; R_4=n-Pr	0.001	0.003	-	0
(32) R_1=H; R_2,R_3=Me; R_4=Et	0.003	0.002	-	0
(32) R_1=H; R_2=Et; R_3,R_4=Me	0	0	-	0
(32) R_1=H; R_2=n-Pr; R_3,R_4=Me	0	0	-	0

Neither Yamamoto nor von Euler have prepared compounds of type:-



(33) R_1=Me; R_2-R_7=H

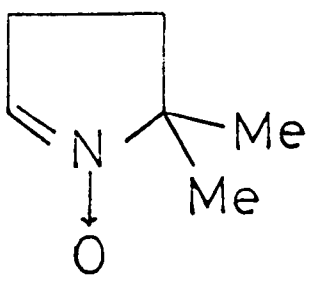
(34) R_1-R_5=H; R_6=R_7=Me

(35) R_1=H; R_2=Me; R_3-R_7=H

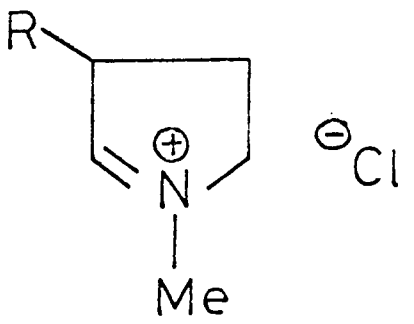
where R_1 to R_7 can be either hydrogen or an alkyl group.

Hankins[123] has reported the preparation of (34) by treating cotinine (8) with a five molar excess of methyl magnesium iodide. He does not characterise the free base but gives melting points for a dihydrochloride and a dipicrate. The latter value (210-212°) is not in agreement with the

value obtained by Rosnati[124] (225-226°) who reports the synthesis of (34) from 3-pyridyl lithium and 5,5-dimethyl-1-pyrroline-1-oxide (36). Neither report gives data on the insecticidal activity of (34).



(36)



(37) R=H
(38) R=Me

Rapoport[126] has shown 1-methyl-1-pyrrolinium chloride (37) to be an efficient precursor of the pyrrolidine ring of nicotine when administered to Nicotiana and more recently[125] by feeding 1,3-dimethyl-1-pyrrolinium chloride (38) to Nicotiana he has obtained 3'-methyl nicotine (35), but again no biological evaluation has been reported.

Castagnoli[140] has synthesised trans - (35) from N-3-pyridylidenemethylamine and succinic anhydride and shown it to be identical with the metabolite obtained by Rapoport.

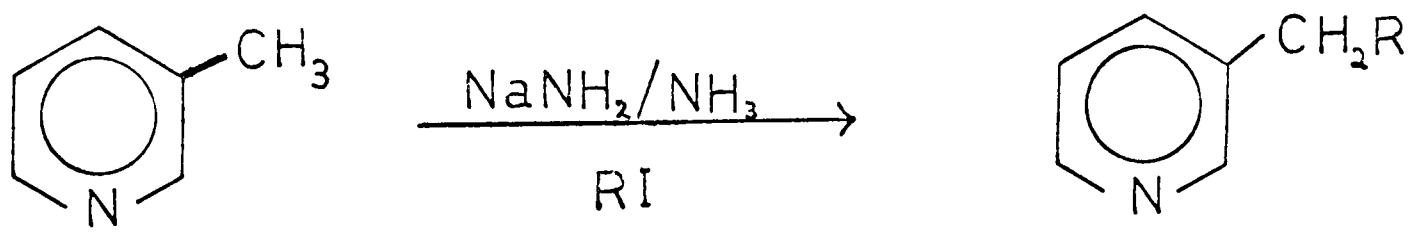
Thus scope exists for further work, in particular replacement of hydrogen atoms on carbon atoms 2' and 4' of nicotine by alkyl groups would lead to interesting compounds.

Attempted Preparation of 2'-Methylnicotine

Increase in steric crowding in a biologically active compound often causes an increase in the specificity of the activity. Molecular models show that (33) would be crowded at carbon atom 2' and rotation between the rings

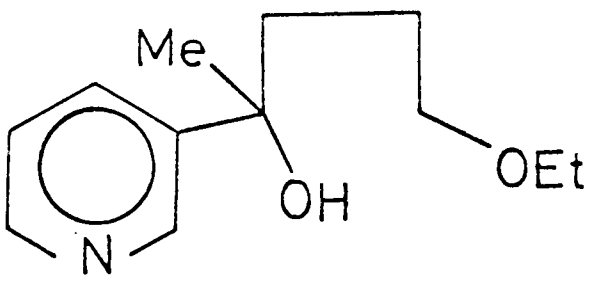
could be considerably restricted. Thus the synthesis of (33) was attempted.

Brown[141] has shown that the alkyl hydrogen atoms of 3-picoline are sufficiently acidic to be replaced by alkyl groups on treatment with sodamide in ammonia, followed by addition of an alkyl halide.



By analogy the 2' hydrogen atom of nicotine would be expected to be replaceable under similar conditions. However nicotine failed to react and it seems likely that the adjacent electron rich pyrrolidine nitrogen atom causes a reduction in acidity of the 2' hydrogen.

Attempted synthesis of (33) first involved reaction of 3-acetylpyridine with 3-ethoxypropylmagnesium bromide to give 1-methyl-1-(3-pyridyl)-4-ethoxybutanol (39).



(39)

It was hoped that hydrolysis of the ether and alcohol functions with concentrated hydrobromic acid would give the dibromo compound which could cyclize with methylamine to the required alkylnicotine.

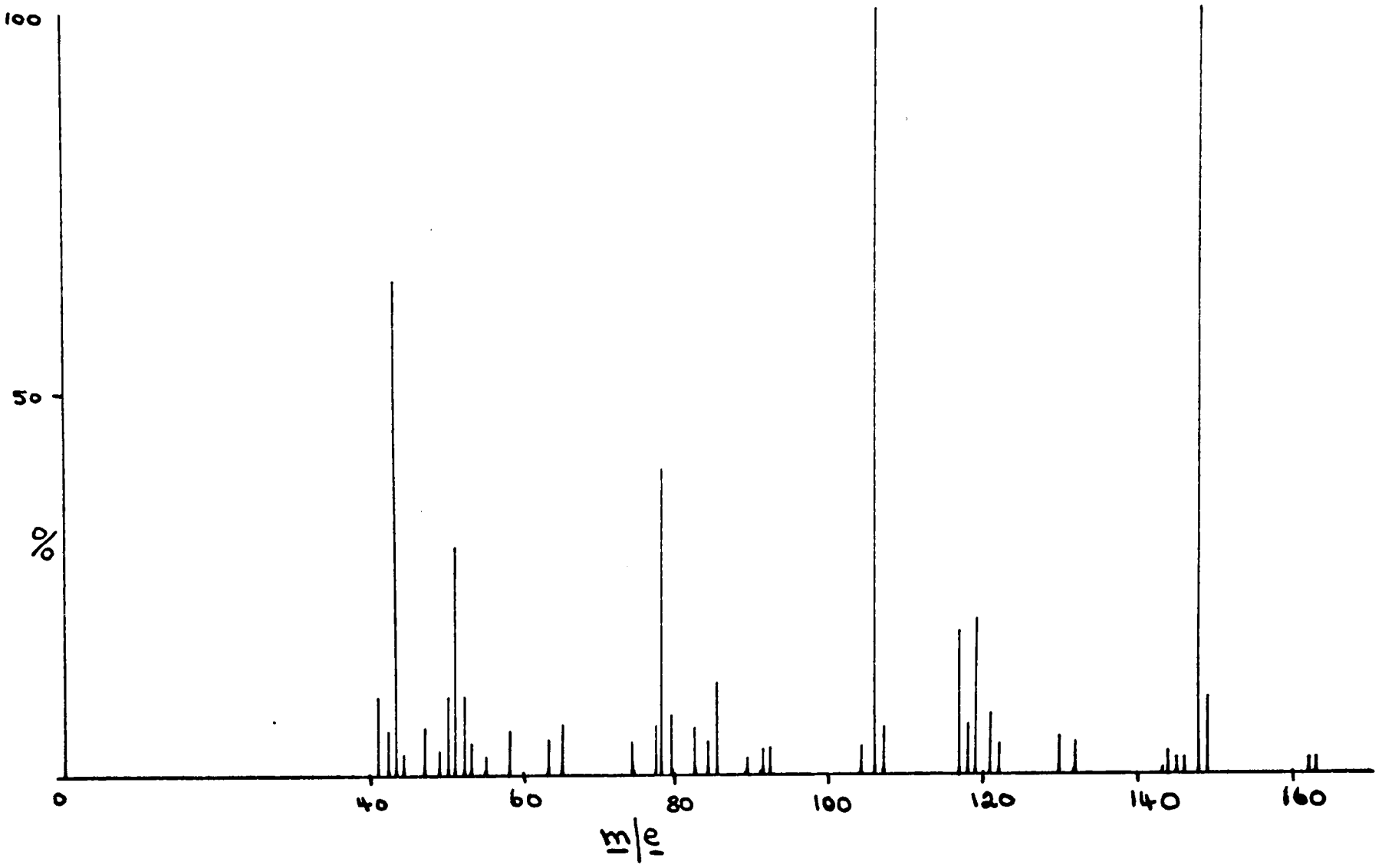


Fig.1 Mass Spectrum of 2-Methyl-2-(3-pyridyl)tetrahydrofuran (40)

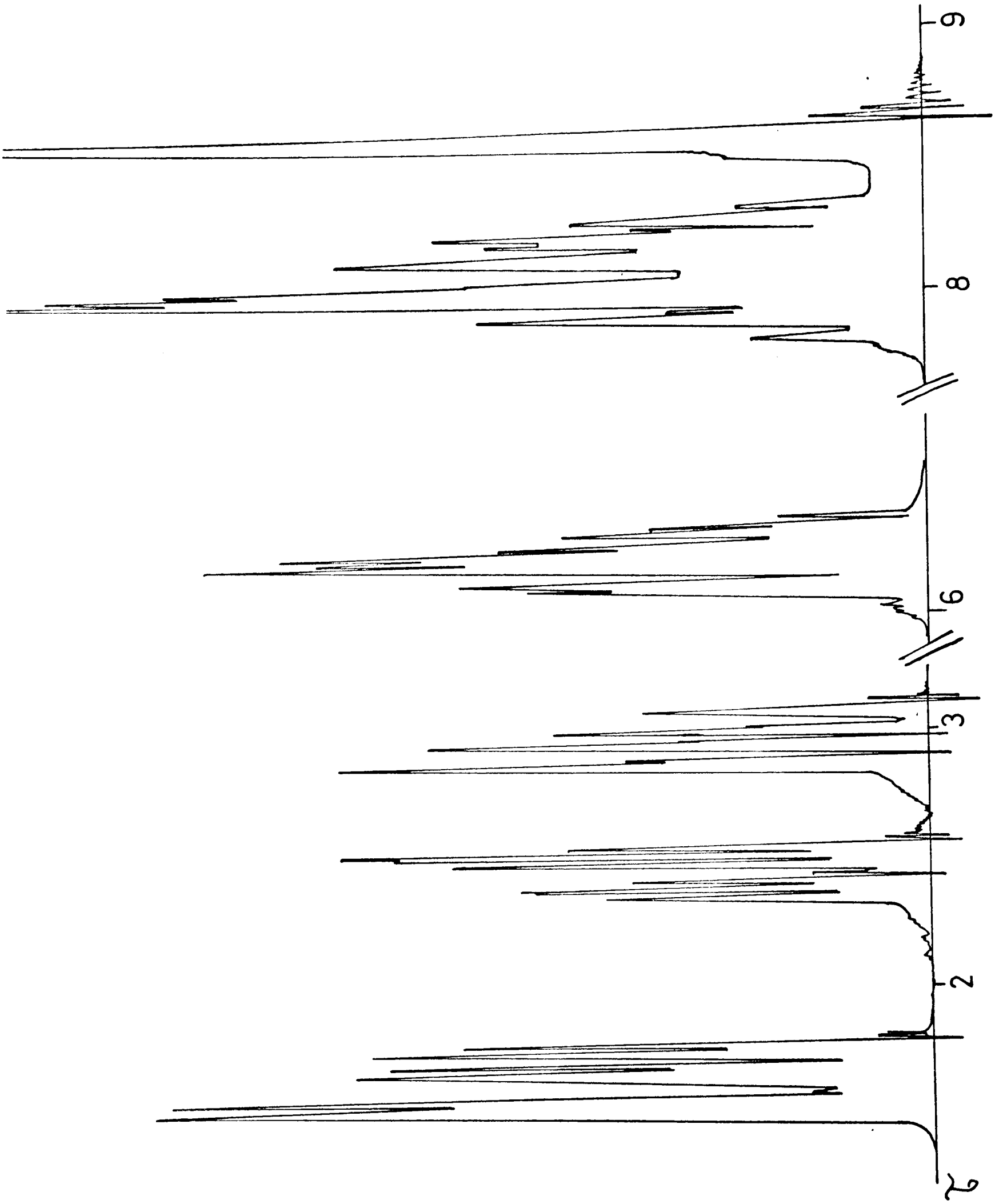
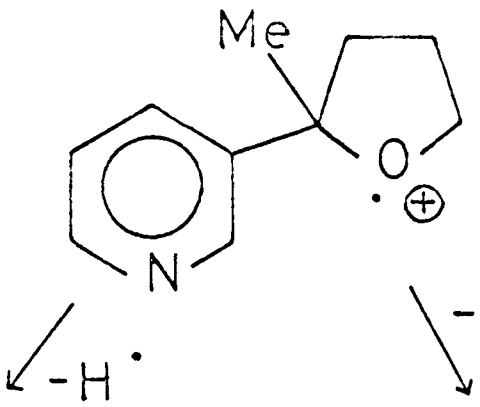
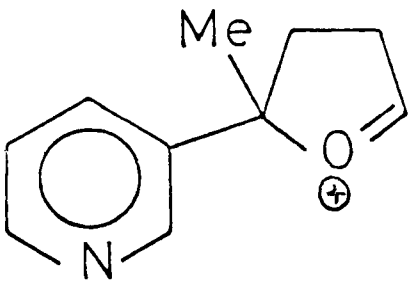


Fig. 2 N.m.r. Spectrum of 2-Methyl-2-(3-pyridyl)tetrahydrofuran (40)

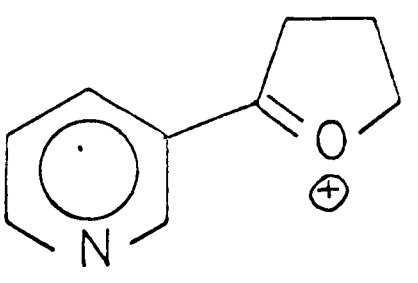
Scheme 4



m/e 163

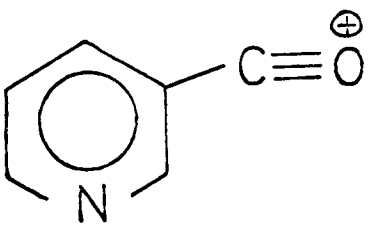


m/e 162



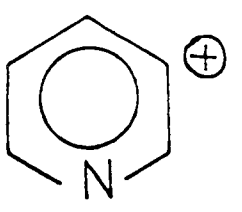
m/e 148

↓ $-C_3H_6$



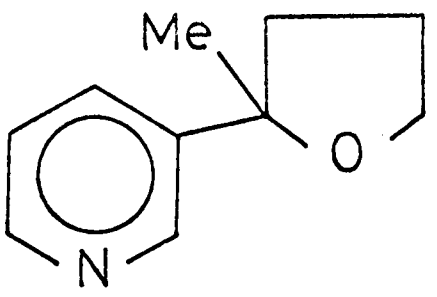
m/e 106

↓ -CO



m/e 78

However, the above procedure gave, along with a large quantity of tar, a compound whose structure was assigned as (40) on the basis of analytical and spectral evidence.

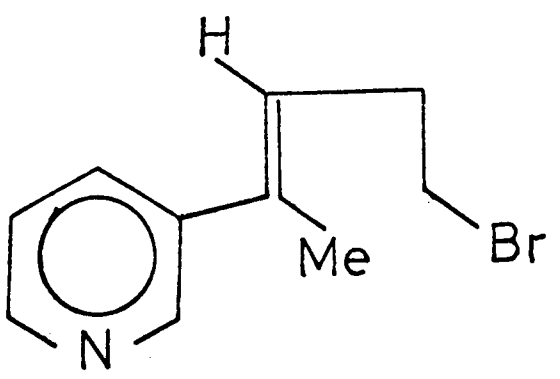


(40)

The mass spectrum (Fig. 1) shows a molecular ion at m/e 163 (1%). Peaks at m/e 162 (1%), m/e 148 (100%), m/e 106 (89%) and m/e 78 (40%) can be rationalised as shown in Scheme 4.

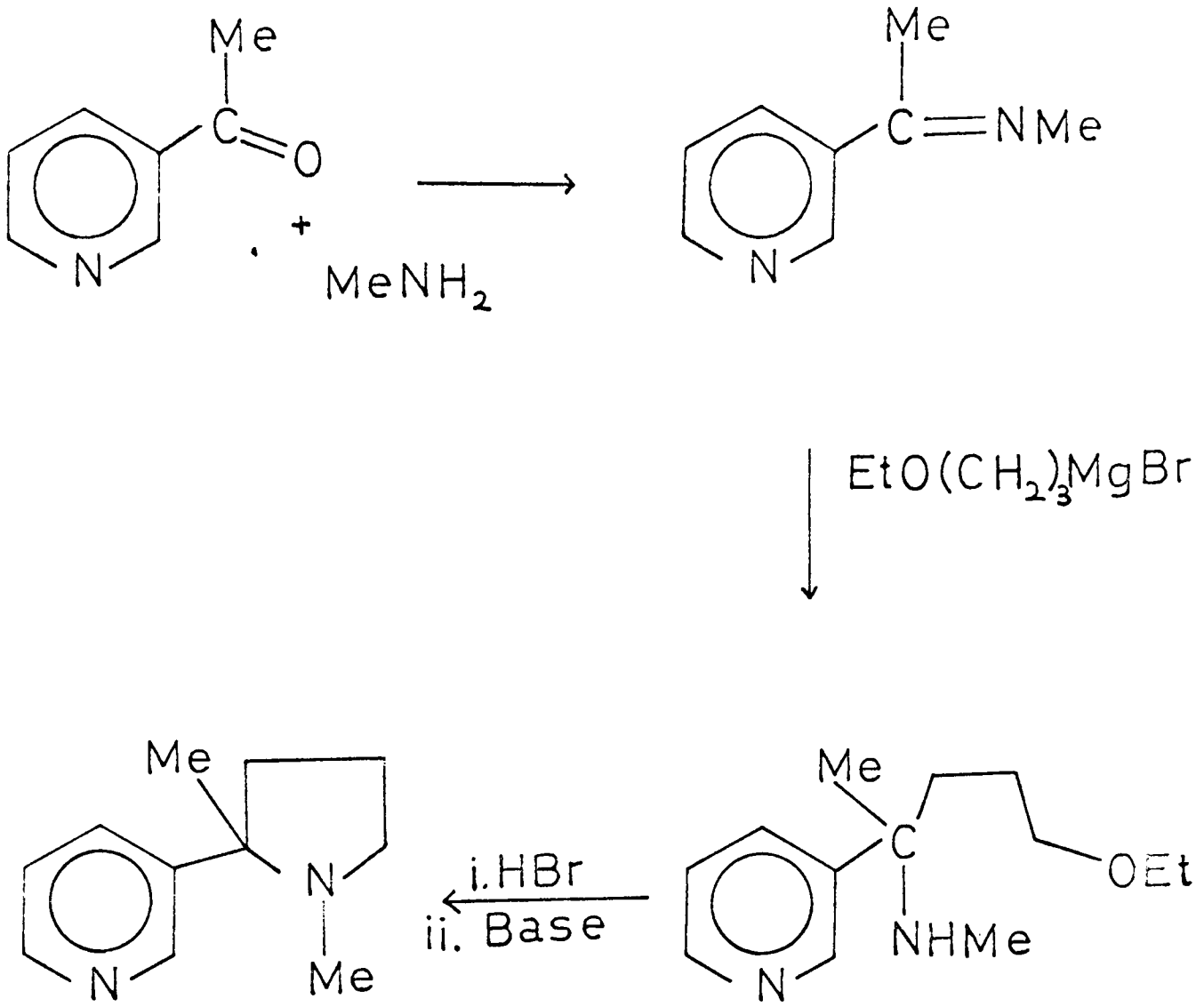
The n.m.r. spectrum (Fig. 2) shows the aromatic signals expected for a 3-pyridyl group. The ∝ protons of the tetrahydrofuran appear as a complex multiplet at τ 6.15 (tetrahydrofuran shows absorption at τ 6.25[156]). The aliphatic C-methyl group is at τ 8.56.

The n.m.r. spectrum of the reaction product before distillation contains, besides the signals for (40), a triplet further split at τ 4.3 and a singlet at τ 8.00; the aliphatic region is also more complex but the aromatic region unchanged. These signals can be rationalised by the presence of (41) in the reaction product. The vinyl hydrogen being at



(41)

Scheme 5


Me
C
O
N
MeNH2
Me
C
NMe
N
EtO(CH2)3MgBr
Me
N
Me
i. HBr
ii. Base
Me
C
OEt
NHMe
N

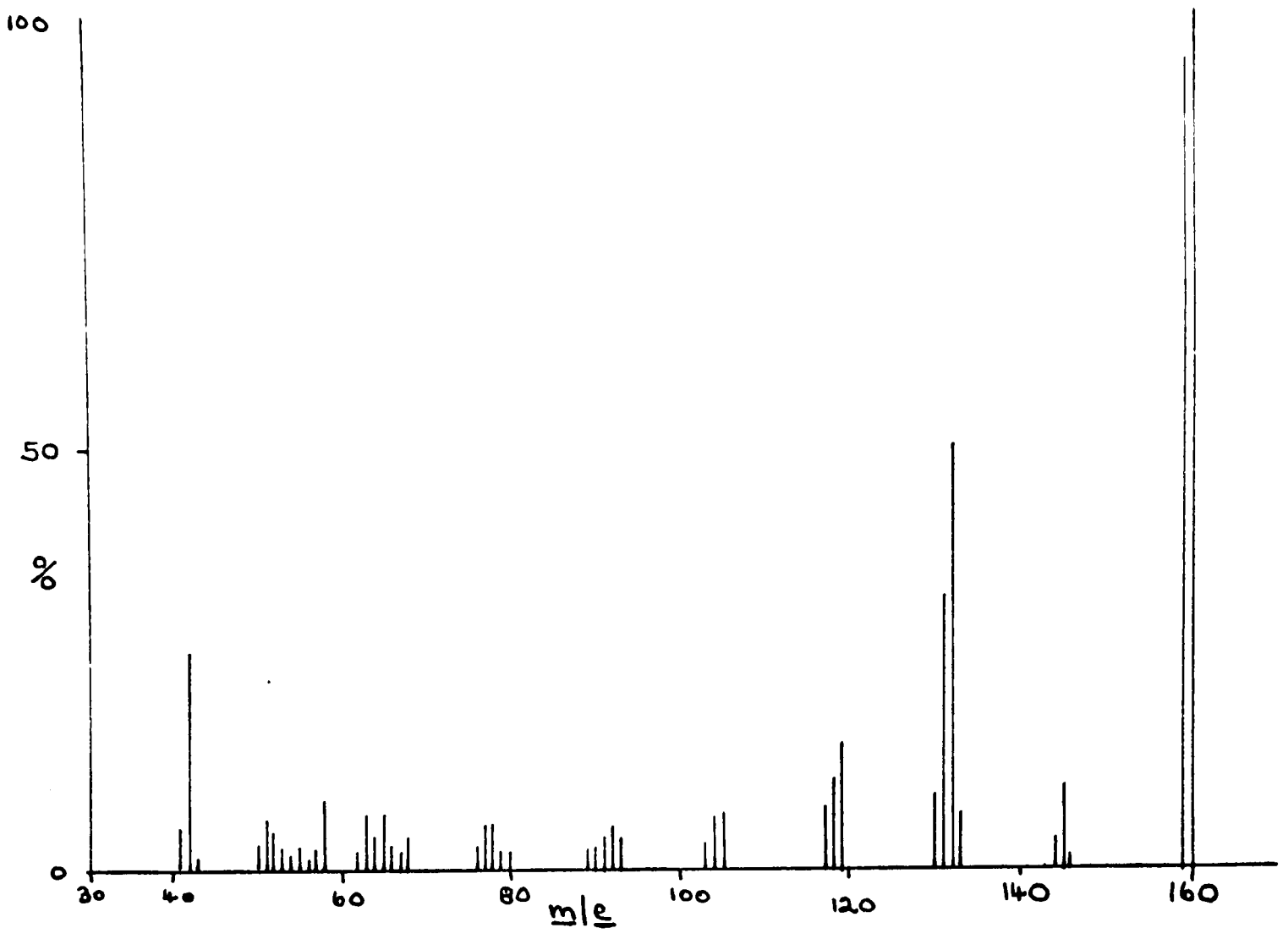


Fig. 3 Mass Spectrum of 4-Methylmyosmine (42)

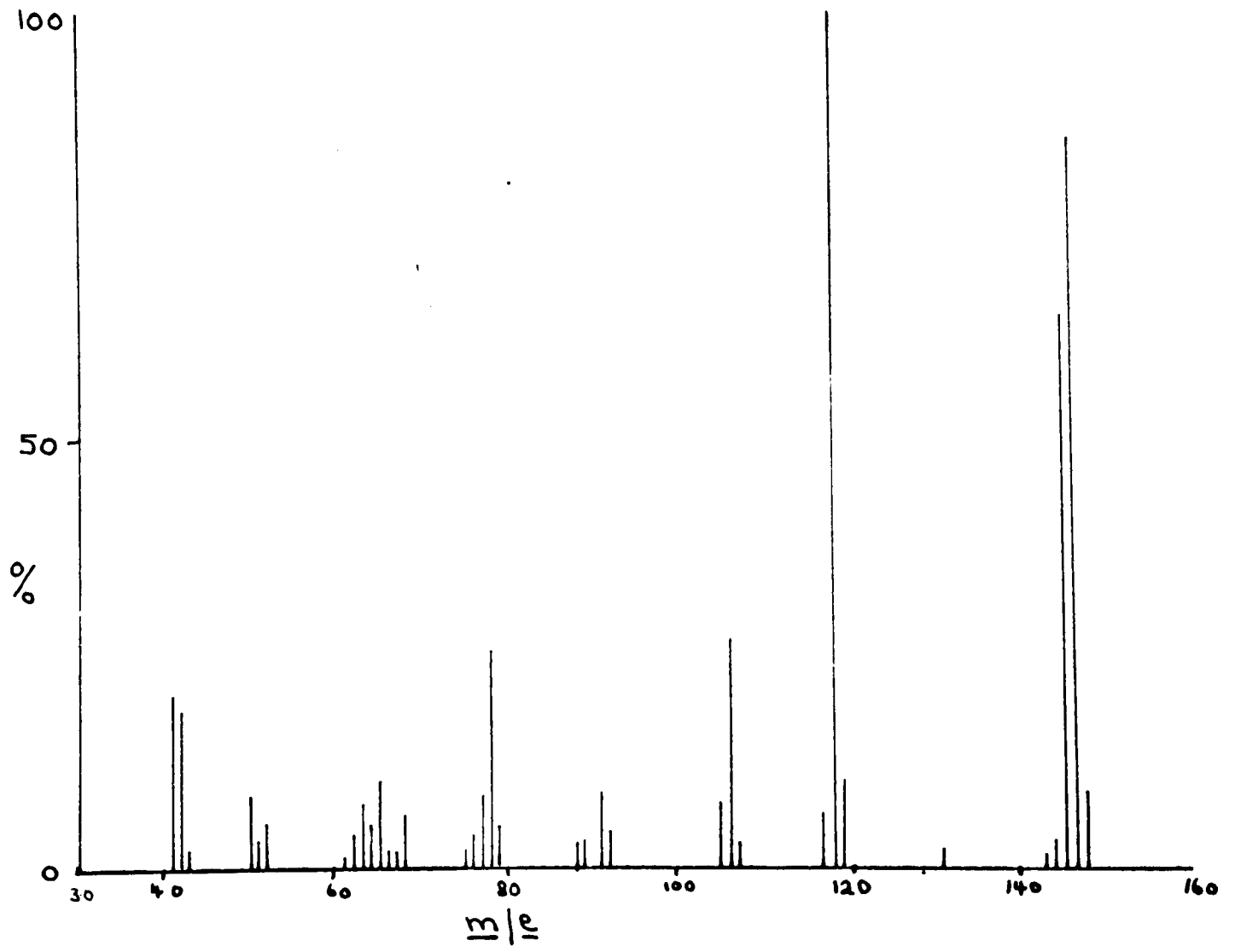


Fig. 4 Mass Spectrum of Myosmine (6)

τ 4.3 and the vinyl methyl group at τ 8.00. Analysis of the integral trace gives the ratio of (41) to (40) as 3:1. Upon distillation (41) almost certainly loses hydrogen bromide from the terminal carbons and polymerization results. Hence the low yield of (40).

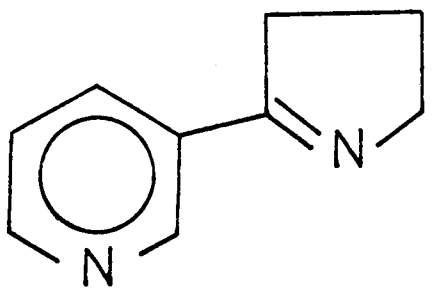
Thus the synthetic scheme, although not giving the required alkyl nicotine gave the oxygen analogue.

Preliminary screening results indicate interesting activity for this compound, further strengthening the belief that 2'-methylnicotine will be interesting biologically.

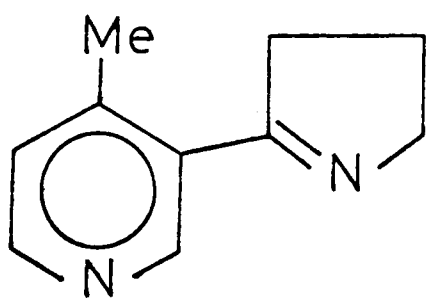
Another attempted synthesis is shown in Scheme 5.

Although 3-acetylpyridine readily condensed with methylamine to give the required imine , reaction with the Grignard reagent gave ethyl n-propyl ether as the only isolable product.

Myosmine (6), a naturally occuring cyclic imine surprisingly gave

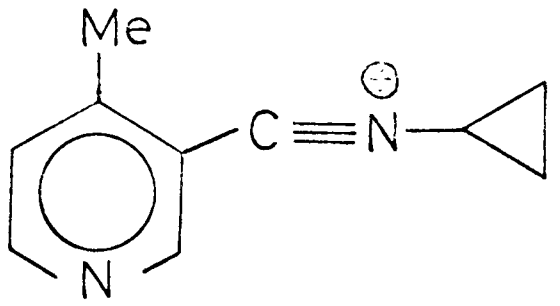


(6)



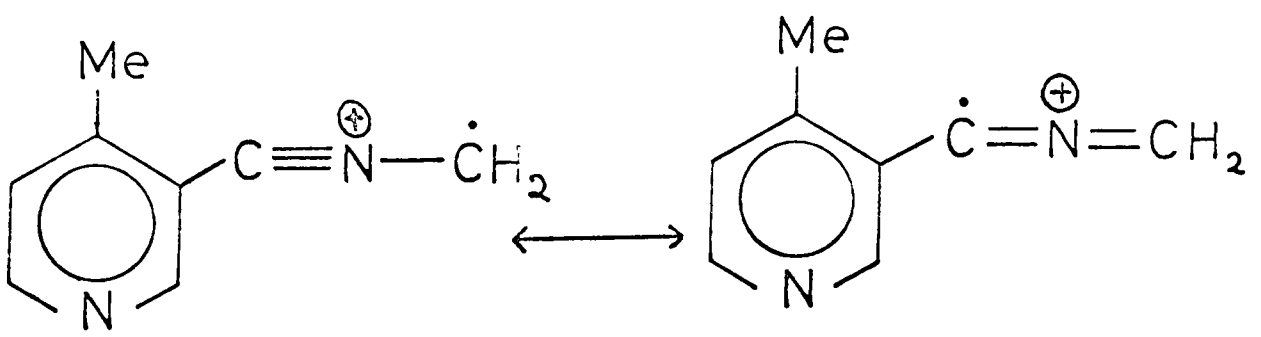
(42)

4-methylmyosmine when reacted with methyl magnesium iodide. The mass spectrum of the product (Fig. 3) gives the molecular weight as 160. Loss of H• readily occurs to give



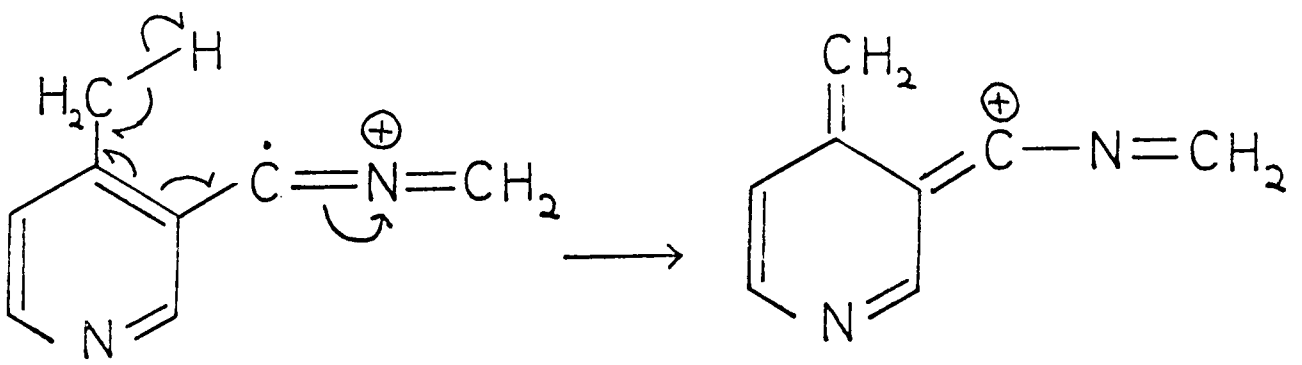
m/e 159 (90%)

and a peak at m/e 132 (48%) can be assigned to



The mass spectrum readily correlates with that for myosmine (Fig. 4) as interpreted by Djerassi.[95]

A peak at m/e 131 has no corresponding peak in the spectrum of myosmine and may result from the fragmentation below, although this is by no means a satisfactory explanation.



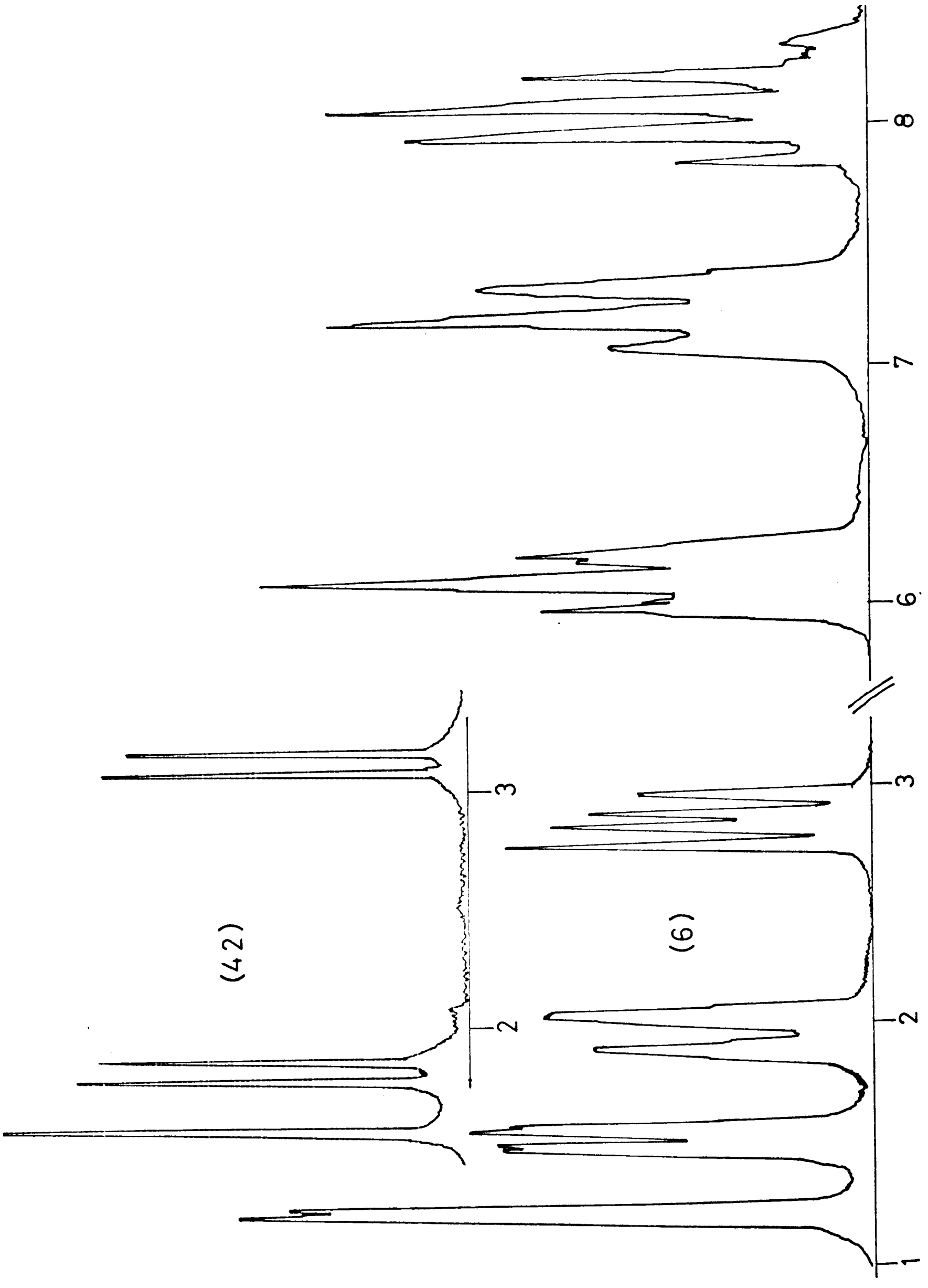


Fig. 5 N.m.r Spectra of Myosmine (6) and the aromatic region of 4-Methylmyosmine (42)

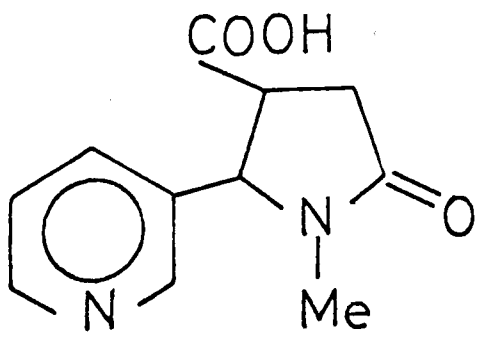
N.m.r. spectral comparison of (42) with myosmine (Fig. 5) shows the Δ' pyrrolenine proton resonances (τ 6-8) to be almost identical in shape and position. The aromatic region now shows only three resonances. The proton at C-5 having moved upfield by 0.15 ppm and the proton at C-6 by 0.16 ppm. These shifts and the observed coupling constants are in agreement with the substitution of a methyl group at C-4 in pyridine and nicotine.

	τ Values			
	2-H	3-H	5-H	6-H
Pyridine	1.50	2.94		
4-Methylpyridine[157]	1.66	3.02		
Nicotine			2.89	1.58
4-Methylnicotine[90]			2.94	1.62
Myosmine			2.79	1.46
4-Methylmyosmine			2.94	1.62

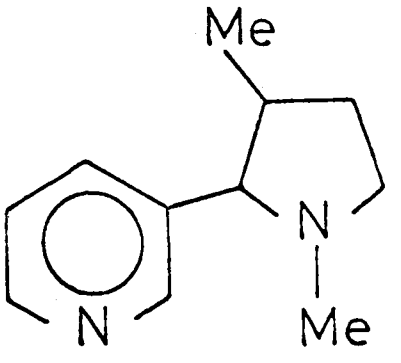
The aromatic methyl group is observed at τ 6.98.

Grignard addition to imines has been investigated[158,159,160] and the reaction found to proceed in a manner analogous to Grignard addition to carbonyl compounds. Thus it is surprising that the imine function in myosmine is inert to Grignard reagents. Undoubtedly the imino double bond is stabilised by conjugation with the pyridine ring; attack at C-4 maintaining this stabilization. Formation of a bulky magnesium complex at the pyridine nitrogen may prevent attack at C-2 and C-6.

Castagnoli[140] reacted N-3-pyridylidenemethylamine and succinic anhydride to give (43) which he then reduced by a number of steps to trans - (35). Attempts to react imine (44) in a similar manner gave only tar. It seems probable that the required product (45) would be too crowded at C-2' and was thus not obtained.



(43)



(35)

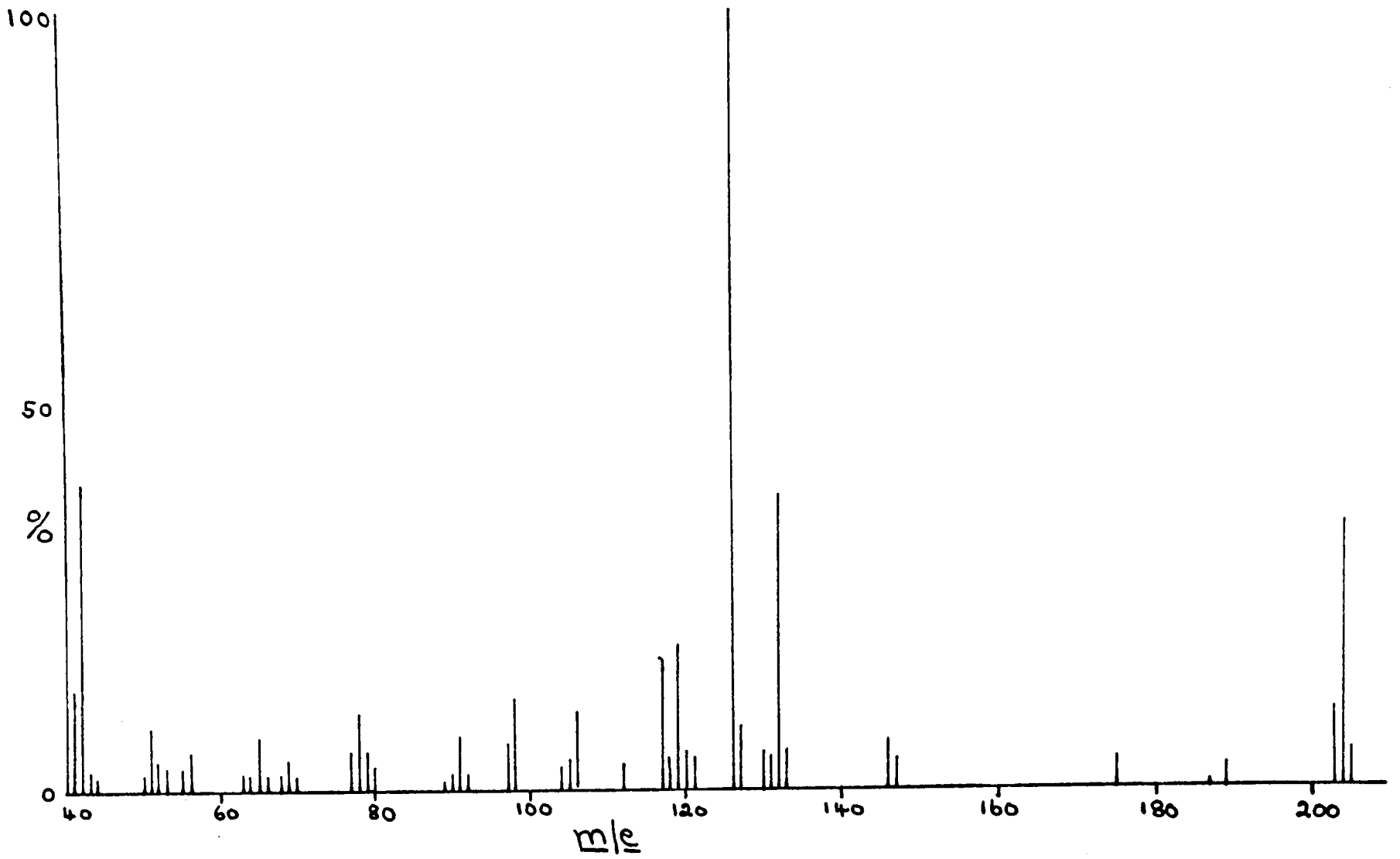


Fig. 6 Mass Spectrum of 3',3'-Dimethylcotinine (46)

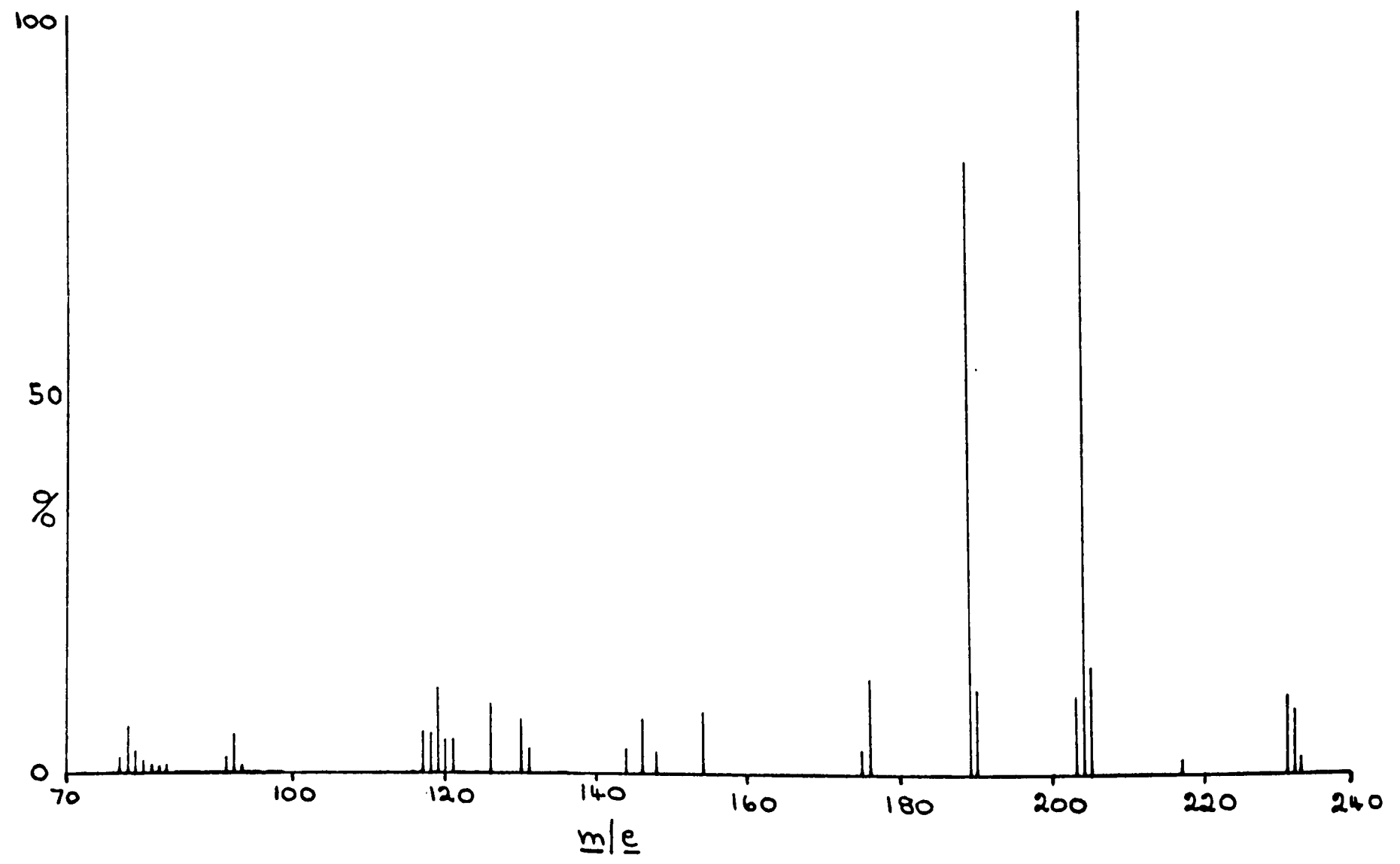


Fig. 7 Mass Spectrum of 3',3'-Diethylcotinine (47)

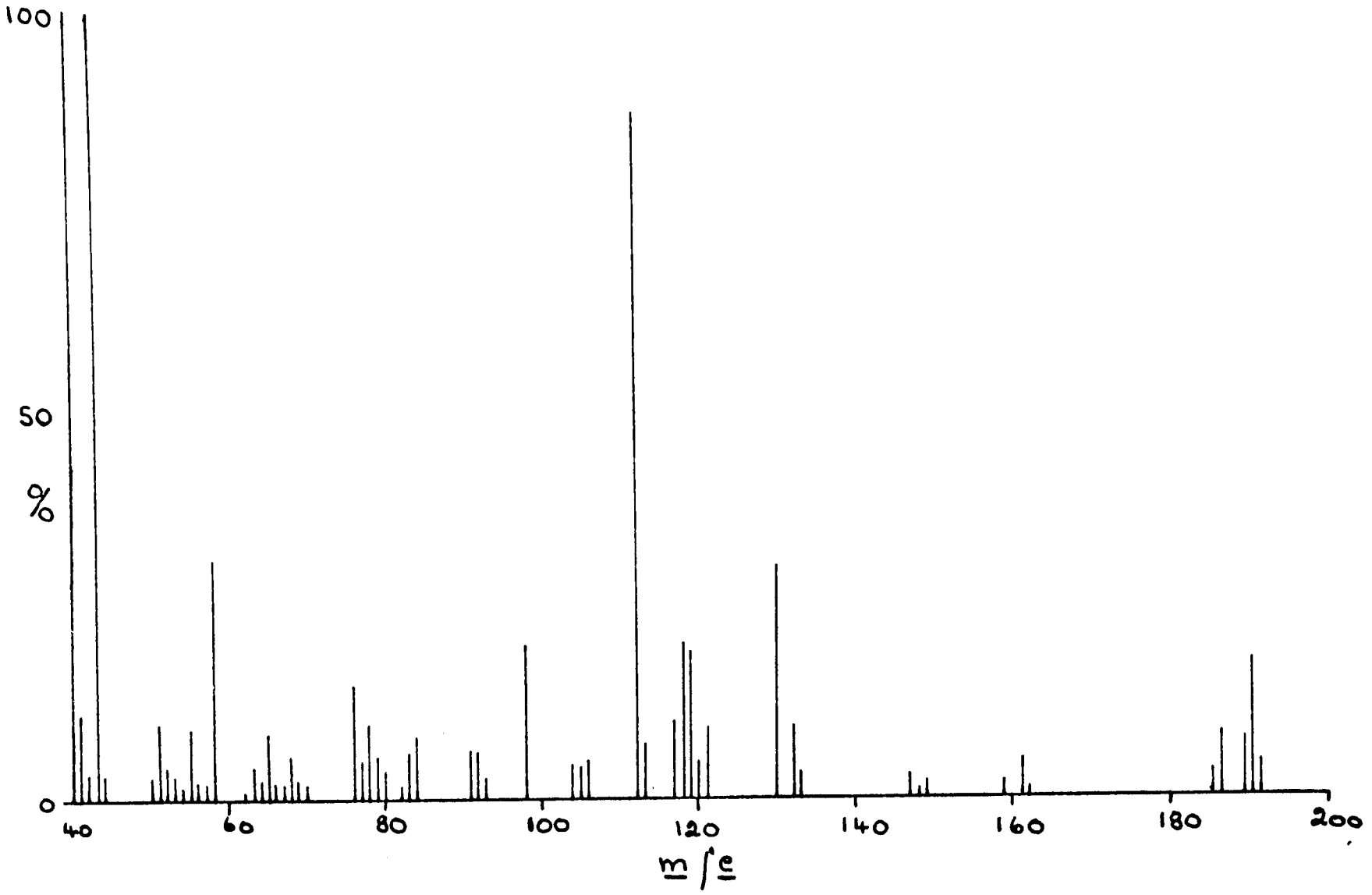


Fig. 8 Mass Spectrum of 3'-Monomethylcotinine (48)

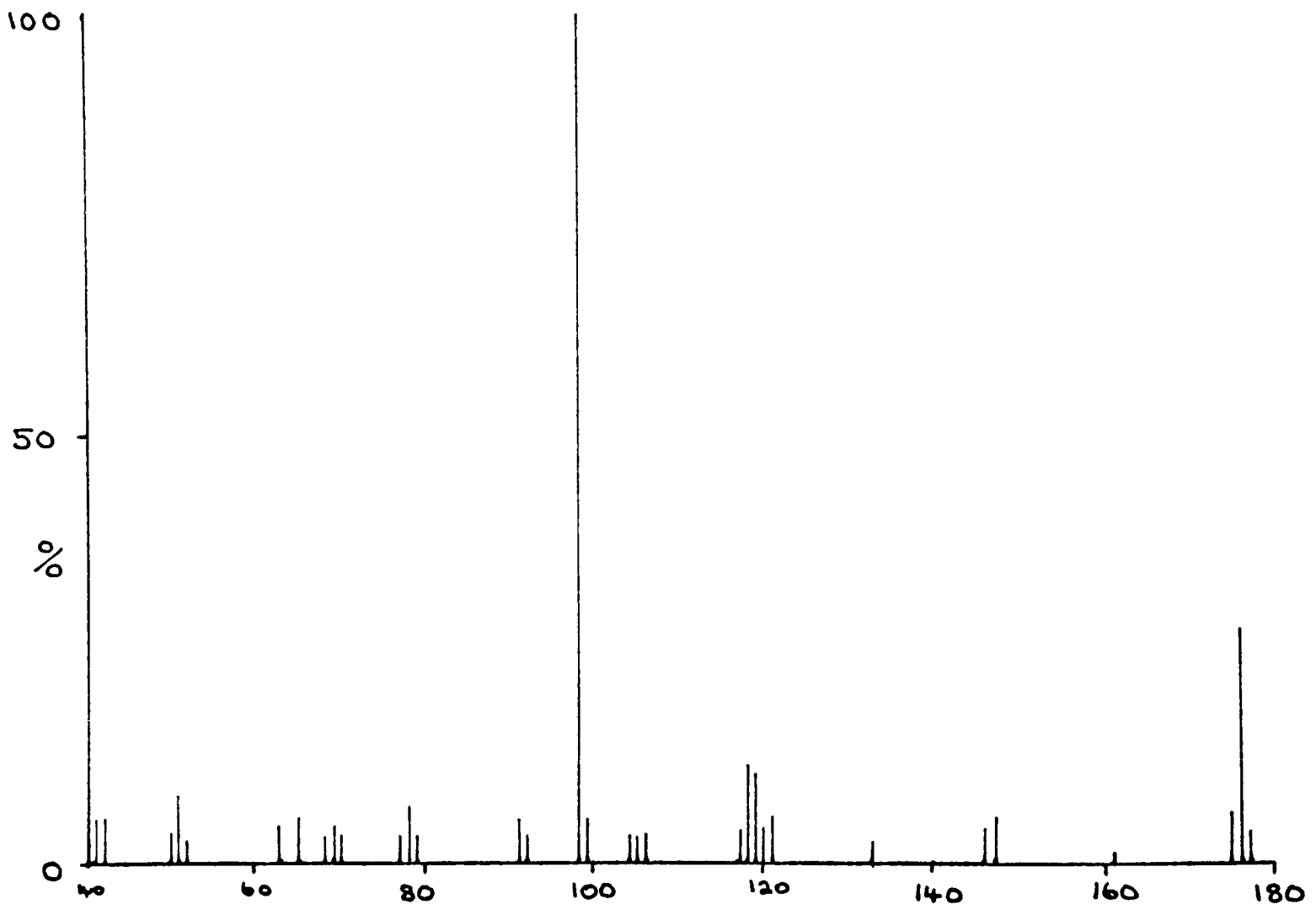
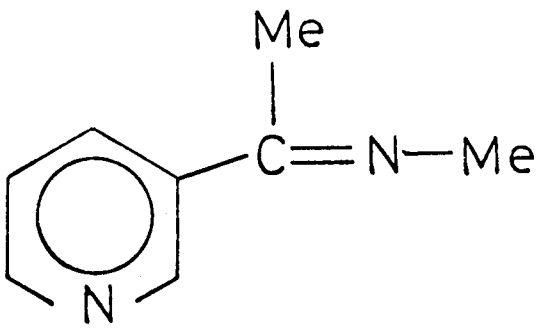
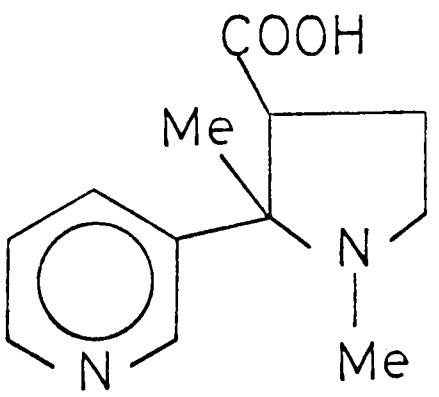


Fig. 9 Mass Spectrum of Cotinine (8)



(44)



(45)

The synthesis of (33) has not been further investigated.

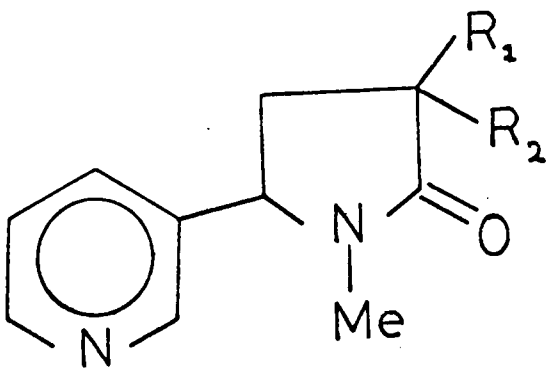
Preparation of 4'-Alkyl- and 4',4'-Dialkyl nicotines

Replacement of the 4' hydrogen atoms of nicotine was accomplished without difficulty.

Cotinine contains two activated hydrogen atoms adjacent to the amidic carbonyl group. These were successively removed and replaced by alkyl groups on treatment with a three molar excess of sodamide in ammonia followed by addition of alkyl halide. A molar equivalent of cotinine, sodamide and methyl iodide gave the mono-alkyl derivative.

The structures readily follow from analytical and spectral data.

The mass spectra for (46) and (48) (Figs 6 and 8) correlate well with cotinine (Fig. 9) as reported by Djerassi.[95]



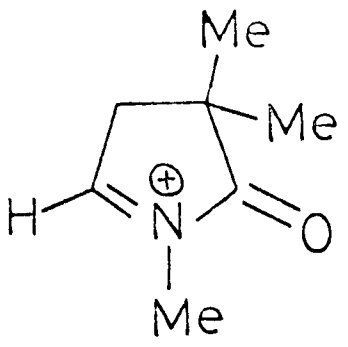
(46) $R_1 = R_2 = Me$

(47) $R_1 = R_2 = Et$

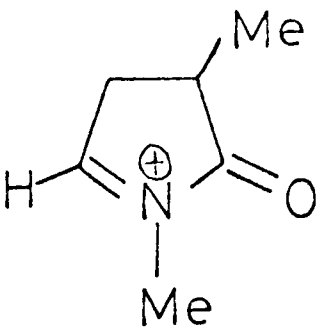
(48) $R_1 = H$; $R_2 = Me$

(8) $R_1 = R_2 = H$

Thus (46) shows a molecular ion at m/e 204 (34%). The base peak at m/e 126 can be assigned to fragment (a).



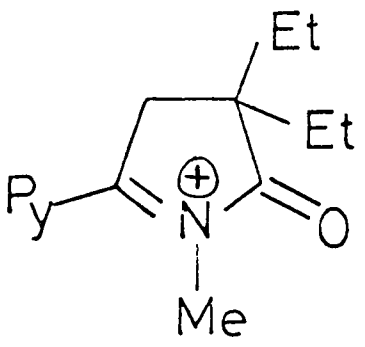
(a)



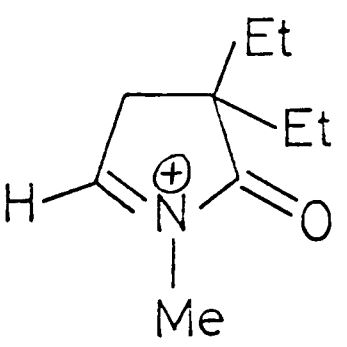
(b)

Likewise a peak at m/e 112 in the mass spectrum of (48) results from fragment (b).

3',3'-Diethylcotinine (47) shows an entirely different fragmentation pattern (Fig. 7). The molecular ion is observed at m/e 232; peaks at m/e 231 and a small peak at m/e 154 (8%) correspond to fragments (c) and (d) respectively.



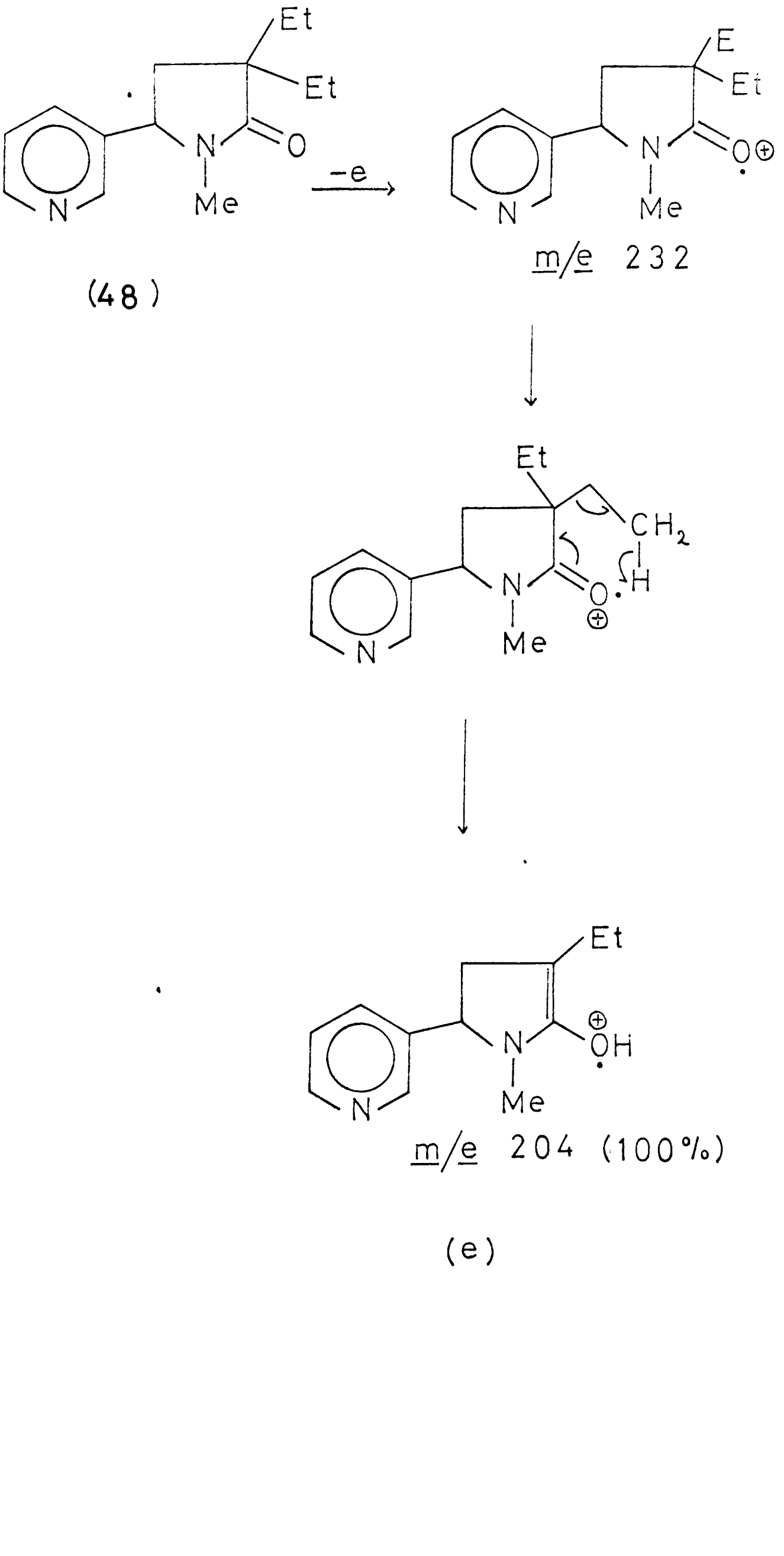
(c)



(d)

However it seems probable from the observed spectrum that the main fragmentation pathway is as in Scheme 6.

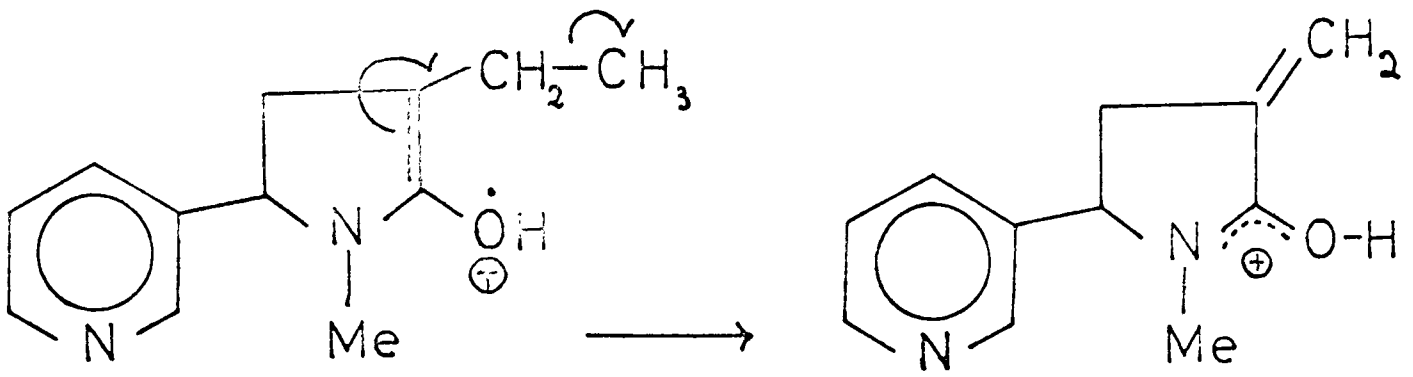
Scheme 6



(48)

(e)

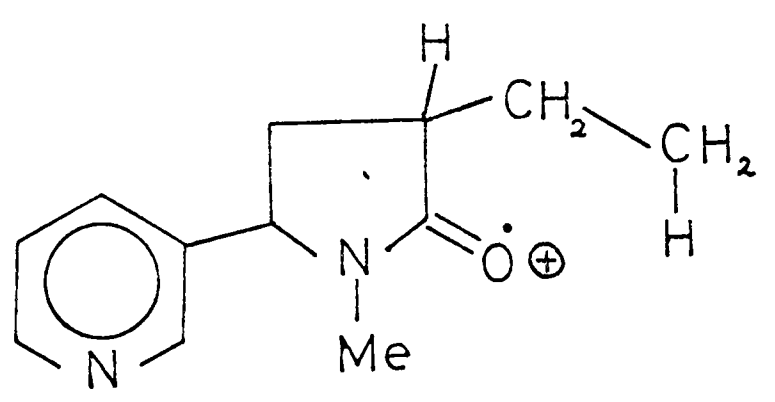
Thus fragment (e) arises by a McLafferty rearrangement of the molecular ion. Fragment (e) appears to break down in two ways, the most favourable being loss of •Me.



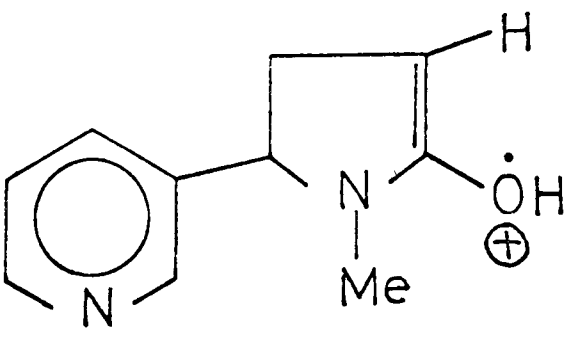
(e)

m/e 189 (80%)

However it seems (e) also rearranges to give :



which undergoes a second McLafferty rearrangement to give :



m/e 176 (13%)

Further fragmentation cannot be traced.

