ATTESTS TOWARDS THE SYNTHESIS OF SUBSTITUTED PYREOLINES

A Thesis presented to
the School of Graduate Studies
Addis Ababa University

In Partial Fulfillment of
the Requirements for the Degree
Master of Science in Chemistry

by

Wendimagegn Mammo

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To my father Mammo Deneke,
my mother Gezashign Asrat,
my brothers and sister

I express my deepest gratitude to my research advisor, Dr. Errnias Dagne, for his conception of this problem, for his patience, guidance and encouragement during the course of this work.

I also wish to express my sincere gratitude to Ato Yohannes Fassil, Dr. Jo Leibscher, Ato Esayas Berhanu and Ato Berhane Tecle for their encouragement and support. Special thanks are given to W/t Atsede Tesfaye and W/t Elizabet Kebede for their encouragement and W/t Amsale Tessema for typing this thesis.

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Abstract

Attempts Towards the Synthesis of

Substituted Pyrrolines

by

Wendimagegn Hamroo

Advisor Dr. Ermias Dagne

In this project, the reactions of several functionalized compounds possessing the nicotine skeleton have been investigated. Studies also have been conducted on the cycloaddition reactions of C-pyridyl-h-methylnitrone with three olefinic compounds namely, allyl chloride, allyl bromide and allyl alcohol. Plausible mechanisms have been suggested for the formation of nicotine and nicotyrine by the reduction of 5-methoxycotinine and related compounds with lithium aluminum hydride.

In the course of this work four new compounds, namelp 4-hydroxynicotine, 4-chloronicotine, 4-hydroxy-l-methyl-2-phenylpyrrolidine and 4-methoxy-l-methyl-2-phenylpyrrolidine, have been synthesized and their structures established.

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CHAPTER I

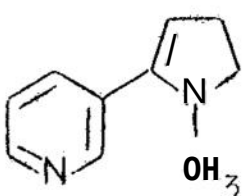
1. Introduction

Nicotine (6) is the principal alkaloid of tobacco, occuring throughout the plant and especially in the leaves of the well known plant nicotinia tabacum.[1,5p] Nicotine is said to be named after Jean Nicot, the French ambassador to Portugal who first sent tobacco seeds to Paris in 1550.[1]

Nicotine (6) was first observed by Vauquelin in 1809 and was isolated in a pure form nineteen years later by Posselt and Peimann.[3] The correct empirical formula was established in 1843 by Melsens and the structural formula was proposed by Pinner in 1895.[3] The first laboratory synthesis was reported by Pictet in 1904[3] and unequivocal proof of the structure of nicotine was established by total synthesis by Spath and Bretschneider in 1928.[4]

Nicotine in the form of tobacco is used extensively in modern society. Pharmacologically it belongs to a group of alkaloids which possesses the common property of inducing an initial and transient stimulation followed by depression and finally paralysis.[1] The pure alkaloid is highly toxic.[5] It is used as an insecticide and a veterinary vermifuge.[1,5]

a review of the literature concerning the syntohetda and characterization of 1 and 2 is given in the following section.



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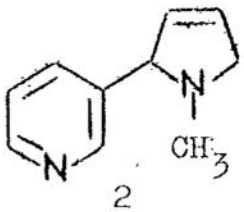

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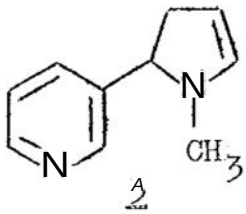

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2. Survey of the literature Concerning the Synthesis and Structure Assignments of li-ilethylmyosmine and Dihydronicotyrine.

N-Methylmyosmine (1) and dihydronicotyrine (2) were first reported in the literature over eighty years ago. However, considerable confusion concerning their structures have persisted.

Dihydronicotyrine is strongly insecticidal.[3] Its insecticial properties are even stronger than those of nicotine.[4] When injected into oncopeltus fascistus, it was found to be three times more toxic than nicotine[6] It also showed a higher toxicity than nicotine to house flies.[12]

Nicotine is actively metabolised both in the intact growing plant and during the processing of the leaf. During the fermentation of tobacco, nicotine is degraded to N-methylnicotinamide (7) and nicotinamide (8) presumably via the intermediate N-methylmyosmine (I).[13,14] The hydrated form of *1* is converted to 3-pynidylpropylketone (9) which is degraded further with the formation of 3-acetylpyridine (10) and nicotinic acid (hi). Support that H-methylmyosrnine (1) is an intermediate in the degradation of nicotine was obtained from oxidation reactions carried out *in vitro*. Thus treatment of N-methylmyosmine (JL) with hydrogen peroxide afforded N-methy-Inicotinaraide (7), nicotinamide 08), 3-pyridylpropylketone (0), 3-acetylpyridine (10) and nicotinic acid (11). These same compounds were obtained as minor components along with the major formation of nicotine N-oxide (12) and cotinine (13) when nicotine itself was treated with hydrogen peroxide.[14]

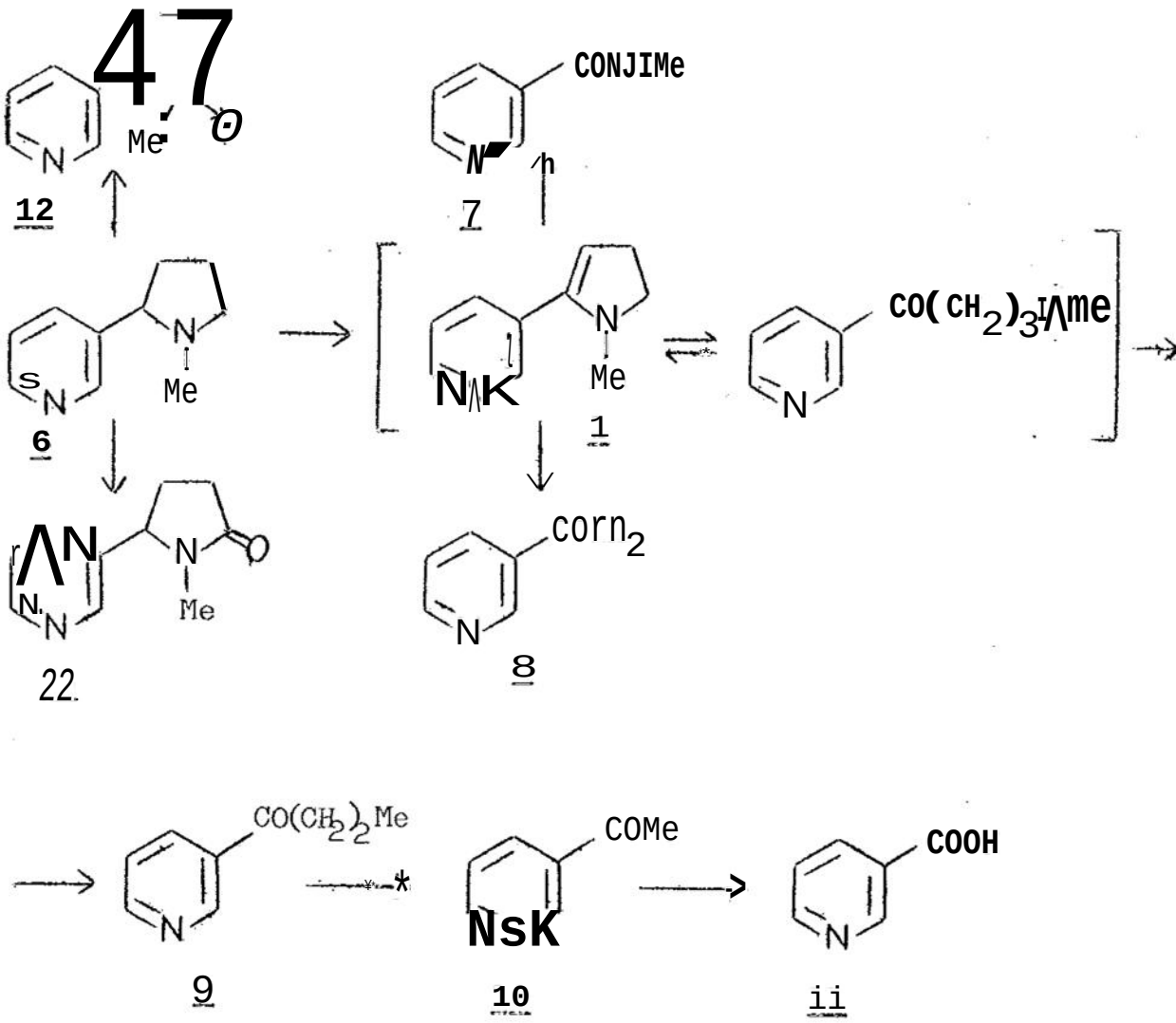
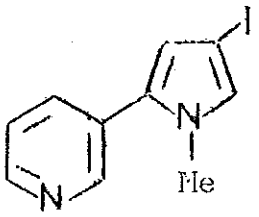


Figure I Degradation of nicotine during fermentation

As early as 1898, Pictet reported the first synthesis of a dehydronicotine (or dihydronicotyrine) by the reduction of iodonicotyrine (4) with zinc and hydrochloric acid.[3] This reaction was a major step in the first total synthesis of nicotine (6). Dihydronicotyrine was assigned structure 1 which Pictet later altered to 2.



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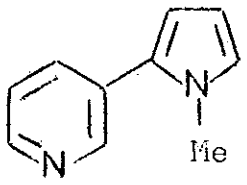

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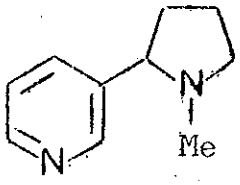

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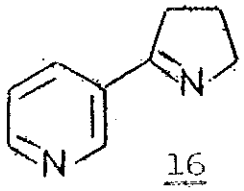

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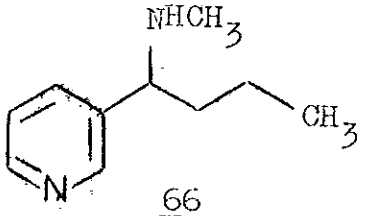

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In 1932, Wibaut and Hackmann[15] prepared a dihydronicotyrine of uncertain structure by the reduction of nicotyrine (5) with a large excess of 20% hydrochloric acid and zinc dust. The catalytic hydrogenation of the dihydronicotyrine with platinum oxide as a catalyst gave nicotine (6), nicotyrine (5) and dihydrometanicotine (66). For the formation of the dihydrometanicotine(66), the opening of the 5-membered ring was assumed while the formation of nicotyrine (5) was explained by a disproportionation of a pyrroline derivative into a pyrrole and a pyrrolidine derivative.[15] The disproportionation was also brought about by Pt and acetic acid with the formation of nicotine (6) and nicotyrine (5).

Dihydronicotyrine was considered to possess any one of the structures 1, 2, or 3.

Of the three possible structures suggested by Wibaut and Hackman,[15] only compound 1 is not resolvable into optical antipodes. Both 2 and 3 retain the chiral center present in nicotine and should be resolvable into their corresponding enantiomers. Osterhuis and Wibaut(1936)[16] attempted to resolve dihydronicotyrine, prepared by the partial reduction of nicotyrine (5), with bromocamphorsulfonic acid and obtained a material with only weak optical rotatory power. They concluded, however, that dihydronicotyrine is a racemic mixture and therefore proposed 2 or 3 as the structure of this compound. Later(1938) Spath and co-workers[17] repeated the resolution experiment with 4,6,4',6'-tetranitro-2,2'-diphenic acid, but again, the free base obtained showed a very small optical activity ($[\alpha]_D$ - 1.4). When the inactive dihydronicotyrine was converted into its picrate, it was observed that the melting range was rather broad (110 - 140°C). Fractional crystallization from methanol yielded nicotine dipicrate and nicotyrine picrate. Thus the dihydronicotyrine, which was originally pure, had disproportionated into nicotine (6) and nicotyrine (5). This result deprived the resolution experiments of all value in establishing the structure of dihydronicotyrine.

Spath and co-workers[17] proposed structure 1 for dihydronicotyrine on the basis that 2-methylaminopropanoic acid (14) was formed when dihydronicotyrine, freshly prepared according to the method of Wibaut and Hackmann,[15] was oxidized with potassium permanganate in dilute sulfuric acid. Moreover, these workers reported that dihydronicotyrine was obtained by repeated distillation of 3-pyridyl-3-methylaminopropylketone (15) under high vacuum.

$CH_3NH-CH_2-CH_2-COOH$

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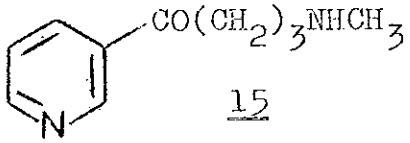

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According to Spath and co-workers,[17] the dihydronicotyrine prepared by Pictet through reduction of iodonicotyrine (4) and by Wibaut and Hackman[15] by the partial reduction of nicotyrine (5) are identical with N-methylmyosmine (1).

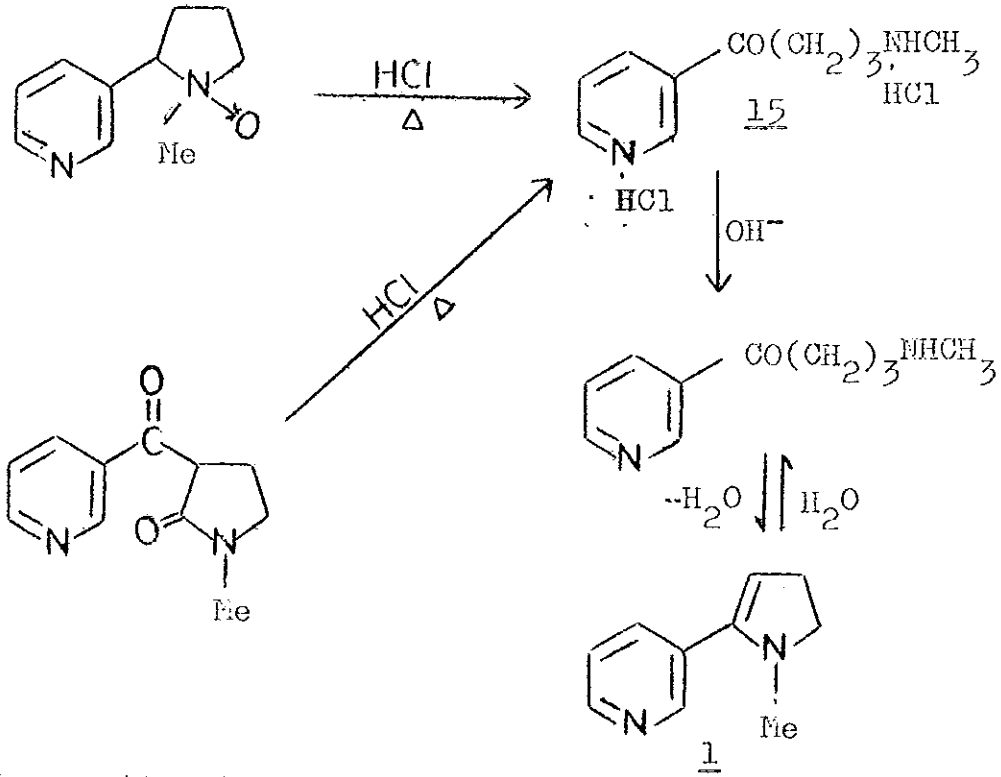
In 1949 Swain and co-workers[18] on the basis of UV-spectroscopic measurements, showed that there is no conjugation of the pyridine ring with the dehydrogenated pyrrolidine ring of dihydronicotyrine ("N-methylmyosmine"). A spectral curve similar to that of myosmine (16) was expected from dihydronicotyrine whose structure was proposed as 1 by Spath and

co-workers.[17] However an absorption curve essentially identical with that of nicotine (6) was obtained. Spectral evidence for the presence of an unconjugated double bond in dihydronicotyrine was indicated by the heightened end absorption in the neighbourhood of 210 nm which is not present in the spectrum of nicotine. The observed absorption characteristics could be explained if dihydronicotyrine possesses structure 2 or 3 .

N-Methylmyosmine and the dihydronicotyrine, prepared by the partial reduction of nicotyrine (5), were shown to be different by Haines and Eisner in 1950. N-Methylmyosmine (1) was prepared by cyclization of 3-pyridyl-3-methylaminopropylketone obtained by treatment of the dihydrochloride salt (15) with base. Attempted distillation of 1 caused polymerization of the product. A mixture of N-methylmyosmine picrate (m.p. 158-160°C) with dihydronicotyrine picrate (m.p. 159-161°C) had a melting point of 140 - 145°C thus indicating that these two picrates are not identical. Moreover, N-Methylmyosmine underwent ready polymerization on standing whereas dihydronicotyrine did not.

If the double bond of dihydronicotyrine were located in the 4,5-position of the pyrroline ring, facile hydrolysis to an aminoaldehyde and subsequent reaction with 2,4-dinitrophenylhydrazine would be expected.[19] Haines

and Eisner[19] did not obtain a 2,4-dinitrophenylhydrazone upon treatment of dihydronicotyrine with this reagent and therefore concluded that the double bond is in the 3,4-position of the pyrroline ring.

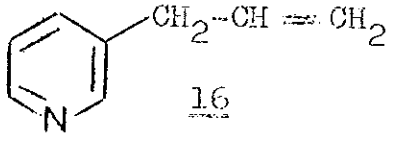


1

In an attempt to determine if isomerisation of dihydronicotyrine into N-methylmyosmine (1) could be observed, Haines and Eisner[19] subjected these compounds to several treatments with acid and alkali. A solution of dihydronicotyrine in dilute aqueous alkali remained unchanged after a month at room temperature but refluxing the dihydronicotyrine with a solution of sodium hydroxide in ethylene glycol produced a crude materal from which nicotine (6) picrate could be isolated. The formation

of nicotine (6) was thought to be due to the disproportionation of dihydronicotyrine. After heating dihydronicotyrine with concentrated HBr for 12 hours followed by treatment of the resulting reaction mixture with picric acid, a mixture of products were obtained melting at 150 - 175°C which could not be purified by crystallization. These workers could find no clear cut evidence of isomerization of dihydronicotyrine into N-methylmyosmine (1).

A comparative study on dihydronicotyrine, 3-allylpyridine (16) and 3-vinylpyridine (17) was carried out by Wibaut and Beyerman[20] in 1951 in their attempts to establish the



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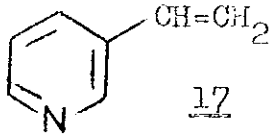

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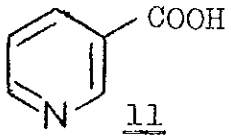
structure of the dihydronicotyrine obtained by the partial reduction of nicotyrine (5). Oxidation of dihydronicotyrine with ozone and further with 3% H_2O_2 gave nicotinic acid (11) whereas the oxidation of 3-allylpyridine gave 3-pyridylacetic acid (18). Compound 1 seemed to be the favoured structure based on the ozonolysis experiments however, this conclusion was incompatible with the ultra violet spectra of the three compounds which indicate that the double bond is not



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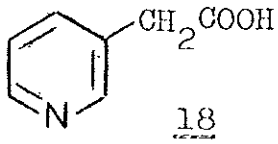

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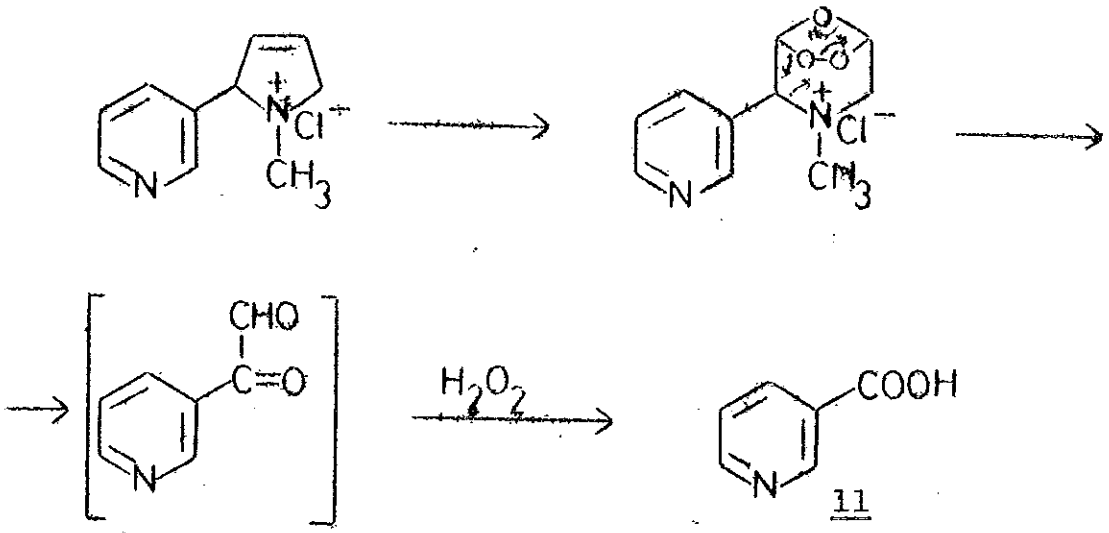
in conjugation with the pyridine ring.

