SYNTHESIS AND REACTIONS OF OXAZOLOPYRIDINIUM SALTS AND RELATED HETEROCYCLIC SYSTEMS

by

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A thesis submitted to the University of Keele in partial fulfilment of the requirements for the Degree of Doctor of Philosophy

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SUMMARY

2-Substituted oxazolo[3,2-a]pyridinium salts have been synthesised starting from the appropriate 2-(4-ethoxybutyryl) oxazoles, which are treated with hydrobromic acid and then cyclised and aromatised by boiling acetic anhydride. Attempts to synthesise 2-substituted oxazoles suitable for the synthesis of the parent oxazolopyridinium salt were not successful. Catalytic reduction of two oxazolopyridinium salts leads to ring opening giving N-substituted-2-piperidones.

Attempts to prepare the parent isoxazolo[2,3-a]-pyridinium ion by the same route have led to the isolation of a compound of unknown structure. The reactions and properties of this compound have been investigated and proposed structures are discussed.

The first synthesis of a substituted isoxazolo[2,3-a]-pyridinium salt is reported using a synthetic route that involves the elimination of hydrogen bromide from the appropriate α,α-dibromoketone.

ACKNOWLEDGMENTS

I am indebted to Dr. G. Jones for his guidance and encouragement during this work.

I would like to thank Professor H.D. Springall and the University of Keele for the provision of laboratory facilities and the Science Research Council for financial support.

I would also like to thank Mrs P. Bebb for the typing of this thesis.

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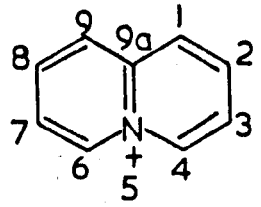
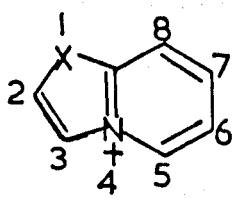
INTRODUCTION

Nomenclature

Throughout the following thesis the name quinolizinium ion will be used to designate the bicyclic napthalenic ring system containing a quaternary nitrogen atom (1). The systems (2, X = S, O) in which a sulphur or oxygen atom replaces two adjacent CH units in the quinolizinium ion (1) have systematic names of thiazolo- and oxazolo[3,2-a]pyridinium salts respectively. Similarly, system (3) is referred to as the isoxazolo[2,3-a]-pyridinium system.



(1)



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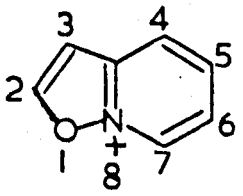


(3)

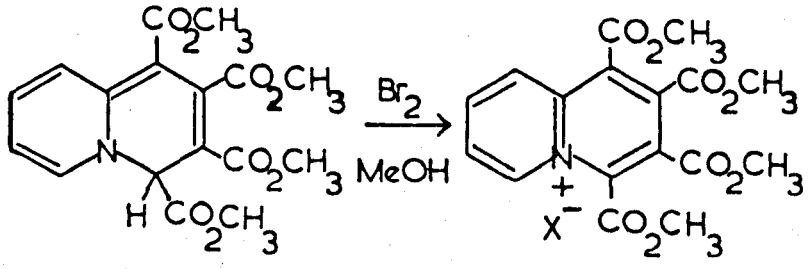
Both the numbering and the naming of all the systems follow the rules set out in the American Chemical Society Ring Index.

Historical Review

The quinolizinium nucleus (1) is known to occur in a number of alkaloids. The work of Perkin et al.[1] on the berberine alkaloids and more recently by Woodward and co-workers[2] on sempervirine has led to considerable interest in this system.

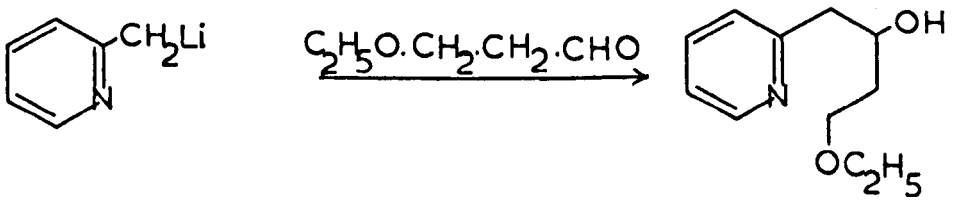
The synthesis of the quinolizinium ion (1) has shown the basic stability of this particular system and has led to the possibility of synthesising isoelectronic analogues.

The first quinolizinium derivatives were reported by Diels and Alder.[3] They reacted pyridine with dimethyl acetylenedicarboxylate to give a stable adduct formulated as 1,2,3,4-tetracarbomethoxy-9aH-quinolizine. Recent work[4,5,6] has however proved that the 9aH isomer is originally formed but converts readily to the 4H isomer (4). Oxidation of (4) by bromine in methanol gave the 1,2,3,4-tetracarbomethoxy-quinolizinium perbromide (5, X = Br_3). The bromide (5, X = Br) was generated on boiling in acetone.



(4) (5)

The parent quinolizinium system was first prepared by Beaman and Woodward[7] using an extension of their synthesis of sempervirine. 2-Picolyllithium was treated with 3-isopropoxy-acrolein and the intermediate cyclised with acid to the quinolizinium ion. The product however was only isolated with great difficulty and in poor yield. By replacing the 3-isopropoxyacrolein with the more readily available 3-ethoxy-propionaldehyde, Boekelheide and Gall[8] were able to obtain the quinolizinium iodide (8) in workable quantities. The 2-hydroxy-1,2,3,4-tetrahydroquinolizinium iodide (7) underwent dehydration followed by a troublesome dehydrogenation stage to produce the quinolizinium iodide (8) in an overall yield of 10%.



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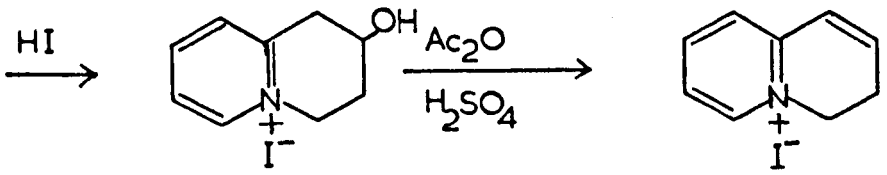

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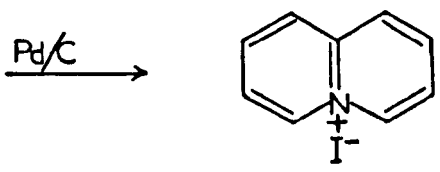
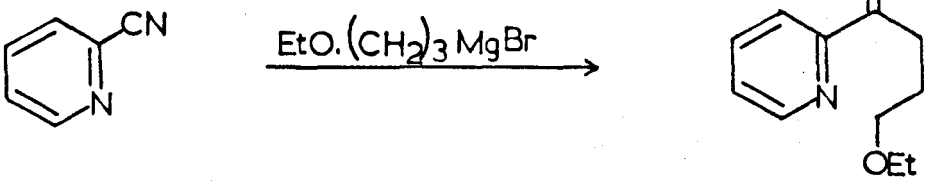


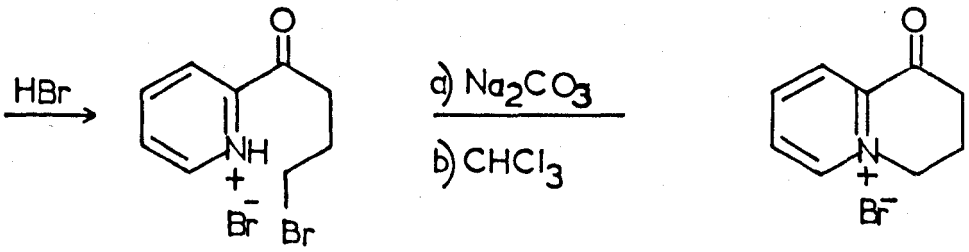
(8)

Synthesis of quinolizinium salts in good yield was first made possible by the route of Glover and Jones[9] in 1958.

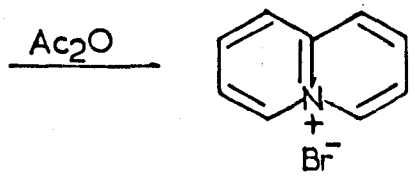
2-Cyanopyridine was treated with the Grignard compound of 3-ethoxypropyl bromide to give 2-(4-ethoxybutyryl)pyridine (9). This was boiled with 48% hydrobromic acid to form 2-(4-bromobutyryl)-pyridine hydrobromide (10). Neutralisation liberated the free base which underwent cyclisation in boiling chloroform to give 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (11). Finally, aromatisation in boiling acetic anhydride gave the quinolizinium bromide (12) in an overall yield of 48%.


CN
N
EtO.(CH2)3MgBr
O
N
OEt

(9)


HBr
O
NH
+
Br⁻
Br
a) Na2CO3
b) CHCl3
O
N
+
Br⁻

(10) (11)


Ac2O
N
+
Br⁻

(12)

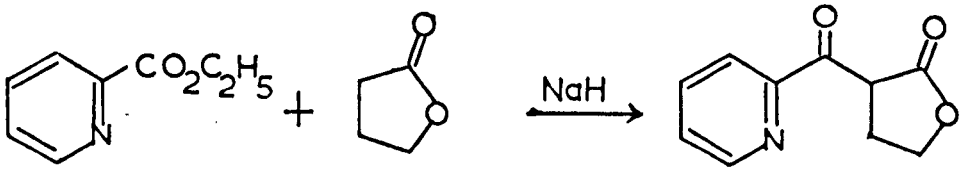
Recent work by Hough and Jones[10] has reported a 60% overall yield of quinolizinium bromide by direct treatment of the crude hydrobromide (10) with boiling acetic anhydride. Presumably the acylpyridine, which is known to be only weakly basic, undergoes dissociation, cyclisation and aromatisation to the bicyclic system (12).

By using substituted 1-bromo-3-ethoxypropanes, many 2, 3 and 4 substituted quinolizinium salts[9,11] have been synthesised in good yield.

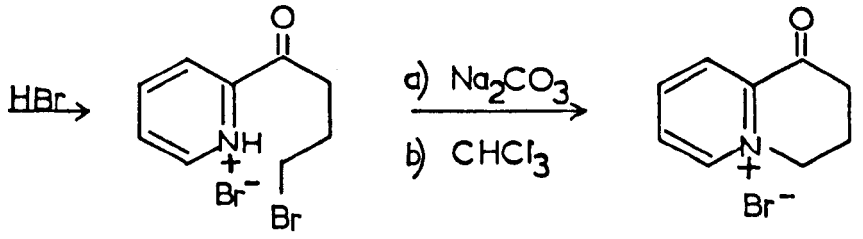
Moynehan, Schofield, Jones and Katritzky[12] have prepared the four monomethyl derivatives starting from the corresponding methyl cyanopyridines.

The mechanism of aromatisation has been studied and is reported in detail later.

Other routes to quinolizinium salts include an alternative synthesis of 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (11) reported by Miyadera and Iwai[13] in 1964. Condensation of ethyl picolinate with γ-butyryl-lactone in the presence of sodium hydride or potassium, gave the substituted lactone (13). Treatment of the lactone (13) with boiling hydrobromic acid led to ring cleavage followed by decarboxylation to the bromo-ketone hydrobromide (10). Basification and cyclisation as described previously yielded the cyclised ketone (11).



(13)

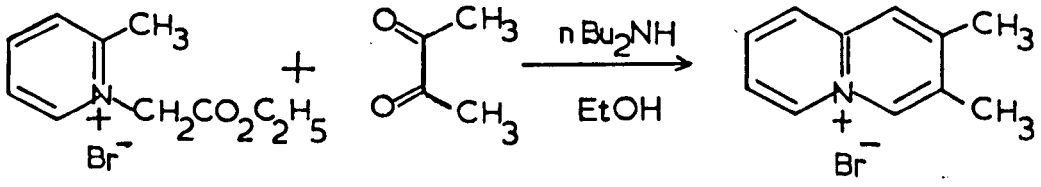


(10) (11)

The cyclised ketone (11) could then be aromatised by the method of Glover and Jones[9] to quinolizinium bromide (12). The overall yield compares favourably with the previous method and in some cases starting materials are more readily available. Miyadera and Iwai synthesised all four monomethyl analogues by suitable variation of starting materials.

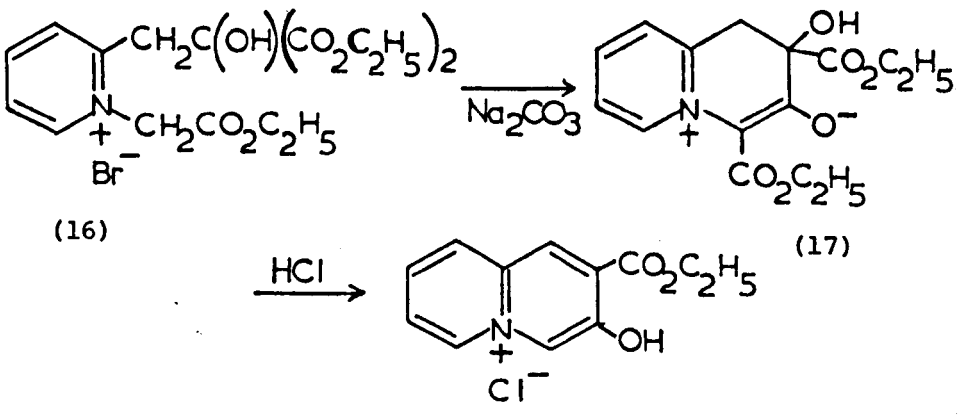
A convenient route to a number of quinolizinium salts was described by Westphal, Jann and Heffe.[14] They initially quaternised a suitable amine with ethyl bromoacetate to produce a picolinium salt which contained an active methylene group adjacent to the quaternary nitrogen atom. The salt readily undergoes condensation with an α-diketone in the presence of dibutylamine to give a high yield of the quinolizinium salt. For example the

quaternary salt (14), formed from ethyl bromoacetate and 2-picoline, when cyclised with diacetyl yields 2,3-dimethylquinolizinium bromide (15) in an overall yield of 60%.



(14) (15)

Finally a recent synthesis of substituted quinolizinium salts was reported by Carelli, Liberatore and Casini.[15] The picolinium salt (14) was again used as intermediate and undergoes a base catalysed condensation with di-ethyl mesoxalate in chloroform solution to give a high yield of the N-substituted-2-(2,2-dicarbethoxy-2-hydroxy)ethylpyridinium bromide (16). Neutralisation of the bromide (16) yielded the cyclic betaine (17) which when boiled in hydrochloric acid underwent aromatisation to the 2,3 disubstituted quinolizinium chloride (18).



(16)

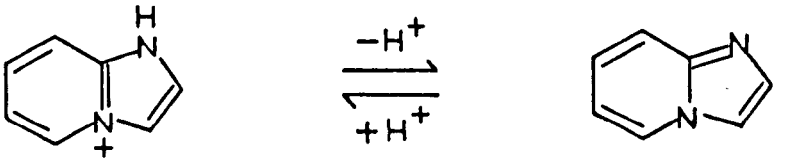
(17)

(18)

The stability of the quinolizinium cation has suggested the possible existence of other iso-π-electronic heterocyclic systems containing a bridgehead nitrogen atom. Replacement of one of the ring CH units by a tertiary nitrogen atom forms another 6,6-bicyclic system. Replacement of two adjacent CH units by a second hetero atom (e.g. N, S or O) results in a 5,6 system. A further substitution produces a 5,5-bicyclic system. The scope of the following review is however limited to those systems containing two hetero atoms resulting in a 5,6-bicyclic system.

Of the possible 5,6 systems, all three nitrogen analogues are known. However the free bases, rather than the pyridinium salts, are preferentially prepared. An example of this is pyrimidazole (20) which is formed by the loss of a proton from the secondary nitrogen

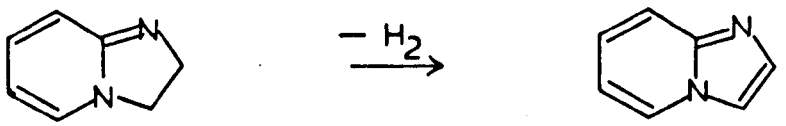
atom of the imidazo[1,2-a]pyridinium ion (19).



(19) (20)

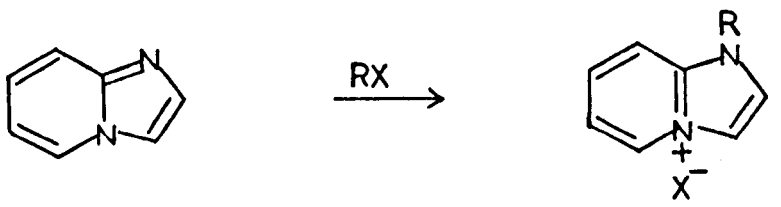
Pyrimidazole (20) was first synthesised by Tschitschibabin[16] in 1925. It was prepared by heating 2-aminopyridine with bromo-acetaldehyde in a sealed tube at 250°.

More recent syntheses are only modifications of this method.[17,18,19] Bower[20] however has obtained pyrimidazole by dehydrogenation of 2,3-dihydropyrimidazole (21) with potassium ferri-cyanide or lead tetra-acetate.



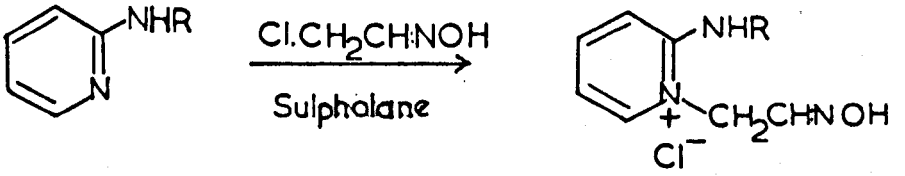
(21) (20)

Imidazo[1,2-a]pyridinium compounds substituted in the 1-position (22) are prepared by the action of alkyl halides on pyrimidazole.[21,22,23]



(20) (22)

An alternative synthesis was reported by Bradsher, Litzinger and Zinn[23] using the reaction of 2-alkylamino and 2-arylamino-pyridines with chloraldoxime. Quaternisation to the intermediate oxime (23) was effected in sulpholane solution at 0° for one week. The oxime was cyclised in boiling hydrobromic acid to give the substituted imidazo[1,2-a]pyridinium bromide (22, X = Br).



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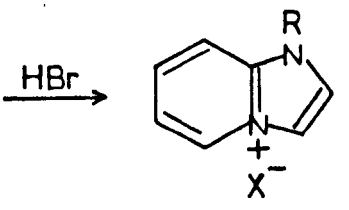
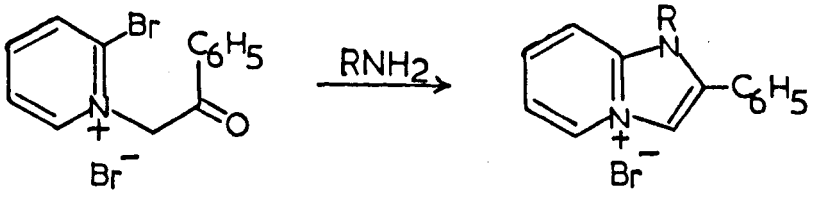


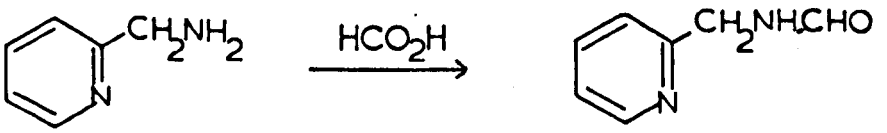
(22)

More recently Bradsher et al.[24] have prepared N-substituted-2-phenylimidazo[1,2-a]pyridinium salts (25) by heating 2-bromo-1-phenacylpyridinium bromide (24) with arylamines, acethydrazide or butylamines in acetonitrile solution. Higher yields of product were obtained when a primary amine was employed.



(24) (25)

Imidazo[1,5-a]pyridine (27) was first reported by Bower and Ramage[25] in 1957. 2-Picolylamine was boiled in 98% formic acid to give 2-formamidomethylpyridine (26). Cyclisation with phosphoryl chloride in boiling benzene yielded imidazo[1,5-a]-pyridine (27).



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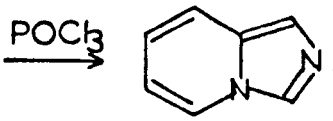
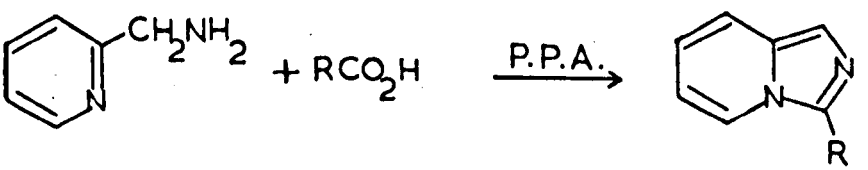


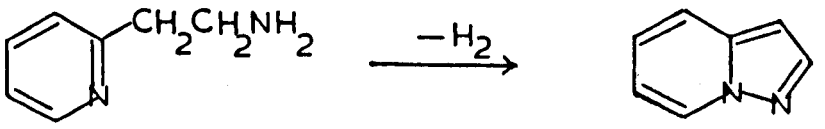
(27)

More recently Winterfeld and Franzke[26] have reported a one stage synthesis of 3-substituted imidazo[1,5-a]pyridines (28) by cyclising carboxylic acids with 2-picolylamine in polyphosphoric acid.



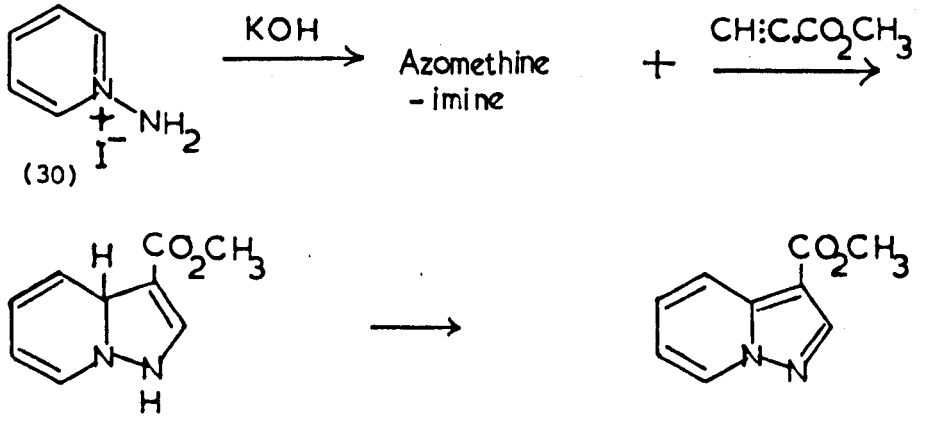
(28)

A synthesis of pyrazolo[1,5-a]pyridine (29) was first reported by Bower and Ramage[27] in 1957. Dehydrogenation of 2-(2-pyridyl)ethylamine with potassium ferricyanide gave the aromatic system (29) in reasonable yield.



(29)

An alternative preparation was reported in 1962 by Huisgen, Grashey and Krischke.[28] N-Aminopyridinium iodide (30) in dimethyl formamide was treated with powdered potassium hydroxide or potassium carbonate to give a deep blue solution of an azomethine-imine. This compound contains a CN double bond in the aromatic ring which can take part in a 1,3 dipolar addition with extremely active multiple bonded compounds. Treatment of the pyridinimine with excess methyl propiolate gave 1-carbomethoxy-pyrazolo[1,5-a]pyridine (32) in 34% yield via the intermediate (31).



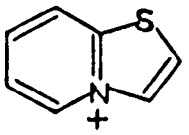
(30)

(31)

(32)

The analogous addition of methyl acetylenedicarboxylate resulted in a 22% yield of the dicarbomethoxy derivative.

If we now consider the three isomeric thiazolopyridinium salts; thiazolo[3,2-a]pyridinium (33), thiazolo[3,4-a]pyridinium (34), and isothiazolo[2,3-a]pyridinium (35), only the latter salt has yet to be synthesised.



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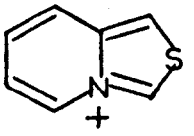

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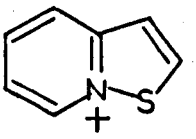
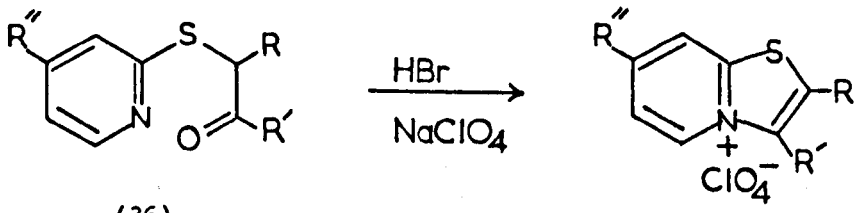


(35)

The synthesis of thiazolo[3,2-a]pyridinium salts was first reported simultaneously by Bradsher and Lohr,[30,31] in the U.S.A.; and by Babichev and Bubnovskaya[29] in Russia. The Russian workers heated 2-mercapto-pyridine or 2-mercapto picoline with α-halo carbonyl compounds in alcohol or acetone to give α-(2-pyridylthio)-carbonyl derivatives (36). These compounds underwent cyclodehydration in boiling hydrobromic acid to yield the products, isolated as their perchlorate salts (37).

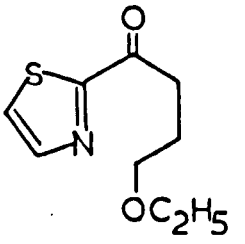


(36) (37)

Bradsher and Lohr[30,31] made the α-(2-pyridylthio) carbonyl derivatives (36) by reacting the sodium salt of 2-mercapto-pyridine with a suitable α-haloketone in methanol solution. The sulphide (36) was in this case cyclised in concentrated sulphuric acid to the thiazolo[3,2-a]pyridinium salt (37) isolated as the perchlorate. In the preparation of the parent bicyclic system (37, R=R'=R"=H) the α-haloketone used was chloroacetaldehyde dimethyl acetal. Treatment of this halide with 2-mercaptopyridine gave the acetal of 2-pyridylthioacetaldehyde in 32% yield. Hydrolysis to the aldehyde (36, R=R'=R"=H) and cyclisation gave an 85% yield of the isolated thiazolo[3,2-a]pyridinium perchlorate (37, R=R'=R"=H) based on the intermediate acetal.

As a further extension of the Glover and Jones[9] synthesis for the preparation of quinolizinium salts; Jones and Jones[32] have prepared the parent thiazolo[3,2-a]pyridinium salt. 2-Cyanothiazole reacted with 3-ethoxypropylmagnesium bromide to give the 2-thiazolyl ketone (38). In boiling hydrobromic acid the ether group was cleaved

and on evaporation a high yield of 8-oxo-5,6,7,8-tetrahydro-thiazolo[3,2-a]pyridinium bromide (39) was obtained. In the quinolizinium series[9] evaporation of the hydrobromic acid solution gave the pyridinium hydrobromide and subsequent basification to the free amine was necessary before cyclisation would occur. Presumably the weaker basicity of the thiazole leads to dissociation of the hydrobromide during evaporation, with simultaneous cyclisation. The cyclic ketone (39) gave an almost quantitative yield of the thiazolo[3,2-a]pyridinium bromide (40, R'=R"=H) on treatment with boiling acetic anhydride.



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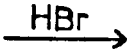

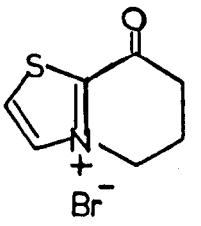

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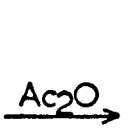
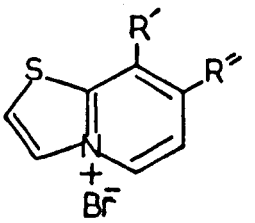
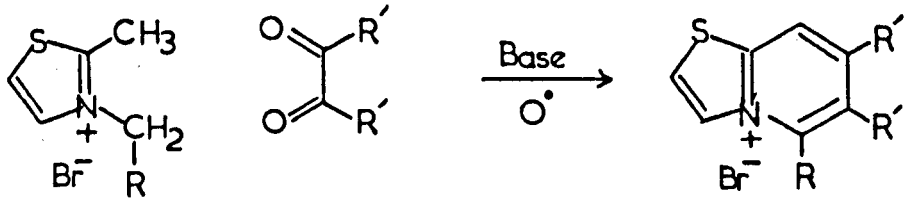




(40)

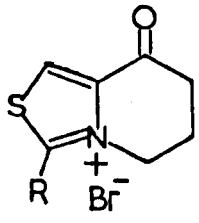
Several 7 and 8 substituted thiazolo[3,2-a]pyridinium salts (40) have been prepared using the same route.

A convenient synthesis of thiazolo[3,2-a]pyridinium salts was reported by Westphal and Joos in 1969,[33] and was an extension of their earlier reported work on quinolizinium salts.[14] Condensation of N-substituted-2-methylthiazolium salts (41) and 1,2 diketones in a solution of dibutylamine and acetone leads to high yields of substituted thiazolo[3,2-a]pyridinium salts (42).



(41) (42)

Attempts by Jones and Jones[34] to synthesise thiazolo[3,4-a]pyridinium (34) and isothiazolo[2,3-a]pyridinium (35) salts by dehydration with boiling acetic anhydride of the cyclic ketones (43 and 44) respectively failed.



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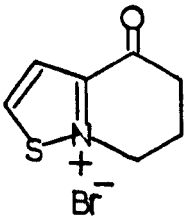
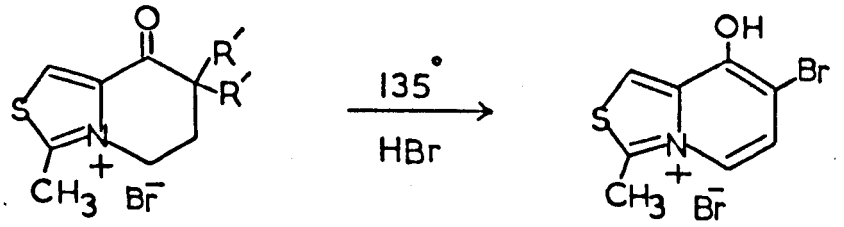


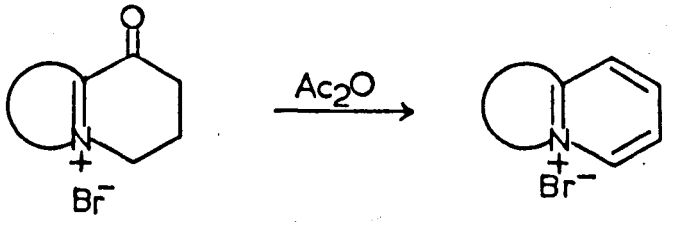
(44)

The same authors however have prepared a substituted thiazolo[3,4-a]pyridinium salt by an alternative route. The methyl ketone (45, R'=H) was brominated to give the dibromoketone (45, R'=Br). Dehydrobromination in a stream of nitrogen at 135° led to the formation of 7-bromo-8-hydroxythiazolo[3,4-a]pyridinium bromide (46) in good yield.



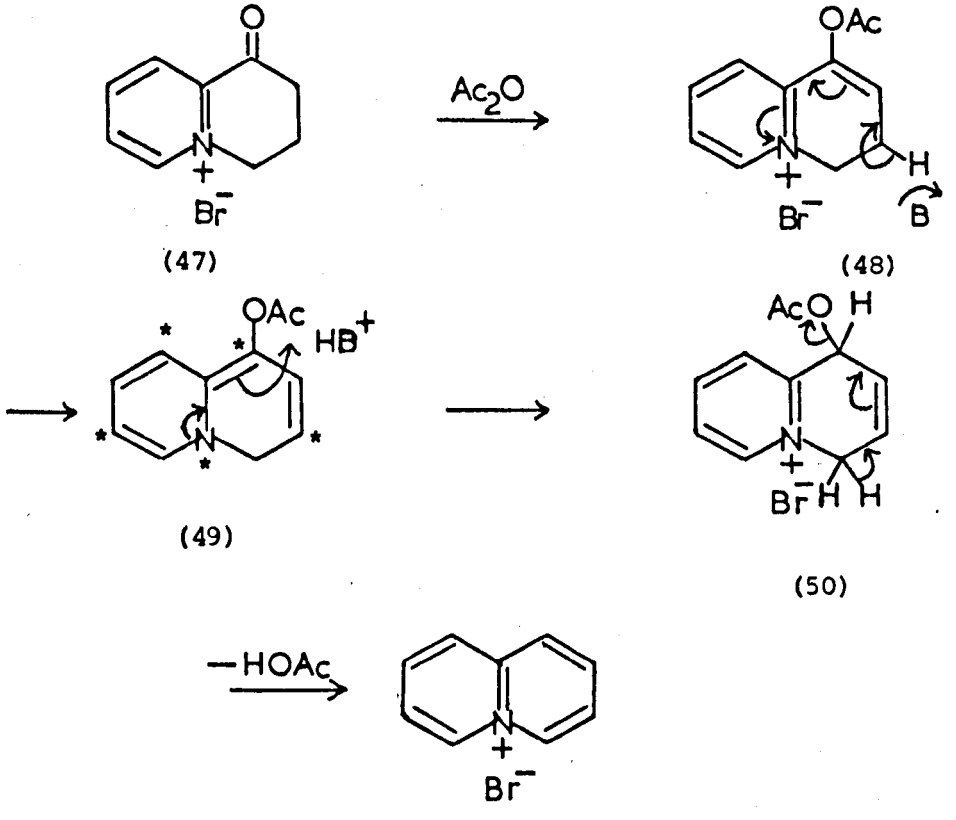
(45) (46)

The successful synthesis of a substituted thiazolo[3,4-a]-pyridinium salt (46) has led to a consideration of the mechanism of aromatisation of cyclic ketones of general type (A) to the corresponding aromatic compound (B).



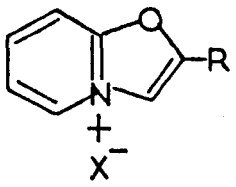
(A) (B)

The mechanism was discussed with regard to the quinolizinium series. Jones and Jones[34] postulate initial enolisation of the cyclic ketone (47), followed by acetylation to give the enol acetate (48). Double bond isomerisation was next suggested to give a neutral quinolizine (49). Protonation of the neutral species (49) could take place at any of the starred positions; of these the two most likely are positions 1 and 3. Protonation at 3 would regenerate the intermediate (49). Protonation at 1 would yield the salt (50) which can lose acetic acid via a 1,4 elimination to give the quinolizinium salt (51).



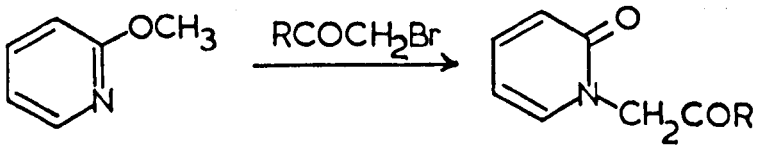
(47) (48) (49) (50) (51)

A further series of analogues isoelectronic to the quinolizinium system result when the sulphur atom in systems (33 - 35) is replaced by an oxygen atom; of these only the oxazolo[3,2-a]pyridinium salts (52, X = ClO_4) were known.

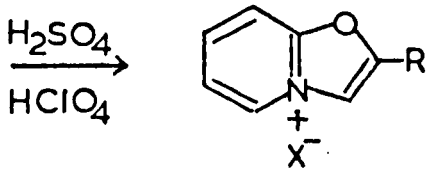


(52)

Bradsher and Zinn[35,36] have reported a synthesis of several 2-substituted oxazolo[3,2-a]pyridinium salts (52, X = ClO_4). 2-Methoxypyridine reacts with α-haloketones to form N-substituted pyridones (53) which readily cyclised in concentrated sulphuric acid at room temperature to give the oxazolo[3,2-a]pyridinium salts, isolated as the perchlorates, in yields ranging between 19 - 90%.