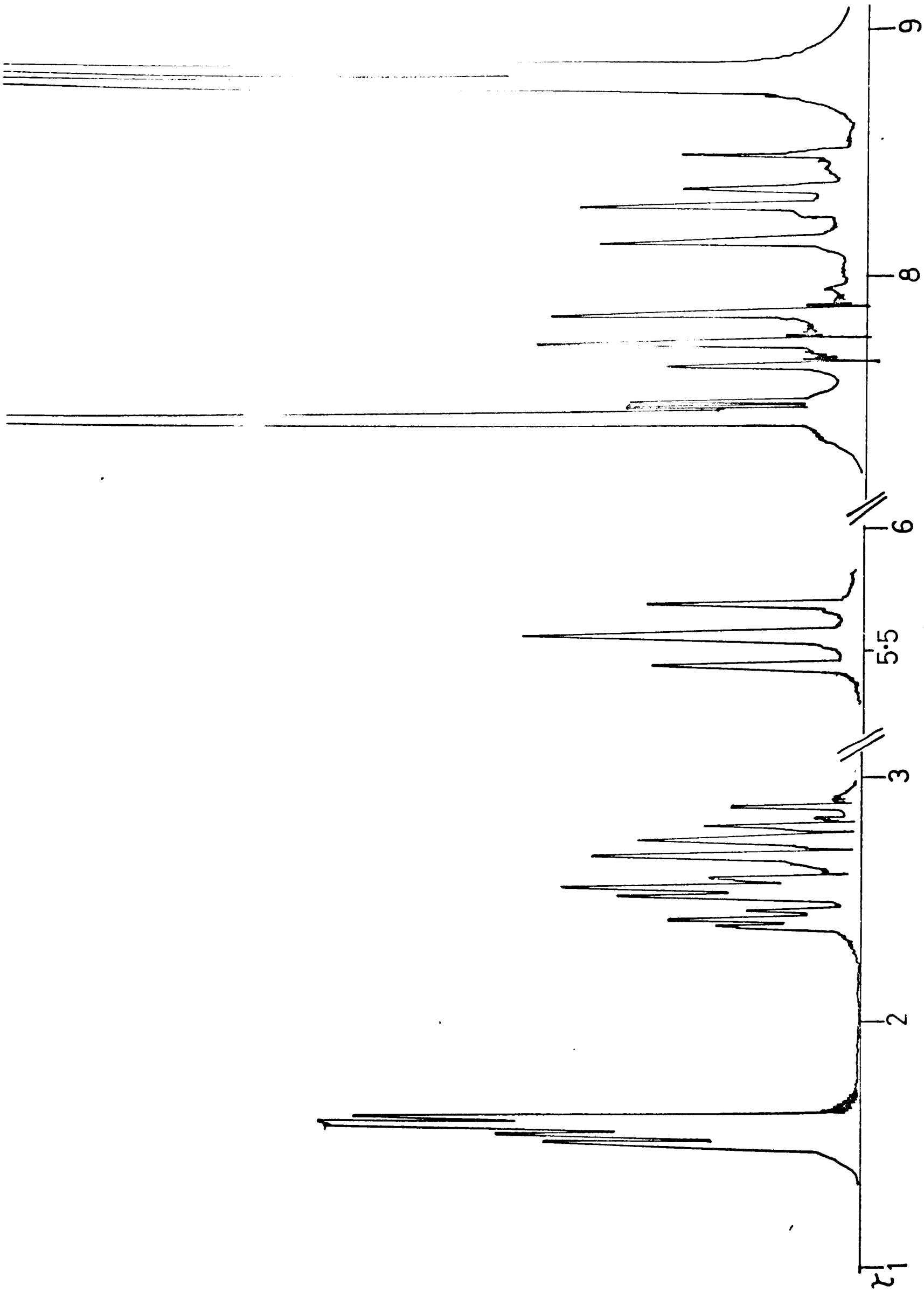


Fig. 10 N.m.r. Spectrum of 3',3'-Dimethylcotinine (46)

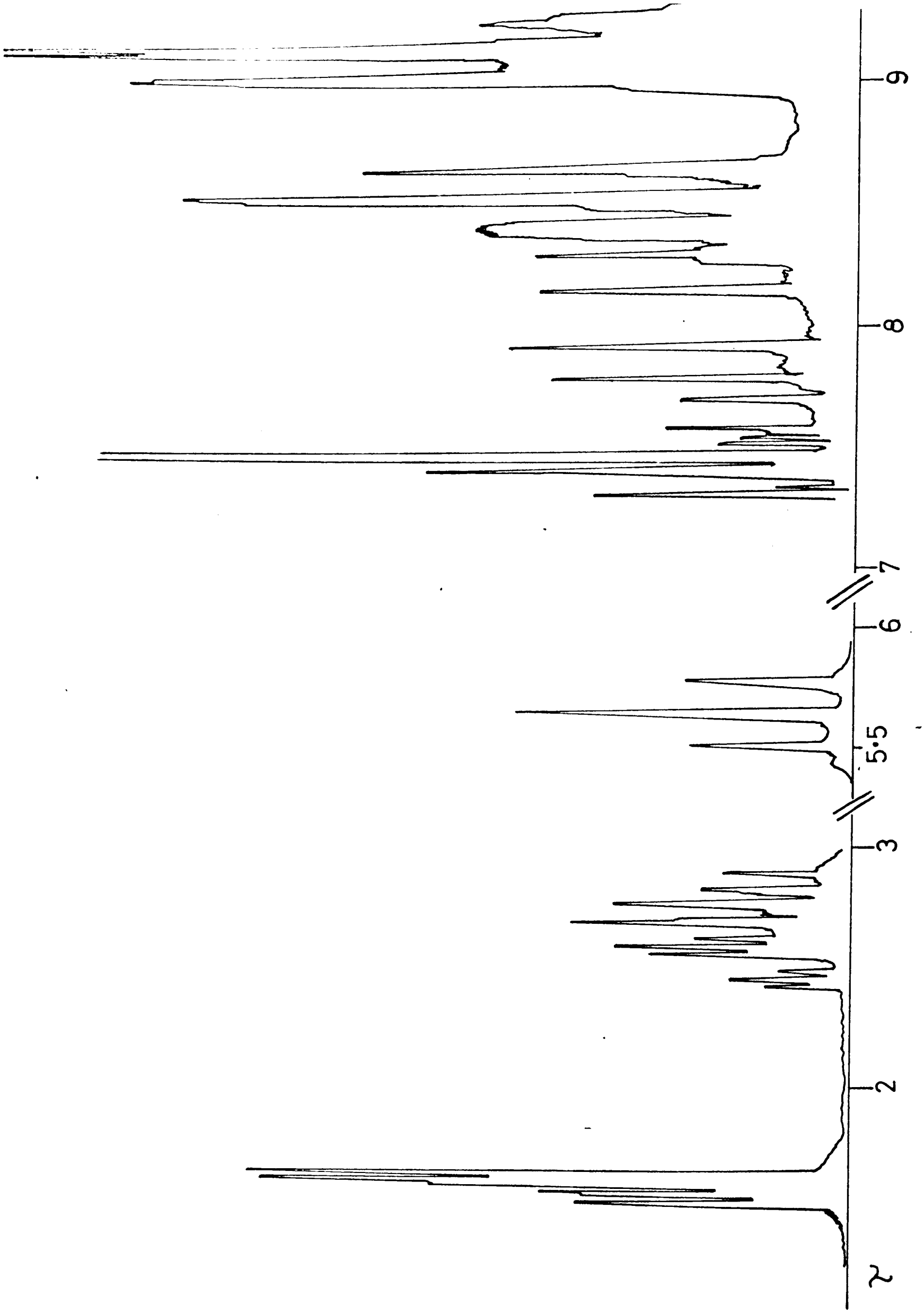


Fig. 11 N.m.r. Spectrum of 3',3'-Diethylcotinine (47)

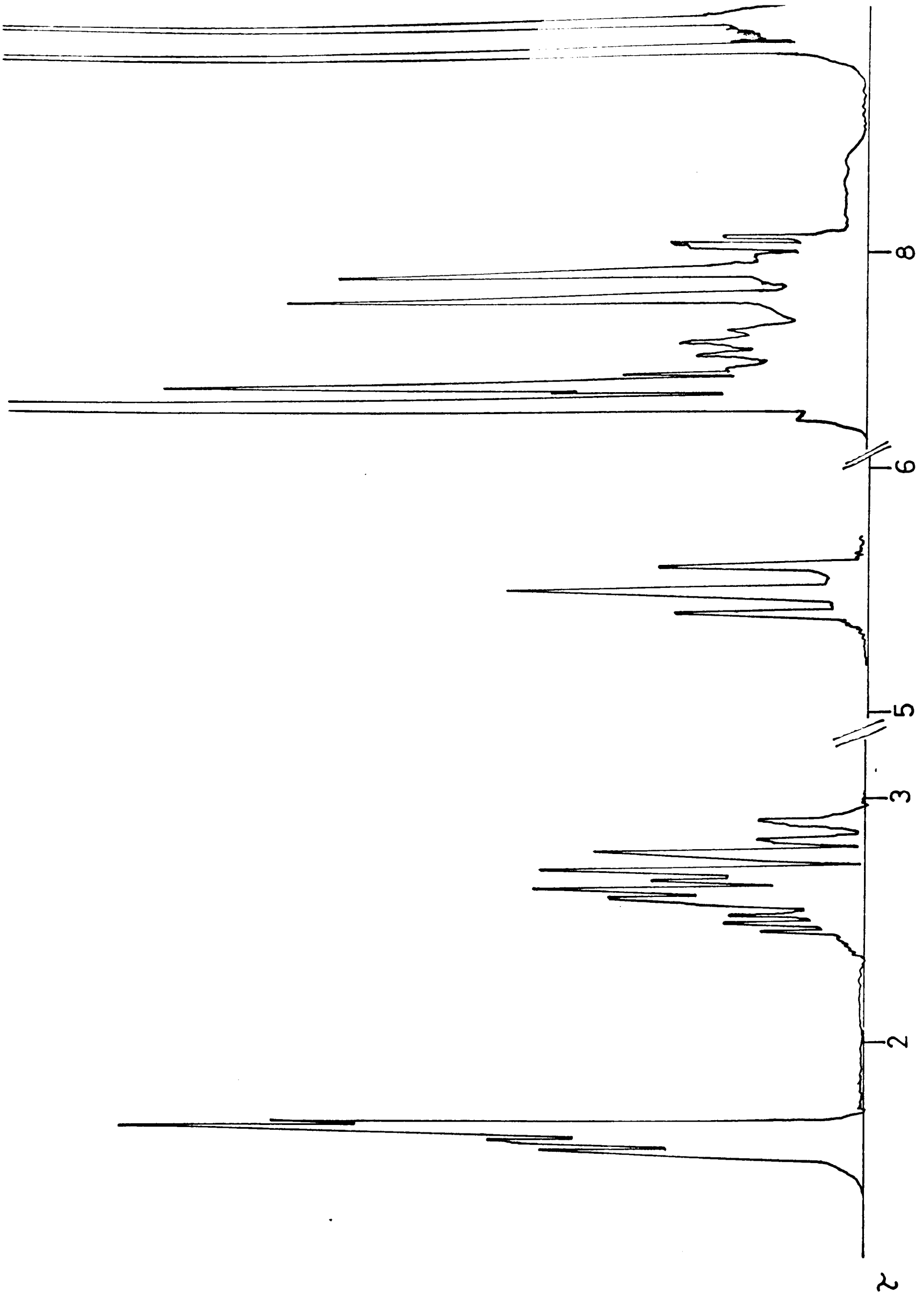


Fig. 12 N.m.r. Spectrum of 3′-Monomethylcotinine (48)

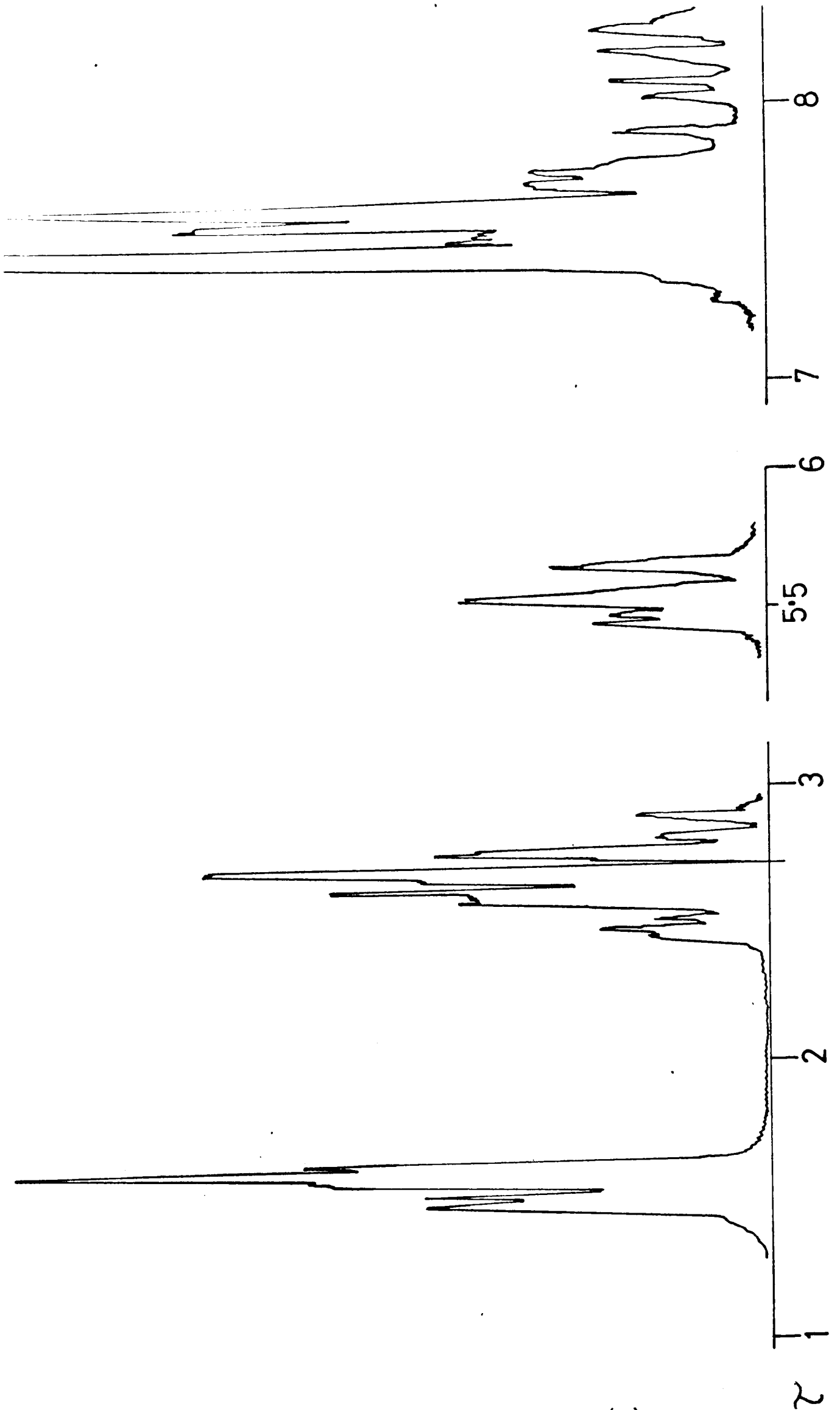


Fig. 13 N.m.r. Spectrum of Cotinine (8)

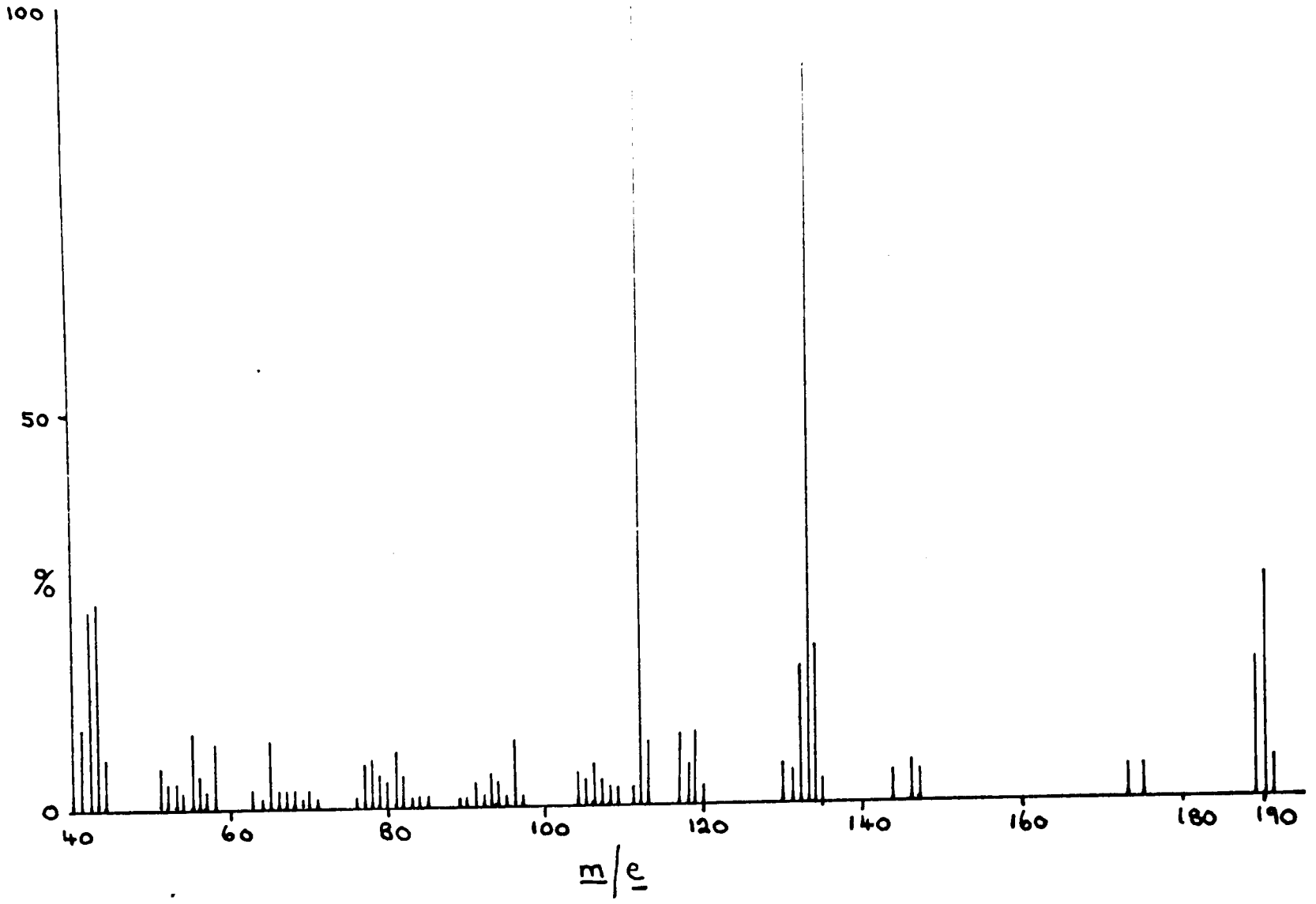


Fig. 14 Mass Spectrum of 4′,4′-Dimethylnicotine (49)

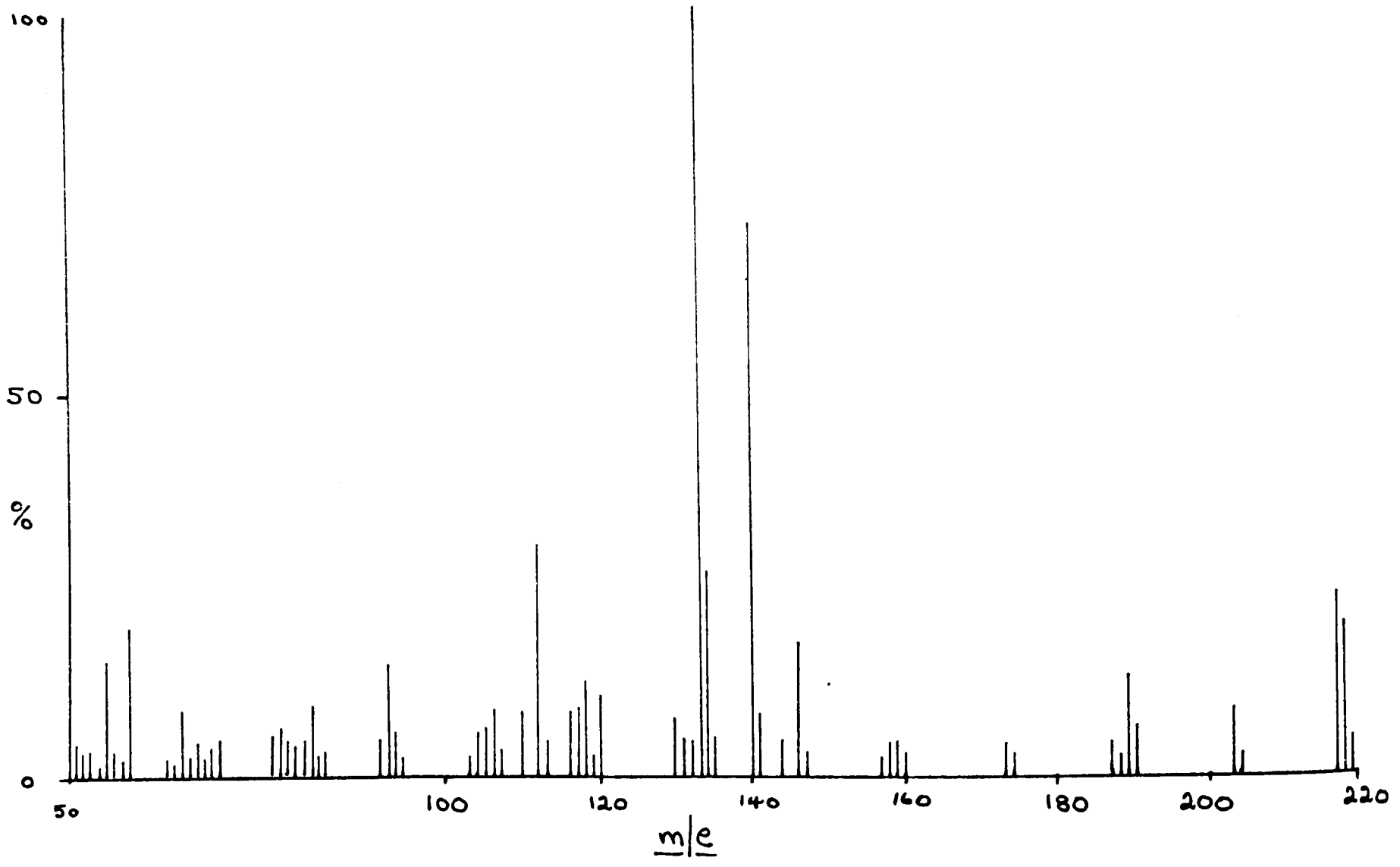


Fig. 15 Mass Spectrum of 4′,4′-Diethylnicotine (50)

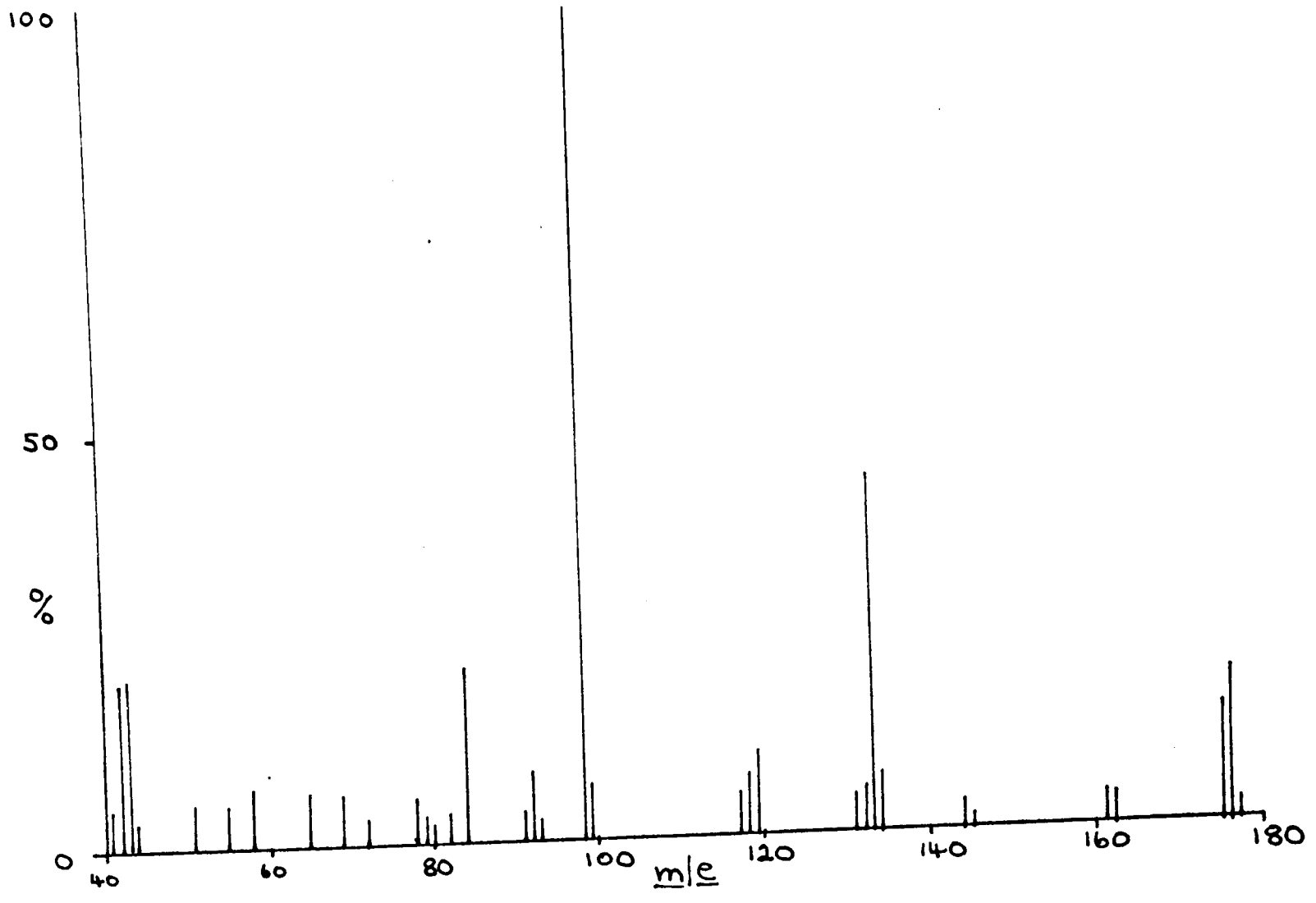


Fig. 16 Mass Spectrum of 4'-Monomethylnicotine (51)

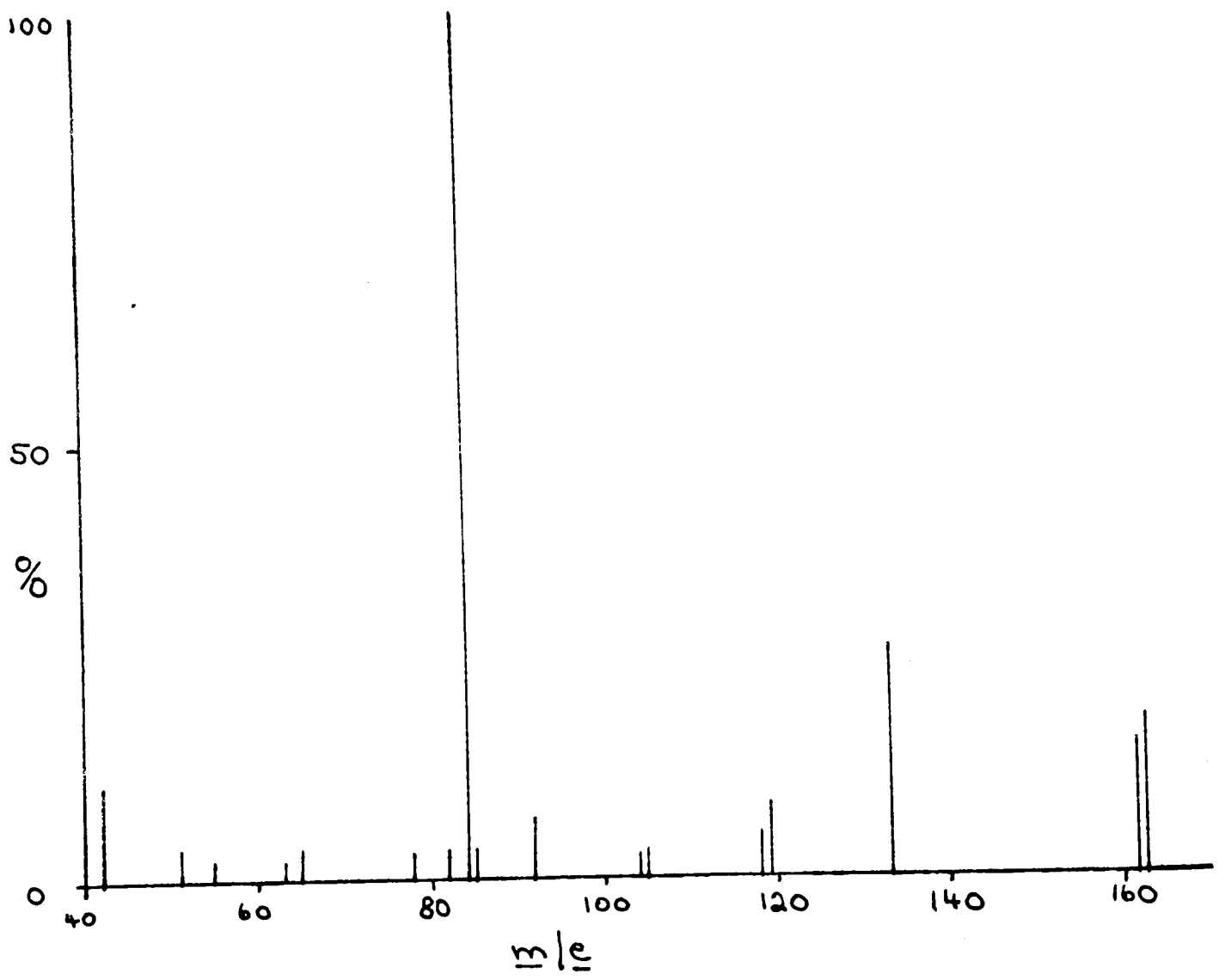
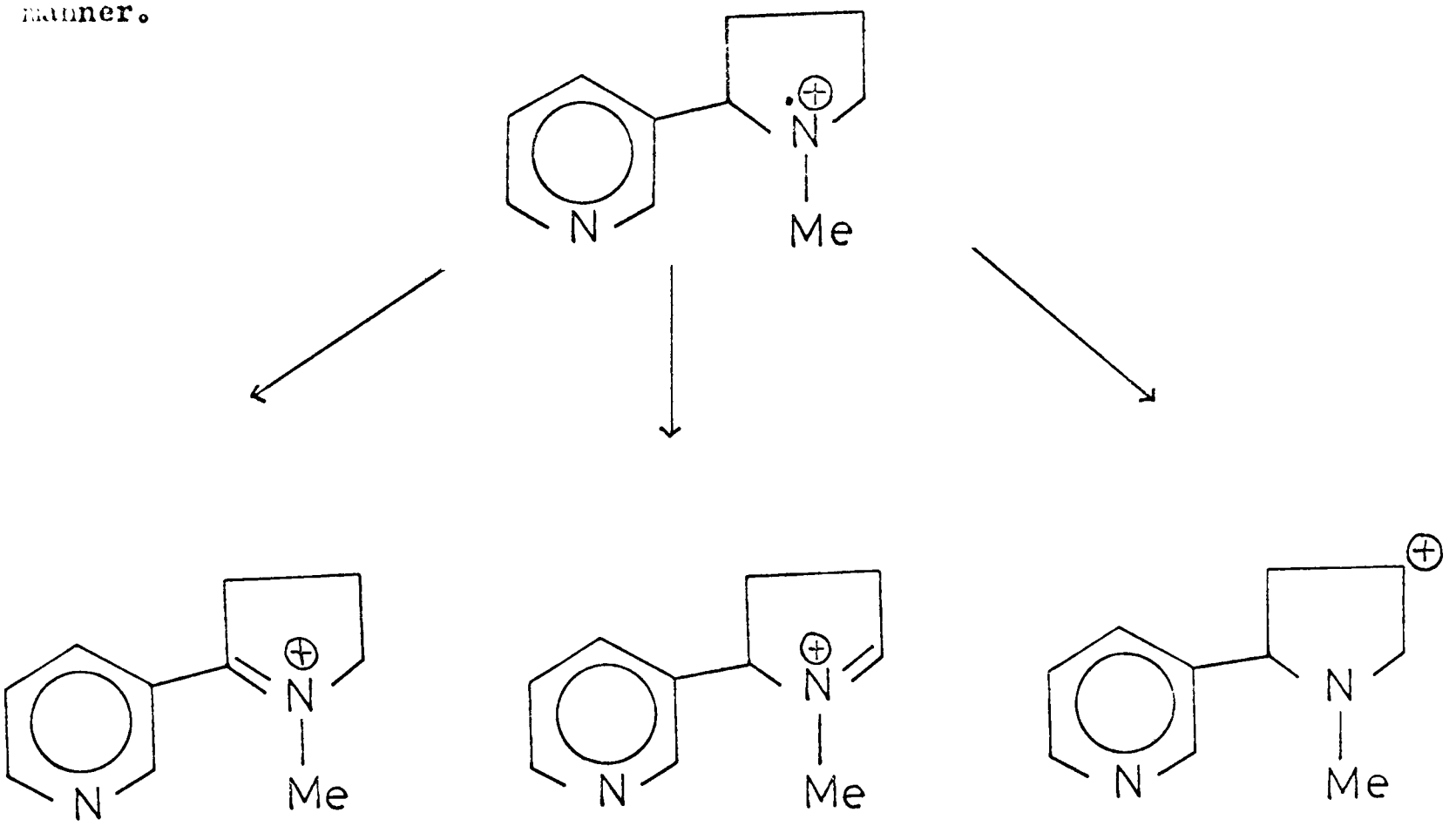


Fig. 17 Mass Spectrum of Nicotine (1)

The mass spectra (Figs 14, 15 and 16) all correlate with that for nicotine (Fig. 17) as reported and analysed by Djerassi.[95] By preparing and recording the mass spectra of 4',4'-dideuteronicotine and 5',5'-dideuteronicotine Djerassi believes nicotine to fragment in the following manner.

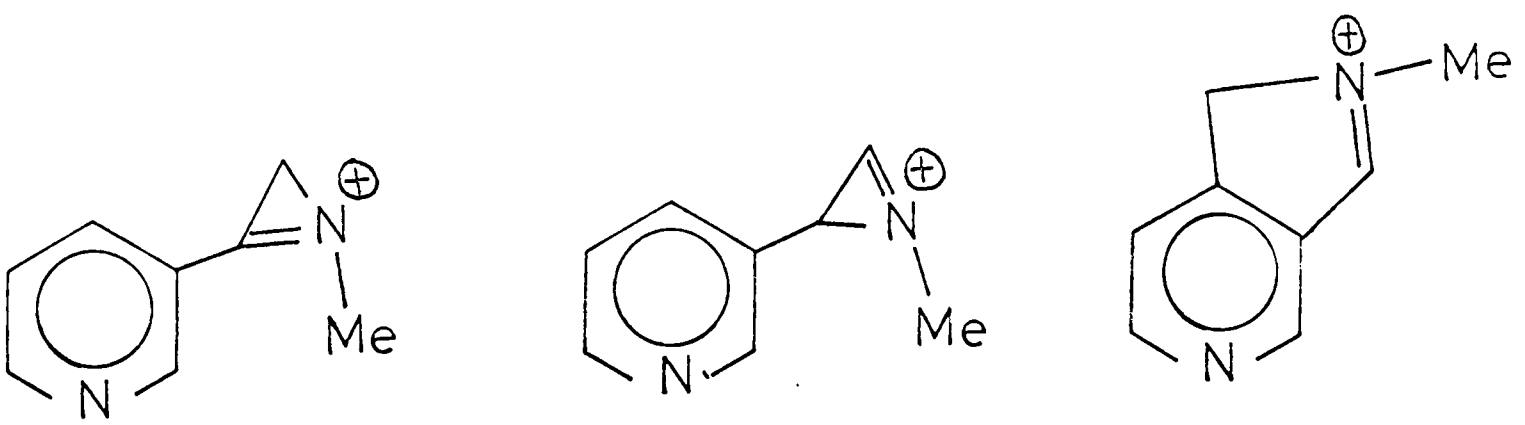


(f)

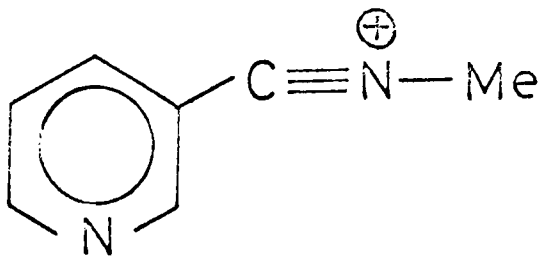
40% 15% 10%

The percentages given record the relative probability of each loss, the remainder being due to hydrogen loss at C-3', C-4 and C-2.

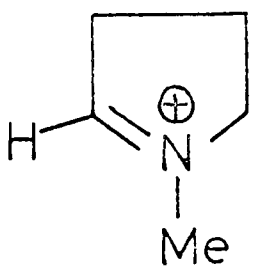
The peak at m/e 133 Djerassi assigns to the three fragments below.



The peak at m/e 119 is believed to be :

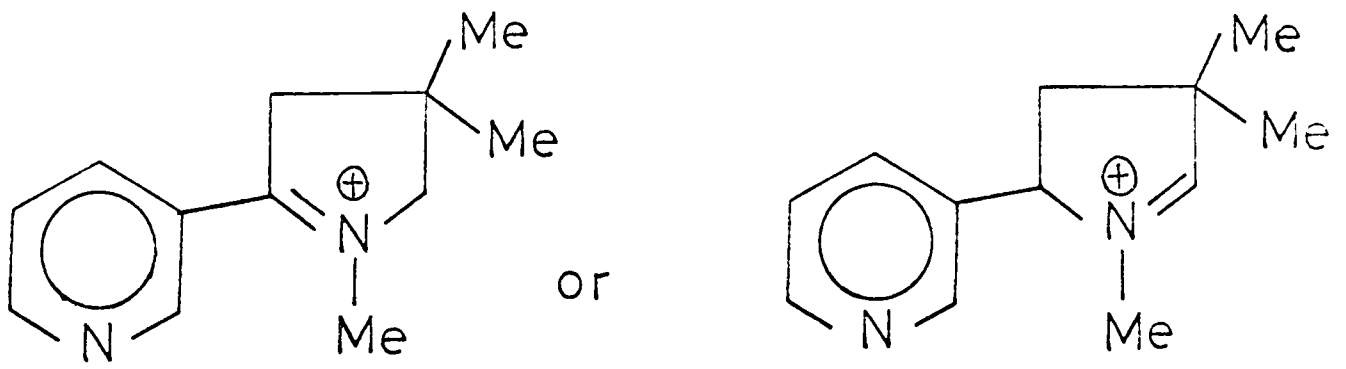


and the base peak at m/e 84 has been ascribed to :

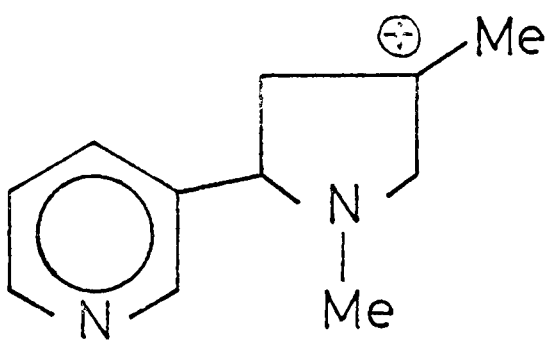


It is now believed that considerable scrambling of deuterium and ^{13}C labels may occur in the mass spectrometer prior to fragmentation thus rendering the precise conclusions by Djerassi suspect. The total randomization of all seven carbon atoms and all eight hydrogen atoms prior to the fragmentation of toluence being a well studied example.[220]

Compound (49) (Fig. 14) fragments by initial loss of •H giving a fragment of type:-



No loss of 15 mass units from the molecular ion is observed, showing that fragment (g) is not formed,

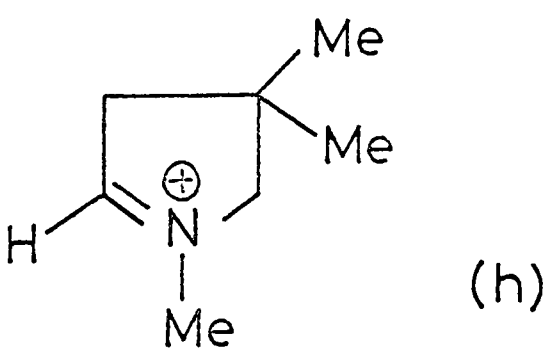


(g)

(formation of (g) would be expected to be a more favourable process than the formation of (f). Thus the existence of (f) is suspect.

A peak at m/e 133 is undoubtedly identical to that observed in nicotine and interpreted by Djerassi[95] as loss of C-3' and C-4'. The absence of peaks in the spectrum of (49) corresponding to m/e 133+14 and m/e 133+28 supports this assumption.

As with nicotine , the base peak arises by loss of a 3-pyridyl radical to give fragment (h).



(h)

The mass spectrum of (34) would help to clarify the loss of either C-3' and C-4' or C-4' and C-5' as discrete units. (page 25)

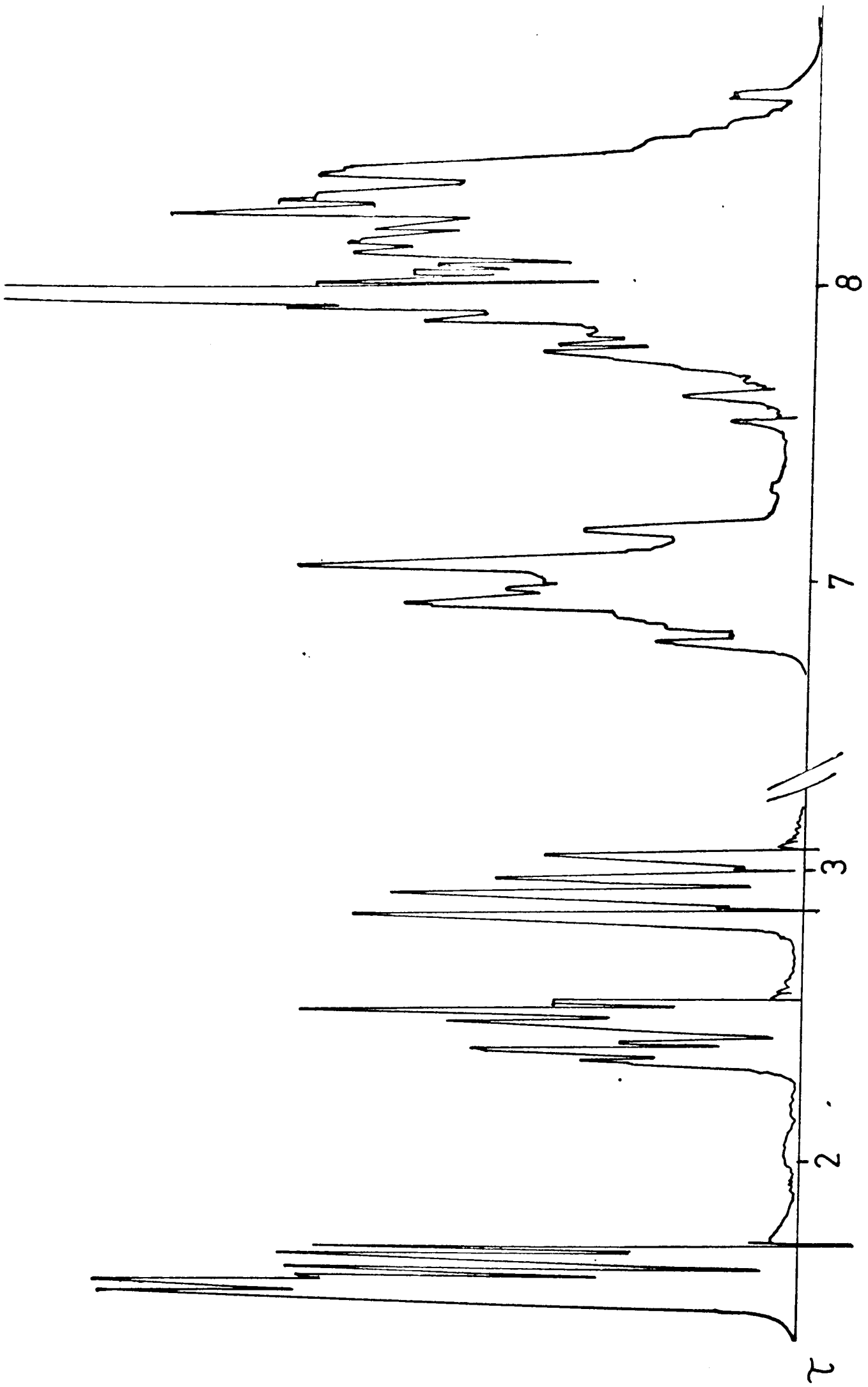


Fig. 18 N.m.r. Spectrum of Nicotine (1)

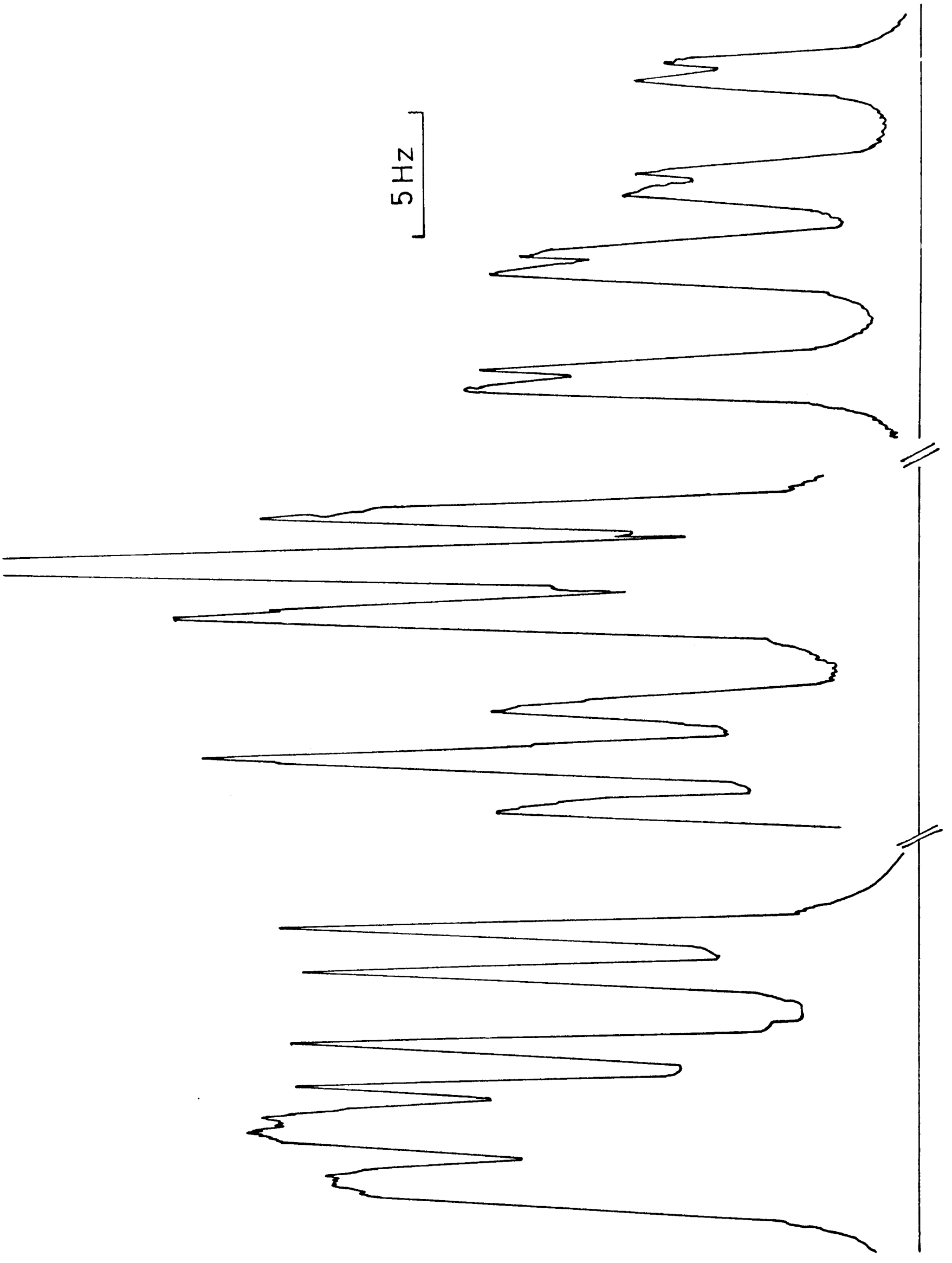


Fig. 18a N.m.r. Spectrum of Nicotine, Expansion of Aromatic Region.

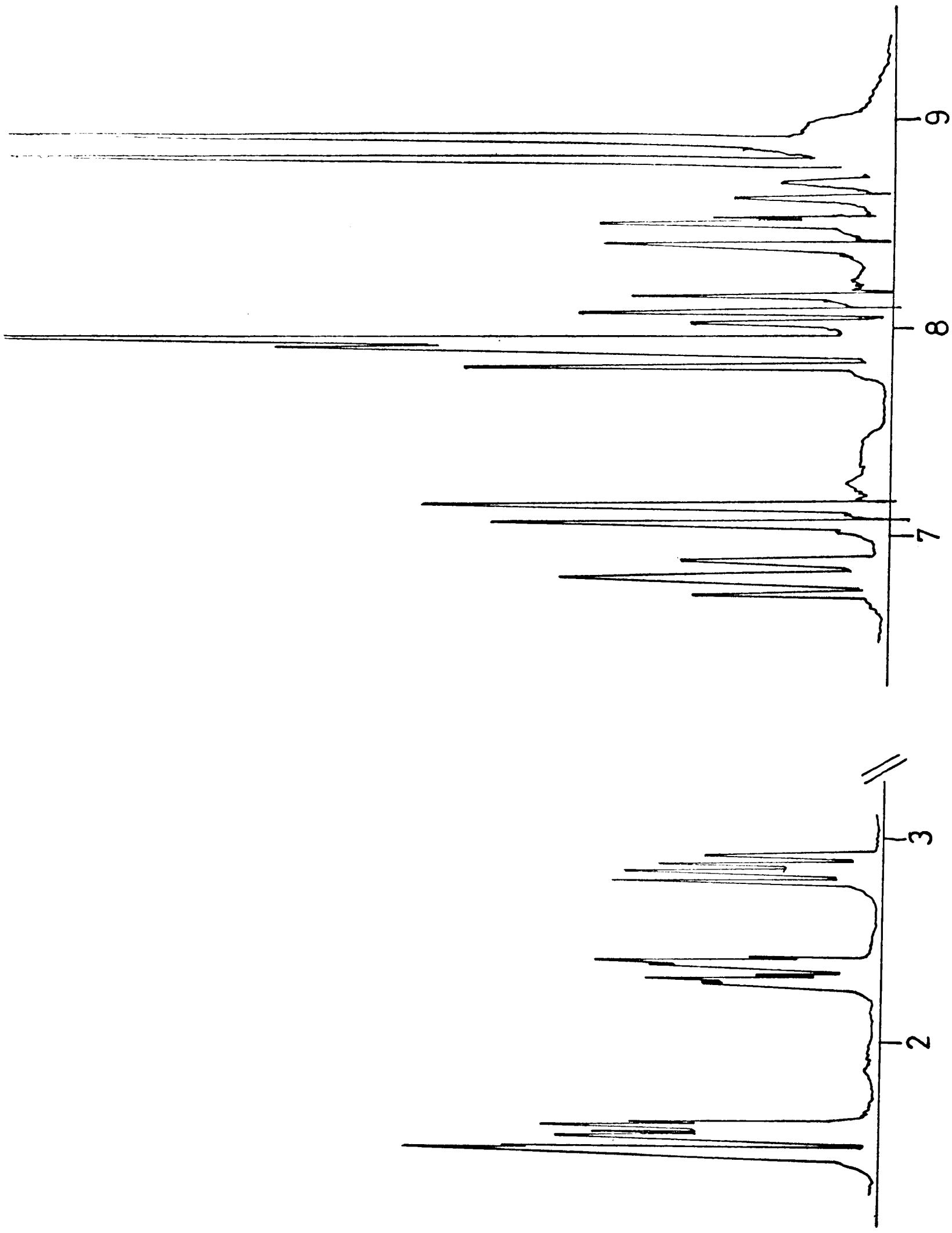


Fig. 19 N.m.r. Spectrum of 4',4'-Dimethylnicotine (49)

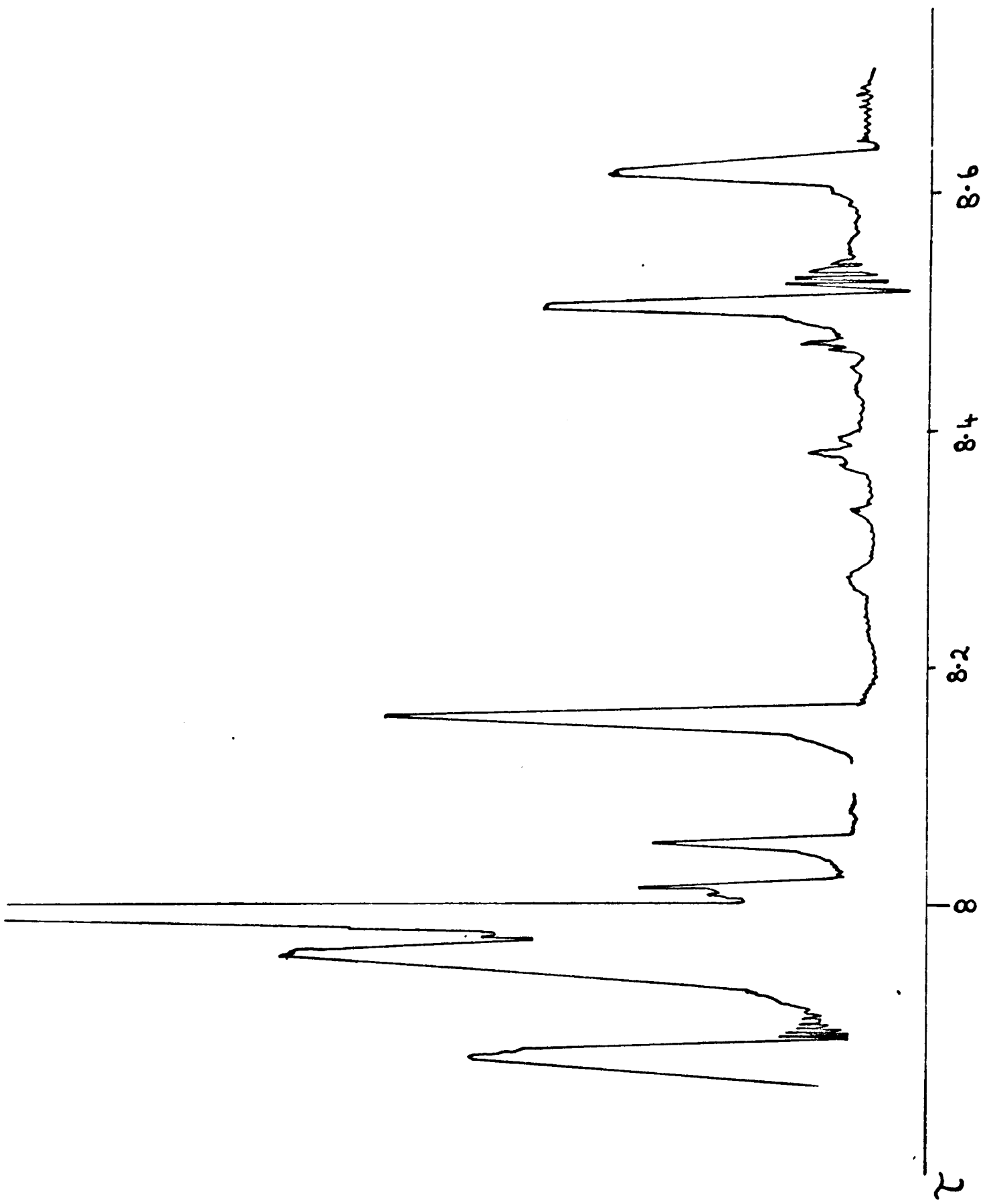


Fig. 19a Frequency sweep 100MHz n.m.r. spectrum of 4',4'-Dimethylnicotine. (7·8 – 8·8τ region whilst irradiating triplet at 6·84τ.

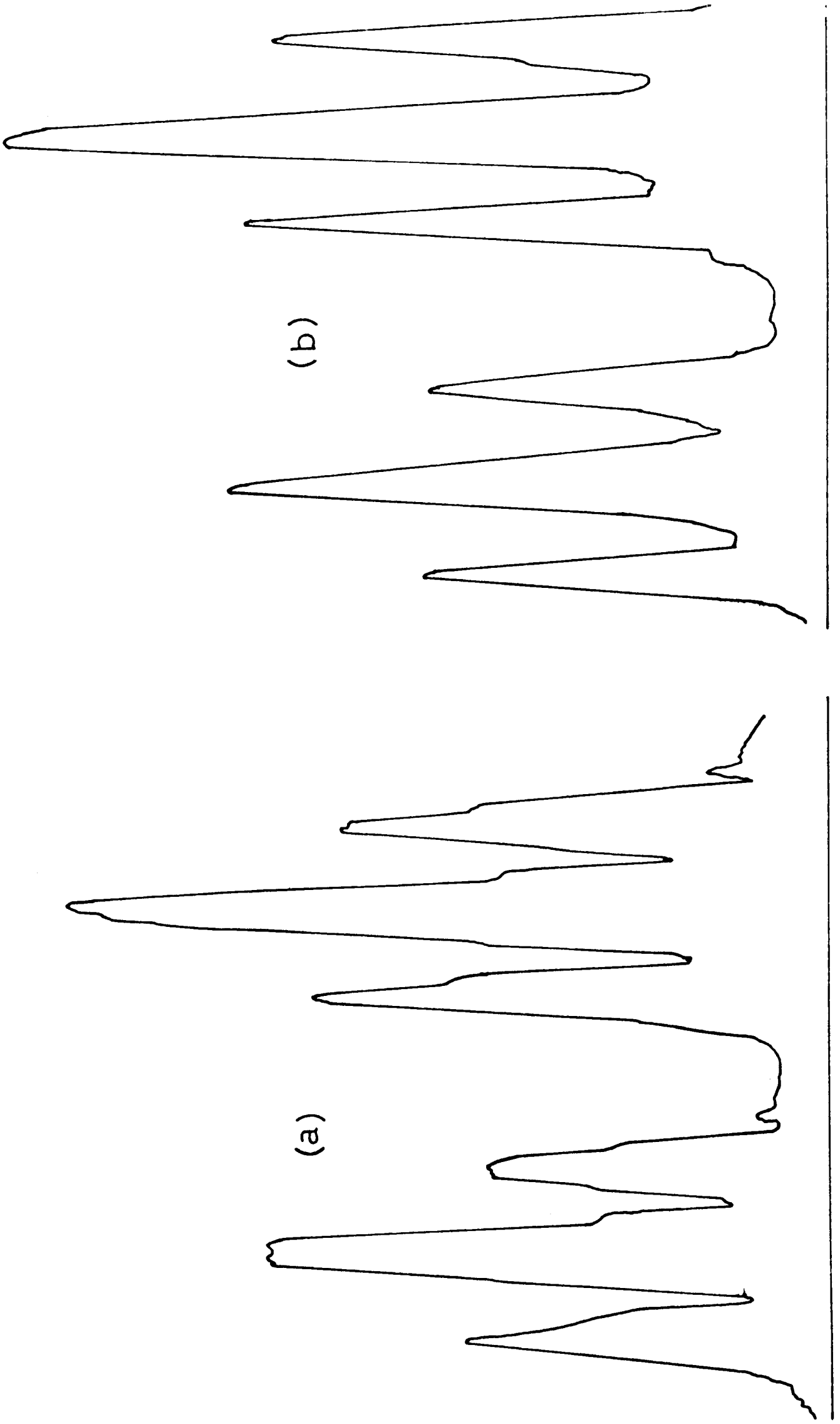
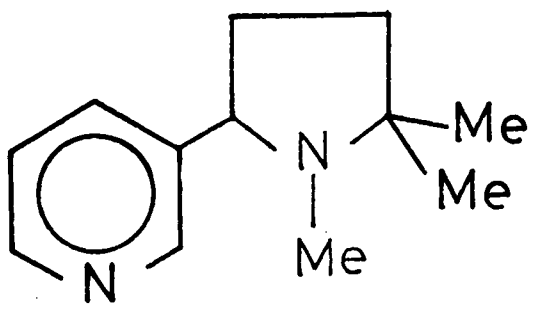


Fig. 19b Frequency sweep 100MHz n.m.r. Spectrum of 4',4'-Dimethylnicotine. (2·4τ region whilst irradiating triplet at 6·84τ.

(a) before irradiation

(b) whilst irradiating



(34)

The mass spectrum of (50) (Fig. 15) follows from that of (49). However the base peak now corresponds to the fragment with m/e 133. This pathway may be favoured by increased stability of the expelled fragment arising from alkyl substitution at C-4'.

4'-Methylnicotine (51) (Fig. 16) fragments in a completely analogous manner.

The n.m.r. spectra of (49), (50) and (51) lend further support to the analysis by Craig[29] and Crain[93] of the n.m.r. spectrum of nicotine (Fig. 18 and 18a). Craig believes the multiplet at τ6.8 to be due to the superimposition of a triplet (2'-H) and a multiplet (5'-H), the 3'-H_2, 4'-H_2 and remaining 5'-H resonating between τ 7.5 - 8.5.

4',4'-Dimethylnicotine (Fig. 19) has a much simpler spectrum than nicotine. The multiplet at τ 6.8 has now become a broad triplet and a doublet which can be assigned respectively to the 2'proton (τ 6.84) and the 5' proton (τ 7.13). The remaining 5' proton appears as a doublet at τ 7.87 and the 3' protons become a series of sharp peaks with the N-methyl and two C-methyl peaks superimposed.

Irradiation at τ 6.84 caused the complex pattern between τ 8-9 to collapse to two doublets (Fig. 19a) arising from coupling of the 3'-protons (J 11 Hz), the highfield 5'-proton at τ 7.87 remaining unaffected.

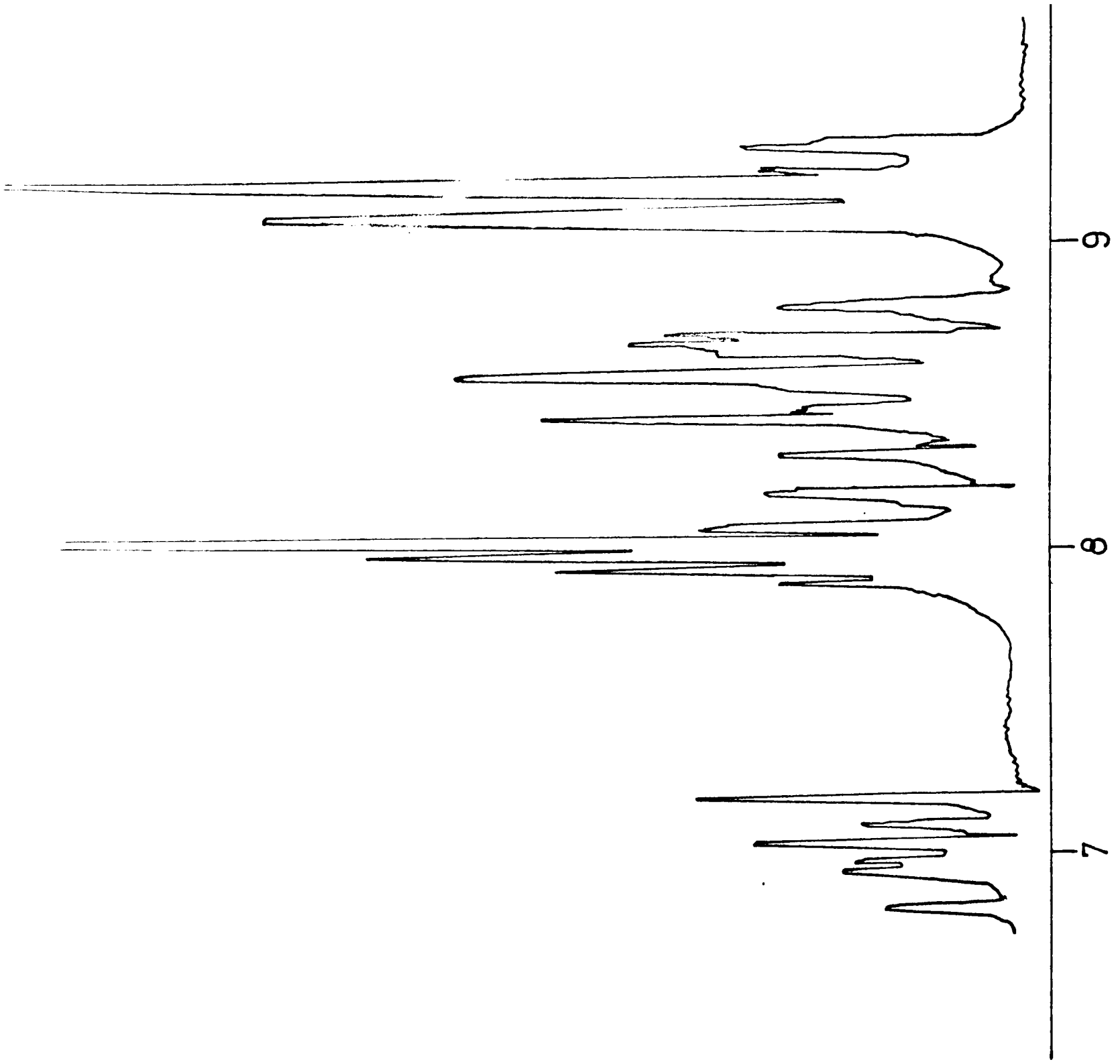


Fig. 20 N.m.r. Spectrum of 4′,4′-Diethylnicotine (50)
(aromatic region not included)

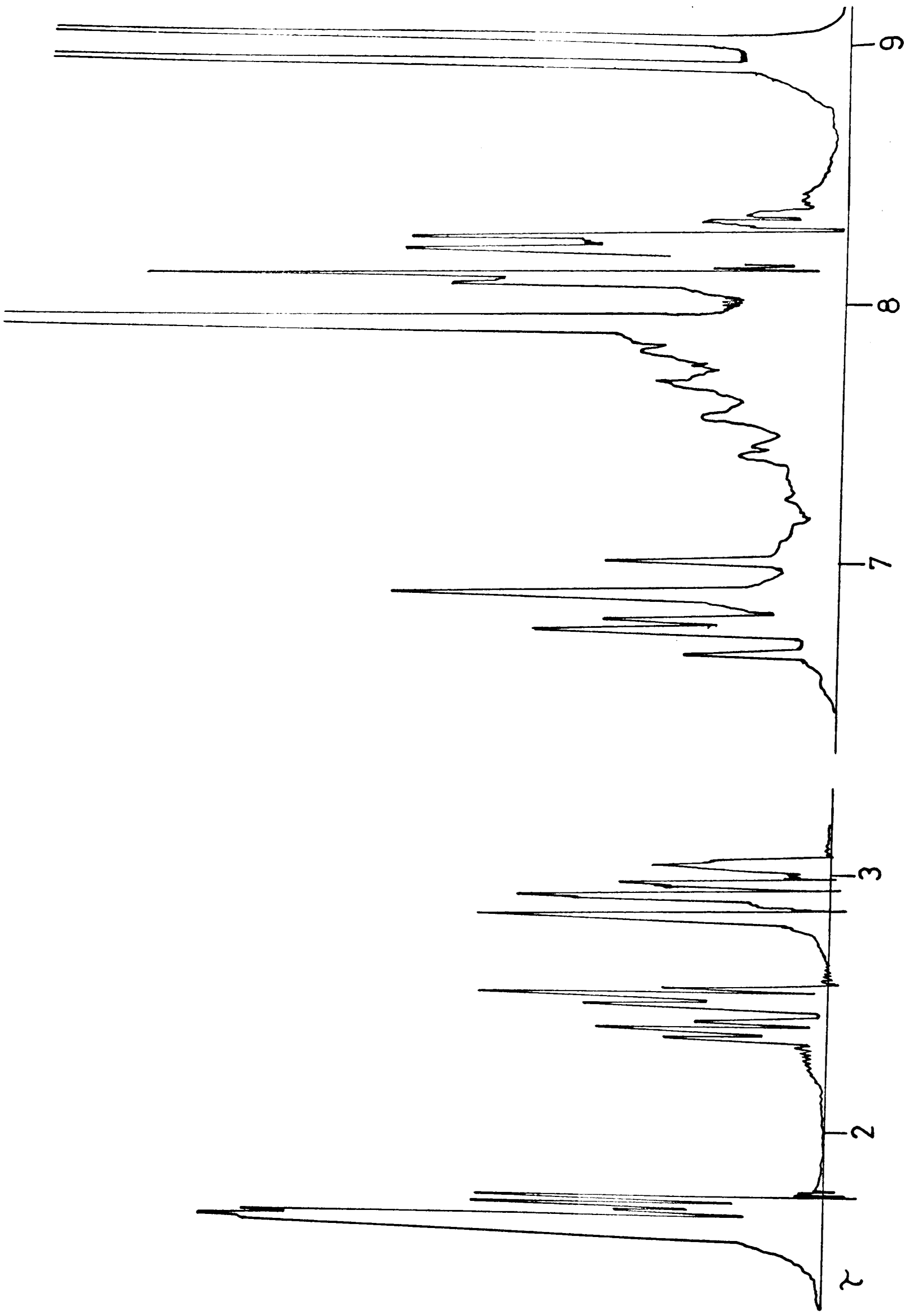


Fig. 21 N.m.r. Spectrum of 4'-Monomethylnicotinc (51)

The 4'-proton appears as a doublet of triplets, as expected, but further splitting ($\underline{J}$ 0.45 Hz) is clearly observed at 60 MHz. At 100 MHz (Fig. 19b) the splitting is less well resolved but irradiation of the 2'-proton (τ 6.8) produces considerable sharpening of the triplets, indicating long range coupling between the 4- and 2'-protons.

For 4',4'-diethylnicotine (50) (Fig. 20) the 2' proton appears as a quartet ($\underline{J}$ 9.6 Hz and 7.5 Hz) indicating that the 3'-protons are not seen to be equivalent by the 2'-proton. The low field 5' proton again appears as a doublet ($\underline{J}$ 9.2 Hz). The τ 8–9.5 region is complicated by resonances due to the methylene protons of the ethyl groups.

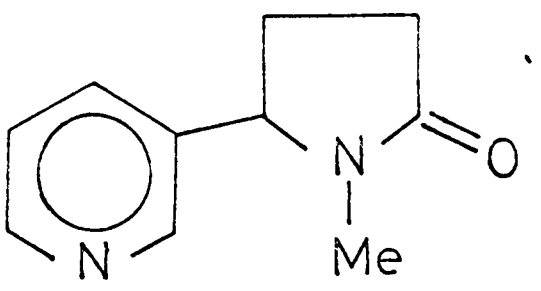
The monomethyl derivative (51) (Fig. 21) shows increased complexity, probably due to virtual coupling of the 2'-proton and the 4'-proton and increased splitting of the 3'-protons by the 4'-proton. Although at 60 MHz the 6–7 region can be rationalized as a quartet and a triplet, at 100 MHz the resonance form is far more complex.

Molecular analysis of the bases or picrates and the i.r. spectra of compounds (46) to (51) are in full agreement with the proposed structures.

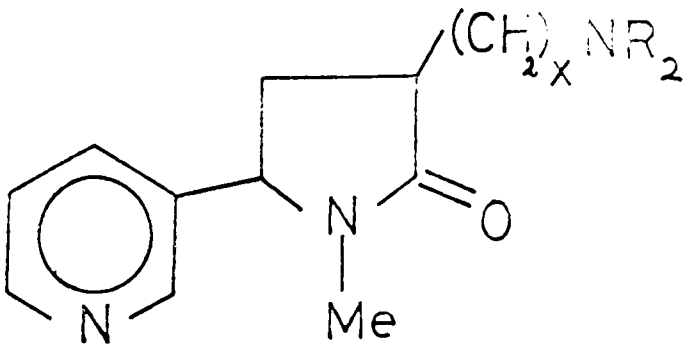
Compounds (46) to (51) and (42) were submitted for biological evaluation, the results of which are in section 6.

Section 2 The Oxidation of Nicotine and the Reactions of Some Oxidation Products

Cotinine (8)



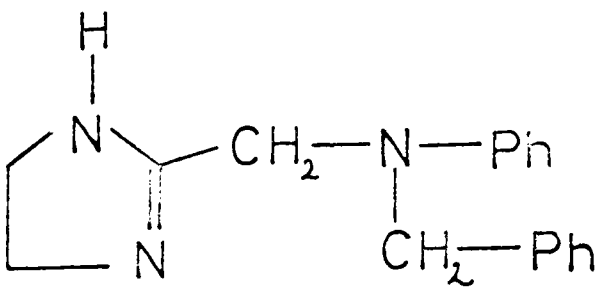
(8)



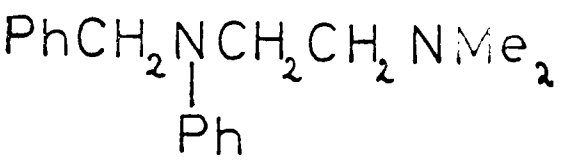
(52)

The bromine/acetic acid oxidation of nicotine to the lactam cotinine (8) has been well documented, more recent work[18,48,49] clarifying the early work of Pinner.

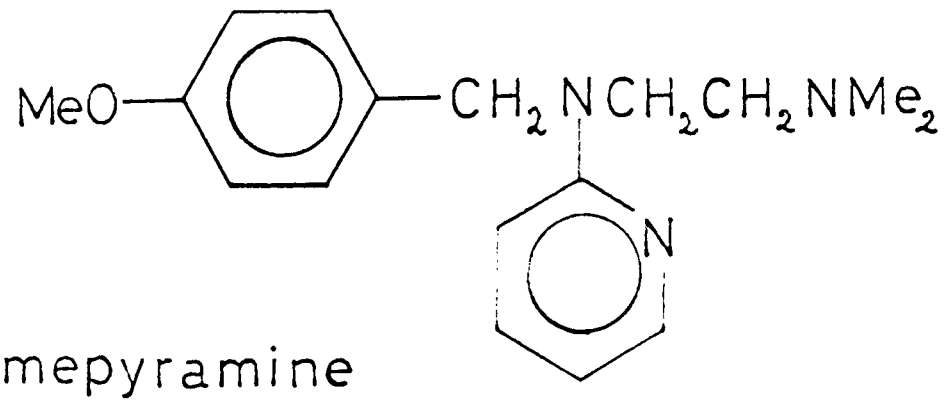
Section 1 shows the preparation of 3',3'-dialkyl- and 3'-alkyl- cotinines from cotinine. Using similar experimental conditions it was hoped to prepare 3'-dialkylaminoalkyl cotinines (52) (and thence by reduction 4'-dialkylaminoalkyl nicotines) which would be potential antihistamines; the exocyclic tertiary amino function being common to many antihistamines.[221]



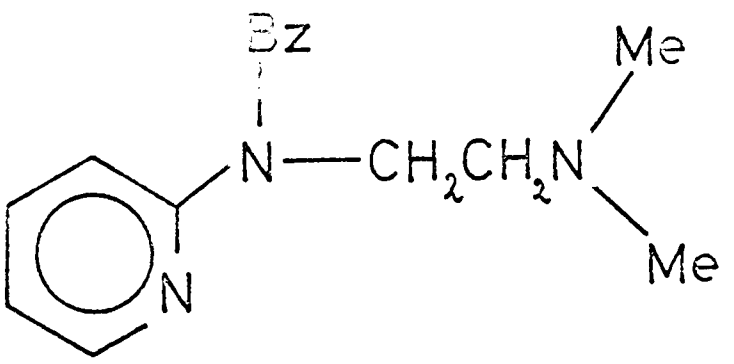
antazole



Antergan



mepyramine

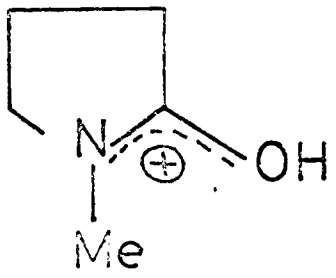


tripelennamine

However no compounds could be isolated from the glues obtained.

Sodium Tetraphenylboron adducts

Sodium tetraphenylboron has been shown to precipitate many amines of sufficient basicity in acid solution.[163] The adduct from N-methylpyrrolid-2-one (53) compares favourably with cetylpyridinium chloride in activity against gram +ve bacteria and fungi.[163]



(53)

$B(Ph)_4$

Cotinine and sodium tetraphenylboron gave a non-stoichiometric precipitate which became a glue on attempted crystallisation. Quantitative precipitation could not be obtained and it is probable that crowding at the 5' position (by the pyridine ring) hinders approach of the bulky tetraphenylboron anion. A similar reason has been proposed to explain why 5-methylpyrrolid-2-one gives no precipitate at all with sodium tetraphenylboron.[163]

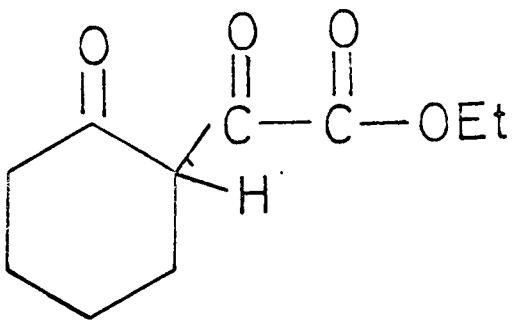
Biological evaluation of the non-stoichiometric adduct showed some activity but because of characterization difficulties the reaction was not further investigated.

Amination of Cotinine

Attempts to aminate cotinine with sodamide by methods applicable to nicotine[87] gave tar, the vigorous reaction conditions almost certainly removing the protons ∝ to the carbonyl group with consequent polymerization.

Acylation of Cotinine

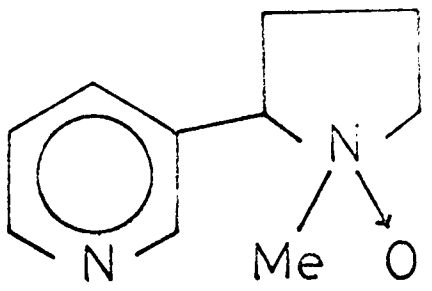
Acylation of carbonyl compounds containing active hydrogen atoms is readily accomplished with dimethyl or diethyl oxalate in the presence of base. Thus cyclohexanone and diethyl oxalate give (54).[164]



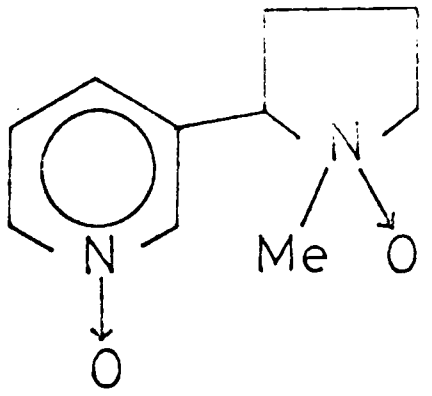
(54)

Cotinine with dimethyl oxalate or diethyl oxalate in the presence of sodium ethoxide or sodium hydride gave only glues from which no acylated products could be obtained.

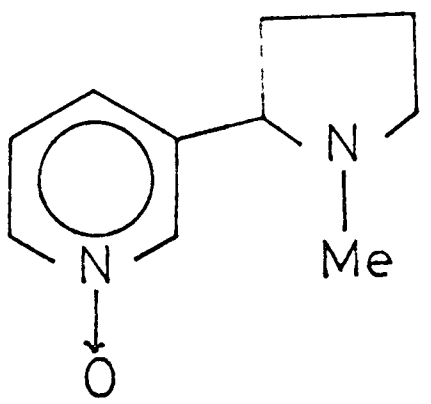
The N-Oxides of Nicotine



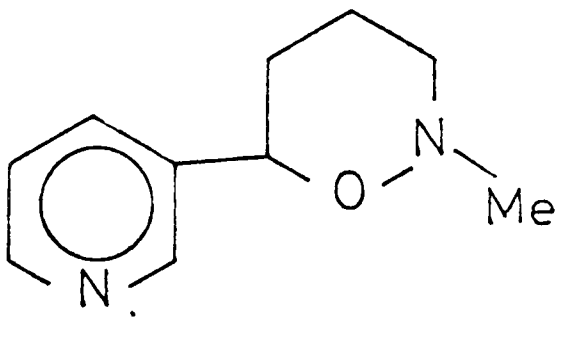
(13)



(14)



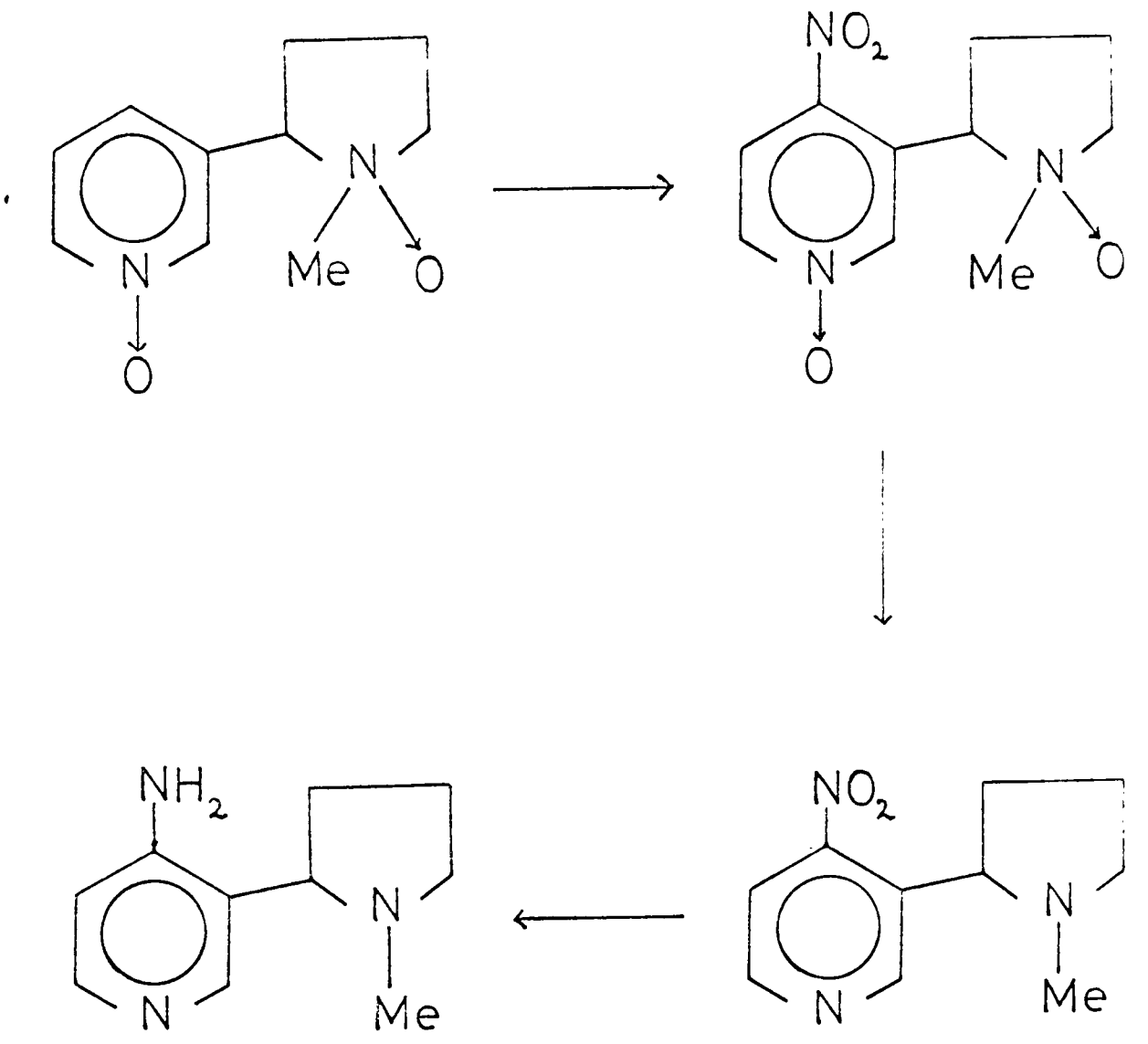
(55)



(56)

Depending on the reaction conditions nicotine mono-N-oxide (13) and nicotine di-N-oxide (14) have both been prepared from nicotine and hydrogen peroxide,[131,132,165] nicotine and perlauric acid,[132] and nicotine and m-chloroperbenzoic acid.[62] Reduction of (14) with sulphur dioxide has given a compound believed to have structure (55). The melting point of the dipicrate has been reported as 147-148°[131], 155-156°[132] and 161°[165] but no other data have been obtained. Johnson[131] has attempted to nitrate and mercurate (55) by the usual methods for pyridine N-oxide[166] but without success.

