O'Keane, John (1971) *Oxidative coupling reactions of pyridine.* PhD thesis.

http://theses.gla.ac.uk/2109/

Copyright and moral rights for this thesis are retained by the author

A copy can be downloaded for personal non-commercial research or study, without prior permission or charge

This thesis cannot be reproduced or quoted extensively from without first obtaining permission in writing from the Author

The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the Author

When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given

Glasgow Theses Service
http://theses.gla.ac.uk/
theses@gla.ac.uk

OXIDATIVE COUPLING
REACTIONS OF PYRIDINE.

JOHN O'KEANE.

A Thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy of the University of Glasgow.

JULY 1971.

ACKNOWLEDGEMENT.

I would like to express my gratitude to my supervisor, Professor D.W.A. Sharp, for his guidance and encouragement during the course of my research project.

I also appreciate the advice of Dr. A.L. Porte on the treatment of the nuclear magnetic resonance spectra of pyridinium salts.

A Science Research Council (C.A.P.S.) award for the period October 1968 to October 1971 is gratefully acknowledged.

[redacted]

-CONTENTS-

GENERAL INTRODUCTION :

CHAPTER I :

(I) Oxidative coupling of pyridine by metal halides :

(II) Reactions of pyridine with transition metal halides.

CHAPTER II :

Reactions of N(4-pyridyl) pyridinium salts.

CHAPTER III:

^{1}H n.m.r. spectra of N(4-pyridyl) pyridinium salts.

CHAPTER IV :

(I) Thermal / Catalytic dehydrogenation of pyridine.

(II) Gas phase halogenation of pyridine.

ABSTRACT

The dimerisation of pyridine, to form 4,4'bipyridyl, has been investigated thoroughly and attempts have been made to prepare this dimer by several routes.

Since it was known that low oxidation state metal halides act as coupling agents in the formation of 2,2' bipyridyl, these particular reactions, and those of pyridine with high oxidation state halides, were studied with a view to finding a practicable route to 4,4'bipyridyl. It was found that, under the action of high oxidation state halides, pyridine is successfully coupled at elevated temperatures, forming 4,4'bipyridyl. The essential differences between 2,2' and 4,4' modes of coupling were investigated from a mechanistic viewpoint and it was found that the formation of 4,4'bipyridyl relied on the intermediate existence of N(4-pyridyl) pyridinium salts. No such salt was detected in the reactions of pyridine with low oxidation state halides and therein lies the reason for the different bipyridyl isomers produced by each type of halide.

The mechanism of conversion of N(4-pyridyl) pyridinium chloride to 4,4'bipyridyl was studied by deuterium labelling and a re-arrangement process, involving dissociation of the salt is proposed. It was also found in this study, that the reaction of 4-halopyridines with pyridine produced N(4-pyridyl) pyridinium halides or 4,4'bipyridyl depending on temperature. At temperatures in the vicinity of 80°C

the reaction produces the pyridyl pyridinium halides quantitatively, whereas considerable amounts of 4,4'bipyridyl result when temperature is raised to 180°C. Mechanistic details are proposed for these two processes.

Having established that the formation of N(4-pyridyl) pyridinium halides, and hence that of 4,4'bipyridyl, relies on the γ-halogenation of pyridine by high oxidation state halides, attempts were made to reproduce these conditions in a series of reactions directed at the gas phase halogenation of pyridine.

With chlorine, insignificant amounts of 4-halopyridines were observed. Other products included 2,2' bipyridyl, pyridine hydrochloride and several chloropyridines. These compounds are thought to arise from the pyrolysis of the chlorine / pyridine adduct $C_5H_5N.Cl_2$, which is formed initially in the reaction. When bromine was used, the degree of 4-halogenation occurring was slightly better than in the case of chlorine, but the process was still far from efficient. The bromopyridines identified were also thought to be derived from the molecular adduct $C_5H_5N.Br_2$

The ^1H n.m.r. spectra of N(4-pyridyl) pyridinium salts were studied by computer techniques. These compounds were shown to give rise to two independent contributions, one from each ring. The N(4-pyridyl) substituent was found to generate a spectrum of the B_2X_2 type while the spectrum of the pyridinium ring was analysed successfully

as an AB_2X_2 spin system. The spectra of other pyridinium compounds were recorded and the resonance frequencies found for the pyridyl pyridinium salts correlated with these and published spectra.

GENERAL INTRODUCTION

Bipyridyl synthesis by conventional organic routes.

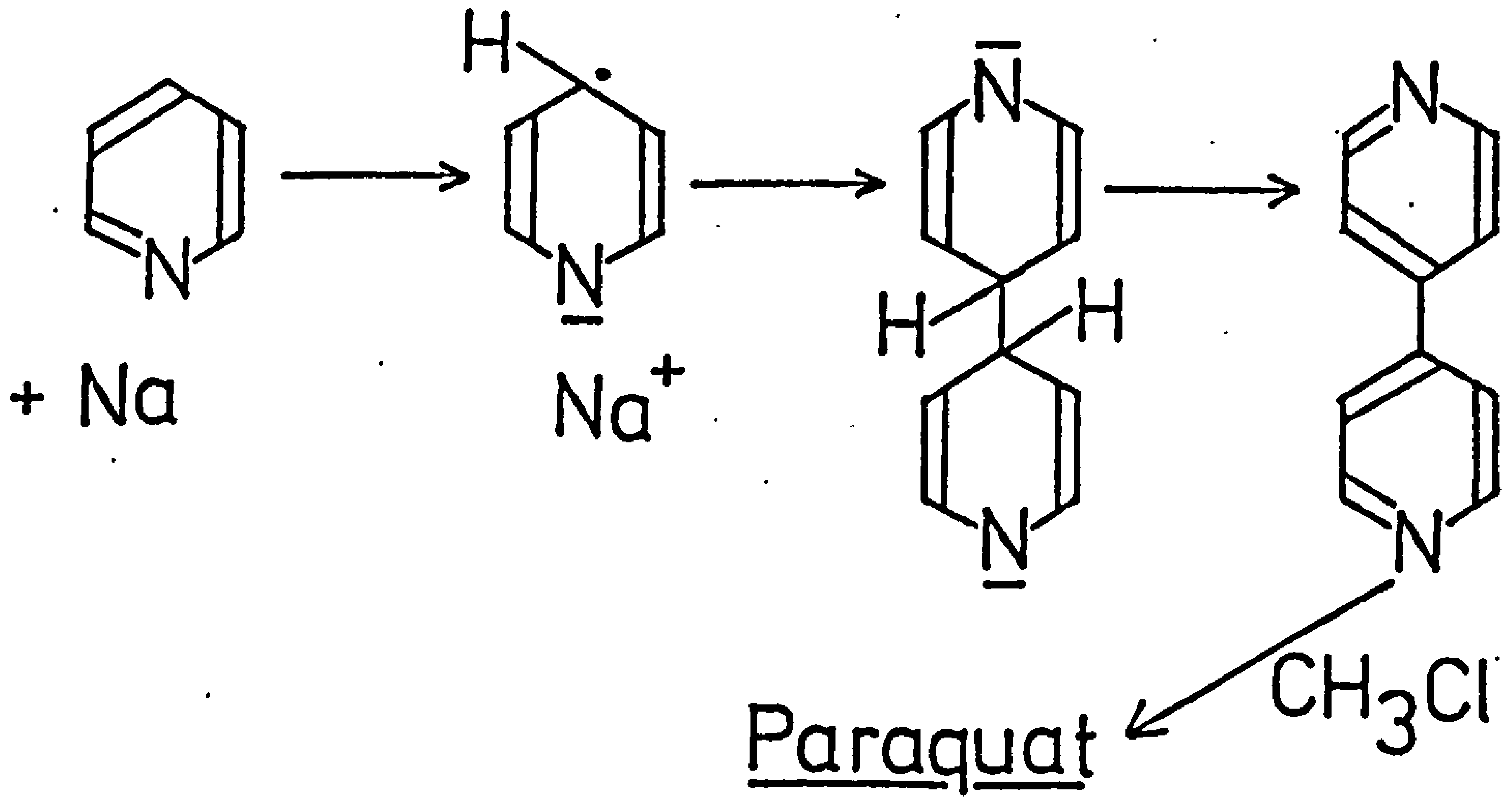
GENERAL INTRODUCTION.

Ever since the first reported synthesis of a bipyridyl in 1888 by Blau (1), there has been considerable interest in these compounds, particularly with regard to transition metal chemistry where they have been used extensively as chelating ligands. Of all the bipyridyls, the 2,2' isomer has probably received most attention in this respect (2,3,4). The need for bipyridyls therefore grew rapidly as the volume of work in this field expanded and consequently, suitable syntheses were sought.

In more recent years the success of non-selective herbicides, based on bipyridylium ions, has also added to the demand for simple, efficient routes to bipyridyls. The present work was undertaken with this in mind.

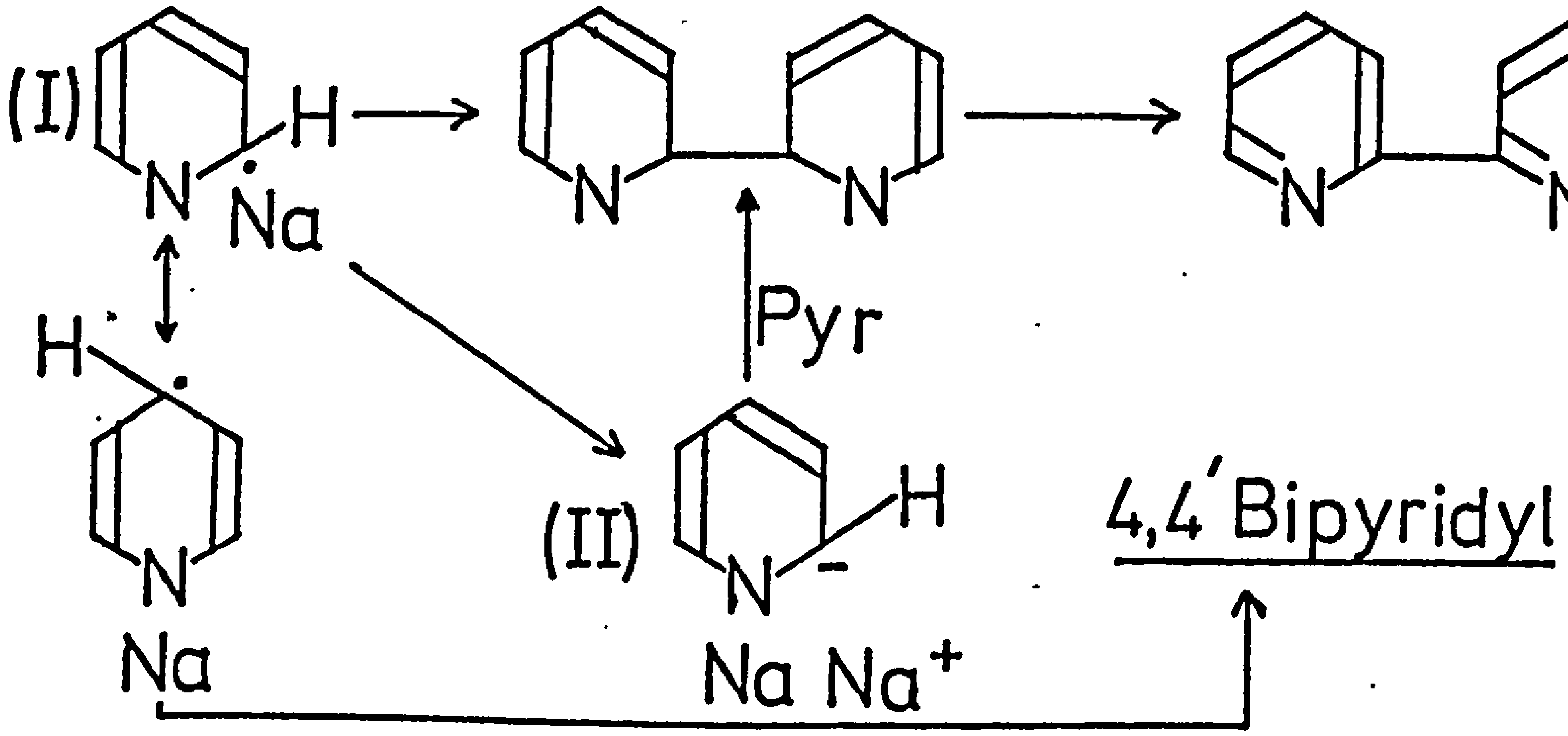
1,1'dimethyl 4,4'bipyridylium ion, Paraquat, has been shown to be a most effective herbicide. It will kill all green tissue to which it is applied and is rendered inactive, almost instantaneously, by the soil; its high activity means that relatively small amounts are required in any practical usage. By employing Paraquat in weed control, the need for mechanical ploughing no longer exists, thus obviating problems of soil erosion in certain parts of the world. It is now believed that Paraquat acts by what is really a catalytic process, by the normal photosynthetic pathway, producing concentrations of hydrogen peroxide too high for disposal by the plant. This arises from the reduction of Paraquat in the presence of oxygen and light, which results in a Paraquat free radical. Subsequent oxidation of the radical is accompanied by the formation of hydrogen peroxide.

Of the existing routes to 4,4'bipyridyl, that involving the reaction of pyridine with sodium and liquid ammonia, or simply sodamide, provides the most direct approach (5,6).



In both cases 4,4'bipyridyl is the only pyridine dimer isolated. By-products include 2-amino and 4- amino pyridines as well as the unreacted base.

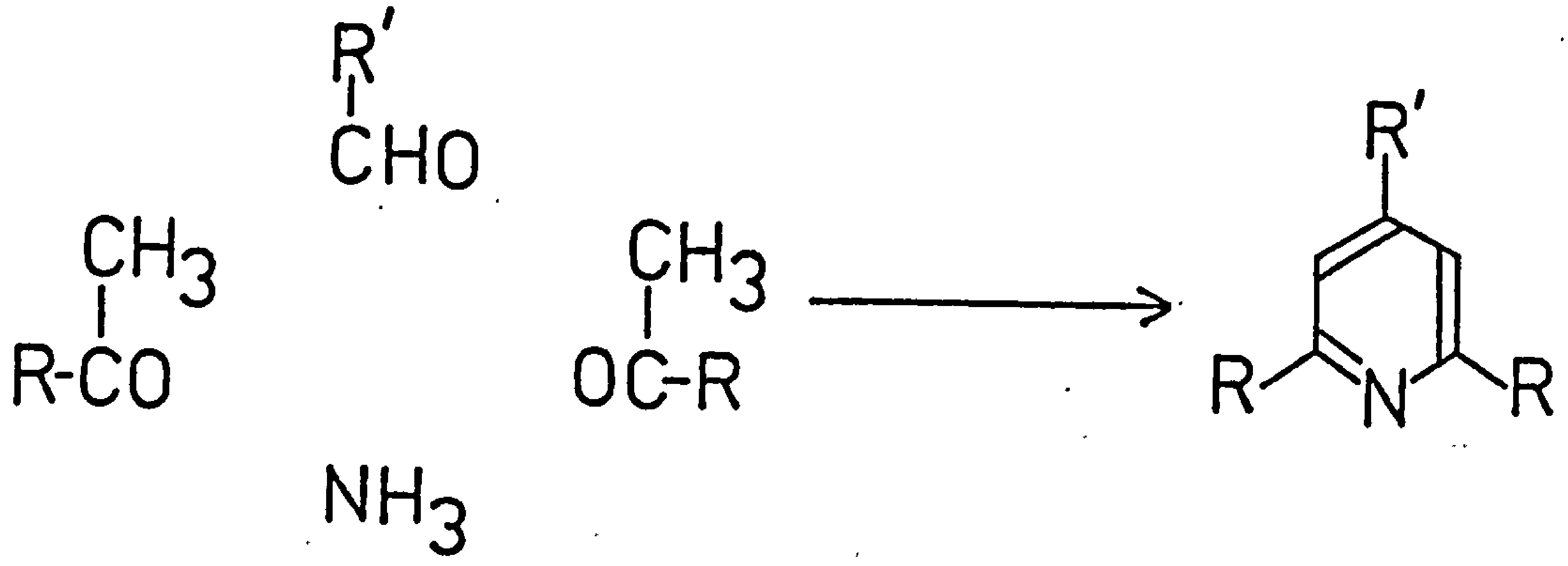
If sodium and dry pyridine are allowed to react at room temperature and the reaction mixture decomposed by water, 2,2' and 4,4'bipyridyls result (7). Apparently these are formed either by the coupling of two monosodium adducts (I) of pyridine or by the addition of a di-sodium (II) adduct to free pyridine. The latter process is similar to the reaction of other organometallic compounds with pyridine. However, the addition of organometallics yields mainly the 2-substituted pyridine. In this case, the major product is 4,4'bipyridyl.



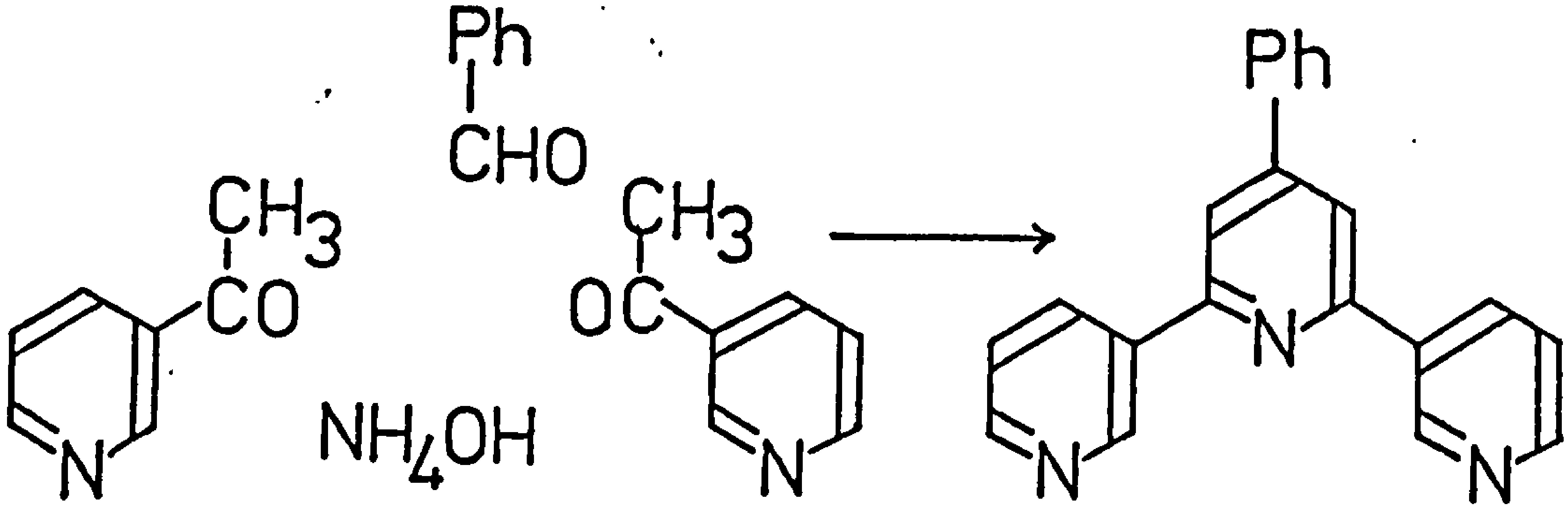
If the monosodium adduct has all seven unshared electrons in π-orbitals, coupling would be possible at both 2 and 4 positions but would be more rapid at the relatively unhindered position 4.

The fact that bipyridyls joined at position 3 can be isolated from the reaction at 100°C indicates that, with sufficient energy, sodium can bond to carbon rather than nitrogen.

Tschichibabin syntheses of pyridines can be regarded as Aldol condensations, generally in conjunction with Michael type reactions, of aldehydes, ketones, $\alpha\beta$ unsaturated carbonyls, or various derivatives of such compounds, followed by a ring closure reaction involving ammonia. In its simplest form, the sequence can be represented as follows :



It has been shown that this synthesis can be adapted to produce bipyridyl derivatives by using pyridyl aldehydes and ketones as starting compounds rather than the normal alkyl or aryl carbonyls (8-11). A series of poly-pyridines and aryl poly-pyridines has been prepared by this method. An example of this approach, from published results (8), is shown below :



The Dimroth reaction, normally used to prepare 4-alkyl and 4-acyl pyridines (12,13), can be modified to produce 4,4'bipyridyl (14,15). The process involves the reaction of an acid halide or anhydride with pyridine, in the presence of zinc dust. By stopping the reaction after the first stage, and oxidising the intermediate product, a 1,1',4,4' tetrahydro 4,4'bipyridyl can be isolated.

Pyrolysis of 2-halopyridines in the presence of copper dust (Ullman reaction) can lead to the formation of 2,2'bipyridyl. It has been shown (16,17), that bromopyridines are much more amenable than either iodo- or chloropyridines are to this treatment. Unfortunately, 4-halopyridines do not produce 4,4'bipyridyl under the same conditions.

Phenanthrolines, by removal of the C_2 bridge between the outer phenyl rings, will yield bipyridyls (18). Naturally, the structure of the resultant bipyridyl is determined by the carbon skeleton of the initial phenanthroline. Hence, the structure of 2,3'bipyridyl was established by oxidising 1,7 phenanthroline in the above manner (19). Pyrolysis of the alkaloid anabasine also yields 2,3'bipyridyl (20).

Most promising of the existing routes to bipyridyls appeared to be those involving dehydrogenation of pyridine. Hein and Retter (21) showed that the action of anhydrous ferric chloride on pyridine, at temperatures in excess of 300°C, afforded 2,2'bipyridyl in about 50% yield. This line was pursued by Morgan and Burstall (22) who reported that this reaction produced all possible bipyridyls with the exception of the 4,4' isomer. They also detected varying amounts of alkyl-pyridines, amino-pyridines and terpyridyls - an indication of the severity of the reaction conditions. Iodine and nickel catalysts have been used to great effect in the dehydrogenation of pyridine, again generating 2,2'bipyridyl in reasonable yields. Case (16) has extended this method to picolines, the degree of conversion to bipyridyl being smaller than for pyridine itself. By reacting β and γ picolines with ferric chloride, he showed that the products were respectively 5,5'dimethyl 2,2'bipyridyl and 4,4'dimethyl 2,2'bipyridyl.