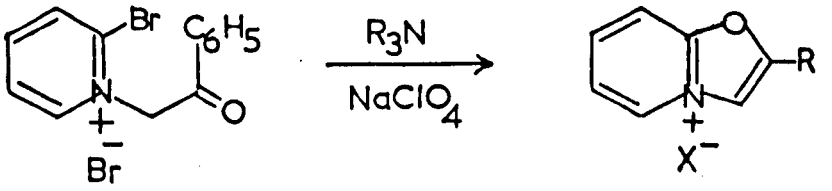


(53)



(52)

A more recent paper by Bradsher et al.[24] has reported a similar synthesis of 2-phenyloxazolo[3,2-a]pyridinium perchlorate (52, X = ClO_4 , R = Ph) by heating the intermediate 2-bromo-1-phenacylpyridinium bromide (54) in dry acetonitrile with bases. Yields in excess of 60% were obtained when tertiary amines were employed.



(54) (52)

However as mentioned earlier, when a primary base such as n-butylamine or an arylamine is used substituted imidazo[1,2-a]pyridinium salts (25) are preferentially formed.

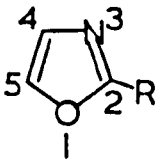
PART I

DISCUSSION

INTRODUCTION

The previous review has described syntheses by Bradsher and co-workers[24,35,36] for the preparation of 2-substituted oxazolo[3,2-a]pyridinium salts (52). These routes however, failed to yield the parent aromatic system (52, R = H). The synthesis of the parent thiazolo[3,2-a]pyridinium system (33) using a modification of the Glover and Jones quinolizinium route[9] has led to the possibility of synthesising the parent oxazolopyridinium system (52, R = H). The unknown 2-cyano-oxazole (55) was therefore required as starting material from which the parent bicyclic system would follow. Once the system was prepared its reactions and spectral properties could be studied in detail and comparisons made with the quinolizinium system (1).

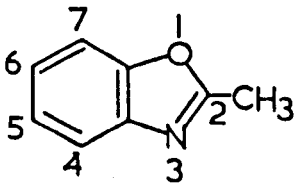
Schemes (a - f) in this discussion are concerned with attempts that have been made to synthesise 2-cyano-oxazole (55). The oxazole ring when unsubstituted in the 4 and 5 positions is cleaved readily by oxidative and hydrolytic reagents.[37] It was therefore necessary to attempt synthetic routes that avoided such reactions.



(55) R = CN

(56) R = CH_3

(61) R = -CH = NOH



(57)

A suitable starting material chosen for research was 2-methyloxazole (56) and preparation via a lengthy literature route gave an overall yield of 18%.[38]

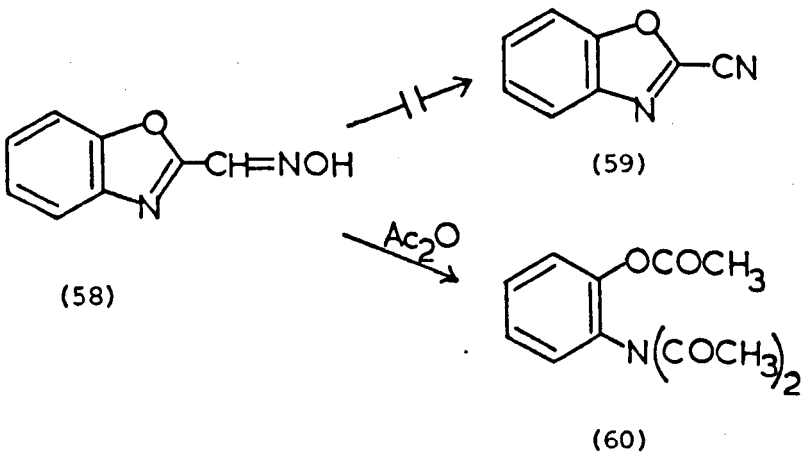
2-Methylbenzoxazole (57) was obtained more conveniently using a one stage synthesis in 75% yield.[39]

Reaction schemes (a), (b) and (c) were initially attempted using 2-methylbenzoxazole (57) as a model.

Scheme (a)

The first route envisaged for the preparation of the 2-cyano-oxazoles (55 and 59) involved the initial preparation of the carboxaldehyde oximes (61 and 58) followed by dehydration to the corresponding nitriles.

Forman[40] has successfully oximinated several alkyl-substituted hetero-aromatic compounds in liquid ammonia at -33° with sodamide and an alkyl nitrite. 2-Hydroxyiminomethylbenzoxazole (58) was obtained in 55% yield and subjected to known dehydrating conditions in an attempt to prepare 2-cyanobenzoxazole (59).



(58) (59) (60)

A portion of the oxime (58) was treated with boiling acetic anhydride for 1 hr. Work up gave a brown solid which showed strong carbonyl bands at 1767, 1726 and 1702 cm^{-1} in the infrared. The melting point and micro-analysis data were in agreement with the formulation of N,N,O-tri-acetyl-2-aminophenol (60).[41]

Treatment of the oxime (58) at lower temperatures with acetic anhydride led to a decreased yield of the tri-acetyl derivative (60) with starting material predominating.

Treatment of the oxime (58) with redistilled thionyl chloride gave either unchanged starting material or polymeric material depending on whether the reaction was performed in boiling ether or dimethoxyethane.

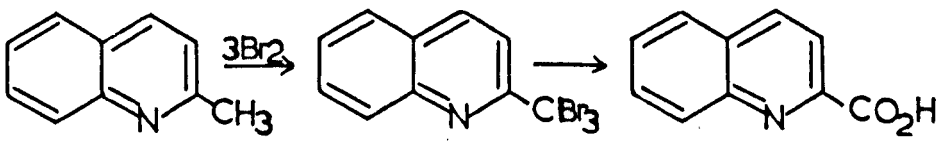
Although the model experiments using 2-hydroxyimino-methylbenzoxazole (58) had been discouraging, 2-methyloxazole (56) was treated with sodamide and pentyl nitrite in liquid ammonia at -33^{o}. After work up however, only a 1% yield of 2-hydroxy-

iminomethyloxazole (61) was obtained. Attempts to oximinate using sodium hydride as base in dimethoxyethane led only to an unidentifiable brown tar. This approach to 2-cyano-oxazole (55) was abandoned due to the small yield of the intermediate oxime (61).

Scheme (b)

The next attempted route involved the conversion of the methyl group of the oxazole to the carboxylic acid via the tribromomethyl derivative.

Hammick[42] has brominated quinaldine in a sodium acetate/glacial acetic acid medium at 100° to yield the ω-tribromoquinaldine (62). Hydrolysis gave quinaldic acid (63) in good yield.

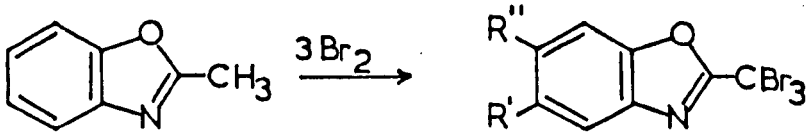


(62) (63)

A similar bromination was attempted on 2-methylbenzoxazole (57). Examination of the solid product by thin layer chromatography (t.l.c.), using toluene as eluent, indicated the presence of three

components. The mixture was separated using Preparative Layer Chromatography (P.L.C.). The fastest running material (Band I) was shown to be a tetrabromo derivative (41% of separated material) as was the middle band (II, 9%). The slowest moving band (III, 50%) was the desired tribromo derivative (64).

The n.m.r. spectra in deuterochloroform of the tetra-bromo-isomers both contain an aromatic ring proton absorption showing only meta-coupling indicating they are the 5-bromobenzoxazole (65) and the 6-bromobenzoxazole (66). Newbury and Phillips[43] have shown that nitration of benzoxazole occurs in the 6- and the 5-positions in a ratio of 4:1. The major isomer (Band I) was therefore assumed to be the 6-bromobenzoxazole derivative (66), and the minor isomer (Band II) the 5-bromobenzoxazole (65). The n.m.r. spectrum of the tribromo derivative (64) shows the expected four proton multiplet in the aromatic region.



(57)

(64) R' = R'' = H

(65) R' = Br, R'' = H

(66) R' = H, R'' = Br

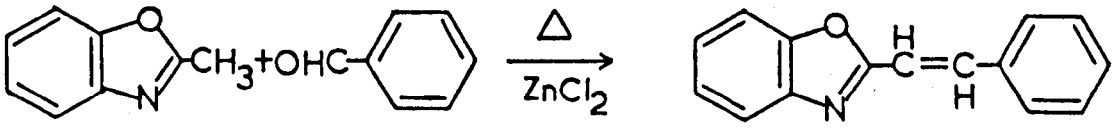
It was thought that the possibility of further substitution in the ring of 2-methyloxazole (56) would not constitute a problem due to its inability to undergo normal substitution reactions.[44] Bromination of 2-methyloxazole (56) and work up as before gave a negligible yield of a yellow solid that quickly decomposed to a brown intractable tar. The n.m.r. spectrum in trifluoro-acetic acid indicated loss of aromaticity with only a methyl singlet at δ2.3 p.p.m. visible. The infrared spectrum showed the loss of absorptions at 3135, 1590 and 1530 cm^{-1} (aromatic) and the appearance of a weak carbonyl band at 1730 cm^{-1}. The oxazole ring appears to be unstable under these conditions and attempts to brominate the methyloxazole (56) using carbon tetrachloride as solvent also failed to give an identifiable product. Cass[47a] has reported ring opening of 2-aryloxazoles on heating with bromine water.

Scheme (c)

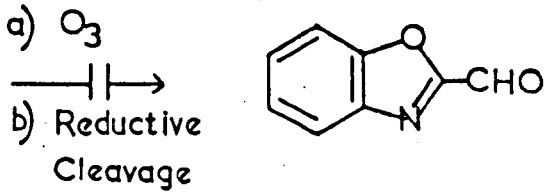
Attempts were next made to prepare the 2-formyloxazoles by ozonolysis of the corresponding 2-styryloxazoles. Again 2-methylbenzoxazole (57) was used as a model for the attempted synthesis.

2-Styrylbenzoxazole (67) was prepared by condensation of 2-methylbenzoxazole (57) with benzaldehyde in the presence of zinc

chloride as catalyst at 177° for 10 hr. The unchanged benzaldehyde was removed to leave a brown residue which on purification gave the product in 51% yield. The yield compares favourably with that obtained in a sealed tube reaction by Brown and Kon.[45] The n.m.r. spectrum of the product contains two aromatic doublets centred at δ7.15 and 7.95 p.p.m. with coupling constants of 17 Hz consistent with trans olefinic protons.



(57) (67)



(68)

Ozonolysis was expected to form a stable ozonide across the styryl double bond, which on reductive cleavage would afford a mixture of 2-formylbenzoxazole (68) and benzaldehyde.

An equivalent quantity of ozonised oxygen was bubbled

through a solution of 2-styrylbenzoxazole (67) at -20°. A sample of the solution on evaporation gave a residue that was shown to be starting material by t.l.c.

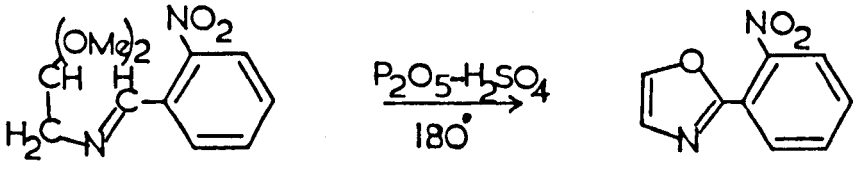
Another equivalent of ozonised oxygen was bubbled through the same solution at 0°. The original yellow colour was discharged and the solvent removed under reduced pressure. Reductive work up as described by Stilbe and Foster[46] gave the product as a yellow oily solid. Examination by t.l.c. eluting with benzene indicated the presence of a complex mixture. The mixture was chromatographed on a column of alumina (activity IV) and eluted with benzene-ether mixtures. The only products separated in identifiable quantities were benzoic acid and benzaldehyde. No 2-formylbenzoxazole (68) was isolated and this approach was abandoned.

Scheme (d)

Schemes (a), (b) and (c) have apparently failed due to the instability of the oxazole ring towards the reaction conditions employed. In all cases the methyl group at position 2 has been difficult to convert to a suitable carboxylic acid derivative which would easily convert to the corresponding nitrile.

Attempts have been made in schemes (d) and (e) at a direct synthesis of an oxazole-2-carboxylic acid derivative by cyclisation of a suitably substituted amino-acetal.

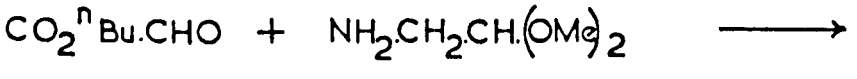
Cass and co-workers[47a,47b] have synthesised a small number of 2-aryloxazoles in 40-50% yield by cyclisation of their corresponding amino-acetals. For example, 2-(2-nitrophenyl)-oxazole (70) was obtained in 55% yield by cyclisation of 2-nitrobenzalamino-acetal (69) in phosphorus pentoxide/sulphuric acid mixture at 180°.



(69) (70)

Several attempts were made to extend this route to the synthesis of oxazole-2-carboxylates.

The acetal (71) was prepared by condensation of n-butyl-glyoxylate[49] and amino-acetaldehyde dimethylacetal in boiling benzene.



(71) (72)

The product (71) was obtained as a brown viscous oil which could not be induced to crystallise. A sample on attempted distillation at 5.3×10^{-5} mm. pressure showed considerable decomposition on heating in excess of 150°. The infrared spectrum of the crude product showed peaks at 1730 and 1650 cm^{-1} consistent with the compound containing both an α,β-unsaturated ester group and a C=N bond respectively. The crude amino-acetal (71) was therefore used in the following attempted cyclisations to the oxazole ester (72).

Cyclisation of (71) in a phosphorus pentoxide/sulphuric acid mixture at $75-80^{\circ}$ led on work up to a black intractable tar which contained no aromatic protons in its n.m.r. spectrum.

The severity of the cyclising conditions was decreased by repeating the cyclisation in the same medium at 0°. On work up a small quantity of starting material was obtained.

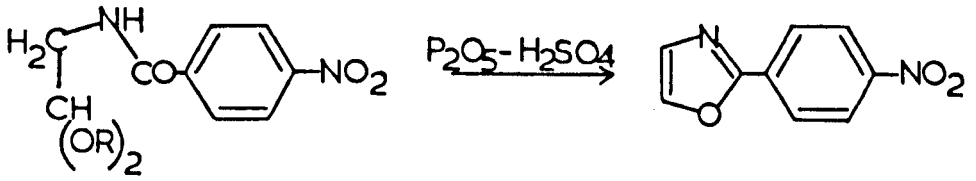
Treatment of the amino-acetal (71) with phosphoryl chloride in boiling benzene led to the recovery of unchanged starting material.

These results appear to confirm the report[48] that this reaction scheme is limited to the preparation of 2-aryloxazoles.

Scheme (e)

As a further extension of their earlier work Cass and

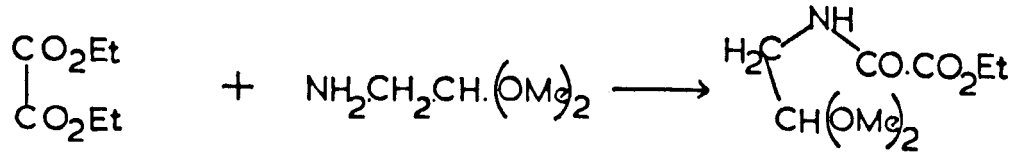
Rosenbaum[47b] have cyclised 4-nitrobenzamido-acetal (73) to 2-(4-nitrophenyl)oxazole (74) in 45% yield.



(73) (74)

An ester group has again replaced the aryl substituent and attempts at cyclisation have been made.

Palamidessi and Pannizzi[50] have reported the synthesis of ethoxalylamino-acetaldehyde dimethylacetal (75) from diethyloxalate and amino-acetaldehyde dimethylacetal in ethanol solution.



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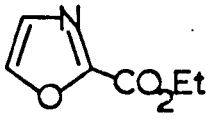

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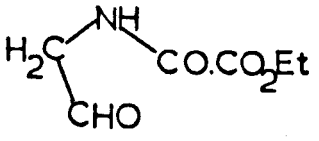


(77)

The acetal (75) was formed in lower yield on heating ethoxalyl chloride and amino-acetaldehyde dimethylacetal in boiling benzene.

The following attempts were made to cyclise the acetal (75) to the 2-carbethoxy-oxazole (76).

Treatment of (75) with a phosphorus pentoxide/concentrated sulphuric acid mixture at 160° (or 100°) led on work up to no isolatable product.

A solution of the acetal (75) and phosphoryl chloride in benzene was boiled for 2 hr. Work up gave a small quantity of a black intractable tar which could not be characterised.

Attempts were next made at hydrolysis of the acetal (75) to its corresponding aldehyde (77) which it was envisaged may undergo cyclisation more readily.

Treatment of the acetal (75) with dilute acid at room temperature gave unchanged starting material. If heat was applied to the reaction mixture difficulty was encountered in separating any product using extraction techniques. Removal of the aqueous solution under reduced pressure followed by extraction of the residue led only to polymeric material.

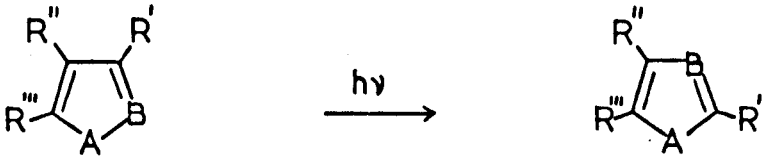
Presumably if the aldehyde (77) was formed it would be fairly soluble in aqueous solution and may polymerise on evaporation of the solvent. Hence this route to simple oxazoles was discontinued.

Scheme (f)

Studies on the synthesis of simple oxazoles using photochemical techniques

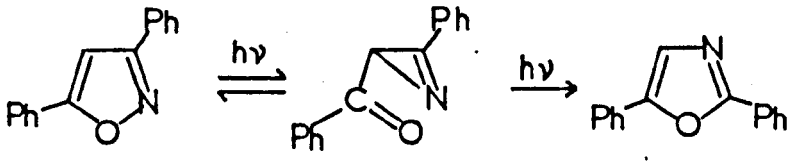
Review

The photochemistry of many different five-membered hetero-atomic aromatic compounds has been widely studied in recent years. Compounds of type (X), where A and B are hetero-atoms, on irradiation, isomerise to compound (Y).



(X) (Y)

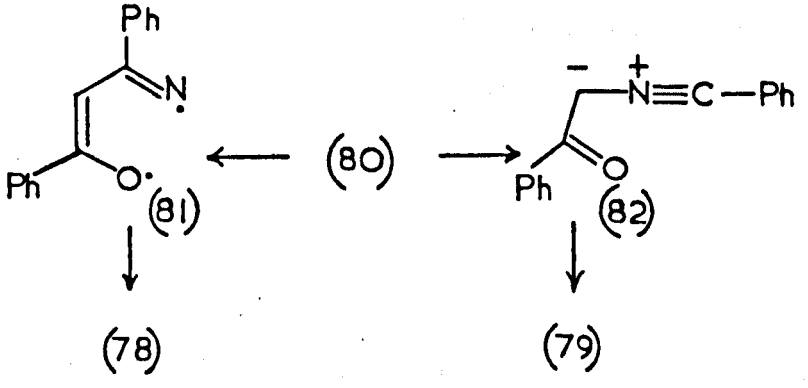
Of particular interest has been the work reported simultaneously by Singh and Ullman[51,52] and by Kurtz and Schechter.[53] The former authors irradiated an ethereal solution of 3,5 diphenyl-isoxazole (78) with 254 nm. light to give a 50% yield of 2,5 diphenyloxazole (79). The same authors have investigated the mechanism of isomerisation and have isolated an intermediate azirine (80). The structure of (80) was confirmed by spectral analysis and chemical conversions.



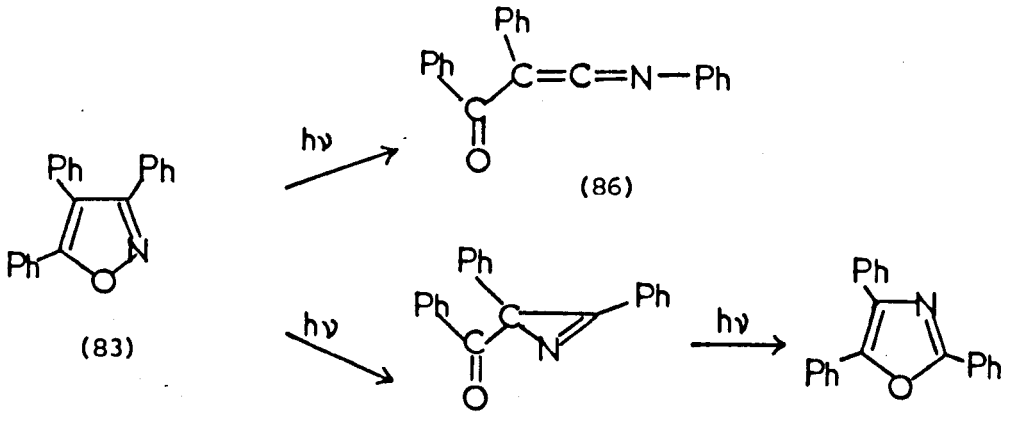
(78) (80) (79)

Further studies showed that the azirine (80) was converted back to the isoxazole (78) with light of 334 nm. wavelength, while irradiation of (80) with light of 313 nm. wavelength gave a good conversion to the oxazole (79).

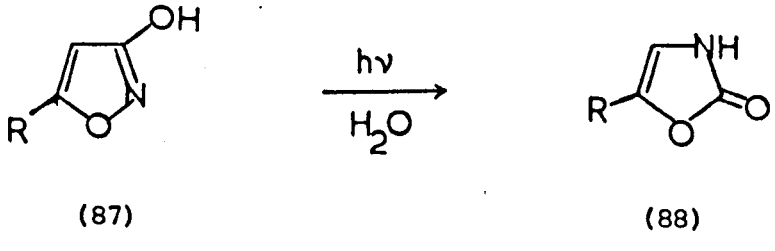
The wavelength dependence of the azirine has been interpreted in terms of specific and localised $n \rightarrow \pi^*$ excitation of its carbonyl or imine groups. The intermediate nitrene (81) was formulated as a triplet in the production of (78) whereas the ketenimine (82) was a singlet intermediate in the formation of (79).



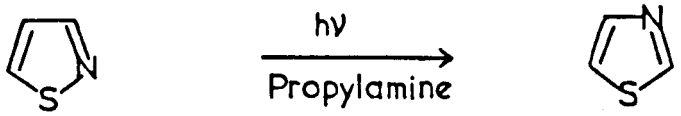
Kurtz and Schechter[53] observed a similar isomerisation on irradiation of triphenylisoxazole (83). In addition to the formation of the azirine (84) and oxazole (85), a ketenimine (86) was also produced.



The ring-contraction ring-expansion process in these reactions can also be applied to the photorearrangements of other isoxazoles. For example Göth et al[54] have isomerised a hydroxy-isoxazole (87) to a 2(3) oxazolone (88).



Finally more recent work by Lablanche-Combier and co-workers[55] has shown that isothiazole (89) can be photo-isomerised to thiazole (90) in a yield of 7% together with numerous other unknown products.

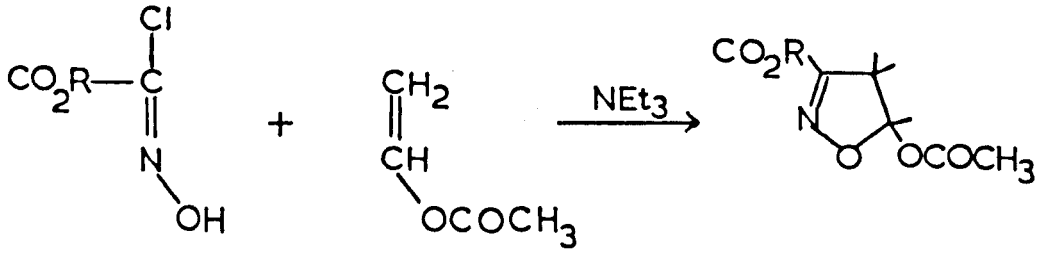


(89) (90)

Scheme (f) Discussion

The review to this section suggested the possibility of photolytically isomerising a simple 3-substituted isoxazole to a 2-substituted oxazole. The most relevant isoxazole derivatives that could be used for photo-isomerisation were the 3-substituted nitrile or carboxylic ester. Fortunately a method for the synthesis of 3-carbethoxy and 3-carbomethoxyisoxazole (95) and (96) was recently reported by Micetich.[56]

The isoxazole esters were obtained in high yield via a two stage synthesis. The ethyl or methyl ester of chloraldoxime (91) or (92) underwent a cyclo-addition reaction with excess vinyl acetate in the presence of base to form the intermediate isoxazolines (93) and (94). Heating the cyclic intermediates at 180° led to loss of acetic acid and formation of the isoxazole esters (95) and (96).

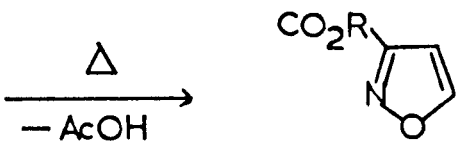


(91) R = Et

(92) R = Me

(93) R = Et

(94) R = Me

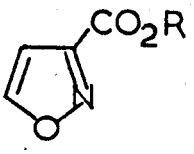


(95) R = Et

(96) R = Me

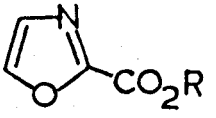
Initial photolyses were carried out on a solution of 3-carbomethoxyisoxazole (96) in anhydrous ether. Irradiation was effected using a Hanovia medium pressure mercury lamp and the course of the photolyses monitored by both t.l.c. and n.m.r. After 0.5 hr. irradiation, t.l.c. revealed the presence of one photo-product, unchanged isoxazole ester (96) and polymeric material at the base line. The n.m.r. spectrum confirmed the presence of a product with broad singlets at δ7.3 and 7.8 p.p.m. indicative of oxazole ring protons. Samples were taken during further irradiations and the proportion of product was observed to rise slowly to a maximum after $1\frac{1}{2}$ hr. (see Table 1). The formation of polymer however, was increasing at a higher rate. After 5 hr. irradiation,

the yield of product had decreased to less than 1% with almost complete conversion to polymeric material. Molecular weight determinations show a molecular weight of 780 (± 2%) indicative of a hexamer.



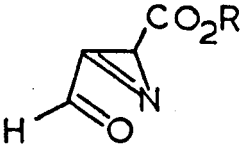
(95) R = Et

(96) R = Me



(97) R = Et

(98) R = Me



(99)

TABLE 1

Photolysis of 3-carbomethoxyisoxazole (96)

Time of Photolysis (hr)	Product % (98)	Starting Material %	Polymer %
0.5	2.5	57.5	40.0
0.75	3.0	53.0	44.0
1.0	5.0	42.0	53.0
1.5	5.4	37.6	57.0
2.0	4.0	20.0	76.0
5.0	< 1	4.0	~ 95

An irradiation time of 1.5 hr. appeared the optimum and evaporation of the solvent at this time, followed by purification using P.L.C., gave a 5.4% yield of the product. The n.m.r. spectrum in deuterochloroform indicated the product to be 2-carbomethoxyoxazole (98). The two broadened singlets centred at δ7.3 and 7.8 p.p.m. were assigned to the 4 and 5 oxazole protons respectively. The chemical shifts compare with δ7.0 and 7.55 p.p.m. observed for the same protons in 2-methyloxazole (56). Oxazoles are known to possess coupling constants of less than 1 Hz between protons 4 and 5 and they appear as broadened singlets in n.m.r. spectra.[57] The ester methyl group is shown as a singlet at δ4.0 p.p.m. The infrared spectrum showed a carbonyl band at 1739 cm^{-1} which was identical with the value observed for 5-benzyl-2-carbethoxyoxazole (45, Part II).

Irradiations of the ethyl ester (95) under the same conditions gave comparable yields of the 2-carbethoxyoxazole (97). The yields of product were too low to be of practical significance and this led to certain modifications. As mentioned previously the conversion of the intermediate azirine (80) to the oxazole (79) proceeded in good yield only when light of ≃ 313 nm. wavelength was employed. The azirine (99) has not been isolated but it may exist as a reaction intermediate. The absence of the more stabilizing phenyl groups would probably prevent its isolation.

The absorption maxima of the diphenylisoxazole (78) at 245 and 265 nm. differs from that observed for the isoxazole esters (95) and (96) at ~ 230 nm. The proposed intermediate azirine (99) would be expected to display absorption maxima at lower wavelength than 247 and 324 (sh) nm. observed for the more conjugated aromatic azirine (80).[52]

The Hanovia medium pressure mercury lamp transmits ultraviolet light mainly of 254 (2.2%), 265 (2.6%), 297 (3.3%), 303 (4.6%), 313 (9.2%) and 366 (16.4%) nm. wavelength. Removal of the abundant 366 nm. band, which was reported to increase polymer formation,[52] would leave the relevant wavelengths required for the isomerisation to the isoxazole esters (95) and (96).

Kasha[58] has reviewed several chemical solution filters, which are reported to be the best method of procuring high intensity ultraviolet light in a selected region when used in conjunction with a suitable source.

Potassium chromate has a good transmission maximum at 313 nm. Curve 1, Figure 1 shows the transmission spectrum of a 1 cm. path of an aqueous solution containing potassium chromate (0.2 g./l). The curve shows complete absorption of the light of 366 nm. wavelength and transmission maxima at 313 nm. (60%) and 230 nm. (15%).

Irradiation of an ethereal solution of the isoxazole ester

(95) using the filter solution led to a considerably slower photo-isomerisation owing to the reduced intensity of the transmitted light. After 25 hr. irradiation, evaporation followed by purification using P.L.C. afforded an 8% yield of oxazole ester (97) (spectroscopic measurement).

Irradiation for longer periods did not lead to increased yields but only to a higher proportion of polymer. The use of a pyrex instead of the original quartz sleeve resulted in unchanged isoxazole ester. Curve 2, Figure 1 shows that only light above 280 nm. wavelength was transmitted.

The absorption curve (3, Figure 1) of the isoxazole ester (95) suggests that excitation is possible in the 230 nm. wavelength region or in the carbonyl $n \rightarrow \pi^*$ region at 316 nm.

Consideration of curves 1 and 2 (Figure 1) indicates that only light of 218 - 245 nm. wavelength is causing the isomerisation. The extremely slow conversion to oxazole appears to be due to the low transmittance at these wavelengths.

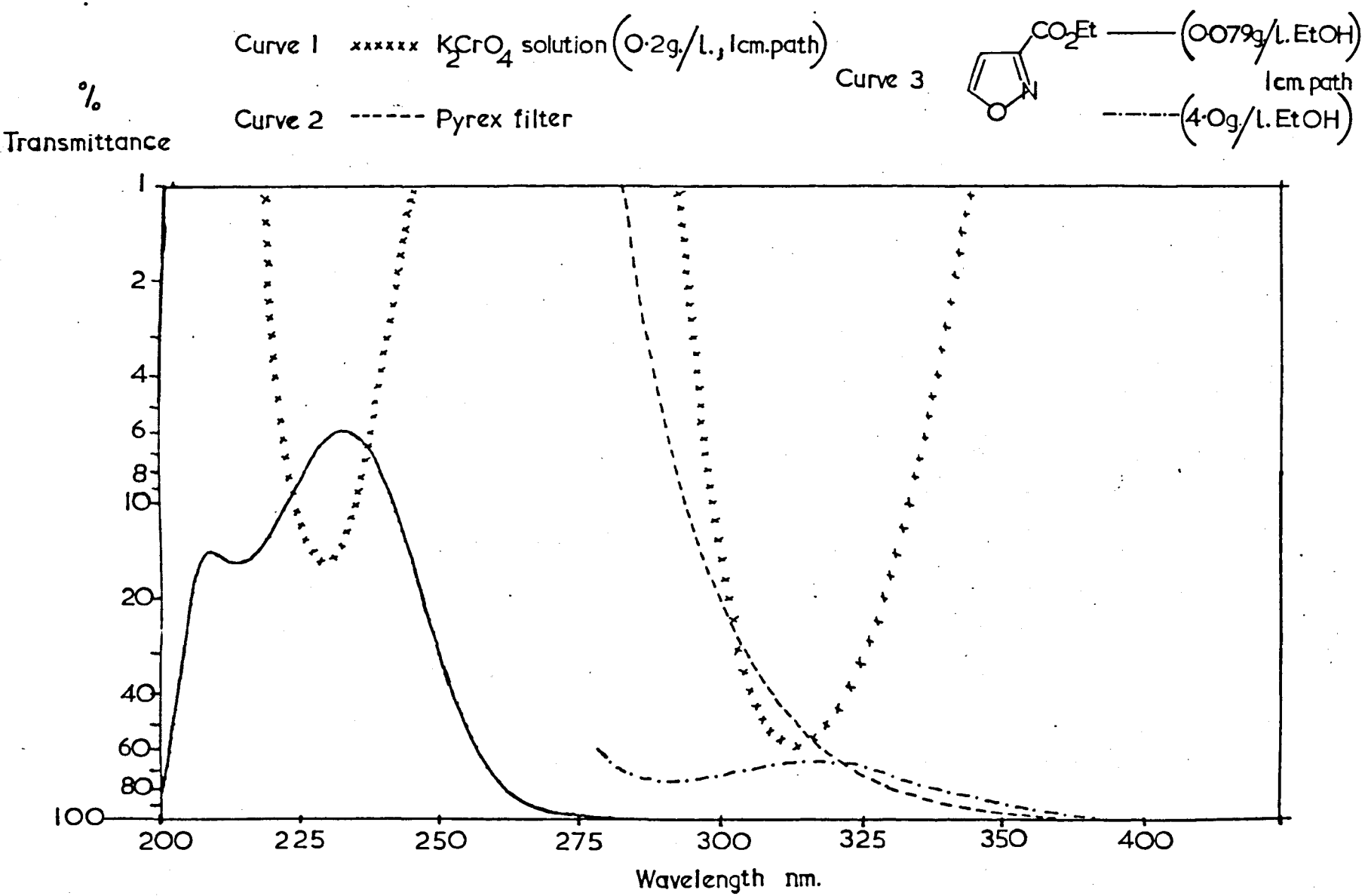

Curve 1 ×××××× K_2CrO_4 solution (0·2g./l., 1cm.path)
Curve 2 ------ Pyrex filter
Curve 3
CO_2Et —— (0·079g./l. EtOH)
1cm. path
-·-·-·- (4·0g./l. EtOH)
%
Transmittance
1
2
4
6
8
10
20
40
60
80
100
200
225
250
275
300
325
350
400
Wavelength nm.

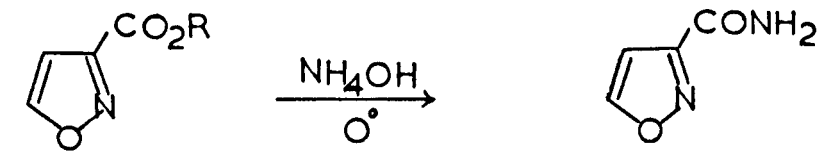
Figure 1

When acetone or acetophenone were used as triplet sensitizers in conjunction with the filter solution only a higher proportion of polymer was isolated and no oxazole ester (97).

Increasing the concentration of the isoxazole ester from 1-3 g. led to considerable polymer formation.

In all these photolyses the formation of polymer on the sleeve surrounding the light source decreased the possible rate of isomerisation. It has been suggested[59] that workable quantities of the oxazole esters could be obtained using a falling film photochemical reactor which prevents the interference of any polymer formed during irradiation.

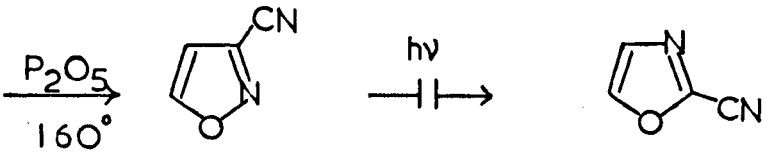
A final attempt was made at the photo-isomerisation of 3-cyano-isoxazole (101) to the 2-cyano-oxazole (55). 3-Cyano-isoxazole (101) was obtained from the 3-isoxazole carboxylic esters (95) and (96) via the carboxamide (100) by treatment with concentrated ammonia solution at 0^{o}. Dehydration of the carboxamide (100) with phosphorus pentoxide at 160^{o} gave an 86% overall yield of the nitrile (101).



(95) R = Et

(96) R = Me

(100)



(101)

(55)

Irradiation of an ethereal solution of 3-cyano-isoxazole (101) with or without the filter solution led to the rapid formation of a black polymeric material and no isolatable product.

