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THE SYNTHESIS

OF

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

BY

D. H. CORR, A.R.I.C.

A THESIS

submitted to the

UNIVERSITY OF DURHAM

for the degree of

MASTER OF SCIENCE

Constantine College
of Technology,
Middlesbrough.

August, 1965.



SUMMARY

The methods of synthesis of quinolizinium and pyrazidiinium salts are briefly reviewed.

The object of this work was to establish satisfactory and if possible, general methods of synthesis of dipyrdo [1,2-a:2',1'-c] pyrazidiinium salts and some of their alkyl and aryl derivatives in quantities which permit a detailed study of their herbicidal and chemical properties.

An attempted synthesis of dipyrdo [1,2-a:2',1'-c] pyrazidiinium salts by the dehydrogenation of 6,7-dihydrodipyrdo [1,2-a:2',1'-c] pyrazidiinium salts was unsuccessful. The system was successfully synthesised by the dehydration, using phosphorus tribromide, of 6-hydroxy 6,7-dihydrodipyrdo [1,2-a:2',1'-c] pyrazidiinium dibromide formed by the cyclisation of the monoquaternary salt, obtained by quaternising 2,2'-bipyridyl with α -bromoacetaldehyde oxime.

By a similar route, using phenacyl bromide and bromoacetone as the quaternising agent, 6-methyl and 6-phenyl-dipyrdo [1,2-a:2',1'-c] pyrazidiinium salts were obtained.

The structures of the aromatic dications were established spectroscopically and by hydrogenation to the corresponding saturated bases.

The synthesis and attempted isolation of stereoisomeric forms of perhydro-6-oxodipyrdo [1,2-a:2',1'-c] pyrazine and the corresponding perhydro-base are described.

The reactions of 6-hydroxy and 6,7-dihydrodipyrido [1,2-a:2',1'-c] pyrazidiinium salts with sodium borohydride is described.

ACKNOWLEDGEMENTS

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

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He would also like to thank Dr. Gurnos Jones, University of Keele, for the determination of his n.m.r. spectra.

His thanks are also due to Middlesbrough Education Committee for the provision of research facilities at Constantine College of Technology and for the award of a Research Assistantship, and to Miss P. Moon and Mrs. A. Bailey for the typescript of this thesis.

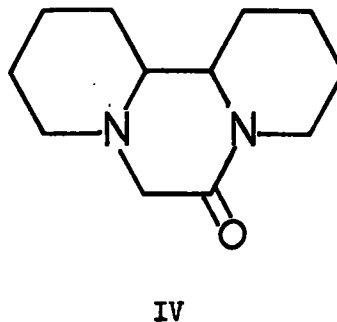
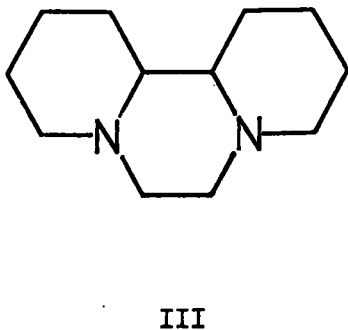
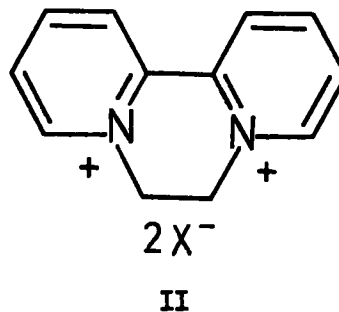
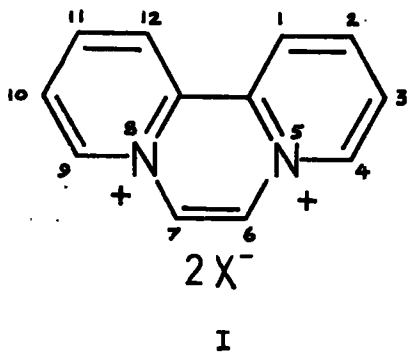
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INTRODUCTION

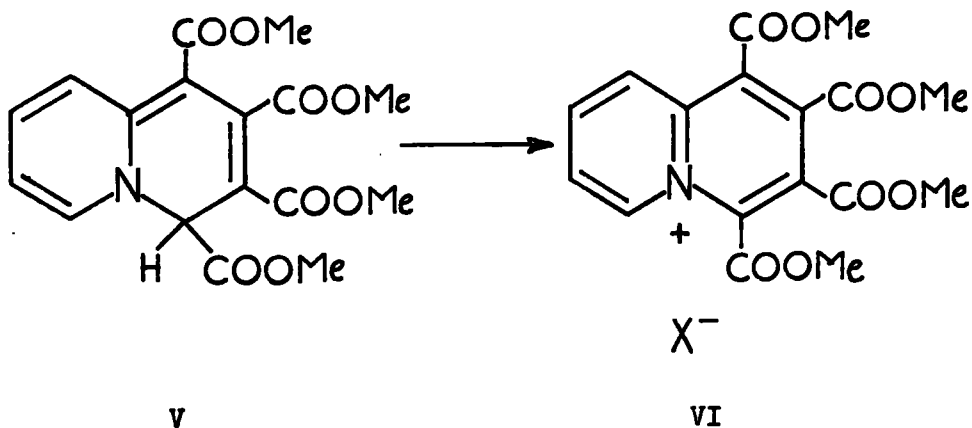
NOMENCLATURE

The name dipyrido [1,2-a: 2',1'-c] pyrazidiinium ion has been adopted to describe the tricyclic fused ring system in which the 8a and 10a bridgehead carbon atoms in phenanthrene have been replaced with quaternary nitrogen atoms. Thus, salts of the type (I) and (II) will be referred to as dipyrido [1,2-a: 2',1'-c] pyrazidiinium salts, and 6,7-dihydrodipyrido [1,2-a: 2',1'-c] pyrazidiinium salts respectively. Compounds of the type (III) and (IV) will be referred to as substituted pyrazines, i.e. perhydrodipyrido [1,2-a: 2',1'-c] pyrazine (III), and perhydro-6-oxodipyrido [1,2-a: 2',1'-c]pyrazine (IV).

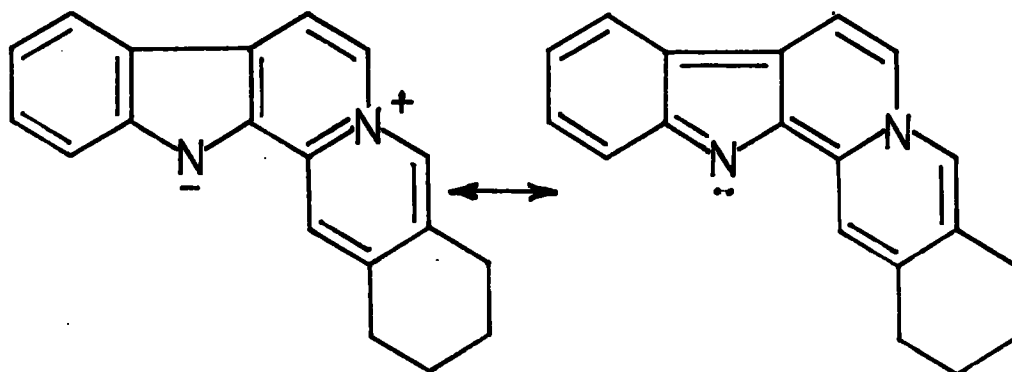


HISTORICAL INTRODUCTION

The earliest synthesis of quinolizinium derivatives was recorded by Diels and Alder¹. While investigating the reactions between the dimethyl ester of acetylene-dicarboxylic acid and pyridine, they obtained three products, an unstable red compound, a stable yellow compound, and the so called, Kashimoto's compound. The stable yellow compound, which has recently been shown^{2,3} to be tetramethyl 4H-quinolizine 1,2,3,4-tetracarboxylate (V), when reacted with bromine in methanol, gave the corresponding quinolizinium perbromide (VI; X = Br₃), which was converted to the bromide by boiling with acetone.

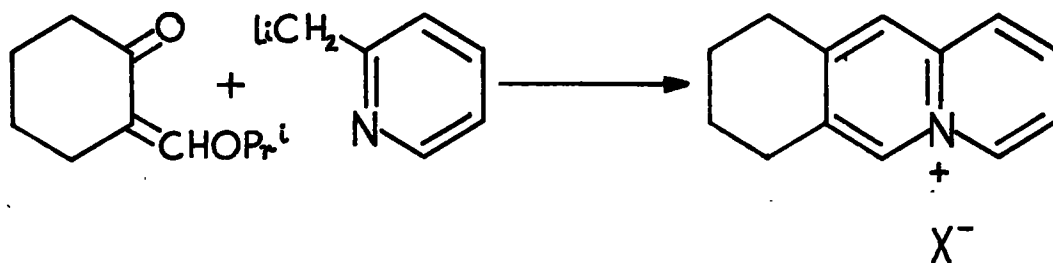


Some years later, in 1949, it was shown^{4,5} that the naturally occurring alkaloid sempervirine contained the quinolizinium nucleus.



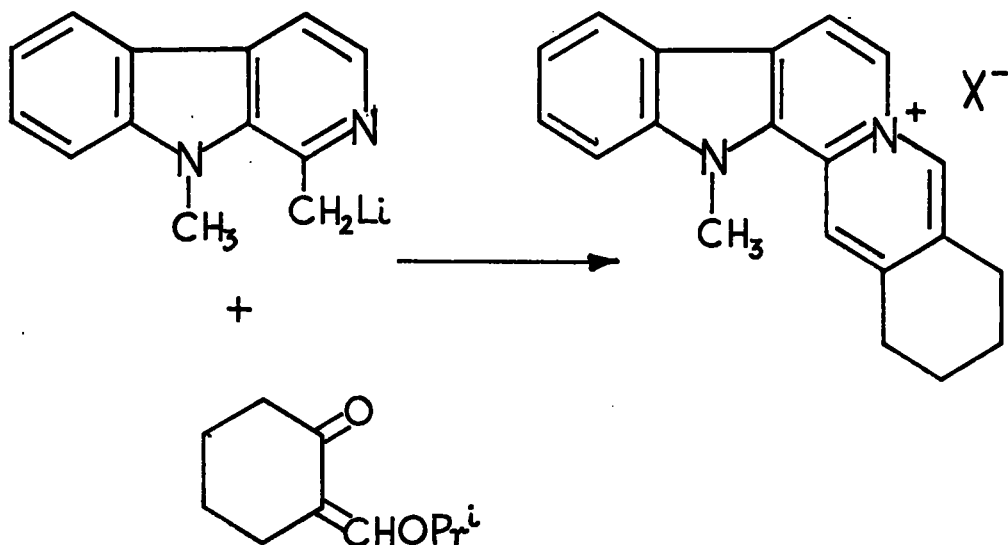
sempervirine

In establishing the structure of the alkaloid, Woodward and McLamore⁵ developed a method for the unambiguous synthesis of the quinolizinium nucleus, which was the basis of many other syntheses of quinolizinium compounds. They condensed 2-picolylium and 2-isopropoxy methylene cyclohexanone, and on subsequent cyclisation obtained 7,8,9,10-tetrahydro benzo [b] quinolizinium picrate (VII; X = picrate) in 51% yield.

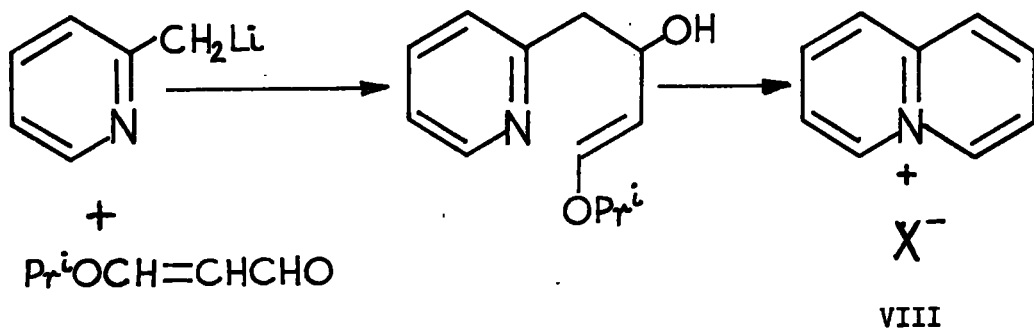


VII

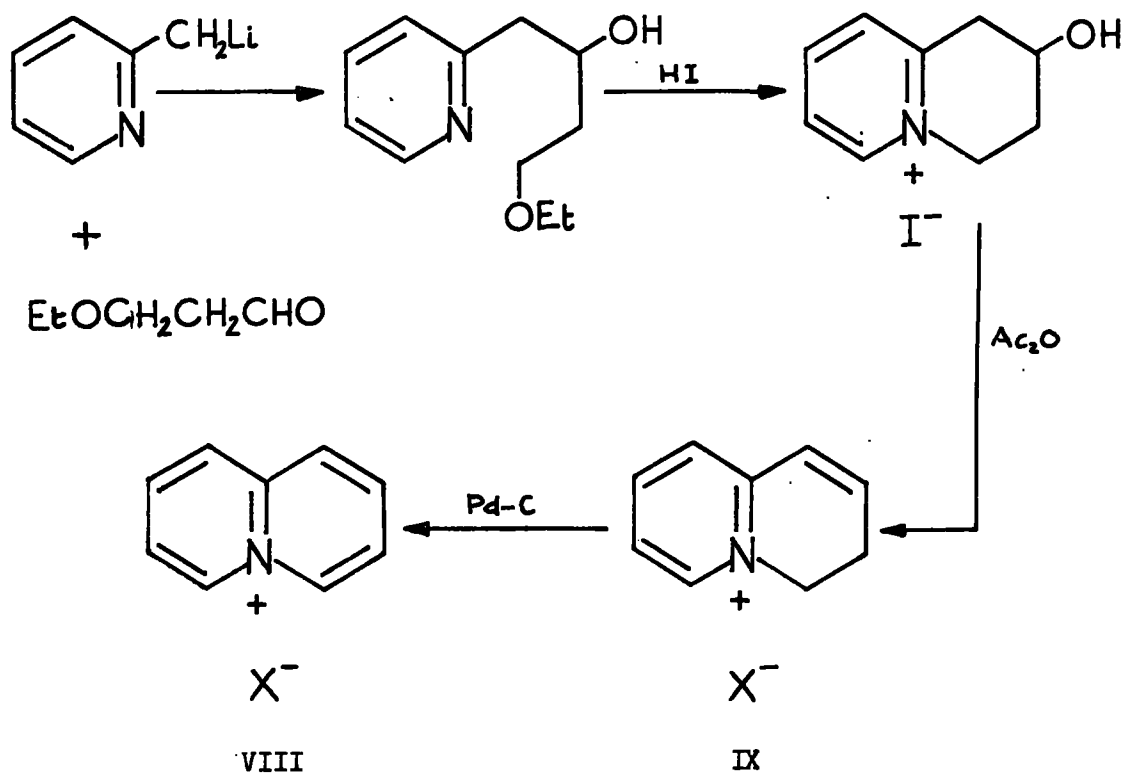
They synthesised the methochloride of sempervirine by condensing 2-isopropoxy methylene cyclohexanone with the lithium derivative of N-methylharman.



Using a modification of this method, Woodward and Beaman⁶ achieved the first synthesis of the simple quinolizinium ion in very low yield. They first condensed 3-isopropoxyacrolein with 2-picolyllithium and then cyclised the intermediate.

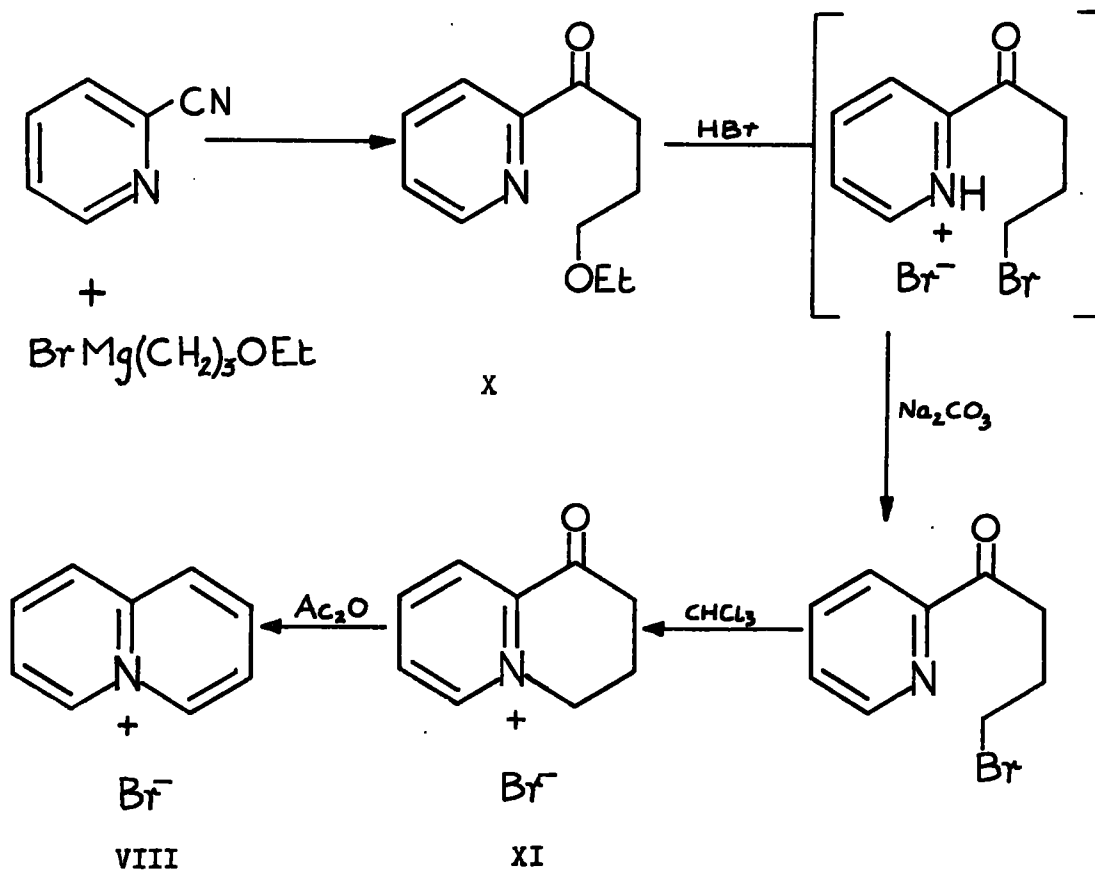


Boekelheide and Gall⁷ improved the method by using 2-ethoxypropionaldehyde as starting material and dehydrogenating the intermediate dihydroquinolizinium iodide (IX; X = I) with palladium-charcoal, or chloranil in butanol. The product was isolated as the picrate (VIII; X = picrate).



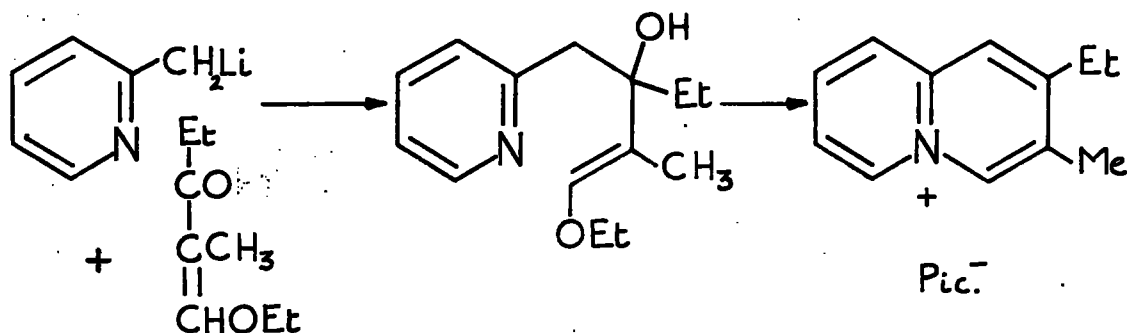
The dehydrogenation of (IX) was difficult, the best yield of quinolizinium picrate (VIII; X = picrate) being obtained when dihydroquinolizinium picrate (IX; X = picrate) was heated with palladium-charcoal in butanol⁸. This procedure has also been successfully applied⁸ to the synthesis of 4-methylquinolizinium salts, by starting with the mono-lithium derivative of 2,6-lutidine.

Glover and Jones^{9,10} avoided the dehydrogenation stage by using 2-cyanopyridine and 3-ethoxypropyl magnesium bromide as starting materials. The condensation product (X) when boiled under reflux with hydrobromic acid was converted to the corresponding bromoamine hydrobromide. This salt was not isolated but converted to the free base which, when dissolved in chloroform and boiled under reflux, cyclised to give 1,2,3,4-tetrahydro-1-oxoquinolizinium bromide (XI). This, when boiled under reflux with acetic anhydride, was dehydrated to quinolizinium bromide in 96% yield. This represents a 48% overall yield, based on the 2-cyanopyridine.



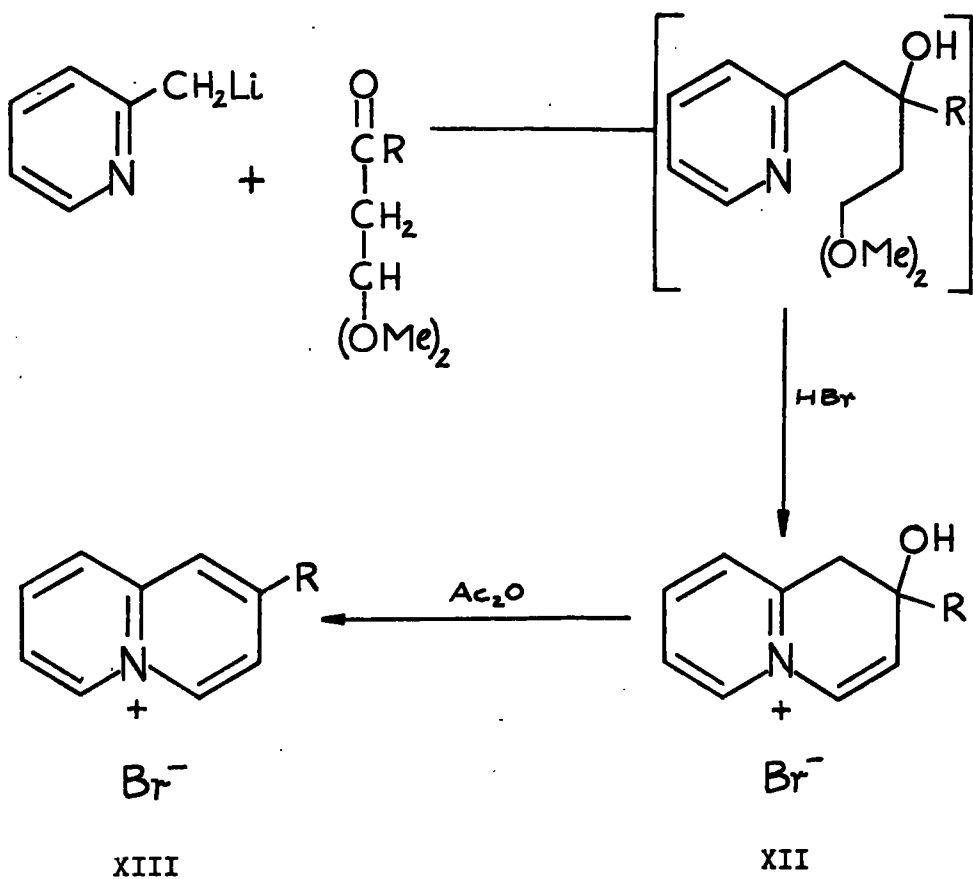
Similarly, the same authors¹⁰ prepared 2-,3-, and 4-alkyl and aryl substituted quinolizinium salts by suitable modification of the aliphatic precursor. Other workers^{11,12} have prepared 1,2,3,4-tetrahydro-1-oxoquinolizinium bromide (XI) by a similar route. Moynehan et. al.¹³ have used this method to prepare 1-,2-,3- and 4-methylquinolizinium bromides, and more recently Miyadera and Iwai¹⁴ have modified the method, improving the yields, in their preparation of quinolizinium and 1,2,3,- and 4-methylquinolizinium bromides.

