The synthesis and properties of some pyrido [1, 2-a] Pyrazinum Salts

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THE SYNTHESIS AND PROPERTIES

OF

SOME PYRIDO [1, 2-a] PYRAZINIUM SALTS

BY

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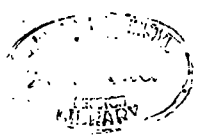

SYNOPSIS

The methods of synthesis of salts containing the quinolizinium nucleus, the pyrazinium nucleus and the pyrazidi-inium nucleus are reviewed.

The object of this work was to establish satisfactory, and if possible, general methods of synthesis of pyrido[1, 2-a]pyrazinium salts and some oxygenated derivatives in quantities sufficient to permit a study of their properties.

The method envisaged for the synthesis of pyrido[1, 2-a]pyrazinium salts was the hydrolysis of the monoquaternary salt between 2-(1, 3-dioxolan-2-yl) pyridine and bromoacetaldehyde oxime followed by cyclodehydration of the resulting di-aldehyde with ammonium acetate. The product of the hydrolysis of the quaternary salt with mineral acid was not the expected di-aldehyde but pyrido[1, 2-a]pyrazinium bromide 2-oxide, which was deoxygenated with phosphorus tribromide to pyrido[1, 2-a]pyrazinium bromide. The 1-methyl- and 1-phenyl-pyrido [1, 2-a]pyrazinium bromide 2-oxides were similarly prepared from suitable precursors whilst 1-bromo-pyrido[1, 2-a]pyrazinium bromide 2-oxide was prepared by the bromination of pyrido[1, 2-a]pyrazinium bromide 2-oxide. Treatment of the 1-phenyl and 1-bromo 2-oxides with phosphorus tribromide afforded the 1-substituted pyrido[1, 2-a] pyrazinium salts but attempts to deoxygenate the 1-methyl 2-oxide were unsuccessful.

1, 4-Dihydro-1-imino-pyrido[1, 2-a]pyrazinium bromide 2-oxide was prepared by treating 2-cyanopyridine with bromoacetaldehyde oxime.

When a solution of the 1-imino 2-oxide in concentrated hydrobromic acid was boiled under reflux the product was 1, 2-dihydro-1-oxo-pyrido [1, 2-a] pyrazinium bromide.

The reaction between picolinic acid amide and ethyl bromoacetate afforded 1, 3-dioxo-1, 2, 3, 4-tetrahydro-pyrido [1, 2-a] pyrazinium bromide which was converted to a bicyclic betaine on treatment with concentrated aqueous or alcoholic ammonia. Hydrolysis of this bicyclic betaine gave 1-carboxymethyl-2-amidopyridinium betaine.

Catalytic hydrogenation of pyrido [1, 2-a] pyrazinium bromide 2-oxide, the 1-bromo 2-oxide or 1, 4-dihydro-1-imino-pyrido [1, 2-a] pyrazinium bromide 2-oxide afforded perhydropyrido [1, 2-a] pyrazine which was also prepared by the action of lithium aluminium hydride on 1, 3-dioxo-1, 2, 3, 4-tetrahydro-pyrido [1, 2-a] pyrazinium bromide and subsequent catalytic hydrogenation of the intermediate compound. Catalytic hydrogenation of 1, 2-dihydro-1-oxo-pyrido [1, 2-a] pyrazinium bromide yielded 1-oxo-perhydropyrido [1, 2-a] pyrazine.

ACKNOWLEDGEMENTS

The author is grateful to Professor W. K. R. Musgrave for the opportunity to carry out this work.

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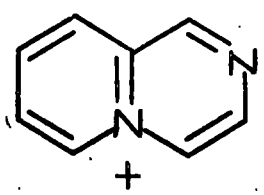
CONTENTS

INTRODUCTION

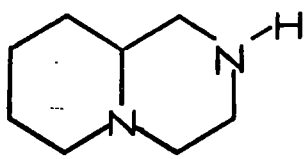
NOMENCLATURE

The nomenclature and abbreviations used in this thesis are those recommended in the Handbook for Chemical Society Authors 1961, published by the Chemical Society. The ring index system will be used throughout for the naming of fused cyclic systems.

The bicyclic fused ring system in which the 4a bridgehead and 2 carbon atoms have been replaced, respectively, by a quaternary and tertiary nitrogen atom will be designated the pyrido [1, 2 - a] pyrazinium ion (i). The corresponding saturated base (ii) will be referred to as perhydropyrido [1, 2 - a] pyrazine.



(i)

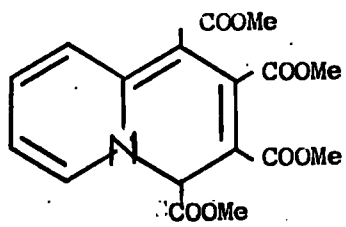


(ii)

It should be noted that the cation (i) has also been referred to as the 2-azaquinolizinium ion[1,2,3].

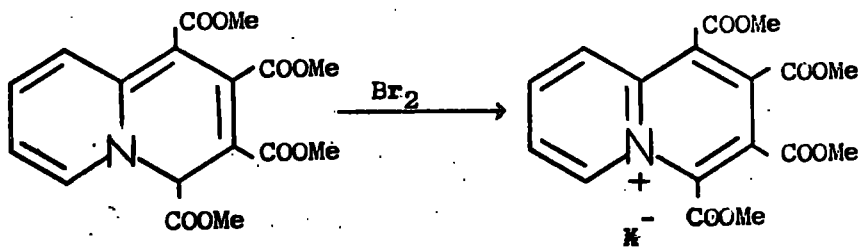
HISTORICAL INTRODUCTION

The earliest synthesis of a quinolizinium derivative was recorded by Diels and Alder[4]. Whilst investigating the reaction between pyridine and the dimethyl ester of acetylene dicarboxylic acid they isolated three products, one of which they believed to be tetramethyl 10H-quinolizine-1,2,3,4-tetracarboxylate but which was later shown by Acheson and Taylor[5] and by Jackman and Tebby[6] to be the 4H-isomer (iii)



(iii)

Oxidation of (iii) with bromine in methanol gave the quaternary salt (iv; X = Br_3) which was converted to the bromide (iv; X = Br) by boiling in acetone.



(iii) (iv)

The "Diene Synthesis" used by Diels and Alder[4] to synthesise compounds containing the quinolizinium nucleus is limited to a few compounds because of the relative instability of the intermediate addition products formed and the ease with which they can be converted to indolizine derivatives.

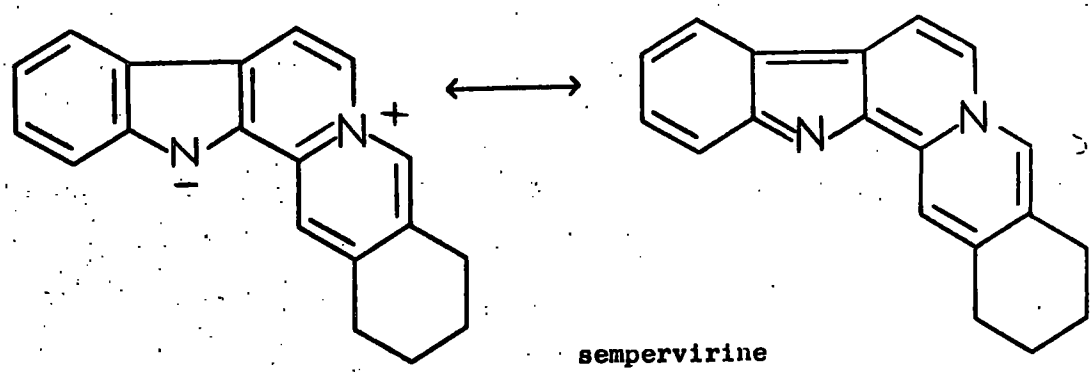
Excluding this synthesis, the methods recorded for the synthesis of quinolizinium and related cations fall essentially into three classes and these will be considered individually.

METHOD 1

This involves the attachment of a suitable side chain to the carbon atom adjacent to the nitrogen atom of a pyridine ring followed by ring closure onto the pyridine nitrogen atom.

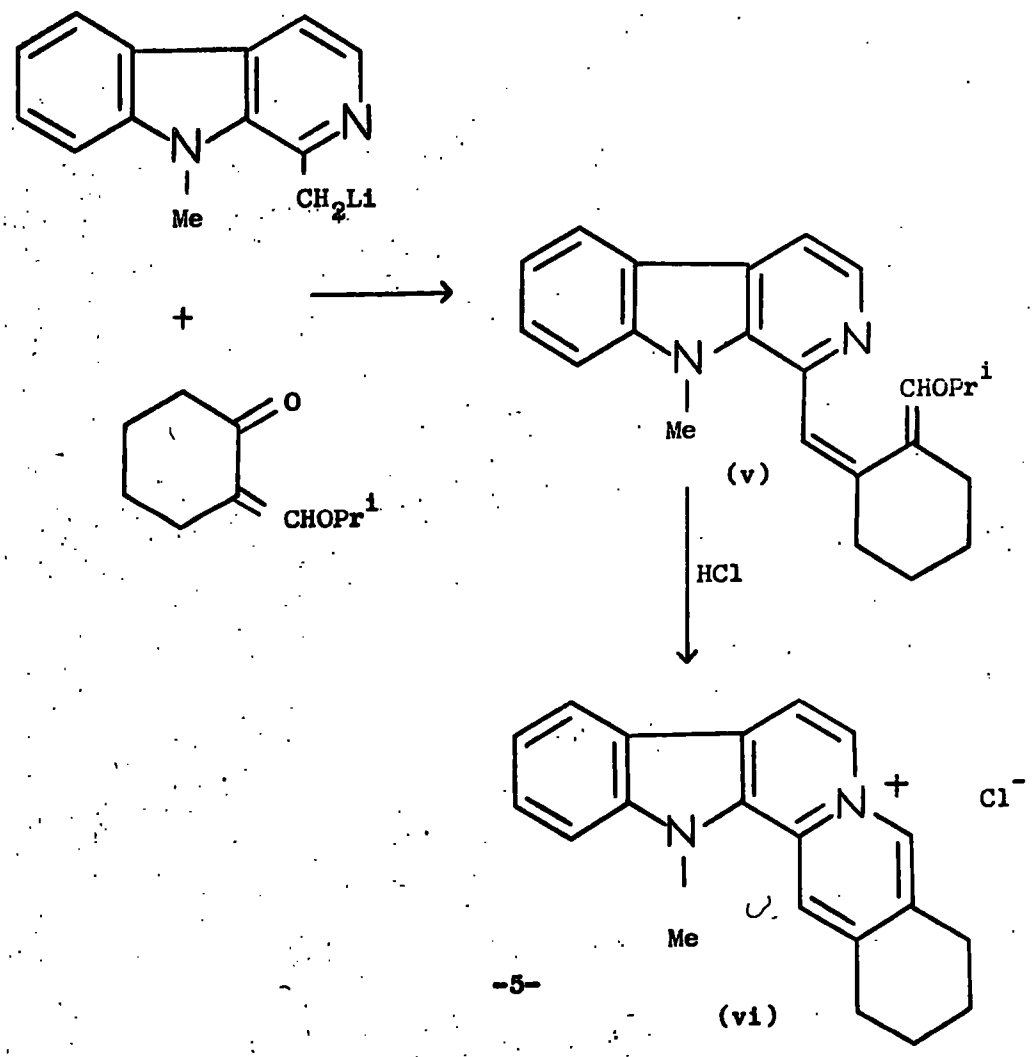
THE QUINOLIZINIUM NUCLEUS

In 1949 it was shown[7,8] that the alkaloid sempervirine contained the quinolizinium nucleus.

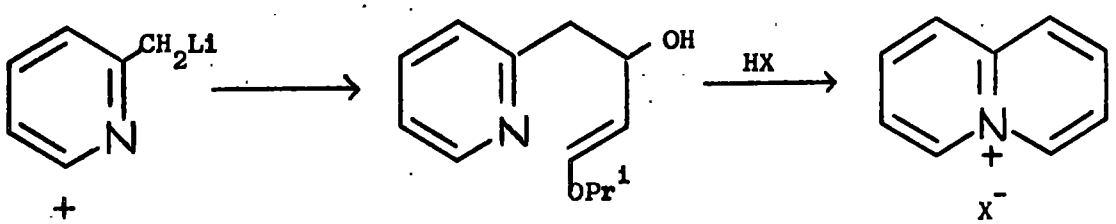


sempervirine

The method of synthesis developed by McLamore and Woodward[8] for the preparation of sempervirine has since been adapted for the preparation of many quinolizinium salts. They condensed 2-isopropoxymethylenecyclohexanone[9] with the lithium derivative of N-methylharman and cyclised the intermediate compound (v) with mineral acid to obtain the methochloride of sempervirine (vi).

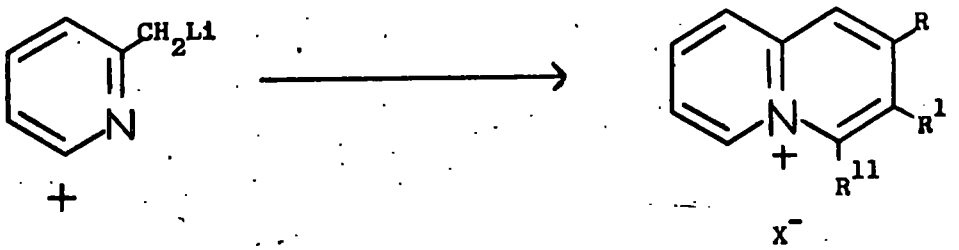


The first synthesis of an unsubstituted quinolizinium salt (vii) was achieved by Beaman and Woodward[10]. The method entailed the treatment of 2-picolyl lithium with 3-isopropoxyacreolin and cyclisation of the intermediate vinyl ether (viii) with mineral acid to give the required quinolizinium salt (vii) in low yield.



$Pr^{i}OCH = CHCHO$ (viii) (vii)

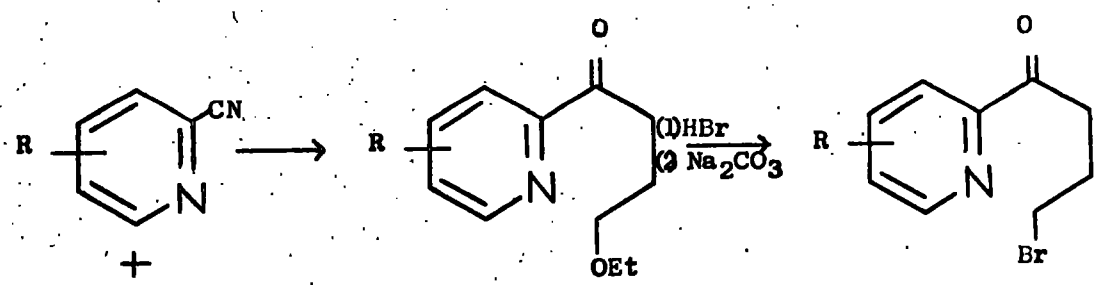
Several modifications[11,12] have been made to the general reaction sequence of McLamore and Woodward[8] and a general scheme, devised by Richards and Stevens[13] uses 2-picolyl lithium and enol ethers, monoketals or β-diketones to give 2-, 3-, or 4-alkyl and aryl substituted quinolizinium salts (ix).

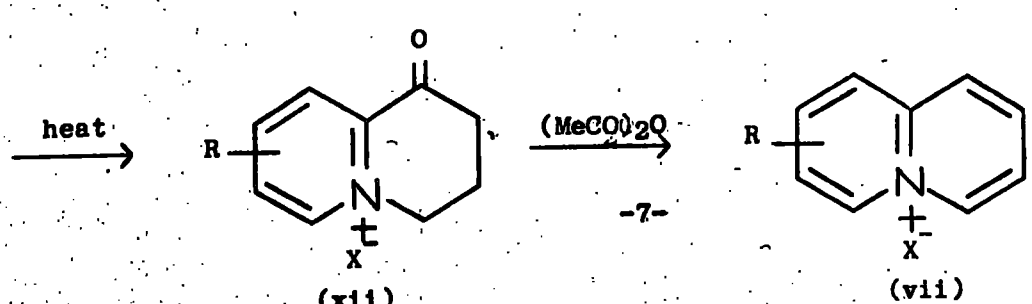


$RCOCHR^{1}CR^{11}(OAlk)_2$ (ix)

By using 2, 6-lutidyl lithium and the appropriate protected β-diketone, Amstutz and Hansen[14] were able to synthesise 4, 6-dimethylquinolizinium salts by analogous reaction sequences.

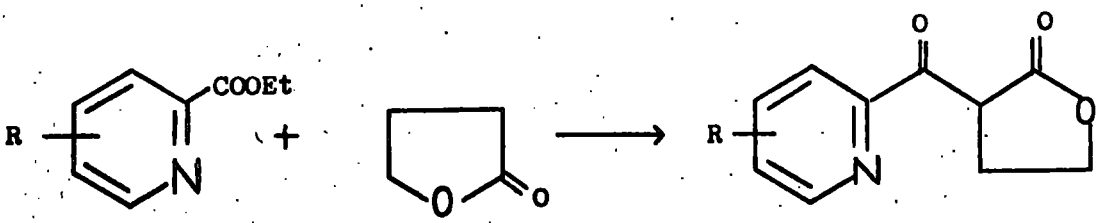
The first synthesis of quinolizinium salts in appreciable yield was recorded by Glover and Jones[15] who treated 2-cyanopyridine with the Grignard reagent from 3-ethoxypropyl bromide and obtained 2-4'-ethoxybutyrylpyridine (x; R = H)[16]. The ether was cleaved using hydrobromic acid and cyclisation effected by heating the resulting bromo compound (xi; R = H) in chloroform to give 1-oxo-1,2,3,4-tetrahydro-quinolizinium bromide (xii; R = H, X = Br). Dehydration by boiling under reflux in acetic anhydride as solvent afforded quinolizinium bromide (vii; R = H, X = Br) in 48% overall yield based on 2-cyanopyridine.





The reaction was shown to be of a general nature by the same authors[15,17] who synthesised a number of 2-, 3-, and 4-alkyl and aryl substituted quinolizinium salts from suitable precursors.

A further synthesis of quinolizinium bromide, together with several methyl derivatives, has been reported by Iwia and Myadera[18]. They condensed ethyl picolinate, or a suitably ring substituted derivative, with 2-oxotetrahydrofuran and obtained the ketolactone (xiii) which, on treatment with concentrated hydrobromic acid, underwent decarboxylation giving the bromoketone (xi). Boiling in chloroform followed by dehydration with acetic anhydride yielded the quinolizinium bromide (vii; R = H or Me; X = Br).



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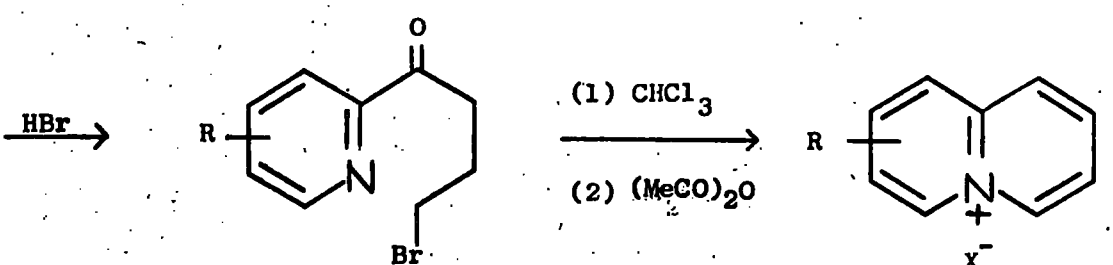
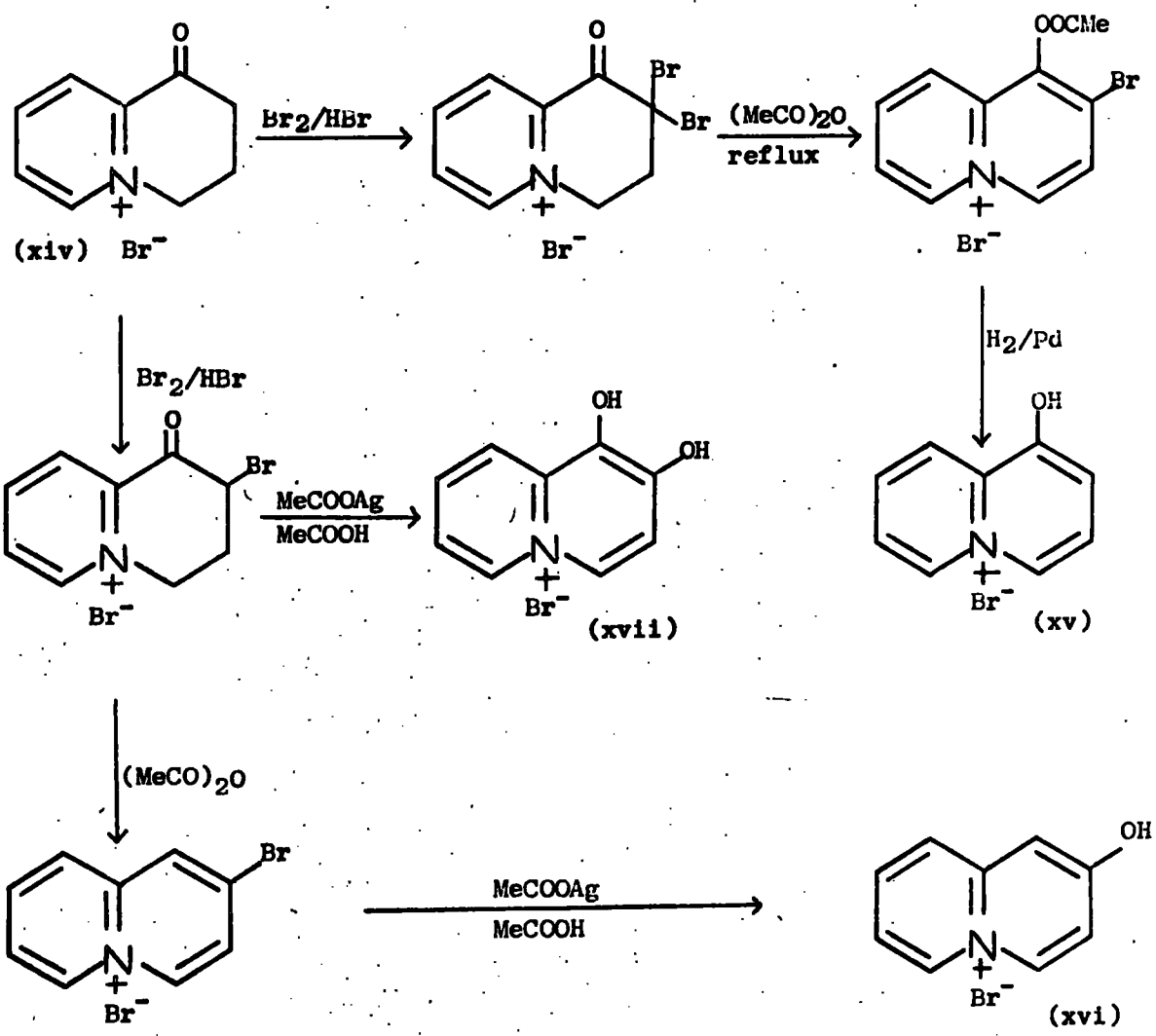


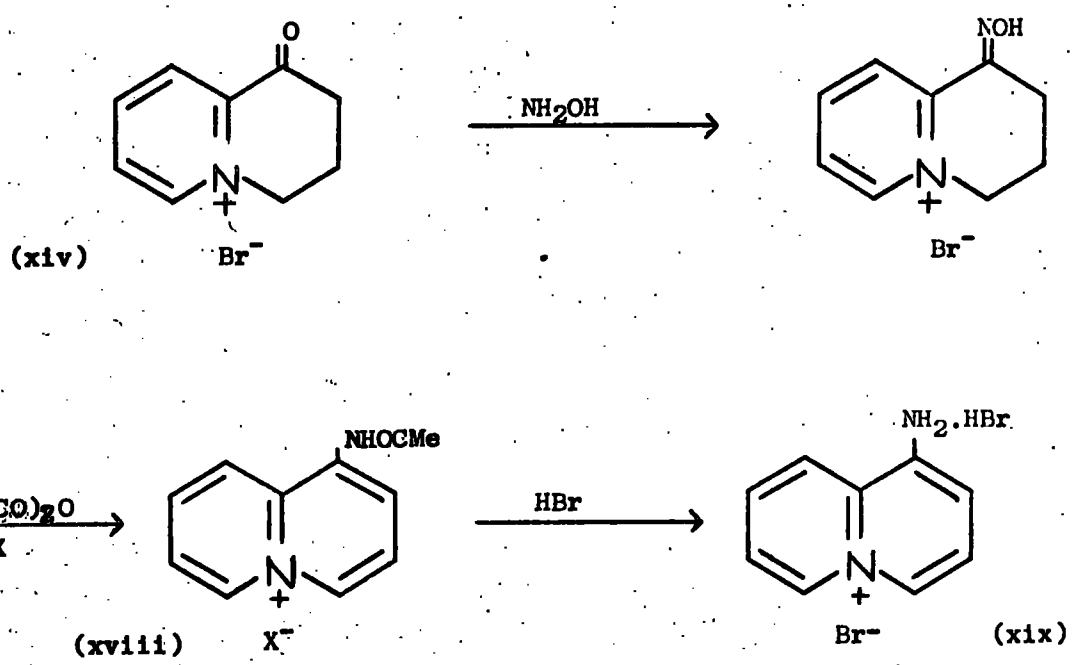
(xi) (vii)

Dehydrogenation[19] of 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (xiv) yielded the 1-hydroxyquinolizinium salt (xv) in low yield; it was isolated as the picrate (xv; X = picrate). Fozard and Jones[20,21] later synthesised the 1-hydroxy[20], 2-hydroxy[21] and the 1,2-dihydroxyquinolizinium[20] salts (xv), (xvi) and (xvii) respectively from the same precursor in accordance with the reaction sequence below.