EXPERIMENTAL

Preliminary Notes

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Infrared absorption spectra were measured on a Perkin Elmer 257 spectrophotometer. The spectra of solids were determined as Nujol mulls, indicated by (Nujol) or in solution (e.g. $CHCl_3$) or as a KBr disc (KBr). The spectra of liquids were determined as liquid films (Film).

Electronic absorption spectra were recorded on a Unicam SP 800 instrument.

Nuclear magnetic resonance (n.m.r.) spectra, unless stated otherwise were recorded on a Perkin Elmer R10 60 MHz. instrument and are quoted as 'delta' (δ) values in p.p.m. using a tetramethylsilane standard (δ0.00 p.p.m.). When spectra were determined in deuterium oxide the standard was recorded externally in a solution of carbon tetrachloride. In all other cases the standard was used internally. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet and br = broadened.

Micro-analyses were carried out on an F and M carbon/hydrogen/nitrogen analyser at the University of Keele, and by

Dr. F.B. Strauss of Oxford.

Mass spectra were determined on a Hitachi-Perkin Elmer RMU-6 instrument; exact mass determinations were performed on an A.E.I. MS 902 machine. The molecular weight was determined by Mr. C. Swinnerton of I.C.I. Limited, on a "Mechrolab", vapour pressure osmometer, model 502.

Column chromatography was carried out using either deactivated Woelm alumina or Davison Silica gel, Grade 923, 100-200 mesh.

Thin layer chromatography (t.l.c.) was carried out on 7.5 x 2.5 cm. microscope slides coated with Kieselgel PF_{254} (Merck). The components were visualised under ultraviolet light or developed in iodine vapour.

Preparative layer chromatography (P.L.C.) was carried out on 40 x 20 cm. glass plates coated with a 1.5 mm. layer of Kieselgel PF_{254}. The separated components, visualised as for t.l.c., were isolated by scraping off the silica and extracted with hot methanol. The filtered methanol solution was evaporated to leave a residue which contained silica. The residue was then dissolved in chloroform filtered and evaporated. When separated bands are reported, the least polar bands are described first.

Photolytic work was performed under an atmosphere of nitrogen using a Hanovia Photochemical reactor (medium pressure) mainly transmitting light of 254, 265, 297, 313 and 366 nm. wavelength.

2-Methyloxazole (56)

Prepared as described by Cornforth and Cornforth.[38]

2-Methylbenzoxazole (57)

Prepared from 2-aminophenol and acetic anhydride as described by Hewitt and King.[39]

2-Hydroxyiminomethylbenzoxazole (58)

Prepared from 2-methylbenzoxazole (57) as described by Forman.[40]

Attempted dehydration of 2-hydroxyiminomethylbenzoxazole (58)

The following reagents and reaction conditions were tried.

(a) Boiling acetic anhydride

A solution of the oxime (58) (3.2g.) in acetic anhydride (25 ml.) was heated under reflux for 1 hr. The acetic anhydride was removed under reduced pressure and the residue treated with ice/water and extracted with chloroform. The chloroform extracts were dried (Na_2SO_4), filtered and evaporated to leave a brown solid. Extraction of the solid with hot petroleum ether (b.p. 60-80°) and cooling of the extracts gave N,N,O-triacetyl-2-aminophenol (60) as pale yellow needles (3.5g., 75%) m.p. 76-78° (lit.,[41] m.p. 78-79°).

$\nu_{max.}$ (Nujol) 1767, 1726 and 1702 $cm.^{-1}$ (CO).

n.m.r. ($CDCl_3$) : δ 2.16 (3H, s), 2.20 (6H, s), 7.1-7.5 (4H, m) p.p.m.

(b) Acetic anhydride at room temperature

The oxime (58) (0.1g.) was added to a stirred solution of acetic anhydride (1 ml.) at room temperature. After stirring for 10 minutes the solvent was removed under reduced pressure at room temperature to leave a brown solid. Spectral evidence, particularly infrared, indicated a mixture of unchanged oxime (58) and triacetyl compound (60).

(c) Thionyl chloride in refluxing ether

A solution of the oxime (58) (0.1g.) in anhydrous ether (5 ml.) was treated dropwise with freshly distilled thionyl chloride (2 ml.). The mixture was heated under reflux for 1 hr. before the solvent was removed under reduced pressure to leave unchanged oxime.

(d) Thionyl chloride in refluxing dimethoxyethane

A solution of thionyl chloride (6 ml.) in anhydrous dimethoxyethane (10 ml.) was added slowly to a hot solution of the oxime (58) (2.0g.) in dimethoxyethane (10 ml.) at such a rate that reflux conditions were maintained. The mixture was heated under reflux for a further 2 hr. The solvent was removed under reduced pressure to leave a black intractable tar which could not be characterised.

2-Hydroxyiminomethyloxazole (61)

Prepared by a modification of Forman's method.[40] 2-Methyloxazole (56) (3g.) was added dropwise to a solution of sodium amide prepared from sodium (0.83g.) in refluxing liquid ammonia (50 ml.) at -33°. After stirring for 1 hr., pentyl nitrite (5.5g.) was added slowly. After further stirring for 1 hr., the addition of a solution of ammonium sulphate (9.5g.) in water (15 ml.) was made as rapidly as possible followed by ether (50 ml.). The temperature of the reaction mixture was allowed to rise to room temperature (overnight). The ether layer was separated and the aqueous/solids layer again extracted with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated. Trituration of the viscous brown residue with chloroform gave a small quantity of the oxime (61) (0.02g., 1%) as a pale yellow solid m.p. 143-144°.

Found: C, 42.30; H, 3.45; N, 24.30%

$C_4H_4N_2O_2$ requires: C, 42.85; H, 3.55; N, 25.00%

$\nu_{max.}$ (Nujol) 3145, 1625 and 928 $cm.^{-1}$

$\lambda_{max.}$ (95% EtOH) 257 nm. ($\log_{10}\varepsilon$, 4.16).

$\lambda_{max.}$ (95% EtOH/NaOH) 280 nm. ($\log_{10}\varepsilon$, 4.07).

Bromination of 2-methylbenzoxazole (57)

Bromine (9.6g.) was added dropwise to a stirred solution of 2-methylbenzoxazole (57) (2.66g.) and sodium acetate (20 g.) in

glacial acetic acid (50 ml.). The mixture was then heated at 100° for 1 hr. On cooling, water (100 ml.) was added and the white precipitate was filtered and dried (4.73g.). T.l.c., eluting with toluene, showed the presence of three components.

A sample of the mixture (0.15g.) was separated by P.L.C. eluting with toluene and the following bands obtained.

Band I (9.3 mg.) was isolated as a colourless solid, recrystallised from petroleum ether (b.p. 60-80°) as colourless needles, m.p. 103-105°. The spectra were consistent with those expected for 5-bromo-2-tribromomethylbenzoxazole (65).

Found: C, 21.0; H, 0.65; N, 3.0%

$C_8H_3Br_4NO$ requires: C, 21.4; H, 0.65; N, 3.1%

$\lambda_{max.}$ (95% EtOH) 253, 292 nm. ($\log_{10}\varepsilon$, 4.33, 4.18).

n.m.r. ($CDCl_3$) : δ 7.65-7.8 (2H, m), 8.1-8.22 (1H, m) p.p.m.

Band II (43.1 mg.) was isolated as a colourless solid, recrystallised from petroleum ether (b.p. 60-80°) as colourless needles, m.p. 99-101°. The spectra were consistent with those expected for the isomeric 6-bromo-2-tribromomethylbenzoxazole (66).

Found: C, 21.4; H, 0.70; N, 3.1%

$C_8H_3Br_4NO$ requires: C, 21.4; H, 0.65; N, 3.1%

$\lambda_{max.}$ (95% EtOH) 260, 290 nm. ($\log_{10}\varepsilon$, 4.29, 4.37).

n.m.r. ($CDCl_3$) : δ 7.7-7.85 (2H, m), 7.95 (1H, d, J = 2Hz) p.p.m.

Band III (52.8 mg.) was isolated as a colourless solid, recrystallised from petroleum ether (b.p. 60-80°) as colourless needles, m.p. 118.5-120°. Spectral data indicated it to be 2-tribromomethylbenzoxazole (64).

Found: C, 25.5; H, 1.15; N, 3.8%

$C_8H_4Br_3NO$ requires: C, 25.95; H, 0.80; N, 3.8%

$\lambda_{max.}$ (95% EtOH) 258, 278 nm. ($\log_{10}\varepsilon$, 4.28, 4.30).

n.m.r. ($CDCl_3$) : δ 7.45-8.1 (4H, m) p.p.m.

Attempted bromination of 2-methyloxazole (56)

Freshly distilled 2-methyloxazole (56) (1.49g.) was added to a saturated solution of sodium acetate (15g.) in glacial acetic acid (80 ml.). Bromine (8.5g.) was added dropwise to the solution which was stirred for a further 1 hr. at room temperature by which time the bromine colour had greatly diminished. Water (100 ml.) was added and the solution cautiously neutralised using 20% sodium hydroxide solution. The precipitated white solid was removed by filtration and dried (0.39g.). On standing in a dessicator the white solid quickly decomposed to a brown tar that could not be characterised.

$\nu_{max.}$ (Nujol) 1730 $cm.^{-1}$ (CO).

n.m.r. (T.F.A.) : δ 2.3 (s) p.p.m.

Bromination using carbon tetrachloride as solvent led to a dark brown intractable tar which again could not be characterised.

2-Styrylbenzoxazole (67)

Freshly crushed zinc chloride (1g.) was rapidly added to a mixture of 2-methylbenzoxazole (57) (16.5g.) and benzaldehyde (17g.) contained in a tube suspended in a constant temperature apparatus. The initially well shaken mixture was heated at 177° (boiling p-cymene) for 10 hr. The brown mixture was then warmed under reduced pressure to remove unchanged benzaldehyde. Water was added to the cooled residue and the organic material extracted with ether. The ether extracts were dried (Na_2SO_4) and evaporated. Extraction of the residue with boiling petroleum ether (b.p. 40-60°) gave the styryloxazole (67) on cooling (14.0g., 51%). Recrystallisation from petroleum ether (b.p. 40-60°) gave pale yellow prisms, m.p. 78-80° (lit.,[45] m.p. 81-82°).

$\lambda_{max.}$ (95% EtOH) 225, 322 nm. ($\log_{10}\varepsilon$, 4.04, 4.54).

n.m.r. ($CDCl_3$) : δ 7.15 (1H, d, J = 17 Hz), 7.28-7.95 (4H, m), 7.95 (1H, d, J = 17 Hz) p.p.m.

Attempted ozonolysis of 2-styrylbenzoxazole (67)

(a) At -20°

An equivalent of ozonised oxygen was bubbled through a solution of 2-styrylbenzoxazole (67) (2.21g.) in anhydrous ethyl acetate (30 ml.) at -20°. No apparent uptake of ozone was observed.

(b) At 0°

Ozonised oxygen was again bubbled through the same solution and this time a definite change of colour was observed after an equivalent of ozone had been added. The solvent was removed under reduced pressure at 0° and the orange residue treated with methanol (10 ml.), potassium iodide (1.5g.) and glacial acetic acid (5 ml.) under an atmosphere of nitrogen to prevent oxidation. The mixture was stirred for 1 hr. at room temperature when sufficient sodium thiosulphate solution was added to remove the dark colouration due to iodine. The methanol was removed under reduced pressure and the mixture extracted with ether. The ether extracts were dried (Na_2SO_4) and evaporated to leave a yellow oily solid (1.2g.) which on examination by t.l.c. eluting with benzene showed a complex mixture.

The mixture was dissolved in benzene and run onto a column of activated alumina (Woelm, grade IV). The column was eluted successively with benzene and benzene-ether mixtures and the following fractions were collected.

Fraction	Solvent	Weight in grams
1,2	Benzene	0.05
3-5	"	0.161
6-16	"	0.445
17-24	20% Ether-benzene	0.268
25	Ether	0.164

T.l.c. analysis showed single spots for fractions 3-5 and 25 only. T.l.c. and infrared spectra confirmed that the two collective fractions were benzaldehyde and benzoic acid respectively. The other residues were examined by n.m.r. and infrared and confused spectra resulted, none of which suggested the formation of 2-formylbenzoxazole (68).

n-Butyl-2,2-dimethylimino-acetate (71)

n-Butylglyoxylate (26g.)[49] and amino-acetaldehyde dimethylacetal (21g.) were heated under reflux in anhydrous benzene (125 ml.). Water was removed using a Dean and Stark water separator. When the theoretical quantity of water had been collected (3.6 ml.) the benzene was removed under reduced pressure to leave a brown oil (43g., Quantitative) which could not be induced to crystallise. The spectral evidence was consistent with the desired product (71).

$\nu_{max.}$ (Film) 1730 (CO), 1650 $cm.^{-1}$ (C = N).

n.m.r. (CCl_4) : δ 1.0 (3H, brt), 1.2-1.8 (4H, m), 3.4 (3H, s), 3.45 (3H, s), 3.1-3.6 (2H, m), 3.9-4.8 (4H, m) p.p.m.

Attempted distillation (200°, 5.3 x 10^{-5} mm.) of the product gave only a dark brown oil whose n.m.r. spectrum showed a certain amount of decomposition had occurred.

Attempted cyclisation of n-butyl-2,2-dimethoxyethylimino-acetate (71)

(a) The acetate (71) (2.0g.) was added dropwise to concentrated sulphuric acid (10 ml.) at 0°. The dark red acid solution was then cautiously added to a mixture of phosphorus pentoxide (4.0g.) in concentrated sulphuric acid (10 ml.) at 0°. The mixture was stirred for a further 0.5 hr. before adding slowly to ice/water (50 g.). The aqueous layer was extracted with both ether and chloroform. Both extracts were dried (Na_2SO_4) and evaporated to leave a negligible quantity of oil (0.03g.). N.m.r. analysis of the residue indicated unchanged starting material. Extraction of the neutralised solution gave no product.

(b) A similar reaction performed at 75-80° gave a black intractable tar.

(c) Treatment of the acetate (71) with phosphoryl chloride (3 ml.) in boiling benzene (30 ml.) for 2 hr. gave a dark brown oil

on evaporation. The oil was treated with ice/water (50g.) and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to leave a brown oil. The n.m.r. spectrum indicated unchanged starting material.

Ethoxalylamino-acetaldehyde dimethylacetal (75)

(a) Prepared from diethyloxalate as described by Palamidessi and Pannizzi[50] in 90% yield.

(b) Also prepared in 25% yield by heating ethoxalyl chloride and amino-acetaldehyde dimethylacetal in boiling benzene.

Attempted cyclisation of the acetal (75)

(a) The acetal (75) (0.5g.) was dissolved in anhydrous benzene (20 ml.) and treated with phosphoryl chloride (2 ml.) before heating at reflux for 2 hr. The solvent was removed under reduced pressure and the residue treated with ice-cold water and extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to leave a small quantity of black tar which could not be characterised.

(b) The acetal (75) (1g.) was treated with concentrated sulphuric acid (10 ml.) and heated briefly on a steam bath and stood overnight at room temperature. Treatment with ice and extraction with ether gave no product on evaporation.

(c) Similar treatment at 160° also gave no product.

Attempted hydrolysis of the acetal (75) to the aldehyde (77)

(a) A solution of the acetal (75) (0.5g.) in methylene chloride (25 ml.) was treated with 2N hydrochloric acid (3 ml.). The mixture was shaken vigorously for 12 hr. at room temperature. The chloroform layer was dried (Na_2SO_4) and evaporated to leave unchanged acetal.

(b) The acetal (75) (0.23g.) was added to 2N hydrochloric acid (10 ml.) and heated on a steam bath for 1 hr. The mixture was cooled and continuously extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to leave a negligible quantity of a dark intractable tar.

3-Carbethoxy- (95) and 3-carbomethoxyisoxazole (96)

Prepared as described by Micetich.[56]

Irradiation of 3-carbomethoxyisoxazole (96)

A solution of 3-carbomethoxyisoxazole (96) (1.0g.) in anhydrous ether (800 ml.) contained in a 1 l. Pyrex flask was flushed with nitrogen. The solution was exposed to radiation from a mercury lamp (Hanovia, medium pressure) and the photolysis monitored using both n.m.r. and t.l.c. After 0.75 hr. irradiation, an aliquot of the mixture (100 ml.) was removed, evaporated to dryness and extracted with anhydrous ether. The polymeric material was insoluble and was removed by filtration (0.04g.). The ether

filtrate was evaporated and gave a pale yellow oil (0.06g.). T.l.c., eluting with chloroform indicated the presence of starting material and one product. An n.m.r. spectrum of the same sample gave an indication of the product to starting material ratio from their integrations. Taking into account the polymer formation, after 0.75 hr. there was 3% product present in the mixture. The ether soluble sample was returned to the photochemical reactor, the volume of solvent replenished and further irradiations performed. Similar work up gave the conversions listed in Table I (p. 41) in the discussion.

After irradiation for the optimum time of 1.5 hr. the ether was removed under reduced pressure and the sticky residue extracted with anhydrous ether to leave the insoluble polymer. The filtrate was evaporated to leave a brown oil (0.6g.). The mixture was applied to two preparative layer plates and eluted with chloroform.

Band I (0.25g.) isolated as a pale yellow oil whose spectral properties indicated unchanged starting material, 3-carbomethoxy-isoxazole (96).

Band II (0.054g.) isolated as an almost colourless solid. Triturated with petroleum ether (b.p. 60-80^{o}) to give a solid which recrystallised from petroleum ether (b.p. 60-80^{o}) as colourless needles, m.p. 86-87^{o}. Spectral evidence indicated the

product to be 2-carbomethoxyoxazole (98).

Found: C, 47.3; H, 4.4; N, 11.2%

$C_5H_5NO_3$ requires: C, 47.25; H, 4.95; N, 11.0%

$\nu_{max.}$ ($CHCl_3$) 1739 $cm.^{-1}$ (CO).

$\lambda_{max.}$ (95% EtOH) 244 nm. ($\log_{10}\varepsilon$, 3.93).

Mass spectrum $^m/_e$ 127 (M^+), 112, 97, 96, 83, 82, 59, 54.

n.m.r. ($CDCl_3$) : δ 4.0 (3H, s), 7.3 (1H, brs), 7.8 (1H, brs) p.p.m.

Band III (0.21g.) isolated as a brown solid and indicated from molecular weight determinations to be a hexamer. (M.wt. = 780 ± 2%).

Irradiation of 3-carbethoxyisoxazole (95)

3-Carbethoxyisoxazole (95) was similarly irradiated and gave comparable yields of 2-carbethoxyoxazole (97). The product was isolated using P.L.C. as a brown oil. Trituration with petroleum ether (b.p. 60-80°) gave the product as almost colourless needles, m.p. 84-85°. The n.m.r. and mass spectral data confirmed the product was 2-carbethoxyoxazole (97).

$\nu_{max.}$ ($CHCl_3$) 1736 $cm.^{-1}$ (CO).

$\lambda_{max.}$ (95% EtOH) 247 nm. ($\log_{10}\varepsilon$, 4.02).

Mass spectrum $^m/_e$ 141 (M^+), 112, 97, 86, 82, 69, 68, 59, 54.

n.m.r. ($CDCl_3$) : δ 1.4 (3H, t, J = 7Hz), 4.42 (2H, q), 7.3 (1H, brs), 7.76 (1H, brs) p.p.m.

3-Carboxamido-isoxazole (100)

3-Carbethoxyisoxazole (95) (26g.) was dissolved in a minimum of methanol and added dropwise to a stirred solution of concentrated ammonia (s.g. 0.88) at 0°. The mixture was stood for 3 days at 0°. The precipitated amide was filtered, washed with water, dried (20.6g., quantitative), and recrystallised from ethyl acetate as colourless plates, m.p. 146° (lit.,[60] m.p. 143°).

Similarly prepared in quantitative yield from 3-carbomethoxyisoxazole (96).

3-Cyano-isoxazole (101)

A finely ground mixture of the amide (100) (15.5g.) and phosphorus pentachloride (35g.) was heated at 160° under nitrogen for 0.5 hr. On slight reduction of the pressure, the nitrile distilled over and was collected in an ice-cooled receiver. Redistillation gave pure 3-cyano-isoxazole (101) (11.1g., 85%) as a colourless liquid, b.p. 160°/500 mm. (lit.,[61] b.p. 70°/25 mm.). $\nu_{max.}$ (Film) 2260 cm.$^{-1}$ (CN).

Irradiation of 3-cyano-isoxazole

Similar irradiation of an ethereal solution of 3-cyano-isoxazole (101) (1.0g.) gave considerable darkening in colour after

1 hr.

Evaporation of the ether left a dark brown intractable tar (0.95g.). The n.m.r. spectrum indicated polymeric material and a small quantity of starting material (101).

Irradiation with the filter solution led to slower formation of the polymer.

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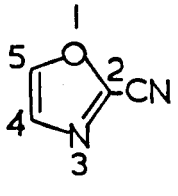
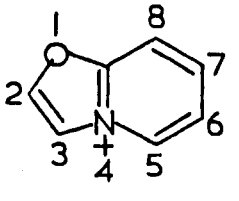
P A R T I I

DISCUSSION

It has been shown in Part I that attempts to synthesise 2-cyano-oxazole (1) have been unsuccessful. This is perhaps attributable to the instability of the oxazole ring when the 4,5 bond is unsubstituted. When an alkyl or aryl substituent is present at the 5-position the stability of the oxazole ring appears to be enhanced. This has led to the synthesis of a number of oxazolo[3,2-a]pyridinium salts[1] which have been prepared using the Glover and Jones[2] quinolizinium route. The description of their preparation and also the attempts to obtain the parent system (2) are discussed below.



(1)

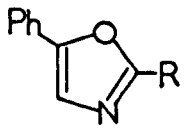


(2)

Synthesis of 2-phenyloxazolo[3,2-a]pyridinium salts. (2, R = Ph)

The starting material for this synthesis, 2-cyano-5-phenyl-oxazole (3) has been prepared from 2-carbethoxy-5-phenyloxazole (4) by some Russian workers.[3] The oxazole ester (4) was synthesised as

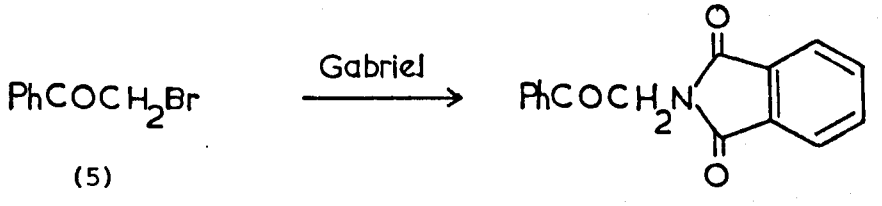
outlined below.



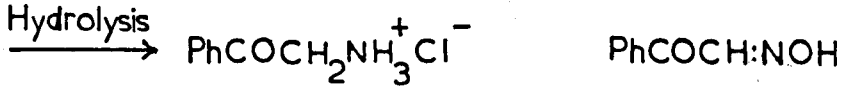
(3) R = CN

(4) R = CO_2Et

ω-Amino-acetophenone hydrochloride (7) was obtained via a Gabriel synthesis[4] on ω-bromo-acetophenone (5)[5] followed by hydrolysis of the resulting phthalimido-acetophenone (6) with boiling hydrochloric acid. The hydrolysis was a modification of Ellinger and Goldbergs[6] method. The actual period of hydrolysis was extended to 4 days and this gave a 40% overall yield of the amine hydrochloride (7) which compares well with a reported yield of 40% via isonitroso-acetophenone (8).[7]

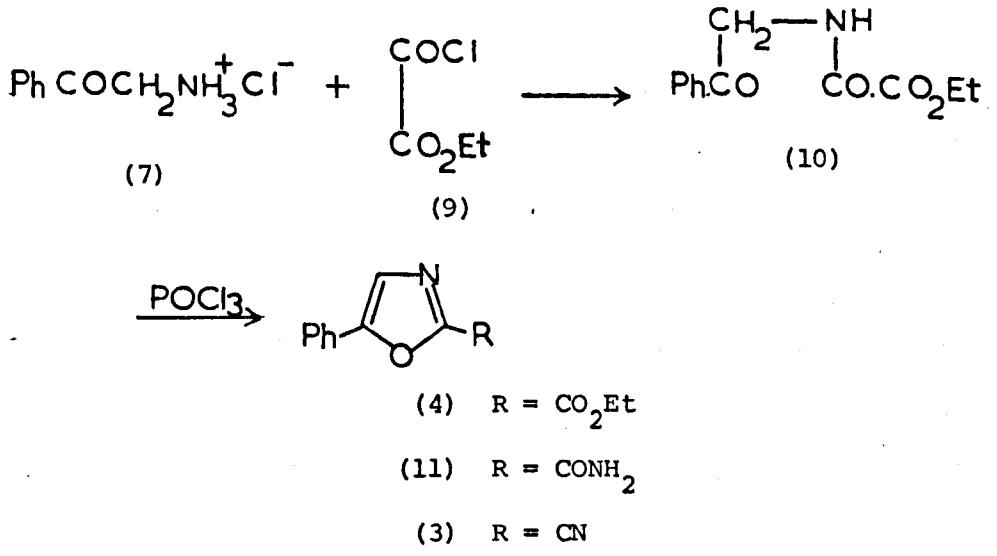


(5) (6)



(7) (8)

Treatment of the amine hydrochloride (7) with ethoxalyl chloride (9)[8] as described by Saito and Tanaka[9] gave the amido-ester (10). Cyclisation of (10) to the oxazole ester (4) as reported by the same authors was improved from 69-74% yield by dehydration with phosphoryl chloride in boiling benzene.



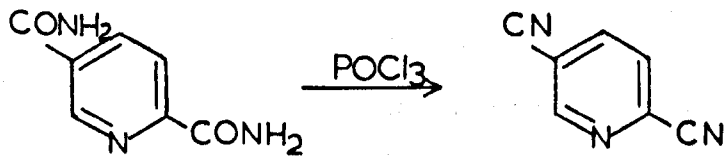
(4) R = CO_2Et

(11) R = $CONH_2$

(3) R = CN

The ester (4) was converted to the amide (11) in methanolic ammonia and dehydrated with phosphorus pentoxide to the nitrile (3)[3] in 70% yield.

Pavlov et al[10] have dehydrated pyridine-2,5-dicarboxamide (12) by treatment with phosphoryl chloride in boiling anhydrous pyridine to the corresponding dicyanopyridine (13).



(12) (13)

Similar treatment of the oxazole derivative (11) gave a 40% yield of product (3).

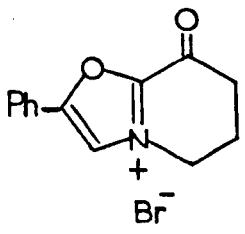
The 2-cyano-5-phenyloxazole (3) was then treated at 0° with the Grignard reagent prepared previously from 3-ethoxypropyl bromide. The mauve coloured complex was stirred overnight before decomposing with an excess of concentrated hydrochloric acid. The mixture was stirred for a further hour to ensure complete hydrolysis of the intermediate imine (14) to the ketone (15). The product, 2-(4-ethoxybutyryl)-5-phenyloxazole (15) was obtained in 60% yield.

(14) (15)

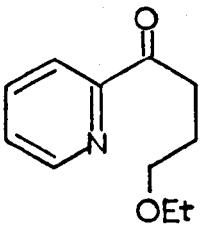
The n.m.r. spectrum in carbon tetrachloride was consistent with the structure of the butyryloxazole (15) and the infrared spectrum showed a strong carbonyl band at 1697 cm.$^{-1}$.

Boiling the keto-ether (15) in 48% hydrobromic acid for 1 hr. and removing the acid under reduced pressure led to a high yield of almost pure 5,6,7,8-tetrahydro-8-oxo-2-phenyl-oxazolo[3,2-a]pyridinium bromide (16). This was in agreement with that observed for the cyclisation of the corresponding butyryl-thiazole. However in the case of the pyridine ketone (17),[2] corresponding to the oxazole (15), the bromoketone hydrobromide (18) was formed. It was found that the ketone hydrobromide (18) had first to be basified to the free amine before cyclisation in boiling chloroform would occur to give the bicyclic ketone (19).

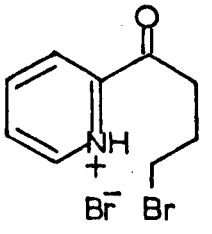
The hydrobromide of 2-(4-bromobutyryl)-5-phenyloxazole was presumably too unstable to be isolated as a solid, due to the weak basicity of the oxazole system compared with the pyridine system (pKa pyridine 5.2, thiazole 2.4 and oxazole 0.8).[12] During the removal of the hydrobromic acid, the hydrobromide must dissociate to the bromoketone which spontaneously undergoes cyclisation to the cyclic ketone (16).



(16)



(17)



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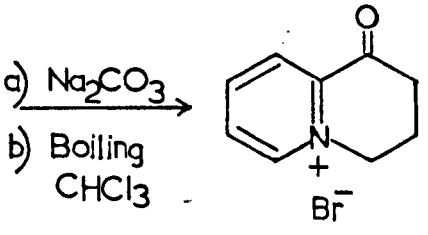
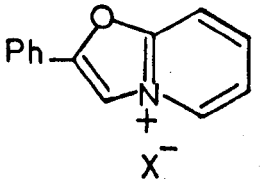


(19)



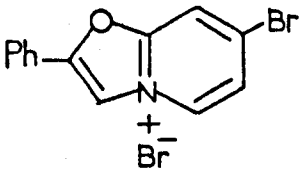
(20)

Treatment of the cyclic ketone (16) with boiling acetic anhydride led to an 85% yield of 2-phenyloxazolo[3,2-a] pyridinium bromide (20, X = Br).

The physical data of the bromide (20, X = Br) and perchlorate (20, X = ClO_4) entirely agreed with those reported by Bradsher and Zinn,[13] and a direct comparison proved their identity when a sample of the perchlorate was generously supplied to us by Professor Bradsher. The n.m.r. data are shown in Table 1 (p. 89) and are discussed later together with the spectra of the other aromatic salts that have been synthesised.

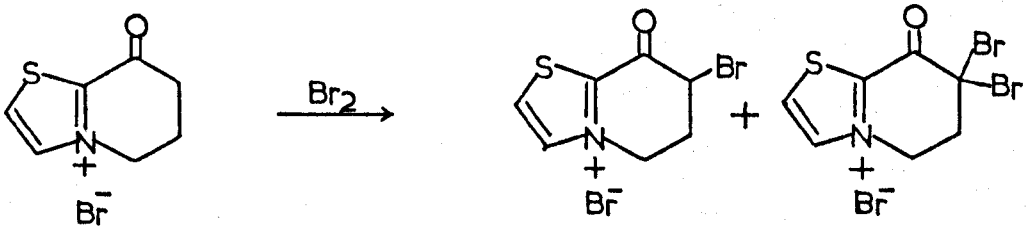
Synthesis of 7-bromo-2-phenyloxazolo[3,2-a]pyridinium bromide. (21)

As a first extension of the synthesis, 7-bromo-2-phenyl-oxazolo[3,2-a]pyridinium bromide (21) was prepared.



(21)

In the thiazole series[11] the cyclic ketone (22) was brominated with bromine in hydrobromic acid to give a mixture of mono- (23) and dibromoketones (24). The monobromoketone could be isolated by virtue of its greater solubility in ethanol.

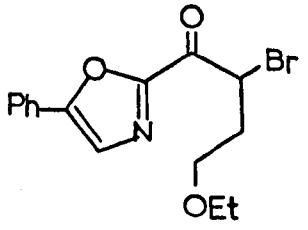


(22) (23) (24)

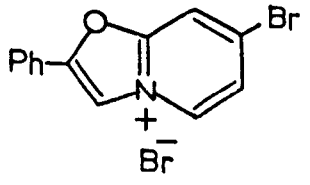
Bromination of the oxazole ketone (16) with one mole of bromine gave a similar mixture of products. However, a sufficiently

pure sample of the monobromo compound, necessary for aromatisation, could not be separated. Instead the ethoxybutyryloxazole (15) was monobrominated.

Marquet and co-workers[14] have successfully used phenyltrimethylammonium tribromide in tetrahydrofuran for the selective α-bromination of a ketone in the presence of double bonds. Treatment of the oxazole ketone (15) in dry tetrahydrofuran with an equimolar amount of phenyltrimethylammonium tribromide afforded a 61% yield of the monobromoketone (25). Its n.m.r. spectrum in deuterochloroform showed the disappearance of the two proton triplet at δ3.18 p.p.m. and the formation of a one proton triplet centred at δ5.58 p.p.m. which is consistent with the expected absorption when a bromine atom occupies an α-position to a carbonyl group.



(25)



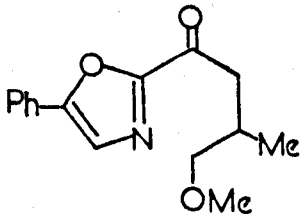
(21)

Cyclisation and aromatisation of the bromoketone (25) as described previously gave 7-bromo-2-phenyloxazolo[3,2-a]pyridinium bromide (21) in 86% yield. The n.m.r. details are given later in Table 1 (p. 89).

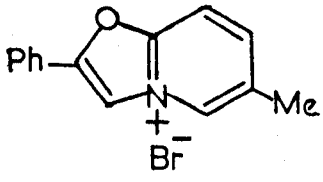
Synthesis of 6-methyl-2-phenyloxazolo[3,2-a]pyridinium bromide (27)

In the quinolizinium series Grignard reagents other than 3-ethoxypropyl bromide have been used in order to vary the position of substituents in the final aromatic salts.[2]

2-Cyano-5-phenyloxazole (3) was treated with 3-methoxy-2-methylpropylmagnesium chloride[2] to produce the crude methoxybutyryloxazole (26).



(26)



(27)

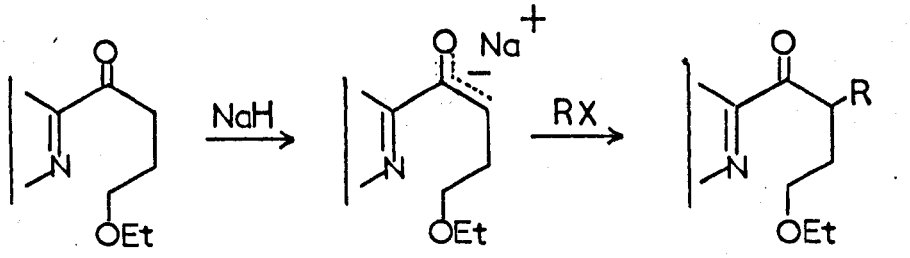
Attempts to purify the product by distillation only led to considerable decomposition. T.l.c. showed the presence of one major component with a minor component near the base line of the plate. The crude product was chromatographed on a column of silica gel. Elution with toluene-chloroform mixtures gave the product almost pure in a yield of 27%. The formation of the methoxybutyryloxazole (26) was confirmed by its n.m.r. spectrum in carbon tetrachloride which showed two methylene doublets at δ2.88 and 3.22 p.p.m.

Cyclisation followed by aromatisation in boiling acetic

anhydride gave an almost quantitative yield of 6-methyl-2-phenyloxazolo[3,2-a]pyridinium bromide (27). The n.m.r. spectrum (Table 1) (p. 89) confirms the structure of the product.

Attempted synthesis of 7-alkyl-2-phenyloxazolo[3,2-a]pyridinium salts

It has been previously reported in the quinolizinium[15] and the thiazolopyridinium series[11] that the intermediate ethoxybutyryl derivatives of the same type as compound (15) can be alkylated. The reaction pathway proceeded via an enolate ion (28) which was treated with an alkyl halide to form the 2-(2-alkyl-4-ethoxybutyryl)pyridine or thiazole (29).

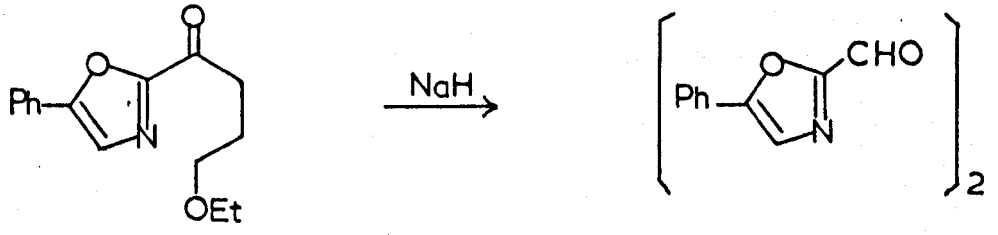


(28) (29)

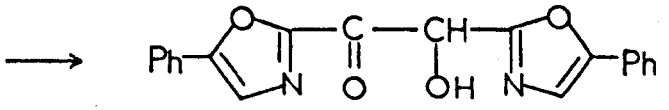
Treatment of 2-(4-ethoxybutyryl)-5-phenyloxazole (15) with sodium hydride in boiling dimethoxyethane and subsequent

addition of one mole of benzyl bromide led to a product containing no aliphatic protons in the n.m.r. spectrum. The infrared spectrum showed strong absorptions at 3380 cm^{-1} and 1730 cm^{-1}, and the mass spectrum, a molecular ion at 346. This corresponded to a formula of $C_{20}H_{14}N_2O_4$ and the product was formulated as the oxazoloin (31).

