SYNTHETIC APPROACHES TOWARDS DENDROBINE

A THESIS
SUBMITTED TO THE
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FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

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NCL, Poona 411 008
January 1980

(Ramesh Anna Joshi)

SUMMARY

S U M M A R Y

The problem deals with the development of synthetic methodology for the total synthesis of some nitrogen alkaloids, like Dendrobine, mainly using internal cycloaddition reactions. Stereochemical complexity of many natural products can be best reproduced by synthesis where internal Diels-Alder and 1,3-cycloadditions are used to fix many stereochemical features unambiguously. This aspect is being studied with particular relevance to 'Dendrobine', a natural product (nitrogen alkaloid) having interesting biological activity.

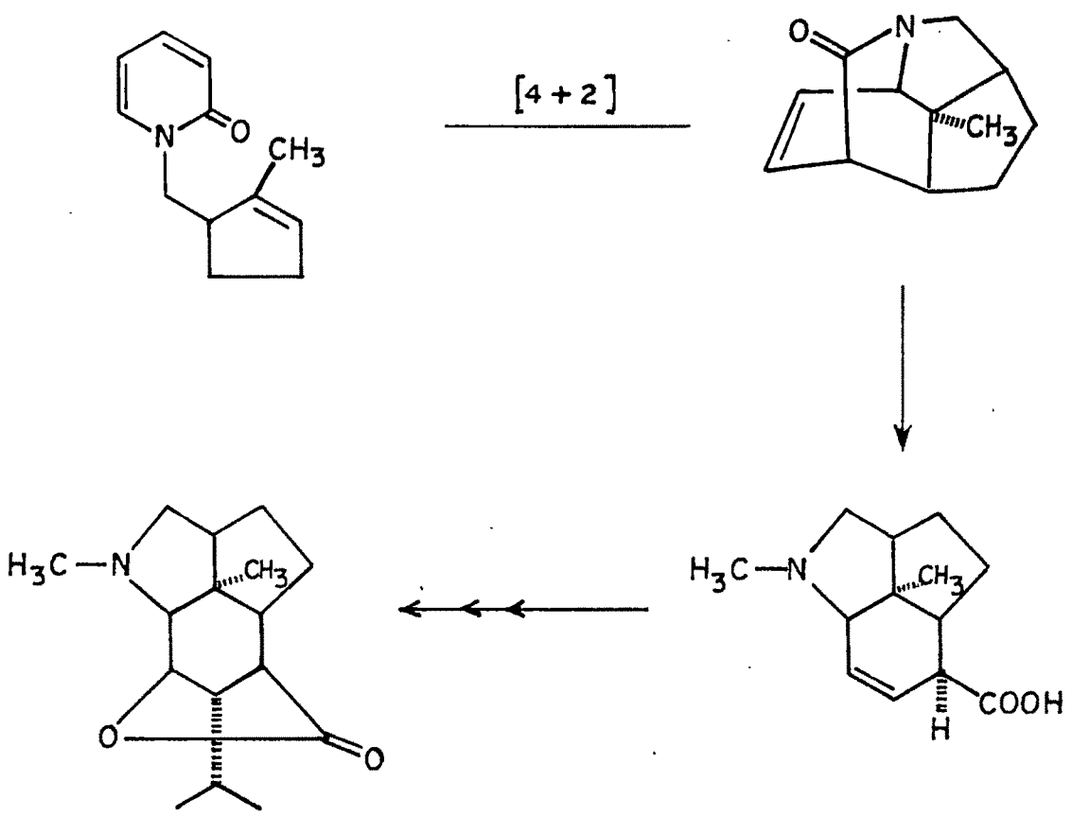
CHAPTER I: PARTIAL AND TOTAL SYNTHESIS OF DENDROBINE - A REVIEW

Dendrobine's interesting structure has elicited considerable attention from synthetic chemists, resulting in four total syntheses of the alkaloid itself and two partial synthesis. The reported syntheses are discussed in this Chapter.

CHAPTER II: INTRAMOLECULAR DIELS-ALDER ADDITIONS OF N-ALKENYL PYRIDONES AS AN APPROACH FOR THE SYNTHESIS OF DENDROBINE SKELETON

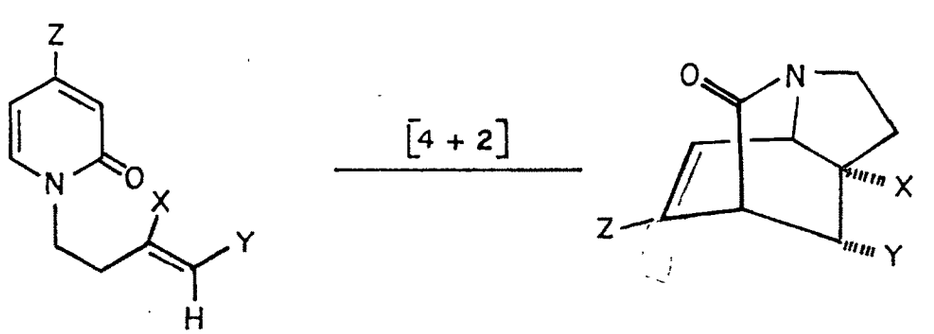
An introduction to internal (4 + 2) cycloaddition reactions which are effectively used for stereospecific synthesis of natural products is given. Also literature on the reaction of pyridones as the diene component in Diels-Alder reaction is presented. Syntheses of Dendrobine

SCHEME 1



DENDROBINE

SCHEME 2.



	X	Y	Z
1	H	CH_3	H
2	H	CH_3	$COCH_3$
3	$COOCH_3$	H	H

reported so far involve very large number of steps and are not stereospecific. Our attempted methodology involved the use of cycloaddition which in the present case would fix five out of seven stereochemical centres unambiguously (Scheme 1).

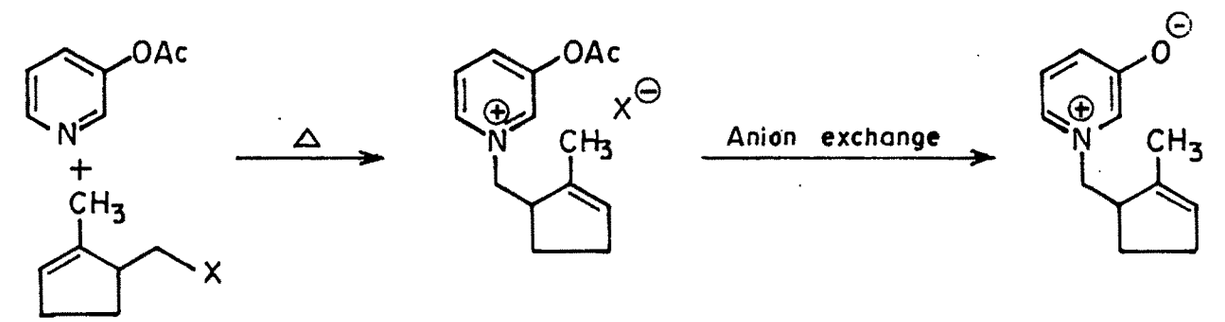
In this connection pyridone derivatives were made and their Diels-Alder reaction was studied (Scheme 2). N-Homoallyl pyridones were subjected to Diels-Alder reaction under Lewis-acid catalysed and uncatalysed conditions without success.

CHAPTER III: INTRAMOLECULAR 1,3-DIPOLAR ADDITIONS OF N-ALKENYL PYRIDINIUM BETAINES AS AN APPROACH FOR THE SYNTHESIS OF DENDROBINE

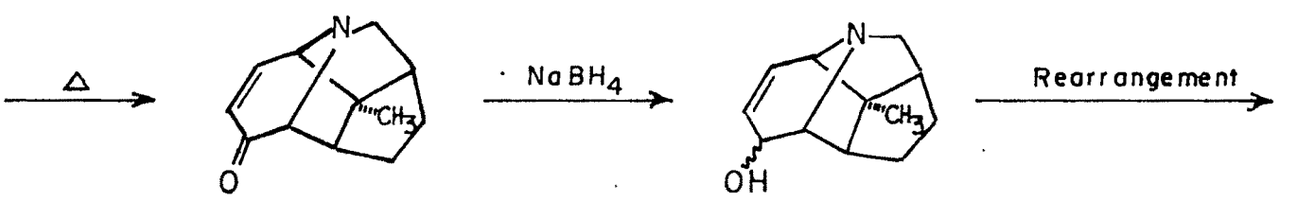
The nature and scope of intermolecular and internal (3 + 2) cycloadditions are discussed. The chemistry of various acyclic and heterocyclic dipoles with regard to their stereospecific reaction with dipolarophiles is presented. The high stereoselectivity and regiospecificity with which the 1,3-dipoles undergo cycloadditions with dipolarophiles led us to investigate the following reaction sequence which would lead to synthesis of Dendrobine. The internal 1,3-dipolar cycloaddition of pyridine system with cyclopentene double bond is the key step (Scheme 3).

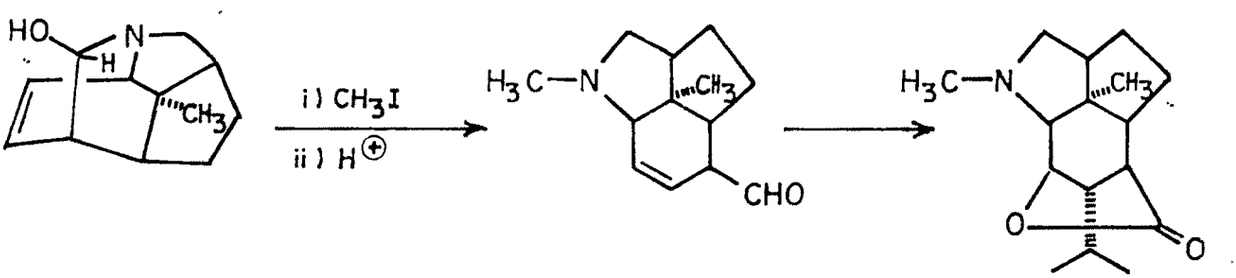
The N-homoallyl-3-oxopyridinium betaines were synthesised and their cycloaddition reaction was studied

SCHEME 3.



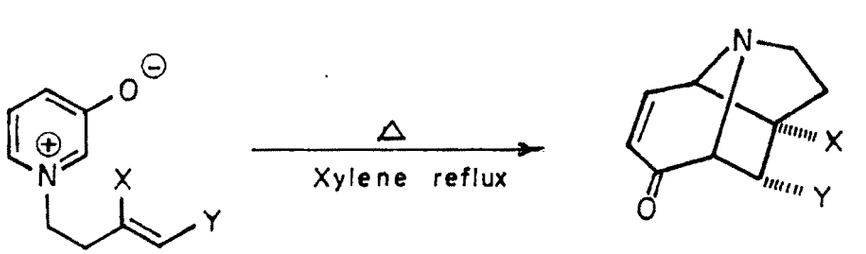
X = leaving gr.





DENDROBINE

SCHEME 4.

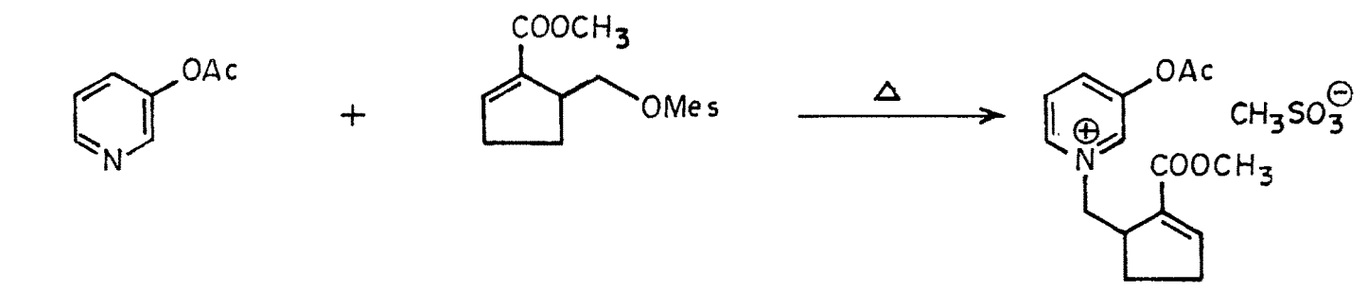


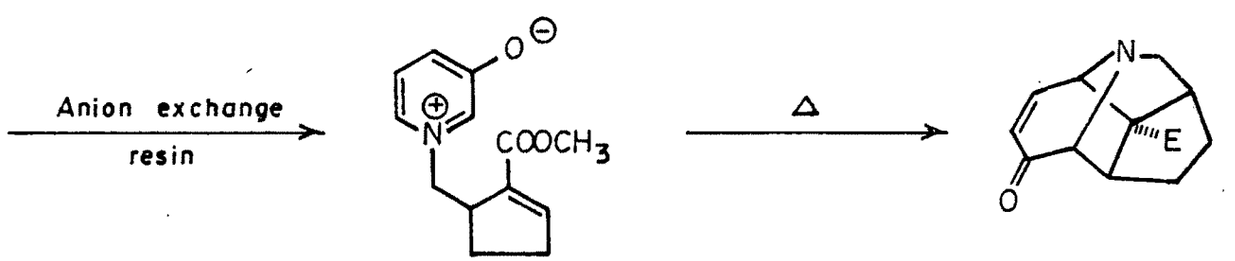
1 X = $COOCH_3$ Y = H

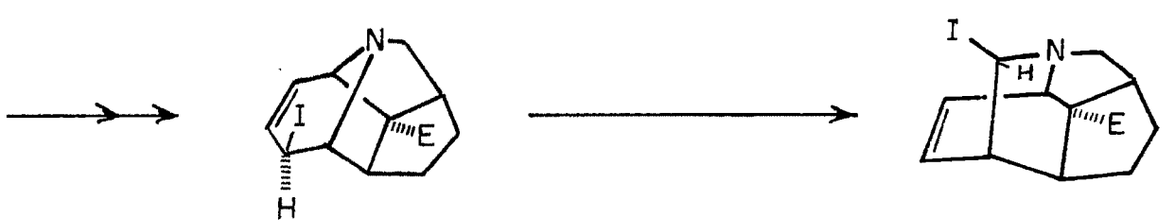
2 Y = CH_3 X = H

(Scheme 4). With the successful cycloaddition reaction on these model compounds, the cyclopentene derivative required for Dendrobine was synthesised and the cycloaddition was studied (Scheme 5). The enone cycloadduct was converted to the β-iodide as shown, by conventional methods. This iodide was found to be unstable with respect to its rearrangement to (2·2·2) azabicyclooctane system. The latter would serve as a key intermediate for elaboration into Dendrobine in a highly stereoselective fashion.

SCHEME 5 .







E = $COOCH_3$

GENERAL REMARKS

1. Proton Magnetic Resonance spectra were recorded either on a Varian T-60 spectrometer or a Bruker WH-90 FT NMR spectrometer. Unless otherwise stated carbon tetrachloride was used as the solvent and tetramethylsilane as the internal standard.

2. Infra Red spectra were scanned on a Perkin-Elmer Infracord 137 spectrophotometer.

3. Ultra Violet spectra were recorded either on a Perkin-Elmer 350 spectrophotometer or a Carl Zeiss Jena Specord UV-Vis Mod. No.445069 spectrophotometer.

4. Mass spectra were recorded on a CEC-21-110B double focussing mass spectrometer operating at 70 eV using a direct inlet system.

5. Melting points and boiling points are uncorrected.

CHAPTER I

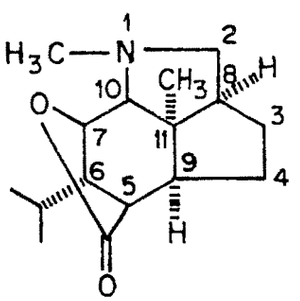
PARTIAL AND TOTAL SYNTHESIS OF DENDROBINE: A REVIEW

INTRODUCTION

The sesquiterpene alkaloid dendrobine 1 (Chart 1) occurs as a component of the Chinese drug Chin-Shih-Hu, which is prepared from the ornamental orchid Dendrobium nobile (Orchidaceae). It was first isolated from the stem of the plant by Suzuki and coworkers[1]. Recently, the alkaloid, as well as a number of its congeners, has been extensively investigated by Hirata[2], Inubushi[3] and Okamoto[4], who have determined the stereostructure shown in 1. A more recent examination of the genus Dendrobium has shown that the widespread Dendrobium nobile LINDL. contains not only dendrobine but other alkaloids nobiline 2 [2,4], dendroxine[5], dendramine[6] and dendrine[7]. Dendrobine's interesting structure (Chart 1) which is closely related to that of picrotoxinin 3 [8] and tutin 4 [9] possessing a very powerful neurophilic activity, has elicited considerable attention from synthetic chemists, resulting in four total syntheses[10-13] of the alkaloid itself as well as several partial syntheses[14-16].

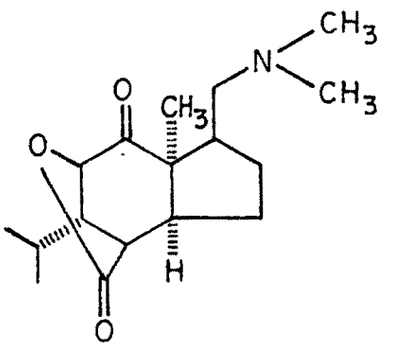
The pharmacological action of dendrobine[17], is nearly identical with that of picrotoxin. Dendrobine has slight but demonstrable analgesic and antipyretic actions, although much weaker than those of aminopyrines; it produces moderate hyperglycemia; diminishes cardiac activity; lowers blood pressure and suppresses respiration. Large doses cause

CHART – 1



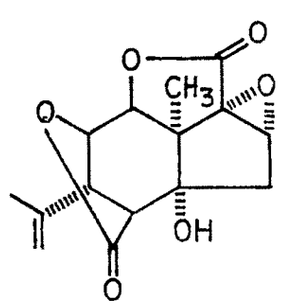
1

DENDROBINE



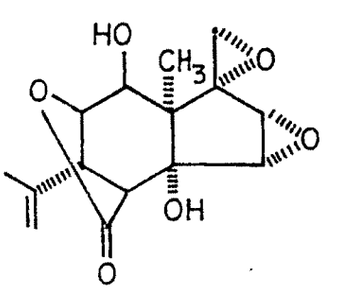
2

NOBILINE



3

PICROTOXININ



4

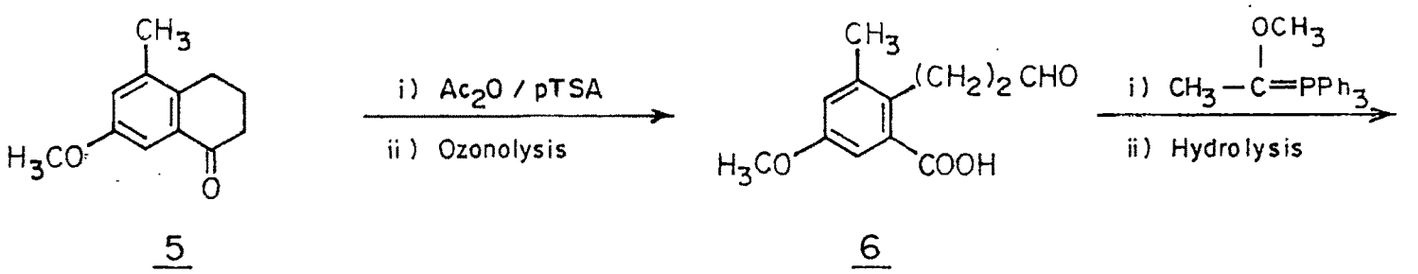
TUTIN

death preceded by convulsions of central origin. Dendrobine also has analeptic action and is effective in antidoting barbiturate intoxication.

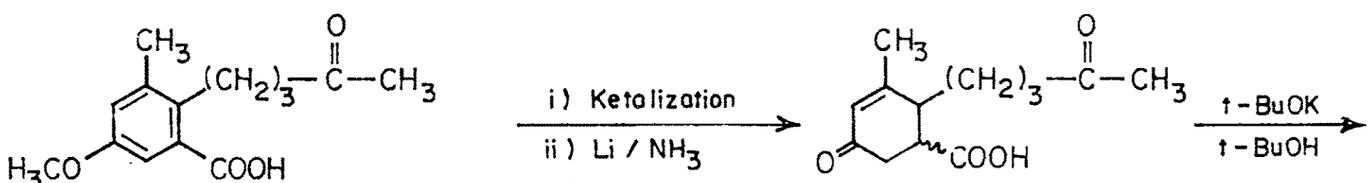
The features of the dendrobine molecule are the cis-hydrindan unit, the N-methylpyrrolidine ring, the γ-lactone ring and the isopropyl unit. In the design of the synthetic scheme of dendrobine, sufficient attention must be paid to stereochemical problems. There are seven asymmetric centers in the molecule, out of which six are in a contiguous array on a cyclohexane ring. So any synthesis should bring about the required carbon configuration in minimum number of steps.

Yamada et al.[10], have reported the first synthesis of (dl)-dendrobine (scheme 1.1). An ingenious method of constructing a cis-hydrindan system stereoselectively by intramolecular Michael addition was employed. 3,4-Dihydro-7-methoxy-5-methyl-1(2H)-napthalenone 5 was converted to the acid 6 via its enol acetate by ozonolysis. The Wittig reaction of 6 with α-methoxyethyltriphenylphosphonium chloride and methylsulfinyl carbanion followed by treatment with aqueous oxalic acid afforded the ketoacid 7. The reduction of ethylene ketal of ketoacid 7 with lithium in liquid ammonia gave the dihydro-derivative, which on hydrolysis, deketalization and acid treatment afforded the oily diketoacid 8. Cyclization of the

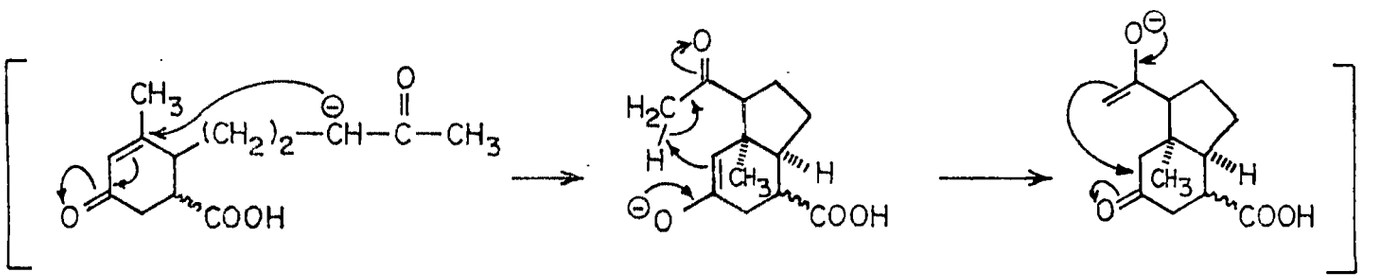
SCHEME 1·1



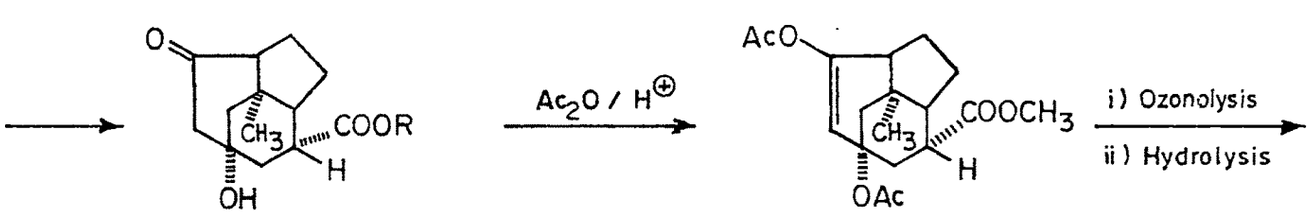
5 6



7 8



9 10 11



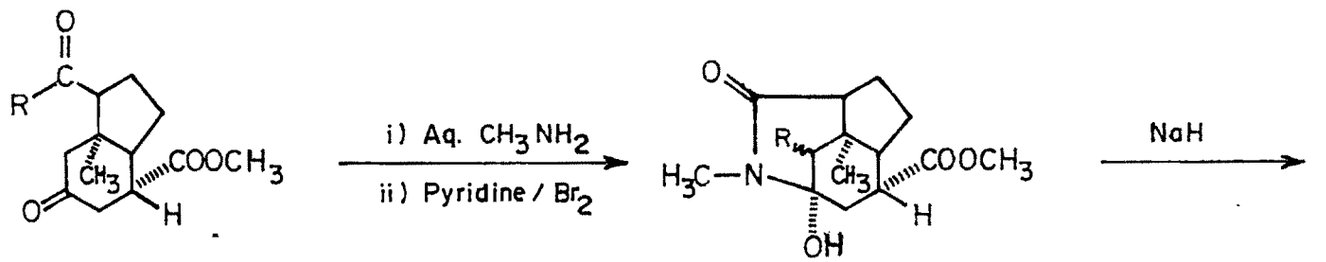
12 a R = H
12 b R = CH3

13

— contd p-13 →

diketoacid 8 with potassium t-butoxide in t-butanol gave a mixture of two products epimeric at C-5, but mainly consisting of ketolacid 12a, which was purified by crystallisation. Treatment of the diketoacid 8 with potassium t-butoxide gave the anion 9 which underwent Michael addition to give the enolate anion 10. This underwent proton transfer to give the more stable anion 11 which gave two C-5 epimeric ketolacids. The ketolacid 12a was esterified (diazomethane) and the resulting ester 12b was acetylated to give the diacetate 13. Ozonolysis of the diacetate 13 followed by treatment with water afforded the acid 14a. A mixture of the acid 14a and N,N'-carbonyldiimidazole was heated at 80° for 5 minutes without solvent and the crude imidazole 14b was converted to the lactam 15a by treatment with aqueous methylamine. The lactam 15a was converted to the bromo derivative 15b (pyridinium bromide perbromide). Treatment of bromide 15b with sodium hydride in glyme followed by acidification with anhydrous oxalic acid yielded the oily pyrrolidone 16, which was transformed ($HCOOCH_3$-$NaOCH_3$-B_z) into a mixture of 17 and 18, the former being readily convertible to the latter (diazomethane). The oily compound 18 on treatment with n-butanethiol gave a sulfide, which on treatment with lithium dimethylcuprate in ether gave the ester 19. Isomerization of 19 was effected by sodium hydride in glyme affording a mixture of 20 and 19

SCHEME 1·1 (contd)

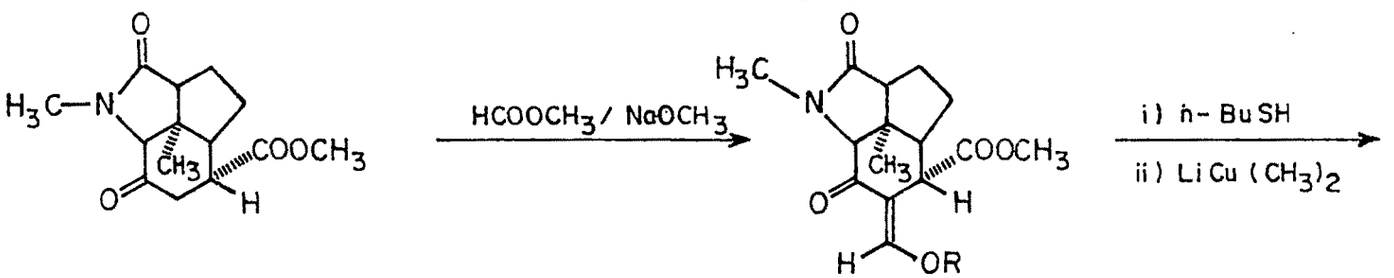


14a R = OH

14b R = 

15a R = H

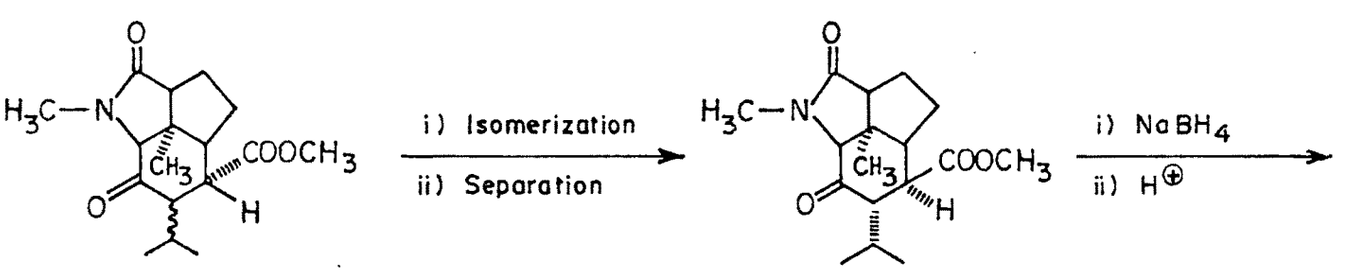
15b R = Br



16

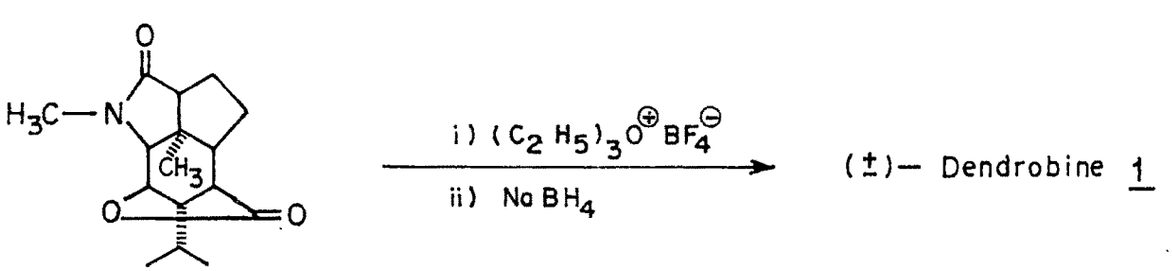
17 R = H

18 R = CH_3



19

20



21

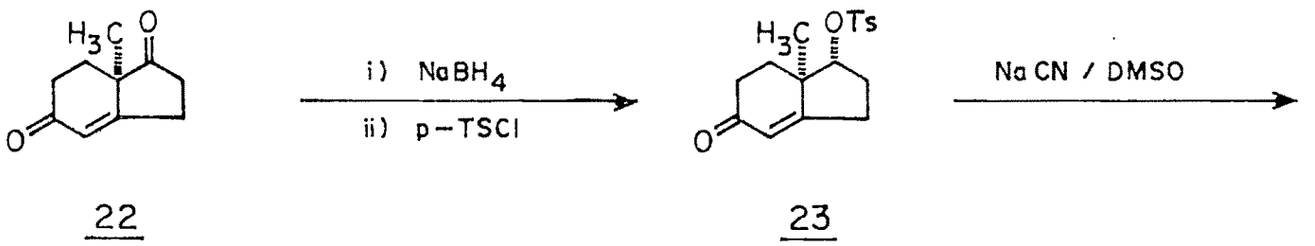
which was separated by preparative TLC. Reduction of 20 with ethanolic sodium borohydride followed by acidification afforded (±)-oxodendrobine 21. Treatment of oxodendrobine with triethyloxonium fluroborate in dichloromethane followed by sodium borohydride reduction yielded an oily product as a boron complex; which was purified and then passed, as a pyridine solution through a column of anion exchange resin to afford (±)-dendrobine 1.

The above sequence of reactions became particularly long because of the wrong orientation of C-5 ester group after the Michael-cum-aldol reaction (8 to 12a). This wrong orientation resulted in further complications later during the introduction of isopropyl group at C-6. The correction of stereochemistry at C-5 and C-6 necessitated an isomerization followed by separation (19 to 20) resulting in poor yields.

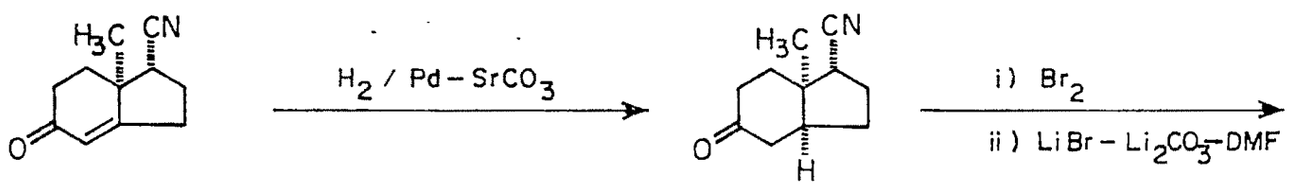
Inubushi et al.[11] have reported a synthesis of dendrobine involving the construction of a cis-hydrindan derivative with functions present at suitable positions for the subsequent reactions for formation of the pyrrolidine ring (Scheme 1.2).

The ketol obtained from the diketone 22, by reduction with sodium borohydride, was converted to its tosylate 23. This

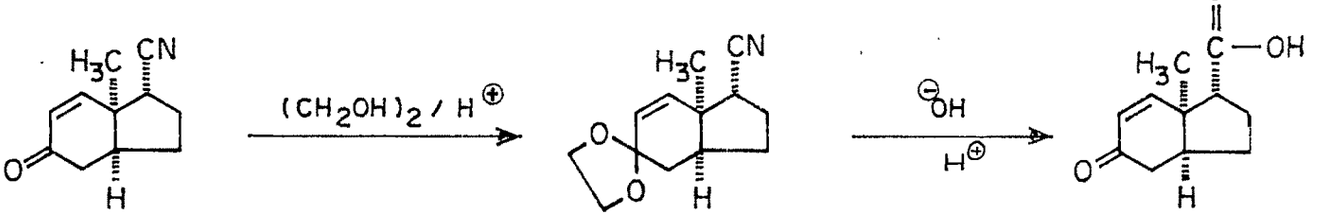
SCHEME 1·2.



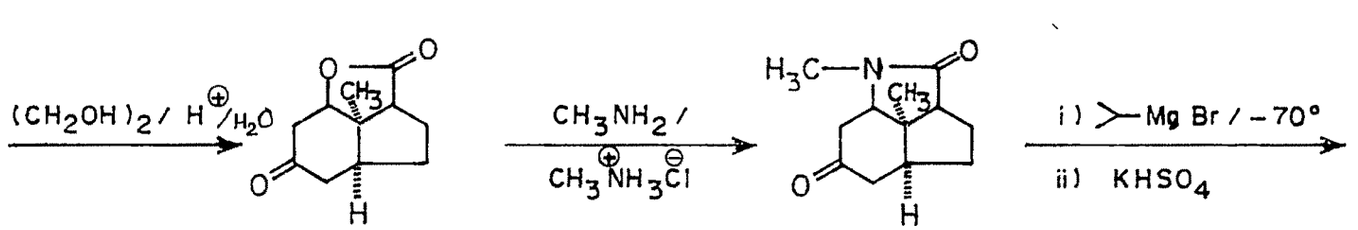
22 23



24 25



26 27 28

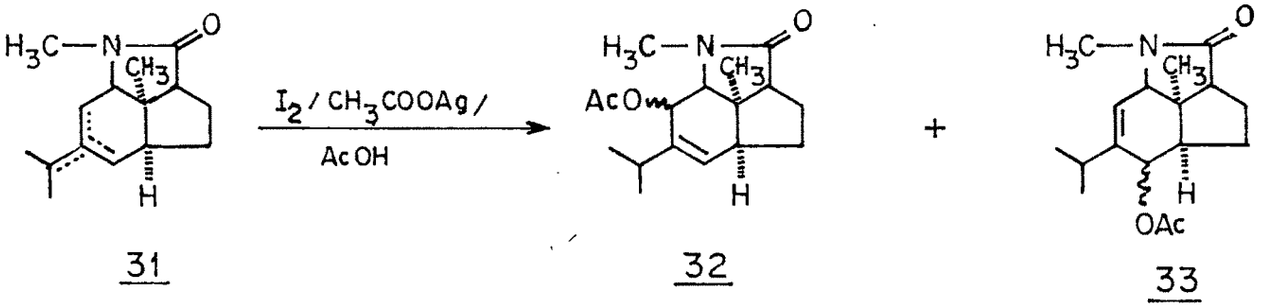


29 30

— contd p·17 →

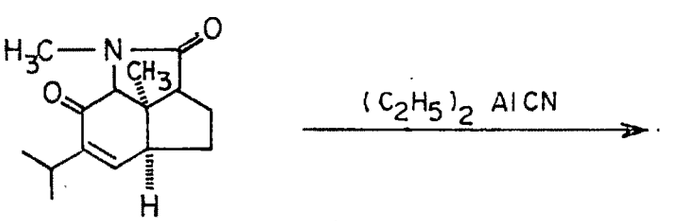
was treated with sodium cyanide in dimethyl sulfoxide to give the ketonitrile 24, surprisingly with retention of stereochemistry. Details of this substitution reaction remain unclear. Catalytic hydrogenation of the nitrile 24 provided mainly cis-hydrindan derivative 25. The ketone 25 on reaction with one molar equivalent of bromine, followed by heating with lithium bromide-lithium carbonate in dimethyl formamide, afforded two enones 26 and 24 in a ratio of 3-4:1. The ethylene ketal 27 of ketone 26, on alkaline hydrolysis of cyano group and subsequent hydrolysis of ketal group afforded the ketoacid 28. On refluxing the ketoacid 28 in ethyleneglycol with 25% sulfuric acid, the lactonization took place affording the ketolactone 29. This lactonization is preceded by epimerization of carboxyl function. The stereochemical requirements for this lactonization also warrant this epimerization. When the lactone 29 was heated with aqueous methylamine in the presence of methylamine hydrochloride the ketolactam 30 was obtained. The Grignard reaction of the ketolactam 30 with isopropylmagnesium bromide afforded the alcohol, which on dehydration (potassium hydrogen sulfate) gave three kinds of olefins 31 in almost quantitative yield. This olefin mixture was treated with iodine-silver acetate in acetic acid, which provided two kinds of allyl acetates 32 and 33 in 10% and 20%

SCHEME 1·2 (contd.)

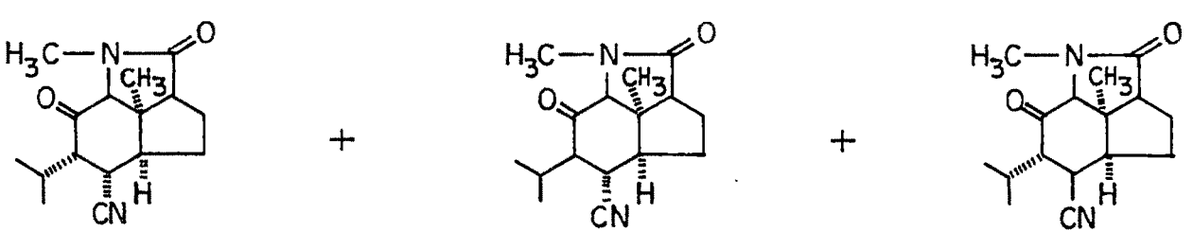


31 32 33

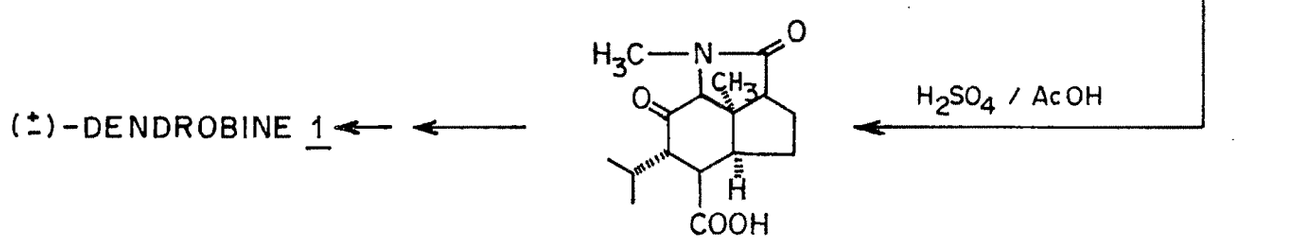
i) Saponification
ii) CrO_3



34



35 36 37



21

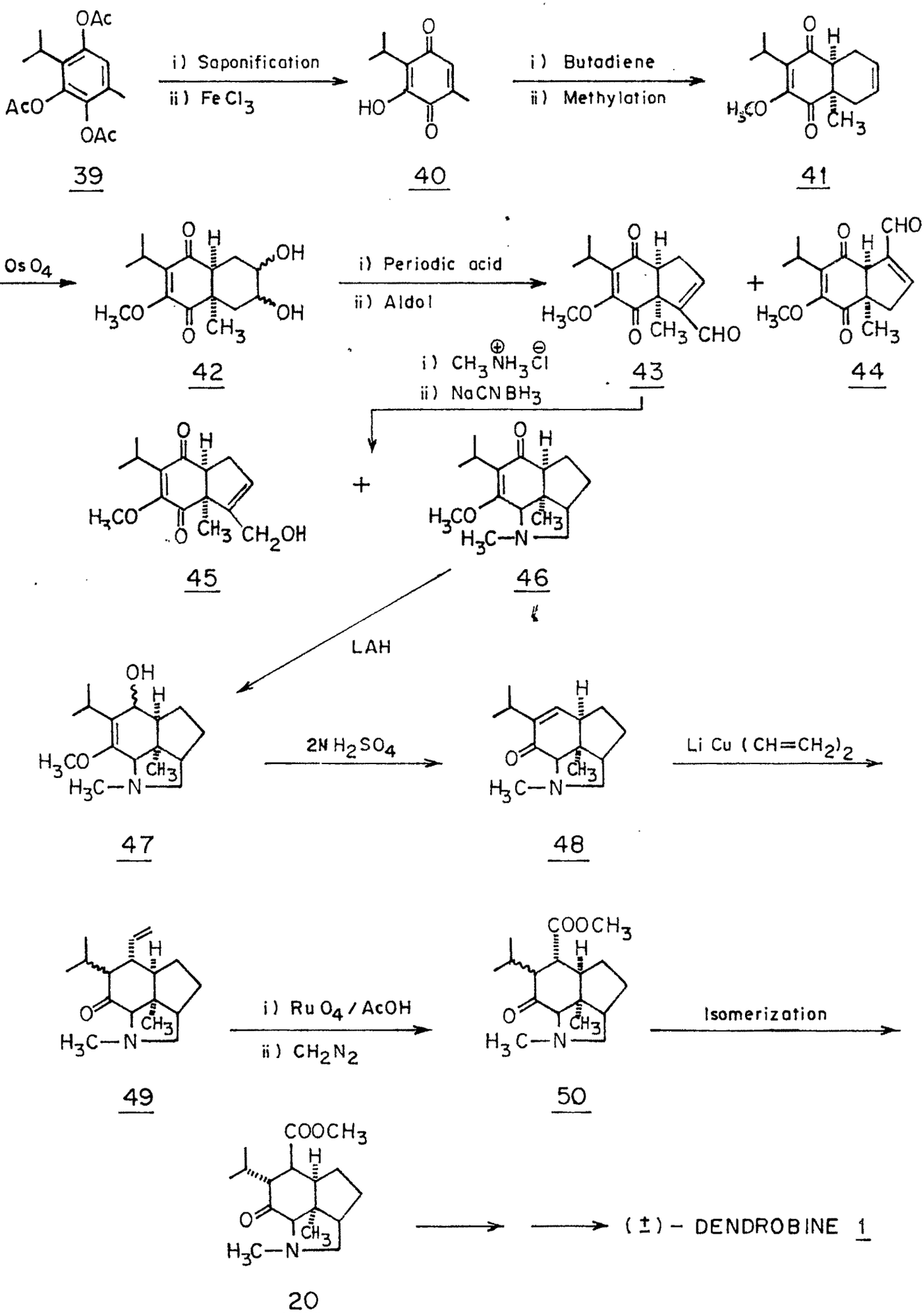
yields respectively. Hydrolysis of the acetate 32 with aqueous methanolic potassium hydroxide gave an alcohol, which was then oxidized with chromium trioxide-pyridine complex to afford the enone 34. The hydrocyanation reaction of 34 with diethylaluminium cyanide yielded three cyanoketones 35, 36 and 37. Treatment of the ketone 36 with sodium methoxide in benzene gave the ketone 35 in 80% yield which was isomerized with sodium methoxide in methanol to the ketone 37, in 20% yield. Hydrolysis of the cyanoketone 37 with sulfuric acid-acetic acid followed by esterification with diazomethane gave the ketoester 20. Reduction of the ester 20 with sodium borohydride proceeded stereoselectively to give the hydroxyester which on hydrolysis with potassium hydroxide and acidification gave (±)-oxodendrobine 21. Treatment of ketone 21 with triethyloxonium fluoroborate followed by reduction with sodiumborohydride provided (±)-dendrobine 1.

This sequence of operations is again longwinded and involves nonregiospecific operations like dehydration leading to mixture of olefins 31 and allylic oxidation to a mixture of allyl acetates 32 and 33 in poor yields. Also in the latter the minor fraction 32 is only to the extent of 10% which is taken for further elaboration. Again in the hydrocyanation step we find lack of stereospecificity

where the stereoisomers have to be equilibrated in two steps to give 20% yield of 37 which has the right orientation of isopropyl and nitrile functions.

Kende et al.[12] have reported a total synthesis of dendrobine in which the Diels-Alder reaction fixes the cis-stereochemistry of the hydrindan derivative (scheme 1.3). The readily available triacetate 39 formed the starting point of the synthesis. Saponification and ferric chloride oxidation of 39 gave 100% of the quinone 40, which with butadiene in ethanol yielded the Diels-Alder adduct. The methyl ether 41 of the latter was selectively hydroxylated at the isolated double bond to give the diol 42. Cleavage of the diol 42 with periodic acid in tetrahydrofuran followed by aldol cyclization with pyrrolidine acetate in benzene gave a 1:1 mixture of the aldehydes 43 and 44. Reductive amination of 43 gave 30% of alcohol 45 and 35% of a crystalline amine 46. Lithium aluminium hydride reduction of 46 gave the carbinols 47 which in cold 2N sulfuric acid produced 80% of the enone 48. Lithium divinylcuprate conjugate addition gave 86% of the ketone 49. Ruthenium tetroxide in acetic acid cleaved the vinyl group which with diazomethane gave the ketoester 50. Reflux of ketoester 50 for three days in anhydrous 0.3M sodium methoxide in methanol effected partial isomerisation

SCHEME - 1·3


OAc
AcO
OAc
i) Saponification
ii) Fe Cl3
HO
i) Butadiene
ii) Methylation
H3CO
CH3
39
40
41
OsO4
OH
i) Periodic acid
ii) Aldol
CHO
42
43
44
i) CH3 NH3 Cl
ii) NaCN BH3
CH2OH
45
46
LAH
47
2N H2SO4
48
Li Cu (CH=CH2)2
49
i) Ru O4 / AcOH
ii) CH2N2
COOCH3
50
Isomerization
20
(±) - DENDROBINE 1

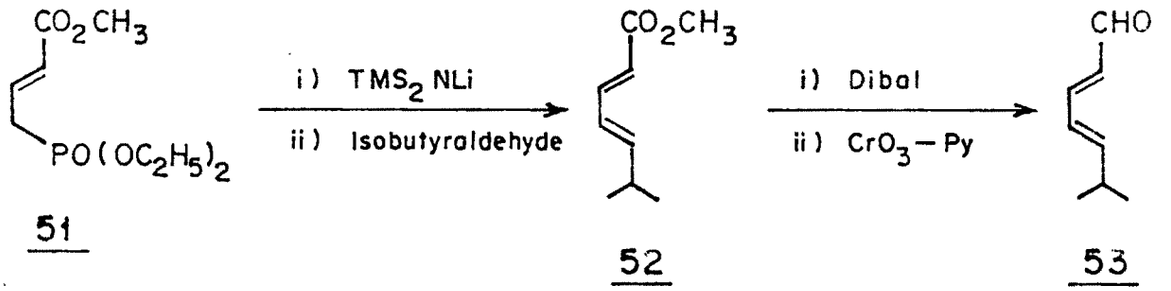
to the ketone 20. The sodium borohydride reduction of the ketone gave an alcohol, which spontaneously cyclised to give (±)-dendrobine 1.

This is the first synthesis reported involving the Diels-Alder reaction which has fixed the cis-ring fusion of the hydrindanone derivatives 43 and 44, but the aldol condensation was not orientation specific and gave equal mixtures of the required aldehyde 43 and unrequired aldehyde 44. Again in the later stages the introduction of carbomethoxy group *via* vinylation and oxidation sequence gave the wrong orientation, necessitating an isomerization step which was found to be inefficient.