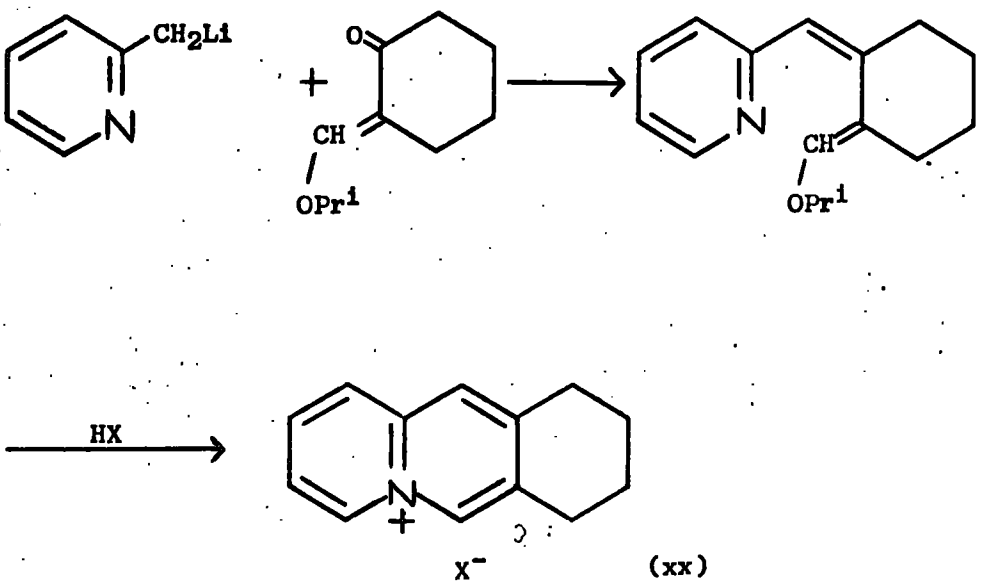
Some alkyl and aryl substituted 1-hydroxyquinolizinium salts[22] have also been prepared, and many are listed in a review by Krönhke[1,2].

The 1-aminoquinolizinium salts reported by Collicut and Jones[23] are the only aminoquinolizinium salts known. They were also prepared from the cyclic ketone (xiv) by conversion to the oxime and thence to the 1-acetamido compound (xviii) by boiling with acidified acetic anhydride. Hydrolysis of this salt (xviii) with concentrated hydrobromic acid yielded the 1-amino salt as the hydrobromide (xix).



BENZOQUINOLIZINIUM SALTS

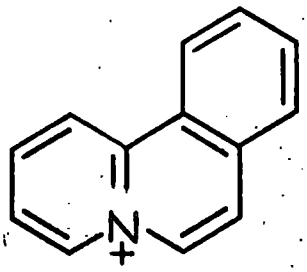
The synthesis developed by McLamore and Woodward[8] for the preparation of the methochloride of sempervirine (p. 5) was similar to the reaction sequence which they used to prepare tetrahydrobenzo [b] quinolizinium picrate (xx; X = picrate). They treated 2-picolyl lithium with 2-isopropoxymethylenecyclohexanone[9] and cyclised the intermediate compound with mineral acid to give the required salt (xx).



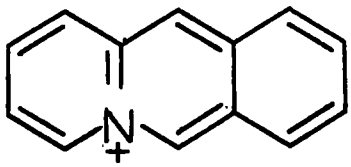
(xx)

The three isomeric benzoquinolizinium salts have been prepared by Glover and Jones[15] who extended their general method for the synthesis of quinolizinium salts described previously (p. 7).

Using 1-cyanoisoquinoline, 3-cyanoisoquinoline or 2-cyanoquinoline together with the Grignard reagent from 3-ethoxypropyl bromide they synthesised benzo [a] quinolizinium salts (xxi), benzo [b] quinolizinium salts (xxii) and the benzo [c] isomer (xxiii).



(xxi)



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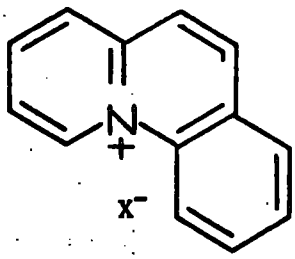
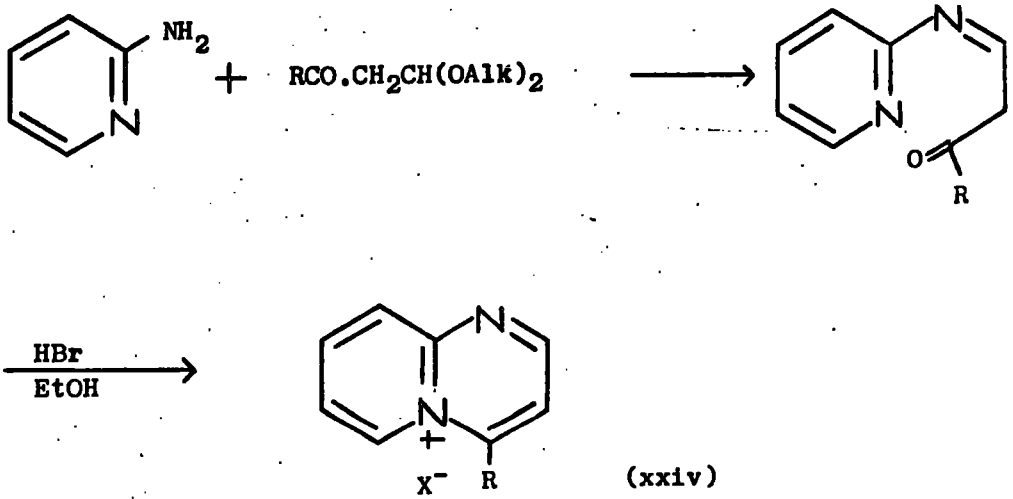


(xxiii)

AZAQUINOLIZINIUM SALTS

At the time of writing this review, no unsubstituted pyrido [1, 2 - a] pyrimidinium salts have been reported, whilst only recently have unsubstituted pyrido [1, 2 - a] pyrazinium salts been prepared[24].

Nesmeyanov et al[25] prepared 4-alkyl-pyrido [1, 2 - a] pyrimidinium salts (xxiv) in moderate overall yield by heating 2-aminopyridine with α-acylacetals in sealed tubes and cyclising the resulting 2-acylanils (xxv) with ethanolic hydrobromic acid.



(xxiv)

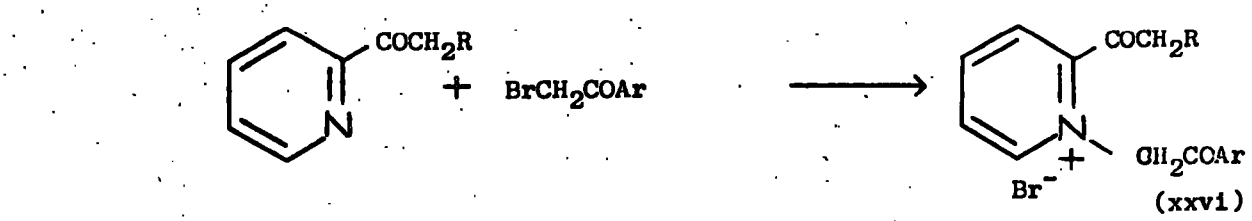
The yield was later improved to 80% by Nesmeyanov and Rybinskaia[26] who allowed a mixture of 2-aminopyridine and an acyl substituted vinyl chloride to stand for several days in methanolic perchloric acid. The bicyclic salts were isolated as the perchlorates (xxiv; X = ClO_4).

METHOD II

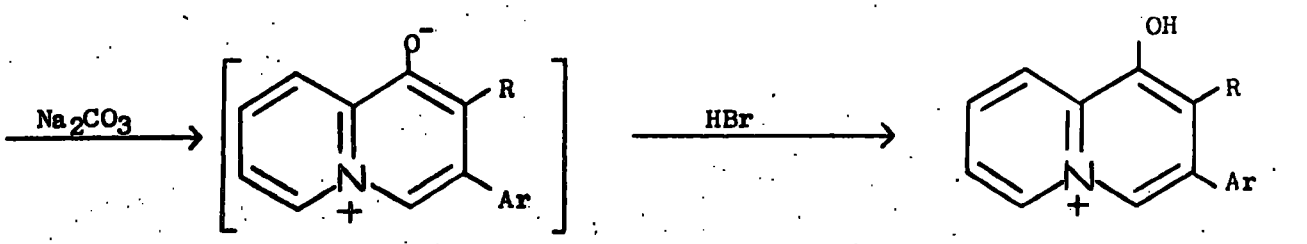
This method involves quaternisation of a suitable 2-substituted pyridine with a substituted alkyl halide containing a group capable of condensing with the 2-substituent. A modification of this technique is to cyclise the 1-substituent of the quaternary salt onto the unsubstituted 2 carbon atom of the pyridine ring.

QUINOLIZINIUM SALTS

This general method of preparation has been used by Kröhnke[1,2] to prepare 1-hydroxy-3-arylquinolizinium salts and their 2-alkyl derivatives. Quaternisation of 2-acylpyridines with ω-bromoacetophenone or a suitably substituted derivative gave the monoquaternary salts (xxvi) which, on treatment with sodium carbonate cyclised to the zwitterionic forms of the 1-hydroxybromides (xxvii).

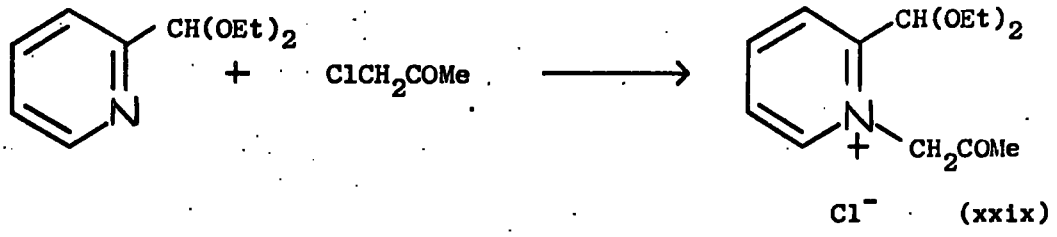


(xxvi)

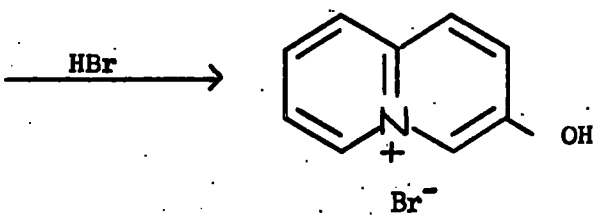


(xxvii)

3-Hydroxyquinolizinium bromide (xxviii) has been synthesised by Schraufstätter[27] by the cyclodehydration of the quaternary salt (xxix) formed by the action of chloroacetone on 2-diethoxymethylpyridine.



(xxix)

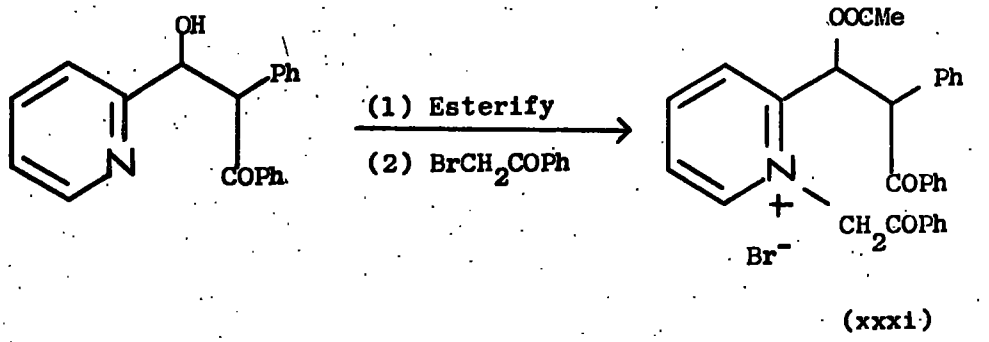


(xxviii)

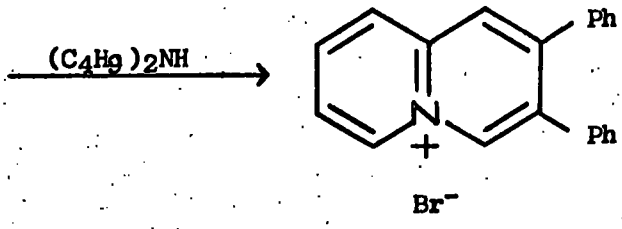
Duke, Fozard and Jones[28] used 2-(1,3-dioxolan-2-yl)pyridine and bromoacetone to prepare the 3-hydroxy salt (xxviii) by a similar procedure.

A specific reaction sequence for the synthesis of 2,3-diphenylquinolizinium bromide (xxx) was devised by Feix and Westphal[29] who coupled pyridine 2-aldehyde with phenyl benzyl ketone, esterified the product, and quaternised the ester with ω-bromoacetophenone. Cyclisation of the monoquaternary salt (xxxi) was achieved by boiling under reflux in a solution of

dibutylamine in acetone.



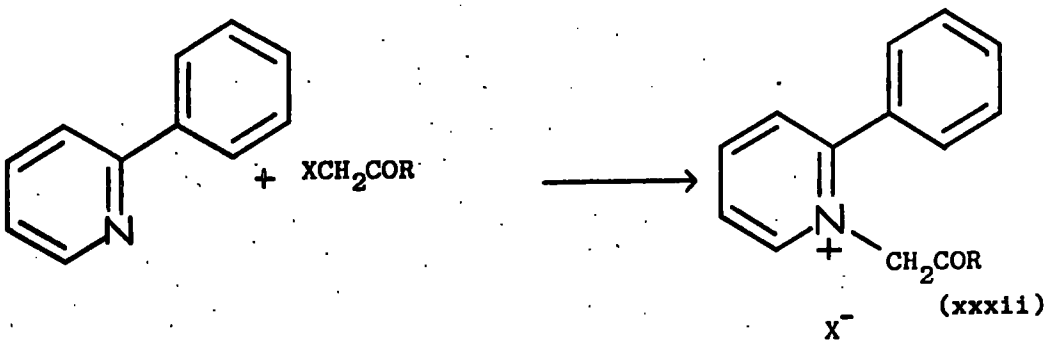
(xxxi)



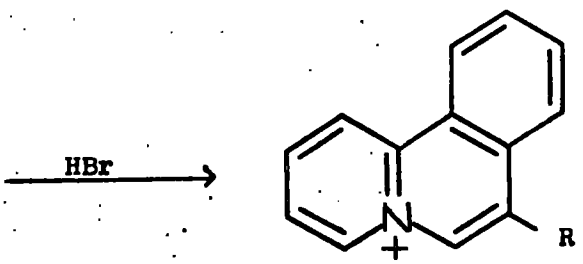
(xxx)

BENZOQUINOLIZINIUM SALTS

Bradsher and Beavers[30] used 2-phenylpyridine and iodoacetone or ω-bromoacetophenone to obtain the monoquaternary salts (xxxii; R = Me, X = I or R = Ph, X = Br) which were cyclised with concentrated hydrobromic acid to give the 7-methyl and 7-phenyl derivatives respectively of benzo [a] quinolizinium bromide (xxxiii; R = Me or Ph)



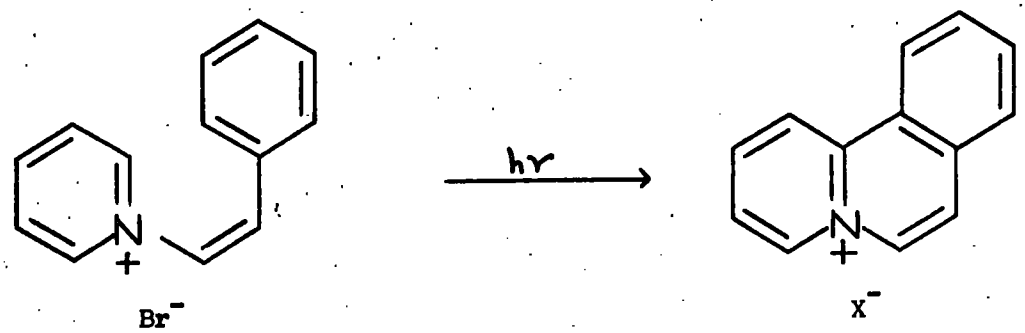
(xxxii)



(xxxiii)

A modification[31] of this method used chloroacetaldehyde oxime as the quaternising agent to give the unsubstituted salt (xxxiii; R = H).

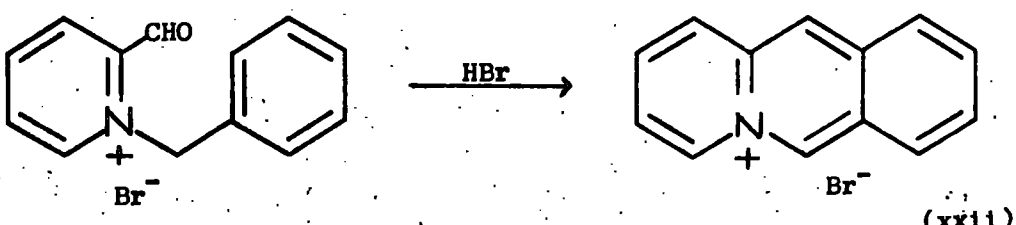
Bradsher and Doolittle[32] treated pyridine with ω-bromostyrene to obtain the monoquaternary salt (xxxiv). Irradiation with ultraviolet light of a solution of this salt (xxxiv) in alcohol containing a trace of iodine afforded the benzo [a] quinolizinium salt (xxi) which was isolated as the perchlorate (xxi; X = ClO_4).



(xxxiv) (xxi)

Some substituted derivatives of the benzo [a] salt (xxi) were also prepared[32] from suitable precursors by similar procedures.

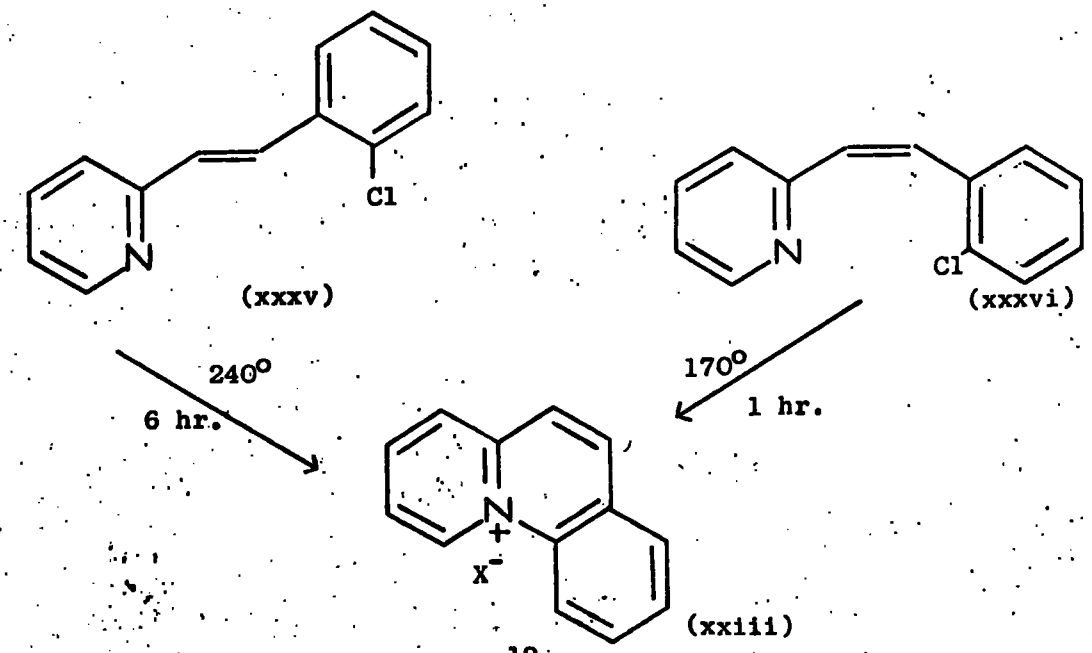
Benzo [b] quinolizinium bromide (xxii; X = Br) was prepared by Bradsher and Beavers[33] by the cyclisation with concentrated hydrobromic acid of the quaternary salt between pyridine 2-aldehyde and benzyl bromide.



(xxii)

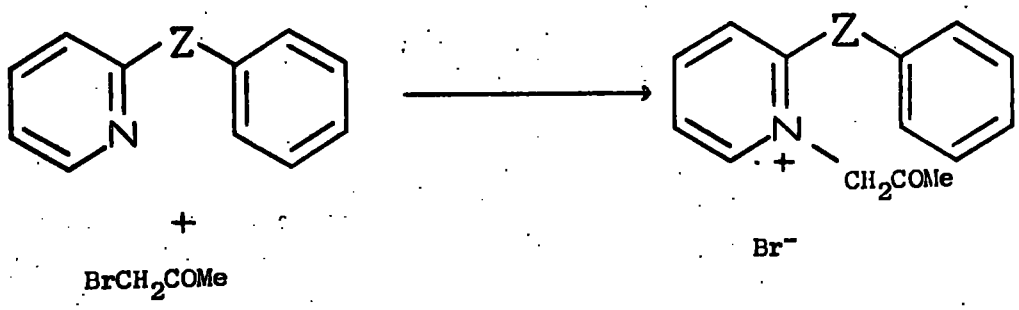
Bradsher et al[34,35,36,37,38,39,40,41,42] have since prepared many substituted benzo [b] quinolizinium salts by quaternising suitable α-haloalkylarenes with derivatives of pyridine 2-aldehyde, 2-acetylpyridine or 2-benzoylpyridine, and cyclodehydrating these quaternary salts.

Bradsher and Fozard[43] have recently reported the synthesis of benzo [c] quinolizinium salts. They prepared trans2'-chloro-2-stilbazole (xxxv) which was converted to the cis isomer (xxxvi) by irradiation with ultraviolet light. On heating the cis isomer at 170° cycloquaternisation occurred to give benzo [c] quinolizinium chloride (xxiii; X = Cl). They later found that the trans isomer (xxxv) could be directly converted to the benzo [c] salt (xxiii) by heating at 240° in the presence of iodine. The salt was isolated as the perchlorate (xxiii; X = ClO_4). Several substituted benzo [c] quinolizinium salts were also prepared.

