BICYCLIC HETEROCYCLIC SYSTEMS DERIVED FROM 1,3,4-TRISUBSTITUTED PYRIDINES

By

ARTHUR BRADLEY

A thesis presented for the degree of

DOCTOR OF PHILOSOPHY

in the

University of Aston in Birmingham

THESIS
547.82
BRA
15Oct 73 165980

June, 1973.

Department of Pharmacy

University of Aston in Birmingham.

SUMMARY

The preparation of 1,3,4-trisubstituted pyridines and their conversion into bicyclic systems are reviewed.

The work described in this thesis concerned the preparation of 1,3,4-trisubstituted pyridines, by both existing and novel routes, and the conversion of these precursors into bicyclic systems.

Nucleophilic displacement of the nitro group in 4-nitronicotinic acid 1-oxide by amines and alcohols gives a series of 3,4-disubstituted pyridine 1-oxides; with methyl hydrazine as the nucleophile, ring closure occurs to give 3-hydroxy-2-methylpyrazolo[4,3-c]pyridine 5-oxide.

Several new 1,3,4-trisubstituted-1,2,5,6-tetrahydropyridines are prepared by reduction of the appropriate pyridinium iodides with sodium borohydride. The reduction of 3,4-dimethoxycarbonyl-1-methyl pyridinium iodide by sodium borohydride gives the expected tetrahydro derivative and 3,4-dimethoxycarbonyl-1-methylpyrid-6-one; the pyridone was also prepared by oxidation of the quaternary salt using potassium ferricyanide. The reaction of 3,4-diethoxycarbonyl-1-methyl pyridinium iodide and 1-ethyl-3,4-dimethoxycarbonyl pyridinium iodide with sodium borohydride gave the corresponding pyrid-6-ones. An investigation into the unexpected course of this reaction is described, and a possible mechanism is proposed.

Two main routes are employed for the synthesis of pyrido[4,3-d]pyrimidine 6-oxides. Condensation of 4-aminonicotinic acid 1-oxide with formamide and urea gives the corresponding pyridopyrimidinones. Treatment of 4-aminonicotinic acid 1-oxide with aroyl halides gives the appropriate 2-arylpyrido[4,3-d][1,3]oxazin-4-one 6-oxides; the reaction of the pyrido-oxazine 6-oxides with ammonia generally gives the diamides, whereas reaction with hydrazine under similar conditions gives the 3-aminopyrido[4,3-d]

pyrimidin-4(3H)-one 6-oxides. The mechanisms of these reactions are discussed.

The reaction of substituted pyridine o-diesters with hydrazine gives the corresponding pyrido[3,4-d]pyridazinones, and the ring closure of 4-N-(3-tolyl)aminonicotinic acid 1-oxide and 4-N-(3-methoxyphenyl)nicotinic acid 1-oxide using sulphuric acid gives the appropriate benzonaphthyridines.

The infrared spectra of the substituted pyridines and of the bicyclic systems, and some of the n.m.r. spectra, are recorded.

The mass spectra of the substituted pyridines and of the bicyclic systems are recorded, and possible fragmentation pathways for several of these compounds are suggested.

The author would like to thank Professor D.G. Wibberley for his help and encouragement during the course of this work, Dr. W.J. Irwin and Dr. A.Z. Britten for useful discussion, and Allen and Hanbury's Ltd., for the award of a research grant.

TO LINDA

CONTENTS

Page Number

SUMMARY

INTRODUCTION

SYNTHESIS OF 1,3,4-TRISUBSTITUTED PYRIDINES

a) 3,4-Disubstituted Pyridine 1-oxides 2

b) 3,4-Disubstituted Pyridinium Quaternary Salts 8

c) 1,3,4-Trisubstituted-1,2,5,6-Tetrahydropyridines 9

SYNTHESIS OF BICYCLIC SYSTEMS

a) From 1,3,4-Trisubstituted Pyridines 12

b) From 1,3,4-Trisubstituted-1,2,5,6-Tetrahydropyridines .. 14

DISCUSSION

SYNTHESIS OF 1,3,4-TRISUBSTITUTED PYRIDINES

i) 3,4-Disubstituted pyridine 1-oxides 22

ii) Tetrahydropyridines. 36

BICYCLIC SYSTEMS DERIVED FROM 1,3,4-TRISUBSTITUTED PYRIDINES.

a) Pyrido[4,3-d]pyrimidines 51

i) From 1,3,4-trisubstituted pyridines. 51

ii) Via pyrido[4,3-d][1,3]oxazin-4-ones. 55

b) Pyrazolopyridines 69

c) Pyrido[3,4-d]pyridazines 74

d) 1,6-Naphthyridine 6-oxides 77

MASS SPECTRA

i) 4-Substituted nicotinic acid 1-oxides 82

ii) 4-Amidonicotinamide 1-oxides 86

iii) N-Alkyl-3,4-disubstituted pyrid-6-ones. 88

Page Number

iv) 2-Arylpyrido[4,3-d][1,3]oxazin-4-one 6-oxides. 89

v) Pyrido[4,3-d]pyrimidine 6-oxides. 91

vi) Pyrido[3,4-d]pyridazines. 92

EXPERIMENTAL

SYNTHESIS OF 1,3,4-TRISUBSTITUTED PYRIDINES

i) 3,4-Disubstituted pyridine 1-oxides 95

ii) 1,2,5,6-Tetrahydropyridines 105

BICYCLIC SYSTEMS DERIVED FROM 1,3,4-TRISUBSTITUTED PYRIDINES 117

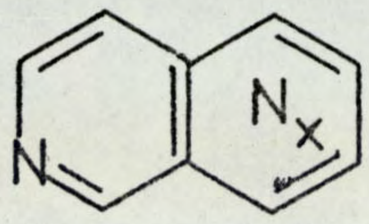
MASS SPECTRAL DIAGRAMS 134

MASS SPECTRAL TABLES 146

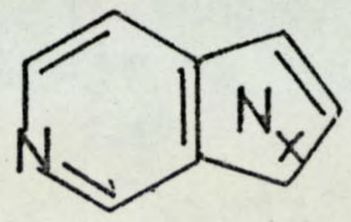
BIBLIOGRAPHY 155

INTRODUCTION

Because of their close structural relationship to the important naturally occurring pteridines and purines, many bicyclic heterocyclic compounds of general formula (1) and (2), where x=1 or 2, containing a pyridine ring fused across the 3,4-bond, have been synthesised from



(1) x = 1 or 2



(2) x = 1 or 2

3,4-disubstituted pyridines for biological studies. The preparation of suitable 3,4-disubstituted pyridine precursors, however, often involves several stages and overall yields are low.[1,2]

The susceptibility of the 4-position of pyridine 1-oxides to both electrophilic and nucleophilic attack has been utilised to prepare 1,3,4-trisubstituted pyridines.[3] Few examples of the use of such derivatives as precursors in the preparation of systems such as (1) or (2), having either a substituted or unsubstituted pyridine nitrogen have, however, been reported. 1,3,4-Trisubstituted piperidines have been used to prepare some biologically active tetrahydro-[4,3-d]-pyrimidines,[4-10] but an alternative route from 1,3,4-trisubstituted pyridines has not been investigated.

The aim of the work to be described later in this thesis was the synthesis of bicyclic N-heteroaromatic compounds of general formula (1) or (2) from appropriate 1,3,4-trisubstituted pyridines. Previous syntheses of 1,3,4-trisubstituted pyridines and the reported conversion of such compounds into bicyclic ring systems are discussed within this section.

1,3,4-Trisubstituted Pyridines

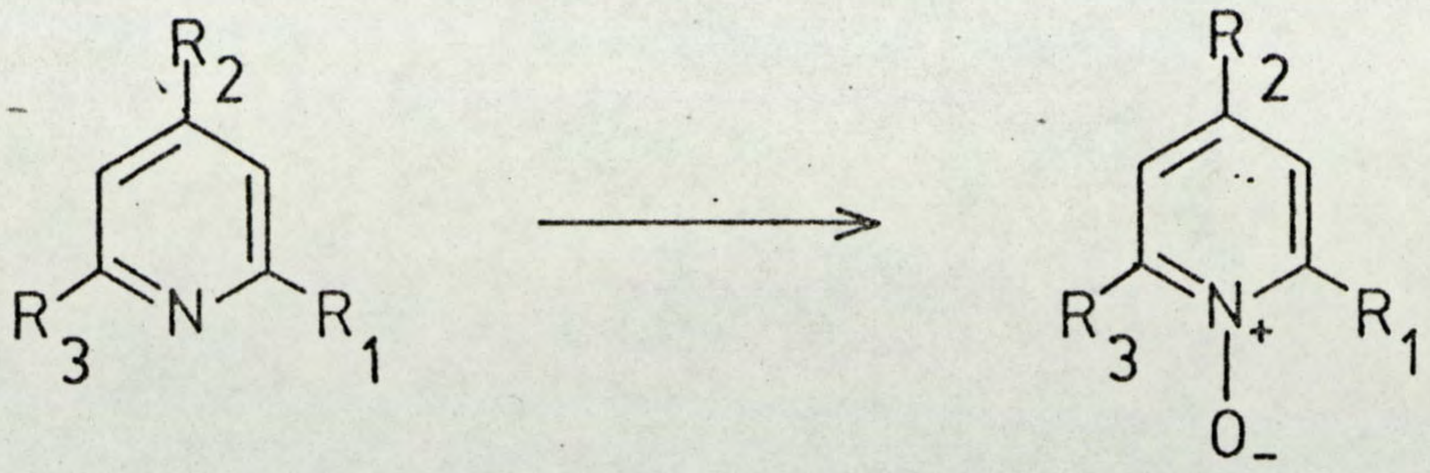
The preparation of the parent 1,3,4-trisubstituted pyridines requires the utilisation of the lone pair of the pyridine nitrogen atom, yielding a positively charged species, and is thus governed by the availability of the lone pair of electrons. Electron donating substituents, suitably orientated on the pyridine ring, will thus enhance donation, and electron withdrawing groups will give decreased availability of the lone pair. The presence of substituents in the 2 and 6 positions of the pyridine ring will sterically hinder any reaction at the 1 position, and quaternisation with methyl iodide has been shown to be more sensitive to steric interference than N-oxidation.[11]

a) 3,4-Disubstituted Pyridine 1-oxides.

i) N-oxidation of 3,4-disubstituted pyridines

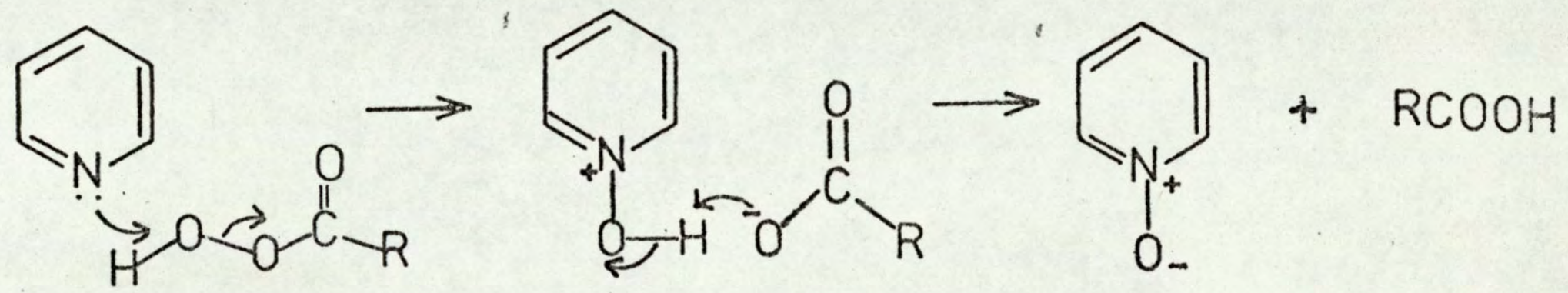
Kinetic studies[12] on the oxidation of pyridine in aqueous dioxan by perbenzoic acid have shown the reaction to be second order and pH dependant, involving the pyridine as free base and the per-acid as free acid. At low pH, the rate falls due to pyridinium cation formation, and at high pH the rate decreases due to the production of the per-acid anion.

Work on a wide variety of alkyl and monochloro-substituted pyridines has shown a satisfactory linear relationship between rate constants and pKa values,[13] with the exception of 2,6-disubstituted pyridines, where steric hindrance interferes.

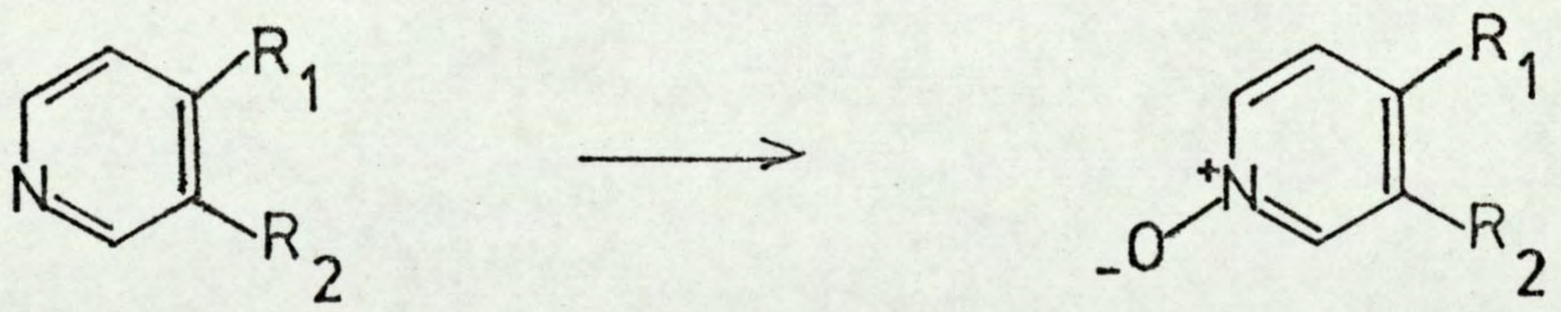


SUBSTITUENTS	pKa	RATE ($Kx10^3 sec.^{-1} mole^{-1}/l$).
(3) $R_1=R_2=R_3=H$	5.17	4.80
(4) $R_1=R_3=H$, $R_2=CH_3$	6.02	7.25
(5) $R_1=R_2=CH_3$, $R_3=H$	6.71	10.2
(6) $R_1=R_2=R_3=CH_3$	7.50	10.2

The above findings indicate the most likely mechanism for N-oxidation to be:



The oxidation of 3,4-dialkyl substituted pyridines (7) with peracetic acid proceeds smoothly and in good yield.[14,15]



(7) $R_1=R_2$=alkyl

(8) R_1=alkyl, R_2=halogen

(9) R_1=alkyl, R_2=formamido

(10) R_1=acetamido, R_2=alkyl

(11) R_1=(4'-pyridyl), $R_2=CH_3$

(12) R_1=ethoxy, R_2=(4-ethoxy-3-pyridylethyl)

(13) $R_1=R_2$=alkyl

(14) R_1=alkyl, R_2=halogen

(15) R_1=alkyl, R_2=formamido

(16) R_1=acetamido, R_2=alkyl

(17) R_1=(4'-pyridyl), $R_2=CH_3$

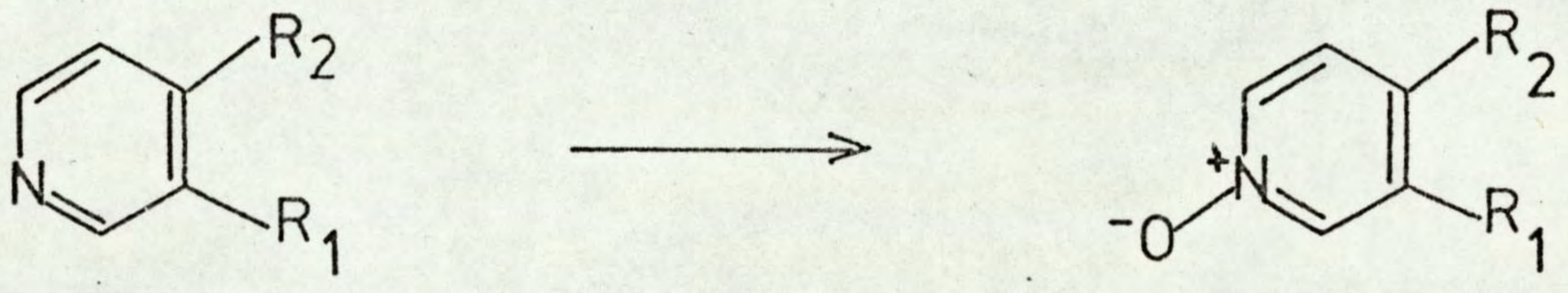
(18) R_1=ethoxy, R_2=(4-ethoxy-3-pyridylethyl).

4-Alkyl-3-halogenopyridine 1-oxides (14) were prepared by oxidation of the appropriate 3,4-disubstituted pyridines (8) with perbenzoic acid,[16]

whereas peracetic acid was used to prepare 4-alkyl-3-formamidopyridine 1-oxides[17] (15) and 4-acetamido-3-alkylpyridine 1-oxides (16) from the corresponding 4-alkyl-3-formamido- (9), and 4-acetamido-3-alkyl pyridines (10).[18]

The oxidation of 3-methyl-4-(4'-pyridyl)-pyridine (11) with perbenzoic acid in chloroform gave only the mono-oxide (17),[19] although the peracetic acid oxidation of 4-ethoxy-3-(2-[4-ethoxy-3-pyridyl]ethyl)pyridine (12)yielded the di-oxide (18).[20]

Although electron withdrawing groups decrease the availability of the nitrogen lone pair for N-oxide formation, the oxidation of 3-alkyl-3-cyano-pyridines (19)[21] and 4-alkylnicotinic acids (20)[22] with peracetic acid was successful.



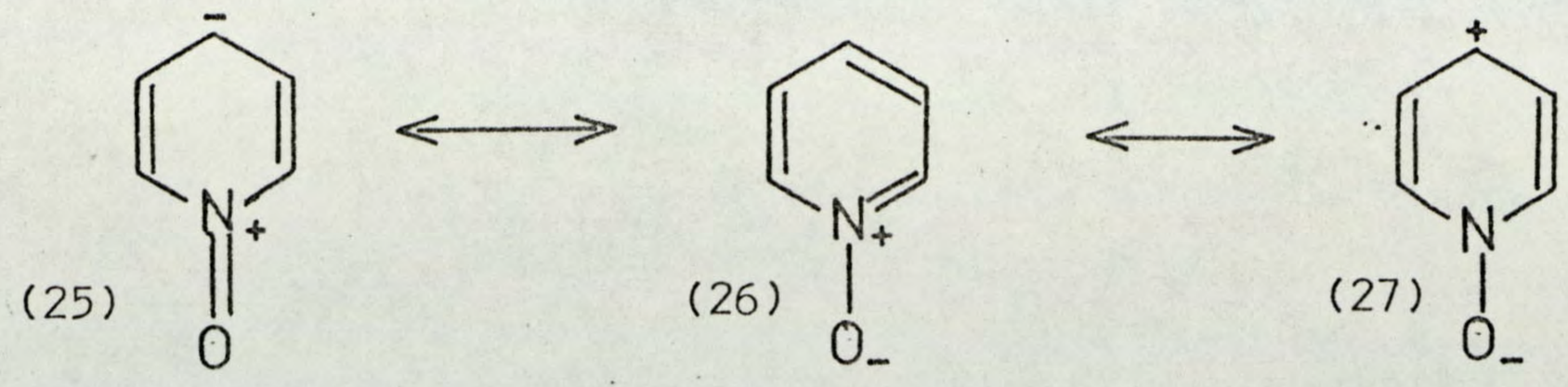
(19) R_1=alkyl, R_2=CN
(20) R_1=COOH, R_2=alkyl
(21) R_1=R_2=COOH

(22) R_1=alkyl, R_2=CN
(23) R_1=COOH, R_2=alkyl
(24) R_1=R_2=COOH

The peracetic acid oxidation of picolinic acid,[23] 2,5- and 2,6-pyridine dicarboxylic acids were all unsuccessful,[24] but pyridine 3,4-dicarboxylic acid (21) was oxidised in 47% yield.[19]

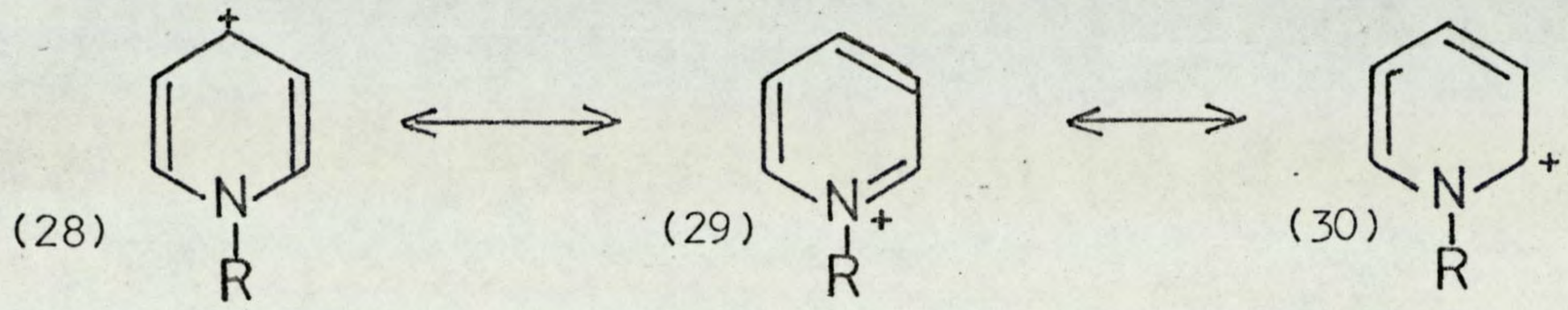
ii) Preparation of 3,4-disubstituted pyridine N-oxides by electrophilic substitution of monosubstituted pyridine N-oxides.

The fundamental difference between pyridine 1-oxides and other 1-substituted pyridines is the ability of the N-oxide group, $=\overset{+}{\underset{|}{N}}-O^-$, to behave as an electron donor as well as an electron acceptor. Thus, canonical forms of types (25) and (27) contribute to the resonance hybrid, whereas in 1-substituted pyridine salts, such as quaternary salts and co-ordination



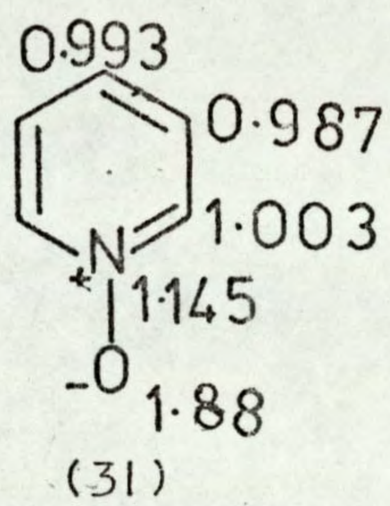
(25) (26) (27)

complexes, any significant resonance is limited to canonical forms of types (28) and (30).



(28) (29) (30)

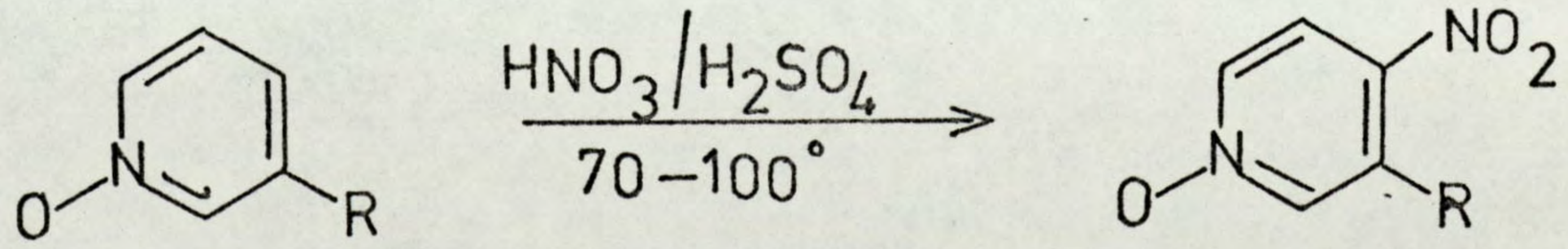
Molecular orbital calculations on pyridine 1-oxide gave the following π-electron densities (31),[25] and recent work[26] indicates that the N-oxide



(31)

group increases the aromaticity of the pyridine ring.

Dipole moment measurements[27] confirmed that there was considerable back polarisation of electrons from the N-oxide group into the pyridine ring, and this observation led to two independent discoveries[28,29] of the relative ease of nitration of pyridine 1-oxide. Nitration at the 4-position has subsequently been shown to proceed smoothly with alkyl,[30] alkoxy,[31] and halogenopyridine 1-oxides.[32]

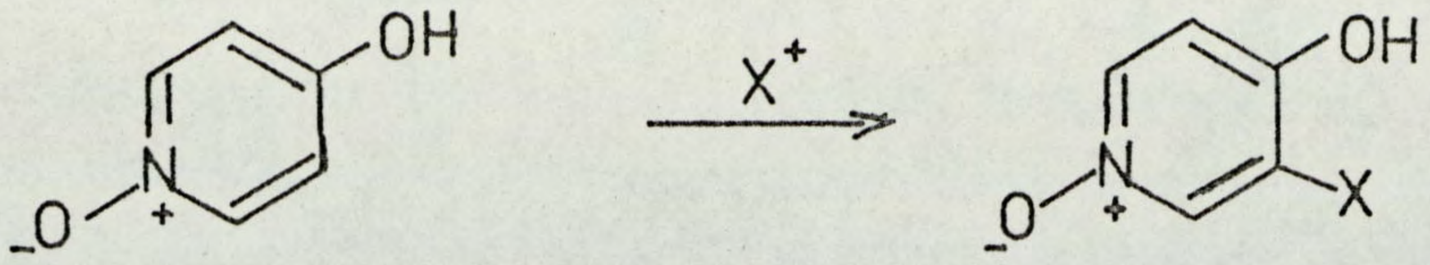


(32) R=alkyl
(33) R=alkoxy
(34) R=halogen

(35) R=alkyl
(36) R=alkoxy
(37) R=halogen

If the 4-position is blocked, nitration usually fails, but if the 4-substituent is sufficiently activating, nitration can occur in the 3 position.[33] Thus, as well as halogenation,[34] and mercuration,[35] 4-hydroxy-

pyridine 1-oxide (38) undergoes nitration in the 3-position.[33]



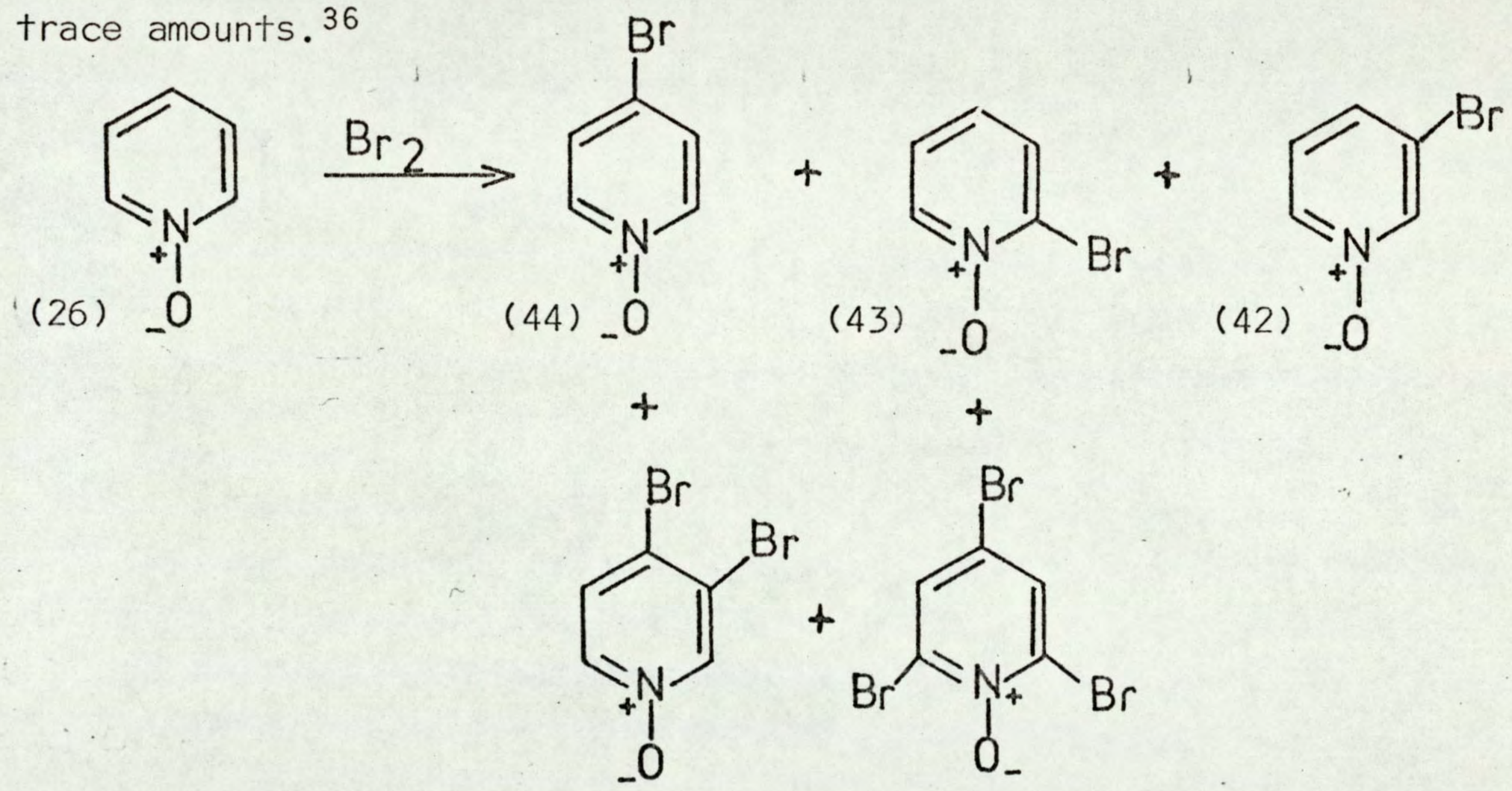
38

(39) X=halogen

(40) X=HgOAc

(41) $X=NO_2$

The bromination of pyridine 1-oxide (26) in 65% oleum gave a mixture of mono-, di-, and tri-brominated products, the major product being the 3-bromo derivative (42) with 3,4-dibromopyridine 1-oxide (45) present in trace amounts.[36]



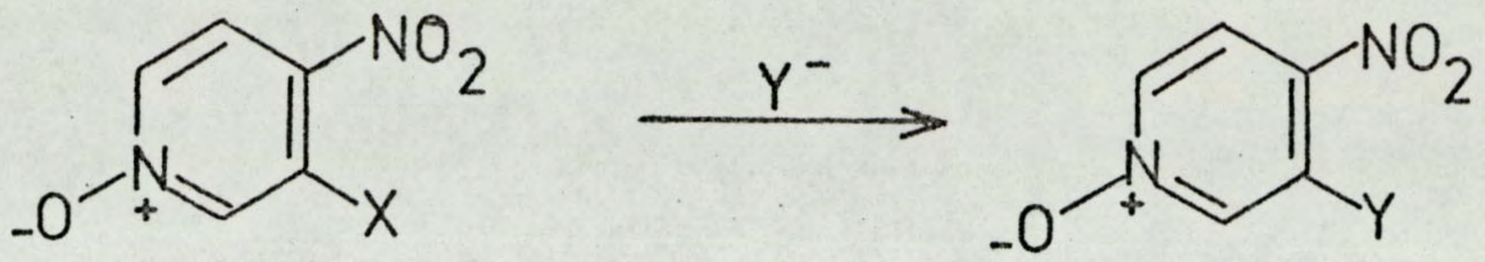
(26) (44) (43) (42) (45) (46)

iii) Nucleophilic substitution as a route to 3,4-disubstituted pyridine N-oxides.

There are no examples of the use of nucleophilic substitution in the preparation of 3,4-disubstituted pyridine 1-oxides from 3-substituted pyridine 1-oxides; nucleophilic substitution into a pyridine N-oxide ring is normally accompanied by deoxygenation. Nucleophilic displacement reactions have, however, been used to prepare a wide range of 3,4-di-

substituted pyridine 1-oxides.

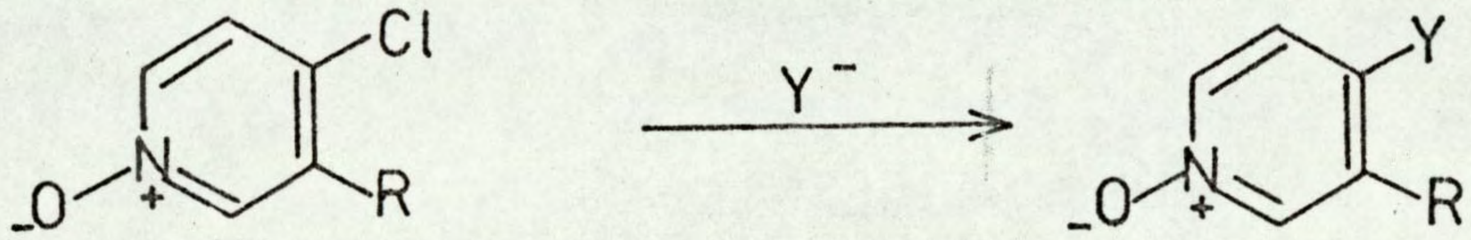
3-Amino- and 3-alkoxy substituted 4-nitropyridine 1-oxides can be readily prepared from 3-halogeno-4-nitropyridine 1-oxides.[37-41]



X=halogen

Y=NHalkyl, NHaryl, $NHNH_2$, Oalk, PhS, OH, $N(alk)_2$, NH-C(=S)-NH_2.

The chloro- group in 3-alkyl-4-chloropyridine 1-oxides (47) and 4-chloronicotinic acid 1-oxide (48) also undergoes displacement by nucleophiles in good yield.



(47) R=alkyl

(48) R=COOH

(49) R=alkyl, $Y=NHCH_3$[42]

(50) R=alkyl, Y=O alkyl[20]

(51) R=alkyl, $Y=OSO_2$[43]

(52) R=COOH, $Y=NH_2$[44]

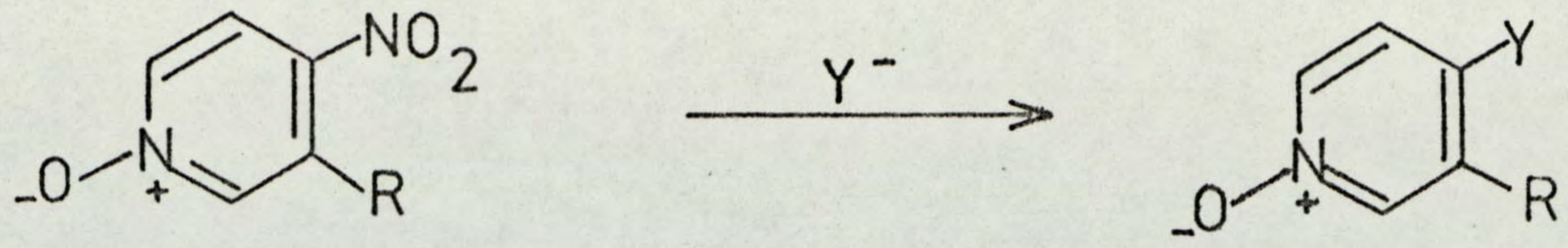
(53) R=COOH, Y=NHNHR[45]

(54) R=COOH, $Y=NHCH_3$[46]

(55) R=COOH, Y=SH[46]

(56) R=COOH, Y=OH[46]

4-Nitrosubstituted pyridine 1-oxides also readily undergo nucleophilic displacement reactions.



(35) R=alkyl

(57) R=COOH

(58) R=alkyl, Y=halogen

(59) R=alkyl, Y=OH

(60) R=alkyl, Y=OCH_2Ph[47]

(61) R=COOH, Y=halogen[48]

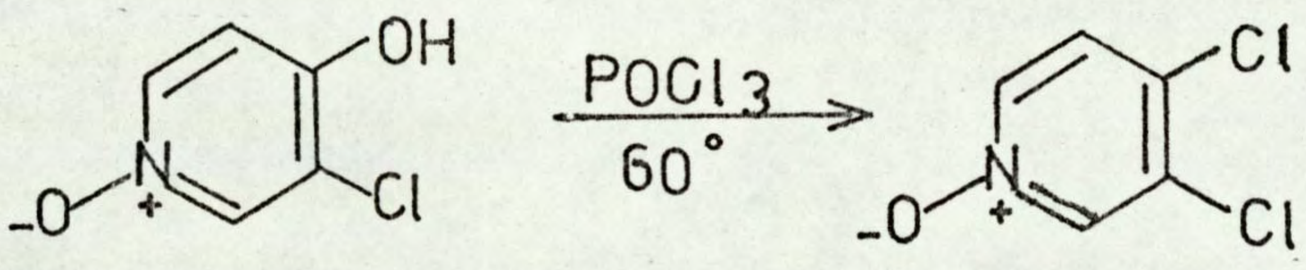
(62) R=COOH, Y=OCH_2Ph

(63) R=COOH, Y=OCH_3

(64) R=COOH, Y=$NHNH_2$[44]

(65) R=COOH, Y=NHPh[49]

3,4-Dichloropyridine 1-oxide (67) has been prepared from 3-chloro-4-hydroxypyridine 1-oxide (66).[50]



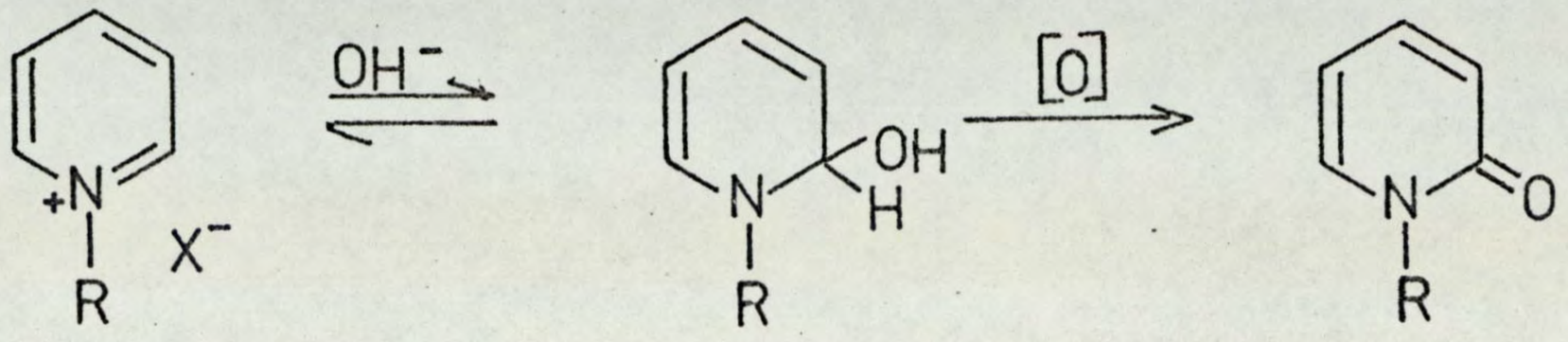
(66) (67)

b) 3,4-Disubstituted Pyridinium Quaternary salts.

The preparation of pyridinium quaternary salts is a well established method for the classification and identification of pyridine derivatives, and many examples of 3,4-disubstituted pyridinium quaternary salts are known.[51] As in N-oxidation, quaternisation is governed by the availability of the nitrogen lone pair, and the ability to donate the lone pair will be enhanced by suitably orientated electron donating substituents, and reduced by electron withdrawing substituents. The presence of large substitutents in the 2 and 6 positions of the ring sterically hinders quaternary salt

formation.

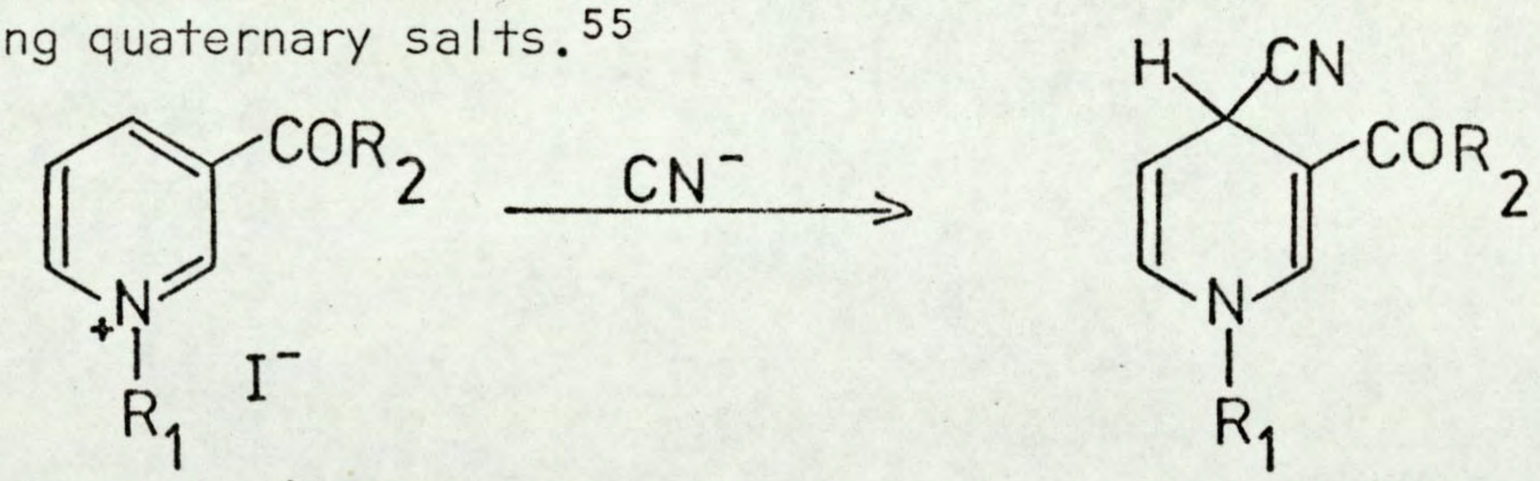
In alkaline solutions, quaternary salts are present as the quaternary hydroxides (67), and the presence of any oxidising agent causes the formation of pyrid-2-ones (68).[52]



(66) (67) (68)

The preparation of pyrid-4-ones by alternative attack at C_4 has not been reported.[52]

Nucleophilic attack on pyridinium quaternary salts occurs predominantly at the 2-position, although it has been suggested[53,54] that those reagents which readily form charge-transfer complexes with pyridinium salts attack at position 4. Cyanide ion attacks at the 4 position, and the 1,3,4-trisubstituted pyridine derivatives (71) and (72) were prepared from the corresponding quaternary salts.[55]



(69) $R_1=CH_3$, $R_2=NH_2$

(70) $R_1=PhCH_2$, $R_2=CH_3$

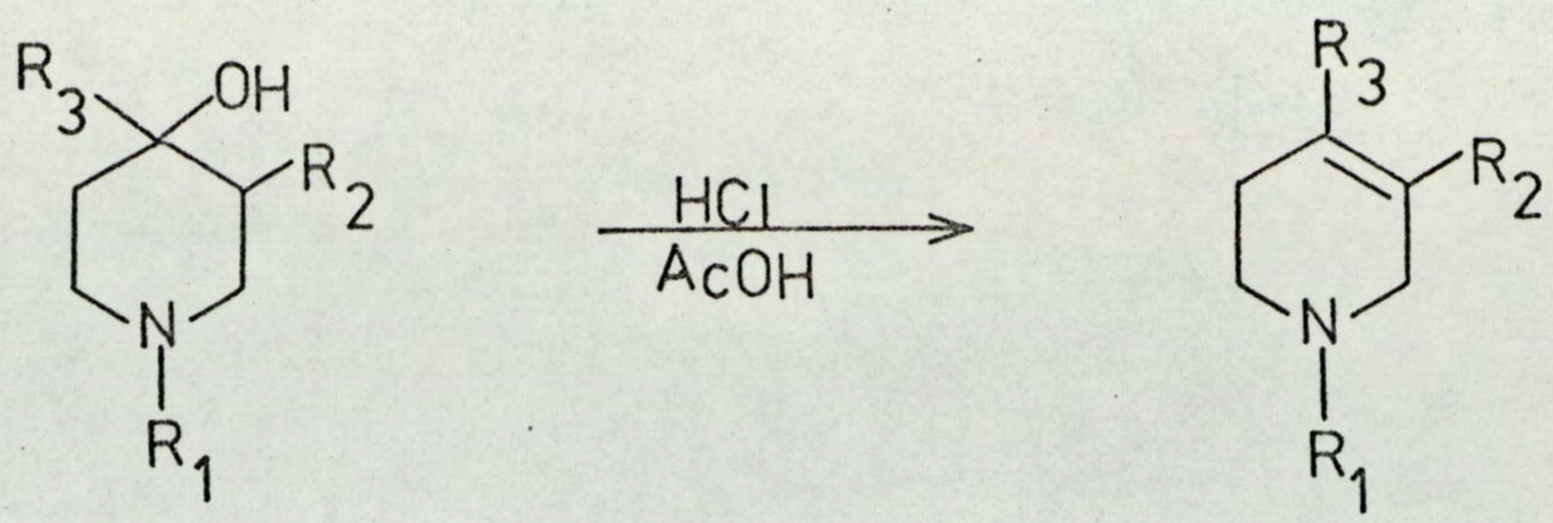
(71) $R_1=CH_3$, $R_2=NH_2$

(72) $R_1=PhCH_2$, $R_2=CH_3$

c) 1,3,4-Trisubstituted-1,2,5,6-Tetrahydropyridines

i) From piperidines and aliphatic amines

The dehydration of 1,3-disubstituted-4-piperidinols has been used to prepare 4-alkyl and 4-aryl substituted 1,2,5,6-tetrahydropyridines[56,57,58].



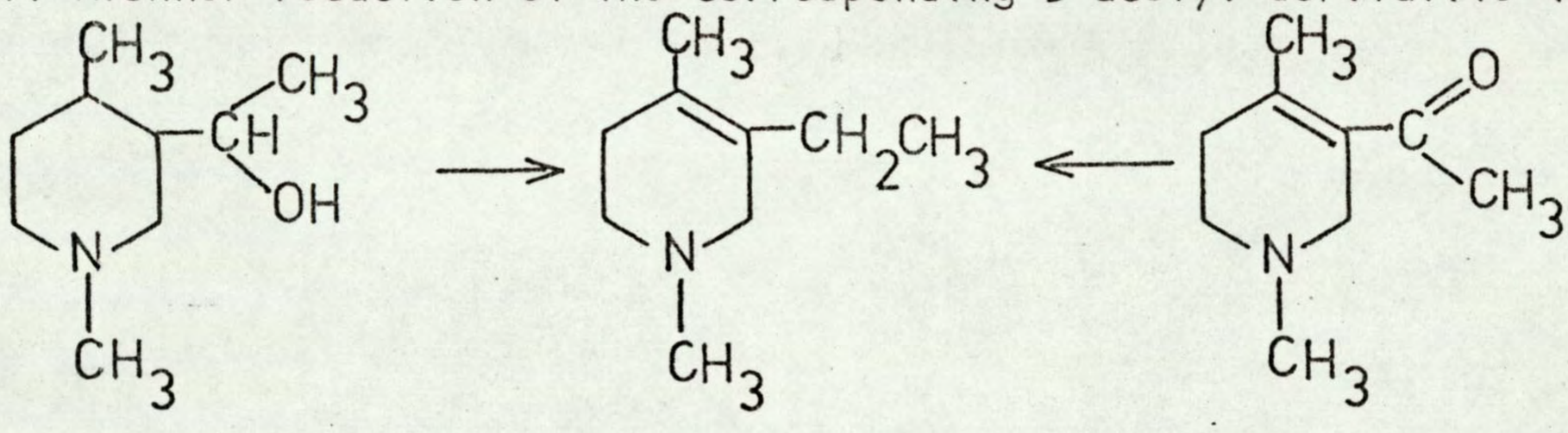
(73) R_1=alkyl, R_2=CH_3, R_3=aryl

(74) R_1=R_3=CH_3, R^2=$COCH_3$

(75) R_1=alkyl, R_2=CH_3, R_3=aryl

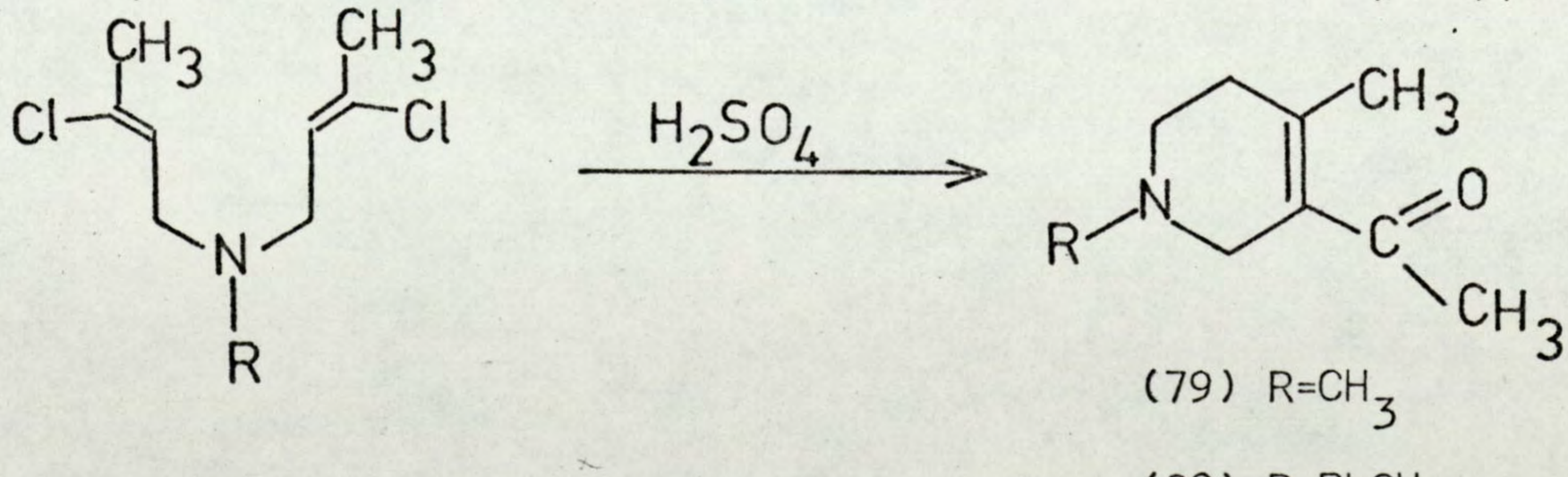
(76) R_1=R_3=CH_3, R_2=$COCH_3$

3-Ethyl-1,4-dimethyl-1,2,5,6-tetrahydropyridine (78) has been prepared by dehydration of 3-(1-hydroxymethyl)-1,4-dimethylpiperidine (77)[59] and by Wolff-Kishner reduction of the corresponding 3-acetyl derivative (79).[60]



(77) (78) (79)

The reaction of N-substituted derivatives of bis(2-chlorocrotyl)amine with sulphuric acid afforded 1,3,4-trisubstituted tetrahydropyridines.[61]



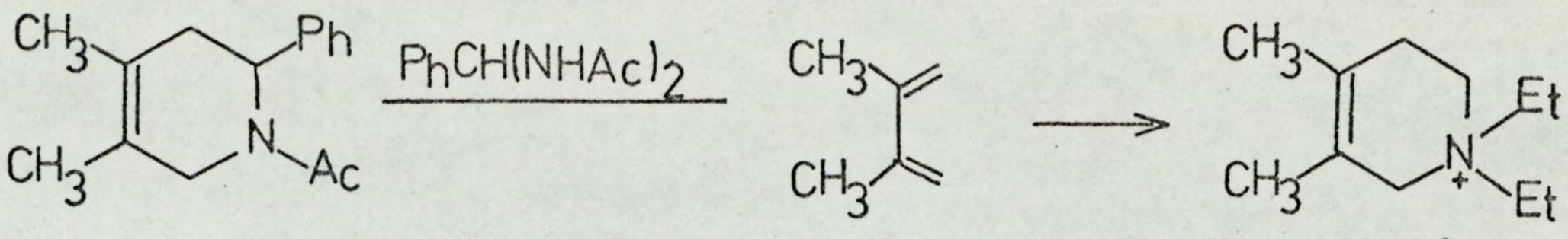
(79) R=CH_3

(80) R=$PhCH_2$

(81) R=COPh

(82) R=p-toluenesulphonyl

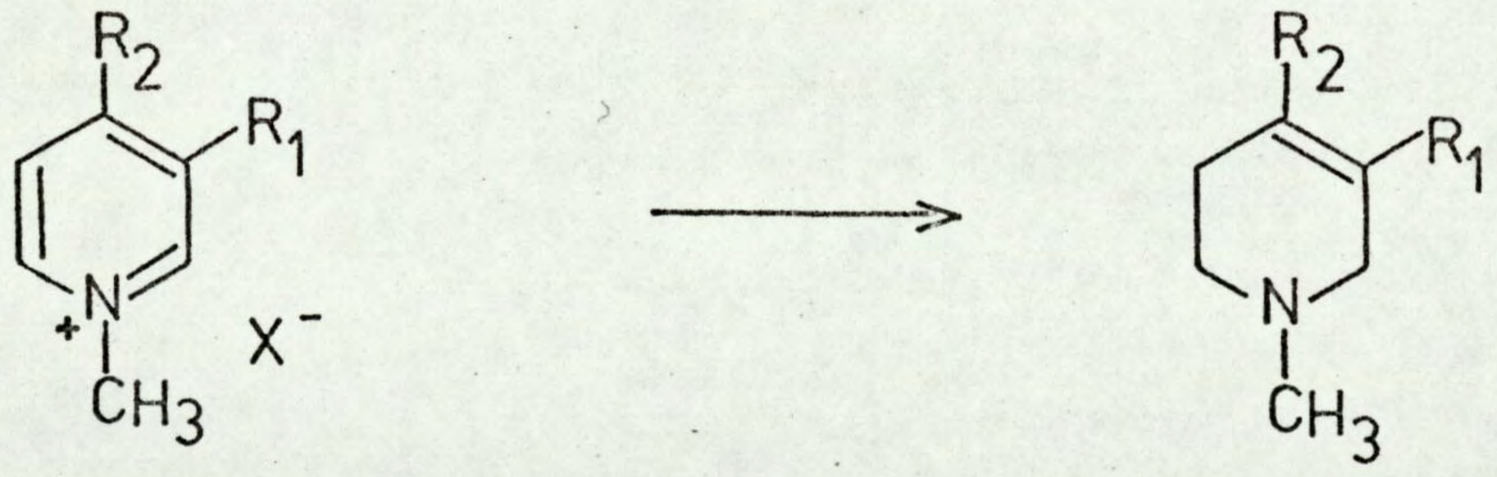
2,3-Dimethylbuta-1,3-diene (84) has proved useful in the preparation of tetrahydropyridines.[62,63]



83 84 85

ii) From pyridinium salts

The reduction of pyridinium salts by complex metal hydrides, notably sodium borohydride, has proved a useful preparative route to tetrahydropyridines.[64,65] The only examples of the preparation of 1,3,4-trisubstituted tetrahydropyridines by reduction of the corresponding pyridinium salts which have been reported, are the reduction of 3,4-dialkyl-1-methylpyridinium iodides[66-70] and methosulphates.[71,72] The quaternary iodides were reduced with sodium borohydride; the methosulphates



(86) $R_1=R_2=CH_3$, X=I

(87) $R_1=R_2=CH_3$, $X=OSO_2OCH_3$

(88) $R_1=R_2=CH_2CH_3$, X=I

(89) $R_1=CH_3$, $R_2=CH_2CH_3$, X=I

(90) $R_1=CH_3$, $R_2=CH_2CH_3$, $X=OSO_2CH_3$

(91) $R_1=CH_2CH_3$, $R_2=CH_3$, X=I

(92) $R_1=R_2=CH_3$

(93) $R_1=R_2=CH_2CH_3$

(94) $R_1=CH_3$, $R_2=CH_2CH_3$

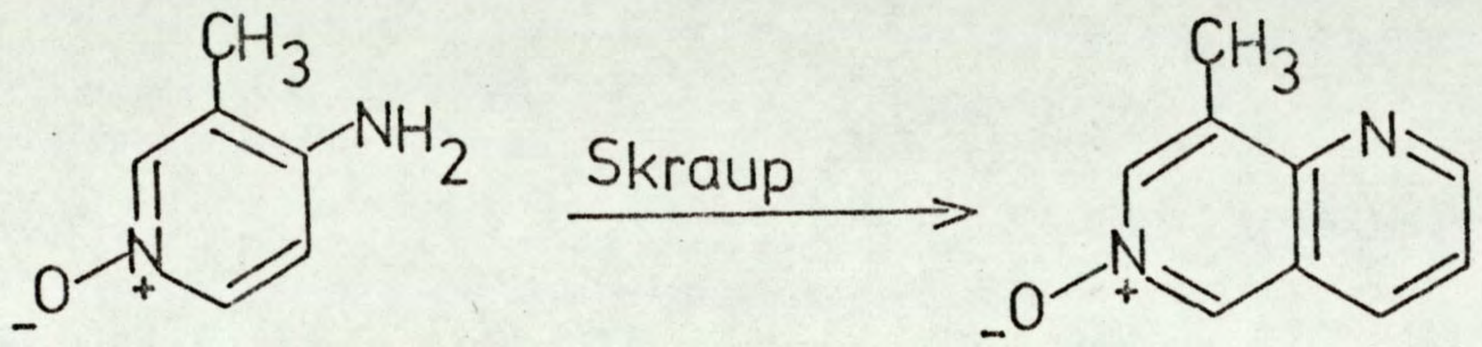
(95) $R_1=CH_2CH_3$, $R_2=CH_3$

were reduced using aluminium hydride, sodium borohydride, and by electrolytic methods.

Bicyclic Heterocyclic Systems

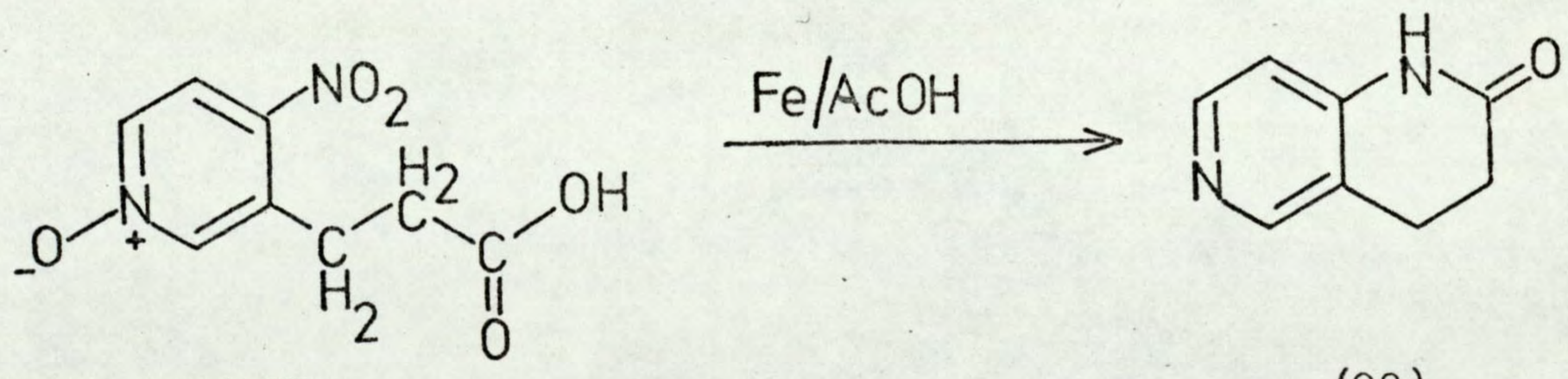
a) From 1,3,4-Trisubstituted Pyridines

The failure of the Skraup reaction in the preparation of 1,6-naphthyridines[73,74] from 4-aminopyridines, was attributed by Kato et. al.[75] to the reduced nucleophilicity of the amino group. The use of 4-aminopyridine 1-oxides in which the amino group is more nucleophilic proved successful, however, in the synthesis of the parent 1,6-naphthyridine 1-oxide and several methyl derivatives.



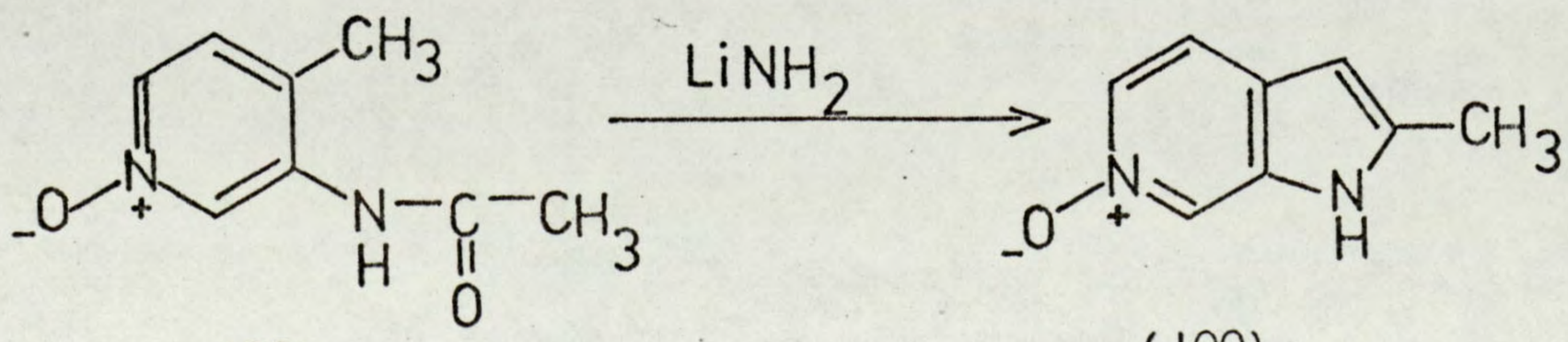
(95) (96)

1,2,3,4-Tetrahydronaphthyrid-2-one (98) was produced by an intramolecular cyclisation when the nitro group of the substituted propionic acid (97) was reduced with an iron/acetic acid mixture.[76]



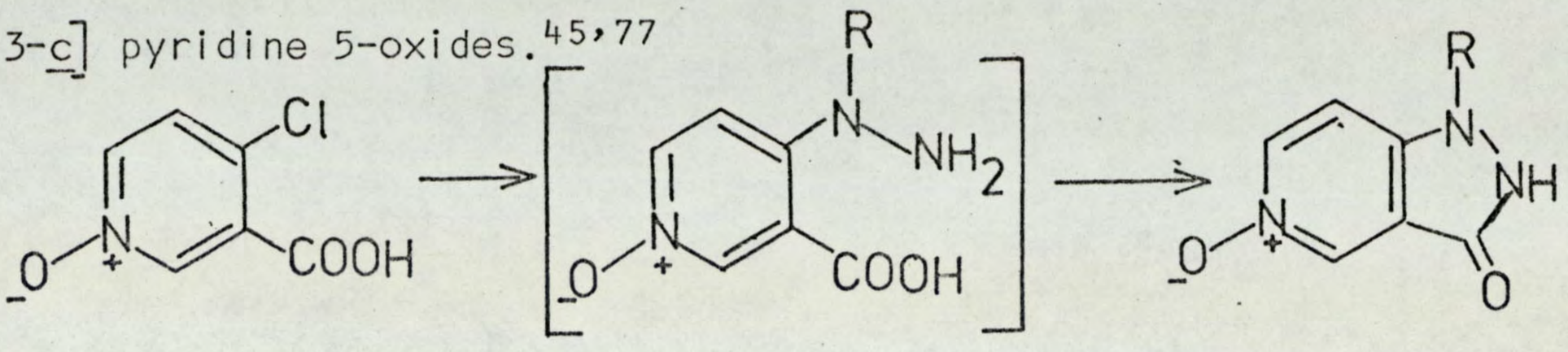
(97) (98)

The active methyl group in the 4-position of pyridine 1-oxides was utilised by Herz and Murty in the preparation of 2-methylpyrrolo [2,3-c] pyridine 6-oxide (100) from 3-acetamido-4-methylpyridine 1-oxide (99).[17]



(99) (100)

Cyclisation of the 4-α-substituted hydrazinonicotinic acid 1-oxides (101), obtained from the reaction of 4-chloronicotinic acid 1-oxide (48) with a substituted hydrazine, gave the required 1-substituted pyrazolo [4, 3-c] pyridine 5-oxides.[45,77]



(48) (101)

(102) R=CH_3

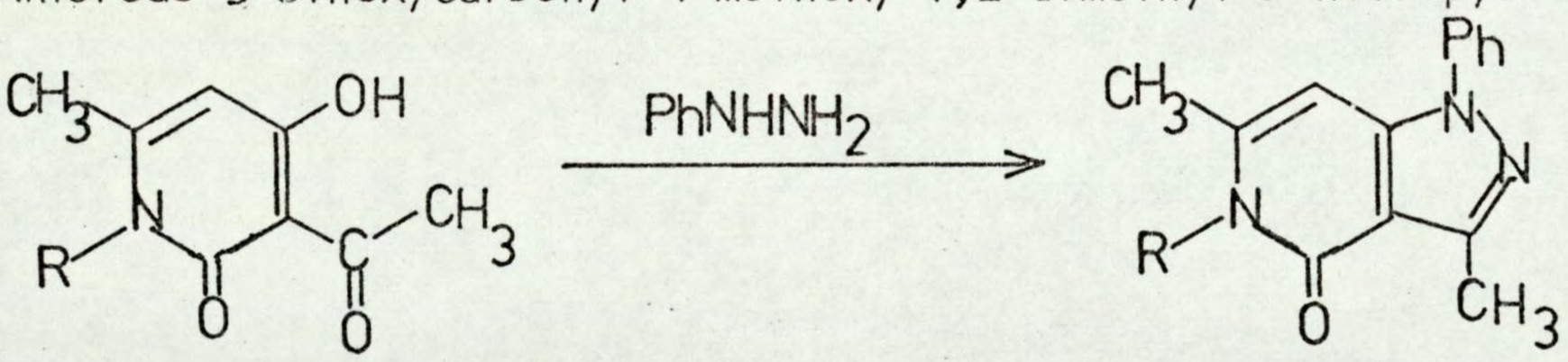
(103) R=Ph

(104) R=p-chlorophenyl

(105) R=p-bromophenyl

(106) R=p-fluorophenyl

1-Substituted pyrazolo [4,3-c] pyridin-4-ones were obtained from N-substitued-3-acetyl-4-hydroxy-6-methylpyrid-2-ones and phenylhydrazine,[78] whereas 3-ethoxycarbonyl-4-methoxy-1,2-dimethyl-5-nitropyrid-6-one (111) and



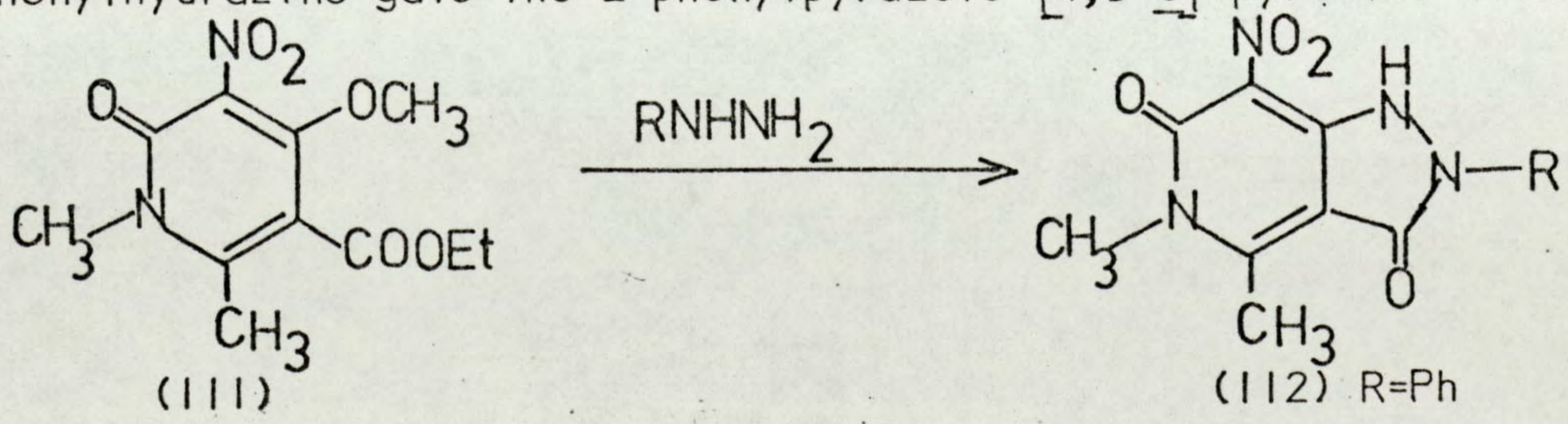
(107) R=CH_3

(108) R=Ph

(109) R=CH_3

(110) R=Ph

phenylhydrazine gave the 2-phenylpyrazolo [4,3-c] pyridine (112)[79]

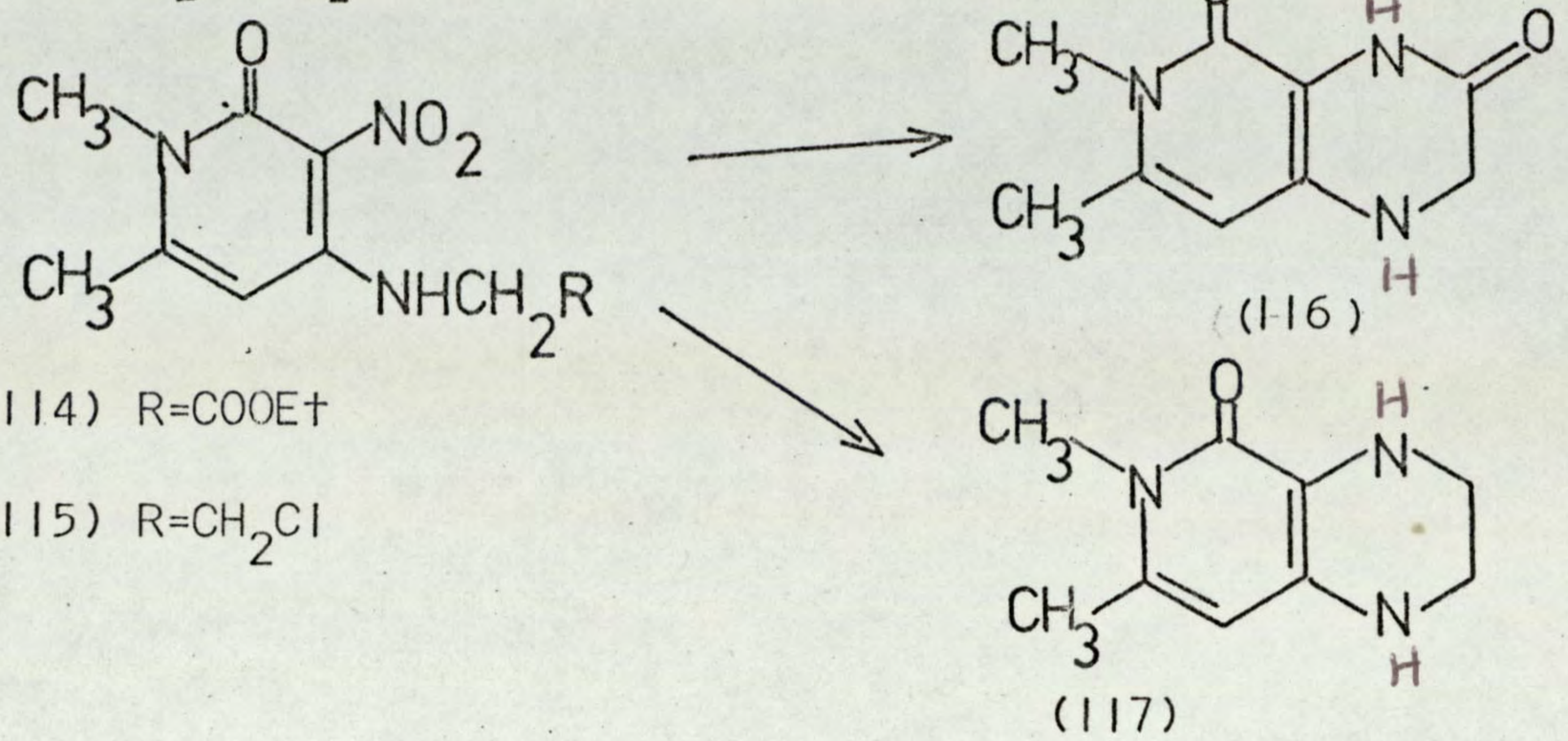


(111)

(112) R=Ph

(113) R=H

The reduction of the nitro group in the pyridones (114) and (115) using hydrogen and a palladium catalyst, gave the intramolecularly cyclised pyrido [3,4-b] pyrazines (116) and (117)[79]



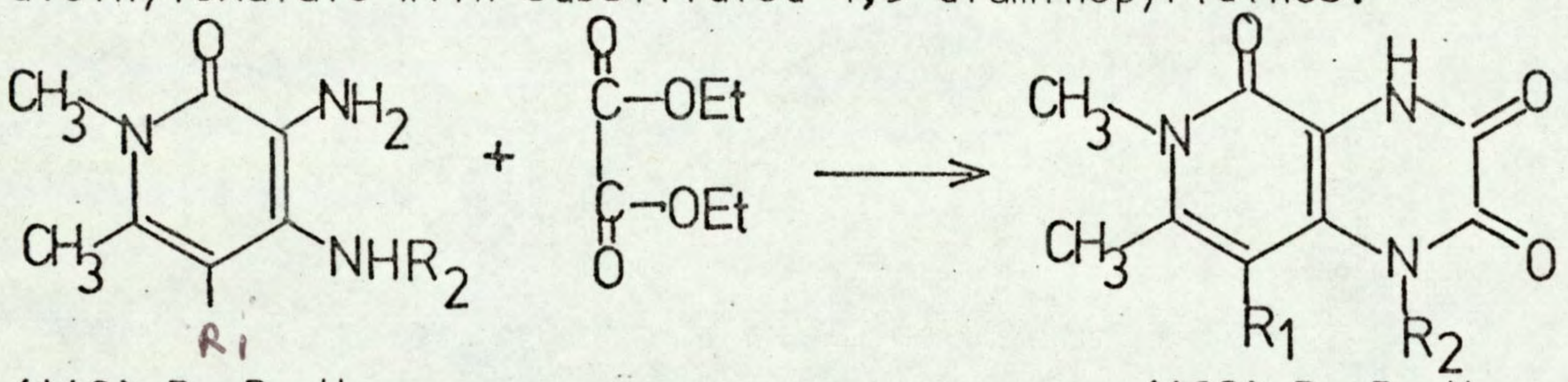
(114) R=COOEt

(115) R=CH_2Cl

(116)

(117)

Pyrido [3,4-b] pyrazines were also produced from the reaction of diethyloxalate with substituted 4,5-diaminopyridines.[79]



(118) $R_1=R_2=H$

(119) $R_1=H$, $R_2=C_4H_9$

(120) $R_1=H$, $R_2=CH_2CH_2OH$

(121) $R_1=COOCH_2CH_3$, $R_2=H$

(122) $R_1=R_2=H$

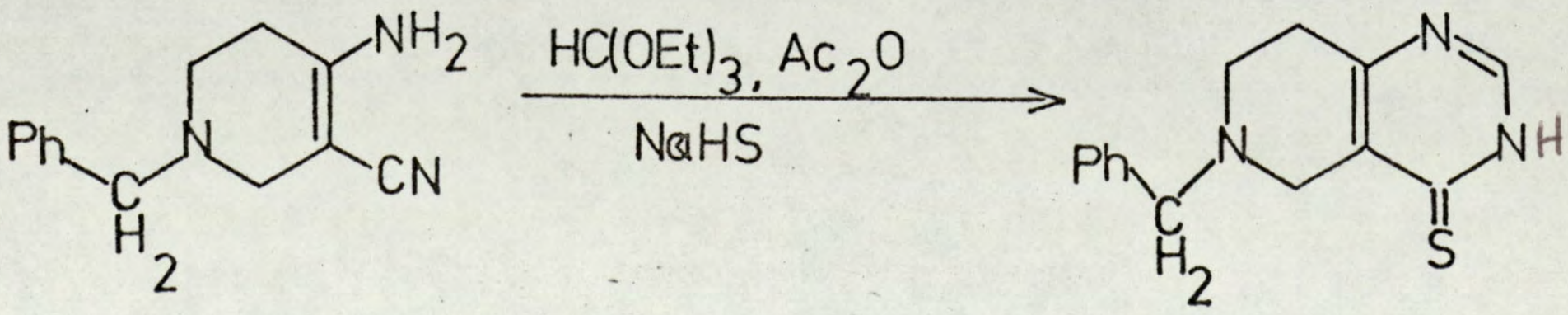
(123) $R_1=H$, $R_2=C_4H_9$

(124) $R_1=H$, $R_2=CH_2CH_2OH$

(125) $R_1=COOCH_2CH_3$, $R_2=H$

b) From 1,3,4-Trisubstituted-1,2,5,6-Tetrahydropyridines

6-Benzyl-5,6,7,8-tetrahydropyrido [4,3-d] pyrimidin-4(3H)-thione (127) has been prepared from 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydropyridine (126)[80]

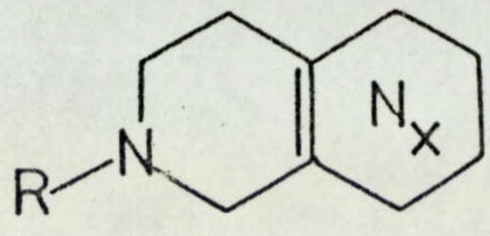


(126)

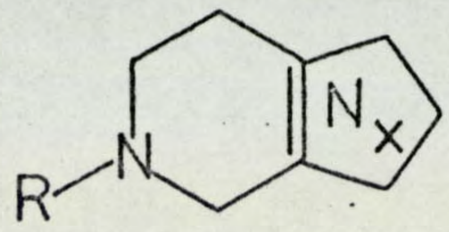
(127)

c) From substituted piperidones

Although there is only one report in the literature[80] of the preparation of a bicyclic system such as (128) from a tetrahydropyridine, other ring systems such as (128) and (129), which comprise a tetrahydropyridine ring



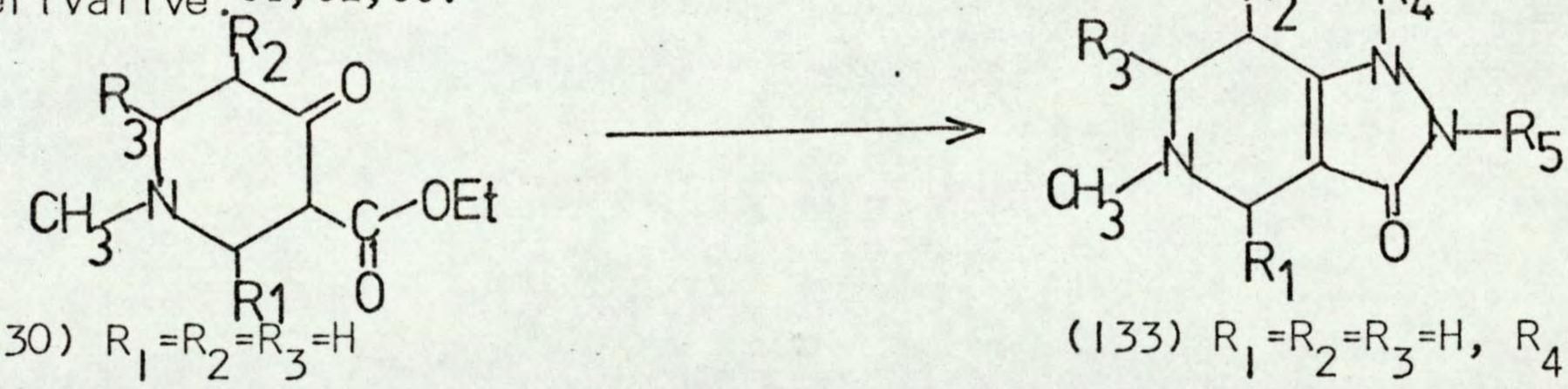
(128) x = 1 or 2



(129) x = 1 or 2

fused across the 3,4-bond, some possessing biological activity, have been prepared from substituted piperidones.

