

Durham E-Theses

Some new aromatic diquatery salts of pyrazine

T. R. Thomas

How to cite:

Thomas, T. R. (1966) Some new aromatic diquatery salts of pyrazine. Masters thesis, Durham University.

Use policy

The full-text may be used and/or reproduced, and given to third parties in any format or medium, without prior permission or charge, for personal research or study, educational, or not-for-profit purposes provided that:

- a full bibliographic reference is made to the original source
- a <https://etheses.durham.ac.uk/id/eprint/9904/> is made to the metadata record in Durham E-Theses
- the full-text is not changed in any way

The full-text must not be sold in any format or medium without the formal permission of the copyright holders.

Please consult the [full Durham E-Theses policy](#) for further details.

SOME NEW AROMATIC DIQUATERNARY SALTS
OF PYRAZINE

BY

T.R. THOMAS

A THESIS

submitted to the
UNIVERSITY OF DURHAM
for the degree of
MASTER OF SCIENCE

CONSTANTINE COLLEGE
OF TECHNOLOGY

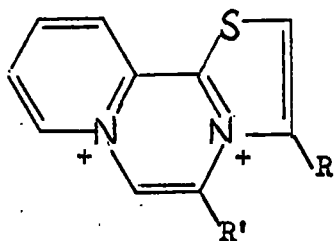
December, 1966



SUMMARY

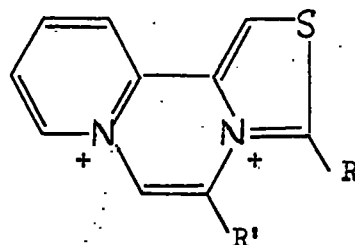
The methods of synthesis of quinolizinium, pyrazidi-inium and other salts containing quaternary bridgehead nitrogen atoms are reviewed.

The object of this work was to establish satisfactory, and if possible, general methods of synthesis of the aromatic bridged diguaternary salts (I, II, LXXXIII, LXXXIV) and some of their alkyl and aryl derivatives, in quantities which permit a study of their chemical properties and possible herbicidal activity.



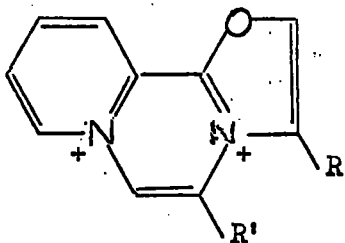
$2x^-$

I



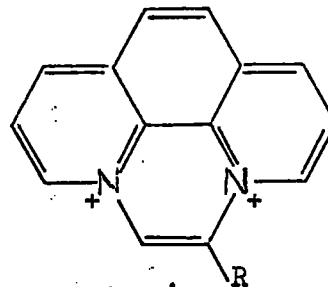
$2x^-$

II



$2x^-$

LXXXIII



$2x^-$

LXXXIV

2-(2-Pyridyl)thiazole (LXXXV; R=H) was synthesised by treating picolinic acid thioamide with bromoacetal.

2-Methyl-4-(2-pyridyl)thiazole (XC; R=Me) was prepared by treating ω -bromoacetylpyridine with thioacetamide.

Quaternisation of these bases with bromoacetaldehyde oxime, bromoacetone and ω -bromoacetophenone and subsequent cyclodehydration of the resulting monoquaternary salts, afforded the pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium salts (I; R=H, Me, R'=H, Me or Ph) and the pyrido [1,2-a] thiazolo [4,3-c] pyrazidi-inium salts (II; R=Me, R'=H, Me or Ph) respectively.

The synthesis of bridged aromatic diquaternary salts of 4-phenyl-2-(2-pyridyl)thiazole was unsuccessful. The 3-phenyl-5,6-dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium salt (LXXXIX; R=Ph, X=Br) was the only diquaternary derivative of this base isolated.

Aromatic bridged diquaternary salts of the analogous base 4-methyl-2-(2-pyridyl)thiazole (LXXXV; R=Me) are described.

The attempted synthesis of aromatic bridged diquaternary salts of 1,10-phenanthroline is described, only the phenyl substituted derivative (LXXXIV; R=Ph) was isolated.

Several attempts were made to synthesise 2-(2-pyridyl)oxazole (CI; R=H), however the quantity of base obtained did not permit the preparation of bridged aromatic diquaternary salts.

ACKNOWLEDGEMENTS

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

He is particularly indebted to Dr. E.E. Glover for his excellent supervision, and constant encouragement.

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

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

CONTENTS

	<u>Page</u>
TITLE	(i)
SUMMARY	(ii)
ACKNOWLEDGEMENTS	(iv)
CONTENTS	(v)
INTRODUCTION	1
Nomenclature	2
Historical Introduction	3
DISCUSSION	52
ILLUSTRATIONS	87
Ultraviolet spectra of:-	
2-(2-pyridyl) thiazole and 2-methyl-4-(2-pyridyl) thiazole ..	88
Pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium dibromide and 3-Methyl-pyrido [1,2-a] thiazolo [4,3-c] pyrazidi-inium dibromide .	89
5,6-Dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium dibromide and 3-Methyl-5,6-dihydro-pyrido [1,2-a] thiazolo [4,3-c] pyrazidi -inium dibromide	90
EXPERIMENTAL	91
BIBLIOGRAPHY	116
INDEX OF COMPOUNDS DESCRIBED IN THE EXPERIMENTAL SECTION	122

INTRODUCTION

1
21 SEP 1967
LIBRARY

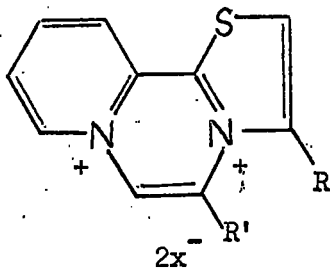
NOMENCLATURE

In accordance with the recommendations of the Chemical Society,¹ the ring index system will be used throughout for the naming of fused cyclic systems.

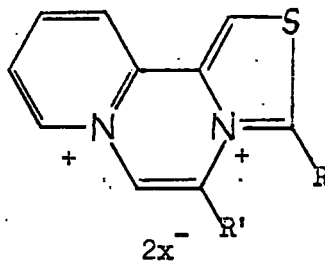
The name pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium ion has been adopted to describe the tricyclic fused ring system (I; R=R'=H). When the sulphur atom is replaced with an oxygen atom the system is referred to as the pyrido [1,2-a] oxazolo [2,3-c] pyrazidi-inium dication (LXXXIII, R=R'=H).

Similarly the name pyrido [1,2-a] thiazolo [4,3-c] pyrazidi-inium ion is used to describe the tricyclic fused ring system (II; R=R'=H).

Benzo[b]dipyrido[1,2-a : 2',1'-c]pyrazidi-inium dication (LXXXIV; R=H) is the name used to describe the tetracyclic system pyrene, where the 3a and 5a bridgehead carbon atoms have been replaced with quaternary nitrogen atoms.



I

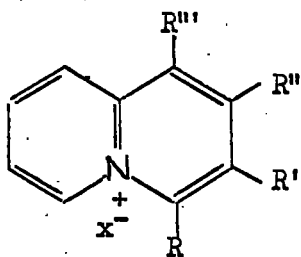


II

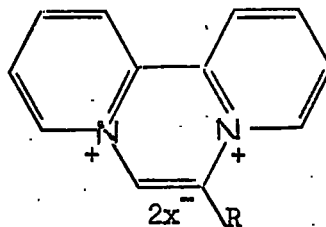
HISTORICAL INTRODUCTION

The most widely studied of all the bridgehead nitrogen compounds are those in which the bridgehead nitrogen atom is quaternary.

In an aromatic cation of this type, the presence of the positively charged nitrogen confers π -deficient² properties on the compound, examples of such cations are the quinolizinium cation (III) and the dipyridopyrazidi-inium dication (IV). The extremely π -deficient compounds of this type are reviewed in the first part of the introduction.

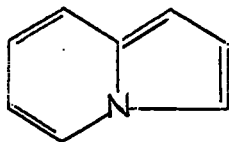


III



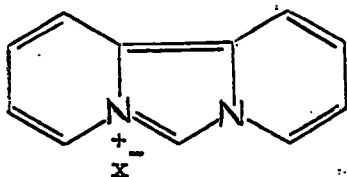
IV

Another group of bridgehead nitrogen compounds is that in which the nitrogen donates two electrons to the aromatic π electron system. Compounds of this type are called π -excessive systems and are exemplified by indolizine (V), but their chemistry, unlike that of the π -deficient compounds mentioned, has not been widely studied.

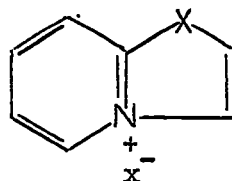


V

Those compounds falling between these two extremes may be expected to show both π -excessive and π -deficient properties, for example, ring systems with a quaternary and a tertiary bridgehead nitrogen atom, exemplified by the dipyrido [1,2-c : 2',1'-e] imidazolium cation³ (VI), and those with a quaternary bridgehead nitrogen atom but possessing other ring heteroatoms, as in the case of the isoelectronic pyridothiazolium⁴ (VII; X=S), pyridoxazolium⁵ (VII; X=O), and pyridoimidazolium⁶ (VII; X=NR) cations.



VI



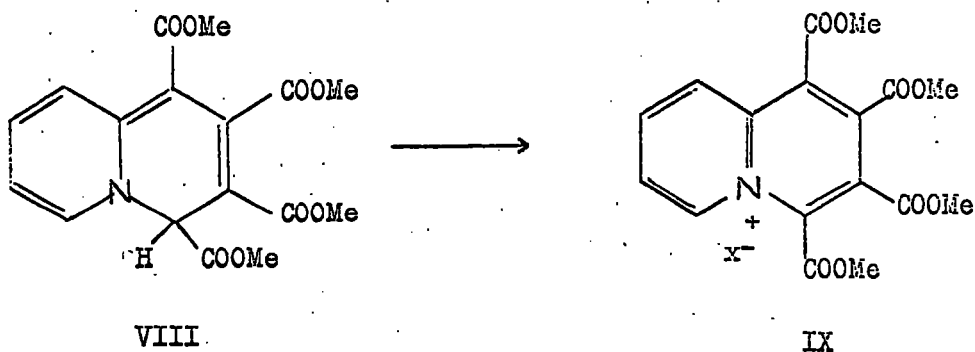
VII

These compounds are reviewed in part two of the introduction.

1. Π -Deficient Aromatic Quaternary Bridgehead Nitrogen Compounds

(i) Quinolizinium salts

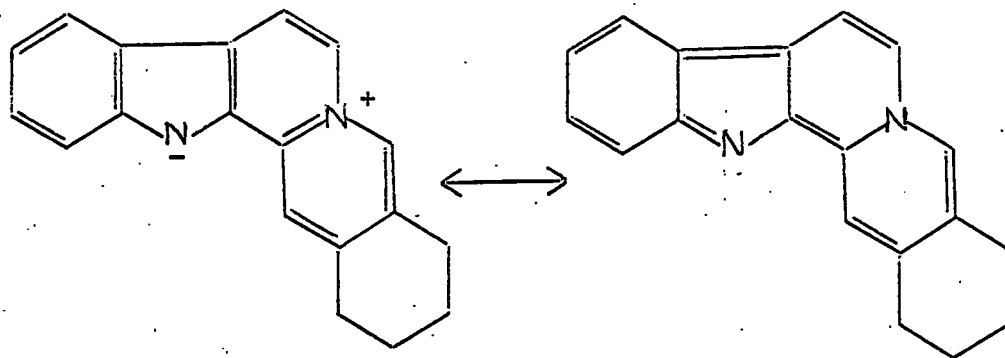
Prior to 1954, the only reported synthesis of a quinolizinium compound having no additional fused rings, was that recorded by Diels and Alder⁷ in 1931. From the reaction between pyridine and the dimethyl ester of acetylene dicarboxylate, these authors obtained three products, one of which, a stable yellow compound, has since been shown^{8,9} to be tetramethyl 4H-quinolizine 1,2,3,4-tetracarboxylate (VIII). When the quinolizine derivative (VIII) was treated with bromine in methanol, the quinolizinium perbromide (IX; X=Br₃) was obtained which yielded the bromide (IX; X=Br) on boiling with acetone.



When Thyagarajan¹⁰ reviewed quinolizine chemistry in 1954, the work necessarily contained few references to the fully aromatic quinolizinium cation (III) and its homologues. Since then, however, much progress has been made in quinolizinium ion chemistry.

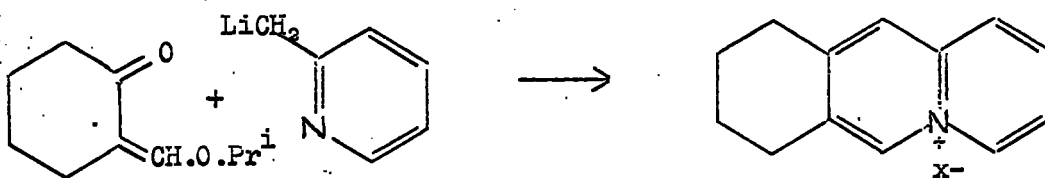
Excluding the diene synthesis described by Diels and Alder⁷, there are essentially two ways of synthesising quinolizinium and related cations. The first method involves attachment of a suitable side-chain onto the carbon adjacent to the pyridine nitrogen atom, cyclisation is then achieved by intramolecular quaternisation. The second method employs quaternisation of a 2-substituted pyridine with an agent capable of condensing with the 2-substituent. As an extension of these general methods, certain workers^{11,12,13} devised modified procedures involving a second component capable of condensing with the 2-substituted quaternised pyridine.

McLamore and Woodward¹⁴ arrived at a synthesis of the quinolizinium nucleus as a result of their work in establishing the structure of the alkaloid sempervirine (X), and this has been the basis of many other syntheses of quinolizinium compounds.



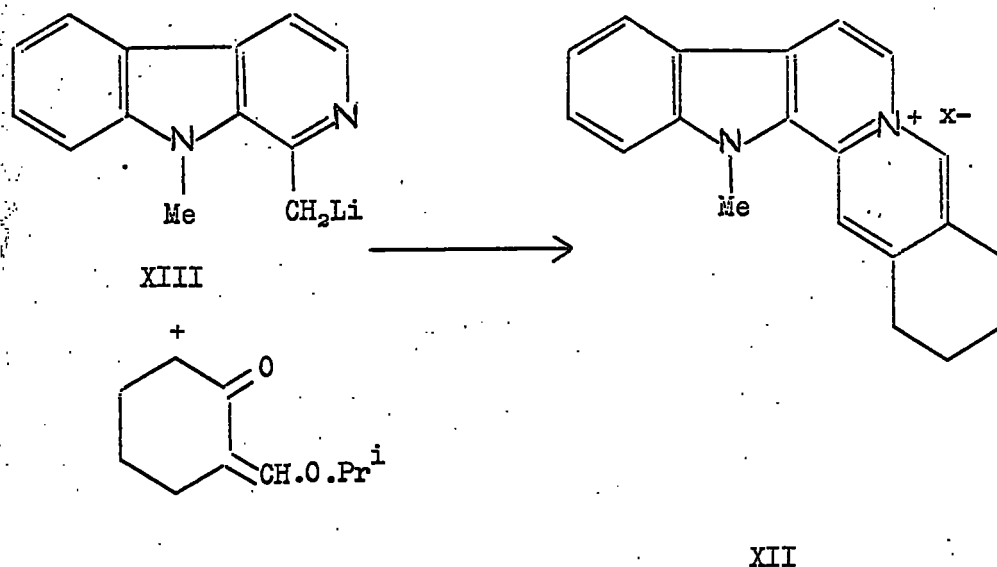
X

The procedure they employed involved the condensation of 2-picolyllithium with 2-isopropoxymethylenecyclohexanone, the cyclisation taking place in the presence of mineral acid to afford a 51% yield of 7,8,9,10-tetrahydrobenzo[b]quinolizinium picrate (XI; X=picrate).

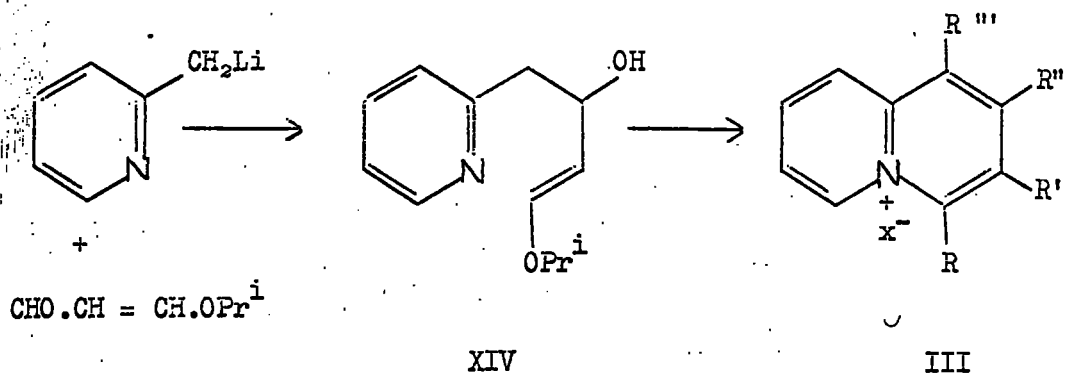


XI

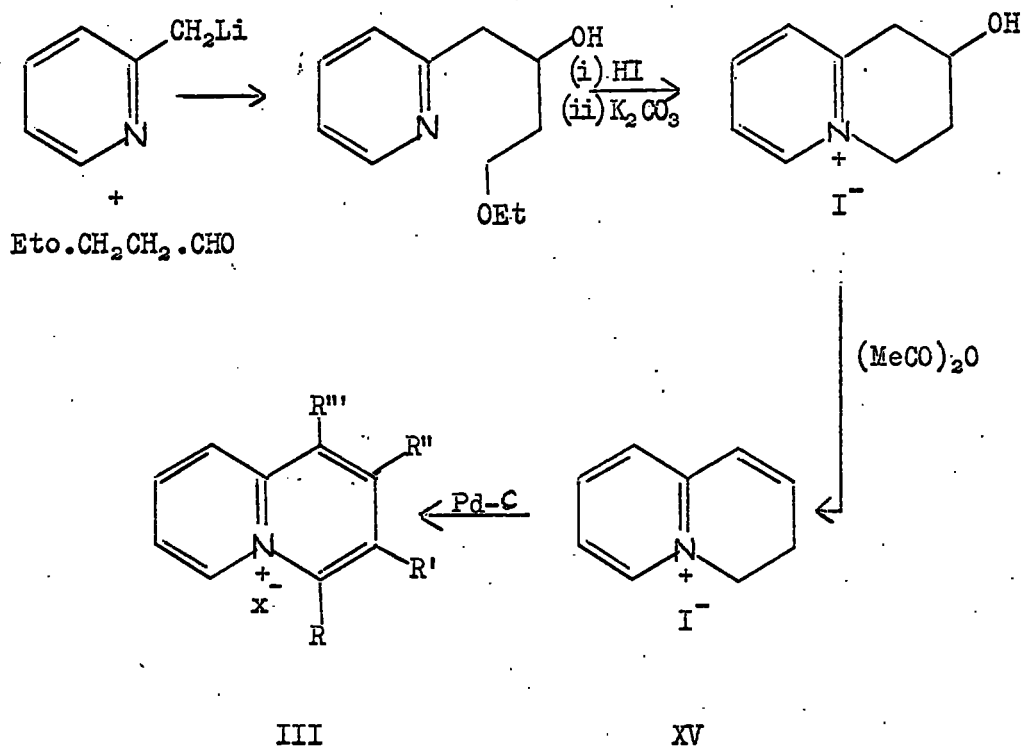
The method was extended to the synthesis of the methochloride of sempervirine (XII; X=Cl) by the condensation of 2-isopropoxy-methylenecyclohexanone with the lithium derivative of N-methylharman (XIII). Subsequent cyclisation afforded 13-methyl-1,2,3,4-tetrahydrobenz [g]indolo [2,3-a]quinolizinium chloride (XII; X=Cl).



The simple quinolizinium ion (III; R=R'=R''=R'''=H) was first synthesised by Beaman and Woodward¹⁵ who obtained a low yield from a modification of the previous method. The condensation was analogous in so much as 2-picolylium-lithium and 3-isopropoxyacrolein were the starting materials, the intermediate (XIV) subsequently undergoing cyclisation with acid to afford the required quinolizinium salt (III; R=R'=R''=R'''=H).

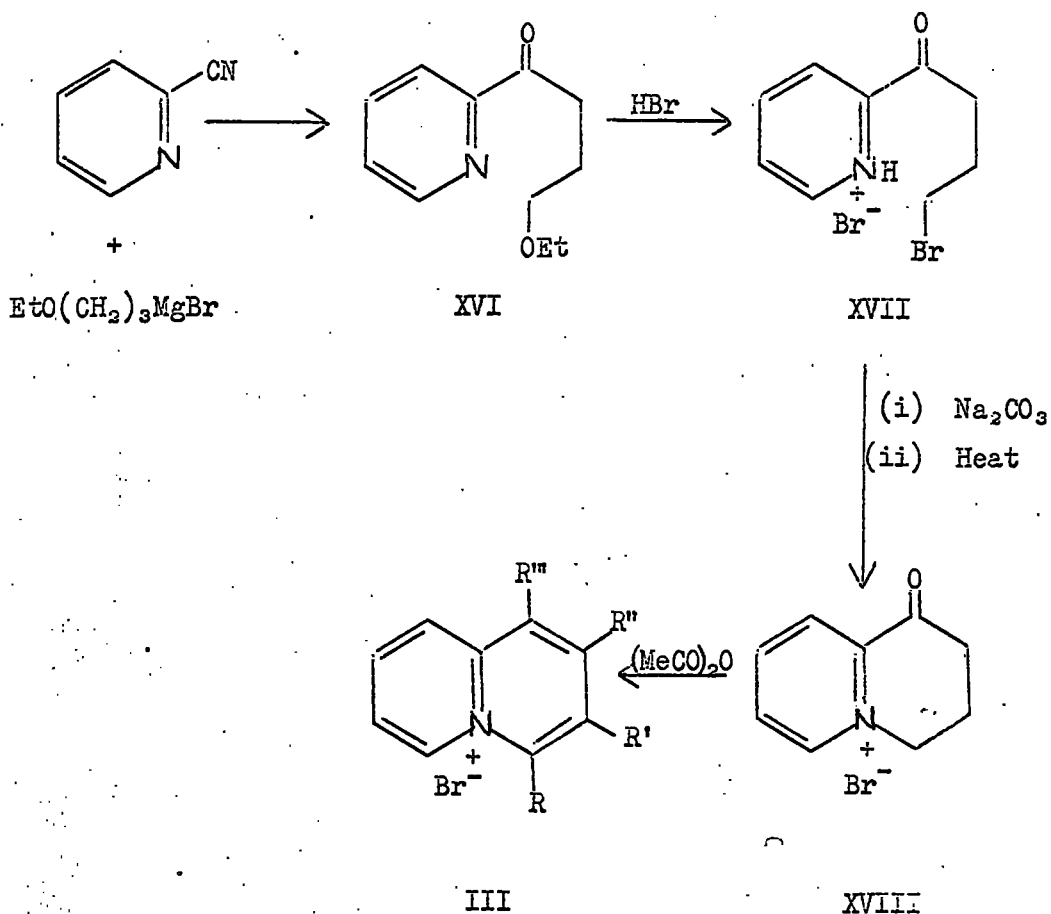


Boekelheide and Gall¹⁶, by replacing the 3-isopropoxyacrolein with 3-ethoxypropionaldehyde, obtained the 3,4-dihydroquinolizinium salt (XV), which, on subsequent dehydrogenation, gave the aromatic salt (III; $R=R'=R''=R'''=H$, X =picrate), isolated as the picrate in 10% overall yield.



Later, Boekelheide and Ross¹⁷ extended the procedure to prepare 4-methylquinolizinium salts (III; R=Me, R'=R''=R'''=H) by starting with the mono-lithium derivative of 2,6-lutidine and dehydrogenating the intermediate dihydro compound.

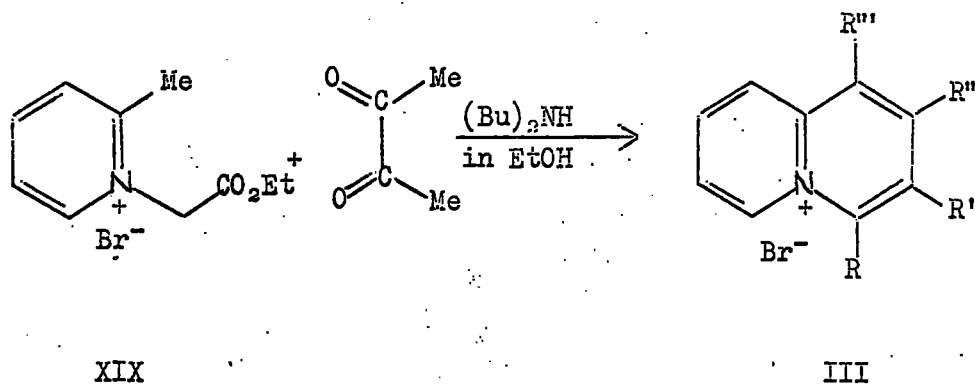
The first synthesis of quinolizinium salts in appreciable yield was recorded by Glover and Jones^{18,19}. Treatment of 2-cyanopyridine with the Grignard reagent from 3-ethoxypropylbromide gave 2-4'-ethoxybutyrylpyridine²⁰ (XVI) which after cleavage with hydrobromic acid and subsequent basification yielded the bromoketone (XVII). Cyclisation was effected by boiling the bromo compound (XVII) in chloroform affording 1,2,3,4-tetrahydro-1-oxo-quinolizinium bromide (XVIII). This cyclic ketone was then dehydrated to quinolizinium bromide (III, R=R'=R''=R'''=H) by boiling under reflux with acetic anhydride. An overall yield of 48% was recorded, based on the starting 2-cyanopyridine.



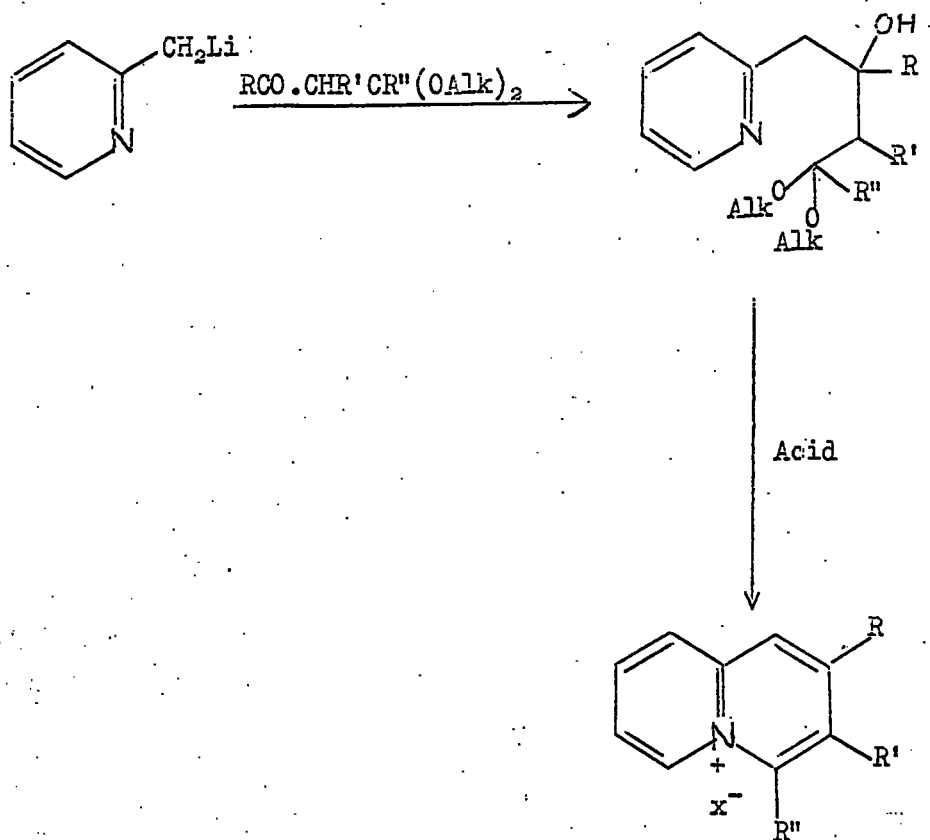
Using this general method the same authors¹⁹ prepared 2-, 3- and 4-alkyl and aryl substituted quinolizinium salts by suitably modifying the aliphatic precursor.