It was hoped to obtain 4-substituted nicotines by preparing 4-substituted N-oxides and removing the oxide functions. Thus a scheme giving 4-nitro- and 4-aminonicotine can be visualized as:

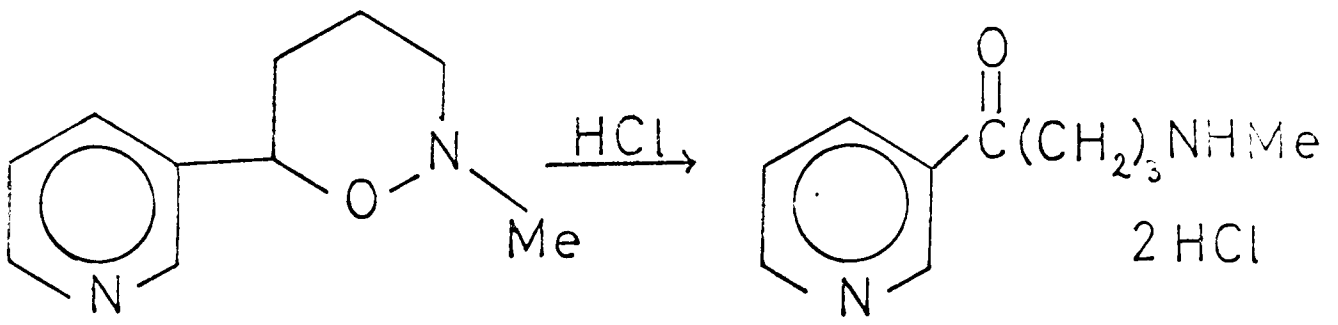


Unfortunately treatment of (14) with the usual nitrating mixtures[166] gave only tars and the scheme was abandoned.

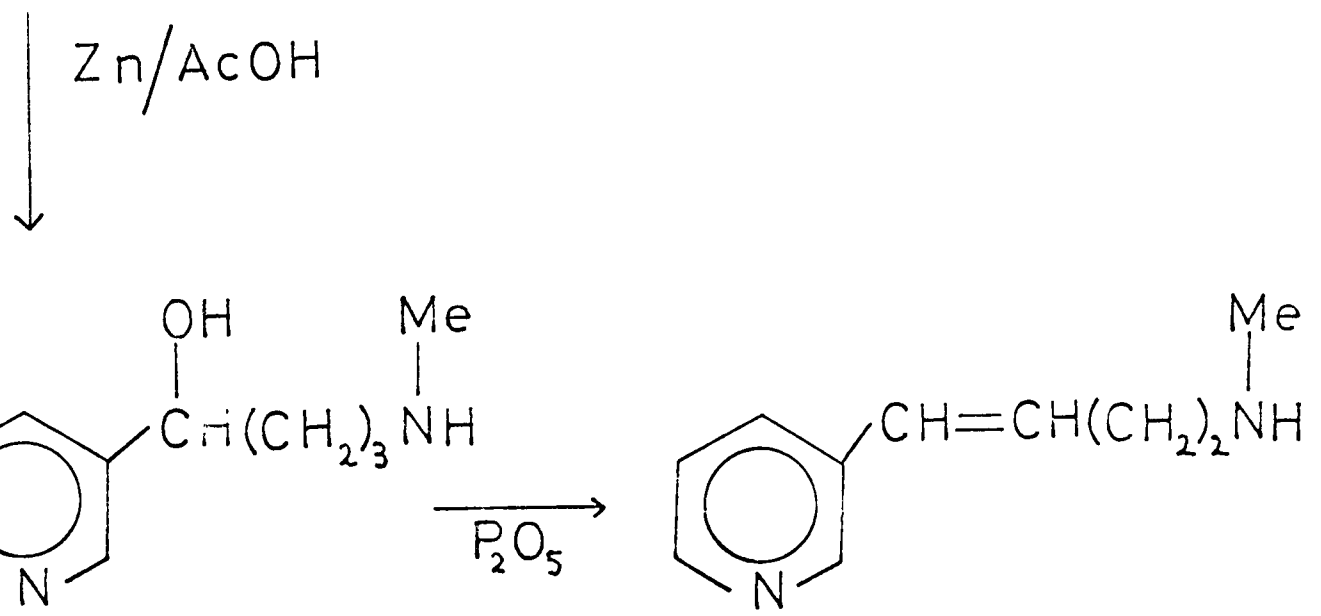
2-Methyl-5-(3-pyridyl)tetrahydrooxazine (56)

Pyrolysis of (13) gives (56),[135] the structure being established by degradation (Scheme 7) and by analogy with similar rearrangements. Thus methylallylaniline N-oxide on pyrolysis gives methyl O-allyl-phenylhydroxylamine.[167]

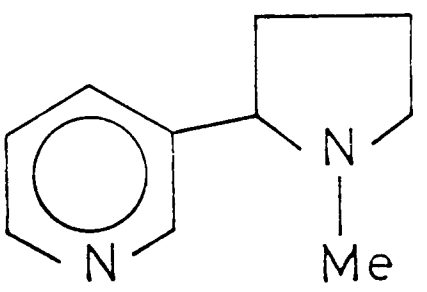
Scheme 7



(56)



+



(D,L)

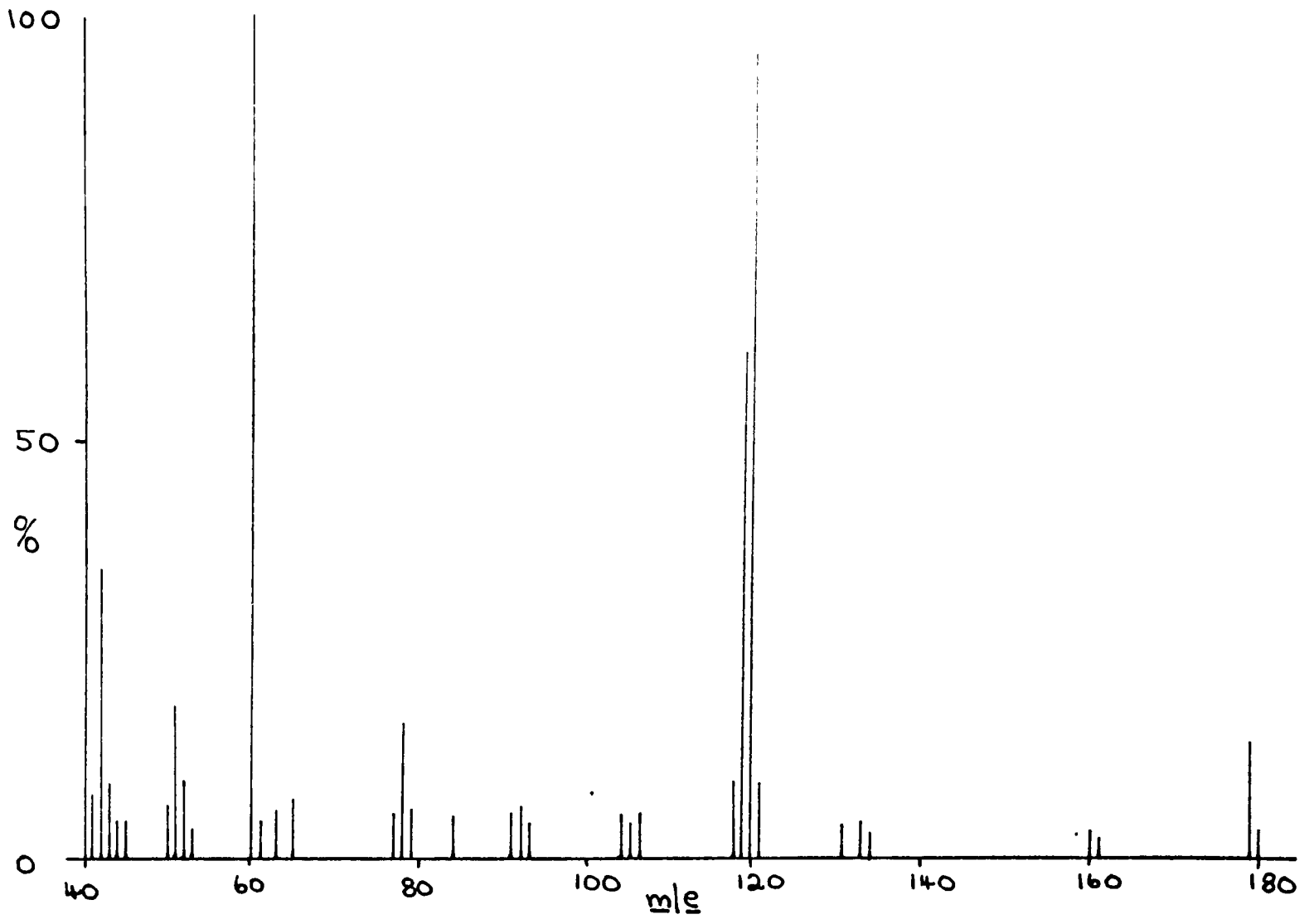
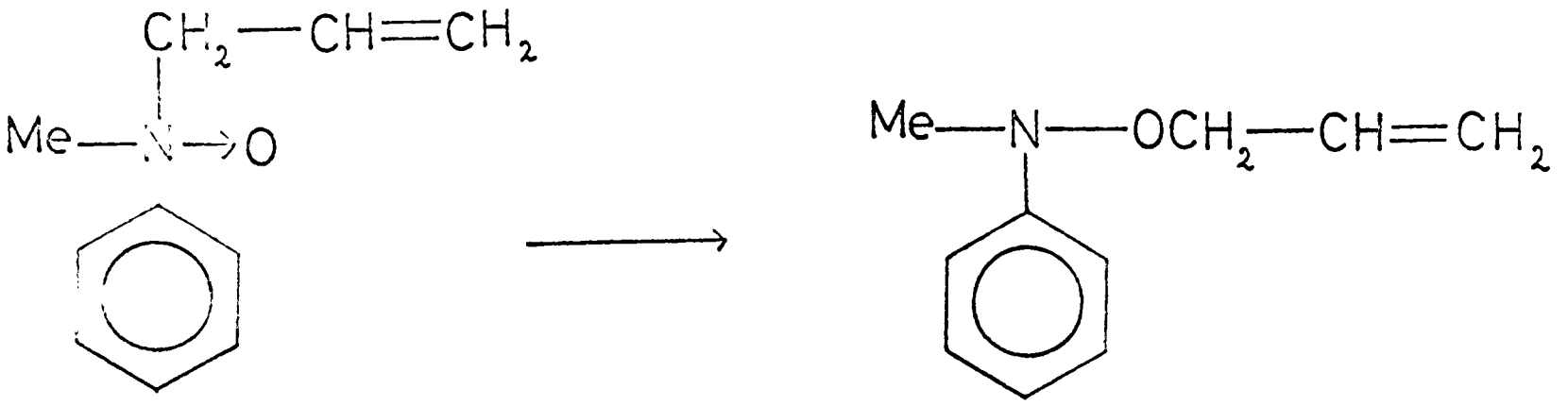
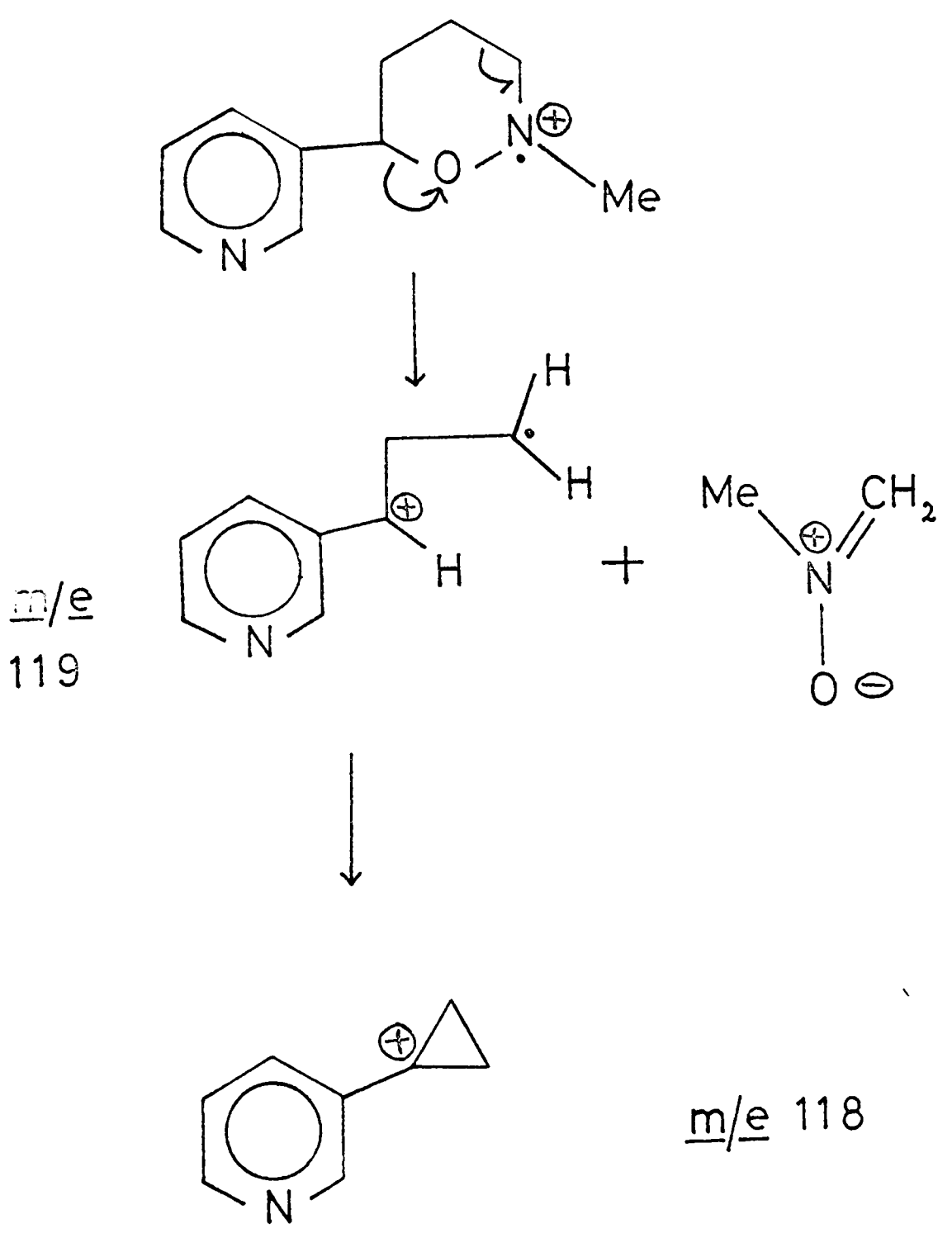


Fig. 22 Mass Spectrum of 2-Methyl-6-(3-pyridyl)tetrahydro-1,2-oxazine (56)



The mass spectrum of (56) (Fig. 22) gives the expected molecular weight (178).

The first major loss gives a peak at m/e 119 (95%) and can be rationalized as below.



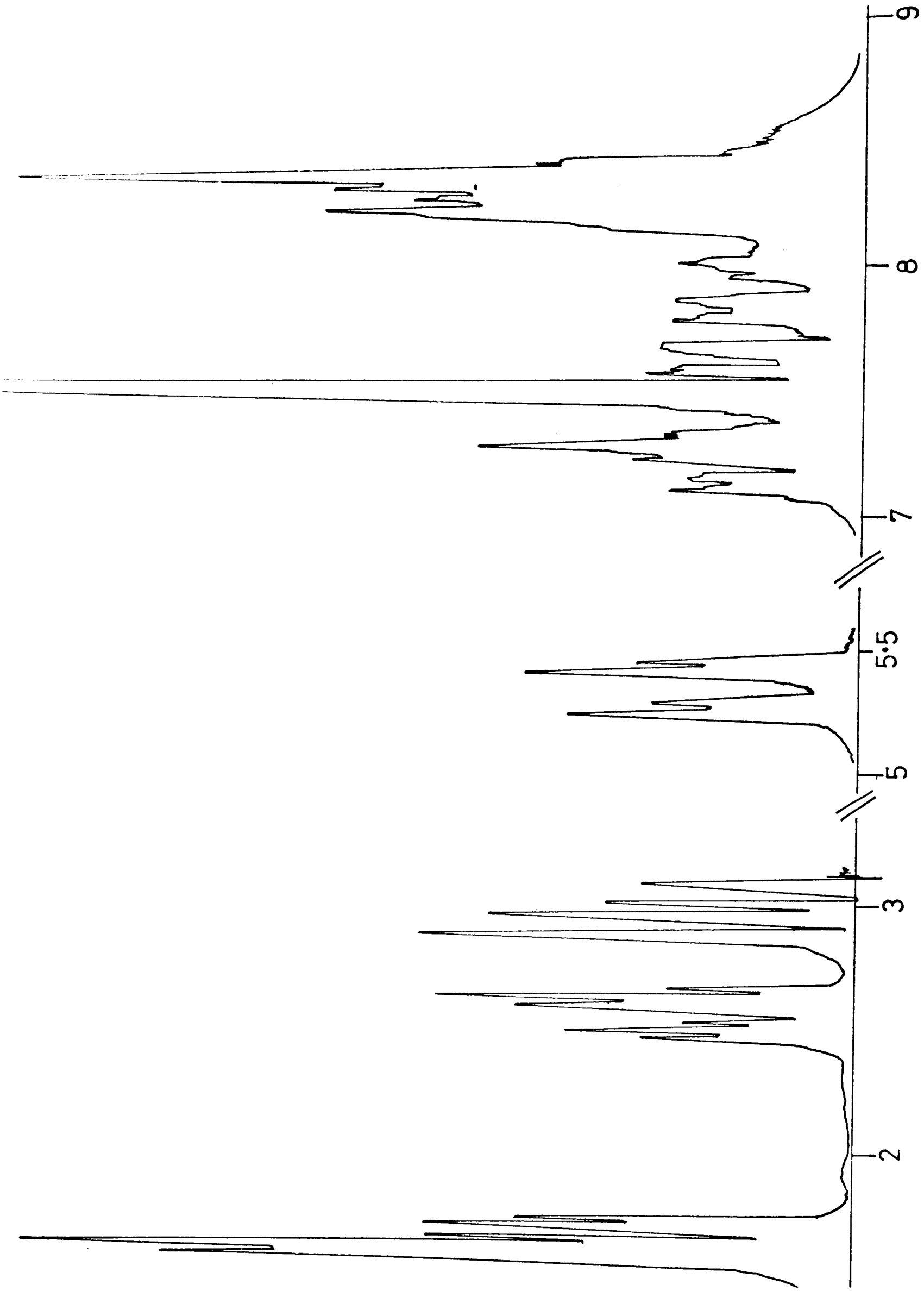
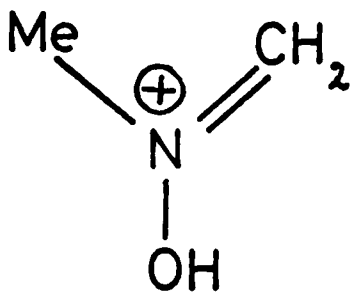


Fig. 23 N.m.r. Spectrum of 2-Methyl-6-(3-pyridyl)tetrahydro-1,2-oxazine (56)

The base peak at m/e 60 arises by protonation of the N-oxide by an unidentified proton donor to give (i).



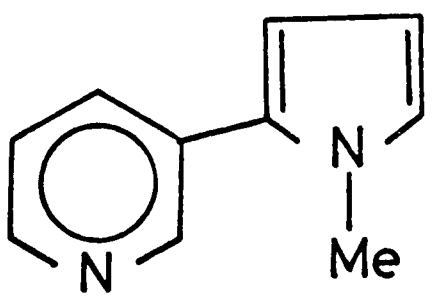
(i)

The n.m.r. spectrum (Fig. 23) shows the resonances expected for a 3 substituted pyridine. A quartet at τ 5.31 can be assigned to the 6' proton with vicinal splitting from the two 5' protons. (J 10 Hz and 2.8 Hz). The 3', 4' and 5' protons give a complex pattern between τ 7-9.

Reaction of (56) with dimethyl acetylenedicarboxylate is reported in section 5.

Nicotyrine (3)

Catalytic dehydrogenation of nicotine with palladium/asbestos is reported to give nicotyrine.[85,168]



(3)

No dehydrogenation occurred with the literature catalyst but palladium charcoal effected smooth dehydrogenation to (3); the reported by-products were

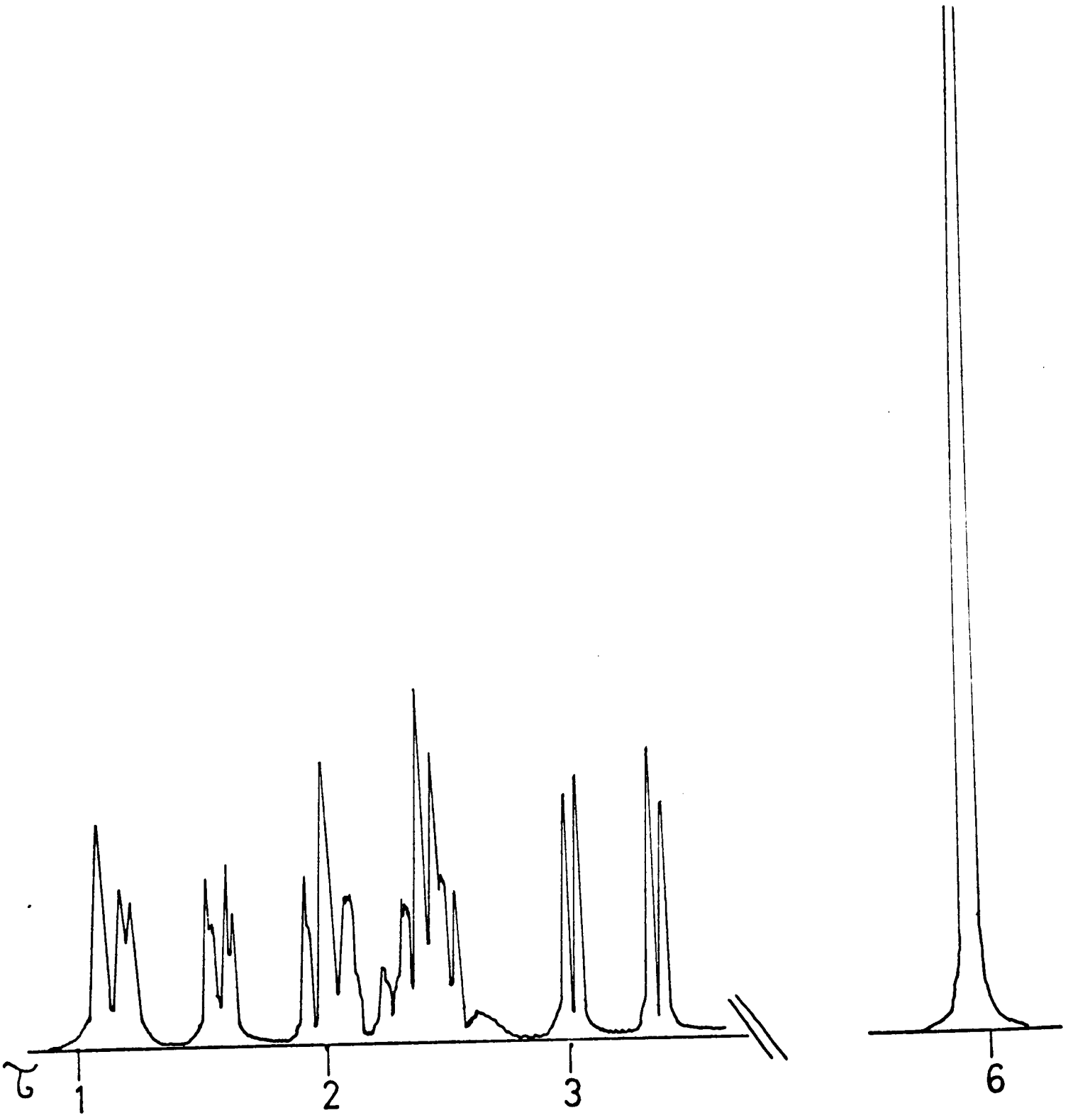
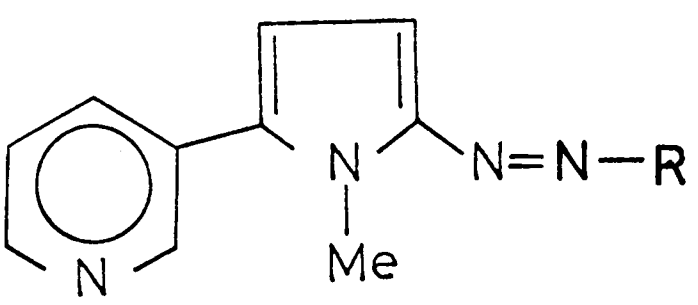


Fig. 24 N.m.r. Spectrum of Diazo-compound (57)

obtained (see experimental).

The coupling of nicotyrine with diazonium salts has been investigated,[17] coupling at the 5' position being assumed by analogy with pyrrole.[169,170] The compounds shown below were obtained[17] and slight activity against black beetle carpet larvae demonstrated.



R = o-C_6H_4COOH (57)
p-$C_6H_4SO_3Na$
m-$C_6H_4NO_2$
p-$C_6H_4NO_2$ (58)
p-C_6H_4COOH
β-$C_{10}H_7$

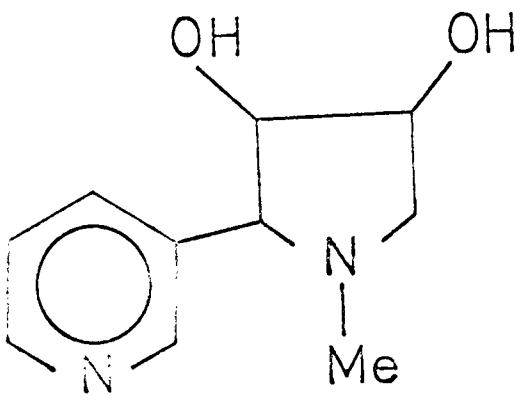
To obtain more complete activity screening (58) was prepared and submitted for evaluation along with a new compound (57). No useful activity was found so further derivatives were not prepared.

The n.m.r. spectrum of (57) (Fig. 24) clearly shows two olefinic protons mutually coupled (J 4.5 Hz) readily assignable as the nicotyrine 3' and 4' protons (c.f. Dithiodinicotyrine, Fig. 31).

Pyrrole is very reactive in the Friedel Crafts reaction, giving 2-acetylpyrrole with acetic anhydride in the absence of catalyst. Nicotyrine however gave only tars under a variety of acylation conditions, no characterizable compounds being obtained.

Reduction of nicotyrine (3) to dihydronicotyrine (5) according to Eisner[85] gave, along with (5), 20% nicotine as contaminant. Confusion concerning the structure of (5) was abolished in 1963 by n.m.r. spectral analysis.[86]

Osmium tetroxide catalysed sodium chlorate oxidation of the isolated double bond of (5) according to established methods[171,172] failed, starting material being recovered. The expected diol (59) would contain the stereochemical and electronic parameters believed necessary for activity



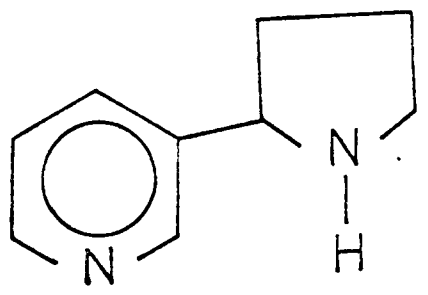
(59)

(section 1) and the functionality at positions 3' and 4' could be used to give new biologically interesting compounds.

The preparation of (59) merits further consideration.

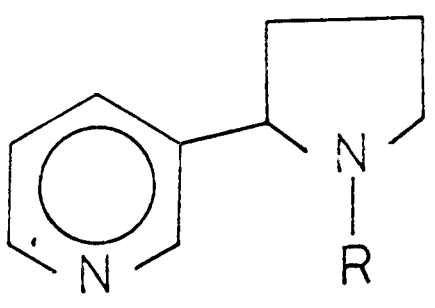
Attempted De-N-Methylations of Nicotine

N-Substituted nicotines can readily be prepared from nornicotine (2).



(2)

The compounds below have all been obtained and in some cases biological activity demonstrated.[187]



R = Et [173]

allyl [173]

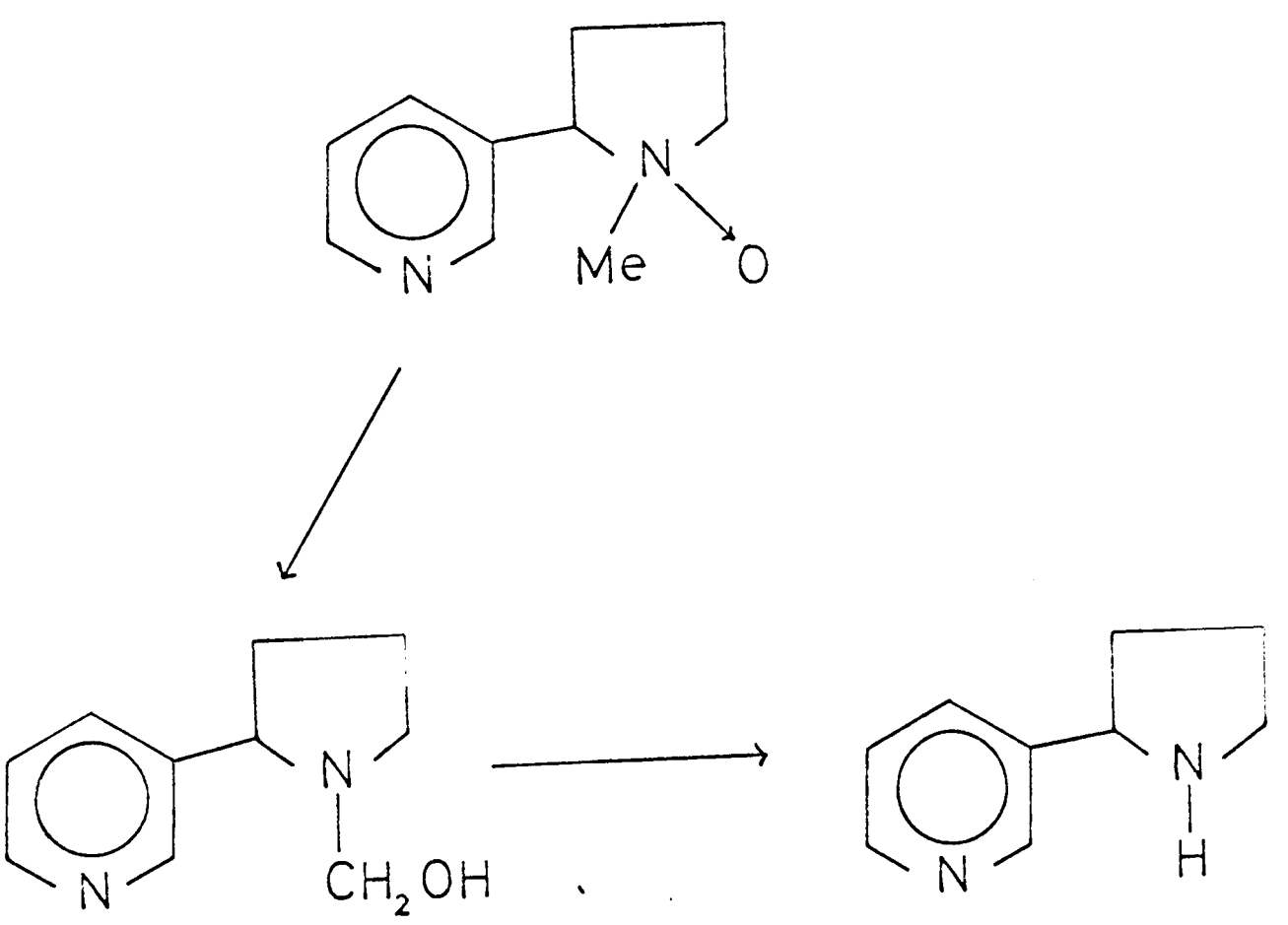
acetyl [173]

amino [175]

formyl [174]

In order to obtain more compounds of this type from nicotine a facile de-N-methylation procedure was needed as nornicotine is not as easily obtained as nicotine.

Craig[161] has investigated the oxidative demethylation of nicotine *in vivo* and *in vitro* and believes nicotine N'-oxide to be involved as an intermediate, oxygen migration to carbon being followed by loss of formaldehyde to give nornicotine.



The *in vitro* reaction studied by Craig involved a g.l.c. determination of the alkaloid products obtained when nicotine N'-oxide was treated with an iron III tartaric acid system at pH 6.3, and is of no preparative value.

Very low yields of nornicotine from nicotine and hydrocinnamic acid,[76] silver oxide[77] and potassium permanganate[77] have been reported.

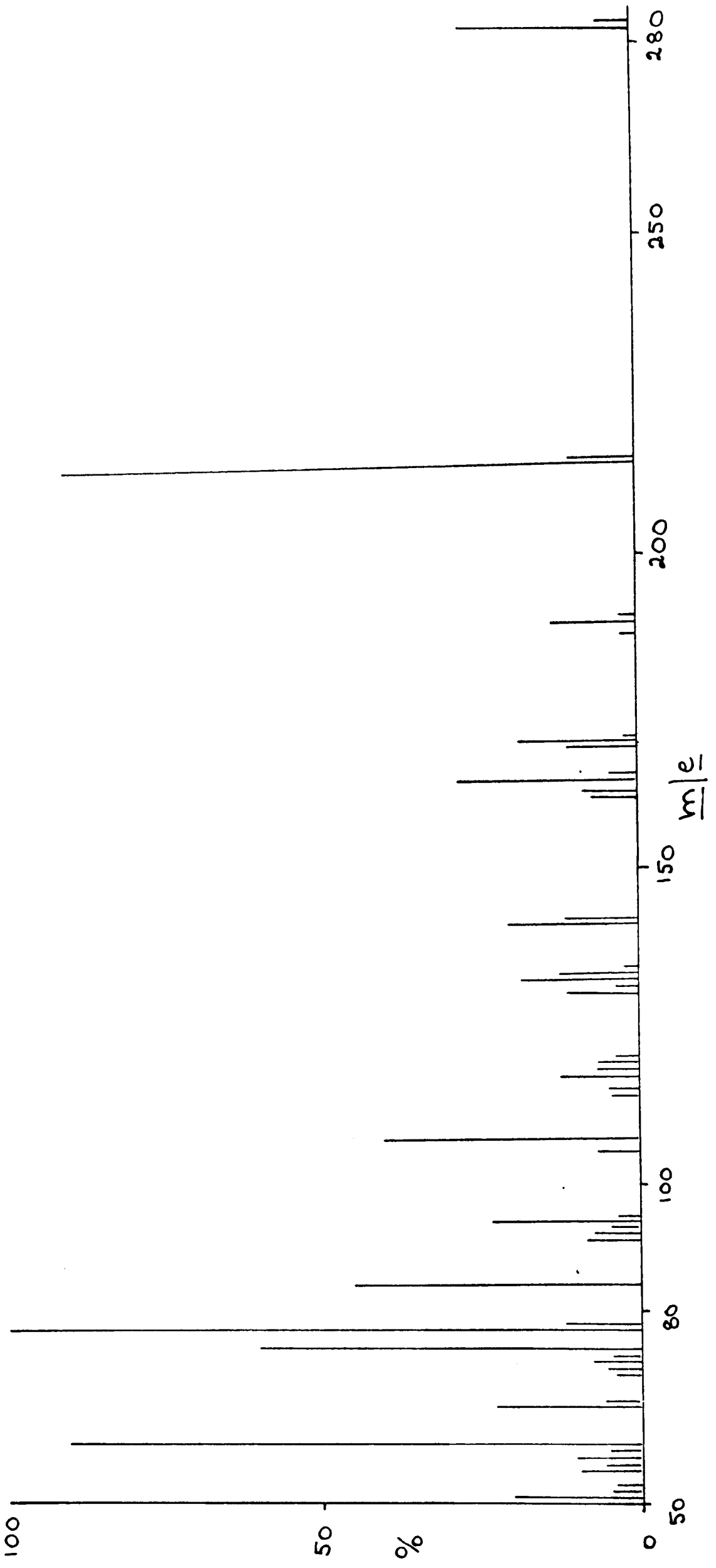
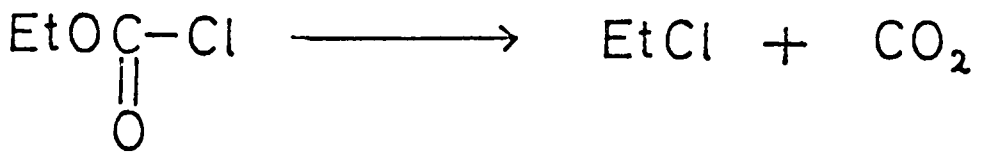


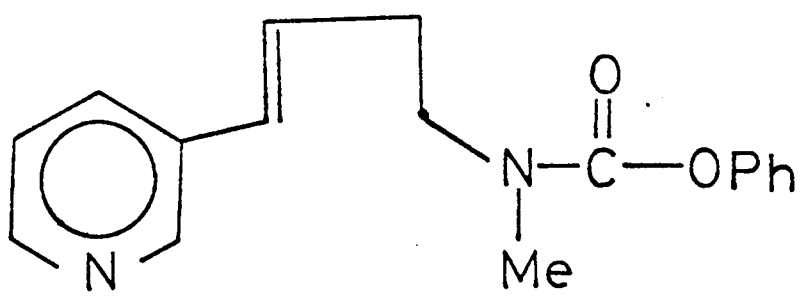
Fig. 25 Mass Spectrum of Δ^4-1-Methyl-1-phenoxycarbonyl-5-(3-pyridyl)butylamine (60)

Nicotine and selenium dioxide in dioxan at 150° (autoclave not mentioned) have been reported to give 50% nornicotine.[58] Repetition using dioxane at 100° and diphenyl ether at 150° (both at atmospheric pressure) gave only starting material.

Thus the following methods were attempted. Chloroformate esters are useful demethylating reagents. Thus ethyl chloroformate gives nortropine from tropine in 16% yield.[176] Phenyl chloroformate has been shown to be preferable in many cases to ethyl chloroformate as loss of carbon dioxide from the reagent is suppressed. Phenyl chloroformate gives phenyl piperidine



N-carboxylate from N-methyl piperidine in 92% yield.[177] Nicotine and phenyl chloroformate under identical conditions gave (60) the structure being assigned on the basis of analytical and spectral data.



(60)

The mass spectrum (Fig. 25) gives the molecular weight as 282. Loss of •OPh from the molecular ion is indicated by a peak at m/e 189 (13%). The base peak is at m/e 77 showing that a major fragmentation mode is:

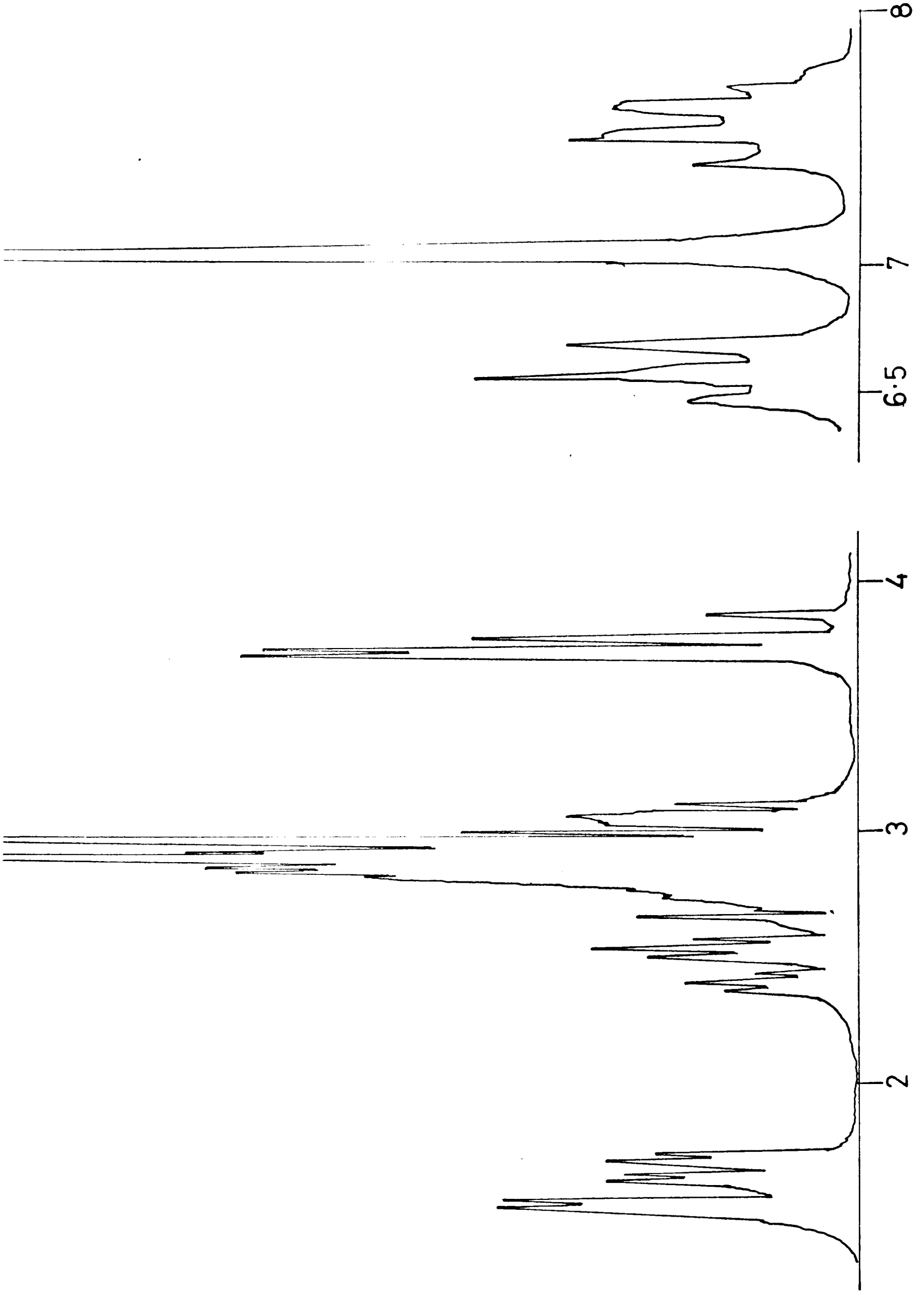
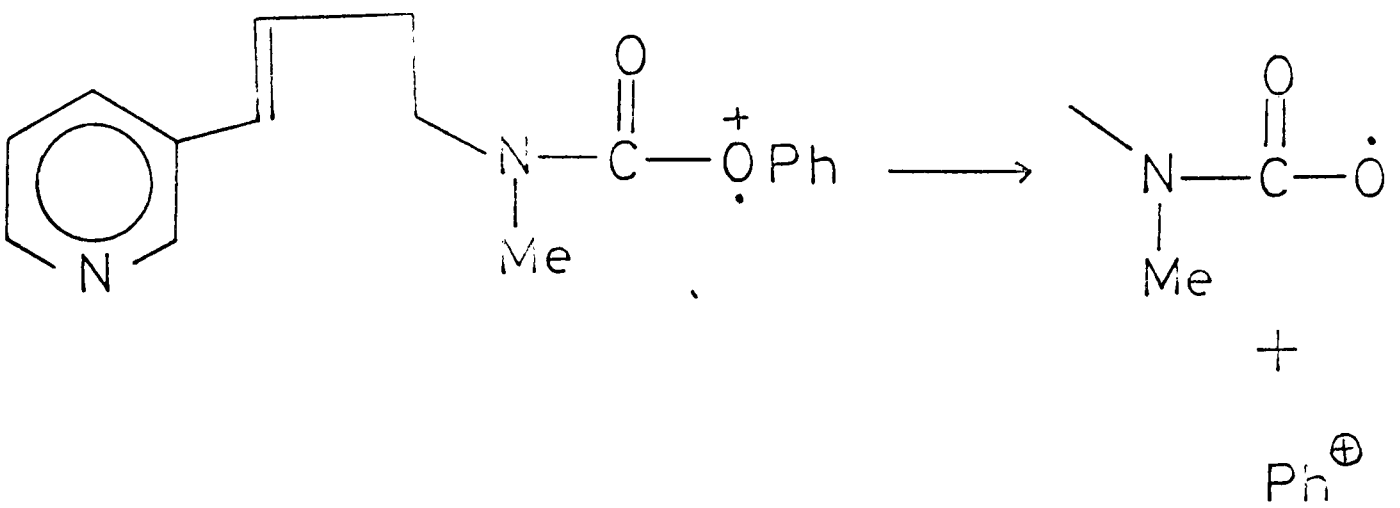


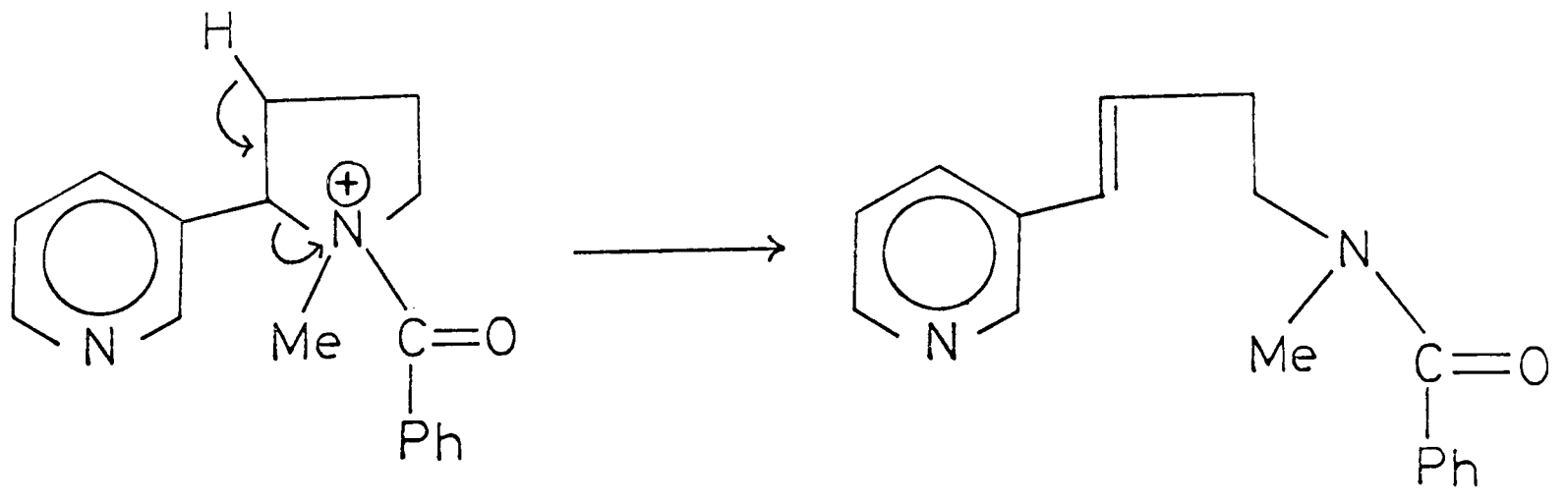
Fig. 26 N.m.r. Spectrum of Δ^4-1-Methyl-1-phenoxycarbonyl-5-(3-pyridyl)butylamine (60)



A peak at m/e 214 corresponds to loss of 68 mass units from the molecular ion. This loss cannot be satisfactorily explained and is quite probably preceded by molecular rearrangement.

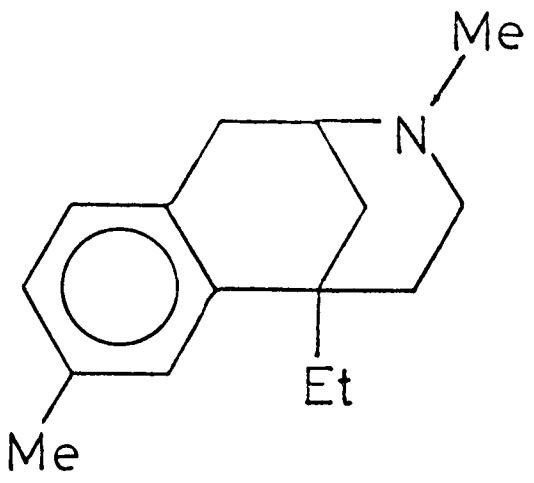
The n.m.r. spectrum (Fig. 26) is in full accord with the structure, the vinyl protons giving a multiplet between τ3.6 - 3.8.

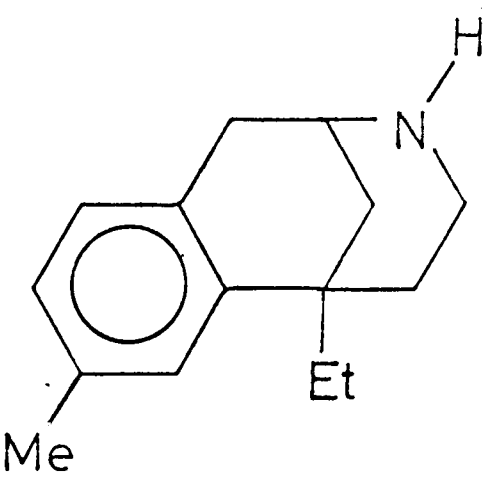
Similar pyrrolidine ring opening reactions of nicotine are well characterized,[212] benzoyl chloride giving N-benzoyl metanicotine,[147] loss of the β proton leading to ring rupture.



The reactions of cyanogen bromide with tertiary amines were first investigated by von Braun[178] and by Scholl and Nörr.[179] Thus N-methyl piperidine has given N-cyano piperidine and N,N-dimethyl piperidinium bromide. More recently 5-methyl-2'-methoxy-2-methyl-6,7-benzomorphan on

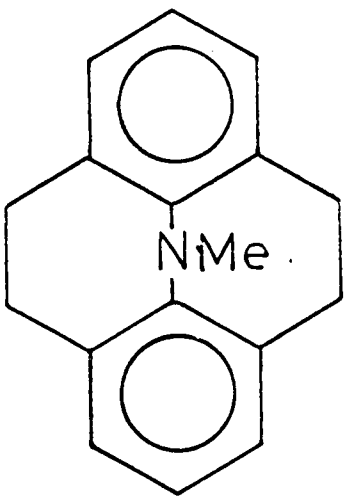
treatment with cyanogen bromide followed by hydrochloric acid has given 5-ethyl-2'-methoxy-6,7-benzomorphan.[213]





Nicotine however gave only tars, no characterizable compounds being obtained.

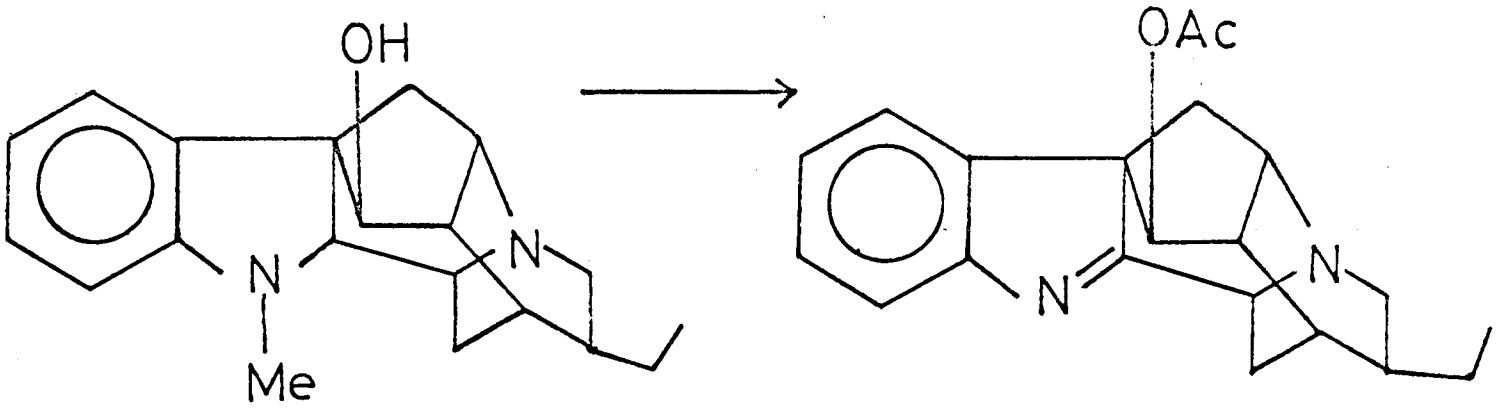
By bubbling oxygen through an ethanolic solution of N-methyl 8,16-imino [2.2] metacyclophane (below) , Boekelheide[180] has obtained 70%



yield of the corresponding de-methyl compound.

Likewise platinum catalysed oxidation of N-methyl piperidine has given N-formyl piperidine.[181] Unfortunately in both cases very dilute solutions were used and equal quantities (by weight) of catalyst employed. As the reaction would be of no large scale synthetic value attempts were made to effect demethylation of nicotine with true catalytic amounts of platinum black and palladium on carbon but with no success, nicotine being recovered unchanged.

Lead tetraacetate has found use as a demethylating reagent, a number of ajmaline derivatives giving the corresponding 1-demethyl - Δ^1 compounds.[182]



No identifiable compounds were obtained from nicotine and lead tetraacetate.

In alkaline solution potassium ferricyanide functions as a complex electron abstracting ion and Perrine[67] has obtained nortropine from tropine with this reagent. Attempts to induce nicotine to react failed, in agreement with Perrine who also obtained no demethylnicotine but observed that the ferricyanide was rapidly reduced. Perrine believes that if the N-methyl group is attached to one or two primary carbon atoms the reaction fails.

Henbest[183] has shown active manganese dioxide to give N-formyl compounds from N-methyl compounds; thus tri-n-alkylamines are oxidised to N-formyl-

$$R_1R_2NMe \longrightarrow R_1R_2NCHO$$

dialkylamines.[184]

Nicotine under similar conditions was unaffected by the reagent.

3-Nitro-5-(3-pyridyl)pyrazole

In 1931 a crystalline solid was isolated as by-product when nicotine was oxidised by nitric acid to nicotinic acid.[131] Its structure was assigned

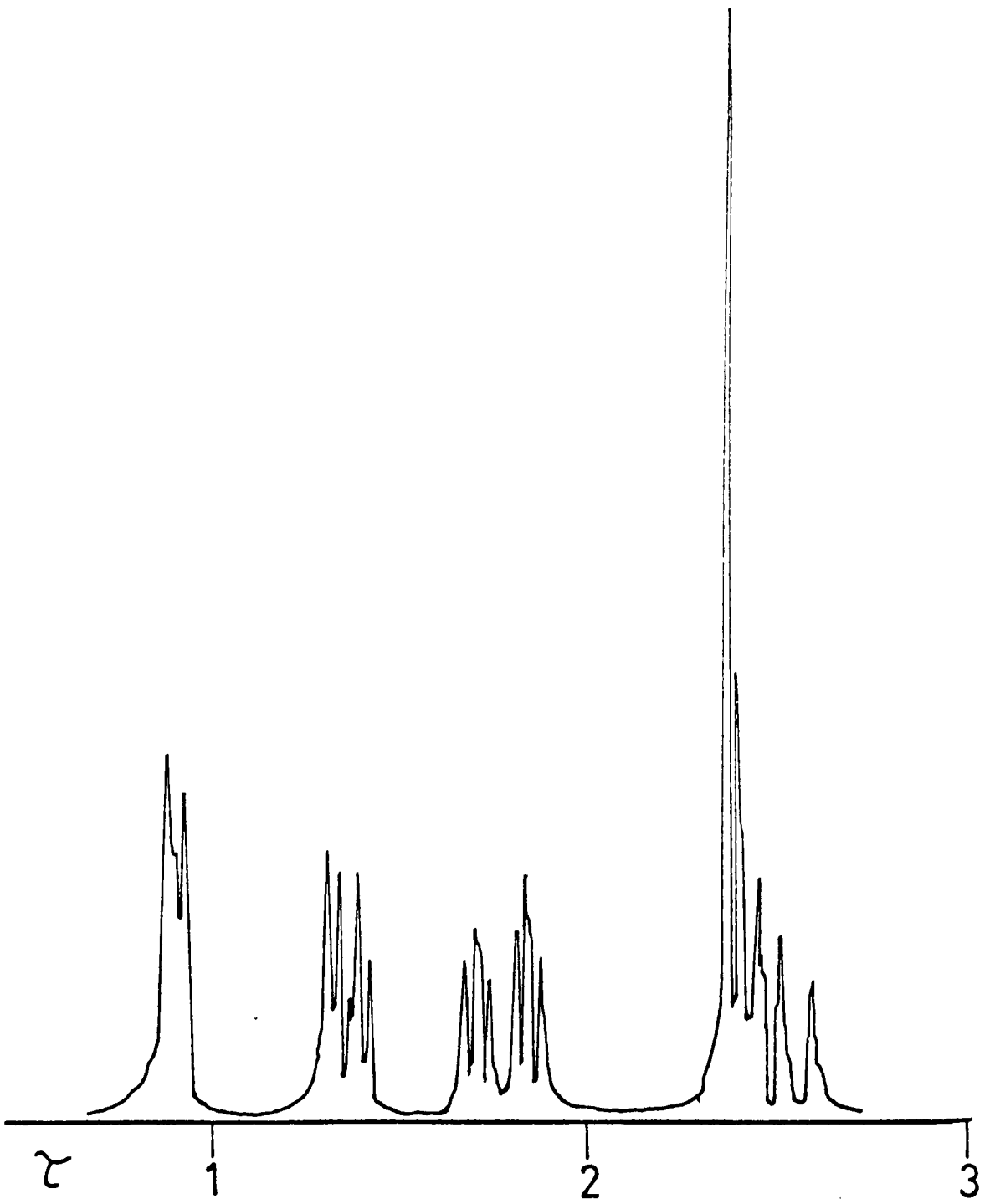


Fig. 27 N.m.r. Spectrum of 3-Nitro-5-(3-pyridyl)pyrazole (15)

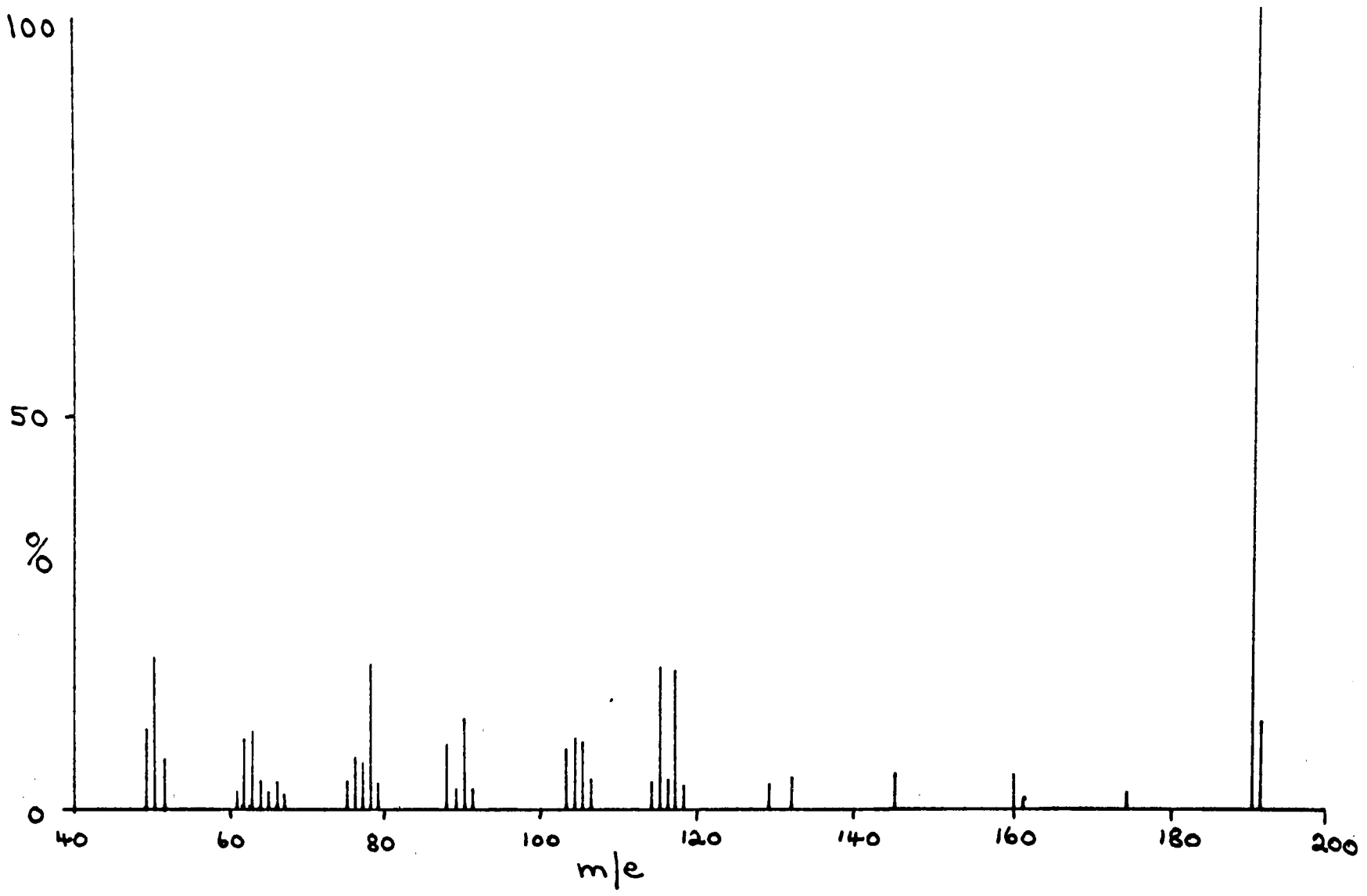
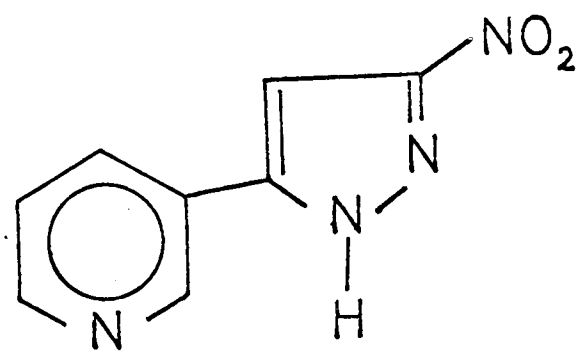


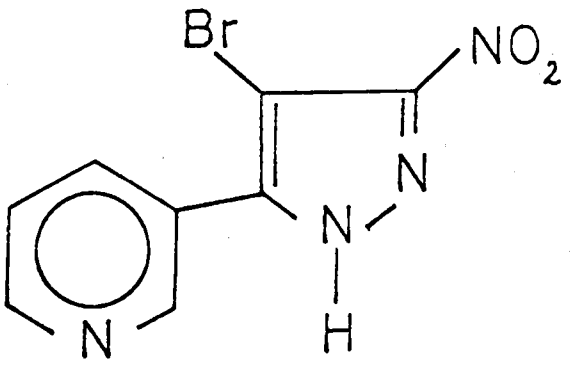
Fig. 28 Mass Spectrum of 3-Nitro-5-(3-pyridyl)pyrazole (15)

4-nitro-5-(3-pyridyl)pyrazole and a bromo derivative as 3-bromo-4-nitro-5-(3-pyridyl)pyrazole. Lund[65] later suggested the structure may be 3-nitro-5-(3-pyridyl)pyrazole and this was proved by Clemo and Holmes[66] when they prepared 3-amino-5-(3-pyridyl)pyrazole from the known 5-(3-pyridyl)pyrazole-3-carboxylate and showed it to be identical with the amino compound produced by reduction of the nitro pyrazole obtained from nicotine.

3-Nitro-5-(3-pyridyl)pyrazole and the 4-bromo derivative (to which structures (15) and (61) have been given[66]) were prepared and subjected to spectral analysis.



(15)



(61)

The n.m.r. spectrum of (15) (Fig. 27) shows signals expected for the 3-pyridyl group. The 4 proton appears as two quartets and not two triplets as usually observed for nicotine derivatives, showing a substantial difference in electronic environment for the 2- and 6-protons; the former being at unusually low field (τ 0.91). The olefinic proton appears as a singlet at τ 2.38, solvent exchange $[(CD_3)_2SO]$ rendering the N-H proton unobserved.

The mass spectrum (Fig. 28) shows the molecular ion at m/e 190 (100%), a peak at m/e 160 probably indicates loss of •NO, the nitro group isomerizing to nitrite before fragmentation.

The i.r. spectrum (recorded in nujol) shows a (very sharp) N-H stretch at 3122 cm^{-1}, indicative of hydrogen bonding and structure (62).

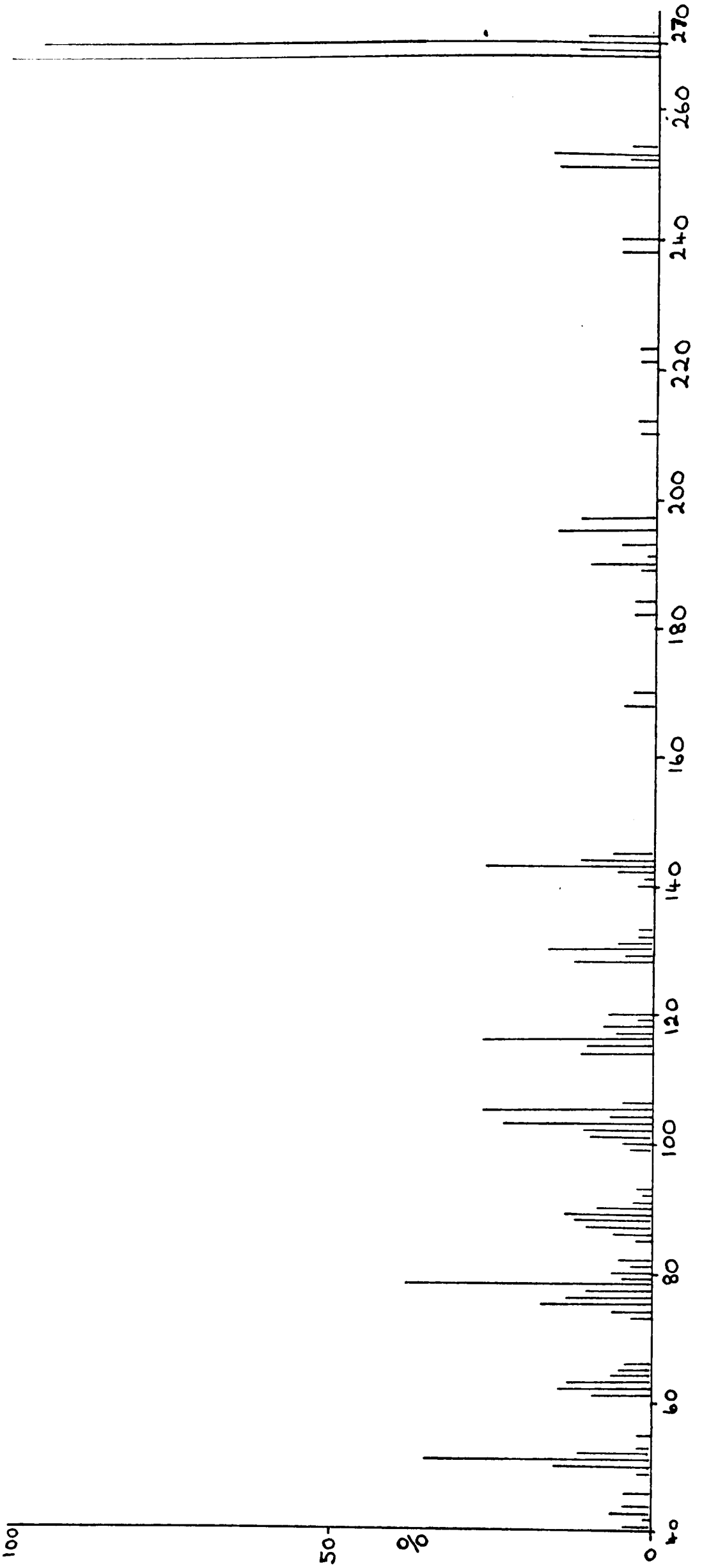
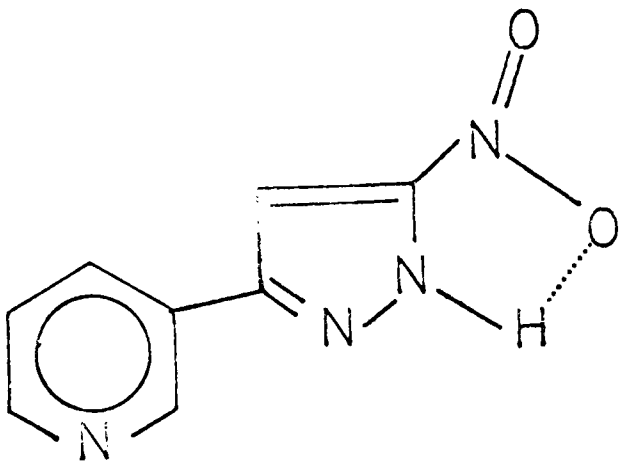


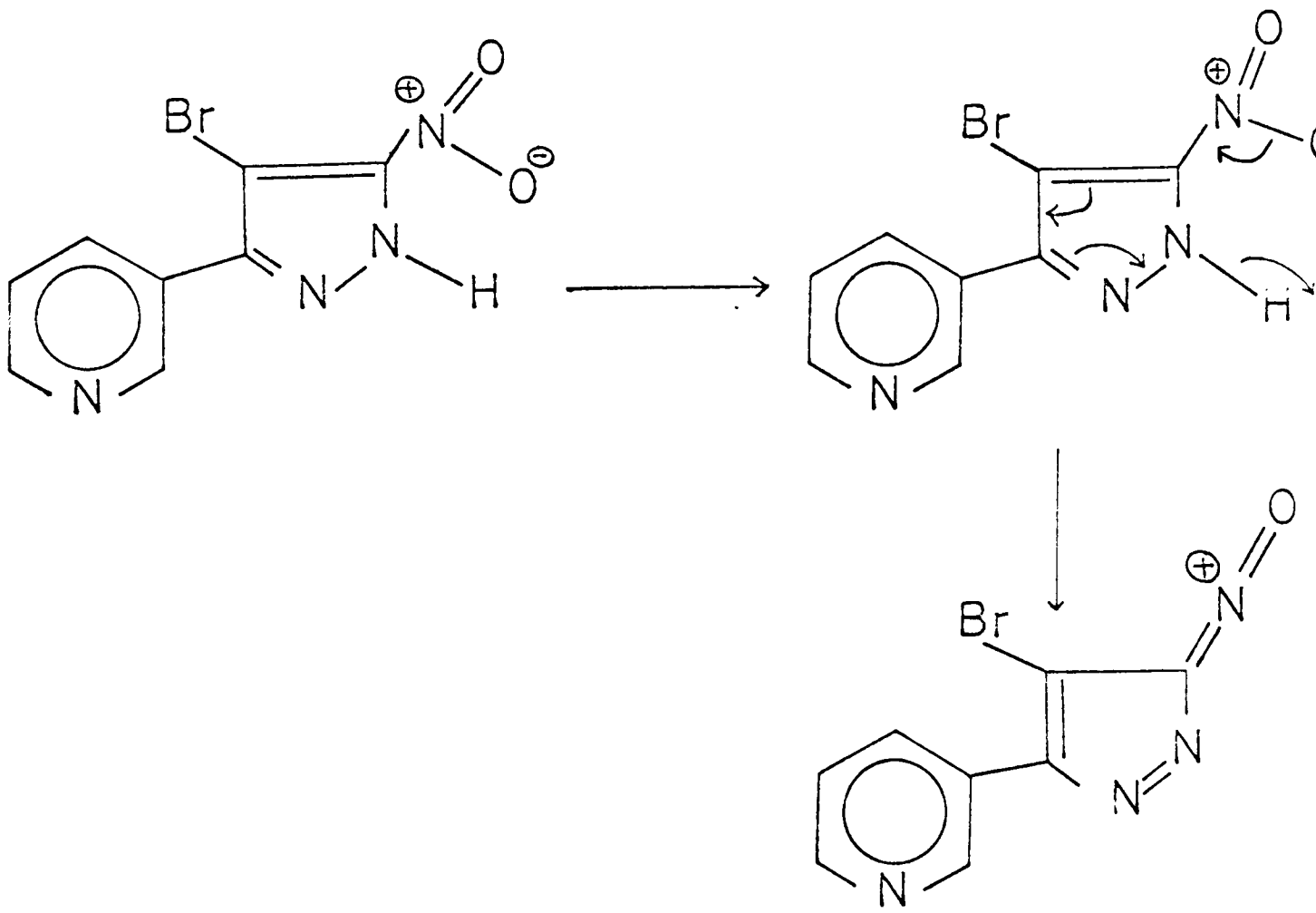
Fig. 29 Mass Spectrum of 4-Bromo-3-nitro-5-(3-pyridyl)pyrazole (61)



(62)

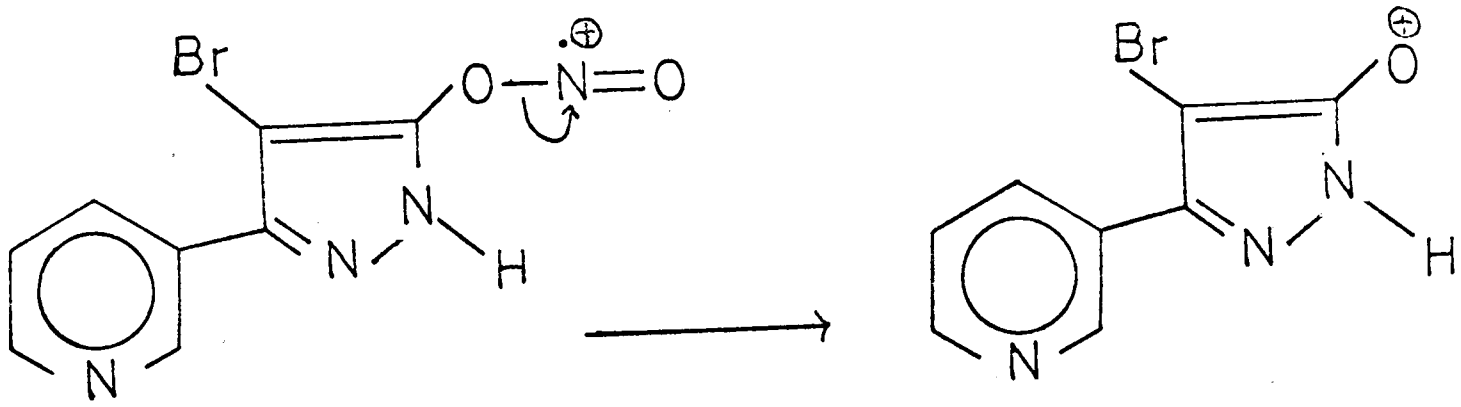
Bromocompound (**61**) shows a (broad) N–H stretching absorption at higher wavenumber (3543 cm^{-1}) indicating no hydrogen bonding. Quite probably the nitro group is being forced out of the pyrazole ring plane by the adjacent bulky bromine atom, thus preventing formation of a hydrogen bond.

The mass spectrum (Fig. 29) gives the molecular ion as base peak at m/e 270, 268. Loss of 17 mass units from the molecular ion, can be assigned to loss of a hydroxyl radical, the scheme below offers a possible explanation.



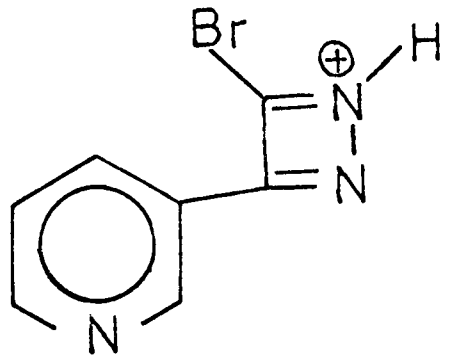
Loss of 30 mass units from the molecular ion is also observed and can

be rationalised as nitro-nitrite isomerization followed by loss of •NO.



m/e 240, 238

Further loss of 28 mass units is probably due to loss of carbon monoxide with subsequent ring contraction giving (j).



(j)

Dithiodinicotyrine

In 1880 Cahours and Etard[69] obtained a yellow solid from nicotine and sulphur which they called thiotetrapyridine. Later Morton and Horvitz[97] obtained the same compound by refluxing nicotine and sulphur in toluene, which they renamed thiodinicotyrine but gave no structure. Obtaining the molecular weight as 303 and 314 by boiling point elevations in benzene they suggested the molecule contained one atom of sulphur and two substituted nicotyrine units (MW 346).