	λ min	λmax	
3-allylpyridine	237-8	256	261
dihydronicotyrine	230	257	263
3-vinylpyridine	266	238	278

Thus 3-vinylpyridine has a strong absorption peak at 278 nm while 3-allylpyridine has maxima at 257 and 263nm and dihydronicotyrine has no peak in the 278 nm region, although it has maxima at 256 and 261 nm. The marked resemblence of the dihydronicotyrine and 3-allylpyridine (16) spectra suggested that 2 was the more likely structure for dihydronicotyrine. The misleading ozonolysis experiment was thought to be due to an abnormal reaction which probably proceeds as shown below.[23]



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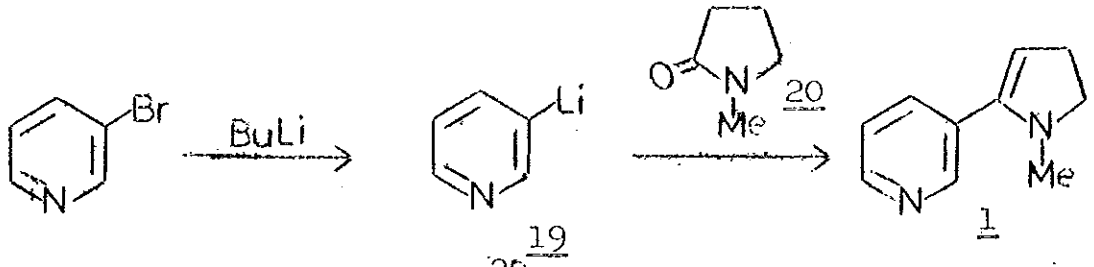
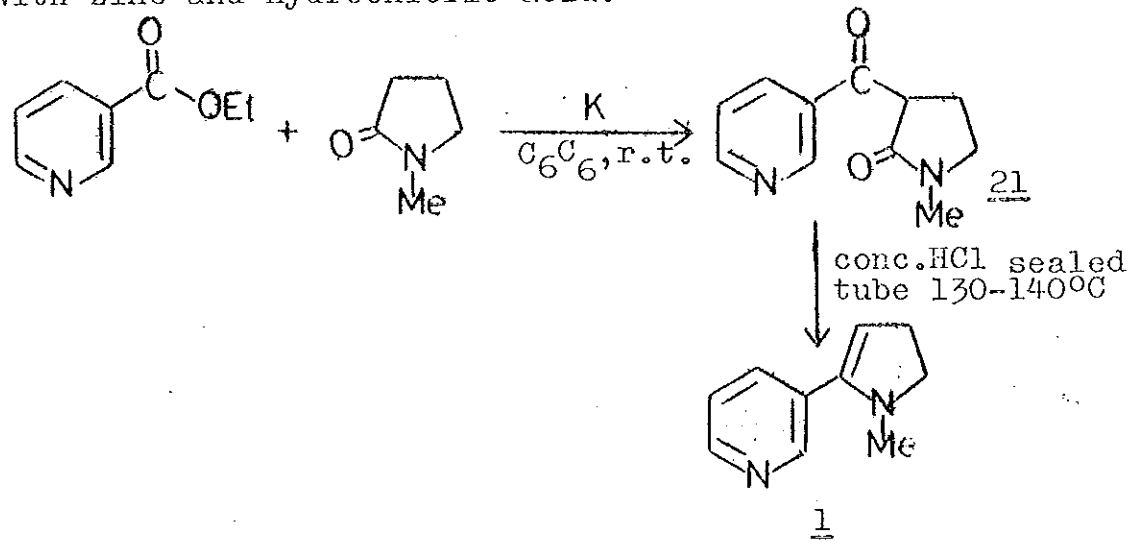
The synthesis of N-methylmyosmine (1) by the condensation of 3-pyridyllithium 19 with N-methylpyrrolidone 20 was

reported by Lukes and Cervinka[21] in 1961. The workers regarded their product to be identical with the dihydronicotyrine prepared by the partial reduction of nicotyrine (5) according to Wibaut and Hackmann.[15] However, spectroscopic examination of dihydronicotyrine prepared by earlier workers[18,20] showed no evidence of a double bond in conjugation with the pyriding ring.

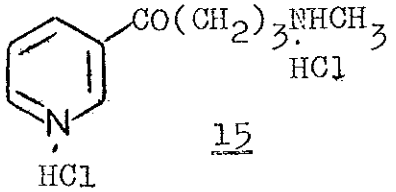


Korte and Schulze-Steinen[28] reported the preparation of N-methylmyosmine (1) by the rearrangement of 3-nicotinoyl-N-methyl-2-pyrrolidinone (21) with concentrated hydrochloric acid in a sealed tube at 130-140°C. The product was characterized by elemental analysis, UV and IR spectroscopy and was shown to be different from the product obtained by the partial reduction of nicotyrine (5) with zinc and hydrochloric acid.



In 1963, Mechoulam and Gaoni[23] proposed that 2 is the favoured structure of the reduction product of nicotyrine (5) based on ^{1}H-NMR spectroscopic grounds. The NMR spectra of nicotine (6) and dihydronicotyrine are identical in the aromatic proton region below 7.0 ppm but are different in the other regions. The NMR spectrum of dihydronicotyrine shows complex patterns centered at δ = 5.75 and 6.06 ppm which are due to two olefinic protons. The presence of two olefinic protons is incompatible with structure 1. The chemical shifts of the two olefinic protons are not sufficiently different to make structure 3 acceptable since in the latter structure one of the two olefinic protons is α to the amine nitrogen and subject to deshielding.

Very recently, a group of Japanese workers[24] reported the synthesis of N-methylmyosmine (1) by a cyclocondensation reaction of pseudooxynicotine dihydrochloride (15) with NaOH. The product was found to be very unstable and was hydrolyzed to 22 by acid. This method of synthesis is essentially identical with that reported by Haines and Eisner[19] in 1950. The same workers[25] have



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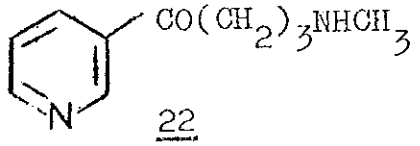

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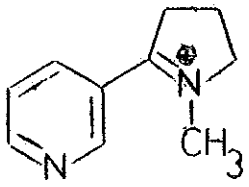
studied the pH induced structural forms of 1. At pH < 4 and pH > 5 the molecular species in aqueous solution are 22 and 1 , respectively. Nicotine-1'-iminium ion(23) exists in equilibrium with 1 and 22 at pH 2-9.5.



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It is apparent from the above discussion covering the literature up to 1981, that little systematic work has been done in the attempts to establish the structures of 1 and 2. A considerable amount of effort has been directed at elucidating the structure of the reduction product of nicotyrine (5), however, unequivocal proof of the structure by an independent synthesis has not been reported up to this time. Moreover no reported synthesis of compound 3 is available in the literature. Inorder to solve the problem of the structures of the pyrrolines (1,2,3,), the need for a more systematic work is obvious.

This project was undertaken with the view of synthesizing each of the pyrrolines 1, 2 and 3 by independent synthetic routes and providing unequivocal proofs of their structures. The results obtained in the course of this work are discussed in the following section.

CHAPTER II

RESULTS AND DISCUSSION

1. Attempts to dehydrohalogenate (S)-3,3-dibromocotinine (24)

The oxidative bromination of nicotine (6) with bromine and acetic acid yields (S)-3,3-dibromocotinine (24)[27] which has found interesting applications in the synthesis of the major nicotine metabolite cotinine (13)[27] and 5-hydroxycotinine (27),[28,29] a secondary metabolite of nicotine. L.Lindblom[30] has suggested the plausible mechanism shown in Figure II for the formation of 24 from nicotine.

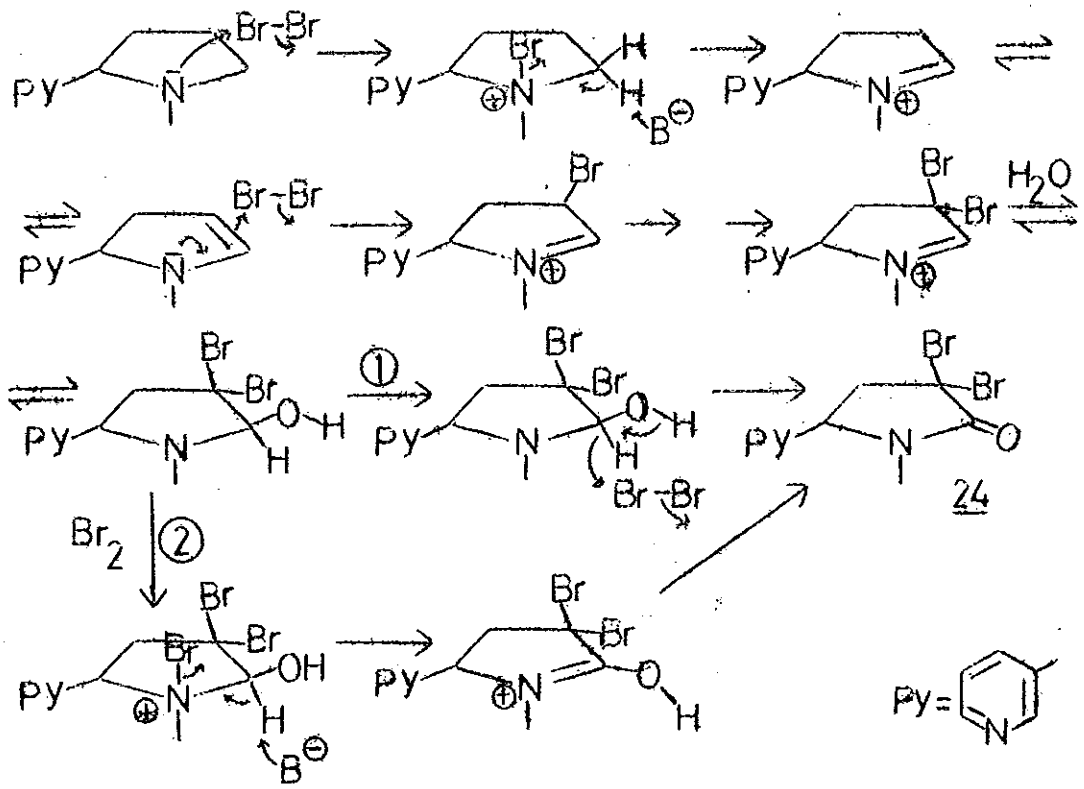


Figure II. Possible mechanism(s) for the formation of (S)-3,3-dibromocotinine from nicotine.

The synthesis of 5-hydroxycotinine (27)[29] from (S)-3,3-dibromocotinine (24) involved several steps. In methanolic KOH 24 undergoes a series of reactions to yield 1-methyl-5-methoxy-5-(3'-pyridyl)-2-pyrrolinone(25). The O-CH_3 bond in 25 was cleaved in hydrobromic acid. Catalytic hydrogenation of 1-methyl-5-hydroxy-5-(3'-pyridyl)-2-pyrrolinone (26) afforded 5-hydroxycotinine (27) as a white crystalline solid.

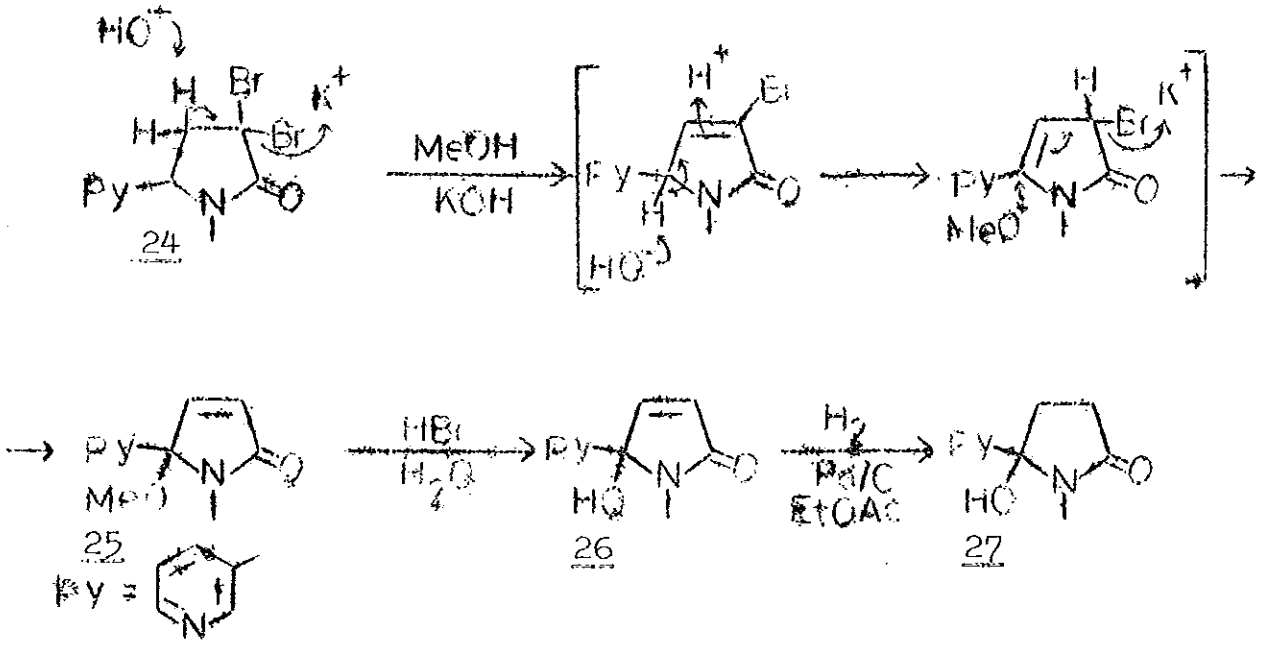
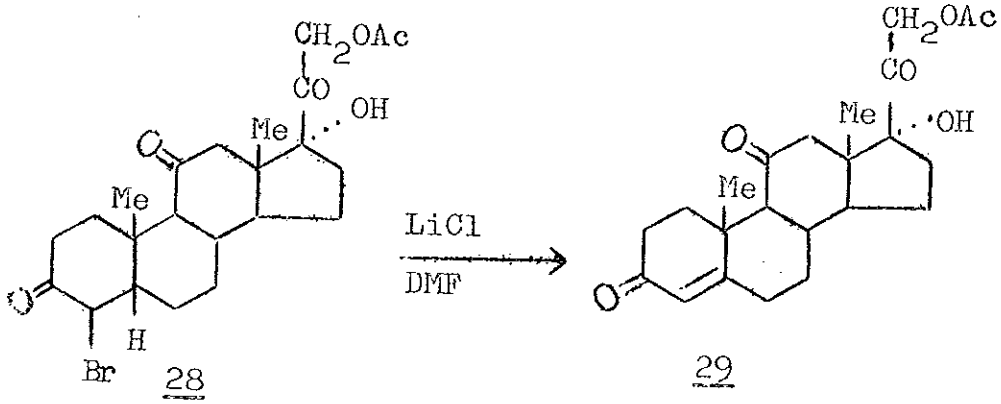


Figure III. Synthetic scheme for the synthesis of 5-hydroxycotinine(27)

With the aim of synthesizing suitable intermediates that may lead to the pyrrolines 1,2 and 3, we first sought to examine the reactions of (S)-3,3-dibromocotinine (24) with some reagents that are known to effect dehydrohalogenation.

Certain weak bases in dipolar aprotic solvents are effective reagents for dehydrohalogenation.[32] Among those most often used for synthetic purposes are LiCl, Li_2CO_3 and Li_2CO_3 - LiBr in dimethyl formamide.[31,32]

A.P. Holysz[33] found LiCl in dimethyl formamide to be an effective reagent for the elimination of the elements of hydrogen bromide from 4-bromodihydrocortisone-21-acetate (28). The reaction yielded cortisone-21-acetate (29) in a 73% yield.



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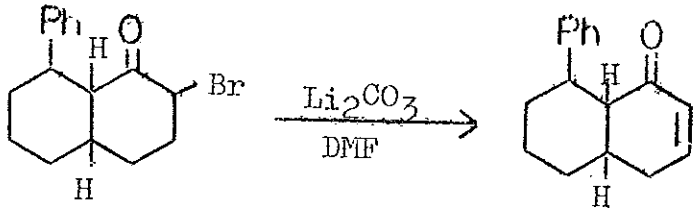
Li_2CO_3 in refluxing dimethylformamide was used by H.O. House and R.W.Bashe[35] to effect dehydrobromination of the bromoketone (30) to give the product (31).



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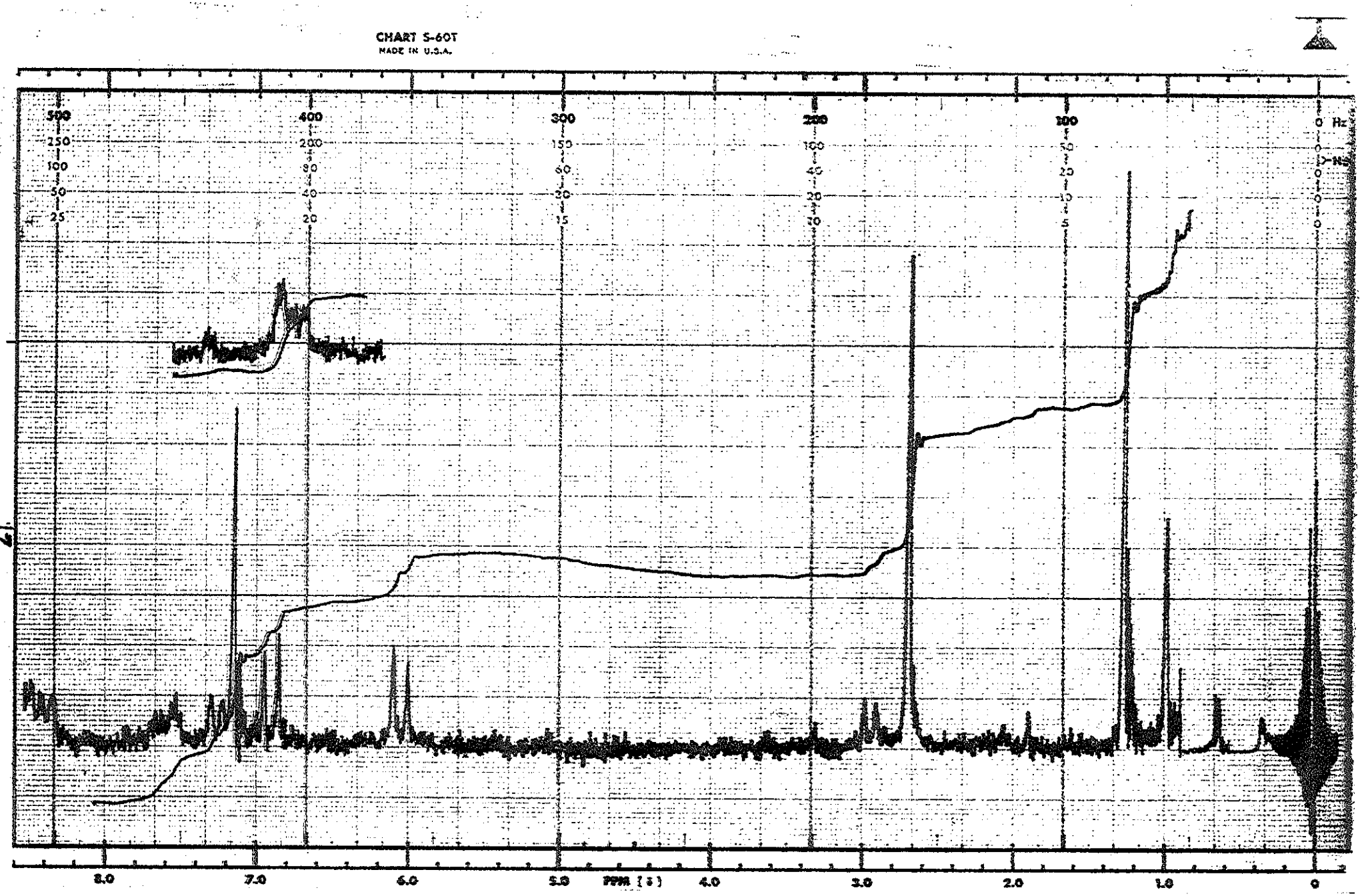
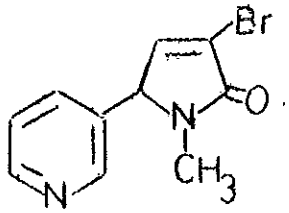


Figure IV. The NMR spectrum of the reaction product of 3,3-dibromocotinine and Li_2CO_3 after purification by preparative tlc.

There are numerous references in the literature where potassium t-butoxide in different solvent systems was used to effect dehydrohalogenations.[36,38] Several attempts were made to remove the elements of HBr from 24 inorder to obtain the pyrrolinone 32 by using potassium t-butoxide. The reactions of 24 with KOt-Bu were studied in four solvent systems viz, t-butyl alcohol, diglyme, tetrahydrofuran, and DMSO.



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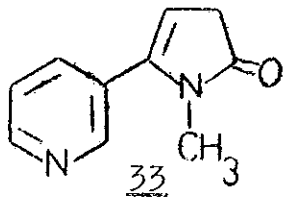
A mixture consisting of at least four components was obtained when the reaction of 24 with KOt-Bu was conducted in refluxing t-butyl alcohol. No indication of olefin formation was shown by the NMR spectrum of the crude product. Compound 24 was recovered unchanged when the same reaction was performed at room temperature.

The reaction of 24 with KOt-Bu in both diglyme and tetrahydrofuran gave back the unreacted starting material. On the contrary, a complex mixture was obtained when the reaction was conducted at elevated temperature using DMSO as the reaction solvent.

2. Attempts to Dehydrate 5-Hydroxycotinine :

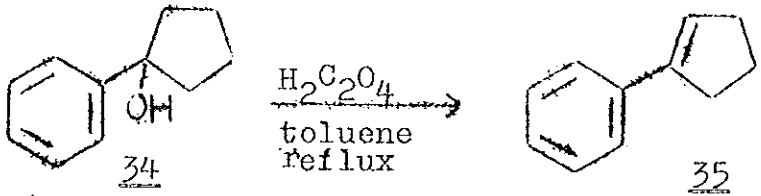
In an attempt to synthesize the pyrrolinone 33 from 5-hydroxycotinine (27) by dehydration, the reactions of 27 with some dehydrating agents were studied. In one approach using phosphorous oxycloride ($POCl_3$) and pyridine,[39,40] a mixture consisting of at least five components was obtained. The NMR spectrum of the crude product showed signals in the olefinic region. Attempts to separate the mixture by silica gel column chromatography were unsuccessful.



33

Another attempt to dehydrate 27 using thionyl chloride and pyridine[41] yielded a mixture consisting of at least six components.

Y. Amiel et al [42] have reported the use of anhydrous oxalic acid as a dehydrating agent for the preparation of 35 from the alcohol 34. The reaction was conducted in toluene with a continuous removal of water by azeotropic distillation.



34 35

Following similar procedure to that given by Amiel et al,[42] the dehydration of 27 was attempted. A solid product which had a very broad melting range (132-145°C) was obtained. Attempts to purify this product by crystallization proved unsuccessful. Examination of the NMR spectrum of the product proved that it was not the pyrrolinone 33. Identification of this compound was not possible based on its IR and NMR spectra.