CHAPTER I

(I) Oxidative coupling of pyridine by metal halides

(II) Reactions of pyridine with transition metal halides

Oxidative coupling of pyridine by metal halides

INTRODUCTION

After the initial work of Hein and Retter (24) and Morgan and Burstall (25), the level of interest in the reactions of pyridine with metal halides fell off to almost nil. They had demonstrated a facile dimerisation of pyridine under the action of anhydrous ferric chloride and Morgan and Burstall investigated the product mixture rather more thoroughly. Although no mechanistic conclusions were drawn or implied by either group, the original efforts of these workers were pursued only after a further 25 years.

At this point, largely due to the development of bipyridylium herbicides, fresh interest arose in this approach to pyridine dimerisation. Indeed, a rather extensive survey of metal halide coupling agents was reported (26), in which those of ferrous and ferric iron, zinc, copper, cobalt and nickel were shown to be suitable agents in the 2,2' coupling of pyridine. It was also noted that the pyrolysis of pyridinium salts and their mixtures with pyridine resulted in the formation of reasonable amounts of 2,2' bipyridyl.

In a similar fashion, it has been shown that the action of an alkaline solution of potassium persulphate on pyridine would produce 2,2'bipyridyl in about 50% yield (27). Subsequent work (28) has indicated that an enormous range of low oxidation state metal halides are capable of coupling pyridine by an oxidative process. The noble metals of Group VIII were shown to be especially suitable in this respect in the form of their halides, nitrates, sulphates, acetates and as complex salts. Apart from the work of Morgan and Burstall (22), there have been no reports of any side reactions or by-products, but it seems likely that this type of reaction is more complex than a simple dehydrogenation or dimerisation. It is noteworthy that in none of these reports is there any evidence for the formation of 4,4' bipyridyl. In contrast, 2,2'bipyridyl appears to be formed with remarkable ease under almost any conditions and indeed, as has been mentioned, can be produced merely by heating pyridine in a quartz tube (29).

It has been suggested (30) that the function of the metal halide in the formation of 2,2'bipyridyl is to complex the products of pyridine dimerisation, thereby preventing such products from taking part in any further reaction. Although the exact mechanism of 2,2' coupling is not yet clear, it is probably relevant to note that despite the fact that oxidation of pyridine does occur, none of the halides used are recognised as oxidising agents of any great strength. It is possible that the metal halides effect coupling by an initial step of nuclear chlorination. Both ferric chloride and antimony pentachloride have been studied in their halogenation ability towards benzene (31), halobenzenes (32) and alkyl benzenes (33) and an electrophilic mechanism is suspected (34). In a similar manner, electrophilic chlorination of coordinated pyridine by a metal halide would generate the 2-halo-pyridine more readily than any other isomer due to the proximity of the α-position of the ring to the chlorinating species. Subsequent thermal dimerisation of the chloropyridine (Ullman Reaction) would result in the formation of 2,2'bipyridyl. A mechanism of this type could therefore readily explain the preponderance of this particular isomer in the product mixtures.

A survey of higher oxidation state halides was undertaken in order to compare their action on pyridine with that of lower halides. In particular, the nature of the bipyridyls generated by these reactions was studied in order to understand the formation of pyridine dimers under such conditions.

EXPERIMENTAL

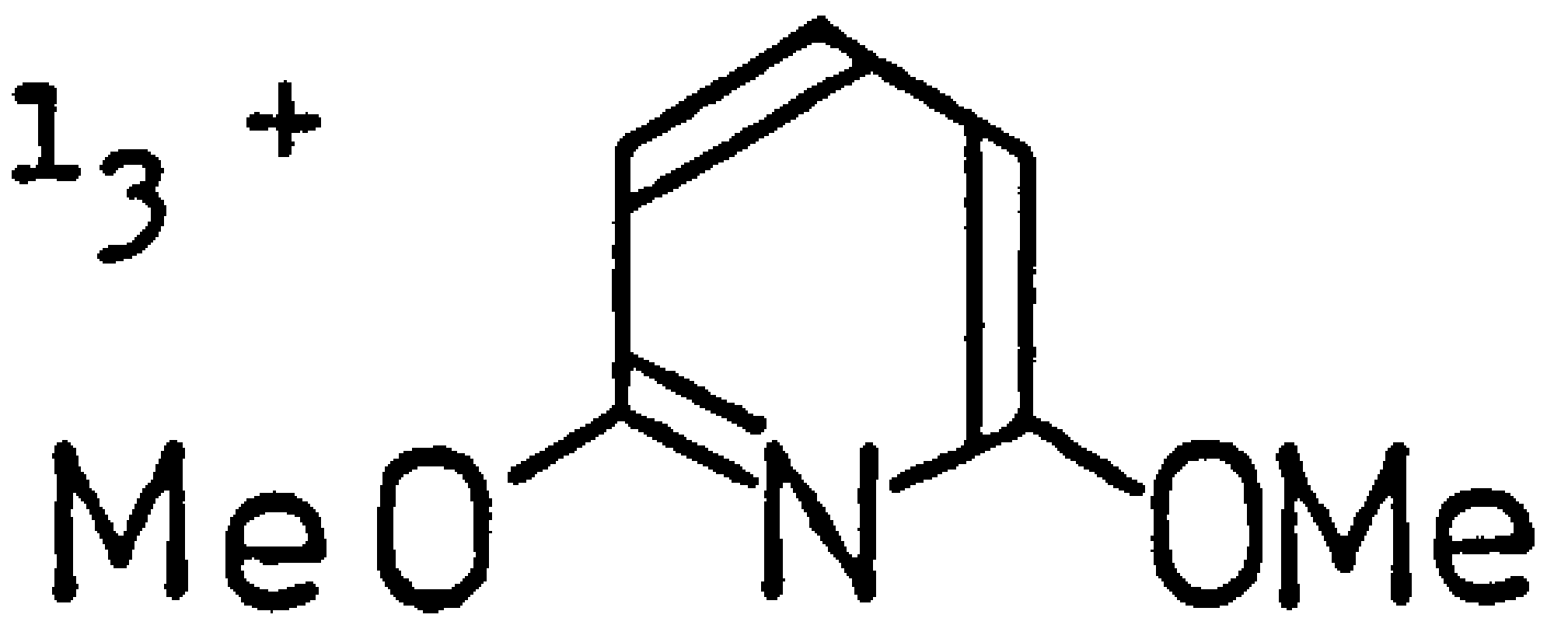
In all reactions, dry, degassed pyridine was added to high purity metal halides by vacuum distillation. All reactions were conducted in silica glass Carius tubes (8" × 1") which had been previously filled under anhydrous conditions, out-gassed and sealed. After heating for the required period of time, the tube was allowed to cool, and the contents washed out with aqueous sodium hydroxide (10mls , 4M) and diluted with water (30 mls). Extraction into hydrocarbon solvents, notably benzene and toluene, isolated the requisite fraction which was analysed for bipyridyls on a Perkin-Elmer F.11 Gas Chromatograph. Separation of the isomers was achieved on a stainless steel column (1m. × 2mm.), at 180°C with nitrogen as the carrier gas. The stationary phase comprised 5% sodium dodecyl benzene sulphonate on 72 - 85 mesh Celite, treated with 10% aqueous potassium hydroxide.

For the purposes of quantitative work, the column was calibrated against an internal standard of 5,6 benzoquinoline. Small amounts of the bipyridyl isomers (20 - 65 mgs) were weighed into a dry volumetric flask (10 mls). A 1% solution of 5,6 benzoquinoline was added (9.5 mls) and the volume made up to 10 mls with more Analar methanol. A 1 microlitre sample of this solution was analysed on the chromatograph and the percentage peak height ratio calculated for each bipyridyl over a range of concentrations.

i.e. $\%\ \text{peak height ratio} = \frac{\text{Peak height of bipyridyl}}{\text{'' \quad '' \quad '' \quad ''}} \times 100$

A calibration graph was then prepared by plotting the peak height ratio against the concentration of the bipyridyls (mgs / 10 mls). Consequently, a direct estimate of the amount of each isomer present in any sample was then possible merely by measuring its g.l.c. peak height.

The results of the survey of higher oxidation state metal halides are presented in tabular form and the bipyridyl products identified. Where significant, the yield of 4,4' bipyridyl is added in parenthesis. This figure is based on the total amount of pyridine included in the reaction mixture. Trace amounts of 4,4'bipyridyl are also denoted by parenthesis, placed around the isomer itself.

Reactants		Temp. (°C)	Time (hours)	Bipyridyls		
Pyr : PyrHCl : $FeCl_3$						
5 : 1 : 1		320	6	2,2',	2,3',	3,3'
9 : 1 : 1		"	"	"	"	"
15 : 1 : 1		"	"	"	"	"
24 : 1 : 1		"	"	"	"	-
Pyr : PyrHCl : $FeCl_2$						
5 : 5 : 1		"	"	"	"	
$FeCl_2Py_2$	(35)	"	"	"	"	
$FeCl_2Py_4$	(36)	"	"	"	"	
$FeCl_3Py_{3/2}$	(37)	"	"	"	"	
$FeCl_3$ + 		"	"	No bipyridyls		

Reactants	Temp. (^{o}C)	Time (hours)	Bipyridyls
Pyridine alone	320	6	2,2', 2,3', (4,4'), 3,3'
Pyr + sand	320	20	2,2', 2,3', 3,3'
Pyr + carbon	"	"	2,2', 2,3', 3,3'
Pyr + Al_2O_3	"	"	2,2', 2,3',
Pyr + WCl_6 + O_2	290	10	2,2', 4,4' (1.6%)
Pyr : WCl_6			
10 : 1	"	"	4,4' (3.2%)
12 : 1	"	"	4,4' (3.0%)
15 : 1	"	"	4,4' (2.5%)
Pyr + $WOCl_4$	300	8	2,2' (trace)
Pyr : $NbCl_5$			
10 : 1	290	10	2,2', 2,4', 4,4' (1.8%)
12 : 1	"	"	2,2', 2,4', 4,4' (1.5%)
15 : 1	"	"	2,2', 2,4', 4,4' (1.4%)
Pyr + PyrHCl + $NbCl_5$	290	20	2,2'
PyrHCl + $NbCl_5$	"	"	2,2'
Pyr + $TiCl_4$	290	15	2,2'
Pyr + PyrHCl + $TiCl_4$	"	"	2,2'
Pyr + PyrHCl + $TaCl_5$	"	"	2,2', 2,4'
Pyr : $TaCl_5$			
15 : 1	"	"	2,2', 2,4', (4,4')
10 : 1	"	"	2,2', 2,4', 4,4'(0.5%)
Pyr : UCl_6			
10 : 1	290	10	2,2', 2,4', (4,4')

Reactants	Temp. (^{o}C)	Time (hours)	Bipyridyls
Pyr : $MoCl_5$			
5 : 1	200	24	4,4' (1%)
7 : 1	"	"	4,4' (2.5%)
10 : 1	290	16	4,4' (3.2%)
15 : 1	"	"	4,4' (3.5%)
15 : 1	290	10	4,4' (3.0%)
Pyr + WCl_5 (39)	200	24	4,4' (2.5%)
WCl_4Py_2 (40)	300	10	2,2', 2,3', 3,3'
4-OH Pyr + Pyr	"	"	No bipyridyls
N(4-pyridyl) pyridinium chloride (PPC)	180	4	4,4' (6.0%)
PPC + Pyr	"	"	4,4' (10.%)
N(methyl) pyridinium chloride	"	"	No bipyridyls

As can be seen from the Table, the most effective 4,4' coupling agents were $MoCl_5$ and WCl_6 which gave the 4,4' isomer as the sole product. In the cases where no trace of this isomer could be found, 2,2' bipyridyl was by far the major product, appearing in about 20% yield in most of these reactions. Titanium tetrachloride appeared to be eminently suited to this, producing 2,2'bipyridyl in roughly 30% yield. In contrast, where 4,4' coupling does occur, the extent of 2,2' formation is reduced markedly and, in fact, falls to zero in the cases of $MoCl_5$ and WCl_6 when air is completely excluded. The cases of $NbCl_5$ and $TaCl_5$ are rather more complex and will be treated in full at a later point. Pyrolysis of metal halide complexes of pyridine proved to be totally unsuccessful in producing bipyridyls, but it does appear that the reaction of pyridine with high oxidation state halides provides a route to 4,4'bipyridyl at elevated temperatures.

A discussion of these findings would be rather fruitless at this point and will therefore be held over for correlation with the results of the ensuing section

Reactions of pyridine with transition metal halides

INTRODUCTION

Pyridine is known to coordinate to a wide range of transition metals and in this respect has been investigated rather extensively (41). However, the focus of this work has generally been the metal / pyridine complex and few efforts have been made to discover the nature of any by-products or side reactions. This particular feature is of cardinal importance when discussing the reactions of amines with high oxidation state halides, since the process generally involves some degree of reduction of the metal and corresponding oxidation of the amine. This effect is not limited to pyridine but has been observed in the reaction of trimethylamine with titanium tetrachloride (42), where reduction of Ti^{IV} to Ti^{III} accounted for 10% of the products. Pyridine was also shown to reduce Ti^{IV} halides. The reduction of various metals by ammonia and amines has been widely reported (43, 44, 45) but the oxidation products of such reactions were not positively characterised.

Generally, the metal must be in the maximum valence state consistent with the stability of the halide before reduction will take place. If the amine has an available hydrogen (i.e. primary or secondary) then the metal - halogen bond may be broken by solvolysis of the type :

$$MX_n.NHR_2 + NHR_2 \longrightarrow MX_{(n-1)}.NR_2 + \overset{+}{N}H_2R_2.\overset{-}{X}$$

In comparison, the absence of an acidic hydrogen, as with pyridine and other tertiary amines, leads to cleavage of the metal halogen bond by reduction :

$$MX_n.NR_3 \longrightarrow MX_{(n-1)}NR_3 + X^- \qquad \text{etc.}$$

This hypothesis is borne out by experiment since it is found that only tertiary amines react by reduction whereas primary and secondary amines do so by solvolysis.

The reduction of WCl_6 by pyridine has been investigate thoroughly by McCarley and Brown and the results correlated with those of the analogous reactions of the Nb^V halides (47). The stoichiometry of the former was shown to be :

$$WCl_6 + 5Py \longrightarrow WCl_4Py_2 + \overset{+}{Py}Py\overset{-}{Cl} + PyHCl$$

the oxidation product, N(4-pyridyl) pyridinium chloride, being characterised by its ultraviolet spectrum. By similar methods (weight gain), the stoichiometry of the reactions of the Nb^V halides with pyridine was also determined and the N(4-pyridyl) pyridinium ion again detected. In this case, reduction to Nb^{IV} was not complete and significant amounts of the 1 : 1 adducts NbX_5Py (X = Cl, Br) were observed.

In contrast, the reaction of pyridine with lower oxidation state halides does not lead to reduction of the metal but results in the formation of halide / pyridine adducts of varying compositions. Indeed, tetrachlorobis-pyridine tungsten^{IV}, formed by the reaction of pyridine with WCl_6, can be recovered easily from a mixture of pyridine and tungsten^{IV} chloride. Such examples are well known and widely documented for such metals as Mn^{II}, Fe^{II}, Co^{II}, Ni^{II},

Cu^{II} and Zn^{II} (41).

In summary, it is to be noted that the reaction of pyridine with high oxidation state metal halides results not only in reduction of the metal, but also in the formation of a distinct pyridine oxidation product. The analogous reactions of lower halides yield only adducts. With this essential distinction in mind, the reactions of pyridine with several high oxidation state halides were examined more closely as possible starting points in the oxidative coupling of pyridine to 4,4'bipyridyl.

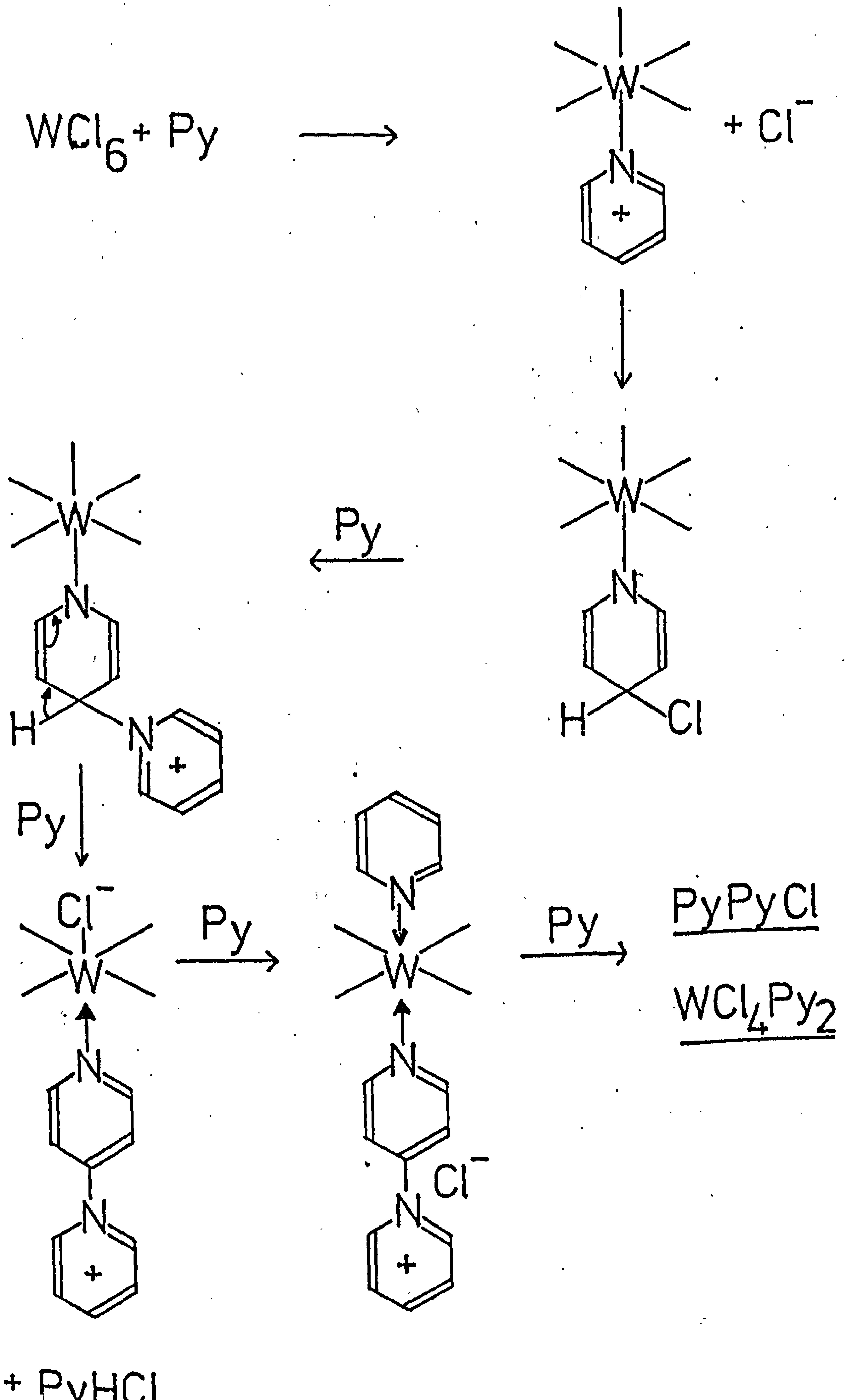
DISCUSSION

As was suggested earlier, the reactions of pyridine with metal halides are of two types, the distinction relying on the oxidation state of the metal. From an extensive survey of the transition series, it appeared that those metals in a high oxidation state produced significant amounts of 4,4' bipyridyl on heating with pyridine. In contrast, 2,2', 2,3' and 3,3'bipyridyls were the usual pyridine dimers produced by lower oxidation state halides. Additionally, it was observed that, in the presence of inert additives (sand, Al_2O_3, carbon), pyrolysis of pyridine again resulted in 2,2', 2,3' and 3,3'bipyridyls. It is proposed that the mechanism of dimerisation operating in these latter cases is one involving the thermal coupling of adsorbed pyridine-like species. It is conceivable that these species may be of a free radical nature. With high oxidation state halides, a definite reduction of the metal occurs on reaction with pyridine at room temperature. Pyridine is oxidised by a two electron process thereby affording N(4-pyridyl) pyridinium salts. This has been demonstrated conclusively for WCl_6 and $MoCl_5$ and implied for WCl_5, UCl_6 and $NbCl_5$.

N(4-pyridyl) pyridinium chloride was successfully isolated from the product mixture after the reaction of pyridine with WCl_6 at room temperature. Bearing in mind that these two reactants generate 4,4'bipyridyl when heated strongly in a Carius tube, the individual products of the reaction at room temperature were investigated in order to ascertain the source of the 4,4' dimer. Neither WCl_4Py_2 nor pyridine hydrochloride produced 4,4'bipyridyl but resulted in the formation of a mixture of 2,2', 2,3' and 3,3' isomers. By heating N(4-pyridyl) pyridinium chloride however, 6% conversion to the 4,4' product was observed. The pyridyl pyridinium salt was therefore judged to be the origin of 4,4'bipyridyl. The room temperature reaction of pyridine with WCl_6 produced 24% N(4-pyridyl) pyridinium chloride , by weight (from the stoichiometry) : reaction of N(4-pyridyl) pyridinium chloride with pyridine in a Carius tube resulted in a 10% yield of 4,4'bipyridyl. By combining these figures, one can predict that the reaction of WCl_6 and pyridine in a Carius tube will yield 2.4% of 4,4'bipyridyl as the only pyridine dimer.