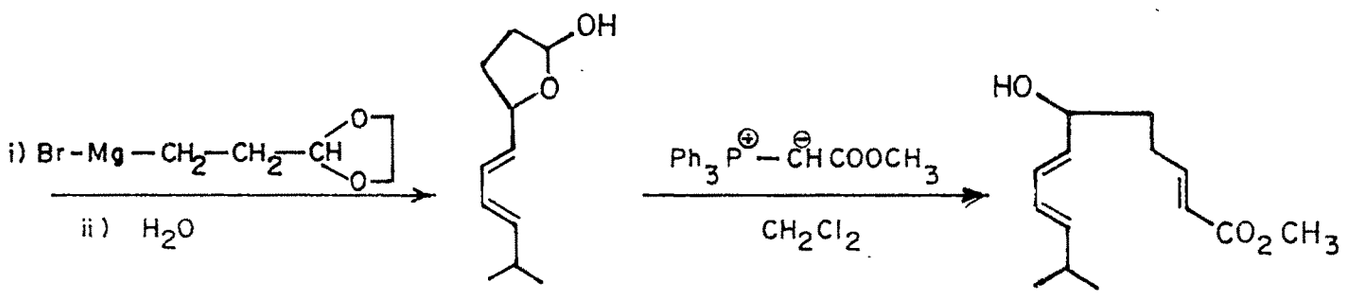
Recently W. Roush[13] has reported a synthesis of dendrobine by a stereoselective route, which utilizes an intramolecular Diels-Alder addition as the key skeleton forming reaction (Scheme 1.4).

Condensation of the stabilized anion of 51 with isobutyraldehyde gave mainly the diene 52. Reduction of the diene 52 with dibal followed by oxidation with chromium trioxide-pyridine complex afforded trans, trans aldehyde 53. The aldehyde 53 on Grignard reaction and subsequent hydrolysis afforded the lactol 54. The Wittig reaction of lactol 54 with carbomethoxymethylenetriphenylphosphorane gave a triene

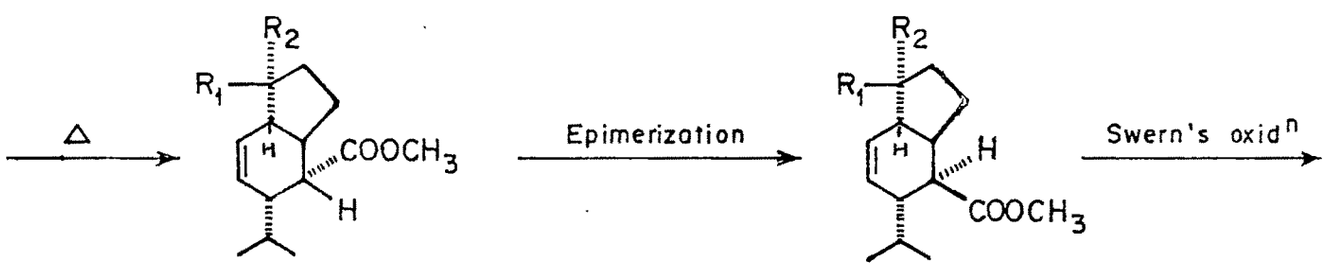
SCHEME 1·4.



51 52 53

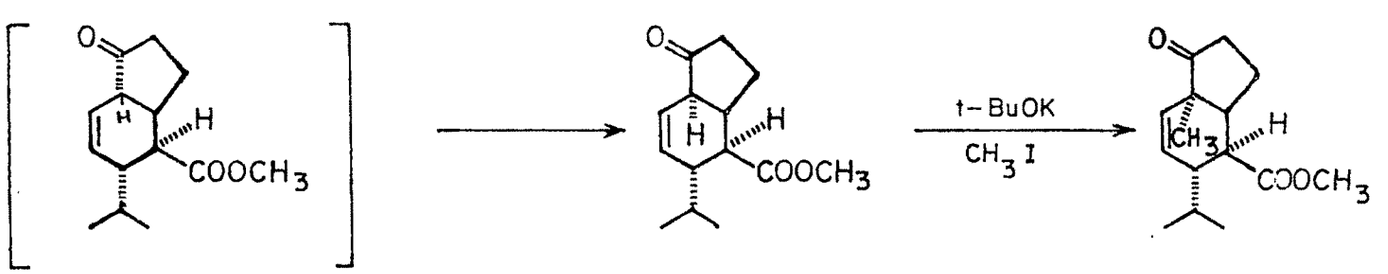


54 55



56a R_1=H, R_2=OH
56b R_1=OH, R_2=H

57a R_1=H, R_2=OH
57b R_1=OH, R_2=H

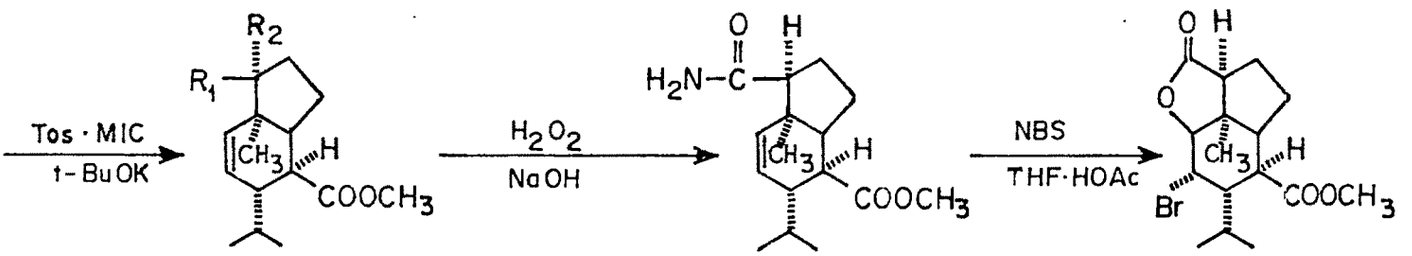


58 59 60

— contd p 24 →

mixture which was mainly 55 (trans, trans, trans). Cyclization of this by refluxing a 0.2M toluene solution of the corresponding trimethylsilyl ether for 85 hrs afforded perhydroindanols, after acid hydrolysis which was mainly 56a and 56b. Treatment of either 56a or 56b with sodium methoxide in methanol resulted in partial epimerization of the C-4 carbomethoxy group giving 57a and 57b. Oxidation of either 57a or 57b with Swern's reagent afforded an unstable ketone 58 which upon silica gel chromatography isomerized to 59. Angular methylation of the ketone 59 afforded a single alkylation product 60. Reductive cyanation of ketone 60 gave a mixture of nitriles 61a and 61b in which the latter was the minor component. Hydrolysis of the nitrile 61a afforded an amide 62 which was oxidized with N-bromosuccinimide to the bromolactone 63. Reduction of the lactone 63 with zinc in refluxing acetic acid and subsequent treatment of the acid 64 obtained, with oxalyl chloride and then lithium tri-t-butoxyaluminium hydride gave the alcohol 65. Mesylation of 65 followed by displacement with methylamine provided the amine 66. Treatment of the amine 66 with trichloroethyl chloroformate and pyridine afforded an urethane which was epoxidized to give 67a and 67b. Deprotection of 67a occurred with concommitant epoxy ring opening to afford the alcohol 68. Oxidation of the alcohol 68

SCHEME-1·4 (contd)

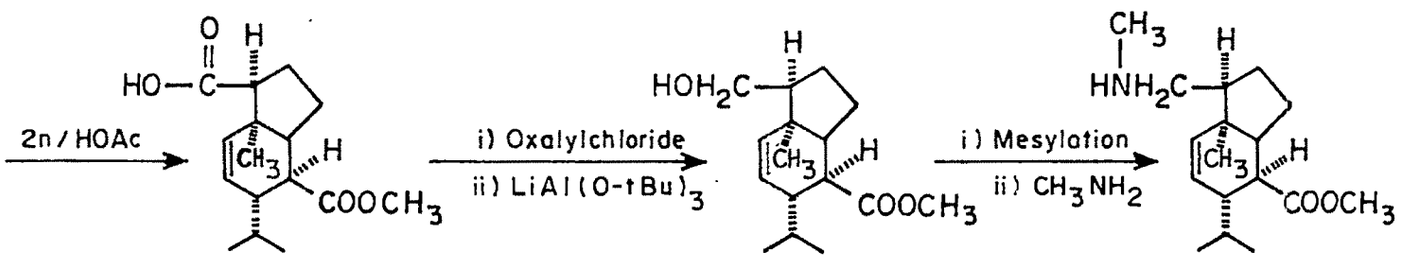


61 b $R_1 = H$, $R_2 = CN$

61 a $R_1 = CN$, $R_2 = H$

62

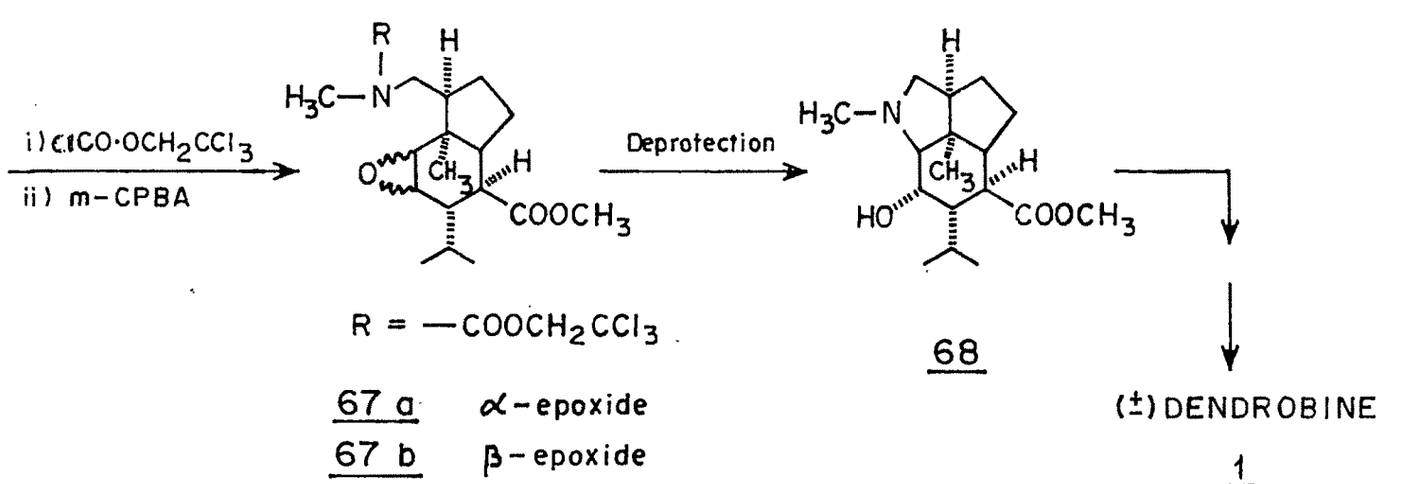
63



64

65

66



R = $-COOCH_2CCl_3$

67 a α-epoxide

67 b β-epoxide

68

(±) DENDROBINE

1

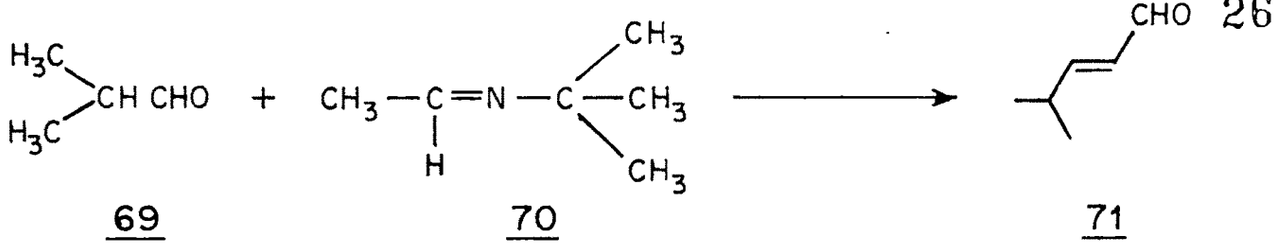
with excess of Jones' reagent at 0° gave a ketone, which on sodium borohydride reduction followed by silica gel chromatography gave (±)-dendrobine 1.

In the above synthesis the intramolecularity of the Diels-Alder reaction gave a high degree of stereoselectivity but again requiring isomerization of carbomethoxy group (56 to 57), which occurs inefficiently. Further, nonselective epoxidation of 66 to 67 resulted in a large amount of unwanted β-epoxide 67b.

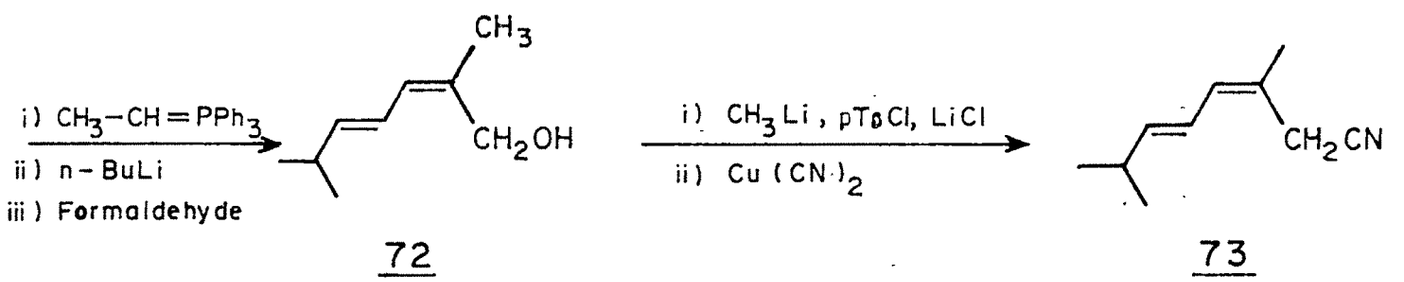
An attempted synthesis of dendrobine by Borch et al.[14] via intramolecular Diels-Alder cyclization led to 6-epidendrobine 80. Inversion of stereochemistry at C-6 is believed to occur as a consequence of diene isomerization under Diels-Alder conditions (Schème 1.5).

The directed aldol condensation of isobutyraldehyde 69 and ethylidine-t-butylamine 70 produced the trans aldehyde 71. This was treated with ethylidenetriphenylphosphine at -78° followed by gaseous formaldehyde to give mainly 72 in 32% yield along with isomeric alcohols. The alcohol 72 was treated sequentially with methyllithium, p-TSCl and lithium chloride to give a chloride. The crude chloride on treatment with lithium iodide and cuprous cyanide afforded the nitrile 73. Alkylation of nitrile 73

SCHEME 1·5.

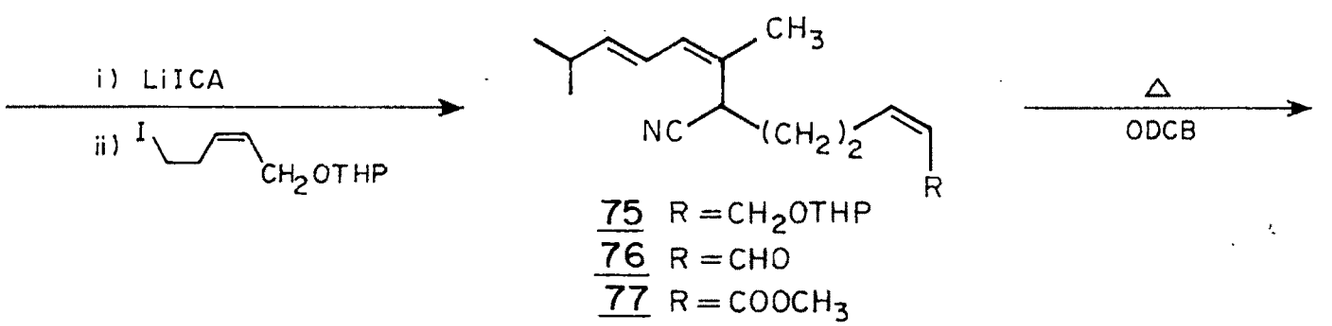


69 + 70 → 71



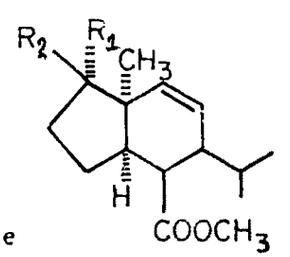
i) $CH_3-CH=PPh_3$ ii) n-BuLi iii) Formaldehyde → 72

i) CH_3Li, pTsCl, LiCl ii) $Cu(CN)_2$ → 73



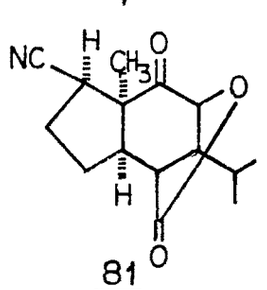
i) LiICA ii) $I-CH_2OTHP$ → 75 R = CH_2OTHP; 76 R = CHO; 77 R = $COOCH_3$

Δ, ODCB



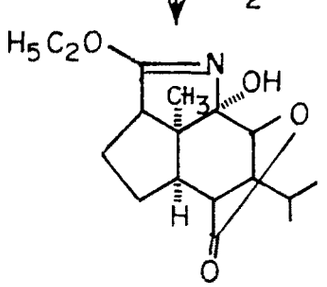
78 a R_1 = H, R_2 = CN
78 b R_1 = CN, R_2 = H
78 c R_1 = H, R_2 = CH_2NHCH_3

i) LiI / Lutidine ii) mCPBA iii) Jones reagent



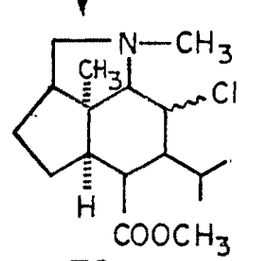
81

$SnCl_2$ / HCl



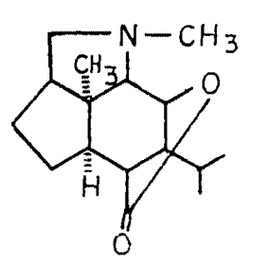
82

$TiCl_3$ / AcOH



79

LiI / Lutidine



80

i) Methylation ii) $NaCNBH_3$

6-epi-Dendrobine

with iodide 74 (prepared by a four step synthesis from propargyl THP ether) afforded the THP ether 75. Deprotection and oxidation of the THP ether 75 gave the trienealdehyde 76. This was converted to methyl ester 77 by reaction with sodium cyanide, glacial acetic acid and activated manganese dioxide in methanol. The ester 77 on refluxing in o-dichlorobenzene for three days afforded two products 78a and 78b differing in the orientation of the nitrile group. Reaction of 78a with dimethylbromonium hexafluroantimonate in liquid sulfur dioxide followed by addition of methanol and reduction with sodium cyanoborohydride afforded the desired amine 78c. When a solution of 78c in aqueous acetic acid was reacted with excess of titanium trichloride a crude chloroamine, presumed to be 79, was obtained. This was treated with lithium iodide in refluxing lutidine to give 80.

The relative stereochemistries of 80 and dendrobine 1 were established as identical at all asymmetric centers except at C-6 bearing the isopropyl group.

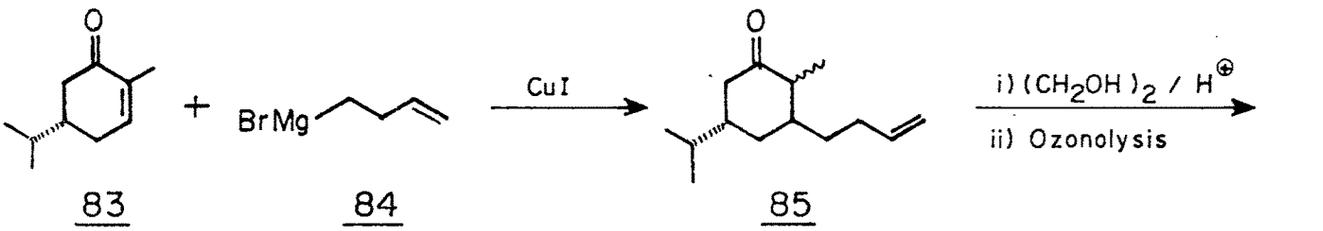
6-epi-Dendrobine has also been synthesised by the following reaction sequence from the same intermediate 78a. Conversion of the ester 78a (Scheme 1.5) to the corresponding acid (lithium iodide in refluxing lutidine) followed by reaction with m-chlorobenzoic acid afforded the hydroxy-

lactone which on Jones' oxidation gave the ketolactone 81. When the ketolactone 81 was subjected to the Stephen reduction ($SnCl_2$-HCl-ether/ethanol) the carbinolamine was obtained.[2] Methylation of amine 82 82/with methyl fluorosulfonate in chloroform gave iminium salt which on reduction with sodium cyanoborohydride in acidic methanol gave 6-epi-dendrobine 80.

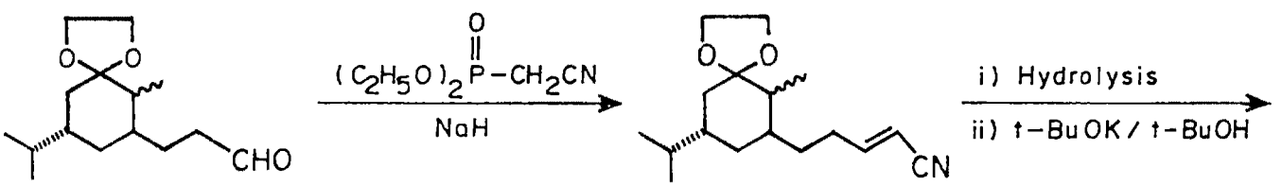
In this reaction sequence at one stage the unwanted nitrile isomer 78b (along with 78a) is formed in equal amounts just to be discarded. The conformation required for the Diels-Alder cyclization of the triene 77 does not give opportunity for any secondary orbital overlap between the carbomethoxy group and the diene system. Hence, reaction takes place only at high temperature (170°), which results in initial isomerization of methyl bearing double bond from Z to E. This isomerization allows the abovesaid secondary overlap but with the unfortunate wrong orientation of the isopropyl group and results in the exclusive formation of 6-epi-dendrobine 80.

Another synthetic approach for the dendrobine framework based on an intramolecular Michael cyclization was studied by Heathcock and Brattesani[15] (scheme 1.6). Intramolecular Michael cyclization of the unsaturated ketonitrile 87 yields only one stereoisomer 88. Addition of 4-butenylmagnesium bromide 84 onto (+)-carvotanacetone 83 gave the

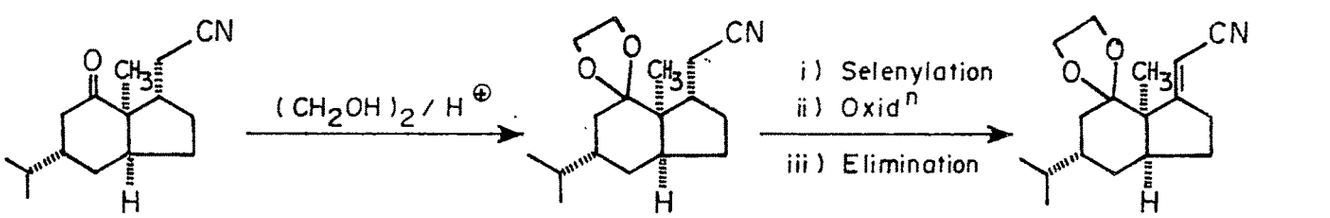
SCHEME 1·6 .



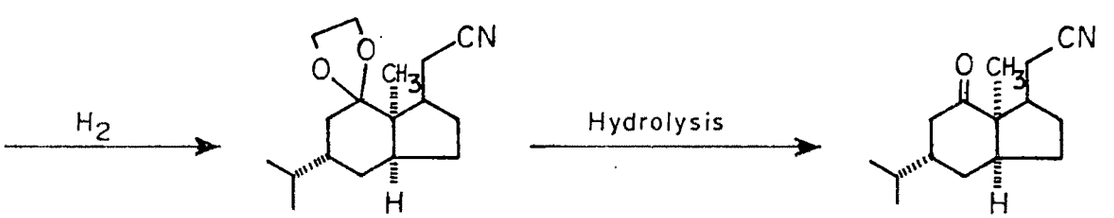
83 84 85



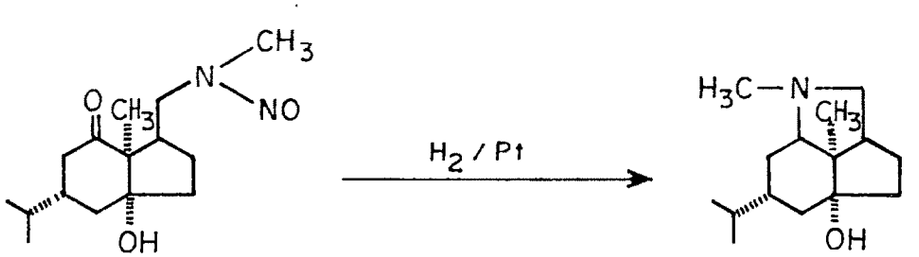
86 87



88 89 90



91 92



93 94

N—Nitroso—6—hydroxy nornobilonine Dendramine

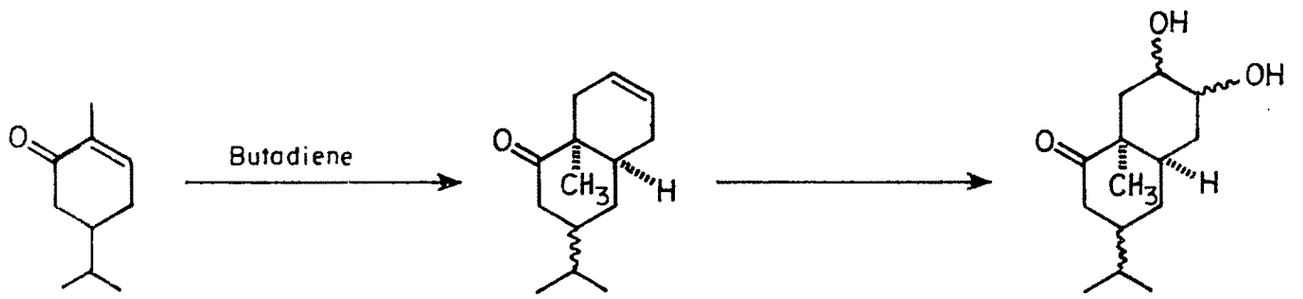
conjugate addition product 85. The ketal of the adduct 85 on ozonolysis gave the aldehyde 86. Condensation of the aldehyde 86 with diethyl cyanomethylphosphonate gave the unsaturated ketonitrile 87. Hydrolysis of the latter gave the corresponding ketonitrile, which on treatment with potassium t-butoxide in t-butanol gave the hydrindanone 88. The ketonitrile 88, however, failed to cyclize. This failure must be due to the cis orientation of the cyanomethyl sidechain and the angular methyl group. For a similar compound having trans stereochemistry of angular methyl group and side chain has been cyclized. Thus, N-nitroso-6-hydroxynornobilonine 93 was cyclised to dendramine 94 by treatment with hydrogen at atmospheric pressure over Adam's catalyst. The epimerization of the ketonitrile 88 to the ketonitrile 92 was achieved by a six step sequence involving ketalization, selenylation, oxidation of the selenide to selenoxide, elimination of selenoxide, catalytic hydrogenation of the double bond obtained and deketalization. However, further elaboration on this intermediate 92 was not studied by the authors.

A synthesis of dendrobine skeleton has been reported by Yamamoto et al.[16] (scheme 1.7). Carvotanacetone 95 was condensed with butadiene in presence of aluminium chloride to afford the adduct 96. The adduct 96 was then

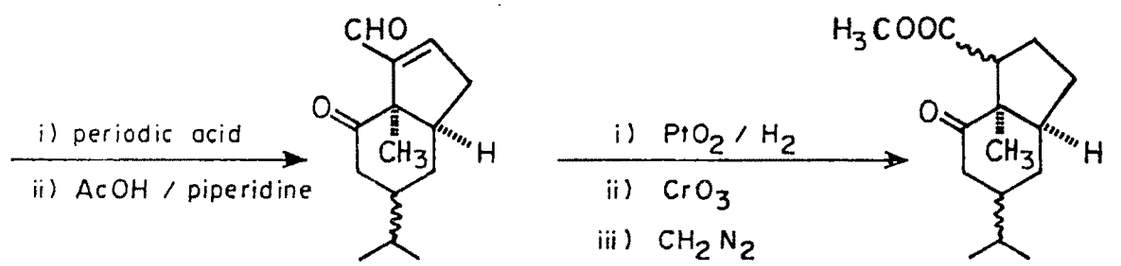
converted to the cis diol 97. Cleavage of the diol 97 with periodic acid in tetrahydrofuran-water solution at room temperature and subsequent treatment with acetic acid and piperidine in benzene solution afforded α-β-unsaturated aldehyde 98. The aldehyde 98 was hydrogenated in the presence of platinum oxide in ethanol at room temperature. The reduction products were oxidised with chromium trioxide in acetic acid and esterified with diazomethane to give the stereoisomeric mixture of ketoesters 99. The cis isomer (substituent at C-1 and C-8) was isomerised to trans isomer by treatment with sodium in boiling methanol. The trans isomer 99 was ketalised with ethyleneglycol using p-TSA and ethyl orthoformate as a catalyst to give 100. Treatment of ketalester 100 with 30% methylamine in ethanol solution at 100° gave the crude amide 101. Reduction of the amide 101 with lithium aluminium hydride in tetrahydrofuran and subsequent treatment with dilute hydrochloric acid gave the aminoketone 102. The hydrogenolysis of the compound 102 in the presence of platinum oxide in ethanol at 200° under 50 atm. pressure afforded an isomeric mixture of 103.

From the foregoing review it appears that cis-hydrindan derivatives are often the key intermediates in the total synthesis of dendrobine. But, invariably, there

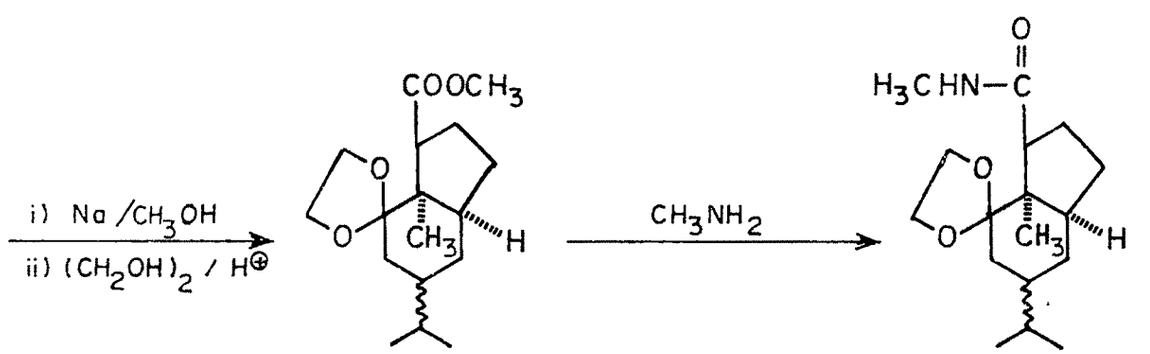
SCHEME 1·7



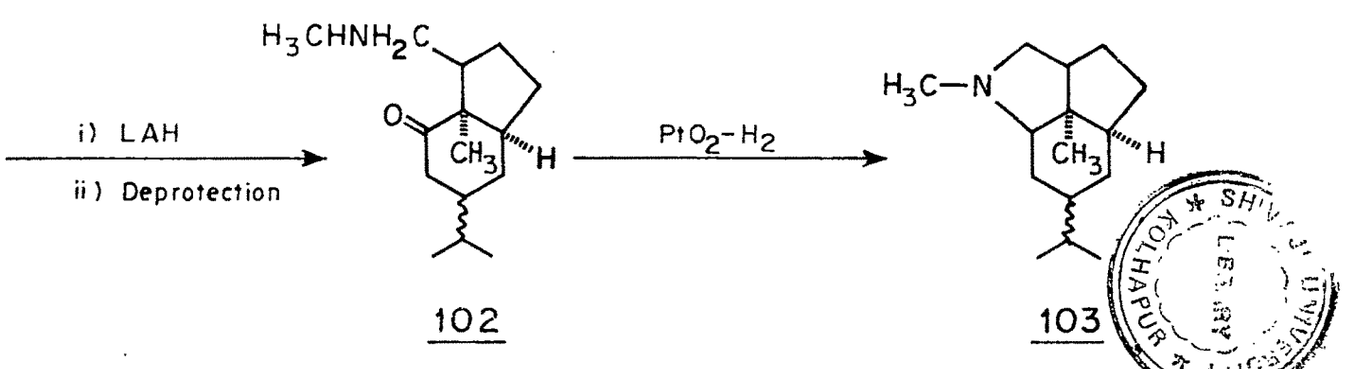
95 96 97



98 99



100 101



102 103

is not enough stereochemical control in many cases during further elaboration of the framework. In the cases where the Diels-Alder reaction are used, complete stereospecificity of more than two stereocenters is not achieved. Even in cases where intramolecular Diels-Alder reaction are employed, the reaction sequences are quite long because of the need of correction of the orientation of groups on asymmetric centers appearing on further elaboration of the framework. Hence, it was decided to plan a strategy using cycloaddition reaction for the synthesis of dendrobine which would involve maximum stereochemical control and minimum number of steps. This strategy in principle should be adaptable for the synthesis of other alkaloids also.

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CHAPTER II

INTRAMOLECULAR DIELS-ALDER ADDITIONS OF N-ALKENYL PYRIDONES AS AN APPROACH FOR THE SYNTHESIS OF DENDROBINE SKELETON

INTRAMOLECULAR CYCLOADDITION OF N-ALKENYL PYRIDONES

2.1 General Introduction

Diels-Alder cycloaddition reaction is one of the most important reactions used in organic synthesis. This reaction consists of thermally induced addition of 1,3-dienes to multiple bonds leading to a six-membered ring with the simultaneous formation of two σ bonds, via a highly ordered aromatic transition state. The great preparative importance of this reaction is shown by a multitude of fascinating applications to the synthesis of complex molecules[1].

From investigations carried out in recent years it follows that the synthetic potential of such cycloadditions is decisively increased by the principle of intramolecularity, compared to the corresponding bimolecular reactions. These intramolecular reactions take place under considerably milder conditions than those required for the analogous bimolecular reactions. The entropic assistance for these reactions is quite considerable and free activation energies in some cases are less by 5 to 7 Kcal/mol than those for the corresponding intermolecular (4 + 2) additions[2]. For the same reason not only unactivated dienophiles (e.g. isolated olefins, oxime ethers and nitriles) but also unreactive (e.g. cis-substituted) 1,3-dienes undergo smooth intramolecular /

additions[3].

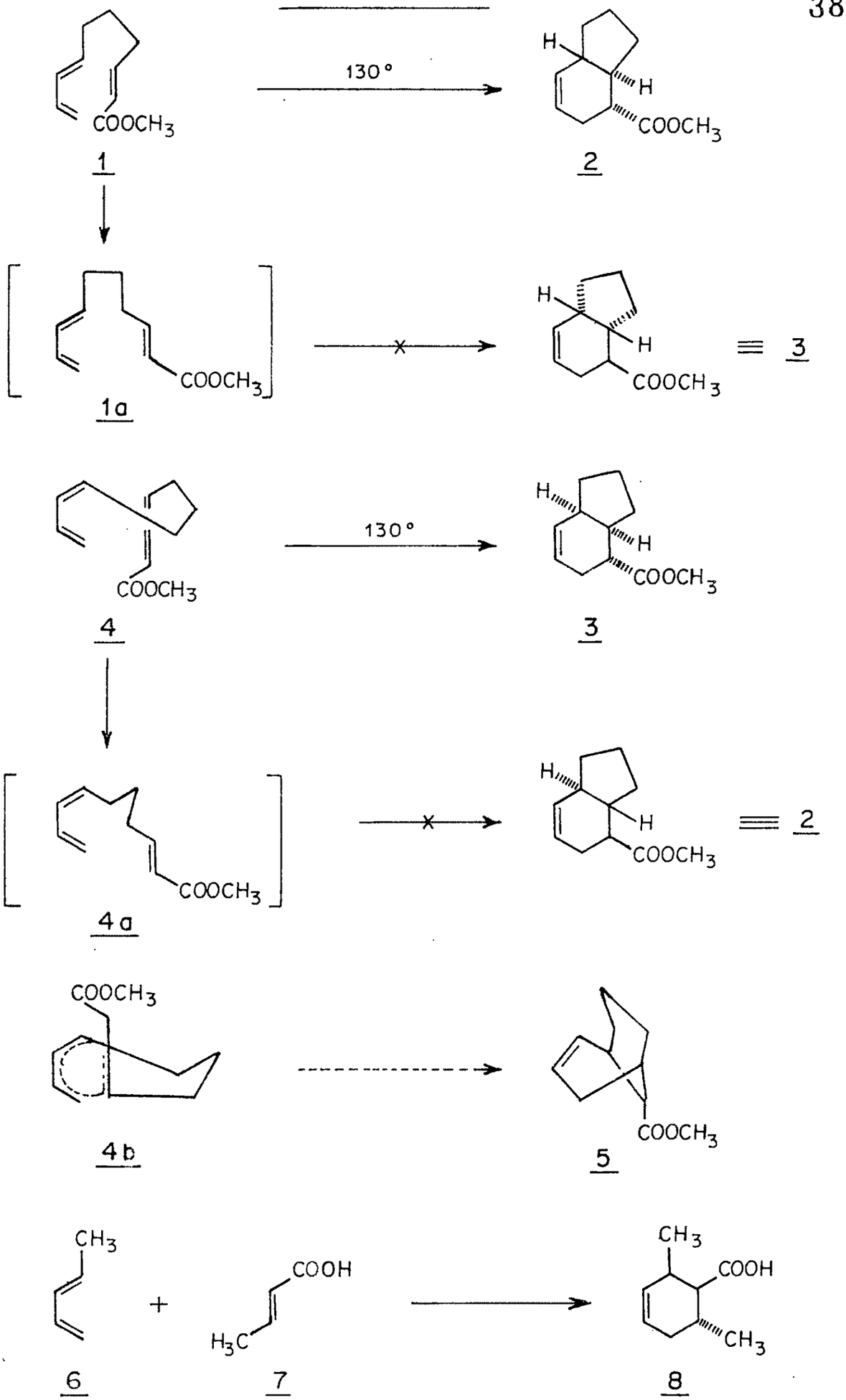
Bimolecular

Intramolecular

For example when 1 is heated to 130° the trans diene unit adds smoothly to the double bond of the acrylic ester linked to the diene by a bridge of three carbon atoms leading to the trans annelated hydrindane derivative 2 (Scheme2.1)[4]. Surprisingly, under the same conditions the cis annelated diene 4 reacts in a similar manner, but with exclusive formation of the cis annelated product 3. In view of the fact that cis substituted open chain 1,3-dienes usually undergo bimolecular Diels-Alder reactions only with difficulty, it shows that the reaction 4 → 3 profits from entropy factors due to spatial proximity of the reaction partners.

Intramolecular [4 + 2] addition is influenced by factors promoting the formation of annelated products. The reaction of the cis diene 4 gave no trace of bridged positional isomer 5. In fact the intramolecular reactions 1 → 2 and 3 → 4 takes place in opposite direction to that strongly favoured in the bimolecular reactions 6 + 7 → 8 [5] leading exclusively to annelated structures. Models show that the

SCHEME 2·1.



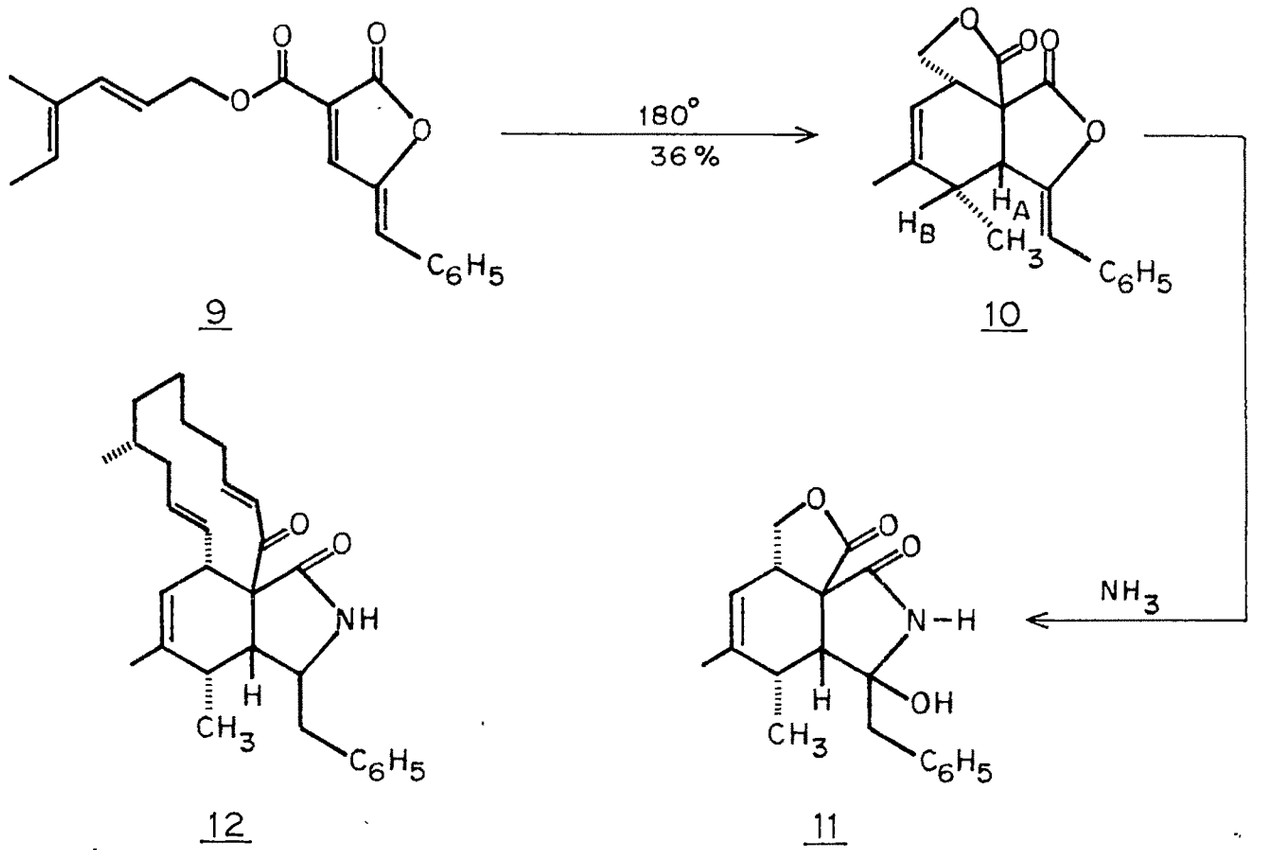
formation of the bridged adduct 5 from 1 is blocked by strain, whereas the formation of transition state 4b from 4 does not require any deformation of bond angles. Still the formation of 5 on thermolysis of 4 is not observed and hence this may be due to other causes, presumably the (entropically favoured) easier closure of a five-membered ring than that of a six-membered ring.

In the exclusive formation of 2 from 1 and 3 from 4, the endo position of the ester group in the transition state appears to be decisive. This becomes obvious from examination of the models of 1a and 4a with the ester group exo, in the transition state which would have resulted in the formation of 3 from 1 and 2 from 4.

From the foregoing discussion, it becomes clear that the intramolecularity of the cycloaddition helps in getting faster reaction and preference of getting annelated structures over bridge structures. These features in conjunction with the stereospecificity of the reactions in general cycloaddition reactions make the intramolecular cycloaddition reactions useful in solution of specific structural problems.

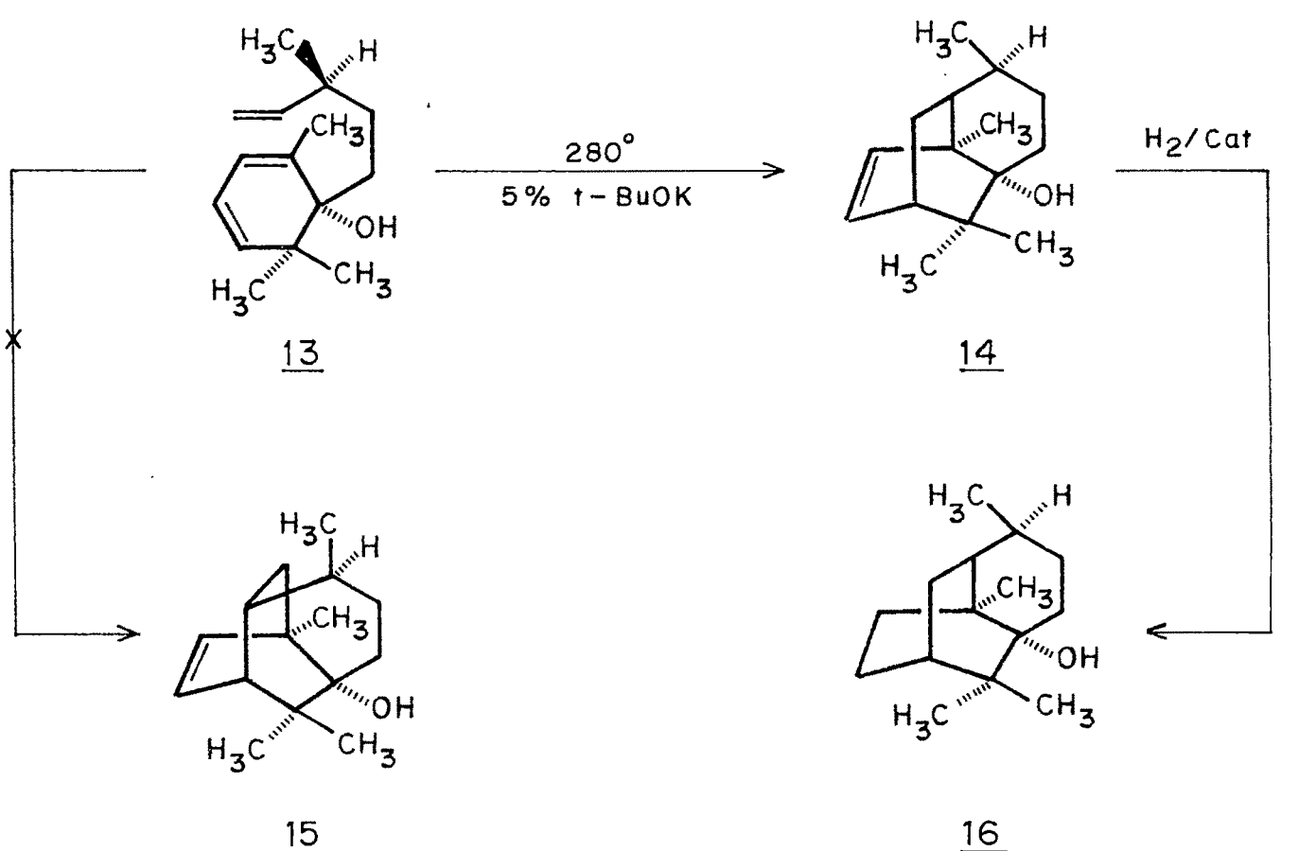
In the thermal conversion of 9 to 10, which was conceived as the key step for the construction of proxiphomine 12[6], a microbial metabolite, the NMR showed (J_{AB} = 7)

SCHEME 2·2



9 10 11 12

SCHEME 2·3



13 14 15 16

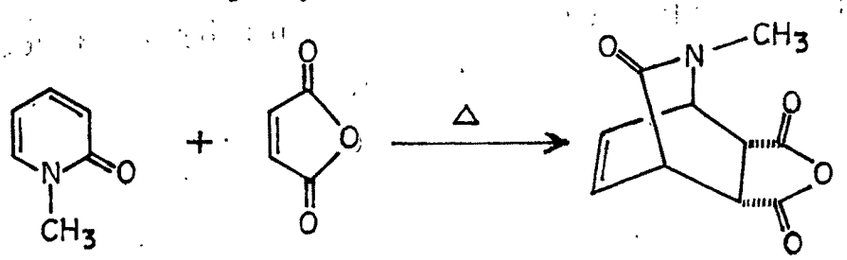
the adduct to be having the correct relative configuration of the natural product 12 with respect to all four chiral centers (Scheme 2.2).

The regioselectivity seen in the earlier reactions 4 → 3, also characterizes the intramolecular cycloaddition 13 → 14 (Scheme 2.3) which provides the complex skeleton 14 (and not 15) of the sesquiterpene patchoulol in a single step[7]. The racemic natural product 16 is obtained by simple hydrogenation of the adduct 14. In comparison with several multistage synthesis of patchoulol[8], this reaction sequence demonstrates the effectiveness of intramolecular cycloadditions.

2.2 Cycloaddition of pyridones

2.2.1 Introduction

N-alkyl pyridones are also diene systems capable of cycloadditions with dienophiles. N-Methyl 2-(1H)pyridone 17 reacts with maleic anhydride 18 to give a cycloadduct 19 on refluxing toluene for 72 hrs[9]. Similar reactions are also seen when N-phenyl maleimide is used[10].