Presumably the hydride ion leads to production of 2-formyl-5-phenyloxazole (30), which like pyridine-2-aldehyde undergoes very rapid self condensation to the acyloin (31).



(15) (30)



(31)

In order to prevent the formation of oxazoloin (31) the hydride was added in small portions to a solution of the butyryl ketone (15) and excess benzyl bromide in dimethoxyethane.

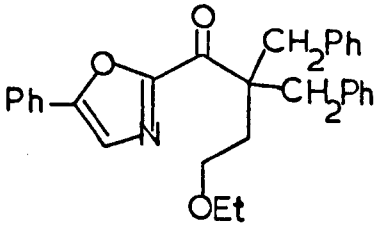
The enolate ion once formed would preferentially undergo alkylation in the presence of an alkyl halide. Working up in the usual way led to the isolation of a viscous oil. T.l.c. indicated a mixture that included starting material. A sample was separated by P.L.C. using a chloroform-ether mixture as eluent.

The fastest running band (I) was identified from its n.m.r. spectrum as benzyl bromide.

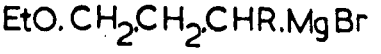
Band (II) was isolated as a colourless oil. The spectral evidence was consistent with the formation of 2-(2,2-dibenzyl-4-ethoxybutyryl)-5-phenyloxazole (32). The infrared spectrum showed a carbonyl absorption at 1690 cm^{-1}. The mass spectrum showed a molecular ion at 439 which agrees with the formula $C_{29}H_{29}NO_3$ and had a prominent peak at $^{m}/e = 91$ due to a benzyl or tropylium ion. Finally the n.m.r. spectrum showed the two benzyl methylene protons as two singlets at $\delta 3.55$ and $\delta 4.71$ p.p.m. The difference in chemical shifts is presumably attributable to the stereochemistry of the molecule, one of the methylene groups being deshielded by the anisotropic effect of the carbonyl group. A model of the structure suggests this possible stereochemistry.

The isolation of dibenzylated compound (32) and starting ketone (15) is presumably due to the mono-alkylated ketone undergoing an extremely rapid second alkylation.

This route to 7-substituted oxazolopyridinium salts was not further pursued. Such compounds could be alternatively prepared via the reaction of 5-phenyl-2-cyano-oxazole (3) with the Grignard reagent from a 1-substituted-3-ethoxypropyl bromide (33).



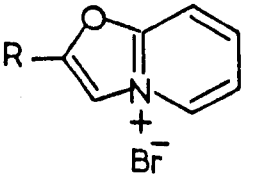
(32)



(33)

Synthesis of 2-methyl- (34) and 2-benzyloxazolo[3,2-a]pyridinium salts (35)

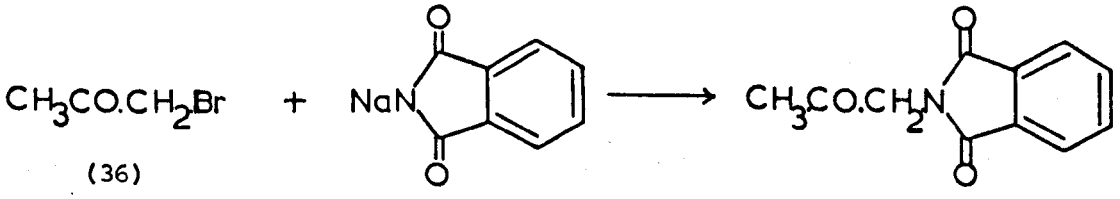
A similar reaction route to that described previously for the synthesis of 2-phenyloxazolo[3,2-a]pyridinium salts (20) has been used for the preparation of the 2-methyl- (34) and the 2-benzyl-substituted aromatic salts (35).



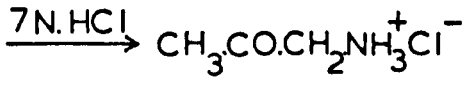
(34) R = CH_3

(35) R = CH_2Ph

Amino-acetone hydrochloride (38) was prepared in good yield by an improved Gabriel synthesis.[16] Sodium phthalimide was generated in boiling dimethoxyethane by the action of sodium hydride on phthalimide. Bromo-acetone (36)[17] was then added slowly to the boiling solution and subsequent concentration of the reaction mixture afforded a good yield of phthalimido-acetone (37). Amino-acetone hydrochloride (38) was formed on hydrolysis of the crude phthalimido-acetone (37) as described by Ellinger and Goldberg.[6]



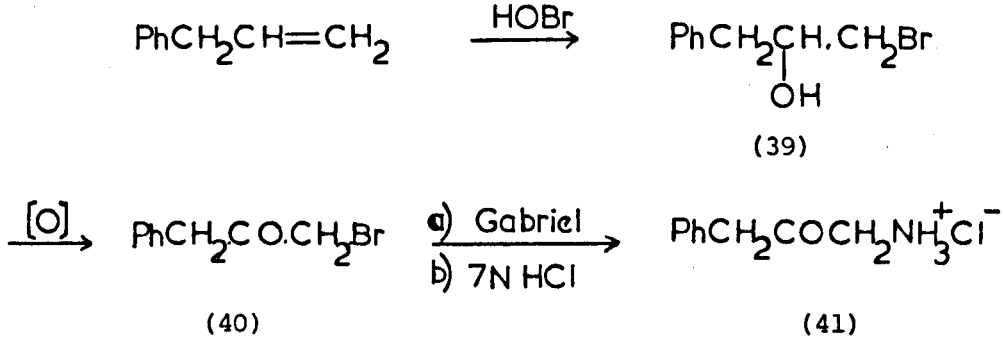
(36) (37)



(38)

The only reported route to 1-amino-3-phenylpropan-2-one hydrochloride (41) has given poor yields.[18]

However, good overall yields have been obtained from allylbenzene, via the bromohydrin (39), the bromoketone (40) and a Gabriel synthesis.



(39)

(40) (41)

Raphael[19] has reported the use of a slightly acidic solution containing N-bromosuccinimide as a convenient source of HOBr which could be added across isolated double bonds to form bromohydrins.

Treatment of allylbenzene with the same reagent has led to an 80% yield of the bromohydrin (39). The product was distilled under nitrogen in a darkened apparatus due to its sensitivity to both light and air.

Oxidation of 3-bromo-1-phenylpropan-2-ol (39) gave the bromoketone (40) in yields of 33-88%.

All reactions were carried out at 0° during addition of oxidising mixture and then completed at room temperature. The following conditions were tried:

(a) A solution of the bromohydrin (39) in benzene was oxidised using an aqueous solution containing sodium dichromate, sulphuric acid and acetic acid.[20] The two phase system led to an excellent

recovery of product (40) (88%) which was indicated to be pure by t.l.c. and n.m.r. The melting point of the semicarbazone agreed with that reported in the literature.[32]

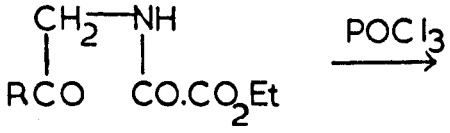
(b) An acetone solution of the bromohydrin (39) was treated with an 8N chromic acid solution[21] to afford a 48% yield of bromoketone (40) identical with that obtained in (a).

(c) Treatment of the bromohydrin (39) in glacial acetic acid with chromium trioxide[22] led on work up to a 33% yield of the bromoketone (40).

The bromoketone (40) underwent a Gabriel synthesis as described for ω-bromo-acetophenone (5).[4] Hydrolysis using the method described by Ellinger and Goldberg[6] gave 1-amino-3-phenylpropan-2-one hydrochloride (41) in an overall yield of 47% from the bromoketone (40).

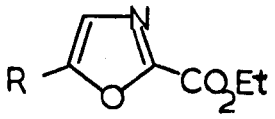
Treatment of the amine hydrochlorides (38) and (41) with ethoxalyl chloride afforded the amides (42) and (43) which cyclised in phosphoryl chloride and boiling benzene to yield the corresponding 2-carbethoxyoxazoles (44) and (45).

The esters (44) and (45) were converted into the corresponding amides (46) and (47) which underwent dehydration to the nitriles (48) and (49) on heating with phosphorus pentoxide.



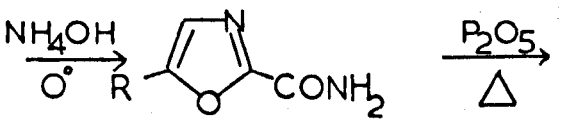
(42) R = CH_3

(43) R = CH_2Ph



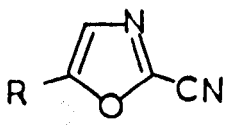
(44) R = CH_3

(45) R = CH_2Ph



(46) R = CH_3

(47) R = CH_2Ph



(48) R = CH_3

(49) R = CH_2Ph

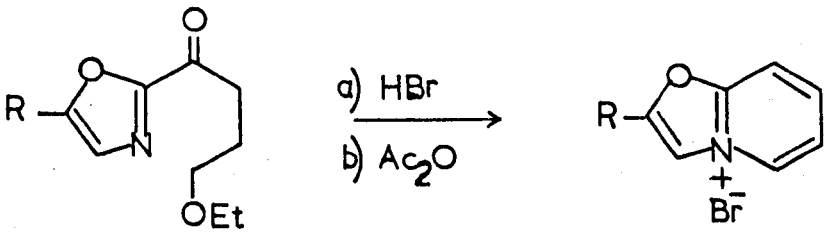
Both nitriles reacted with 3-ethoxypropylmagnesium bromide to yield the respective ethoxybutyryl oxazoles (50) and (51) in yields of 52% and 27% respectively.

The low yield of the benzyl derivative (49) was attributable to some decomposition occurring on distillation. A higher yield was indicated when a small sample of the crude product was chromatographed on a column of silica gel eluting with toluene-chloroform mixtures.

Both the ethoxybutyryl oxazoles (50) and (51) were converted into the aromatic salts by treatment with aqueous hydrobromic acid, evaporation, and treating the crude intermediates with boiling

acetic anhydride. Respective yields of 100% and 71% of the 2-methyl (34) and the 2-benzyloxazolo[3,2-a]pyridinium bromides (35) were obtained.

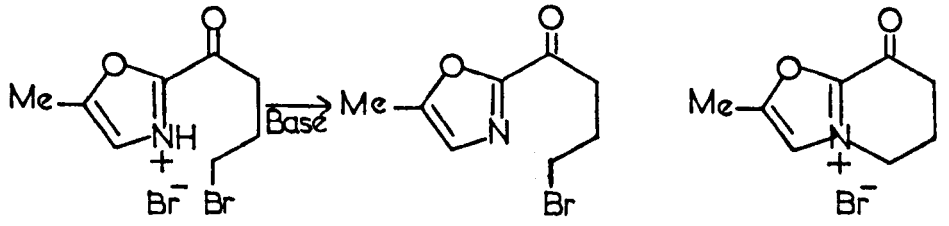
The n.m.r. spectra, which will be discussed collectively later, (p. 87) show the expected pattern for aromatic systems (34) and (35).



(50) R = CH_3 (34) R = CH_3

(51) R = CH_2Ph (35) R = CH_2Ph'

An examination of the n.m.r. spectrum in deuterium oxide of the crude intermediate, obtained by the treatment of 2-(4-ethoxybutyryl)-5-methyloxazole (50) with boiling hydrobromic acid, indicated a mixture of the uncyclised bromobutyryl compound (52) and the cyclic ketone (53). Comparison of the integrations of the methyl singlets for (52) and (53) suggested a 1:1 ratio of products.



(52) (54) (53)

Prolonged boiling in hydrobromic acid did not increase the yield of cyclic ketone (53). As mentioned previously the analogous pyridine derivative (17) on similar treatment gave only the uncyclised hydrobromide (18).

It has been shown by Brown and Ghosh[12] that the presence of a methyl group in an oxazole ring can increase the pKa by approximately 1 unit due to hyperconjugation as compared with that of a phenyl substituted oxazole. This increase in basicity may be sufficient to partially inhibit the bromobutyryl oxazole from undergoing dissociation followed by cyclisation to the cyclic ketone (53). In this respect the 2-(4-ethoxybutyryl)-5-methyloxazole (50) has a behaviour midway between that of the corresponding parent thiazole and pyridine derivatives.

The bromobutyryl ketone (54) was isolated by chloroform extraction of a basic solution of the ketone mixture. The n.m.r. spectrum in carbon tetrachloride showed the expected three absorptions due to the methylene groups and the mass spectrum contained a molecular ion peak at $^{m}/e$ 232 consistent with the suggested formula.

Evaporation of the basic solution followed by extraction with ethanol gave the cyclic ketone (53) as a deliquescent solid which could not be purified for analysis, although the spectral properties were consistent with those expected.

The rate of cyclisation of the bromobutyryloxazole (54)

was extremely slow in boiling chloroform or absolute ethanol which was in direct contrast to the behaviour of the bromobutyryl-pyridines. Cyclisation and aromatisation did however occur in quantitative yield by treatment of the mixture of ketones with boiling acetic anhydride.

N.m.r. spectra of the substituted oxazolo[3,2-a]pyridinium salts

The chemical shifts and coupling constants of the substituted oxazolo[3,2-a]pyridinium salts are recorded in Table 1. For completeness the 60 MHz spectra have been obtained in both deuterium oxide and trifluoroacetic acid. The 100 MHz spectrum of 2-methyl-oxazolo[3,2-a]pyridinium bromide (34) has been recorded in deuterium oxide and is shown in Figure 1. Double irradiation studies are shown in Figure 2. The methyl compound was studied in most detail as the aromatic pattern was unobscured.

The one proton broadened doublet furthest downfield at δ8.75 p.p.m. (see Figure 1) is due to proton 5 which has coupling constants $J_{5,6}$ = 6.5 Hz and $J_{5,7}$ = 1.5 Hz. The absorption of proton 7 is shown as a multiplet centred at δ8.3 p.p.m. with coupling constants $J_{6,7}$ = 6.5 Hz, $J_{7,8}$ = 9 Hz and $J_{5,6}$ = 1.5 Hz. The broadened singlet at δ8.13 p.p.m. is due to the 3-proton on the oxazole ring. The 8-proton absorption is shown as a slightly broadened doublet centred at δ8.03 p.p.m. with coupling constants $J_{7,8}$ = 9 Hz and $J_{6,8}$ = 1 Hz.

Finally, the 6-proton absorption is shown as a broadened triplet centred at δ7.73 p.p.m., coupling with all three ring protons.

Figure 2 shows the spectrum of the aromatic protons when the methyl absorption at δ2.58 p.p.m. was irradiated. The proton 3 absorption is now shown as a sharp singlet indicating coupling with the methyl protons at position 2. A similar irradiation of the broadened singlet due to proton 3 at δ8.13 p.p.m. led to the methyl proton absorption appearing as a sharp singlet instead of the original finely split singlet of coupling J_{CH_3,H_3} = 1 Hz. This evidence indicates allylic character in the 2,3-double bond.

The other mono-substituted salts (20) and (35) contain similar aromatic splitting patterns with the 5,6 and 6,7 couplings approximately equal (6-7 Hz) and the 7,8 coupling larger (8-9 Hz). Similar coupling constants have been reported for indolizines,[23] triazolopyridines[24] and thiazolo[3,2-a]pyridinium salts.[11]

Where substituents are contained in the six-membered pyridinium ring in salts (21) and (27) the substitution pattern of the remaining protons confirms the structure.

The n.m.r. spectrum of 7-bromo-2-phenyloxazolo[3,2-a]-pyridinium bromide (21) in deuterium oxide clearly shows the one proton broadened singlet at δ8.22 p.p.m. due to the 8-proton absorption. Similarly the spectrum of 6-methyl-2-phenyloxazolo[3,2-a]-pyridinium bromide (27) shows the 5-proton absorption as a broadened singlet furthest downfield at δ8.46 p.p.m.

N.m.r. spectrum of 2-methyloxazolo[3,2-a]pyridinium bromide (34) in D_2O (aromatic region)

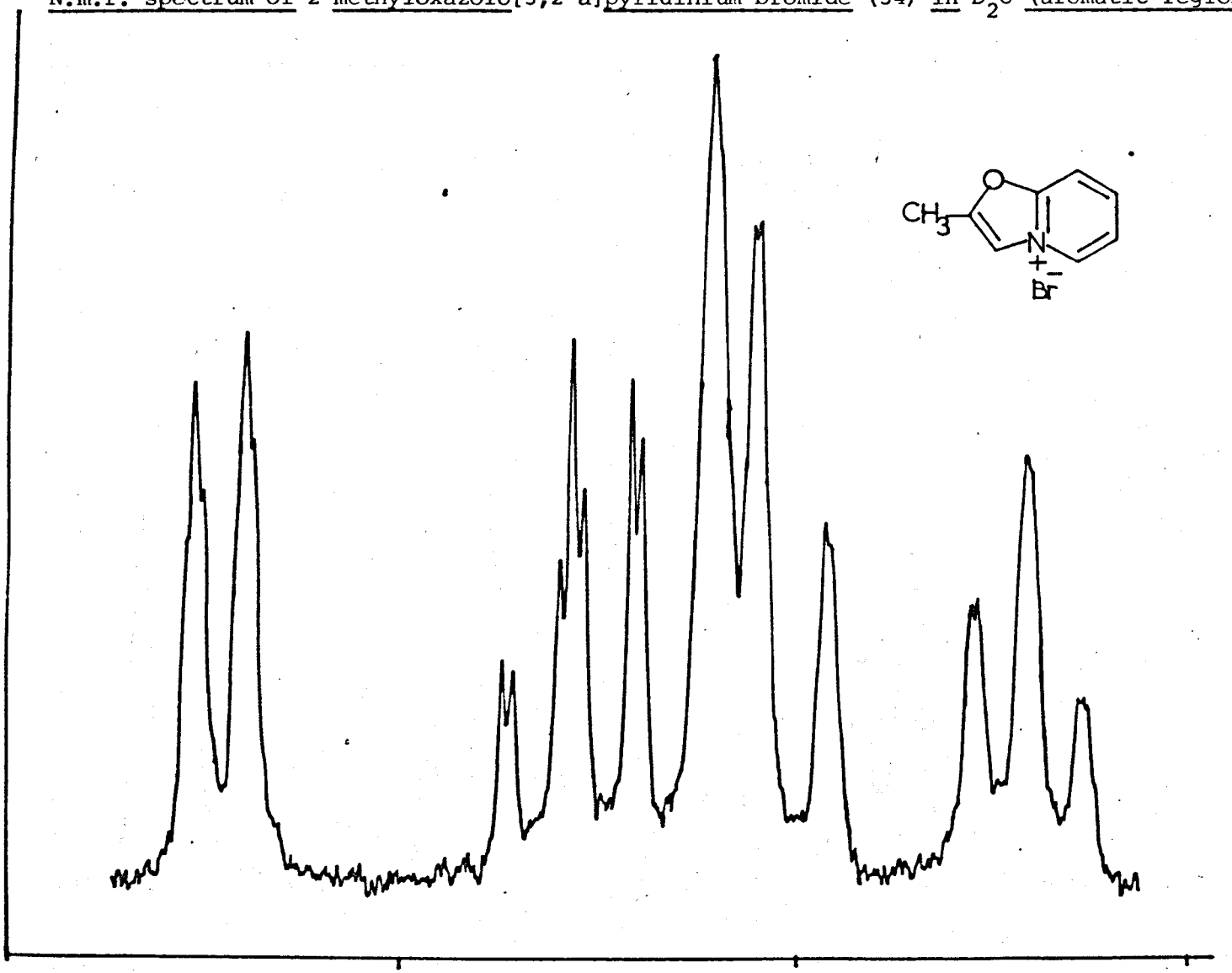


Figure 1

N.m.r. spectrum of 2-methyloxazolo[3,2-a]pyridinium bromide (34) in D_2O.

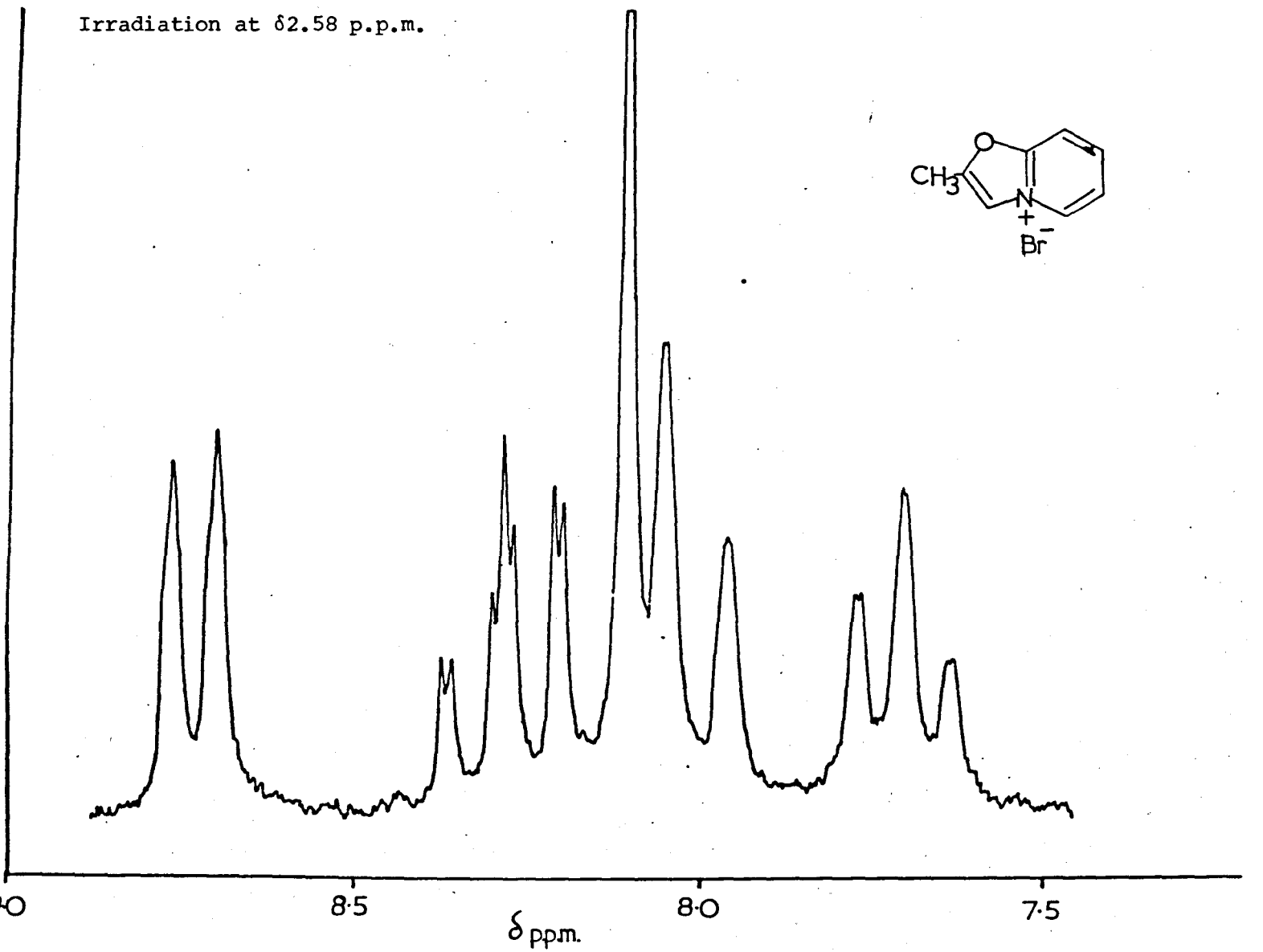


Figure 2

TABLE I

N.m.r. Details[a] of Oxazolo[3,2-a]pyridinium Salts

Cpd	Solvent[b]	H-3	H-5	H-6	H-7	H-8	Other resonances	Coupling Constants (Hz)
20	D	8.52s	8.72brd	7.1-7.8	8.20m	8.0brd	7.1-7.8 (5H,Ph)	$J_{5,6}$ 7; $J_{5,7}$ 1; $J_{6,7}$ 7; $J_{6,8}$ 1; $J_{7,8}$ 8
20	T	8.62s	8.95q	7.4-8.1	8.30m	7.75-8.10	7.4-8.1 (5H,Ph)	
21	D	8.49s	8.59d	7.93m	-	8.22brs	7.14-7.7 (5H,Ph)	$J_{5,6}$ 7; $J_{6,8}$ 1
21	T	8.63d	8.85d	7.4-8.1	-	8.33brs	7.4-8.1 (5H,Ph)	
27	D	8.36s	8.46s	-	8.07q	7.77d	2.41 (3H,s,Me) 7.06-7.66 (5H,Ph)	$J_{5,6}$ 1; $J_{7,8}$ 8
27	T	8.55s	8.71brs	-	8.26d	8.14d	2.66 (3H,s,Me) 7.4-8.1 (5H,Ph)	
34	D[c]	8.13brs	8.75brd	7.73m	8.30m	8.03d	2.58 (3H,brs,Me)	$J_{5,6}$ 6.5; $J_{5,7}$ 1.5; $J_{6,7}$ 6.5; $J_{6,8}$ 1; $J_{7,8}$ 9; $J_{3,Me}$ 1
34	T	8.12s	8.86brd	7.84m	8.43m	8.04brd	2.71 (3H,s,Me)	
35	D	8.12s	8.70brd	7.70m	8.27m	7.88d	4.16 (2H,s,CH_2) 7.22 (5H,Ph)	$J_{5,6}$ 6.5; $J_{6,8}$ 1
35	T	8.02s	8.85brd	7.85m	8.44m	8.07brd	4.28 (2H,s,CH_2) 7.39 (5H,brs,Ph)	

[a] Values given are δ in p.p.m. from Me_4Si; 60MHz spectra

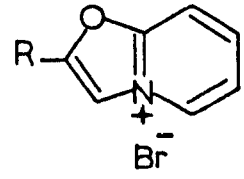
[b] D = D_2O, T = CF_3CO_2H

[c] 100MHz spectrum; double irradiation at 2.58 p.p.m. confirms H-3, CH_3 coupling

Studies on the synthesis of the parent oxazolo[3,2-a]pyridinium salts from the substituted salts (34) and (35)

Scheme (a)

Both the 2-methyl (34) and the 2-benzyloxazolopyridinium salts (35) were potential sources of the unsubstituted oxazolo-[3,2-a]pyridinium salt (2) which has not yet been prepared.



(34) R = CH_3

(35) R = CH_2Ph

Quinolizinium salts, on account of the delocalised positive charge carried by the cation, are resistant to electrophilic attack. The introduction of a powerfully electron-donating group, however, modified the resistance of the quinolizinium system sufficiently to allow electrophilic substitution to occur.[25]

The stability of the quinolizinium ion to electrophilic attack suggests the possibility of brominating the methyl or benzylic methylene groups in the salts (34) and (35). The brominated products are possible precursors for the preparation of the 2-carboxylic acid and 2-benzoyl substituted aromatic salts which could both yield the

parent system (2).

However the two oxazolo[3,2-a]pyridinium salts were recovered unchanged when treated under the following conditions:

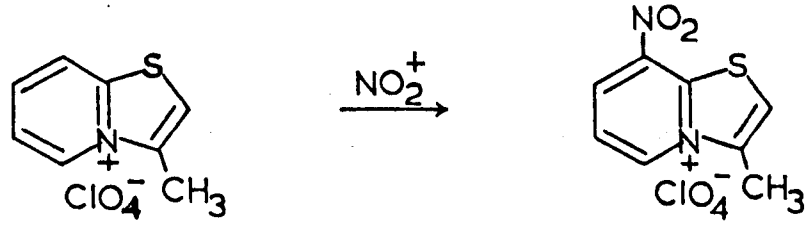
(a) Bromine in water at 100°.

(b) Bromine in 48% hydrobromic acid at 100° or at the boiling point.

(c) Bromine in glacial acetic acid at 100°.

These results indicate the stability of the oxazolopyridinium salts against electrophilic attack. However it must be noted that the 2-position may be most favoured towards electrophilic substitution due to the close proximity of the negative hetero-atom. Further evidence for the stability of the oxazolopyridinium system against electrophilic attack was obtained when 2-phenyloxazolo[3,2-a]pyridinium perchlorate (20, X = ClO_4) was subjected to nitration.

Bradsher and Lohr[26] have successfully nitrated 3-methylthiazolo[3,2-a]pyridinium perchlorate (55) in boiling concentrated nitric acid containing several pieces of anthracite. Nitration occurred at the 8-position (56) in a yield of 14%.



(55) (56)

Nitration of 2-phenyloxazolo[3,2-a]pyridinium perchlorate (20, X = ClO_4) under the same conditions produced a dark brown solid indicating that a certain amount of carbonisation had occurred. The n.m.r. spectrum was similar to that of the starting material.

Scheme (b)

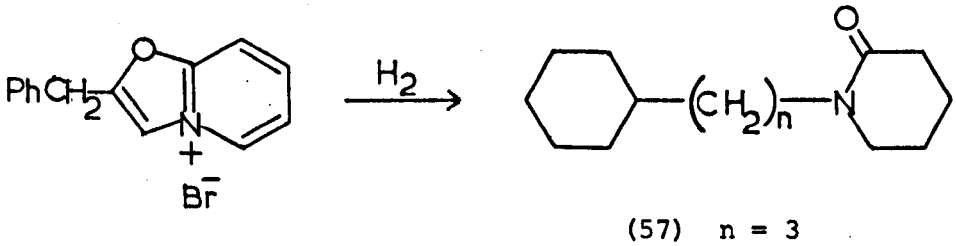
Attempts have been made to remove the benzyl group from the aromatic salt (35) by reductive cleavage. Benzyl groups have been removed from oxygen, sulphur and nitrogen atoms using catalytic hydrogenation. 3-Methylthiazolo[3,2-a]pyridinium perchlorate (55) was unaffected by catalytic reduction at atmospheric pressure using Adams' catalyst.[26]

Reduction of the aromatic salt (35) with palladium-charcoal and hydrogen in ethanol at atmospheric temperature and pressure was ineffective. Reduction however with Adams' catalyst in ethanol led to uptake of seven molar equivalents of hydrogen giving a crude liquid. Purification using P.L.C. gave a colourless liquid that was bulb-tube distilled to obtain a sample of analytical purity. The infrared spectrum showed a strong absorption at 1640 cm^{-1} which led to the suspicion of an α-piperidone type structure being present.

Edwards and Singh[27] have reported the infrared spectra of saturated N-alkyl six membered lactams. They observed a strong carbonyl band near 1640 cm^{-1} when in the liquid (Film) or solid (Nujol, KBr disc) state and an absorption at 1620 cm^{-1} in chloroform solution.

The isolated product had similar carbonyl absorptions at 1640 cm^{-1} (film) and 1620 cm^{-1} ($CHCl_3$). The mass spectrum (see Figure 3) showed a molecular ion at $^m/e$ 223 which corresponded to a formula of $C_{14}H_{25}NO$ and suggested the compound was 1-(3-cyclohexylpropyl)-2-piperidone (57).

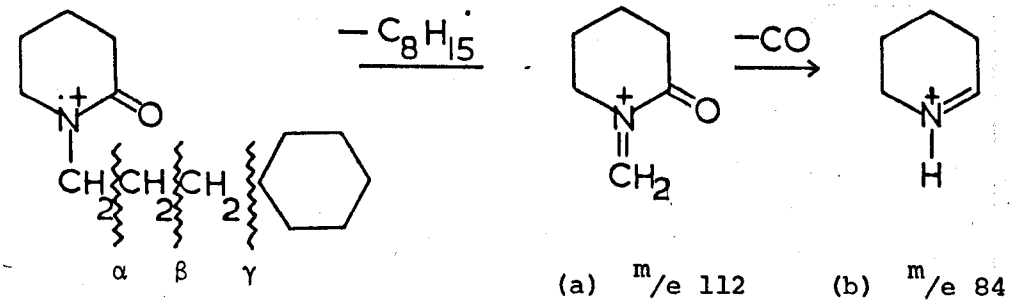
The mass spectrum suggests the main fragment ($^m/e$ 112) was formed by α-cleavage, with β-($^m/e$ 126) and γ-fissions ($^m/e$ 140) occurring as well. A similar breakdown has been observed for N-alkyl-2-pyrrolidones.[28] Elimination of carbon monoxide from structure (a) resulted in an ion of mass 84 which may possess the ring expanded structure (b). The n.m.r. spectrum in deuterochloroform showed a four proton multiplet centred at δ3.3 p.p.m. due to the two methylene groups adjacent to the tertiary nitrogen. A similar two proton absorption centred at δ2.2 p.p.m. was assigned to the methylene group adjacent to the carbonyl. The remaining nineteen protons appeared as a complex multiplet between δ0.8-2.4 p.p.m.



(35)

(57) n = 3

(58) n = 2



(57)

A similar hydrogenation of 2-phenyloxazolo[3,2-a] pyridinium bromide (20, X = Br) gave 1-(2-cyclohexylethyl)-2-piperidone (58). The mass spectrum (Figure 4) showed a molecular ion at $^{m}/e$ 209 and a similar breakdown pattern as compound (57) thus confirming the structure of compound (58).

The instability towards reduction is in contrast to the thiazolo[3,2-a]pyridinium salt (55)[26] and is apparently due to the weak C5-oxygen bond in the oxazole ring.