Another modification of the Woodward and McLamore synthesis was that due to Richards and Stevens¹⁵, who were the first to synthesise simple alkyl quinolizinium derivatives. They prepared 2-ethyl 3-methyl-quinolizinium picrate by condensing 2-picolyllithium with 1-ethoxy 2-methyl pent-1-ene-3-one and cyclising the intermediate with alcoholic picric acid.



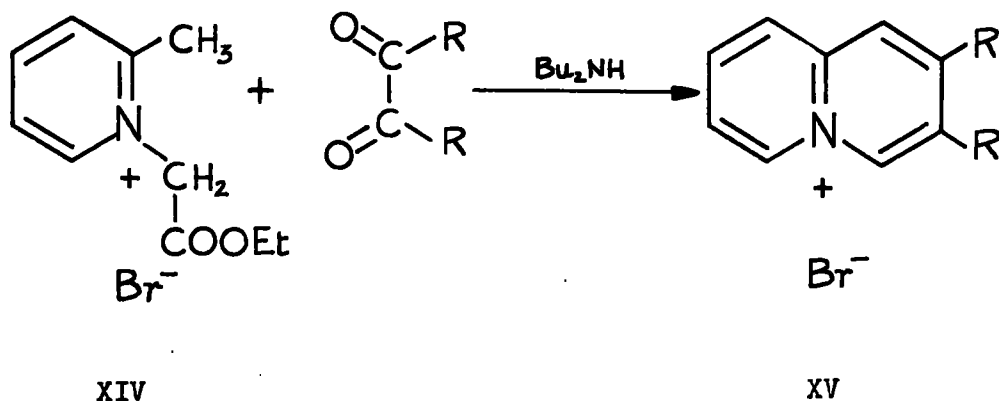
They later¹⁶ extended this synthesis to include various 2-,3-, and 4-substituted alkyl and aryl quinolizinium salts. Hansen and Amstutz¹⁷ further extended it to synthesise 2,4,6-trimethyl- and 2-phenyl 4,6-dimethylquinolizinium salts.

A specific synthesis of 2-substituted quinolizinium salts was reported by Nesmeyanov and Rybinskaia¹⁸ who condensed 2-picolyl-lithium with certain acylacetals and on subsequent cyclisation obtained the corresponding hydroxy- compounds (XII). These were dehydrated with acetic anhydride to give the 2-substituted quinolizinium salts (XIII; R = Me., Prⁿ, Ph.).

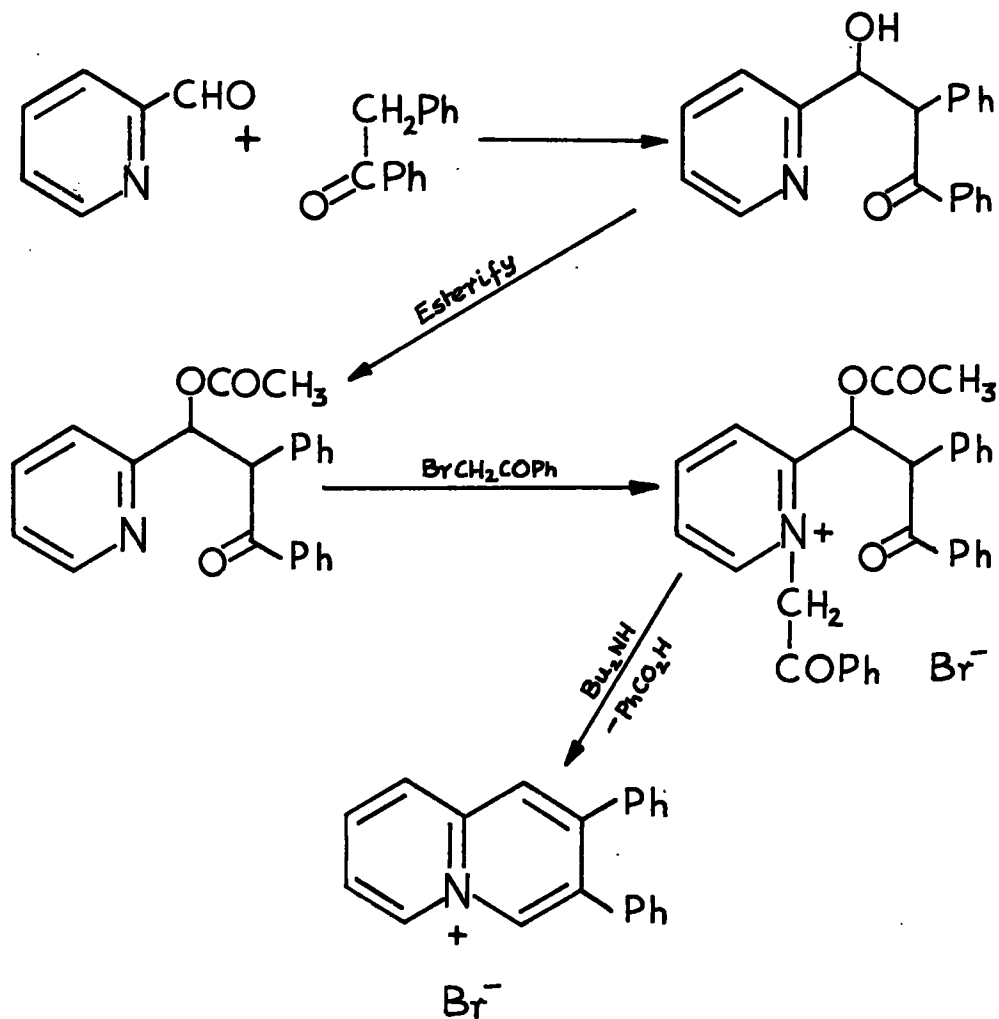


A similar method for the synthesis of 1-alkyl- and 1-aryl quinolizinium salts has been reported by Glover and Jones¹⁹.

Westphal et. al.²⁰ have described a comprehensive synthesis of the quinolizinium ring system. In this, 2-picolinium salts (XIV) with an activated methylene group were condensed with 1,2-diketones in the presence of weakly basic agents, such as dibutylamine or sodium carbonate, to give 2,3-disubstituted quinolizinium derivatives (XV).

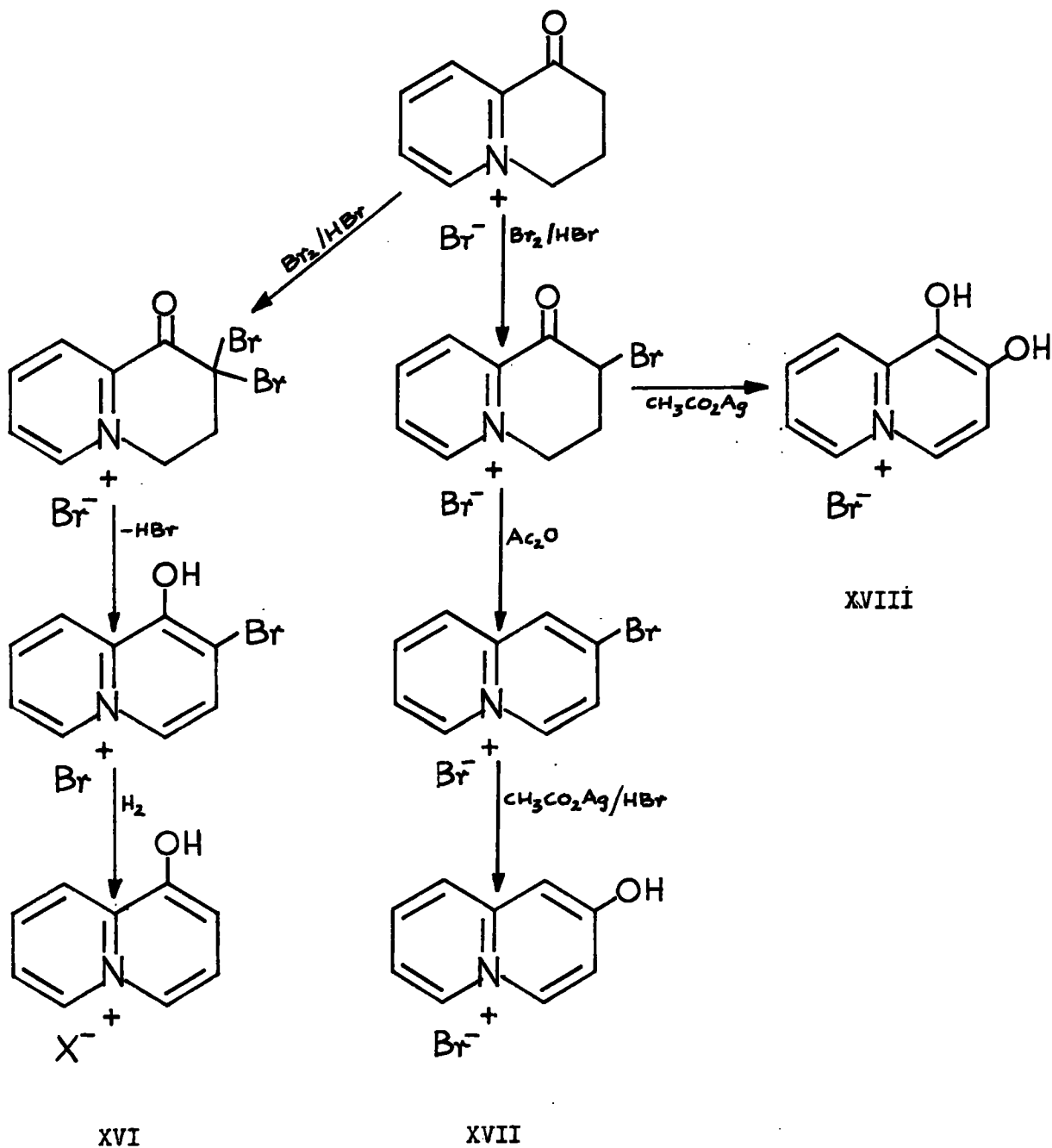


Many derivatives have been prepared²¹ using this procedure, including more highly substituted compounds, with substituents other than alkyl or aryl groups. A slight variation²² on this method is to use two components, each containing ketonic and active methylene groups, e.g.

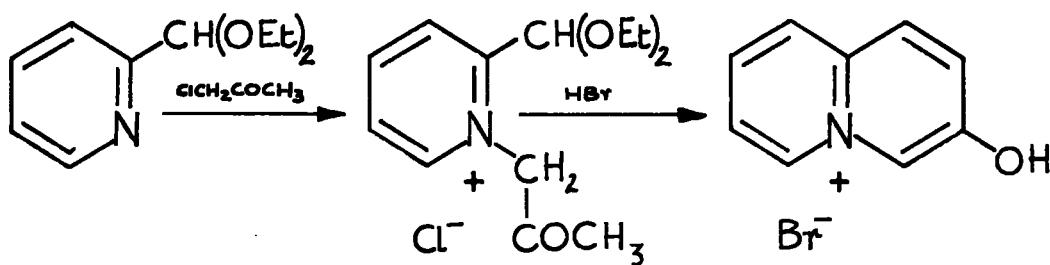


Several hydroxyquinolizinium salts have been prepared. The 1-hydroxyquinolizinium derivative (XVI; X = picrate) was first prepared by Glover and Jones²³ by dehydrogenation of 1,2,3,4-tetrahydro-1-oxoquinolizinium bromide (XI) with palladium-charcoal. The yield was low and only the picrate was isolated. The picrate has also been isolated²⁴ from the products of diazotisation and hydrolysis of 1-aminoquinolizinium chloride. Fozard and Jones^{25,26}

have since prepared the 1-hydroxy-²⁵ (XVI; X = Br), the 2-hydroxy-²⁶ (XVII), and the 1,2-dihydroxy-²⁵ (XVIII) quinolizinium bromides in good yields, via the following series of reactions:-

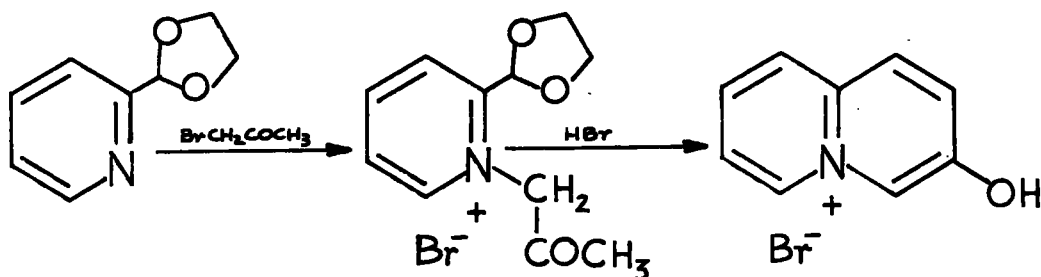


3-Hydroxyquinolizinium bromide (XIX) has been prepared by Schraufstätter²⁷, who first quaternised pyridine-2-aldehyde diethyl acetal with chloroacetone, and then cyclised the product with hydrobromic acid.

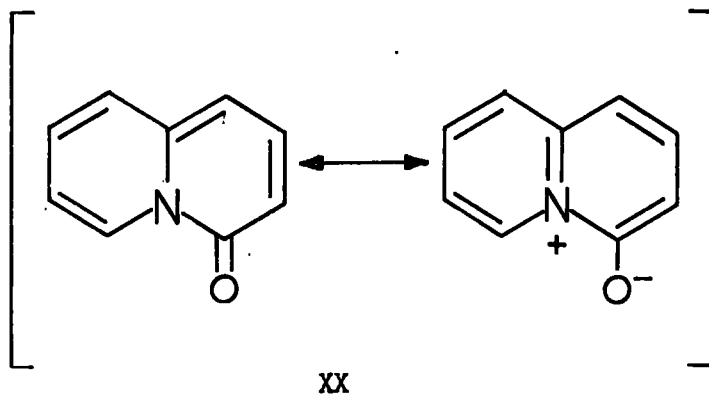


XIX

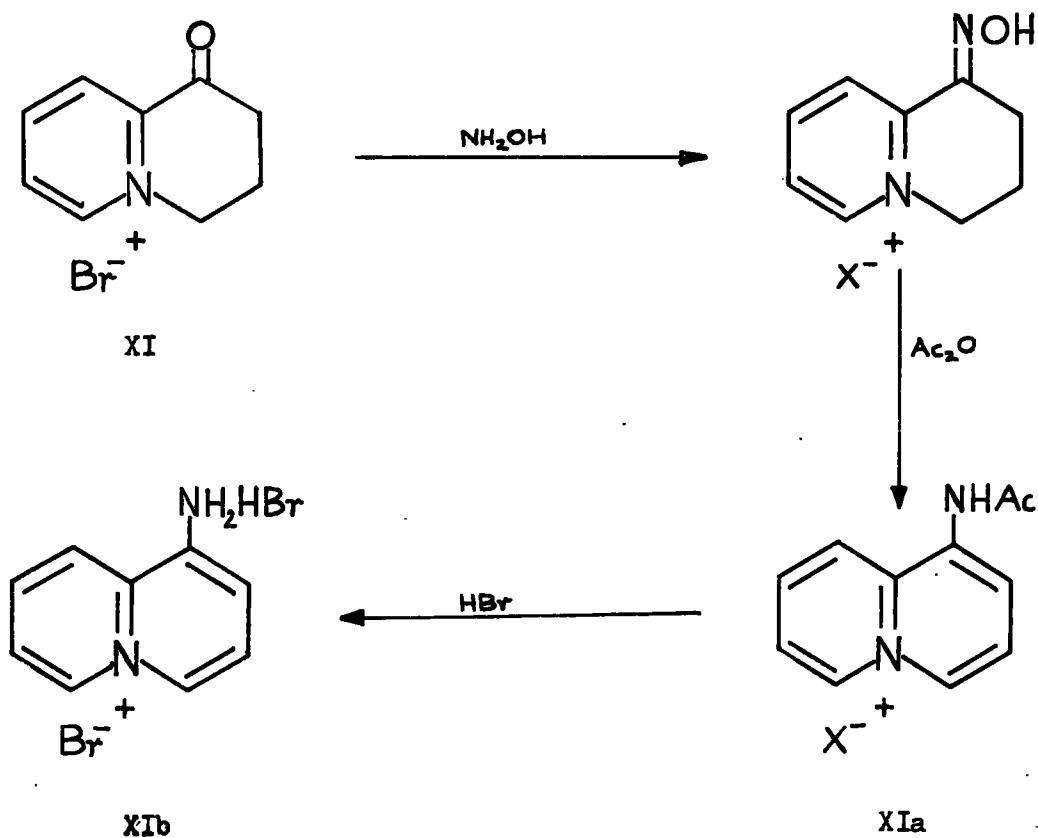
It has also been prepared²⁸ by quaternising 2-(1,3-dioxolan-2-yl)pyridine with bromoacetone and cyclising the intermediate with hydrobromic acid.



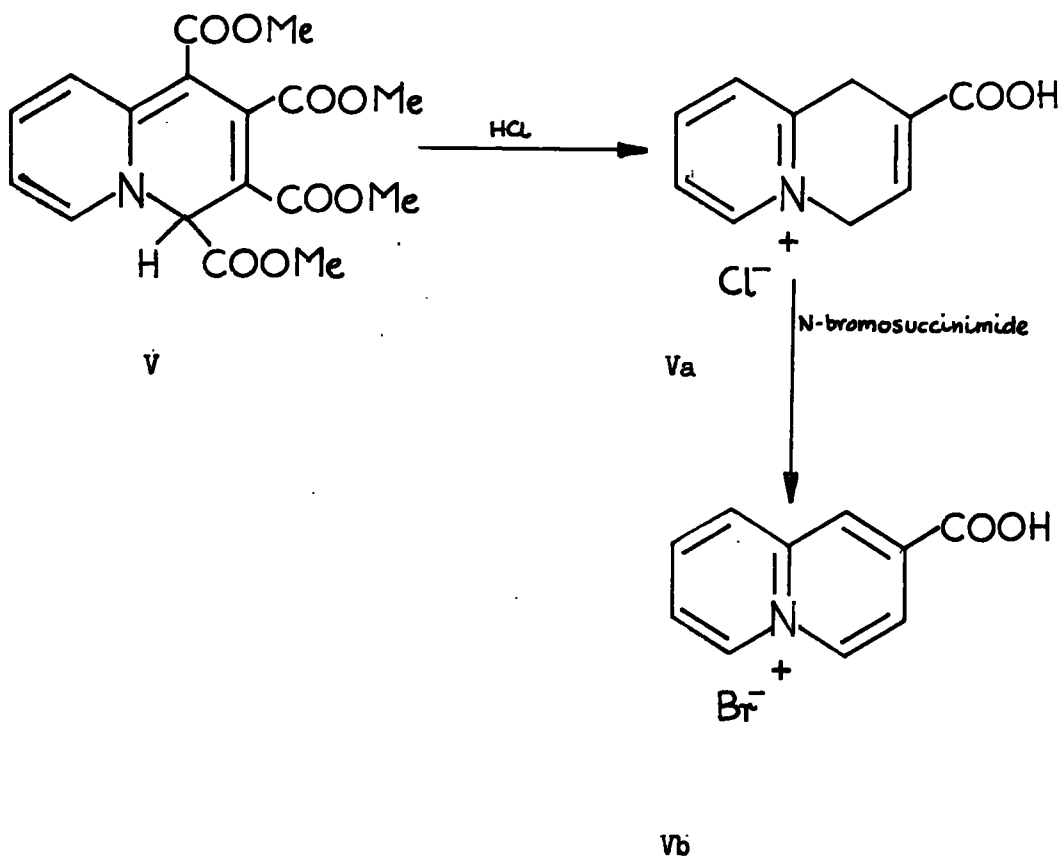
Boekelheide and Lodge²⁹ have prepared 4-quinolizone (XX) but were unable to isolate salts of the mesomeric 4-hydroxyquinolizinium ion. Physical measurements indicate that the lactam is the predominant form.



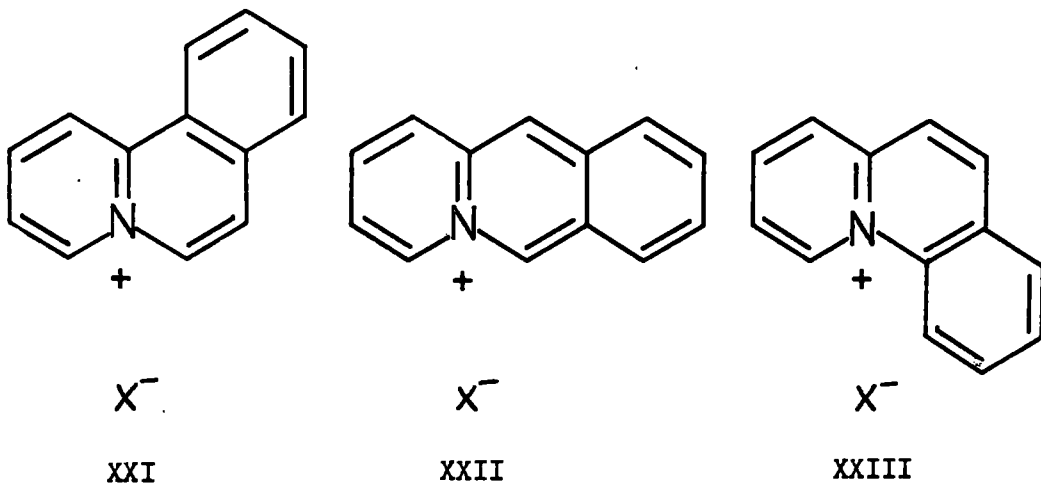
Some alkyl and aryl substituted 1-hydroxyquinolizinium salts have been prepared³⁰, and many are listed in a review by Kröhnke^{31,49}. Other simple substituted quinolizinium compounds prepared include the 1-aminoquinolizinium salt²⁴, and the 2-carboxyquinolizinium salt³². The 1-amino compound (XIb) was prepared as follows: 1,2,3,4-tetrahydro-1-oxoquinolizinium bromide (XI) was converted into its oxime with hydroxylamine, then this was aromatised by boiling under reflux with acetic anhydride containing a drop of concentrated sulphuric acid, to give the 1-acetamidoquinolizinium salt (XIa). This salt (XIa) was then converted to the 1-aminoquinolizinium bromide hydrobromide (XIb) by boiling with concentrated hydrobromic acid.



