The synthesis and oxidation of some n-amino compounds

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THE SYNTHESIS AND OXIDATION OF SOME N-AMINO COMPOUNDS

by

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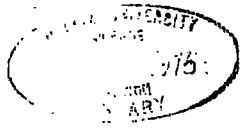
A thesis submitted to the UNIVERSITY OF DURHAM
for the degree of MASTER OF SCIENCE



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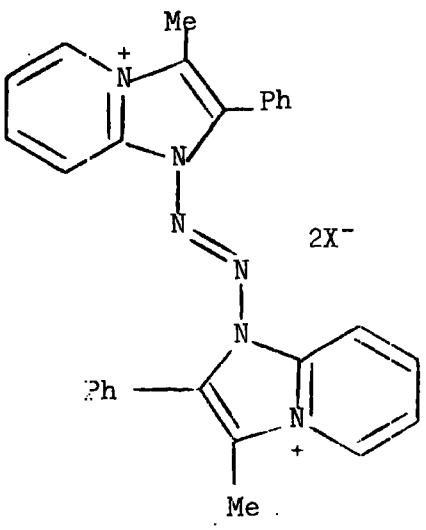
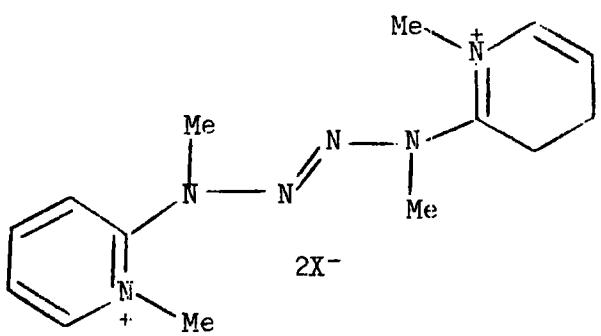
SUMMARY

The aim of this work was the preparation of a series of compounds having similar structural features to the highly active neuromuscular blocking agent (i).

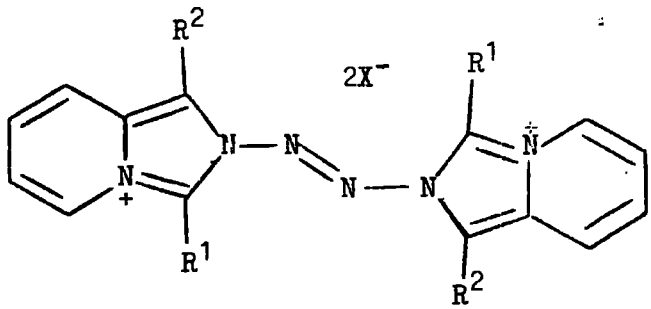


(i)

In view of the current interest in diquaternary tetrazenes as short-acting non-depolarising neuromuscular blocking agents, the synthesis of the diquaternary salts (ii) incorporating two 2-methylaminopyridine units joined by an azo link, and the diquaternary salts (iii) - (vi) incorporating two imidazo [1,5-a] pyridine heterocyclic systems joined by an azo link was undertaken.



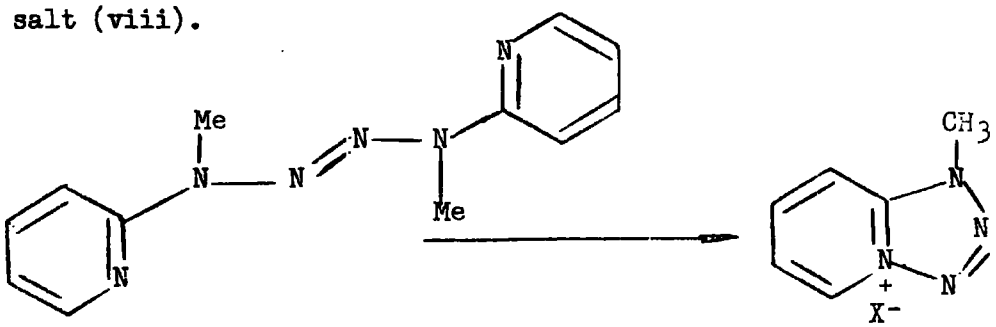
(ii)



	R^1	R^2
(iii)	H	H
(iv)	Ph	H
(v)	H	Ph
(vi)	Me	H

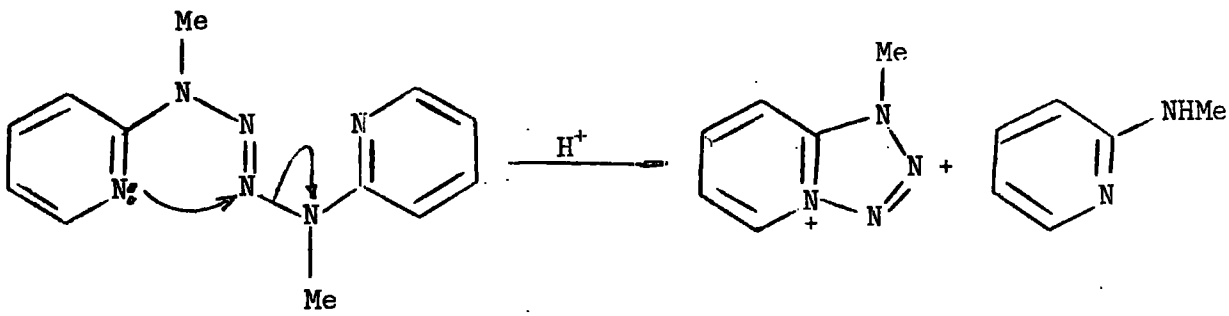
DIQUATERNARY COMPOUNDS CONTAINING THE 2-METHYLAMINOPYRIDINE SYSTEM AND A TETRAZENE LINKAGE (ii)

Attempted synthesis of the diquaternary tetrazene (ii) by the methylation of the tetrazene base (vii) gave the tetrazolopyridinium salt (viii).



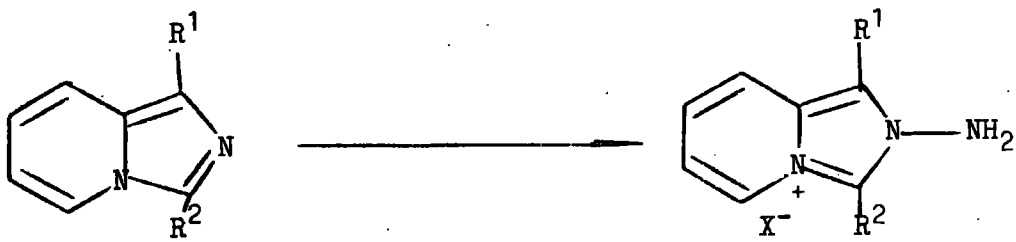
(vii) (viii)

Cyclisation of tetrazene (vii) to the tetrazolopyridinium bromide (viii; X = Br) was also effected by boiling ethanolic hydrobromic acid and the isolation of 2-methylaminopyridine from such a cyclisation confirmed the mechanism as shown below.

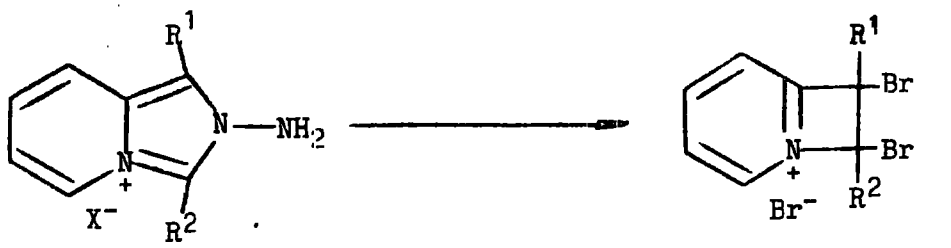


DIQUATERNARY COMPOUNDS CONTAINING IMIDAZO[1,5-a] PYRIDINE HETEROCYCLIC SYSTEMS AND A TETRAZENE LINKAGE (iii) - (vi)

The attempted synthesis of diquaternary tetrazenes (iii) - (vi) by the oxidation of the N-amino salts (xiii) - (xvi), with saturated aqueous bromine gave the respective 1,2-dihydroazeto[1,2-a] pyridinium bromides (xvii) - (xx). The N-amino salts (xiii) - (xvi) were obtained by treating the parent imidazo[1,5-a] pyridines (ix) - (xii) with O-p-tolylsulphonylhydroxylamine.

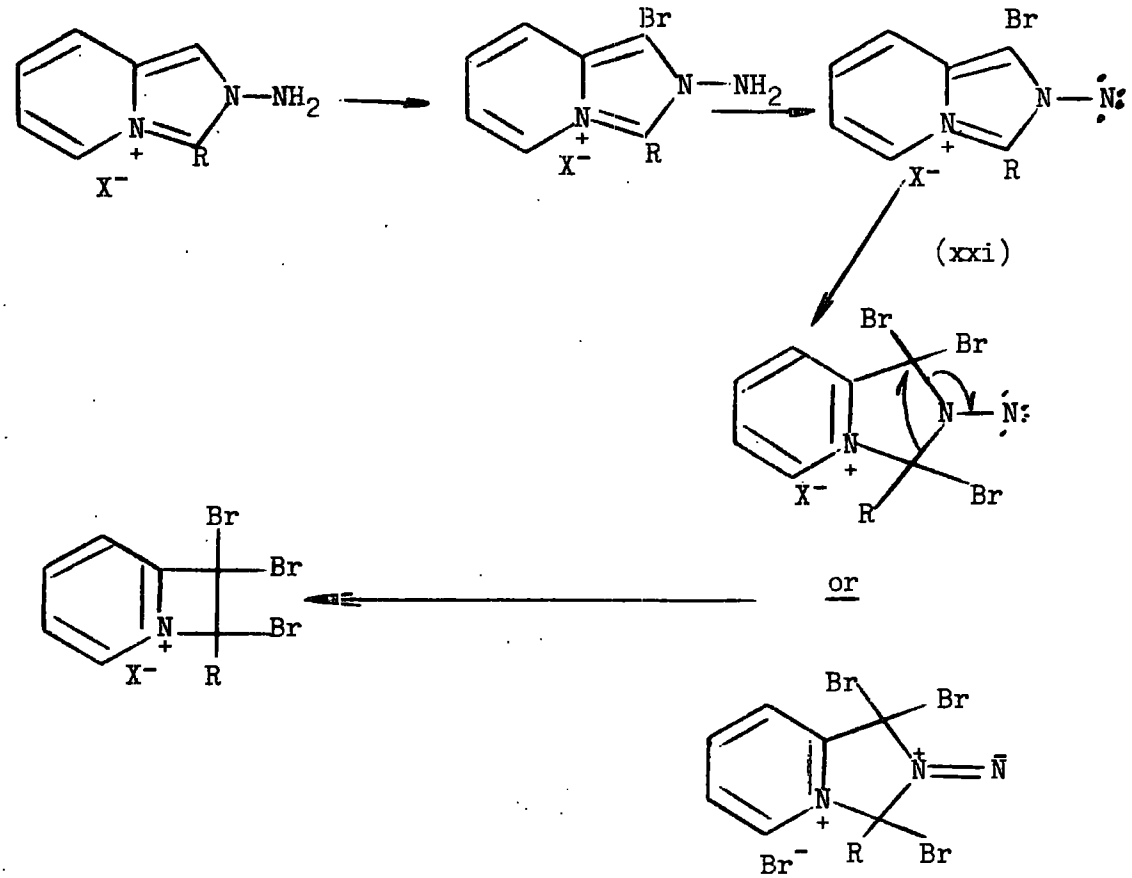


	R^1	R^2		R^1	R^2
(ix)	H	H	(xiii)	H	H
(x)	H	Ph	(xiv)	H	Ph
(xi)	Ph	H	(xv)	Ph	H
(xii)	H	Me	(xvi)	H	Me

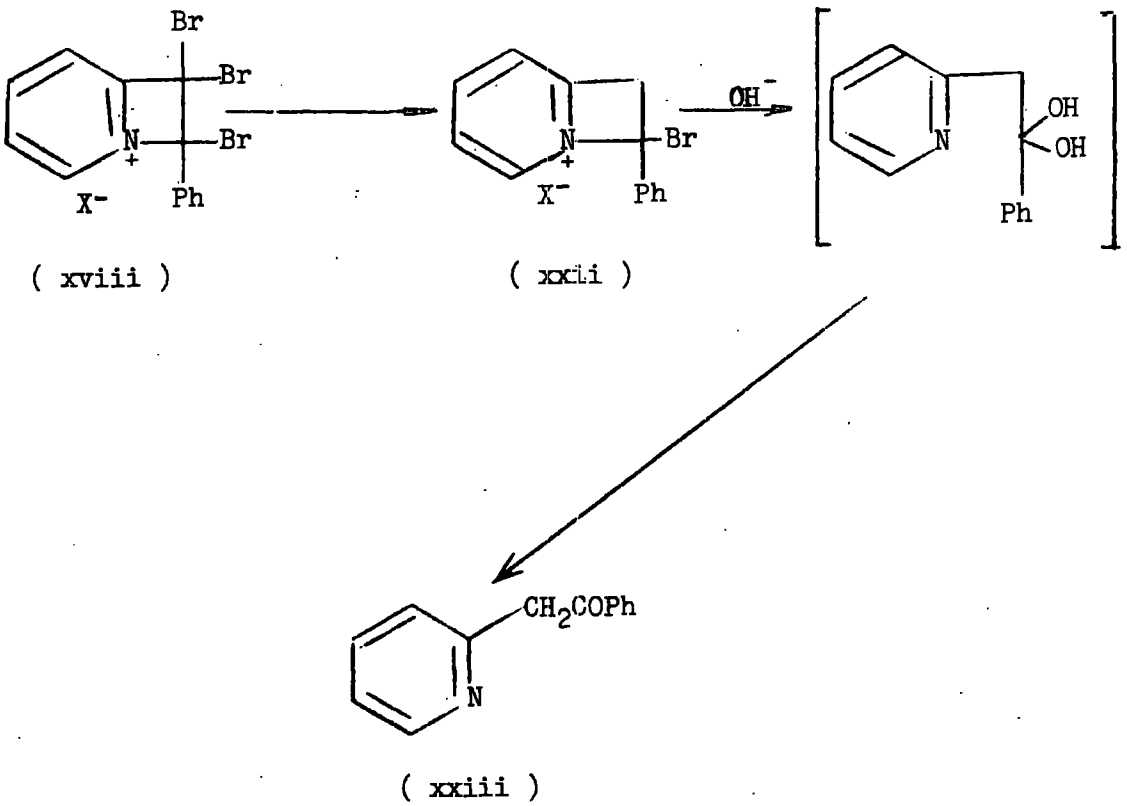


	R^1	R^2		R^1	R^2
(xiii)	H	H	(xvii)	Br	Br
(xiv)	H	Ph	(xviii)	Br	Ph
(xv)	Ph	H	(xix)	Ph	Br
(xvi)	H	Me	(xx)	Br	Me

The suggested course of reaction is via initial bromination at the free position of the imidazo ring followed by oxidation of the amino function yielding the amino nitrene (xxi). The 1,4 addition of bromine in the five membered ring followed by nitrogen loss then gives the 1,2-dihydroazeto[1,2-a] pyridinium bromide as shown below.



Hydrogenation of the tribromo-2-phenyldihydroazetopyridinium salt (xviii) over palladium charcoal resulted in the uptake of approximately two molecular equivalents of hydrogen and subsequent basification gave phenyl-2-pyridylmethylketone (xxiii) presumably via the intermediate monobromo compound (xxii) as shown below.



(xviii) (xxii) (xxiii)

ACKNOWLEDGEMENTS

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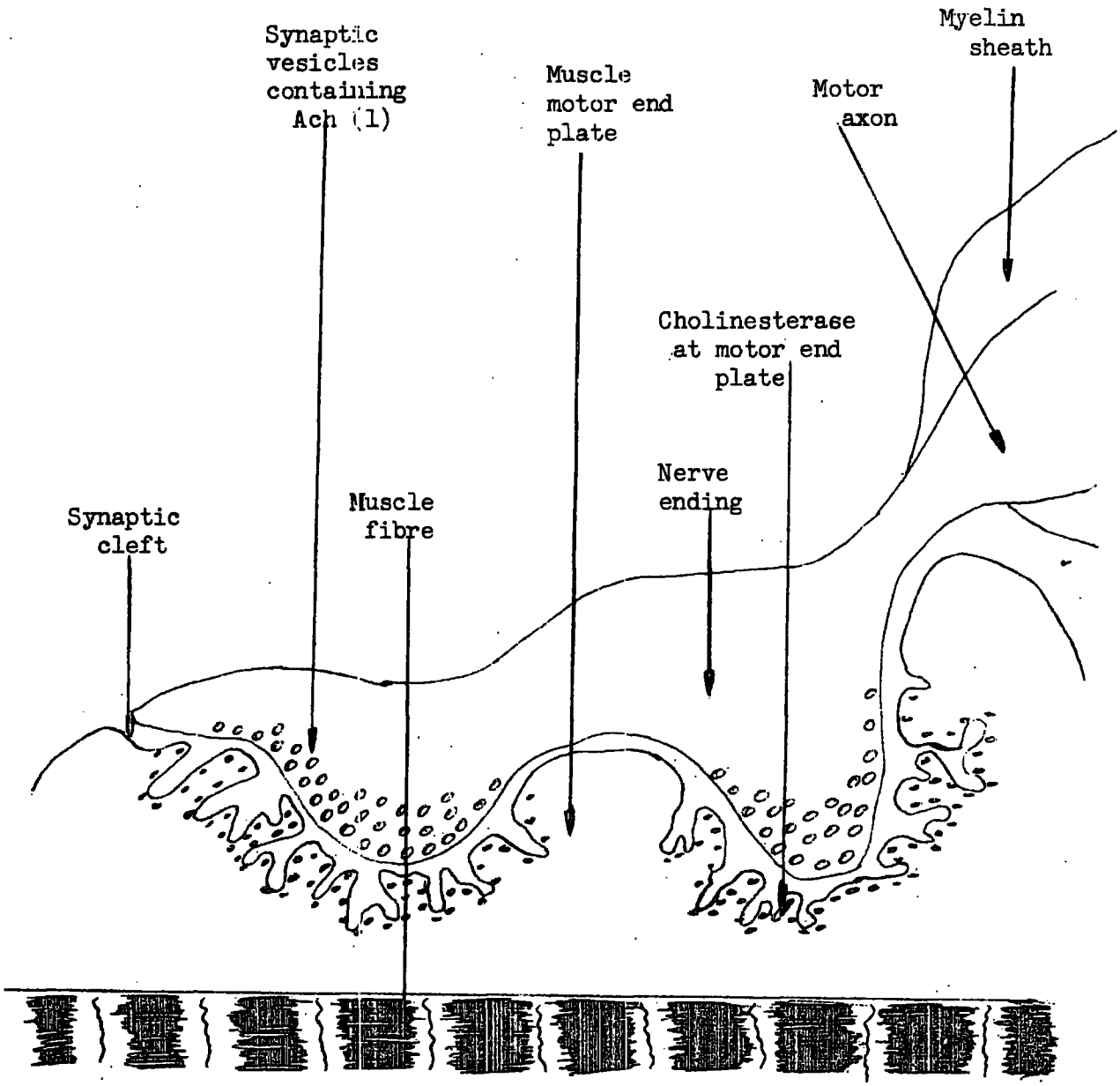
INTRODUCTION

NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking agents interrupt the normal operation of the nerve-voluntary muscle transmission at the neuromuscular junction. Also they can affect the conduction of the nerve impulse along the motor axons, but they do not affect the contractile power of the muscle[1].