3. The Reduction of 5-Methoxycotinine and Related Compounds with $LiAlH_4$

The reduction of cyclic amides (lactams) containing a tertiary nitrogen atom by lithium aluminum hydride(LAH) has been extensively studied and in most cases the cyclic amines were formed.[43] However, various N-substituted amides can undergo a reductive cleavage to give the corresponding aldehyde as well as the amine. In general, reduction with a large excess of LAH gives the corresponding amine.[43,44]

Nguyen Thi[45] reported a 55 % yield of (S)-nicotine-5', 5'-d_2 (36) by reduction of (S)-cotinine (13) with lithium aluminum deuteride in tetrahydrofuran.

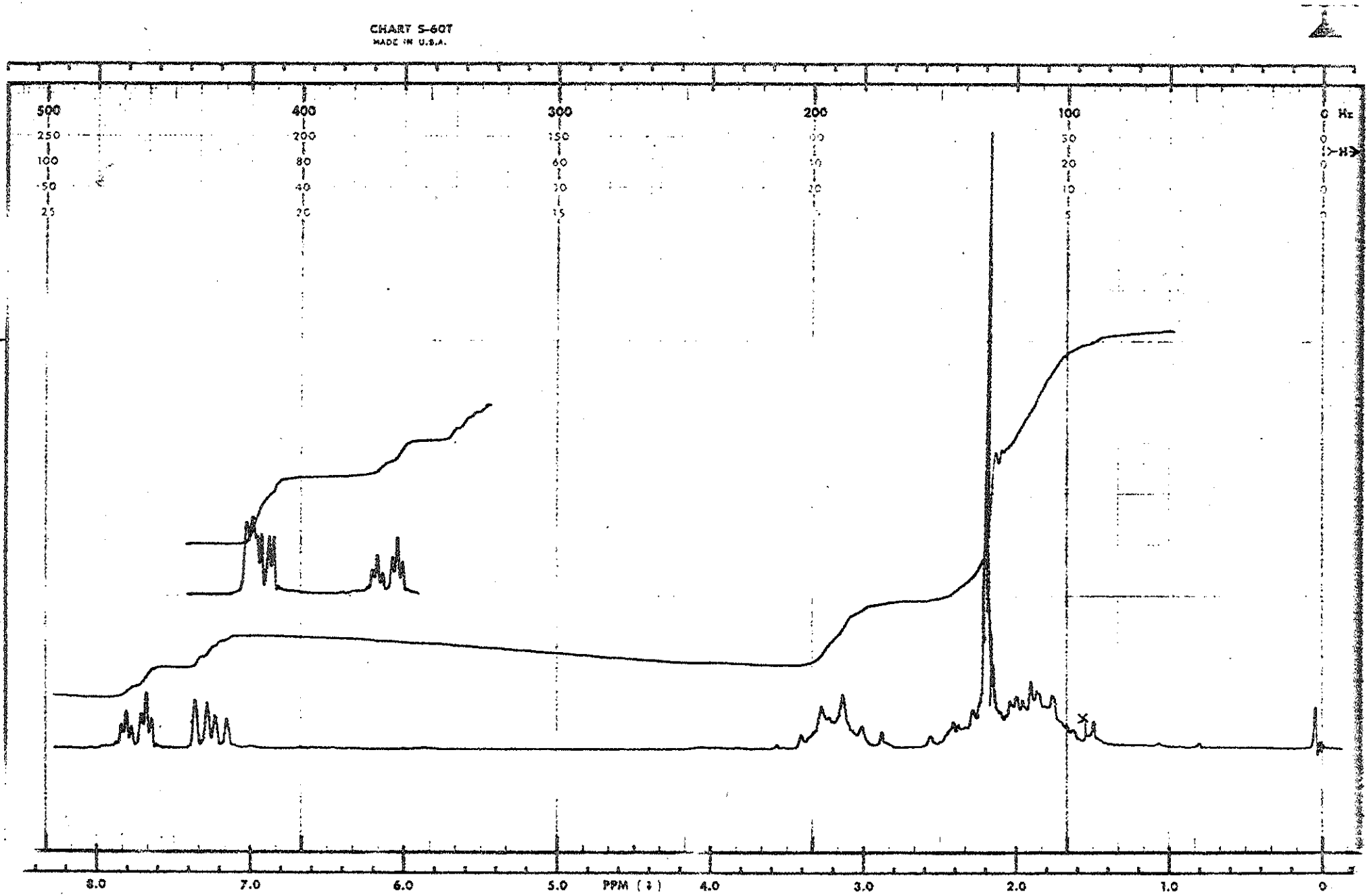


Figure VI. The NMR spectrum of nicotine(6).

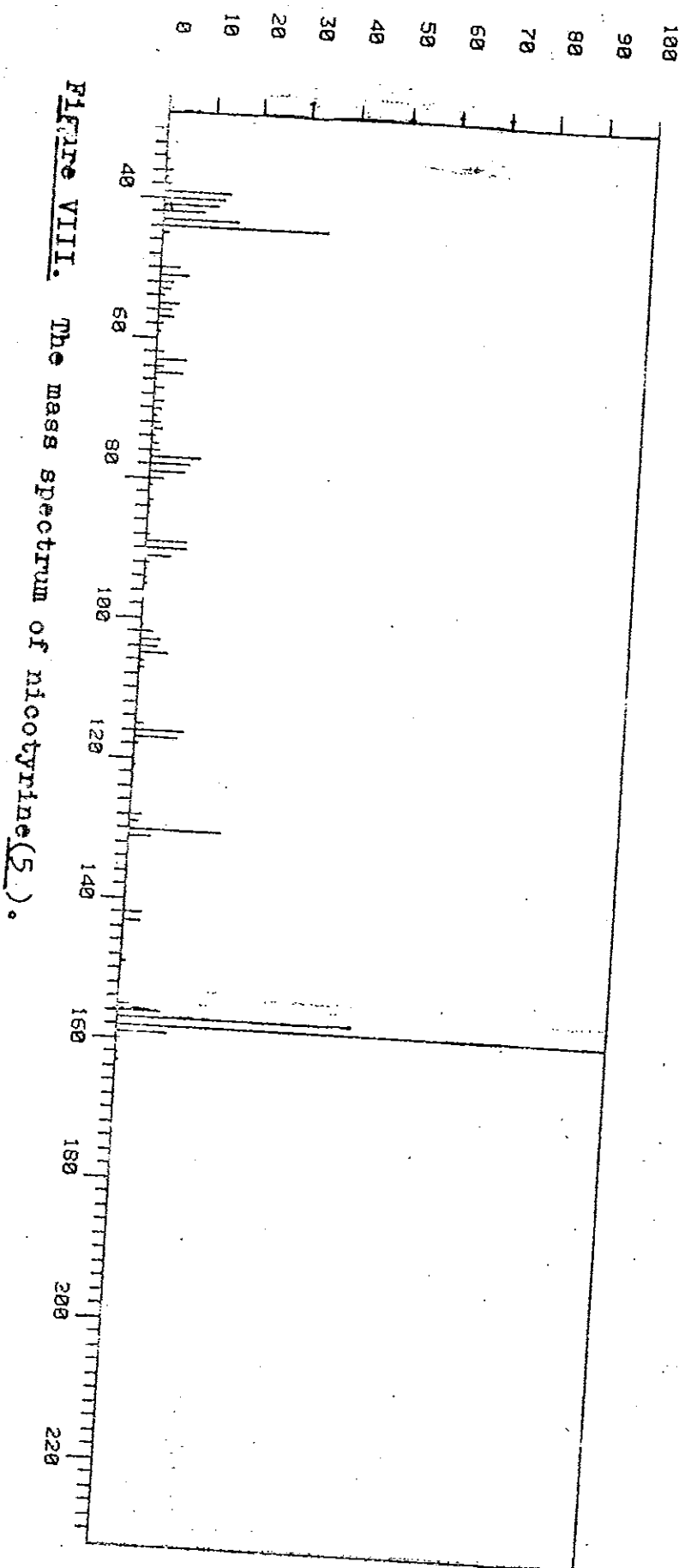


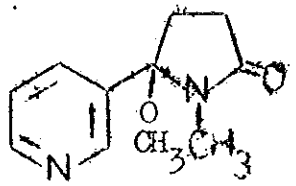
Figure VIII. The mass spectrum of nicotyrine(5).

The second major component of the mixture had a GC-retention time of 0.46 min (10% carbowax on $^{100}/_{120}$ Gaschrom Q OV. 200°C). The comparison of the gas chromatogram of the mixture with that of an authentic sample of nicotine revealed that the retention time of this major component was identical with that of nicotine. Moreover, it was also evident from the NMR spectrum of the mixture that this major component was nicotine (6).

From a comparison of the GC-peak areas of nicotine and nicotyrine and from the integrations in the NMR spectrum of the mixture, it could be observed that nicotine and nicotyrine were formed in the ratio of approximately 1:3.

Identification of the other three minor products was not possible since they could not be obtained in pure forms.

5-methoxy-1-methyl-5-(3'-pyridyl)-2-pyrrolidinone (5-methoxycotinine, 37) was prepared from 25 by catalytic hydrogenation in ethyl acetate using 5% Pd on carbon as a catalyst. The NMR spectrum (Fig IX) displayed the



37

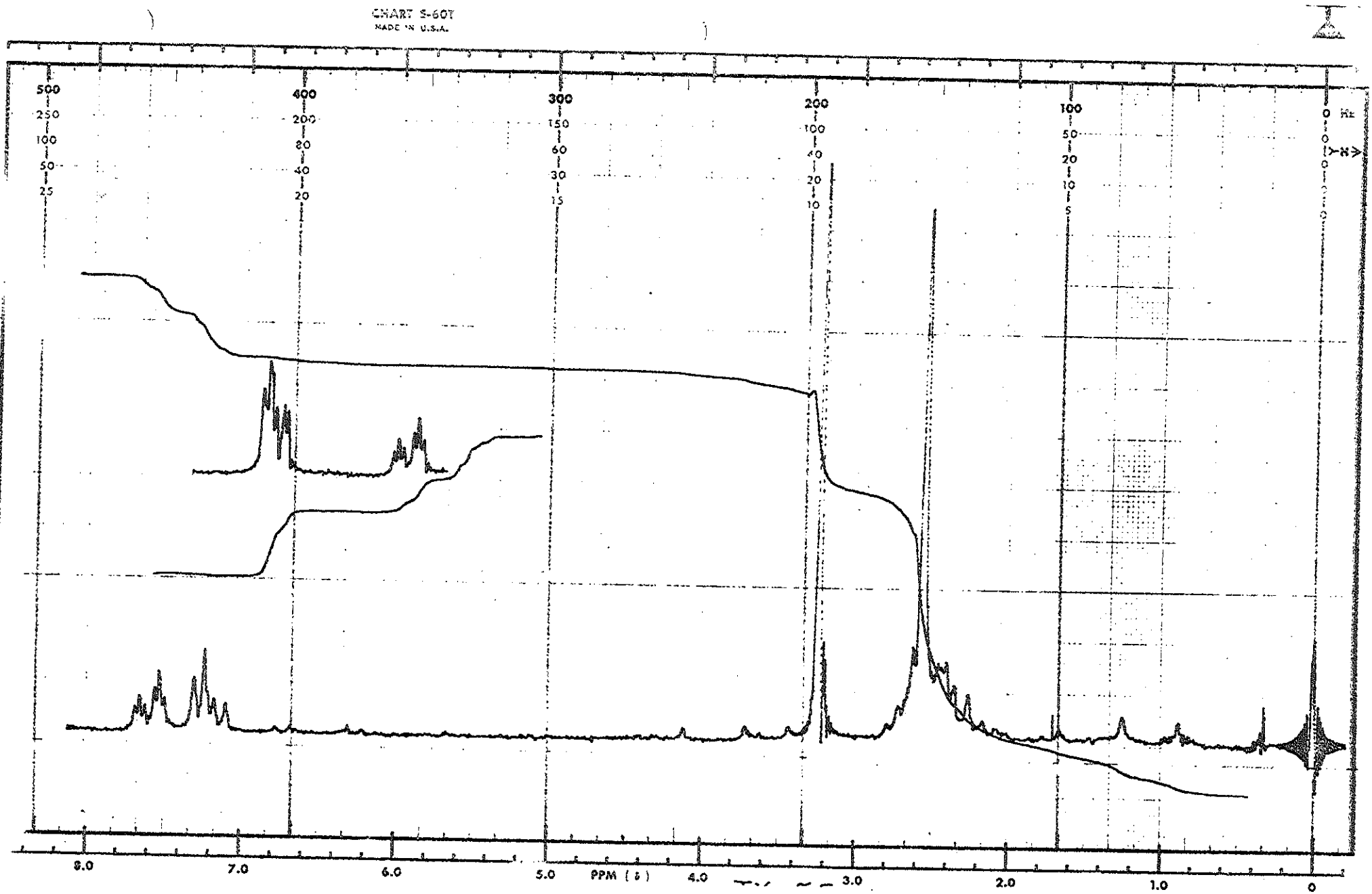


Figure IX. The NMR spectrum of 5-methoxycotinine(37).

disappearance of the olefinic protons of 25 and the appearance of a multiplet centered at 2.5 ppm due to the newly introduced protons at C-3 and C-4. The white crystalline product had a melting point of 63-65°C.

The reduction of 37 with lithium aluminum hydride in refluxing THF overnight yielded a mixture of products which was shown by GC (Figure X) to contain five components. Attempt was made to separate the mixture by preparative TLC. It was only possible to obtain two of the components with GC-retention times of 1.5 min and 5.8 min in pure forms.

The compound with a GC-retention time of 1.5 min was identified to be β-nicotyrine (5) based on its NMR spectrum and a comparison of its GC-retention time with that of an authentic sample of β-nicotyrine.

The second pure compound (R_t = 5.8 min) had an NMR spectrum (Figure XI) that displayed a multiplet between 1.4 and 1.87 ppm, a singlet at 2.2 ppm, a broad peak at 3.2 ppm exchangeable with D_2O, a multiplet at 3.57 ppm and the signals due to the pyridine ring protons below 7.0 ppm. A high resolution mass spectral analysis (Figure XII) gave an empirical formula of $C_{11}H_{16}N_2O$ with a molecular ion peak at m/e 192 (5.84%) and a base peak at m/e 121 (100%). The

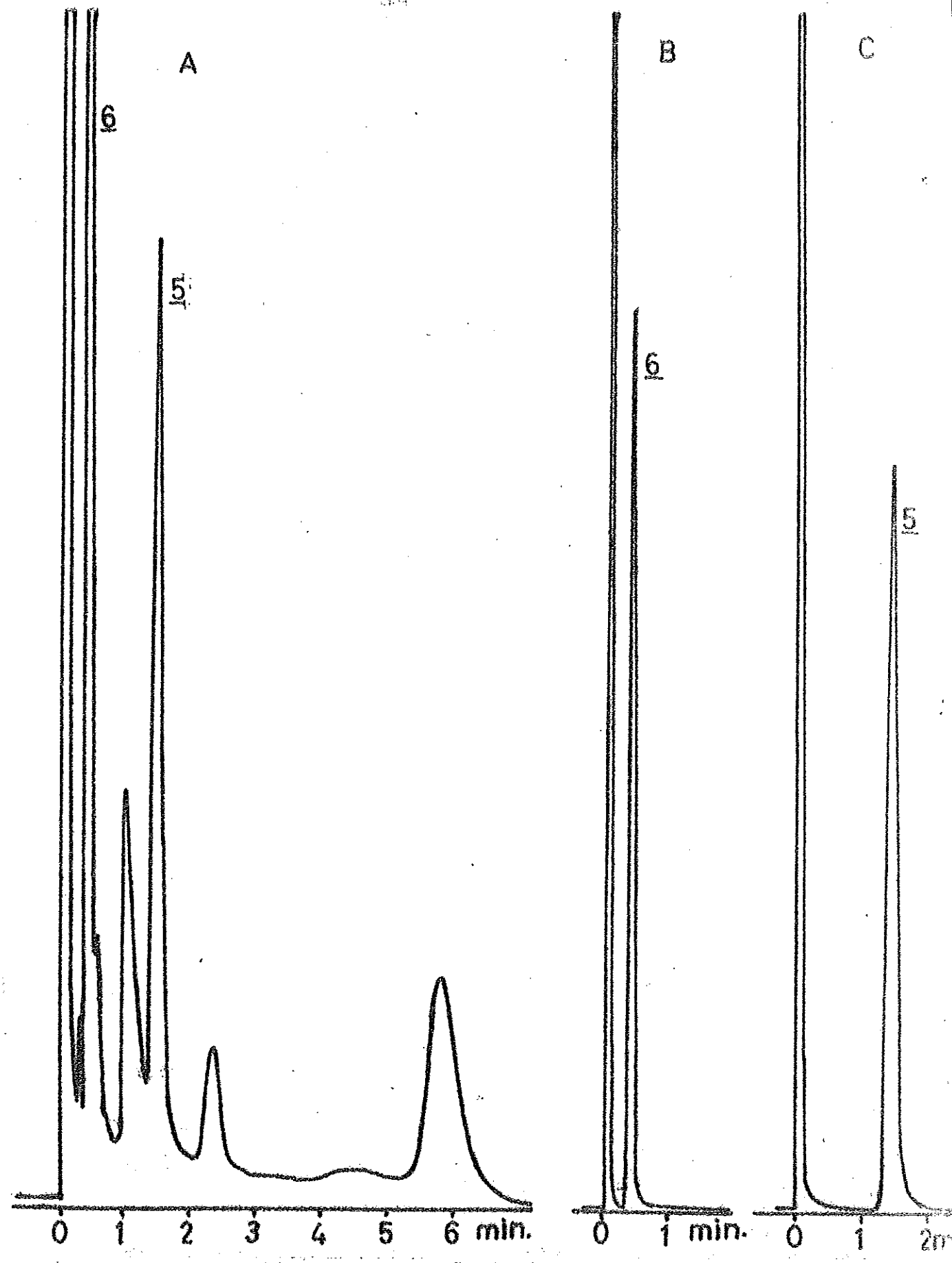
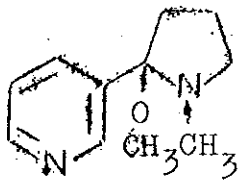


Figure X. The GC tracings (10% Carbowax 20M on 100/120 Gaschrom Q OV 200 isothermal) of (A) the product mixture obtained after the reduction of 5-methoxycotinine (37) with $LiAlH_4$, (B) nicotine(6), (C) nicotyrine(5).

expected structure for this compound was 38, however, the NMR spectrum did not show the sharp singlet for an $-OCH_3$ group below 3.0 ppm.



38

Unambiguous structural assignment was not possible based on the spectral data available for the compound.

The major product (R_t 0.46 min) was identified as nicotine based on its R_f (0.44; silica gel, benzene ethanol 8:2) on a fluorescent plate and its GC-retention time.

Nicotine and β-nicotyrine were the two major products of the reduction of 37 with LAH. The relative ratio of nicotine to β-nicotyrine was estimated from the GC-peak areas, to be approximately 3:2.

A result essentially similar to the above two cases was obtained when the reduction of 5-hydroxy-1-methyl-5-(3'-pyridyl)-2-pyrrolinone (26) with lithuim aluminum hydride was studied. A mixture consisting of more than five components was obtained where two of the components were major and the others were formed in trace amounts. The two major components of the mixture were identified

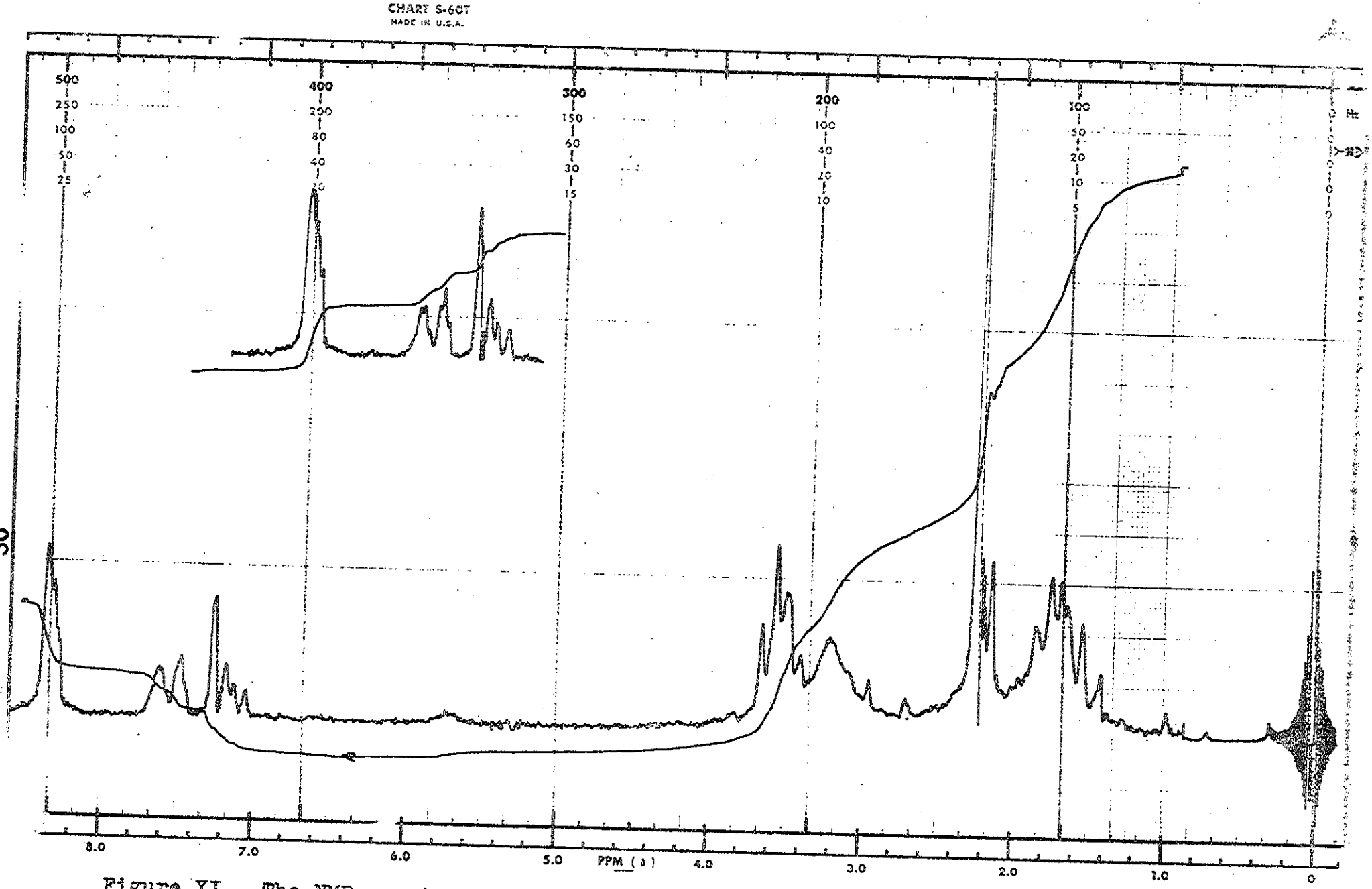


Figure XI. The NMR spectrum of the unidentified compound isolated in pure form from the product mixture obtained by the reduction of 5-methoxycotinine(37) with $LiAlH_4$.