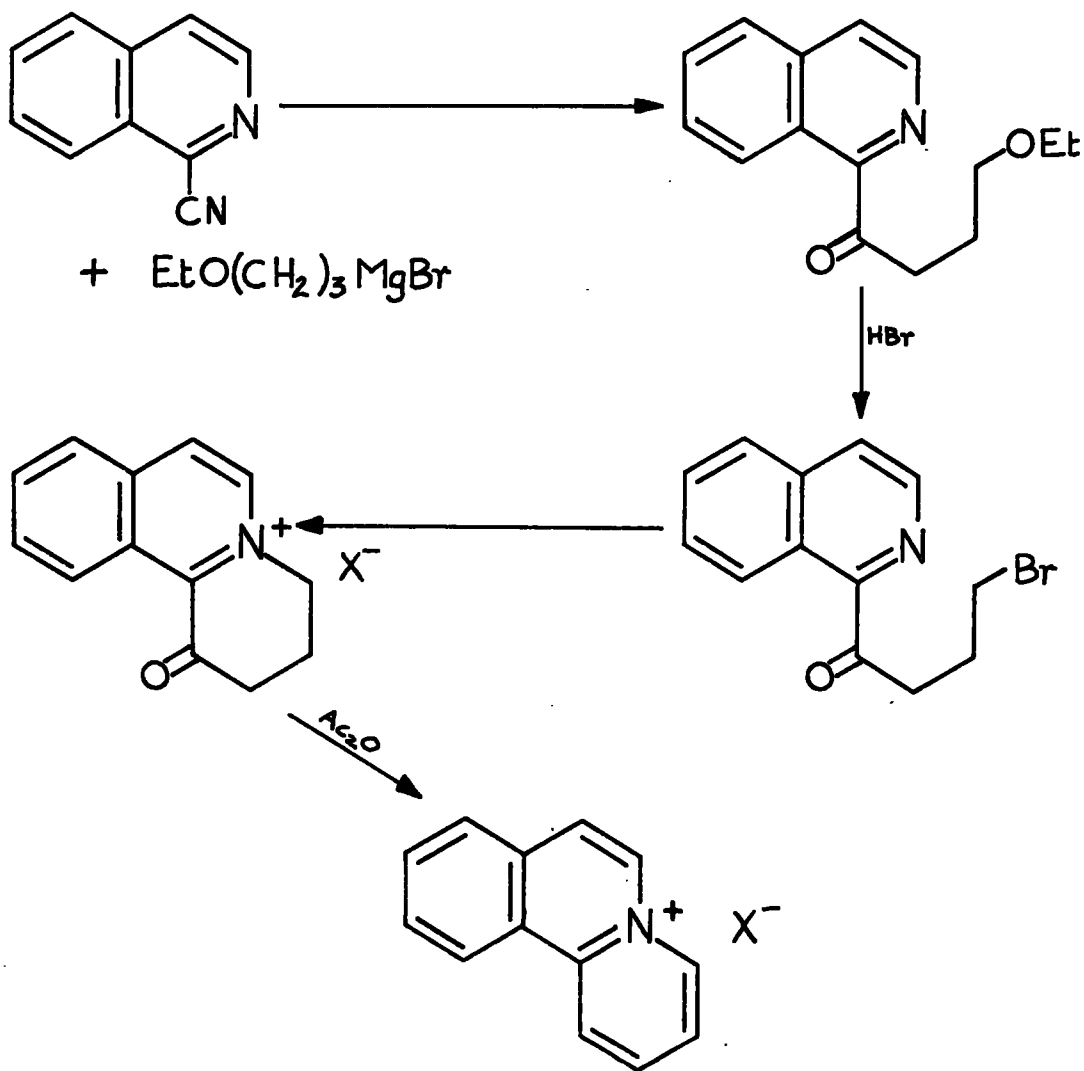
The 2-carboxy compound (Vb) was prepared from tetramethyl 4H-quinolizine 1,2,3,4-tetracarboxylate (V). When this was boiled with dilute hydrochloric acid two products were obtained. One, a substituted indole, was removed by extraction with chloroform leaving 2-carboxy 1,4-dihydroquinolizinium chloride (Va) in solution. Treatment of the solution with N-bromosuccinimide, using aqueous dioxan as solvent, gave 2-carboxyquinolizinium bromide (Vb).



BENZOQUINOLIZINIUM SALTS

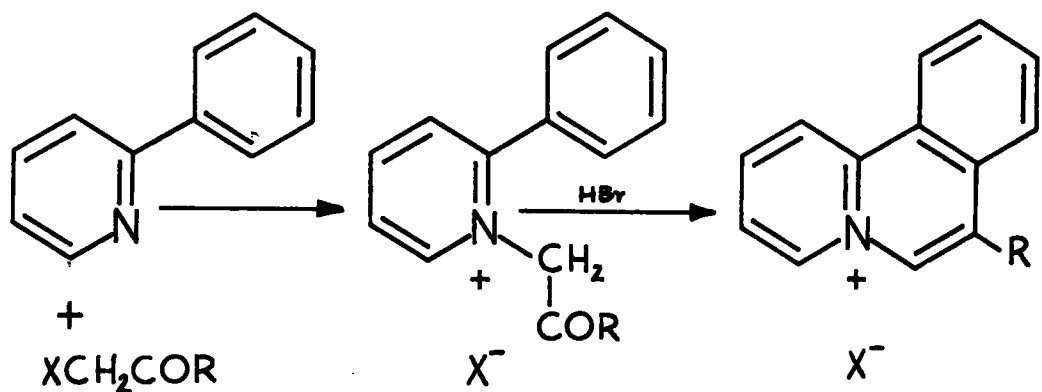


By using 1-cyanoisoquinoline, 3-cyanoisoquinoline and 2-cyanoquinoline as starting materials, Glover and Jones¹⁰ adapted their general method of synthesis of quinolizinium salts, to the synthesis of the isomeric benzo [a] -, benzo [b] -, and benzo [c]-quinolizinium salts (XXI, XXII, XXIII). The following reaction scheme illustrates the formation of the benzo [a] quinolizinium compound (XXI), the two other isomers being prepared in an analogous manner.

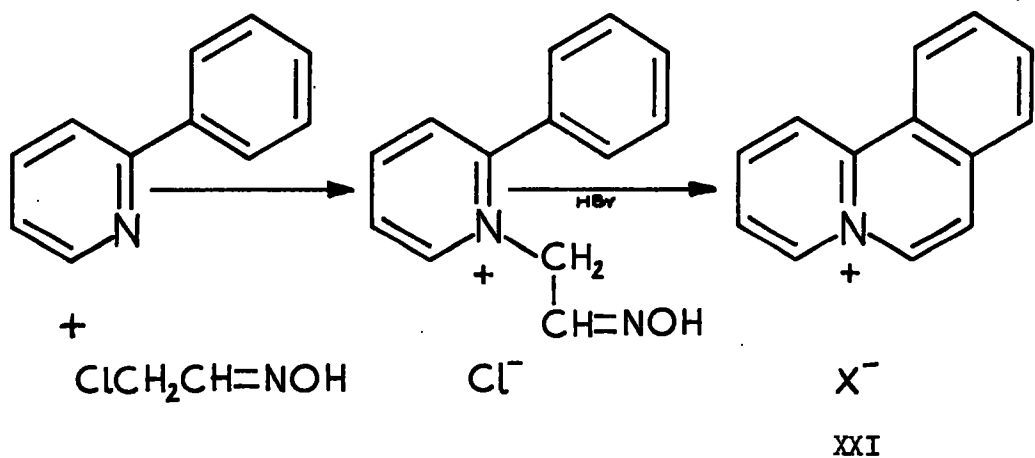


XXI

Substituted benzo [a] quinolizinium salts have also been prepared by Bradsher and Beavers³³ who, using 2-phenylpyridine and iodoacetone, or phenacyl bromide, formed the quaternary salt and then by cyclodehydration obtained 7-methyl or 7-phenyl benzo[a]quinolizinium salts respectively.



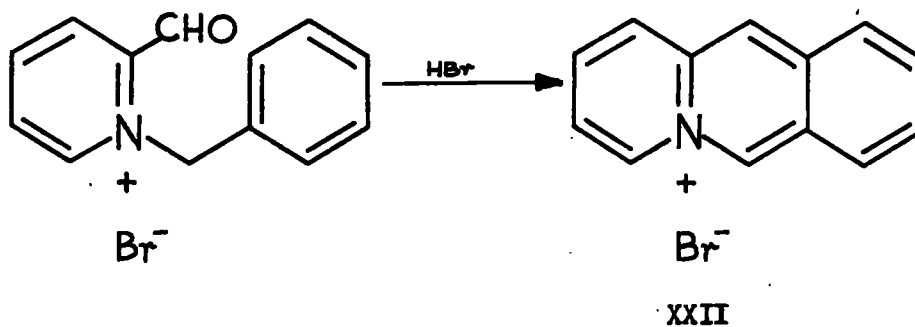
By using chloroacetaldoxime and 2-phenylpyridine as starting materials Kimber and Parham³⁴ have prepared unsubstituted benzo [a] quinolizinium salts in a similar manner.



Other substituted benzo [a] quinolizinium salts including some with a β -ethylcarbethoxy group in the 7-position have been prepared^{34,35}.

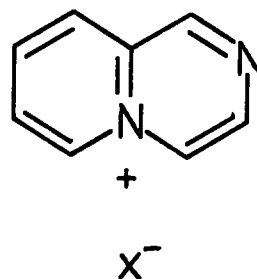
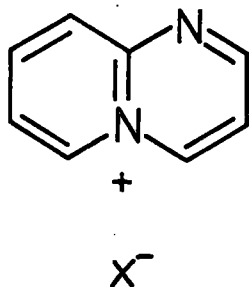
Benzo[b] quinolizinium bromide (XXII; X = Br) was originally prepared by Bradsher and Beavers³⁶, by the cyclodehydration of

N-(benzyl) 2-aldopyridinium bromide with concentrated hydrobromic acid.

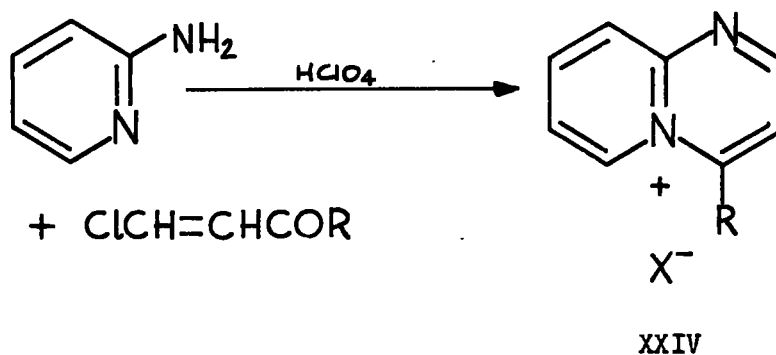


By quaternising suitable α -haloalkylarenes with derivatives of pyridine 2-aldehyde, 2-acetylpyridine, and 2-benzoylpyridine, followed by cyclodehydration, Bradsher et. al.^{37,38,39,40,41,42,43,44,45} prepared many substituted benzo[b] quinolizinium salts.

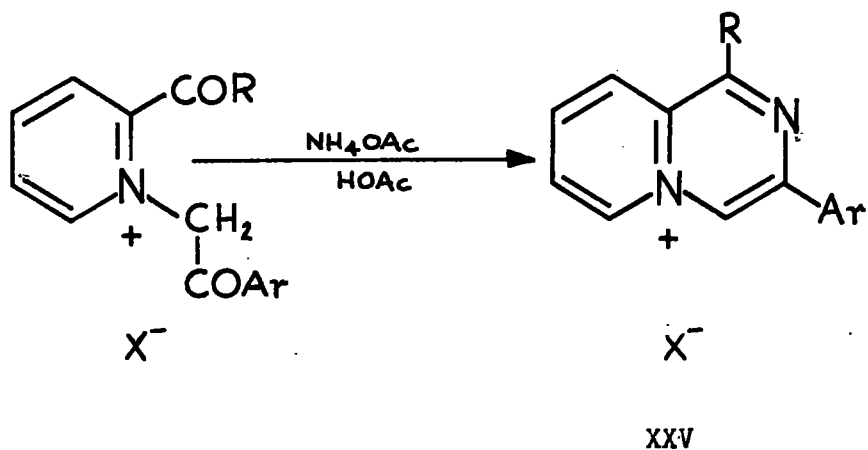
BICYCLIC AZAQUINOLIZINIUM SALTS



Alkyl substituted 1-azaquinolizinium salts (XXIV; R = Me, Et, Prⁿ) have been prepared by Nesmeyanov et. al.⁴⁶ by condensing 2-aminopyridine with β -ketoacetals in a sealed tube, and then cyclising the product with ethanolic hydrobromic acid. They later⁴⁷ improved the method by using β -chlorovinyl ketones and 2-aminopyridine; the condensation and cyclisation stages occurring together under the influence of perchloric acid. This latter method also gives the 4-phenyl-1-azaquinolizinium salt (XXIV; R = Ph).

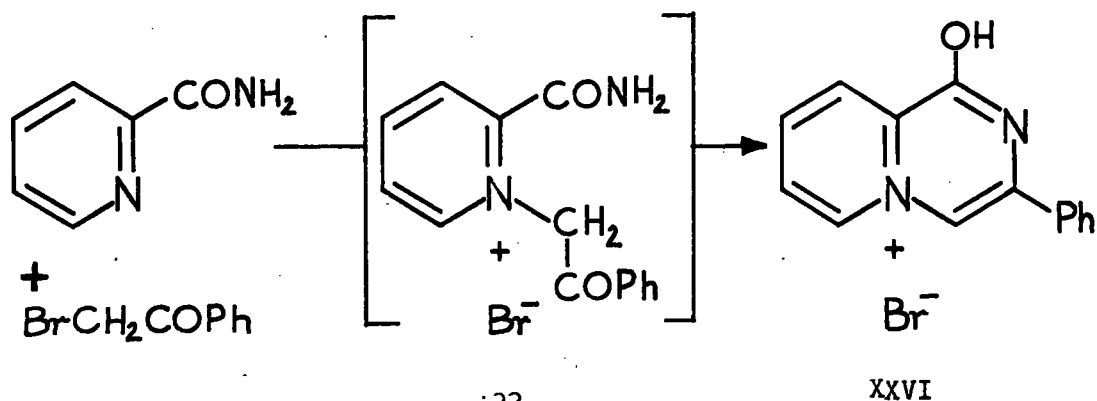


Kröhnke⁴⁸ reported the synthesis of 1-alkyl- and 1-aryl, 3-aryl-2-azaquinolizinium salts (XXV) in excellent yields, by heating N-(phenacyl)-2-acylpyridinium salts with ammonium acetate in acetic acid.



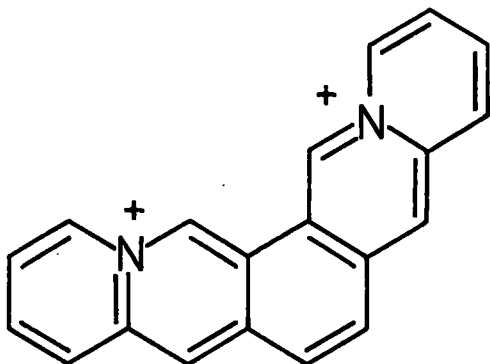
Later, Kröhnke et. al.⁴⁹ showed that 1-hydroxy 3-phenyl-2-azaquinolizinium salts (XXVI) can be prepared in the same way, by heating 1-phenacyl-2-carbethoxy pyridinium salts with ammonium acetate in acetic acid. However, if 2-picolinic acid amide, or 2-cyanopyridine is heated with phenacyl bromide in acetonitrile then 1-hydroxy 3-phenyl-2-azaquinolizinium salts (XXVI) are formed directly.

e.g.



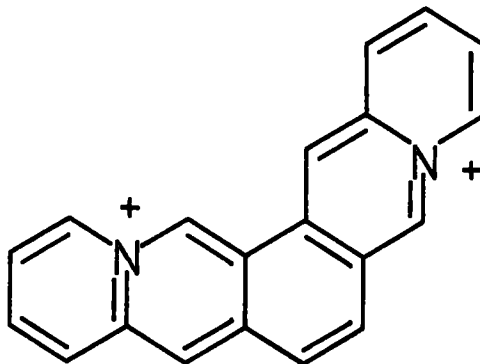
- So far, neither unsubstituted 1-aza-, nor 2-azaquinolizinium salts
have been prepared.

DIAZONIAPENTAPHENE SALTS



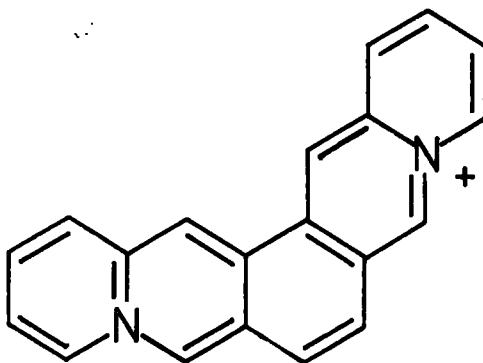
$2X^-$

XXVII



$2X^-$

XXVIII

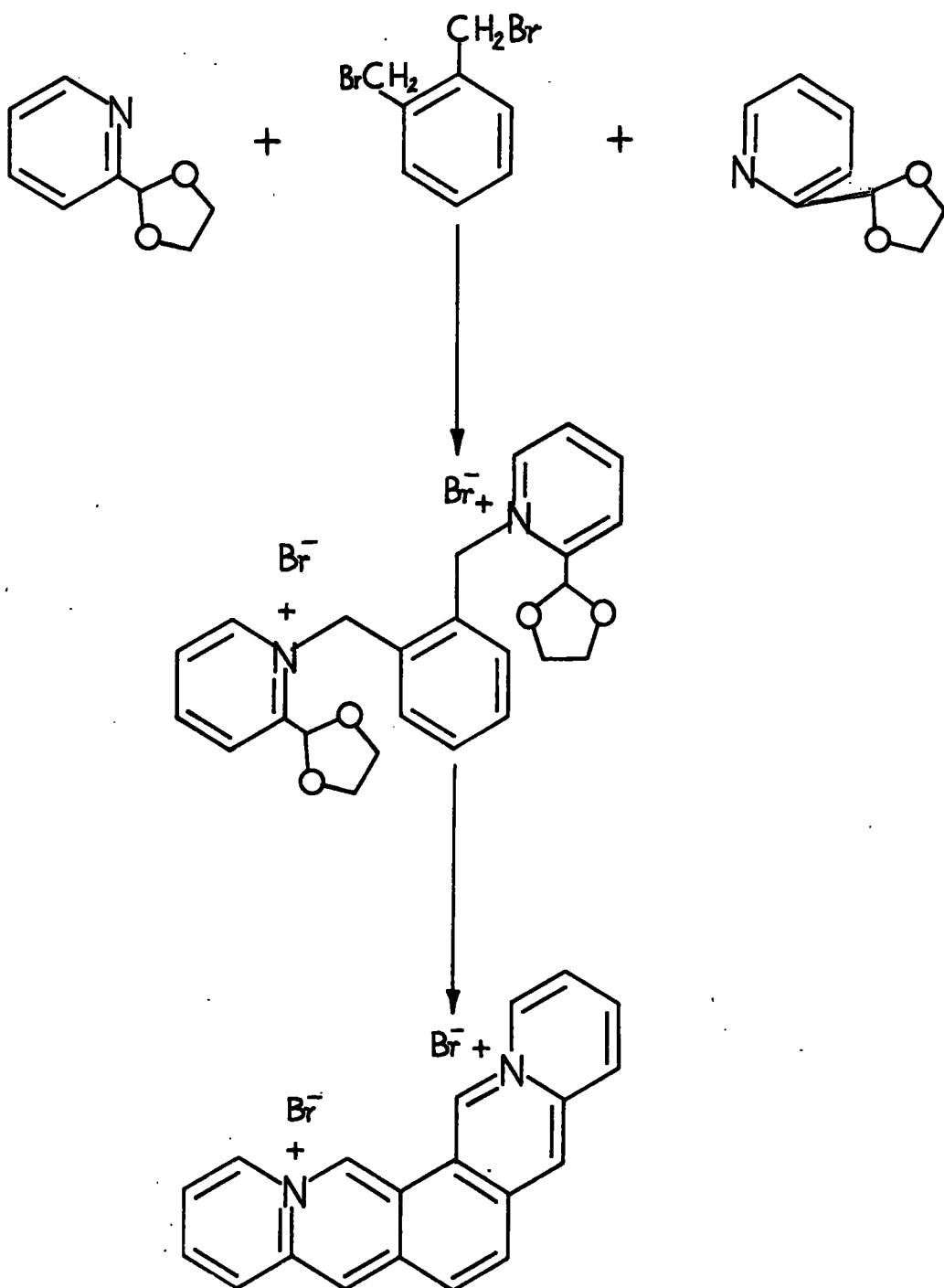


$2X^-$

XXIX

The first fully aromatic compounds to contain two quaternary nitrogen atoms, in bridgehead positions, but in different rings, were the diazoniapentaphene salts. The three isomeric, 12a, 14a- (XXVII), 4a, 12a- (XXVIII), and 4a, 8a- (XXIX) diazoniapentaphene salts have been prepared by Bradsher and Parham⁵⁰. They quaternised 2-(1,3-dioxolan-2-yl) pyridine with the appropriate α, α' -dibromoxylene, and cyclised the intermediate product by heating with polyphosphoric acid.

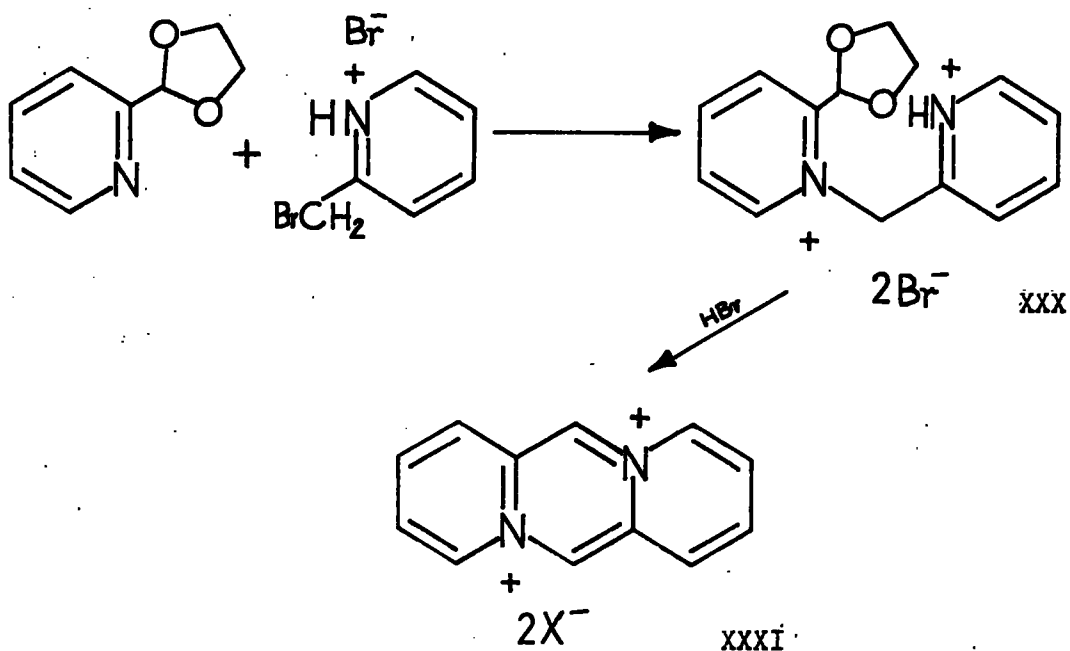
e.g.