PHYSIOLOGY OF NEUROMUSCULAR TRANSMISSION

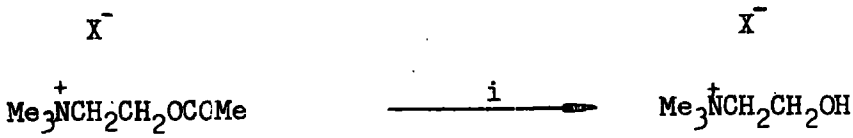


NEUROMUSCULAR JUNCTION

It is possible to measure the potential difference in various cells and muscles, by using microelectrodes. The resting potential of a muscle varies from one organism to another and is generally in the range 60 - 90 mV, with the inside invariably being negative with respect to the outer surface. Such potentials remain stable for long periods of time, so long as no impulse is travelling through the muscle[2].

Stimulation of the muscle membrane results in the inner surface becoming approximately 10 mV positive (end plate potential) due to a temporary increase in the permeability of the muscle membrane to sodium ions which pass through the membrane from the extracellular fluid[3]. This localised area of depolarisation produces an outward current flow into the adjacent polarised membrane, resulting in its depolarisation[3]. This wave of depolarisation and repolarisation is propagated along the muscle and is known as the muscle action potential and it causes contraction of the muscle. On removal of the stimulus, the muscle regains its polarisation initially by the outward flow of intracellular potassium ions to the external surface of the muscle membrane. This localised area of polarisation produces an inward current flow in the adjacent depolarised membrane, resulting in its repolarisation. Small constantly recurring potentials, which are localised and non-propagated, are exhibited at the resting muscle fibre adjacent to the nerve endings[3]. These minute potentials are attributed to the release of small amounts of acetylcholine (Ach(l)) from the synaptic vesicles of the nerve endings which diffuse across the synaptic cleft and are believed to combine momentarily with an unidentified receptor substance producing depolarisation in the region of the end plate. The small end plate potentials produced are not of sufficient amplitude to depolarise the muscle membrane and hence initiate a muscle action potential[3].

When the nerve impulse reaches the motor nerve ending a very large amount of Ach(1) is released and produces an end plate potential of sufficient amplitude to depolarise the muscle membrane around the end plate. This initiates the muscle action potential, which is propagated as a wave of depolarisation along the muscle fibre surface. The Ach(1) released is rapidly hydrolysed by the enzyme cholinesterase, and the potential difference across the muscle membrane is then restored[3].



(1) (2)

i Cholinesterase

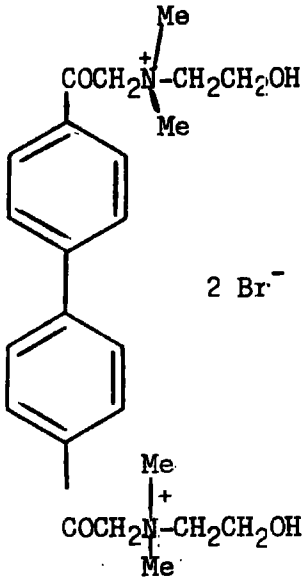
Neuromuscular blocking agents are classified into two main divisions :-

(i) those which act presynaptically, i.e. the drug acts at or around the motor nerve terminals

(ii) those which act postsynaptically, i.e. the drug acts at the muscle end plate.

PRESYNAPTIC NEUROMUSCULAR BLOCKING DRUGS

Certain drugs are believed to interfere with the synthesis and storage of Ach(1). Hemicholinium dibromide (3)[4] inhibits the synthesis of Ach(1) at the nerve endings and it has been postulated that it interferes with the transport of choline (2) to the site of Ach(1) synthesis, resulting in very little Ach(1) being released. The block produced by hemicholinium dibromide (3) is slow in onset and is antagonised by choline (2) and to a lesser extent by analogues and esters of choline.



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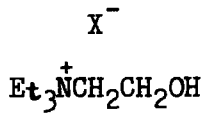
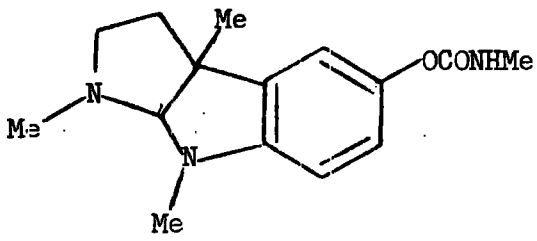


(4)

Triethylcholine (4)[4] has a similar action to that of hemicholinium dibromide (3). Both hemicholinium dibromide (3) and triethylcholine (4) depress the motor end plate sensitivity to Ach(1), but higher concentrations of the drugs are required to produce neuromuscular block by this latter action than by their presynaptic effect[4]. High concentrations of eserine (5), tetraethylammonium salts (6), digitalis compounds (7) or sodium ion deficiency inhibit Ach(1) synthesis, but it has not been demonstrated that this occurs at the neuromuscular junction[3].



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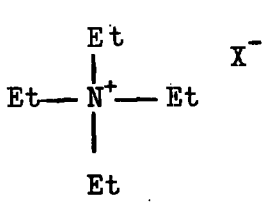

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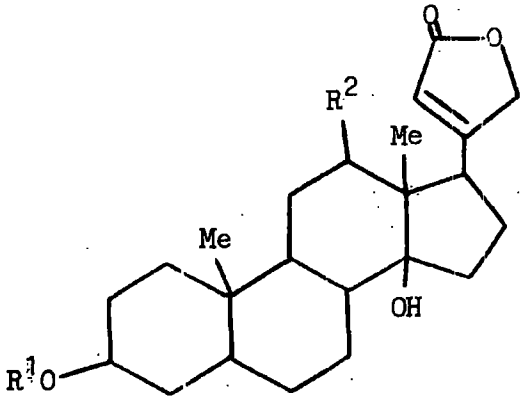


(7)

	R^1	R^2
Digoxin	OH	$C_{18}H_{31}O_9$
Digitoxin	H	$C_{18}H_{31}O_9$
Acetyldigitoxin	H	$C_{18}H_{30}O_9$ - COMe

The raising of the magnesium ion concentration or the lowering of the calcium ion concentration, in the extracellular plasma, blocks neuromuscular transmission by reducing the amounts of Ach(1) released at the nerve endings[4].

Certain toxins, clostridium botulinum[4], puffer fish toxin[5], and the toxin secreted in the salivary glands of the Rocky Mountain wood tick, prevent release of Ach(1) from the nerve endings. The block resembles that exhibited by calcium ion deficiency.

Large dosages of some antibiotics such as neomycin, streptomycin and kanamycin produce neuromuscular block similar to that produced by the depression of Ach(1) release, or by calcium ion deficiency[4].

The antibiotics have little clinical value as neuromuscular blocking agents because large doses are necessary.

A number of phenols, such as catecholamines, increase the quantity of Ach(1) released per nerve impulse and so accelerate the run down of Ach(1) stores. Some local and general anaesthetics, cardine glycosides, and 2,4-dinitrophenol are believed to reduce the release of Ach(1) by inhibition of the selective sodium ion conductance change, responsible for the initiation of the muscle action potential, resulting in neuromuscular block[4].

POSTSYNAPTIC NEUROMUSCULAR BLOCKING DRUGS

There are two main types of postsynaptic neuromuscular blocking agents :-

(i) depolarising agents, which act by depolarising the end plate

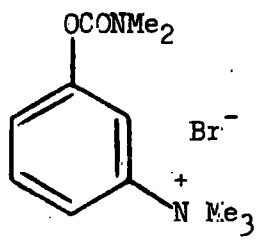
(ii) non-depolarising agents, which act by occupying the receptor sites on the motor end plate and so inhibit the action of Ach(1) on them.

Taylor and Nedergaard[6] have emphasised that depolarising blocking drugs enter the muscle membrane through the motor end plate region. Non-depolarising drugs are unable to enter the muscle, but by combining with the receptors on the motor end plate, are able to prevent the action of Ach(1) and other depolarising drugs. Generally depolarising drugs have a slender flexible structure whereas non-depolarising drugs are relatively large, bulky and rigid molecules. The potency of the two types of postsynaptic blocking drugs has been attributed to the rate of association and dissociation of the drug with the receptors on the motor end plate[7], non-polarising drugs have a low rate of dissociation, whilst the depolarising drugs have a high rate.

DEPOLARISING NEUROMUSCULAR BLOCKING AGENTS

This type of block is due to the abnormally prolonged depolarisation in the region of the end plate and has the following characteristics. The block is preceded by an increase in motor activity due to initial end plate depolarisation and there is no decrease in the depolarising action of Ach(1) or anticholinesterase compounds, in fact these have an additive effect, intensifying the block. The block may be reversed by the injection of a non-depolarising blocking agent, such as (+)-tubocurarine chloride (8). However there is no suitable antagonist of depolarising block as the dose is too critical to be of clinical value.

Various drugs, such as anticholinesterase compounds like neostigmine bromide (9), edrophonium chloride (10), decamethonium dibromide (11)[8] and succinylmonocholine dichloride (12)[7], all produce neuromuscular block by depolarisation of the motor end plate.



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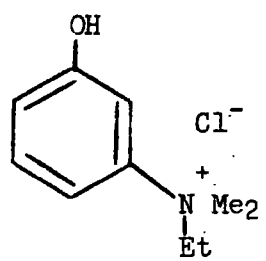

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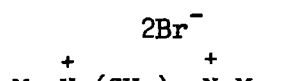

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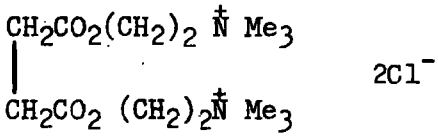


(12)

In man intra-arterial injections of Ach(1) have been observed to produce a transient stimulating effect followed by a brief depressant effect and then by a more prolonged and less marked depressant effect[9], which has the properties of a depolarising block. Ach(1) is not used clinically to produce neuromuscular block as huge doses are required, its actions are too widespread and full inhibition of cholinesterase is necessary.

Intra-arterial administration of choline (2) in man produces depression of muscle action potentials evoked by nerve stimulation. Moderate degrees of block produced by choline (2) have properties of the depolarising type, but marked degrees of block have properties of the non-depolarising type[4].

The main disadvantages of the depolarising drugs are :-

(i) there are no suitable antagonists should the need arise

(ii) powerful muscle fasciculations which precede the block may cause damage to the muscle fibres and result in severe deep muscle ache after the operation.

These disadvantages restrict their use to short-lasting operations.

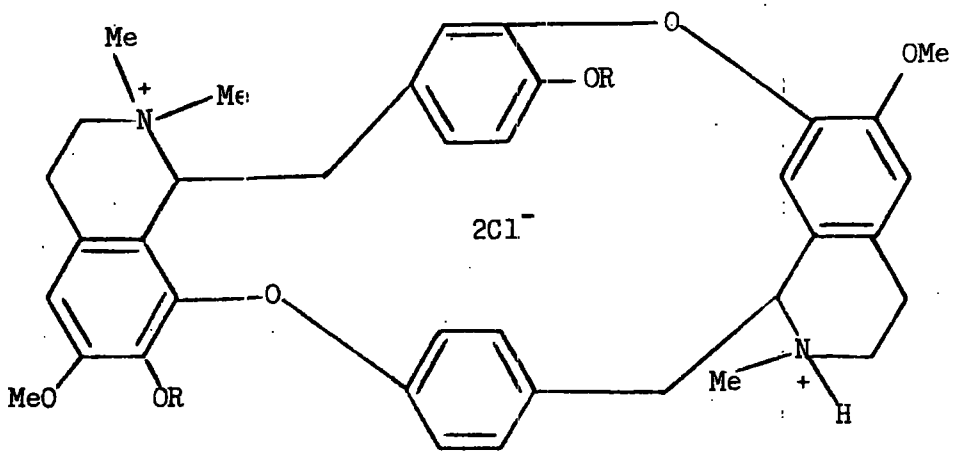
NON-DEPOLARISING NEUROMUSCULAR BLOCKING AGENTS

This type of block is due to inhibition of the depolarising action of the transmitter on the motor end plate. It occurs without change in the resting potential of the muscle membrane and is reversible by Ach(1) or an anticholinesterase compound. The block is not preceded by an increase in motor activity and there is a decline in the muscle action potentials in response to two or more stimuli[3].

The best known neuromuscular drug of this type is (+)-tubocurarine chloride (8), which was probably first used by South American indians, who used the crude curare as an arrow poison. Crude curare contains a number of closely related alkaloids that have a

similar action but attention is focused mainly on (+)-tubocurarine chloride (8) a quaternary ammonium base. King[10] separated (+)-tubocurarine chloride (8) from crude tubocurare, and later Wintersteiner and Dutcher[11] isolated it from a specific menispermaceous plant, Chondodendron Tomentosum.

Using n.m.r. spectroscopy, Everett et al[12] have shown (+)-tubocurarine chloride (8) to contain one quaternary centre and not two as previously believed.



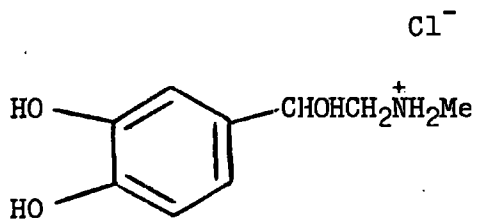
R

(8) H

(13) Me

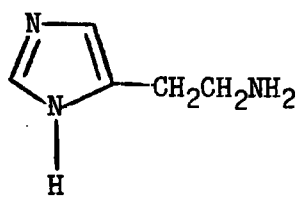
The mechanism of the block produced by (+)-tubocurarine chloride (8) is that it competes, in a reversible manner, with Ach(1) for the occupation of the receptor sites on the motor end plate of the muscle, and hence blocks the transmitter action of Ach(1) thereby preventing depolarisation of the motor end plate. The motor end plate still retains its normal permeability to potassium ions and the muscle still responds to direct electrical stimulation. The block can be antagonised by depolarising neuromuscular drugs, such as Ach(1) and succinylcholine dichloride (12), the dose is critical since such

drugs themselves produce neuromuscular block. The cooling of the muscle, the presence of excess potassium ions, adrenaline hydrochloride (14), tetraethylammonium salts (6), and also anticholinesterase drugs antagonise the block by depolarisation.



(14)

The main disadvantage of (+)-tubocurarine chloride (8) as a neuromuscular blocking drug is that it produces bronchoconstriction and lowering of the blood pressure, which is due to the liberation of histamine (15).



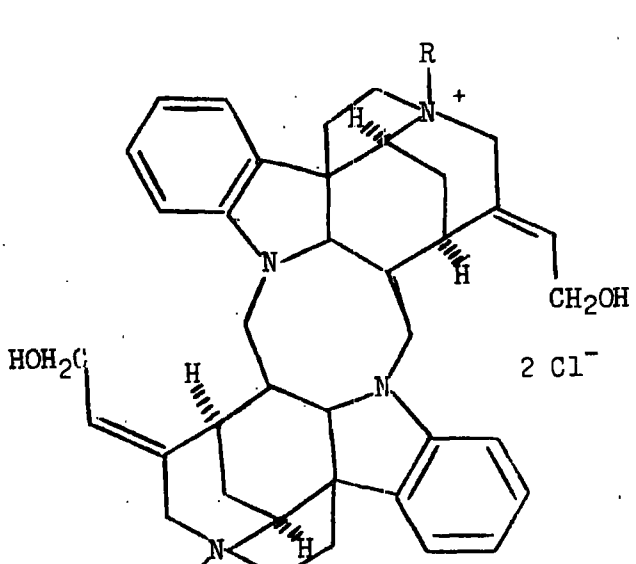
(15)

In man the dimethylether (13) of (+)-tubocurarine is approximately twice as potent as (+)-tubocurarine chloride (8) itself, however (-)-tubocurarine is much less active.

Calabash curare (another form of crude curare), the most active type, is produced from different species of Strychnos and many alkaloids have been isolated from it by Wieland et al[13,14], Karrer et al[15,16,17], Battersby and Hodson[18] and various other workers.

Of the fifty different compounds isolated only ten possessed

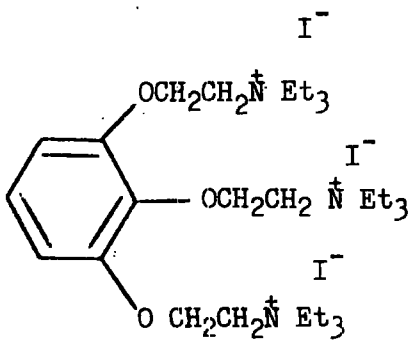
any curare like activity in particular, C-toxiferine dichloride (16) was very active. By substitution of the quaternary methyl groups in C-toxiferine dichloride (16) some derivatives were obtained of which N,N'-diallyl-bis-nortoxiferine dichloride (17)[19] was found to be the most useful clinically.



	R
(16)	CH_3
(17)	$-CH_2CH = CH_2$

Both C-toxiferine (16) and N,N'-diallyl-bis-nortoxiferine dichloride (17) have the advantage of high selectivity, no depression of blood pressure, no bronchoconstriction and no liberation of histamine (15) compared to the other curare compounds. C-Toxiferine dichloride (16) has a fairly long duration of action whilst that of N,N'-diallyl-bis-nortoxiferine dichloride (17) is fairly short.

The expense and difficulty of obtaining pure alkaloids from natural sources led to the efforts to prepare synthetic neuromuscular blocking agents. Three curarimetric drugs that have been introduced into clinical practice are, like (+)-tubocurarine chloride (8), phenolic ethers. They are gallamine triethiodide (18)[20], diplacine bromide (19)[21] and mediational iodide (20)[22].



