THE SYNTHESIS AND PROPERTIES OF QUINOLIZINIUM AND RELATED COMPOUNDS

A THESIS

by

ALAN FOZARD

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SUMMARY

The work describes the preparation and properties of several simple quinolizinium salts particularly hydroxyquinolizinium derivatives. 1- and 2-Hydroxyquinolizinium salts have been prepared in high yields from 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide. The 2-hydroxyquinolizinium ion has also been converted to the related compound, 2-quinolizone. Some 1,2-dihydroxyquinolizinium salts have been prepared.

1-Hydroxyquinolizinium salts are shown to be phenolic, readily undergoing acetylation, bromination and coupling with diazotised aniline. However, nitration is abnormal giving a series of compounds having zwitterionic structures. The 2-hydroxyquinolizinium salts behave to some extent as phenols but 2-quinolizone, as expected, has properties resembling the 2- and 4-pyridones.

The rearrangements of 1-oximino-1,2,3,4-tetrahydroquinolizinium bromide have been investigated and total syntheses of both possible Beckmann rearrangement products are reported. Under certain acid conditions the oxime rearranges to give aminohydroxyquinolizinium salts. These have been formulated as 1-amino-2-hydroxy and 1-amino-4-hydroxyquinolizinium compounds.

Attempts have been made to synthesise the 1- and 3-oxo pyrido[1,2a]-azepinium systems. Although the preparation of the unsubstituted compounds has not been successful several compounds in the 1-oxo pyrido[1,2a]-azepinium series have been synthesised.

ACKNOWLEDGMENTS

I am indebted to Professor H. D. Springall and the University of Keele for providing facilities for carrying out this work.

I would particularly like to thank my supervisor, Dr. Gurnos Jones, for his invaluable help and encouragement.

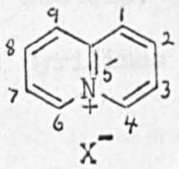
My thanks are also due to Dr. R. J. Highet of the National Institutes of Health, Maryland, U. S. A. for carrying out the nuclear magnetic resonance spectra.

CONTENTS

INTRODUCTION

Nomenclature

Throughout the course of this work the term quinolizinium ion will be used to describe the bicyclic naphthalenic ring system in which one of the bridgehead carbon atoms has been replaced by a quaternary nitrogen atom (I). The equivalent reduced systems (II) will be termed quinolizidines and salts of type (III) will be referred to as 1,2,3,4-tetrahydroquinolizinium salts. The heterocyclic system (IV) is one (10 - H) of several isomers known as quinolizines.



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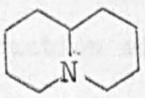

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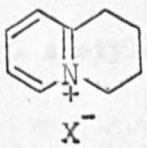

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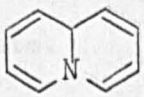


IV

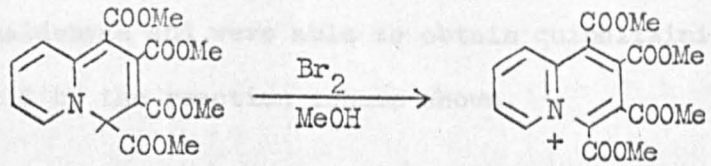
Survey of Previous work

(a) Syntheses of Quinolizinium Compounds.

Although a considerable amount of work has been carried out on substances containing quinolizidine (II) and quinolizine (IV) systems, comparatively little has been done on the fully aromatic quinolizinium cation and its derivatives.

Previous to 1954 the only reported synthesis of a quinolizinium compound having no additional fused rings was the 1,2,3,4-tetramethoxy

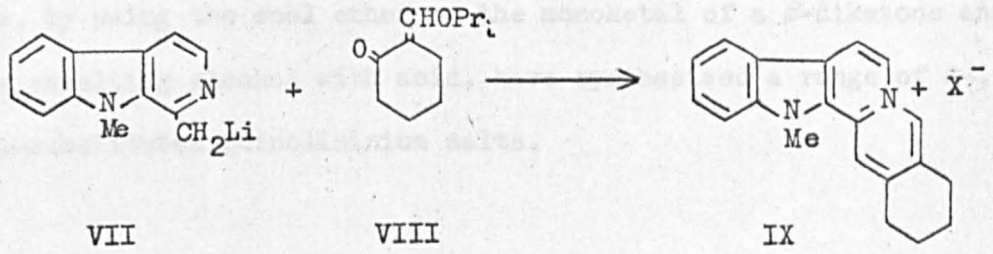
carbonyl compound (VI) which had been prepared by Diels and Alder[1] from tetramethyl-4H-quinolizine-1,2,3,4-tetracarboxylate (V). The quinolizine (V) had been obtained as one of the products of the reaction between pyridine and dimethyl acetylenedicarboxylate. Although the structure of this compound (V) was first given as the 10 - H isomer, recent work by Acheson and Taylor,[2] and Jackman, Johnson and Tebby,[3] has proved the structure to be tetramethyl-4H-quinolizine-1,2,3,4-tetracarboxylate (V). The quinolizinium derivative (VI) was obtained by oxidation of the quinolizine (V) with bromine in methanol, giving the perbromide (VI, X = Br_3). This could be converted to the perchlorate (VI, X = ClO_4) by addition of perchloric acid,[1] or to the bromide (VI, X = Br) by refluxing with acetone.[2] Similar compounds have been obtained[3] by using substituted pyridines in the reaction with dimethyl acetylenedicarboxylate.



V VI

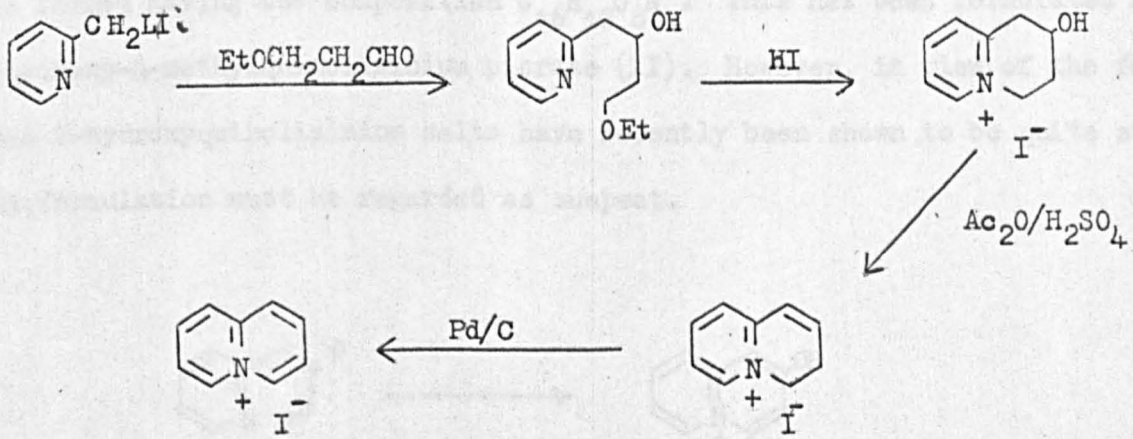
Quinolizinium salts have been known to exist in certain complex alkaloids for some time. In 1949 Bentley and Stevens[4] and McLamore and Woodward[5] simultaneously established the presence of the quinolizinium nucleus in the alkaloid sempervirine. McLamore and Woodward also synthesised a number of sempervirine metho-salts by a process which involved reaction of

2-isopropoxy methylene cyclohexanone (VIII) with the lithium reagent of N-methyl harman (VIII), subsequent cyclisation giving 13-methyl-1,2,3,4-tetrahydrobenzo-indolo [2,3a] quinolizinium chloride (IX).

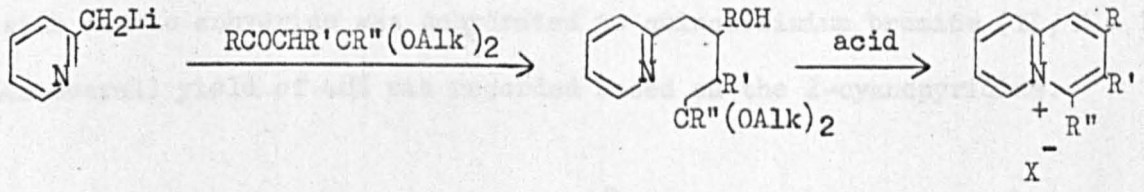


VII VIII IX

Using a modification of this method, Beamann and Woodward [6] achieved the first synthesis of an unsubstituted quinolizinium salt. The method involved the treatment of 2-picolyl lithium with 3-isopropoxyacrolein, subsequent cyclisation of the initially formed product with acid giving the required quinolizinium salt in very poor yield. The method has been elaborated by Boekelheide and Gall [7] who replaced the 3-isopropoxyacrolein with 3-ethoxypropionaldehyde and were able to obtain quinolizinium salts in 10% overall yield by the reaction scheme shown.

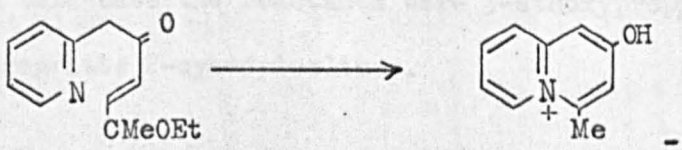


By using the monolithium reagent of 2.6-lutidine in place of 2-picolyl lithium, Boekelheide and Ross[8] were also able to prepare 4-methylquinolizinium salts. A further refinement has been made by Richards and Stevens,[9] who, by using the enol ether or the monoketal of a β-diketone and cyclising the resulting alcohol with acid, have synthesised a range of 2-, 2,3-, and 2,4-substituted quinolizinium salts.



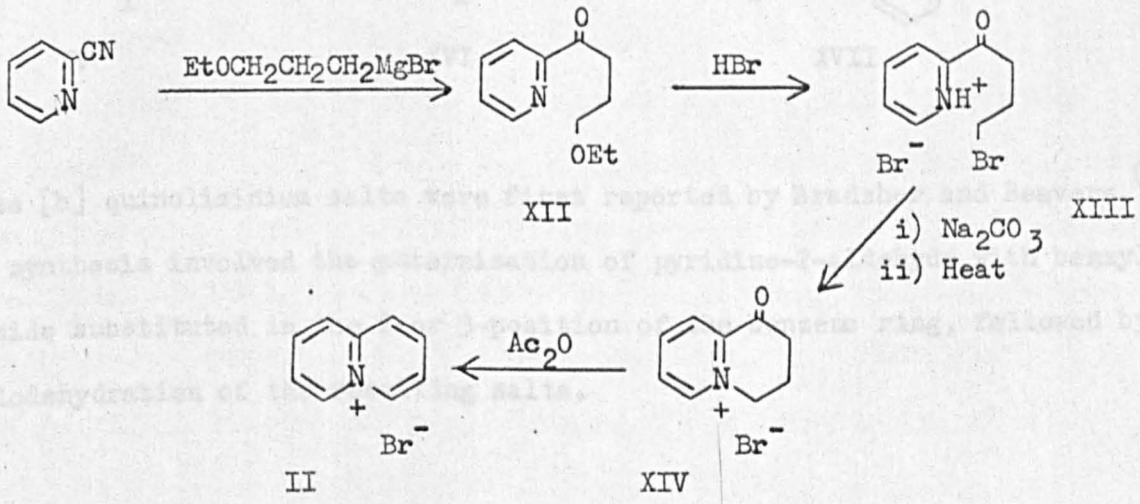
This synthesis has also been used by Hansen and Amstutz[10] to form 4,6-dimethylquinolizinium salts. This has been accomplished by the reaction of 2,6-lutidyl lithium with the appropriate protected β-diketone.

In an attempt to prepare a quinolizinium salt unsubstituted in position 2, Richards and Stevens[9] reacted 2-picolyl lithium with ethyl β-ethoxy crotonate giving compound (X). With picric acid an unstable picrate was formed having the composition $C_{16}H_{12}O_8N_4$. This has been formulated as 2-hydroxy-4-methylquinolizinium picrate (XI). However, in view of the fact that 2-hydroxyquinolizinium salts have recently been shown to be quite stable,[11] the formulation must be regarded as suspect.



X XI

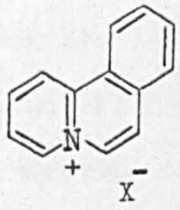
A synthesis by Glover and Jones[12] was the first to produce the quinolizinium cation in appreciable quantities. By treating 2-cyanopyridine with the Grignard reagent from 3-ethoxypropyl bromide, 2(4'-ethoxy butyryl) pyridine[13] (XII) was obtained. Cyclisation was then effected by splitting the ether (XII) with hydrobromic acid and heating the resulting bromo ketone (XIII) in chloroform to give 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XIV). The cyclic ketone (XIV) when boiled under reflux with acetic anhydride was dehydrated to quinolizinium bromide (II, X = Br). An overall yield of 48% was recorded based on the 2-cyanopyridine.



The method is a general one and by using suitable starting materials the same authors[12,14] have synthesised a number of 2-, 3- and 4-alkyl and aryl substituted quinolizinium salts. Moynehan, Schofield, Jones and Katritzky[16] have also used this method to synthesise the four methyl quinolizinium derivatives. In this case the reactants were 3-ethoxypropyl magnesium bromide and the appropriate 2-cyanopicolines.

Syntheses of 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XIV) have since been reported by Prasad and Swan[17] and Elderfield, Lagouski, McCurdy and Wythe,[18] though yields are lower than in the preparation described.

The three isomeric benzo-quinolizinium derivatives, benzo [a] (XV), benzo [b] (XVI), and benzo [c] (XVII) quinolizinium salts have all been prepared.



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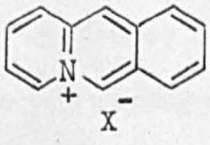
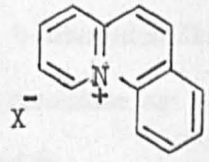
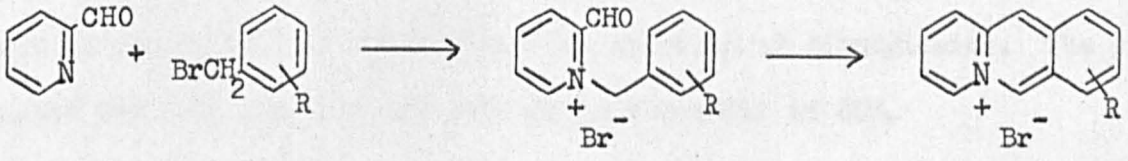


XVI



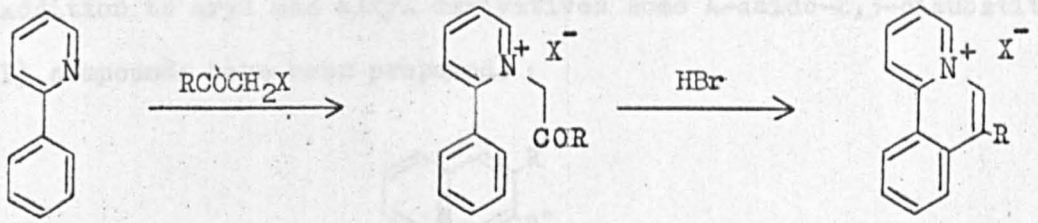
XVII

Benzo [b] quinolizinium salts were first reported by Bradsher and Beavers.[19] The synthesis involved the quaternisation of pyridine-2-aldehyde with benzyl bromide substituted in the 2-or 3-position of the benzene ring, followed by cyclodehydration of the resulting salts.



By a similar method Bradsher and Jones[20] prepared a number of substituted benzo [a] quinolizinium salts. In this, 2-phenyl pyridine was quaternised with phenacyl bromide or iodoacetone, and the resulting quaternary salts boiled under reflux in hydrobromic acid to yield 7-phenyl and 7-methyl

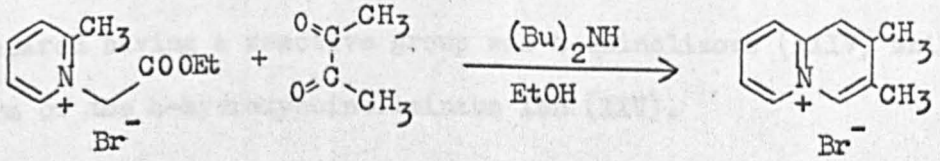
benzo [a] quinolizinium bromides (XVIII) respectively.



XVIII

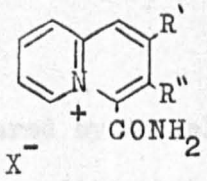
Glover and Jones[14] have extended their general method of preparation of quinolizinium salts to the synthesis of the three benzoquinolizinium isomers. The starting materials are the appropriate cyanoquinoline or isoquinoline and the Grignard reagent from 3-ethoxy propyl bromide.

Another process by which substituted quinolizinium compounds have been prepared, is one which involves cyclodehydration of suitable pyridinium salts. Westphal, Jann and Heffe[21] have prepared several 2,3-disubstituted quinolizinium salts by condensation of compounds having two adjacent oxo groups, with a suitably activated picolinium salt. 2,3-Dimethylquinolizinium bromide (XX) is thus formed by reaction of the quaternary salt of ethyl bromo-acetate and 2-picoline (XIX) with diacetyl. The cyclisation is carried out by heating in an ethanolic solution of dibutylamine. The yields quoted for this reaction are usually in the order of 80%.



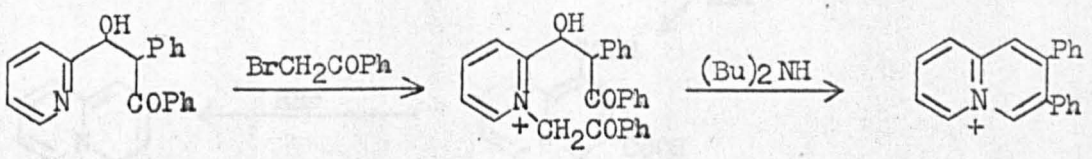
XIX XX

A recent patent application[22] lists many compounds prepared in this manner. In addition to aryl and alkyl derivatives some 4-amido-2,3-disubstituted (XXI) compounds have been prepared.



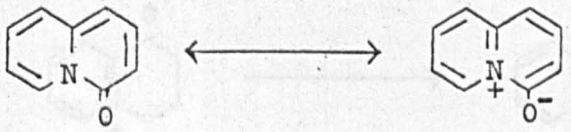
XXI

Westphal and Feix[23] have used a modification of this method in a synthesis of 2,3-diphenylquinolizinium bromide. The first step is a reaction between 2-pyridine aldehyde and phenyl benzyl ketone. The product (XXII) is quaternised with phenacyl bromide and the resulting pyridinium salt (XXIII) is cyclised by refluxing with a solution of dibutylamine in acetone.



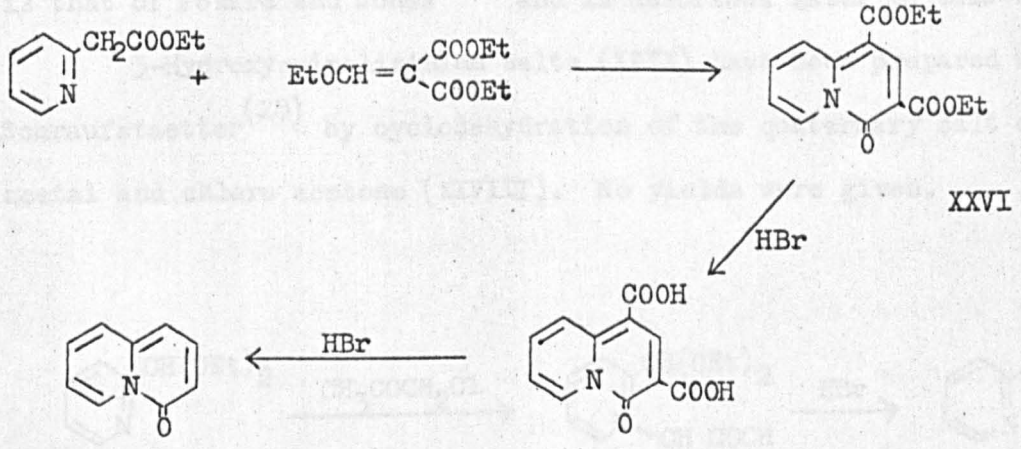
XXII XXIII

Apart from the alkyl and aryl derivatives described, few simple quinolizinium derivatives have been reported. The first simple quinolizinium compound prepared having a reactive group was 4-quinolizone (XXIV) which is the stable form of the 4-hydroxyquinolizinium ion (XXV).



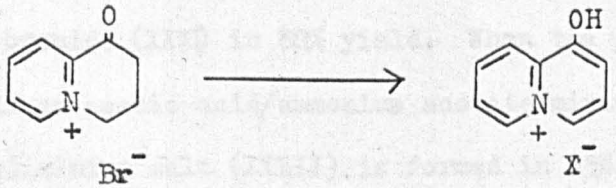
XXIV XXV

4-Quinolizone (XXIV) was prepared by Boekelheide and Lodge[24] by condensation of ethyl pyridylacetate and diethyl ethoxymethylene malonate to 1,3-dicarbethoxy-4-quinolizone (XXVI). Treatment of this with hydrobromic acid gave the unsubstituted quinolizone.



XXVI

The three other hydroxyquinolizinium compounds are now known. 1-Hydroxyquinolizinium picrate (XXVII, X=Picrate) was first prepared by Glover and Jones[25] by dehydrogenation of 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XIV) with palladium charcoal. The yield was poor and only the picrate could be obtained.

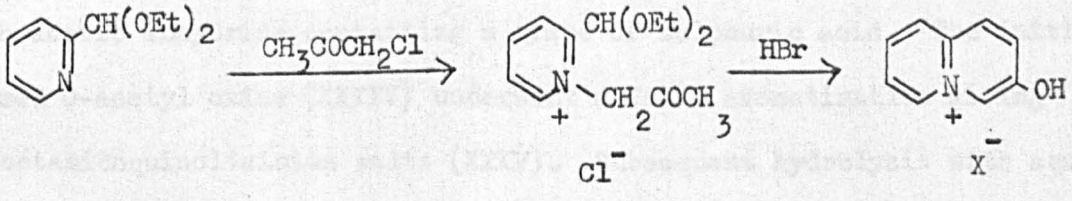


XIV XXVII

Fozard and Jones[26] have also synthesised the bromide (XXVII , X = Br). Details of this appear later.

The only reported synthesis to date of 2-hydroxyquinolizinium salts is that of Fozard and Jones[27] and is described later in this work.

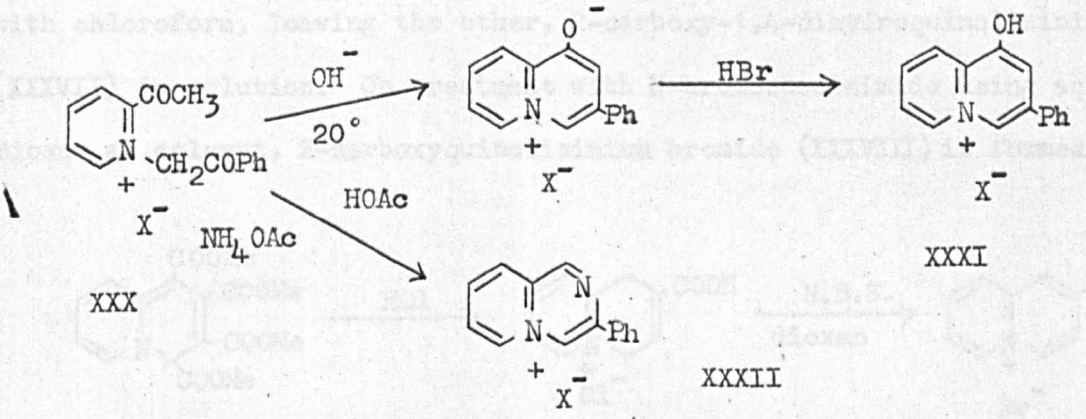
3-Hydroxyquinolizinium salts (XXIX) have been prepared by Schraufstaetter[28] by cyclodehydration of the quaternary salt of 2-pyridine acetal and chloro acetone (XXVIII). No yields were given.



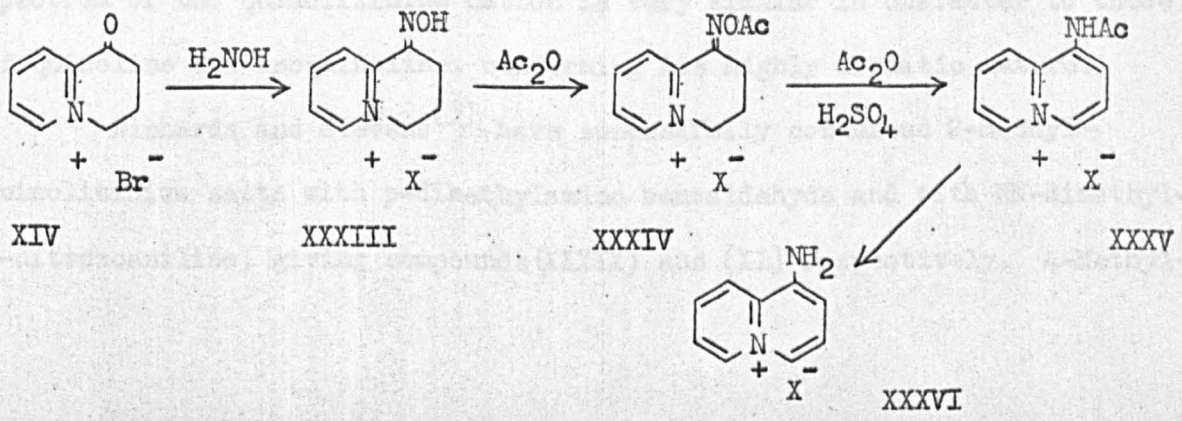
XXVIII XXIX

In a review on pyridinium salts Krohnke[29] gives details of a yet unpublished synthesis of substituted 1-hydroxyquinolizinium salts originated by Weis.[30] The quaternary salt of 2-acetyl-pyridine and bromo acetophenone (XXX) on treatment with base gives the zwitterion form of the 1-hydroxy salt. This is not

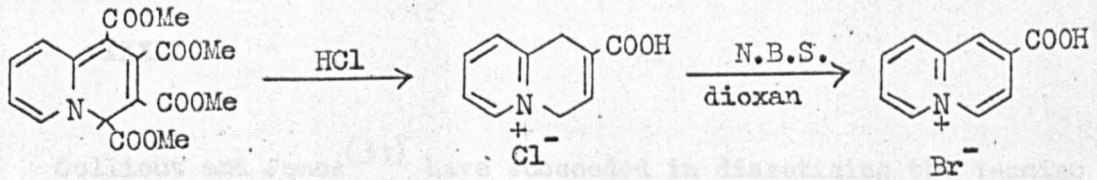
isolated but is treated with hydrobromic acid to give 1-hydroxy-3-phenyl-quinolizinium bromide (XXXI) in 80% yield. When the pyridinium salt (XXX) is treated with an acetic acid/ammonium acetate mixture at 130°C, a 2-aza-3-phenyl-quinolizinium salt (XXXII) is formed in 95% yield.



Only one amino-quinolizinium derivative is known this being 1-aminoquinolizinium bromide (XXXVI, X = Br), obtained by Collicut and Jones[31] from 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XIV). The ketone (XIV) was first converted to the oxime (XXXIII) with hydroxylamine, and then refluxed with acetic anhydride containing a trace of sulphuric acid. The initially formed O-acetyl oxime (XXXIV) underwent a Wolff aromatisation giving 1-acetamidoquinolizinium salts (XXXV). Subsequent hydrolysis with aqueous hydrobromic acid gave the 1-amino derivative as the hydrobromide (XXXVI, X = Br as hydrobromide).