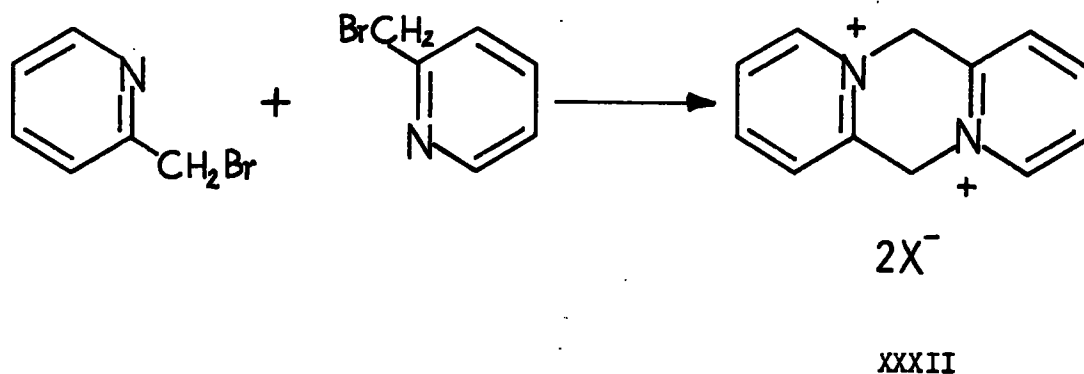
XXVII

DIPYRIDOPYRAZIDIINIUM SALTS

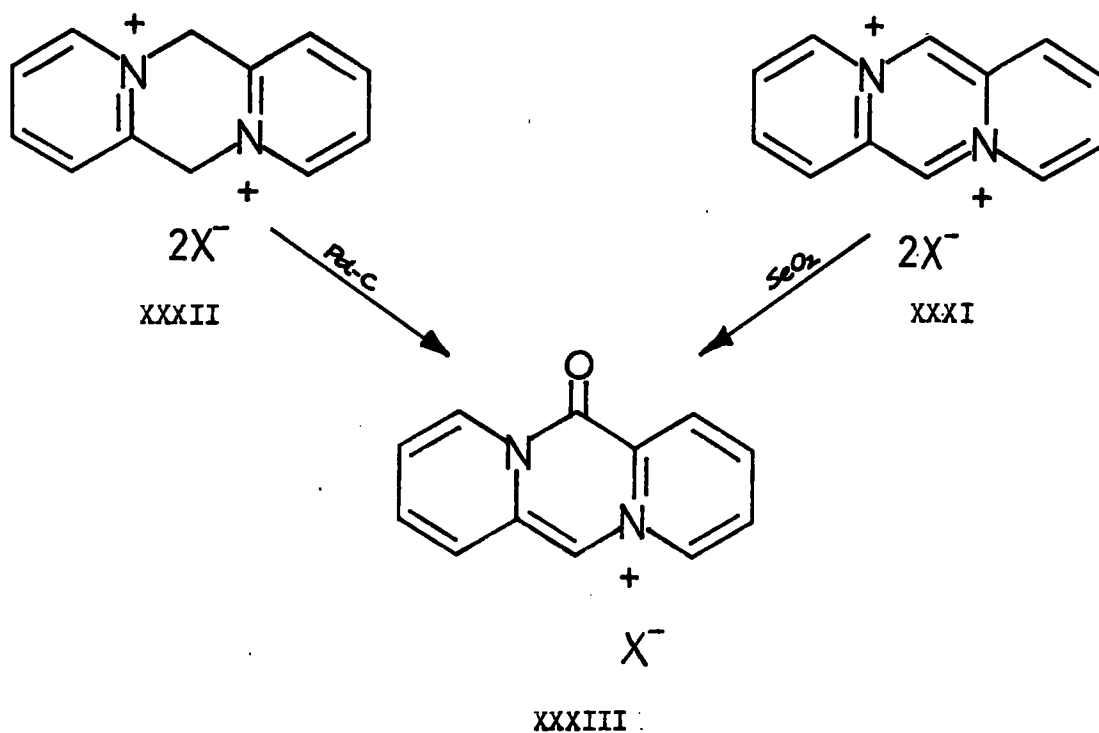
The first fully aromatic compounds to contain two quaternary nitrogen atoms, in bridgehead positions, in the same ring, were the dipyridopyrazidiinium salts. The synthesis of dipyrido [1,2-a: 1',2'-d] pyrazidiinium salts (XXXI) have been reported by Glover and Morris⁵¹. They quaternised 2-(1,3-dioxolan-2-yl) pyridine with 2-pyridylmethyl bromide hydrobromide in tetramethylene sulphone and obtained the salt (XXX) as a red oil. This salt (XXX) was cyclised by boiling with concentrated hydrobromic acid, giving the aromatic diquaternary salt (XXXI).



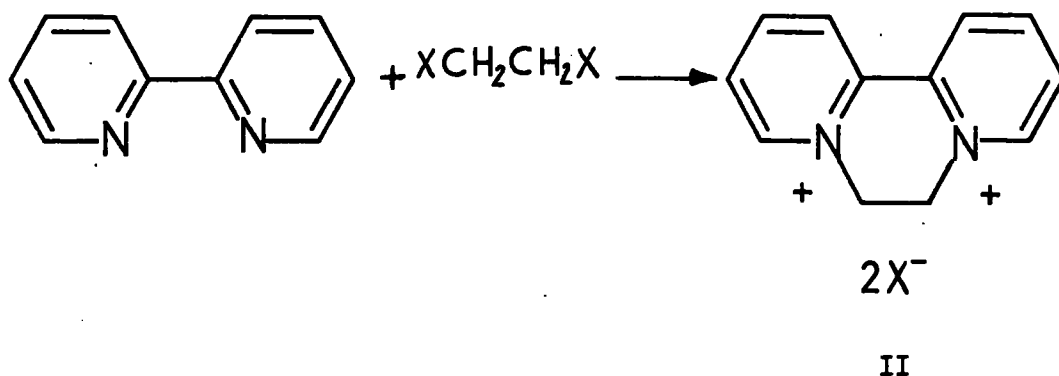
6,12-Dihydrodipyrido [1,2-a: 1',2'-d] pyrazidiinium salts (XXXII) have also been prepared^{52,53,54,55}. These salts have been synthesised by heating 2-pyridylmethyl bromide in benzene as solvent.



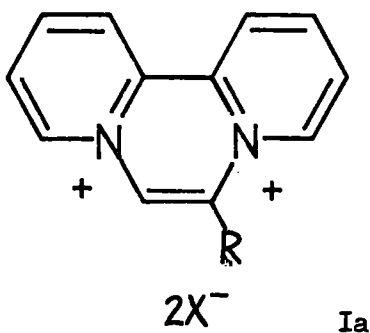
The 12-oxo-12H-dipyrido [1,2-a: 1',2'-d] pyrazin-5-ium salt (XXXIII) has been prepared by the action of palladium-charcoal in nitromethane on the dihydro-diquaternary salt⁵⁵ (XXXII; X = picrate), and by the oxidation of the aromatic diquaternary salt (XXXI; X = Br) with selenium dioxide⁵¹.



The major interest in this type of compound has been shown in the 6,7-dihydrodipyrido [1,2-a: 2',1'-c] pyrazidiinium salts (II) and its derivatives,^{56,57,58,59,60} since these compounds exhibit herbicidal activity. It, and its derivatives, have been prepared by quaternising 2,2'-bipyridyl (or a substituted 2,2'-bipyridyl) with methylene dihalides.



The synthesis of the 6-methyl-, the 6-phenyl-, and the unsubstituted dipyrdo [1,2-a: 2',1'-c] pyrazidiinium salts (Ia; R = Me, Ph or H, X = Br) has been reported^{61,62}; details of which will be given in this thesis. The 6-methyl derivative (Ia; R = Me, X = Br) has been simultaneously reported by Calder and Sasse⁶³.



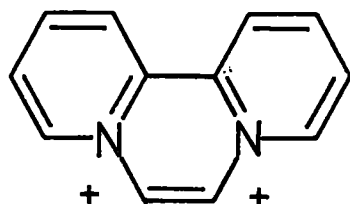
DISCUSSION

DISCUSSION

The preparation of aromatic compounds, containing one and two quaternary nitrogen atoms at bridgehead positions in fused six-membered ring systems, has been outlined in the introduction. As an extension of this sequence, the following work is concerned with the preparation of dipyrido [1,2-a:2',1'-c] pyrazidiinium compounds (I).

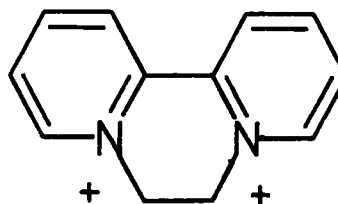
In an investigation of bipyridyl diquaternary salts as herbicidal agents Homer et.al.^{57,58,64} found that 6,7-dihydrodipyrido [1,2-a:2',1'-c] pyrazidiinium (II) salts were active. They formulated certain properties⁶⁴ of the diquaternary salts which must be fulfilled before herbicidal activity could be shown by the compounds. Among these, it was shown that the compound must be easily and reversibly reduced, adding on a single electron, to give a stable water soluble free radical. The stability of the free radical depended upon the delocalisation of the odd electron over the whole molecule, and hence upon the coplanarity of the molecule.

A comparison of the structures of dipyrido (I) and 6,7-dihydrodipyrido [1,2-a:2',1'-c] pyrazidiinium (II) salts leads to the conclusion that in the case of the former, the derived free radical should be more stable since it contains a larger π -electron system, allowing for a greater delocalisation of the odd electron.



$2X^-$

I



$2X^-$

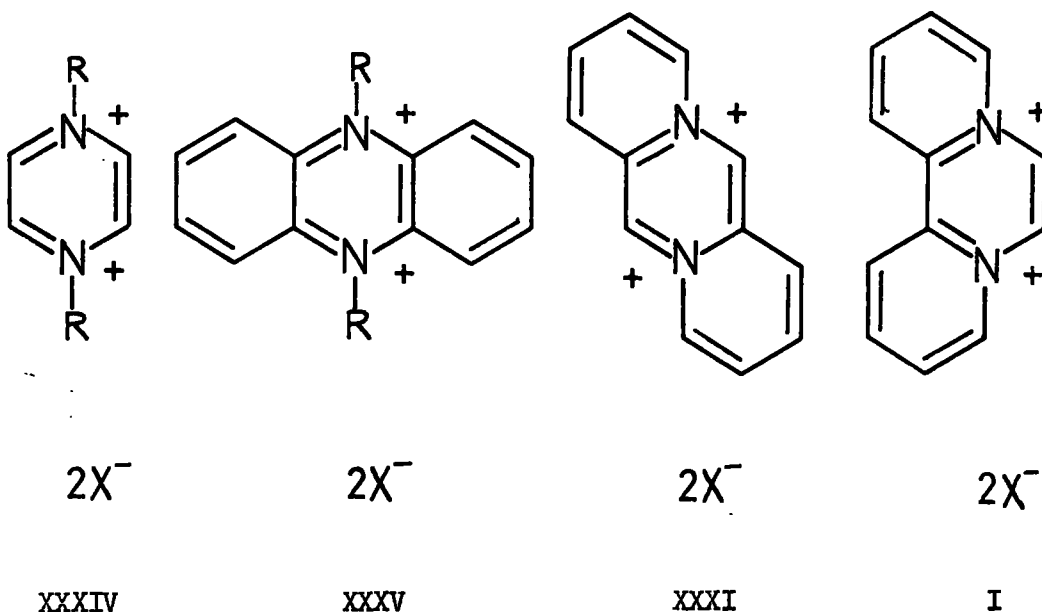
II

Although the herbicidal properties of dipyrido [1,2-a: 2',1'-c] pyrazidiinium salts were not of prime interest, tentative experiments indicate that it is easily reduced in aqueous solution with zinc dust to give a highly coloured solution, probably due to free radical formation. Furthermore, when a leaf of *Epilobium angustifolium* was dipped into an aqueous solution of the salt it was killed within 36 hours.

The utility of these herbicides⁶⁴ is due firstly, to their non-selective action, and secondly, to the fact that on contact with the soil they are immediately adsorped and have no residual herbicidal effect. The adsorption of the highly polar herbicide is found to be due to an ion-exchange mechanism.

The herbicidal activity of dipyrido [1,2-a: 2',1'-c] pyrazidiinium dibromide (I; X=Br) and its 6-substituted derivatives (Ia; X=Br; R=Me or Ph) is being further investigated.⁶⁵

The dipyrido [1,2-a: 2',1'-c] pyrazidiinium salts form part of the series: pyrazidiinium (XXXIV)⁶⁶, phenazidiinium (XXXV)⁶⁷, dipyridopyrazidiinium (XXXI and I)⁵¹ salts.



The weakness of pyrazine as a diacidic base is well known and only recently have diquatery salts been recorded.⁶⁶ Phenazine is, however, a stronger base than pyrazine⁶⁸ and diquatery salts of phenazine have long been known.⁶⁷ The greater basic strength of phenazine compared with pyrazine is probably due to stabilisation of the cation and dication by increased charge distribution over the more extended π -electron system. It seemed likely, therefore, that the title compounds (I) in which both the nitrogen atoms of the

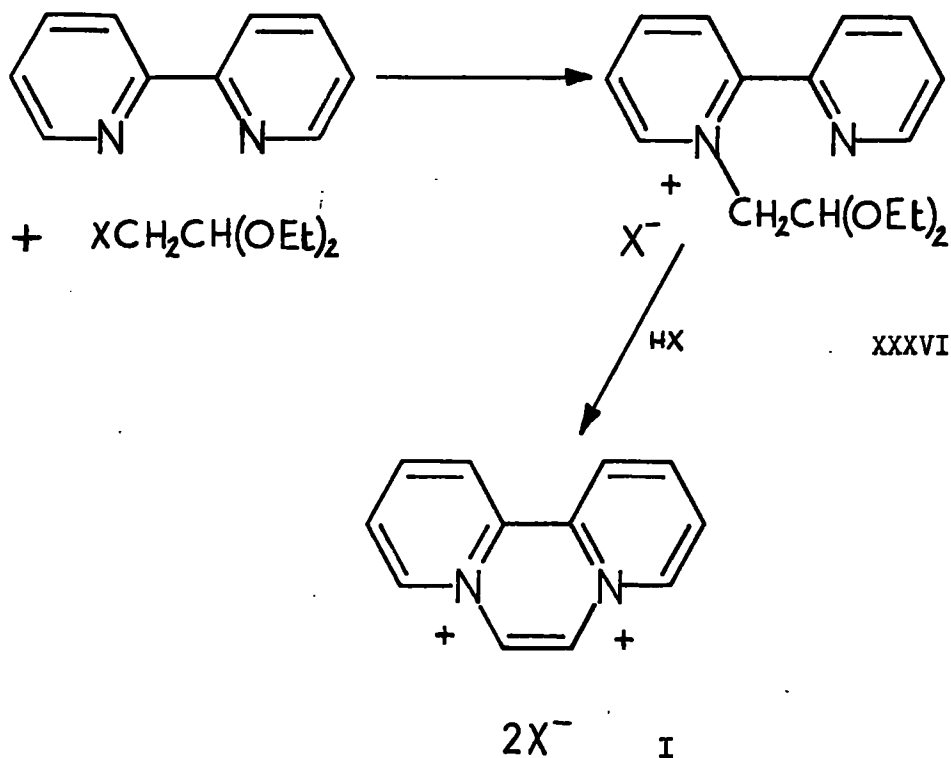
central pyrazine ring are quaternary, would be stable and of interest as new aromatic systems.

The following description outlines the preparation of dipyrido [1,2-a: 2',1'-c] pyrazidiinium dibromide (I; X=Br) and its 6-methyl- and 6-phenyl - derivatives (Ia; X=Br; R=Me or Ph).

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

The first attempt to prepare the title compound (I) involved the dehydrogenation of 6,7-dihydrodipyrido [1,2-a:2',1'-c] pyrazidiinium dipicrate (II; X=picrate). This was boiled under reflux for several hours with palladium-charcoal in nitromethane as solvent. However, after filtration of the palladium-charcoal, and evaporation of the solvent the starting material was recovered unchanged.

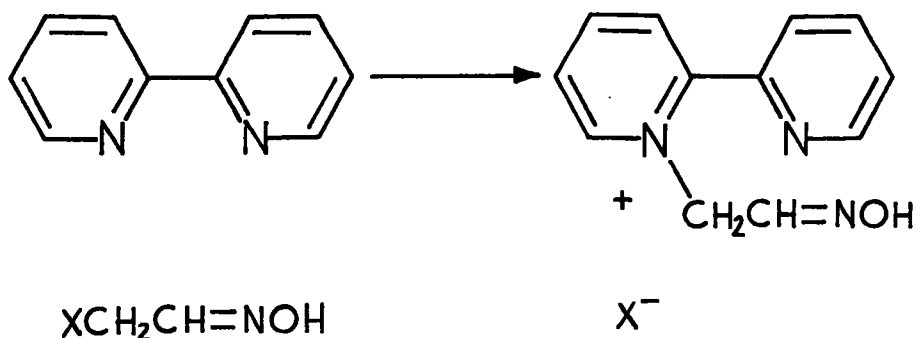
Another likely route to the dipyrido [1,2-a:2',1'-c] pyrazidiinium salt (I) seemed to be via the acid catalysed cyclisation of the monoquaternary salt (XXXVI), formed between diethyl α -haloacetaldehyde acetal and 2,2'-bypyridyl.



However, neither diethyl α -chloroacetaldehyde acetal nor the corresponding bromo compound, would quaternise with 2,2'-bipyridyl, even after heating them together for several hours.

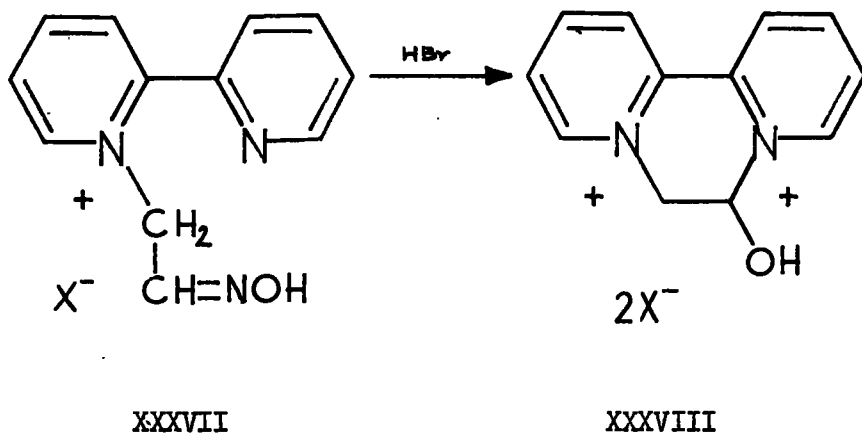
To overcome the difficulty of quaternisation, other derivatives of α -haloacetaldehyde were tried. One of them: α -chloroacetaldehyde-2,4-dinitrophenylhydrazone was a solid, which was too insoluble in most solvents to be of use. There was some reaction between 2,2'-bipyridyl and a dilute solution of the hydrazone in boiling methanol, but the amount of product was negligible.

Successful quaternisation was achieved by heating α -bromoacetaldehyde oxime (or the corresponding chloro compound) with 2,2'-bipyridyl for about two minutes on a water-bath. The resulting product was a gum, assumed to be the monoquaternary salt (XXXVII).



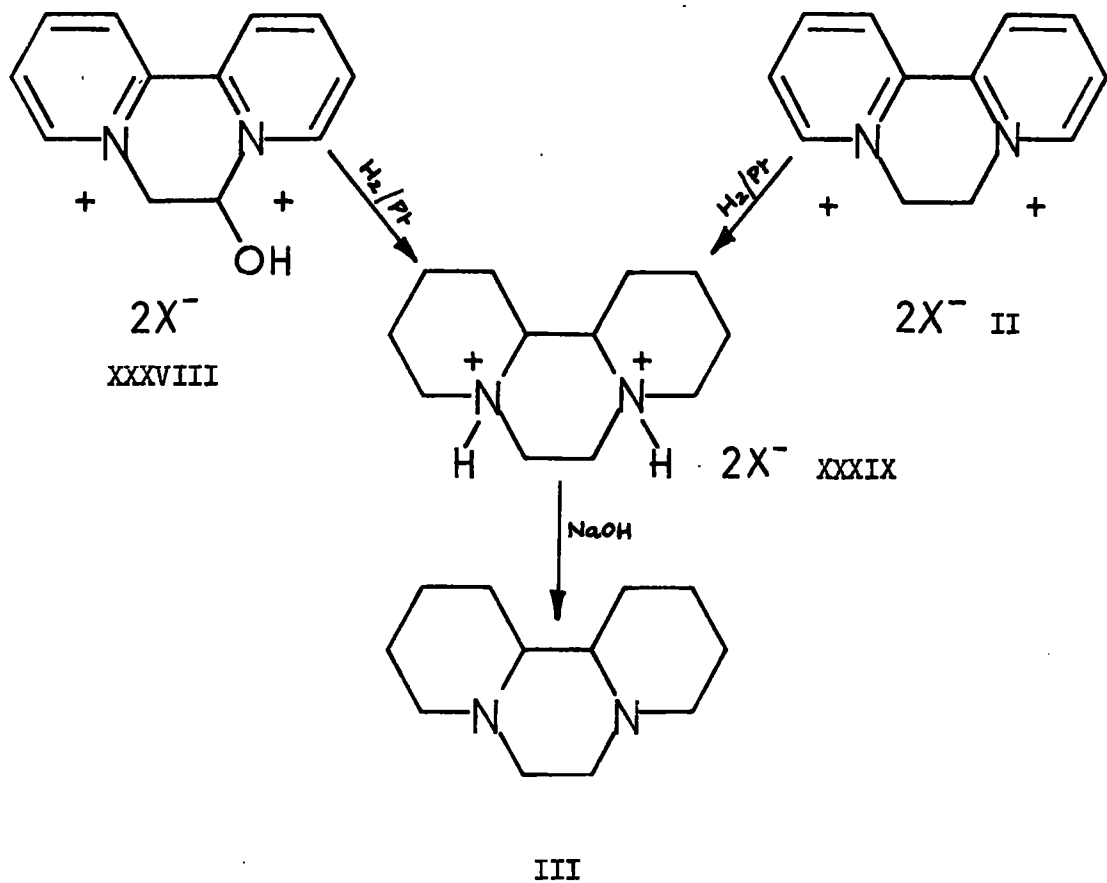
XXXVII

This monoquaternary salt (XXXVII) was cyclised in good overall yield, by boiling under reflux with concentrated hydrobromic acid, to give the hydroxy dibromide⁶³(XXXVIII; X=Br). The hydroxy dibromide analysed as a monohydrate and its derived dipicrate (XXXVIII; X=picrate) was anhydrous.