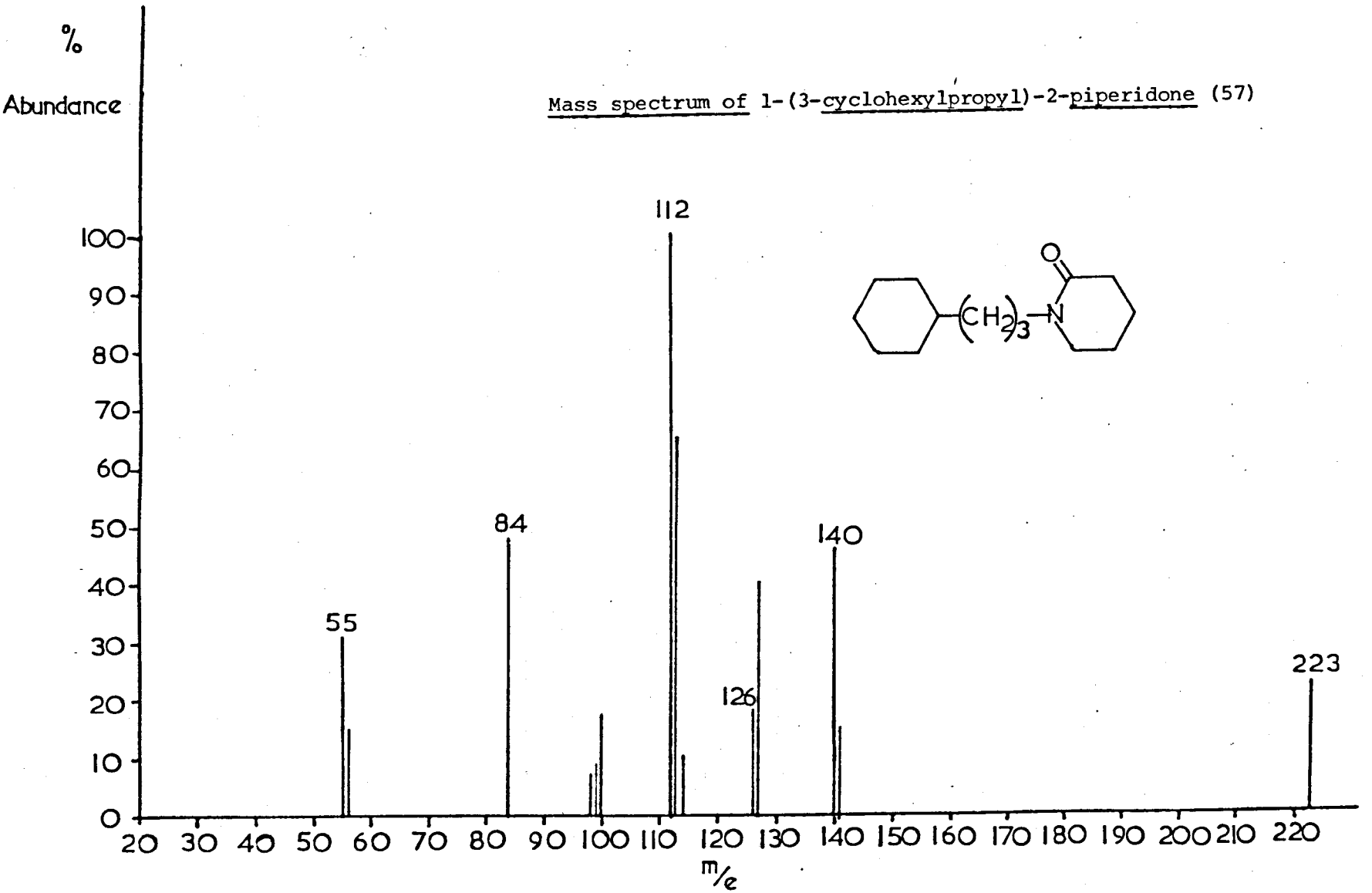

%
Abundance
Mass spectrum of 1-(3-cyclohexylpropyl)-2-piperidone (57)
112
84
55
140
126
223
100
90
80
70
60
50
40
30
20
10
0
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220
m/e
O
(CH2)3
N

Figure 3

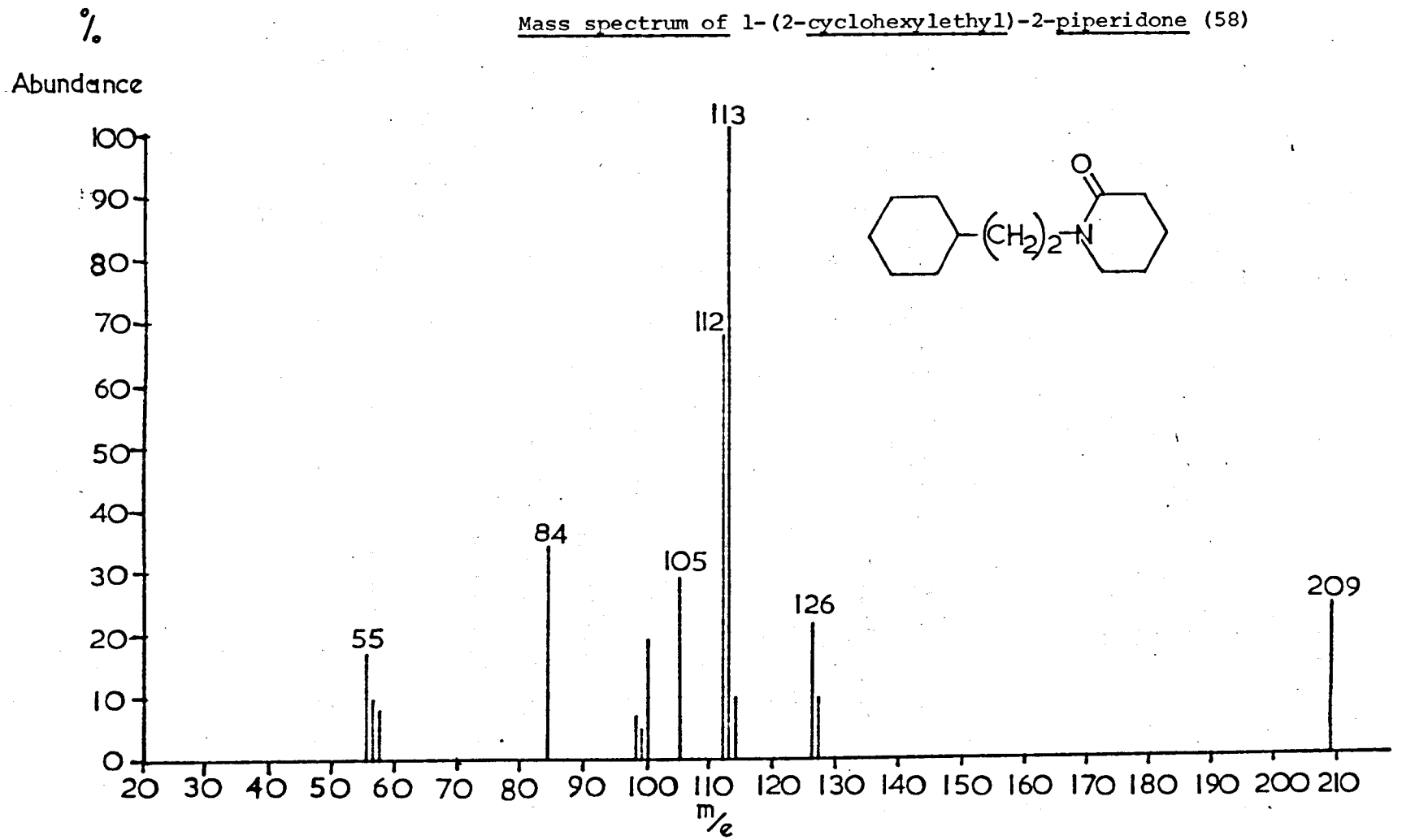
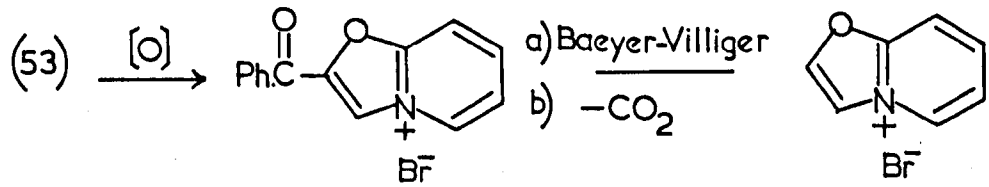

Mass spectrum of 1-(2-cyclohexylethyl)-2-piperidone (58)
%
Abundance
100
90
80
70
60
50
40
30
20
10
0
113
112
84
105
126
209
55
O
(CH2)2
N
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210
m/e

Figure 4

Scheme (c)

Another route envisaged for the preparation of the parent compound (2) involved initial oxidation of the benzyl group in compound (35) to the benzoyl group (59). A subsequent Baeyer-Villiger oxidation may conceivably lead to the acid which on decarboxylation would afford the parent compound (2).



(59) (2)

Oxidation of 2-benzyloxazolo[3,2-a]pyridinium bromide (35) with selenium dioxide in anhydrous pyridine at 115°[29] led to a black intractable tar. The n.m.r. spectrum was ill-defined indicating that decomposition had occurred. Oxidation at 100° gave a similar product. Attempts to purify the product failed,

The oxazolopyridinium system appears to be unstable towards both reduction and oxidation and attempts to synthesise the parent system was discontinued.

EXPERIMENTAL

ω-Bromo-acetophenone (5)

Prepared from acetophenone as described by Cowper and Davidson.[5]

Phthalimido-acetophenone (6)

Prepared using an improved Gabriel synthesis as described by Sheehan and Bolhofer.[4]

ω-Amino-acetophenone hydrochloride (7)

Prepared by an adaptation of Ellinger and Goldberg's method.[6] A solution of phthalimido-acetophenone (6) (115g.) in 7N hydrochloric acid (500 ml.) was boiled for 4 days. Work up gave ω-amino-acetophenone hydrochloride (7) as a pale yellow solid, m.p. 185-187° (lit.,[30] m.p. 188.5°).

The amine hydrochloride was isolated in an overall yield of 45% starting from acetophenone. A yield of 40% has been reported[7] via isonitroso-acetophenone (8).

Ethoxalyl chloride (9)

Prepared from diethyl oxalate as described by Kindler et al.[8]

Ethoxalylamino-acetophenone (10)

Prepared from ω-amino-acetophenone hydrochloride (7) and ethoxalyl chloride (9) by the method of Saito and Tanaka.[9]

2-Carbethoxy-5-phenyloxazole (4)

The acetophenone (10) was cyclised by the method of Saito and Tanaka.[9] An increased yield of product was obtained by boiling rather than gentle heating of the reaction mixture, (74%) m.p. 61-3° (lit.,[9] m.p. 60-61°, yield 69%).

5-Phenyloxazole-2-carboxamide (11)

The amide (11) was prepared using the method of Sycheva et al.[3] A virtually quantitative yield was obtained by dissolving the ester (4) in a minimum of methanol, adding the solution to ice-cold ammonia (s.g. 0.88) and standing the mixture at 0° for 1-3 days. Recrystallisation from methanol gave colourless prisms of the amide (11), m.p. 189-192° (lit.,[3] m.p. 189-191°, yield 84.5%).

2-Cyano-5-phenyloxazole (3)

(a) The amide (11) was dehydrated using phosphorus pentoxide as described by Sycheva et al[3] to give the cyano compound (3) in 70% yield.

(b) Also prepared using the method of Pavlov et al.[10] A mixture

of 5-phenyloxazole-2-carboxamide (1.0g.) and phosphoryl chloride (2 ml.) in anhydrous pyridine (10 ml.) was heated under reflux for 2 hr. The solvents were removed under reduced pressure and the residue treated with ice-water and extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and evaporated to leave almost pure nitrile (3) (0.36g., 48%).

2-(4-Ethoxybutyryl)-5-phenyloxazole (15)

A solution of the Grignard reagent from 3-ethoxypropyl bromide (18.4g.) and magnesium (2.88g.) in anhydrous ether (200 ml.) was added slowly with stirring (3 hr.) under nitrogen to an ice-cold solution of 2-cyano-5-phenyloxazole (3) (17g.) in ether (150 ml.). Stirring was continued overnight at room temperature. Ice-cold 12N hydrochloric acid (30 ml.) was added slowly to the reaction mixture which quickly changed from a mauve to a brick-red colour. The ethereal layer was separated and re-extracted with further acid. The combined acid extracts were diluted to dissolve suspended solids, and stirred at room temperature (1 hr.) to ensure complete hydrolysis of the imine intermediate (14). The solution was basified by the cautious addition of ammonia (s.g. 0.88) at 0° and ether extracted. The dried ether extracts were evaporated, and the solid residue extracted with boiling petroleum ether (b.p. 60-80°). From the cooled extracts the butyryl

oxazole (15) was obtained (15.5g., 60%). Recrystallised from petroleum ether as colourless plates m.p. 70-71°.

Found: C, 69.5; H, 6.55; N, 5.3%

$C_{15}H_{17}O_3N$ requires: C, 69.5; H, 6.6; N, 5.4%

$\nu_{max.}$ (Nujol) 1697, 1124 cm.$^{-1}$ (CO).

$\lambda_{max.}$ (95% EtOH) 233, 250(sh), 313 nm. ($\log_{10}\varepsilon$, 3.89, 3.81, 4.27).

n.m.r. (CCl_4) : δ 1.1 (3H, t, $\underline{CH_3}CH_2$), 1.97 (2H, m, $CH_2\underline{CH_2}CH_2$), 3.08 (2H, t, $COCH_2$, J = 7Hz), 3.39 (2H, q, OCH_2CH_3, J = 6.5Hz), 3.44 (2H, t, OCH_2CH_2) 7.2-7.9 (6H, m) p.p.m.

2-Phenyloxazolo[3,2-a]pyridinium bromide (20, X = Br)

A solution of the butyryloxazole (15) (5g.) in 48% hydrobromic acid (100 ml.) was boiled under reflux for 1 hr., allowing the ethyl bromide initially formed to escape from the system. The hydrobromic acid was removed under reduced pressure and the solid residue dissolved in absolute ethanol and re-evaporated (twice). The crude cyclic ketone showed a carbonyl band at 1728 cm.$^{-1}$ in the infrared. The crude ketone was treated with boiling acetic anhydride (50 ml.) for 2 hr. The acetic anhydride was evaporated and the residue dissolved in ethanol and re-evaporated to remove traces of acetic anhydride. Trituration of the residual solid with dry

acetone (A.R.) gave almost pure 2-phenyloxazolopyridinium[3,2-a]-bromide (20, X = Br) (4.52g., 85%). Recrystallisation from absolute ethanol/ethyl acetate gave almost colourless prisms m.p. 196-197° (lit.,[13] m.p. 197.5-199.5°).

Found: C, 53.5; H, 4.05; N, 4.8%

$C_{13}H_{10}NOBr.H_2O$ requires: C, 53.1; H, 4.1; N, 4.75%

$\lambda_{max.}$ (95% EtOH) 236, 286(sh), 301 nm. ($\log_{10}\varepsilon$, 4.33, 4.27, 3.98).

$\lambda_{max.}$ (95% EtOH/aq.NaOH) 245(sh), 294, 414 nm. ($\log_{10}\varepsilon$, 4.32, 4.03, 3.90).

The n.m.r. details are given in Table I (p. 89).

Picrate

Recrystallised from absolute ethanol, m.p. 204-205°.

Found: C, 53.4; H, 2.8; N, 13.0%

$C_{19}H_{12}O_8N_4$ requires: C, 53.8; H, 2.85; N, 13.2%

Perchlorate

Prepared from the bromide by anionic exchange on amberlite (I.R.A. 400) resin, recrystallised from methanol as colourless needles, m.p. 216-218° (lit.,[13] 218-222°).

Found: C, 52.8; N, 3.4; N, 4.6%

$C_{13}H_{10}ClNO_5$ requires: C, 52.8; H, 3.4; N, 4.75%

Phenyltrimethylammonium tribromide

Prepared from dimethylaniline as described by Marquet et al.[14]

2-(2-Bromo-4-ethoxybutyryl)-5-phenyloxazole (25)

Phenyltrimethylammonium tribromide (0.145g.) was added to a solution of the ethoxybutyryloxazole (15) (1g.) in anhydrous tetrahydrofuran (15 ml.) at room temperature. The mixture was set aside with occasional shaking for 6 hr. It was then filtered, the insoluble quaternary salt was washed with a little tetrahydrofuran and the combined filtrates evaporated under reduced pressure to give a brown oil which was shaken with water and ether. The ethereal extracts were dried (Na_2SO_4) and evaporated, and the residual oil extracted with hot petroleum ether (b.p. 60-80°) to give the bromobutyryloxazole (25) on cooling as a pale yellow solid (0.8g., 61%). Recrystallised from petroleum ether (b.p. 60-80°) as colourless cubes, m.p. 73-74°.

Found: C, 53.25; H, 4.75; N, 4.15%

$C_{15}H_{16}BrNO_3$ requires: C, 53.5; H, 5.05; N, 4.1%

$\nu_{max.}$ (Nujol) 1700, 1101 $cm.^{-1}$ (CO).

$\lambda_{max.}$ (95% EtOH) 241, 329 nm. ($\log_{10}\varepsilon$, 3.95, 4.22).

n.m.r. ($CDCl_3$) : δ 1.1 (3H, t, $OCH_2\underline{CH_3}$), 2.22-2.78 (2H, m, $CH(Br)\underline{CH_2}CH_2$), 3.35 (2H, t, $OCH_2\underline{CH_2}$, J = 7Hz), 3.52 (2H, q, $OCH_2\underline{CH_3}$), 5.58 (1H, t, $CO\underline{CH}BrCH_2$,

J = 7Hz), 7.30-7.80 (6H, m) p.p.m.

7-Bromo-2-phenyloxazolo[3,2-a]pyridinium bromide (21)

Cyclisation and aromatisation as described for compound (20) gave from the bromobutyryloxazole (25) (1g.) the 7-bromo-2-phenyloxazolopyridinium bromide (21) (0.9g., 86%). Recrystallised from absolute ethanol/acetone, m.p. 218-220°.

Found: C, 43.9; H, 3.05; N, 3.8%

$C_{13}H_9Br_2NO$ requires: C, 44.0; H, 2.55; N, 3.95%

$\lambda_{max.}$ (95% EtOH) 228, 287(sh), 309 nm. ($\log_{10}\varepsilon$, 4.08, 4.20, 4.35).

$\lambda_{max.}$ (95% EtOH/aq.NaOH) 242, 287(sh), 307 nm. ($\log_{10}\varepsilon$, 4.21, 3.77, 3.79).

The n.m.r. details are given in Table I (p. 89).

3-Methoxy-2-methylpropyl chloride

Prepared from methyl methacrylate as described by Glover and Jones.[2]

2-(4-Methoxy-3-methylbutyryl)-5-phenyloxazole (26)

Prepared as described for compound (15), but using the Grignard reagent from 3-methoxy-2-methylpropyl chloride. Attempts to distil the product led to considerable decomposition. T.l.c., eluting with chloroform showed the presence of one major component

with one minor component remaining at the base line of the plate.

The mixture (3.4g.) was dissolved in toluene and run onto a column of silica gel (Davison, grade 923, 100g.). The column was eluted with toluene-chloroform mixture gradually increasing the proportion of chloroform. The product was obtained as a viscous oil which was extracted with hot petroleum ether (b.p. 60-80°) to give 2-(4-methoxy-3-methylbutyryl)-5-phenyloxazole (26) (2.69g., 27%) as a pale yellow solid on cooling. Recrystallised from petroleum ether (b.p. 60-80°) as colourless needles, m.p. 53-54°.

Found: C, 69.4; H, 6.4; N, 5.7%

$C_{15}H_{17}O_3N$ requires: C, 69.5; H, 6.6; N, 5.4%

$\nu_{max.}$ (Nujol) 1694 $cm.^{-1}$ (CO).

$\lambda_{max.}$ (95% EtOH) 233, 313 nm. ($\log_{10}\varepsilon$, 3.88, 4.25).

n.m.r. (CCl_4) : δ 1.0 (3H, d, $\underline{CH_3}CH$, J = 6Hz), 2.22-2.73 (1H, m, $CH_2\underline{CH}(CH_3)CH_2$), 2.88 (2H, d, $COCH_2\underline{CH}$), 3.2 (3H, s, OCH_3), 3.22 (2H, d, $CHCH_2O$, J = 6Hz), 7.2-7.8 (6H, m) p.p.m.

6-Methyl-2-phenyloxazolo[3,2-a]pyridinium bromide (27)

The methoxybutyryloxazole (26) (0.67g.) was cyclised and aromatised as described previously for the preparation of 2-phenyloxazolopyridinium bromide (20, X = Br). 6-Methyl-2-phenyloxazolo-[3,2-a]pyridinium bromide (27) was obtained as a light brown solid

(0.71g., 95%). Recrystallised from absolute ethanol/ethylacetate as buff prisms m.p. 204-206°.

Found: C, 51.0; H, 4.75; N, 4.3%

$C_{14}H_{12}BrNO.2H_2O$ requires: C, 51.5; H, 4.95; N, 4.3%

$\lambda_{max.}$ (95% EtOH) 231, 288(sh), 299 nm. ($\log_{10}\varepsilon$, 4.00, 4.19, 4.2).

$\lambda_{max.}$ (95% EtOH/aq.NaOH) 239, 300(sh), 412 nm. ($\log_{10}\varepsilon$, 4.07, 3.65, 3.77).

The n.m.r. details are given in Table I (p.89).

Reaction of sodium hydride with 2-(4-ethoxybutyryl)-5-phenyloxazole (15)

A solution of the butyryloxazole (15) (0.5g.) and sodium hydride (0.2g., 50% dispersion in oil) in dry dimethoxyethane (40 ml.) was stirred and boiled under an atmosphere of nitrogen. The progress of the reaction was monitored using t.l.c. After 4 hr., the solvent was removed under reduced pressure, and the residue treated with ice-cold 12N hydrochloric acid and ether extracted to remove the parrafin oil. The acid extracts were basified with ammonia (s.g. 0.88) and extracted with ether. The dried ethereal extracts were evaporated to leave an oily solid (0.35g.). T.l.c. eluting with chloroform-25% carbon tetrachloride indicated the presence of starting material and one other component.

The mixture (0.3g.) was applied to the base of one

preparative chromatography plate and eluted with chloroform - 25% carbon tetrachloride.

The following bands were obtained.

Band I (0.19g.) N.m.r. and melting point were identical with that of starting material.

Band II (0.045g.) isolated as a viscous oil which was purified by bulb-tube distillation, b.p. 85-90°/0.1 mm., m.p. 37-39°. Spectral evidence indicated the compound to be oxazoloin (31).

Found: N, 8.0%

$C_{20}H_{14}N_2O_4$ requires: N, 8.1%

$\nu_{max.}$ ($CHCl_3$)	3380, 1730 $cm.^{-1}$
$\lambda_{max.}$ (95% EtOH)	260, 268, 280(sh) nm. ($\log_{10}\varepsilon$, 4.64, 4.6, 4.35).
Mass spectrum m/e	346, 302, 248, 145, 117, 105 (M^+ requires 346).
n.m.r. ($CDCl_3$) :	δ 7.42-7.95 (12H, m), 8.1 (2H, s, oxazole H-4) p.p.m.

Attempted alkylation of 2-(4-ethoxybutyryl)-5-phenyloxazole (15)

Sodium hydride (0.106g.) was added in small portions under nitrogen to a boiling mixture of benzylbromide (0.68g.) and the ethoxybutyryl oxazole (15) (0.52g.) in dry dimethoxyethane (40 ml.). After boiling and stirring for a further 4 hr., the solvent was

removed under reduced pressure and the cooled residue treated with concentrated hydrochloric acid and ether. The acid extracts were separated and basified with ammonia (s.g. 0.88) and extracted with ether. The dried ethereal extracts were evaporated to leave an oil. T.l.c. eluting with chloroform indicated a complex mixture which included some starting material. The n.m.r. spectrum indicated a mixture of benzylated butyryl-oxazoles.

Bulb-tube distillation (200°; 0.1 mm.) of a sample of the mixture gave only a small quantity of benzyl bromide. A black polymeric residue remained in the distillation tube.

The mixture (0.3g.) was separated by P.L.C. (eluting with chloroform:ether; 7:1) into the following bands.

Band I (0.02g.) was shown to be benzyl bromide.

Band II (0.12g.) was isolated as a colourless oil and shown to be the dibenzyl compound (32).

Found: N, 3.2%

$C_{29}H_{29}NO_3$ requires: N, 3.2%

$\nu_{max.}$ (Film)	1690 cm.$^{-1}$ (CO).
$\lambda_{max.}$ (95% EtOH)	239, 301 nm. ($\log_{10}\varepsilon$, 3.92, 4.26).
Mass spectrum m/e	439, 348, 302, 248, 91 (M^+ requires 439).
n.m.r. ($CDCl_3$) :	δ 1.12 (3H, t, J = 6Hz), 2.55 (2H, t, $OCH_2.\underline{CH_2}$-C, J = 6Hz), 3.11-3.5 (4H, m, $O(\underline{CH_2}\text{-})_2$), 3.55 (2H, s), 4.71 (2H, s), 7.02-7.62 (16H, m) p.p.m.

Band III (0.053g.) shown from t.l.c. and mass spectral data to be mainly starting material (15) and dibenzyl compound (32).

Bromo-acetone (36)

Prepared from acetone by the method of Levene.[17]

Amino-acetone hydrochloride (38)

A mixture of dry phthalimide (77g.) and sodium hydride (24g., 50% dispersion in oil) in dimethoxyethane (500 ml.) was boiled and stirred under nitrogen for 2 hr. Bromo-acetone (36) (70g.) was added slowly over a period of 2-3 hr. and boiling and stirring of the mixture was continued overnight. Concentration under reduced pressure gave almost pure phthalimido-acetone (37) on filtration. Hydrolysis of the unpurified phthalimido-acetone as described by Ellinger and Goldberg[6] gave amino-acetone hydrochloride (38) (47g., 50%) as a viscous oil which failed to crystallise.

3-Bromo-1-phenylpropan-2-ol (39)

A mixture of allyl benzene (23.6g.), finely powdered N-bromosuccinimide (48.8g.) and water (100 ml.) containing a few drops of glacial acetic acid was shaken at room temperature for 24 hr. The mixture was extracted with ether (3 x 40 ml.). The

combined ethereal extracts were shaken with sodium meta-bisulphite solution, sodium bicarbonate solution, and finally water. The dried ethereal extracts were distilled under nitrogen and the 3-bromo-1-phenylpropan-2-ol (39) (35g., 81%) b.p. 81-84°/0.05 mm. collected in a darkened receiver.

Found: C, 50.1; H, 4.95%

$C_9H_{11}BrO$ requires: C, 50.25; H, 5.15%

$\nu_{max.}$ (Film) 3400 cm.$^{-1}$ (OH).

n.m.r. ($CDCl_3$) : δ 2.7-4.4 (6H, m), 7.45 (5H, s) p.p.m.

3-Bromo-1-phenylpropan-2-one (40)

(a) A solution of sodium dichromate (24g.) in sulphuric acid (30 ml.), water (100 ml.), and acetic acid (10 ml.)[20] was added over a period of 2 hr. at 0° to a solution of 3-bromo-1-phenylpropan-2-ol (39) (40g.) in benzene (300 ml.). After 15 hr. stirring at room temperature the mixture was separated, the aqueous layer diluted with an equal volume of water and extracted with benzene. The benzene extracts were combined and washed well with water, sodium carbonate solution and finally salt solution. The dried benzene extracts were then evaporated to give virtually pure 3-bromo-1-phenylpropan-2-one (40) (35g., 88%). Distillation gave the pure ketone, b.p. 100-105°/0.35 mm.

$\nu_{max.}$ (Film) 1720 cm.$^{-1}$ (CO).

n.m.r. ($CDCl_3$) : δ 3.95 (2H, s), 4.0 (2H, s), 7.43 (5H, s) p.p.m.

The semicarbazone had m.p. 230-232° (lit.,[31] m.p. 225-8°).

(b) Oxidation of the propan-2-ol (39) in acetone solution with an 8N chromic acid solution[21] initially at 0° and then at room temperature (12 hr.) gave the propan-2-one (40) in 48% yield identical with that obtained in (a).

(c) Oxidation of the propan-2-ol (39) with chromium trioxide in glacial acetic acid[22] at room temperature for 16 hr. gave the propan-2-one (40) in 33% yield.

1-Amino-3-phenylpropan-2-one hydrochloride (41)

(a) A solution of 3-bromo-1-phenylpropan-2-one (40) (100g.) in dry dimethylformamide (D.M.F.) (100 ml.) was added rapidly under nitrogen to a stirred suspension of potassium phthalimide (100g.) in dry D.M.F. (200 ml.). The temperature rose rapidly to 70° and was maintained by external heating at this temperature for 1 hr. The mixture was next concentrated under reduced pressure to 30% of its original volume, chloroform (200 ml.) added and the mixture poured into water (1 l.). The aqueous layer was separated and further extracted with chloroform. The combined chloroform extracts were dried (Na_2SO_4) and evaporated to give the crude phthalimide derivative. Hydrolysis as described for compound (6) gave the amine hydrochloride (41) (42g., 47%), which was

recrystallised from absolute ethanol as colourless needles, m.p. 196.5-197.5°, (lit.,[18] 190-3°).

(b) The amine hydrochloride (41) was prepared in 30% yield using the method described for the preparation of amino-acetone hydrochloride (38).

Ethoxalylamino-acetone (42)

Ethoxalyl chloride (9) (80g.) was added to a stirred suspension of amino-acetone hydrochloride (38) (63g.) in anhydrous benzene (200 ml.) and the mixture was heated under reflux for 5 hr. The benzene was removed under reduced pressure and the residue treated with ice-water (200 g.) and chloroform extracted. The combined chloroform extracts were dried (Na_2SO_4) and distilled. The ethoxalylamino-acetone (42) had b.p. 124-130°/0.3 mm. (85-90%).

$\nu_{max.}$ (Film) 1740-1690 $cm.^{-1}$ (CO).

n.m.r. ($CDCl_3$) : δ 1.4 (3H, t), 2.3 (3H, s, $\underline{CH_3}CO$), 4.35 (2H, d, $\underline{CH_2}N$), 4.45 (2H, q), 7.95 (1H, brs, $\underline{NH}$) p.p.m.

1-Ethoxalylamino-3-phenylpropan-2-one (43)

A mixture of 1-amino-3-phenylpropan-2-one hydrochloride (41) (36.8g.) and ethoxalyl chloride (9) (30g.) in dry benzene (500 ml.) was heated under reflux for 12 hr. The solvent was

removed under reduced pressure to give almost pure product (42.6g., 86%). Recrystallisation from carbon tetrachloride gave the ketone (43) as colourless needles, m.p. 65-67°.

Found: C, 62.6; H, 6.1; N, 5.7%

$C_{13}H_{15}NO_4$ requires: C, 62.65; H, 6.05; N, 5.6%

$\nu_{max.}$ (Nujol) 1746-1680 $cm.^{-1}$ (CO).

n.m.r. ($CDCl_3$) : δ 1.35 (3H, t), 3.75 (2H, s, $\underline{CH_2}CO$), 4.21 (2H, d, $NH.\underline{CH_2}.CO$, J = 5Hz), 4.33 (2H, q), 7.32 (5H, s), 7.75 (1H, brs, NH) p.p.m.

2-Carbethoxy-5-methyloxazole (44)

A solution of ethoxalylamino-acetone (42) (10g.) and phosphoryl chloride (20g.) in dry benzene (120 ml.) was boiled for 12 hr. The solvent was removed under reduced pressure and the cooled residue treated with ice-water and chloroform. An emulsion resulted which was separated using a two-phase filter paper. The chloroform extracts were dried (Na_2SO_4) and distilled; 2-carbethoxy-5-methyloxazole (44) had b.p. 85-90°/0.45 mm. (4.48g., 50%). The higher b.p. distillate contained a certain quantity of unchanged ethoxalylamino-acetone (42) which could be used in subsequent cyclisations thus making the overall yield in excess of 50%.

$\nu_{max.}$ (Film) 1740 cm.$^{-1}$ (CO).

$\lambda_{max.}$ (95% EtOH) 255 nm. ($\log_{10}\varepsilon$, 3.34).

n.m.r. (CCl_4) : δ 1.45 (3H, t), 2.47 (3H, s), 4.55 (2H, q), 7.13 (1H, s, oxazole H-4) p.p.m.

Mercuric chloride complex

A sample of freshly distilled oxazole (44) was dissolved in a minimum of 95% ethanol and the solution added to cold, aqueous mercuric chloride to produce an immediate white precipitate of the mercuric chloride complex. Recrystallisation from 95% ethanol gave colourless needles, m.p. 110-113°.

Found: C, 11.4; H, 1.2; N, 1.95%

$C_7H_9NO_3.2HgCl_2.H_2O$ requires: C, 11.7; H, 1.55; N, 1.95%

2-Carbethoxy-5-benzyloxazole (45)

A solution of the amido ketone (43) (30g.) and phosphoryl chloride (60g.) in dry benzene (250 ml.) was boiled for 12 hr. Work up as described for compound (44) gave an oil which on distillation gave the 5-benzyloxazole ester (45) (17.25g., 62%), b.p. 134-136°/0.05 mm.

Found: C, 67.4; H, 5.65; N, 6.0%

$C_{13}H_{13}NO_3$ requires: C, 67.5; H, 5.65; N, 6.05%

$\nu_{max.}$ (Film) 1740 cm.$^{-1}$ (CO).

$\lambda_{max.}$ (95% EtOH) 261 nm. ($\log_{10}\varepsilon$, 4.01).

n.m.r. ($CDCl_3$) : δ 1.37 (3H, t), 4.03 (2H, s, $PhCH_2$), 4.39 (2H, q), 6.88 (1H, s, oxazole H-4), 7.22 (5H, brs) p.p.m.

5-Methyloxazole-2-carboxamide (46)

Freshly distilled 5-methyloxazole ester (44) (20g.) was dissolved in a minimum of methanol and added dropwise to a stirred solution of ammonia (150 ml., s.g. 0.88) at 0°. After 3 days standing at 0° the solid was separated, washed well with water and dried giving almost pure amide (46) (16.25g., quantitative). Recrystallisation from absolute ethanol gave colourless prisms, m.p. 163° (sublimes).

Found: C, 47.8; H, 4.75; N, 22.6%

$C_5H_6O_2N_2$ requires: C, 47.6; H, 4.75; N, 22.2%

$\nu_{max.}$ (Nujol) 1675, 1120 cm.$^{-1}$ (CO).

$\lambda_{max.}$ (95% EtOH) 225(sh), 255 nm. ($\log_{10}\varepsilon$, 3.69, 3.98).

n.m.r. (D_2O) : δ 2.17 (3H, s), 6.92 (1H, s, oxazole H-4) p.p.m.

(T.F.A.) : δ 2.65 (3H, s), 7.58 (1H, s), 8.1 (2H, brs, NH_2) p.p.m.

5-Benzyloxazole-2-carboxamide (47)

Prepared in quantitative yield using the same method as described for compound (46). Recrystallised from methanol as colourless plates, m.p. 189-190°.

Found: C, 65.1; H, 4.9; N, 13.8%

$C_{11}H_{10}N_2O_2$ requires: C, 65.3; N, 5.0; N, 13.85%

$\nu_{max.}$ (Nujol) 1703 cm.$^{-1}$ (CO).

$\lambda_{max.}$ (95% EtOH) 255 nm. ($\log_{10}\varepsilon$, 3.95).

n.m.r. (T.F.A.) : δ 4.36 (2H, s, $PhCH_2$), 7.54 (6H, brs, aromatic), 8.4 (2H, brs, NH_2) p.p.m.

2-Cyano-5-methyloxazole (48)

A dry well-ground mixture of 5-methyloxazole-2-carboxamide (46) (19g.) and phosphorus pentoxide (38g.) was heated at 160° under nitrogen for 1 hr. On slight reduction of the pressure, the nitrile slowly distilled, and was collected in an ice-cold receiver. Redistillation gave pure nitrile (48) (8g., 49%), b.p. 160°/450 mm.

Found: C, 55.1; H, 3.70%

$C_5H_4N_2O$ requires: C, 55.55; H, 3.75%

$\nu_{max.}$ (Film) 2260 cm.$^{-1}$ (CN).

$\lambda_{max.}$ (95% EtOH) 254 nm. ($\log_{10}\varepsilon$, 4.05).

n.m.r. (CCl_4) : δ 2.55 (3H, s), 7.2 (1H, s, oxazole H-4) p.p.m.

2-Cyano-5-benzyloxazole (49)

A similar mixture of 5-benzyloxazole-2-carboxamide (47) (16g.) and phosphorus pentoxide (32g.) was heated at 180° under nitrogen. Slight reduction of the pressure enabled the nitrile (49) to distil over and collect in an ice-cold receiver (5.0g., 41%). The pure 2-cyano-5-benzyloxazole (49) had b.p. 154°/30 mm.

Found: C, 71.8; H, 4.6; N, 15.2%

$C_{11}H_8N_2O$ requires: C, 71.7; H, 4.4; N, 15.2%

$\nu_{max.}$ (Film) 2260 cm.$^{-1}$ (CN).

$\lambda_{max.}$ (95% EtOH) 255 nm. ($\log_{10}\varepsilon$, 4.09).

n.m.r. ($CDCl_3$) : δ 4.15 (2H, s), 7.1 (1H, s, oxazole H-4), 7.48 (5H, s) p.p.m..

2-(4-Ethoxybutyryl)-5-methyloxazole (50)

This was prepared using the method described previously in the preparation of compound (15). The butyryloxazole (50) had b.p. 100°/0.1 mm., (8.5g., 52%).

Found: C, 60.9; H, 7.8; N, 7.2%

$C_{10}H_{12}NO_3$ requires: C, 60.9; H, 7.65; N, 7.1%

$\nu_{max.}$ (Film) 1700, 1115 cm.$^{-1}$ (CO).

$\lambda_{max.}$ (95% EtOH) 276 nm. ($\log_{10}\varepsilon$, 4.01).

n.m.r. (CCl_4) : δ 1.1 (3H, t), 1.95 (2H, m, $CH_2\underline{CH_2}CH_2$), 2.46 (3H, s), 3.06 (2H, t, $COCH_2CH_2$, J = 7Hz), 3.45 (2H, q), 3.5 (2H, t, OCH_2CH_2, J = 6.5Hz), 7.14 (1H, s, oxazole H-4) p.p.m.

5-Benzyl-2-(4-ethoxybutyryl)oxazole (51)

Prepared as described for compound (15). The butyryl-oxazole (51) had b.p. $170^{o}/0.2 \times 10^{-2}$ mm. (decomp.) (27.2%).