Acheson, Gagan and Taylor[32] have described a method of formation of 2-carboxyquinolizinium bromide (XXXVIII). When tetramethyl-4H-quinolizine-1,2,3,4-tetracarboxylate (V) is refluxed with dilute hydrochloric acid, two products are formed. One, a substituted indole, can be removed by extraction with chloroform, leaving the other, 2-carboxy-1,4-dihydroquinolizinium chloride (XXXVII) in solution. On treatment with N-bromosuccinimide using aqueous dioxan as solvent, 2-carboxyquinolizinium bromide (XXXVIII) is formed.



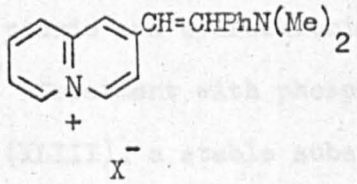
V XXXVII XXXVIII

b) Properties

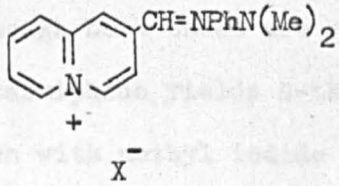
Little is known of the properties of the quinolizinium cation or its derivatives, but it should be a π deficient aromatic substance very susceptible to nucleophilic substitution in the 2- and 4-positions. Electrophilic attack should take place much less readily than either pyridine or quinoline due to the positive charge carried. The ultraviolet absorption spectrum of the quinolizinium cation is very similar in character to those of quinoline and isoquinoline, confirming its highly aromatic nature.

Richards and Stevens[9] have successfully condensed 2-methyl-quinolizinium salts with p-dimethylamino benzaldehyde and with NN-dimethyl-p-nitrosoaniline, giving compounds (XXXIX) and (XL) respectively. 4-Methyl-

quinolizinium bromide also undergoes a similar condensation with NN-dimethyl-p-nitrosoaniline.[15] These methyl salts thus show some analogy with the 4-methyl substituent in a pyridine ring.

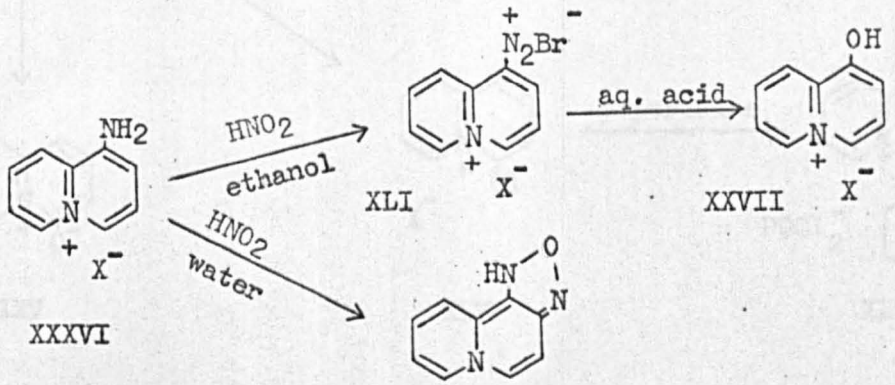


XXXIX



XL

Collicut and Jones[31] have succeeded in diazotising the 1-amino compound (XXXVI) though only in ethanolic solution. The diazonium compound (XLI) will couple with 2-naphthol to give an azo dye and on refluxing in aqueous acid a 1-hydroxy salt (XXVII) is obtained. In aqueous solution diazotising conditions gave an insoluble compound of composition $C_9H_7N_3O$. This has been formulated as a furazan (XLII). Presumably, the formation of such a compound would go via a nitroso intermediate. Although this is unexpected due to the electrophilic mechanism of nitrosation, it will be seen later that 1-hydroxyquinolizinium salts readily undergo electrophilic substitution in the 2-position.



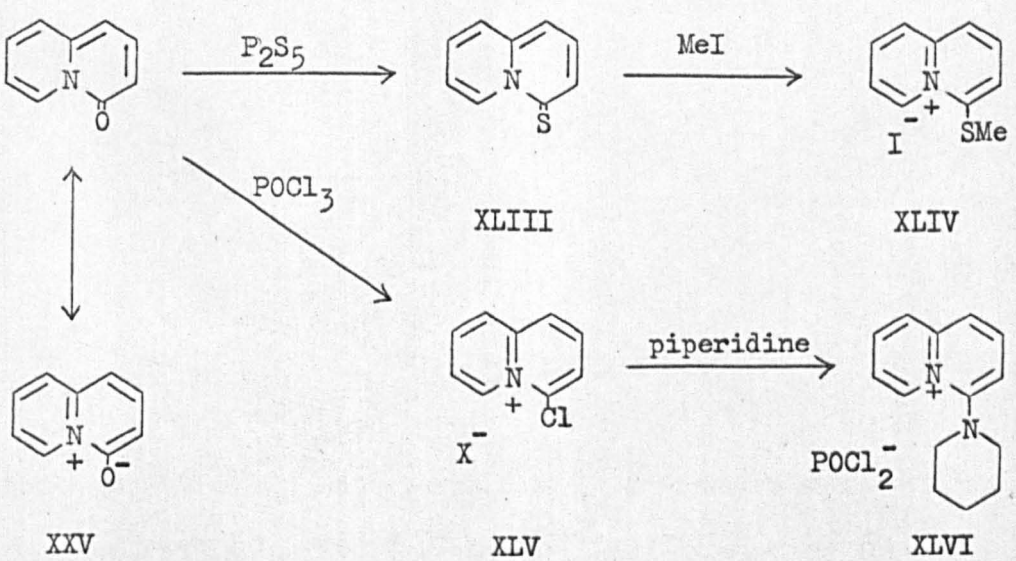
XXXVI

XLI

XXVII

XLII

Of all quinolizinium salts and related compounds, the chemistry of 4-quinolizone (XXIV) has been most studied. Both its properties and ultraviolet absorption spectrum suggest that it is a resonance hybrid to which the 4-hydroxyquinolizinium cation (XXV) is a major contributor. Thus it gives a deep red colour with ferric chloride solution and forms crystalline salts with picric and hydrochloric acids though both these are very unstable.[24] Treatment with phosphorus pentasulphide yields 4-thioquinolizone[24] (XLIII), a stable substance which with methyl iodide gives 4-methylmercaptoquinolizinium iodide (XLIV), a stable crystalline salt.[33] Van Allan and Reynolds[34] have reacted phosphorus oxychloride with 4-quinolizone and obtained an almost quantitative yield of 4-chloroquinolizinium dichlorophosphate (XLV, X = $POCl_2$). This may be converted to the perchlorate (XLV, X = ClO_4) with perchloric acid. The same authors have also found that the chlorine atom in (XLV, X = $POCl_2$) is replaced by piperidine to give 4-piperidinoquinolizinium dichlorophosphate (XLVI) in poor yield.



PART I

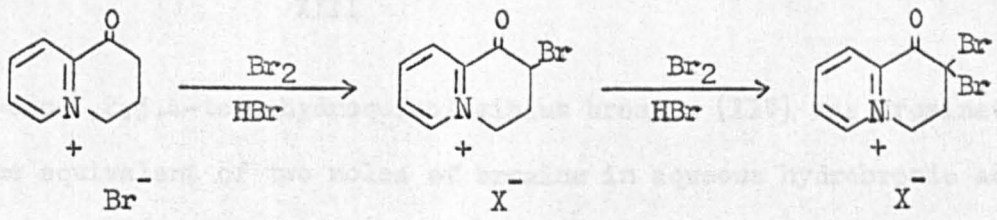
The Preparation and Properties of Hydroxyquinolizinium Salts

Discussion

Of the four possible mono-hydroxyquinolizinium salts the 2- and 4-isomers should be abnormal, the more stable form being an "amide" type tautomer. 1- and 3-hydroxy-salts should behave as normal phenols like the 3- and 5-hydroxypyridines. The chemistry of 4-hydroxyquinolizinium derivatives has been investigated and as expected reveals a certain amide character.[24,33,34] 3-Hydroxyquinolizinium salts have recently been prepared but their properties have not yet been investigated. This section describes the preparation of 1- and 2- hydroxyquinolizinium salts and gives an account of their properties. The synthesis of 1,2-dihydroxy salts is also recorded.

a) The bromination of 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XIV)

The tetrahydro-ketone (XIV), prepared by the method of Glover and Jones,[12] was brominated in concentrated hydrobromic acid to give 2-bromo-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XLVII, X = Br), a pale yellow salt, in 90% yield.

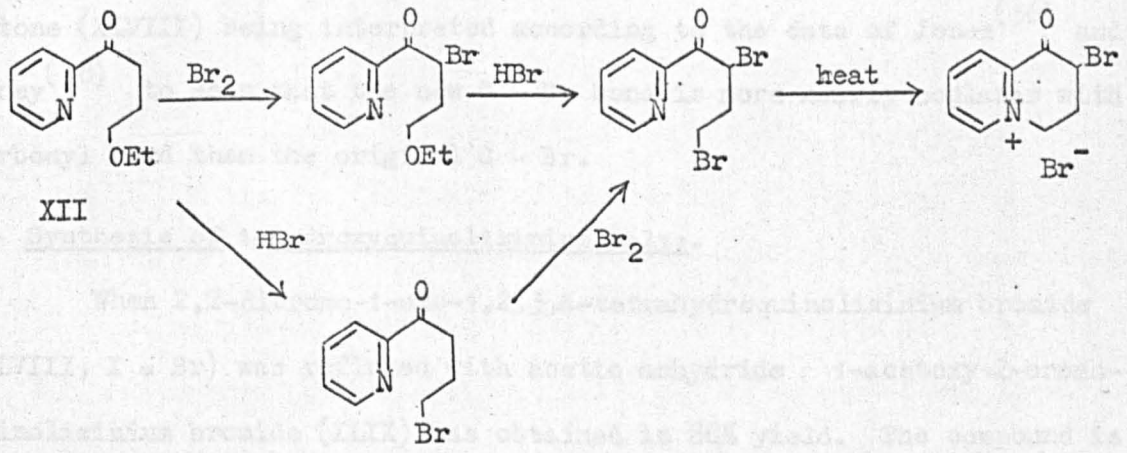


XIV XLVII XLVIII

Although by analogy with 1-tetralone,[35] bromination would be expected to give the 2-bromo derivative, the carbonyl stretching frequency of the

brominated ketone differed very little from that of the starting material. As halogenation in the 2-position relative to a carbonyl often produces a large shift of carbonyl absorption,[36] substitution at position 4 could not be excluded.

In order to confirm that the compound was in fact the 2-bromo derivative, the uncyclised ketone (XII) was brominated before and after conversion to the bromo ketone (XIII). Under these conditions bromination would occur in the position adjacent to the carbonyl group. Subsequent cyclisation in both cases gave compound (XLVII, X = Br).



When 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XIV) was brominated with the equivalent of two moles of bromine in aqueous hydrobromic acid, a dibromo ketone (XLVIII, X = Br) was formed in 90% yield. The carbonyl stretching frequency of this compound differed appreciably (20 $cm.^{-1}$) from that of the tetrahydro ketone. Again by analogy with 1-tetralone[37] the 2,2-dibromo compound is indicated and this was confirmed by a comparison

of the nuclear magnetic resonance spectra of the mono (XLVII) and dibromo (XLVIII) ketones. Both spectra showed a triplet centred at 5.1 τ (relative to tetra-methyl silane) assigned to the two protons at position 4. The mono-bromo ketone (XLVII) had a broad quartet centred at 7.1 τ assigned to the two protons at position 3. In the dibromo ketone (XLVIII) these appear as a triplet centred at 6.65 τ , the additional chemical shift being due to the extra bromine atom on the adjacent carbon 2.

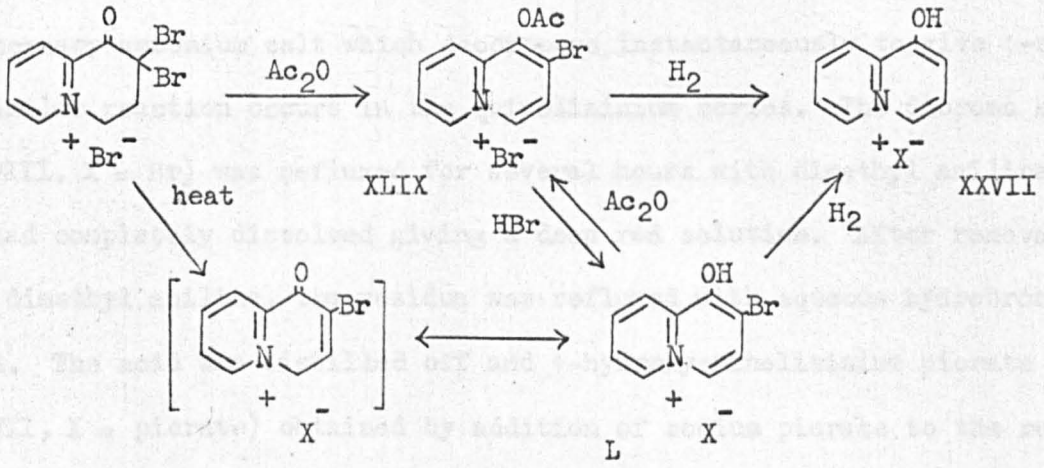
The positions of the carbonyl stretching absorptions may be explained by assuming that the first bromine atom substitutes the 2-position quasi-axially. The significantly larger shift observed for the dibromo ketone (XLVIII) being interpreted according to the data of Jones[36] and Corey[38] to mean that the new C - Br bond is more nearly coplanar with the carbonyl bond than the original C - Br.

b) Synthesis of 1-hydroxyquinolizinium salts.

When 2,2-dibromo-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XLVIII, X = Br) was refluxed with acetic anhydride 1-acetoxy-2-bromo-quinolizinium bromide (XLIX) was obtained in 86% yield. The compound is notable for its unusually high carbonyl stretching frequency in the infrared (1785 cm.$^{-1}$).

Catalytic hydrogenation of this compound (XLIX) would be expected to yield the 1-acetoxy salt. When hydrogenation was carried out in an ethanolic solution using 10% palladium on charcoal catalyst, an uptake of one mole equivalent of hydrogen was noted. However, the product isolated was the monohydrate of 1-hydroxyquinolizinium bromide (XXVII, X = Br), hydrolysis of the acetyl group having occured. The yield was 86%. The anhydrous

picrate (XXVII, X = picrate) could be obtained by addition of aqueous sodium picrate to an aqueous solution of the bromide.

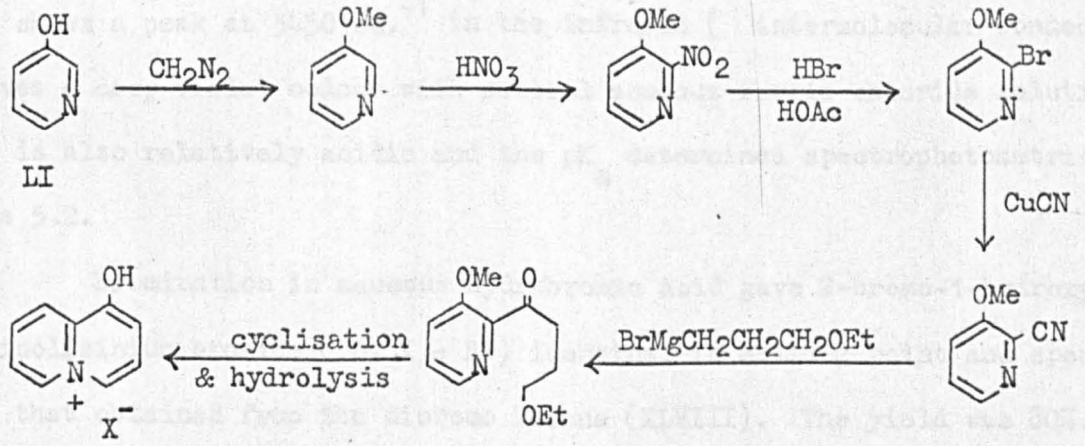


When the dibromo ketone (XLVIII, X = Br) was refluxed with 50% aqueous hydrobromic acid a bromo-hydroxyquinolizinium bromide (L, X = Br) was isolated in 70% yield. Treatment of the acetoxy compound (XLIX, X = Br) with aqueous hydrobromic acid gave an identical product. The same compound (L, X = Br) was later found to be formed in quantitative yield by heating the dibromo ketone (XLVIII, X = Br) at 150-160°C, copious fumes of hydrogen bromide being evolved. The bromo-hydroxy compound is thus 1-hydroxy-2-bromoquinolizinium bromide (L, X = Br), the reaction proceeding via the removal of a molecule of hydrogen bromide from the dibromo ketone (XLVIII, X = Br) followed by immediate enolisation to the hydroxy-bromo compound (L, X = Br). Catalytic reduction of (L, X = Br) gave again 1-hydroxyquinolizinium bromide (XXVII, X = Br) in 86% yield. By this reaction an overall yield of 75% was obtained based on the tetrahydro ketone (XIV).

The hydroxy compound (XXVII, X = picrate) could also be obtained

directly from the dibromo ketone (XLVIII, X = Br). Krollpfeiffer and Muller[40] report that 2,2-dibromo-1-tetralone forms 1-naphthol when refluxed with dimethyl aniline. The reaction involves the formation of a quaternary ammonium salt which decomposes instantaneously to give 1-naphthol. A similar reaction occurs in the quinolizinium series. The dibromo ketone (XLVIII, X = Br) was refluxed for several hours with dimethyl aniline until it had completely dissolved giving a deep red solution. After removal of the dimethyl aniline, the residue was refluxed with aqueous hydrobromic acid. The acid was distilled off and 1-hydroxyquinolizinium picrate (XXVII, X = picrate) obtained by addition of sodium picrate to the residue dissolved in water. The salt was identified by analysis, ultraviolet spectrum and a mixed melting point with an authentic specimen of 1-hydroxyquinolizinium picrate.

In one early unsuccessful attempt to prepare 1-hydroxyquinolizinium salts it was intended to carry out the following scheme of reactions.



3-Hydroxypyridine (LI) was converted to the 3-methoxy compound by methylation as described by Prins.[41] Nitration according to the method of Bernstein

et al[42] gave 3-methoxy-2-nitropyridine in good yield. This was heated in a sealed tube with a saturated solution of hydrogen bromide in glacial acetic acid to give 2-bromo-3-methoxypyridine in 25% yield. In the next stage, a Rosemund-Von Braun nitrile conversion to the 2-cyano derivative, an extremely vigorous reaction occured, the reactants charring before any of the nitrile could be distilled. As no more of the 2-bromo-3-methoxypyridine was available the reaction was not repeated.

c) The properties of 1-hydroxyquinolizinium bromide (XXVII, X = Br)

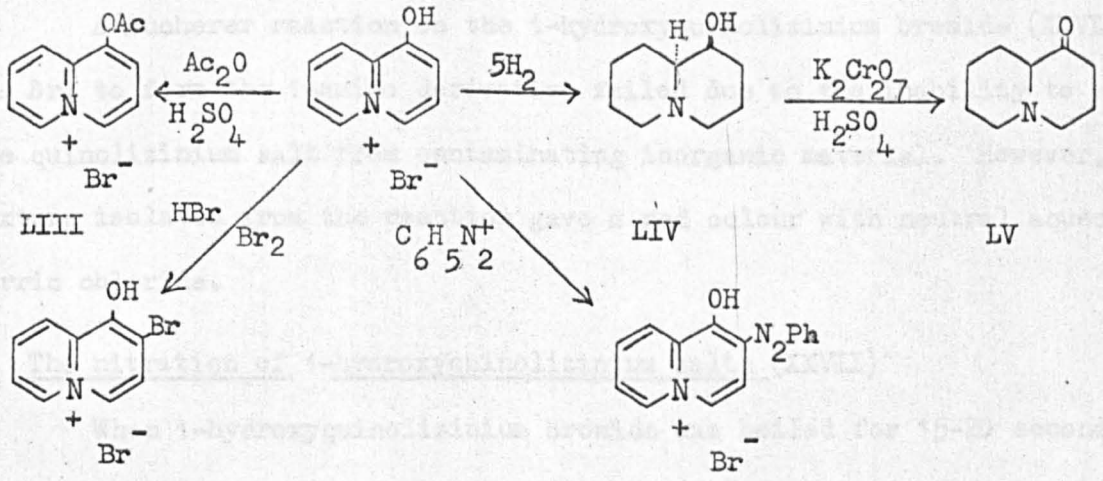
Although the quinolizinium ion is a π-deficient system, the hydroxyl group is a fairly strong electron donor and would be expected to modify the resistance of the quinolizinium system to electrophilic attack. In order to compare the properties of 1-hydroxyquinolizinium salts and phenolic hydroxy compounds of other π-deficient nitrogen heterocyclic systems, a range of reactions characteristic of phenols has been carried out.

1-Hydroxyquinolizinium bromide (XXVII, X = Br) is a colourless solid. It shows a peak at 3450 $cm.^{-1}$ in the infrared (intermolecular bonded OH) and gives a deep violet colour with neutral aqueous ferric chloride solution. It is also relatively acidic and the pK_a determined spectrophotometrically was 5.2.

Bromination in aqueous hydrobromic acid gave 2-bromo-1-hydroxy-quinolizinium bromide (L, X = Br) identical in melting point and spectra to that obtained from the dibromo ketone (XLVIII). The yield was 80%. The ready substitution is surprising in view of the positive charge carried by the ring system. The phenol (XXVII, X = Br) also coupled with diazotised

aniline, presumably in the 2-position, to give a deep red azo dye (LII). Unfortunately no suitable solvent was found for recrystallisation and no analysis of the dye was obtained. Nitration was abnormal and a number of complex products were obtained. A full description of these appears in the next section.

1-Hydroxyquinolizinium bromide (XXVII, X = Br) was readily acetylated with acetic anhydride to which a drop of sulphuric acid had been added, giving 1-acetoxyquinolizinium bromide (LIII). The infrared spectrum of this compound, like that of the acetoxy-bromo compound (XLIX), was characterised by a high carbonyl absorption frequency (1785 cm.$^{-1}$).



On catalytic hydrogenation using Adams' platinum oxide catalyst, 1-hydroxyquinolizinium bromide (XXVII, X = Br) was reduced to 1-hydroxyquinolizidine (LIV). The quinolizidine (LIV) was very soluble in aqueous media and as isolation required basification by aqueous sodium carbonate, the yield after purification was comparatively low (33%), although the theoretical amount of hydrogen had been absorbed. The melting point, 78°C, corresponded

with one of the isomers of 1-hydroxyquinolizidine obtained by Swan.[43]

Attempts to oxidise the quinolizidine (LIV) to 1-quinolizidone (XLV) proved difficult. Several methods were tried; oxidation by chromium trioxide in glacial acetic acid, by Jones reagent, by chromic acid, etc. The most successful was that using chromic acid. Even so, it was necessary to repeat the oxidation several times until the appearance of a strong carbonyl stretching in the infrared showed the reaction to be substantially complete. The picrate (LV) obtained from the oxidation product by addition of ethanolic picric acid proved to be impure and its melting point could not, therefore, be compared with that of authentic 1-quinolizidone picrate.

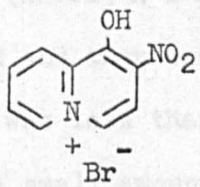
A Bucherer reaction on the 1-hydroxyquinolizinium bromide (XXVII, X = Br) to form the 1-amino derivative failed due to the inability to separate the quinolizinium salt from contaminating inorganic material. However, the mixture isolated from the reaction gave a red colour with neutral aqueous ferric chloride.

d) The nitration of 1-hydroxyquinolizinium salts (XXVII)

When 1-hydroxyquinolizinium bromide was boiled for 15-20 seconds with 7% aqueous nitric acid and then immediately cooled in ice cold water, a bright red insoluble compound melting at 234°C was obtained. This compound will be referred to as NI. If the nitric acid solution was boiled for a longer period (3-5 mins) an orange compound (NII) was formed. The infrared spectra of the two compounds were very similar. Both compounds were rather insoluble in polar solvents and completely insoluble in the usual non-polar solvents. However, by using large quantities of solvent NI was successfully

recrystallised from 80% ethanol and NII from acetone.

The analysis of NI corresponded roughly with the expected 2-nitro-1-hydroxyquinolizinium bromide (LVI) but with a hydrogen content 1% below that required.



LVI

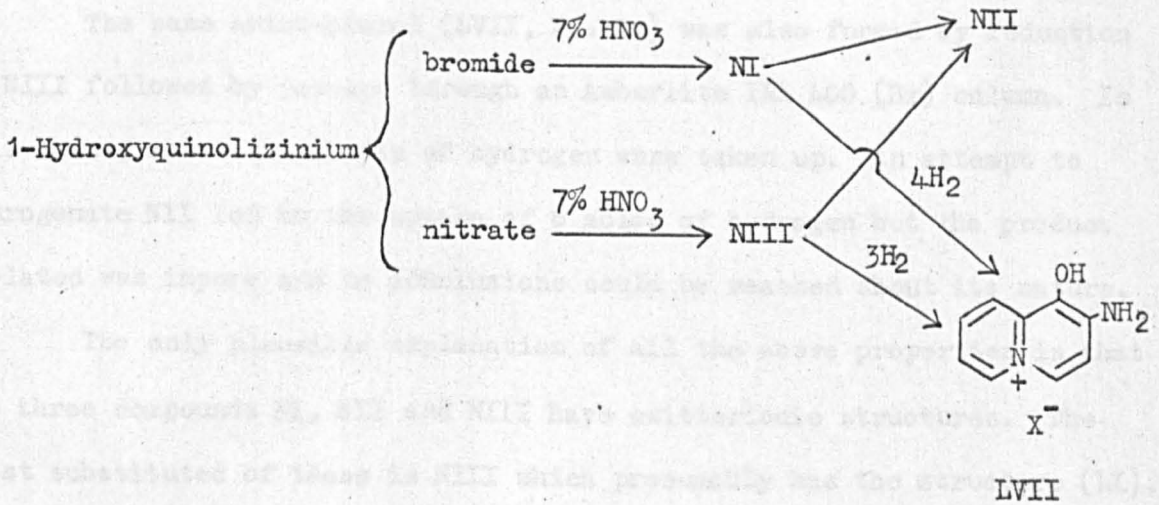
Significantly, NI gave no precipitate with a solution of silver nitrate in dilute nitric acid indicating the absence of ionic bromide. The compound did however give a very positive Beilstein test indicating that halogen was present and an approximate quantitative measurement gave the bromine content as 29%. The infrared spectrum of NI showed no trace of hydroxyl stretching but showed strong peaks at 1580 $cm.^{-1}$ and 1330 $cm.^{-1}$ attributed to a nitro group.[44] The ultraviolet absorption spectrum had a strong absorption at 4570 Å which suggested that a high degree of resonance was occuring.

Difficulty was experienced in obtaining a nuclear magnetic resonance spectrum of NI due to its insolubility in normal solvents. A saturated solution in sulphur dioxide was eventually used and the spectrum showed the presence of aromatic protons only. These appeared as a complex multiplet centred at 1.7 τ .

In an attempt to prepare an analogue of NI without any halogen

present, 1-hydroxyquinolizinium bromide (XXVII, X = Br) was converted to the nitrate (XXVII, X = NO_3). This was achieved by adding an equivalent amount of silver nitrate to an aqueous solution of the bromide (XXVII, X = Br), filtering off the silver bromide and evaporating the filtrate.