The cyclisation product (XXXVIII; X=Br) was at first considered⁶¹ to be the dihydrate of dipyrido [1,2-a:2',1'-c] pyrazidiinium dibromide (I; X=Br), and its dipicrate derivative (XXXVIII; X=picrate) to be the monohydrate of dipyrido [1,2-a: 2',1'-c] pyrazidiinium dipicrate (I; X=picrate). This conclusion was based mainly upon the smooth hydrogenation of the cyclisation product to the dihydrobromide (XXXIX; X=Br) of the perhydro-base (III). Since, at that time it was not realised that hydrogenolysis of the hydroxyl group of the hydroxy dibromide (XXXVIII; X=Br) had occurred. The perhydro-base (III) and its derived dipicrate were identical with those obtained by the hydrogenation of the 6,7-dihydro-dibromide

(II; X=Br)^{61,57}



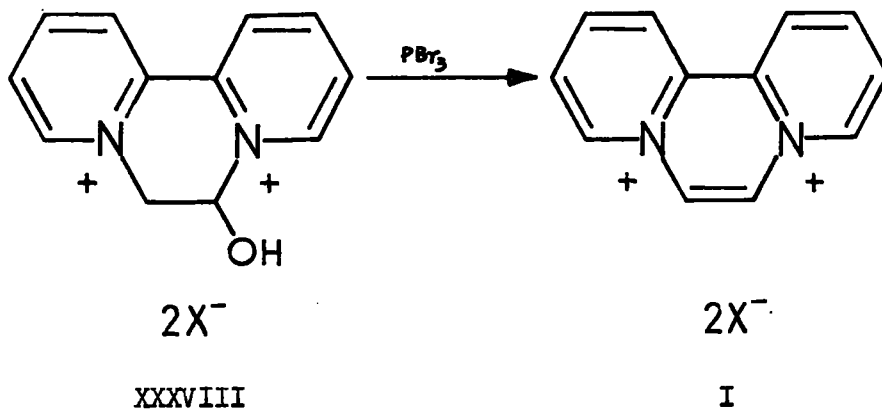
Furthermore, the hydroxy dibromide (XXXVIII; X=Br) and the 6,7-dihydro dibromide (II; X=Br) gave the same octahydrodipyrido [1,2-a:2',1'-c] pyrazine base on reduction with sodium borohydride reagent (see p. 54).

These salts have now been shown⁶¹ to be the dibromide monohydrate and the dipicrate of the hydroxy compound (XXXVIII). The structure of this hydroxy dibromide (XXXVIII; X=Br) was confirmed by its n.m.r. spectrum in D₂O which showed a triplet centred at τ 3.0 corresponding

to the proton on the hydroxylated carbon atom, a doublet centred at τ 4.5 corresponding to the methylenic protons, together with a collection of eight protons in the region τ 0.4 - 1.8.

The ultraviolet spectrum of the hydroxy dibromide (XXXVIII; X=Br) has been determined in hydrochloric acid (A), in water immediately after preparation of the solution (B), and again in water after the solution had been standing for three hours (C). The variation in results is illustrated in (Figure 1).⁶¹ (See p. 59).

The hydroxy dibromide (XXXVIII; X=Br) was dehydrated by boiling under reflux with phosphorus tribromide to give dipyrido [1,2-a:2',1'-c] pyrazidiinium dibromide (I; X=Br).



The structure of the aromatic dication was confirmed by its n.m.r. spectrum in trifluoroacetic acid which showed only a collection of ten protons in the region τ 0.4 - 1.8. Chemical evidence for the structure of the aromatic dication (I) was obtained by catalytic hydrogenation in methanol. This yielded the dihydrobromide

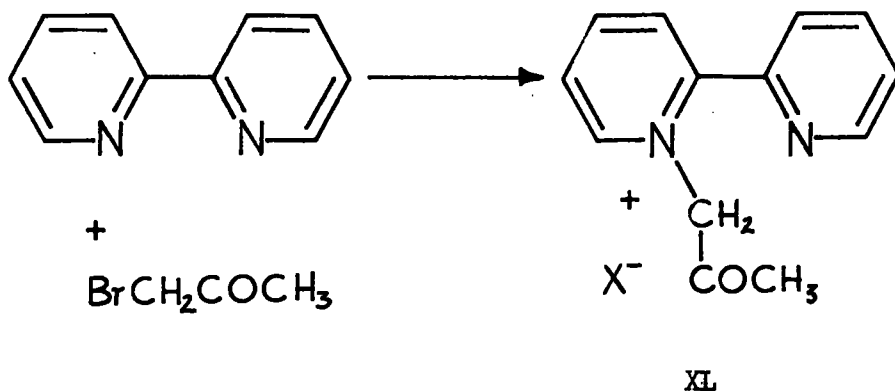
(XXXIX; X=Br) of the perhydro-base (III) characterised as its
dipicrate.⁶¹

Immediately after preparation, the aromatic compound (I; X=Br) consisted of bright yellow crystals, which on exposure to the atmosphere quickly faded in colour, due to the absorption of moisture. With alkali the aromatic compound gave a deep red solution, and with zinc dust in aqueous solution was readily reduced giving the same deep red colour. In the latter case the colour is probably due to free radical formation.⁶⁴

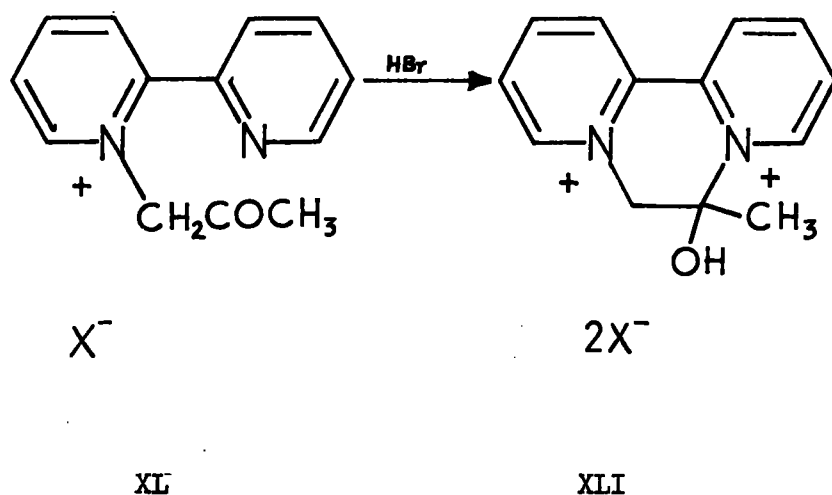
6-METHYLDIPYRIDO [1,2-a:2',1'-c] PYRAZIDIINIUM SALTS

The method chosen to synthesis the 6-methyldipyrido [1,2-a:2',1'-c] pyrazidiinium salts (Ia; X=Br; R=Me) was similar to that outlined in the previous section for the preparation of the unsubstituted compound (I).

Quaternisation of 2,2'-bipyridyl with bromoacetone gave a brown solid in high yield, which was assumed to be the acetonyl quaternary salt (XL; X=Br), and characterised as its picrate (XL; X=picrate).

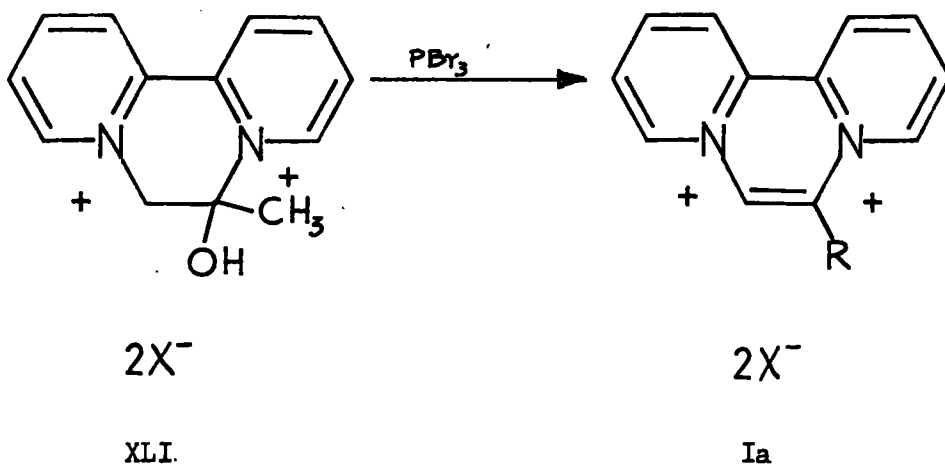


Cyclisation of the acetonyl quaternary salt (XL) was achieved by boiling under reflux with concentrated hydrobromic acid. On cooling, the methyl hydroxy dibromide⁶³ (XLI; X=Br) was precipitated from solution, in good yield, with acetone.

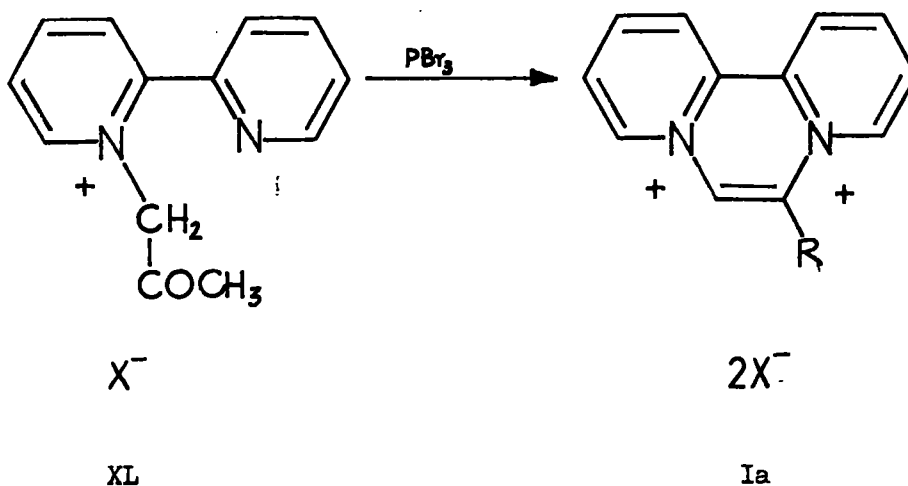


The n.m.r. spectrum of the methyl hydroxy dibromide (XLI; X=Br) in D_2O showed singlets at $\tau 7.95$ and $\tau 4.45$ corresponding to the methyl and methylenic protons respectively, together with a collection of eight protons in the region $\tau 0.3 - 1.7$. Catalytic hydrogenation of this salt (XLI; X=Br) over Adam's catalyst gave, after basification, 6-methyl-perhydrodipyrido [1,2-a:2',1'-c] pyrazine (XLII), showing that hydrogenolysis of the hydroxyl group had occurred.

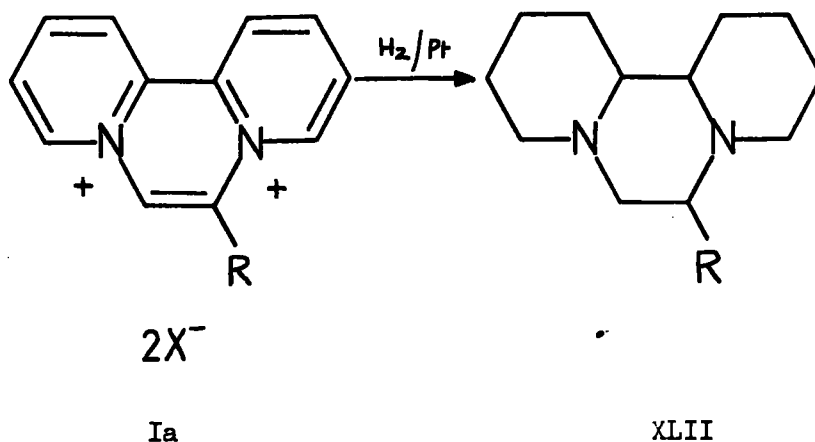
The methyl hydroxy dibromide (XLI; X=Br) was dehydrated by boiling in phosphorus tribromide, yielding the 6-methyl aromatic dibromide⁶³ (Ia; R=Me; X=Br).



A more convenient route to the 6-methyl aromatic compound (Ia; R=Me) was by the cyclisation of the acetylpyridinium salt (XL; X=Br) in boiling phosphorus tribromide. This procedure gave a higher overall yield, eliminated one stage, and required a shorter reflux time with phosphorus tribromide.



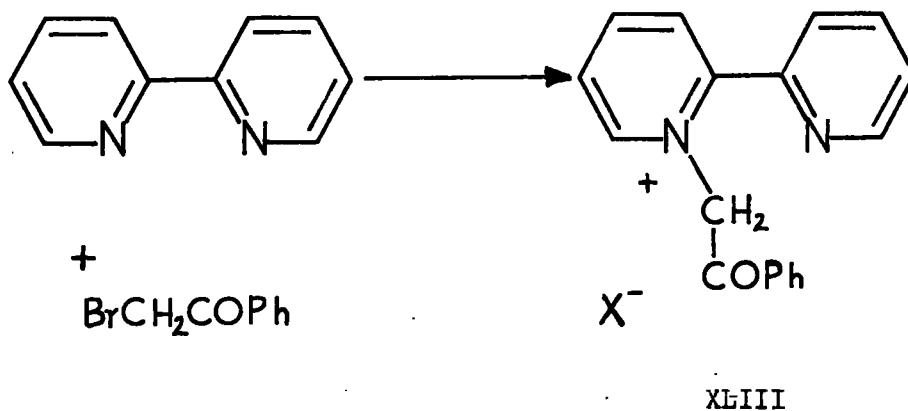
The structure of the 6-methyl aromatic dication (Ia; R=Me) was confirmed by its n.m.r. spectrum in D_2O which showed a 3 proton singlet at $\tau 6.8$ corresponding to the methyl protons, and a collection of nine protons in the region $\tau 0 - 1.4$. Chemical evidence was obtained by hydrogenation of the 6-methyl aromatic dibromide (Ia; R=Me; X=Br) over Adam's catalyst, yielding, after basification, 6-methyl-perhydrodipyrido [1,2-a:2',1'-c] pyrazine⁶³ (XLII; R=Me)



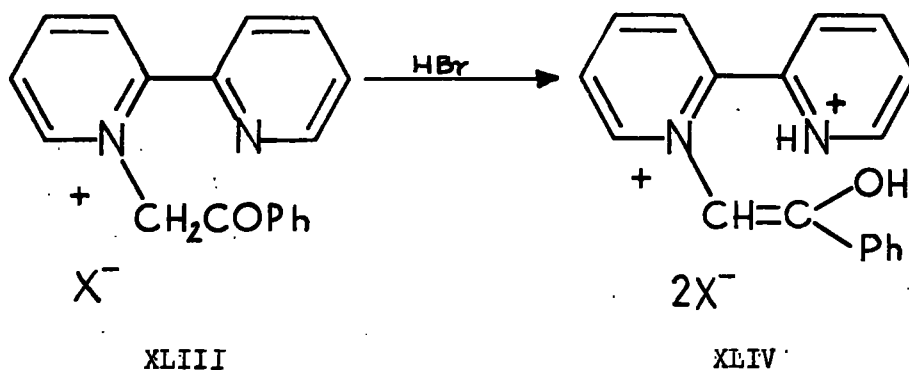
6-PHENYLDIPYRIDO [1,2-a:2',1'-c] PYRAZIDIINIUM SALTS

The method of synthesis of 6-phenyldipyrido [1,2-a:2',1'-c] pyrazidiinium salts (Ia; R=Ph) followed the same pattern as described for the 6-methyl compound, except that no equivalent hydroxy compound was formed.

The monoquaternary salt N-phenacyl-2-(2'-pyridyl)pyridinium bromide (XLIII; X=Br) was prepared in good yield from 2,2'-bipyridyl and phenacyl bromide.

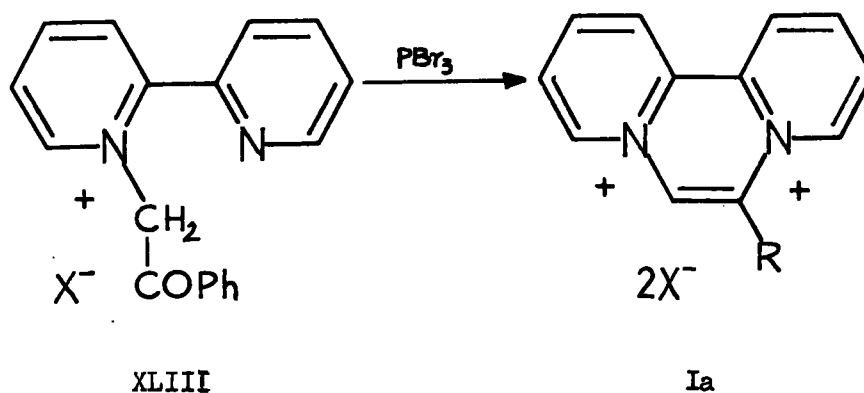


Attempted cyclisation of the phenacyl quaternary salt (XLIII; X=Br) with concentrated hydrobromic acid gave the enolic compound (XLIV; X=Br).



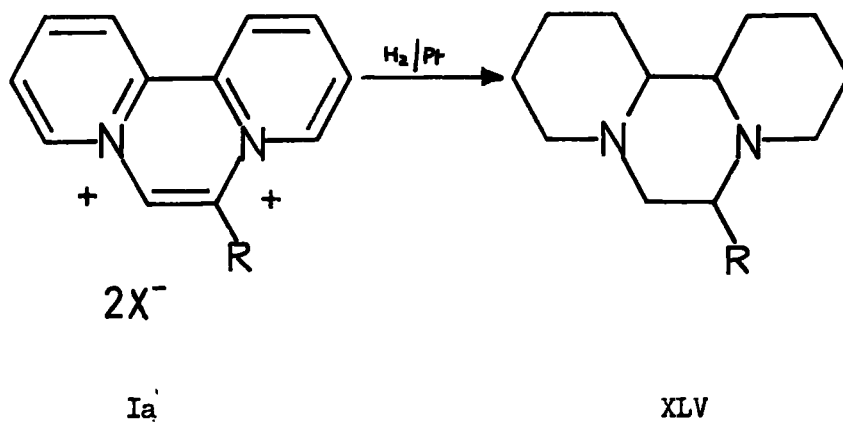
The infrared spectrum of this compound (XLIV) showed no absorption between 1620 cm^{-1} and a broad band in the region $2600 - 3100\text{ cm}^{-1}$. The n.m.r. spectrum of (XLIV) in D_2O showed only a single proton peak at $\tau 3.75$ which slowly disappeared over a period of $1\frac{1}{2}$ hours, together with a collection of thirteen protons in the region $\tau 0.8 - 2.8$. Treatment of the enolic compound (XLIV) with picric acid gave the monoquaternary picrate (XLIII; X=picrate) confirming that cyclisation of the phenacyl quaternary salt (XLIII) had not occurred on treatment with hydrobromic acid.

Cyclisation of the phenacyl quaternary salt (XLIII; X=Br) was achieved by boiling with phosphorus tribromide, giving the 6-phenyl aromatic dibromide (Ia; R=Ph; X=Br) in good yield.



The n.m.r. spectrum of this salt (Ia; R=Ph; X=Br) in trifluoroacetic acid showed a singlet at $\tau 2.6$ corresponding to the phenyl protons and a collection of nine protons in the region $\tau 0 - 1.4$. Hydrogenation of the 6-phenyl aromatic diquaternary salt (Ia; R=Ph; X=Br) and subsequent basification gave the 6-phenyl-perhydrodipyrido

[1,2-a:2',1'-c] pyrazine (XLV).

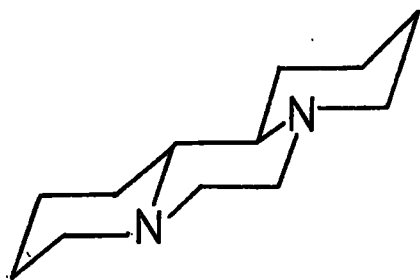


The infrared spectra of all three aromatic diquaternary salts showed a new band at 1680 cm^{-1} .

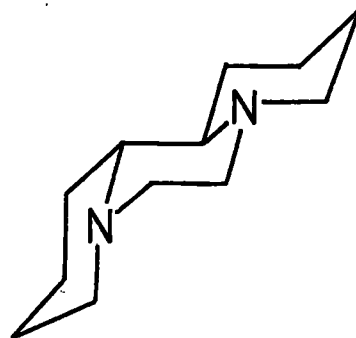
The chemistry of all three aromatic diquaternary salts is to be further studied.

PERHYDRODIPYRIDO [1,2-a:2',1'-c] PYRAZINE.

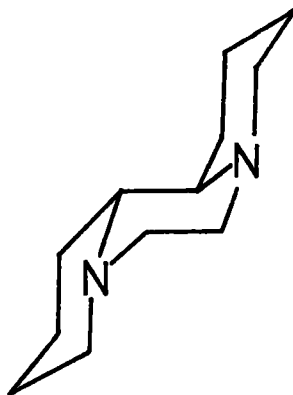
A study of the conformation of the perhydrodipyrido [1,2-a:2',1'-c] pyrazine ring system indicated that stereoisomerism, depending upon the mode of ring fusion, was possible. Also, by analogy with the perhydrophenanthrenes,⁶⁹ the three most stable isomers were expected to be, trans - trans (IIIa), cis - trans (IIIb), and cis - cis (IIIc) respectively; each ring being in the chair form.



IIIa



IIIb



IIIc

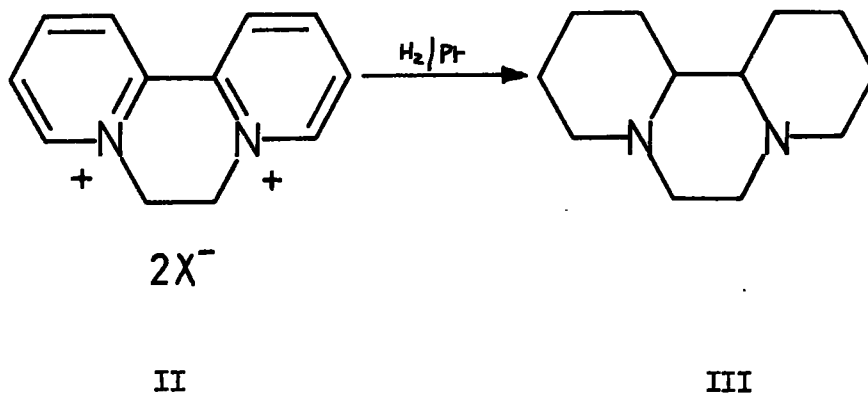
As a guide to the recognition of such isomers Bohlmann⁷⁰ has shown that trans - quinolizidines with at least two axial hydrogen atoms adjacent to the nitrogen, show a prominent band in the infrared at 2800 - 2700 cm^{-1} . Thus, those isomeric bases showing a Bohlmann band in the infrared are considered to have at least one trans ring fusion.

The corresponding perhydrodipyrido [1,2-a:1',2'-d] pyrazines have been studied⁷¹ and the three most stable isomers, trans - trans, cis - trans and cis - cis respectively, have been isolated. The trans-trans perhydrodipyrido [1,2-a:1',2'-d] pyrazine isomer was isolated by two methods. The first, involved the catalytic hydrogenation of 6,12-dihydrodipyrido [1,2-a:1',2'-d] pyrazidinium dibromide (XXXII; X=Br), and the second, the lithium aluminium hydride reduction of the lactam; trans - trans perhydro-6-oxodipyrido [1,2-a:1',2'-d] pyrazine. The cis - trans perhydrodipyrido [1,2-a:1',2'-d] pyrazine isomer was prepared similarly by reducing cis - trans perhydro-6-oxodipyrido [1,2-a:1',2'-d] pyrazine with lithium aluminium hydride. Finally, the cis - cis perhydrodipyrido [1,2-a:1',2'-d] pyrazine isomer was obtained via the isomerisation of the cis - trans perhydro-base on an alumina packed chromatography column.