7-Ethoxycarbonyl-4,5,6-trimethyl-4,5,6,7-tetrahydropyrazolo [4,3-c]-1(H)-pyridine (134), 5-methyl-2,6-, and 5-methyl-1,2-diphenyl-4,5,6,7-tetrahydropyrazolo [4,3-c]-1(H)-pyridines (135), (136), were prepared from the corresponding 3-ethoxycarbonyl-4-piperidones and a suitable hydrazine derivative.[81,82,83].



(130) $R_1=R_2=R_3=H$

(131) $R_1=R_3=CH_3$, $R_2=COOCH_2CH_3$

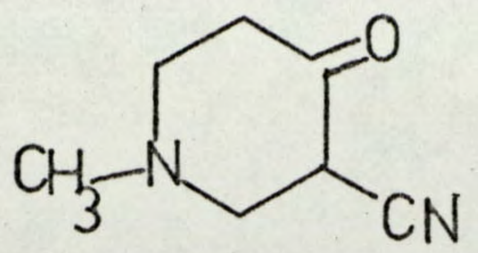
(132) $R_1=R_2=H$, $R_3=Ph$

(133) $R_1=R_2=R_3=H$, $R_4=R_5=Ph$

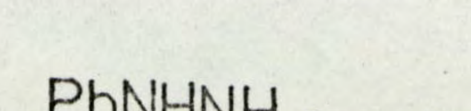
(134) $R_1=R_3=CH_3$, $R_2=COOCH_2CH_3$, $R_4=R_5=H$.

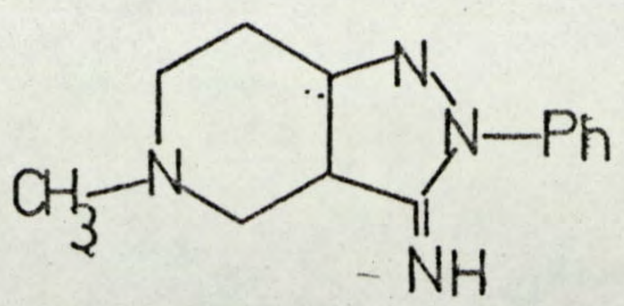
(135) $R_1=R_2=R_4=H$, $R_3=R_5=Ph$

Other 3-substituted-4-piperidones which have been used to prepare 4,5,6,7-tetrahydropyrazolo[4,3-c]-1(H)-pyridines are 3-cyano-, (136),[84] 3-(4-methylbenzoyl)-, (138),[85] and 3-hydroxymethyl-4-piperidone (139).[86]

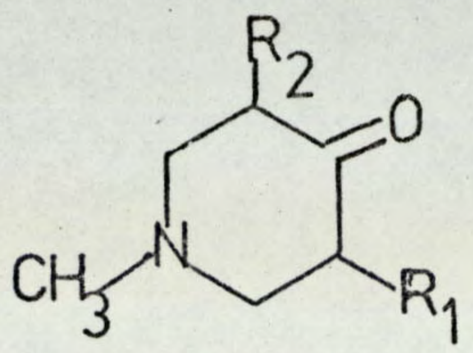


(136)



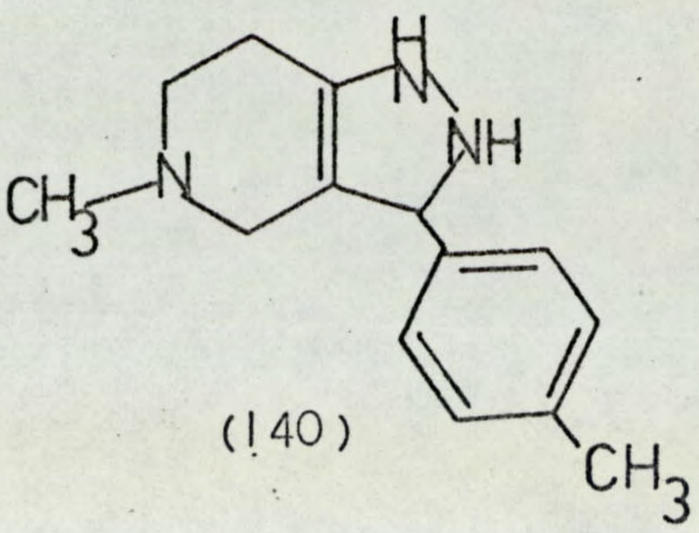


(137)

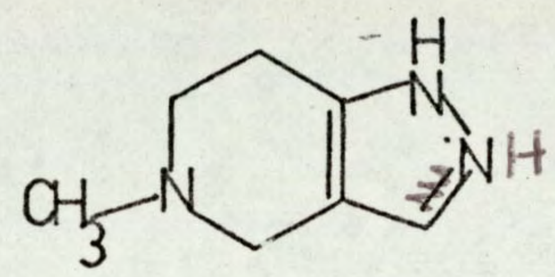


(138) R_1=p-methylbenzoyl, R_2=CH_3

(139) R_1=CH_2O^-, R_2=H

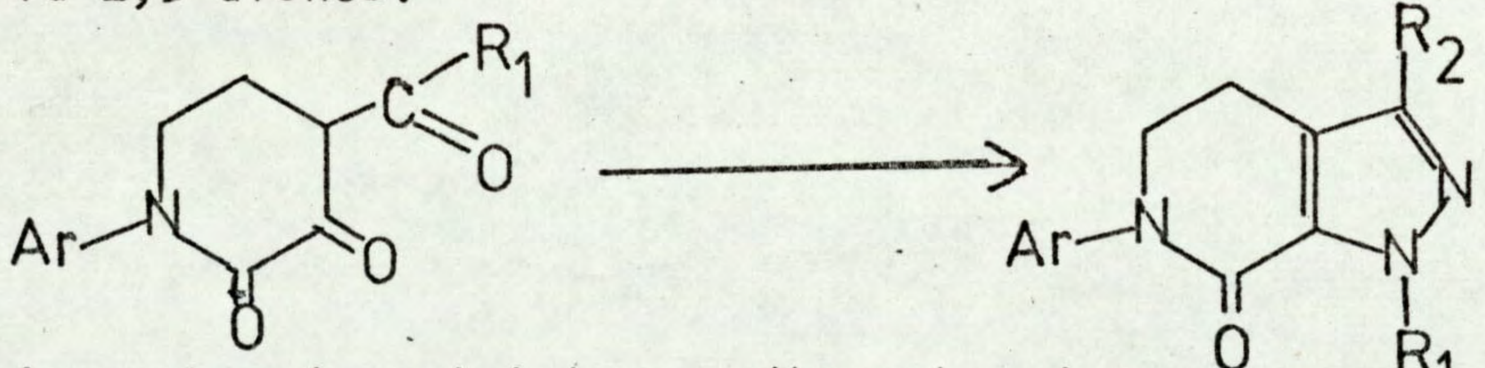


(140)



(141)

A number of 4,5,6,7-tetrahydropyrazolo [3,4-c]-1(H)-pyridin-7-ones, which exhibit anti-inflammatory properties, have been prepared from piperid-2,3-diones.[87,88]

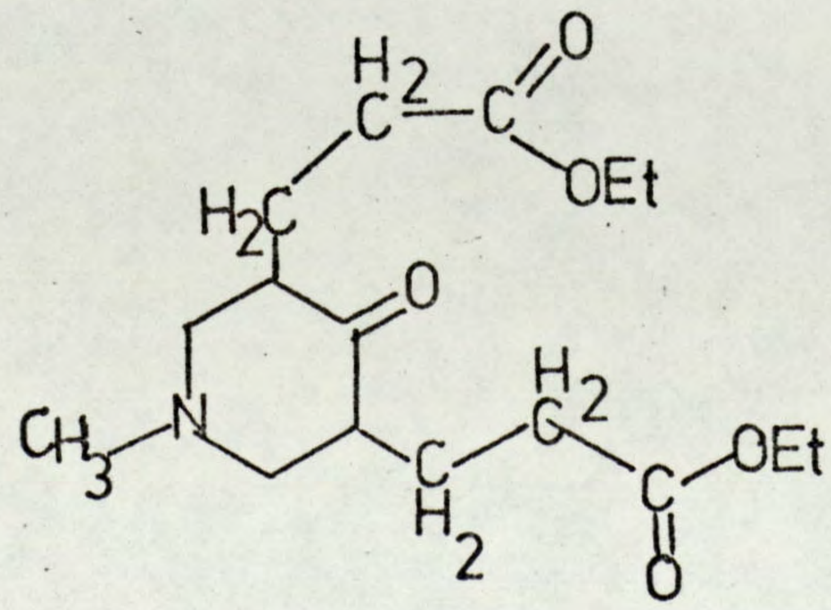


Ar = phenyl, p-tolyl, p-methoxyphenyl

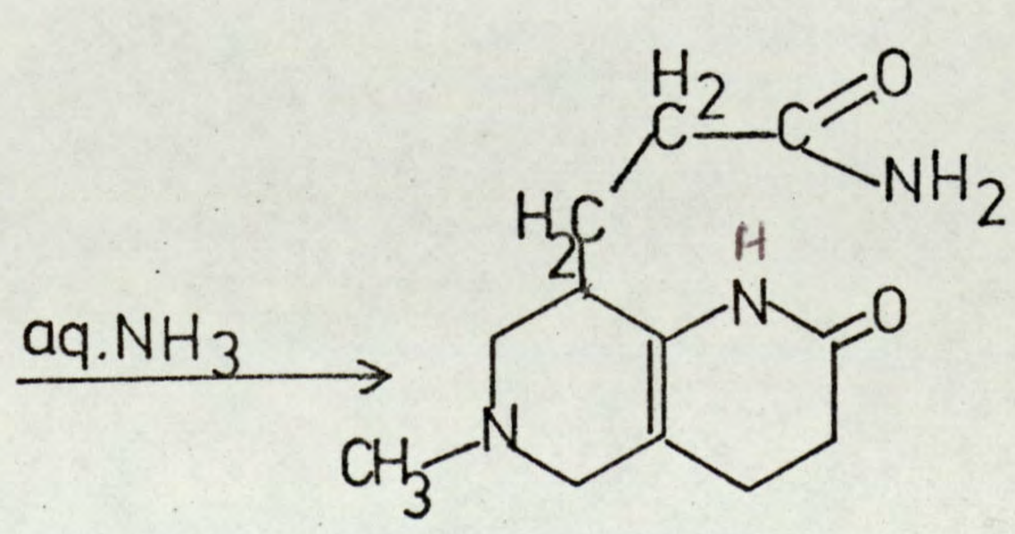
R_1 = H, p-tolyl, p-fluorophenyl, p-chlorophenyl

R_2 = CH_3, CH_2CH_3, $CH_2CH_2CH_3$, Ph, NH_2.

3,5-Bis-(2-ethoxycarbonylethyl)-1-methyl-4-piperidone (142) gives the octahydronaphthyridine (143) on treatment with ammonia solution.[89]

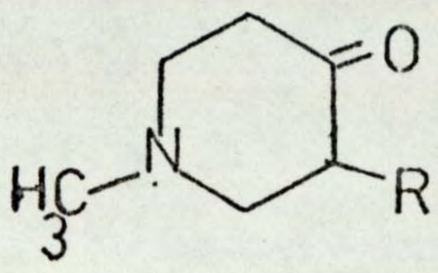


(142)



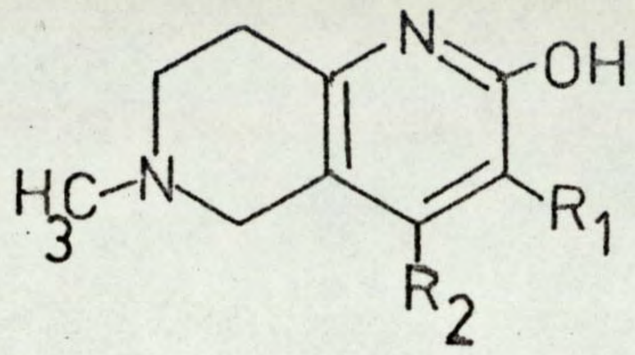
(143)

Cyanoacetamide may be caused to condense with 1-methylpiperid-3-al-4-one (144) to give the tetrahydronaphthyridine (146),[90] and 2-hydroxy-6-methyl-4-phenyl-5,6,7,8-tetrahydro-1,6-naphthyridine (147), an intermediate in the preparation of the pharmacologically active 2-acyloxy- (148) and 2-acyloxy-6-methyl-4-phenyl-5,6,7,8-tetrahydro-1,6-naphthyridines (149), was prepared from 1-methylpiperid-4-one (145) and 1-benzyl-1-cyanomethane.[91]



(144) R=CHO

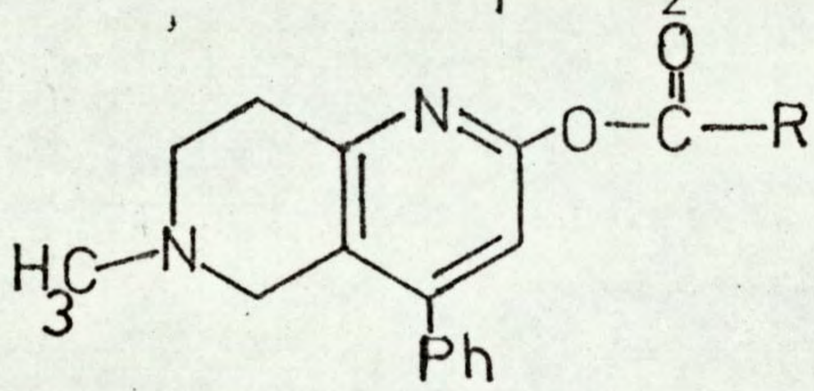
(145) R=H



(146) R_1=CN, R_2=H

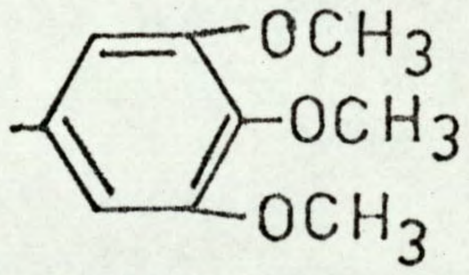
(147) R_1=H, R_2=Ph.

(147) $\xrightarrow{RCOCl}$

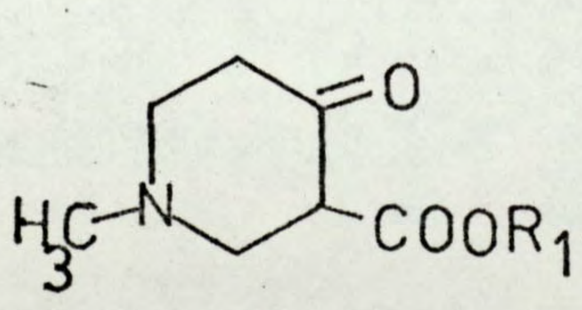


(148) R=H

(149) R=



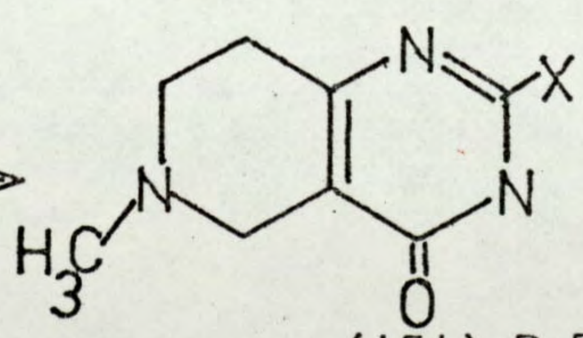
Cook and Reed[4] showed that 4-piperidone-3-carboxylates condense with amidines to give tetrahydropyrido [4,3-d]pyrimidines.



(150) R=CH_3

(130) R=CH_2CH_3

$X-C(=NH)-NH_2$



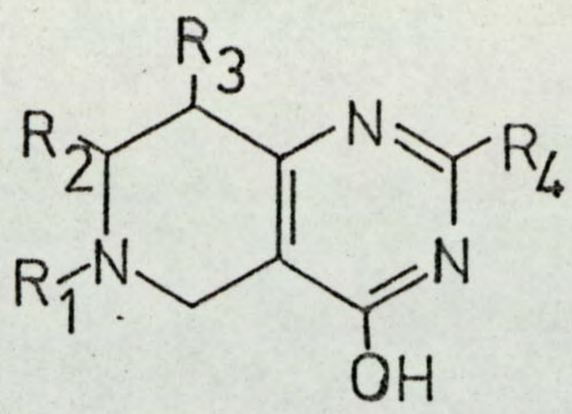
(151) R=Ph

(152) R=NH_2

(153) R=OH

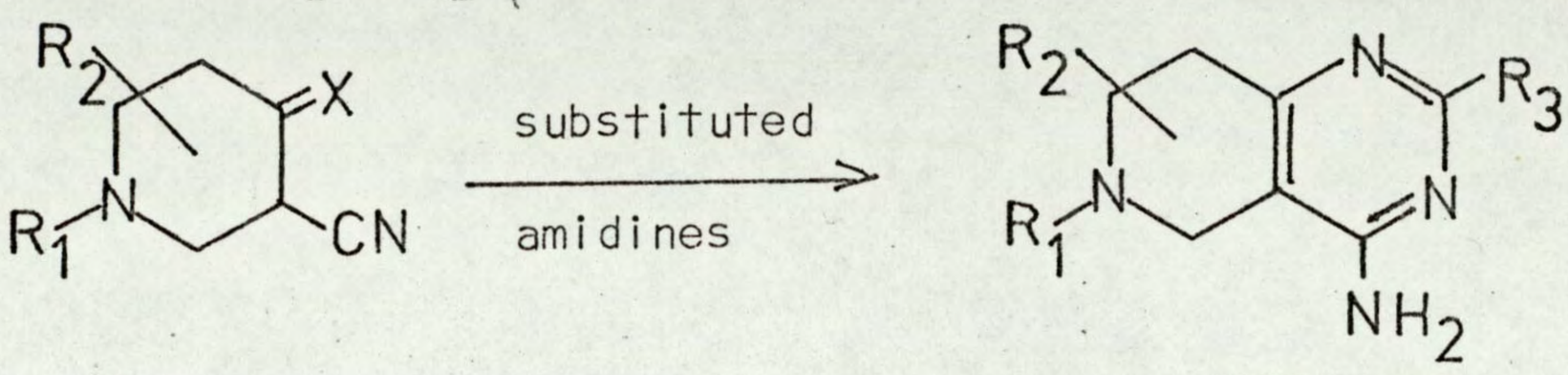
This type of condensation has been extended, and several hundred tetrahydropyrido [4,3-d] pyrimidines of general formula (154) have been

prepared.[5-10]



(154)

The same amidines were also made to condense with a series of 3-cyano-4-imino- and 3-cyano-4-oxo-piperidines to give 4-amino-5,6,7,8-tetrahydropyrido [4,3-d] pyrimidines (155).[92]

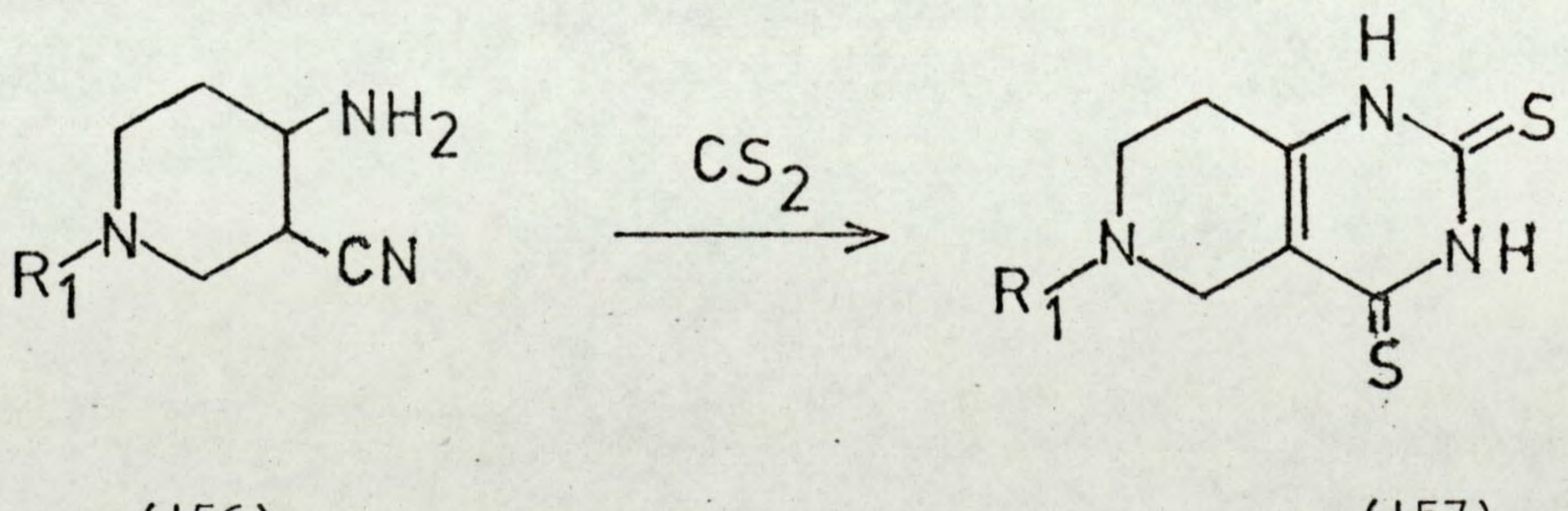


X=O, NH

(155)

The tetrahydropyrido [4,3-d] pyrimidines prepared by the above methods were claimed to possess antiphlogestic, antipyretic, diuretic, bacteriostatic, sedative, and coronary dilatory properties.

Tetrahydropyrido [4,3-d] pyrimidines have also been prepared by the reaction of piperidine o-aminonitriles with orthoformates and carbon disulphide.[80,93,94,95]

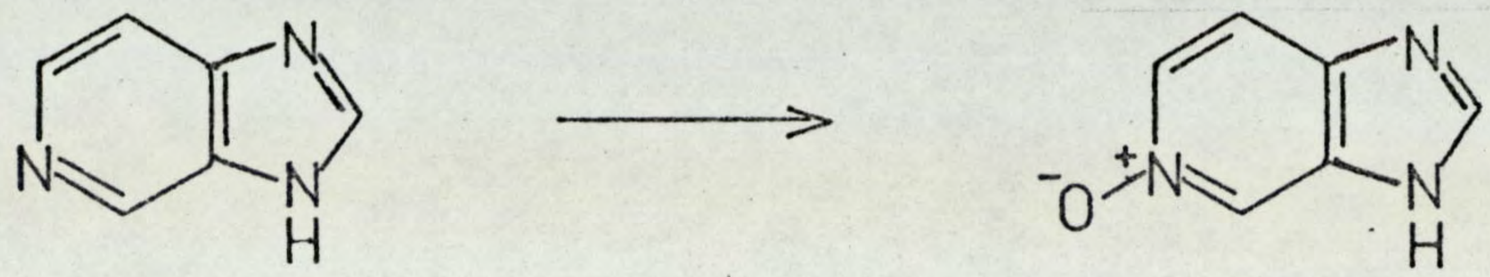


(156)

(157)

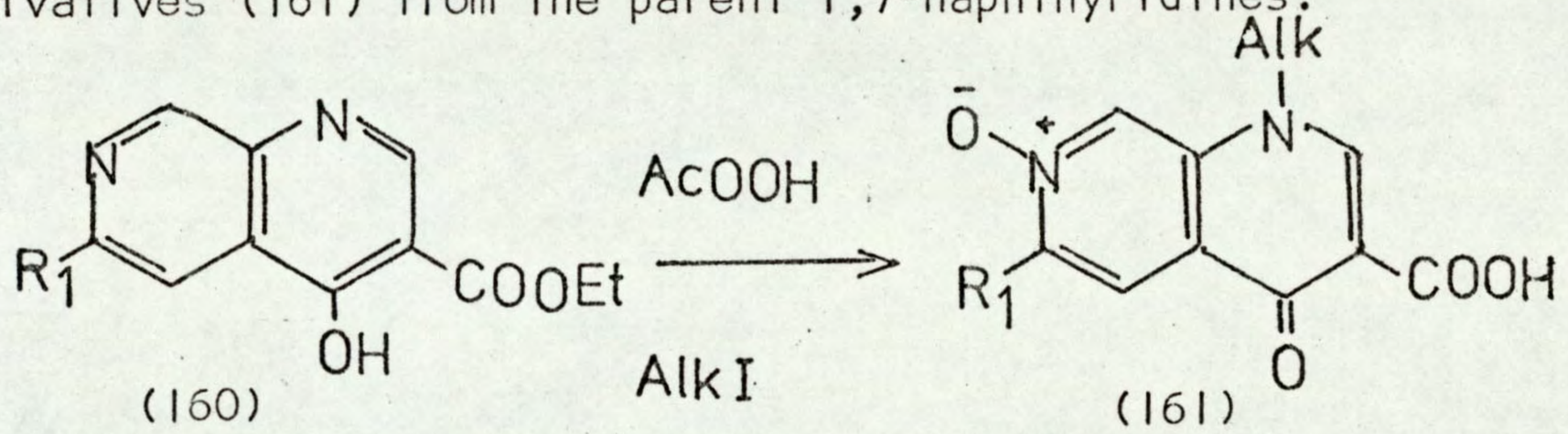
d) Other routes

The N-oxide derivatives of imidazo-[4,5-c]-pyridine (159)[96], 1,6-, 1,7-, and 2,7-naphthyridines[97,98] have been prepared, but both pyrido-[3,4-b] pyrazine and pyrido [4,3-b] pyrazine failed to give N-oxides.



(158) (159)

The antibacterial activity exhibited by the 1,7-naphthyridine-3-carboxy-7-oxide structure led to the synthesis of a number of 1-alkyl derivatives (161) from the parent 1,7-naphthyridines.[99,100]

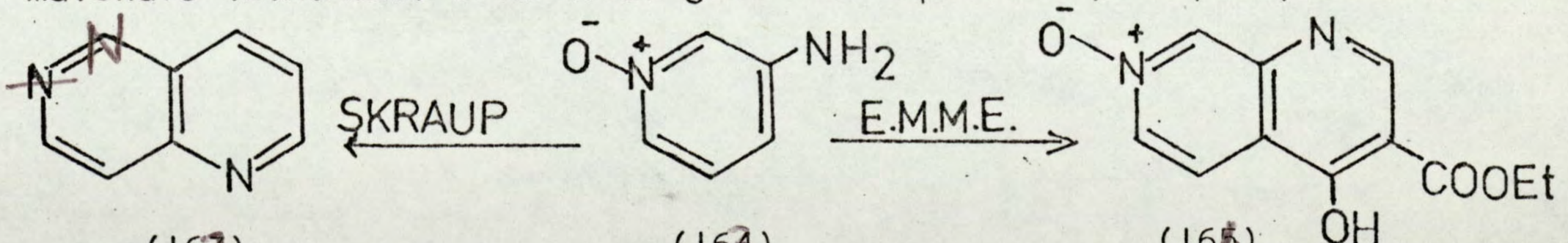


(160) (161)

(161) - Alk=CH_3, CH_2CH_3, CH_3CHCH_3, $CH_2CH_2CH_2CH_3$

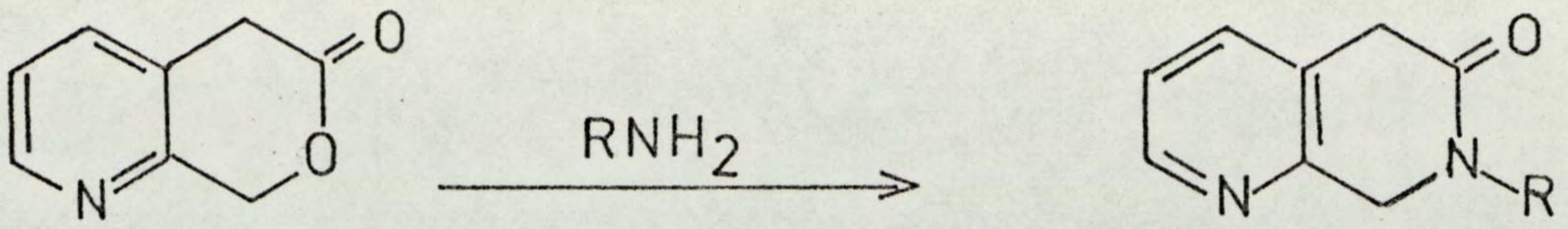
R_1 =H, CH_3.

The Skraup reaction on 3-aminopyridine 1-oxide (163) afforded 1,5-naphthyridine (162)[101], whereas condensation of diethylethoxymethylene-malonate (E.M.M.E.) with (163) gave the expected 1,7-naphthyridine (164)[102]



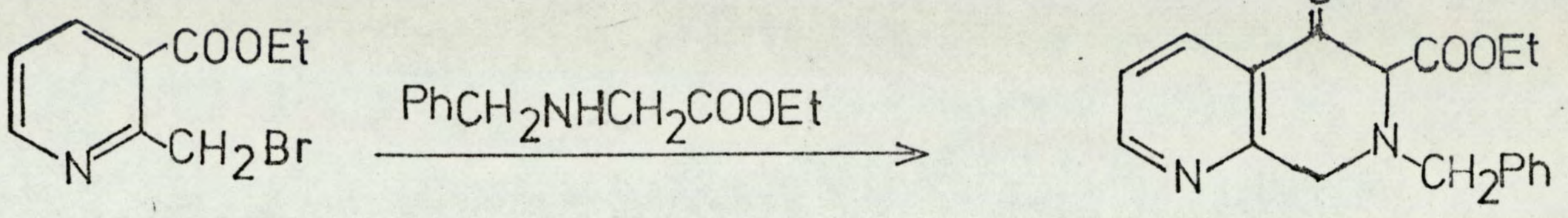
(163) (164) (165)

5,6,7,8-Tetrahydro-1,7-naphthyridines have been prepared from 2-hydroxymethylpyridyl-3-acetic acid lactone (165);[103] and from ethyl-2-bromomethylnicotinate (167).[104]



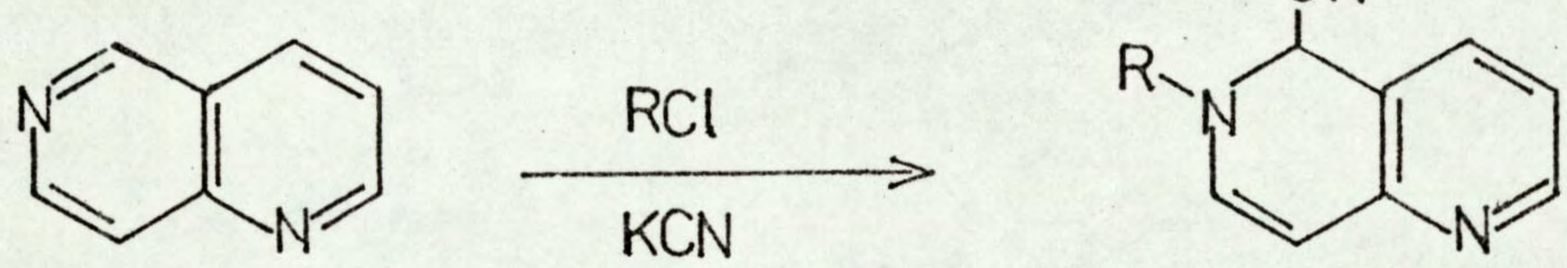
(165) (166)

(166)- R=$(CH_3)_2N(CH_2)_2$, Ph, $PhCH_2$, $Et_2N(CH_2)_2$, $(CH_3)_2CH)_2N(CH_2)_2$



(167) (168)

The potential antibacterials (169) and (170) were prepared from the parent 1,6-naphthyridine by the action of potassium cyanide and an acyl or alkyl halide[105]



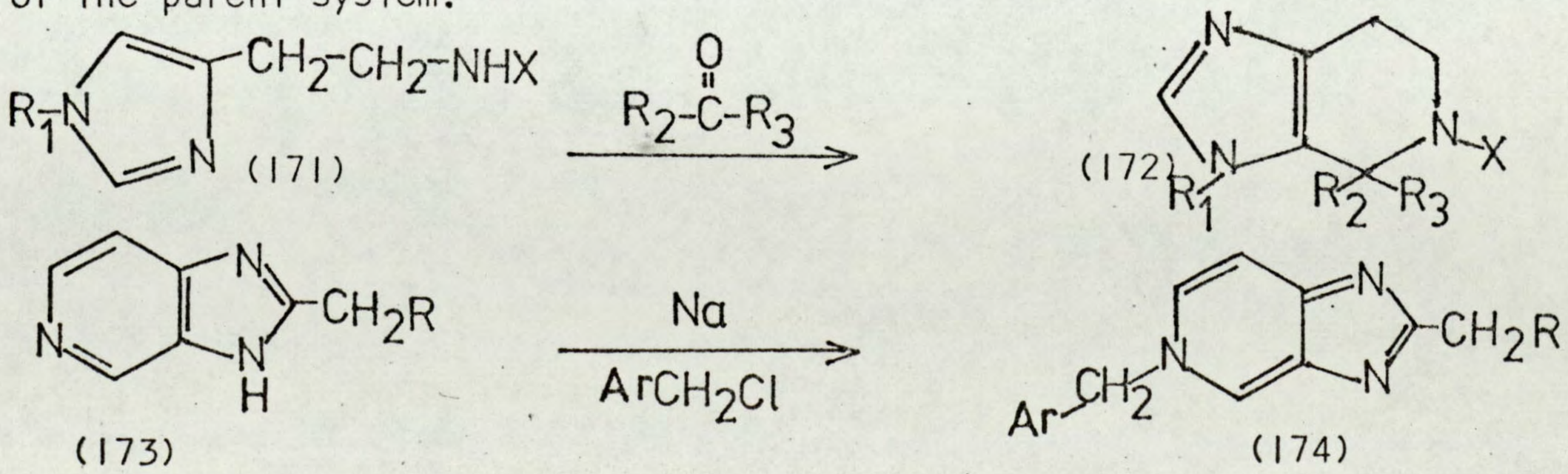
(~~162~~)

(169) R=acyl

(170) R=$PhCH_2$

tetrahydro

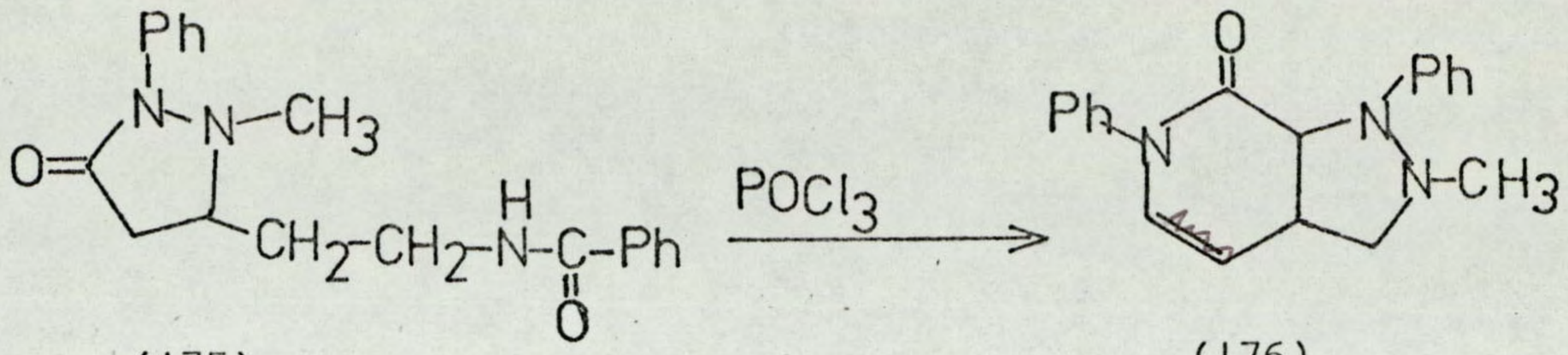
5-substituted imidazo-[4,5-c]-pyridines (172) were synthesised by the condensation of histamine derivatives (171) with ketones, and by alkylation of the parent system.[108]



(171) (172)

(173) (174)

The ring closure of (175) with phosphorus oxychloride gave the pyrazolopyridine (176), which on hydrogenation in the presence of



(175) (176)

aromatic esters, gave a series of compounds with antipyretic and analgesic properties.[109]

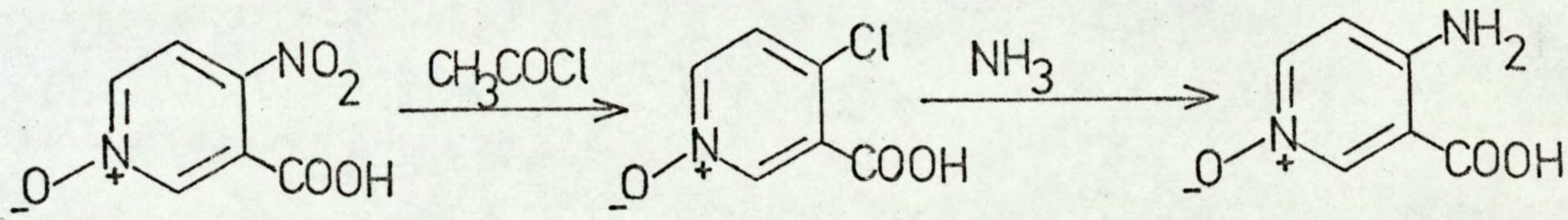
DISCUSSION

The synthesis of 1,3,4-trisubstituted pyridines, and known examples of their conversion into bicyclic heterocyclic systems have been reviewed in the Introduction. The aim of the work to be described in this section was to examine the routes to suitable 1,3,4-trisubstituted pyridine precursors, and to investigate their utility in the preparation of bicyclic systems.

The Synthesis of 1,3,4-Trisubstituted Pyridines.

i) 3,4-Disubstituted Pyridine 1-oxides.

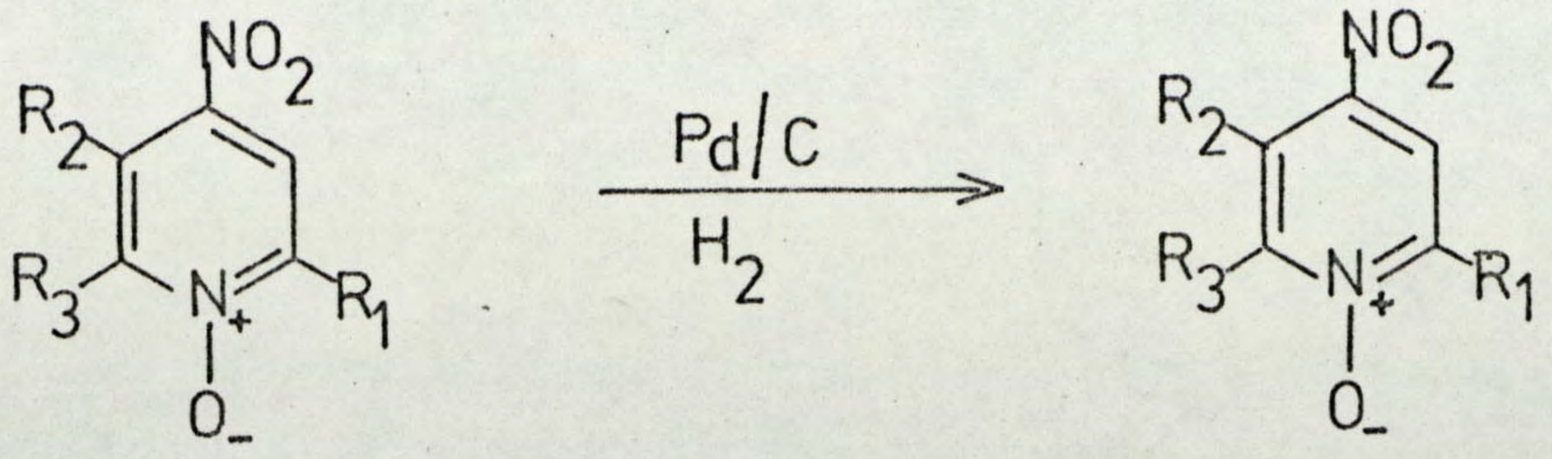
The method of Herz & Murty[49] was used in the preparation of 4-nitronicotinic acid 1-oxide (57) by the oxidation of 4-nitro-3-picoline 1-oxide (32) with chromic acid. 4-Aminonicotinic acid 1-oxide (52) has previously been prepared by a two stage reaction, with an overall yield of 30%.[110]



(57) (48) (52)

Because of the instability of 4-chloronicotinic acid 1-oxide (48) reported by Taylor, and the low overall yield, it was decided to investigate alternative routes to 4-aminonicotinic acid 1-oxide.

Experimental evidence concerning the catalytic hydrogenation of nitro N-oxides indicates that the nitro group is reduced at a rate comparable to that of the N-oxide function.[3] Although nickel catalysts favour initial reduction of the N-oxide, palladium catalysts favour reduction of the nitro group with the N-oxide function being reduced only on prolonged reaction.[111, 112] Catalytic reduction of 4-nitropyridine 1-oxides to the corresponding 4-amino compounds, with retention of the N-oxide group, has been reported for unsubstituted and alkyl substituted 4-nitropyridine 1-oxides.[113-115]



(177) $R_1=R_2=R_3=H$

(178) R_1=alkyl, $R_2=R_3=H$

(179) $R_1=R_2$=alkyl, $R_3=H$

(180) $R_1=R_3$=alkyl, $R_2=H$

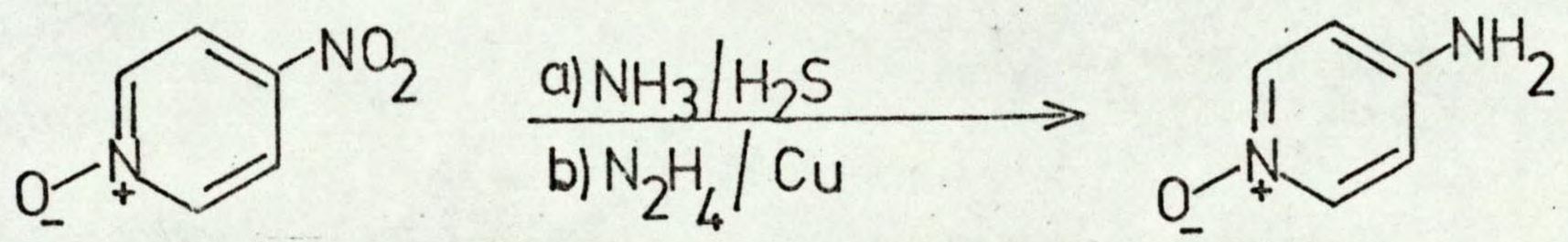
(181) $R_1=R_2=R_3=H$

(182) R_1=alkyl, $R_2=R_3=H$

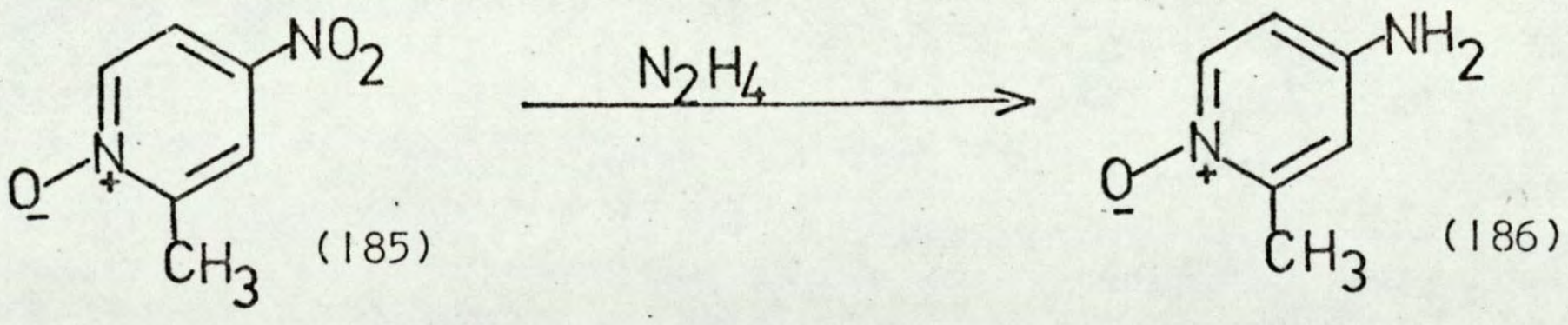
(183) $R_1=R_2$=alkyl, $R_3=H$

(184) $R_1=R_3$=alkyl, $R_2=H$

Chemical reduction of 4-nitropyridine 1-oxides to the corresponding amino 1-oxides has been successful for 4-nitropyridine 1-oxide (177) and for 2-methyl-4-nitropyridine 1-oxide (185);[116,117] although a small amount of 4-aminonicotinic acid 1-oxide (52) was isolated as a by-product from

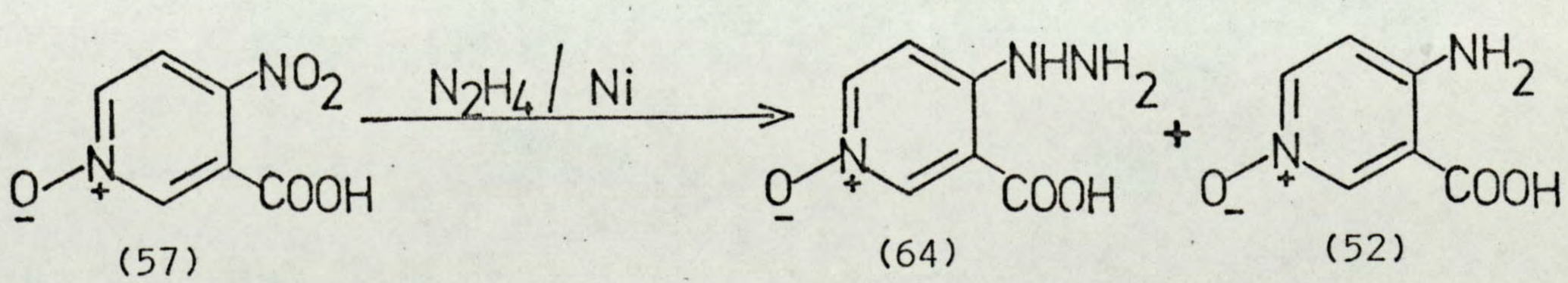


(177) (181)



(185) (186)

the attempted reduction of 4-nitronicotinic acid 1-oxide (57) using hydrazine hydrate and a Raney nickel catalyst, the major product being 4-hydrazino-

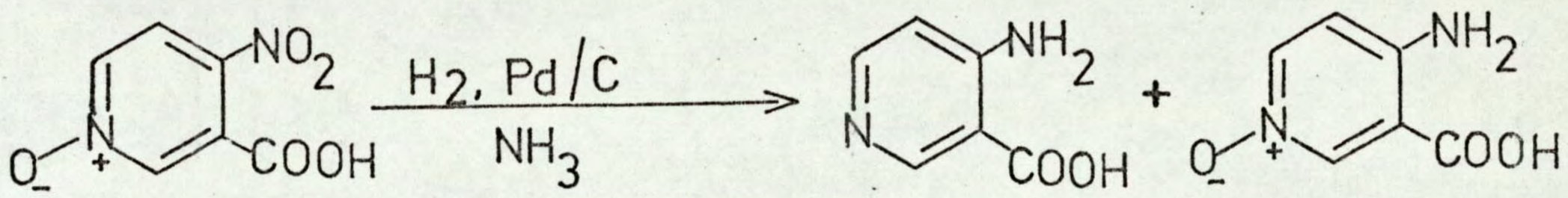


(57) (64) (52)

nicotinic acid 1-oxide.[118]

An attempt at a direct nucleophilic displacement of the nitro group in (57) by ammonia was reported to be unsuccessful.[119]

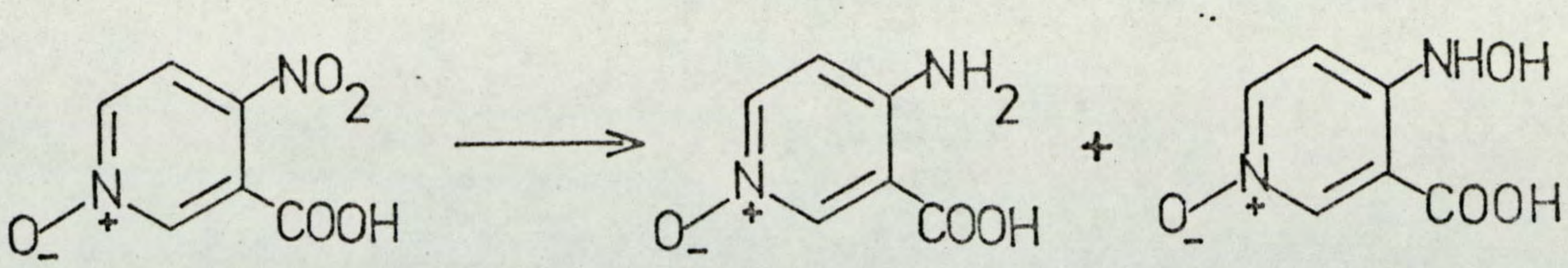
The catalytic reduction of the nitro group of 4-nitronicotinic acid 1-oxide (57) over a palladium catalyst appeared to be a feasible route to 4-aminonicotinic acid 1-oxide (52). The reduction of a solution of the nitro-acid, (57) in dilute ammonia solution (pH 10), under a pressure of 345 k.N.m.$^{-2}$ of hydrogen for 2 hours gave, as the only product, a compound with melting point and infrared spectrum identical to those of 4-aminonicotinic acid (187).[49] Less forcing conditions, using a lower pressure of hydrogen (300 k.N.m.$^{-2}$), a smaller quantity of catalyst, and a shorter reaction time (0.5 h) gave both the amino-acid (187) in 40% yield, and the required 4-aminonicotinic acid 1-oxide (52) in 33% yield.



(57) (187) (82)

The melting point of the N-oxide (52) was identical to that quoted by Taylor,[110] and the infrared spectrum showed the expected absorptions at 3310 and 3400cm^{-1} due to the asymmetrical and symmetrical N-H stretching vibrations, and at 1660cm^{-1} due to the carbonyl stretching vibration. The strong absorption at 1280cm^{-1} was assigned to the N^{+}-O^{-} stretching vibration,[118] and the mass spectrum showed the expected initial loss of oxygen to give the base peak at m/e 138.

The isolation of mixtures (of (187) and (52)) suggested that reduction at a lower hydrogen pressure, where the uptake of hydrogen could be monitored more accurately would be more suitable. The reduction of a basic solution of the nitro-acid N-oxide (57) under atmospheric conditions, with the reaction stopped after the uptake of 2 moles of hydrogen, gave 4-aminonicotinic acid 1-oxide (52) in 53% yield, and 4-hydroxyaminonicotinic acid 1-oxide (188).

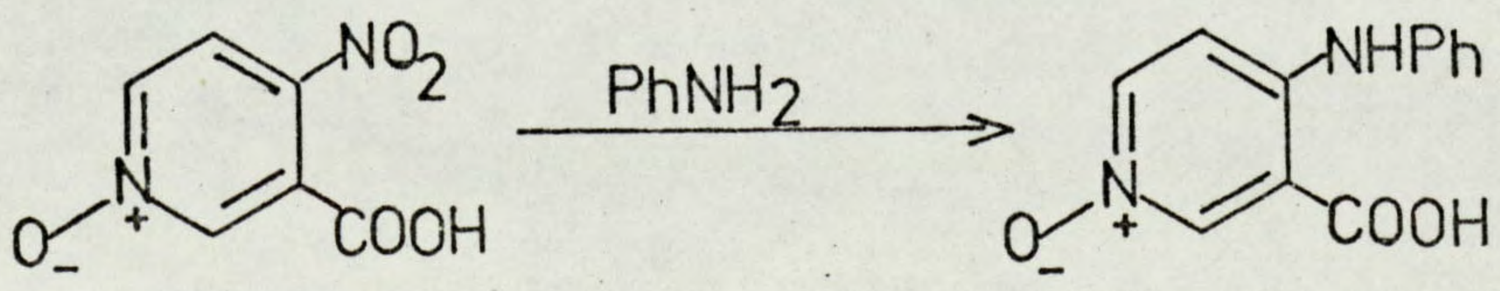


(57) (52) (188)

Chemical reductions of aromatic nitro groups to amines by means of hydrazine and palladium charcoal,[120] sodium borohydride and palladium charcoal,[121] and cyclohexene and palladium charcoal[122] have been reported. The application of these methods to the reduction of the nitro-acid (57) gave as the product a solid whose infrared and mass spectra bore similarities to the respective spectra of the amino-acid (52), but from which the required product could not be isolated.

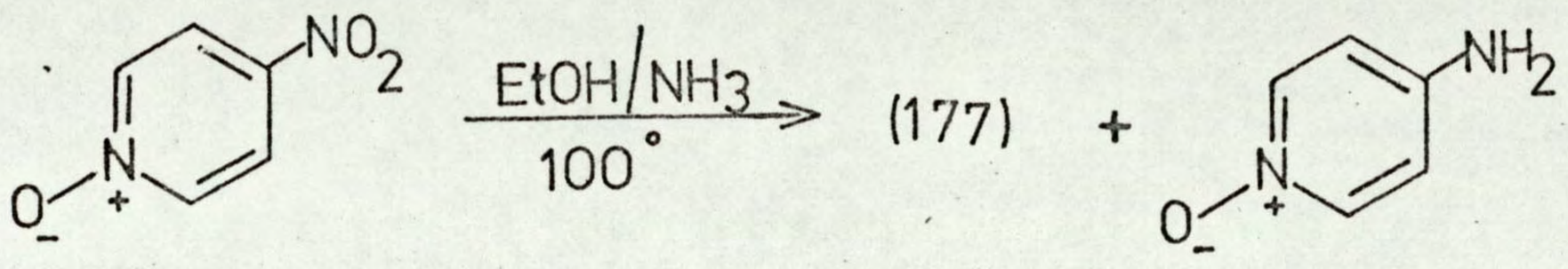
The unsatisfactory overall yield of 4-aminonicotinic acid 1-oxide (52) by the above methods, and the known susceptibility of the nitro group in the 4-position of pyridine 1-oxides to nucleophilic displacement, prompted a re-investigation into the reported failure of the direct nucleophilic substitution of the nitro-acid (57) by ammonia.[119] An attempted direct amination of 4-nitropyridine 1-oxide (177) using ethanolic ammonia by Ochiai and co-workers, resulted in 75% recovery of the starting material, and the formation of 4,4'-azopyridine 1-,1'-dioxide (189) together with a trace amount of 4-aminopyridine 1-oxide (181)[123]

Herz and Murty[49] obtained 4-anilinonicotinic acid 1-oxide (65) on heating 4-nitronicotinic acid 1-oxide (57) with aniline in an attempted



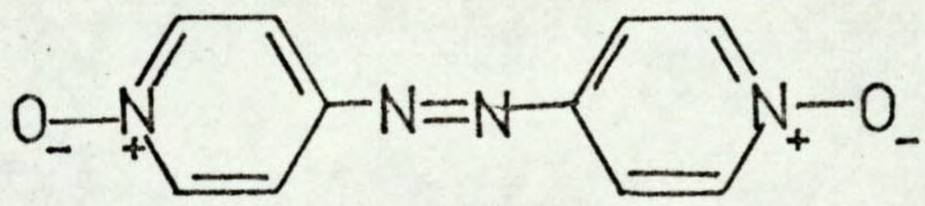
(57) (65)

deoxygenation reaction.[124] These authors also reported the failure of both 4-nitropyridine 1-oxide (177) and 4-nitronicotinic acid to give a nucleophilic displacement reaction, with the comparatively weak nucleophile aniline, under similar conditions, indicating that the displacement of the nitro group in (57) is due to the combined effect of both the N-oxide and the carboxylic acid group.



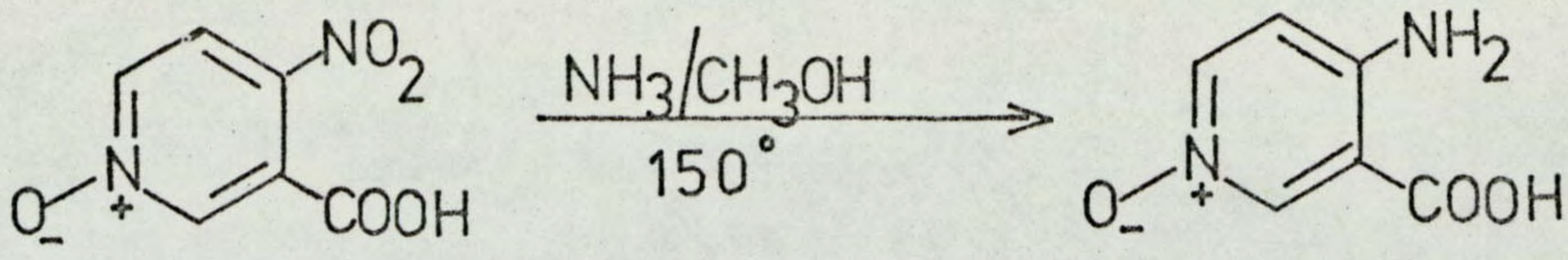
(177) (181)

+



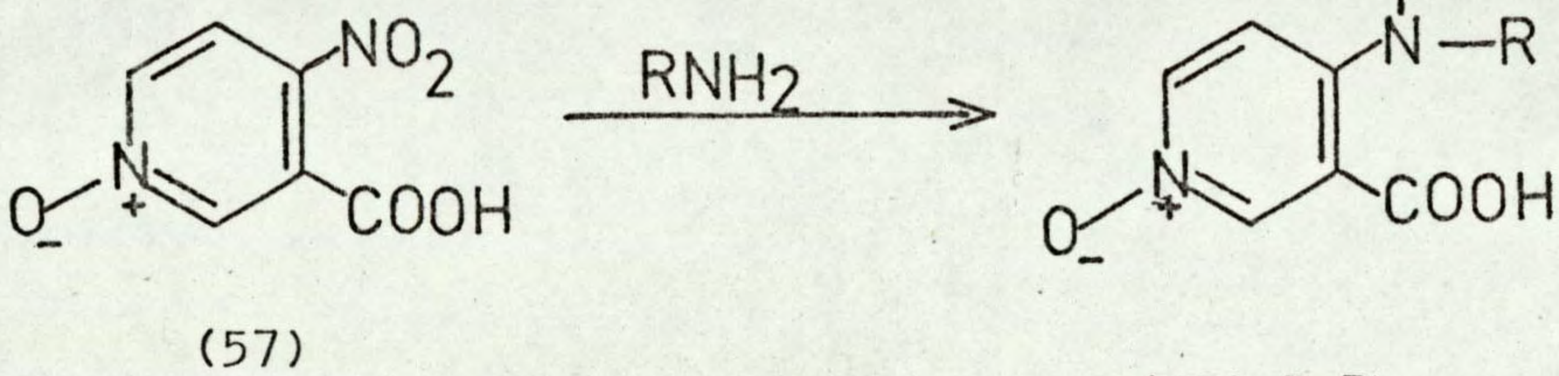
(189)

The evidence from the above two groups of workers[49,123] appeared to indicate that the direct substitution of the nitro acid (57) by ammonia should be feasible. Accordingly, a solution of the 4-nitro acid (57) in methanol was saturated with ammonia, and was heated under pressure at 150° in a steel bomb for 4 hours. Evaporation of the methanol then gave the required amino-acid 1-oxide (52) in 80% yield.



(57) (52)

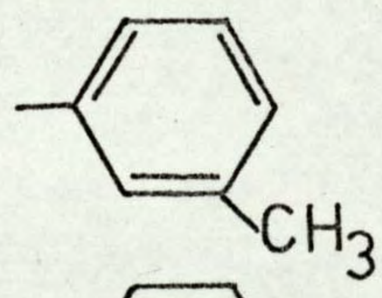
The nucleophilic displacement of the nitro-group in (57) by amines has now been extended to the preparation of other 4-N-substituted amino-pyridine 1-oxides. 4-Nitronicotinic acid 1-oxide (57) when heated at 100° with an excess of the appropriate amine, gave the required 4-amino-nicotinic acid 1-oxides.

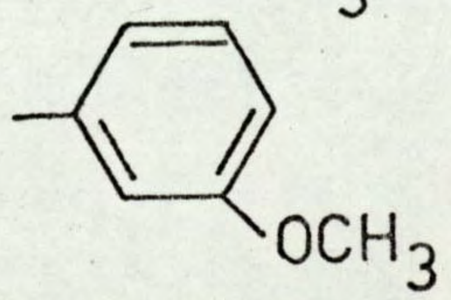


(57)

(65) R=Ph

(190) R=$PhCH_2$

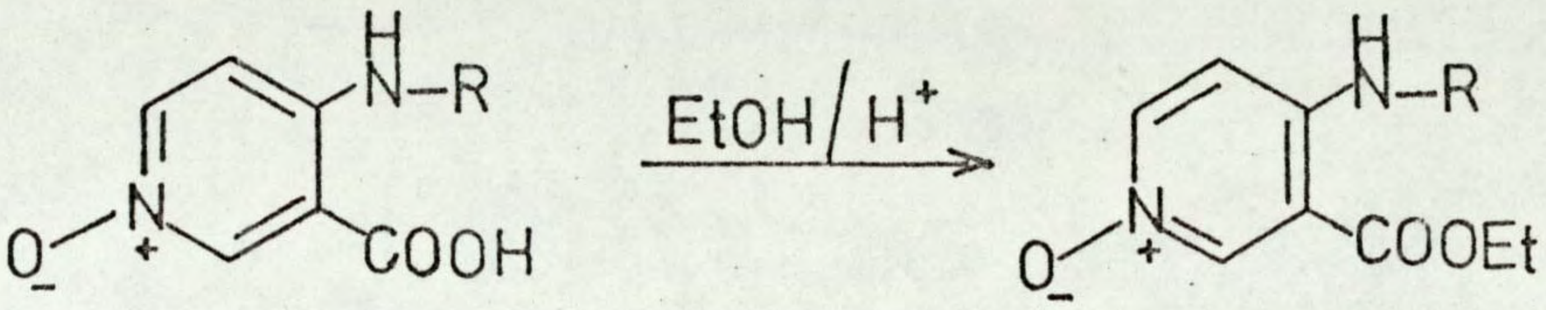
(191) R= 

(192) R= 

The amino-acid N-oxides were practically insoluble in most organic solvents and were recrystallised from aqueous dimethylformamide. The infra-red spectra all showed a peak at 3150cm^{-1} due to the bonded N-H stretching vibration, and a broad peak centred around 1680cm^{-1} due to the carbonyl stretching vibration. The n.m.r. spectra of the amino acid N-oxides (65) and (190) in trifluoroacetic acid both showed a characteristic splitting pattern due to the 2-, 5-, and 6- protons. The 2- proton appears as a doublet at τ0.91 ($\underline{J}$ 2.0Hz), the 6- proton as a quartet at τ1.73 ($\underline{J}_{5,6}$ 7.0Hz,

$\underline{J}_{2,6}$ 2.0Hz), and the 5-H appears as a doublet at τ2.82 ($\underline{J}_{5,6}$ 7.0Hz). The methylene protons in 4-benzylaminonicotinic acid 1-oxide (190) appear as a broad doublet at τ5.14 (-NH$\underline{CH_2}$Ph, $\underline{J}$ 5.0Hz).

Ethyl 4-anilinonicotinate 1-oxide (194) and ethyl 4-benzylamino-nicotinate 1-oxide (195) were prepared by heating the appropriate amino-acid N-oxide with ethanol and a catalytic amount of sulphuric acid under reflux for 3 days. The preparation of ethyl 4-aminonicotinate 1-oxide (193) under the same conditions required 10 days.



(52) R=H

(65) R=Ph

(190) R=$PhCH_2$

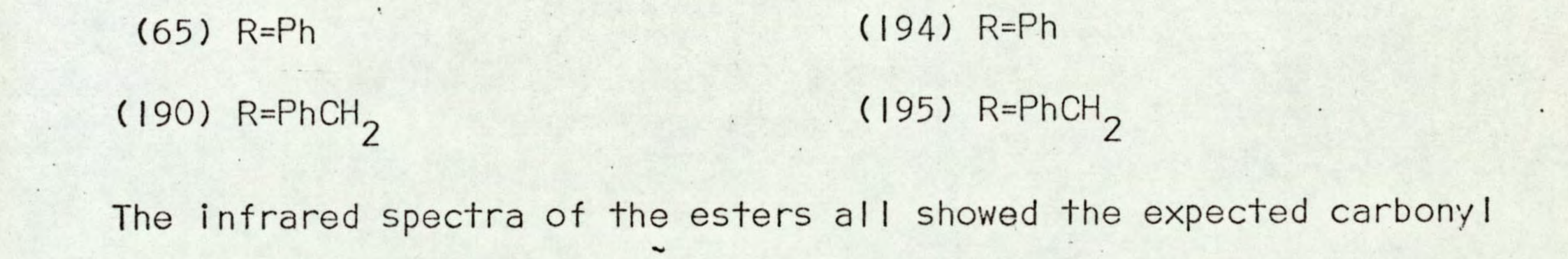
(193) R=H

(194) R=Ph

(195) R=$PhCH_2$

The infrared spectra of the esters all showed the expected carbonyl stretching vibration at 1720cm^{-1}.

The 4-amido acid 1-oxides (196 - 201) were isolated from the reaction of 4-aminonicotinic acid 1-oxide (52) with 2 moles of the appropriate acid chloride, during the preparation of pyrido[4,3-$\underline{d}$] [1,3]oxazin-4-one 6-oxides (202). This reaction will be discussed in more detail on p.58.



(52)

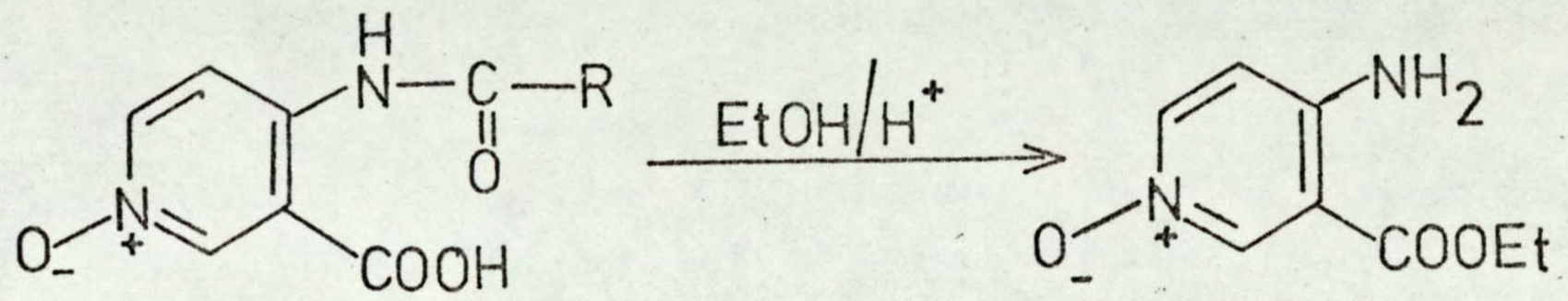
(196) R=Ph
(197) R=p-methoxyphenyl
(198) R=p-tolyl
(199) R=p-fluorophenyl
(200) R=3,4-dichlorophenyl
(201) R=p-nitrophenyl

(202) R=aryl

4-Anilinonicotinic acid 1-oxide (65) and 4-benzylaminonicotinic acid 1-oxide (190) both failed to react with acetic anhydride, acetyl chloride, and benzoyl chloride under similar conditions to those above, and under more forcing conditions.

Pyridine o-amido-esters have been shown to be useful intermediates in the synthesis of pyrido [4,3-d] pyrimidines.[125]

The attempted esterification, using ethanol and an acid catalyst, of 4-acetamidonicotinic acid 1-oxide (203) and 4-benzamidonicotinic acid 1-oxide (196) gave ethyl 4-aminonicotinate 1-oxide (204) in both cases.

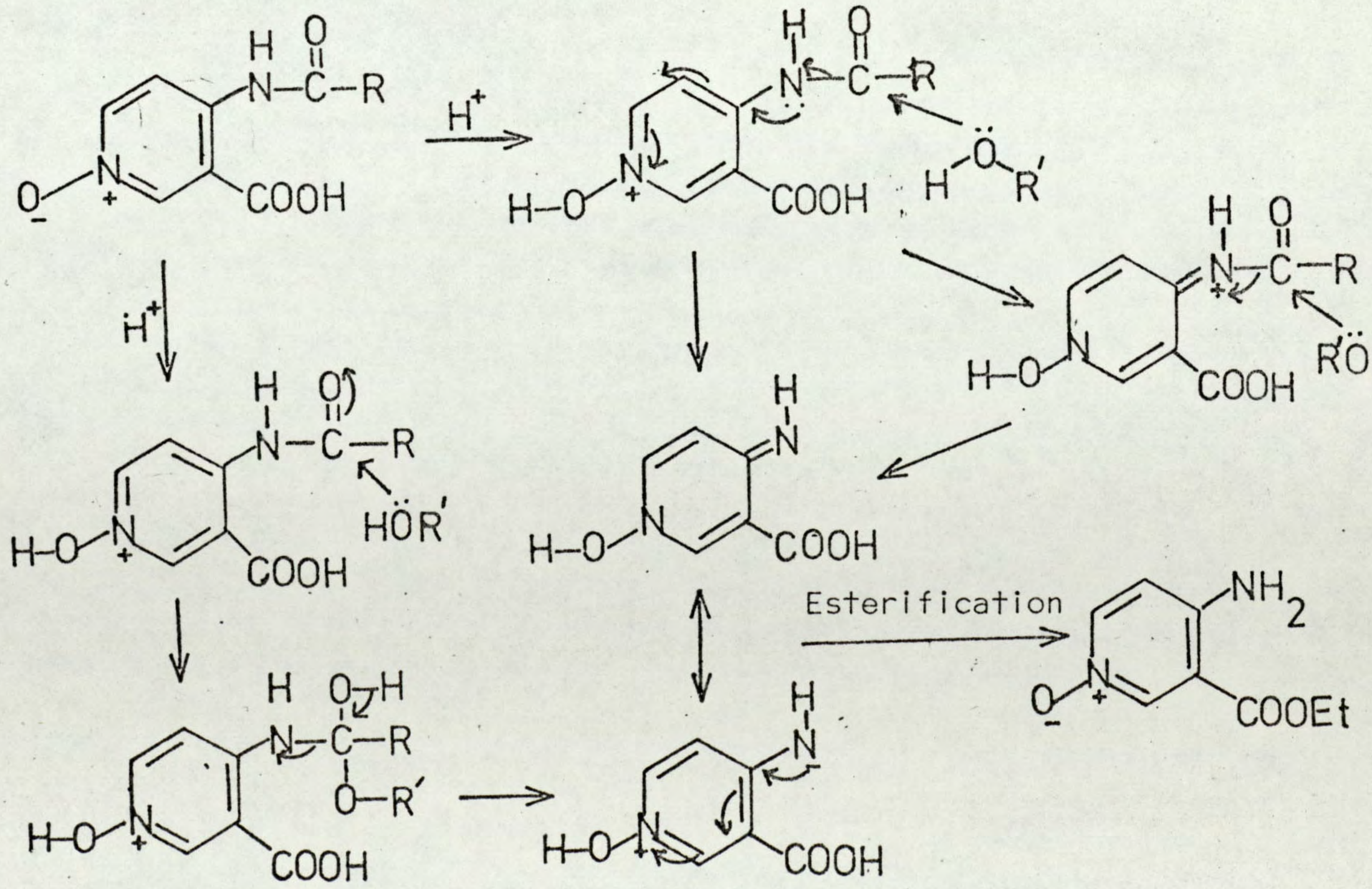


(203) R=CH_3

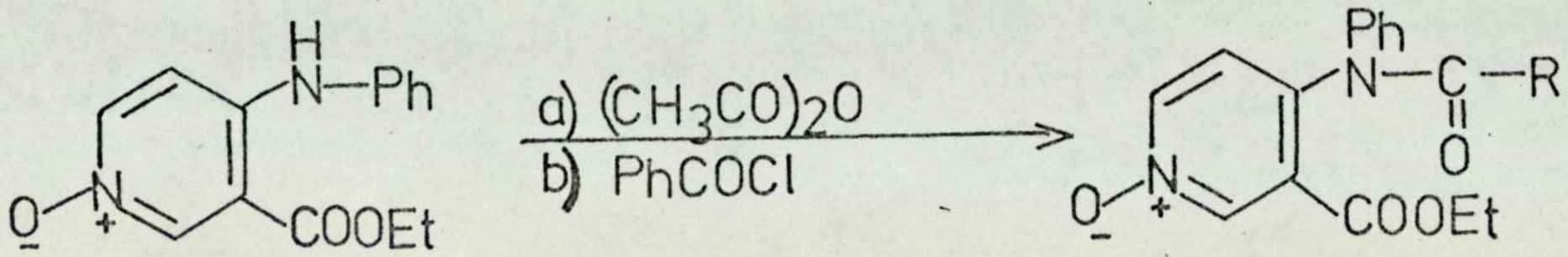
(196) R=Ph

(204)

The following mechanisms appear feasible:-



Ethyl 4-(N-phenylacetamido)nicotinate 1-oxide (205) was prepared by heating the anilino-ester with acetic anhydride at 100° for 36 hours, followed by chromatographic separation of the amido ester. The benzamido ester (206) was prepared by stirring the anilino-ester with benzoyl chloride



(194)

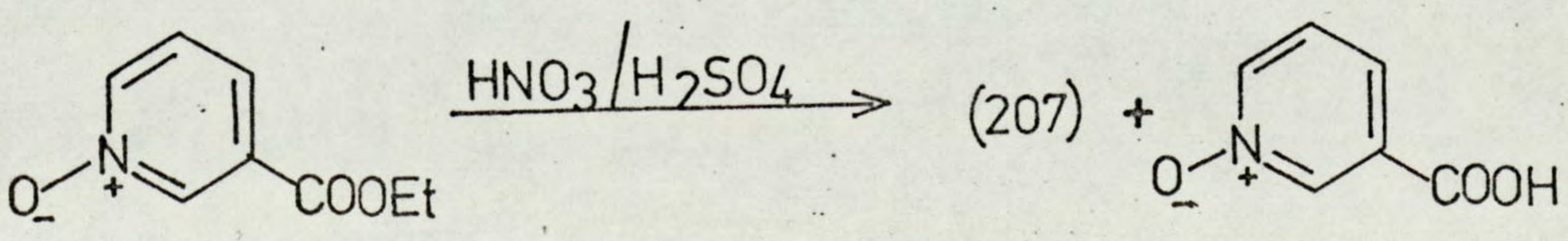
(205) R=CH_3
(206) R=Ph

for 8 hours at 25°. The infrared spectra of the amido-esters showed a carbonyl stretching vibration at 1720cm^{-1} due to the ester carbonyl, and a second carbonyl peak at 1660cm^{-1} due to the amide carbonyl.

Two routes were employed in the attempted preparation of the ethyl and methyl esters of 4-nitronicotinic acid 1-oxide (57), which were considered to be useful precursors for bicyclic systems.

Previous attempted nitrations of pyridine 1-oxides containing electron withdrawing substituents have proved unsuccessful; 3-cyano,-3-carboxy-,[32] and 2-carboxy-5-methoxycarbonyl-pyridine 1-oxides[126] have all proved resistant to nitration.

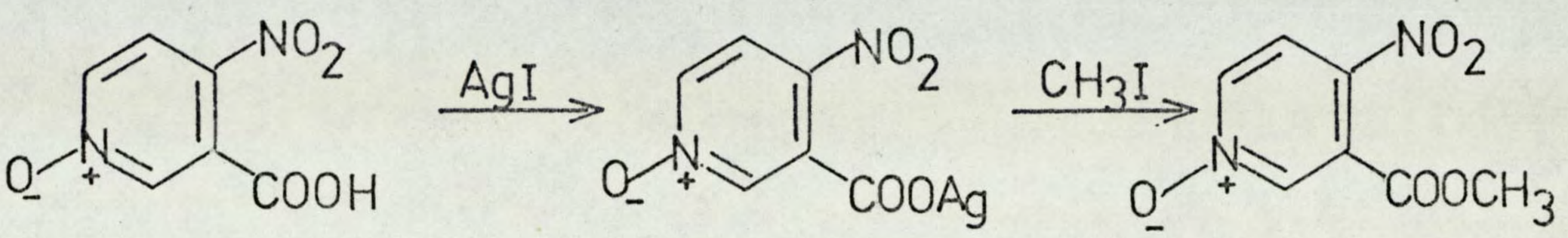
Ethyl nicotinate 1-oxide (207) has now also been shown to be resistant to nitration; the ester (207) was treated with concentrated nitric and sulphuric acids under forcing conditions, but the required nitro-ester was not isolated, the product being a mixture of the starting material and nicotinic acid 1-oxide (208).