Found: C, 69.9; H, 6.85; N, 5.1%

$C_{16}H_{19}NO_3$ requires: C, 70.3; H, 7.05; N, 5.15%

$\nu_{max.}$ (Film) 1692, 1110 cm.$^{-1}$ (CO).

$\lambda_{max.}$ (95% EtOH) 276 nm. ($\log_{10}\varepsilon$, 4.19).

n.m.r. (CCl_4) : δ 1.12 (3H, t), 2.0 (2H, m, $CH_2.\underline{CH_2}.CH_2$), 3.11 (2H, t, $COCH_2CH_2$, J = 7Hz), 3.48 (2H, q), 3.54 (2H, t, OCH_2CH_2, J = 6.5Hz), 4.15 (2H, s), 7.01 (1H, s, oxazole H-4), 7.48 (5H, brs) p.p.m.

Purification of the crude product was effected using column chromatography and therefore avoided the possibility of decomposition on distillation. A proportion of the crude mixture (5.5g.) was dissolved in a minimum of toluene and applied to a column of silica gel (250g., Davison, grade 923, 100-200 mesh). The column was eluted with toluene-chloroform mixtures and gave 2.73g. of

the oxazole (51) pure enough for cyclisation.

2-Methyloxazolo[3,2-a]pyridinium bromide (34)

Prepared from 2-(4-ethoxybutyryl)-5-phenyloxazole (50) (0.9g.) using the method described previously for the synthesis of 2-phenyloxazolo[3,2-a]pyridinium bromide (20, X = Br). The crude product was triturated with acetone to give almost pure bromide (34) (0.98g., quantitative). Recrystallisation from absolute ethanol/ethyl acetate gave the bromide (34) as colourless prisms, m.p. 233-234°.

Found: C, 44.7; H, 3.65; N, 6.5%

C_8H_8BrNO requires: C, 44.9; H, 3.75; N, 6.55%

$\lambda_{max.}$ (95% EtOH) 261 nm. ($\log_{10}\varepsilon$, 3.04).

$\lambda_{max.}$ (95% EtOH/aq.NaOH) 306 nm. ($\log_{10}\varepsilon$, 2.79).

The n.m.r. details are given in Table I (p. 89).

Perchlorate

Recrystallised from absolute ethanol as colourless rhombs, m.p. 130-131° (lit.,[13] m.p. 130-133°).

Found: C, 41.2; H, 3.7; N, 5.9%

$C_8H_8ClNO_5$ requires: C, 41.1; H, 3.45; N, 6.0%

2-(4-Bromobutyryl)-5-methyloxazole (54) and 5,6,7,8-tetrahydro-2-methyl-8-oxo-oxazolo[3,2-a]pyridinium bromide (53)

A solution of the ethoxybutyryloxazole (50) (1.5g.) in 48% hydrobromic acid (60 ml.) was boiled for 2.5 hr., allowing the ethyl bromide formed initially to escape from the system. The acid was removed under reduced pressure and the residue dried by adding absolute ethanol and redistilling. Trituration of the oily residue with acetone gave a light brown solid. This solid was dissolved in a minimum of water and treated with solid sodium carbonate until effervescence ceased. Extraction with chloroform separated the uncyclised from the cyclised material. The chloroform extracts were dried (Na_2SO_4) and evaporated under reduced pressure giving the crude product as a light brown oil (0.6g.). T.l.c. of the product, eluting with chloroform, showed one major component.

A sample of the crude oil (0.18g.) was applied to one preparative plate and eluted with chloroform. The bromobutyryl-oxazole (54) was obtained as a colourless oil (0.088g.).

Found: C, 41.25; H, 4.5; N, 5.7%

$C_8H_{10}BrNO_2$ requires: C, 41.4; H, 4.3; N, 6.05%

$\nu_{max.}$ (Film) 1700 $cm.^{-1}$ (CO).

Mass spectrum $^m/_e$ 234 (M+2), 232 (M^+), 177, 175, 152, 151, 149, 125, 123, 121, 97, 69, 41.

n.m.r. (CCl_4) : δ 2.32 (2H, m, $CH_2.\underline{CH_2}.CH_2Br$), 2.51 (3H, brs, CH_3), 3.25 (2H, t, $\underline{CH_2}CO$, J = 7Hz), 3.58 (2H, t, CH_2Br), 7.08 (1H, s, oxazole H-4) p.p.m.

Evaporation of the aqueous layer, extraction of the residual solid with absolute ethanol and evaporation gave a deliquescent solid whose n.m.r. spectrum was that expected for the cyclic ketone (53).

n.m.r. (D_2O) : δ 2.2-2.5 (2H, m), 2.3 (3H, s), 3.07 (2H, t, $CO\underline{CH_2}$, J = 6Hz), 4.27 (2H, t, $\overset{+}{N}CH_2$, J = 5Hz), 7.8 (1H, s, oxazole H-4) p.p.m.

Attempted cyclisation of 2-(4-bromobutyryl)-5-methyloxazole (54)

A solution of the bromo-amine (54) (0.1g.) in absolute ethanol (10 ml.) was boiled for 6 hr. Evaporation under reduced pressure gave a brown oil (0.09g.). T.l.c. and n.m.r. analysis indicated unchanged starting material.

Conversion of the salt mixture (52) and (53) to 2-methyloxazolo-[3,2-a]pyridinium bromide (34)

The mixture of cyclised (53) and uncyclised ketones (52) (1.14g.) was treated with boiling acetic anhydride (50 ml.) for 2 hr. The acetic anhydride was removed under reduced pressure, the residue

boiled with absolute ethanol and re-evaporated to remove traces of acetic anhydride. The crude residue was triturated with pure acetone to give almost pure 2-methyloxazolo[3,2-a]pyridinium bromide (34) (0.9g., quantitative).

The product was identical with samples obtained directly from 2-(4-ethoxybutyryl)-5-methyloxazole (50).

2-Benzyloxazolo[3,2-a]pyridinium bromide (35)

Prepared from 5-benzyl-2-(4-ethoxybutyryl)oxazole (51) (1.0g.) using the method described previously for the synthesis of compound (20, X = Br). The crude product was triturated with acetone to give an almost colourless solid (0.76g., 72%). Recrystallisation from absolute ethanol gave colourless prisms of the bromide (35), m.p. 190-192°.

Found: C, 56.5; H, 4.4; N, 4.5%

$2C_{14}H_{12}BrNO.H_2O$ requires: C, 56.20; H, 4.35; N, 4.7%

$\lambda_{max.}$ (95% EtOH) 264 nm. ($\log_{10}\varepsilon$, 3.09).

$\lambda_{max.}$ (95% EtOH/aq.NaOH) 305 nm. ($\log_{10}\varepsilon$, 3.73).

Details of n.m.r. in Table I (p. 89).

Attempted bromination of 2-methyl- (34) and 2-benzyloxazolo-[3,2-a]pyridinium bromide (35)

Both the 2-methyl- (34) and the 2-benzyl (35) aromatic salts were treated under the following conditions:

(a) Bromine in boiling water for 2 hr.

(b) Bromine in boiling 48% hydrobromic acid for 2 hr.

(c) Bromine in glacial acetic acid at 100° for 2 hr.

Under all conditions the aromatic salts were recovered unchanged.

Hydrogenations of 2-benzyloxazolo[3,2-a]pyridinium bromide (35)

(a) A solution of 2-benzyloxazolopyridinium bromide (35) (0.29g.) in 95% ethanol (20 ml.) containing 10% palladium on charcoal catalyst (0.1g.) was hydrogenated at atmospheric temperature and pressure for 2 hr. No absorption of hydrogen was observed and unchanged starting material was recovered.

(b) A solution of the bromide (35) (0.435g.) in 95% ethanol (30 ml.) containing Adams' catalyst (0.1g.) was similarly hydrogenated until the uptake of hydrogen ceased (7 molar equivalents). The catalyst was filtered off and the filtrate evaporated under reduced pressure to leave a pale yellow oil. T.l.c. eluting with benzene - 50% acetone showed the presence of one major component and a minor component that remained at the base of the plate.

The mixture (0.3g.) was applied to one preparative plate and eluted with benzene - 50% acetone. The major band was separated as a colourless oil.

Bulb-tube distillation gave 1-(3-cyclohexylpropyl)-2-piperidone (57) b.p. 140°/0.07 mm., (0.13g., 40%).

Found: N, 6.1%

$C_{14}H_{25}NO$ requires: N, 6.25%

$\nu_{max.}$ (Film) 1640 cm.$^{-1}$, ($CHCl_3$) 1620 cm.$^{-1}$

n.m.r. (CCl_4) : δ 0.8-2.0 (19H, m), 2.2 (2H, m, $COCH_2$), 3.2 (4H, m, $N(CH_2)_2$) p.p.m.

Mass spectrum $^m/e$ 223, 140, 127, 126, 113, 112, 84 (requires M^+ 223).

Hydrogenation of 2-phenyloxazolo[3,2-a]pyridinium bromide (20, X = Br)

A solution of the bromide (20, X = Br) (0.522g.) was similarly hydrogenated using Adams' catalyst (0.1g.) in 95% ethanol. Usual work up gave an almost colourless oil which was purified using P.L.C. eluting with acetone twice.

Bulb-tube distillation gave 1-(2-cyclohexylethyl)-2-piperidone (58) with b.p. 125°/0.1 mm. (0.18g., 46%).

Found: C, 74.2; H, 11.2; N, 6.2%

$C_{13}H_{23}NO$ requires: C, 74.6; H, 11.1; N, 6.7%

$\nu_{max.}$ (Film) 1642 cm.$^{-1}$, ($CHCl_3$) 1622 cm.$^{-1}$

n.m.r. (CCl_4) : δ 0.8-2.0 (19H, m), 2.2 (2H, m, $COCH_2$), 3.15-3.5 (4H, m, $N(CH_2)_2$) p.p.m.

Mass spectrum $^m/e$ 209, 148, 126, 113, 112, 105, 100, 84 (requires M^+ 209).

Attempted oxidation of 2-benzyloxazolo[3,2-a]pyridinium bromide (35)

(a) A mixture of the bromide (0.145g.), selenium dioxide (0.083g.) and pyridine (20 ml.) was stirred at room temperature for 2 hr. Evaporation under reduced pressure gave unchanged starting material.

(b) Similar quantities as in (a) were stirred and heated at 115° for 1 hr. Evaporation under reduced pressure gave a black intractable tar. The spectral characteristics of this residue were ill defined and attempts at purification failed. No further investigations were pursued.

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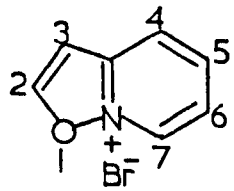
P A R T I I I

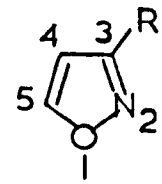
DISCUSSION

Studies on the synthesis of Isoxazolo[2,3-a]pyridinium salts (1)

As mentioned previously in the introduction, no synthesis of an isoxazolo[2,3-a]pyridinium salt (1), or any substituted analogues, has so far been reported. The iso-electronic relationship with the quinolizinium and oxazolo[3,2-a]pyridinium systems (see introduction) suggest that it should be stable. Initially an attempt has been made to synthesise the parent system (1) by application of the Glover and Jones quinolizinium route[1] starting from 3-cyano-isoxazole (2).



(1)



(2) R = CN

(3) R = CO_2Et or CO_2Me

(4) R = $CONH_2$

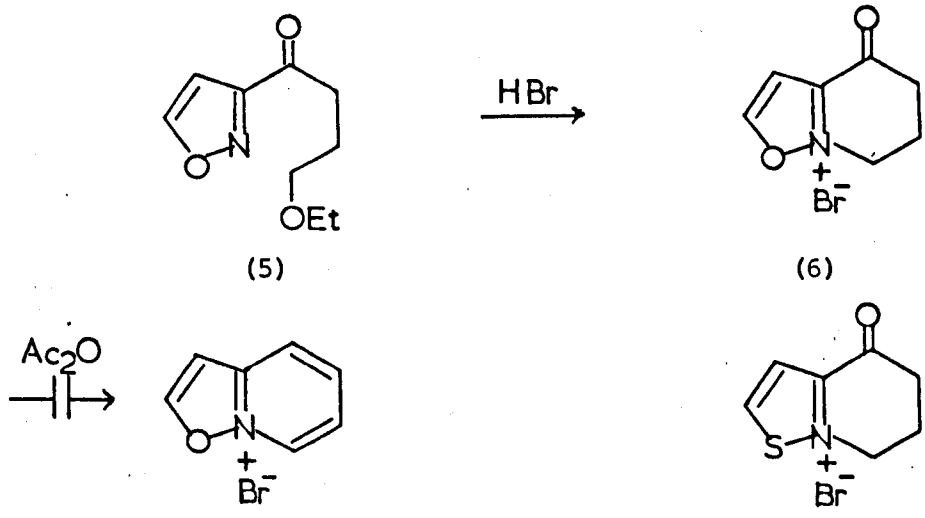
The 3-cyano-isoxazole (2) was obtained in good yield from the isoxazole esters (3) via the intermediate 3-carboxamide (4) as described in Part I of this thesis.

Due to the known sensitivity of isoxazoles towards nucleophiles,[2] an ethereal solution of 3-cyano-isoxazole (2) was treated with 3-ethoxypropylmagnesium bromide at -12° giving 3-(4-ethoxybutyryl)isoxazole (5) in 52% yield. The n.m.r. spectrum in carbon tetrachloride was consistent with the structure of the butyrylisoxazole (5) and the infrared spectrum showed a strong carbonyl band at 1703 cm^{-1}.

Treatment of the keto-ether (5) with boiling 48% hydrobromic acid and usual work up gave 4,5,6,7-tetrahydro-4-oxo-isoxazolo[2,3-a]pyridinium bromide (6) in high yield. The structure of the product (6) was confirmed by the n.m.r. spectrum in trifluoroacetic acid. The 5 and 7 methylene groups were shown as triplets at δ3.05 and 5.03 p.p.m. respectively with a coupling of 6 Hz. The multiplet centred at δ2.82 p.p.m. was assigned to the absorption of the 6 methylene group. The two remaining finely split singlets at δ7.48 and 9.06 p.p.m. are due to the absorptions of the isoxazole 3 and 2 protons respectively with a coupling $J_{2,3}$ = 2 Hz. The infrared spectrum showed a carbonyl band at 1725 cm^{-1}.

Treatment of the cyclic ketone (6) with boiling acetic anhydride led to an immediate darkening of the mixture. After 5 minutes boiling the solvent was removed and a dark brown oil/solid was isolated. The crude product was insoluble in water, soluble in organic solvents and showed a broad infrared absorption at 1768 cm^{-1} assigned initially to the carbonyl stretching of an acetoxy group.

The n.m.r. spectrum in deuterochloroform showed no absorptions due to aromatic protons.



(5) (6)

(1) (7)

Jones and Jones[3] have reported that treatment of the corresponding isothiazolo ketone (7) with boiling acetic anhydride gave a similar crude product that contained a carbonyl band at 1760 cm^{-1} in the infrared. They suggested that the isothiazolium ring was degraded under these conditions and a pure product was not isolated.

Examination of the crude product from the attempted aromatisation of the cyclic ketone (6) by t.l.c. showed the presence of one major and one minor component with a considerable amount of

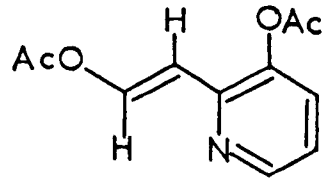
polymeric material remaining at the base line.

The components were separated by P.L.C. eluting with chloroform-10% ethyl acetate.

The upper band (I) was isolated as a black tar which showed a poorly resolved n.m.r. spectrum, but its aromatic pattern and two methyl ester singlets at δ2.2 and 2.35 p.p.m. suggested the product to be 3-acetoxy-2(2-acetoxyvinyl)pyridine (8).

The major band (II, 47%) was isolated as a pale yellow solid which showed infrared absorptions at 1778, 1684 and 1590 cm^{-1}. The ultraviolet spectrum showed an irreversible change on addition of base to the solution. The micro-analytical and mass spectral data confirm the molecular formula of the product to be $C_9H_9NO_3$. Further structural evidence was obtained from the mass spectrum (Figure 1), which showed a M-42 peak at $^m/e$ 137 and the base peak at $^m/e$ 43 indicative of an acetate group. The n.m.r. spectrum of this product, which will be referred to as compound A, is shown in Figure 2. The n.m.r. data are discussed below in the light of the proposed structures (9), (10) and (11).

The remaining material on the base line of the plate appeared to be polymeric in nature and constituted approximately 50% of the mixture.



(8)

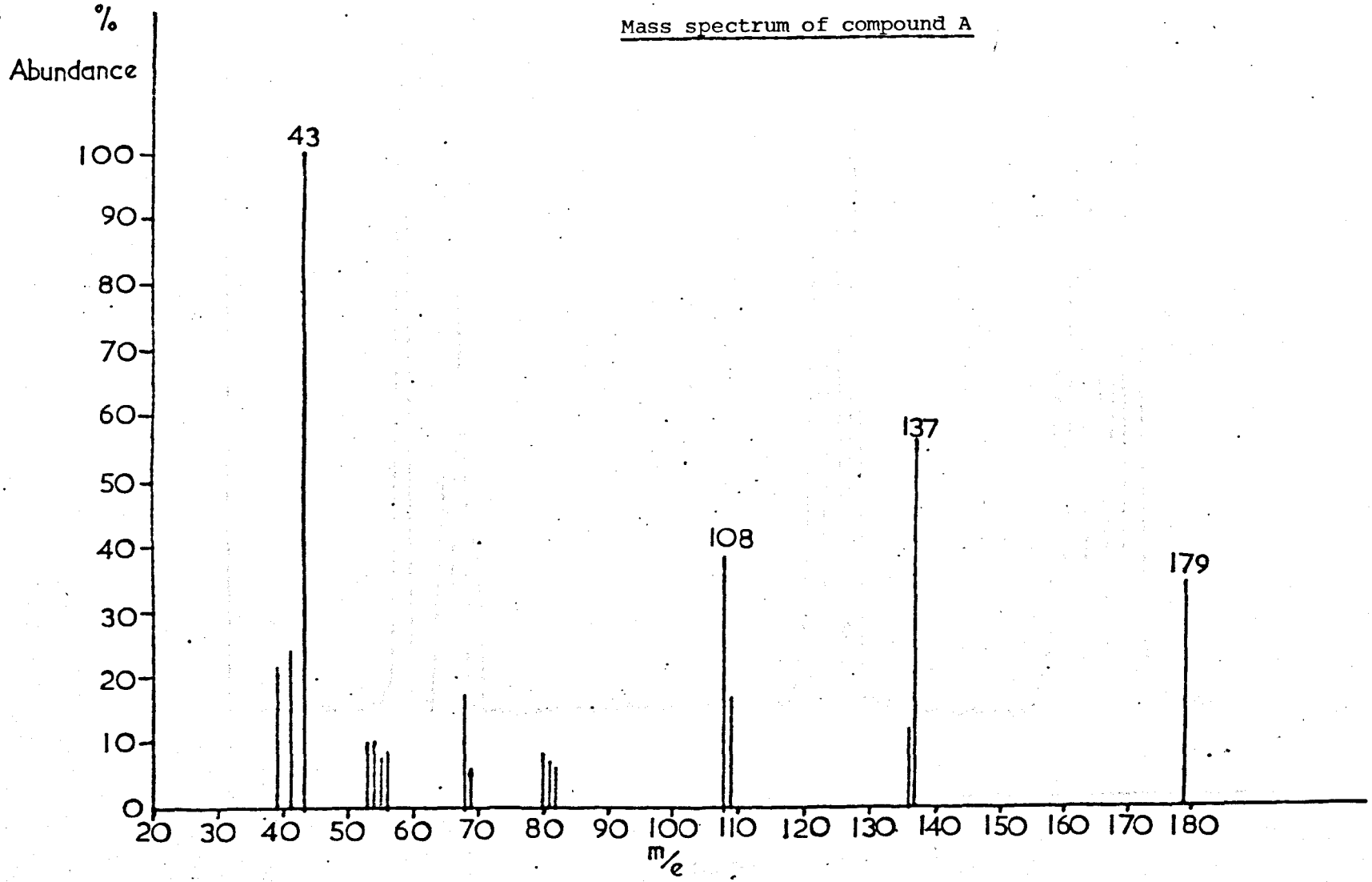

Mass spectrum of compound A
%
Abundance
100
90
80
70
60
50
40
30
20
10
0
43
108
137
179
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
m/e

Figure 1

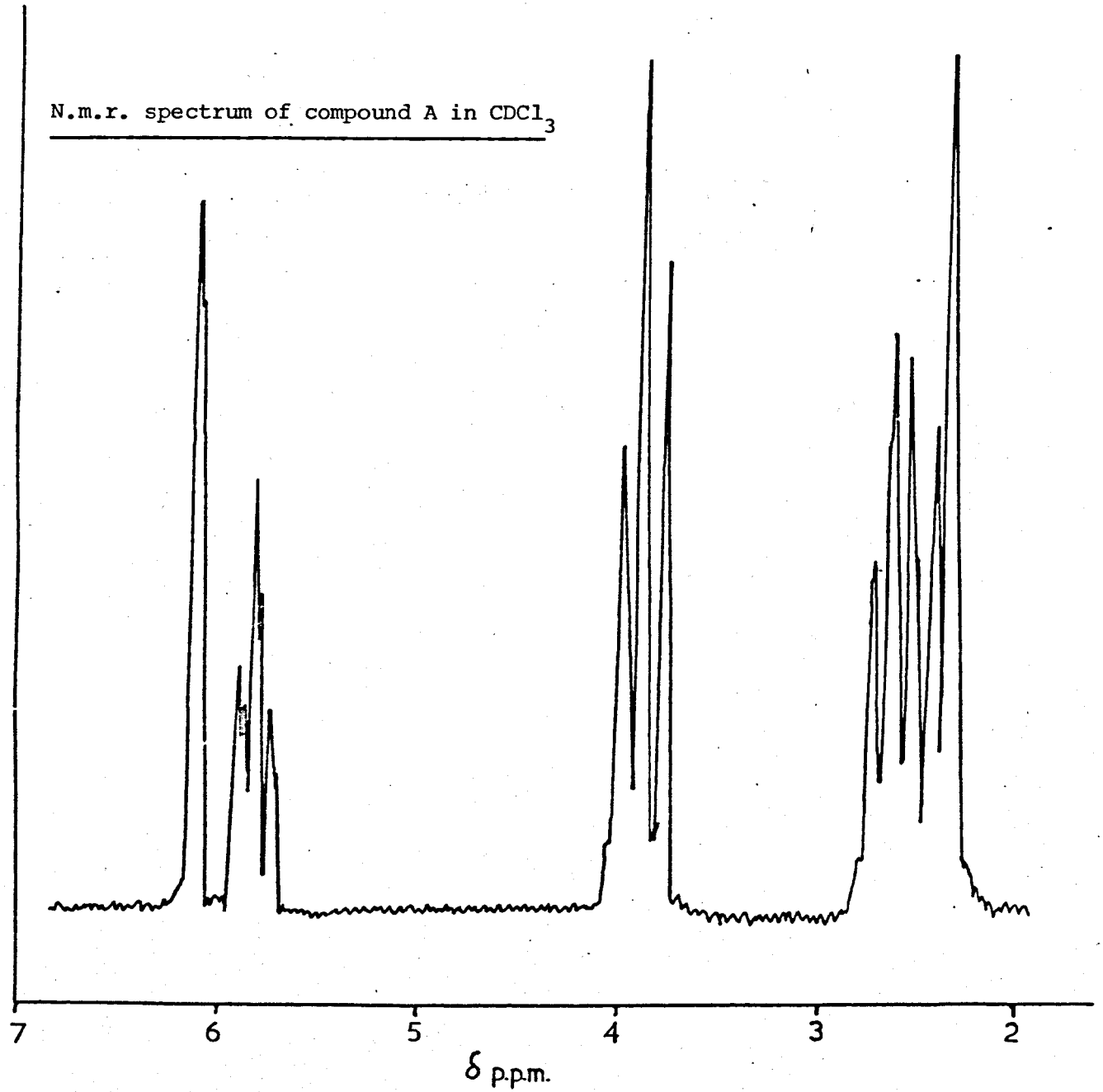
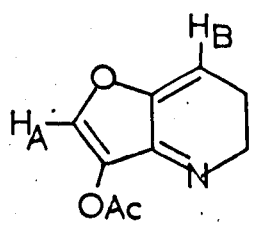


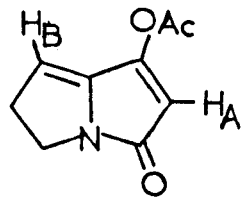
Figure 2

Studies on the elucidiation of the structure of compound A

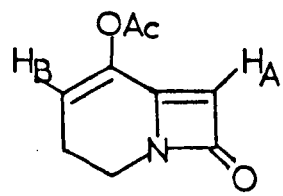
The three isomeric structures shown by compounds (9), (10) and (11) were proposed for compound A on the basis of the original spectral evidence.



(9)



(10)



(11)

All three compounds have structures that contain acetate groups indicated by the three proton absorption at δ2.34 p.p.m. in the n.m.r. spectrum (Figure 2). Each structure has protons H_A and H_B capable of the long range coupling of 1 Hz shown by the one proton absorptions at δ6.1 and 5.8 p.p.m. The latter absorption at δ5.8 p.p.m. is shown as a broadened triplet (J = 5 Hz) suggesting a methine proton adjacent to a methylene group.

The chemical shift of the two proton absorption at δ3.9 p.p.m. shown as a triplet (J = 6 Hz) indicated a methylene group situated between a nitrogen and another methylene group. The latter methylene absorption would then explain the remaining two proton multiplet at δ2.6 p.p.m. which appears to be deshielded by neighbouring unsaturation.

Reactions of compound A

The structure of compound (9) contains a dihydropyridine ring which would be expected to readily undergo dehydrogenation to the corresponding pyridine. In order to test the validity of this structure, compound A was subjected to dehydrogenation using 2,3-dicyano-5,6-dichloro-1,4-benzoquinone in boiling benzene. After 16 hr. compound A was recovered unchanged.

A dihydropyridine structure containing cis double bonds would also be expected to undergo a Diels-Alder addition with a suitable dienophile. Treatment of compound A with dimethylacetylene dicarboxylate in boiling benzene gave unchanged starting material after 20 hr.

The failure of compound A to undergo either dehydrogenation or addition reactions rules out the possibility of compound A having the dihydropyridine structure shown by compound (9).

Compound A was next subjected to a series of reactions to enable a further investigation of its structure. The implications from the results are discussed later in the light of the proposed structures (10) and (11).

(a) An ethanolic solution of compound A was treated dropwise with dilute sodium hydroxide solution and the rapid course of the reaction monitored using ultraviolet spectroscopy. On work up a

pale yellow solid was obtained. Exact mass determinations confirmed a molecular formula of $C_7H_7NO_2$, and indicates a loss of $-COCH_2$ from the original compound A. The complete breakdown pattern, shown in Figure 3, contains peaks at $^m/_e$ 108 and $^m/_e$ 80 indicating loss of a CHO fragment and further loss of CO. Comparison of the n.m.r. spectrum (Figure 4) with that of compound A (Figure 2) showed loss of an acetate methyl absorption at δ2.34 p.p.m. and the appearance of a one proton broad multiplet centred at δ6.00 p.p.m. which exchanged on addition of deuterium oxide. The finely split one proton singlet originally at δ6.1 p.p.m. in compound A is now shown at δ4.72 p.p.m. Presumably the loss of the acetyl group has led to the removal of its anisotropic deshielding effect on this proton. The remaining absorptions are shown as multiplets centred at δ2.5 and 3.4 p.p.m. both integrating for two protons. The infrared spectrum shows strong absorptions at 3420, 1768 and 1620 cm^{-1} indicative of a compound containing a hydroxyl group, a carbonyl group and possessing some degree of unsaturation.

Mass spectrum of hydrolysis product (from compound A).

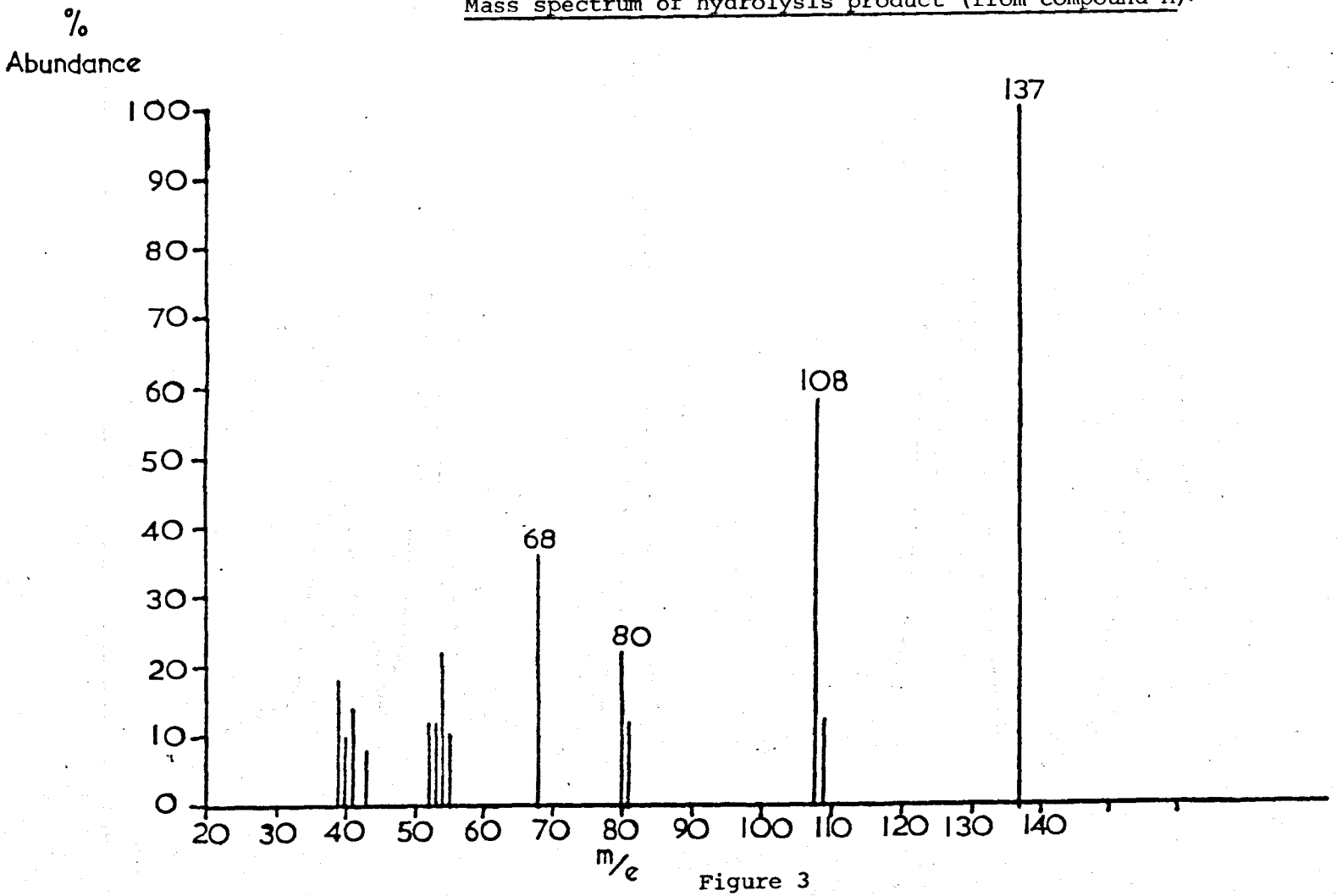


Figure 3

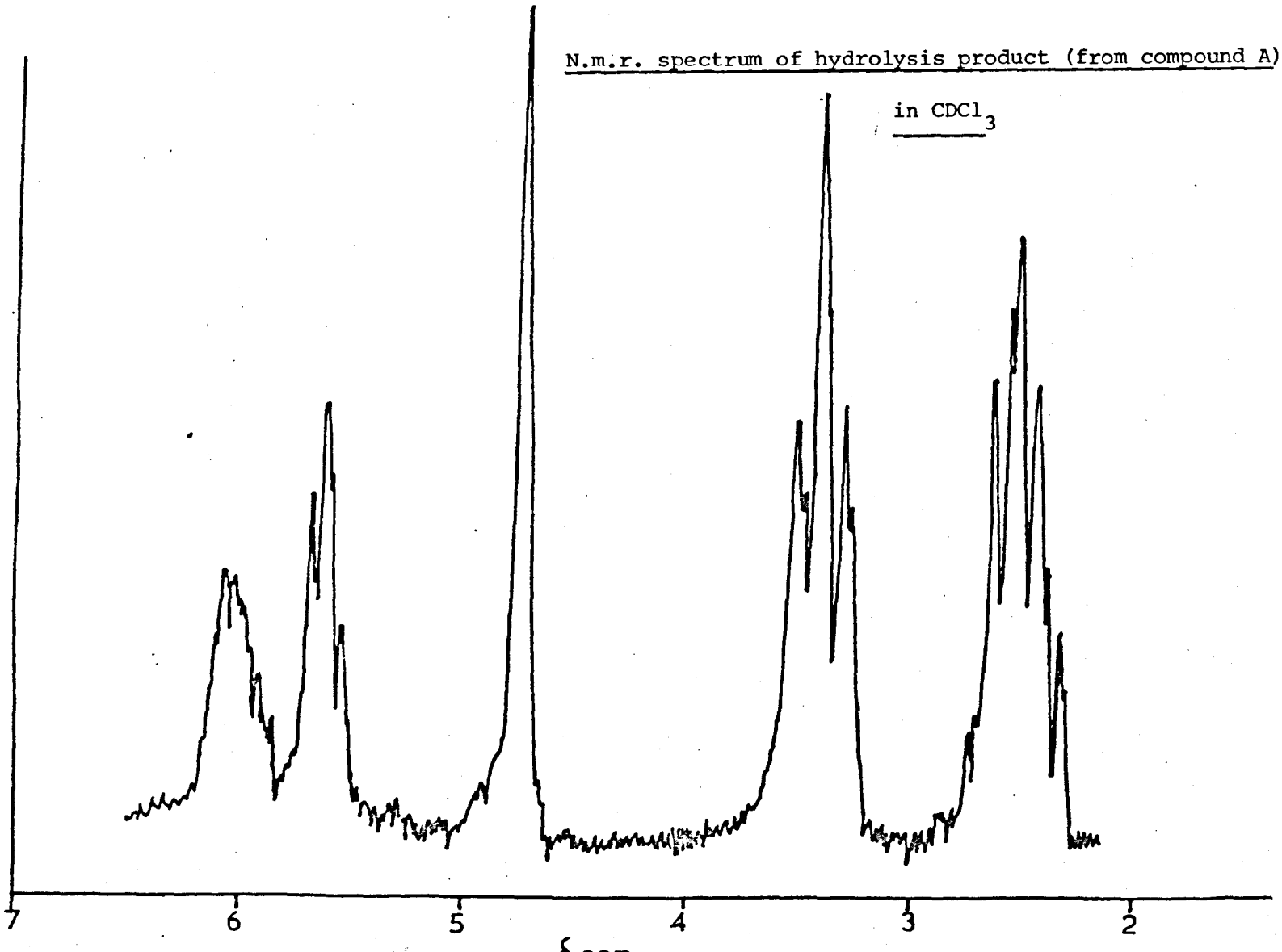

N.m.r. spectrum of hydrolysis product (from compound A)
in $CDCl_3$
7
6
5
4
3
2
δ p.p.m.

Figure 4

(b) Hydrogenation of compound A using 10% palladium on charcoal led to absorption of one mole of hydrogen. Purification of the product using P.L.C. gave a colourless solid (compound B). The analytical and mass spectral data both confirmed the uptake of one mole of hydrogen with a formula of $C_9H_{11}NO_3$. The n.m.r. spectrum of compound B in deuterochloroform (Figure 5) shows a similar one proton broadened singlet and acetate methyl absorption at δ5.9 and 2.3 p.p.m. to that observed in the spectrum of compound A (Figure 2). The three multiplets centred at δ1.93, ~ 2.5 (obscured) and 3.8 p.p.m. each integrate for two protons. The remaining one proton absorption at δ4.85 p.p.m. consists of two broadened doublets with coupling of 6 Hz. The ultraviolet spectrum showed an irreversible change on addition of base. The infrared spectrum shows strong absorptions at 1740, 1687 and 1610 cm^{-1}.