It was considered that a likely route to the preparation of isomeric perhydrodipyrido [1,2-a:2',1'-c] pyrazine bases would be to follow a similar procedure to that outlined above.

The first step involved the catalytic hydrogenation of 6,7 - dihydrodipyrido [1,2-a:2',1'-c] pyrazidinium dibromide (II; X=Br) in

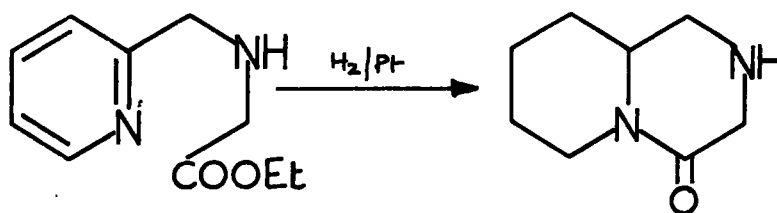
methanol. The dibromide having been prepared by heating together 2,2'-bipyridyl and dibromoethane in a sealed tube.



The base isolated in this manner was a liquid, which showed a Bohlmann band in the infrared; it gave a single dipicrate and dimethiodide, and was thus considered to be the trans - trans isomer.

The next step was an attempt to prepare and separate the isomeric lactams (IV) i.e. the perhydro-6-oxodipyrido [1,2-a:2',1'-c] pyrazines.

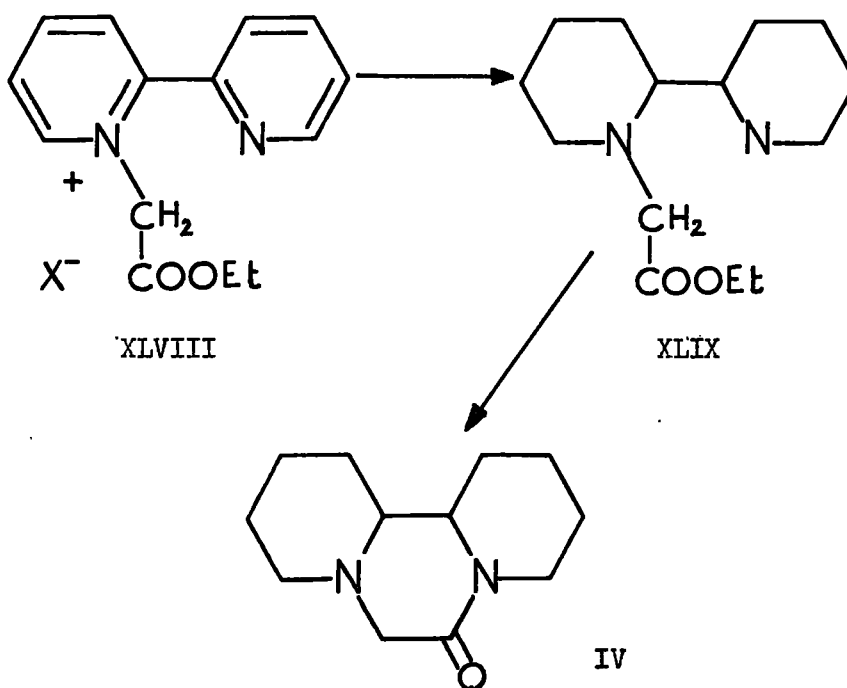
Use was made of the general method of preparing lactams, as exemplified by the preparation⁷² of perhydro-4-oxopyrido [1,2-a] pyrazine (XLVII) via the catalytic hydrogenation of ethyl N-(2-pyridylmethyl) glycinate (XLVI).



XLVI

XLVII

Thus, N-(carbethoxymethyl)-2-(2'pyridyl) pyridinium bromide (XLVIII; X=Br), prepared by heating 2,2'-bipyridyl with ethyl bromoacetate, was catalytically hydrogenated in glacial acetic acid as solvent.

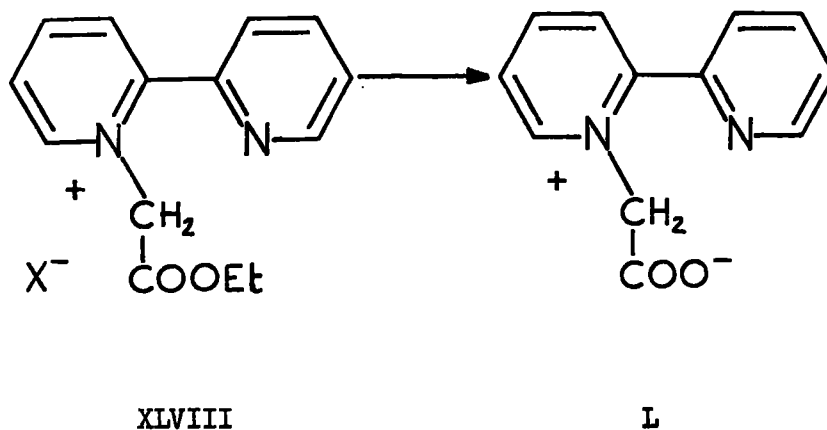


XLVIII

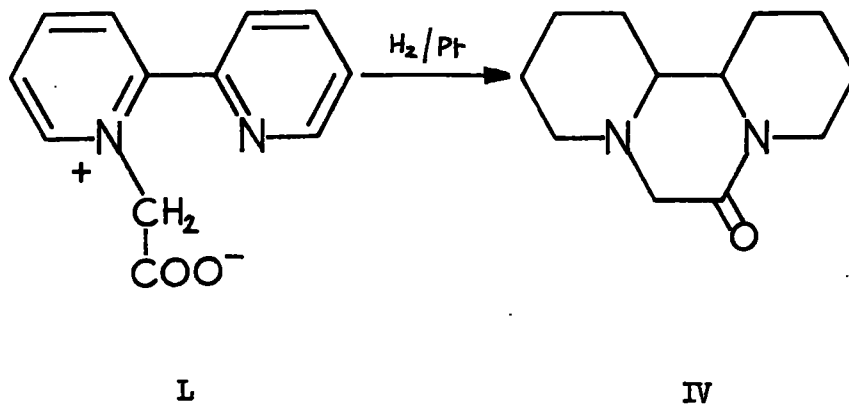
XLIX

IV

However, at this stage, the N-(carbethoxymethyl)-2-(2'-pyridyl) pyridinium bromide (XLVIII; X=Br) could only be prepared as a gum, purification being difficult, consequently the product appeared to be a mixture of the saturated ester (XLIX) and the lactam (IV). This conclusion was supported by its infrared spectrum which showed both an ester carbonyl absorption peak and a lactam carbonyl peak. Later, the quality of the N-(carbethoxymethyl)-2-(2'-pyridyl) pyridinium bromide was improved by allowing 2,2'-bipyridyl and ethyl bromoacetate to stand together at room temperature for several days. By this time, it was found that a better method of obtaining the lactam (IV) was from the betaine (L). This could be prepared in good yield and quality by passing an aqueous solution of the impure monoquaternary bromide (XLVIII; X=Br) down an anion-exchange column and evaporating the eluate to dryness.

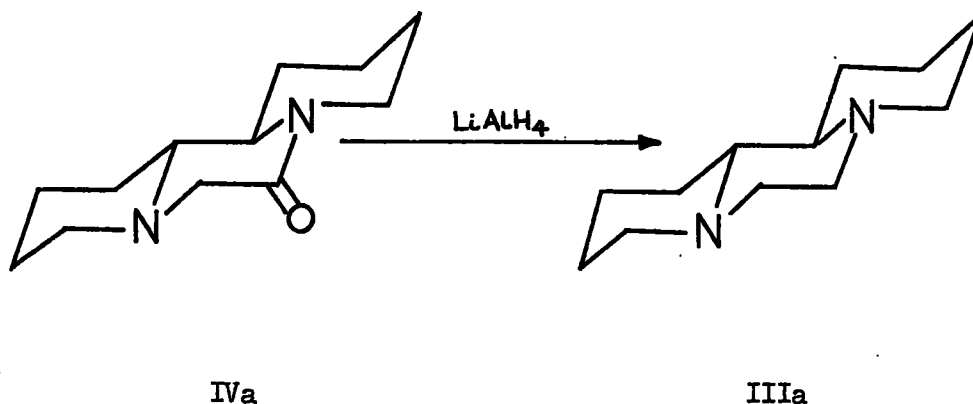


The betaine (L) was hydrogenated over Adam's catalyst in glacial acetic acid as solvent, giving after basification, the lactam (IV). The infrared spectrum of the lactam showed an absorption peak in the 1650 cm^{-1} region characteristic of six-membered lactams.⁷³



The lactam prepared in this way was a solid melting at $25 - 30^{\circ}\text{C}$. which on repeated sublimation gave a solid melting finally at $52 - 54^{\circ}\text{C}$., indicating that the initial sample was a mixture of isomers. Furthermore, the lactam, immediately after preparation, gave two picrates upon treatment with alcoholic picric acid. The picrates differed in solubility in ethanol and melted at $168 - 69^{\circ}\text{C}$. and $215 - 219^{\circ}\text{C}$. respectively. Analytical figures for both the picrates were consistent with the formula $\text{C}_{18}\text{H}_{13}\text{N}_5\text{O}_8$ corresponding with the dipicrate of the lactam (IV). Preliminary attempts to separate the mixture of isomeric lactams by passing them, in ether, down an alumina packed chromatography column have, so far, been unsuccessful.

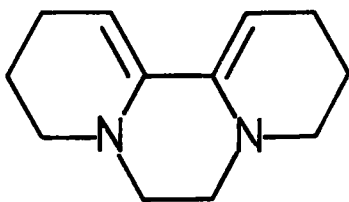
The higher melting lactam was reduced with lithium aluminium hydride to give the trans - trans perhydrodipyrdo [1,2-a:2',1'-c] pyrazine base (IIIa) identical with that obtained by the catalytic hydrogenation of 6,7-dihydrodipyrdo [1,2-a:2',1'-c] pyrazidiinium dibromide (II; X=Br). This suggests that the lactam m.p. 52 - 54° is the trans - trans isomer (IVa).



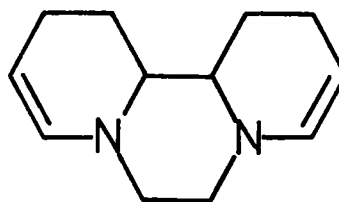
This work remains to be completed, but it is obvious that a better method of separation of the isomeric lactams and bases is necessary. By analogy with the work on perhydrodipyrdo [1,2-a:1',2'-d] pyrazine it seems likely that separation might be effected using gas-liquid chromatography.

SODIUM BOROHYDRIDE REDUCTION

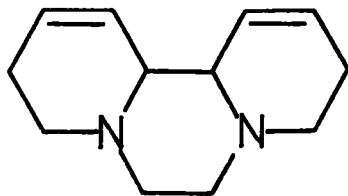
An initial programme to study the effect of chemical reagents on some of the compounds prepared in this work was begun. The first reagent to be considered was sodium borohydride, and the first two compounds to be reduced were the 6-hydroxy-(XXXVIII; X=Br) and 6,7-dihydrodipyrido [1,2-a:2',1'-c] pyrazidiinium (II; X=Br) dibromides.



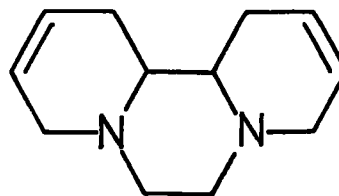
LI



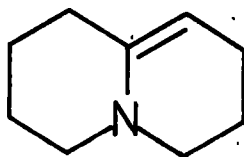
LII



LIII

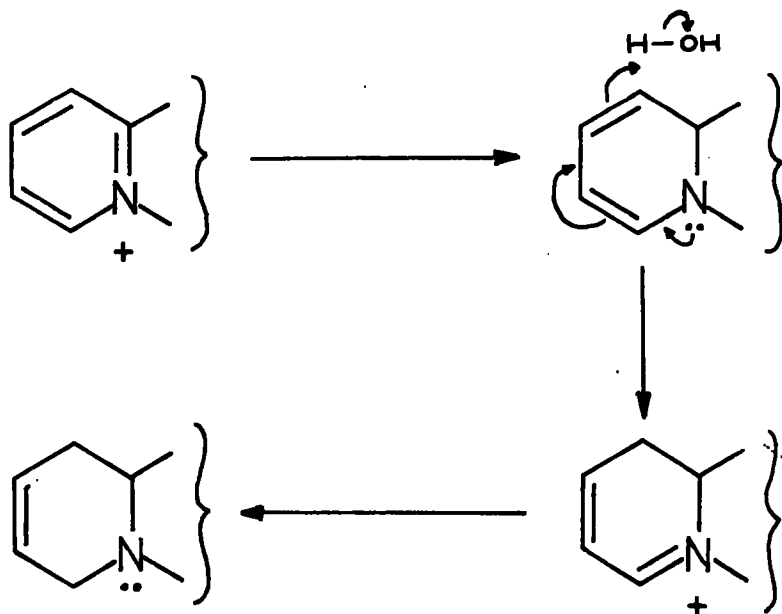


LIV

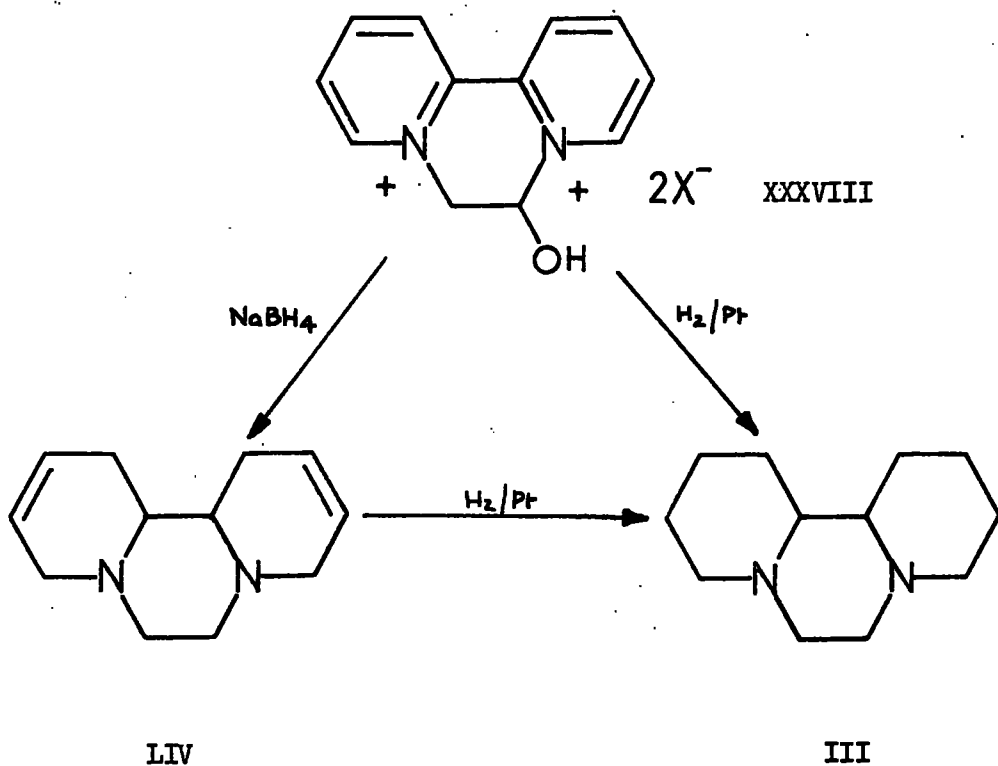


LV

The reduction of the dihydro compound (II) using sodium borohydride gave an octahydrodipyrido [1,2-a:2',1'-c] pyrazine; the four most likely structures of the base being (LI), (LII), (LIII) and (LIV). The ultraviolet absorption spectrum of the base showed no appreciable absorption above 220 $m\mu$, whereas the ultraviolet spectra of cyclic enamines show a band of medium intensity between 220 - 240 $m\mu$ ⁷⁴. The enamine $\Delta^{1(10)}$ dehydroquinolizidine (LV), a suitable model, has an ultraviolet absorption maximum at 228 $m\mu$ ⁷⁵, so precluding (LI) and (LII) as possible structures for the basic product of the borohydride reduction. Of the structures (LIII) and (LIV) the latter is considered to be the more likely since its formation is consistent with the mechanism proposed by Mirza⁷⁶ for the reduction of cyclic quaternary ammonium salts by sodium borohydride, and by Miyadera and Kishida⁷⁷ for the sodium borohydride reduction of quinolizinium salts.



The 6-hydroxy compound (XXXVIII; X=Cl) on borohydride reduction gave the same octahydro base (LIV). This rapidly darkened on standing and was characterised as its dimethiodide and dipicrate. On catalytic hydrogenation in methanol, the octahydro base (LIV) gave the perhydro base (III) identical with that obtained from the 6,7-dihydro-compound (II).



The reduction of the 6-hydroxy compound (XXXVIII) to the octahydro base (LIV) can be compared with its catalytic hydrogenation to give the perhydro-base (III); hydrogenolysis of the hydroxyl group occurring in both cases.

This work remains to be completed, and the action of sodium borohydride on dipyrido [1,2-a:2',1'-c] pyrazidiinium dibromide (I; X=Br) has yet to be tried. However consideration of the above mechanism^{76,77} suggests that the same octahydro base (LIV) would be obtained.

ILLUSTRATIONS

FIGURE 1

Ultraviolet spectrum of:-

6-hydroxy 6,7-dihydrodipyrido [1,2-a:2',1'-c] pyrazidiinium

dibromide, determined in hydrochloric acid (A), in water immediately after preparation of the solution (B), and again in water after the solution had been standing for three hours (C).

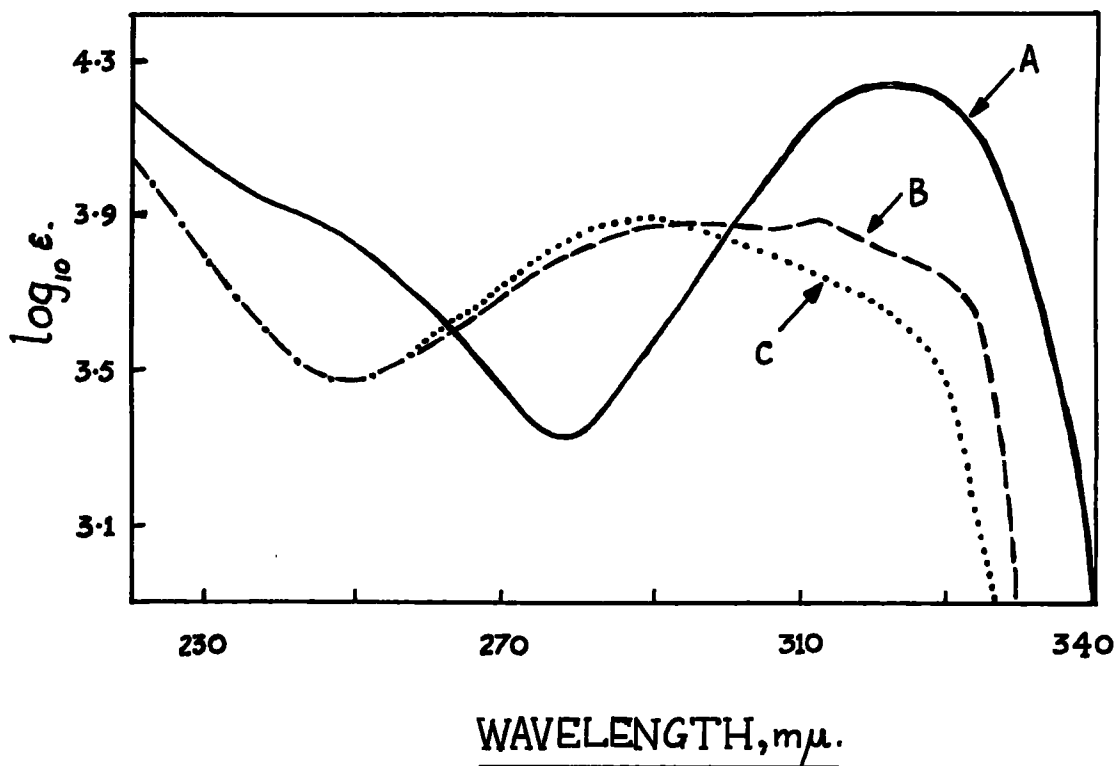


FIGURE 2

Ultraviolet spectrum of:-

6,7-dihydrodipyrdo [1,2-a:2',1'-c] pyrazidiinium dibromide.