(207)

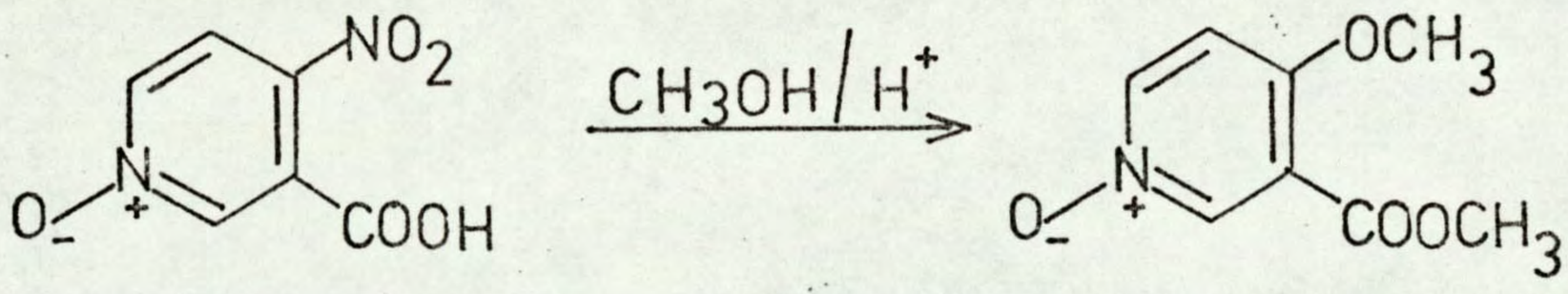
(208)

The preparation of the required nitro-esters by a normal esterification procedure using alcohol and an acid catalyst has not been reported, but Herz & Murty[49] prepared methyl 4-nitronicotinate 1-oxide (210) from the nitro-acid (57) via the intermediate silver salt (209) in an overall yield of 20%.



(57) (209) (210)

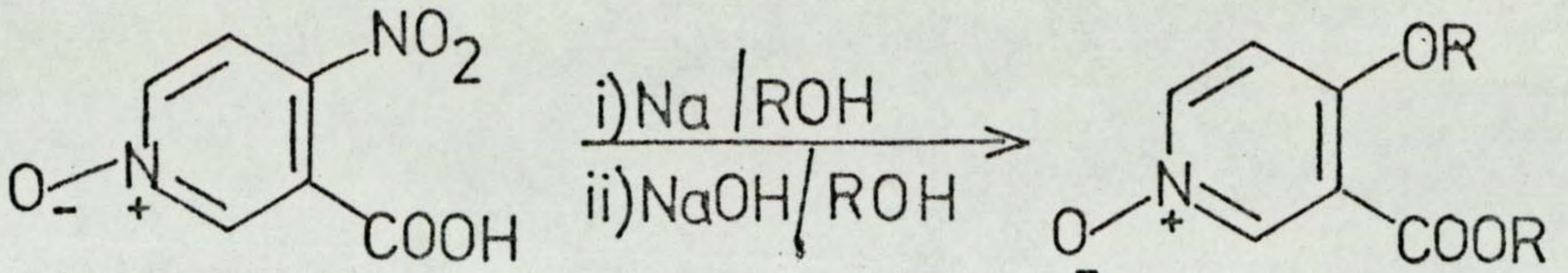
Esterification of the nitro-acid (57) using an alcohol and an acid catalyst has now been shown to be unsuccessful. The nitro-acid (57) was heated with methanol and an acid catalyst at 60° for 6 hours. Esterification of the carboxyl group occurred, but was accompanied by nucleophilic displacement of the nitro group to give methyl 4-methoxynicotinate 1-oxide (211).



(57) (211)

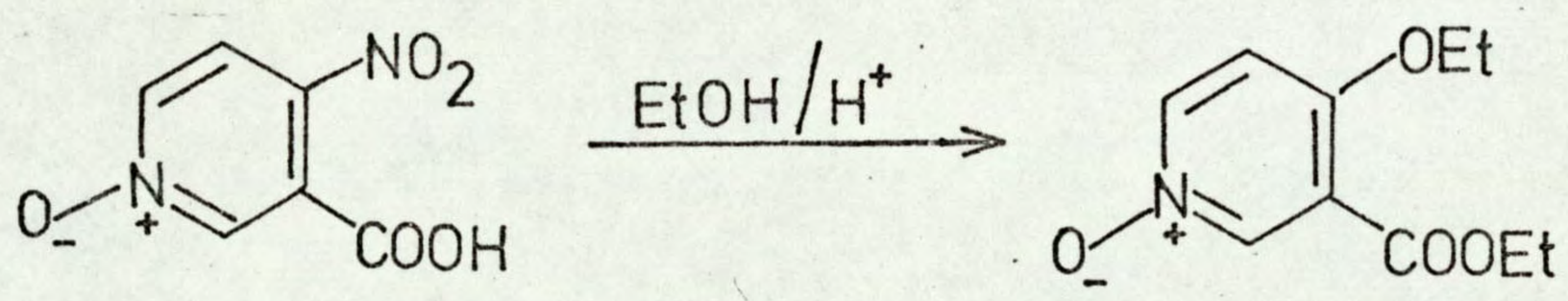
The n.m.r. spectrum of the methoxy-ester (211) in deuterochloroform showed the methyl group as singlets at τ6.01(-O<u>CH</u>$_3$) and τ6.1(-COO<u>CH</u>$_3$). The infra-red spectrum showed the expected absorption at 1720cm^{-1} due to the carbonyl stretching vibration; the peaks at 1530cm^{-1} and 1350cm^{-1} in the starting material were not present in the product, indicating that the nitro group had been replaced.

Previous nucleophilic displacements of the nitro-group in the nitro-acid (57) by alkoxide groups have been performed in basic media, using either sodium and the appropriate alcohol, or a solution of sodium hydroxide in an alcohol;[3] Taylor and Crovetti[110] prepared methyl 4-nitronicotinate 1-



(57) (212)

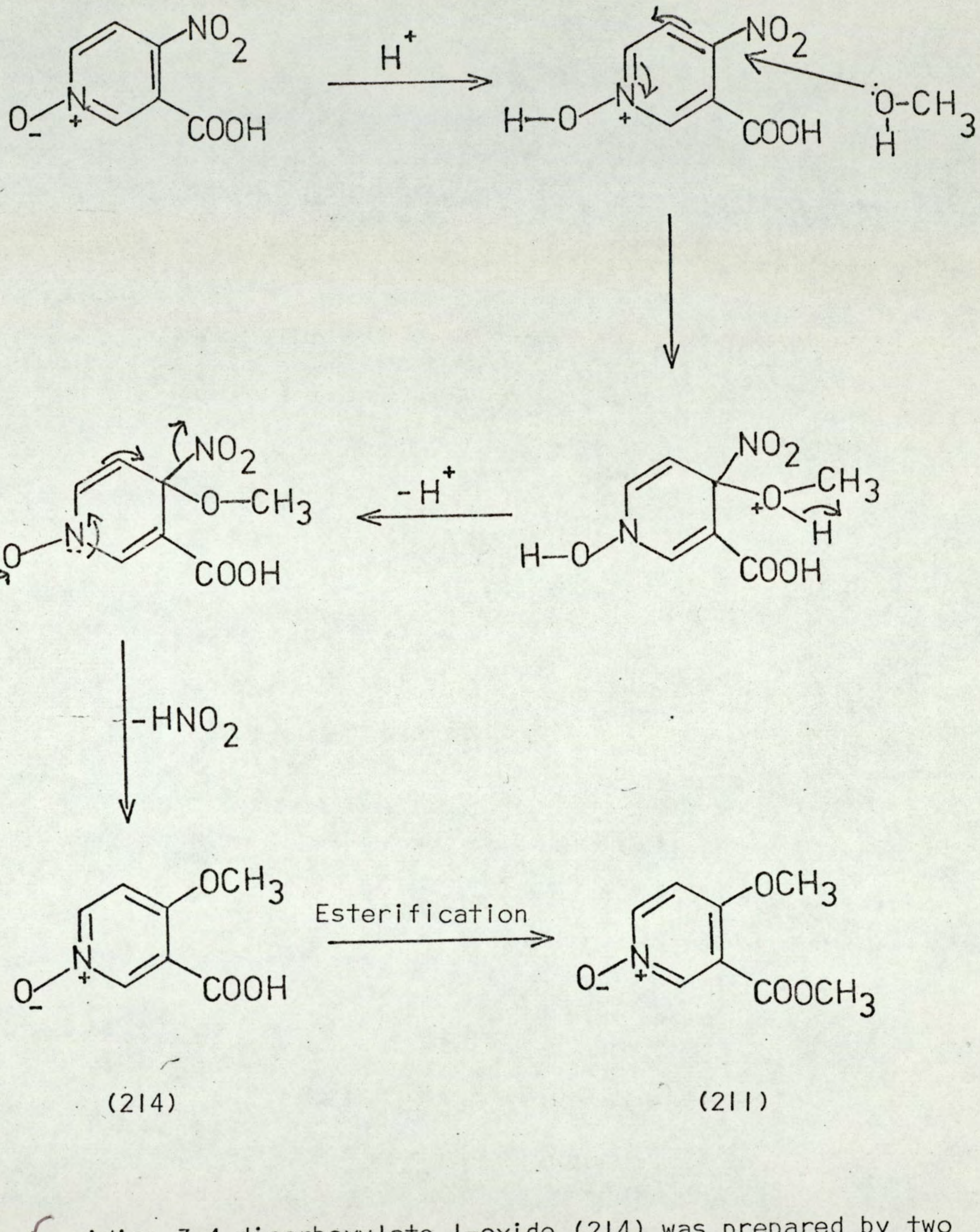
oxide (211) by a nucleophilic displacement reaction on the nitro-acid (57) using sodium methoxide, but were unable to re-crystallise the material, and classified the compound via the picrate. The material obtained from the attempted esterification was recrystallised from an ethanol/ether mixture and a correct analysis obtained. The replacement of methanol by ethanol gave the corresponding ethyl 4-ethoxycarbonyl nicotinate 1-oxide.



(57) (213)

A plausible mechanism for the nucleophilic displacement of the nitro-group in (57) by methanol under acidic conditions is shown on page 33.

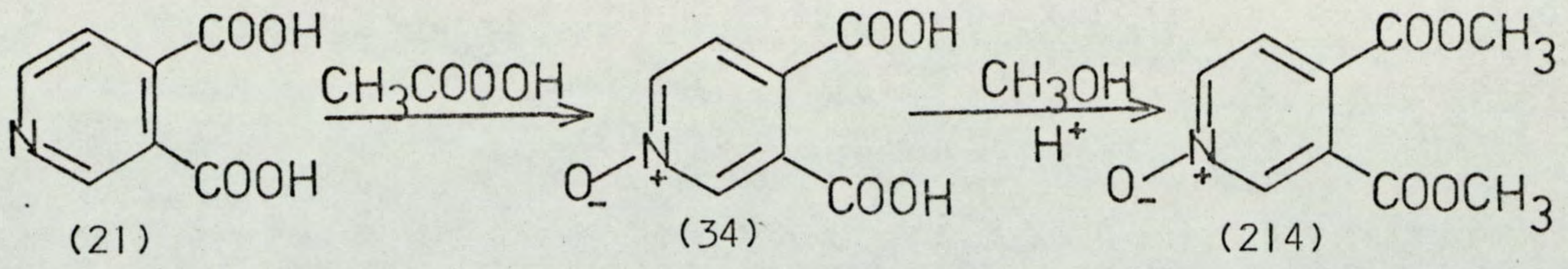
The first step is protonation of the N-oxide oxygen atom. The next stage is the nucleophilic attack of the methanol at the 4-position, deprotonation, followed by loss of nitrous acid to give the 4-methoxy acid (214). A normal esterification reaction then gives the methoxy-ester (210). The role of the protonation step was demonstrated by heating a solution of the nitro-acid in methanol under reflux for 24 hours. Methyl 4-methoxy nicotinate 1-oxide was not isolated from the resinous product.



(214) (211)

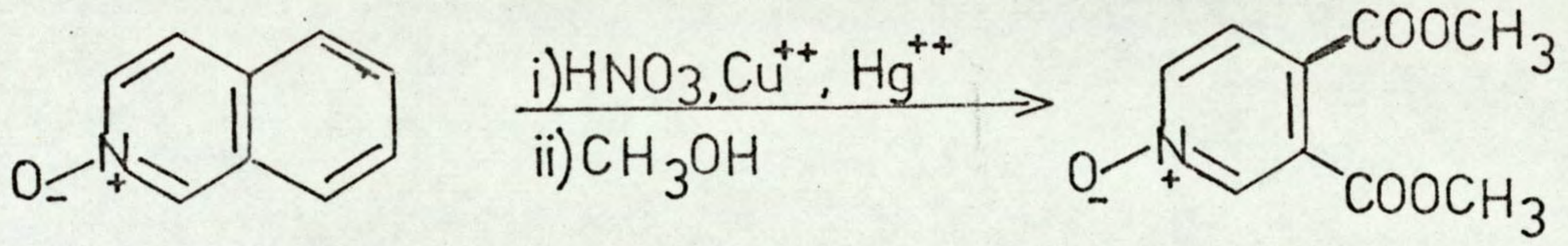
Methyl pyridine 3,4-dicarboxylate 1-oxide (214) was prepared by two routes. Pyridine 3,4-dicarboxylic acid 1-oxide (24) was prepared by oxidation of pyridine 3,4-dicarboxylic acid (21) according to the method of Bain & Saxton,[19] but with more forcing conditions. The di-ester (214) was prepared by heating the di-acid (24) under reflux with methanol and

sulphuric acid for 3 days. The infrared spectrum showed the expected

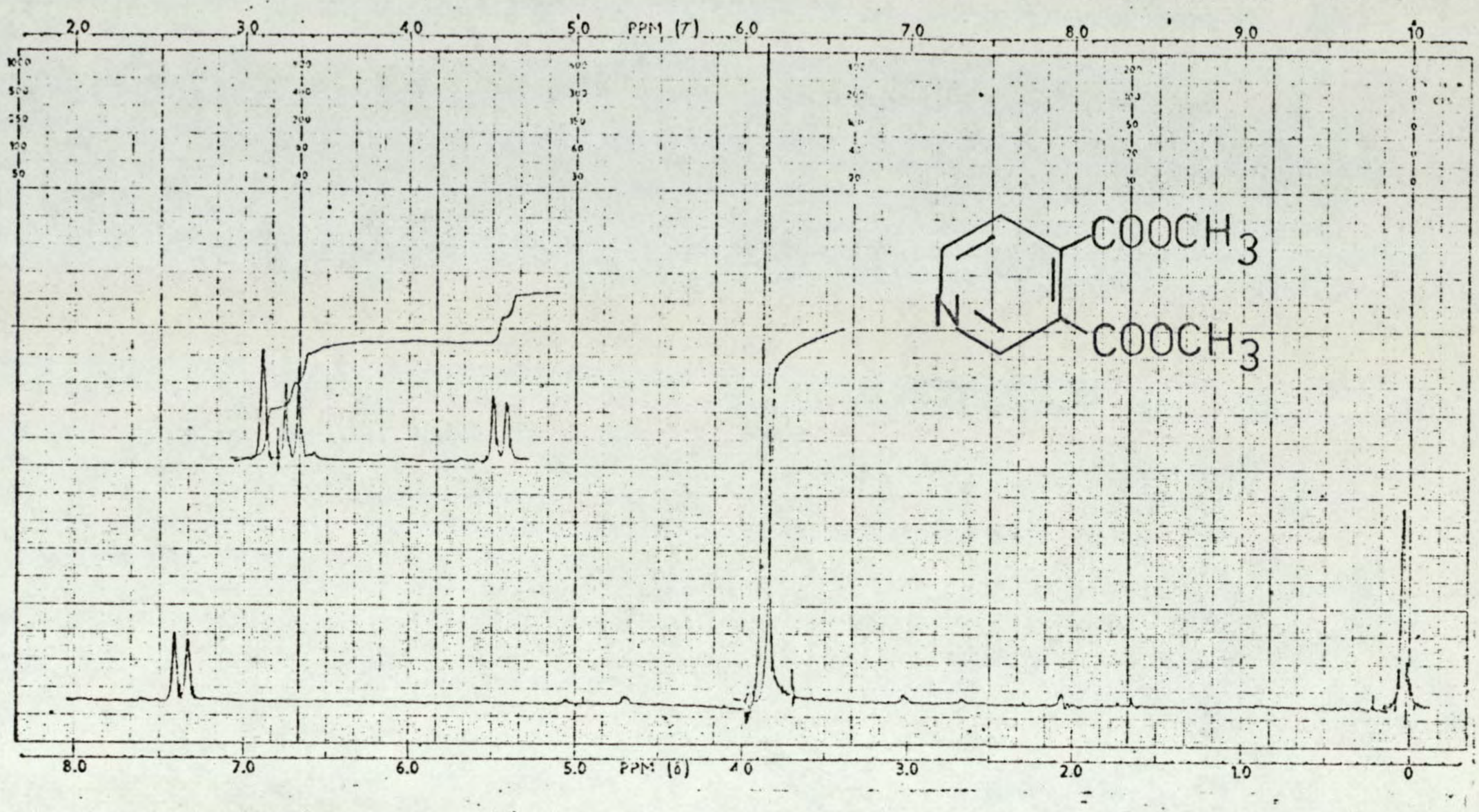


(21) (34) (214)

absorption at 1720cm^{-1} due to the carbonyl stretching vibration. Methyl-pyridine 3,4-dicarboxylate has been prepared by the oxidation of isoquinoline by nitric acid in the presence of mercury and copper salts, and direct esterification of the products.[127] This oxidation procedure has now been applied to isoquinoline N-oxide to give methyl pyridine 3,4-dicarboxylate 1-oxide (214) in 40% yield.



The shielding effect of the N-oxide group on the α-hydrogen atoms is illustrated by the n.m.r. spectra of methylpyridine 3,4-dicarboxylate and methylpyridine 3,4-dicarboxylate 1-oxide (214) in Fig. 1. Both spectra were determined in deuterochloroform. The 2-hydrogen atom in the N-oxide appears at τ1.9 compared with τ1.05 for the equivalent proton in methyl-pyridine 3,4-dicarboxylate, and the 6-hydrogen appears at τ1.95 in the N-oxide compared with τ1.22 when the N-oxide is absent.


2.0
3.0
4.0
5.0
PPM (δ)
6.0
7.0
8.0
9.0
10
COOCH3
COOCH3
N
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

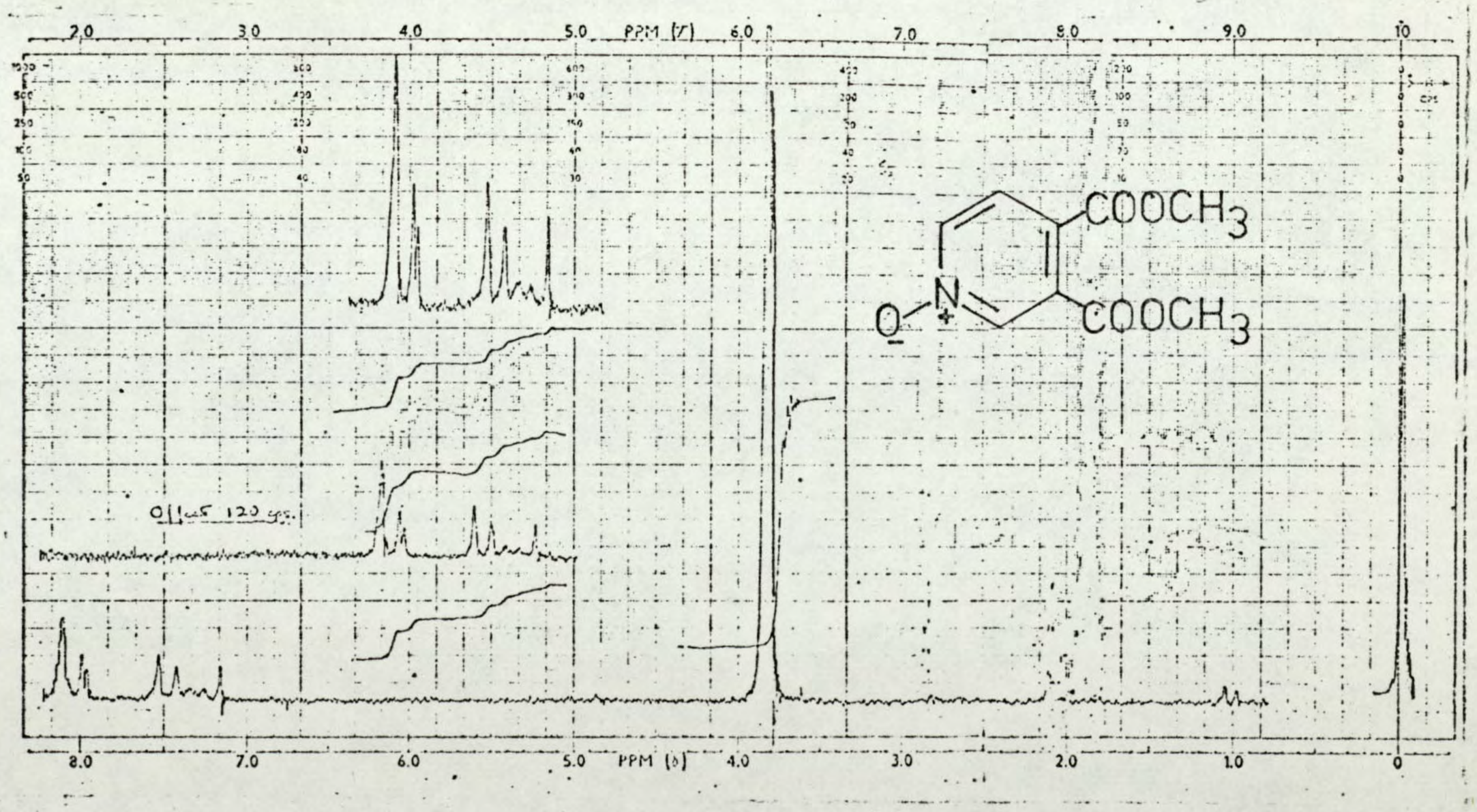
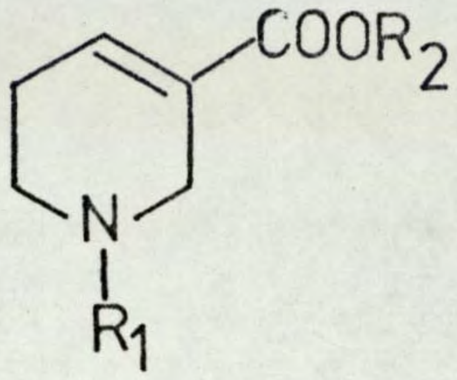

2.0
3.0
4.0
5.0
PPM (δ)
6.0
7.0
8.0
9.0
10
COOCH3
COOCH3
O
N
Oil at 120 °.
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

Fig. 1.

ii) Tetrahydropyridines

Interest in the chemistry of 1,2,5,6-tetrahydropyridines (3-piperideines) is mainly due to the existence of several alkaloids containing this structure. Jahns[65] isolated arecoline (216), arecaidine (217), guvacine (218), and guvacoline (219), and the alkaloids anatabine (220), N-methylanatabine (221),

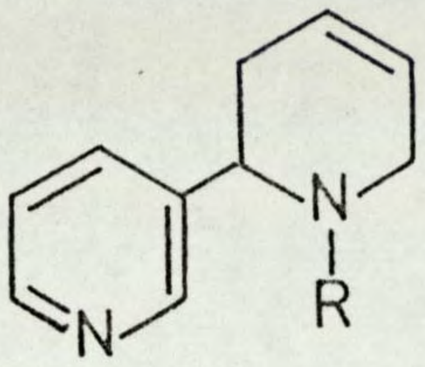


(216) $R_1=R_2=CH_3$

(217) $R_1=CH_3, R_2=H$

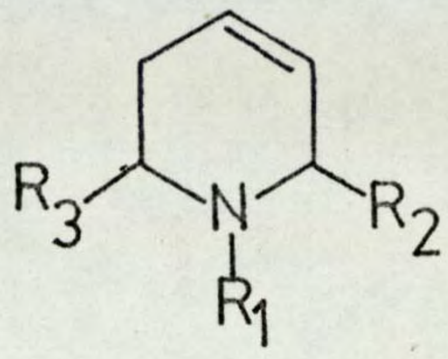
(218) $R_1=R_2=H$

(219) $R_1=H_1, R_2=CH_3$



(220) R=H

(221) $R=CH_3$



(222) $R_1=R_3=H$, $R_2=COOH$

(223) $R_1=CH_3$, $R_2=CH_2CHCH_2CH_3$ (OH)

$R_3=CH_2COPh$

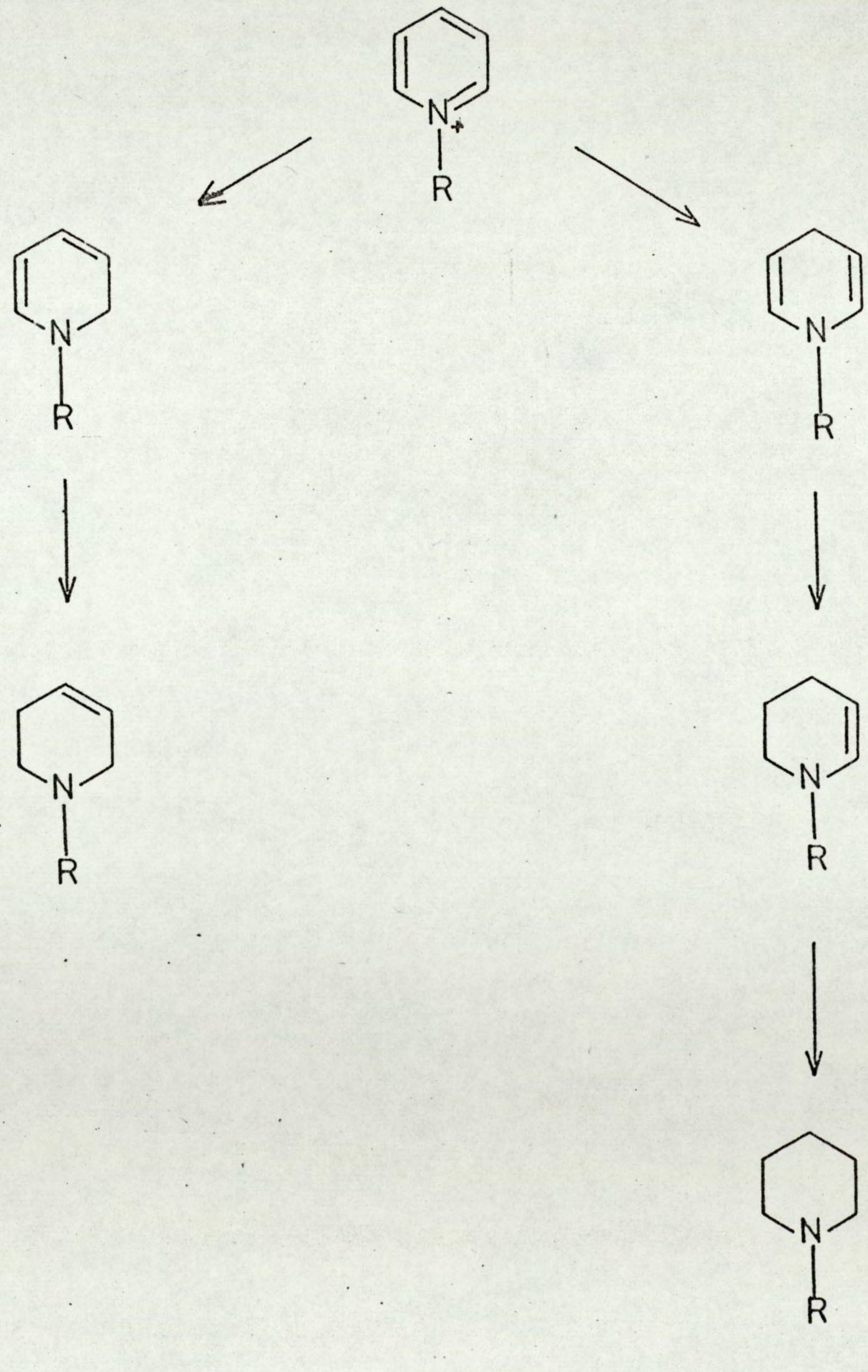
baikiain(222), lobinine and its stereoisomer iso-lobinine (223), contain the 3-piperideine system, which is also found in the ergot alkaloids.

Synthetic modifications of the arecaidine system have been reported,[65] including derivatives prepared by the reduction of pyridinium quaternary salts by sodium borohydride. The only reported reductions of 1,3,4-tri-substituted pyridinium quaternary salts have been limited to alkyl substituted compounds.

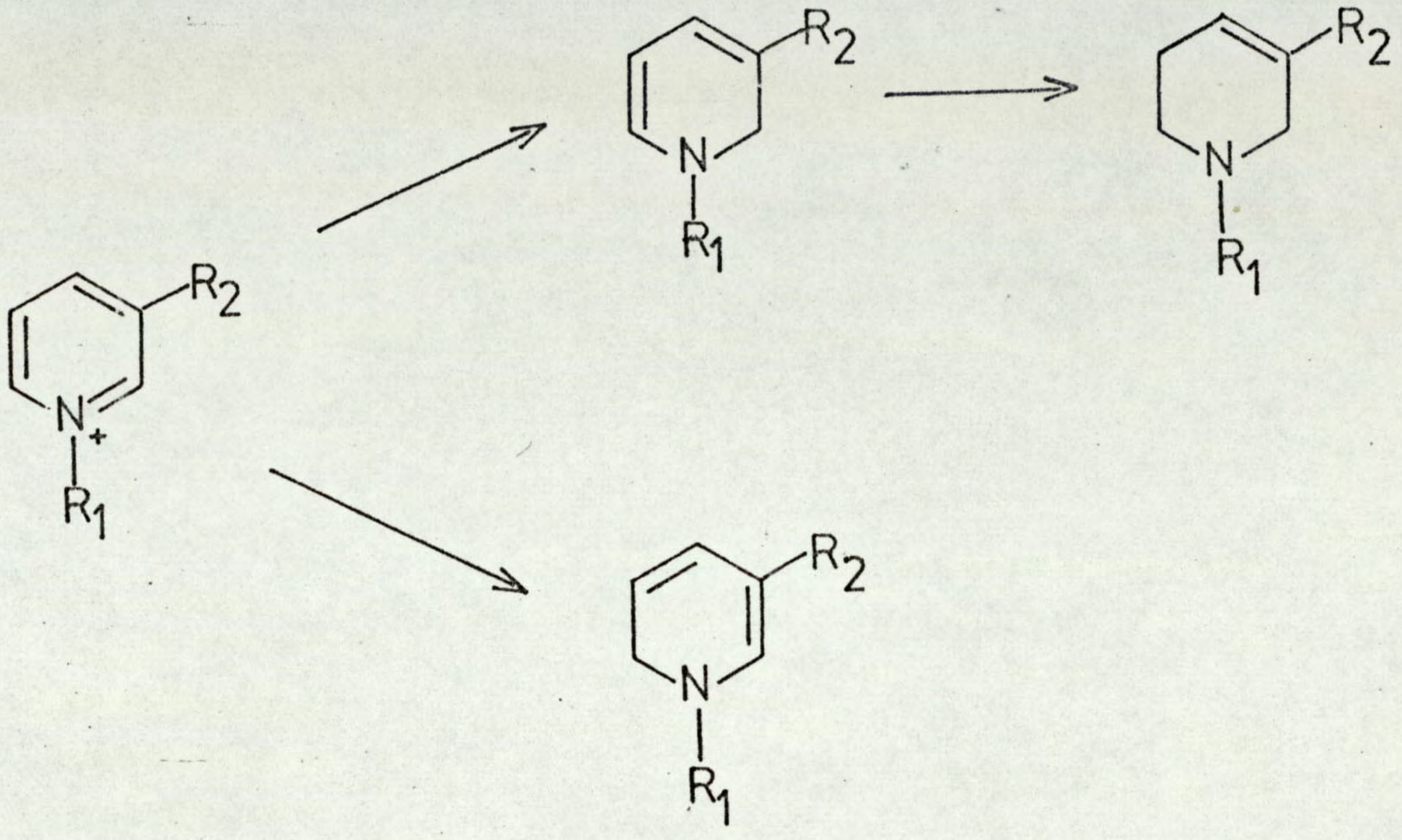
Although numerous bicyclic compounds containing a 3-piperideine ring fused across the 3,4 bond have been prepared, only 1 example has been prepared directly from a tetrahydropyridine.[80] An alternative route to bicyclic systems from suitably substituted tetrahydropyridines was considered feasible, and the synthesis of suitable precursors was attempted.

In their investigation into the mechanism of the reduction of pyridinium quaternary salts by sodium borohydride, Anderson and Lyle demonstrated that

initial attack of hydride ion at the 2 or 6 position resulted in the formation of tetrahydropyridines,[64] and they confirmed the postulation of Ferles,[128] that initial attack at the 4 position resulted in the formation of piperidines. Increasing the size of the R group resulted in increasing preferential attack at position 4.



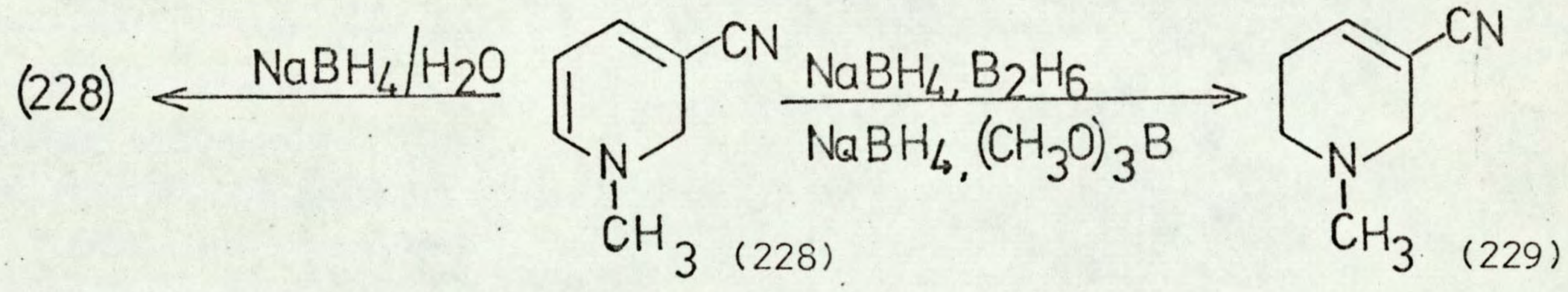
Reduction of 3-substituted pyridinium quaternary salts demonstrated that initial attack at the 2 position resulted in tetrahydropyridine formation, whereas attack at the 6 position gave 1,6-dihydropyridines.[64]



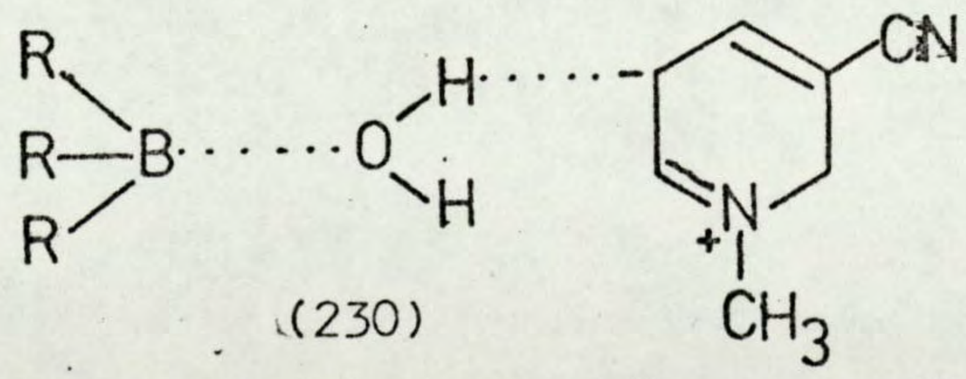
In accordance with the above observations, the following mechanism for the formation of tetrahydropyridines was proposed:-

(224) (225) (226) (227)

Initial attack of the hydride ion occurs at the 2 position to give the 1,2-dihydropyridine (225). Protonation at the 5 position gives the immonium cation (226) which is further reduced by the attack of hydride ion at the 6 position giving the tetrahydropyridine (227). After initial hydride ion attack at the 6 position, the presence of the substituent in the 3 position, at the centre of the dienamine system, inhibits the protonation step and results in the isolation of a 1,6 dihydropyridine. The protonation step was suggested to occur by direct attack of the solvent, water. Liberatore et. al.[129] have since demonstrated that 3-cyano-1-methyl-1,2-dihydropyridine (228) is not reduced by sodium borohydride under aqueous conditions, thus excluding a direct protonation by water. The reduction of the di-hydropyridine (228) with sodium borohydride in the presence of trimethoxyborane or



externally generated diborane, however, gives the tetrahydropyridine (229). It was suggested that the protonating species is one of the adducts formed in the gradual hydrolysis of borane, and that the protonation proceeds



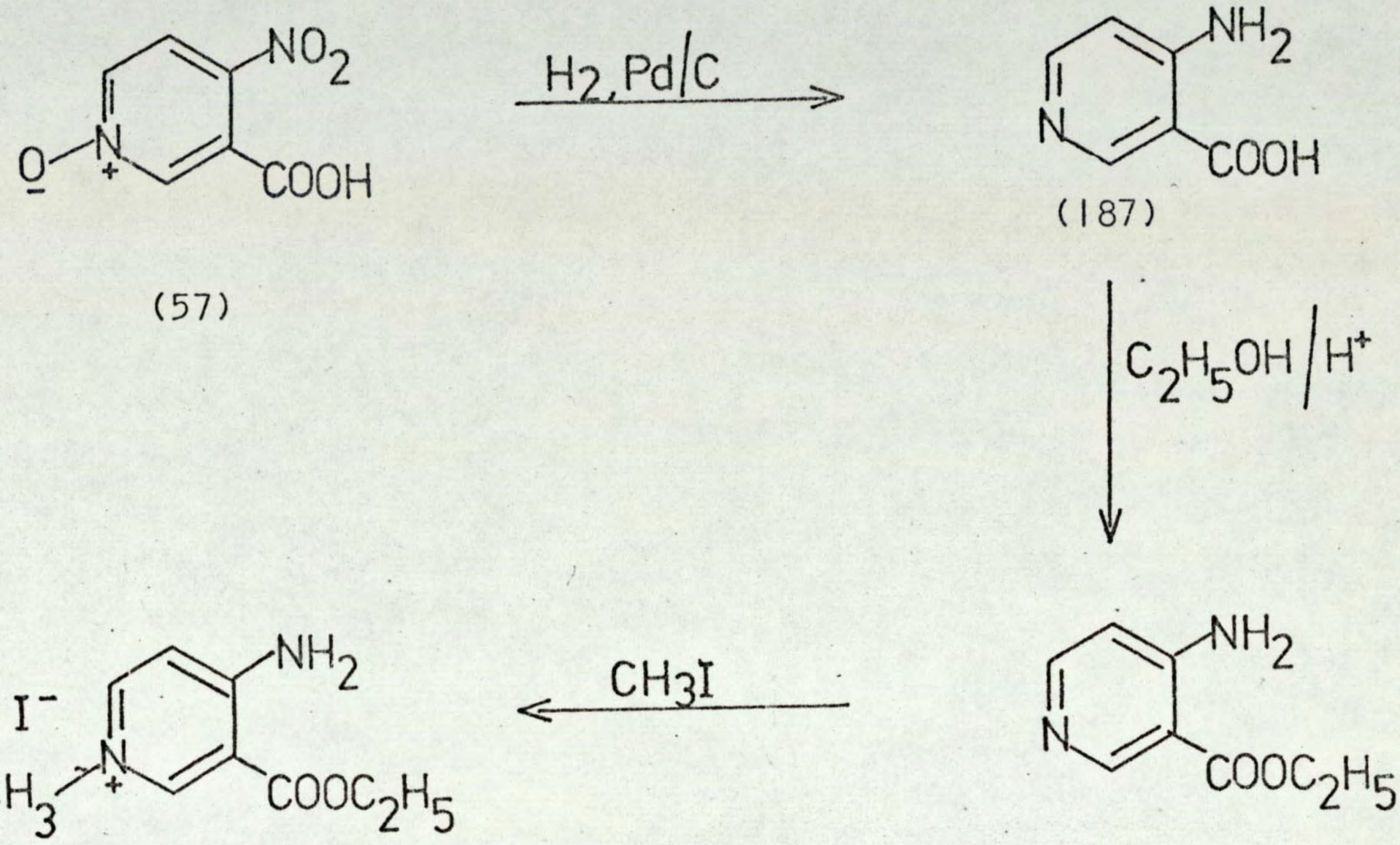
(230)

through a borane-water-1,2-dihydropyridine transition state (230).

Pyridine o-aminoacids and o-aminoesters have previously been shown to be useful intermediates in the preparation of bicyclic systems;[130] tetrahydropyridine o-aminoesters and di-esters appeared to be useful intermediates.

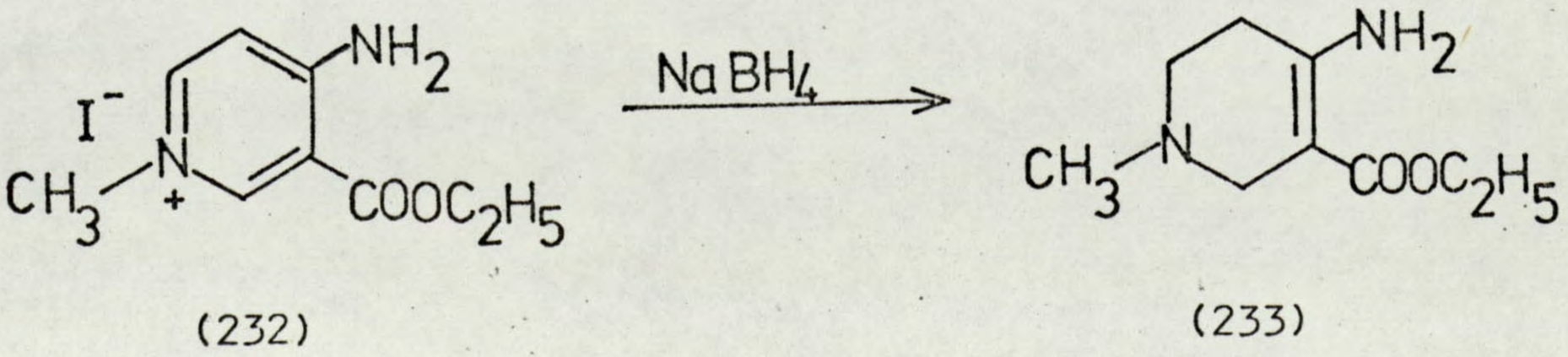
4-Aminonicotinic acid (187) was prepared by the reduction of 4-

nitronicotinic acid 1-oxide (57); esterification using ethanol and sulphuric acid gave the amino-ester (231). The methiodide (232) was prepared by



(57) (187) (231) (232)

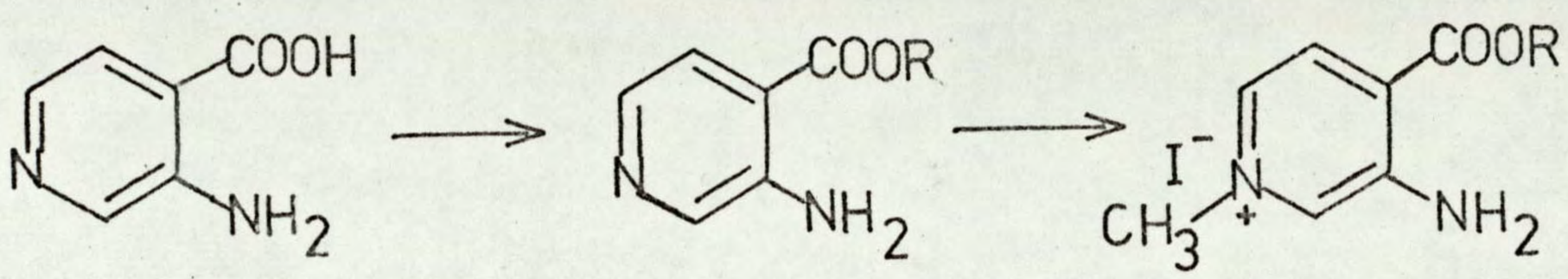
heating the ester with methyl iodide in ethanol under reflux for 1 hour. The reduction of an aqueous solution of 1 mole of the methiodide (232) by 0.5 moles of sodium borohydride at room temperature for 2 hours gave the tetrahydroaminoester (233) in 96% yield. The infrared spectrum showed the expected absorption at $3400cm^{-1}$ and $3250cm^{-1}$ due to the asymmetrical



(232) (233)

and symmetrical N-H stretching vibrations and an absorbance at 2600cm^{-1} due to the N-CH_3 stretching vibration. The carbonyl stretching vibration appeared at 1720cm^{-1} and the absorbance due to the double bond stretching vibration appeared at 1610cm^{-1}. The absence of any absorbance due to an olefinic proton in the n.m.r. spectrum, and the close similarity in the ultra-violet spectra obtained for both the ortho-aminoester (233) and ethyl-β-aminocrotonate indicated the double bond to be in the 3,4 position.

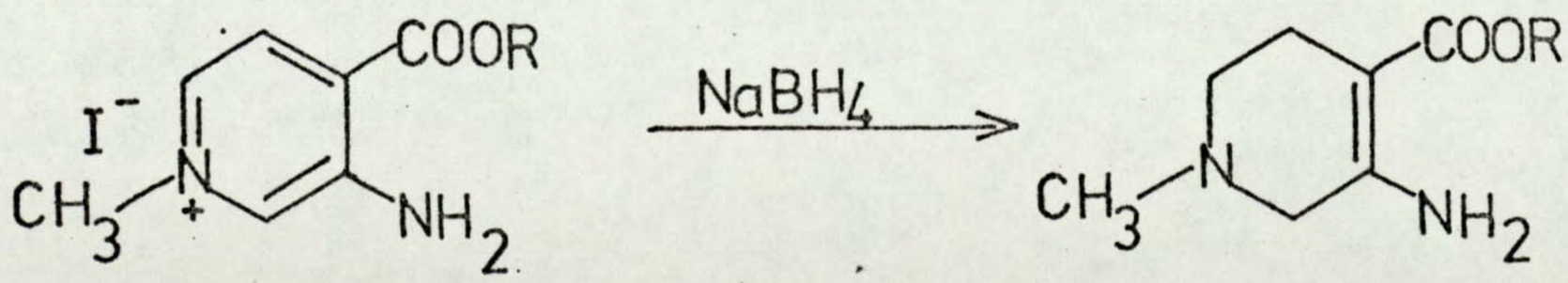
The methyl and ethyl esters (235) and (236) were prepared by heating



(234) (235) R=CH_3 (237) R=CH_3

(236) R=C_2H_5 (238) R=C_2H_5

the amino-acid (234) with the appropriate alcohol and sulphuric acid under reflux for 3 days. The methiodides (237) and (238) were prepared by heating the apporpriate amino-ester, methyl iodide, and ethanol under reflux for 1 hour. The reduction of aqueous solutions of the methiodides (237) and (238) containing 1 mole of the quaternary salt with 0.5 mole of sodium borohydride, at room temperature for 2 hours, gave the tetrahydroamino-



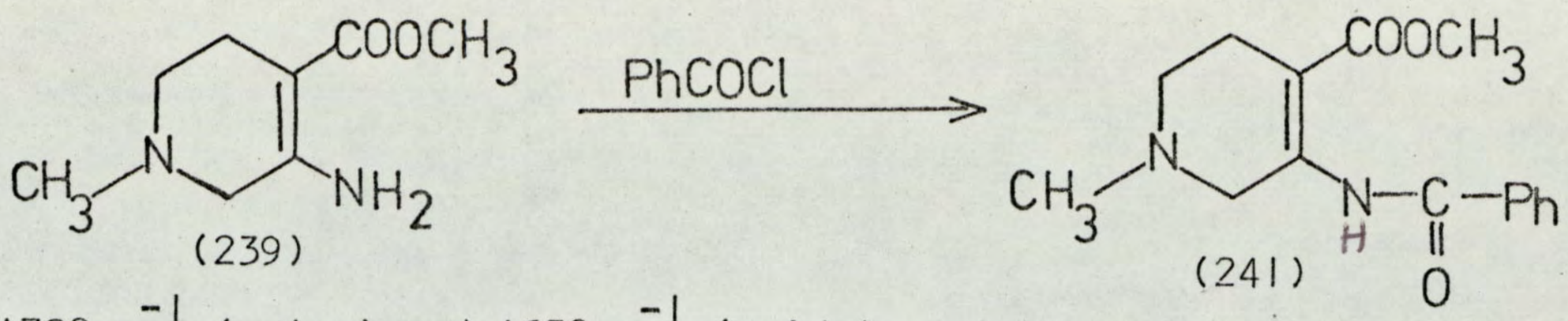
(237) R=CH_3 (239) R=CH_3

(238) R=C_2H_5 (240) R=C_2H_5

esters (239) and (240) in good yield.

The reaction of 3-amino-4-methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine (239) with benzoyl chloride, in pyridine, gave the 3-benzamido-

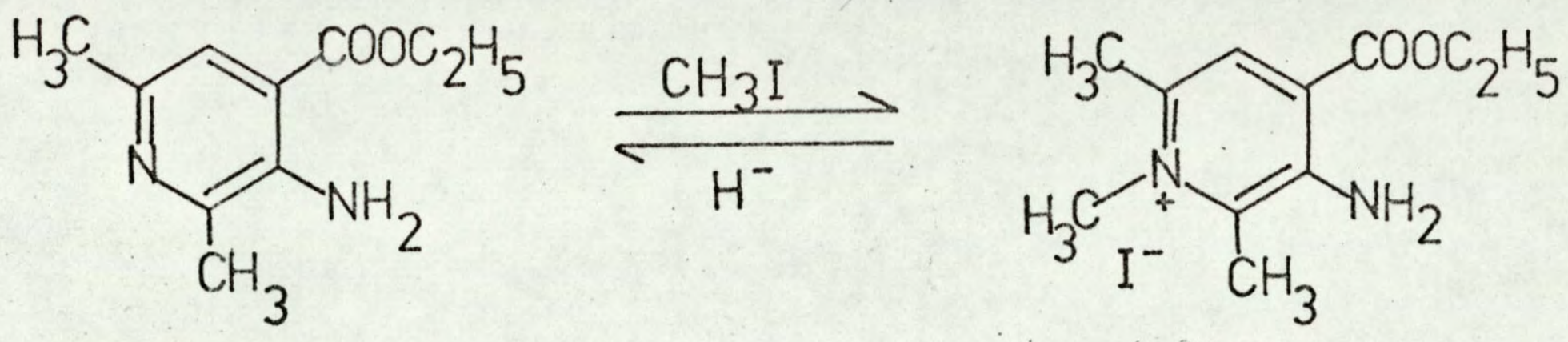
ester (241). The infrared spectrum showed the carbonyl stretching vibrations



(239) (241)

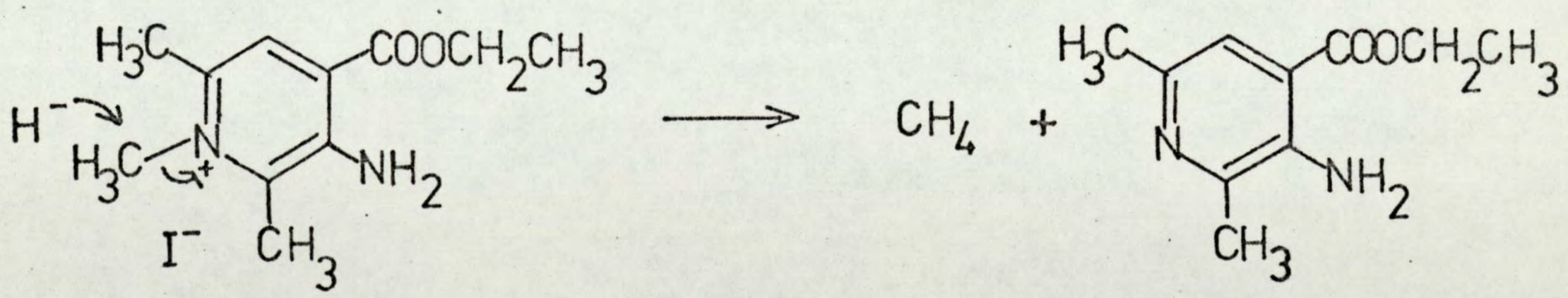
at 1720cm^{-1} (ester) and 1650cm^{-1} (amide).

Due to the steric hindrance of the 2- and 6- methyl groups in 3-amino-4-ethoxycarbonyl-2,6-dimethylpyridine (242), preparation of the methiodide (243) required more forcing conditions. A solution of the amino-ester (242) and methyl iodide in ethanol was heated under reflux for 60 hours to



(242) (243)

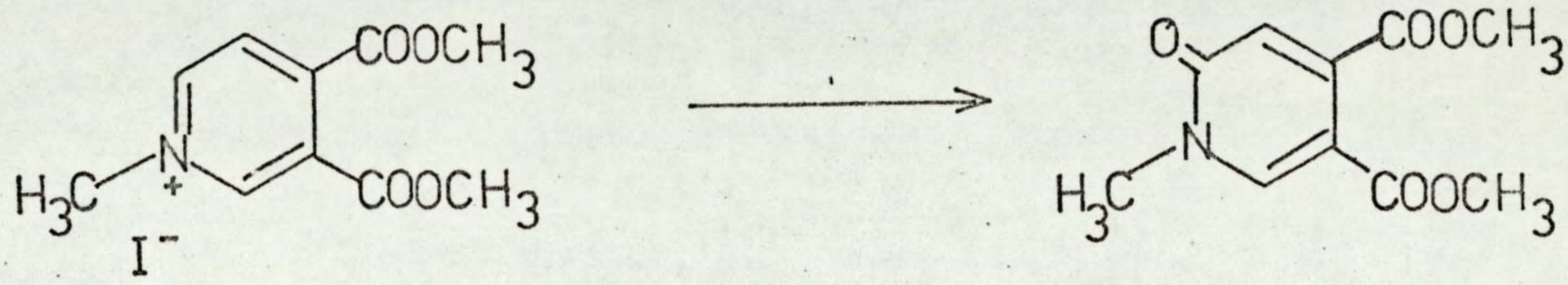
give the methiodide (243) in 43% yield. The addition of sodium borohydride to an aqueous solution of the quaternary salt (243) resulted in the immediate precipitation of a solid with melting-point and infrared spectrum identical to those of the amino-ester (242). Stirring for 3 hours at room temperature resulted in 96% recovery of the de-methylated aminoester (242). The de-methylation of quaternary salts by lithium aluminium hydride has



(243) (242)

been reported[131] to yield a tertiary amine and methane. The de-methylation of the quaternary salt (243) by sodium borohydride presumably proceeds by a similar mechanism.

The reduction of an aqueous solution of 1 mole of 3,4-dimethoxycarbonyl-1-methylpyridinium iodide (244) by 0.5 mole of sodium borohydride at room temperature for 4 hours, and extraction of the resultant solution with chloroform followed by evaporation of the dried chloroform solution, gave an amber oil which began to crystallise on standing. Trituration of the mixture with ether gave a yellow solid, which was identified as 3,4-dimethoxycarbonyl-1-methylpyrid-6-one (245), and a red oil. Thin-layer chromatography of the oil indicated 3 major components, although no pure

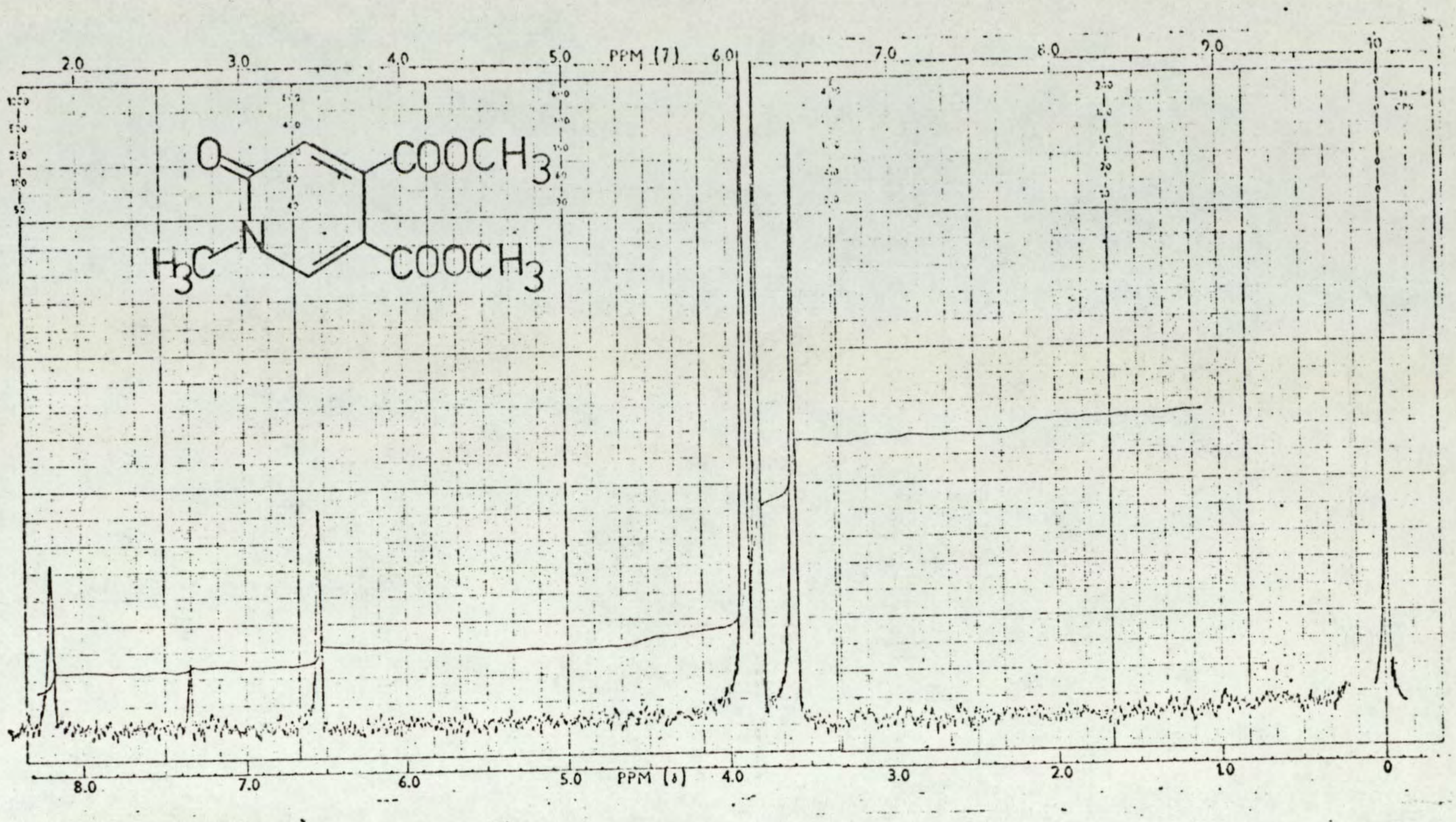


(244) (245)

material was isolated by column chromatography.

The infrared spectrum of the pyridone (245) showed absorptions at 1715cm^{-1} and 1705cm^{-1} due to stretching vibrations of the ester carbonyl groups, and a peak at 1665cm^{-1} due to the stretching vibrations of the amide carbonyl group.

The n.m.r. spectrum, see Fig. 2., showed the oxo group to be in the 6 rather than the 2 position. The singlet at τ1.81 was attributed to the 2 proton, and the singlet at τ3.45 was attributed to the 5 proton. The singlets at τ6.09 (3H, 4-COO$\underline{CH}_3$) and τ6.17 (3H, 3-COO$\underline{CH}_3$) were attributed to the ester methyl groups, and the singlet at τ6.40 (3H, -N-$\underline{CH}_3$) was assigned to the N-methyl group. The overall yield of the oxidised product was 30%.


O
COOCH3
N
H3C
COOCH3
PPM (δ)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0

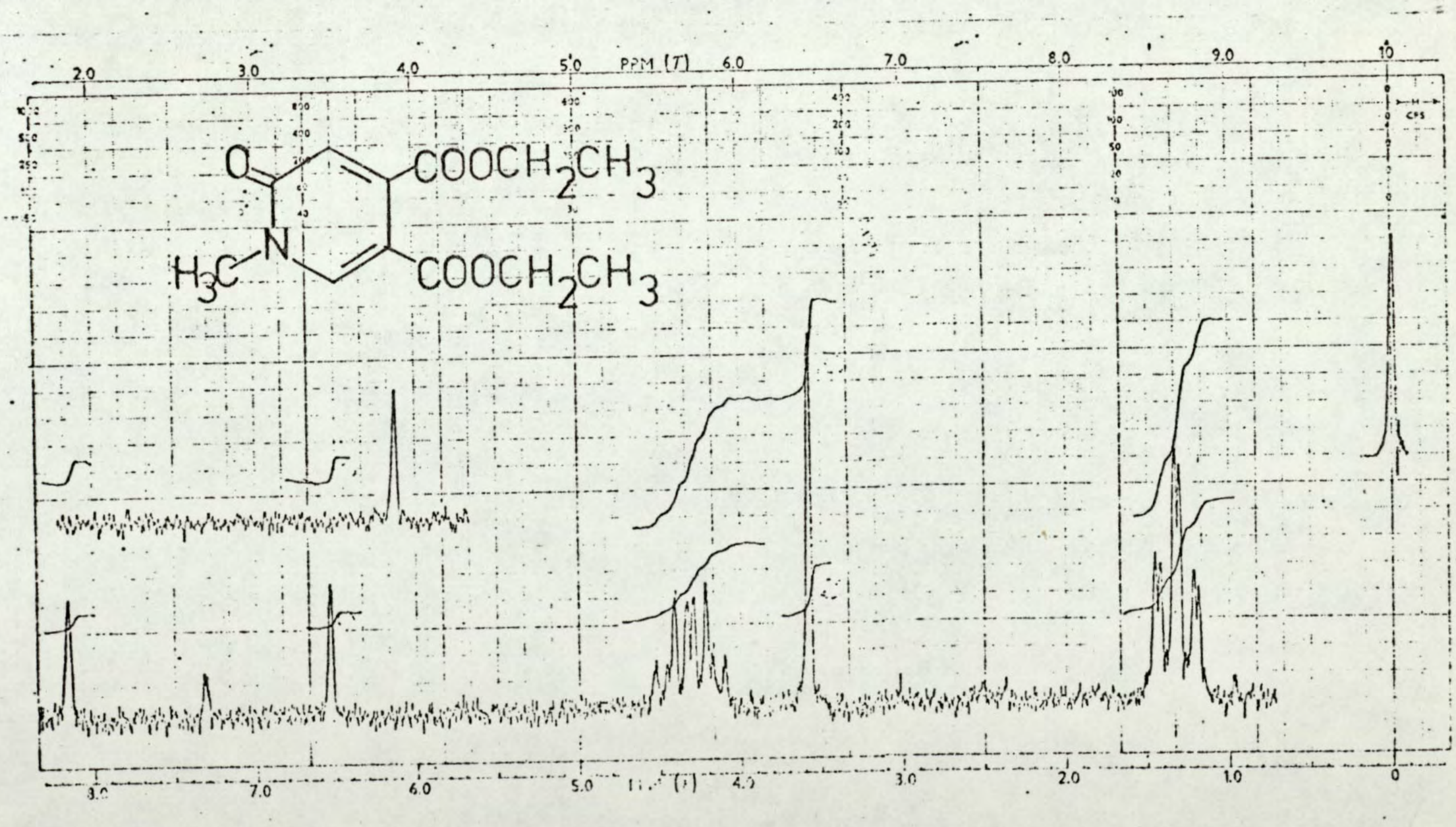
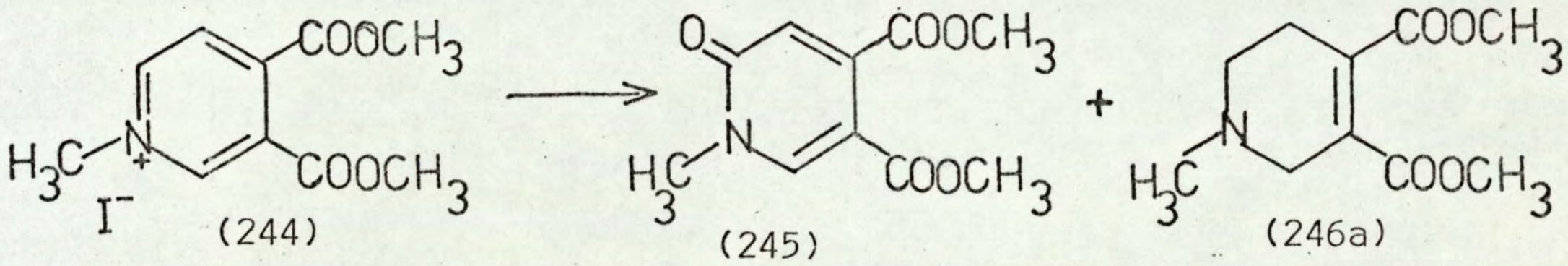

O
COOCH2CH3
N
H3C
COOCH2CH3
PPM (δ)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0

Fig. II.

Repitition of the reaction with heating of the reaction mixture under reflux after the addition of the borohydride, gave a small yield of a dark red oil, which was shown to be a mixture of seven components none of which could be isolated in a pure form. The reaction at room temperature was repeated, but with stirring for 24 hours. Extraction of the mixture again gave the pyridone (245), in 34% yield. Thin-layer and gas-liquid chromatography of the amber oil remaining after removal of the pyridone, indicated only one major component. The oil could not be made to crystallise, but the hydrochloride salt was prepared from an ethanolic solution using dry HCl gas, and careful addition of ether. Spectroscopic and analytical evidence showed the material to be 3,4-dimethoxycarbonyl



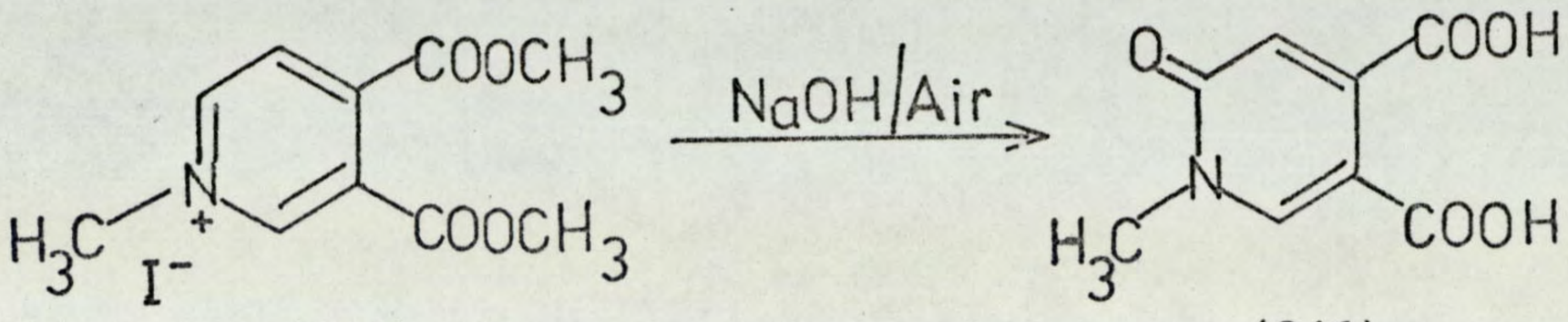
(244) (245) (246a)

-1-methyl-1,2,5,6-tetrahydropyridine hydrochloride (246a) in overall yield of 52%.

The infrared spectrum of the tetrahydro compound (246a)showed the expected absorption at 1710cm^{-1} due to the stretching vibration of the ester carbonyl groups, an absorption at 1650cm^{-1} due to the double bond stretching vibration, and a series of peaks in the 2500cm^{-1} region due to the hydrochloride. The absence of any absorption due to an olefinic proton in the n.m.r. spectrum showed the double bond to be in the 3-4 position.

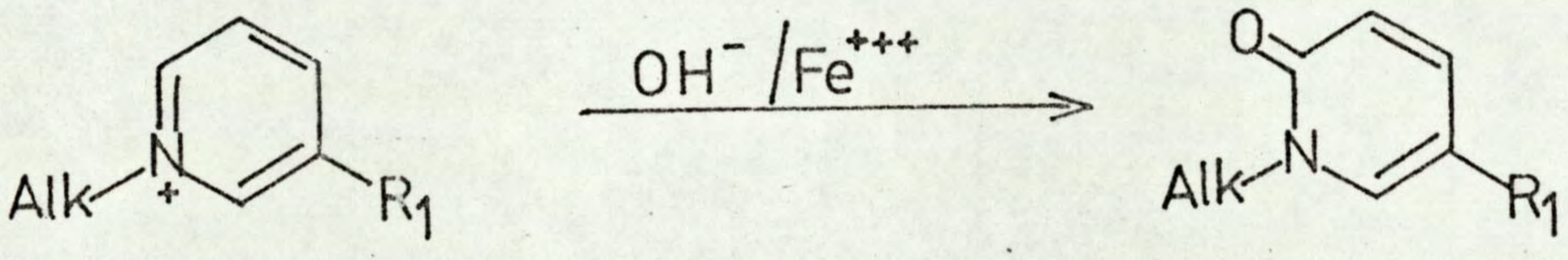
When the reaction was repeated using methanol as solvent, the yield of the pyridone was 17%. The pyridone (245) was also isolated from the reaction of sodium borohydride with solutions of the methiodide (244) in both methanol and water, under an atmosphere of nitrogen.

Air was drawn through a solution of the quaternary salt (244) in water for 6 hours at room temperature; no 3,4-dimethoxycarbonyl-1-methyl-pyrid-6-one (245) was isolated from the resulting solution, although a 5% yield of the corresponding di-acid (246) was isolated.



(244) (246)

3,4-Dimethoxycarbonyl-1-methylpyrid-6-one (245) was prepared by an alternative route. The oxidation of quaternary salts to pyridones is a well established procedure;[132] although alkyl-substituted pyridinium salts normally give the pyrid-2-ones, 3-carboxy- (248) and 3-cyano (247) - pyridinium salts have been shown to proceed to the pyrid-6-ones (251) and



(247) R_1=CN

(248) R_1=COOH

(249) R_1=$CONH_2$

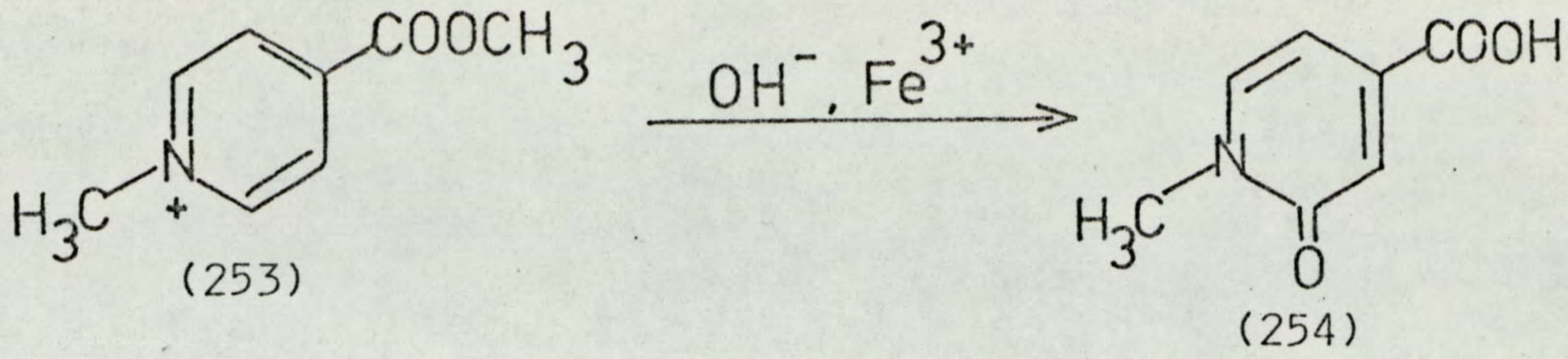
(250) R_1=CN

(251) R_1=COOH

(252) R_1=$CONH_2$

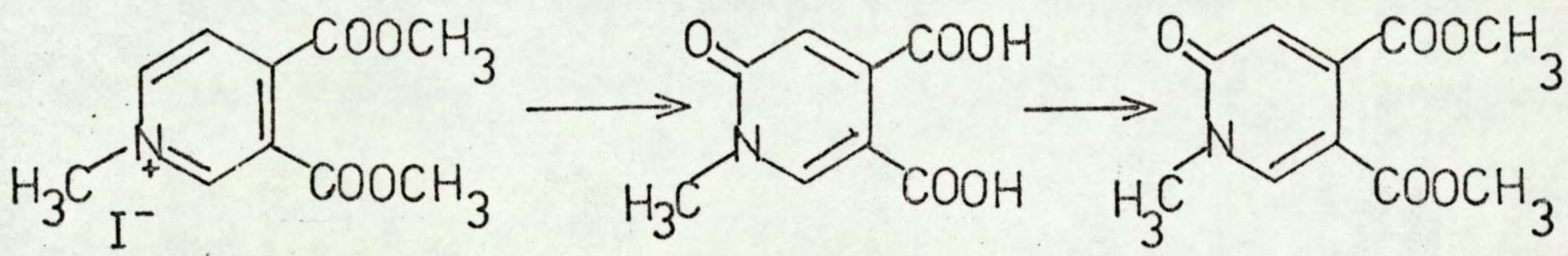
(250),[133] whereas nicotinamide methiodide (249) was reported to give both the 2- and 6- one depending upon the extraction procedure used.[134]

Frank and Mosher[135] obtained 4-carboxy-1-methylpyrid-2-one (254) by the action of alkaline ferricyanide solution on 4-methoxycarbonyl-1-methylpyridinium iodide (253).



(253) (254)

The conditions used by Frank and Mosher[135] have now been employed for the oxidation of 3,4-dimethoxycarbonyl-1-methylpyridinium iodide. Careful addition of separate solutions of sodium hydroxide and potassium ferricyanide to a warm aqueous solution of the methiodide, followed by acidification of the resultant mixture, gave 3,4-dicarboxy-1-methylpyrid-6-one (246) in 40% yield.

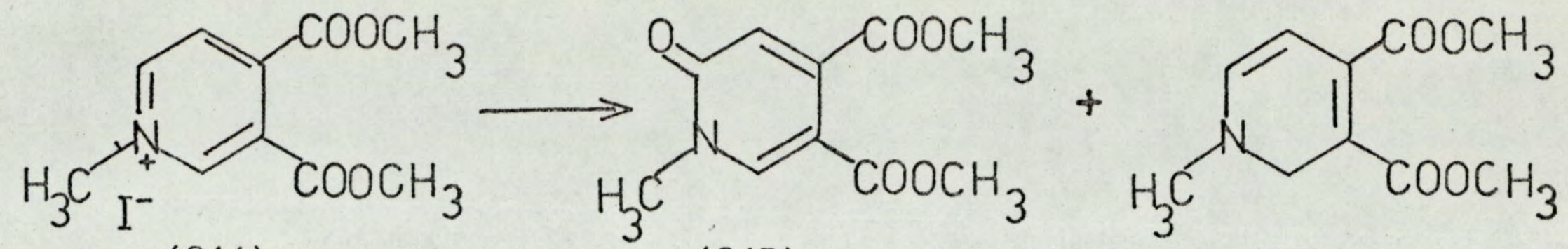


(244) (246) (245)

The infrared spectrum of the di-acid (246) had a broad band in the 3450-3500cm^{-1} region of the spectrum due to the OH stretching vibration, two peaks at 1710cm^{-1} and 1690cm^{-1} due to the carbonyl stretching vibrations, and a peak at 1640cm^{-1} due to the amide carbonyl stretching vibration. Esterification of the di-acid using methanol and sulphuric acid gave the expected di-ester, the material being identical to that obtained from the reaction of the quaternary (244) with sodium borohydride.

To investigate the reaction further, sodium borohydride was added to a solution of the quaternary salt (244) in water, and an identical reaction was performed simultaneously using sodium borodeuteride and a solution of the quaternary (244) in D_2O. Both reaction mixtures were extracted with chloroform after 15 minutes; the chloroform extracts were dried and evaporated, and the pyridone (245), which crystallised in both cases, was

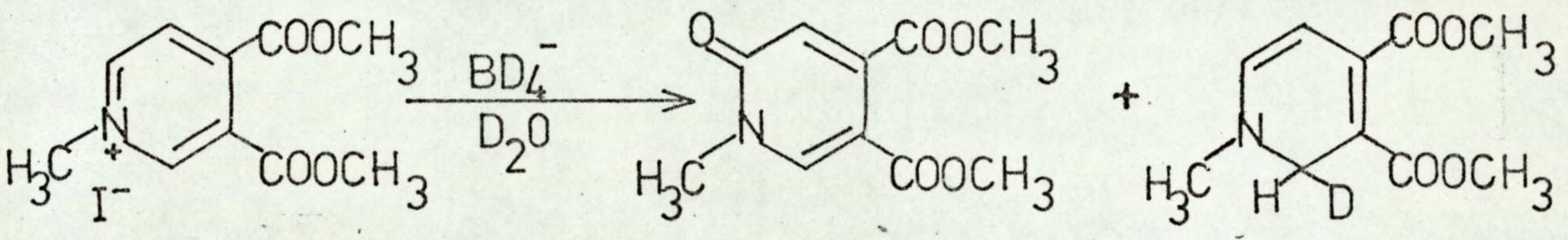
removed. A mass spectrum of the resultant oil from the sodium borohydride reaction indicated the major component to be a dihydropyridine (255); the



(244) (245) (255)

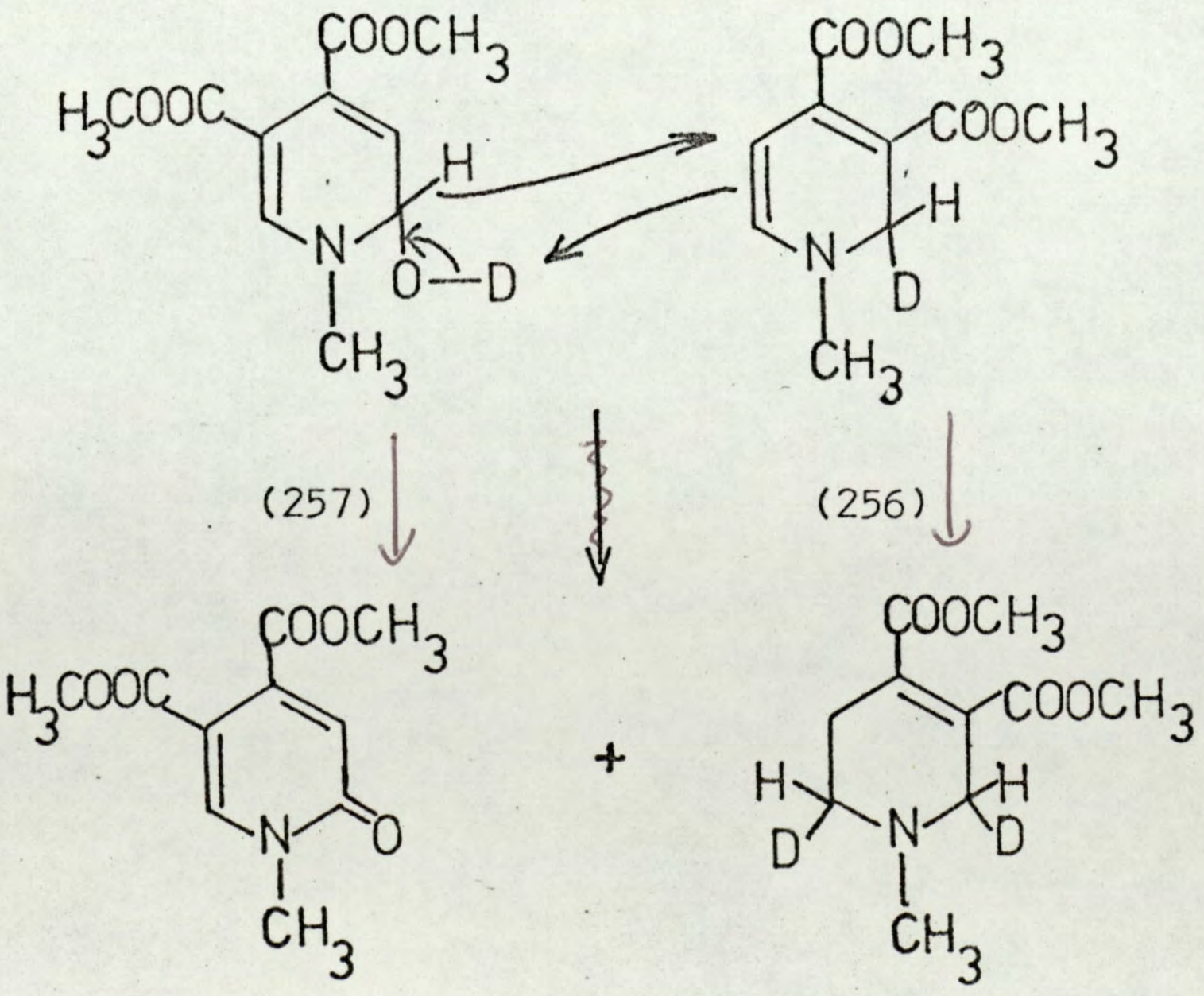
absence of a fragment at m/e 213 indicated that no tetrahydropyridine (246) was present.