Katritzky et al²¹ used a modification of this method to synthesise 1-, 2-, 3-, and 4-methylquinolizinium bromides, but a more convenient procedure has been devised by Iwai and Miyadera²² which affords the intermediate ketone (XVIII) in higher yield.

As an extension of the two basic methods mentioned previously (page 6) certain authors¹¹ prepared several 2,3-disubstituted quinolizinium salts (III; R=R''=H, R'=R'''=Me) by the condensation of quaternary salts of α -picoline with compounds having two adjacent oxo-groups. Thus 2,3-dimethylquinolizinium bromide (III; R=R''=H, R'=R'''=Me) was obtained by the action of diacetyl on the quaternary salt (XIX) formed between ethyl bromoacetate and α -picoline, cyclisation was achieved by heating in ethanolic dibutylamine. The yields reported for this reaction are usually in the order of 80%.



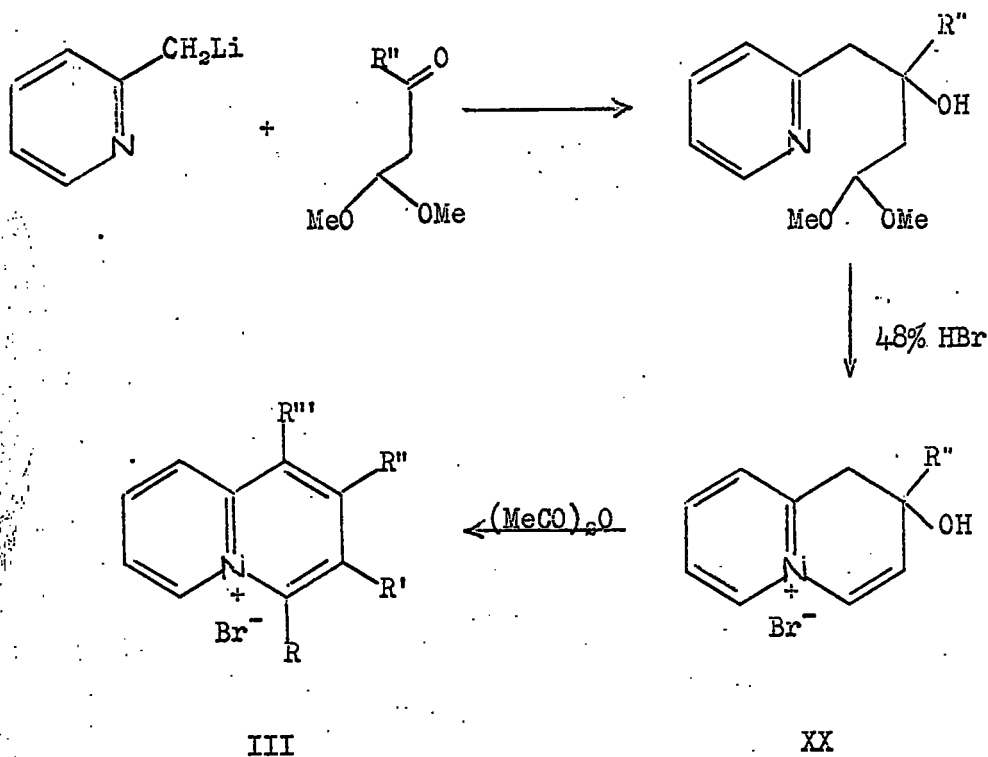
A range of 2-, 3-, and 4-alkyl and aryl substituted quinolizinium salts have been prepared by Richards and Stevens²³, by treating the enol ether or the monoketal of a β -diketone with 2-picoyl-lithium, and cyclising the resulting alcohols with acid.



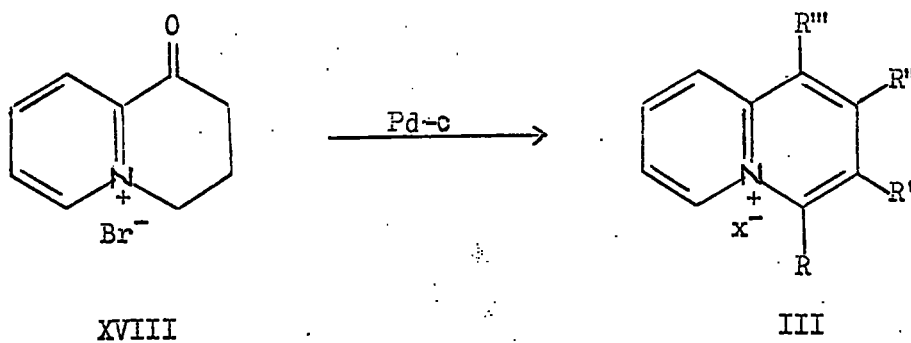
By an extension of the Richards and Stevens procedure and using 2,6-lutidyl-lithium with the appropriate protected β -diketones, Amstutz and Hansen²⁴ synthesised 2,4,6-trimethyl-, and 2-phenyl-4,6-dimethylquinolizinium salts.

Nesmayanov and Rybinskaya²⁵ have reported a procedure for the specific synthesis of 2-substituted quinolizinium salts which avoids the dehydrogenation stage used by Boekelheide et al^{16,17}. They treated 2-picolyllithium with 2-acylacetals, cyclisation being effected by boiling under reflux with 48% hydrobromic acid.

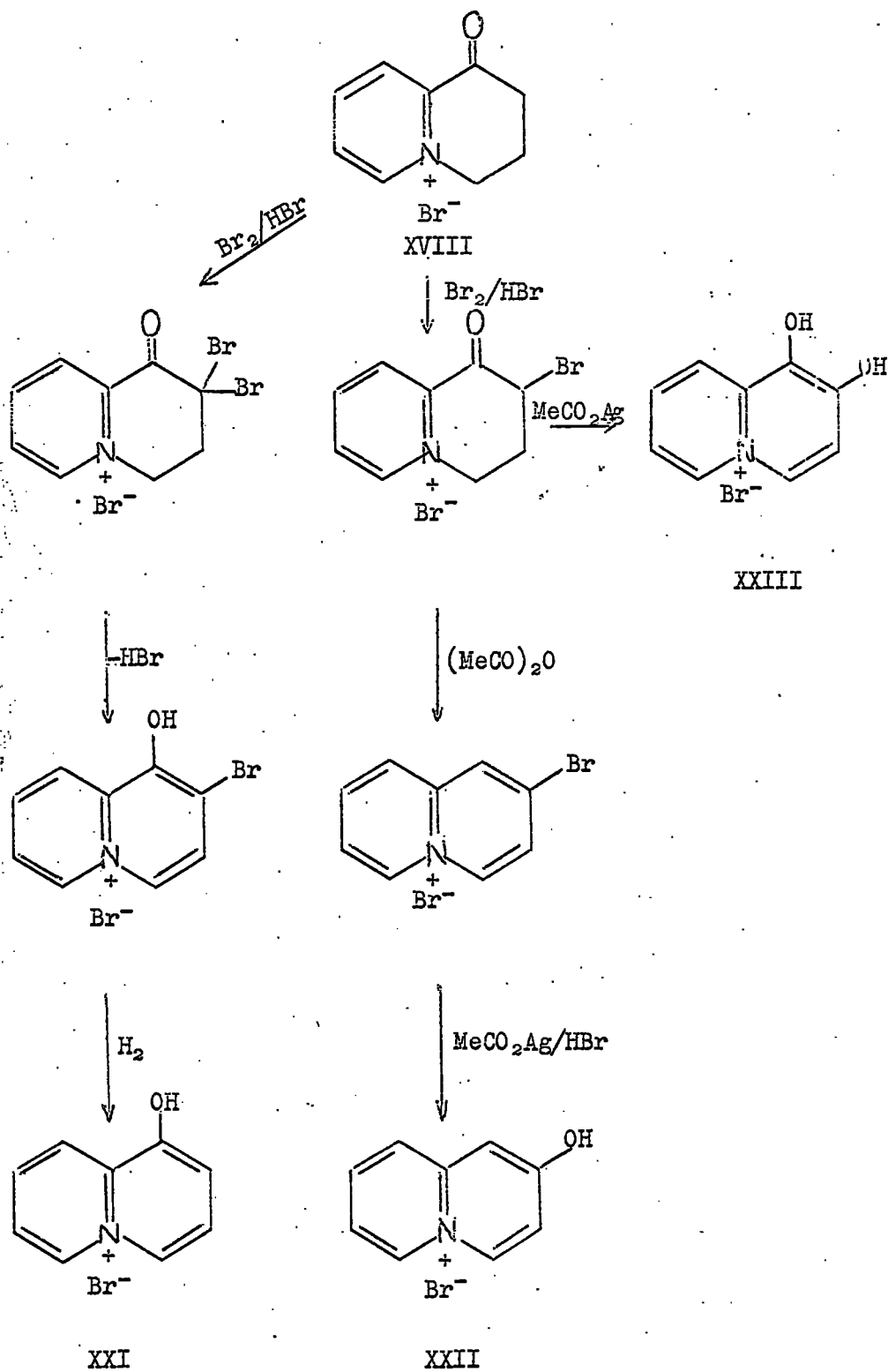
Dehydration of the resulting alcohols (XX) with acetic anhydride readily produced the quinolizinium salts (III; $R=R'=R''=H$, $R''=Me$, Pr^n or Ph) in high yield.



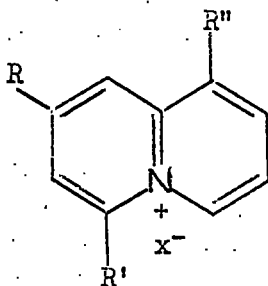
Three mono-hydroxyquinolizinium compounds are now known. 1-Hydroxyquinolizinium picrate (III; $R=R'=R''=H$, $R''=OH$) was first prepared by Glover and Jones²⁶ by dehydrogenation of 1,2,3,4-tetrahydro-1-oxoquinolizinium bromide (XVIII) using palladium charcoal as catalyst. The yield was poor and only the picrate was obtained.



Later, Fozard and Jones^{27,28} synthesised 1-hydroxyquinolininium bromide (XXI), the 2-hydroxybromide (XXII) and the 1-,2-dihydroxy bromide (XXIII) via the following series of reactions and starting with the cyclic ketone (XVIII).

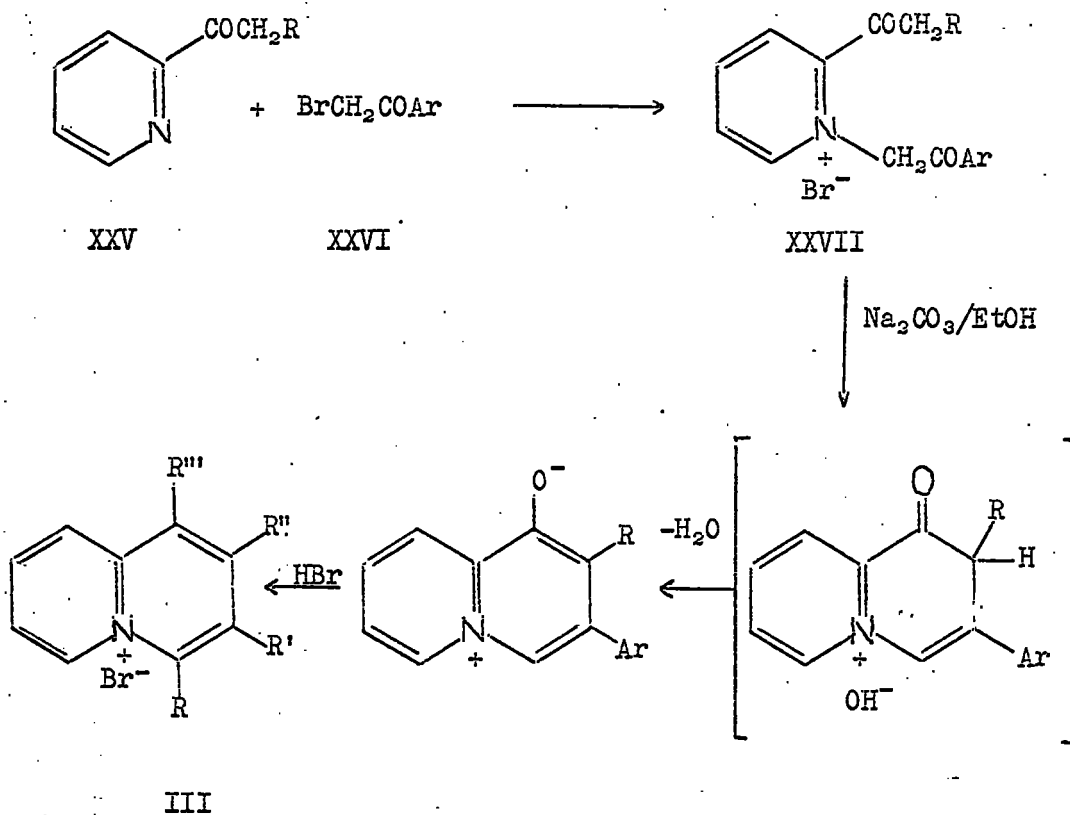


Furthermore these authors have reported²⁹ the synthesis of 6-methyl-1-hydroxy (XXIV; R=H, R'=Me, R''=OH) and 8-methyl-1-hydroxy quinolizinium salts (XXIV; R'=H, R=Me, R''=OH) by a modification of the above reaction sequence.

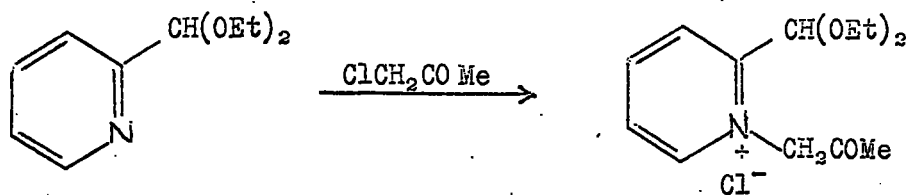


XXIV

The details of the preparation of 1-hydroxy-3-aryl quinolizinium salts and their 2-alkyl derivatives (III; R=H, R'=Ar, R''=Alkyl, R'''=OH) have been reported by Kröhnke^{12,13}. The synthesis involved quaternisation of a 2-acylpyridine (XXV) with ω -bromoacetophenone or a suitably substituted derivative (XXVI). The resulting monoquaternary salt (XXVII) when treated with a base, afforded the zwitterion form of the 1-hydroxy salt which was not isolated but treated with hydrobromic acid to yield the substituted 1-hydroxy quinolizinium salt (III; R=H, R'=Ar, R''=Alkyl, R'''=OH).

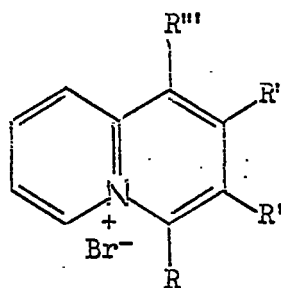


3-Hydroxyquinolizinium salts (III; $\text{R}=\text{R}'=\text{R}''=\text{H}$, $\text{R}'=\text{OH}$) have been prepared by Schraufstätter³⁰ by treating the quaternary salt (XXVIII) between α -diethoxymethylpyridine and chloroacetone, with hydrobromic acid.



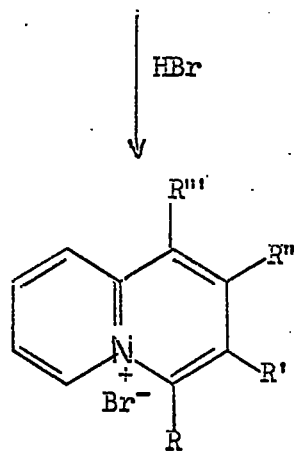
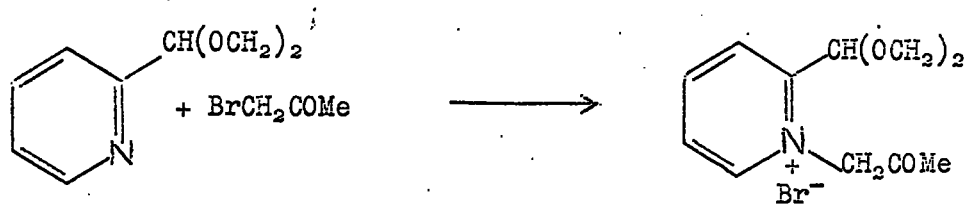
XXVIII

HBr



III

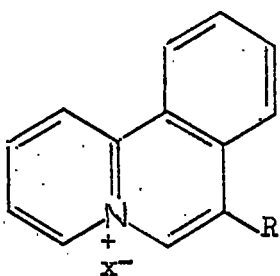
Using a similar cyclodehydration procedure, Duke, Fozard and Jones³¹ have reported the synthesis of the 3-hydroxyquinolizinium bromide (III; $\text{R}=\text{R}'=\text{R}''=\text{H}$, $\text{R}'=\text{OH}$). These workers treated the quaternary salt formed between 2-(1,3-dioxolan-2-yl)pyridine and bromoacetone with hydrobromic acid.



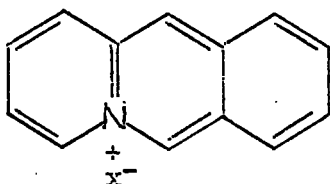
III

(ii) Benzoquinolizinium salts

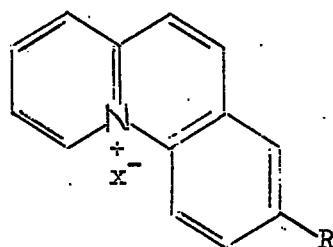
The three benzoquinolizinium systems benzo[a](XXIX; R=H) benzo[b](XXX) and benzo[c]quinolizinium salts (XXXI) have all been prepared.



XXIX

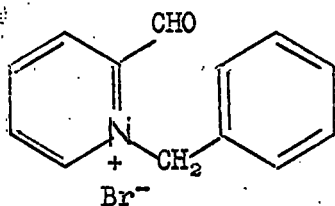


XXX

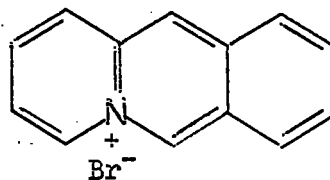
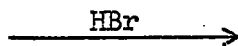


XXXI

Bradsher and Beavers^{32,33} reported the first synthesis of benzo[b](XXX) and substituted benzo[a](XXIX) quinolizinium salts. The preparation of the benzo[b] salts involved the cyclodehydration of N-benzyl-2-formylpyridinium bromide (XXXII) with concentrated hydrobromic acid.



XXXII

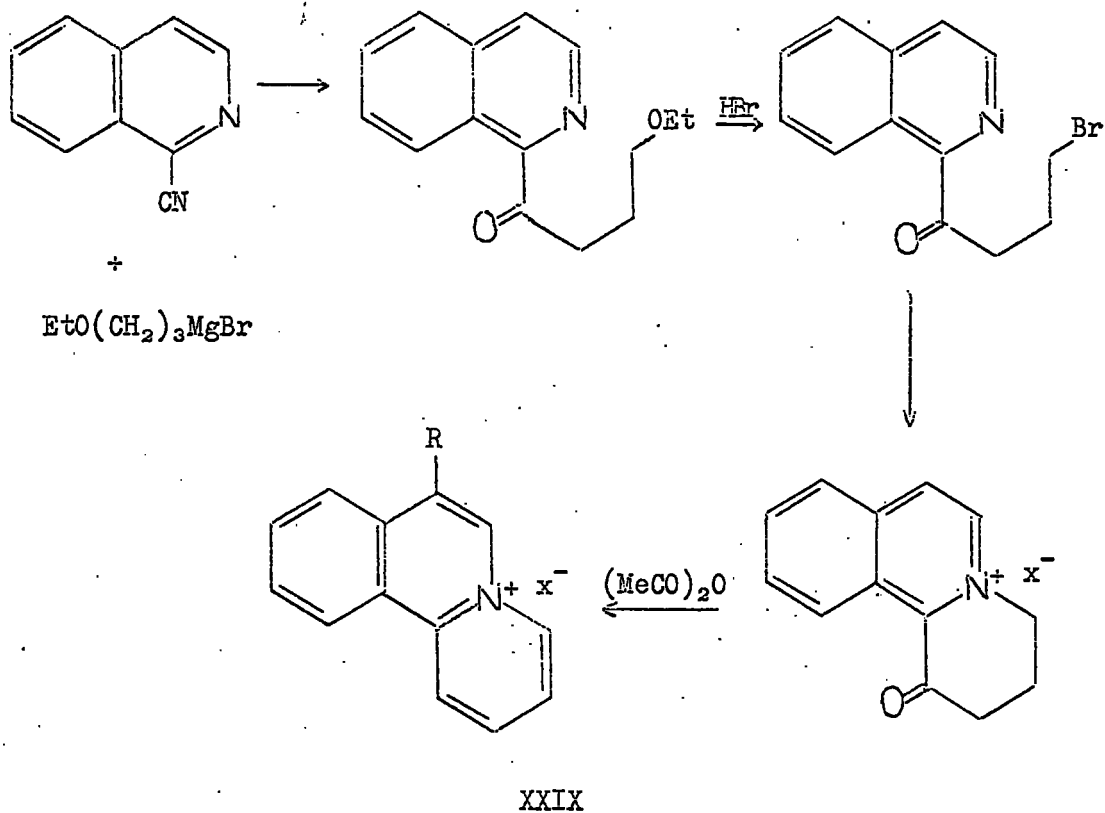


XXX

Quaternisation of 2-phenylpyridine with ω -bromoacetophenone or iodoacetone, followed by treatment with hydrobromic acid effected cyclodehydration and afforded the benzo[a]quinolizinium salt (XXIX; R=Me or Ph).

Benzo[a]quinolizinium salts³⁴ (XXIX; R=H) and numerous substituted derivatives have been prepared^{34,35} using a modification of the original cyclodehydration method described by Bradsher and Beavers³².

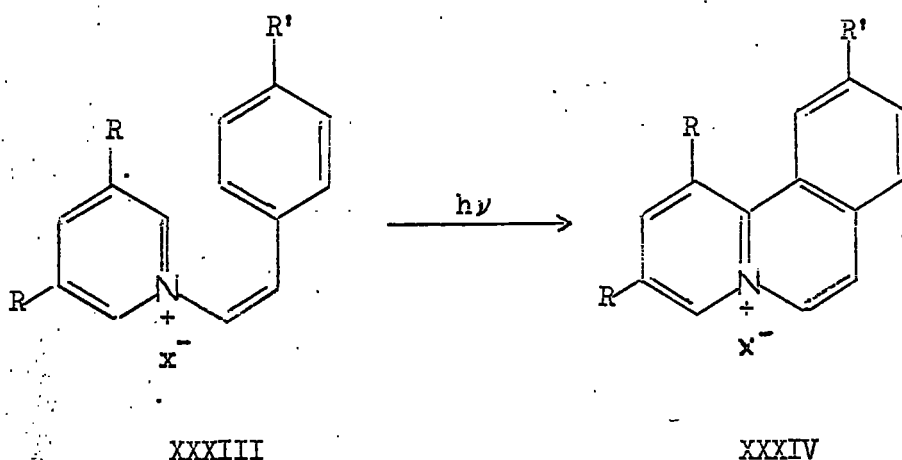
The procedure described by Glover and Jones¹⁸ for the synthesis of quinolizinium salts was adapted by the same authors for the preparation of the three benzoquinolizinium salts¹⁹. Starting with 1-cyanoisoquinoline, and 2-cyanoquinoline, the three isomers were prepared in a manner analogous to the following reaction scheme.



Bradsher et al^{36,37,38,39,40,41,42,43} prepared many substituted benzo[b] quinolizinium salts, including quinones, by quaternising derivatives of pyridine-2-aldehyde, 2-acetylpyridine, and 2-benzoylpyridine with suitable α -haloalkylarenes. Cyclo-dehydration of the resulting salts afforded the required benzo[b] quinolizinium compounds.

Recently a photochemical cyclisation technique has been utilized for the synthesis of benzo[a] and benzo[c] quinolizinium salts. Bradsher and Doolittle⁴⁴ quaternised pyridine with

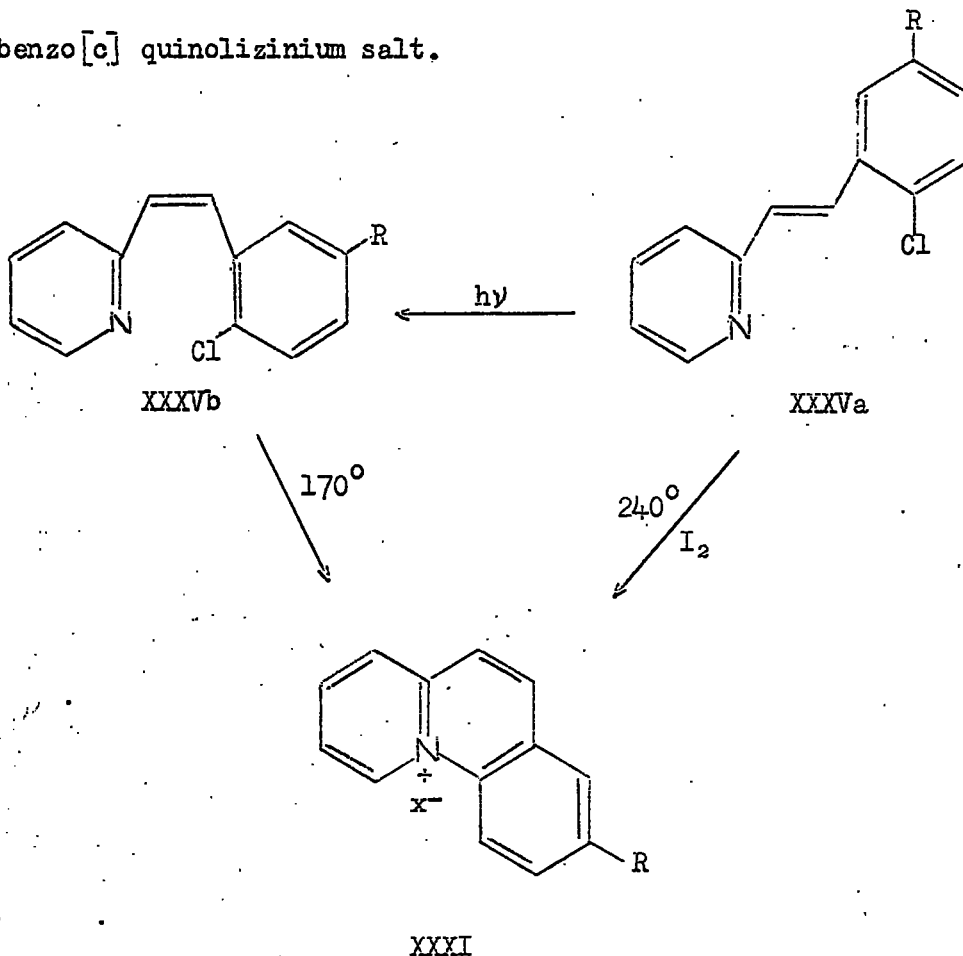
ω -bromostyrene to afford the 1-styrylpyridinium salt (XXXIII; $R=R'=H$, $X=Br$). Ultraviolet irradiation of this salt in alcohol containing a trace of iodine yielded the benzo[a]quinolizinium salt (XXXIV; $R=R'=H$, $X=ClO_4$) isolated as the perchlorate.



Two substituted derivatives have also been synthesised (XXXIV; $R=Me$, $R'=H$ or $R=H$, $R'=Cl$, $X=ClO_4$).