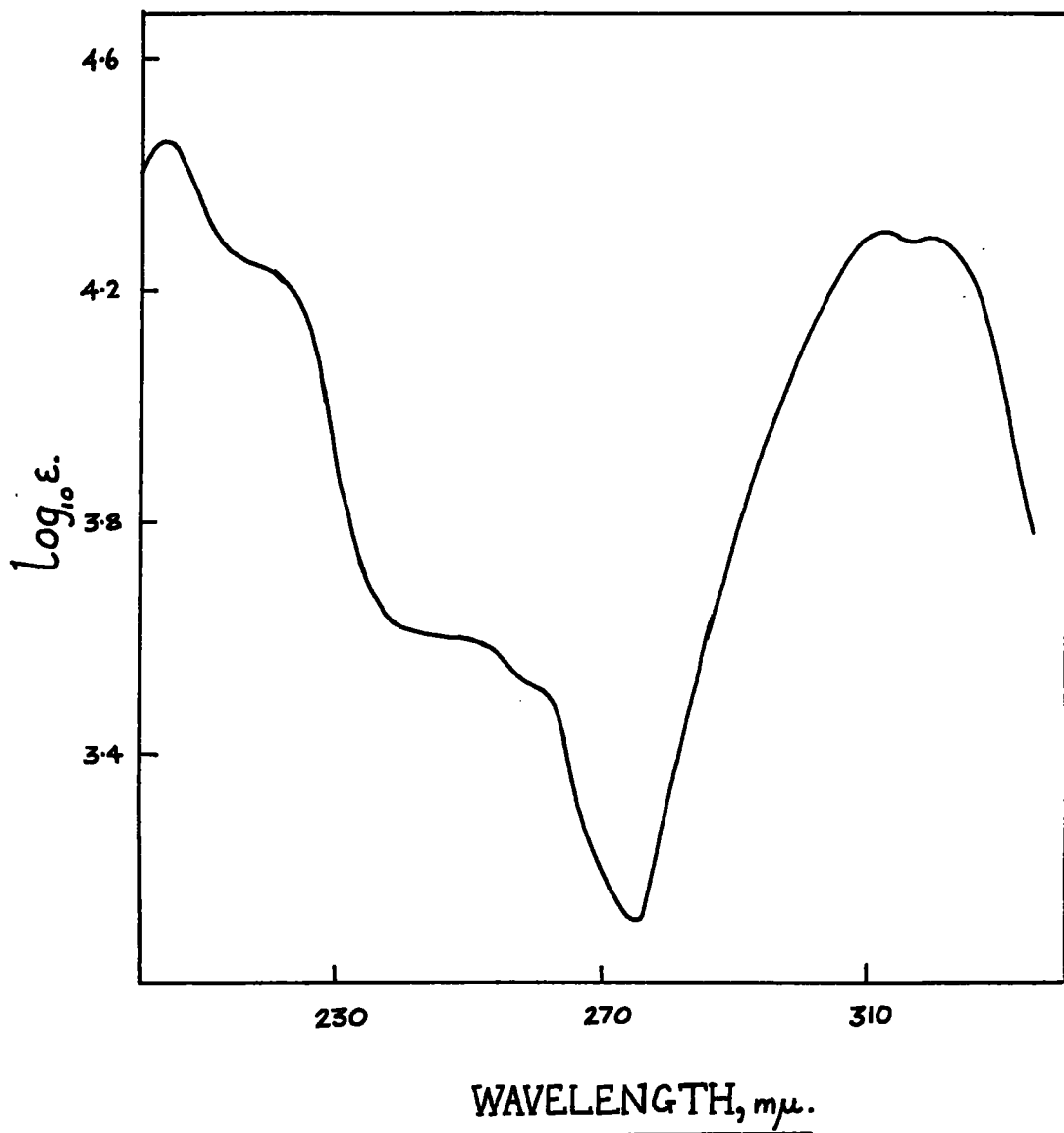


FIGURE 3

Ultraviolet spectrum of:- phenanthrene

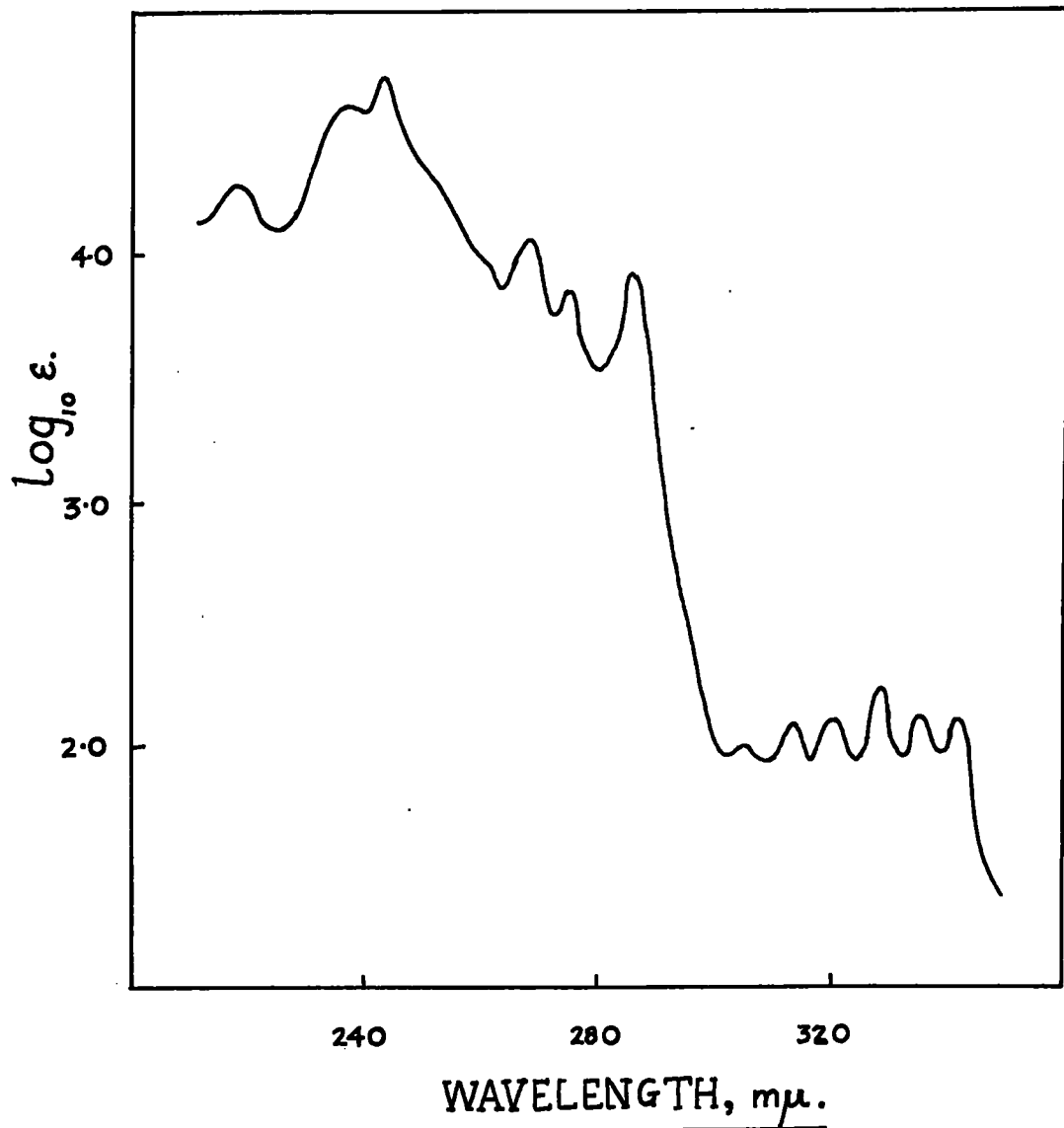


FIGURE 4

Ultraviolet spectrum of:-

dipyrido [1,2-a:2',1'-c] pyrazidiinium dibromide

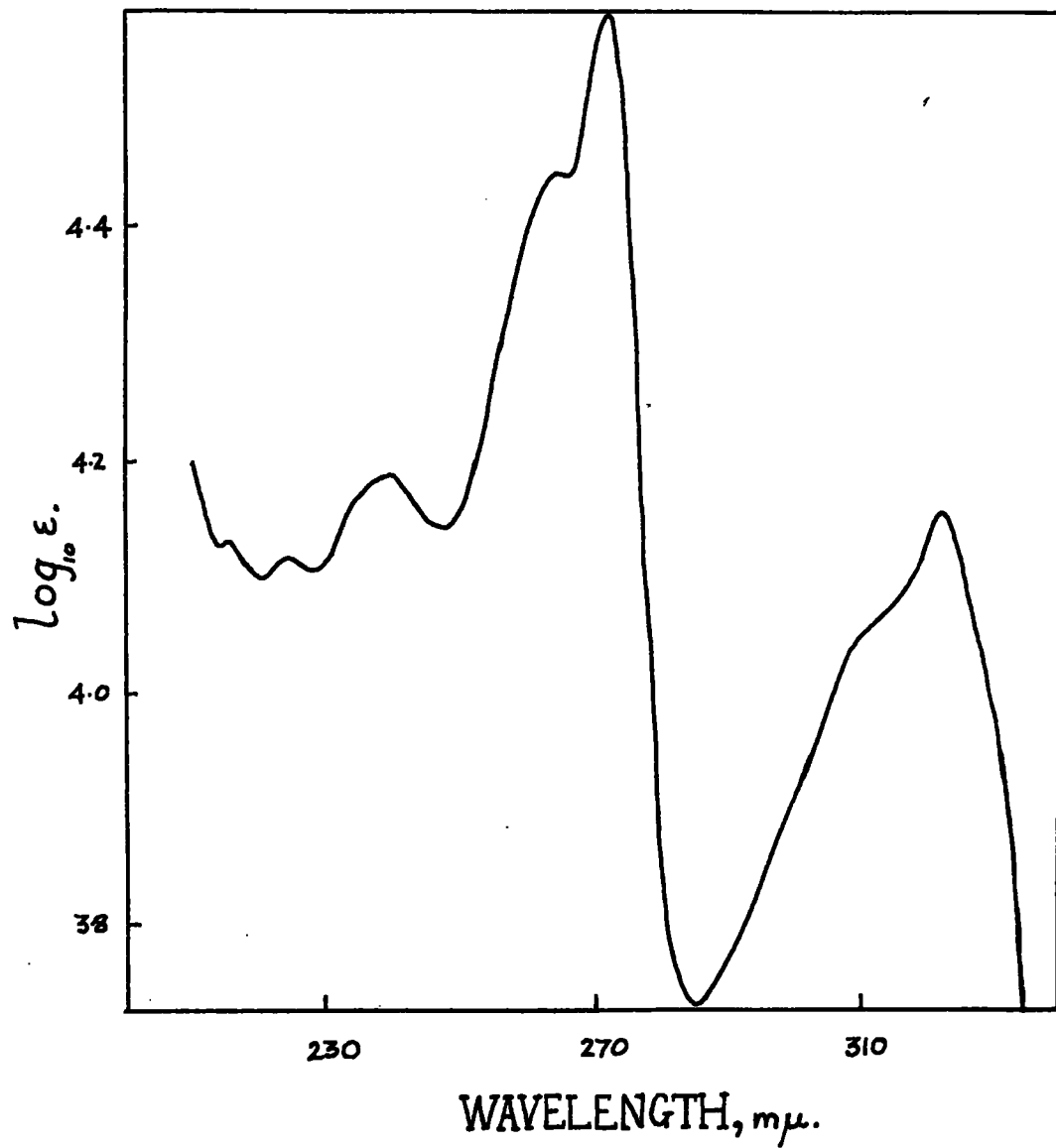


FIGURE 5

Ultraviolet spectrum of:-

6-methyl-dipyrido [1,2-a:2',1'-c] pyrazidinium dibromide

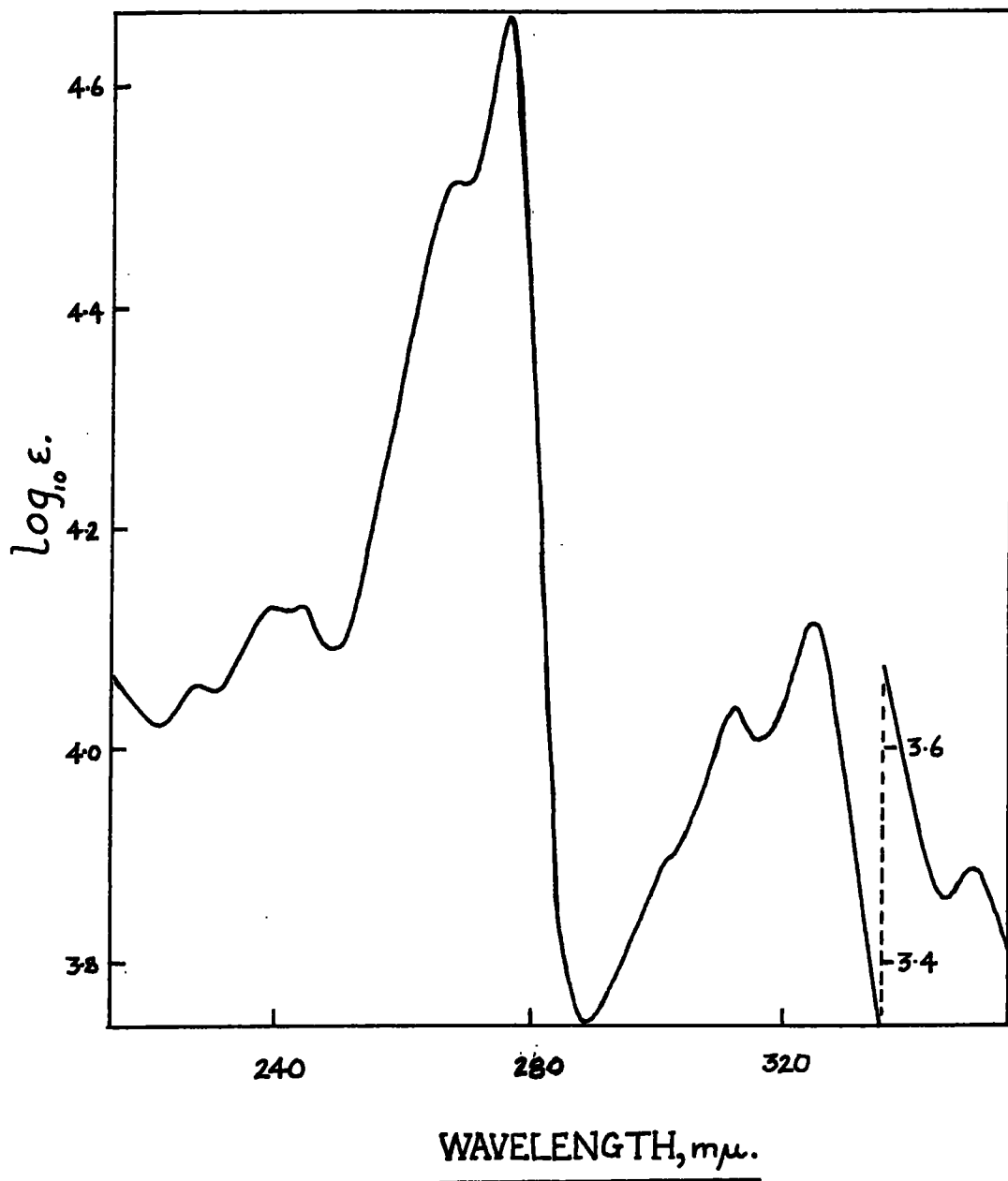
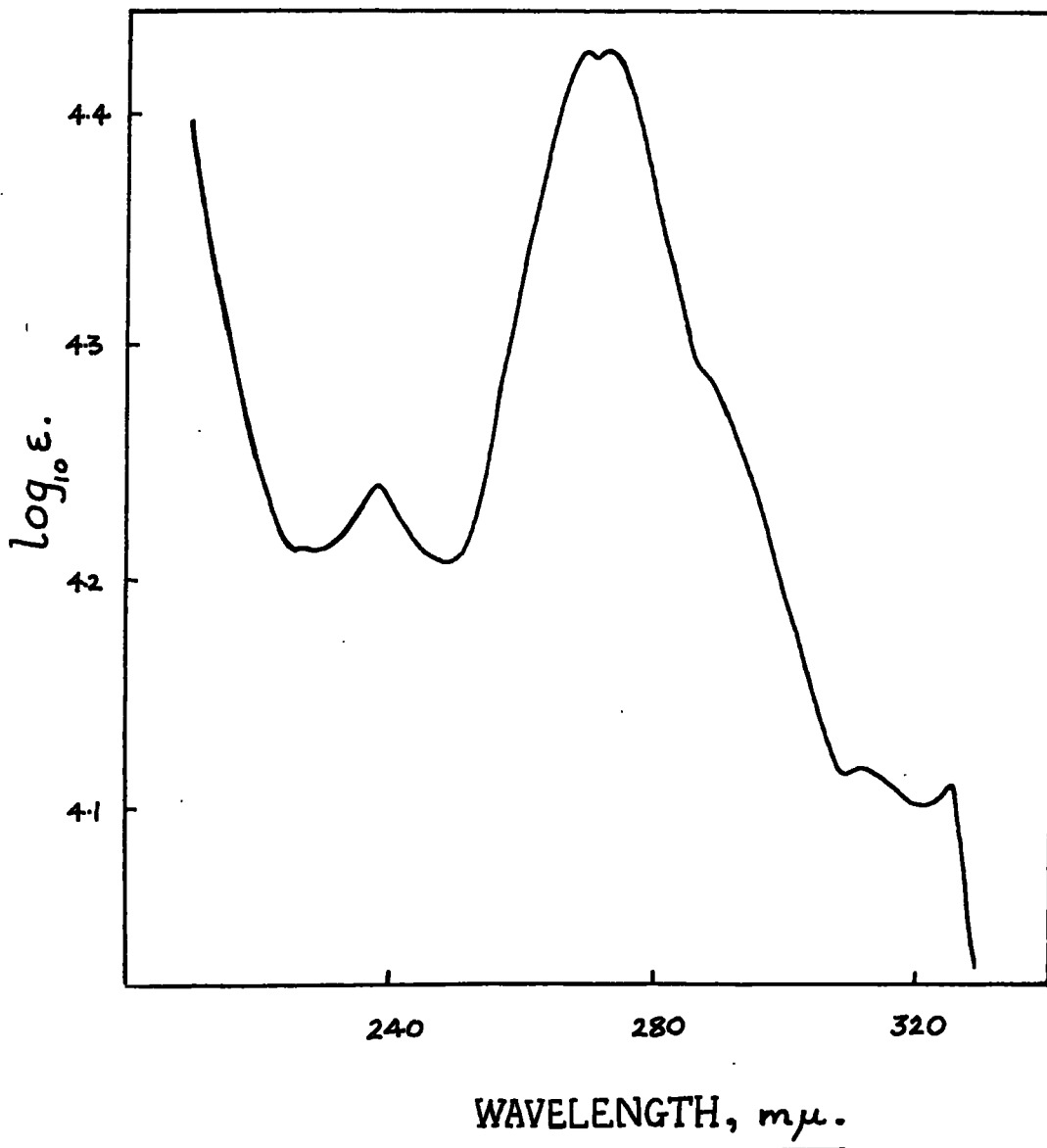


FIGURE 6

Ultraviolet spectrum of:-

6-phenyl-dipyrido [1,2-a:2',1'-c] pyrazidiinium dibromide



EXPERIMENTAL

EXPERIMENTAL

All melting points were determined on a Kofler block.

Infrared absorption spectra were determined on a Perkin-Elmer 237 spectrophotometer, ultraviolet absorption spectra on a Unicam S.P. 500 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, Microanalytical Laboratory, Banbury, Oxford.

6,7- Dihydrodipyrido [1,2-a: 2',1'-c] pyrazidiinium Dibromide

(II; X = Br). - A mixture of 2,2'- bipyridyl (4.5g.) and 1,2- dibromoethane (5.4g.) was heated in a sealed tube at 150° for 24 hrs. The resulting solid crystallised from methanol as pale green prisms, m.p. > 350° (lit.,⁵⁷ m.p. > 320°), (7.7g., 77%).

The dipicrate, obtained by the addition of aqueous sodium picrate to the dibromide, crystallised from water as yellow needles, m.p. 247-249°.

Found: C, 45.1; H, 2.4%

$C_{24}H_{16}N_8O_{14}$ requires : C, 45; H, 2.5%

Attempted Dehydrogenation of 6,7- Dihydrodipyrido [1,2-a: 2',1'-c]

pyrazidiinium Dipicrate (II; X = picrate). - A solution of the dihydro dipicrate (II; X = picrate) in nitromethane (60 ml.) was boiled under reflux for 5 hrs. with 10% palladium-charcoal (0.3g.). The solution was then filtered hot, concentrated by evaporation, and cooled. The starting dihydro dipicrate crystallised as yellow-brown plates, m.p. 246-247°. Recrystallised from water, as orange

needles, it had a m.p. 246-248°, and mixed m.p. 246-248°, and was identical with that prepared above.

Attempted Quaternisation of 2,2'-Bipyridyl with Diethyl

α -Chloroacetaldehyde Acetal. - A solution of 2,2'-bipyridyl (0.1g.) in diethyl α -chloroacetaldehyde acetal (0.1g.) was boiled under reflux for 6 hrs. The solution darkened, but remained liquid; on cooling, ether was added precipitating only a slight amount of black gum.

Attempted Quaternisation of 2,2'-Bipyridyl with α -Chloroacetaldehyde-

2,4-Dinitrophenylhydrazone. - 2, 2'-Bipyridyl (0.1g.) was boiled under reflux for 3 hrs. with a saturated solution of α -chloroacetaldehyde-2,4-dinitrophenyl hydrazone in hot methanol (5 ml.). The solution was then cooled, and ether added, precipitating only a slight amount of black gum.

Bromoacetaldehyde Oxime was prepared using the method described by Kimber and Parham³⁴ for the preparation of the chloro compound.

Attempts to distil the bromo-oxime at atmospheric pressure resulted in its violent decomposition.

6-Hydroxy-6,7-dihydrodipyrido [1,2-a: 2',1'-c] pyrazidinium Dibromide

(XXXVIII; X = Br). - A mixture of bipyridyl (1g.) and bromoacetaldehyde oxime (1g.) was warmed until homogeneous and then allowed to stand at room temperature for 2 days. The resulting gum was washed with ether and dissolved in 48% hydrobromic acid (4 ml.). The solution was boiled for 2 min., cooled and acetone added. The precipitated dibromide⁶¹ crystallised from methanol-ether as pale yellow prisms, m.p. 272-273° (decomp.) (0.89g., 37%).

Found: C, 38.4; H, 3.7; N, 7.6%

$C_{12}H_{12}Br_2N_2O \cdot H_2O$ requires C, 38.1; H, 3.7; N, 7.4%

The dipicrate,⁶¹ obtained by the addition of aqueous sodium picrate to the dibromide, crystallised from water or nitromethane as yellow needles, m.p. 185-186°.

Found: C, 44.1; H, 2.6; N, 17.7%

$C_{24}H_{16}N_8O_{15}$ requires: C, 43.9; H, 2.5; N, 17.1%

Dipyrido [1,2-a: 2',1'-c]pyrazidiinium Dibromide (I; X = Br). - A suspension of the hydroxy dibromide (XXXVIII; X = Br) (1.58g.) in phosphorus tribromide (15 ml.) was boiled under reflux for 1½ hr. The mixture was cooled and filtered. Crystallisation of the residue from methanol-ether gave the dibromide as yellow needles (1.02g., 68%) which rapidly became paler on exposure to the atmosphere. The yellow colour was restored on drying in vacuo. The dibromide had m.p. > 350°.

Found: C, 40.3; H, 3.4; N, 7.7%

$C_{12}H_{10}Br_2N_2 \cdot H_2O$ requires C, 40; H, 3.4; N, 7.8%

λ_{max} in water 2150, 2240, 2390, 2650, 2720, 3100sh., 3220Å.

$\log_{10} \epsilon$ 4.13, 4.11, 4.19, 4.44, 4.58, 4.05, 4.15.

The dichloride crystallised from methanol-ether as white needles, m.p. > 350°.

Found: C, 53.3; H, 4.4; N, 10.2%

$C_{12}H_{10}Cl_2N_2 \cdot H_2O$ requires C, 53.1; H, 4.4; N, 10.3%

The dipicrate, obtained by the addition of aqueous sodium picrate to the dibromide, crystallised from water as yellow needles, m.p. 265-269° (decomp.).

Found: C, 45.2; H, 2.1; N, 18.1%

$C_{24}H_{14}N_8O_{14}$ requires C, 45.1; H, 2.2; N, 17.6%

Perhydrodipyrido [1,2-a: 2',1'-c] pyrazine (III). - (i) A solution of the 6,7- dihydro dibromide (II; X = Br) (0.71g.) in methanol (25 ml.) was hydrogenated to completion over Adam's catalyst at atmospheric temperature and pressure. The catalyst was filtered off and the solvent evaporated under reduced pressure. The residue was crystallised from methanol-ether giving the dihydrobromide⁵⁷ as colourless prisms, m.p. > 350° (0.59g., 80%).

Found: C, 40.4; H, 7; N, 8%

Calc. for $C_{12}H_{22}N_2 \cdot 2HBr$: C, 40.4; H, 6.8; N, 7.9%

An aqueous solution of the dihydrobromide was basified, ether extracted and the dried ether extract evaporated under reduced pressure. The residue was distilled from a bulb tube giving the free base⁵⁷ b.p. 90-92°/2 mm. (bath temp.).

Found: C, 74.1; H, 12.1; N, 14.3%

Calc. for $C_{12}H_{22}N_2$: C, 74.2; H, 11.4; N, 14.4%

The monomethiodide, obtained by the action of methyl iodide on the base, crystallised from methanol-ether as white needles, m.p. 218-219°.