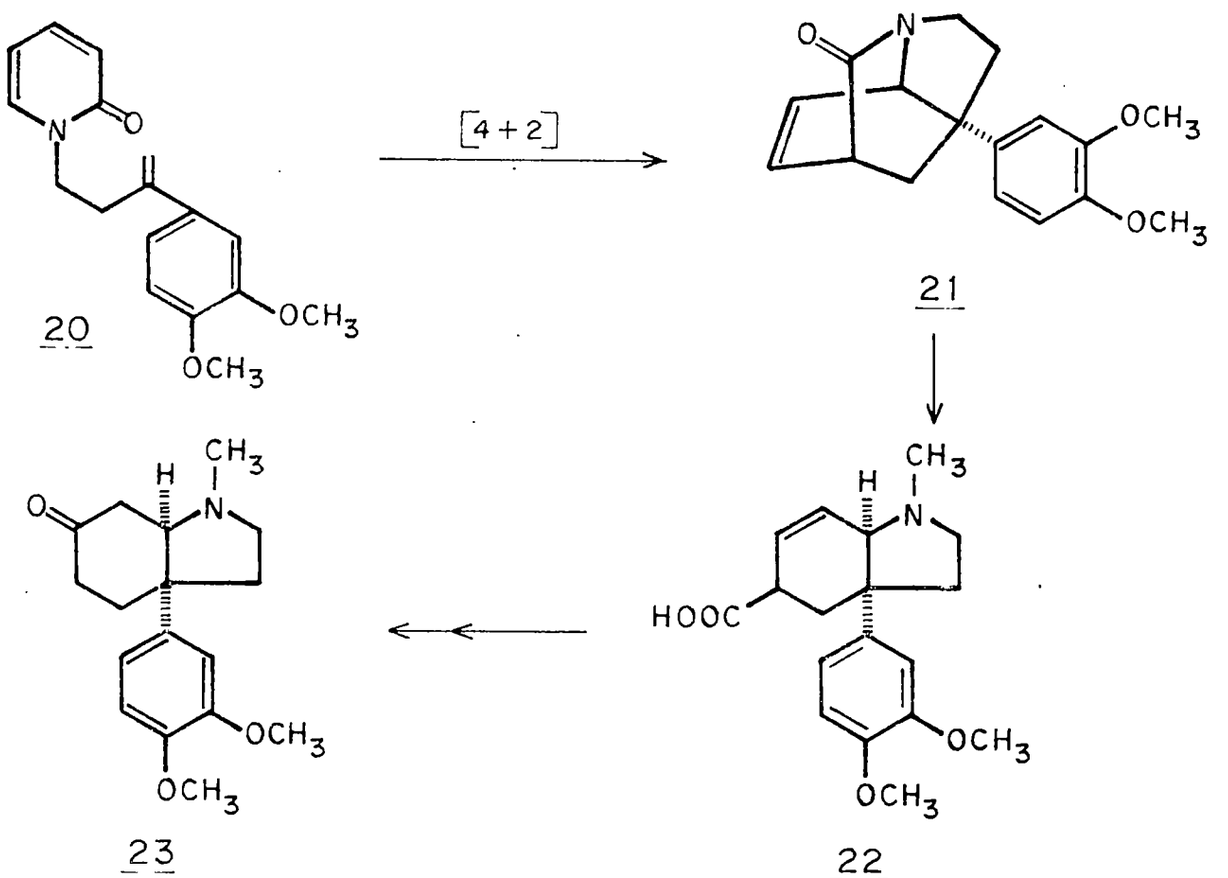


17 18 19

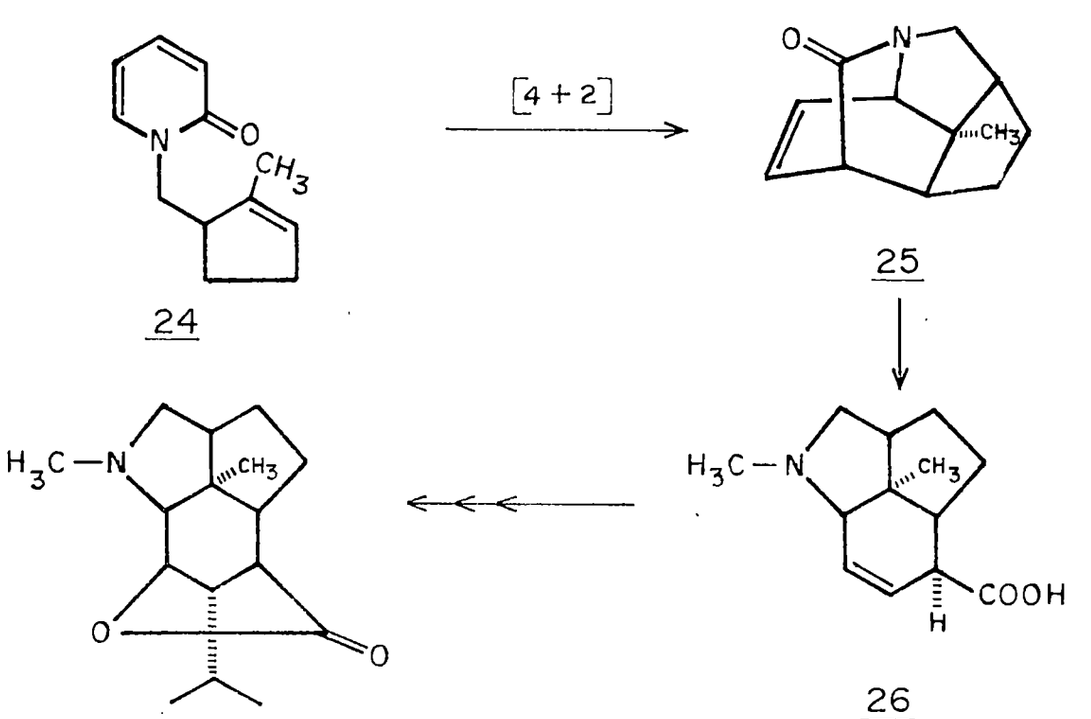
Adduct

However these reactions are carried out under fairly drastic conditions even when the dienophile is reactive one, revealing the poor diene reactivity of N-alkyl pyridones. Other reactions reported, where N-alkylpyridone is a diene partner, are reactions with benzyne[11] and N-phenyl triazolinedione[12]. The poor reactivity of N-alkyl pyridones may be attributed to the fact that the diene system in N-alkyl pyridone is conjugated with amide carbonyl group, so the electron availability on diene is less. Since intramolecular addition takes place even between unactivated dienophiles and unreactive 1,3-dienes, we wanted to see whether N-alkyl

SCHEME 2·4



SCHEME 2·5

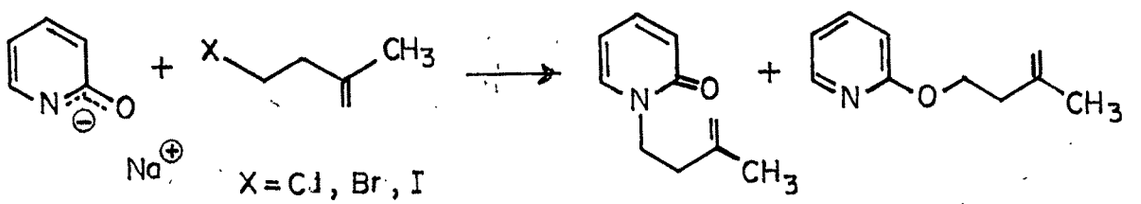


pyridones can undergo cycloaddition under intramolecular situations. A proper N-alkyl group containing the dienophile was thought to be capable of undergoing intramolecular cycloadditions. This would pave the way for the synthesis of many complex natural products like mesembrine 23, dendrobine 27 etc. For example the cycloaddition of 20 and 24 would give key intermediates which could be further elaborated easily into alkaloids (Scheme 2.4 and 2.5).

2.2.2 Present Work

To study the above intramolecular reactions we chose a pyridone 30 with an N-alkenyl group as a model compound. N-Alkyl pyridones can be obtained from several methods i.e. N-Alkylation of 2(1H)-pyridone[13], quaternisation of pyridine with alkyl halide and subsequent oxidation with ferricyanide[14] or quaternisation of 2-alkoxypyridine with alkyl halide[15].

In the alkylation of 2(1H)-pyridone there is always a competition between N-alkylation and O-alkylation. N-Alkylation can be obtained in maximum yields by a proper choice of cation (K^+, Na^+ or Tl^+) and solvent (DMF, MeOH). Solvent has the larger effect on silversalt alkylation where alkoxy pyridine formation is favoured in poor ionsolvating media.

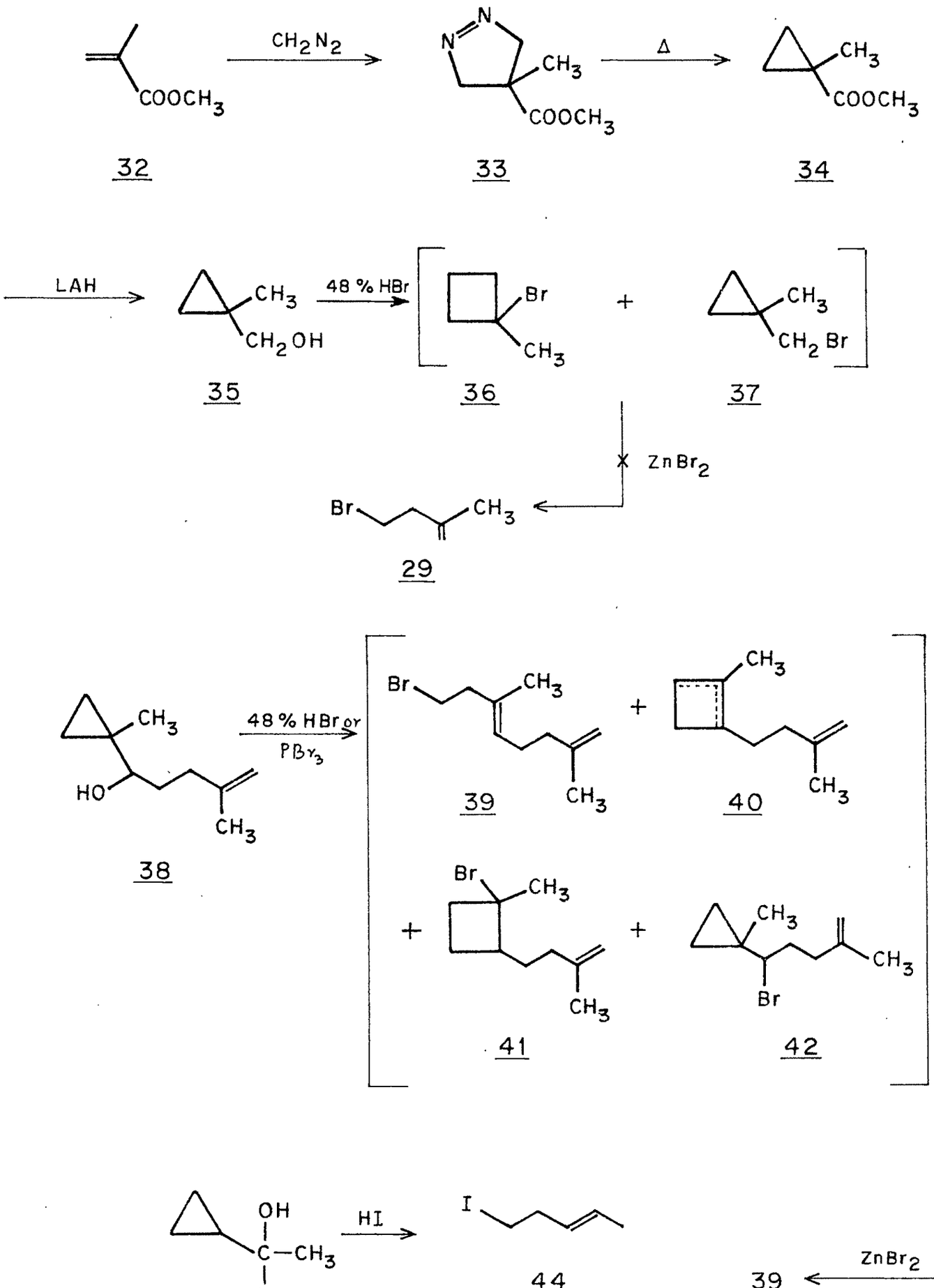


28 29 30 31

In the case of sodium salts of pyridones, reaction in DME gives maximum N-alkylation. For the synthesis of the model pyridone 30 the alkenyl halide 29 is required. For the synthesis of homoallylhalide 29 we followed Julia's[16] method, which involves the use of cyclopropyl alkyl carbinols. Cyclopropyl carbinols on treatment with 48% HBr give homoallylbromide. For bromide 29 the cyclopropylcarbinol required was synthesised by the following scheme (Scheme 2.6).

Addition of diazomethane on methyl methyacrylate 32 and subsequent thermolysis of the adduct gave the ester 34[17]. Lithium aluminium hydride reduction of the ester 34 gave the carbinol 35[18]. Treatment of the carbinol 35 under Julia's conditions failed to give the homoallyl bromide 29 inspite of variations in temperature, solvent and HBr quantity. This reaction gave only mixtures of bromides 36 and 37 from spectral evidences. In the cases where such mixtures are expected to result on rearrangement, further treatment with $ZnBr_2$ converts them into homoallyl halide[19]. For example it is known that treatment of carbinol 38 with PBr_3/collidine

SCHEME 2.6



32 33 34 35 36 37 29 38 39 40 41 42 43 44

at 0° afforded a mixture of bromides 39, 40, 41 and 42 (Scheme 2.5). This bromide mixture on further treatment with $ZnBr_2$ gave exclusively the homoallyl bromide 39. However, the mixture of bromides 36 and 37 did not equilibrate to homoallyl bromide 29 in the present case.

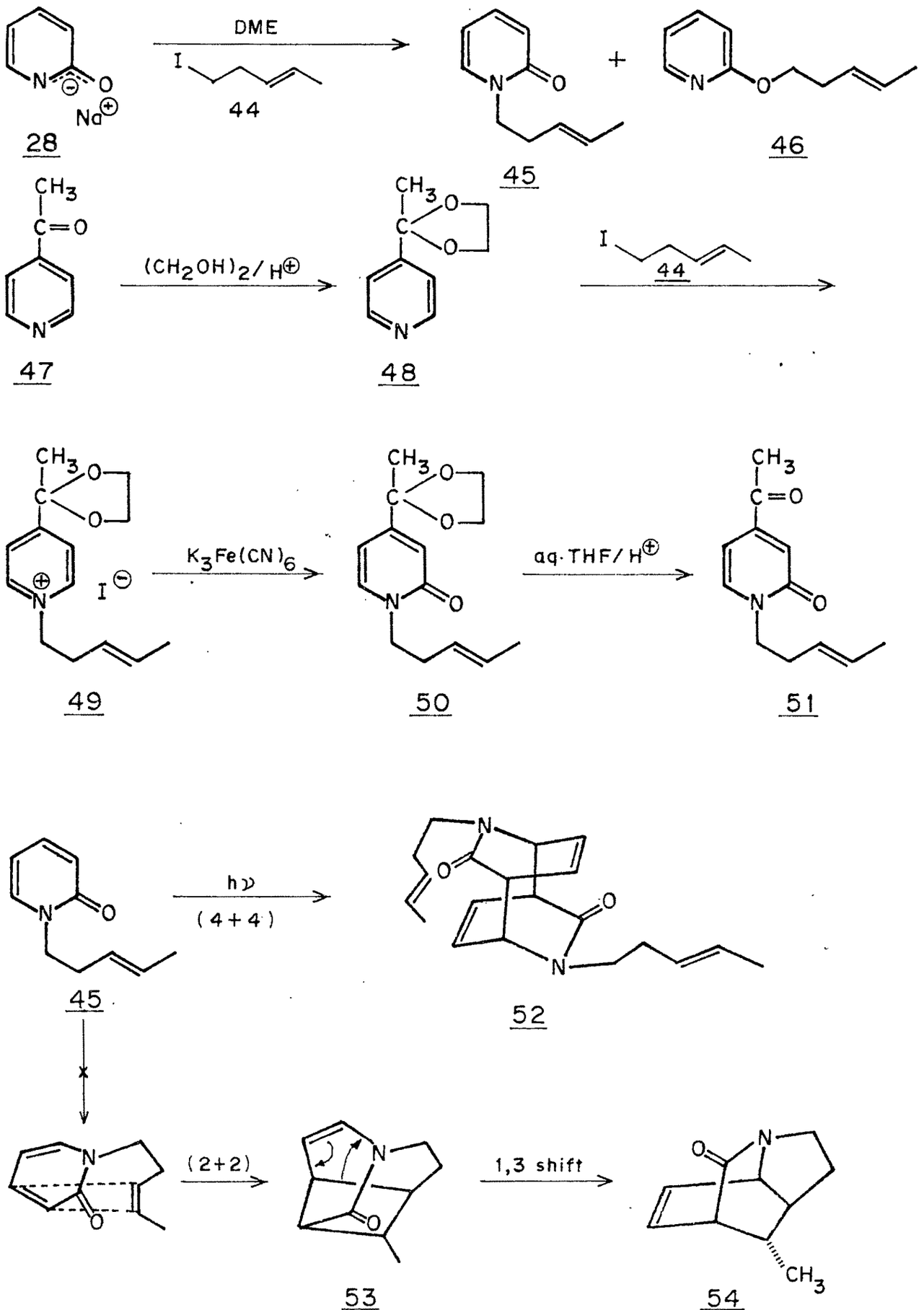
But the alkenyl halide 44 could be easily made from methyl cyclopropyl carbinol 43 and hydroiodic acid (cf. Ref.20) and this was used in the alkylation.

Alkylation of 2(1H)-pyridone was done by treating the sodium salt of 2(1H)-pyridone 28 (prepared from 2(1H)-pyridone and sodium methoxide) with 44 in DME. The mixture of N- and O-alkylpyridones (84:16) was resolved by chromatography on silica gel (Scheme 2.7).

The pyridone 45 was subjected to thermolysis to effect (4 + 2) cycloaddition. A 10% solution of pyridone in different solvents i.e. xylene, ODCB and diphenyl ether failed to give any reaction. The use of Lewis acids also was without success. Heating the pyridone 45 with catalytic amount of hydroquinone at 250° - 300° for 1-2 hrs produced no change. But, on longer heating polymerization took place.

The poor reactivity of pyridone may be attributed to the dienamide structure. To see whether the introduction of an acetyl group at four position in pyridone helps in

SCHEME 2·7


DME
44
28
45
46
$(CH_2OH)_2/H^{\oplus}$
47
48
$K_3Fe(CN)_6$
aq·THF/$H^{\oplus}$
49
50
51
hν
(4+4)
52
(2+2)
1,3 shift
53
54

the cycloaddition, we took up the synthesis of N-(3'-pentenyl) 4-acetyl-2(1H)-pyridone 51.

This pyridone was synthesised from 4-acetylpyridine. Ethylene-dioxy ketal 48 of 4-acetyl pyridine was prepared from 4-acetyl pyridine and ethylene glycol using pTSA as a catalyst. The quaternary salt 49 was obtained by heating neat mixture of ketal 48 and iodide 44. This salt on oxidation with potassium ferricyanide and subsequent hydrolysis gave pyridone 51 (Scheme 2.7).

This pyridone was subjected to thermolysis in different solvents to effect (4 + 2) cycloaddition without success. Even the use of Lewis acids did not help. This pyridone seems to be too stable to undergo cycloaddition under the conditions tried.

The pyridone 45 was photolysed to see whether it undergoes (2 + 2) intramolecular cycloaddition and then further (1-3) shift to give the required cycloaddition product (Scheme 2.7). But on photolysis the pyridone 45 gave only the intermolecular photo-dimer, which is a (4+4) cycloaddition product 52, as found to be in other N-alkyl derivatives.

To effect the intramolecular cycloaddition of N-alkyl pyridone, we thought that a more reactive dienophile might help. Since electron withdrawing functions like carbomethoxy,

aldehyde or acid chloride increases the dienophilic reactivity of the double bond, we wanted to study reactions of pyridone 57 as a model.

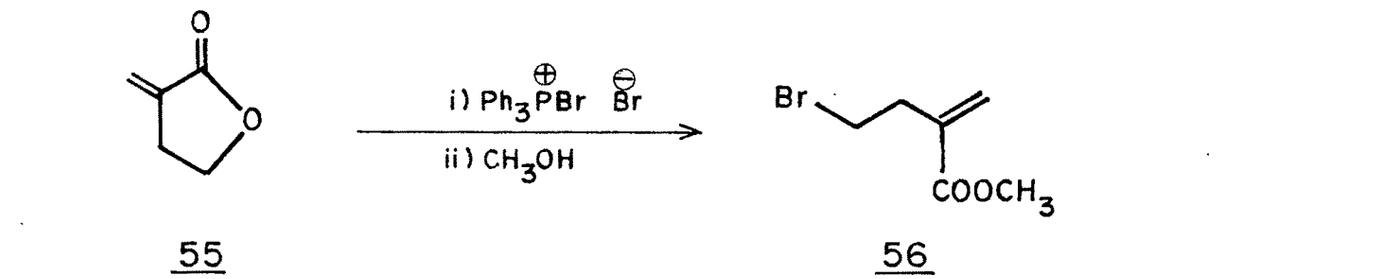
Synthesis of the required alkyl halide 56 was achieved from α-methylene butyrolactone 55. Treatment of lactone 55 by triphenylphosphine dibromide in acetonitrile, followed by methanol gave the bromide 56 in about 30% yield (cf.Ref.21).

Alkylation of 2(1H)-pyridone using bromide 56, however gave the rearranged product 59, although it was found to be an exclusive N-alkylation (Scheme 2.8). This was due to an initial Michael addition followed by ring closure of ester enolate as shown. To circumvent this difficulty we tried an alternative method of N-alkylation.

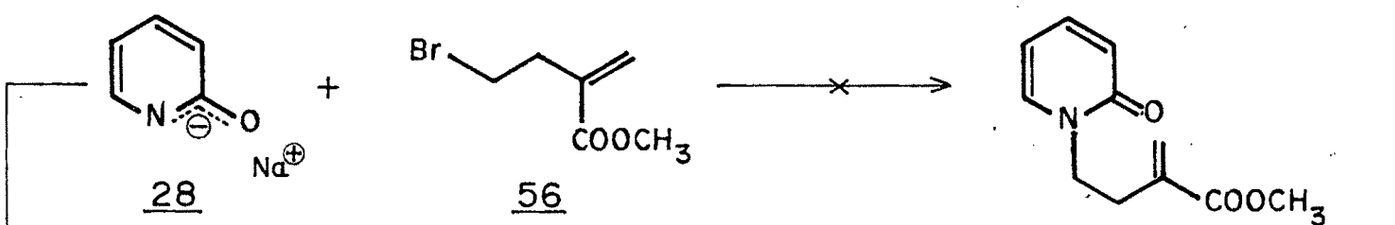
2-Ethoxypyridine (prepared from 2-chloropyridine and sodium ethoxide) was quaternized with bromide 56. The quaternary compound eliminated ethyl bromide readily, forming the required pyridone 57. This pyridone was also subjected to thermolysis with and without Lewis acid catalysis to effect cycloaddition without success. Conversion of carbomethoxy group to acid chloride via acid by triphenylphosphine-carbon-tetrachloride did not help in favouring cycloaddition.

It is reported[22] that the pyridinium salt 63 on reduction with basic sodium borohydride gives the dihydro-

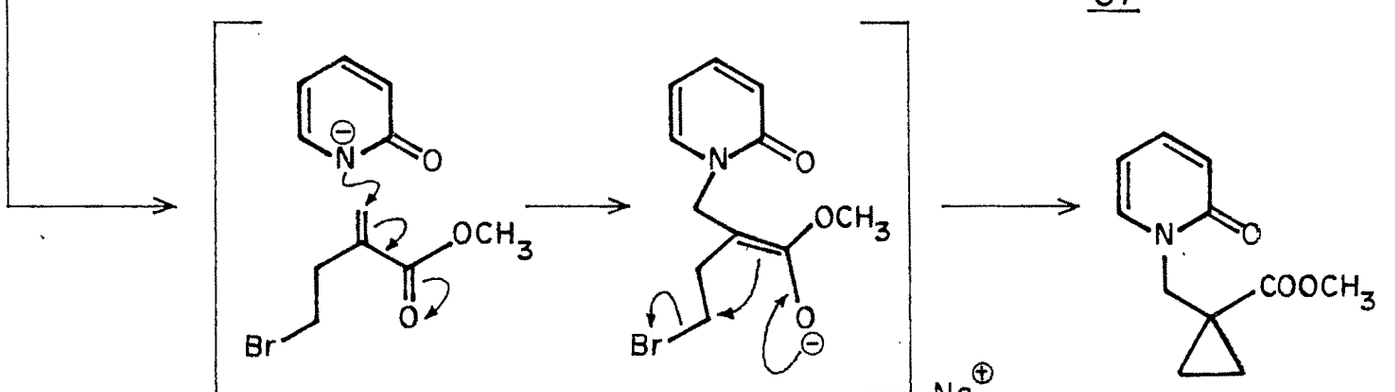
SCHEME 2·8



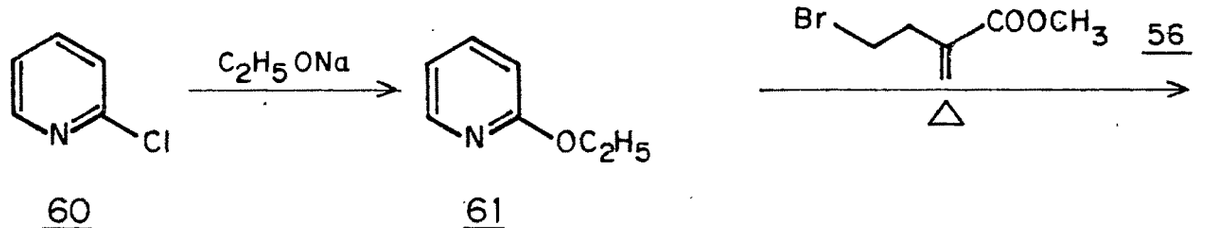
55 56



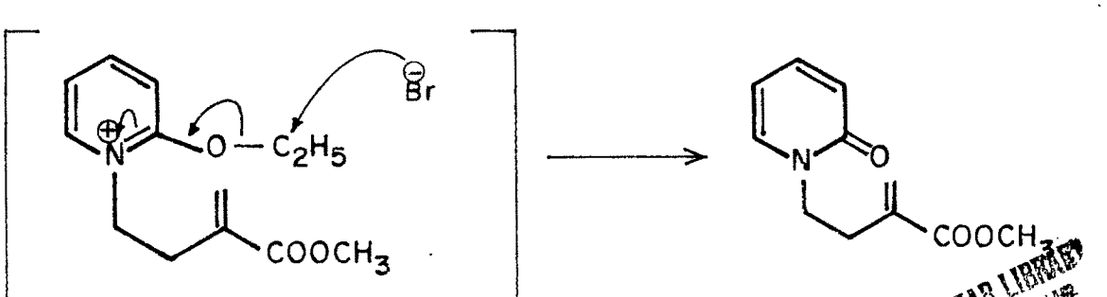
28 56 57



58 59



60 61



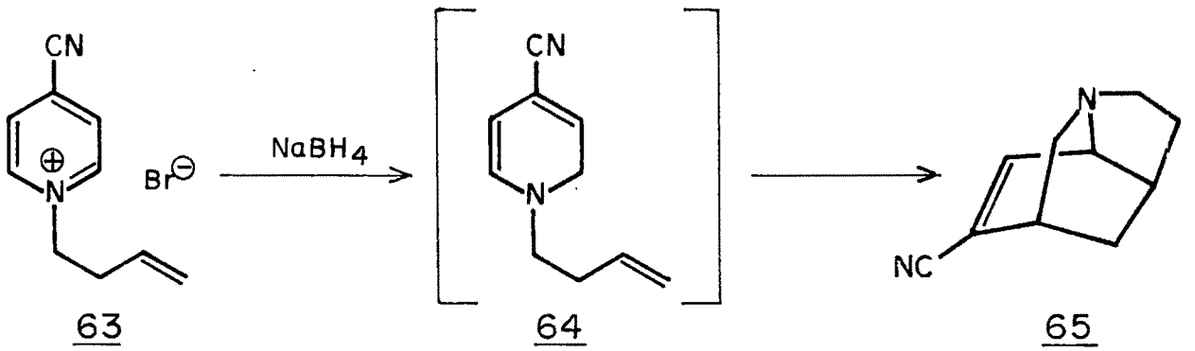
62 57

pyridine 64 which on heating undergoes Diels-Alder reaction to yield the adduct 65 (Scheme 2.9). Since dihydropyridine undergoes Diels-Alder reaction much more easily than pyridones, we prepared 4-acetyl pyridinium salt 66 and reduced the salt with basic sodium borohydride (1 equivalent) at low temperature hoping to get dihydropyridine derivative 67 or its adduct. But the product was a mixture of reduced pyridine derivatives and dihydropyridine 67 could not be isolated.

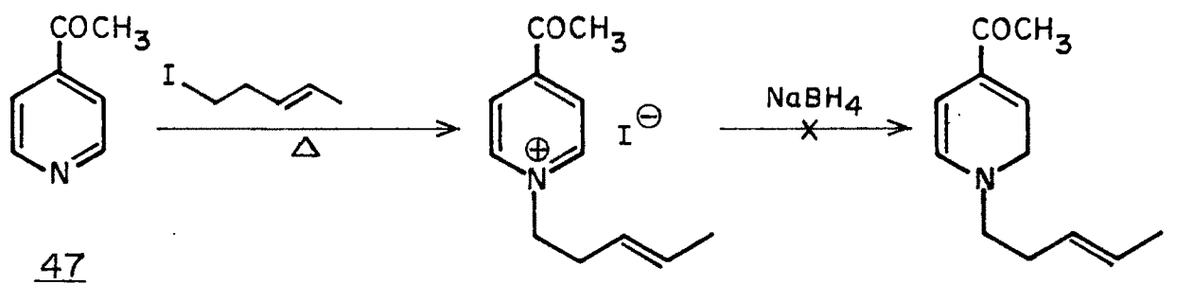
Attempts to make other dihydropyridine derivatives from 2-methoxypyridinium salts were also made. Since N-substituted lactams can be converted to acetals by first treatment with dimethyl sulfate followed by alcohol in presence of triethyl amine[23], a corresponding acetal formation was tried on pyridone 45. Instead of methanol as nucleophile, hydride ($LiAl(OtBu)_3H$) was also used. But the corresponding acetal 70 or aminal 69 was not formed, instead only starting pyridone 45 was recovered. The intermediate 2-methoxypyridinium salt 68 was also obtained by treatment of 45 by Meerwein reagent $(CH_3)_3O^{\oplus}\ BF_4^{\ominus}$. The change of anion also did not help only the pyridone 45 was obtained on subsequent treatment with nucleophiles.

An alternative method of getting lactam acetal was tried based on the reported conversion of chloropyridinium salts to the corresponding acetal with sodium methoxide (Scheme 2.9).

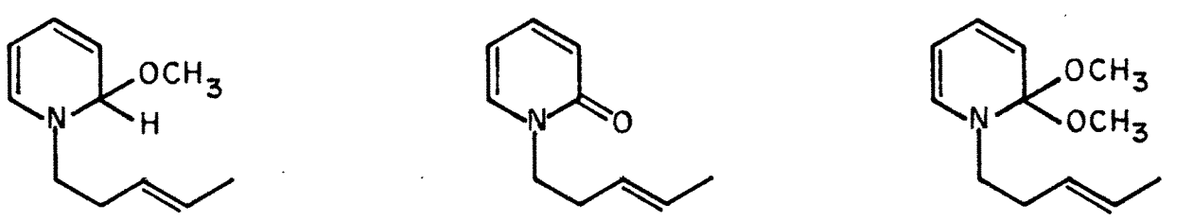
SCHEME 2·9



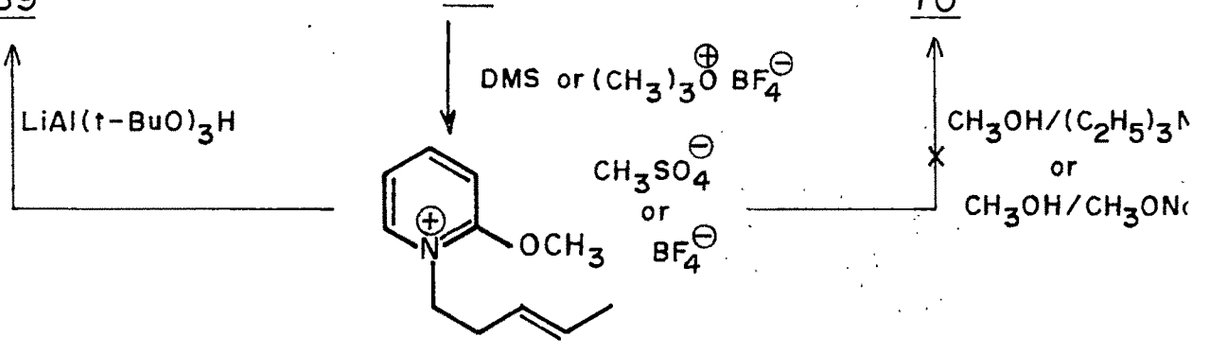
63 64 65



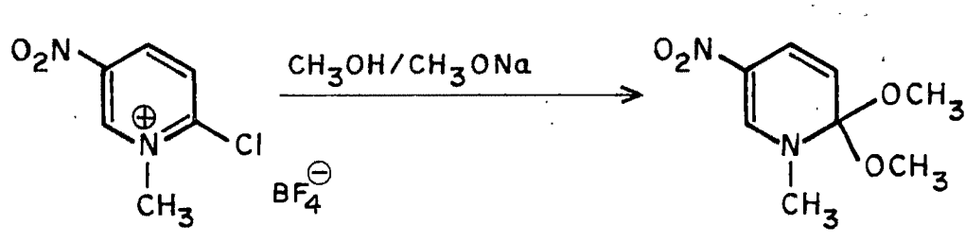
47 66 67



69 45 70



68



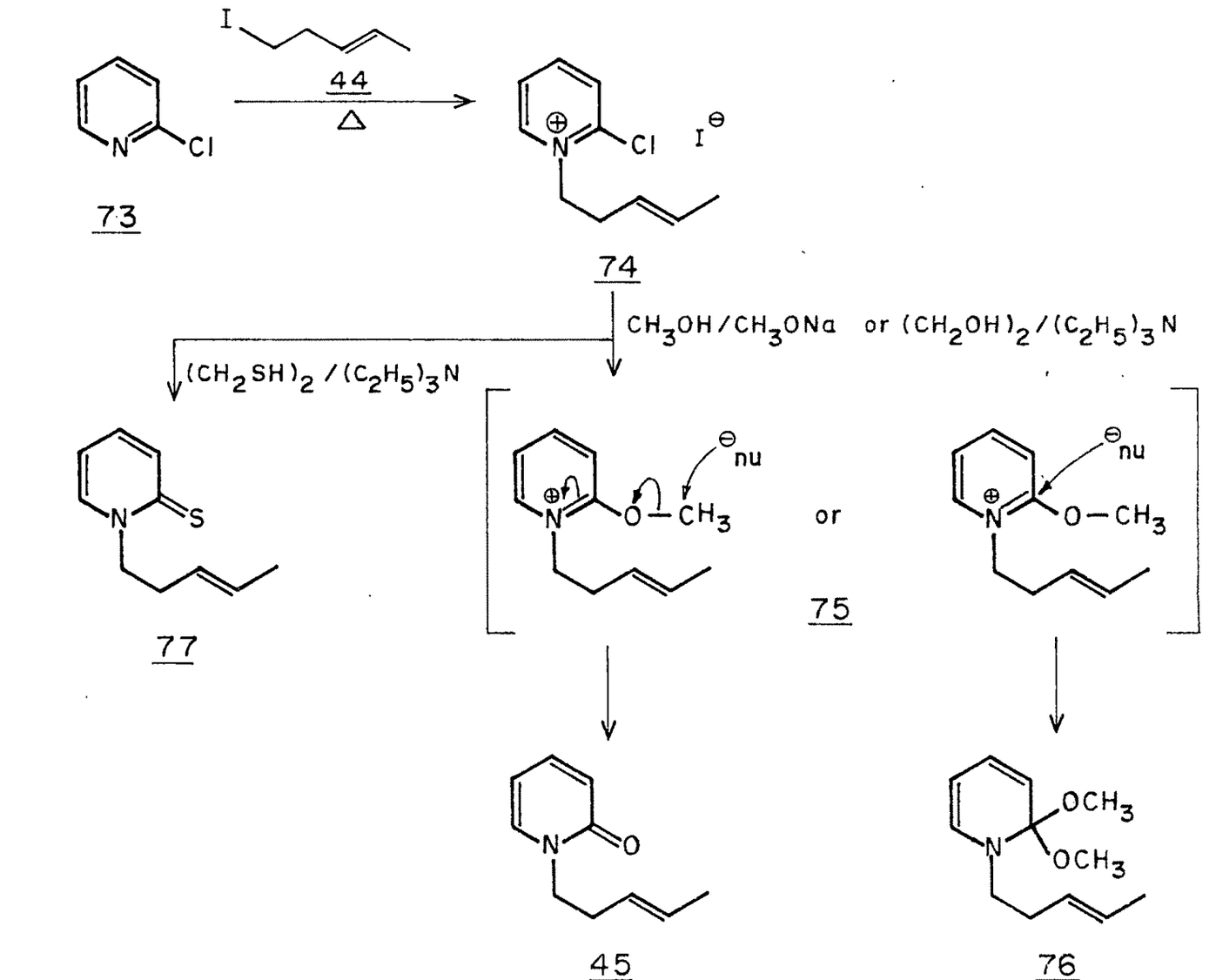
71 72

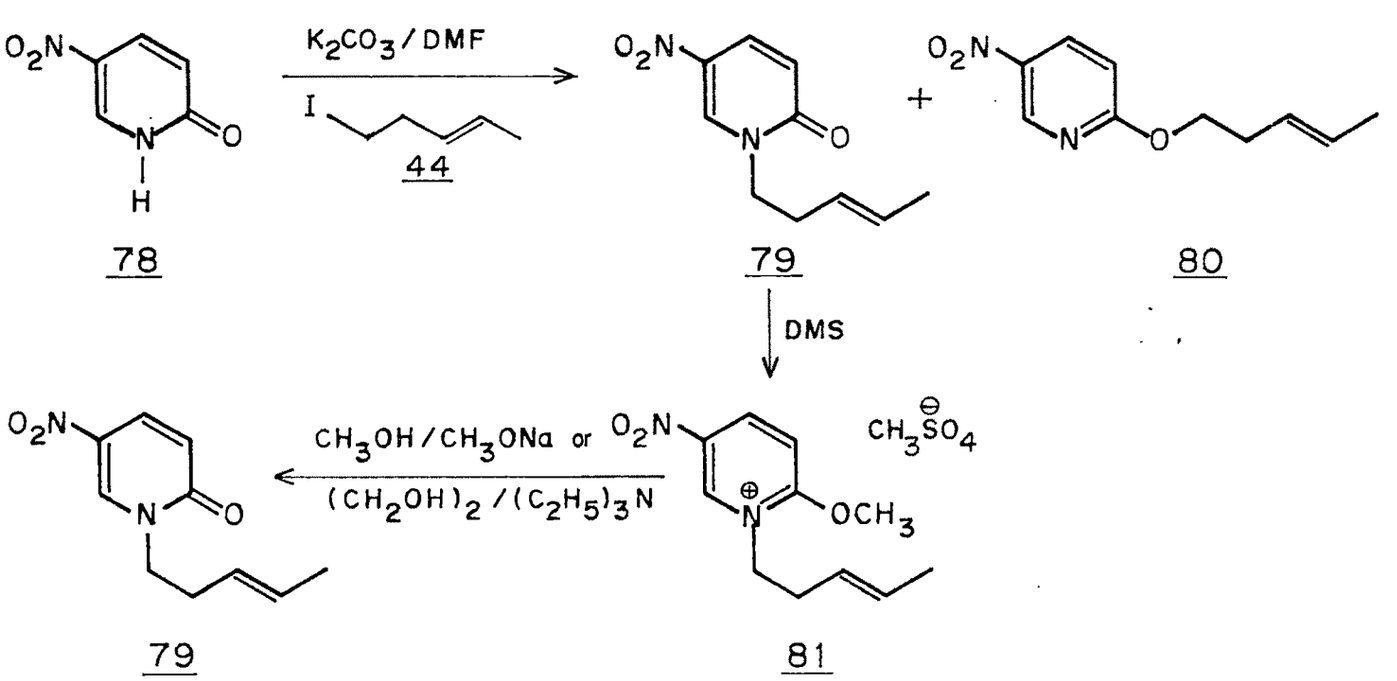
N-Methyl-2-chloro-5-nitropyridinium tetrafluoroborate 71 on treatment with sodium methoxide was reported to give the dimethyl acetal of N-methyl pyridone 72[24]. 2-Chloropyridine was quaternized with iodide 44 and the resulting salt 74 was treated with sodium methoxide in methanol, but the only product isolated was pyridone 45. Quaternization of 4-nitro-2-chloropyridine with iodide 44 was also tried in the hope of subsequent ketalisation but this reaction did not proceed even on heating the neat mixture of nitrochloropyridine and iodide. Use of solvent like DMF resulted in the formation of 2-dimethylamino 5-nitropyridine.

Since 2-chloro-5-nitropyridine could not be quaternised, synthesis of 79 as an intermediate for acetalisation was achieved via N-alkylation of 5-nitro-2(1H)pyridone with iodide 44 and methylation of resulting pyridone 79 with dimethyl sulfate. But subsequent treatment of 81 with sodium methoxide in methanol or ethylene glycol-triethylamine failed to form the acetal instead only the pyridone 79 was obtained. The latter pyridone 79 was also thermolysed to see any Diels-Alder reaction, but found to be unreactive.

In all the above cases the intermediate 2-methoxypyridinium salts appeared to be strong methylating agent and the reaction product always found to be starting pyridone. The above acetal preparation starting from 2-chloropyridinium

SCHEME 2·10


I
44
Δ
Cl
I⊖
73
74
CH3OH/CH3ONa or (CH2OH)2/(C2H5)3N
(CH2SH)2/(C2H5)3N
nu⊖
or
75
77
45
76
OCH3
OCH3


O2N
K2CO3/DMF
I
44
78
79
80
DMS
CH3OH/CH3ONa or
(CH2OH)2/(C2H5)3N
CH3SO4⊖
OCH3
79
81

salt was also tried using ethyleneglycol, thioethanol and ethylenedithiol. In these cases also only pyridone 45 was obtained except with ethylenedithiol which gave thiopyridone 77. The thiopyridone 77 was also subjected to thermolysis with and without Lewis acid catalysis and found to be equally unreactive as pyridones.

From the foregoing discussion it is seen that several N-alkenyl derivatives of 2-(1H)pyridone (45, 51, 57 and 79) failed to undergo Diels-Alder cycloaddition. Neither activation of dienophile (substitution of carbomethoxy group on the double bond), nor substitution of nitro or acetyl group in the pyridone ring system helps the cycloaddition. Thiopyridone also behaved similar to pyridone.

E X P E R I M E N T A L

Purification and drying of solvents and reagents: Dichloromethane and acetonitrile were distilled from phosphorous pentoxide. DMF was distilled from calcium hydride under reduced pressure prior to use. Xylene, petrolium ether, diphenyl ether were distilled and stored over sodium wire. DME and diglyme were distilled from lithium aluminium hydride. Methanol was dried by refluxing over and then distilling from freshly burnt calcium oxide and then from magnesium turnings and traces of iodine.

Preparation of intermediates

1-Methyl-1-carbomethoxycyclopropane 34: This was prepared from methyl methacrylate (20 g, 0.2 mole) according to reported procedure[17]. B.p. 120-123° (lit.[17] 123-126°).

Yield: 10 g (44%).

NMR:(δ):0.5-0.7 (m, 2H), 1.1 - 1.3 (m, 2H), 1.1 (s, 3H) and 3.6 (s, 3H).

Cyclopropyl carbinol 35: This was prepared from 1-methyl-1-carbomethoxycyclopropane 34 (4.2 g, 0.05 mole) according to reported procedure[18], b.p. 125° (lit.[18] 125-128°).

Yield: 2 g (61%).

NMR (δ): 0.2 - 0.5 (m, 4H), 1.2 (s, 3H), 3.3 (s, 2H) and 4.3 (s, OH exchanging with D_2O).

I R (smear): 3350 cm^{-1}.

Rearrangement reactions of carbinol 35: The reaction was conducted under acid catalysis on 3 m.mole scale in different solvents. The results are tabulated below.

Entry	Reagent	Conditions	Product
1	5 ml 48% HBr/ 4 ml DME	0° 2 hrs	Cyclobutane and cyclopropyl derivatives.
2	i) 5 ml 48% HBr ii) $ZnBr_2$/ether	0° 1 hr	" "
3	i) PBr_3/ether ii) $ZnBr_2$/ether	0° 1 hr	" "
4	5 ml 56% HI	0° 1 hr	" "

Cyclopropyl carbinol 43: Sodium borohydride (9 g, 0.24 mol) was added in small lots to cyclopropyl methyl ketone (8.2 g, 0.097 mol) in methanol (25 ml) and stirred for 1 hr. Methanol was removed, complex was decomposed with water, carbinol was extracted with ether and dried over anhydrous sodium sulfate. The solvent was evaporated to yield the carbinol (5.2 g 60%). b.p. 120° (lit.[28] 122.5 - 123.5°).

NMR (δ): 0.1 - 0.6 (m, 4H); 0.6 - 1.0 (m, 1H); 1.3 (d, 3H); 2.8 - 3.3 (quintet, 1H); 3.9 (s, 1H, exchanges with D_2O).

IR (smear): 3450 cm^{-1} (-OH).

Iodide 44: Carbinol 43 (8.6 g, 0.10 mol) was added to a mixture of 40% hydriodic acid (70 ml) and DME (70 ml) kept

cooled in an icebath and stirred overnight at room temperature. It was diluted with water (150 ml) and extracted with ether. The ether extract was washed with water, sodium bicarbonate, sodiumthiosulfate and finally with water. It was dried over anhydrous sodium sulfate. The solvent was removed and the product was distilled. Yield: 14 g (71.5%). b.p. 100° (bath temp.)/60 mm.

NMR (δ): 1.5 - 1.8 (m, 3H); 2.3 - 2.8 (m, 2H); 3.0 - 3.3 (m, 2H); 5.1 - 5.9 (m, 2H).

IR (smear): 980 cm^{-1} (trans double bond).

Pyridone 45: Sodium salt of 2(1H) pyridone was prepared from 2(1H)pyridone (2.3 g, 23 m.mole) and 23 ml of 1N sodium methoxide in methanol. Solvent was distilled and the salt was taken in anhydrous DME (23 ml). Iodide 44 (4.528 g, 23 m.mole) in DME (10 ml) was slowly added at room temperature. The stirring was continued for 24 hrs. TLC in 5% ethyl acetate/benzene showed presence of two products. The reaction mixture was diluted with water and extracted with ether. Organic extract washed with water and brine, dried over anhydrous sodium sulfate. Evaporation of the solvent afforded crude product (3.75 g, 90%). This was resolved on silica gel.

Pyridone 45: Yield (3.15 g 84%).

NMR: Fig. .1

IR: Fig. .2

O-Alkylated product 46: yield (0.600 g,16%).

NMR: Fig.3.

IR (smear): 1600 cm^{-1} (Aromatic C=C), 980 cm^{-1} (trans double bond).

Photodimer of pyridone 52: The cyclohexane solution (200 ml) of pyridone 45 (0.490 g, 3 m.mole) was irradiated with UV radiations for 10 hrs. The cyclohexane solution on evaporation of solvent afforded crude product. This was resolved on silica gel.

Dimer 52: Yield: 0.200 g.

NMR: Fig. 4

IR: Fig. 5

Also the unreacted starting material (280 mg) was recovered.

Pyridone 51

a) 4-(1',1'-Ethylenedioxyethyl) pyridine 48: This was prepared according to reported procedure[26] from 12.1 g (100 m.mole) of 4-acetylpyridine. Yield: 16 g (96%).

b.p. 85°/1 mm (Lit.[26] b.p.[34] 137-138°).

NMR (δ): 1.6 (s, 3H), 3.4 - 4.1 (m, 4H) and 7.3 (broad s, 4H).

IR ($CHCl_3$): 1040 cm^{-1} (ethylene ketal).

b) Quaternary salt 49: The ketal 48 (3.2 g, 20 m.mole) and iodide 44 (3.92 g, 20 m.mole) were mixed and heated at 100° for three hours. The reaction mixture was used for ferricyanide oxidation without purification.

c) Pyridone 50: The quaternary salt from the previous reaction was oxidized according to the reported general procedure.

The quaternary salt 49 (7.12 g, 20 m.mole) was dissolved in 40 ml water. Separate solutions of potassium ferricyanide (13.16 g, 40 m.mole) in 25 ml water and potassium hydroxide (4.5 g, 80 m.mole) in 10 ml water, were added dropwise from two separatory funnels to the well stirred solution of pyridinium salt at 0°. The mixture was stirred for one hr at 0° and overnight at room temperature. The reaction mixture was extracted with benzene. The combined organic extract washed with water, brine and dried over anhydrous sodium sulfate. On evaporation of solvent under reduced pressure, an oil was obtained. Yield: (6 g, 72%).