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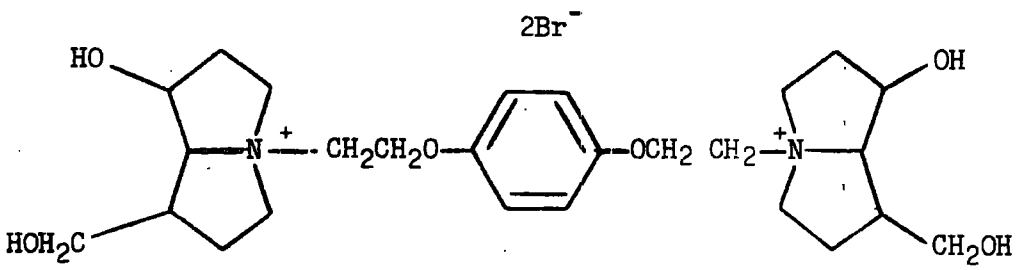

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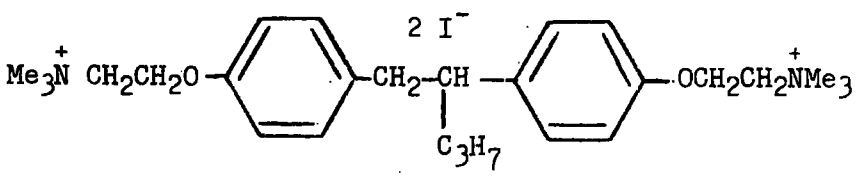


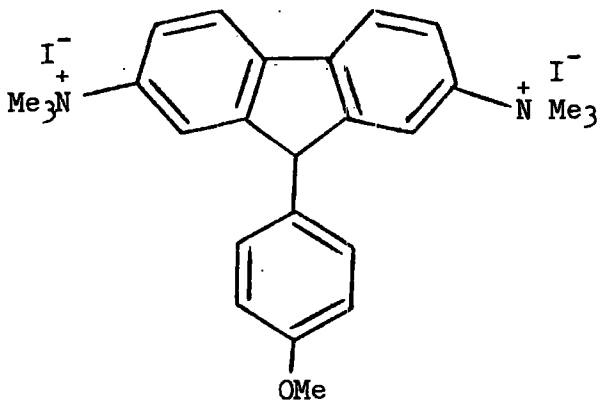
(20)

Gallamine triethiodide (18) was the first synthetic relaxant to be introduced into clinical practice and is still widely used. It is about one fifth as potent as (+)-tubocurarine chloride (8) and has a much shorter duration of action.

Some diquaternary compounds possessing a rigid structure were synthesised, so that the distance or the number of intermediate atoms

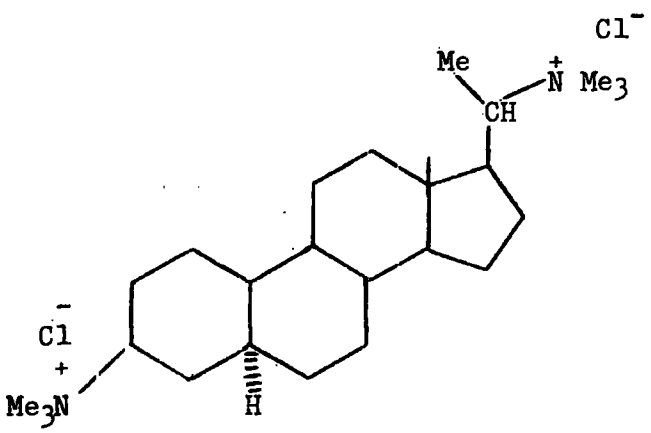
between the positively charged nitrogen centres were similar to those of (+)-tubocurarine chloride (8) or C-toxiferine dichloride (16).

Medesan and Stoica[23] found that fluorene derivatives (21), which posses a rigid structure and seven interonium carbon atoms, possessed neuromuscular blocking activity greater than that of (+)-tubocurarine dichloride (8).



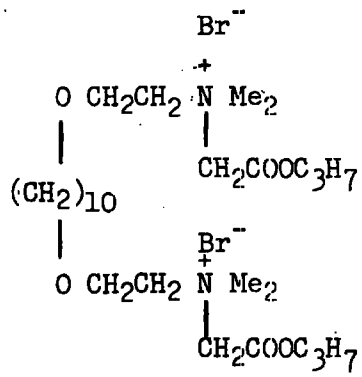
(21)

In the case of Malouetine dichloride (22)[24,25], the two quaternary centres are separated by ten carbon atoms. Although the centre of the molecule is rigid, the rotation of the side chain enables the distance between the two quaternary centres to vary from 11 to 12.5 Å. Its activity is comparable to that of (+)-tubocurarine chloride (8).



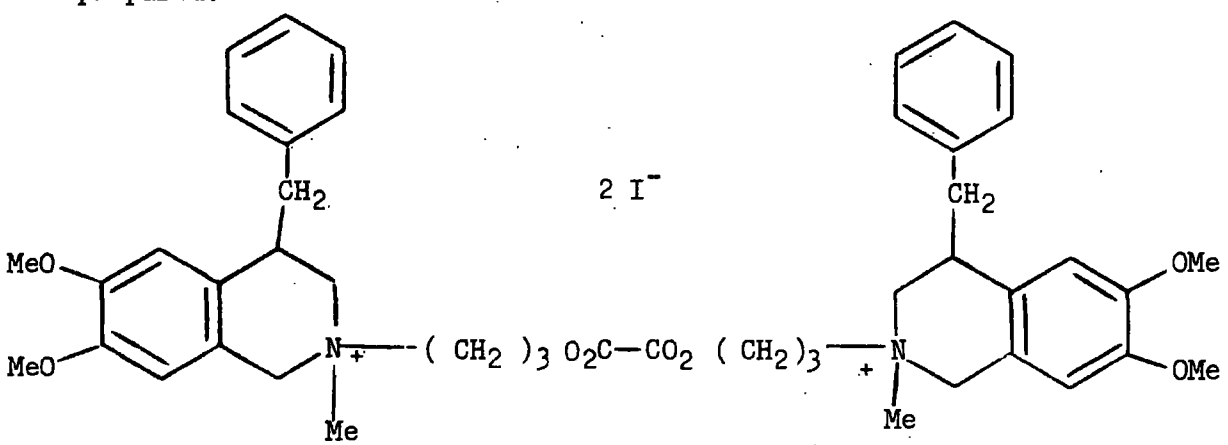
(22)

Because of the inconveniences associated with the depolarisation mechanism of action of succinylcholine dichloride (12), many attempts have been made to develop short-acting neuromuscular drugs with a competitive action. The first solution to the problem was provided by the synthesis of procedonium bromide (23)[26].



(23)

Subsequently, a series of compounds combining the properties of succinylcholine dichloride (12) with those of bistetrahydroisoquinolinium derivatives (24)[27] and bispiperidinium salts (25)[28] were prepared.



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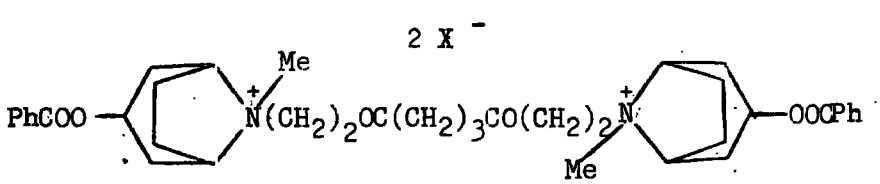

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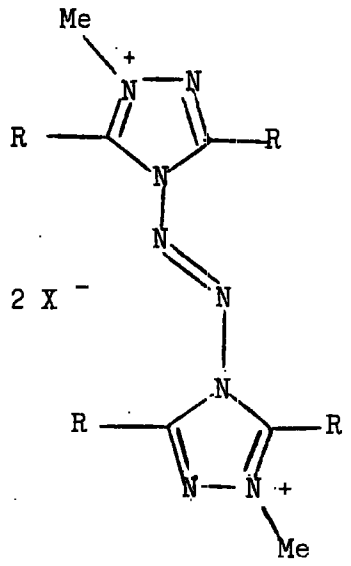
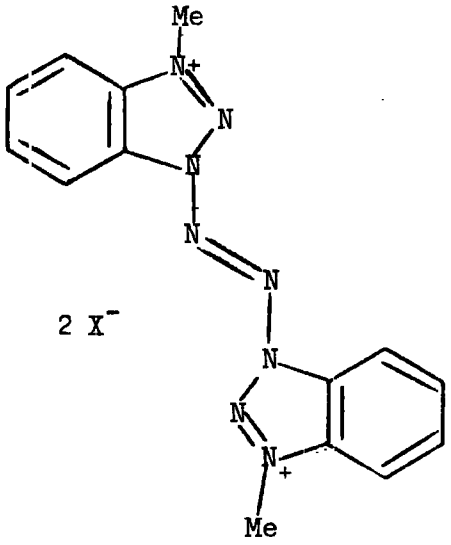


(28)

Glover and Rowbottom[33,34] have prepared some azo-1,2,4-triazolium salts (28), the 1,1-azobenzotriazolium salt (29) and also some 3,3-dimethyl-1,1-azobenzimidazolium salts (30), which possessed some neuromuscular blocking activity.



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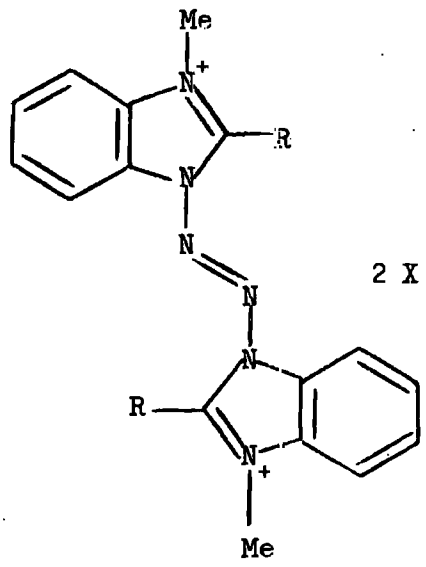


$2X^-$

R

H

Me

Ph

p - Me OC_6H_4

(30)

The remainder of this thesis describes a programme of work devised to investigate some of the structural features thought to be necessary for the desirable biological activity shown by the diquaternary compounds (27).

The most prominent feature of the imidazopyridinium salts (27) is the diquaternary nature of the system, a characteristic repeatedly, though not always, encountered in compounds having neuromuscular blocking activity.

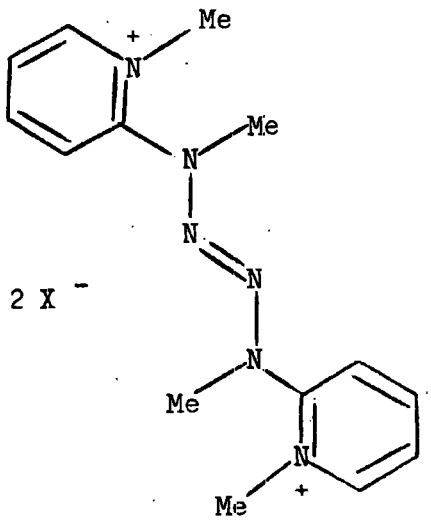
Previously[23], the distance separating the positively charged centres has been suggested as important in determining the degree of activity of diquaternary salts showing neuromuscular blocking properties.

In the powerfully active imidazo[1,2-a] pyridinium salts (27) the bridgehead nitrogen atoms, which may be regarded as the most highly positive atoms, are separated by a total of seven bonds.

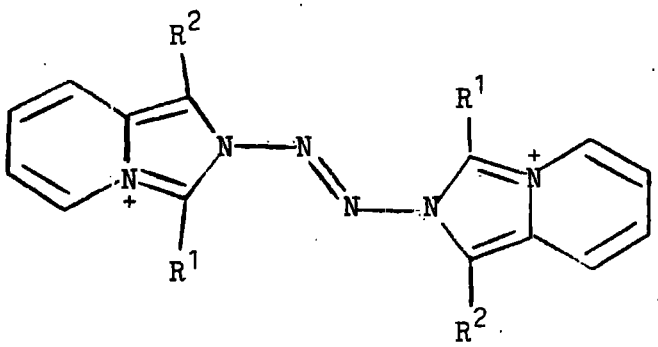
The tetrazene linkage, a feature of imidazo[1,2-a] pyridinium salts (27) is believed to be fairly labile in biological systems and this was postulated as having some connection with the short-

lasting property of the neuromuscular blocking agents.

The synthesis of diquaternary compounds containing an azo linkage joining the following heterocyclic systems, methyl-2-pyridylamine(I), and imidazo[1,5-a] pyridine (II) was attempted.



(I)

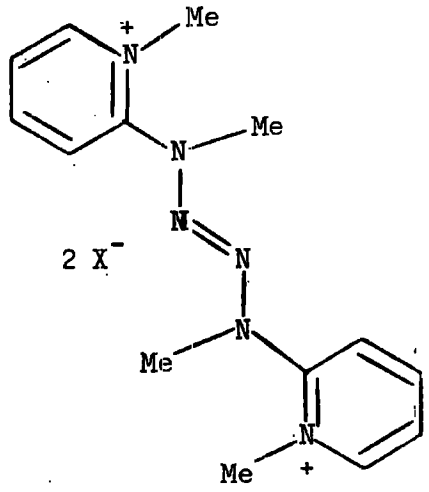


(II)

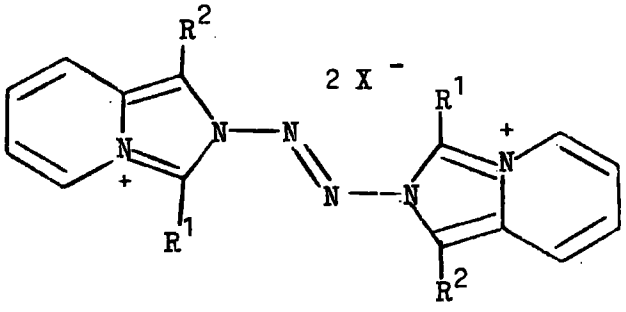
DISCUSSION

The aim of this work was the synthesis of a series of diquaternary compounds incorporating a potentially biologically labile tetrazene linkage, the compounds to be prepared having, whenever possible, the following additional general features (i) two quaternary centres and (ii) a seven bond length separation between positive centres.

As compounds having these requirements, the synthesis of diquaternary salts incorporating methyl-2-pyridyl amine (I) and imidazo [1,5-a] pyridine (II) heterocyclic systems was undertaken.



(I)



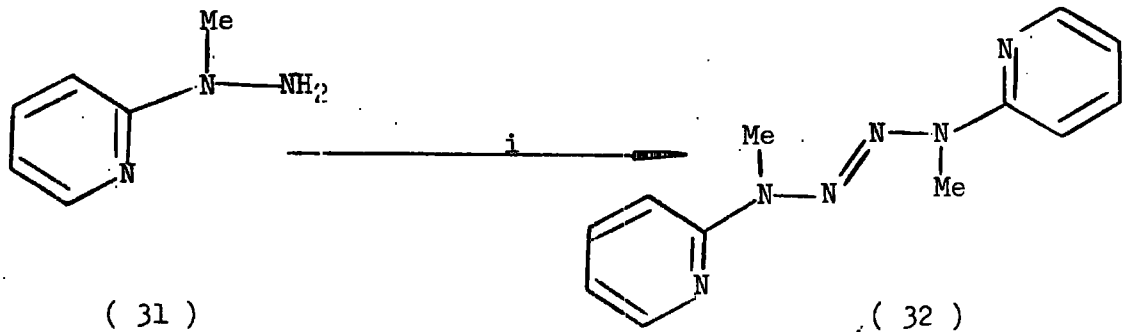
(II)

R^1	R^2
H	H
Ph	H
H	Ph
Me	H

METHYL-2-PYRIDYLAMINE DERIVATIVES (I)

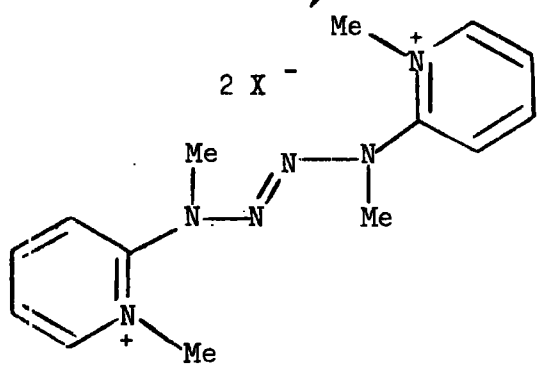
THE ATTEMPTED SYNTHESIS OF 1,4-DIMETHYL-1,4-DI(2-PYRIDYL)-2-TETRAZENE DIQUATERNARY SALTS (34)

The synthetic route proposed for the introduction of the tetrazene linkage, was the oxidation of hydrazine (31) followed by the quaternisation of the resulting tetrazene (32) to afford the required diquaternary salt (34).