The oxidation of pyridine by WCl_6 at room temperature can be represented by the mechanism shown overleaf. Chlorination of the coordinated pyridinium ring is proposed, the nucleophilic species being a chloride ion already displaced by the affixation and subsequent oxidation of pyridine. This step results in a 4-chloro-dihydropyridine which is susceptible to attack by the nitrogen atom of a free pyridine whereas the original coordinated pyridinium species is not. This hypothesis is borne out by the fact that the reaction of pyridine with N(methyl) pyridinium chloride does not produce either a pyridyl pyridinium salt or 4,4' bipyridyl.

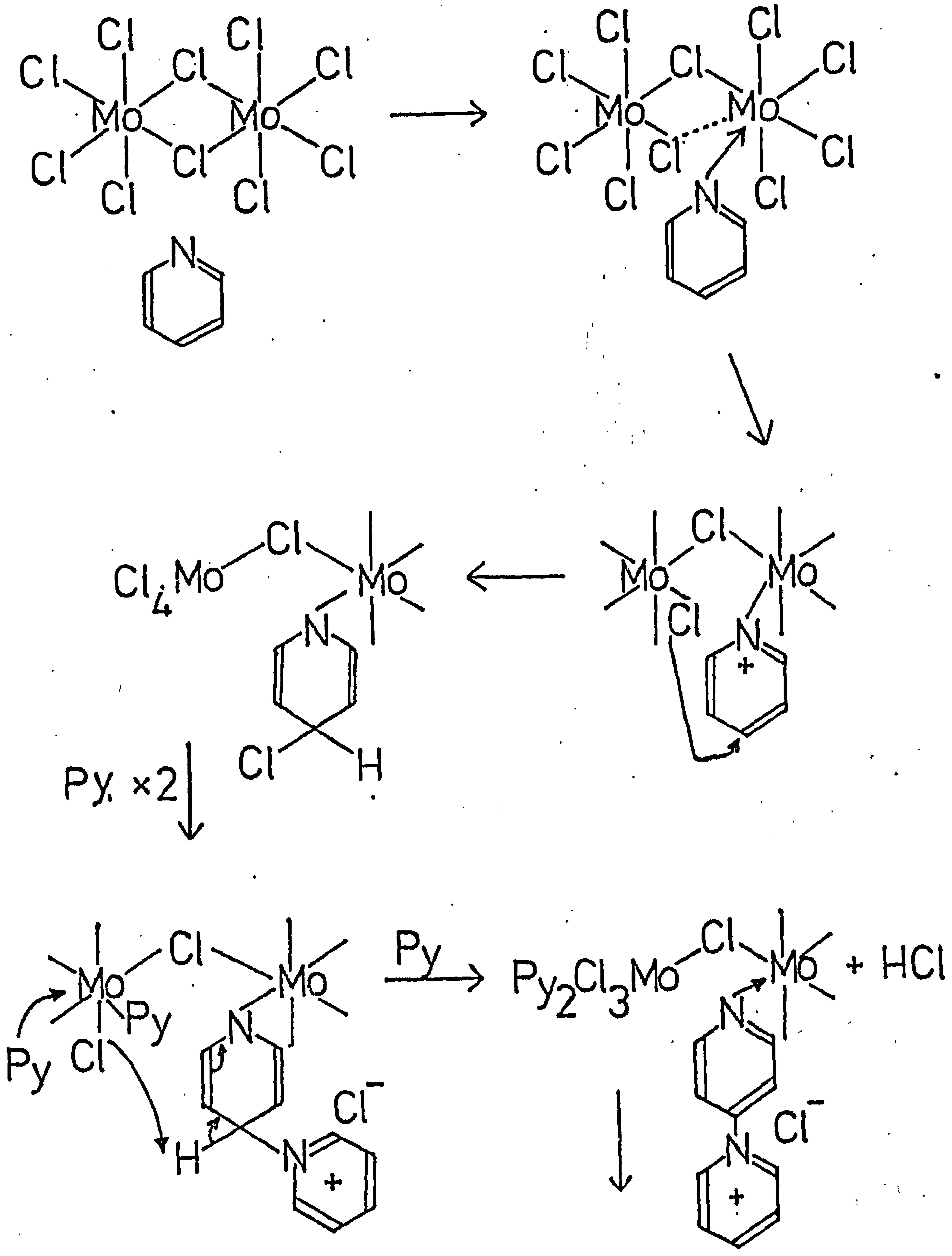
$$WCl_6 + 5Py \longrightarrow WCl_4Py_2 + PyPyCl + PyHCl$$



A similar mechanism can be proposed to satisfy the observed products and stoichiometry in the reaction of pyridine with $MoCl_5$ and is outlined on the following page. Again, chlorination of a coordinated pyridinium species is envisaged. The initial step in the sequence involves the the coordination of pyridine at a molybdenum atom which subsequently cleaves one of the Mo - Cl - Mo bridges. Thereafter the reaction pathway is entirely similar to that proposed for WCl_6.

Reaction of pyridine with $NbCl_5$, $TaCl_5$ and UCl_6 produces a mixture of 2,2', 2,3' and 3,3'bipyridyls. McCarley (47) has already demonstrated the partial reduction of $NbCl_5$ by pyridine at room temperature and has shown that no reduction at all occurs with $TaCl_5$, the adduct $TaCl_5$.Py being the sole product. In a manner similar to that described for WCl_6 and $MoCl_5$, it is thought that the presence of 4,4' bipyridyl after heating the niobium, tantalum and uranium halides with pyridine is due to formation of amounts of an N(4-pyridyl) pyridinium salt. This has been shown to occur at room temperature for $NbCl_5$ and it is thought that, on heating, some degree of reduction of Ta^{V} to Ta^{IV} does occur, thereby generating the intermediate compound N(4-pyridyl) pyridinium chloride. It is further suggested that the existence of amounts of unreduced metal in the form of the adducts MCl_5.Py (M = Nb, Ta), contributes to the formation of 2,2'bipyridyl. This feature will be discussed

$$2MoCl_5 + 9Py. \longrightarrow 2MoCl_4Py_3 + PyPyCl + PyHCl$$

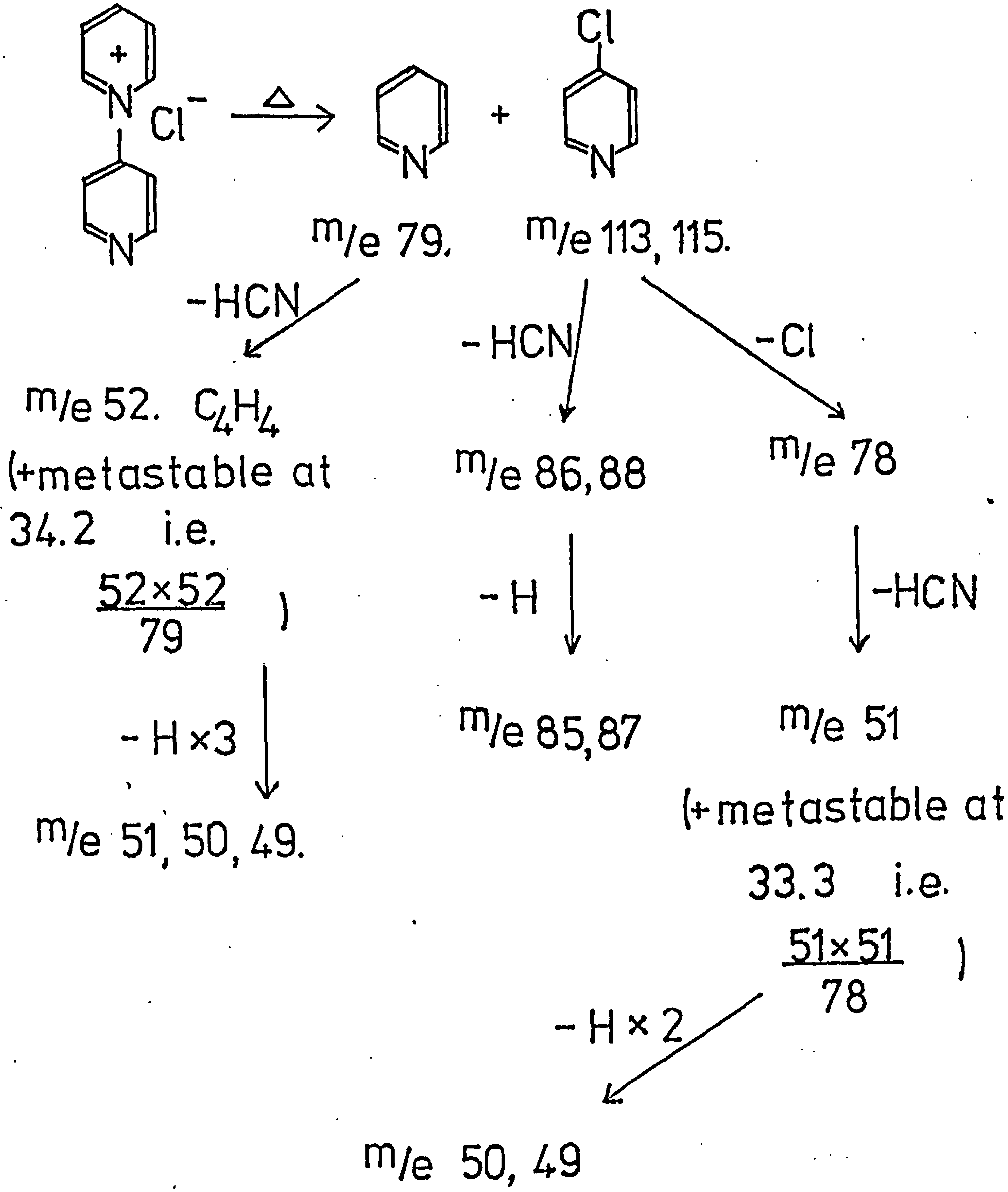


$$\begin{tikzcd} {} \arrow[r, "Py \times 3"] & 2MoCl_4Py_2 + \underline{PyPyCl} + \underline{PyHCl} \arrow[d, "Py \times 2"] \\ & \underline{2MoCl_4Py_3} \end{tikzcd}$$

later with reference to the reactions of pyridine with lower oxidation state halides.

The room temperature reaction of pyridine with UCl_6 was not investigated but the mixture of bipyridyls identified from their reaction at higher temperature (2,2', 2,4', 4,4') leads one again to the conclusion that reduction of the metal by pyridine is incomplete and that some adduct formation does occur. This reaction is thought to be rather more complex than those observed for the other halides in view of the variation in the possible coordination number of uranium and, hence, the series of tenable complexes of pyridine and the halide.

A useful synthetic route to pyridyl pyridinium salts was also found. By reacting liquid pyridine with 4-chloropyridine hydrochloride, quantitative conversion to N(4-pyridyl) pyridinium chloride was effected. Reaction was accomplished at 70°C and problems in isolation and purification of the product were not encountered. By using pyridine d_5, the semi-deuterated N(4-pyridyl) pyridinium chloride d_5 was also prepared almost quantitatively from the same reaction. The

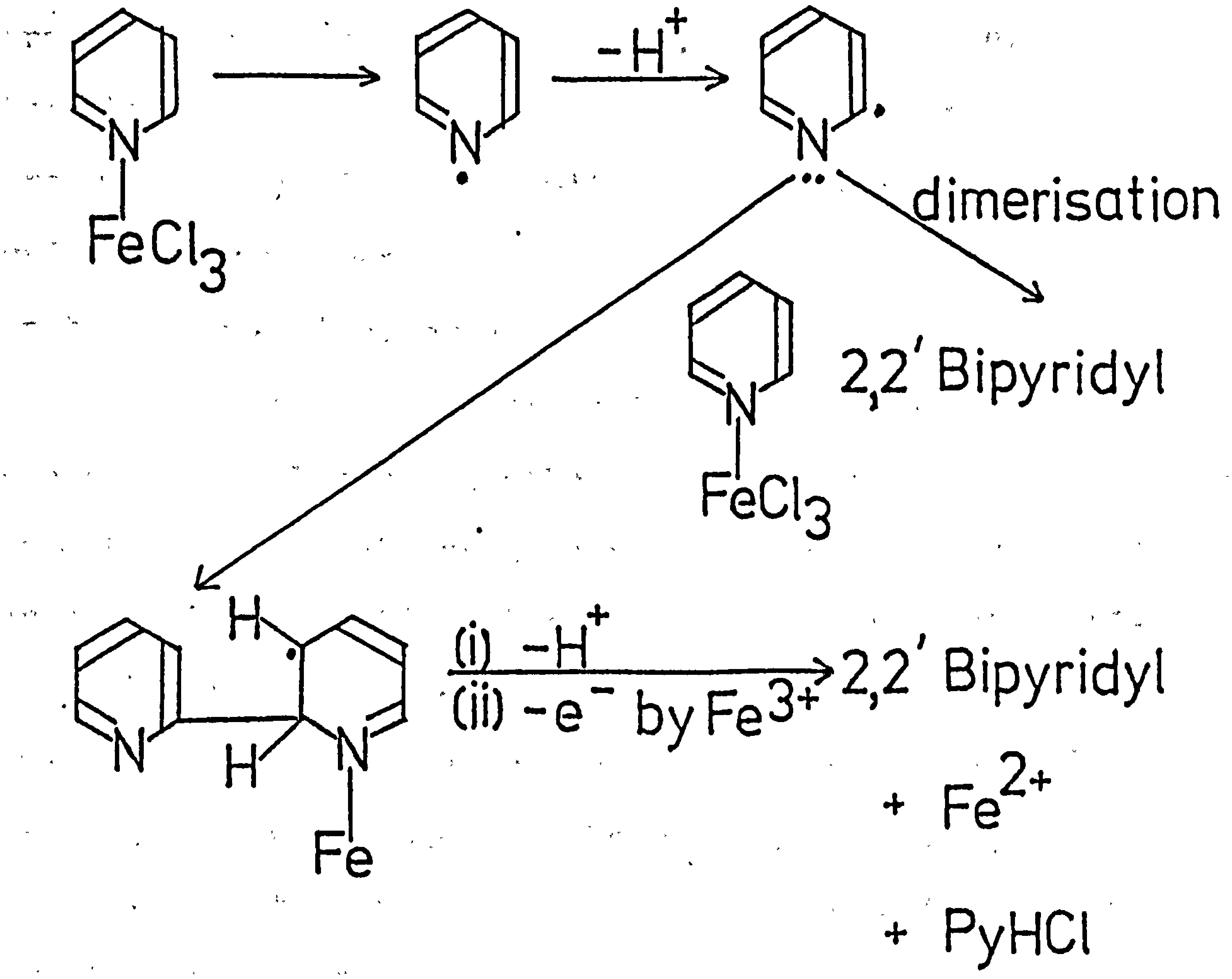

+
N
Cl⁻
N
Δ
+
N
Cl
N
m/e 79.
m/e 113, 115.
-HCN
-HCN
-Cl
m/e 52. C₄H₄
(+metastable at
34.2 i.e.
52×52 / 79)
m/e 86,88
m/e 78
-H
-HCN
-H×3
m/e 85,87
m/e 51
(+metastable at
33.3 i.e.
51×51 / 78)
m/e 51, 50, 49.
-H×2
m/e 50, 49

^{1}H n.m.r. spectra of these compounds are discussed fully in a later chapter. The mass spectra of both compounds were recorded at 180°C, and for the undeuterated molecule, the fragmentation pattern (see preceding page) showed no molecular ion corresponding to the empirical formula $C_{10}H_9ClN_2$. The peaks of highest mass were observed at m/e 113 and 115, indicating a monochloropyridine. In addition, an abundant species was observed at m/e 79 and was presumed to be the pyridine molecular ion. Accordingly, a thermal dissociation of the pyridyl pyridinium salt is proposed whereby it reverts to the component species, pyridine and 4-chloropyridine. This pattern (m/e 113, 115 and 79) was also evident when a mixture of $MoCl_4Py_3$ and N(4-pyridyl) pyridinium chloride was examined by mass spectrometry, thus confirming the presence of the salt. A parallel mode of fragmentation was recorded for the deuterated analogue N(4-pyridyl) pyridinium chloride d_5 whose spectrum showed metastable peaks in the expected positions, viz. m/e 37.2, m/e 34.2 .

As was noted previously, a 6% yield of 4,4'bipyridyl can be obtained by heating N(4-pyridyl) pyridinium chloride to 180°C. This figure rises to 10% if liquid pyridine is included in the reaction mixture. The role of pyridine in the reaction is not clear at this juncture but was examined by isotopic methods and is reported in the next Chapter.

The reactions of pyridine with lower oxidation state metal halides were also studied, both at room and elevated temperatures. The latter reactions produced no 4,4'bipyridyl and usually generated considerable amounts of 2,2' and 2,3' isomers. The reaction of ferric chloride and pyridine was investigated closely in an attempt to elucidate the mechanism of bipyridyl formation with low oxidation state halides and ascertain the differences between this mode of coupling and that observed with the high oxidation state halides. At room temperature, this reaction was found to produce an adduct of empirical formula $FeCl_3Py_{3/2}$. Confirmation of the totally ferric nature was obtained by treating the adduct with an acidified solution of potassium iodide and titrating the iodine liberated against standard thiosulphate. It was also found possible to prepare the complex in solution ($EtOH / Et_2O$) and to recover it unchanged from ethanol. On heating mixtures of pyridine and ferric chloride to 300°C, in a sealed glass tube, considerable amounts of 2,2'bipyridyl, along with smaller quantities of the 2,3' and 3,3' isomers were detected. By isolating the crude product mixture after one of these reactions, pyridine hydrochloride was recovered by sublimation and the iron was found to be present exclusively as the ferrous oxidation state.

The proposed mechanism entails the homolytic fission of an iron - nitrogen bond previously formed by the coordination of pyridine. Loss of a proton from the pyridine residue produces a 2-pyridyl radical species which will either dimerise or react further with a coordinated pyridine molecule thus generating 2,2'bipyridyl, ferrous iron and pyridine hydrochloride. Further evidence of the radical nature of this reaction was provided by Morgan and Burstall who detected amounts of molecular hydrogen in the products (22). Although no provision is made for this in the mechanism below, the extreme conditions of temperature and pressure render such a process entirely possible.



Such a mechanism not only allows for 2,2' coupling but also predicts the formation of pyridine hydrochloride and ferrous iron. Further, due to the proposed radical nature of the reaction, lesser amounts of 2,3' and 3,3' bipyridyls might be expected as a result of some scrambling of the exact position of the radical centre on the ring. Convincing support for this type of mechanism was derived from the reaction of ferric chloride and 2,6 di-methoxy pyridine. After heating the reactants at 320°C, for six hours, no trace of any bipyridyl was found. In this case, there is the obvious implication that the effect of the methoxyl groups is to inhibit the initial formation of a 2-pyridyl radical thereby rendering pyridine dimerisation impossible at the α-position, or at any other position.

This type of mechanism is proposed to account for the products observed in the reactions of pyridine with low oxidation state halides in general, where either complete or partial adduct formation occurs at room temperature. It is of interest to note that when WCl_6 and pyridine were heated together in the presence of oxygen, some 2,2'bipyridyl was formed, in addition to the predominant 4,4' isomer. It is known, that in oxygen contaminated solvents, WCl_6 will undergo the reaction :

$$WCl_6 + O_2 \longrightarrow WOCl_4$$

Having formed some of the oxychloride by this route, pyridine coupling will now occur in a manner similar to that proposed for $FeCl_3$ and other low oxidation state halides, resulting in the generation of small amounts of 2,2'bipyridyl. This hypothesis was checked by heating pyridine with tungsten oxytetrachloride whereupon small amounts of 2,2'bipyridyl were detected by gas chromatography. In addition, by completely removing oxygen from the system, WCl_6 and pyridine react at high temperature to produce only 4,4'bipyridyl.

In conclusion, it appears that the greater acidity of the high oxidation state halides contributes to the withdrawal of an electron from a coordinated pyridine. The resulting pyridinium species is then susceptible to nucleophilic substitution by a displaced chloride ion at the γ-position. Subsequent attack of free pyridine on the 4-chloropyridine generates the reduced metal and a pyridyl pyridinium salt. The route to 4,4'bipyridyl from this point will be discussed in the following Chapter.

By way of contrast, it is thought that the lower halides react by a free radical process at elevated temperatures. The coordination bond between the metal and pyridine is broken homolytically, probably by a thermal process, and the resulting radical can either dimerise or combine with a coordinated pyridine thereby producing 2,2' bipyridyl.

In those cases where the initial reduction of the halide is incomplete, the observed bipyridyls are a result of the combination of the above routes.

EXPERIMENTAL

Reaction of pyridine with tungsten hexachloride (46)

The stoichiometry of this reaction was checked by a determination of the weight gain.

Tungsten hexachloride (33.18 gms, 0.0844 moles) was placed in a 250 ml. round bottomed flask, under an atmosphere of dry nitrogen, and dry, degassed pyridine added in excess by vacuum distillation. The mixture was allowed to come to room temperature and stirred constantly for one week. Unreacted pyridine was removed by vacuum distillation and the solid product finally dried under high vacuum. By reweighing the apparatus at this point, the gain in weight was found to be 32.54 gms. This increase is attributable to incorporation of pyridine and represents 0.41 moles, thus indicating a reactivity ratio of 1 : 4.9 = WCl_6 : Pyr. The reaction was repeated under identical conditions, with a smaller amount of the halide (17.28 gms, 0.0437 moles). The weight gain was found to be 16.9 gms (0.214 moles) of pyridine. These figures therefore indicate a reactivity ratio of 1 : 4.9 .