A similar technique has been used by Bradsher and Fozard⁴⁵ to prepare benzo[c]quinolizinium salts. 2-chloro-5-nitrobenzaldehyde was boiled under reflux with 2-picoline in acetic anhydride to afford the trans-stilbazole (XXXVa; $R=NO_2$). Ultraviolet irradiation of this isomer in benzene solution gave the benzo[c]quinolizinium salt (XXXI; $R=NO_2$) isolated as the chloride. Ultraviolet irradiation of trans-2'-chloro-2-stilbazole (XXXVa; $R=H$) resulted in the formation of cis-2'-chloro-2-stilbazole (XXXVb; $R=H$). Heating

this isomer at 170°C for 1 hour yielded the unsubstituted benzo[c]quinolizinium salt (XXXI; R=H, X=Cl). By heating the trans-2'-chloro-2-stilbazole (XXXVa; R=H) at 240° for 6 hours in the presence of iodine these workers isolated the unsubstituted benzo[c]quinolizinium salt.

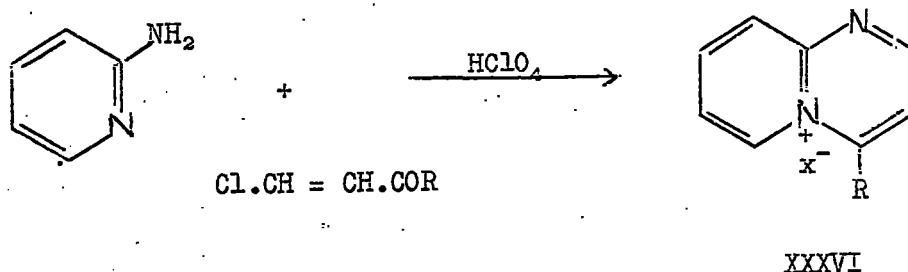


Some substituted benzo[c]quinolizinium salts⁴⁵ have also been prepared.

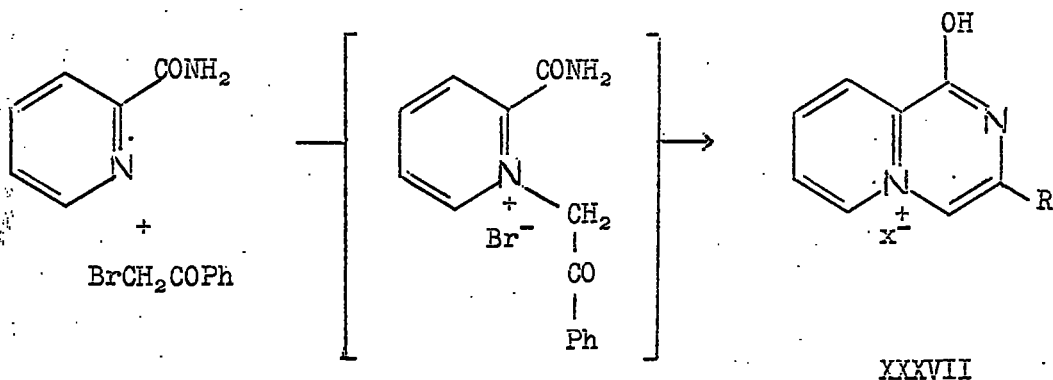
(iii) Bicyclic azaquinolizinium salts

Prior to the recent work of Glover and Loadman⁴⁶, none of the possible unsubstituted azaquinolizinium ions had been reported, only alkyl- and aryl-substituted salts being known. Nesmeyanov et al^{47,48} prepared 4-alkyl substituted 1-azaquinolizinium salts (XXXVI; R=Me, Et or Prⁿ; X=Cl) by condensing 2-aminopyridine with β -ketoacetals in sealed tubes and cyclising the products with ethanolic hydrobromic acid. By using β -chlorovinyl ketones and 2-aminopyridine Nesmeyanov and Rybinskaya improved this method, the condensation and cyclisation stages occurring together under the influence of perchloric acid.

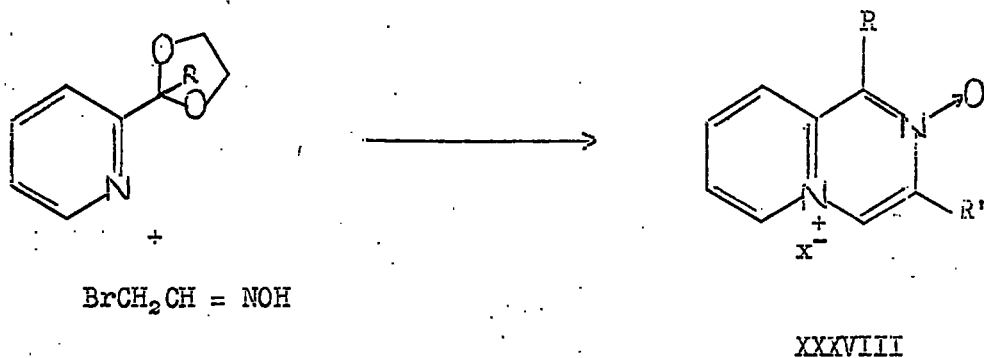
This method also provides a route to the 4-phenyl-1-azaquinolizinium salt (XXXVI; R=Ph, X=Cl).



Kröhnke et al^{12,13} have synthesised 1-alkyl-3-aryl, and 1,3-diaryl-2-azaquinolizinium salts in excellent yields by heating N-phenacyl-2-arylpiperidinium salts with ammonium acetate in acetic acid solution. If 2-picolinic acid amide, or 2-cyanopyridine, is heated with ω -bromoacetophenone in acetonitrile then 1-hydroxy-3-phenyl-2-azaquinolizinium bromide (XXXVII; R=Ph, X=Br) is formed directly.

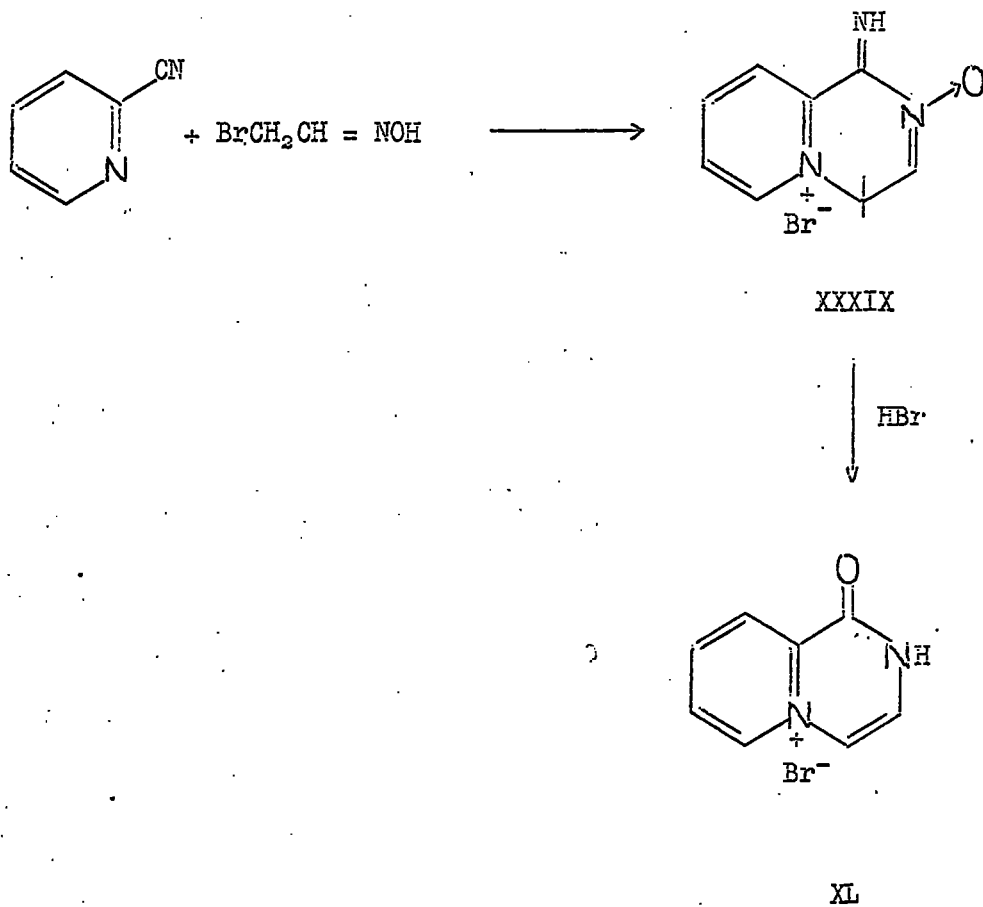


Details of the synthesis of 1-alkyl and 1-aryl-2-azaquinolizinium-2-oxide salts (XXXVIII; R¹=H, R=H, Me or Ph, X=Br) have recently been given by Glover and Loadman^{4,6}. 2-(1,3-Dioxolan-2-yl)pyridine or 2-[2-methyl(1,3)dioxolan-2-yl]pyridine was quaternised with bromoacetaldehyde oxime and the resulting salts cyclised with concentrated hydrobromic acid, resulting in the formation of the 2-oxide derivatives (XXXVIII; R¹=H, R=H or Me, X=Br) in good yields.

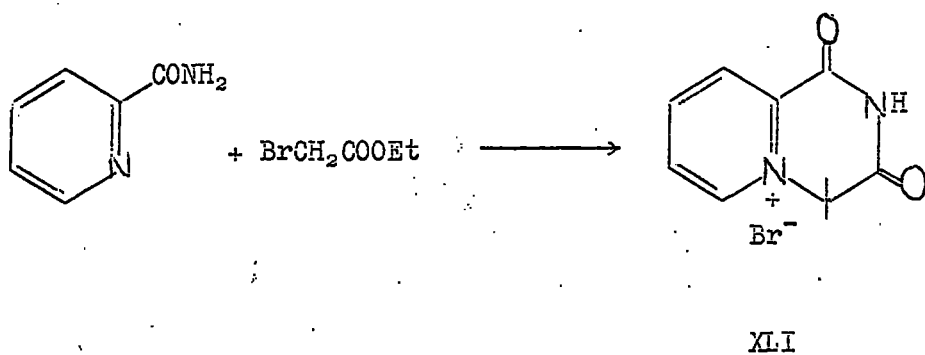


The same authors obtained the 1-phenyl derivative (XXXVIII; R'=H, R=Ph, X=Br) directly by quaternising 2-benzoylpyridine with bromoacetaldehyde oxime.

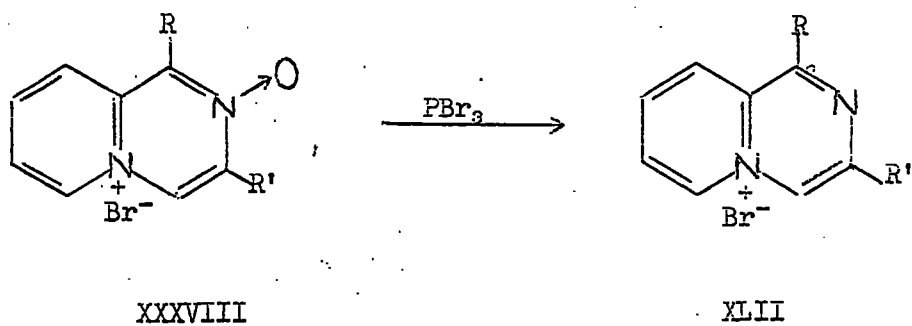
By quaternising 2-cyanopyridine with bromoacetaldehyde oxime, and boiling the resulting 1-imino 2-oxide salt (XXXIX) under reflux with hydrobromic acid, the same workers isolated 1-oxo-1,2-dihydro-pyrido [1,2-a] pyrazinium bromide (XL).



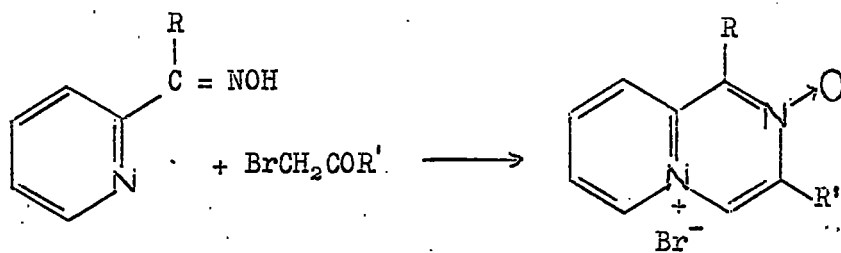
By an extension of the previous method they have also isolated the 1,3-dioxo-1,2,3,4-tetrahydro-pyrido[1,2-a]pyrazinium bromide (XLI). Treatment of 2-picolinic acid amide with ethyl bromoacetate afforded the 1,3-dioxobromide (XLI) in high yield.



While investigating the chemistry of the 2-azaquinolizinium salts, Glover and Loadman obtained the first unsubstituted 2-azaquinolizinium compounds (XLII; R=R'=H) by boiling the unsubstituted 2-oxide (XXXVIII; R=R'=H, X=Br) under reflux with phosphorus tribromide.



Bradsher and Telang⁴⁹ have also recently reported the synthesis of the N-oxides of 2-azaquinolizinium salts (XXXVIII; R=H or Me, R'=Me) by the action of bromoacetone on a solution of picolinaldoxime or 2-acetylpyridine oxime, in acetone or tetramethylenesulphone.

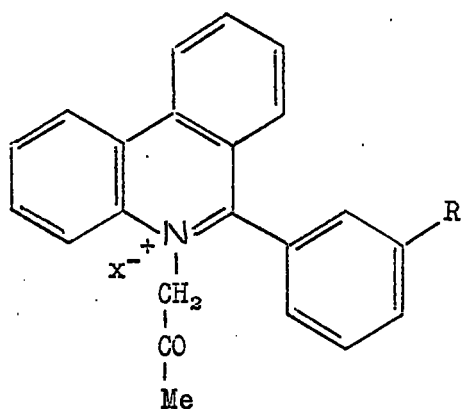


XXXVIII

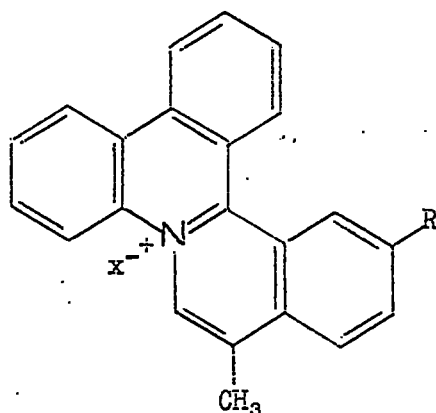
The 3-phenyl derivative (XXXVIII; R=H, R'=Ph) has also been synthesised by treating the quaternary salt, formed between picolinaldoxime and ω -bromoacetophenone, with hydrobromic acid. The same workers⁴⁹ obtained several benzologues using a similar procedure.

5a-Azonia-acephenanthrylene salts

It has been shown by Bradsher and Moser⁵⁰ that 6-phenylphenanthridinium systems with an activating methoxyl on the phenyl group (XLIII; R=OMe, X=Br) will undergo cyclisation to yield 11-methyldibenzo[a,c]phenanthridizinium salts (XLIV; R=OMe, X=Br).

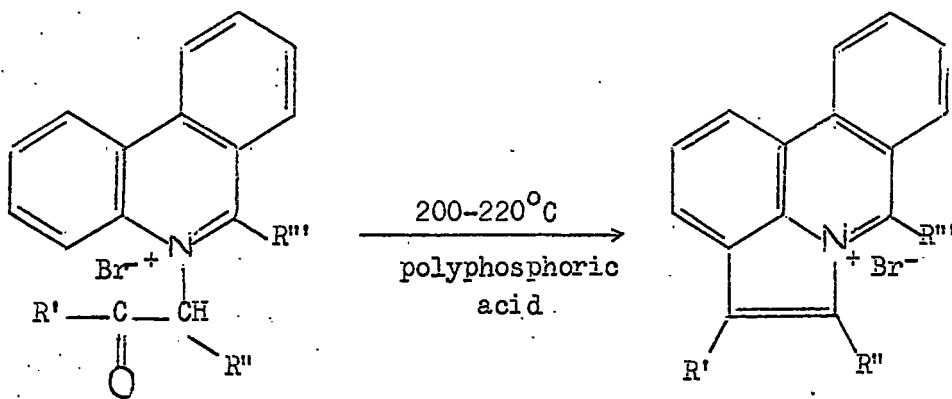


XLIII



XLIV

However, when Bradsher and Kimber⁵¹ attempted the synthesis of the unsubstituted phenanthridizinium salt (XLIV; R=H) they obtained the 5a-azonia-acephenanthrylene salt (XLV; R¹=Me, R²=H, R³=Ph) in low yield, cyclisation not occurring onto the 6-phenyl group.

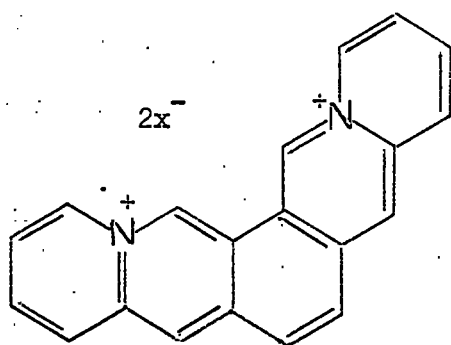


XLV

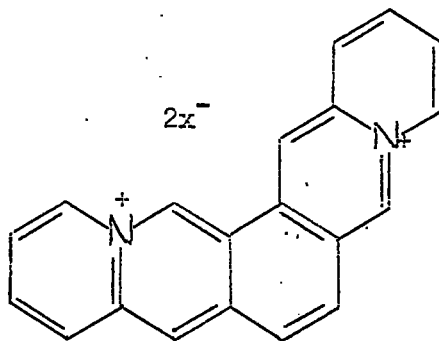
The same authors have also obtained the 4,5-dimethyl salt
 (XLV; $\text{R}'=\text{R}''=\text{Me}$, $\text{R}'''=\text{Ph}$) in 43% yield.

Diazoniapentaphene salts

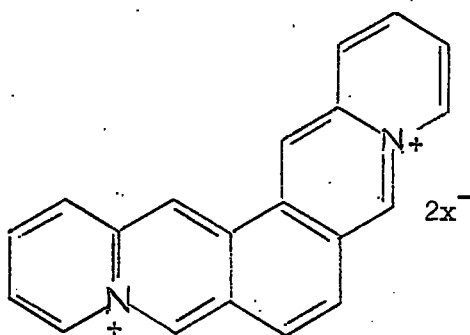
The first fully aromatic compounds with quaternary nitrogen atoms at two bridgehead positions were the diazoniapentaphene salts (XLVI, XLVII, XLVIII) which were prepared by Bradsher and Parham⁵².



XLVI

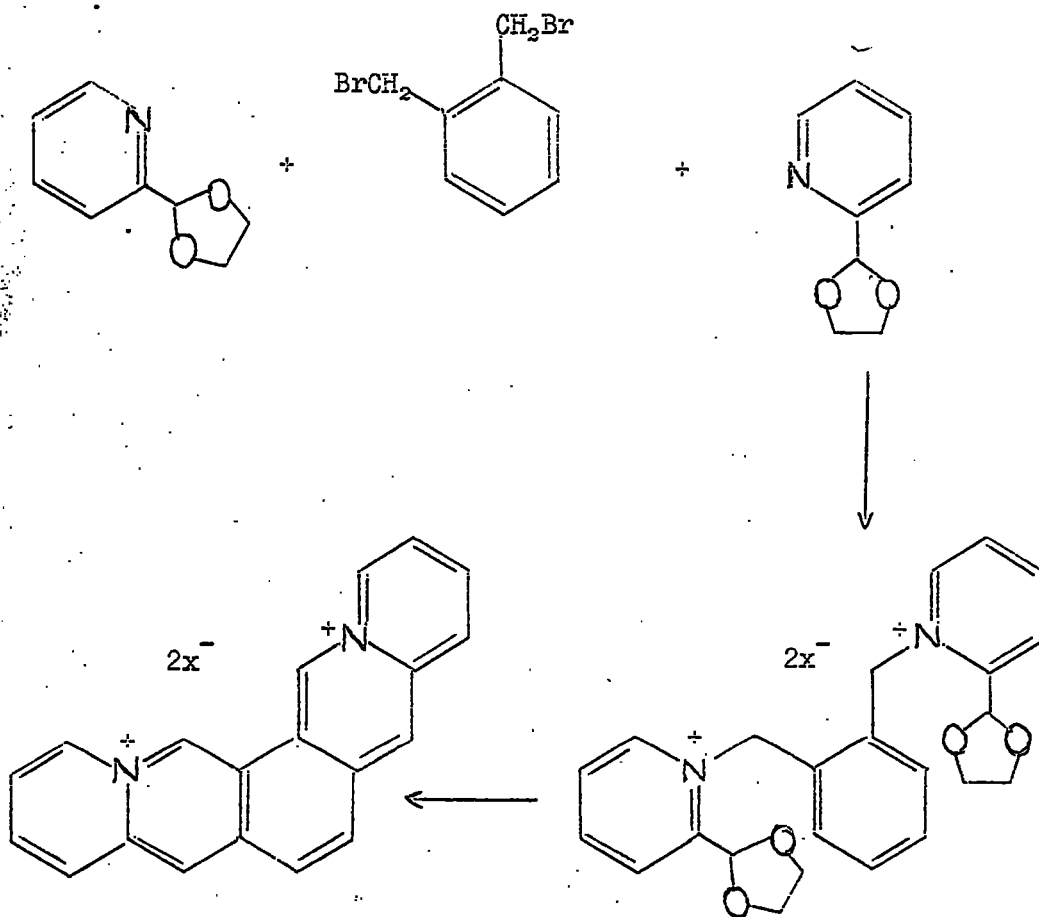


XLVII



XLVIII

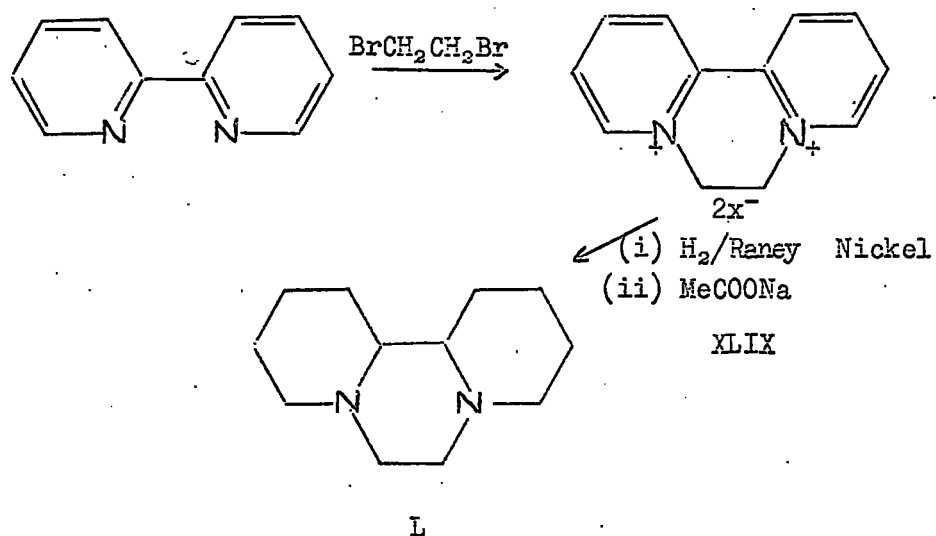
These workers synthesised several isomeric diazoniapentaphene salts (XLVI, XLVII, XLVIII) by quaternising 2-(1,3-dioxolan-2-yl) pyridine in tetramethylenesulphone, with α, α' -dibromoxylenes and cyclising the resulting salts with polyphosphoric acid.



XLVI

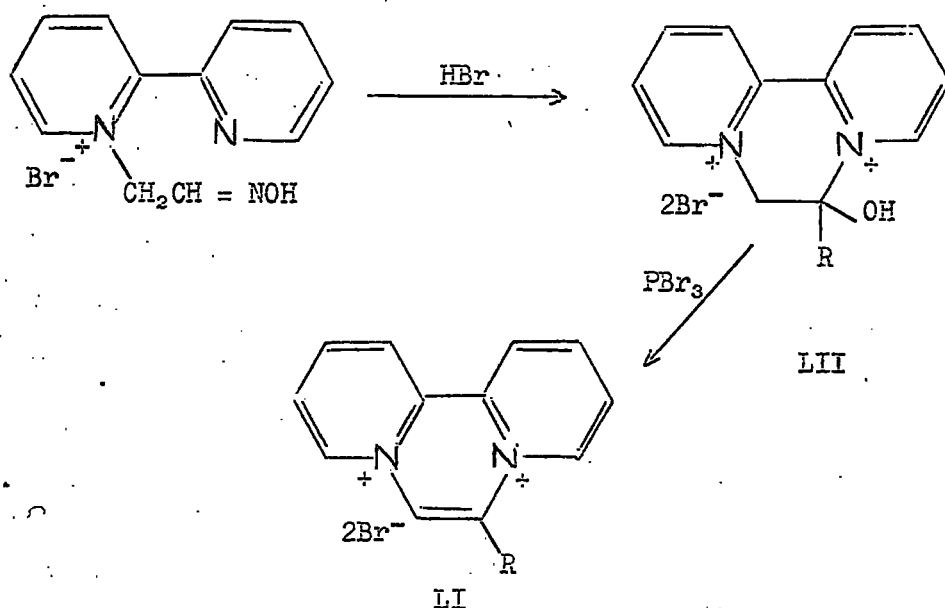
Dipyrido[1,2-a : 2',1'-c]pyrazidi-inium salts

6,7-dihydro-dipyrido[1,2-a : 2',1'-c]pyrazidi-inium dibromide (XLIX) was obtained by Fielden, Homer and Jones⁵³ by the quaternisation of 2,2'-bipyridyl with ethylene dibromide. The catalytic hydrogenation of (XLIX) in alkaline solution afforded perhydrodipyrido[1,2-a : 2',1'-c]pyrazine (L).

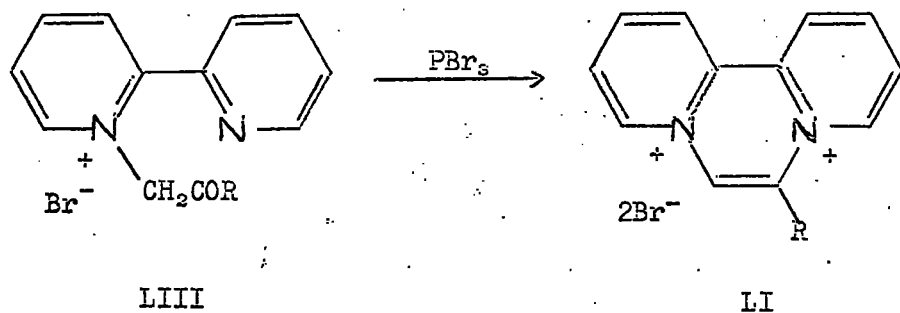


Much interest has been shown in the 6,7-dihydro-dipyrido[1,2-a : 2',1'-c]pyrazidi-inium salts (XLIX) due to their herbicidal activity and many derivatives have been synthesised^{54,55,56,57}.

Corr and Glover^{58,59} synthesised dipyrido[1,2-a : 2',1'-c]pyrazidi-inium salts (LI; $\text{R}=\text{H}$) by cyclising, with hydrobromic acid, the quaternary salt formed between 2,2'-bipyridyl and bromoacetaldehyde oxime. Aromatization of the resulting hydroxy compound (LII; $\text{R}=\text{H}$) was effected by boiling phosphorus tribromide.