Found: C, 46.1; H, 7.5; N, 8.7%

$C_{13}H_{25}N_2I$ requires: C, 46.4; H, 7.5; N, 8.3%

The dipicrate,⁶¹ obtained by the addition of alcoholic picric acid to the base, crystallised from water as yellow plates, m.p. 248-252° (decomp.).

Found: C, 44.1; H, 4.3; N, 17.4%

$C_{12}H_{22}N_2, C_{12}H_6N_6O_{14}$ requires C, 44.2; H, 4.3; N, 17.2%

(ii) A solution of the hydroxy dibromide (XXXVIII; X = Br) (0.34g.) in glacial acetic acid (10 ml.) and water (2 ml.) was hydrogenated to completion over Adam's catalyst at atmospheric temperature and pressure. The catalyst was filtered off and the solvent evaporated under reduced pressure. The residue was converted to the dipicrate which crystallised from water as yellow plates identical with the sample described above, m.p. and mixed m.p. 248-252° (decomp.).

(iii) A solution of the aromatic dibromide (I; X = Br) was hydrogenated to completion over Adam's catalyst at atmospheric temperature and pressure. The catalyst was filtered off and the solvent evaporated. The residue was converted to the dipicrate which crystallised from water as yellow plates identical with the sample described above, m.p. and mixed m.p. 248-252° (decomp.)

(iv) A solution of the lactam (IV) (0.5g.) in dry ether (50 ml.) was slowly added to a stirred suspension of lithium aluminium hydride (1.0g.) in dry ether (50 ml.), and the resulting mixture boiled under

reflux for 17 hrs., cooled and the excess hydride decomposed with water. The ether layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. The residual liquid was distilled from a bulb tube giving the free base b.p. $60-65^\circ/0.4$ mm. (bath temp.) (0.37g., 80%).

The dipicrate, obtained by the action of alcoholic picric acid on the base, crystallised from water as yellow plates identical with the sample described above m.p. and mixed m.p. $248-252^\circ$ (decomp.)

The infrared spectrum of the base showed a Bohlmann⁷⁰ band at 2770 cm^{-1} .

1-Acetyl-2-(2'-pyridyl) pyridinium Bromide (XL; X = Br). - A mixture of 2,2'-bipyridyl (1.94g.) and bromoacetone (1.71g.) was warmed until homogeneous and then allowed to stand at room temperature for 3 weeks. The resulting solid was washed with ether giving a brown solid (2.84g., 78%) which crystallised from ethanol-ether as very hygroscopic buff prisms, m.p. $162-164^\circ$.

The picrate, obtained by the addition of aqueous sodium picrate to the brown solid, crystallised from water as yellow needles, m.p. $132-134^\circ$.

Found: C, 51.9; H, 3.4; N, 16.2%

$\text{C}_{19}\text{H}_{15}\text{N}_5\text{O}_8$ requires C, 51.7; H, 3.4; N, 15.9%

6-Hydroxy-6-methyl-6,7-dihydrodipyrido [1,2-a: 2',1'-c] pyrazidinium Dibromide (XLI; X = Br). - A solution of the acetyl quaternary salt (XL; X = Br) (0.77g.) in 48% hydrobromic acid (4 ml.) was boiled for

2 min., cooled and acetone added. The precipitated dibromide crystallised from acetone - 48% hydrobromic acid as pale yellow prisms, m.p. 220-222° (decomp.), lit.⁶³, m.p. 220-225°, (0.75g., 76%).

Found: C, 42.1; H, 3.9; N, 7.8%

Calc. for $C_{13}H_{14}Br_2N_2O$ C, 41.7; H, 3.8; N, 7.5%

The dipicrate, obtained by the addition of aqueous sodium picrate to the dibromide, crystallised from water as yellow needles, m.p. 66-68°.

Found: C, 43.9; H, 2.9; N, 16.5%

$C_{25}H_{18}N_8O_{15}, H_2O$ requires C, 43.6; H, 2.9; N, 16.3%

6-Methyldipyrido [1,2-a: 2',1'-c] pyrazidiinium Dibromide (Ia; R = Me,

X = Br). - (i) A suspension of the acetyl quaternary salt (XL; X = Br)

(0.5g.) in phosphorus tribromide (4 ml.) was boiled under reflux for 15 mins. The mixture was filtered and the residue digested with hot ethanol. After filtration the residue was crystallised from methanol-ether giving the dibromide as yellow prisms, m.p. > 350° (lit.⁶³, m.p. 300-305° decomp.), (0.37g., 60%).

Found: C, 43.8; H, 3.6; N, 7.9%

Calc. for $C_{13}H_{12}Br_2N_2$: C, 43.8; H, 3.4; N, 7.9%

λ_{max} in water 2270, 2380, 2435, 2680, 2760, 3005sh., 3125, 3250, 3505 Å.

$\log_{10} \epsilon$ 4.06, 4.12, 4.12, 4.52, 4.66, 3.89, 4.03, 4.11, 3.49.

The dipicrate, obtained by the addition of aqueous sodium picrate to the dibromide, crystallised from water as yellow plates, m.p. 249-251° (decomp.) (lit.⁶³, m.p. 243-245° decomp.).

Found: C, 46.2; H, 2.5; N, 16.8%

Calc. for $C_{25}H_{16}N_8O_{14}$: C, 46; H, 2.5; N, 17.2%

(ii) A suspension of the 6-methyl hydroxy dibromide (XLI; X = Br) (0.58g.) in phosphorus tribromide (5 ml.) was boiled under reflux for 30 mins. The mixture was cooled and filtered, the residue washed with ether and crystallised from methanol-ether giving the aromatic dibromide (0.33g., 60%) the infrared spectrum of which was identical with that of the above sample.

6-Methyl-perhydrodipyrido [1,2-a: 2',1'-c] pyrazine (XLII). - (i) The aromatic dibromide (Ia; R = Me, X = Br) (0.36g.) in methanol (50 ml.) was hydrogenated to completion over Adam's catalyst at atmospheric temperature and pressure. The catalyst was filtered off, the solvent evaporated under reduced pressure, and the hygroscopic residue dissolved in water. The aqueous solution was basified, ether extracted and the dried ether extract evaporated under reduced pressure. The residue was distilled from a bulb tube giving the free base b.p. $73-78^{\circ}/0.1$ mm. (bath temp.)(lit.⁶³, b.p. $80-82^{\circ}/0.2$ mm.) (0.14g., 67%).

Found: C, 75.1; H, 11.4; N, 13.4%

Calc. for $C_{13}H_{24}N_2$: C, 74.9; H, 11.6; N, 13.4%

The dipicrate, obtained by the action of alcoholic picric acid on the base, crystallised from nitromethane as yellow prisms, m.p. $267-268^{\circ}$ (decomp.) (lit.⁶³, m.p. $263-264^{\circ}$).

Found: C, 44.5; H, 4.5; N, 17.2%

Calc. for $C_{13}H_{24}N_2, C_{12}H_6N_6O_{14}$: C, 45; H, 4.5; N, 16.8%

(ii) A solution of the 6-methyl hydroxy dibromide (XLI; X = Br) (0.36g.) in methanol (15 ml.) was hydrogenated to completion over Adam's catalyst at atmospheric temperature and pressure. The catalyst was filtered off and the solvent evaporated under reduced pressure. The residue was converted to the dipicrate which was crystallised from nitromethane as yellow prisms identical with the sample described above, m.p. and mixed m.p. 267-268° (decomp.).

1-Phenacyl-2-(2'-pyridyl) pyridinium Bromide (XLIII; X = Br). - A mixture of 2,2'-bipyridyl (2g.) and phenacyl bromide (2.64g.) was warmed on a water-bath for 45 min. and then allowed to stand at room temperature for 2 days. The solid product was crystallised from ethanol-ether giving the bromide as colourless prisms, m.p. 174-176° (2.9g., 64%).

Found: C, 60.4; H, 4.6; N, 8.1%

$C_{18}H_{15}BrN_2O$ requires: C, 60.9; H, 4.3; N, 7.9%

The picrate, obtained by the addition of aqueous sodium picrate on the bromide, crystallised from nitromethane/di-isopropyl ether as yellow needles, m.p. 164-165°.

Found: C, 57.3; H, 3.4; N, 13.6%

$C_{24}H_{17}N_5O_8$ requires: C, 57.3; H, 3.4; N, 13.9%

The bromide hydrobromide, obtained by dissolving the bromide in 48% hydrobromic acid and precipitating with acetone, crystallised from acetone-hydrobromic acid (48%) as yellow prisms, m.p. 136-138°.

Found: C, 47.3; H, 4.2%

$C_{18}H_{15}BrN_2 \cdot HBr \cdot H_2O$ requires C, 47.6; H, 4.0%

6-Phenyldipyrido [1,2-a: 2',1'-c] pyrazidiinium Dibromide (Ia; R = Ph, X = Br). - A suspension of the phenacyl monoquaternary salt XLIII; X = Br) (2.9g.) in phosphorus tribromide (15 ml.) was boiled under reflux for 15 min. The mixture was cooled, filtered and the black residue washed with ether. Crystallisation from methanol/di-isopropyl ether gave a green solid (2.16g., 58%). Recrystallisation from the same solvent gave the analytical sample of the dibromide as yellow prisms which rapidly became paler on exposure to the atmosphere. The yellow colour returned when the sample was dried in vacuo. The dibromide had m.p. 212-214°.

Found: C, 47.6; H, 3.9; N, 6.8%

$C_{18}H_{14}Br_2N_2 \cdot 2H_2O$ requires C, 47.6; H, 4.0; N, 6.2%

λ_{max} . in water 2260, 2380, 2690, 2720, 2870sh., 3120, 3260 Å.

$\log_{10} \epsilon$ 4.21, 4.24, 4.43, 4.43, 4.29, 4.12, 4.11.

The dipicrate, obtained by the addition of sodium picrate to the dibromide, crystallised from water as yellow needles, m.p. 241-243° (decomp.).

Found: C, 50.2; H, 2.6; N, 15.9%

$C_{30}H_{18}N_8O_{14}$ requires C, 50.4; H, 2.5; N, 15.7%

6-Phenyl-perhydrodipyrido [1,2-a: 2',1'-c] pyrazine (XLV). - A solution of the aromatic dibromide (Ia; R = Ph, X = Br) (0.5g.) in methanol (20 ml.) was hydrogenated over Adam's catalyst at atmospheric temperature and pressure until the hydrogen uptake ceased. The catalyst

was filtered off, the solvent evaporated and the hygroscopic solid residue dissolved in water. The solution was basified, ether extracted and the ether extract dried and evaporated. The residue was chromatographed in ether on an alumina column giving the colourless base (0.22g., 74%). The analytical sample was obtained by sublimation at 250° and 0.5 mm. and had m.p. 110-115°.

Found: C, 79.6; H, 9.8; N, 9.9%

$C_{18}H_{26}N_2$ requires: C, 80; H, 9.7; N, 10.4%

The dipicrate, obtained by the addition of alcoholic picric acid to the base, crystallised from nitromethane as yellow prisms, m.p. 215-217° (decomp.).

Found: C, 49.3; H, 4.3; N, 14.9%

$C_{18}H_{26}N_2, C_{12}H_6N_6O_{14}$ requires C, 49.5; H, 4.4; N, 15.4%

N-(Carbomethoxymethyl)-2-(2'-pyridyl) pyridinium Bromide (XLVIII; X = Br). -

A mixture of 2,2'-bipyridyl (1.45g.) and ethyl bromoacetate (1.62g.) was warmed until homogeneous and then allowed to stand at room temperature for 4 weeks. The resulting solid was washed with ether giving a buff coloured solid (2.1g., 68%) which crystallised from dry acetone as very hygroscopic buff prisms, m.p. 154-156° (decomp.).

The picrate, obtained by the addition of aqueous sodium picrate to the bromide, crystallised from ethanol as yellow needles, m.p. 125-126°.

Found: C, 51.2; H, 3.5; N, 14.9%

$C_{20}H_{17}N_5O_9$ requires C, 51; H, 3.6; N, 14.9%

Hydrogenation of N-(Carbethoxymethyl)-2-(2'-pyridyl) pyridinium Bromide (XLVIII; X = Br). - A solution, in glacial acetic acid (25 ml.), of the monoquaternary bromide (XLVIII; X = Br), prepared by heating together 2,2'-bipyridyl (1.3g.) and ethyl bromoacetate (1.3g.) for 4 hrs. and washing the tar-like product with ether, was hydrogenated to completion over Adam's catalyst at atmospheric temperature and pressure. The catalyst was filtered off, the solvent evaporated under reduced pressure, and the hygroscopic solid residue dissolved in water. The solution was basified, ether extracted and the ether extract dried (Na_2SO_4) and evaporated. The residual liquid was distilled from a bulb tube giving a clear liquid (small amount b.p. $95-100^\circ/1 \text{ mm.}$ $\approx 0.1\text{g.}$, and majority b.p. $135-140^\circ/1 \text{ mm.}$, 0.6g.). The infrared spectrum of the liquid showed an absorption peak at 1750 cm.^{-1} corresponding to an ester carbonyl, and another at 1660 cm.^{-1} corresponding to a lactam carbonyl.

2-(2'-Pyridyl) pyridine Betaine (L). - A solution of the monoquaternary bromide (XLVIII; X = Br) (1.0g.) in water (10 ml.) was passed through Amberlite I.R.A. - 400(OH) (25 cm. x 1 cm.). The column was eluted with water (25 ml.) and the eluate was evaporated to dryness. The residual light brown solid (0.53g., 80%) crystallised from ethanol/di-isopropyl ether giving the betaine as colourless prisms, m.p. $214-216^\circ$.

Found: C, 64.8; H, 5.2; N, 13.2%

$\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_2 \cdot \frac{1}{2}\text{H}_2\text{O}$ requires C, 64.6; H, 5; N, 12.6%

The picrate, obtained by the addition of alcoholic picric acid to the betaine, crystallised from alcohol/di-isopropyl ether as yellow prisms, m.p. 155°.

Found: C, 48.8; H, 2.7; N, 16 %

$C_{18}H_{13}N_5O_9$ requires C, 48.8; H, 3; N, 15.8%

Perhydro-6-oxodipyrido [1,2-a: 2',1'-c] pyrazine (IV). - A solution of the betaine (L) (0.51g.) in glacial acetic acid (15 ml.) was hydrogenated to completion over Adam's catalyst at atmospheric temperature and pressure. The catalyst was filtered off, the solvent evaporated under reduced pressure, and the liquid residue dissolved in water. The solution was basified, ether extracted and the ether extract dried (Na_2SO_4) and evaporated. The residual solid (m.p. 25-30°) was sublimed at 100° and 0.5 mm. giving the lactam as a white solid, m.p. 52-54° (0.21g., 42%).

Found: C, 68.8; H, 10 ; N, 13.9%

$C_{12}H_{20}N_2O$ requires C, 69.2; H, 9.7; N, 13.5%

Two picrates, obtained by the action of alcoholic picric acid on the lactam (m.p. 25-30°) were separated by fractional crystallisation from ethanol.

Picrate (1) crystallised from ethanol as yellow prisms, m.p. 168-169°.

Found: C, 49.3; H, 5.6%

$C_{12}H_{20}N_2O, C_6H_3N_3O_7$ requires C, 49.5; H, 5.3%

Picrate (2) crystallised from water as yellow prisms,
m.p. 215-219°.

Found: C, 49.9; H, 5.4%
 $C_{12}H_{20}N_2O_6, C_6H_3N_3O_7$ requires C, 49.5; H, 5.3%

1,4,6,7,9,12,12a,12b - Octahydrodipyrido [1,2-a:2',1'-c] pyrazine (LIV). -

(i) Sodium borohydride (lg.) was slowly added to a stirred solution of the 6,7-dihydro-compound (II; X = Br) (lg.) in methanol (10 ml.) and water (1 ml.). The mixture was boiled under reflux for 10 mins., cooled and the excess hydride decomposed with water (50 ml.). The ethereal extract of the aqueous solution was dried (Na_2SO_4) and the solvent removed by evaporation under reduced pressure. The residual liquid was distilled from a bulb tube to give the octahydro base b.p. 90-95°/0.9 mm. (0.42g., 76%). The base quickly darkened on standing.

The dipicrate, obtained by the action of alcoholic picric acid on the base, crystallised from nitromethane as yellow prisms, m.p. 247-248°.

Found: C, 44.2; H, 3.8; N, 17.1%
 $C_{12}H_{18}N_2, C_{12}H_6N_6O_{14}$ requires C, 44.4; H, 3.7; N, 17.3%

The dimethiodide, obtained by the action of methyl iodide on the base, crystallised from methanol/di-isopropyl ether as colourless prisms, m.p. 225-227°.

Found: C, 36; H, 5.6; N, 5.9%
 $C_{14}H_{24}N_2I_2, CH_4O$ requires C, 35.6; H, 5.6; N, 5.5%

A solution of the octahydro base (0.286g.) in methanol (30 ml.) was hydrogenated to completion over Adam's catalyst at atmospheric temperature and pressure. The base (LIV) absorbed 67 mls. of hydrogen (measured at N.T.P.) this being equivalent to 2 moles of hydrogen per 1 mole of base, i.e. two double bonds. The catalyst was filtered off and the solvent was evaporated under reduced pressure. The residual liquid (0.292g., 100%) was converted to the dipicrate which crystallised from water as yellow plates identical with perhydrodiprido [1,2-a: 2',1'-c] pyrazine (III) dipicrate, m.p. and mixed m.p. 248-252° (decomp.).

(ii) The 6-hydroxy compound (XXXVIII; X = Cl) (1g.) was reduced with sodium borohydride (1g.), as described above, the octahydro base (LIV) (0.5g., 71%) being converted to the dipicrate and dimethiodide. The dipicrate crystallised from nitromethane as yellow prisms, identical with the sample described above, m.p. and mixed m.p. 247-248°.

The dimethiodide crystallised from methanol/di-isopropyl ether as colourless prisms identical with the sample described above, m.p. and mixed m.p. 225-227°.

The ultraviolet spectrum of the octahydro base (LIV) was determined in cyclohexane, and showed no maxima between 220 and 240 m μ .

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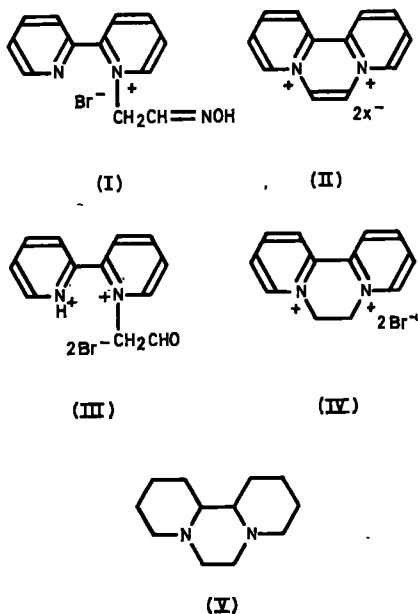
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Dipyrido [1,2-a: 2',1'-c] pyrazidiinium Salts

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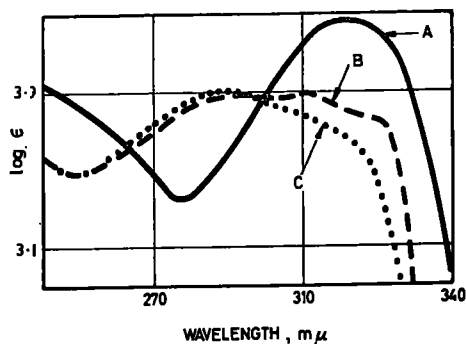
As far as we know the only completely aromatic condensed benzenoid systems with two quaternary nitrogen atoms at bridgehead positions are the diazoniapentaphene salts.¹ We record here the synthesis of the title compounds in which both quaternary bridgehead nitrogen atoms are in the same ring.



Treatment of 2,2'-bipyridyl with bromoacetaldoxime gave the monoquaternary salt (I) as a gum. The gum was boiled with 48% hydrobromic acid for 2 min., the solution cooled and the diquaternary salt (II, X=Br) precipitated with acetone. This salt crystallised from methanol-ether as the dihydrate (m.p. 272-273° decomp.) (pure, 37%). The dipicrate crystallised as a monohydrate (m.p. 185-186°).

The structure of (II, X=Br) was confirmed by hydrogenation yielding the dihydrobromide of the

perhydro base (V). The infrared spectrum of this dihydrobromide (m.p. >350°) was identical with that of the salt obtained by the hydrogenation of the



Spectrum of the diquaternary salt (II, X=Br): A, in 32% hydrochloric acid; B, in water immediately after preparation of the soln; C, in water after standing for 3 hours.

dihydrodiquaternary salt (IV).^{2,3} Further the dihydrobromides obtained from both (II) and (IV) gave the same perhydro-base² on basification (m.p. and mixed m.p. of the dipicrates 248-252° decomp.).

As expected the diquaternary salts are susceptible to attack by nucleophiles. Although the dibromide (II, X=Br) can be precipitated unchanged after boiling for 6 hours with concentrated hydrobromic acid, in dilute neutral aqueous solution, an equilibrium exists in favour of the aldehyde (III) as shown by the ultraviolet absorption spectrum (see Fig.). Evaporation of these dilute aqueous solutions leaves the diquaternary salt (II, X=Br), the infrared spectrum of which contains no bands attributable to either -CHO or =NH.

Satisfactory analyses have been obtained for the compounds reported here.

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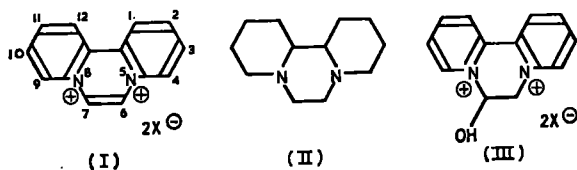
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Dipyrido[1,2-a:2',1'-c]pyrazidiinium Salts: A Correction

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Recently¹ we reported the synthesis of what we considered to be the title compounds (I) as the dibromide and dipicrate, the salts being described as a dihydrate and a monohydrate respectively. The structure of these salts was based mainly on the smooth hydrogenation of the dibromide to the dihydrobromide of the perhydro-base (II).



These salts have now been shown to be the dibromide and dipicrate of the hydroxy-compound (III). The N.M.R. spectrum of the hydroxy-dibromide (III, X=Br) in D₂O showed a triplet centred at τ 3.0 corresponding to the proton on the hydroxylated carbon atom, a doublet centred at τ 4.5 corresponding to the protons of the methylene group, together with a collection of eight protons in the region τ 0.4-1.7.

The hydroxy-dibromide (III, X=Br) was dehydrated by boiling under reflux in phosphorus tribromide for 1.5 hr, giving the aromatic dibromide (I, X=Br) which crystallised from methanol-ether as the monohydrate (68%), m.p. $>350^\circ$, λ_{\max} . 2150, 2240, 2390, 2650, 2720, 3100sh., 3220 Å ($\log_{10}\epsilon$ 4.13, 4.11, 4.19, 4.44, 4.58, 4.05, 4.15) in H₂O.

The dipicrate (I, X=picrate) crystallised from water and had m.p. 265-269° (decomp.); the dried sample gave analytical results consistent with an anhydrous salt.

The N.M.R. spectrum of the cation (I) in trifluoroacetic acid showed a collection of 10 protons in the region τ 0.4-1.8. Hydrogenation of the dibromide (I, X=Br) followed by basification gave the perhydro-base (II), characterised as the dipicrate, m.p. 248-252° (decomp.).¹

We thank Dr Gurnos Jones for the determination and interpretation of the N.M.R. spectra.

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