When the nitrate (XXVII, X = NO_3) was boiled for approximately 15 seconds in 7% nitric acid and then cooled, a third nitration product (NIII) was isolated. The yield was less than that of NI and the compound appeared to be contaminated with a small amount of NII. On further heating in dilute nitric acid both NI and NIII formed NII.



LVII

Although it was difficult to get an analytically pure specimen of NIII analysis gave the empirical formula $C_9H_6N_2O_3$. NII analysed exactly to $C_9H_5N_3O_5$.

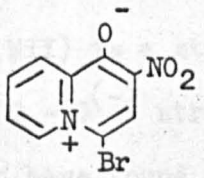
When a solution of NI in 80% aqueous ethanol was hydrogenated using a 10% palladium on charcoal catalyst, 3 molar equivalents of hydrogen were quickly absorbed and then a fourth much more slowly. Isolation of the product gave a yellow compound m.p. 181° which analysed as an aminohydroxy-

quinolizinium bromide (LVII, X = Br). This compound (LVII, X = Br) gave a jade green colour with aqueous ferric chloride solution and could be diazotised and coupled with alkaline 2-naphthol to give a violet coloured azo dye. The infrared spectrum was compatible with that of a primary amine. With aqueous cupric acetate the amino-phenol (LVII, X = Br) gave a deep red-brown colour which was attributed to complexing of adjacent amino and hydroxyl groups with a copper atom. With silver nitrate in dilute nitric acid a precipitate of silver bromide formed indicating the presence of ionic bromide. The compound (LVII, X = Br) was thus assigned the structure (LVII, X = Br), i.e. 2-amino-1-hydroxyquinolizinium bromide.

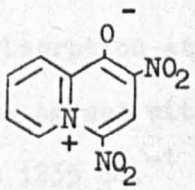
The same amino-phenol (LVII, X = Br) was also formed by reduction of NIII followed by passage through an Amberlite IRA 400 (Br) column. In this case 3 mole equivalents of hydrogen were taken up. An attempt to hydrogenate NII led to the uptake of 6 moles of hydrogen but the product isolated was impure and no conclusions could be reached about its nature.

The only plausible explanation of all the above properties is that the three compounds NI, NII and NIII have zwitterionic structures. The least substituted of these is NIII which presumably has the structure (LX). The nitro group would appear to be in the 2-position because of complexing of the amino-phenol (LVII, X = Br) with cupric acetate. ~~The~~ NI in addition has a bromine substituted in the ring and in (LVIII) it is shown in the 4 position. This is probable because the 4 position which is adjacent to the positively charged nitrogen atom would be expected to undergo nucleophilic substitution (e.g. with Br^-) fairly easily. NII which analyses

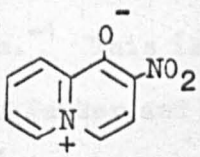
as a dinitro compound is represented by structure (LIX).



LVIII

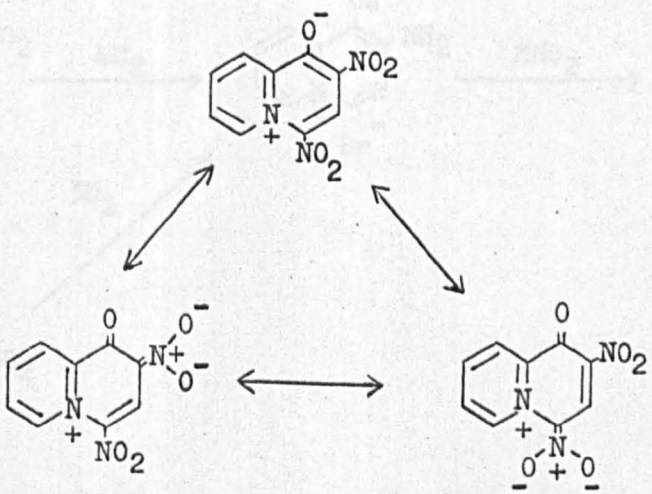


LIX



LX

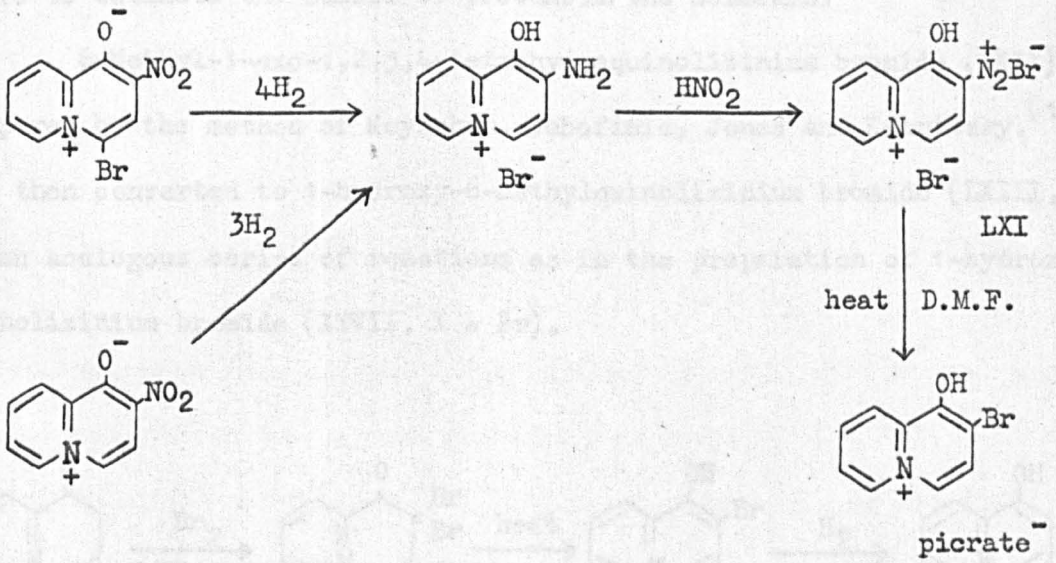
Obviously resonance can occur between the various tautomeric forms as is shown in the case of NII (LIX).



Although NI, NII and NIII all have similar infrared spectra that of NII differs in that it has a strong absorption at 1655 cm.$^{-1}$ typical of a carbonyl stretching. This can be explained if the phenolate form makes only

a minor contribution to the resonance hybrid and it is significant that NII absorbs at a lower wavelength than NI in the visible region of the spectrum. Common to all three infrared spectra (though to a lesser extent to NII) is a strong broad absorption at 1260-1265 cm.$^{-1}$ This is attributed to C - O$^{(-)}$ stretching which agrees with the work of Parker and Kirschenbaum[39] who have found a shift from 1235 cm.$^{-1}$ to 1262 cm.$^{-1}$ for the C - O stretching absorption in phenol and the phenolate ion.

The position of the nitro group in NI (LVIII) and NIII (LX) and presumably one of the groups in NII (LIX) was confirmed by their conversion into 1-hydroxy-2-bromoquinolizinium picrate (L, X = picrate) the preparation of which has been described previously. The reaction sequence is given below.

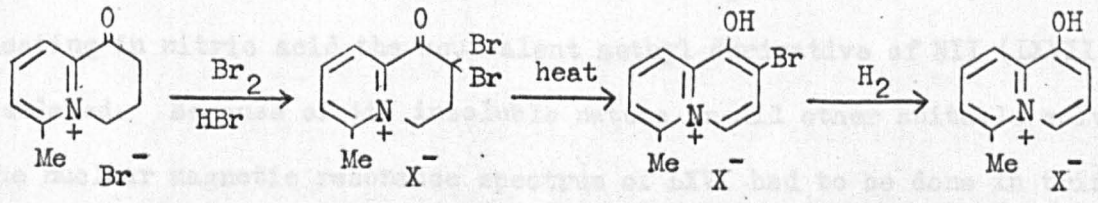


NI (LVIII) was reduced catalytically to 2-amino-1-hydroxyquinolizinium bromide (LVII, X = Br). Diazotisation of this in aqueous solution at -8°C

gave an orange precipitate of 1-hydroxyquinolizinium-2-diazonium dibromide (LXI) which was filtered off and dried. This compound was relatively stable at room temperature and its infrared spectrum showed a doublet at 2120 $cm.^{-1}$ ($N \equiv N^{+}$). It gave a violet azo dye when added to a solution of 2-naphthol. Finally, by heating in pure dry dimethyl formamide, a technique which is described in greater detail in the next part of this thesis (p. 77) 1-hydroxy-2-bromoquinolizinium picrate (L, X = picrate) was obtained. This was identified by its infrared spectrum and a mixed melting point with an authentic specimen.

As the N.M.R. spectrum gave little help in evaluating the number of protons in NI, it was decided to prepare a methyl homologue. The three protons incorporated could thus be used as a standard in the integration curve to estimate the number of protons in the molecule.

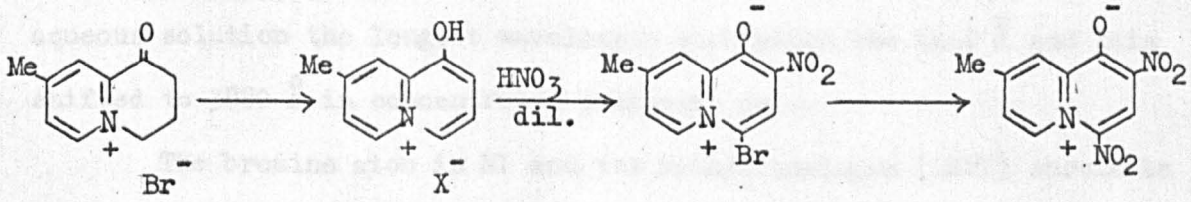
6-Methyl-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (LXII) was prepared by the method of Moynehan, Schofield, Jones and Katritzky.[16] It was then converted to 1-hydroxy-6-methylquinolizinium bromide (LXIII, X = Br) by an analogous series of reactions as in the preparation of 1-hydroxyquinolizinium bromide (XXVII, X = Br).



LXII LXIII

However, treatment of the 1-hydroxy-6-methyl compound (LXIII, X = Br) with nitric acid in the standard manner failed to give any of the expected product. This indirectly gives confirmation of the 4-bromo substituent in NI since it seems probable that the methyl in position 6 sterically hinders the attack of the bromide ion on position 4.

A further attempt to make a homologue of NI was made using 1-hydroxy-8-methylquinolizinium bromide (LXV, X = Br) which had been prepared from 8-methyl-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (LXIV) by the same sequence of reactions as the 6-methyl compound (LXIII). The tetrahydro ketone (LXIV) was again prepared by the method of Moynehan et al.[16]



LXIV LXV LXVI LXVII

1-Hydroxy-8-methylquinolizinium bromide (LXV, X = Br) as expected when treated with dilute nitric acid formed a homologue of NI (LXVI). On further heating in nitric acid the equivalent methyl derivative of NII (LXVII) was isolated. Because of its insoluble nature in all other suitable solvents the nuclear magnetic resonance spectrum of LXVI had to be done in trifluoracetic acid solution. A small amount of the dinitro compound (XLVII) was probably present in the sample since not all the solid dissolved in the

solvent.

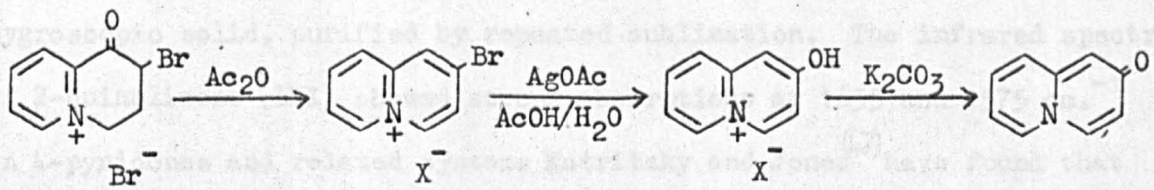
The spectrum showed an unsplit aromatic methyl peak at 7.08 τ and a complex multiplet centred at 1.25 τ due to the aromatic protons. A high resolution spectrum of this multiplet showed a strong single peak at 1.25 τ which presumably was due to the isolated proton on C 3. It was also possible to assign (though not definitely) the remaining peaks to the other protons in the molecule. However, from the integration curve the ratio methyl:aromatic protons was 3:5 whereas the molecule as depicted (LXVI) should only have 4 aromatic protons. This extra proton must be due to protonation of the molecule in the acid solution. Confirmation that protonation does occur is given by the considerable difference of ultra-violet spectrum of the compound (LXVI) in neutral and acid solution. In aqueous solution the longest wavelength absorption was 4440 Å and this shifted to 3880 Å in concentrated sulphuric acid.

The bromine atom in NI and its methyl analogue (LXVI) should be fairly easily replaced by nucleophilic reagents. Reactions to this end have been attempted but have been unsuccessful. In a reaction with silver acetate in glacial acetic acid, NI was recovered unchanged. However, with phenyl hydrazine, reduction occured and only the amino-hydroxy compound (LVII) was isolated.

e) Synthesis and properties of 2-hydroxyquinolizinium bromide (LXIX, X = Br).

The mono-bromo ketone (XLVII) when boiled with acetic anhydride gave 2-bromoquinolizinium bromide (LXVIII, X = Br) in 75% yield. As halogen atoms in the 2- and 4-positions of pyridine are very prone to nucleophilic replacement it would be expected that halogens

in the equivalent positions in a quinolizinium salt might also be replaced. An attempt was therefore made to replace the bromine atom in the 2-bromo-quinolizinium system (LXVIII) with a hydroxyl group.

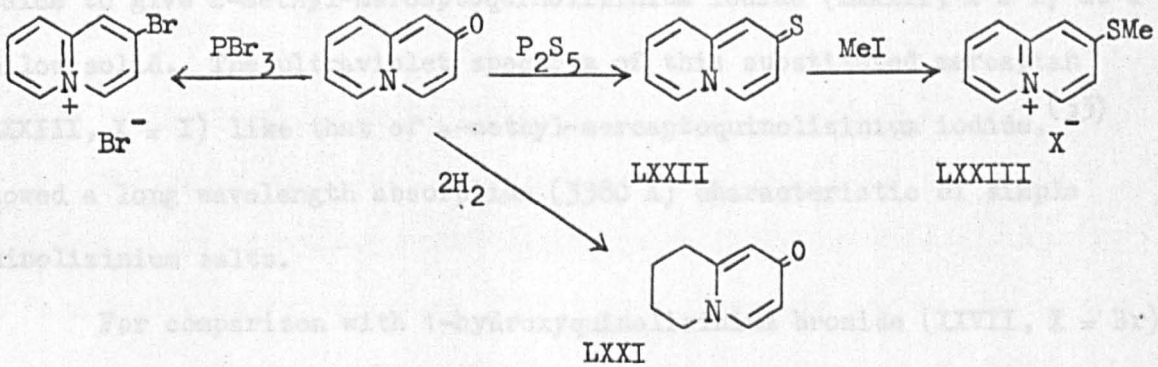


LXVIII LXIX LXX

2-Bromoquinolizinium bromide (LXVIII, X = Br) was boiled with an equivalent amount of silver acetate in acetic acid for 40 hrs., cooled, filtered and treated with acid. Working up gave 2-hydroxyquinolizinium bromide (LXIX, X = Br) in 90% yield. If the reaction time was shortened to 15 hrs. only approximately 50% conversion occured and the product was a mixture of the hydroxy and bromo derivatives. The bromine atom is thus less readily replaced than might be expected.

2-Hydroxyquinolizinium bromide (LXIX, X = Br) is a stable white solid unlike the equivalent 4-hydroxyquinolizinium salts. It gave a red colour with neutral aqueous ferric chloride and its infrared spectrum showed an absorption at 3350 $cm.^{-1}$ (hydrogen bonded OH). The pK_a was determined by a spectroscopic method to be approximately 4. The anhydrous picrate (LXIX, X = picrate) was obtained by addition of aqueous sodium picrate to the bromide (LXIX, X = Br).

The hydroxy compound (LXIX, X = Br) was easily converted to 2-quinolizone (LXX) by treatment with alkali. On adding the bromide to a saturated solution of potassium carbonate, effervesence occured and yellow oily droplets formed. The solution was extracted with chloroform and evaporation of the extracts gave 2-quinolizone (LXX), a yellow hygroscopic solid, purified by repeated sublimation. The infrared spectrum of 2-quinolizone (LXX) showed strong absorptions at 1635 and 1575 $cm.^{-1}$ In 4-pyridones and related systems Katritzky and Jones[47] have found that the lower of these two frequencies is due to carbonyl stretching, the higher value being due to ring stretching of the molecule. The low value of the carbonyl stretching is apparently due to the high contribution of single bond character in the link. Another absorption at 3350 $cm.^{-1}$ (hydrogen bonded OH) may have been due to the presence of water.

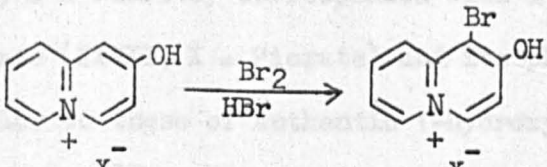


On heating with phosphorus tribromide 2-quinolizone (LXX) formed 2-bromo-quinolizinium bromide (LXVIII, X = Br). This was identified by its spectrum and melting point. The comparatively low yield (27%) from this reaction was probably due to the small scale of the experiment and the difficulty of working up. When 2-quinolizone (LXX) was catalytically reduced using

Adams' platinum oxide catalyst an uptake of only 2 mole equivalents of hydrogen was noted. The product (LXXI) had an infrared spectrum which showed a strong absorption at 1640 $cm.^{-1}$ (ring stretching) and another very strong absorption at 1550 $cm.^{-1}$ (C=O stretching). Both these peaks are characteristic of 4-pyridones and the reduction product is thus 6,7,8,9-tetrahydro-2-quinolizone (LXXI). The ultraviolet spectrum showed a single peak at 2620 Å shifting to 2390 Å in acid. This may be compared with N-methyl-4-pyridone which absorbs at 2600 Å shifting to 2370 Å on acidification.(48)

Treatment of 2-quinolizone with phosphorus pentasulphide gave a product which showed a thione (C = S) stretching in the infrared. This compound, 2-thioquinolizone (LXXII), could not be satisfactorily purified due to its hygroscopic nature. It was therefore treated with methyl iodide to give 2-methyl-mercaptoquinolizinium iodide (LXXIII, X = I) as a yellow solid. The ultraviolet spectrum of this substituted mercaptan (LXXIII, X = I) like that of 4-methyl-mercaptoquinolizinium iodide,(33) showed a long wavelength absorption (3380 Å) characteristic of simple quinolizinium salts.

For comparison with 1-hydroxyquinolizinium bromide (XXVII, X = Br), some electrophilic reactions were attempted on the 2-hydroxy isomer. Bromination of 2-hydroxyquinolizinium bromide (LXIX, X = Br) in hydrobromic acid gave 1-bromo-2-hydroxyquinolizinium bromide (LXXIV, X = Br) in high yield. The compound (LXXIV, X = Br) was identical to that obtained by another route which is described in Part II of this thesis.



LXXIV

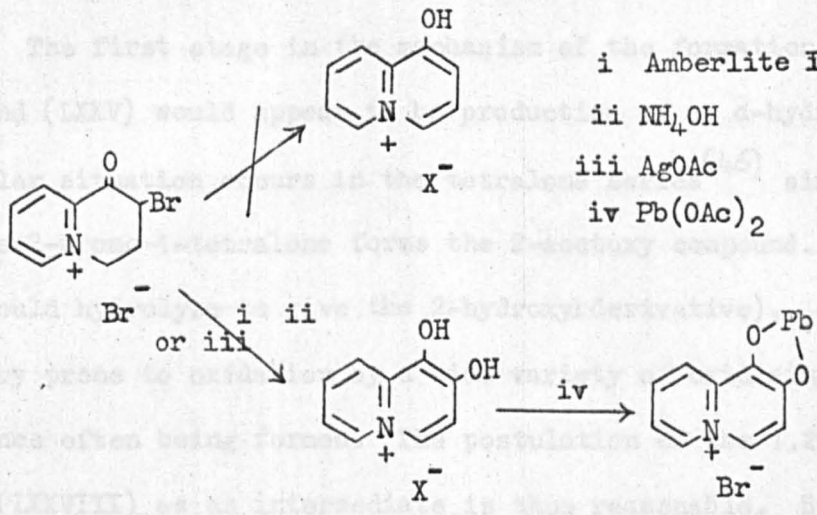
With dilute nitric acid the 2-hydroxy compound (LXIX, X = Br) unexpectedly gave a good yield of 1-bromo-2-hydroxyquinolizinium nitrate (LXXIV, X = NO_3). However, this is not an unknown situation as Finar and Millar[45] have reported that bromination can occur in high yields in the presence of nitric acid.

An attempt to introduce a cyano group into the 1-position by boiling 2-hydroxyquinolizinium bromide (LXIX, X = Br) in nitric acid containing an excess of cyanide failed and only 2-hydroxyquinolizinium nitrate (LXIX, X = NO_3) was recovered.

f) <u>The synthesis of 1,2-dihydroxyquinolizinium bromide</u> (LXXV, X = Br)

Dehydrobromination of the mono-bromo ketone (XLVII) would be expected to give 1-hydroxyquinolizinium salts (XXVII). Initial attempts to form the 1-hydroxy compound (XXVII) were therefore dehydrobromination reactions on the bromo ketone (XLVII, X = Br). Because of the difficulty of separating quinolizinium salts from contaminating inorganic materials, the base used was the strongly basic resin Amberlite IRA 400 (OH) in boiling methanol. The methanolic solution gave a deep jade green colour with neutral ferric chloride solution indicating the presence of a phenol. This was isolated as the picrate (LXXV, X = Picrate). The analysis of

this picrate (LXXV, X = Picrate) corresponded with a hydrate of 1-hydroxyquinolizinium picrate (XXVII, X = Picrate) and its physical characteristics were somewhat similar to these of authentic 1-hydroxyquinolizinium picrate obtained from the diazotisation of 1- aminoquinolizinium bromide (XXXVI, X = Br). However, the compound was subsequently shown to be 1,2-dihydroxyquinolizinium picrate (LXXV, X = Picrate). The same picrate (LXXV, X = Picrate) was obtained by treatment of the 2-bromo ketone (XLVII, X = Br) with hot aqueous ammonia. All attempts to convert this compound to the bromide (LXXV, X = Br) by ion exchange were unsuccessful, the picrate being recovered unchanged.



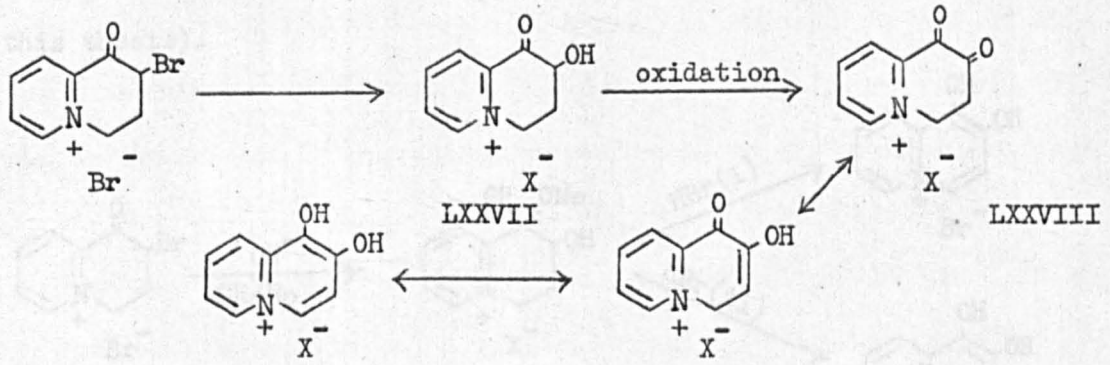
LXXV LXXVI

In another reaction the 2-bromo ketone (XLVII, X = Br) was treated with hot aqueous silver acetate. After passing the filtered solution through an Amberlite IRA 400 (Br) column, a deliquescent solid was isolated. This could be obtained in the anhydrous state by refluxing with acetic anhydride. The compound analysed as a dihydroxyquinolizinium salt, presumably

1,2-dihydroxy quinolizinium bromide (LXXV, X = Br). It gave a very deep jade green colour with neutral aqueous ferric chloride solution and its picrate (LXXV, X = Picrate) was found to be identical with the picrates obtained by treatment of the bromo ketone (XLVII, X = Br) with base. The ultraviolet spectrum of the dihydroxy compound (LXXV, X = Br) showed a long wavelength absorption (3250 Å) characteristic of the fully aromatic quinolizinium system.

Final proof of the structure of this compound (LXXV) was given by the precipitation of a lead salt (LXXVI) on addition of aqueous lead acetate to a solution of the bromide (LXXV, X = Br). This is characteristic of ortho dihydroxy phenols.

The first stage in the mechanism of the formation of the dihydroxy compound (LXXV) would appear to be production of an *a*-hydroxy ketone (LXXVII). A similar situation occurs in the tetralone series[46] since with sodium acetate 2-bromo-1-tetralone forms the 2-acetoxy compound. (In aqueous solution this would hydrolyse to give the 2-hydroxyl derivative). *a*-Hydroxy ketones are very prone to oxidation by a wide variety of oxidising agents, 1,2-diketones often being formed. The postulation of the 1,2-dicarbonyl compound (LXXVIII) as an intermediate is thus reasonable. Silver acetate is an oxidising agent but the oxidation in the case of the alkaline reactions is assumed to occur by atmospheric oxidation. The final stage will be enolisation followed by a 1 $\longrightarrow$ 4 proton shift.

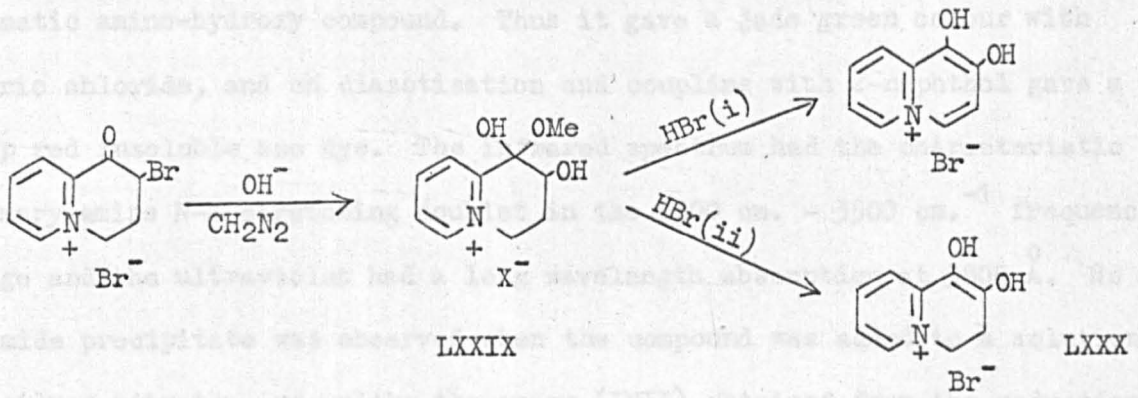


The possibility that dehydrobromination to the 1-hydroxy salt (XXVII) was the first stage, then followed by hydroxylation, was eliminated by treating 1-hydroxyquinolizinium bromide (XXVII, X = Br) with Amberlite IRA 400 (OH) in boiling methanol. 1-Hydroxyquinolizinium picrate (XXVII, X = picrate) was recovered.