(31)

(32)

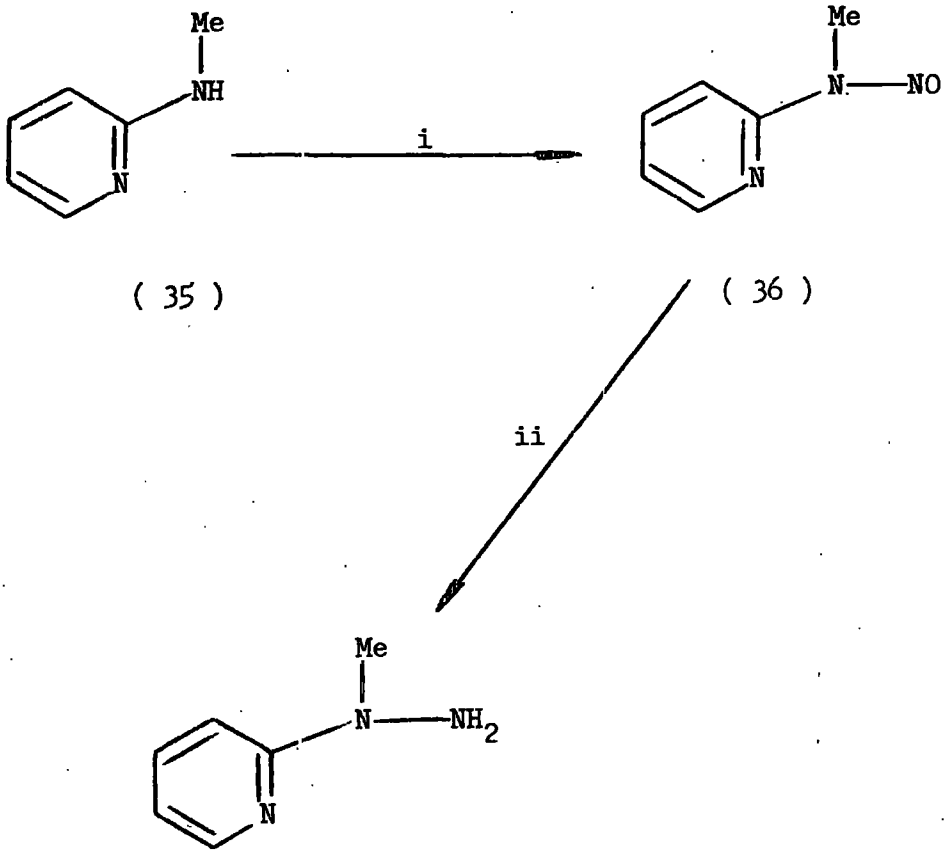


(34)

Reagents proposed : i, Oxidising agent

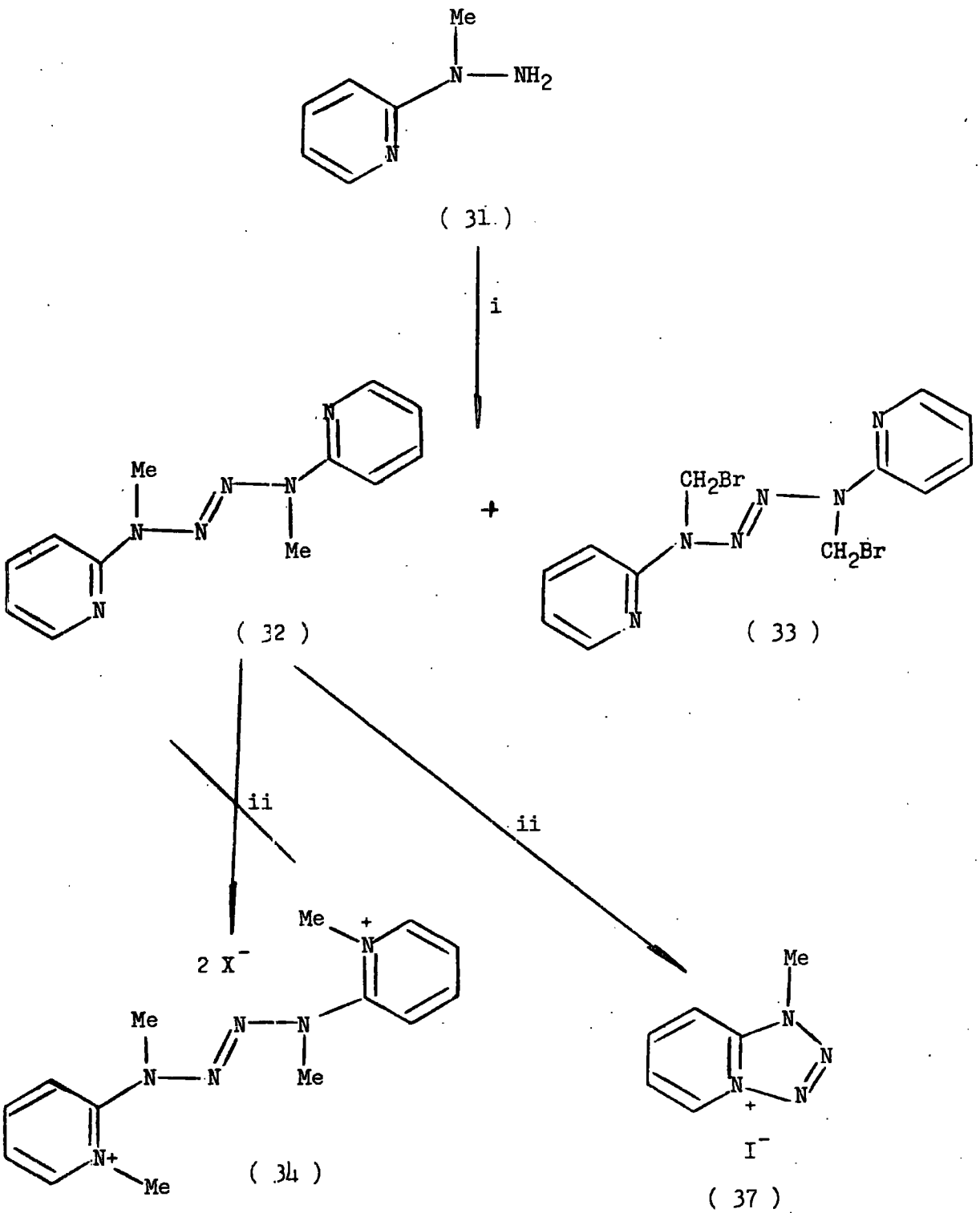
ii, MeX

2-Methylaminopyridine (35) was prepared using essentially the same procedure as Tschitschibabin and Knunianz[35]. Nitrosation of the 2-methylaminopyridine (35) and the subsequent reduction of the resulting nitrosamine (36) gave the required hydrazine (31).



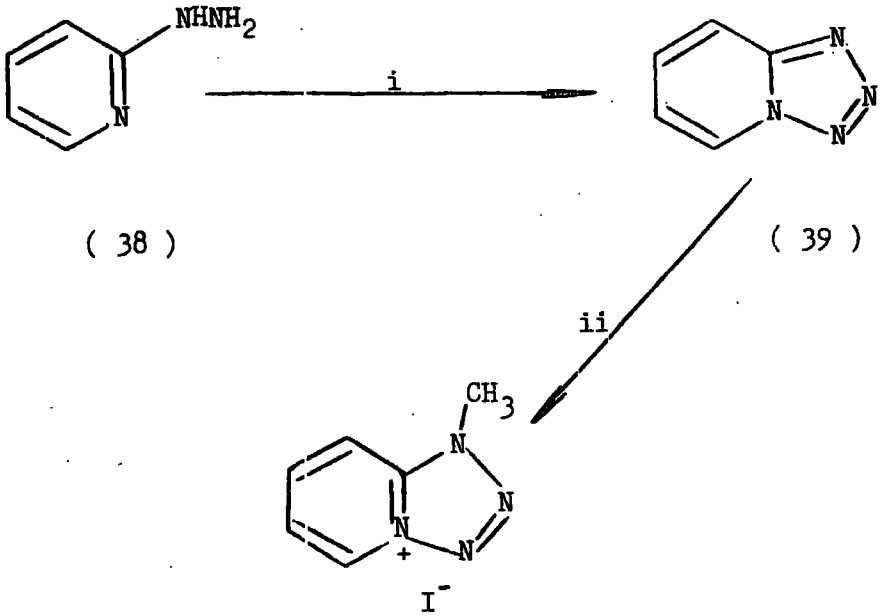
Reagents used : i, $NaNO_2$ - HCl at 0^o
ii, Zn - CH_3COOH

Oxidation of the hydrazine (31) with saturated aqueous bromine gave the tetrazene (32) in 39% yield, a small amount of the bromo substituted tetrazene (33) being also obtained. However, treatment of the tetrazene (32) with methyl iodide gave 1-methyltetrazolo[1,5-a] pyridinium iodide (37) instead of the expected tetrazene diquaternary salt (34; X = I).



Reagents used : i, saturated aqueous bromine
ii, CH_3I

The methyltetrazolopyridinium salt (37) was identical with a sample obtained by the treatment of tetrazolopyridine (39), obtained[36] by the diazotisation of 2-hydrazinopyridine (38), with methyl iodide.



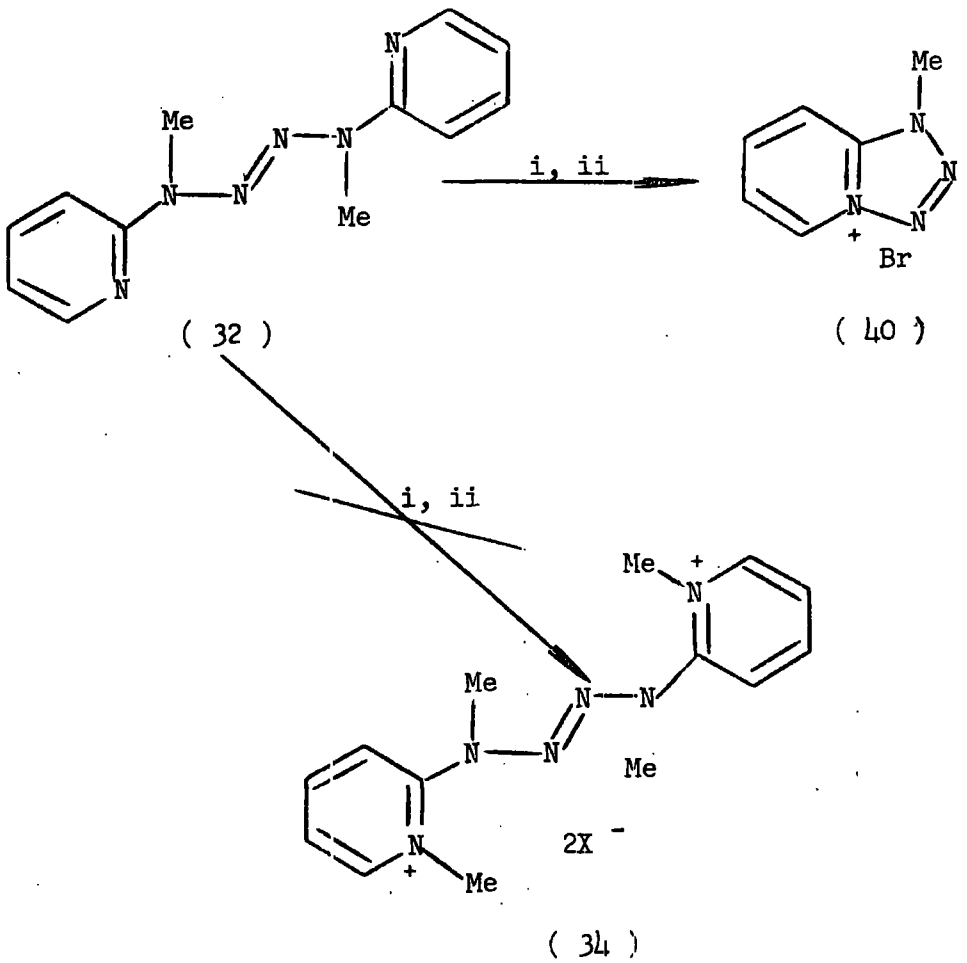
(38) (39)

(37)

Reagents used : i, 50% CH_3COOH $-NaNO_2$

ii, MeI

Quaternisation of the tetrazene (32) with methyl fluorosulphonate likewise gave the corresponding 1-methyltetrazolo[1,5-a] pyridinium salt, which was converted to the bromide (40) by ion exchange, instead of the expected tetrazene diquaternary bromide salt (34; X = Br).



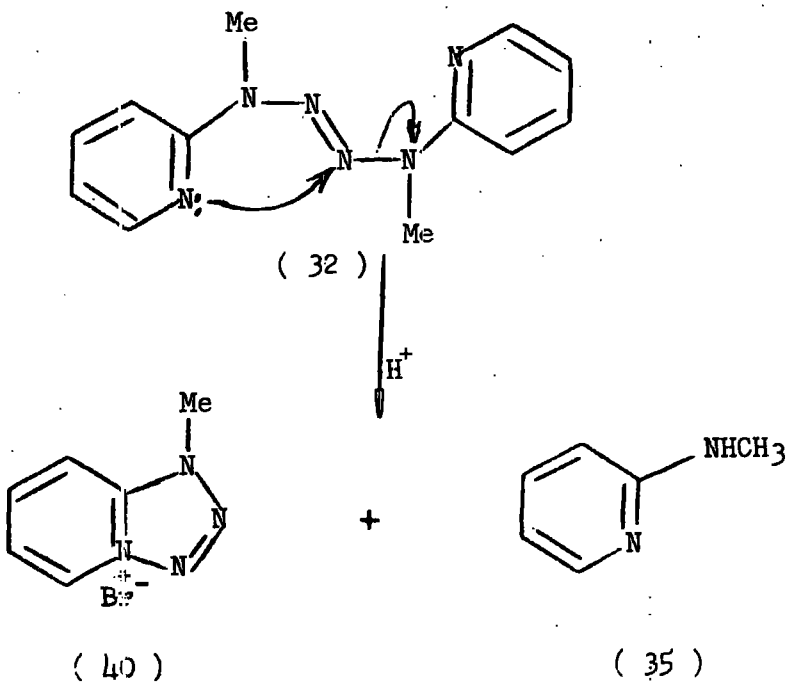
(32) (40)

(34)

Reagents used : i, CH_3OSO_2F

ii, Amberlite IRA 400(Br)-methanol

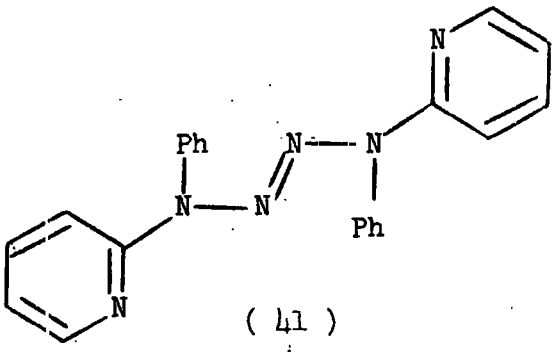
Cyclisation of the tetrazene (32) to the tetrazolopyridinium bromide (40), was better effected using boiling ethanolic hydrobromic acid. The isolation of 2-methylaminopyridine (35) from such a cyclisation confirmed the mechanism to be as that shown in Scheme 1.



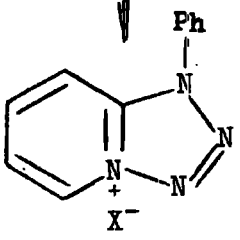
SCHEME I

In addition to establishing the position of alkylation of tetrazolo[1,5-a] pyridine the reaction also provides a route to the otherwise inaccessible 1-aryltetrazolo[1,5-a] pyridinium salts.

Accordingly the 1-phenyltetrazolo [1,5-a] pyridinium bromide (42; X= Br) was prepared by boiling the 1,4-diphenyl-1,4-di(2-pyridyl)-2-tetrazene (41) in ethanolic hydrobromic acid and the system (42; X = ClO_4) further characterised by conversion to the perchlorate salt by ionexchange.



(41)



(42)

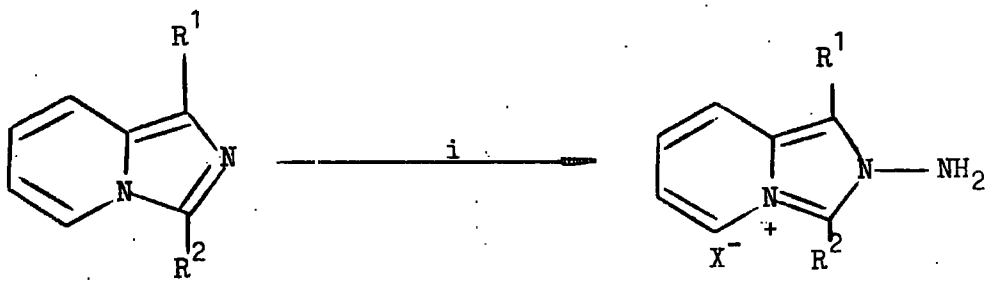
Reagents used : i, Ethanol - HBr

The 1-phenyltetrazolo[1,5-a] pyridinium perchlorate (42; X = ClO_4), was prepared by refluxing tetrazine (41) with methyl iodide, the iodide (42; X = I) being converted to the perchlorate salt by ionexchange[37].

IMIDAZO[1,5-a] PYRIDINE DERIVATIVES (II)

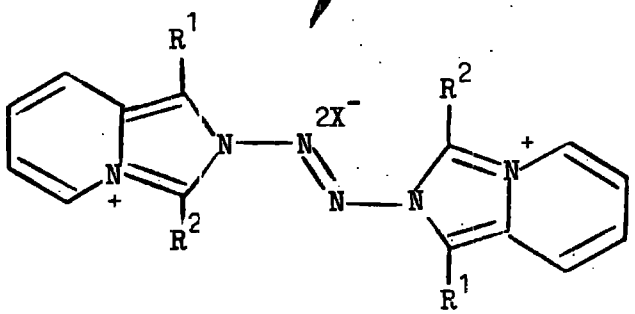
2,2'-AZOIMIDAZO[1,5-a] PYRIDINIUM SALTS (53) - (57)

The synthetic route proposed for the introduction of the tetrazene linkage was by direct N-amination of the imidazo[1,5-a] pyridines (43) - (47) followed by oxidation of the resulting N-amino compounds (48) - (52) to the required diquaternary tetrazenes (53) - (57).



	R^1	R^2
(43)	H	H
(44)	Ph	H
(45)	H	Ph
(46)	H	Me
(47)	Br	Me

	R^1	R^2
(48)	H	H
(49)	Ph	H
(50)	H	Ph
(51)	H	Me
(52)	Br	Me

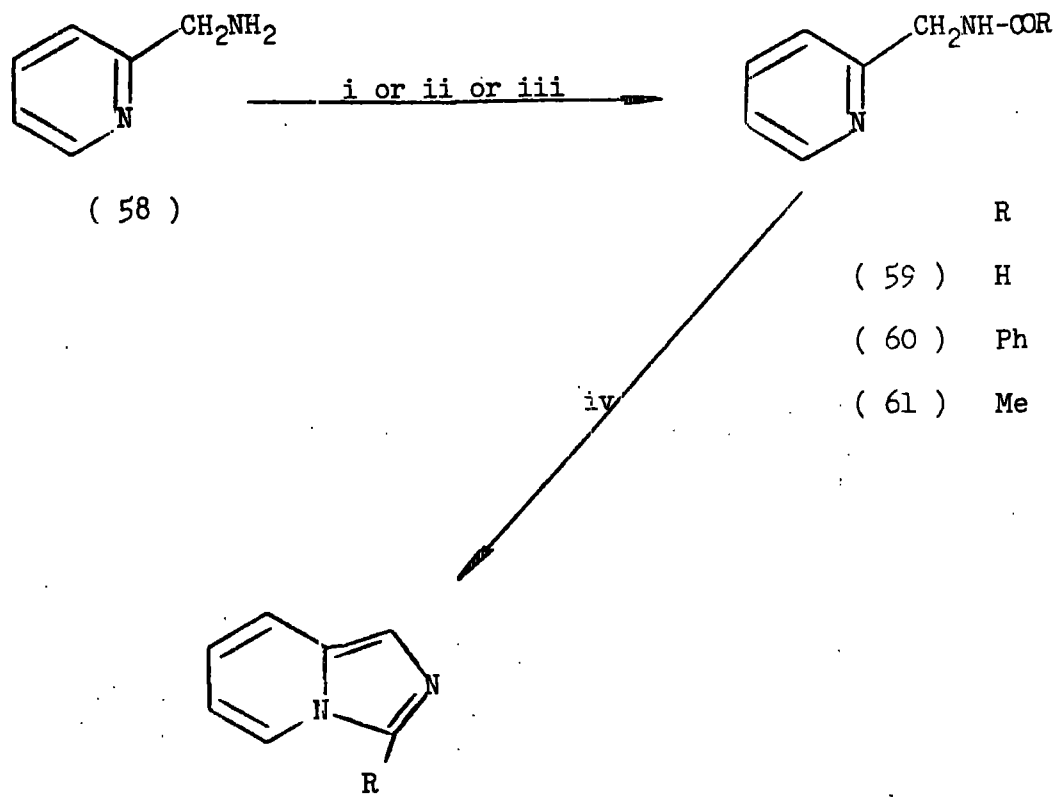


	R^1	R^2
(53)	H	H
(54)	Ph	H
(55)	H	Ph
(56)	H	Me
(57)	Br	Me

Reagents used : i, N - Aminating agent

ii, Oxidising agent

Imidazo[1,5-a] pyridine (43), 3-phenylimidazo[1,5-a] pyridine (45) and 3-methylimidazo[1,5-a] pyridine (46) were prepared using essentially the same procedure as that described by Bower and Ramage[38]. Cyclisation of the formyl-(59), the benzoyl-(60) and the acetyl-(61) derivatives of 2-pyridylmethylamine (58) was affected by refluxing in a mixture of phosphorus oxychloride and benzene, producing imidazo[1,5-a] pyridine (43), 3-phenylimidazo[1,5-a] pyridine(45) and 3-methylimidazo[1,5-a] pyridine (46) respectively.