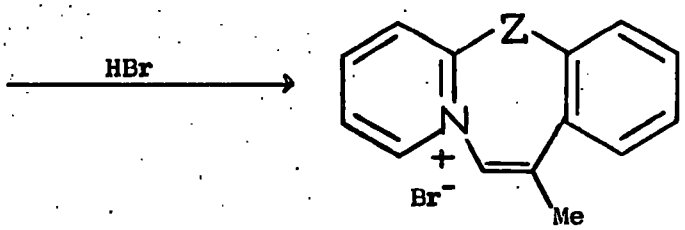


MORPHANTHRIDIZINIUM SALTS

7-Methylmorphanthridizinium salts (xxxvii; Z = CH_2)[44] and the analogous heterocyclic systems (xxxvii; Z = O)[45] and (xxxvii; Z = S)[46] have been synthesised by Bradsher et al[44,45,46]. They treated an appropriately 2-substituted pyridine with bromoacetone and cyclodehydrated the quaternary salt (xxxviii; Z = CH_2, O or S) with concentrated hydrobromic acid, to yield the tricyclic salt (xxxvii; Z = CH_2, O or S).



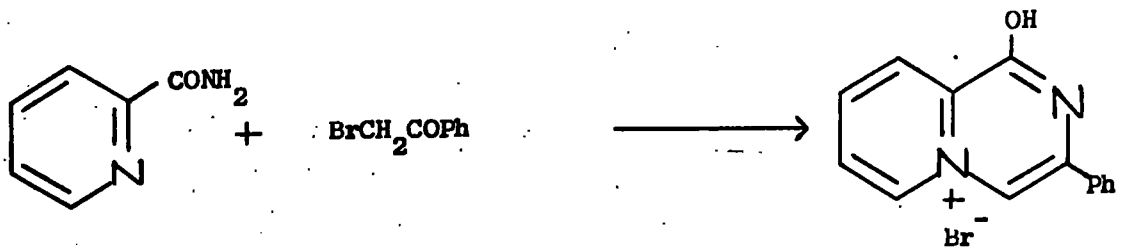
(xxxviii)



(xxxvii)

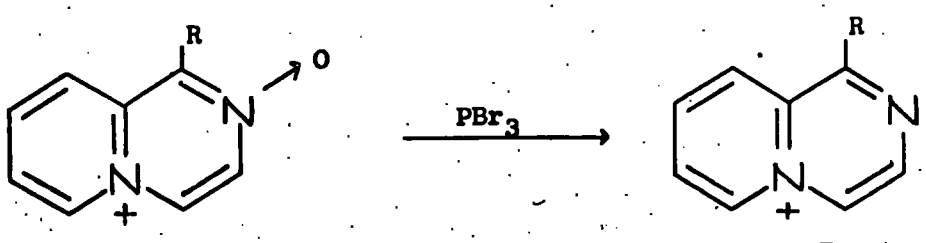
AZAQUINOLIZINIUM SALTS

Kröhnke has shown that when ω-bromoacetophenone was heated with 2-cyanopyridine or picolinic acid amide in acetonitrile as solvent, quaternisation and cyclodehydration occurred yielding 1-hydroxy-3-phenylpyrido [1, 2 - a] pyrazinium bromide (xxxix).



(xxxix)

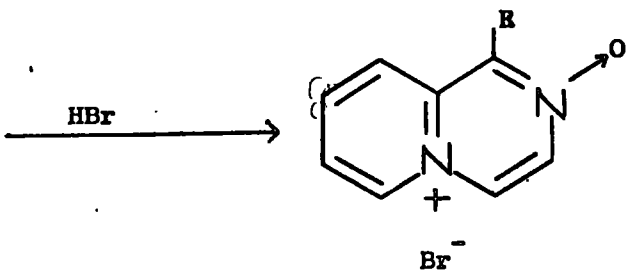
The synthesis of the 2-oxides of some pyrido [1, 2 - a] pyrazinium salts (xl; R = H, Me, Ph or Br) and their conversion by boiling phosphorus tribromide into the corresponding pyrido [1, 2 - a] pyrazinium salts (xli; R = H, Ph, or Br) has recently been reported by the Author[24], and is the subject of the first part of the discussion of this thesis.



(xl) (xli)

Bradsher and Telang[3] have also recently reported the synthesis of the 2-oxide (xl; R = H) by treating 2-oximinomethylpyridine with chloroacetaldehyde oxime and cyclising the monoquaternary salt (xlii) with concentrated hydrobromic acid.

(xlii)

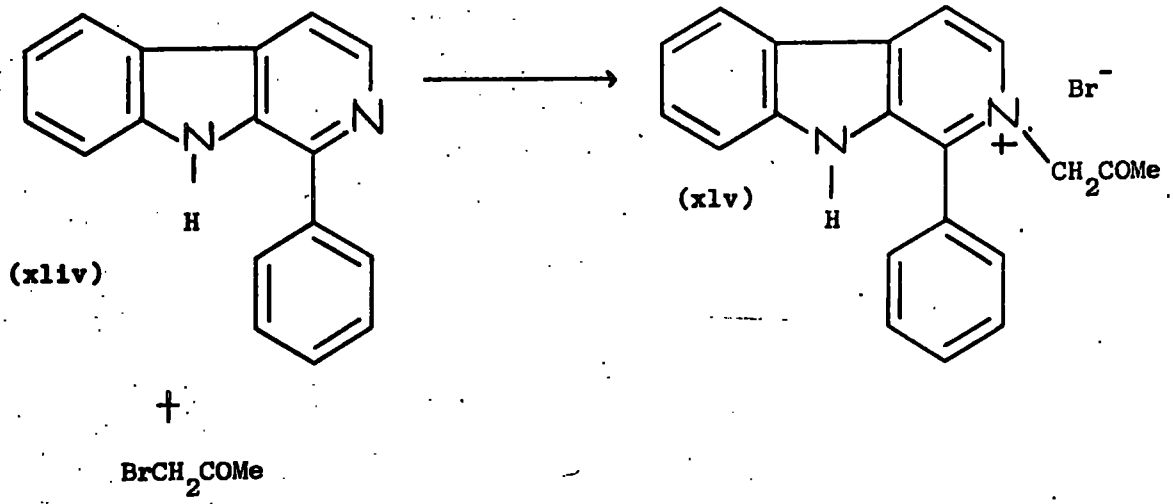


(xl)

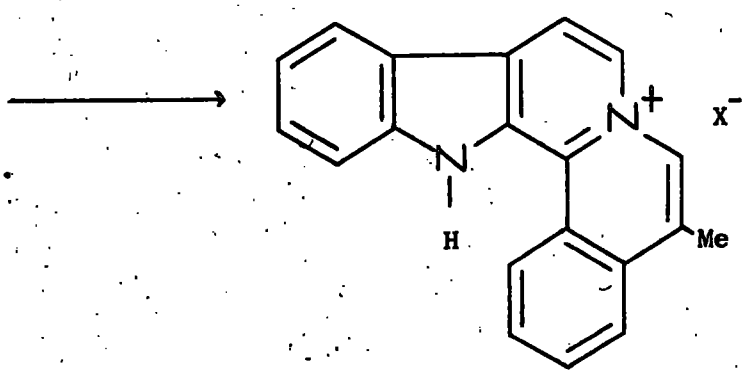
3-Substituted and 1, 3-disubstituted 2-oxides were also prepared[3] from suitable precursors.

BENZO [h] INDOLO [2, 3 - a] QUINOLIZINIUM SALTS

The 9-methyl derivative of benzo [h] indolo [2, 3 - a] quinolizinium perchlorate (xliii; X = ClO_4) was synthesised by Bradsher and Litzinger[47]. Treatment of 1-phenyl-9H-pyrido [3, 4 - b] indole (xliv) with bromoacetone followed by cyclisation of the monoquaternary salt (xlv) by heating in phosphoric acid yielded the required salt (xliii) which was characterised as the perchlorate (xliii; X = ClO_4).



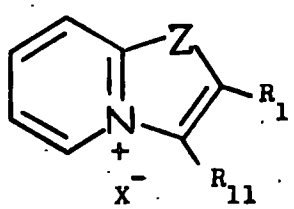
(xliv) + $BrCH_2COMe$ → (xlv)



(xliii)

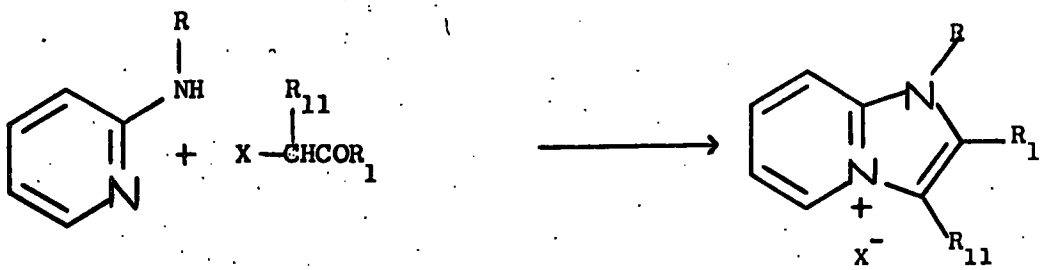
IMIDAZO [1, 2 - a] PYRIDINIUM SALTS AND RELATED COMPOUNDS

A series of salts of general formula (xlvi; Z = N - R, O or S) have been prepared by Bradsher et al[48, 49, 50].



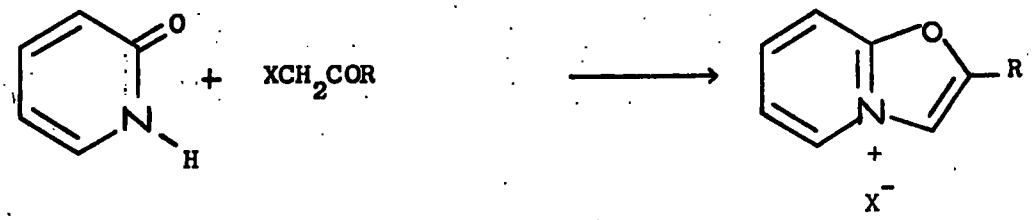
(xlvi)

2-Alkylamino and 2-arylaminopyridines were boiled under reflux with α-haloketones in acetone as solvent. The solids which separated from the solutions were the trisubstituted imidazo [1, 2 - a] pyridinium salts (xlvi; Z = N - R)[48].

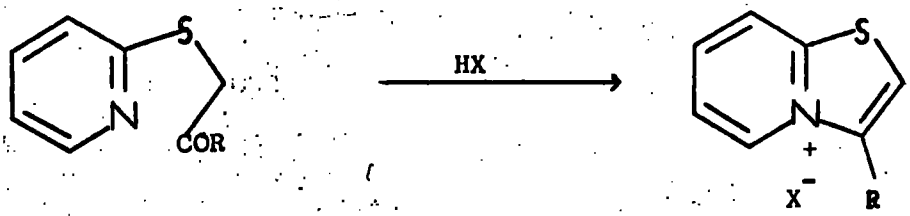


The use of chloroacetaldehyde oxime in place of the α-haloketone afforded, after hydrolysis and cyclisation of the intermediate monoquaternary salt, the 1-substituted salt (xlvi; Z = N - R, $R_1 = R_{11} = H$).

When a 2-pyridone was treated with α-haloketones in acetone as solvent, 2-substituted pyrido [2, 1 - b] oxazolium salts (xlvi; Z = O, R_{11} = H) were produced[49].

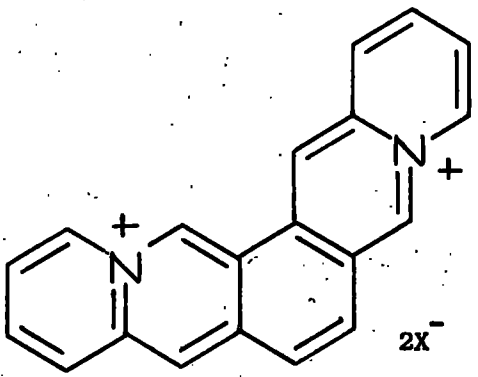


The analogous pyridothiazolium salts (xlvi; Z = S, R_1 = H, R_{11} = H or Me) were prepared by Bradsher and Lohr[50] from 2-pyridyl sulphides having a carbonyl function beta to the sulphide linkage. In the presence of mineral acid cyclodehydration occurred yielding the 3-substituted pyrido [2, 1 - b] thiazolium salts (xlvi; Z = S, R_1 = H, R_{11} = H or Me).

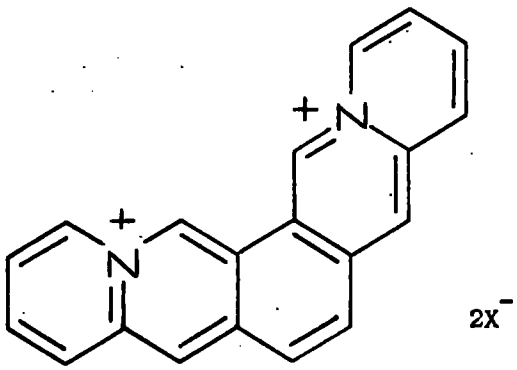


DIAZONIAPENTAPHENE SALTS

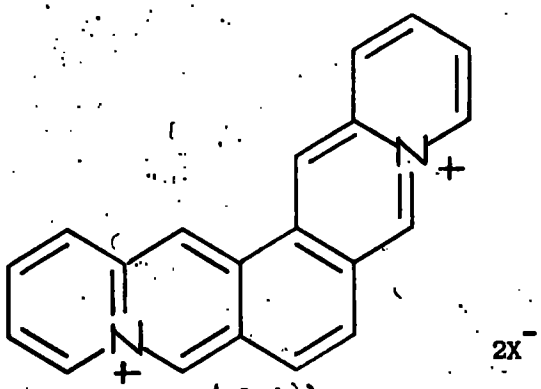
The first fully aromatic fused ring systems containing two quaternary bridgehead nitrogen atoms were synthesised by Bradsher and Parham[51]. They cyclised the quaternary salts formed between 2-(1, 3-dioxolan-2-yl) pyridine and the three 1, 1'-dibromoxylenes with polyphosphoric acid, and obtained the three isomeric diazoniapentaphene salts (xlvii), (xlviii) and(xlxix).



(xlvii)



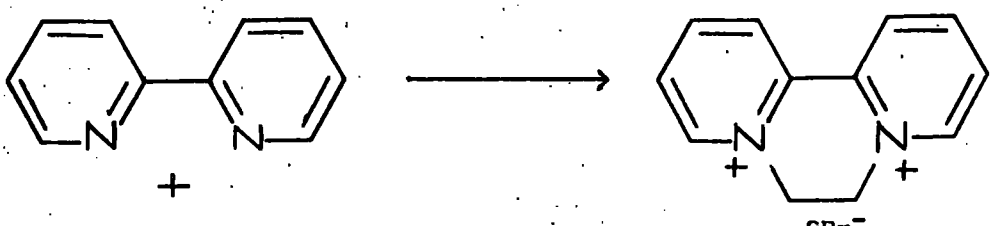
(xlviii)



(xlxix)

DIPYRIDO [1, 2 - a:2', 1' - c] PYRAZIDI-INIUM SALTS

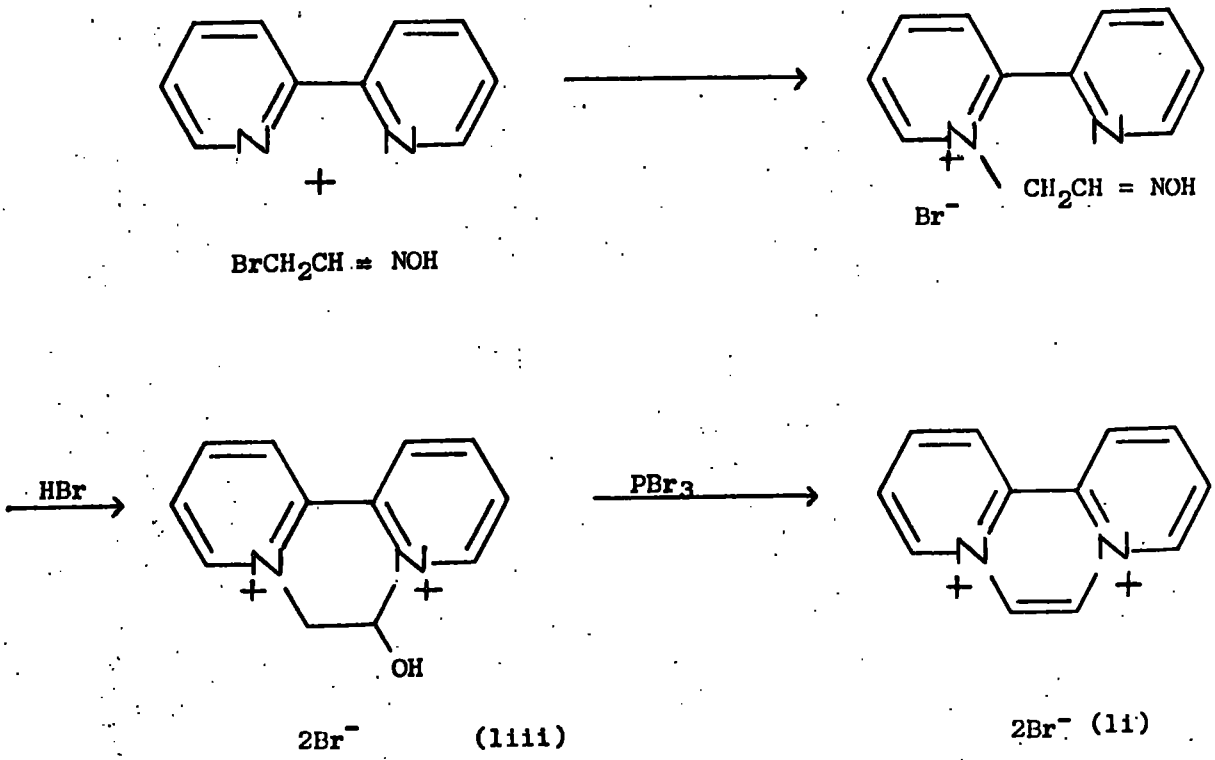
6, 7-Dihydrodipyrido [1, 2 - a:2', 1' - c] pyrazidi-inium dibromide (1) was synthesised by Fielden, Homer and Jones[52] who quaternised 2, 2'-bipyridyl with ethylene dibromide.



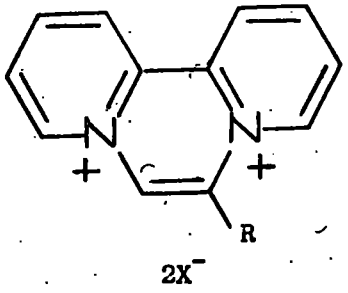
(1)

Similar diquaternary salts have also been prepared[53,54,55,56] using various α,ω-polymethylene dihalides.

The preparation of the fully aromatic system (1i) has been reported by Corr and Glover[57]. They treated 2, 2'-bipyridyl with bromoacetaldehyde oxime and cyclised the monoquaternary salt (1ii) with concentrated hydrobromic acid to the hydroxy dibromide (1iii). Dehydration with boiling phosphorus tribromide effected the conversion to dipyrido [1, 2 - a:2', 1' - c] pyrazidi-inium dibromide (1i).



Substituted dipyrido [1, 2 - a: 2', 1' - c] pyrazidi-inium salts have also been reported by the same authors[57] who, using 2, 2'-bipyridyl and bromoacetone or ω-bromoacetophenone, formed the monoquaternary salts which were cyclodehydrated to the 7-methyl or 7-phenyl derivatives (liv; R = Me or Ph) respectively with boiling phosphorus tribromide.

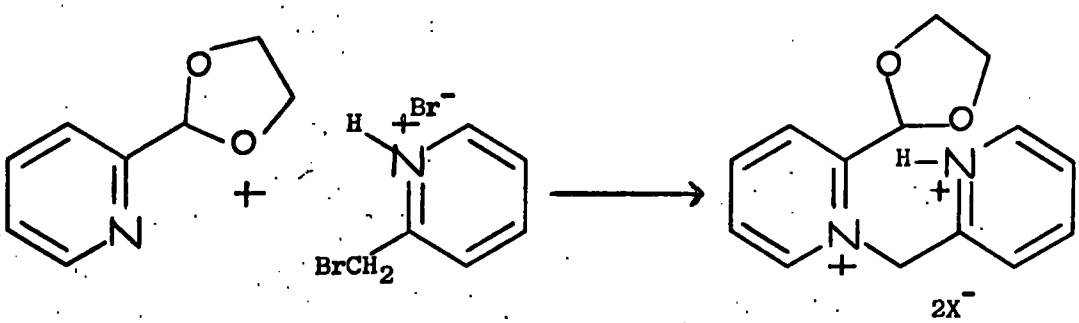


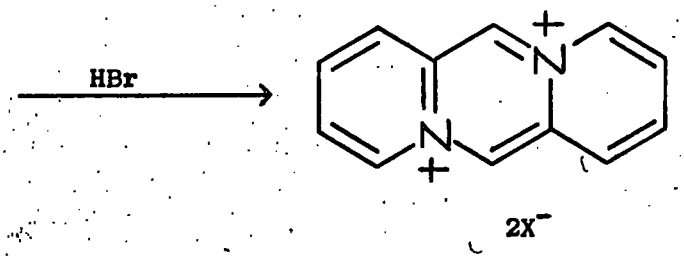
(liv)

Synthesis of the aromatic diquaternary salts (liv; R = H or Me) have recently been reported by Calder and Sasse[58].

DIPYRIDO [1, 2 - a:1', 2' - d] PYRAZIDI-INIUM SALTS

Glover and Morris[59] synthesised dipyrido [1, 2 - a:1',2' - d] pyrazidi-inium salts (1v) by treating 2-(1, 3-dioxolan-2-yl)pyridine with the hydrobromide of 2-pyridylmethyl bromide in tetramethylenesulphone as solvent. The monoquaternary salt was isolated as a red oil which readily yielded the aromatic diquaternary salt (1v; X = Br) on warming with concentrated hydrobromic acid. The salt was characterised as the anhydrous diperchlorate (1v; X = ClO_4).

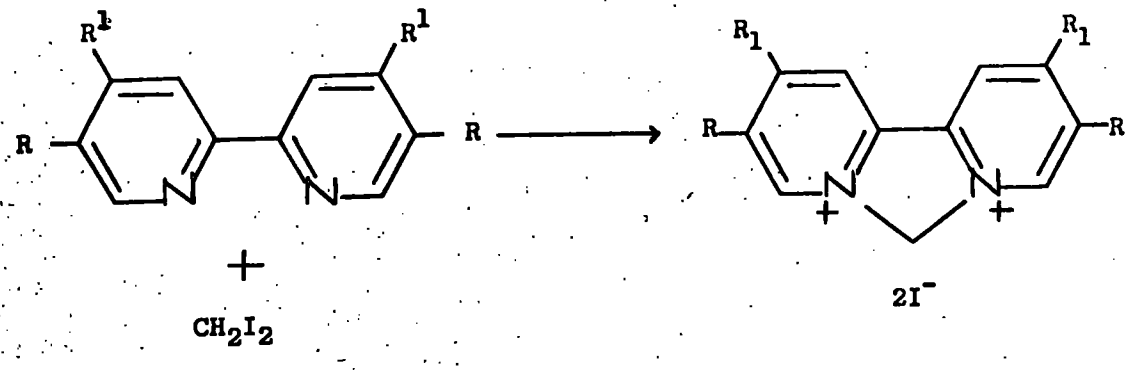




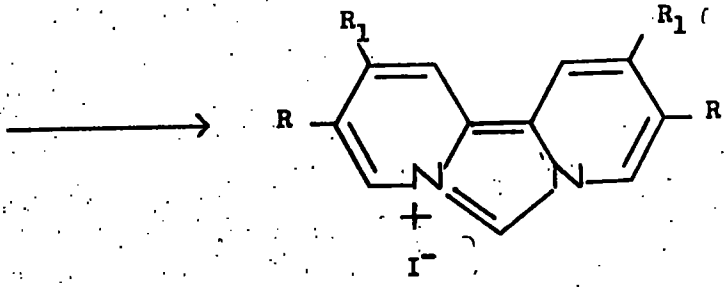
(1v)

DIPYRIDO [1, 2 - c:2', 1' - e] IMIDAZOLIUM SALTS

The synthesis of these salts (lvi) has been reported by Calder and Sasse[60] who treated 2,2'-bipyridyl or a substituted derivative with methylene di-iodide in acetonitrile as solvent. They suggested the formation of the intermediate diquaternary salts (lvii) which in ethanolic solution underwent conversion to the monoquaternary salts (lvi).