The solid reaction mixture was then extracted thoroughly with boiling acetonitrile (3 x 50 mls) and the insoluble residue, a buff coloured powder, was removed by filtration and dried under high vacuum. Its melting point was not recorded precisely but was found to be above 300°C. Microanalysis of a sample revealed the following composition:

Found :

%C = 25.1 ; %H = 2.5 ; %N = 5.6 ; %Cl = 30.0 ; %W = 36.85 :

Calculated for WCl_4Py_2 :

%C = 24.8 ; %H = 2.4 ; %N = 5.8 ; %Cl = 29.4 ; %W = 38.0 :

This compound appears to be tetrachloro-bispyridine tungsten^{IV}, although slightly impure. The infra-red spectrum was recorded as a Nujol mull on KBr plates and the following frequencies observed (cm $^{-1}$) :

1601(m) ; 1443(s) ; 1260(w) ; 1209(m) ; 1150(w) ; 1061(m) ;
1044(w) ; 1008(w) ; 960(w) ; 874(w) ; 827(m) ; 766(m) ;
753(m) ; 675(s) ; 640(m) ; 609(w) ; 560(m) ; 441(s) ;

The spectrum was also recorded as a KBr disc :

1601(s) ; 1441(s) ; 1264(w) ; 1206(m) ; 1150(w) ; 1057(s) ;
1044(m) ; 1006(m) ; 956(m) ; 854(w) ; 825(w) ; 778(m) ;
750(s) ; 686(s) ; 636(m) ; 603(w) ; 554(m) ; 438(s) ;

The original acetonitrile washings were combined and the solvent removed. The solid residue was thoroughly dried and sublimed under vacuum (70°C, 10^{-2}mm.). A white volatile solid was readily isolated by this method and its mass spectrum recorded. A molecular ion, m/e 79, and a metastable ion, m/e 34.2, indicated the presence of pyridine. Additional peaks at m/e 36 and 38 implied hydrogen chloride. The sublimate was therefore presumed to be pyridine hydrochloride.

Residual traces of the hydrochloride were removed from the involatile solid by further sublimation. The ultraviolet spectrum was recorded after the addition of concentrated sodium hydroxide and maxima were observed at 430 and 365 mμ. These figures are consistent with those reported (47) for the N(4-pyridyl) pyridinium ion. The melting point of the solid was recorded as 212°C and elemental analysis showed the following composition :

Found :

%C = 62.0 ; %H = 4.8 ; %N = 14.6 ; %Cl = 18.52 ;

Calculated for $C_{10}H_9ClN_2$:

%C = 62.3 ; %H = 4.7 ; %N = 14.6 ; %Cl = 18.46 ;

This compound was consequently identified as N(4-pyridyl) pyridinium chloride.

The complex tetrachloro-bispyridine tungsten^{IV} was refluxed in pyridine for several hours and further reaction occurred. Around 75°C both the solid and the supernatant liquid became considerably darker in colour, the latter assuming an almost permanganate purple. On cooling the mixture, the colour faded slightly but the remaining solid was now black in colour. The composition of the solid was determined for two separate experiments :

Found :

(i) %W = 32.7 ; %Cl = 23.8 ;

(ii) %W = 33.0 ; %Cl = 25.0 ;

Calculated for WCl_4Py_3 :

%W = 32.7 ; %Cl = 25.2 ;

Further refluxing of this solid in pyridine, for three days , resulted in a black powder whose composition proved to be :

$$\%W = 49.05 \; ; \; \%Cl = 3.2 :$$

Although no meaningful conclusions can be drawn from these figures, its is clear that the system does undergo further reaction. However, in view of its seeming complexity, this line was not pursued further.

Reaction of pyridine with molybdenum pentachloride.

Molybdenum pentachloride (22.01 gms, 0.0806 moles) was placed in a 250 ml. round bottomed flask, equipped with stirrer bar and stopcock adapter, under an atmosphere of dry nitrogen. Dry, degassed pyridine was then added in excess by vacuum distillation and the resultant slurry stirred continuously for 72 hours at room temperature. After this time, unreacted pyridine was removed by vacuum distillation and the residual solid dried under high vacuum. By reweighing the apparatus and products, the gain in weight was found to be 27.5 gms. Assuming that all weight gain can be attributed to incorporation of pyridine, this figure represents 0.35 moles. Consequently, the overall stoichiometry of the reaction can be written as

0.0806 moles of $MoCl_5$ + 0.35 moles of pyridine.

i.e. $2\ MoCl_5 + 9\ Py$

This procedure was repeated in two separate experiments and the reactivity ratios were calculated as :

(i) $1\ MoCl_5 \ : \ 4.42\ Py$

(ii) $1\ MoCl_5 \ : \ 4.45\ Py$

The solid product of the reaction was then sublimed ($70^{o}C$, 10^{-2}mm.) and a white volatile product isolated under dry nitrogen. The mass spectrum of this compound was recorded and showed simply the spectrum of pyridine (molecular ion at m/e 79 and metastable at m/e 34.2) along with HCl peaks at m/e 36 and 38 in the ratio of 3 : 1. The compound was presumed to be pyridine hydrochloride and comparison of its ^{1}H n.m.r. spectrum with that of an authentic sample confirmed this.

By extracting the original reaction mixture with warm chloroform, a similar isolation of the hydrochloride was effected. After removal of pyridine hydrochloride, the remaining solid was analysed elementally with the following results from two separate experiments :

Found :

(i) %C = 42.06 ; %H = 3.59 ; %N = 9.71 ; %Cl = 27.67 :

(ii) %C = 41.86 ; %H = 3.58 ; %N = 9.92 ; %Cl = 27.52 :

The mass spectrum of this solid was also recorded and showed essentially the spectrum of pyridine with the important addition of lines at m/e 113 and 115. Their intensities were in the ratio of 3 : 1 indicating the probable presence of a monochloro-pyridine. Assuming that the stoichiometry of the overall reaction can be represented by :

$$2\ MoCl_5 + 9\ Py \longrightarrow 2\ MoCl_4Py_3 + PyPyCl + PyHCl$$

then the above solid should consist of a 2 : 1 molar mixture of tetrachloro-trispyridine molybdenum^{IV} and N(4-pyridyl) pyridinium chloride. The composition of such a mixture was calculated to be

$$\%C = 42.06 \; ; \; \%H = 3.40 \; ; \; \%N = 10.5 \; ; \; \%Cl = 27.9 \; :$$

A comparison of these figures with those already found (above) indicates that the proposed stoichiometry does hold and that the initial washing with chloroform does not separate N(4-pyridyl) pyridinium chloride and the molybdenum /pyridine complex. The appearance of a monochloro-pyridine in the mass spectrum also confirms this supposition, as was shown in Discussion of the spectrum of N(4-pyridyl) pyridinium chloride. As final confirmation, it was also found that chloroform did not dissolve N(4-pyridyl) pyridinium chloride, as was suggested above.

Reaction of pyridine with 4-chloro-pyridine hydrochloride.

Dry, degassed pyridine (8 mls) was distilled under vacuum into a flask fitted with a stopcock adapter and containing 4-chloro-pyridine hydrochloride (1.7 gms). The reaction mixture was stirred at 80°C for five hours and unreacted pyridine removed under vacuum. The residual buff coloured solid was then thoroughly dried on a high vacuum line. The product was isolated under dry nitrogen and its melting point determined as 202 - 206 °C. Reaction had obviously occurred since the melting point of the original hydrochloride was 158 - 160 °C.

The reaction was repeated at 80 °C for 24 hours and the hot mixture filtered. White, plate-like crystals formed in the filtrate on cooling and these were isolated and dried under vacuum. This solid (m. pt. 140 - 142 °C) was analysed by mass spectrometry and n.m.r. and the spectra were found to correspond exactly to those of pyridine hydrochloride. The initial reaction mixture was reduced to dryness by removing excess pyridine under vacuum. The solid which remained was sublimed (80 °C, 10^{-2}mm.) and the volatile fraction isolated and identified, as before, as pyridine hydrochloride.

N.m.r. spectra of the remaining, involatile solid were recorded in D_2O and were in no way similar to that of pyridine hydrochloride. The solid was found to melt at 212 -213 °C and microanalysis showed the following composition Found. :

%C = 62.1 ; %H = 4.9 ; %N = 14.7 ; $\%Cl^-$ = 18.5 :

Calculated for N(4-pyridyl) pyridinium chloride :

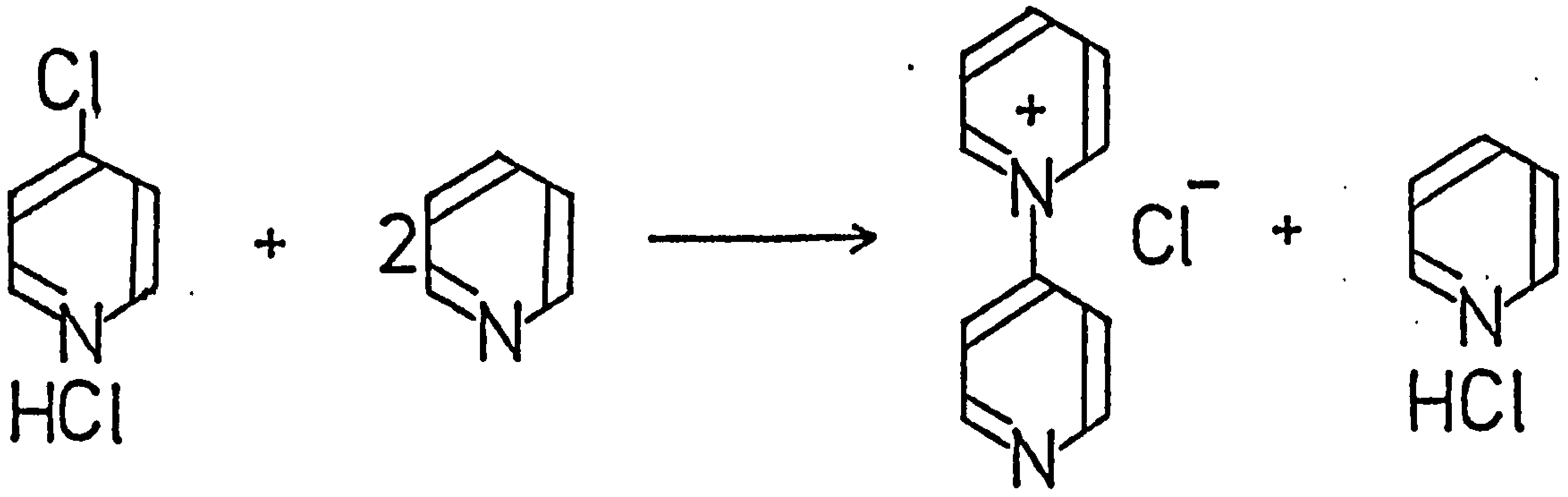
%C = 62.3 ; %H = 4.7 ; %N = 14.6 ; $\%Cl^-$ = 18.5 :

A repeat of the reaction under the same conditions gave a quantitative yield of the pyridyl pyridinium salt whose melting point was determined as 214 °C, the sharpness of the phase change indicating a high degree of purity :

Found :

%C = 62.2 ; %H = 5.0 ; %N = 14.6 ; $\%Cl^-$ = 18.5 :

Additionally, by determining the weight gain during reaction, it was found that 1 mole of 4-chloro-pyridine hydrochloride required 1.96 moles of pyridine for complete reaction, indicating a stoichiometric equation of the form :



By using pyridine d_5 instead of the fully protonated analogue, the semi-deuterated compound N(4-pyridyl) pyridinium chloride d_5 was prepared, the experimental conditions and isolation procedure being exactly as has been outlined. The melting point of the product was determined as 212 - 213°C and ^{1}H n.m.r. and mass spectra were recorded. Microanalysis of a sample produced the following results :

Found :

%C = 59.9 ; %(H + D) = 6.5 ; %N = 14.7 ; %Cl$^-$ = 18.2 :

Calculated for $C_{10}H_4D_5ClN_2$:

%C = 60.8 ; %(H + D) = 7.1 ; %N = 14.2 ; %Cl$^-$ = 17.8 :

Again, the yield was almost quantitative and the product isolated in reasonable purity. A similar white sublimate was obtained and was identified as pyridine hydrochloride d_5 from its mass spectrum.

<u>Reaction of pyridine with ferric chloride</u>.

Anhydrous ferric chloride was added to the apparatus, a 50 ml. round bottomed flask fitted with a stopcock adapter, under an atmosphere of dry nitrogen. Dry, degassed pyridine was added in excess, by vacuum distillation at -196°C, and the apparatus allowed to come to room temperature gradually. Care was taken to prevent the mixture over-heating due to the exothermic nature of the reaction. The brown / red slurry was stirred continuously for seven days. Excess pyridine was removed slowly on a high vacuum line and the product allowed to crystallise. The solid residue was thoroughly dried and rust brown crystals, which appeared to be stable in air, were isolated. The composition of the solid was determined by microanalysis and corresponded to an empirical formula of $FeCl_3Py_{3/2}$.

Calculated.:

%C = 32.0 ; %H = 2.7 ; %N = 7.45 ; %Cl = 37.7 :

Found :

%C = 31.4 ; %H = 3.2 ; %N = 7.43 ; %Cl = 37.7 :

A small sample of this compound dissolved in water was treated with an acidified solution of potassium iodide. Liberation of iodine was quite definite, as was indicated by the purple colour of a chloroform extract of the solution. By titrating the iodine produced against a standard solution of thiosulphate, it was found that all the iron in the sample was present as the ferric oxidation state. The compound therefore appears to be an adduct of ferric chloride and pyridine, mentioned previously about 50 years ago (48), and presumably similar in nature to the di-alcoholate found by Lloyd and co-workers (49) and the ethyl etherate investigated by

Forster (50).

Adduct formation was also attempted in solution. Ferric chloride was dissolved in boiling ether and the solution treated with a mixture of pyridine in boiling ethanol Reaction was immediate and vigarous resulting in the formation of dark brown crystals. Treatment of these with acidified potassium iodide produced a recognisable amount of free iodine. The composition was found, by analysis, to be :

%C = 31.3 ; %H = 3.1 ; %Cl = 36.9 ; %Fe = 19.9 :

Calculated for $FeCl_3Py_{3/2}$:

%C = 32.0 ; %H = 2.7 ; %Cl = 37.8 ; %Fe = 19.9 :

The mass spectrum of this compound was recorded at temperatures between 90 and 110 °C and, on all occasions, showed only the spectrum of pyridine. The infrared spectrum was recorded as a Nujol mull, on KBr plates, and the following frequencies were observed (cm^{-1}) :

1627(w) ; 1598(m) ; 1528(s) ; 1484(s) ; 1479(s) ; 1439(w) :
1036(w) ; 1002(m) ; 866(s) ; 762(s) ; 707(m) ; 690(m) :
678(s) ; 630(m) ; 369(s) ; 317(s) :

This complex was recrystallised, apparently unchanged, from ethanol. In view of the known existence of a di-alcoholate and an ethyl etherate (49, 50), it now seems likely that the pyridine adduct is more stable than either of these and is therefore formed preferentially in solution.

Reaction of 4-picoline with ferric chloride.

Anhydrous ferric chloride was placed in the apparatus as in the previous experiment. 4-Picoline was distilled onto the halide at -196 °C and the mixture allowed to reach room temperature. The resultant slurry was then stirred continuously for four days and unreacted picoline was removed by vacuum distillation. The products could not be dried completely due to the great difficulty encountered in removing the final traces of picoline. At this point, the product was a thick red tar and weight gain data, which indicated a stoichiometry of $FeCl_3$: 4 Picoline , were deemed unreliable. The addition of hot ethanol to this tar caused the immediate deposition of a buff coloured solid which was removed by filtration and dried under vacuum. By microanalysis, the composition was found to be :

%C = 49.9 ; %H = 5.3 ; %N = 9.5 ; %Cl = 23.5 ; %Fe = 12.7 :

Calculated for $FeCl_3(Pic)_3$:

%C = 49.1 ; %H = 4.9 ; %N = 9.5 ; %Cl = 24.1 ; %Fe = 12.7 :

The mass spectrum of this compound was recorded and consisted essentially of that of a picoline. The molecular ion was observed at m/e 93 and a metastable ion at m/e 47 was attributed to the process involving loss of HCN from the picoline molecule :

$$C_6H_7N \text{ (m/e 93)} \longrightarrow C_5H_6\text{(m/e 66)} + \text{metastable at m/e 47}$$

$$\text{i.e. at } \frac{66 \times 66}{93}$$

Reaction of pyridine with niobium pentachloride (47).

A sample of the halide was transferred to the reaction flask in a glove-box, under an atmosphere of nitrogen. The flask, fitted with a stopcock adapter, was then evacuated thoroughly and an excess of pyridine condensed on to the halide. The mixture was then stirred for 72 hours at room temperature. Unreacted pyridine was distilled from the flask and the resultant yellow solid dried under high vacuum. Bearing the results of McCarley's work (47) in mind, a sample of the total product was analysed, with the following outcome :

%Cl = 36.5 ; %N = 7.3 ; %Nb = 19.9 :

This composition agrees well with that calculated for the mixture of products proposed by McCarley :

%Cl = 37.1 ; %N = 7.7 ; %Nb = 19.4 :

The total product mixture was then washed with anhydrous acetonitrile and the insoluble portion dried under vacuum. Analysis of a sample showed the following composition :

%Cl = 36.2 ; %N = 7.1 ; %Nb = 23.7 :

Since these figures also agree well with those predicted on the basis of McCarley's stoichiometry, further confirmation was not sought.

Chemicals.

In all cases, Analar grade pyridine was used. This had been redistilled onto sodium hydroxide and thence onto activated molecular sieves (Linde Type 4A) where it was stored for subsequent use. Pyridine d_5 (99.5% isotopically pure) was purchased from Prochem Ltd.

With the exception of ferric chloride, which was Analar grade, all halides were purchased from Ralph N. Emmanuel, and were stored in a glove box.

Analar grade solvents were used for all operations and were dried by the appropriate methods where necessary.

CHAPTER II

Reactions of N(4-pyridyl) pyridinium salts.

INTRODUCTION

Pyridyl pyridinium salts have been used extensively as intermediate compounds in the preparation of aminopyridines pyridones and deutero-pyridines (51, 52) especially when substitution α or γ to nitrogen is intended. In this respect, N(4-pyridyl) pyridinium chloride has received considerable attention.

The preparation of its hydrochloride, by the action of thionyl chloride on pyridine (51), was reported around 1930. Its formation was presumed to be due to the interaction of free pyridine with an intermediate 4-chloropyridine species which is generated in situ. This report also notes the existence of two distinct crystalline modifications, a finding which as yet remains unsubstantiated. Other routes to N(4-pyridyl) pyridinium salts rely on the dimerisation of 4-halo- and 4-nitropyridines (53). McCarley (54, 55) noted its formation from the reactions of pyridine with $NbCl_5$ and WCl_6. McElvain and Goese (56) detected N(3-bromo-4-pyridyl) 3-bromo-pyridinium bromide in the product mixture after the gas phase bromination of pyridine. They propose that this compound results from the autoquaternisation of 3-bromo- and 3,4 dibromopyridines. Dimerisation of 4-chloropyridine (57) has been shown to produce N(4-pyridyl) 4-chloro-pyridinium chloride which, on basic hydrolysis, yields N(4-pyridyl) 4-pyridone. 4-Bromopyridine is thought to react similarly (58).

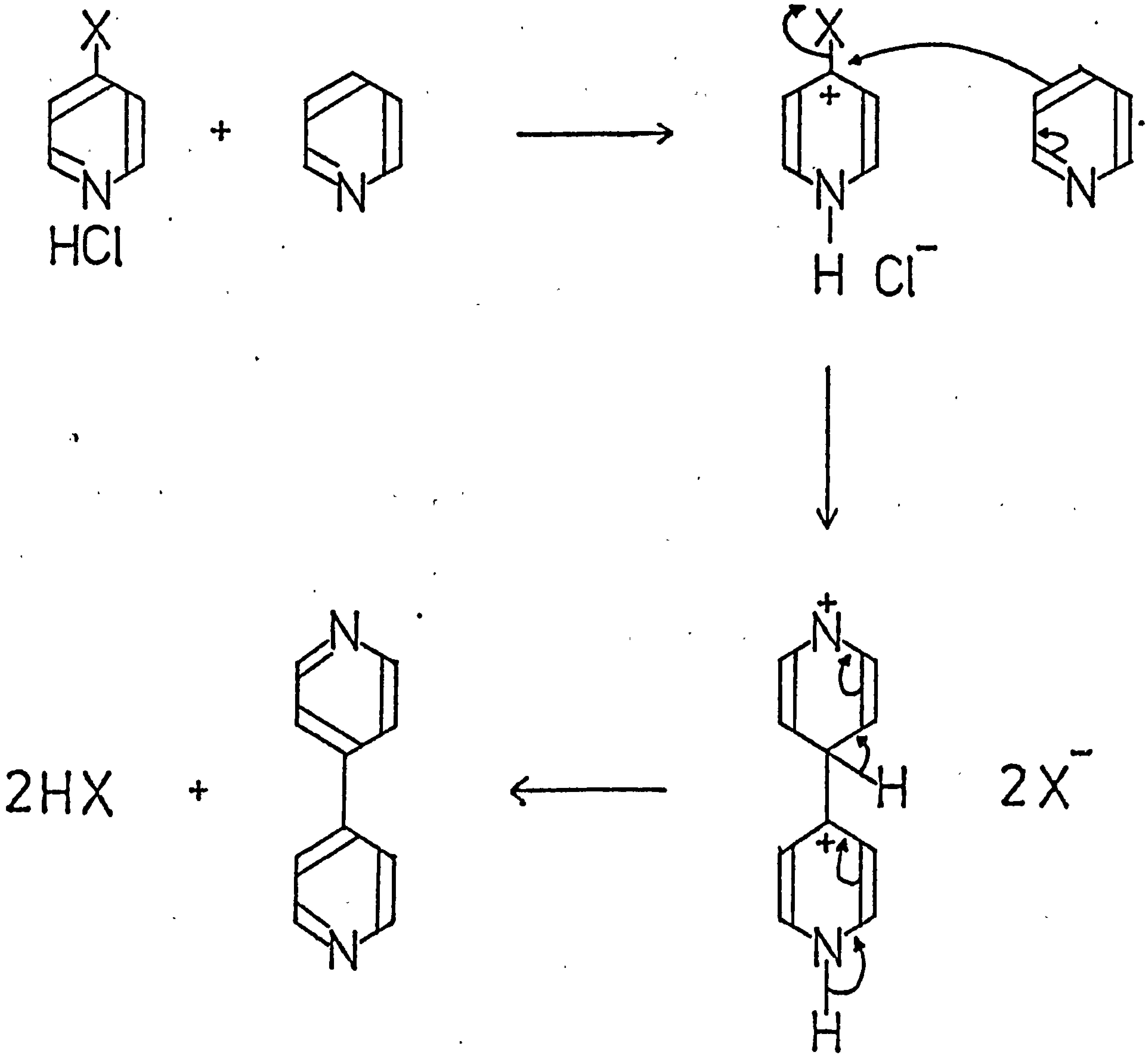
Apart from these few reports, very little is known of the general chemistry of these salts. Their reactions at high temperature, in the presence and absence of several solvents, were investigated in order to establish the mechanism of their conversion to 4,4'bipyridyl. The results of this study are presented in this Chapter.