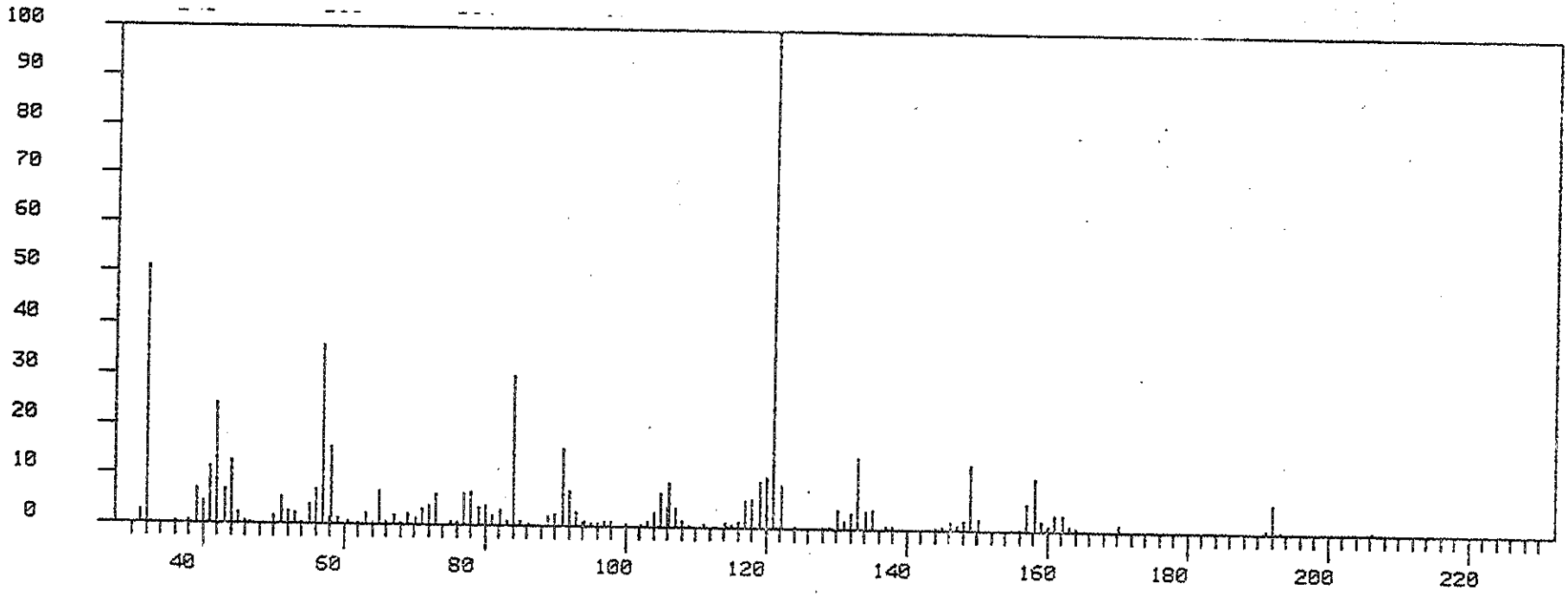


Figure XII. The mass spectrum of the unidentified compound isolated in pure form from the product mixtureobtained bytthe reduction of 5-methoxycotinine(37) with $LiAlH_4$.

as nicotine and β-nicotyrine based on their R_f values GC-retention times and NMR spectra. The relative ratio of β-nicotyrine to nicotine was approximately 1:8 based on the integrations in the NMR spectrum of the mixture.

It was surprising to observe that in all the three cases investigated, nicotine and β-nicotyrine were major products, together with smaller quantities of other compounds. It can be concluded therefore that the mechanism of the formation of nicotine and β-nicotyrine may follow the same pathways with 25 and 26 where as with 37 a different mechanism may be operating.

The mechanism of the formation of nicotine from 25 and 26 (Figure XIII) may involve 1,4-addition of hydride to the α,β-unsaturated lactam upon treatment with LAH to give the enol form of the corresponding reduced form. Elimination of the group at the 5-position followed by reduction of the resulting iminium ion may give the adduct 69 which may be readily converted to the keto form 70 which can be further reduced by LAH to the methylene group.

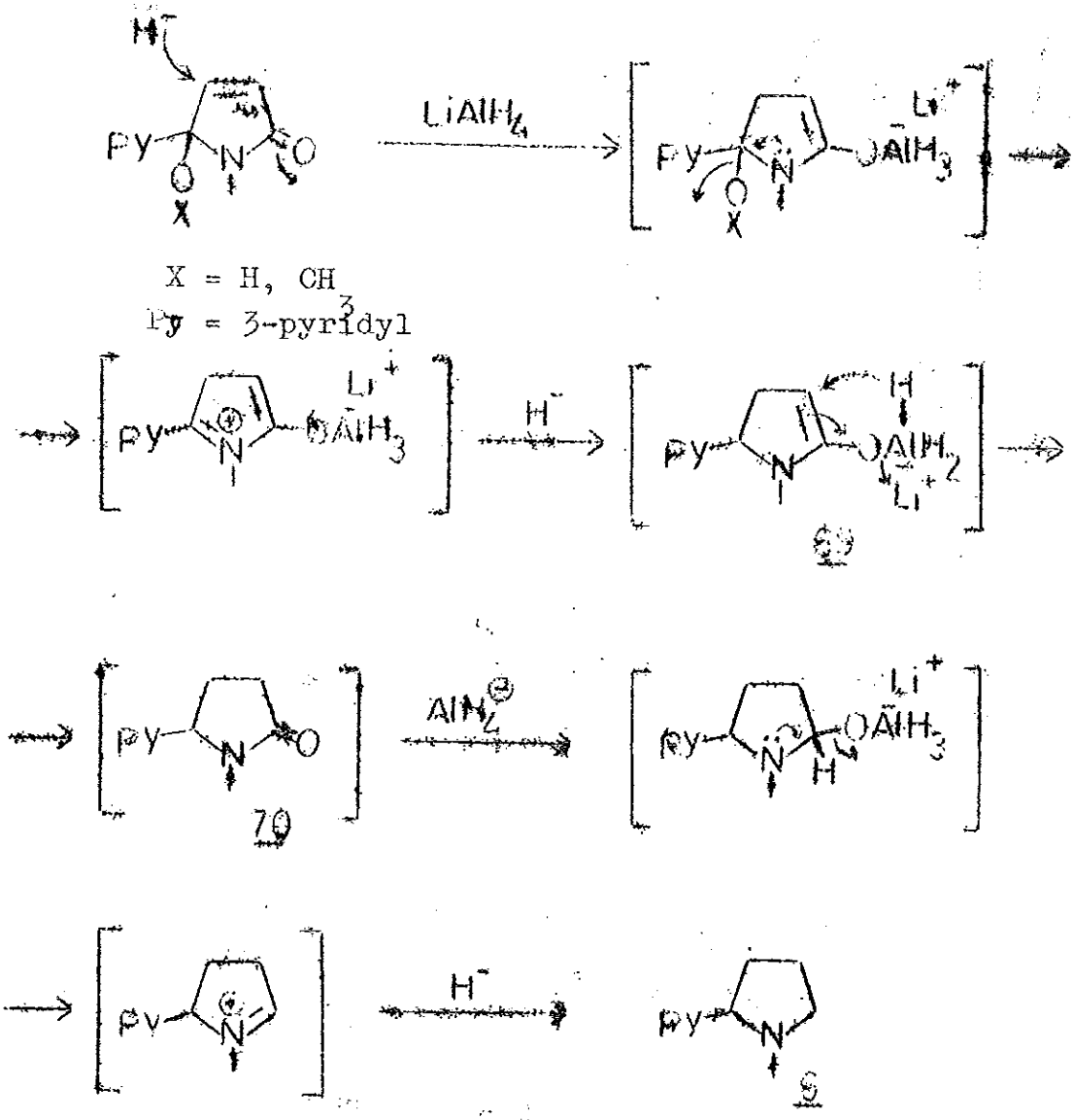


Figure XIII Probable mechanism for the formation of nicotine from 25 and 26

The formation of β-nicotyrine may involve an initial 1,4-addition to the α,β-unsaturated lactam followed by an E-2 type elimination of the group at the 5-position. The adduct 39 may rearrange to the keto form (40) which may be further reduced to the iminium

ion 42 via the adduct 41. The iminium ion may then lose a proton to give β-nicotyrine.

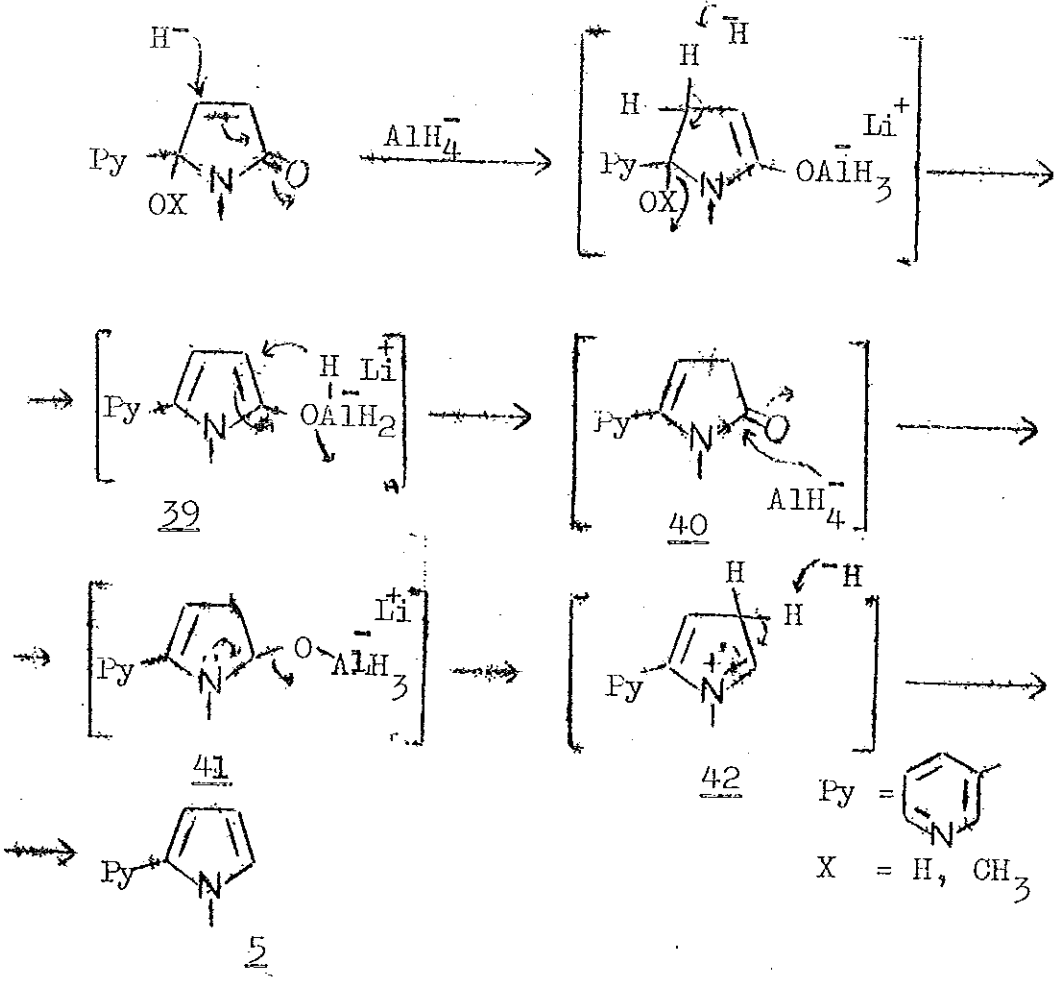
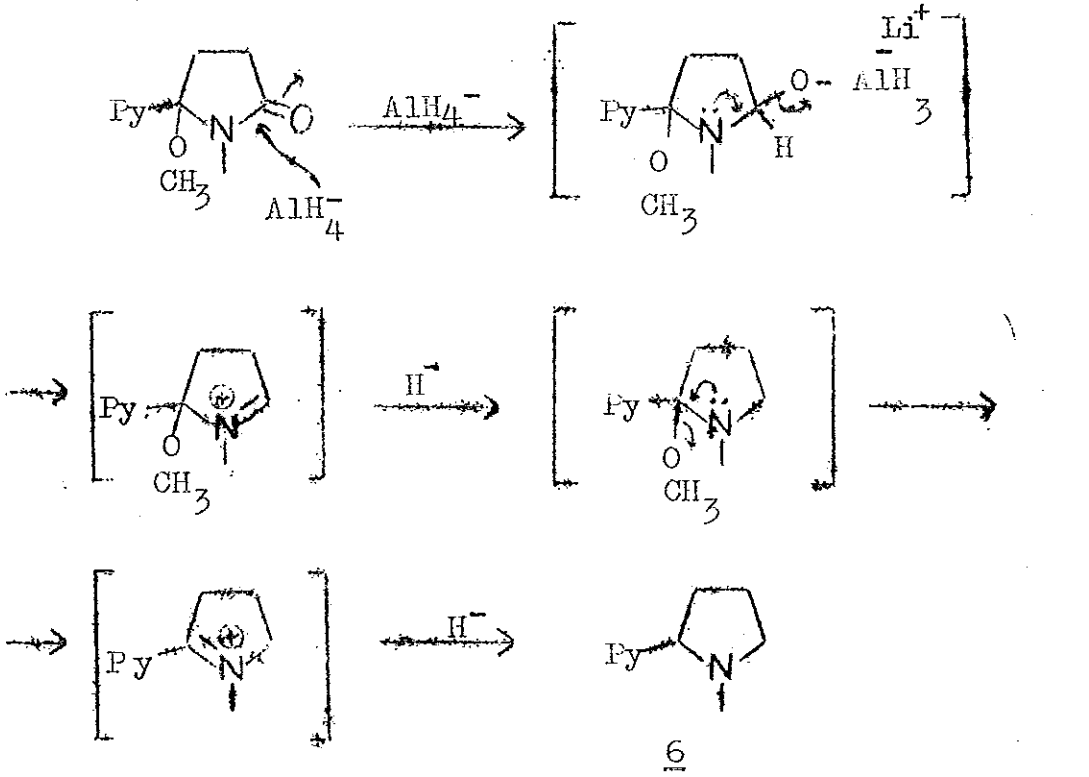


Fig XIV. Probable mechanism for the formation of β-nicotyrine from 25 and 26.

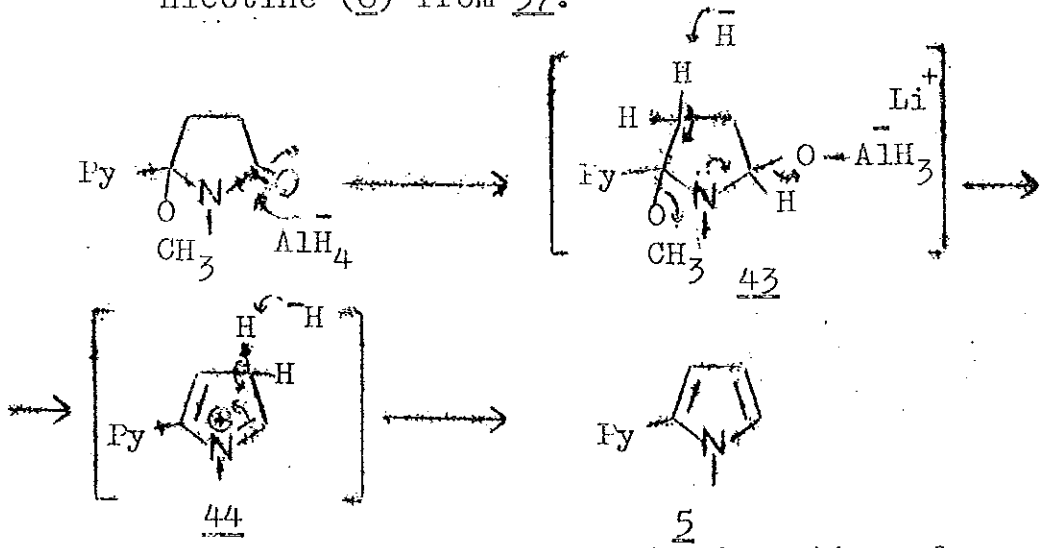
In the case of the reduction of 5-methoxycotinine (37) to nicotine, the mechanism of the reaction may involve elimination of the OCH_3 group and reduction of the lactam carbonyl to a methylene group (Fig XV). The formation of β-nicotyrine probably proceeds by addition to the carbonyl group of the lactam (1,2-addition) to give the adduct 43 which may lose a molecule

of methanol and eliminate the $-OAlH_3$ to form the iminium salt 44 which probably is transformed to ℓ-nicotyrine by a hydride ion.



6

Fig XV. Probable mechanism for the formation of nicotine (6) from 37.

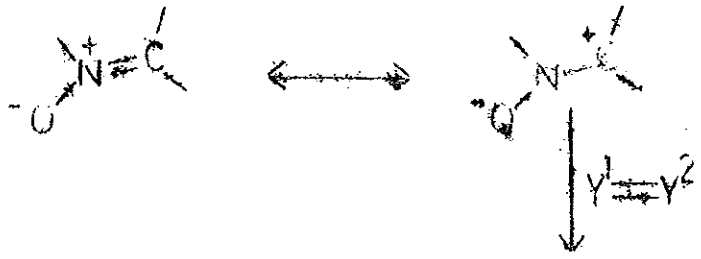


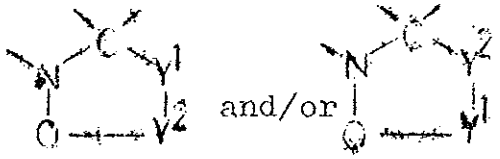
43 44 5

Fig XVI. Probable mechanism for the formation of nicotyrine from 37.

4. Studies on Isoxazolidines for the Synthesis of 4-Hydroxynicotine (47)

Nitrones are well known to behave as 1,3-dipolar reagents in thermal cycloaddition reactions.[47] A 1,3-dipdar reagent is a compound which undergoes 1,3-cycloadditons and is described by a zwitterionic octet structure.[48]





1,3-Dipolar cycloadditions of nitrones have been reported with a variety of dipolarophiles and have been widely used in the construction of a variety of five membered heterocyclic ring systems.[47] However, the cycloadducts are not stable in all cases and sometimes undergo interesting transformations.[47]

In the addition of an unsymmetrical dipolarophile to a nitrone, two orientations of addition are possible.[43-52]

Both steric and electronic factors are important and in general the more hindered end of the dipolarophile adds to the nitrone oxygen.[49]

In the attempts to synthesize suitably substituted nicotine analogs that may lead to the pyrrolines 1, 2, and 3, the reactions of C-pyridyl-N-methylnitrone (45) with three olefinic compounds, viz allyl chloride, allyl bromide and allyl alcohol, were investigated. The main focus in this investigation was the synthesis of 4-hydroxynicotine (59) which was hoped to be a suitable intermediate that could dehydrate to yield the pyrroline 2 or 3. The synthetic plan (Fig XXVII) involved thermal cyclization of the nitrone 45 with the olefinic compound to form the isoxazolidine 46, cleavage of the N-O bond of the isoxazolidine by catalytic hydrogenation and cyclization of the resulting open chain compound.

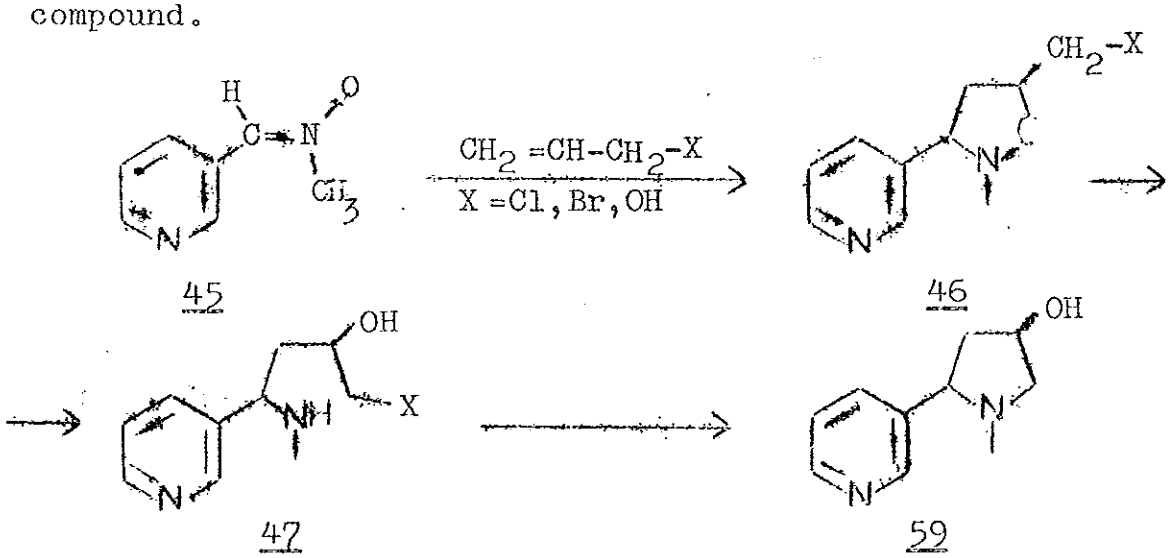


Fig XVII. Synthetic plan for the synthesis of 59

The reaction of the nitrone 45 with allyl chloride in refluxing benzene was carried out and the progress of the reaction was monitored by TLC.