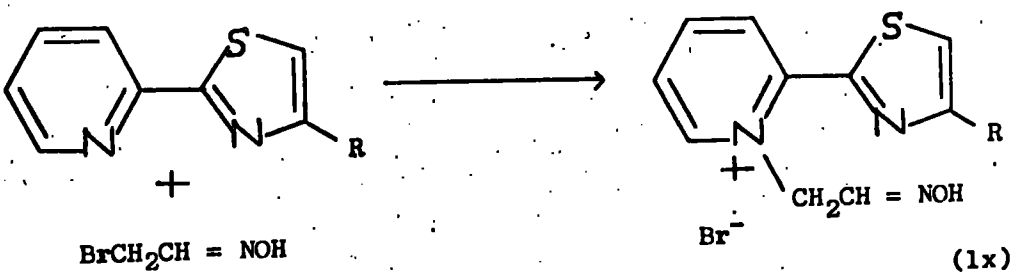
(lvii)



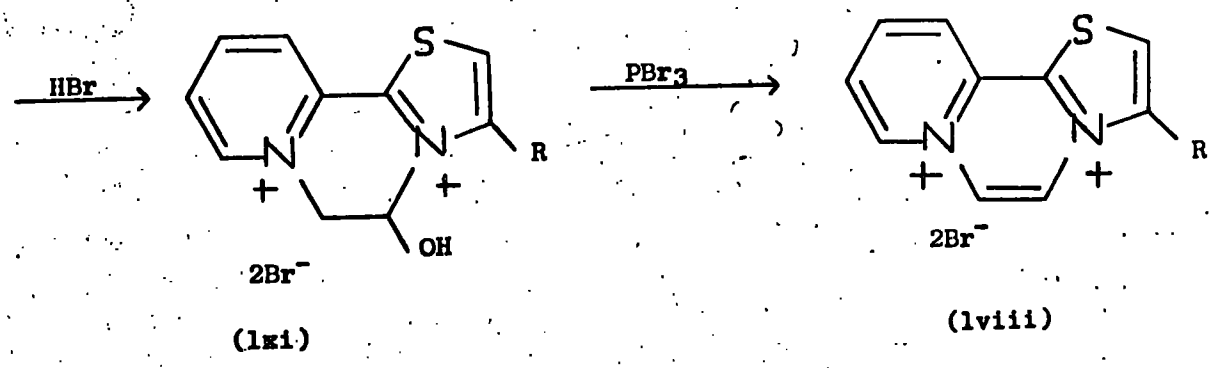
(lvi)

PYRIDO THIAZOLO PYRAZIDI-INIUM SALTS

The syntheses of pyrido [1, 2 - a] thiazolo [2, 3 - c] pyrazidi-inium salts (lviii) and pyrido [1, 2 - a] thiazolo [4, 3 - c] pyrazidi-inium salts (lix) have recently been reported by Glover and Thomas[61]. Treatment of 2-(2-pyridyl)thiazole, or the 4-methyl derivative with bromoacetaldehyde oxime gave the monoquaternary salts (lx; R = H or Me), which, when warmed with concentrated hydrobromic acid yielded the hydroxy diquaternary salts (lxi; R = H or Me). Conversion to the fully aromatic systems (lviii; R = H or Me) was accomplished by boiling under reflux suspensions of the hydroxy salts (lxi; R = H or Me) in phosphorus tribromide.



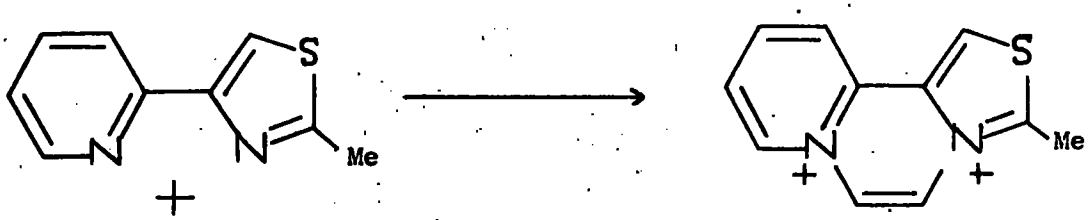
(lx)



(lxi)

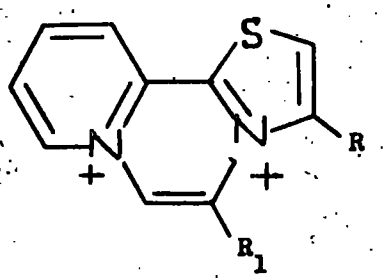
(lviii)

3-Methyl-pyrido [1, 2 - a] thiazolo [4, 3 - c] pyrazidi-inium salts (lix) were prepared by a similar procedure using 2-methyl-4-(2-pyridyl)thiazole as a precursor.

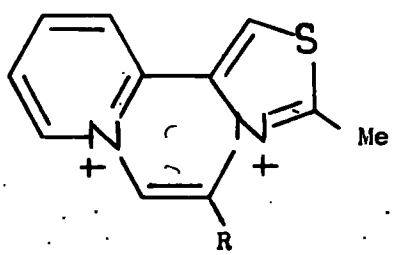


(lix)

The monoquaternary salts formed between the pyridylthiazoles and bromoacetone or ω-bromoacetophenone could be cyclodehydrated with phosphorus tribromide to yield the 5-methyl derivatives (lxii; R = H or Me, R_1 = Me) and (lxiii; R = Me) or the 5-phenyl derivatives (lxii; R = H or Me, R_1 = Ph) and (lxiii; R = Ph) of the aromatic diquaternary salts (lviii) and (lix) respectively.



(lxii) 2Br⁻



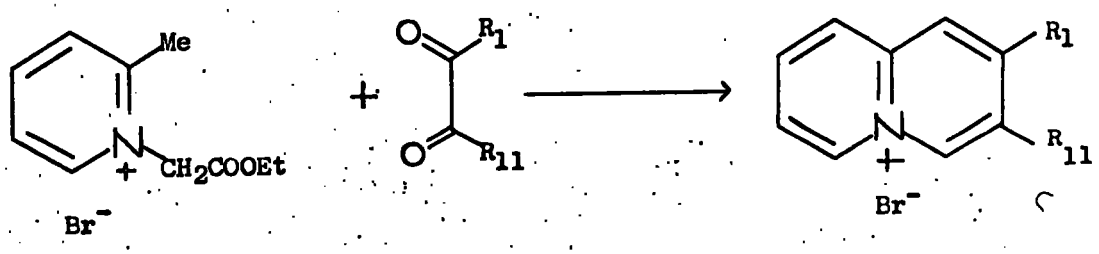
2Br⁻ (lxiii)

METHOD III

The third method which has been used for the synthesis of the quinolizinium nucleus involves the intermolecular condensation of a suitable quaternary salt of a 2-substituted pyridine with a second component.

QUINOLIZINIUM SALTS

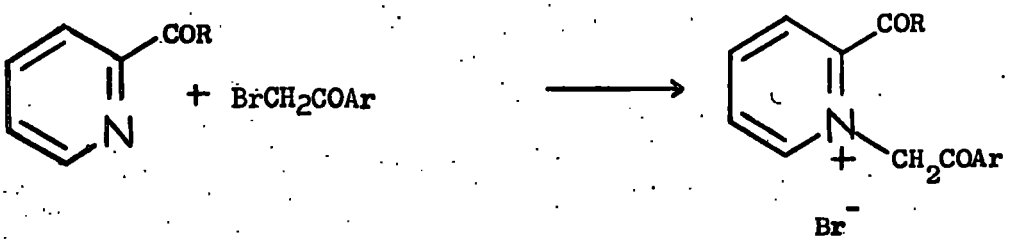
Several 2, 3-dialkylquinolizinium salts have been prepared by Heffe, Jann and Westphal[62] using this method. They treated the monoquaternary salt between 2-picoline and ethyl bromoacetate with α-dicarbonyl compounds in ethanolic dibutylamine as solvent to obtain the substituted quinolizinium salts (lxiv).

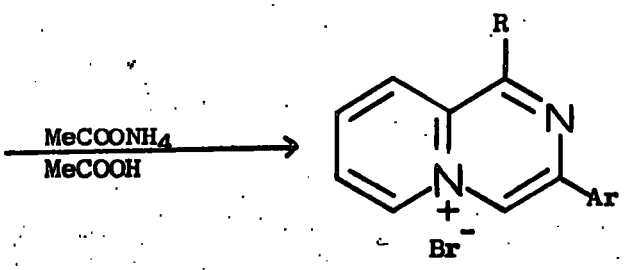


(lxiv)

PYRIDO [1, 2-a] PYRAZINIUM SALTS

The preparation of several 1-alkyl-3-aryl- and of 1-aryl-3-aryl-pyrido [1, 2-a] pyrazinium salts (lxv) has been reported by Kröhnke[1,2]. The monoquaternary salts between 2-acylpyridines and ω-bromoacetophenone were heated with ammonium acetate in acetic acid solutions to obtain the required salts (lxv).





(lxv)

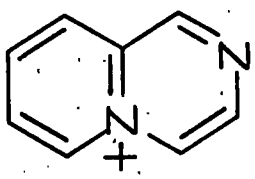
DISCUSSION

PART I

THE SYNTHESIS OF SOME PYRIDO [1, 2-a] PYRAZINIUM 2-OXIDE SALTS AND THEIR CONVERSION TO PYRIDO [1, 2-a] PYRAZINIUM SALTS

The preparation of compounds containing one or two quaternary nitrogen atoms at bridgehead positions in fused aromatic ring systems has been outlined in the introduction and it has been shown how the methods available for the synthesis of these systems fall essentially into three classes. The first involves the attachment of a suitable side chain to the carbon atom adjacent to the nitrogen atom of a pyridine ring followed by ring closure onto the pyridine nitrogen atom, whilst the second approach is to quaternise a suitably 2-substituted pyridine with a substituted alkyl halide containing a group capable of condensing with the 2-substituent. The third method involves the intermolecular condensation of a suitable quaternary salt of a 2-substituted pyridine with a second component. Typical examples of these reactions are those described by Nesmeyanov and Rybinskaia[26] (p. 13), Bradsher and Beavers[30] (p. 17) and Krönhke[1,2] (p. 34) respectively.

No unsubstituted pryido [1, 2-a] pyrazinium salts (lxvi) have yet been reported and their synthesis was accordingly undertaken.

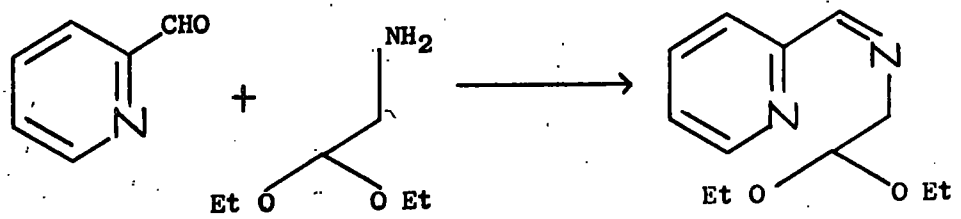


X^-

(lxvi)

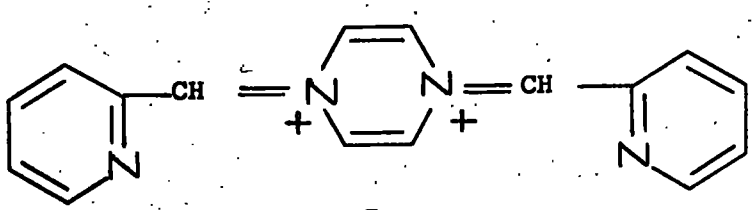
PYRIDO [1, 2-a] PYRAZINIUM BROMIDE 2-OXIDE (lxvii)

A convenient method for the synthesis of unsubstituted pyrido [1, 2-a] pyrazinium salts would be the cyclisation in acid media of the anil (lxviii) formed by the condensation of aminoacetal with pyridine 2-aldehyde.



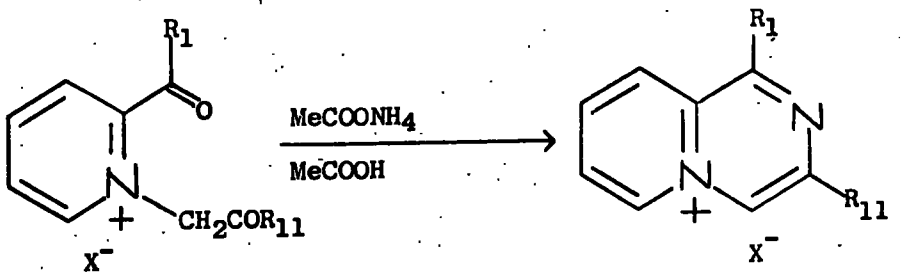
(lxviii)

It has been shown by Glover, Jones and Trenholm[63], however, that anils of the type (lxviii) undergo intermolecular condensation in the presence of mineral acid; the anil (lxviii) yielding 1, 4-di-(2-pyridylmethylene)pyrazidi-inium salts (lxix).



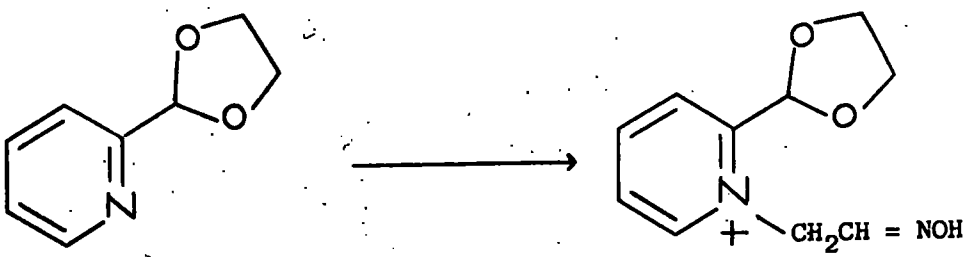
(lxix)

Kröhnke[1,2] described the synthesis of some 1,3-disubstituted pyrido [1,2-a] pyrazinium salts (lxv) by the intermolecular condensation of the quaternary salt (lxx) with ammonium acetate in acetic acid as solvent.



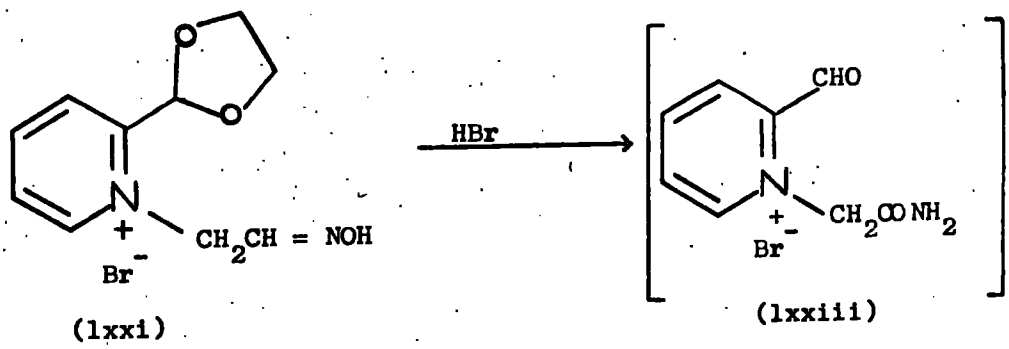
(lxx) (lxv)

It seemed therefore, that a possible route to the unsubstituted salt (lxv; $R_1 = R_{11} = H$) would be via the monoquaternary salt (lxx; $R_1 = R_{11} = H$), resulting from the hydrolysis of quaternary salt (lxxi) between 2-(1, 3-dioxolan-2-yl)pyridine and bromoacetaldehyde oxime.

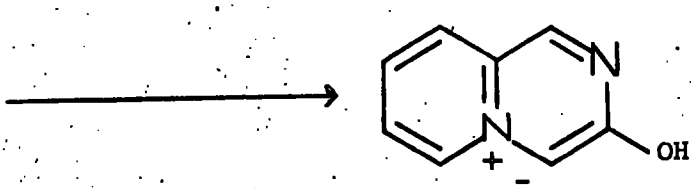


(lxxi)

In an attempt to effect hydrolysis of both the acetal and oximino functions, the salt (lxxi) was heated with concentrated hydrobromic acid. Instead of the expected dicarbonyl compound (lxx, $R_1 = R_{11} = H$) the product was a compound of molecular formula $C_8H_7BrN_2O$. The infra-red spectrum showed no bands which could be attributed to a carbonyl group whilst the ultra-violet spectrum extended to 3600 A°, (Fig. 1, p. 65) suggesting the possible presence of a fused bicyclic aromatic system containing an additional chromophore. A possible structure is 3-hydroxy-pyrido[1, 2-a]pyrazinium bromide (lxxii). A reaction sequence could be postulated involving hydrolysis of the acetal function and a Beckmann type rearrangement of the oximino function giving the intermediate 1-amidomethyl quaternary salt (lxxiii). Intramolecular condensation would then yield the 3-hydroxy salt (lxxii).



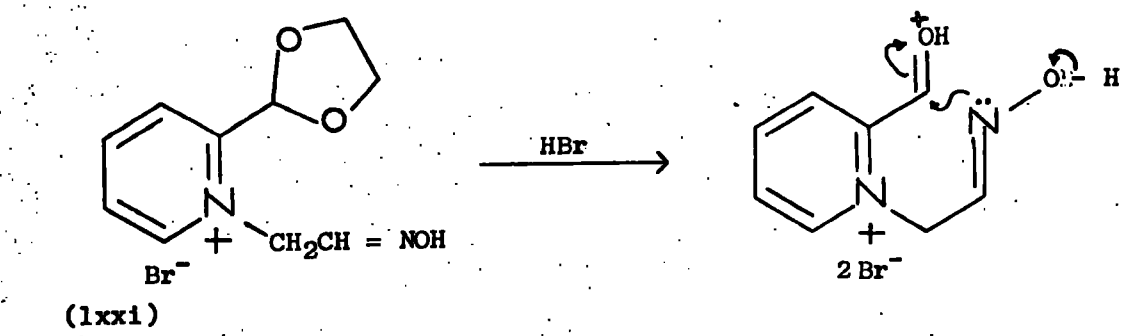
(lxxi) (lxxiii)



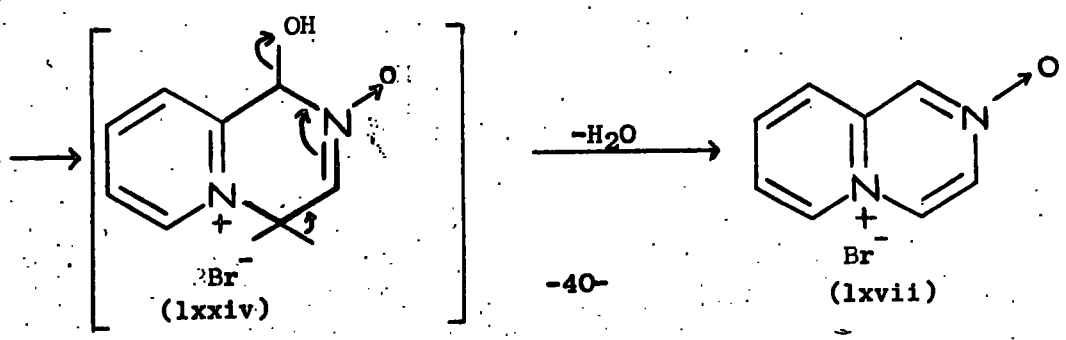
(lxxii)

A precedent for the cyclodehydration step was recorded by Krönhke[1,2] who prepared 1-hydroxy-3-phenyl-pyrido[1, 2-a]pyrazinium salts from picolinic acid amide and ω-bromoacetophenone. However, attempts to test this hypothesis by treating the quaternary salt between 2-(1, 3-dioxolan-2-yl)pyridine and chloroacetamide with concentrated hydrobromic acid were unsuccessful, no products being isolated from the resulting solutions.

Further consideration of the available data lead to the conclusion that the salt of molecular formula $C_8H_7BrN_2O$ was pyrido[1, 2-a]pyrazinium bromide 2-oxide (lxvii). Acid hydrolysis of the acetal function would give a protonated carbonyl oxygen atom; subsequent donation of the nitrogen lone pair of electrons onto the electron deficient carbon atom and expulsion of a proton would give the alcohol (lxxiv) which on dehydration would give the 2-oxide (lxvii).

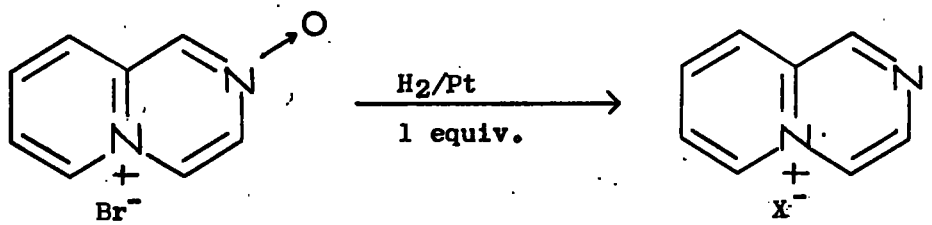


(lxxi)



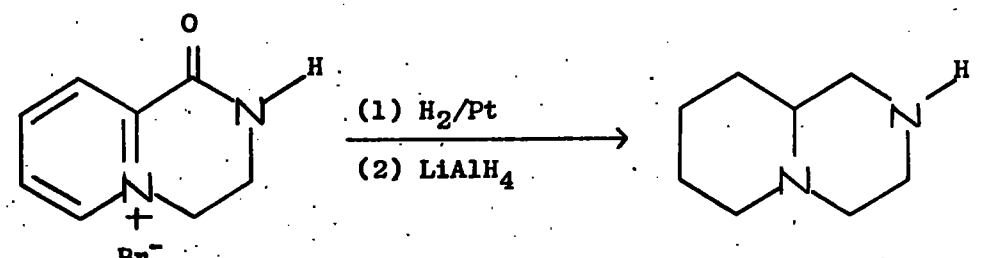
(lxxiv) (lxvii)

Ishii[64] has reported that catalytic hydrogenation of pyridine N-oxides affords the deoxygenated pyridine derivatives. Controlled hydrogenation of the salt (lxvii) with one equivalent of hydrogen yielded pyrido[1, 2-a]pyrazinium bromide (lxvi; X = Br) giving support for the proposed 2-oxide structure.



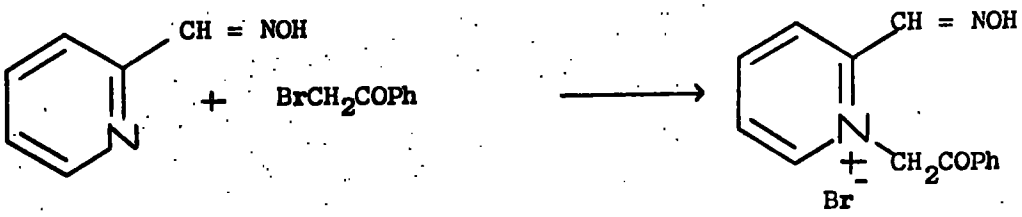
(lxvii) (lxvi)

Complete hydrogenation of the 2-oxide over Adams' catalyst gave perhydropyrido[1, 2-a] pyrazine (II) the dipicrate of which melted with decomposition at 275° - 278°. Melting points of 240°[65] and 250° - 260°[3,66] have been reported for this dipicrate but although the sample darkened at 250° a definite fusion occurred at 275° - 278°. It was therefore compared and found to be identical with a sample[63] derived from the lactam (lxxv) by hydrogenation and subsequent reduction with lithium aluminium hydride.