Repetition of the literature method[97] gave a compound of identical

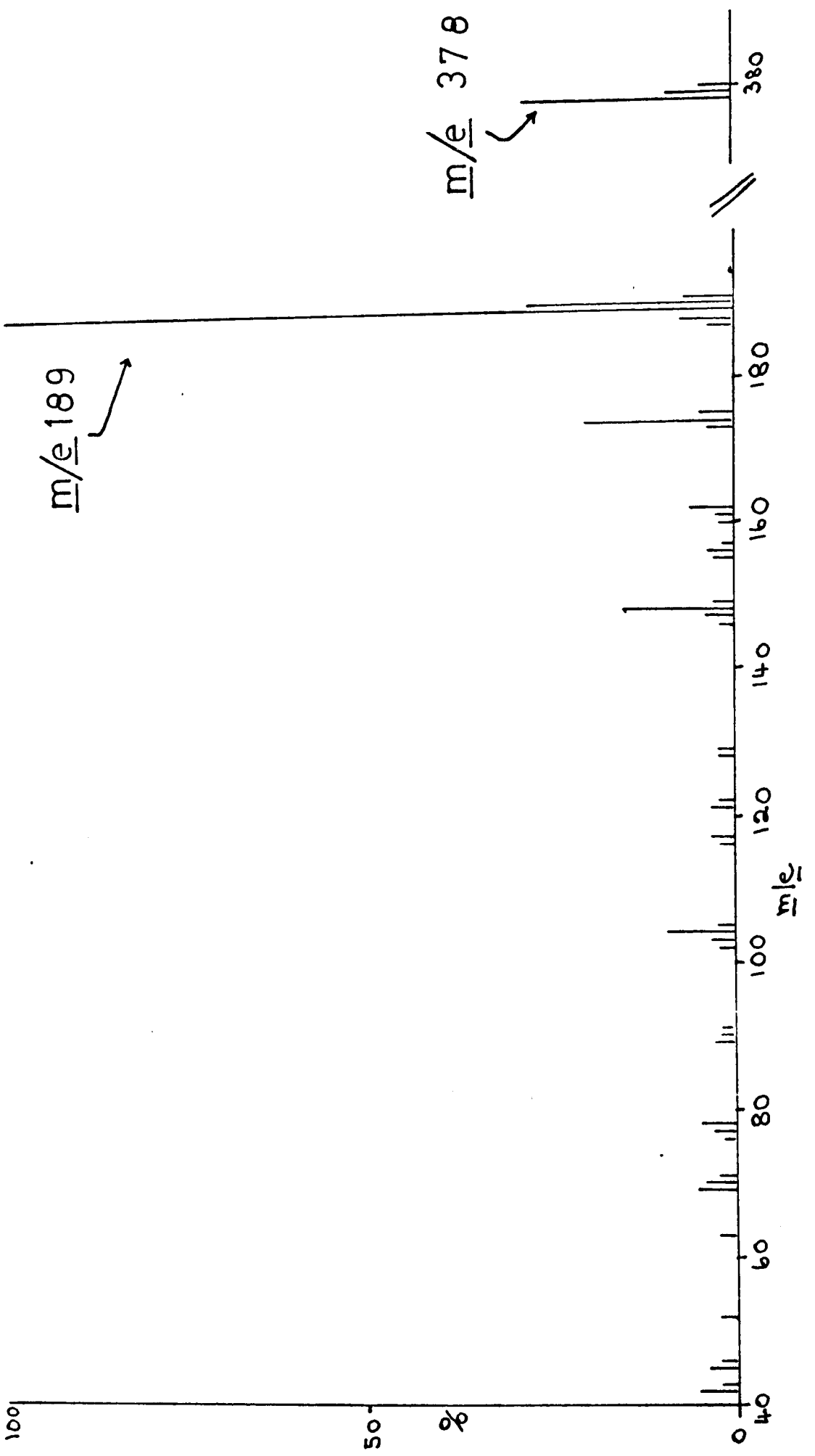


Fig. 30 Mass Spectrum of Dithiodinicotyrine (24)

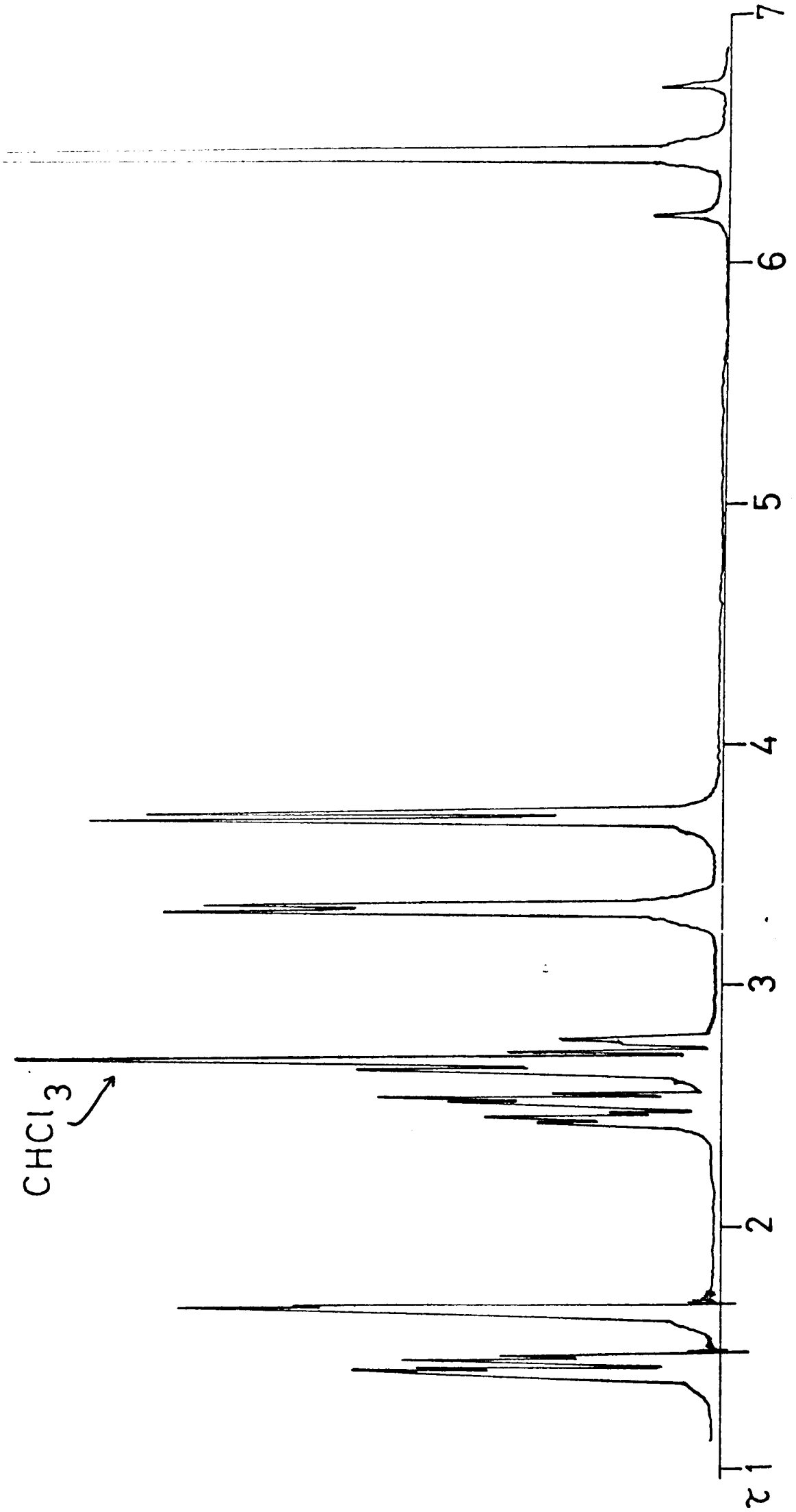


Fig.31 N.m.r. Spectrum of Dithiodinicotyrine (24) 100MHz.

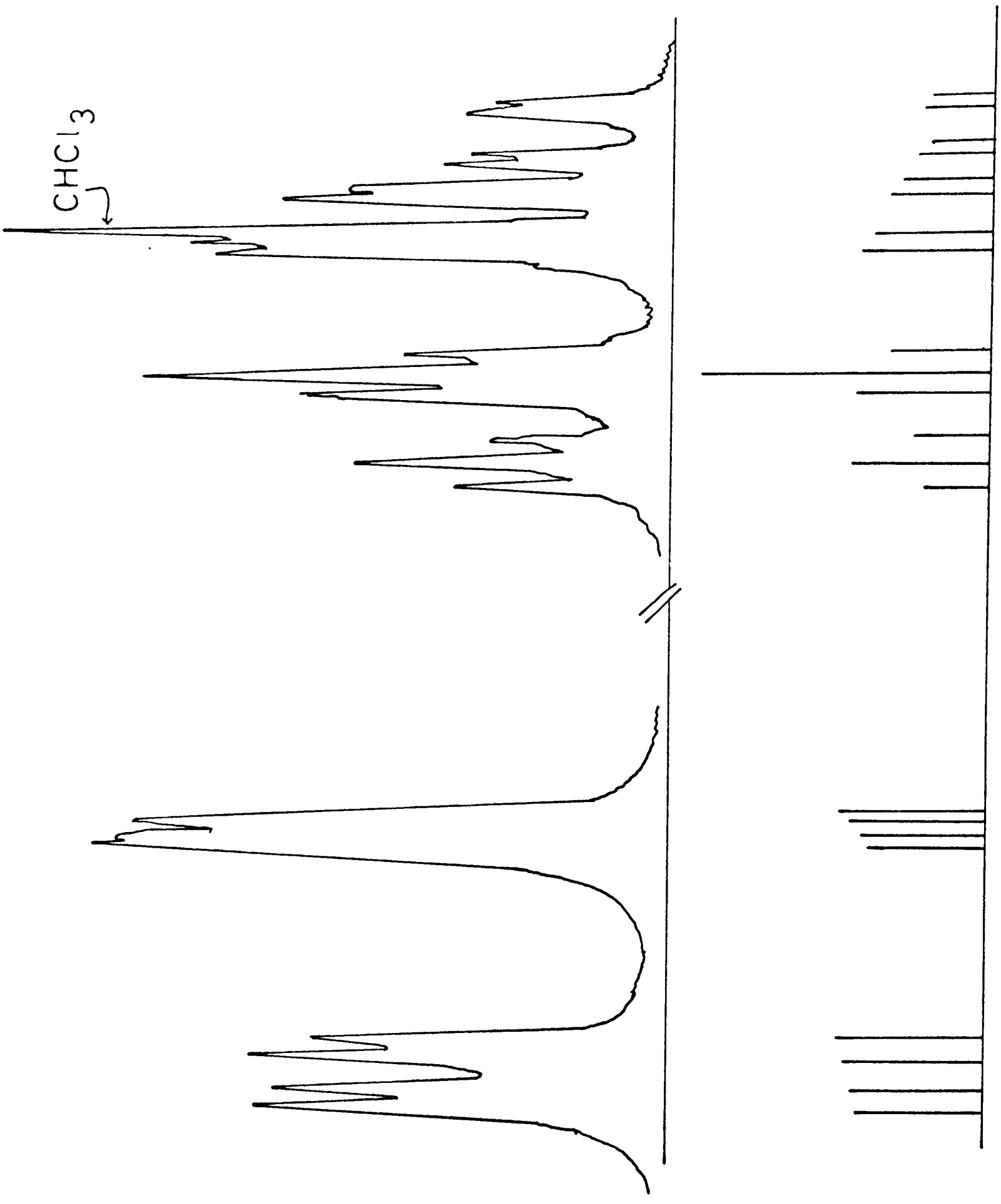


Fig. 31a Experimental (upper) and Computed n.m.r. Spectrum of the aromatic region of Dithiodinicotyrine (24)

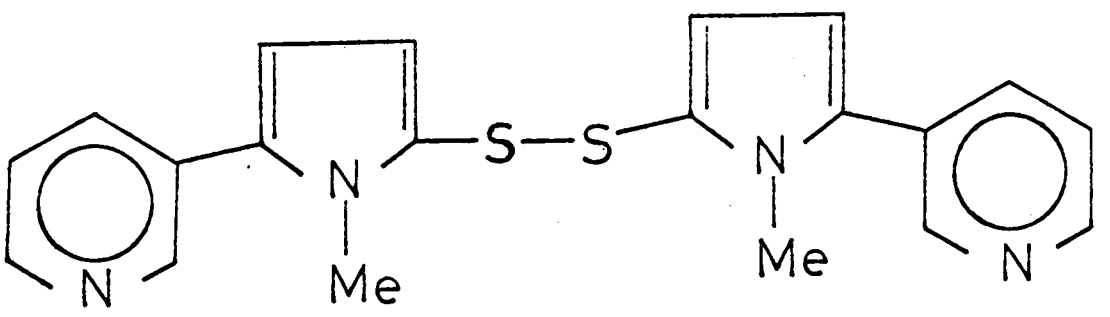
melting point. Analysis showed two atoms of sulphur and two substituted nicotyrine units giving a molecular weight of 378. Mass spectrometry gave a molecular ion at m/e 378 (28%) (Fig. 30). The base peak at m/e 189 almost certainly arising by cleavage of the sulphur—sulphur bond.

The n.m.r. spectrum (Fig. 31) shows the resonances expected for a 3 substituted pyridine ring, a computer simulation of which was successful (Fig. 31 and n.m.r. table). Two doublets at τ3.32 and τ3.68 ($\underline{J}$ 3 Hz) being assignable to the 3' and 4'-protons of a nicotyrine unit. The only other peak (τ 6.43) corresponds to an N-methyl group.

The n.m.r. spectrum of nicotyrine shows a singlet at τ3.35 (1H) and a multiplet at τ3.85 (2H), being assigned to the 3'H and superimposed 4'-H and 5'-H.

Desulphurization with Raney nickel gave nicotyrine in good yield confirming the integrity of the nicotyrine unit.

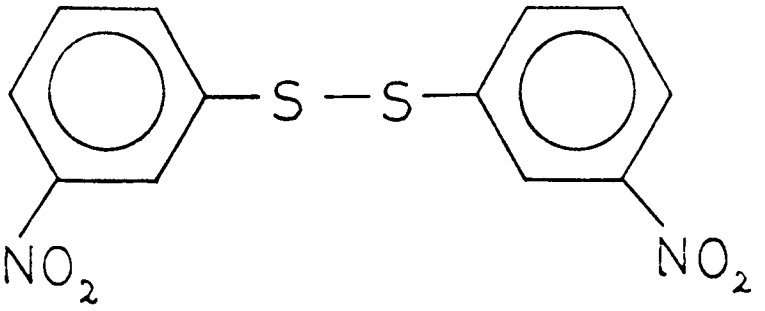
Thus the structure below is proposed.



(24)

Reduction of (24) with zinc and acetic acid gave only tars.

Disulphide (24) was submitted for testing as a number of important active compounds contain disulphide linkages, thus nitrophenide is an anticoccidal.[219]

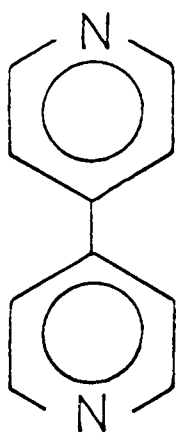


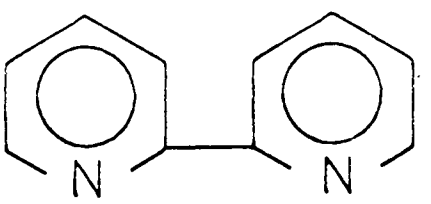
nitrophenide

Selenium would not couple with or dehydrogenate nicotine, even under forcing conditions.

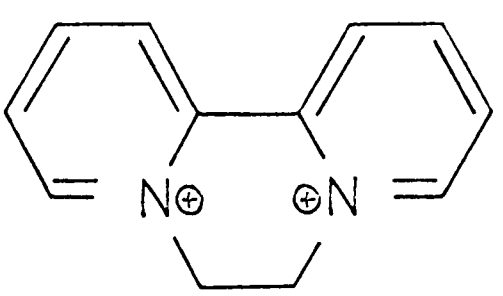
Nicotine with sodium

Pyridine when treated with sodium sand and the product added to water in air, couples to give bipyridyls.[185]

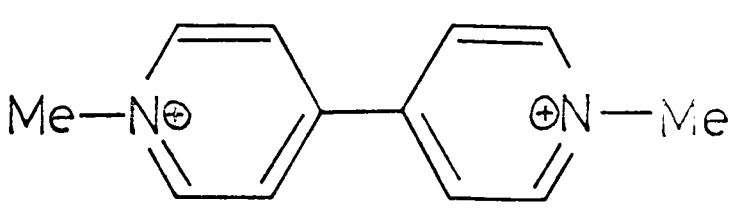




A number of dipyridyl ammonium salts are used as systemic herbicides,[219,220] e.g.



diquat



paraquat

Nicotine and sodium under identical conditions gave some tar along with recovered nicotine, no coupling products being obtained.

N-Bromosuccinimide

Nicotine and N-bromosuccinimide in carbon tetrachloride gave red gums. It was hoped to exchange the 2'-hydrogen for bromine by this procedure as methyl hydrogen atoms in 3-picoline are known to be acidic.[141] These findings are in agreement with Waters[186] who obtained red gums from N-bromosuccinimide and N-methylpiperidine and which he believed to be perbromides.

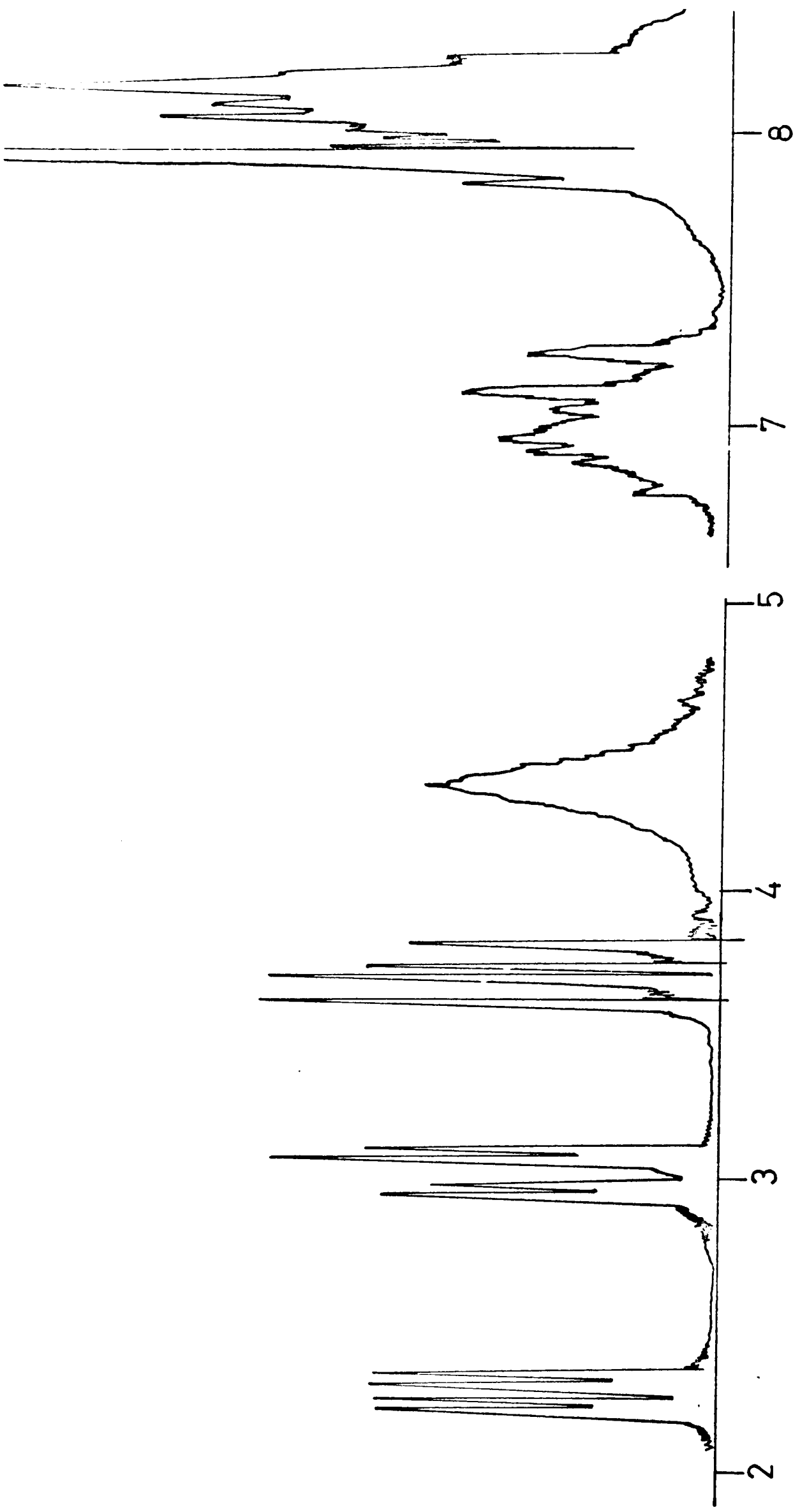


Fig. 32 N.m.r. Spectrum of 2-Aminonicotine (18)

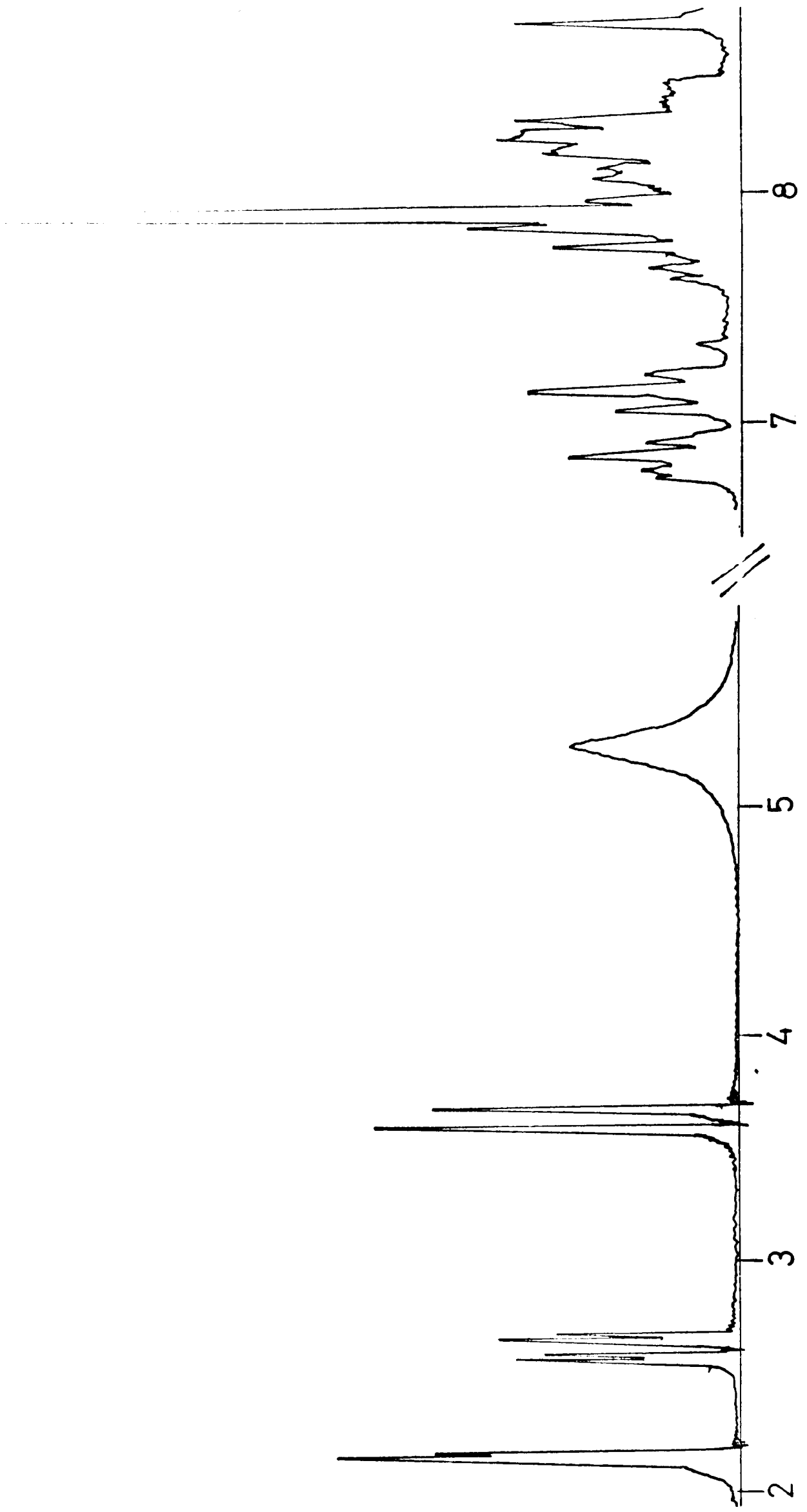
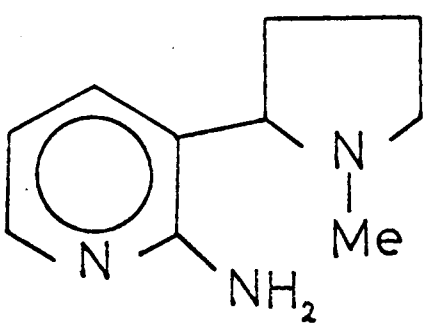


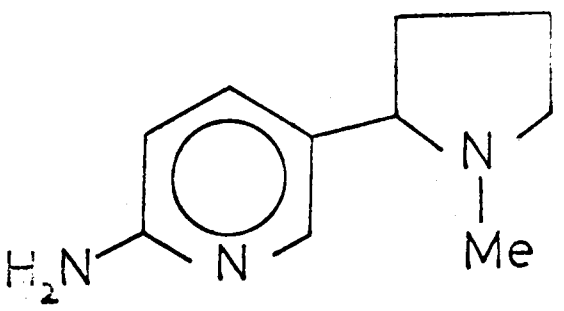
Fig. 33 N.m.r. Spectrum of 6-Aminonicotine (19)

Section 3. Some Reactions of 2- and 6-Aminonicotine

In 1924 Tschitschibabin[87] reacted nicotine with sodamide and obtained two isomeric aminonicotines to which he gave structures (18) and (19), the former being insoluble in water and readily separable from the latter.



(18)



(19)

N.m.r. and mass spectral data for (18) and (19), prepared according to Tschitschibabin,[87] confirm the structures.

The n.m.r. spectrum of (18) (Fig. 32) shows the 6-proton as a quartet (J 5 Hz and 2 Hz) at τ 2.16. The 5-proton is a quartet at τ 3.63 (J 7.5 Hz and 5 Hz) and the 4-proton a quartet at τ 2.93 (J 7.5 Hz and 2 Hz).

The N-H absorption is at τ 4.29. The multiplet centred at τ 6.97 is almost certainly due to the 2'- and one of the 5'-protons, as observed in nicotine.

The n.m.r. spectrum of (19) (Fig. 33) shows the 2-proton as a doublet at τ 2.12, the 4-proton as a quartet at τ 2.60 and the 5-proton as a doublet at τ 3.60 (there is no observed splitting between the 2- and 5-protons). The N-H absorption is at τ 5.26. The multiplet observed at τ 6.97 in the n.m.r. spectrum of (18) now appears as two triplets, centred at τ 6.97, in all probability this line shape is fortuitous.

The mass spectrum of (19) (Fig. 34) is very similar to that of nicotine as would be expected since aromatic amino-groups are quite stable to

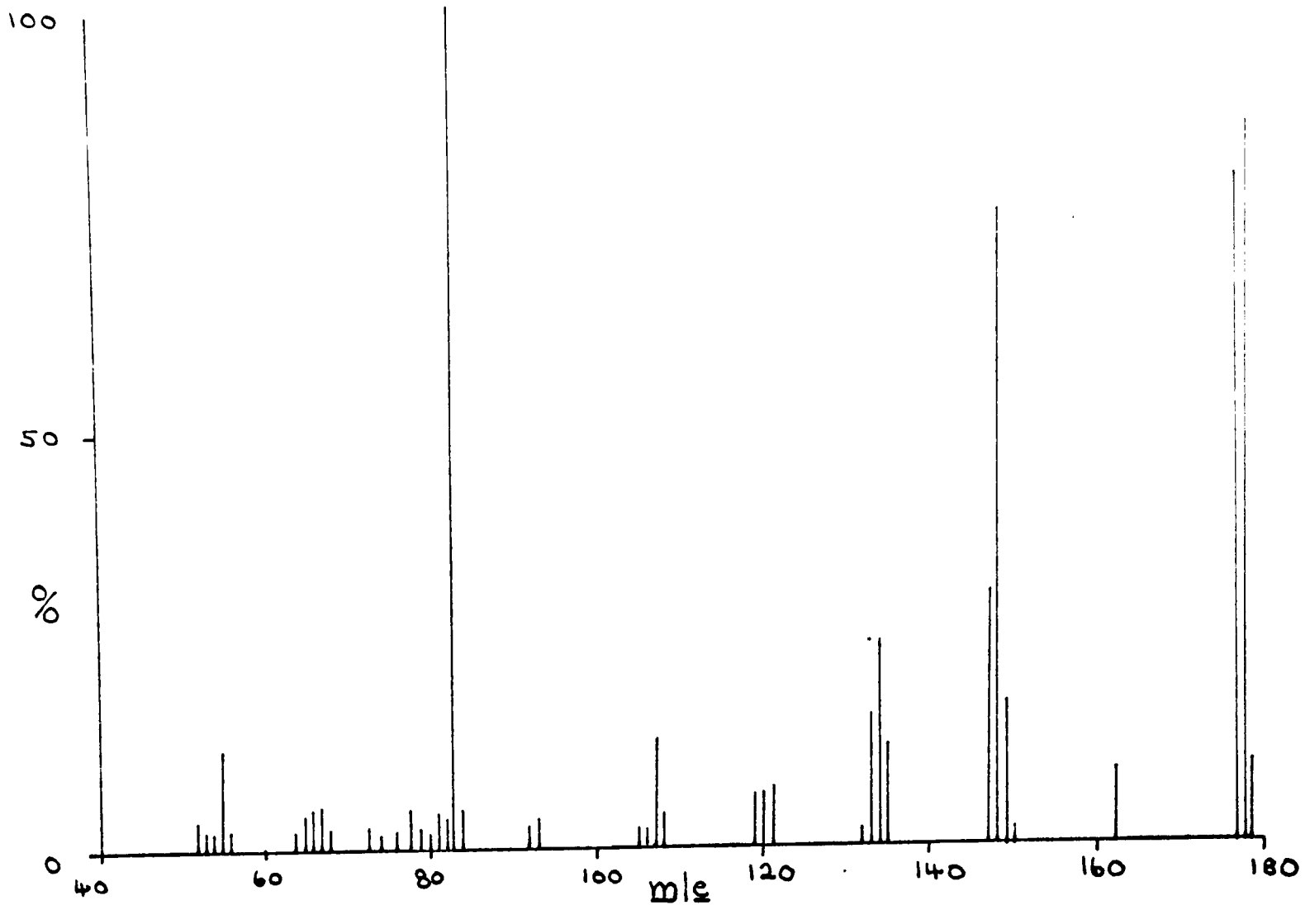


Fig. 34 Mass Spectrum of 6-Aminonicotine (19)

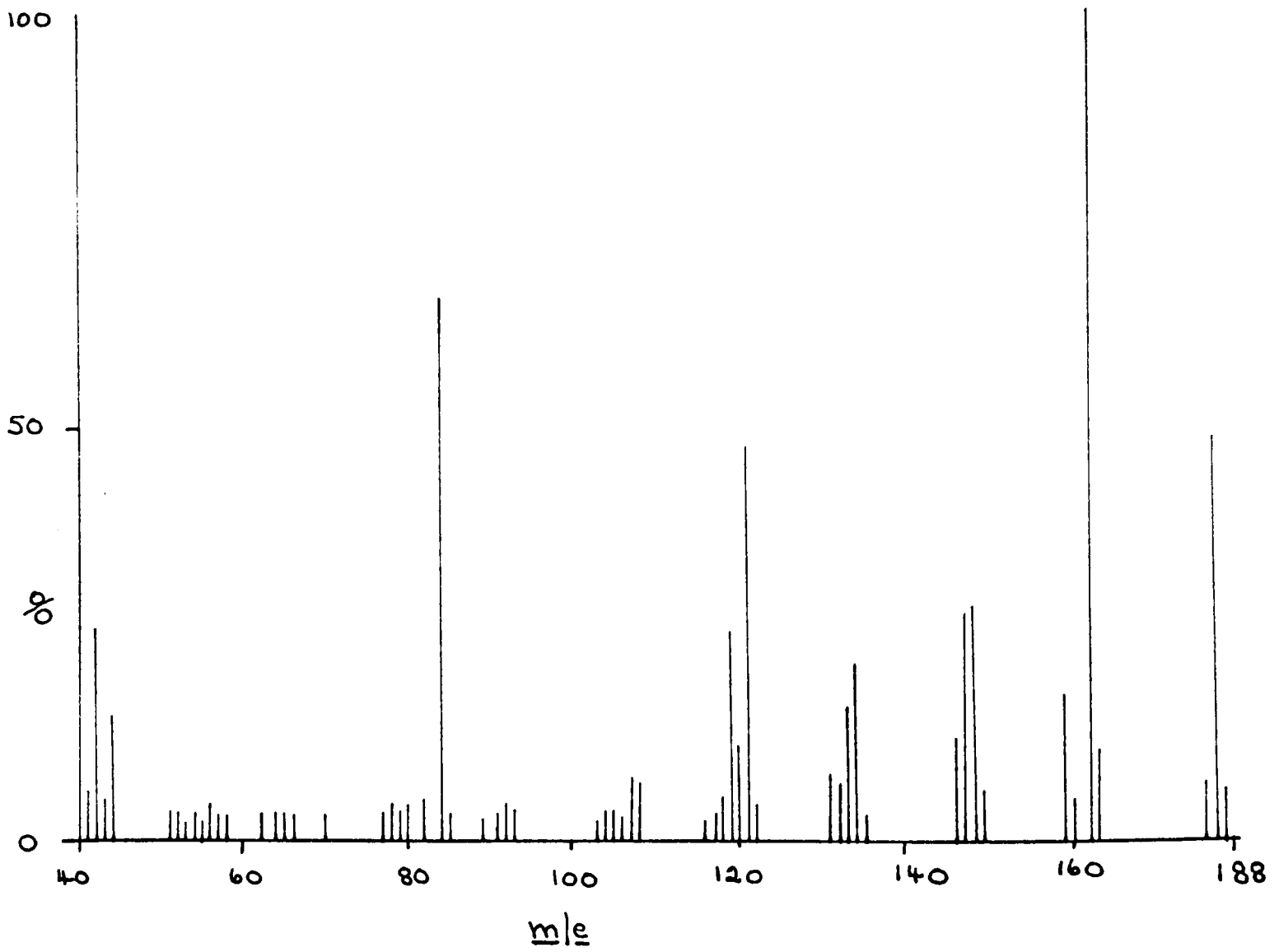
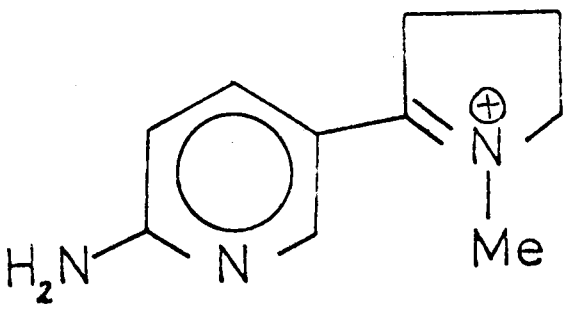
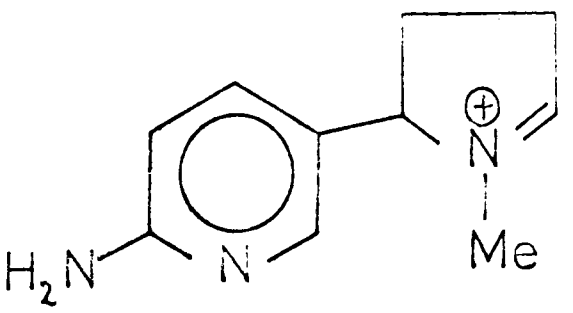


Fig. 35 Mass Spectrum of 2-Aminonicotine (18)

fragmentation. The molecular ion loses a hydrogen radical to give either

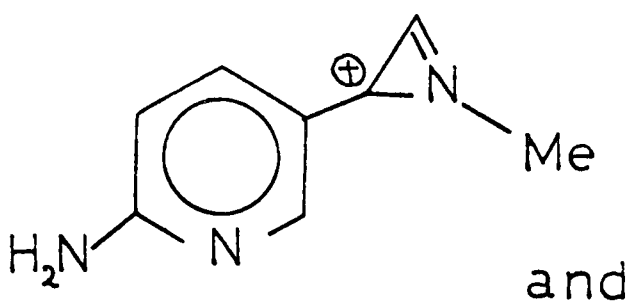


or

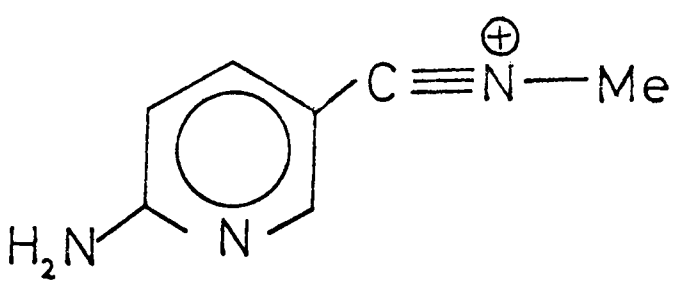


m/e 176 (79%)

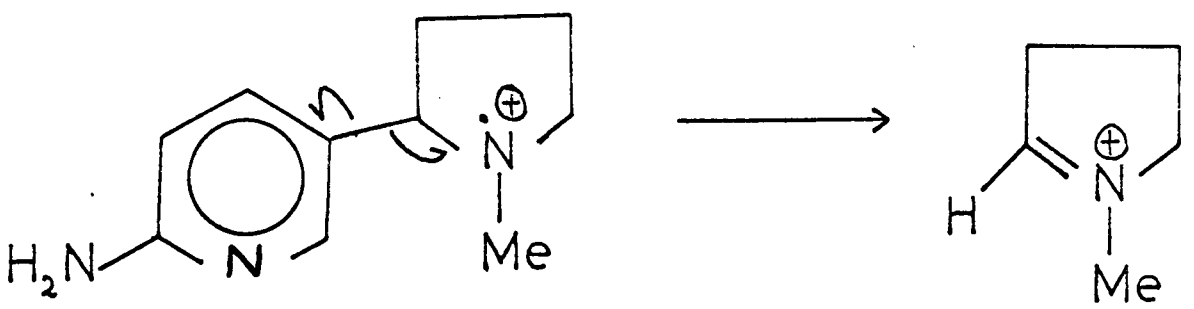
Peaks at m/e 148 (75%) and m/e 134 (24%) arise from



and



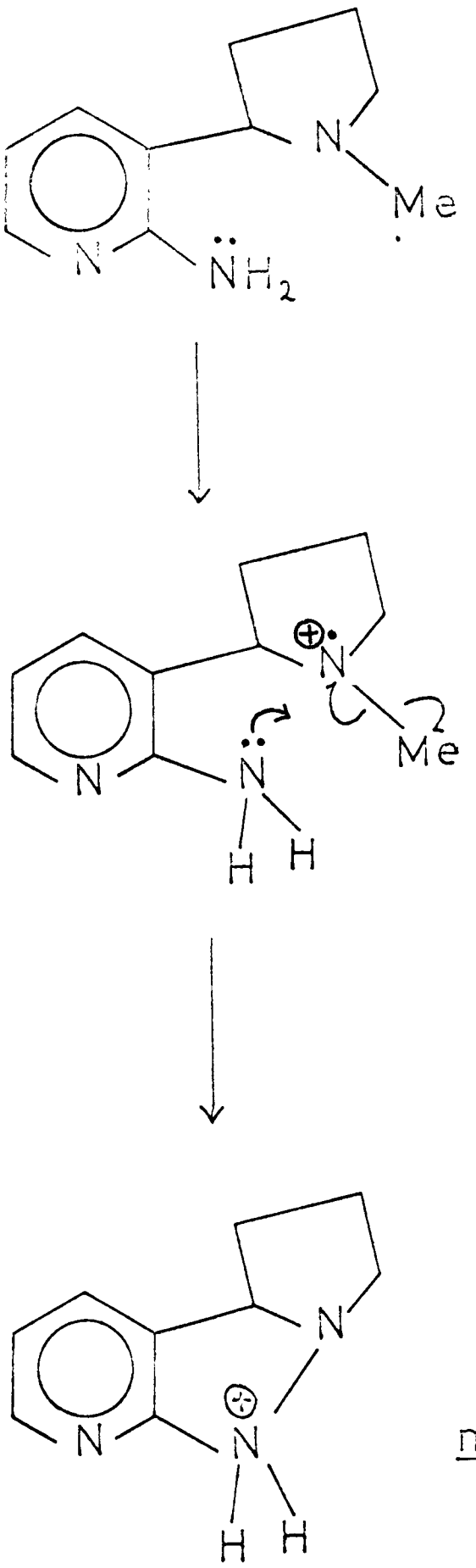
A second decomposition pathway giving the base peak at m/e 84 arises by fission of the 3-2' bond, as is observed in the mass spectrum of nicotine.



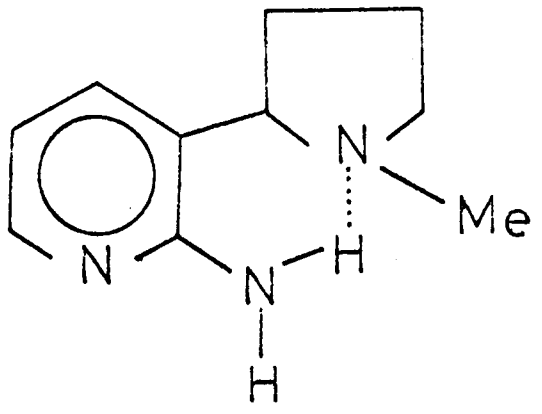
The mass spectrum of (18) (Fig. 35) shows along with the fragmentation pathways observed for (19) a peak at m/e 162, which arises by loss of a methyl radical from the molecular ion. A possible pathway involves participation by the non-bonded electrons of the amino group and is shown in Scheme 8.

The i.r. spectrum of (18) in carbon tetrachloride shows a sharp band at 3492 cm^{-1} and a broad band at 3408 cm^{-1}, broadening probably being caused by hydrogen bonding between the amino hydrogen and the pyrrolidine nitrogen.

Scheme 8



m/e 162



The i.r. spectrum of (19) shows two sharp N-H stretching absorptions at 3508 and 3420 cm^{-1} in agreement with the i.r. spectrum of 2-aminopyridine[188] (3509 and 3411 cm^{-1}).

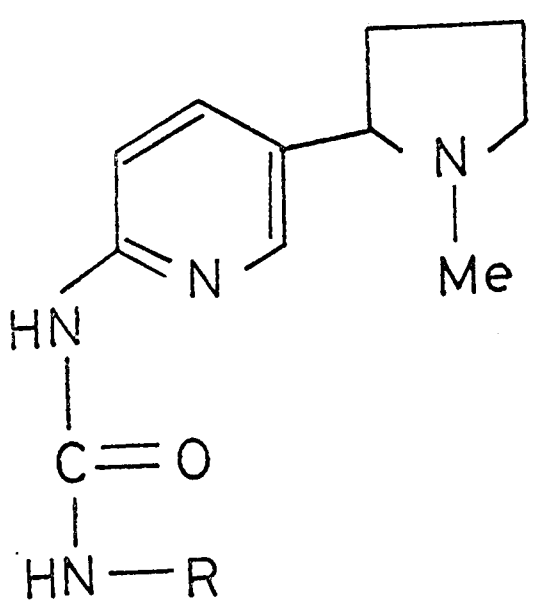
The hydrochloride salt obtained from 6-aminonicotine had identical melting point to that obtained by Tschitschibabin,[87] but, whereas Tschitschibabin reports the salt to be a dihydrochloride, rigorous elemental analysis shows it to be $C_{10}H_{15}N_3$. 2 HCl. $1\frac{1}{2}$ H_2O. The salt only crystallized from ethanol if water was present, use of anhydrous ethanol as recommended by Tschitschibabin gave no precipitate. The preparation of 6-aminonicotine, uncontaminated with 2-aminonicotine, has been reported[88] by heating nicotine and sodamide in an autoclave. Repetition gave a low yield of an approximately equally proportioned mixture of (18), (19) and unreacted nicotine. The method offered no preparative advantages over that of Tschitschibabin and was not further investigated.

Ureas and Thioureas

A number of ureas and thioureas were prepared from (18) and (19) as biological activity is often associated with this type of structure.[219,221]

Some ureas havediuretic properties and cause reduction of intracranial and intraocular pressure. Many ureas are weak hypnotics but can be useful as sedatives e.g. carbomal

$$Et_2 \quad \begin{matrix} C \\ | \\ Br \end{matrix} — CONHCONH_2$$

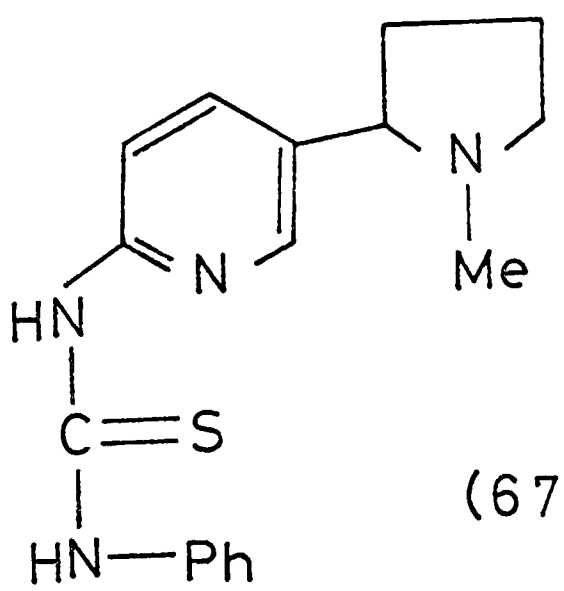


(63) R= Ph

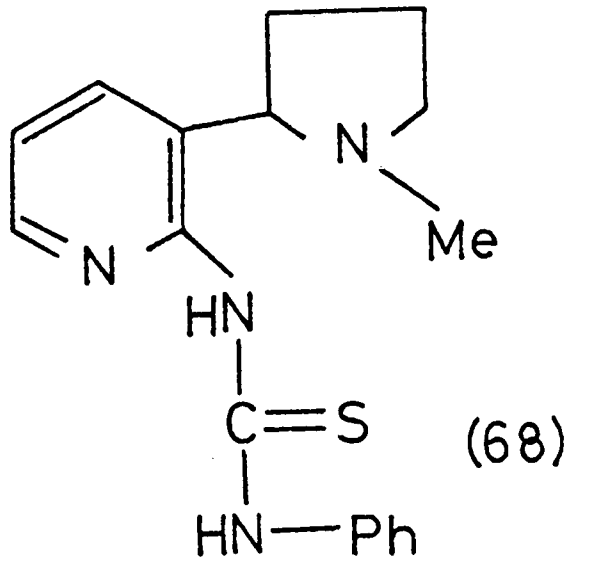
(64) R= o-chlorophenyl

(65) R=m-chlorophenyl

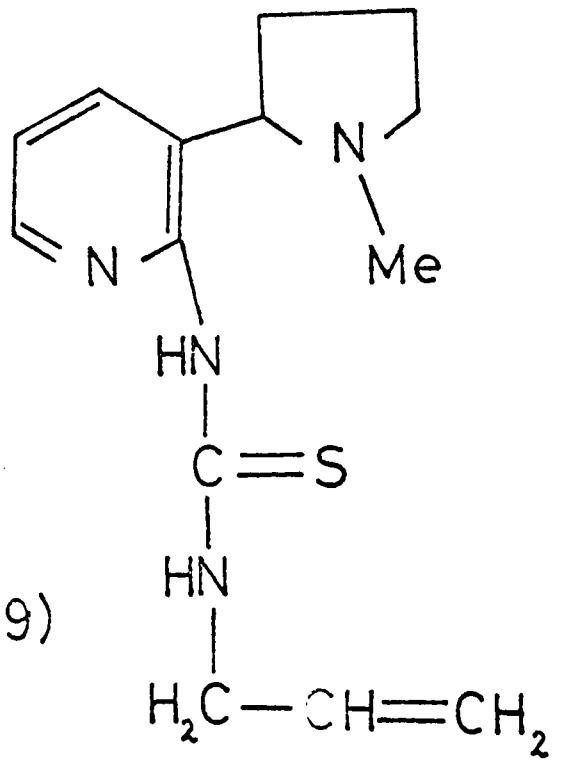
(66) R=p-chlorophenyl



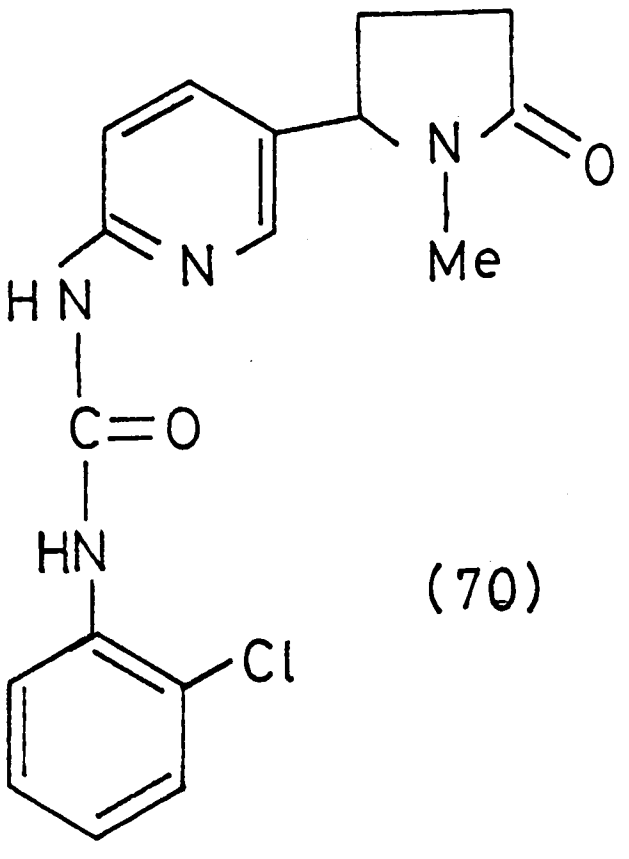
(67)



(68)



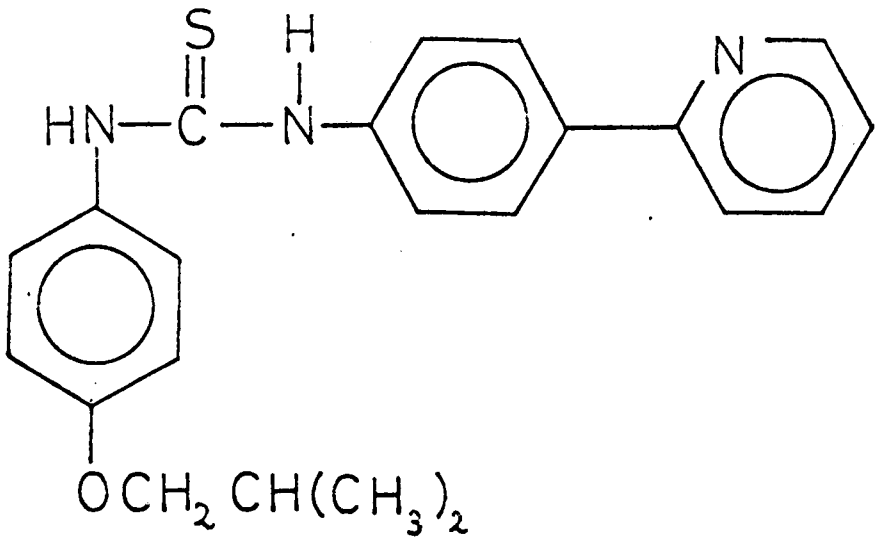
(69)



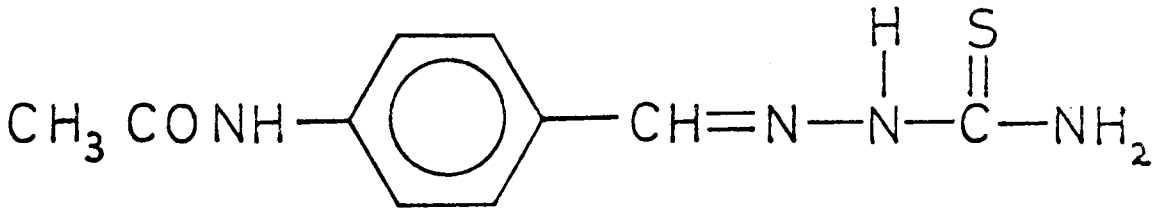
(70)

Thioureas are used in hyperthyroidism, congestive heart failure and in healing ulcers.

Thiocarbamidin is used in treating tuberculosis.[219]



A number of thiosemicarbazones have anti-viral properties,[219] e.g. thiacetazone.



6-Aminonicotine gave the expected ureas with phenyl isocyanate, o-chlorophenyl, m-chlorophenyl and p-chlorophenyl isocyanate and the expected thiourea with phenyl isothiocyanate. Reaction with allyl isothiocyanate gave only tars. Conversely 2-aminonicotine and allyl isothiocyanate gave the corresponding thiourea, likewise with phenyl isothiocyanate. However 2-aminonicotine would not react with phenyl isocyanate, diphenyl urea being obtained.

All spectral data obtained for the ureas and thioureas were in full accord with the expected structures.

2- and 6-Aminocotinine

Oxidation of the pyrrolidine ring of 6-aminonicotine (19) and 2-aminonicotine (18) with bromine and acetic acid, under conditions similar to those used for

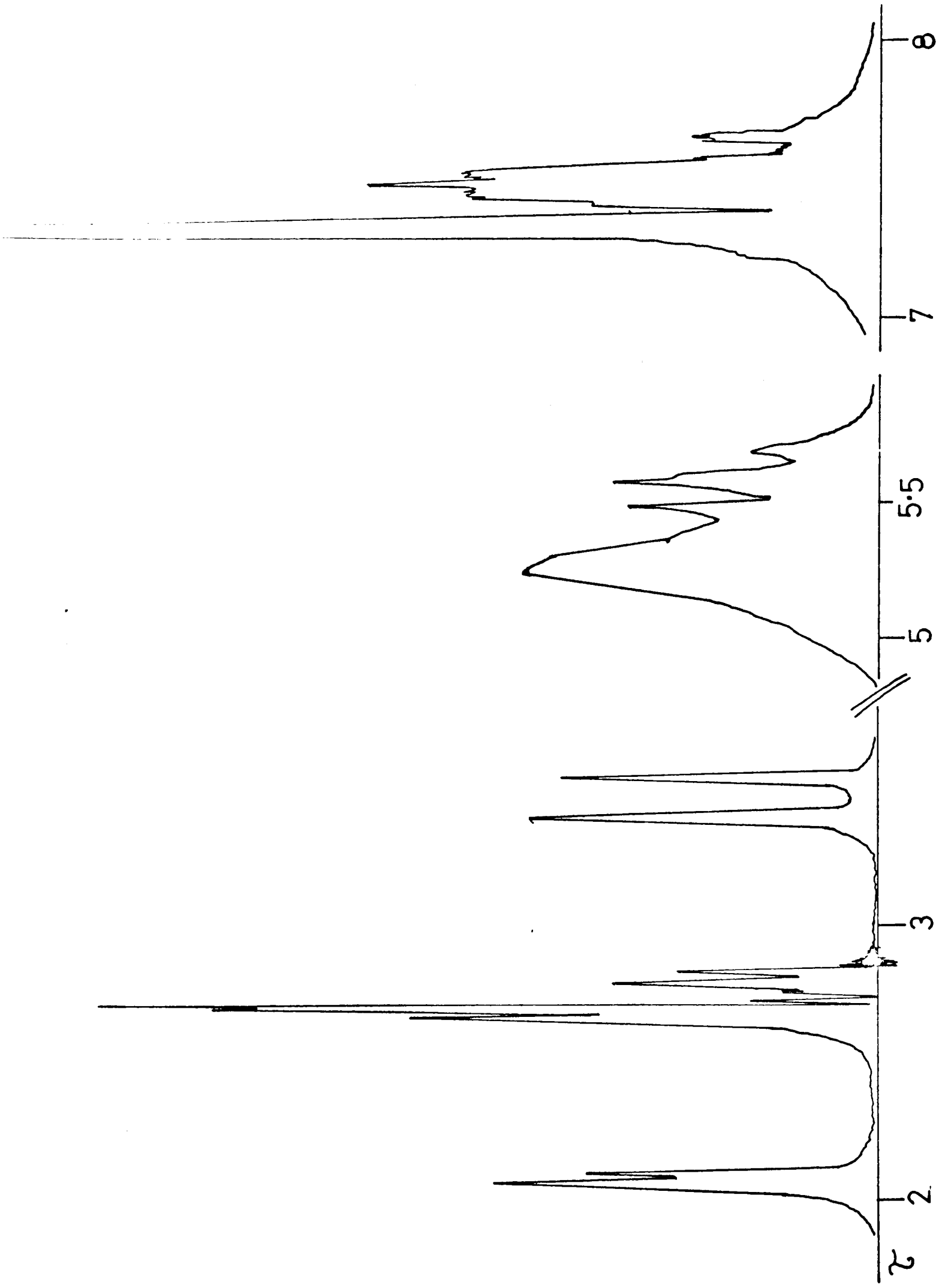


Fig. 36 N.m.r. Spectrum of 6-Aminocotinine (71)

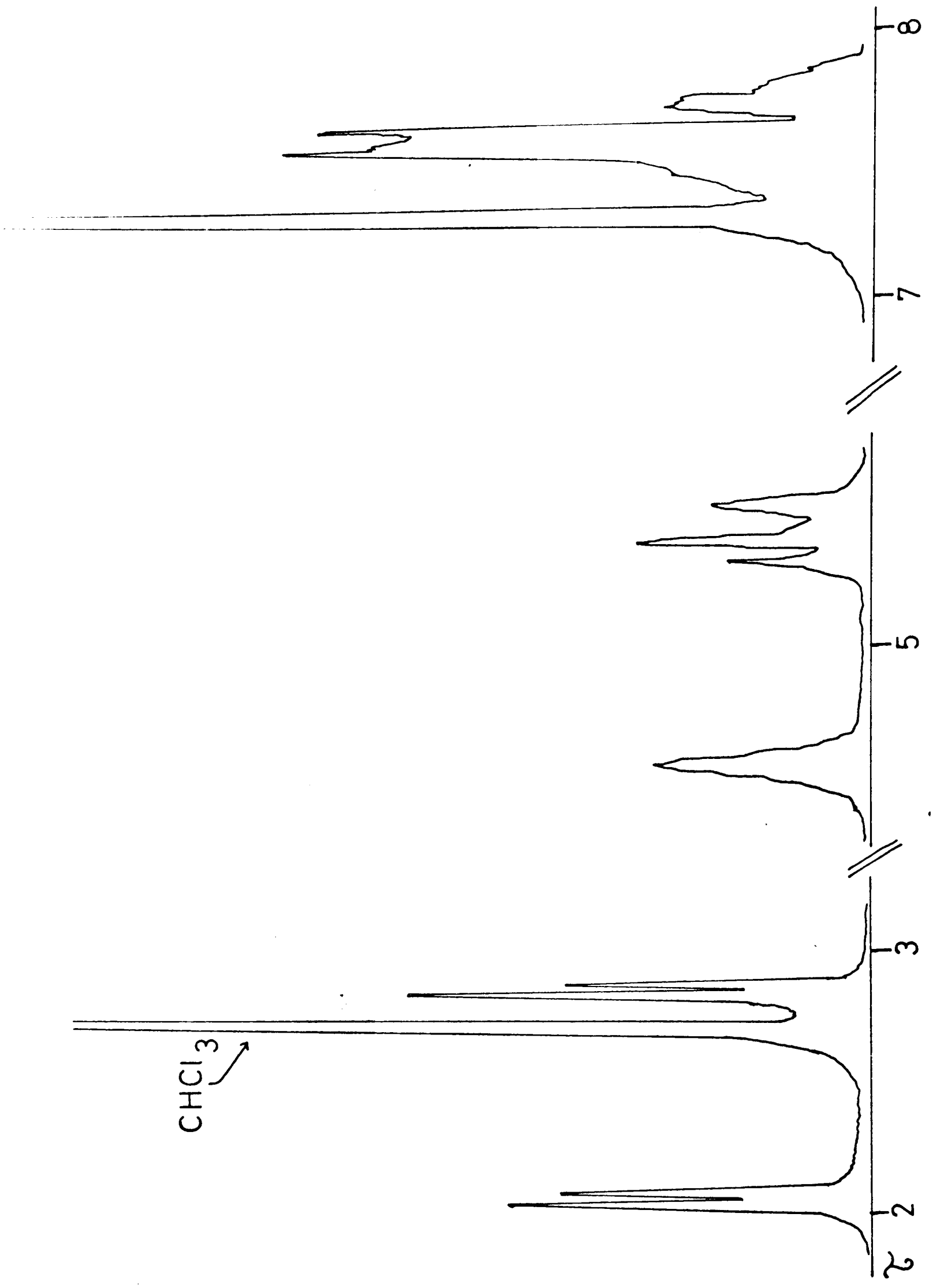


Fig. 37 N.m.r. Spectrum of 2-Amino-5-bromocotinine (72)

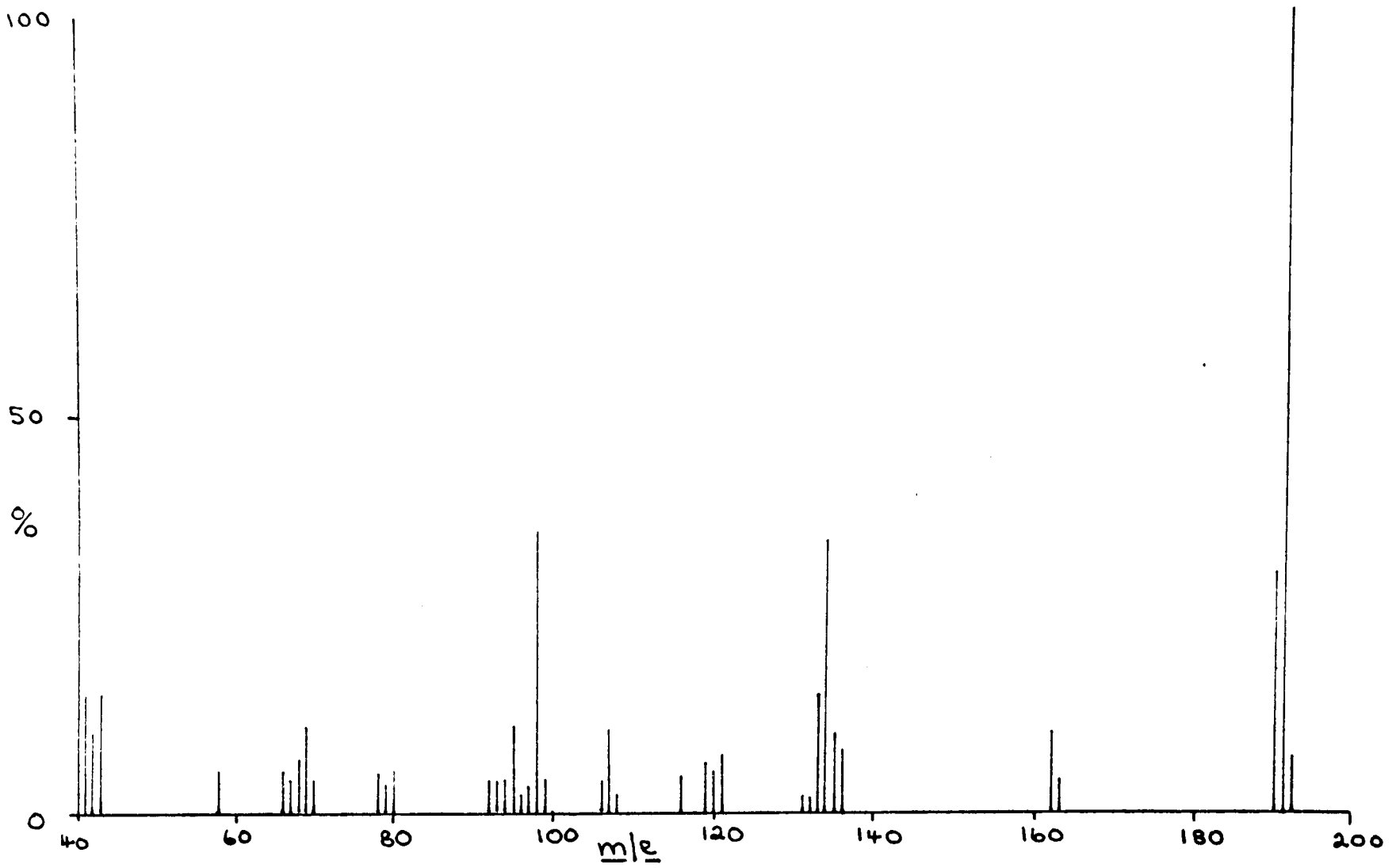
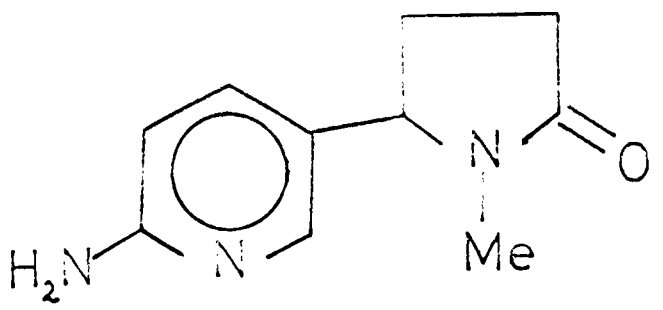
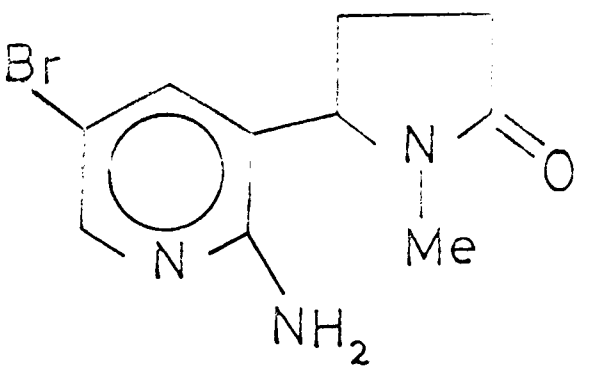


Fig. 38 Mass Spectrum of 6-Aminocotinine (71)

the oxidation of nicotine to cotinine gave lactams (71) and (72) respectively, in the latter case bromination para to the amino group having taken place.



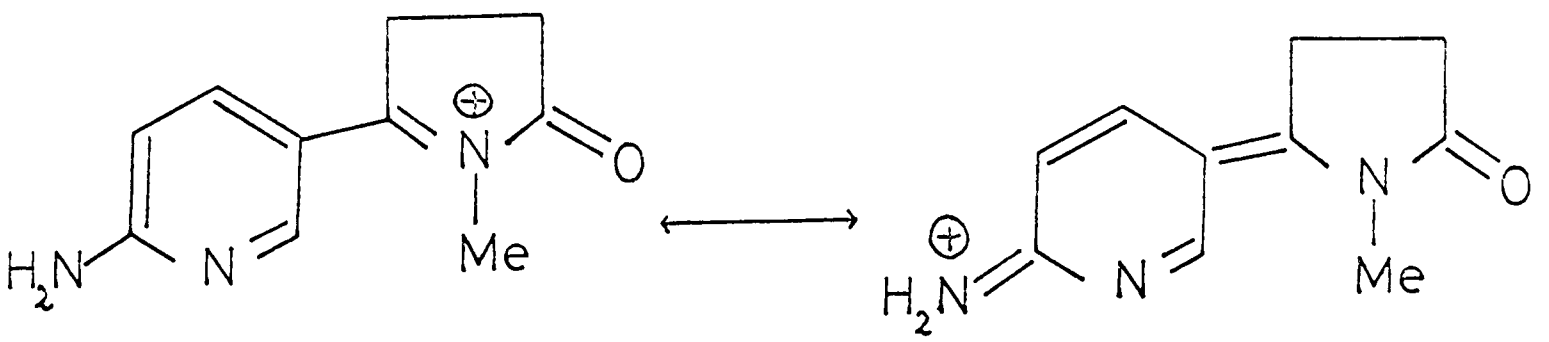
(71)



(72)

The n.m.r. spectrum of (71) (Fig. 36) is virtually identical to that for (19) (Fig. 34) in the aromatic region. A multiplet centred at τ 5.64 can be assigned to the 5'-proton.

The n.m.r. spectrum of (72) (Fig. 37) however shows only two aromatic signals, a doublet at τ 2.05 (J 2 Hz) for the 6-proton and a doublet at τ 2.85 (J 2 Hz) for the 4-proton. The 5'-proton multiplet is centred at τ 5.42. The mass spectrum of (71) (Fig. 38) shows the molecular ion as base peak at m/e 191. Loss of a hydrogen radical gives a peak at m/e 190 (30%) the resultant fragment most probably being (k).



(k)

Resonance stabilization of (k) as shown may explain why this fragment is much more significant than in the mass spectrum of cotinine (Fig. 9). Loss of 28 mass units from m/e 190 gives a peak at m/e 162 (10%) which then loses

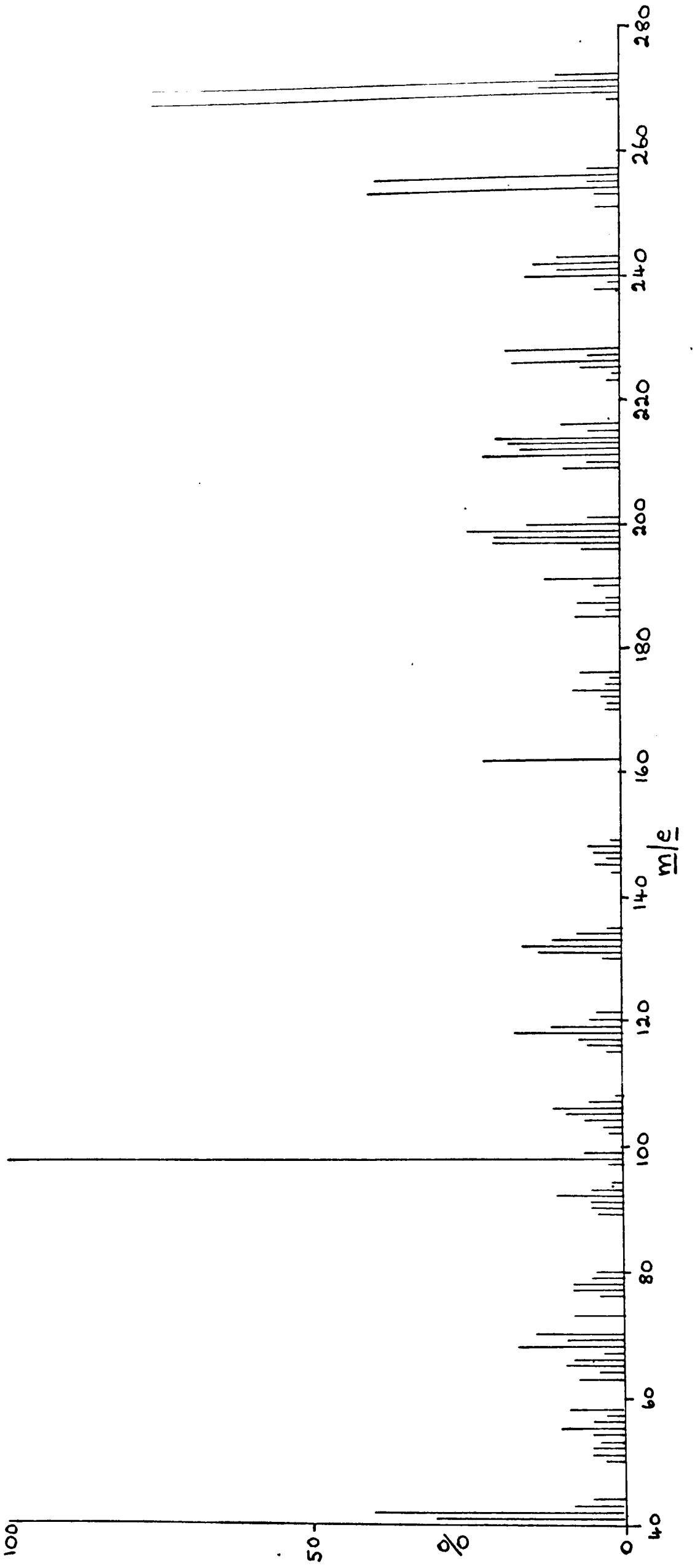
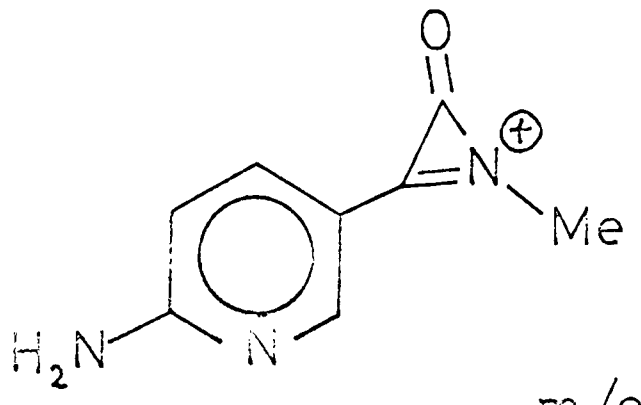
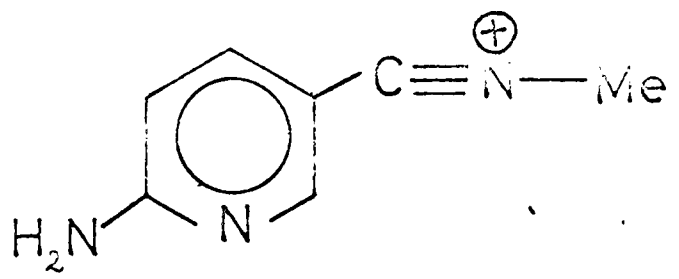


Fig. 39 Mass Spectrum of 2-Amino-5-bromocotinine (72)



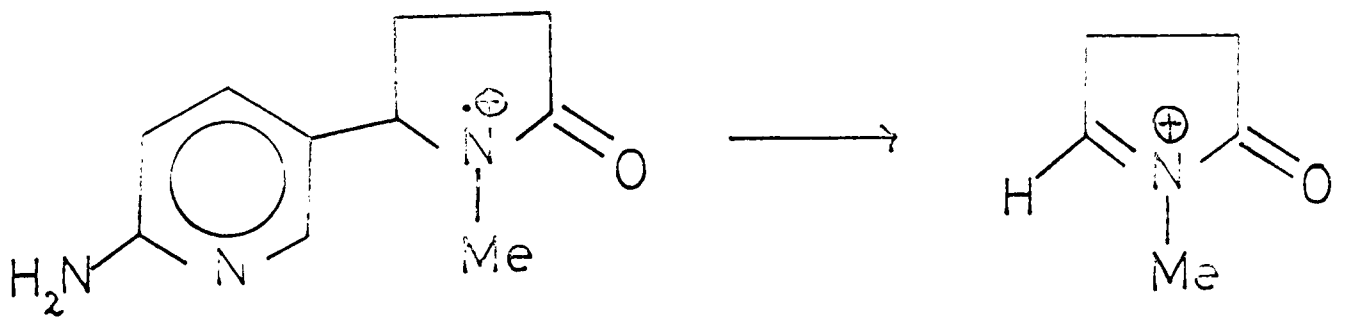
m/e 162

carbon monoxide to give



m/e 134 (34%)

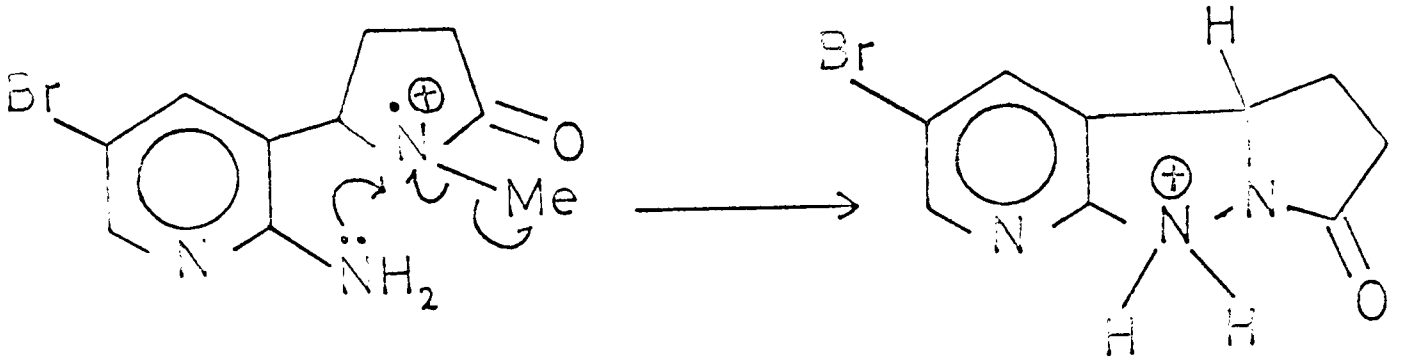
A peak at m/e 98 (the base peak for cotinine (8)) is only 35% and arises by expulsion of a 2-aminopyridyl radical.