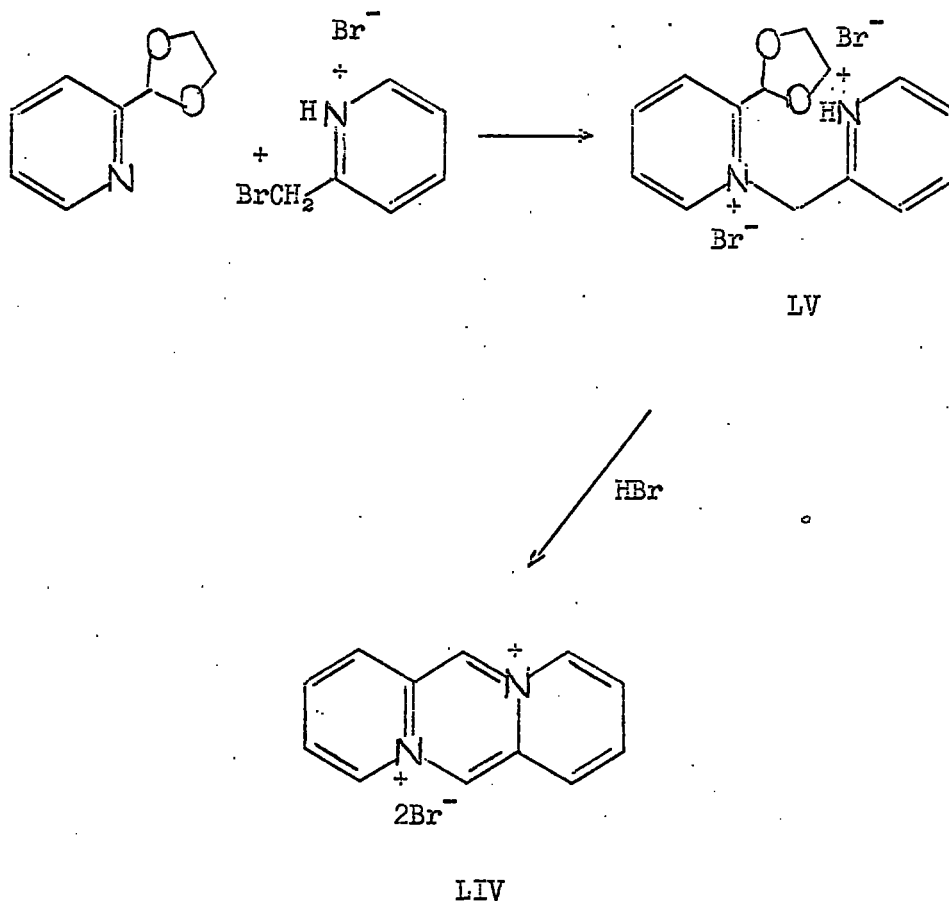
The same authors have isolated the 6-methyl- and 6-phenyl-dipyrido [1,2-a : 2',1'-c] pyrazidi-inium salts (LI; R=Me or Ph) treating the monoquaternary salts (LIIII; R=Me or Ph) formed between 2,2'-bipyridyl and bromoacetone or ω-bromoacetophenone, with phosphorus tribromide.



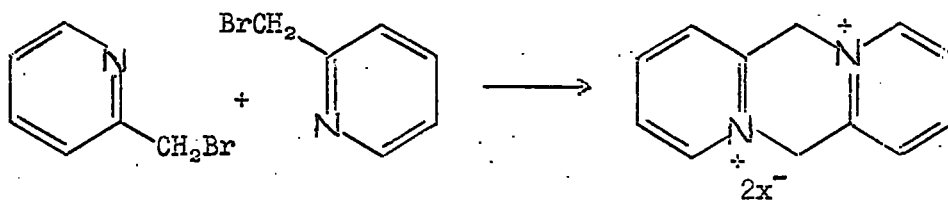
The 6-methyl derivative (LI; R=Me) was simultaneously reported by Calder and Sasse⁶⁰.

Dipyrido[1,2-a : 1',2'-d]pyrazidi-inium salts

The synthesis of dipyrido[1,2-a : 1',2'-d]pyrazidi-inium salts (LIV; X=Br) has been achieved by Glover and Morris⁶¹; 2-(1,3-dioxolan-2-yl) pyridine was treated with 2-pyridylmethylbromide hydrobromide in tetramethylenesulphone giving the intermediate salt (LV) as a red oil. Treatment of the oil with hydrobromic acid afforded the aromatic diquaternary salt (LIV) which was isolated as the dibromide.

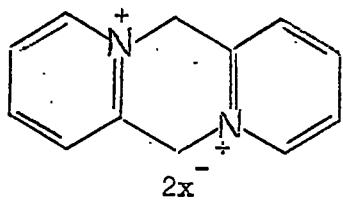


6,12-Dihydro-pyrido[1,2-a : 1',2'-d]pyrazidi-inium salts (LVI) have also been prepared^{62,63} by the intermolecular quaternisation of 2-pyridylmethyl bromide in boiling benzene.

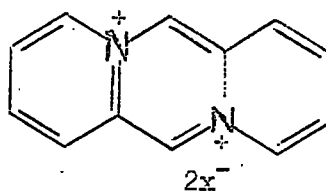


LVI

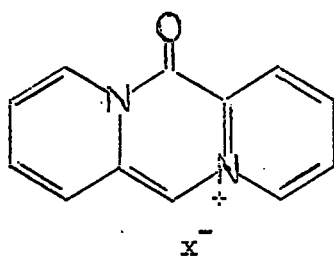
It has been shown by Glover and Morris^{61,64} that treatment of the dihydrodiaternary salt (LVI; X=picrate), in nitromethane with palladium charcoal, afforded 12-oxo-12H-dipyrido[1,2-a : 1',2'-d]pyrazin-5-ium salt (LVIII); the same product was obtained by the selenium dioxide oxidation of the aromatic diquaternary salt (LIV).



LVI



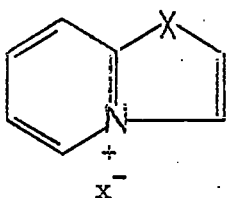
LIV



LVII

2. π -Intermediate Aromatic Quaternary Bridgehead Nitrogen Compounds

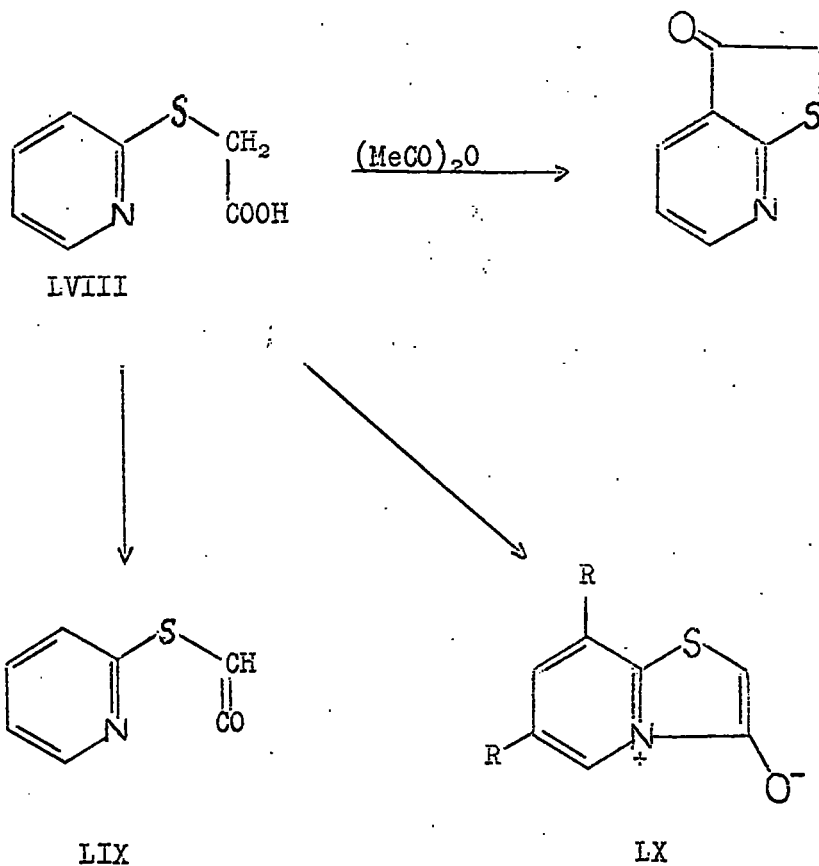
Aromatic cations of the type shown (VII; X=NH,O,S) containing a quaternary bridgehead nitrogen atom and an additional heteroatom will have their π -electron deficient properties modified by the additional heteroatom. Such compounds will be referred to as π -intermediate.



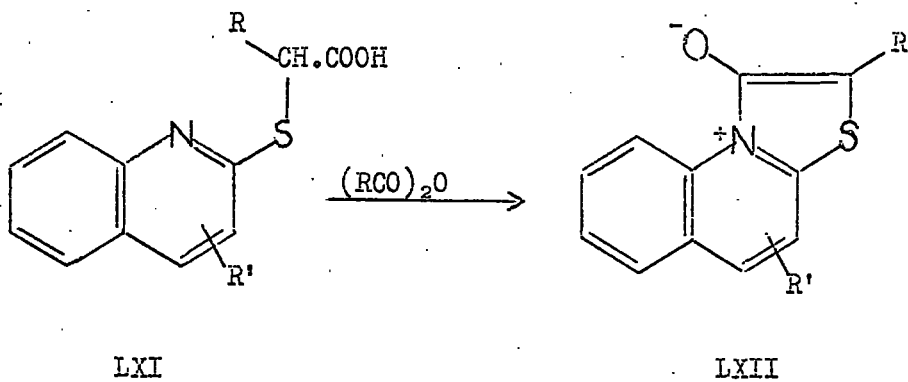
VII

Pyridothiazolium salts

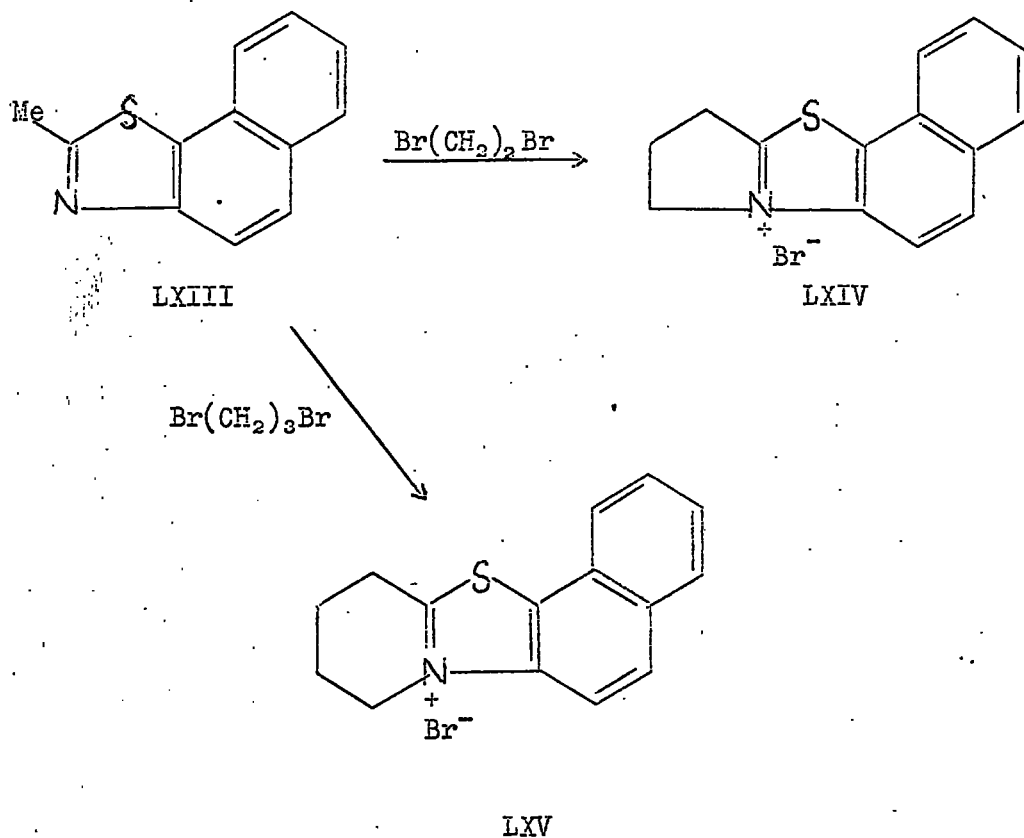
In 1924 Koenigs and Geisler⁶⁵ obtained a yellow compound from the reaction between pyridyl 2-thioacetic acid (LVIII) and acetic anhydride. The structure initially assigned to it by these authors was later precluded by Tschitschibabin and Woroshtow⁶⁶ who favoured the monocyclic keten structure (LIX). However, Duffin and Kendall⁶⁷ suggested that the compound may be more satisfactorily formulated as the mesoionic pyridothiazolium system (LX).



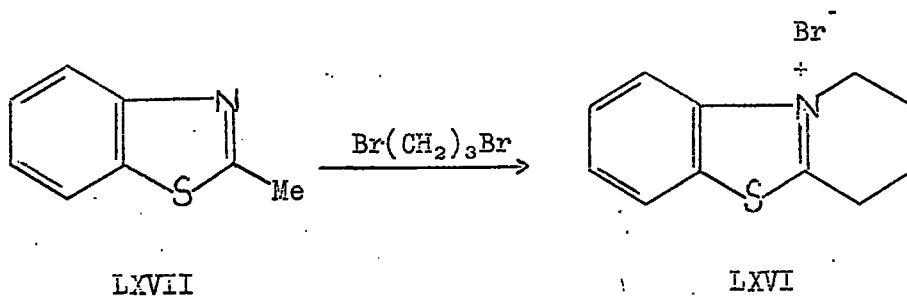
These latter authors⁶⁷ found that similar acids (LXI; R=H, R¹=5-Me) were cyclodehydrated by boiling in acetic or propionic anhydride affording the yellow products (LXII; R=H, R¹=Me).



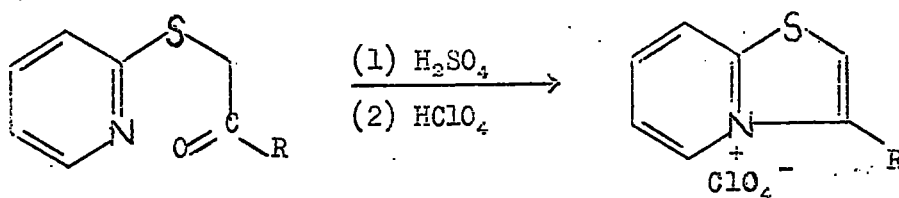
A series of bridgehead nitrogen compounds, based on thiazole, have been synthesised by DeSmet and Schwarz⁶⁸. These authors treated the naphthothiazole (LXIII) with 1,2-dibromoethane and isolated the quaternary pyridothiazole (LXIV), and by a similar procedure obtained the quaternary pyridothiazole (LXV) by treating the naphthothiazole with trimethylene dibromide.



The same workers synthesised the quaternary salt (LXVI)⁶⁸ by heating a mixture of the benzothiazole (LXVII) and trimethylene dibromide.



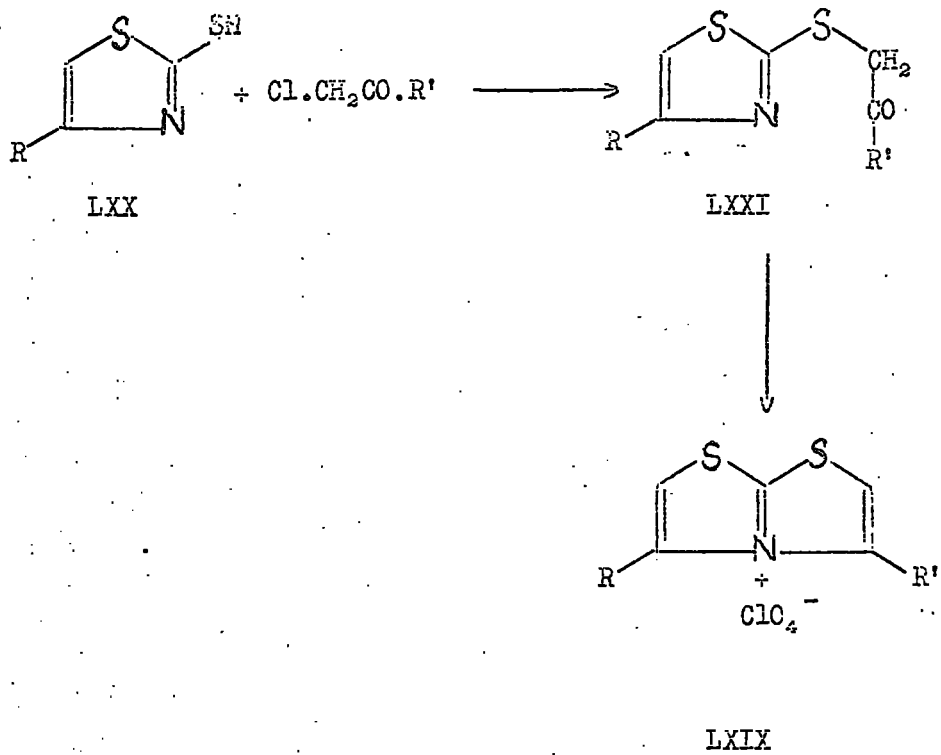
Pyridothiazolium salts (LXVIII; R=H or Me) recently reported by Bradsher and Lohr⁴, were prepared by treating with mineral acid, 2-pyridyl sulphides having a carbonyl function beta to the sulphide link. Cyclodehydration occurred affording the required aromatic quaternary salt (LXVIII).



LXVIII

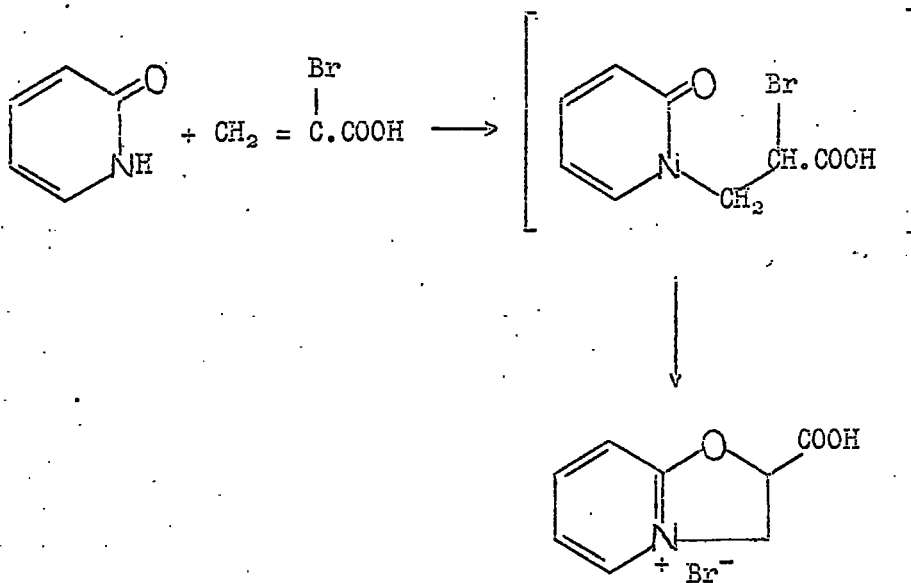
The synthesis of the pyridyl sulphides was achieved by treating the sodium salt of 2-mercapto pyridine with the appropriate α -haloketone.

Recently Bradsher et al⁶⁹ have reported the preparation of the thiazolo[2,3-b]thiazolium cation (LXIX). Treatment of 2-mercaptothiazoles (LXX) with α -chloroketones afforded the sulphides (LXXI), which when treated with concentrated sulphuric acid at 100°C cyclodehydrated to yield the required aromatic systems (LXIX; R=R'=Me, R=R'=Ph or R=Me; R'=Ph) isolated as the perchlorates.



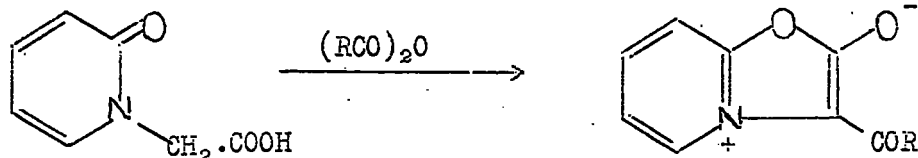
Pyrido-oxazolium salts

While investigating the structure of the adduct formed between 2-pyridone and 1-bromoacrylic acid, Adams and Pachter⁷⁰ isolated an acid (LXXII) to which they assigned the dihydro structure (LXXII).



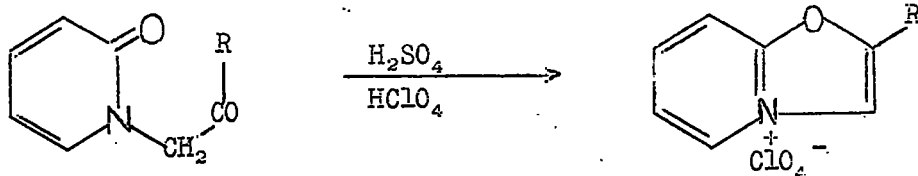
LXXII

Lawson and Miles⁷¹ have reported the synthesis of the meso-ionic pyrido-oxazolium derivative (LXXIII; R=Me or Et). They treated 2-pyridone N-acetic acid with hot acetic or propionic anhydride in accordance with the following reaction scheme.



LXXIII

More recently Bradsher and Zinn⁵ have synthesised 2-substituted pyrido-oxazolium salts (LXXIV; R=Me, Ph or p-BrC₆H₄). The synthesis was achieved by boiling 2-methoxypyridine with the appropriate acyl halides in acetone solution. Treatment of the resulting pyridone (LXXV) with mineral acid effected cyclisation affording the required aromatic quaternary salt (LXXIV) which was isolated as the perchlorate.

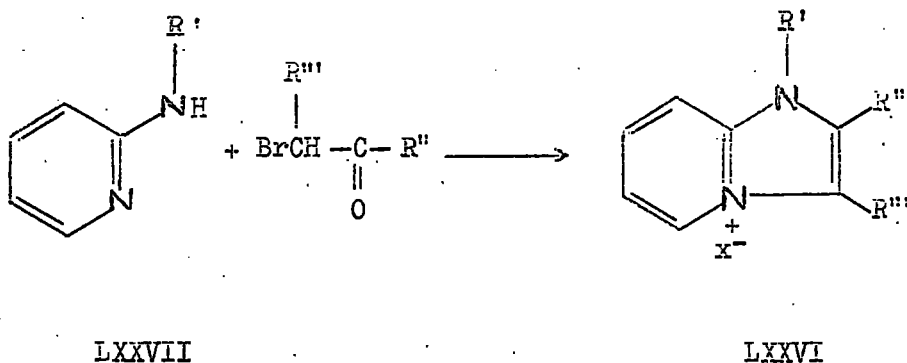


LXXV

LXXIV

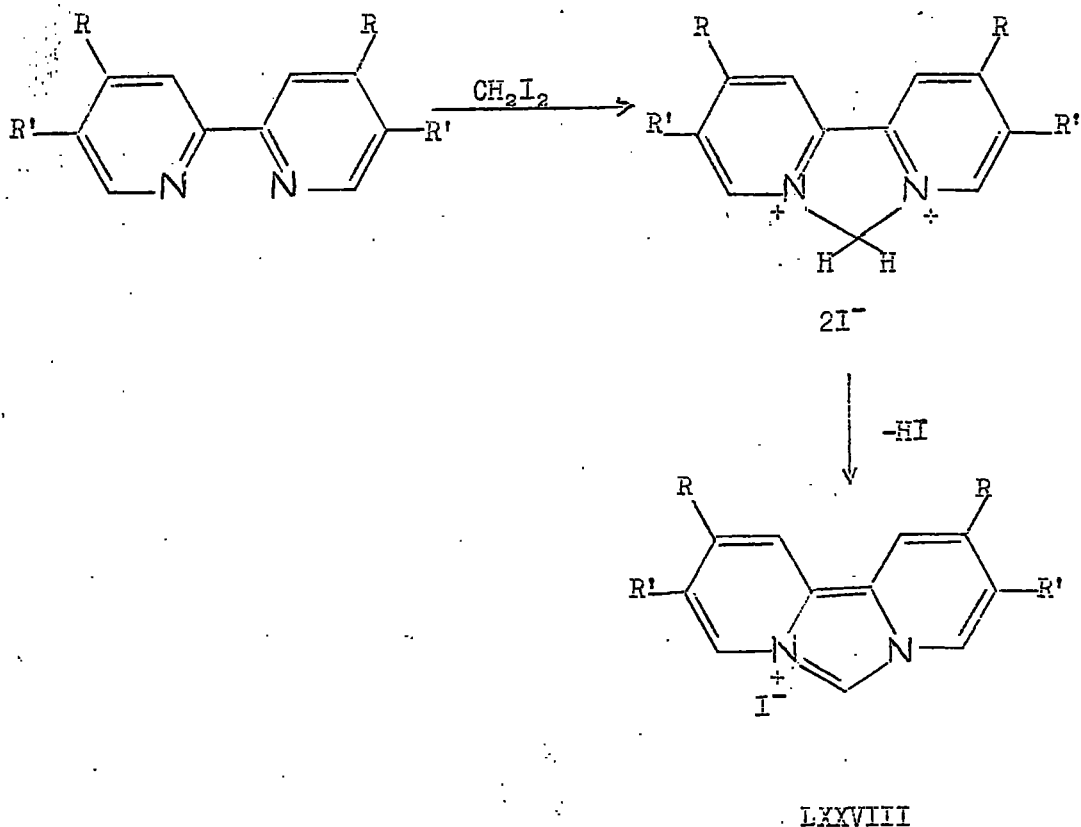
Pyridoimidazolium salts

Many systems containing the pyrido[2,1-a]imidazolium nucleus are known⁷² but little attention had been given to the 1-alkyl and 1-aryl salts (LXXVI) until recently when Bradsher et al⁷³ prepared a variety of 2-substituted 1-alkyl- and 1-aryl-pyrido[2,1-a]imidazolium salts. These authors treated 2-alkylaminopyridines (LXXVII) with 1-haloketones to afford the required aromatic salts (LXXVI) according to the following reaction sequence.

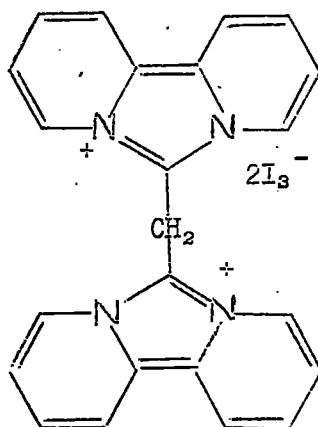


Dipyridoimidazolium salts

This series of compounds, iso-electronic with dipyridic pyrazidi-inium salts, is based on indolizine, and it might be expected that they would exhibit "π intermediate" properties. Calder and Sasse³ have recently reported the synthesis of compounds of this type. By the treatment of 2,2'-bipyridyls with gem dihalides they obtained dipyrido[1,2-c : 2',1'-e]imidazolium salts (LXXVIII; R=R'=H).



The same workers describe alkylations occurring at the 6-position in the parent cation (LXXVIII; R=R'=H) the feasibility of these alkylations being supported by the isolation of the bis-tri-iodide (LXXIX) when the parent cation (LXXVIII; R=R'=H) was treated with methylene di-iodide in benzonitrile at 160°C.



LXXIX

DISCUSSION

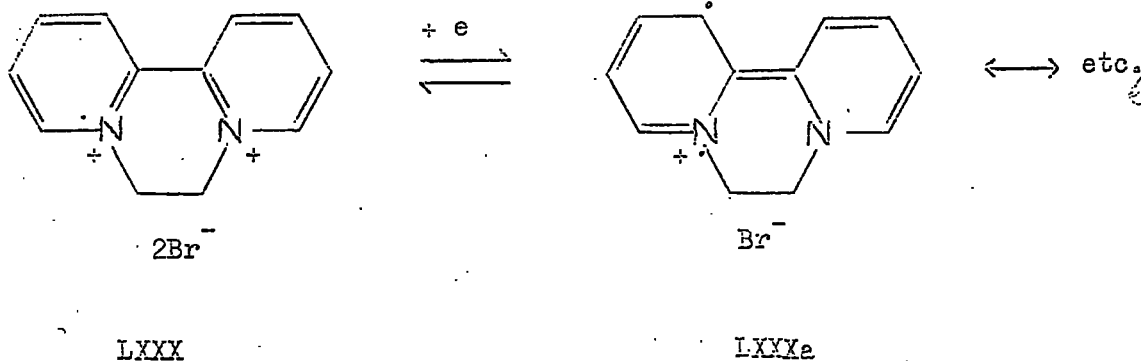
DISCUSSION

The pyrido thiazolo pyrazidi-inium salts (I,II), the synthesis of which form the basis of the following discussion, are included in the same category as those π -intermediate compounds, reviewed in the second part of the introduction (page 41).