NMR (δ): 1.5 (s, 3H), 1.5-1.8 (m, 3H), 2.1-2.4 (m, 2H), 3.5-4.1 (m, 6H), 5.2 - 5.6 (m, 2H), 6.1 (d.d 1H, J = 8, 2 Hz), 6.4 (d, 1H J = 2 Hz) and 7.2 (d, 1H, J = 8 Hz).

IR (smear): 1666 cm^{-1} (cyclic amide carbonyl), 1040 cm^{-1} (ethylene ketal) and 980 cm^{-1} (trans double bond).

d) Pyridone 51: THF solution (20 ml) of pyridone 50 (2.49 g, 10 m.mole) was treated with 20 ml of 3% hydrochloric acid at 60° for 14 hrs. The reaction mixture was neutralised with potassium carbonate, saturated with sodium chloride and extracted with ether.

Organic extract washed with water, brine and dried over sodium sulfate. Solvent removed under reduced pressure to afford pyridone.

Yield: 2 g (90%).

NMR (δ): Fig.6

IR (smear): 1685 cm^{-1} (carbonyl), 1650 cm^{-1} (cyclic amide carbonyl) and 980 cm^{-1} (trans double bond).

Bromide 56: (a) α-Methylene-γ-butyrolactone[25] 55: This compound was prepared according to reported procedure from butyrolactone in three steps.

B.p. 70°/2 mm (Lit.[25] b.p. 50-53°/0.45 mm).

NMR (δ): 2.9 - 3.0 (m, 2H), 4.3 (t, 2H, J = 7 Hz), 5.6 - 5.7 (t, 1H, J = 3 Hz) and 6.0 - 6.1 (t, 1H, J = 3 Hz).

IR ($CHCl_3$): 1765 cm^{-1} (C=O) and 1670 cm^{-1} ($=CH_2$).

(b) Bromide 56: Triphenylphosphine-dibromide was prepared from triphenylphosphine (1.841 g, 7 m.mole) and bromine (1.120 g, 7 m.mole) in anhydrous acetonitrile (14 ml). The lactone 55 (670 mg, 7 m.mole) in anhydrous acetonitrile (5 ml) was slowly added to triphenylphosphinedibromide solution at room temp. The resulting reaction was refluxed for six hrs. At the end of this period 3 ml of methanol was added and further refluxed for half hr. Solvents were evaporated under reduced pressure and residue extracted with pet. ether (60-80°) several times. Pet. ether extract on evaporation of solvent

afforded crude product which was purified by passing through a short silica gel column. Yield: 400 mg (28%).

NMR (δ): Fig.7

IR (smear): 1725 cm^{-1} ($\alpha\beta$-unsaturated ester).

Pyridone 59: This was prepared from 2(1H)-pyridone (100 mg, 1 m.mole) and bromide 56 (193 mg, 1 m.mole) by the procedure used for pyridone 45.

Yield: 350 mg (84%).

NMR (δ): Fig.8

IR: Fig.9

Pyridone 57: 2-Ethoxypyridine (615 mg, 5 m.mole) and the bromide 56 (965 mg, 5 m.mole) were mixed and heated at 130-140° for 6 hrs. The TLC in 5% methanol-ethyl acetate showed mixture of product. This crude product was resolved on silica gel column to afford pyridone 57. Yield: 650 mg(63%).

NMR(δ): Fig.10

IR(smear): 1666 cm^{-1} (cyclic amide carbonyl) and 1725 cm^{-1} ($\alpha\beta$-unsaturated ester).

Pyridone 79: Potassium salt of 5-nitro-2(1H) pyridone was prepared from 5-nitro-2(1H)pyridone (1.40 g, 10 m.mole)and potassium carbonate (2.8 g, 20 m.mole) in anhydrous DMF (10 ml). The resulting salt was treated with iodide 44 (1.96, 10 m.mole) with stirring at room temperature. After stirring for 16 hrs

the reaction mixture was diluted with water and extracted with ethyl acetate. Organic extract washed with water, brine and dried over anhydrous sodium sulfate. On evaporation of solvents under reduced pressure, the ethyl acetate extract afforded an oil (2.0 g). This was resolved on silica gel to yield the desired pyridone 79. Yield 1.664 g (80%).

NMR: Fig. 11

IR (smear): 1681 cm^{-1} (cyclic amide carbonyl), 1333 cm^{-1} (nitro) and 960 cm^{-1} (trans double bond).

O-Alkylated product 80: Yield 208 mg (10%).

NMR (δ) 1.5-1.8 (m, 3H), 2.3-2.7 (m,2H), 4.3-4.6 (t, 2H, J=7 Hz), 5.3-5.7 (m, 2H), 6.7 (d, 1H, J=10 Hz). 8.3 (dd, 2H, J=10,3 Hz) and 9.0 (d, 1H, J=3 Hz).

Pyridone 77: The pyridinium salt 74 was prepared by heating neat mixture of 2 chloropyridine 73 (100 mg, 1 m.mole) and the iodide 44 (196 mg, 1 m.mole) at 100° for 12 hrs. The solution of the salt 74 in anhydrous acetonitrile (1 ml) was cooled to 0° and triethylamine (202 mg, 2 m.mole) was added followed by ethylene dithiol (94 mg, 1 m.mole). Reaction mixture was warmed to room temperature and stirred for 3 hrs. Reaction mixture was made alkaline (sodium bicarbonate) and extracted with ethyl acetate. Organic extract was washed with water, brine and dried over anhydrous

sodium sulfate. Evaporation of solvents under reduced pressure, the organic extract gave pyridone as an oil. Yield: 142 mg (71%).

NMR: Fig. 12

IR(CCl_4): 1100 and a shoulder at 1124 cm^{-1}, 960 cm^{-1} (trans double bond) [cf. Ref. 27].

General procedure for the Diels-Alder reaction of pyridones:

Method (a): A 10% solution of the pyridone in xylene was refluxed for 6 hrs. At the end of this period TLC showed no progress in the reaction. The solvent was evaporated under reduced pressure. The unreacted starting material was obtained, as shown by spectral studies.

This reaction was repeated in diglyme and diphenyl ether with similar results.

Method (b): To a solution of pyridone (1 m.mole) in xyleme (3 ml) one equivalent of Lewis acid ($AlCl_3$, $SnCl_4$ or BF_3.etherate) was added and the solution was refluxed for one hr. Again no reaction took place.

The reaction was repeated in dichloromethane with similar results.

Method (c): A mixture of pyridone (1 m.mole) and hydroquinone (5 mg) was heated in a sealed tube at 250-300°. No reaction took place, but prolonged heating caused polymerization.

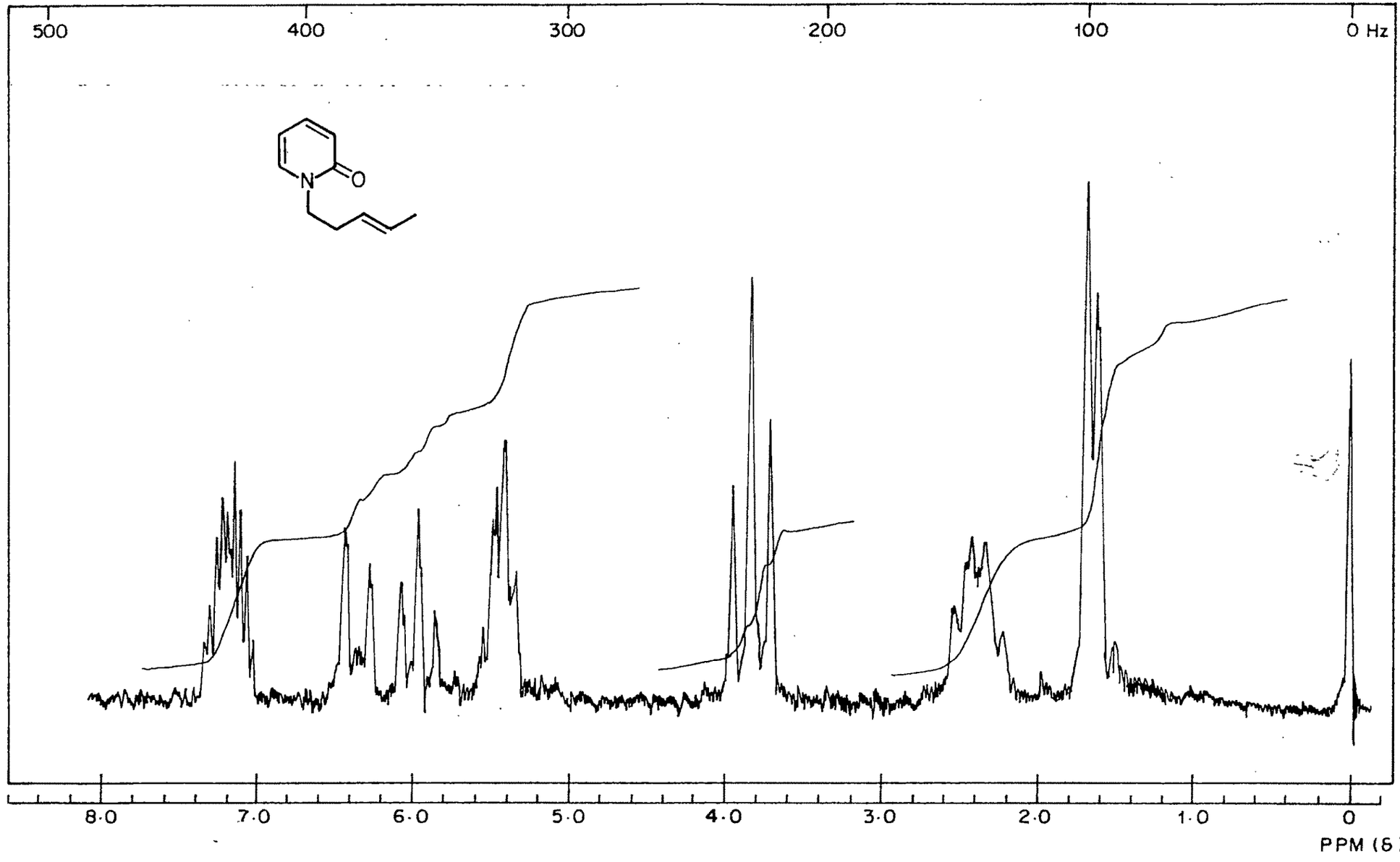


FIG. NO. 1. NMR SPECTRUM OF PYRIDONE 45

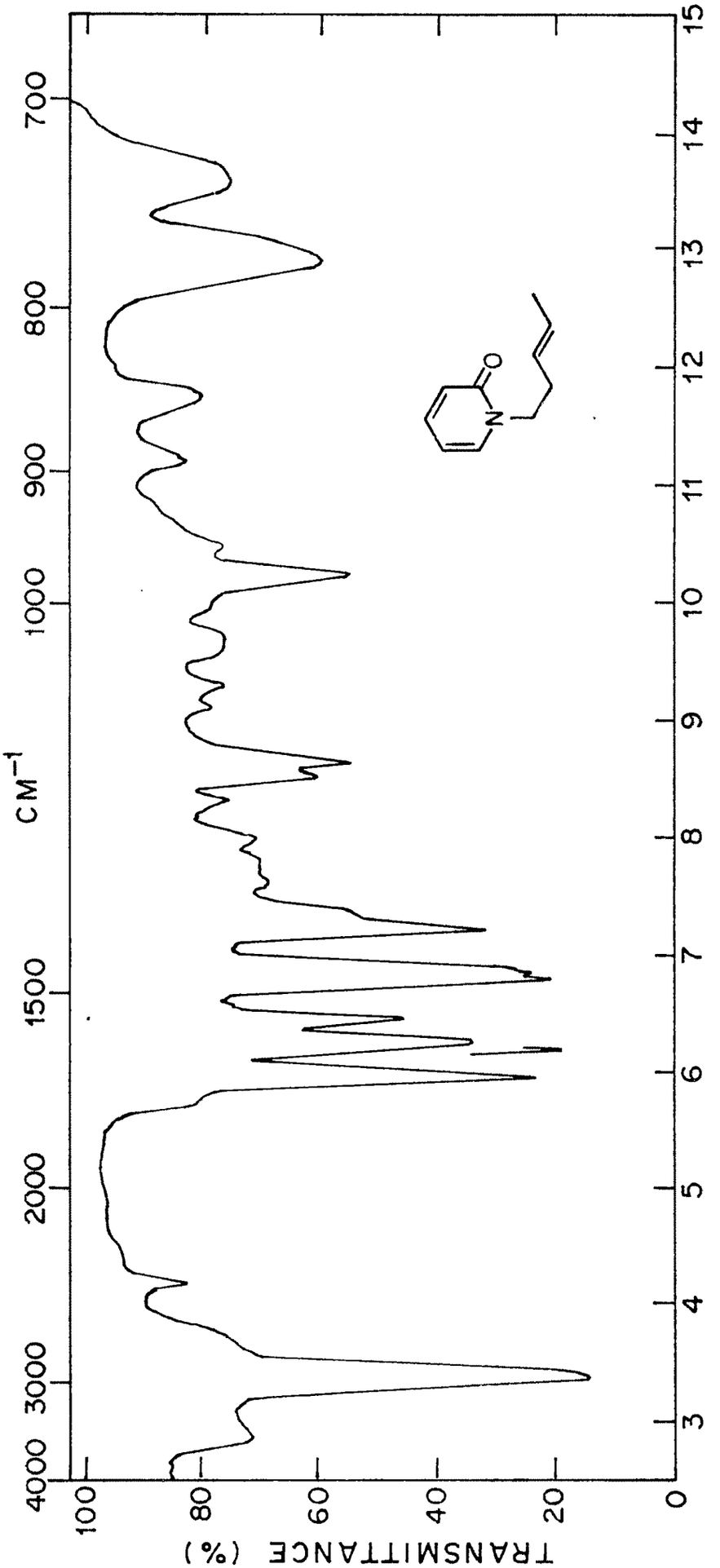


FIG. NO. 2. IR SPECTRUM OF PYRIDONE 45

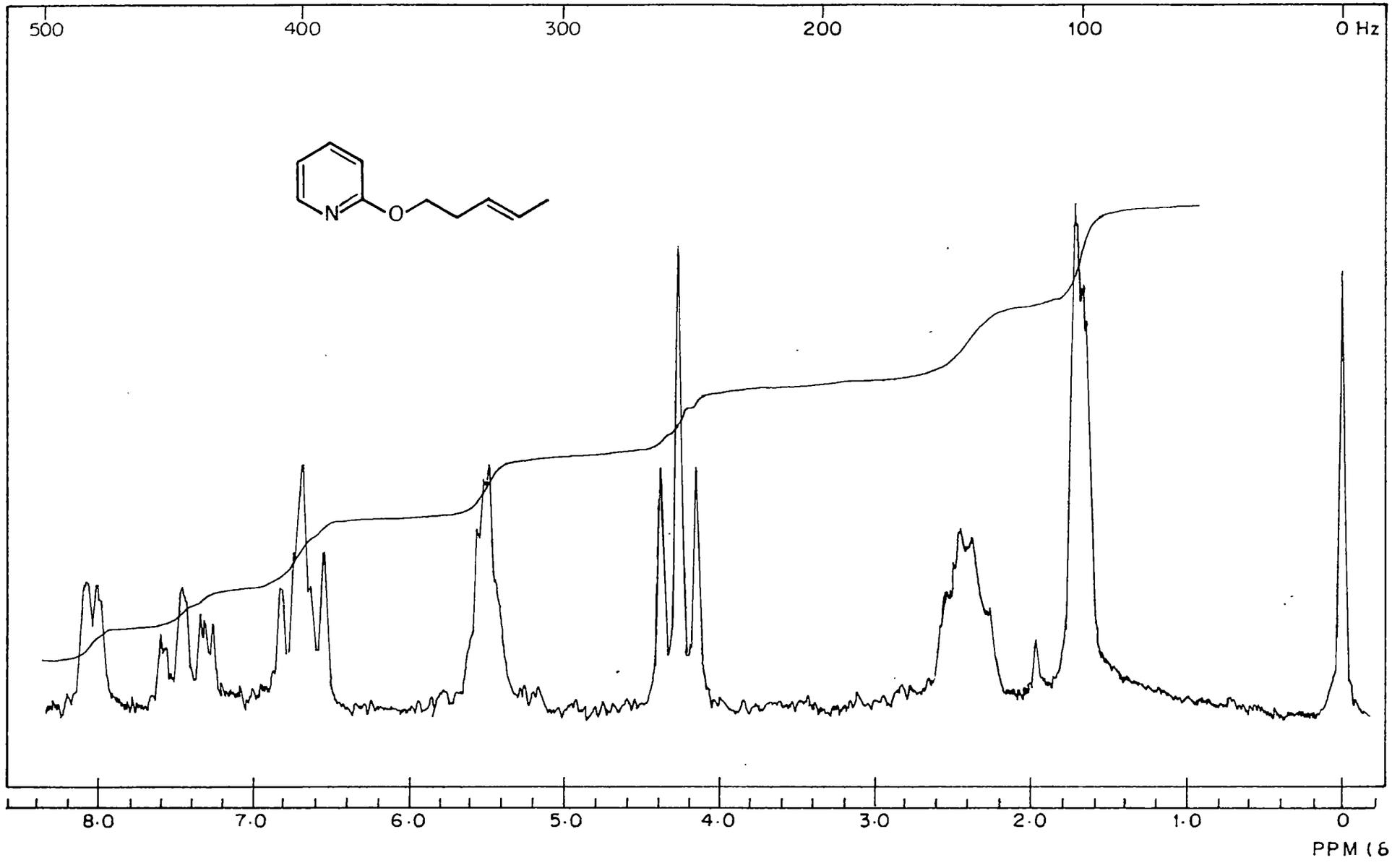


FIG. NO. 3. NMR SPECTRUM OF 46.

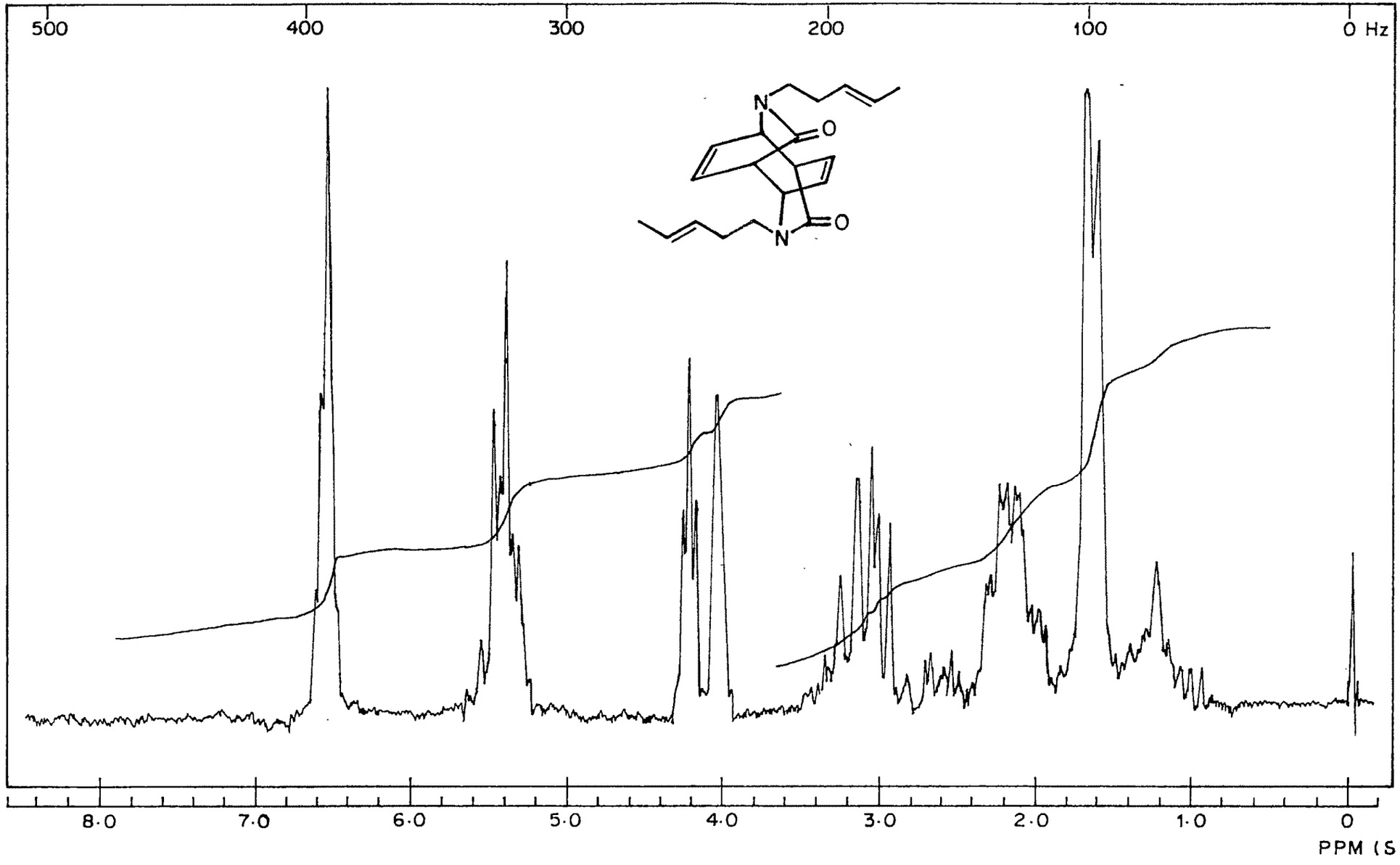


FIG. 4. NMR SPECTRUM OF DIMER 52

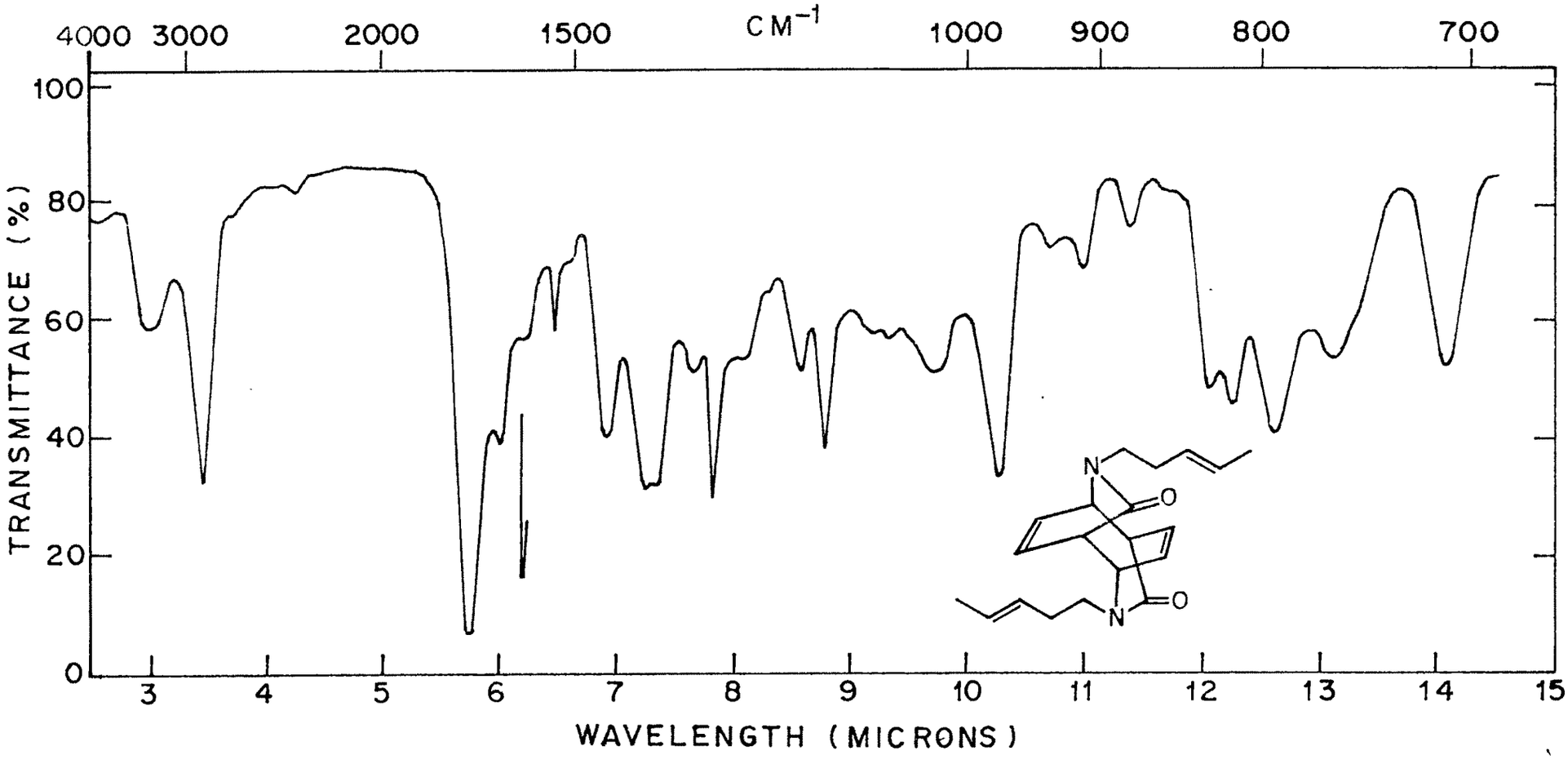


FIG. 5. IR SPECTRUM OF DIMER 52

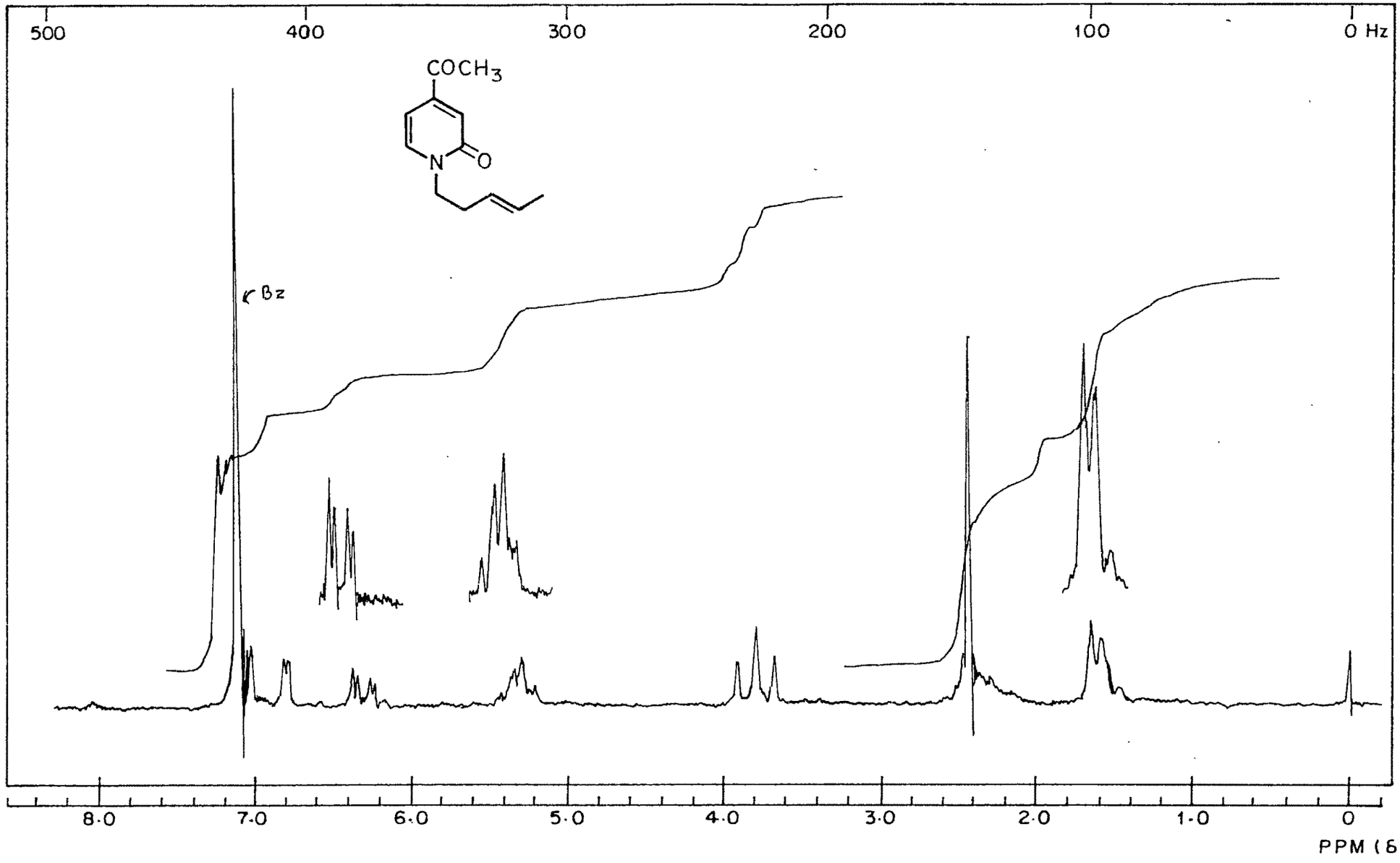


FIG. NO. 6. NMR SPECTRUM OF PYRIDONE 51

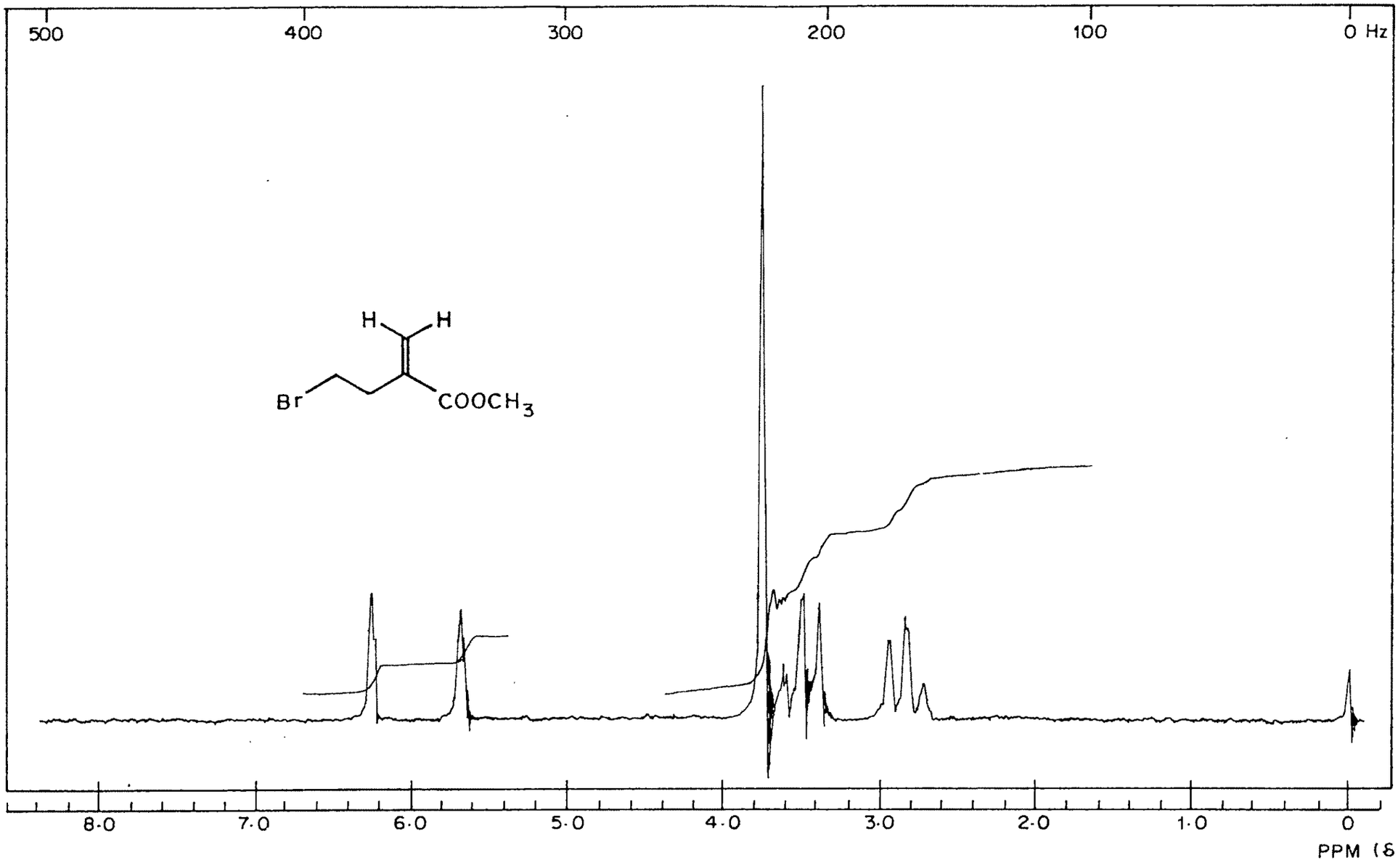


FIG. NO. 7. NMR SPECTRUM OF BROMIDE 56.

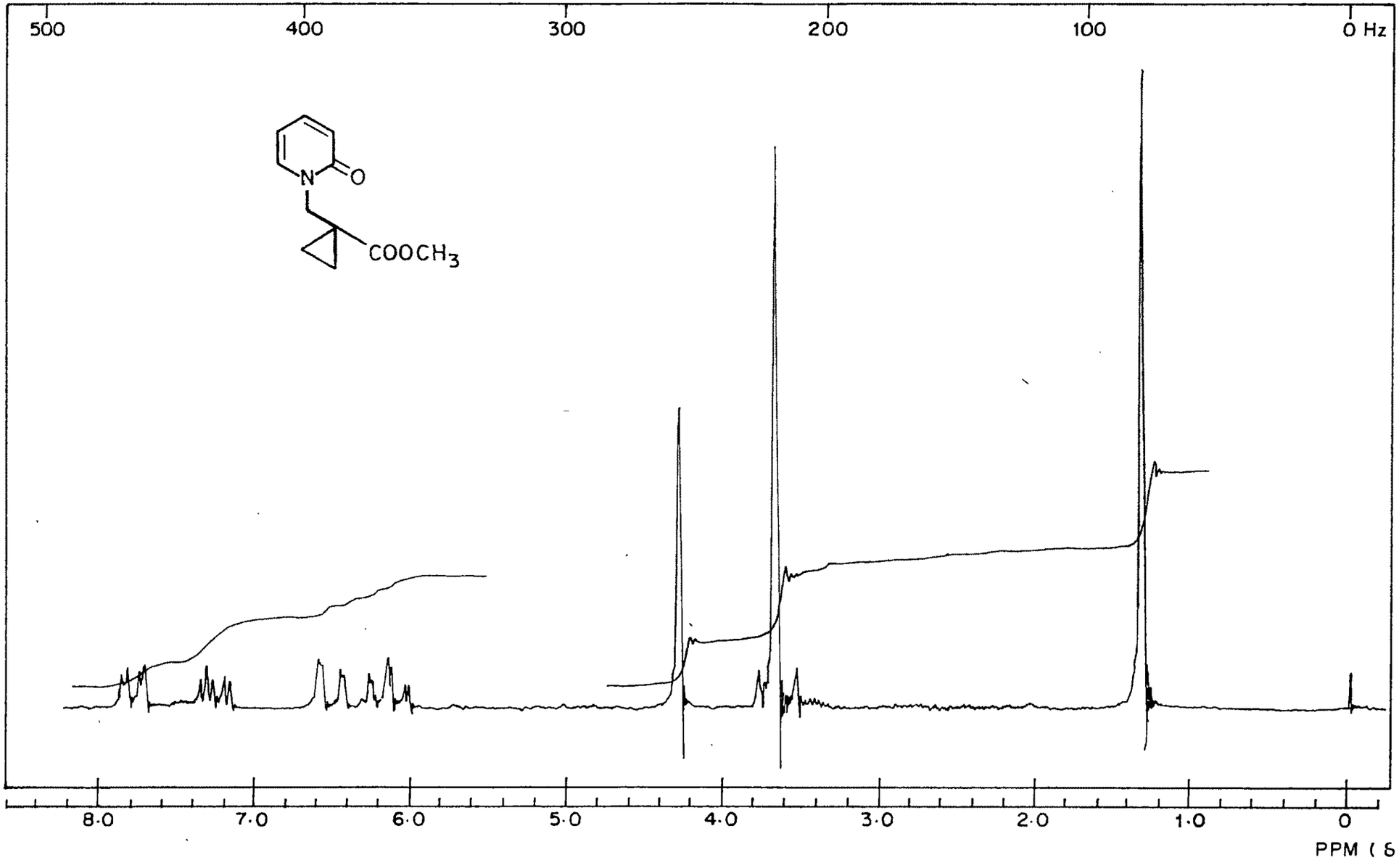


FIG. NO. 8. NMR SPECTRUM OF PYRIDONE 59

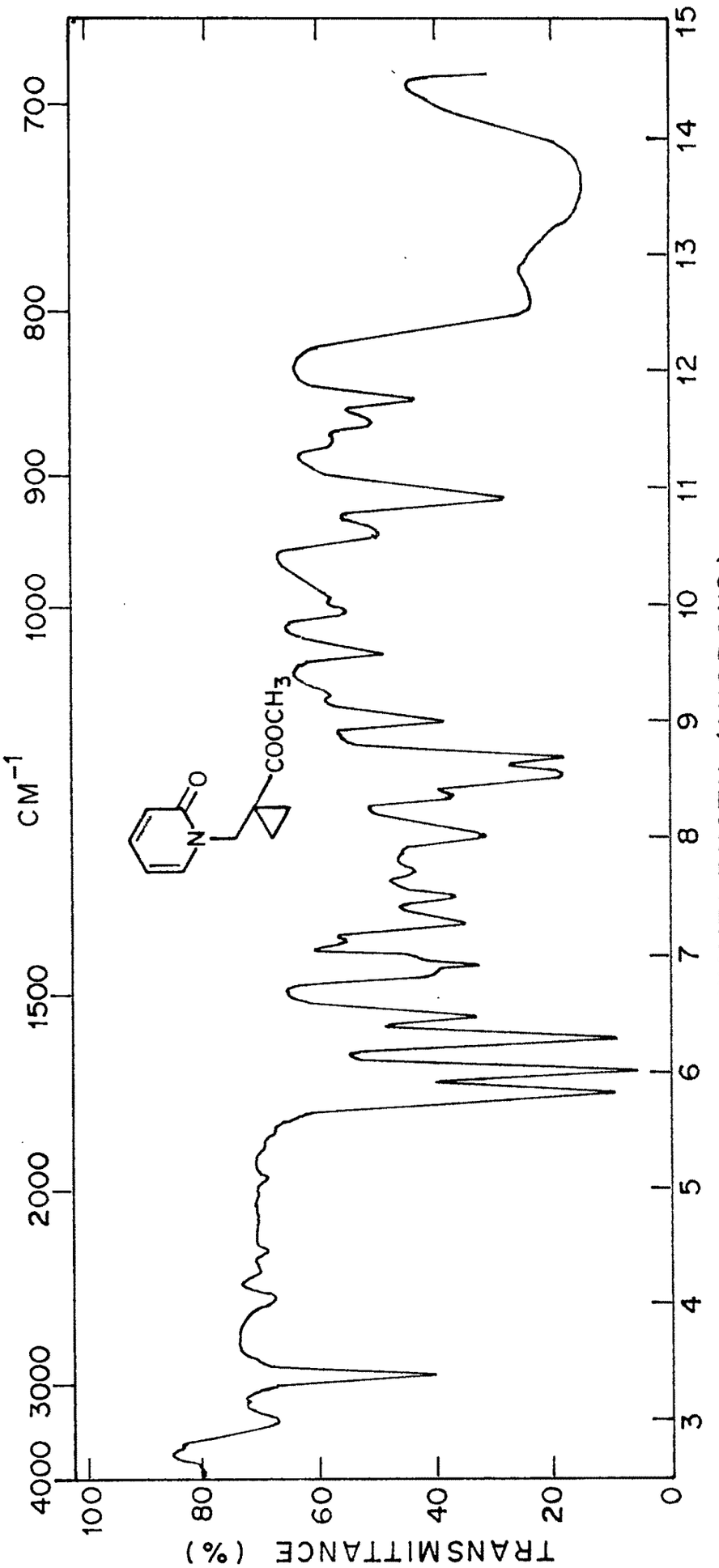


FIG. 9. IR SPECTRUM OF PYRIDONE 59

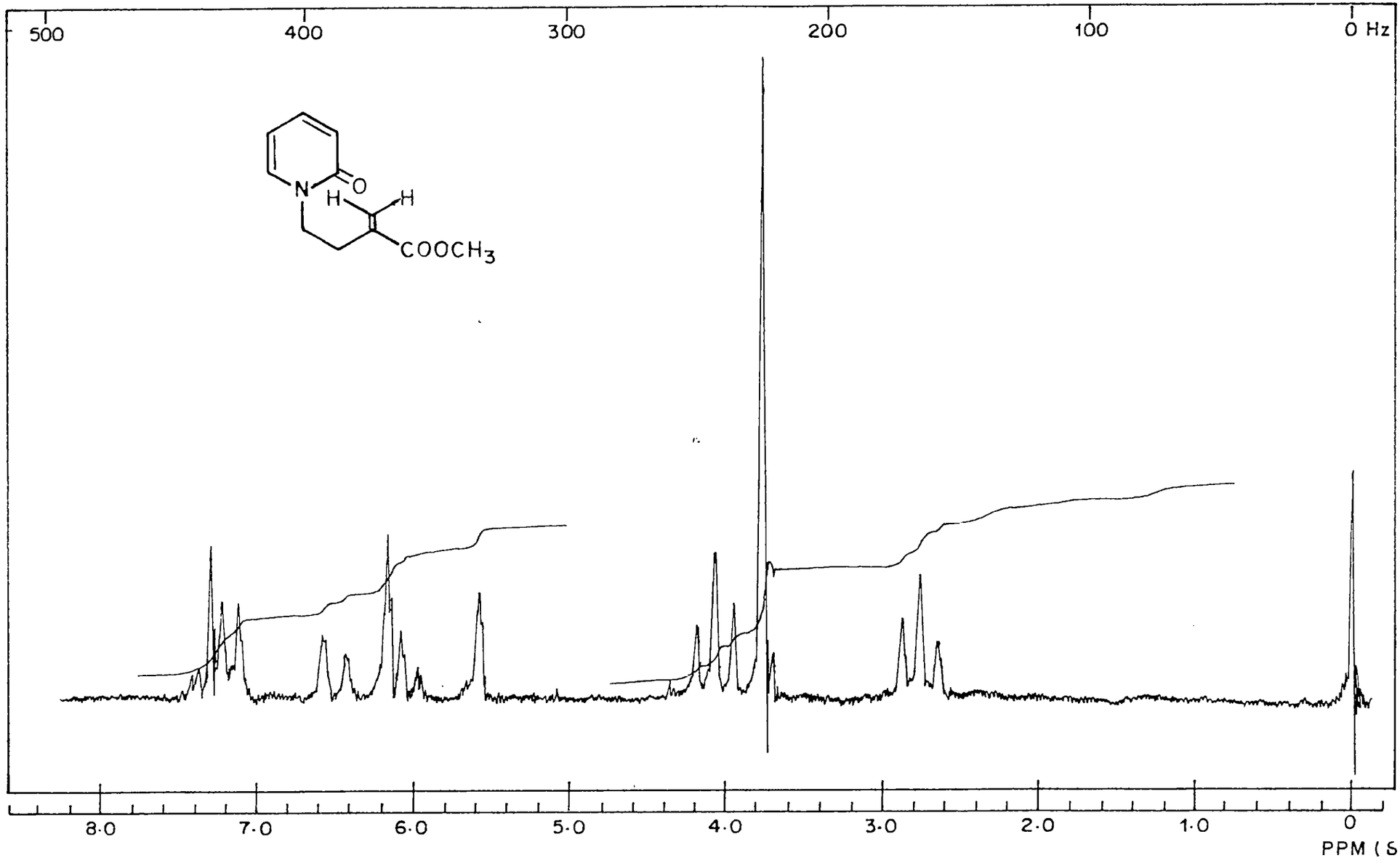


FIG. NO. 10. NMR SPECTRUM OF PYRIDONE 57

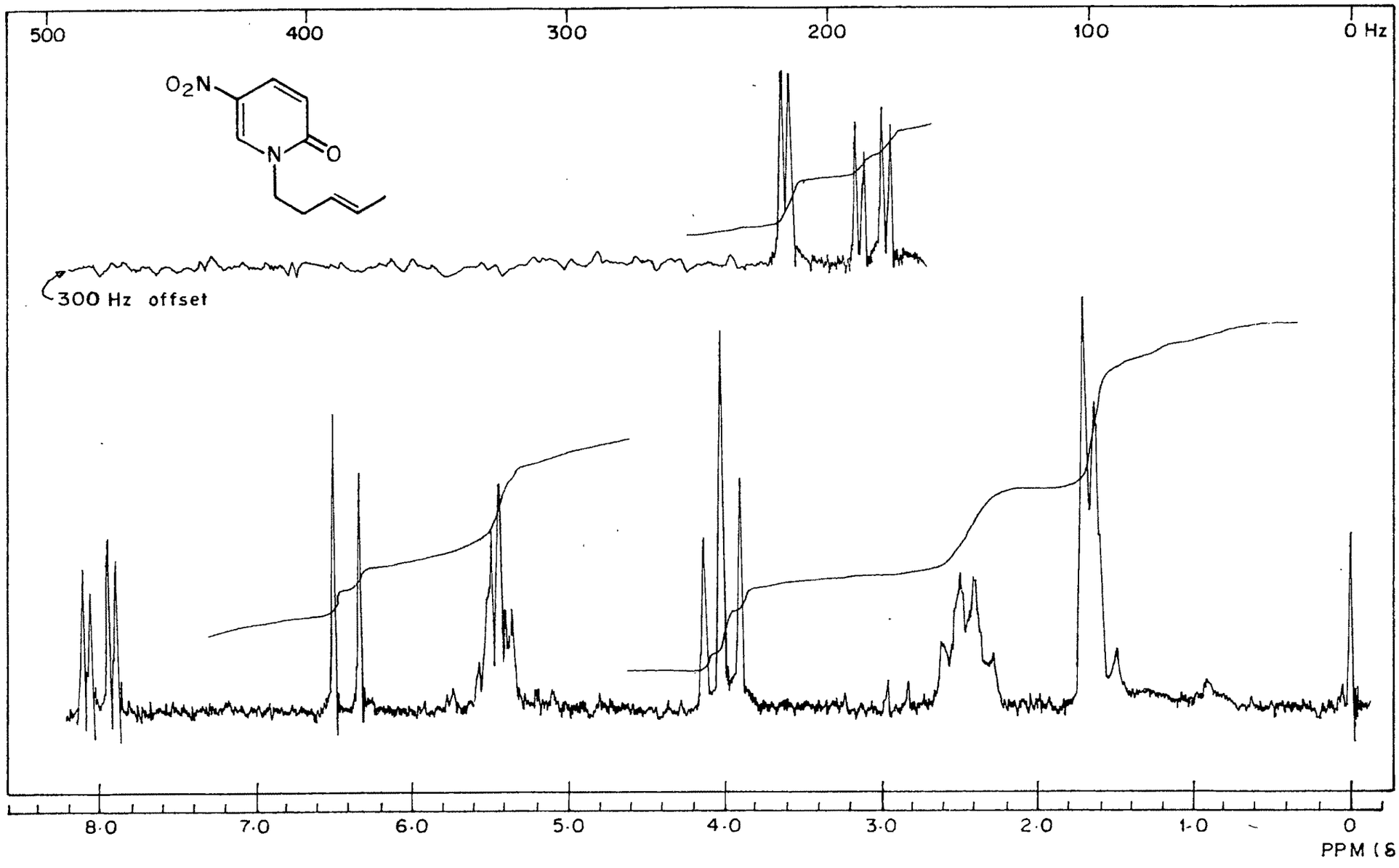


FIG. NO. 11 . NMR SPECTRUM OF PYRIDONE 79.