In early attempts to obtain the dihydroxy bromide (LXXV, X = Br) the crude methanolic solution from the Amberlite reaction with the bromo ketone (XLVII) was methylated with diazomethane. A picrate analysing for $C_{16}H_{16}N_4O_{10}$ (LXXIX, X = picrate) was isolated in 20% yield and this could be converted to the bromide (LXXIX, X = Br) by passage through an Amberlite IRA 400 (Br) column. The bromide (LXXXIX, X = Br) had an ultra-violet spectrum with a single peak at 2630 Å resembling the spectra of tetrahydroquinolizinium salts. Its infrared spectrum showed a strong absorption at 1070 $cm.^{-1}$ which was interpreted to be the C-O stretching of an aliphatic ether.

Stevens, Beereboom and Rutherford[49] report that treatment of 2-bromo-1-tetralone with sodium methoxide gives an α-hydroxy ketal. It seems probable therefore that the product of methylation is an α-hydroxy-hemiketal (LXXIX), a conclusion which is supported by the formation of hemiketals in similar compounds in the pyrido-azepinium series (Part III

of this thesis).



LXXIX LXXX

When the hemiketal (LXXIX, X = Br) was heated with aqueous hydrobromic acid 1,2-dihydroxyquinolizinium bromide (LXXV, X = Br) was obtained, identical in melting point and spectra with a specimen from the silver acetate reaction. It is assumed here that the trace of bromine in the acid caused oxidation the mechanism otherwise being as before.

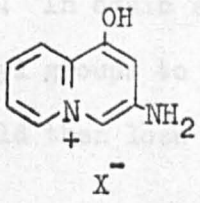
In one reaction with hydrobromic acid another product was isolated. This gave a jade green colour with ferric chloride solution but its ultraviolet spectra suggested that it was not a fully aromatic quinolizinium system. Its analysis was concordant with that of 1,2-dihydroxy-3,4-dihydroquinolizinium bromide (LXXX).

g) The reaction of 2,2-dibromo-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XLVIII, X = Br) with ammonia.

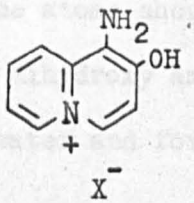
When concentrated aqueous ammonia was added to the dibromo ketone (XLVIII, X = Br), a vigorous exothermic reaction occured, the solution turning a deep brown colour. The ammonium bromide formed during the reaction was removed by passing the solution through an Amberlite IRA 400 (OH) column and boiling to expel the liberated ammonia. From the reaction mixture was

isolated a yellow compound m.p. 182°C which had characteristics of an aromatic amino-hydroxy compound. Thus it gave a jade green colour with ferric chloride, and on diazotisation and coupling with 2-naphthol gave a deep red insoluble azo dye. The infrared spectrum had the characteristic primary amine N-H stretching doublet in the 3300 cm. - 3500 $cm.^{-1}$ frequency range and the ultraviolet had a long wavelength absorption at 3800 Å. No bromide precipitate was observed when the compound was added to a solution of silver nitrate, and unlike the amine (LVII) obtained from the reduction of the nitro compound NI, it did not give any colour change with aqueous cupric acetate. The analysis coincided with that of an amino-hydroxyquinolizinium hydroxide.

On account of the properties listed above, it was first formulated as 3-amino-1-hydroxyquinolizinium hydroxide (LXXXI, X = OH). In fact this deduction was wrong and the compound should be written as 1-amino-2-hydroxyquinolizinium hydroxide (LXXXII, X = OH). The proof of this structure is given in Part II(b).



LXXXI

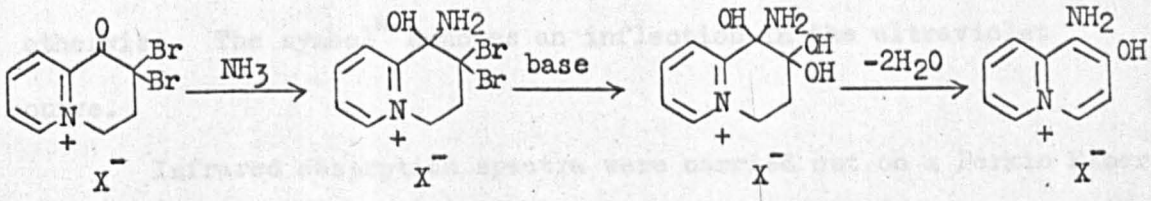


LXXXII

In order to establish whether 2-bromo-1-hydroxyquinolizinium salts (L) were intermediates in the reaction, 2-bromo-1-hydroxyquinolizinium bromide (L, X = Br) was treated with hot concentrated aqueous ammonia

solution. A yellow solid was immediately precipitated. However, spectroscopic and analytical evidence showed this to be 2-bromo-1-hydroxyquinolizinium hydroxide (L , X = OH).

A suggested mechanism which explains the formation of this aminophenol (LXXXII) is given below.



LXXXIIa LXXXIIb LXXXII

With ammonia the dibromoketone is assumed to form the amino carbinol (LXXXIIa). In basic solution the bromine atoms should easily be replaced by hydroxyl groups to give the unstable dihydroxy amino carbinol (LXXXIIb) which would then lose two molecules of water and form the amino phenol (LXXXII).

PART I

EXPERIMENTAL

All melting points were determined on a Kofler block. Ultraviolet absorption spectra were determined on a Unicam S.P. 700 automatic spectrophotometer and in aqueous solution unless indicated otherwise. The symbol ^{inf} denotes an inflection in the ultraviolet curve.

Infrared absorption spectra were carried out on a Perkin Elmer Infracord spectrophotometer.

The nuclear magnetic resonance spectra were determined on a Varian A 60 instrument at the National Institutes of Health, Maryland, U. S. A.

Micro analyses have been carried out by Drs. G. Weiler and F. B. Strauss, Oxford.

EXPERIMENTAL

1-Oxo-1,2,3,4-tetrahydroquinolizinium Bromide (XIV, X = Br)

This was prepared in 66% yield from 2-(4'ethoxybutyryl) pyridine by the method of Glover and Jones.[12]

2-Bromo-1-oxo-1,2,3,4-tetrahydroquinolizinium Bromide (XLVII, X = Br)

(a) To a vigorously stirred solution of 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XIV, X = Br) (8.0 g.) in 50% aqueous hydrobromic acid (50 ml.) was added a solution of bromine (5.8 g.) in hydrobromic acid (20 ml.). During the addition a yellow solid precipitated. Stirring was continued for 5 min. after the addition was complete, and the mixture was heated until all the solid had dissolved. Evaporation under reduced pressure gave a solid residue which was crystallised from absolute ethanol to give the bromo-ketone bromide (XLVII, X = Br) as pale yellow needles, m.p. 159-60°C (9.52 g., 89%).

Found: C, 35.7; H, 3.15; N, 4.4; Br, 51.7

$C_9H_9Br_2NO$ Requires: C, 35.25; H, 2.95; N, 4.55; Br, 52.05%

λ_{max} 2440, 2730, 3450 Å ($\log_{10} \varepsilon$ 3.64, 3.83, 3.21)

ν_{max} 1695 $cm.^{-1}$ (C=O stretching).

The picrate prepared by the addition of saturated methanolic picric acid to a methanolic solution of the bromide, recrystallised from methanol as yellow rhombs m.p. 153°C.

Found: C, 39.9; H, 2.5; N, 11.9

$C_{15}H_{11}BrN_4O_8$ Requires: C, 39.6; H, 2.4; N, 12.5%

(b) A solution of 2-(4'ethoxybutyryl) pyridine (1.9 g.) in chloroform (25 ml.) was treated with bromine (1.7 g.) in chloroform (25 ml.) and stood for 3 hr., then heated on a boiling water bath. After the chloroform had distilled off the residue was taken up in concentrated aqueous hydrobromic acid and boiled under reflux for 1 hr. Cyclisation as described by Glover and Jones[12] gave the bromo ketone bromide.

(c) A solution of the 2-(4'ethoxybutyryl) pyridine (4.5 g.) in concentrated hydrobromic acid was boiled under reflux for 0.5 hr. The solution was cooled, and bromine (4 g.) in concentrated hydrobromic acid (10 ml.) was added with stirring. The mixture was heated, evaporated to dryness and cyclised.

Specimens from (a) (b) and (c) were identical.

2,2-Dibromo-1-oxo-1,2,3,4-tetrahydroquinolizinium Bromide (XLVIII, X = Br)

To 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XIV, X = Br) (5.0 g.) in 50% aqueous hydrobromic acid (75 ml.) was added bromine (10 g.) in hydrobromic acid (20 ml.). Vigorous stirring was maintained for the addition and for 15 min. subsequently. The mixture was warmed until the precipitate dissolved and then evaporated to dryness under reduced pressure. The residual solid was treated with boiling ethanol and filtered to give the dibromo ketone bromide (XLVIII, X = Br), m.p. 236-7°C (7.63, 91%). A portion was recrystallised from absolute ethanol as yellow needles m.p. 236-7°C.

Found: C, 28.1; H, 2.1; N, 3.55; Br, 61.8

$C_8H_8Br_3NO$ requires: C, 28.0; H, 2.1; N, 3.6 ; Br, 62.1%

λ_{max} 2680 Å ($\log_{10} \varepsilon$ 3.78) ν_{max} 1720 cm.$^{-1}$

The Picrate (XLVIII, X = picrate) prepared by addition of saturated methanolic picric acid to a solution of the bromide in methanol was recrystallised from methanol as yellow rhombs m.p. 133°C (dec.).

Found: C, 34.3; H, 2.0; N, 11.0

$C_{15}H_{10}Br_2N_4O_6$ requires: C, 33.7; H, 1.9; N, 10.5%

1-Acetoxy-2-bromoquinolizinium Bromide (XLIX, X = Br)

A suspension of the dibromo ketone bromide (XLVIII, X = Br) (10.0 g.) in acetic anhydride (150 ml.) was boiled under reflux for 1.5 hr. Evaporation under reduced pressure gave a solid which was washed with ethyl acetate and then recrystallised from absolute ethanol:ethyl acetate to give 1-acetoxy-2-bromoquinolizinium bromide (XLIX, X = Br) as buff rhombs, m.p. 193-5 - 194°C (7.71 g., 86%).

Found: C, 38.2; H, 2.35; N, 3.8

$C_{11}H_9Br_2NO_2$ requires: C, 38.1; H, 2.6; N, 4.0%

λ_{max} 2130, 2330, 2930, 3210, 3360 Å ($\log_{10}\varepsilon$ 4.67, 4.62, 3.76, 4.32, 4.45).

ν_{max} 1785 $cm.^{-1}$ (C=O stretching) 1180 $cm.^{-1}$ (C-O stretching).

2-Bromo-1-hydroxyquinolizinium Bromide (L, X = Br).

(a) A solution of the dibromo ketone bromide (XLVIII, X = Br) (0.3 g.) in 50% hydrobromic acid (15 ml.) was boiled under reflux for 4 hrs. The solution was evaporated to dryness under reduced pressure and the residual solid suspended in a mixture of ethanol:ethyl acetate. Filtration gave 2-bromo-1-hydroxyquinolizinium bromide (L, X = Br), m.p. 226-229° (dec.) (0.271 g. 70%) which was recrystallised from absolute ethanol to give a buff microcrystalline solid m.p. 227.5 - 229.5°C (dec.).

Found: C, 35.4; H, 2.25; N, 4.1

$C_9H_7Br_2NO$ requires: C, 35.4; H, 2.3; N, 4.6%

$\lambda_{max.}$ 2160, 3830 Å ($\log_{10}\varepsilon$ 4.49, 4.09)

The picrate (L, X = picrate) crystallised from ethanol as yellow needles m.p. 176-176.5°C.

Found: C, 40.2; H, 2.2

$C_{15}H_9BrN_4O_7$ requires: C, 39.75; H, 2.0

(b) The dibromo-ketone bromide (XLVIII, X = Br) (5.00 g.) was heated at 150-160°C (oil bath) until the evolution of hydrogen bromide ceased. The product (3.95 g., 100%) was pure 2-bromo-1-hydroxyquinolizinium bromide m.p. 234°C. The spectra of the compound were identical to those produced in (a) and in the infrared it showed no carbonyl stretching.

(c) A solution of 1-acetoxy-2-bromoquinolizinium bromide (XLIX, X = Br) (0.3 g.) in 50% aqueous hydrobromic acid (10 ml.) was boiled under reflux for 1.5 hr. Evaporation to dryness was followed by solution of the residue in water and the solution was again evaporated. The residue after crystallisation from ethyl acetate:ethanol gave the bromide (0.15 g., 57%) identical to that produced in (a) and (b).

1-Hydroxyquinolizinium Salts (XXVII)

(a) 1-Acetoxy-2-bromoquinolizinium bromide (XLIX, X = Br) (7.0 g.) in 95% ethanol (100 ml.) with 10% palladium on charcoal catalyst (1 g.) was hydrogenated at atmospheric temperature and pressure, one mole of hydrogen being absorbed. The mixture was filtered and concentrated and on cooling gave 1-hydroxyquinolizinium bromide (XXVII, X = Br) as the monohydrate, m.p. 184-5°C (4.2 g., 86%) (colourless plates).

Found: C, 44.3; H, 4.1; N, 5.4

$C_9H_8BrNOH_2O$ requires: C, 44.3; H, 4.1; N, 5.7%

$\lambda_{max.}$ 2370, 3450 Å ($\log_{10}\varepsilon$ 4.15, 4.17) $\nu_{max.}$ 3350 $cm.^{-1}$ (OH stretching).

An aqueous solution gave a deep purple colour with neutral aqueous ferric chloride.

The picrate (XXVII, X = picrate), obtained by adding aqueous sodium picrate to a solution of the bromide, crystallised from ethanol as yellow needles m.p. 218-9°C (dec.).

Found: C, 48.3; H, 2.9

$C_{15}H_{10}N_4O_8$ requires: C, 48.15; H, 2.7%

λ_{max} 2370, 3460 Å ($\log_{10}\varepsilon$ 4.39, 4.40).

(b) A solution of 2-bromo-1-hydroxyquinolizinium bromide (L, X = Br) (0.95 g.) in 95% ethanol (50 ml.) was hydrogenated using 10% palladium on charcoal catalyst. One mole equivalent of hydrogen was absorbed. Isolation as described above gave 1-hydroxyquinolizinium bromide m.p. 183-5°C (0.65 g., 86%).

(c) The dibromo-ketone (XLVIII, X = Br) (2.0 g.) in dimethyl aniline (30 ml.) was refluxed for 4.5 hr. giving a deep red solution. The amine was distilled off under reduced pressure and the residue treated three times with water which was successively distilled off. The residue was dissolved in water and the remaining amine was removed by extraction from the aqueous solution with ether. The aqueous layer was evaporated to dryness under reduced pressure and 50% hydrobromic acid (20 ml.) added. After refluxing the mixture for 1.5 hr. the acid was removed by evaporation to dryness under reduced pressure. The residue was taken up in water and again evaporated to dryness. The residual solid was dissolved in methanol and the solution treated with decolourising charcoal. After filtering, the methanol was boiled off and the residue taken up in water. Treatment of

this solution with aqueous sodium picrate gave 1-hydroxyquinolizinium picrate (1.4 g.) recrystallised from acetone as yellow plates m.p. 221-3°C (dec.) identical to that produced previously.

Found: C, 48.55; H, 2.85; N, 14.85

Calculated for $C_{15}H_{10}N_4O_8$: C, 48.15; H, 2.7; N, 14.95%

3-Methoxy Pyridine was prepared from 3-hydroxypyridine by the method of Prins.(41)

3-Methoxy-2-Nitropyridine was prepared as described by Bernstein et al.(42) from 3-methoxy-pyridine. The yield was 81%.

2-Bromo-3-methoxypyridine

3-Methoxy-2-nitropyridine (5 g.) in a saturated solution of hydrogen bromide in glacial acetic acid (15 ml.) was put in a sealed tube and heated in a furnace at 125° for three hours. The resulting solution was evaporated to approximately a third bulk under reduced pressure and basified with 50% aqueous potassium hydroxide. The free amine was extracted with ether which was dried over sodium sulphate, filtered and distilled. 2-Bromo-3-methoxy-pyridine was collected at 130°/10 mm. (1.85 g., 30%). The hydrobromide was prepared by the addition of cold 50% aqueous hydrobromic acid to a portion of the bromide. Recrystallised from acetone as very small colourless needles m.p. 191°C.

Found: C, 26.5; H, 2.4; N, 5.75

$C_6H_7Br_2NO$ requires: C, 26.75; H, 2.6; N, 5.2%

Attempted preparation of 2-cyano-3-methoxypyridine

2-Bromo-3-methoxy-pyridine (5.5 g.) and cuprous cyanide (2.5 g.)

were heated until fusion occured. The apparatus was fitted up for reduced pressure distillation and the mixture again heated. A vigorous reaction occured, the solid mass charring before the nitrile could be distilled over.

Bromination of 1-hydroxyquinolizinium Bromide (XXVII, X = Br)

A solution of bromine (0.20 g.) in 50% aqueous hydrobromic acid (5 ml.) was added to a stirred solution of the 1-hydroxyquinolizinium bromide (XXVII, X = Br) (0.24 g.). A yellow solid separated but this dissolved on heating the mixture on a water bath. The solution was evaporated under reduced pressure, water added, and the solution again evaporated to give a solid. The solid was dissolved in absolute alcohol and precipitated with ethyl acetate, giving 2-bromo-1-hydroxyquinolizinium bromide (L, X = Br) m.p. 228°C (dec.) (0.245 g., 80%) identical with that obtained by the methods previously described.

1-Acetoxyquinolizinium Bromide (LIII, X = Br)

A solution of 1-hydroxyquinolizinium bromide (XXVII, X = Br) (0.30 g.) in acetic anhydride (10 ml.) with one drop of concentrated sulphuric acid was heated under reflux for 2.5 hr. The acetic anhydride was distilled off under reduced pressure, the residue dissolved in absolute alcohol and cleaned with decolourising charcoal. Precipitation with ethyl acetate gave 1-acetoxyquinolizinium bromide (LIII, X = Br) (0.12 g., 36%). Recrystallised from ethyl alcohol:ethyl acetate as colourless needles m.p. 185-7°C.

Found: C, 49.0; H, 3.9; N, 5.4

$C_{11}H_{10}NOBr$ requires: C, 49.25; H, 3.75; N, 5.2%

λ_{max} 2090, 2300, 2900, 3160, 3290 Å ($\log_{10} \varepsilon$ 4.54, 4.26, 3.56, 4.00, 4.20)

ν_{max} 1785 $cm.^{-1}$ (C=O), 1180 $cm.^{-1}$ (C-O).

Reaction of 1-hydroxyquinolizinium Bromide (XXVII, X = Br) and diazotised aniline.

A solution of diazotised aniline (0.100 g.) in dilute (3N) hydrochloric acid (4 ml.) was added to a solution of the phenol (0.105 g.) in 20% aqueous potassium hydroxide (3 ml.) A deep red solid was precipitated (0.097 g.).

Reduction of 1-hydroxyquinolizinium bromide (XXVII, X = Br).

A solution of 1-hydroxyquinolizinium bromide (XXVII, X = Br) (2.3 g.) in 95% ethanol (100 ml.) was hydrogenated using Adams' catalyst (75 mg.) at atmospheric temperature and pressure. Two mole equivalents of hydrogen were rapidly absorbed and a further three moles much more slowly. The mixture was filtered and evaporated to dryness. The residual solid (hydrobromide) was basified with an ice cold saturated solution of sodium carbonate and extracted with chloroform. The chloroform extracts were dried (K_2CO_3) and evaporated, the last traces of chloroform being removed by blowing a stream of air over the solution. The residue was sublimed giving 1-hydroxyquinolizidine (LIV) (0.47 g.) as a colourless solid m.p. 75-77°C. Repeated sublimation gave a m.p. 76-78°C. Swan[43] gives a m.p. of 80°C for the trans isomer of 1-hydroxyquinolizidine.

Found: C, 69.1; H, 10.7

Calculated for $C_9H_{17}NO$: C, 69.6; H, 11.0%

1-Ketoquinolizidine (LV)

1-Hydroxyquinolizidine (LIV) (0.45 g.) in ether (10 ml.) was added to a mixture of sodium dichromate (0.6 g.) and sulphuric acid (0.5 g.). After the initial vigorous reaction the ether was evaporated and the residual mixture heated on a boiling water bath for 30 min.

On basification with saturated aqueous sodium carbonate and extraction with chloroform a product was obtained which showed strong absorption in the -OH stretching region of the infrared (3450 $cm.^{-1}$). This was reoxidised for periods of 2 and 3 hours until the appearance of a strong carbonyl stretching absorption at 1730 $cm.^{-1}$ showed the oxidation to be substantially complete. The isolated material after basification and extraction with chloroform was distilled on to a cold finger condenser. 1-Ketoquinolizidine was a colourless liquid which rapidly turned brown in air. A portion with saturated methanolic picric acid gave an impure picrate.

Bücherer reaction on 1-hydroxyquinolizinium Bromide

To the phenol (0.500 g.) in an unsealed Carius tube was added a solution of ammonia (s.g. 0.88) (5 ml.) in which sulphur dioxide (0.5 g.) had been dissolved. The tube was then sealed and heated at 180° for 20 hrs. The resulting solution was evaporated to dryness under reduced pressure, water added and evaporated again to dryness. After dissolving the resultant solid in water the solution was passed through an Amberlite IRA 400 (OH) column. The ammonia liberated was removed by evaporation, the solution then being taken to dryness. The residue was taken up in ethanol and passed through an Amberlite IRA 400 (Br) column. Evaporation of the

effluent gave a solid consisting mainly of inorganic material which gave a red colour with neutral aqueous ferric chloride.

1-Hydroxyquinolizinium nitrate (XXVII, X = NO_3)

1-Hydroxyquinolizinium bromide (XVII, X = Br) (0.500 g.) dissolved in water was treated with silver nitrate (0.360 g.) in water (5 ml.). The silver bromide was filtered off and the filtrate evaporated to dryness under reduced pressure. The white solid residue remaining was suspended in an ethanol:ethyl acetate solution and filtered. 1-Hydroxyquinolizinium nitrate (XVII, X = NO_3) was a white solid purified from ethanol:ethyl acetate as a white amorphous solid m.p. 170-1°.

The nitrate (XXVII, X = NO_3) gave a red colour with neutral ferric chloride solution and its infrared spectrum showed a strong broad absorption at 1400-1260 cm.$^{-1}$ (NO_3^-).

Found: C, 52.05; H, 3.9

$C_9H_8N_2O_4$ requires: C, 51.9; H, 3.85%

Nitration of 1-hydroxyquinolizinium bromide (XXVII, X = Br)

1) The phenol (1.00 g.) was dissolved in 7% aqueous nitric acid (20 ml.) and the solution boiled for 15-20 seconds. The hot solution was cooled in ice cold water and a red solid NI (LVIII) precipitated. This was filtered off and washed with water (0.625 g., 57%) m.p. 232° (dec.). Recrystallised from 80% aqueous ethanol as small red needles m.p. 234° (dec.).

Found: C, 40.25; H, 2.2; N, 10.3

$C_9H_5BrN_2O_3$ requires: C, 40.15; H, 1.9; N, 10.4%

λ_{max} 2070, 2680, 3230, 4570 Å ($\log_{10}\varepsilon$ 4.55, 4.33, 3.86, 4.48).

ν_{max} 1580, 1330 (NO_2) 1260 (C-O$^-$).

2)a The phenol (0.50 g.) was dissolved in 10% nitric acid (10 ml.) and boiled under reflux for 5 mins. On cooling in ice a yellow crystalline solid was obtained (0.086 g., 18%). The compound, NII (LIX), was recrystallised from acetone as pale orange rhombs m.p. 292° (dec.).

Found: C, 45.95; H, 2.15; N, 17.55

$C_9H_5N_3O_5$ requires: C, 45.95; H, 2.1; N, 17.85%

λ_{max} 2080, 2540, 4200 Å ($\log_{10} \varepsilon$ 4.25, 3.98, 4.33).

ν_{max} 1655 cm.$^{-1}$ (C=O) 1585, 1385 cm.$^{-1}$ (NO_2) 1255 (C-O$^-$).

2)b 1-Hydroxyquinolizinium Bromide (0.45 g.) was suspended in acetic anhydride (10 ml.) at 0°C. A solution containing concentrated nitric acid (s.g. 1.43) (1.5 ml.), glacial acetic acid (3.5 ml.) and acetic anhydride (5 ml.) was added to the stirred suspension over 20 mins. During the addition the phenol dissolved giving an orange solution and towards the end of the addition a yellow solid precipitated. This was filtered off and washed with ether giving 0.045 g. of NII (LIX) m.p. 292°C.

Nitration of 1-hydroxyquinolizinium nitrate (XXVII, X = NO_3)

The phenol nitrate (XXVII, X = NO_3) (0.25 g.) in 7% nitric acid (5 ml.) was boiled for 15 seconds and immediately cooled in ice water. The deep orange coloured crystals of NIII (LX) which formed were filtered and washed with water. (0.070 g. 31%). Recrystallisation from 80% aqueous ethanol gave orange rhombs which charred at temperatures greater than 300°C. but did not melt under 340°.

Found: C, 56.15; H, 2.85; N, 14.8

$C_9H_6N_2O_3$ requires: C, 56.85; H, 3.2; N, 14.7%

λ_{max} 2120, 2290, 2570, 4290 Å ($\log_{10}\varepsilon$ 4.21, 4.10, 4.03, 4.24)

ν_{max} 1575 cm.$^{-1}$ (NO_2) 1260 cm.$^{-1}$ (C-O$^-$).

2-Amino-1-Hydroxyquinolizinium Bromide (LVII, X = Br)

(a) The nitration product NI (LVIII) (0.75 g.) was dissolved in 80% aqueous ethanol (200 ml.) and hydrogenated using 10% palladium on charcoal catalyst (0.75 g.). The solution quickly took up three mole equivalents of hydrogen and then a fourth much more slowly. The solution was filtered and evaporated leaving an oily residue. Trituration with acetone gave 2-amino-1-hydroxyquinolizinium bromide (LVII, X = Br) as a yellow solid which was then filtered. (0.515 g., 77%). Recrystallisation from absolute ethanol:ethyl acetate gave a m.p. 180-1°C.

Found: C, 44.45; H, 3.9; N, 11.1

$C_9H_9BrN_2O$ requires: C, 44.8; H, 3.75; N, 11.6%

λ_{max} 2160, 2345, 3230, 3570 Å ($\log_{10}\varepsilon$ 4.30, 4.25, 3.88, 3.89)

The compound (LVII, X = Br) gave a jade green colour with neutral aqueous ferric chloride. With aqueous cuprous acetate a deep red-brown colour was obtained. Diazotisation of an aqueous solution of the amino compound with nitrous acid and subsequent coupling with alkaline 2-naphthol gave a violet insoluble azo dye. Treatment with silver nitrate:nitric acid solution gave a precipitate of silver bromide.

The picrate (LVII, X = picrate) prepared by the addition of aqueous sodium picrate to an aqueous solution of the amine recrystallised from ethanol as

yellow needles m.p. 211-3°C.