One of the major factors governing the ease of quaternisation of nitrogen heterocycles is the basic strength of the nitrogen atom involved. Thus the facility with which this reaction can be carried out, with a given quaternising agent, can be taken as a reasonable indication of the availability of the nitrogen lone pair for bonding. For example electrophilic attack will occur more readily at a pyridine nitrogen than at a thiazole nitrogen. The stronger basic nature of pyridine compared to thiazole was shown by the formation of monopicates of the pyridyl thiazole bases (LXXXV, XC), the evidence being in favour of the pyridine ring as the location of the picrate residue. The nitrogen in pyridine depletes the π -electron cloud rendering pyridine π -deficient but five membered heteroaromatic systems containing a 'doubly bound' nitrogen atom, as well as a singly bound heteroatom, maintain their π -excessive nature⁷⁴.

It has been shown⁷⁵ that the coplanar nature of salts such as "Diquat", 6,7-dihydro-dipyrido [1,2-a : 2',1'-c] pyrazidi-inium dibromide (LXXX) is a necessary feature for herbicidal activity, since the facile reduction of these compounds to produce a stable

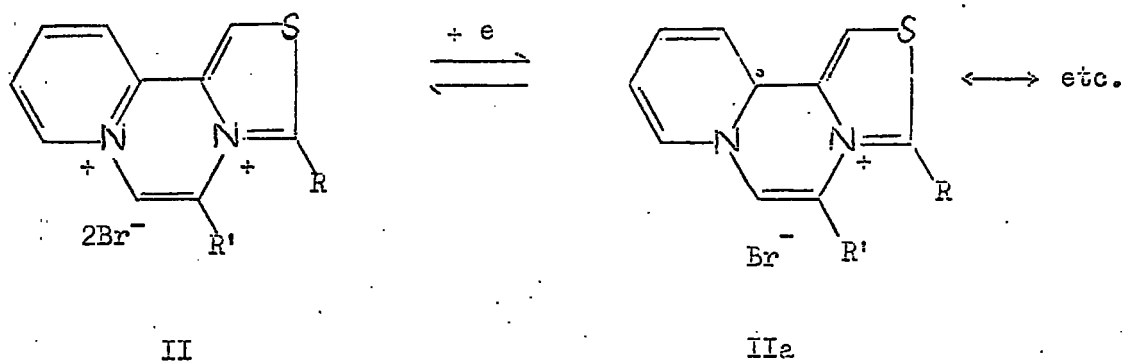
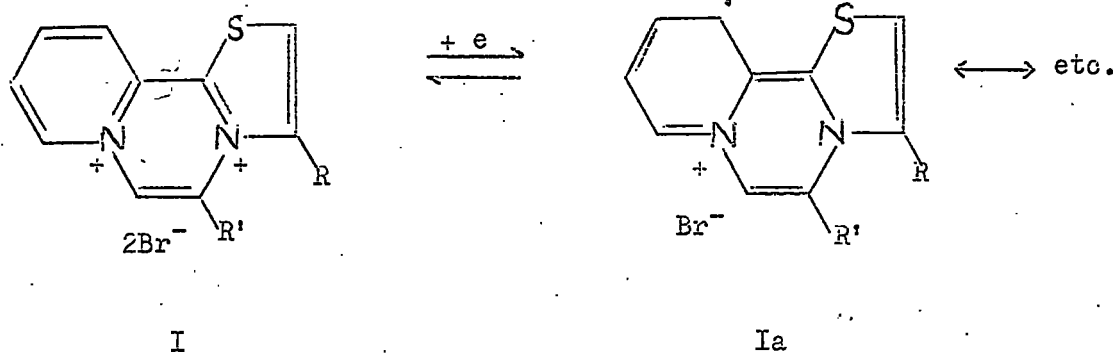
water soluble free radical (LXXXa) is favoured by delocalisation of the odd electron over the whole molecule.



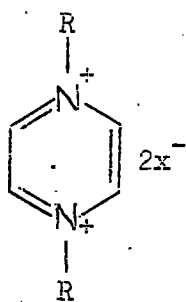
There is an indication that the pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium bromides (I) are similarly easily reduced. When aqueous solutions are treated with zinc dust a coloured solution results presumably due to the formation of a water soluble free radical. A quantitative assessment⁷⁶ of the herbicidal properties of 3,5-dimethyl-pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium dibromide (I; R=R'=Me) however, showed only weak activity. The herbicidal properties of other unsubstituted pyrido thiazolo pyrazidi-inium salts have yet to be studied.

It may be expected that the pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium compounds would exhibit greater herbicidal activity than the pyrido[1,2-a]thiazolo[4,3-c]pyrazidi-inium salts (II). The greater stability of the free radical (Ia) produced by one

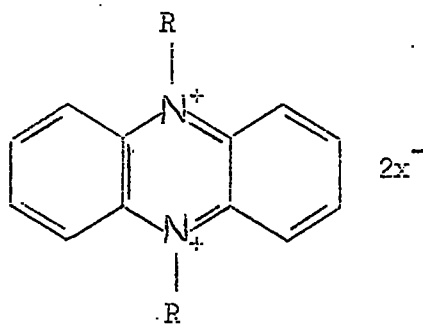
electron reduction of the former system (I) follows from its increased mesomeric stabilization, compared with the radical (IIa) derived from the latter system (II).



The stability of diquaternary salts of phenazine⁷⁷ (LXXXI) has been attributed to the distribution of charge over the π -electron system, hence the reluctance of pyrazine (LXXXII) to form diquaternary salts⁷⁸ can be explained in terms of reduced stability of the dication by virtue of the smaller aromatic system over which the charge is distributed.



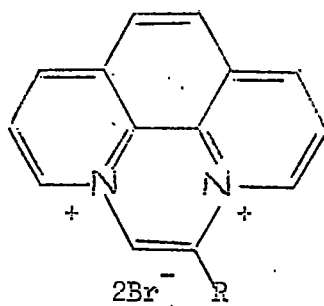
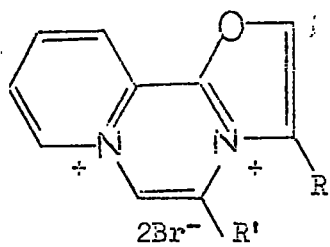
LXXXII



LXXXI

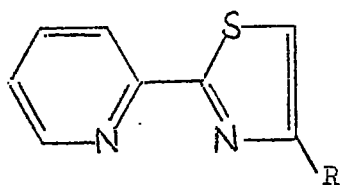
Dipyrido pyrazidi-inium (IV) and pyrido thiazolo pyrazidi-inium (I,II) dications are related to the π -deficient diquaternary salts but it may be expected that the latter group would show π -intermediate character.

The work was then extended and the synthesis of the bridged aromatic diquaternary salt of phenanthroline (LXXXIV; R=Ph, X=Br) achieved. The attempted synthesis of pyrido[1,2-a]oxazolo[2,3-c]pyrazidi-inium salts (LXXXIII) is also described.

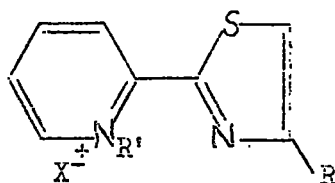


PYRIDO [1,2-a]THIAZOLO [2,3-c]PYRAZIDI-INIUM SALTS

Details of the synthesis of 4-methyl-2-(2-pyridyl) thiazole (LXXXV; R=Me) have been given by Karrer and Schukri⁷⁹, and of 4-phenyl-2-(2-pyridyl) thiazole (LXXXV; R=Ph) by Knott and Breckenridge⁸⁰. These latter authors have also reported the synthesis of the parent base (LXXXV; R=H) although insufficient was obtained for analysis. The base was prepared in fair yield however, by heating a mixture of bromoacetal and picolinic acid thioamide.



LXXXV

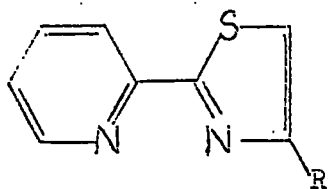


LXXXVa

The preparation of the parent pyrido [1,2-a]thiazolo [2,3-c] pyrazidi-inium salt (I, R=R'=H, X=Br) was similar to the method described by Glover and Corr⁵⁸ for the synthesis of dipyrido [1,2-a : 2',1'-c]pyrazidi-inium dibromide (IV; R=H). 2-(2-Pyridyl) thiazole (LXXXV; R=H) was heated with bromoacetaldehyde

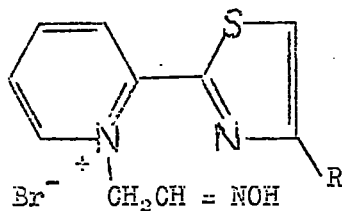
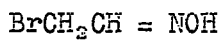
oxime for several hours and the resulting crude monoquaternary oxime (LXXXVI; R=H) cyclised with concentrated hydrobromic acid to afford the 5-hydroxy dibromide (LXXXVII; R=R'=H). The yield of the hydroxy salt was low, 9%.

Attempted dehydration with phosphorus tribromide was unsuccessful only unchanged hydroxy compound was recovered. Dehydration to the aromatic dibromide (I; R=R'=H) was finally achieved in moderate yield by boiling the hydroxy salt under reflux with phosphorus tribromide containing a trace of phosphoric acid. A better yield was obtained by using thionyl chloride as dehydrating agent.



LXXXV

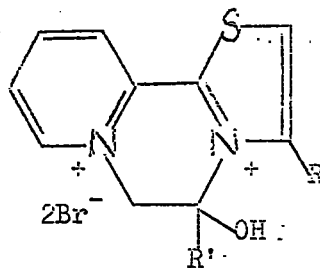
+



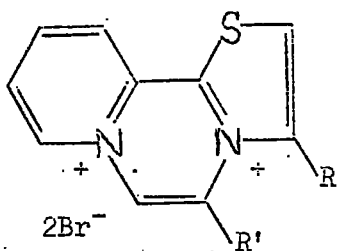
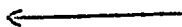
LXXXVI



HBr



LXXXVII



I

3-Alkyl and 3-Aryl-pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium salts

The preparation of the 3-methyl substituted system (I; R=Me, R'=H, X=Br) followed the same general procedure used for the parent aromatic dibromide. A mixture of the methyl base (LXXXV; R=Me) and bromoacetaldehyde oxime was heated on a boiling water bath for $\frac{1}{2}$ hour and the resulting monoquaternary oxime (LXXXVI; R=Me) allowed to stand at room temperature in concentrated hydrobromic acid for 3 hours. A 5% yield of the 5-hydroxy bromide (LXXXVII; R'=H, R=Me) was obtained. Treatment of this salt with boiling phosphorus tribromide did not effect dehydration; only the unreacted hydroxy compound was recovered. The aromatic dibromide (I; R=Me, R'=H) was obtained in high yield however by boiling the 5-hydroxy salt under reflux with thionyl chloride.

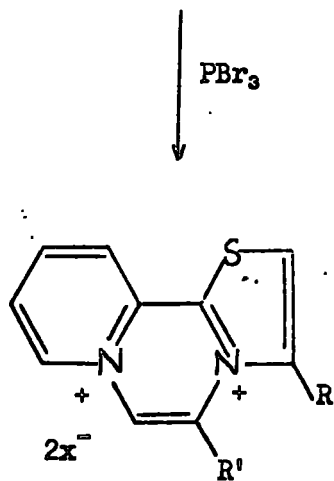
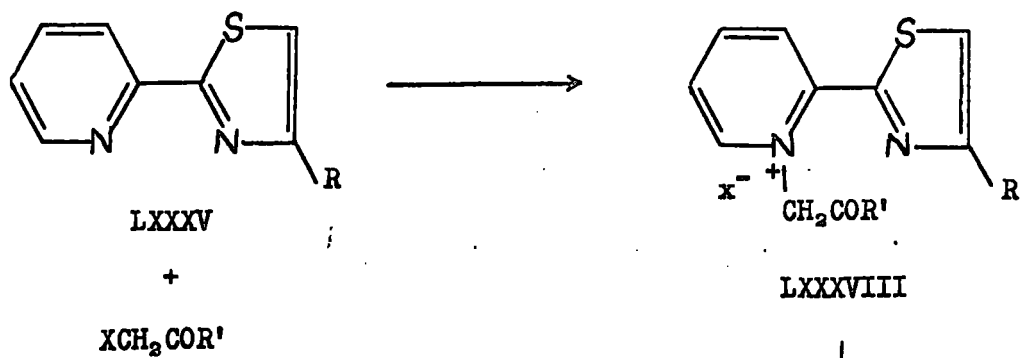
The synthesis of the corresponding 3-phenyl aromatic dibromide was attempted in the same way but the addition of acetone to the hydrobromic acid solution of the gum obtained by heating a mixture of the phenyl base (LXXXV; R=Ph) with bromoacetaldehyde oxime, precipitated only the hydrobromide of the phenyl base (LXXXVa; R=Ph, R'=H, X=Br) cyclisation to the 5-hydroxy salt (LXXXVII; R=Ph, R'=H) not having occurred.

5-Alkyl and 5-Aryl-pyrido [1,2-a]thiazolo [2,3-c]pyrazidi-inium salts

The synthesis of the 5-substituted pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium salts was carried out using a method similar to that described by Glover and Corr⁵⁹ for the preparation of 6-alkyl and 6-aryl-dipyrido [1,2-a : 2',1'-c] pyrazidi-inium salts (IV; R=Me or Ph).

The 1-acetyl and 1-phenacyl monoquaternary salts (LXXXVIII; R=H, R'=Me or Ph) of the parent base (LXXXV; R=H) were prepared by heating the base with bromoacetone or ω -bromoacetophenone on a water bath. After heating for 7 hours, a 48% yield of the 1-phenacyl bromide was obtained, however the corresponding 1-acetyl salt could not be isolated as a solid and was characterised as the picrate (LXXXVIII; R=H, R'=Me, X=picrate).

Cyclisation of the 1-acetyl salt to the aromatic dibromide (I; R=H; R'=Me) was effected by boiling the monoquaternary bromide gum (LXXXVIII; R=H, R'=Me) under reflux with phosphorus tribromide. A yield of 10% based on the starting 2-(2-pyridyl) thiazole was recorded. Treatment of the 1-phenacyl bromide (LXXXVIII; R=H, R'=Ph, X=Br) with boiling phosphorus tribromide afforded the 5-phenyl aromatic salt (I; R=H, R'=Ph, X=Br) in 38% yield.



3,5-Disubstituted pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium salts

The same procedure, used previously for the synthesis of the 5-substituted pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium salts, was used for the preparation of the 3,5-disubstituted systems (I; R=Me, R'=Me or Ph, X=Br).

A 64% yield of the 1-acetyl salt of the methyl base (LXXXVIII; R=R'=Me, X=Br) was obtained after heating a mixture of the base (LXXXV; R=Me) and bromoacetone for 5½ hours on a water bath. The 1-phenyl salt (LXXXVIII; R=Me, R'=Ph, X=Br) was isolated in 62% yield after heating the base with ω -bromoacetophenone for 26 hours. Both these salts were obtained as crystalline solids and both were cyclised to the corresponding aromatic systems (I; R=Me, R'=Me or Ph, X=Br) in fair yield by boiling under reflux with phosphorus tribromide.

In an attempt to reduce the 3,5-dimethyl-pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium dibromide (I; R=R'=Me, X=Br) an aqueous solution of the salt was hydrogenated over a platinum catalyst. Basification of the resulting solution and subsequent ether extraction did not afford the expected product. No identifiable compound was isolated.

Quaternisation of the phenyl base (LXXXV; R=Ph) with bromoacetone or ω -bromoacetophenone afforded respectively the 1-acetyl salt (LXXXVIII; R=Ph, R'=Me, X=Br) in 73% yield after heating for

$\frac{1}{2}$ hour, and the 1-phenacyl bromide (LXXXVIII; R=R'=Ph, X=Br) in 53% yield after $3\frac{1}{2}$ hours heating on a water bath. Neither of these colourless crystalline solids could be cyclised to diquaternary salts. When the 1-acetonyl bromide (LXXXVIII; R=Ph, R'=Me, X=Br) was boiled under reflux with phosphorus tribromide only the base hydrobromide (LXXXVa; R=Ph, R'=H, X=Br) was isolated from the reaction mixture, in 45% yield. Similarly, attempts to cyclise the 1-acetonyl salt to the hydroxy compound (LXXXVII; R=Ph, R'=Me, X=Br) using concentrated hydrobromic acid afforded only the hydrobromide of the phenyl base in 79% yield.

The base hydrobromide was the only product isolated from the reaction mixture when the 1-phenacyl monoquaternary salt of the phenyl base (LXXXVIII; R=R'=Ph, X=Br) was boiled under reflux with phosphorus tribromide. This monoquaternary salt was recovered unchanged and in high yields after being boiled under reflux in concentrated hydrobromic acid for $\frac{1}{2}$ hour.

The location of the quaternary nitrogen in the pyridine ring of the monoquaternary salts is suggested since pyridine is a stronger base than thiazole⁸².

The reluctance of the phenyl base (LXXXV; R=Ph) to form bridged diquaternary salts can be attributed to the steric effect of the 2-phenyl group and the more weakly basic nature of the thiazole nitrogen. Additional evidence in support of the

pyridinium structure for the monoquaternary salts (LXXXVIII) is to be found in the formation of only monopicates of the pyridyl thiazole bases, and in the n.m.r. spectrum of the 1-acetyl salt of the methyl base (LXXXVIII; R=R'=Me, X=Br). The n.m.r. spectrum of the methyl base in CCl₄ solution shows a signal in the region τ 7.5 attributed to the protons of the thiazole 3-methyl group, and the 1-acetyl salt (LXXXVIII; R=R'=Me) in D₂O solution showed a signal at τ 7.45 attributed to the protons of the thiazole 3-methyl group. A singlet at τ 7.4 was also observed, attributed to the ketonic methyl group of the acetyl function. Had the thiazole nitrogen been quaternary a greater shift downfield would have been expected for the signal attributed to the 3-methyl protons, the negligible difference in the signals suggests that the quaternary nitrogen is in the pyridine ring.

The infrared spectra of all the aromatic bromides (I) prepared showed a band in the region 1660 - 1680 cm.⁻¹ and attributed to the -C=C- of the central diquaternary pyrazine ring.

They are all pale yellow solids when prepared but on exposure to the atmosphere the colour fades due to absorption of moisture. Aqueous solutions of the aromatic dibromides developed a russet colouration of varying intensity when treated with zinc dust, indicating that reduction occurs probably with the formation of water soluble free radicals.

The physical constants of the pyrido[1,2-a]thiazolo
[2,3-c]pyrazidi-inium salts (I) are listed in Table I (page 68).

TABLE I - PYRIDO [1,2-a]THIAZOLO [2,3-c]PYRAZIDI-INIUM SALTS (I)

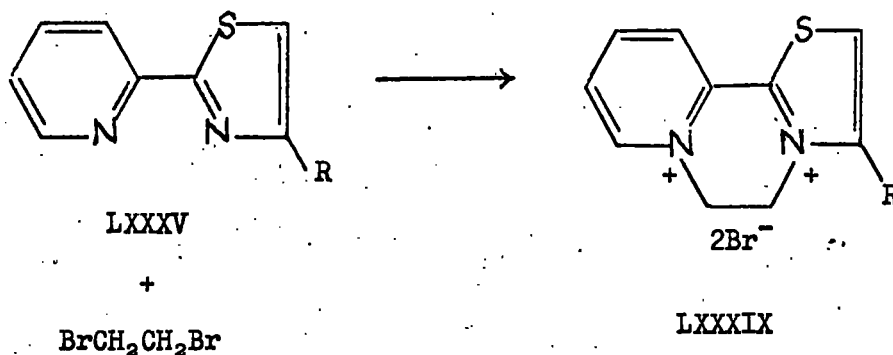
R	R'	X	MP (°C)	Yield %	λ max. (Å)	$\log_{10} \epsilon$
H	H	Br	320 ^a	69	2290, 2500sh., 2630, 2670, 2730, 3260, 3330, 3500	3.89, 4.02, 4.2, 4.23, 4.24, 4.11, 4.16, 4.09
H	H	Picrate	262-263	-		
H	Me	Br	320 ^a	10 ^b	2290sh., 2480, 2710sh., 2770, 3290, 3400, 3570	3.9, 4.0, 4.37, 4.41, 4.23, 4.22, 4.01
H	Ph	Br	340 ^a	38	2420sh., 2780, 3390	4.08, 4.28, 4.23
H	Ph	Picrate	220-222	-		
Me	H	Br	325 ^a	85	2260, 2490, 2700sh., 2770, 3400, 3560	3.92, 3.99, 4.19, 4.23, 4.22, 4.23
Me	H	Picrate	273 ^d	-		
Me	Me	Br	350 ^a	59	2500, 2830, 3450, 3550sh.	3.92, 4.22, 4.21, 4.18
Me	Me	Picrate	258	-		
Me	Ph	Br	320 ^a	57	2510, 2830, 3510sh., 3610	4.03, 4.26, 4.26, 4.29
Me	Ph	Picrate	228-230	-		

a - These compounds slowly charred without melting below the temperature indicated

b - Yield based on the starting 2-(2-pyridyl)thiazole.

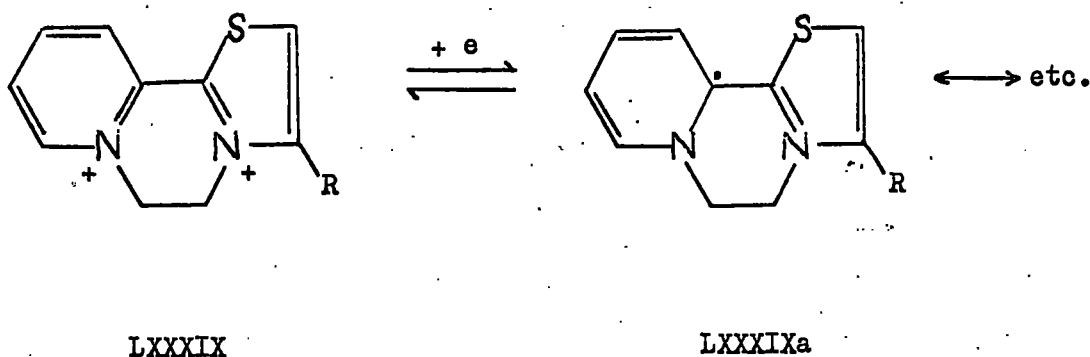
5,6-Dihydro pyrido [1,2-a] thiazolo[2,3-c] pyrazidi-inium salts

By heating the 2-(2-pyridyl) thiazole bases (LXXXV; R=H,Me or Ph) with dibromoethane in sealed tubes at 120°C, it was possible to isolate the 5,6-dihydro dibromides (LXXXIX; R=H,Me or Ph) from the reaction mixtures as yellow crystalline solids.



The ultraviolet spectra of these salts were determined and the spectrum of the dihydro compound derived from the phenyl base (LXXXIX; R=Ph) showed the expected bathochromic shift compared to the monomethiodide of the base (LXXXVa; R=Ph, R'=Me, X=I). It has been shown⁵⁶, that the bathochromic shift observed in compounds of this type results from the near coplanarity of the aromatic rings in these bridged diquaternary systems. It might be expected that these dihydro compounds, like the analogous salts of bipyridyl (LXXX), would exhibit herbicidal activity. The ready formation of stable water soluble free radicals was indicated by the

colouration produced when an aqueous solution of the salt was treated with zinc dust, and the near flat nature of the molecules inferred from the ultraviolet spectra and the number of possible structures which can be formulated for the mesomeric radicals (LXXXIXa; R=H, Me or Ph) obtained by one electron reduction of the dihydro salts.



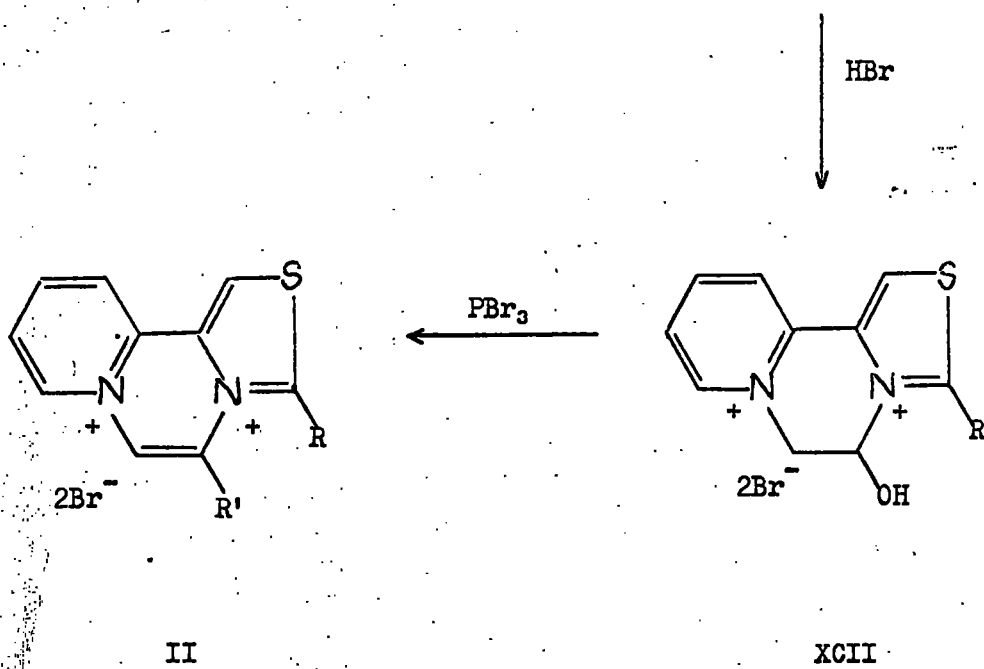
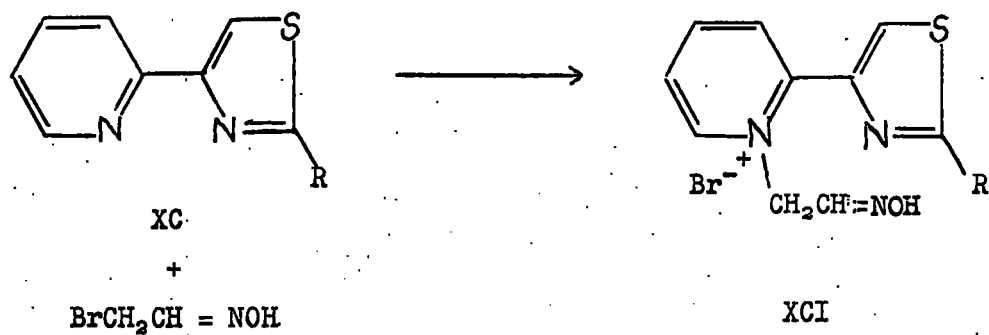
Except for the 5-hydroxy-5,6-dihydro salts (LXXXVII) the only other partially reduced systems obtained were the 5,6-dihydro-pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium salts. In the case of the phenyl base (LXXXV; R=Ph) the 5,6-dihydro derivative (LXXXIX; R=Ph, X=Br) was the only bridged diquaternary salt to be isolated.

Pyrido[1,2-a]thiazolo[4,3-c]pyrazidi-inium salts

2-Methyl-4-(2-pyridyl) thiazole (XC; R=Me) was prepared by heating thioacetamide with ω -bromoacetylpyridine⁸³ using a procedure similar to that described by Knott and Breckenridge⁸⁰ for the preparation of the parent base (XC; R=H).

Quaternisation of the methyl base with bromoacetaldehyde oxime yielded the crude monoquaternary oxime (XCI; R=Me, X=Br) which, when allowed to stand in concentrated hydrobromic acid for 5 hours, afforded a 34% yield of the 5-hydroxy dibromide (XCII; R=Me).