For cotinine the expulsion of a 3-pyridyl radical is much more highly favoured than expulsion of a hydrogen radical, but for 6-aminocotinine each pathway is approximately equally favoured. Resonance stabilization in fragment (k) in all probability causing the observed difference.

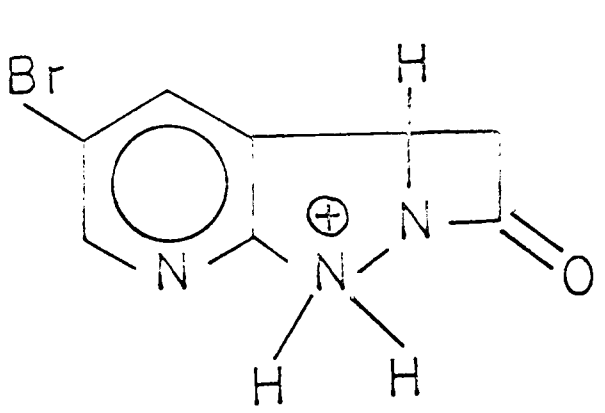
The mass spectrum of (72) (Fig. 39) shows a quite different fragmentation from that of (71). The first major loss is 15 mass units, the

non-bonded electrons of the amino group almost certainly participating in a manner similar to that proposed for 2-aminonicotine (Fig. 55).

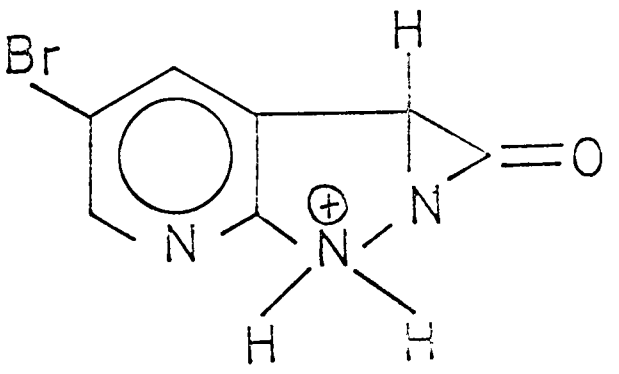


(1)

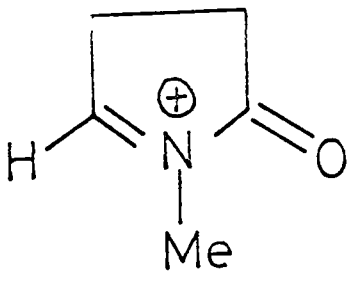
Peaks at m/e 242, 240 (14%) and m/e 228, 226 (17%) seem best explained by loss of CH_2 and $C_5H_4(CH_2 + CH_2)$ from (1) giving



and

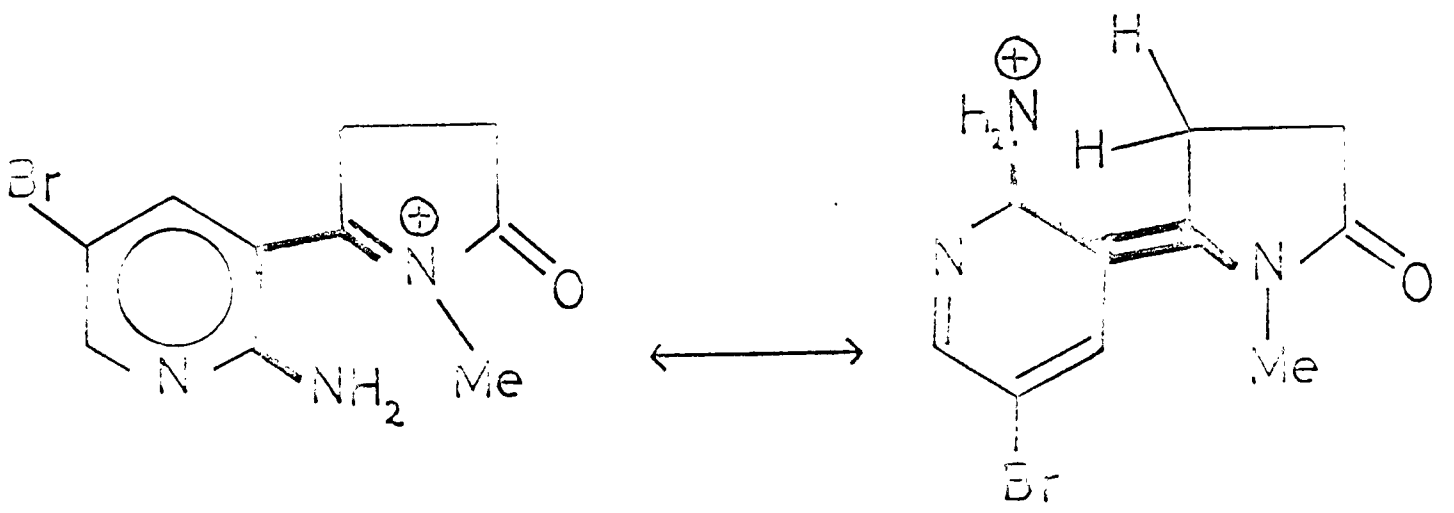


The base peak is at m/e 98 and corresponds to



as observed for cotinine. There is no peak corresponding to loss of •H from the molecular ion, a favourable process in the fragmentation of (71).

Such fragmentation in (72) would give an ion of structure:

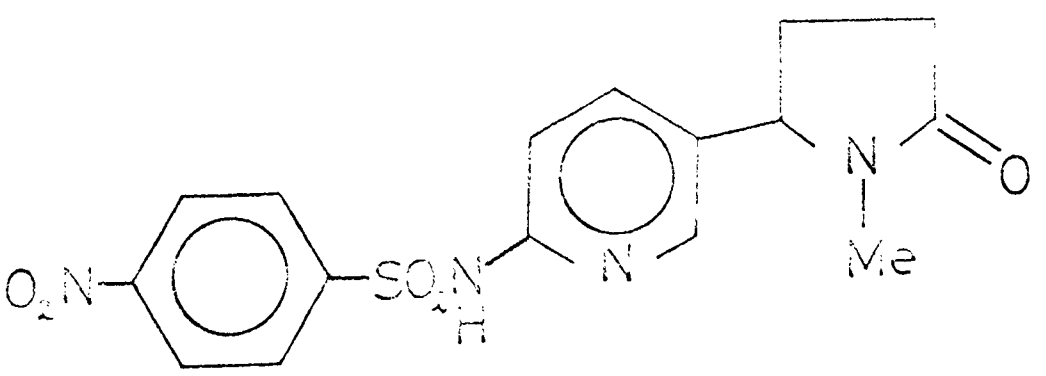


The necessary planarity of the bonds shown as thick lines would lead to considerable crowding and hence destabilization, thus favouring the alternative fragmentation.

Acylation, Arylations and Sulphonylations of the 2- and 6-aminogroups

Attempts to react acetyl chloride or acetic anhydride with either 2- or 6-aminonicotine gave tars, the reaction almost certainly being complicated by attack at the basic pyrrolidine nitrogen atom to give ring opened products, as observed with nicotine.

However, reaction of (71) with p-nitrobenzenesulphonyl chloride in acetone or caustic soda gave starting amine and p-nitrobenzenesulphonic acid. When the reaction was carried out in a large excess of pyridine the expected sulphonamide (73) was obtained but in very low yield.

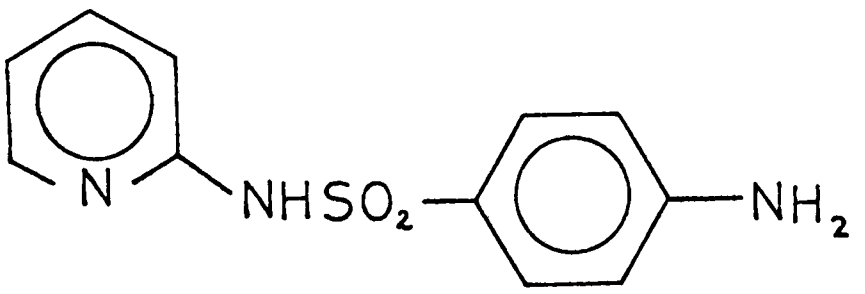


(73)

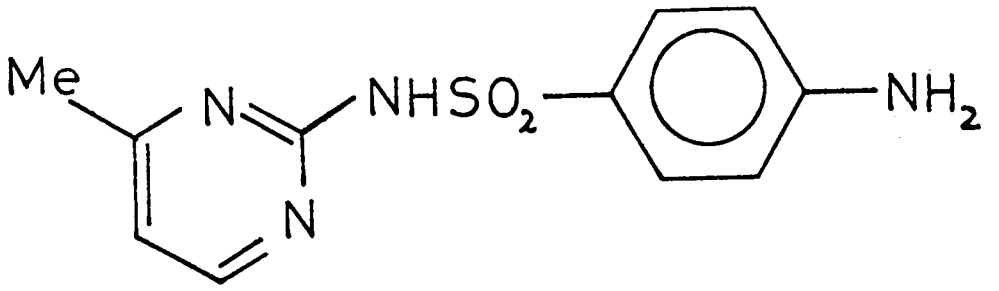
Although (73) gave a very accurate elemental analysis the mass spectrum could not be rationalised.

Reduction of the nitro group to give a p-aminobenzenesulphonamide would give a compound of great biological interest as many antibacterial drugs contain this grouping.[221]

e.g. sulphapyridine



and sulphamethazine.



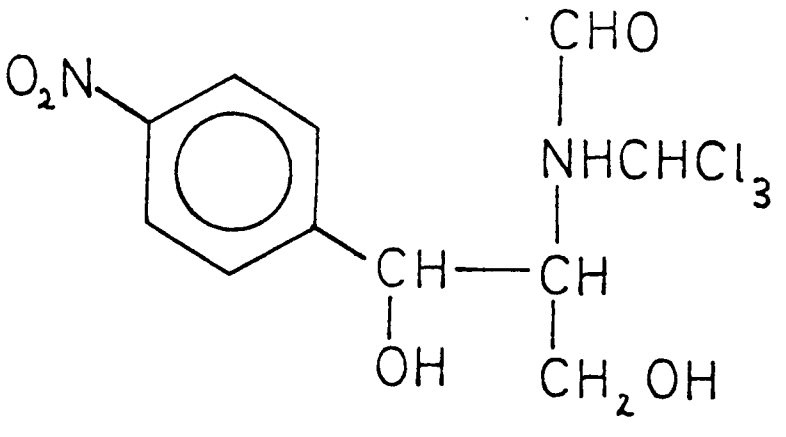
Furthermore reduction of the lactam to a pyrrolidine ring would give the sulphonamide derived from 6-aminonicotine, another biologically interesting molecule.

Paucity of material prevented these reductions being investigated, this area merits further investigation.

2- and 6-Nitronicotine

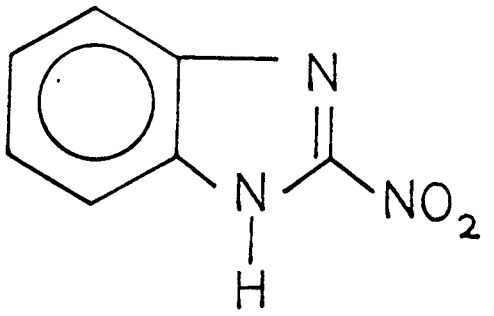
Aminopyridines can readily be oxidised by sulphuric acid and hydrogen peroxide to nitropyridines.[189,190] Many important biologically active compounds contain nitro groups.[219]

Chloramphenicol is a broad spectrum antibiotic,

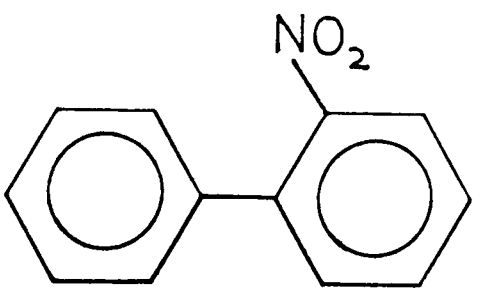


active against gram positive and gram negative bacteria.

Azomycin is an antibiotic nitrobenzimidazole.



o-Nitrobiphenyl is a fungicide



and dinitro-o-cresol a versatile weed killer.

Oxidation of 2-aminonicotine (18) and 6-aminonicotine (19) to the corresponding nitronicotines (75) and (74) was successfully accomplished with hydrogen peroxide and concentrated sulphuric acid and the products characterized by spectral and analytical evidence.

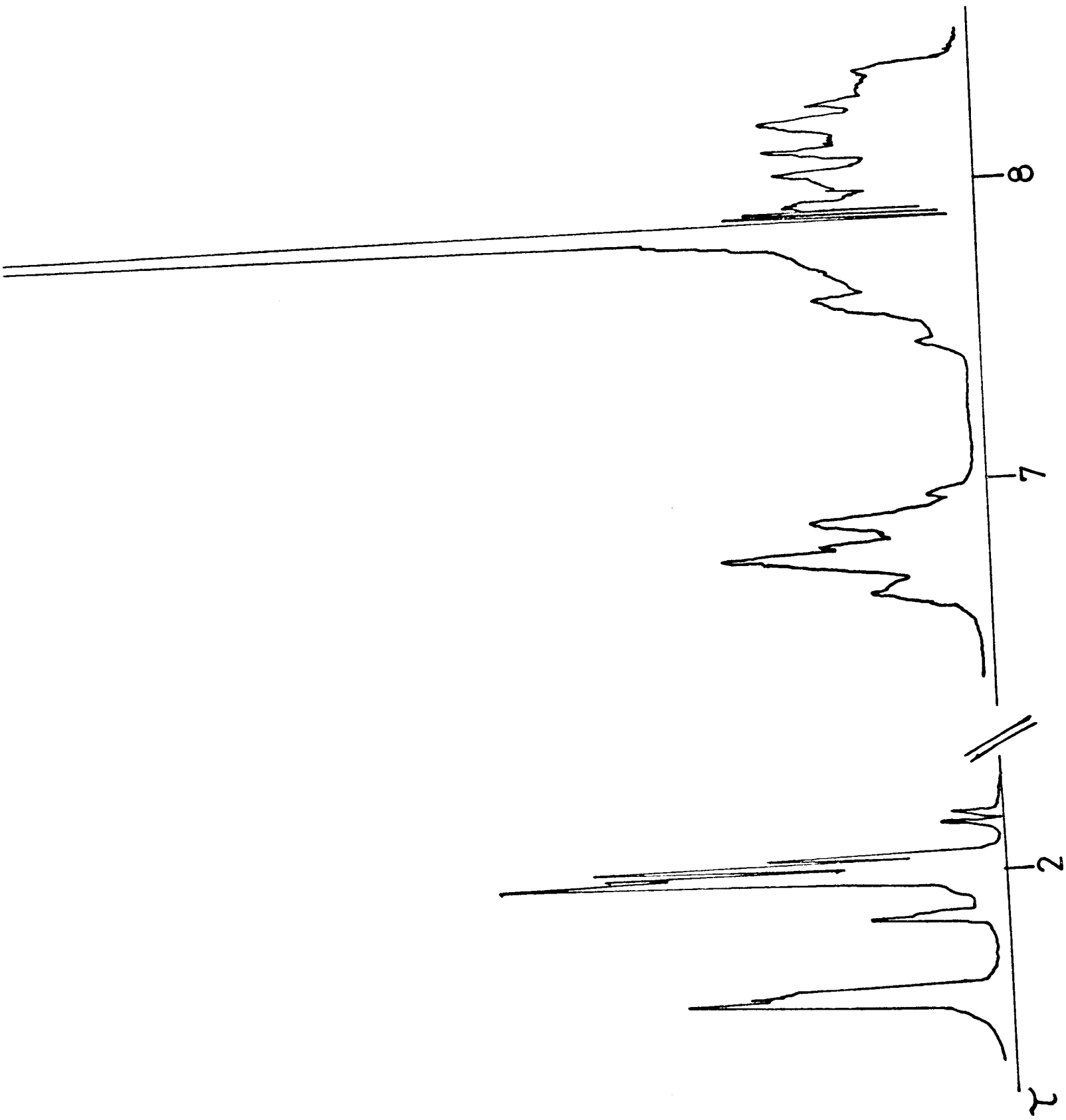


Fig. 40 N.m.r. Spectrum of 6-Nitronicotine (74)

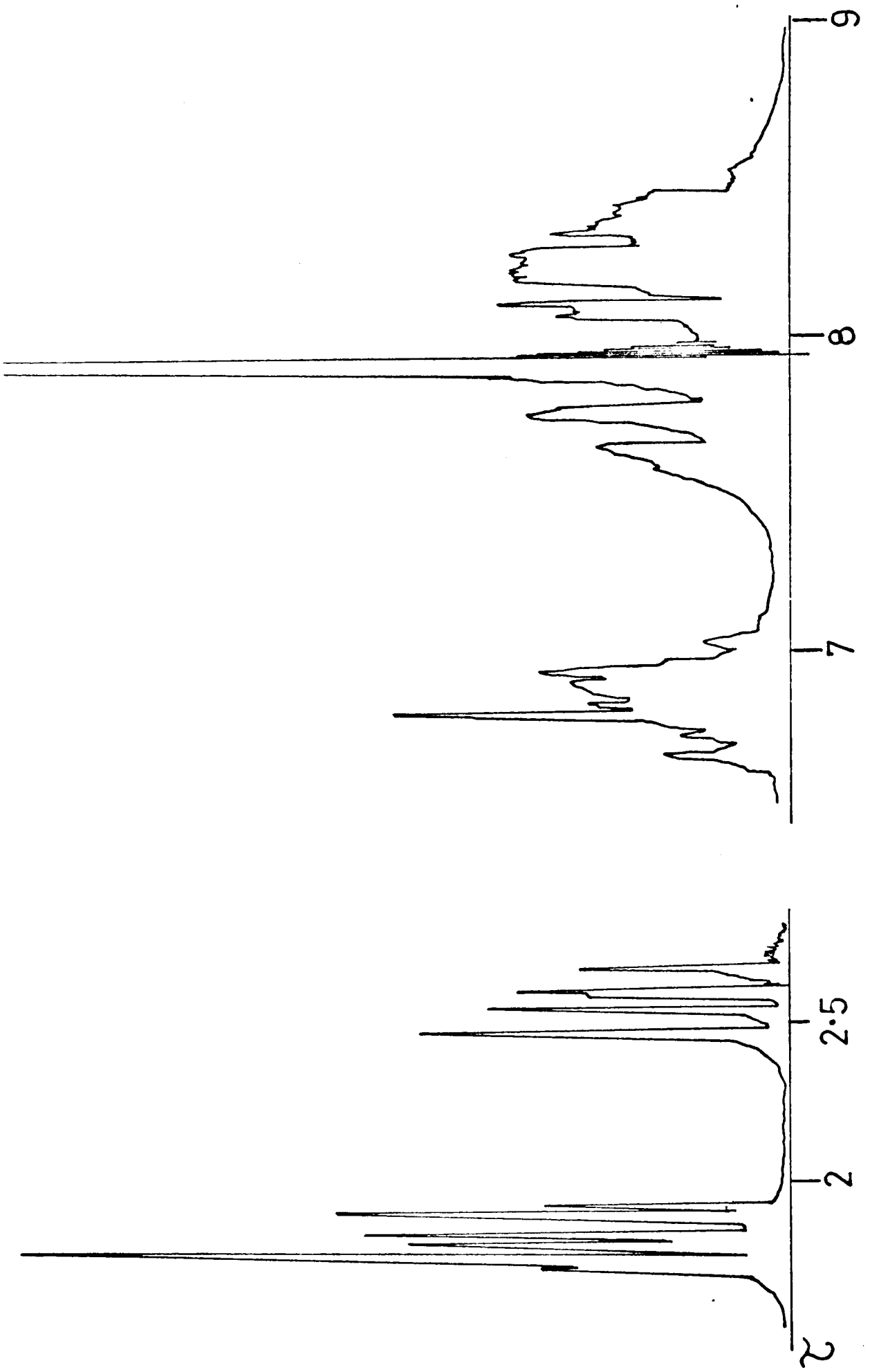


Fig. 41 N.m.r. Spectrum of 2-Nitronicotine (75)

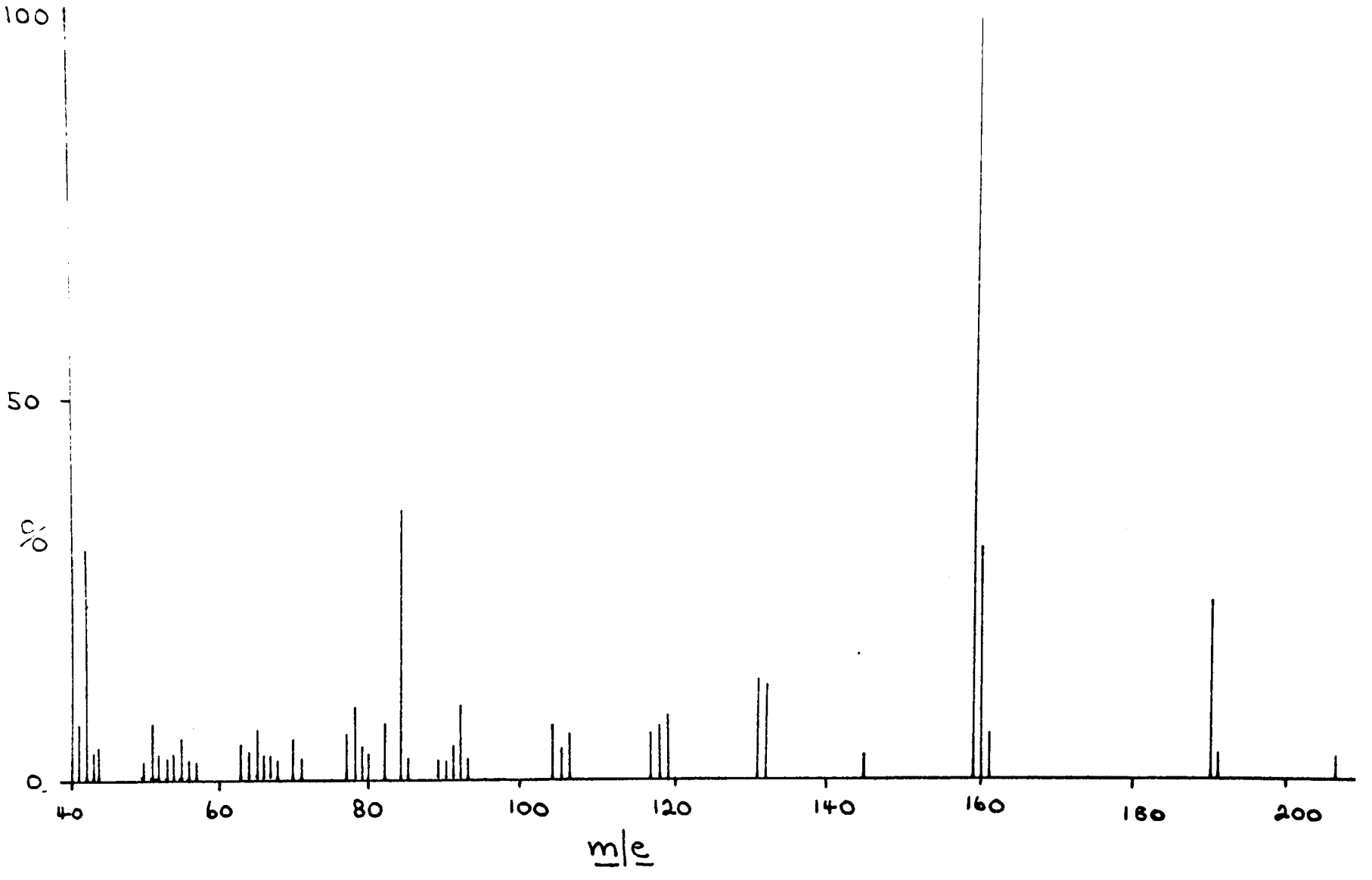


Fig. 42 Mass Spectrum of 2-Nitronicotine (75)

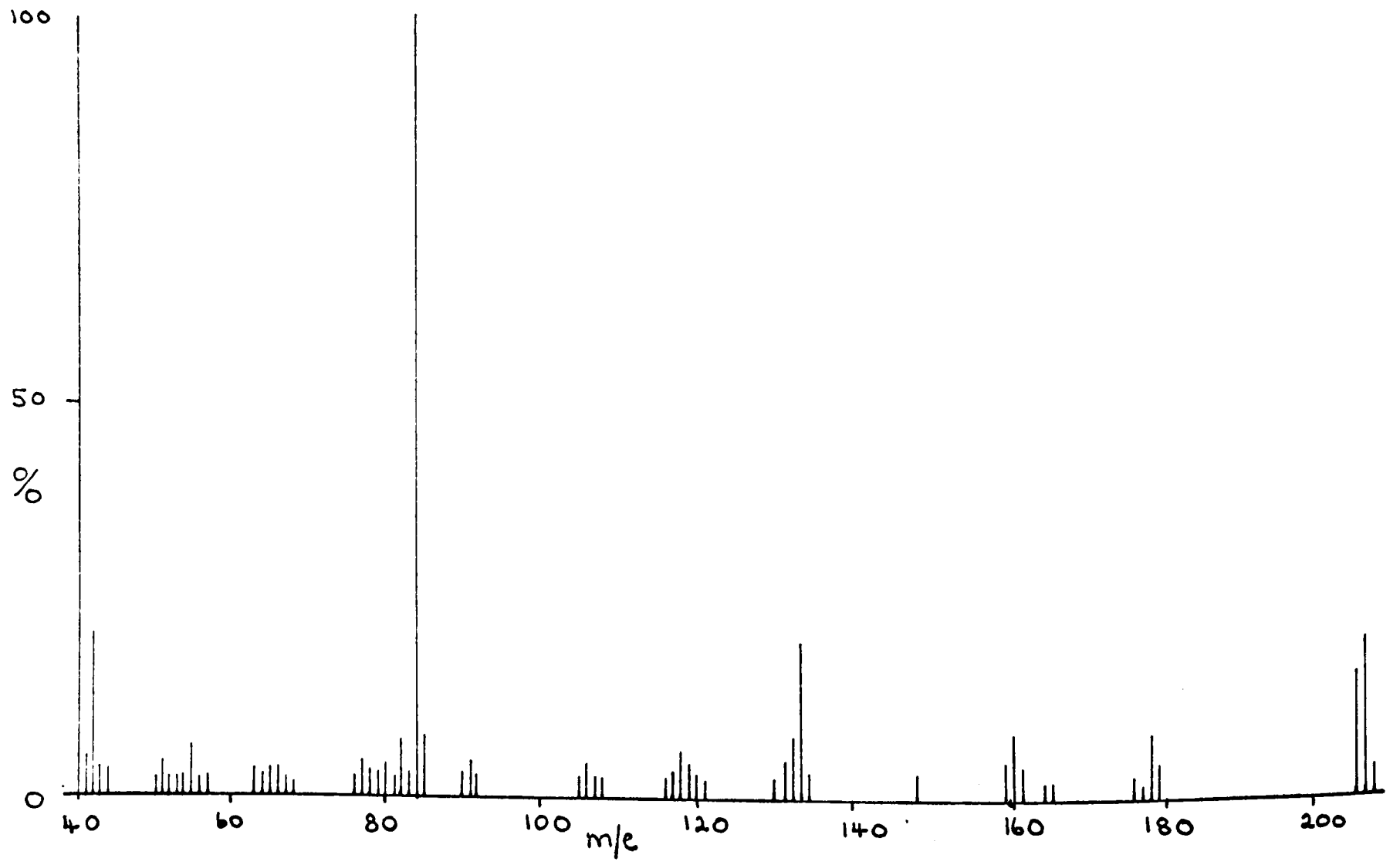
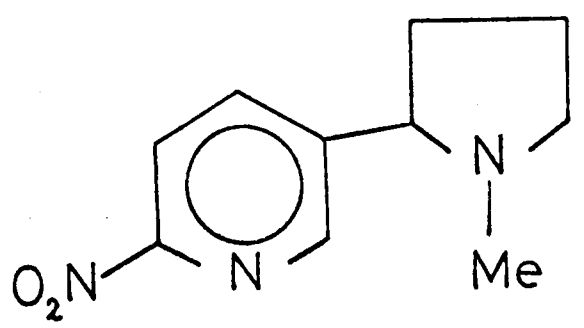
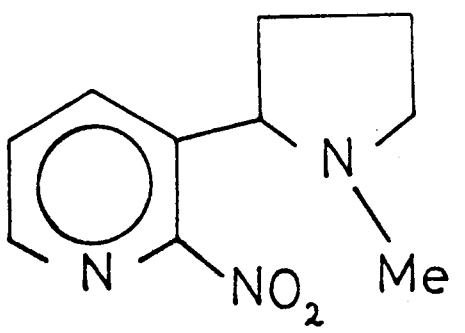


Fig. 43 Mass Spectrum of 6-Nitronicotine (74)



(74)

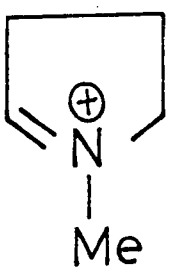


(75)

The n.m.r. spectrum of (74) (Fig. 40) shows the 2-proton as a fairly broad singlet with some further splitting at τ 1.59. The 4-proton and 5-proton are somewhat superimposed but it is possible to assign the quartet centred at τ 2.11 to the 4-proton (J 8 Hz and 2.1 Hz) and the quartet at τ 1.90 to the 5-proton (J 8 Hz and 1.2 Hz). It is interesting to note that whereas in 6-aminonicotine (Fig. 33) no splitting was observed between the 2-H and 5-H, for (74) the splitting is 1.2 Hz. A multiplet at τ 6.77 almost certainly corresponds to the 2'- and one of the 5'-protons.

The n.m.r. spectrum of (75) (Fig. 41) is less precise. The 5-proton is seen clearly as a quartet of doublets at τ 2.52 (J 7.7 Hz, 4.5 Hz and 0.5 Hz), the coupling probably being with the 2'-proton. The 5-H and 6-H form a complex pattern between τ 1.7 and τ 1.9. The 2'-H 5'-H multiplet is seen at τ 6.80.

The mass spectrum of (74) (Fig. 43) shows the molecular ion at m/e 207 (19%). Loss of a hydrogen radical gives a peak at m/e 206 (15%). The base peak arises by expulsion of the 6-nitro-pyridyl radical to give (m) at

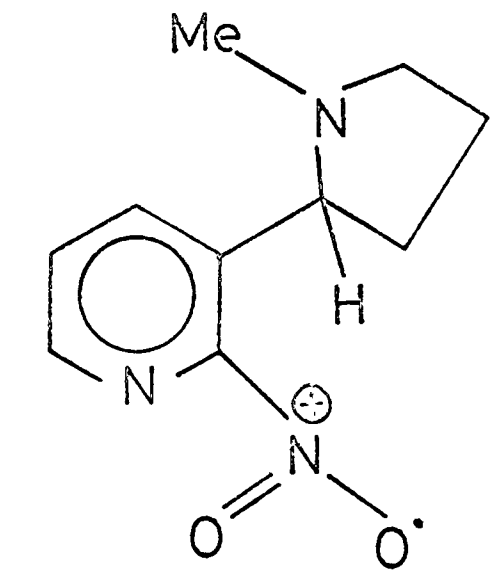


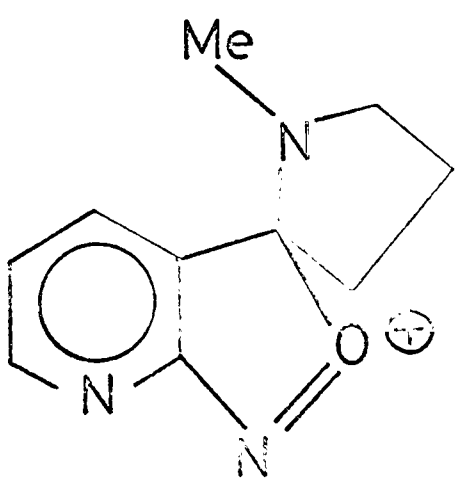
(m)

2-Nitronicotine (75) (Fig. 42) shows a very different mass spectrum. The molecular ion is only 3%; loss of 17 mass units giving a peak at m/e 190 (23%), and the base peak is at m/e 159.

The N-methylpyrrolidinyl cation is now 35% at m/e 84. A peak at m/e 160 (30%) shows loss of either NO from the fragment with m/e 190 or loss of HNO_2 directly from the molecular ion.

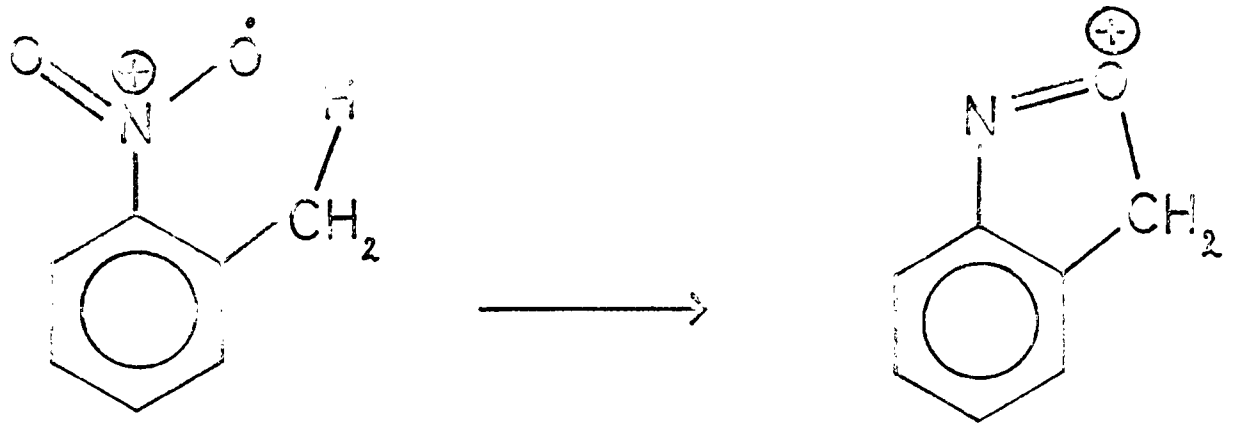
A possible fragmentation for loss of 17 mass units from the molecular ion is shown below.





m/e 190

A similar fragmentation has been shown for o-nitrotoluene.[220]



Dicyclohexylcarbodiimide

Amines react with carboxylic acids in the presence of dicyclohexylcarbodiimide to give amides, usually in good yield,[197] the diimide removing the elements of water to form dicyclohexylurea. Attempts to induce either (18) or (19) to condense with benzoic acid or acetic acid failed, the only isolated product being n-benzoyl dicyclohexylurea or n-acetyl dicyclohexylurea.

Miscellaneous Reactions of 2- and 6-Aminonicotine

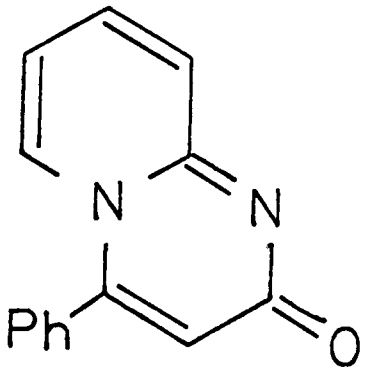
2-Aminopyridine readily gives 2-amino-5-iodo-pyridine on iodination.[196] 2-Aminonicotine however would not react under the published conditions and was recovered from the reaction mixture.

Attempts to repeat a number of diazotization reactions of (18) and (19) as described by Tschitschibabin[87] failed. Thus both (18) and (19) were diazotized[87] with sodium nitrite and sulphuric acid to the pyridones, repetition gave only starting materials. Diazotization of (18) and (19) in concentrated hydrochloric acid is reported to give the respective chloronicotine, repetition again gave starting material.

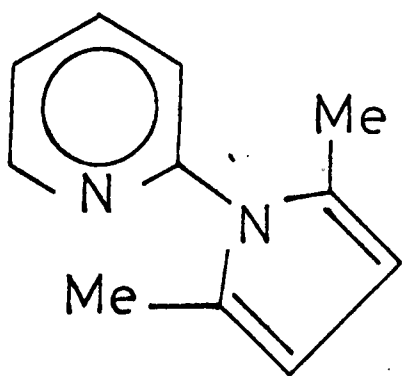
6-Aminonicotine, concentrated sulphuric acid, sodium nitrite and ethanol gave none of the expected 6-ethoxynicotine,[203] starting amine was recovered in good yield.

Use of iso-amyl nitrite in concentrated sulphuric acid likewise gave only starting amine.

Aminopyridines condense with β-keto esters and β-and γ-diketones to give heterocyclic products. Thus 2-aminopyridine and ethyl benzoylacetate give 2-oxo-4-phenylpyrido [1,2-a] pyrimidine.[199]



2-Aminopyridine and diethyl malonate give anhydro(2-hydroxy-4-oxopyrido [1,2-a] pyrimid-1-inium hydroxide.[200,201] 2-Aminopyridine and 2,5-hexanedione gives 1-(2-pyridyl)-2,5-dimethylpyrrole.[195]



However only tars were obtained when 2- (18) or 6-aminonicotine (19) were reacted with diethyl malonate, 2,5-hexanedione or acetylacetone under

similar conditions.

However a number of early Russian papers[191,192,193,202] describe reactions of (18) and (19) and their hydrochloride salts with α-haloketones and keto-esters. Thus 6-aminonicotine and bromopyruvic ester are reported to give 5-(1-methyl-2-pyrrolidyl)-2(or 3)carbethoxypyrimidazole, 2-aminonicotine and acetoacetic ester are alleged to give 1,2-[1'-(1-methyl-2-pyrrolidyl)-divinylene]-6-methyl-4-pyrimidone or 4-methyl-6-pyrimidone and chloroacetone with 2- and 6-aminonicotine are reported to give 7-(N-methyl-α-pyrrolidyl)-2 (or 3)methylpyrimidazole and 5-(N-methyl-α-pyrrolidyl)-2- (or 3) methylpyrimidazole respectively.

However reaction of (18) or (19) with either 2-chloroacetone or acetoacetic ester under the published conditions has given only tars.

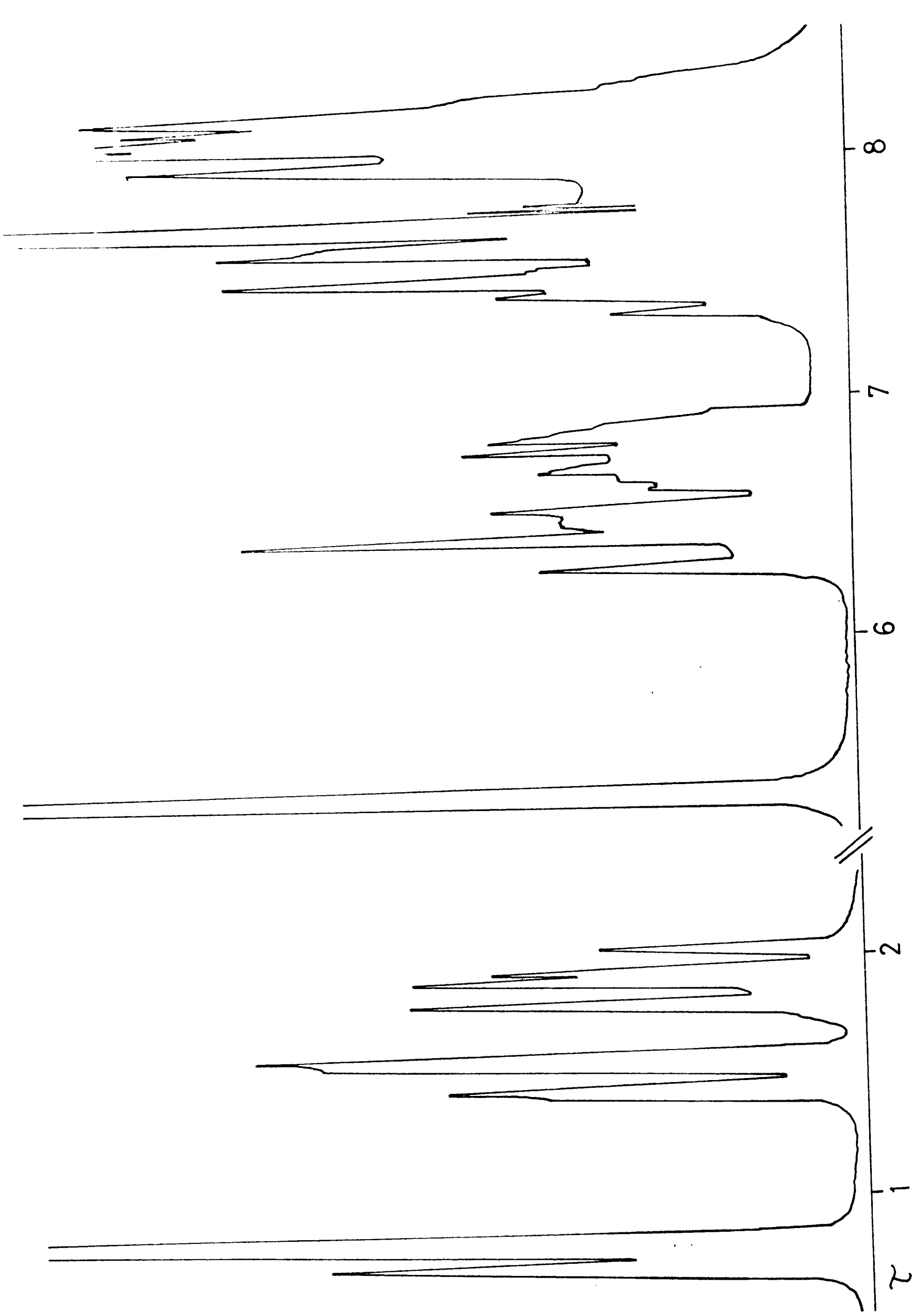
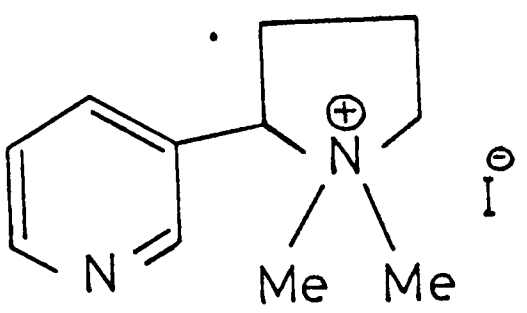


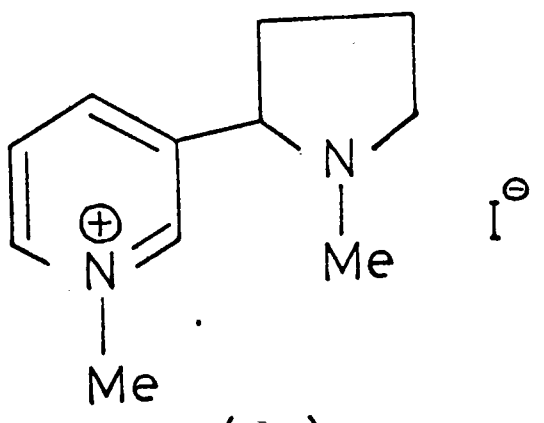
Fig. 44 N.m.r. Spectrum of Nicotine iso-methiodide (77)

Section 4. Preparation and Reactions of Some Nicotinium Salts

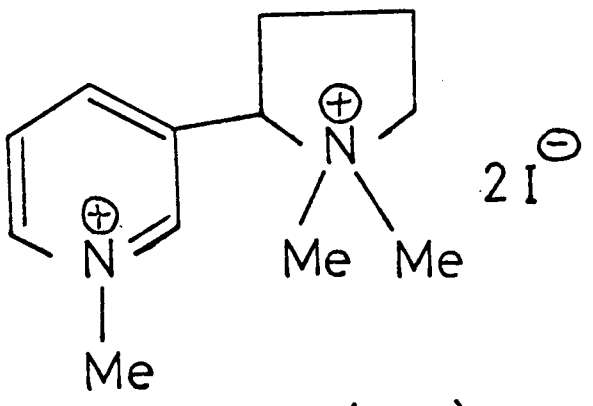
Nicotine, containing two basic nitrogen atoms forms two isomeric monomethiodides (76) and (77) and one dimethiodide (78).



(76)



(77)

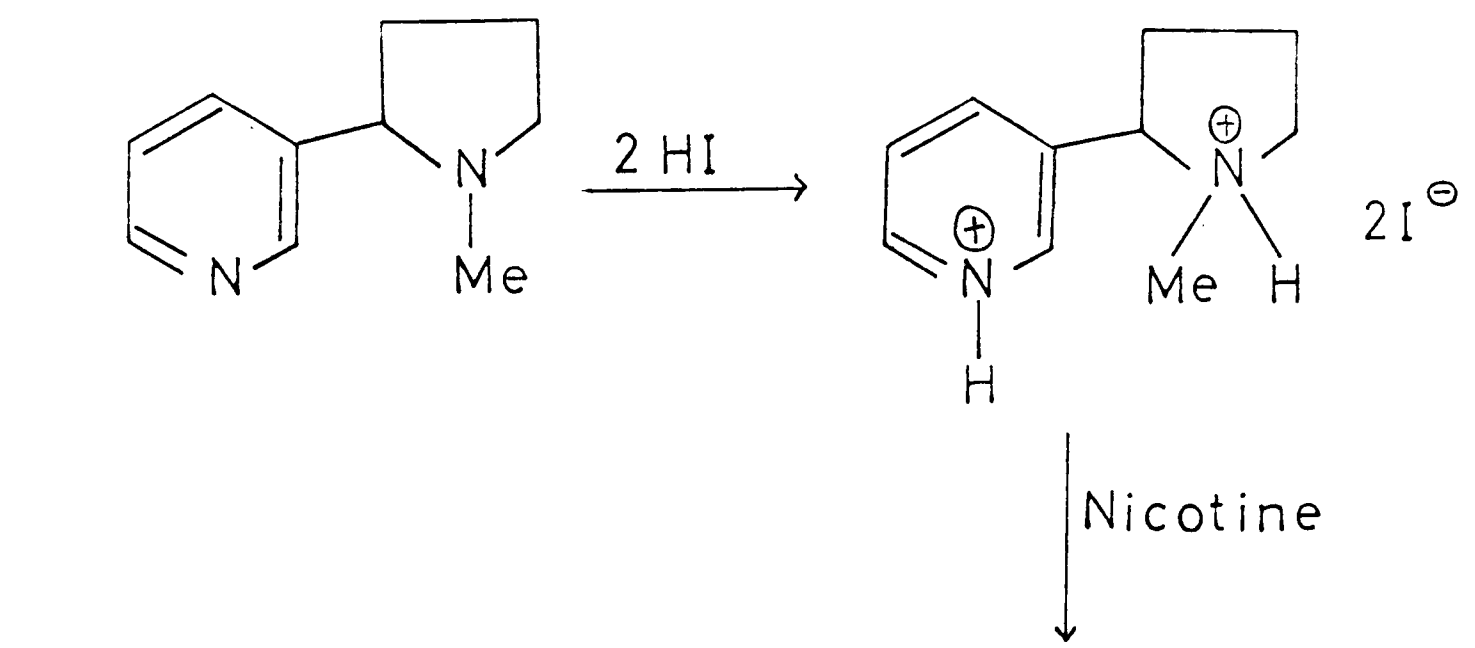


(78)

Their preparation has been reported,[127] (76) is obtained simply by the addition of nicotine (1 mole) to methyl iodide (1 mole) in methanol (ether as solvent is reported to give a mixture of all three salts). Dimethiodide (78) is prepared by adding a three molar excess of methyl iodide to nicotine in methanol. Iso-methiodide (77) requires a more complex reaction sequence which is shown in Scheme 9.

The n.m.r. spectrum of (77) (Fig. 44) shows the superimposed 2-H and 6-H at quite low field (τ 0.8) as would be expected with a positive charge on the adjacent nitrogen atom. The 4 proton is a doublet of triplets τ 1.49

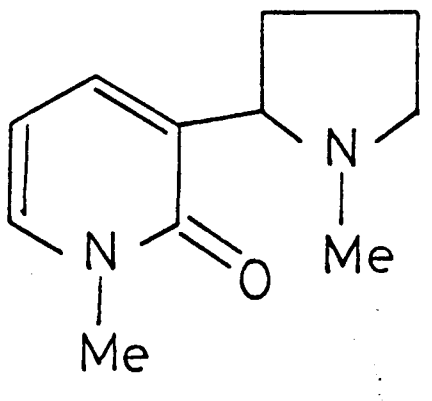
Scheme 9



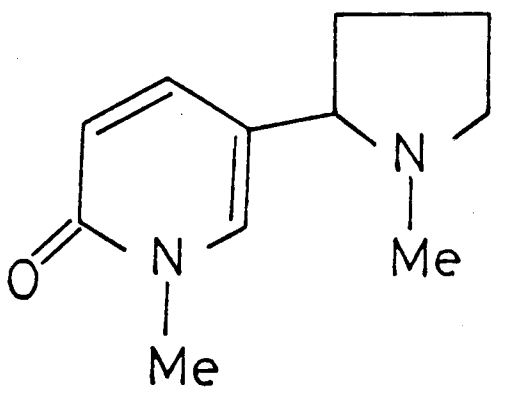
(77)

(J 8.7 and 1.5 Hz) and the 5 proton a quartet at τ1.93 (J 7.9 and 6.5). The singlet at τ5.36 is assigned to the pyridine N-methyl group; the pyrrolidine N-methyl is at τ7.76. The multiplet usually found between τ6.5 - 7.0 in nicotine derivatives and assignable to the 2'-proton and one of the 5'-protons now appears to have separated into a triplet at τ6.42 (J 7 Hz) and a complex multiplet at τ6.75. The 2'-proton being closer to the positively charged pyridinium cation has, it seems, been pulled downfield relative to the 5'-proton.

Karrer[99,204] has shown that potassium ferricyanide oxidises (77) to (79).



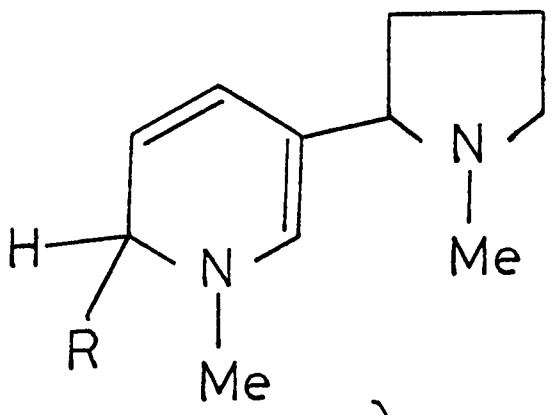
(79)



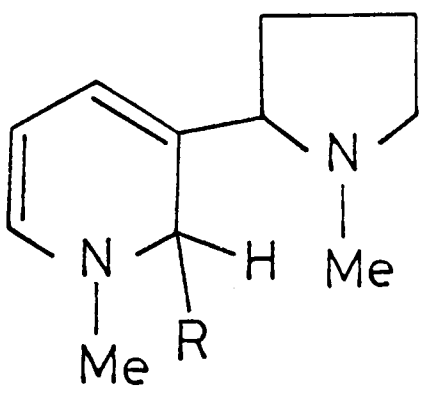
(80)

Conversion to the corresponding chlorocompound with phosphorus pentachloride followed by oxidation to the known 2-chloronicotinicacid serves to disprove structure (80).

Karrer has also investigated the reaction of (77) with methyl, ethyl n-propyl and n-butyl magnesium iodide,[205] and has obtained very low yields of compounds the structures of which he believes to be either (81) or (82).



(81)



(82)

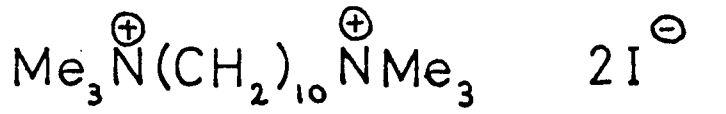
Repetition of Grignard reaction with methyl magnesium iodide gave only tars, insolubility of the methiodide (77) in the usual solvents most probably causing unsatisfactory reaction.

Biological Implications

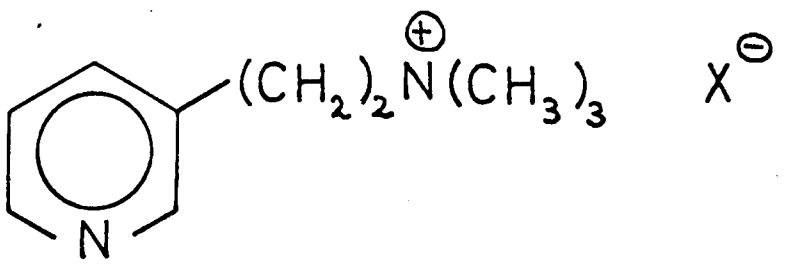
Quaternization of the pyrrolidine ring of nicotine appears to slightly diminish the stimulant properties but increases the nerve impulse blocking properties.

A number of compounds very similar to quaternised nicotines have useful biological activity.

In 1948 Barlow and Ing[223] showed that decamethonium iodide strongly inhibits the passage of nerve impulses at the synapses by acting as an acetylcholine analogue.



β-(3-Pyridyl)ethyl-trimethylammonium salts are more active than nicotine in stimulating chick biventer cervicis muscles.

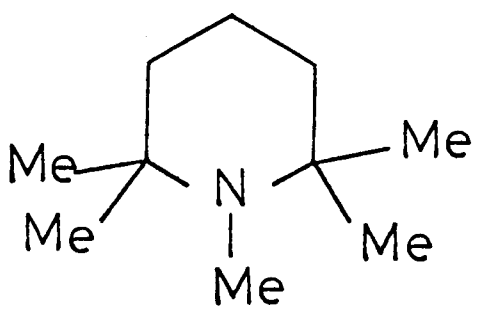


The dimethiodide of dithiodinicotyrine (24), the dimethiodide of 2-methyl-6-(3-pyridyl)tetrahydro-1,2-oxazine (56) and the dimethiodide of

1-methyl-3-(1-methyl-pyrrolid-2-yl)-1,2,5,6-tetrahydropyridine (**87**) (see below) were prepared from their respective bases and submitted for testing.

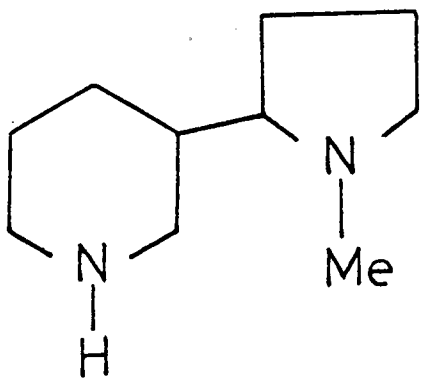
Reduction of Nicotine iso-methiodide

The ganglion blocking agent pempidine contains a completely reduced pyridine ring,[219] thus reduction of the pyridine ring of nicotine was investigated.

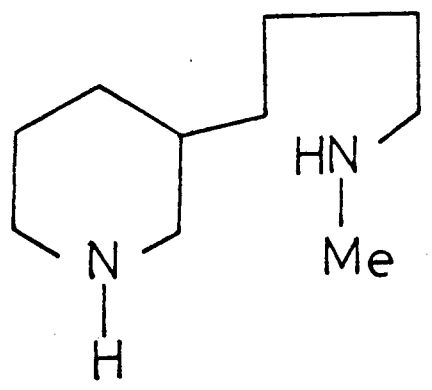


pempidine

Catalytic reduction of nicotine gives hexahydro-(16) and octahydronicotine (17);[25,80-83] these reactions are well documented and were not further considered.

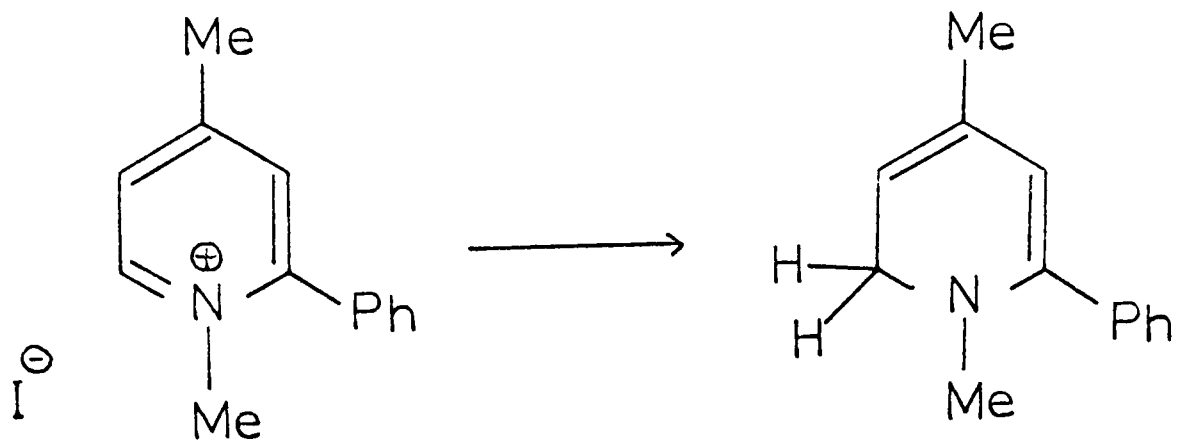


(16)



(17)

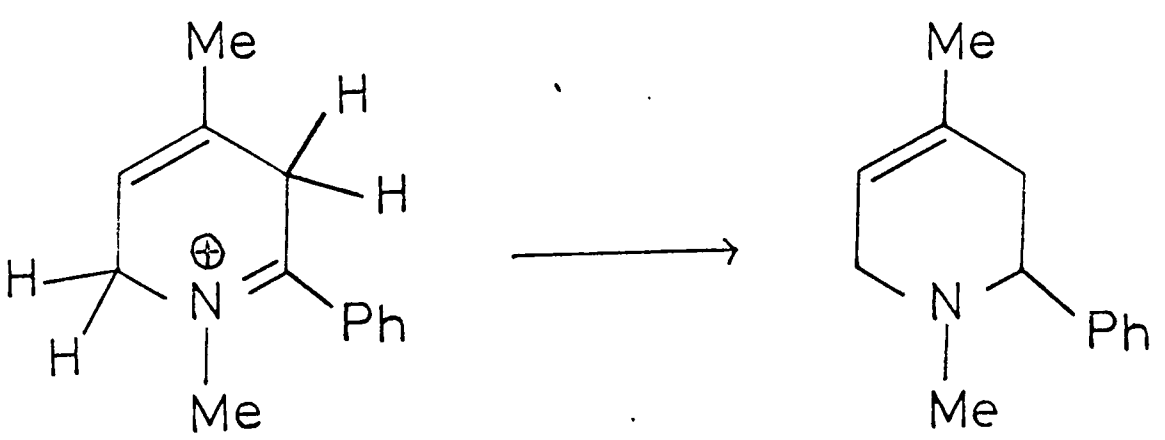
1-Methylpyridinium iodide is reduced by alkaline sodium borohydride to give a 1,2,5,6-tetrahydropyridine,[207] the mechanism of which has been investigated using the model compound 1,4-dimethyl-2-phenylpyridinium iodide (**83**).[208,209]



(83)

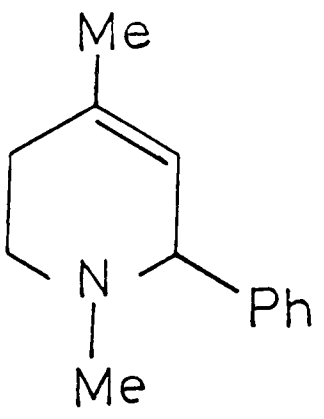
(84)

Intermediate (84) was isolated and its structure verified. Further reduction then takes place by nucleophilic attack at C-3 to give (85), the structure of which has been proved by n.m.r. spectroscopy; attack at C-5

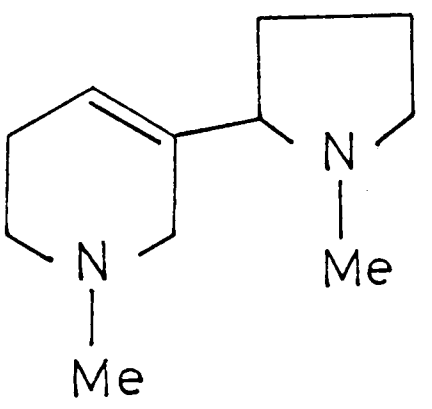


(85)

would have given (86).



(86)



(87)

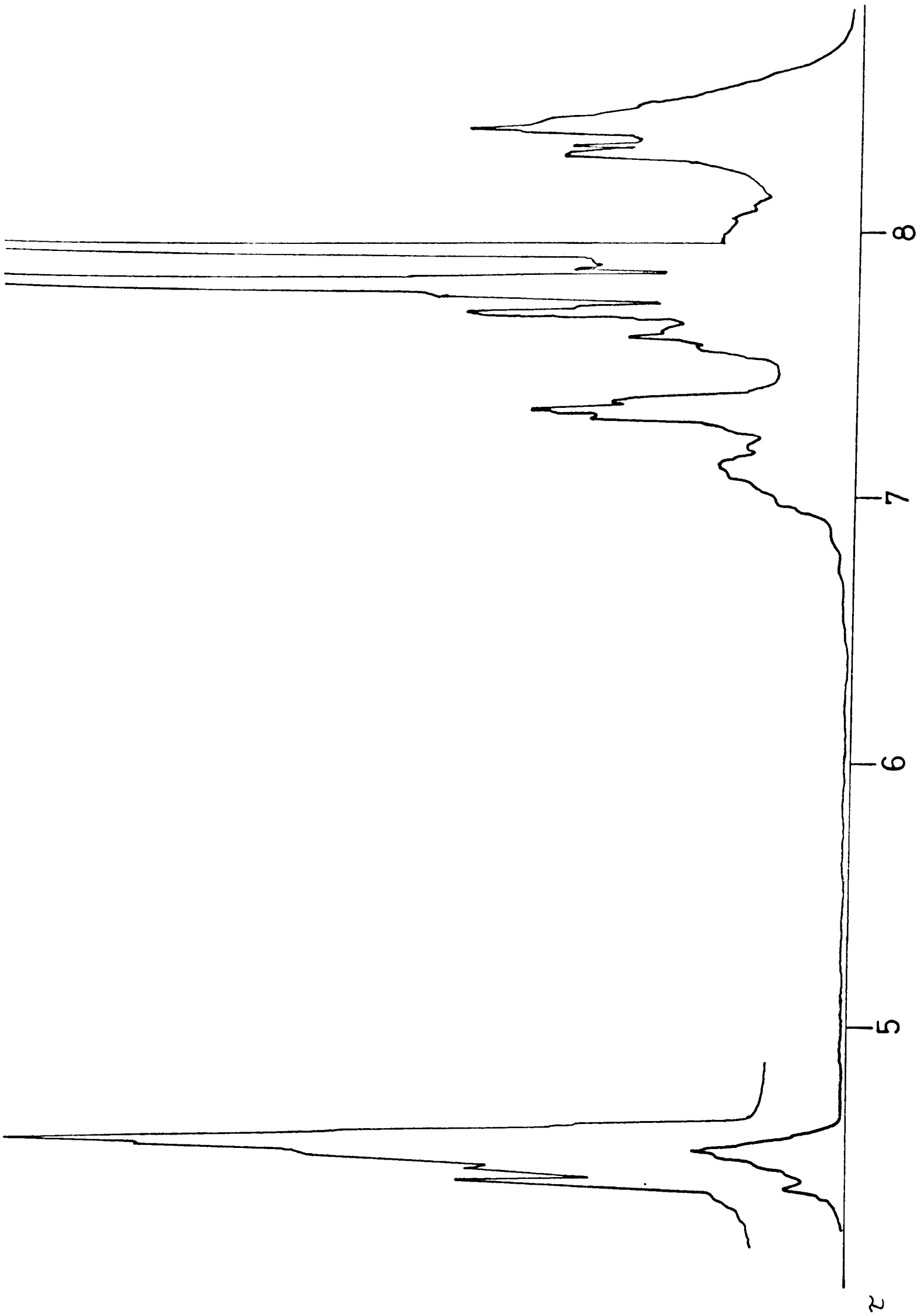


Fig. 45 N.m.r. Spectrum of 1-Methyl-3-(1-methylpyrrolid-2-yl)-1,2,5,6-tetrahydropyridine (87)

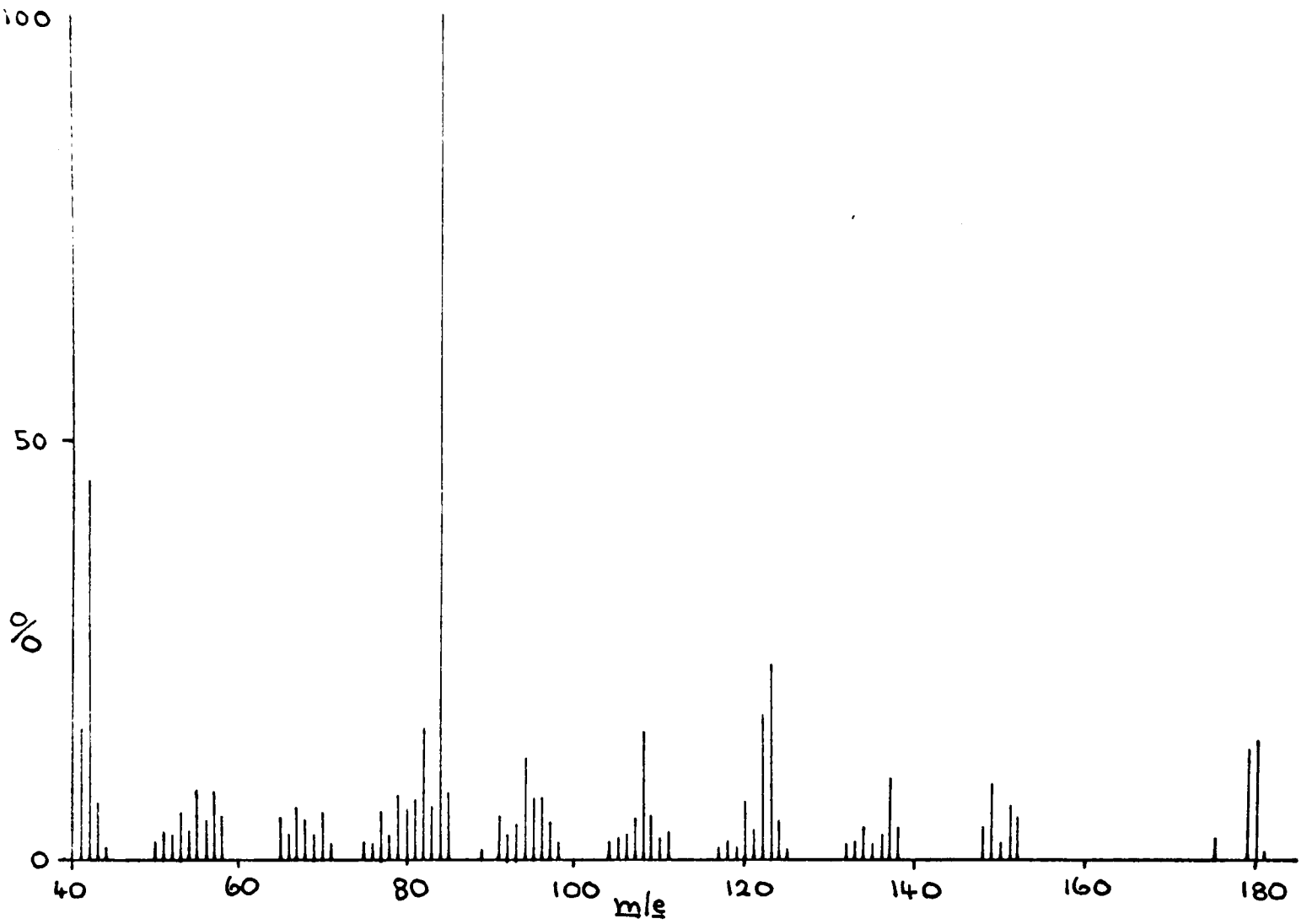
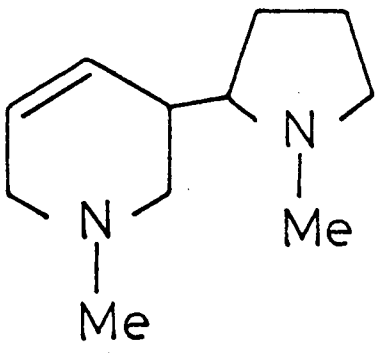


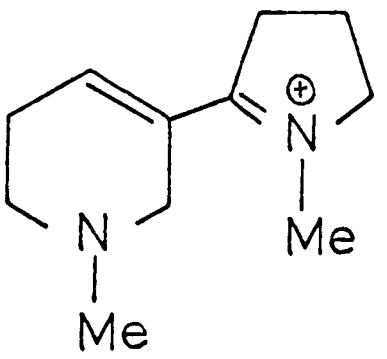
Fig. 46 Mass Spectrum of 1-Methyl-3-(1-methylpyrrolid-2-yl)-1,2,5,6-tetrahydropyridine (87)

Nicotine iso-methiodide and sodium borohydride gave (87), the appearance of only one olefinic proton in the n.m.r. spectrum (Fig. 45) serving to exclude (88).

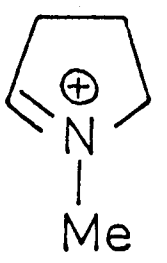
The mass spectrum of (87) (Fig. 46) shows the molecular ion at m/e 180 (14%), loss of a hydrogen radical (m/e 179, 13%) giving fragment (n).



(88)



(n)



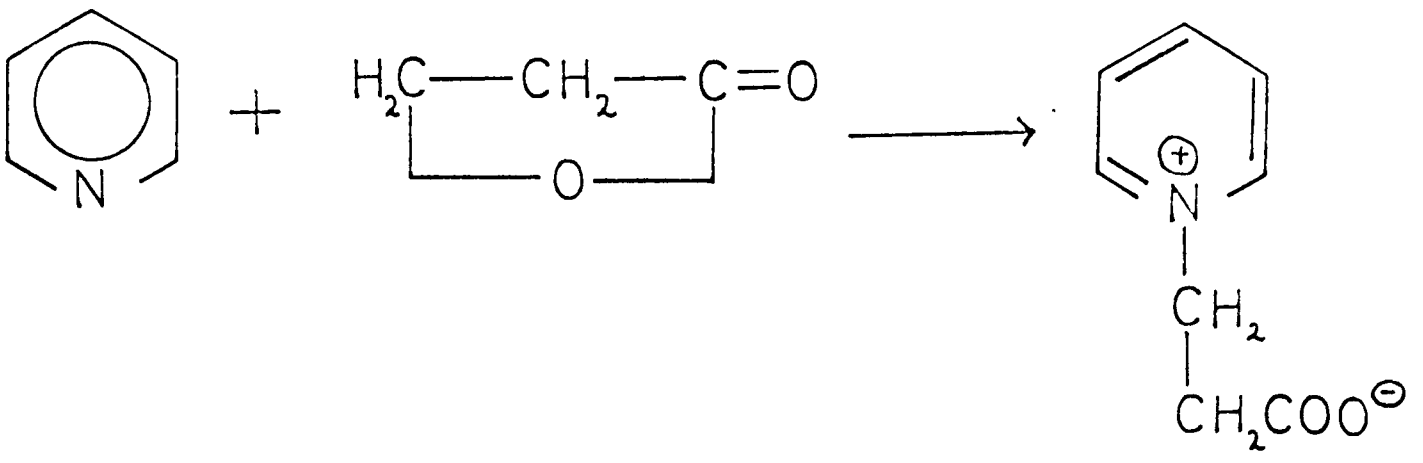
(o)

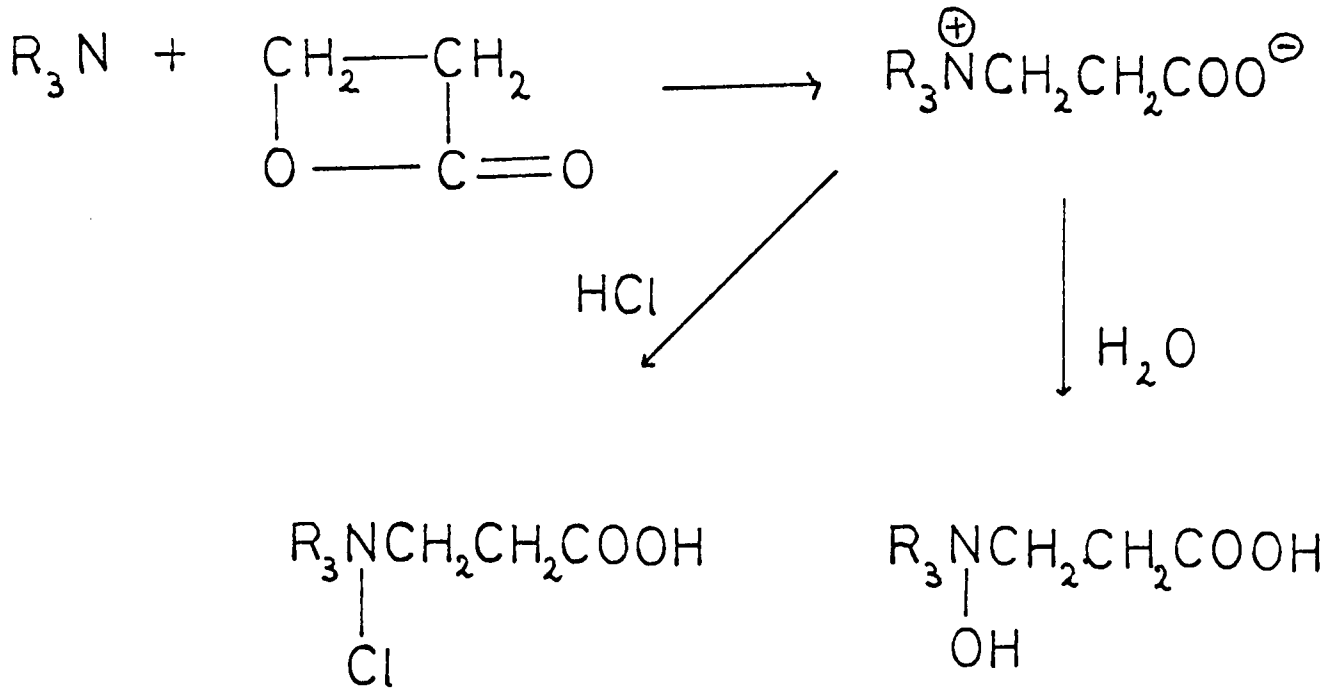
The only other significant peak is the base peak at m/e 84 corresponding to fragment (o).

Sodium hydrosulphite has been used extensively for the reduction of pyridinium salts to 1,4-dihydropyridines[210], the reaction being similar to the enzymatic reduction of dihydrophosphopyridine nucleotide $(DPN)^+$ and triphosphopyridine nucleotide. Thus the methylammonium salt of nicotinamide gives the 1,4 dihydronicotinamide.[210]

Nicotine iso-methiodide and sodium hydrosulphite gave a complex product mixture from all reaction attempts. 1-Methyl-1,4-dihydropyridine is unstable in air, stability being conferred by electron withdrawing groups at positions 3 or 5.

Pyridine and tertiary amines react with β-propiolactone to give betaines.[211]





Attempts to induce nicotine and nicotine <u>iso</u>-methiodide to react with β-propiolactone gave glues which could not be characterised.

Likewise glues were obtained when nicotine and cetyl bromide were heated, no crystalline quaternary cetylammonium salts were obtained.

Section 5. Reactions of Dimethyl Acetylenedicarboxylate with Nicotine Derivatives

Historical Introduction

Acheson[144] has reviewed the reactions of dimethyl acetylenedicarboxylate with nitrogen containing heterocycles.

Diels[145] first isolated two adducts from pyridine and dimethyl acetylenedicarboxylate in ether and termed them "labile" and "stable". The labile adduct has been obtained only once since;[214] it rapidly isomerizes to the stable adduct which is known to have structure (89).

However quinolizines (90), (91) and (92) have been obtained from 3-methylpyridine and dimethyl acetylenedicarboxylate.

Stable adduct (90) can also be obtained by thermal isomerization of labile adduct (91), the mechanism and kinetics of the isomerization for the 7-methyl derivative of (91) have been studied[153] and the following data obtained.