Found: C, 46.3; H, 3.4; N, 18.3

$C_{15}H_{11}N_5O_8$ requires: C, 46.3; H, 2.85; N, 18.0%

(b) The nitro compound NIII (LX) (0.225 g.) dissolved in 75% ethanol (100 ml.) was hydrogenated using 10% palladium charcoal catalyst. Three mole equivalents of hydrogen were absorbed. After filtering, the solution was passed down an Amberlite IRA 400 (Br) column. Evaporation followed by trituration with acetone gave a yellow solid (0.142 g., 45%) identical in spectra and properties to that prepared in (a) above.

Attempted reduction of NII (LIX)

NII (LIX) (0.35 g.) suspended in 75% aqueous ethanol (130 ml.) was hydrogenated using 10% palladium charcoal catalyst (0.300 g.). Six mole equivalents of hydrogen were absorbed in 10 hrs., the uptake then ceasing. Filtration followed by evaporation to dryness gave an oily residue which could be solidified by trituration with acetone (0.085 g.). This gave a very indistinct melting point and infrared spectrum and was not further purified.

1-Hydroxyquinolizinium-2-diazonium Dibromide (LXI, X = Br)

2-Amino-1-hydroxyquinolizinium bromide (LVII, X = Br) (0.50 g.) in 15% aqueous hydrobromic acid (12 ml.) was cooled to -8°C and treated dropwise with sodium nitrite solution until the nitrite was in excess. The orange solid which came out of solution was filtered and dried in a vacuum desiccator at room temperature. (0.38 g., 55%).

ν_{max} 2130, 2095 cm.$^{-1}$ ($N \equiv N^+$).

The compound (LXI, X = Br) darkened on standing in sunlight and when added

to alkaline 2-naphthol gave a violet azo dye. On standing in water at room temperature a deep violet coloured precipitate was formed. This was presumably due to some type of azo coupling.

Replacement of the diazo group in (LXI) by bromine

The diazonium compound (LXI) (0.345 g.) suspended in pure dry dimethyl formamide (5 ml.) was heated to 120°C (oil bath) at which temperature the solid dissolved (giving a jade green solution) and nitrogen was evolved. When the evolution of nitrogen had subsided the solution was cooled and the dimethyl formamide removed by distillation at reduced pressure. The residue was dissolved in ethanol, treated with charcoal and re-evaporated leaving a semi-solid residue. This was dissolved in water and a picrate precipitated by addition of aqueous sodium picrate. The picrate (L, X = picrate) was identified as 2- bromo-1-hydroxyquinolizinium picrate by its m.p. (170.5 - 3.5°) and infrared spectrum. A mixed melting point with an authentic specimen gave no depression.

6-Methyl-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (LXII) was prepared from 5-methyl-2-(4'ethoxybutyryl) pyridine by the method of Moynehan, Schofield, Jones and Katritzky.[16] The yield was 65.5%.

2,2-Dibromo-6-methyl-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide

To the ketone (3.5 g.) dissolved in 50% aqueous hydrobromic acid was added bromine (6.0 g.) in hydrobromic acid (25 ml.). The solution was stirred during the addition and for 15 mins. subsequently. After heating on a water bath for 15 mins. the solution was evaporated to dryness under reduced pressure. Water was added to the residue and the solution

again evaporated leaving a pale yellow solid which was suspended in acetone and filtered (4.96 g., 85%). Recrystallisation from ethanol gave microcrystalline yellow needles, m.p. 228-229.5°C.

Found: C, 30.2; H, 3.05

$C_{10}H_{10}Br_2NO$ requires: C, 30.0; H, 2.50%

$\lambda_{max.}$ 2760 Å ($\log_{10} \varepsilon$ 3.83).

2-Bromo-1-hydroxy-6-methylquinolizinium Bromide.

The 2,2-dibromo-6-methyl ketone (4.00 g.) was heated to 160° (oil bath) at which temperature copious fumes of hydrogen bromide were evolved. Heating was continued until the evolution of hydrogen bromide ceased. The solid remaining was pure 2-bromo-1-hydroxy-6-methylquinolizinium bromide (3.16 g., 100%). It crystallised from ethanol as white microcrystalline needles m.p. 228-229°.

Found: C, 36.1; H, 3.0

$C_{10}H_9Br_2NO.H_2O$ requires: C, 35.65; H, 3.3%

$\lambda_{max.}$ 2160, 3680 Å ($\log_{10} \varepsilon$ 4.45, 4.12).

The compound gave a deep violet colour with neutral ferric chloride solution.

1-Hydroxy-6-methylquinolizinium bromide (LXIII, X = Br)

2-Bromo-1-hydroxy-6-methylquinolizinium bromide (2.75 g.) in 95% ethanol was hydrogenated using 10% palladium charcoal catalyst (0.75 g.). One mole equivalent of hydrogen was absorbed. Filtration followed by evaporation gave an oily residue which crystallised on cooling (1.98 g. 92%)

as hemihydrate). It recrystallised from ethanol as white platelets m.p. 281-3° (with charring).

Found: C, 47.95; H, 4.5; N, 5.7

2 $C_{10}H_{10}BrNO \cdot H_2O$ requires: C, 48.2; H, 4.4; N, 5.6%

λ_{max} 2050, 2400, 3410 Å ($\log_{10} \varepsilon$ 4.52, 4.07, 4.14).

The picrate (LXIII, X = Br) crystallised from ethanol as yellow rhombs m.p. 232-4°.

Found: C, 49.5; H, 3.2

$C_{16}H_{12}N_4O_8$ requires: C, 49.5; H, 3.1%

Attempted nitration of 1-hydroxy-6-methylquinolizinium bromide (LXIII, X = Br).

The phenol (0.25 g.) in 7% aqueous nitric acid (5 ml.) was boiled for 15 seconds and cooled in ice cold water. A small amount (5 mg.) of an impure orange solid came out of solution and was filtered off. The filtrate was boiled for longer periods but no other product was isolated.

8-Methyl-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (LXIV) was prepared by the method of Moynehan, Schofield, Jones and Katritzky from 4-methyl-2-(4-ethoxybutyryl)pyridine. The yield was 80%. The 2-cyano-4-methyl-pyridine used in the preparation of the ethoxy butyryl pyridine was itself prepared from 4-picoline by the method of Feely and Beavers.(50)

2,2-Dibromo-8-methyl-1-oxo-1,2,3,4-tetrahydroquinolizinium Bromide was prepared in an identical manner to the 6-methyl derivative but using the 8-methyl ketone (LXIV) (4.1 g.). 6.1 g. (90%) of the 8-methyl dibromo ketone was obtained. It was recrystallised from ethanol as small yellow

blunt needles m.p. 221-3°.

Found: C, 30.75; H, 3.0

$C_{10}H_{10}Br_3NO$ requires: C, 30.0; H, 2.5

λ_{max} 2600 ($\log_{10}\varepsilon$ 3.74)

2-Bromo-1-hydroxy-8-methylquinolizinium Bromide was prepared in 100% yield by heating the 8-methyl dibromo ketone at 160°C until evolution of hydrogen bromide ceased. It was purified from ethanol as a white amorphous solid m.p. 225-6° (with charring).

Found: C, 37.9; H, 3.2

$C_{10}H_9Br_2NO$ requires: C, 37.65; H, 2.85%

λ_{max} 2160, 3650 ($\log_{10}\varepsilon$ 4.61, 4.18).

1-Hydroxy-8-methylquinolizinium Bromide (LXV, X = Br)

2-Bromo-1-hydroxy-8-methylquinolizinium bromide (4.00 g.) in ethanol (100 ml.) was hydrogenated using palladium charcoal catalyst (0.7 g.). Working up in a similar manner to the 6-methyl analogue (LXIII, X = Br) gave the phenol (LXV, X = Br) as colourless rhombs m.p. 210-11.5°C (2.72 g., 85% as monohydrate).

Found: C, 47.0; H, 4.65; N, 5.8

$C_{10}H_{10}BrNO \cdot H_2O$ requires: C, 46.55; H, 4.7; N, 5.4

λ_{max} 2070, 2300, 3370 Å ($\log_{10}\varepsilon$ 4.65, 4.18, 4.19).

The picrate (LXV, X = Picrate) recrystallised from ethanol as blunt yellow needles m.p. 228-32°.

Found: C, 49.5; H, 3.3

$C_{16}H_{12}N_4O_8$ requires: C, 49.5; H, 3.1%

Nitration of 1-hydroxy-8-methylquinolizinium bromide (LXV, X = Br)

(a) The phenol (0.5 g.) in 7% nitric acid (10 ml.) was heated to boiling. The solution became deep red and a solid precipitated after boiling for approximately 5 seconds. The solution was cooled in ice water and filtered giving the zwitterion form of the 4-bromo-1-hydroxy-8-methyl-2-nitroquinolizinium cation (LXVI) (0.305 g., 55%). This recrystallised from 80% aqueous ethanol giving feathery red crystals which charred but did not melt below 340°.

Found: C, 43.0 ; H, 2.45; N, 10.1

$C_{10}H_7BrN_2O_3$ requires: C, 42.45; H, 2.4; N, 9.9%

λ_{max} 2100, 2410, 3250, 3790, 4440 Å ($\log_{10}\varepsilon$ 4.45, 4.19, 3.66, 3.94, 4.31)

λ_{max} (H_2SO_4) 2600, 3440, 3980 Å

(b) The filtrate from the above reaction was boiled for a further 3 mins. and cooled. A yellow solid (0.05 g.) which came out of solution was the methyl analogue of NII (LXVII). It recrystallised from acetone as microcrystalline yellow needles. It did not melt below 340°.

Found: C, 48.2; H, 2.9 ; N, 17.1

$C_{10}H_7N_3O_5$ requires: C, 48.20; H, 2.85; N, 16.85%

λ_{max} (75% EtOH) 2150, 2570, 4320 ($\log_{10}\varepsilon$ 4.33, 3.99, 4.42)

ν_{max} 1560, 1330 $cm.^{-1}$ (NO_2) 1250 $cm.^{-1}$ (CO^-)

Action of silver acetate on NI (LVIII)

The nitro compound NI (LVIII) (1.00 g.) and silver acetate (0.75 g.) suspended in glacial acetic acid (200 ml.) were stirred and boiled under

reflux for 48 hrs. The suspension was cooled and filtered and the filtrate evaporated to dryness. The residue was dissolved in water and heated on a boiling water bath for 0.25 hr. Evaporation to dryness gave a residue of unchanged NI identified by its infrared spectrum.

Action of phenyl hydrazine on NI (LVIII)

A solution of NI (LVIII) (0.28 g.) in redistilled phenyl hydrazine (10 ml.) was warmed on a water bath for 0.5 hr. The phenyl hydrazine was removed by distillation under reduced pressure and the residue taken up in water. This was boiled down to a third bulk which removed the last traces of the hydrazine. The solution was evaporated to dryness under reduced pressure. The oily residue solidified on treatment with acetone. This was filtered and identified as 2-amino-1-hydroxyquinolizinium bromide (LVII, X = Br) by its infrared spectrum (0.07 g., 28%).

2-Bromoquinolizinium Bromide (LXVIII, X = Br)

2-Bromo-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XLVII, X = Br) (5.0 g.) and acetic anhydride (150 ml.) were refluxed for 2 hr. The solution was evaporated to dryness under reduced pressure, crystals of 2-bromoquinolizinium bromide (LXVIII, X = Br) coming out of solution during the evaporation. The residue was suspended in a little acetic anhydride, filtered and washed with a small amount of absolute alcohol (3.4 g., 75%). It recrystallised from ethanol as colourless needles m.p. 257-9°C.

Found: C, 37.4; H, 2.45

$C_9H_7Br_2N$ requires: C, 37.55; H, 2.3%

λ_{max} 2800, 2905, 3050, 3170, 3240, 3310 Å ($\log_{10}\varepsilon$ 3.50, 3.56, 3.79, 4.10, 4.09, 4.38).

The picrate (LXVIII, X = picrate) was obtained by adding saturated ethanolic picric acid to an alcoholic solution of the bromide. Recrystallised from methanol as yellow needles m.p. 185.5 - 186.5°C.

Found: C, 41.3; H, 2.1

$C_{15}H_9BrN_4O_7$ requires: C, 41.15; H, 2.25%

2-Hydroxyquinolizinium Bromide (LXIX, X = Br)

A suspension of silver acetate (3.25 g.) in glacial acetic acid (100 ml.) was added to 2-bromoquinolizinium bromide (LXVIII, X = Br) (2.50 g.) in acetic acid (50 ml.) and the mixture stirred and boiled under reflux for 40 hr. After cooling in ice water the mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in 50% aqueous hydrobromic acid and warmed on a water bath for 0.25 hr. The solution was then evaporated to dryness under reduced pressure, water added and the solution again evaporated to give a solid. The solid residue was suspended in absolute ethanol, cooled in ice water and filtered. More solid was obtained by addition of ethyl acetate to the filtrate. The yield of almost pure 2-hydroxyquinolizinium bromide hemi-hydrate (LXIX, X = Br) was 1.76 g. (90%). Recrystallisation from ethanol: ethyl acetate gave white blunt needles m.p. 258-63°C.

Found: C, 45.75; H, 3.7; N, 6.05

$2\,C_9H_8BrNO \cdot H_2O$ requires: C, 46.0; H, 3.85; N, 5.95%

λ_{max} 2250, 2980, 3240* Å ($\log_{10} \varepsilon$ 4.55, 4.05, 3.86)

ν_{max} 3250 cm.$^{-1}$ (hydrogen bonded OH), 1650 cm.$^{-1}$ (cyclic amide C=O).

The picrate (LXIX, X = picrate) was prepared by addition of aqueous sodium picrate to an aqueous solution of the hydroxy bromide (LXIX, X = Br) and

crystallised from acetone as small yellow prisms.

Found: C, 48.5; H, 2.7; N, 15.0

$C_{15}H_{10}N_4O_8$ requires: C, 48.15; H, 2.7; N, 15.0%

The bromide (LXIX, X = Br) gave a deep red colour with aqueous ferric chloride.

2-Quinolizidone (LXX)

2-Hydroxyquinolizinium bromide (LXIX, X = Br) (4.50 g.) was treated with cold saturated aqueous potassium carbonate solution (20 ml.). Effervescence occured andyellow oily droplets were formed. The solution was extracted several times with chloroform and the chloroform extracts dried (Na_2SO_4). Evaporation of the chloroform gave a residue which sublimed to give 1.325 g. (49%) of 2-quinolizone (LXX) as thick yellow crystals m.p. 127.5° (change of crystal form at 65-67°). After two more sublimations the m.p. was 128-129.5° (65-67°).

Found: N, 9.7

C_9H_7NO requires: N, 9.65%

λ_{max} 2260, 2990, 3250* Å ($\log_{10}\varepsilon$ 4.50, 4.00, 3.75)

λ_{max} (H_2SO_4 conc.) 2160, 2870*, 3130, 3210 Å ($\log_{10}\varepsilon$ 4.50, 3.84, 4.07, 4.06)

ν_{max} 1634 $cm.^{-1}$. The pK_a determined spectrophotometrically was 4 (± 0.5).

6,7,8,9-Tetrahydro-2-Quinolizone (LXXI)

2-Quinolizone (0.35 g.) in 95% ethanol (25 ml.) was hydrogenated at atmospheric pressure using Adams' platinum oxide catalyst (0.100 g.). Two molar equivalents of hydrogen were quickly (0.5 hr.) absorbed, absorption then ceasing. The solution was filtered and the filtrate evaporated to dryness. The oily residue crystallised on treatment with petroleum ether

[40-60] and was filtered to give 0.324 g. (93%) of 6,7,8,9-tetrahydro-2-quinolizone. Sublimation gave colourless blunt needles m.p. 133-5° (Change of crystal form 55-7°).

Found: N, 9.05

$C_9H_{11}NO$ requires: N, 9.4%

λ_{max} (MeOH) 2600 Å ($\log_{10}$ ε 4.17).

λ_{max} (MeOH + 1 drop concentrated aqueous HCl) 2390 Å ($\log_{10}$ ε 3.98)

ν_{max} 1645 cm.$^{-1}$ (C=C stretching), 1550 cm.$^{-1}$ (pyridone C=O stretching).

2-Methyl mercaptoquinolizinium iodide (LXXIII, X = I)

2-Quinolizone (LXX) (0.60 g.) and phosphorus pentasulphide (0.29 g.) were heated for 0.75 hr. in a sublimation apparatus at 150°C (oil bath). The temperature was then raised to 170° and the pressure reduced to 0.2 mm., a small amount of oily material subliming. The residue was extracted several times with chloroform and evaporated leaving an oily residue which had the same infrared spectrum as the sublimate and showed a strong absorption at 1080 cm.$^{-1}$ (C=S stretching). The residue was taken up in the minimum quantity of absolute ethanol and warmed with methyl iodide. On evaporation and cooling, 2-methyl mercaptoquinolizinium iodide (LXXIII, X = I) was obtained. This was suspended in ethanol:acetone and filtered. Purification from ethanol:ethyl acetate gave a yellow amorphous solid m.p. 196-201°.

Found: C, 39.6; H, 3.3; N, 4.4

$C_9H_{10}INS$ requires: C, 39.4; H, 3.6; N, 4.45%

λ_{max} 2130, 2580, 3380 Å ($\log_{10}$ ε 4.55, 4.25, 4.33).

The picrate (LXXIII, X = picrate) crystallised from ethanol as yellow rhombs

m.p. 183-7° (softening at 170°).

Found: C, 47.35; H, 3.05; N, 14.2

$C_{15}H_{12}O_7N_4S$ requires: C, 47.55; H, 3.4; N, 13.85

Reaction of 2-Quinolizone with phosphorus tribromide.

Phosphorus tribromide (2 ml.) and 2-quinolizone (LXX) (0.300 g.) were boiled under reflux for 2 hr. After cooling the excess phosphorus tribromide was decanted and the brown solid residue washed with dry ether and dissolved in absolute ethanol. Partial evaporation of the ethanolic solution gave on cooling, crystals of 2-bromoquinolizinium bromide (LXVIII, X = Br) (0.17 g., 27%) m.p. 257°. The infrared spectrum of this sample was identical with that produced as described previously.

1-Bromo-2-hydroxyquinolizinium Bromide (LXXIV, X = Br)

Bromine (0.25 g.) in 50% aqueous hydrobromic acid was added to a stirred solution of 2-hydroxyquinolizinium bromide (LXIX, X = Br) (0.250 g.). During the addition a solid yellow perbromide came out of solution. The mixture was stirred for 1 hr., heated on a water bath until all the solid had dissolved and then evaporated to dryness under reduced pressure. The solid residue was suspended in an ethanol:ethyl acetate mixture and filtered giving 1-bromo-2-hydroxyquinolizinium bromide (0.207 g., 67%). Recrystallisation from ethanol gave small colourless rhombs m.p. 295-7° dec. (charring above 270°).

Found: C, 35.3; H, 2.55; N, 4.95

$C_9H_7Br_2NO$ requires: C, 35.45; H, 2.3; N, 4.6%

λ_{max} 2360, 3050, 3520 Å ($\log_{10} \varepsilon$ 4.49, 4.13, 3.89).

The infrared spectrum was identical with that of a sample prepared by another route (part IIb. p. 87)

1-Bromo-2-hydroxyquinolizinium nitrate (LXXIV, X = NO_3)

2-Hydroxyquinolizinium bromide (LXIX, X = Br) (0.25 g.) in 7% nitric acid (5 ml.) was boiled for 15 seconds and immediately cooled in ice cold water. The pale yellow solid which came out of solution was filtered (0.225 g., 79%). Recrystallisation from ethanol gave small colourless needles m.p. 158-159°.

Found: C, 38.2; H, 2.4; N, 9.85

$C_9H_7BrN_2O_4$ requires: C, 37.9; H, 2.5; N, 9.8%

ν_{max} 1400-1340 cm.$^{-1}$, 815 cm.$^{-1}$ (NO_3^-).

On passing an aqueous solution of the nitrate (LXXIV, X = NO_3) through a column of Amberlite IRA 400 (Br) exchange resin, the bromide (LXXIV, X = Br) was obtained.

Attempted formation of 1-cyano-2-hydroxyquinolizinium salts.

2-Hydroxyquinolizinium bromide (LXIX, X = Br) (0.25 g.) and sodium cyanide (0.35 g.) in 7% nitric acid (5 ml.) were boiled for 15 seconds and cooled in water. The solid which came out of solution was filtered off (0.107 g., 49%) and was identified as 2-hydroxyquinolizinium nitrate (LXIX, X = NO_3). It recrystallised from ethanol as colourless rhombs m.p. 188-92°.

Found: C, 51.75; H, 4.3

$C_9H_8N_2O_4$ requires: C, 51.9; H, 3.85%

1,2-Dihydroxyquinolizinium salts (LXXV)

(a) A solution of the bromo ketone bromide (XLVII, X = Br) (1.0 g.)

in methanol (50 ml.) was stirred and boiled under reflux with Amberlite IRA 400 (OH) (15 ml.) for 1.5 hr. The cooled mixture was filtered and evaporated to small bulk. A small portion when treated with aqueous neutral ferric chloride solution gave a deep jade green colour.

Picric acid (0.75 g.) in methanol (5 ml.) was added to the remainder. Concentration of the resulting solution to 2.5 ml. followed by the addition of ether gave an oily solid which was washed several times with ether by decantation. The crude picrate was dissolved in methanol, heated with decolourising charcoal, filtered and evaporated to dryness. The residue crystallised from water as orange prisms m.p. 180° (hydrated). Recrystallisation from acetone gave 1,2-dihydroxyquinolizinium picrate (LXXV, X = picrate) m.p. 223-5°C (dec.) (0.35 g., 20%).

Found: C, 46.5; H, 2.55

$C_{15}H_{10}N_4O_9$ requires: C, 46.25; H, 2.55

λ_{max} 2130, 2350, 3310, 3500 Å ($\log_{10}\varepsilon$ 4.59, 4.52, 4.28, 4.29).

(b) A solution of the bromo ketone bromide (XLVII, X = Br) (0.500 g.) in water (10 ml.) was treated with aqueous ammonia (s.g. 0.88) (10 ml.), the solution turning deep red in colour. The mixture was heated on a water bath for 0.5 hr., then boiled to remove ammonia. The aqueous solution was passed down a column of Amberlite IRA 400 (OH) and boiled to remove liberated ammonia. Evaporation to dryness under reduced pressure gave a solid which was dissolved in absolute ethanol and precipitated by careful addition of ethyl acetate as an extremely hygroscopic brown solid. Purification of this proved impossible. The picrate was formed by addition of aqueous sodium picrate and recrystallised from acetone to give orange prisms m.p. 226-8°C (dec.) identical to that produced in method (a) above.

(c) The mono-bromo ketone bromide (XLVII, X = Br) (1.0 g.) in water (20 ml.) was mixed with a solutionof silver acetate (2.0 g.) in water (130 ml.) and the mixture stirred and boiled under reflux for 2 hours. The cooled mixture was filtered, evaporated under reduced pressure and the residue dissolved in water. The aqueous solution was passed through a column of Amberlite IRA 400 (Br) and again evaporated. The picrate (LXXV, X = picrate), prepared from the residue (A) by treatment with aqueous sodium picrate, was crystallised from absolute ethanol as yellow needles m.p. 223-7°C (dec.).

The residue (A) was hygroscopic and could not be crystallised but after treatment with boiling acetic anhydride (2.5 hr.) a solid bromide (LXXV, X = Br) was isolated and recrystallised (using decolourising charcoal) from absolute ethanol:ethyl acetate as flesh coloured cubes m.p. 227°C (dec.) (0.20 g., 25%).

Found: C, 44.7; H, 3.7; N, 5.3

$C_9H_8BrNO_2$ requires: C, 44.65; H, 3.35; N, 5.8%

λ_{max} 2120, 2354, 3250 Å ($\log_{10} \varepsilon$ 4.41, 4.35, 4.01).

With a neutral solution of ferric chloride the bromide (LXXV, X = Br) gave a very intense jade green colour.

The picrate (LXXV, X = picrate) was prepared by adding saturated aqueous sodium picrate to the bromide. Recrystallised from ethanol as yellow needles m.p. 225-7°C identical to that produced before treatment of the residue (A) with acetic anhydride and with that in methods (a) and (b).

Found: C, 46.2; H, 2.8; N, 13.9

$C_{15}H_{10}N_4O_9$ requires: C, 46.25; H, 2.55; N, 14.15

The lead salt of 1,2-dihydroxyquinolizinium bromide (LXXVI) was prepared by addition of an aqueous solution of lead acetate to a solution of the bromide (LXXV, X = Br) in water. Recrystallised from water as yellow needles m.p. 339-42°C.

Found: C, 24.7; H, 1.4; N, 3.25

$C_9H_6BrNO_2Pb$ requires: C, 24.2; H, 1.35; N, 3.15%

λ_{max} 2140, 2340, 3410, 3700 Å ($\log_{10}\varepsilon$ 4.27, 4.17, 3.75, 3.53).

1,2-Dihydroxy-1-methoxy-1,2,3,4-tetrahydroquinolizinium salts (LXXIX)

2-Bromo-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XLVII, X = Br) (1.0 g.) in methanol (50 ml.) was stirred and boiled under reflux with Amberlite IRA 400 (OH) (15 ml.) for 1 hr. The cooled mixture was filtered and further cooled to between 0 and 5°C. To this methanolic solution was added an ethereal solution of diazo methane (from 1.5 g. of nitroso dimethyl urea) and the resulting solution left for 0.3 hr. After concentration to small bulk, methanolic picric acid was added and the picrate so obtained recrystallised from methanol to give orange rhombs m.p. 191.5-192.5°. The yield of unrecrystallised picrate (LXXIX, X = picrate) was 0.34 g.) (25%).

Found: C, 45.4; H, 4.1; N, 13.3

$C_{16}H_{16}N_4O_{10}$ requires: C, 45.4; H, 3.8; N, 13.2%

λ_{max} 2550, 3570 Å ($\log_{10}\varepsilon$ 4.37, 4.38).

The bromide (LXXIX, X = Br) was prepared by passing an ethanolic solution of the picrate through an Amberlite IRA 400 (Br) column. Recrystallisation from ethanol:ethyl acetate gave colourless needles m.p. 158-60°.

Found: C, 42.15; H, 4.9

2 $C_{10}H_{14}BrNO_3 \cdot H_2O$ requires: C, 42.25; H, 5.3%

λ_{max} 2630 Å ($\log_{10} \varepsilon$ 3.81) ν_{max} 1070 $cm.^{-1}$ (C-O).

No colour was obtained with neutral aqueous ferric chloride.

Reaction of 1,2-dihydroxy-1-methoxy-1,2,3,4-tetrahydroquinolizinium bromide (LXXIX, X = Br) with aqueous hydrobromic acid.

(a) The hemi-ketal bromide (0.1 g.) in 25% aqueous hydrobromic acid (10 ml.) was boiled under reflux for 4 hours. The solution was evaporated under reduced pressure, the residue dissolved in water and again evaporated. The residual solid was crystallised from absolute ethanol: ethyl acetate (charcoal) to give 1,2-dihydroxyquinolizinium bromide (LXXV, X = Br) m.p. 219-223°C characterised by melting point, infrared and ultraviolet spectra.

(b) Experiment (a) repeated but the solution refluxed for 2.5 hrs. Crystallisation from absolute ethanol:ethyl acetate gave a solid presumed to be 1,2-dihydroxy-3,4-dihydroquinolizinium bromide (LXXX) (0.06 g.). Further recrystallisation from absolute ethanol:ethyl acetate gave m.p. 192-4°C.