The mass spectrum of the resultant oil from the sodium borodeuteride reduction also indicated the major product to be a dihydropyridine (256), and the absence of any fragment of m/e 215 indicated no tetrahydropyridine



(244) (245) (256)

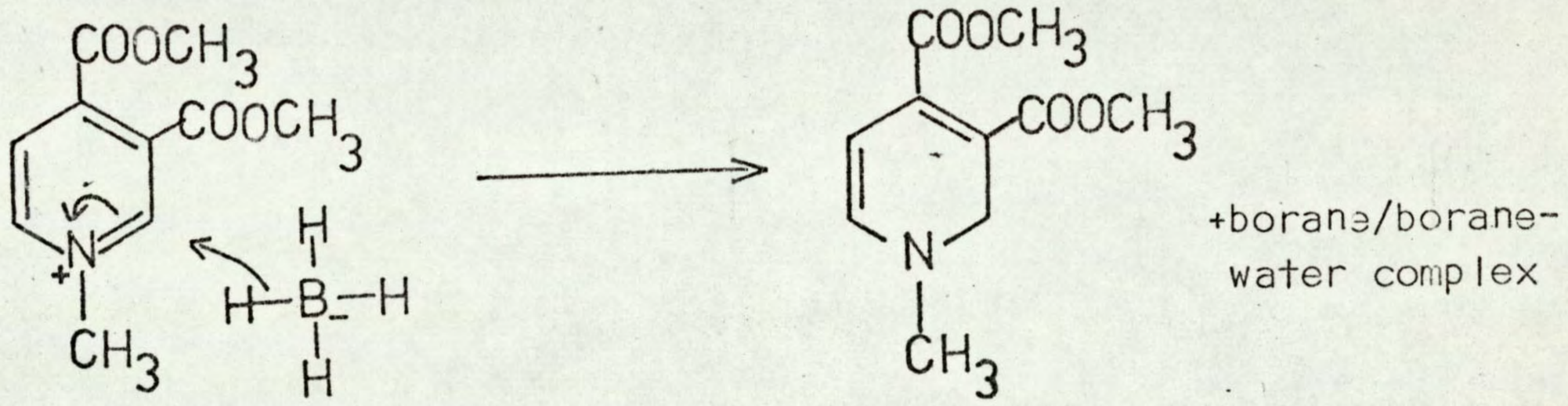
formation, and also eliminated the possibility of the formation of the



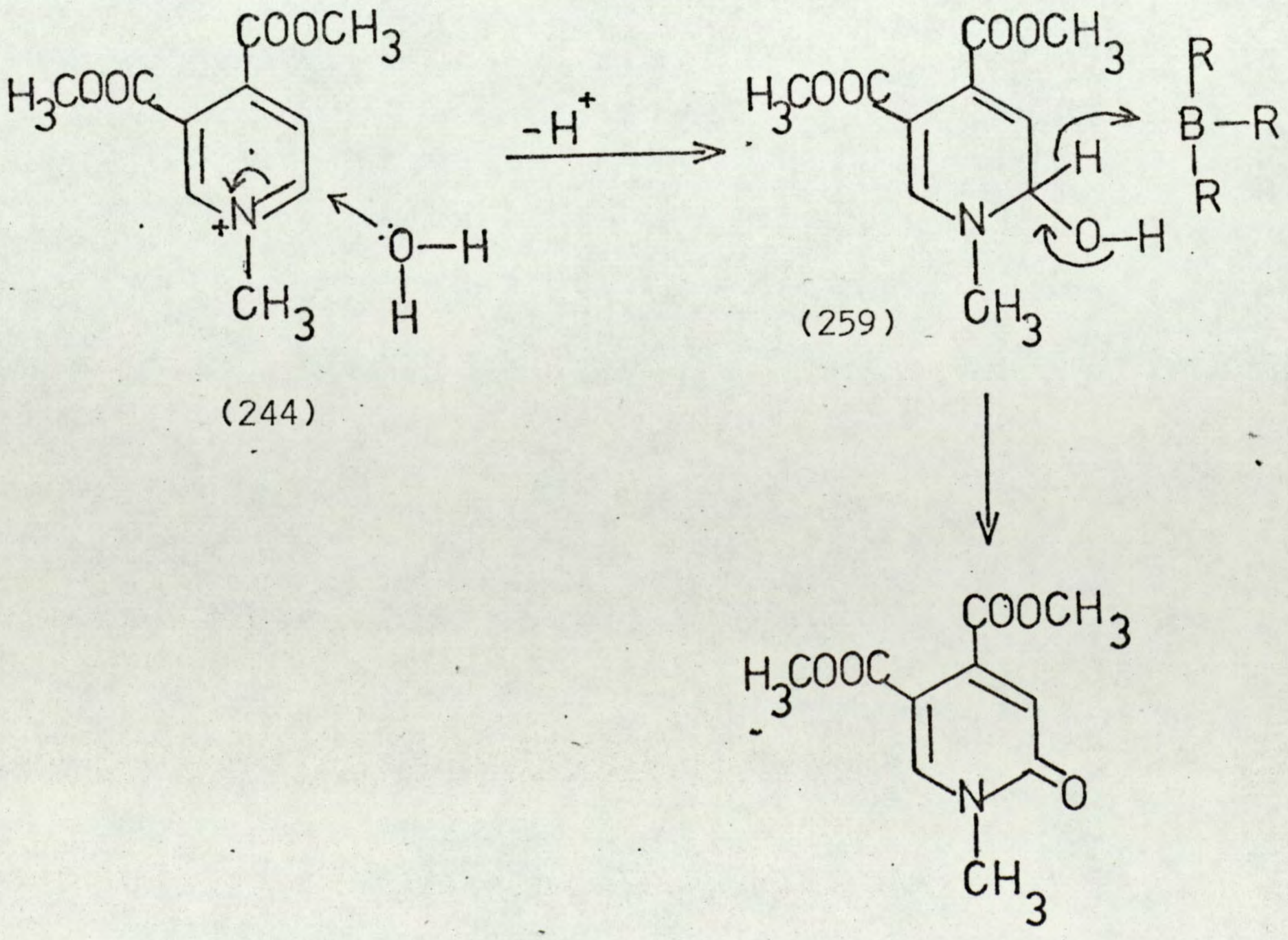
(245) (258)

pyridone via a transfer hydrogenation reaction involving the intermediate dihydropyridine, such as (257) → (258).

In view of the known electron deficiency of many boron compounds and complexes,[136] it seems possible that, after the initial attack of a hydride ion on the quaternary (244) to give the dihydropyridine (255), and nucleophilic attack of the solvent on the quaternary (244) to give the pseudo-base (259), the reaction proceeds by the abstraction of a hydride ion from the pseudo base (259) by an electron deficient boron complex or

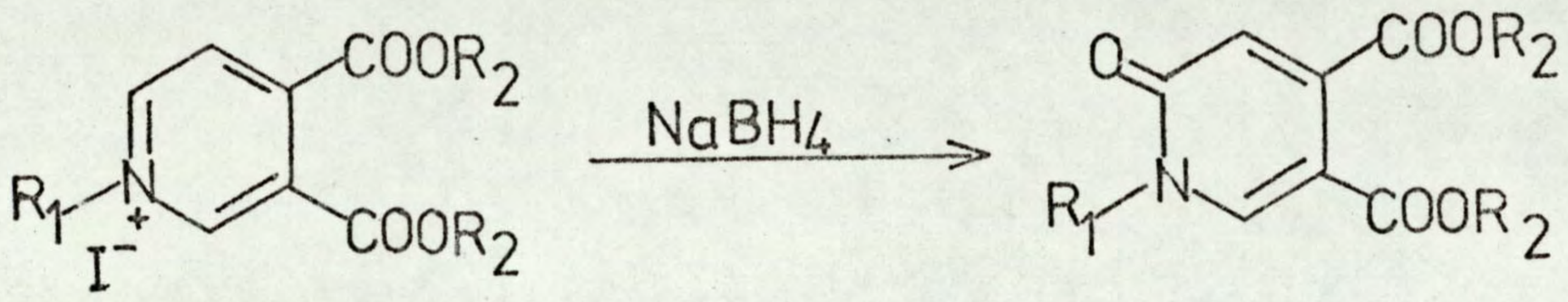


(244) (255)



borane. The isolation of 3,4-dicarboxy-1-methylpyrid-6-one (246) from the oxidation of the quaternary (245) with potassium ferricyanide shows that pseudo-base formation occurs in the 6 rather than the 2 position, and the isolation of only the tetrahydropyridine (246) and the pyridone (245) from the reduction of the quaternary (244) over 24h. shows, from the known mechanism of the reduction of quaternary salts by borohydride,[64] that initial attack of hydride ion occurs at the 2 and not the 6 position.

3,4-Diethoxycarbonyl-1-methylpyrid-6-one (262) was isolated in 30% yield from the treatment of 3,4-diethoxycarbonyl-1-methylpyridinium iodide



(260) $R_1=CH_3$, $R_2=C_2H_5$ — (262) $R_1=CH_3$, $R_2=C_2H_5$

(261) $R_1=C_2H_5$, $R_2=CH_3$ — (263) $R_1=C_2H_5$, $R_2=CH_3$

(260) by sodium borohydride, and 1-ethyl-3,4-dimethoxycarbonylpyrid-6-one (263) was isolated in 14% yield from the treatment of 1-ethyl-3,4-dimethoxycarbonylpyridinium iodide (261) by borohydride; the lower yield obtained in the case of the N-ethyl quaternary salt (261) is presumably due to the increased steric hindrance of the ethyl group. The location of the oxo group in the 6 position was indicated by the n.m.r. spectrum.

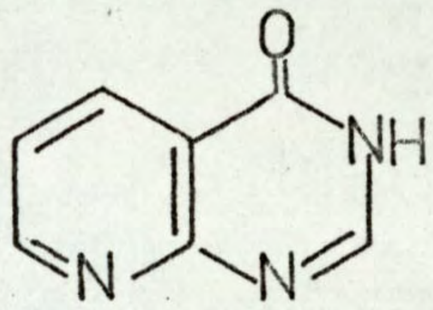
Bicyclic Systems derived from 1,3,4-Trisubstituted Pyridines.

a) Pyrido[4,3-d]Pyrimidines

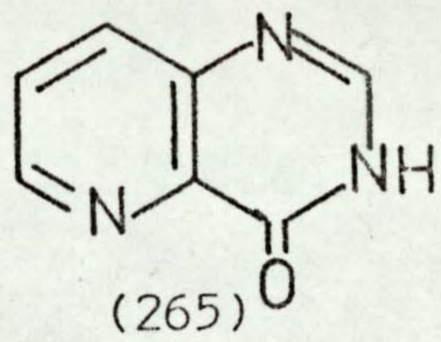
i) From 1,3,4-trisubstituted Pyridines

Pyrido pyrimidines have been prepared by condensation of o-amino-pyridine carboxylic acids with formamide, urea, and other suitably substituted amides, using an extension of the von Niementowskii quinazolone synthesis.[130]

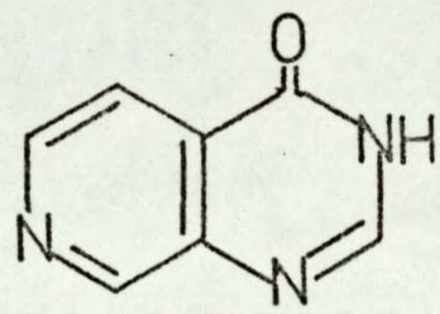
The reaction of 2-aminonicotinic acid, 3-aminopicolinic acid, and 3-aminoisonicotinic acid with formamide all gave the respective pyrido-



(264)



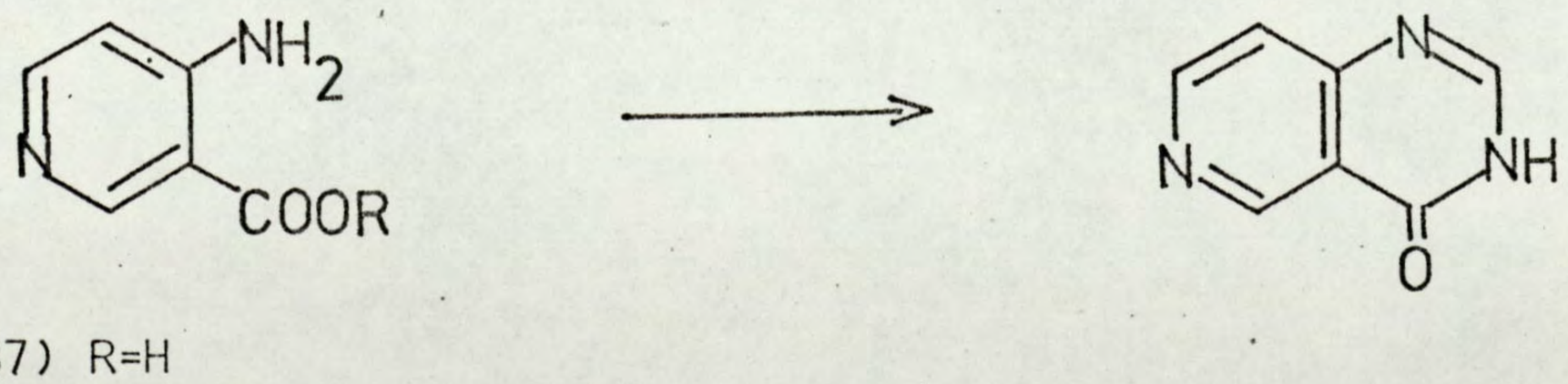
(265)



(266)

pyrimidinones (264), (265) and (266).

Substitution of formamide by urea gave the corresponding diones. Fusion of both 4-aminonicotinic acid (187) and methyl 4-aminonicotinate (267) with formamide failed to give the expected product (268),[137] but the condensation of ethyl 4-aminonicotinate (231) with formamide gave the required pyrido [4,3-d] pyrimidine -4(3H)-one (268).



(187) R=H

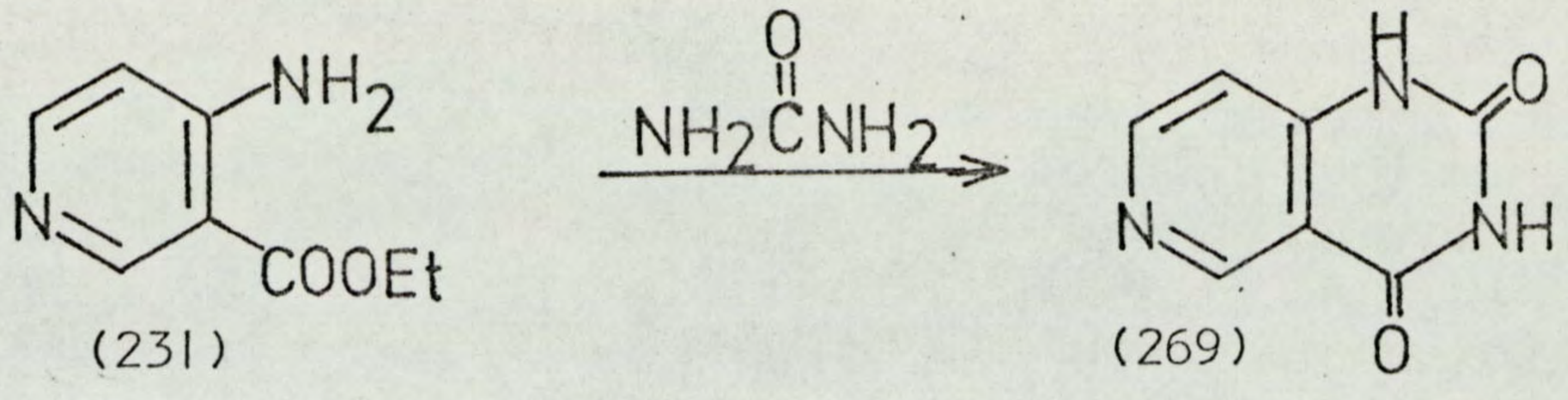
(267) R=CH_3

(231) R=C_2H_5

(268)

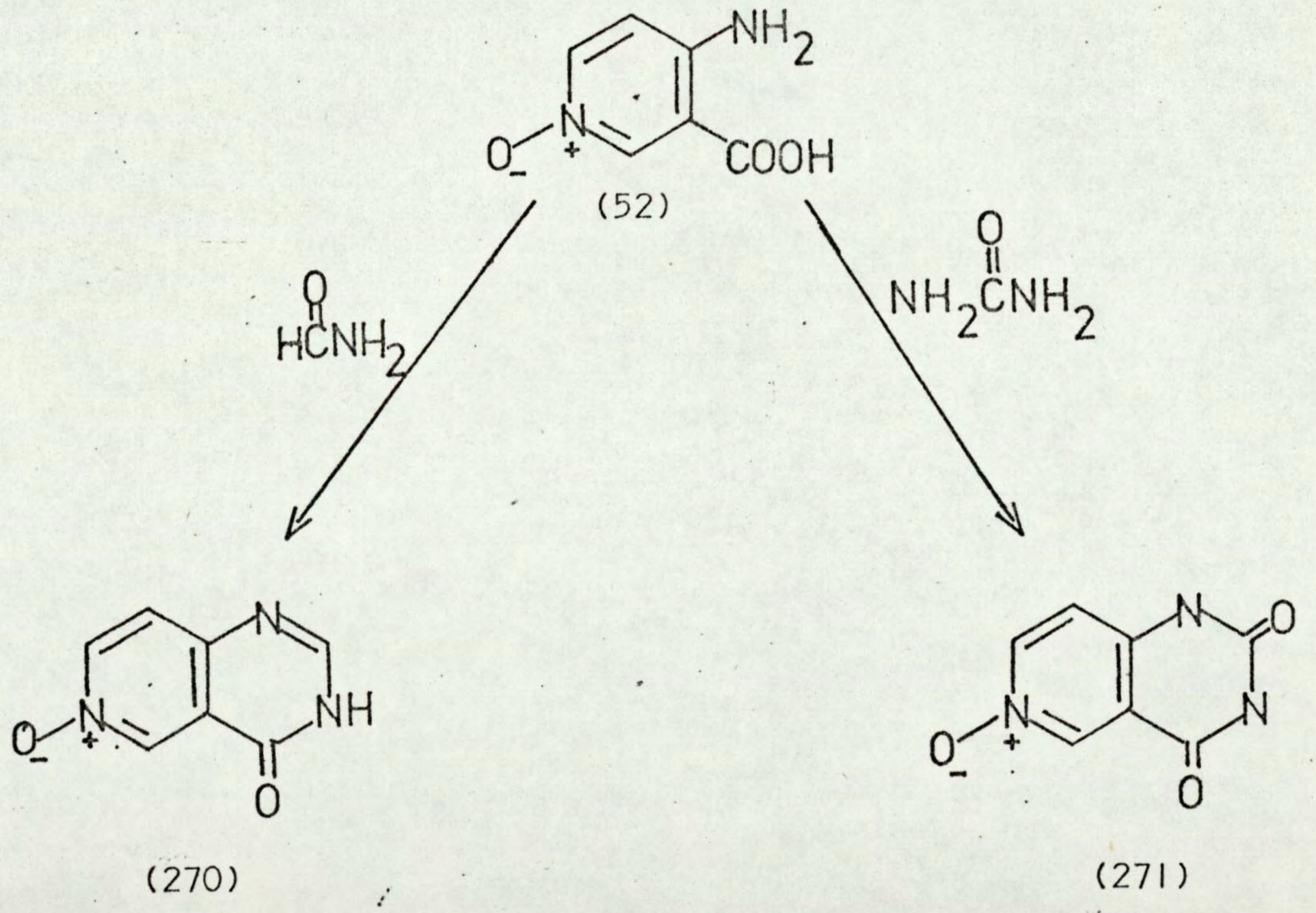
The reaction between the amino-ester (231) and urea gave a compound which was classified as the dione (269), but a pure sample could not be

isolated.[138]



(231) (269)

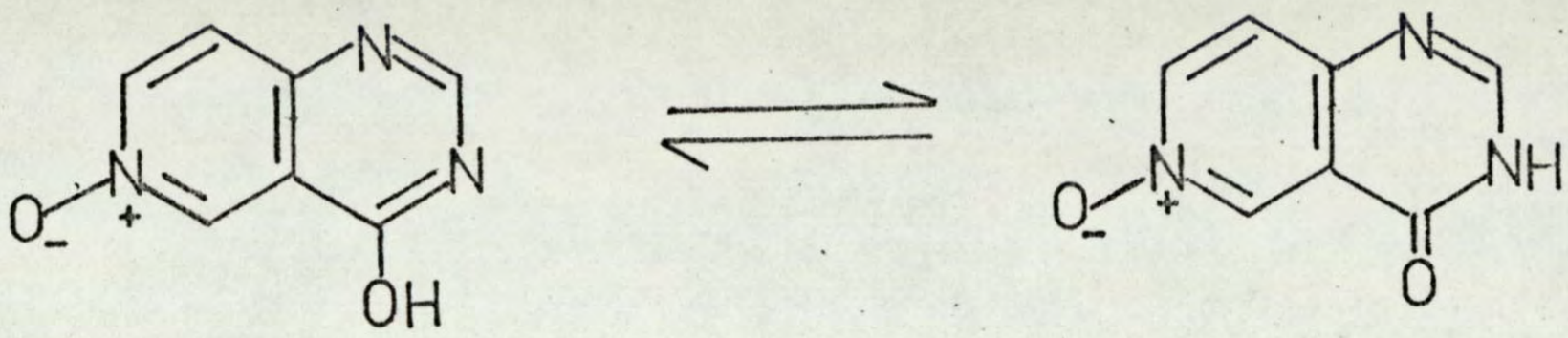
The route has now been extended to the preparation of pyrido [4,3-d] pyrimidinone 6-oxides. Fusion of the 4-aminonicotinic acid 1-oxide (52) with formamide at 170° gave pyrido [4,3-d] pyrimidine-4 (3H)-one 6-oxide (270). Replacement of formamide by urea gave pyrido [4,3-d] pyrimidin-2,4(1H,3H)-dione 6-oxide (271) under the same conditions.



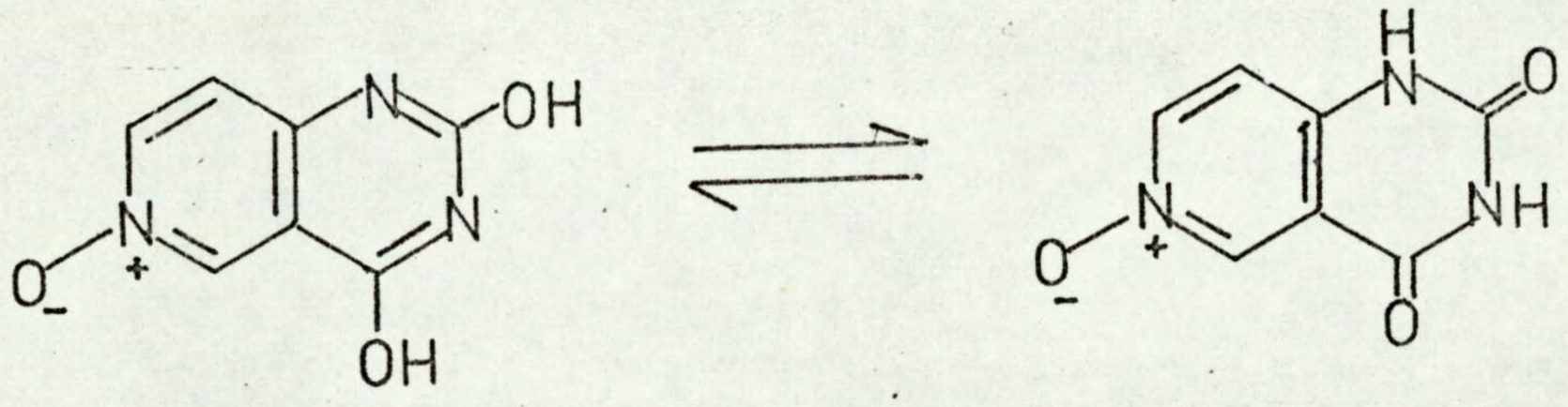
4-Aminonicotinic acid 1-oxide (52) and ethyl 4-aminonicotinate 1-oxide (193) both failed to react with formanilide under similar conditions.

The carbonyl stretching vibration in the 1680-1700cm^{-1} region of the

infrared spectrum, together with the presence of N-H vibrations, indicates that the compounds exist predominantly in the tautomeric oxo forms (270) and (271). The predomination of the oxo form has been observed in other series of pyridopyrimidines.[130]



(272) (270)



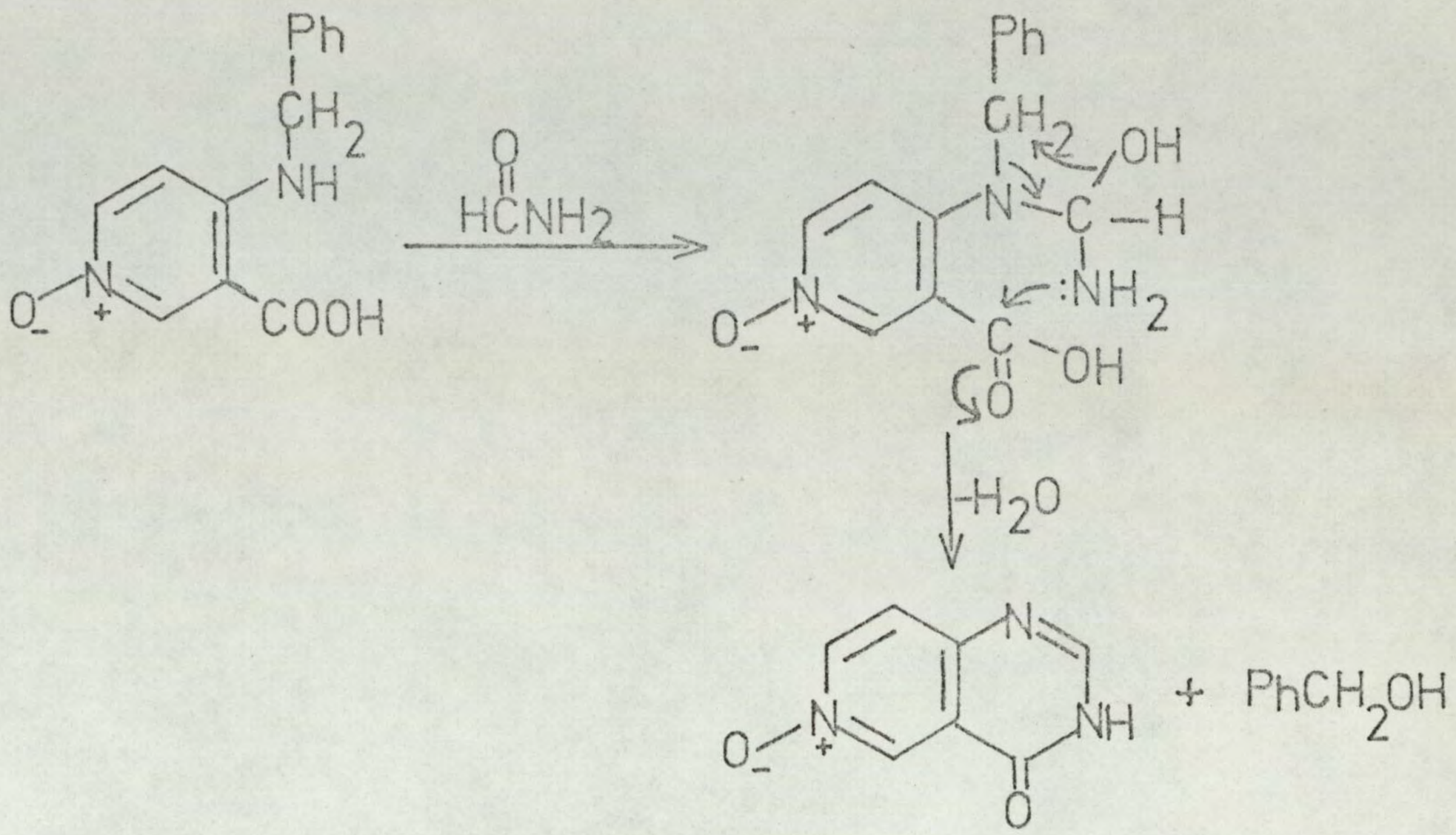
(273) (271)

The mass spectra of the pyridopyrimidinone N- oxides showed an initial loss of oxygen to give the base peak at M-16 in both cases.

4-Anilinonicotinic acid 1-oxide (65) could not be made to condense with formamide or urea on fusion at temperatures up to 250°; the failure to react is presumably due to the decreased nucleophilicity of the amine nitrogen atom.

The fusion of 4-benzylaminonicotinic acid 1-oxide (190) with formamide at 170° for 2 hours, gave a mixture of the starting material and a de-

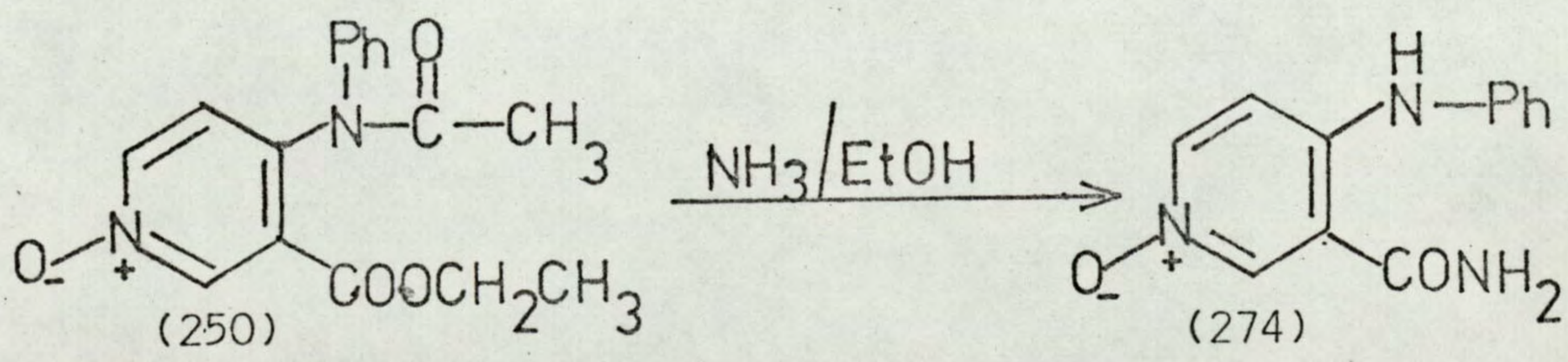
benzylated product with infrared and mass spectra identical to those of pyrido [4,3-d] pyrimidin-4(3H)-one 6-oxide (270).



3-amino-4-ethoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine (240)

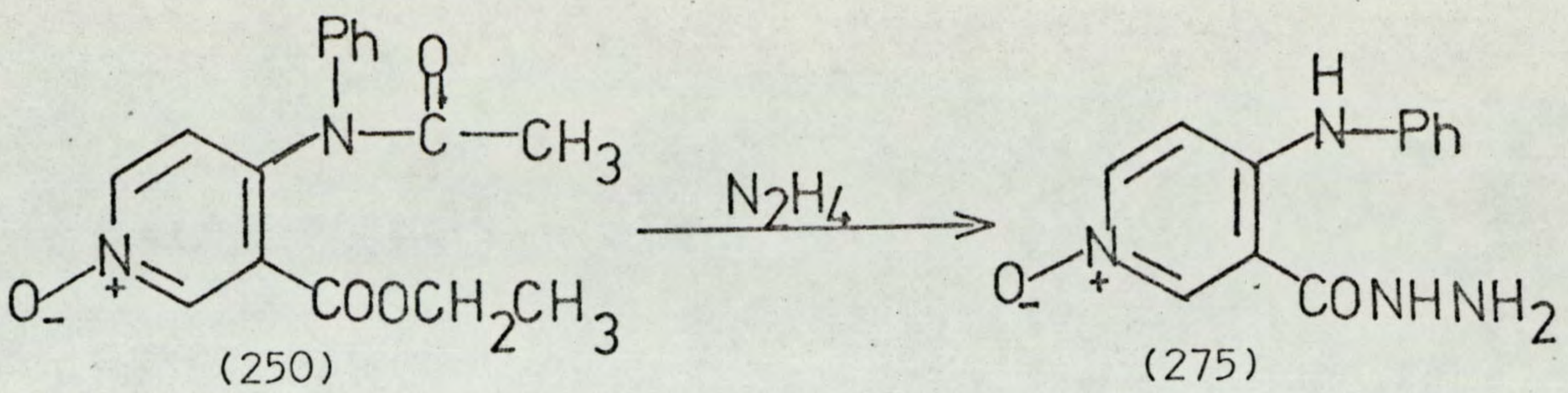
could not be made to condense with formamide; fusion at 150° for 2 hours gave unchanged starting material; fusion at 180° for 6 hours gave an intractable tar.

The reaction of 3-ethoxycarbonyl -4- (N-phenylacetamido)-pyridine 1-oxide (250), with a solution of ammonia in ethanol, under pressure in a



(250) (274)

steel bomb gave a mixture from which 4-anilinonicotinamide 1-oxide (274) was isolated. The same product was obtained by stirring the amido-ester (250) in a solution of ammonia in ethanol at room temperature for 30 days. The reaction of the amido-ester with hydrazine hydrate in ethanol at room temperature for 36 hours gave a mixture from which a small amount of a solid which was identified as 4-anilinonicotinic acid hydrazide 1-oxide (275) was isolated.

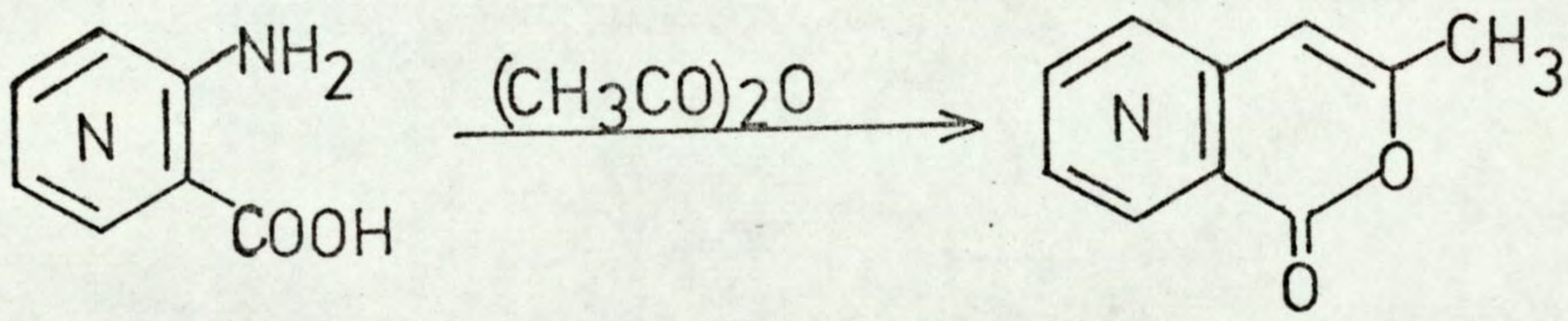


(250) (275)

3-Benzamido-4-ethoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine (241) when reacted with hydrazine hydrate in ethanol for 36 hours gave an oil from which no pure material could be isolated.

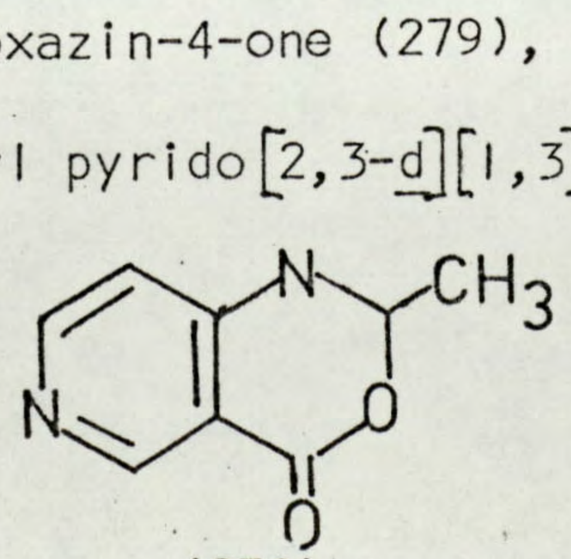
ii) Via pyrido [4,3-d] [1,3] oxazin-4-ones

Pyrido [1,3] oxazin -4-ones have proved useful intermediates in the preparation of 2- and 3- substituted pyrido pyrimidines.[130] Little and Allen[139] showed that the condensation of the appropriate aminopyridine carboxylic acids (276) with acetic anhydride afforded the corresponding 2-methylpyrido [1,3] oxazin -4-ones. (277).

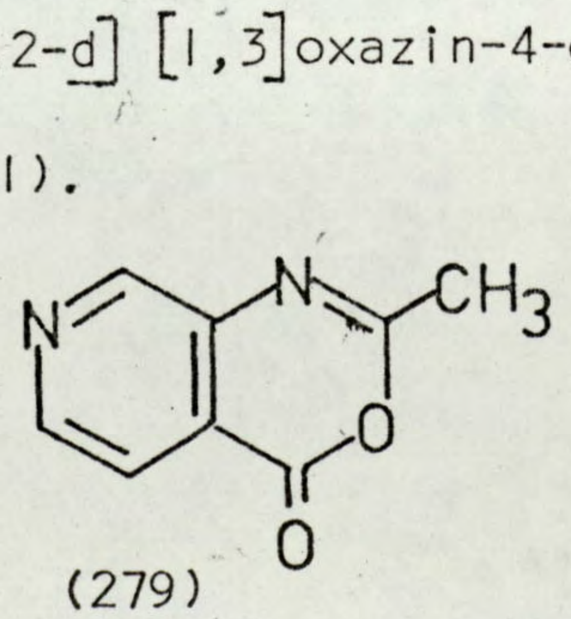


276 277

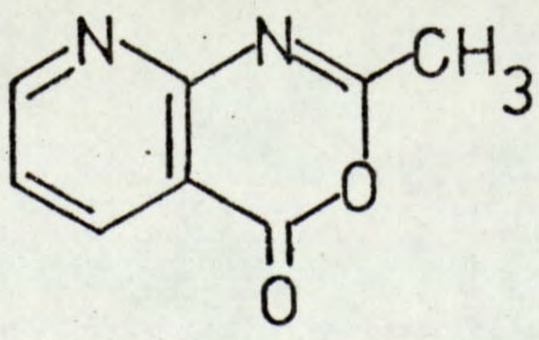
The method yielded the four 2-methylpyrido[1,3]oxazin-4-ones:- 2-methylpyrido[4,3-d][1,3]-oxazin-4-one (278), 2-methylpyrido[3,4-d] [1,3] oxazin-4-one (279), 2-methylpyrido[3,2-d] [1,3]oxazin-4-one(280), and 2-methyl pyrido[2,3-d][1,3]oxazin-4-one (281).



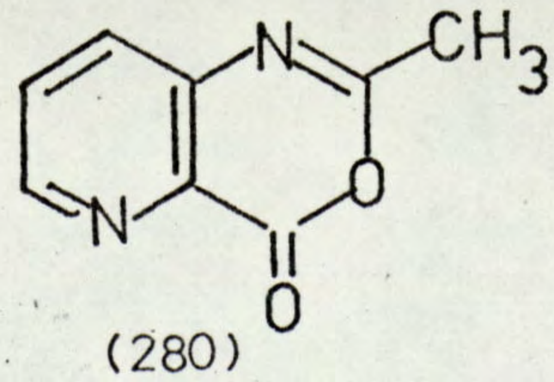
(278)



(279)



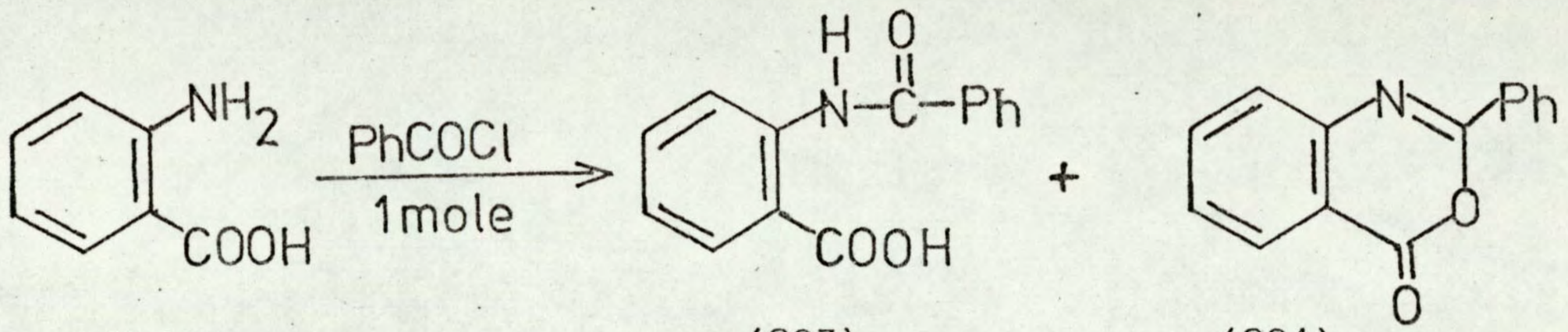
(281)



(280)

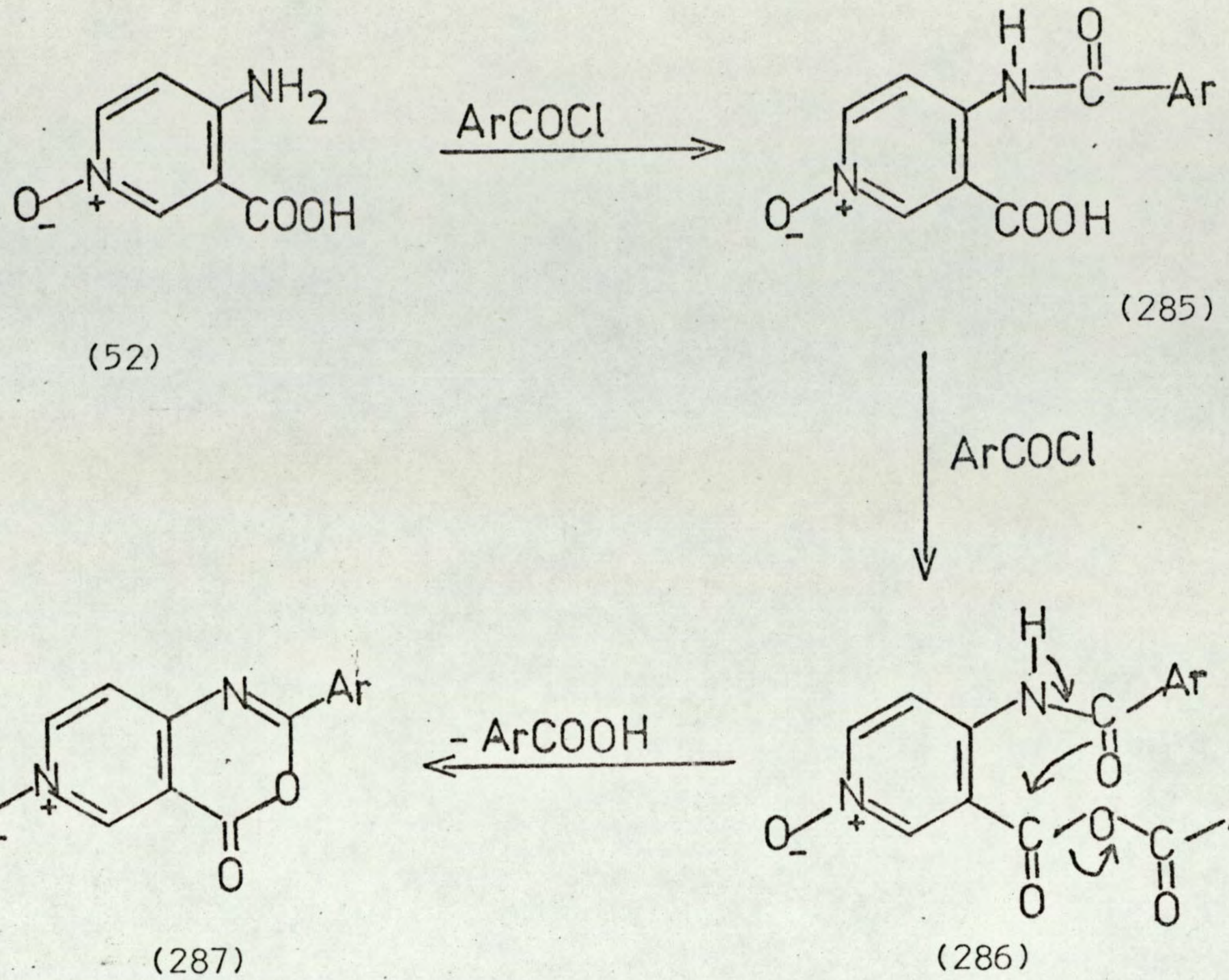
The scope of the reaction has been extended to include the 2-aryl derivatives of pyrido[3,2-d][1,3]oxazin-4-one, and pyrido[3,4-d][1,3]-oxazin-4-one.[130] The reaction of 4-aminonicotinic acid with benzoyl chloride failed to give the expected 2-phenylpyrido[4,3-d][1,3] oxazin-4-one.[125]

In their investigation into the mechanism of the formation of the benzoxazine (284) from anthranilic acid (282) and benzoyl chloride, Bain and Smalley isolated N-benzoylanthranilic acid (283) and the benzoxazine (284) when only 1 mole of benzoyl chloride was used.[140]



(282) (283) (284)

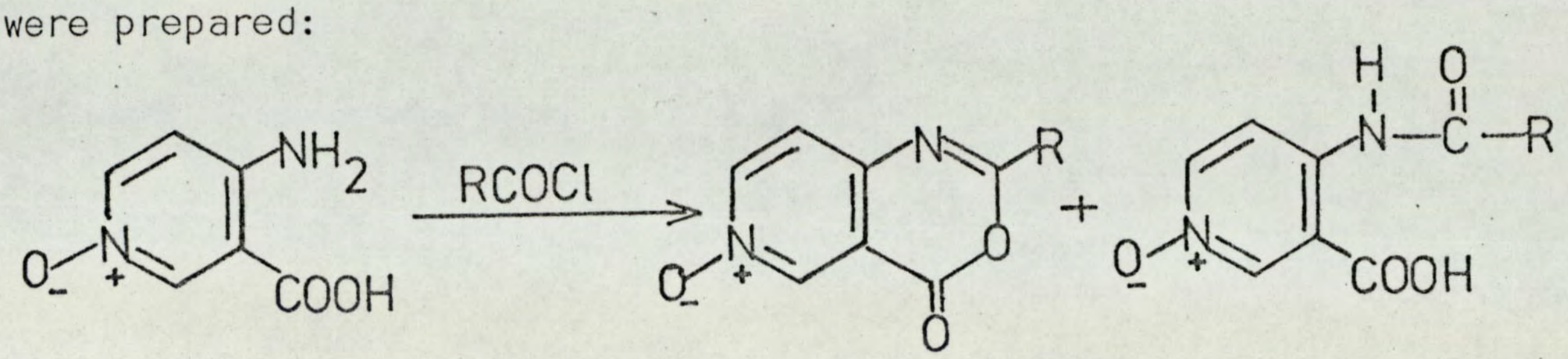
When 2 moles of benzoyl chloride were used, the benzoxazine (284) was formed in 95% yield. The mechanism for the above reaction and that postulated for the formation of 2-phenylpyrido[3,4-d][1,3]oxazin-4-one from 3-aminoisonicotinic acid and benzoyl chloride,[141] seemed most likely to be also applicable in the formation of 2-aryl substituted pyrido [4,3-d][1,3]oxazin-4-one 6-oxides (287) from 4-aminonicotinic acid 1-oxide (52) and aroyl halides. The route was therefore investigated.



By analogy with the benzoxazines, it can be assumed that the first mole of acid chloride reacts with the amino group to give the amido-acid (285). The second mole of acid chloride will then undergo a normal acid chloride reaction[142] with a carboxylic acid group to give the unsymmetrical anhydride (286), which then undergoes an intramolecular nucleophilic displacement reaction to give the oxazinone (287).

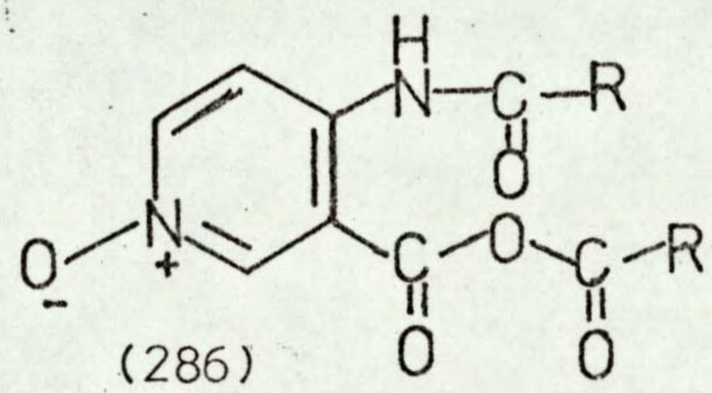
Less forcing conditions than those employed for the preparation of 2-arylbenzoxazines and 2-phenylpyrido[3,4-d][1,3]oxazin-4-ones were used in the synthesis of 2-arylpyrido[4,3-d][1,3]oxazin-4-ones 6-oxides. Dropwise addition of two moles of the appropriate acid chloride to a suspension of 1 mole of 4-aminonicotinic acid 1-oxide (52) in pyridine, and extraction of the resultant slurry with boiling benzene after stirring for fifteen minutes at room temperature, gave the required oxazinones. The material

which was insoluble in benzene was boiled with ethanol and acetic acid, and the insoluble amido-acids collected. The following pyrido-oxazinones were prepared:



(57) (287) (285)

It can be seen from the table (P. 59) that better yields of the oxazinones were obtained from compounds where the substituent R in the intermediate (286) is electron releasing towards the amide carbonyl, and



(286)

the lowest yields were obtained from the compounds where R is electron withdrawing.

The infrared spectra of the 2-arylpyrido[4,3-d][1,3]oxazin-4-one 6-oxides (287) all showed the expected carbonyl stretching vibration of an unsaturated δ-lactone in the 1760-1780cm^{-1} region of the spectrum. An analytically pure sample of the product from the reaction of 4-nitrobenzoyl chloride and 4-aminonicotinic acid 1-oxide (52) could not be obtained, although the infrared spectrum indicated the presence of the pyrido-oxazinone system.

The reaction of acetic anhydride with 4-aminonicotinic acid 1-oxide under the conditions employed above, and under conditions more forcing than those used by Little and Allen,[139] did not give the expected 2-methylpyrido[4,3-d][1,3]oxazin-4-one 6-oxide. 4-Acetamidonicotinic acid 1-oxide (288) was obtained as the only product in 93%yield.

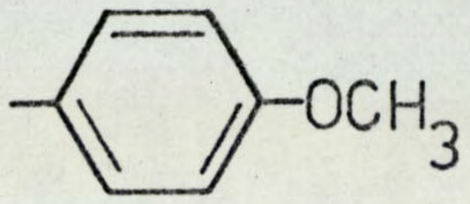
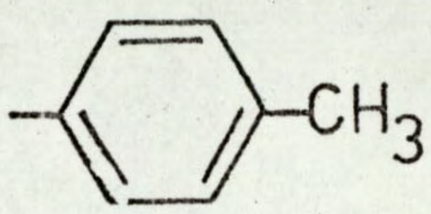
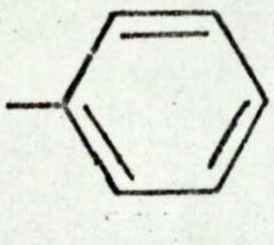
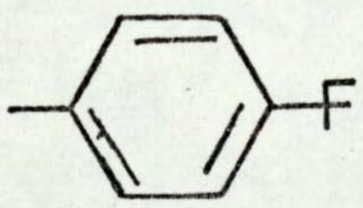
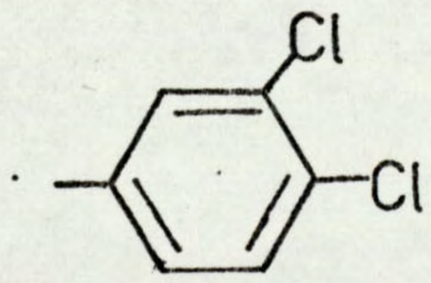
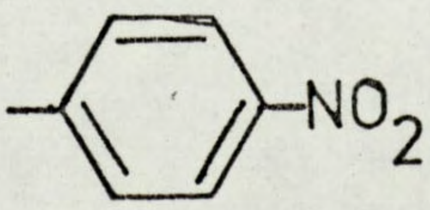
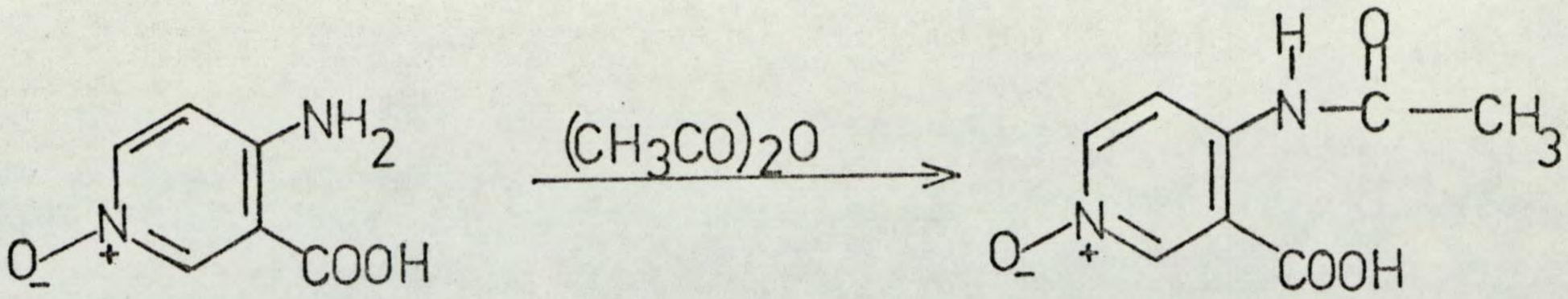
Substituent R	Yield % Oxazinone (287)	Amido-acid (285)
	56	21
	35	23
	32	30
	31	30
	19.9	43.8
	-	-

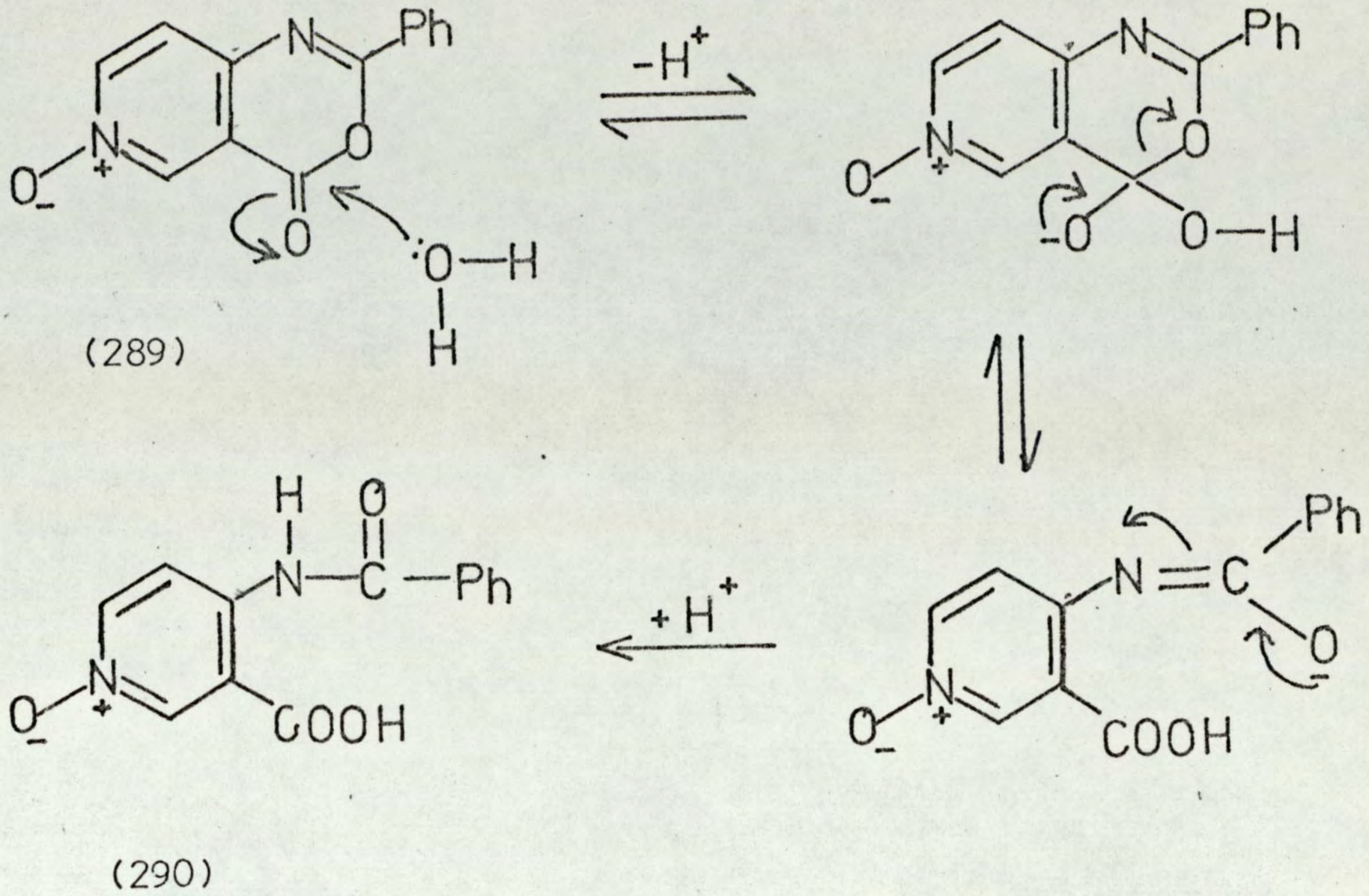
TABLE I



(52) (288)

Replacement of acetic anhydride by acetyl chloride resulted in a vigorous reaction and the production of an intractable tar. The addition of acetyl chloride to a suspension of the amino-acid N-oxide (52) in pyridine which had been cooled to -80^{o}, resulted in the formation of a yellow solid. After allowing the mixture to come to room temperature however, a tar was formed, from which the required 2-methylpyrido[4,3-d][1,3]oxazin-4-one 6-oxide could not be isolated. An attempt to extract the suspected oxazinone from the cooled reaction mixture was unsuccessful, and an attempt to react any oxazinone 'in situ' with aniline was also unsuccessful.

2-Methylpyrido-oxazinones have been shown to be less stable and more susceptible to hydrolysis than the corresponding 2-aryl pyrido-oxazinones.[141] The 2-arylpyrido[4,3-d][1,3]-oxazin-4-one 6-oxides (287) were recovered unchanged from water at room temperature after 24 hours, and showed no indication of hydrolysis after exposure to the atmosphere for 3 days. An infrared spectrum of 2-phenylpyrido[4,3-d][1,3]oxazin-4-one 6-oxide (289) after several weeks exposure to the atmosphere showed the emergence of a broad peak at $1680cm^{-1}$, due to the amide and carboxylic acid stretching vibrations of the hydrolysed product (290). The probable mechanism for the hydrolysis of 2-phenylpyrido[4,3-d][1,3]oxazin--4-one 6-oxide (289) to the amido-acid (290) is as follows:

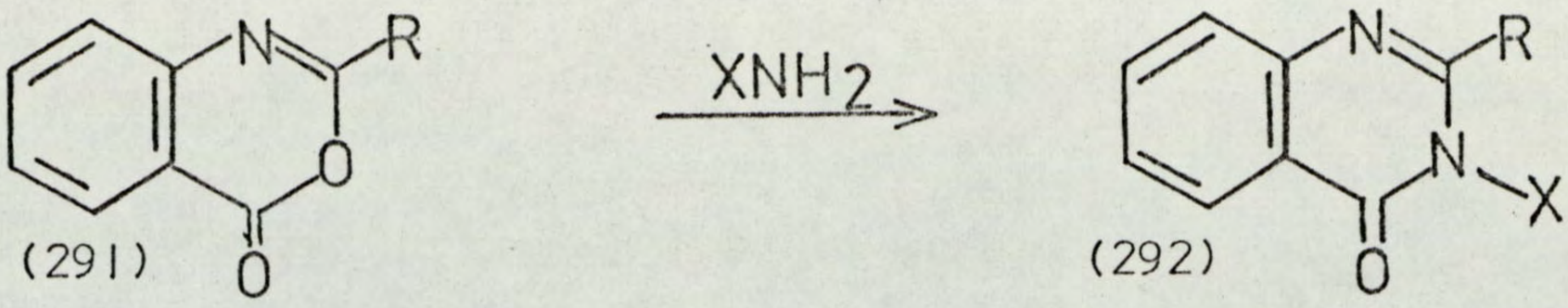


(289)

(290)

The yields of the 4-amido-acid 1-oxides (285) isolated from the reaction of 4-aminonicotinic acid 1-oxide (52) with the appropriate aryl chloride are summarised in table 1. The amido-acids were practically insoluble in all organic solvents, and were recrystallised with difficulty from boiling acetic acid. The infrared spectra of the amido-acids all showed a broad carbonyl stretching vibration centred about 1680cm^{-1}, due to the amide and carboxylic acid carbonyl groups, and a peak at 3150cm^{-1} due to a bonded N-H stretching vibration.

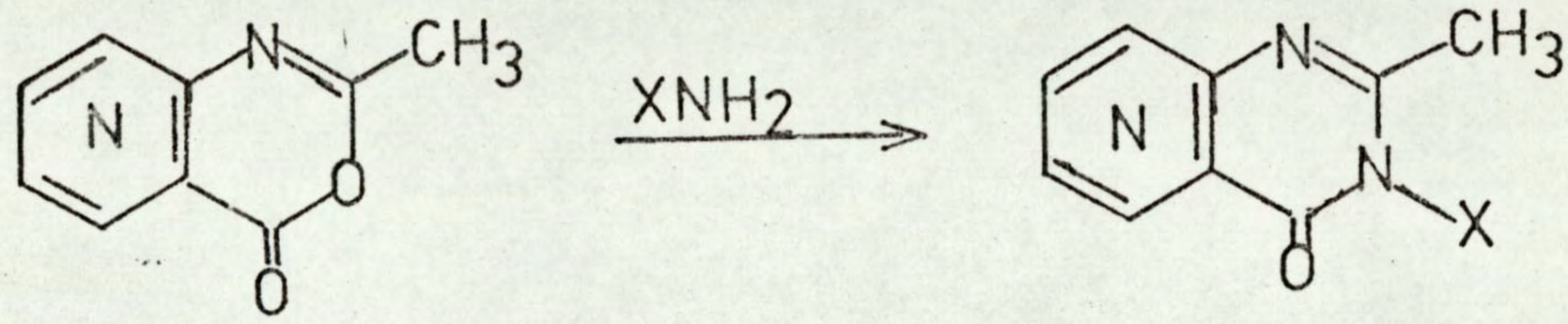
Benz-1,3-oxazin-4-ones (291) react exothermally with ammonia in aqueous media to give high yields, of quinazolones (292).[143-145] A wide variety of amines have been successfully used, including aliphatic, aromatic, heterocyclic amines and hydrazine.



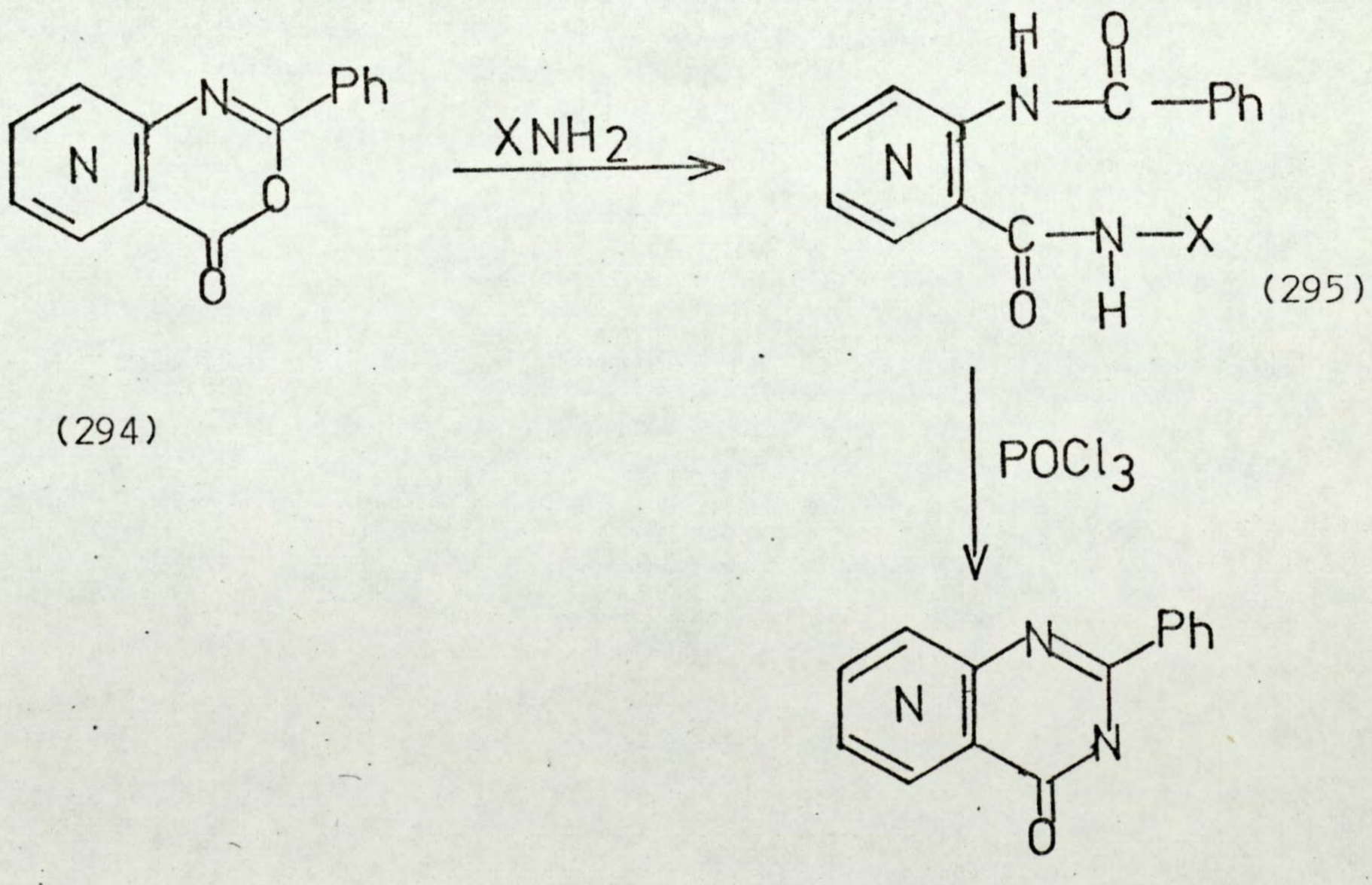
(291) (292)

This route has been extended to the synthesis of pyridopyrimidines.[130]

The 2-methyl substituted derivatives of pyrido[2,3-d][1,3]oxazin-4-one (281) pyrido[3,2-d][1,3]oxazin-4-one (280), pyrido[3,4-d][1,3]oxazin-4-



(277) (293)

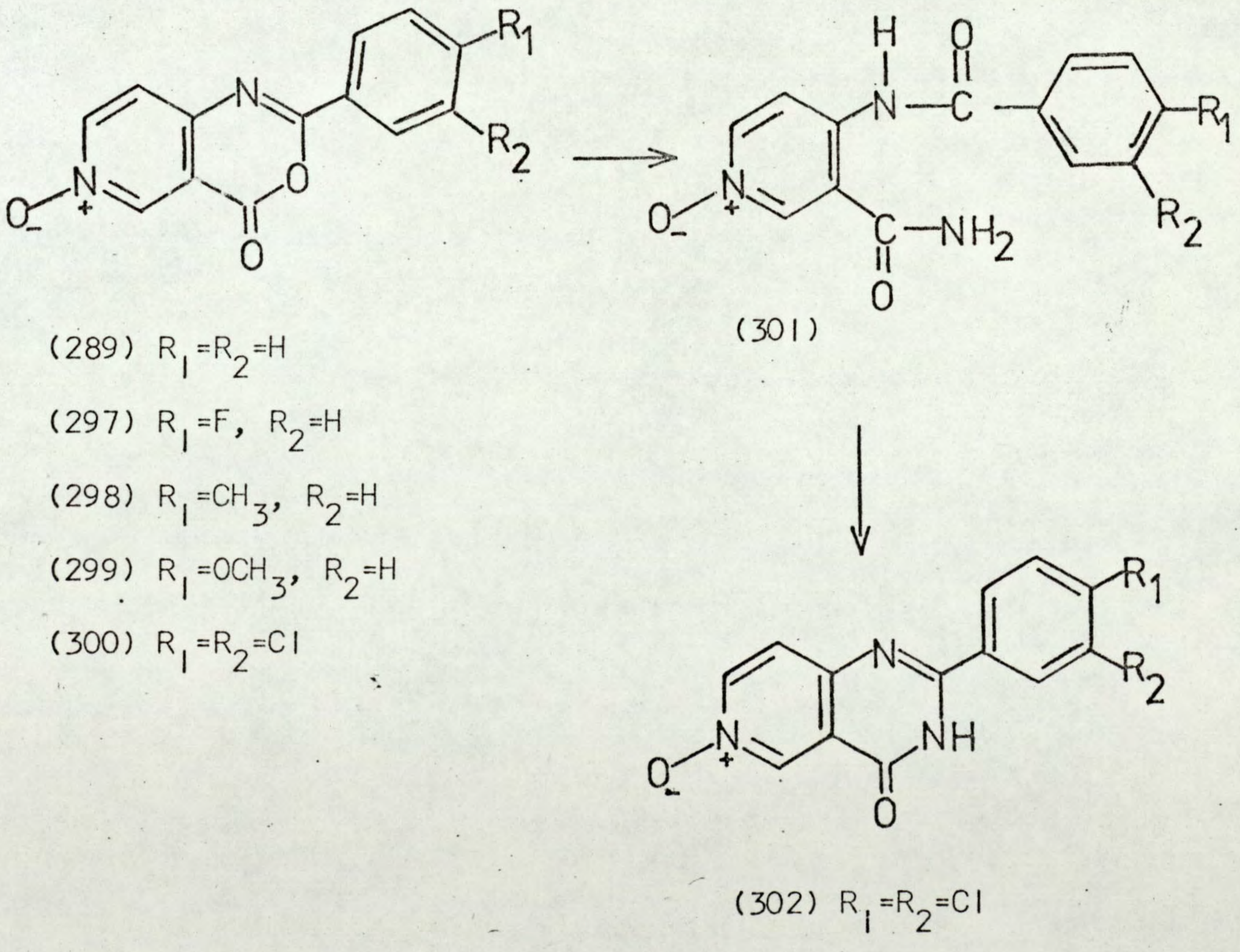


(294) (295) (296)

one (279), and pyrido[4,3-d][1,3]oxazin-4-one (278), all gave the corresponding 2-methyl-3-substituted pyridopyrimidines (293) on reaction with suitable amine derivatives. 2-Phenylpyrido[3,2-d][1,3]oxazin-4-ones and 2-phenylpyrido[3,4-d][1,3]oxazin-4-ones both gave the intermediate diamides (295) as products. The diamides were cyclised to the pyridopyrimidines (296) by dissolution in phosphoryl chloride or by heat.

This method of synthesis has now been applied to the pyrido[4,3-d]pyrimidine 6-oxide system.

The 2-arylpyrido[4,3-d][1,3]oxazin-4-one-6-oxides on stirring with aqueous ammonia at room temperature for up to nine days, gave the diamides



(289) $R_1=R_2=H$

(297) $R_1=F$, $R_2=H$

(298) $R_1=CH_3$, $R_2=H$

(299) $R_1=OCH_3$, $R_2=H$

(300) $R_1=R_2=Cl$

(301)

(302) $R_1=R_2=Cl$

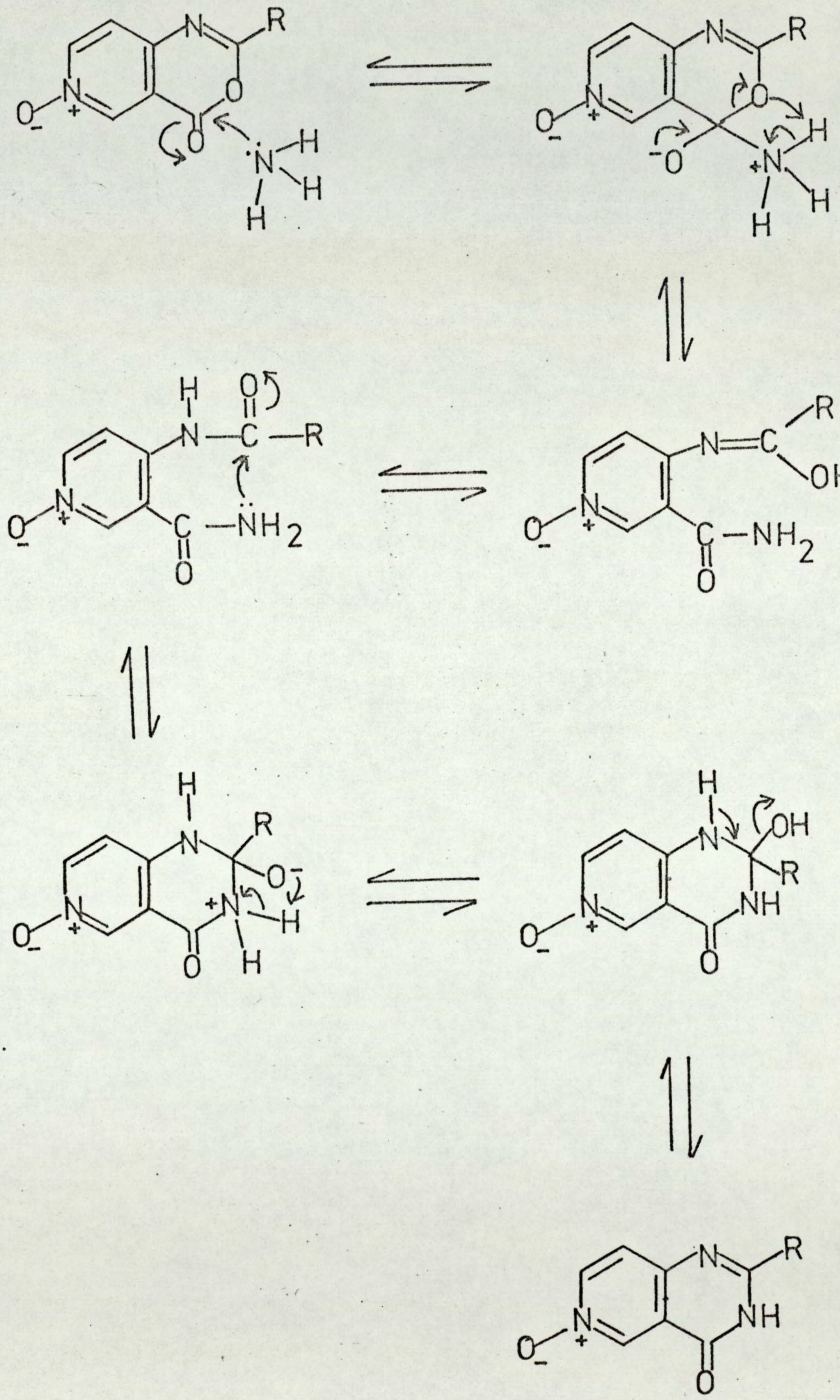
(301); 2-(3,4-dichlorophenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (300), however, gave the required pyridopyrimidine (302). The diamides were

insoluble in almost all organic solvents and were recrystallised from boiling acetic acid. Attempted thermal cyclisation was unsuccessful; heating the diamides at 240^{o} for up to 10 hours gave unchanged starting material, heating at higher temperatures caused decomposition of the product. The preparation of pyrido pyrimidines from oxazines has been shown to proceed through the diamides, and the most probable mechanism is shown on P. 65.

The initial step is the nucleophilic attack by the lone pair of electrons on the nitrogen atom of the amine at the exocyclic C=O bond of the pyrido-oxazine.