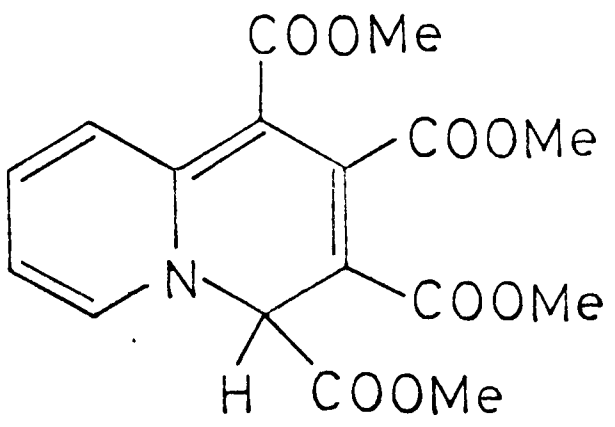
(i) When carried out in $^{2}[H]$ ethanol deuterium is not incorporated at the 4 position.

(ii) The activation energy and activation entropy for the isomerization of the 7,9-dimethyl-9a<u>H</u>-quinolizine were determined as 24.8 kcal/mol and -8.6 ± 2.6 e.u. respectively.[153]

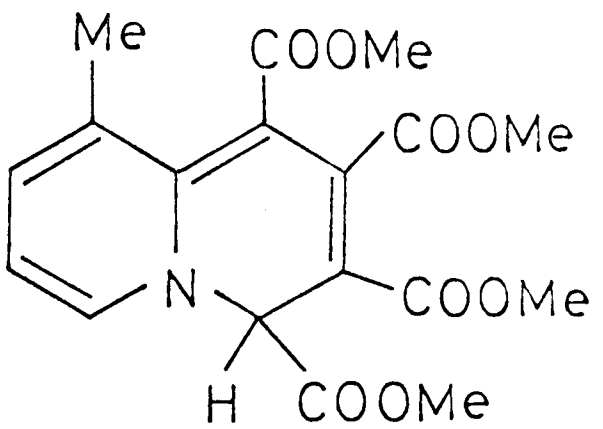
(iii) Tetramethyl 7,9-dimethyl-9a<u>H</u>-[6,9a-$^{2}H_{2}$] quinolizine-1,2,3,4-tetracarboxylate showed a kinetic isotope effect of 5.98 ± 0.05 for isomerization to the 4 <u>H</u> isomer.

These facts are all characteristic of 1,5-hydrogen shifts[154] permitted for concerted suprafacial thermal reactions according to the Woodward-Hoffmann rules.[155]

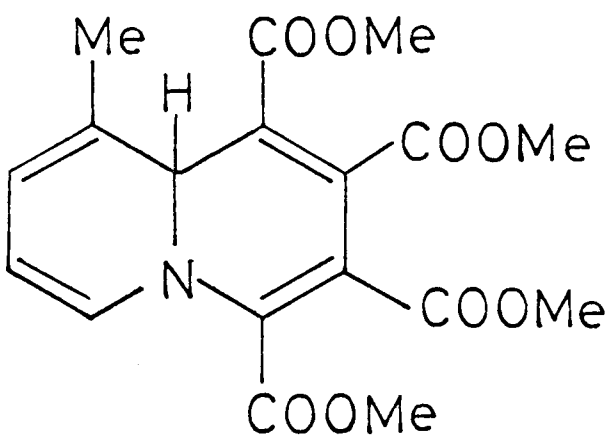
The mechanism of the addition of dimethyl acetylenedicarboxylate to pyridines is believed to be a stepwise Michael type addition of two molecules


COOMe
COOMe
COOMe
N
H
COOMe

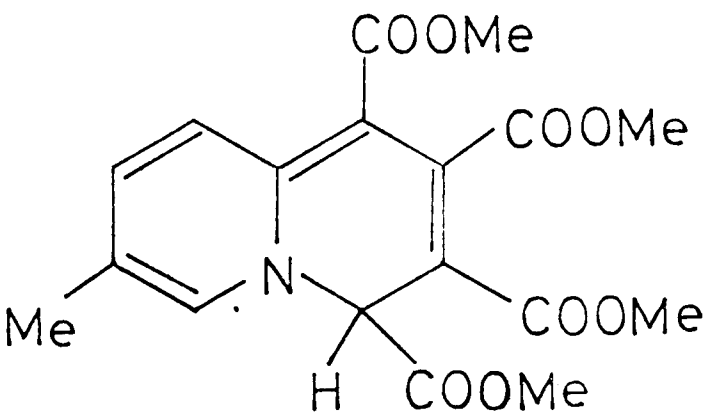
(89)


Me
COOMe
COOMe
COOMe
N
H
COOMe

(90)

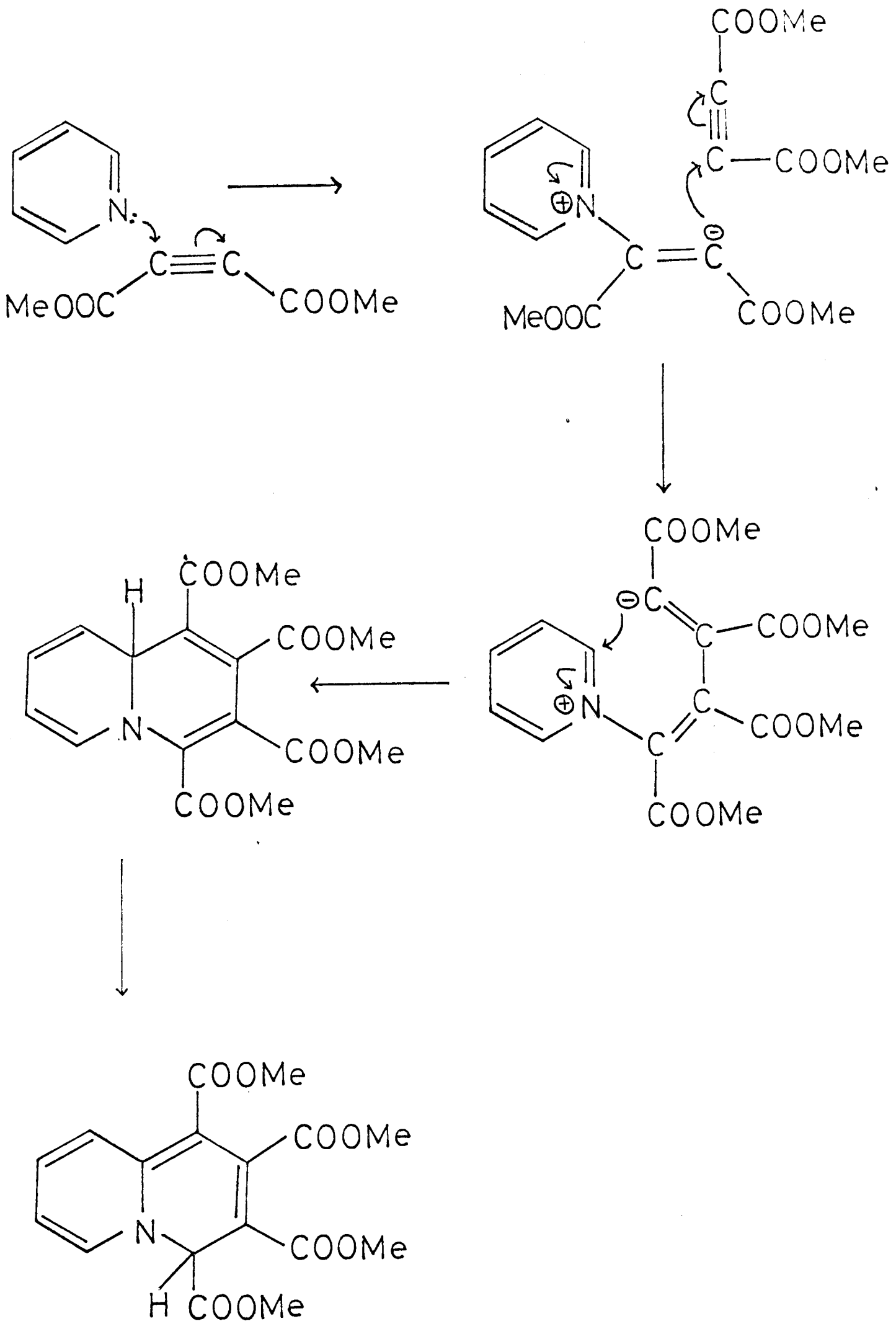

Me
H
COOMe
COOMe
COOMe
N
COOMe

(91)


COOMe
COOMe
COOMe
N
Me
H
COOMe

(92)

Scheme 10


N:
C
C
MeOOC
COOMe
COOMe
C
C
COOMe
⊕N
C
C
MeOOC
COOMe
COOMe
⊖C
C
COOMe
⊕N
C
C
COOMe
C
COOMe
H
COOMe
COOMe
N
COOMe
COOMe
H
COOMe
COOMe
N
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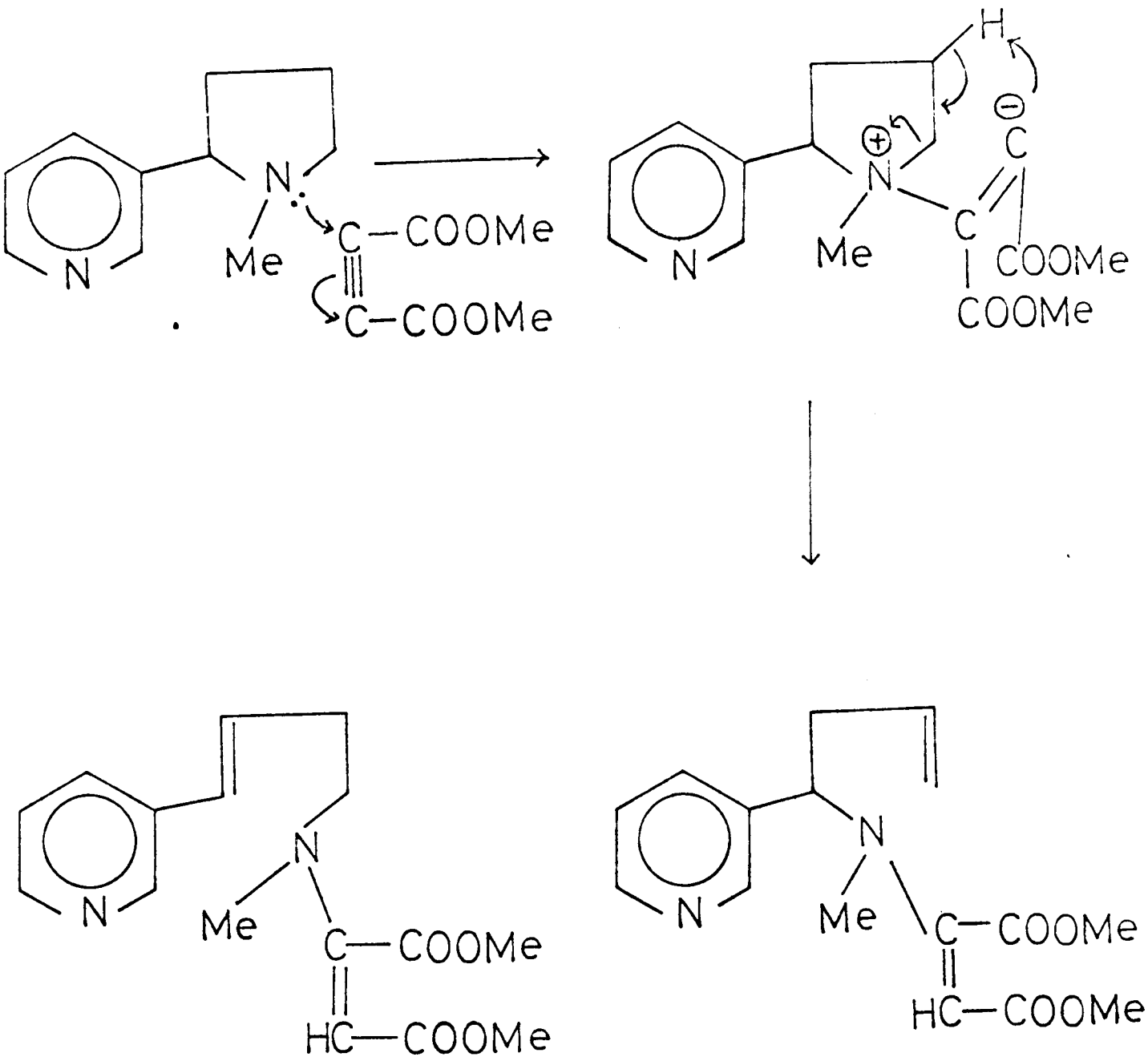
H
COOMe

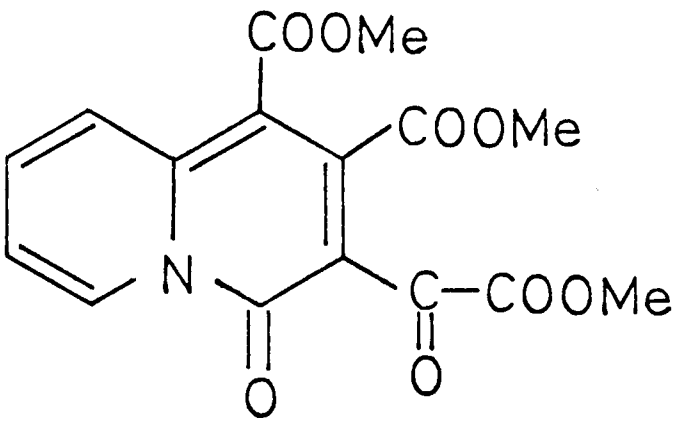
Scheme 11


N
Me
C—COOMe
C—COOMe
H
C
COOMe
COOMe
N
Me
C—COOMe
HC—COOMe
N
Me
C—COOMe
HC—COOMe

of the diester (Scheme 10).

A minor product sometimes isolated from the reaction of pyridines with dimethyl acetylenedicarboxylate is the Kashimoto compound. Woodward and Kornfeld have shown the structure to be (93). Two possible pathways for

(93)



its formation are described by Acheson.[144]

Biological Implications and Results

Increasing the degree of crowding in a biologically active molecule which has relatively free rotation often leads to an increase in the specificity or strength of the biological response caused by the compound.

Addition of a 5-, 6- or 7-membered ring to the pyridine ring of nicotine could probably lead to useful modifications of its biological activity, by interfering with rotation between the rings, especially so if the 9-substituted quinolizines were obtained.

It was hoped that nicotine would react with dimethyl acetylenedicarboxylate to give the adducts expected for a 3-substituted pyridine; however no solid products were obtained.

It seems likely that nucleophilic attack by the highly basic pyrrolidine nitrogen at the ester triple bond is being followed by abstraction of pyrrolidine protons leading to ring opened products which polymerize (Scheme 11)

Triethylamine has been shown to react with dimethyl acetylenedicarboxylate in the presence of a proton source (triethylamine hydrobromide) to give

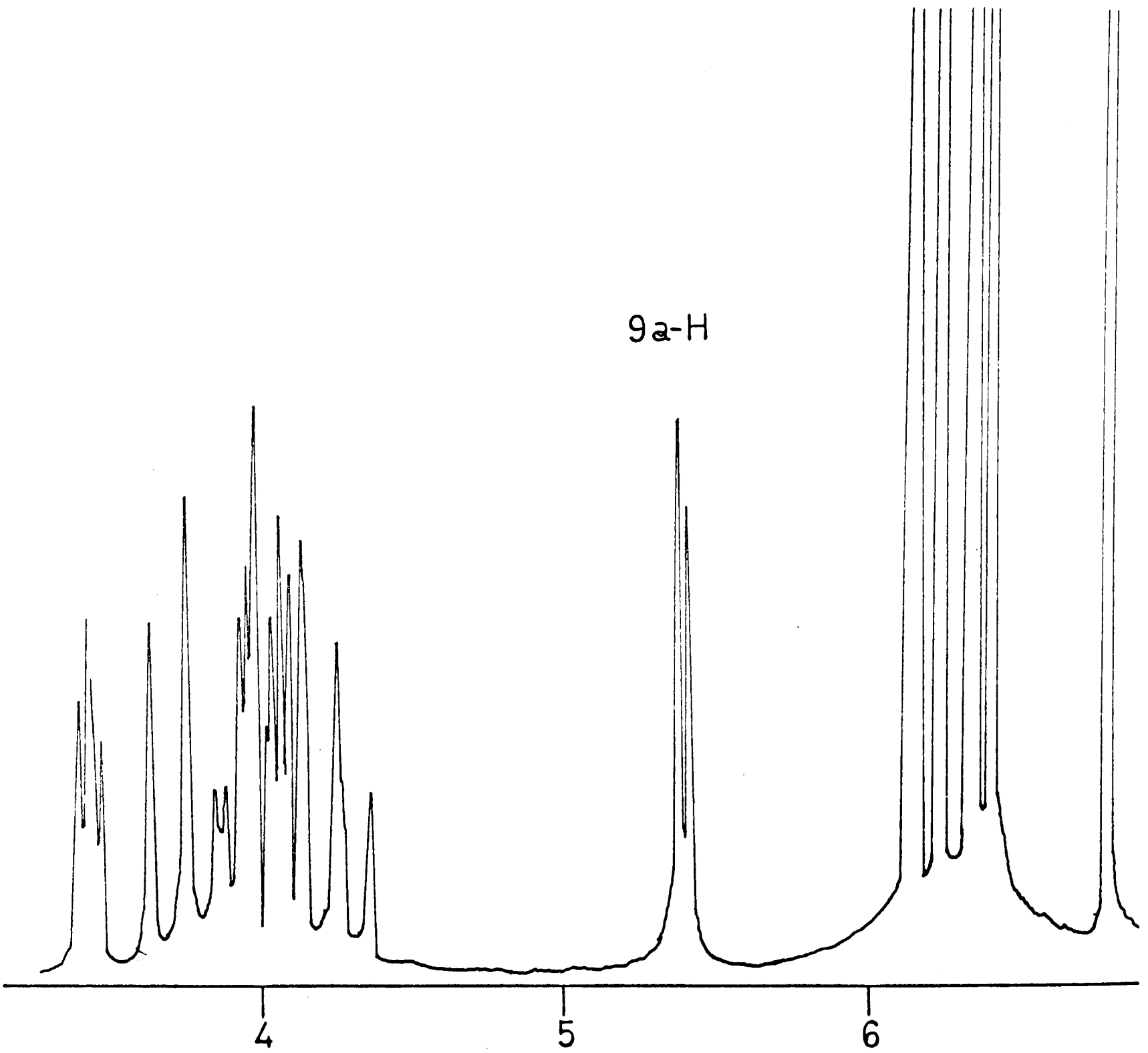


Fig. 47 N.m.r.Spectrum of Tetramethyl 9-(1-methylpyrrol-2-yl)-9a<u>H</u>-quinolizine-1,2,3,4-tetracarboxylate (94)

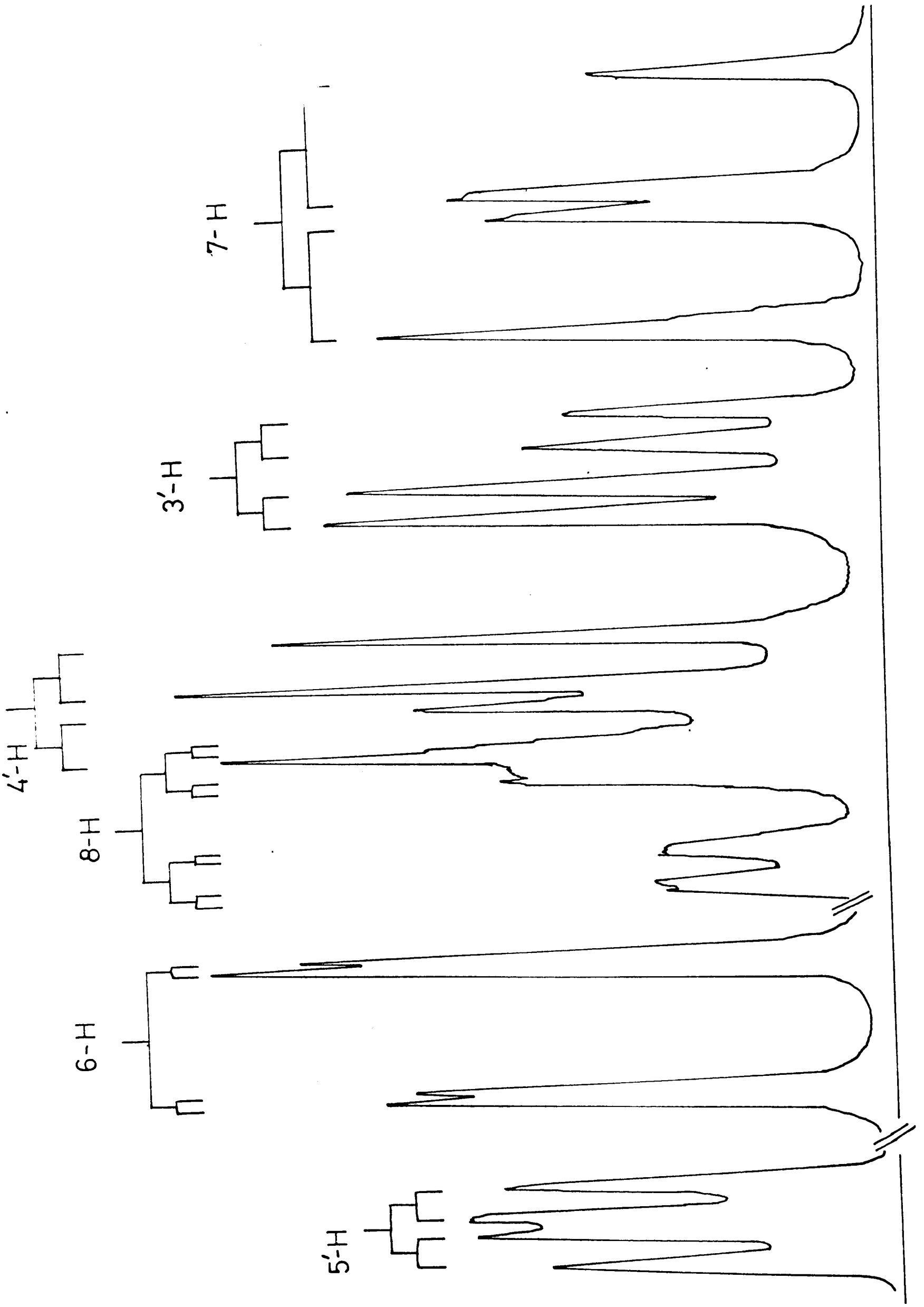
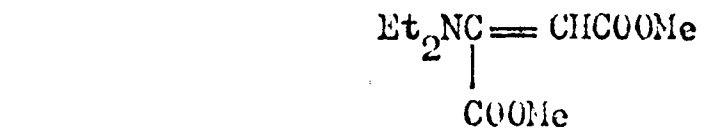


Fig. 48 N.m.r. Spectrum (100MHz) of the τ 3-5 region of (94)



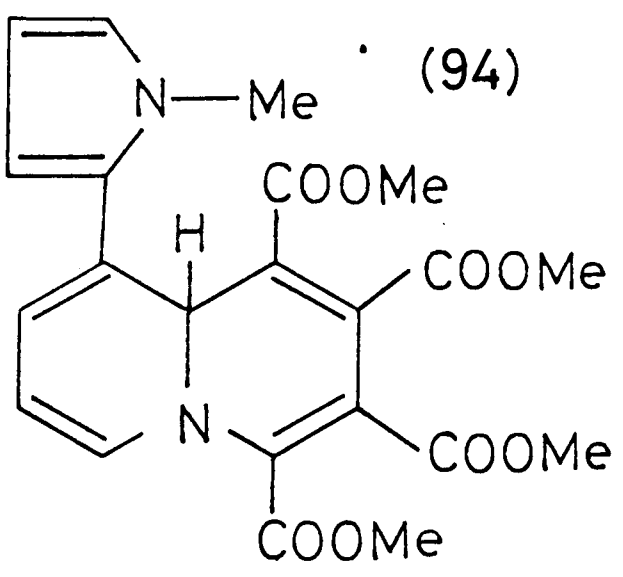
in quantitative yield.[215] In the absence of a proton source polymeric products are obtained.

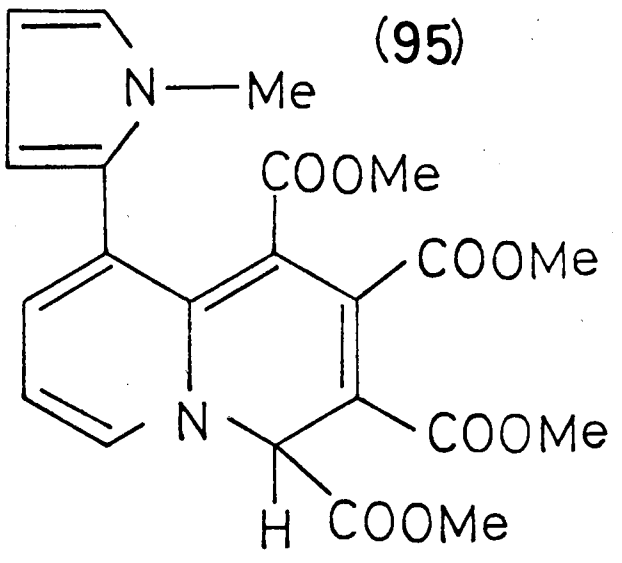
No attempts were made to react nicotine with the ester in the presence of a proton source.

Thus reduction of the basicity of the pyrrolidine nitrogen could lead to preferential reaction at the pyridine nitrogen and the production of the expected quinolizines.

Nicotyrine with Dimethyl acetylenedicarboxylate

Nicotyrine, which is readily available from nicotine, contains an N-methylpyrrole ring, the pK_a of the 1'-nitrogen being small (nicotine~8.0) and gave the expected 9aH quinolizine with dimethyl acetylenedicarboxylate (94), no (95) being isolated.





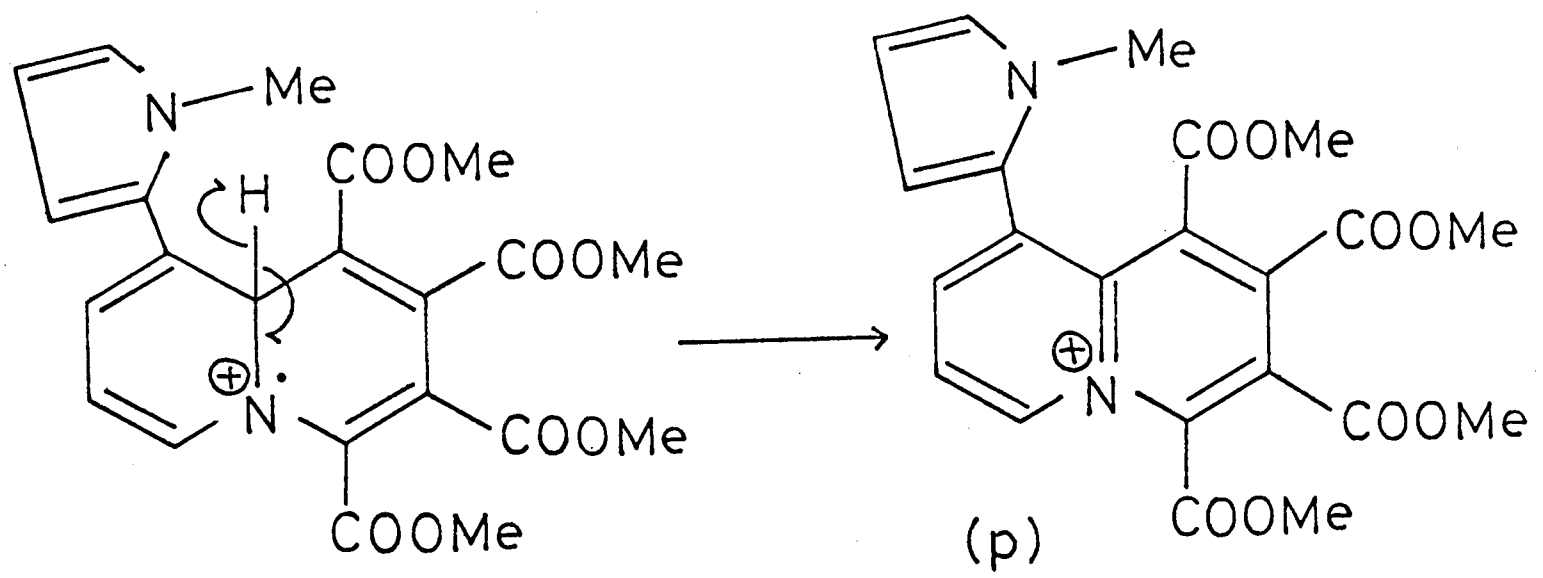
The structure follows from comparison of the n.m.r. spectrum (Figs. 47 and 48) with that of the 9-methyl-9aH-quinolizine (91),[147,152] obtained from 3-methylpyridine; the relevant assignments are shown in Table 8.

Table 8. N.m.r. Spectra of Dimethyl Acetylenedicarboxylate Adducts

Compound	4-H	6-H	7-H	8-H	9-H	9aH	Ester Me's
(94)		3.65q (J 7.2,0.5)	3.99q (J7.2,6.2)	3.87q of d (J 7.2,1.1,0.5)		5.35d (J 1.7)	6.14, 6.21, 6.32, 6.38
(91)[152]		3.78d (J 7)	4.05 - 4.22m			5.01d (J 1)	6.09, 6.09, 6.24, 6.29
(95)	3.85	2.32q (J 8, 1)	3.06q (J 8, 6)	3.55 (J 6, 1)			6.07, 6.22, 6.28, 6.48
(90)[152]	3.89	2.48q (J + J 8)	3.07t (J + J 14)	2.33q (J + J 8)			6.06, 6.24, 6.27, 6.31
(96)		4.1	4.1		3.70d (J 8)	5.17d	6.01, 6.11, 6.19, 6.28
(97)	4.06s	2.70	2.70d (J 9)		1.36d (J 9)		6.14, 6.27, 6.31, 6.33
(92)	3.89	2.62d (J 1)	2.52q (J + J 10)		1.38d (J 9)		6.05, 6.18, 6.23, 6.26
(101)		4.1-4.3	4.1 - 4.3		3.78d (J 8)	5.13s	6.09, 6.09, 6.27, 6.29
(102)	3.95s	2.4 - 2.7	2.4 - 2.7		1.36d (J 9)		6.07, 6.22, 6.24, 6.27

The n.m.r. spectrum of (94) is complicated by superimposition of the pyrrole protons, thus the quartet at τ3.39 is assigned to 5'-H ($J_{4',5'}$ 2.6; $J_{5',5'}$ 1.6 Hz), quartet at τ3.93 to 4'-H ($J_{3',4'}$ 3.9 Hz) and the quartet at τ4.05 to 3'-H. The 9a proton at τ5.35 is coupled to the 8 proton (J 1.8 Hz).

The mass spectrum is in full agreement with the structure, the molecular ion being at m/e 442 (24%). A peak at m/e 441 (12%) is due to loss of the 9a proton as a hydrogen radical to give the corresponding quinolizinium cation (p).



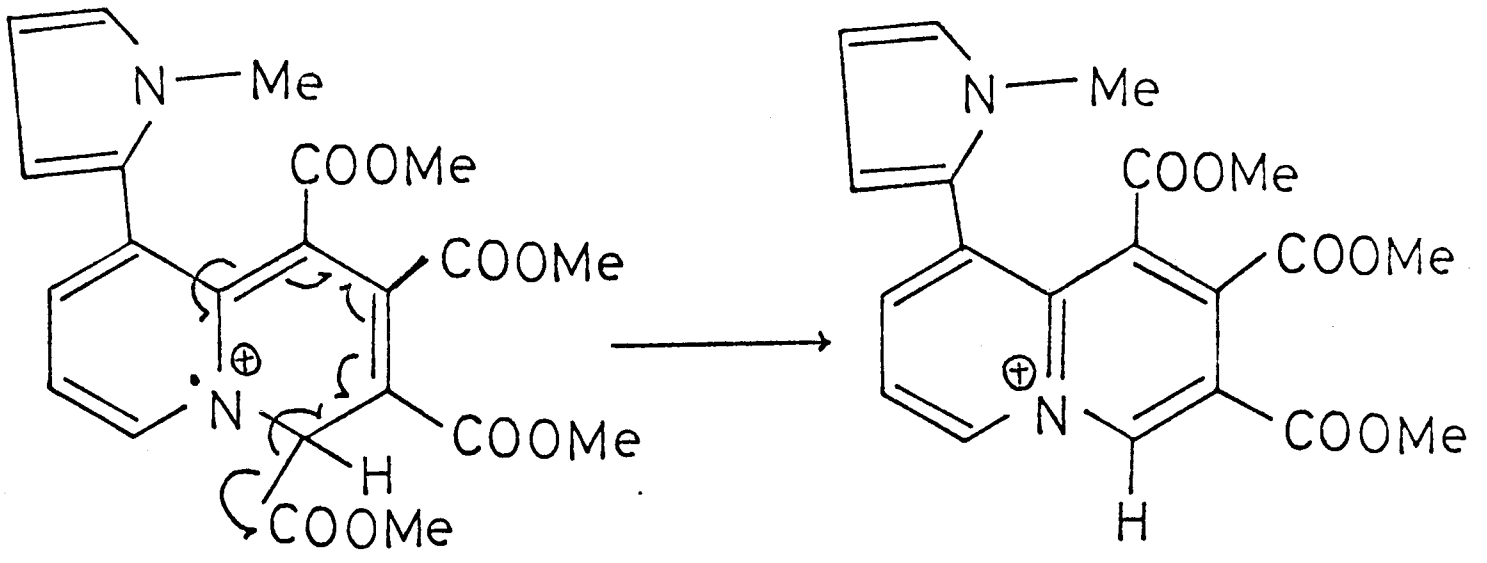
(p)

The isomeric 4H-quinolizines show no loss of •H, thus this peak serves to readily distinguish the two compounds.

The base peak in the mass spectrum of (94) is at m/e 383 and corresponds to loss of methoxycarbonyl group.

Thermal isomerization of the 9aH-isomer gave the 4H isomer (95). The n.m.r. spectrum (Table 8) being in good agreement with that of the 9-methyl 4H-quinolizine (90).

The mass spectrum showed the molecular ion at m/e 442 (8%), the base peak at m/e 383 almost certainly arising by loss of the 4-methoxycarbonyl group giving the quinolizinium cation (q).

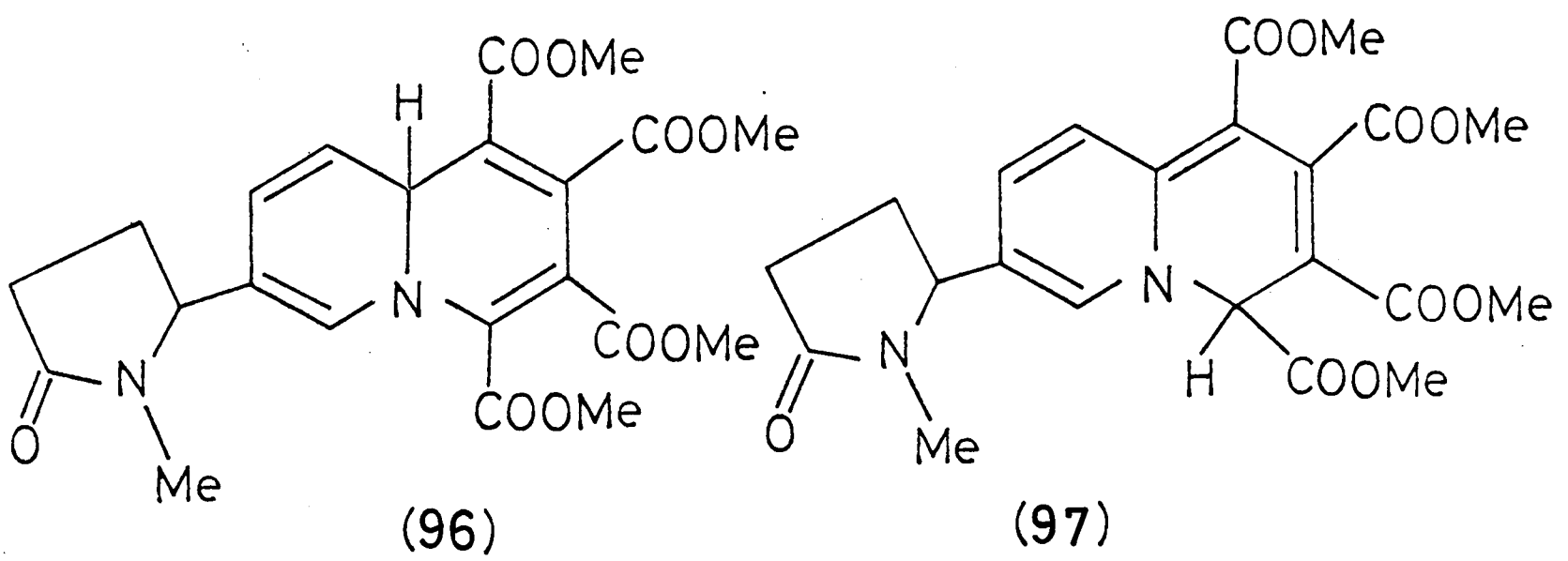


(9)

The u.v. spectra of both isomers are as expected and compare favourably with the 9-methyl analogues (Table 9).

Cotinine with Dimethyl Acetylenedicarboxylate

Cotinine (8) which contains a lactam function reacted with dimethyl acetylenedicarboxylate to give a 9aH-quinolizine. The only solid compound isolated was formed by cyclization in the opposite sense to the nicotyrine adducts to give tetramethyl 7-(1-methylpyrrolid-2-one-5-yl)-9aH-quinolizine-1,2,3,4-tetracarboxylate (96), no 4H-quinolizine was observed.



(96) (97)

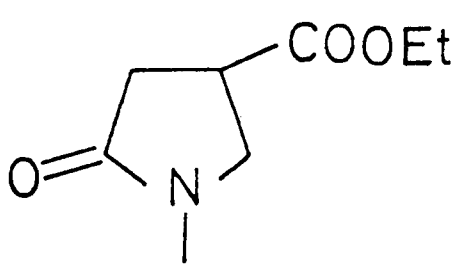
The n.m.r. spectrum was in full agreement with the proposed structure and the relevant values are shown in Table 8.

Table 9. U.v. Spectral Data of 9aH and 4H Quinolizines ($10^{-4}\varepsilon$ in brackets)

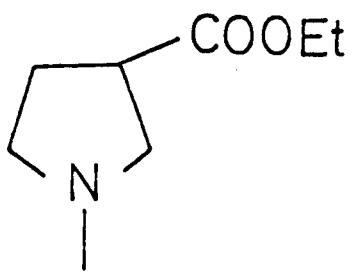
(94)	280(1.57)	331(1.92)	462(0.57)	
(91)[216]	281(1.24)	338(0.50)	420(0.6)	
(95)	259(1.40)	327(1.02)	381(1.34)	461(1.09)
(90)[217]	262(0.74)	311(1.00)	360(1.30)	439(0.97)
(96)	280(1.30)	330(0.40)	435(0.44)	
(97)	265(1.10)	309(1.80)	352(1.06)	442(1.08)
(92)[217]	263(0.91)	307(1.44)	347(1.16)	445(1.10)
(101)	236(1.66)	292(1.64)	442(0.66)	
(102)	264(1.01)	308(1.56)	351(1.21)	445(1.17)

Thermal isomerization of (96) gave the 4H isomer (97). The n.m.r. spectrum (Table 8) compares favourably with that for the corresponding 7-methyl 4H-quinolizine (92). The mass spectrum shows the molecular ion at m/e 460 (5%), no loss of a hydrogen radical being observed. The base peak at m/e 401 corresponds to the expected loss of a methoxycarbonyl group. Table 9 contains the u.v. absorption data.

Brown and Heim[150] have shown that diborane is an excellent reducing agent for amides and more recently Kornet[151] has shown that ethyl 1-benzylpyrrolid-2-one-4-carboxylate (98) is reduced specifically to ethyl 1-benzylpyrrolidine-3-carboxylate (99) by diborane.

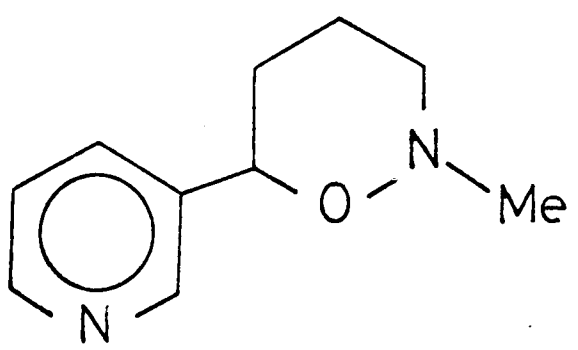


(98)

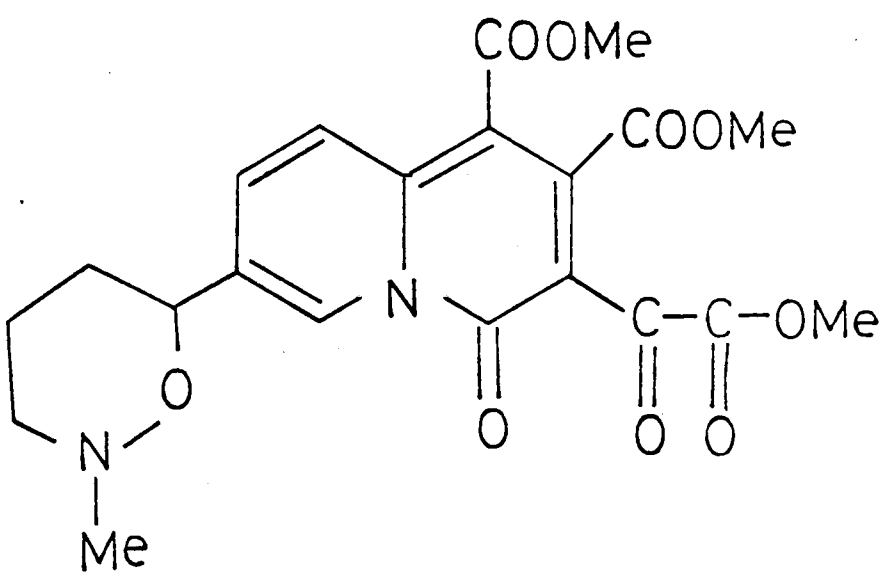


(99)

It was hoped to reduce the lactam function of (97) to the pyrrolidine, thus giving the 7-substituted 4H-quinolizine adduct theoretically obtainable from nicotine and dimethylacetylenedicarboxylate. Unfortunately the lactam proved inert to diborane and was recovered unchanged.



(56)



(100)

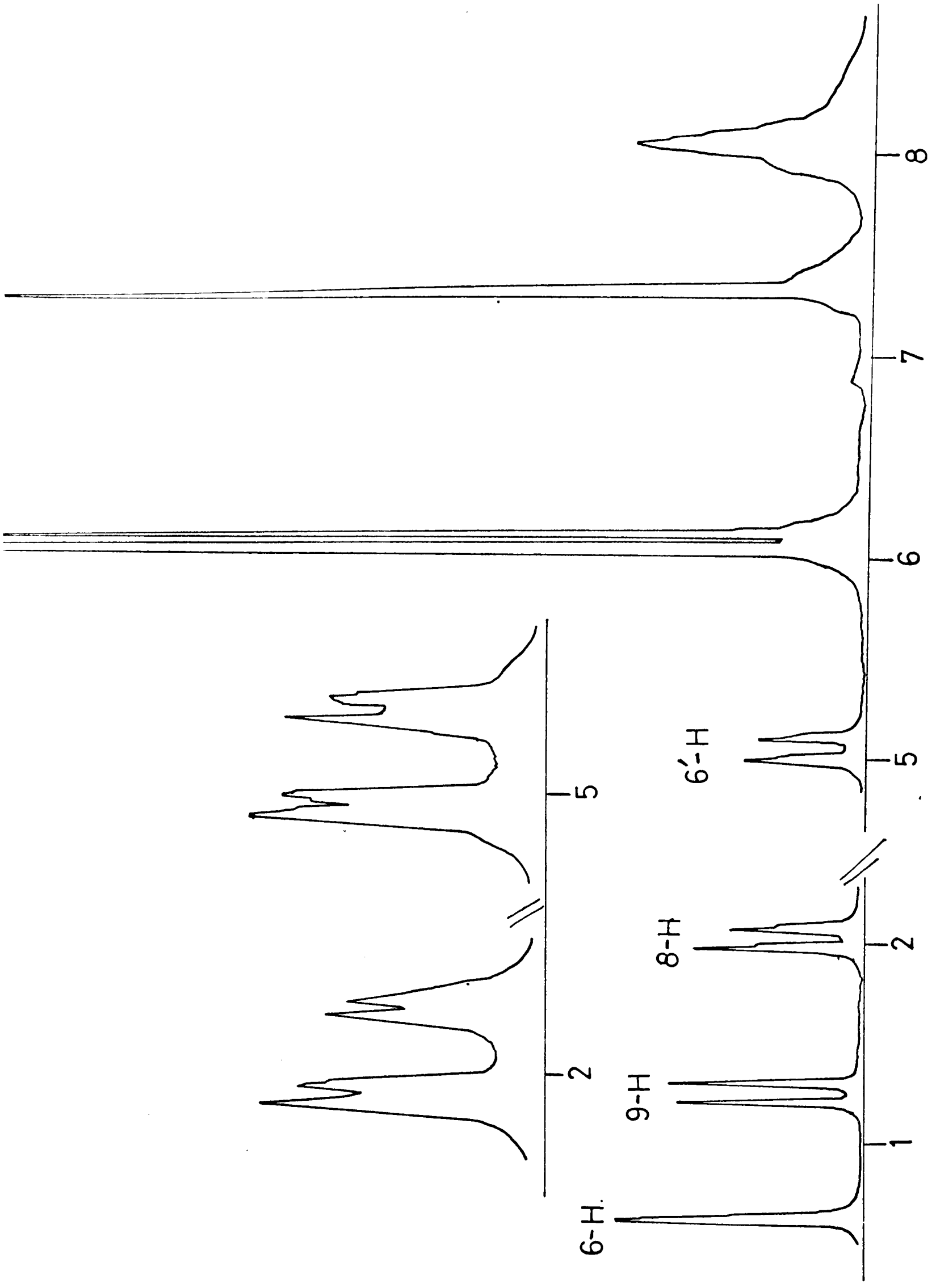


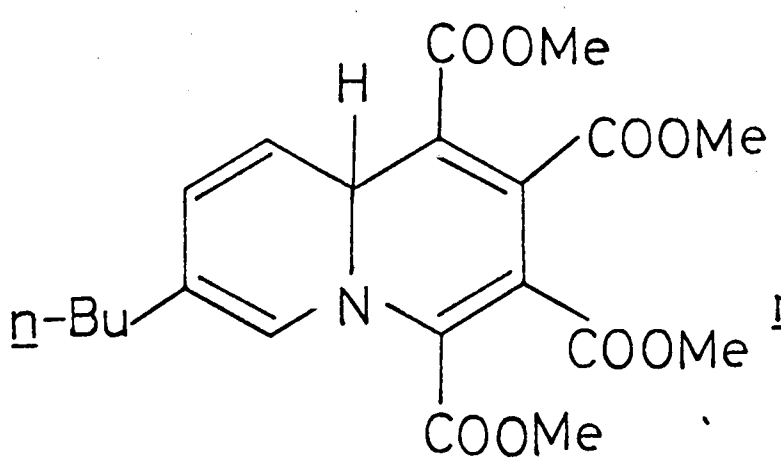
Fig. 49 N.m.r. Spectrum (100 MHz) of Methyl 1,2-dimethoxycarbonyl-7-(2-methyltetrahydrooxazin-6-yl)-4-oxoquinolizine-3-glyoxalate (**100**)

2-Methyl-6-(3-pyridyl)tetrahydro-1,2-oxazine with Dimethyl Acetylenedicarboxylate

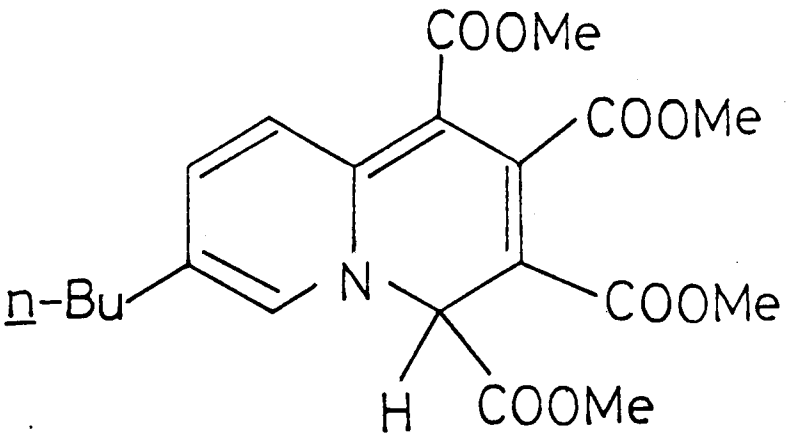
2-Methyl-6-(3-pyridyl)tetrahydro-1,2-oxazine (**56**) obtained by pyrolysis of nicotine 1'-oxide[135] gave one isolable adduct with dimethyl acetylenedicarboxylate.

Elemental and spectral analysis showed it to have the structure of a Kashimoto compound, methyl 1,2-dimethoxycarbonyl-7-(2-methyloxazine-6-yl)-4-oxoquinolizine-3-glyoxalate (**100**). The n.m.r. spectrum (Fig. 49) shows the 6-proton at τ 0.62 ($J_{6,8}$ 1.0), the 8-proton as a quartet at τ 2.03 ($J_{8,9}$ 9.25 Hz), and the 9-proton (doublet) at τ 1.23. Three ester group resonances are observed (two of which are superimposed at τ6.08, the other being at τ6.14). The 6'-proton appears as a broad doublet at τ5.05.

The mass spectrum gives the molecular ion at m/e 446 (42%) being sixteen mass units lower than expected for the 9aH or 4H quinolizine. A peak at m/e 428 (5%) corresponds to loss of water and is also observed in the mass spectrum of the starting oxazine. The base peak (m/e 387) arises by loss of a methoxycarbonyl group from the molecular ion.



(101)



(102)

3-n-Butylpyridine with Dimethyl Acetylenedicarboxylate

Whereas 3-methylpyridine gives the 9-methyl-9aH and 4H-quinolizines also with some 7-methyl-4H-quinolizine ,[146,148] 3-n-butylpyridine (obtained by dehydrogenation of nicotine [136]) gave tetramethyl 7-n-butyl-9aH-quinolizine-1,2,3,4- tetracarboxylate (**101**) and 7-n-butyl-4H-quinolizine-1,2,3,4-

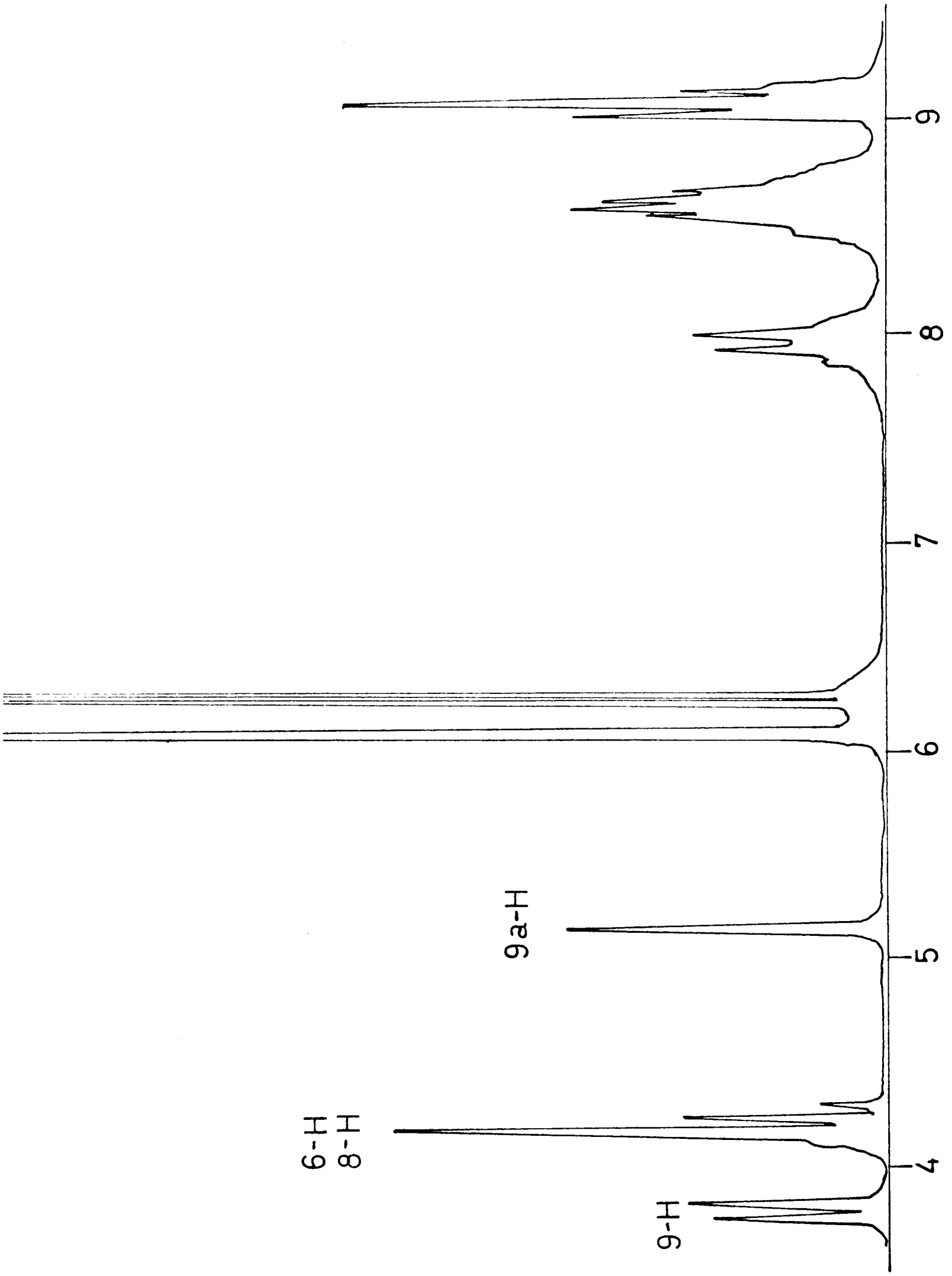


Fig. 50 N.m.r. Spectrum of Tetramethyl 7-n-butyl-9aH-quinolizine-1,2,3,4-tetracarboxylate (101)

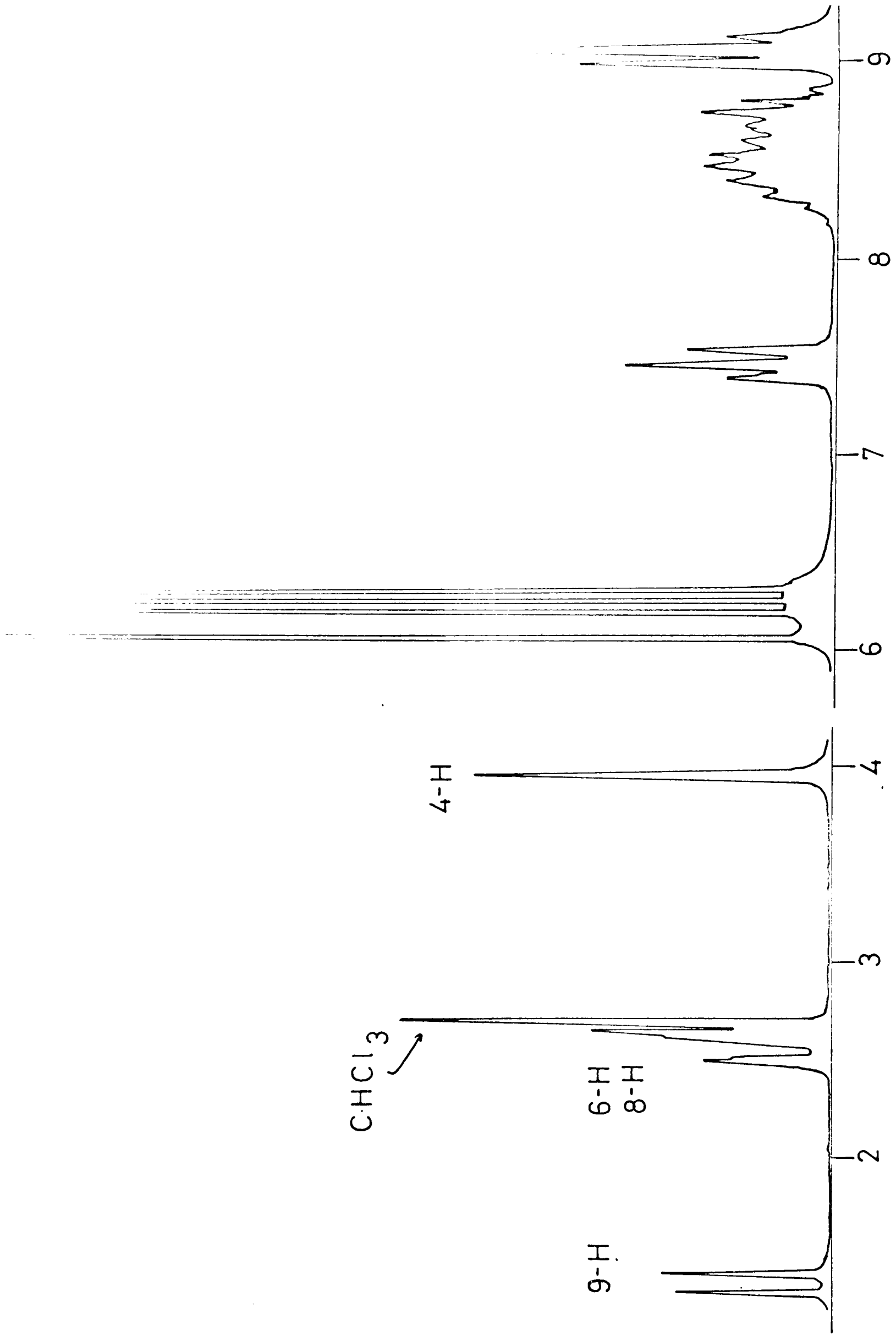


Fig. 51 N.m.r. Spectrum of Tetramethyl 7-n-butyl-4H-quinolizine-1,2,3,4-tetracarboxylate (102)

tetracarboxylate (102). No 9-n-butylquinolizines were isolated or detected. Their structures follow by comparison of their n.m.r. spectra (Figs 50 and 51 and Table 8) with those of the corresponding pyridine and 3-methylpyridine adducts. Compound (101) could readily be isomerized to (102) in refluxing benzene.

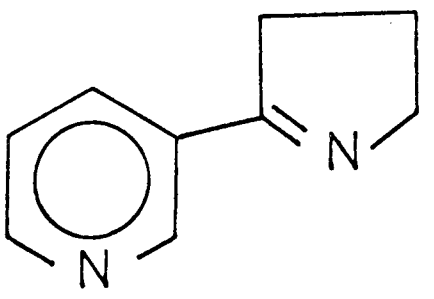
The mass spectrum of (101) gives the molecular ion at m/e 419, loss of a hydrogen radical giving the base peak at m/e 418. Also of 100% intensity is the peak at m/e 360 which corresponds to loss of the methoxycarbonyl group from the molecular ion.

The mass spectrum of (102) shows the molecular ion at m/e 419 (4%) and the base peak at m/e 360 as the only significant peaks.

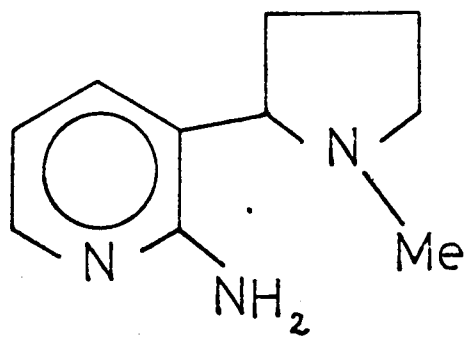
The u.v. spectrum of adduct (102) (Table 9) is in full agreement with that reported for the corresponding 7-methyl-4H-quinolizine (92).

Attempted Reactions with Dimethyl Acetylenedicarboxylate

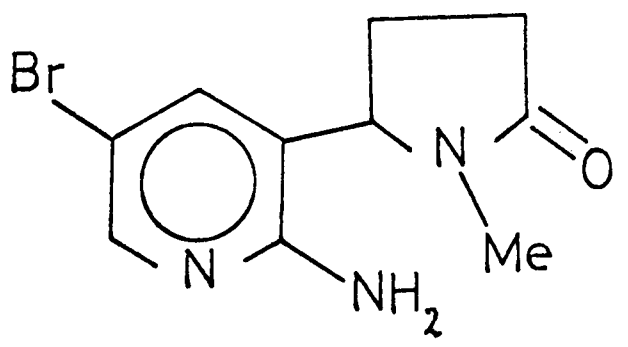
Myosmine (6), 2-aminonicotine (18) and 2-amino-5-bromocotinine (72) all gave tars with dimethyl acetylenedicarboxylate.



(6)



(18)



(72)

Section 6. Biological Evaluation of Compounds Prepared

The testing was conducted by Imperial Chemical Industries and the results can conveniently be divided into three sections, each being obtained from a separate division of I.C.I.

Plant Protection Limited at Bracknell provided the bulk of the Insecticidal Screening, Table 10 shows a representative sample of the results obtained and gives an indication of the tests conducted. Compounds not in the table showed no activity.

The majority of the tests involve spraying an aqueous solution (when water soluble) or an oil dispersion either directly onto the species or onto its food, the latter usually being the plant on which it feeds.

Although activity was observed in a number of cases, this was not considered to be of a useful kind.

The Pharmaceutical Division at Alderley Park provided the testing outlined in Table 11. Again activity was found for a number of compounds but did not prove significant. A blank indicates that the compound was not tested.

The Central Nervous System screen merits further discussion.

Sub-heading T is for temperature, the body temperature of the species (usually mouse or rat) is recorded before and at periods after injection of the test compound. Any unusual variance with a control animal is noted.

Ag refers to the agility test. A number of mice are each placed on long metal rods, some of which have received a dose of the test compound. The length of time each animal remains on the rod is recorded and any variance between controls and test animals noted. The test examines those areas of the CNS which affect balance.

Ax is the Anorexia spaghetti test. A number of rats and mice are allowed to feed for seven days on measured rods of dry spaghetti only, some

animals having received the test compound. The food intake each day is simply obtained by measuring the length of spaghetti remaining. Thus any affect a compound may have on the feeding habits or hunger drive of an animal is obtained.

An refers to analgesia. The study animal is injected with a standard amount of a known compound which causes it to feel pain and thus quirm. The degree of squirming in control animals is compared with those who have received an injection of the test compound previous to the squirm inducing drug. The test gives an indication of the ability of a compound to reduce pain.

EP means electroinduced pain and is of a similar nature. In this test the pain is produced by administering small electric shocks to the animals.

RHA is the Reserpine Hypothermia Antagonism test. The lowering of body temperature is a well known effect on administration of reserpine, the degree to which the test compound augments or diminishes this effect shows the amount of synergism or antagonism to reserpinised mice.

LAR is the locomotor activity ratio. The caged animal is automatically monitored for general movement before and after drug administration, thus the degree to which the drug affects the liveliness of the animal can be readily obtained.

The final series of tests were conducted at The IndustrialHygiene Research Laboratories at Alderley Park, the results are in Table 12. This test is at present being evaluated as to its ability for giving results of a qualitative nature.

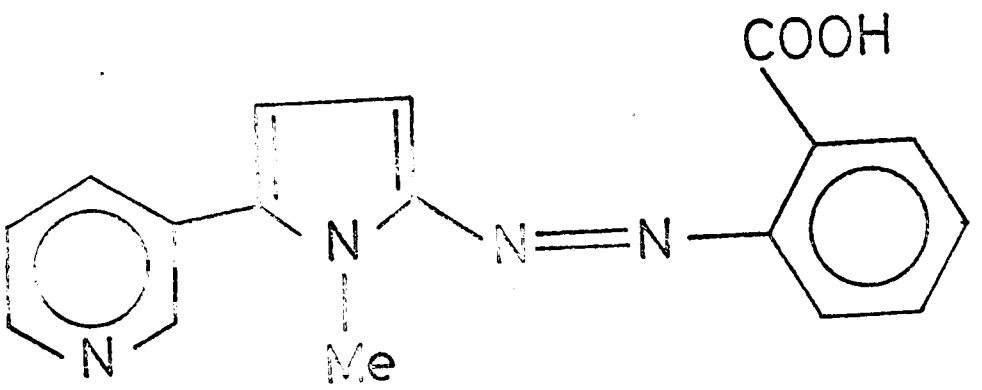
The test animal and control are observed for a number of days prior to drug administration and their behaviour noted. This will include (a) number of times drink is taken per day; (b) amount of food eaten and how much at each session; (c) general activity, waking and sleeping periods, amount of walking and exploring.

The test animal is then given the drug and both it and the control are placed in new cages. Their behaviour is again noted and the drugged animal

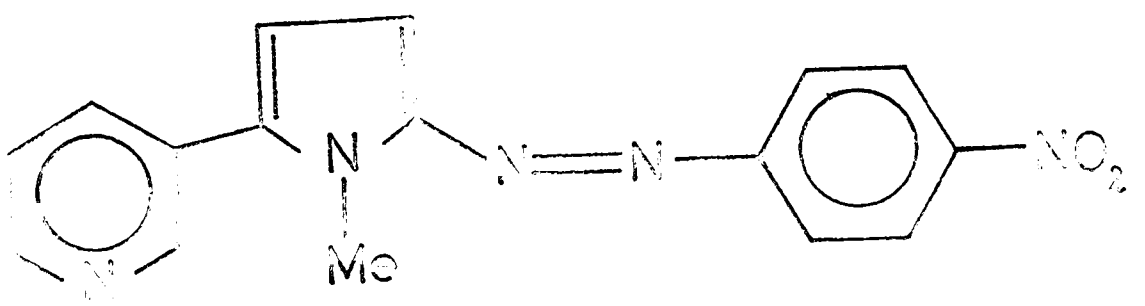
compared with the control.

The test does not give quantitative results but it is hoped that it may provide a speedy, efficient and inexpensive method for exposing activity of almost any kind. Activity found in this test will naturally require a full and complete investigation but lack of activity at this stage may enable many time consuming and expensive tests to be dispensed with.

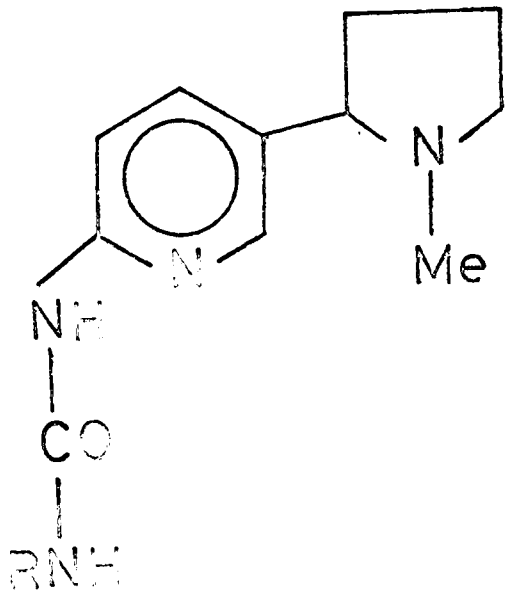
Structures for Section 6 which are not included in the Table of N.M.R spectra (page 149).



(57)



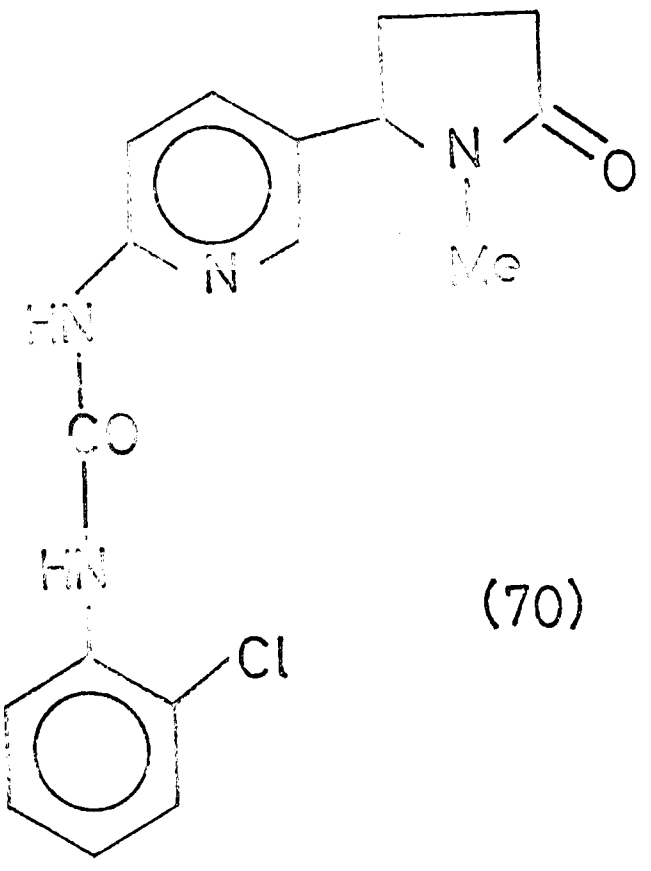
(58)



(64) R = o-chlorophenyl

(65) R = m-chlorophenyl

(66) R = p-chlorophenyl



(70)

Table 10. Insecticidal Screening Results from Plant Protection Limited

	(15)	(46)	(47)	(49)	(50)	(56)	(87)	(87) 2MeI
Phytotoxicity (French bean)	-	-	-	-	-	-	-	100
Acarina (spider mites)								
Adult	-	-	-	-	-	20	-	-
Organophosphate synergist	-	75	-	-	-	40	-	70
Aphid								
Aphis fabae	-	-	-	-	-	-	-	-
Megoura viciae	-	-	-	-	-	-	-	-
Aedes (mosquito)								
Larvae	-	-	-	-	-	-	-	-
Adult	-	-	-	-	-	-	-	-
Musca (house fly)								
Contact (flying)	-	-	-	-	-	20	-	-
Treated surface	-	-	-	-	-	-	-	-
Batella (German cockroach)								
Contact	-	25	-	-	-	-	-	-
Pieris (cabbage white caterpillar)								
Systematic	-	-	- (LNE)	-	- (LNE)	-	-	-
Contact	-	50 (LNE)	100	100	100	-	-	-
Plutella (caterpillar)								
Systematic	-	-	- (LNE)	-	- (LNE)	-	-	-
Contact	-	- (LNE)	-	-	- (LNE)	-	-	-

	(15)	(46)	(47	(49)	(50)	(56)	(87)	(87) 2MeI
Tme (. tard beetle)								
Systematic	-	-	- (LNE)	-	- (LNE)	-	- (LNE)	-
Contact	-	-	-	-	-	-	-	-
Cal (grain weevil)	-	-	-	-	-	-	-	-
Fri (flour beetle)	-	-	-	-	-	-	-	-
Agric (grey field slug)	-	-	-	-	-	50	-	-

The figure shows the number of kills at 1000 ppm. (total kill = 100).

LNE = leaf not eaten (antifeeding effect).

Table 11. Testing Results from Pharmaceuticals Division

	(15)	(18)	(19)	(24)	(24) 2MeI	(46)	(47)	(48)	(49
Insecticide	-		-	-	-	-	-		-
Virus			-	-	-				
Coccidiosis	-		-	-	-	-	-	-	
Antibacterial	**		-	-	-		-	-	
Fungicidal									
Antiseptic	-		-	-	-	-	-	-	
Antidiabetic									
Antidepressant						**	**		
Analgesic	-					**	-	-	
Antihelminth	-						-		
Liver fluke									
Sedative							**		
Central Nervous System									
T		0_{100}	-	-	-				
Ag		0_{100}	-	0_{100}	-				
Ax		-	0_{30}	-	-		**		
Ac		-	-	-	-				
An		-	0_{30}	-	-				
MA		0_{100}	-	-	*				
LAR		-	-	-	-				
EP		-	-	-	-				

	(50)	(51)	(56)	(56) MeI	(57)	(58)
Insecticide	-			-	-	-
Virus					-	-
Coccidiosis	-	-		-	-	-
Antibacterial	-			-	-	-
Fungicidal						
Antiseptic	-	-		-	-	-
Antidiabetic						
Antidepressant						
Analgesic	-	-		-		
Antihelminth				-		
Liver fluke		-		-		
Sedative	**					
Central Nervous System						
T	-				-	-
Ag	-				-	-
Ax	-				-	-
Ac	-				-	-
An	-				-	-
DHA	-				-	-
LAR	-				-	-
EP	-				-	-

	(60)	(63)	(64)	(65)	(66)	(67)	(68)	(69)	(70)
Insecticide		-	-	-	-	-	-	-	
Virus		-	-	-	-	-	-	-	
Coccidiosis	-	-	-	-	-	-	-	-	-
Antibacterial	-	-	-	-	-	-	-	-	**
Fungicidal									
Antiseptic	-	-	-	-	-	-	-	-	-
Antidiabetic									-
Antidepressant	**								-
Analgesic	**								-
Antihelminth									-
Liver fluke									
Sedative		-	-	-	-	-	-	-	
Central Nervous									
System									
T	O_{10}	O_{100}	-	-	O_{100}	-	-		
Ag	-	O_{100}	-	-	O_{100}	-	-		
Ax		-	-	-	O_{100}	-	-		
Ac	O_{30}	-	-	-	-	-	-		
An	O_{30}	-	-	-	-	-	-		
INA	-	-	-	-	-	-	-		
LAR	-	-	-	-	-	-	-		
EP	-	-	-	-	-	-	-		

	(71)	(72)	(74)	(75)	(87)	(87) 2MeI
Insecticide	-	-	-	-	-	-
Virus		-				
Coccidiosis	-	-			-	-
Antibacterial	-	-			-	-
Fungicidal	-					
Antiseptic	-	-			-	-
Antidiabetic	-					
Antidepressant					-	-
Analgesic					-	-
Antihelminth					-	-
Liver fluke						
Sedative						
Central Nervous System						
T			-	-	-	
Ag			-	-	-	
Ax			-	-	-	
Ac			-	-	-	
An			-	-	-	
IMA			-	-	-	
IAR			-	-	-	
EP			-	-	-	

** Activity, but not of useful kind.

0 Not active at level shown but active above this level

- Not active

Table 12. Exploration-Thirst Activity.

Preliminary Screening at Industrial Hygiene Research Laboratory

	Latency Day		Activity Day		Other CNS effects
	1	2	1	2	
(15)	-	-	-	-	-
(18)	-	-	-	-	-
(19)	-	-	-	-	**
(24)	-	-	0_1	0_1	-
(46)	-	-	-	-	-
(47)	-	-	-	-	-
(48)					
(49)	-	-	* 12	-	**
(50)					
(51)					
(56)					
(56)dimethiodide	* 25	-	-	* 25	-
(57)	-	-	-	-	-
(58)	-	-	0_1	0_1	
(60)					
(63)	-	-	-	-	-
(64)	-	* 25	-	-	-
(65)	-	-	-	-	-
(66)	-	-	-	-	-
(67)	-	-	-	* 20	-
(68)					
(69)	* 25	* 25	-	-	-
(70)					

	Latency Day		Activity Day		Other CNS effects
	1	2	1	2	
(71)	-	-	-	-	-
(72)	-	* 25	-	-	-
(74)	*	0_5	0_5	-	**
(75)	0_5	-	0_5	-	**
(87)	-	-	-	-	-
(87) 2 MeI	* 25	-	-	-	-

\- Not active

* Active at level shown (mg./kg.)

0 Not active at level shown but active above this level

* Toxic at concentrations tested

** Activity but not of a useful kind.

EXPERIMENTAL

Melting points were recorded on a Kofler hot stage and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 257 Infracord with polystyrene film as standard. U.v. spectra were recorded in 1 cm cells on a Perkin-Elmer 137-UV machine fitted with a deuterium lamp. Methanol was used as solvent, being distilled slowly from magnesium methoxide before use. N.m.r. spectra were recorded on Perkin-Elmer R14 and (by the author) R12 spectrometers, with tetramethylsilane as internal standard ($\tau = 10$). Coupling constants (J) are given in Hz and the abbreviations s, singlet; d, doublet; q, quartet and m, multiplet employed. Mass spectra were recorded by the author on A.E.I. MS - 9 and Varian-Atlas CH-7 machines (ionizing potential 70 eV). Micro-analyses were by Dr. Strauss at Oxford.

Spence grade H alumina was used for chromatography (100-200 mesh), deactivated with water (5% v/v) to give deactivated basic alumina (pH 10), and with 10% acetic acid aq. (5% v/v) for deactivated neutral alumina. Deactivation involved shaking for 2 hours and standing for 12 hours before use. Thin layer chromatographic plates used for routine monitoring were MN Polygram Sil N-HR/UV 254 (Machery-Nagel and Co., Duren) containing a 254 nm fluorescent indicator and inspected by a UV lamp.