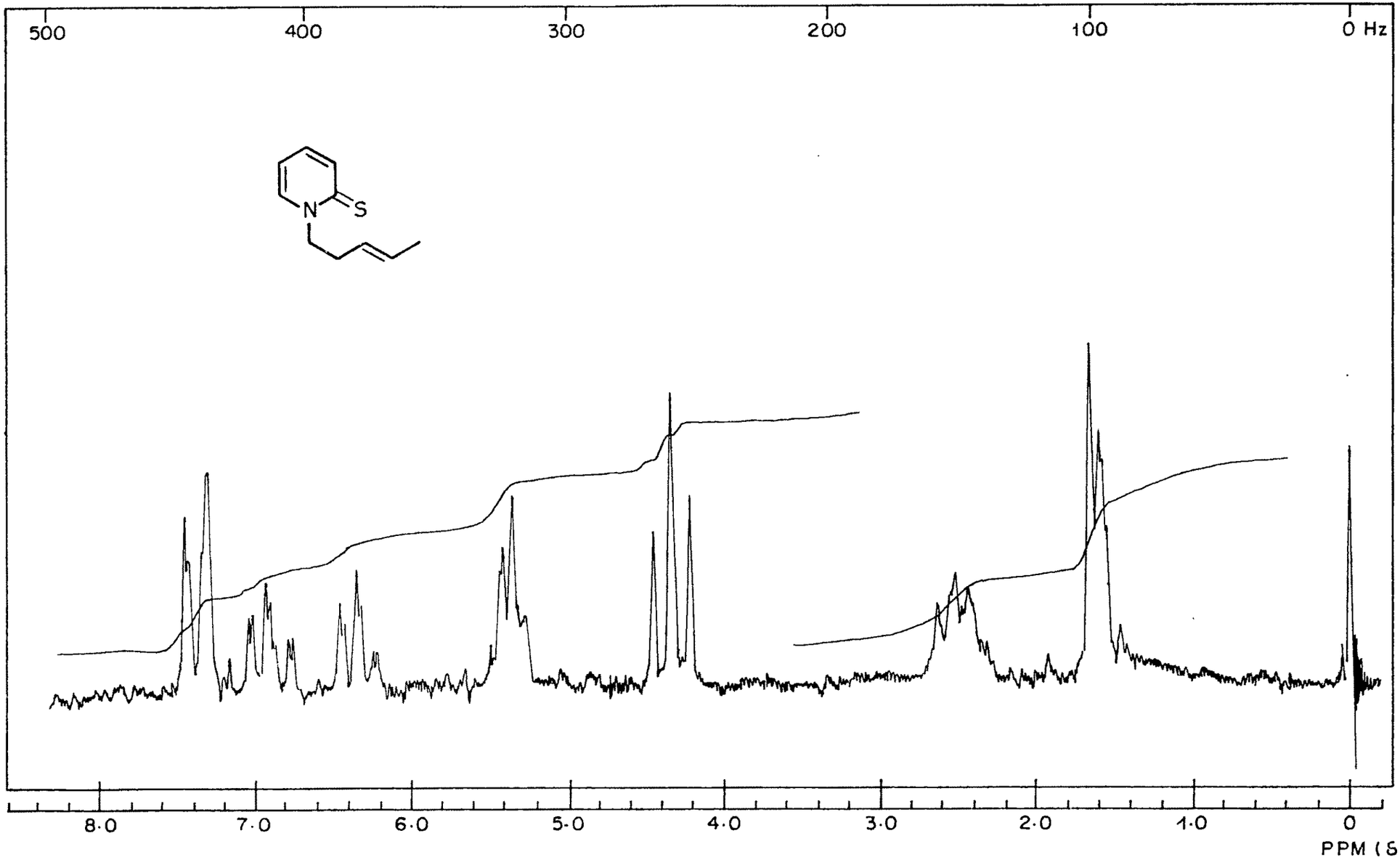


FIG. NO. 12. NMR SPECTRUM OF THIOPYRIDONE 77

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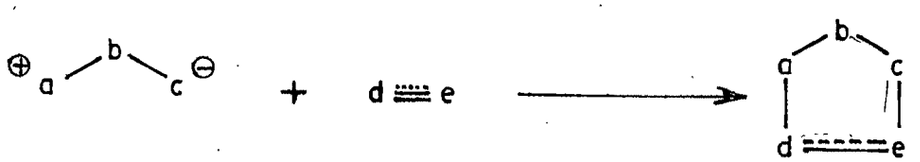
CHAPTER III

INTRAMOLECULAR 1,3-DIPOLAR ADDITIONS OF N-ALKENYL PYRIDINIUM BETAINES AS AN APPROACH FOR THE SYNTHESIS OF DENDROBINE

INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION REACTIONS

3.1 General Introduction

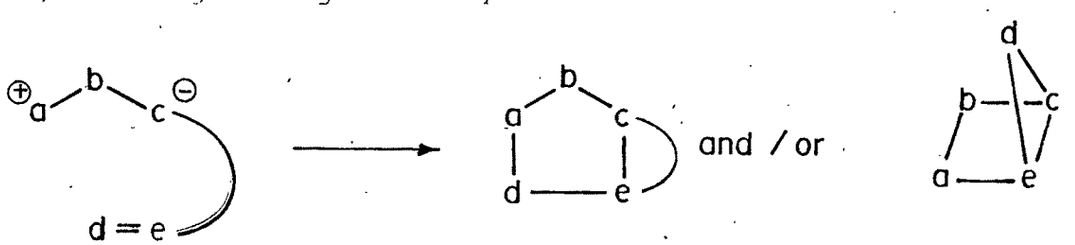
1,3-Dipolar cycloaddition is a reaction of considerable scope for the synthesis of five-membered heterocyclic rings[1]. 1,3-Dipolar cycloadditions are bimolecular in nature and involve the addition of a 1,3-dipole to a multiple bond system leading to five membered heterocycles.



A 1,3-dipole is a system of three atoms over which are distributed four π electrons. The three atoms can be a wide variety of combinations of C, O and N. The dipolarophile can be any double or triple bond. Majority of 1,3-cycloadditions, the reaction rate is not markedly influenced by the dielectric constant of the solvent-medium in which the reaction is conducted. In most of the instances of 1,3-dipolar cycloaddition reactions, when two isomers are possible as a result of the use of unsymmetrical reagents, one isomer usually predominates, often to the exclusion of the other. The independence of the solvent polarity, the negative entropies of activation and the stereospecificity and regiospecificity point to a highly ordered transition

state. The mechanism of the cycloaddition is that of a single step, four center, "no mechanizm" cycloaddition, in which the two new bonds are both partially formed in the transition state, although not necessarily to the same extent[2]. A symmetry energy correlation diagram reveals that such a thermal cycloaddition reaction is an allowed process.

Intramolecular 1,3-dipolar cycloaddition is an extremely versatile and important reaction. The range of synthetic possibilities which it opens for the construction of fused heterocycles is extremely large. 1,3-Dipoles bearing a functional group able to behave as a dipolarophile are extremely interesting substrates. The intramolecular cycloaddition of a properly functionalized 1,3-dipole represents a general scheme for the synthesis of novel fused and/or bridged ring heterocycles.



3.2 Acyclic Dipoles

Nitrones, diazoalkanes, azides, azomethine imines, nitrile ylides, carbonyl oxides and nitrile oxides are known to undergo 1,3.dipolar cycloadditions. Nitrones occupy

a special place among the 1,3-dipoles because of their easy accessibility and the facility with which their adducts can be modified.

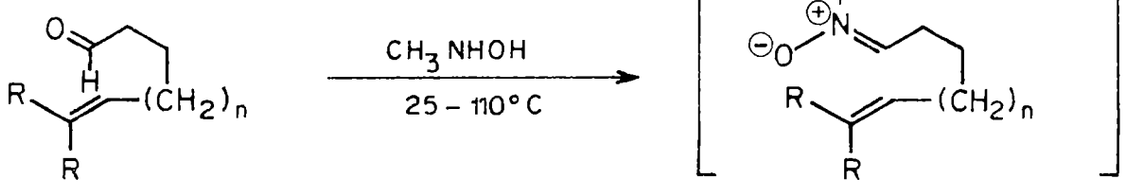
3.2.1 Nitrones

LeBel et al.[3,4] showed that intramolecular additions of intermediate C-alkenyl nitrones can be easily effected if olefinic aldehydes 1 are condensed with N-alkyl hydroxylamines, annelated isoxazolidines 3 and/or 4 are obtained in this way (Scheme 3.1).

It is interesting that many of these intramolecular additions to unactivated C-C double bonds take place smoothly at 25°, whereas the bimolecular additions require a higher temperature and/or activation of the olefinic component[5]. This difference reflects the entropic influence in the intramolecular reactions. It is also worth noting the regioselectivity of the additions of 2 leads mainly to annelated adducts. An exception is provided by the formation of bridged isoxazolidines such as 5 from C-alkenylketonitrones, probably owing to non-bonding interactions of the substituents.

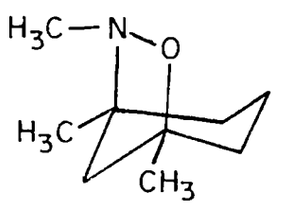
It appears that the C-(4-alkenyl)nitrones 2a react highly selectively to give cis-condensed isoxazolidines 3a. The kinetically controlled reaction of the homologous C-(5-alkenyl)nitrone 2b occurs less selectively[6]; the trans adducts 4b are the main products, along with varying amounts

SCHEME 3·1.

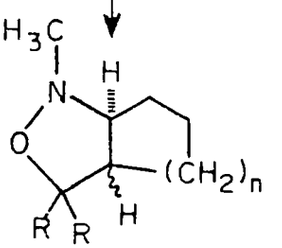


1

2 a) n = 1 b) n = 2

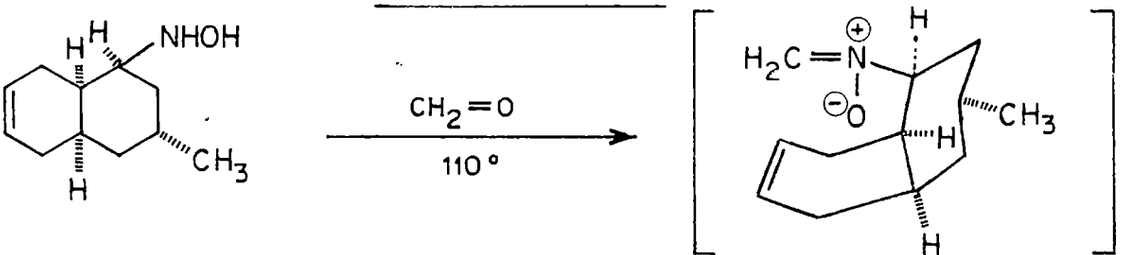


5



3 cis a) n=1.
4 trans b) n=2

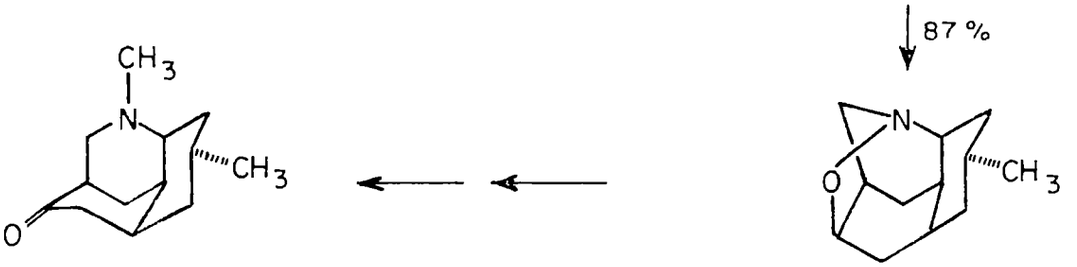
SCHEME 3·2.



6

7

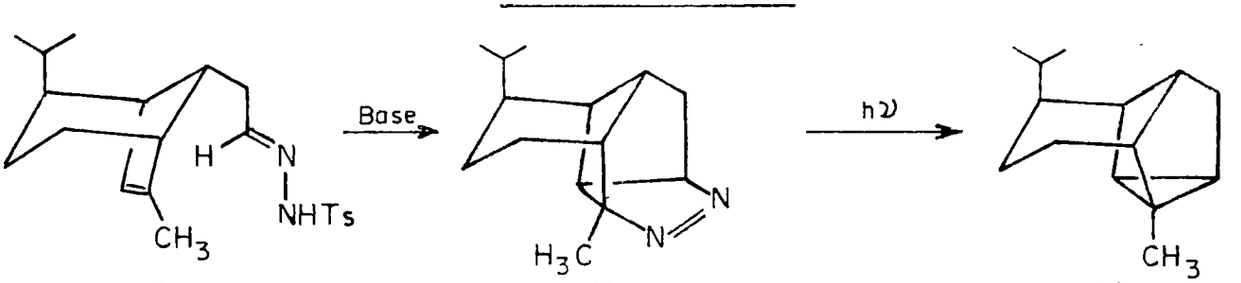
87 %



9
LUCIDULINE

8

SCHEME 3·3.



10 11 12

CYCLOCOPACAMPHENE

of the cis-isomers 3b. However at higher temperatures (180° - 300°C) equilibrium of the trans and cis adducts 4b and 3b occurs, presumably by 1,3-dipolar cycloreversion, to afford finally the thermodynamically stable isomer 3b.

The ready accessibility of N-(4-alkenyl)nitrones (from N-alkenyl hydroxylamines) and the unequivocal direction of their intramolecular additions to non-conjugated "symmetric" C=C bonds recently allowed a simple and regioselective synthesis of the lycopodium alkaloid Luciduline 9 (Scheme 3.2)[7]. Heating the easily available hydroxylamine 6 with an excess of paraformaldehyde and molecular sieves in toluene furnished directly an 87% yield of the isoxazolidine 8, which on methylation, reduction and oxidation gave the alkaloid 9 in high yield. Comparison with another multistage preparation of racemic 9[8] demonstrated for the first time in the synthesis of natural products a superiority of the intramolecular nitrone additions over other types of reactions.

3.2.2 Diazoalkanes

Diazoalkanes also act as 1,3-dipole. The lithium salt of tosylhydrazone 10 when heated at 120°, an internal cycloaddition occurs (Scheme 3.3)[9]. The cycloadduct obtained 11 was converted into cyclocopacamphene 12 on further photolysis. The facile intramolecular 1,3-dipolar cycloaddition of the intermediate olefinic diazoalkane to give 11 is presumably related to the proximity of the two

reacting functional groups and to the fairly strained nature of the double bond.

3.2.3 Azides

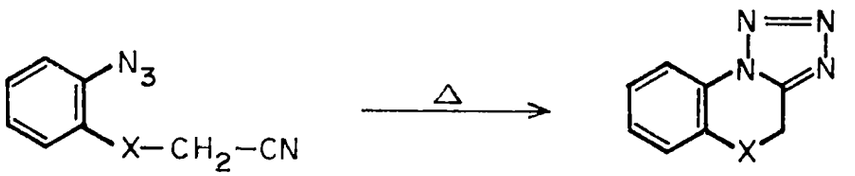
Organic azides are well known to behave as 1,3-dipoles in thermal cycloaddition reactions. The ring closure of azidonitrile system 13 gives tetrazole derivative 14, which is an intramolecular 1,3-dipolar cycloaddition (Scheme 3.4)[10]. In intermolecular terms, only nitrile groups activated by electronwithdrawing substituents have been shown to behave as dipolarophiles towards azides[11], but in the present case the mutual ortho disposition of the two interacting groups in 13 provides a favourable stereochemical relationship for intramolecular cycloaddition.

3.2.4 Azomethine imines

Azomethine imines, which can act as 1,3-dipoles are normally not isolable, but their facile preparation *in situ* from storable precursors make them easy to use (Scheme 3.5).

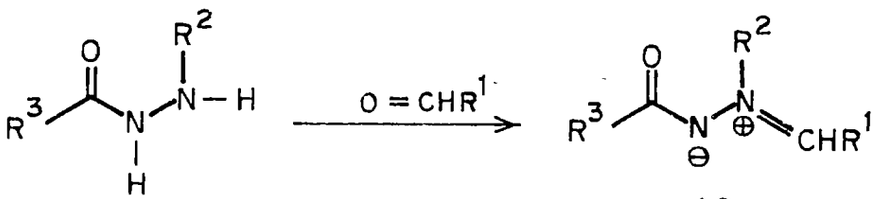
Azomethine imines were obtained from N-acyl-N'N'-dimethyl hydrazines *via* mercury compounds[12] or preferably by condensation of aldehydes with N-acyl-N'alkylhydrazines[13]. Subsequent trapping of 16 by bimolecular additions to dipolarophiles furnished pyrazolidines in high yields. The simple reaction 15 → 16 allows olefinic substituents R^1R^2 and R^3 to be introduced specifically into the three positions

SCHEME 3·4.

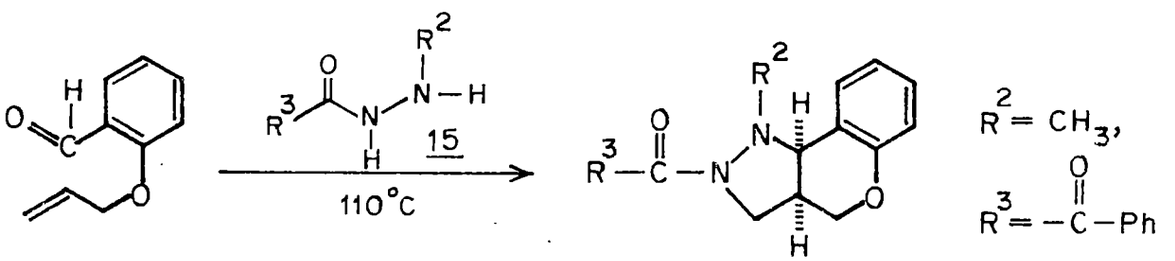


13 X = O, CH_2 14

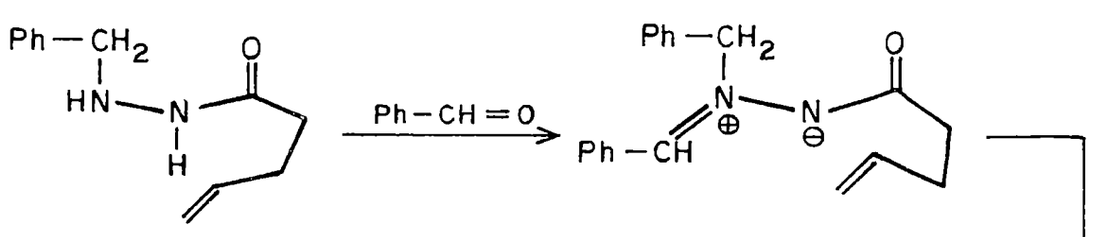
SCHEME 3·5.



15 16



17 18



19 20 21 22

of dipole.

For intramolecular version of the above reaction, the C-alkenylazomethine imines required are conveniently made *in situ* by condensing olefinic aldehydes with N-acyl-N'alkylhydrazines 15 which undergoes a spontaneous, regioselective addition to 18[14]. Formation of 18 is regio and stereoselective.

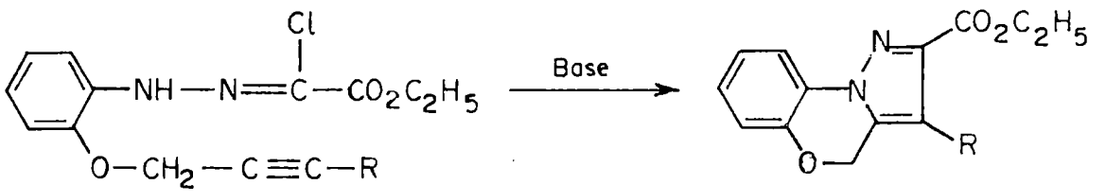
N-Alkenoyl azomethine imines also undergo dipolar additions. A reaction of this type can be smoothly effected by heating N-alkenoyl-N'alkyl hydrazines together with aldehydes as shown by regio and stereoselective conversion 19 → 20 → 21 [15]. The sole product is the annelated product 21 with no trace of bridged isomer 22 (Scheme 3.5).

3.2.5 *Nitrile imines*

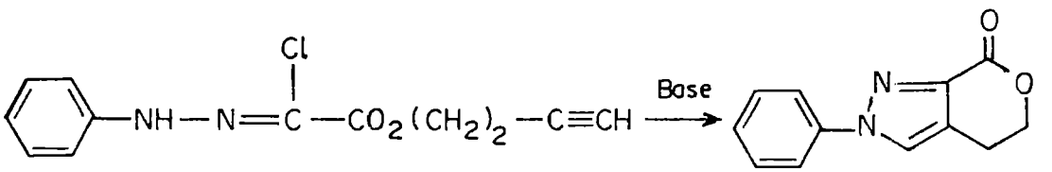
Nitrile imines are compounds containing the grouping $R-\bar{N}-\overset{+}{N} \equiv C-R^1$. The most convenient method for generation of this class of 1,3-dipoles involves the action of tertiary bases of hydrazidoyl halides such as 23 and 25 (Scheme 3.6)[16]. The 1,3-dipole cannot be isolated and the external dipolarophile must be present in the reaction. Treatment of 23 with base leads to a nitrile imine which gets readily intercepted by the adjacent acetylenic functionality present in the molecule to give the pyrazole 24[17].

Similarly, treatment of 25 with base affords cyclo-

SCHEME 3·6.

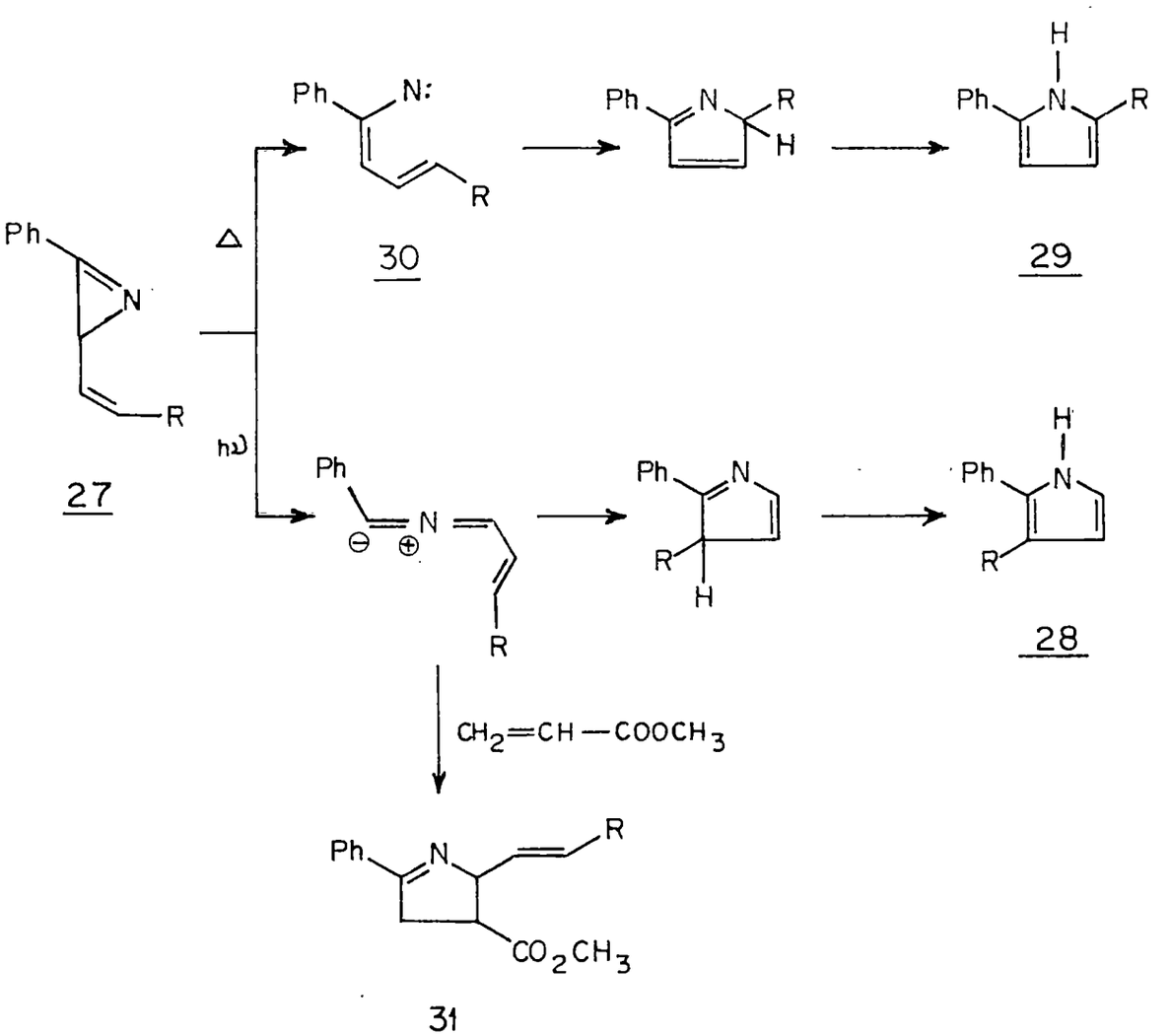


23 24



25 26

SCHEME 3·7.



adduct 26. These ring closures are particularly interesting in that they involve cycloadditions with unconjugated alkynes, substrates which are generally unreactive towards nitrile imines[18].

3.2.6 Nitrile Ylides

Padwa et al.[19] and Schmid et al.[20] have independently shown that irradiation of 2H-azirines lead to irreversible ring opening and the formation of nitrile ylides as intermediates. These species may be intercepted with a wide variety of dipolarophiles to form five-membered heterocycles (Scheme 3.7).

2-Vinyl azirine 27 on irradiation in benzene afforded a 2,3-disubstituted pyrrole 28, while thermolysis gave a 2,5-disubstituted pyrrole 29[21,22].

The thermal transformations observed have been rationalized in terms of an equilibrium of the 2H-azirine with a transient vinyl nitrine 30 which subsequently rearranges to the 2,5-disubstituted pyrrole. But the evidences obtained clearly indicated that the photorearrangement of 27 proceeded by a mechanizm which involved a nitrile ylide intermediate. This conclusion was reached by carrying out the irradiation of 27 in the presence of trapping agent methyl acrylate. Under these conditions, the formation of the 2,3-disubstituted pyrrole 31, which is formed in high yield in absence of a

trapping reagent, is entirely suppressed.

3.2.7 Carbonyl oxides

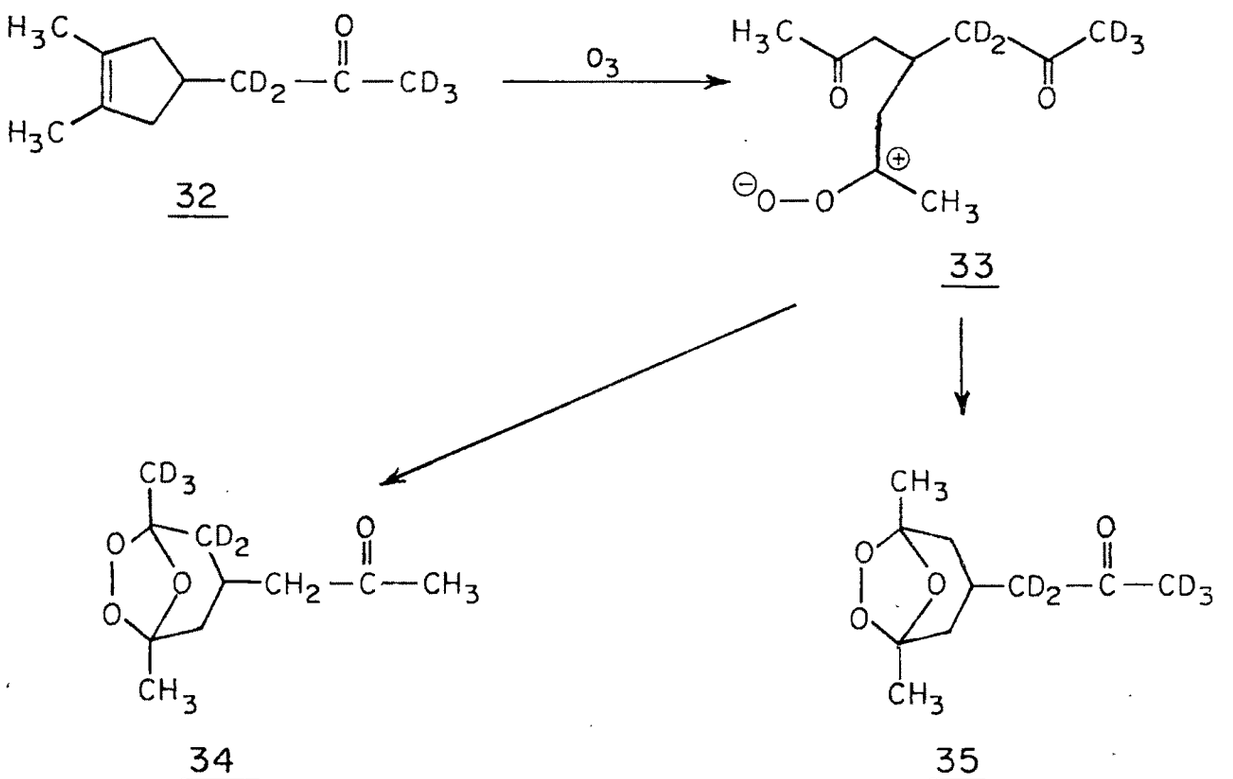
Criegee[23] has shown that the ozonolysis of 1,2-disubstituted-1-cyclopentenes e.g. 32, containing different substituents at 4 position of the ring produces carbonyl oxides such as 33 as reaction intermediates (Scheme 3.8). These dipoles undergo intramolecular 1,3-dipolar cyclo-addition with each of the two C=O functional groups present giving 34 and 35.

3.2.8 Nitrile oxide

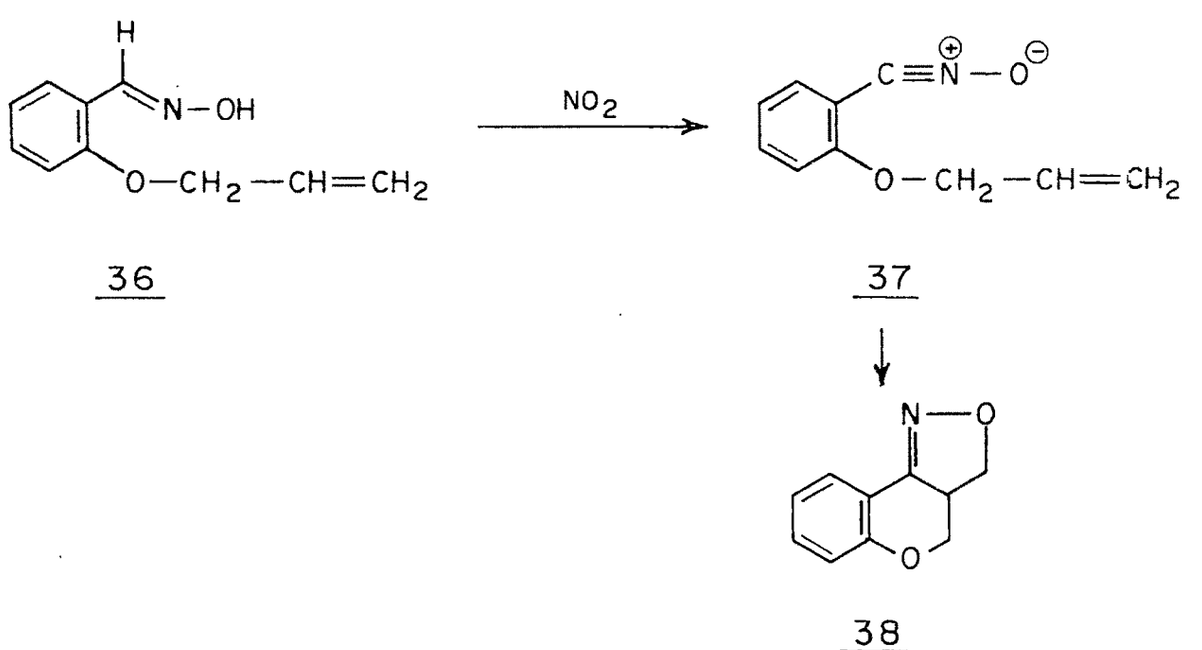
Nitrile oxides can be conveniently generated by the base treatment of hydroxamic acid chlorides or by oxidation of aldoxines (Scheme 3.9). Oxidation of 2-allyl-oxybenzaldehyde oxime 36 by nitrogen dioxide has been reported to give the fused ring compounds 38, the product of an intramolecular cycloaddition of the intermediate nitrile oxide 37 [24].

Nitrile oxides generally undergo bimolecular 1,3-dipolar cycloaddition with terminal double bonds to give 5-substituted 2-isoxazolines[25,26,27]. Obtainment of the 4-substituted 2-isoxazoline 38 in the intramolecular cyclo-addition of 36 indicates that geometrical factors can force the reaction to occur in the opposite manner from that normally encountered.

SCHEME 3·8.



SCHEME 3·9.



3.3 Heterocyclic dipoles

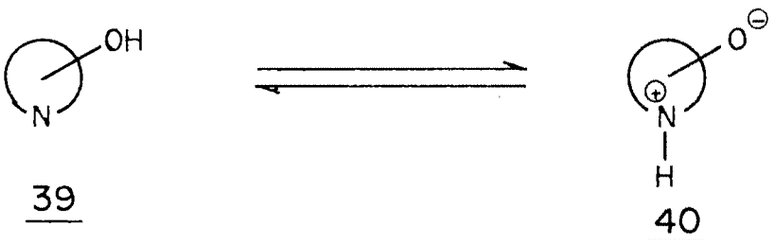
3.3.1 General introduction

Heterocycles containing a ring nitrogen atom and a substituent hydroxyl group 39 are in tautomeric equilibrium with species 40 in which the proton has been transferred to the nitrogen atom (Chart 1)[28]. In the case of 4-pyridinol 41, the zwitterionic form 42 is a resonance structure of a carbonyl compound, 4-pyridone 43. However, when the hydroxyl group is situated β to the nitrogen, as in 3-pyridinol 44 the alternative tautomeric form 45 has to be written in betaine form. Similar possibilities exist in the five-membered ring series. 4-Hydroxy pyrazoles 46 have zwitterionic tautomer 47. Structures like 45 and 47 show dipolarophilic activity.

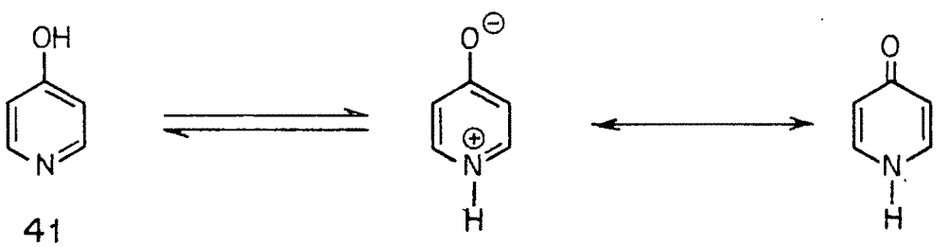
3.3.2 Sydnones

Heteroaromatic betaines with five-membered rings have the property of behaving as 1,3-dipoles and undergo 1,3-dipolar additions with a great variety of dipolarophiles. For example, on heating N-phenyl-C methyl sydnone 48 with dimethyl acetylenedicarboxylate for one hour at 120°C, CO_2 is evolved and an almost quantitative yield of dimethyl 1-phenyl 5-methyl/3,4-dicarboxylate (pyrrazole) 49 is obtained (Scheme 3.10)[29]. In this reaction an initial rate determining 1,3-addition is followed by a rapid rearomatization with ejection of carbon dioxide.

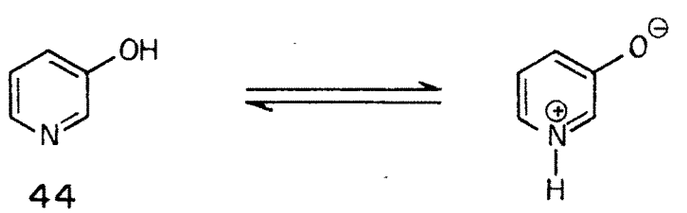
CHART 1.



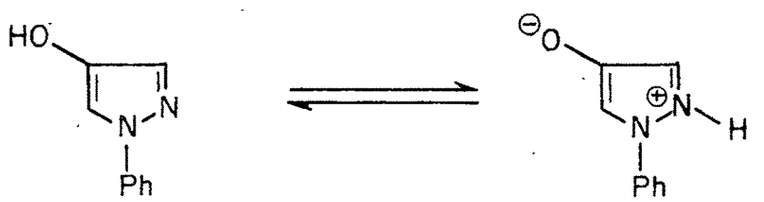
39 40



41 42 43

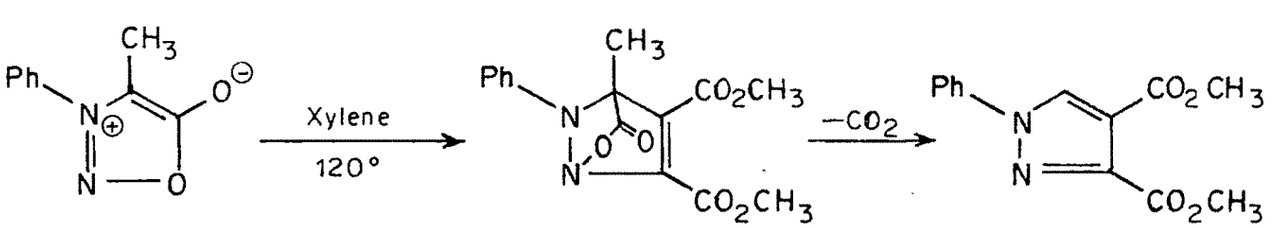


44 45



46 47

SCHEME 3·10.



48 + $H_3CO_2C-C\equiv C-CO_2CH_3$

49

The azomethine imines resulting from decarboxylation of the primary adduct (sydnone and alkene) are capable of adding onto a second molecule of alkene via a 1,3-dipolar addition. For example, N-phenyl sydnone is heated with excess acenapthylene for 30 minutes at 150°, the product isolated consists of 49% of the 1:2 adduct 53 and 41% of the 1:1 adduct 52 (Scheme 3.11)[30].

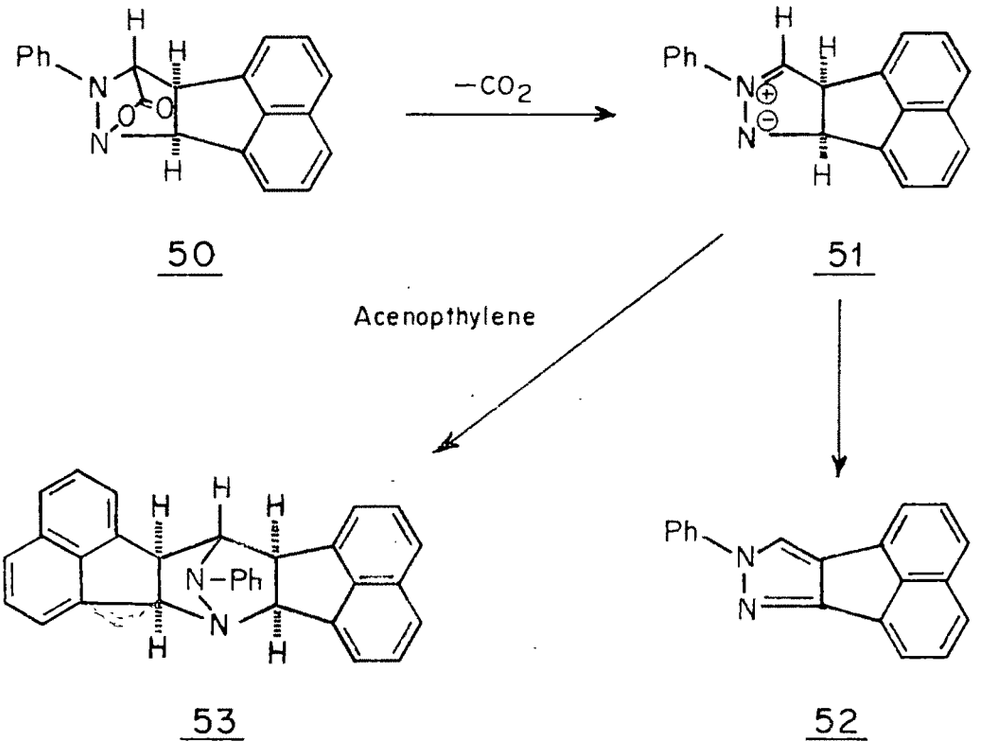
3.3.3 Pyridinium betaines

Katritzky has extensively studied the hetero-aromatic betaines, behaving as 1,3-dipoles and their cyclo-addition reactions[31]. 1-Methyl-3 pyridiniumolate 54 was prepared from 3-pyridinol via the quaternary salt 53, which is most conveniently converted into 54 using an anion exchange resin. Betaine 54 shows 1,3-dipolar activity and undergoes reactions with acrylonitrile, methyl acrylate, methyl vinyl ketone and methyl methacrylate (Scheme 3.12).

With each of these unsymmetrical dipolarophiles there are four conceivable reaction products that can be formed, but the reaction proceeds regiospecifically to produce a mixture of endo 55 and exo 56 isomers. The two alternative regioisomers 57 were not detected in any of these reactions.

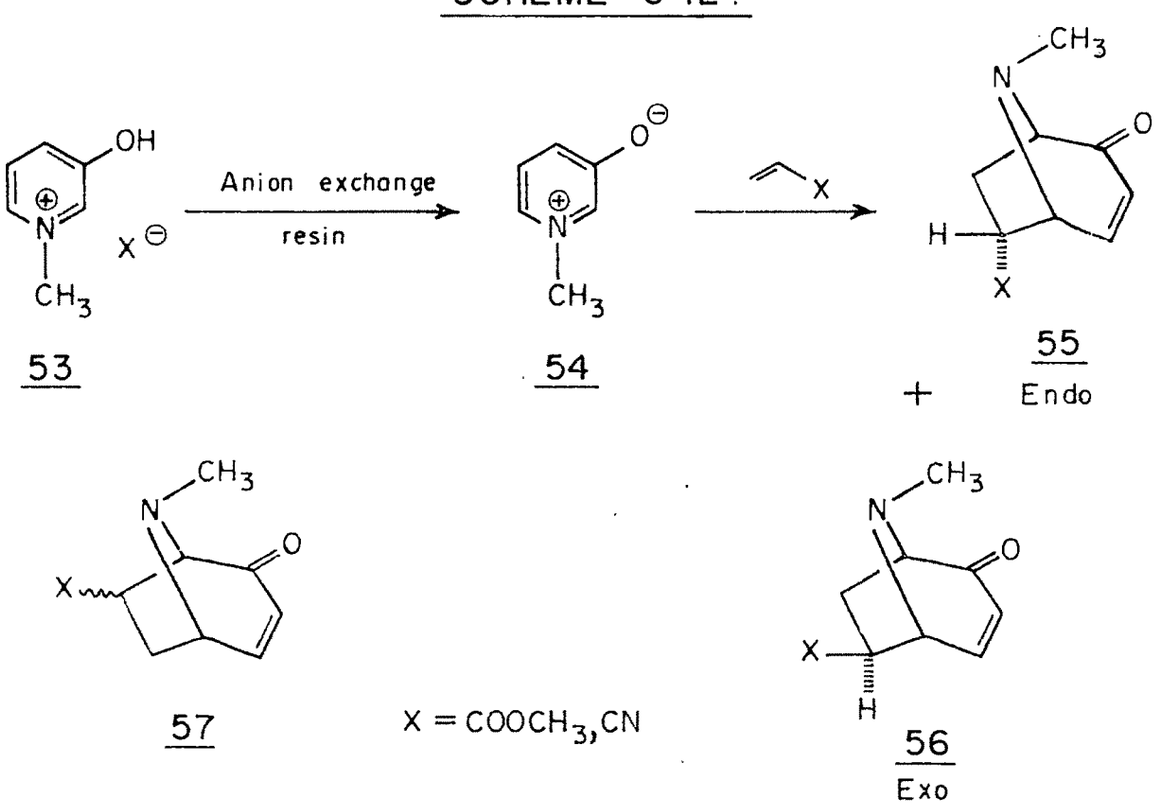
Reactions were successful only with olefinic dipolarophiles containing a strongly electron-withdrawing

SCHEME 3·11.



50 51 53 52

SCHEME 3·12.



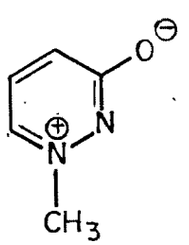
53 54 55 Endo

57 56 Exo

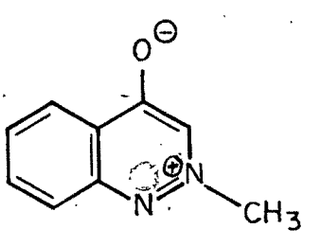
group, other olefins do not yield adducts.

These cycloadducts have been converted to tropone derivatives i.e. tropones, tropolone, benzotropones, aryl-substituted tropolones. In this synthesis, it is not necessary to separate the two stereoisomeric adducts. The mixture of adducts from methyl acrylate 58 is converted into mixed methiodides 59, which on reaction with silver oxide or sodium hydrogen carbonate gives dimethyl amino tropone 60 and further hydrolysis gives tropolone 61 (Scheme 3.13).

However, the placement of further nitrogen atoms in the ring appears to seriously decrease the reactivity[32]. Thus the methyl pyridazinium betaine 62 is unreactive toward a wide range of dipolarophiles, although the benzoanalogs i.e. phthalazinium betaine 63[33] and cinnolinium betaine 64[34,35] do show reactivity as 1,3-dipoles. The pthalazinium betaine 63 reacts with diphenyl acetylene to give the adduct 65 (Scheme 3.14)[34].



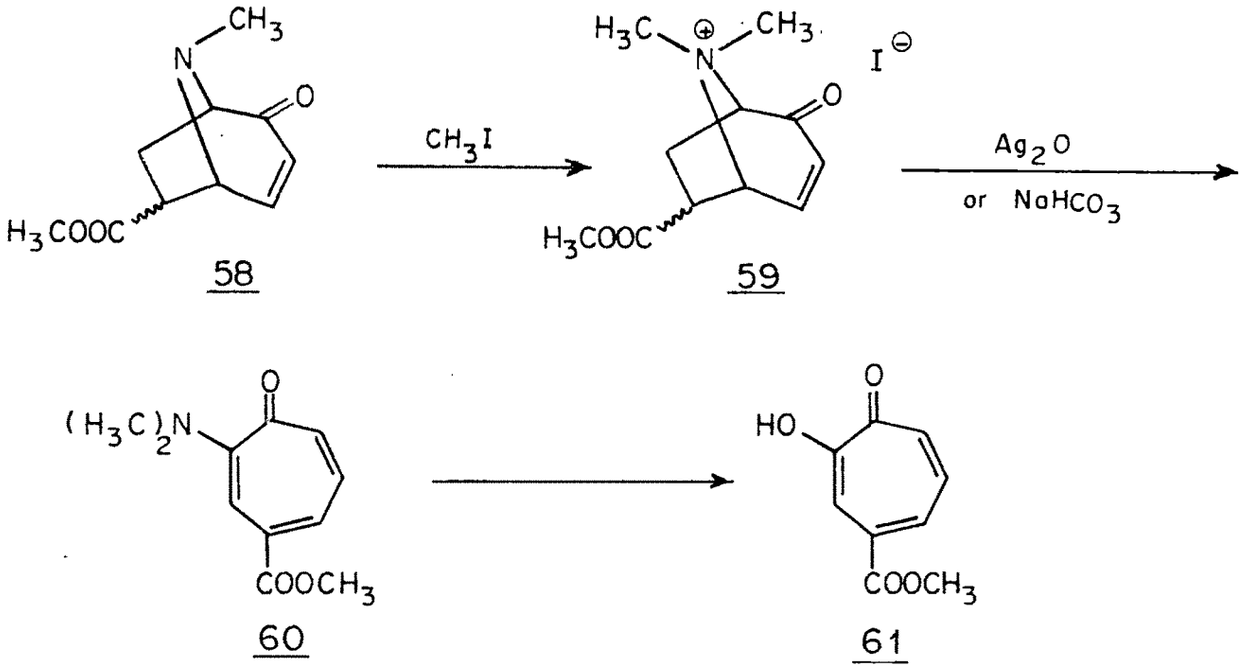
62



64

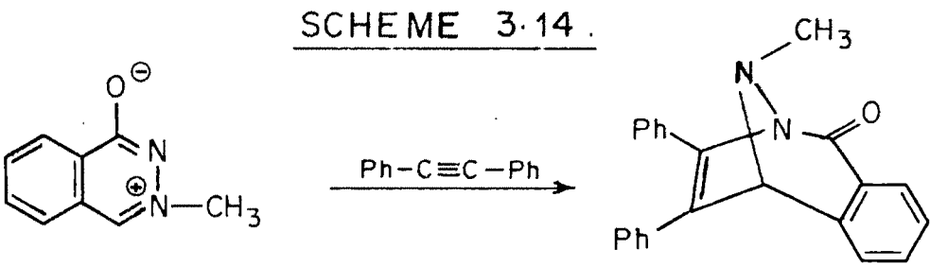
3-Pyridinol 44 is a tautomeric compound in equilibrium

SCHEME 3·13.