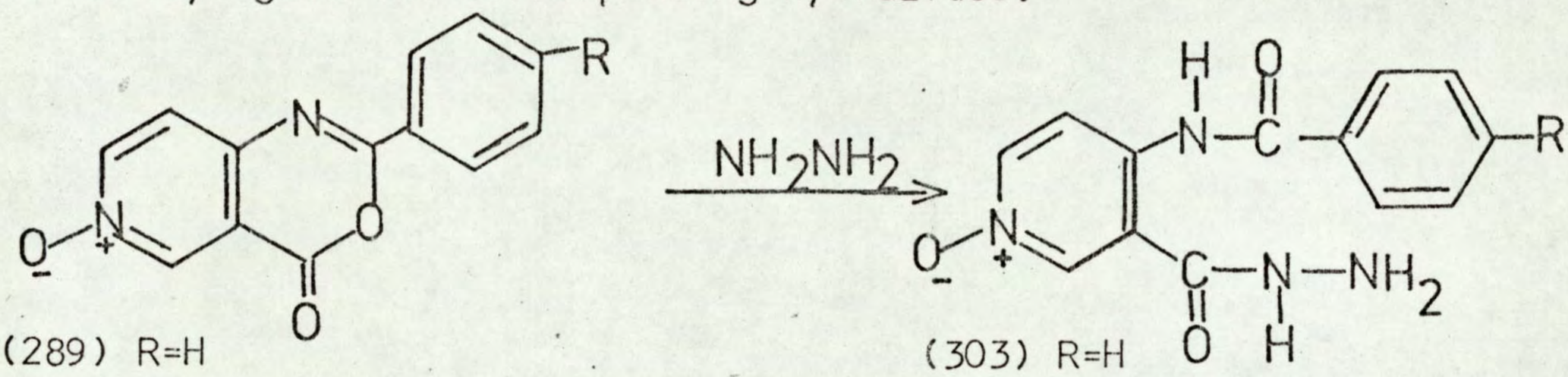
Previous workers have proposed the overall rate determining step to be the attack of the nitrogen atom of the 3-amido group on the carbonyl carbon of the 4-amido group. In the pyrido[3,4-d]pyrimidine series, the reaction of 2,6,8-trimethylpyrido[3,4-d][1,3]oxazin-4-one with a series of amines demonstrated the relationship of the rate of reaction with the basic strength of the amine.[141] Ammonia yielded the corresponding pyrido-pyrimidine in 12 hours at room temperature, while with less basic amines, longer reaction times were required. In conjunction with the nucleophilicity of the amine, the electrophilicity of the carbonyl group should also be a factor in the rate determining step.

It can be seen from the reactions of aqueous ammonia with the series of 2-arylpyrido[4,3-d][1,3]oxazin-4-one 6-oxides (287) above, that pyrido-pyrimidine formation occurred only in the use of 2-(3,4-dichlorophenyl) pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (300), which had the greatest electron-withdrawal away from the 4-amido carbonyl group.



The infrared spectra of the diamides all showed absorptions in the 3300cm^{-1} and 3100cm^{-1} region due to the symmetrical and assymmetrical NH stretching vibrations, and absorptions at 1685cm^{-1} and 1675cm^{-1} due to the amide carbonyl stretching vibrations. The infrared spectrum of 2-(3,4-dichlorophenyl)pyrido[4,3-d]pyrimidin-4(3H)-one 6-oxide (302) had no peaks in the region of 3300cm^{-1}, and the carbonyl absorption occurred at 1690cm^{-1}. The mass spectrum of the pyridopyrimidine (302) did not contain the fragment at M-33 which occurred in the breakdown of the diamides.

The reaction of 2-phenyl- (289) and 2-(4-fluorophenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxides (297) with hydrazine hydrate at room temperature for 3 days gave the corresponding hydrazides.



(289) R=H

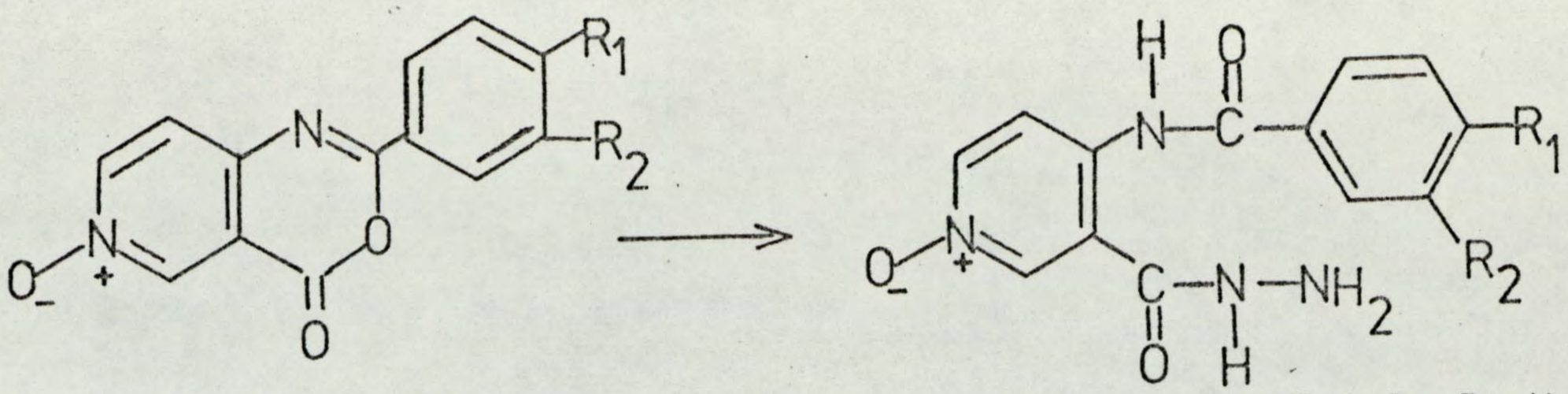
(297) R=F

(303) R=H

(304) R=F

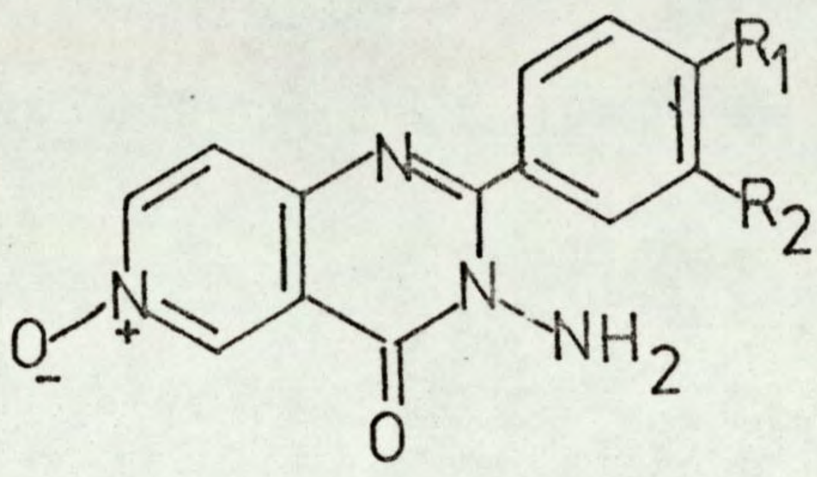
Both hydrazides showed two peaks at 1680cm^{-1} and 1655cm^{-1} due to the amide carbonyl groups in their infrared spectra.

The reaction between the 2-phenyl oxazine (289) and hydrazine was repeated with a longer reaction time, 9 days, and the required 3-amino-2-phenylpyrido[4,3-d]pyrimidin-4(3H)-one 6-oxide (308) was produced. The reaction was repeated for other 2-aryl substituted pyrido-oxazines and the corresponding 3-aminopyridopyrimidines were isolated.



(289) $R_1=R_2=H$
(298) $R_1=CH_3$, $R_2=H$
(299) $R_1=OCH_3$, $R_2=H$
(300) $R_1=R_2=Cl$

(303) $R_1=R_2=H$
(305) $R_1=CH_3$, $R_2=H$
(306) $R_1=OCH_3$, $R_2=H$
(307) $R_1=R_2=Cl$



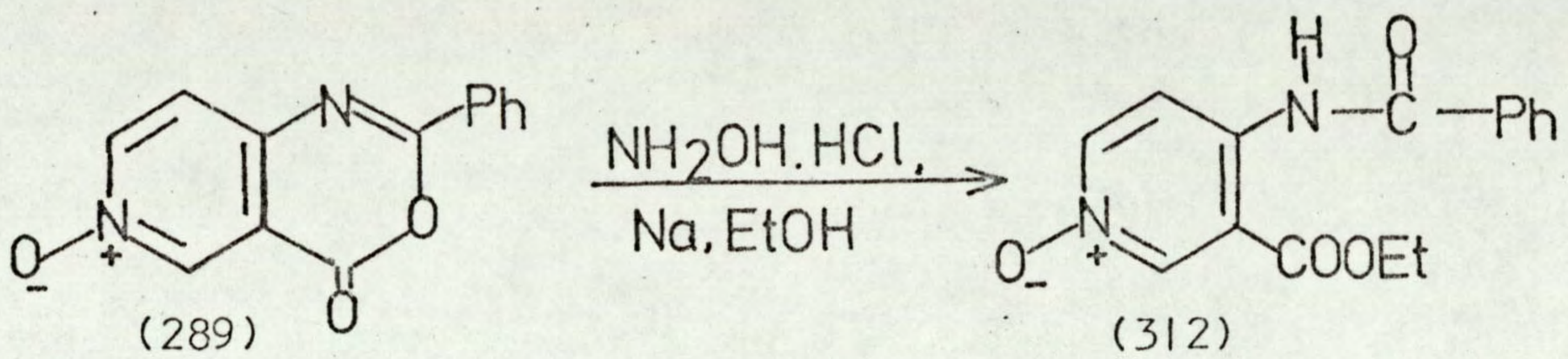
(308) $R_1=R_2=H$
(309) $R_1=CH_3$, $R_2=H$
(310) $R_1=OCH_3$, $R_2=H$
(311) $R_1=R_2=Cl$

The infrared spectra of the pyridopyrimidines all had a sharp peak at 1690cm^{-1} due to the carbonyl stretching vibrations. The occurrence of the carbonyl peak in the pyridopyrimidines at a higher wavenumber than the corresponding diamides has also been noted in other pyridopyrimidine systems.

The relationship between the availability of the lone pair of electrons on the nitrogen atom of the 3-amido group and the rate of ring closure in the rate determining stage, has previously been demonstrated. It seems probable that,although hydrazine(pKb 5.52)is a weaker base than aqueous ammonia (pKb 4.74), ring closure occurred in the hydrazine series because of the partial solubility of the intermediate hydrazides in the reaction solvent, alcohol, whereas in the ammonia series, the intermediate diamides were almost totally insoluble in the reaction solution and were precipitated

on formation. Evaporation of the filtrate from the preparation of 4-benzamidonicotinic acid hydrazide 1-oxide (303) resulted in the recovery of 15% of the hydrazide; no material was recovered by evaporation of the filtrate from the corresponding diamide preparation.

The reaction between the 2-phenyloxazinone (289) and hydroxylamine gave ethyl 4-benzamidonicotinate 1-oxide (312) and not the expected 3-hydroxypyridopyrimidine. The reaction presumably occurs by attack of ethoxide ion on the oxazinone system; the ethoxide ion was probably present

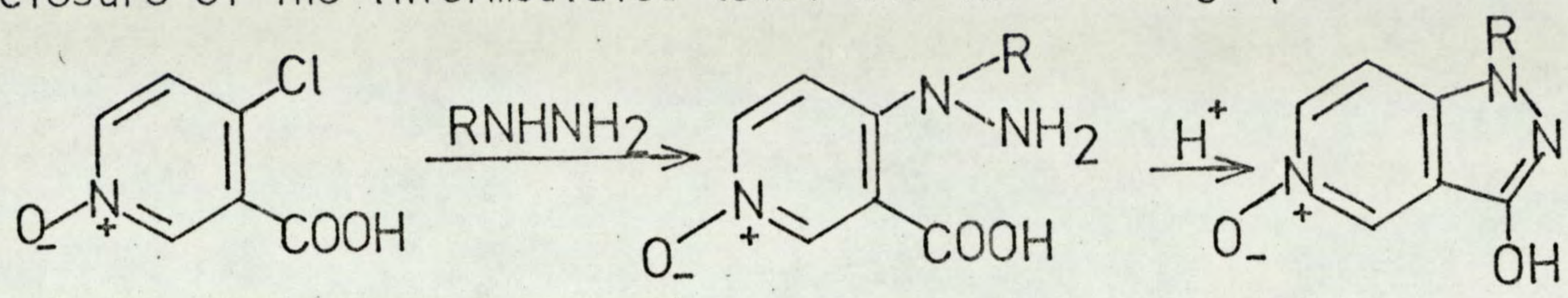


(289) (312)

due to incomplete reaction during the preparation of the hydroxylamine by the reaction of hydroxylamine hydrochloride with sodium in ethanol.

b) Pyrazolo-Pyridines.

Badger and Rao[45] reported the preparation of 3-hydroxy-1-methyl-pyrazolo[4,3-c]pyridine 5-oxide (102) and 3-hydroxy-1-phenylpyrazolo[4,3-c] pyridine 5-oxide (103) by a nucleophilic substitution reaction on 4-chloro-nicotinic acid 1-oxide (48) using the appropriate hydrazine, and ring closure of the intermediates (313) and (314) using hydrochloric acid.



(48)

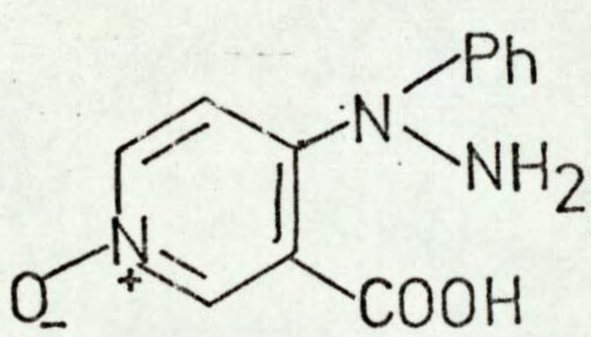
(313) R=CH_3

(314) R=Ph

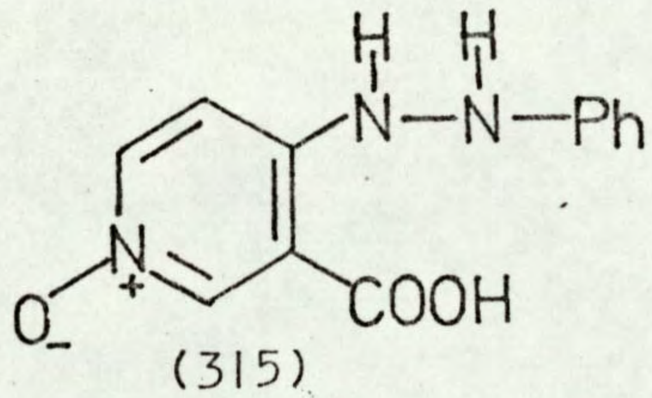
(102) R=CH_3

(103) R=Ph

The intermediate from the phenylhydrazine reaction was assigned the structure (314) rather than the expected phenylhydrazino acid (315) on



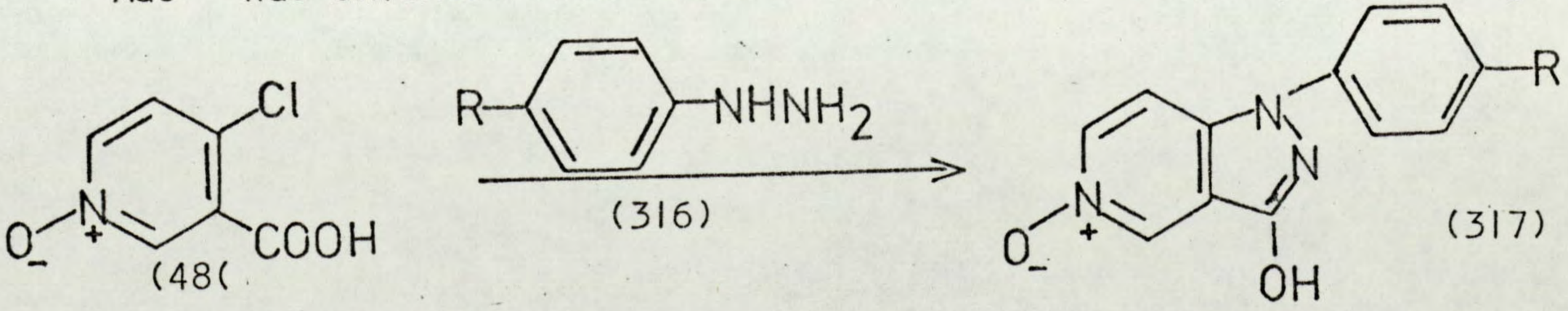
(314)



(315)

the evidence of the infrared spectrum, which was reported to exhibit two bands characteristic of a primary amino group, and on the evidence of a positive Liebermann reaction, although this reaction is normally characteristic of secondary amines.

Rao[77] has extended this route to other 1-aryl-3-hydroxypyrazolo[4,3-c] pyridine 5-oxides (317).



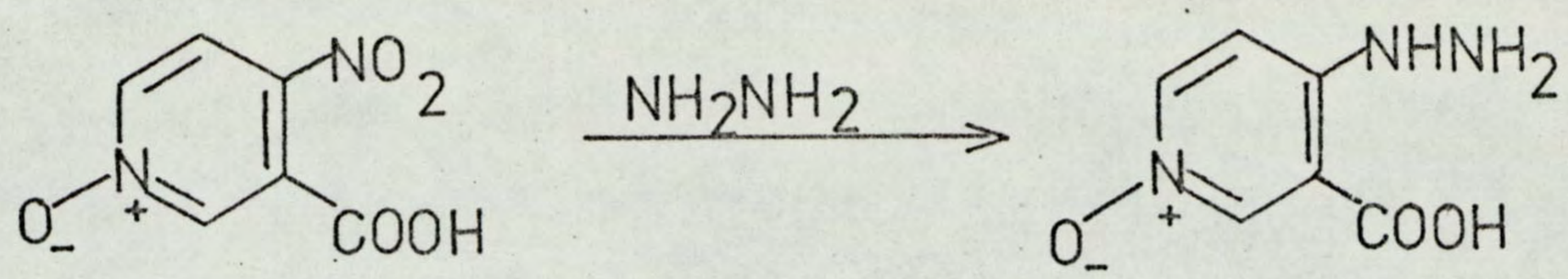
(48(

(316)

(317)

The substitution of 4-nitronicotinic acid 1-oxide (57) by substituted hydrazines has not been reported, although Taylor and Driscoll[44] obtained

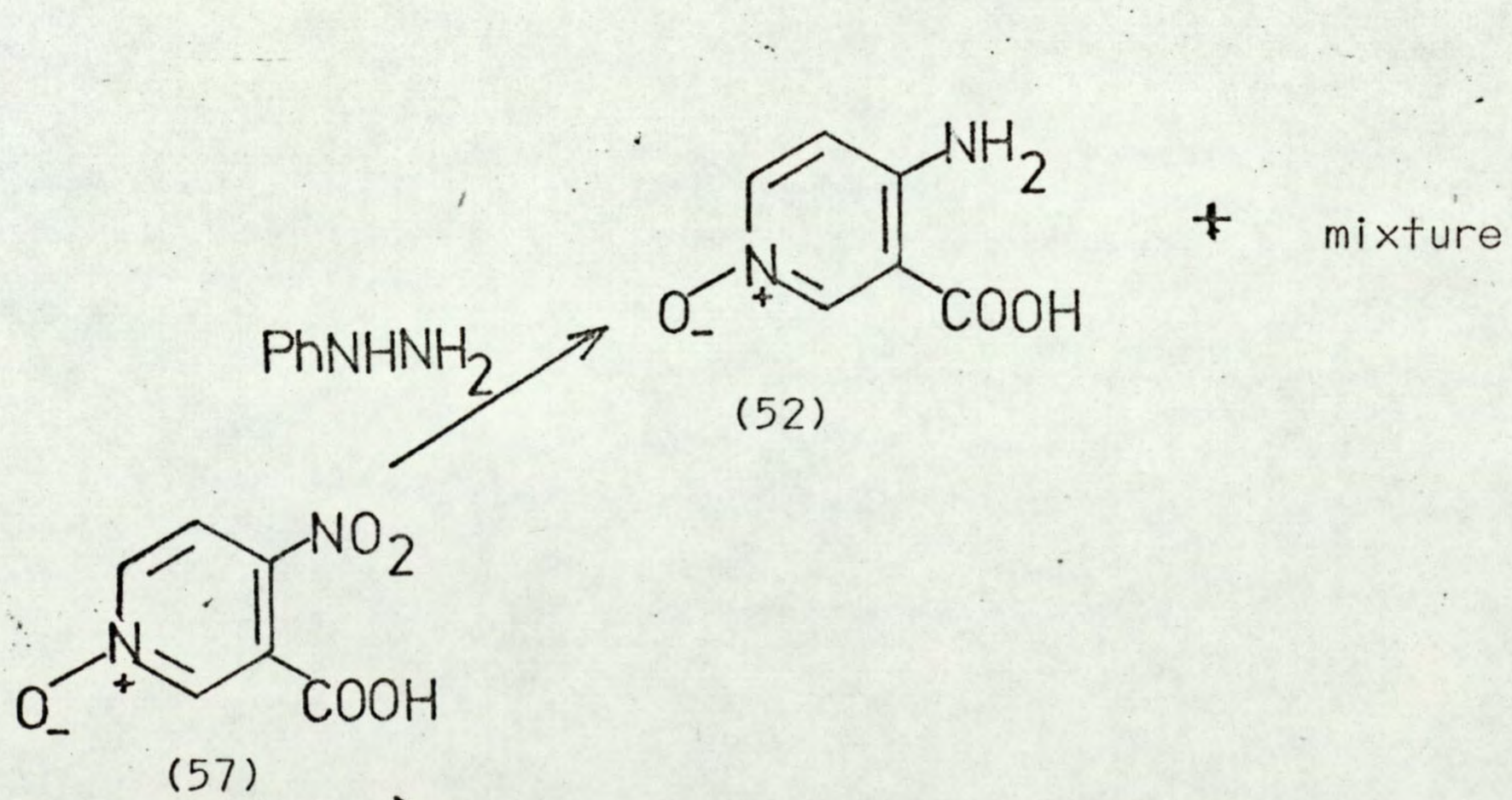
4-hydrazinonicotinic acid 1-oxide (64) in poor yield from the 4-nitro acid (57) and hydrazine.



(57) (64)

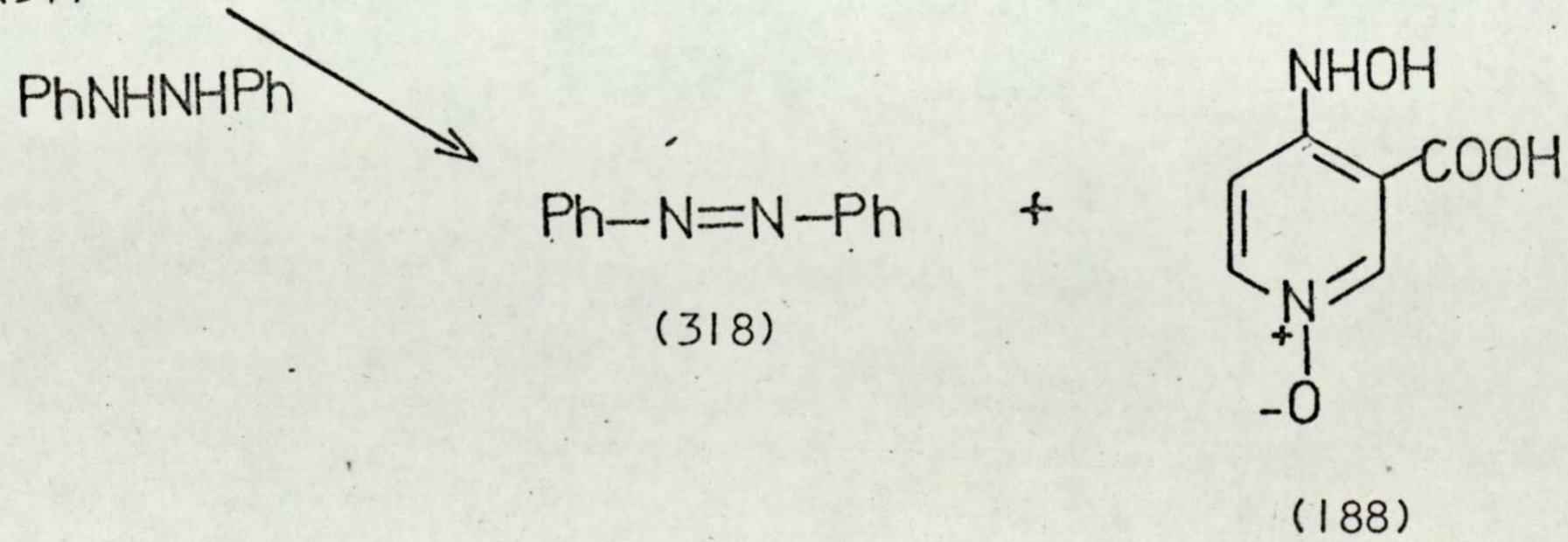
The use of 4-nitronicotinic acid 1-oxide (57) as a precursor in the preparation of pyrazolopyridines has now been investigated.

The reaction of the 4-nitro acid (57) with phenylhydrazine under the conditions employed by Badger and Rao,[45] gave a mixture from which the required substitution product was not obtained. Spectroscopic evidence indicated one of the components to be 4-aminonicotinic acid 1-oxide (52) and it seems probable that reduction had occurred rather than substitution.



(52) + mixture

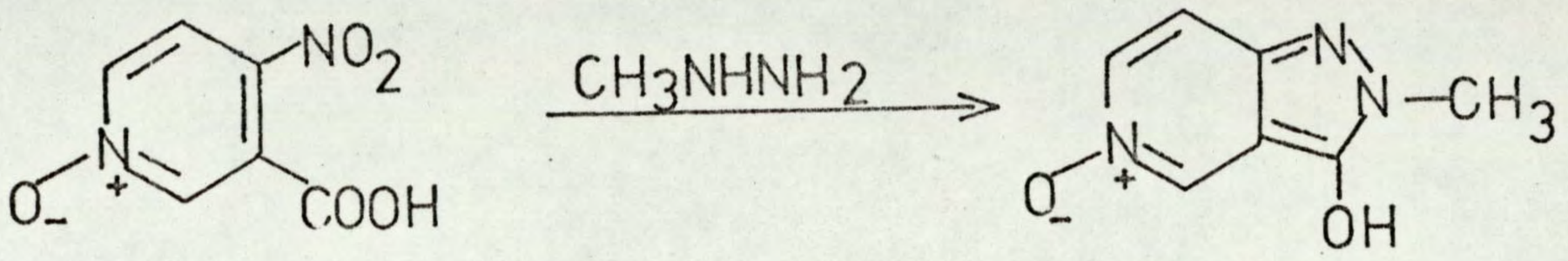
(57)



(318) (188)

Replacement of phenylhydrazine with diphenylhydrazine gave azobenzene (318) and a mixture from which the required substitution product was not obtained, although a small amount of 4-hydroxylaminonicotinic acid 1-oxide (188) was isolated.

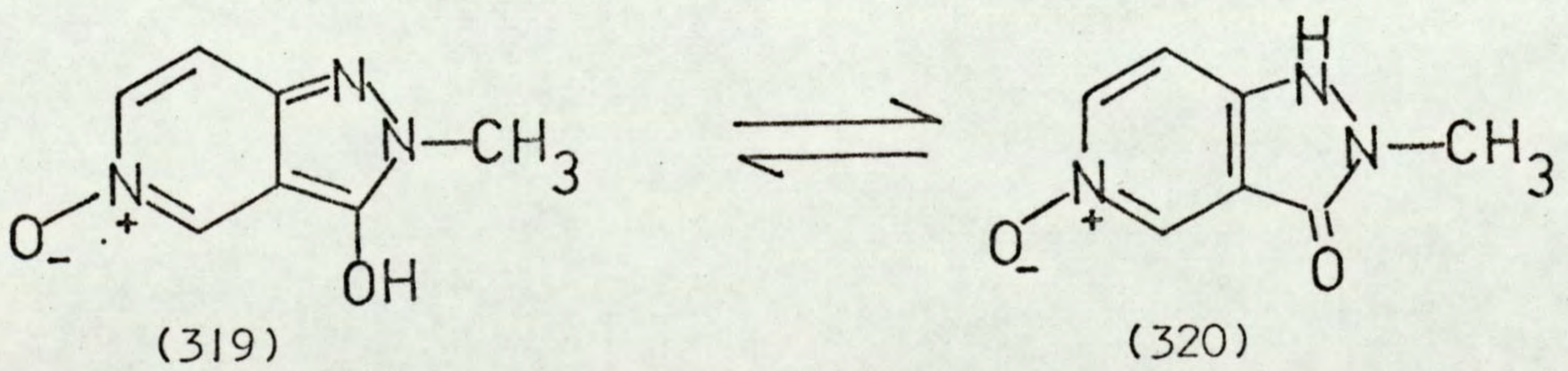
The reaction of the 4-nitro acid (57) with methylhydrazine gave a product which has been assigned as 3-hydroxy-2-methylpyrazolo[4,3-c] pyridine 5-oxide (319). The product had a melting point of 241.5-243°, and



(57) (319)

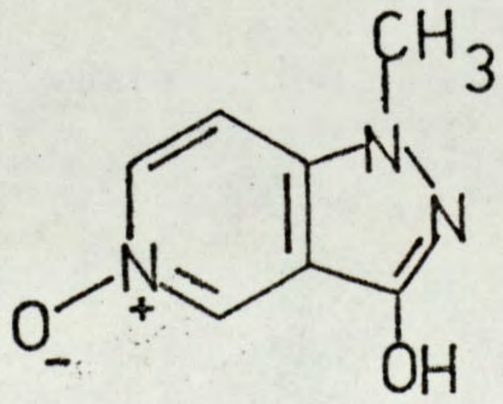
U.V. maxima at 267nm. and 313nm.; the product obtained by Badger and Rao[45] from the reaction of 4-chloronicotinic acid 1-oxide (48) and methylhydrazine had a melting point of 236-238° and u.v. maxima at 265nm. and 321nm.

The presence of a rather weak absorption in the carbonyl region of the infrared spectrum of the product (319) indicates, in agreement with the observations of Badger and Rao,[45] that the lactim tautomer predominates.

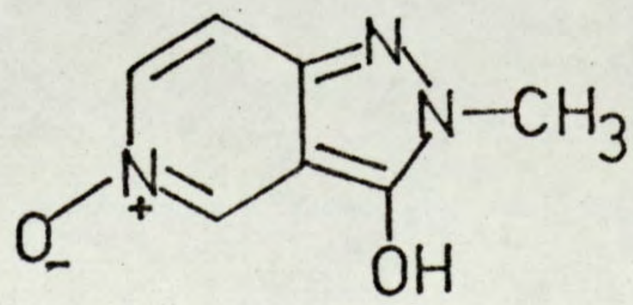


(319) (320)

Badger and Rao[45] proposed structure (102) for the product obtained



(102)

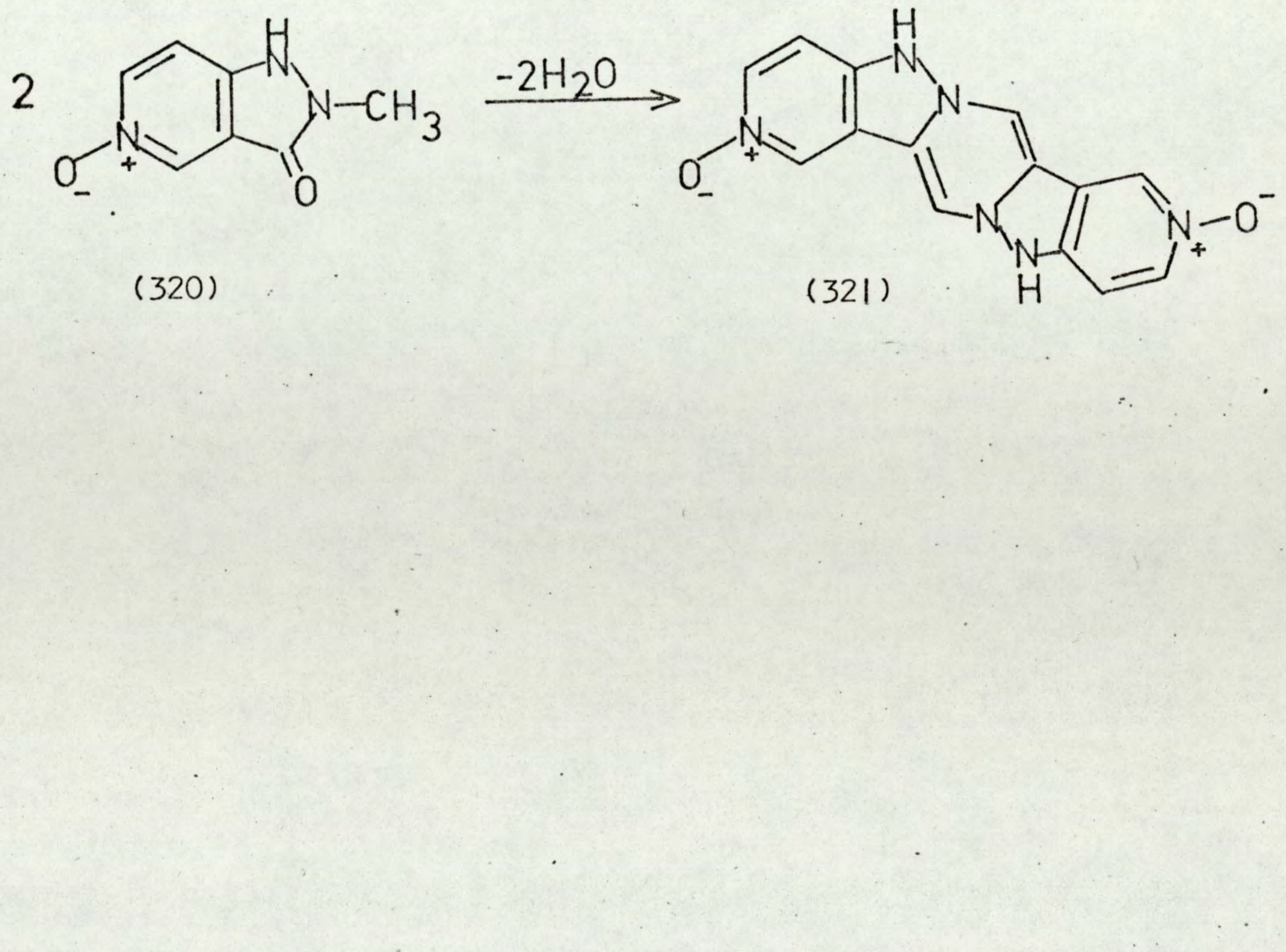


(319)

from 4-chloronicotinic acid 1-oxide (48) and methyl hydrazine, with the methyl group in the 1-position. Mass spectral evidence indicates that the product obtained from 4-nitronicotinic acid 1-oxide (57) and methylhydrazine has structure (319) with the methyl group in the 2-position.

The mass spectrum of the pyrazolopyridine (319) contained the molecular ion at m/e 165, the base peak at m/e 149, and a fragment at m/e 294. An accurate mass determination on the fragment at m/e 294 gave the molecular formula as $C_{14}H_{10}N_6O_2$, indicating that dimerisation may have occurred with the loss of two molecules of water. When the spectrum was run at 100°, no fragment occurred at m/e 294; on increasing the temperature to that of the melting point, the fragment at m/e 294 appeared, and the relative abundance of the molecular ion peak at m/e 165 decreased.

An examination of the structures (319) and (102) indicates that structure (319) is suitably orientated for condensation to occur to give the possible product (321), whereas the structure containing a 1-methyl group is not suitably orientated.

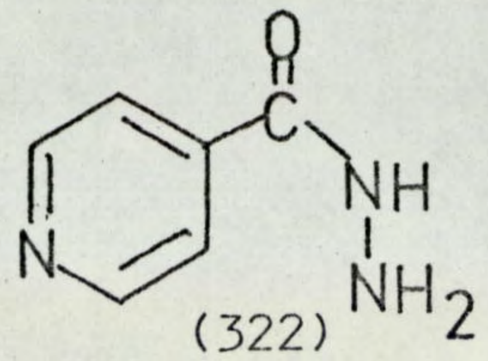


(320) (321)

An attempt to prepare the condensation product (321) by pyrolysis of the pyrazolopyridine (319) was unsuccessful; decomposition of the starting material occurred.

c) Pyrido-pyridazines

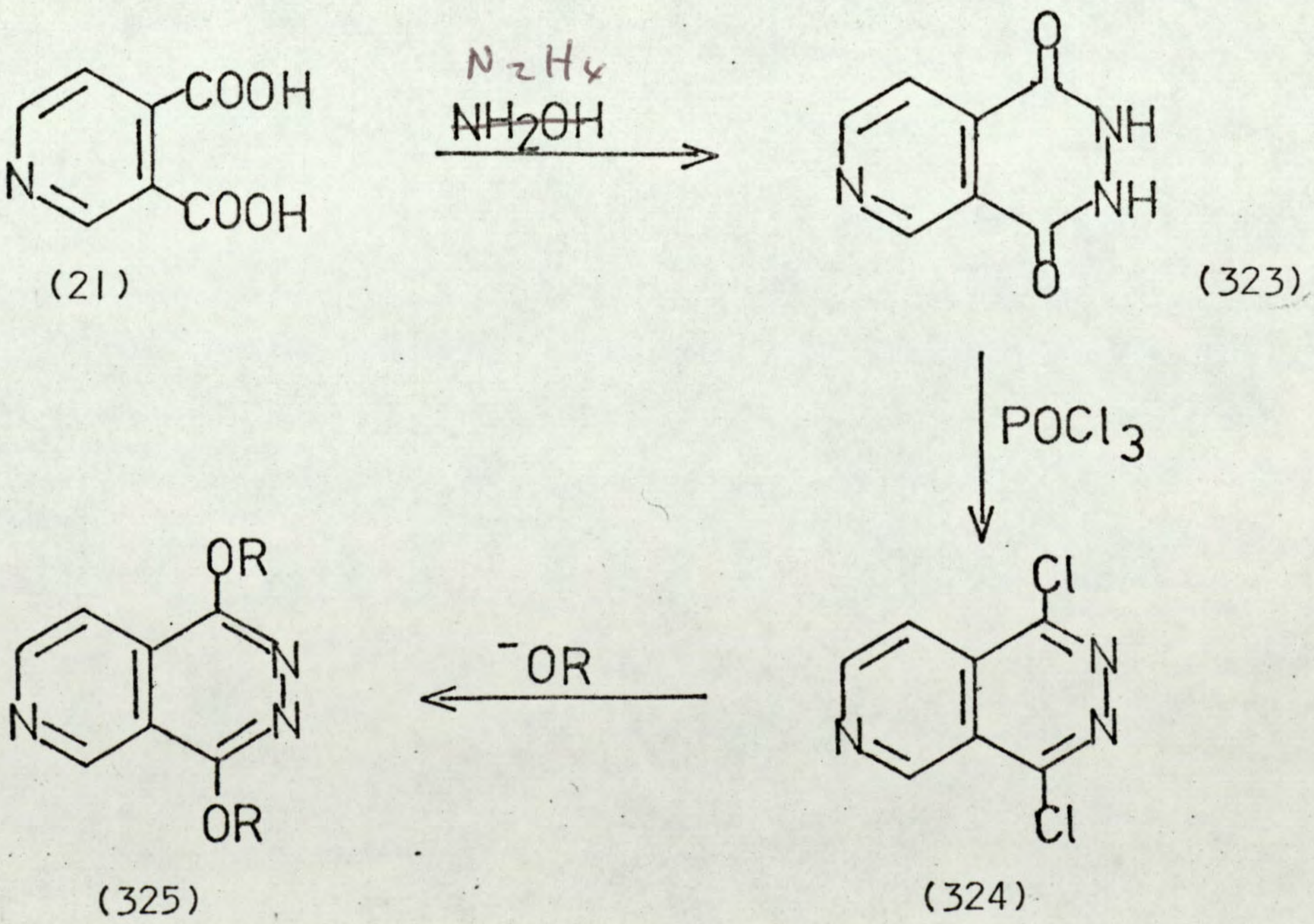
The activity of isonicotinic acid hydrazide (322) against tuberculosis has led to the synthesis of several pyridine carboxylic acid hydrazides



(322)

and related compounds such as the pyridopyridazines.[146]

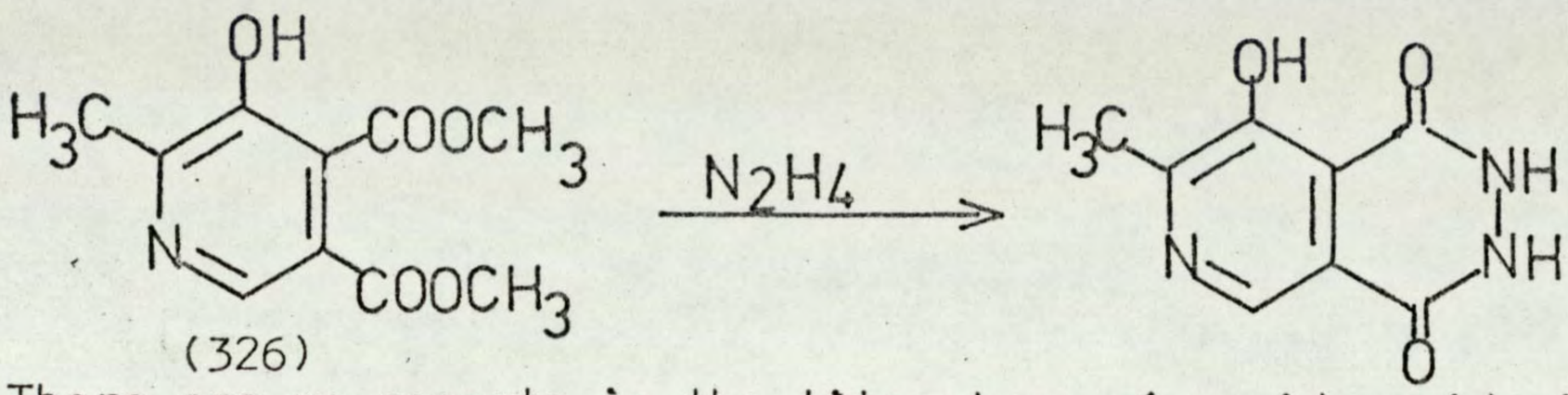
Recent Japanese work[147,148] has resulted in the preparation of a number of pyrido[3,4-d]pyridazines with reported anti-inflammatory, anti-depressant, and anti-spasmodic properties. These workers prepared the anti-spasmodic 1,4-dialkoxypyrido[3,4-d]pyridazines (325) by a 3 stage process from pyridine 3,4-dicarboxylic acid; treatment of the 1,4 dione (323), prepared from the di-acid (21) and hydroxylamine, with phosphorous



(21) (323) (324) (325)

oxychloride, gave the 1,4-dichloro deriviative (324) from which the alkoxy compounds (325) were prepared by a nucleophilic displacement reaction.

Takuichi and Tasuki[147] prepared 8-hydroxy-7-methyl-1,2,3,4-tetrahydropyrido[3,4-d]pyridazin-1,4-dione (327), a useful anti-inflammatory agent and blood pressure depressant, from the di-ester (326) and hydrazine.



(326) (327)

There are no reports in the literature of pyridopyridazines containing a pyridine ring fused across the 3,4 bond with a substituent on the pyridine nitrogen atom. In view of the reported biological activity of several compounds containing the pyrido[3,4-d]pyridazine system, the conversion of available suitably substituted pyridine derivatives into pyrido[3,4-d]pyridazines was investigated.

Pyridopyridazines have usually been prepared by the reaction of ortho-dicarbonyl or ortho-cyano-carbonyl pyridine derivatives with hydrazine hydrate.

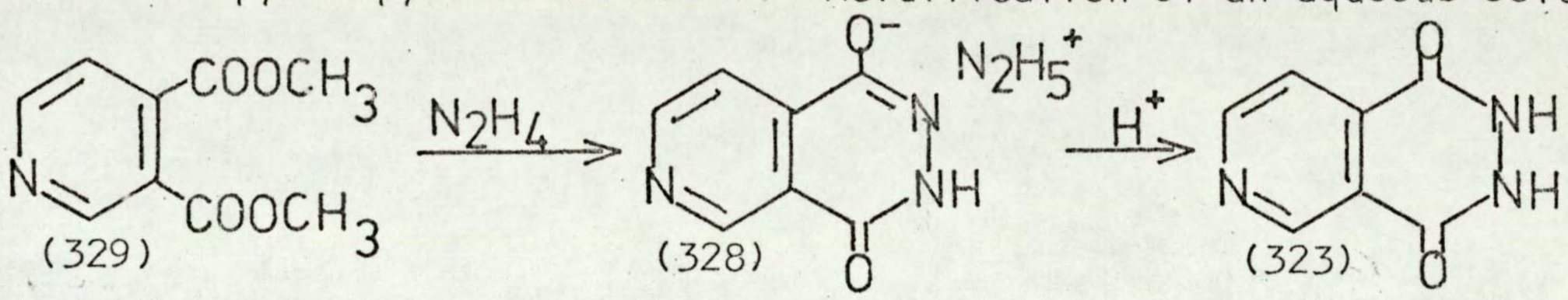
Meyer and Mally[149] prepared pyrido[4,3-d]pyridazin-1,4-dione (323) by the pyrolysis of 3-carboxyisonicotinic acid hydrazide, which was reported by these authors to be the product obtained by heating methyl-pyridine 3,4-dicarboxylate with hydrazine hydrate in ethanol.

Yale[146] and co-workers later prepared the hydrazine salt of the 1,4-dione (328) by heating the di-ester (329) with hydrazine hydrate in alcohol under reflux for 6 hours; acidification of the salt with acetic acid gave the pyridopyridazine (323). Jones[150] reported the synthesis of a number of pyridopyridazines using conditions less vigorous than those

employed by Yale et. al.[146]

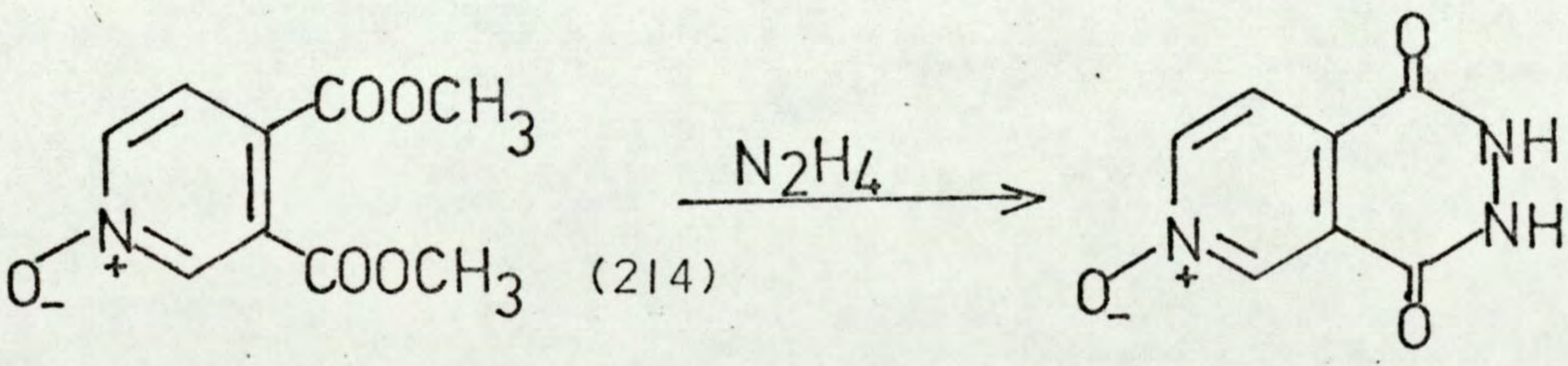
The conditions proposed by Jones[150] have now been employed for the synthesis of the 1,4-dione (323).

Methyl pyridine 3,4-dicarboxylate (329) and hydrazine hydrate were mixed in ethanol and warmed on a steam bath for 10 minutes; a yellow solid began to separate from the solution, and precipitation was complete after 30 min . The reaction was also completed after 10 hours at room temperature. The water soluble, high melting, solid was identified as the hydrazine salt of the pyridopyridazine (328): Acidification of an aqueous solution

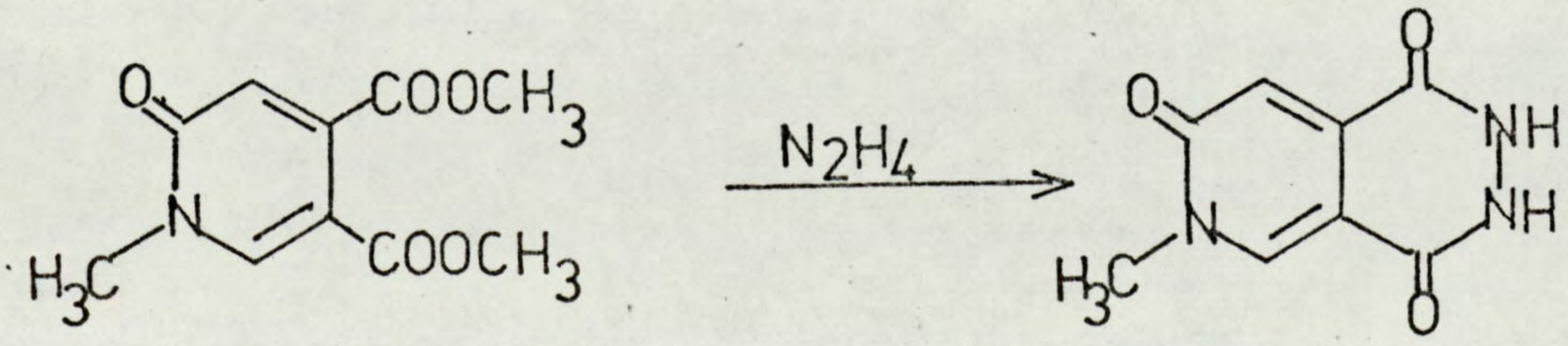


(329) (328) (323)

of the salt gave pyrido[3,4-d]pyridazin 1,4-dione (323). The fragment of m/e 32 which was the base peak in the mass spectrum of the salt (328), was absent in the mass spectrum of the free base (323). Methyl pyridine-3,4-dicarboxylate 1-oxide (214) gave the corresponding pyrido[3,4-d] pyridazin. 1,4-dione 6-oxide (330) after 4 hours at room temperature, and 1-methyl-3,4-dimethoxycarbonyl 6-pyridone (245) gave the corresponding 6-methylpyrido[3,4-d]pyridazin 1,4,7-trione (331) on heating with hydrazine



(214) (330)

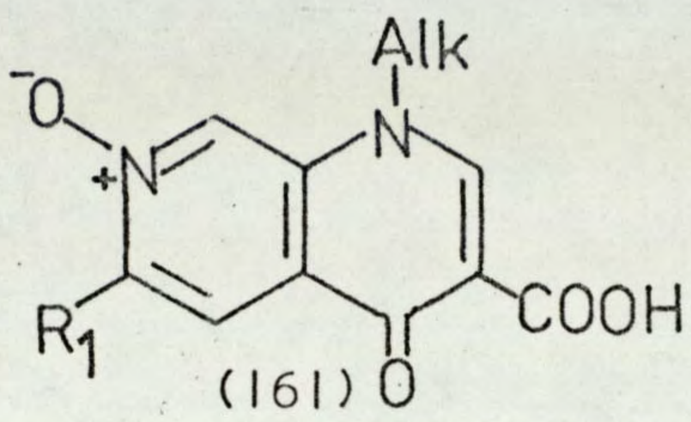


(245) (331)

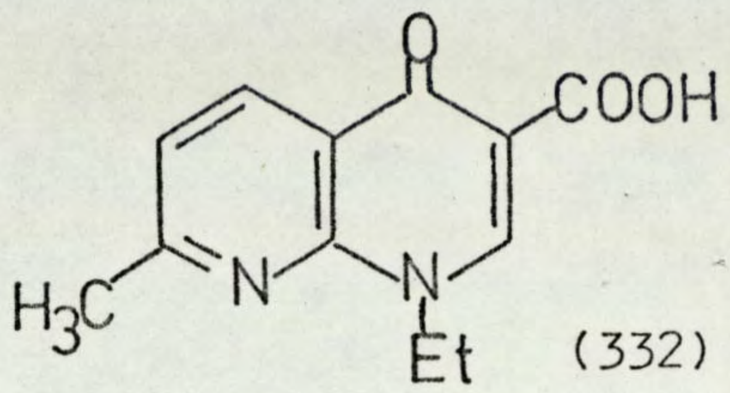
hydrate under reflux for 1 hour in ethanol.

1,6-Naphthyridine 6-oxides

Several naphthyridine derivatives including the 1,7-naphthyridine 7-oxides (161), and more notably the 1,8-naphthyridine (nalidixic acid) (332) have been shown to possess antibacterial properties.[151] Other naphthyridine



(161)

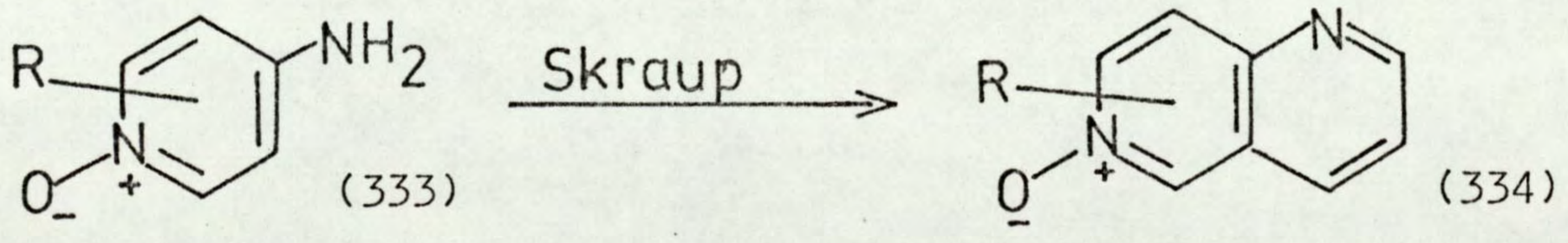


(332)

derivatives have been reported to show hypotensive and antitubercular activity.[151]

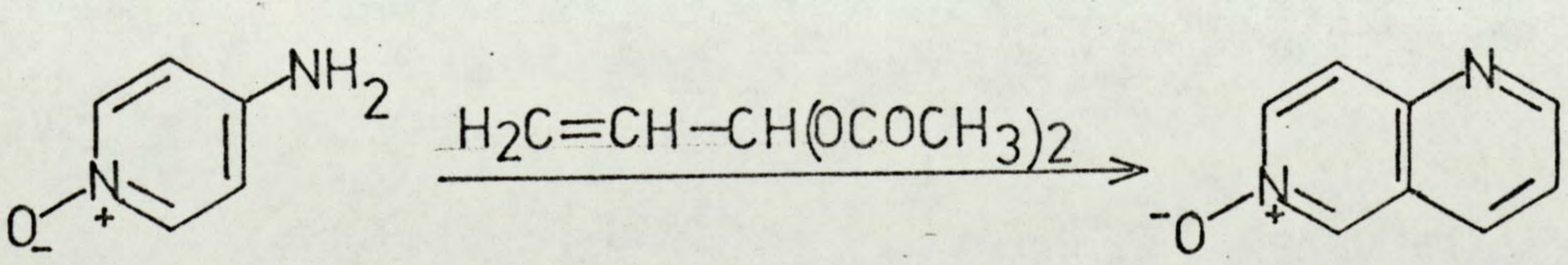
Although the 1,7-naphthyridine 7-oxides (161) were prepared by oxidation of the parent ring system, the use of substituted pyridine 1-oxides in the preparation of naphthyridine N-oxides has also been reported.

The Skraup reaction on 4-aminopyridine 1-oxide and some of its methyl derivatives (333) gave the 1,6-naphthyridine 6-oxides (334),[75] although the reported yields were less than 5%. The synthesis of 1,6-naphthyridine



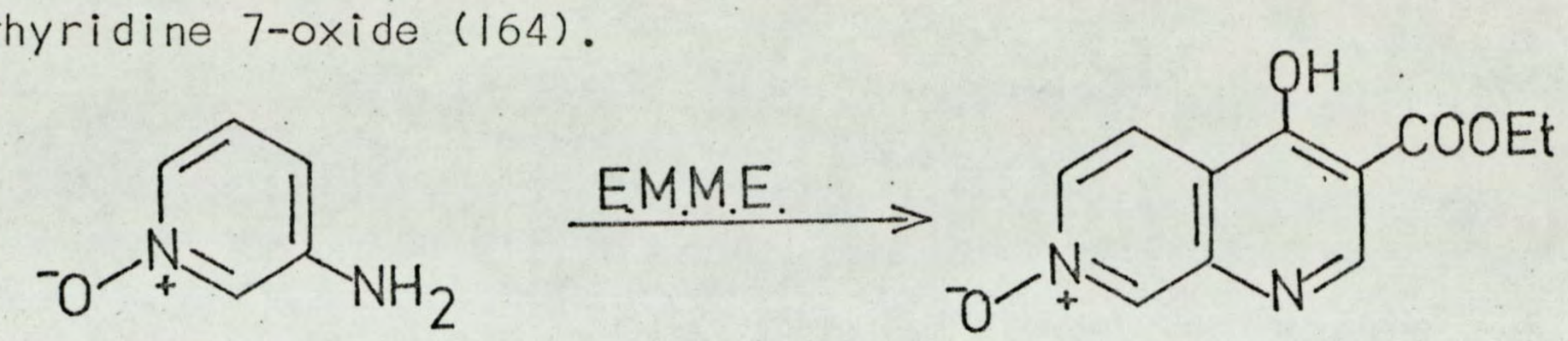
(333) (334)

6-oxide (335) by the reaction of the amino N-oxide (181) and 1,1-diacetoxy-2-propene has also been recorded.[151]



(181) (335)

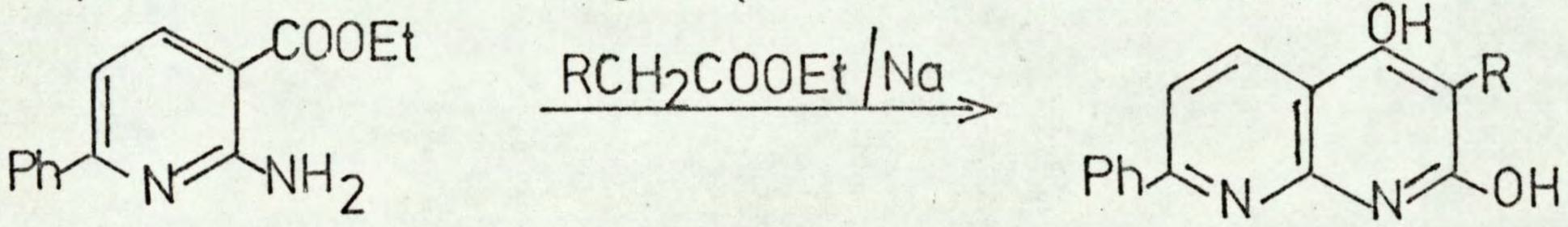
Murray and Hauser[101] have shown that condensation of 3-aminopyridine 1-oxide (163) with diethylethoxymethylenemalonate (EMME) gives the 1,2-naphthyridine 7-oxide (164).



(163) (164)

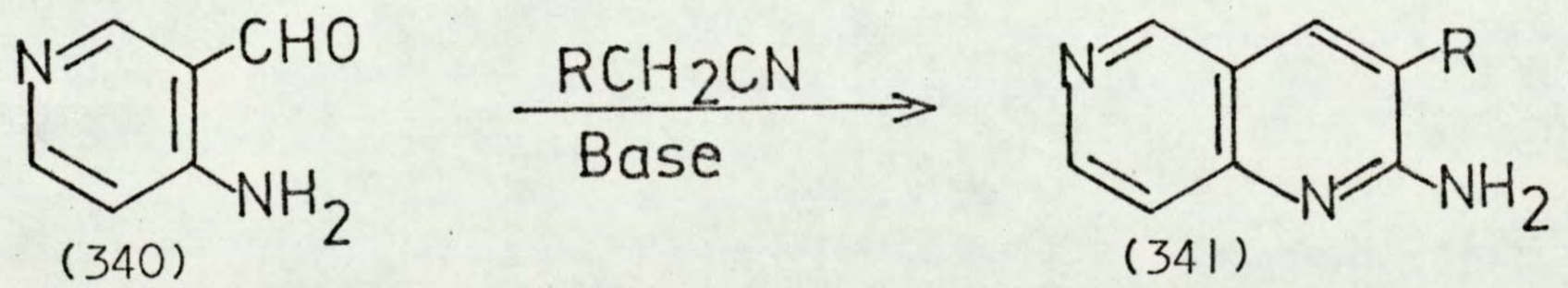
Following the preparation of suitable 3,4-disubstituted pyridine 1-oxides, which have been described earlier in this discussion, the conversion of these compounds into naphthyridine derivatives has now been attempted.

Hawes and Wibberley[152] reported the preparation of the 1,8-naphthyridine -2,4-diols (337-339) in good yield from the o-aminoester (336). Hawes[153]



(336) (337) R=H, (338) R=CH_3, (339) R=Ph

has also reported the preparation of 2-amino-1,6-naphthyridines (341) from 4-aminonicotinaldehyde (340) and substituted acetonitriles, and has



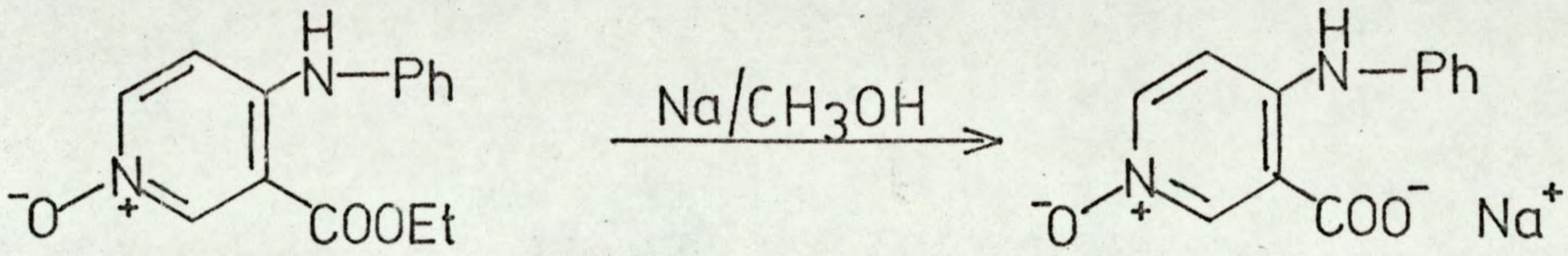
(340) (341)

demonstrated that the rate of reaction is related to the activity of the methylene group of the substituted acetonitrile, and that the addition of the anion of the methylene group precedes the addition of the primary amine to the nitrile.

The above types of condensation have now been applied to ethyl 4-anilinonicotinate 1-oxide (194) in an attempt to prepare a series of 1-

phenyl-1,6-naphthyridine 6-oxides.

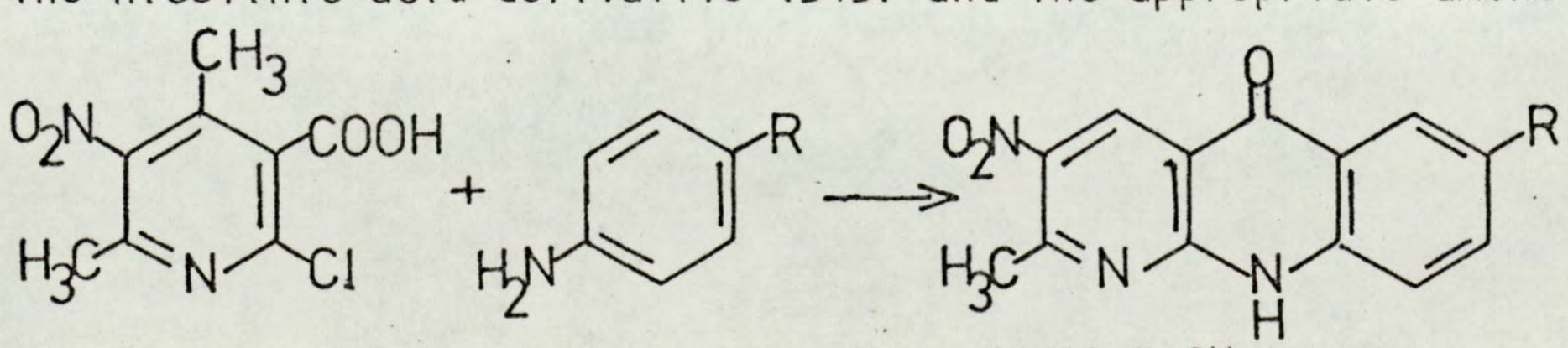
The reaction of the anilino-ester (194) with cyanoacetamide in the presence of piperidine at 100° for 3 hours gave unchanged starting material. The reaction of the anilino-ester (194) with ethylacetate, ethyl phenyl acetate, cyanoacetamide, and malononitrile, in the presence of sodium, gave the same product for each reaction. The same product was obtained from the reaction of the ester (194) with sodium in methanol, and chemical and spectroscopic evidence indicated the product to be the sodium salt of the anilino acid (342).



(194) (342)

The infrared spectrum showed a broad band centred at 1510cm^{-1} due to the carbonyl stretching vibration of the carboxylate anion. The n.m.r. spectrum showed the characteristic splitting of a 3,4-disubstituted pyridine 1-oxide, and the mass spectrum, after the initial loss of CO_2 and oxygen, closely resembled the corresponding part of the spectrum obtained from 4-anilinonicotinic acid 1-oxide (65).

Singh and co-workers[154] reported the preparation of the benzo-naphthyridines (345) and (346) by the reaction of equimolar amounts of the nicotinic acid derivative (343) and the appropriate amine (344).



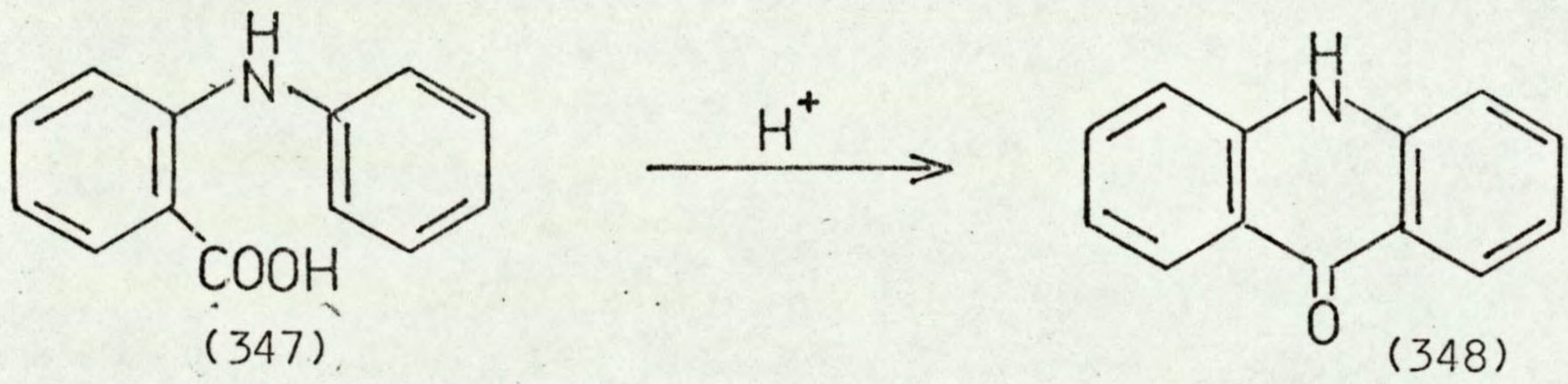
(343) (344) (345) R=CH_3

(346) R=OCH_3

The conditions used in the above reaction have now been applied to the reaction of 4-nitronicotinic acid 1-oxide (57) and suitable aromatic amines. A mixture of equimolar amounts of the nitro-acid (57) and m-toluidine, when warmed on a steam bath, gave a vigorous reaction with evolution of nitrogen dioxide, and resulted in the production of an intractable tar. The reaction under more controlled conditions gave a dark-red mixture as the product, but the required benzonaphthyridine could not be isolated.

An attempted ring closure of 4-anilinonicotinic acid 1-oxide (65) by heating at 250° for 10 hours gave only unchanged starting material.

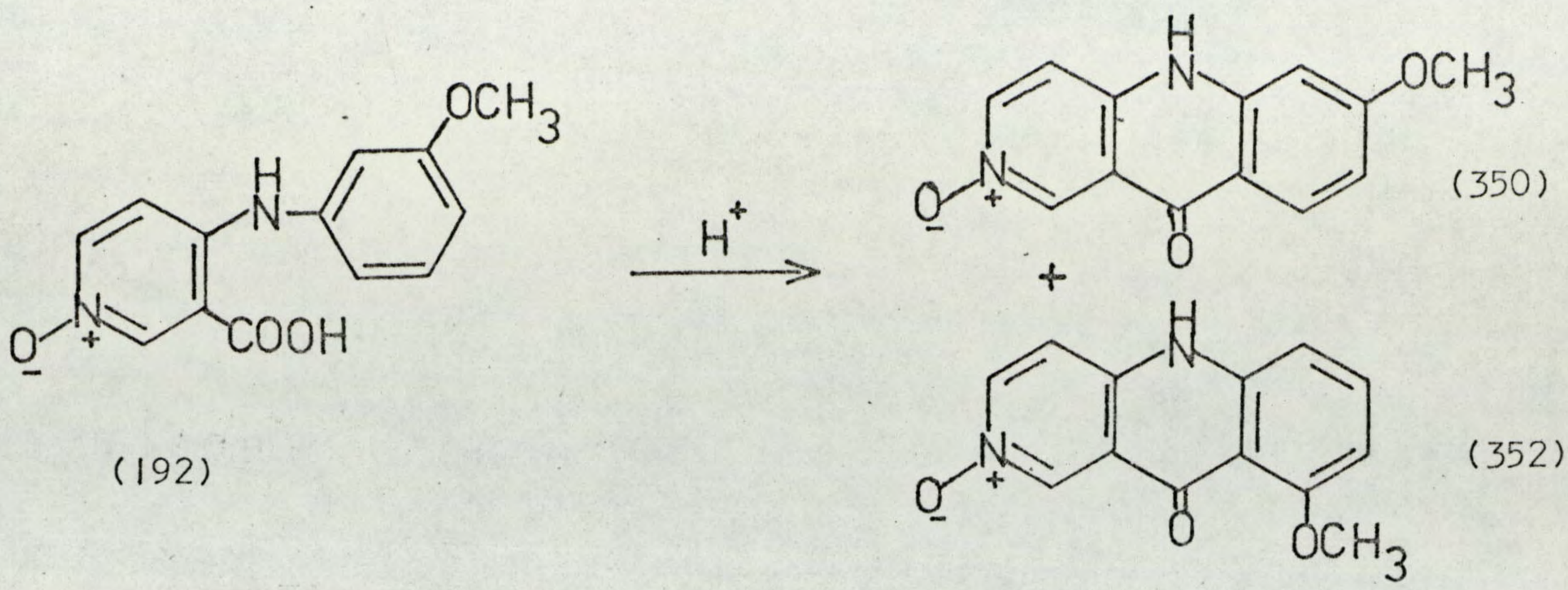
The most useful method for the synthesis of acridones,[155] first performed by Jourdan,[156] has been reported to be the ring closure of



(347) (348)

diphenylamine 2-carboxylic acids (347) using sulphuric acid or phosphorus oxychloride.

This method of synthesis has now been extended to the cyclisation of 4-N-(3-methoxyphenyl)aminonicotinic acid 1-oxide (192) and 4-N-(3-tolyl)aminonicotinic acid 1-oxide (191). The reaction of the amino-acid N-oxides with concentrated sulphuric acid for 4 hours gave the benzo-naphthyridine N-oxides.



(192) (350) (352)

(191) (349) (351)

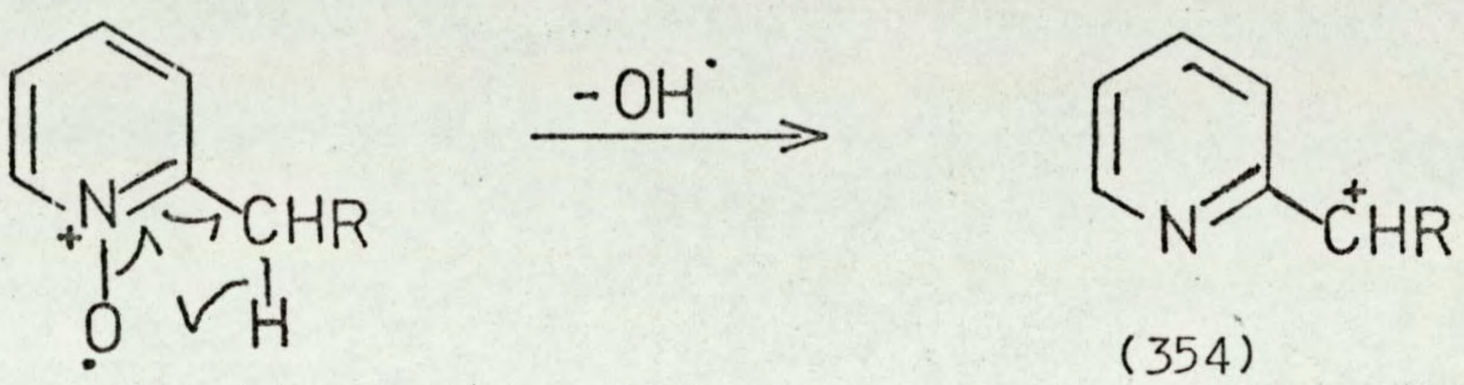
The benzonaphthyridine N-oxides were insoluble in all organic solvents; an n.m.r. spectrum could not be obtained, and the ratio 7 and 9 substituted isomers (349:351), (350:352) was not determined.

Earlier workers[155] have shown that the position of ring closure in the synthesis of acridones is governed by the mesomeric effect. The ring closure of 3'-methoxy diphenylamine 2-carboxylic acid was reported to give 60% of the 3-isomer and 40% of the 1-isomer, whereas the corresponding 3'-methyl derivative gave 20% of the 3-isomer and 80% of the 1-isomer. By analogy with this evidence, it seems probable that in the preparation of the methoxybenzonaphthyridine N-oxide, the predominant isomer will be the 7-methoxy derivative (350), and the predominant isomer derived from 4-N-(3-tolyl)aminonicotinic acid 1-oxide (191) will be the 9-isomer (351).

MASS SPECTRA

Heterocyclic N-oxides.

An important characteristic of the mass spectra of heterocyclic N-oxides is the presence of an (M-16) peak, which has been suggested as a diagnostic test for the N-oxide group.[159] In 2-alkyl substituted pyridine 1-oxides (353) an ortho-effect causes the reduction of the (M-16) peak in favour of a peak at (M-17).[160]



(353) (354)

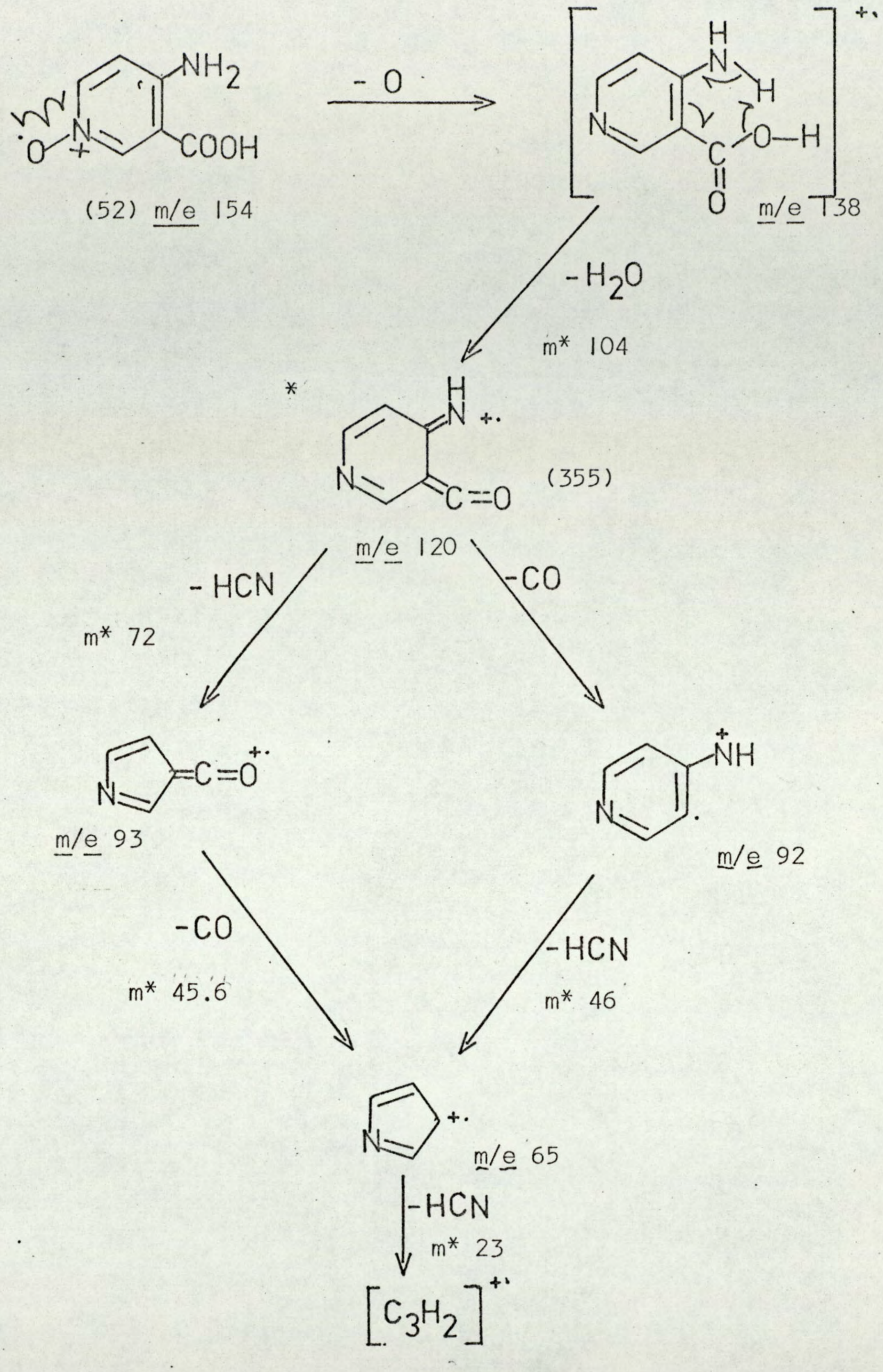
The mass spectrum of quinoline 1-oxide contains a fragment at (M-16) and also a peak at (M-28) due to loss of carbon monoxide by a molecular rearrangement; a similar rearrangement in isoquinoline 1-oxide gives a fragment at (M-27) due to loss of HCN.[161] Molecular rearrangements have been observed for other bi- and tri-cyclic heterocyclic N-oxides. The loss of COCl in the high temperature mass spectrum of pentachloropyridine 1-oxide has been suggested to occur via an oxaziridine ring.[162]

Mantsch[163] reported the presence of a meta-stable peak for the process $(M)^{+\cdot} \rightarrow (M-16)^{+}$ in the mass spectrum of acridine 10-oxide; this is the only report in the literature of a meta-stable peak for this process.

i) 4-Substituted nicotinic acid 1-oxides.