Found: C, 44.05; H, 4.3

$C_9H_{10}BrNO_2$ requires: C, 44.3; H, 4.15%

The bromide (LXXX) gave a jade green colour with neutral aqueous ferric chloride

λ_{max} 2650, 3330 Å ($\log_{10} \varepsilon$ 3.82, 3.25).

Action of Amberlite IRA 400 (OH) on 1-hydroxyquinolizinium bromide (XXVII, X = Br).

The phenol bromide (XXVII, X = Br) (0.5 g.) in methanol (30 ml.) was refluxed with Amberlite IRA 400 (OH) (10 ml.) for 0.75 hr. The solution was then cooled, filtered and evaporated to dryness. The residue was dissolved in water and aqueous sodium picrate added precipitating only 1-hydroxyquinolizinium picrate m.p. 219-21°C.

1-Amino-2-hydroxyquinolizinium Hydroxide (LXXXII, X = OH).

The dibromo ketone (XLVIII, X = Br) (1.0 g.) reacted exothermically with aqueous ammonia (s.g. 0.88) (15 ml.) to give a deep brown solution. After the initial violent reaction was over the solution was heated on a water bath for 0.5 hr., and then evaporated to dryness. After dissolving the residue in a small amount of water the solution was passed down a column of Amberlite IRA 400 (OH) and boiled to remove liberated ammonia. The solution was evaporated to dryness under reduced pressure, the residue dissolved in absolute ethanol, and the ethanolic solution treated with decolourising charcoal. On concentration of the solution 1-amino-2-hydroxyquinolizinium hydroxide (LXXXII, X = OH) (0.125 g., 48%) crystallised as yellow needles. Recrystallisation from acetone gave m.p. 179-82°C.

Found: C, 60.8; H, 5.8; N, 15.7

$C_9H_9N_2O_2$ requires: C, 60.65; H, 5.65; N, 15.7%

λ_{max} 2160, 3330 Å ($\log_{10} \varepsilon$ 4.43, 4.03).

The hydroxide (LXXXII, X = OH) gave a green colour with ferric chloride and after treatment with pentyl nitrite and HCl at 0°C gave a

deep red insoluble azo compound with alkaline 2-naphthol. No colouration was observed with aqueous cupric acetate and the compound did not give a precipitate with aqueous silver nitrate and nitric acid.

The picrate (LXXXII, X = picrate) crystallised from methanol as yellow needles m.p. 215-7°C.

Found: C, 45.35; H, 3.15

$C_{15}H_{12}N_5O_8.CH_3OH$ requires: C, 45.6; H, 3.6%

Action of ammonia on 2-bromo-1-hydroxyquinolizinium bromide (L, X = Br).

To the bromo-hydroxy bromide (0.75 g.) dissolved in water (2 ml.) was added ammonia (5 ml., s.g. 0.88). A yellow precipitate formed. The mixture was heated on a water bath for 0.5 hr. and cooled. The yellow solid was filtered off and crystallised from acetone to give yellow needles of 2-bromo-1-hydroxyquinolizinium hydroxide (L, X = OH), m.p. 220.5-221°, (0.49 g., 83%).

Found: C, 45.1; H, 3.3; N, 5.75

$C_9H_8BrNO_2$ requires: C, 44.65; H, 3.3; N, 5.8%

$\lambda_{max.}$ 2160, 3800 Å ($\log_{10}\varepsilon$ 4.47, 4.06).

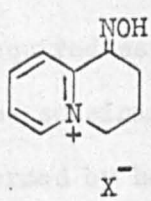
PART II

The Rearrangements of 1-Oximino-1,2,3,4-tetrahydroquinolizinium Bromide

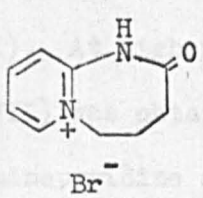
Discussion

(a) The Beckmann rearrangement.

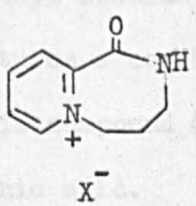
In one of the Wolff aromatisation reactions carried out by Collicut and Jones[31] on 1-oximino-1,2,3,4-tetrahydroquinolizinium bromide (XXXIII, X = Br) an isomer of the oxime was isolated. As the conditions used for this reaction (boiling in an acetic anhydride-sulphuric acid mixture) were known to favour Beckmann rearrangements, the product was assumed to be one of the two possible rearrangement products. (LXXXIII or LXXXIV).



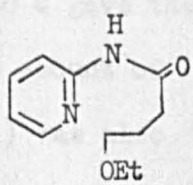
XXXIII



LXXXIII



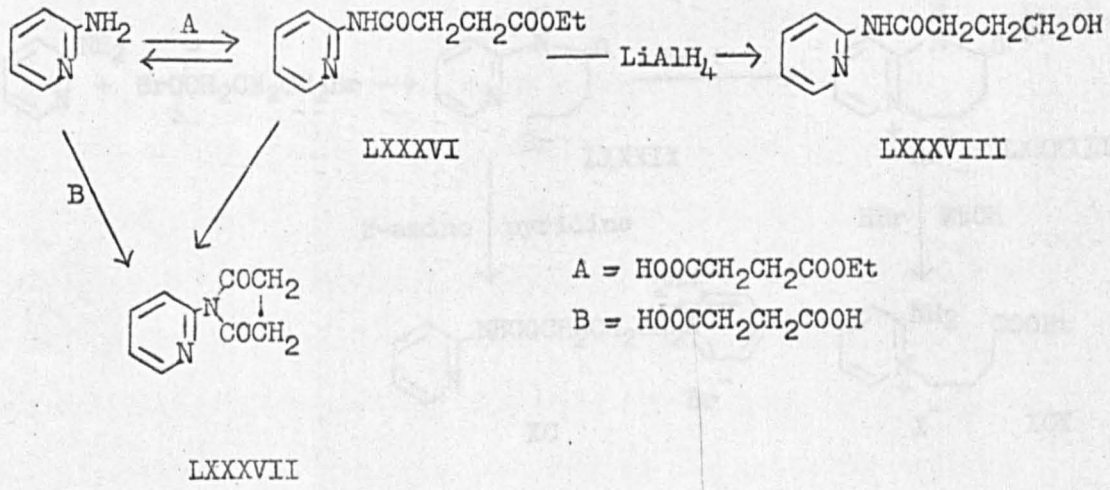
LXXXIV



LXXXV

An attempt by the same authors to prepare the lactam (LXXXIII) by cyclisation of the substituted amide (LXXXV) was unsuccessful because of the ready hydrolysis of the amide group under acid conditions. In this section the preparation of both cyclic amides (LXXXIII and LXXXIV) is reported and an account of their behaviour on hydrolysis is given.

Initially it was proposed to synthesise LXXXIII by formation of ethyl N-2-pyridyl succinimate (LXXXVI) followed by its reduction with lithium aluminium hydride to the hydroxy amide (LXXXVIII). Conversion of this to the bromo compound with phosphorus tribromide and subsequent cyclisation should then give the required product.



LXXXVI

LXXXVIII

LXXXVII

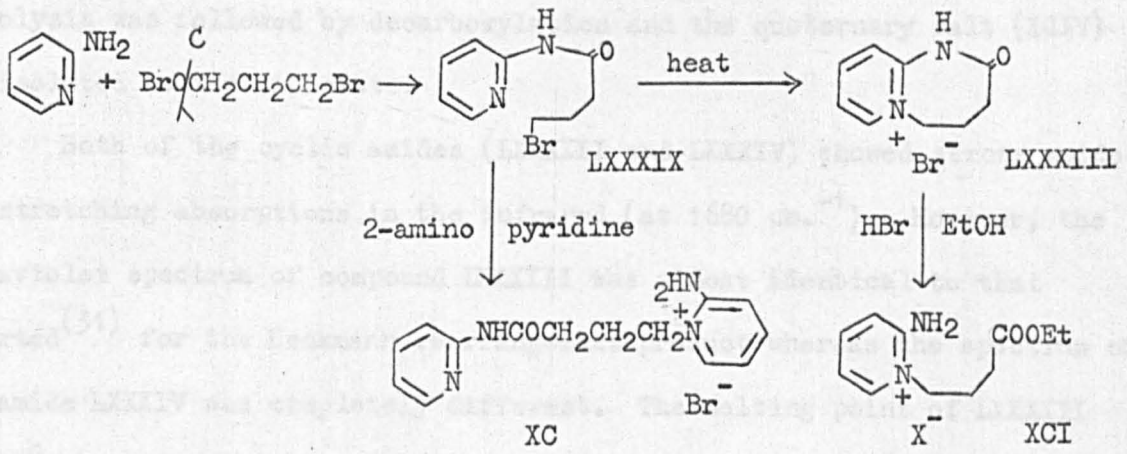
A = $HOOCCH_2CH_2COOEt$

B = $HOOCCH_2CH_2COOH$

Heating 2-aminopyridine with mono ethyl succinate at 130°C gave the required ester (LXXXVI). At higher temperatures a considerable amount of the succinimide (LXXXVII) was obtained. This compound (LXXXVII) was also formed by heating 2-aminopyridine and succinic acid.

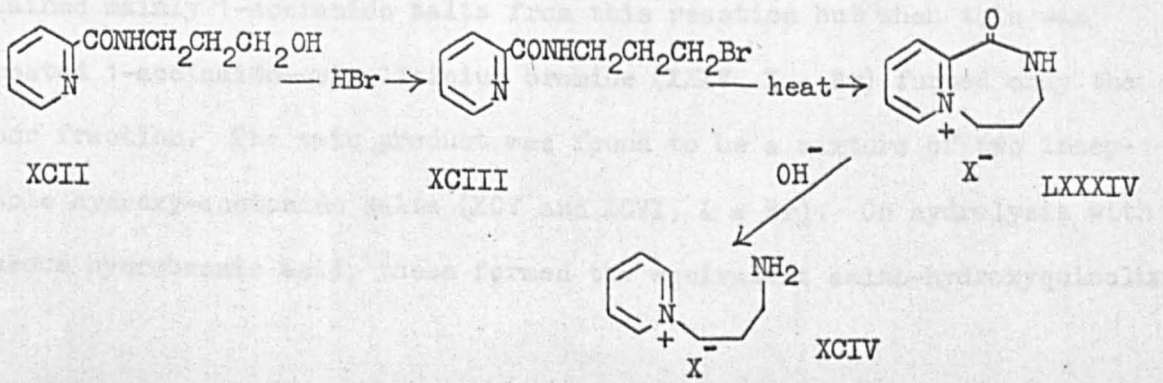
All attempts to reduce the ester (LXXXVI) to the hydroxy-amide failed because of hydrolysis of the amide link. Only 2-aminopyridine was recovered.

A direct method of preparation of the bromo-amide (LXXXIX) was eventually used. γ-Bromobutyryl bromide prepared by reaction of γ-bromo-butyric acid and phosphorus tribromide was added to 2-aminopyridine. The bromo-amide which formed was not isolated, but instead, the crude material was heated in order to induce cyclisation. The product, as expected, was the lactam (LXXXIII). However, if an excess of 2-aminopyridine was used in the reaction, a quaternary salt could be isolated which from its analysis and infrared spectrum had the structure XC.



Hydrolysis of the cyclic amide (LXXXIII) gave the quaternary salt XCI which was isolated as the picrate (X = picrate). For comparison, this compound (XCI, X = picrate) was also prepared by direct quaternisation of 2-amino-pyridine with ethyl γ-bromobutyrate. The two specimens obtained were identical.

The other possible Beckmann product (LXXIV, X = Br) was prepared from the hydroxy-amide (XCII). This had been prepared by Jones[51] by direct heating of 2-picolinic acid and 3-amino-propanol. Treatment of the hydroxy-amide (XCII) with phosphorus tribromide gave the bromo-amide (XCIII) which again was not isolated, but was heated under anhydrous conditions to give the cyclic amide (LXXXIV, X = Br).



When this compound (LXXXIV) was hydrolysed under alkaline conditions, hydrolysis was followed by decarboxylation and the quaternary salt (XCIV) was isolated as the dipicrate.

Both of the cyclic amides (LXXXIII and LXXXIV) showed strong amide C=O stretching absorptions in the infrared (at 1680 $cm.^{-1}$). However, the ultraviolet spectrum of compound LXXXIII was almost identical to that reported[31] for the Beckmann rearrangement product whereas the spectrum of the amide LXXXIV was completely different. The melting point of LXXXIII was 20^{o} higher than that reported but even so the available evidence indicates that, contrary to the prediction of Bauer and Hewitson,[52] the Beckmann product has structure LXXXIII.

In order to finalise the position several attempts have been made to isolate a Beckmann product from the oxime (XXXIV, X = Br). Although rearrangements have occured in acid solutions (see next section), it has proved impossible to repeat the Beckmann rearrangement.

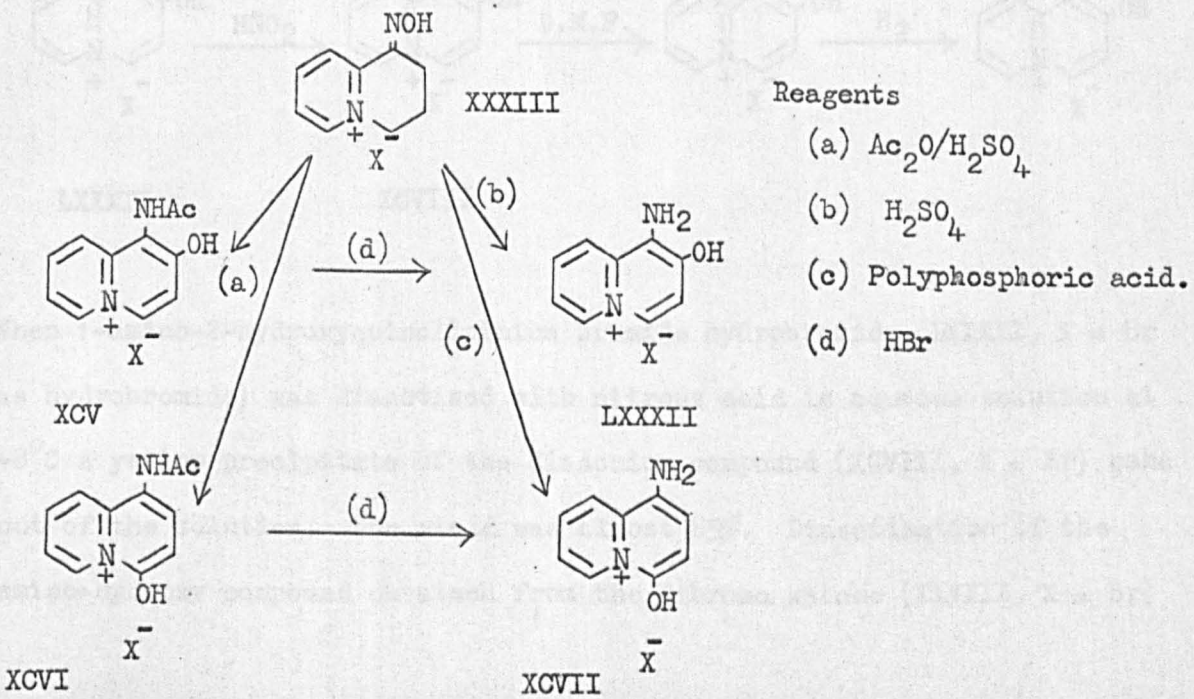
(b) Acid catalysed rearrangements.

The reaction of the oxime (XXXIII, X = Br) with acetic anhydride containing a trace of sulphuric acid has been repeated many times in an attempt to isolate the Beckmann product. All were unsuccessful and only acetamido quinolizinium salts were isolated. Collicut and Jones[31] obtained mainly 1-acetamido salts from this reaction but when this was repeated 1-acetamido-quinolizinium bromide (XXXV, X = Br) formed only the minor fraction. The main product was found to be a mixture of two inseparable hydroxy-acetamido salts (XCV and XCVI, X = Br). On hydrolysis with aqueous hydrobromic acid, these formed the equivalent amino-hydroxyquinolizinium

salts as the hydrobromides. The two amino compounds had different solubilities in ethanol and consequently it was possible to separate the mixture into its two components. The infrared spectrum of both compounds showed the characteristic fine structure of amine salts between 3000 - 2500 cm.$^{-1}$ and a medium intensity band at about 2000 cm.$^{-1}$. (This last absorption is mentioned[53] as being present in amino acid hydrochlorides and it has been found to occur in all quinolizinium amine salts described in this work). The two compounds were also found to give colours with neutral ferric chloride solution indicating a phenolic hydroxyl group.

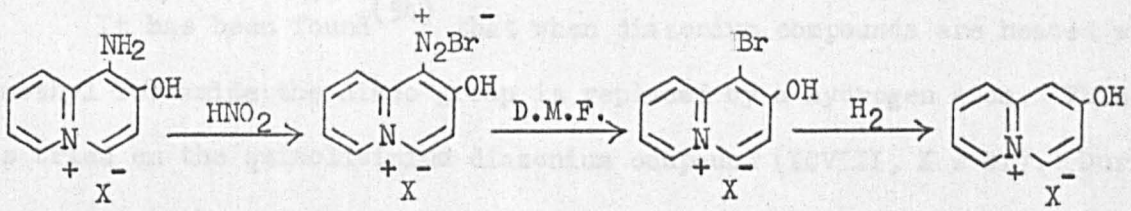
A very small yield of one of these compounds (XCVII, X = Br) was obtained when the oxime (XXXIII, X = Br) was heated with polyphosphoric acid. It is assumed that the major product was the other (more soluble) hydroxy-amine but that it could not be isolated.

On treating the oxime (XXXIII, X = Br) with hot sulphuric acid a good yield of the more soluble hydroxy-amino-quinolizinium salt (LXXXII, X = Br)



was obtained. Comparison of the picrates showed this to be the same compound as was obtained in the reaction of 2,2-dibromo-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XLVIII, X = Br) with ammonia (see p. 39)

From the nature of the formation of these compounds (under Wolff aromatisation conditions) it would appear that the amine group is in position 1. It therefore remained to deduce the position of the hydroxyl group in the molecules. Using the reaction sequence shown below the product from the sulphuric acid reaction was identified as 1-amino-2-hydroxyquinolizinium bromide hydrobromide (LXXXII, X = Br as hydrobromide). The other amino-hydroxy compound (XCVII) is considered to be the 4-hydroxy derivative because of its similarity to LXXXII (X = Br) and because its infrared spectrum shows the hydroxyl group to have amide character. (A strong peak at 1650 $cm.^{-1}$ corresponds to amide C=O stretching).



LXXXII XCVIII

When 1-amino-2-hydroxyquinolizinium bromide hydrobromide (LXXXII, X = Br as hydrobromide) was diazotised with nitrous acid in aqueous solution at $-8^{\circ}C$ a yellow precipitate of the diazonium compound (XCVIII, X = Br) came out of the solution. The yield was almost 85%. Diazotisation of the amino-hydroxy compound obtained from the dibromo ketone (XLVIII, X = Br)

also gave the same diazonium salt.

The product (XCVIII, X = Br) showed a doublet in the infrared at 2150, 2179 cm.$^{-1}$ ($N \equiv N^+$ stretching) and on addition to alkaline 2-naphthol it precipitated a violet azo dye. It was also remarkably stable and only started to decompose above 130°C. It had a definite melting point (272°C) and it could be recrystallised from boiling methanol or hot water with only slight change in its infrared spectrum.

Several attempts were made to convert the diazonium compound (XCVIII, X = Br) into the bromo-hydroxy derivative (LXXXIV, X = Br). These included Gatterman reactions and reactions with hydrobromic acid. All gave mixtures of products which could not be separated. In one reaction the diazonium compound (XCVIII, X = Br) was boiled with hydriodic acid in an attempt to obtain the iodo analogue. However, reduction took place and only the amino-hydroxy compound (LXXXII, X = I as hydriodide) was isolated.

It has been found[54] that when diazonium compounds are heated with dimethyl formamide the diazo group is replaced by a hydrogen atom. This was tried on the quinolizinium diazonium compound (XCVIII, X = Br). During the reaction the evolution of nitrogen was noted. The product was not the expected hydroxy salt (LXIX, X = Br) but the bromo-hydroxy compound (LXXIV, X = Br) and was identical with the product from the bromination of 2-hydroxyquinolizinium bromide (LXXIV , X = Br) (p. 33).

Reduction to the 2-hydroxy compound (LXIX, X = Br) by catalytic hydrogenation was rather slow and the product was a mixture of the bromo-hydroxy (LXXIV, X = Br) and hydroxy (LXIX, X = Br) compounds. These were separated by fractional crystallisation from ethanol and 2-hydroxyquinolizinium

bromide (LXIX, X = Br) identified by analysis, melting point and spectra.

The mechanism of formation of the amino-hydroxy compounds (LXXXII and XCVII) from the oxime (XXXIII, X = Br) is somewhat difficult to explain. It is possible that the first stage is a Wolff aromatisation to the 1-amino derivative followed by substitution in the 2- or 4-position of the ring system. In the case of the sulphuric acid reaction the hydroxyl group would be formed by replacement in the working up, but in the acetic anhydride reaction such a replacement seems very unlikely.

Other attempts to get the oxime (XXXIII, X = Br) to undergo a Beckmann reagent have included reactions with acetic acid and sulphur dioxide. In both only the unchanged oxime was recovered.

PART II

EXPERIMENTAL

N-2-Pyridylsuccinimide (LXXXVII)

A mixture of 2-aminopyridine (4.7 g.) and succinic acid (6.4 g.) was heated under reflux at 200° (oil bath) for 40 min. The mixture was then distilled at 15 mm. to a bath temperature of 220° and the residue crystallised from methanol, giving colourless needles of N-2-pyridyl-succinimide (LXXXVII). m.p. 138° (lit.[55] 137°) (6.45 g., 73%).

Found: C, 60.85; H, 4.65; N, 15.8

Calculated for $C_9H_8N_2O_2$ C, 61.35; H, 4.55; N, 15.9

λ_{max} 2580 Å ($\log_{10} \varepsilon$ 3.51) ν_{max} 1700 cm.$^{-1}$ (amide CO).

Ethyl N-2-Pyridylsuccinimate (LXXXVI).

A mixture of 2-aminopyridine (4.7 g.) and ethyl hydrogen succinate (11.0 g.) was heated at 130° (oil bath) for 5 hr., cooled, and distilled under reduced pressure. Ethyl N-2-pyridyl succinamate (LXXXVI) was collected at 95-105°/0.1 mm. and was recrystallised from ethanol:ethyl acetate as colourless needles m.p. 71.5 - 72°. (8.8 g., 73%).

Found: C, 55.1; H, 6.6; N, 11.8

$C_{11}H_{14}N_2O_3 \cdot H_2O$ requires: C, 55.0; H, 6.7; N, 11.7%

λ_{max} (95% EtOH) 2330, 2940 Å ($\log_{10} \varepsilon$ 3.98, 3.50).

ν_{max} 1740 cm.$^{-1}$ (ester CO), 1685 cm.$^{-1}$ (amide CO.)

On heating 2-aminopyridine and the succinic ester at higher temperatures than 130°C the product was mainly the succinimide (LXXXVII).

Attempted reduction of Ethyl N-2-Pyridylsuccinimate.

To a stirred solution of the ester (LXXXVI) (5.5 g.) in ether (300 ml.) was added a slurry of lithium aluminium hydride (0.55 g.) in ether (100 ml.)

at a rate sufficient to maintain gentle boiling. After the addition the mixture was stirred for 0.5 hr. and then water (30 ml.) was added slowly. The mixture was filtered, the ether layer separated, dried (Na_2SO_4), and evaporated. The residue was distilled under nitrogen and had b.p. 72°/ 2.5 mm. The infrared spectrum and m.p. showed it to be 2-aminopyridine.

γ-Bromobutyryl Bromide

γ-Bromobutyric acid (10.0 g.) and phosphorus tribromide (10.0 g.) were heated together at 130° for 4 hr. After cooling, the liquid was decanted and distilled, giving γ-bromobutyryl bromide, b.p. 104-5°/15 mm (10.2 g., 74%).

2-Oxo-1,3,4,5-tetrahydro-2H-pyrido[1,2-a][1,3]-diazepinium Bromide (LXXXIII)

γ-Bromobutyryl bromide (13.8 g.) was added to 2-aminopyridine (2.8 g.) and an exothermic reaction with copious evolution of hydrogen bromide occurred. After the initial reaction, the mixture was heated on a water bath for 1 hr., cooled, and basified with saturated aqueous sodium carbonate solution. The alkaline mixture was extracted with chloroform, the chloroform solution dried (Na_2SO_4) and evaporated. The residue was heated at 140° (oil bath) for 0.5 hr., cooled, and triturated with absolute alcohol, giving the cyclic amide bromide (LXXXIII) (0.48 g., 7.3%) (m.p. 225-228°), recrystallised from ethanol as colourless prisms m.p., 232-233°C.

Found: C, 45.05; H, 4.85; N, 11.2

$C_9H_{11}BrN_2O$ requires: C, 44.65; H, 4.55; N, 11.55%

$\lambda_{max.}$ 2310, 2900 Å ($\log_{10} \varepsilon$ 4.02, 4.04)

$\lambda_{max.}$ (95% EtOH) 2360, 2950 Å ($\log_{10} \varepsilon$ 3.98, 4.0)

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

2-Amino-1,3'-ethoxycarbonylpropylpyridinium Picrate (XCI, X = picrate)

a) The cyclic amide (LXXXIII) (0.25 g.) in 50% hydrobromic acid (15 ml.) was boiled for 2 hr., the solution becoming bright red. The solution was evaporated to dryness under reduced pressure, the residue dissolved in water and again evaporated. Several repetitions of this process using absolute ethanol gave a yellow hygrosoopic solid which was suspended in ethyl acetate and filtered (0.224 g.). A picrate (XCI, X = picrate) was prepared by adding an aqueous solution of the crude solid to saturated sodium picrate solution and recrystallised from absolute alcohol as yellow needles m.p. 147-151°.

Found: C, 46.65; H, 4.40.

$C_{17}H_{19}N_5O_9$ requires: C, 46.65; H, 4.35

$\lambda_{max.}$ 2320, 3140,* 3550 Å ($\log_{10}\varepsilon$ 4.35, 4.03, 4.20).

$\nu_{max.}$ 3450 cm.$^{-1}$ (NH) 1715 cm.$^{-1}$ (ester CO).

b) A solution of 2-aminopyridine (1.94 g.) and ethyl γ-bromobutyrate (4.0 g.) in tetramethylene sulphone (5 ml.) was kept at 40° for 5 days. The viscous oil was triturated with ether (50 ml.) and twice with ethyl acetate (50 ml.). The oil was dissolved in water and converted into the picrate (XCI, X = picrate) by addition of aqueous sodium picrate (6.79 g., 75%). A sample recrystallised from ethanol showed no depression in a mixed m.p. determination with that obtained by method (a), and the infrared spectra were identical.

2-Amino-1-γ-[N-2'-pyridyl]butramidopyridinium Bromide (XC)

2-Aminopyridine (6.0 g.) and γ-bromobutyryl bromide (9.2 g.) were mixed and heated as described in the preparation of the cyclic amide

(LXXXIII). The residue from the chloroform extraction was dissolved in 95% ethanol and boiled for 15 hr., the ethanol distilled off, and the residue dissolved in the minimum quantity of methanol. After cooling, small colourless crystals were obtained m.p. 214-216°C. Recrystallisation from ethanol gave colourless rhombs of the pyridinium bromide (XC) (1.0 g., 10%) m.p. 216-217°C.