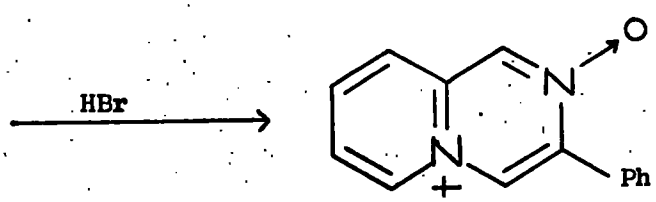


(lxxv) (ii)

Further support for the 2-oxide structure was given by Bradsher and Telang[3] (p. 22) who reported the synthesis of several substituted pyrido[1, 2-a] pyrazinium 2-oxide salts. One of the salts, prepared by the cyclisation in acid media of the quaternary salt (lxxvi) between 2-oximinomethylpyridine and ω-bromoacetophenone was 3-phenyl-pyrido[1, 2-a]pyrazinium bromide 2-oxide (lxxvii) thus precluding the 3-hydroxy structure for the salt (lxvii).



(lxxvi)

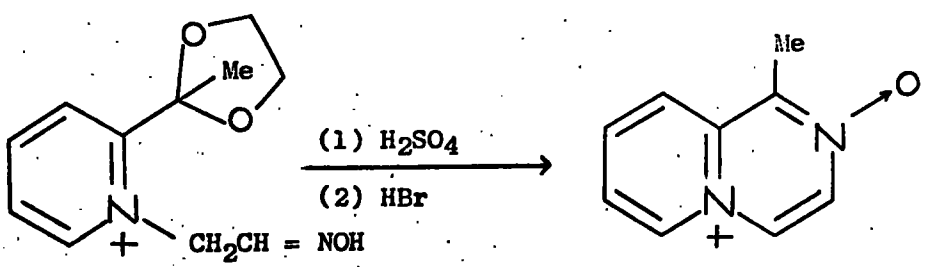


(lxxvii)

1-METHYL-PYRIDO[1, 2-a] PYRAZINIUM BROMIDE 2-OXIDE (lxxviii)

Initial attempts to prepare the 1-methyl 2-oxide (lxxviii) by treating 2-acetylpyridine with bromoacetaldehyde oxime afforded a crystalline solid in low yield (4%). The infra-red spectrum of this salt suggested that it was the 1-methyl 2-oxide (lxxviii).

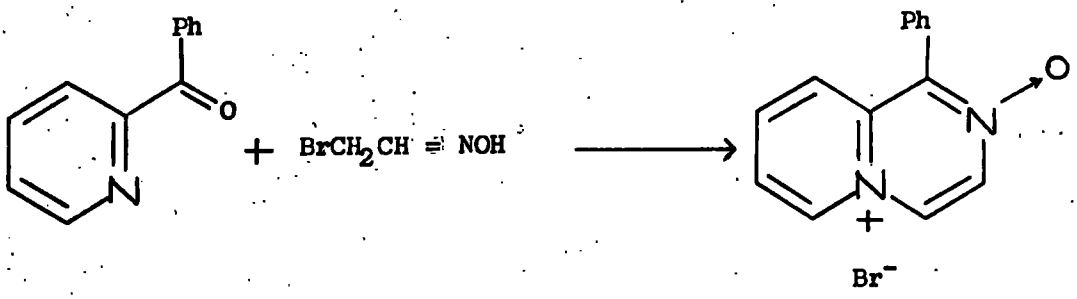
In an attempt to synthesise the required salt (lxxviii) in good yield, the monoquaternary salt (lxxix) between 2-(2-methyl [1, 3] dioxolan-2-yl)pyridine and bromoacetaldehyde oxime was prepared and treated with concentrated hydrobromic acid. Cyclisation to the 1-methyl 2-oxide occurred but again in poor yield (10%). Hydrolysis of the acetal function and subsequent cyclodehydration was eventually accomplished using concentrated sulphuric acid. After washing the reaction mixture with ether, the residual oil was treated with concentrated hydrobromic acid to give 1-methyl-pyrido[1, 2-a] pyrazinium bromide 2-oxide (lxxviii) in good yield (84%). The structure was confirmed by elemental analysis and by its infra-red and ultra-violet absorption spectra; the ultra-violet spectrum is illustrated in Fig. 1. (p. 65).



(lxxix) (lxxviii)

1-PHENYL-PYRIDO[1, 2-a] PYRAZINIUM BROMIDE 2-OXIDE (lxxx)

1-Phenyl-pyrido[1, 2-a]pyrazinium bromide 2-oxide (lxxx) was prepared in moderate yield by warming a mixture of 2-benzoylpyridine and bromoacetaldehyde oxime.



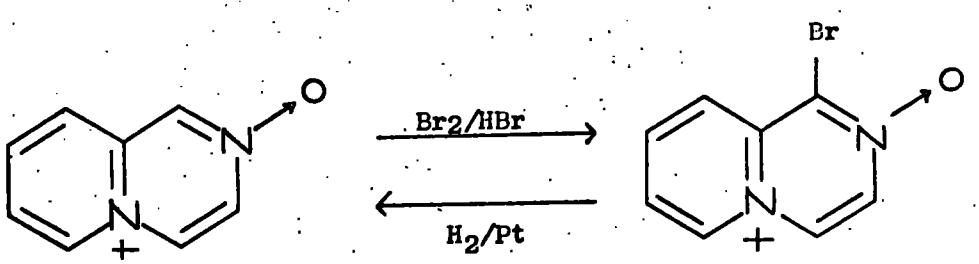
(lxxx)

The ultra-violet spectrum of the salt (lxxx) was similar to those of the unsubstituted 2-oxide (lxvii) and the 1-methyl derivative (lxxviii) with the general loss of fine structure associated with a phenyl substituted compound (Fig. 1, p. 65).

1-BROMO-PYRIDO[1, 2-a] PYRAZINIUM BROMIDE 2-OXIDE (lxxxi; X = Br)

Bromination of pyrido[1, 2-a] pyrazinium bromide 2-oxide (lxvii) was accomplished by stirring a suspension of the 2-oxide (lxvii) in a cold solution of bromine in concentrated hydrobromic acid. The solution was boiled to destroy any perbromide (lxxxi; X = Br_3) formed, and the bromo compound (lxxxi; X = Br) isolated.

Controlled hydrogenation of the bromo salt (lxxxi; X = Br) with one equivalent of hydrogen gave the parent 2-oxide (lxvii) indicating a monobrominated derivative; this was confirmed by mass spectroscopic analysis[67] of the picrate (lxxxi; X = picrate) which gave the mass number of the cation as 225 (^{79}Br). The n.m.r. spectrum of the bromo salt (lxxxi; X = Br) in trifluoracetic acid as solvent showed a two proton signal in the region τ 0.2 - 0.4 assigned to the protons on C_4 and C_6, a one proton doublet centred at τ 0.9 assigned to the proton on C_3 and a three proton signal in the region τ 1.2 - 1.8 attributed to the protons on C_7, C_8, and C_9, showing the salt to be 1-bromo-pyrido[1, 2-a] pyrazinium bromide 2-oxide (lxxxi; X = Br).



(lxvii) (lxxxi)

PYRIDO[1,2-a] PYRAZINIUM SALTS

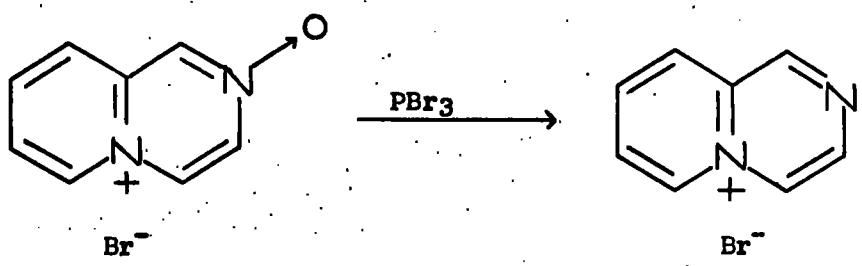
Ochiai and Naito[68] have shown that a solution of phosphorus trichloride in chloroform can be used to deoxygenate pyridine N-oxides.

To avoid the possibility of a mixture of anions in the product, phosphorus tribromide was used to prepare pyrido[1, 2-a] pyrazinium bromide (lxvi; X = Br) from the 2-oxide (lxvii). A suspension of pyrido[1, 2-a] pyrazinium bromide 2-oxide (lxvii) in phosphorus tribromide was boiled under reflux, cooled, and the insoluble product isolated. Elemental analysis gave the molecular formula as $C_8H_7BrN_2$. The wavelengths of the absorption maxima in the ultra-violet spectrum of the product (Fig. 2, p.66) closely resembled those of the pyrido[1, 2-a] pyrimidinium salts prepared by Nesmeyanov et al[25]. The molecular extinction coefficients were, however, not reported:

Absorption maxima of pyrido[1, 2-a] pyrazinium bromide (lxvi; X = Br) A^{o} 3360, 3220, 3100, 2870, 2760, 2320.

Absorption maxima of pyrido[1, 2-a] pyrimidinium salts A^{o} 3360, 3180, 3120, 3040, 2740, 2280.

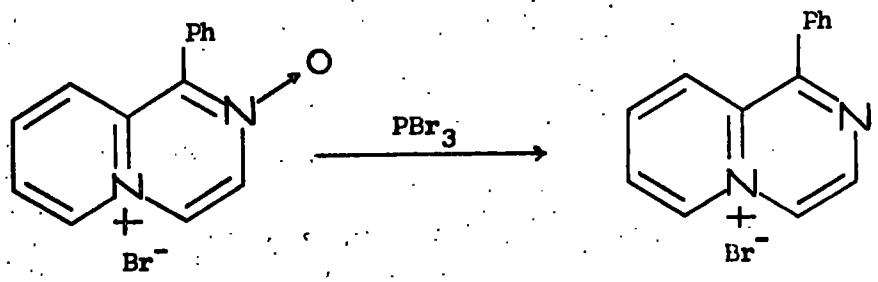
The infra-red spectrum of this salt (lxvi; X = Br) was identical to that of the sample obtained by the controlled catalytic hydrogenation of the 2-oxide (lxvii).



(lxvii) (lxvi)

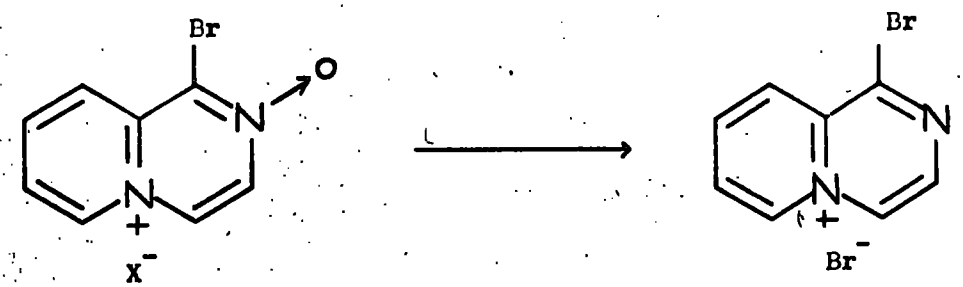
Treatment of 1-methyl-pyrido[1, 2-a] pyrazinium bromide 2-oxide (lxxviii) with phosphorus tribromide did not effect deoxygenation and the 2-oxide was recovered unchanged. The use of thionyl chloride afforded an intractable gum. Bradsher and Telang[3] reported that they were unable to deoxygenate 3-methyl-pyrido[1, 2-a]pyrazinium bromide 2-oxide by boiling under reflux a suspension of the salt in phosphorus trichloride.

The 1-phenyl 2-oxide (lxxx) readily afforded 1-phenyl-pyrido[1, 2-a] pyrazinium bromide (lxxxii) on treatment with phosphorus tribromide. The ultraviolet spectrum was comparable to that of the unsubstituted salt (lxvi; X = Br) with the expected loss of fine structure.



(lxxx) (lxxxii)

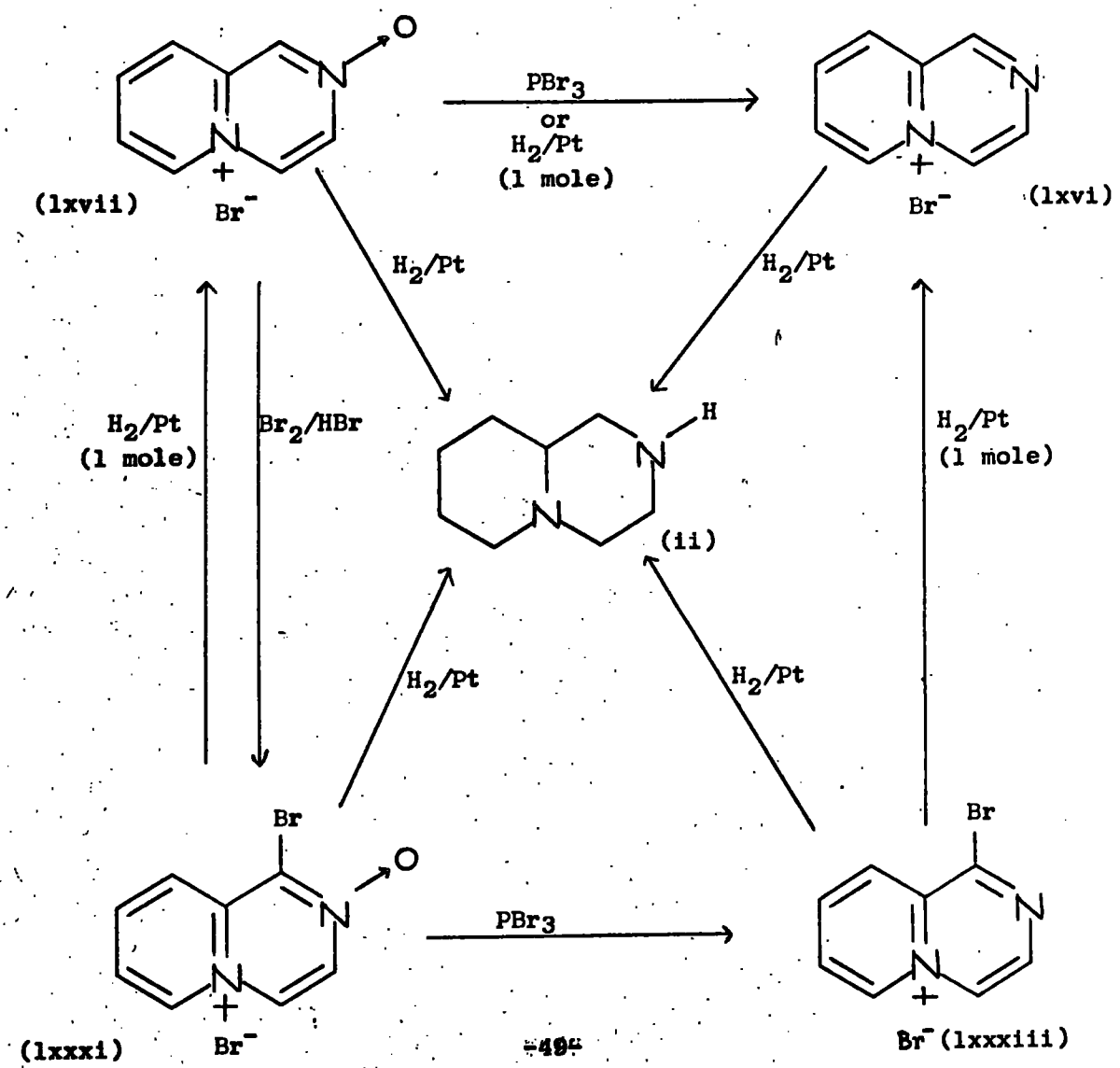
1-Bromo-pyrido[1, 2-a]pyrazinium bromide (lxxxiii) was also prepared from the 1-bromo 2-oxide (lxxxi; X = Br) using phosphorus tribromide. The ultra-violet spectrum was similar to that of the unsubstituted salt (lxvi) with the characteristic bathochromic shift associated with a nuclear bromo substituent.



(lxxxi) (lxxxiii)

Controlled hydrogenation of the bromo salt (lxxxiii) with one equivalent of hydrogen afforded pyrido[1, 2-a]pyrazinium bromide (lxvi).

SUMMARY OF THE REACTIONS OF PYRIDO[1, 2-a] PYRAZINIUM BROMIDE 2-OXIDE



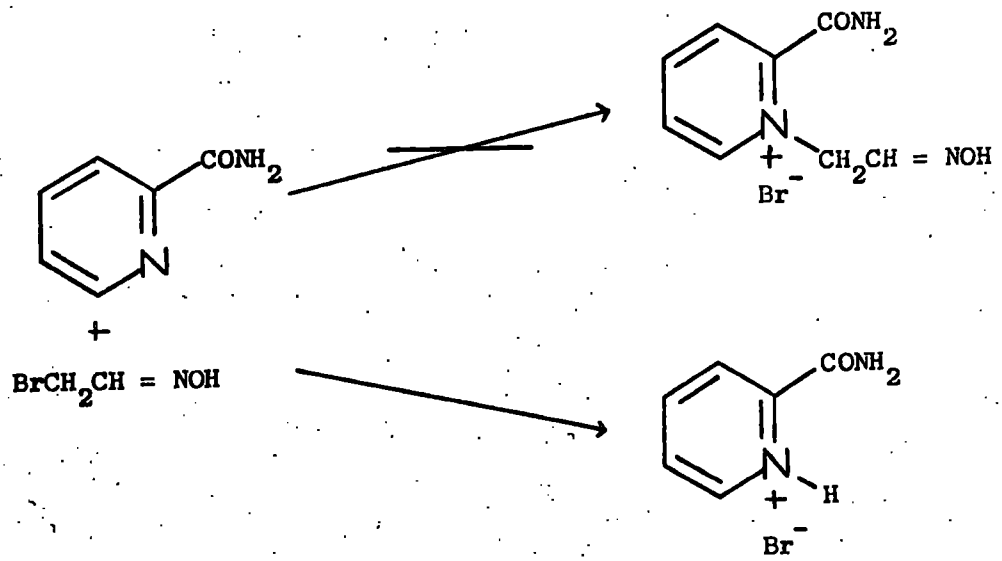
PART II

SOME OXYGENATED DERIVATIVES OF PYRIDO[1, 2-a]PYRAZINIUM SALTS

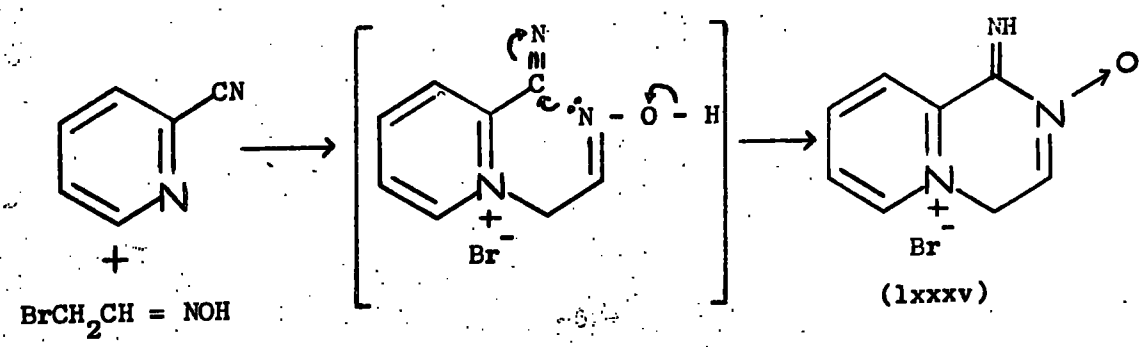
1, 2-DIHYDRO-1-OXO-PYRIDO[1, 2-a] PYRAZINIUM BROMIDE (lxxxiv)

Krönhke has described the preparation of 1-hydroxy-3-phenyl-pyrido [1, 2-a] pyrazinium salts by the treatment of picolinic acid amide or 2-cyanopyridine with ω-bromoacetophenone (p. 21). A possible route to 1-hydroxy-pyrido[1, 2-a] pyrazinium bromide would therefore be via the hydrolysis and subsequent cyclisation in acid media of the monoquaternary salts between picolinic acid amide or 2-cyanopyridine and bromoacetaldehyde oxime.

A mixture of picolinic acid amide and bromoacetaldehyde oxime was warmed until homogeneous and allowed to stand at room temperature for fourteen days. The reaction mixture was washed with acetone and the residual solid purified by sublimation. Elemental analysis indicated that the salt was picolinic acid amide hydrobromide and this was confirmed by comparison of the infra-red spectrum of the salt with that of an authentic sample prepared by the addition of hydrobromic acid to picolinic acid amide.



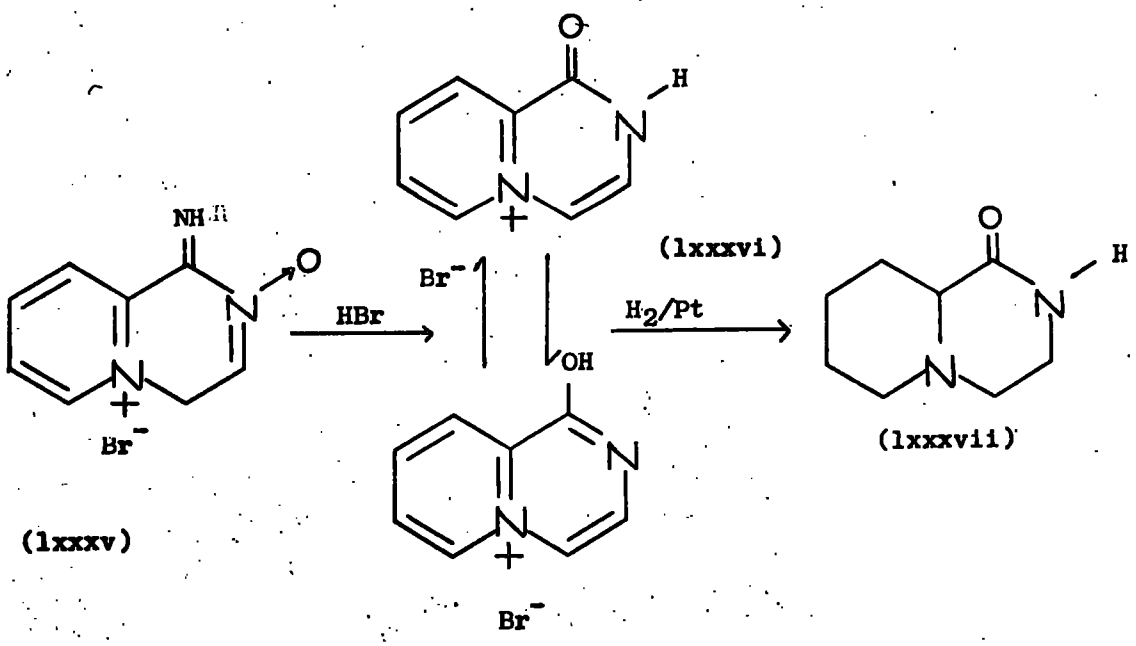
Initial attempts to bring about a reaction between 2-cyanopyridine and bromoacetaldehyde oxime by heating a mixture of the two compounds either alone, or in tetramethylenesulphone as solvent were unsuccessful. Quaternisation was eventually achieved by allowing a solution of 2-cyanopyridine and bromoacetaldehyde oxime to stand at room temperature. After three days yellow crystals separated from the solution but only after thirty days was an appreciable yield obtained. Elemental analysis of the new quaternary salt indicated a molecular formula of $C_8H_8BrN_3O$ whilst catalytic hydrogenation afforded a base, the infra-red spectrum and dipicrate of which were identical to those of perhydropyrido[1, 2-a] pyrazine. The ultra-violet spectrum of the salt showed no appreciable absorption beyond 3000 A° indicating the absence of a fully aromatic fused bicyclic system whilst the infra-red spectrum showed a band at 3220 cm^{-1} attributed to an imino group. It was therefore concluded that the salt was 1, 4-dihydro-1-imino-pyrido [1, 2-a]pyrazinium bromide 2-oxide (lxxxv).



(lxxxv)

A possible mechanism would involve donation of the oxime nitrogen lone pair of electrons onto the electron deficient nitrile carbon atom followed by proton migration to give the imine (lxxxv).