The major fragmentation pathway of 4-aminonicotinic acid 1-oxide (52), after the initial loss of oxygen atom to give the base peak at $(M-16)^{+\cdot}$ is similar to that of 4-aminonicotinic acid (Scheme 1). The water loss which occurs in both these compounds is a common feature of aromatic acids with a hydrogen bearing ortho-substituent.[164]

The radical ion at m/e 120 (355) eliminates either a molecule of CO



Scheme I

* The structure shown for this and subsequent fragments represents only one of several possible forms.

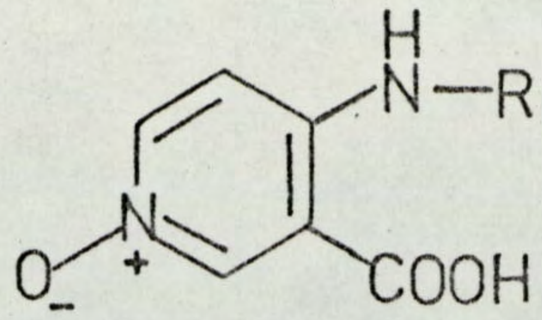
to give the fragment at m/e 92, or a molecule of HCN to give the fragment at m/e 93. Loss of HCN from the fragment at m/e 92, and loss of CO from the fragment at m/e 93 then gives the same ion at m/e 65.

Three minor fragmentation pathways were observed; loss of water occurred from the molecular ion to give a peak at $(M-18)^{+\cdot}$, followed by loss of oxygen to give the fragment at m/e 120 (355) shown in scheme 1. Loss of carbon dioxide from the molecular ion, followed by loss of oxygen gave a fragment of $(M-60)^{+\cdot}$, which also occurred by loss of CO_2 from the fragment of m/e 138 shown in scheme 1.

The relative abundances of the molecular ions and the fragments (M-16), (M-17), (M-18), and (M-60) of a number of 4-substituted nicotinic acid 1-oxides are summarised in Table 1, together with the corresponding peaks for nicotinic acid 1-oxide[165] and 4-aminonicotinic acid.

As can be seen from Table 1, the low abundance of the molecular ions in the majority of cases indicates that the 4-substituted nicotinic acid 1-oxides are relatively unstable to electron impact compared with 4-aminonicotinic acid (187), and nicotinic acid 1-oxide, where the molecular ion is the base peak. The amino-acid N-oxides lose an oxygen atom to give a substantial peak at $(M-16)^{+\cdot}$. The abundance of the molecular ions of both 4-anilino- (65) and 4-benzylamino-nicotinic acid 1-oxide (190) was less than 0.1%, and a spectrum of the benzylamino acid (190) run at low ionising voltage did not show any significant molecular ion (<0.1%).

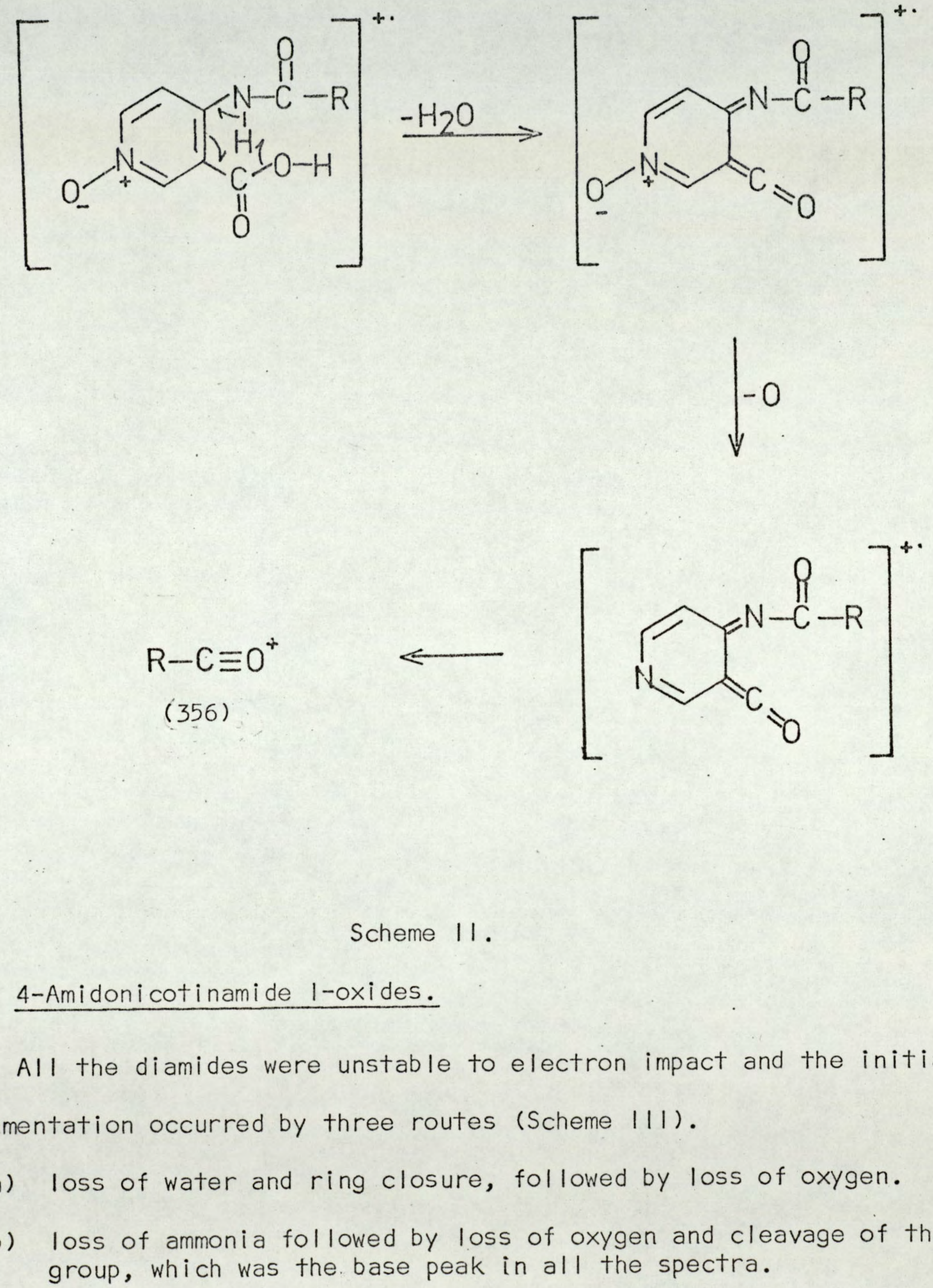
The major fragmentation pathway of the 4-amidonicotinic acid 1-oxides was by loss of water from the molecular ion and not by loss of oxygen; loss of oxygen occurred in all cases from the $(M-18)^{+\cdot}$ fragment. The acyl ion



	Relative Abundances					
R	M	M-16	M-17	M-18	M-60	Base Peak
$COCH_3$	-	-	4	45	40	43
p-fluorobenzoyl	2	15	3	16	24	123
p-methoxybenzoyl	1	-	2	15	2	135
3,4-dichlorobenzoyl	2	8	4	25	18	173
p-methylbenzoyl	1	3	-	4	9	119
H	24	100	5	15	33	138
Ph	-	52	-	-	70	196
CH_2Ph	-	57	6	-	16	91
m-anisoyl	4	88	-	-	100	200
m-tolyl	40	18	-	-	18	91
4-aminonicotinic acid	100	-	11	93	11	138
Nicotinic acid 1-oxide	100	72	3	-	unknown	139
4-Nitronicotinic acid 1-oxide	3	-	-	-	10	39

Table 1

(356) was the base peak in all the amido-acids. (Scheme II).



Scheme II.

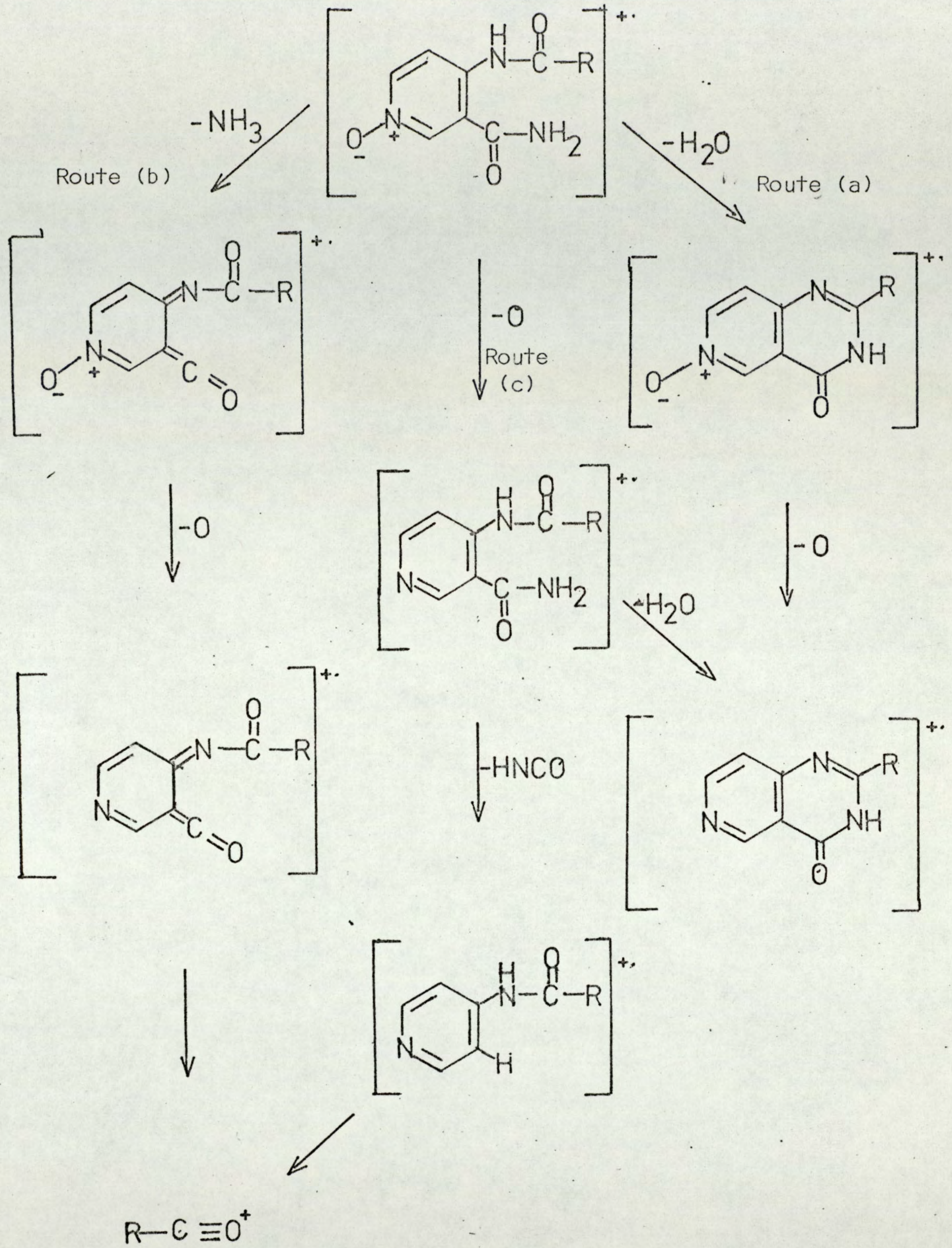
ii) 4-Amidonicotinamide 1-oxides.

All the diamides were unstable to electron impact and the initial fragmentation occurred by three routes (Scheme III).

a) loss of water and ring closure, followed by loss of oxygen.

b) loss of ammonia followed by loss of oxygen and cleavage of the acyl group, which was the base peak in all the spectra.

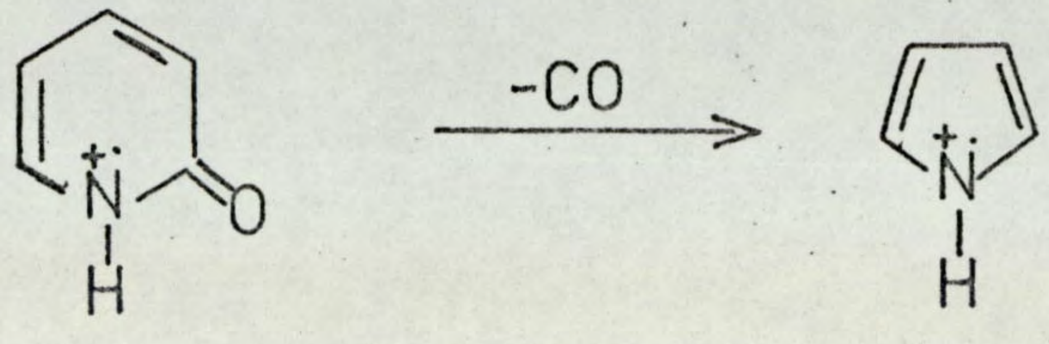
c) loss of oxygen followed by either loss of water or loss of HNCO.



SCHEME III

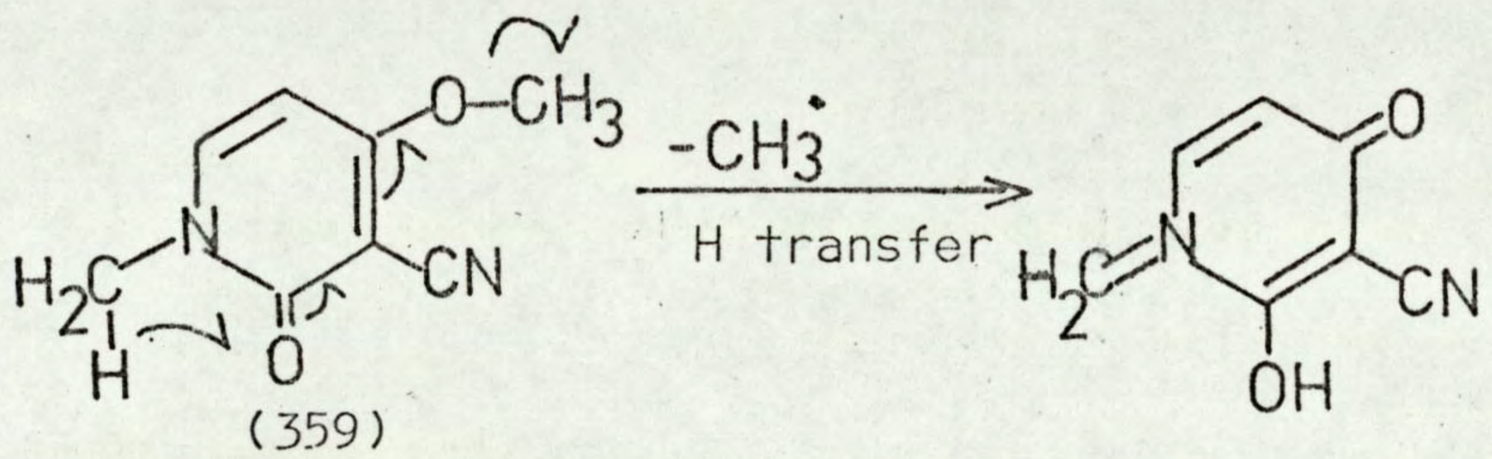
iii) N-Alkyl-3,4-disubstituted pyrid-6-ones.

2-Pyridone (357) fragments by loss of CO to give the pyrrole radical-ion (358); but substitution of the pyridone ring has a pronounced effect on the mass spectrum.[165]



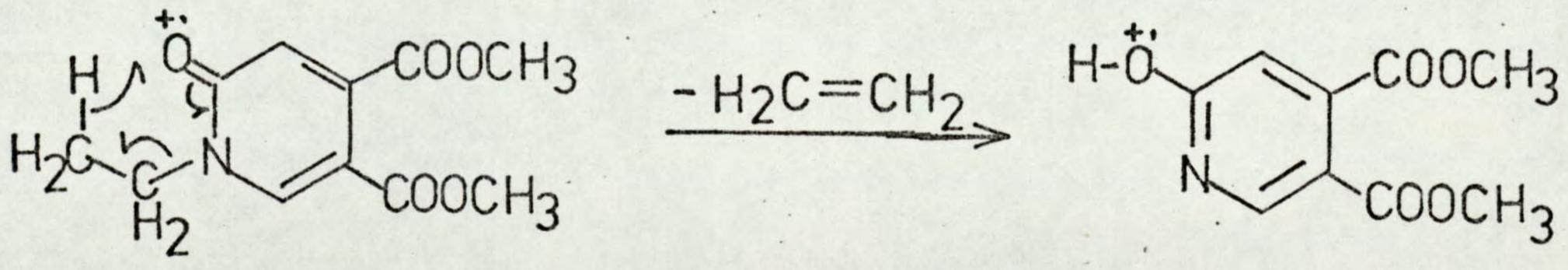
(357) (358)

Hydrogen transfer from an N-alkyl group to the pyridone oxygen atom has been observed in the mass spectrum of ricinine (359).[165]



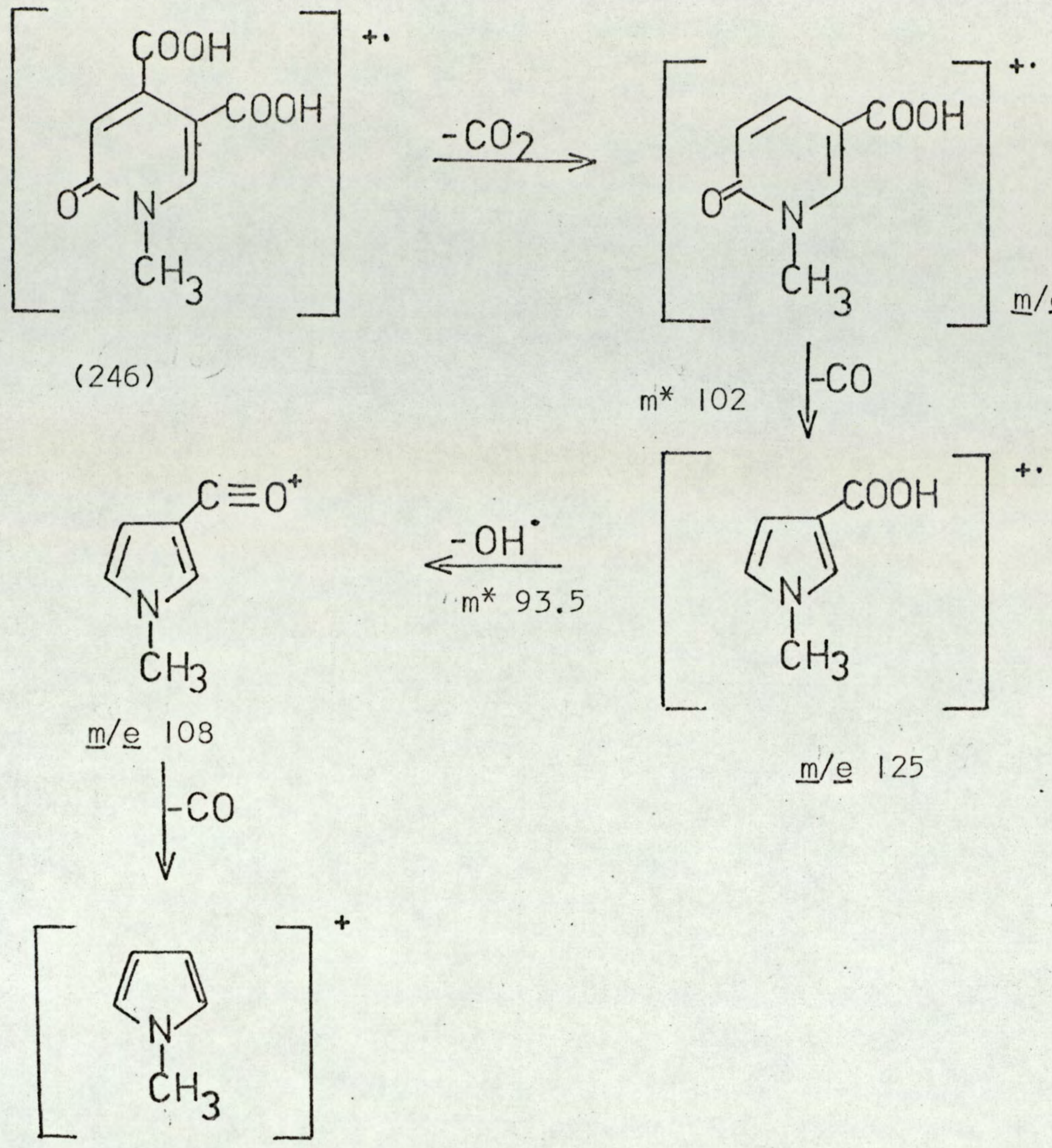
(359) (360)

The 3,4-dialkoxycarbonyl-N-alkyl-pyrid-6-ones all fragment via the alkoxycarbonyl groups, with loss of an alkoxy group followed by loss of CO. An alternative pathway in the case of 3,4-dimethoxycarbonyl-1-ethyl-pyrid-6-one (263) was by loss of ethylene, presumably via a McLafferty rearrangement.



(263) (361)

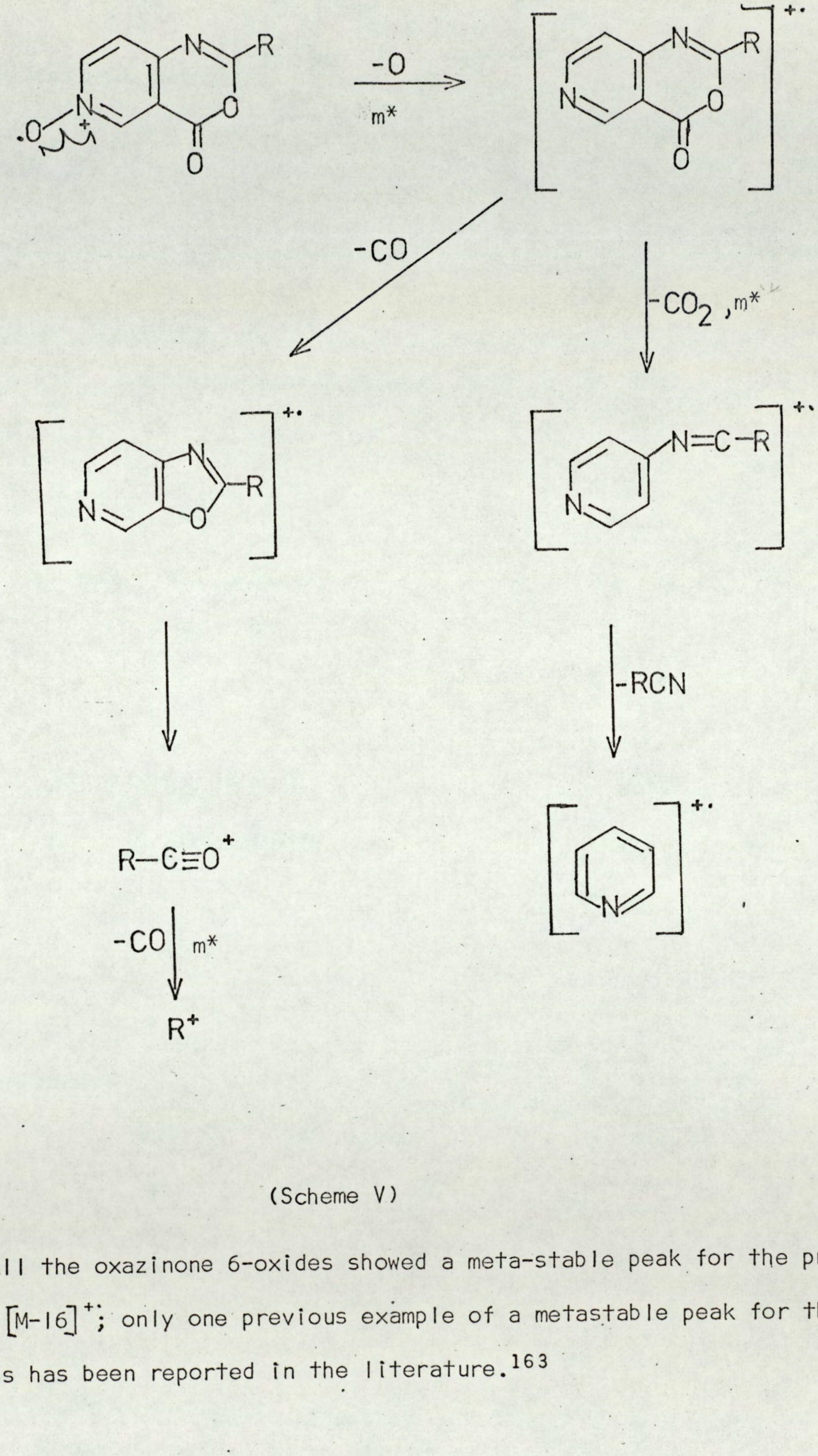
The major fragmentation pathway of 3,4-dicarboxy-1-methyl pyrid-6-one (246) was by loss of CO_2 to give the radical ion at m/e 153; this was followed by successive loses of CO, OH, and CO to give the ion at m/e 80 (Scheme IV).



Scheme IV

iv) 2-Aryl-pyrido[4,3-d][1,3] oxazin-4(3H)-one 6-oxides

The major fragmentation pathway of the pyrido-oxazinone 6-oxides was by loss of an oxygen atom, followed by either loss of CO and subsequent loss of the ($R-C\equiv O^+$) ion, which was the base peak in all the compounds studied, or by loss of CO_2 and subsequent loss of $(R-CN)^+$ (Scheme V).

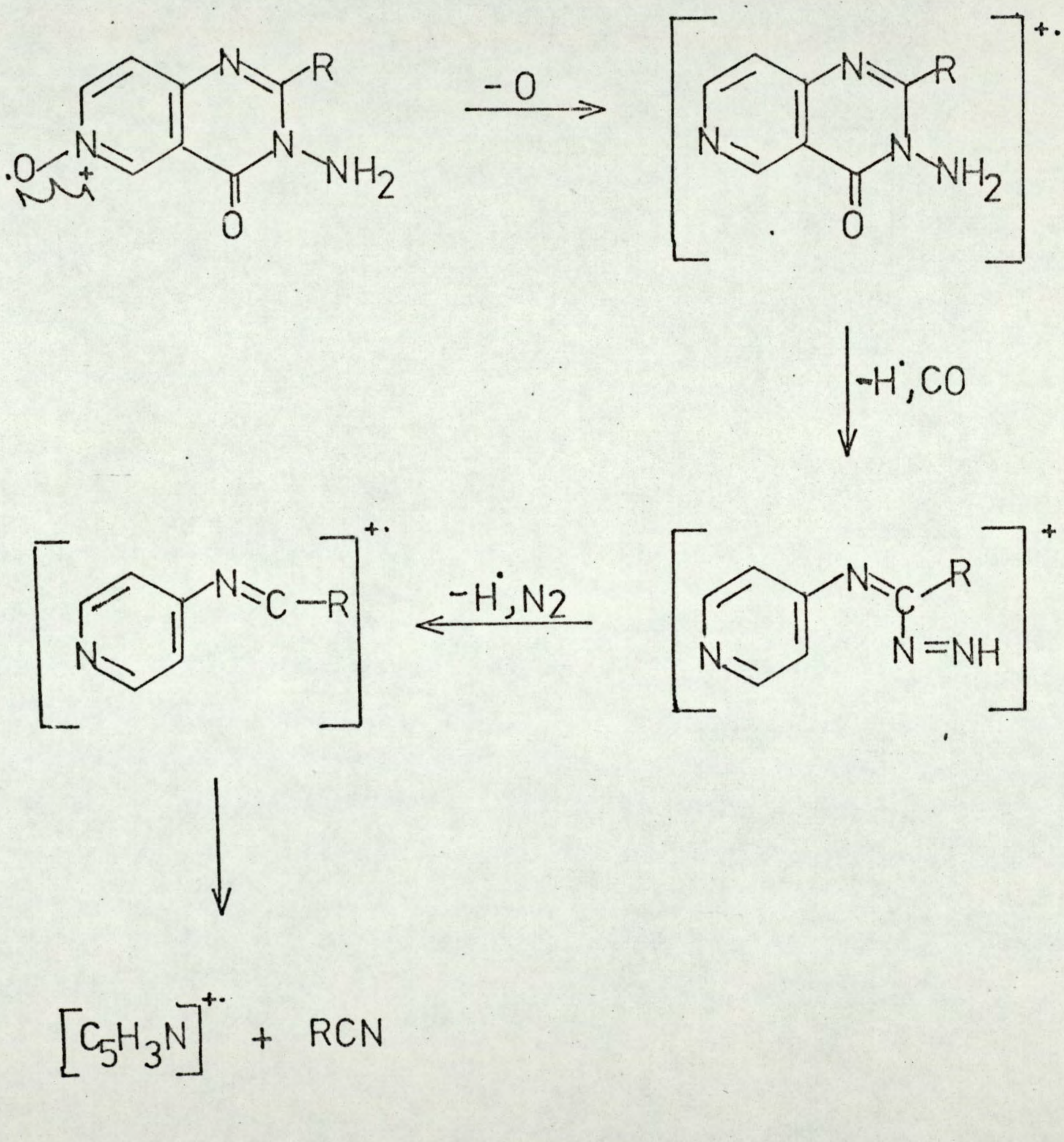


(Scheme V)

All the oxazinone 6-oxides showed a meta-stable peak for the process $M^{+\cdot} \rightarrow [M-16]^{+\cdot}$; only one previous example of a metastable peak for the process has been reported in the literature.[163]

v) Pyrido-pyrimidine 6-oxides

The fragmentation pathway of pyridopyrimidin-4(3H)-ones and pyrido-pyrimidin-2,4(1H,3H)-diones have been reported.[166] In both pyrido[4,3-d] pyrimidin-4(3H)-one 6-oxide (270) and pyrido[4,3-d]pyrimidin-2,4(1H,3H)-dione 6-oxide (271) the base peak was the ion at $(M-16)^{+\cdot}$; the subsequent fragmentation patterns were the same as those recorded in the literature.[166]

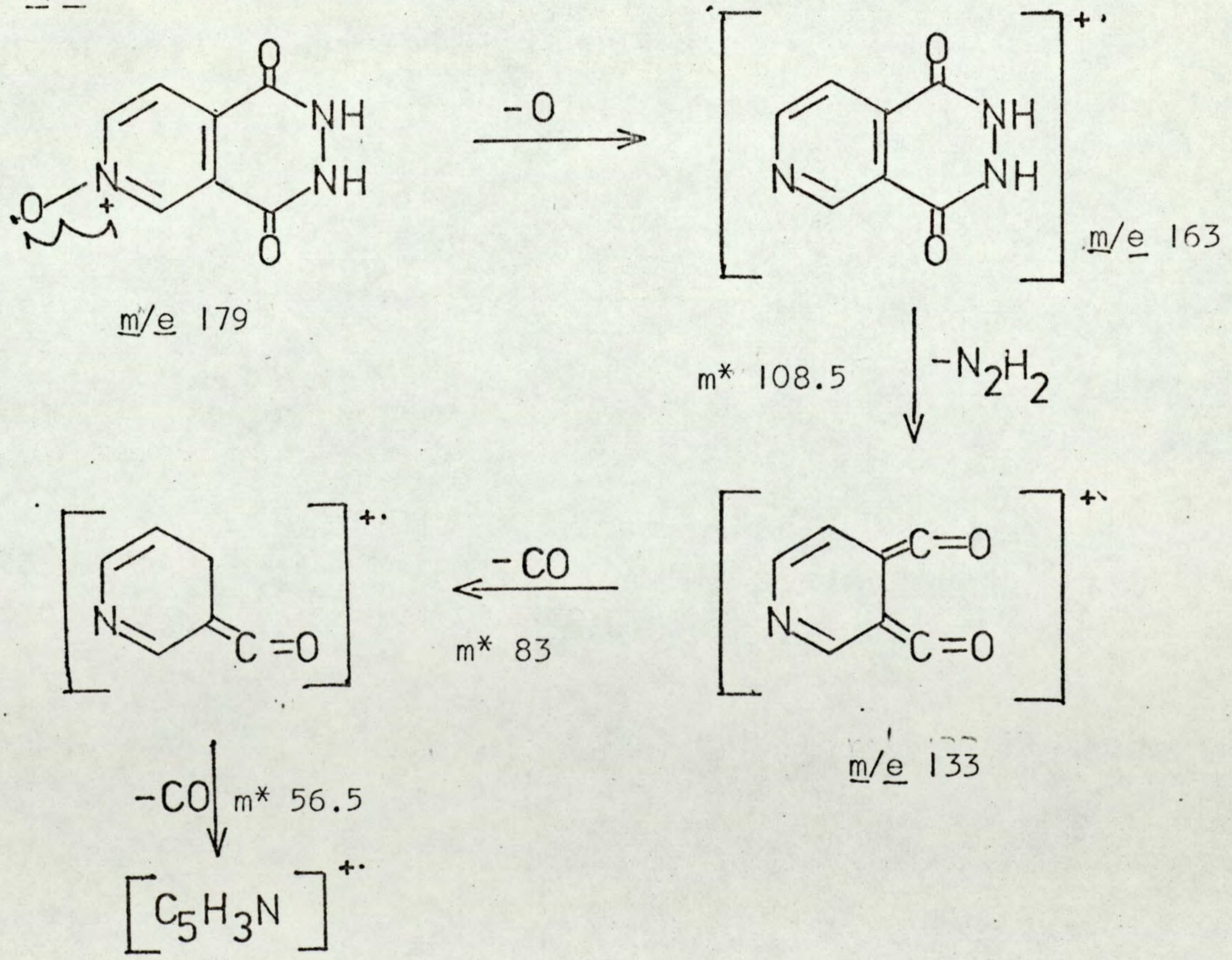


SCHEME VI

The major fragmentation pathway of the 3-amino-2-arylpyrido[4,3-d]pyrimidin 4-(3H)-one 6-oxides, after the initial loss of oxygen, closely resembled that previously reported for 3-aminopyrido[4,3-d]pyrimidin-4(3H)-ones;[138] the ion $(M-16)^+$ fragments by loss of H· and CO, and then by subsequent loss of H·, nitrogen and RCN (Scheme VI).

vi) Pyrido-pyridazines.

Previous reports on the mass spectra of pyrido[3,4-d]pyridazines[167] have shown that the diones fragment by loss of N_2H_2 followed by successive losses of two molecules of CO; any loss of nitrogen usually indicates an -N=N- linkage. This breakdown pattern was observed in both pyrido[3,4-d]pyridazin-1,4(2H,3H)-dione (323) and the corresponding 6-oxide (330). Loss of oxygen occurred in the pyridopyridazine 6-oxide (330) to give the base peak at m/e 163 (Scheme VII).



SCHEME VII

All the bicyclic heterocyclic N-oxide systems studied were more stable to electron impact than the disubstituted pyridine N-oxides, and showed significant abundances for the respective molecular ion peaks.

EXPERIMENTAL

Infrared spectra were determined as Nujol mulls, unless otherwise stated, with a Unicam S.P. 200 spectrophotometer.

Nuclear magnetic resonance spectra were determined with tetramethylsilane as internal standard, on a Varian A60-A spectrometer. All the peaks are assigned in terms of τ values. Abbreviations used in the interpretation of n.m.r. spectra are:

s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet;

J = coupling constant.

Mass spectra were determined on an A.E.I. MS 9 spectrometer, operating at 100 μa and 70 eV. $\underline{M}^+$ signifies the molecular ion peak.

Melting points are uncorrected. Reaction temperatures are those of an external oil bath.

1,3,4-TRISUBSTITUTED PYRIDINES

i) 3,4-disubstituted pyridine 1-oxides.

4-Nitro-3-picoline 1-oxide. - 3-picoline 1-oxide (85g) was added to sulphuric acid ($310cm^3$., d. 1.84), cooled to 5^o. Fuming nitric acid ($240cm^3$., d. 1.85) was added gradually with shaking and the mixture heated under reflux for 2.5h., cooled, poured onto crushed ice (1kg) and neutralised with sodium carbonate. After allowing to stand overnight, the yellow precipitate was collected and extracted with boiling chloroform. The filtrate was also extracted with chloroform ($600cm^3$) and the combined extracts were dried ($MgSO_4$) and evaporated to dryness to give the nitro compound (75.0g, 62.5%) m.p. 132-133° (from acetone), (lit[137] 131-134°). νmax. 1530 and 1350 (NO_2)cm^{-1}.

4-Nitronicotinic Acid 1-oxide (57). - A solution of 4-nitro-3-picoline 1--oxide (10g) in sulphuric acid ($35cm^3$, d. 1.84) was added dropwise over 2h to an ice-cold solution of sodium dichromate (24 g) in sulphuric acid ($35cm^3$, d. 1.84). During the addition the temperature of the reaction mixture was raised to 45-55° and maintained for 6h. The solution was poured onto crushed ice (250g) and left overnight. The resulting precipitate was collected, washed with ice water, dissolved in dilute ammonia and the product precipitated by the addition of dilute hydrochloric acid to give the nitro-acid (13.5g, 75.3%) m.p. 172° (decomp) (lit.[49] 172° [decomp.]).

$\nu_{max.}$ 2650-2500 (O-H), 1670(C=O), 1560 and 1380(NO_2),

$\nu_{max.}$ 1270(C-O)cm^{-1}.

Catalytic Hydrogenation of 4-Nitronicotinic acid 1-oxide.

Method A. 4-Nitronicotinic acid 1-oxide (1g) was suspended in water ($20cm^3$) and the pH adjusted to 10 with ammonia solution (d 0.88). Palladium-charcoal (0.5g) was added, and the mixture was shaken with hydrogen under a pressure of 344.74 $k.N.m.^{-2}$ for 2h. The solution was filtered and the solvent removed under reduced pressure to give 4-aminonicotinic acid (187) (0.5g, 66.7%) m.p. 334-336° (decomp.). (lit.[137] 335-336° [decomp.]). The infrared and n.m.r. spectra were identical with an authentic sample.

Method B. The 4-nitro acid (1g) was suspended in water ($20cm^3$) and the pH adjusted to 10 with ammonia solution (d. 0.88). Palladium-charcoal (0.25g) was added, and the mixture was shaken with hydrogen under a pressure of 310.3 $k.N.m.^{-2}$ for 0.5h. The solution was filtered and the solvent was removed under reduced pressure until crystallisation occurred. The resulting solid was filtered and identified as 4-aminonicotinic acid (0.32g, 40.8%) m.p. 334-337°.

The filtrate was evaporated to dryness under reduced pressure. The residue was boiled with ethanol and filtered to give 4-aminonicotinic acid 1-oxide (152) (0.28g, 33.3%) m.p. 272-273° (lit[110] 273°).

ν_{max} 3400, 3310 (NH_2), 1660 (C=O), 1280($\overset{+}{N}$-O^-)cm^{-1}.

Method C. The nitro-acid (1g) in dilute ammonia solution ($20cm^3$, pH 10) and palladium-charcoal (0.3g) were shaken under hydrogen at atmospheric pressure until the required volume of hydrogen (2 moles) had been absorbed. The solution was filtered and evaporated under reduced pressure to give the aminoacid 1-oxide (0.45g, 53.6%) m.p. 271-273°.

Further reduction of the resultant filtrate resulted in the crystallisation of 4-hydroxyaminonicotinic acid 1-oxide (188) (0.09g, 9.8%) m.p. 213-214° (lit.[110] 215-217°).

ν_{max} 3500 2600 (OH), 3280(NH), 1660(C=O)cm^{-1}.

Chemical Reduction of 4-nitronicotinic acid 1-oxide

The 4-nitro acid (10) was added to a solution of palladium-charcoal (0.1g) in methanol ($20cm^3$) contained in a 3 necked round-bottomed flask. A stream of nitrogen was passed through the solution, which was heated vigorously under reflux. Hydrazine hydrate ($0.75cm^3$) was added dropwise down the condenser to the refluxing solution. When all the hydrazine was added, the mixture was heated under reflux for 10min., cooled, filtered, and the filtrate evaporated under reduced pressure to give a brown solid. The solid could not be purified by recrystallisation and fractional crystallisation, although the infrared spectrum showed close similarities to that of 4-aminonicotinic acid 1-oxide.

The above method was repeated using sodium borohydride and cyclohexene as the reducing agents, but no pure material could be isolated from either reaction.

4-Aminonicotinic Acid 1-oxide (32). - Ethanol ($30cm^3$) was saturated at 0° with ammonia, and 4-nitronicotinic acid 1-oxide (2.0g) was added to the solution. The mixture was heated in a steel bomb at 160° under pressure for 3h, cooled, and the solution filtered to give the amino acid (1.45g, 86.8%) plates, m.p. 273° (from ethanol) (lit.[110] 273°)

$\nu_{max.}$ 3400 and 3310 (NH_2), 1660(C=O)cm^{-1}. 3500 - 2600 (olt)

4-Anilinonicotinic Acid 1-oxide (65). - 4-nitronicotinic acid 1-oxide (2.0g) and aniline ($25cm^3$) were heated on a steam bath for 4h and poured into aqueous sodium hydroxide (10%, $50cm^3$). The aqueous layer was separated, washed with ether, and carefully acidified to give the amino-acid (2.33g, 93.2%) needles, m.p. 249-250° (from aqueous dimethylformamide). (lit.[49] 242-244°).

$\nu_{max.}$ 3090(N-H), 1680(C=O)cm^{-1}.

τ(T.F.A.) 2.78(d, 1H, J 8.0Hz, 5-H), 2.58(s, 5H, N-Ph), 1.8(q, 1H, $J_{5,6}$

8.0Hz, $\underset{\sim}{J}_{2,6}$ 2.0Hz, 6-H) 1.23(d, 1H, $\underset{\sim}{J}_{2,6}$ 2.0Hz, 2-H). ..

4-Benzylaminonicotinic Acid 1-oxide (190). - 4-nitronicotinic acid 1-oxide (4.0g) and benzylamine (25cm^3) were heated at 120° for 4h. The resultant solid was washed with boiling acetone and filtered to give the amino-acid (2.1g 39.6%) needles, m.p. 249-250° (from aqueous acetone).

(Found: C, 63.84; H, 5.10; N, 11.38; $C_{13}H_{12}N_2O_3$

requires: C, 64.0; H, 4.92; N, 11.49).

$\nu_{max.}$ 3250 (N-H). 1675 (C=O)cm^{-1} 3500 - 2600 (OH)

τ(T.F.A.) 5.14(d, 2H, $\underset{\sim}{J}$ 5.0Hz, N-CH_2- Ph.), 2.82(d, 1H, $\underset{\sim}{J}_{5,6}$ 8.0Hz, 5-H),

2.48(s, 5H, CH_2-Ph), 1.74(q, 1H, $\underset{\sim}{J}_{5,6}$ 8.0Hz, $\underset{\sim}{J}_{2,6}$ 2.0Hz, 6-H),

0.91(d, 1H, $\underset{\sim}{J}_{2,6}$ 2.0Hz).

4-N-(3-Tolyl)aminonicotinic Acid 1-oxide (191). - 4-Nitronicotinic acid 1-oxide (1.5g) and m-toluidine (25cm^3) were heated on a steam bath for 3h and poured into aqueous sodium hydroxide (10%, 50cm^3). The aqueous layer was separated, washed with ether, and acidified to give the amino-acid (1.85g, 93.0%) needles, m.p. 268-268.5° (from aqueous dimethylformamide)

(Found: C, 63.85; H, 5.10; N, 11.51; $\underset{\sim}{M}^+$244.084786; $C_{13}H_{12}N_2O_3$

requires: C, 63.93; H, 4.92; N, 11.48; $\underset{\sim}{M}^+$244.083915).

$\nu_{max.}$ 3060 (N-H), 1660 (C=O)cm^{-1}. 3500 - 2600 (OH)

4-N-(3-Methoxyphenyl)aminonicotinic Acid 1-oxide (192). - 4-Nitronicotinic acid 1-oxide (1.5g) and m-anisidine (20cm^3) were heated on a steam bath for 3h and poured into aqueous sodium hydroxide (10%, 50cm^3). The aqueous layer was separated, washed with ether, and acidified to give the amino-acid (1.8g, 84.9%) needles, m.p. 253.5-254.5 (from aqueous dimethyl formamide).

(Found: C, 59.96; H, 4.69; N, 10.63; $C_{13}H_{12}N_2O_4$

requires: C, 60.00; H, 4.62; N, 10.77).

$\nu_{max.}$ 3150 (N-H), 1660 (C=O)cm^{-1}. 3500 - 2600 (OH)

Ethyl 4-anilinonicotinate 1-oxide (194). - A solution of 4-anilino nicotinic acid 1-oxide (3.5g), ethanol ($50cm^3$), and sulphuric acid ($5cm^3$, d. 1.84) was heated under reflux for 3 days, poured onto ice, neutralised with sodium carbonate, and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated under reduced pressure to give the ester (1.99g, 50.6%) yellow needles, m.p. 77.5-78° (from ether).

(Found: C, 65.39; H, 5.43; N, 10.42; M^+ 258.100435; $C_{14}H_{14}N_2O_3$ requires: C, 65.2; H, 5.44; N, 10.86; M^+ 258.100347).

$\nu_{max.}$ 3350 (N-H), 1695 (C=O)cm^{-1}.

$\tau(CDCl_3)$ 8.61(t, 3H, J 8.0Hz, $-CH_2\underline{CH_3}$), 5.52(q, 2H, J 8.0 Hz, $\underline{CH_2}CH_3$), 2.96(d, 1H, $J_{5,6}$ 7.0Hz, 5-H), 2.65(s, 5H, N-Ph), 1.9(q, 1H, $J_{5,6}$ 7.0Hz, $J_{2,6}$ 2.0Hz, 6-H), 1.21(d, 1H, $J_{2,6}$ 2.0Hz, 2-H) 0.34(broad s, 1H, N-H).

Ethyl 4-Aminonicotinate 1-oxide (193). - a) 4-aminonicotinic acid 1-oxide (1g), ethanol ($50cm^3$) and sulphuric acid ($2cm^3$, d. 1.84) were heated under reflux for 5 days. The mixture was poured onto ice, basified with sodium carbonate, and extracted with chloroform to give the amino-ester (0.17g, 9.4%) plates, m.p. 187-188° (from ether).

(Found: M^+ 182.069137, $C_8H_{10}N_2O_3$ requires: M^+ 182.069140).

b) The above method was repeated, with the reaction time extended to 10 days to give the amino-ester (0.5g, 42.4%).

$\nu_{max.}$ 3450 and 3300 (NH_2), 1710 (C=O)cm^{-1}

$\tau(CDCl_3)$ 8.68(t, 3H, J 7.0Hz, $-CH_2-\underline{CH_3}$), 5.77(q, 2H, J 7.0Hz, $-\underline{CH_2}-CH_3$), 3.1(d, 1H, $J_{5,6}$ 7.0Hz, 5-H), 2.5(broad s, 2H, $\underline{NH_2}$), 2.24(q, 1H, $J_{5,6}$ 7.0Hz, $J_{2,6}$ 2.0Hz, 6-H), 1.41(d, 1H, $J_{2,6}$ 2.0Hz, 2-H).

Ethyl 4-Benzylaminonicotinate 1-oxide (195). - 4-benzylaminonicotinic acid 1-oxide (4g), ethanol ($50cm^3$) and sulphuric acid ($2cm^3$) were heated under reflux for 3 days, poured onto ice, neutralised with sodium carbonate, and extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give an amber oil, which was triturated with ether to yield the amino-ester (2.8g, 62.8%), needles, m.p. 66-67° (from ether).

(Found: C, 62.69; H, 6.66; N, 10.58; M^+ 272.116084; $C_{15}H_{16}N_2O_3.H_2O$ requires: C, 62.1; H, 6.21; N, 9.7; M^+ 272.114998).

$\nu_{max.}$ 3400 (N-H), 1700 (C=O), 1220 (C-O)cm^{-1}.

$\tau(CDCl_3)$ 8.63(t, 3H, J 7.5Hz, $-CH_2-CH_3$), 5.7(q, 2H, J 7.5Hz, CH_2CH_3) 5.5(d, 2H, J 5.5Hz, CH_2-Ph), 3.43(d, 1H, $J_{5,6}$ 7.0Hz, 5-H), 2.71(s, 5H, CH_2-Ph), 1.95(q, 1H, $J_{5,6}$ 7.0Hz, $J_{2,6}$ 2.0Hz, 6-H), 1.5(broad s, 1H, NH-CH_2), 1.35(d, 1H, $J_{2,6}$ 2.0Hz, 2-H).

Attempted preparation of Ethyl-4-acetamidonicotinate 1-oxide. - 4-acetamidonicotinic acid 1-oxide (0.5g), ethanol ($50cm^3$) and sulphuric acid ($2.0cm^3$) were heated under reflux for 36h. The mixture was poured into ice, basified with sodium carbonate, and extracted with chloroform. Evaporation of the dried ($MgSO_4$) chloroform extract gave ethyl-4-amino-nicotinate 1-oxide (0.2g, 41.6%) m.p. 187-188°.

ν_{max} 3450 and 3300 (NH_2), 1715 (C=O)cm^{-1}.

Attempted preparation of ethyl-4-benzamidonicotinate 1-oxide. - 4-Benzamidonicotinic acid 1-oxide (0.4g). ethanol ($50cm^3$), and sulphuric acid ($2.0cm^3$) were heated under reflux for 36h. The mixture was poured onto ice, basified with sodium carbonate, and extracted with chloroform. Evaporation of the dried ($MgSO_4$) chloroform extract gave ethyl-4-amino-nicotinate 1-oxide (0.16g, 35%) m.p. 187-188°.

Ethyl 4-(N-Phenylacetamido)nicotinate 1-oxide. - Ethyl 4-anilinonicotinate 1-oxide (0.5g) and acetic anhydride ($10cm^3$) were heated under reflux for 36h. The excess anhydride was removed under reduced pressure to give a brown oil, which was chromatographed on a column of basic alumina with chloroform as eluent. Collection of the yellow band which developed, and removal of the solvent gave the amido-ester (0.18g, 31.0%) yellow needles, m.p. 143-144° (from ether).

(Found: C, 63.33; H, 5.79; N, 9.02; M^+, 300.110999; $C_{16}H_{16}N_2O_4$ requires: C, 64.00; H, 5.34; N, 9.34; M^+, 300.110283).

$\nu_{max.}$ 1730 (ester C=O), 1670 (amide C=O)cm^{-1}.

Ethyl 4-(N-Phenylbenzamido)nicotinate 1-oxide. - Ethyl-4-anilinonicotinate 1-oxide (0.5g), pyridine ($2cm^3$), and benzoyl chloride (0.35g) were stirred for 8h at room temperature. Water ($30cm^3$) was added, and the mixture was extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and evaporated under reduced pressure to give an oil, which on trituration with ether gave the amido-ester (0.2g, 28.6%) needles, m.p. 179-180° (from ether).

(Found: C, 68.66; H, 4.81; N, 7.76; M^+362.126648; $C_{21}H_{18}N_2O_4$ requires: C, 69.61; H, 4.97; N, 7.74; M^+362.127692).

$\nu_{max.}$ 1720(ester C=O), 1655(amide C=O)cm^{-1}.

Attempted preparation of Ethyl-4-Nitronicotinate 1-oxide. - Ethyl nicotinate 1-oxide (2.0g), sulphuric acid ($10cm^3$) and fuming nitric acid ($10cm^3$) were heated under reflux for 24h. The mixture was poured onto ice, neutralised with sodium carbonate, and extracted with chloroform. Evaporation of the chloroform extract gave 0.02g of an unidentifiable oil. The aqueous layer was evaporated to dryness and extracted with boiling ethanol. Fractional crystallisation of the ethanol gave ethyl nicotinate 1-oxide (1.2g) and nicotinic acid 1-oxide (0.3g, 14%). Melting points and infrared spectra were identical with those of authentic samples.

Attempted preparation of Methyl 4-Nitronicotinate 1-oxide. - 4-nitronicotinic acid 1-oxide (0.75g), methanol ($25cm^3$) and sulphuric acid ($1cm^3$) were heated under reflux for 6h. The solution was poured onto ice, basified with sodium carbonate and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated under reduced pressure to give a white solid, which was shown to be methyl-4-methoxynicotinate 1-oxide (0.49g, 66.2%) needles m.p. 139.5-140°.

(Found: C, 51.94; H, 5.04; N, 7.50; M^+ 183.053152; $C_8H_9NO_4$ requires: C, 52.46; H, 4.92; N, 7.65; M^+ 183.052635).

$\nu_{max.}$ 1715 (C=O) 1230 (C-O)cm^{-1}

$\tau(CDCl_3)$ 6.1(s, 3H, $COO\underline{CH_3}$), 6.0(s, 3H, $O\underline{CH_3}$) 2.95(d, 1H, J 7.0Hz, 5-H), 1.64(q, 1H, $J_{5,6}$ 7.0Hz, $J_{2,6}$ 2.0Hz, 6-H), 1.4(d, 1H, $J_{2,6}$ 2.0Hz, 2-H).

Attempted preparation of Ethyl 4-Nitronicotinate 1-oxide. - 4-nitronicotinic acid 1-oxide (0.75g), ethanol ($20cm^3$) and sulphuric acid ($1cm^3$, d. 1.84) were heated at 60° for 8h. The solution was poured onto ice, basified with sodium carbonate, and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated under reduced pressure to give a white solid, which was shown to be ethyl-4-ethoxynicotinate 1-oxide (0.54g, 62.8%) needles, m.p. 51-52° (from ether).

(Found: C, 48.48; H, 6.68; N, 5.60; M^+ 211.084451; $C_{10}H_{13}NO_4 2H_2O$. requires: C, 48.58; H, 6.88; N, 5.67; M^+ 211.083705).

$\nu_{max.}$ 1710 (C=O), 1230 (C-O)cm^{-1}

$\tau(CDCl_3)$ 8.5(t, 6H, J 7.0Hz, $-CH_2\underline{CH_3}$), 5.6(q, 4H, J=7.0Hz, $\underline{CH_2}-CH_3$), 2.9(d, 1H, J=7.0Hz, 5-H), 1.6(d, 1H, J 7.0hz, 6-H), 1.39(s, 1H, 2-H).

Attempted esterification of 4-nitronicotinic acid 1-oxide. - Nitronicotinic acid 1-oxide (1.0g) and methanol ($30cm^3$) were heated under reflux

for 24h. Evaporation of the solvent gave an amber resin which could not be made to crystallise by trituration with ether. Extraction of an aqueous emulsion of the resin with chloroform, followed by evaporation of the chloroform extract gave a dark brown gum from which no solid material could be isolated.

Pyridine-3,4-dicarboxylic Acid 1-oxide. - Pyridine-3,4-dicarboxylic acid (5g), glacial acetic acid (15cm^3), and hydrogen peroxide (15cm^3, 40%) were heated on a steam bath for 10h. The solvent was evaporated under reduced pressure, and the residue recrystallised from water to give the N-oxide (3.8g, 69.3%) plates, m.p. 249-250^o (from water). (lit.[19] 249-250^o).

$\nu_{max.}$ 1710 and 1650 (C=O)cm^{-1}.

Methyl pyridine-3,4-dicarboxylate 1-oxide - Method A. Sulphuric acid (12cm^3, d. 1.84) was added dropwise to a mixture of ice cold iso-quinoline N-oxide (5g), annydrous copper sulphate (0.14g) and mercuric nitrate monohydrate (0.3g) with cooling. Nitric acid (14cm^3, d. 1.4) was added dropwise (to the mixture) at 210-230^o over a period of 2h. Air was then drawn through for a further 0.5h and the solution cooled. Urea (1.5g) was added and the mixture heated at 100^o for 0.5h. Methanol (20cm^3) and benzene (15cm^3) were added and the solution was heated under reflux for 7h. The resulting solution was poured onto ice and the pH adjusted to 10 with ammonia solution (d. 0.88). The benzene layer was separated off, and the aqueous layer extracted with chloroform. The chloroform layer was washed with aqueous sodium carbonate solution and water. The combined residues from the chloroform extraction and the benzene layer were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a brown oil, which on trituration with ether gave the di-ester-N-oxide (2.8g, 38.5%) off-white needles, m.p. 98-100^{o}C (from ether).

(Found: C, 51.36; H, 4.45; N, 6.78; $\underline{M}^+$211.048066; $C_9H_9NO_5$ requires: C, 51.18; H, 4.27; N, 6.64; $\underline{M}^+$211.048485).

ν_{max} 1735 & 1720 (C=O), 1320 (N-O), 1250 (C-O)cm^{-1}

τ_{CDCL_3} 6.19(s, 6H, $O\underline{CH_3}$), 2.54(d, 1H, $\underline{J}$ 6.5Hz, 5-H), 1.98(q, 1H, $\underline{J}_{5,6}$ 6.5Hz, $\underline{J}_{2,6}$ 2Hz, 6-H), 1.92(s, 1H, 2-H).

Method B. Pyridine-3,4-dicarboxylic acid 1-oxide (4g), methanol ($25cm^3$) and sulphuric acid ($2cm^3$, d. 1.84) were heated under reflux for 30h. The mixture was poured onto ice, basified with sodium carbonate, and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated under reduced pressure to give an amber oil, which on trituration with ether gave the di-ester-N-oxide (1.8g, 39.0%). The m.p. and infrared spectrum were identical to the product obtained by Method A.

ii) 1,2,5,6-tetrahydropyridines

Ethyl 4-Aminonicotinate (231). - 4-Aminonicotinic acid (0.4g), ethanol (50cm^3) and sulphuric acid (2cm^3, d. 1.84) were heated under reflux for 3 days. The solution was poured onto ice, basified with ammonia solution (d. 0.88) and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated under reduced pressure to give the ester (0.4g, 66.7%) m.p. 104-106° (lit.[138] 100-105°).

$\nu_{max.}$ 3400 and 3200 (NH), 1695(C=O), 1260 (C-O)cm^{-1}.

τ_{CDCl_3} 8.63(t, 3H, J 8.0Hz, CH_2-CH_3), 5.61(q, 2H, J 8.0Hz, CH_2-CH_3), 3.38(d, 1H, J 6.0Hz, 5-H), 2.91(broad s, 2H, NH_2), 1.81(d, 1H, J 6.0Hz, 6-H), 1.08(s, 1H, 2-H).

4-Amino-3-ethoxycarbonyl-1-methyl Pyridinium Iodide.(232) - Ethyl-4-aminonicotinate (0.4g), methyl iodide (0.5g) and ethanol (10cm^3) were heated under reflux for 3h. The solvent was removed under reduced pressure, and trituration of the resultant oil with ether gave the methiodide (0.5g, 67.6%) needles, m.p. 164-165°C.

$\nu_{max.}$ 3380 and 3190 (NH_2), 1710 (C=O), 1290 (C-O)cm^{-1}.

4-Amino-3-ethoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine (233). 4-Amino-3-ethoxycarbonyl-1-methyl pyridinium iodide (0.5g) was dissolved in water (20cm^3) and sodium borohydride (0.11g) added slowly. The solution was stirred at room temperature for 2h and extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and the solvent removed under reduced pressure to give a yellow oil, which was triturated with ether to give the tetrahydropyridine (0.29g, 96.7%) needles, m.p. 47-49° (from ether).

(Found: C 58.57; H, 8.62; N, 15.31; $C_9H_{16}N_2O_2$

requires: C, 58.7; H, 8.7; N, 15.23).

$\nu_{max.}$ 3450 and 3330 (NH), 2800 ($N-CH_3$), 1720 (C=O),

$\nu_{max.}$ 1620 (C=O), 1240 (C-O)cm^{-1}.

$\tau(CDCl_3)$ 8.72(t, 3H, J 7.5Hz, $CH_2-\underline{CH_3}$), 7.68(s, 3H, $N-\underline{CH_3}$), 7.6(m, 4H, $=C-\underline{CH_2}-\underline{CH_2}-N$), 6.92(s, 2H, $-N-\underline{CH}-C=$), 5.91(q, 2H, J 7.5Hz, $\underline{CH_2}-CH_3$), 3.6(broad s, 2H, $\underline{NH_2}$).

Methyl Pyridine-3,4-dicarboxylate. - Sulphuric acid (240cm^3, d. 1.84) was added dropwise to a mixture of isoquinoline (106.4g), anhydrous copper sulphate (2.8g) and mercuric nitrate monohydrate (6.0g) cooled by an external ice-salt bath. Nitric acid (284 cm^3, d. 1.40) was added dropwise to the mixture at 210 - 230° over a period of 2.5h. Air was then drawn through for a further 0.5h and the solution cooled. Urea (30.0g) was added and the mixture heated at 100° for 0.5h and then cooled to room temperature. Methanol (360cm^3) and benzene (240cm^3) were added and the solution heated under reflux for 7h. The resulting solution was poured onto ice and the pH adjusted to 10.0 with ammonia solution (d. 0.88). The benzene layer was separated off, and the aqueous layer extracted with chloroform (3 x 360cm^3). The chloroform layer was washed with aqueous sodium carbonate solution and water. The combined benzene and chloroform extracts were distilled under reduced pressure to give the ester (74.0g, 46.0%) b.p. 98-105°/1.5m.m. (lit.[127] 95-100°/1.5mm).

$\nu_{max.}$ 1730 (C=O)cm^{-1}.

3,4-Dimethoxycarbonyl-1-methyl pyridinium iodide (244). - Methyl pyridine 3,4-dicarboxylate (10g) methyl iodide (12cm^3) and ethanol (5cm^3) were stirred at room temperature for 3hrs. The resultant yellow solid was filtered to give the quaternary (16.7g 96.6%) m.p. 150-151° (from ethanol).

Pyridine-3,4-dicarboxylic Acid. - Methyl pyridine-3,4-dicarboxylate (74.0g) and hydrochloric acid (230cm^3, 3.5N) were heated under reflux for 4h. Evaporation to dryness under reduced pressure gave the acid (60.5g, 95.4%) m.p. 252-254° (lit.[127] 253-255°).

$\nu_{max.}$ 1710 (C=O)cm^{-1}. 1260 (C-O)

Cinchomeronimide. - Pyridine-3,4-dicarboxylic acid (22.5g) and acetic anhydride (75cm^3) were heated together under reflux for 3h. The mixture was distilled until 37cm^3 of acetic acid and acetic anhydride had been collected, acetamide (14.0g) was added, and the mixture heated at 120-125° for 8h. The solution was cooled to give the imide (16.2g, 81.2%) m.p. 228-230° (from ethanol) (lit.[141] 229-230°).

$\nu_{max.}$ 2750 (NH), 1720 (C=O)cm^{-1}.

3-Aminopyridine-4-carboxylic Acid(234). - Finely powdered cinchomeronimide (10.0g) was dissolved in a well stirred, ice cold, solution of potassium hypobromite, prepared from bromine (4.6g) and aqueous potassium hydroxide solution (75cm^3, 10%). After 2h a further 40cm^3 of the potassium hydroxide solution was added, and the mixture was heated on a steam bath for 10 minutes. The solution was acidified with hydrochloric acid (d. 1.16) and evaporated to dryness under reduced pressure. The residue was extracted with boiling absolute ethanol and the filtered solution concentrated to a small volume to give the amino-acid dihydrochloride (7.3g, 78.3%), m.p. 243-244° (lit.[141] 244-245°).

$\nu_{max.}$ 3330 and 3430 (NH), 1690 (C=O)cm^{-1}.

Methyl 3-Aminoisonicotinate (235). - 3-Aminoisonicotinic acid (0.5g), methanol ($20cm^3$), benzene ($20cm^3$) and sulphuric acid ($2cm^3$) were heated under reflux for 3 days, the water produced being removed by a Dean and Stark apparatus. The solution was poured onto ice, basified with sodium carbonate, and extracted with chloroform. The chloroform solution was dried, and the solvent removed under reduced pressure to give the ester (0.32g, 58.2%) m.p. 85-86° (lit.[168] 86-87°).

$\nu_{max.}$ 3400 and 3250 (NH_2), 1740 (C=O)cm^{-1}.

Ethyl 3-aminoisonicotinate (236). - 3-Aminoisonicotinic acid (2.5g) ethanol ($40cm^3$) and sulphuric acid ($2cm^3$, d. 1.84) were heated under reflux for 3h. The solution was poured onto ice, basified with ammonia solution (d. 0.88) and extracted with ether. The ether extract was dried ($MgSO_4$) and the solvent removed to give the ester (1.85g, 61.7%) m.p. 100-107°.

$\nu_{max.}$ 3450 and 3200 (NH) 1710 (C=O), 1240(C-O)cm^{-1}.

3-Amino-4-methoxycarbonyl-1-methyl Pyridinium Iodide (237). - Methyl-3-aminoisonicotinate (0.3g), methyl iodide (0.5g) and ethanol ($10cm^3$) were heated under reflux for 1h. Cooling gave the methiodide (0.62g, 63.9%), needles, m.p. 169-171° (from ethanol).

(Found: C, 32.75; H, 3.94; N, 9.28; I, 43.51; $C_8H_{11}N_2O_2I$ requires: C, 32.7; H, 3.64; N, 9.52; I, 43.2.).

ν_{max} ($CHCl_3$) 3450 and 3400 (N-H), 1730 (C=O), 1290 (C-O)cm^{-1}.

3-Amino-4-ethoxycarbonyl-1-methyl Pyridinium Iodide (238). - Ethyl-3-aminoisonicotinate (1.5g), methyl iodide (2.0g) and ethanol ($10cm^3$) were heated under reflux for 1h., cooled, and the methiodide filtered off. (2.2g, 79.4%) m.p. 129-131°.

$\nu_{max.}$ 3390 and 3210 (NH), 1690 (C=O)cm^{-1}.

3-Amino-4-methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine (239). - 3-Amino-4-methoxycarbonyl-1-methyl pyridinium iodide (0.3g) was dissolved in

water ($10cm^3$) and sodium borohydride (0.04g) added slowly. The mixture was stirred at room temperature for 2h and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and the solvent removed under reduced pressure to give the tetrahydropyridine (0.13g, 83.9%) needles, m.p. 121-122° (from ether).

(Found: C, 54.68; H, 7.90; N, 15.60; $C_8H_{14}N_2O_2$ requires: C, 56.4; H, 8.23; N, 16.45).

$\nu_{max.}$ 3450 and 3200 (NH), 1740 (C=O), 1270(C-O)cm^{-1}.

3-Amino-4-ethoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine (240). - 3-Amino-4-ethoxycarbonyl-1-methyl pyridinium iodide (0.9g) was dissolved in water and sodium borohydride (0.22g) was added slowly. The solution was stirred for 2h, extracted with chloroform, and the chloroform solution was dried and evaporated under reduced pressure to give a pale yellow oil. The oil was triturated with ether to give the tetrahydropyridine (0.52g, 96.3%), needles, m.p. 65-66° (from ether).

(Found: C, 58.95; H, 8.59; N, 15.15; $C_9H_{16}N_2O_2$ requires: C, 58.7; H, 8.7; N, 15.23.).

$\nu_{max.}$ 3400 and 3290 (NH), 2850 ($N-CH_3$), 1710 (C=O), 1620 (C=C)cm^{-1}.

$\lambda_{max.}$ 285 n.m.

$\tau(CDCl_3)$ 8.79(t, 3H, J 7.0Hz, $CH_2-\underline{CH_3}$), 7.79(s, 3H, $N-\underline{CH_3}$), 7.65(m, 4H, $=C-\underline{CH_2}-\underline{CH_2}-CH-N-$), 7.14(s, 2H, $-N-\underline{CH_2}-C=$), 5.92(q, 2H, J 7.0Hz, $\underline{CH_2}-CH_3$), 3.9(broad s, 2H, $\underline{NH_2}$).

3-Benzamido-4-methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine hydrochloride (241). - 3-Amino-4-methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine (0.09g), pyridine (0.1g), and benzoyl chloride (0.15g) were stirred at room temperature for 0.25h. The resultant precipitate was collected, dissolved in absolute ethanol and precipitated by the addition of ether to give the amido-ester (0.07g, 43.8%), needles, m.p. 194-195° (from ethanol).

(Found: C, 56.36; H, 6.63; N, 7.96; $C_{15}H_{19}N_2O_3Cl.H_2O$ requires: C, 54.80; H, 6.39; N, 8.52.).

νmax. 3150 (N-H), 2500-2400 ($=N^+(H)-$), 1710 (C=O),

$\nu_{max.}$ 1270 (C-O)cm^{-1}.

3-Amino-4-ethoxycarbonyl-1,2,6-trimethyl pyridinium iodide (243). - 3-Amino-2,6-dimethyl-4-ethoxycarbonyl pyridine (1g), methyl iodide (1.5g) and ethanol (10cm^3) were heated under reflux for 60h. The excess solvent was removed, and the residual oil was triturated with ether to give the methiodide (0.75g, 43.4%), needles, m.p. 194-195° (from ethanol).

$\nu_{max.}$ 3400 and 3300 (NH_2), 2700 ($N-CH_3$), 1695 (C=O), 1240 (C-O)cm^{-1}.

Attempted preparation of 3-amino-4-ethoxycarbonyl-1,2,6-trimethyl-1,2,5,6-tetrahydropyridine. - 3-Amino-4-ethoxycarbonyl-1,2,6-trimethyl pyridinium iodide (0.4g) was dissolved in water (20cm^3) and sodium borohydride (0.1g) added slowly. The solution was stirred at room temperature for 3h and the precipitated yellow solid was filtered. This solid was shown to be 3-amino-2,6-dimethyl-4-ethoxycarbonyl pyridine by mixed melting point and identical infrared spectrum with an authentic sample (0.18g, 78.3%).

The filtrate was extracted with chloroform, the chloroform solution was dried and evaporated under reduced pressure to give a yellow oil, which on trituration with ether gave a further 0.04g (12.4%) of 3-amino-

2,6-dimethyl-4-ethoxycarbonyl pyridine.

Reduction of 3,4-dimethoxycarbonyl-1-methyl pyridinium iodide by sodium borohydride. - i) Sodium borohydride (0.38g) was added slowly to a solution of 3,4-dimethoxycarbonyl-1-methyl pyridinium iodide (3.36g) in water ($25cm^3$), and the mixture was stirred at room temperature for 4h. The solution was extracted with chloroform, and the dried ($MgSO_4$)chloroform extract was evaporated under reduced pressure to give an amber oil, which began to crystallise on standing. Trituration with ether gave a solid which was identified as 3,4-dimethoxycarbonyl-1-methylpyrid-6-one (0.69g, 30.8 %), needles, m.p. 162-163° (from ethanol).

(Found: C, 53.43; H, 5.02; N, 6.40; M^+225.063716; $C_{10}H_{11}NO_5$ requires: C, 53.4; H, 4.90; N, 6.22; M^+225.063195).

$\nu_{max.}$ 1715, 1705 (ester C=O), 1665 (amide C=O)cm^{-1}.

$\tau(CDCl_3)$ 6.4(s, 3H, N-CH_3), 6.17(s, 3H, 3-COOCH_3), 6.09(s, 3H, 4-COOCH_3), 3.45(s, 1H, 5-H), 1.81(s, 1H, 2-H).

Thin-layer chromatography of the oil after removal of the pyridone, on silica gel with ether as eluant, indicated 3 components. Column chromatography gave 2 oils from which no pure material could be isolated.

ii) Sodium borohydride (0.38g) was added to a solution of the quaternary salt (3.36g) in water ($25cm^3$) and the mixture was heated under reflux for 10h. Extraction of the cooled solution with chloroform, followed by evaporation of the dried ($MgSO_4$) chloroform extract, gave a dark red oil. Thin-layer chromatograph on silica gel using ether:benzene, 3:1 as eluant indicated seven components.

iii) Sodium borohydride (0.38g) was added to a solution of the methiodide (3.36g) in water ($25cm^3$) and the solution was stirred at room temperature for 24h. The solution was extracted with chloroform and the dried ($MgSO_4$) chloroform extract was evaporated under reduced pressure to give an amber

oil. Trituration with ether gave a solid with m.p. and infrared spectrum identical to those of 3,4-dimethoxycarbonyl-1-methylpyrid-6-one(0.77g, 34.2%).

Thin layer chromatography on silica gel with ether as eluant, and gas-liquid chromatography on Carbowax 20M KOH, both showed the remaining oil to contain 1 major component. The oil was dissolved in ethanol, and dry hydrogen chloride was bubbled through the solution. The solution was reduced to small volume and trituration with ether gave a white precipitate of 3,4-dimethoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine hydrochloride (1.29g,52.1%), needles, m.p. 182-183° (from ethanol).

(Found: C, 47.90; H, 6.32; N, 5.83; Cl 14.15; $C_{10}H_{15}NO_4Cl$ requires: C, 48.15; H, 6.41; N, 5.62; Cl 14.22).

$\nu_{max.}$ 1710 (C=O), 1645 (C=C)cm^{-1}

$\tau_{(D_2O)}$ 6.94(s, 3H, N-CH_3) 6.5-7.1(m, 6H, =C-CH_2-CH_2-N-CH_2)
6.16(s, 3H, 3-COOCH_3), 6.14(s, 3H, 4-COOCH_3).

iv) Sodium borohydride (0.38g) was added to a solution of the methiodide (3.36g) in methanol ($30cm^3$) and the mixture was stirred for 24h. Excess solvent was removed, water ($50cm^3$) was added and the solution was extracted with chloroform. The dried ($MgSO_4$) chloroform extract was evaporated under reduced pressure to give an amber oil; trituration with ether gave 3,4-dimethoxycarbonylpyrid-6-one (0.38g, 16.8%) m.p. 162-163°.

v) The above reaction was repeated, with the reaction mixture maintained in an atmosphere of nitrogen; the yield of the pyridone was 11.4%.

vi) The reaction under nitrogen was repeated with water as the solvent; the yield of the pyridone was 27.4%.

vii) The reaction between sodium borohydride (0.38g) and the quaternary salt (3.36g) in aqueous solution was repeated, but the mixture was extracted with chloroform after 15 minutes. Evaporation of the chloroform extract gave an amber oil which on trituration gave the pyridone.

The pyridone was removed and the ether evaporated to give a residual amber oil. A mass spectrum of the oil showed no fragment of m/e 213, indicating no tetrahydropyridine formation; the fragment at m/e 211 indicated the presence of a dihydropyridine.

viii) The above procedure was repeated using sodium borodeuteride and deuterium oxide. The corresponding mass spectrum showed no fragment at m/e 215, indicating no tetrahydropyridine containing two deuterium atoms.

3,4-Dicarboxy-1-methylpyrid-6-one

1-Methyl Pyridine-3,4-dicarboxylate-6-one (246) - Method A. Sodium hydroxide solution (4.0cm^3, 0.0242M) and warm potassium ferricyanide solution (12.0cm^3, 0.019M) were added during 3h, with shaking, to a solution of 1-methyl-3,4-dimethoxycarbonyl pyridinium iodide (1.8g in 10cm^3 water). After the final addition of ferricyanide, the solution was maintained at 40-55° for 1h., cooled, and acidified with hydrochloric acid (6N) to give a white solid and a dark green solution. The solid was boiled with absolute ethanol and the inorganic material was filtered off. The filtrate was evaporated to dryness under reduced pressure to give the pyridone (0.42g, 39.9%), needles, m.p. 261-262° (from ethanol).

(Found: C, 44.49; H, 4.31; N, 6.88; M^+ 197.032029; $C_8H_7NO_5.H_2O$ requires: C, 44.65; H, 4.19; N, 6.51; M^+ 197.032417).

$\nu_{max.}$ 3450-3500 (OH), 1710, 1690 (acid C=O), 1640 (amide C=O), 1270 (C-O)cm^{-1}.

Method B. 1-Methyl-3,4-dimethoxycarbonyl pyridinium iodide (0.95g) was added to aqueous sodium hydroxide (20cm^3, 8%) and air was drawn through the well stirred solution for 6h. The basic solution was extracted with chloroform, and the chloroform extract was dried ($MgSO_4$) and the solvent removed to give a dark brown oil which could not be identified (0.01g). The basic solution was acidified with hydrochloric acid (50%) and the precipitate which formed on standing was collected. The solid

had m.p. and I.R. spectrum were identical with those of the material prepared by Method A. (0.03g, 5.4%).

3,4-Dimethoxycarbonyl-1-methyl-6-pyridone (245). - 1-Methyl pyridine-3,4-dicarboxylate-6-one (0.1g), methanol ($40cm^3$) and sulphuric acid ($0.5cm^3$ d. 1.84) were heated under reflux for 36h. The excess methanol was evaporated under reduced pressure, and the solution was poured onto ice and basified with sodium carbonate. The basic solution was extracted with chloroform, and the chloroform solution was dried ($MgSO_4$) and evaporated under reduced pressure to give a pale yellow oil. Trituration with ether gave the pyridone di-ester which had m.p., I.R., and mass spectra identical with those of the product obtained by the reaction of sodium borohydride on 3,4-dimethoxycarbonyl-1-methyl pyridinium iodide (0.08g, 70.0%), needles, m.p. 162-163°.

$\nu_{max.}$ 2800 ($N-CH_3$), 1720, 1700 (ester C=O), 1665

$\nu_{max.}$ (amide C=O), 1260 (C-O)cm^{-1}.

$\tau(CDCl_3)$ 6.4(3H, s, $N-\underline{CH_3}$), 6.18(3H, s, $4-COO\underline{CH_3}$), 6.09(3H, s, $3-COO\underline{CH_3}$), 3.46(1H, s, 5-H), 1.82(1H, s, 2-H).

Ethyl Pyridine 3,4-dicarboxylate. - Pyridine 3,4-dicarboxylic acid (5g), ethanol ($100cm^3$) and sulphuric acid ($5cm^3$, d. 1.84) were heated under reflux for 3 days. The excess solvent was removed and the mixture was poured onto ice, neutralised with sodium carbonate, and extracted with chloroform. Evaporation of the dried ($MgSO_4$) chloroform extract gave the di-ester (6g, 89.9%) b.p. 160°/14mm. (lit.[168] 172°/21mm).

$\nu_{max.}$ 1720 (C=O)cm^{-1}.