Found: C, 50.3; H, 5.15; N, 16.3

$C_{14}H_{17}BrN_4O$ requires: C, 49.9; H, 5.05; N, 16.6%

$\lambda_{max.}$ 2300, 2750, 2970 Å ($\log_{10}\varepsilon$ 4.15, 3.83, 3.86)

$\nu_{max.}$ 3300 cm.$^{-1}$ (NH), 1660 cm.$^{-1}$ (amide CO).

N-2-Hydroxypropylpicolinamide (XCII)

3-Aminopropanol (10.0 g.) and picolinic acid (8 g.) were mixed and the mixture boiled for 1 hr. Distillation under reduced pressure gave the picolinamide (XCII) b.p. 147-153°/0.1 mm.,(11 g., 92%)

Found: C, 60.3; H, 6.75

$C_9H_{12}N_2O_2$ requires: C, 60.0; H, 6.7%

$\lambda_{max.}$ 2170, 2630 Å ($\log_{10}\varepsilon$ 3.99, 3.73).

$\nu_{max.}$ 3390 cm.$^{-1}$ (H bonded OH), 1665 cm.$^{-1}$ (amide I), 1527 cm.$^{-1}$ amide II 1055 cm.$^{-1}$ (CO stretching primary acyclic alcohol).

1-Oxo-2,3,4,5-tetrahydro-pyrido[1,2-a][1,4]-diazepinium Bromide (LXXXIV, X = Br).

Phosphorus tribromide (2.1 g.) was added to the hydroxyamide (XCII) (3.5 g.) in benzene (30 ml.) with stirring. The mixture was boiled for

4 hr., cooled, and the benzene evaporated. The residue was treated with a saturated aqueous solution of sodium carbonate, and extracted several times with chloroform. The chloroform extracts were dried (Na_2SO_4) and the chloroform removed. The residue was heated at 130-140° (oil bath) for 1 hr., cooled, dissolved in the minimum quantity of absolute ethanol, and kept at -5° overnight, giving a crystalline solid. Recrystallised from ethanol this gave colourless rhombs of the cyclic amide bromide, (LXXXIV, X = Br), m.p. 218-219° (1.03 g., 22%).

Found: C, 41.6; H, 4.85; N, 10.3

$C_9H_{11}BrN_2O.H_2O$ requires: C, 41.4; H, 5.0; N, 10.7%

$\lambda_{max.}$ 2780 Å ($\log_{10} \varepsilon$ 3.56) in 95% EtOH

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

The picrate (LXXXIV) was recrystallised from acetone:ethanol to give microcrystalline yellow needles, m.p. 206.5-109°

Found: C, 45.85; H, 3.5; N, 17.6

$C_{15}H_{13}N_5O_8$ requires: C, 46.05: H, 3.35; N, 17.9%

γ-Aminopropylpyridinium Dipicrate (XCIV, X = picrate)

The amide (LXXXIV, X = Br) (0.45 g.) in 95% ethanol (25 ml.) and 50% aqueous sodium hydroxide (five drops) was boiled overnight, the solution turning dark red. The mixture was cooled, neutralised with 50% aqueous hydrobromic acid and evaporated to dryness under reduced pressure. The residue was dissolved in water and treated with a queous sodium picrate. The picrate obtained (0.230 g.) recrystallised from acetone as yellow rhombs m.p. 206-209°C.

Found: C, 40.8; H, 3.15; N, 19.0

$C_{20}H_{18}N_8O_{14}$ requires: C, 40.4; H, 3.05; N, 18.85%

$\lambda_{max.}$ 2100, 2480, 3530 Å ($\log_{10}$ ε 4.47, 4.32, 4.41).

1-Oximino-1,2,3,4-tetrahydroquinolizinium Bromide (XXXIII, X = Br) was prepared from 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (XIV) by the method of Collicut and Jones.[31]

1-Amino-2-hydroxyquinolizinium salts (LXXXII)

A solution of the oxime bromide (XXXIII, X = Br) (2.0 g.) in concentrated sulphuric acid (25 ml.) was heated at 130-140° (oil bath) for 30 min., cooled, and carefully poured into dry ether (300 ml.) at -10°. The precipitated solid was filtered off, dissolved in water, and passed through a column of Amberlite IRA 400 (Br). Evaporation under reduced pressure gave a yellow solid, which was suspended in absolute ethanol and filtered (1.46 g., 55%). Recrystallisation from absolute ethanol:ethyl acetate containing a drop of hydrobromic acid gave pale yellow plates of the hydroxyamine hydrobromide (LXXXII, X = Br as hydrobromide), m.p. 205-215° (dec.).

Found: C, 34.35; H, 3.05; N, 9.2

$C_9H_{10}Br_2NO$ requires: C, 33.6; H, 3.15; N, 8.7%

$\lambda_{max.}$ 3320, 3610 Å ($\log_{10}$ ε 3.90, 3.93)

$\nu_{max.}$ 2000 cm.$^{-1}$ (NH^+).

An aqueous solution of the hydrobromide gave a deep green colour with neutral aqueous ferric chloride.

The picrate (LXXXII, X = picrate) crystallised from ethanol as yellow needles, m.p. 215°.

Found: C, 45.7; H, 2.35

Calculated for $C_{15}H_{11}N_5O_8$: C, 46.25; H, 2.85

A mixed melting point with a sample prepared from the dibromo-ketone (XLVIII, X = Br) showed no depression.

1-Amino-4-hydroxyquinolizinium bromide Hydrobromide (XCVII, X = Br as hydrobromide.)

The oxime bromide (XXXIII, X = Br) (1.0 g.) was heated with polyphosphoric acid (6 g.) for 15 min. at 120-130° (oil bath). The mixture was cooled, and 95% ethanol (100 ml.) was added. An insoluble oil formed and was separated, dissolved in water, and percolated through a column of Amberlite IRA 400 (Br). The effluent was evaporated under reduced pressure and the residue purified from ethyl acetate:absolute ethanol as a pale yellow amorphous powder m.p. > 340°C (with charring).

Found: C, 33.9; H, 3.9; N, 9.05

$C_9H_{10}Br_2N_2O$ requires: C, 33.6; H, 3.15; N, 8.7

Hydroxy-1-acetamidoquinolizinium salts (XCV and XCVI).

The oxime bromide (XXXIII, X = Br) (2.0 g.) in acetic anhydride (220 ml.) containing 4 drops of concentrated sulphuric acid was boiled for 4 hours. The solution was cooled and evaporated under reduced pressure. The oily residue was triturated with acetone giving a solid mixture of 2- and 4-hydroxy-1-acetamidoquinolizinium bromides (XCV and XCVI, X = Br) which was then filtered (0.92 g. 39%). Evaporation of the filtrate gave

0.17 g. (8%) of 1-acetamidoquinolizinium bromide (XXXV, X = Br).

The mixture of hydroxy-acetamidoquinolizinium salts was purified with ethanol:ethyl acetate before analysis.

Found: C, 46.65; H, 4.45

$C_{11}H_{11}BrN_2O_2$ requires: C, 46.65; H, 3.95%

$\nu_{max.}$ 3450 cm.$^{-1}$ (H bonded OH), 1655 cm.$^{-1}$ (amide I), 1520 cm.$^{-1}$ (amide II).

Hydrolysis of the hydroxy-1-acetamidoquinolizinium salts

The mixture of the two hydroxy-acetamido salts (XCV and XCVI) (0.55 g.) was boiled with 50% aqueous hydrobromic acid for 1 hr. The solution was then evaporated to dryness under reduced pressure, dissolved in water and re-evaporated. The solid residue was suspended in acetone and filtered (0.38 g., 56%).

Separation of the two constituents of the product was achieved by fractional crystallisation from ethanol. The more soluble component was 2-hydroxy-1-aminoquinolizinium bromide hydrobromide (LXXXII, X = Br as hydrobromide) and the other was 4-hydroxy-1-aminoquinolizinium bromide hydrobromide (XCVII, X = Br as hydrobromide). Both were identified by their infrared spectra.

2-Hydroxyquinolizinium-1-diazonium Dibromide (XCVIII, X= Br).

a) The hydrobromide (LXXXII, X = Br as hydrobromide) (1.25 g.) in 25% hydrobromic acid (17 ml.) was cooled to -8°C. Aqueous sodium nitrite was added until in excess when a yellow solid precipitated. The mixture was left for 1 hr. and then filtered. The diazonium salt (XCVIII,

X = Br) (1.07 g., 83%) showed signs of decomposition above 130°, but melted at 270-2°.

Found: N, 12.2

$C_9H_7Br_2N_3O$ requires: N, 12.6%

$\lambda_{max.}$ (95% EtOH) 2310, 2480,* 2780, 3600 Å ($\log_{10}\varepsilon$ 4.16, 3.99, 3.70, 3.75)

$\nu_{max.}$ 2150, 2179 $cm.^{-1}$ ($N\equiv N$).

b) 1-Amino-2-hydroxyquinolizinium hydroxide (LXXXII, X = OH) prepared from the dibromo ketone (XLVIII, X = Br) was dissolved in 25% hydrobromic acid and treated as above. The diazonium salt (0.173 g., 71%) was identical in spectra and in melting point with that prepared as in a).

Action of Hydriodic acid on the Diazonium salt (XCVIII, X = Br)

The diazonium salt (XCVIII, X = Br) (0.62 g.) was dissolved in 55% hydriodic acid (20 ml.) and the solution boiled for 1.5 hr. Evaporation to dryness and treatment of the residue with ethanol:ethyl acetate gave an orange solid (0.1 g.). The infrared spectrum of this solid was identical with that of 1-amino-2-hydroxyquinolizinium bromide hydrobromide (LXXXII, X = Br as hydrobromide) and it is assumed to be the hydriodide.

1-Bromo-2-hydroxyquinolizinium Bromide. (LXXIV, X = Br)

The diazonium compound (XCVIII, X = Br) (0.755 g.) was dissolved in dry redistilled dimethyl formamide (10 ml.) and heated to 130° (oil bath) at which temperature nitrogen was evolved. After the nitrogen evolution was complete the solution was cooled, and evaporated under reduced pressure. The residue was suspended in a small amount of absolute ethanol and filtered (0.40 g., 56%). Recrystallisation from ethanol gave the bromohydroxy

bromide (LXXIV, X = Br) m.p. 266-272° (dec.), identical in infrared absorption spectrum with the compound obtained from bromination of 2-hydroxyquinolizinium bromide.

Reduction of 1-Bromo-2-hydroxyquinolizinium Bromide (LXXIV, X = Br)

The bromide (LXXIV, X = Br) (0.47 g.) in 95% ethanol (100 ml.) was hydrogenated at atmospheric pressure with 10% palladium charcoal (0.25 g.). Uptake of hydrogen was slow, but approximately 1 mole of hydrogen was absorbed. The mixture was filtered, and the filtrate evaporated. The solid residue was separated by fractional crystallisation from absolute ethanol, the less soluble fraction being unchanged bromohydroxy bromide (LXXIV, X = Br). The major (more soluble) product was 2-hydroxyquinolizinium bromide (LXIX, X = Br), showing no depression in a mixed melting point determination with a sample prepared from 2-bromoquinolizinium bromide (LXIX, X = Br). The infrared spectra of the two samples were identical.

Found: C, 44.35; H, 3.8; N, 5.2

Calculated for $C_9H_8BrNO \cdot H_2O$: C, 44.3; H, 4.15; N, 5.75%

Attempted Beckamnn Rearrangement of 1-oximino-1,2,3,4-tetrahydroquinolizinium salts.

a) To the oxime chloride (XXXIII, X = Cl) (1.0 g.) in liquid SO_2 (100 ml.) thionyl chloride (3 g.) was added. The sulphur dioxide was allowed to evaporate, and the residue was unchanged oxime (XXXIII, X = Cl).

b) The oxime bromide (XXXIII, X = Br) (1.0 g.) was dissolved in hot glacial acetic acid containing 5 drops of concentrated sulphuric acid

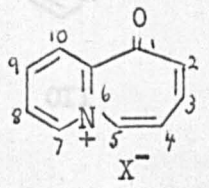
and the solution boiled for 4 hr. After evaporation of the acetic acid under reduced pressure the residue was dissolved in ethanol and percolated through an Amberlite IRA 400 (Br) column, to give the oxime bromide (XXXIII, X = Br).

PART III

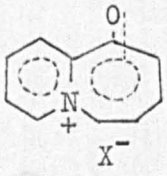
The Synthesis of Pyrido[1,2a]azepinium Salts

Discussion

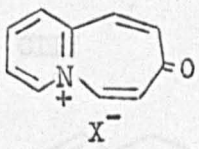
The 1- and 3-oxo pyrido[1,2a]azepinium systems can be represented either by the classical structures (XCIXa and Ca) or by the pseudo-aromatic structures (XCIXb and Cb).



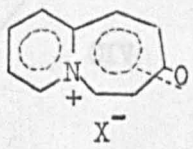
XCIXa



XCIXb

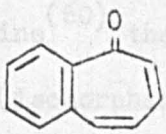


Ca

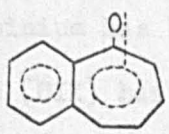


Cb

Oxo-pyrido[1,2a]azepinium salts could thus have considerable aromatic character. However, the properties of the equivalent benzo-tropone (CI)[56,57] show it to behave rather as a conjugated dienone system (CIa) than as an aromatic compound (represented by CIb). It is thus of considerable interest to prepare the pyrido-azepinium derivatives (XCIX and C) and to examine their properties for evidence of aromaticity.



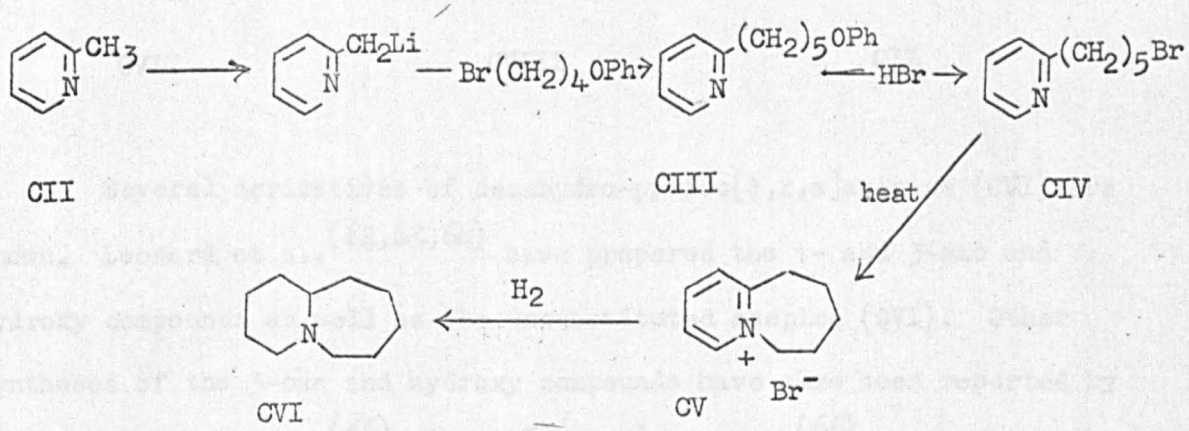
CIa



CIb

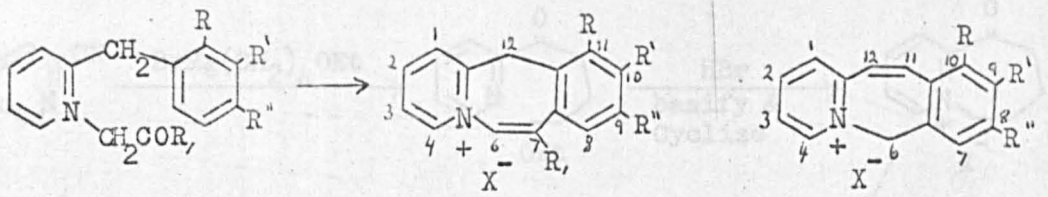
Only one bicyclic pyrido[1,2a]azepinium salt has been reported in the

literature. 2H-1,3,4,5-Tetrahydropyrido[1,2a]azepinium bromide (CV) has been synthesised from 2-picoline (CII) by Morikava[58] in 10% overall yield. The reaction sequence is given below.



2-Picoline was converted to 2-picolyl lithium and then treated with 1-bromo-4-phenoxybutane to give 2-(5' phenoxypentyl)pyridine (CIII). This was boiled with aqueous hydrobromic acid and the bromo compound (CIV) which formed was cyclised to the pyridoazepinium salt (CV). Catalytic hydrogenation gave the decahydro derivative (CVI).

Bradsher and Moser[59] have synthesised a number of substituted 12 H-pyridobenzazepinium salts (CVIII) by cyclisation of 1-acetonyl-2-benzylpyridines (CVII). Because of the relation of the system (CVIII) to morphanthridine[60] the name morphanthridizinium has been proposed. The isomeric 6H-(isomorphanthridizinium) system (CIX) has also been synthesised[61] by quaternisation of 2-acetonylpyridine and the appropriate benzyl halide followed by cyclisation of the product.



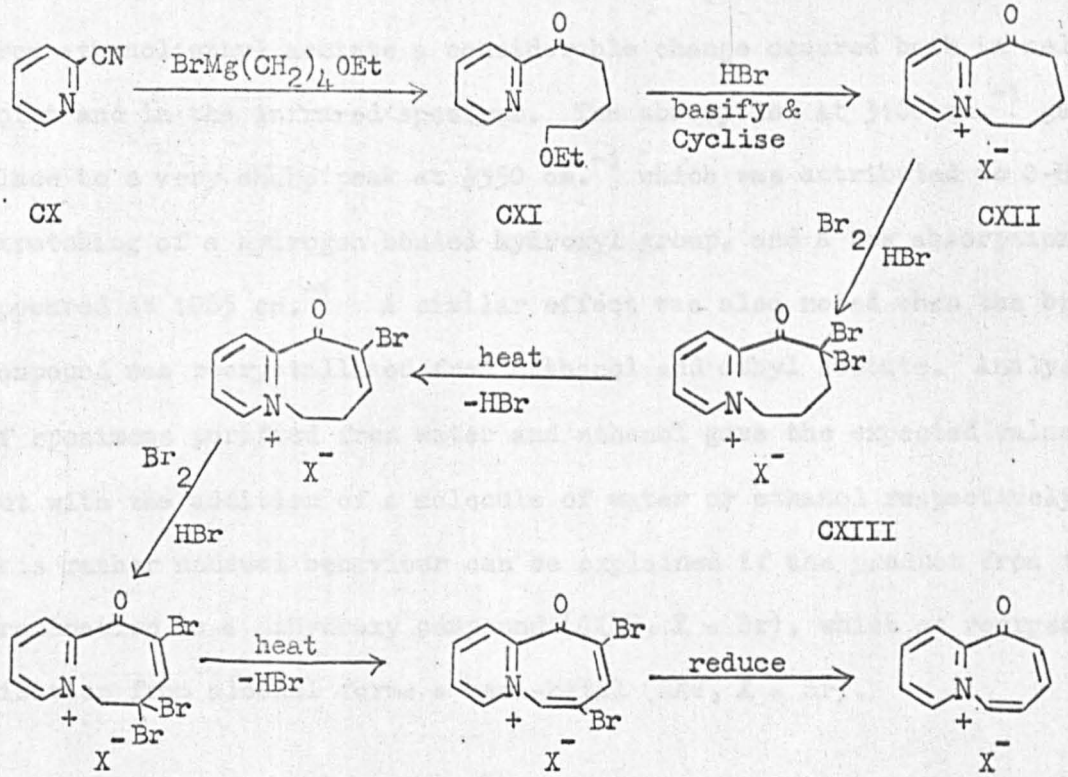
CVII CVIII CIX

Several derivatives of decahydro-pyrido[1,2,a]azepine (CVI) are known. Leonard et al.(62,63,64) have prepared the 1- and 3-oxo and hydroxy compounds as well as the unsubstituted azepine (CVI). Other syntheses of the 3-oxo and hydroxy compounds have also been reported by Winterfield and Muller(65) and Lukeš and Červinka.(66)

The following two sections of this work describe attempts to synthesise the unsubstituted 1- and 3-oxo pyrido[1,2,a]azepinium systems (XCIX and CI).

a) The preparation of 1-oxo-pyrido[1,2,a]azepinium derivatives

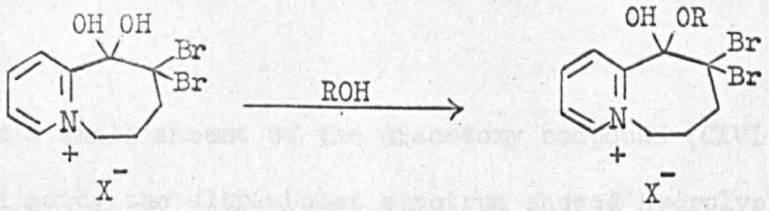
The route envisaged for the preparation of the 1-oxo compound (XCIX) was somewhat similar to that of the preparation of 1-hydroxyquinolizinium salts (XXVII) (p. 17). 2-(5' Ethoxy-valeryl)pyridine (CXI) was prepared by the reaction of the Grignard reagent of 4-bromo-1-ethoxy butane and 2-cyanopyridine (CX) under the same conditions used in the preparation of 2(4'-ethoxybutyryl)pyridine.(14) The yield was 54%.



Cyclisation to the ketone (CXII, X = Br) proved more difficult than expected. The usual method of boiling the bromo ketone (from CXI) in chloroform gave mainly an oily product which would not crystallise. However, if this oil was heated for approximately 30 minutes at 130-140° the cyclic ketone (CXII, X = Br) could be isolated in 55% yield.

Bromination of the ketone (CXII, X = Br) with bromine in hydrobromic acid to form the dibromo ketone (CXIII, X = Br) appeared to go well, and the product was obtained in 90% yield. Unexpectedly, the infrared spectrum showed no carbonyl absorption. There was however, a broad indistinct band at 3100 $cm.^{-1}$ and very strong bands at 1150 and 1045 $cm.^{-1}$

(C-O vibration and stretching). When the compound was recrystallised from ethanol:ethyl acetate a considerable change occured both in melting point and in the infrared spectrum. The absorption at 3100 $cm.^{-1}$ gave place to a very sharp peak at 3350 $cm.^{-1}$ which was attributed to O-H stretching of a hydrogen bonded hydroxyl group, and a new absorption appeared at 1065 $cm.^{-1}$ A similar effect was also noted when the bromo compound was recrystallised from methanol and ethyl acetate. Analysis of specimens purified from water and ethanol gave the expected value but with the addition of a molecule of water or ethanol respectively. This rather unusual behaviour can be explained if the product from the bromination is a dihydroxy compound (CXIV, X = Br), which on recrystallisation from alcohol forms a hemi-ketal (CXV, X = Br).

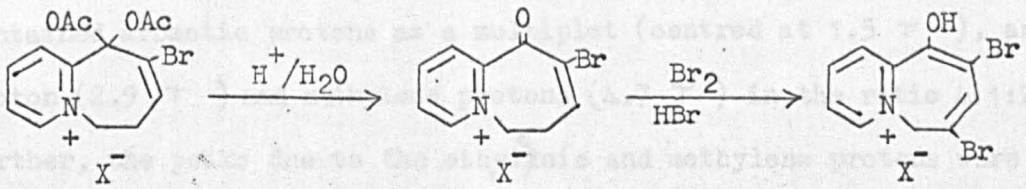


CXIV CXV

If the bromo-hydroxy compound (CXIV, X = Br) was heated at 140-150° vigorous evolution of hydrogen bromide occured accompanied by considerable charring of the solid. At the end of evolution all that remained was a black charred solid from which nothing could be isolated.

In another attempt to dehydrobrominate CXIV (X = Br) the bromo compound was boiled with acetic anhydride. Working up gave a product

which had a fairly long wavelength absorption in the ultraviolet region of the spectrum, and which showed absorption at 1780 $cm.^{-1}$ (acetyl C=O) and 1170 $cm.^{-1}$ (C-O stretching) in the infrared. This product could be purified by crystallisation from ethanol:acetone but only with considerable loss. The analysis indicated that it was the diacetoxy compound (CXVI, X = Br).



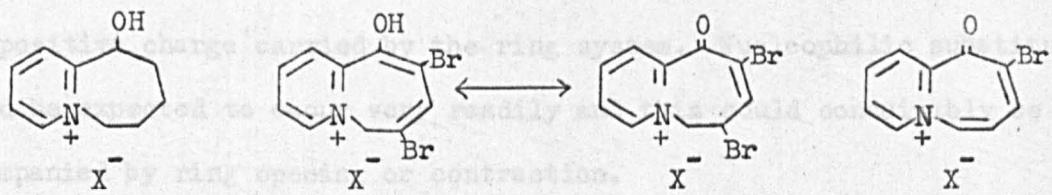
CXVI CXVII CXVIII

When a small amount of the diacetoxy compound (CXVI, X = Br) was treated with acid, the ultraviolet spectrum showed hydrolysis to be complete after about 10 mins. The new spectrum had a longer wavelength than the original compound (3530 Å) and this was taken to mean that an extension of the conjugated system had occured, presumably to the ketone (CXVII). The reaction was repeated on a larger scale but only oily residues were isolated. It was therefore decided to brominate the product of hydrolysis in situ.

The bromination was carried out in hydrobromic acid solution and the product which formed was isolated fairly readily and purified from

ethanol as a yellow crystalline solid. Although sufficient bromine was added for dibromination to have occured, analysis indicated that only one bromine atom had entered the ring and gave the empirical formula $C_{10}H_8Br_3NO$. The compound (CXVIII, X = Br) gave a deep jade green colour with neutral ferric chloride solution characteristic of an enolic or phenolic hydroxyl group and also had a very long wavelength absorption in the visible spectrum (4130 Å). Its structure was shown to be CXVIII (X = Br) from its N.M.R. spectrum which was run in D_2O. The spectrum contained aromatic protons as a multiplet (centred at 1.5 τ), an olefinic proton (2.9 τ) and methylene protons (4.7 τ) in the ratio 4:1:2. Further, the peaks due to the ethylenic and methylene protons were singlets which could only be explained if there were no adjacent protons available to cause splitting. The other proton, the hydroxyl proton, was not detected in the spectrum and it was assumed that either deuterium exchange had occured or that the absorption was coincident with that of HDO.

Other evidence as to the structure of the molecule (CXVIII, X = Br) was given by its reduction to 1-hydroxy-2-H-1,3,4,5-tetrahydro-pyrido[1,2a]azepinium bromide (CXIX, X = Br). On hydrogenation, 4 mole equivalents of hydrogen were taken up, and these corresponded to reduction of two double bonds (1-2 and 3-4) and replacement of the two bromine atoms on positions 2 and 4. The same compound (CXIX, X = Br) was also formed by hydrogenation of the diacetoxy-bromo compound (CXVI, X = Br) and the cyclic ketone (CXII, X = Br) with uptakes of 3- and 1 mole equivalents of hydrogen respectively.



CXIX CXX CXXI

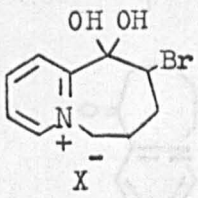
An ultraviolet spectrum of the bromo-hydroxy compound (CXVIII, X = Br) in concentrated sulphuric acid showed a shift to shorter wavelengths, the compound presumably existing as the keto tautomer (CXX). Elimination of hydrogen bromide from this should give the fully aromatic pyrido [1,2a] azepinium derivative (CXXI). Several attempts at achieving this have been carried out.