DISCUSSION

The reaction of 4-chloropyridine hydrochloride with pyridine, previously shown to produce N(4-pyridyl) pyridinium chloride at 80 °C, was found to follow a different path when temperature was raised to 180 °C. In this latter case, 4,4'bipyridyl was detected in yields ranging between 45 and 50%. 4-Bromopyridine reacted similarly with pyridine on heating, producing 4,4'bipyridyl in even greater yields (55 - 60%).

Since N(4-pyridyl) pyridinium chloride will provide 4,4'bipyridyl in only 10% yield, at best, when heated with pyridine, it appears that the above reactions do not depend on the intermediate formation of pyridyl pyridinium salts at higher temperatures. Consequently, two distinct mechanisms are envisaged for this reaction, one allowing for the formation of a pyridyl pyridinium salt at low temperature and the other providing a direct route to 4,4' bipyridyl on heating to around 180 °C. The precise mechanism of each reaction will be discussed at a later point.

It is further thought that the direct formation of 4,4'bipyridyl from pyridine and a 4-halopyridine is governed to some extent by the strength of the carbon - halogen bond. Consequently, the higher yield of bipyridyl derived from the reaction of 4-bromopyridine hydrochloride can be attributed to the greater ease of cleavage of the of the C - Br bond as compared with the energy required to break the C - Cl bond (59). Thus, any tenable mechanism for this reaction must make provision for rupture of the carbon - halogen bond. Apart from one of simple dimerisation of 4-pyridyl radicals, the most plausible mechanism for direct formation of 4,4'bipyridyl appears to be :



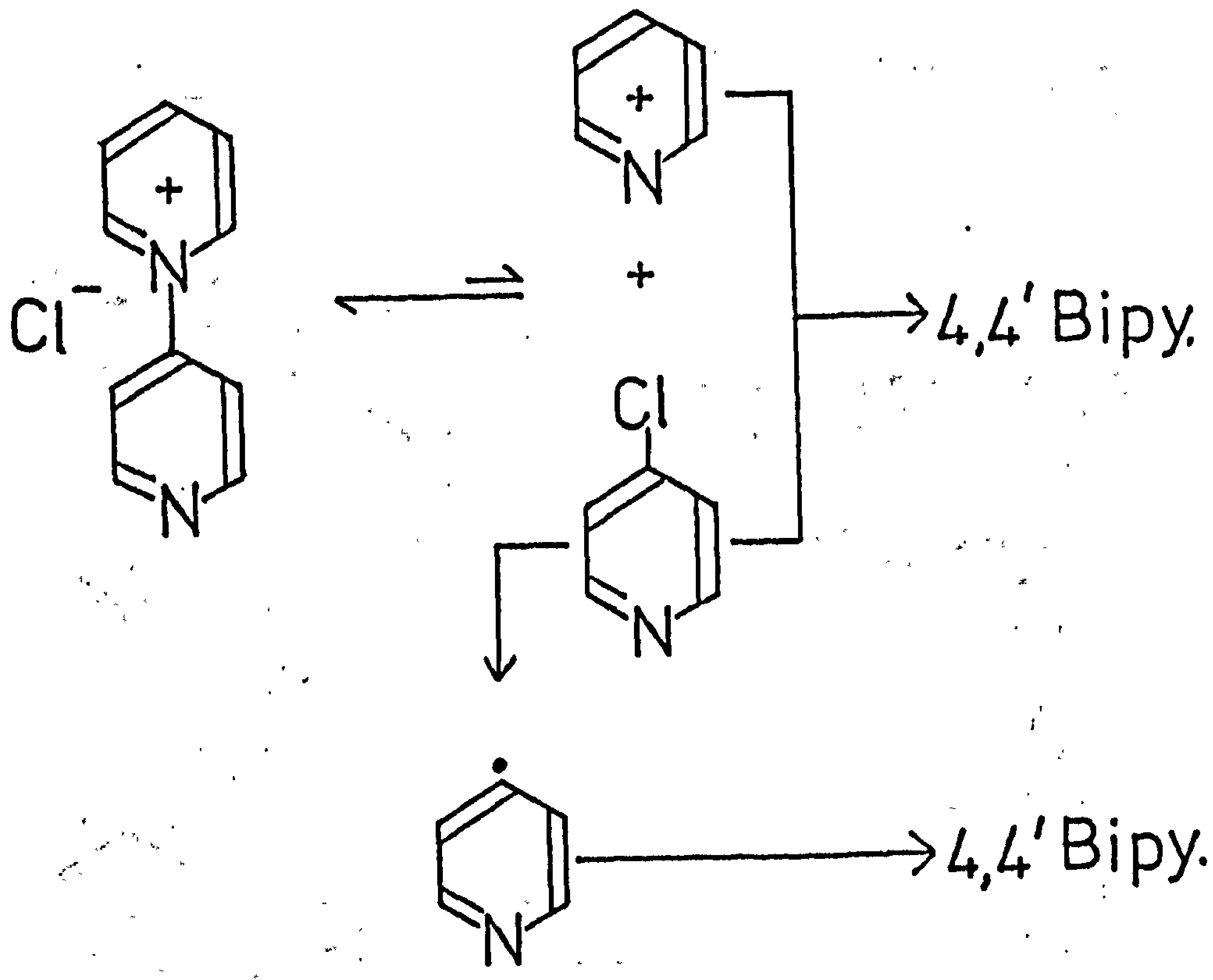
Furthermore, it was shown that the addition of methanol or acetic acid greatly inhibited the extent of bipyridyl formation and in fact, in the latter case, reduced it to zero. This not unexpected on the basis of the above mechanism, since any protonation of pyridine would discourage the initial nucleophilic attack on the 4-halopyridine. A similar investigation of the reaction of α-picoline with 4-chloropyridine showed that the predominant product, by far, was 2-methyl 4,4'bipyridyl. Trace amounts of the unsubstituted 4,4'bipyridyl were also detected, indicating that a small degree of self-coupling of the 4-halopyridine does occur. It is more than likely that this process depends on the dimerisation of 4-pyridyl radicals which are produced as a result of the relatively high reaction temperature.

A significant increase in the yield of bipyridyl was detected when N(4-pyridyl) pyridinium chloride was heated in the presence of free pyridine. This reaction generated 10% 4,4'bipyridyl, whereas by heating the pyridyl pyridinium salt alone only 6% conversion was observed. Although it seems clear that the added pyridine is directly involved in the formation of 4,4'bipyridyl, the precise nature of its participation is not yet apparent. Similar treatment of N(4-pyridyl) pyridinium chloride hydrochloride showed the same trend in the bipyridyl yields, but the overall conversion to bipyridyl was substantially greater in this case than for N(4-pyridyl) pyridinium chloride. This result will be treated in full at a later point.

In order to elucidate the mechanism whereby N(4-pyridyl) pyridinium chloride produces 4,4'bipyridyl, a series of reactions was conducted involving deuteropyridine and deuterated pyridyl pyridinium salts. The degree of deuterium incorporation in the bipyridyl products was monitored by mass spectrometry and this is given as a percentage of the total 4,4'bipyridyl in Table I.

Bearing in mind the nature of the deuterated products (Table I), it is proposed that the thermal conversion of N(4-pyridyl) pyridinium salts to bipyridyl is governed by two independent mechanisms. In the absence of pyridine, the pyridyl pyridinium salt dissociates on heating yielding the component molecules pyridine and 4-chloropyridine. 4,4'Bipyridyl is formed by the dimerisation of thermally produced 4-pyridyl radicals and by the reaction of pyridine and 4-chloropyridine already outlined in this Chapter (p 48). When pyridine is present, both of these mechanisms apply, but only represent a small fraction of the total reaction. The predominant reaction operating in the presence of pyridine does not rely on dissociation of the pyridyl pyridinium salt but on the nucleophilic attack of pyridine and subsequent re-arrangement of the salt. These two routes are shown pictorially overleaf.

Dissociative



Associative

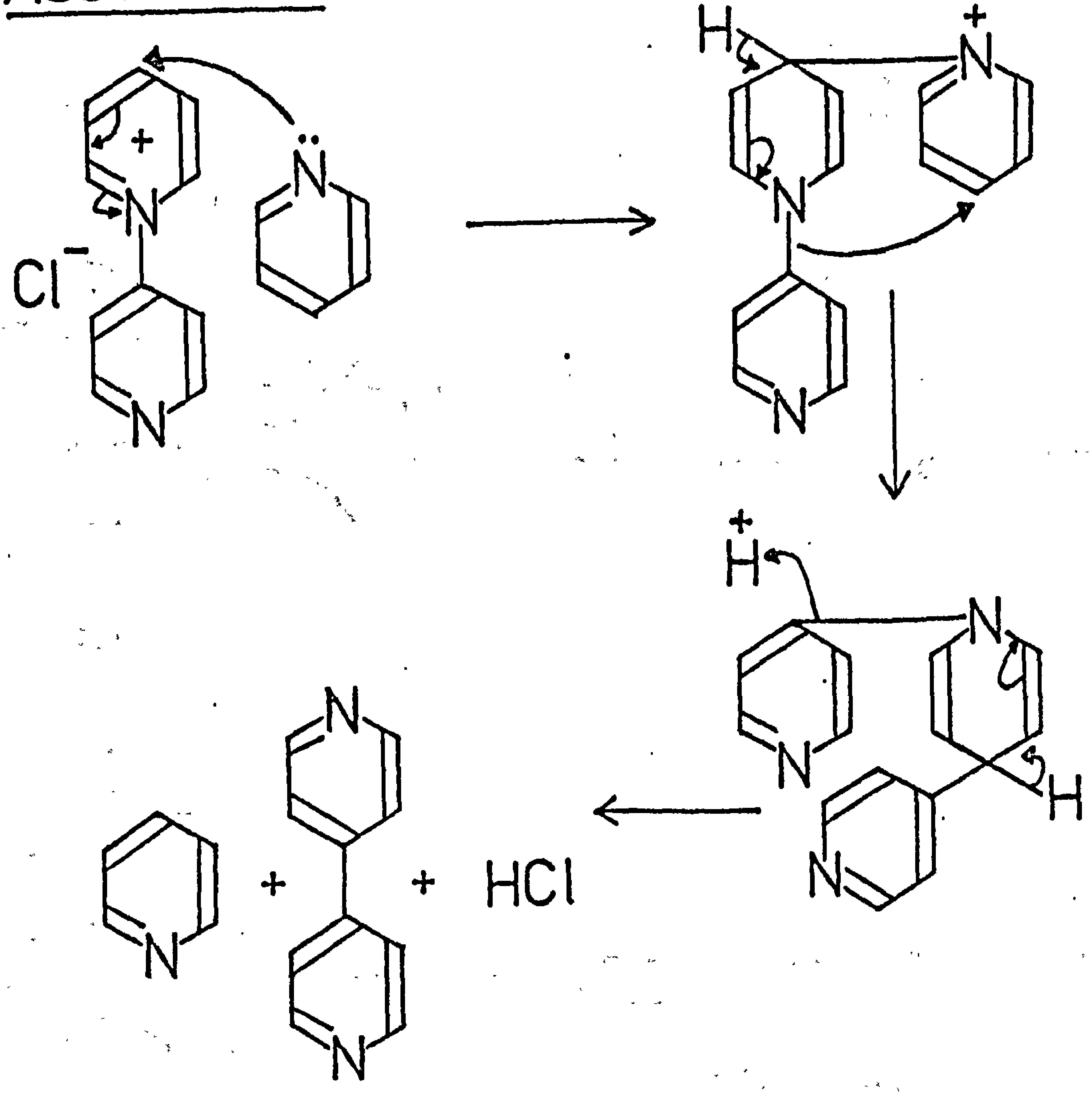
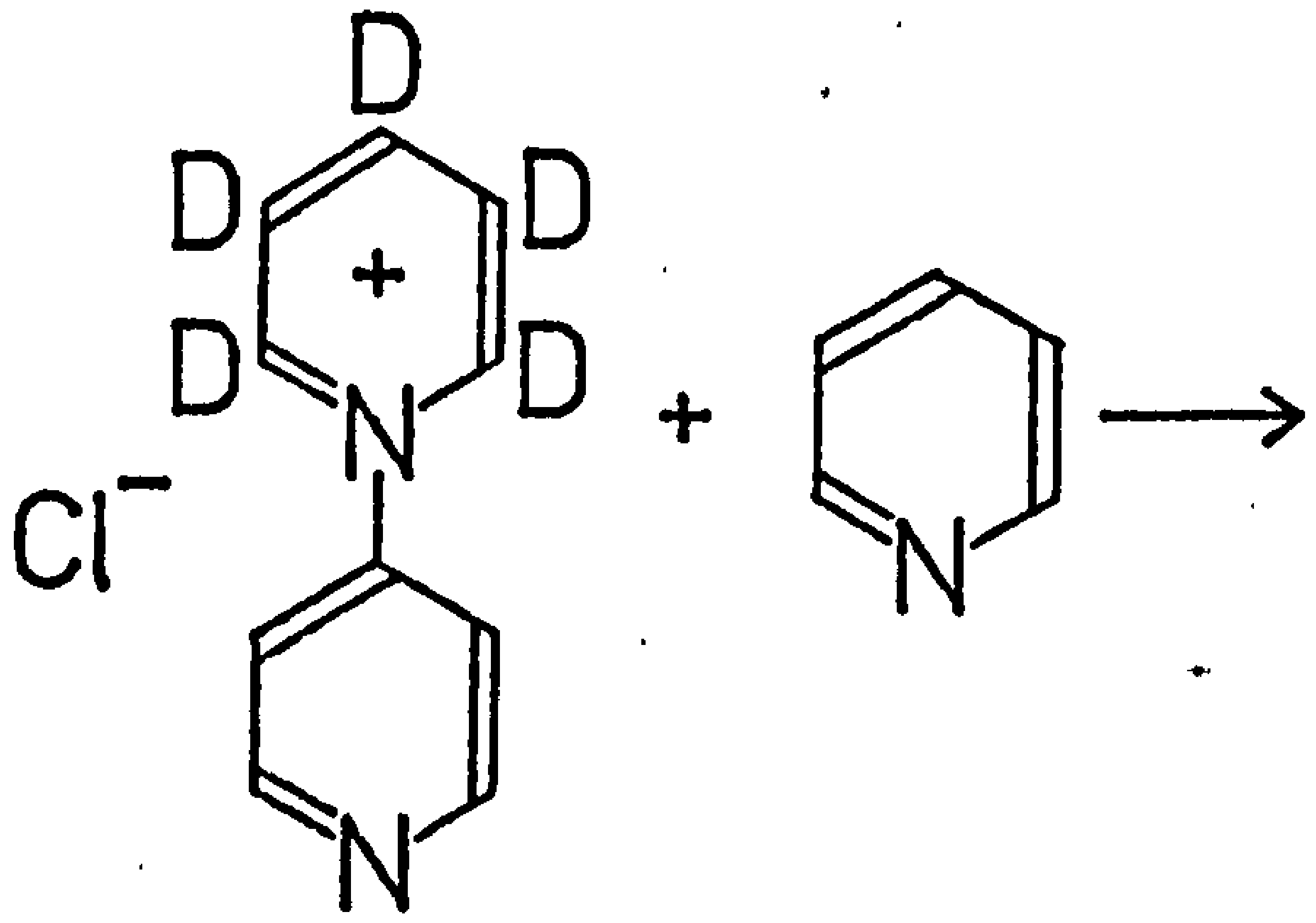
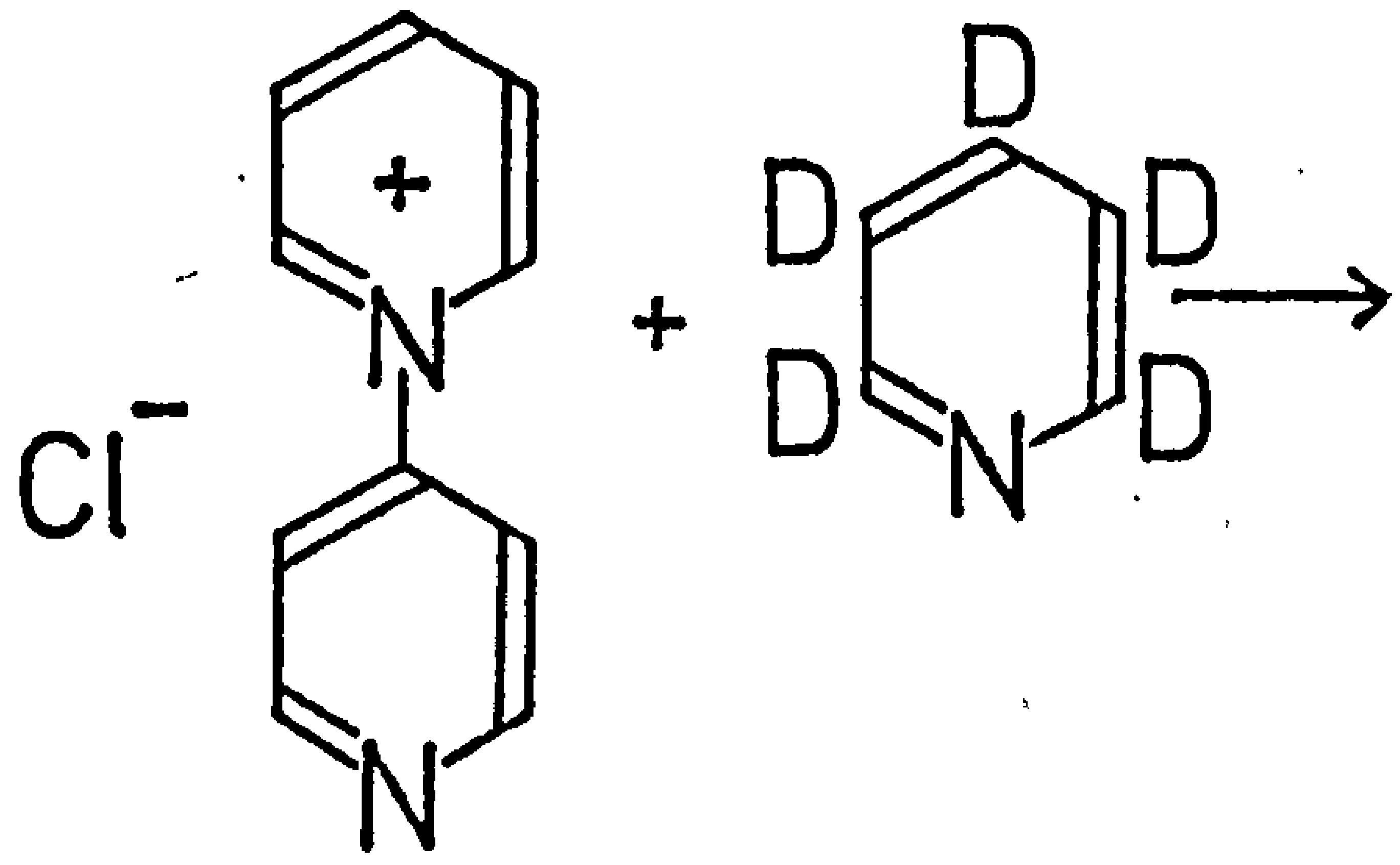
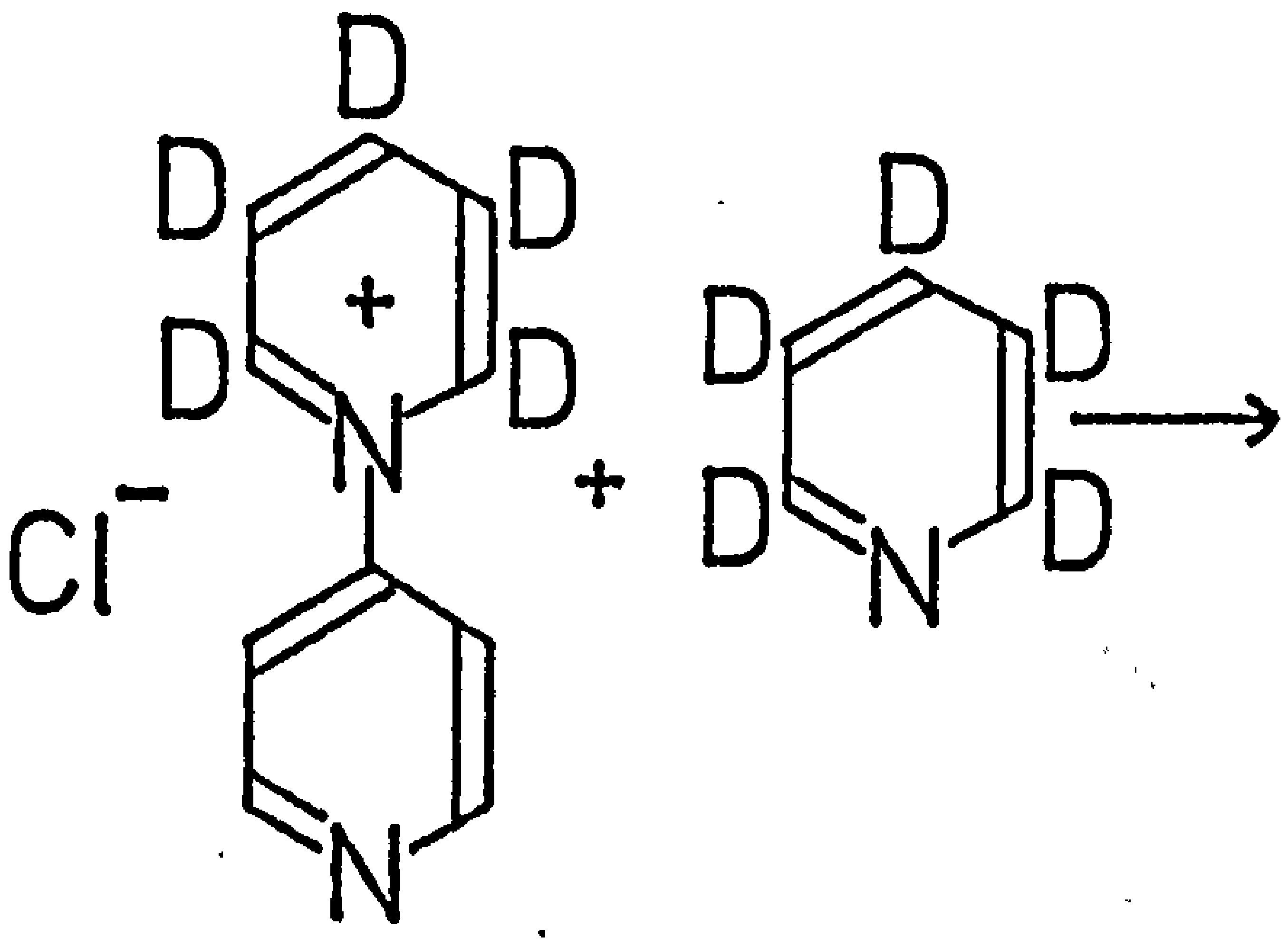
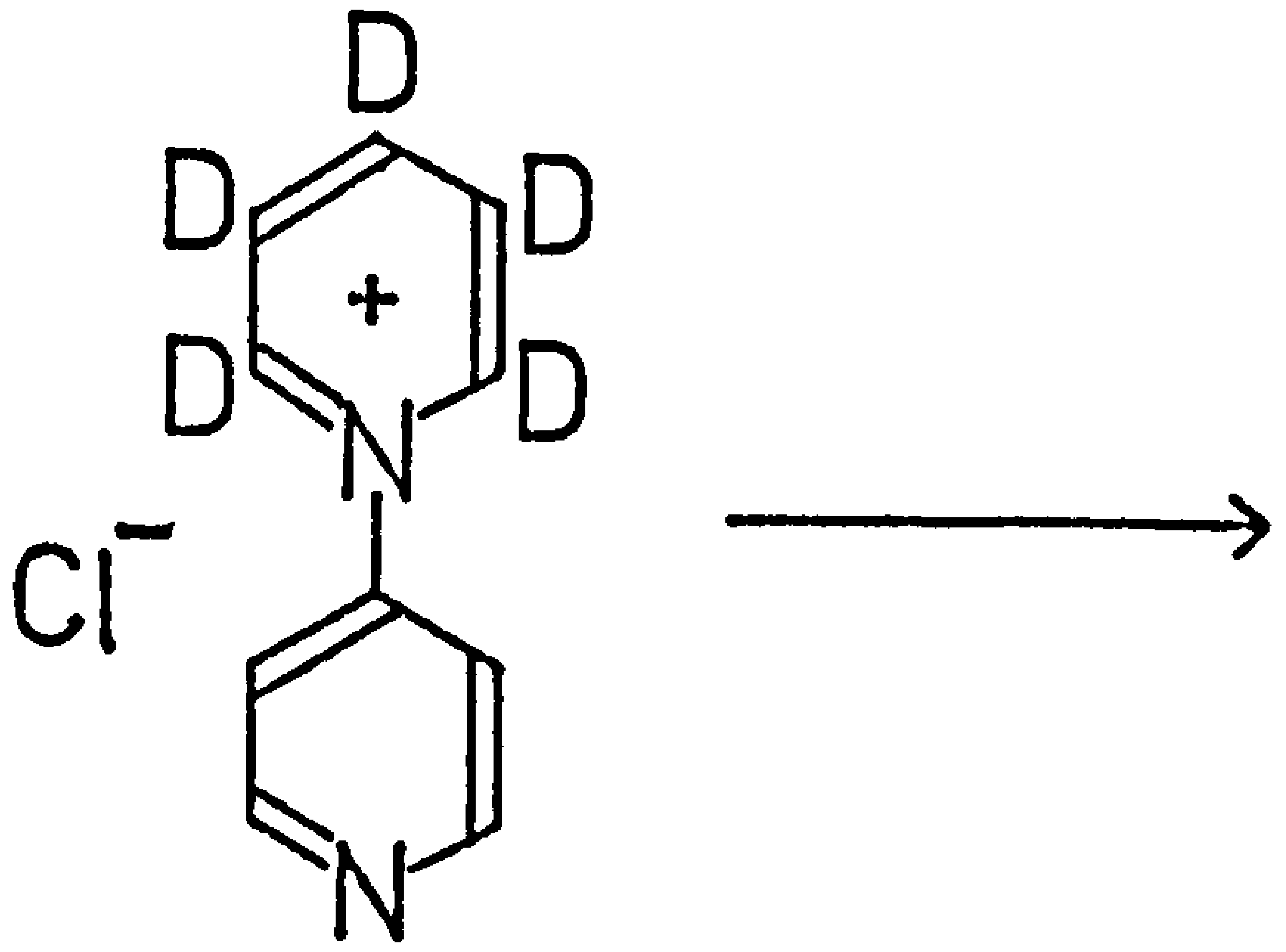
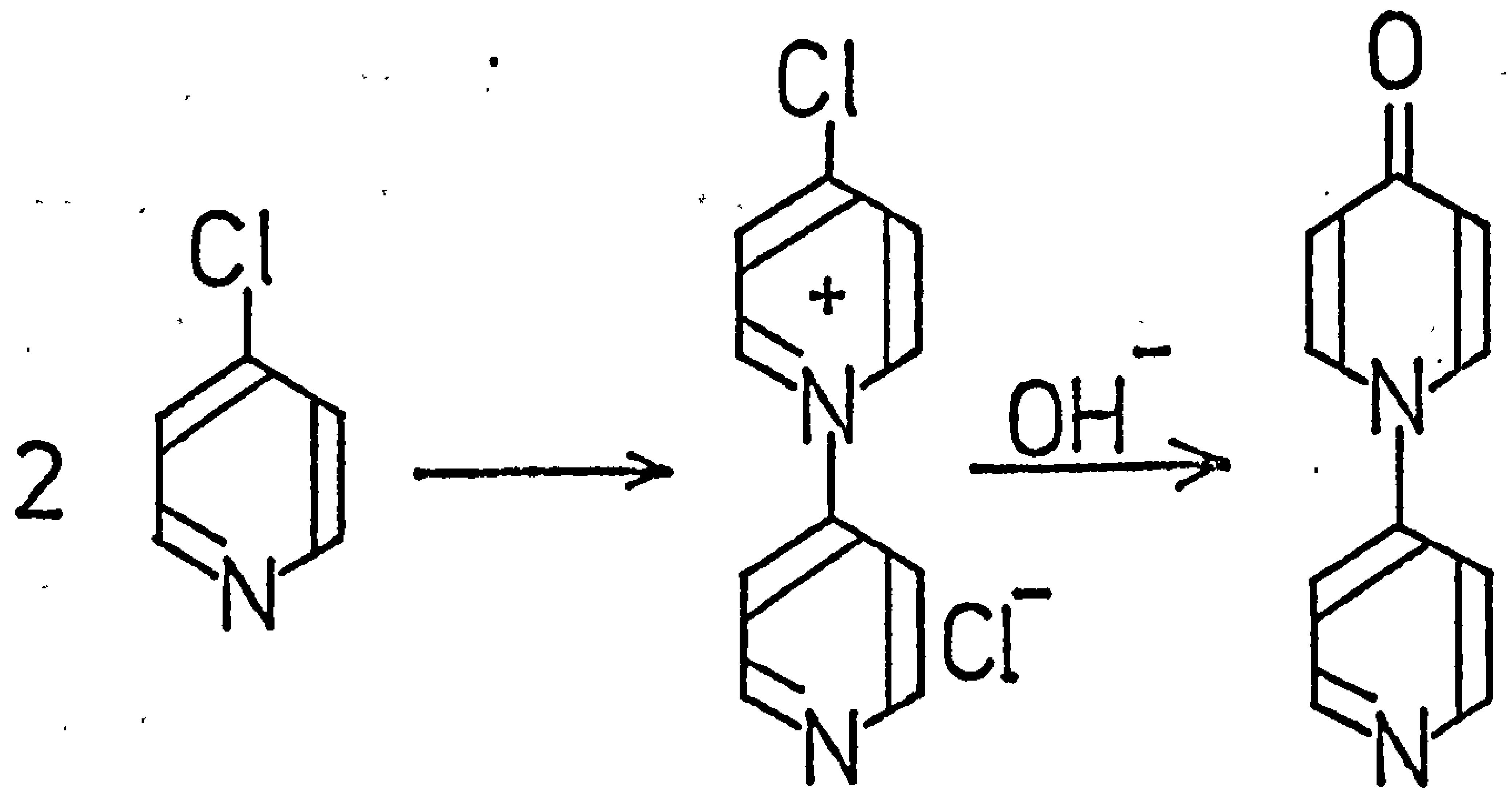