$\tau(CDCl_3)$ 8.68(t, 6H, J 7.0Hz, $CH_2-\underline{CH_3}$), 5.6(q, 4H, J 7.0Hz, $\underline{CH_2}-CH_3$), 2.5(d, 1H, J 5.0Hz, 5-H), 1.21(d, 1H, J 5.0Hz, 6-H), 0.92(s, 1H, 2-H).

3,4-Diethoxycarbonyl-1-methyl pyridinium iodide (260). - Ethyl pyridine 3,4-dicarboxylate (6g), methyl iodide (6g) and ethanol ($5cm^3$) were warmed on a steam bath for 1h. Evaporation of the solvent and trituration with ether gave the quaternary (69g, 91.8%) m.p. 96-97°.

3,4-Diethoxycarbonyl-1-methyl-6-pyridone (262). - 3,4-Diethoxycarbonyl-1-methyl pyridinium iodide (3.60g) was dissolved in water ($20cm^3$) and sodium borohydride (0.38g) was added slowly. The solution was stirred for 2h, extracted with chloroform, and the chloroform extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residual amber oil was triturated with ether to give the pyridone (0.36, 29.4%) plates, m.p. 170-171° (from ethanol).

(Found: M^+, 253.095014; $C_{12}H_{15}NO_5$ requires: M, 253.096848).

$\nu_{max.}$ 1715-1705 (ester C=O), 1660 (amide C=O), 1260 (C-O)cm^{-1}.

τ_{CDCl_3} 8.7(t, 3H, J 7.0Hz, 3-$COOCH_2\underline{CH_3}$), 8.67(t, 3H, J 7.0Hz, 4-$COOCH_2\underline{CH_3}$), 6.42(s, 3H, N-$\underline{CH_3}$), 5.73(q, 2H, J 7.0Hz, 3-$COO\underline{CH_2}CH_3$), 5.65(q, 2H, J 7.0Hz, 4-$COO\underline{CH_2}CH_3$), 3.46(s, 1H, 5-H), 1.85(s, 1H, 2-H).

1-Ethyl-3,4-dimethoxycarbonyl Pyridinium Iodide (261). - Methyl pyridine 3,4-dicarboxylate (5g), ethyl iodide (6g) and absolute ethanol ($10cm^3$) were heated under reflux for 1h. The ethanol was removed under reduced pressure and the residual oil was triturated with ether to give the methiodide (8.2g, 91.1%) needles, m.p. 128-130° (from ethanol).

$\nu_{max.}$ 1720 (C=O), 1270 (C-O)cm^{-1}.

1-Ethyl-3,4-dimethoxycarbonyl-6-pyridone. - Sodium borohydride (0.19g) was added to a solution of 1-ethyl-3,4-dimethoxycarbonyl pyridinium iodide (1.75g) in water ($10cm^3$) and the mixture stirred for 8h. The solution was extracted with chloroform and the chloroform solution was dried ($MgSO_4$) and

evaporated under reduced pressure to give an amber oil. Trituration with ether gave the pyridone (0.16g, 13.6%) m.p. 168-169° (from ethanol).

(Found: M^+, 239.079365; $C_{11}H_{13}NO_5$ requires: M, 239.078432).

$\nu_{max.}$ 2800 ($N-CH_2$), 1730-1720 (ester C=O), 1670 (amide C=O), 1275 (C-O)cm^{-1}.

τ_{CDCl_3} 8.61(t, 3H, J 7.0Hz, $-CH_2-CH_3$), 6.16(s, 3H, $4-COOCH_3$), 6.1(s, 3H, $3-COOCH_3$), 5.96(q, 2H, J 7.0Hz, $N-CH_2-CH_3$), 3.44(s, 1H, 5-H), 1.81(s, 1H, 2-H).

Bicyclic Systems Derived from 1,3,4-trisubstituted pyridines.

Pyrido[4,3-d]pyrimidin-4(3H)-one 6-oxide (270). - 4-Aminonicotinic acid 1-oxide (0.6g) and formamide (1.8g) were heated together at 170-180° for 2h., cooled, and triturated with absolute ethanol. The insoluble brown solid was collected and sublimed under vacuum to give the pyrido-pyrimidine (0.35g, 55.6%), colourless plates, m.p. 337-338° (from acetic acid).

(Found: M^+, 163.037115; $C_7H_5N_3O_2$ requires: M^+ 163.038173).

$\nu_{max.}$ 2650 (N-H), 1690 (C=O)cm^{-1}.

Pyrido[4,3-d]pyrimidin-2,4(1H,3H)-dione 6-oxide (271). - An intimate mixture of 4-aminonicotinic acid-1-oxide (0.6g) and urea (0.3g) was heated at 160-170° for 1.5h, cooled, and triturated with absolute ethanol. The insoluble brown solid was collected and recrystallised from acetic acid to give the dione (0.36g, 51.4%), plates, m.p. >360° (from acetic acid).

(Found: C, 46.51; H, 3.02; N, 23.43; M^+ 179.033087; $C_7H_5N_3O_3$ requires: C, 46.92; H, 2.79; N, 23.46; M^+ 179.032544)

$\nu_{max.}$ 2850 (N-H), 1720, 1700 (C=O)cm^{-1}.

Attempted preparation of 3-phenylpyrido[4,3-d]pyrimidin-2,4,(1H,3H)-dione 6-oxide. - Method A. An intimate mixture of 4-aminonicotinic acid 1-oxide (0.15g) and formanilide (0.2g) was heated at 170° for 2h., and cooled. Trituration with absolute ethanol gave a product with m.p. and I.R. spectrum identical to those of the starting material (0.13g).

Method B. The reation was repeated with heating at 200° for 6h. Trituration with ethanol gave unchanged starting material.

Method C. 0.15g of 4-aminonicotinic acid 1-oxide, and 0.2g of formanilide were fused at 180°C for 18h. The resultant solid was extracted with

boiling absolute alcohol (5 x 25cm^3) and the ethanolic solution was evaporated to dryness under reduced pressure to give a solid whose m.p. and I.R. spectrum were identical with those of the starting material (0.11g). The solid which was insoluble in ethanol was sublimed under vaccuum to give colourless crystals, with m.p. and I.R. spectrum identical to those of 4-aminonicotinic acid (0.02g., 14.9%) m.p. 333-335° (decomp.) (lit. 335-336°)

$\nu_{max.}$ 3325 and 3200 (N-H), 2750 (bonded OH),

$\nu_{max.}$ 1690 (C=O) 1240 (C-O)cm^{-1}.

Method D. Ethyl 4-aminonicotinate 1-oxide (0.15g) and formanilide (0.3g) were heated at 180° for 4h. The mixture was cooled and triturated with benzene to give a brown solid (0.12g) with m.p. and I.R. spectrum identical to those of the starting material.

Attempted preparation of 1-phenyl substituted pyridopyrimidinones.

(A) From 4-Anilinonicotinic acid.

i) Fusion of 4-anilinonicotinic acid 1-oxide (1.0g) with formamide (1.5g) at 180° for 2h. gave unchanged starting material.

ii) Fusion at 240° for 6h gave unchanged 4-anilinonicotinic acid 1-oxide.

iii) Fusion at 250° for 16h gave starting material and a black oil which could not be identified.

(iv) 4-Anilinonicotinic acid and urea, heated at 170° for 8h gave unchanged starting material.

(B) From o-amido esters

i) Methanol (20cm^3) was saturated at 0° with ammonia, and 3-ethoxycarbonyl-4-(N-phenylacetamido)pyridine 1-oxide (100mg) was added. The mixture was heated in a steel bomb at 160°, under pressure, for 5h, cooled and the excess solvent evaporated under reduced pressure. Trituration of the resultant oil with ether gave a yellow solid which was identified as 4-anilinonicotinamide 1-oxide (0.01g, 13.1%) m.p. 280-282°.

$\nu_{max.}$ 3400 and 3280 (NH_2), 1645 (amide C=O)cm^{-1}.

ii) 3-Ethoxycarbonyl-4-(N-phenylacetamido)pyridine 1-oxide (0.05g) was stirred in a solution of ammonia in ethanol at room temperature for 30 days. The solution was extracted with chloroform, dried ($MgSO_4$), and the solvent removed under reduced pressure. Trituration of the resultant oil with ether gave a yellow solid with m.p., I.R., and mass spectra identical to those of 4-anilinonicotinamide 1-oxide (0.005g, 14.3%).

iii) 3-Ethoxycarbonyl-4-(N-phenylacetamido)pyridine 1-oxide (0.1g) and hydrazine hydrate ($1cm^3$) reacted under the above conditions gave 4-anilino-nicotinic acid hydrazide 1-oxide (0.01g, 12.3%) m.p. 220-221°C.

(Found: $(M-16)^+$ 228.101105; $C_{12}H_{12}N_4O$

requires: $(M-16)^+$ 228.100361),

$\nu_{max.}$ 3420 and 3290 (NH_2), 1650 (amide C=O)cm^{-1}.

iv) 3-Benzamido-4-ethoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine (0.15g), hydrazine hydrate ($1cm^3$) and ethanol ($5cm^3$) were heated at 60° for 36h. Evaporation of the excess solvent gave a gum from which no pure material could be isolated.

Attempted preparation of 1-benzylpyrido[4,3-d]-pyrimidin-4-one 6-oxide.

Method A. - 4-Benzylaminonicotinic acid 1-oxide (0.5g) and formamide (2g) were heated at 170° for 2h and cooled. The resultant solid, which had a strong characteristic odour, was boiled with absolute ethanol and the insoluble material collected. The solid had a m.p., I.R. spectrum, and mass spectrum identical with that of pyrido [4,3-d]pyrimidin-4(3H)-one 6-oxide (0.11g, 32.9%) m.p. 336-337°.

$\nu_{max.}$ 2650(N-H), 1690(C=O)cm^{-1}.

The filtrate was evaporated under reduced pressure to give a dark brown oil which on trituration with ether gave a solid with m.p. and I.R. spectrum identical to those of the starting material. (0.15g) m.p. 285°C.

$\nu_{max.}$ 2650(N-H), 1690(C=O)cm^{-1}.

Method B. 4-Benzylaminonicotinic acid 1-oxide (0.23g) and formamide (0.30g) were heated at 200° for 6h. and cooled. The mixture was boiled with absolute ethanol and the insoluble material, which had m.p. and I.R. spectrum were identical to pyrido[4,3-d]pyrimidin-4(3H)-one-6-oxide, was collected (0.04g, 26.0%).

The filtrate was reduced to half volume under reduced pressure, cooled, and the resultant precipitate collected. The mass spectrum of the material showed a molecular ion the same as that to be expected of the desired product (0.01g, 4.2%)

m.p. 276-280°

$\nu_{max.}$ 1660 (C=O)cm^{-1}.

Further evaporation of the filtrate yielded a brown solid whose m.p. and I.R. spectrum were identical with those of the starting material (0.10g).

The above conditions were repeated on a larger scale, but the required product could not be obtained.

Increasing the reaction temperature and extending the reaction time gave the starting material and pyrido[4,3-d]pyrimidin-4(3H)-one-6-oxide as the only isolatable products.

2-(4-Methoxyphenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (299). - 4-Aminonicotinic acid 1-oxide (1.0g), dry pyridine (1.0g) and 4-methoxybenzoyl chloride (1.75g) were stirred at room temperature for 0.25h., and then warmed in a steam bath for a further 0.5h. The mixture was filtered, and the resultant solid was washed with water and extracted with boiling benzene (3 x 100cm^3). The benzene solution was dried ($MgSO_4$), excess solvent removed under reduced pressure, and the mixture cooled to yield the

oxazine (0.98g, 55.9%) needles, m.p. 258-259° (from benzene).

(Found: C, 61.11; H, 3.73; N, 9.89; $\underline{M}^+$270.064051; $C_{14}H_{10}N_2O_4$ requires: C, 62.22; H, 3.70; N, 10.37;$\underline{M}^+$270.062499).

νmax. 1770 (C=O), 1260 (C-O)cm^{-1}.

The material insoluble in benzene was boiled with ethanol and filtered to give the amido-acid (0.4g, 21.4%), prisms, m.p. 275-276° (from acetic acid)

(Found: C, 56.92; H, 4.24; N, 9.14; $\underline{(M-H_2O)}^+$ 270.064051; $C_{14}H_{12}N_2O_5$ requires: C, 58.33; H, 4.17; N, 9.72; $\underline{(M-H_2O)}^+$ 270.064583).

$\nu_{max.}$ 3150 (N-H), 1680 (C=O), 1265(C-O)cm^{-1}.

2-(4-Methylphenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (298). - 4-Aminonicotinic acid 1-oxide (1.0g), dry pyridine (1.0g), and 4-toluoyl chloride (2.0g) were stirred at room temperature for 0.25h., and then warmed on a steam bath for 0.5h. The mixture was filtered, and the resultant solid was washed with water and extracted with boiling benzene (3 x 100cm^3). The benzene solution was dried ($MgSO_4$), excess solvent removed under reduced pressure, and the mixture cooled to yield the oxazine (0.58g, 35.2%), needles, m.p. 246.5-247.5° (from benzene).

(Found: C, 66.12; H, 4.08; N, 10.82; $\underline{M}^+$254.069137; $C_{14}H_{10}N_2O_3$ requires: C, 66.1; H, 3.94; N, 11.04; $\underline{M}^+$254.068519).

$\nu_{max.}$ 1760 (C=O), 1260 (C-O)cm^{-1}.

The material which was insoluble in benzene was boiled with ethanol and filtered to give the amido-acid (0.4g, 22.6%), prisms, m.p. 280-281 (from acetic acid).

Found(C, 61.45; H, 4.67; N, 10.54; $C_{14}H_{14}N_2O_4$ requires:C, 61.76; H, 4.41; N, 10.29).

$\nu_{max.}$ 3180 (N-H), 1660 - 1680 (C=O)cm^{-1}.

2-Phenylpyrido[4,3-d][1,3]oxazin-4-one 6-oxide (289). - 4-Amino-nicotinic acid 1-oxide (1.5g), dry pyridine (1.0g), and benzoyl chloride (3.0g) were stirred at room temperature for 0.5h., and then warmed on a steam bath for 0.5h. The mixture was filtered, and the resultant solid was washed with water and extracted with boiling benzene (3 x 100cm^3). The benzene solution was dried ($MgSO_4$) and excess solvent removed under reduced pressure to give the pyrido-oxazine (0.75g, 32.1%), needles, m.p. 240-241° (from benzene).

(Found: C, 64.59; H, 3.55; N, 11.90; $C_{13}H_8N_2O_3$ requires: C, 64.7; H, 3.3; N, 11.6).

$\nu_{max.}$ 1765 (C=O), 1250 (C-O)cm^{-1}.

The pyrido-oxazine was not hydrolysed by stirring with water for 24h.

The material which was insoluble in benzene was boiled with ethanol and filtered to give the amido-acid (0.75g, 29.9%) m.p. 283-284°.

(Found: $\underline{(M-H_2O)}^+$ 240.053489; $C_{13}H_{10}N_2O_4$ requires: $\underline{(M-H_2O)}^+$ 240.053368).

$\nu_{max.}$ 3200(N-H), 1660 - 1680 (C=O)cm^{-1}.

2-(4-Fluorophenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (297). - 4-Aminonicotinic acid 1-oxide (0.15g), dry pyridine (0.5g), and 4-fluorobenzoyl chloride (0.32g), were stirred at room temperature for 0.25h, and then warmed on a steam bath for 0.5h. The mixture was filtered, and the resultant solid was washed with water and extracted thrice with boiling benzene. The benzene solution was dried ($MgSO_4$) and evaporated under reduced pressure to give the pyrido-oxazine (0.08g, 32.0%), needles, m.p. 259-260° (from benzene).

(Found: C, 60.24; H, 2.69; N, 10.72; F, 7.61; $C_{13}H_7N_2O_3F$ requires: C, 60.5; H, 2.62; N, 10.85; F, 7.38).

$\nu_{max.}$ 1765 (C=O), 1250 (C-O)cm^{-1}.

The material which was insoluble in benzene was boiled with ethanol and filtered to give the amido-acid (0.08g, 29.6%) prisms, m.p. 280° (from acetic acid).

$\nu_{max.}$ 3150 (N-H), 1670 (C=O)cm^{-1}.

2-(3,4-Dichlorophenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide. (300) - 4-Aminonicotinic acid 1-oxide (1.0g), dry pyridine (1.0g), and 3,4-dichlorobenzoyl chloride (2.72g), were stirred at room temperature for 0.25h., and warmed on a steam bath for a further 0.5h. The mixture was filtered, and the resultant solid was washed with water, and extracted with boiling benzene (3 x 100cm^3). The benzene solution was dried ($MgSO_4$), excess solvent removed under reduced pressure, and the mixture cooled to give the oxazine (0.4g, 19.9%), needles, m.p. 277.5-278° (from benzene).

(Found: C, 50.23; H, 2.01; N, 8.85; M^+ 307.975301; $C_{13}H_6N_2O_3Cl_2$ requires: C, 50.48; H, 1.94; N, 9.06; M^+ 307.975544).

$\nu_{max.}$ 1770 (C=O), 1260 (C-O)cm^{-1}.

The material which was insoluble in benzene was boiled with ethanol and filtered to give the amido-acid (0.93g, 43.8%), prisms, m.p. 287-288° (from acetic acid).

(Found: $(M-H_2O)^+$ 307.975544; $C_{13}H_8N_2O_4Cl_2$ requires: $(M-H_2O)^+$ 307.975906).

$\nu_{max.}$ 3200 (N-H), 1670 (C=O)cm^{-1}.

2-(4-Nitrophenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide. - 4-Aminonicotinic acid 1-oxide (1.0g), dry pyridine (1.0g), and 4-nitrobenzoyl chloride (2.8g), were stirred at room temperature for 0.5h., and warmed in a steam bath for 0.25h. The mixture was filtered, and the resultant solid was washed with water, and extracted with boiling benzene. Evaporation of the dried ($MgSO_4$) benzene gave a yellow solid (0.15g). The infrared

spectrum of the solid contained a high carbonyl absorption at 1765cm^{-1}, and a second absorption at 1670cm^{-1}. The material could not be purified by recrystallisation from benzene, or by extracting a benzene solution with sodium hydroxide.

$\nu_{max.}$ 1765 and 1670 (C=O)cm^{-1}.

4-Acetamidonicotinic Acid 1-oxide (288). - 4-Aminonicotinic acid 1-oxide (0.15g) and acetic anhydride (10cm^3) were stirred at room temperature for 1h. The resulting precipitate was filtered, washed with water, and recrystallised from acetic acid to give the amido-acid (0.18g, 93.0%) m.p. 277-278^{o} (from acetic acid).

(Found: C, 48.12; H, 3.99; N, 13.51; $C_8H_8N_2O_4$ requires: C, 48.9; H, 4.08; N, 14.28).

$\nu_{max.}$ 1690 (acid and amide C=O), 1230 (C=O), 3080 (NH)cm^{-1}

The same product was obtained in 86% yield on heating the amino-acid N-oxide and acetic anhydride under reflux for 10h.

Attempted preparation of 2-Methylpyrido[4,3-d][1,3]oxazin-4-one 6-oxide. Method A. Acetyl chloride (0.16g) was added dropwise to a mixture of 4-aminonicotinic acid (0.15g) in pyridine (0.5g) at room temperature. A black oil was formed immediately from which no solid material could be isolated.

Method B. The above reaction was repeated at ca. -80^{o}. The yellow solid which was produced on addition of the acid chloride, decomposed on warming to room temperature to give an intractable tar.

Method C. The reaction was repeated at ca. -80^{o}C and the reaction mixture was extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and the solvent removed under reduced pressure to give a dark brown oil, which on trituration with ether gave unreacted 4-aminonicotinic acid 1-

oxide (0.07g).

4-Benzamidonicotinamide 1-oxide. - 2-Phenylpyrido[4,3-d][1,3]oxazin-4-one 6-oxide (0.4g) and ammonia solution ($10cm^3$, d. 0.88) were stirred at room temperature for 8 days. The resultant precipitate was collected, washed with absolute alcohol, and recrystallised from acetic acid to give the diamide (0.3g, 69.8%), needles, m.p. 300-300.5° (from acetic acid).

(Analysis was not satisfactory. Calculated for $C_{13}H_{11}N_3O_3$ M^+, 257.079877; Found: M^+, 257.080035).

$\nu_{max.}$ 3350, 3100 (NH_2) 1685(amide I, C=O), 1675(amide II C=O)cm^{-1}.

The diamide was recovered unchanged after heating at 240° for 10h.

4-(4-Fluorobenzamido)nicotinamide 1-oxide. - 2-(4-Fluorophenyl)pyrido [4,3-d][1,3]oxazin-4-one 6-oxide (0.2g) and ammonia solution ($10cm^3$, d, 0.88) were stirred at room temperature for 4 days. The resultant precipitate was collected, washed with water, and recrystallised from acetic acid to give the diamide (0.18g, 85.7%), needles, m.p. 313-314°C (from acetic acid).

(Found: C, 56.02; H, 3.84; N, 14.41; $C_{13}H_{10}N_3O_3F$ requires: C, 56.7; H, 3.64; N, 15.3).

$\nu_{max.}$ 3250, 3080 (NH_2) 1690 (amide I and amide II C=O)$_{cm}^{-1}$.

4-(4-Methylbenzamido)nicotinamide 1-oxide. - 2-(4-Tolyl) pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (0.25g) and ammonia solution ($10cm^3$, d 0.88) were stirred at room temperature for 9 days. The resultant precipitate was collected, washed with water, and recrystallised from acetic acid to give the diamide (0.20g, 75.0%), plates, m.p. 323-325° (from acetic acid).

(Found: C, 60.54; H, 4.62; N, 14.49; M^+271.094688; $C_{14}H_{13}N_3O_3$ requires: C, 61.99; H, 4.80; N, 15.50; M^+271.095684).

$\nu_{max.}$ 3250, 3100 (NH_2) 1680 (amide I and amide II C=O)cm^{-1}.

4-(4-Methoxybenzamido)nicotinamide 1-oxide. - 2-(4-Methoxyphenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (0.17g) and ammonia solution ($10cm^3$, d. 0.88) were stirred at room temperature for 8 days. The resultant precipitate was collected, washed with water and recrystallised from acetic acid to give the diamide (0.15g, 83.0%) plates, m.p. 314-315° (from acetic acid).

(Found: C, 57.67; H, 4.71; N, 14.44; $C_{14}H_{13}N_3O_4$ requires: C, 58.54; H, 4.53; N, 14.63).

$\nu_{max.}$ 3330, 3150 (NH_2), 1685 (amide I C=O), 1670 (amide II C=O)cm^{-1}.

2-(3,4-Dichlorophenyl)pyrido[4,3-d]pyrimidin-4(3H)-one 6-oxide (302).

2-(3,4-Dichlorophenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (0.05g) and ammonia solution ($10cm^3$, d. 0.88) were stirred at room temperature for 8 days. The resultant suspension was filtered, and the solid was washed with water and recrystallised from acetic acid to give the pyridopyrimidine (0.042g, 84.3%), plates, m.p. 318-320 (from acetic acid). (An analysis was not obtained. Calculated for $C_{13}H_7N_3O_2Cl_2$: $\underline{M}^+$, 306.992554; Found: $\underline{M}^+$, 306.991528

$\nu_{max.}$ 1680 (C=O)cm^{-1}.

4-Benzamidonicotinic acid hydrazide 1-oxide (303). - 2-Phenylpyrido[4,3-d][1,3]oxazin-4-one 6-oxide (0.25g), absolute ethanol ($10cm^3$) and hydrazine hydrate (0.5g) were stirred at room temperature for 84h. The resultant suspension was filtered, and the solid was washed with water and recrystallised from ethanol/water to give the hydrazide (0.24g, 61.7%), plates, m.p. 269-270° (from ethanol/water).

(Found: C, 53.96; H, 4.89; N, 19.22; $C_{13}H_{12}N_4O_3.H_2O$ requires: C, 53.79; H, 4.83; N, 19.31)

$\nu_{max.}$ 3360, 3180(NH_2), 1690 (hydrazide C=O), 1655 (amide C=O).

$\nu_{max.}$ 1250 (C-O)cm^{-1}.

Evaporation of the filtrate gave a further 0.06g (15.4%) of the hydrazide.

4-(4-Fluorobenzamido)nicotinic acid hydrazide 1-oxide (304). - 2-(4-Fluorophenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (0.15g), hydrazine hydrate (0.6cm^3), and absolute ethanol (15cm^3) were stirred at room temperature for 3 days. The resultant precipitate was collected and washed with ethanol/water to give the hydrazide (0.14g, 82.4%), plates, m.p. 276-277^{o} (from ethanol/water).

(Found: C, 53.87; H, 3.86; N, 19.21; $C_{13}H_{11}N_4O_3F$ requires: C, 53.8; H, 3.8; N, 19.3).

$\nu_{max.}$ 3300, 3220 (NH_2), 3100 (NH), 1675 (hydrazide C=O), $\nu_{max.}$ 1660 (amide C=O)cm^{-1}.

3-Amino-2-phenylpyrido[4,3-d]pyrimidin-4(3H)-one 6-oxide (308). - 2-phenylpyrido[4,3-d][1,3]oxazin-4-one 6-oxide (0.33g), absolute ethanol (15cm^3) and hydrazine hydrate (2cm^3) were stirred at room temperature for 8 days. The resultant solid was collected, and sublimed under vacuum to give the pyridopyrimidine (0.25g, 71.6%), plates, m.p. 238-239^{o}C (by vaccuum sublimation).

(Found: C, 62.88; H, 4.26; N, 22.81; M$^+$254.080370; $C_{13}H_{10}N_4O_2$ requires: C, 61.5; H, 3.94; N, 22.05; M$^+$254.080501).

$\nu_{max.}$ 3350, 3100 (NH_2), 1680 (C=O)cm^{-1}.

3-Amino-2-(4-tolyl)pyrido[4,3-d]pyrimidin-4(3H)-one 6-oxide (309). - 2-(4-Tolyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (0.25g), hydrazine hydrate (1cm^3) and absolute ethanol (10cm^3) were stirred at room temperature for 9 days. The resultant precipitate was collected, washed with water, and recrystallised from acetic acid to give the pyridopyrimidine (0.25g,

94.8%), plates, m.p. 253-254° (from acetic acid). (A satisfactory analysis was not obtained. Calculated for $C_{14}H_{12}N_4O_2$: $\underline{M}^+$, 268.095267; Found: M^+,268.096019) $\nu_{max.}$ 3300, 3100 (NH_2) 1680 (C=O)cm^{-1}.

3-Amino-2-(4-methoxyphenyl)pyrido[4,3-d]pyrimidin-4(3H)-one 6-oxide (310). - 2-(4-Methoxyphenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (0.25g), hydrazine hydrate ($1cm^3$) and absolute ethanol ($10cm^3$) were stirred at room temperature for 8 days. The resultant precipitate was collected, washed with water, and recrystallised from acetic acid to give the pyridopyrimidine (0.2g 80,2%), plates, m.p. 224-225° (from acetic acid).

(Found: C, 54.59; H, 4.59; N, 17.68; $\underline{M}^+$284.090933; $C_{12}H_{12}N_4O_3.H_2O$ requires: C, 55.6; H, 4.64; N, 18.6; $\underline{M}^+$284.089529).

$\nu_{max.}$ 3300, 3130 (NH_2) 1690 (C=O)cm^{-1}.

3-Amino-2-(3,4-dichlorophenyl)pyrido[4,3-d]pyrimidin-4(3H)-one 6-oxide (311 2-(3,4-Dichlorophenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (0.05g), hydrazine hydrate ($0.5cm^3$) and absolute ethanol ($5cm^3$) were stirred at room temperature for 8 days. The resultant precipitate was collected, washed with water, and recrystallised from acetic acid to give the pyrido-pyrimidine (0.04g, 76.5%) plates, m.p. 298-299° (from acetic acid).

(An analysis was not obtained. Calculated for $C_{13}H_8N_4O_2Cl_2$: $\underline{M}^+$, 322.000536; Found: $\underline{M}^+$, 322.002427).

$\nu_{max.}$ 3300, 3100 (NH_2) 1680 (C=O)cm^{-1}.

Attempted Preparation of 3-Hydroxy-2-phenylpyrido[4,3-d]pyrimidin-4(3H)-one 6-oxide.

Hydroxylamine hydrochloride (0.28g) was added to a solution of sodium (0.02g) in ethanol ($10cm^3$). The precipitated sodium chloride was removed and 2-phenylpyrido[4,3-d][1,3]oxazin-4-one 6-oxide (0.35g) was added. The mixture was stirred at room temperature for 24h. and filtered.

Evaporation of the filtrate gave ethyl 4-benzamidonicotinate 1-oxide (0.19g, 60.2%) m.p. 210-211° (from ethanol).

(Found: C, 62.76; H, 4.97; N, 9.75; $\underline{M}^+$ 286.095349; $C_{15}H_{14}N_2O_4$ requires: C, 63.0; H, 4.90; N, 9.80; $\underline{M}^+$ 286.093379).

$\nu_{max.}$ 1720 (ester C=O), 1660 (amide C=O)cm^{-1}.

Attempted nucleophilic displacement reactions on 4-nitronicotinic acid 1-oxide using hydrazines.

i) 4-Nitronicotinic acid 1-oxide (2.0g) and phenylhydrazine ($10cm^3$) were heated at 100° for 5h., cooled, and the precipitated solid removed (1.32g). The infrared and mass spectra closely resembled the corresponding spectra of 4-aminonicotinic acid 1-oxide, but no pure material could be obtained after four recrystallisations from ethanol.

ii) 4-Nitronicotinic acid 1-oxide (2.0g), diphenylhydrazine (2.0g) and methanol ($20cm^3$) were heated under reflux for 16h., cooled and the precipitated brown solid was removed. Fractional crystallisation from ethanol gave 4-hydroxylaminonicotinic acid 1-oxide (0.02g, 3.1%) m.p. 212-214° (lit.[110] 215-217°). Evaporation of the filtrate from the reaction mixture gave azobenzene (1.5g, 75.2%) m.p. 67-68° (lit.[51] 68°).

3-Hydroxy-2-methylpyrazolo[4,3-c]pyridine 5-oxide (319). - 4-Nitronicotinic acid 1-oxide (1.5g) was added slowly to methylhydrazine ($10cm^3$) and the mixture was heated under reflux for 6h. Evaporation of the excess methylhydrazine under reduced pressure gave an amber oil, which on trituration with acetonegave the pyrazolopyridine (0.83g, 61.7%), plates, m.p. 241.5-243° (from ethanol [charcoal]).

(Found: C, 50.64; H, 4.45; N, 25.46; $\underline{M}^+$ 165.053871; $C_7H_7N_3O_2$ requires: C, 50.91; H, 4.24; N, 25.45; $\underline{M}$ 165.053822).

ν_{max} 1640 (C=O)cm^{-1}.

λ_{max} (H_2O) 205, 256, 284 n.m.

λ_{max} (NaOH, 1M) 225, 267, 311 n.m.

$\tau_{(T.F.A.)}$ 6.93 (s, 3H, N-$\underline{CH}_3$), 3.2 (d, 1H, $\underline{J}$ 7Hz, 7-$\underline{H}$),

2.55(q, 1H, $\underline{J}_{6,7}$ 7Hz, $\underline{J}_{4,6}$ 1.0Hz, 6-$\underline{H}$),

1.68(d, 1H, $\underline{J}$ 1.0Hz, 4-$\underline{H}$).

Pyrido[3,4-d]pyridazin-1,4(2H,3H)-dione (323). - Methyl pyridine 3,4-dicarboxylate (3.9g), hydrazine hydrate (1.0g), and ethanol (10cm^3) were warmed on a steam bath for 10 minutes and the resultant pyridopyridazine salt removed (3.1g, 86.1%) m.p. >360°).

The salt was dissolved in water, acetic acid (5.0cm^3) added, and the precipitated pyridopyridazinone removed (2.41g, 95.9%) m.p. >360° (lit.[146] >360°).

(Found: $\underline{M}^+$ 163.038173; $C_7H_5N_3O_2$ requires: $\underline{M}^+$ 163.038407).

ν_{max} 1660 (C=O)cm^{-1}.

Pyrido[3,4-d]pyridazin-1,4(2H,3H)-dione 6-oxide (330). - Methyl pyridine 3,4-dicarboxylate 1-oxide (0.5g), hydrazine hydrate (0.3g) and ethanol (10cm^3) were stirred at room temperature for 4h. and the precipitated pyridopyridazinone collected (0.35g, 82.5%) yellow powder, m.p. 320° (decomp.) (from water).

(Found: C, 40.15; H, 4.23; N, 32.94; $\underline{M}^+$ 179.033087; $C_7H_5N_3O_3.N_2H_4$ requires: C, 39.81; H, 4.27; N, 33.18; $\underline{M}^+$ 179.033594).

$\nu_{max.}$ 1660-1630 (C=O)cm^{-1}.

6-Methylpyrido[3,4-d]pyridazin-1,4,7(2H,3H,6H)-trione (331). - 1-Methyl-3,4-dimethoxycarbonyl-6-pyridone (0.225g), hydrazine hydrate (0.05g) and ethanol (10cm^3) were heated under reflux for 1h. The mixture was cooled and the resultant precipitate was collected and washed with ethanol to give the pyrido-pyridazine (0.18g, 94.7%), yellow powder, m.p. >360°

(decomp.) (from ethanol).

(Found: $\underline{M}^+$ 193.048736; $C_8H_7N_3O_3$ requires: $\underline{M}$ 193.047743).

$\nu_{max.}$ 3300 (N-H), 1650 (C=O)cm^{-1}.

Attempted preparation of 1-Phenyl-1,6-naphthyridin-2,4(1H,3H)-dione 6-oxide.

Method (A) Ethyl 4-anilinonicotinate 1-oxide (0.096g) was added to a solution of ethyl acetate (1.0cm^3) and piperidine (2cm^3) and the mixture was heated under reflux for 6h. Evaporation of the solvent gave unchanged starting material.

Method (B) Ethyl 4-anilinonicotinate 1-oxide (0.096g) was added to a solution of sodium (0.018g) in ethyl acetate (0.5cm^3). The mixture was heated under reflux for 60h, cooled, and the precipitated solid collected to give sodium 4-anilinonicotinate 1-oxide (0.065g, 73.7%), m.p. >360° (decomp.).

$\nu_{max.}$ 1510 (C=O)cm^{-1}.

$\tau_{(D_2O)}$ 2,83(d, 1H, $J_{5,6}$ 7.0Hz, 5-H), 2.56(m, 5H, N-Ph), 2.0(q, 1H, $J_{5,6}$ 7.0Hz, $J_{2,6}$ 2.0Hz, 6-H), 1.43(d, 1H, $J_{2,6}$ 2.0Hz, 2-H)

Attempted preparation of 1,3-diphenyl-1,6-naphthyridine-2,4(1H,3H)-dione-6-oxide. - Ethyl 4-anilinonicotinate 1-oxide (0.09g) was added to a solution of sodium (0.08g) in ethyl phenyl acetate (1cm^3) and the mixture heated at 140° for 6h. The solution was cooled, and the resultant precipitate collected and washed with absolute ethanol to give sodium 4-anilinonicotinate 1-oxide (0.06g, 72.6%) m.p. >360°.

Attempted preparation of 2-Amino-3-cyano-1,6-naphthyridine-4(1H)-one 6-oxide. - Ethyl 4-anilinonicotinate 1-oxide (0.39g) was added to a solution of sodium (0.07g) in methanol ($10cm^3$) and malononitrile (0.19g). The mixture was heated on a steam bath for 2h, cooled, and the precipitate collected to give sodium 4-anilinonicotinate 1-oxide (0.27g, 75.4%). The m.p., I.R. and n.m.r. spectra were identical with those of a previously obtained sample.

Attempted preparation of 3-Amido-2-amino-1-phenyl-1,6-naphthyridine-4(1H)one 6-oxide. - Ethyl 4-anilinonicotinate 1-oxide (0.39g) was added to a solution of sodium (0.07g) in methanol ($10cm^3$) and cyanoacetamide (0.25g). The mixture was heated on a steam bath for 2h, cooled, and the resulting precipitate collected to give sodium 4-anilinonicotinate-1-oxide (0.25g, 69.9%) m.p. $>360^{o}$ (from ethanol). The I.R. and n.m.r. spectra were identical with those of the salt obtained previously.

Sodium 4-anilinonicotinate 1-oxide (342). - Ethyl 4-anilinonicotinate 1-oxide (0.1g), sodium (0.08g) and methanol ($10cm^3$) were heated under reflux for 2h. The mixture was cooled, and the resultant precipitate collected and washed with absolute ethanol to give the salt (0.075g, 77.2%) m.p. $>360^{o}$.

ν_{max} 1510 (C=O)cm^{-1}

$\tau_{(D_2O)}$ 2.83(d, 1H, $J_{5,6}$ 7.0Hz, 5-H), 2.56(m, 5H, N-Ph), 2.0(q, 1H, $J_{5,6}$ 7.0Hz, $J_{2,6}$ 2.0Hz, 6-H), 1.43(d, 1H, $J_{2,6}$ 2.0Hz, 2-H).

7 and 9-Methoxybenzo [b]-1,6-naphthyridin-10(5H)-one 2-oxide. - 4-N-(3-Methoxyphenyl)aminonicotinic acid 1-oxide (0.2g) and sulphuric acid ($5cm^3$, d. 1.84) were heated on a steam bath for 4h. The mixture was carefully poured into hot water ($100cm^3$) and the solution was evaporated to half volume under reduced pressure. The resultant precipitate was collected and washed with water to give the naphthyridine (0.09g, 48.3%),

m.p. >360°.

(Found: $\underline{M}^+$, 226.073454; $C_{13}H_{10}N_2O_2$ requires: M^+, 226.074222).

ν_{max} 1670 (C=O), 1230 (C-O)cm^{-1}

λ_{max} 196, 227, 239, 302, 325, 385 n.m.

An n.m.r. spectrum was not obtained since no suitable solvent was available.

7 and 9-Methoxybenzo[b]-1,6-naphthyridine-10(5H)-one 2-oxide.

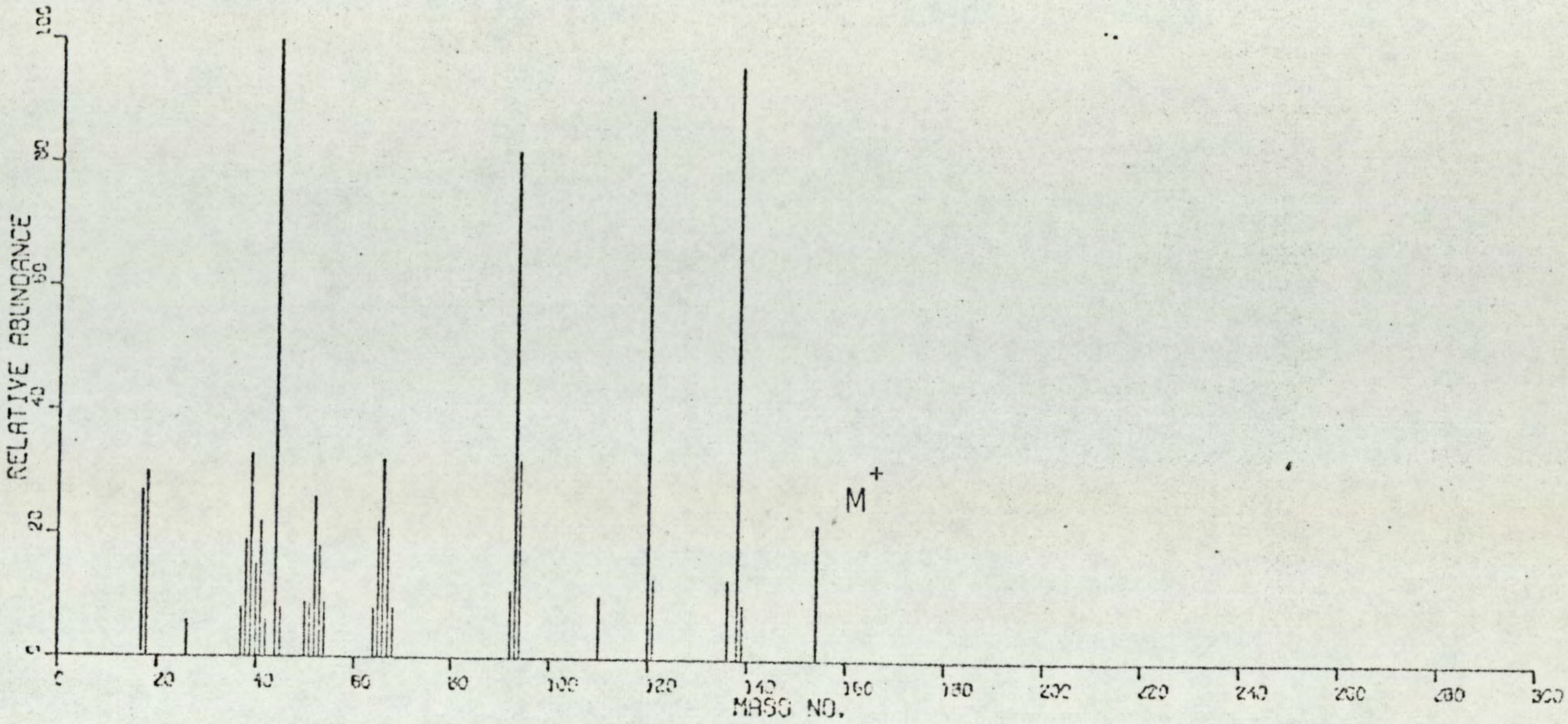
- 4-N-(p-tolyl)aminonicotinic acid 1-oxide (0.2g) and sulphuric acid ($5cm^3$, d. 1.84) were heated at 100° for 5h. The mixture was carefully poured into hot water ($100cm^3$) and the solution was concentrated to small volume under reduced pressure. The resultant precipitate was collected and washed with water to give the naphthyridine (0.07g, 37.8%) m.p. 345-346° (decomp.).

(Found: $\underline{M}^+$, 226.074646; $C_{13}H_{10}N_2O_2$ requires: $\underline{M}^+$, 226.074222).

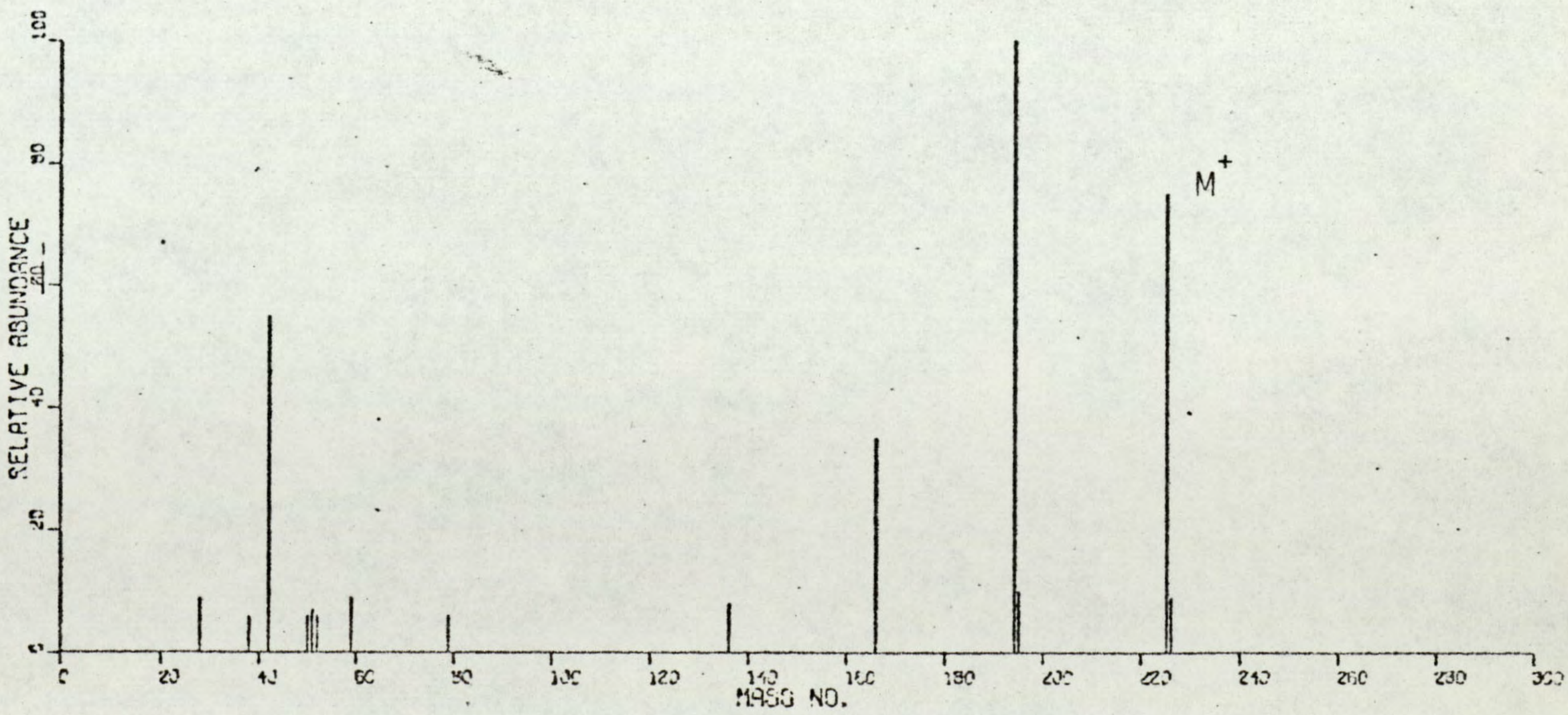
ν_{max} 1670 (C=O), 1240 (C-O)cm^{-1}.

$\lambda_{max.}$ 200, 251, 257, 264, 275, 320 n.m.

4-Aminonicotinic acid 1-oxide (52).

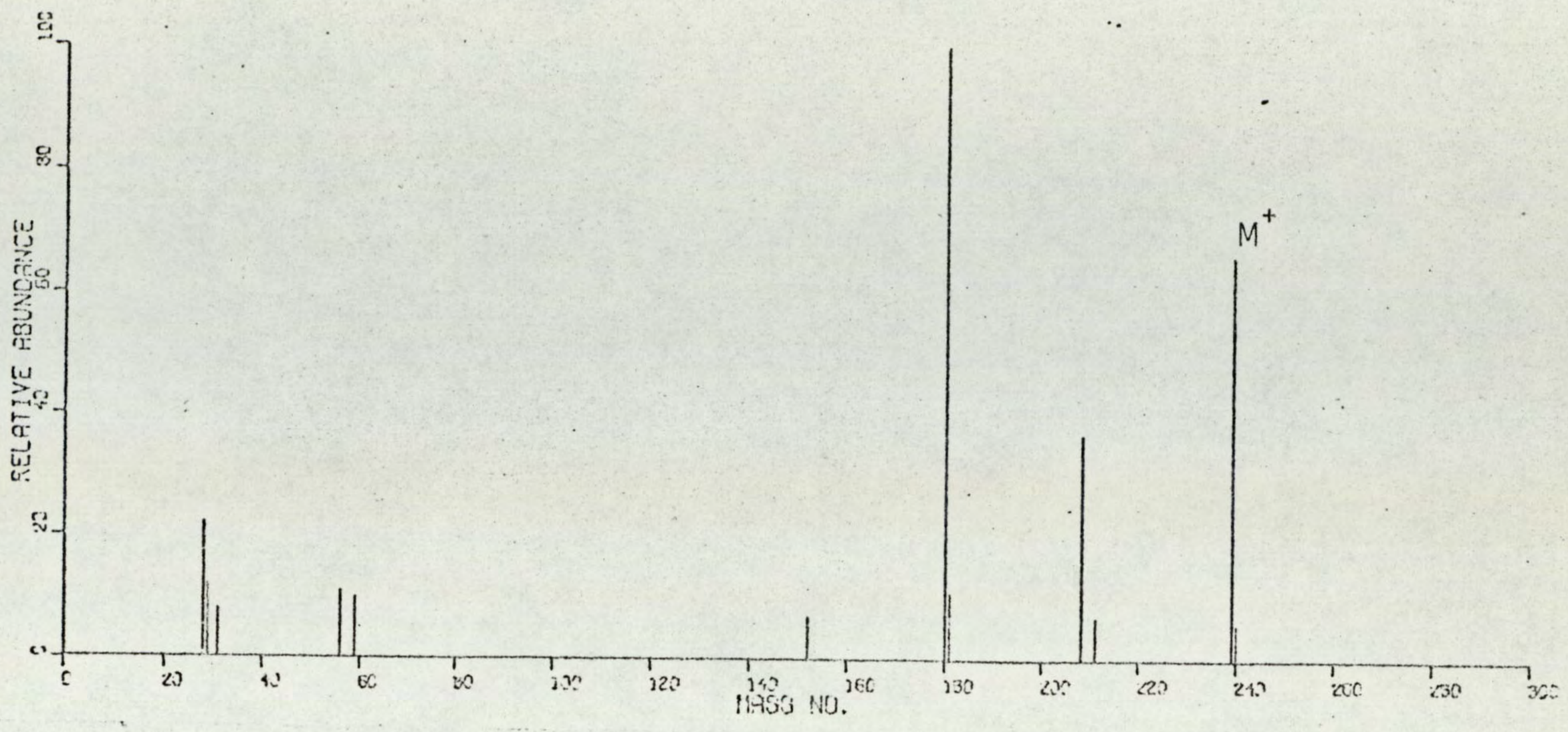


3,4-Dimethoxycarbonyl-1-methylpyrid-6-one (245).



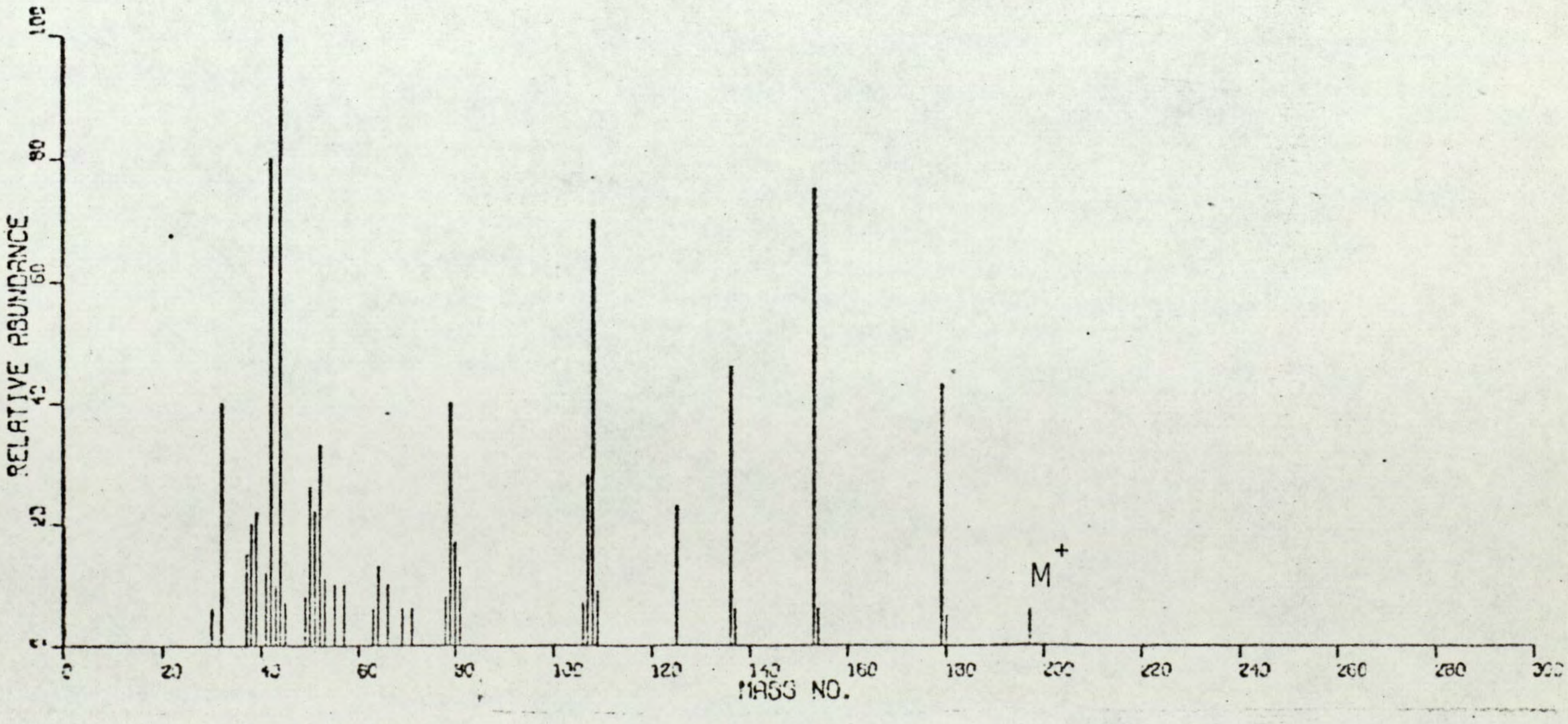
m* 167(225→94), 142(194→166), 111.5(166→136).

1-Ethyl-3,4-dimethoxycarbonylpyrid-6-one (263).



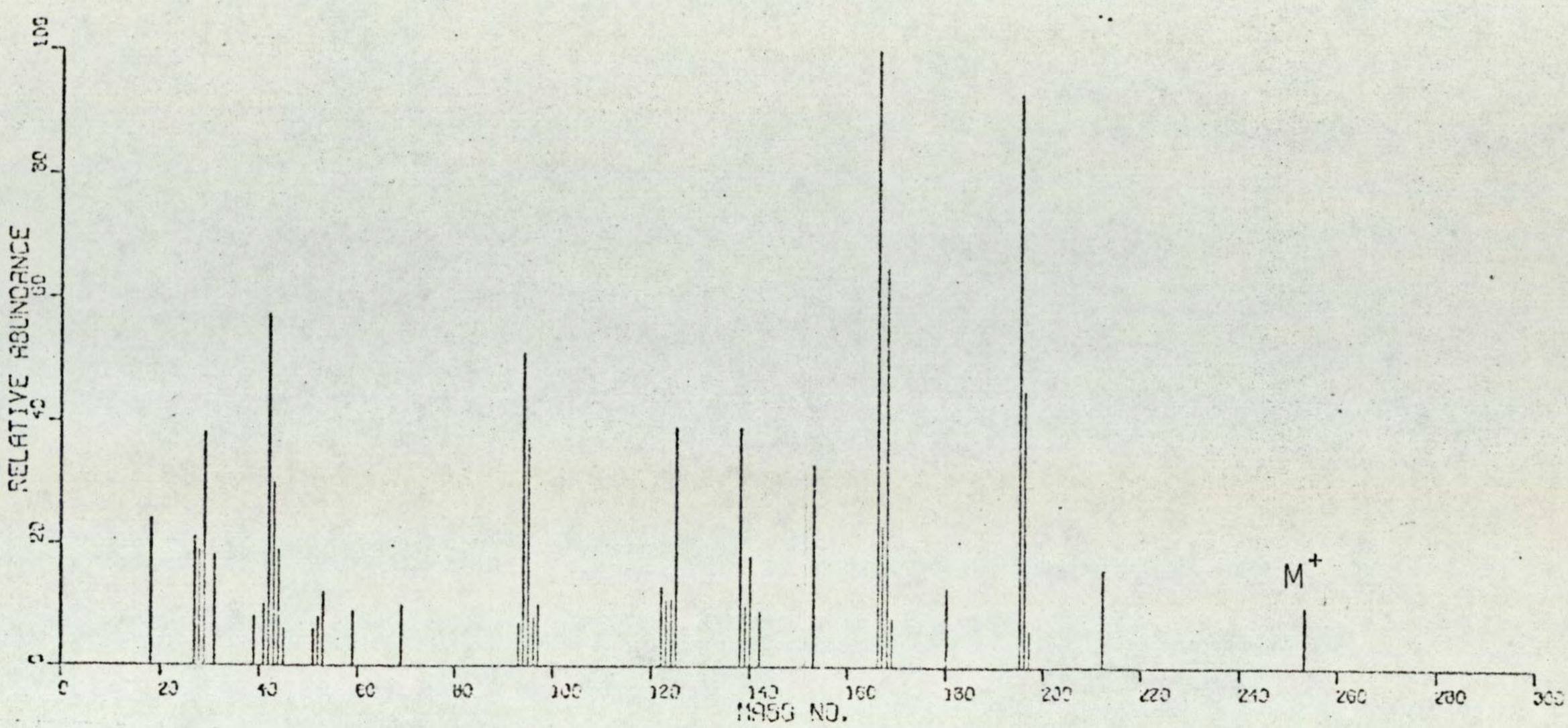
m* 187(239→211), 181(239→208), 156(208→180), 128(180→152)

3,4-Dicarboxy-1-methylpyrid-6-one (246).



m* 102(153→125), 93.5(125→108), 38.9(79→52)

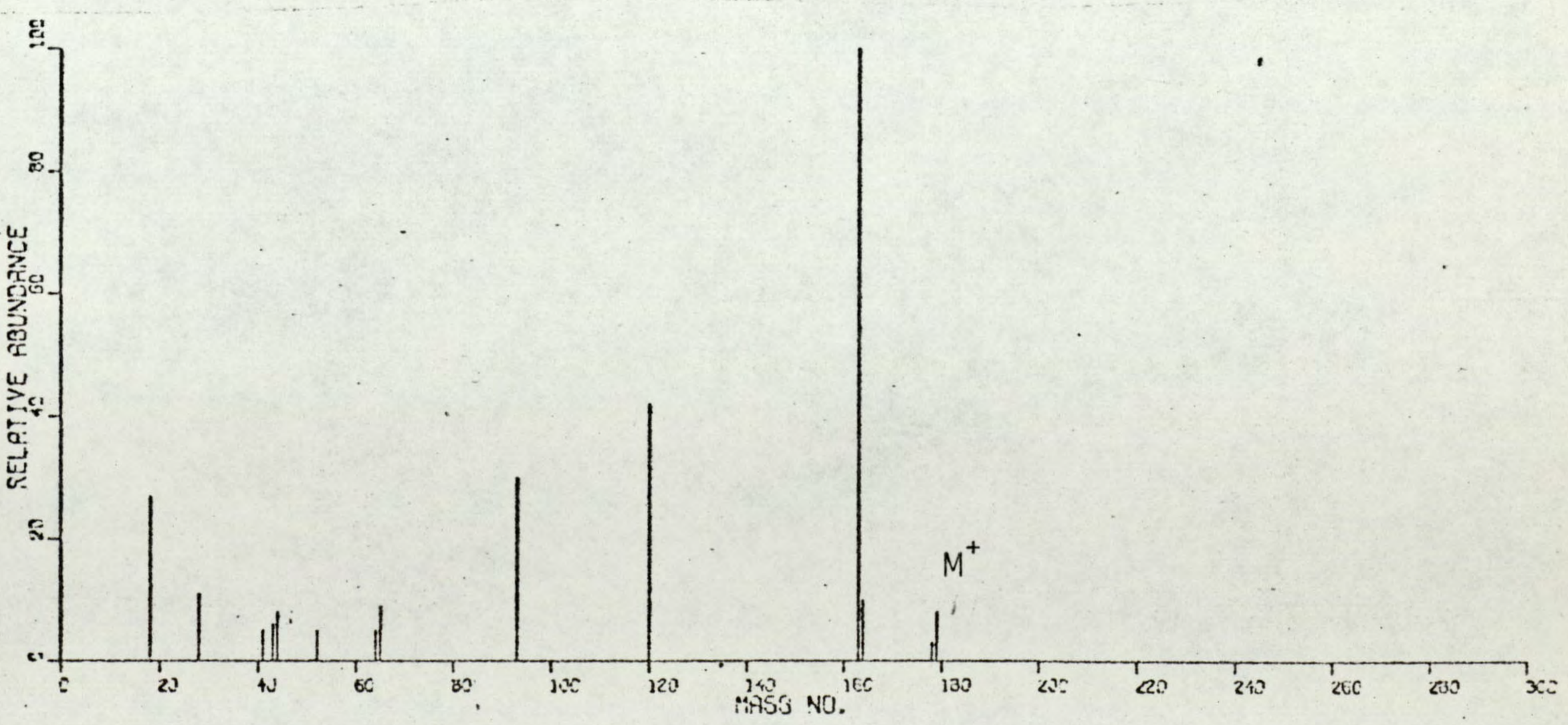
3,4-Diethoxycarbonyl-1-methylpyrid-6-one (262).



M* 165(196→180), 141(195→166), 130(180→153), 119.5(196→153),

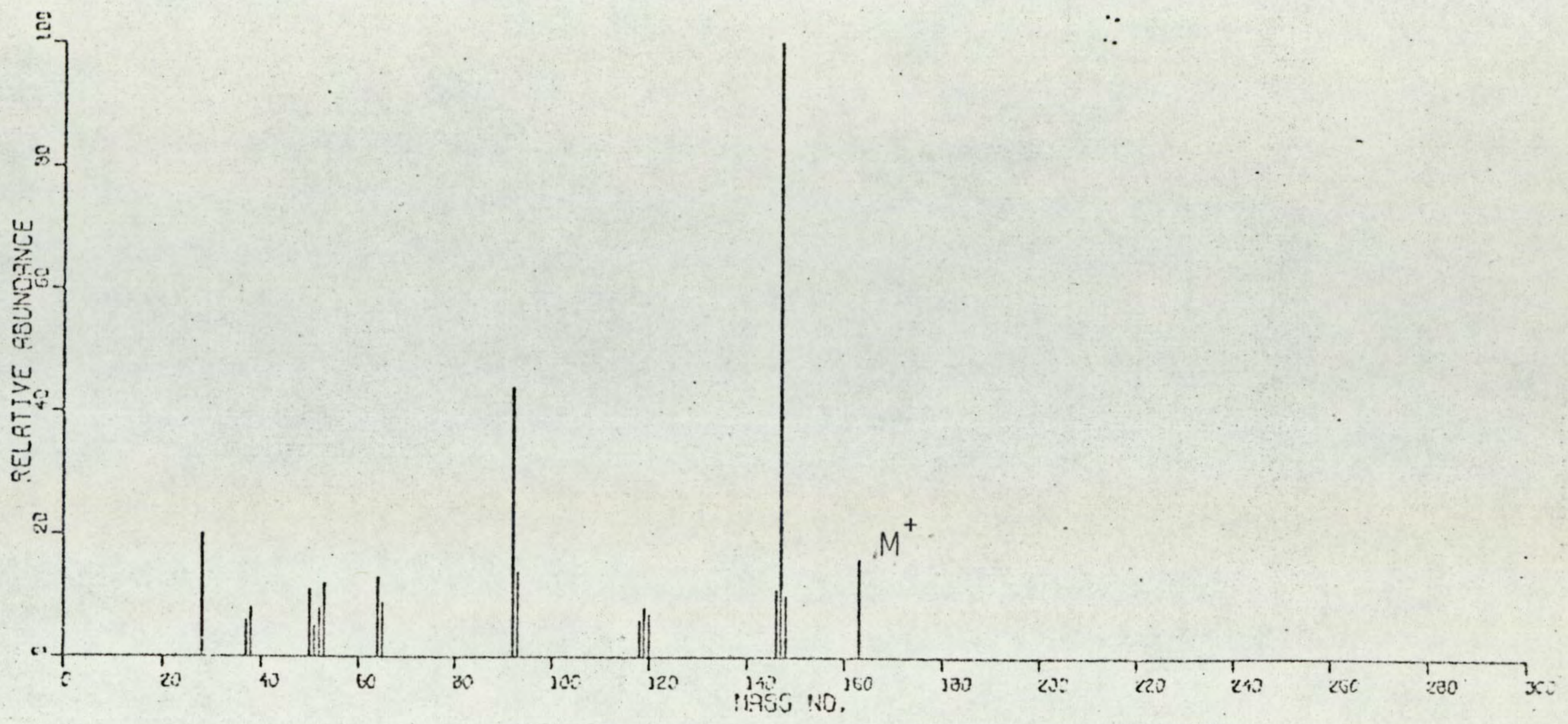
116(168→140), 102(153→125), 93.4(168→125)

Pyrido[4,3-d]pyrimidin-2,4(1H,3H)dione (271).



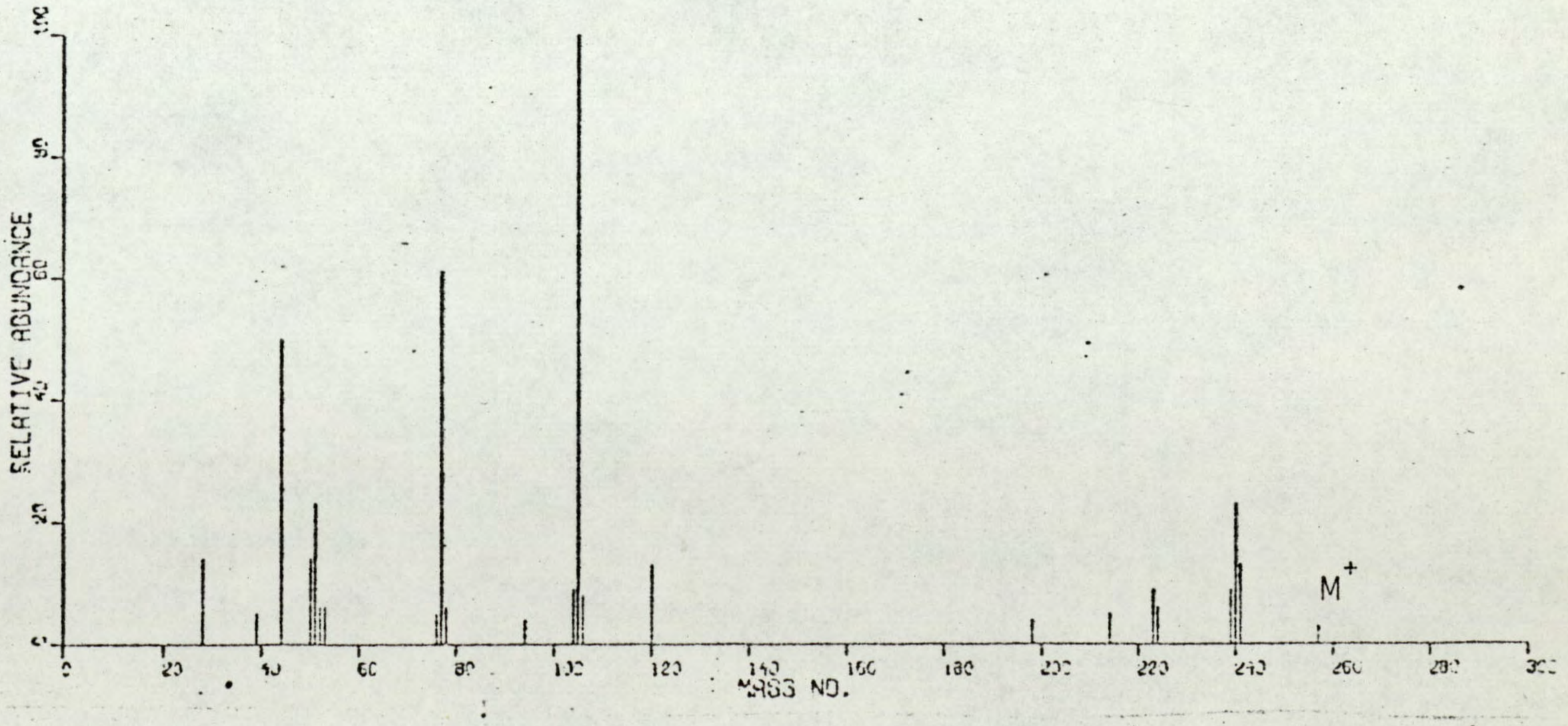
m* 88.5(163→120), 72(120→93)

Pyrido[4,3-d]pyrimidin-4(3H)one 6-oxide (270).



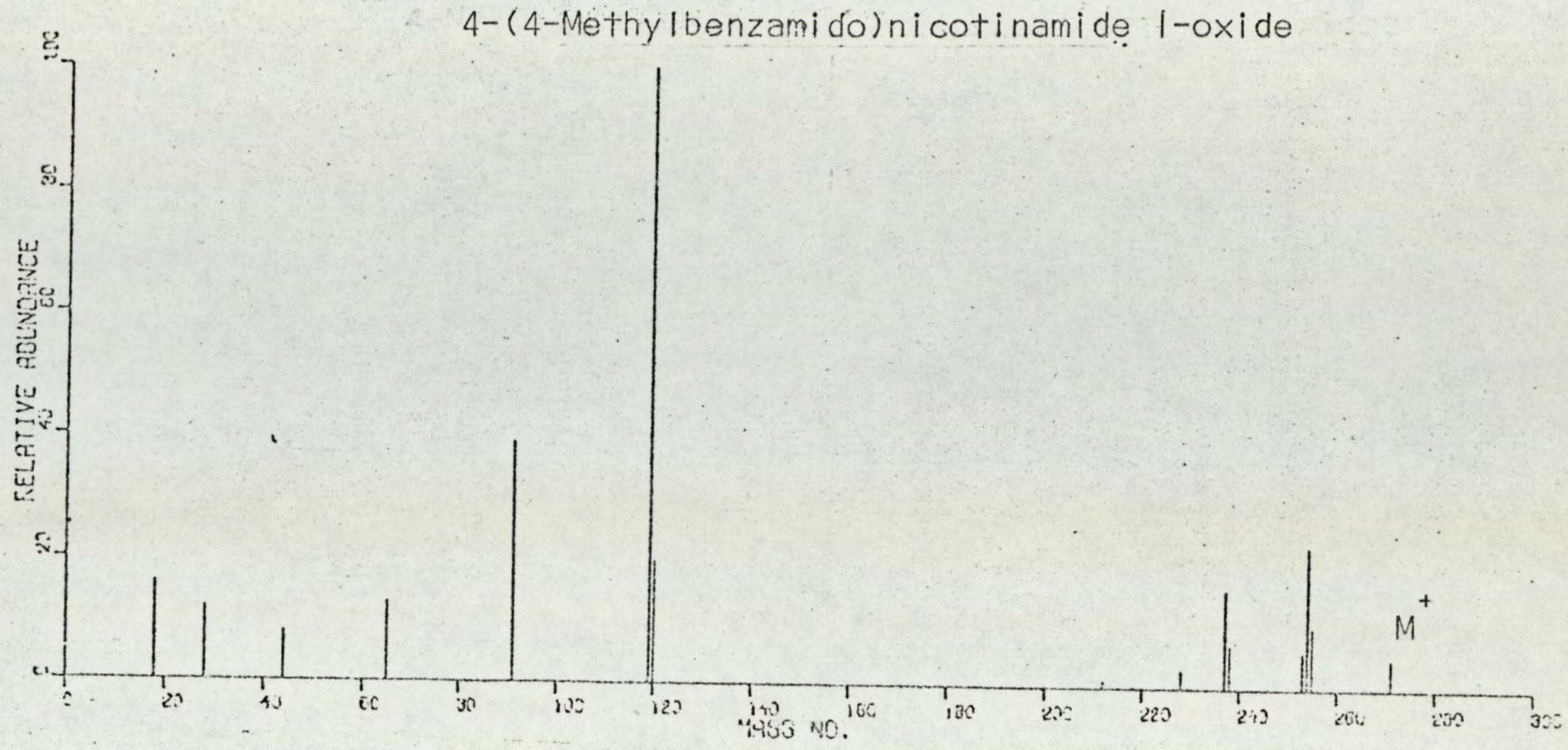
m* 96.3(147→119), 71.1(119→92).

4-Benzamidonicotinamide 1-oxide



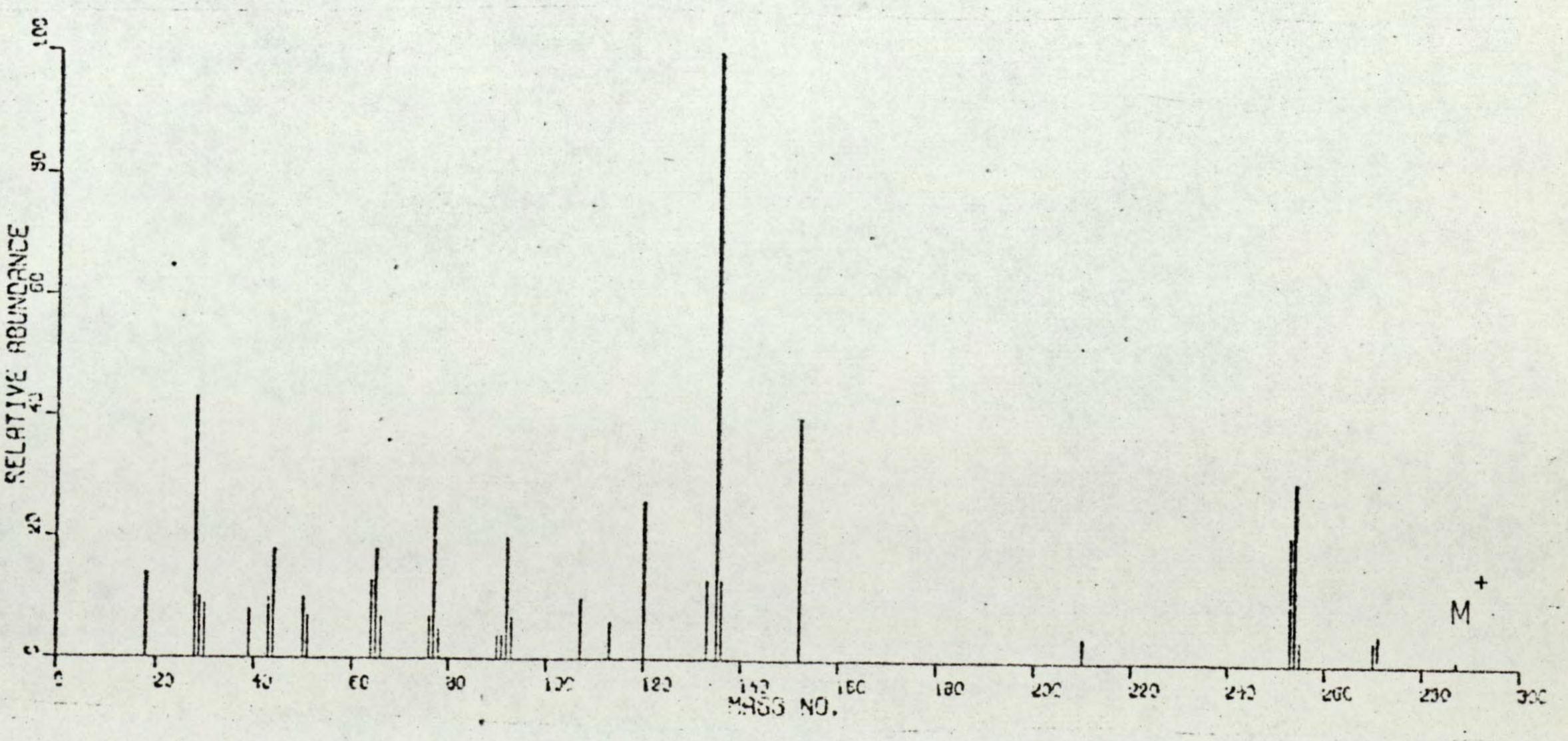
m* 161(241→198), 56.5(105→77)

4-(4-Methylbenzamido)nicotinamide 1-oxide



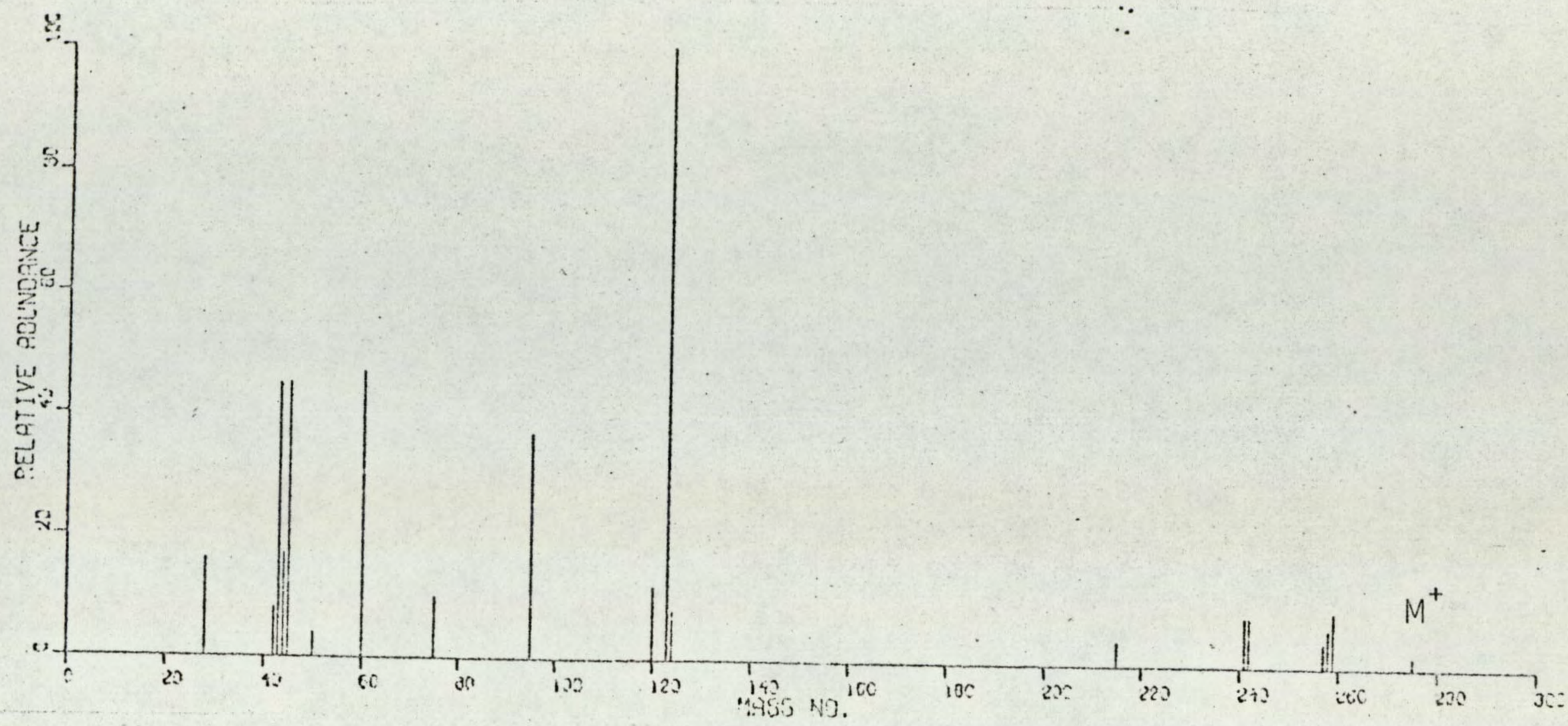
m* 221.1(254→238), 174.6(255→211), 69.5(119→91), 46.4(91→65)

4-(4-Methoxybenzamido)nicotinamide 1-oxide.