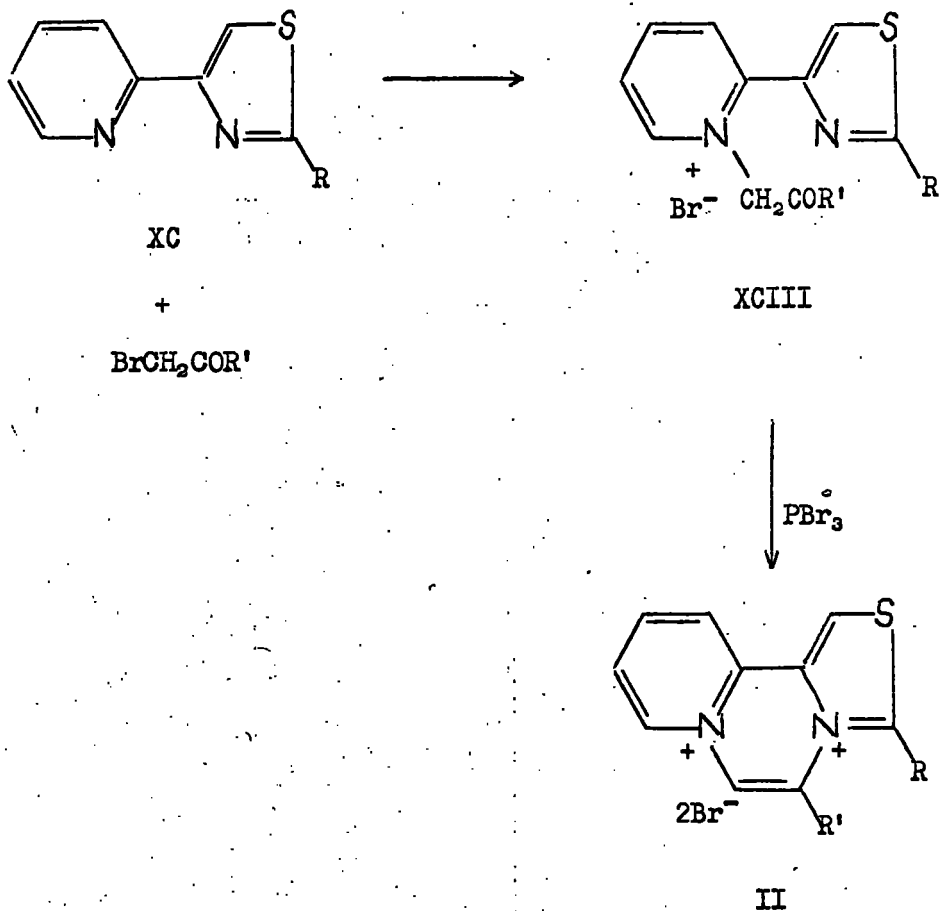
Dehydration of this hydroxy compound was achieved by boiling a suspension under reflux in phosphorus tribromide for 1½ hours when a high yield of the aromatic dibromide (II; R=Me, R'=H) was obtained.



5-Alkyl and 5-Aryl-pyrido[1,2-a]thiazolo[4,3-c]pyrazidi-inium salts

The 5-methyl and 5-phenyl aromatic dibromides (II; R=Me, R'=Me or Ph) were prepared in the same way as the corresponding 5-substituted pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium salts (I).

The 1-acetyl and 1-phenacyl monoquaternary salts (XCIII; R=Me, R'=Me or Ph, X=Br) were prepared in high yield by heating the base (XC; R=Me) with bromoacetone or ω -bromoacetophenone. Both these colourless crystalline solids were cyclised in moderate yield to the corresponding aromatic dibromides (II; R=Me, R'=Me or Ph, X=Br) by boiling under reflux with phosphorus tribromide.



Picrates of these aromatic diquaternary salts (II; R=Me, R'=Me or Ph, X=picrate) were obtained initially as yellow crystalline solids, but on attempted recrystallisation from a variety of solvents they subsequently decomposed.

The infrared spectra of these aromatic dibromides showed an absorption band in the region of 1660 - 1680 cm^{-1} attributed to the -C=C- of the central diquaternary pyrazine ring.

The instability of these compounds towards nucleophilic solvents was shown on attempted recrystallisation from aqueous or alcoholic solution, when intractable solids were obtained. Crystallisation from concentrated hydrobromic acid-acetone mixtures however, afforded the salts cleanly and with little loss.

When the ultraviolet spectra of these diquaternary compounds were determined in neutral aqueous solution, it was observed that on standing decomposition occurred with the appearance of a yellow colouration. The appearance of this colour coincided with a decrease in the intensity of the absorption maximum at 300 $\text{m}\mu$ and the appearance of a new maximum at 400 $\text{m}\mu$. In order to ensure that the compounds did not decompose the spectra were determined of solutions of the salts in dilute mineral acid.

The physical constants of the pyrido[1,2-a]thiazolo[4,3-c]pyrazidi-inium salts (II) are listed in Table II (page 76).

TABLE II - PYRIDO [1, 2-a] THIAZOLO [4, 3-c] PYRAZIDI -INIUM SALTS (II)

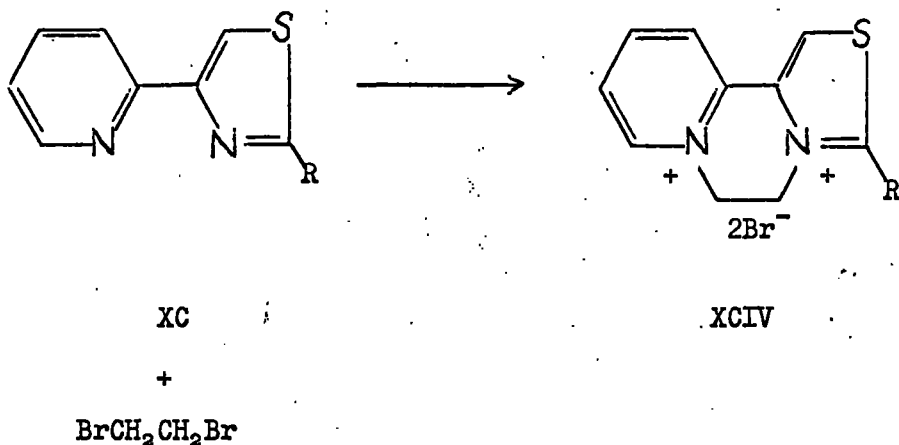
R	R'	X	MP (°C)	Yield %	λ max. (Å)	$\log_{10} \epsilon$
Me	H	Br ^c	320 ^a	86	2520, 2580sh., 2760sh., 3060, 3185	4.52, 4.47, 4.22, 3.84, 3.87
Me	Me	Br ^c	291d	52	2560, 2630, 2790, 3220	4.61, 4.58, 4.24, 3.98
Me	Ph	Br ^c	263-264	45	2560, 2780sh., 3260	4.52, 4.31, 4.0

a - This compound slowly charred without melting below the temperature indicated

c - These U.V. spectra were recorded of solutions in N. hydrochloric acid

5,6-Dihydro-pyrido[1,2-a]thiazolo[4,3-c]pyrazidi-inium salts

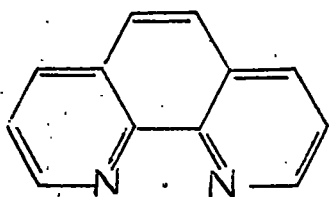
The dihydro compound (XCIV; R=Me, X=Br) was obtained in 50% yield by heating a mixture of the base (XC; R=Me) and dibromoethane at 120°C for 4 days.



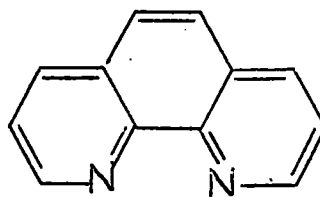
The picrate of this compound, like the picrates of the aromatic system (II) also decomposed on attempted recrystallisation. Like the other bridged diquaternary salts of this base the dihydro dibromide was crystallised from concentrated hydrobromic acid-acetone to prevent decomposition which occurred in alcoholic and neutral aqueous solution.

Benzo[b] dipyrido[1,2-a : 2',1'-c]pyrazidi-inium salts

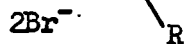
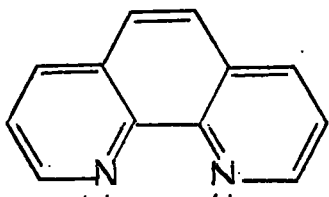
The synthesis of the parent aromatic dibromide (LXXXIV; R=H, X=Br) was attempted using the procedure described for the preparation of the parent pyrido thiazolo pyrazidi-inium systems (I,II; R=R'=H, X=Br). 1,10-phenanthroline was quaternised with bromoacetaldehyde oxime and the resulting crude monoquaternary salt gum (XCV; X=Br) treated with concentrated hydrobromic acid. When acetone was added to this solution a brown solid was precipitated which was assumed to be the hydroxy dibromide (XCVI). Crystallisation of this salt proved difficult and attempted dehydration to the aromatic diquaternary salt (LXXXIV; R=H, X=Br) with phosphorus tribromide afforded a reaction mixture from which no identifiable compound could be isolated.



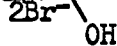
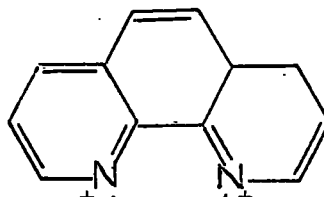
+



XCV



LXXXIV



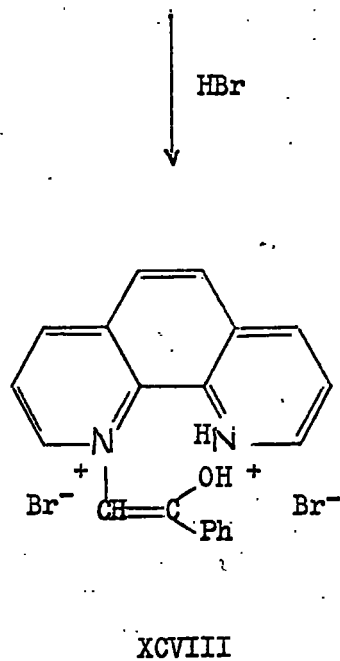
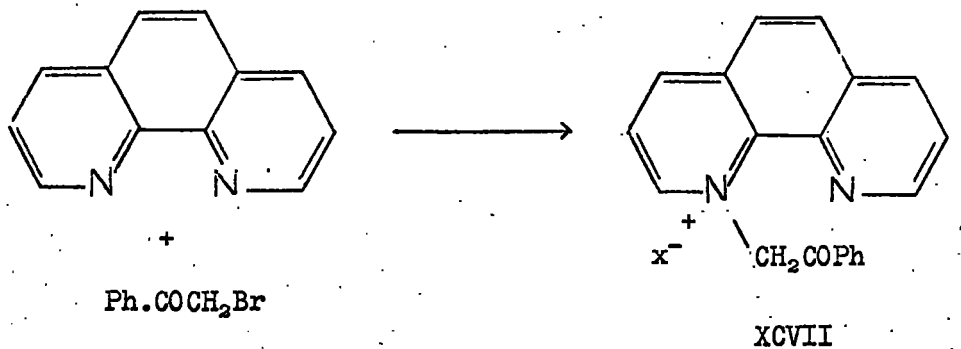
XCVI

5-Alkyl and 5-Aryl-benzo[b] dipyrido[1,2-a : 2',1'-c]pyrazidi-inium salts

The quaternisation of phenanthroline with bromoacetone was carried out using the general method for preparing acetyl quaternary salts. When the dark red reaction mixture was washed with ether, and dissolved in methanol, a dark intractable mass was obtained.

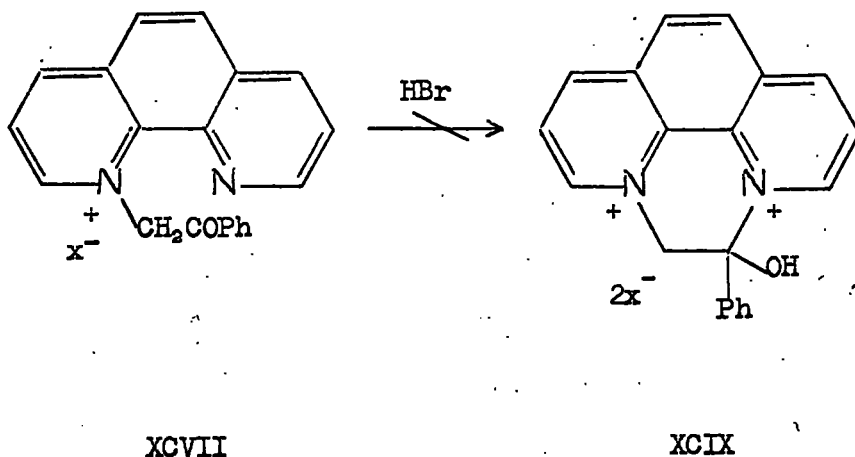
The 1-phenacyl monoquaternary salt (XCVII; X=Br) was similarly prepared by heating an equimolecular mixture of phenanthroline and ω -bromoacetophenone. Crystallisation of this salt from methanol solution proved to be much easier than for the 1-acetyl analogue and afforded a moderate yield of the phenacyl monoquaternary salt (XCVII; X=Br).

When the monoquaternary bromide (XCVII; X=Br) was heated with concentrated hydrobromic acid for several minutes, the addition of acetone to the cooled reaction mixture precipitated an enolic compound (XCVIII).

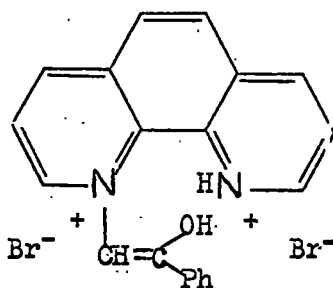
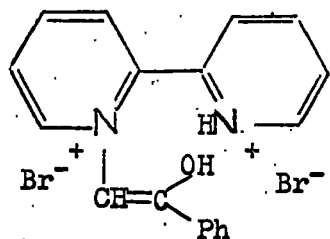


The infrared spectrum of this enolic salt (XCVIII) showed no absorption between 1620 cm^{-1} and 2500 cm^{-1} indicating the absence of a carbonyl function.

Treatment of this compound with aqueous sodium picrate afforded the 1-phenacyl monoquaternary picrate (XCVII; X=picrate) showing that hydrobromic acid had not effected cyclisation to the 5-hydroxy diquaternary salt (XCIX; X=Br).



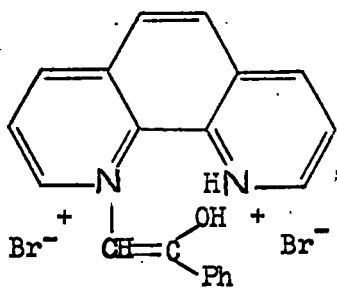
The structure of the compound(XCVIII) is analogous to that of the hydrobromide of the phenacyl monoquaternary salt of 2,2'-bipyridyl recently reported by Corr and Glover⁵⁹, and which was also shown to be enolic. These authors report the n.m.r. spectrum of the bipyridyl analogue (C) in D₂O as showing a single proton peak at τ 3.75 attributed to the enolic proton, the peak slowly disappeared during a period of 1½ hours.



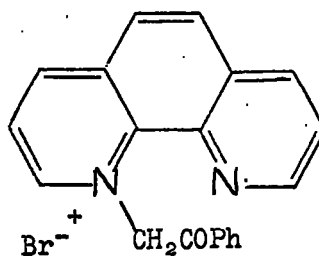
C

XCVIII

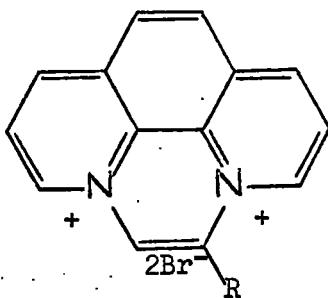
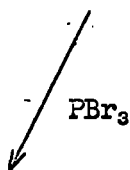
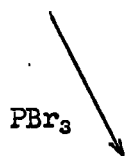
The enolic compound (XCVIII) was dehydrated to the aromatic dibromide (LXXXIV; R=Ph) by boiling phosphorus tribromide. A more convenient route to this salt however was by the direct cyclisation of the 1-phenacyl monoquaternary bromide (XCVII; X=Br) with boiling phosphorus tribromide. This procedure avoids one stage and the reflux time is shorter.



XCVIII



XCVII

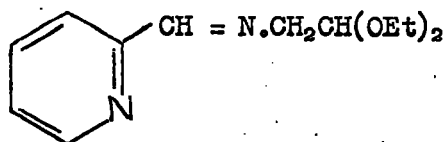


LXXXIV

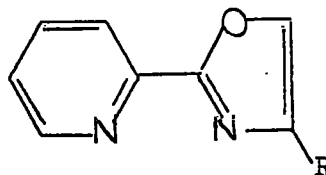
Pyrido [1,2-a] oxazolo [2,3-c] pyrazidi-inium salts

The synthesis of the 2-(2-pyridyl) oxazole was attempted using the method described by Dadkhah and Prijs⁸⁴ and reported as affording a 47% yield of the base (CI; R=H). Pyridine-2-aldehyde was condensed with aminoacetal and the resulting azomethine (CII) cyclised with oleum. After basification and subsequent ether extraction, only a small amount of dark oil was isolated which produced a tar on attempted distillation.

Another method⁸⁴, similarly utilized cyclisation of the azomethine (CII) but employed phosphorus pentoxide and concentrated sulphuric acid as the cyclising agent. A 10% yield was reported for this method, but only a very small amount of pyridyl oxazole was obtained.



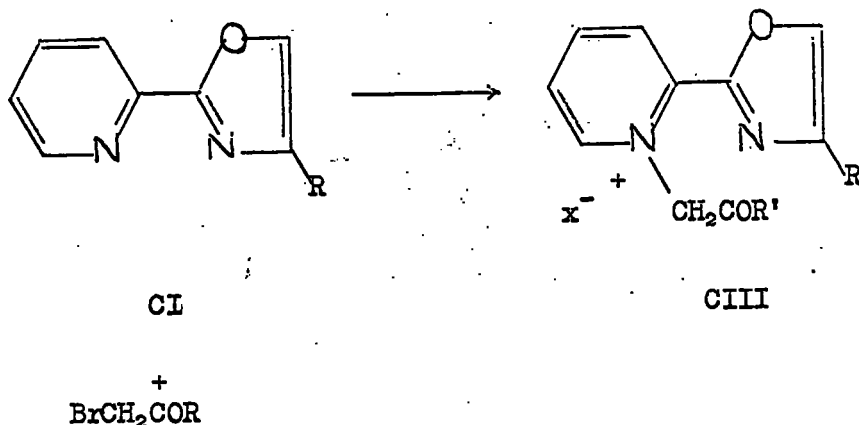
CII



CI

By heating this base with an excess of ω -bromoacetophenone it was possible to isolate a colourless crystalline solid, the infrared spectrum of which was very similar to the analogous 1-phenacyl-2-(2-thiazolyl) pyridinium bromide (LXXXVIII; R=H, R'=Ph, X=Br).

Characterisation of the suspected monoquaternary bromide (CIII; R=H, R'=Ph, X=Br) was attempted by preparing the picrate (CIII; R=H, R'=Ph, X=picrate) which was obtained as a stable yellow crystalline solid. The quantity produced was, however, after recrystallisation from ethanol, insufficient for elemental analysis.



It would appear that further investigation into the preparation of the pyridyl oxazole base is required, in order that a viable yield may be obtained. More work on this topic would almost certainly be fruitful, as the facile quaternisation with ω -bromoacetophenone has indicated a convenient route to the pyrido[1,2-a]oxazolo[2,3-c]pyrazidinium salts (LXXXIII).

ILLUSTRATIONS

FIGURE 1

Ultraviolet spectra of:-

2-(2-pyridyl) thiazole, A, and 2-methyl-4-(2-pyridyl) thiazole, B.

both in ethyl alcohol

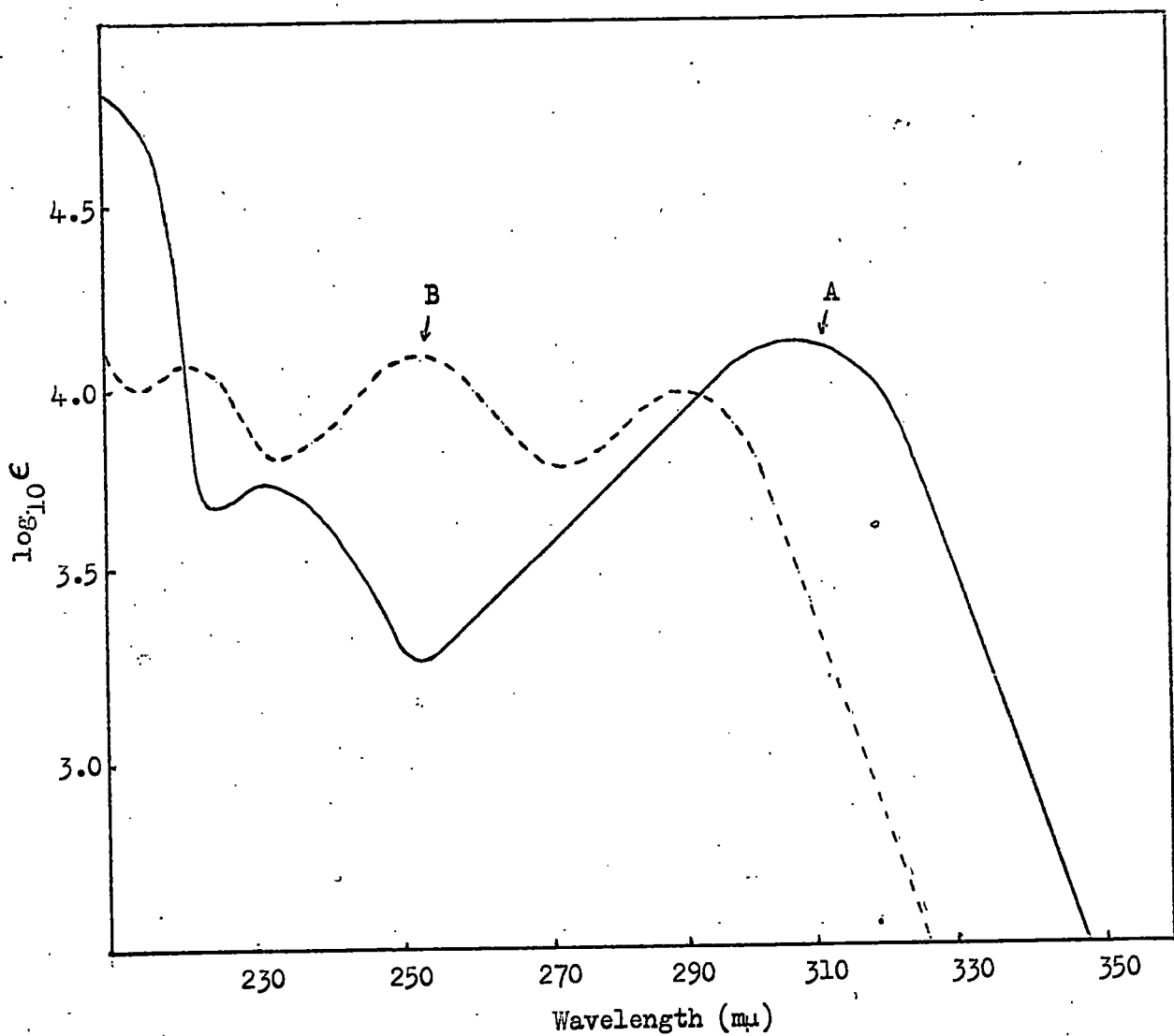


FIGURE 2

Ultraviolet spectra of:-

pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium dibromide, A, in neutral aqueous solution and 3-methylpyrido[1,2-a]thiazolo[4,3-c]pyrazidi-inium dibromide, B. in N. hydrochloric acid solution

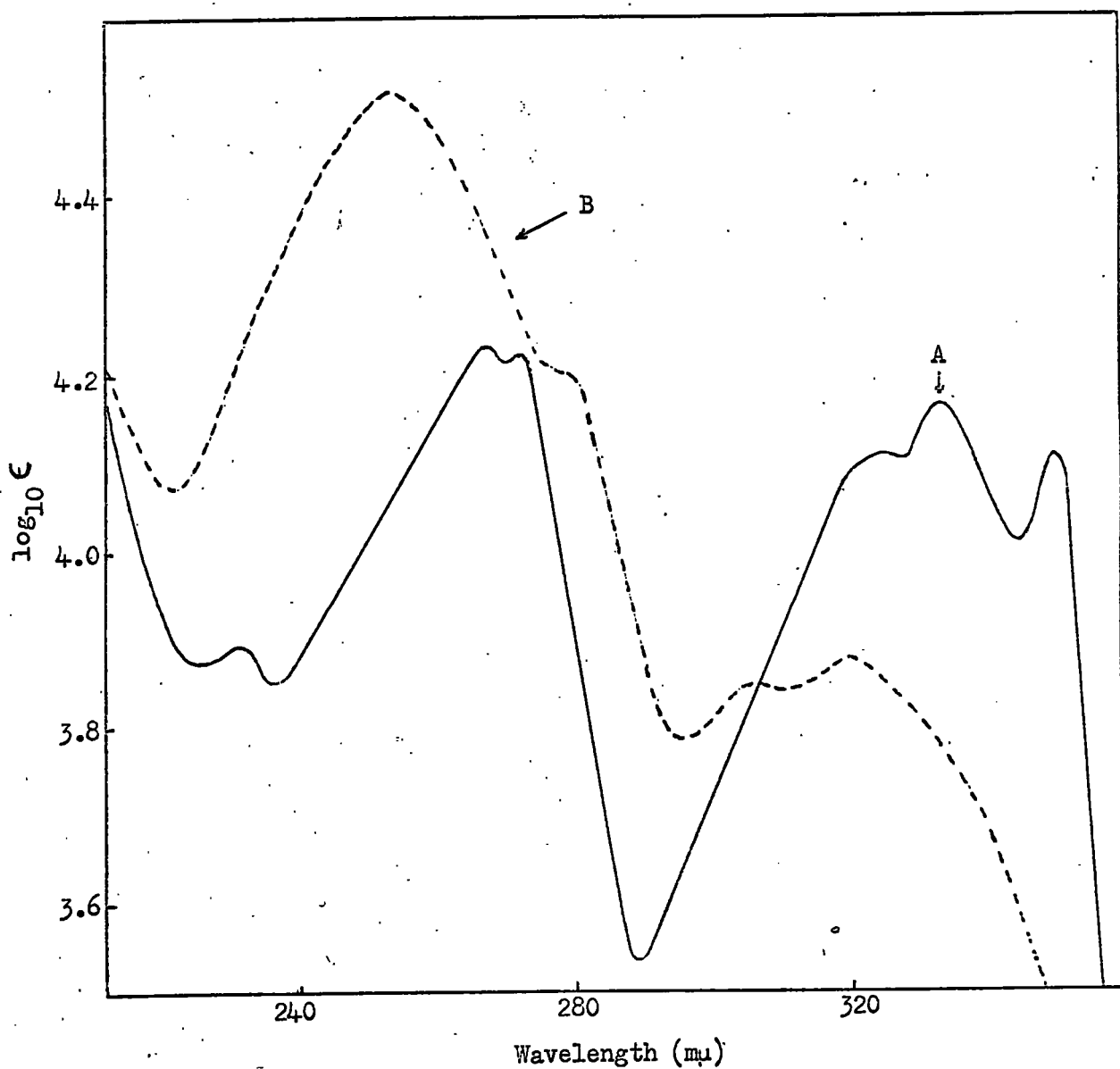


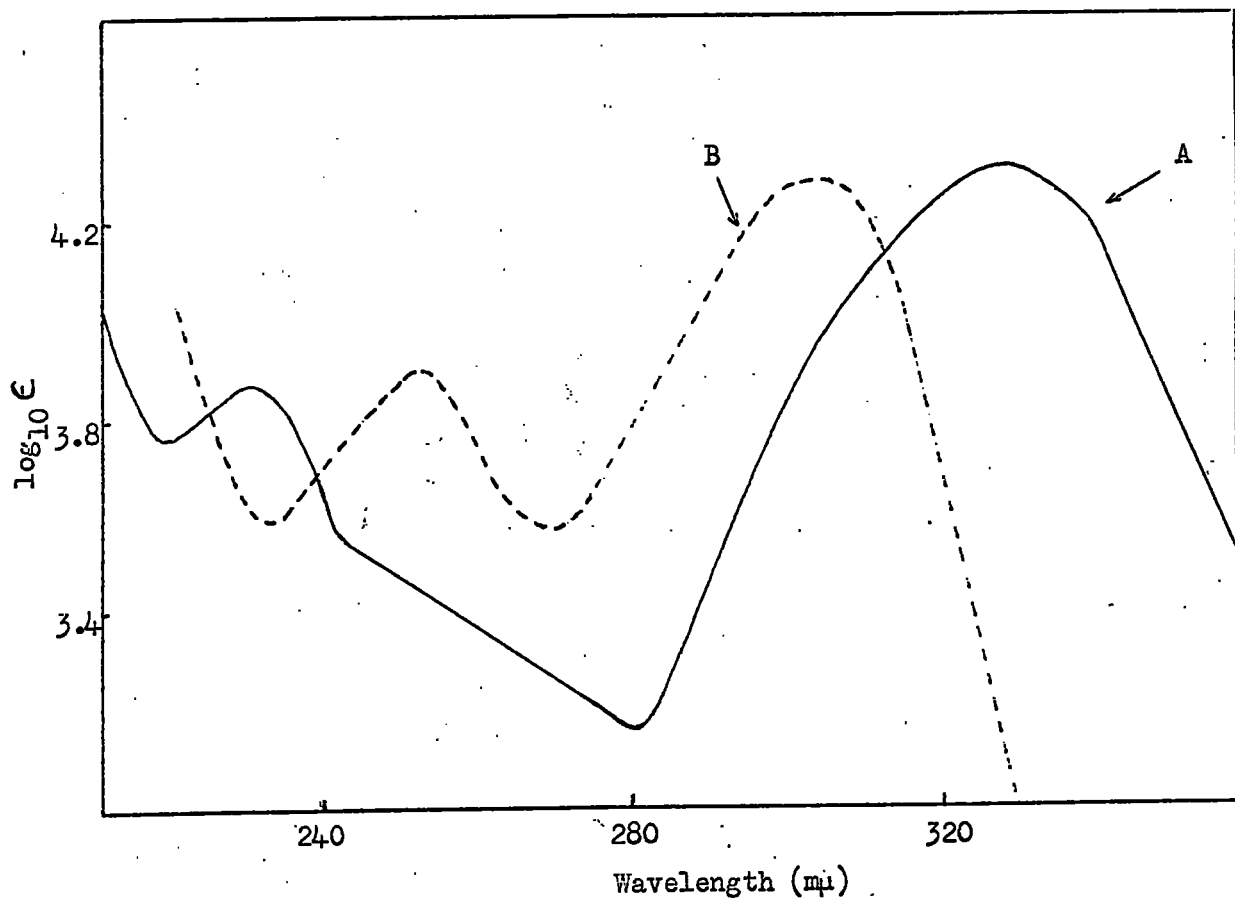
FIGURE 3

Ultraviolet spectra of:-

5,6-Dihydro-pyrido [1,2-a]thiazolo[2,3-c]pyrazidi-inium dibromide, A,

and 3-methyl-5,6-dihydro-pyrido [1,2-a]thiazolo[4,3-c]pyrazidi-inium

dibromide, B, in neutral aqueous solution



EXPERIMENTAL

EXPERIMENTAL

All melting points were determined on a Kofler block.