(58)

	R
(59)	H
(60)	Ph
(61)	Me

	R
(43)	H
(45)	Ph
(46)	Me

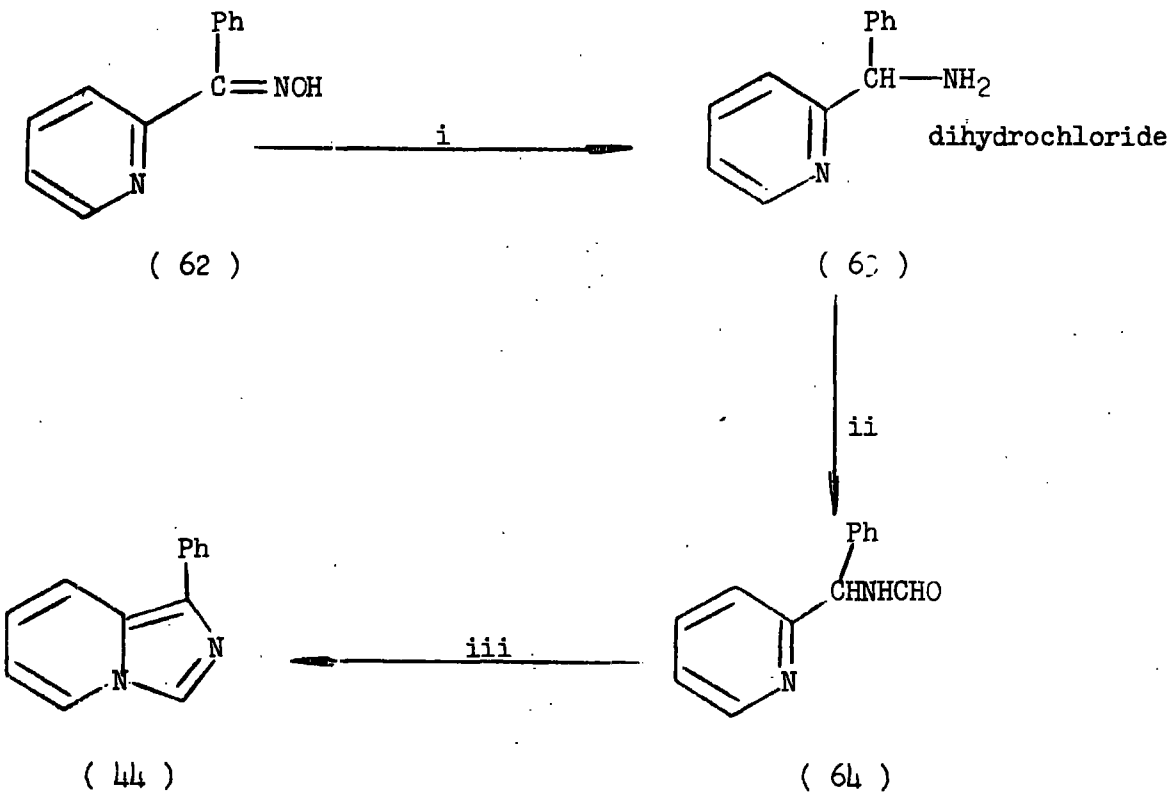
Reagents used : i, HCOOH

ii, benzoyl chloride

iii, Ac_2O and CH_3COOH

iv, $POCl_3$ and benzene

1-Phenylimidazo[1,5-a] pyridine (44) was prepared using the same procedure as that described by Glover and Vaughan[39]. Phenyl-2-pyridylamine (63) was prepared by the reduction of 2-benzoylpyridine oxime (62) with zinc and ammonium hydroxide using the procedure described by Jochims[40] for the preparation of diphenylmethylamine. Treatment of base (63) with formic acid gave the formyl derivative (64) which underwent cyclisation with phosphorus oxychloride in boiling benzene yielding the required 1-phenylimidazo[1,5-a] pyridine (44).



(62) (63) (64) (44)

Reagents used : i, Zn - NH_4OH; HCl

ii, HCOOH

iii, $POCl_3$ - benzene

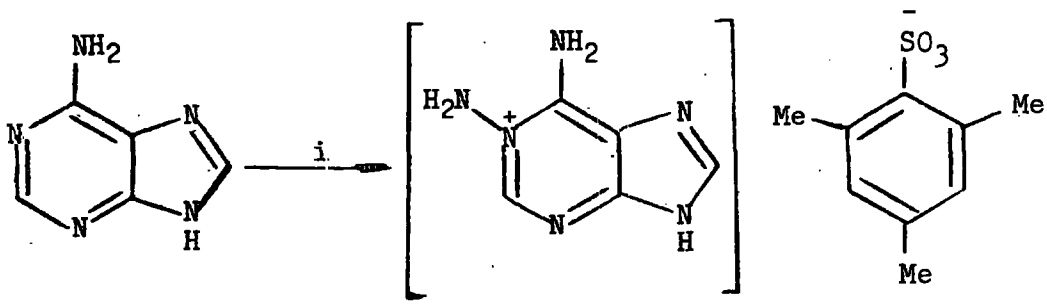
N-AMINATION PROCEDURES

Chloramine and hydroxylamine-O-sulphonic acid[42] (H.S.A.) are the traditional reagents used for N-aminations. Recently Tamura et al[41] have successfully carried out N-aminations using O-mesitylene-sulphonylhydroxylamine (M.S.H.) on a number of heterocyclic compounds, and found the yield obtained to be much higher than using H.S.A.[42] (see table 1).

base	M.S.H. %yield N-amino salt	H.S.A. %yield N-amino salt
pyridine	80	63 - 72
2-picoline	94	57
2,6-lutidine	89	34
quinoline	67	32

TABLE 1

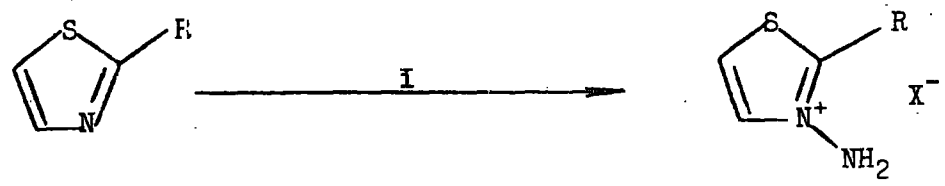
Wiemer et al[43] failed to aminate adenine (65) with H.S.A., but with M.S.H. in methanol 1-amino-adeninium mesitylenesulphonate (66), was obtained in 65% yield.



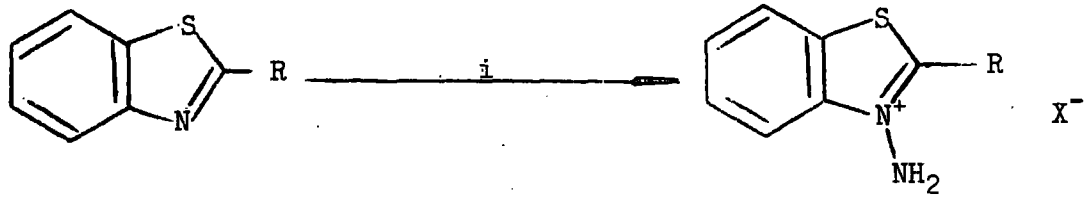
(65) (66)

Reagents used : i, MSH./methanol

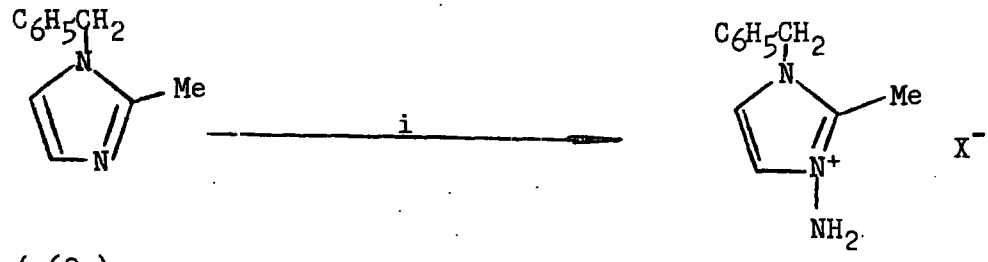
Koga et al[44] reported that the N-amination of thiazoles (67), benzothiazoles (68) and the imidazole (69) using M.S.H. gave the corresponding N-aminothiazolium (70), N-aminobenzothiazolium (71) and N-aminoimidazolium (72) compounds respectively in good yields.



(67) (70)



(68) (71)

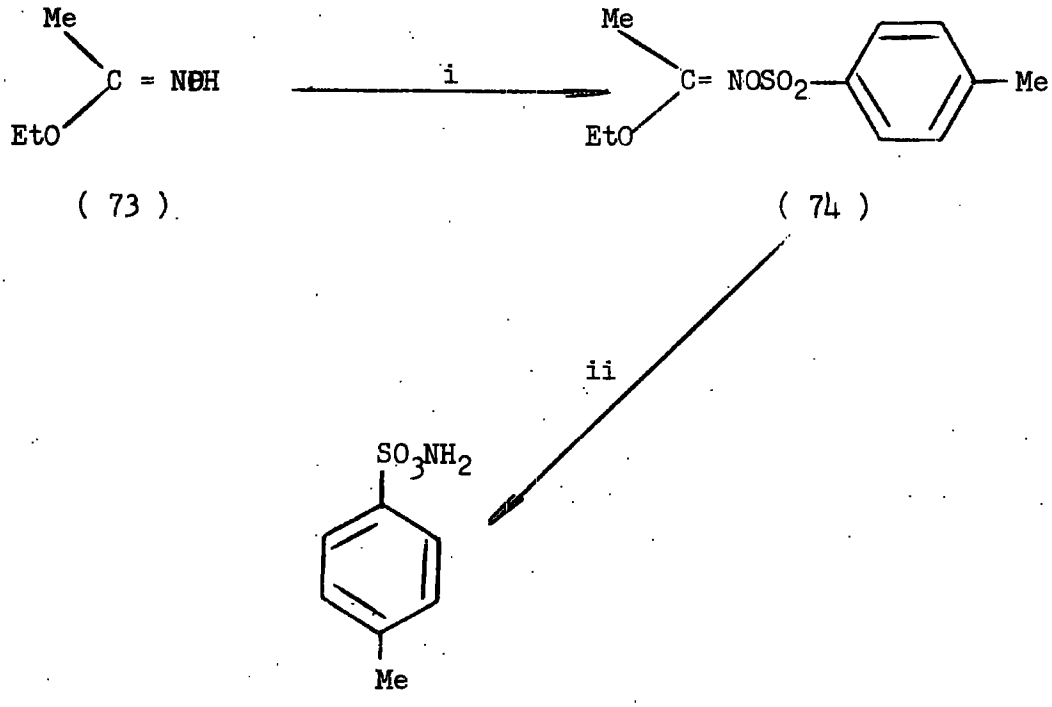


(69) (72)

Reagent used : i, M.S.H.

N-Aminations have successfully been carried out by Glover and Rowbottom[45], in high yield, using M.S.H. and O-p-tolylsulphonylhydroxylamine (T.S.H.) as the N-aminating agents. Both M.S.H. and T.S.H. are very powerful N-aminating agents giving good yields. The T.S.H. is less stable than M.S.H. but has the advantage of being derived from cheap and readily available p-toluenesulphonylchloride.

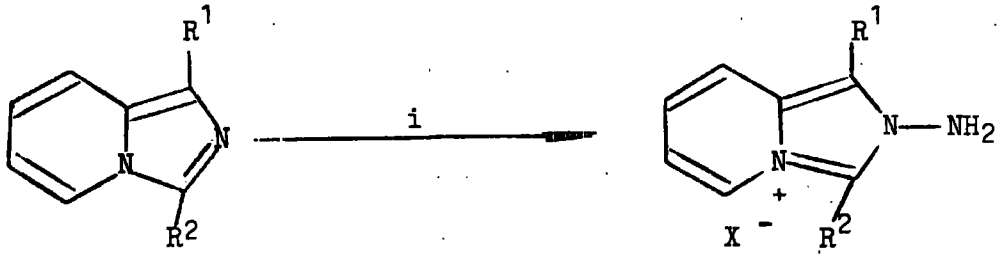
The parent imidazopyridines (43) - (47) were all N-aminated in good yield using O-p-tolylsulphonylhydroxylamine (75)[45] giving the N-amino salts (48) - (52) respectively. The O-p-tolylsulphonylhydroxylamine (75) was prepared by treating ethylacetohydroxamate (73) with p-toluenesulphonylchloride to produce the O-p-tolylsulphonylhydroxamate (74), which was then stirred with perchloric acid affording O-p-tolylsulphonylhydroxylamine (75) which was extracted into chloroform or methylene chloride.



(73) (74) (75)

Reagents used : i, p.- tolylsulphonylchloride

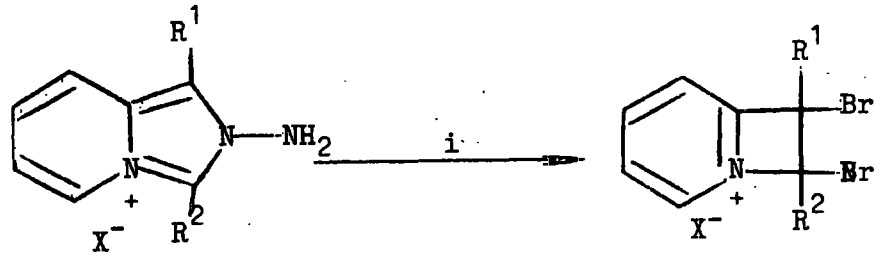
ii, 60% $HClO_4$



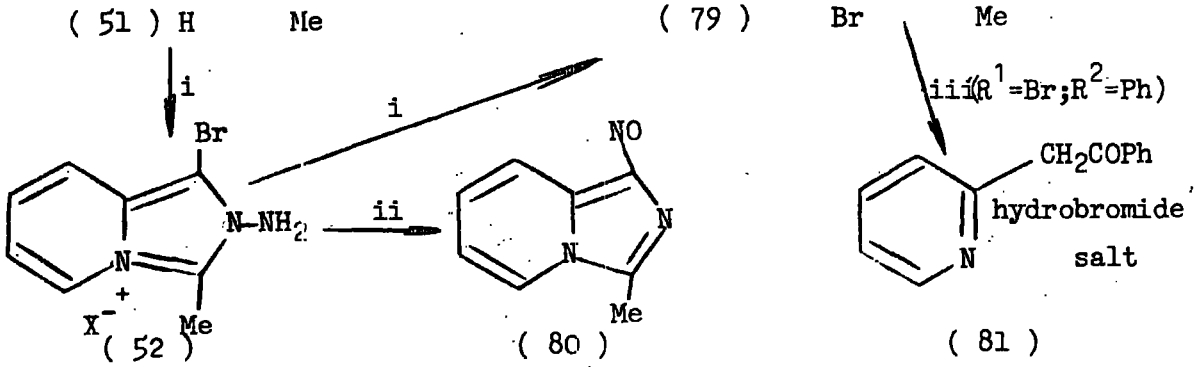
	R^1	R^2		R^1	R^2
(43)	H	H	(48)	H	H
(44)	Ph	H	(49)	Ph	H
(45)	H	Ph	(50)	H	Ph
(46)	H	Me	(51)	H	Me
(47)	Br	Me	(52)	Br	Me

Reagents used : i, T.S.H./$CHCl_3$ or T.S.H./CH_2Cl_2

Oxidation of the phenyl substituted N-amino compounds (49) and (50) with saturated aqueous bromine gave, instead of the expected corresponding diquaternary tetrazene salts (54) and (55), the corresponding tribromo-1,2-dihydroazeto[1,2-a] pyridinium bromides (77) and (78).

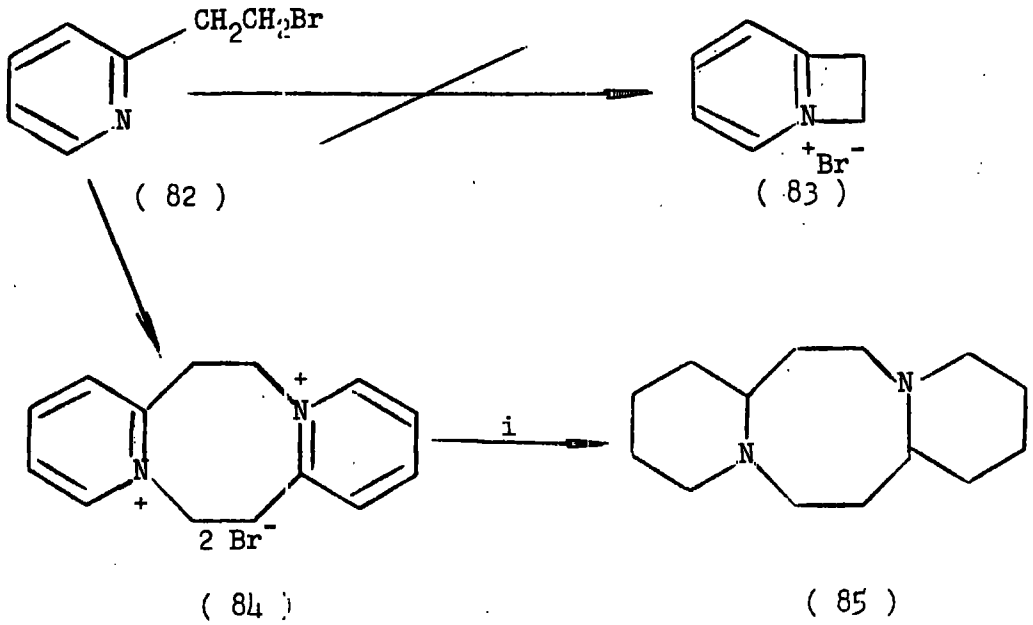


	R^1	R^2		R^1	R^2
(48)	H	H	(76)	Br	Br
(49)	Ph	H	(77)	Ph	Br
(50)	H	Ph	(78)	Br	Ph
(51)	H	Me	(79)	Br	Me



Reagents used : i, saturated aqueous bromine
ii, $NaNO_2$ - HCl
iii, H_2/Pd charcoal - basification

In the early work of Loffler the cyclisation of 2-(β-haloethyl) pyridine (82) is reported to give pyridinium salts to which structure (83) was assigned[46]. A number of such compounds appeared in the literature[47-50] and their structural assignments were generally accepted. Boekelheide et al[51] reported that the pyridinium bromide, prepared as described by Loffler[46], when subjected to hydrogenation over platinum, gave an oil b.p. 100°/0.2mm having a composition equivalent to $(C_7H_{13}N)_x$. The high boiling point of the oil indicated it to be the dimer (85) and determination of its molecular weight confirmed this. Thus the most likely structure of Loffler's pyridinium bromide is (84).