When heated at 160°C the bromo-hydroxy compound (CXVIII, X = Br) lost hydrogen bromide. The solid remaining after heating was, however, very charred and was insoluble in all the usual polar solvents. The same thing occured when the compound was boiled in acetic anhydride or heated with concentrated sulphuric acid. Heating with Amberlite IRA 400 (OH) suspended in methanol gave a deep red solution but on working up only oily residues were obtained. A reaction with silver acetate on boiling acetic acid also failed to give any identifyable product.

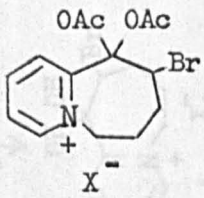
The final stage to the fully aromatic system has thus not been achieved. As hydrogen bromide is evolved from the bromo-hydroxy compound (CXVIII, X = Br) on heating, it is evident that the pyrido-azepinium salt which presumably first forms, is somewhat unstable. Indeed, the probability

that such a system can exist is open to doubt, particularly in view of the positive charge carried by the ring system. Nucleophilic substitution would be expected to occur very readily and this could conceivably be accompanied by ring opening or contraction.

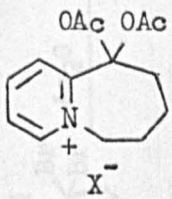
A few other reactions have been carried out on compounds in this series. When the cyclic ketone (CXII, X = Br) was monobrominated the monobromo derivative (CXXII, X = Br) was obtained. On boiling with acetic anhydride this gave the diacetoxy compound (CXXIII, X = Br). A similar compound (CXXIV, X = Br) also formed when the unsubstituted ketone (CXII, X = Br) was treated with acetic anhydride.



CXXII

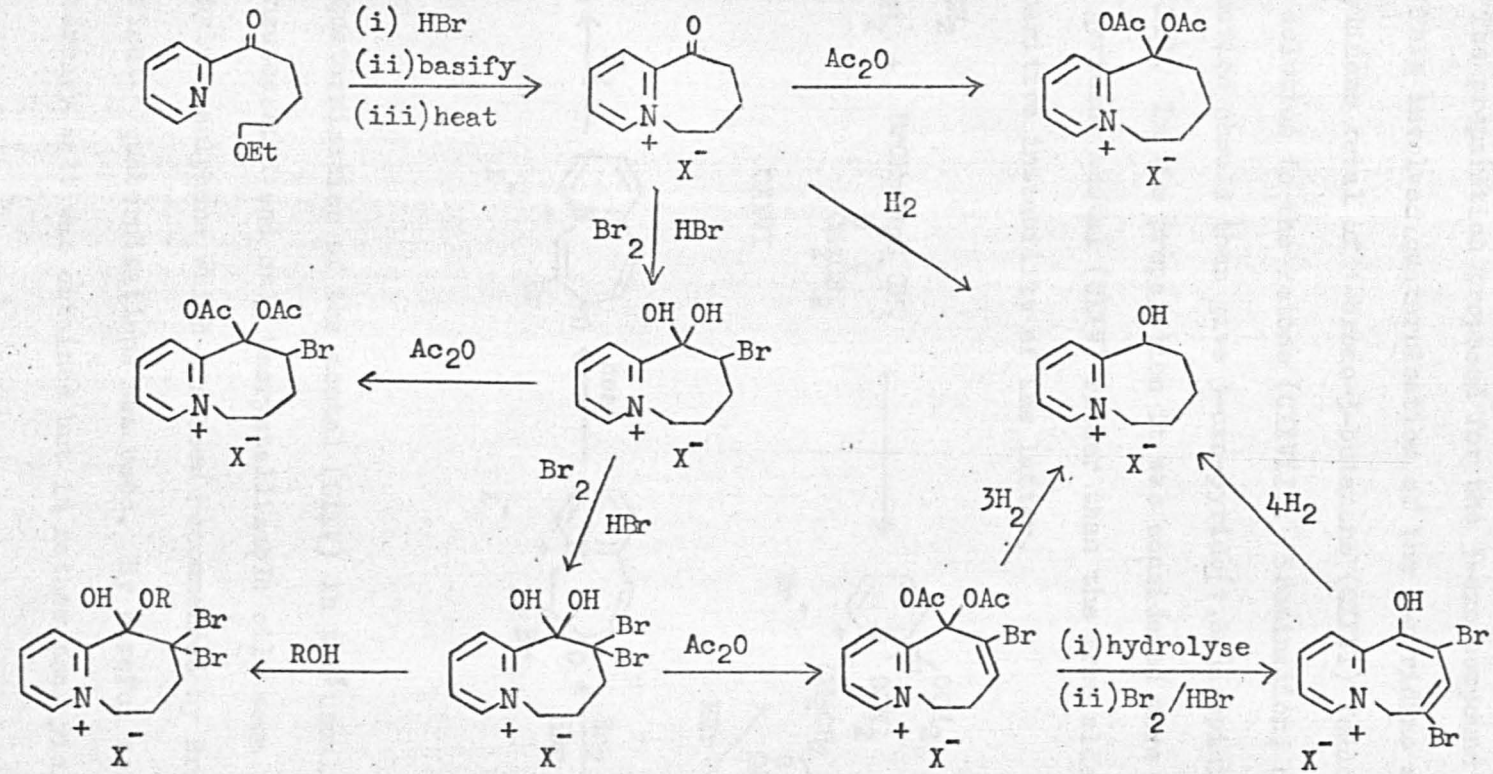


CXXIII



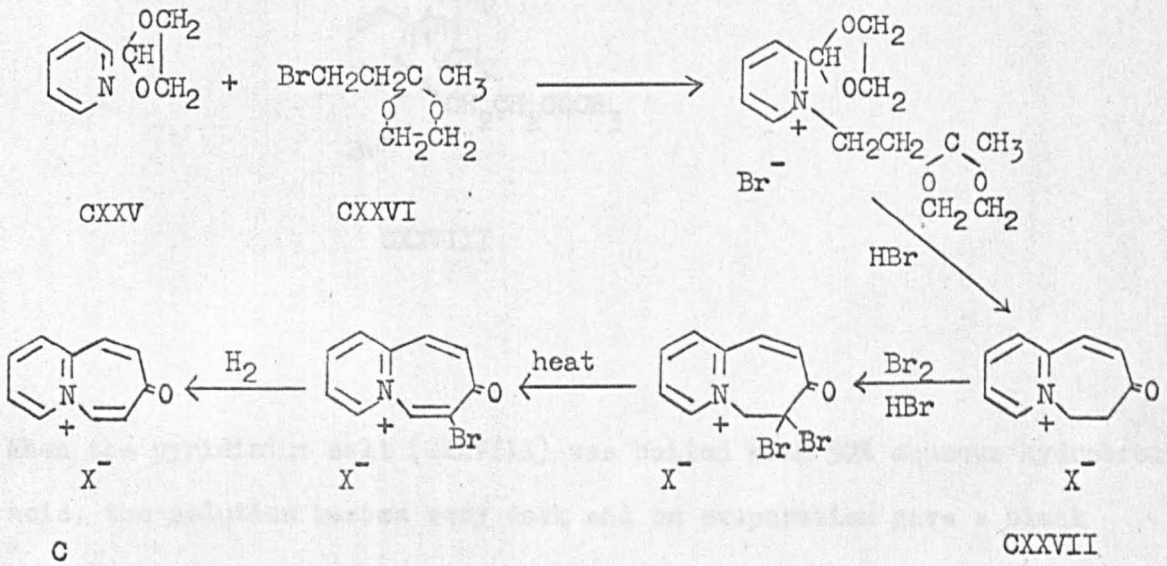
CXXIV

Summary of reactions in the 1-oxo pyrido[1,2a]azepinium series



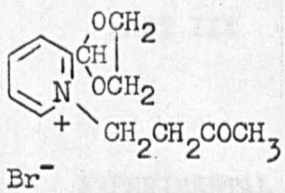
b) Attempted synthesis of 3-oxo pyrido[1,2a]azepinium compounds.

The preparation proposed for the 3-oxo compound (C) is outlined below. This involved quaternisation of the 2-pyridine acetal (CXXV) with the ethylidene ketal of 1-bromo-3-butanone (CXXVI) followed by cyclisation in acid solution to the ketone (CXXVII). Bromination, dehydrobromination and reduction should then give 3-oxo-pyrido[1,2a]azepinium bromide (C, X = Br). In the preparation it was considered more convenient to use the pyridine acetal (CXXV) rather than the free aldehyde because of the comparitive instability of the latter.



Quaternisation of the acetal (CXXV) in the usual solvents was rather unsuccessful and only uncrystallisable oils were formed. Eventually, tetramethylene sulphone which has been recommended by Bradsher and Parham[67] for 'difficult' quaternisations was used. By careful working up a crystalline quaternary salt was obtained but in rather poor yield. The product

had an infrared spectrum which showed both a carbonyl (1710 $cm.^{-1}$) and an acetal (C-O) (1120 $cm.^{-1}$) stretching, the last in the same position as the acetal stretching in 2-pyridine acetal (CXXV). Analysis gave the formula $C_{12}H_{16}BrNO_3$ which would indicate that hydrolysis of either the acetal or ketal group had occured. Because of the extreme ease of hydrolysis of the bromo ketal (CXXVI) the pyridinium salt was assigned structure CXXVIII. This was later confirmed by preparing it directly from the acetal (CXXV) and bromo-butan-2-one.



CXXVIII

When the pyridinium salt (CXXVIII) was boiled with 50% aqueous hydrobromic acid, the solution became very dark and on evaporation gave a black hygroscopic solid which could not be purified. Other attempts at cyclisation ended similarly.

PART III

EXPERIMENTAL

4-Ethoxybutyl bromide was obtained from tetramethylene glycol in 48% yield by an analagous procedure to that described for 3-ethoxypropyl bromide.[68] B.p. 167-72° (lit[69] 169°).

2-(5'-Ethoxyvaleryl) pyridine (CXI).[70]

The Grignard reagent from 4-ethoxybutyl bromide (70 g.) and magnesium (12 g.) in ether (650 ml.) was added slowly to 2-cyanopyridine (40 g.) in ether (300 ml.) under an atmosphere of nitrogen. Vigorous stirring was maintained throughout the addition. After leaving overnight the complex was hydrolysed by the addition of 5 N. aqueous hydrochloric acid and then made alkaline with ammonia (s.g. 0.88). The ether layer was separated, dried (Na_2SO_4) and the excess ether distilled. The residue was distilled under reduced pressure under nitrogen. B.p. 158-62°/10 mm. Yield 42.6 g (54%).

Found: C, 69.6; H, 8.4; N, 6.8

$C_{12}H_{17}NO_2$ requires: C, 69.5; H, 8.3; N, 6.7%

$\lambda_{max.}$ (95% EtOH) 2300, 2700 Å ($\log_{10} \varepsilon$ 3.94, 3.68)

$\nu_{max.}$ 1710 $cm.^{-1}$ (C = O) 1115 $cm.^{-1}$ (C - O).

1-Oxo-2-H-1,3,4,5-tetrahydropyrido[1,2a]azepinium bromide (CXII, X = Br)

2-(5'-Ethoxyvaleryl) pyridine (CXI) (20.0 g.) in 50% aqueous hydrobromic acid (200 ml.) was boiled under reflux for 1 hr. (The ethyl bromide which formed was periodically allowed to escape by removal of the condenser). Evaporation under reduced pressure gave a residue which was dissolved in water and treated dropwise with aqueous sodium carbonate, the liberated bromo-amine being extracted with chloroform. The chloroform

extract was dried (Na_2SO_4) and distilled. The residue was then heated for 1 hr. at 130-140° (oil bath), cooled, and the viscous solid dissolved in ethanol. Evaporation of the solution to small bulk followed by cooling gave a crystalline solid which was suspended in acetone and filtered (12.75 g., 54%) m.p. 151-4°C. Recrystallisation from ethanol:acetone gave flesh coloured rhombs m.p. 154-6°C.

Found: C, 49.4; H, 5.1; N, 6.2

$C_{10}H_{12}BrNO$ requires: C, 49.6; H, 5.0; N, 5.8%

$\lambda_{max.}$ 2680 Å ($\log_{10} \varepsilon$ 3.83)

$\nu_{max.}$ 1700 $cm.^{-1}$ (C = O).

The picrate (CXII, X = picrate) prepared by addition of aqueous sodium picrate to the bromide (CXII, X = Br) recrystallised from ethanol as yellow needles m.p. 116-117°C.

Found: C, 48.9; H, 3.7; H, 14.3

$C_{16}H_{14}N_4O_8$ requires: C, 49.25; H, 3.6; N, 14.35%

2,2-Dibromo-1,1-dihydroxy-2 H-1,3,4,5-tetrahydro pyrido[1,2a]azepinium bromide (CXIV, X = Br).

To a stirred solution of the ketone bromide (CXII, X = Br) (10.0 g.) in 50% aqueous hydrobromic acid (100 ml.) was added bromine (15.0 g.) in hydrobromic acid (40 ml.). An oily yellow solid came out of solution during the addition. Stirring was continued for 15 min. after the bromine had been added and then the mixture was warmed on a boiling water bath for 20 min. Evaporation under reduced pressure gave a fawn solid which was treated with water and re-evaporated. The solid was suspended in a 50:50

acetone:water mixture and filtered. (13.85 g., 80%). m.p. 165° (dec.). A portion recrystallised from water for analysis gave colourless microcrystalline needles m.p. 163.5 - 4.5° (dec.).

Found: C, 28.6; H, 2.8; N, 3.65

$C_{10}H_{12}Br_3NO_2$ requires: C, 28.7; H, 2.85; N, 3.4%

$\lambda_{max.}$ 2670 Å ($\log_{10} \varepsilon$ 3.88)

$\nu_{max.}$ 3100 cm.$^{-1}$ (OH) 1150 cm.$^{-1}$ and 1045 cm.$^{-1}$ (CO stretching and vibration?).

The picrate (CXIV, X = picrate) crystallised from acetone as yellow needles, m.p. 139.5-140°.

Found: C, 35.35; H, 2.35; N, 9.85

$C_{16}H_{12}Br_2NO_8$ requires: C, 35.05; H, 2.2; N, 10.2%

$\nu_{max.}$ 1695 cm.$^{-1}$ (C=O stretching).

Recrystallisation of the bromide (CXIV, X = Br) from ethanol:ethyl acetate gave 2,2-dibromo-1-ethoxy-1-hydroxy-2 H-1,3,4,5-tetrahydropyrido[1,2a]-azepinium bromide (CXV, X = Br, R = Et) as small colourless rhombs m.p. 110-111°C.

Found: C, 30.55; H, 3.6; N, 3.4

$C_{12}H_{16}Br_3NO_2.H_2O$ requires: C, 31.15; H, 3.9; N, 3.0

$\lambda_{max.}$ 2700 Å ($\log_{10} \varepsilon$ 3.90)

$\nu_{max.}$ 3300 cm.$^{-1}$ (OH) 1070 cm.$^{-1}$ (aryl ether C-O stretching).

The methoxy derivative (CXV, X = Br, R = Me) was similarly prepared by recrystallisation from methanol:ethyl acetate, m.p. 107-9°C (colourless

rhombs).

Found: C, 29.2; H, 4.15; N, 2.8

$C_{11}H_{14}Br_3NO_2.H_2O$ requires: C, 29.35; H, 3.6; N, 3.1

$\lambda_{max.}$ 2650 Å ($\log_{10}\epsilon$ 3.76)

2-Bromo-1,1-diacetoxy-1 H-4,5-dihydropyrido[1,2a]azepinium bromide (CXVI, X = Br).

The dibromo hydroxy compound (CXIV, X = Br) (5.00 g.) was boiled with acetic anhydride (100 ml.) for 0.75 hr. and the acetic anhydride distilled off under reduced pressure. The dark solid residue (4.24 g., 85%) was purified from ethanol:acetone with the use of charcoal, giving a flesh coloured amorphous solid m.p. 171° (2.34 g., 46%).

Found: C, 40.35; H, 3.55; N, 3.3

$C_{14}H_{15}Br_2NO_4$ requires: C, 39.95; H, 3.6; N, 3.3%

$\lambda_{max.}$ 2440, 3170 Å ($\log_{10}\epsilon$ 4.02, 4.07)

$\nu_{max.}$ 1780 cm.$^{-1}$ (acetyl C=O) 1165 cm.$^{-1}$ (C-O).

On heating a small amount of the diacetoxy compound (CXIV, X = Br) for 10 mins. with hydrobromic acid on a water bath the ultraviolet spectrum of the solution had $\lambda_{max.}$ 2530 and 3530 Å. Attempts at isolation of a product at this stage gave only oily residues.

2,4-Dibromo-1-hydroxy-5 H-pyrido[1,2a]azepinium bromide (CXVIII, X = Br)

The crude diacetoxy compound (CXVI, X = Br) (4.00 g.) in 50% aqueous hydrobromic acid (80 ml.) was heated on a boiling water bath for 1 hr. and cooled. To the stirred solution was added bromine (6 g.) in hydrobromic

acid (20 ml.). During the addition a yellow perbromide separated. The mixture was heated on a water bath for 15 min. and then evaporated to dryness under reduced pressure. The residue was taken up in water and re-evaporated. Several repetitions of this process gave a solid which was suspended in ethyl acetate and filtered. The crude material was recrystallised from ethanol (charcoal) as yellow green rhombs m.p. 183-5° (1.72 g., 45%).

Found: C, 30.2; H, 2.5; N, 3.45

$C_{10}H_8Br_3NO$ requires: C, 30.15; H, 2.05; N, 3.5%

$\lambda_{max.}$ 2580, 3110, 4100 Å ($\log_{10} \varepsilon$ 3.98, 3.78, 3.74)

$\lambda_{max.}$ (conc. H_2SO_4) 2570, 3540 Å

The compound (CXVIII, X = Br) gave a deep jade green colour with neutral aqueous ferric chloride.

The picrate (CXVIII, X = picrate) recrystallised from acetone as yellow rhombs m.p. 146-8°.

Found: C, 36.35; H, 2.2

$C_{16}H_{10}Br_2N_4O_8$ requires: C, 35.85; H, 1.9%

1-Hydroxy-2 H-1,3,4,5-tetrahydropyrido[1,2a]azepinium bromide (CXIX, X = Br)

a) 2,4-Dibromo-1-hydroxy-5 H-pyrido[1,2a]azepinium bromide (CXVIII, X = Br) (0.50 g.) in 95% ethanol (100 ml.) was hydrogenated at atmospheric temperature and pressure using 10% palladium charcoal catalyst (0.3 g.). The absorption was equivalent to 4-mole equivalents of hydrogen. The solution was filtered and evaporated. Cooling gave crystals of

1-hydroxy-2 H-1,3,4,5-tetrahydropyrido[1,2a]azepinium bromide (CXIX, X = Br) which was suspended in ethyl acetate and filtered (0.225 g., 74%). Crystallisation from ethanol:ethyl acetate gave flesh coloured rhombs m.p. 172-3.5°C.

Found: C, 49.3; H, 5.75; N, 5.75

$C_{10}H_{14}BrNO$ requires: C, 49.2; H, 5.75; N, 5.7%

$\lambda_{max.}$ 2680 Å ($\log_{10} \varepsilon$ 3.79)

$\nu_{max.}$ 3250 $cm.^{-1}$ (OH).

b) The cyclic ketone (1.00 g.) (CXII, X = Br) in 95% ethanol (100 ml.) with 10% palladium charcoal (0.5 g.) was hydrogenated. One mole equivalent of hydrogen was absorbed. Working up as above gave the 1-hydroxy compound (CXIX, X = Br) (0.8 g., 80%) m.p. 171°. The spectra were identical with those of the compound prepared from the bromo-hydroxy derivative (CXVIII, X = Br).

c) The diacetoxy compound (CXVI, X = Br) (0.40 g.) in 95% ethanol (100 ml.) was hydrogenated with the use of 10% palladium charcoal catalyst (0.30 g.). The uptake of three mole equivalents of hydrogen was noted. After filtration and evaporation a product was isolated by careful addition of ethyl acetate followed by filtration of the precipitated solid. The infrared spectrum showed it to be the 1-hydroxy compound (CXIX, X = Br).

Attempted dehydrobromination of 2,4-dibromo-1-hydroxy-5 H-pyrido[1,2a]-azepinium bromide (CXVIII, X = Br)

a) The bromo compound (CXVIII, X = Br) (0.40 g.) was heated at 160°C (oil bath) for two hours during which hydrogen bromide was given off.

The solid remaining after the evolution was charred and would not dissolve in polar solvents.

b) The compound (CXVIII, X = Br) (0.50 g.) in acetic anhydride (30 ml.) was boiled under reflux for two hours. After evaporation under reduced pressure there remained a black solid residue which could not be purified, and which was not soluble in the normal polar solvents.

c) The bromo compound (CXVIII, X = Br) in methanol (50 ml.) and Amberlite IRA 400 (OH) (20 ml.) was boiled with stirring for 0.75 hr., the solution turning deep red. After cooling and filtration the solution was evaporated to dryness leaving a black uncrystallisable oil.

d) The compound (CXVIII, X = Br) (1.5 g.) and silver acetate (2.25 g.) in glacial acetic acid (125 ml.) was boiled under reflux for 40 hrs. The mixture was then cooled, filtered and evaporated to dryness under reduced pressure. 50% Aqueous hydrobromic acid (50 ml.) was added to the residue and the solution heated on a boiling water bath for 0.25 hr. Evaporation to dryness under reduced pressure gave a black solid residue which could not be purified.

2-Bromo-1,1-dihydroxy-2 H-1,3,4,5-tetrahydropyrido[1,2a]azepinium bromide (CXXII, X = Br).

To a stirred solution of the cyclic ketone (CXII, X = Br) (1.0 g.) in 50% aqueous hydrobromic acid (25 ml.) was added bromine (0.68 g.) in hydrobromic acid (10 ml.) . Working up as in the case of the dibromo-dihydroxy compound (CXIV, X = Br) gave the mono-bromo compound (CXXII, X = Br) (1.2 g., 85%). It recrystallised from an 80% acetone:water solution

as flesh coloured blunt needles m.p. 135.5-6°.

Found: C, 35.55; H, 3.95; N, 4.6

$C_{10}H_{13}Br_2NO_2$ requires: C, 35.4; H, 3.85; N, 4.15%

$\lambda_{max.}$ 2670 Å ($\log_{10} \varepsilon$ 3.72)

$\nu_{max.}$ 3250 $cm.^{-1}$ (H bonded OH).

2-Bromo-1,1-diacetoxy-2 H-1,3,4,5-tetrahydropyrido[1,2a]azepinium bromide (CXXIII, X = Br).

A solution of the bromo-dihydroxy bromide (CXXII, X = Br) in acetic anhydride (120 ml.) was boiled under reflux for 1 hr. Cooling followed by evaporation to dryness gave an oily residue which could be crystallised by trituration with acetone (0.62 g., 4%). Crystallisation from ethanol: acetone gave flesh coloured microcrystalline rhombs m.p. 183-3.5°.

Found: C, 39.9; H, 3.8; N, 3.85

$C_{14}H_{17}Br_2NO_4$ requires: C, 39.75; H, 4.05; N, 3.30%

$\lambda_{max.}$ 2670 Å ($\log_{10} \varepsilon$ 3.67)

$\nu_{max.}$ 1780 $cm.^{-1}$ (acetyl C=O) 1175 $cm.^{-1}$ (C-O stretching).

1,1-Diacetoxy-2 H-1,3,4,5-tetrahydropyrido[1,2a]azepinium bromide (CXXIV, X = Br).

The cyclic ketone (CXII, X = Br) (0.50 g.) in acetic anhydride (25 ml.) was boiled under reflux for 2 hr., cooled and then evaporated to dryness. The oily residue was taken up in absolute ethanol (charcoal) and a solid precipitated by careful addition of ethyl acetate (0.165 g., 24%). Crystallisation from ethanol: ethyl acetate gave small colourless rhombs m.p. 158-60°.

Found: C, 48.7; H, 5.35; N, 4.4

$C_{14}H_{18}BrNO_4$ requires: C, 48.85; H, 5.25; N, 4.05%

$\lambda_{max.}$ 2420, 3000 Å ($\log_{10} \varepsilon$ 3.88, 4.07)

$\nu_{max.}$ 1760 $cm.^{-1}$ (acetyl C=O) 1210 $cm.^{-1}$ (CO stretching).

4-Bromo-butan-2-one ethylene ketal (CXXVI) was prepared according to Jones' modification[71] of the method of Schinz and Williman[72] from ethyl acetoacetate except that the final basification stage was carried out with sodium bicarbonate instead of pyridine. The product consisted of the ketal (b.p. 88-94 /17 mm.) (19% overall yield) and 4-bromo-butan-2-one (b.p. 84-8°C/17 mm. (10% overall yield). The ketal (CXXVI) was very prone to hydrolysis and was kept over calcium chloride.

2-(1,3-Dioxolan-2-yl)pyridine (CXXV) was prepared by the method of Bradsher and Parham[68] from 2-pyridine aldehyde and ethylene glycol. The yield was 69% based on the aldehyde.

1-(3'-oxo)butyl-2-(1,3-dioxolan-2-yl)pyridinium bromide (CXXVIII)

a) The pyridine acetal (CXXV) (6.00 g.) and the ethylene ketal of 4-bromo-butan-2-one (CXXVI) (8.1 g.) in tetramethylene sulphone (10 ml.) were heated on a water bath for 2.5 hr. giving a viscous red oil. This was poured into ethyl acetate (150 ml.) and the excess ester decanted off. The oily residue was washed with ethyl acetate (50 ml.) and then three times with dry ether (50 ml. portions). Trituration with acetone followed by careful addition of absolute alcohol gave a colourless crystalline solid m.p. 127-9° which recrystallised from ethanol:ethyl acetate as blunt needles m.p. 129°. (2.20 g., 18%).

Found: C, 47.6; H, 5.45; N, 4.95

$C_{12}H_{16}BrNO_3$ requires: C, 47.7; H, 5.35; N, 4.65%

$\lambda_{max.}$ 2650 Å ($\log_{10}$ ε 3.83)

$\nu_{max.}$ 1710 $cm.^{-1}$ (C=O) 1120 $cm.^{-1}$, 1040 $cm.^{-1}$ (CO stretching and vibration)

b) The acetal (CXXV) (6.00 g.) and 4-bromo-butan-2-one (6.8 g.) in tetramethylene sulphone (10 ml.) heated on water bath for 2.5 hr. Working up as described above gave the pyridinium salt (CXXVIII) (1.2 g., 10%) identical to that obtained previously.

Attempted cyclisation of the pyridinium salt (CXXVIII)

a) The quaternary compound (CXXVIII)(0.50 g.) in 50% hydrobromic acid (10 ml.) was boiled under reflux for 2 hr. during which the solution turned a deep brown colour. Cooling followed by evaporation gave a hygroscopic black solid which could not be crystallised.

b) The salt (CXXVIII)(0.40 g.) dissolved in acetic anhydride (10 ml.) to which concentrated sulphuric acid (5 drops) had been added was boiled under reflux for 3 hr. Cooling and then addition of ethyl acetate precipitated a black intractable solid.

c) The pyridinium salt (CXXVIII)(0.5 g.) in concentrated sulphuric acid (7.5 ml.) was heated for 2 hr. at 80-90° (oil bath). The solution was cooled and poured into dry ether (100 ml.) at -10°. A black solid precipitated.

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