Infrared absorption spectra were determined on a Perkin-Elmer 237 spectrometer, ultraviolet absorption spectra on a Unicam SP700C spectrophotometer and n.m.r. spectra on a Perkin-Elmer Model R10 spectrometer.

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

Bromoacetaldehyde oxime was prepared using the method described by Kimber and Parham³⁴ for the synthesis of the chloro compound. A mixture of bromoacetaldehyde dimethylacetal (26 g.) and hydroxylamine hydrochloride (48 g.) in water (60 ml.) was stirred until an homogeneous solution was obtained. This solution was continuously extracted with ether for 72 hr., the ether extract washed with water (2 ml.) and then dried with sodium sulphate. The ether was removed by rotary evaporation to afford the bromoacetaldehyde oxime.

2-(ω -Bromoacetyl) pyridine was prepared using the method described by Clemo et al.⁸³. A solution of bromine (31.8 g.) in benzene (151.2 ml.) was added gradually to a well stirred solution of 2-acetylpyridine (24 g.) in benzene (240 ml.) and glacial acetic acid (60 ml.). The resulting colourless precipitate was collected and treated with an excess of saturated potassium carbonate solution to yield an oil. The oil was extracted with ether and the extract dried with sodium sulphate. Distillation of the oil under reduced pressure afforded 2-acetylpyridine, b.p. 35-40°/1 mm. (4.4 g.), and 2-(ω -bromoacetyl) pyridine, b.p. 89-90°/1 mm. (12.1 g.).

Bromoacetone was prepared by the method of P.A. Levene⁸¹. A mixture of acetic acid (74 ml.), acetone (100 ml.) and water (320 ml.) was heated in a round bottomed flask with stirring at 65°, while bromine (70 ml.) was added dropwise. This solution was then diluted with water (160 ml.) at 10°, before neutralising to Congo Red with sodium carbonate. The resulting oil was collected in a

separating funnel and dried with calcium chloride (16 g.) before distillation. The fraction boiling 38-48°/13 mm. was collected for redistillation under vacuum when the 40-42° fraction at 13 mm. was retained for use.

Thiopicolinamide was prepared using the method described by Karrer and Schukri⁷⁹. 2-Cyanopyridine (10 g.) in ethanol (20 ml.) was added to a solution (80 ml.) of ethanol saturated with ammonia. When this mixture was saturated with hydrogen sulphide the crude thioamide gradually separated from the solution. The thioamide was crystallised from ethanol as pale yellow needles, m.p. 138° (5.6 g.).

4-Methyl-2-(2-pyridyl) thiazole (LXXXV; R=Me) was prepared according to the method of Karrer and Schukri⁷⁹. A solution of thiopicolinamide (1 g.) and chloroacetone (1 g.) in ethanol (3-4 ml.), was boiled under reflux for 8-10 hr. The base hydrochloride was obtained from the cold alcohol solution as colourless needles, m.p. 170-172°.

The free base was obtained by dissolving the hydrochloride (1 g.) in water (5-7 ml.), basifying with sodium hydroxide and extracting with ether. Evaporation of the ether yielded the crude base which crystallised from 40-60° petrol-acetone and had m.p. 84-84.5°;

λ_{max} (in EtOH) 2330, 3090 Å ($\log_{10} \epsilon$ 3.78, 4.19).

4-Phenyl-2-(2-pyridyl) thiazole (LXXXV; R=Ph) was prepared using the method described by Knott and Breckenridge⁸⁰. A solution of thiopicolinamide (1.5 g.) and ω -bromoacetophenone (1.7 g.) in ethanol (10 ml.) was boiled under reflux for 2 hr. The solution was evaporated to half its original volume and cooled. The base hydrobromide (LXXXVa; R=Ph, R'=H, X=Br) was washed with dilute potassium hydroxide solution giving the free base which was crystallised from ligroin-ether and had m.p. 71°; λ_{\max} (in EtOH) 2510, 2590_{sh.}, 2840_{sh.}, 3240 Å ($\log_{10} \epsilon$ 4.46, 4.39, 4.02, 4.08).

The monomethiodide, (LXXXVa; R=Ph, R'=Me, X=I) of the phenyl base was prepared by treating a solution of the base in tetramethylenesulphone with methyl iodide. The monoquaternary iodide crystallised from methanol-ether as yellow needles, m.p. 202° (Found: N, 7.4, 7.7. C₁₅H₁₃IN₂S requires N, 7.4%); λ_{\max} (in H₂O) 2160_{sh.}, 2570, 3470 ($\log_{10} \epsilon$ 4.42, 4.31, 3.82).

2-(2-Pyridyl) thiazole (LXXXV; R=H)

A mixture of thiopicolinamide (2 g.) and bromoacetal (2.6 g.) was heated on a boiling water bath for 16 hr. The reaction mixture was cooled, washed with ether, dissolved in water, and basified with dilute sodium hydroxide solution. This solution was extracted with ether and the extract dried with sodium sulphate before evaporation to low volume. The residual crude base was chromatographed in ether solution on an alumina column and the

eluate evaporated. Crystallisation of the residue from 40-60° petroleum ether gave the chemically pure base (1.1 g., 47%). The analytical sample of the colourless base was obtained by sublimation at 70-80° / 0.5 mm., m.p. 59-61° (Found: C, 59.0; H, 3.8; N, 17.25. $C_8H_6N_2S$ requires C, 59.3; H, 3.7; N, 17.3%); λ_{\max} (in EtOH) 2300_{sh.}, 2390_{sh.}; 3080 Å ($\log_{10} \epsilon$ 3.61, 3.52, 4.13).

The picrate, prepared by the addition of alcoholic picric acid to the base, crystallised from ethanol as yellow prisms, m.p. 155-157° (Found: C, 42.85; H, 2.1; N, 18.0. $C_8H_6N_2S$, $C_6H_3N_3O_7$ requires C, 43.0; H, 2.3; N, 17.9%).

2-Methyl-4-(2-pyridyl) thiazole (XC; R=Me)

A mixture of 2-(ω -bromoacetyl) pyridine (1.0 g.) and thioacetamide (0.35 g.) was heated on a boiling water bath for 3 hr., cooled and washed with ether. The residual gum was basified and extracted with ether. The dried extract was evaporated to low volume and chromatographed in ether solution on an alumina column to yield the base (0.43 g., 49%). The analytical sample, obtained by sublimation at 85° and 3.5 mm., had m.p. 43°. (Found: C, 61.3; H, 4.5; N, 15.4. $C_9H_8N_2S$ requires C, 61.35; H, 4.6; N, 15.9%); λ_{\max} (in EtOH) 2210, 2530, 2900 Å ($\log_{10} \epsilon$ 4.08, 4.10, 3.98).

The picrate, prepared by the addition of alcoholic picric acid to the base, crystallised from ethanol as yellow needles,

m.p. 195° (decomp.). (Found: C, 44.3; H, 2.7; N, 17.15).

$C_9H_8N_2S$, $C_6H_5N_3O_7$ required C, 44.5; H, 2.7; N, 17.3%.

5-Hydroxy-5,6-dihydro-pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium
Dibromide (LXXXVII; R=R'=H, X=Br)

A mixture of the base (LXXXV; R=H) (1.18 g.) and bromoacetaldehyde oxime (1.5 g.) was heated on a hot water bath for 3 hr. The reaction mixture was cooled and washed with ether. The residue was dissolved in concentrated hydrobromic acid (2 ml.) and allowed to stand at room temperature for 1½ hr. The addition of acetone precipitated the crude hydroxy diquaternary salt which was filtered off. The analytical sample of the hydroxy dibromide crystallised from concentrated hydrobromic acid-acetone and had m.p. >340° (decomp.) (0.228 g., 9%). (Found: C, 33.25; H, 2.65; N, 7.7. $C_{10}H_{10}Br_2N_5O_5$ requires C, 32.8; H, 2.75; N, 7.65%.)

Addition of aqueous sodium picrate to the dibromide afforded the dipicrate which was crystallised from nitromethane-ether and had m.p. 176-178°. (Found: C, 40.0; H, 2.25. $C_{22}H_{14}N_8O_{15}S$ requires C, 39.9; H, 2.1%.)

Pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium Dibromide (I; R=R'=H, X=Br)

A suspension of the hydroxy dibromide (LXXXVII; R=R'=H, X=Br) (0.35 g.) in thionyl chloride (6 ml.) was boiled under reflux for 1 hr. The reaction mixture was cooled, filtered and the residue which was crystallised from concentrated hydrobromic acid - acetone afforded

the dibromide, m.p. $> 320^{\circ}$ (decomp.) (0.216 g., 69%) (Found: C, 33.1; H, 3.1; N, 7; 0. $C_{10}H_8Br_2N_2S$. H_2O requires C, 32.8; H, 2.75; N, 7.65%); λ_{max} (in H_2O) 2290, 2500 $\underline{sh.}$, 2630 $\underline{sh.}$, 2670, 2725, 3260, 3330, 3500 \AA ($\log_{10} \epsilon$ 3.89, 4.02, 4.20, 4.23, 4.24, 4.11, 4.16, 4.09).

The dipicrate, prepared by the addition of aqueous sodium picrate to the dibromide, crystallised from nitromethane - ether and had m.p. 262-263 $^{\circ}$ (Found: C, 41.2; H, 2.0; N, 17.3.

$C_{22}H_{12}N_8O_{14}S$ required C, 41.0; H, 1.9; N, 17.4%).

5,6-Dihydro-pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium Dibromide
(LXXXIX; R=H, X=Br)

A mixture of the unsubstituted base (LXXXV; R=H) (0.98 g.) and dibromoethane (1.25 g.) was heated in a sealed tube at 120 $^{\circ}$ for 3 days. The reaction product was washed with ether and crystallised from concentrated hydrobromic acid - acetone giving the dibromide m.p. $> 320^{\circ}$ (0.55 g., 48%) (Found: C, 34.5; H, 3.0; N, 8.3.

$C_{10}H_{10}Br_2N_2S$ required C, 34.3; H, 2.9; N, 8.0%); λ_{max} (in H_2O) 2290, 3280 \AA ($\log_{10} \epsilon$ 3.86, 4.28).

The dipicrate, prepared by treating the dibromide with aqueous sodium picrate was crystallised from nitromethane and had m.p. 255-257 $^{\circ}$. (Found: C, 41.05; H, 2.2; N, 17.3. $C_{22}H_{14}N_8O_{14}S$ requires C, 40.9; H, 2.2; N, 17.3%).

1-Acetyl-2-(2-thiazolyl) pyridinium Bromide (LXXVIII; R=H, R'=Me, X=Br)

2-(2-Pyridyl) thiazole (0.22 g.) and bromoacetone (0.22 g.) were heated together on a boiling water bath for 3 hr. The resulting gum was washed with ether but no solid material could be isolated; the cation was therefore characterised as the picrate. The crude mono-quaternary bromide was treated with aqueous sodium picrate and the resulting monopicrate crystallised from ethanol giving yellow needles, m.p. 145-146° (0.05 g., 8%, based on the starting 2-(2-pyridyl) thiazole). (Found: C, 45.45; N, 2.95; S, 15.6. $C_{17}H_{15}N_5O_8S$ requires C, 45.6; H, 2.9; N, 15.65%).

5-Methyl-pyrido [1,2-a]thiazolo[2,3-c]pyrazidi-inium Dibromide (I; R=H, R'=Me, X=Br)

A mixture of bromoacetone (1.06 g.) and 2-(2-pyridyl) thiazole (0.85 g.) was heated on a boiling water bath. The resulting gum was washed with ether and then boiled under reflux with phosphorus tribromide (5 ml.) for 5 min. After cooling, the residue was filtered off and washed free of phosphorus tribromide with acetone. The dibromide crystallised from concentrated hydrobromic acid - acetone as pale yellow plates, m.p. >320° (decomp.) (0.17 g., 10%, based on the starting 2-(2-pyridyl) thiazole) (Found: C, 32.7; H, 3.7; N, 6.6. $C_{11}H_{10}Br_2N_2S \cdot 2H_2O$ requires C, 33.2; H, 3.5; N, 7.0%); λ_{max} (in H_2O) 2290_{sh.}, 2490_{sh.}, 2710_{sh.}, 2770, 3290, 3400, 3570 ($\log_{10} \epsilon$ 3.90, 4.0, 4.37, 4.41, 4.23, 4.22, 4.01).

1-Phenacyl-2-(2-thiazolyl) pyridinium Bromide (LXXXVIII; R=H, R'=Ph, X=Br)

2-(2-Pyridyl) thiazole (1.08 g.) and ω -bromoacetophenone (1.33 g.) were heated together on a hot water bath at 80° for 7 hr. The reaction mixture was cooled and washed with ether. Recrystallisation of the residue from ethanol-ether afforded the monoquaternary bromide as pale yellow plates, m.p. 178-179° (1.16 g., 48%) (Found: C, 53.1; H, 3.6; N, 8.3. $C_{16}H_{13}BrN_2OS$ requires C, 53.2; H, 3.6; N, 7.8%).

The picrate, prepared by the addition of aqueous sodium picrate to the monoquaternary bromide, crystallised from ethanol and had m.p. 162° (Found: C, 52.2; H, 2.9; N, 14.2. $C_{22}H_{15}N_5O_8S$ requires C, 51.9; H, 3.0; N, 13.75%).

5-Phenyl-pyrido [1,2-a]thiazolo [2,3-c]pyrazidi-inium Dibromide (I; R=H, R'=Ph, X=Br)

A suspension of the monoquaternary bromide (LXXXVIII; R=H, R'=Ph) (1.23 g.) in phosphorus tribromide (10 ml.) was boiled under reflux for 5 min., and the reaction mixture cooled, filtered and washed with acetone. The residue was crystallised from methanol-ether yielding the dibromide, m.p. >340° (0.55 g., 38%) (Found: C, 44.7; H, 3.0; N, 6.8. $C_{16}H_{12}Br_2N_2S \cdot \frac{1}{2} H_2O$ requires C, 44.35; H, 3.0; N, 6.5%); λ_{max} (in H_2O) 2420 $\underline{sh.}$, 2780, 3390 ($\log_{10} \epsilon$ 4.08, 4.28, 4.25).

The dipicrate, prepared by the addition of aqueous sodium picrate to the dibromide, was crystallised from nitromethane-ether, and had m.p. 220-222° (Found: C, 46.3; H, 2.4; N, 15.7. $C_{28}H_{16}N_8O_{14}S$ requires C, 46.7; H, 2.2; N, 15.55%).

5-Hydroxy-3-methyl-5,6-dihydro-pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium Dibromide (LXXXVII; R=Me, R'=H, X=Br)

A mixture of the methyl base (LXXXV; R=Me) (0.86 g.) and bromoacetaldehyde oxime (0.8 g.) was heated on a water bath at 80° for 30 min. The reaction mixture was cooled, washed with ether, the residue dissolved in concentrated hydrobromic acid (2 ml.) and allowed to stand at room temperature for 3 hr. The addition of acetone precipitated the hydroxy dibromide which, when filtered off and crystallised from concentrated hydrobromic acid - acetone had m.p. 253° (0.10 g., 5%) (Found: C, 34.9; H, 3.1; N, 7.5. $C_{11}H_{12}Br_2N_2OS$ requires C, 34.75; H, 3.2; N, 7.4%).

Attempted dehydration of 5-Hydroxy-3-methyl-5,6-dihydro-pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium Dibromide (LXXXVII; R=Me, R'=H, X=Br)

A suspension of the hydroxy dibromide (0.14 g.) in phosphorus tribromide (5 ml.) was boiled under reflux for 2½ hr. The reaction mixture was cooled and filtered, and the residue washed with acetone. Recrystallisation of the residue from concentrated hydrobromic acid - acetone gave only the starting hydroxy dibromide (0.11 g., 78%).



3-Methyl-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide

(I; R=Me, R'=H, X=Br)

A suspension of the hydroxy dibromide (LXXXVII; R=Me, R'=H, X=Br) (0.18 g.) in thionyl chloride (5 ml.) was boiled under reflux for $1\frac{1}{4}$ hr. The reaction mixture was cooled, filtered, washed with acetone, and the residue dissolved in concentrated hydrobromic acid. The addition of acetone precipitated the aromatic dibromide which was recrystallised from concentrated hydrobromic acid - acetone giving pale yellow plates, m.p. $>325^{\circ}$ (0.15 g., 85%) (Found: C, 34.5; H, 3.5; N, 7.85. $C_{11}H_{10}Br_2N_2S$. H_2O requires C, 34.75; H, 3.2; N, 7.4%); λ_{max} (in H_2O) 2260, 2490, 2700_{sh.}, 2770, 3400, 3560 Å ($\log_{10} \epsilon$ 3.92, 3.99, 4.19, 4.23, 4.22, 4.23).

The dipicrate, prepared by the addition of aqueous sodium picrate to the dibromide, crystallised from nitromethane-ether, and had m.p. 260° (decomp.) (Found: C, 42.1; H, 2.4. $C_{23}H_{14}N_8O_{14}S$ requires C, 41.95; H, 2.1%).

3-Methyl-5,6-dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium

Dibromide (LXXXIX; R=Me, X=Br)

A sealed tube containing a mixture of the methyl base (LXXXV; R=Me) (0.65 g.) and dibromoethane (1.49 g.) was heated at 120° for 6 days. The reaction mixture was cooled, washed with ether and the residue crystallised from methanol-ether to afford the

bridged dibromide, m.p. $>300^{\circ}$ (0.28 g., 21%) (Found: C, 36.2; H, 3.2; N, 7.6. $C_{11}H_{12}Br_2N_2S$ requires C, 36.3; H, 3.3; N, 7.7%); λ_{max} (in H_2O) 2330, 3430 \AA ($\log_{10} \epsilon$ 3.79, 4.29).

The dipicrate, prepared by the addition of aqueous sodium picrate to the dibromide, crystallised from water as yellow needles, m.p. 273° (decomp.) (Found: C, 42.4; H, 2.7; N, 17.1.

$C_{23}H_{14}Br_2N_8O_{14}S$ requires C, 42.8; H, 2.5; N, 16.6%).

1-Acetyl-2-[2-(4-methylthiazolyl)]pyridinium Bromide (LXXXVIII; R=R'=Me, X=Br)

A mixture of the methyl base (LXXXV; R=Me) (3.72 g.) and bromoacetone (2.8 g.) was heated on a water bath at 80° for $5\frac{1}{2}$ hr.

The reaction mixture was washed with ether and yielded a solid which crystallised from methanol-ether as colourless plates, m.p. 216° (4.24 g., 64%) (Found: C, 45.2; H, 4.4; N, 8.5.

$C_{12}H_{13}BrN_2OS \cdot \frac{1}{2}H_2O$ requires C, 44.7; H, 4.4; N, 8.7%).

The picrate, prepared by the addition of aqueous sodium picrate to the bromide, crystallised from ethanol-water as yellow needles, m.p. $178-180^{\circ}$ (Found: C, 47.1; H, 3.6; N, 14.9.

$C_{18}H_{15}N_5O_8S$ requires C, 46.9; H, 3.3; N, 15.2%).

3,5-Dimethyl-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide (I; R=R'=Me, X=Br)

A suspension of the 1-acetyl monoquaternary salt (LXXXVIII; R=R'=Me, X=Br) (0.62 g.) in phosphorus tribromide (10 ml.) was

boiled under reflux for 5 min. The reaction mixture was cooled, filtered and the residue washed with acetone and ether. Crystallisation of the residue from methanol-ether gave the aromatic dibromide, m.p. $>350^{\circ}$ (0.44 g., 59%) (Found: C, 35.35; H, 3.65; N, 6.8. $C_{12}H_{12}Br_2N_2S \cdot 2H_2O$ requires C, 35.0; H, 3.9; N, 6.8%); λ_{max} (in H_2O) 2500, 2825, 3450, 3550sh. \AA ($\log_{10} \epsilon$ 3.92, 4.22, 4.21, 4.18).

The dipicrate, prepared by the addition of aqueous sodium picrate to the bromide, crystallised from water as yellow plates, m.p. 258° (decomp.) (Found: C, 43.2; H, 2.2. $C_{24}H_{16}N_8O_{14}S$ requires C, 42.9; H, 2.4%).

1-Phenacyl-2-[2-(4-methylthiazolyl)]pyridinium Bromide (LXXXVIII; R=Me, R'=Ph, X=Br)

A mixture of 4-methyl-2-(2-pyridyl) thiazole (0.85 g.) and ω -bromoacetophenone (0.96 g.) was homogenized on a boiling water bath and then allowed to stand at room temperature for 26 hr. The reaction product was washed with ether and recrystallised from methanol-ether affording the monoquaternary bromide as colourless plates, m.p. 236° (1.1 g., 62%) (Found: C, 53.2; H, 4.3; N, 7.2. $C_{17}H_{15}BrN_2O \cdot \frac{1}{2}H_2O$ requires C, 53.1; H, 4.2; N, 7.3%).

3-Methyl-5-phenyl-pyrido [1,2-a]thiazolo [2,3-c]pyrazidi-inium Dibromide (I; R=Me, R'=Ph, X=Br)

A suspension of the monoquaternary bromide (LXXXVIII; R=Me, R'=Ph) (0.61 g.) in phosphorus tribromide (10 ml.) was boiled under reflux for 5 min. The reaction product was cooled, filtered and washed free

of phosphorus tribromide with acetone. Crystallisation of the residue from methanol-ether gave the dibromide as pale yellow plates m.p. $>320^{\circ}$ (decomp.) (0.4 g., 57%) (Found: C, 45.8; H, 3.4; N, 6.45. $C_{17}H_{14}Br_2H_2S \cdot \frac{1}{2}H_2O$ requires C, 45.65; H, 3.6; N, 6.3%); λ_{max} (in H_2O) 2510, 2830, 3510 $\underline{sh.}$, 3610 $\overset{\circ}{A}$ ($\log_{10} \epsilon$ 4.03, 4.26, 4.26, 4.29).

The dipicrate, prepared by the addition of aqueous sodium picrate to the dibromide, crystallised from nitromethane-ether as yellow plates, m.p. 228-230 $^{\circ}$ (Found: C, 47.1; H, 2.9; N, 15.4.

$C_{29}H_{18}N_8O_{14}S$ requires C, 47.4; H, 2.5; N, 15.3%).

Attempted synthesis of 5-Hydroxy-3-Phenyl-5,6-dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide (LXXXVII; R=Ph, R'=H, X=Br)

A mixture of the phenyl base (LXXXV; R=Ph) (0.48 g.) and bromoacetaldehyde oxime (0.28 g.) was heated on a hot water bath for 4 hr. The reaction mixture was cooled, washed with ether and the gum dissolved in concentrated hydrobromic acid (5 ml.). Acetone was added to the mixture but the precipitated solid proved to be the hydrobromide of the base (LXXXVa; R=Ph, R'=H, X=Br).

3-Phenyl-5,6-dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide (LXXXIX; R=Ph, X=Br)

A sealed tube containing 4-phenyl-2-(2-pyridyl) thiazole (0.5 g.) and dibromoethane (0.5 g.) was heated at 120 $^{\circ}$ for 4 days. The tube was cooled and the contents washed with ether. Crystallisation of the residue from methanol-ether afforded the dihydrodibromide (LXXXIX; R=Ph) as yellow plates, m.p. 297-299 $^{\circ}$ (decomp.) (0.16 g., 18%)

(Found: C, 43.9; H, 3.6; N, 6.5. $C_{16}H_{14}Br_2N_2S \cdot \frac{1}{2}H_2O$ requires C, 44.2; H, 3.5; N, 6.4%); λ_{max} (in H_2O) 2240, 3030_{sh.}, 3550 Å ($\log_{10} \epsilon$ 4.27, 3.67, 4.17).

The dipicrate was prepared by treating the bromide with aqueous sodium picrate and crystallised from nitromethane as yellow needles, m.p. 220-222° (Found: C, 46.5; H, 2.8; N, 15.2. $C_{28}H_{18}N_8O_{14}S$ requires C, 46.5; H, 2.5; N, 15.5%).

1-Acetyl-2-[2-(4-phenylthiazolyl)]pyridinium Bromide (LXXXVIII; R=Me, R=Ph, X=Br)

A mixture of the phenyl base (LXXXV; R=Ph) (0.52 g.) and bromoacetone (0.9 g.) was heated on a boiling water bath for 30 min. The reaction mixture was cooled, washed with ether and the residue crystallised from methanol-ether yielding the monoquaternary bromide as golden plates, m.p. 184-185° (0.61 g., 74%) (Found: C, 52.75; H, 4.2; N, 7.1. $C_{17}H_{15}BrN_2OS \cdot \frac{1}{2}H_2O$ requires C, 53.1; H, 4.2; N, 7.3%).

The picrate, prepared by treating the bromide with aqueous sodium picrate, crystallised from ethanol-water as yellow needles, m.p. 190° (Found: C, 52.3; H, 3.4; N, 13.4. $C_{23}H_{17}N_5O_8S$ requires C, 52.8; H, 3.3; N, 13.4%).

Attempted synthesis of 5-Methyl-3-phenyl-pyrido [1,2-a]thiazolo [2,5-c]pyrazidi-inium Dibromide (I; R=Ph, R'=Me, X=Br).