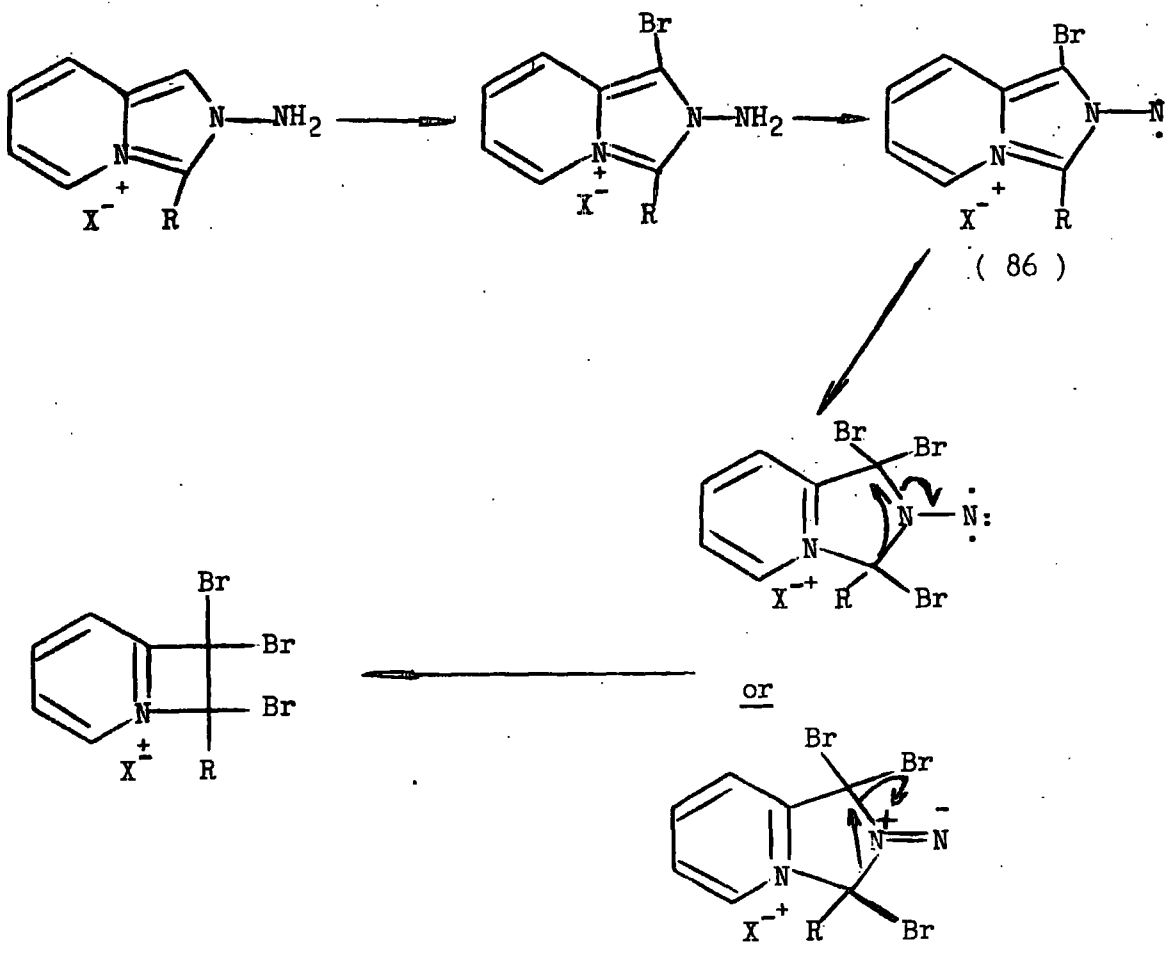
(82) (83)

(84) (85)

Reagents used : i, Pt/H_2

The fused 6:4 ring structure is assigned to (77) and (78) on the basis of the absence of $\nu(\overset{+}{N}\text{-H})$ bands in their infrared spectra, the conversion of the salt (77) to the corresponding monoperchlorate and the hydrogenation and subsequent basification of (78) which yielded phenyl-2-pyridylmethylketone (81) isolated as the hydrobromide.

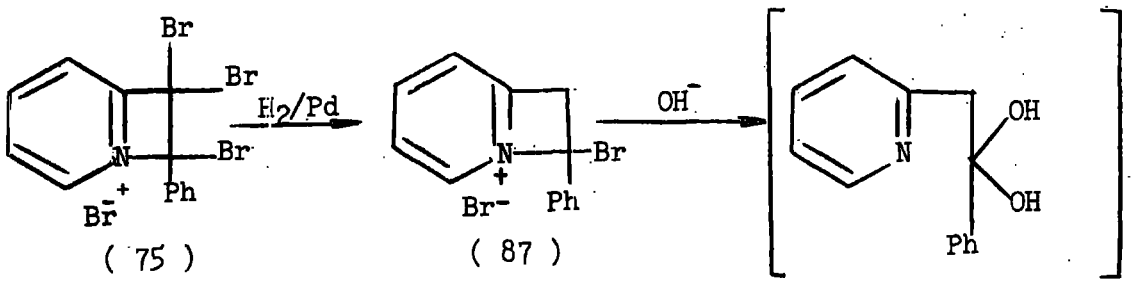
The suggested course of the reaction is via initial bromination at the free position of the imidazole ring followed by oxidation of the amino function yielding the amino-nitrene (86). The 1,4 addition of the bromine in the five membered ring followed by nitrogen loss then gives the tribromo-1,2-dihydroazeto-pyridinium bromide as shown in scheme 2.



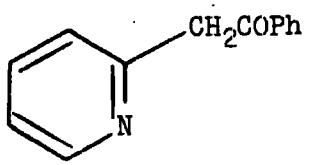
SCHEME 2

Evidence of the initial electrophilic bromination stage was obtained by the isolation of the bromo substituted N-amino salt (52) when 2-amino-3-methylimidazo[1,5-a] pyridinium bromide (51; X = Br) was treated with saturated aqueous bromine. The 2-amino-1-bromo-3-methylimidazo[1,5-a] pyridinium bromide (52) was also obtained by the N-amination of the 1-bromo-3-methylimidazo[1,5-a] pyridine (47). Deamination of (52) with nitrous acid gave the nitroso compound (80) and further treatment of (52) with aqueous bromine gave the corresponding tribromo-1,2-dihydroazetopyridinium bromide salt (79).

Hydrogenation of the 1,1,2-tribromo-2-phenyl-1,2-dihydroazetopyridinium bromide (78) over palladium charcoal resulted in the uptake of approximately two molecular equivalents of hydrogen and subsequent basification gave phenyl-2-pyridylmethylketone (81) presumably via the intermediate monobromo compound (87) as shown in scheme 3 .



(75) (87)



(81)

SCHEME 3

The oxidation of the N-amino salt (48) of the parent imidazopyridine (43) gave 1,1,2,2-tetrabromo-1,2-dihydroazeto[1,2-a] pyridinium bromide (76) probably via initial electrophilic bromination at both of the free positions of the five membered ring.

EXPERIMENTAL

All melting points were determined on a Kofler hot-stage and are uncorrected. N.m.r. spectra were determined on a Perkin-Elmer R12A spectrometer. I.r. spectra were determined on a Perkin-Elmer 237 spectrometer. Microanalyses were carried out by Dr. F.B. Strauss.

2-Methylaminopyridine (35) was prepared according to the method described by Tschitchibabin and Knuniang[35].

Powdered sodamide (39g) was covered with absolute ether and a solution of 2-aminopyridine (94g) in absolute ether (1ℓ) was slowly added dropwise. After the vigorous evolution of ammonia, the mixture was boiled under reflux for 1.5h on a water bath. A solution of dimethyl sulphate (63g) in absolute ether (200 ml) was slowly added to the reaction mixture with stirring. After addition the reaction mixture was boiled for a further 1h and then allowed to stand overnight.

The mixture was washed with water and the aqueous washings extracted twice with ether. The combined ether extracts were then extracted with dilute hydrochloric acid. The acid extracts were basified with 25% aqueous sodium hydroxide, and then extracted with ether, the extract being dried over potassium hydroxide pellets. The solvent was removed under reduced pressure and the residual oil (63g) was dissolved in pyridine (150ml) and then slowly treated with benzoyl chloride (190g). After addition the mixture was heated on a water bath for 0.5h, cooled, and ice cold 10% hydrochloric acid was added with thorough mixing. The acid solution was filtered, and the filtrate was basified with potassium hydroxide pellets, the oil which separated was extracted into ether. The extract was dried over potassium hydroxide pellets before fractionally distilling the 2-benzoylmethylaminopyridine (41.0g, 20%) b.p. 190°/10mm (lit[35]., b.p. 200°/1mm).

A mixture of 2-benzoylmethylaminopyridine (41g) in 20% hydrochloric acid solution was boiled under reflux for 0.5h. After cooling the benzoic acid was filtered off and the filtrate was basified with 25% aqueous sodium hydroxide and then extracted

with ether. Fractional distillation of the ether extract yielded 2-methylaminopyridine (35) (12.1g, 57%) b.p. 82-84°/7mm (lit[35]., b.p. 90°/9mm).

2-(N-Nitrosomethylamino) pyridine (36)

An ice cold solution of 2-methylaminopyridine (35) (5g) in 20% hydrochloric acid (30 ml) was treated dropwise with a solution of sodium nitrite (3.5g) in water (10 ml). The reaction mixture was allowed to stand for 0.5h in ice water before it was treated with ammonia. The liberated nitrosamine, which separated as an oil, was extracted into ether, the extract being dried over potassium hydroxide pellets. The solvent was removed under reduced pressure and the residual green yellow nitrosamine (36) was fractionally distilled (4.7g, 74%) b.p. 86-88°/5.5 mm (lit[35]., b.p. 123-4°/30mm).

1-Methyl-1-(2-pyridyl) hydrazine (31)

A solution of the nitrosamine (36) (4g) in 80% acetic acid (15g) was added in small portions to a stirred aqueous suspension of zinc powder (18g), the reaction mixture being maintained at 10 - 15°. After addition of the nitrosamine solution, the reaction mixture was stirred at room temperature for 3h before being filtered and the residue being washed with 2M acetic acid. The combined washings and filtrate were basified with 25% sodium hydroxide solution. The separating oil was extracted into ether, the extract being dried over potassium hydroxide pellets. The solvent was then removed under reduced pressure and the residual oil was fractionally distilled yielding the pure hydrazine (31) (2.9g, 81%) b.p. 90-92°/8.5mm (lit[35]., b.p. 105°/10mm).

1,4-Dimethyl-1,4-di(2-pyridyl)-2-tetrazene (32)

Saturated aqueous bromine (30 ml) was added in bulk to a stirred solution of hydrazine (31) (2g) in methanol (3 ml). The mixture was basified with 2M aqueous sodium hydroxide solution, trituration of the mixture yielded a white solid which was filtered off. Recrystallisation of the white solid from methanol yielded the tetrazene (32) as colourless crystals (0.43g, 22%) m.p. 137-138°. (Found: C,59.2; H, 5.9; N, 34.4. $C_{12}H_{11}N_6$ requires C,59.5; H, 5.8%; N, 34.7%).

On recrystallisation of the tetrazene (32) from methanol a small amount of methanol insoluble material was obtained. Recrystallisation of this methanol insoluble product from chloroform gave a colourless compound m.p. 243°, in very low yield, analytical data for which was consistent with structure (33).
(Found: C, 36.0; H, 3.1; N, 21.5. $C_{12}H_{12}Br_2N_6$ requires, C, 36.0; H, 3.0; N, 21.0%).

1-Methyltetrazolo[1,5-a]pyridinium iodide(37) prepared from tetrazene (32).

A mixture of the tetrazene (32)(0.3g), methyliodide (3 ml) and methanol (3 ml) was boiled under reflux for 17h and then cooled. Addition of ether to the reaction mixture caused precipitation of the tetrazolo iodide (37) (0.06g, 39%) which was filtered off. Evaporation of the filtrate and recrystallisation of the residue from aqueous methanol gave the starting tetrazene (32)(0.16g). The yield to the reaction, is before recrystallisation and is based on starting material consumed. The tetrazolo salt (37) was recrystallised from nitromethane-ether in poor yield m.p. 199°.
(Found: C, 27.6; H, 2.95; N, 21.2. $C_6H_7IN_4$ requires, C, 27.5; H, 2.7; N, 21.4%).

Tetrazolo [1,5-a] pyridine (39) was prepared according to the method described by Fargher and Furness[36].

2-Pyridylhydrazine (38)(1g)was dissolved in 50% aqueous acetic acid (20 ml) and the resulting solution was cooled in an ice bath and then treated with sodium nitrite (0.8g). The reaction mixture was neutralised with 2M sodium hydroxide solution and then extracted with chloroform. The solvent was removed under reduced pressure and the residue obtained was crystallised from water yielding the tetrazolo [1,5-a] pyridine (39) as colourless crystals (0.6g, 54%) m.p. 156° (lit[36]., m.p. 159°).

1-Methyltetrazolo [1,5-a] pyridinium iodide (37) prepared from tetrazolo [1,5-a] pyridine.

A mixture of tetrazolo [1,5-a] pyridine (39) (0.2g) and methyl iodide (2 ml) was heated in a sealed tube at 100° for a period of 20h. The resulting solution was evaporated under reduced pressure and the residue obtained recrystallised from methanol-ether yielding the iodide (37) as colourless crystals (0.26g, 60%) m.p. 200°.

(Found: C, 27.6; H, 2.7; N, 21.4%. $C_6H_7IN_4$ requires C, 27.5; H, 2.7; N, 21.4%).

1-Methyltetrazolo [1,5-a] pyridinium bromide (40) was prepared by using two different procedures :-

(i) A mixture of the tetrazene (32) (0.29g) in chloroform (5 ml) and methylfluorosulphonate (2 ml) was heated on a boiling water bath for 4 - 5 minutes. The precipitate which separated was filtered off and washed with ether. No suitable crystallising solvent was found to recrystallise the precipitate obtained. A methanolic solution of the precipitate

was eluted through an ion exchange column of Amberlite IRA400(Br). The volume of the methanolic solution obtained after elution was decreased under reduced pressure. The remaining methanolic solution (~20ml) was boiled under reflux for 20h. Ether was added to the resulting solution until it became slightly turbid and on cooling a solid precipitated from the solution. The precipitate was filtered from the solution and then recrystallised from methanol-ether yielding the bromide (40) as a pale yellow crystalline solid (0.09g, 35%) m.p. 232°.
(Found: C, 33.3; H, 3.1; N, 25.8. $C_6H_7BrN_4$ requires C, 33.5; H, 3.3; N, 26.1%)

(ii) A mixture of the tetrazene (32) (0.1g), ethanol (20 ml) and 48% hydrobromic acid (0.07 ml) was boiled under reflux for 2h. The reaction mixture was cooled and ether was added until precipitation occurred. The precipitate was filtered off and recrystallised from methanol-ether, yielding the bromide (40) as a pale yellow crystalline solid (0.075g, 84%) m.p. 234°.
(Found: C, 33.3; H, 3.1; N, 25.8. $C_6H_7BrN_4$ requires C, 33.5; H, 3.3; N, 26.1%)

The filtrate was evaporated to dryness under reduced pressure and the residue obtained dissolved in water and basified with 10% aqueous sodium hydroxide solution. The basic solution was extracted with ether, the combined ether extracts being dried over anhydrous sodium sulphate. The solvent was removed from the dried ether extract under reduced pressure and the residue obtained was treated with alcoholic picric acid which yielded the picrate of 2-methylaminopyridine (35) m.p. 189-190°, identical with an authentic sample.

2-(N-Nitrosophenylamino) pyridine

A solution of sodium nitrite (8.5g) in water (20 ml) was added dropwise to a vigorously stirred solution of 2-(phenylamino) pyridine (17.0g) in concentrated hydrochloric acid (10 ml) immersed in a water bath at 70°. The solution was cooled, the product filtered off and recrystallised from methanol yielding 2-(N-nitroso-phenylamino) pyridine as yellow prisms, m.p. 99° (15.7g, 79%). (lit[37]., m.p. 99-100°, 80%).

1-Phenyl-1-(2-pyridyl) hydrazine

A solution of 2-(N-nitrosophenylamino) pyridine (4.0g) in methanol (60 ml) and glacial acetic acid (10g) was added dropwise over a period of 1h to a stirred suspension of zinc powder (18g) in water (20 ml) immersed in an ice bath. The suspension was stirred for a further 1h then filtered and the residue washed with methanol (10 ml). The combined filtrate and washings were basified with 25% aqueous sodium hydroxide solution to pH 11 and extracted with ether (2 x 200 ml), each extract in turn being washed with water (15 ml); the ether extract was evaporated and the resulting aqueous mixture was extracted with ether (3 x 50 ml). The dried ether extract (anhydrous sodium sulphate) was evaporated under reduced pressure and the residual oil was fractionally distilled yielding 1-phenyl-1-(2 pyridyl) hydrazine (1.15g, 31%) (b.p.135-139°/1.5 mm) (lit[37]., b.p. 123°/0.6 mm., 25%).