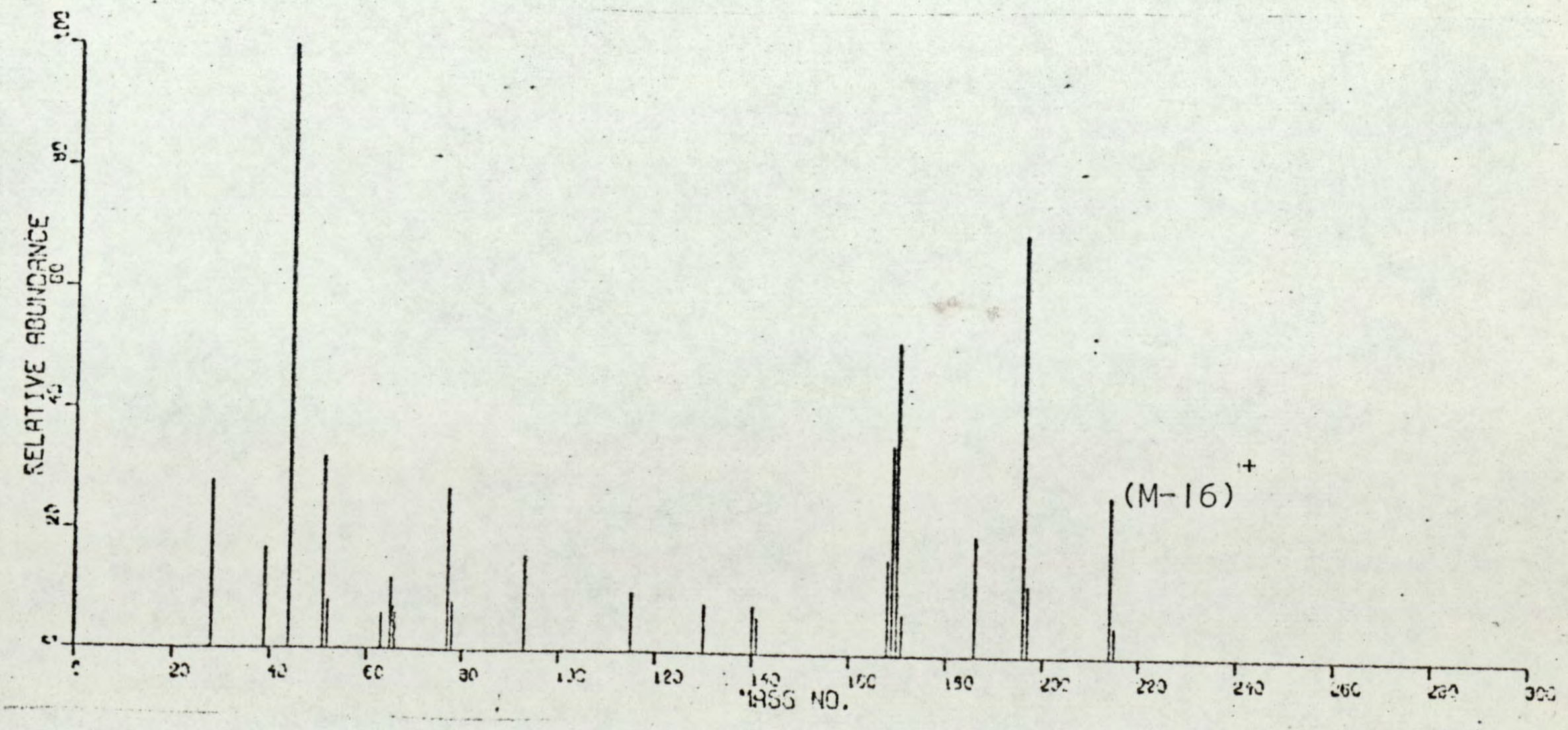
m* 119.9(152→135), 84.8(135→107), 55.4(107→77)

4-p-Fluorobenzamidonicotinamide 1-oxide



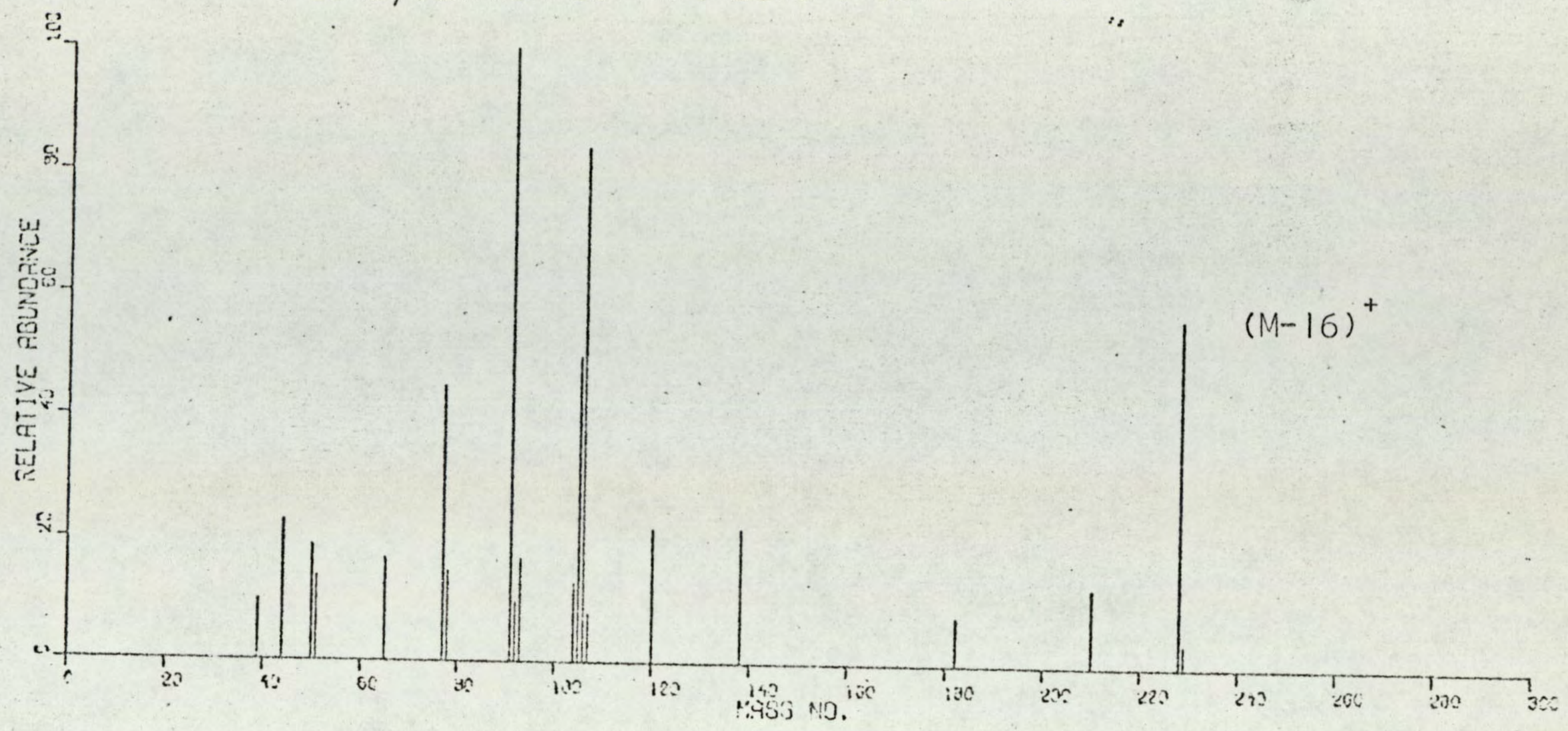
m* 178.5(259→215), 73.5(123→95), 59(95→75)

4-Anilinonicotinic acid 1-oxide (65).



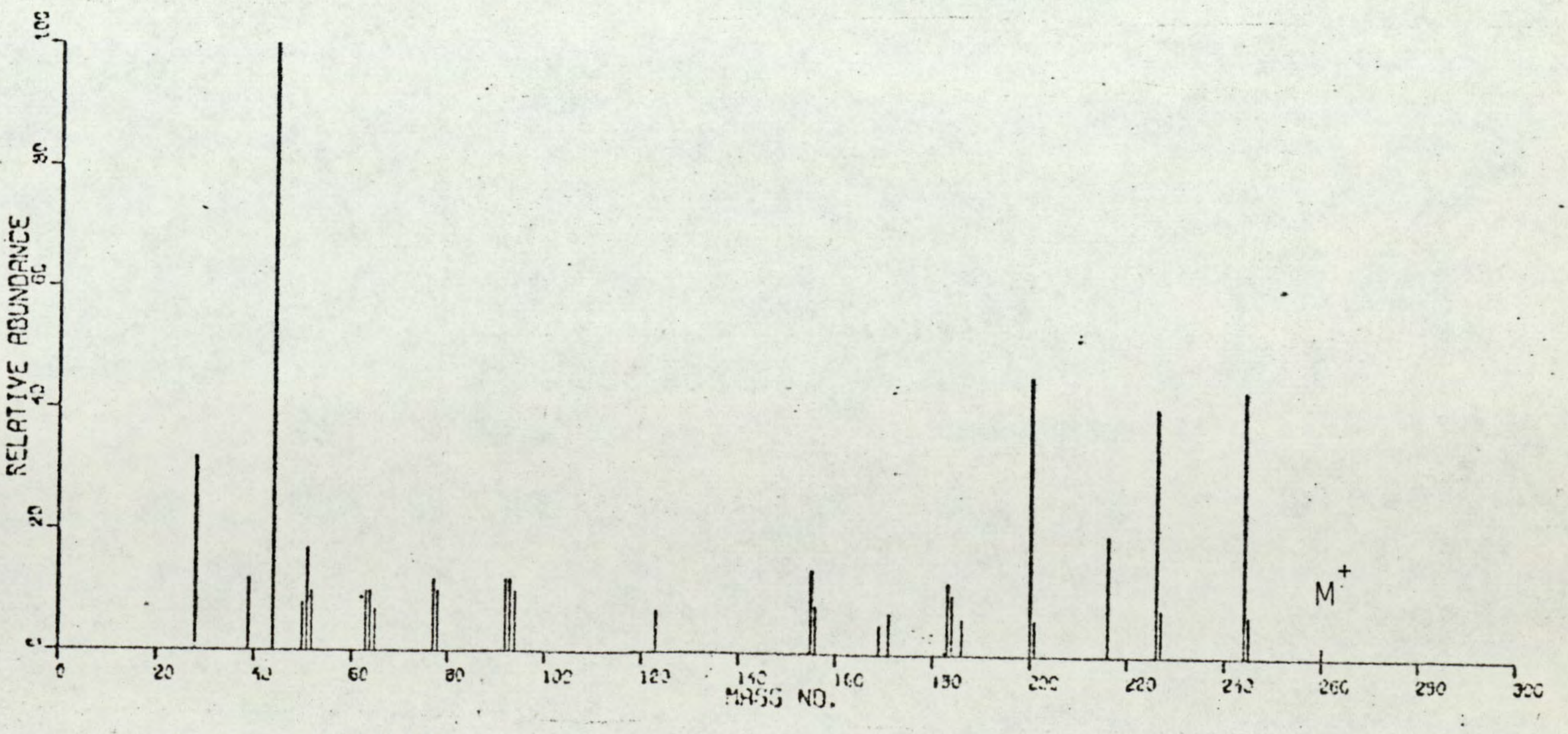
m* 180(214→196), 168(170→169), 144(196→168), 34(77→51)

4-Benzylaminonicotinic acid 1-oxide (190)



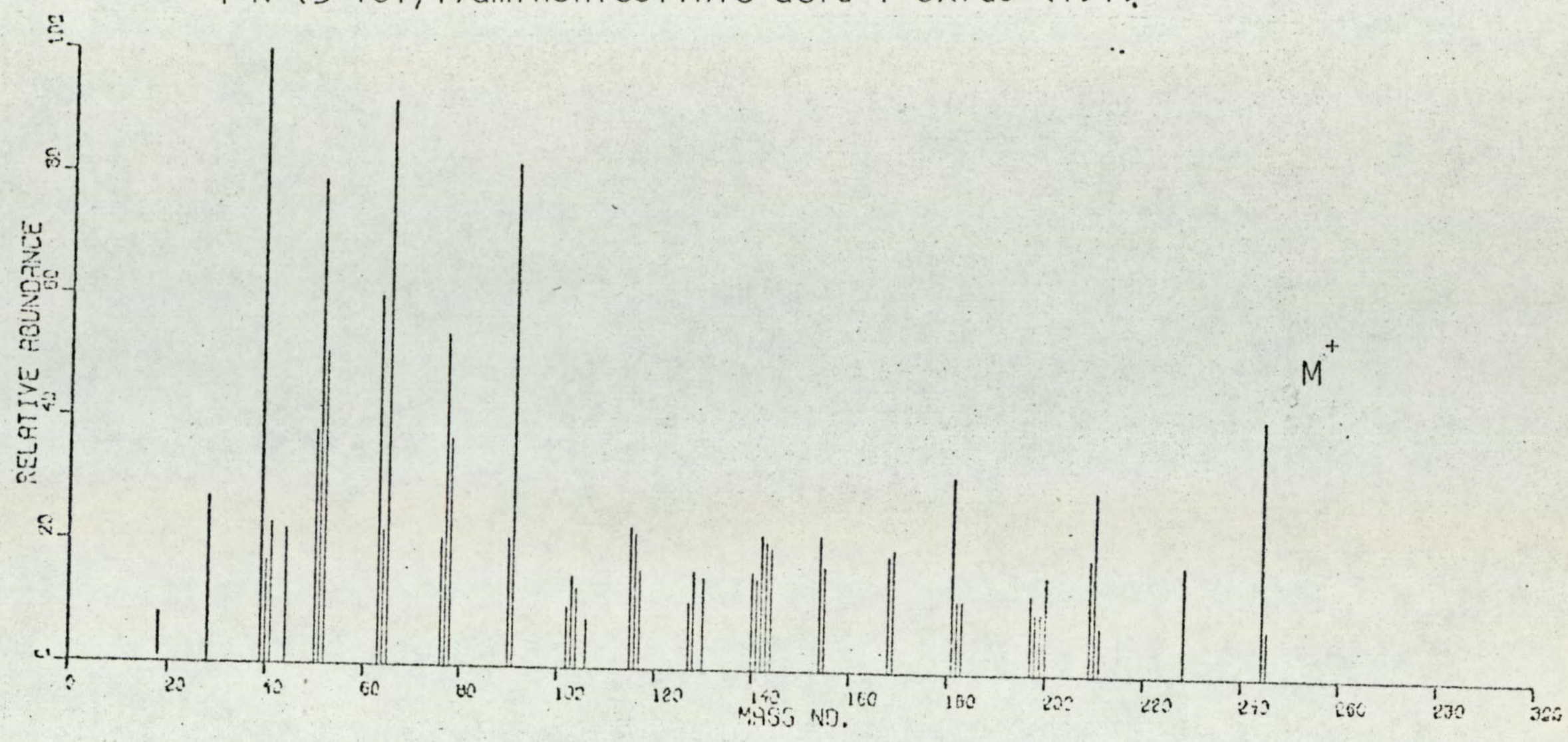
m* 193(228→210), 72(120→93), 56.5(105→77)

4-N-(3-methoxyphenyl)aminonicotinic acid 1-oxide (192)



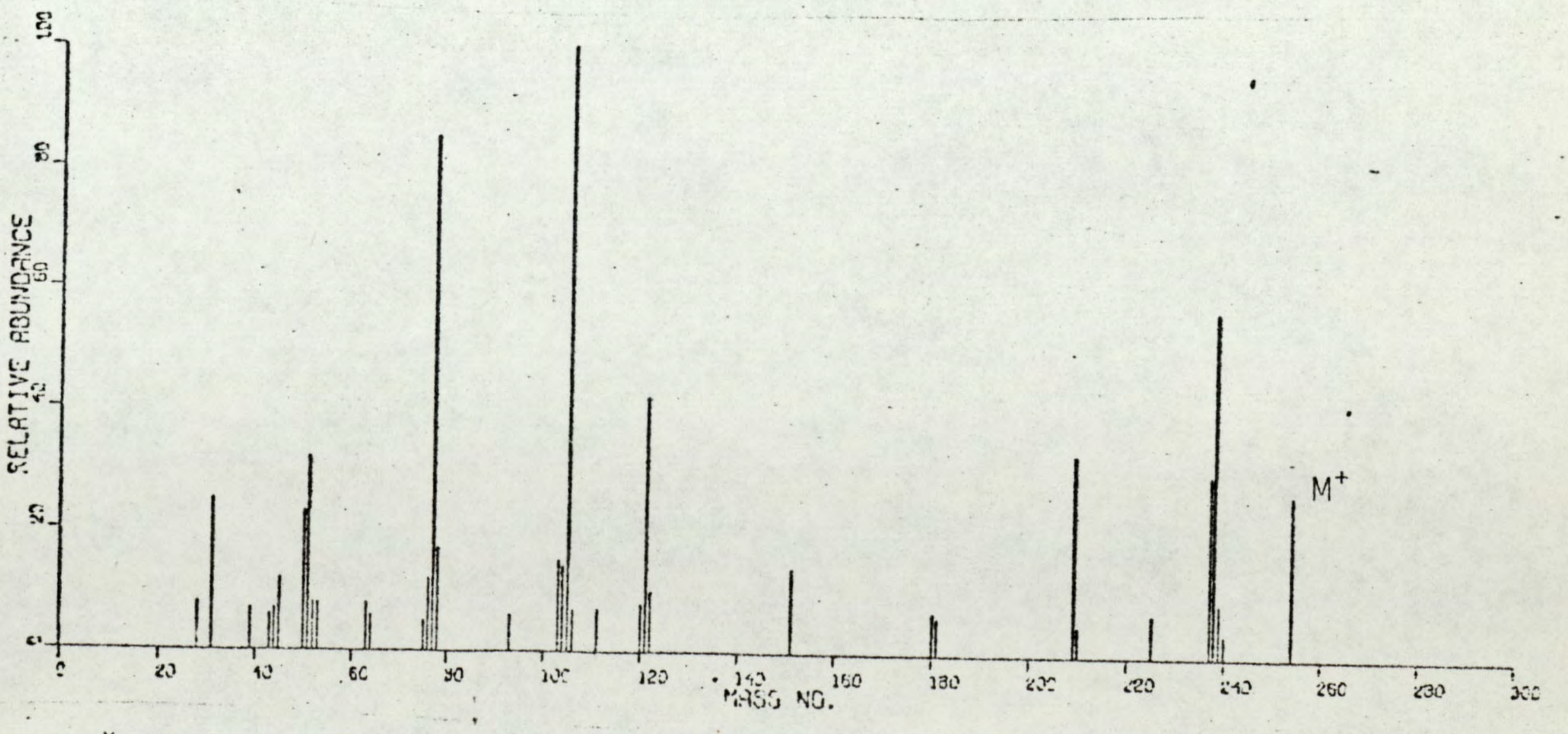
m* 209.3(244→226)

4-N-(3-Tolyl)aminonicotinic acid 1-oxide (191).



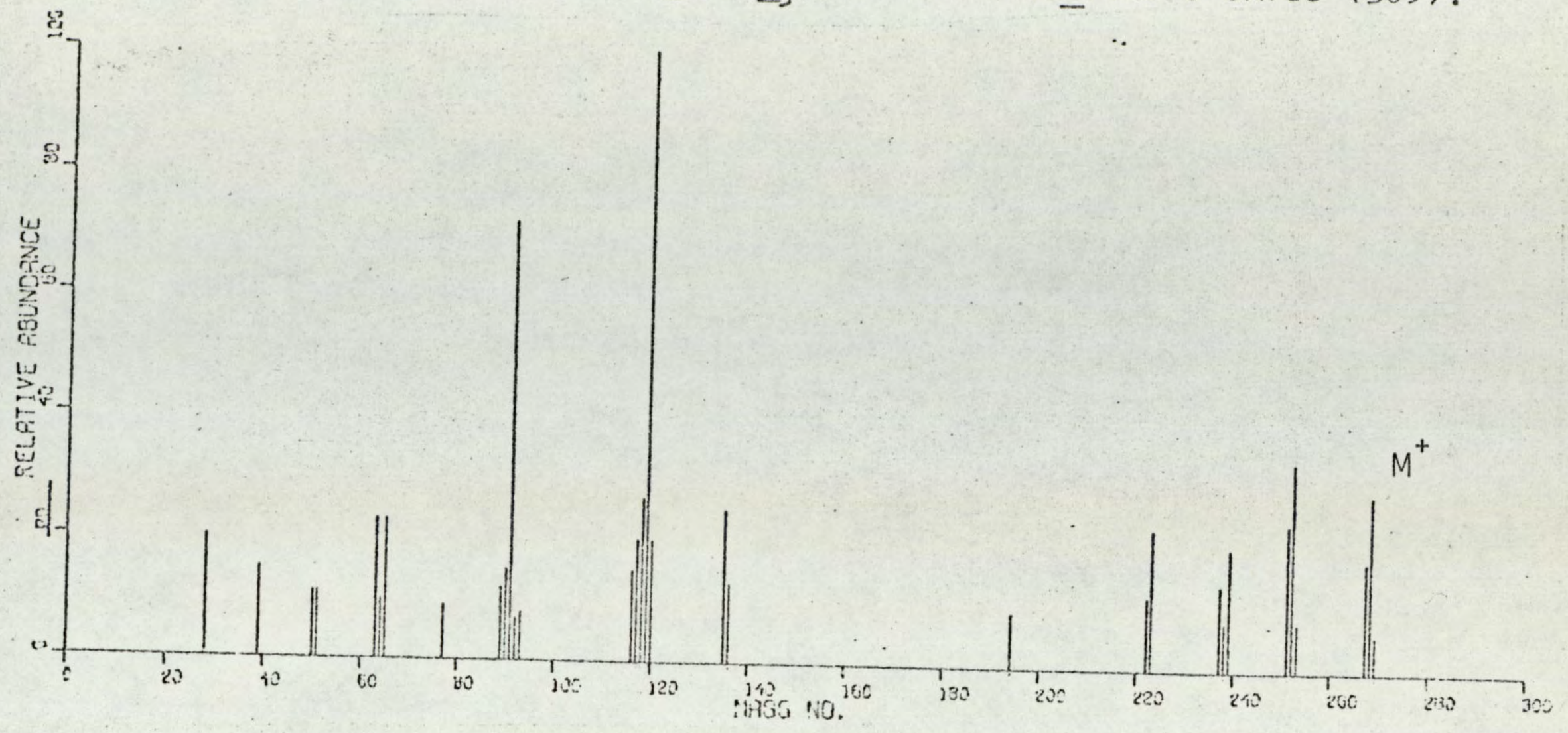
m* 46.5(91→65)

3-Amino-2-phenylpyrido|4,3-d|pyrimidin-4(3H)one 6-oxide (308).



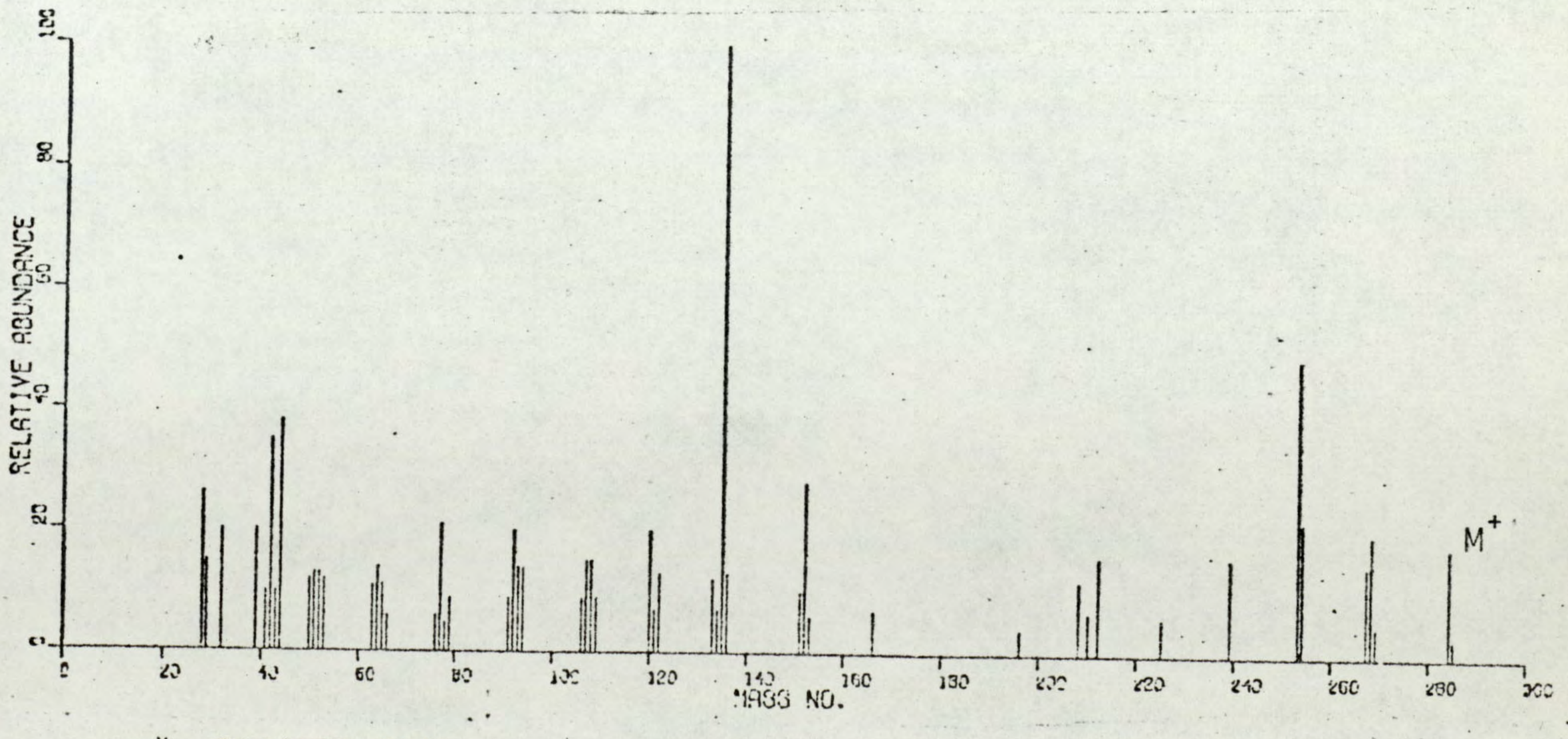
m* 236(238→237), 183(238→209), 157(208→181), 56.5(105→77)

3-Amino-2-*p*-tolylpyrido[4,3-*d*]pyrimidin-4(3*H*)one 6-oxide (309).



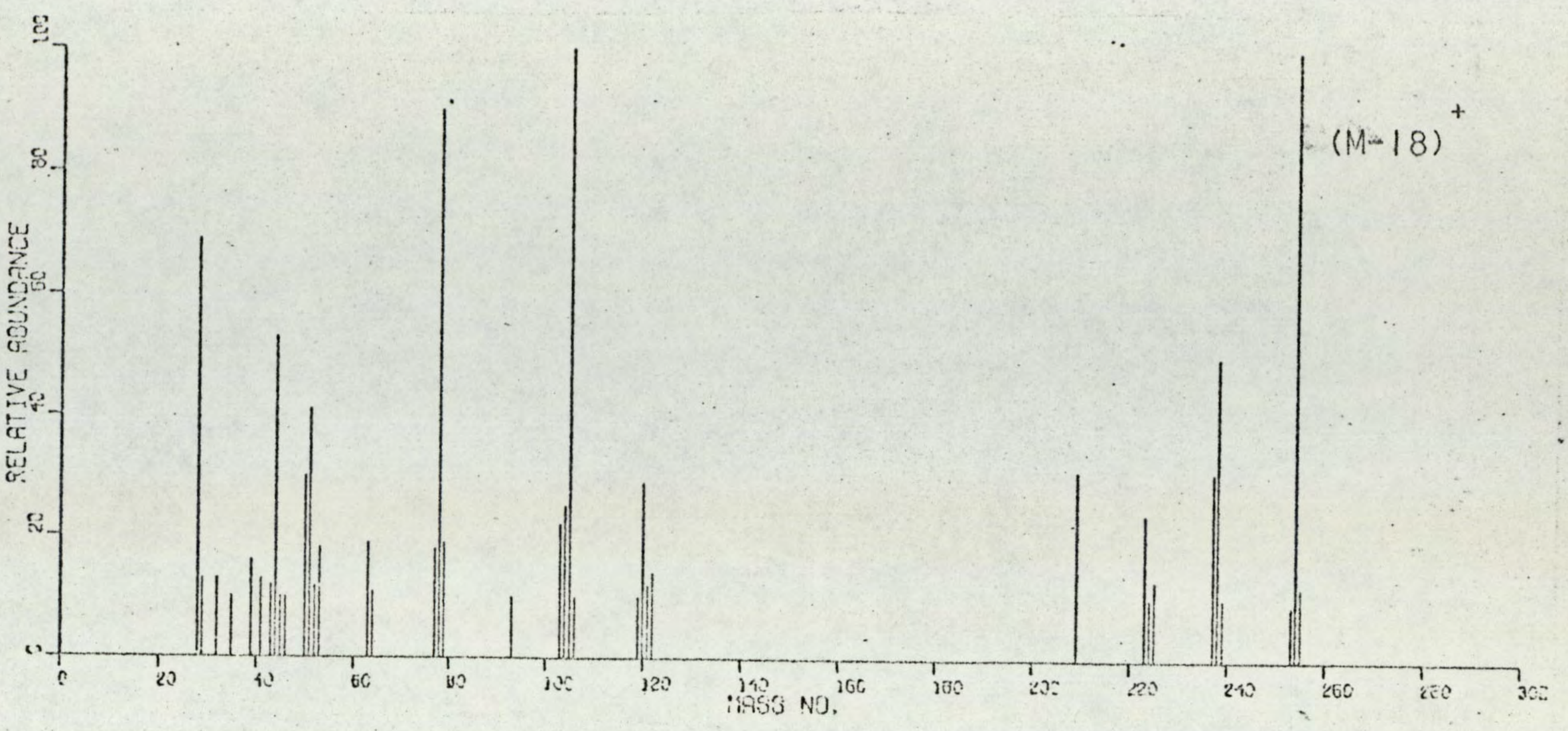
m* 266(268→267), 213(268→239), 69.5(119→91)

3-Amino-2-(4-methoxyphenyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)one 6-oxide (310).



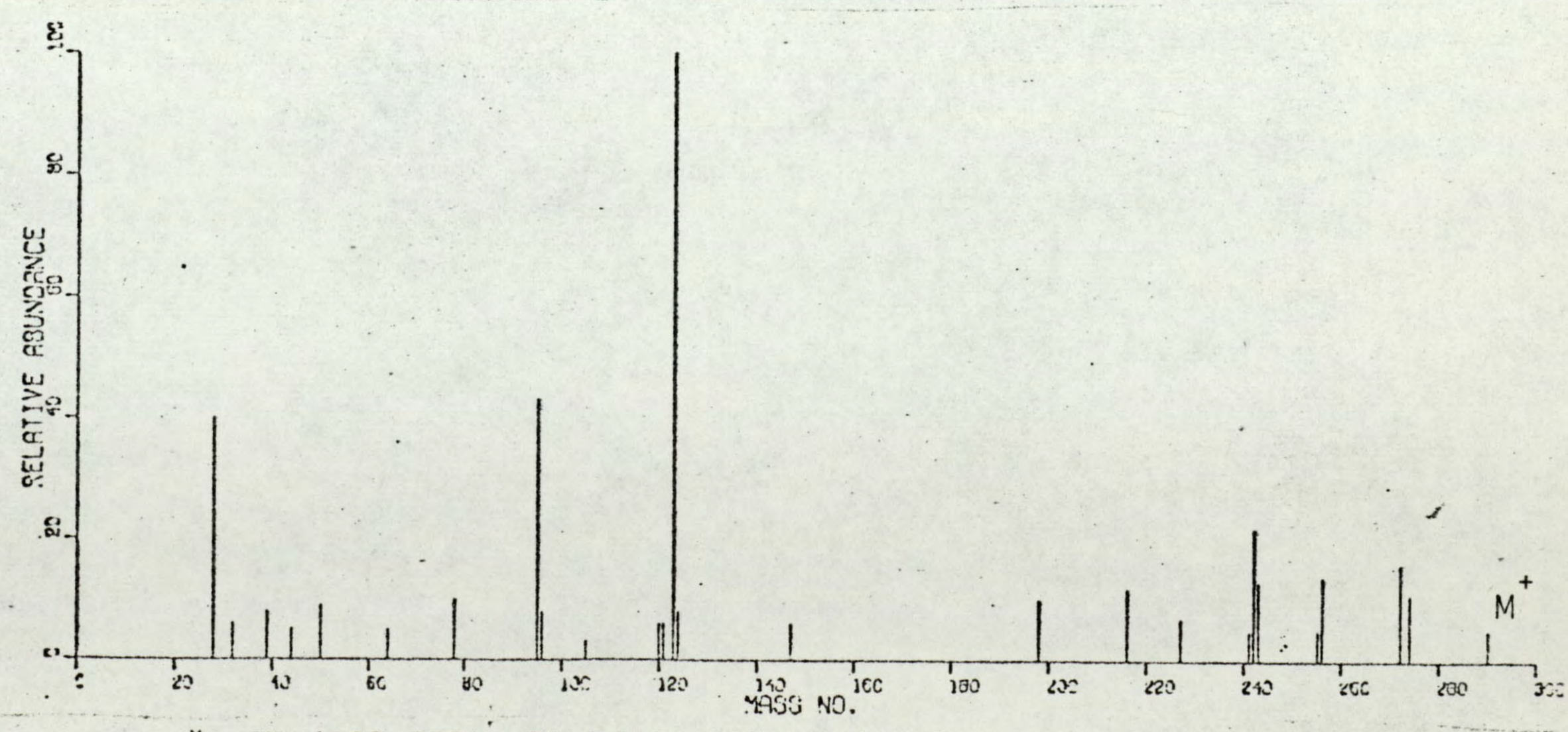
m* 266(302→284)

4-Benzamidonicotinic acid hydrazide 1-oxide (303).



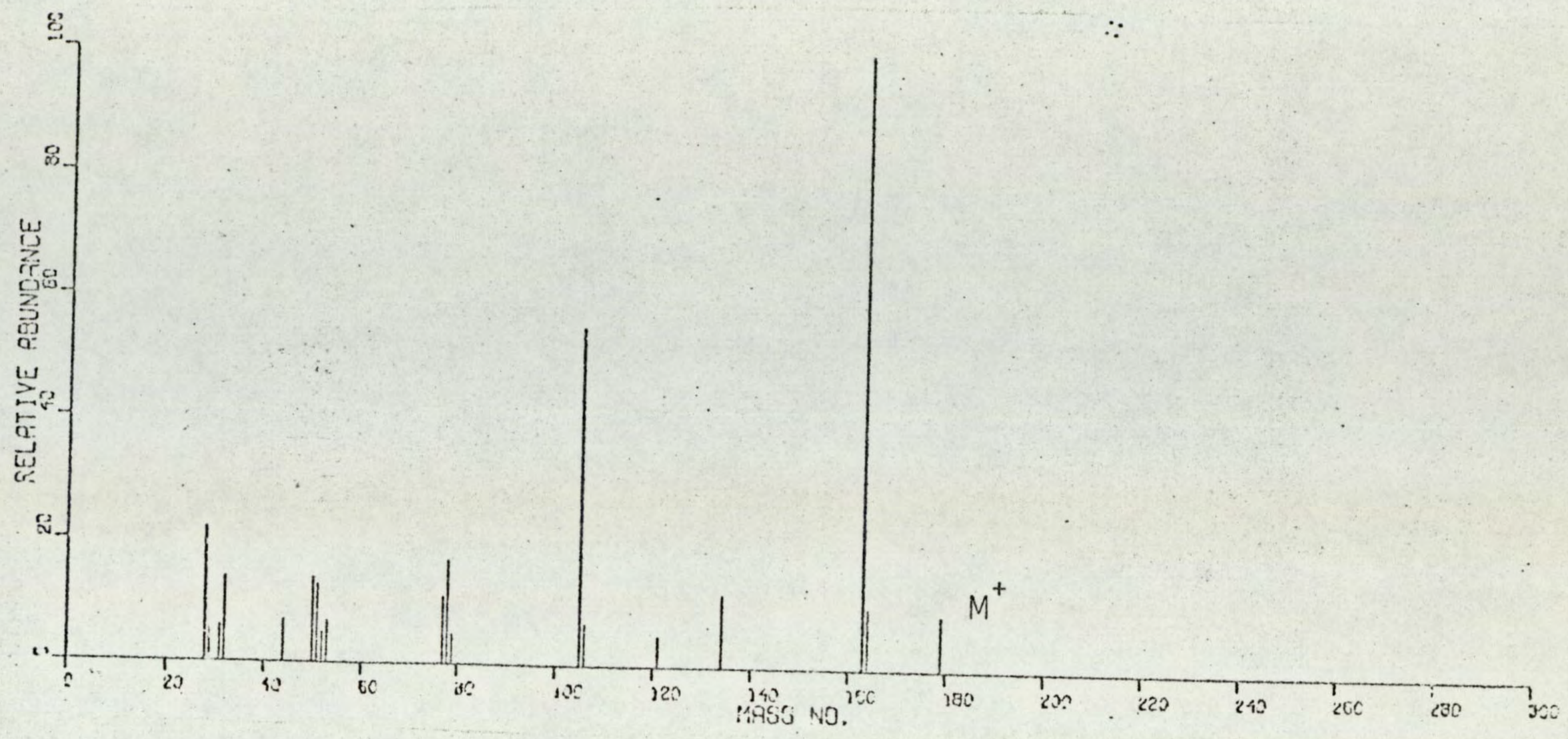
m* 252(254→253), 236(272→254), 199.5(254→225), 56.5(105→77)

4-p-Fluorobenzamidonicotinic acid hydrazide 1-oxide (304).



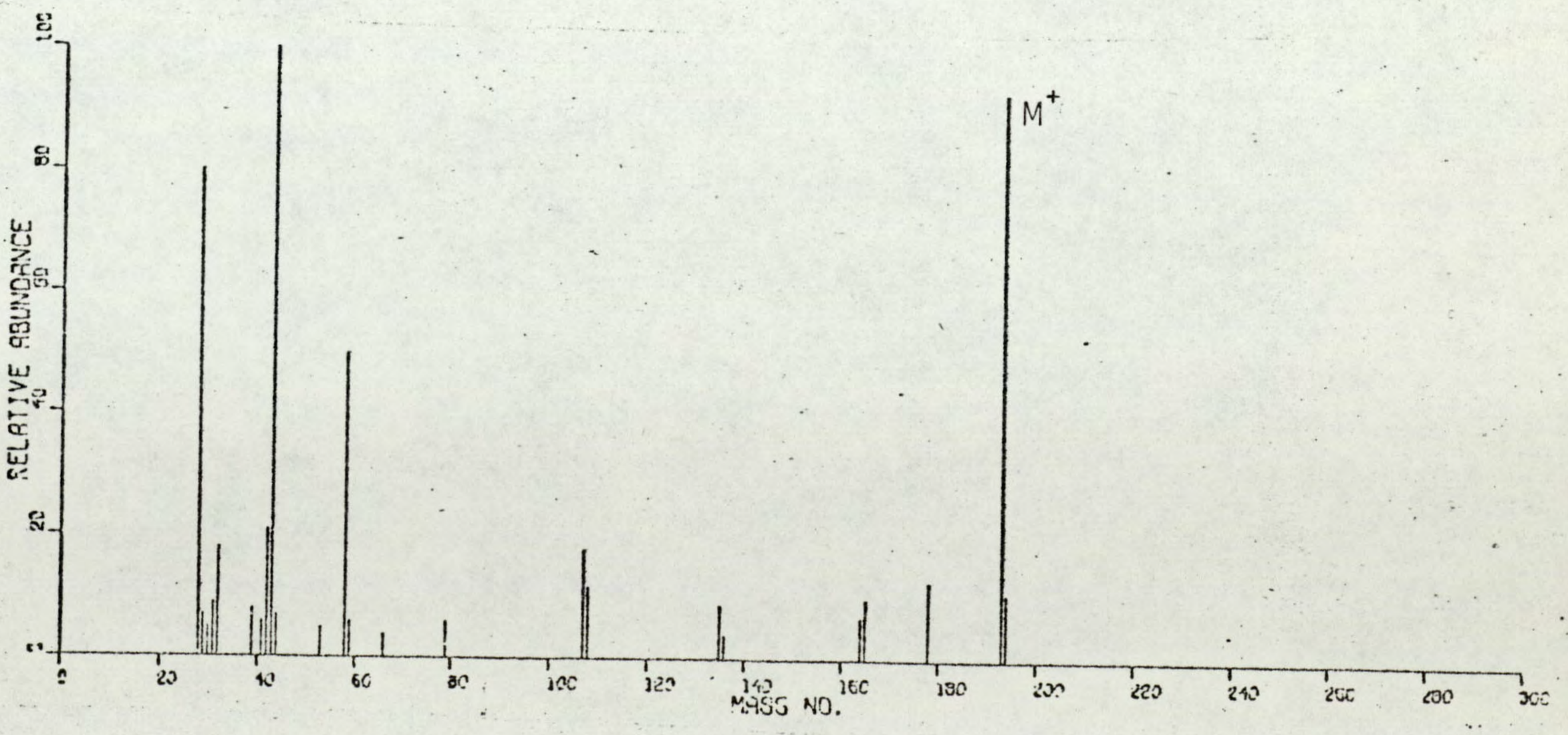
m* 254(290→272), 73.5(123→95), 59(95→75)

Pyrido[3,4-d]pyridazin-1,4(2H,3H)dione 6-oxide (330).



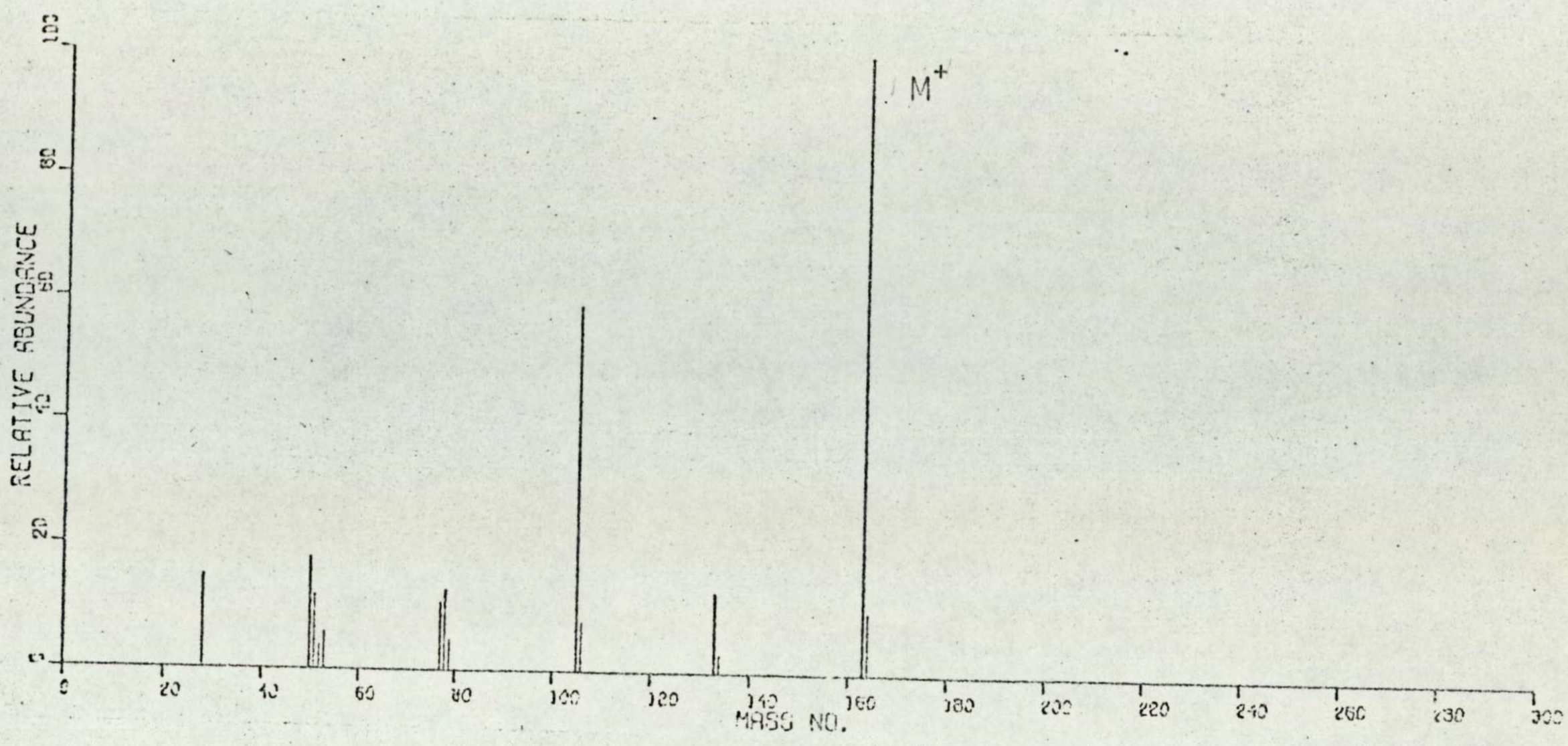
m* 108.5(163→133), 83(133→105), 56.5(105→777)

6-Methylpyrido[3,4-d]pyridazin-1,4,7(2H,3H,6H)trione (331).



m* 141(193 - 165)

Pyrido[3,4-d]pyridazin-1,4(2H,3H)dione (323).



m* 108.5(163→133), 83(133→105), 56.5(105→77)

4-Nitronicotinic acid 1-oxide (57).

m/e	184(M^+)	140	124	111	110	94	92	84	82	78	76
1%	3	50	6	3	44	7	3	3	5	12	4

m/e	75	68	64	63	62	61	58	54	53	52	51	50	49	44
1%	4	4	22	42	17	5	7	5	16	8	37	39	7	64

m/e	43	39	38	37	30	29	28	27	17
1%	35	100	33	11	71	34	13	13	47

m* 86.5 (140 → 110)

Ethyl 4-aminonicotinate 1-oxide (193).

m/e	183	182(M^+)	167	166	154	138	137	136	122	121	120	109
1%	9	87	8	76	30	20	19	97	8	63	100	13

m/e	108	94	93	92	81	79	78	68	67	66	65	64	54	53	52
1%	5	20	57	8	9	10	7	9	8	37	18	55	10	31	43

m/e	51	50	46	45	44	43	41	40	39	38	31	29	28	27	26
1%	7	6	8	18	13	10	10	8	34	40	24	24	20	30	10

m* 130.5(182 → 154), 89(166 → 121), 72(120 → 93), 47(93 → 66).

Ethyl 4-anilinonicotinate 1-oxide (194).

m/e	258(M^+)	241	242	230	214	197	196	169	168	167	149	141
1%	11	8	45	5	3	23	100	6	14	4	7	5

m/e	140	115	93	78	77	65	51	44	39	31	29	28
1%	7	7	9	4	17	6	12	4	6	11	10	16

m* 205(258 → 230), 159(242 → 196), 144(196 → 168).

Ethyl 4-benzylaminonicotinate 1-oxide (195).

m/e	272(M^+)	257	256	228	227	225	211	210	209	182	181	133	106	105
1%	12	12	60	6	36	7	11	19	93	14	16	13	27	10

m/e	104	92	91	79	78	77	65	51	44	43	39	29	28
1%	12	9	100	6	12	8	15	10	22	12	6	20	22

m* 201.7(256 → 278), 192.5(227 → 209), 173(256 → 210).

4-Benzamidonicotinic acid 1-oxide (196).

m/e	240	225	224	180	167	150	147	138	122	121	120	119	106	105	104
1%	29	14	33	16	14	35	15	9	30	10	14	9	11	100	20

m/e	93	92	78	77	76	75	74	65	64	52	51	50	44	39	30	28
1%	10	11	10	66	29	14	9	17	10	8	29	27	15	11	8	27

m* 96(150 → 120)

4-(p-Methoxybenzamido)nicotinic acid 1-oxide (197).

m/e	288(M^+)	270	254	244	229	152	136	135	121	107	92	77	76	64
1%	1	13	4	4	1	4	10	100	2	7	13	17	3	7

m/e	63	50	44	28
1%	5	2	12	3

m* 84.8(135 → 107), 119.9(152 → 135), 55.4(107 → 77).

4-(p-Methylbenzamido)nicotinic acid 1-oxide (198).

m/e	272(M^+)	254	238	228	212	138	121	120	105	93	92	91	90	79	78	77
1%	1	4	5	5	6	6	13	100	5	4	4	40	4	16	10	4

m/e	65	52	51	50	44	41	39	38	36	28
1%	15	9	7	4	15	4	9	6	22	10

m* 46.5(91 → 65), 69.8(120 → 91).

4-(p-Fluorobenzamido)nicotinic acid 1-oxide (199).

m/e	276(M^+)	260	258	230	216	214	199	124	123	96	95	94	75	51
1%	2	16	16	5	24	5	5	18	100	5	66	5	15	4

m/e	50	44	39	38
1%	5	18	3	10

m* 179(260 → 216), 73.5(123 → 95), 59(95 → 75).

4-(3,4-Dichlorobenzamido)nicotinic acid 1-oxide (200).

m/e	328(M^+)	326	310	309	308	294	293	292	283	268	266	177	175	174	173
1%	3	7	23	14	26	8	8	9	6	7	10	18	58	18	100

m/e	154	147	145	139	138	136	121	120	110	109	94	93	75	67	66	65	54	53
1%	42	22	32	13	95	22	16	97	25	15	21	63	15	13	25	17	13	22

m/e	52	51	50	44	41	39	38	37	32	28
1%	27	19	21	10	30	24	17	16	10	14

m* 104.3(138 → 120), 72(120 → 93).

4-Acetamidonicotinic acid 1-oxide (288).

m/e	178	162	152	147	138	136	120	119	110	94	93	67	66	64	60	53	52
1%	60	17	9	9	10	37	12	8	23	29	12	11	8	8	24	15	9

m/e	51	50	45	44	43	42	41	39	28
1%	8	9	29	32	100	9	8	8	23

m* 104(178 → 36), 96.3(147 → 119).

Ethyl 4-(N-phenylacetamido)nicotinate 1-oxide (205).

m/e	300(M^+)	284	259	258	243	242	239	230	197	196	195	185	170	169
1%	8	5	18	82	13	7	8	8	23	100	8	7	6	31

m/e	168	154	140	129	128	118	115	103	93	79	78	51	44	43
I%	12	6	6	7	6	12	5	5	7	6	28	17	9	46

m/e	39	32	29	28
I%	5	9	15	11

m* 222.8(300 → 259), 205(258 → 230), 195.5(197 → 196).

Ethyl 4-(N-phenylbenzamido)nicotinate 1-oxide (206).

m/e	363	362(M^+)	346	273	197	196	180	169	168	149	106	105
I%	3	13	12	3	5	4	7	8	4	5	9	100

m/e	78	77	51	31	29	28
I%	4	39	7	4	6	7

m* 56.5(105 → 77), 33.9(77 → 51).

Methyl 4-methoxynicotinate 1-oxide (211).

m/e	184	183(M^+)	168	167	166	153	152	150	138	137	136	135	134	125	123
I%	10	100	8	41	9	5	18	6	11	22	92	9	23	5	6

m/e	110	109	106	94	93	92	80	79	78	77	71	69	68	67	66	65	64	63
I%	8	5	11	11	18	5	5	17	75	11	9	10	17	6	10	8	8	7

m/e	59	55	54	53	52	51	50	45	44	43	42	41	40	39	38	37
I%	13	8	10	55	10	32	18	12	16	9	7	13	7	24	23	5

m/e	32	31	30	29	28	27	26
I%	5	5	17	22	20	13	12

m* 138.3(167 → 152), 44.6(78 → 59).

Ethyl 4-ethoxynicotinate 1-oxide (213).

m/e	211(M^+)	195	183	166	150	148	137	134	123	122	121	94	93
1%	22	11	13	13	32	28	100	13	10	45	34	18	15

m/e	53	44	43	39	32	29	28
1%	23	12	13	12	44	29	18

m* 141.4(195 → 166), 131.5(211 → 166), 99.5(150 → 122).

Methylpyridine 3,4-dicarboxylate 1-oxide (214).

m/e	212	211(M^+)	195	194	181	180	165	164	163	137	136	133	122	106	105
1%	10	88	8	10	10	100	29	90	9	5	4	5	7	7	16

m/e	93	78	77	63	59	53	51	50	44	39	28
1%	11	29	8	11	13	8	10	19	5	10	14

m* 193(195 → 194), 153.6(211 → 180), 112.8(164 → 136).

4-Amino-3-ethoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine (233).

m/e	184(M^+)	183	156	155	139	138	137	112	111	110	109	96	95	94	82	81
1%	18	30	4	51	18	12	100	8	52	8	8	13	6	6	5	3

m/e	80	70	69	68	67	55	54	53	52	44	43	42	41	39	31	30	29	28	27	26
1%	4	6	14	15	4	8	16	4	10	25	7	44	13	5	15	6	10	16	13	5

m* 131(184 → 156), 121.3(155 → 137), 102.5(183 → 137), 79.5(155 → 111).

3-Amino-4-methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine (239).

m/e	171	170(M^+)	141	139	137	128	127	112	111	110	109	99	96	95	94	82	70	69	68
1%	5	50	3	13	5	8	100	8	11	7	9	13	6	16	10	6	5	66	17

m/e	67	66	57	55	54	53	52	44	43	42	41	40	39	30	28	27	18
1%	8	4	5	11	6	5	19	46	6	40	16	5	10	6	13	5	11

m* 77(127 → 99), 48.2(99 → 69), 37.5(127 → 69).

3-Benzamido-4-methoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine (241).

m/e	274(M^+)	243	215	170	169	105	94	80	79	78	77	53	52	51	50	49
I%	5	2	3	1	8	8	4	6	100	14	8	9	80	34	22	5

m/e	44	42	39	38	36	35	28	26
I%	4	5	10	12	38	6	14	12

m* 215.5(274 → 243), 34.2(79 → 52).

3,4-Dimethoxycarbonyl-1-methyl-1,2,5,6-tetrahydropyridine hydrochloride (246a)

m/e	213(M^+)	212	198	183	182	181	180	170	166	164	155	154	153	152	140	139	138	1
I%	5	3	7	4	31	89	9	5	8	3	11	100	19	53	6	68	19	

m/e	123	122	111	95	94	93	83	66	65	59	53	52	51	45	44	43	42	41	40	39
I%	17	17	17	38	62	8	8	5	5	20	10	10	10	9	14	48	82	16	5	13

m/e	38	36	35	29	28	27
I%	17	44	5	6	31	6

m* 129.8(182 → 154), 106(182 → 139), 96.7(154 → 122), 88.5(139 → 111), 83.5(181 → 123), 57.5(154 → 94).

4-Anilinonicotinamide 1-oxide (274).

m/e	229(M^+)	213	212	211	197	196	195	194	182	170	169	168	167	142	141
I%	5	25	5	17	10	64	100	28	5	17	17	14	7	5	6

m/e	140	117	115	114	103	93	78	77	76	75	66	65	64	63	52	51	50	48
I%	13	5	7	5	5	8	7	31	11	5	19	13	10	7	8	28	12	8

m/e	44	43	41	39	38	28
I%	25	8	7	17	5	14

m* 144.1(196 → 168), 193.2(195 → 194).

4-Anilinonicotinic acid hydrazide 1-oxide (275).

m/e	244(M^+)	228	197	94	93	92	78	77	67	66	65	63	54	52	51	50	46	41	40
I%	2	2	4	7	100	10	2	2	5	31	18	6	5	6	5	5	8	6	5

m/e	39	38	28
I%	15	6	10

m* 46.8(93 → 66).

2-(4-methoxyphenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (299).

m/e	271	270(M^+)	255	254	253	226	210	136	135	133	119	107	92	77	64
I%	11	80	7	33	6	2	2	10	100	7	2	6	17	20	10

m/e	63	53	50	44	32	28
I%	11	5	5	9	10	17

m* 239(270 → 254), 84.9(135 → 107), 67.5(270 → 135).

2-(4-tolyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (298).

m/e	255	254(M^+)	239	238	237	223	210	209	194	120	119	117	105	92	91
I%	7	34	6	34	5	2	4	2	10	9	100	5	4	5	65

m/e	90	89	78	77	65	64	63	58	51	50	39	32	28
I%	6	6	5	6	20	5	9	4	5	5	10	13	18

m* 223.5(254 → 238), 158(238 → 194), 69.5(119 → 91), 46.5(91 → 65).

2-(4-Fluorophenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (297).

m/e	258(M^+)	243	242	214	198	182	181	154	153	152	141	140	139	138	130	124
I%	21	7	50	5	15	10	24	37	6	17	6	5	18	6	5	7

m/e	123	122	121	111	96	95	94	93	79	78	75	59	53	52	51	50	44	43	42	41
I%	100	6	5	5	4	43	12	5	11	5	11	6	6	8	9	10	18	13	21	7

m/e	39	36	32	29	28	27
I%	7	12	10	6	20	7

m* 226.7(258 → 242), 73.5(123 → 95)

2-(3,4-Dichlorophenyl)pyrido[4,3-d][1,3]oxazin-4-one 6-oxide (300).

m/e	311	310(M^+)	309	308	294	292	248	177	176	175	174	173	147	145	111	110	109
I%	6	45	12	68	10	16	6	12	6	66	10	100	32	45	9	10	21

m/e	93	75	74	64	63	62	53	51	50	44	38	36	32	28
I%	6	15	11	6	15	6	13	5	12	10	6	10	6	18

m* 276.8(308 → 292), 123.5(175 → 147), 121.5(173 → 145)

2-(3,4-Dichlorophenyl)pyrido[4,3-d]pyrimidin-4(3H)-one 6-oxide (302).

m/e	309(M^+)	307	293	292	291	175	174	173	172	147	145	120	93	44	32	28
I%	23	37	39	20	60	14	13	25	16	9	14	100	14	14	18	27

3-Amino-2-(3,4-dichlorophenyl)pyrido[4,3-d]pyrimidin-4(3H)-one 6-oxide (311).

m/e	324(M^+)	322	310	309	308	307	306	305	295	294	293	292	291	279	277
I%	30	44	9	14	37	26	48	18	12	16	36	22	42	20	30

m/e	242	192	190	175	174	173	172	171	147	145	138	136	135	121	120	119	111	109
I%	12	12	20	54	16	100	14	24	24	34	10	12	14	24	68	16	10	16

m/e	93	92	78	75	74	64	51	50	44	36	32	28
I%	16	10	10	14	12	14	10	20	34	16	16	18

m* 157.5(190 → 173)

Ethyl 4-benzamidonicotinate 1-oxide (312).

m/e	286(M^+)	270	240	224	122	120	106	105	78	77	51	50	44	29
I%	15	7	6	4	14	3	8	100	4	47	12	5	6	10

m* 90.6(122 → 105), 56.5(105 → 77), 33.8(77 → 51).

3-Hydroxy-2-methylpyrazolo[4,3-c]pyridine 5-oxide (319).

m/e	294	278	223	165(M^+)	150	149	148	147	135	134	121	120	119	107	106	105	94
I%	18	2	4	32	10	100	27	7	10	11	5	7	6	5	25	10	10

m/e	93	92	79	78	77	76	67	66	65	64	63	53	52	51	50	44	43	42	41	40
I%	17	7	12	29	12	8	15	15	7	7	5	8	12	26	25	26	19	6	5	4

m/e	39	38	37	32	31	29	28	27	26	18
I%	15	12	5	7	7	6	12	15	5	34

m* 147(149 → 148), 120.5(149 → 134), 57.3(106 → 178).

Sodium 4-anilinonicotinate 1-oxide (342)

m/e	186	185	171	170	169	168	142	115	93	78	77	66	65	51	44
I%	3	4	10	22	100	10	3	7	5	5	9	5	6	17	46

m/e	39	28
I%	6	12

m* 119.3(169 → 142).

7- and 9- methoxybenzo[b]1,6-naphthyridine-10(5H)-one 2-oxide.

m/e	242(M^+)	226	225	212	196	186	80	77	76	66	64	48	44	36	32	28
I%	2	7	5	10	3	2	3	4	2	6	100	38	15	4	7	24

7- and 9-methylbenzo[b]1,6-naphthyridine-10(5H)-one 2-oxide.

m/e	226(M^+)	225	211	210	209	194	184	183	182	181	153	152	105	91	77	76	66
I%	5	2	7	33	11	3	17	7	5	7	3	4	3	5	5	7	16

m/e	64	58	57	56	51	50	48	44	43	42	41	39	34	32	31	30	29	28
I%	100	6	13	6	6	5	65	26	10	5	8	8	9	12	5	6	5	27

m* 208(210 → 209).

References

1. R.C. Elderfield, A.C. Mehta, Heterocyclic Compounds, (1967), 1, 1.

2. W.L.F. Armarego, Advan.Heterocyclic Chem., (1963), 1, 253 - 309.

3. "Chemistry of the Heterocyclic N-oxides". A.R. Katritzky, J.M. Lagowskii, Academic Press, (1971).

4. A.H. Cook, R.J. Reed, J.Chem.Soc. (1945), 399.

5. G. Ohnacker, U.S. Patent 3,186,991 (1965); Chem.Abstr., (1965), 63, 4312.

6. G. Ohnacker, U.S. Patent 3,306,901 (1967); Chem.Abstr., (1967), 67, 73618.

7. K. Thomae, Fr. Patent M2450, (1964); Chem.Abstr., (1964),61, 8307.

8. K. Thomae, Fr. Patent M2798, (1964); Chem.Abstr., (1965) 62, 6493.

9. K. Thomae, Fr. Patent M2928, (1964); Chem.Abstr., (1965), 62, 9150.

10. K. Thomae, Neth. Patent 6,400,580, (1966); Chem.Abstr., (1966), 64, 5111.

11. J. Foucart, J. Nasielski, E. Van der Douckt, Bull.Soc.Chim.Belges., (1966), 75, 17.

12. G. Modena, P.E. Todesco, Gazz.Chim.Italia.,(1960), 90, 702.

13. A. Dondoni, G. Modena, P.E. Todesco, Gazz.Chim.Italia., (1961), 91, 613.

14. F.D. Popp, W.D. McEwen, J.Amer.Chem.Soc., (1958), 80, 1181.

15. P.F. Holt, H. Lindsay, J.Chem.Soc.(B)., (1969), 54.

16. R.J. Martens, H.J. den Hertog, Rec.Trav.Chim., (1967), 86, 655.

17. W. Herz, D.R.K. Murty, J.Org.Chem., (1960), 25, 2242.

18. W. Herz, D.R.K. Murty, J.Org.Chem., (1961), 26, 418.

19. B.M. Bain, J.E. Saxton, J.Chem.Soc., (1961), 5216.

20. E.C. Taylor, J.S. Driscoll, J.Org.Chem., (1961), 26, 3796.

21. S. Furukaw, J.Pharm.Soc.Japan., (1959), 79, 492; Chem. Abstr., (1959), 53, 18029.

22. T.R. Govindachari, K. Nagarajan, S. Rajappa, J.Chem.Soc., (1957), 551.

23. E. Profft, W. Steinka, J.Prakt.Chem., (1961) 13, 58.

24. D.L. Heywood, J.T. Dunn, J.Org.Chem., (1959), 24, 1569.

25. R.A. Barnes, J.Amer.Chem.Soc., (1959), 81, 1935.

26. J. Devanneaux, J.-F. Labarre, J.Chim.Phys., (1969), 66, 1174.

27. E.P. Linton, J.Amer.Chem.Soc., (1940), 62, 1945.

28. E. Ochiai, M.O. Ishikawa, Proc.Japan.Acad., (1942), 18, 561.

29. H.J. den Hertog, J. Overhoff, Rec.Trav.Chim., (1950), 69, 468.

30. E.V. Brown, J.Amer.Chem.Soc., (1954), 76, 3167.

31. H.J. den Hertog, C.R. Kalder, W.P. Combe, Rec.Trav.Chim., (1951), 70, 591.

32. R. Jujo, J.Pharm. Soc.Japan., (1946), 66, 21. Chem.Abstr., (1951), 45, 6637.

33. E. Hayashi, J.Pharm.Soc.Japan., (1950), 70, 145; Chem.Abstr., 1950, 44, 5881.

34. E. Hayashi, J.Pharm.Soc.Japan., (1951), 71, 213.

35. H.J. den Hertog, J. Maas, C.R. Kalder, W.P. Combe, Rec.Trav.Chim., (1955), 74, 1171.

36. M. Van Ammers, H.J. den Hertog, B. Haase, Tetrahedron, (1962), 18, 227.

37. J.W. Clark-Lewis, R.P. Singh, J.Chem.Soc., (1962) 2379.

38. T. Talik, Roczniki Chem., (1963), 37, 495.

39. T. Talik, Z. Talik, Roczniki Chem., (1962), 36, 539.

40. M. Bellas, H.Suschitzky, J.Chem.Soc., (1965), 2096.

41. Z. Talik, B. Brekieoz, Roczniki Chem., (1967), 41, 279.

42. J.M. Essery, K. Schofield, J.Chem.Soc., (1960), 4953.

43. Y. Suzuki, J.Pharm.Soc.Japan., (1961), 81, 917.

44. E.C. Taylor, J.S. Driscoll, J.Amer. Chem.Soc., (1960), 82, 3141.

45. G.M. Badger, R.P. Rao, Austral.J.Chem., (1965), 18, 379.

46. G.M. Badger, R.P. Rao, Austral.J.Chem., (1964), 17, 1399.

47. T. Hai, H. Ogura, J.Pharm.Soc.Japan., (1955), 78, 292.

48. T. Wieland, H. Bierer, Chem.Ber., (1963), 96, 266.

49. W. Herz, D.R.K. Murty, J.Org.Chem., (1961), 26, 122.

50. H.J. den Hertog, J. Maas, C.R. Kalder, W.P. Combe, Rec.Trav.Chim., (1955), 74, 59.

51. "A Text Book of Practical Organic Chemistry" A.I. Vogel, London(1964).

52. R.A. Abramovitch, J.G. Saha, Advan.Heterocyclic.Chem., (1966), 6, 333.

53. E.K. Kosower, S.W. Bauer, J.Amer.Chem.Soc., (1956), 78, 3497.

54. E.K. Kosower, S.W. Bauer, J.Amer.Chem.Soc., (1960), 82, 2191.

55. M. Marti, M. Viscontini, P. Karrer, Helv.Chim.Acta., (1956), 39, 1451.

56. A.F. Casey, A.H. Beckett, M.A. Ioria, H.Z. Youseff, Tetrahedron, (1965), 21, 3387.

57. A.F. Casey, A.H. Beckett, M.A. Ioria, Tetrahedron, (1967), 23, 1405.

58. R. Lukes, M. Hudlicky, Z. Janu, Coll.Czech.Chem.Comm., (1956), 21, 140.

59. V. Prelog, E. Moor, Helv.Chim.Acta., (1945), 28, 182.

60. V. Prelog, A. Kamzak, Ber., (1941), 74, 1705.

61. O. Wichterle, M. Hudlicky, Coll.Czech.Chem.Comm., (1941), 12, 101.

62. H. Bohme, K. Hartke, A. Muller, Ber., (1963), 96, 5607.

63. R. Merton, G. Muller, Angew.Chem., (1962), 74, 866.

64. R.E. Lyle, P.S. Anderson, Advan.Heterocyclic Chem.,(1966) 6, 45.

65. M. Ferles, J. Pliml, Advan.Heterocyclic Chem., (1970), 12, 43-101.

66. E.M. Fry, E.L. May, J.Org.Chem., (1957), 22, 1366.

67. E.M. Fry, E.L. May, J.Org.Chem. (1961), 26, 2592.

68. J.H. Ager, E.L. May, J.Org.Chem., (1962), 27, 245.

69. J.H. Ager, E.L. May, S.E. Fullerton, J.Org.Chem., (1962), 27, 2554.

70. E.M. Fry, J.Org.Chem., (1963), 28, 1869.

71. A. Silhankova, M. Holik, M. Ferles, Coll.Czech.Chem.Comm., (1968), 33, 2499.

72. Z. Vondrackova, M. Kovarick, M. Ferles, Coll.Czech.Chem.Comm., (1966), 31, 1348.

73. B. Bobranski, E. Sucharda, Chem.Ber., (1926), 60, 1081.

74. B. Bobranski, E. Sucharda, Roczniki Chem., (1927), 7, 192.

75. T. Kato, F. Hamaguchi, T. Oiwa, Chem.Pharm.Bull.(Tokyo), (1956), 4, 178.

76. B.M. Ferrier, N. Campbell, Proc.Roy.Soc.Edinburgh Sect.A., (1960), 65, 231.

77. R.P. Rao, J.N. Singh, Labdev Part A, (1969), 7, 126.

78. N.S. Viel'fson, G.M. Sukhotina, Izv.Akad.Nauk.S.S.R. Ser.Khim., (1966), 1785.

79. A. Dornow, H.W. Plessen, Ber., (1966), 99, 244.

80. E.C. Taylor, A. McKillop, S. Vromen, Tetrahedron, (1967), 23, 885.

81. T. Takahashi, K. Kanematsu, Yakugoku Zashi., (1958), 78, 787.

82. S. Hunig, G. Kobrich, Ann., (1958), 617, 181.

83. K. Hohenlohe-Oehringen, D. Saffer, G. Sporidi, H. Bretschreider, Monatsh, (1967), 92, 313.

84. U. Horlein, Ber., (1954), 87, 463.

85. E.V. Heyringen, J.Amer.Chem.Soc., (1957), 60, 156.

86. L.H. Schlager, Arch.Pharm., (1963), 296, 756.

87. Neth. Patent 6,511,645, (1966); Chem.Abstr., (1966), 65, 2269.

88. H.M. Blutter, U.S. Patent 3,423,414 (1969); Chem.Abstr. (1969), 70, 68361.

89. K. Tsuda, S. Saeki, S. Imura, S. Okuda, Y. Sato, H. Mishima, J.Org.Chem., (1956), 21, 1481.

90. F. Haglid, Ark.Kemi., (1967), 26, 489.

91. J.H. Diebold, M. Wolf, U.S. Patent 3,555,034, (1966); Chem.Abstr., (1966), 65, 5871.

92. G. Ohnacker, U.S. Patent 3,248,395, (1966); Chem.Abstr., (1966), 65, 3888.

93. E.C. Taylor, A. McKillop, S. Vromen, A.V. Ravindranathan, Angew.Chem. Int.Ed., (1965), 5, 308.

94. E.C. Taylor, A. McKillop, R.N. Warrener, Tetrahedron, (1967), 23, 891.

95. A. Aviran, S. Vroman, Chem.and Ind., (1967), 1452.

96. Y. Mizureo, T. Itoh, K. Saito, Chem.Pharm.Bull.(Tokyo), (1964), 12, 866.

97. W.W. Paudler, D.J. Podkorny, S.J. Cornish, J.Heterocyclic.Chem., (1970), 7, 291.

98. T. Torizo, H. Yoshiti, T. Isao, U. Hideko, Yakugaku Zasshi., (1969), 89, 1260.

99. Sterling Drug Co., Brit. Patent 1,022,214, (1966); Chem.Abstr., (1966), 64, 19618.

100. G.Y. Lesher, U.S. Patent 3,429,887 (1969); Chem.Abstr., (1969), 70, 106489.

101. J.G. Murray, C.A. Hauser, J.Org.Chem., (1954), 19, 2008.

102. A.H. Gawer, B.P. Dailey, J.Chem.Phys., (1965), 43, 2658.

103. Y. Sato, T. Iwashige, T. Miyadera, Chem.Pharm.Bull. (Tokyo). (1960), 8, 427.

104. F. Zymalkowski, P. Messinger, Arch.Pharm., (1967), 300, 91.

105. Y. Hamada, T. Takeuchi, H. Mitsuoka, Chem.Pharm.Bull.(Tokyo), (1970), 18, 1026.

106. T. Vitali, G. Bertaccini, Gazz.Chim.Italia., (1964), 94, 296.

107. T. Vitali, G. Bertaccini, F. Mossini, Farmaco.Ed.Sci., (1967), 22, 821.

108. G. Cleve, H. Gibian, G.A. Hayer, D. Rahtz, E. Schroeder, G. Schulz, Ann., (1971), 747, 158.

109. S. Sugasawa, N. Yoneda, Chem.Pharm.Bull. (Tokyo), (1956), 4, 360.

110. E.C. Taylor, A.J. Crovetti, J.Amer.Chem.Soc., (1956), 78, 214.

111. S. Mitsui, T. Sakai, H. Saito, Nippon Kagaku Zasshi, (1965), 86, 409.

112. T. Sakai, C. Kaneko, S. Mitsui, Nippon Kagaku Zasshi, (1965), 86, 1328.

113. E. Ochiai, I. Suzuki, J.Pharm.Soc.Japan, (1947), 67, 158; Chem.Abstr., (1951), 45, 9541.

114. J.A. Berson, T. Cohen, J.Org.Chem., (1955), 20, 1461.

115. T. Kato, T. Niitsuma, Chem.Pharm.Bull.(Tokyo) (1965), 13, 963.

116. E. Ochiai, M. Katada, J.Pharm.Soc.Japan (1943), 63, 186.

117. S. Kubota, T. Akita, J.Pharm.Soc.Japan (1968), 78, 248.

118. "Aromatic Amine Oxides", E. Ochiai, Elsevier,(1967).

119. R.P. Rao, J.Sci.Indust.Res.India, (1967), 26, 333.

120. M.J.S. Dewar, T. Mole, J.Chem.Soc. (1956), 2556.

121. T. Neilson, H.G.S. Wood, A.G. Wylie, J.Chem.Soc. (1962), 371.

122. E.A. Braude, R.P. Linstead, K.R.H. Woolridge, J.Chem.Soc., (1954), 3586.

123. E. Ochiai, M. Katada, J.Pharm.Soc.Japan (1943), 63, 265.

124. I.J. Pachter, M.C. Koetzel, J.Amer.Chem.Soc., (1952), 74, 971.

125. A.G. Ismail, D.G. Wibberley, J.Chem.Soc.(C)., (1967), 2613.

126. M.L. Peterson, J.Org.Chem., (1960), 25, 657.

127. W.L.F. Armarego, R.F. Evans, J.Appl.Chem., (1962), 12, 45.

128. M. Ferles, Coll.Czech.Chem.Comm., (1958), 23, 479.

129. F. Liberatore, V. Corelli, M. Cardellini, Tetrahedron Letters, (1968). 4375.

130. W.J. Irwin, D.G. Wibberley, Advan.Heterocyclic Chem. (1968), 10, 149.

131. A.C. Cope, E. Ciganak, L.J. Fleckenstein, M.A.P. Meisinger, J.Amer. Chem.Soc. (1960), 82, 4651.

132. "Organic Synthesis Coll. Vol. II" J. Wiley & Sons, New York, (1955), 419.

133. H.L. Bradlow, C.A. Van der Werff, J.Org.Chem., (1951), 16, 73.

134. M.E. Pullman, J.P. Colowick, J.Biol.Chem., (1954), 206, 121.

135. M.H. Frank, H.S. Mosher, J.Org.Chem., (1959), 24, 196.

136. "The Chemistry of Boron and its Compounds", E.L. Muetterties, J. Wiley and Sons, New York, (1967).

137. W.L.F. Armarego, J.Chem.Soc. (1962), 4094.

138. A.G. Ismail, Ph.D. Thesis, University of Aston in Birmingham, (1968).

139. R.E. Little, D.S. Allen Jnr., J.Med.Chem., (1965), 8, 722.

140. D.I. Bain, R.K. Smalley, J.Chem.Soc., (1968), 1593.

141. I.R. Gelling, Ph.D. Thesis, University of Aston in Birmingham, (1970).

142. C.F.H. Allen, C.J. Kibler, D.M. McLachlin, C.V. Wilton, "Organic Synthesis Coll. Vol. III", (1955), 28.

143. D.T. Zentmeyer, E.C. Wagner, J.Org.Chem., (1949) 14, 967.

144. M.T. Bogart, H.A. Seil, J.Amer.Chem.Soc., (1905); 27, 1305.

145. M.T. Bogart, V.J. Chambers, J.Amer.Chem.Soc., (1905), 27, 649.

146. H.L. Yale, K. Losee, J. Martins, M. Holsing, F.M. Perry, J. Bernstein, J. Amer.Chem.Soc., (1953), 75, 1933.

147. M. Takuichi, M. Tasuki, Japan.Patent 70,18458 (1970); Chem.Abstr. (1970), 73, 77268.

148. M. Ikutoshi, Japan Patent, 70 33186 (1970); Chem.Abstr., (1970), 74, 76436.

149. H. Mayer, J. Mally, Monatsh, (1912), 33, 393.

150. R.G. Jones, J.Amer.Chem.Soc., (1956), 78, 159.

151. W.W. Paudler, T.J. Kress, Advan.Heterocyclic Chem., (1970), 11, 124-177.

152. E.M. Hawes, D.G. Wibberley, J.Chem.Soc.(C), (1966), 315.

153. E.M. Hawes, D.K.J. Gorecki, J.Heterocyclic Chem., (1972), 703.

154. S. Singh., R.S. Tanya., K.S. Narang, Indian J.Chem. (1968), 6, 11.

155. "The Acridones", A. Albert, Arnold. London,(1966).

156. W. Jourdan, Ber., (1885), 18, 1444.

157. W. Glenn, K. Nietszche, J.Prakt.Chem., (1939), 153, 200.

158. O. Lehmstedt, M. Schrader, Ber., (1937), 70, 838.

159. T.A. Bryce, J.R. Maxwell, Chem.Comm., (1967), 206.

160. R. Grigg, R.G. Odell, J.Chem.Soc. (B), (1966), 218.

161. O. Buchardt, A.M. Duffield, R.H. Shapiro, Tetrahedron, (1968), 24, 3139.

162. S.M. Roberts, H. Suschitzky, Chem.Comm., (1967), 893.

163. H.H. Mantsch, Rev.Roum.Chem., (1969), 549.

164. H. Budzikiewicz, C. Djerassi, D.H. Wiliams, "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, (1967).

165. Q.N. Porter, J. Boldas, "Mass Spectrometry of Heterocyclic Compounds", Wiley and Sons, (1971).

166. I.R. Gelling, W.J. Irwin, D.G. Wibberley, J.Chem.Soc. (B), (1969), 513.

167. J. Bowie, R.G. Cooks, P.F. Donaghue, J.A. Halleday, H.J. Rodda, Austral.J.Chem., 1967, 20, 2677.

168. "Dictionary of Organic Compounds". Eyre and Spottiswoode, London, (1965).