A suspension of the monoquaternary bromide (LXXXVIII; R=Ph, R'=Me) (0.29 g.) in phosphorus tribromide (5 ml.) was boiled under reflux for 5 min. The reaction mixture was cooled and washed with acetone and

and ether. Crystallisation of the residue from ethanol-water yielded yellow plates, m.p. 180° (0.11 g., 45%). The infrared spectrum of this salt showed no carbonyl absorption band, and was identical with the spectrum obtained for the base hydrobromide (LXXXVa; R=Ph, R'=H, X=Br).

A second attempt was made to cyclise the monoquaternary salt. A suspension of the bromide (LXXXVIII; R=Ph, R'=Me) (0.34 g.) in concentrated hydrobromic acid (9 ml.) was boiled under reflux for 30 min. On cooling the reaction mixture, yellow needles crystallised from the solution. The crystalline solid was filtered off and recrystallised from ethanol yielding the base hydrobromide (LXXXVa; R=Ph, R'=H, X=Br) (0.26 g., 79%). The infrared spectrum of this salt was identical with that obtained previously for the base hydrobromide of the phenyl base (LXXXVa; R=Ph, R'=H, X=Br).

1-Phenacyl-2-[2-(4-phenylthiazolyl)]pyridinium Bromide (LXXXVIII; R=R'=Ph, X=Br)

A mixture of the phenyl base (LXXXV; R=Ph) (1.17 g.) and ω -bromoacetophenone (1.07 g.) was heated on a boiling water bath for $3\frac{1}{2}$ hr. The reaction mixture was washed with ether and the residue crystallised from methanol affording the monoquaternary bromide as yellow plates, m.p. 205° (1.13 g., 53%) (Found: C, 60.1; H, 4.1; N, 6.5. $C_{22}H_{17}N_2BrOS$ requires C, 60.4; H, 4.0; N, 6.4%).

The picrate, obtained by treating the bromide with aqueous sodium picrate, crystallised from ethanol-water as yellow needles, m.p. 157°

(Found: C, 57.0; H, 3.4; N, 12.35. $C_{28}H_{19}N_5O_8S$ requires C, 57.4; H, 3.3; N, 12.0%).

Attempted synthesis of 3,5-Diphenyl-pyrido[1,2-a]thiazolo[2,3-c]pyrazidi-inium Dibromide (I; R=R'=Ph, X=Br)

A suspension of the monoquaternary bromide (LXXXVIII; R=R'=Ph, X=Br) (0.11 g.) in phosphorus tribromide (3 ml.) was boiled under reflux for 1 hr. The reaction mixture was cooled and filtered, the residue washed with acetone and crystallised from ethanol giving yellow needles (0.03 g., 41%). Subsequent infrared analysis showed that this salt was the base hydrobromide (LXXXVa; R=Ph, X=Br)

A suspension of the phenacyl monoquaternary bromide (LXXXVIII; R=R'=Ph, X=Br) (0.30 g.) in concentrated hydrobromic acid (5 ml.) was boiled under reflux for 30 min., and cooled. The crystals which separated from the solution were filtered off, washed and then crystallised from methanol giving the starting monoquaternary salt (0.24 g., 80%). The infrared spectrum of the product was identical with that of the starting phenacyl monoquaternary salt (LXXXVIII; R=R'=Ph, X=Br). The high yield was indicative of the recovery of unchanged starting material. Further attempts at cyclisation were unsuccessful.

5-Hydroxy-3-methyl-5,6-dihydro-pyrido[1,2-a]thiazolo[4,3-c]pyrazidi-inium Dibromide (XCII; R=Me, X=Br)

A mixture of 2-methyl-4-(2-pyridyl) thiazole (XC; R=Me) (0.85g.)

and bromoacetaldehyde oxime (0.76 g.) was heated on a boiling water bath for $1\frac{1}{2}$ hr., and then allowed to stand at room temperature for 23 hr. The resulting gum was washed with ether and dissolved in concentrated hydrobromic acid (2 ml.). This solution was set aside for 5 hr. at room temperature when the addition of acetone precipitated the crude hydroxy dibromide (XCII; R=Me, X=Br). The analytical sample of the dibromide was crystallised from concentrated hydrobromic acid-acetone, and had m.p. $253-255^{\circ}$ (0.63 g., 34%) (Found: C, 33.5; H, 3.7; N, 6.8. $C_{11}H_{12}Br_2N_2OS$. $1H_2O$ requires C, 33.2; H, 3.5; N, 7.0%).

3-Methyl-5,6-dihydro-pyrido[1,2-a]thiazolo[4,3-c]pyrazidi-inium Dibromide (XCIV; R=Me, X=Br)

A sealed tube containing a mixture of the base (XC; R=Me) (1.72 g.) and dibromoethane (2.05 g.) was heated for 4 days at 120° . The reaction mixture was cooled, washed with ether and the residue crystallised from concentrated hydrobromic acid-acetone affording the bridged dibromide as colourless plates, m.p. 278° (1.75 g., 49%) (Found: C, 36.1; H, 3.4; N, 8.2.

$C_{11}H_{12}N_2Br_2S$ requires C, 36.3; H, 3.3; N, 7.7%; λ_{max} (in H_2O) $2490_{sh.}$, 2530, 3030 μ ($\log_{10} \epsilon$ 3.87, 3.88, 4.27).

3-Methyl-pyrido[1,2-a]thiazolo[4,3-c]pyrazidi-inium Dibromide (II; R=Me, R'=H, X=Br)

A suspension of the hydroxy dibromide (XCII; R=Me, X=Br)

(0.46 g.) in phosphorus tribromide (5 ml.) was boiled under reflux for $1\frac{1}{2}$ hr. The reaction mixture was cooled and filtered and the residue washed with acetone. Crystallisation of the residue from concentrated hydrobromic acid-acetone afforded the aromatic dibromide, m.p. $>320^{\circ}$ (decomp.) (0.38 g., 86%) (Found: C, 35.5; H, 3.2; N, 7.4. $C_{11}H_{10}Br_2N_2S \cdot \frac{1}{2}H_2O$ requires C, 35.6; H, 3.0; N, 7.55%); λ_{max} (in N.HCl) 2520, 2580_{sh.}, 2760, 3060, 3190 Å ($\log_{10} \epsilon$ 4.52, 4.47, 4.22, 3.84, 3.87).

1-Acetyl-2-[4-(2-methylthiazolyl)]pyridinium Bromide (XCIII; R=R'=Me)

A mixture of the base (XC; R=Me) (0.54 g.) and bromoacetone (0.51 g.) was homogenised on a hot water bath and set aside for 14 days at room temperature. The reaction mixture was washed with ether and the residue crystallised from methanol-ether yielding the monoquaternary bromide as colourless plates, m.p. 200° (0.85 g., 87%) (Found: C, 45.75; H, 4.3; N, 8.8. $C_{12}H_{13}BrN_2OS$ requires C, 46.0; H, 4.2; N, 8.95%).

The picrate, prepared by treating the bromide with aqueous sodium picrate, crystallised from ethanol-water as yellow needles, m.p. 157° (Found: C, 46.4; H, 3.1; N, 15.35. $C_{18}H_{15}N_5O_8S$ requires C, 46.9, H, 3.3; N, 15.25%).

3,5-Dimethyl-pyrido[1,2-a]thiazolo[4,3-c]pyrazidinium Dibromide

(II; R=R'=Me, X=Br)

A suspension of the 1-acetyl monoquaternary salt (XCIII; R=R'=Me, X=Br

(0.36 g.) in phosphorus tribromide (5 ml.) was boiled under reflux for 5 min. The reaction mixture was cooled, filtered and the residue washed with acetone. Crystallisation of the residue from concentrated hydrobromic acid-acetone afforded the aromatic dibromide (II; R=R'=Me, X=Br) m.p. 291° (decomp.) (0.23 g., 52%) (Found: C, 37.4; H, 3.55. $C_{12}H_{12}Br_2N_2S \cdot \frac{1}{2}H_2O$ requires C, 37.4; H, 3.4%); λ_{max} (in N.HCl) 2560, 2630, 2790_{sh.}, 3220 Å ($\log_{10} \epsilon$ 4.61, 4.58, 4.24, 3.98).

1-Phenacyl-2-[4-(2-methylthiazolyl)]pyridinium Bromide (XCIII; R=Me, R'=Ph, X=Br)

A mixture of the base (XC; R=Me) (0.89 g.) and ω -bromoacetophenone (1.09 g.) was heated on a boiling water bath for 2 hr. The reaction mixture was washed with ether; the residue crystallised from methanol-ether as colourless needles, m.p. 220-221° (1.43 g., 75%) (Found: C, 54.2; H, 4.1; N, 7.35. $C_{17}H_{15}BrN_2OS$ requires C, 54.4; H, 4.0; N, 7.5%).

The picrate, prepared by the addition of aqueous sodium picrate to the bromide, crystallised from ethanol as yellow needles, m.p. 194-195° (Found: C, 53.3; H, 3.0; N, 13.2. $C_{23}H_{17}N_5O_8S$ requires C, 52.8; H, 3.3; N, 13.4%).

3-Methyl-5-phenyl-pyrido[1,2-a]thiazolo[4,3-c]pyrazidi-nium Dibromide (II; ; R=Me, R'=Ph, X=Br)

A suspension of the 1-phenacyl monoquaternary salt (XCIII; R=Me, R'=Ph, X=Br) (0.27 g.) in phosphorus tribromide (5 ml.) was boiled under

reflux for 5 min. The reaction mixture was cooled, filtered and the residue washed with acetone. Crystallisation of the residue from concentrated hydrobromic acid-acetone yielded the pale yellow aromatic dibromide, m.p. 263-264° (decomp.) (0.12 g., 45%) (Found: C, 44.1; H, 3.9; N, 5.3. $C_{17}H_{14}Br_2N_2S \cdot \frac{1}{2}H_2O$ requires C, 43.9; H, 3.7; N, 6.0%); λ_{max} (in N.HCl) 2560, 2780_{sh.}, 3260 Å (log₁₀ ε 4.52, 4.31, 4.0).

Attempted synthesis of Benzo[b]dipyrido[1,2-a : 2',1'-c]pyrazidi-inium Dibromide (LXXXIV; R=H, X=Br)

A mixture of phenanthroline (1 g.) and bromoacetaldehyde oxime (0.78 g.) was homogenized on a boiling water bath and allowed to stand at room temperature for 2 days. The resulting gum was washed with ether, dissolved in concentrated hydrobromic acid (4 ml.), and heated on a boiling water bath for 2 min. The addition of acetone precipitated the crude hydroxy dibromide which proved difficult to crystallise and when a suspension in phosphorus tribromide was boiled under reflux an intractable dark solid was obtained.

Attempted synthesis of 5-Methyl-benzo[b]dipyrido[1,2-a : 2',1'-c]pyrazidi-inium Dibromide (LXXXIV; R=Me, X=Br)

A mixture of phenanthroline (0.98 g.) and bromoacetone (0.87 g.) was heated on a boiling water bath until homogeneous, and then set aside at room temperature for 24 hr. The dark red product was washed with ether and an attempted crystallisation from methanol-ether afforded an intractable tarry mass.

1-Phenacyl-1,10-phenanthroline Bromide (XCVII; R=Ph, X=Br)

A mixture of phenanthroline (1 g.) and ω -bromoacetophenone (1 g.) was homogenized on a hot water bath and then set aside for 2 days at room temperature. At the end of this time dark red crystals had appeared which were washed with ether and crystallised from methanol containing decolourising charcoal. Recrystallisation from methanol afforded the bromide as colourless plates, m.p. 246-247° (1 g., 47%) (Found: C, 63.0; H, 4.0; N, 7.7. $C_{20}H_{15}BrN_2O$ requires C, 65.3; H, 4.0; N, 7.4%).

The picrate, prepared by treating the bromide with aqueous sodium picrate, crystallised from ethanol as yellow needles, m.p. 213-214° (Found: C, 58.8; H, 3.2; N, 12.7. $C_{26}H_{17}N_5O_8$ requires C, 59.2; H, 3.25; N, 13.3%).

The hydrobromide (XCVIII; R=Ph, X=Br) was prepared by heating a suspension of the monoquaternary bromide (0.15 g.) in concentrated hydrobromic acid (4 ml.) on a boiling water bath for 2 min. The reaction mixture was cooled when the addition of acetone afforded the bromide hydrobromide which crystallised from concentrated hydrobromic acid-ethanol as yellow plates, m.p. 220° (decomp.) (0.16 g., 88%) (Found: C, 50.5; H, 3.6; N, 6.15. $C_{20}H_{16}Br_2N_2O \cdot H_2O$ requires C, 50.2; H, 3.8; N, 5.9%); λ_{max} (in H_2O) 2620_{sh.}, 2720 Å ($\log_{10} \epsilon$ 4.51, 4.60).

The monopicrate, obtained from the bromide hydrobromide, by addition of aqueous sodium picrate to the hydrobromide, crystallised

from ethanol as brown needles. (Found: C, 58.9; H, 3.25; N, 13.5. $C_{26}H_{17}N_5O_8$ requires C, 59.2; H, 3.25; N, 13.3%).

This picrate was found to be identical with the picrate obtained directly from the 1-phenacyl monoquaternary salt (LXX; R=Ph, X=Br).

5-Phenyl-benzo[b] dipyrido[1,2-a : 2',1'-c] pyrazidi-inium Dibromide (LXXXIV; R=Ph, X=Br)

A suspension of the 1-phenacyl monoquaternary bromide (0.49 g.) in phosphorus tribromide (5 ml.) was boiled under reflux for 5 min. The reaction mixture was cooled, filtered, and the residue leached with ethanol before recrystallising from methanol. The aromatic dibromide crystallised as brown plates, m.p. 270° (decomp.) (0.44 g., 77%) (Found: C, 50.3; H, 3.5; N, 6.1. $C_{20}H_{14}Br_2N_2 \cdot 2H_2O$ requires C, 50.2; H, 3.8; N, 5.9%); λ_{max} (in H_2O) 2550sh., 2700sh., 2870, 3200sh., 3580 \AA ($\log_{10} \epsilon$ 4.18, 4.29, 4.50, 3.60, 3.66).

2-(2-Pyridyl) oxazole (CI; R=H)

The synthesis of this base was first attempted using the method described by Dadkhah and Prijs⁸⁴, and, although these authors report a yield of 47%, only a very small amount of black oil was obtained after several attempts. The oil could not be distilled, as a tar was formed on heating.

Another procedure, a patented method⁸⁵, involved a slight modification of the previous preparation, and using this latter process it proved possible to prepare a small amount of pyridyl oxazole.

The azomethine (CII) (10 g.) was treated with concentrated sulphuric acid (42 ml.) at 0°C and phosphorus pentoxide (17 g.). After heating the mixture at 120° for 20 min., crushed ice was added (500 g.) and the solution neutralised with concentrated ammonium hydroxide before steam distillation.

The distillate was extracted with ether and the extract evaporated yielding a very small amount of the base. By heating a mixture of the base and ω -bromoacetophenone a colourless crystalline solid was obtained, crystallising from methanol. The infrared spectrum of this salt compared well with the analogous 1-phenacyl-2-(2-thiazolyl) pyridinium Bromide (CIII; R=H, R'=Ph, X=Br). The bromide was treated with aqueous sodium picrate and the precipitate crystallised from ethanol but there proved to be insufficient material for analytical purposes.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Handbook for Chemical Society Authors, 1961.
2. Adrien Albert, "Heterocyclic Chemistry".
3. I.C. Calder and W.H.F. Sasse, Aust. J. Chem., (1965) 18, 1819-33.
4. C.K. Bradsher and D.F. Lohr, Chem. and Ind., (1964) 1801.
5. C.K. Bradsher and M.F. Zimm, J. Hetero. Chem., (1964) 1, 219.
6. C.K. Bradsher, E.F. Litzinger, Jr., and M.F. Zimm, J. Hetero. Chem., (1965) 2, 4, 331-334.
7. O. Diels and K. Alder, Annalen., (1931) 490, 267. O. Diels, K. Alder, W. Friedrichsen, H. Klare, H. Winkler and H. Schrum, ibid., (1933) 505, 103.
8. R.M. Acheson and G.A. Taylor, J., (1960) 1691.
9. L.M. Jackman, A.W. Johnson and J.C. Tebby, J., (1960) 1579.
10. B.S. Thyagarajan, Chem. Reviews, (1954) 54, 1019.
11. O. Westphal, K. Jann and W. Heffe, Arch. Pharm., (1961) 294, 37.
12. F. Kröhnke, Angew. Chem., (1963) 75, 181.
13. F. Kröhnke, H. Schnegelberger and W. Weiss, Ber., (1964) 97, 3566.
14. W.M. McLamore and R.B. Woodward, J. Amer. Chem. Soc., (1949) 71, 379.
15. A.G. Beaman and R.B. Woodward, A.G. Beaman, Phd. thesis, (1951), J. Amer. Chem. Soc., (1954), 76, 1832.
16. V. Boekelheide and W.G. Gall, J. Amer. Chem. Soc., (1954) 76, 1832.
17. V. Boekelheide and J.M. Ross, ibid., (1955) 77, 5691.
18. E.E. Glover and G. Jones, Chem. and Ind., (1956) 1456.
19. Idem., J., (1958) 3021.
20. L.C. Craig, J. Amer. Chem. Soc., (1934) 56, 1144.

21. R. Jones, A.R. Katritzky, T.M. Moynihan and K. Schofield, J., (1962) 2637.
22. I. Iwai and T. Miyadera, Chem. Pharm. Bull. (Japan), (1964) 12, 1338.
23. A. Richards and T.S. Stevens, J., (1958) 3067.
24. E.D. Amstutz and H.V. Hansen, J. Org. Chem., (1963) 28, 393.
25. A.N. Nesmeyanov and M.I. Rybinskaya, Doklady Akad. Nauk. S.S.S.R., (1957) 116, 93. Chem. Abs., (1958) 52, 6349.
26. E.E. Glover, Phd. Thesis, University of London, 1959.
27. A. Fozard and G. Jones, J., (1963) 2203.
28. Idem, ibid, (1964) 2760.
29. Idem, ibid, (1964) 3030.
30. E. Schraufstätter, Angew. Chem., (1962) 74, 874.
31. P.A. Duke, A. Fozard and G. Jones, J. Org. Chem., (1965) 30, 526.
32. C.K. Bradsher and L.E. Beavers, J. Amer. Chem. Soc., (1955) 77, 453.
33. Idem, ibid, (1955) 77, 4812.
34. R.W.L. Kimber and J.C. Parham, J. Org. Chem., (1963) 28, 3205.
35. C.K. Bradsher and N.L. Yarrington, ibid, (1963) 28, 81.
36. C.K. Bradsher and J.H. Jones, ibid, (1957) 79, 6033.
37. C.K. Bradsher and N.L. Yarrington, J. Org. Chem., (1960) 25, 294.
38. Idem, ibid, (1963) 28, 78.
39. C.K. Bradsher and J.C. Parham, ibid, (1963) 28, 83.
40. Idem, J. Hetero. Chem., (1964) 1, 30.
41. Idem, ibid, (1964) 1, 121-4.
42. C.K. Bradsher and M.W. Barker, J. Org. Chem., (1963) 28, 1669.

43. Idem, ibid, (1964) 29, 61.
44. C.K. Bradsher and R.E. Doolittle, Chem. and Ind., (1965) 38, 1631.
45. C.K. Bradsher and A. Fozard, J. Org. Chem., (1966) 31, 2316.
46. E.E. Glover and M.J.R. Loadman, in the press.
47. A.N. Nesmeyanov, M.I. Rybinskaya and N.K. Bel'skii, Doklady Akad. Nauk., S.S.S.R. (1957) 113, 343, Chem. Abs. (1957) 51, 14712.
48. A.N. Nesmeyanov and M.I. Rybinskaia, ibid, (1958) 118, 297, Chem. Abs. (1958) 52, 10080.
49. C.K. Bradsher and S.A. Telang, J. Org. Chem., (1966) 31, 941.
50. C.K. Bradsher and K.B. Moser, J. Amer. Chem. Soc., (1959) 81, 2547.
51. C.K. Bradsher and R.W.L. Kimber, J. Hetero. Chem., (1964) 1, 208.
52. C.K. Bradsher and J.C. Parham, J. Org. Chem., (1964) 29, 856.
53. R.J. Fielden, R.F. Homer and R.F. Jones, British Patent, 785, 732. Chem. Abs., (1958) 52, 6707.
54. R.C. Brian, R.F. Homer, J. Stubbs and R.F. Jones, Nature (1958) 181, 446.
55. W.R. Boon and R.F. Homer, Brit. Pat., 815, 348. Chem. Abs. (1959) 53, 20679.
56. R.F. Homer and T.E. Tomlinson, J., (1960) 2498.
57. R.F. Homer, Brit. Pat., 857, 501, Chem. Abs. (1961) 55, 12430.
58. D.H. Corr and E.E. Glover, Chem. and Ind., (1964) 2128; (1965) 847.
59. Idem, J., (1965) 5816.
60. I.C. Calder and W.H.F. Sasse, Tet. Letters, (1964) 3871.
61. E.E. Glover and G.H. Morris, J., (1965) 3885.
62. F. Šorm and L. Sedivy, Coll. Czech. Chem. Comm., (1948) 13, 283.
63. Tetsuzo Kato, J. Pharm. Soc. (Japan), (1958) 75, 1239.

64. E.E. Glover and G.H. Morris, J., (1964) 3366.
65. E. Koenigs and H. Geisler, Ber., (1924) 57, 2076.
66. A.E. Tschitschibabin and N.N. Woroshtow, Ber., (1933) 66, 364.
67. G.F. Duffin and J.D. Kendall, J. Chem. Soc., (1951) 734.
68. P. DeSmet and G. Schwarz, Brit. Pat., 587, 434. Chem. Abs., (1948) 42, 619. Natuurw Tijdschr., (1940) 21, 271. Chem. Abs., (1940) 34, 3603. Brit. Pat., 615, 205. Chem. Abs., (1949) 43, 8293.
69. C.K. Bradsher, D.F. Lohr, Jr., and W.J. Jones, Jr., Tet. Letters, (1965) 22, 1723.
70. R. Adams and I.J. Pachter, J. Amer. Chem. Soc., (1952) 74, 4906.
71. A. Lawson and D.H. Miles, Chem. and Ind., (1958) 461.
72. W.L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms" Interscience Publishers, (1961), Part 1, Ch. V.
73. C.K. Bradsher, E.F. Litzinger, Jr., and M.F. Zinn, J. Hetero. Chem., (1965) 2, 4, 331.
74. A.R. Katritzky, "Physical Methods in Heterocyclic Chemistry", Academic Press, London, (1963) Vol. I, p.47.
75. R.F. Homer, G.C. Mees and T.E. Tomlinson, J. Sci. Food Agric., (1960) 11, 309. W.R. Boon, Chem. and Ind., (1965) 782.
76. Personal communication with J.A. Farrington, I.C.I. Ltd., Jealott's Hill Res. Stn. Berks.
77. H. Hilleman, Ber., (1938) 71B, 34.
78. T.J. Curphey, J. Amer. Chem. Soc., (1965) 87, 2063.
79. P. Karrer and J. Schukri, Helv. Chim. Acta., (1945) 28, 820.
80. R.F. Knott and J.G. Breckenridge, Canad. J. Chem., (1954) 32, 512.
81. A.H. Blatt, "Organic Synthesis", John Wiley & Sons, (1955) Collective Vol. II, page 88.

82. A. Albert, R. Goldacre and J. Phillips, J. Chem. Soc., (1948) 2270.
83. G.R. Clemo, W.M. Morgan and R. Raper, J. Chem. Soc., (1937) 965.
84. M. Dadkhah and B. Prijs, Helv. Chim. Acta., (1962) 45, 375-81.
Chem. Abs. (1962) 57, 3426g.
85. Ciba Ltd., (H. Erlenmeyer), GER. 1,112,076, 1961, Chem. Abs.,
(1966), 64, 5100c.

INDEX OF COMPOUNDS DESCRIBED IN THE EXPERIMENTAL SECTION

Index of compounds described in the experimental section

	<u>Page</u>
1-Acetylonyl-2-[2-(4-methylthiazoly)] pyridinium Bromide -	No. 103
1-Acetylonyl-2-[2-(4-methylthiazoly)] pyridinium Picrate -	103
1-Acetylonyl-2-[4-(2-methylthiazoly)] pyridinium Bromide -	110
1-Acetylonyl-2-[4-(2-methylthiazoly)] pyridinium Picrate -	110
1-Acetylonyl-2-[2-(4-phenylthiazoly)] pyridinium Bromide -	106
1-Acetylonyl-2-[2-(4-phenylthiazoly)] pyridinium Picrate -	106
1-Acetylonyl-2-(2-thiazoly) pyridinium Bromide -	99
1-Acetylonyl-2-(2-thiazoly) pyridinium Picrate -	99
Bromoacetaldehyde oxime -	93
Bromoacetone -	93
2-(ω -Bromoacetyl) pyridine -	93
5,6-Dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide -	98
5,6-Dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dipicrate -	98
3,5-Dimethyl-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide -	103
3,5-Dimethyl-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dipicrate -	104
3,5-Dimethyl-pyrido [1,2-a] thiazolo [4,3-c] pyrazidi-inium Dibromide -	110
5-Hydroxy-5,6-dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide -	97
5-Hydroxy-5,6-dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dipicrate -	97
5-Hydroxy-3-methyl-5,6-dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide -	101
5-Hydroxy-3-methyl-5,6-dihydro-pyrido [1,2-a] thiazolo [4,3-c] pyrazidi-inium Dibromide -	108
3-Methyl-5,6-dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide -	102
3-Methyl-5,6-dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dipicrate -	103

	<u>Page</u>
	No.
3-Methyl-5,6-Dihydro-pyrido [1,2-a] thiazolo [4,3-c] pyrazidi-inium Dibromide -	109
3-Methyl-5-phenyl-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide -	104
3-Methyl-5-phenyl-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dipicrate -	105
3-Methyl-5-phenyl-pyrido [1,2-a] thiazolo [4,5-c] pyrazidi-inium Dibromide -	111
3-Methyl-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide -	102
3-Methyl-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dipicrate -	102
3-Methyl-pyrido [1,2-a] thiazolo [4,3-c] pyrazidi-inium Dibromide -	109
5-Methyl-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide -	99
2-Methyl-4-(2-pyridyl) thiazole -	96
2-Methyl-4-(2-pyridyl) thiazole Picrate -	96
4-Methyl-2-(2-pyridyl) thiazole -	94
4-Methyl-2-(2-pyridyl) Monohydrochloride -	94
1-Phenacyl-2-[2-(4-methylthiazolyl)] pyridinium Bromide -	104
1-Phenacyl-2-[4-(2-methylthiazolyl)] pyridinium Bromide -	111
1-Phenacyl-2-[4-(2-methylthiazolyl)] pyridinium Picrate -	111
1-Phenacyl-1,10-phenanthroline Bromide -	113
1-Phenacyl-1,10-phenanthroline Picrate -	113
1-Phenacyl-1,10-phenanthroline Hydrobromide -	113
1-Phenacyl-2-[2-(4-phenylthiazolyl)] pyridinium Bromide -	107
1-Phenacyl-2-[2-(4-phenylthiazolyl)] pyridinium Picrate -	107
1-Phenacyl-2-(2-thiazolyl) pyridinium Bromide -	100
1-Phenacyl-2-(2-thiazolyl) pyridinium Picrate -	100
5-Phenyl-benzo[b] dipyrido [1,2-a : 2',1'-c] pyrazidi-inium Dibromide -	114

	<u>Page</u>
	No.
3-Phenyl-5,6-dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide -	105
3-Phenyl-5,6-dihydro-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dipicrate -	106
5-Phenyl-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide -	100
5-Phenyl-pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dipicrate -	101
4-Phenyl-2-(2-pyridyl) thiazole -	95
4-Phenyl-2-(2-pyridyl) thiazole Monohydrobromide -	95
4-Phenyl-2-(2-pyridyl) thiazole Monomethiodide -	95
Pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dibromide -	97
Pyrido [1,2-a] thiazolo [2,3-c] pyrazidi-inium Dipicrate -	98
2-(2-Pyridyl) oxazole -	114
2-(2-Pyridyl) thiazole -	95
2-(2-Pyridyl) thiazole Picrate -	96
Thiopicolinamide -	94