Treatment of the imine (lxxxv) with concentrated hydrobromic acid afforded 1, 2-dihydro-1-oxo-pyrido[1, 2-a]pyrazinium bromide (lxxxvi), catalytic hydrogenation of which gave 1-oxo-perhydropyrido [1, 2-a]pyrazine (lxxxvii) as a colourless crystalline solid which was purified by sublimation. The structure of the base was confirmed by comparing its infra-red spectrum with that of an authentic sample[24,63] prepared by the catalytic hydrogenation of the lactam (lxxv); the spectra were identical.

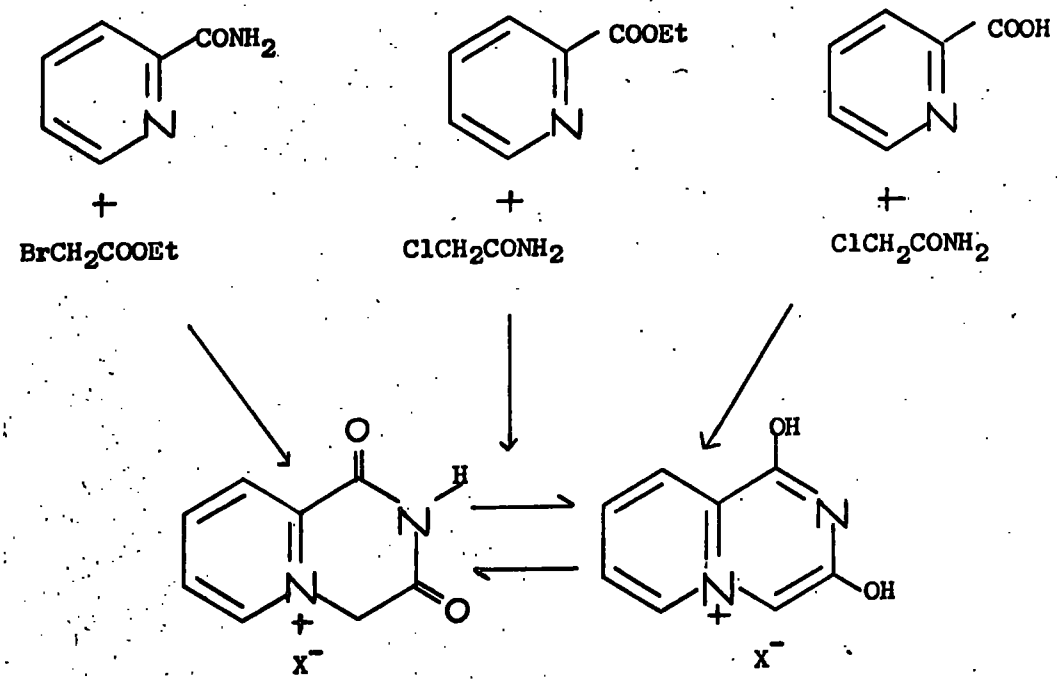


The salt (lxxxvi) is potentially tautomeric as illustrated, however, the predominance of the carbonyl form was shown by its infra-red spectrum which showed a band at 1690 cm^{-1} corresponding to an α, β -unsaturated six membered lactam[69]. This band can be related to the one occurring at 1650 cm^{-1} in the infra-red spectrum of the base (lxxxvii) and attributed to the carbonyl group of a saturated six membered lactam[69]. It has been found[70] that the ultra-violet spectra of acidic solutions of potentially tautomeric systems such as 1-hydroxyisoquinoline in which the carbonyl form is preferred, show no bathochromic shifts relative to those determined in neutral aqueous solution. This is suggested to be due to the non-basic nature of the ring nitrogen atom present in the lactam form. Systems such as 5-hydroxyquinoline in which conversion to the lactam form is not possible do exhibit such shifts due to protonation of the basic ring nitrogen atoms in acidic solution. The ultra-violet spectrum of the salt (lxxxvi) in neutral aqueous solution showed an absorption maximum at 3450 A^{o} which gave no shift upon acidification, thus further supporting the proposed carbonyl form.

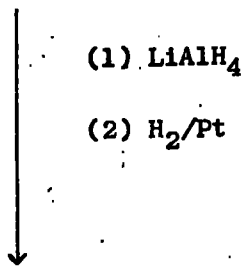
1, 3-DIOXO-1,2,3,4-TETRAHYDRO-PYRIDO[1, 2-a] PYRAZINIUM BROMIDE (lxxxviii; X = Br)

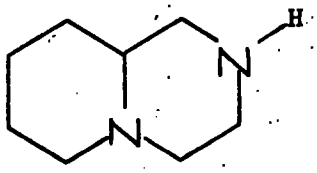
The bromide (lxxxviii; X = Br) was initially prepared by warming a mixture of picolinic acid amide and ethyl bromoacetate, the maximum yield being obtained after heating the mixture for three days. The resulting solid was washed with acetone and crystallised from hydrobromic acid-acetone. It was also found that the salt (lxxxviii; X = Cl) could be prepared, in a lower yield, by heating ethyl picolinate or picolinic acid with chloroacetamide in a sealed tube and crystallising the product from hydrobromic acid-acetone. This salt (lxxxviii) is also potentially tautomeric, however, its infra-red spectrum showed bands at 1740 cm^{-1} and 1720 cm^{-1} characteristic of the carbonyl groups of six membered cyclic imides[69], whilst the ultra-violet spectrum of the salt, determined in 0.1N hydrochloric acid, showed only two absorption bands at 2270 A^{o} and 2720 A^{o} (Fig. III, p. 67); the absence of any significant longer wave absorption supporting the dicarbonyl structure (lxxxviii). The n.m.r. spectrum in trifluoracetic acid as solvent showed a four proton signal in the region τ 0.5 - τ 1.5 attributed to the protons on C_6, C_7, C_8 and C_9 together with a two proton signal at τ 3.9 corresponding to the methylene group adjacent to the quaternary bridgehead nitrogen atom.

Reduction of the imide (lxxxviii; X = Br) with lithium aluminium hydride, followed by catalytic hydrogenation of the intermediate compound which was not isolated yielded perhydropyrido[1, 2-a] pyrazine (ii).


CONH2
+
BrCH2COOEt
COOEt
+
ClCH2CONH2
COOH
+
ClCH2CONH2
O
H
N
N
O
+
X-
OH
N
N
OH
+
X-

(lxxxviii)


(1) LiAlH4
(2) H2/Pt


H
N
N

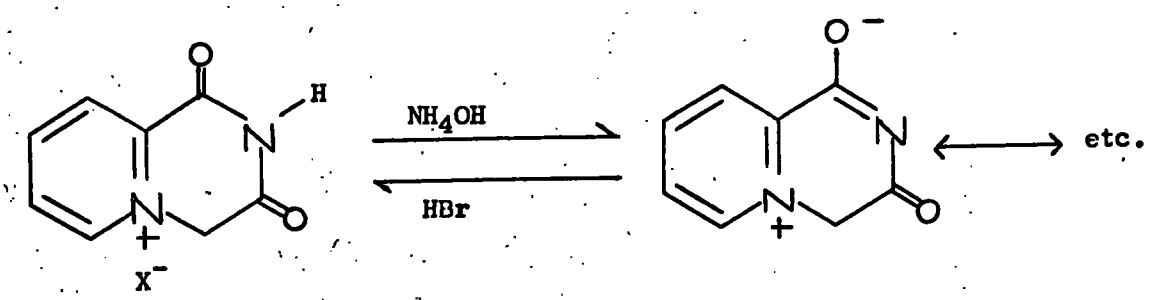
(ii)

1, 3-DIOXO-1,2,3,4-TETRAHYDRO-PYRIDO[1, 2-a] PYRAZINIUM BETAINE (lxxxix)

Attempts to crystallise the imide (lxxxviii; X = Br) from water or alcohol resulted in its gradual decomposition, yielding first a yellow compound and subsequently a red compound. Prolonged boiling of the yellow compound in aqueous solution afforded a new colourless compound.

When a concentrated aqueous solution of the yellow compound was boiled for a short time, a red solid was produced in low yield. The infra-red and ultra-violet spectra of this compound were similar to those of the yellow compound although the ultra-violet spectrum of the red compound extended to 4400 A^{o} compared with 4100A^{o} for the yellow compound. Attempts to crystallise the red compound resulted in its conversion to the colourless compound. It was therefore not further investigated.

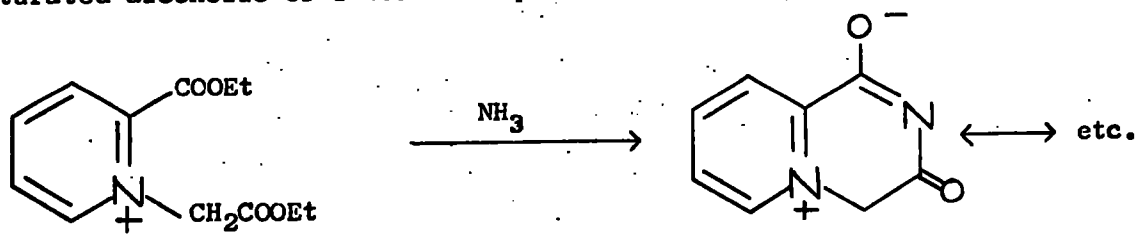
When the imide (lxxxviii; X = Br) was treated with cold concentrated aqueous ammonia the yellow compound was produced in high yield , the reaction being reversed by the addition of concentrated hydrobromic acid. Elemental analysis and the spectroscopic properties of the yellow compound showed it to be the mesomeric betaine (lxxxix).



(lxxxviii) (lxxxix)

Determination of the n.m.r. spectrum of the betaine (lxxxix) was not possible due to its low solubility in the available solvents. The ultra-violet spectrum of the betaine (lxxxix) in neutral aqueous solution (Fig. III, p. 67) showed the expected bathochromic shift relative to the spectrum of the imide (lxxxviii; X = Br) in 0.1 N acidic solution. A comparison of the ultra-violet spectrum of the betaine (lxxxix) with that of the imide (lxxxviii; X = Br) in neutral aqueous solution showed them to be similar, differing only in the molar extinction coefficients, the difference probably being due to the existence of an equilibrium in neutral solution between the salt (lxxxviii) and its betaine (lxxxix).

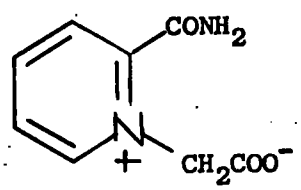
The betaine (lxxxix) was also produced when the monoquaternary salt between ethyl picolinate and ethyl bromoacetate was treated with saturated alcoholic or saturated aqueous ammonia.



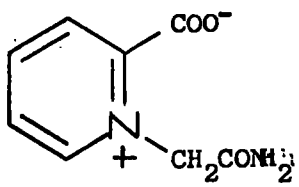
(lxxxix)

When the yellow betaine (lxxxix) was boiled under reflux in aqueous solution, and subsequently acetone added, a colourless solid of molecular formula $C_8H_8N_2O_3$ slowly crystallised from the solution.

The ultra-violet spectrum of this solid showed no absorption beyond 2770 A^{o} whilst the infra-red spectrum showed a band at 1710 cm^{-1} attributed to an amide carbonyl group. Additional bands at 1630 cm^{-1} and 1620 cm^{-1} were attributed to a carboxylate function. It was concluded therefore that hydrolysis of the yellow betaine (lxxxix) had occurred to give either the betaine (xc a) or (xc b).

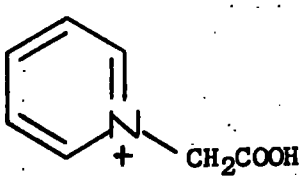


(xc a)

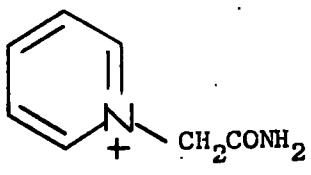


(xc b)

It was considered that a possible difference between the two betaine structures (xc a) and (xc b) would be found in the chemical shifts of the methylene groups adjacent to the quaternary nitrogen atom. Accordingly the model compounds pyridine betaine hydrobromide (xci) and 1-amidomethylpyridinium chloride (xcii) were prepared and their n.m.r. spectra determined.

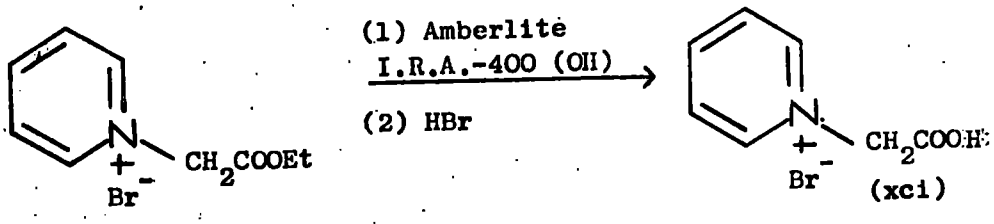


(xci)

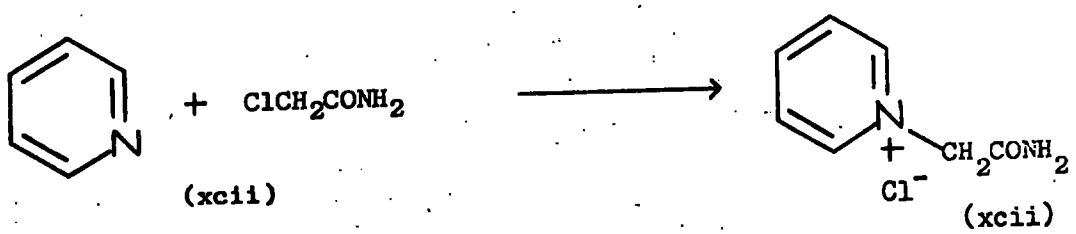


(xcii)

Pyridine betaine hydrobromide (xci) was prepared by treating pyridine with ethyl bromoacetate and passing the resulting mono-quaternary salt down an ion exchange column (Amberlite I.R.A. -400 (OH)) to give pyridine betaine; acification with hydrobromic acid followed by the addition of acetone precipitated the hydrobromide (xci) which crystallised from water as colourless plates.



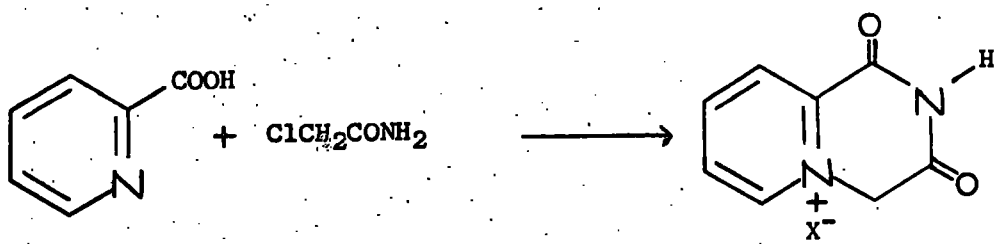
1-Amidomethylpyridinium chloride (xcii) was prepared by heating a mixture of pyridine and chloroacetamide in a sealed tube.



Comparison of the n.m.r. spectra of the two model compounds (xci) and (xcii) in trifluoracetic acid as solvent showed that the signals corresponding to the methylene groups adjacent to the quaternary nitrogen atom occurred at τ 3.9 and τ 4.0 respectively, whilst the corresponding signal in the n.m.r. spectrum of the betaine (xc).

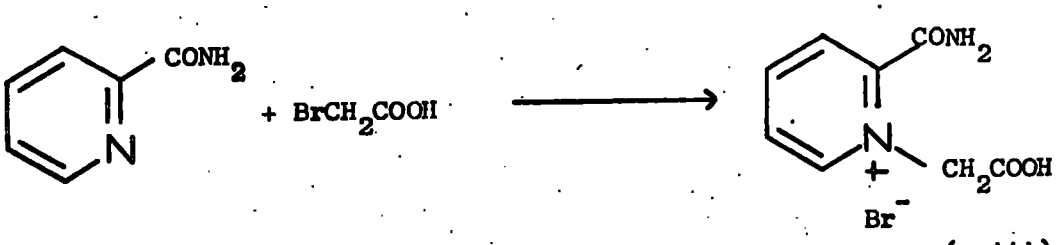
occurred at τ 4.0. This difference in τ values was considered too slight to be significant. The signal due to the methylene group of 1-amidomethylpyridinium chloride (xcii) was very sharp whilst those due to the methylene groups of pyridine betaine hydrobromide (xci) and the unknown betaine (xc) were broader, giving a preference for the structure (xc a) for the betaine. To confirm the suggested structure (xc a) for the betaine, the unambiguous syntheses of the two betaines (xc a) and (xc b) were attempted.

The method envisaged for the synthesis of the betaine (xc b) was to treat picolinic acid with chloroacetamide and pass the resulting monoquaternary salt down an ion exchange column (Amberlite I.R.A. - 400 (OH)), However, when a mixture of picolinic acid and chloroacetamide was heated in a sealed tube, the product was the imide (lxxxviii; X = Cl).

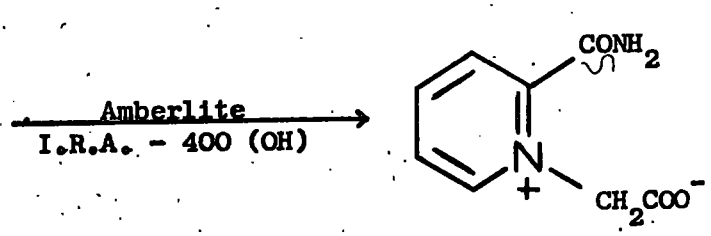


(lxxxviii)

The synthesis of 1-carboxymethyl-2-amidopyridinium betaine (xc a) was achieved by heating a mixture of picolinic acid amide and bromoacetic acid on a water bath and treating the crude reaction product with an aqueous slurry of ion exchange resin (Amberlite I.R.A. - 400 (OH)). The solution was filtered and the addition of acetone to the filtrate precipitated a colourless solid, the infra-red spectrum of which was identical to the product of the hydrolysis of the yellow betaine (lxxxix). Additional confirmation of the betaine structure (xc a) was obtained by treating the betaine (xc a) with cold hydrobromic acid followed immediately by a large excess of acetone. The solid which precipitated from the solution was identical to the product of the reaction between picolinic acid amide and bromoacetic acid; 1-carboxymethyl-2-amidopyridinium betaine hydrobromide (xciii). Attempts to crystallise this salt were unsuccessful; from neutral aqueous or alcoholic solution the product was the betaine (xca) whilst from dilute acid the imide (lxxxviii) was produced.

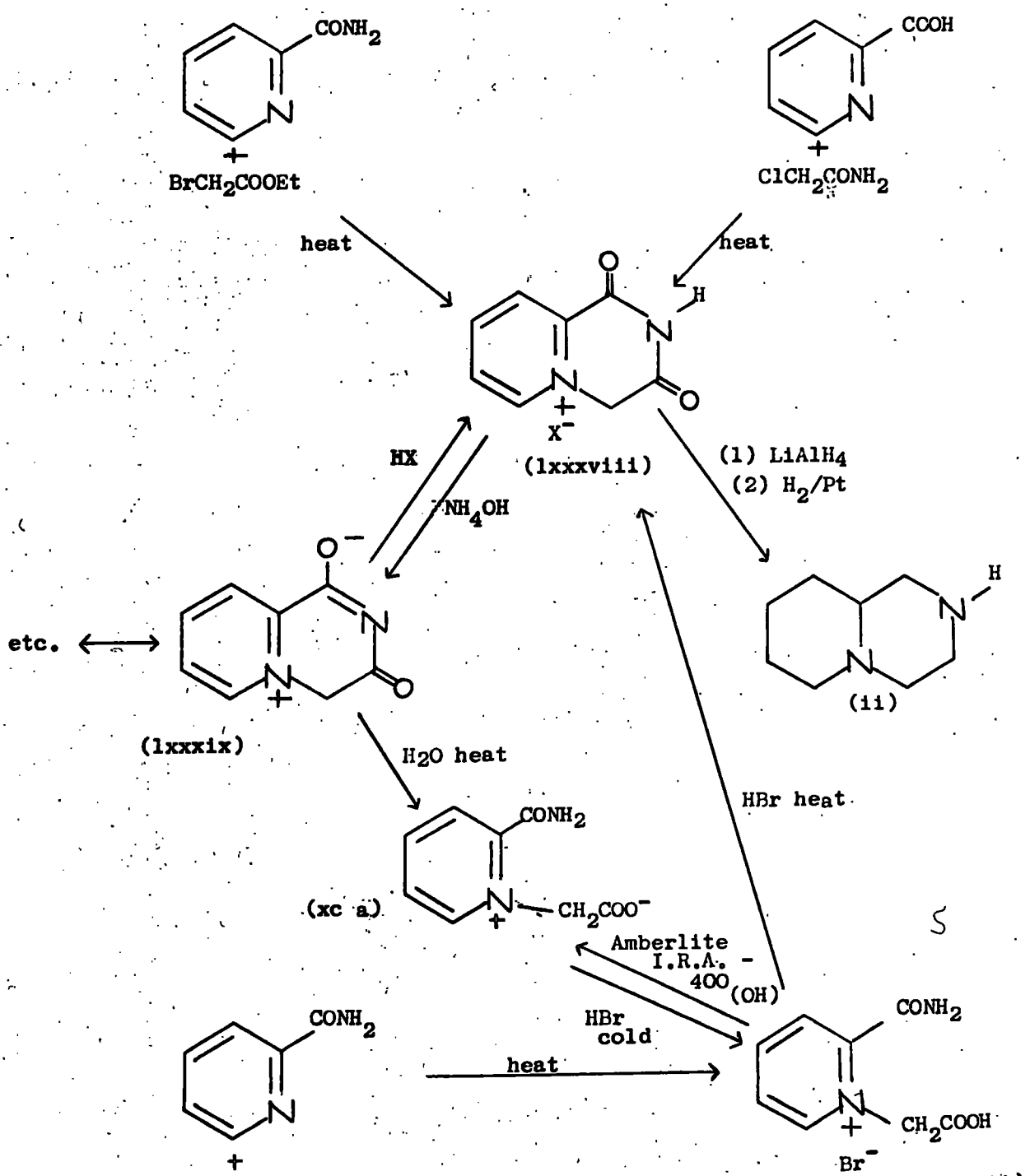


(xciii)



(xca)

SUMMARY OF THE REACTIONS OF 1,3-DIOXO-1,2,3,4-TETRAHYDROPYRIDO [1, 2-a] PYRAZINIUM BROMIDE (lxxxviii; X = Br)



ILLUSTRATIONS

Figure I

Ultra-violet spectra of aqueous solutions of:-

A. Pyrido[1, 2-a] pyrazinium bromide 2-oxide.

B. 1-Methyl-pyrido[1, 2-a] pyrazinium bromide 2-oxide.

C. 1-Phenyl-pyrido[1, 2-a] pyrazinium bromide 2-oxide.

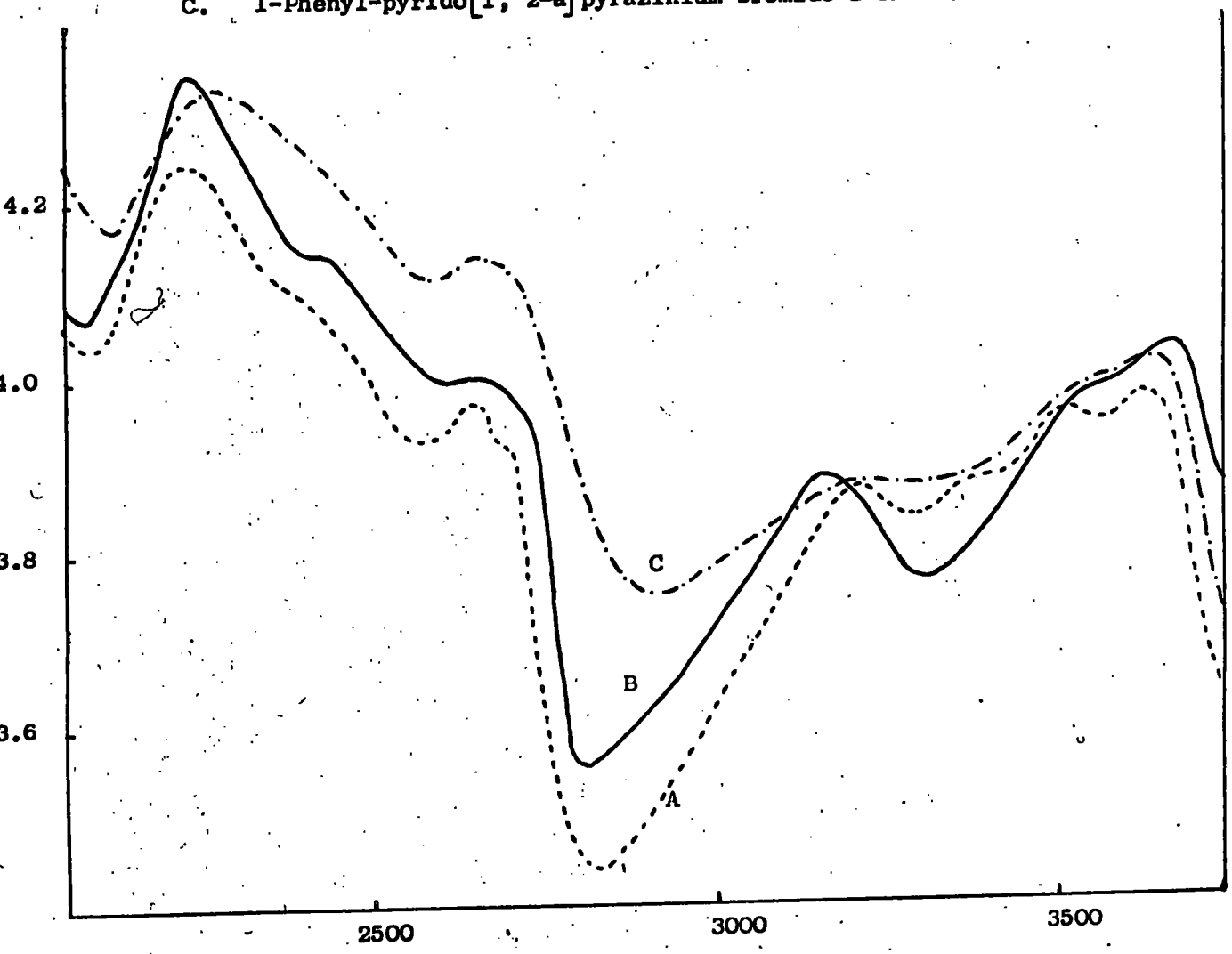


Figure II

Ultra-violet spectrum of an aqueous solution of:-

Pyrido[1, 2-a]pyrazinium bromide.