Table I

	H_4D_4	H_5D_3	H_6D_2	H_7D_1	H_8	
	10.5	0.91	0.45	3.65	85.0	%
	+ m/e 172					
	42.0	18.6	7.6	4.5	27.4	%
	+ m/e 172					
	65.0	22.0	7.8	1.7	2.6	%
	+ m/e 172					
	70.0	12.0	0	3.6	13.8	%
	+ m/e 172					

From the last two reactions recorded in Table I, it can be seen that the amount of 4,4'bipyridyl arising from the dimerisation of 4-pyridyl radicals is vanishingly small in the presence of pyridine but is quite significant when free pyridine is absent. This difference is probably due to the extent of dissociation of N(4-pyridyl) pyridinium chloride, the process being inhibited by the addition of pyridine. In the cases where the products were examined by mass spectrometry, an unexpected compound was observed in minute quantities at m/e 172. This product was also noted when 4-chloropyridine was heated in a Carius tube. It is thought that this compound is N(4-pyridyl) 4-pyridone, originating from the 4-chloropyridine dimer in a manner already suggested by Wibaut (53) :



Clearly, dissociation of N(4-pyridyl) pyridinium chloride would give rise to this compound via the dimerisation and subsequent hydrolysis of 4-chloropyridine.

As was noted earlier, the use of N(4-pyridyl) pyridinium chloride hydrochloride resulted in an increased yield of 4,4'bipyridyl. On the basis of the mechanism suggested this is not altogether unexpected, since quaternisation of the second nitrogen atom would greatly facilitate the nucleophilic attack of free pyridine by providing an additional electron deficient centre.

From the foregoing discussion, it appears that the conversion of the pyridyl pyridinium salts to bipyridyl, by a dissociative route, is limited only by the degree of dissociation of the salt. In contrast, when pyridine and 4-chloropyridine, the products of such a dissociation, are heated together, conversion to 4,4'bipyridyl is far more efficient. Two separate mechanisms are proposed for these cases. However, from the results of experiments on isotopic labelling, it appears that, in the presence of pyridine, an associative mechanism predominates rather than any other in the conversion of N(4-pyridyl) pyridinium salts to 4,4'bipyridyl.

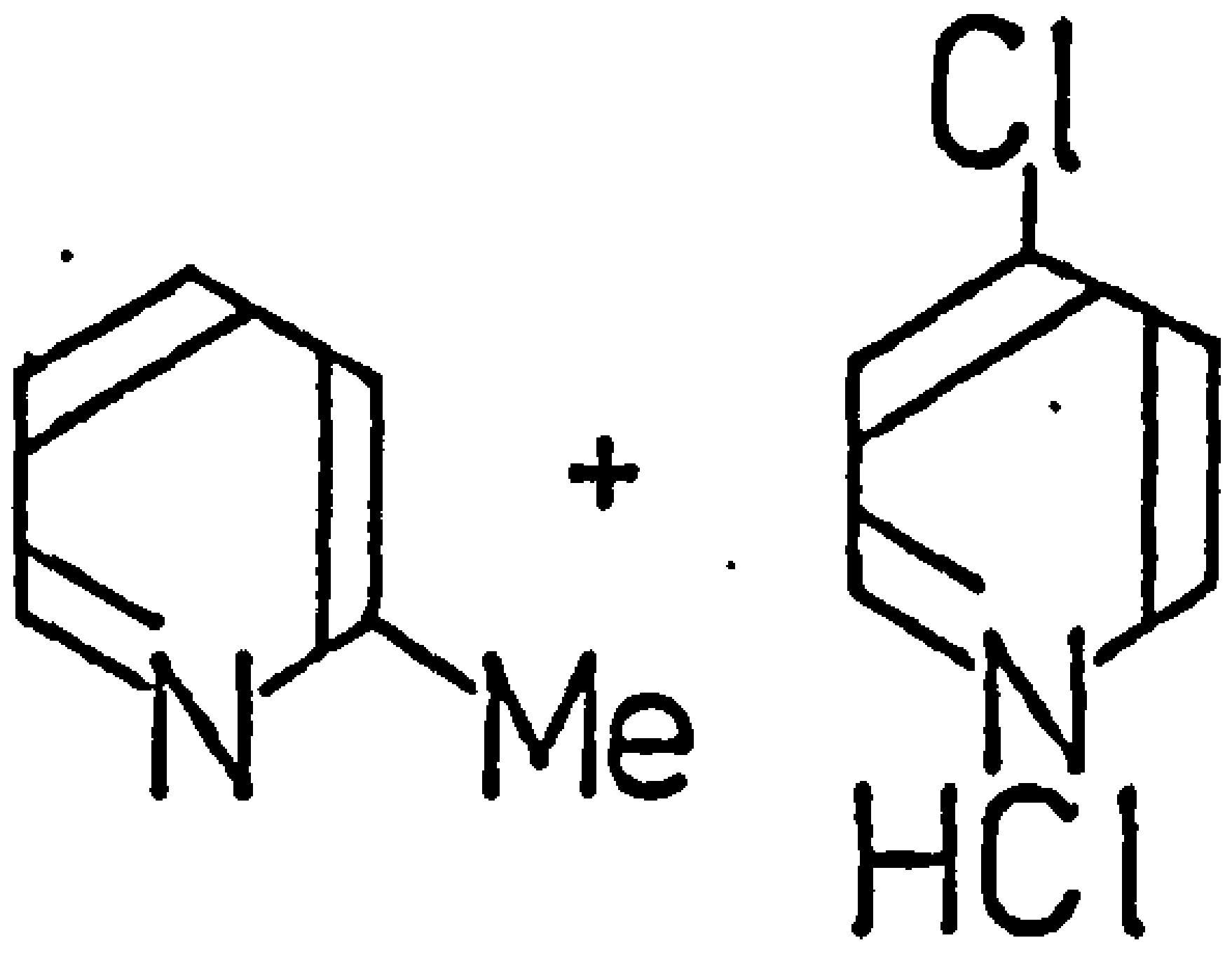
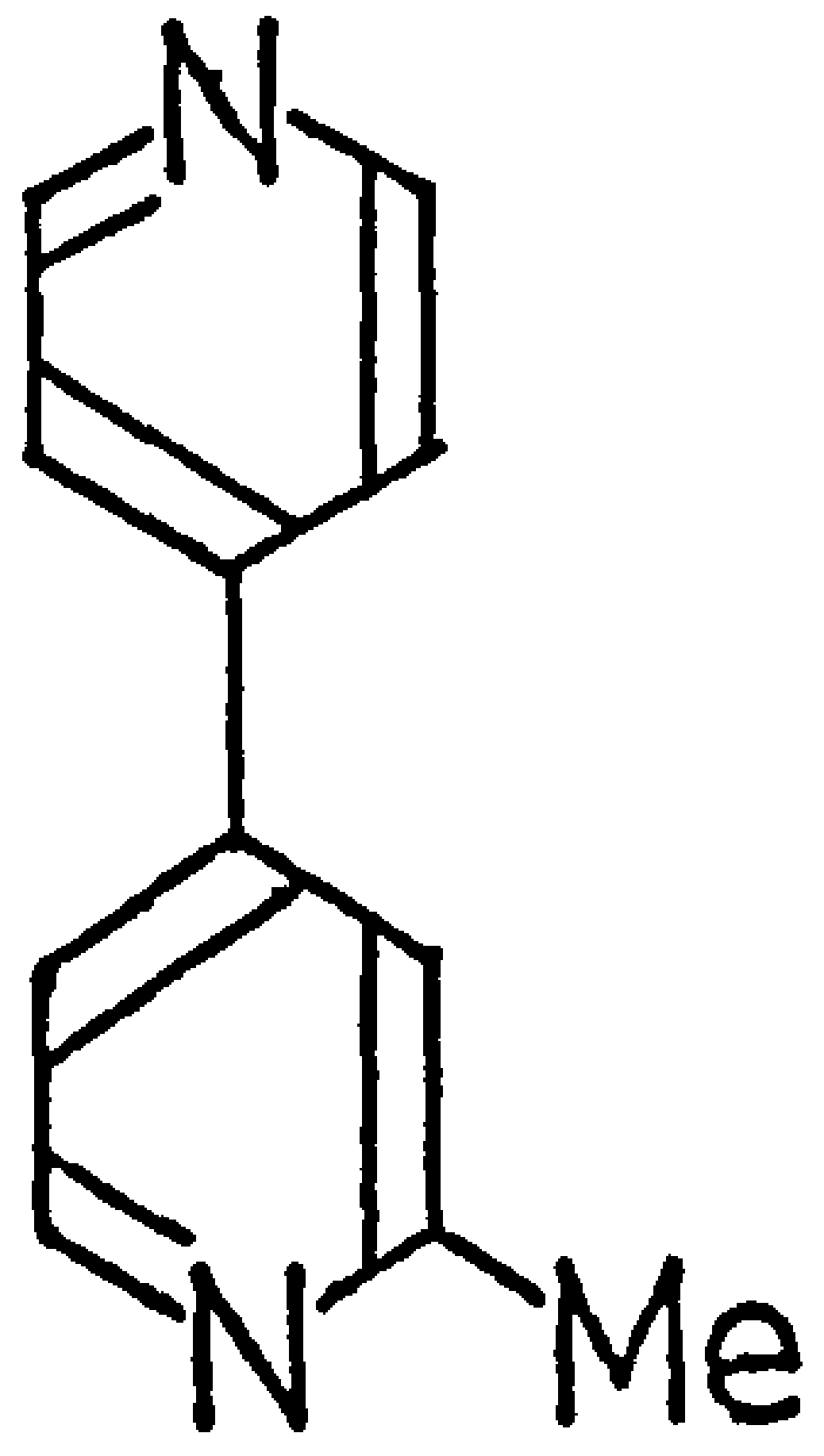
EXPERIMENTAL

All reactions were conducted in silica glass Carius tubes. The reactants were added under an atmosphere of anhydrous nitrogen and the tubes sealed under vacuum. After reaction was complete, the volatile products (gases and excess pyridine) were removed under vacuum and the residue analysed either by mass measurement or by the gas chromatographic techniques outlined in Chapter I. In those cases where deuteropyridines were involved, analysis by mass measurement was employed and the yields of each bipyridyl product were determined by the relative abundances of their molecular ions. Otherwise, bipyridyls were identified by gas chromatography and their yields calculated from the peak height of the product.

Analar pyridine, redistilled twice and stored over sodium hydroxide was used on all occasions. Pyridine d_5 (99.5% isotopically pure) was purchased from Prochem Ltd. 4-Chloropyridine hydrochloride and N(4-pyridyl) pyridinium chloride hydrochloride were purchased from Koch-Light Laboratories Ltd. All other materials used were Analar grade.

A general survey of the reactions of pyridyl pyridinium salts was conducted and the results appear in Table II. A more precise investigation of the thermal decomposition of N(4-pyridyl) pyridinium chloride was under taken using pyridine d_5. Samples of N(4-pyridyl)

Table II.

Reactants	Temp. (°C)	Time (hours)	Products (%)
Pyr + 4-ClPyrHCl	180	4	4,4'bipyr (45 - 50%)
Pyr + 4-BrPyrHCl	"	"	4,4'bipyr (55 - 60%)
Pyr/4-ClPyrHCl/HOAc	"	"	No bipyridyls
Pyr/4-ClPyrHCl/MeOH	"	"	4,4'bipyr (13%)
N(4-pyridyl) pyridinium chloride (PPC)	"	"	4,4'bipyr (6%)
PPC + Pyr	"	"	4,4'bipyr (10%)
PPC.HCl (alone)	"	"	4,4'bipyr (9%)
PPC.HCl + Pyr	"	"	4,4'bipyr (18%)
PPC.HCl + H_2O	"	"	4,4'bipyr (9%)
4-ClPyrHCl	"	"	m/e 172 and a trace of 4,4'bipyr
	"	"	 + trace 4,4'bipyr

pyridinium chloride d_5, used in this series of reactions were prepared by the method already outlined in Chapter I. (p 36). Molar ratios of 1 : 1 were used in all cases and the results are those previously reproduced in Table I.