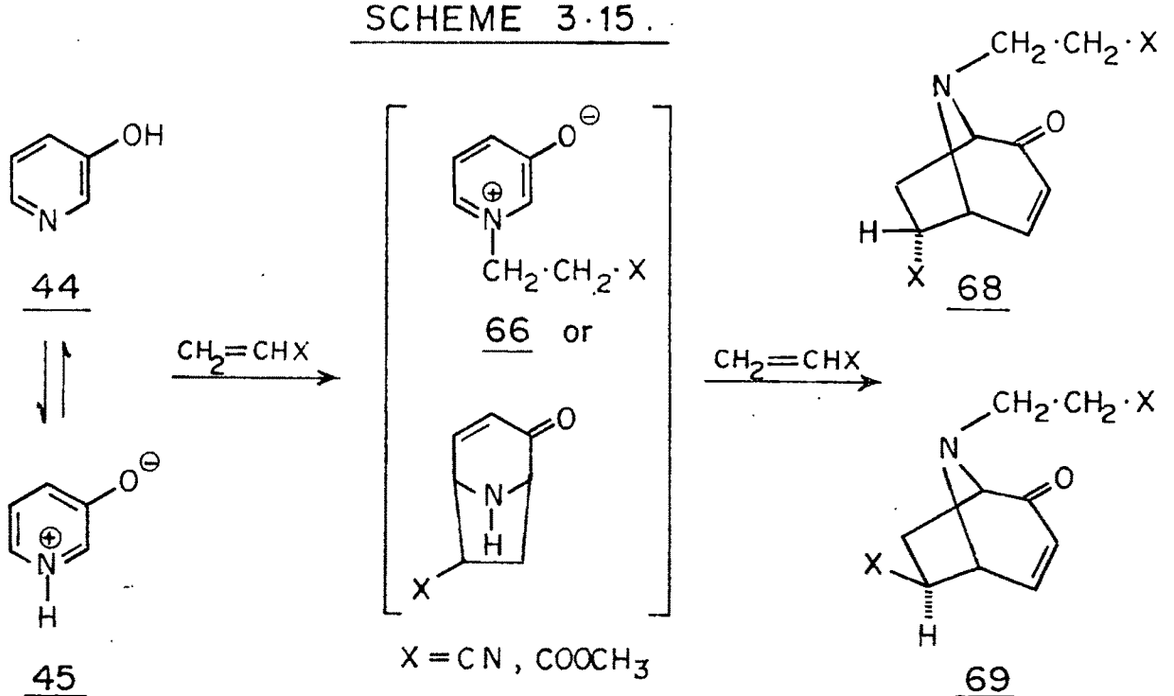
58 59 60 61

SCHEME 3·14.



63 65

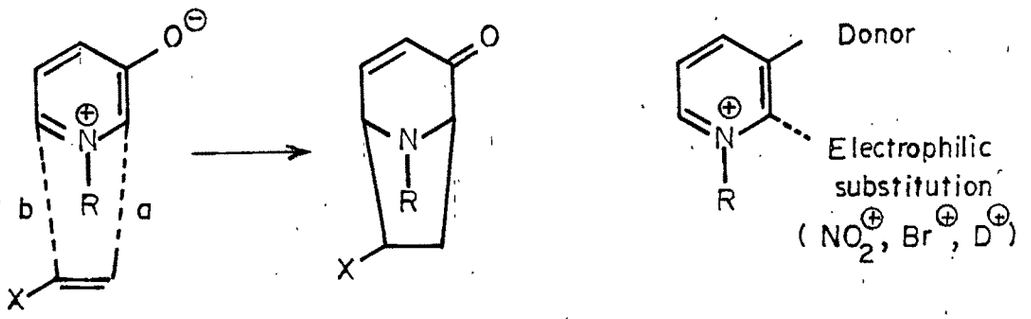
SCHEME 3·15.



44 45 66 or 67 68 69

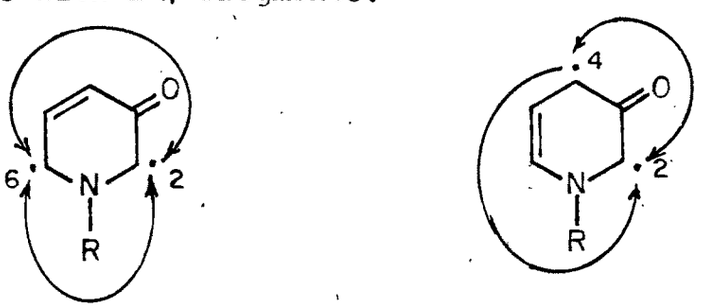
with the zwitterionic form 45. This reacts with acrylonitrile and methyl acrylate to give high yields of the endo 68 and exo 69 adducts (Scheme 3.15)[28]. Both adducts contain two molecules of the dipolarophile. Two routes are possible: either the initial Michael addition at the cyclic nitrogen atom to give 66 followed by dipolar addition with a second mole of dipolarophile, or alternatively dipolar addition with the betaine to give 67 followed by a Michael type addition at the nitrogen atom of 67. No direct evidence is available to distinguish these possibilities in this system.

The regiospecificity of the cycloaddition 70 → 71 (R = methyl, phenyl or hydrogen) together with the fact that group x of the dipolarophile needs to be an electron-withdrawing substituent can be explained. In the pyridinium compounds 72 the carbon atom at position 2 behaves as the most nucleophilic of the ring carbon atoms. Thus, electrophilic substitution of compounds of this type always occurs at C-2[36]. Calculations show that this position has the highest π-electron density. Evidently the bond a in 70 between C-2 of the betaine and the C-β of the dipolarophile is formed before bond b. A driving force in the reaction is the donation of electrons from the betaine to the dipolarophile.



70 71 72

For the additions at the 2,6-positions these betaines are 4 π fragments, they can be considered as 5 atom fragments bridged by nitrogen or alternatively as 3 atom fragments bridged by a 3-carbon unit (cf. 73). They are thus expected to undergo thermally allowed suprafacial pericyclic reactions with 2 π fragments.



73 74

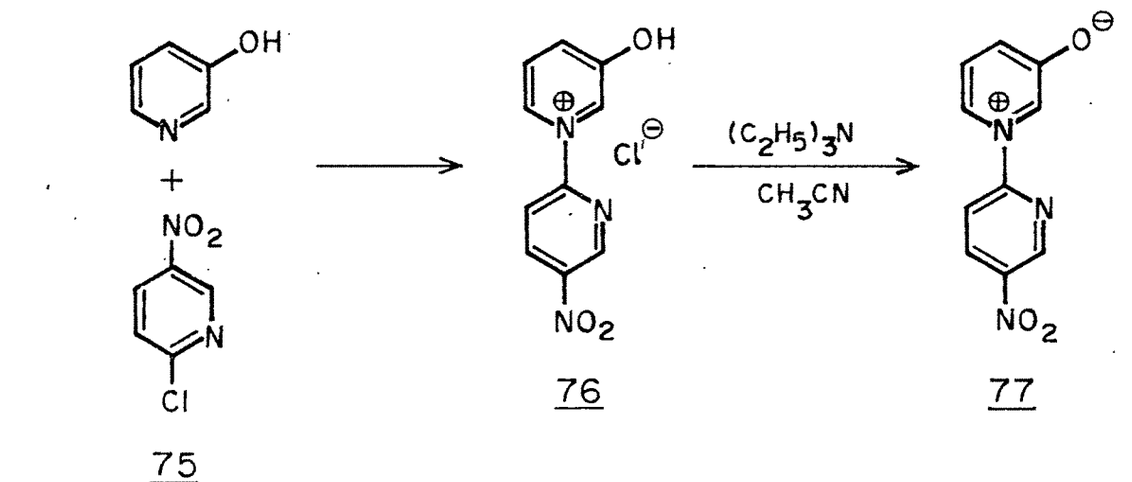
These betaine systems can also add at 2,4-positions. For this additions across the 2,4-positions 74 the betaine can be considered either to be a 6π electron 5 atom fragment with a one carbon atom bridge, or as a 2 π electron 3-atom fragment with a two-carbon and one nitrogen atom bridge. Hence these systems can undergo thermal cycloaddition with

4 π systems. For example 2-chloro 5-nitropyridine 75 reacts readily with 3-pyridinol to give the quaternary salt 76 and the betaine 77 liberated spontaneously dimerizes to the compound 78. This dimerization involves the addition of the 2,6-positions of one betaine to the 2,4-positions of a second molecule in the sense of 79 (Scheme 3,16)[37].

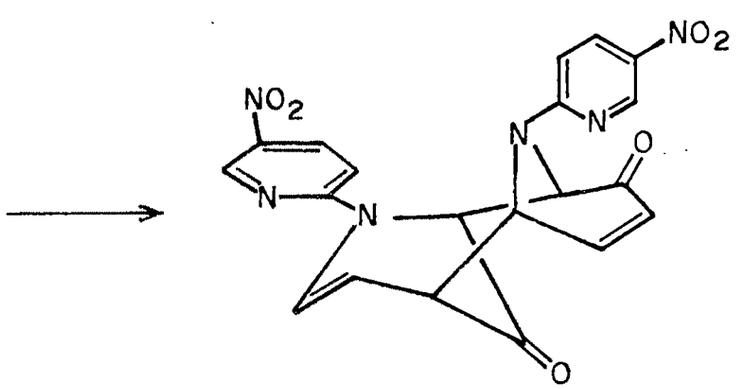
Dimer 78 dissociates reversibly at 100° to the monomer, for under these conditions it reacts readily with a wide variety of dipolarophiles to give adducts in good yields[38]. This dimer also reacts with a variety of 1,3-dienes across the 2,4-positions. In these reaction mixtures, the alternative possibility of the diene reacting as a mono-ene across the 2,6-positions also occurs. If the reaction of 78 with cyclopentadiene is carried out at a high temperature: heating the two dimers together at 100°C the product 80 is formed. The initial step of the reaction is an addition of the diene as mono-ene across the 2,6-positions; this is followed by a Diels-Alder addition to give the final product. On the other hand, if the reaction between the two monomers (i.e. cyclopentadiene and betaine 77)is carried out at 20°C, a mixture of the two expected initial products of addition across the 2,4 and 2,6-positions is formed.

The nitropyridyl betaine 77 reacts with dimethyl-

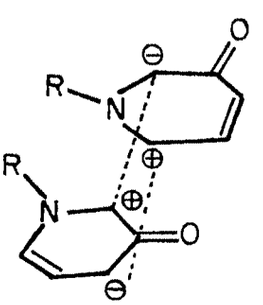
SCHEME 3·16.



75 76 77



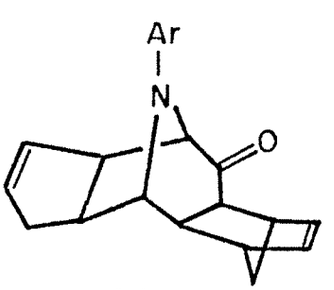
78



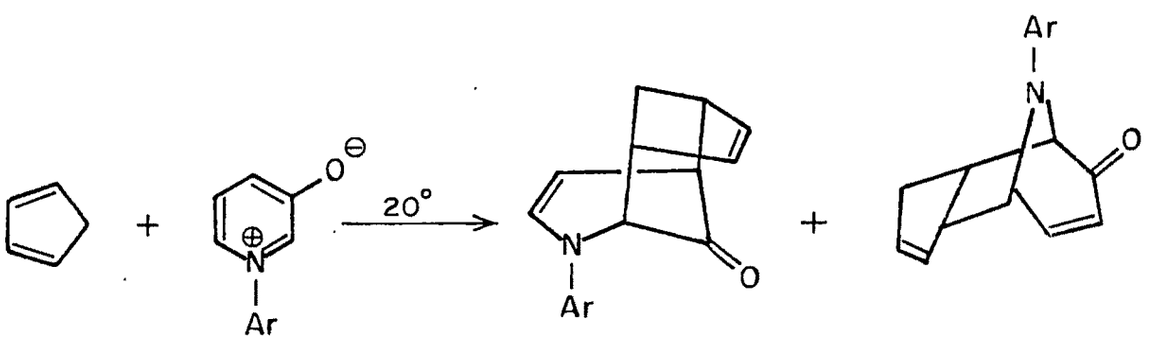
79

Cyclopentadiene dimer + Betaine dimer → (100°C) → 80

78



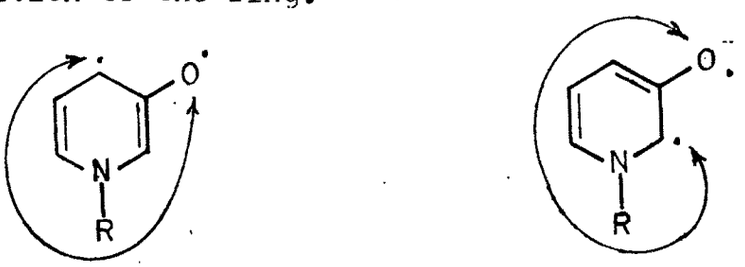
80



77 81 82

fulvene in the sense of 83 (4π, 6π cycloaddition) the initial adduct 84 isomerises spontaneously to the end product 85 (Scheme 3.17).

Another mode of cycloaddition is seen, in which the betaine acts as a 8π component either across the oxygen atom and the 4-position, or across the oxygen atom and the 2-position of the ring.

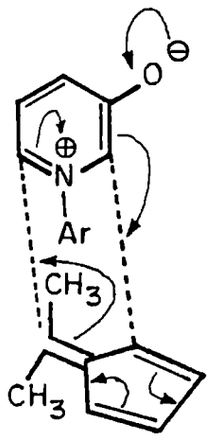


86

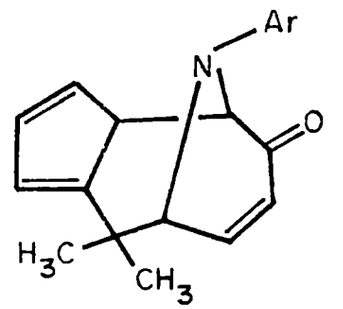
Certain 2π components can add across the oxygen and ring 4 position or ring 2 position (cf. 86)[39]. Dichloroketene cycloadds with 3-oxopyridiniums to yield the new bicyclic compounds 89 via intermediates 88 which spontaneously lose HCl (Scheme 3.18). By reacting the betaine 90 with α-bromophenylketene and by hydrolysis of the intermediate 91 it has been possible to convert 3-hydroxypyridine to 2-benzyl-3-hydroxypyridine 92 (Scheme 3.19).

Change of oxygen carrying the negative charge to sulphur, nitrogen or carbon (cf. 93) indicate that this type of variation in the structure is not advantageous. One of the reasons is the formation of a C=X bond which is

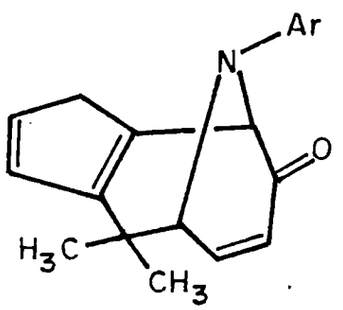
SCHEME 3·17.



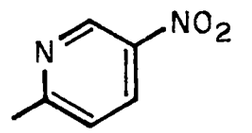
83



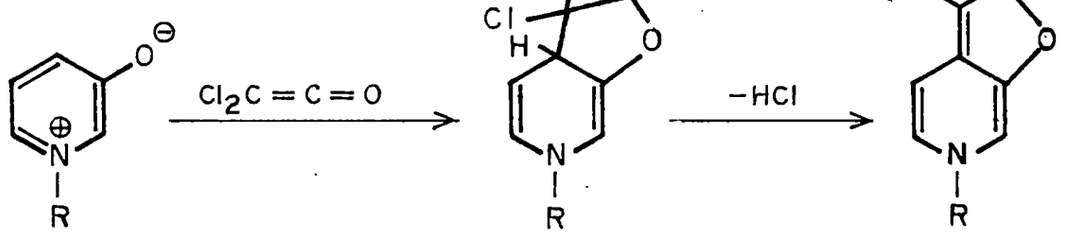
84



85

Ar = 

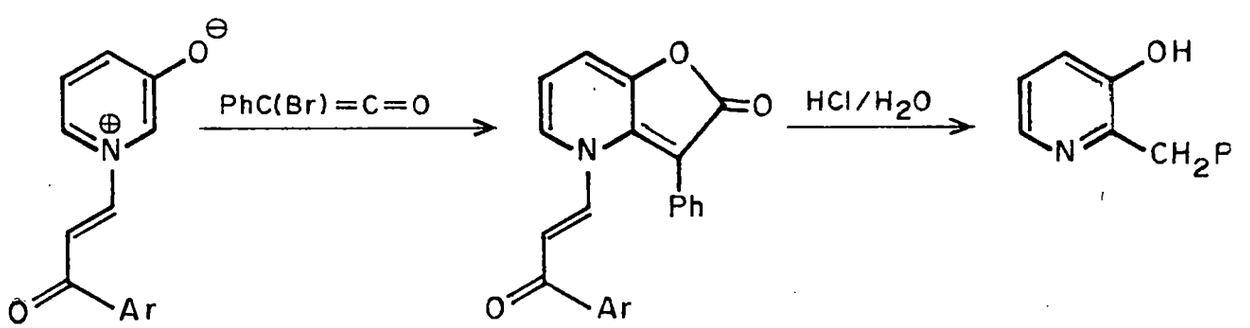
SCHEME 3·18.



87 88 89

R = CH_3, $PhCH_2$–, Ph

SCHEME 3·19



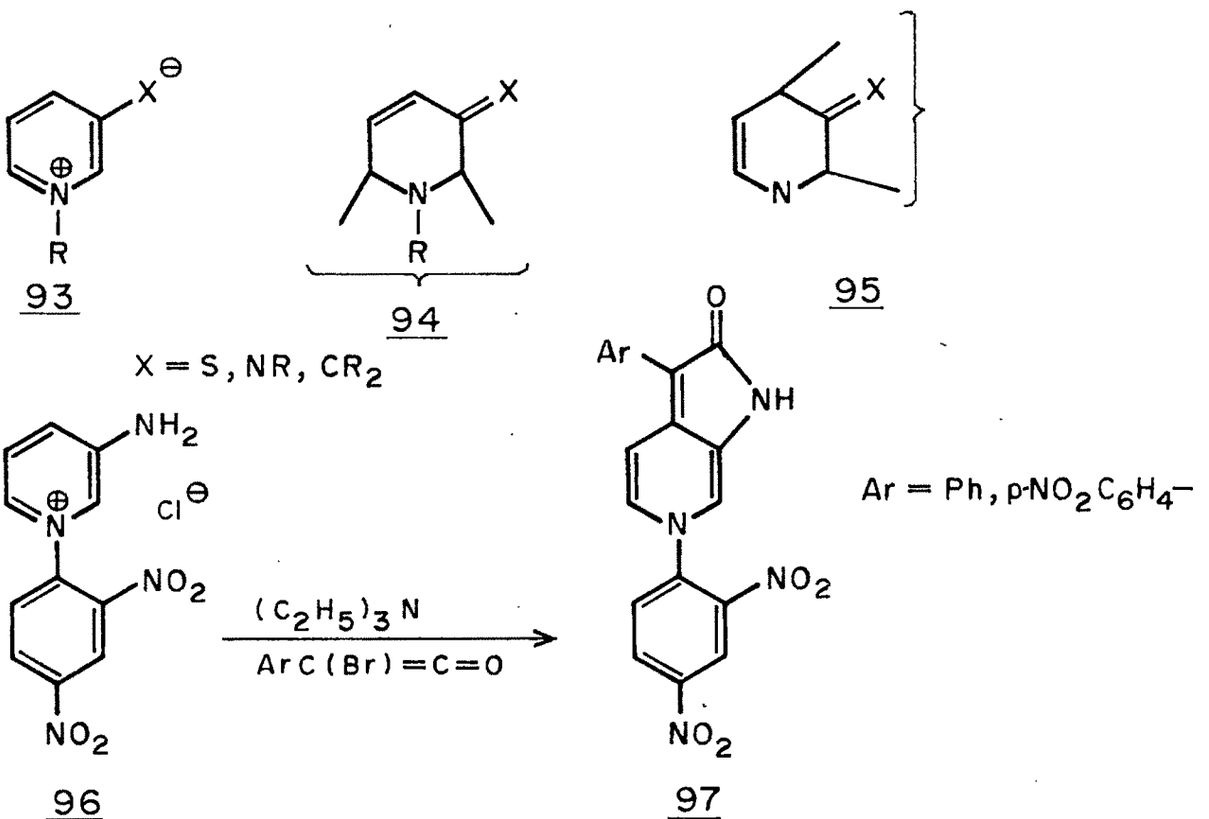
90 91 92

involved (cf 94, 95) is much less stable when X is sulphur, nitrogen or carbon atom than when it is oxygen. The only successful reaction of compounds of type 93 have been where reaction has taken place across the nitrogen and the 4 position of the ring (Scheme 3.20).

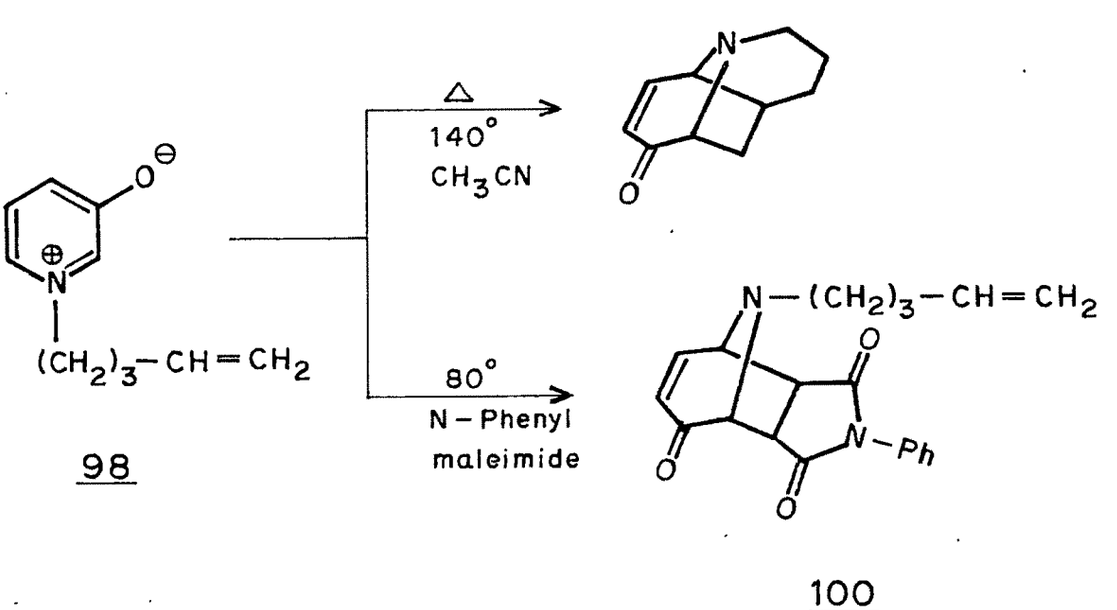
Pyridinium betaines having methyl or phenyl group as substituent on nitrogen yield the cycloadduct in 30-40% showing the poor reactivity of this type of betaines. N-phenyl group is not easy to remove if necessary for further elaboration of cycloadduct. 5-Nitro-2-pyridyl or 2-triazinyl as the N-substituent increases the reactivity of betaines giving 90% of cycloadduct[40]. These type of nes are very reactive systems which possesses the tage of ready availability, ease of activation. Some e nitrogen substituents (triazinyl) are quite easy to e by hydrolysis.

Recently Sammer and Watt[41] have shown that N-alkenyl- idiniumolate undergoes intramolecular cycloaddition nactivated olefins (Scheme 3.21). Thermolysis of the he 98 in acetonitrile at 140° for 24 hrs gave the adduct 99. This bridged troponoid derivative was regeoselectively. This cycloaddition was found to latively slow, in that competition reactions gave l cycloadducts, N-phenylmaleimide reacted with the ine 98 at 80°C to give the adduct 100 only.

SCHEME 3·20.



SCHEME 3·21.



3.4 PRESENT WORK

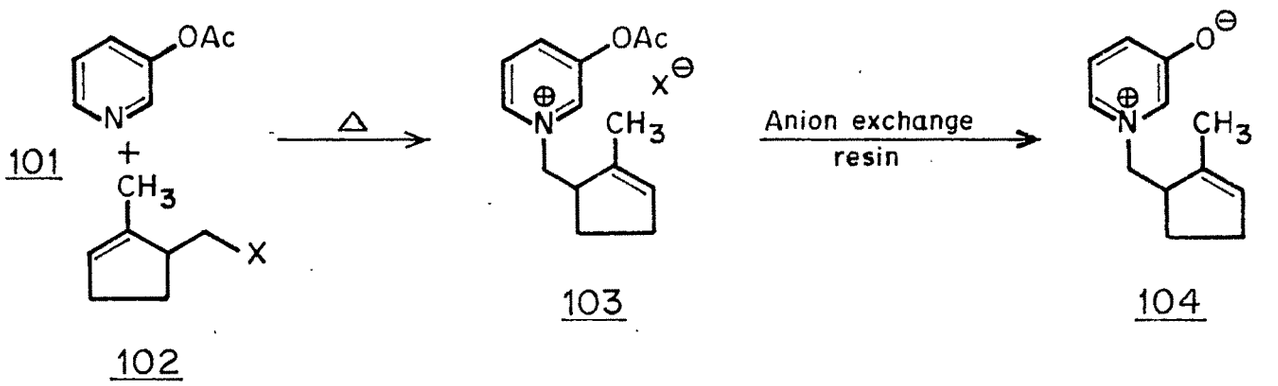
3.4.1 Introduction

The high stereoselectivity and regioselectivity with which the 1,3-dipoles undergo cycloaddition with dipolarophiles led us to investigate the following reaction sequence leading to synthesis of Dendrobine, an alkaloid having seven chiral centers. An internal 1,3-dipolar cycloaddition of pyridinium system with cyclopentene double bond is the key step (Scheme 3.22).

In the above sequence the intramolecular cycloaddition of betaine 104 fixes five out of seven stereo centers in dendrobine skeleton and remaining two can be fixed with the functions already present. To study the above cycloaddition reaction we conducted the study on the model compounds with acylic N-alkenyl substituents (Scheme 3.23, 3.24).

The salt obtained from heating 3-pyridonol acetate 101 and 5-iodo 3-pentene 110 on treatment with anion exchange resin gave the betaine 112. Heating the betaine in refluxing xylene gave the cycloadduct 113 regioselectively in about 20% yield. Making the dipolarophile more reactive by using electron withdrawing substituent on the double bond increases the yield (Scheme 3.24). The betaine obtained from the salt 115 on heating in refluxing xylene gave the cycloadduct 117

SCHEME 3·22.

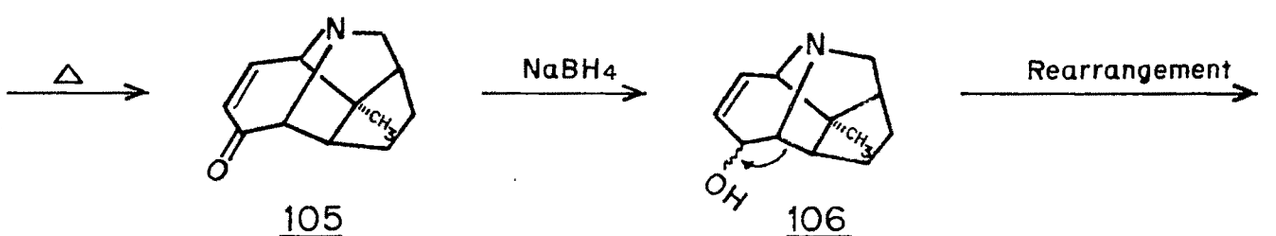


102

X = leaving gr.

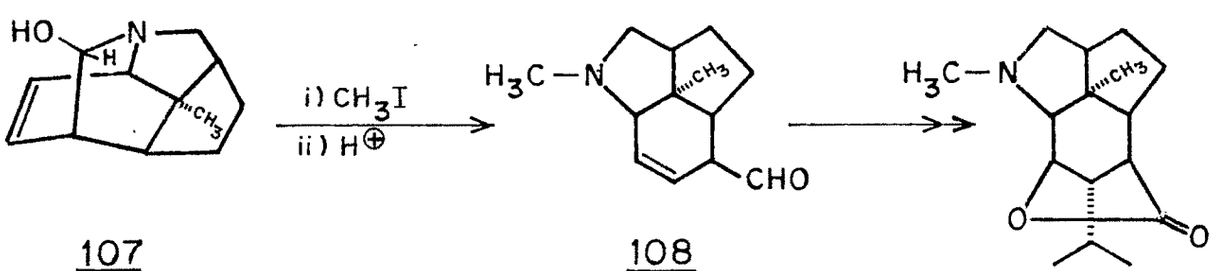
103

104



105

106



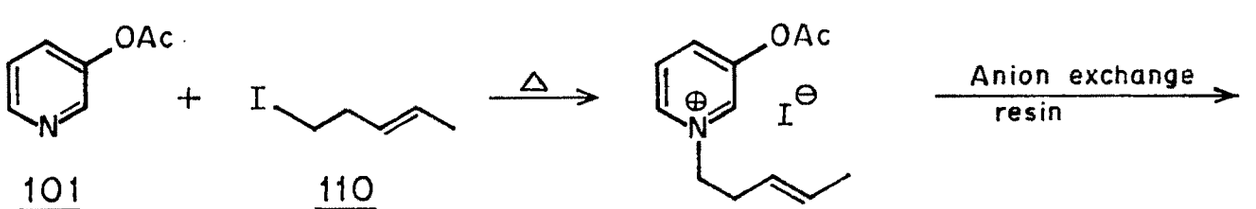
107

108

109

DENDROBINE

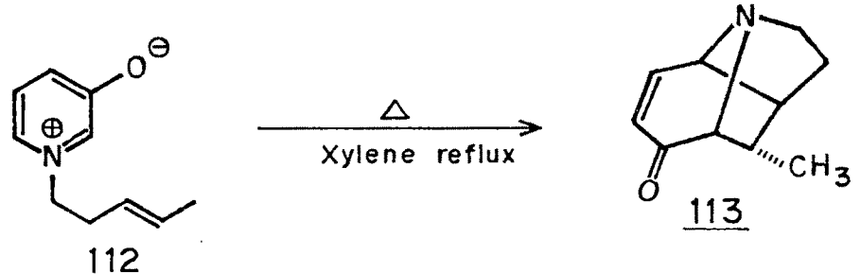
SCHEME 3·23.



101

110

111



112

113

in 38% yield.

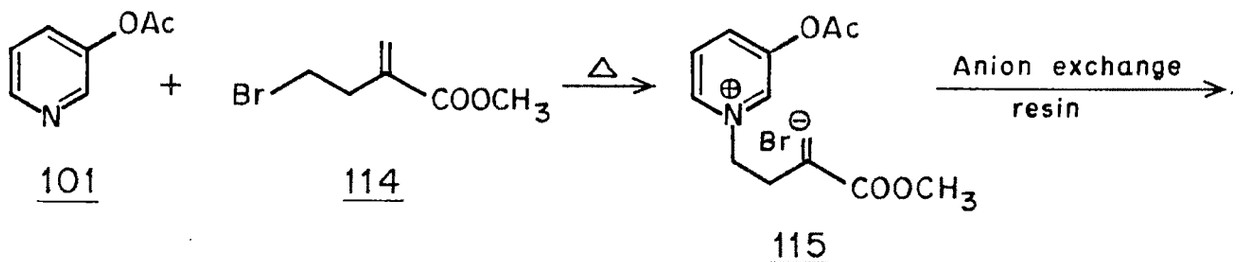
Several synthetic routes can be thought of for the synthesis of cyclopepentene derivative, required for the above methodology of dendrobine synthesis. The most simple reaction would be Prins reaction of the corresponding cyclopentene derivative. Δ^3-Carene 118 reacts with paraformaldehyde in warm glacial acetic acid to give the alcohol and acetate 119[42]. Similar treatment of 1-methyl-cyclopentene 120 did not give the corresponding alcohol 121 (Scheme 3.25).

The reported vinyl cyclopropyl rearrangement to cyclopentene derivative (Scheme 3.26) in our hands failed to produce practical yields even with modification in reaction conditions[43].

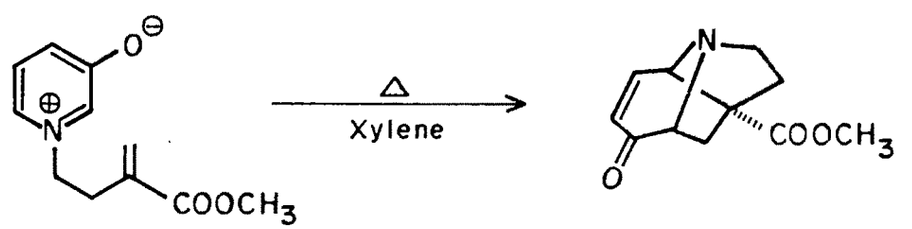
From the studies on solvolysis of bicyclo(3.1.0)hexanyl 2-chlorides (both exo and endo) which gives mainly bicyclohexanols and some cyclohex 3-ene ols it was concluded that the intermediate 2-bicyclohexyl cation is nonclassical with positive character at C-5[44]. The intermediacy of a bicyclobutonium type of cation was ruled out because of the absence of cyclopentenyl as well as bicyclo(2.2.0) hexan 2ols. Since the deamination reactions of bicyclohexanyl amines also gave similar results, it was thought that this reaction is an S_{N_1} type 124 → 126 + 127.

In this connection we wanted to see any change in the

SCHEME 3·24.

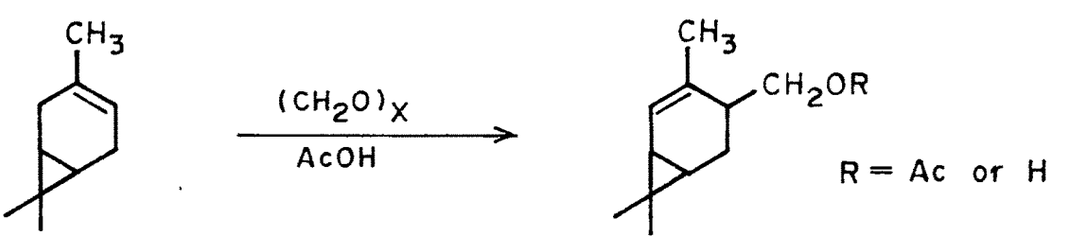


101 114 115

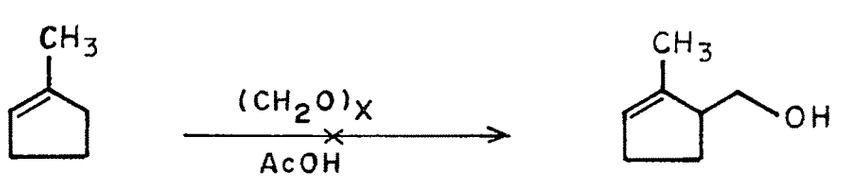


116 117

SCHEME 3·25.

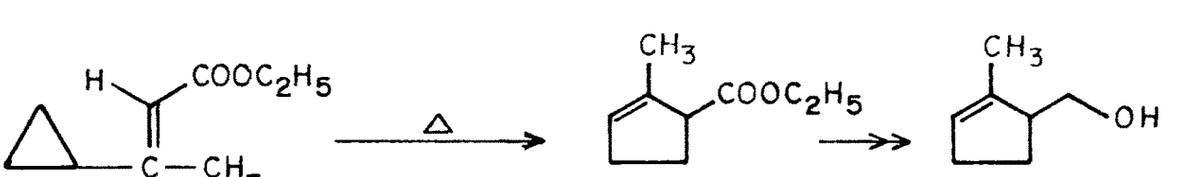


118 119



120 121

SCHEME 3·26.



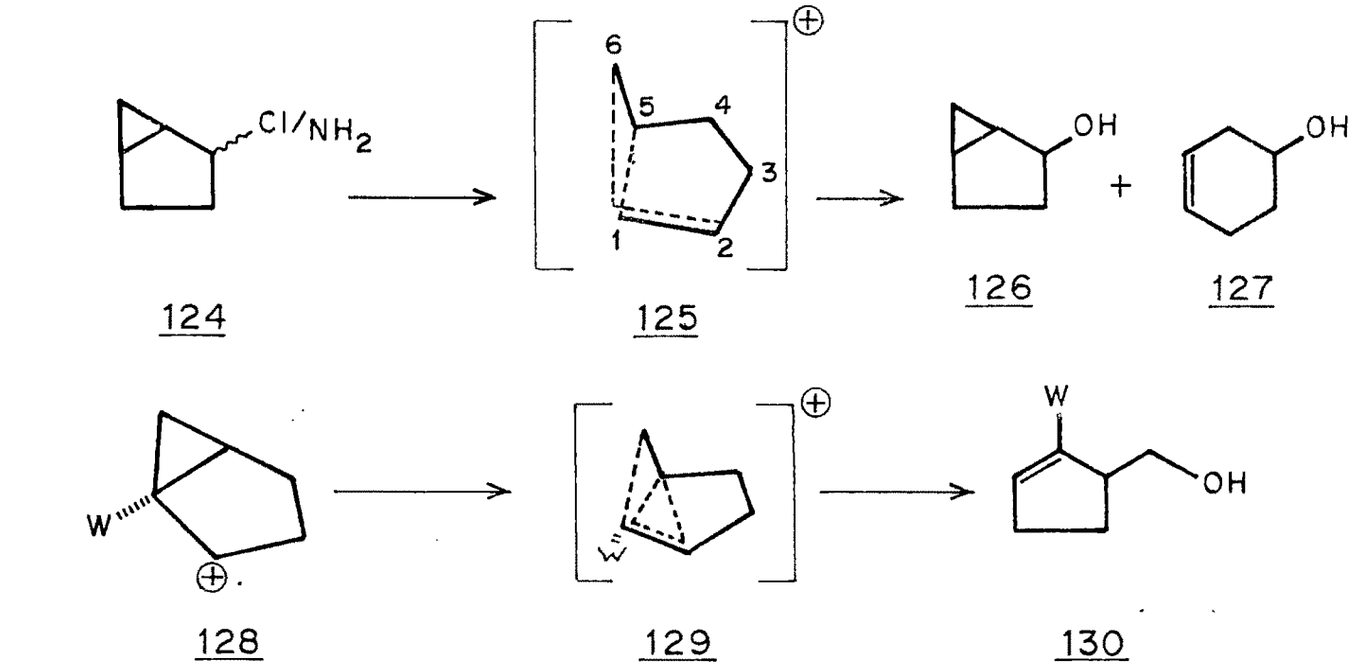
122 123 121

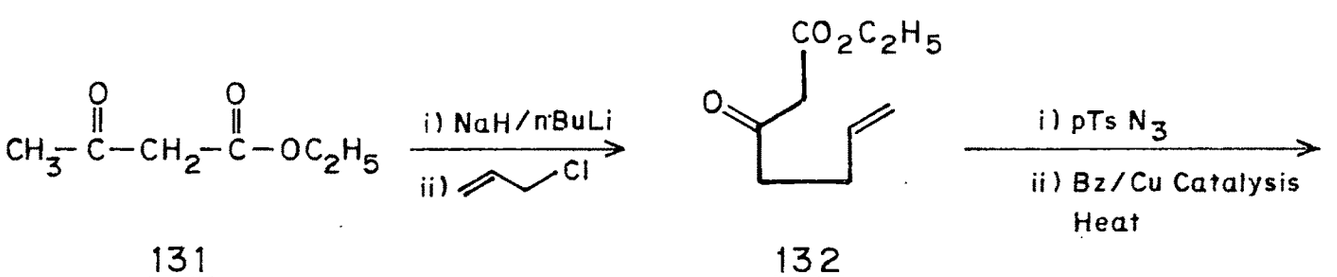
pattern of solvolysis when the bicyclic system is substituted by an electron withdrawing group 128 at C-1.. Involvement of a bicyclobutonium intermediate 129 in these cases might lead to the required cyclopentenyl carbinyl derivative (Scheme 3.27). For this we made 1-substituted bicyclo(3.1.0) hexane 2ol 135 and treated with strong acids to generate the carbonium ion.

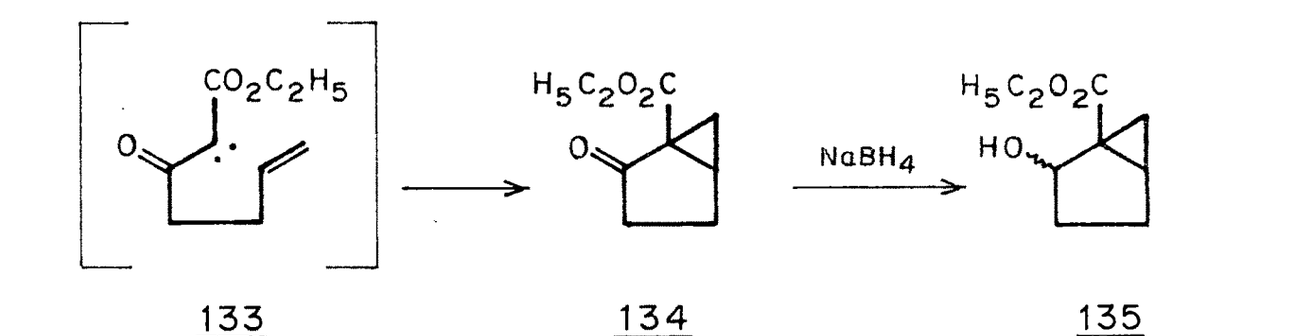
1-Carbeethoxy bicyclo(3.1.0)hexane 2-one was prepared by the following sequence of reactions (Scheme 3.26). Allylation of ethyl acetoacetate dianion gave ethyl 3-oxo-6-heptenoate 132. The diazo compound obtained from the reaction of diketone with p-toluenesulfonazide, on heating in benzene solution with copper catalysis gave the expected 1-carboethoxy bicyclo(3.1.0)hexane-2-one 134. The ketone was reduced with sodium borohydride to corresponding alcohol 135.

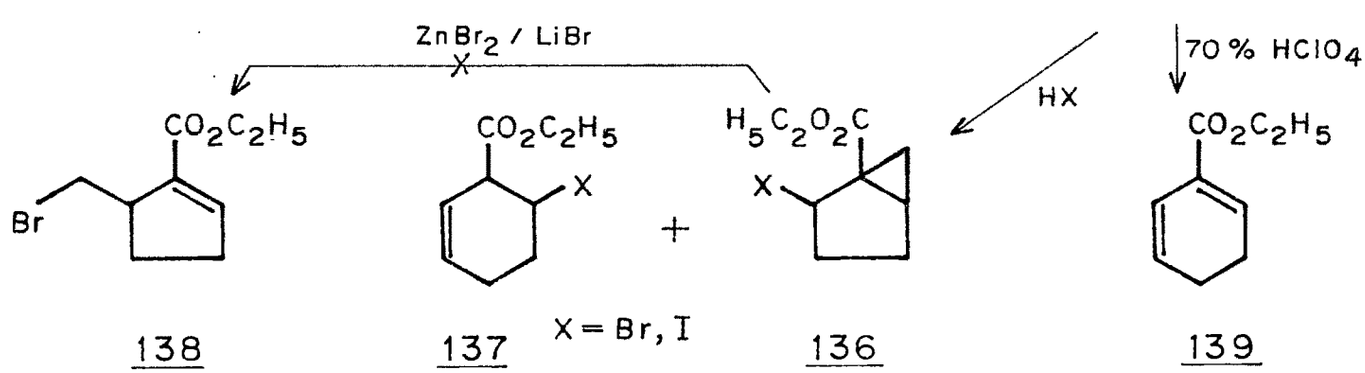
Rearrangement of the bicyclic alcohol 135 under different conditions were tried. Treatment with protic acids like 48% hydrobromic acid or hydriodic acid gave mixture of products. From NMR spectra it seemed to be a mixture of bicyclohexylhalide and cyclohexenyl halide 136, 137. Triphenylphosphinedibromide or triphenylphosphine-carbontetrachloride mainly gave bicyclohexylhalide 136 without rearrangement. This halide 136 on treatment with

SCHEME 3·27.


Cl/NH2
6
5
4
3
1
2
OH
OH
+
124
125
126
127
W
W
OH
128
129
130


CH3–C(=O)–CH2–C(=O)–OC2H5
i) NaH/nBuLi
ii)
Cl
CO2C2H5
O
i) pTs N3
ii) Bz/Cu Catalysis
Heat
131
132


CO2C2H5
O
H5C2O2C
O
NaBH4
H5C2O2C
HO
133
134
135


ZnBr2 / LiBr
X
70 % HClO4
HX
CO2C2H5
Br
CO2C2H5
X
H5C2O2C
X
+
CO2C2H5
138
137
X = Br, I
136
139

zinc chloride and lithium chloride did not produce cleanly any product. 1-Carboethoxy- 1,5-cyclohexadiene 139 was obtained on treatment of alcohol with 70% perchloric acid.

The above observations lead to the conclusion that even with electronwithdrawing substituent at one position, the formation of bicyclobutonium intermediate is not taking place and the intermediate carbonium ion species are very similar to those involved in the solvolysis of 124.

It is reported[45] that 1-carboethoxybicyclo(3.1.0) hex$^{an}_{\wedge}$2-one can be opened with strong nucleophiles like CN^- or PhS^- to give cyclopentanone derivatives. If the ketone is opened by PhS^-, the resulting sulfide can be converted to halide via ternerization. Corey et al.[46] have reported that phenyl alkyl sulfide with methyl iodide and lithium iodide in refluxing dimethyl formamide gives the alkyl iodide via ternary salt. Also the ketone enolate obtained can be alkylated to get finally 2-methyl-2 cyclopentyl carbinyl iodide (Scheme 3.28).

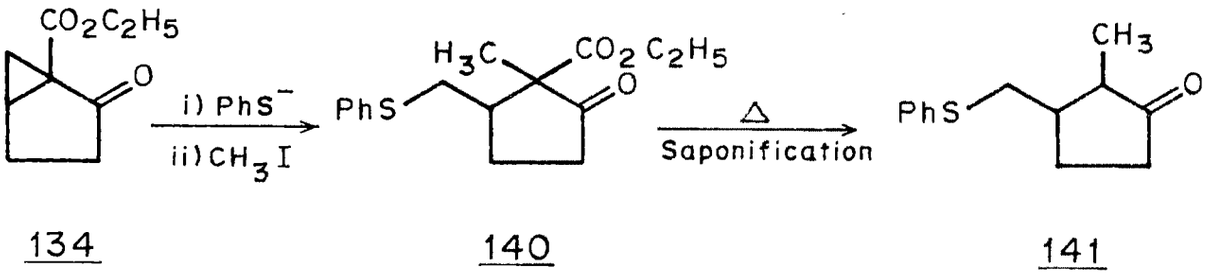
1-Carboethoxybicyclo(3.1.0)hex$^{an}_{\wedge}$2-one 134 on treatment with thiophenoxide anion and quenching the anion with methyl iodide gave the methylated ketone 140. This was saponified and decarboxylated to give ketosulfide 141. This sulfide failed to give ternary salt with methyl iodide and further iodide 144. However the ternerisation was

achieved by treatment with dimethyl sulfate, but this did not undergo cleavage by iodide anion. This sulfide was stable towards Pummerer reaction conditions or bromination with N-bromosuccinimide.

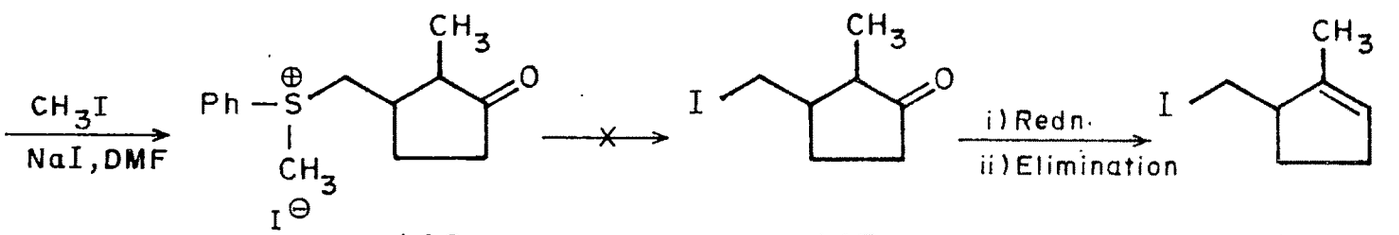
If the bicyclic ketone 134 can be opened by thiol acetic acid anion instead of thiophenoxide anion, it will give the protected thiol, subsequently the thiol can be converted to the halide[47] to give the required cyclopentene derivative (Scheme 3.29). The bicyclic ketone 134 was opened with thiolacetic acid anion and the reaction mixture was quenched with methyl iodide to give methylated product 145. It was thought that the carboxylic ester will saponify faster than the thio ester. But when the protected thiol 145 was subjected to saponification it seemed that both the esters were undergoing saponification and the product appeared to be thiolactone 148 from the NMR spectra.

Another approach for making the methyl cyclopentenyl carbinol 121 was attempted starting from 2-methyl-cyclo-pent-2 enone 149 via oxirane 150 (Scheme 3.30). Reductions of oxiranes normally lead to mixture of primary and secondary alcohols, but use of aluminium hydride or LAH and $AlCl_3$ mainly gives primary alcohol[48]. The cyclopentenone 149 was prepared from cyclopentanone by a reported procedure[49].