N.m.r. spectrum of compound B in $CDCl_3$

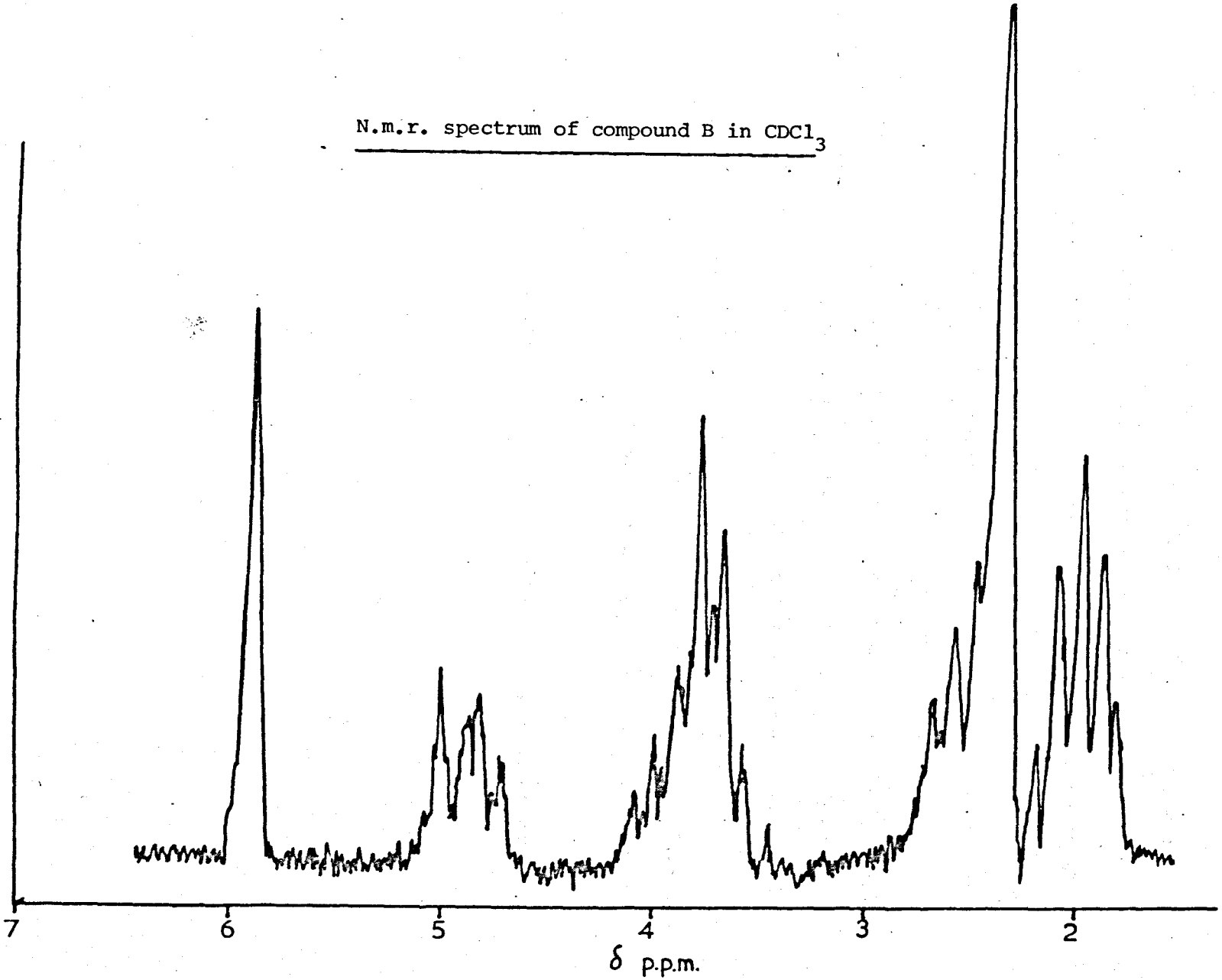


Figure 5

(c) A similar rapid base hydrolysis of compound B was monitored using ultraviolet spectroscopy. After work up the product was obtained as a colourless solid. The mass spectral and micro-analytical data confirmed a formula $C_7H_9NO_2$ indicating the loss of an acetyl group. The n.m.r. spectrum in deuterochloroform (Figure 6) showed the loss of the acetate methyl absorption and the appearance of an exchangeable hydroxyl group at δ6.18 p.p.m. Again the loss of the anisotropic effect of the acetyl carbonyl has resulted in the one proton absorption originally at δ5.9 p.p.m. moving upfield to δ4.63 p.p.m. The remaining absorptions are shown as complex multiplets at δ1.2-2.65 p.p.m. and at δ3.3 p.p.m. integrating for four and two protons respectively.

The infrared spectrum contained absorptions at 3395, 1720 and 1620 cm^{-1}.

N.m.r. spectrum of hydrolysis product (from compound B) in $CDCl_3$

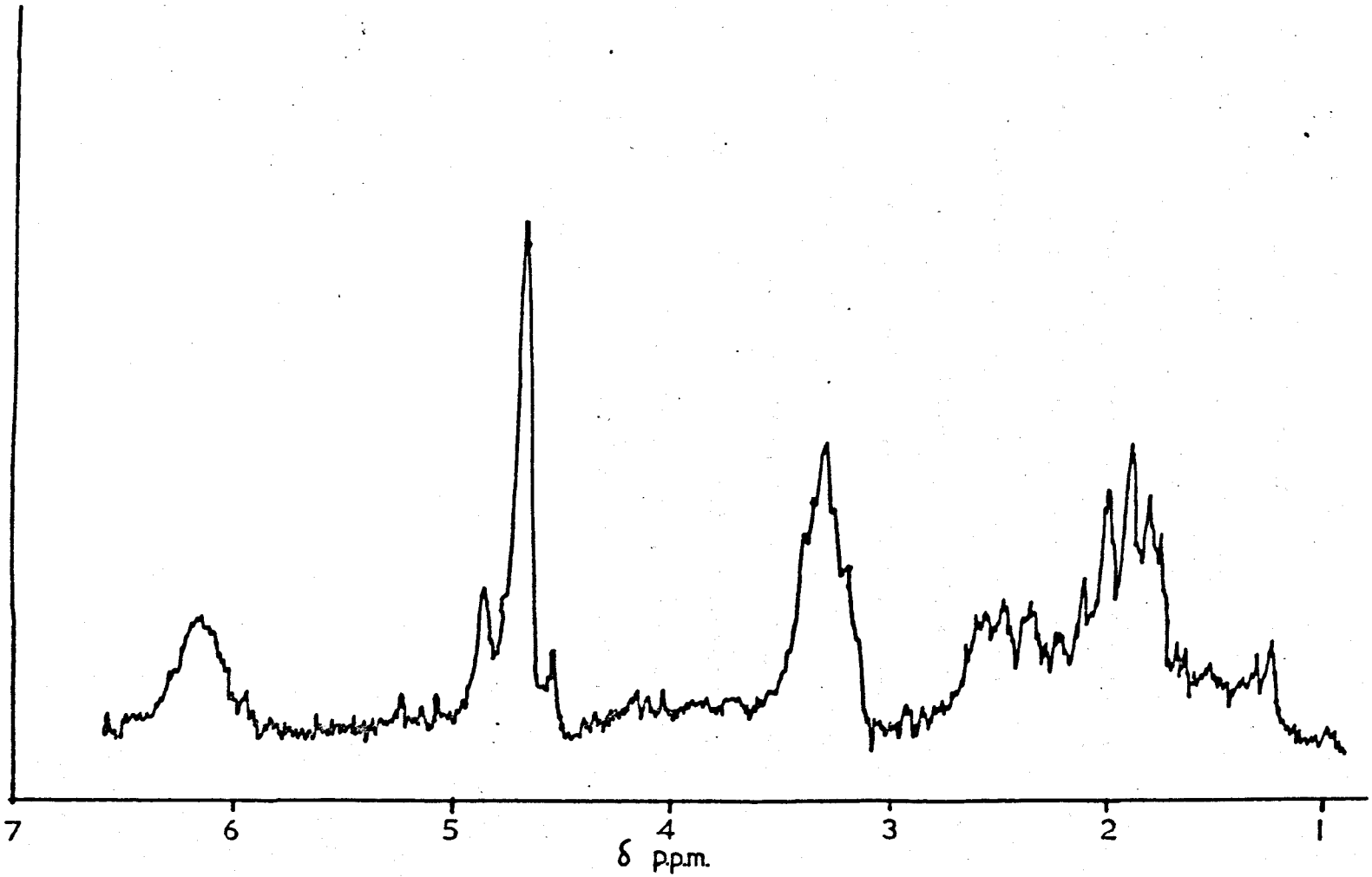


Figure 6

(d) Hydrogenation of compound A using Adams' catalyst led to the uptake of 3 molar equivalents of hydrogen. Accurate mass determinations showed a molecular ion corresponding to the formula $C_9H_{15}NO_3$ thus confirming the absorption of three moles of hydrogen. The n.m.r. spectrum of the purified hydrogenation product (compound C) in deuterochloroform is shown in Figure 7. The most noticeable feature was the predominance of complex multiplets between δ2.4 and 5.4 p.p.m. indicating non equivalence of the protons. The broad absorption at δ1.25 p.p.m. integrates for six protons and suggests three methylene groups having a similar environment. The one proton absorption at δ9.6 p.p.m. was exchangeable and its chemical shift indicated the presence of a secondary amide NH. The infrared spectrum showed strong absorptions at 1710 and 1620 cm^{-1} and a broad absorption between 3100 to 3340 cm^{-1}.

N.m.r. spectrum of compound C in $CDCl_3$

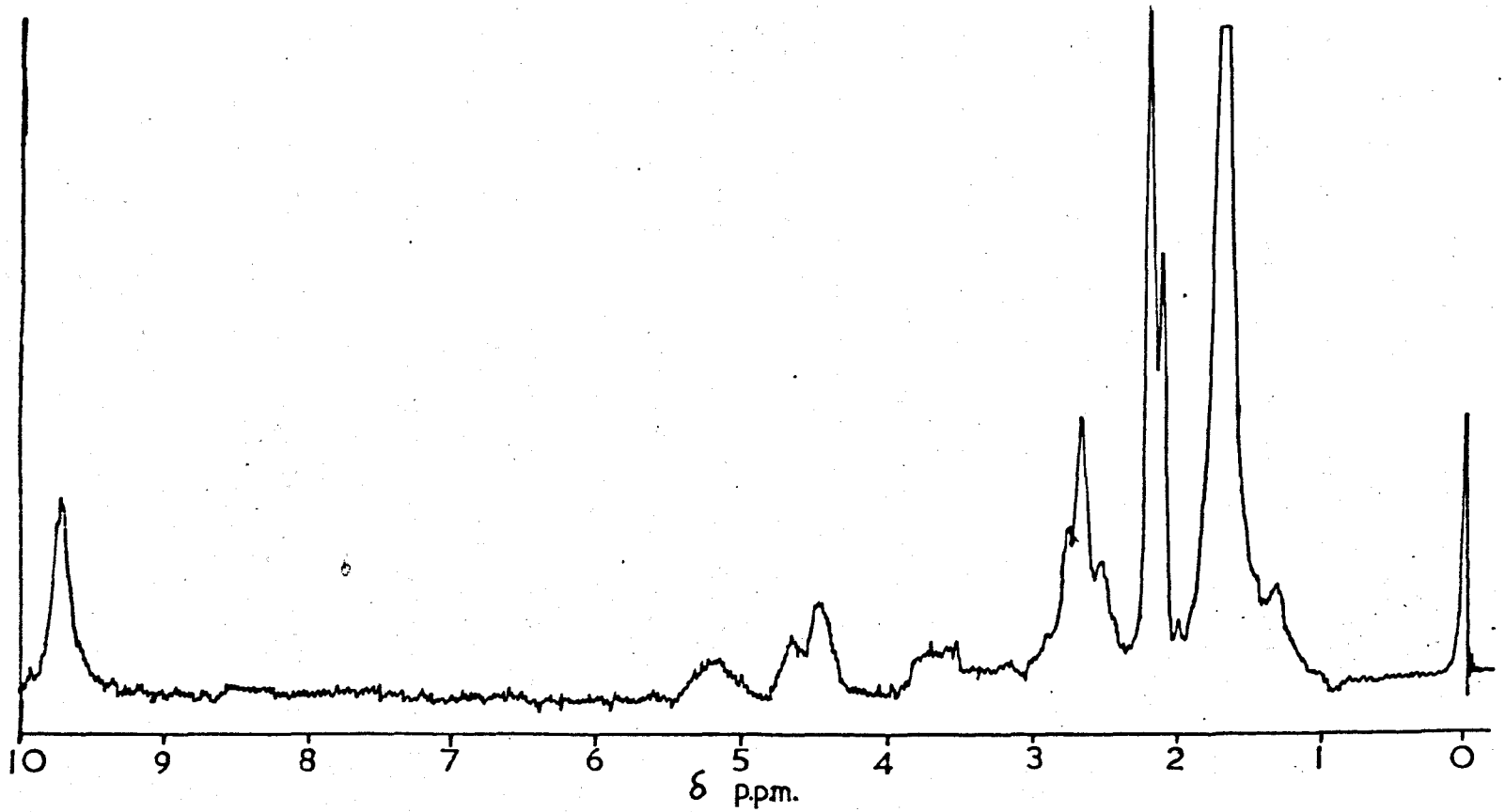
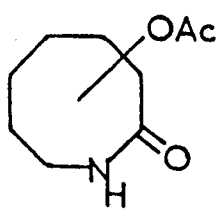


Figure 7

(e) Hydrolysis of compound C was ineffective using ethanolic sodium hydroxide solution at room temperature. However treatment of compound C with base and ethanol at 100° for 2 hr. afforded a colourless glass. The infrared showed loss of the carbonyl band at 1710 cm^{-1} but retention of the absorption at 1610 cm^{-1}. The n.m.r. and mass spectra were ill defined and failure to purify the product indicated polymerisation may have occurred.

It was still possible to explain the majority of reactions on compound A in terms of the structures of compounds (10) and (11). However reaction (d) in which compound A was hydrogenated using Adams' catalyst appeared to be more novel. The n.m.r. spectrum of the product (compound C) showed a broad six proton absorption at δ1.25 p.p.m. which indicated a long saturated hydrocarbon chain. The infrared spectrum showed an absorption at 1620 cm^{-1} that was consistent with a cyclic amide of up to eight members. Huisgen et al[4] have shown that cyclic amides of this size exist in the cis configuration and that the amide II band (~ 1520 cm^{-1}) is absent from cis lactams. On consideration of the molecular formula $C_9H_{15}NO_3$, the substituted cyclic amide (12) was tentatively assigned as the structure of compound C.



(12)

Cyclic amides of this structure are known to undergo polymerisation on heating and this presumably explains the inability of compound C to produce an identifiable product on attempted hydrolysis.

A search of the literature on analogous compounds produced no evidence for the possible conversion of the unsaturated pyrrolizidone structure (10) or the azetinone structure (11) to a cyclic amide structure (12) by hydrogenation. It was therefore convenient to synthesise reported compounds of similar structure to compounds (10) and (11) and to study the effect of hydrogenation. 3-Pyrrolizidone (13) was chosen as a suitable compound for comparison with the properties of compounds A and B and was prepared by the following route.

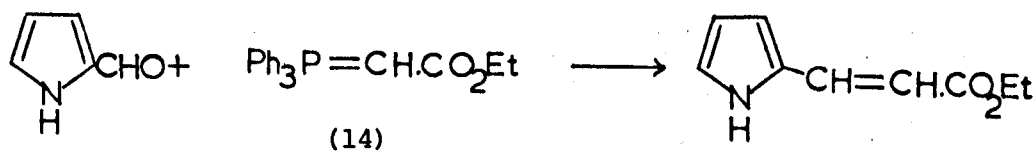
(a) Synthesis and properties of 3-pyrrolizidone (13)

Ethyl 3-(2-pyrrolyl) acrylate (15) was synthesised from 2-formylpyrrole and the phosphorane (14)[5] using a Wittig reaction.[6]

The acrylate (15) was hydrogenated to completion (3 molar equivalents) in glacial acetic acid in the presence of Adams' catalyst. Work up gave a quantitative yield of almost pure ethyl 3-(2-pyrrolidyl)propionate (16).

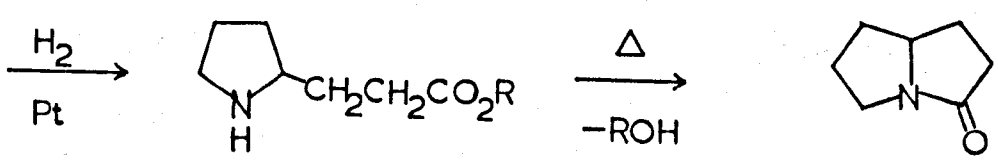
Galinovsky and Reichard[7] have hydrolysed the ester (16) to the carboxylic acid (17) which they then heated at 200° to give 3-pyrrolizidone (13) in an overall yield of 33%. The route has

been modified by heating the ester (16) in boiling xylene to give the pyrrolizidone (13) directly in an improved yield of 43%. Spectral evidence confirmed the formation of 3-pyrrolizidone (13). The mass spectrum showed the expected molecular ion at $^{m}/_{e}$ 125 and the infrared spectrum showed the presence of a tertiary amide carbonyl absorption at 1675 cm^{-1}.



(14)

(15)



(16) R = Et

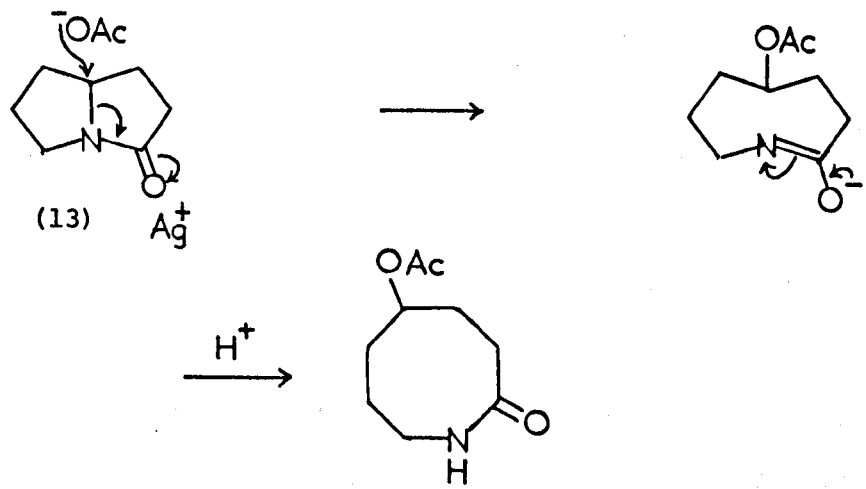
(17) R = H

(13)

Hydrogenation of 3-pyrrolizidone (13) in the presence of Adams' catalyst led to complete recovery of starting material. Kochetkov and Likhoshertov[8] have similarly found a retention of the same 5,5 ring system on reduction with lithium aluminium hydride.

Evidence therefore suggested that if compound A had the 5,6 dihydropyrrolizine type structure (10), reduction to an eight membered lactam would not proceed via the pyrrolizidone.

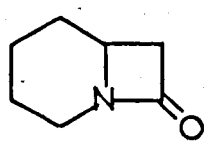
Reaction of silver acetate in glacial acetic acid on 3-pyrrolizidone (13) was also attempted but proved unsuccessful with the recovery of starting material. It was hoped that the acetate anion may have substituted at the 7a position leading to breakage of the CN bond and formation of the 5-acetoxy-2-oxo-heptamethylene-imine (18).



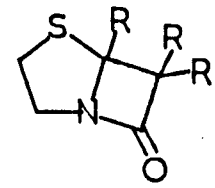
(18)

(b) Attention was next directed towards a consideration of the azetinone structure (11) proposed for compound A.

A search of the literature showed that the nearest known compound of this type was reported by Moll in 1966.[9] 1-Aza-bicyclo[4,2,0]octan-2-one (19) was reported to show an infrared carbonyl absorption at 1756 cm^{-1}. Work on the penicillins[10] has produced many compounds of structure (20), which show a strong carbonyl absorption at 1775 cm^{-1}. The position of this absorption corresponds closely to the absorption at 1778 cm^{-1} shown by compound A.



(19)



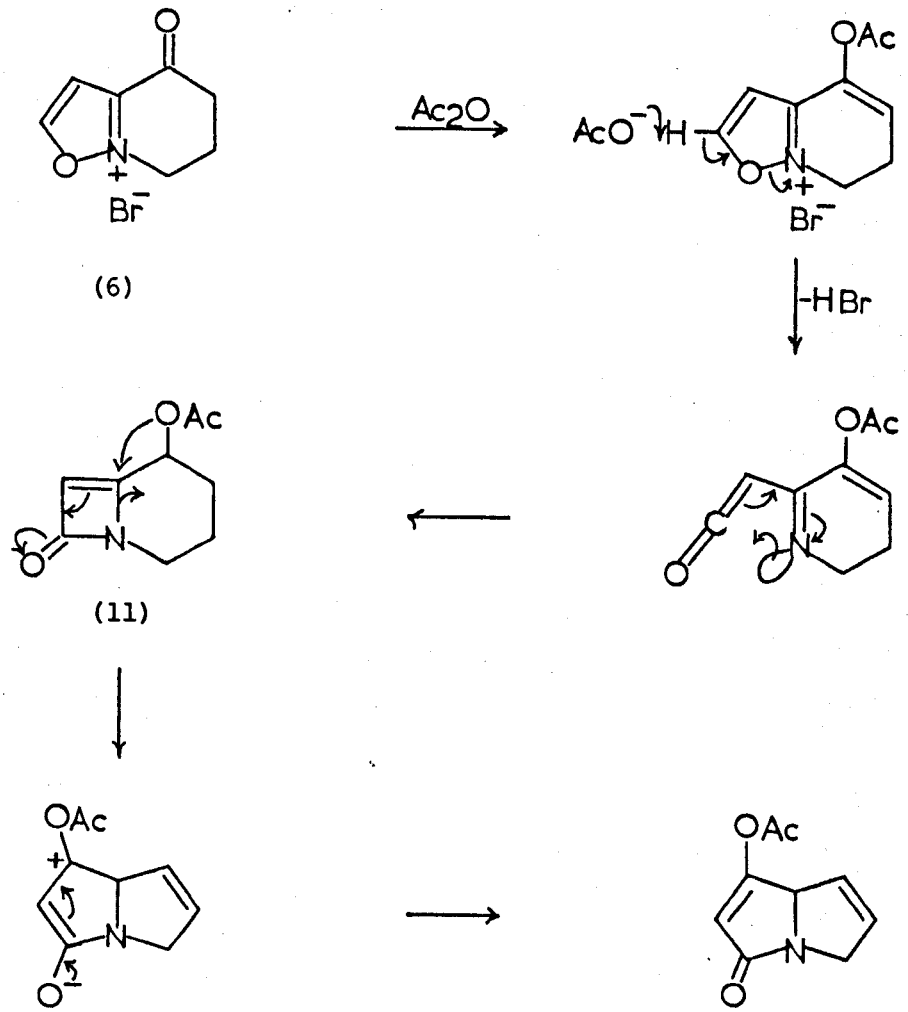
(20)

At this stage it was not possible to assign a preferred structure to compound A although the infrared characteristics indicated the azetinone structure (11). However, proposed mechanisms are tentatively suggested for the conversion of the cyclic ketone (6) to compounds (10) and (11).

The first proposed step involves enolisation of the keto group of compound (6) followed by acetylation to the enol acetate.

Similar enol acetates have been isolated in the quinolizinium series on brief boiling of the corresponding ketones with acetic anhydride.[3] The acetate anion abstracts a proton from C2 and subsequent cleavage of the weak N-O bond would then form the intermediate ketene. Cyclisation occurs by nucleophilic attack of the nitrogen onto the electron deficient carbon atom of the ketene and subsequent double-bond isomerisation yields the azetinone (11).

The formation of the 5,5 bicyclic system (10) is postulated to proceed via the azetinone (11). Nucleophilic attack by the acetate anion onto the developing carbonium ion at the bridgehead position followed by bond rearrangement yields the charged pyrrolizidol which would exist as the preferred pyrrolizidone (10).



(6)

(11)

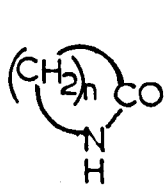
(10)

(c) Attempts have also been directed towards the synthesis of the substituted lactam (12) which has the proposed structure for compound C. The starting material required was 2-oxoheptamethylene-imine (21) which was conveniently prepared via a Schmidt reaction on cycloheptanone.[11]

The lactam (21) was brominated using a modification of the method described by Brenner and Rickenbacher[12] for the halogenation of 2-oxohexamethylene-imine (22). Bromination followed by work up gave an orange oily solid which on examination with t.l.c. indicated a mixture of two components. Separation by P.L.C. gave the dibromo compound (23) in a yield of 17%. The remaining band was shown to be unchanged starting material (21). The structure of the dibromo compound (23) was assigned from its n.m.r. spectrum that showed two complex multiplets at δ2.94-3.15 p.p.m. and δ3.38-3.75 p.p.m. corresponding to the methylene groups adjacent to nitrogen and a brominated methylene group. The structure was confirmed by the mass spectral data which showed the expected M, (M + 2), and (M + 4) peaks in the ratio of 1:2:1 which are characteristic of dibromo compounds.

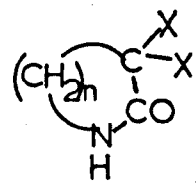
Brenner and Rickenbacher[12] have successfully removed one chlorine atom from 3,3-dichloro-2-oxohexamethylene-imine (24) using hydrogen and Raney nickel in the presence of one molar equivalent of tri-ethanolamine.

Similar hydrogenation of the dibromoketone (23) gave a 22% yield of the monobromoketone (25) first synthesised by Ottenheym and Garritsen in 1964.[13]



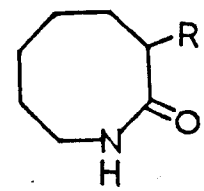
(21) n = 6

(22) n = 5



(23) n = 5, X = Br

(24) n = 4, X = Cl



(25) R = Br

(12) R = OAc

There are several reports in the literature of nucleophilic displacements where an alkyl halide is converted to an acetate by the action of silver acetate.

Treatment of the monobromoketone (25) with silver acetate in glacial acetic acid at 100° overnight gave no conversion.[14]

A similar reaction was attempted using acetic anhydride as solvent.[15] After boiling for 1 hr., evaporation and work up gave a brown tar which showed a rather ill-defined n.m.r. spectrum. The cyclic amide is presumably degraded under these conditions.

Treatment of 5-bromo-4,5,6,7-tetrahydro-4-oxo-isoxazolo[2,3-a]-pyridinium bromide (26) with acetic anhydride

Further to the previous work reported on the attempted aromatisation of the cyclic ketone (6) a similar investigation has been made on the action of acetic anhydride on the monobromoketone (26).

The cyclic ketone (6) was brominated with one mole of bromine in hydrobromic acid to give the monobromoketone (26). Treatment of the ketone (26) with boiling acetic anhydride resulted in an immediate darkening of the reaction mixture. After boiling for 2 min. work up gave a dark brown viscous oil. T.l.c. indicated the presence of three components which were separated using P.L.C. Elution with chloroform-20% ethyl acetate gave two identifiable bands.

The fastest running band (I) was isolated as a brown viscous oil of which there was insufficient to purify. Spectral evidence however, showed the structure to be 3-(1-acetoxy-2-bromo-1,3-butadien-1-yl) isoxazole (27). The mass spectrum shows the M, and (M + 2) peaks at $^{m}/e$ 257 and 259 consistent with the monobromo compound (27). The n.m.r. spectrum in deuterochloroform is shown in Figure 8 and is consistent with the formulation of the structure (27). The isoxazole protons were shown as doublets at δ6.45 and

8.54 p.p.m. with coupling of 2 Hz. The terminal vinyl protons (H_a and H_b) appear as doublets centred at δ5.62 and 5.97 p.p.m. with coupling constants $J_{Ha,Hc}$ = 10 Hz and $J_{Hb,Hc}$ = 16 Hz consistent with cis and trans olefin protons. The remaining absorption due to H_c is shown between δ7.12-7.56 p.p.m. as two doublets with the expected coupling. Only a small geminal coupling (0.5 Hz) is visible for the H_a and H_b protons. The infrared spectrum showed a strong ester carbonyl absorption at 1770 cm^{-1}.

Band II was isolated as a dark brown tar which was shown from spectral evidence to be 3-acetoxy-2-(2-acetoxyvinyl)-4-bromo-pyridine (28). The mass spectrum showed a molecular ion at $^m/e$ 299 with the expected M + 2 peak at $^m/e$ 301. Loss of two fragments of 42 from the molecular ion and a base peak at 43 indicated the presence of two acetate groups. A strong peak at $^m/e$ 78 indicates the presence of a pyridine ring. The n.m.r. spectrum in deuterochloroform is shown in Figure 9. The two absorptions at δ2.21 and 2.42 p.p.m. each integrate for three protons and are assigned to two acetate methyls. The two doublets centred at δ7.48 and 8.3 p.p.m. with coupling constants of 5 Hz are assigned to the pyridine protons H_a and H_b. The remaining two doublets centred at δ6.5 and 8.6 p.p.m. are assigned to the two vinyl protons H_d and H_c respectively with coupling $J_{c,d}$ = 12 Hz indicative of trans olefinic protons. Proton H_c is thought to be deshielded by the effect of the lone pair of the nitrogen.

N.m.r. spectrum of 3-(1-acetoxy-2-bromo-1,3-butadien-1-yl) isoxazole (27) in $CDCl_3$

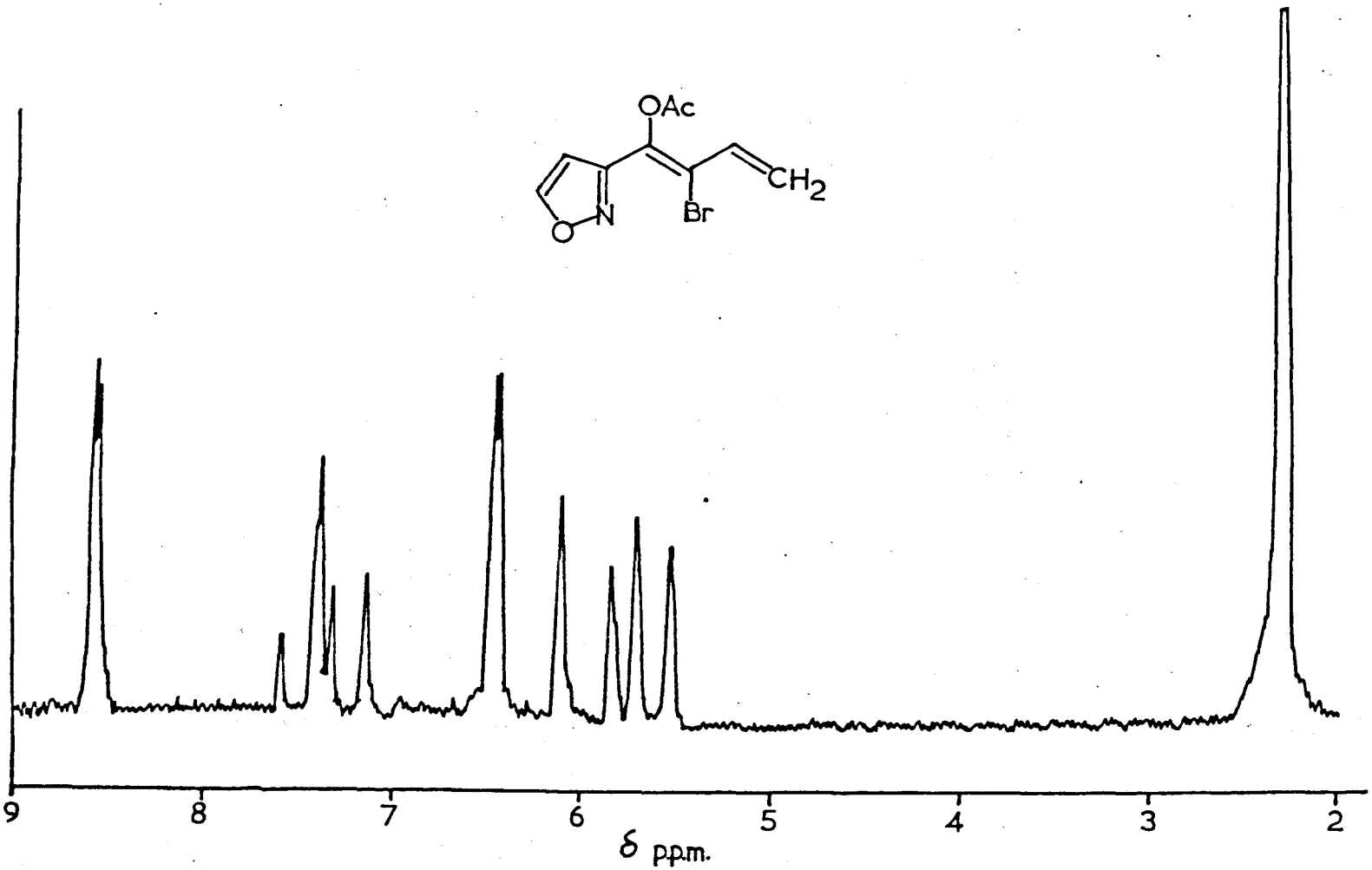


Figure 8

N.m.r. spectrum of 3-acetoxy-2-(2-acetoxyvinyl)-4-bromopyridine (28) in $CDCl_3$

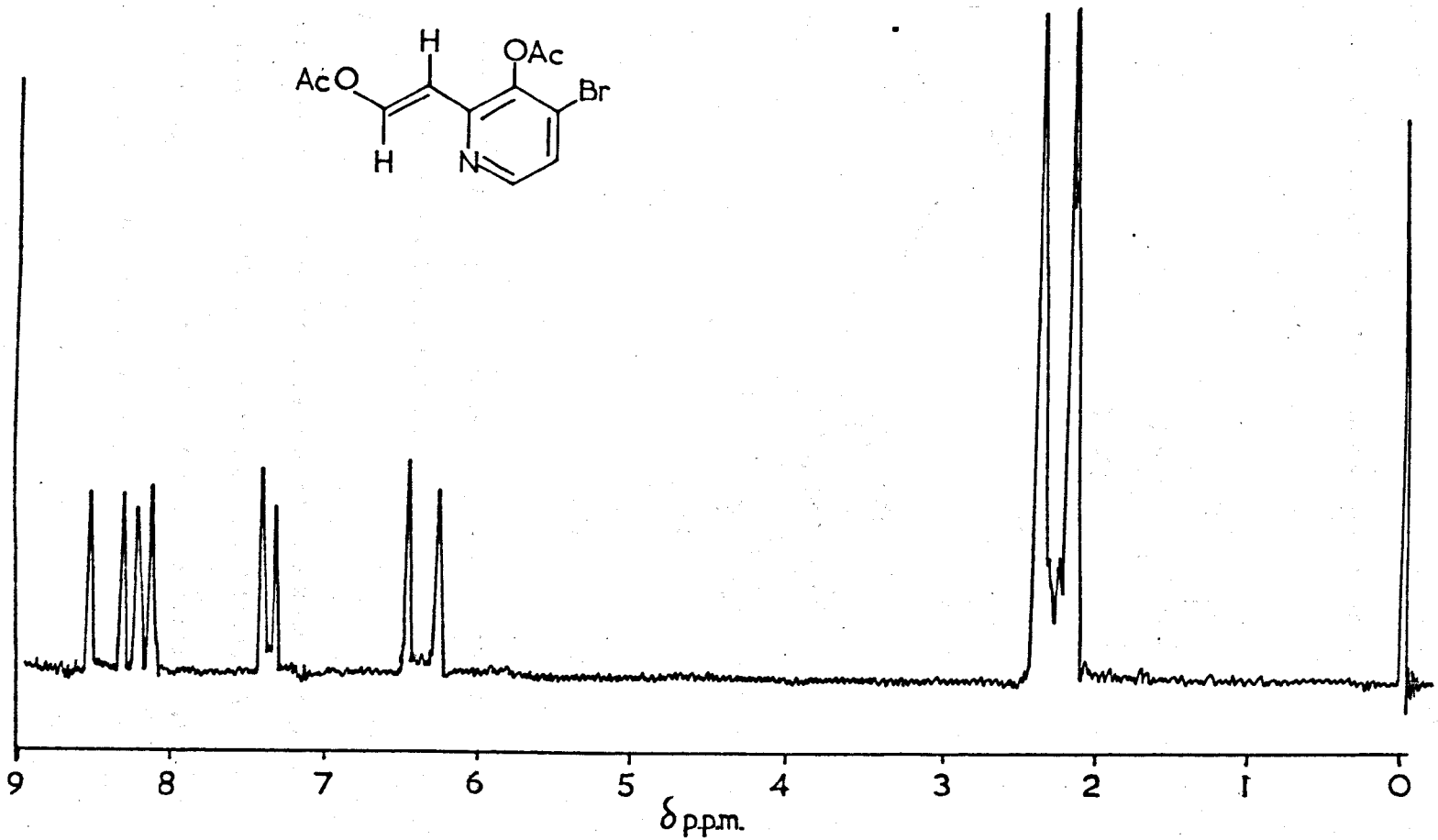
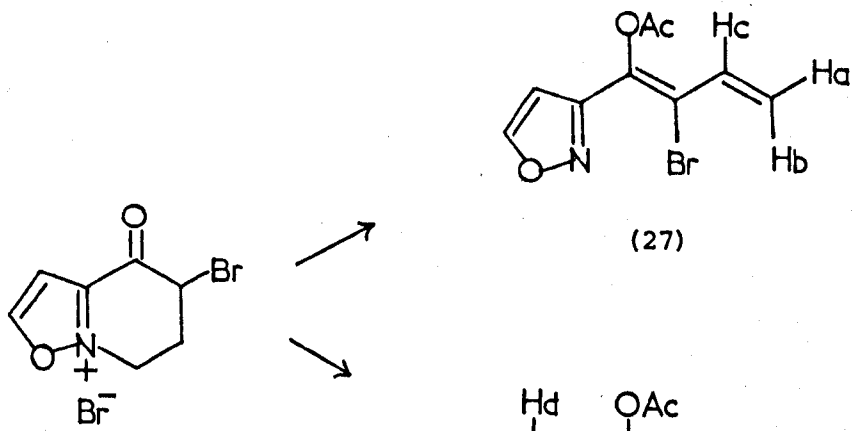


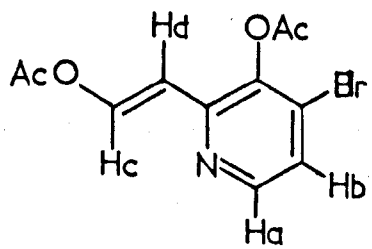
Figure 9

The infrared spectrum contained strong absorptions at 1760 cm^{-1} and 1646 cm^{-1} indicative of an acetate carbonyl and unsaturation respectively.