As the reaction proceeded, a brownish solid (compound I) began to precipitate. The formation of a second compound (compound II) with a greater R_f than the strating material also was detected. The reaction was stopped at the end of 72 hours and compound I was separated by filtration. Distillation of the filtrate under reduced pressure afforded a yellow oil which consisted of compound II and some unreacted nitrone. Separation of the nitrone and compound II was achieved by means of silica gel column chromatography. Compound II was obtained in a pure form as a light yellow oil.

Compound II had an NMR spectrum consistent with the isoxazolidine 48. The NMR spectrum (Fig XVIII) displayed in addition to the chracteristic signals of the protons of a 3-substituted pyridine (7.0 to 9.0 ppm) a complex pattern centered at 2.1 ppm integrating for one proton H_b or H_c), a singlet at 2.5 ppm integrating for three protons (N-CH_3), a multiplet at 3.0 ppm integrating for one proton (H_b or H_c), a complex pattern at 3.6 integrating for three protons (Ha and -CH_2-Cl) and a multiplet at 4.33 ppm integrating for one proton (Hd).

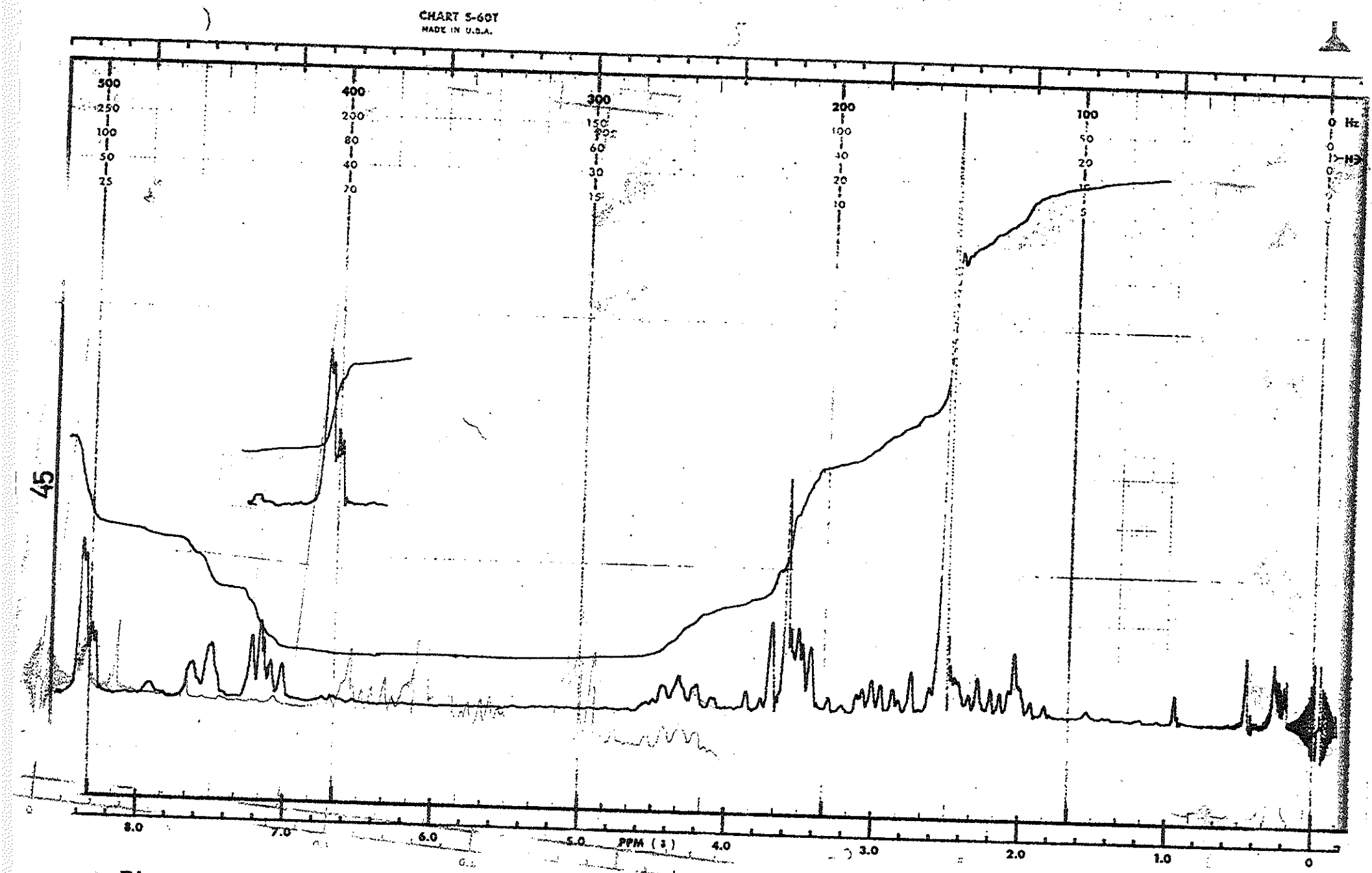


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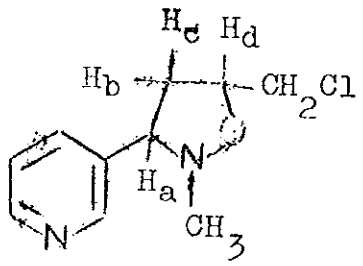
Figure XVIII. The NMR spectrum of 5-chloromethyl-2-methyl-3(3'-pyridyl)isoxazolidine(48).



48

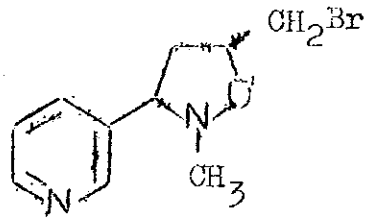
Identification of compound I was not possible on the basis of its IR and NMR spectra. It was however suspected to be a pyridinium salt based on the observation that it was extremely hygroscopic, insoluble in most organic solvents and soluble in water.

Catalytic hydrogenation of the isoxazolidine 48 in ethyl acetate over W-2 Raney Nickel[53] catalyst at a hydrogen pressure of 30 lb/in^2 for 20 hours gave back the unchanged starting material. On the contrary, a complex mixture of products was obtained when the hydrogenation of 48 was carried out in absolute ethanol over 5% Pd on carbon.

As opposed to the case of the allyl chloride-nitrone reaction, the reaction of the nitrone 45 with allyl bromide in refluxing benzene resulted in only one product. This product separated as a brown solid as the reaction proceeded.

It was extremely hygroscopic and turned into dark red oil when exposed to air. The IR spectrum showed a broad peak at 3400 cm^{-1} and other major peaks at 1600, 1500,

1420 and 1190 cm^{-1}. The NMR spectrum (D_2O - DSS) displayed a singlet at 5.37 ppm a triplet at 4.47 ppm, a doublet at 3.4 ppm, a multiplet between 1.4 and 2.0 ppm, a doublet at 1.17 ppm and a triplet at 0.87 ppm. It was obvious from the NMR spectrum that the product obtained was not the isoxazolidine 49. Identification of this compound was not however possible on the basis of the available information.

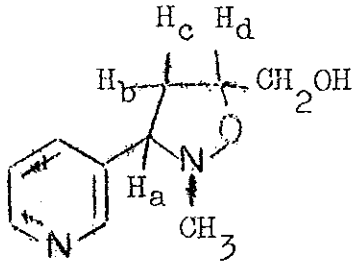


49

Contrary to the above two cases, the cyclization of the nitrone 45 with allyl alcohol gave rise to the isoxazolidine 50 which was identified by its IR and NMR spectra.

The cyclization was conducted in excess boiling allyl alchol and the progress of the reaction was monitored by TLC. The reaction was complete after heating under reflux for 50 hours and a yellow oil (R_f 0.4, benzene-ethanol 8:2) was obtained whose NMR spectrum (Fig XIX) was consistent with the isoxazolidine 50. The NMR spectrum displayed a one proton multiplet between 1.83

and 2.4 ppm (H_b or H_c), a three ptoron singlet at 2.53 ppm (N-CH_3), a one proton multiplet between 2.67 and 3.17 ppm (H_b or H_c), a three proton multiplet between 3.43 and 3.9 ppm (-CH_2OH and H_a), a one proton multiplet between 4.13 and 4.5 ppm (H_a), a broad peak at 4.6 ppm (-OH) and the typical 3-substituted prydine pattern between 7.0 and 8.6 ppm integrating for four protons.



50

The catalytic hydrogenation of the isoxazolidine 50 in absolute ethanol over freshly prepared W-2 Raney Nickel catalyst afforded an oil which had a lower R_f (0.15, benzene: ethanol 8:2) than the starting material. The IR spectrum showed a very broad -OH absorption band (3700-2400 cm^{-1}) and broad absorption at 1100 - 1040 cm^{-1} (doublet) consistent with a glycol. The NMR spectrum (Figure XX) displayed in addition to the pyridine ring protons below 7.0 ppm, a triplet at 1.83 ppm integrating for two protons, a singlet at 2.17 ppm integrating for three protons, a multiplet between 3.4 and 4.0 ppm integrating for four protons and a broad peak at 4.2 ppm.

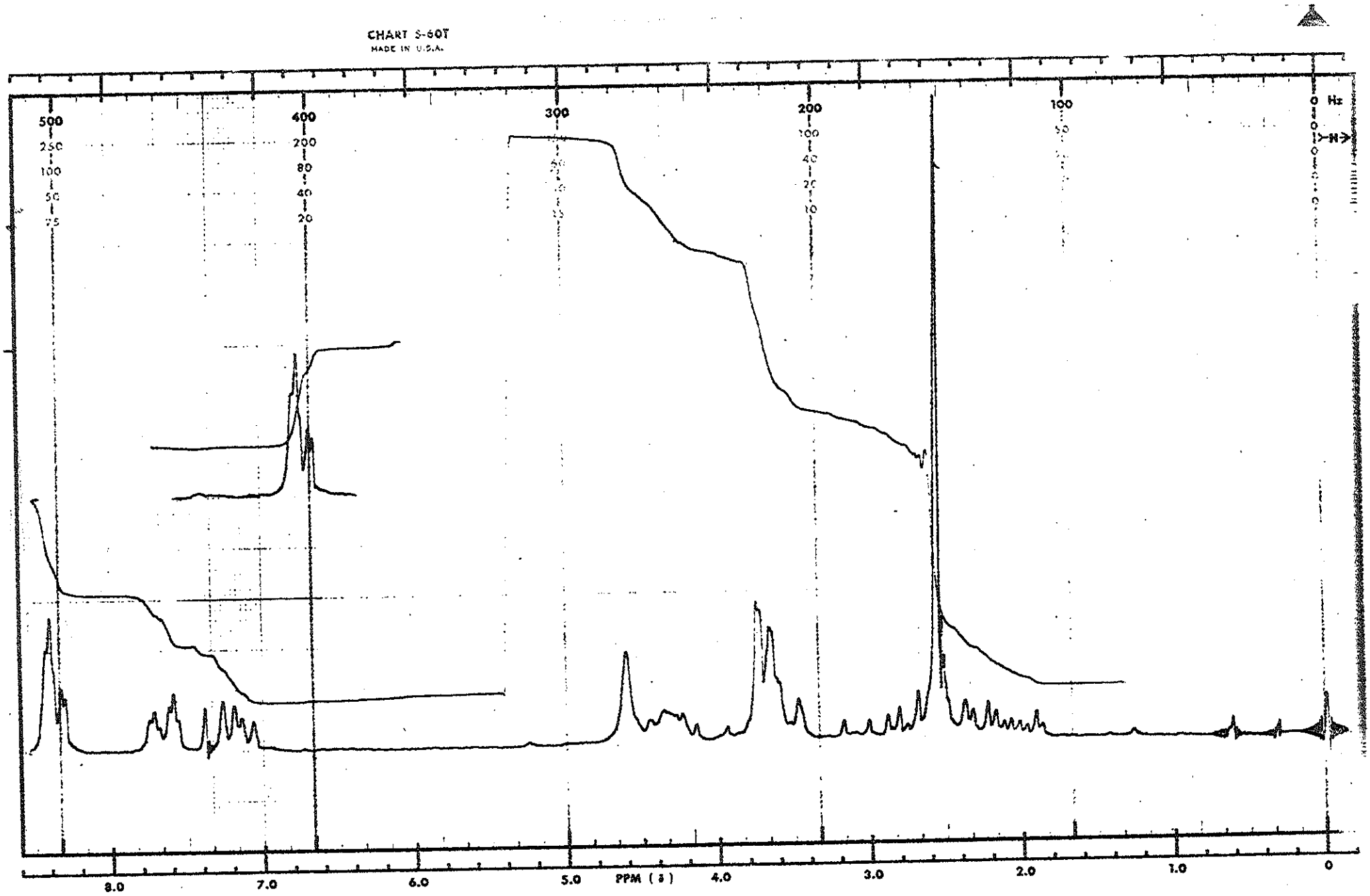
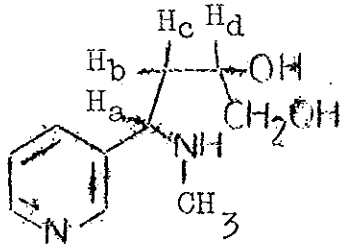


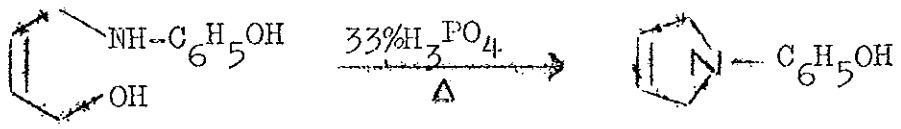
Figure XIX. The NMR spectrum of 5-hydroxymethyl-2-methyl-3-(3'-pyridyl)isoxazolidine(50).

Based on the NMR and IR spectra, structure 51 was assigned to this compound.



51

O.Wichterle and M.Vavruska[54] reported the cyclization of the amino alcohol 52 to the pyrroline 53 with 33% H_3PO_4. A 35% yield of the pyrroline 53 was reported.



52 53

An analogous reaction of compound 51 with 33% H_3PO_4 at 70 - 80°C overnight did not effect the anticipated cyclization; the strating material was recovered unchanged.

The reaction of compound 51 with thionyl chloride afforded a mixturé consisting of at least three products. The TLC of the mixture suggested that the components with R_f 0.57 and 0.45 were the major products. The component with R_f 0.45 was obtained in a pure form as a solid (m.p 165 - 166°C) when the mixture was taken up in ethanol hexane. Identification of this

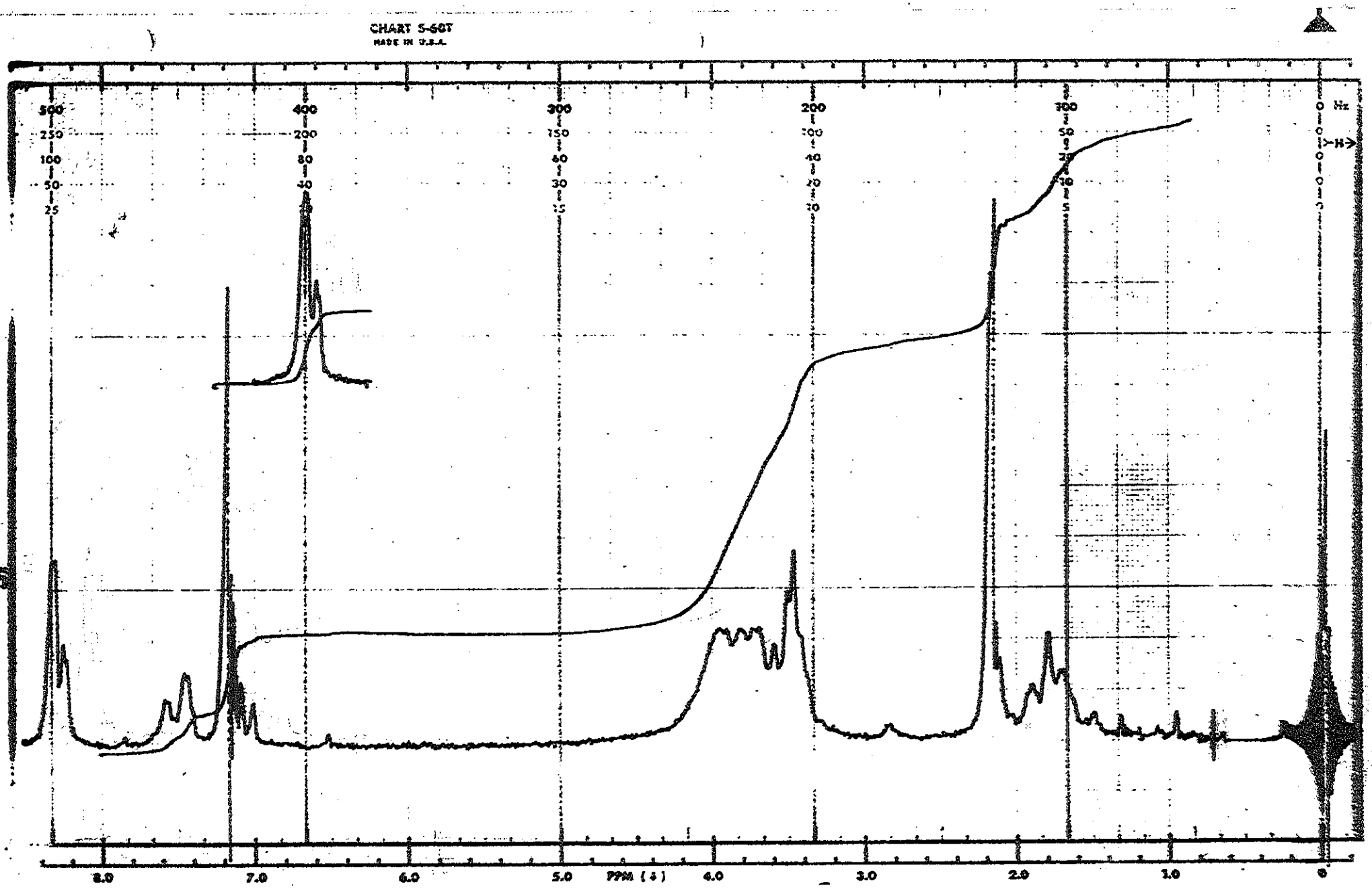
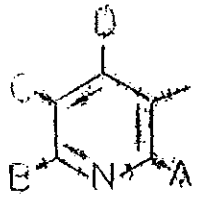


Figure XX. The NMR spectrum of compound 51.

compound was not however possible on the basis of its NMR and IR spectra.

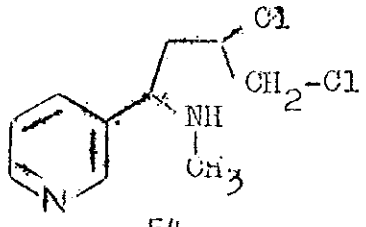
The second major component (R_f 0.57) was separated in a pure form by preparative TLC (silica gel, benzene: ethanol 8:2). The NMR spectrum of this compound displayed a doublet at 2.17 ppm, a series of multiplets between 2.27 and 3.83 ppm, a multiplet at 4.4 ppm and the signals due to the pyridine ring protons below 7.0 ppm. It was observed, however, that the proton D on the pyridine ring was split into three triplets rather than the normally expected splitting into two triplets. This behavior was difficult to rationalize.



The splitting of the N-CH_3 signal at 2.17 ppm into a doublet is suggestive of a secondary amine structure where the methyl protons couple with the proton on the nitrogen atom. The absorption band at 3400 cm^{-1} in the IR spectrum of the compound may be due to an N-H stretching vibration.

The unknown compound gave a positive Beilestein's test and showed in its IR spectrum absorption bands at 1280 and 720 cm^{-1} suggesting the presence of chlorine. The number of chlorine atoms present, however, could not be determined.

An unequivocal structural assignment was not possible based on the available informations. However, 54 was thought to be the most probable structure based on NMR and IR spectroscopic grounds.



54

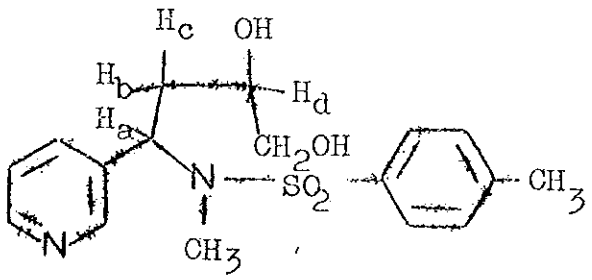
The reaction of compound 51 with p-toluenesulfonyl chloride in triethyl amine afforded a mixture of products which was shown by TLC to contain one major component. Separation of the major product was effected by preparative TLC (silica gel, 2 mm plate, benzene: ethanol 8:2).

It was obtained in a pure form and displayed in its NMR spectrum (Figure XXI) the presence of two methyl signals at 2.33 and 2.57 ppm and signals due to phenyl ring protons at 7.5 and 7.1 ppm in addition to the signals due to the pyridine ring protons. The incorporation of only one tosyl group could be deduced from the integrations in the NMR spectrum. The IR spectrum showed a broad absorption band at 3700 - 2500 cm^{-1} and other strong absorption bands at 1340 and 1160 cm^{-1}.

The unknown compound was found to be very stable to both acid (HCl) and alkali (NaOH) treatments at high temperatures. It was therefore rationalized that this compound

should be a sulfonamide (reaction at N) rather than a tosylate (reaction at O). If the compound were a tosylate, hydrolysis back to the starting material should have taken place upon treatment with acid and base. Since the compound was stable to these forcing conditions this possibility was discarded.