Petrol refers to that fraction of boiling point 60-80°, unless otherwise stated.

Nicotine was supplied by British Nicotine Ltd. and slowly distilled at 118-120°/17 mm under a nitrogen atmosphere before use.

Myosmine was supplied by the Imperial Tobacco Group of Great Britain and purified by recrystallization from petrol (b.p. 80-100°).

Experimental for Section 1. Alkyl Derivatives of Nicotine

Cotinine dibromide hydrobromide perbromide. - This salt was prepared according to McKinnis.[48] Bromine (198 ml, 5.76 mol) in acetic acid (80%, 480 ml) was added to L-nicotine (88 g, 0.538 mol) in acetic acid (80%, 400 ml) over 2 h with stirring. Water (1800 ml) was added and the two phase system vigorously stirred and heated to 80° when homogeneity resulted. After 30 min at 80° cooling whilst stirring gave orange needles of cotinine dibromide hydrobromide perbromide, $C_{10}H_9N_2OBr_2.HBr.Br_2$ (174 g, 73%) m.p. 141-145° (lit.[18] 141-144°).

1-Methyl-5-(3-pyridyl)pyrrolid-2-one (8). - Zinc dust (125 g) was added over 3 h to a mixture of cotinine hydrobromide dibromide perbromide (100 g, 0.174 mol), acetic acid (50%, 1250 ml) and concentrated hydrochloric acid (65 ml) following McKinnis[48] to give cotinine (30.4 g, 0.172 mol, 98%) b.p. 145-150°/0.7 mm. Cotinine is very hygroscopic and would not give a reliable analysis. Methiodide (prepared in and recrystallized from acetonitrile) m.p. 147-148°. (Found: C, 41.9; H, 4.9; N, 8.6. Calc. for $C_{11}H_{15}N_2OI$: C, 41.5; H, 4.7; N, 8.8%).

1,3,3-Trimethyl-5-(3-pyridyl)pyrrolid-2-one (46). - Cotinine (8.8 g, 0.05 mol) in ether (50 ml, sodium dried) was slowly added to sodamide (from 4.6 g sodium) in liquid ammonia (150 ml). Methyl iodide (28 g, 0.2 mol) in ether (50 ml) was slowly added to the resulting rusty brown solution which became dark green. Ammonia was allowed to evaporate and water (50 ml) and chloroform (50 ml) were added. The organic layer was

separated, dried (magnesium sulphate) and the solvent removed to give a light yellow oil. Trituration with petrol gave a white solid which recrystallized from petrol as fine white needles (8.2 g, 80%). Sublimation (90-100°/20 mm) gave an analytical sample, m.p. 95-97° (Found: C, 70.5; H, 7.7; N, 13.7. $C_{12}H_{16}N_2O$ requires: C, 70.6; H, 7.8; N, 13.7%) ν_{max} (nujol) 1678s, 1592w, 1578w, 1393s, 1076s, 1025s, 919m, 885w, 819m, 758m, 739m and 721s $cm.^{-1}$ m/e (%) 204(34, M^+), 203(10,M^+-1), 189(3, M^+-15), 175(4, M^+-29), 161(1, M^+-43), 146(6, M^+-58), 132(28, M^+-72), 126(100, M^+-78), 119(19, M^+-85), 117(17, M^+-87).

3,3-Diethyl-1-methyl-5-(3-pyridyl)pyrrolid-2-one (47). - Ethyl bromide instead of methyl iodide as in the previous reaction gave the title compound as a yellow oil (9.0 g, 77.5%) b.p. 130-134°/1.0 mm (Found: C, 72.2; H, 8.6; N, 11.9. $C_{14}H_{20}N_2O$ requires: C, 72.5; H, 8.6; N, 12.1%) ν_{max} (liquid film) 2984s, 2970w, 2941m, 1679s, 1591w, 1578m, 750s, 714m, and 661m $cm.^{-1}$ m/e (%) 232(8, M^+), 231(10, M^+-1), 217(2, M^+-15), 204(100, M^+-28), 189(80, M^+-43), 176(13, M^+-56), 154(8, M^+-78).

1,3-Dimethyl-5-(3-pyridyl)pyrrolid-2-one (48). - Cotinine (8.8 g, 0.05 mol) in ether (50 ml, sodium dried) was added with vigorous stirring to sodamide (from 1.15 g sodium) in liquid ammonia (100 ml). Methyl iodide (8.0 g, 0.06 mol) was added immediately, the ammonia was allowed to evaporate, water (50 ml) added and the mixture chloroform extracted (2 x 50 ml). Drying (magnesium sulphate), solvent removal and distillation of the resulting yellow oil (b.p. 123-130°/1.0 mm) gave colourless viscous oil (5.5 g, 59%). A satisfactory analysis could not be obtained. ν_{max} (liquid film) 3035w, 2985s, 2968s, 2939m, 1690s, 1591m, 1576m, 1395s, 1023m, 812m and 716s $cm.^{-1}$ m/e (%) 190(17, M^+), 189(7, M^+-1), 186(7, M^+-4), 166(1, M^+-24), 161(4.5, M^+-29), 130(30, M^+-60), 119(19, M^+-71), 118(20, M^+-72), 112(87, M^+-78), 98(20, M^+-92), 58(31, M^+-132), 43(100, M^+-147).

1,4,4-Trimethyl-2-(3-pyridyl)pyrrolidine (49). - 1,3,3-Trimethyl-5-(3-pyridyl)pyrrolid-2-one (2.0 g, 0.01 mol) in ether (50 ml, sodium dried) was slowly added to lithium aluminium hydride (0.75 g) in ether (40 ml), so maintaining a gentle reflux by spontaneous reaction; heating then maintained reflux for 3 h. After cooling excess hydride was destroyed by consecutive addition of wet ether, ethyl acetate and water. Ether extraction drying (magnesium sulphate) and solvent evaporation gave a yellow oil which distilled at 128-130°/13 mm to give 1,4,4-trimethyl-2-(3-pyridyl)pyrrolidine (49) (1.5 g, 0.0079 mol, 79%) as a colourless oil. An accurate analysis was not obtained. $\underline{n}_D^{17}$ 1.5032; ν_{max} (liquid film) 3040w, 2960s, 2910w, 2875m, 2842m, 2780s, 2680w, 1592w, 1580m, 1430m, 1368m, 1050m, 1027m, 801m and 719s cm.$^{-1}$ λ_{max} 215, 258 (shoulder), 263, 268 (shoulder) nm. m/e (%) 190(28, M^+), 189(17, M^+-1), 175(4, M^+-15), 173(4, M^+-17), 133(90, M^+-57), 112(100, M^+-78). Dipicrate (prepared in and recrystallized from methanol) m.p. 195-198° (decomp.) (Found: C, 44.5; H, 3.8; N, 17.2. $C_{24}H_{24}N_8O_{14}$ requires: C, 44.5; H, 3.7; N, 17.3%).

4,4-Diethyl-1-methyl-2-(3-pyridyl)pyrrolidine (50). - Reduction of 1-methyl-3,3-diethyl-5-(3-pyridyl)pyrrolid-2-one with lithium aluminium hydride as in the previous experiment gave 4,4-diethyl-1-methyl-2-(3-pyridyl)pyrrolidine (50) as a colourless oil, b.p. 168-170°/13 mm (60% yield). (Found: C, 76.9; H, 10.6; N, 12.7. $C_{14}H_{22}N_2$ requires: C, 77.0; H, 10.1; N, 12.8%). $\underline{n}_D^{17}$ 1.5109; ν_{max} (liquid film) 3090w, 3039w, 2970s, 2945s, 2885w, 2875w, 2840w, 2780m, 1591w, 1578m, 1026m, 955m, 810m and 719 cm.$^{-1}$ λ_{max} 211, 258 (shoulder), 265, 268 nm. m/e (%) 218(19, M^+), 217(23, M^+-1), 203(8, M^+-15), 190(6, M^+-28), 189(12, M^+-29), 173(4, M^+-45), 159(4, M^+-59), 158(4, M^+-60), 146(17, M^+-72), 140(72 M^+-78), 133(100, M^+-85).

1,4-Dimethyl-2-(3-pyridyl)pyrrolidine (51). - Reduction of 1,3-dimethyl-5-(3-pyridyl)pyrrolid-2-one with lithium aluminium hydride as in the above experiment gave, 1,4-dimethyl-2-(3-pyridyl)pyrrolidine (1.3 g, 64%) b.p. 115-119°/13 mm as a colourless oil. An accurate analysis was not obtained. ν_{max} (liquid film) 3039w, 2960s, 2875m, 2840m, 2780s, 1592w, 1578m, 1430m, 1316m, 1024m, 806m and 716 $cm.^{-1}$ m/e (%) 176(18.5, M^+), 175(14, M^+-1), 162(4, M^+-14), 161(4, M^+-15), 144(4, M^+-32), 133(43, M^+-43), 119(10, M^+-57), 118(7, M^+-58), 117(5, M^+-59), 98(100, M^+-78), 84(21, M^+-92). 2.5 Picrate (prepared in and recrystallized from methanol) m.p. 205-207° (decomp.) (Found: C, 41.7; H, 3.2; N, 17.6. $C_{52}H_{45}N_{19}O_{35}$ requires: C, 41.8; H, 3.1; N, 17.8%).

Attempted reduction of 1,3,3-Trimethyl-5-(3-pyridyl)pyrrolid-2-one with Sodium dihydro-bis(2-methoxyethoxy)aluminate. - The pyrrolidone-2 (49) (1.0 g, 0.005 mol) in toluene (20 ml) was added to sodium dihydro-bis(2-methoxyethoxy)aluminate (3.0 g, 0.010 mol) in toluene (40 ml) and the temperature maintained at 110° for 6 h. Cooling, addition of base, removal and drying of the organic phase (magnesium sulphate) gave only starting pyrrolidone-2 (49) as a white solid after solvent removal. Characterised by i.r. and n.m.r.

Attempted Reaction of Nicotine with Sodamide in Ammonia. - Nicotine (16.2 g, 0.1 mol) in ether (20 ml, sodium dried) was slowly added to sodamide (from 4.6 g sodium) in ammonia (150 ml) at -50 to -60°. After addition methyl iodide (28.4 g, 0.2 mol) in ether (40 ml) was added to the resulting yellow mixture which was vigorously stirred (12 h). Addition of water (50 ml), ether extraction, drying and solvent removal gave nicotine b.p. 120-125°/13 mm (13.9 g) (i.r., n.m.r.). Lithium amide under the above conditions gave only nicotine (12.1 g).

3-Ethoxypropyl Bromide. - 3-Ethoxypropanol (135.0 g, prepared from 1,3-propane diol by the method of Noyes,[133]) in carbon tetrachloride (200 ml) was treated over 1 h with phosphorus tribromide (55 ml) in chloroform (200 ml) during which time the temperature was allowed to rise to 40°. The mixture was poured into water (1 l), the chloroform layer separated, dried (magnesium sulphate) and evaporated to leave crude 3-ethoxypropyl bromide. Distillation at 45-49°/13 mm gave the pure bromide as a water white mobile liquid (180 g, 79.7%).

3-Acetylpyridine with 3-Ethoxypropylmagnesium Bromide. - 3-Ethoxypropylmagnesium bromide (0.2 mol, from 4.6 g magnesium and 33.4 g 3-ethoxypropyl bromide) in ether (100 ml, sodium dried) was added over 30 min to 3-acetylpyridine (12.1 g, 0.1 mol) stirred in ether (100 ml, sodium dried). A yellow precipitate formed immediately. After 1 h the mixture was poured into cold 10% ammonium chloride aq., the ether layer separated, water washed, dried (magnesium sulphate) and solvent removed to give a light yellow oil. Distillation gave two fractions, (i) 50-55°/1.0 mm shown by n.m.r and refractive index to be n-propyl ethyl ether (10.0 g) and (ii) 127-133°/1.0 mm shown by n.m.r., mass spectra and analysis to be 1-methyl-1-(3-pyridyl)-4-ethoxybutan-1-ol (39) (12.4 g, 58.5%)(Found: C, 69.1; H, 9.0; N, 6.6. $C_{12}H_{19}NO_2$ requires: C, 69.0; H, 9.1; N, 6.7%). n_D^{19} 1.5038; ν_{max} (liquid film) 3300b, 2980m, 2865m, 1595w, 1580w, 1480w, 1420m, 1379m, 1114bs, 814m and 720s $cm.^{-1}$ m/e (%) 209(0.6, M^+), 195(0.6, M^+-14), 194(3.0, M^+-15), 148(9.5, M^+-61), 122(100, M^+-87), 106(15, M^+-103).

2-Methyl-2-(3-pyridyl)tetrahydrofuran (40). - 1-Methyl-1-(3-pyridyl)-4-ethoxybutan-1-ol (2.9 g) and hydrobromic acid (50 ml, 49%) were stirred at 145° for 10 min. The solution was neutralised with saturated sodium bicarbonate (350 ml), the organic phase chloroform extracted (2 x 50 ml), dried (magnesium sulphate) and solvent removed to give dark brown oil. Distillation at 128-132°/13 mm gave 2-methyl-2-(3-pyridyl)tetrahydrofuran (0.46 g) as a colourless oil (Found: C, 73.3; H, 7.9; N, 8.9. $C_{10}H_{13}NO$ requires C, 73.6; H, 8.0; N, 8.6%). n_D^{19} 1.5199; ν_{max} (liquid film) 2975s, 1720s, 1695s, 1588m, 1574m, 1475m, 1415s, 1270m, 1105m, 1086m and 718s $cm.^{-1}$ m/e (%) 162(1, M^+), 161(1, M^+-1), 148(100, M^+-4), 106(89, M^+-56), 78(40, M^+-84).

4-Methyl myosmine (42). - Myosmine (1.2 g) in ether (50 ml) was added over 1 h to methyl magnesium iodide (from 1.4 g magnesium and 8.3 g methyl iodide) in ether (40 ml). The resulting dark green solution was stirred at 18° for 30 min, poured into ammonium chloride (10%, 200 ml), the ether layer removed and the aqueous layer chloroform extracted. The organic extracts were combined, dried (magnesium sulphate) and evaporated to leave a brown oil which distilled at 132-138°/13 mm to give 4-methyl myosmine as a light yellow oil (0.40 g), an accurate analysis could not be obtained. n_D^{20} 1.5435; ν_{max} (liquid film) 2960b, 2865m, 1610s, 1591m, 1552w, 1432m, 1329m, 1220w, 1039s, 988m, 964m, 831, 802m and 738 $cm.^{-1}$ m/e (%) 160(100, M^+), 159(95, M^+-1), 145(10, M^+-15), 132(48, M^+-28), 131(37, M^+-29), 130(8, M^+-30), 129(15, M^+-31). Dipicrate (prepared in and recrystallized from methanol) m.p. 176-178° (decomp.) (Found: C, 42.6; H, 3.0; N, 18.2. $C_{22}H_{18}N_8O_{14}$ requires C, 42.7; H, 3.0; N, 18.1%).

N-Methyl Nicotinamide. - Methyl nicotinoate (50 g) and methylamine (100 ml of a 33% ethanolic solution) were heated at 100° for 24 h in a stainless steel autoclave. Ethanol was evaporated from the light green resulting solution to give a white solid which recrystallized from benzene as colourless needles of N-methyl nicotinamide (43 g) m.p. 103-104° (lit.,[134] 104-105°).

N-Methyl Nicotinamide with Methylmagnesium Iodide. - Methyl magnesium iodide (0.2 mol, prepared from 4.8 g of magnesium and 28.4 g methyl iodide) in ether (100 ml) was added (1 h) to a vigorously stirred slurry of N-methyl nicotinamide (13.6 g, 0.1 mol) in toluene (500 ml). The resulting light yellow slurry was warmed to 100° and maintained for 3 h. Cooling to 5°, addition of ammonium chloride (200 ml, 10%) and chloroform extraction gave, after solvent removal, starting amide (1.2 g). Basification of the ammonium chloride solution with potassium hydroxide and chloroform extraction gave more starting amide (0.6 g). No other identifiable compounds were obtained.

1-(3-Pyridyl)ethylidenemethylamine. - Methylamine (100 ml of a 33% ethanolic solution) and 3-acetylpyridine (60 g) were stirred in benzene (200 ml) containing molecular sieve (5A, 150 g) for 48 h. Filtration and solvent removal gave an amber liquid which distilled at 116-118°/13 mm to give 1-(3-pyridyl)ethylidenemethylamine (54.2 g, 85%). (Found: C, 71.3; H, 7.6; N, 20.3. $C_8H_{10}N_2$ requires: C, 71.5; H, 7.5; N, 20.1%) n_D^{20} 1.5489. ν_{max} (liquid film) 1691w, 1640s, 1585m, 1572w, 1415s, 1378m, 1294m, 1195w, 1020m, 809 broad m, 709s cm.$^{-1}$ λ_{max} 237(1.0), 267 (0.4)nm. m/e (%) 134(41, M^+), 133(34, M^+-1), 118(100, M^+-16), 105(6, M^+-29), 103(8, M^+-31), 92(10, M^+-42), 78(40, M^+-56), 56(55, M^+-78).

Attempted reaction of 1-(3-Pyridyl)ethylidenemethylamine with 3-Ethoxypropyl Magnesium Bromide - 3-Ethoxypropylmagnesium bromide (from 5.2 g magnesium and 37.6 g 3-ethoxypropyl bromide in 200 ml ether) was treated with 1-(3-pyridyl)ethylidenemethylamine (15.01 g) in ether (200 ml) under nitrogen with constant stirring. The resulting yellow solid was added to ammonium chloride solution (10%, 400 ml) and the ether layer removed. The aqueous solution was basified and chloroform extracted (3 x 100 ml), the organic extracts combined, dried (magnesium sulphate) and the solvent removed. Distillation of the residue at 0.1 mm gave only ethyl n-propyl ether (1.8 g). Much tar remained and no other products were identified or isolated.

Attempted reaction of 1-(3-Pyridyl)ethylidenemethylamine with Succinic Anhydride. - The title imine (26.8 g) and succinic anhydride (20.0 g) were refluxed in xylene (25 ml) for 24 h. The reaction gave only tar, no products could be isolated by a number of work-up procedures.

Repetition using toluene as solvent likewise gave tar but at a slower rate.

Experimental for Section 2. The Oxidation of Nicotine and Reactions of some Oxidation Products

Cotinine (8) with Sodium Tetraphenylboron. - Cotinine (0.352 g, 0.002 mol) in water (160 ml, pH 2 by addn of HCl aq) was treated with a 1% aqueous solution of sodium tetraphenylboron (140 ml, 0.004 mol) at 50°. A white precipitate which immediately formed was filtered with difficulty and dried over phosphorous pentoxide (1.15 g) m.p. 95-98° (resolidifies and decomp. 120-200°). The solid was insoluble in the usual solvents becoming a glue above 70° in solution. Elemental analysis showed non-stoichiometry, the reaction was not further investigated.

Cotinine with N,N-Diethyl-2-chloroethylamine. - Cotinine (4.4 g, 0.025 mol in ether (75 ml, sodium dried) was slowly added to sodamide (from 2.3 g sodium) in ammonia (150 ml) at -50°. N,N-Diethyl-2-chloroethylamine (13.5 g, 0.01 mol), obtained from the hydrochloride immediately prior to use, was then slowly added in petrol (75 ml) and the resulting dark red mixture vigorously stirred for 12 h, allowing ammonia to evaporate. Water was added to the residue and the ether/petrol layer removed. Solvent evaporation and distillation of the residue gave cotinine (0.1 g) (i.r., n.m.r., and t.l.c.). Chloroform extraction of the aqueous phase, drying (magnesium sulphate), filtering and solvent removal gave a dark red glue, which would not crystallize or distil under reduced pressure. T.l.c. of the chloroform extract showed a little cotinine and much immobile material (1 : 9 methanol: chloroform).

Attempted Hydrolysis of Cotinine (8). - Cotinine (1.76 g, 0.01 mol) and potassium hydroxide (0.62 g, 0.011 mol) in 15% aqueous ethanol were refluxed for 16 h. Ether extraction gave cotinine (1.54 g) (i.r., n.m.r. and t.l.c.).

Cotinine (8) with Sodamide. - Cotinine (4.4 g) sodamide (1.2 g) and dimethylaniline (15 ml) were heated at 150°. Vigorous bubbling ceased after 15 min and the resulting brown glue was poured into water (100 ml) and ether extracted. Drying (potassium carbonate) and solvent evaporation gave dimethylaniline (i.r. and n.m.r.). Chloroform extracts from the aqueous phase contained only cotinine (1.4 g, 32%) (i.r., n.m.r. and R_f).

Cotinine (8) with Dimethyl Oxalate. - Sodium metal (0.25 g) was added to cotinine (1.76 g, 0.01 mol) in benzene (10 ml) containing dimethyl oxalate (1.18 g, 0.01 mol). After stirring at 20° for 1 h solvent was removed and the yellow oil acidified with 5% sulphuric acid. Basifying with 30% ammonium hydroxide, chloroform extraction, drying (potassium carbonate) and solvent removal gave cotinine (1.2 g, 68%) (i.r. and n.m.r.). Temperature increase reduced cotinine recovery giving no other products. Diethyl oxalate and sodium hydride also only gave cotinine.

1-Methyl-2-(3-pyridyl)pyrrolidine 1-oxide (13). - Nicotine mono N-oxide was prepared according to Taylor.[132] Thus nicotine (32.4 g) gave 1-methyl-2-(3-pyridyl)pyrrolidine 1-oxide (30.2 g, 85%) as a colourless viscous oil. Picrate (ethanol) m.p. 168-169° (lit.,[132] m.p. 168-169°).

2-Methyl-6-(3-pyridyl)tetrahydro-1,2-oxazine (56). - Nicotine mono-N-oxide (17.8 g) was pyrolysed according to Rayburn et al.[135] to give the title oxazine (56) (16.9 g, 95%); n_D^{25} 1.5254; ν_{max} (liquid film) 3085w, 3030w, 2990w, 2940s, 2865m, 2785w, 1593w, 1578w, 1480m, 1425s and 712s $cm.^{-1}$ m/e (%) 178(14,M^+), 160(2, M^+-18), 159(3, M^+-19), 119(95, M^+-59), 118(60, M^+-60), 78(16, M^+-100), 60(100, M^+-118). Picrate (prepared in and recrystallized from ethanol) m.p. 183-184° (lit.,[135] m.p. 184°). Dimethiodide (prepared in acetonitrile and recrystallized from ethanol) m.p. 141-144° (Found: C, 31.3; H, 4.4; N, 6.1; I, 54.7. Calc. for $C_{12}H_{20}N_2OI_2$: C, 31.3; H, 4.4; N, 6.1; I. 55.0%).

1-Methyl-2-(3-pyridyl 1-oxide)pyrrolidine 1-oxide(14). - Nicotine di-N-oxide was prepared according to Johnson.[131] Thus nicotine (32.5 g) gave the di-N-oxide (35.0 g, 90%) as a clear yellow viscous hygroscopic oil. Picrate m.p. 245-246° (lit.,[131] m.p. 245-246°).

Attempted Nitration of Nicotine di-N-oxide. - Nicotine di-N-oxide (10.0 g) dissolved in conc. sulphuric acid (90 ml) was treated portionwise with potassium nitrate (16 g). The mix was heated to 90° and maintained for 16 h. On cooling the acid solution was poured into ice water (900 ml) and 10 N potassium hydroxide slowly added till the solution became basic. Chloroform extraction, drying (magnesium sulphate) and solvent removal gave a dark brown oil (1.3 g). Purification by standard proceddres failed. Spectroscopic examination of the impure oil (i.r. and n.m.r.) did not aid identification.

The aqueous phase from the chloroform extraction was evaporated to dryness and the resulting solid of potassium sulphate was extracted with hot chloroform. Drying (magnesium sulphate) and solvent evaporation gave further dark brown oil (0.9 g) which likewise could not be purified. I.r. and n.m.r. examination failed to aid identification. No other compounds were obtained or identified from the reaction.

Addition of a nitration mixture of conc. sulphuric acid (30 ml) and fuming nitric acid (12 ml) to nicotine di-N-oxide (10 g) produced an immediate tar. The reaction was not further investigated.

1-Methyl-2-(3-pyridyl)pyrrole (3). - Nicotine (76 g) was oxidised by the method of Frank[17] to give (a) colourless oil (12 g) b.p. 48-50°/2.5 mm, (b) light yellow oil (20.0 g) b.p. 96-108°/2.5 mm and (c) dark yellow oil (15 g) b.p. 190-200°/2.5 mm. Frank and Weatherbee[136] have shown (a) to be 3-n-butylpyridine. Johnson[131] has shown (c) to be methyl di-4-(3-pyridyl)butylamine. Fractional distillation of (b) gave pure nicotyrine (17.5 g, 23.6%) b.p. 98-102°/2.5 mm. Picrate (ethanol) m.p. 168-169° (lit.,[17] 168.5-169°).

2-(4-Nitrophenyl-azo)-1-methyl-5-(3-pyridyl)pyrrole (58). - According to Frank[17] p-nitrobenzenediazonium chloride (6.9 g) and nicotyrine (7.0 g) were coupled to give the title azo compound as dark red crystals from ethanol (14.3 g, 77.6%), m.p. 195-198° (lit.[17] 195-197°) (Found: C, 63.4; H, 4.3; N, 23.1. Calc. for $C_{16}H_{13}N_5O_2$: C, 62.5; H, 4.3; N, 22.8%).

2-(1-Methyl-5-(3-pyridyl)pyrrol-2-yl-azo)-benzoic acid (57). - Anthranilic acid (8.2 g, 0.06 mol) in water (500 ml) containing concentrated hydrochloric acid (32 ml, 0.024 mol) was cooled to 0° and sodium nitrite (5.5 g, 0.08 mol) in water (500 ml) added dropwise with constant stirring. This solution was added with stirring to nicotyrine (7.1 g, 0.04 mol) and sodium acetate (10 g) dissolved in water (500 ml) and ethanol (50 ml) at 0° over 1 h. The resulting red solid recrystallized (ethanol) to give 2-(1-methyl-5-(3-pyridyl)pyrrol-2-yl-azo)-benzoic acid (12.2 g, 0.041 mol, 69%) m.p. 174-175° (Found: C, 65.6; H, 4.6; N, 19.4. $C_{16}H_{14}N_4O_2$: requires: C, 65.3; H, 4.6; N, 19.4%); ν_{max} (nujol) 1710s, 1598w, 1580w, 1510w, 1075s, 1042s, 899m, 783m, 765m and 696m $cm.^{-1}$; λ_{max} 409nm.

Nicotyrine with Acetic Anhydride. - Nicotyrine (1.58 g), acetic anhydride (2.2 ml) and benzene (5 ml) were heated to reflux for 2 h with orthophosphoric acid (1 drop). The resulting dark red solution was cooled and red tar deposited. This was taken up in water/benzene (50 ml of 50:50) and the aqueous layer basified (sodium carbonate). The benzene layer was separated, dried (magnesium sulphate) and evaporated to leave dark yellow oil. Distillation gave nicotyrine (1.2 g) as the only isolable product.

Use of zinc chloride or aluminium trichloride as catalyst gave only intractable tars.

2,5-Dihydro-1-methyl-2-(3-pyridyl)pyrrole (5). - Nicotyrine (15.0 g) was reduced to the title compound (dihydronicotyrine) by the method of Haines and Eisner [85] (7.2 g, 42%) b.p. 114-124°/11 mm. N.m.r. (CCl_4) showed 20% nicotine as impurity (1-methyl resonances). Trial reactions were conducted without further purification.

Dihydronicotyrine with Osmium Tetroxide and Sodium Chlorate. - A mixture of dihydronicotyrine (15 g, containing 20% nicotine), sodium chlorate (12.6 g, 0.12 mol) and osmium tetroxide (0.2 g) was stirred for 48 h at 20°. Water (250 ml) was added, the mixture saturated with sodium carbonate, chloroform extracted, dried (potassium carbonate) and the solvent removed to give a dark brown viscous oil (10.3 g, 31%) b.p. 110-130°/11 mm., shown (n.m.r.) to contain nicotine (30%) and dihydronicotyrine (70%). Repetition at 40° and pH 4 gave identical results.

Nicotine with Phenyl Chloroformate. - Nicotine (16.0 g, 0.1 mol) and phenyl chloroformate (15.6 g, 0.1 mol) in dichloromethane (80 ml) were refluxed for 3 h, the solvent removed and the resulting dark red viscous oil twice distilled at 220-230°/1.5 mm giving colourless Δ^3-N-methyl-N-phenoxycarbonyl-4-(3-pyridyl)butylamine (60) (18.4 g, 65%) (Found: C, 71.8; H, 6.3; N, 10.2. $C_{17}H_{18}N_2O_2$ requires: C, 72.4; H, 6.4; N, 10.0%). ν_{max} (liquid film) 3030m, 2935m, 1719s, 1592m, 1568m, 751m, 708m and 689m cm.$^{-1}$ λ_{max} 247, 282 (shoulder). m/e (%) 282(27, M^+), 214(90, M^+-68), 189(13, M^+-93), 170(18, M^+-112), 164(28, M^+-118), 107(40, M^+-175), 84(46, M^+-198), 77(100, M^+-205), 55(90, M^+-227).

The base would not form a crystalline methiodide, picrate or platinic chloride.

Nicotine with Cyanogen Bromide. - Nicotine (8.1 g, 0.05 mol) in dichloromethane (100 ml) was added over 1 h to a stirred solution of cyanogen bromide (16.0 g, 0.15 mol) in dichloromethane (50 ml) under nitrogen. The solution immediately became dark red and remained so during 3 h reflux. After cooling and solvent removal the oil was refluxed with 6% hydrochloric acid (100 ml) for 24 h. Cooling, neutralizing with 33% ammonium hydroxide, chloroform extraction, drying and solvent evaporation gave a dark yellow oil. Distillation (120-125°/13 mm) gave nicotine (6.3 g), characterised by i.r. and n.m.r. No other products were detected.

Nicotine with Palladium and Oxygen. - Nicotine (50 g), palladium catalyst (0.1 g) and ethanol (100 ml) were refluxed with vigorous stirring under a stream of oxygen for 48 h. Cooling, filtering and solvent removal gave black oil. Distillation at 90-95°/2.5 mm gave nicotine (41 g, 82%) as the only isolable product (i.r., n.m.r. and t.l.c.). Platinum and/or platinum oxide with methanol gave increased recovery of nicotine (90%).

Nicotine with Lead Tetraacetate.- Nicotine (3.2 g) and lead tetraacetate (17.8 g) were stirred together in benzene (100 ml). A small quantity of tarry solid was filtered, and the filtrate evaporated to give a brown oil. Distillation at 68-74°/2.0 mm gave nicotine (2.9 g) characterised by i.r. and n.m.r. No other products were isolated.

Nicotine with Potassium Ferricyanide. - Nicotine was treated with potassium ferricyanide according to Perrine.[67] Work up gave nicotine (64%) characterised by i.r. and n.m.r. in agreement with Perrine.[67]

Nicotine with Manganese Dioxide. - Nicotine (16.0 g) and active manganese dioxide (300 g) were stirred at 16° for 48 h in chloroform (500 ml). Filtering, solvent evaporation and distillation of the resulting brown oil gave nicotine (15.1 g) b.p. 118-120°/17 mm. No other products could be detected by t.l.c., i.r. or n.m.r.

3-Nitro-5-(3-pyridyl)pyrazole (15). - Nicotine (210 g) was oxidised with concentrated nitric acid (2800 ml) according to Gough and King[63] to give 3-nitro-5-(3-pyridyl)pyrazole (11.9 g, 5.1%). Recrystallization from ethanol (charcoal), glacial acetic acid and sublimation (200-230°/13 mm) gave an analytical sample, m.p. 281-282° (lit.,[63] 280-281°) (Found: C, 50.8; H, 3.1; N, 29.3. Calc for $C_8H_6N_4O_2$: C, 50.5; H, 3.1; N, 29.1%); ν_{max} (nujol) 3122m, 1524s, 1336s, 1300m, 826m, 814m, 760m, 703m and 642 $cm.^{-1}$ λ_{max} 251 nm. m/e (%) 190(100, M^+), 174(1, M^+-16), 160(3.5, M^+-30), 149(1.5, M^+-41), 132(3.5, M^+-58), 129(2, M^+-61), 117(17, M^+-73), 115(18, M^+-75).

4-Bromo-3-nitro-5-(3-pyridyl)pyrazole (61). - 3-Nitro-5-(3-pyridyl) pyrazole and bromine gave the title compound according to Gough and King[63] as a white solid (83% yield). Sublimation gave an analytical sample m.p. 242-244° (lit.[63] m.p. 240-242°) (Found, C, 35.4; H, 2.0; N, 20.8; Br, 30.3. Calc. for $C_8H_5N_4O_2Br$: C, 35.6; H, 1.9; N, 20.8; Br, 29.7%). ν_{max} (nujol) 3540b, 1610w, 1575w, 1549s, 1530s, 1395s, 1335m, 1042m, 965m and 834m cm.$^{-1}$ m/e (%) 270, 268(100, M^+), 253, 251(15, M^+-17), 240, 238(5, M^+-30), 223, 221(2, M^+-47), 212, 210(2, M^+-58), 197, 195(15, M^+-73).

Bis-1-methyl-2-(3-pyridyl)pyrrol-5-yl disulphide (24). - Nicotine (30 g) and sulphur (16 g) refluxed in toluene for 16 h according to Morton[97] gave the title compound as golden yellow spangles (8.1 g, 9.1%) m.p. 153-153.5° lit.[97] m.p. 153-154°) (Found: C, 63.5; H, 4.8; N, 15.0; S, 17.0. $C_{20}H_{18}N_4S_2$ requires: C, 63.5; H, 4.79; N, 14.8; S, 16.9%); ν_{max} (nujol) 3100m, 3050m, 1700w, 1592m, 1572s, 1500s, 1460s, 1420s, 1312s and 1184 cm.$^{-1}$ λ_{max} ($10^{-4}\varepsilon$) 219(1.08), 250(0.93), 290(0.64, shoulder). m/e (%) 378(28, M^+), 189(100, M^+-189, 174(20, 189-15), 169(189-20), 156(3, 189-33), 148(15, 189-41).

Dimethiodide (acetonitrile) m.p. 223-225° (Found: C, 40.2; H, 3.8; N, 8.8; S, 9.7; I, 36.8. $C_{22}H_{24}N_4S_2I_2$ requires: C, 40.6; H, 3.8; N, 8.6; S, 9.8; I, 37.2%).

Horton[97] reported the title compound to be a monosulphide, the mass spectrum and elemental analysis indicate a symmetrical disulphide.

Dithiodinicotyrine (24) with Raney Nickel. - Dithiodinicotyrine (0.37 g) was refluxed in methanol (20 ml) with Raney nickel (1.0 g) for 1 h, the mixture was cooled, filtered and the solvent evaporated to give a yellow oil which distilled at 98-104°/2.5 mm giving nicotyrine (0.31 g) (i.r., n.m.r. and mixed m.p. of picrate).

Dithiodinicotyrine (24) with Zinc and Acetic Acid. Zinc (50 g) was added over 2 h to dithiodinicotyrine (3.7 g) in acetic acid (50 g). Yellow amorphous solid was precipitated over 12 h and was filtered but tarred rapidly on exposure to air and could not be characterised. Basification of the filtrate gave only zinc hydroxide.

Nicotine with Selenium. - Nicotine (3.2 g), selenium powder (5.0 g) and diphenyl ether (100 ml) were refluxed for 48 h. Selenium was filtered from the dark brown liquid which was extracted with dilute hydrochloric acid. The extracts were basified and ether extracted. Solvent removal and distillation of residue (80-85°/2.5 mm) gave nicotine only (1.5 g, 47%), characterised by i.r. and n.m.r.

Nicotine with Sodium Sand. - Nicotine (80 g) in ether (50 ml) was added to sodium sand (11.0 g) freshly prepared under xylene (200 ml). After 24 h stirring at 18° the dark green organic phase was decanted from sodium remaining in the flask and evaporated to give a glue. This was taken up in chloroform and water washed. The chloroform solution was dried (magnesium sulphate) and evaporated to give a dark brown oil. Vacuum distillation gave nicotine (45 g) as the only isolable material.

Nicotine with N-Bromosuccinimide. - Nicotine (1.62 g) and N-bromosuccinimide (1.7 g) in carbon tetrachloride (20 ml)were treated with a little benzoyl peroxide and warmed. Solid N-bromosuccinimide became dark orange, then red giving a viscous tar. No identifiable compounds could be isolated from a number of work-up procedures.

Experimental for Section 3. Reactions of Aminonicotines

2- and 6-Aminonicotine (18) and (19). - Nicotine was aminated by the method of Tschitschibabin and Kirssanow[87] giving 2-aminonicotine (22%) and 6-aminonicotine (23%). The former (18) had m.p. 124-125° (lit.[87] m.p. 125°) (Found: C, 68.0; H, 8.4; N, 23.8. Calc for $C_{10}H_{15}N_3$: C, 67.8, H, 8.5; N, 23.7%); ν_{max} (nujol) 3330s, 3167s, 1630s, 1583s, 1477s, 1455s and 775s $cm.^{-1}$ λ_{max} 237, 300 nm. m/e (%) 177(48, M^+), 162(100, M^+-15), 159(17, M^+-18), 148(28, M^+-29), 147(27, M^+-30), 134(21, M^+-43), 121(47, M^+-56), 119(25, M^+-58), 84(64, M^+-93).

The latter amine (19) had b.p. 160-165°/1.0 mm (Found: C, 67.9; H, 8.4; N, 23.6. Calc for $C_{10}H_{15}N_3$: C, 67.8; H, 8.5; N, 23.7%); ν_{max} (nujol) 3470m, 3320s, 3185s, 2785s, 1625s, 1575w, 1506s, 1458m, 1415s and 1358s $cm.^{-1}$ λ_{max} 208, 241, 303 nm. m/e (%) 177(85, M^+), 176(79, M^+-1), 162(9, M^+-15), 148(75, M^+-29), 134(24, M^+-43), 121(7, M^+-56), 120(6, M^+-57), 119(7, M^+-58), 107(13, M^+-70), 84(100, M^+-93).

Hydrochloride (ethanol, trace of water) m.p. 136-138° (lit.[87] m.p. 136°). Tschitschibabin[87] reported this salt to be a dihydrochloride, analysis gives $(6\text{-Aminonicotine})_2$. 4 HCl. $3H_2O$ (Found: C, 43.2; H, 7.4; N, 15.2; Cl, 25.9. $C_{20}H_{40}N_6Cl_4O_3$ requires: C, 43.4; H, 7.3; N, 15.2; Cl, 25.8%).

Nicotine with Sodamide in Autoclave. - Nicotine (90.0 g) and sodamide (50.0 g, Fluka) were heated to 160° for 12 h in an autoclave. After cooling, addition of water, chloroform extraction and drying (potassium carbonate) the organic extracts, solvent removal gave brown viscous oil. Distillation (80-120°/2.5 mm) gave light yellow oil (30.1 g) shown by t.l.c. to contain approximately equal portions of nicotine, 2-aminonicotine and 6-aminonicotine.

6-Aminonicotine with Phenyl Isocyanate (63). - Phenyl isocyanate (1.2 g, 0.01 mol) in dry ether (75 ml) was added dropwise to 6-aminonicotine (1.7 g, 0.01 mol) in ether (50 ml). After 30 min some white precipitate was filtered. Evaporation of filtrate gave a colourless solid which recrystallized (acetonitrile) as colourless needles of N-6-nicotinyl-N'-phenyl urea (2.7 g, 93%), m.p. 171-173° (Found: C, 68.6; H, 6.8; N, 18.8. $C_{17}H_{20}N_4O$ requires: C, 68.8; H, 6.8; N, 18.9%); ν_{max} (nujol) 1700s, 748m and 687m cm.$^{-1}$ λ_{max} 209, 250, 289 nm. m/e (%) 296(43, M^+), 268(4, M^+-28), 267(7, M^+-29), 253,(3, M^+-43), 212(2, M^+-84), 204(8, M^+-92), 203(9, M^+-93), 202(9, M^+-94), 177(30, M^+-119), 176(29, M^+-120), 93(37, M^+-203), 84(100, M^+-212)

Dichloromethane as solvent gave diphenyl urea. 2-Aminonicotine treated as above gave only starting material; reflux with acetonitrile (48 h) gave only diphenyl urea.

6-Aminonicotine with o-, m- and p-chlorophenylisocyanate gave the expected ureas when treated similarly.

N-6-Nicotinyl-N'-o-chlorophenyl urea(64). - Yield 93%, m.p. 197-199° (Found: C, 61.6; H, 5.7; N, 16.8; Cl, 11.2. $C_{17}H_{15}N_4OCl$ requires: C, 61.6; H, 5.7; N,16.9; Cl, 10.8%) ν_{max} (nujol) 1700s, 1585s, 1493m, 1330s, 1080m, 1041m amd 848w $cm.^{-1}$ m/e (%) 332, 330(12, 33, M^+)

N-6-Nicotinyl-N'-m-chlorophenyl urea (65). - Yield 91.5%, m.p. 169-172° (Found: C, 61.9; H, 5.7; N, 16.9; Cl, 11.1%) ν_{max} (nujol) 1700s, 1609s, 1585s, 1495m, 1472m, 1395w, 1370w, 1348w, 1076w, 994w, 879m, 848m, 767m and676 $cm.^{-1}$ m/e (%) 332,330 (13, 41, M^+)

N-6-Nicotinyl-N'-p-chlorophenyl urea (66). - Yield 94%, m.p. 193-197° (Found: C, 61.8; H, 5.7; N, 16.9; Cl, 11.2%); ν_{max} (nujol) 1700s, 1613s, 1585s, 1491s, 1330s, 1089m, 1041w, 1009w, 848w, 822w, 804m, 770w and 738m $cm.^{-1}$ m/e (%) 332, 330 (20, 50, M^+)

2-and 6-Aminonicotine with Phenyl Isothiocyanate. - 6-Amino-nicotine (0.85 g, 0.05 mol) in acetonitrile (150 ml) and phenyl isothiocyanate (1.73 g, 0.13 mol) were refluxed for 4 h, cooled and solvent removed to give brown oil. Trituration (60-80° petrol, drop of ether gave N-6-nicotinyl-N'-phenyl thiourea (67), recrystallized (acetonitrile)as white needles (1.2 g, 77%), m.p. 173-174° (Found: C,65.6; H, 6.4; N, 17.9; S, 10.5.$C_{17}H_{20}N_4S$ requires: C, 65.6 H, 6.4; N,17.9; S, 10.3%). ν_{max} 1189m, 831m,682m, 657m, $cm.^{-1}$ λ_{max} 209, 269, 304nm. m/e (%) 312(80, M^+), 279(8, M^+-33), 220(26, M^+-92), 177(41, M^+-135), 176(35, M^+-136), 149(20, M^+-163), 148(30, M^+-164), 84 (100, M^+-228).

Similarly 2-aminonicotinc gave N-2-nicotinyl-N'-phenyl thiourea (68) (70%) m.p. 130-133° (acetonitrile) (Found: C, 65.3; H, 6.3; N, 17.9; S, 9.9. $C_{17}H_{20}N_4S$ requires: C, 65.6; H, 6.4; N, 19.9; S, 10.3%) ν_{max}(nujol) 1180s, 741s and 691s cm.$^{-1}$ m/e (%) 312(100, M^+), 297(7, M^+-15), 279(25, M^+-33), 256(13, M^+-56), 254(19, M^+-58), 228(17, M^+-84), 222(27, M^+-90), 220(34, M^+-92), 204(59, M^+-108).

2-Aminonicotine with Allyl Isothiocyanate. - 2-Aminonicotine (3.4 g, 0.02 mol) and allyl isothiocyanate (2.0 g, 0.02 mol) were refluxed in acetonitrile for 24 h. Cooling gave colourless crystals of N-2-nicotinyl-N'-allyl thiourea (69) (4.1 g, 76%), recrystallized from acetonitrile m.p. 120-122° (Found: C, 60.6; H, 7.3; N, 20.2; S, 11.3. $C_{14}H_{20}N_4S$ requires C, 60.9; H, 7.3; N, 20.1; S, 11.6%). ν_{max}(nujol) 1644w, 1595s, 1558s, 1520s and 770s cm.$^{-1}$, m/e (%) 276(100, M^+), 262(5, M^+-14), 261(3, M^+-15), 245(10, M^+-31), 243(12, M^+-33), 230(4, M^+-46), 220(60, M^+-56), 218(28, M^+-58), 204(45, M^+-72), 192(18, M^+-84), 186(25, M^+-90), 175(15, M^+-101), 163(35, M^+-113),

6-Aminonicotine and allyl isothiocyanate treated similarly gave no isolable products.

6-Aminocotinine with o-Chlorophenyl isocyanate. - 6-Aminocotinine 1.9 g, 0.01 mol) and o-chlorophenyl isocyanate (2.0 g, 0.012 mol) were stirred in a mixture of ether (200 ml) and acetonitrile (50 ml). Filtering and evaporation of filtrate gave the urea (70) (96%) as brown solid which recrystallized from acetonitrile (charcoal) m.p. 200-204° (Found: C, 59.9; H, 4.9; N, 16.1; Cl, 10.5. $C_{17}H_{17}N_4ClO_2$ requires: C, 59.5; H, 4.94; N, 16.3; Cl, 10.3%). ν_{max}(nujol) 3240 broad w, 3160 broad w, 1690s, 1670s, 1619m, 1586s, 1443m, 1397m, 1312m, 1297m, 1270m, 1234m, 1148w, 1110w, 1058w, 1030w, 949w, 838m, 769s, 758s and 667w cm.$^{-1}$; m/e (%) 336, 334(1,4, M^+), 282, 280(1, 3.5, M^+-54), 245(5, M^+-91, 93), 218(5, M^+-118, 120), 217(29, M^+-119, 121),

216(20, M^+-120, 118), 192(4, M^+-144, 142), 191(27, M^+-145, 143), 190(19, M^+-146, 144), 189(9, M^+-147, 145), 188(24, M^+-148, 146), 162, 160(17, 20, M^+-174); 155, 153(9, 30, M^+-181), 129, 127(30, 100, M^+-207), 98(65, M^+-238, 236).

6-Amino-3-(1-methylpyrrolid-2-one-5-yl)pyridine (71). - Bromine (40 ml) in 80% acetic acid (50 ml) was added over 4 h to a stirred solution of 6-aminonicotine (20.0 g) in 80%acetic acid (250 ml). After 1 h at 20° water (800 ml) was added, the mixture stirred and heated to 85° for 15 min. When cool 80% acetic acid (100 ml), concentrated hydrochloric acid (40 ml) and zinc dust (70 g) were added and the mixture stirred (20 h). After filtering the solution was basified with 0.88 ammonia, chloroform extracted, the extracts dried (magnesium sulphate) filtered and evaporated to give yellow oil, which crystallised from benzene as the title compound (10.0 g, 44%) m.p. 144-146° (Found: C, 62.9; H, 6.8; N, 22.1. $C_{10}H_{13}N_3O$ requires: C, 62.8; H, 6.8; N, 22.0%) ν_{max} 3420s, 3330s, 3200m, 2950m, 1675s, 1621s, 1568m and 1504 m cm.$^{-1}$ λ_{max} 242, 304 nm. m/e (%) 191(100, M^+), 190(30, M^+-1), 162(10, M^+-29), 134(34, M^+-57), 98(35, M^+-93).

2-Amino-5-bromo-3-(1-methylpyrrolid-2-one-5-yl)pyridine (72). - 2-Amino-nicotine was oxidised to the title compound in similar manner to 6-amino nicotine (above) giving white microcrystals from benzene (13.6 g, 51%) m.p. 179-181° (Found: C, 44.7; H, 4.4; N, 15.8; Br, 29.2. $C_{10}H_{12}N_3OBr$ requires: C, 44.4; H, 4.4; N, 15.6; Br 29.6%); ν_{max} (nujol) 3320b, 3200b, 1685b, 1595s, and 753s cm.$^{-1}$ λ_{max} 242, 310 nm. m/e (%) 271, 269(75, 75, M^+), 256, 254(40, 41, M^+-15), 242, 240(14, 15, M^+-29), 228, 226(18, 18, M^+-43), 98(100, M^+-173, 171).

6-Aminocotinine with p-Nitrobenzenesulphonyl Chloride. - 6-Aminocotinine (2.4 g, 0.0125 mol) in pyridine (200 ml) was treated with p-nitrobenzene-sulphonyl chloride (4.0 g, 0.018 mol), stirred for 48 h at 18° and the pyridine removed. The resulting oil was taken up in chloroform (50 ml), water washed (3 x 50 ml) and the organic phase evaporated to leave a white solid. Recrystallization (ethanol) gave the required sulphonamide, m.p. 160-162° (Found: C, 51.2; H, 4.3; N, 14.8; S, 8.2. $C_{16}H_{16}N_4O_5S$ requires: C, 51.1; H, 4.3; N, 14.9; S, 8.5%). ν_{max}(nujol) 1681s, 1646s, 1610m, 1521s, 1453m, 1380 broad s, 1360s, 1350s, 1291m, 1273s, 1145s, 1092s and 982m cm.$^{-1}$ m/e (%) molecular ion not observed, 311(4, M^+-65), 288(50, M^+-88), 273(9, M^+-103), 271(7, M^+-105), 270(27, M^+-106), 260(11, M^+-116), 245(10, M^+-131), 179(16, M^+-197), 178(40, M^+-198), 149(25, M^+-227), 110(100, M^+-266).

6-Nitronicotine (74). - 6-Aminonicotine (4.0 g, 0.0226 mol) was added to concentrated sulphuric acid (10 ml), cooled and 30% hydrogen peroxide (70 ml) in 30% fuming sulphuric acid (50 ml) added. The mixture was cooled (0°) for 3 h, stirred at 20° (48 h), poured into water (300 ml) and basified (50% caustic soda solution). White solid thus precipitated was filtered, dried and recrystallized from petrol at -20° to give 6-nitronicotine (3.6 g, 77%) m.p. 73-75° (Found: C, 57.9; H, 6.4; N, 20.2. $C_{10}H_{13}N_3O_2$ requires: C, 58.0; H, 6.3; N, 20.3%). ν_{max}(nujol) 2770m, 1534s ($ArNO_2$), 1455m, 1360 ($ArNO_2$), 1315m, 1015m, 859s and 693m cm.$^{-1}$; λ_{max} 213, 248, 275 nm. m/e (%) 207(19, M^+), 206(15, M^+-1), 177(7.5, M^+-30), 160(7, M^+-47), 133(19, M^+-74), 84(100, M^+-123).

2-Nitronicotine (75). - 2-Aminonicotine treated as for 6-aminonicotine gave 2-nitronicotine (49%) m.p. 34-35° (Found: C, 57.7; H, 6.3; N, 20.0. $C_{10}H_{13}N_3O_2$ requires: C, 58.0; H, 6.3; N, 20.3%) ν_{max}(nujol) 2818w, 2765m, 1540b ($ArNO_2$), 1455m, 1429m, 1415m, 1378s, 1357s ($ArNO_2$), 1043s, 902s, 854s, 815s and 695m cm.$^{-1}$; m/e (%) 207(2.5, M^+), 190(23, M^+-17), 159(100, M^+-48) 84(35, M^+-123).

6-Aminonicotine and Benzoic Acid with Dicyclohexylcarbodiimide. - 6-Aminonicotine (1.7 g) and benzoic acid (1.2 g) in dichloromethane (20 ml) were treated with dicyclohexylcarbodiimide (2.06 g) in dichloromethane (20 ml). N,N-dicyclohexylurea was filtered after 2 h stirring. Filtrate evaporation gave a white powder which recrystallized (ethanol) as N-benzoyl-N,N'-dicyclohexylurea (1.2 g) m.p. 166-167° (lit.[142] 164-165°) (Found: C, 72.8; H, 8.4; N, 8.6. Calc for $C_{28}H_{28}N_2O_2$: C, 73.2; H, 8.5; N, 8.5%). MW 328 (mass spec.).

Use of tetrahydrofuran or dioxane as solvent gave a similar result.

6-Aminonicotine with Acetyl Acetone. - 6-Aminonicotine (3.5 g) and acetyl acetone (2.2 g) were refluxed for 24 h in toluene (10 ml) containing a drop of concentrated hydrochloric acid.

T.l.c. showed only starting materials to be present. Solvent removal and distillation of the tarry residue gave 6-aminonicotine (2.0 g) 160-170°/ 3.0 mm.

2-Aminonicotine subjected to similar conditions gave starting amine (2.3 g) after solvent removal and extraction with hot petrol (80-100°).

Attempted preparation of 6-Ethoxy nicotine . - Sodium nitrite (2.5 g) was slowly added to a stirred solution of 6-aminonicotine dihydrochloride in ethanol (20 ml) and concentrated hydrochloric acid (10 ml). The mix was warmed to 60° and stirred (12 h), during which time gas evolution occurred and the solution darkened. Neutralization with sodium carbonate, solvent removal, addition of water (100 ml) and basification with 2 N caustic soda (50 ml) gave a white precipitate which extracted into chloroform. Drying (magnesium sulphate) and solvent removal gave 6-aminonicotine (1.6 g) (i.r., n.m.r. and t.l.c.).

Attempted Iodination of 2-Aminonicotine. - 2-Aminonicotine (1.77 g, 0.01 mol), sublimed iodine (1.3 g, 0.01 mol), sodium carbonate (10.0 g) and water (100 ml) were refluxed (5 h) with stirring, cooled, chloroform extracted and the chloroform removed to give a white solid. Recrystallization (acetonitrile) gave 2-aminonicotine (1.2 g), characterised by i.r. and n.m.r. Dioxane/water as solvent and caustic soda as base also gave starting material.

6-Aminonicotine with Nitrous Acid. - Sodium nitrite (16.6 g, 0.24 mol) in water (20 ml) was added over 3 h to 6-aminonicotine (1.7 g, 0.01 mol) in 5% sulphuric acid (20 ml). The mix was slowly raised to 80°, maintained for 1 h, allowed to cool, neutralised with sodium carbonate and extracted with petrol (80-100°). Solvent evaporation and distillation of the residue (159-164°/0.2 mm) gave 6-aminonicotine (1.3 g).

2-Aminonicotine, under similar conditions also failed to react.

6-Aminonicotine with iso-Amyl Nitrite. - 6-Aminonicotine (1.6 g, 0.01 mol), iso-amyl nitrite (2.7 ml, 0.02 mol) and sodium ethoxide (0.02 mol, from 0.46 g of sodium in 20 ml absolute ethanol) were refluxed for 4 h, poured into 1N sulphuric acid (20 ml) and heated to 90° (1 h). Cooling, basifying (0.5N caustic soda), chloroform extraction, drying (potassium carbonate) and solvent evaporation gave yellow oil (1.2 g) which solidified. I.r. and n.m.r. showed it to be starting material.

2-Aminonicotine, similarly treated, failed to react.

6-Aminonicotine with p-Nitrobenzenesulphonyl Chloride. - 6-Aminonicotine (1.7 g, 0.01 mol) in pyridine (50 ml) was treated with p-nitrobenzenesulphonyl chloride (2.21 g, 0.01 mol) at 18° for 30 min then 50° for 1 h. Cooling and pouring into water gave a non-characterisable glue.

Benzene or acetone as solvent (with and without base present) also gave non-characterisable glues.

p-Toluenesulphonyl chloride similarly gave glues, as did acetyl chloride and benzoyl chloride.

Experimental for Section 4. Reactions of Nicotinium Salts

Nicotine iso-methiodide (77). - Nicotine (162 g) reacted according to Pinner[84] gave nicotine iso-methiodide (246 g, 90%) as microcrystals from ethanol/ ether, m.p. 164-165° (lit.[84] m.p. 164°) (Found, C, 43.5; H, 5.6; N, 9.4. Calc. for $C_{11}H_{17}N_2I$: C, 43.5; H, 5.6; N, 9.2%).

1-Methyl-3-(1-methyl pyrrolidin -2-yl)-1,2,5,6-tetrahydropyridine (87). - Sodium borohydride (8.0 g, 0.21 mol) in water (50 ml) was added, all at once, to nicotine iso-methiodide (24.0 g, 0.127 mol) stirred in 1N caustic soda (200 ml). After immediate effervescence (5 min), the solution was warmed to 60° (15 min), cooled, chloroform extracted and the extracts dried (magnesium sulphate) and evaporated giving a yellow oil, b.p. 121-140°/20 mm. Redistillation at 120-122°/20 mm gave 1-methyl-3-(1-methyl pyrrolidin-2-yl)-1,2,5,6-tetrahydropyridine (8.4 g, 37%) as colourless oil. (Found: C, 72.7; H, 11.3; N, 15.0. $C_{11}H_{20}N_2$ requires: C, 73.4; H, 11.1; N, 15.5%); n_D^{20} 1.4924; ν_{max} (liquid film) 2965m, 2938s, 2840m, 2775s and 1450s cm.$^{-1}$; λ_{max} 257 mμ. Dimethiodide , prepared in acetonitrile and recrystallized from acetonitrile/methanol had m.p. 221-224° (Found: C, 33.7; H, 5.7; N, 5.9; I, 54.6. $C_{13}H_{26}N_2I_2$ requires: C, 33.7; H, 5.6; N, 6.0; I, 54.8%).

Nicotine iso-Methiodide with Sodium Dithionite. - Sodium dithionite (3.5 g, 0.02 mol) was added over 5 min to a solution of nicotine iso-methiodide (6.0 g, 0.02 mol) and sodium carbonate (15.0 g) in water (50 ml). The temperature was raised to 50° for 15 min and then the mixture allowed to cool. Basification with caustic soda (pH 12), chloroform extraction, drying the extracts (magnesium sulphate) and solvent removal gave dark yellow oil (3.5 g) which decomposed on distillation and could not be chromatographically purified. Spectroscopic investigation of the crude product showed it to be a multicomponent mixture.

Nicotine iso-methiodide with β-propiolactone. - β-Propiolactone (1.5 g) and nicotine iso-methiodide (6.0 g) in water (20 ml) gave, after 24 h at 18°, only glue on solvent removal, which would not crystallize.

Cotinine similarly gave a glue.

Nicotine with β-propiolactone. - Nicotine (8.1 g, 0.05 mol) in water (10 ml) was added to β-propiolactone (3.85 g, 0.05 mol) and the mix allowed to stand for 24 h. Solvent removal and drying over phosphorus pentoxide gave a non-characterisable glue. The following conditions gave similar glues. (i) ratio of 2 moles β-propiolactone to 1 mole of nicotine, (ii) methanol as solvent and (iii) refluxing (methanol or water) for 24 h.

Nicotine with Cetyl Bromide. - Nicotine (1.62 g, 0.01 mol) and cetyl bromide (6.05 g, 0.02 mol) were refluxed in acetonitrile (50 ml) for 6 h. The dark brown solution so produced could not be induced to crystallize. Solvent removal gave a dark brown non-characterisable oil.

Use of nicotine (1 mol) and cetyl bromide (1 mole) similarly gave a non-characterisable oil.

Treatment of cotinine with cetyl bromide in acetonitrile also gave a non-characterisable oil.

Experimental for Section 5. Reactions of Dimethyl Acetylenedicarboxylate with Nicotine Derivatives

Nicotine with Dimethyl Acetylenedicarboxylate. - Dimethyl acetylenedicarboxylate (40 g) in ether (200 ml) was added over 4 h to nicotine (22.6 g) in ether (100 ml) at -30°. After 1 h stirring the mixture was filtered to remove dark brown solid (tarred on exposure to air), the filtrate evaporated, the residual oil taken up in benzene and passed through basic alumina (500 g). Benzene elution gave yellow oil, b.p. 72-74°/2.5 mm. τ (CCl_4, 100MHz) 5.9(1H, s); 6.19, 6.29, 6.39(3H, singlets, ester methyls).

Benzene: chloroform (90 : 10 to 70 : 30) eluted yellow oil which gave crystals from ethanol (250 mg) m.p. 190-191°. τ (CCl_4) 6.09(s, ester methyl). Mixed m.p. with hexamethyl hexamelitate was undepressed.

Benzene: chloroform (60 : 40 to 10 : 90) eluted red oil which deposited an amorphous red solid from carbon tetrachloride. N.m.r. showed complex ester methyl resonances τ 6-7 but no aromatic signals.

Changes of reaction solvent, temperature, molar ratio and time similarly gave no isolable products.

Use of methyl propiolate likewise gave no isolable products.

Nicotyrine with Dimethyl Acetylenedicarboxylate. - Dimethyl acetylenedicarboxylate (17.1 g, 0.12 mol) in acetonitrile (50 ml) was added over 3 h to nicotyrine (9.5 g, 0.06 mol) in acetonitrile (50 ml), stirred at 0°. After 3 h at 0° the mixture was allowed to warm to 18°, the solvent removed and the resulting red oil chromatographed on alumina (900 g, neutral) prepared in benzene. Pure benzene eluted dimethylfumarate, recrystallized from methanol (mixed m.p. undepressed). Benzene chloroform (90 : 10) eluted red non characterizable oil. Benzene: chloroform (80 : 20 to 10 : 90) eluted red oil which gave dark red crystals from methanol of tetramethyl 9-(1-

methylpyrrol-2-yl)-9aH-quinolizine-1,2,3,4 tetracarboxylate (94) (3.37 g, 6.3%) m.p. 109-110° (Found: C, 59.4; H, 5.0; N, 6.1. $C_{22}H_{22}N_2O_8$ requires: C, 59.7; H, 5.0; N, 6.3%); ν_{max}(nujol) 1749s, 1730m, 1704s cm^{-1}; λ_{max} ($10^{-4}\varepsilon$) 235(2.18), 283(1.57), 333(1.95), 466(0.54) nm (no change with 2 drops of perchloric acid). m/e (%) 442(24, M^+), 441(12, M^+-1), 411(7.5, M^+-31), 383(100, M^+-59), 370(2, M^+-72), 323(10, M^+-119).

The above adduct (1.0 g) was warmed to 60° in benzene (20 ml) for 3 h. Chromatography (30 g neutral alumina, column prepared in benzene) and recrystallization of the resulting yellow oil (methanol) gave tetramethyl 9-(1-methyl pyrrol-2-yl)-4H-quinolizine-1,2,3,4-tetracarboxylate (95) m.p. 135-138° (Found: C, 59.9; H, 5.0; N, 6.1. $C_{22}H_{22}N_2O_8$ requires: C, 59.7; H, 5.0; N, 6.3%); ν_{max}(nujol) 1746s, 1674s and 1622w $cm.^{-1}$ λ_{max}($10^{-4}\varepsilon$) 260(1.41), 325(1.02), 382(1.34), 466(1.09). Addition of 2 drops perchloric acid λ_{max} 308 nm. m/e 442(8, M^+), 411(2, M^+-31), 383(100, M^+-59), 351(5, M^+-91), 323(9, M^+-119).

Cotinine with Dimethyl Acetylenedicarboxylate. - Dimethyl acetylenedicarboxylate (7.1 g, 0.050 mol) in acetonitrile (50 ml) was added (over 3 h) to cotinine (4.4 g, 0.025 mol) in acetonitrile (50 ml) at 0°. After 4 h, solvent was removed and the resulting red oil taken up in benzene and chromatographed on alumina (300 g, neutral, prepared in benzene). Gradient elution (benzene to chloroform, 10 steps each of 200 ml) eluted only one compound (judged by t.l.c.) which gave crystals from methanol (0.2 g, 1.7%) of tetramethyl 7-(1-methylpyrrolid-2-one-5-yl)-9aH-quinolizine-1,2,3,4-tetracarboxylate (96) m.p. 124-125° (slight decomp. at 112°) (Found: C, 57.5; H, 5.1; N, 5.9. $C_{22}H_{24}N_2O_9$ requires: C, 57.4; H, 5.2; N, 6.1%), ν_{max}(nujol) 1725-1765 (broad C=O's), 1700 (broad C=O), 1634m, 1589w, 1525m $cm.^{-1}$; λ_{max} ($10^{-4}\varepsilon$) 436(0.44) nm., (no change with 2 drops perchloric acid). m/e (%) 460(5, M^+), 459(4, M^+-1), 419(6, M^+-41), 401(100, M^+-59), 388(24, M^+-72), 373(2, M^+-87),

371(3, M^+-89), 370(4, M^+-90), 357(9, M^+-103), 343(14, M^+-117), 330(16, M^+-130), 98(46, M^+-362).

The above adduct (1.0 g) was heated at 50° in benzene (50 ml) for 6 h. Chromatography (30 g neutral alumina prepared in benzene) gave tetramethyl 7-(1-methylpyrrolid-2-one-5-yl)-4H-quinolizine-1,2,3,4-tetracarboxylate (97) (0.2 g, 20%) m.p. 112-115° (methanol) ν_{max}(nujol) 1742s, 1693s, 1668s, 1645w, 1575s, 1535w, 1494s, and 1023m cm.$^{-1}$ λ_{max} ($10^{-4}\epsilon$) 265(1.11), 309(1.00), 352(1.06), 449(1.09), nm. Addition of 2 drops perchloric acid gave λ_{max} 261, 310, 448 nm. m/e (%) 460(4, M^+), 429(7, M^+-31), 401(100, M^+-59), 304(7, M^+-156), 284(4, M^+-176), 226(4, M^+-234).

Tetramethyl 7-(1-methylpyrrolid-2-one-5-yl)-4H-quinolizine-1,2,3,4-tetracarboxylate with Diborane. - Diborane prepared according to the literature[143] was passed through a solution of the title adduct (1.0 g) in tetrahydrofuran for 2 h at reflux. Cooling, addition of water, chloroform extraction and chromatography (alumina, basic, 30 g) gave the starting adduct (0.65 g) as the only isolable product.

2-Methyl-6-(3-pyridyl)tetrahydro-1,2-oxazine with Dimethyl Acetylene-dicarboxylate. - Dimethyl acetylenedicarboxylate (5.7 g, 0.04 mol) in ether (50 ml) was added over 4 h to the oxazine (3.6 g, 0.02 mol) in ether (50 ml) at 0°. After 4 h at 0° solvent removal gave red oil which was chromatographed on alumina (200 g, neutral, prepared in benzene). Gradient elution (benzene to chloroform) gave one compound (t.l.c.) as red oil, which was treated with methanol and cooled to -10°. Light yellow crystals which precipitated over 6 months recrystallized (methanol) to give methyl 1,2-methoxycarbonyl-7-(2-methyloxazine-6-yl)-4-oxoquinolizine-3-glyoxalate (100)

(0.75 g, 8.1%) m.p. 158–160° (Found, C, 56.7; H, 4.7; N, 6.2. $C_{21}H_{22}N_2O_9$ requires: C, 56.7; H, 4.9, N, 6.3%) ν_{max}(nujol) 1734s, 1683m, 1655m (broad), 1640m, 1565w, 1530w cm.$^{-1}$; λ_{max} ($10^{-4}\varepsilon$) 273(1.49), 344(0.75), 436(2.56) nm. (no change with 2 drops perchloric acid). m/e (%) 446(42, M^+), 428(5, M^+–18), 415(12, M^+–31), 414(11, M^+–32), 387(100, M^+–59), 370(17, M^+–76), 355(15, M^+–91), 340(8, M^+–106), 328(20, M^+–118), 295(36, M^+–151).

3-n-Butylpyridine with Dimethyl Acetylenedicarboxylate. – Dimethyl acetylenedicarboxylate (14.2 g, 0.1 mol) in acetonitrile (30 ml) was added over 2 h to 3-n-butylpyridine (6.8 g, 0.05 mol) in acetonitrile (50 ml) at 0°. After 4 h, evaporation of solvent gave red oil, which was chromatographed (400 g, neutral alumina, prepared in benzene). Benzene: chloroform (100 : 0 to 80 : 20) gave red oil which deposited orange crystals of tetramethyl 7-n-butyl-9aH-quinolizine-1,2,3,4-tetracarboxylate (101) from methanol (1.2 g, 3.4%) m.p. 88–89° (Found; C, 60.0; H, 5.9; N, 3.4. $C_{21}H_{25}NO_8$ requires: C, 60.0; H, 6.0; N, 3.3%) ν_{max}(nujol) 2960s, 2695s, 2862s, 1745s, 1730s, 1712s, 1623s, 1523s, 1468s, 1448s, 1379s, 1035m, 996m, 939m, 859m, 784m and 726m cm.$^{-1}$ λ_{max} ($10^{-4}\varepsilon$) 236(1.67), 292(1.64), 442(0.66) (no change with 2 drops perchloric acid). m/e (%) 419(34, M^+), 418(100, M^+–1), 415(3.5, M^+– 4), 388(23, M^+–31), 387(20, M^+–32), 386(12, M^+–33), 372(20, M^+–47), 362(26, M^+–57),360(100, M^+–59), 300(27, M^+–119).

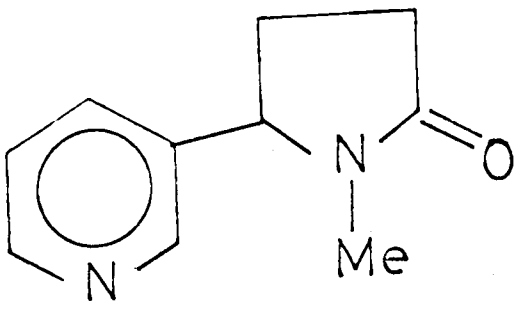
Benzene: chloroform (70 : 30 to 10 : 90) gave red oil which deposited yellow crystals from methanol of tetramethyl 7-n-butyl-4H-quinolizine-1,2,3,4-tetracarboxylate (102) (0.21 g, 0.57%) m.p. 164–167° (Found: C, 59.7; H, 6.1; N, 3.4. $C_{21}H_{25}NO_8$ requires: C, 60.0; H, 6.0; N, 3.3%) ν_{max}(nujol) 1746s, 1690s, 1615s, 1572s and 1502s cm.$^{-1}$ λ_{max} ($10^{-4}\varepsilon$) 266(1.01), 310(1.37), 353(1.21), 466(1.17) nm. Addition of 2 drops perchloric acid: λ_{max} 261 (shoulder), 315, 333 (shoulder) nm. m/e (%) 419(100, M^+), 388(6, M^+–31), 374(2, M^+–45), 360(100, M^+–59).

Myosmine with Dimethyl Acetylenedicarboxylate. - Dimethyl acetylenedicarboxylate (2.84 g, 0.02 mol) in ether (100 ml, sodium dried) was added over 1 h to myosmine (1.46 g, 0.01 mol) in ether (100 ml, sodium dried). After 2 h at 0° the solution was allowed to warm to 18°, the solvent removed and the resulting red oil chromatographed on alumina (120 g, basic), prepared in toluene. Fraction 1-3 (60 ml each, 10% chloroform in toluene) were clear. Fraction 4-15 (60 ml each, 20% chloroform in toluene to 50% chloroform in toluene showed two spots on t.l.c. (R_f 0.5 and 0.7, silica, 10% methanol in chloroform). Fraction 16-21 (60 ml each, 60% chloroform in toluene to 80% chloroform in toluene) gave one spot on t.l.c. R_f 0.7). Fractions 4-15 and 16-21 were separately combined and the solvent removed to leave in each case a dark red tarry oil. Attempts to induce crystallization over 4 weeks failed and subsequent t.l.c. analysis showed both fractions to contain only tar (R_f 0 to 0.2).

2-Aminonicotine with Dimethyl Acetylenedicarboxylate. - Dimethyl acetylenedicarboxylate (7.1 g, 0.05 mol) in ether (750 ml) was added over 3 h to 2-aminonicotine (4.4 g, 0.025 mol) in ether (50 ml) and acetonitrile (80 ml) at -5°. After 3h the dark red solution containing much tar was stripped of solvent. Chromatography on alumina gave no characterisable products.

2-Amino-5-bromocotinine with Dimethyl Acetylenedicarboxylate. - 2-Amino-5-bromocotinine (2.7 g, 0.01 mol) in acetonitrile (250 ml) was treated with dimethyl acetylenedicarboxylate (2.8 g, 0.02 mol) in acetonitrile (50 ml) at -10°. After 4 h the dark red solution was stripped of solvent and the resulting oil containing solid tar chromatographed on alumina. Gradient elution (benzene, chloroform and finally methanol) gave no characterisable products.