(27)

(26)

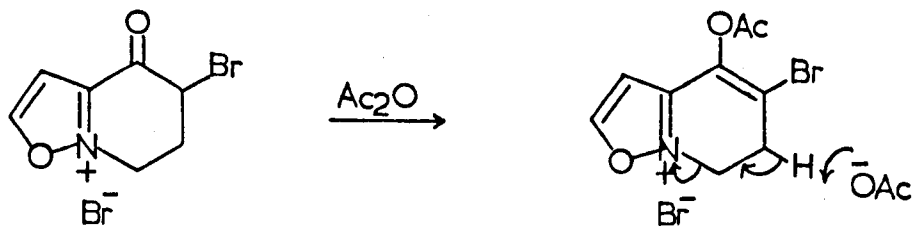


(28)

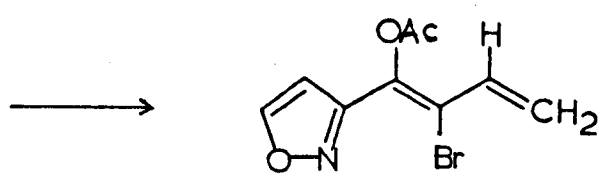
Suggested mechanisms which explain the formation of compounds (27) and (28) are outlined below.

(a) Compound (27)

The first step involves enolisation of the keto group of compound (26) followed by acetylation to the enol acetate. A β-elimination involving the proton at C6 and the quaternary nitrogen results in the formation of the butadienylisoxazole (27).



(26)

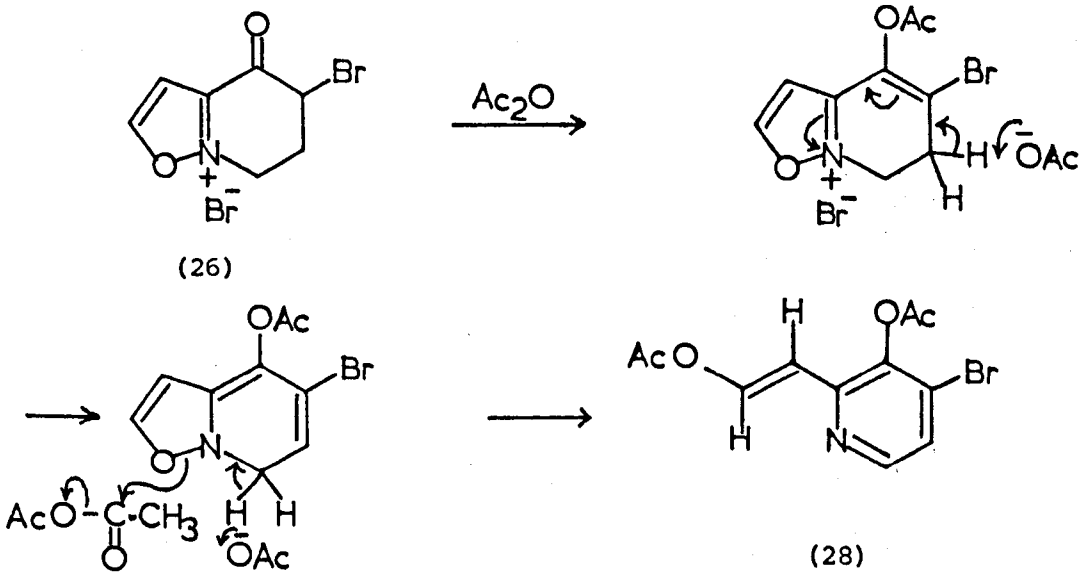


(27)

The work of Miyadera et al[16] has shown that nucleophilic attack of Grignard reagents occurs at position 4 of quinolizinium salts with subsequent ring opening to give pyridyl butadienes.

(b) Compound (28)

The first step involves usual formation of the enol acetate. Involvement of the bridgehead nitrogen as in the quinolizinium series[3] leads to loss of a proton from C6 and double-bond isomerisation to give a neutral species. Abstraction of a proton from C7 of the neutral intermediate is followed by cleavage of the O-N bond and simultaneous O-acetylation to give the vinyl-pyridine (28).

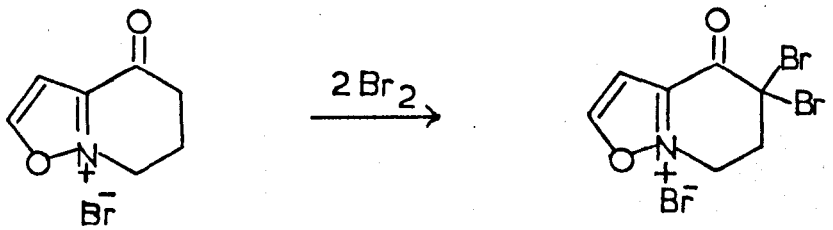


Synthesis of 6-bromo-5-hydroxyisoxazolo[2,3-a]pyridinium bromide (29)

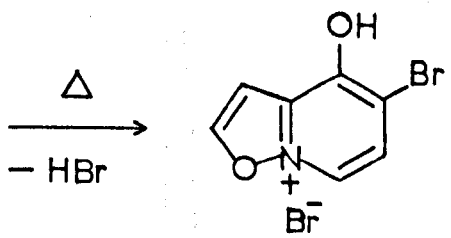
The previous attempt to prepare the parent isoxazolo[2,3-a]-pyridinium salt (1) by application of the Glover and Jones quinolizinium route[1] failed due to the instability of the isoxazole ring. However by a process of bromination and dehydrobromination of the cyclic ketone (6), the first isoxazolopyridinium salt (29) has been synthesised.

The cyclic ketone (6) was brominated with two moles of bromine in hydrobromic acid to give the dibromo ketone (30). Heating of the dibromoketone (30) dry, in a nitrogen stream at 135°, led to

the evolution of hydrogen bromide. The residual solid was the 6-bromo-5-hydroxyisoxazolo[2,3-a]pyridinium bromide (29).



(6) (30)



(29)

The n.m.r. spectrum in trifluoro-acetic acid shown in Figure 10, was in accord with the structure of the aromatic salt (29). The 2 and 3 isoxazole ring absorptions are shown as doublets at δ7.74 and 8.85 p.p.m. with coupling $J_{2,3}$ = 2 Hz. The absorptions due to the 6 and 7 protons appear as doublets at δ8.14 and 8.95 p.p.m. (partly obscured) with coupling $J_{6,7}$ = 8 Hz.

N.m.r. spectrum of 5-bromo-4-hydroxyisoxazolo[2,3-a]pyridinium bromide (29) in CF_3CO_2H

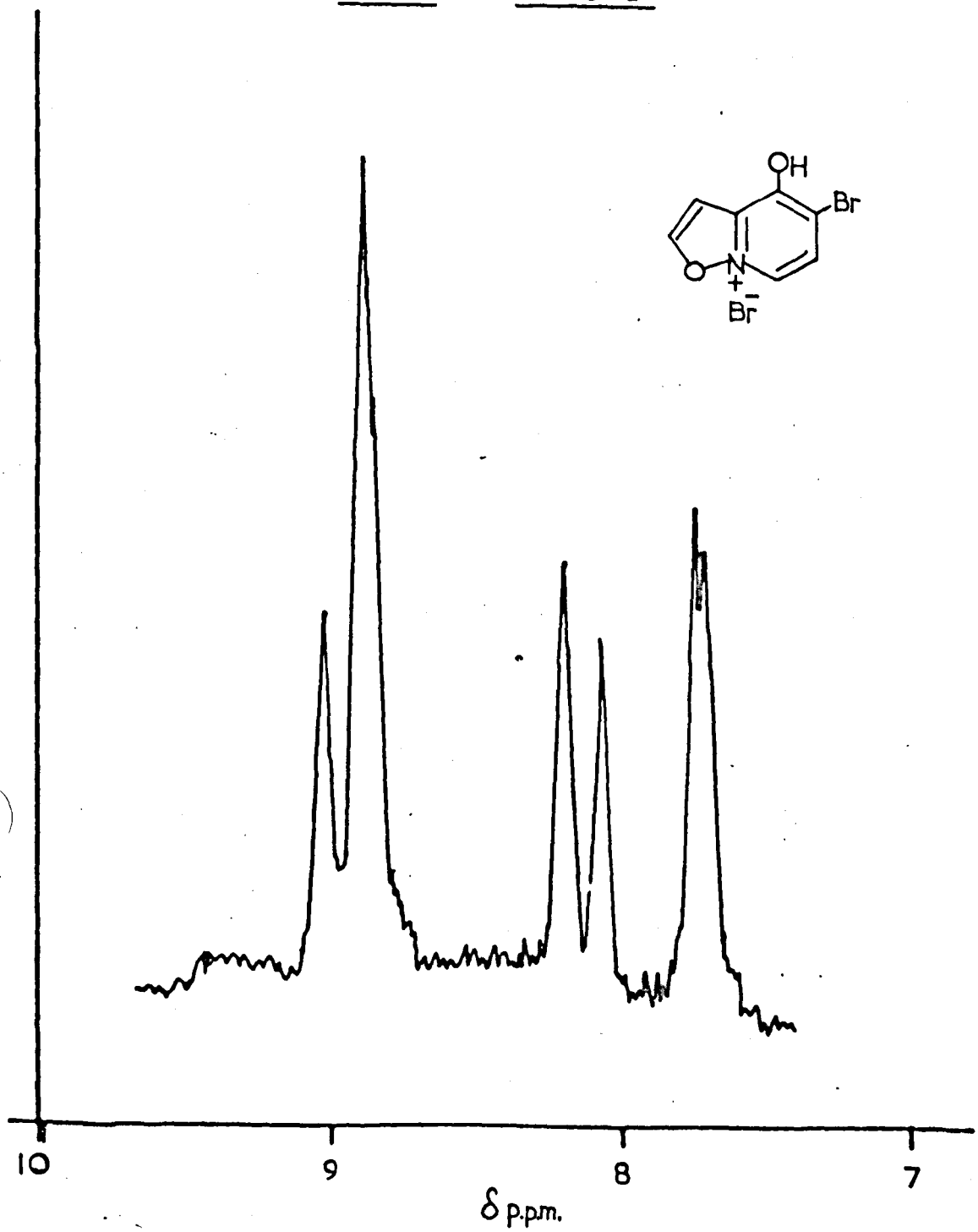


Figure 10

EXPERIMENTAL

3-Cyano-isoxazole (2)

Prepared from the isoxazole ester (3) as described in Part I (p. 62) of this thesis.

3-(4-Ethoxybutyryl)isoxazole (5)

A solution of the Grignard reagent from 3-ethoxypropyl bromide (18.4g) and magnesium (2.88g.) in dry ether (200 ml.) was added slowly with stirring to a cooled solution of 3-cyano-isoxazole (2) (9.4g.) in ether (200 ml.) at -12°. Stirring was continued overnight and usual work up (see Part II, p. 98) gave the product as a clear liquid. The butyrylisoxazole (5) was obtained pure on distillation, b.p. 66°/0.5 mm. (9.6g., 52%).

Found: C, 58.7; H, 7.3; N, 7.8%

$C_9H_{13}NO_3$ requires: C, 59.0; H, 7.15; N, 7.65%

$\nu_{max.}$ (Film) 1703, 1110 cm.$^{-1}$ (CO).

n.m.r. (CCl_4) : δ 1.1 (3H, t, CH_3CH_2), 1.94 (2H, m, $CH_2\underline{CH_2}CH_2$), 3.06 (2H, t, $CO\underline{CH_2}$, J = 7Hz), 3.35 (2H, q, $O\underline{CH_2}CH_3$, J = 6.5Hz), 3.4 (2H, t, $O\underline{CH_2}CH_2$), 6.64 (1H, d, isoxazole, J = 2Hz), 8.41 (1H, d, isoxazole) p.p.m.

4,5,6,7-Tetrahydro-4-oxo-isoxazolo[2,3-a]pyridinium bromide (6)

A solution of the ethoxybutyrylisoxazole (5) (0.5g.) in 48% hydrobromic acid (25 ml.) was heated under reflux for 1 hr., allowing the ethyl bromide initially formed to escape from the system. Evaporation under reduced pressure gave a solid residue, which was dissolved in absolute ethanol and re-evaporated. Trituration of the residue with dry acetone gave almost pure cyclic ketone (6) (0.54g., 91%), which recrystallised from absolute ethanol/ethyl acetate as light brown needles, m.p. >300°.

Found: C, 37.0; H, 3.9; N, 6.0%

$2C_7H_8BrNO.H_2O$ requires: C, 37.1; H, 3.95; N, 6.2%

$\nu_{max.}$ (Nujol) 1725 cm.$^{-1}$ (CO).

n.m.r. (T.F.A.) : δ 2.82 (2H, m, $CH_2\underline{CH_2}CH_2$, J = 6Hz), 3.05 (2H, t, $\underline{COCH_2}$), 5.03 (2H, t, $\underline{\overset{+}{N}CH_2}$), 7.46 (1H, d, isoxazole, J = 2Hz), 9.06 (1H, d, isoxazole) p.p.m.

Attempted aromatisation of 4,5,6,7-tetrahydro-4-oxo-isoxazolo-[2,3-a]pyridinium bromide (6) with boiling acetic anhydride

A solution of the cyclic ketone (6) (2.7g.) in acetic anhydride (20 ml.) was boiled for 5 min. Evaporation under reduced pressure and absolute ethanol treatment gave a dark-brown viscous oil (2.8g.). A sample of the product was run on t.l.c., elution

with chloroform showed the presence of two components with polymeric material remaining at the base line of the plate.

The mixture (2.7g.) was applied to nine preparative plates and elution with chloroform - 10% ethyl acetate gave the following bands.

Band I (0.03g.) isolated as a black tar which showed an n.m.r. spectrum indicating the product to be 3-acetoxy-2-(2-acetoxyvinyl)pyridine (8).

Band II (1.04g., 47%) isolated as a pale yellow solid (compound A), which was recrystallised from benzene as colourless prisms, m.p. 110-112°.

Found: C, 60.2; H, 5.2; N, 7.8%

$C_9H_9NO_3$ requires: C, 60.4; H, 5.05; N, 7.8%

$\nu_{max.}$ ($CHCl_3$)	1778, 1684, 1590 $cm.^{-1}$
$\lambda_{max.}$ (95% EtOH)	276 nm. ($\log_{10}\varepsilon$, 4.24).
$\lambda_{max.}$ (95% EtOH/aq.NaOH)	260, 312 nm. ($\log_{10}\varepsilon$, 3.96, 4.17).
Mass spectrum $^m/_e$	179 (M^+), 137, 108, 80, 68, 53, 43 (base peak).
Metastable	[m^* 105 (179-137)].
n.m.r. ($CDCl_3$) :	δ 2.34 (3H, s), 2.6 (2H, m), 3.9 (2H, t, J = 6Hz), 5.8 (2H, m, J = 5Hz, J = 1Hz), 6.1 (1H, d, J = 1Hz) p.p.m.

Attempted dehydrogenation of compound A using 2,3-dicyano-5,6-dichloro-1,4-benzoquinone (D.D.Q.)

A solution of compound A (0.07g.) and D.D.Q. (0.098g.) in dry benzene (5 ml.) was heated under reflux for 16 hr. EVaporation of the mixture under reduced pressure gave a residue whose n.m.r. spectrum indicated starting material.

Attempted reaction of compound A with dimethylacetylene dicarboxylate

A solution of compound A (0.045g.) and dimethyl acetylene-dicarboxylate in dry benzene (10 ml.) was boiled for 20 hr. Evaporation of the mixture under reduced pressure gave unchanged starting material.

Hydrolysis of compound A

A solution of compound A (0.04g.) in 95% ethanol (20 ml.) was stirred and treated dropwise with N sodium hydroxide solution until complete hydrolysis was indicated by ultraviolet spectroscopy.

The mixture was adjusted to pH 7 using dilute hydrochloric acid and the solvent removed under reduced pressure. The residue was extracted with chloroform and the dried extracts evaporated to leave a yellow solid (0.032g., 96%). Recrystallisation from benzene gave the product as colourless prisms, m.p. 110-111°.

Mass spectrum : M^+ = 137.0480 ($C_7H_7NO_2$ requires 137.0478), 108.0448 (C_6H_6NO requires 108.0449), 80.0500 (C_5H_6N requires 80.0500), 68.0136 (C_3H_2NO requires 68.0136). [m* 88 (137-110)].

$\nu_{max.}$ ($CHCl_3$) 3420, 1750, 1620 $cm.^{-1}$

$\lambda_{max.}$ (95% EtOH) 260, 312 nm. ($\log_{10}\varepsilon$, 3.82, 4.03).

n.m.r. ($CDCl_3$) : δ 2.3-2.7 (2H, m), 3.4 (2H, m), 4.72 (1H, brs), 5.6 (1H, m), 6.0 (1H, m) p.p.m.

Hydrogenation of compound A using 10% palladium on charcoal as catalyst

A solution of compound A (0.179g.) in 95% ethanol (20 ml.) containing 10% palladium on charcoal catalyst (0.02g.) was hydrogenated until the uptake of hydrogen ceased (1 molar equivalent). The catalyst was filtered off and the filtrate evaporated to dryness. Purification of the residue using P.L.C. gave the product (compound B) as a colourless solid (0.068g., 38%), which was recrystallised from benzene/carbon tetrachloride as colourless prisms, m.p. 99-100°.

Found: C, 59.9; H, 6.35; N, 7.7%

$C_9H_{11}NO_3$ requires: C, 59.65; H, 6.1; N, 7.75%

$\nu_{max.}$ ($CHCl_3$) 1740, 1687, 1610 $cm.^{-1}$

$\lambda_{max.}$ (95% EtOH) 264 nm. ($\log_{10}\varepsilon$, 4.18).

$\lambda_{max.}$ (95% EtOH/aq.NaOH) 260 nm. ($\log_{10}\varepsilon$, 4.31).

Mass spectrum $^{m}/e$ 181 (M^{+}), 139, 137, 111, 110, 83, 70, 68, 55, 43.

[m^{*} 88 (139-110)].

n.m.r. ($CDCl_3$) : δ 1.93 (2H, m), 2.3 (3H, s), 2.25-2.65 (2H, m), 3.6-4.0 (2H, m), 4.85 (1H, m, J = 6Hz, J = 1Hz), 5.9 (1H, brs) p.p.m.

Hydrolysis of compound B

Compound B (0.03g.) was hydrolysed as described previously for compound A. The product was isolated as an almost colourless solid (0.023g., Quantitative). Recrystallised from benzene/carbon tetrachloride as colourless needles, m.p. 119-120°.

Found: C, 60.9; H, 6.5; N, 10.2%

$C_7H_9NO_2$ requires: C, 60.4; H, 6.5; N, 10.05%

$\nu_{max.}$ ($CHCl_3$) 3395, 1720, 1625 $cm.^{-1}$

$\lambda_{max.}$ (95% EtOH) 260 nm. ($\log_{10}\varepsilon$, 4.34).

Mass spectrum $^{m}/e$ 139 (M^{+}), 110, 83, 70, 68, 55.

[m^{*} 88 (139-110), 62 (110-83)].

n.m.r. ($CDCl_3$) : δ 1.2-2.65 (4H, m), 3.3 (2H, m), 4.54-4.86 (1H, m), 4.63 (1H, brs), 6.18 (1H, m, exchangeable) p.p.m.

Hydrogenation of compound A using Adams' catalyst

A solution of compound A (0.179g.) in 95% ethanol (20 ml.) containing Adams' catalyst (0.045g.) was hydrogenated until the uptake of hydrogen ceased (3 molar equivalents). The catalyst was removed by filtration and the ethanol filtrate evaporated to dryness to leave the product (compound C) an almost colourless solid (0.178g., 96%). Recrystallised from benzene/carbon tetrachloride as colourless needles, m.p. 102-104°.

Accurate measured mass : M^+ = 185.1052

$C_9H_{15}NO_3$ requires : 185.1052

$\nu_{max.}$ ($CHCl_3$) 1710, 1620 $cm.^{-1}$

Mass spectrum $^m/e$ 185 (M^+), 142, 126, 119, 117, 98, 84, 56, 43.

[m^* 109 (185-142)].

n.m.r. ($CDCl_3$) : δ 1.65 (6H, brs), 2.1-2.18 (4H, m), 2.4-2.8 (2H, m), 3.1-3.8 (1H, m), 4.3-5.4 (1H, m), 9.6 (1H, s, exchangeable) p.p.m.

Attempted hydrolysis of compound C

A solution of compound C (0.09g.) in ethanol (5 ml.) was treated with N sodium hydroxide solution (5 ml.). The mixture was then stirred on a steam bath for 2 hr. The mixture was cooled, adjusted to pH 7 with dilute hydrochloric acid and evaporated to

dryness. The residue was extracted with chloroform and the dried extracts evaporated under reduced pressure to give a colourless glass (0.076g.). Attempts to purify the product failed.

$\nu_{max.}^{(CHCl_3)}$ 3350, 1610 cm.$^{-1}$

Ethoxycarbonylmethylenetriphenylphosphorane (14)

Prepared from triphenyl phosphine and bromo-ethyl acetate by the method of Isler et al.[5]

Ethyl trans-3-(2-pyrrolyl)acrylate (15)

Prepared from the phosphorane (14) and 2-formylpyrrole as described by Jones and Lindner[6] in a yield of 67%, b.p. 125-130°/0.5 mm. (lit.,[6] b.p. 135-140°/2 mm., yield 64%).

Ethyl 3-(2-pyrrolidyl)propionate (16)

A solution of the acrylate (16) (2.0g.) in glacial acetic acid (40 ml.) containing Adams' catalyst (0.09g.) was hydrogenated until uptake of hydrogen ceased (3 molar equivalents). The catalyst was filtered off and the filtrate evaporated to dryness. The residue was treated with ice-water and neutralised to pH 7 using solid sodium bicarbonate. The solution was extracted with ether (3 x 20 ml.). The dried ethereal extracts were evaporated under reduced pressure to leave almost pure product

(16) (2.06g., Quantitative) which was used undistilled for the next stage.

$\nu_{max.}$ (Film)	1730 cm.$^{-1}$
n.m.r. (CCl_4) :	δ 1.2 (3H, t), 1.45-2.05 (6H, m),
	2.3 (2H, t, $\underline{CH_2}CO$, J = 6Hz),
	2.7-3.1 (3H, m), 4.04 (2H, q),
	7.5 (1H, brs, $N\underline{H}$) p.p.m.

3-Pyrrolizidone (13)

A solution of the almost pure ester (16) (2.04g.) in xylene (30 ml.) was boiled for 4 hr. The course of the reaction was monitored using infrared spectroscopy by observing the appearance of the amide carbonyl absorption at 1675 cm.$^{-1}$ and disappearance of the ester carbonyl absorption at 1730 cm.$^{-1}$. The solvent was removed under reduced pressure and the residue distilled (bulb-tube). 3-Pyrrolizidone (13) had a b.p. 150-160°/60 mm., (lit.,[7] 90-100°/10 mm.).

$\nu_{max.}$ (Film)	1675 cm.$^{-1}$ (CO).
Mass spectrum $^{m}/e$	125, 97, 69, 44.

Attempted hydrogenation of 3-pyrrolizidone (13)

A solution of 3-pyrrolizidone (13) (0.125g.) in 95% ethanol (20 ml.) containing Adams' catalyst (0.02g.) was hydrogenated. No uptake of hydrogen was observed and unchanged 3-pyrrolizidone (13) was recovered.

Action of silver acetate on 3-pyrrolizidone (13)

A solution of 3-pyrrolizidone (13) (0.25g.) in glacial acetic acid (15 ml.) was treated with silver acetate (0.334g., 0.002M). The mixture was stirred and heated at 100° for 2 hr. On cooling, the precipitate was removed by filtration and the filtrate evaporated to dryness. The residue was treated with sodium bicarbonate solution and extracted with chloroform. Evaporation of the dried chloroform extracts gave a pale yellow oil (0.22g.), which was starting material.

2-Oxoheptamethylene-imine (21)

Prepared from cycloheptanone as described by Blicke and Doorenbos.[11]

$\nu_{max.}$ (CCl_4) 3420, 3215, 1660 $cm.^{-1}$

3,3-Dibromo-2-oxoheptamethylene-imine (23)

A solution of 2-oxoheptamethylene-imine (21) (1.27g.) in freshly distilled chloroform (15 ml.) was treated dropwise with phosphorus oxychloride (2.3g.) at 10-15°. Phosphorus pentachloride (2.3g.) was added slowly at 10-15° and stirring was continued until all the solid dissolved. Bromine (3.52g.) in chloroform (15 ml.) was next added dropwise at room temperature and the mixture was stirred overnight. The solvent was evaporated under reduced pressure

and the residual oil treated with ice-water. Extraction with chloroform gave an orange oily solid on evaporation (1.5g.). T.l.c., eluting with chloroform indicated the presence of starting material and one product. The mixture was separated using P.L.C., and elution with chloroform gave the following bands:-

Band I (0.5g., 17%) isolated as a yellow solid and shown from spectral evidence to be 3,3-dibromo-2-oxoheptamethylene-imine (23).

$\nu_{max.}$ ($CHCl_3$)	3400, 1665 $cm.^{-1}$
Mass spectrum $^m/_e$	287 (M + 4), 285 (M + 2), 283 (M^+), 206, 204, 189, 187, 178, 176, 135, 133, 121, 119, 107, 105, 99, 81, 71, 56, 55.
n.m.r. ($CDCl_3$) :	δ 1.4-2.0 (6H, m), 2.94-3.15 (2H, m, $\underline{CH_2}N$), 3.38-3.75 (2H, m, $\underline{CH_2}.CBr_2$) p.p.m.

Band II (0.75g.) isolated as a yellow oil and shown from spectral examination to be unchanged 2-oxoheptamethylene-imine (21).

3-Bromo-2-oxoheptamethylene-imine (25)

A modification of the method of Brenner and Rickenbacher[12] was employed.

A solution of the dibromoketone (23) (0.23g.) and triethanolamine (0.16g.) in methanol (20 ml.) containing Raney

nickel catalyst (0.1g.) was hydrogenated until uptake of hydrogen had ceased (1 molar equivalent). The precipitate of triethanolamine hydrobromide was filtered off, the filtrate evaporated under reduced pressure, and the residue extracted with chloroform. The chloroform extracts were washed with dilute hydrochloric acid, dried and evaporated to leave a pale yellow solid. Purification using P.L.C. eluting with chloroform - 10% acetone gave the monobromoketone (25) (0.037g., 22%) as an almost colourless solid, m.p. 160-163° (lit.,[13] m.p. 163-164°).

$\nu_{max.}$ ($CHCl_3$) 3400, 1660 $cm.^{-1}$

Mass spectrum $^m/_e$ 207 (M + 2), 205 (M^+), 178, 176, 127, 99, 98.

n.m.r. ($CDCl_3$) : δ 1.5-2.0 (6H, m), 2.0-2.45 (2H, m, $\underline{CH_2}CHBr$), 3.2-3.6 (2H, m, $\underline{CH_2}N$), 4.9 (1H, t, $\underline{CH}Br$, J = 8Hz), 3.0 (1H, brs) p.p.m.

Attempted preparation of 3-acetoxy-2-oxoheptamethylene-imine (12)

(a) Treatment of the monobromoketone (25) (0.03g.) with silver acetate (0.03g.) in glacial acetic acid (10 ml.) at 100° for 12 hr. gave unchanged starting material.

(b) A solution of the ketone (25) (0.03g.) and silver acetate (0.03g.) in acetic anhydride (10 ml.) was boiled for 1 hr. in the dark. Work up gave a small quantity of a brown tar (0.015g.) which could not be characterised.

$\nu_{max.}$ ($CHCl_3$) 1700 $cm.^{-1}$ (CO).

5-Bromo-4,5,6,7-tetrahydro-4-oxo-isoxazolo[2,3-a]pyridinium bromide (26)

The ketone (6) (1.09g.) was dissolved in 48% hydrobromic acid (20 ml.) and treated with bromine (0.85g.) in hydrobromic acid (10 ml.). The mixture was heated and stirred on a steam bath for 0.5 hr. The acid was removed under reduced pressure, a little water added and the solution re-evaporated. The residue was treated with absolute ethanol and the insoluble dibromoketone (0.2g.) removed by filtration. Evaporation of the filtrate and trituration of the residue with acetone gave the monobromoketone (26) almost pure (1.1g., 70%). Recrystallised from absolute ethanol/ethyl acetate as buff prisms, m.p. >300°.

Found: C, 26.7; H, 3.2%

$C_7H_7Br_2NO_2.H_2O$ requires: C, 26.7; H, 2.85%

n.m.r. (T.F.A.) δ 2.65-3.2 (2H, m, CH_2CHBr), 4.7-5.0 (3H, m), 7.35 (1H, d, isoxazole, J = 2Hz), 9.0 (1H, d, isoxazole) p.p.m.

Treatment of 5-bromo-4,5,6,7-tetrahydro-4-oxo-isoxazolo[2,3-a]-pyridinium bromide (26) with acetic anhydride

A solution of the bromoketone (26) (0.8g.) in acetic anhydride (20 ml.) was boiled for 2 min. The colour of the reaction mixture quickly changed to a dark brown. Evaporation

under reduced pressure and absolute ethanol treatment gave a dark brown viscous oil (0.71g.). T.l.c. of the product, eluting with chloroform - 20% ethyl acetate, showed the presence of three components. The mixture (0.65g.) was applied to two preparative plates and eluted twice with chloroform - 20% ethyl acetate.

The following bands were obtained:-

Band I (0.045g.) isolated as a brown oil that showed spectral evidence consistent with 3-(1-acetoxy-2-bromo-1,3-butadien-1-yl) isoxazole (27).

$\nu_{max.}$ ($CHCl_3$)	1770 $cm.^{-1}$ (CO).
$\lambda_{max.}$ (95% EtOH)	264 nm.
$\lambda_{max.}$ (95% EtOH/aq.NaOH)	221, 262 nm.
Mass spectrum $^m/e$	259 (M + 2), 257 (M^+), 241, 239, 226, 224, 217, 215, 199, 197, 189, 187, 148, 146, 108, 90, 60, 43.
n.m.r. ($CDCl_3$) :	δ 2.32 (3H, s), 5.62 (1H, d, J = 10Hz), 5.97 (1H, d, J = 16Hz), 6.45 (1H, d, J = 2Hz), 7.12-7.56 (1H, m, J = 10Hz, J = 16Hz), 8.54 (1H, d, J = 2Hz) p.p.m.

Band II (0.152g.) shown from spectral evidence to be 3-acetoxy-2-(2-acetoxyvinyl)-4-bromopyridine (28).

$\nu_{max.}$ ($CHCl_3$)	1760, 1646 $cm.^{-1}$

Mass spectrum $^{m}/e$ 301 (M + 2), 299 (M^{+}), 259, 257, 217, 215, 200, 198, 119, 117, 78, 43.

$\lambda_{max.}$ (95% EtOH) 223, 253, 295 nm.

$\lambda_{max.}$ (95% EtOH/aq.NaOH) 221, 245(sh), 288, 311(sh) nm.

n.m.r. ($CDCl_3$) : δ 2.21 (3H, s), 2.42 (3H, s), 6.5 (1H, d, J = 12Hz), 7.48 (1H, d, J = 5Hz), 8.31 (1H, d, J = 5Hz), 8.6 (1H, d, J = 12Hz) p.p.m.

Band III (0.159g.) isolated as a dark brown tar which could not be characterised.

5,5-Dibromo-4,5,6,7-tetrahydro-4-oxo-isoxazolo[2,3-a]pyridinium bromide (30)

A solution of the cyclic ketone (6) (0.87g.) in 48% hydrobromic acid (10 ml.) was treated with bromine (1.4g.) in hydrobromic acid (10 ml.). The mixture was heated on a steam bath for 0.5 hr. Evaporation of the solvent under reduced pressure gave a brown residue that was treated with boiling ethanol and filtered. The filtrate contained the monobromoketone (26). The insoluble solid was the dibromoketone (30) (0.71g., 47%) and was recrystallised from absolute ethanol/ethyl acetate, m.p. 150° (dec.).

Found: C, 21.6; H, 2.25; N, 3.6%

$C_7H_6Br_3NO.H_2O$ requires: C, 21.3; H, 2.3; N, 3.55%

n.m.r. (T.F.A.) : δ 3.5 (2H, t, $\underline{CH_2}CBr_2$, J = 6Hz),
4.95 (2H, t, $\overset{+}{\underline{NCH_2}}$, J = 6Hz),
7.52 (1H, d, isoxazole, J = 2Hz),
9.06 (1H, d, isoxazole, J = 2Hz) p.p.m.

6-Bromo-5-hydroxyisoxazolo[2,3-a]pyridinium bromide (29)

The dibromoketone (30) (0.25g.) was heated in a dry tube under a current of nitrogen at 140°; the effluent gas was tested for hydrogen bromide with moist litmus until evolution ceased. The residue was the bromohydroxy salt (30) (0.17g., 87%), which recrystallised from methanol/ethyl acetate as a light brown solid, m.p. >320°.

Found: C, 28.1; H, 2.1; N, 4.6%

$C_7H_5Br_2NO_2$ requires: C, 28.5; H, 1.7; N, 4.75%

$\lambda_{max.}$ (95% EtOH) 223(sh), 285, 335 nm. ($\log_{10}\varepsilon$, -, 4.02, 3.6).

$\lambda_{max.}$ (95% EtOH/aq.NaOH) 245, 312, 384(sh) nm. ($\log_{10}\varepsilon$, 4.17, 4.13, 3.48).

n.m.r. (T.F.A.) : δ 7.74 (1H, d, H3, J = 2Hz),
8.14 (1H, d, H6, J = 8Hz),
8.85 (1H, d, H2, J = 2Hz),
8.95 (1H, d, H5, J = 8Hz) p.p.m.

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