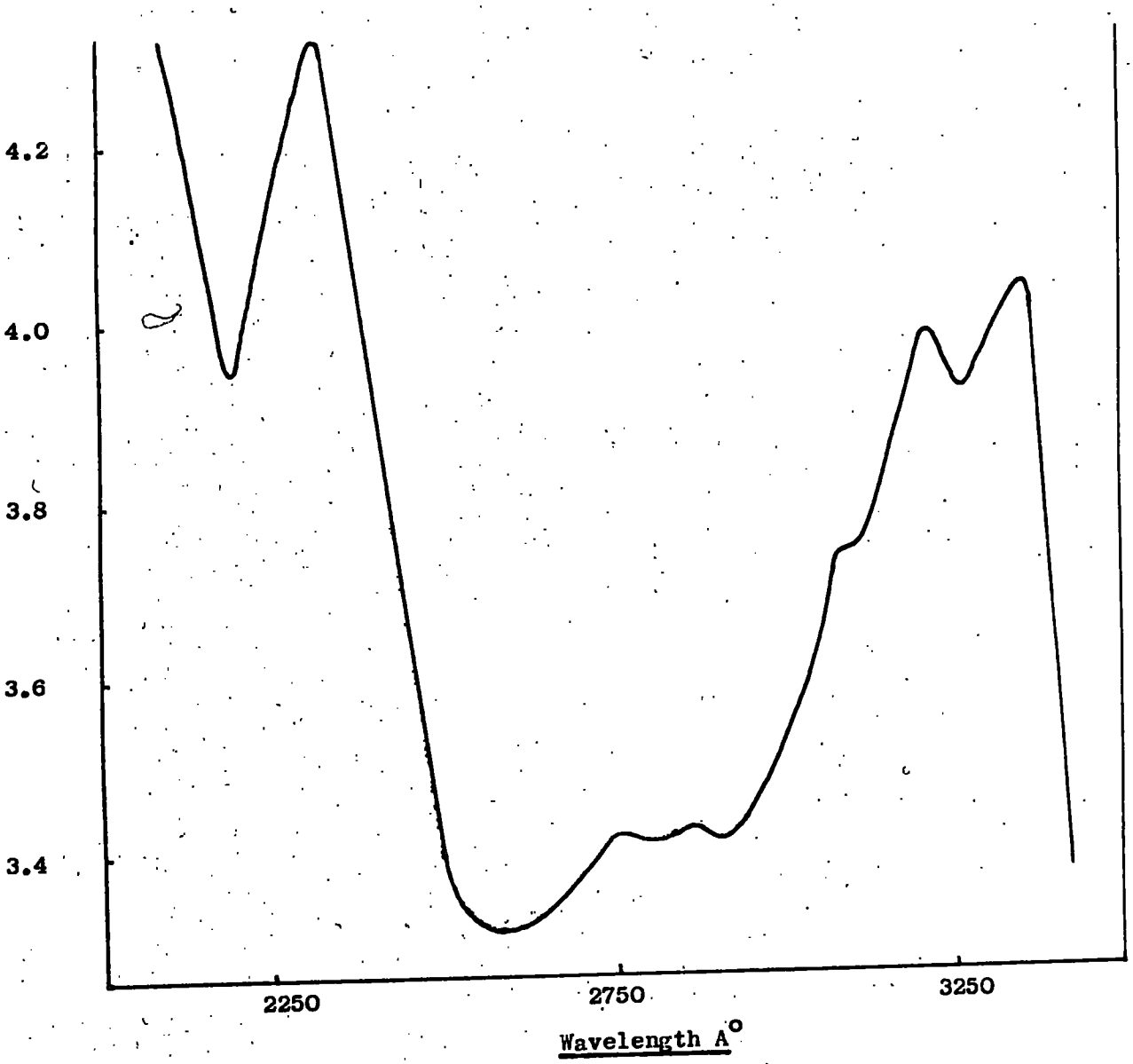


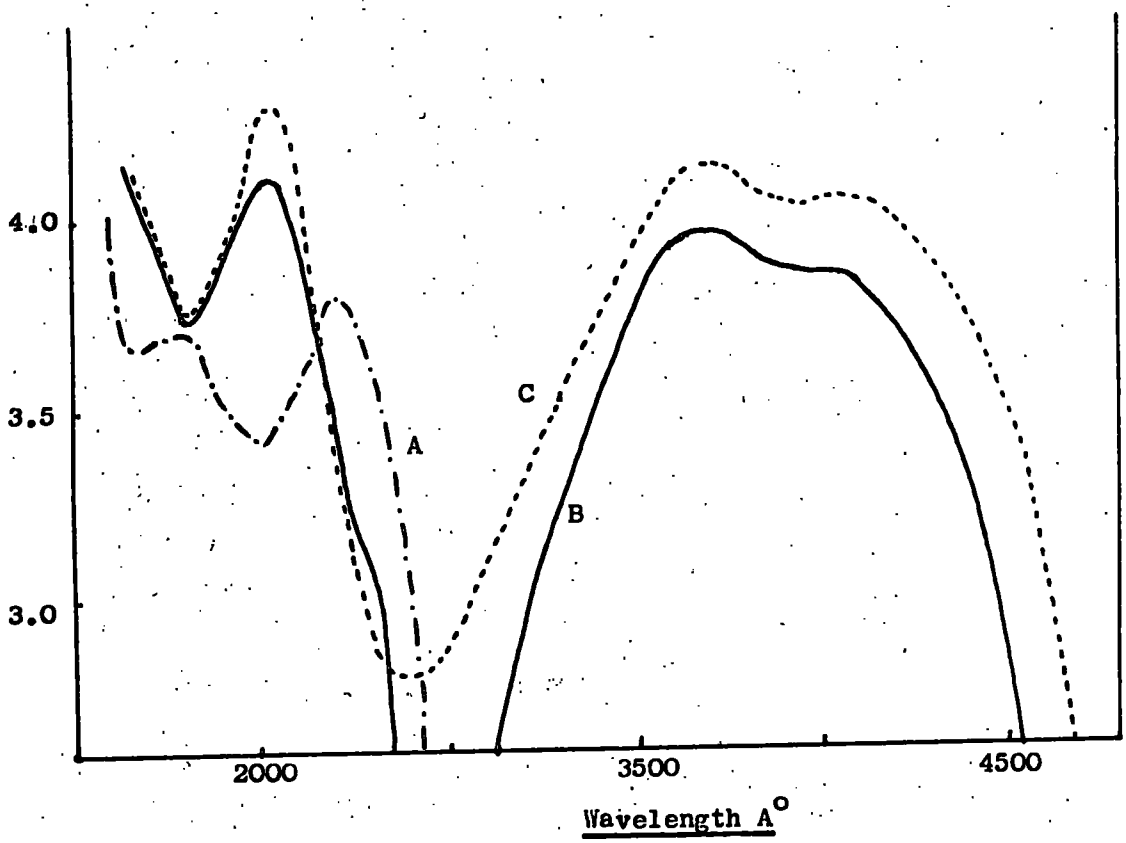
Figure III

Ultra-violet spectra of:-

A. 1, 3-dioxo-1,2,3,4-tetrahydro-pyrido[1,2-a] pyrazinium bromide determined in O.1 N hydrochloric acid.

B. 1, 3-dioxo-1,2,3,4-tetrahydro-pyrido[1, 2-a] pyrazinium bromide determined in aqueous solution.

C. 1, 3-dioxo-1,2,3,4-tetrahydro-pyrido[1, 2-a] pyrazinium betaine determined in aqueous solution.



EXPERIMENTAL

All melting points were determined on a Kofler block.

Infra-red absorption spectra were determined on a Perkin-Elmer 237 spectrometer, ultra-violet absorption spectra on a Unicam SP 700c spectrophotometer and n.m.r. spectra on a Perkin-Elmer Model R.10 spectrometer.

Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss.

BROMOACETALDEHYDE OXIME

Was prepared by the method used by Kimber and Parham[31] for the synthesis of the chloro compound.

2-(1,3-DIOXOLAN-2-YL) PYRIDINE[38]

A solution of pyridine 2-aldehyde (21.4 g.), ethylene glycol (24 ml.) and p. toluene sulphonic acid (10 g.) in benzene (300 ml.) was boiled under reflux with a Dean Stark water separator for 64 hours. The solution was cooled and poured into saturated aqueous sodium carbonate (200 ml.). The benzene layer was separated and the aqueous phase washed four times with benzene (50 ml.). The combined benzene layers were washed once with water (10 ml.) and dried (Na_2CO_3). The solvent was evaporated under reduced pressure to give the acetal as a colourless liquid, b.p. 80°/0.8 mm. (lit.[38], b.p. 122°/4 mm.) (18.46 g., 61%).

1-(2-OXIMINOETHYL)-2-(1,3-DIOXOLAN-2-YL) PYRIDINIUM BROMIDE (lxxi)

A mixture of bromoacetaldehyde oxime (1.46 g.) and 2-(1,3-dioxolan-2-yl) pyridine (1.59 g.) was allowed to stand at room temperature for 48 hr. The resulting solid was washed with acetone leaving the bromide which crystallised from alcohol-ether as colourless needles, m.p. 168 - 169° (1.86 g., 61%).

Found : N, 9.45%

$C_{10}H_{13}BrN_2O$ requires : N, 9.7%

The picrate crystallised from alcohol as yellow needles, m.p. 127°.

Found : C, 43.6; H, 3.7; N, 16.35%

$C_{16}H_{15}N_5O_{10}$ requires: C, 43.9; H, 3.5; N, 16.0%.

PYRIDO[1, 2-a] PYRAZINIUM BROMIDE 2-OXIDE (lxvii)

(a) A solution of the monoquaternary salt (lxxi) (1.38g.) in concentrated (48%) hydrobromic acid (10 ml.) was boiled under reflux for 20 min. Addition of acetone to the cooled solution precipitated the bromide (0.78 g., 72%) which crystallised from methanol as pale yellow prisms, m.p. 283° (decomp.) (lit[3], m.p. 280° decomp.)

Found : C, 42.4; H, 3.3; N, 12.4%

Calc. for $C_8H_7BrN_2O$: C, 42.3; H, 3.1; N, 12.3%

$\lambda_{max}(H_2O)$ 2230, 2410, 2600 sh., 2640, 2700 sh., 3200, 3370, 3510, 3630 A°

($\log_{10}\epsilon$ 4.25, 4.09, 3.94, 3.98, 3.92, 3.88, 3.88, 3.96, 3.98).

(b) A solution of the 1-bromo 2-oxide (lxxxi) (0.278 g.) in 20% aqueous methanol (25 ml.) was hydrogenated over Adams catalyst at atmospheric pressure and temperature until the uptake was 20.5 ml. The catalyst was filtered off and the solvent evaporated under reduced pressure. Addition of acetone to the residue gave the bromide, which, after crystallisation from methanol had a m.p. 283° (decomp.) (0.076 g., 37%).

The picrate crystallised from ethanol as yellow needles, m.p. 199°.

	Found	: C, 45.2; H, 2.85; N, 19.0%
$C_{14}H_9N_5O_8$	requires	: C, 44.8; H, 2.4; N, 18.7%.

2-(2-METHYL[1,3]DIOXOLAN-2-YL) PYRIDINE[38]

Was prepared by the method described for the synthesis of 2-(1,3-Dioxolan-2-yl)pyridine.

1-(2-OXIMINOETHYL)-2-(2-METHYL[1,3]DIOXOLAN-2-YL)PYRIDINIUM BROMIDE (lxxix)

A mixture of 2-(2-methyl[1,3]dioxolan-2-yl)pyridine (0.98 g.) and bromoacetaldehyde oxime (0.79 g.) was allowed to stand at room temperature for 18 hr. The resulting solid was washed with acetone and crystallised from ethanol giving the bromide as colourless needles, m.p. 189 - 190° (decomp.) (1.03 g., 58%).

	Found	: N, 9.0%
$C_{11}H_{15}BrN_2O_3$	requires:	N, 9.2%

The picrate crystallised from ethanol-ether as yellow needles, m.p. 140°.

	Found	: C, 44.7; H, 3.9; N, 16.0%
$C_{17}H_{17}N_5O_{10}$	requires	: C, 45.2; H, 3.8; N, 15.5%.

1-METHYL-PYRIDO[1, 2-a] PYRAZINIUM BROMIDE 2-OXIDE (lxxviii)

A solution of the monoquaternary bromide (lxxix) (1.0 g.) in concentrated sulphuric acid (3 ml.) was heated on a boiling water bath for 2 min., cooled, and ether added. The ether layer was decanted and the residual oil washed with ether, dissolved in concentrated (48%) hydrobromic acid (1 ml.) and acetone added. The precipitated bromide (0.67 g., 84%) crystallised from ethanol as colourless needles, m.p. 254-256° (decomp.).

Found : C, 45.3; H, 3.8; N, 11.7%
$C_9H_9BrN_2O$ requires : C, 44.8; H, 3.8; N, 11.6%

λ_{max}(H_2O) 2230, 2420, 2640, 3150, 3550 sh., 3640 A° ($\log_{10}\epsilon$ 4.34, 4.14, 4.00, 3.87, 3.98, 4.02).

The picrate crystallised from ethanol as yellow needles, m.p. 185 - 186°.

Found : C, 46.1; H, 2.9; N, 17.7%
$C_{15}H_{11}N_5O_8$ requires : C, 46.3; H, 2.85; N, 18.0%.

1-PHENYL-PYRIDO[1,2-a] PYRAZINIUM BROMIDE 2-OXIDE (lxxx)

A mixture of 2-benzoylpyridine (0.95 g.) and bromoacetaldehyde oxime (0.75 g.) was warmed on a boiling water bath for 30 min. The resulting gum was washed with ether, digested with boiling acetone for 30 min., and the acetone decanted. The crude residue was then washed with acetone containing a little methanol and finally crystallised from ethanol, giving the bromide as pale yellow prisms, m.p. 263 - 264° (decomp.) (0.43 g., 27%).

Found : C, 55.25; H, 4.0; N, 9.1%
$C_{14}H_{11}BrN_2O$ requires : C, 55.5; H, 3.7; N, 9.2%.

$\lambda_{max}(H_2O)$ 2260, 2670, 3230, 3570 sh., 3680 A° ($\log_{10}\epsilon$ 4.33, 4.04, 3.88, 4.00, 4.03).

The picrate crystallised from water as yellow plates, m.p. 212 - 213°.

Found : C, 53.1; H, 3.3; N, 16.0%
$C_{20}H_{13}N_5O_8$ requires : C, 53.2; H, 2.9; N, 15.5%.

1-AMIDOMETHYL-2-(1,3-DIOXOLAN-2-YL)PYRIDINIUM CHLORIDE

A mixture of 2-(1,3-dioxolan-2-yl)pyridine (1.51 g.) and chloroacetamide (0.94 g.) was heated in a sealed tube at 118° for 20 hr. The black product was washed with acetone and the residual dark solid crystallised from methanol-ether. Recrystallisation gave the chloride as colourless plates, m.p. 216° (1.89 g., 76%).

Found : C, 48.9; H, 5.3%
$C_{10}H_{13}ClN_2O_3$ requires : C, 49.1; H, 5.4%

The bromide crystallised from ethanol as colourless plates, m.p. 212 - 215°.

Found : C, 41.6; H, 4.4; N, 9.4%
$C_{10}H_{13}BrN_2O_3$ requires : C, 41.5; H, 4.5; N, 9.7%

The picrate crystallised from ethanol as yellow needles, m.p. 182°.

Found : C, 43.8; H, 3.5; N, 15.8%
$C_{16}H_{15}N_5O_{10}$ requires : C, 43.9; H, 3.5; N, 16.0%

1-AMIDOMETHYL-2-(2-METHYL[1,3]DIOXOLAN-2-YL)PYRIDINIUM CHLORIDE

Was prepared from 2-(2-methyl[1,3]dioxolan-2-yl)pyridine (1.65 g.) and chloroacetamide (0.94 g.) using the procedure described for the nonmethylated compound. The chloride crystallised from alcohol as colourless needles, m.p. 252° (1.39 g., 54%).

Found : C, 51.0; H, 5.85; N, 10.65%
$C_{11}H_{15}ClN_2O_3$ requires : C, 51.1; H, 5.85; N, 10.8%.

The picrate crystallised from ethanol as yellow plates, m.p. 141°.

Found : C, 45.25; H, 3.9%
$C_{17}H_{17}N_5O_{10}$ requires : C, 45.2; H, 3.8%

1-BROMO-PYRIDO[1, 2-a]PYRAZINIUM BROMIDE 2-OXIDE (lxxxi; X = Br)

A solution of the 2-oxide (lxvii) (0.5 g.) and bromine (0.5 ml.) in concentrated (48%) hydrobromic acid (7.5 ml.) was stirred at room temperature for 1 hr., heated on a boiling water bath for 2 hr. and cooled. The addition of acetone precipitated the bromide which crystallised from concentrated (48%) hydrobromic acid - acetone as buff needles which charred without melting below 320° (0.62 g., 92%).

Found : C, 30.85; H, 2.4; N, 8.7%
$C_8H_6Br_2N_2O$ requires : C, 31.4; H, 2.0; N, 9.2%.

$\lambda_{max}(H_2O)$ 2190 sh., 2490 sh., 2560, 2630, 2810 sh., 3530, 3750 A°
($\log_{10}\epsilon$ 3.94, 3.90, 3.93, 3.92, 3.56, 3.67, 3.64).

The picrate crystallised from water as golden prisms, m.p. 155 - 156°.

Found : C, 36.6; H, 2.15; N, 15.1%
$C_{14}H_8BrN_5O_8$ requires : C, 37.0; H, 1.8; N, 15.4%

PYRIDO[1, 2-a] PYRAZINIUM BROMIDE (lxvi; X = Br)

(a) A suspension of the 2-oxide (lxvii) (0.48 g.) in phosphorus tribromide (5 ml.) was boiled under reflux for 20 min. The mixture was cooled, filtered, and the residue washed with ether. Recrystallisation from methanol-ether gave the bromide as buff needles, m.p. 272 - 274° (0.26 g., 58%).

Found : C, 43.6; H, 3.7; N, 12.45%
$C_8H_7BrN_2\frac{1}{2}H_2O$ requires : C, 43.7; H, 3.7; N, 12.7%

$\lambda_{max}(H_2O)$ 2320, 2760, 2870, 3100 sh., 3220, 3360 A° ($\log_{10}\epsilon$ 4.31, 3.34, 3.35, 3.73, 3.98, 4.03).

(b) A solution of the 2-oxide (lxvii) (0.436 g.) in methanol (20 ml.) was hydrogenated over Adams catalyst at atmospheric pressure and temperature until the uptake was 43 ml. The catalyst was filtered off and the solvent evaporated under reduced pressure. Crystallisation of the residue from methanol-ether gave the bromide, m.p. 272 - 274° (0.153 g., 36%).

(c) A solution of the 1-bromo compound (lxxxiii; X = Br) (0.21 g.) in methanol (25 ml.) was hydrogenated over Adams catalyst at atmospheric

pressure and temperature until the uptake was 16.2 ml. The catalyst was filtered off and the solvent evaporated under reduced pressure. Crystallisation of the residue from methanol-ether afforded the bromide, m.p. 272 - 274° (0.058 g., 43%).

The picrate crystallised from water as yellow plates, m.p. 192 - 194°.

	Found	: C, 46.4; H, 2.4; N, 19.8%
$C_{14}H_9N_5O_7$	requires	: C, 46.8; H, 2.5; N, 19.5%

1-PHENYL-PYRIDO[1, 2-a]PYRAZINIUM BROMIDE (lxxxii)

A suspension of the 1-phenyl 2-oxide (lxxx) (0.35 g.) in phosphorus tribromide (6 ml.) was boiled under reflux for 20 min. The mixture was cooled and filtered. Crystallisation of the residue from methanol-ether gave the bromide as colourless plates, m.p. 259° (0.18 g., 54%).

	Found	: C, 58.0; H, 4.2; N, 9.8%
$C_{14}H_{11}BrN_2$	requires	: C, 58.5; H, 3.9; N, 9.8%

$\lambda_{max}(H_2O)$ 2350, 3000, 3400 A° ($\log_{10}\epsilon$ 4.32, 3.97, 3.89).

The picrate crystallised from ethanol as yellow needles, m.p. 162 - 164°.

	Found	: C, 55.2; H, 3.4: N, 16.3%
$C_{20}H_{13}N_5O_7$	requires	: C, 55.2; H, 3.0; N, 16.1%

1-BROMO-PYRIDO[1, 2-a] PYRAZINIUM BROMIDE (lxxxiii)

A suspension of the 1-bromo 2-oxide (lxxxi) (0.38 g.) in phosphorus tribromide (6 ml.) was boiled under reflux for 15 min. The mixture was cooled, filtered, and the residue crystallised from methanol-ether, affording the bromide as colourless needles which charred without melting below 320° (0.21 g., 58%).

	Found	: C, 32.9; H, 1.9; N, 9.9%
$C_8H_6Br_2N_2$	requires	: C, 33.1; H, 2.1; N, 9.7%

$\lambda_{max}(H_2O)$ 2450, 2840, 2990, 3390, 3520 A° ($\log_{10}\epsilon$ 4.33, 3.56, 3.51, 3.96, 4.13).

The picrate crystallised from methanol-ether as yellow needles, m.p. 142°.

	Found	: C, 38.2; H, 2.2; N, 15.6%
$C_{14}H_8BrN_5O_7$	requires	: C, 38.4; H, 1.8; N, 16.0%.

1-4,DIHYDRO-1-IMINO-PYRIDO[1, 2-a] PYRAZINIUM BROMIDE 2-OXIDE (lxxxv)

A solution of 2-cyanopyridine (1 g.) and bromoacetaldehyde oxime (1.5 g.) in tetramethylenesulphone (2 ml.) was allowed to stand at room temperature for 30 days. The yellow needles which had crystallised from the solution were filtered off and recrystallised from methanol-ether, affording the bromide as yellow needles, m.p. 268° (0.274 g., 12.5%).