1,4-Diphenyl-1,4-di(2-pyridyl)-2-tetrazene (41)

Saturated aqueous bromine (30 ml) was added bulkwise to a solution of 1-phenyl-1-(2-pyridyl) hydrazine (1.3g) in

methanol (3 ml). The reaction mixture was basified with 10% aqueous sodium hydroxide solution and on trituration gave an amber solid which was filtered off. Recrystallisation from methyl cyanide yielded the tetrazene (41) as colourless needles m.p. 144° (decomp.) (0.2g, 16%) (lit[37]., m.p. 145° (decomp.), 19%).

1-Phenyltetrazolo[1,5-a] pyridinium bromide (42; X = Br)

The tetrazene (41) (0.1g) was dissolved in ethanol (20 ml) and 48% hydrobromic acid (0.11 ml) added, the mixture was boiled under reflux for 7h. The solution was cooled and ether was added until precipitation occurred. The precipitate was filtered off but it became a gum on the filter paper. The gum was recrystallised from methanol-ether giving a brown solid which contained starting meterial (41). Recrystallisation of the brown solid from nitromethane-ether gave the bromide (42; X = Br) as a pale yellow crystalline solid in very poor yield, m.p. 234°.

(Found: C, 46.5; H, 3.8; N, 19.7. $C_{11}H_9BrN_4 \frac{1}{2}H_2O$ requires, C, 46.2; H, 3.5; N, 19.6%).

1-Phenyltetrazolo[1,5-a] pyridinium perchlorate (42; X = ClO_4)

The tetrazene (41) (0.08g), was dissolved in ethanol (20 ml) and 48% hydrobromic acid (0.2 ml) added, the mixture was boiled under reflux for 2.5h and then evaporated to dryness under reduced pressure. Attempts to recrystallise the residue from nitromethane and ether, gave a gum. The gum was dissolved in chloroform (15 ml) and treated with 70% perchloric acid (0.1 ml).

The chloroform was removed under reduced pressure and the residue was recrystallised first from ethanol-ether and then nitromethane-ether yielding the perchlorate (42; X = ClO_4) as a pale yellow crystalline solid (0.02g, 31%) m.p. 241-242° (lit[37]., m.p. 243-244°).

2-Pyridylmethylamine (58) was prepared according to the method described by Craig and Hixon[52]. Zinc dust (280g) and glacial acetic acid (280g) were added in small portions to a stirred solution of 2-pyridinealdoxime (35.0g) in ethanol (525 ml) over a period of several hours. After standing overnight the suspended solid was filtered off and washed with alcohol. The combined filtrate and washings were concentrated under reduced pressure to a thick syrup, water was added and the evaporation repeated three successive times to remove as much of the acetic acid as possible. An 80% aqueous solution of potassium hydr--oxide was added to the residue and the oil, which rose to the surface, was drawn off. The caustic suspension was subjected to steam distillation to remove the retained base, the base being recovered by acidifying the distillate with hydrochloric acid, evaporating off the water and decomposing the residue with 80% aqueous potassium hydroxide. The combined fractions of oil were dried over potassium hydroxide pellets and then fractionally distilled yielding 2-pyridyl-methylamine (58) (15.3g, 68%) b.p. 62 - 64°/3.5 mm (lit[52]., b.p. 91°/15 mm).

2-Formamidomethylpyridine (59) was prepared by essentially the same procedure as that described by Bower and Ramage[38].

A solution of 2-aminomethylpyridine (58) (8.29g) and 98% formic acid (50 ml) was boiled under reflux for 3h. Excess formic acid was removed under reduced pressure and the residual oil was fractionally distilled yielding the base (59) as a yellow oil (8.87g, 85%) b.p. 142-145°/1.5 mm (lit[38]., b.p. 160-161°/4 mm., 77%).

Imidazo[1,5-a] pyridine (43) was prepared according to the method described by Bower and Ramage[38]. A stirred mixture of 2-formamidomethylpyridine (59) (8.87g), phosphorus oxychloride (18 ml) and benzene (55 ml) was boiled under reflux for 4h. Excess phosphorus oxychloride and benzene were removed under reduced pressure and the residual oil was decomposed with ice water and basified with 25% aqueous sodium hydroxide solution. The aqueous mixture was extracted with chloroform, the combined chloroform extracts being dried over calcium chloride. Fractionation of the dried extract gave the base (43) (5.5g, 71%) b.p. 113-115°/2 mm (lit[38]., b.p. 120-125°/3 mm., 71%).

2-Aminoimidazo[1,5-a] pyridinium salts (48)

2-Aminoimidazo[1,5-a] pyridinium-p-tolylsulphonate (48; X=$C_7H_7SO_3$)

To a solution of imidazo[1,5-a] pyridine (43) (5.5g) in chloroform (20 ml), T.S.H.(O-p-tolylsulphonylhydroxylamine) 5% W/V in chloroform (200 ml) was added in bulk and the reaction mixture was stirred for 0.5h. Ether was added to complete precipitation of the product (15g). A small amount of the

p-tolylsulphonate salt (48; X = $C_7H_7SO_3$) (~0.1g) was recrystallised from methanol-ether yielding colourless crystals m.p. 214 - 215°.

(Found: C, 55.1; H, 5.2; N, 13.6. $C_{14}H_{15}N_3O_3S$ requires, C, 55.1; H, 5.0; N, 13.8%).

2-Aminoimidazo[1,5-a] pyridinium bromide (48; X = Br)

A solution of p-tolylsulphonate salt (48; X = $C_7H_7SO_3$) (15g), 48% hydrobromic acid (10 ml) and methanol (150 ml) was boiled under reflux for 4 - 5 minutes. The solution was cooled and ether added to complete the precipitation. The bromide (48; X = Br) was recrystallised from methanol-ether as a colourless crystalline solid (7.5g, 75%) m.p. 219 - 221°.

(Found: C, 39.3; H, 3.8; N, 19.6. $C_7H_8BrN_3$ requires, C, 39.3; H, 3.8; N, 19.6%).

N.B. Overall yield based on the starting imidazopyridine (48) (5.5g).

1,1,2,2-Tetrabromo-1,2-dihydroazeto[1,2-a] pyridinium bromide (76)

Saturated aqueous bromine (75 ml) was added bulkwise to a solution of bromide (48) (0.4g) in water (2 ml). The reaction mixture was stirred for 0.5h after which the red solid which had separated was filtered off, washed with water and dissolved in absolute acetone. The solution was boiled under reflux until a white solid precipitated which was filtered off and recrystallised from acetone-48% hydrobromic acid yielding the bromide (76) as a colourless crystalline solid (0.21g, 22%) m.p. 156 - 158°.

(Found: C, 16.9; H, 1.1; N, 2.8. $C_7H_4Br_5N$ requires, C, 16.8; H, 0.8; N, 2.8%)

2-Benzoylpyridine Oxime (62) was prepared using the procedure described by Huntress and Walter[62].

Sodium hydroxide (9.3g) was slowly added to a stirred solution of 2-benzoylpyridine (9.15g) and hydroxylamine hydrochloride (5.0g) in industrial methylated spirit (20 ml). The mixture was boiled under reflux for 5 minutes, cooled and poured into a solution of concentrated hydrochloric acid (25 ml) and water (160 ml). The solution was neutralised to phenolphthalein with aqueous sodium hydroxide when the oxime (62) precipitated as a colourless solid (8.7g, 88%) (lit[62]., 97%).

Phenyl-2-pyridylmethylamine Dihydrochloride (63) was prepared essentially by the same procedure as that described by J.C. Jochims[40] for the preparation of diphenylamine.

A mixture of 2-benzoylpyridine oxime (62) (20g), zinc dust (30g), ammonium acetate (4g), industrial methylated spirits (100 ml) and concentrated ammonium hydroxide (500 ml) was boiled under reflux for 4h. The reaction mixture was cooled and the solid filtered off and washed with ether. 50% Aqueous sodium hydroxide solution (20.5 ml) was added to the filtrate and the resulting solution extracted with ether. The combined washings and ether extracts were evaporated under reduced pressure giving a yellow oil. The oil was acidifed with concentrated hydrochloric acid and the resulting mixture was then evaporated to dryness under reduced pressure yielding the dihydrochloride (63) 25.5g, 92%) m.p. 245° (lit.[53], m.p. 242 - 244°(decomp.)).

N-(Phenyl-2-pyridylmethyl) formamide (64)

A solution of the phenyl-2-pyridylmethylamine dihydrochloride (63) (45.5g) in formic acid (140 ml) was boiled under reflux for a period of 20h. Excess formic acid was removed under reduced pressure and the residue was basified with 10% aqueous sodium hydroxide solution. The liberated base (64) was extracted into ether (3 x 250 ml) and the combined ether extracts were dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure yielding a solid residue. Recrystallisation of the residue from ether gave the base (64) (21.1g, 56%) as yellow prisms, m.p. 75° (lit.[39], m.p. 75-76°).

1-Phenylimidazo[1,5-a] pyridine (44) was prepared by essentially the same procedure as that described by Glover and Vaughan[39].

A magnetically stirred solution of the substituted formamide (64) (21.1g), phosphorus oxychloride (40 ml) and benzene (80 ml) was boiled under reflux for a period of 20h. Excess phosphorus oxychloride and benzene were removed under reduced pressure, the residual oil was decomposed with ice water and the resulting mixture was basified with 25% aqueous sodium hydroxide solution. The reaction mixture was then extracted with ether, the combined ether extracts were dried over anhydrous sodium sulphate. Evaporation of the dried extract under reduced pressure followed by recrystallisation of the residue from ether gave base (44) (13.5g, 70%) as amber prisms m.p. 105 - 106° (lit.[39], m.p. 102°).

2-Amino-1-phenylimidazo[1,5-a] pyridinium salts (49)

2-Amino-1-phenylimidazo[1,5-a] pyridinium-p-tolylsulphonate (49; X = $C_7H_7SO_3$)

To a solution of 1-phenylimidazo[1,5-a] pyridine (44) (1.14g) in a minimum volume of methylene chloride, T.S.H. 5% W/V in methylene chloride (22 ml) was added in bulk and the resulting mixture was stirred for 0.5h. Ether was added to complete precipitation of the product. Recrystallisation of the precipitate from methanol-ether yielded the p-tolylsulphonate (49; X=$C_7H_7SO_3$) as a colourless crystalline solid (1.72g, 77%) m.p. 164°.
(Found: C, 62.2; H, 5.0; N, 10.5. $C_{20}H_{19}N_3O_3S$ requires, C, 62.9; H, 5.0; N, 11.0%).

2-Amino-1-phenylimidazo[1,5-a] pyridinium bromide (49; X = Br)

To a solution of 1-phenylimidazo[1,5-a] pyridine (44) (10g) in a minimum volume of methylene chloride, T.S.H. 5% W/V in methylene chloride (200 ml) was added in bulk and the resulting mixture was stirred for 1h. Ether was added to complete precipitation of the p-tolylsulphonate salt (49; X=$C_7H_7SO_3$), which was filtered off and converted to the bromide salt (49; X = Br) by dissolution in methanol (50 ml) and 48% hydrobromic acid (10 ml) followed by addition of ether until precipitation occurred. Recrystallisation of the precipitate from methanol-ether yielded the bromide (49; X = Br) as a colourless crystalline solid (10.9g, 73%) m.p. 217°.
(Found: C, 53.9; H. 4.5; N, 14.3. $C_{13}H_{12}BrN_3$ requires C, 53.8; H, 4.2; N., 14.5%)

1,2,2-Tribromo-1-phenyl-1,2-dihydroazeto[1,2-a] pyridinium salts (77)

1,2,2-Tribromo-1-phenyl-1,2-dihydroazeto[1,2-a] pyridinium bromide (77; X = Br)

To a solution of bromide (49; X = Br) (0.5g) in water (2 ml), saturated aqueous bromine (75 ml) was added in bulk. The reaction mixture was stirred for 1h after which the liquid was decanted from the red oil, which had separated. After washing the oil several times with water, the oil was dissolved in absolute acetone and the solution was boiled under reflux until precipitation of a white solid occurred. The solution was cooled and the precipitate was filtered off and recrystallised from methanol-ether yielding the bromide salt (77: X = Br) as a colourless crystalline solid (0.46g, 53%) m.p. 187 - 188°.

(Found: C, 31.4; H, 2.4; N, 2.8. $C_{13}H_9Br_4N$ requires, C, 31.3; H, 1.8; N, 2.8%)

1,2,2-Tribromo-1-phenyl-1,2-dihydroazeto[1,2-a] pyridinium perchlorate (77; X = ClO_4)

To a solution of the bromide salt (77; X = Br) (~0.1g) in methanol (10 ml) - 60% perchloric acid (~0.2 ml) ether was added until precipitation occurred. The precipitate was filtered off and recrystallised from methanol-ether yielding the perchlorate salt (77; X = ClO_4) as a colourless crystalline solid m.p. 177 - 178°.

(Found: C, 30.5; H, 2.1; N, 2.7. $C_{13}H_9Br_3ClNO_4$ requires, C, 30.1; H, 1.8; N, 2.7%)

N-Benzoyl-2-pyridylmethylamine (60) hydrochloride

Benzoylchloride (24.5 ml) was added in small quantities to a solution of 2-pyridylmethylamine (58) (10.3g) in methanol (57 ml) and 10% aqueous sodium hydroxide solution (285 ml), the reaction mixture being shaken vigorously for several minutes after each addition. The aqueous reaction mixture was extracted several times with ether. The combined ether extracts were evaporated under reduced pressure yielding a brown oil which was acidifed with concentrated hydrochloric acid. The acid mixture was evaporated to dryness under reduced pressure. Recrystallisation of the solid residue from ethanol yielded N-benzoyl-2-pyridylmethylamine (60) hydrochloride as colourless needles (23.5g, 94%) m.p. 188 - 189° (lit.[54], m.p. 189°).

3-Phenylimidazo[1,5-a] pyridine (45) was prepared by essentially the same procedure as that described by Bower and Ramage[38].

An aqueous solution of N-benzoyl-2-pyridylmethylamine (60) hydrochloride (23.5g) was basified with 10% aqueous sodium hydroxide solution and extracted with ether. The dried (calcium chloride) extract was evaporated under reduced pressure to give N-benzoyl-2-pyridylmethylamine (60). A magnetically stirred solution of base (60), phosphorus oxychloride (23 ml) and benzene (70 ml) was boiled under reflux for a period of 20h. Excess phosphorus oxychloride and benzene were removed under reduced pressure and the residual oil decomposed with ice water and the resulting mixture was basified with 25% aqueous sodium hydroxide solution. The reaction mixture was extracted with ether, the combined ether extracts being dried over anhydrous sodium sulphate. Evaporation of the dried extract under reduced pressure followed by recrystallisation of the

residue from ether gave base (45) as pale yellow prisms (11.0g, 51%) m.p. 109 - 110° (lit.[38], m.p. 109°, 61%).

2-Amino-3-phenylimidazo[1,5-a] pyridinium salts (50)

2-Amino-3-phenylimidazo[1,5-a] pyridinium-p-tolylsulphonate (50; X = $C_7H_7SO_3$)

To a solution of 3-phenylimidazo[1,5-a] pyridine (45) (5.2g) in a minimum volume of chloroform, T.S.H. 5% W/V in chloroform (104 ml) was added in bulk and the resulting mixture stirred for 1h. Ether was then added to complete the precipitation of the product which was filtered off and washed with ether (7.5g, 73%). Recrystallisation of the precipitate from methanol-ether yielded the p-tolylsulphonate salt (50; X = $C_7H_7SO_3$) as a colourless crystalline solid m.p. 139 - 140°.
(Found: C, 62.7; H. 5.1; N, 11.0. $C_{20}H_{19}N_3O_3S$ requires C, 63.0; H, 5.0; N, 11.0%).

2-Amino-3-phenylimidazo[1,5-a] pyridinium bromide (50; X = Br) was prepared by (i) dissolving the p-tolylsulphonate salt (50; X = $C_7H_7SO_3$) in ethanol - 48% hydrobromic acid and adding ether or (ii) conversion to bromide via ion exchange on (Amberlite IRA 400 (Br)).

(i) A solution of the p-tolylsulphonate salt (50; X = $C_7H_7SO_3$) (11.2g) in methanol (40 ml) - 48% hydrobromic acid (2.5 ml) was boiled under reflux for 4 - 5 minutes. The solution was cooled and ether added to complete precipitation of product which was filtered off and washed with ether. Recrystallisation of the precipitate from methanol-ether yielded the bromide salt (50; X = Br) as a colourless crystalline solid (4.1g, 48%) m.p. 204°.

(ii) A methanolic solution of the p-tolylsulphonate salt (50; X = $C_7H_7SO_3$) (0.5g) was eluted down an ionexchange column of Amberlite IRA400(Br). The volume of the methanolic solution obtained after elution was reduced by evaporation under reduced pressure Ether was added to completely precipitate a green solid which was filtered off and washed with ether. Recrystallisation of the precipitate from methanol-ether yielded the bromide salt (50; X = Br) as a colourless crystalline solid (0.26g, 69%) m.p. 208°.

(Found: C, 53.9; H, 4.2; N, 14.6. $C_{13}H_{12}BrN_3$ requires C, 53.8; H, 4.2; N, 14.5%)

1,1,2-Tribromo-2-phenyl-1,2-dihydroazeto[1,2-a] pyridinium bromide (78) was prepared from (i) p-tolylsulphonate (50; X = $C_7H_7SO_3$) and (ii) bromide (50; X = Br).

(i) To a solution of the p-tolylsulphonate (50; X = $C_7H_7SO_3$) (0.25g) in water (5 ml), saturated aqueous bromine (30 ml) was added in bulk. The reaction mixture was stirred for 0.5h after which the liquid was decanted from the red solid which had separated. After several washings with water the solid was dissolved in absolute acetone and the solution was boiled under reflux until the precipitation of a white solid occurred. The solution was cooled and the precipitate was filtered off and recrystallised from methanol-ether yielding the bromide salt (78) as a colourless crystalline solid (0.22g, 66%) m.p. 104°.

(Found: C, 31.5; H, 2.0; N, 2.5. $C_{13}H_9Br_4N$ requires C, 31.3; H, 1.8; N, 2.8%)

(ii) To a solution of the bromide salt (50; X = Br) (0.5g) in water (5 ml), saturated aqueous bromine (75 ml.) was added in bulk. The reaction mixture was stirred for 0.5h after which the liquid was decanted from the red oil which had separated. After several washings with water the oil was dissolved in absolute acetone and the solution boiled under reflux until a white solid precipitated. The solution was cooled and the precipitate was filtered off and recrystallised from methanol-ether giving the bromide salt (78) as a colourless crystalline solid (0.65g, 75%) m.p. 107 - 108°.
(Found: C, 31.4; H, 1.8; N, 2.7. $C_{13}H_9Br_4N$ requires, C, 31.3; H, 1.8; N, 2.8%).