Sulfonamides are generally not hydrolyzed by alkali treatment, not even with hot concentrated aliali, but acids hydrolyze them, though less readily than they do sulfonate esters.[55] The stability of the unknown compound to both acid and alkali was therefore infavor of a sulfonamide. Based on these grounds, structure 55 was assigned to the major product of the reaction of 51 with tosyl chloride in triethyl amine. Both the IR and NMR spectral data were consistent with this assignment.



55

Protons	δ ppm
Ha	5.33 (m)
Hb & Hc	1.67-2.13 (m)
Hd & CH_2 - OH	3.1-3.5 (m)
N-CH_3	2.6 (s)
Ph-CH_3	2.33 (s)

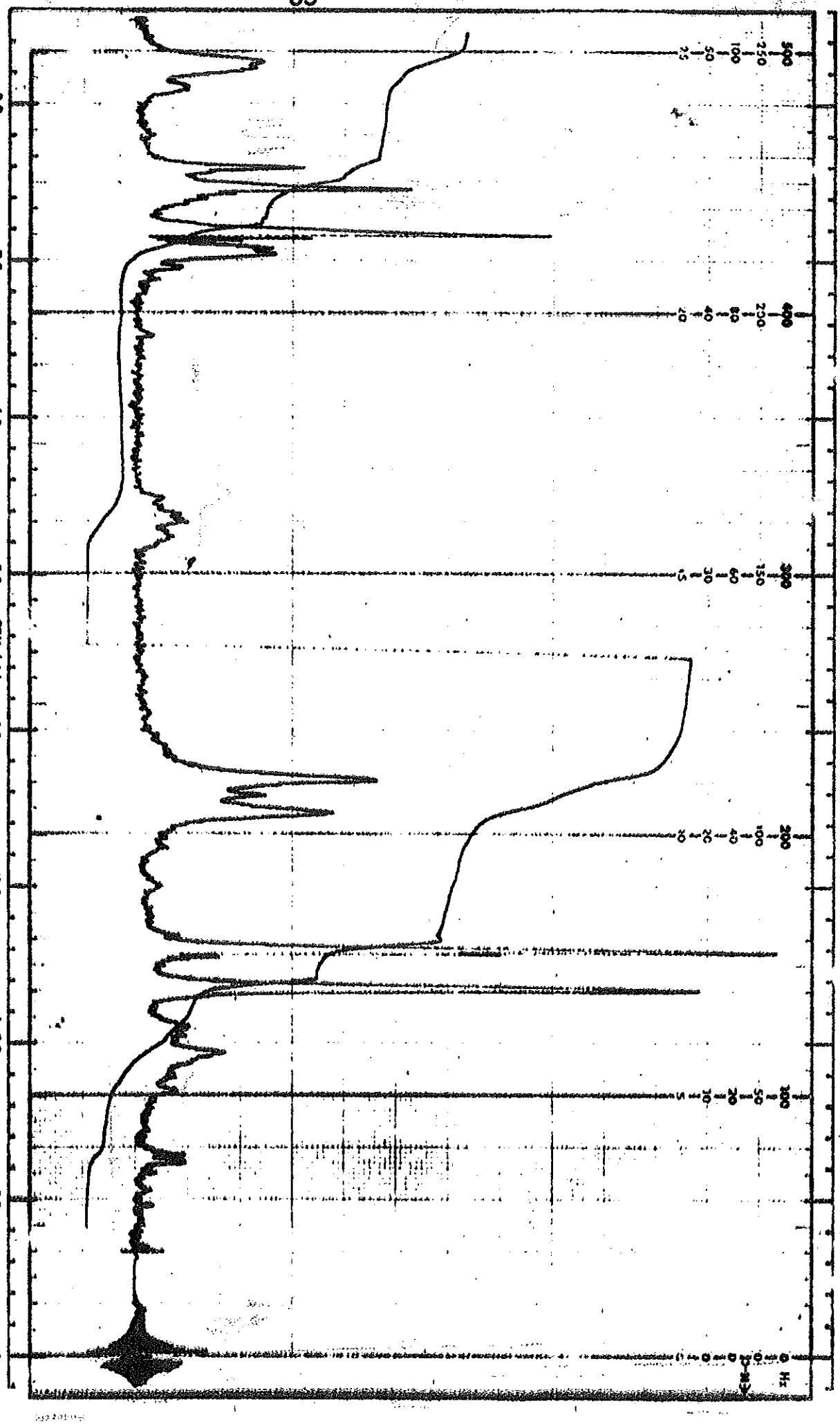


Figure XXI. The NMR spectrum of compound 55.

A similar result was obtained when the reaction of 51 with tosyl chloride was performed in pyridine.

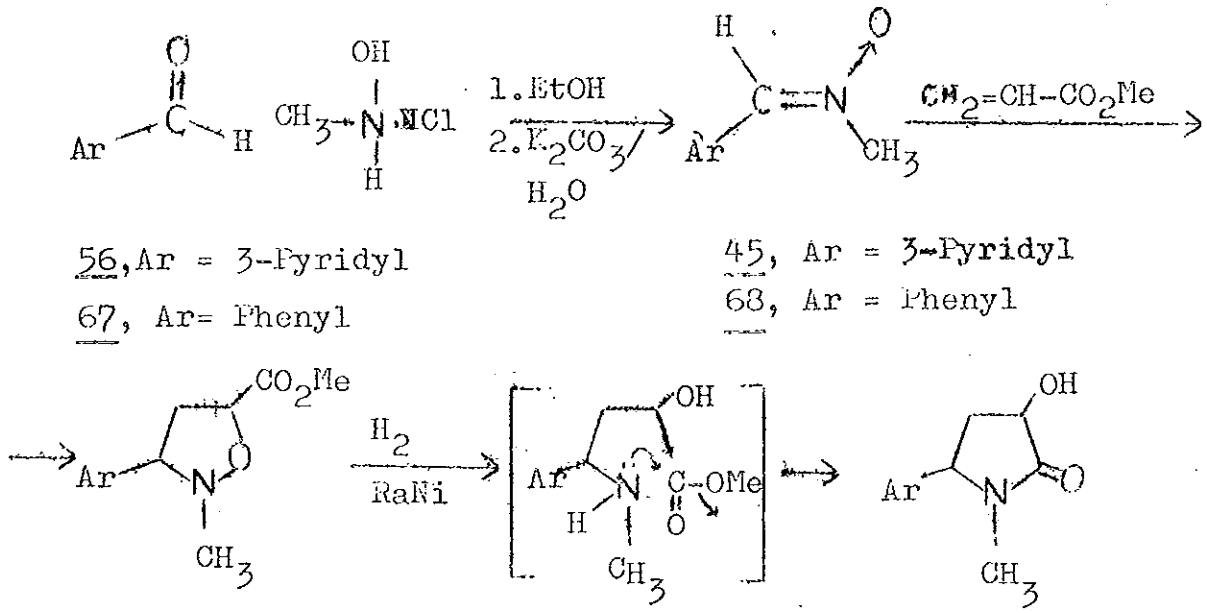
All the above reactions were done in view of effecting a cyclization of 51 to give 4-hydroxynicotine (59). However, it was not possible to obtain the desired product.

5. Studies on 3-hydroxycotinine and its phenyl analog

3-Hydroxycotinine 57 was prepared following the method previously employed by E.Dagne and N.Castagnoli.[56] Treatment of 3-pyridinecarboxaldehyde (56) with N-methylhydroxylamine hydrochloride in absolute ethanol gave the hydrochloride of the nitrone 45 as a white solid. The hydrochloride was dissolved in water saturated with K_2CO_3 and extracted with $CHCl_3$ exhaustively. Removal of the solvent under reduced pressure yielded the nitrone 45. The NMR spectrum displayed a singlet at 3.87 ppm ($N-CH_3$) a multiplet at 7.23 ppm, a doublet at 8.23 ppm and a multiplet at 8.83 ppm, slightly different from what was reported earlier.

The nitrone 45 was heated under reflux in excess methyl acrylate for 2 hours and the crude mixture that resulted was hydrogenated in absolute ethanol over freshly prepared W-2 Raney Nickel catalyst. Separation of the catalyst and removal of the solvent under reduced pressure yielded a yellowish oil which was taken up in acetone and cooled

to give 3-hydroxycotinine (57) as a white crystalline solid (mp 146-148°C; lit[56] mp 149-157°C).



56, Ar = 3-Pyridyl
67, Ar = Phenyl

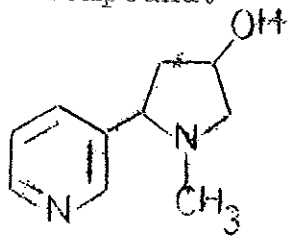
45, Ar = 3-Pyridyl
68, Ar = Phenyl

57, Ar = 3-Pyridyl
58, Ar = Phenyl

Figure XXII. Synthetic scheme for the preparation of 3-hydroxycotinine (57) and its phenyl analog (58)

The reduction of 3-hydroxycotinine (57) with lithium aluminum hydride in refluxing tetrahydrofuran yielded a mixture consisting of four components. Distillation of the mixture under high vacuum gave a light yellow oil which displayed in its IR spectrum a broad -OH absorption band at 3450 cm^{-1} and the absence of the carbonyl absorption band that appeared at 1700 cm^{-1} in the

starting material spectrum. The NMR spectrum (Figure XXIII) showed in addition to the signals due to the pyridine ring protons, a three proton singlet at 2.13 ppm, a series of multiplets between 2.3 and 3.3 ppm integrating for four protons, a one proton multiplet at 3.6 ppm and a broad peak at 4.37 ppm that exchanged with D_2O. Buried under the broad peak at 4.37 ppm was a multiplet integrating for one proton. The mass spectrum of this compound gave a molecular ion peak at m/e 178 (100%) and other prominent peaks at m/e 177 (47%), 164 (16%), 134(7%), 105 (14.3%) and 80 (7.5%). Based on the IR, NMR and mass spectral data, structure 59 was assigned for this compound.



59

The ^{13}C-NMR spectrum (Table I) confirmed this structure. Assignment of the pyridine carbons was straight forward since the chemical shifts were nearly the same as in nicotine (6).[57] The downfield shift of the signal due to the C-4'-carbon atom (69.7 ppm) as compared to that in nicotine (22.61 ppm) is clearly a consquence of the hydroxyl group at the 4'-position. The assignments for all the other carbon atoms are in agreement with the known assignments for the carbon atoms in nicotine.[58] The ^{13}C-chemical shifts and the corresponding ^{1}H-chemical shifts along with the assignments are give in Table I.

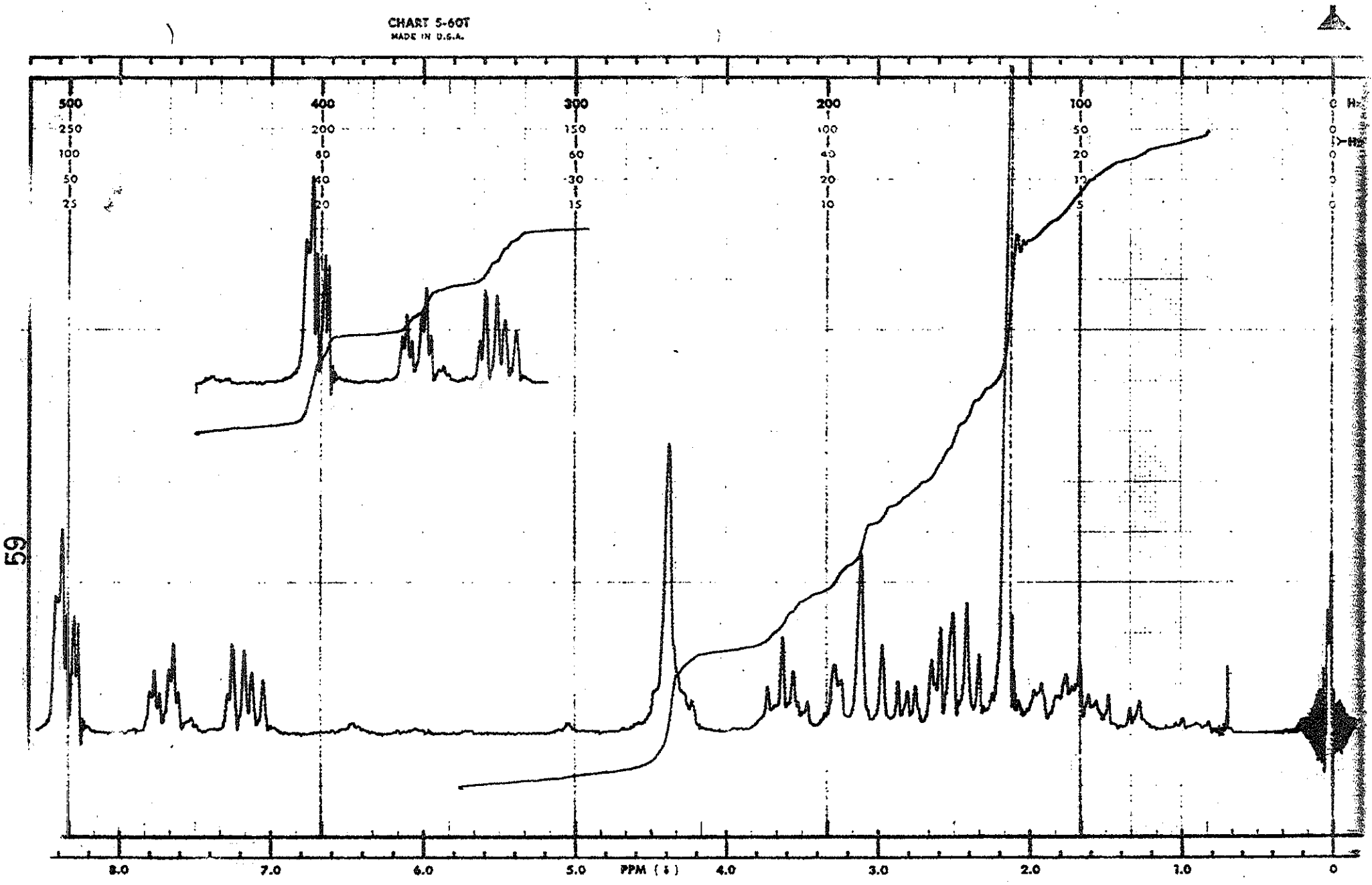
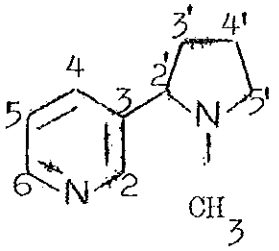
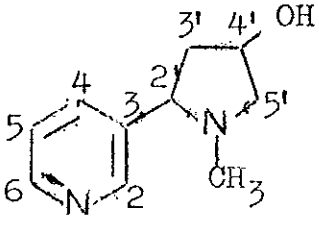
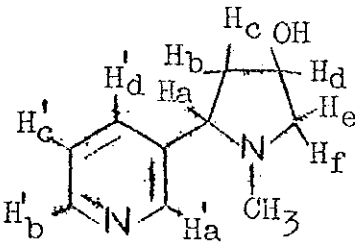


Figure XXIII. The NMR spectrum of 4-hydroxynicotine(59).

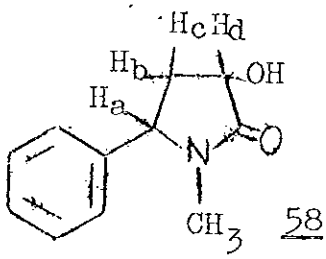






Carbon	δ-ppm	Carbon	δ-ppm	Proton	δ-ppm
2	149.55	2	149.2	Ha' & Hb'	8.33 (m)
3	138.79	3	137.3	Hd'	7.6-7.83 (two triplets)
4	134.75	4	135.3		
5	123.47	5	124.2	Hc'	7.17 (m)
6	148.60	6	149.05	Hd & -OH	4.37 (b)
2'	68.81	2'	68.3	Ha	3.6 (m)
3'	35.27	3'	39.7	He & H_f	2.7-3.3(m)
4'	22.61	4'	69.7	Hb & Hc	2.3-3.7(m)
5'	56.95	5'	65.7	$N-CH_3$	2.13 (s)
$N-CH_3$	40.31	$N-CH_3$	45.5		

Table I. ^{13}C and ^1H NMR data for nicotine and 4-hydroxy-nicotine (59)

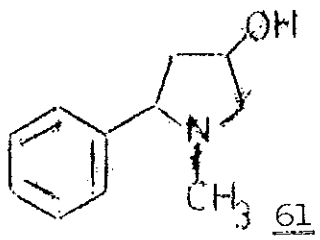


58

multiplet between 4.2 and 4.6 ppm (Ha and Hd). The IR spectrum showed an -OH absorption band at 3300 cm^{-1} and a strong carbonyl absorption band at 1690 cm^{-1}, identical with what was reported earlier.

Reduction of 58 with $LiAlH_4$ in refluxing THF afforded 1-methyl-4-hydroxy-2-phenylpyrrolidine (61)which wad identified by its IR, NMR and mass spectra.

The IR spectrum showed a broad -OH absorption band at 3300 cm^{-1}. The NMR spectrum (Figure XXVI) displayed an N-methyl signal at 2.07 ppm, a one proton multiplet between 1.7 and 2.0 ppm, a series of multiplets between 2.2 and 3.27 ppm, a broad peak at 3.97 ppm which exchanged with D_2O, a one proton multiplet at 4.23 ppm and the signals due to the phenyl ring protons at 7.2 ppm. Based on the known assignments for the pyrrolidinyl protons of nicotine,[55] the multiplets between 1.7 and 2.0 ppm were assigned to H_b, the multiplets between 2.2 and 2.9 ppm were assigned to Hc, He and H_f, the multiplet between 2.97 and 3.27 ppm was assigned to Ha, and the multiplet at 4.23 ppm was assigned to Hd.



61

The mass spectrum (Figure XXVII) displayed a molecular ion peak at m/e 177, a base peak at m/e 132 and other fragments at m/e 176, 159, 133, 100, 91, 77, 44. The fragment at m/e 159 could arise by a loss of H_2O (M^+-18) from the molecular ion and the prominent peak at m/e 100 could be explained as a loss of phenyl radical from the molecular ion.

The base peak at m/e 132 corresponds to a loss of 45 mass units from the molecular ion. This may be rationalized by the mechanism shown in Figure XXV . The fragment ion assignments are shown in Figure XXVIII.

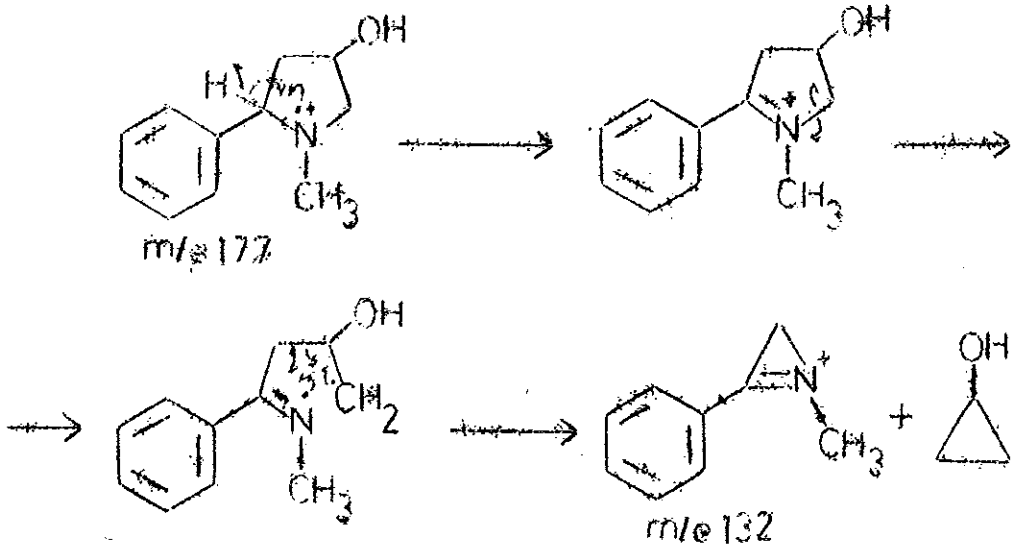


Figure XXV. Possible mechanism for the formation of the base peak from the M^+ peak of compound 61.