SCHEME 3·28.

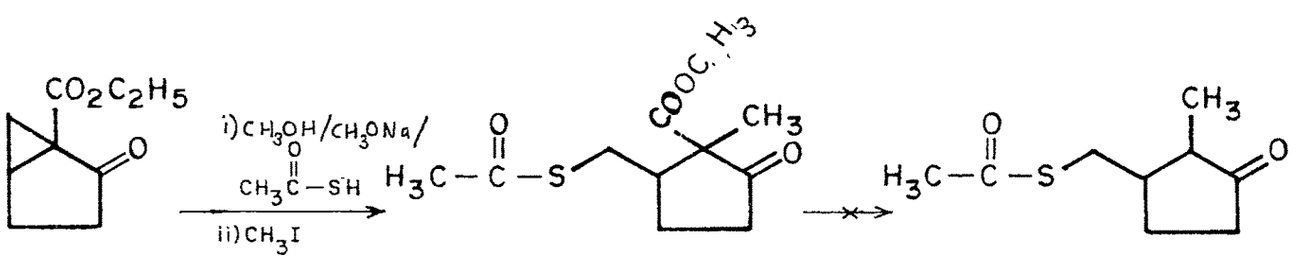


134 140 141

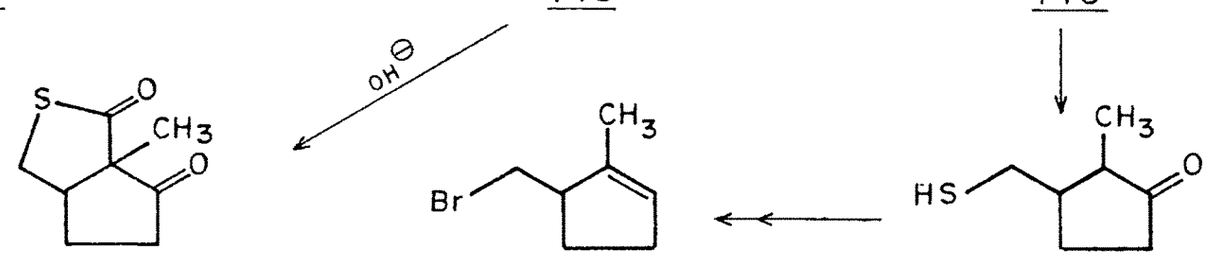


142 143 144

SCHEME 3·29.

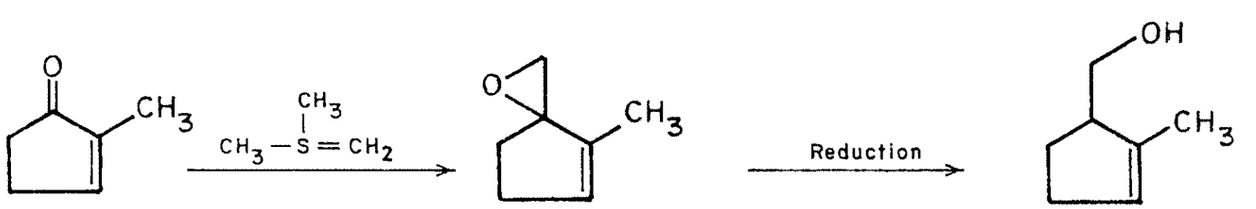


134 145 146



148 138 147

SCHEME 3·30.



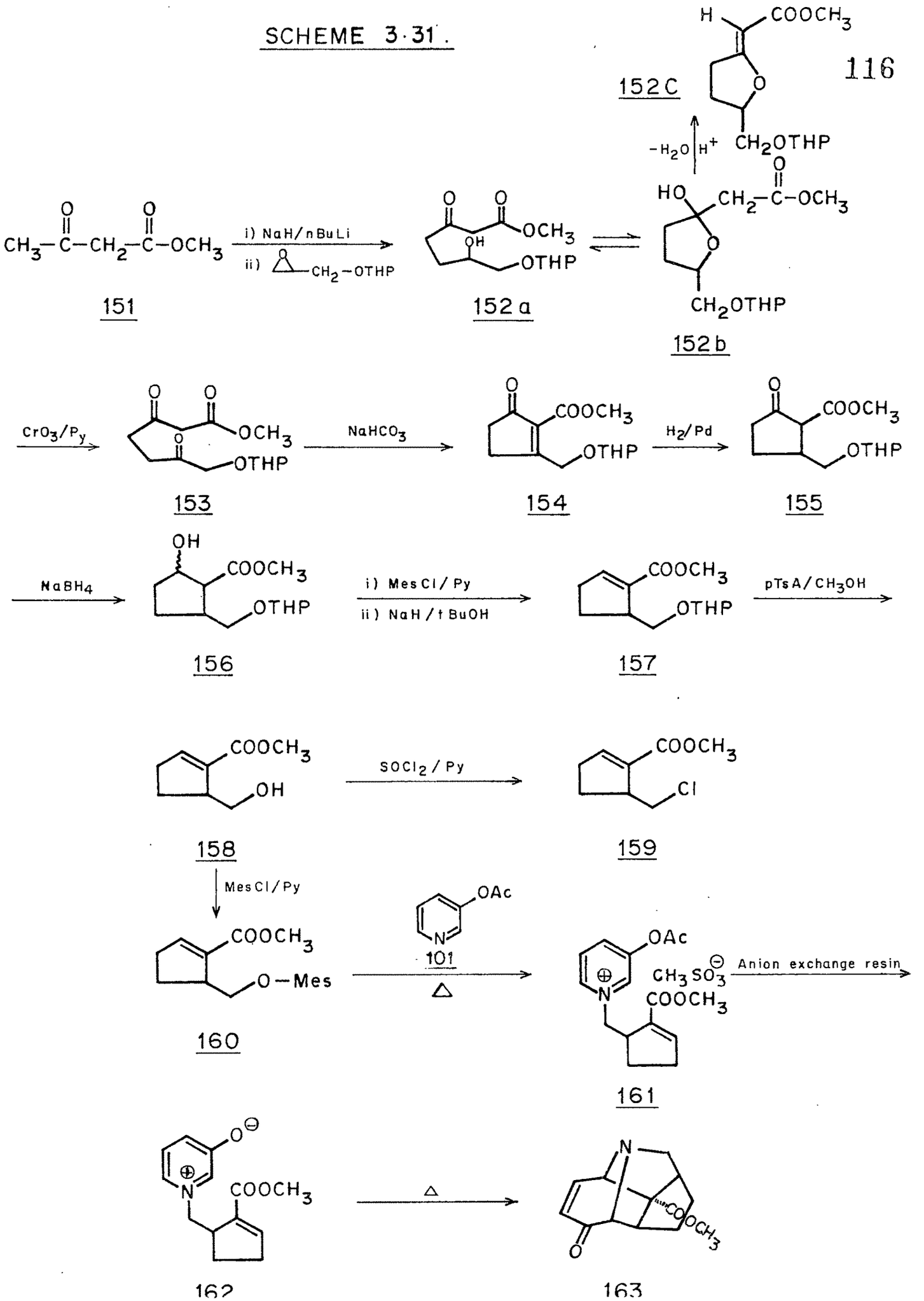
149 150 121

Reaction of cyclopentenone with dimethylsulfonium methylide gave oxirane 150. Reductive opening with LAH-$AlCl_3$ should give a primary alcohol with specific cleavage of allylic -C-O bond. However the cyclopropanation reaction to give 150 did not give clean or reproducible results.

Finally, we succeeded in synthesizing the desired cyclopentene derivative by the following reaction sequence (Scheme 3.31). The nucleophilic opening of the glycidol THP ether with the dianion of methyl acetoacetate afforded the alcohol 152a which also exists in its cyclic form 152b (care was taken during workup of the reaction to avoid dehydration to give tetrahydrofuran derivative 152c). The mixture of alcohols 152a,b was converted to the cyclopentenone 154 by oxidation with Collins reagent, followed by cyclization using sodiumbicarbonate in methylene chloride-water two-phase system. Catalytic hydrogenation and borohydride reduction of the latter gave an alcohol 156 which was converted to cyclopentene derivative 157 via mesylation and elimination. THP ether on treatment with methanol-pTsA gave alcohol 158. This alcohol on treatment with thionyl chloride gave chloride 159 .

The chloride so obtained, however, failed to react with 3-pyridinol acetate under the conditions at which the acyclic halides in the model compounds reacted. On

SCHEME 3·31.


H
COOCH3
152C
O
CH2OTHP
-H2O
H+
HO
CH2-C-OCH3
O
CH2OTHP
CH3-C-CH2-C-OCH3
i) NaH/nBuLi
ii) CH2-OTHP
OH
OCH3
OTHP
151
152a
152b
CrO3/Py
NaHCO3
H2/Pd
153
154
155
NaBH4
156
i) MesCl/Py
ii) NaH/tBuOH
157
pTsA/CH3OH
158
SOCl2/Py
159
Cl
MesCl/Py
O-Mes
160
OAc
101
△
CH3SO3
Anion exchange resin
161
162
163

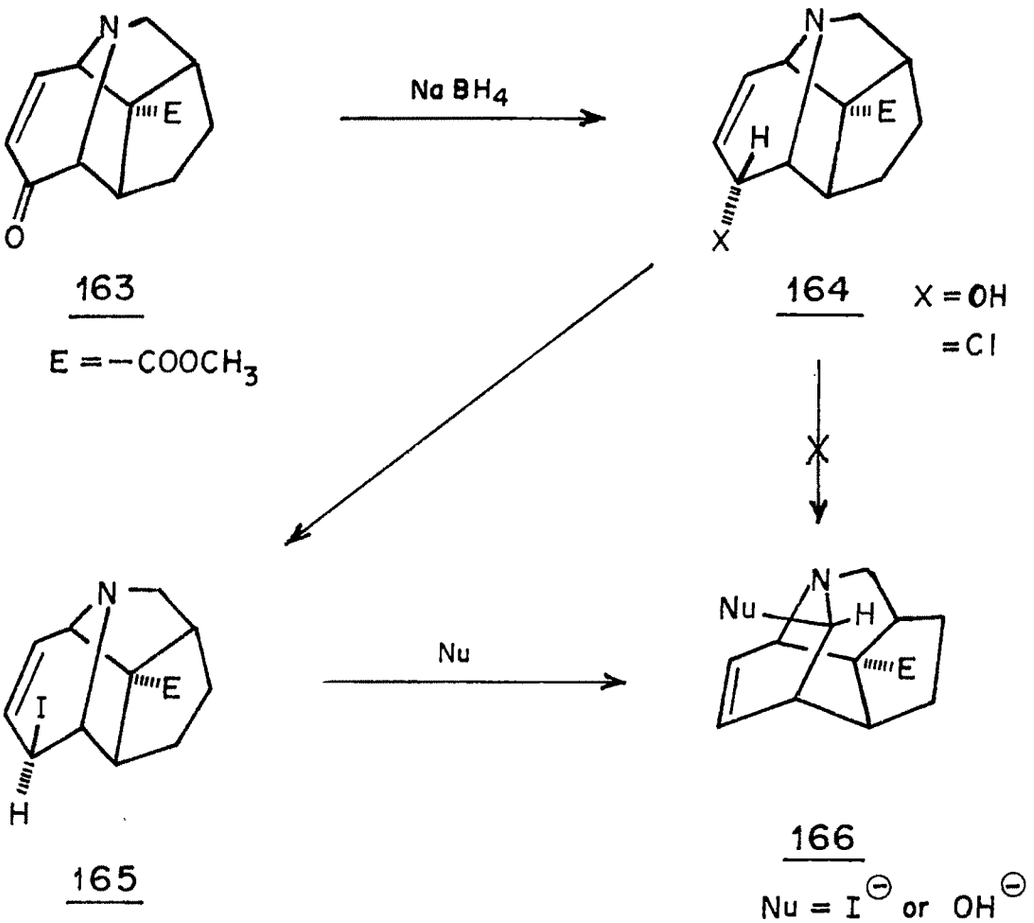
prolonged treatment of temperatures ranging from 100-150° only polymerization took place.

So, we tried to convert the alcohol 158 to the corresponding bromide with triphenylphosphine-bromine complex. But the reaction failed to yield the desired bromide. An unidentifiable mixture was obtained.

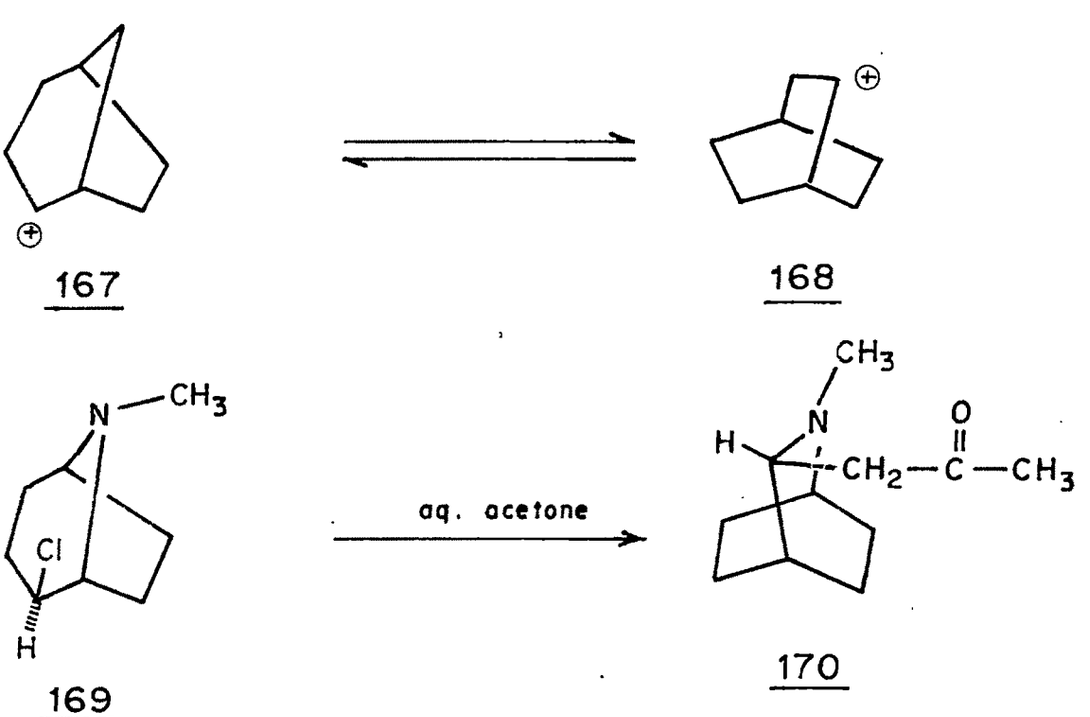
But we could convert the alcohol 158 to its mesylate 160, by treatment with mesyl chloride in pyridine. 160 proved sufficiently reactive towards quaternization. Thus the reaction between 3-pyridinol acetate 101 and the mesylate 160 took place smoothly at 100° affording quaternary salt 161. The salt 161 was converted to betaine 162 by treatment with anion exchange resin. The dipolar cycloaddition of betaine was accomplished by refluxing its solution in xylene to give the cycloadduct 163. On reduction of the enone 163 with sodium borohydride the corresponding alcohol 164 (X=OH) was obtained as a major product (Scheme3·32). This was homogeneous by TLC and gave a clean NMR spectrum showing the exclusive presence of one of the two possible epimers.

In analogy with the known interconversion of (3·2·1) bicyclooctanes to (2·2·2) systems[53], 167 ⇌ 168 (Scheme3·33) it was considered feasible that the carbonium ion from alcohol 164 could rearrange to the required (2·2·2) system 166.

SCHEME 32.



SCHEME 33.



However under varying acid conditions ($HClO_4$, methanolic pTsA etc) the alcohol 164 was found to be stable. Conversion of the alcohol 164 to the corresponding chloride was achieved by thionyl chloride to give cleanly one epimer (164, X=Cl). This was also found to be stable towards solvolytic conditions. Hence this chloride and its precursor alcohol (164 X=OH) were assumed to be α oriented as shown in Scheme 32 (thionyl chloride converts alcohol to chloride with retention of stereochemistry - S_{Ni} mechanism). For a halide to solvolyse with rearrangement, orientation has to be β (as in 165) as shown by earlier studies on the solvolysis of 169 → 170 (Scheme 33)[54]. Hence it was considered imperative that the chloride stereochemistry in 164 has to be inverted. For this alcohol 164 was treated with sodium iodide in acetone to give the β iodide which was as expected found to be unstable with respect to the rearrangement reaction, as shown by TLC and NMR signals for the halogen bearing methine proton. Hence the halide 165 would serve as a useful tricyclic intermediate for rearrangement to 166 and further elaboration to Dendrobine with most of its stereocenters in the right fashion.

E X P E R I M E N T A L

Purification of solvents and reagents: In experiments requiring anhydrous solvents: THF was distilled from benzophenone ketyl under nitrogen prior to use. Pyridine was distilled from calcium hydride. Chromium trioxide was dried over phosphorus pentoxide. t-Butanol was dried by distilling from either metallic sodium or calcium hydride. Methane sulfonyl chloride was distilled under reduced pressure prior to use. For the drying and purification of other solvents and reagents refer to the Experimental Section in Chapter II.

Preparation of cycloadduct 113: 3-Pyridinol acetate 101 (137 mg, 1 m.mole) and the iodide 110 (196 mg, 1 m.mole) were mixed and heated at 100° for 1 hr to obtain the salt 111. The salt was dissolved in 2 ml of methanol and treated with anion exchange resin (as a slurry in methanol) for 0.5 hr with stirring. Reaction mixture was filtered. Evaporation of the solvent from the filtrate gave an oily betaine 112 containing a little water. The crude product was dissolved in chloroform and dried over anhydrous sulfate. Evaporation of chloroform gave the betaine 112. A solution of betaine in xylene (20 ml) containing catalytic amount of hydroquinone (5 mg) was refluxed for six hrs. Xylene was distilled under reduced pressure to obtain an

oil which was resolved on alumina (neutral) column. Chromatography gave the desired cycloadduct 113.

Yield: 30 mg (20%).

NMR ($CDCl_3$, δ): Fig.2, 7.0 (d,d; 1H; J = 10 Hz and 6 Hz $-CH=CH-\overset{O}{\overset{\|}{C}}-$). 6.1 (d, 1H, J = 10 Hz $-CH=CH-\overset{O}{\overset{\|}{C}}-$) and 0.9 (d, 3H, J = 8 Hz $C-CH-CH_3$).

IR($CHCl_3$) cm^{-1}: Fig.3: 1660 α-β -unsaturated carbonyl.

Mass (M^+): 163.

Preparation of the cycloadduct 117: Following the procedure described above the cycloadduct was prepared from (137 mg, 1 m.mole) of 3-pyridinol acetate 101 and 193 mg, 1 m.mole) of the bromide 114.

NMR ($CDCl_3$ δ): Fig.4, 7.0 (d,d; 1H, J = 10 Hz and 6 Hz) $-CH=CH-\overset{O}{\overset{\|}{C}}-$) and 6.1 (d,d; 1H, J = 10 Hz and 0.75 Hz, $-CH=CH-\overset{O}{\overset{\|}{C}}-$).

IR ($CHCl_3$, cm^{-1}): Fig.5, 1680; α-β -unsaturated ketone and 1710 ester.

Mass (M^+): 207.

Preparation of ketone 134: a) Preparation of n-butyl lithium: Prepared according to the reported procedure from lithium (15.4 g, 2.2 moles) and n-butyl chloride (92.5 g 1 mole) in petroleum ether (60-80°) at reflux and estimated by the double titration method of Gilman[50].

b) Preparation of ethyl-3-oxo-6-heptenoate 132: This was prepared by monoallylation of the dianion of ethyl acetoacetate[51] (6.5 g, 50 m.mole). Yield: 5.7 g (66%).

NMR (δ): Fig.6.

IR ($CHCl_3$ cm^{-1}): 1735 ester and 1710 ketone.

c) Preparation of the ketone 134: To the solution of ester 132 (510 mg, 3 m.mole) and triethylamine (303 mg, 3 m.mole) in 5 ml of anhydrous acetonitrile, the p-toluenesulfonazide (590 mg,3 m.mole) in 2 ml anhydrous acetonitrile was added slowly at room temperature with stirring. After 1 hr the solvent was distilled under reduced pressure. The resulting residue was diluted with cyclohexane (30 ml). The separated p-toluenesulfonamide was filtered. The cyclohexane solution was refluxed for six hrs in presence of copper-bronze (6 g). The reaction mixture was filtered. The cyclohexane solution on evaporation of solvent under reduced pressure yielded an oil. This on distillation (130-40° bath temperature at 1 mm Hg) gave ketone 134. Yield: 320 mg (63%).

NMR(δ): Fig.7

IR ($CHCl_3$ cm^{-1}): 1755 ester and 1725 ketone carbonyl.

Mass (M^+): 168

Preparation of the alcohol 135: To the solution of ketone 134 (336 mg, 2 m.mole) in 2 ml of ethanol at 0° sodium borohydride (74 mg, 2 m.mole) was added with stirring. After 1 hr ethanol was evaporated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. Organic extract was washed with small amounts

of water, brine and dried over anhydrous sodium sulfate. Evaporation of solvent under reduced pressure yielded an oil, alcohol 135. (Homogeneous by TLC). Yield: 305 mg (90%).

NMR(δ): Fig.8

IR (CCl_4 cm^{-1}): 1720 ester carbonyl and 3380 -hydroxy.

Rearrangement of alcohol 135: Alcohol (1 m.mole) was subjected to following conditions. The results are tabulated.

Entry	Reactants	Conditions	Products
1	Alcohol + 1 ml THF + 1 ml HI (57%)	0° 1 hr	136 + 137
2	Alcohol + 1 ml THF + 1 ml HBr (48%)	"	-do-
3	Alcohol + 1 ml Bz + 0.5 ml $SOCl_2$	"	-do-
4	Alcohol + Ph_3PBr_2 1 m.mole + 1 ml CH_3CN	"	136
5	Alcohol + 1 ml THF + 1 ml $HClO_4$ (70%)	"	139

Preparation of ketone 140: To a slurry of sodium hydride (150 mg, 80% in oil, 6 m.mole) in anhydrous DMF, thiophenol (702 mg, 6 m.mole) was added with stirring at 0°. After stirring for 0.5 hr, ketone 134 (1.0 g, 6 m.mole) was added at that temperature. This was slowly warmed to room temp.

and methyliodide (3 ml, excess) was added and stirred for 2 hrs. Reaction mixture was diluted with water and extracted with pet. ether. Organic extract was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded an oil. This was resolved on silica gel column to obtain the desired ketone 140. Yield: 1.320 g (76%).

NMR (δ): Fig.10

IR ($CHCl_3$ cm^{-1}): 1760 ester and 1730 ketone carbonyl.

Preparation of ketone 141: A slurry of ester ketone 140 (870 mg, 3 m.mole) and powdered potassium carbonate (2 g.) in methanol (20 ml) was stirred at room temperature for 10 hrs. Methanol was evaporated under reduced pressure and the residue diluted with water, acidified with dilute hydrochloric acid and extracted with ether. Organic extract was washed with water, dried over anhydrous sodium sulfate. Evaporation of ether under reduced pressure yielded the corresponding acid. Yield: 600 mg (86%).

The acid obtained from above reaction was dissolved in xylene (2 ml). The xylene solution was refluxed for 6 hrs with catalytic amount of pTsA (10 mg). Xylene was distilled under reduced pressure. The residue was extracted with pet. ether. The organic extract was washed with water, saturated sodium bicarbonate solution, brine and dried over

anhydrous sodium sulfate. Evaporation of the solvent yielded the ketone 141. Yield: 330 mg (66%).

IR (CCl_4 cm^{-1}): 1740 ketone carbonyl.

Preparation of ketone 145: Following the procedure described for the ketone 140, the ketone 145 was prepared from thiolacetic acid (456 mg, 6 m.mole) and ketone 134 (1.0 g, 6 m.mole) and subsequent treatment with excess of methyl iodide (CH_3OH/CH_3ONa). Yield: 1.1 g (80%).

NMR(δ): Fig.11

IR (CCl_4, cm^{-1}): 1760 ester, 1730 ketone and 1630 thioester carbonyl.

Preparation of oxirane 150: To a stirred suspension of trimethylsulfonium iodide (2.45 g, 12 m.mole) in 12 ml of anhydrous THF cooled to 0°, under nitrogen, a pet-ether solution of n-butyl lithium (13 ml of 6% pet. ether solution, 12 m.mole) was added. The resulting solution was stirred for 10 minutes and then a solution of ketone 149 (.960 mg, 10 m.mole) in 10 ml of THF was added. The reaction was continued for half an hour at 0° and then at room temperature for one hr and quenched with aqueous ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with ether. Organic layer was washed with water, dried over anhydrous sodium sulfate. Evaporation of ether gave an oily crude product 150. This was chromatographed on silica gel to get TLC homogeneous product.

Yield: 620 mg (57%).

NMR (δ): 5.5 (m, 1H, C<u>H</u>=C) and 2.1 (s, 3H, C=C-C<u>H</u>$_3$).

<u>Preparation of the cyclopentanone 155</u>: This was prepared from methyl acetoacetate based on the reported procedure[52].

a) <u>Alcohol 152a,b:</u> Approximately 25 ml of anhydrous THF was distilled from $LiAlH_4$ into a 50 ml flask containing 0.54 g of sodium hydride (50% mineral oil, 11 m.mole). The flask was stoppered with a septum cap, flushed with nitrogen and cooled to 0° (ice). Then 1.16 g of methyl acetoacetate (10 m.mole) was added dropwise and the colourless solution was stirred at 0° for 10 min. To this solution was added dropwise 5.5 ml n-butyllithium (2M, pet.ether solution, 11 m.mole). After stirring for 10 min. at 0°, the reaction mixture was cooled to -78° (dry ice-acetone). The solution of glycidol THP ether (1.58 g, 10 m.mole) in 1 ml of anhydrous THF was added. The reaction mixture was slowly warmed to room temperature (4 hr) and stirred overnight. The reaction mixture was then quenched with 50% aqueous acetic acid. Organic layer was separated and the aqueous layer was extracted with ether. The combined extract washed with water, brine, dried over anhydrous magnesium sulfate. The solvents were evaporated under reduced pressure to obtain crude product. This was resolved on silica gel.

Yield: Alcohol <u>152 a,b</u> 2.3 g (80%).

NMR ($CDCl_3$ δ): 3.47 (s, 2H, $-CO(OH)-CH_2-COOCH_3$ 152a)
2.78 (s, 2H, $-C(OH)-CH_2-COOCH_3$ 152b)

IR ($CHCl_3$ cm^{-1}): 3400 hydroxy.

Dehydrated product 152c

NMR (δ): 5.3 (m, 1H, CH=C), 4.6 (m, 1H, O-CH-O)

IR ($CHCl_3$ cm^{-1}): 1640 vinyl ether, 1690 ester.

UV: λ_{max} (EtOH): 244 nm.

b) Ketone 153: To a solution of Collins reagent from 2.4 g (24 m.mole) of chromium trioxide, 3.8 g (48 m.mole) of pyridine and 50 ml of anhydrous dichloromethane, a solution of alcohol 152 a,b (1.152 g, 4 m.mole) in 5 ml of dichloromethane was added in one portion and kept stirred for 15 min. The resulting reaction mixture was passed through a short silica gel column to remove chromium salts. The dichloromethane solution was diluted with ether and washed with 5% copper sulfate solution, water and brine. The organic extract was dried over anhydrous sodium sulfate. Evaporation of the solvents gave the crude ketone 153. This was resolved on silica gel.

Yield: 600 mg (51%).

NMR(δ): 3.6 (s, 3H, $COOCH_3$), 2.7 (s, 4H $-C(=O)-CH_2-CH_2-C(=O)-$)
3.4 (s, 2H, $CH_2-C(=O)-OCH_3$), 4 (s, 2H, $C(=O)-CH_2-O-$) and
4.6 (m, 1H, O-CH-O).

IR (neat cm^{-1}): 1717, 1725 ketone and 1748 ester carbonyl.

c) Adol cyclization of diketone 153: A solution of diketone 153 (2.72 g, 10 m.mole) in 50 ml of dichloromethane was stirred with sodium bicarbonate solution (2.92 g, 35 m.mole in 720 ml water) for 36 hrs at room temperature. The reaction mixture was acidified (pH = 3) with dilute hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ether. Organic extract was washed with water, brine, dried over anhydrous sodium sulfate. Evaporation of solvent under reduced pressure yielded oily cyclopentenone 154. Homogeneous by TLC.
Yield: 2.3 g (90%).
NMR (δ): 4.66 (m, 1H, O-CH-O), 3.7 (s, 3H, $COOCH_3$).
IR (neat cm^{-1}): 1713 ketone and 1744 ester carbonyl.
UV: λ_{max} (EtOH): 234 nm.

d) Reduction of cyclopentenone 154: The cyclopentenone 154 (2.3 g, 9 m.mole) in 30 ml of ethanol was hydrogenated over 10% Pd-C (200 mg). After the completion of the reaction catalyst was removed by filtration through fluted filter paper and alcohol evaporated off to yield ketone 155. (Homogeneous by TLC silica gel).
Yield: 2.3 g (99%).
NMR (δ): 3.75 (s, 3H, $COOCH_3$) and 4.6 (m, 1H, O-CH-O).
IR (neat cm^{-1}): 1727 ketone and 1755 ester carbonyl.

Alcohol 156: To a cold solution (0^{o}) of ketone 155 (3.840 g, 15 m.mole) in 20 ml of methanol, 0.555 g (15 m.mole)

of sodium borohydride was added with stirring. After 2 hrs at 0°, the reaction mixture was acidified with acetic acid and solvents were evaporated under reduced pressure. The residue was partitioned between water and ether. The ether layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of solvent yielded the alcohol 156. Homogeneous by TLC (silica gel).

Yield: 3 g (79%).

NMR (δ): 3.6 (m, 3H, $COOCH_3$), 4.4 (m, 1H, O-CH-O).

IR (neat cm^{-1}): 1750 ester and 3700 hydroxy.

Preparation of cyclopentene 157

a) Mesylation of alcohol 156: A solution of the alcohol 156 (1.032 g, 4 m.mole) and mesyl chloride (560 mg, 5 m.mole) in 5 ml of pyridine was stirred at room temperature for 3 hrs. The reaction mixture was made alkaline by saturated sodiumbicarbonate solution and extracted with ethyl acetate. Organic extract was washed with saturated copper sulfate solution, water, brine, dried over anhydrous sodium sulfate. Evaporation of solvent yielded an oily mesylate which was purified on silica gel column.

Yield: 1.100 g (75%).

NMR ($CDCl_3$ δ): 2.9 (s, 3H, $-SO_2-CH_3$), 3.6 (s, 3H, $COOCH_3$)
5.1 (m, 1H, SO_2-CH-C) and 4.4 (m, 1H, O-CH-O).

IR (CCl_4 cm^{-1}): 1725 ester and 1370 sulfonate.

b) Elimination of mesylate : To a slurry of sodium hydride (150 mg of 50% mineral oil, 3 m.mole) in 3 ml of t-butanol, the mesylate (1.100 g, 3 m.mole) was slowly added at room temperature. The reaction mixture was stirred for 16 hrs and acidified with glacial acetic acid. t-Butanol was distilled off under reduced pressure, residue diluted with water and extracted with ethyl acetate. Organic extract washed with water, brine, dried over sodium sulfate. Evaporation of solvent yielded crude cyclopentene derivative 157. This was resolved on silica gel to obtain desired product.

Yield: 565 mg (78%).

NMR (δ): 3.7 (s, 3H, $COOCH_3$), 4.6 (m, 1H O-CH-O) and 6.8 (m, 1H, $CH=C-COOCH_3$).

IR:($CHCl_3$ cm^{-1}): 1700 ester.

Deprotection of THP ether 157: To a solution of THP ether 156 (480 mg, 2 m.mole) in 2 ml of anhydrous methanol and a crystal of p-TSA added. After 1 hr at room temperature, 2 drops of saturated sodiumbicarbonate was added. The solvent was removed and the residue partitioned between ethyl acetate and water. Aqueous layer was extracted with ethyl acetate. Combined organic extract was washed with water, brine, dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure yielded alcohol 158, homogeneous by TLC.

Yield: 0.270 g (87%).

NMR ($CDCl_3$ δ): 3.8 (s, 3H, $COOCH_3$) and 6.8 (m, 1H, CH=C). Fig.12

IR ($CHCl_3$ cm^{-1}): 1700 ester and 3400 hydroxy.

Preparation of mesylate 160: Following the procedure described for the mesylation of alcohol 156, the mesylate was prepared from alcohol 158 (156 mg 1 m.mole) and mesyl chloride (148 mg, 3 m.mole). The crude product was chromatographed on silica gel.

Yield: 145 mg (66%).

NMR (δ): 2.8 (s, 3H, $O-SO_2-CH_3$), 3.6 (s, 3H, $COOCH_3$) and 6.8 (m, 1H, CH=C-).

IR ($CHCl_3$ cm^{-1}): 1700 ester and 1370 sulfonate.

Preparation of the cycloadduct 163: Following the procedure described for 113, the cycloadduct 163 was prepared from 3-pyridinol acetate 101 (137 mg, 1 m.mole) and mesylate 160 (224 mg, 1 m.mole), only refluxing time period was increased from 6 to 24 hrs. Yield: 110 mg (48%).

NMR ($CDCl_3$ δ): Fig.13. 7.1 (d,d, 1H J = 14 Hz, 8 Hz $-CH=CH-\overset{\alpha}{C}-$), 6.0 (d,d, 1H, J = 14 Hz. 2 Hz $-CH=CH-\overset{\beta}{C}-$), 3.66 (s, 3H, $COOCH_3$).

IR ($CHCl_3$ cm^{-1}): 1680 α,β-unsaturated ketone, 1710 ester carbonyl. Fig.14.

Mass (M^+): 233.

Preparation of alcohol 164 (X=OH): The cycloadduct 163 (80 mg, 0.3 m.mole) was dissolved in 0.5 ml methanol. This was cooled with ice-salt mixture and sodium borohydride (37 mg, 1.m.mole) was added. After one hr at that temperature one drop of glacial acetic acid was added and methanol was distilled off at reduced pressure. The residue was dissolved in water and extracted with ethyl acetate. Organic extract was washed with water, saturated brine and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure yielded crude alcohol 164. This was chromatographed on silica gel to get TLC pure alcohol. Yield: 50 mg (60%).

NMR ($CDCl_3$ δ): Fig.15. 5.8 (d,d,d 1H, J = 14 Hz, 7 Hz and 2 Hz $-CH=CH-\underset{OH}{\underset{|}{C}}H-$), 5.5 (d,d,d, 1H, J = 14 Hz, 2 Hz and 2 Hz $-CH=\underset{OH}{\underset{|}{C}}H-$), 4.7 (broad m, 1H, $-\underset{OH}{\underset{|}{C}}H-$) and 3.66 (s, 3H, $COOCH_3$).

Preparation of chloride 164 (X = Cl): The alcohol 164 X=OH (37 mg) was dissolved in 0.5 ml benzene and two drops of thionyl chloride was added to this at room temperature. After one hr excess of thionyl chloride and benzene was evaporated and residue was made alkaline with saturated sodium bicarbonate solution. This was extracted with ethyl acetate. Organic extract was washed with small amount of water, dried over anhydrous sodium sulfate. Evaporation of solvent yielded TLC pure chloride 164 (X = Cl). Yield: 35 mg (88%).

NMR ($CDCl_3$ δ): Fig.16, 5.95 (d,d 1H, J = 8 Hz and 4 Hz $\underline{CH}=CH-\underset{Cl}{CH}$), 5.75 (d,d,d 1H, J = 8 Hz, 4 Hz and 2 Hz $CH=\underline{CH}-\underset{Cl}{CH}$), 4.15 (d,d, 1H, J = 4 Hz, 2 Hz $-\underline{CH}-Cl$) and 3.66 (s,3H, $COOC\underline{H}_3$).

Preparation of iodide 165: To the solution of chloride 164 X=Cl (30 mg) in 0.5 ml of acetone powdered sodium iodide (400 mg) was added and the resulting reaction mixture was stirred for one hr. TLC in chloroform was showing the iodide to be faster moving (chloride Rf 0.5, iodide Rf 0.6). Acetone was evaporated and residue dissolved in water and extracted with ethyl acetate. Evaporation of solvent gave iodide 165. Yield: 20 mg (50%).

NMR ($CDCl_3$ δ): 5.8 (m, 2H vinylic protons), 4.7 (broad m, 1H, $\underline{CH}-I$) and 3.66 (s, 3H, $COOC\underline{H}_3$).

The above iodide on keeping in chloroform solution was found to be different from the starting iodide. TLC in chloroform showed it to be much slower moving than the iodide (iodide Rf 0.6 and this compound 0.3). NMR of this compound was now showing the methine proton at 5.6 δ instead of 4.7 δ.