2-Acetaminomethylpyridine (61) was prepared by essentially the same procedure as that described by Bower and Ramage[38].

A mixture of 2-pyridylmethylamine (58) (3.5g), acetic anhydride (5.9 ml) and glacial acetic acid (17.7 ml) were heated on a boiling water bath for 0.5h. Excess acetic acid and acetic anhydride were removed under reduced pressure. The residual oil was fractionally distilled yielding the base (61) as a pale yellow oil (3.4g, 70%) b.p. 130°/2 mm (lit.[38], b.p. 160-163°/5 mm).

3-Methylimidazo[1,5-a] pyridine (46) was prepared by essentially the same procedure as that described by Bower and Ramage[38].

2-Acetaminomethylpyridine (61) (14g), phosphorus oxychloride (16 ml) and benzene (48 ml) were boiled under reflux for 4h, the mixture being magnetically stirred. Excess phosphorus oxychloride and benzene were removed under reduced pressure, the residual oil being decomposed with ice water and

basified with 25% aqueous sodium hydroxide solution. The reaction mixture was extracted with chloroform, the combined chloroform extracts being dried over anhydrous sodium sulphate. Evaporation of the dried extract under reduced pressure followed by fractional distillation of the residual oil yielded the base (46) (8.6g, 70%) b.p. 110 - 114°/4.5 mm (lit.[38], b.p. 112 - 117°/4 mm, 62%).

2-Amino-3-methylimidazo[1,5-a] pyridinium bromide (51; X = Br)

To a solution of 3-methylimidazo[1,5-a] pyridine (46) (2g) in a minimum volume of chloroform, T.S.H. 5% W/V in chloroform (64 ml) was added in bulk and the resulting mixture stirred for 1h. Ether was added to complete the precipitation of the p-tolylsulphonate salt (51; X = $C_7H_7SO_3$), which after recrystallisation from methanol-ether had m.p. 165°. The p-tolylsulphonate (51; X = $C_7H_7SO_3$) was converted to the bromide salt (51; X = Br) by dissolution in ethanol (20 ml) - 48% hydrobromic acid (1 ml) followed by addition of ether until precipitation occurred. Recrystallisation of the precipitate from methanol-ether yielded the bromide salt (51; X = Br) (1.6g, 46%) m.p. 221°.

(Found: C, 41.8; H, 4.6; N, 18.2. $C_8H_{10}BrN_3$ requires C, 42.1; H, 4.4; N, 18.4%).

2-Amino-1-bromo-3-methylimidazo[1,5-a] pyridinium bromide (52; X=Br)

To a solution of bromide salt (51; X = Br) (1g) in water (4 ml), saturated aqueous bromine (100 ml) was added in bulk and the resulting mixture was stirred for 2 - 3 minutes. The solid which separated was filtered off and washed several times with water. The solid obtained was recrystallised from methanol and gave the bromide salt (52; X = Br) (0.32g, 23%)

m.p. 223°.

(Found: C, 31.7; H, 2.8; N, 13.9. $C_8H_9Br_2N_3$ requires C, 31.3; H, 3.0; N, 13.7%).

1-Bromo-3- methylimidazo[1,5-a] pyridine (47) hydrobromide

A solution of bromine (1.5 ml) in methanol (10 ml) was added dropwise to a stirred solution of 3-methylimidazo[1,5-a] pyridine (46) (1.67g) in methanol (10 ml). After the addition was complete the reaction mixture was stirred for a further 1h at room temperature. Ether was then added to precipitate the hydrobromide of the base (47). The hydrobromide of the base (47) was recrystallised from methanol-ether as pale yellow prisms (2.76g, 75%) m.p. 179° (decomp.).

(Found: C, 33.1; H, 3.2; N, 9.5. $C_8H_8Br_2N_2$ requires C, 32.9; H, 2.8; N, 9.6%).

1-Bromo-3-methylimidazo[1,5-a] pyridine (47)

The hydrobromide of base (47) (0.5g) was dissolved in water and basified with 25% aqueous sodium hydroxide solution. The aqueous solution was extracted with ether, the ether extract being dried over anhydrous sodium sulphate. The ether was removed under reduced pressure leaving a solid residue. Vacuum sublimation of the residue yielded the base (47) as a yellow crystalline solid (0.35g, 96%) m.p. 96°C.

(Found: C, 45.8; H, 3.4; N, 13.3. $C_8H_7BrN_2$ requires C, 45.5; H, 3.3; N, 13.3%).

2-Amino-1-bromo-3-methylimidazo[1,5-a] pyridinium bromide (52; X = Br)

The hydrobromide of base (47) (1.7g) was dissolved in water and basified with 25% aqueous sodium hydroxide solution. The aqueous solution was extracted with ether, the ether extract dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure leaving the yellow base (47). The base (47) was dissolved in chloroform (10 ml) and T.S.H. 5% W/V in chloroform (40 ml) added in bulk and the reaction mixture was stirred for 1h. Ether was added to completely precipitate the p-tolylsulphonate salt (52; X = $C_7H_7SO_3$) which after recrystallisation from methanol-ether had m.p. 216° decomp. The p-tolylsulphonate salt (52; X = $C_7H_7SO_3$) was converted to the bromide (52; X = Br) by dissolution in methanol (40 ml) - 48% hydrobromic acid (4 ml) followed by the addition of ether until precipitation occurred. Recrystallisation of the precipitate from methanol yielded the bromide salt (52; X = Br) (0.61g, 34%) m.p. 223°.

(Found: C, 31.5; H, 2.8; N, 13.6. $C_8H_9Br_2N_3$ requires C, 31.3; H, 3.0; N, 13.7%).

1,1,2-Tribromo-2-methyl-1,2-dihydroazeto[1,2-a] pyridinium bromide (79)

The bromide salt (52; X = Br) (0.2g) was dissolved in 50% aqueous methanol (5 ml) and saturated aqueous bromine (30 ml) was added in bulk. The reaction mixture was stirred for 0.5h. after which the liquid was decanted from the red oil which had separated. The oil was washed with water several times and then dissolved in absolute acetone and the solution was boiled under reflux until a white solid precipitated. Recrystallisation

of the solid from methanol-ether yielded the bromide (79) as a crystalline solid (0.05g, 17%) m.p. 142 - 143°.
(Found: C, 22.2; H, 1.8; N, 3.4. $C_8H_7Br_4N$ requires, C, 22.0; H, 1.6; N, 3.2%).

1-Nitroso-3-methylimidazo[1,5-a] pyridine (80)

Deamination of bromide (52; X = Br) treatment with nitrous acid followed by hypophosphorous acid resulted in simultaneous nitrosation to give base (80).

To an ice cold solution of bromide (52; X = Br), (0.2g) in concentrated hydrochloric acid (20 ml), an ice cold solution of saturated sodium nitrite (2 ml) was added over a period of ten minutes, the solution was stirred for a further 0.5h at room temperature. Hypophosphorous acid (3 ml) was added to the solution and the solution was stirred for a further 1h, and then chilled at 0° for 3h. The solution was then basified with 2M sodium hydroxide solution and then extracted with ether. The ether was removed from the dried (sodium sulphate) extract under reduced pressure, the residue obtained was recrystallised from ether yielding base (80) in poor yield m.p. 89°.
(Found: C, 59.4; H, 4.3; N, 26.3 . $C_8H_7N_3O$ requires C, 59.6; H, 4.4; N, 26.1%).

Phenyl-2-pyridylmethylketone (81) hydrobromide

The bromide salt (78) (0.5g) was dissolved in ethanol (75 ml) and 10% palladium-charcoal (0.15g) added to the solution. The mixture was hydrogenated at atmospheric pressure until the uptake of hydrogen ceased. The reaction mixture was then filtered and the solvent removed under reduced pressure. The residue was dissolved in water, basified with 2M sodium hydroxide solution and then ether extracted. The ether was removed from the dried (sodium sulphate) extract under reduced pressure and the residue obtained dissolved in ethanol (20 ml) - 48% HBr (0.5 ml), ether was added and the precipitate was filtered off. The precipitate was recrystallised from ethanol-ether yielding the hydrobromide salt (0.4g, 15%) m.p. 157 - 158°.

Phenyl-2-pyridylmethylketone (81) hydrobromide was prepared essentially by the same procedure as that described by Goldberg et al[55].

Phenyl lithium (0.105 mole) was prepared in absolute ether (125g) from lithium and bromobenzene. 2-Picoline (5g) was added to the phenyl lithium mixture over a period of ten minutes, the mixture then being boiled under reflux for 30 minutes. To the rapidly stirred solution, a solution of ethylbenzoate (4.3g) in absolute ether (25 ml) was added, over a 20 minute period so that the ether refluxed rapidly, the mixture was then boiled under reflux for 0.5h on a water bath. Water (25 ml) was added slowly and the resulting mixture poured on to 6N hydrochloric acid (25 ml) and crushed ice (100g). The ether phase was extracted several times with 6N hydrochloric acid. The combined acidic extracts were

treated with 20% aqueous sodium hydroxide solution until the solution remained slightly acidic, sodium bicarbonate was then added until the solution was basic.

The aqueous solution was extracted with ether, the combined ether extracts were dried over anhydrous sodium sulphate. Evaporation of the dried ether extract under reduced pressure yielded an oil which was fractionally distilled giving phenyl-2-pyridylmethylketone (81) b.p. 155 - 160°/3 mm (lit.[55], b.p. 145 - 153°/ 2 mm).

A small amount of phenyl-2-pyridylmethylketone (81) was dissolved in methanol (10 ml) - 48% hydrobromic acid (0.1 ml) and ether was added until precipitation occurred. The precipitate was recrystallised from methanol-ether yielding the hydrobromide of base (81) as a crystalline solid m.p. 157 - 158° (lit.[56], m.p. 156 - 157°).

Ethylacetimidate Hydrochloride was prepared according to the method described by McElvain and Nelson[57].

Dry hydrogen chloride was passed into an ice cold solution of dry methyl cyanide (20g) in absolute ethanol (22g) and absolute ether (20g) for a period of 4h. The solution was allowed to stand overnight at 0°. The reaction mixture was then cooled to -80° (in a liquid nitrogen bath) and then treated with ether until the product crystallised out as colourless prisms, which were filtered off and washed with ether (52g, 84%) m.p. 110° (lit.[58], m.p. 98 - 100° (decomp.)).

Ethylacetohydroxamate (73) was prepared according to the method described by Millen and Waters[59].

Ethylacetimidate hydrochloride (15g) was added in small portions to a stirred solution of potassium carbonate (34.5g) in water (75 ml) immersed in an ice bath. The mixture was stirred for a further 10 minutes and then extracted with ether (3 X 50 ml). The combined ether extracts were shaken with a solution of hydroxylamine hydrochloride (10.65g) in water (37.5 ml) for 5 minutes, and then the layers were separated. The aqueous phase was extracted again with ether (2 x 40 ml) and the combined ether phases were dried over anhydrous sodium sulphate. Evaporation of the dried ether extracts under reduced pressure gave ethylacetohydroxamate (73) as a colourless oil (8.2g, 66%) (lit.[60], m.p. 25 - 26°).

Ethyl-O-p-tolylsulphonylacetohydroxamate (74)

An ice cold solution of freshly prepared ethylacetohydroxamate (73) (8.2g) and triethylamine (8.2g) in dimethylformamide (55 ml) was treated with p-tolylsulphonylchloride (15.1g) over a period of 10 minutes. The resulting mixture was stirred at room temperature for a further 2h. The triethylamine hydrochloride, which had precipitated from the reaction mixture, was filtered off and washed with ether. Evaporation of the ether washings and the combined filtrate, under reduced pressure, followed by addition of the residual solution to ice cold water (500 ml) gave the hydroxamate (74) (12g, 58%) which crystallised from aqueous methanol as colourless prisms m.p. 70° (lit.[61], m.p. 69 - 71°).

O-p-tolylsulphonylhydroxylamine (75) was prepared according to the procedure described by Glover and Rowbottom[61].

A suspension of the hydroxamate (74) (2.0g) in 60% perchloric acid was stirred at room temperature when the hydroxamate dissolved and a colourless solid separated. The suspension was then poured on to crushed ice and the mixture extracted with methylene chloride. Evaporation of the dried (Na_2SO_4) extract gave the hydroxylamine (75) (1.05g, 74%), m.p. 39° (lit.[61], m.p. 40°, 76%).

The product was too unstable for recrystallisation but could be stored for about one week in chloroform or methylene chloride. On standing ammonium p-tolyl-sulphonate slowly precipitates.

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Action of Acids and Alkylating Agents on 1,4-Di-(2-pyridyl)tetraz-2-enes

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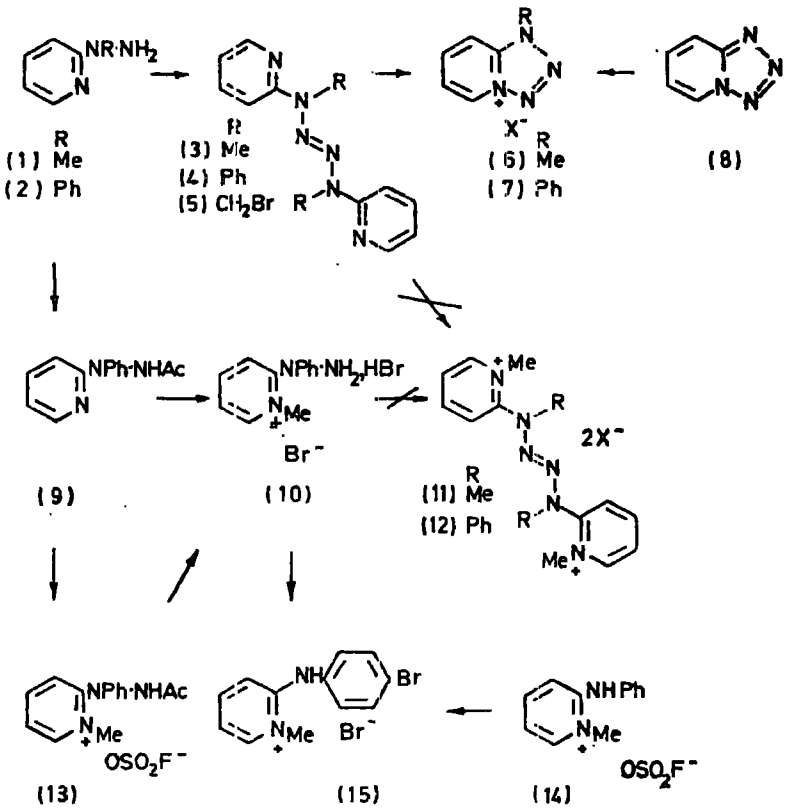

SCHEME 1

TABLE 3

Quaternary salts

Reactants	Product	X	Yield (%)	M.p. (°C)	Cryst. solvent	Found (%) C	Found (%) H	Found (%) N	Rqd. (%) C	Rqd. (%) H	Rqd. (%) N
(9) (0·2 g) + $MeOSO_2F$ [a]	(13)		80	143	MeOH–Et_2O	49·5	4·8	12·2	49·3	4·7	12·3
(13) (0·4 g) + 48% HBr (5 ml) [b]	(10)		28	172—174	EtOH–Et_2O	40·1	4·3	11·8	39·9	4·2	11·6
(9) (0·5 g) + MeI (3 ml) and MeOH (3 ml) [c]	(10)		26	172—174	EtOH–Et_2O						
2-Anilinopyridine (0·85 g) in $CHCl_3$ (10 ml) + $MeOSO_2F$ (0·57 g) [d]	(14)		82	155—156	EtOH	50·9	4·95	9·8	50·7	4·6	9·9
(4) (0·24 g) + MeI (3 ml) and MeCN (3 ml) [e]	(7)	I	38	216—217	$MeNO_2$	40·8	2·5	17·4	40·8	2·8	17·3
(4) (0·08 g) in EtOH (20 ml) and 48% HBr (0·2 ml) [f]	(7)	ClO_4 [g]	31	243—244	$MeNO_2$–Et_2O	44·0	3·3	18·7	44·5	3·1	18·9
	(7)	Br		234	$MeNO_2$–Et_2O	46·2	3·5	19·6	46·5	3·8	19·7 [h]
(3) (0·3 g) + MeI (3 ml) and MeOH (3 ml) [i]	(6)	I [j]	39 [k]	199	$MeNO_2$–Et_2O	27·6	2·95	21·2	27·5	2·7	21·4
(8) [l] (0·2 g) + MeI (2 ml) [i]	(6)	I [j]	60	200	MeOH–Et_2O	27·6	2·7	21·4	27·5	2·7	21·4
(3) (0·1 g) in EtOH (20 ml) and 48% HBr (0·07 ml) [m]	(6)	Br	84	234	MeOH–Et_2O	33·5	3·3	26·05	33·3	3·1	25·8

[a] The reaction mixture was maintained at 0 °C until all the solid had dissolved. Trituration then gave the fluorosulphate which was filtered off. [b] The solution was boiled under reflux for 1 h and evaporated to dryness under reduced pressure. The residue was then recrystallized. [c] The solution was boiled under reflux overnight and evaporated to dryness under reduced pressure. The residue was then boiled with 16% HBr (5 ml) for 5 min and again evaporated to dryness. The residue was then recrystallized. [d] Added dropwise to the stirred solution. The product separated and was filtered off. [e] The solution was boiled under reflux overnight and then cooled, and the product was filtered off. [f] The solution was boiled under reflux for 2·5 h and then evaporated to dryness under reduced pressure. Attempts to recrystallize the residue from nitromethane–ether gave a gum which was dissolved in chloroform (15 ml) and treated with 70% perchloric acid (3 drops). The chloroform was then evaporated off and the residue recrystallized first from ethanol–ether and then from nitromethane–ether. [g] Also obtained from the iodide by treatment with 70% perchloric acid. [h] For the hemihydrate. [i] The solution was boiled under reflux for 17 h and then cooled. Addition of ether precipitated the crude product which was filtered off. Evaporation of the filtrate and recrystallization of the residue from aqueous methanol gave the starting tetrazene (0·16 g). [j] The two samples were identical (i.r. spectra and mixed m.p.). [k] Before recrystallization and based on starting material consumed. [l] The reaction mixture was heated in a sealed tube at 100 °C for 20 h. The solution was then evaporated and the residue recrystallized. [m] The reaction mixture was boiled under reflux for 2 h. The solution was then cooled and ether added to incipient precipitation. The bromide which separated on cooling was filtered off and the filtrate evaporated to dryness. The residue was basified and extracted with ether. Evaporation of the dried extract and treatment of the residue with alcoholic picric acid gave 2-methylaminopyridine picrate, m.p. 189—190°, identical with an authentic sample.

[1] R. G. Fargher and R. Furness, *J. Chem. Soc.*, 1915, 688.