CHAPTER III

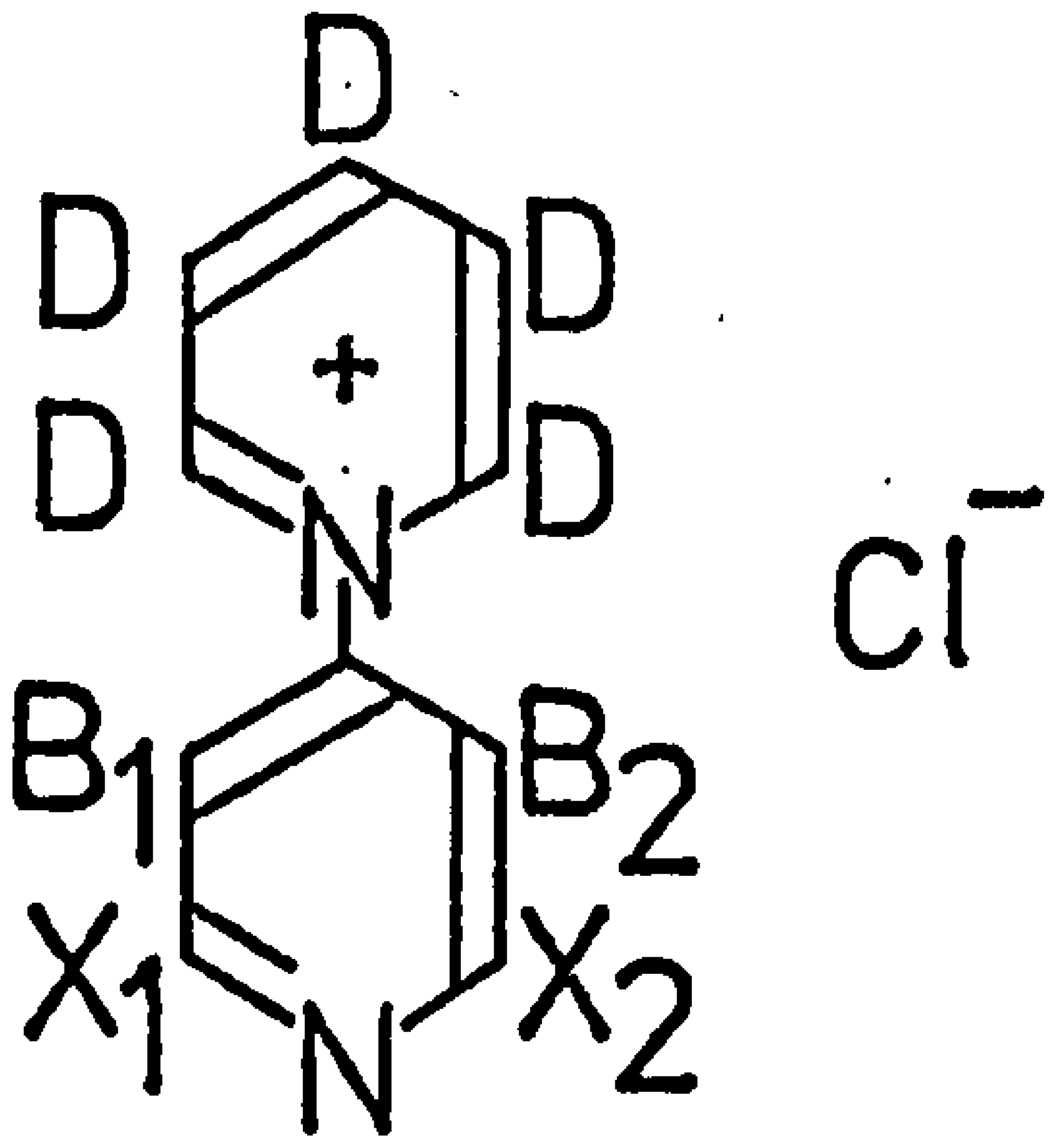
^{1}H n.m.r. spectra of N(4-pyridyl)pyridinium salts.

INTRODUCTION.

The ^{1}H n.m.r. spectra of substituted pyridines have been studied extensively (60) and generally the correlation between recorded and calculated spectra has been very good. The spectra discussed in this Chapter also show reasonable agreement with those predicted on a quantum mechanical basis by McConnell (61) and by Pople (62).

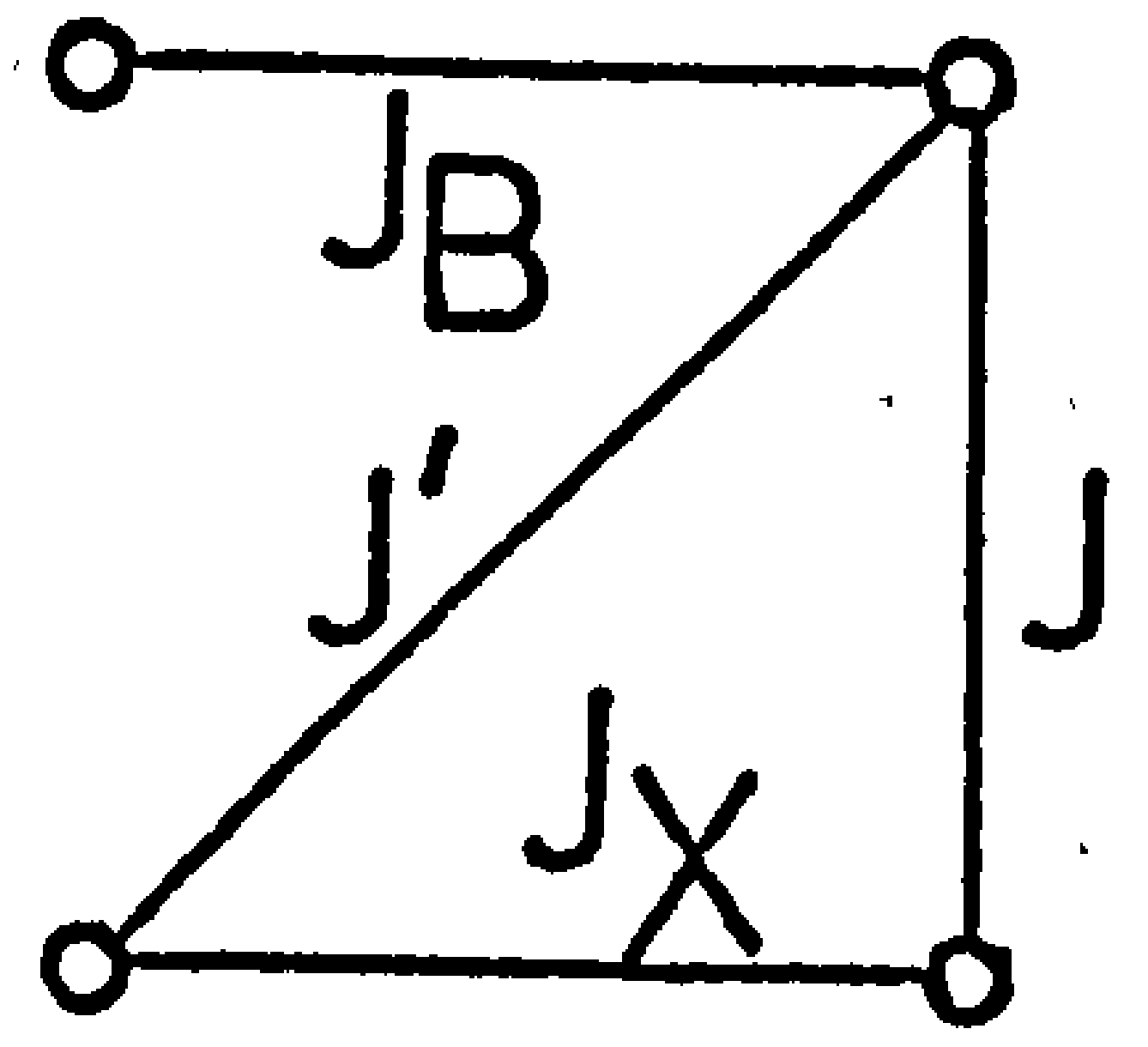
Throughout the discussion which is to follow, the spectra of the pyridyl pyridinium salts were regarded as comprising two distinct parts, representing the non-interacting contributions from each of the heterocyclic rings. Thus, the spectrum of N(4-pyridyl) pyridinium chloride d_5 (I), was analysed as a B_2X_2 spin system, like other 4-substituted pyridines.

(I)

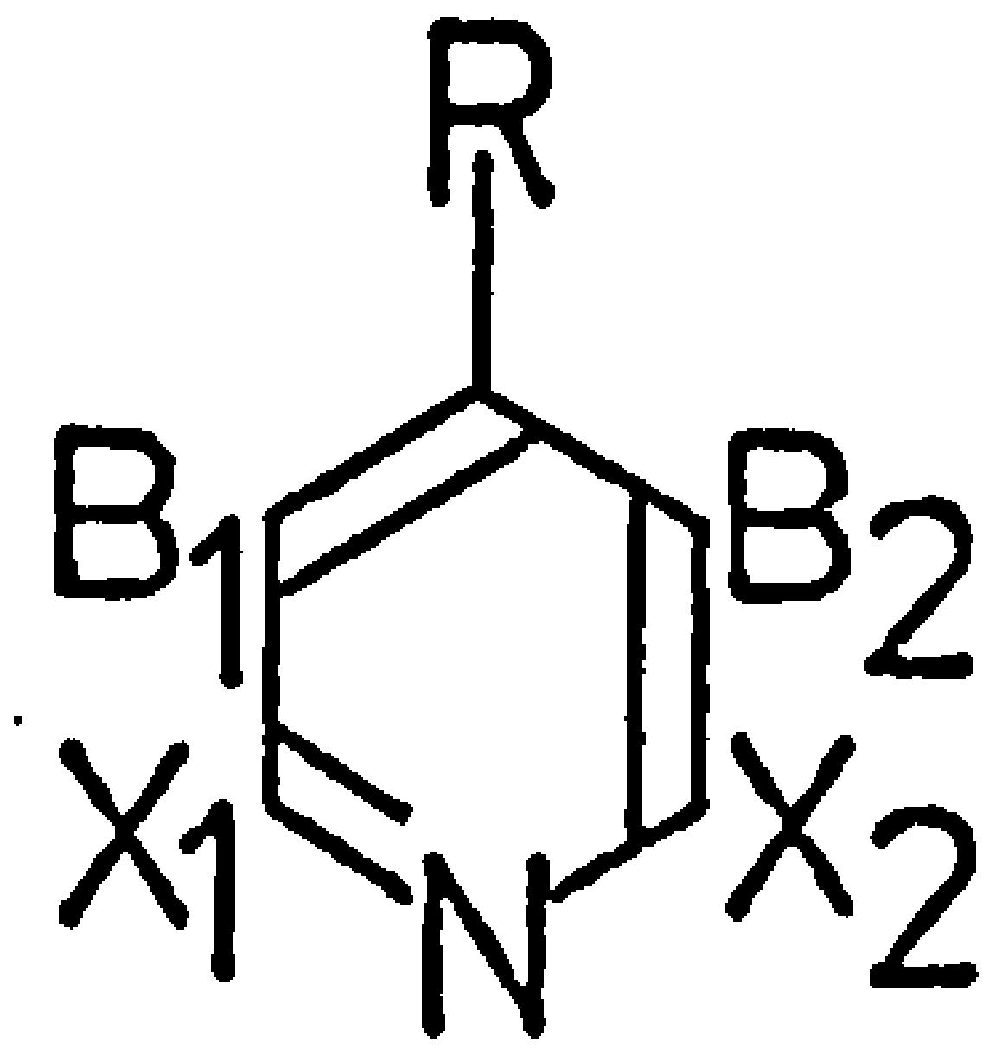


The theoretical background for B_2X_2 was first given by McConnell (63) and the method extended to the general case by Bernstein, Pople and Schneider (64). Analysis of the spectrum of 4-pyridine d_1 was successfully accomplished by this approach (65).

Such a treatment of the B_2X_2 system results in a total of 24 lines, due to equal numbers of B and X transitions. The coupling constants in the general case, and in the present case, are defined by :



and by



A derivation of the spectrum leads to the following relative energies for the B transitions (66) :

	TRANSITION	ENERGY RELATIVE TO ν_B
1.	$1s_1 \longrightarrow s_2$	$\frac{1}{2}N$
2.	$1s_0 \longrightarrow 1s_1$	$\frac{1}{2}N$
3.	$s_{-2} \longrightarrow 1s_{-1}$	$-\frac{1}{2}N$
4.	$1s_{-1} \longrightarrow 2s_0$	$-\frac{1}{2}N$
5.	$3s'_0 \longrightarrow 2s_1$	$\frac{1}{2}K + \frac{1}{2}(K^2 + L^2)^{\frac{1}{2}}$
6.	$2s_{-1} \longrightarrow 4s'_0$	$-\frac{1}{2}K + \frac{1}{2}(K^2 + L^2)^{\frac{1}{2}}$
7.	$4s'_0 \longrightarrow 2s_1$	$\frac{1}{2}K - \frac{1}{2}(K^2 + L^2)^{\frac{1}{2}}$
8.	$2s_{-1} \longrightarrow 3s'_0$	$-\frac{1}{2}K - \frac{1}{2}(K^2 + L^2)^{\frac{1}{2}}$
9.	$2a'_0 \longrightarrow 2a_1$	$\frac{1}{2}M + \frac{1}{2}(M^2 + L^2)^{\frac{1}{2}}$
10.	$2a_{-1} \longrightarrow 1a'_0$	$-\frac{1}{2}M + \frac{1}{2}(M^2 + L^2)^{\frac{1}{2}}$
11.	$1a'_0 \longrightarrow 2a_1$	$\frac{1}{2}M - \frac{1}{2}(M^2 + L^2)^{\frac{1}{2}}$
12.	$2a_{-1} \longrightarrow 2a'_0$	$-\frac{1}{2}M - \frac{1}{2}(M^2 + L^2)^{\frac{1}{2}}$

Where :

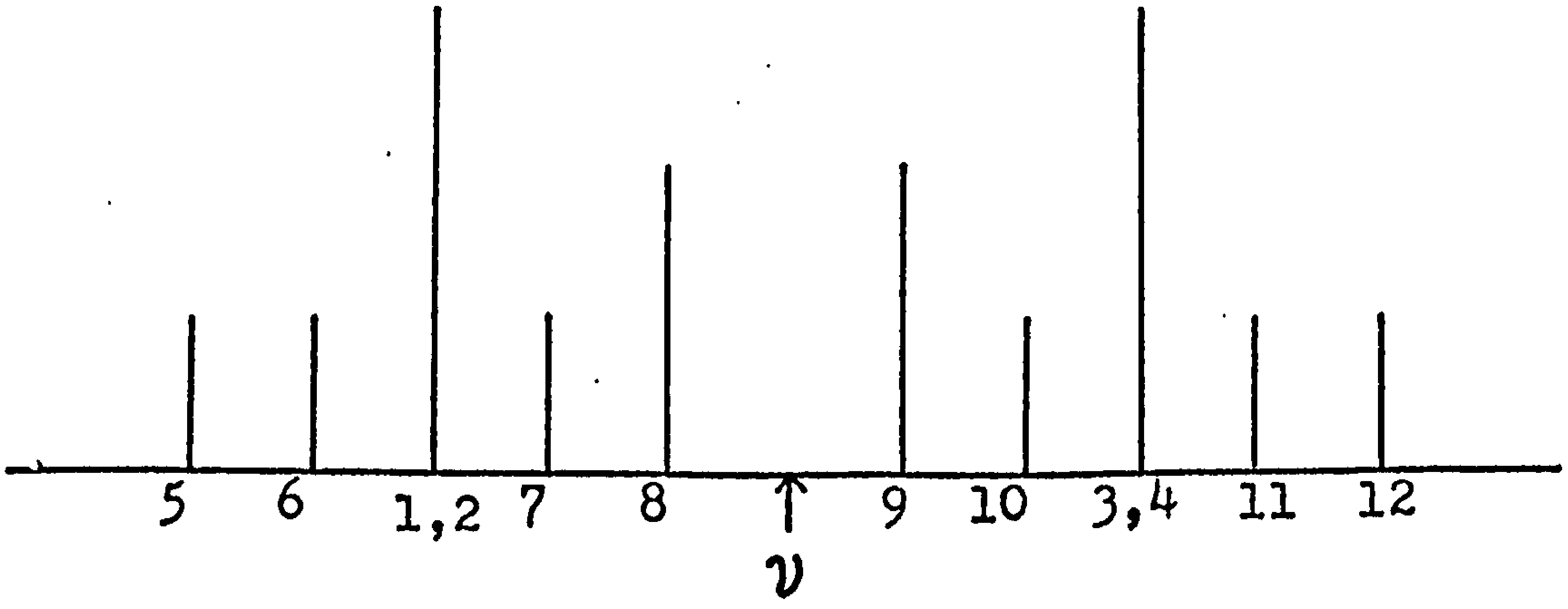
$$K = J_B + J_X \quad ; \quad L = J - J'$$
$$M = J_B - J_X \quad ; \quad N = J + J'$$

An entirely identical pattern can be derived for the twelve X transitions and consequently, both B and X spectra have the same form. By inspection of the table, it will be seen that they comprise :

(1) A strong doublet (lines 1,2,3 and 4), centered on the resonance frequency ν_B (or ν_X), the separation being N.

(2) Two symmetrical quartets (5,6,7,8 and 9,10,11,12) also centered on ν_B (or ν_X). It is generally found that innermost lines are the most intense and hence, can be readily assigned.

The shape of both B and X spectra is therefore of the form :



As has been noted above, the separation of the intense doublet is given by :

$$N = J + J'$$

and in this particular case by :

$$N = J_{23} + J_{25}$$

Thus, by measurement of the doublet separation, this sum can be determined.

Further, if we assume that $J_B = J_X$, it can be shown that the separation of the intense inner lines of the quartets is given by :

$$\left[(J_B + J_X)^2 + (J - J')^2 \right]^{\frac{1}{2}} - (J_B + J_X)$$

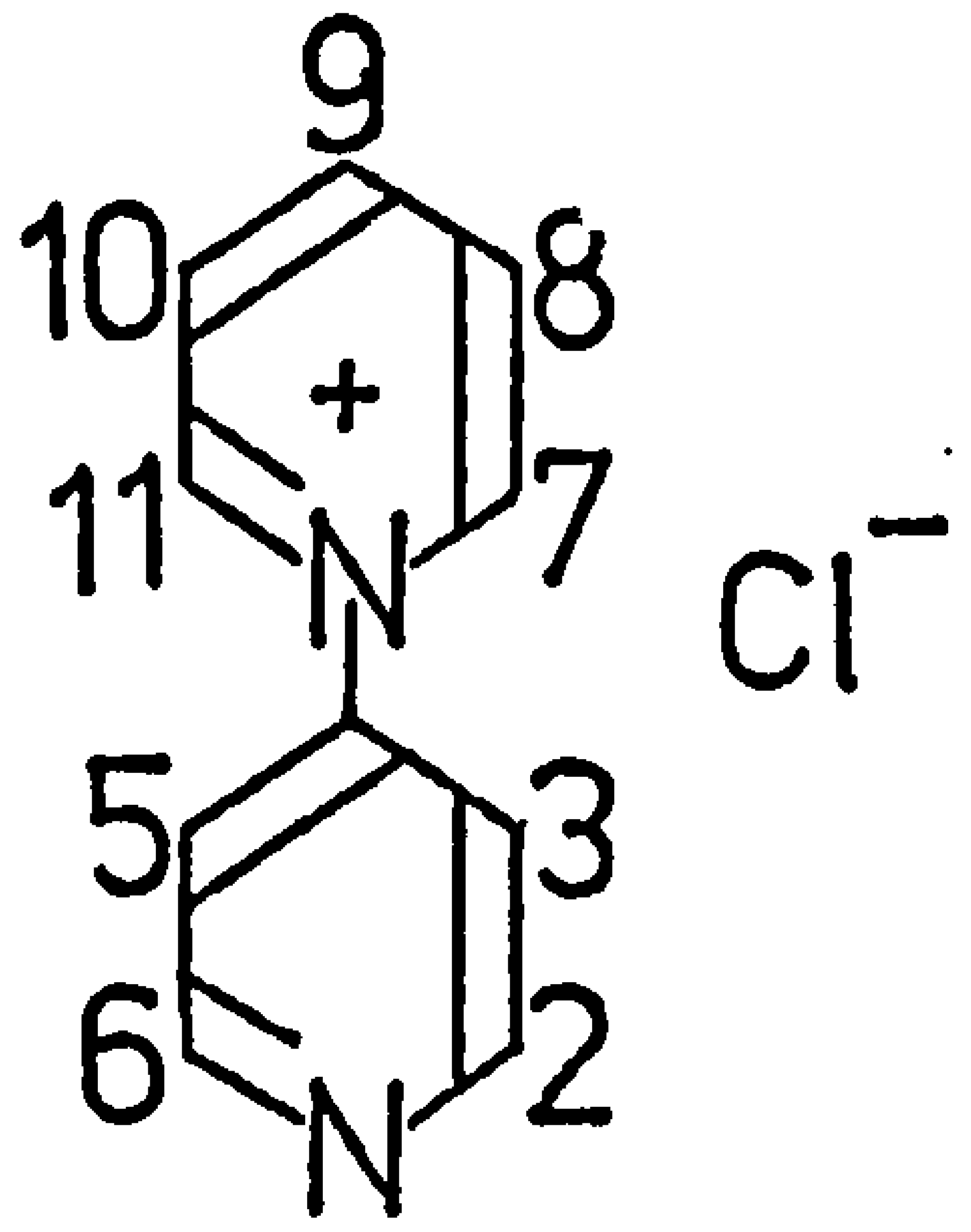
i.e. by :

$$\left[(J_{35} + J_{26})^2 + (J_{23} - J_{25})^2\right]^{\frac{1}{2}} - (J_{35} + J_{26})$$

Again, by measurement of the line spacing and by trial and error methods, we can derive all the coupling constants for this system quite simply. Although not absolutely accurate, these values will be fairly close to the correct coupling constants.