	Found	: C, 40.2; H, 3.4; N, 17.0%
$C_8H_8BrN_3O$	requires	: C, 39.7; H, 3.3; N, 17.4%.

$\lambda_{max}(H_2O)$ 2410, 2810, 2900, 3530, 4130 A° ($\log_{10}\epsilon$ 4.06, 4.29, 4.30, 3.40, 3.40).

The picrate crystallised from methanol-water as red needles, m.p. 212 - 215°.

	Found	: C, 43.2; H, 2.6%
$C_{14}H_{10}N_6O_8$	requires	: C, 43.1; H, 2.6%.

1-2,DIHYDRO-1-OXO-PYRIDO[1, 2-a] PYRAZINIUM BROMIDE (lxxxvii)

A solution of the 1-imino 2-oxide (lxxxv) (0.46 g.) in concentrated (48%) hydrobromic acid (3 ml.) was boiled under reflux for 15 min., cooled, and acetone added. The resulting solid crystallised from methanol-ether giving the bromide as yellow needles which charred without melting below 320° (0.42 g., 91%).

	Found	: C, 41.9; H, 3.2; N, 12.3%
$C_8H_7BrN_2O$	requires	: C, 42.3; H, 3.1; N, 12.3%.

$\lambda_{max}(H_2O)$ 2450, 2570, 3450 A° ($\log_{10}\epsilon$ 4.23, 4.22, 3.97).

The picrate crystallised from methanol-water as yellow needles, m.p. 250 - 254°.

	Found	: C, 44.5; H, 2.1%
$C_{14}H_9N_5O_8$	requires	: C, 44.8; H, 2.4%

1-OXO-PERHYDROPYRIDO[1, 2-a] PYRAZINE (lxxxvi)

A solution of the 1-oxo bromide (lxxxvii) (0.3 g.) in 20% aqueous methanol (25 ml.) was hydrogenated to completion over Adams catalyst at atmospheric pressure and temperature. The catalyst was filtered off

and the methanol evaporated under reduced pressure. The residual aqueous solution was basified (NaOH) and extracted with ether. The ether layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure, leaving the base as a white solid which was purified by sublimination (100°/2 mm), m.p. 131° (lit.[63], m.p. 134 - 134.5°) (0.058 g., 40%). The infra-red spectrum of the base was identical to that of an authentic sample of the base prepared by the catalytic hydrogenation of the lactam (lxxv)[24,63].

PICOLINIC ACID AMIDE[71]

A solution of ethyl picolinate (1 g.) in concentrated aqueous ammonia (5 ml.) was allowed to stand in a stoppered flask for 2 hr. The solution was reduced to half volume by evaporation under reduced pressure when the amide crystallised from the solution as colourless plates (0.6 g.). The filtrate was saturated with ammonia and allowed to stand for a further 2 hr. The solution was heated to boiling, and cooled, yielding a further quantity of the amide (0.076 g., total yield 84%) which crystallised from water as colourless plates, m.p. 107° (lit.[71], m.p. 107°).

PICOLINIC ACID AMIDE HYDROBROMIDE

(a) Picolinic acid amide (0.194 g.) was dissolved in concentrated (48%) hydrobromic acid (1 ml.) and acetone subsequently added precipitating a colourless solid which was filtered and purified by sublimation (120°/0.7 mm) giving the hydrobromide as colourless

needles, m.p. 222-225° (0.311 g, 95.5%)

Found : C, 36.0; H, 3.6; N, 14.2%
$C_6H_7BrN_2O$ requires : C, 35.5; H, 3.5; N, 13.8%

(b) A mixture of picolinic acid amide (1 g.) and bromoacetaldehyde oxime (1.13 g.) was warmed to effect solution and allowed to stand at room temperature for 14 days. The resulting gum was washed with acetone, yielding the hydrobromide which sublimed (120°/0.7 mm) to give colourless needles, m.p. 220 - 225° (1.32 g., 79%). The infra-red spectrum was identical to that of the sample obtained as in (a).

1,3-DIOXO-1,2,3,4-TETRAHYDRO-PYRIDO[1, 2-a] PYRAZINIUM BROMIDE (lxxxviii; X = Br)

(a) A mixture of picolinic acid amide (2.9 g.) and ethyl bromoacetate (4.1 g.) was warmed on a boiling water bath for 70 hr. The resulting deep red solid was washed with acetone and crystallised from concentrated (48%) hydrobromic acid - acetone giving the bromide as colourless needles which charred without melting below 320° (4.93 g., 85%).

Found : C, 39.8, H, 3.2; N, 11.7%
$C_8H_7BrN_2O$ requires : C, 39.5, H, 2.9; N, 11.5%.

λ_{max}(0.1N HCl) 2060, 2260, 2740 A° ($\log_{10}\epsilon$ 4.32, 3.82, 3.85).

(b) A solution of 1-carboxymethyl-2-amidopyridinium betaine (xca) (0.638 g.) in concentrated (48%) hydrobromic acid (2.5 ml.) was boiled under reflux for 1 hr. The addition of acetone precipitated a colourless solid which crystallised from concentrated (48%) hydrobromic acid-acetone giving the bromide as colourless needles (0.305 g., 35.5%). The infra-red spectrum of the salt showed it to be the bromide (lxxxviii; X = Br).

(a) The chloride (lxxxviii; X = Cl) was prepared by heating a mixture of picolinic acid (123 g.) and chloroacetamide (0.935 g.) in a sealed tube at 120° for 18 hr. The resulting black gum was washed with acetone and crystallised from concentrated hydrochloric acid - acetone, affording the chloride as colourless needles which charred without melting below 320° (0.5 g., 25%). The infra-red spectrum of this salt was identical to that of the bromide (lxxxviii; X = Br).

(b) A modification of this reaction, using ethyl picolinate (1.51 g.) in place of picolinic acid (1.23 g.) gave the chloride as colourless needles, (0.595 g., 30%). The infra-red spectrum of this salt was identical to that of the bromide (lxxxviii; X = Br).

The picrate crystallised from nitromethane-ether as yellow needles, m.p. 183 - 185°.

	Found	: C, 43.2; H, 2.6; N, 17.65%
$C_{14}H_9N_5O_9$	requires	: C, 43.0; H, 2.3; N, 17.9%

ETHYL PICOLINATE[72]

A solution of picolinic acid (50 g.) in dry ethanol (150 ml.) and concentrated sulphuric acid (60 ml.) was boiled under reflux for 4 hr.,

cooled, concentrated sulphuric acid (40 ml) added and the solution boiled under reflux for a further 15 min. The cooled solution was poured onto crushed ice (500 g), sodium carbonate (62.5 g) added and the solution basified by the addition of concentrated aqueous ammonia solution (160 ml). The ether extract of the alkaline solution was dried (Na_2SO_4), the solvent removed by evaporation under reduced pressure and the resulting ester distilled under reduced pressure, b.p. 85°/2.5 mm. (lit[72], b.p. 125 - 127°/14 mm) (48.7 g, 68%) (lit,[72] yield 61%).

1-(CARBETHOXYMETHYL)-2-CARBETHOXYPYRIDINIUM BROMIDE

A mixture of ethyl picolinate (3.02 g) and ethyl bromoacetate (3.34 g) was warmed on a water bath (90°) for 70 hr. The resulting black solid was washed with acetone and crystallised from ethanol-ether giving the bromide as colourless needles, m.p. 146° (5.79 g, 91%).

	Found	: C, 45.4; H, 5.2; N, 3.9%
$C_{12}H_{16}BrNO_4$	requires	: C, 45.3; H, 5.1; N, 4.4%

The picrate crystallised from water as yellow needles, m.p. 110°.

	Found	: C, 46.4; H, 4.0; N, 12.0%
$C_{18}H_{18}N_4O_{11}$	requires	: C, 46.35; H, 3.9; N, 12.0%.

1, 3-DIOXO-1,2,3,4-TETRAHYDRO-PYRIDO[1, 2-a]PYRAZINIUM BETAINE (lxxxix)

(a) The bromide (lxxviii; X = Br) (0.11 g.) was added to concentrated aqueous ammonia (1 ml.) and a yellow solid precipitated from the solution. The solid was washed with acetone and crystallised from nitromethane-ether giving the bicyclic betaine as yellow needles which darkened without melting below 320° (0.072 g., 98%).

Found : C, 59.2; H, 3.9; N, 17.35%
$C_8H_6N_2O_2$ requires : C, 59.3; H, 3.7; N, 17.3%

$\lambda_{max}(H_2O)$ 2080, 2550, 3690, 4090 A° ($\log_{10}\epsilon$ 4.21, 4.23, 4.04, 3.94).

(b) A solution of 1-(carbethoxymethyl)-2-carbethoxypyridinium bromide (2 g.) in concentrated aqueous ammonia (10 ml.) was boiled under reflux for 10 min. The solution was reduced to half volume by evaporation under reduced pressure and acetone was added, precipitating the betaine as a yellow solid which crystallised from nitromethane-ether as yellow needles (0.815 g., 80%). The infra-red spectrum of this betaine was identical to that of the betaine (lxxxix) prepared as in (a).

Treatment of the betaine (lxxxix) with saturated alcoholic picric acid afforded the picrate (lxxviii; X = picrate) which crystallised from nitromethane-ether as yellow needles, m.p. 183 - 185°.

1-CARBOXYMETHYL-2-AMIDOPYRIDINIUM BETAINE (xca)

(a) A suspension of the bicyclic betaine (lxxxix) (0.315 g.) in water (10 ml.) was boiled under reflux for 1 hr. when the betaine (lxxxix) slowly dissolved. The volume of the solution was reduced to 2 ml. by evaporation under reduced pressure and acetone added. Crystallisation of the resulting colourless solid from methanol-ether afforded the monocyclic betaine as colourless needles, m.p. 192° (0.325 g., 93%).

Found : C, 53.15; H, 4.7; N, 15.8%
$C_8H_8N_2O_3$ requires : C, 53.3; H, 4.5; N, 15.55%

$\lambda_{max}(H_2O)$ 2120, 2770 A° ($\log_{10}\epsilon$ 3.74, 3.81).

(b) A solution of 1-carboxymethyl-2-amidopyridinium betaine hydrobromide (0.2 g.) in an aqueous slurry of ion exchange resin (Amberlite I.R.A. - 400 (OH)) (2 ml.) was shaken for 2 min. and filtered. The solvent was evaporated under reduced pressure and acetone added, precipitating a colourless solid, crystallisation of which, from methanol-ether, afforded the monocyclic betaine as colourless needles, m.p. 192° (0.083 g., 60%). The infra-red spectrum of this sample was identical to that of the sample obtained as in (a).

The picrate, prepared by the addition of alcoholic picric acid to the betaine (xca), crystallised from alcoholic picric acid as yellow needles, m.p. 176 - 178°.

Found : C, 40.9; H, 2.5; N, 17.3%
$C_{14}H_{11}N_5O_{10}$ requires : C, 41.1; H, 2.7; N, 17.1%

1-CARBOXYMETHYL-2-AMIDOPYRIDINIUM BETAINE HYDROBROMIDE (xciii)

(a) Ice cold concentrated (48%) hydrobromic acid (1 ml) was added to 1-carboxymethyl-2-amidopyridinium betaine (0.5 g) followed immediately by an excess of acetone. The bromide crystallised slowly from the solution as colourless needles, (0.283 g., 39%). Crystallisation of the bromide from ethanol-ether afforded the betaine (xca) whilst from aqueous hydrobromic acid-acetone the product was the imide (lxxxviii; X = Br).

(b) A mixture of picolinic acid amide (1.22 g) and bromoacetic acid (1.39 g) was warmed on a water bath (85°) for 18 hr. The product was washed with acetone and the bromide solidified as a pale yellow mass, (2.395 g., 88%). The infra-red spectrum of this salt was identical to that of the sample prepared as in (a).

The picrate, prepared by the addition of saturated aqueous sodium picrate to the bromide, crystallised from alcoholic picric acid as yellow needles, m.p. 176 - 178° and was identical to the picrate of 1-carboxymethyl-2-amidopyridinium betaine.

PYRIDINE BETAINE HYDROBROMIDE (xci)

A mixture of pyridine (1.58 g) and ethyl bromoacetate (3.34 g) was warmed on a boiling water bath for 5 min., cooled and the resulting solid washed with acetone. Crystallisation of the residue from ethanol-ether afforded 1-carbethoxymethyl pyridinium bromide as colourless needles, m.p. 136° (lit[73], m.p. 135 - 136°).

(4.76 g., 97%). The quaternary ester (1 g.) was dissolved in water (2.5 ml.) and passed down an ion exchange column (Amberlite I.R.A. - 400 (OH)), eluting with water. The eluate, which was deepred, was retained and concentrated (48%) hydrobromic acid (1 ml.) added. Evaporation under reduced pressure, followed by the addition of acetone and crystallisation of the residue from water afforded the hydrobromide as colourless plates, m.p. 199 - 202° (lit[74], m.p. 198 - 200° (decomp.))(0.695 g., 79%).

1-AMIDOMETHYLPYRIDINIUM CHLORIDE (xcii)

A mixture of pyridine (1.58 g.) and chloroacetamide (1.87 g.) was heated in a sealed tube at 100° for 18 hr. The resulting solid was washed with acetone and crystallised from methanol-water giving the chloride as colourless needles, m.p. 209 - 211° (2.48 g., 72%).

Found : C, 48.8; H, 5.1; N, 15.9%
$C_7H_9ClN_2O$ requires : C, 48.7; H, 5.25; N, 16.2%

PERHYDROPYRIDO[1, 2-a] PYRAZINE (ii)

(a) A solution of the 2-oxide (lxvii) (0.4 g.) in 20% aqueous methanol (25 ml.) was hydrogenated to completion over Adams catalyst, filtered and the alcohol evaporated under reduced pressure. The residual aqueous solution was basified (NaOH), the ether extract of the alkaline solution dried (Na_2SO_4) and the solvent evaporated under reduced pressure.

The resulting base was distilled under reduced pressure, b.p. 60°/0.6 mm (lit[75], 98 - 99°/25 mm) (0.098 g., 40%).

Found : C, 68.2; H, 11.7%
calc. for $C_8H_{16}N_2$: C, 68.55; H, 11.5%.

(b) Hydrogenation of 1-bromo-pyrido[1, 2-a]pyrazinium bromide (lxxxiii) (0.18 g.) as described for the 2-oxide (lxvii) afforded the base, b.p. 80°/2 mm (0.037 g., 42.5%).

(c) Hydrogenation of 1, 4-dihydro-1-imino-pyrido[1, 2-a]pyrazinium bromide 2-oxide (lxxxv) (0.3 g.) as described for the 2-oxide (lxvii) gave the base, b.p. 80°/2 mm (0.068 g., 36.5%).

(d) 1, 3-Dioxo-1,2,3,4-tetrahydro-pyrido[1, 2-a]pyrazinium bromide (lxxxviii; X = Br) (0.8 g.) was slowly added to a stirred solution of lithium aluminium hydride (1 g.) in dry ether (50 ml.) and the resulting solution boiled under reflux for 5 hr., cooled, and allowed to stand at room temperature for a further 17 hr. The excess hydride was decomposed with water, the resulting clear ether solution decanted, water (5 ml.) added, and the ether evaporated under reduced pressure. Methanol (20 ml.) was added to the resulting aqueous solution and the intermediate compound was hydrogenated to completion over Adams catalyst. The catalyst was filtered off and the alcohol evaporated from the filtrate under reduced pressure. The residual aqueous solution was basified (NaOH), the etheral extract of the alkaline solution dried (Na_2SO_4) and the ether evaporated under reduced pressure,

leaving the base which was distilled under reduced pressure, b.p. 70°/ 1.7 mm. (0.138 g., 30%).

The infra-red spectra of the bases obtained as in (b), (c) and (d) were identical to that of the base prepared as in (a) and to the infra-red spectrum of an authentic sample of perhydropyrido[1, 2-a] pyrazine[63] prepared by hydrogenation and subsequent lithium aluminium hydride reduction of the lactam (lxxv).

The dipicrate crystallised from water as yellow needles, m.p. 275 - 278° (lit, m.p. 240°[65], 250 - 260°[66]).

Found : C, 40.3; H, 3.8; N, 18.65%
Calc. for $C_8H_{16}N_2 \cdot 2C_6H_3N_3O_7$: C, 40.15; H, 3.7; N, 18.7%.

The melting points of the dipicratesderived from the base prepared as in (a), (b), (c) and (d) were identical.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. F. KRÖHNKE, Angew. Chem, 1963, 75, 181.
2. F. KRÖHNKE, H. SCHNEGELBERGER and W. WEIS, Ber., 1964, 97, 3566.
3. C. K. BRADSHER and S. A. TELANG, J. Org. Chem., 1966, 31, 941.
4. O. DIELS and K. ALDER, Annalen, 1931, 490, 267.
   O. DIELS, K. ALDER, W. FRIEDRICHSEN, H. KLARE, H. WINKLER and H. SCHRAUM, Annalen, 1933, 505, 103.
5. R. M. ACHESON and G. A. TAYLOR, J., 1960, 1691.
6. L. M. JACKMAN, A. W. JOHNSON and J. C. TEBBY, J., 1960, 1579.
7. R. BENTLEY and T. S. STEVENS, Nature, 1949, 164, 141.
8. W. M. MCLAMORE and R. B. WOODWARD, J. Amer. Chem. Soc., 1949, 71, 379.
9. K. von AUWERS, Ber., 1938, 71, 2082.
10. A. C. BEAMAN and R. B. WOODWARD, J. Amer. Chem. Soc., 1954, 76, 1832.
11. V. BOEKELHEIDE and W. G. GALL, J. Amer. Chem. Soc., 1954, 76, 1832
12. V. BOEKELHEIDE and W. G. GALL, J. Amer. Chem. Soc., 1955, 77, 5691.
13. A. RICHARDS and T. S. STEVENS, J., 1958, 3067.
14. E. D. AMSTUTZ and H. V. HANSEN, J. Org. Chem., 1963, 28, 393.
15. E. E. GLOVER and G. JONES, J., 1958, 3021.
16. L. C. CRAIG, J. Amer. Chem. Soc., 1934, 56, 1144.
17. E. E. GLOVER and G. JONES, J., 1959, 1686.
18. I. IWAI and T. MIYADERA, Chem. Pharm. Bull. (Japan), 1964, 12, 1388.
19. E. E. GLOVER, Ph.D. Thesis, University of London, 1959.
20. A. FOZARD and G. JONES, J., 1963, 2203.
21. A. FOZARD and G. JONES, J., 1964, 2760.
22. A. FOZARD and G. JONES, J., 1964, 3030.
23. A. R. COLLICUT and G. JONES, J., 1960, 4101.
24. E. E. GLOVER and M. J. R. LOADMAN, in the press.
25. A. N. NESMEYANOV, M. I. RYBINSKAIA and N. K. BEL'SKII, Docklady Akad. Nauk. S.S.S.R., 1957, 113, 343.
26. A. N. NESMEYANOV, and M. I. RYBINSKAIA, Docklady Akad. Nauk. S.S.S.R., 1958, 118, 297.
27. E. SCHRAUFSTÄTTER, Angew. Chem., 1962, 74, 874.

28. P. DUKE, A. FOZARD and G. JONES, J. Org. Chem., 1965, 30, 526.

29. G. FEIX and O. WESTPHAL, Angew. Chem., 1963, 75, 206.

30. C. K. BRADSHER and L. E. BEAVERS, J. Amer. Chem. Soc., 1955, 77, 453.

31. R. W. L. KIMBER and J. C. PARHAM, J. Org. Chem., 1963, 28, 3205.

32. C. K. BRADSHER and R. E. DOOLITTLE, Chem. and Ind., 1965, 1631.

33. C. K. BRADSHER and L. E. BEAVERS, J. Amer. Chem. Soc., 1955, 77, 4812.

34. C. K. BRADSHER and J. H. JONES, J. Amer. Chem. Soc., 1957, 79, 6033.

35. C. K. BRADSHER and J. H. JONES, J. Org. Chem., 1960, 25, 293.

36. C. K. BRADSHER and N. L. YARRINGTON, J. Org. Chem., 1960, 25, 294.

37. C. K. BRADSHER and N. L. YARRINGTON, J. Org. Chem., 1963, 28, 78.

38. C. K. BRADSHER and J. C. PARHAM, J. Org. Chem., 1963, 28, 83.

39. C. K. BRADSHER and J. C. PARHAM, J. Hetero. Chem., 1964, 1, 30.

40. C. K. BRADSHER and J. C. PARHAM, J. Hetero. Chem., 1964, 1, 121.

41. C. K. BRADSHER and M. W. BARKER, J. Org. Chem., 1963, 28, 1669.

42. C. K. BRADSHER and M. W. BARKER, J. Org. Chem., 1964, 29, 61.

43. C. K. BRADSHER and A. FOZARD, J. Org. Chem., 1966, 31, 2346.

44. C. K. BRADSHER and K. B. MOSER, J. Amer. Chem. Soc., 1959, 81, 2547.

45. C. K. BRADSHER, R. E. LEBLEU and L. D. QUIN, J. Org. Chem., 1961, 26, 2373.

46. C. K. BRADSHER, J. W. McDONALD, R. E. LEBLEU and L. D. QUIN, J. Org. Chem., 1961, 26, 4944.

47. C. K. BRADSHER and E. F. LITZINGER, J. Hetero. Chem., 1964, 1, 168.

48. C. K. BRADSHER, E. F. LITZINGER and M. F. ZINN, J. Hetero. Chem., 1965, 2, 332.

49. C. K. BRADSHER, and M. F. ZINN, J. Hetero. Chem., 1964, 1, 219.

50. C. K. BRADSHER and D. F. LOHR, Chem. and Ind., 1964, 1801.

51. C. K. BRADSHER and J. C. PARHAM, J. Org. Chem., 1964, 29, 856.

52. R. F. FIELDEN, R. F. HOMER and R. F. JONES, British Patent 785,732.

53. R. C. BRIAN, R. F. HOMER, R. F. JONES and J. STUBBS, Nature, 1958, 181, 446.

54. W. R. BOON and R. F. HOMER, British Patent 815, 348. Chem. Abs. 1959, 53, 20679.

55. R. F. HOMER and T. E. TOMLINSON, J., 1960, 2498.

56. R. F. HOMER, British Patent 857, 501, Chem. Abs., 1961, 55, 12430.

57. D. H. CORR and E. E. GLOVER, J., 1965, 5816.

58. I. C. CALDER and W. H. F. SASSE, Tetrahedron Letters, 1965, 20, 1465.

59. E. E. GLOVER and G. H. MORRIS, J., 1965, 3885.

60. I. C. CALDER and W. H. F. SASSE, Austral. J. Chem., 1965, 18, 1819.

61. E. E. GLOVER and T. R. THOMAS, in the press.

62. W. HEFFE, K. JANN and O. WESTPHAL, Arch. Pharm., 1961, 294, 37.

63. G. TRENHOLM, M.Sc. Thesis, University of Durham, 1965.

64. T. ISHII, J. Pharm. Soc. (Japan), 1951, 71, 1092.

65. W. GÖBEL, K. KÜLMER and K. WINTERFELD, Ber., 1959, 92, 1510.

66. G. GIERENZ and K. WINTERFELD, Ber., 1959, 92, 240.

67. Personal Communication from W. A. WOLSTENHOLME, A.E.I. Ltd., Manchester.

68. E. OCHIAI and T. NAITO, J. Pharm. Soc. (Japan), 1943, 63, 210.

69. K. NAKANISHI, Infra-red absorption spectroscopy, p. 47.

70. G. W. EWING and E. A. STECK, J. Amer. Chem. Soc., 1946, 68, 2181.

71. H. MEYER, Rec. Trav. Chim., 1925, 44, 323.

72. A. CAMPS, Arch. Pharm., 1902, 240, 346.

73. F. KRÖHNKE, Ber., 1937, 70B, 543.

74. J. KRÜGER, J. Prakt. Chem., 1891, 43, 294.

75. M. E. FREED and A. R. DAY, J. Org. Chem., 1960, 25, 2108.

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