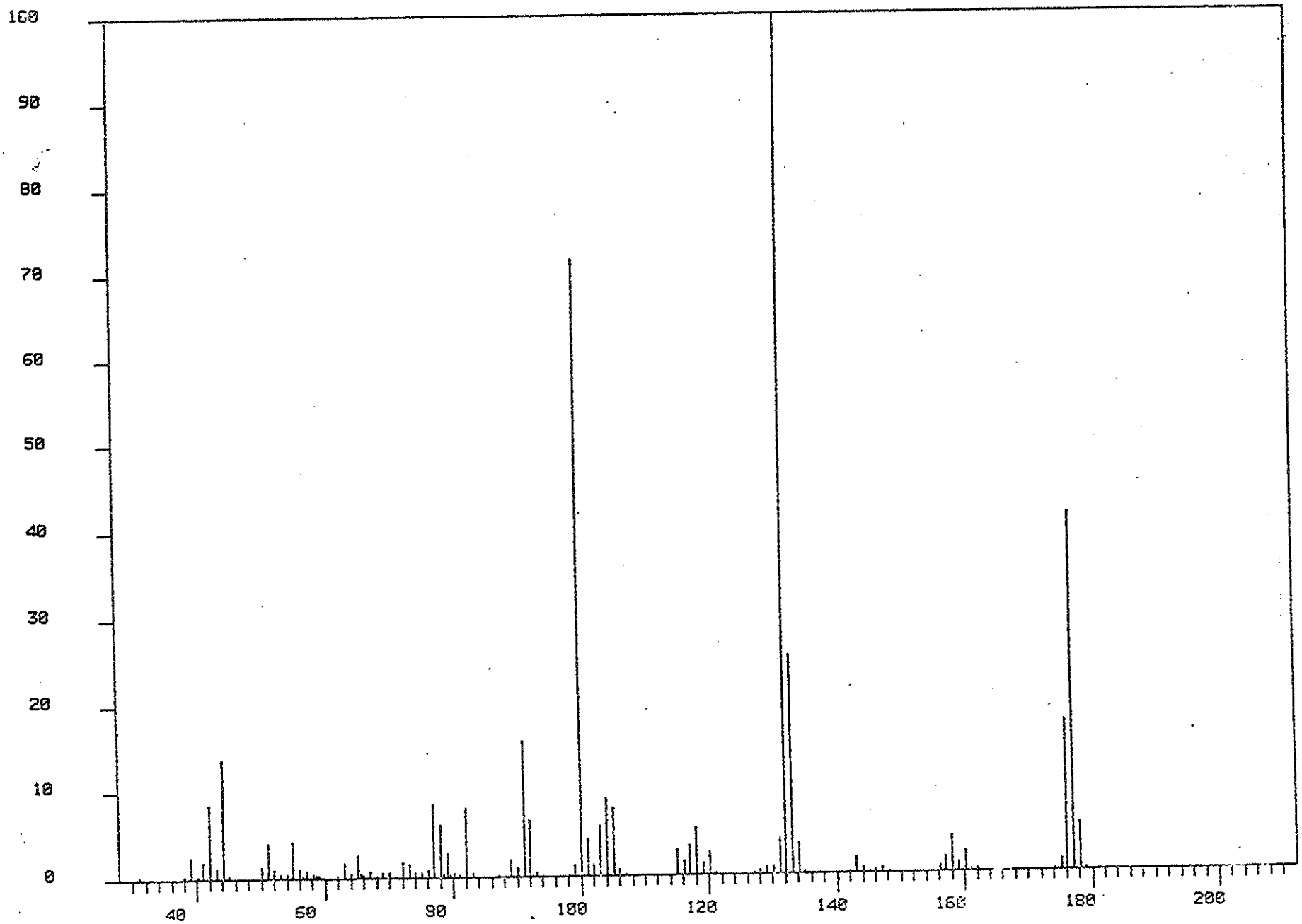
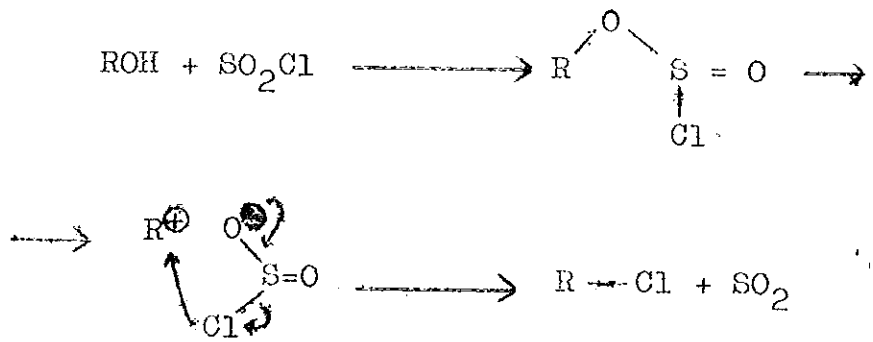
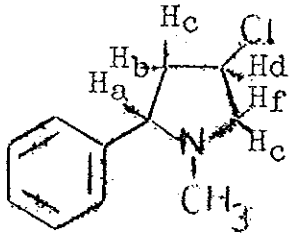


Figure XXVI: The mass spectrum of 4-hydroxy-1-methyl-2-phenylpyrrolidine(61).



4--chloro-1-methyl-2-phenylpyrrolidine (62) was synthesized by heating 61 under reflux in thionyl chloride for 4 hours. Compound 62 gave a positive Beilestein's test and showed no --OH absorption band in its IR spectrum. The NMR spectrum (Figure XXIX) showed a three proton singlet at 2.17 ppm ($N-CH_3$), a two proton multiplet between 2.27 and 2.9 ppm (Hb and Hc), a three proton multiplet between 3.33 and 3.83 ppm (Ha, He and H_f), a one proton quintet centered at 4.4 ppm (Hd), and the signal due to the phenyl ring protons at 7.17 ppm.



62

Phosphorous tribromide and HBr are reagents commonly used to convert alcohols to alkyl bromides.[62] In an attempt to synthesize 4--bromo-1-methyl-2-phenylpyrrolidine (63) the reactions of 61 with PBr_3 and HBr were studied. The reaction of 61 with PBr_3 (prepared from red phosporous and bromine)[63] in pyridine at 0°C afforded a complex mixture of product, whereas, the reaction of 61

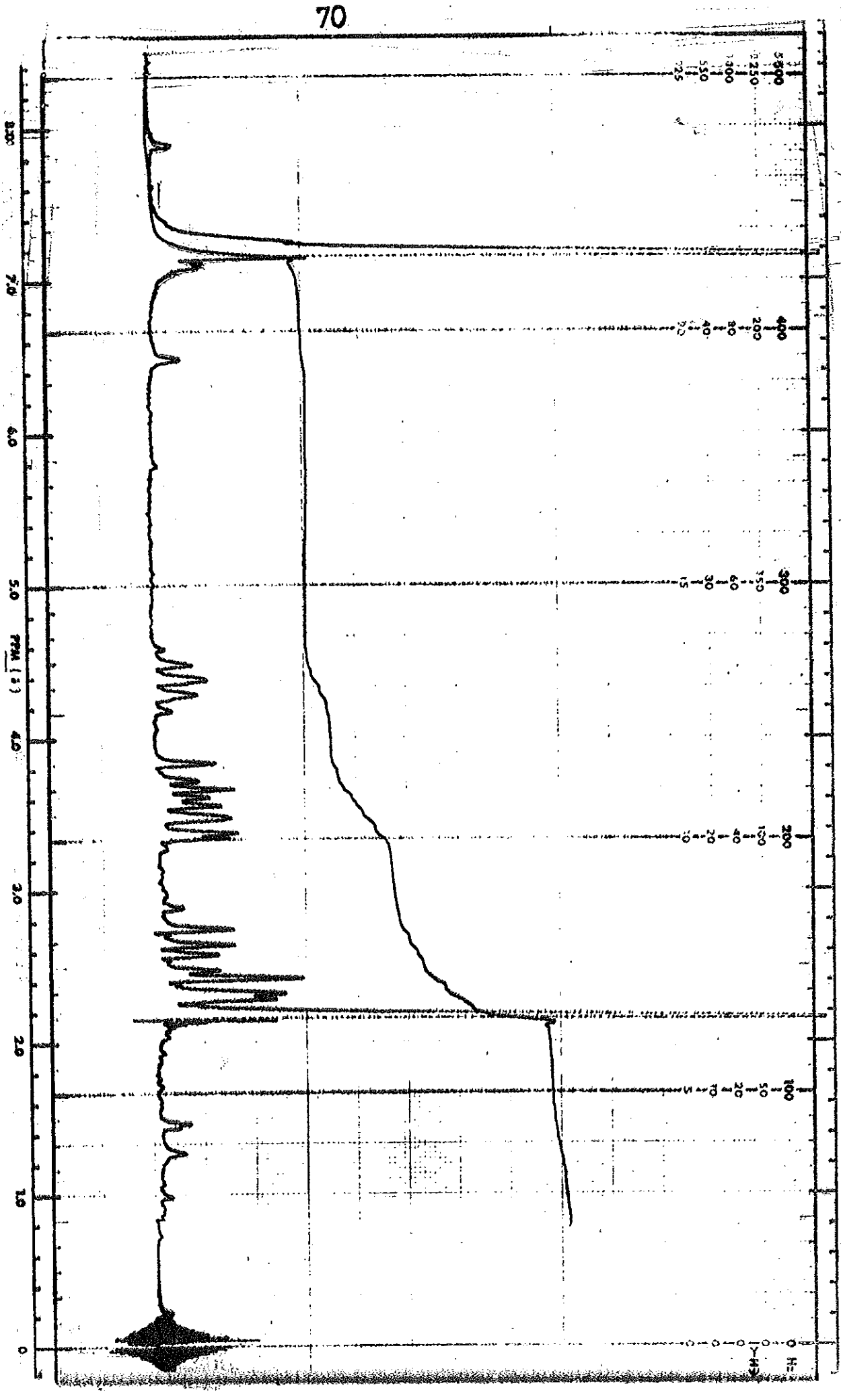
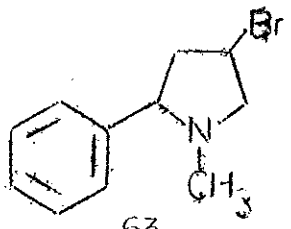


Figure XXIX. The NMR spectrum of 4-chloro-1-methyl-2-phenylpyrrolidine(62).



63

with 48% HBr at reflux overnight gave back the unchanged starting material.

Several attempts were made to introduce a double bond into the pyrrolidine ring by dehydrating 61 and dehydrochlorinating 62 using some of the commonly used methods for effecting dehydrations and dehydrohalogenations.

Treatment of compound 41 with 89% H_3PO_4 at 100°C for 2 hours gave back the unreacted starting material. In another attempt using phosporous oxychloride and pyridine, a brown oil was obtained which showed no signals corresponding to olefinic protons in its NMR spectrum. The NMR spectrum was, however, identical to that of the compound previously identified as 4-chloro-1-methyl-2-phenylpyrrolidine (62). All other attempts to dehydrate 61 using thionyl chloride and pyridine, p-toluenesulfonic acid,[64] trifluoroacetic acid and P_2O_5[65] were unsuccessful.

Attempts to dehydrochlorinate 62 using KOH in methanol and KO*t*Bu in *t*-BuOH proved unsuccessful. Compound 62 was recovered unchanged after treatment with KOtBu in refluxing t-BuOH overnight and the starting material was isolated after 4 hours refluxing in methanolic KOH.

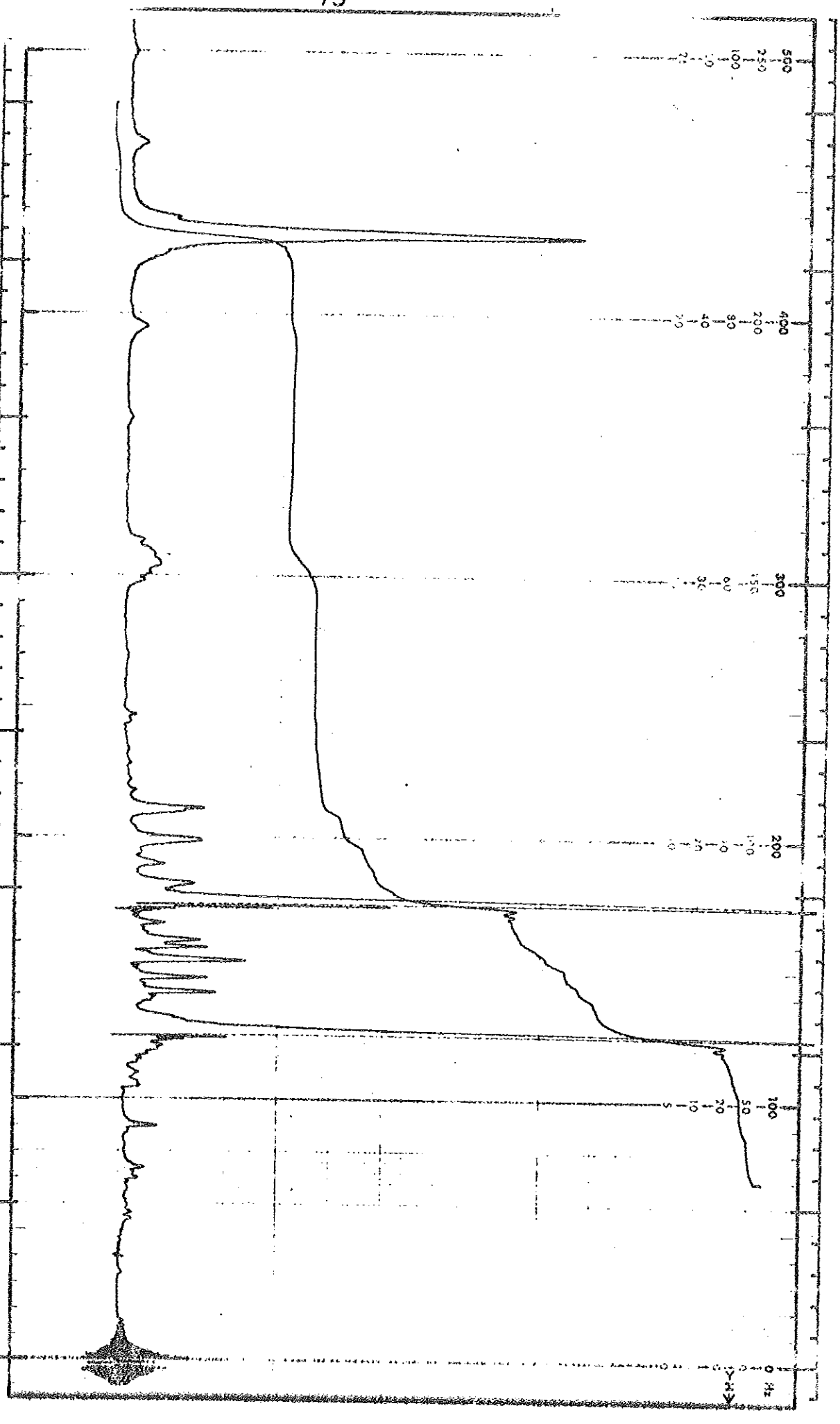
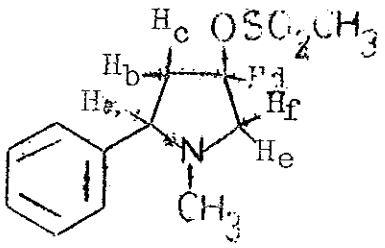
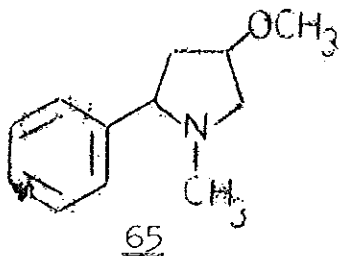


Figure XXX. The NMR spectrum of 4-mesyloxy-4-methyl-2-phenylpyrrolidine (54).

H_d in the product spectrum clearly support the above assignment.



64



65

The reaction of the mesylate 64 with NaOMe in refluxing methanol afforded an oil whose NMR spectrum (Figure XXXI) displayed two methyl signals at 2.1 and 3.23 ppm, a multiplet between 2.27 and 2.77 ppm integrating for 2 protons, another multiplet between 3.33 and 4.07 ppm integrating for 3 protons and the signals due to the phenyl ring protons at 7.17 ppm. The appearance of the three proton singlet downfield from the $S-CH_3$ singlet clearly indicated that the methanesulfonyl group was substituted by an OCH_3 group. Moreover, the signals for H_d appeared at 5.1 ppm in the starting material spectrum, whereas , in the product spectrum the signals for H_d appeared at about 3.8 ppm. This upfield shift could be explained if the more electronegative mesyl group was substituted by the less electronegative $-OCH_3$ group. Based on these grounds, structure 65 was assigned for the product.

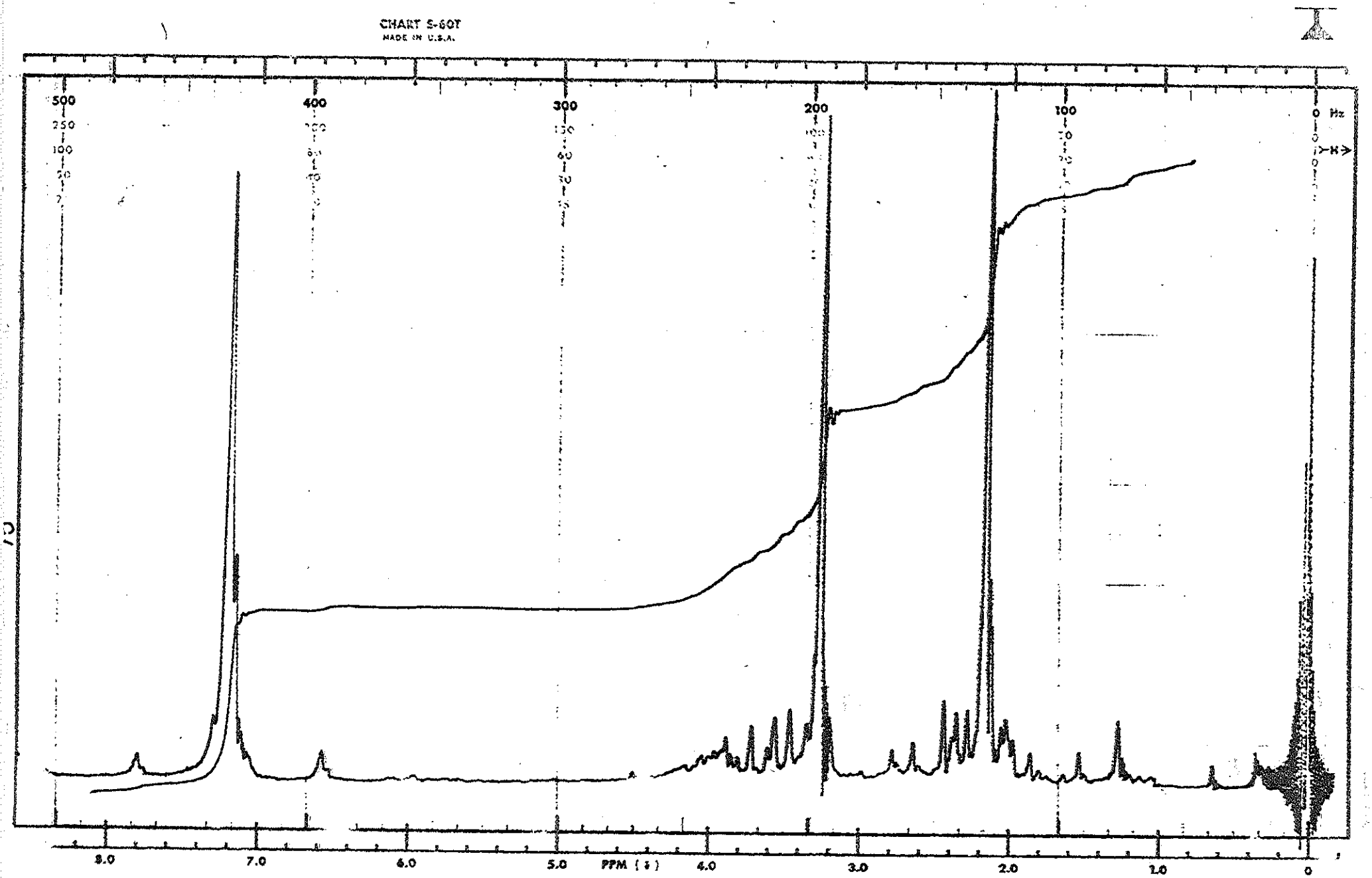


Figure XXXI. The NMR spectrum of 4-methoxy-1-methyl-2-phenylpyrrolidine(65).

CONCLUSION

In the course of this project, the reactions of several functionalized compounds possessing the nicotine basic skeleton have been investigated. Studies have also been conducted on the cycloaddition reactions of C-pyridyl-N-methylnitrone (45) on three olefinic compounds, namely allyl chloride, allyl bromide and allyl alcohol. Even-though our original goal of synthesizing the pyrrolines 1,2 and 3 is not yet accomplished, several interesting and important results have been achieved.

During our attempts to reduce the lactam carbonyl group of compounds 25, 26 and 37 with $LiAlH_4$, we have encountered the known tobacco alkaloid nicotyrine (5) arising from all three lactams. An interesting mechanism for the formation of nicotyrine (5) and nicotine (6) has been proposed. A survey of the literature on the synthesis of nicotyrine (5) reveals that it has been prepared either from nicotine (6) directly by dehydrogenation[67-69] or by coupling the pyridine and the N-methylpyrrole units chemically[70] or photochemically[71]. No reports are available on the synthesis of nicotyrine (5) from functionalized pyridyl-pyrrolidines (or pyridyl-pyrrolines). Another reported route to nicotyrine (5), according to Wibaut and Hackman,[15] is the disproportionation

of dihydronicotyrine to nicotine (6)and nicotyrine (5) upon catalytic hydrogenation with platinum oxide as a catalyst.

Among the major achievements of this project are the synthesis of four new compounds namely 4-hydroxynicotine(59), 4-chloronicotine (60), 4-hydroxy-1-methyl-2-phenylpyrrolidine (61) and 4-methoxy-1-methyl-2-phenylpyrrolidine (62). The structures of these compounds have been unequivocally established by spectral analysis although their stereochemistry have not been taken into account. The preparation of these compounds may be an important addition to the existing nicotine analogs. Moreover, we believe that a test of the physiological activities of these new compounds may be of paramount importance considering the interesting pharmacological properties of nicotine.

III. EXPERIMENTAL

General

Melting points were determined by Thomas- Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were taken on a Perkin Elmer 727B spectrophotometer. A Varian T-60A instrument was used to obtain nuclear magnetic resonance (nmr) spectra. Chemical shifts are given in parts per million (ppm) down field from internal tetramethylsilane (TMS) in $CDCl_3$. Spin multiplicity is given as (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (b) broad. Gas chromatograms were taken on a Hewlett-Packard gas chromatograph with a flame ionization detector using nitrogen as the carrier gas. ^{13}C-nmr was taken at Chemistry Department Boston University by Dr Berharu Abegaz. Mass spectra were taken by Dr.Pascher of Microanalytisches Laboratorium, W.Germany and by Dr.Robert Wernkam, at Purdue University.

3,3-Dibromocotinine hydrobromide perbromide ($\underline{24}.HBr.Br_2$)

A solution of bromine (19.8 ml, 0.38 mol), in aqueous acetic acid (80% v/v, 58 ml) was introduced dropwise into a 1 L. flask containing a stirred solution of nicotine (8.8 ml, 0.054 mol) in aqueous acetic acid (80% $v/_v$, 400 ml). Temperature was maintained between 25 and 43°C and the reaction was complete in 2 hr. Stirring was continued for 1 hr. and then water (100ml) was added. The dark red solution and the viscous bottom layer were heated to 60 - 70°C until the phases become miscible. The mixture was allowed to cool to room temperature slowly where upon reddish orange crystals separated which were collected by suction filteration. Yield of the air dried material was 24 g, 77% mp 142 - 143°C (lit.[26] mp 140 - 150°C).