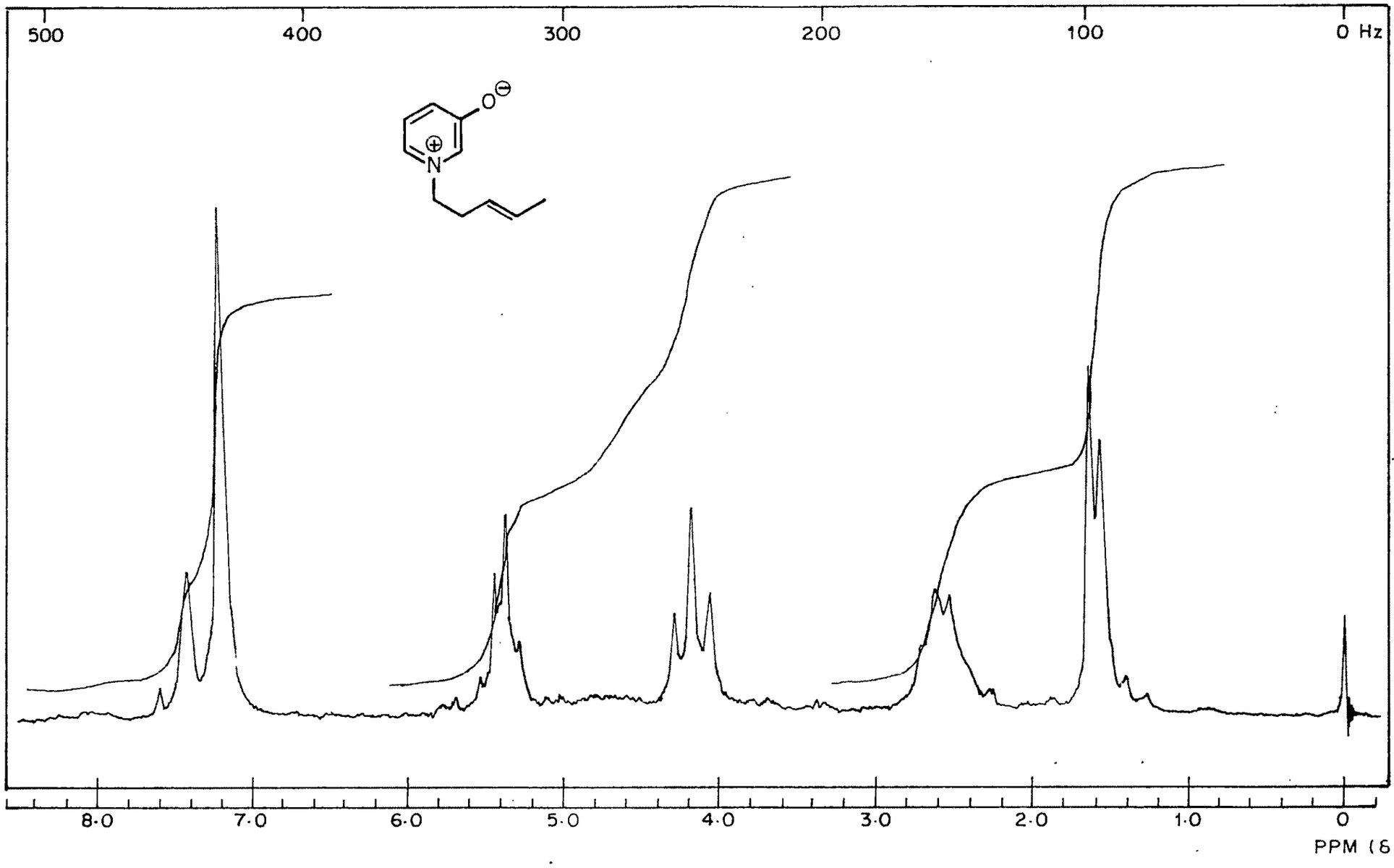


FIG. NO. 1. NMR SPECTRUM OF BETAINE 112

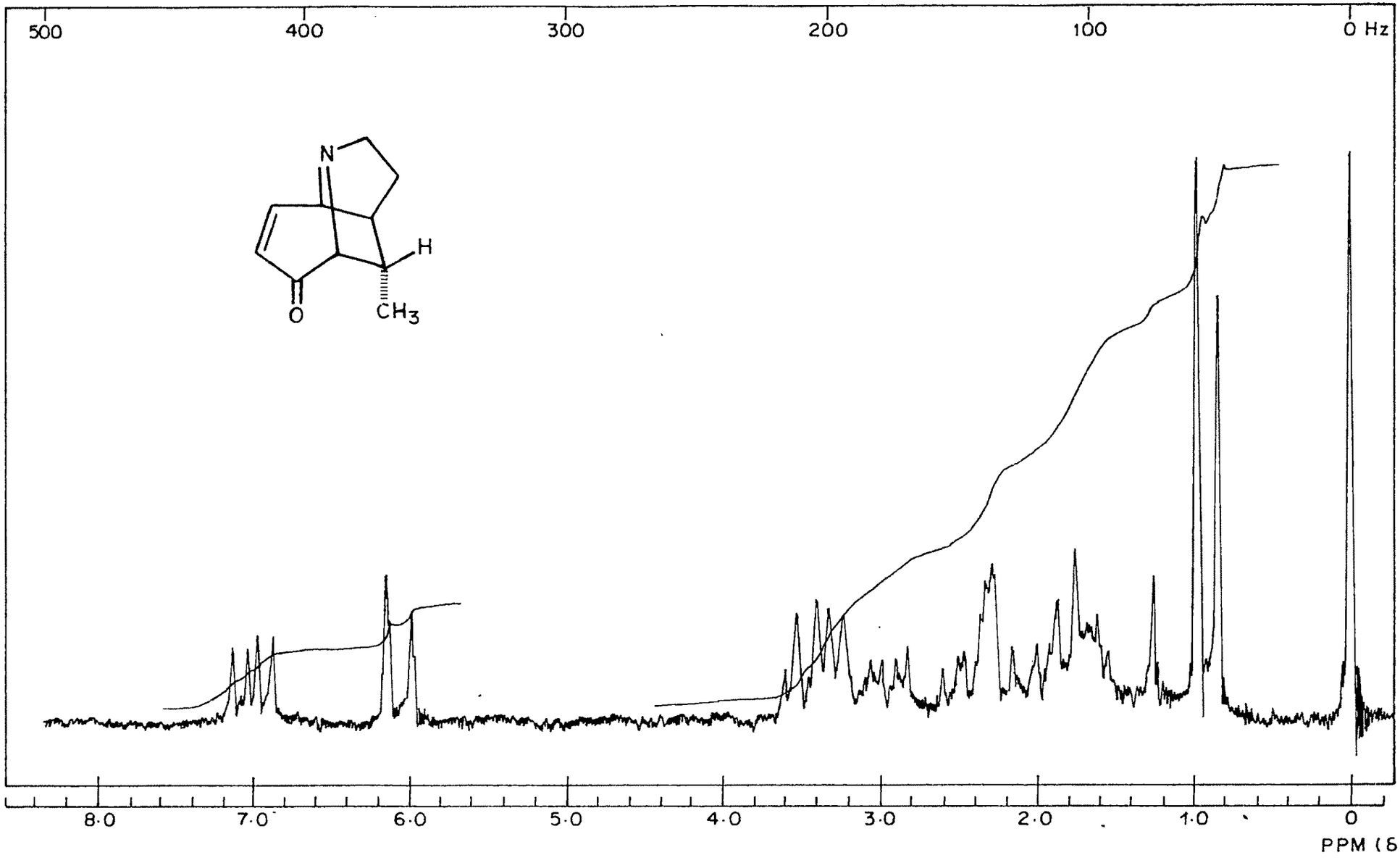


FIG. NO. 2. NMR SPECTRUM OF CYCLOADDUCT 113

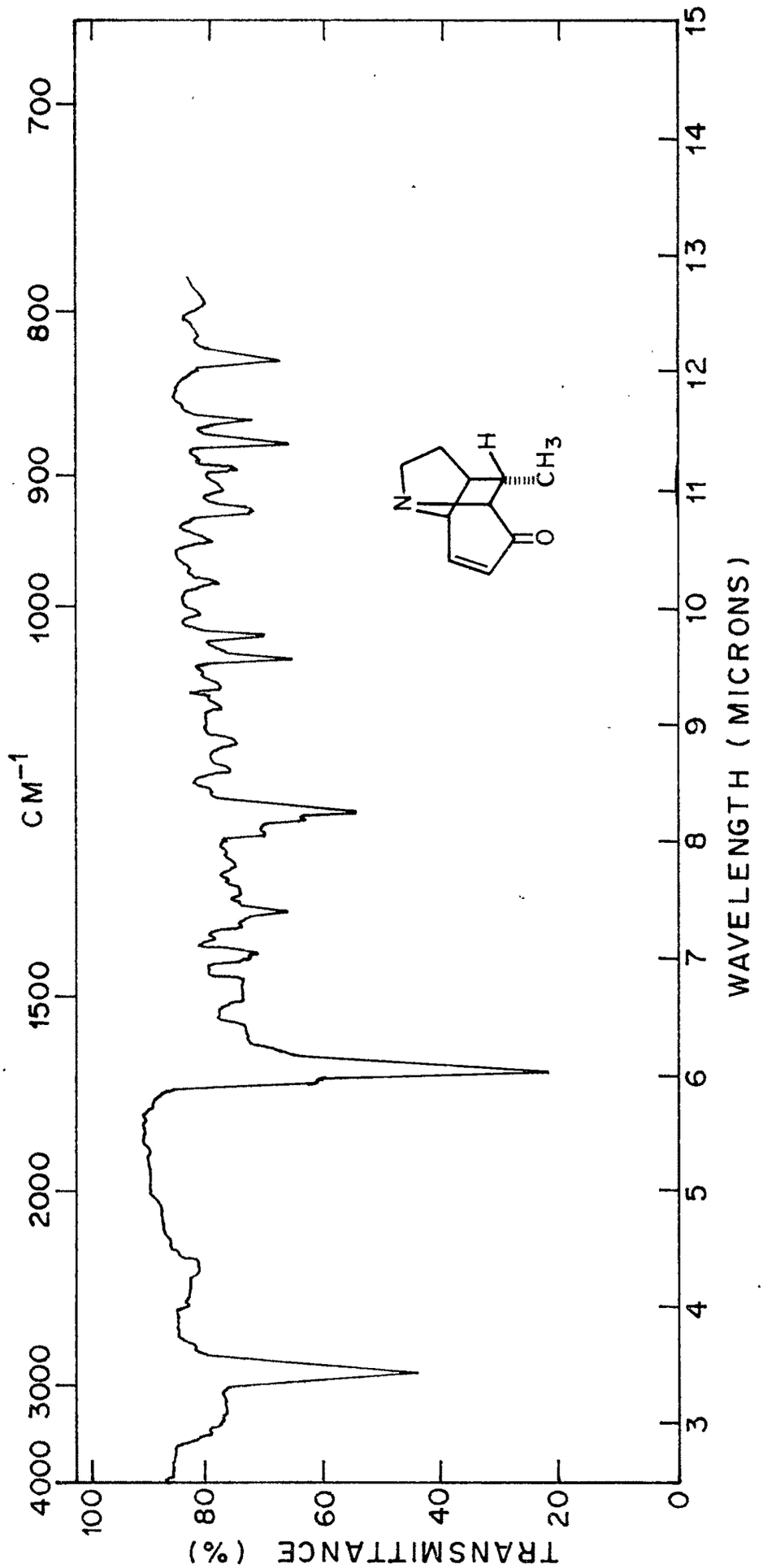


FIG. NO. 3. IR SPECTRUM OF CYCLOADDUCT 113

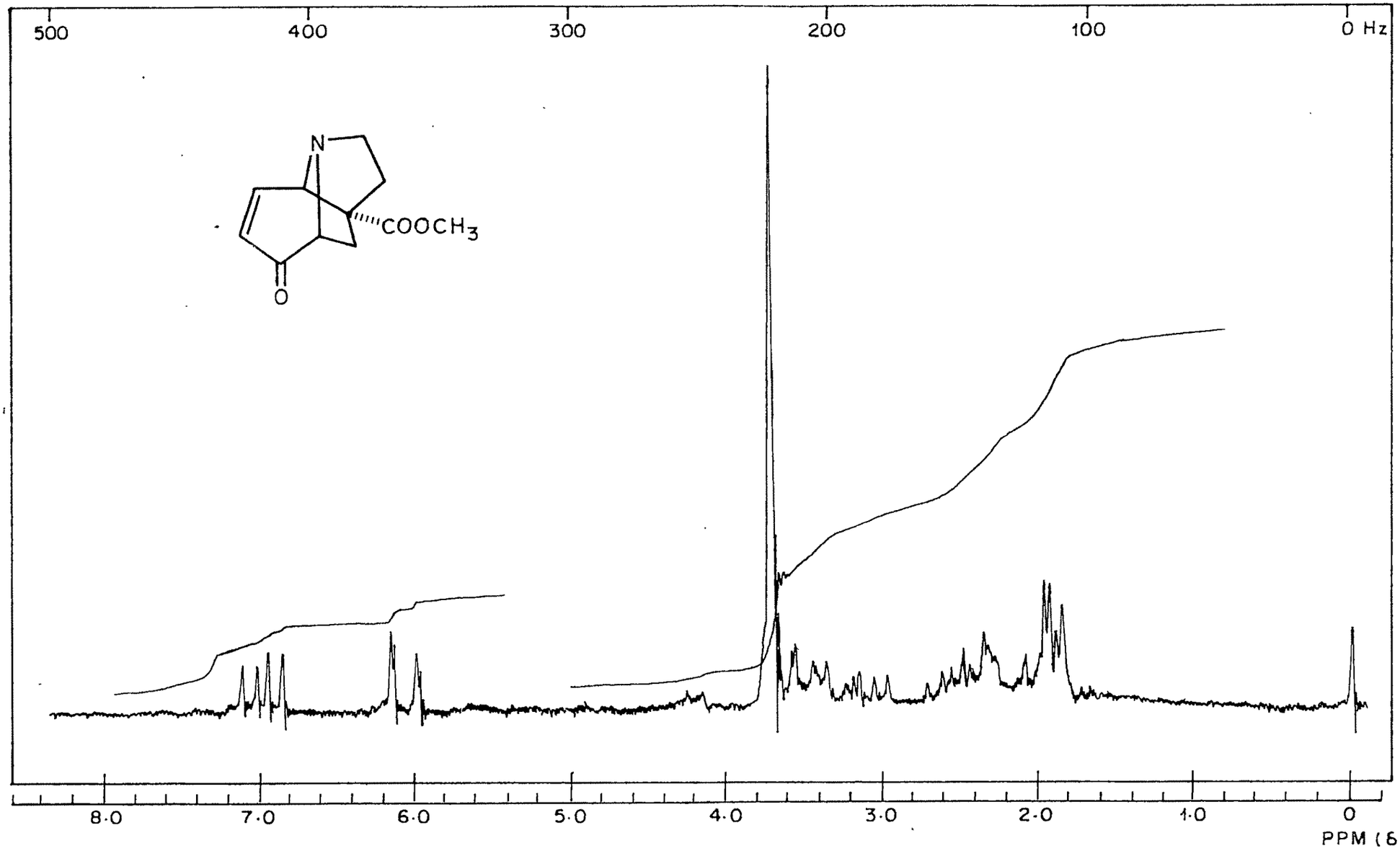


FIG. NO. 4. NMR SPECTRUM OF CYCLOADDUCT 117

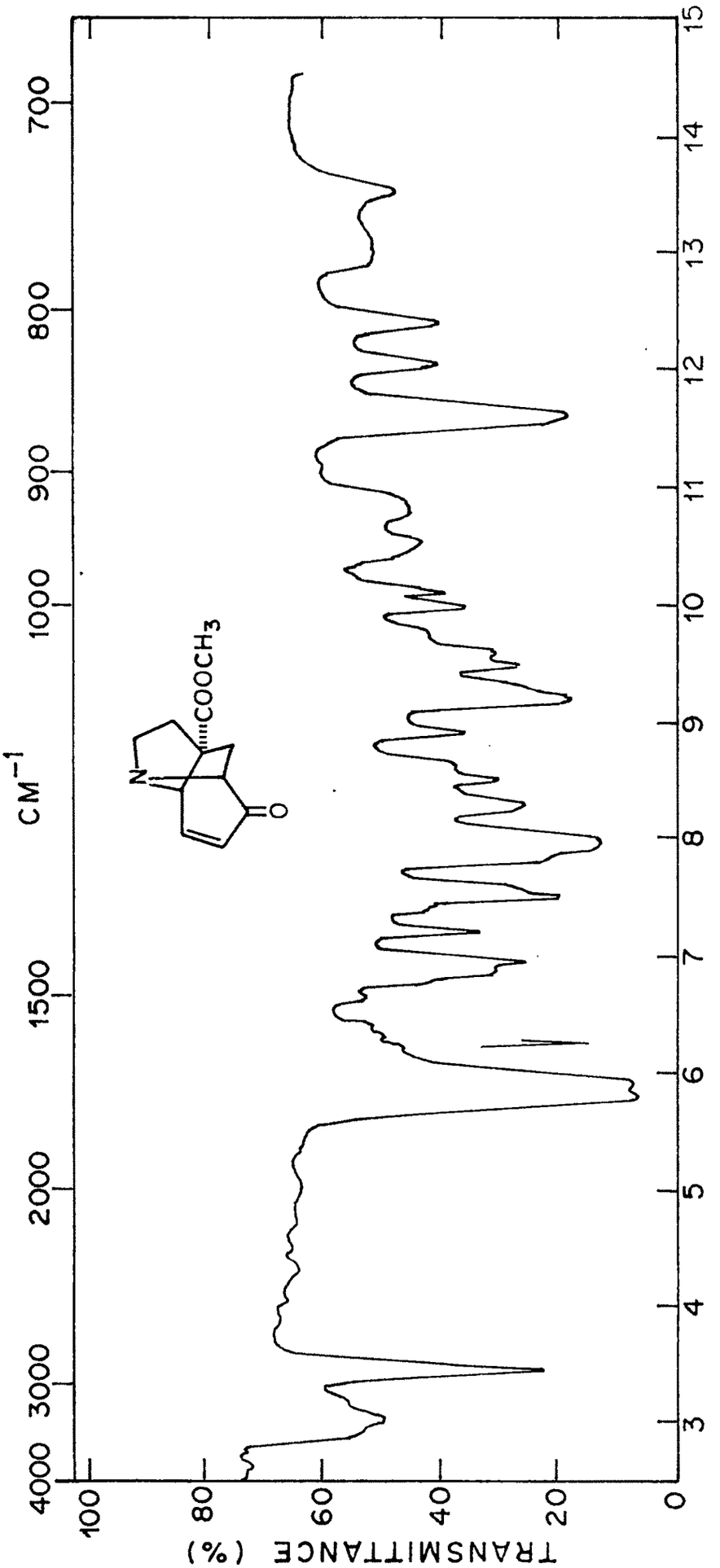


FIG. NO. 5. IR SPECTRUM OF CYCLOADDUCT 117

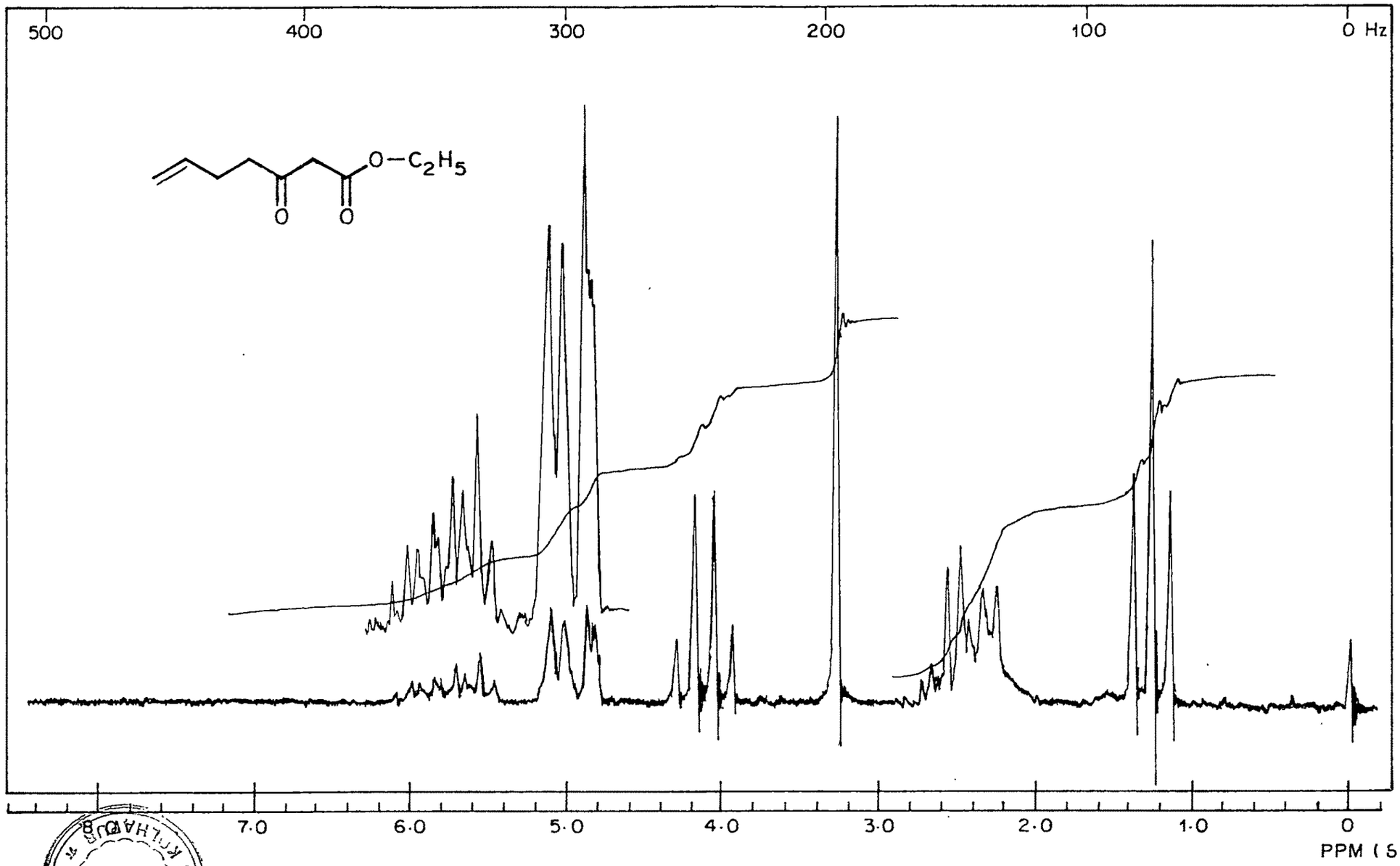


FIG. NO. 6. NMR SPECTRUM OF ESTER 132

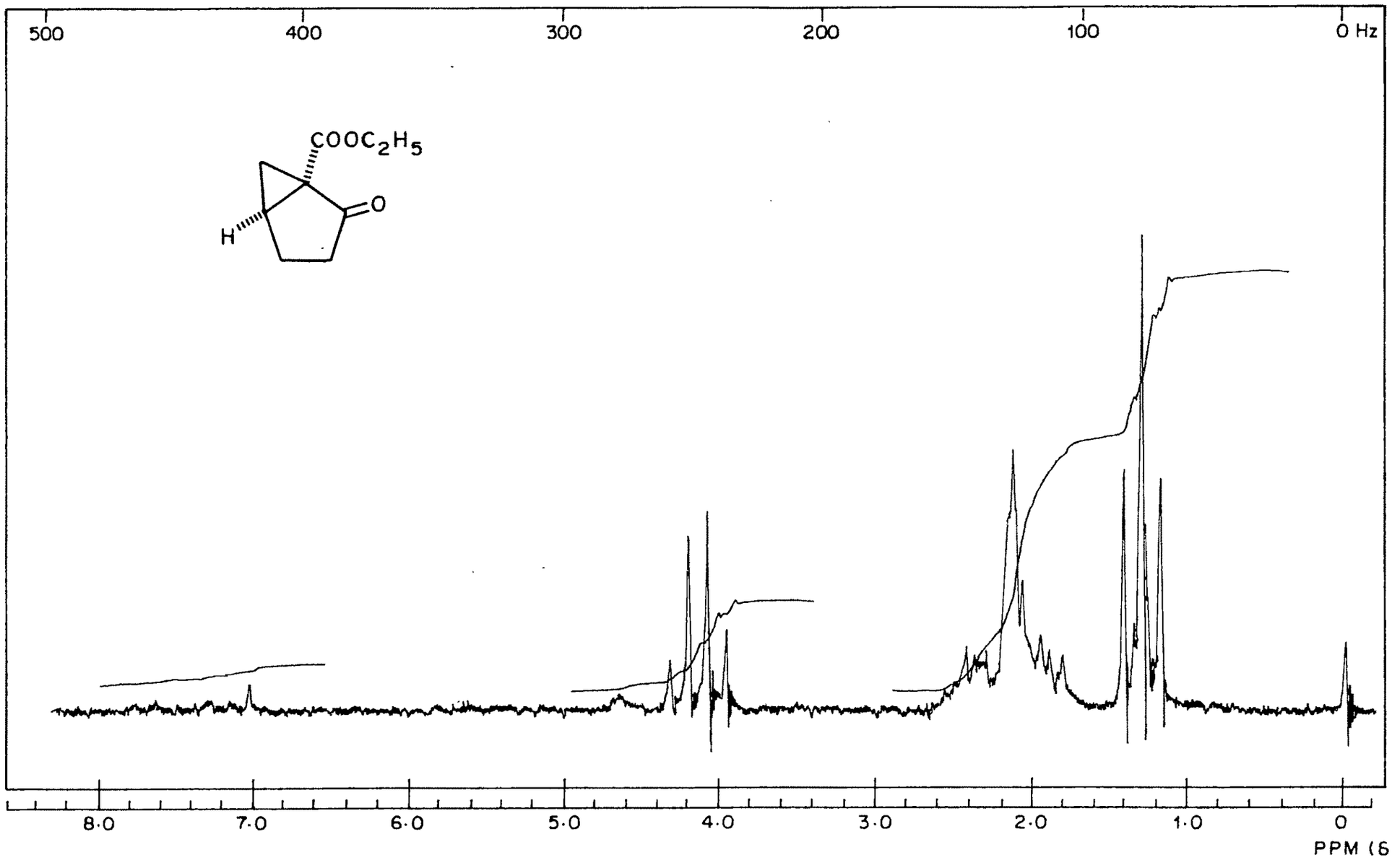


FIG. NO. 7. NMR SPECTRUM OF KETONE 134

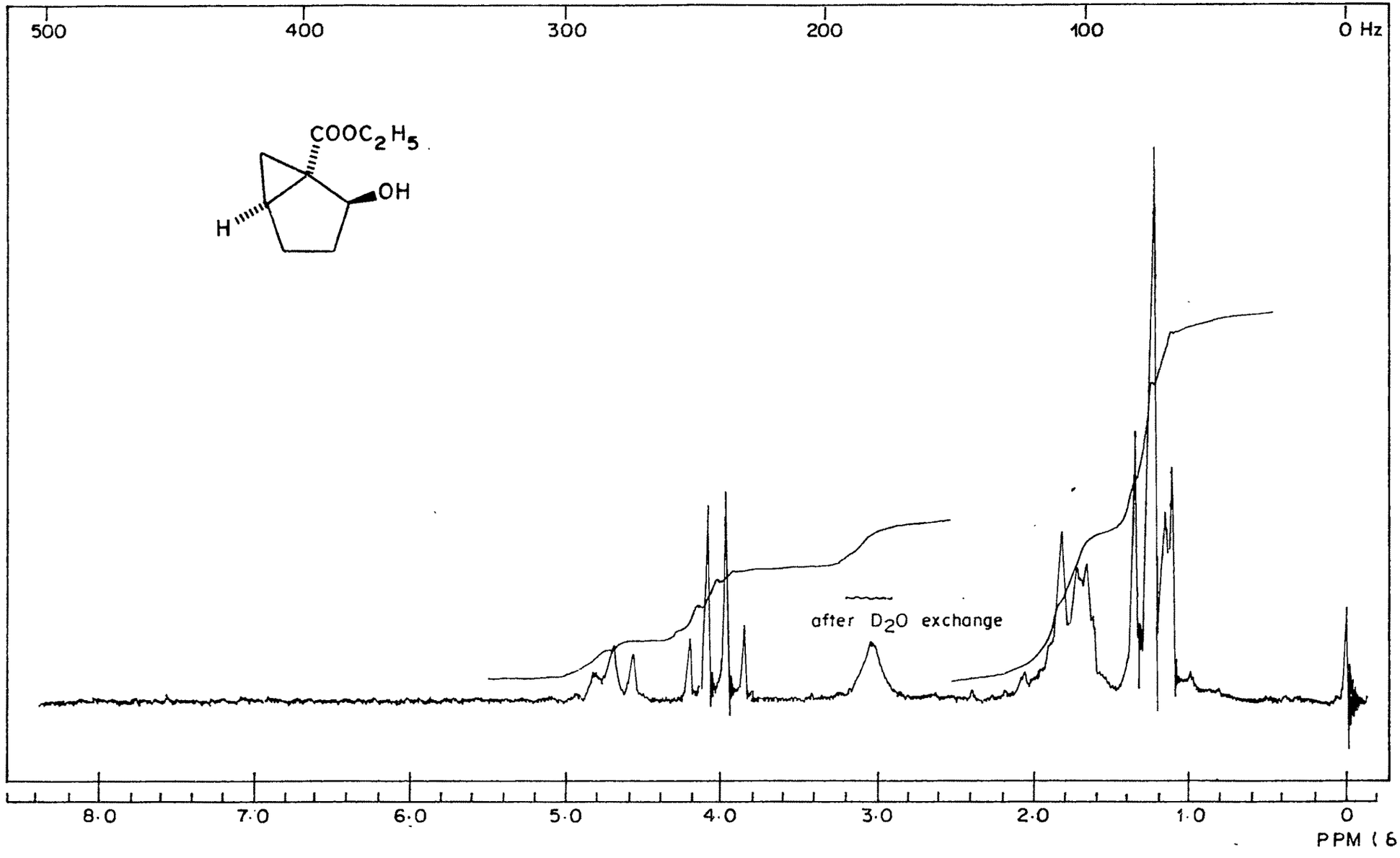


FIG. NO. 8. NMR SPECTRUM OF ALCOHOL 135

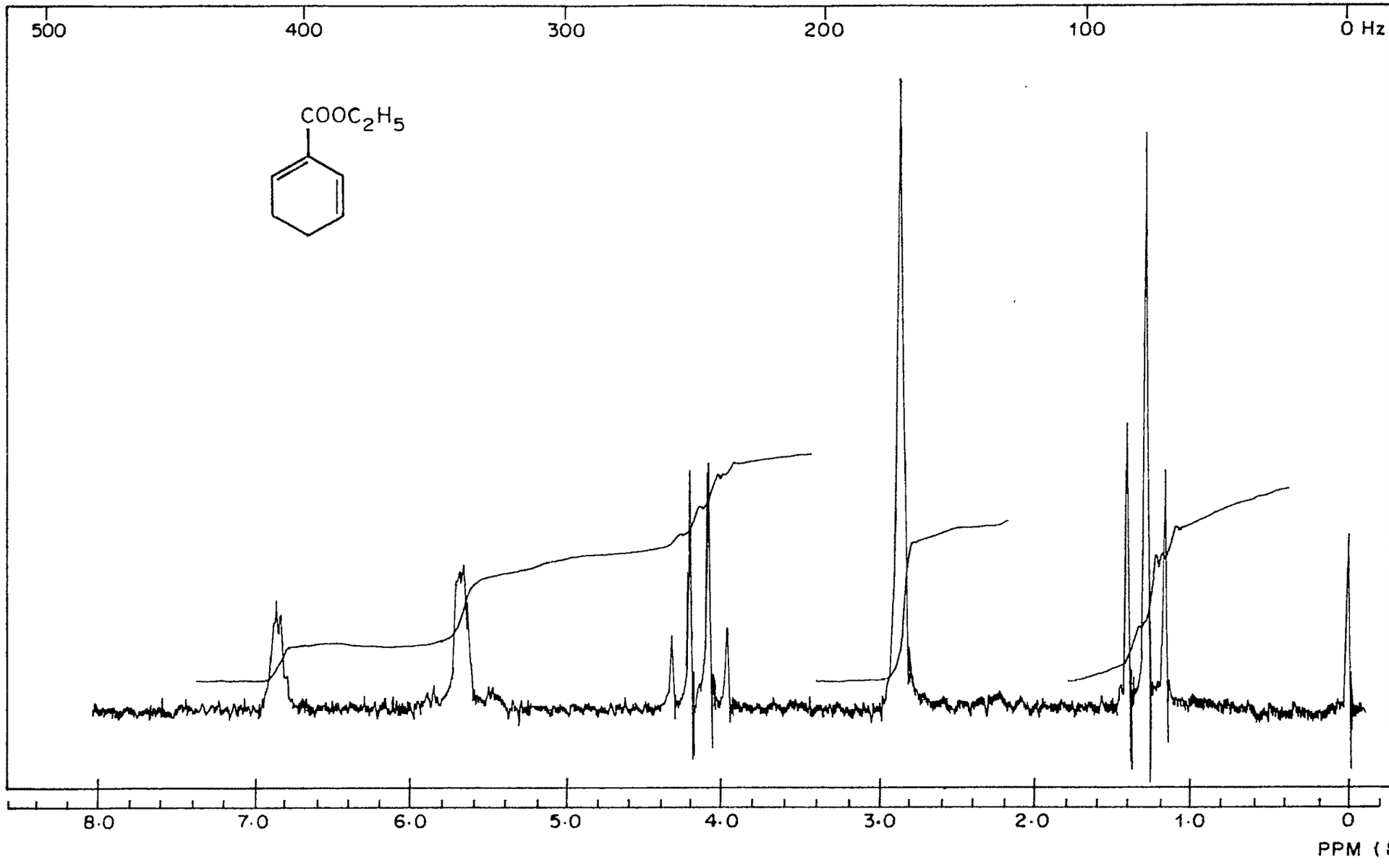


FIG. NO. 9 : NMR SPECTRUM OF REARRANGED PRODUCT 139

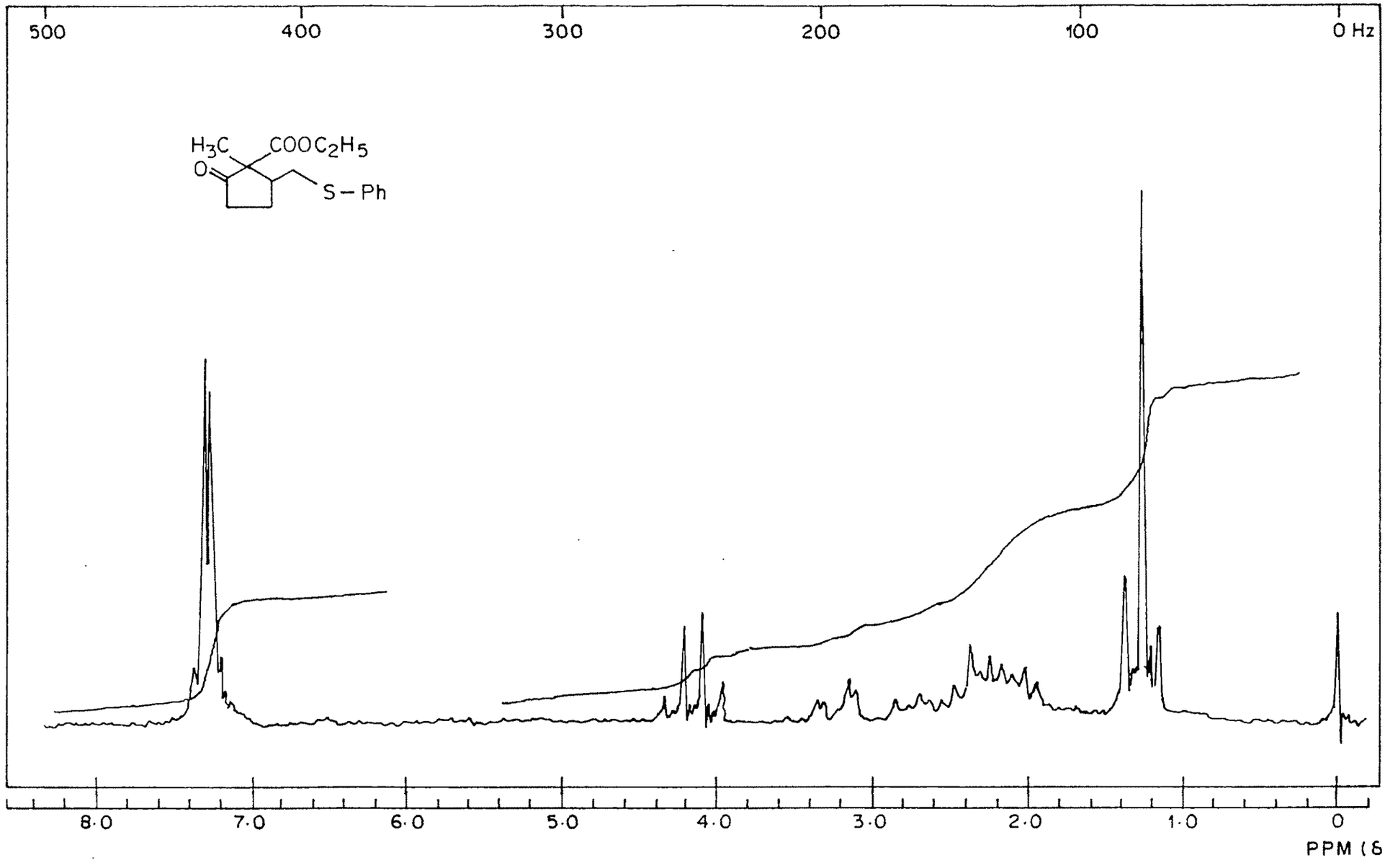


FIG. NO. 10. NMR SPECTRUM OF KETONE 140

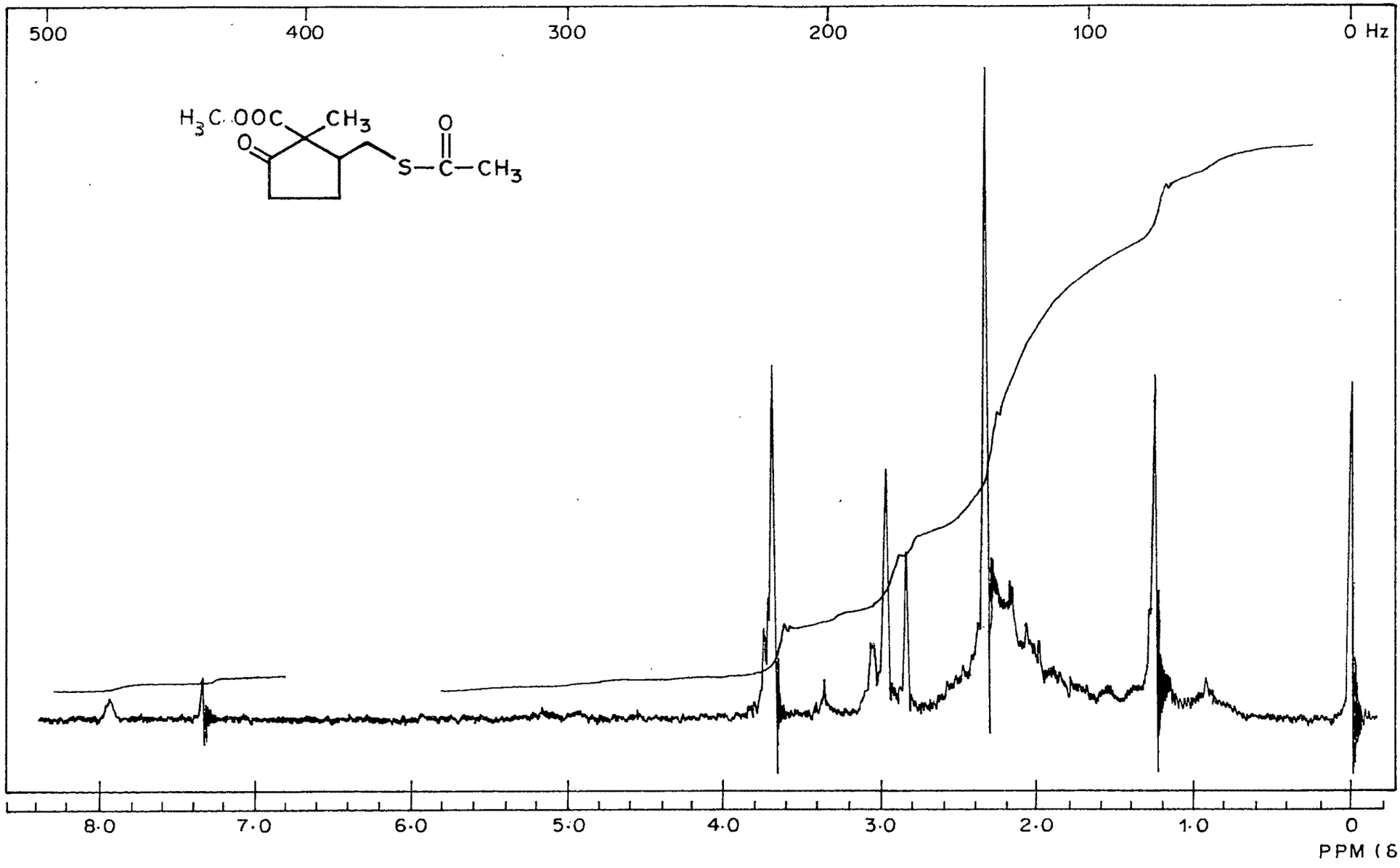


FIG. NO. 11. NMR SPECTRUM OF KETONE 145

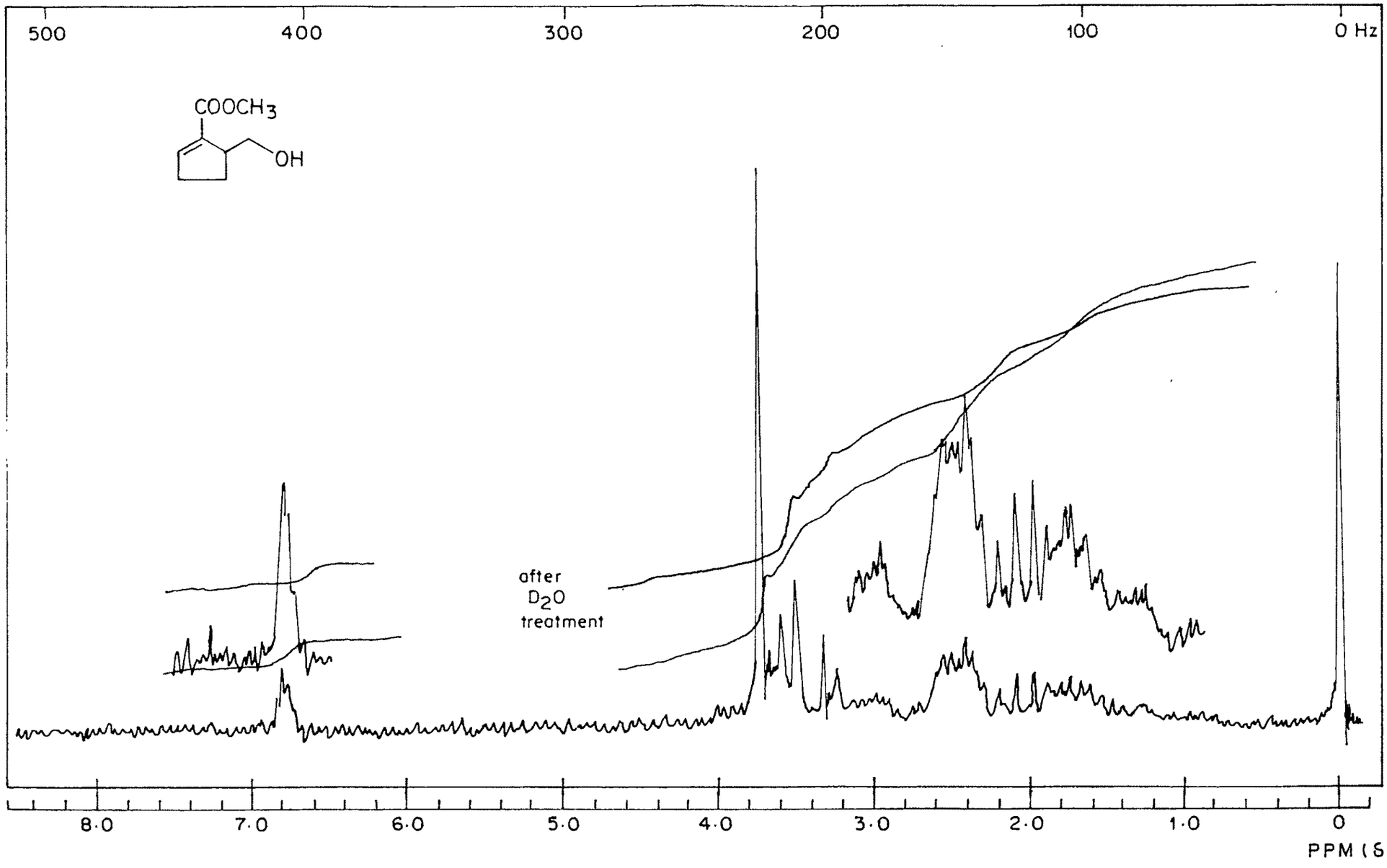


FIG. NO. 12. NMR SPECTRUM OF ALCOHOL 158

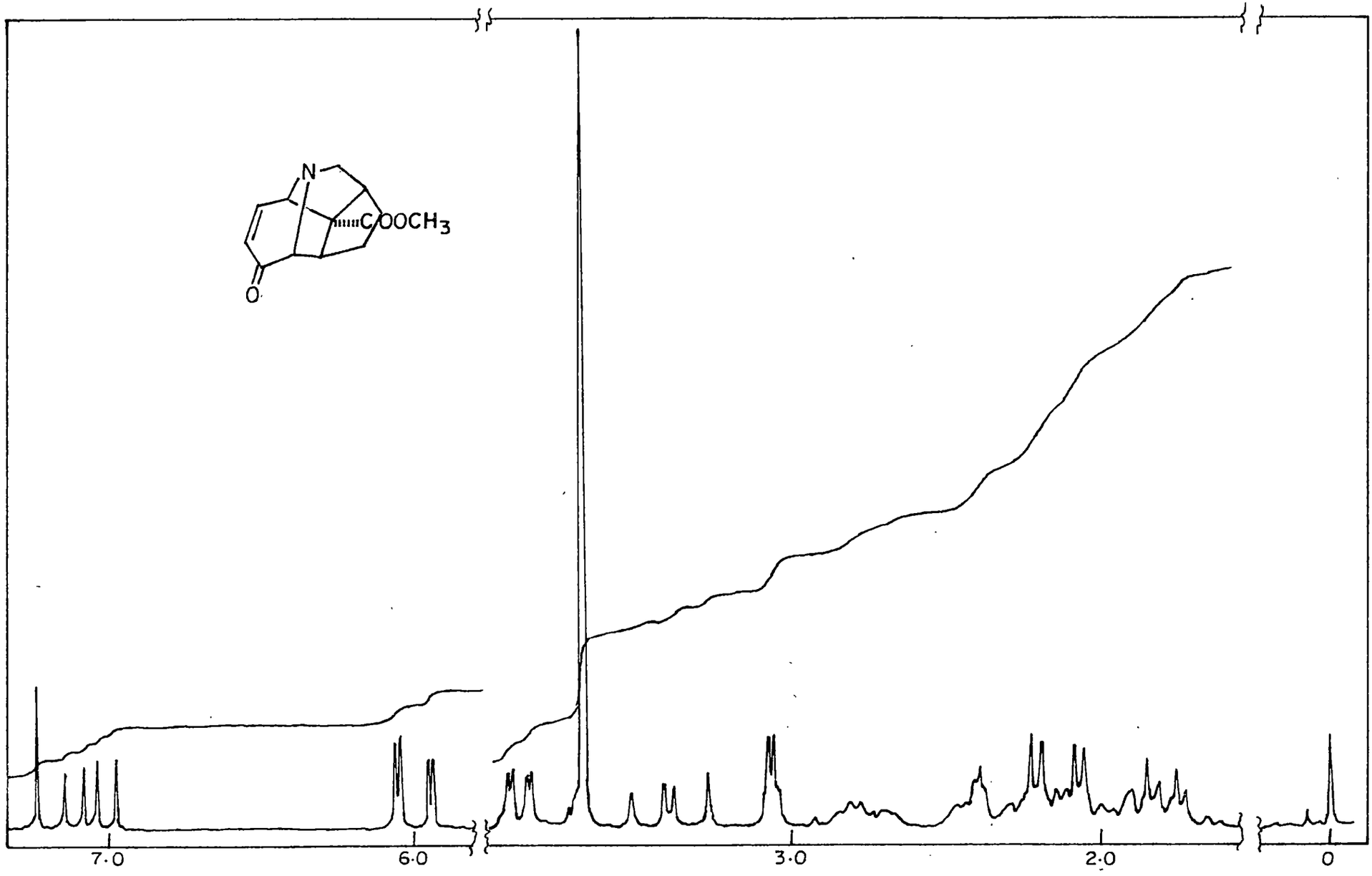


FIG. NO. 13 . NMR SPECTRUM OF CYCLOADDUCT 163 90 MHz

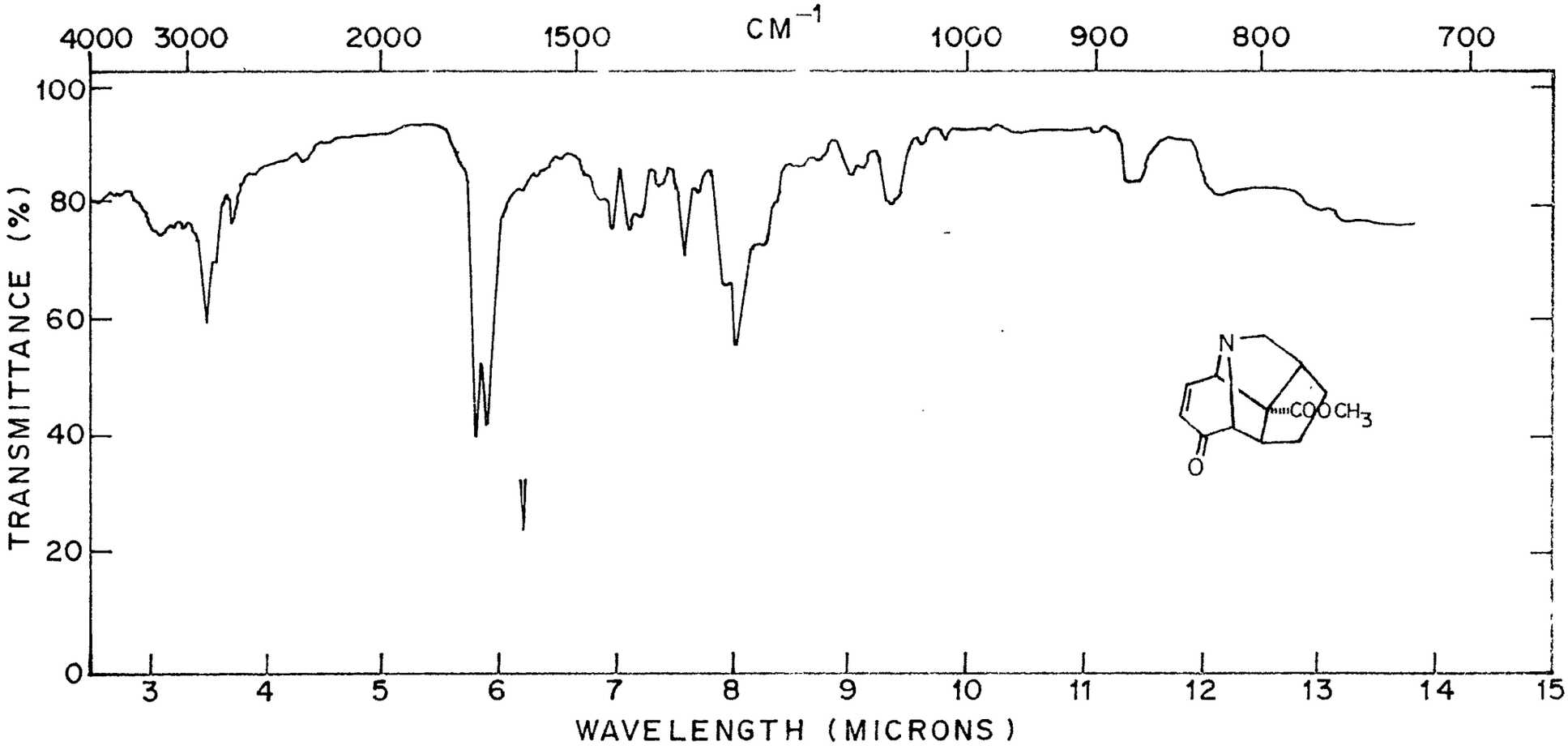


FIG. NO. 14 . IR SPECTRUM OF CYCLOADDUCT 163

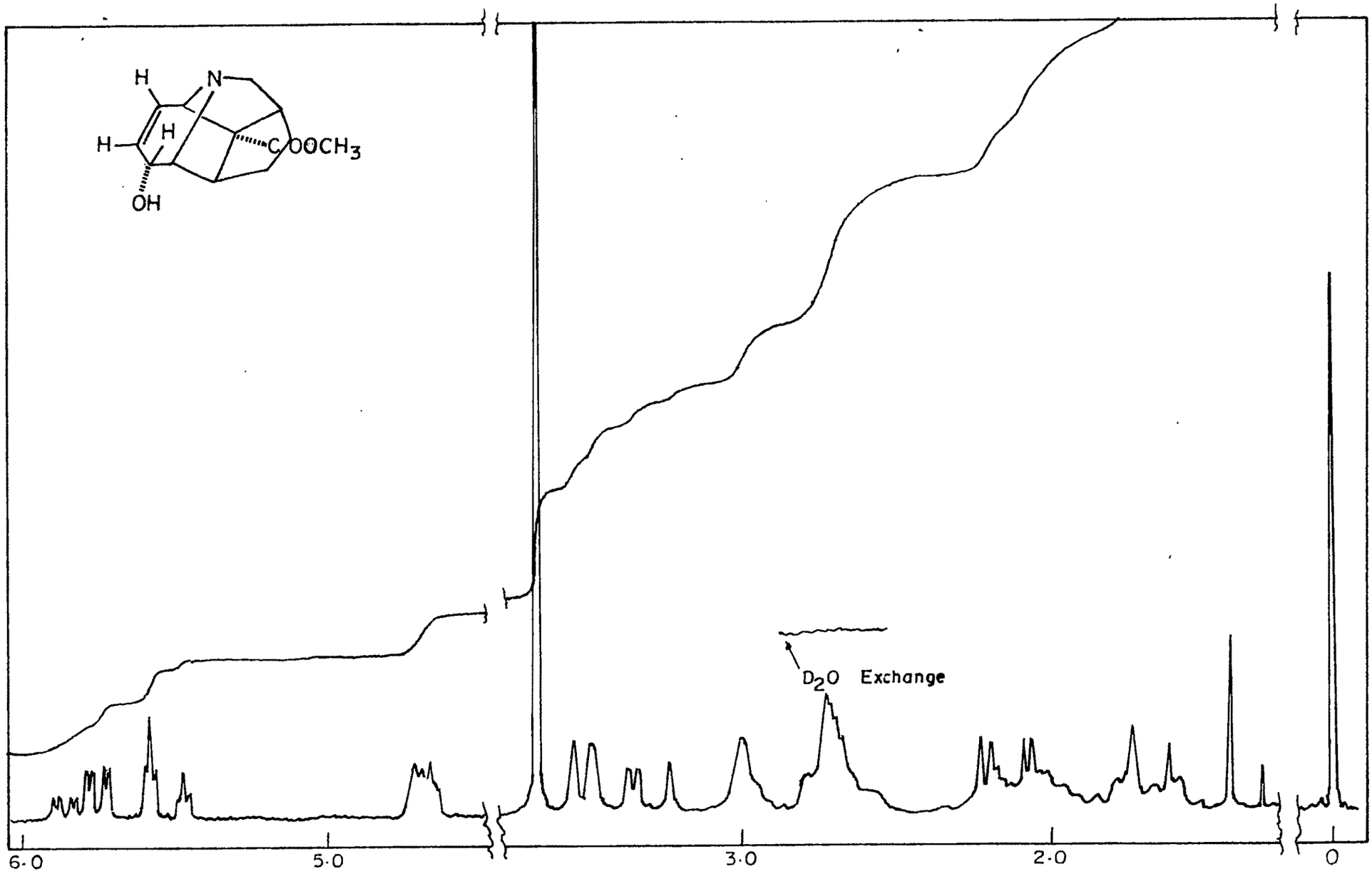


FIG. NO. 15 . NMR SPECTRUM OF ALCOHOL 164 (X = OH) 90 MHz

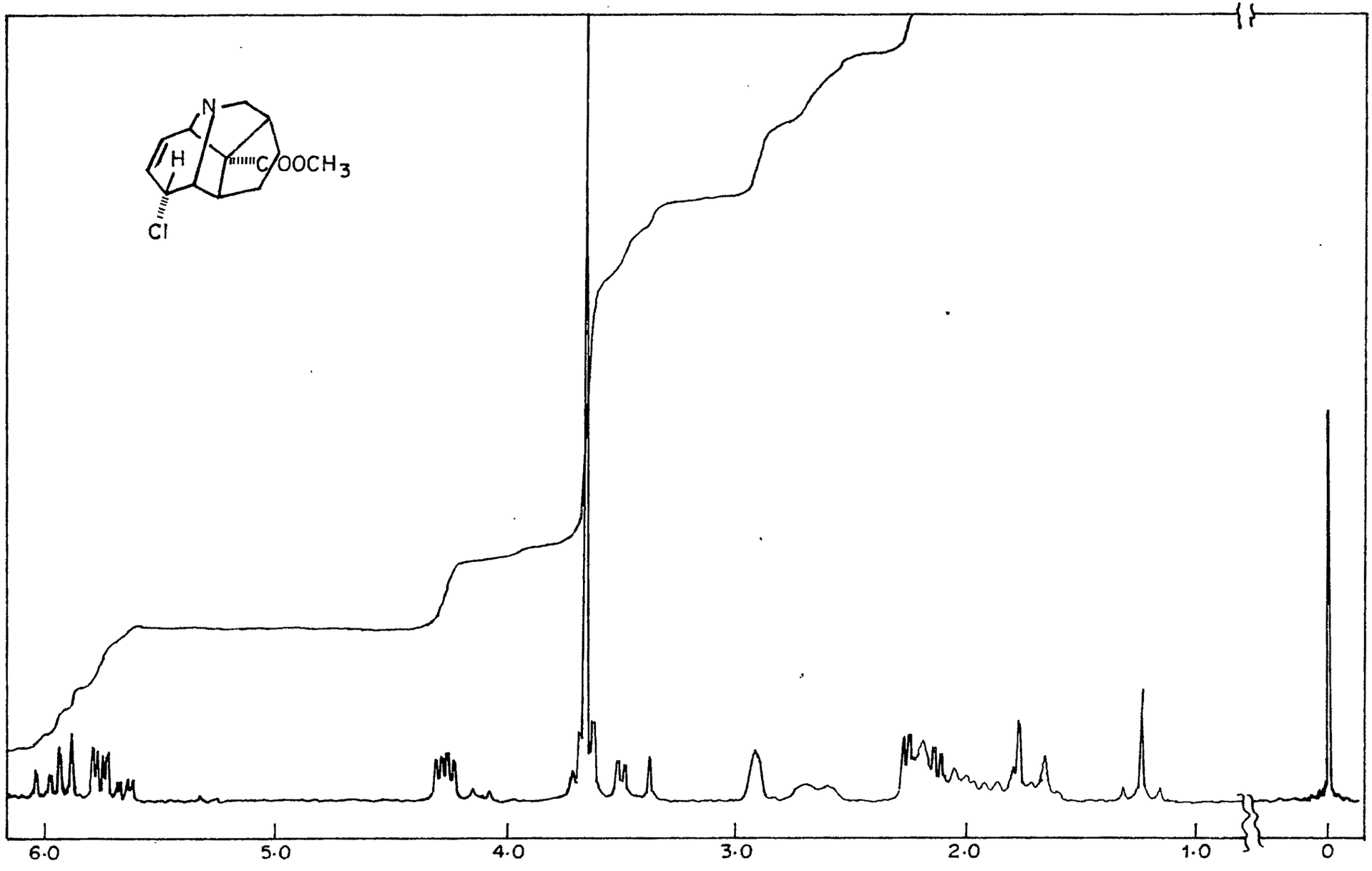


FIG. NO. 16 . NMR SPECTRUM OF CHLORIDE 164 (X = Cl) 90MHz

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