TABLE OF N.M.R. SPECTRA



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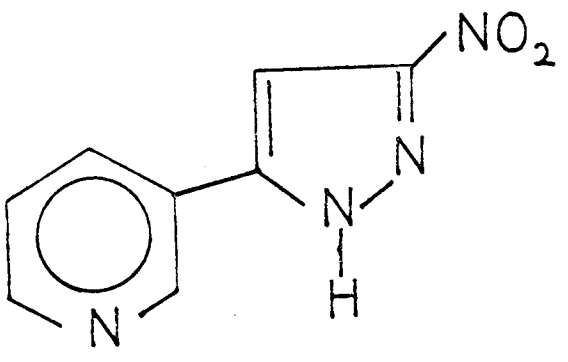

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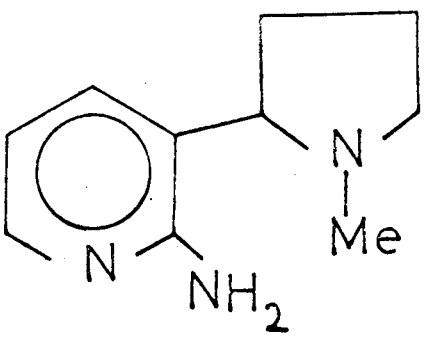

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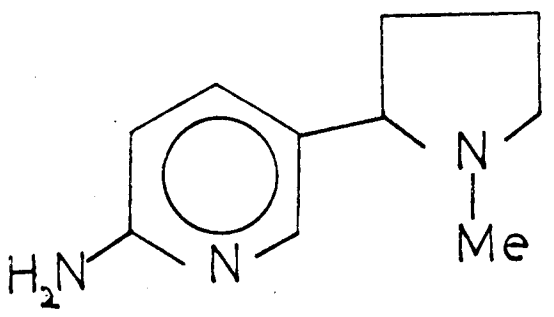

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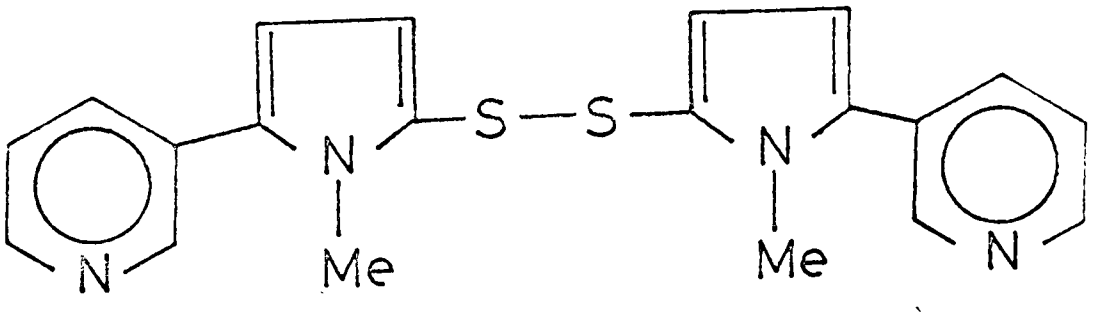
TABLE 13

N.m.r. spectra (τ values; J in Hz; Me_4Si as internal standard)

Compound	Solvent	
(8)	$CDCl_3$	1.34 (1H, d, Pyridine 1-H); 1.46 (1H, m, Pyridine 6-H); 2.25 (2H, m, Pyridine 4-H and 5-H); $J_{2,5}$ 2.5 5.42 (1H, m, Pyrrolidone 5'-H); 7.43-8.27 (4H, m, Pyrrolidone 3'-H_2 and 4'-H_2); 7.35 (3H, s, 1'-CH_3)
(15)	$(CD_3)_2SO$	0.99 (1H, q, Pyridine 2-H); 1.44 (1H, q, Pyridine 6-H); 1.74 (1H, dq, Pyridine 4-H); 2.47(1H, dq, Pyridine 5-H); $J_{2,4}$ 2.4; $J_{2,5}$ 0.9; $J_{4,5}$ 7.9; $J_{4,6}$ 2.4; $J_{5,6}$ 4.8 2.38 (1H, s, Pyrazole 4'-H)
(18)	CCl_4	2.16 (1H, q, Pyridine 6-H); 2.93 (1H, q, Pyridine 4-H); 3.63 (1H, q, Pyridine 5-H); 4.29 (2H, broad s, Pyridine 2-NH_2); $J_{4,5}$ 7.5; $J_{4,6}$ 2.0; $J_{5,6}$ 5.0 6.7-7.4 (2H, m, Pyrrolidine 2'-H and 5'-H); 7.86 (3H, s, 1'-CH_3); 7.8-8.4 (5H, m, Pyrrolidine 3'-H_2, 4'-H_2 and 5'-H)
(19)	CCl_4 (100 MHz)	2.12 (1H, d, Pyridine 2-H); 2.60 (1H, q, Pyridine 4-H); 3.60 (1H, d, Pyridine 5-H); 5.26 (2H, broad s, Pyridine 6-NH_2); $J_{2,4}$ 2.6; $J_{4,5}$ 8.6 6.97 (2H, m, Pyrrolidine 2'-H and 5'-H); 7.91 (3H, s, 1'-CH_3); 7.6-8.7 (5H, m, Pyrrolidine 3'-H_2, 4'-H_2 and 5'-H)



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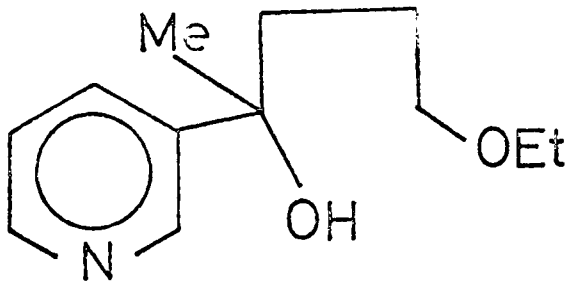

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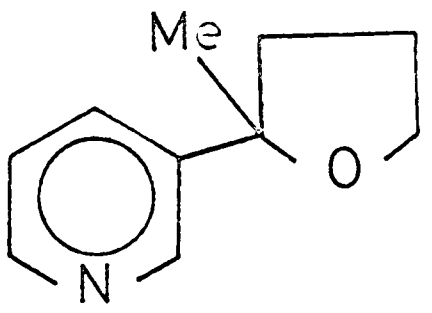


(40)

(24) $CDCl_3$ 1.40 (1H, q, Pyridine 6-H); 1.64 (1H, q, Pyridine 2-H); 2.46 (1H, dt, Pyridine 4-H); 2.68 (1H, dq, Pyridine 5-H); $\underline{J}_{2,4}$ 2.0; $\underline{J}_{2,5}$ 0.9; $\underline{J}_{4,5}$ 6.3; $\underline{J}_{4,6}$ 1.7; $\underline{J}_{5,6}$ 4.7

3.41 (1H, d, Pyrrole 3'-H); 3.70 (1H, d, Pyrrole 4'-H); 6.43 (3H, s, 1'-CH_3); $\underline{J}_{3',4'}$ 3.0

The pyridine region was simulated to 0.1Hz accuracy by use of the following parameters: 1.431 (2-H), 1.645 (6-H), 2.508 (4-H), 2.711 (5-H) $\underline{J}_{2,4}$ 1.9, $\underline{J}_{2,5}$ 1.0, $\underline{J}_{4,5}$ 7.9, $\underline{J}_{4,6}$ 1.5, $\underline{J}_{5,6}$ 4.4

(39) CCl_4 1.47 (1H, broad d, Pyridine 2-H); 1.73 (1H, q, Pyridine 6-H); 2.25 (1H, d of t, Pyridine 4-H); 2.89 (1H, q of d, Pyridine 5-H); $\underline{J}_{2,4}$ 2.4; $\underline{J}_{4,5}$ 8.0 $\underline{J}_{4,6}$ 1.8; $\underline{J}_{5,6}$ 4.6

5.86* (1H, s, $C(CH_3)\underline{O}\underline{H}$); 6.70 (4H, q, $C\underline{H}_2O\underline{C}\underline{H}_2CH_3$); $\underline{J}$ 14 and 7

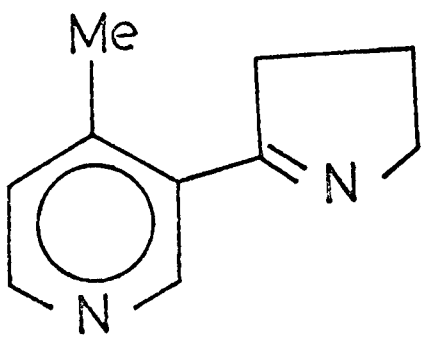
8.53 (3H, s, $C(\underline{C}\underline{H}_3)OH$); 8.90 (3H, t, $OCH_2\underline{C}\underline{H}_3$); $\underline{J}$ 7

8.0-9.2 (4H, broad m, $\underline{C}\underline{H}_2\underline{C}\underline{H}_2CH_2O$)

* Disappears on addition of D_2O

(40) CCl_4 1.49 (1H, q, Pyridine 2-H); 1.65 (1H, q, Pyridine 6-H); 2.38 (1H, d of q, Pyridine 4-H); 2.92 (1H, q of d, Pyridine 5-H); $\underline{J}_{2,4}$ 2.4; $\underline{J}_{2,5}$ 0.8; $\underline{J}_{4,5}$ 7.9; $\underline{J}_{4,6}$ 1.6; $\underline{J}_{5,6}$ 4.6

6.15 (2H, m, Tetrahydrofuran 5'-H_2); 7.6-8.5 (4H, m, Tetrahydrofuran 3'-H_2 and 4'-H_2); 8.56 (3H, s, Tetrahydrofuran 2'-CH_3)



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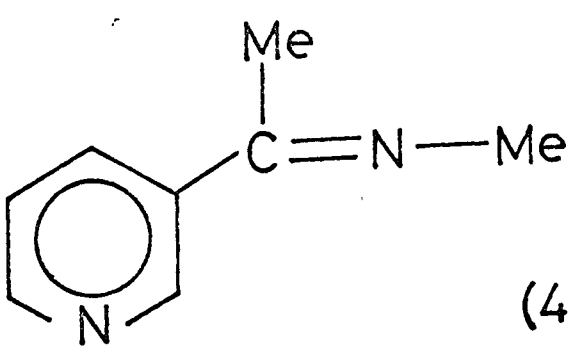

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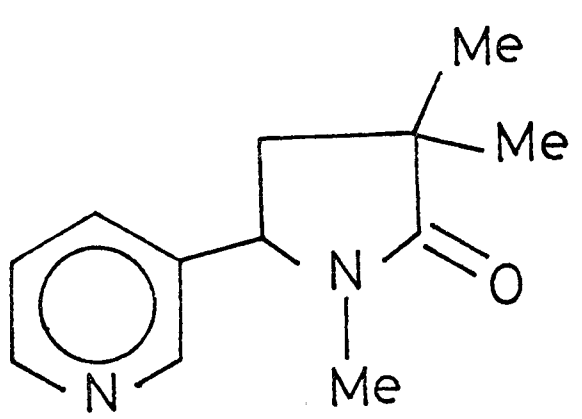
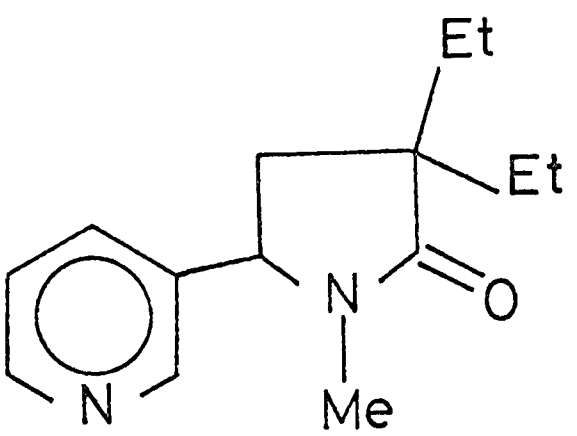


(46)



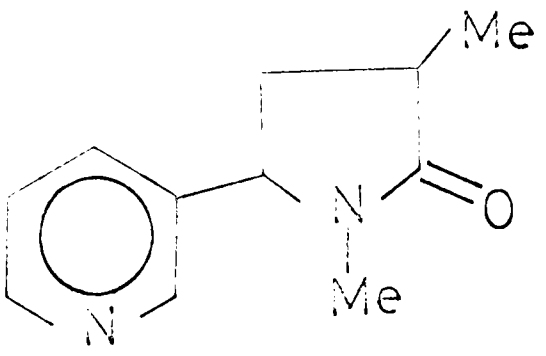
(47)

(42) CCl_4 1.41 (1H, broad s, Pyridine 2-H); 1.02 (1H, d, Pyridine 6-H); 2.94 (1H, d, Pyridine 5-H); $\underline{J}_{5,6}$ 4.8 6.00 (2H, t of t, Pyrroline 5'-H_2); 7.10 (2H, m, Pyrroline 3'-H_2); 8.02 (2H, q with further splitting, Pyrroline 4'-H_2); 6.98 (3H, s, Pyridine 4-CH_3)

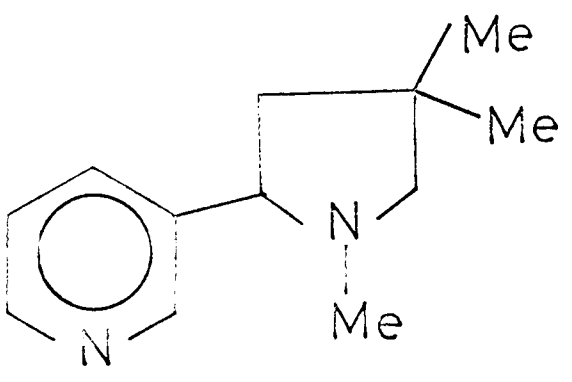
(44) CCl_4 0.99 (1H, d, Pyridine 2-H); 1.45 (1H, d, Pyridine 6-H); 2.00 (1H, d of d, Pyridine 4-H); 2.84 (1H, d of d, Pyridine 5-H); $\underline{J}_{2,4}$ 2.4; $\underline{J}_{2,5}$ 0.8; $\underline{J}_{4,5}$ 8.1; $\underline{J}_{4,6}$ 1.8; $\underline{J}_{5,6}$ 4.8
6.80 (3H, s, N-CH_3); 7.98 (3H, d, C-CH_3); $\underline{J}$ 0.9

(46) CCl_4 1.57 (1H, d, Pyridine 6-H); 1.59 (1H, d, Pyridine 2-H); 2.46 (1H, dt, Pyridine 4-H); 1.77 (1H, dd, Pyridine 5-H); $\underline{J}_{2,4}$ 2.1; $\underline{J}_{2,5}$ 0.8; $\underline{J}_{4,5}$ 7.8; $\underline{J}_{4,6}$ 1.9; $\underline{J}_{5,6}$ 4.8
5.56 (1H, t, Pyrrolidone 5'-H); 7.45 (3H, s, 1'-CH_3); 7.09 (1H, q, Pyrrolidone 4'-H); 8.32 (1H, q, Pyrrolidone 4'-H); 8.83 (3H, s, Pyrrolidone 3'-CH_3); 8.87 (3H, s, Pyrrolidone 3'-CH_3); $\underline{J}_{4',4'}$ 13; $\underline{J}_{4',5'}$ 7.2

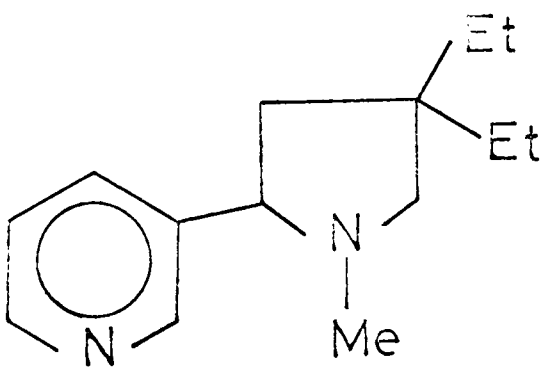
(47) CCl_4 1.51 (1H, d, Pyridine 6-H); 1.59 (1H, d, Pyridine 2-H); 2.47 (1H, dt, Pyridine 4-H); 2.75 (1H, dd, Pyridine 5-H) $\underline{J}_{2,4}$ 2.1; $\underline{J}_{2,5}$ 0.8; $\underline{J}_{4,5}$ 7.8; $\underline{J}_{4,6}$ 1.9; $\underline{J}_{5,6}$ 4.8
5.61 (1H, t, Pyrrolidone 5'-H); 7.46 (3H, s, 1'-CH_3); 7.73 (1H, q, Pyrrolidone 4'-H); 8.3 (1H, q, Pyrrolidone 4'-H); 9.11 (3H, t, Pyrrolidone 3'-$CH_2\underline{CH}_3$); 9.13 (3H, t, Pyrrolidone 3'-$CH_2\underline{CH}_3$); $\underline{J}_{4',4'}$ 13; $\underline{J}_{4',5'}$ 8



(48)



(49)

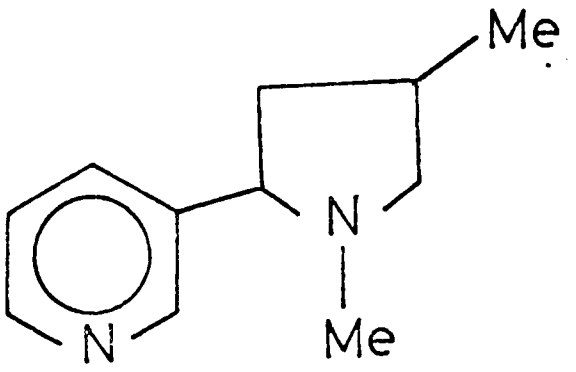


(50)

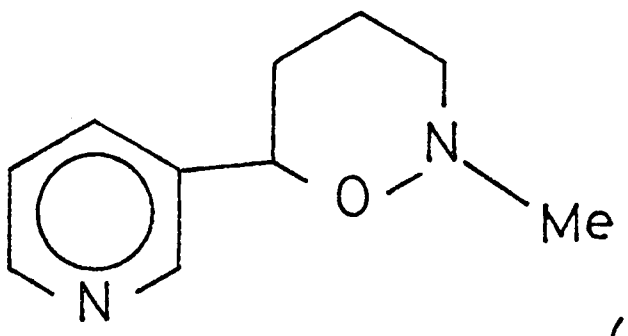
(48) CCl_4 1.50 (1H, q, Pyridine 6-H); 1.58 (1H, d, Pyridine 2-H); 2.49 (1H, dt, Pyridine 4-H); 2.77 (1H, dq, Pyridine 5-H); $\underline{J}_{2,4}$ 2.1; $\underline{J}_{2,5}$ 0.8; $\underline{J}_{4,5}$ 7.8; $\underline{J}_{4,6}$ 1.9; $\underline{J}_{5,6}$ 4.6
5.46 (1H, t, Pyrrolidone 5'-H); 7.37 (3H, s, 1'-CH_3); 7.4-8.1 (2H, m, Pyrrolidone 4'-H); 7.85 (1H, d, Pyrrolidone 3'-H); 8.85 (3H, d, Pyrrolidone 3'-CH_3); $\underline{J}_{4,5}$ 5.6; $\underline{J}_{3,3\text{-Me}}$ 6.6

(49) CCl_4 1.58 (1H, broad d, Pyridine 2-H); 1.62 (1H, q, Pyridine 6-H); 2.40 (1H, dtd, Pyridine 4-H); 2.91 (1H, gq, Pyridine 5-H); $\underline{J}_{2,4}$ 2.6; $\underline{J}_{2,5}$ 0.9; $\underline{J}_{4,5}$ 7.7; $\underline{J}_{4,6}$ 1.8; $\underline{J}_{5,6}$ 4.5; $\underline{J}_{4,5'}$ 0.45
6.84 (1H, t, Pyrrolidine 2'-H); 7.13 (1H, d, Pyrrolidine 5'-H); 7.87 (1H, d, Pyrrolidine 5'-H); 7.91 (3H, s, 1'-CH_3); 7.90-8.55 (2H, m, Pyrrolidine 3'-H); 8.81 (3H, s, Pyrrolidine 4'-CH_3); 8.93 (3H, s, Pyrrolidine 4'-CH_3); $\underline{J}_{4,5}$ 7.8; $\underline{J}_{2,2}$ 8.8

(50) CCl_4 1.58 (1H, broad d, Pyridine 2-H); 1.62 (1H, q, Pyridine 6-H); 2.40 (1H, dt, Pyridine 4-H); 2.92 (1H, dq, Pyridine 5-H); $\underline{J}_{2,4}$ 2.6; $\underline{J}_{2,5}$ 0.9; $\underline{J}_{4,5}$ 7.7; $\underline{J}_{4,6}$ 1.8; $\underline{J}_{5,6}$ 4.5
6.91 (1H, q, Pyrrolidine 2'-H); 7.06 (1H, d, Pyrrolidine 5'-H); 7.85-8.90 (7H, m, Pyrrolidine 5'-H and 3'-H_2, Pyrrolidine 4'-$C\underline{H}_2CH_3$); 7.98 (3H, s, 1'-CH_3); 9.16 (6H, broad t, Pyrrolidine 4'-$CH_2C\underline{H}_3$); $\underline{J}_{4,5}$ 9.6, 7.5; $\underline{J}_{2,2}$ 9.2



(51)



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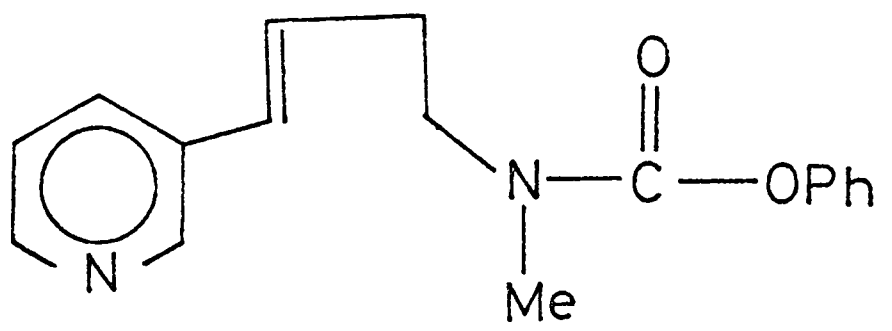

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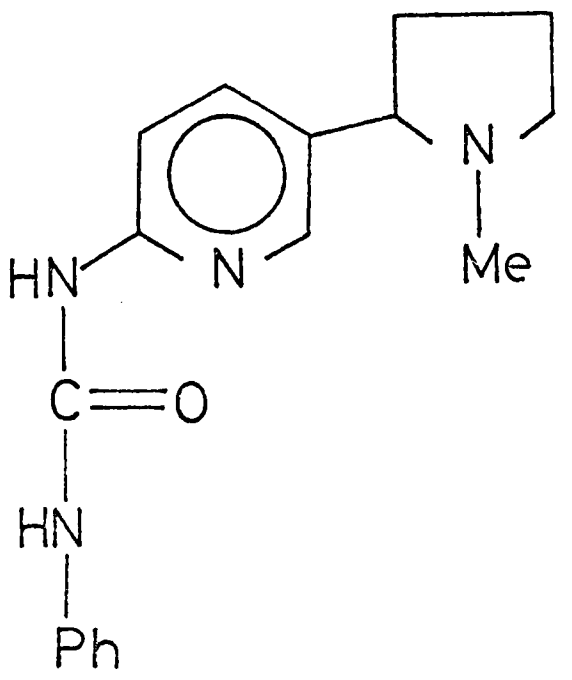


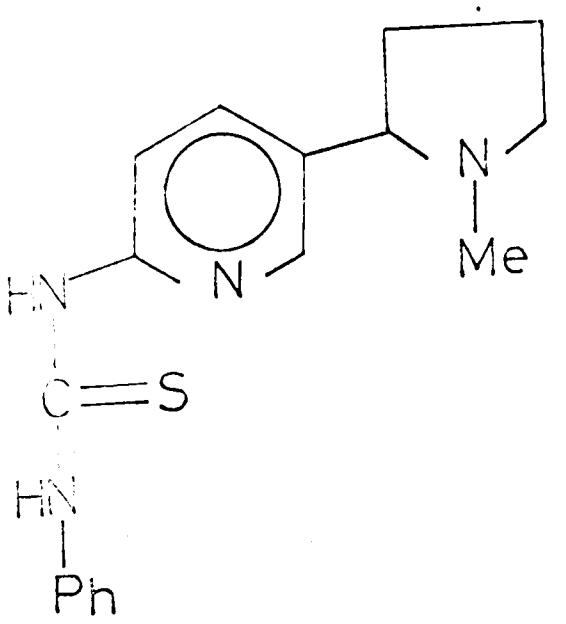
(63)

(51) CCl_4 1.63 (1H, broad d, Pyridine 2-H); 1.77 (1H, q, Pyridine 6-H); 2.45 (1H, dt, Pyridine 4-H); 2.93 (1H, dq, Pyridine 5-H); $J_{2,4}$ 2.6; $J_{2,5}$ 0.9; $J_{4,5}$ 7.7; $J_{4,6}$ 1.8; $J_{5,6}$ 4.5
6.18 (1H, q, Pyrrolidine 2'-H); 6.80 (1H, d, Pyrrolidine 5'-H); 7.5-8.5 (4H, m, Pyrrolidine 5'-H, 3'-H and 4'-H); 7.93 (3H, s, 1'-CH_3); 8.99 (3H, d, Pyrrolidine 4'-CH_3); $J_{4,5}$ 9,6; $J_{2,2}$ 8

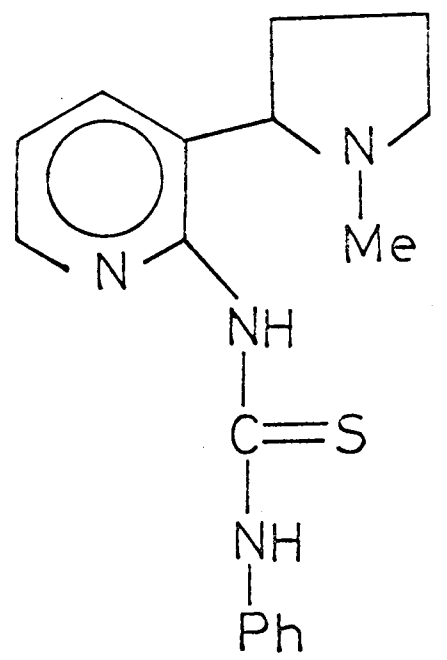
(56) CCl_4 1.54 (1H, d, Pyridine 2-H); 1.63 (1H, q, Pyridine 6-H); 2.50 (1H, dt Pyridine 4-H); 2.94 (1H, q, Pyridine 5-H); $J_{2,4}$ 2.0; $J_{4,5}$ 8.0; $J_{4,6}$ 2.0; $J_{5,6}$ 4.6
5.31 (1H, q, Oxazine 6'-H); 7.0-8.9 (6H, m, Oxazine 3'-H_2,4'-H_2 and 5'-H_2); 7.50 (3H, s, 2'-CH_3); $J_{5,6}$ 10.0, 2.8

(60) $CDCl_3$ 1.46 (1H, d, Pyridine 2-H); 1.66 (1H, q, Pyridine 6-H); 2.42 (1H, dt, Pyridine 4-H); 2.6-3.1 (6H, m, Pyridine 5-H and Phenyl H_5); 3.6-3.7 (2H, m, Olefinic H); 6.56 (2H, m, allyl -CH_2); 7.05 (3H, s, N-CH_3); 7.66 (2H, m, N-CH_2); $J_{2,4}$ 1.8; $J_{4,5}$ 7.7; $J_{4,6}$ 1.8; $J_{5,6}$ 4.8

(63) $(CD_3)_2SO$ -0.57* (1H, s, Pyridine 6-NH); 0.59* (1H, s, Phenyl NH); 1.85 (1H, d, Pyridine 2-H); 2.2-3.2 (7H, m, Phenyl H_5 and Pyridine 4-H and 5-H); $J_{2,4}$ 2
6.7-7.3 (2H, m, Pyrrolidine 2'-H and 5'-H); 7.95 (3H, s, 1'-CH_3); 7.7-8.8 (5H, m, Pyrrolidine 3'-H_2, 4'-H_2 and 5'-H).
*Disappears on addition of D_2O



(67)



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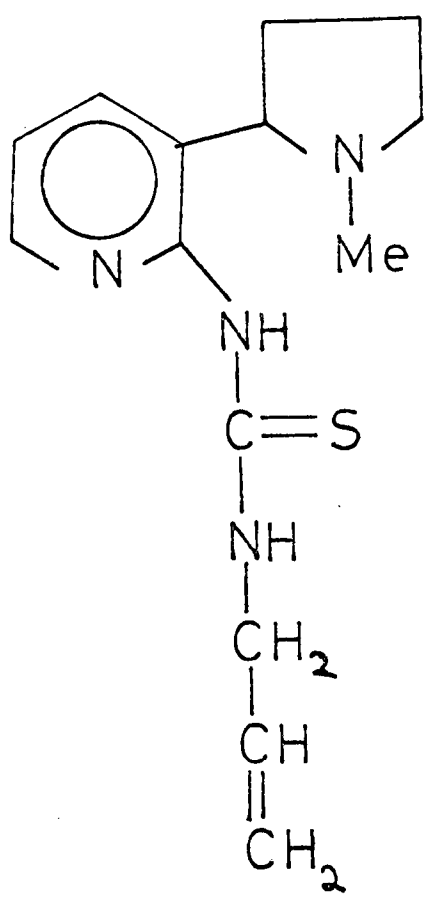


(69)

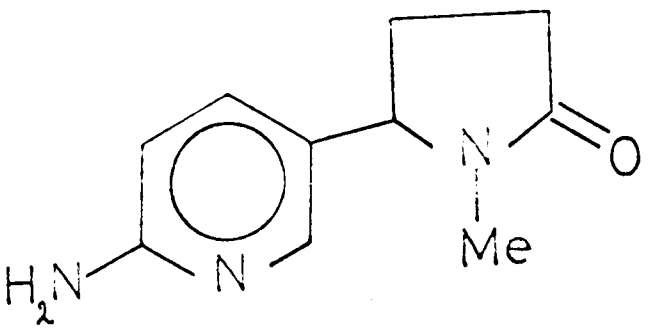
(67) $(CD_3)_2SO$ -3.65* (1H, s, Pyridine 6-NH); -0.79* (1H, s, Phenyl NH); 1.80 (1H, d, Pyridine 2-H); 2.2-2.8 (7H, m, Phenyl H_5 and Pyridine 4-H and 5-H); $J_{2,4}$ 2 6.8-7.2 (2H, m, Pyrrolidine 2'-H and 5'-H); 7.96 (3H, s, 1'-CH_3); 7.6-8.6 (5H, m, Pyrrolidine 3'-H_2, 4'-H_2 and 5'-H)

* Disappears on addition of D_2O

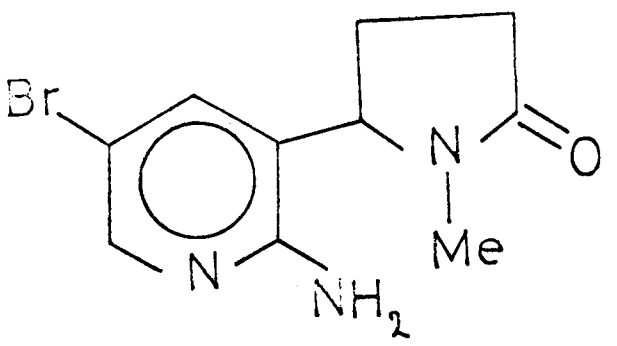
(68) $(CD_3)_2SO$ -3.60* (1H, s, Pyridine 2-NH); -2.20* (1H, s, Phenyl NH); 1.78 (1H, q, Pyridine 6-H); 2.2-3.2 (7H, m, Phenyl H_5 and Pyridine 4-H and 5-H); $J_{4,6}$ 2; $J_{5,6}$ 5 6.5-7.0 (2H, m, Pyrrolidine 2'-H and 5'-H); 7.81 (3H, s, 1'-CH_3); 7.7-8.5 (5H, m, Pyrrolidine 3'-H_2, 4'-H_2 and 5'-H)

* Disappears on addition of D_2O

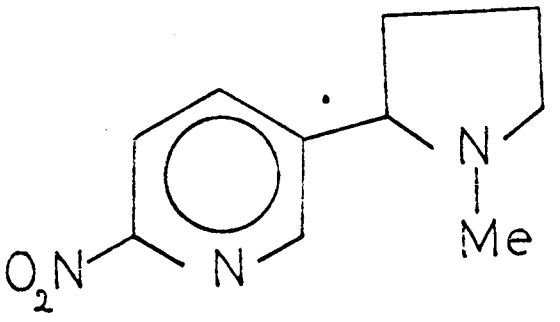
(69) CCl_4 -1.60* (1H, s, Pyridine 2-NH); -1.27 (1H, s, CH_2-NH); 1.98 (1H, q, Pyridine 6-H); 2.64 (1H, s, Pyridine 4-H); 3.28 (1H, q, Pyridine 5-H); $J_{4,5}$ 8; $J_{4,6}$ 2; $J_{5,6}$ 5 4.01 (1H, m, Vinyl CH_2-CH); 4.6-5.1 (2H, m, Vinyl CH_2); 4.5-4.8 (2H, apparent t, allyl CH_2); 6.5-7.0 (2H, m, Pyrrolidine 2'-H and 5'-H); 7.71 (3H, s, 1'-CH_3); 7.6-8.3 (5H, m, Pyrrolidine 3'-H_2, 4'-H_2 and 5'-H)



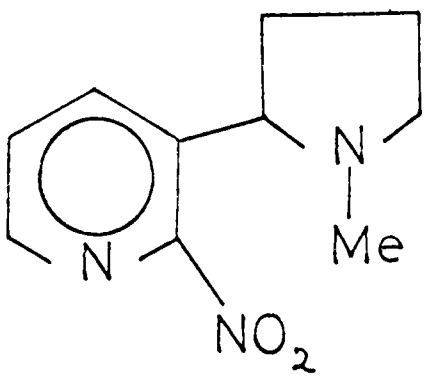
(71)



(72)



(74)



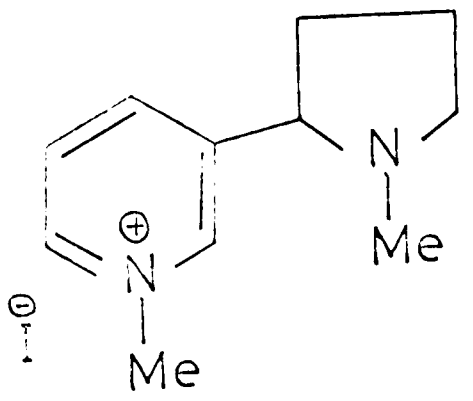
(75)

(71) $CDCl_3$ 2.13 (1H, d, Pyridine 2-H); 2.74 (1H, q, Pyridine 4
3.51 (1H, d, Pyridine 3-H); 5.31 (2H, broad s, Pyri
6-NH_2); $J_{2,4}$ 3; $J_{4,5}$ 9
5.64 (1H, m, Pyrrolidone 5'-H); 7.40 (3H, s, 1'-CH_3
7.4-8.5 (4H, broad m, Pyrrolidone 3'-H_2 and 4'-H_2)

(72) $(CD_3)_2SO$ 2.05 (1H, d, Pyridine 6-H); 2.85 (1H, d, Pyridine 4
4.67 ($\frac{1}{2}$H*, broad s, Pyridine 2-NH_2); $J_{4,6}$ 2
5.42 (1H, broad m, Pyrrolidone 5'-H); 7.31 (3H, s,
1'-CH_3); 7.4-8.3 (4H, m, Pyrrolidone 3'-H_2 and 4'-H_2
* Partial exchange with solvent

(74) CCl_4 1.59 (1H, s, Pyridine 2-H); 1.90 (1H, q, Pyridine
2.11 (1H, q, Pyridine 4-H); $J_{2,4}$ 2.1; $J_{2,5}$ 1.0; J_4
8.0
6.77 (2H, broad m, Pyrrolidine 2'-H and 5'-H); 7.8
(3H, s, 1'-CH_3); 7.4-8.6 (5H, m, Pyrrolidine 3'-H_2
4'-H_2 and 5'-H)

(75) CCl_4 1.65-1.90 (2H, m, Pyridine 4-H and 6-H); 2.54 (1H,
Pyridine 5-H); $J_{4,5}$ 7.7; $J_{4,6}$ 4.5
6.6-7.0 (2H, m, Pyrrolidine 2'-H and 5'-H); 7.5-8.
(5H, m, Pyrrolidine 3'-H_2, 4'-H_2 and 5'-H); 7.89 (
s, 1'-CH_3)
* This signal further split by 0.5 Hz.



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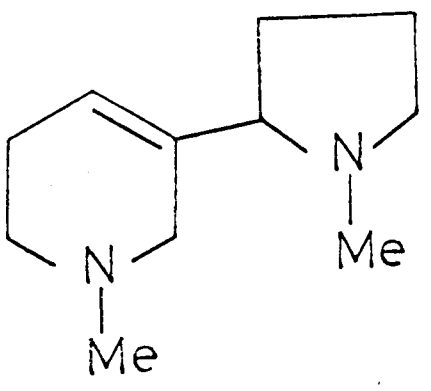
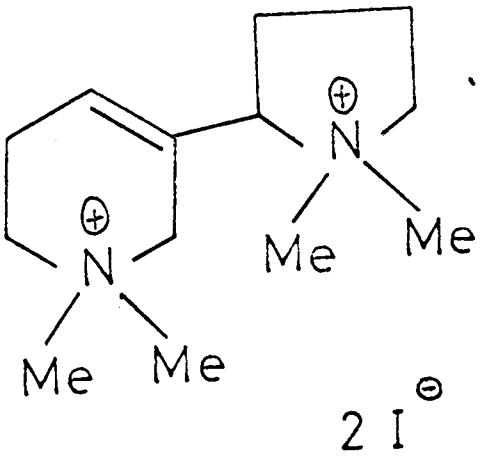
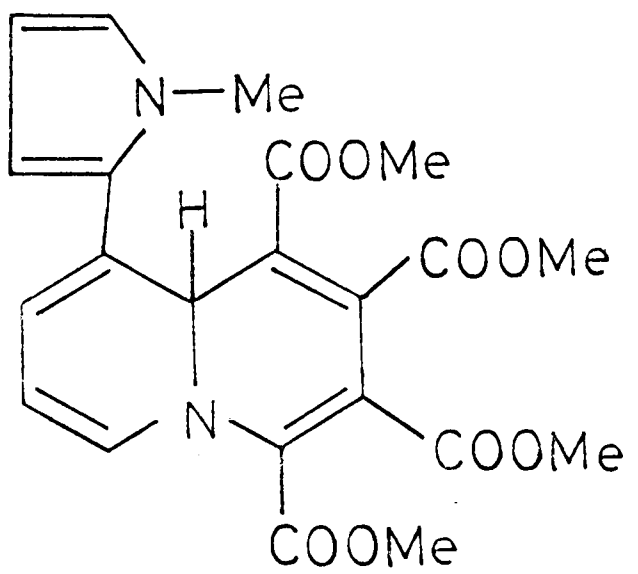


(87)



(87)
2MeI



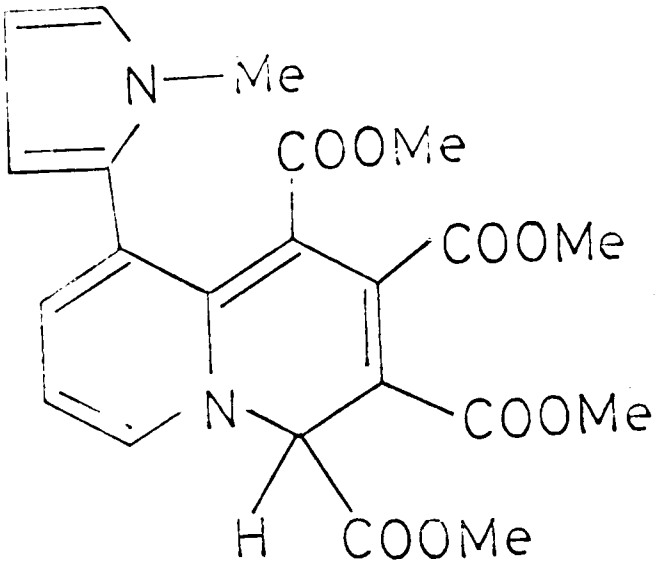
(94)

(77) D_2O 1.15 (1H, d, Pyridine 2-H); 1.18 (1H, q, Pyridine 6-H); 1.38 (1H, dt, Pyridine 4-H); 1.87 (1H, q, Pyridine 5-H); 5.54 (3H, s, Pyridine 1-CH_3); $J_{2,4}$ 1.5; $J_{4,5}$ 8; $J_{4,6}$ 1.5; $J_{5,6}$ 6.0
6.0-7.0 (2H, m, Pyrrolidine 2'-H and 5'-H); 7.1-8.3 (5H, m, Pyrrolidine 3'-H_2, 4'-H_2 and 5'-H); 7.73 (3H, s, Pyrrolidine 1'-CH_3)

(87) CCl_4 4.51 (1H, m, Tetrahydropyridine 4-H); 7.0-8.7 (13H, m, 2-H_2, 5-H_2, 6-H_2, 2'-H, 3'-H_2, 4'-H_2, 5'-H_2); 7.81 (3H, s, Tetrahydropyridine 1-CH_3); 7.95 (3H, s, Pyrrolidine 1'-CH_3)

(87) 2MeI D_2O 3.39 (1H, m, Tetrahydropyridine 4-H); 6.80 (6H, s, Tetrahydropyridine 1-$(CH_3)_2$); 6.82 (3H, s, Pyrrolidine 1'-CH_3); 7.06 (3H, s, Pyrrolidine 1'-CH_3); 5.90-8.10 (13H, m, 2-H_2, 5-H_2, 6-H_2, 2'-H, 3'-H_2, 4'-H_2, 5'-H_2)

(94) $CDCl_3$ 3.39 (1H, q, Pyrrole 5'-H); 3.65 (1H, q, Quinolizine 6-H); 3.87 (1H, q of d, Quinolizine 8-H); 3.99 (1H, q, Quinolizine 7-H); 4.01 (1H, q, Pyrrole 4'-H); 4.10 (1H, q, Pyrrole 3'-H); 5.35 (1H, d, Quinolizine 9aH); 6.14, 6.21, 6.32, 6.38 (3H each, s, ester CH_3); 6.74 (3H, s, Pyrrole 1'-CH_3); $J_{6,7}$ 7.2; $J_{6,8}$ 0.5; $J_{7,8}$ 6.2; $J_{8,9a}$ 1.7; $J_{3',4'}$ 3.9; $J_{3',5'}$ 1.7; $J_{4',5'}$ 2.6


N—Me
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COOMe
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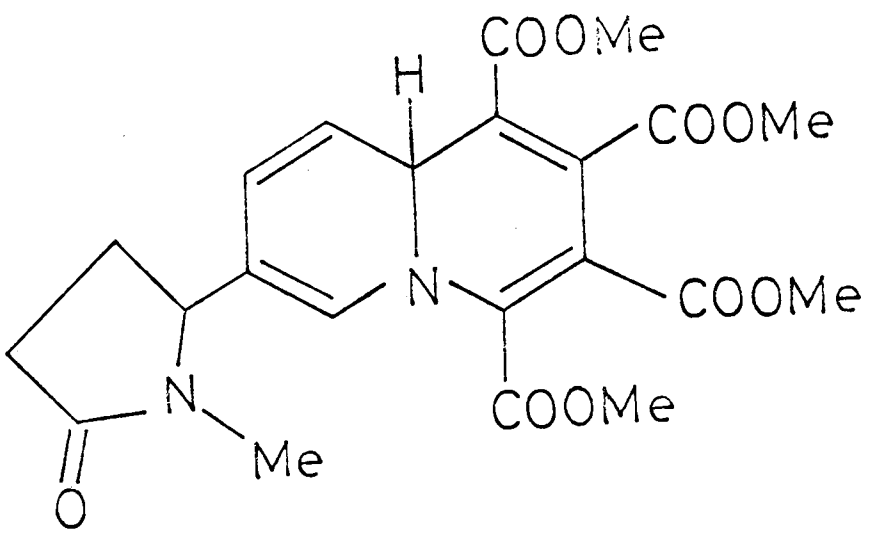
COOMe

(95)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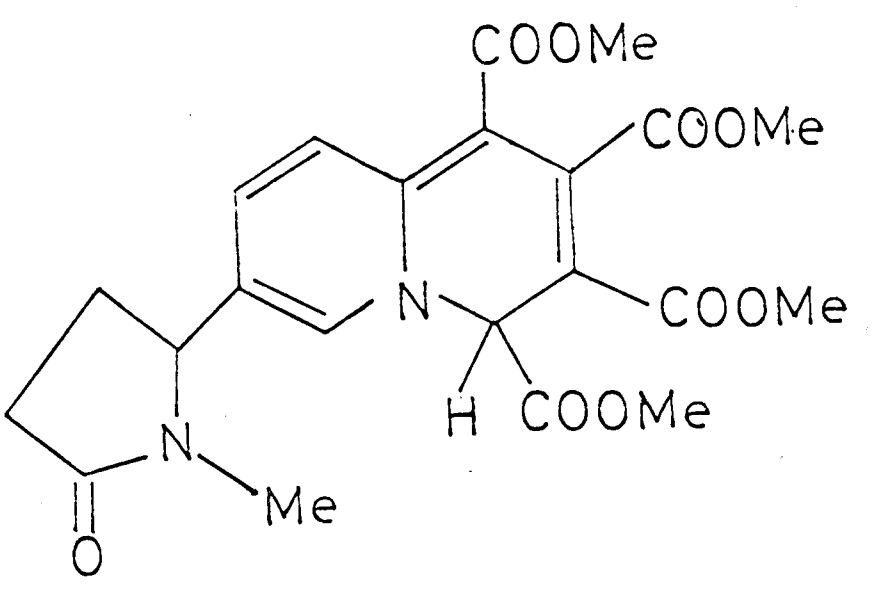
(96)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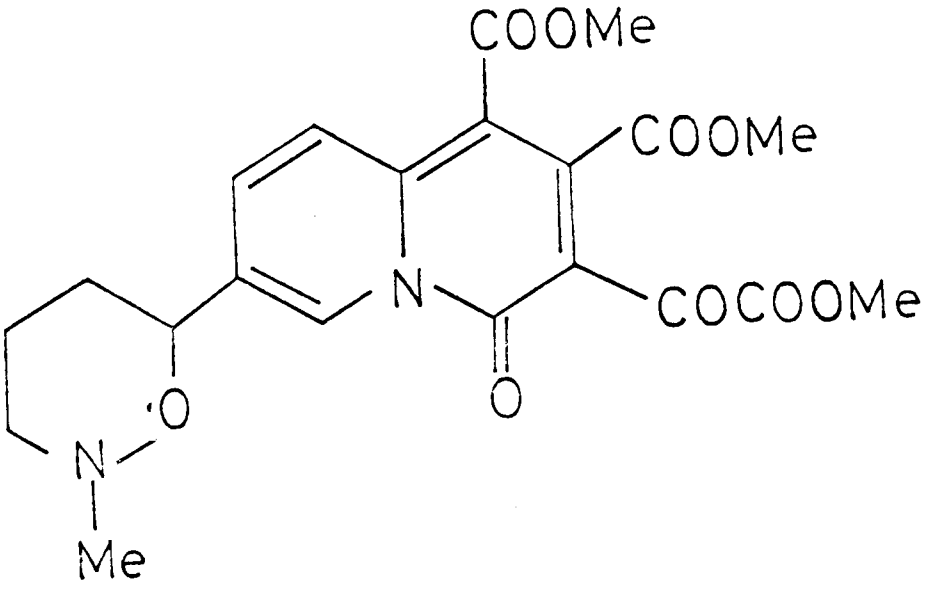
(97)


COOMe
COOMe
N
COCOOMe
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Me

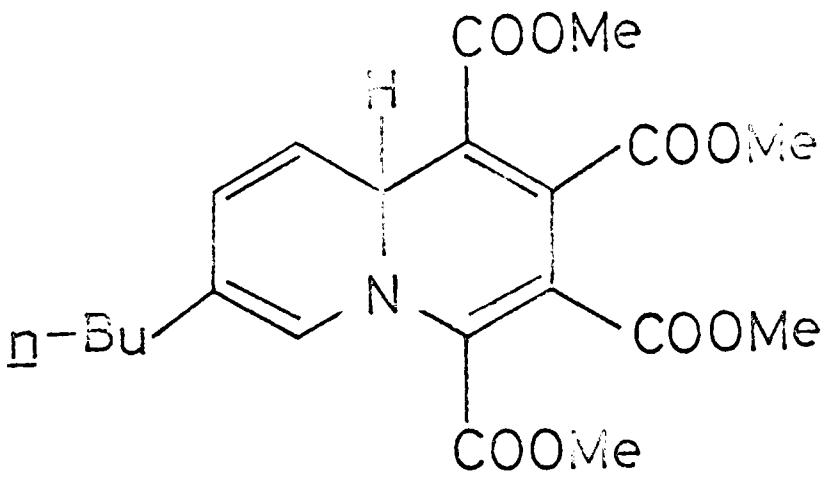
(100)

(95) $CDCl_3$ 2.32 (1H, q, Quinolizine 6-H); 3.55 (1H, q, Quinolizine 8-H); 3.06 (1H, t, Quinolizine 7-H); 3.3[illegible] (1H, t, Pyrrole 5'-H); 3.85 (3H, apparent broad d, Quinolizine 4-H and Pyrrole 3'-H and 4'-H); 6.07, 6.22, 6.28, 6.48 (3H each, s, ester CH_3); 6.92 (3H, s, Pyrrole 1'-CH_3); $J_{6,7}$ 8; $J_{6,8}$ 1; $J_{7,8}$ 6; $J_{3',4'}$ 4; $J_{3',5'}$ 2 ; $J_{4',5'}$ 3

(96) $CDCl_3$ 3.70 (1H, d, Quinolizine 9-H); 4.10 (2H, m, Quinolizine 6-H and 8-H); 5.17 (1H, d, Quinolizine 9a-H); 6.01, 6.11, 6.19, 6.28 (3H each, s, ester CH_3's); 7.28 (3H, d, Pyrrolidone 1'-CH_3); 7.0-8.0 (5H, m, Pyrrolidone 3'-H_2, 4'-H_2 and 5'-H); $J_{8,9}$ 6

(97) $CDCl_3$ [illegible].36 (1H, d, Quinolizine 9-H); 2.70 (2H, m, Quinolizine 6-H and 8-H); 4.06 (1H, s, Quinolizine 4-H); 6.14, 6.27, 6.31, 6.33 (3H each, s, ester CH_3's) 7.32 (3H, d, Pyrrolidone 1'-CH_3); 7.0-8.0 (5H, m, Pyrrolidone 3'-H_2, 4'-H_2 and 5'-H); $J_{8,9}$ 9

(100) $CDCl_3$ 0.62 (1H, q, Quinolizine 6-H); 1.23 (1H, q, Quinolizine 9-H); 2.03 (1H, q, Quinolizine 8-H); 6.08 (6H, apparant s, Quinolizine 1-$COOCH_3$ and 2-$COOCH_3$); 6.14 (3H, s, $OCOOCH_3$); 7.34 (3H, s, Oxazine 2'-CH_3); 7.7-8.5 (7H, m, Oxazine 3'-H_2, 4'-H_2, 5'-H_2 and 6'-H); $J_{6,8}$ 1.0; $J_{6,9}$ 0.45; $J_{8,9}$ 9.25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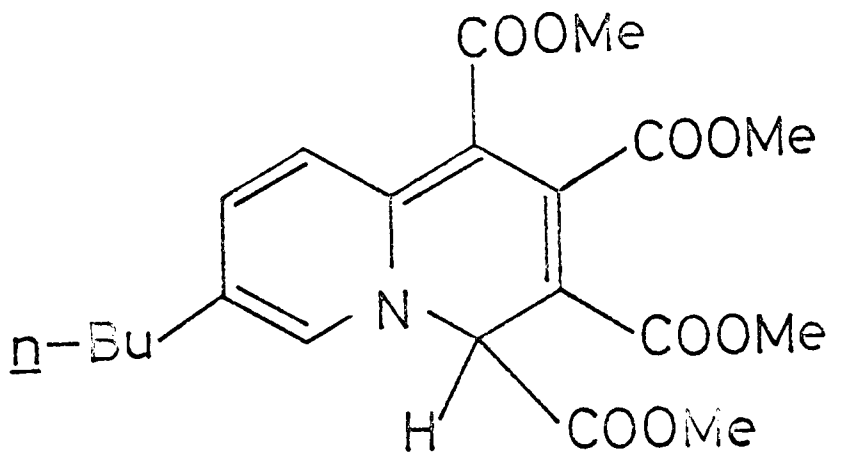
(101)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(102)

(101) $CDCl_3$ (100 MHz) 3.78 (1H, d, Quinolizine 9-H); 4.1-4.3 (2H, m, Quinolizine 6-H and 8-H); 5.13 (1H, s, Quinolizine 9a-H); 6.09, 6.09, 6.27, 6.29 (3H each, s, ester CH_3's); 7.95 (2H, m, $CH_3CH_2CH_2\underline{CH_2}CH_2$); 8.70 (4H, m, $CH_3\underline{CH_2}\underline{CH_2}CH_2$); 9.10 (3H, m, $\underline{CH_3}CH_2CH_2CH_2$); $\underline{J}_{6,9}$ 8

(102) $CDCl_3$ (100 MHz) 1.36 (1H, d, Quinolizine 9-H); 2.4-2.7 (2H, m, Quinolizine 6-H and 8-H); 3.95 (1H, s, Quinolizine 4-H); 6.07, 6.22, 6.24, 6.27 (3H each, s, ester CH_3's); 7.50 (2H, apparent t, $CH_3CH_2CH_2\underline{CH_2}$); 8.6 (4H, broad m, $CH_3\underline{CH_2}\underline{CH_2}CH_2$); 9.06 (3H, unsymmetrical t, $\underline{CH_3}CH_2CH_2CH_2$); $\underline{J}_{6,9}$ 9

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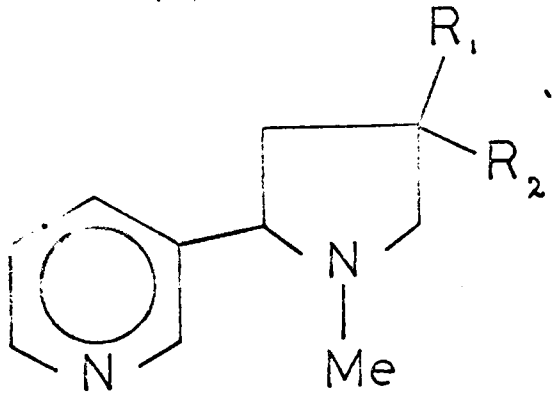
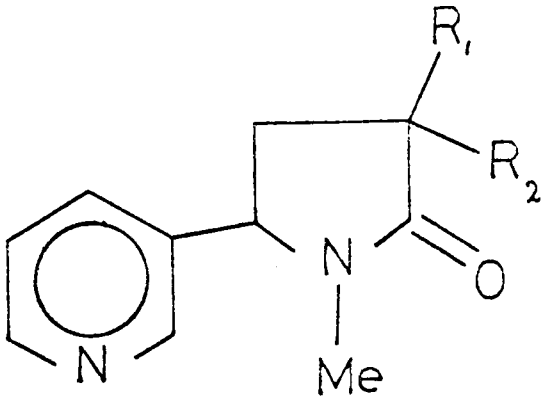
A B S T R A C T

The thesis consists of an Introduction, a Discussion (divided into 6 sections) and an Experimental chapter (for sections 1 to 5 of the Discussion).

The Introduction contains the justification for this work, the aim of which is to prepare new potentially valuable biologically active compounds from the readily available but highly toxic alkaloid nicotine (1). The chemistry, biological activity and metabolism of nicotine in man and animals is described.

Section 1 of the Discussion reports the synthesis of alkylnicotines, prepared with the aims (a) to obtain new compounds but preserve the electronic and stereochemical parameters considered[1] necessary for nicotine-like insecticidal activity, and (b) to prevent or reduce the rate of metabolic oxidative degradation of nicotine to the non-toxic nicotinic acid and cotinine (2).





(1) $R_1 = R_2 = H$

(2) $R_1 = R_2 = H$

(3) $R_1 = R_2 = Me$

(4) $R_1 = R_2 = Me$

(5) $R_1 = R_2 = Et$

(6) $R_1 = R_2 = Et$

(7) $R_1 = H$; $R_2 = Me$

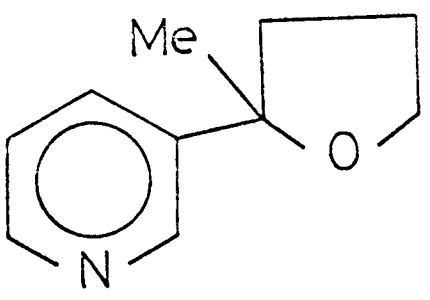
(8) $R_1 = H$; $R_2 = Me$

Nicotine analogues (3), (5) and (7) have been prepared by reduction of the corresponding carbonyl compounds (4), (6) and (8), which were synthesised from nicotine.

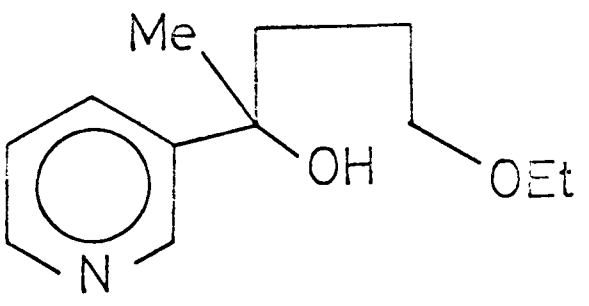
The n.m.r. spectra of (3) to (8) are discussed and corroborate Craig's[2] assignments for the n.m.r. spectrum of nicotine, a double irradiation n.m.r. spectrum of (3) supporting these assignments.

The mass spectra of (3) to (8) have been recorded and interpreted with regard to the fragmentation modes for nicotine (1) and cotinine (2) as discussed by Djerassi.[3] Compound (6) undergoes a double McLafferty rearrangement in the mass spectrometer.

The 1'-oxo analogue (9) of 2'-methylnicotine has been prepared by cyclization of (10) with hydrobromic acid.

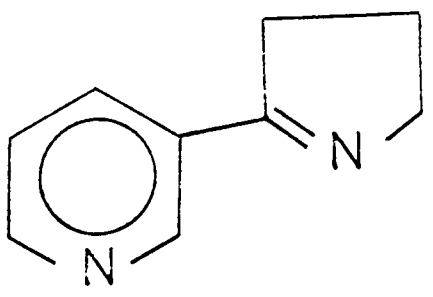


(9)

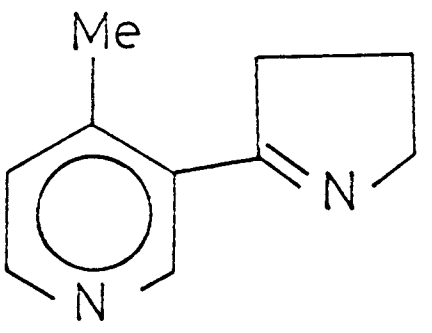


(10)

Myosmine (11) and methyl magnesium iodide have given 4-methylmyosmine (12) and its mass spectrum and n.m.r. spectrum are interpreted in terms of those obtained for (11).



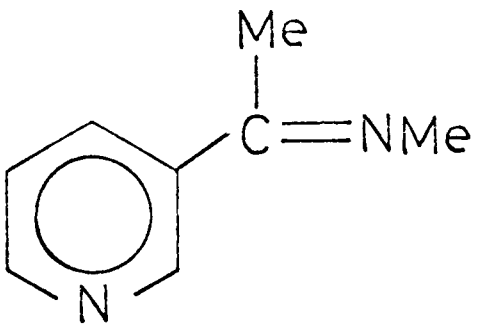
(11)



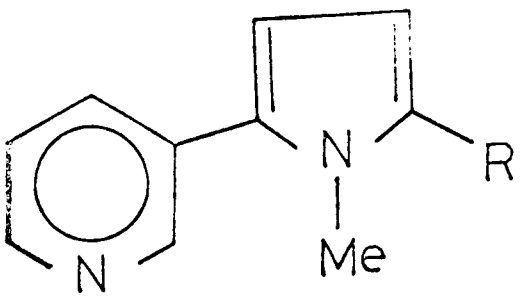
(12)

1-(3-Pyridyl)ethylideneamethylamine (13) has been prepared from

3-acetylpyridine and methylamine, but attempts to convert it to 2'-methyl-nicotine failed.



(13)



(14) R = H

(15) R = o-HOOC$C_6H_4N_2$

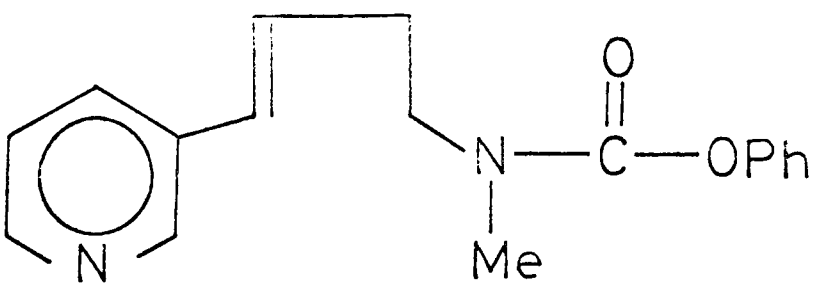
(16) R = p-$O_2NC_6H_4N_2$

Section 2 deals with oxidised nicotines.

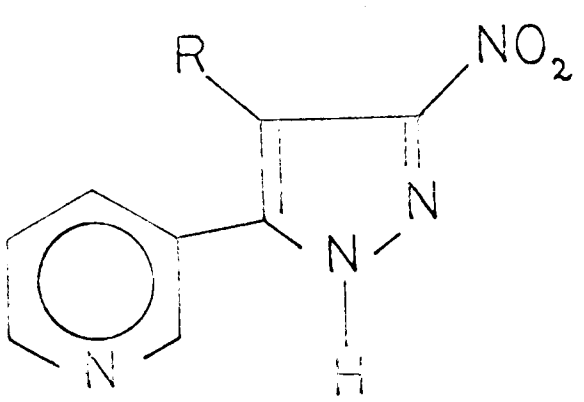
Nicotyrine[4] (14) has been coupled with the diazonium compounds obtained from anthranilic acid and from p-nitroaniline to give (15) and (16) respectively. Although (16) appears[4] to be active against black carpet beetle larvae neither (15) nor (16) showed useful activity in our screens.

Nicotine with phenyl chloroformate gave Δ^3-1-methyl-1-phenoxycarbonyl-5-(3-pyridyl)butylamine (17).

(17)

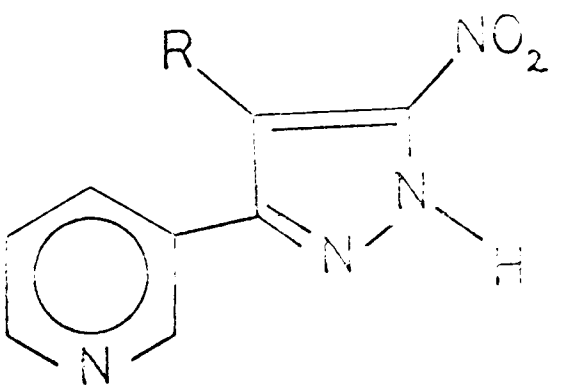


The structure of pyrazole[5,6] (18) obtained from nicotine and nitric acid is discussed with reference to its mass spectrum and i.r. spectrum, the latter showing a strongly hydrogen bonded N-H stretching absorption implying structure (18b) and not (18a) as earlier supposed.[6]



(18a) R=H

(19a) R=Br



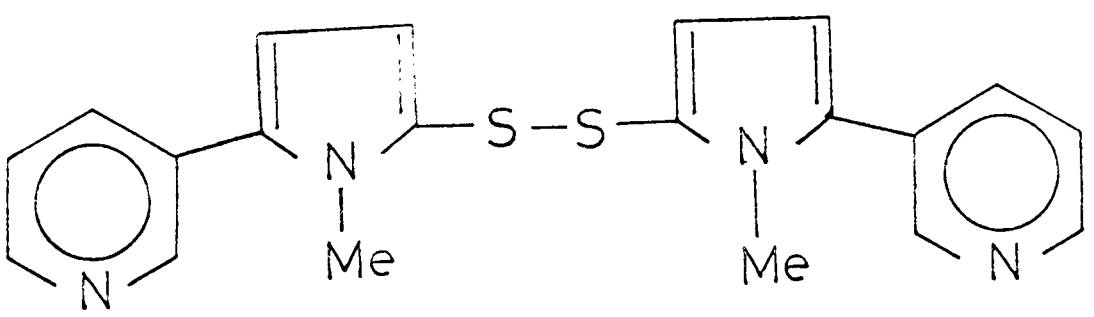
(18b) R=H

(19b) R=Br

Monobromo compound (19) has likewise been investigated.

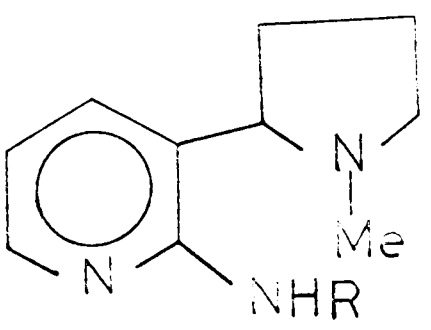
Nicotine and sulphur react to give dithiodinicotyrine (20) and not thiodinicotyrine as alleged earlier.[7] A satisfactory computer simulation of the pyridine protons of (20) has been performed.

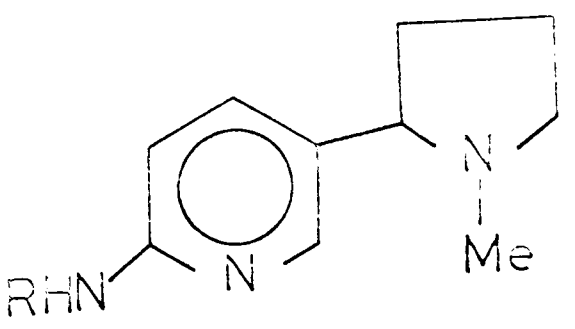
Desulphurization of (20) with Raney Nickel has given nicotyrine (14).



(20)

The reactions of 2- (21) and 6-aminonicotine (22)[8] are considered in Section 3.





(for key see over page)

(21) R = H

(23) R = PhNHCS

(25) R = allylNHCS

(22) R = H

(24) R = PhNHCS

(26) R = o-C_6H_4NHCS

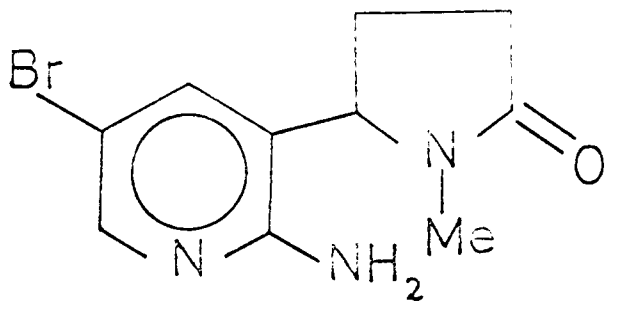
(27) R = m-C_6H_4NHCS

(28) R = p-C_6H_4NHCS

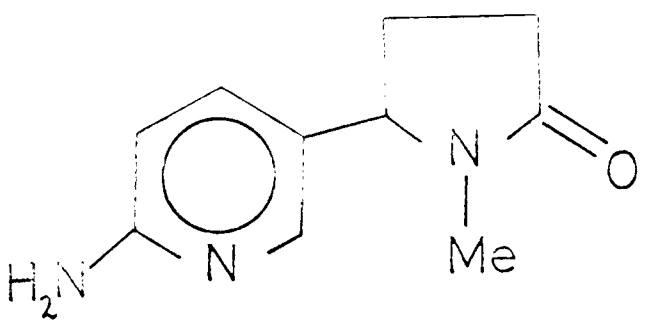
(29) R = PhNHCO

As some ureas have diuretic properties and cause reduction of intracranial and intraocular pressure compounds (23)to (29) were synthesised from (21) and (22) with the appropriate isocyanates and isothiocyanates.

The amine (21) with bromine in acetic acid has given (30) whilst (22) under the same conditions has given (31).



(30)

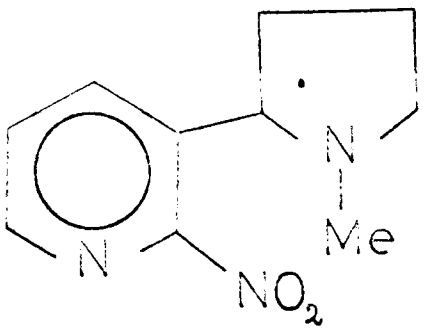


(31)

Compound (31) was converted to the urea with o-chlorophenyl isocyanate and to the expected amide with p-nitrobenzenesulphonyl chloride.

Whereas the mass spectrum of (22) is similar to that of nicotine[3] the mass spectrum of (21) shows loss of a methyl radical ascribed to participation of the nonbonded electrons of the amino group. Likewise the mass spectrum of (31) is similar to that of cotinine[3] but the mass spectrum of (30) shows loss of a methyl radical, a similar fragmentation mechanism to that of (21) is proposed.

The aminonicotines (21) and (22) have been oxidised by hydrogen peroxide and concentrated sulphuric acid to (32)and (33) respectively.



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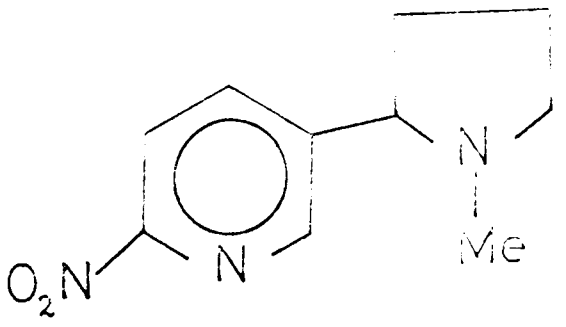
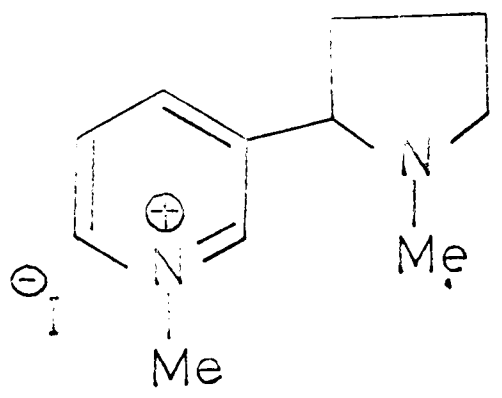


(33)

The mass spectrum of (33) is very similar to that of nicotine but the mass spectrum of (32) is much more complex.

Section 4 describes attempts to obtain compounds of similar structure and electronic constitution to known acetylcholine mimicks.

Nicotine iso-methiodide[9] (34) has been reduced with sodium borohydride to (35) and its dimethiodide prepared.



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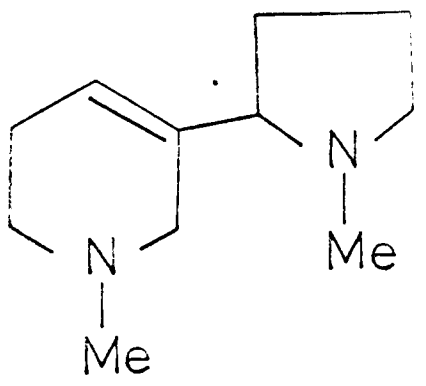
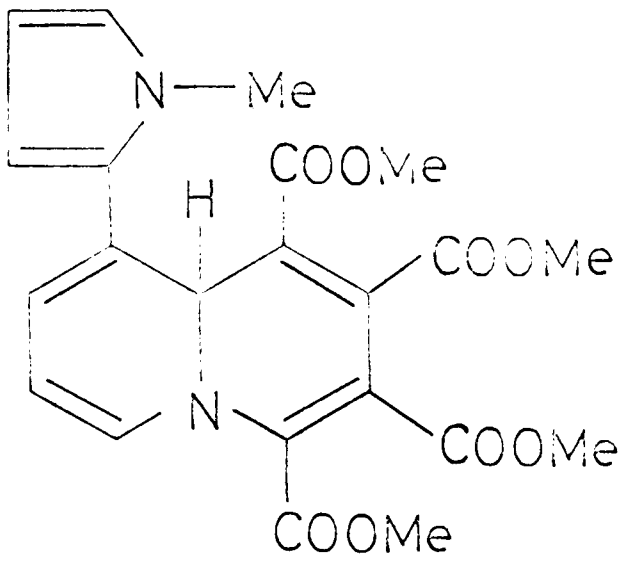


(35)

The reactions of nicotine derivatives with dimethyl acetylenedicarboxylate are described in Section 5.

Dimethyl acetylenedicarboxylate[10] with nicotine gave only tars but with nicotyrine tetramethyl 9-(1-methylpyrrol-2-yl)-9a*H*-quinolizine-1,2,3,4-tetracarboxylate (36) was obtained and isomerized to the 4*H*-isomer (37) by heating.



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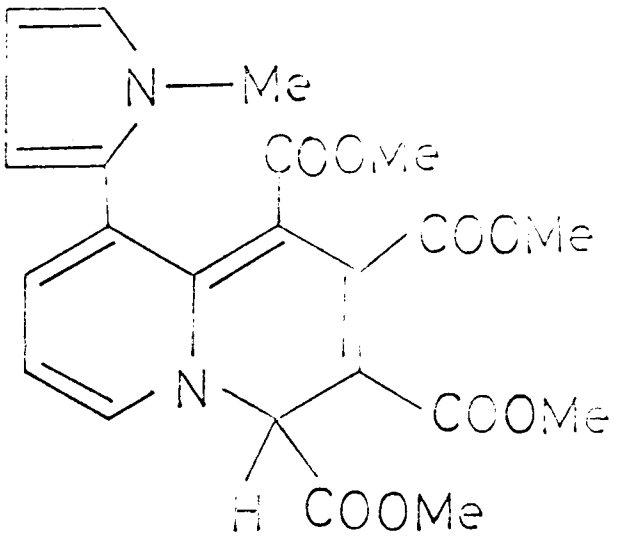
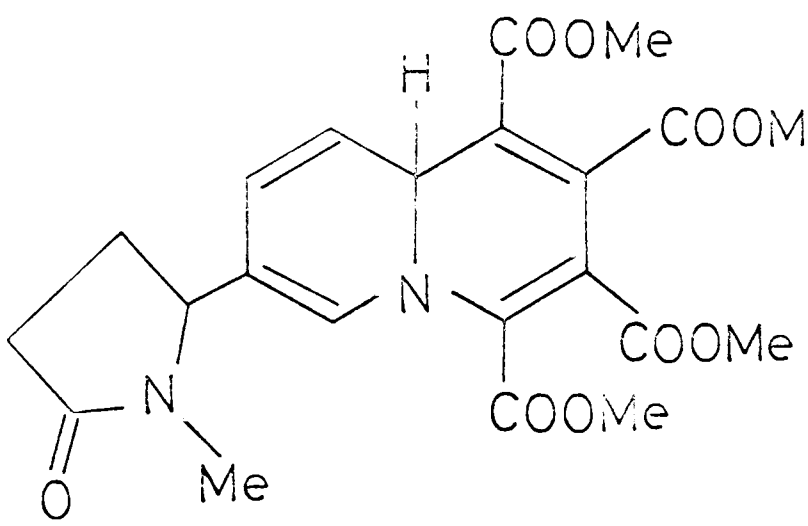
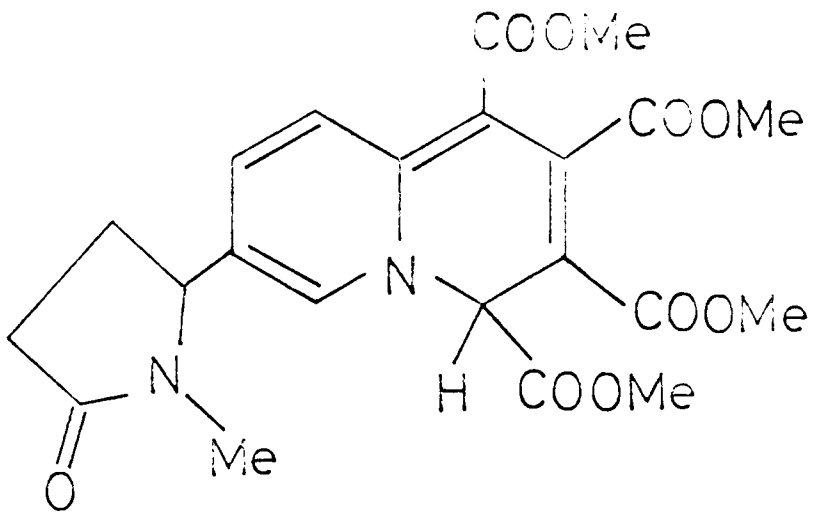


(37)

Cotinine (8) with the ester in contrast gave the 7-substituted-9a<u>H</u>-quinolizine (38) which isomerized on heating to (39).

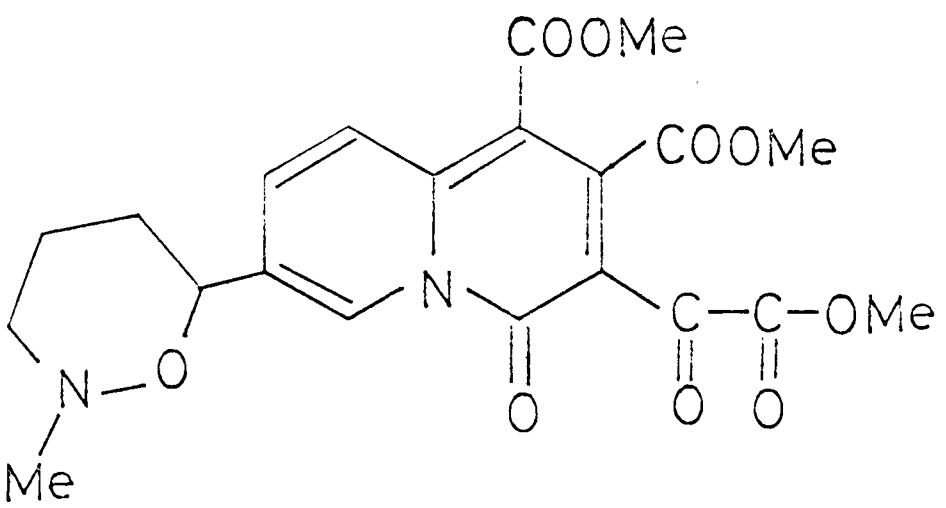


(38)



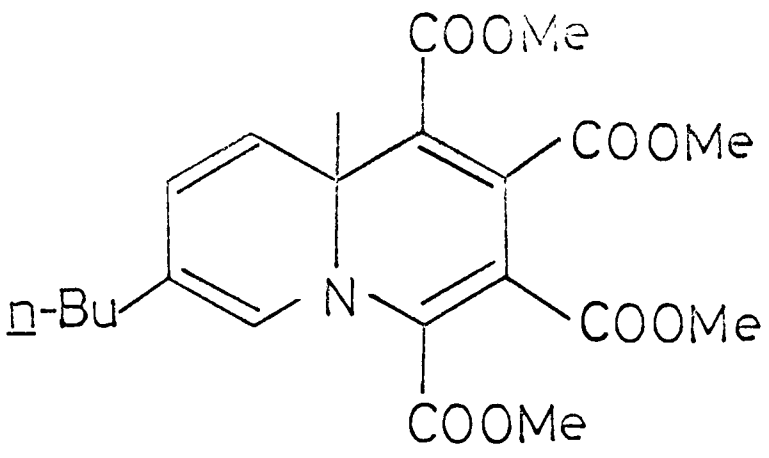
(39)

6-(3-Pyridyl)-2-methyltetrahydro-1,2-oxazine, obtained by pyrolysis of nicotine 1'-oxide,[11] reacts with the ester to give methyl 1,3-methoxycarbonyl-7-(2-methyltetrahydro-1,2-oxazine-6-yl)-4-oxoquinolizine-3-glyoxalate (40) as the only crystalline product, identified from its n.m.r. spectrum which includes the very low field 6-proton.

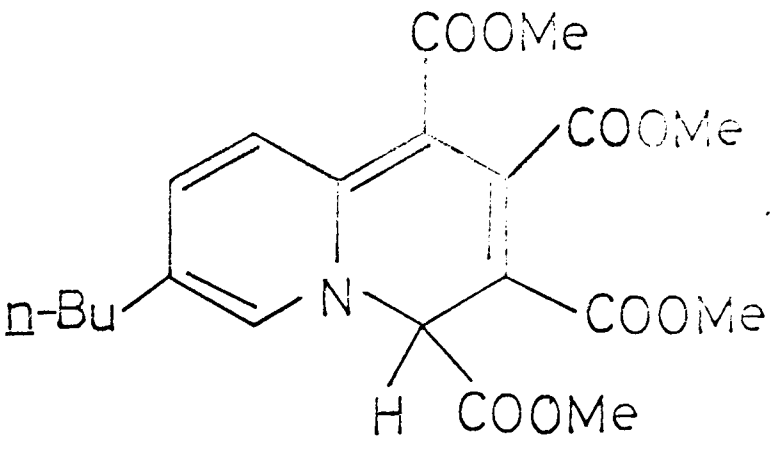


(40)

3-n-Butylpyridine[12] reacts with the ester to give tetramethyl 7-n-butyl-9aH-quinolizine-1,2,3,4-tetracarboxylate (41) and the 4H-isomer (42).



(41)



(42)

Section 6 contains the biological evaluation results obtained by Imperial Chemical Industries. No significant activity has been found.

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