3,3-Dibromocotinine (24)

To 3,3-dibromocotinine hydrobromide perbromide (24g) in water (100 ml) was added Na_2SO_3 gradually with stirring until the bromine color disappeared. A slightly yellowish homogeneous solution resulted which was neutralized by the addition of Na_2CO_3 in small portions. The resulting solid was filtered by suction and washed with water and recrystallized from aqueous ethanol

yielding 3,3-dibromocotinine (11g) as white needles, mp 123 - 125°C (lit[27] mp 125°C): nmr ($CDCl_3$, TMS) δ 2.73 (S,3H,N-CH_3), 3.0 (2d,1H, C_4), 3.5(2d,1H,C_4), 4.6 (2d, 1H, C_5), 7.0-9.0 (a typical 3-substituted pyridine pattern); ir (Pellet KBr) 1700 cm^{-1} (lactam C=O).

1-Methyl-5-methoxy-5-(3'-pyridyl)-3-pyrrolin-2- one (25)

To ice cold methanol (50 ml) was added 3,3-dibromocotinine (24, 4 g, 12 mmol) and KOH (1.7 g, 30 mmol) with stirring. When all the KOH had dissolved, the mixture was allowed to warm to room temperature. After 2 hr the KBr precititate was removed by filteration and the methanol was removed by rotary evaporation at reduced pressure. To the residue was added $CHCl_3$ (25ml) and the insoluble KBr was separated by filtration. The $CHCl_3$ solution was washed once with water, decolorized with activated charcoal dried over molecular sieves and evaporated to give 25 as a light yellow oil (1.7 g, 70% lit[28] 90%): ir(neat) 1700 cm^{-1} (S, C=O)

1-Methyl-5-hydroxy-5-(3'pyridyl)-3-pyrrolin-2·one (26)

Compound 25 (2.0 g, 9.8 mmol) in 15% aqueous HBr (15.3 ml) was heated at 95°C for 2 hr. The reaction mixture was then cooled, neutralized with $NaHCO_3$,

and extracted with CH_2Cl_2. The combined extracts were decolorized on charcoal and the solvent was removed by rotary evaporation. A light yellow oil (1.2g, 64.5%) was obtained which solidified on standing in the fridge: mp 143 - 145°C (lit[28] mp 145 - 146°C); ir 3600 - 2400 cm^{-1} (broad, OH), 1700 cm^{-1} (lactam C=O)

1-Methyl-5-hydroxy-5-(3'-pyridyl)-2- pyrrolidinone (5-Hydroxycotinine 27)

Compound 26 (1.5 g, 7.9 mmol) dissolved in EtOA (100ml) was reduced with H_2 (20 lb/in^2) using 5% Pd/C (500 gm) as catalyst. At the end of 25 hr the mixture was filtered. Upon removal of the EtOAC a white crystalline solid (1.0 g, 66%) was obtained mp 120 - 123°C(lit[28] mp 126 - 127°C); nmr ($CDCl_3$, TMS) δ 2.3 - 3.0 (a complex multiplet and an intense singlet, 7H, C_3, C_4 and N-CH_3), 5.83 (broad S, O-H), 7.1 - 9.0 (4H, a typical 3-substituted pyridine pattern)

1-Methyl-5-methoxy-5-(3'-pyridyl)-2- pyrrolidinone (37)

Compound 25 (0.74 g, 3.6 mmol) dissolved in EtOAc (30 ml) was reduced with H_2 (25 lb/in^2) using 5% Pd/C 200mg) as a catalyst. At the end of 22 hr. the mixture was filtered. Upon removal of the solvent a crystalline solid (0.7g, 94%) was obtained: mp 63 - 65°C; ir, 1700 cm^{-1} (lactam C=0; nmr ($CDCl_3$, TMS) δ 2.0 - 2.9 (a complex multiplet and a sharp singlet, 7H, N-CH_3

C_3 and C_4), 3.23 (S, 3H, OCH_3), 7.0 - 9.0 (4H, a typical 3-substituted pyridine pattern).

Attempts to dehydrohalogenate 3,3-dibromocotinine (24)

Several attemps were made to convert 3,3-dibromocotinine to the pyrrolinone 32:

a) 3,3-dibromocotine (0.5g, 1.5 mmol) and Li_2CO_3 (1.11g, 15 mmol) in DMF (15 ml) was refluxed under nitrogen atmosphere for 3½ hr. The mixture was cooled and filtered to remove the Li_2CO_3. To the filtrate, water (20 ml) was added and was wased with ether (2 x 25 ml) followed by exhaustive extraction with $CHCl_3$. The $CHCl_3$ extracts were combined, decolorized with charcoal, dried over Na_2SO_4 and the solved was removed under reduced pressure to yield a yellow oil (0.23 g). The product was a mixture consisting of two major and other minor components.

The nmr spectrum of the crude product showed signals due to olefinic protons at δ 6.07 (d) and 6.9 (d). Attempts to separate the olefinic compound by preparative TLC (silica gel 2.0 mm thick; benzene - ethanol 8:2) did not give a pure compound.

b) A mixture of products was isolated from the reaction of 3,3-dibromocotinine (24) with LiCl in DMF at 100°C for 2 hr. The NMR spectrum of the crude product showd signals due to olefinic protons at δ6.07 (d) and 6.87 ppm. Attempt was not made to separate the mixture since the olefinic compound was a minor product.

c) Only starting material was isolated from a reaction mixture containing KOt-Bu and 3,3-dibromocotinine (24) in diglyme (stirred at room temperature overnight).

d) Treatment of 24 with KOt-Bu in t-BuOH at room temperature gave back the unchanged starting material.

e) A mixture consisting of more than four components was obtained when the reaction of 24 with KOt-Bu in refluxing t-BuOH was performed. The NMR spectrum of the product mixture showed no signals due to olefinic protons.

f) A mixture consisting of more than five components was isolated when the reaction of 24 with KOt-Bu in DMSO was conducted at 100°C for 2 hr.

g) The unreacted starting material was recovered after treatment of 3,3-dibromocotinine (24) with KOt-Bu in THF both at room temperature and under reflux.

Attempts to dehydrate 5-hydroxycotinine (27) to the pyrrolinone (33)

a) 5-Hydroxycotinine (27, 300mg) was dissolved in pyridine (2ml) at 0°C and $POCl_3$ (0.1 ml) was added dropwise. After the addition was complete, the mixture was stirred for 1 hr and poured into a beaker containing cracked ice. Neutralization of the mixture with $NaHCO_3$ followed by extraction with CH_2Cl_2 yielded a dark brown gummy product (0.17g) consisting of more than five components. Attempt at separating the mixture by silica gel column chromatography using benzene and ethanol in different proportions as eluent was unsuccessful.

b) To a stirred solution of 5-hydroxycotinine (27, 200 mg) in pyridine (2ml) at 0°C was added dropwise, a solution of thionyl chloride (0.1 ml) in pyridine (2ml). The mixture was stirred under nitrogen for 1 hr and was poured into a beaker containing ice cold water and allowed to stand for 2 hr. Neutralization with $NaHCO_3$ and exhaustive extraction with CH_2Cl_2 yielded a yellow oil (0.13 g) which consisted of more than six components.

c) Attempt to dehydrate 27 with anhydrous oxalic acid in toluene following the procedure given by Y.Amiel et al[42] did not give the pyrrolinone 33.

An unidentified solid compound (mp 132 - 145°C) was obtained.

Reduction of 1-methyl-5-methoxy-5-(3'-pyridyl)-2-pyrrolidinone (37) with $LiAlH_4$

In a 100 ml 3-necked flask equipped with a reflux condenser, a pressure equalizing dropping funnel and a magnetic stirrer was suspended $LiAlH_4$ (200 mg 5.3 mmol) in 10 ml of freshly distilled THF. The reaction flask was cooled in a water bath while compound 37 (1.1 g, 5.3 mmol) in 2 ml of THF was introduced slowly dropwise. When the addition was complete, the reaction mixture was stirred under reflux overnight. The reaction mixture was chilled in an ice bath, then 0.2 ml of water was added followed by 0.2 ml of 15% NaOH and finally 1 ml of water was added slowly. The resulting mixture was stirred until white salts were formed. It was then filtered and dried over molecular sieves. The solvent was removed under reduced pressure to yield a yellow oil (0.75g) consisting of five components (GC. 10% carbowax 20 M on 100/120 Gaschrom Q OV 200°C isothermal). Attempts to separate the mixture by preparative TLC (silica gel 2 mm thick, benzene-ethanol 8:2) gave only two of the components with GC retention times of 1.5 min and 5.8 min in pure forms. The major product had a GC retention time of 0.46 min and was identified as

nicotine (6), by comparison with an autentic sample of nicotine. Identification of the compound with Rt 5.8 min was not possible based on its nmr, ir and mass spectra (see text). The compound with R_t 1.5 was identified as nicotyrine (5): nmr ($CDCl_3$ TMS) δ 3.6 (S, 3H, N-CH_3), 6.17 (m, 2H, C_3 and C_4), 6.67(t, 1H, C_5) 7.0 - 9.0 (4H, a typical 3-substituted pyridine pattern); ms m/e (relative intensity) M^+ 158(100%), 157 (43%), 130 (19%), 117 (9%), 116 (10%), 105 (6%), 91 (5%), 89(8.6%), 77(10%).

Reduction of 1-methyl-5-methoxy-5-(3'-pyridyl)-3-pyrrolin-2-one (25) with $LiAlH_4$

Compound 25 was reduced in the same manner described for the reduction of 37 above. A yellow oil consisting of five components was obtained (GC 10% carbowax 20 M on 100/120 Gaschrom Q, CV 200°C). Attempts to separate the mixture by preparative TLC (silica gel 2 mm thick benzene-ethanol 8:2) gave only the component with R_t 1.5 min in a pure form. This compound was identified as nicotyrine (5) based on its nmr and mass spectra. Nicotine (R_t = 0.46) was identified by comparison with an authentic sample.

Reduction of 1-methyl-5-hydroxy-5-(3'-pyridyl)-3-pyrrolin-2-one (26) with $LiAlH_4$

This compound was reduced in the same manner described for the reduction of compound 37. A mixture consisting of more than five compounents was obtained. Nicotine (6) and nicotyrine (5) were identified as the two major components based on their GC retention times and the NMR spectrum.

3-Hydroxycotinine (57)

This compound was synthesized according to the procedure of E.Dagne and N.Castagnoli[56].

i) α-3-Pyridyl-N-methylnitrone (25)

A solution of pyridine-3-carboxaldehyde (56) (12.8g, 120 mmol) and N-methylhydroxylamine hydrochloride (10.0g, 120 mmol) in abs. EtOH (100 ml) was stirred 18 hr at room temperature.

The solid which formed (16.14 g, lit[56] 15.6 g) was collected and combined with an additional 3.55g obtained by concentrating the mother liquor. The total nitrone. HCl (19.69 g, 86.6%, lit[56] 81%) was dissolved in water saturated with K_2CO_3. Exhaustive extraction with $CHCl_3$ gave 13.2 g (81%, lit[56] 69%) of the free base: mp 72 - 75°C (lit[56] mp 74-76°C); nmr ($CDCl_3$ TMS)

slowly followed by 0.2 ml 15% NaOH and finally 1 ml of water. The mixture was stirred until white salts were formed. It was then filtered, and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded a yellow oil (600 mg) which was shown by TLC (silica gel, benzene-ethanol 8:2) to consist of four products. Distillation of the crude product under high vacuum (150°C, 0.5 atm) yielded a faint yellow oil (300 mg, 36%): nmr ($CDCl_3$ TMS, figure XXIII) δ 2.13 (S,3H, NCH_3) 2.3 - 2.7 (m,2H, H_b and H_c), 2.7 - 3.3 (m,2H, He and H_f), 3.6 (m,1H, Ha), 4.37(b,Hd and OH), 7.0 - 9.0 (4H, a typical 3-substituted pyridine pattern); ms m/e (relative intensity) M^+ 178 (100%), 177 (47%) 164 (16%), 134 (7%), 105 14.3%), 80(7.5%).

4-Chloronicotine (60)

To 4-hydroxynicotine (59, 140 mg, 0.79 mmol) dissolved in pyridine (0.2 ml) was added dropwise $POCl_3$ (0.2 ml) at room temperature. The mixture was stirred for 2 hr and was poured into ice-cold water. It was basified with 15% NaOH and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried (molecular sieves) and removal of the solvent under reduced pressure yielded a yellow oil (100 mg, 61%): nmr ($CDCl_3$TMS) δ 2.2 (S,3H, N-CH_3), 2.3 - 2.9 (m,2H,H_b and H_c) 3.3 - 3.9 (m,3H, Ha, He and H_f) 4.4 (m,1H, Hd) 7.0 - 9.0 (4H,

typical 3-substituted pyridine pattern).

1-Methyl-3-hydroxy-5-phenyl-2-pyrrolidinone (58)

This compound was synthesized following the procedure of E.Dagne[29].

i) C-Phenyl-N-methylnitrone (66)

A solution of benzaldehyde (5 g, 47.2 mmol) and N-methylhydroxylamine hydrochloride (3.94 g, 47.2 mmol) in abs.EtOH(40 ml) was stirred 18 hr at room temperature. Removal of the solvent gave a white crystalline solid. It was dissolved in water saturated with K_2CO_3 and exhaustively extracted with $CHCl_3$. Removal of the solvent gave 5.24 g (82%) of the free base 66: mp 77-82°C.

ii) 1-Methyl-3-hydroxy-5-phenyl-2-pyrrolidinone (58)

A solution of C-phenyl-N-methylnitrone (66, 5.24 g, 39 mmol) in methyl acerylate (30 g, 349 mmol) was heated under reflux for 2 hr. After removal of the solvent, a yellowish oil (7.97 g) was obtained which was hydrogenated (35 lb/in^2) in abs.EtOH(75 ml) over W-2 Raney Nickel for 20 hr. The catalyst was separated by filteration and the solvent was removed under reduced pressure. The resulting oil was taken up in acetone and upon cooling a white crystalline solid (2.19 g, 32%) separated which was collected by filteration. mp 140 - 142°C (lit[29] mp 148-149°C);

ir 3300 cm^{-1} (OH) 1690 cm^{-1} (lactam C = O); nmr ($CDCl_3$ TMS) δ 2.0 (m,1H, $\underline{H}_b$), 2.6(S,3H, N-$C\underline{H}_3$) 2.73-3-06 (m,1H, $\underline{H}_c$) 4.2 - 4.6 (m,2H, Ha and Hd) 7.17 (5H, aromatic protons)

1-Methyl-4-hydroxy-2-phenylpyrrolidine (61)

This compound was prepared by the reduction of 58 with $LiAlH_4$ in the same manner described for the preparation of compound 59. A slightly yellowish oil was obtained in a yield of 86%: ir 3300 cm^{-1} (OH); nmr ($CDCl_3$ TMS) δ 2.07 (S,3H, $NC\underline{H}_3$), 1.7 - 2.0 (m, 1H, $\underline{H}_b$) 2.2 - 2.9 (m,3H, Hc, He and $\underline{H}_f$), 2.97 - 3.27 (m,1H, Ha) 4.23(m,1H Hd), 7.2(5H, Aromatic protons); m.s m/e M^+ 177, 176, 159, 133, 132 (100%), 100, 91, 77, 44.

Attempts to dehydrate 1-methyl-4-hydroxy-2-phenylpyrrolidine (61)

a) A solution of 61, in 89% H_3PO_4 was heated at 100°C for 2 hr. After work - up the unreacted starting material was obtained.

b) Compound 61 was recovered unchanged after treatment with P_2O_5 in refluxing benzene overnight.

c) Distillation of compound 61 over P_2O_5 under high vacuum gave back the unchanged starting material

4-Chloro-1-methyl-2-phenylprrolidine (62)

1-methyl-4-hydroxy-2-phenylpyrrolidine (61 , 600 mg, 3.4 mmol) in $SOCl_2$ (3.28 g, 27.6 mmol) was heated under reflux for 4 hr. The excess $SOCl_2$ was removed under reduced pressure and the residue was neutralized with 10% Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was decolorized on charcoal and the solvent was removed under reduced pressure to yield an oil (610 mg, 92%); nmr ($CDCl_3$ TMS) δ 2.17 (s, 3H, N-CH_3) 2.27-2.9 (m, 2H, H_b and H_c) 3.33 - 3.83 (m, 3H, Ha, He and H_f), 4.44 (m, 1H, Hd), 7.17 (5H, aromatic protons).

Attempts to dehydrohalogenate 4-chloro-1-methyl-2-phenylpyrrolidine (62)

a) Compaund 62 (300 mg) and KOt-Bu (300 mg) in t-BuOH (10 ml) was stirred and refluxed overnight. Work-up gave back the unchanged starting material.

b) The starting material was recovered unchanged after treatment of 62 with KOH in refluxing MeOH for 4hr.

c) Compound 62 was recovered unchanged after refluxing in triethylamine overnight.

4-Mesyloxy-1-methyl-2-phenylpyrrolidine (64)

To 4-hydroxy-1-methyl-2-phenylpyrrolidine (61 , 300 mg, 1.7 mmol) and triethylamine (260 mg, 2.6 mmol) in dichloromethane (15 ml) at 0°C was added mesyl chloride (300 mg, 3.4 mmol) dropwise over a period of 10 min. The reaction

mixture was stirred for 30 min longer at 0°C. It was then transferred into a separatory funnel with the aid of more CH_2Cl_2 and washed with water and 10% Na_2CO_3. The organic layer was dried over molecular sieves and removal of the solvent under reduced pressure yielded the mesylate 64 (350 mg, 73%) as a yellow oil: nmr ($CDCl_3$ TMS) δ 2.1 (S, 3H, NCH_3), 2.5 (m,2H, H_b and H_c), 2.93 (S, 3H, S-CH_3) 3.25(m,3H, Ha, He and H_f), 5.1 (m,1H, Hd) , 7.2 (5H, phenyl ring protons).

4-methoxy-1-methyl-2-phenylpyrrolidine (65)

The mesylate 64 (200 mg, 0.7 mmol) and NaOMe (100 mg, 4.2 mmol) in MeOH (11 ml) was heated under reflux for 4 hr. The solvent was removed under reduced pressure and the residue was dissolved in water and exhaustively extracted with $CHCl_3$. The $CHCl_3$ extracts were combined and dried over molecular sieves. Removal of the solvent yielded 65 (100 mg, 75%) as a yellow oil: nmr ($CDCl_3$ TMS) δ 2.1 (S, 3H, N-CH_3), 3.2 (S, 3H, O-CH_3), 1.8 - 2.8 (m,3H, H_b, H_c, H_e), 3.3 - 4.07 (m, 3H, Ha, Hd and H_f), 7.17 (5H, phenylring protons).

Reaction of C-pyridyl-N-methylnitrone (45) with allyl chloride

The nitrone 45 (2 g, 14.7 mmol) and allyl chloride (10 g, 131 mmol) in benzene (20 ml was heated under

reflux following the progress of the reaction by TLC (benzene-ethanol 8:2). As the reaction proceeded, a brown solid began to separate. The formation of a second compound (R_f 0.6) was detected by TLC. At the end of 72 hr the reaction was stopped and the brown solid was separated by filtration. The filtrate was distilled under reduced pressure to give a yellowish oil (1.29 g) which consisted of the unreacted nitrone and the product. The oil (1.29 g) was applied to a column packed with silica gel (30g) and was eluted with benzene-ethanol (8:2). Fractions 3 and 4 contained the desired product (0.8 g 34%) which was identified to be the isoxozolidine 48: nmr ($CDCl_3$TMS) δ 2.1(m,1H, H_b or H_c) 2.5(S, 3H, N-CH_3), 3.0 (m,1H, H_b or H_c), 3.6 (m,3H, Ha and CH_2 — Cl), 4.33(m,1H, Hd) 7.0 - 9.0 (4H, a typical 3-substituted pyridine pattern).

5-Hydroxymethyl-2-methyl-3-(3'-pyridyl) isoxazolidine (50)

The nitrone 45 (500 mg,3.67 mmol) in allyl alcohol (10g, 172.4 mmol) was heated under reflux following the progress of the reaction by TLC (benzene-ethanol 8:2). At the end of 50 hr all the starting material had disappeared. The excess allyl alcohol was removed under reduced pressure to yield an oil (600 mg, 84.5%); ir 3700-2400 cm^{-1} (-OH); nmr ($CDCl_3$ TMS) δ 1.83 - 2.4 (m, 1H, H_b or H_c), 2.53 (S, 3H, N-CH_3), 2.67-3.17 (m,1H, H_b or H_c), 3.43 - 3.9

(m,3H, Ha and CH_2-OH), 4.13 - 4.5 (m, 1H, Ha), 4.6 (b, 1H, OH), 7.0 - 9.0 (4H, typical 3-substituted pyridine pattern).

Catalytic hydrogenation of 4-hydroxymethyl-2-methyl-3-(3'-pyridyl) isoxazolidine (50)

Compound 50 (600 mg, 3 mmol) dissolved in abs EtOH (35 ml) was hydrogenated (33 lb/in^2) over freshly prepared W-2 Raney Nickel for 13 hr. The mixturewas filtered and the solvent removed under reduced pressure to yield 51 as an oil (510 mg, 83.6%): ir 3700 - 2400 cm^{-1} (OH); nmr ($CDCl_3$ TMS) δ1.83 (t,2H, H_b and H_c), 2.17 (S, 3H, N-CH_3), 3.4 - 4.0 (m,4H, Ha, Hd, and CH_2- OH), 7.0 - 9.0 (4H, pyridine ring protons).

Reaction of compound 51 with thionyl chloride

Compound 51 , (1.6g) in thionyl chloride (16g) was heated at 60-70°C for 2 hr. The excess thionyl chloride was removed under reduced pressure and to the residue was added H_2O (10 ml) and was neutralized with Na_2CO_3. It was then extracted with $CHCl_3$, dried over molecular sieves and removal of the solvent yielded a dark red oil (1.26 g). The resulting oil was taken up in ethanol hexane to give a white solid (mp 165 - 166°C, compound I) which was separated by filtration. The filtrate was concentrated and the resulting oil was applied on a 2 mm silica gel plate and eluted with

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