Having derived approximate values for all coupling constants in the N(4-pyridyl) substituent in (I), it was then assumed that they would also apply in the case of the non-deuterated molecule, N(4-pyridyl) pyridinium chloride (II)

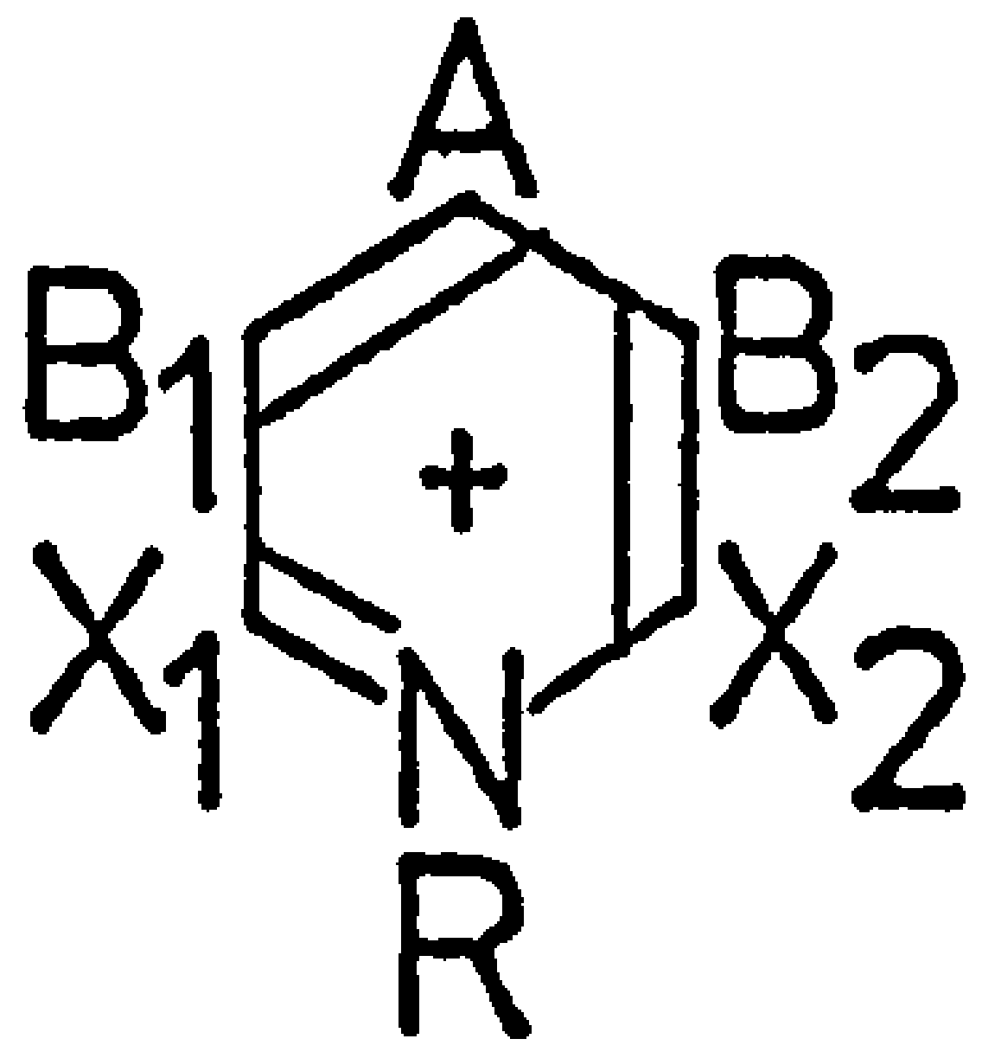
(II)



This type of approach has already been used successfully, notably in the analysis of the spectrum of pyridine itself (67). The authors of this work used data derived from the spectra of partially deuterated pyridines in order to complete the rather difficult analysis of the pyridine spectrum. Pyridine was shown to give rise to a spectrum of the AB_2X_2 type.

The spectrum of N(4-pyridyl) pyridinium chloride is considerably simplified if one can subtract those signals due to the B_2X_2 contribution from the N(4-pyridyl) substituent

Such a step then leaves the spectrum of the upper, pyridinium ring, which can be regarded as an AB_2X_2 type, thus :



Due to the complexity of this particular type, analysis of the spectrum relied on computer simulation by successive approximation to the correct coupling constants. By trial and error methods, plausible values for the coupling constants were used until an exact duplicate of the recorded spectrum was calculated by the computer. At this point, the selected values were taken as the best possible approximations to the correct coupling constants.

RESULTS AND DISCUSSION.

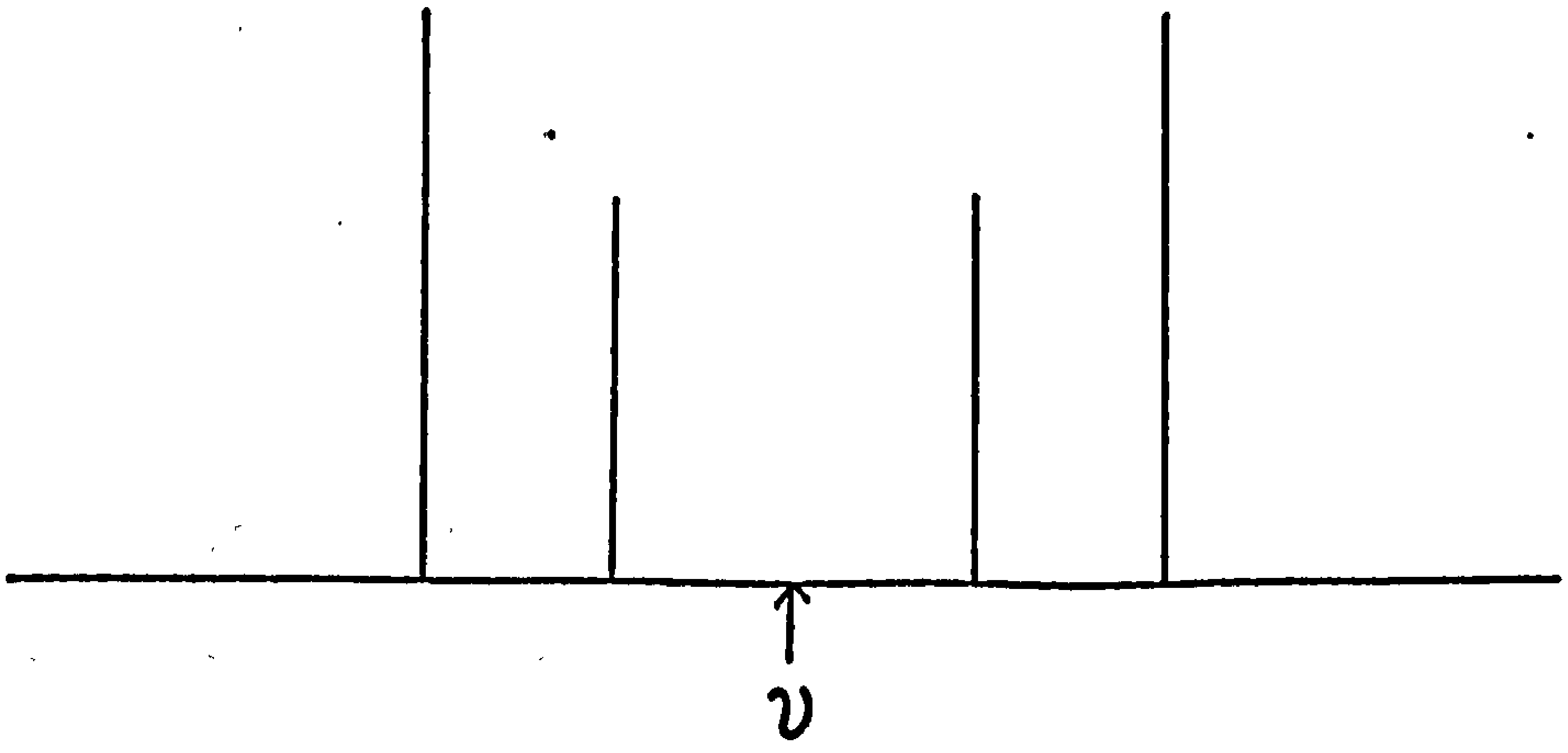
(1) N(4-pyridyl) pyridinium chloride d_5

The chemical shifts, as measured in D_2O, were :

$$\nu_X = 1.02\tau.$$
$$\nu_B = 2.06\tau.$$

and the separation of B and X spectra was measured as 62 Hz.

As was noted earlier, calculation of the theoretical spectrum of a B_2X_2 spin system results in two identical groups of lines, each comprising twelve transitions. In practice however, both B and X spectra are considerably simplified since all but the four strongest lines are not generally observed. These four lines correspond to the strong doublet centered on the resonance frequency and the innermost lines of each quartet. The usual form of both B and X spectra is thus reduced to :



Inspection of the observed spectrum showed clearly that these four lines were the predominant features of the B and X signals. In addition, some of the lesser lines of each quartet were clearly discernible either as distinct peaks or as shoulders. The complete spectrum of

N(4-pyridyl) pyridinium chloride d_5 is shown in Fig. 1. and these minor transitions are readily visible.

By utilising the four main transitions, as indicated in the Introduction, approximate values for the coupling constants can be derived from their separations.

(1) The strong doublet separation was measured as :

$$N = J_{23} + J_{25} = 6.4 \text{ Hz.}$$

(2) The separation of the two inner lines was found to be :

$$X = \left[(J_{35} + J_{26})^2 + (J_{23} - J_{25})^2\right]^{\frac{1}{2}} - (J_{35} + J_{26})$$
$$= 3.0 \text{ Hz.}$$

(3) And further, by closer inspection, the separation Y, probably the difference between lines 9 and 11 (from the table), was found to be 2.6 Hz.

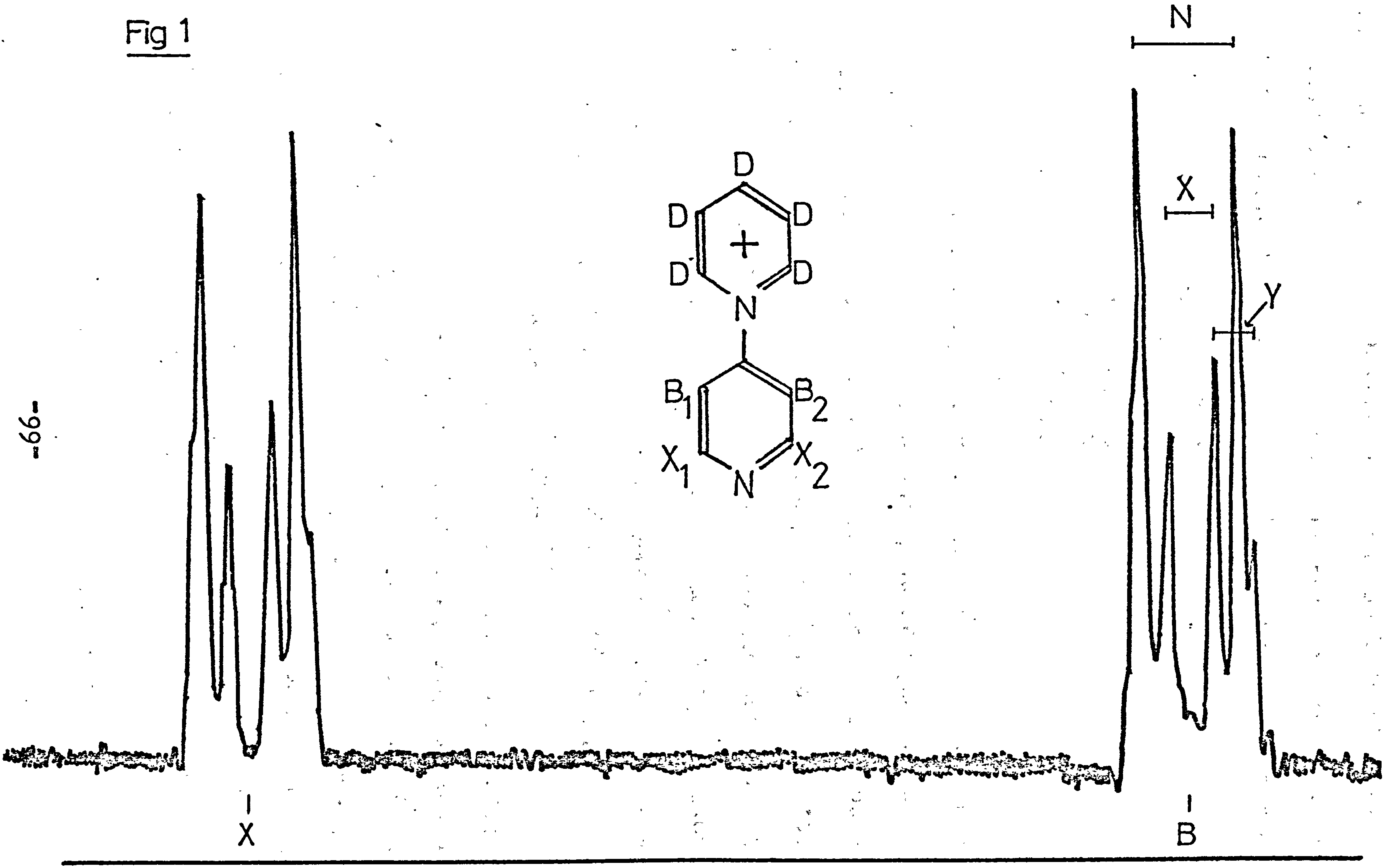
Bearing in mind the assumption already stated, namely that $J_{35} = J_{26}$, the best fit of foreseeable coupling constants proved to be :

$$J_{23} = 5.45 \text{ Hz.} \qquad J_{25} = 0.95 \text{ Hz.}$$
$$J_{35} = J_{26} = 0.9 \text{ Hz.}$$

It is to be emphasised that these values, however close they may be to the correct coupling constants, are only good approximations in view of the assumption already made.

When the spectrum was recorded at higher concentrations (up to 60%), pronounced changes occurred in the form of the spectrum. Firstly, there was a considerable shift to lower

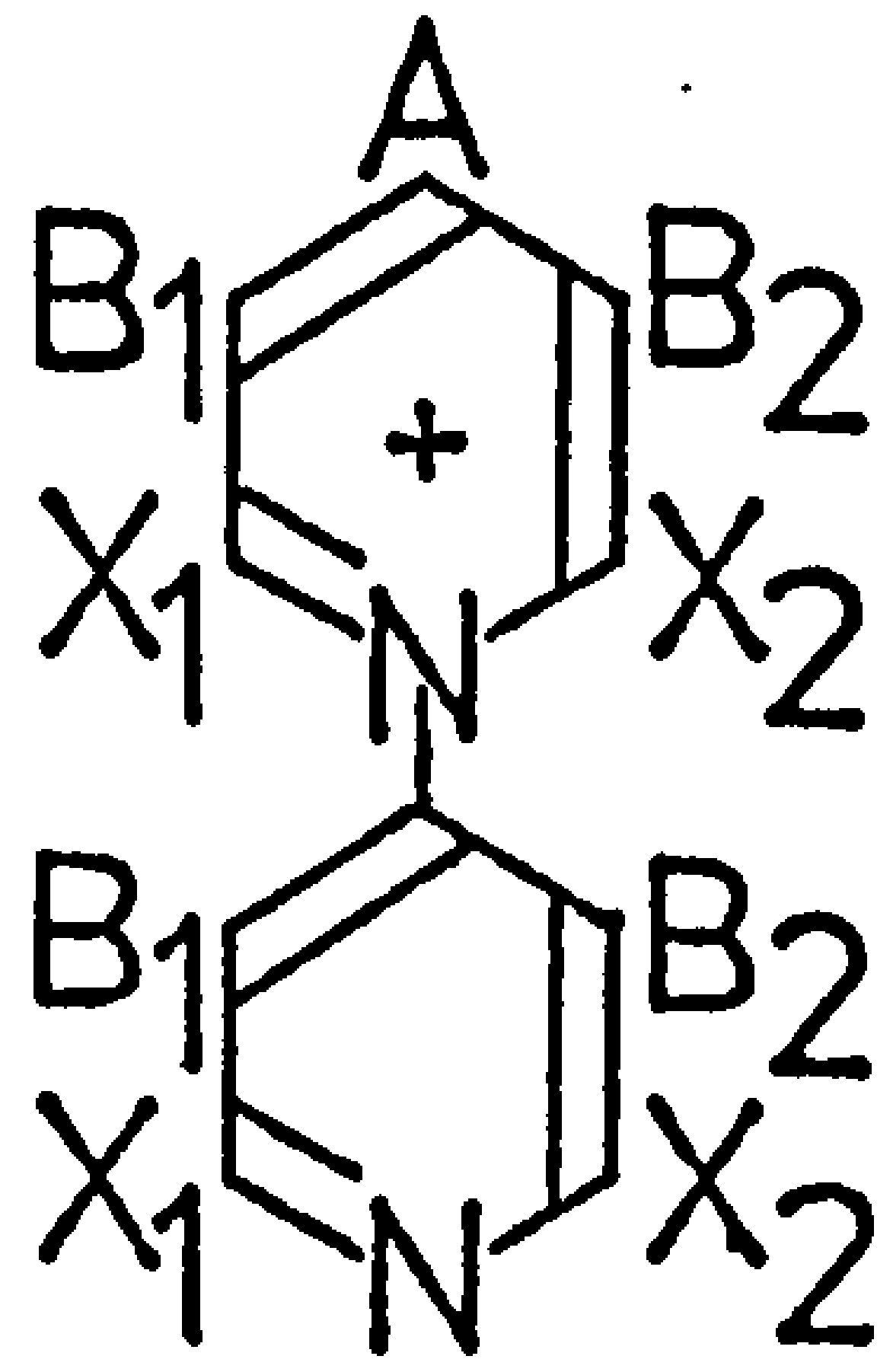
Fig 1



field ($\upsilon_X = 0.98; \upsilon_B = 1.94\tau$). Secondly, the fine structure of the X spectrum dissappeared altogether such that only two broad bands remained. The form of the B spectrum did not alter significantly as concentration increased. These data would seem to indicate an assocation between the nitrogen atom on the lower ring and some other species, resulting in the broadening of the X lines only. It is possible that the chloride counter-ion could cause such an effect at higher concentrations.

(2) N(4-pyridyl) pyridinium chloride

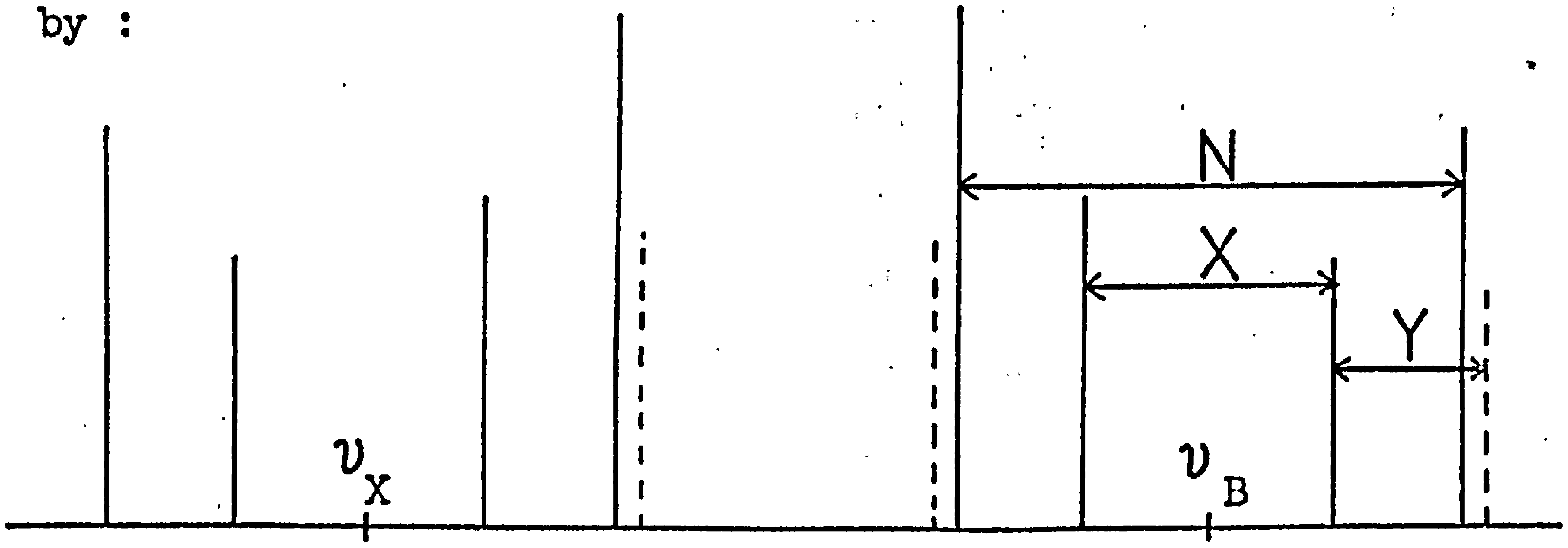
Naively, one might expect that the spectrum of this compound would consist simply of the super-imposed contributions from upper and lower rings, with little or no interaction between the two. In fact, this appears to be so, and the B_2X_2 spectrum of the lower ring is easily recognised. Consequently, we may regard the spectrum of this molecule as an AB_2X_2 contribution from the pyridinium ring, and a B_2X_2 part due to the lower ring :



The B_2X_2 spectrum of the N(4-pyridyl) substituent is an exact replica of that recorded for the deuterated analogue. Again, several of the less intense lines of the quartets are visible, particularly in the B spectrum. The observed resonance frequencies were :

$$\nu_X = 1.03\ \tau$$
$$\text{and } \nu_B = 2.03\ \tau$$

The small differences between these values and those recorded for the partially deuterated molecule may be ascribed to minor variations in the concentrations of the samples. The overall form of this part of the spectrum can be represented by :



The broken lines indicate the presence of the less intense transitions within the outer quartets. It will be noted also that the intensities of corresponding lines in the B and X spectra bear a mirror-image relationship to each other. This is commonly found in spectra of this type.

Measurement of the separations N, X and Y gave precisely the same values as those noted for N(4-pyridyl) pyridinium chloride d_5 , viz.

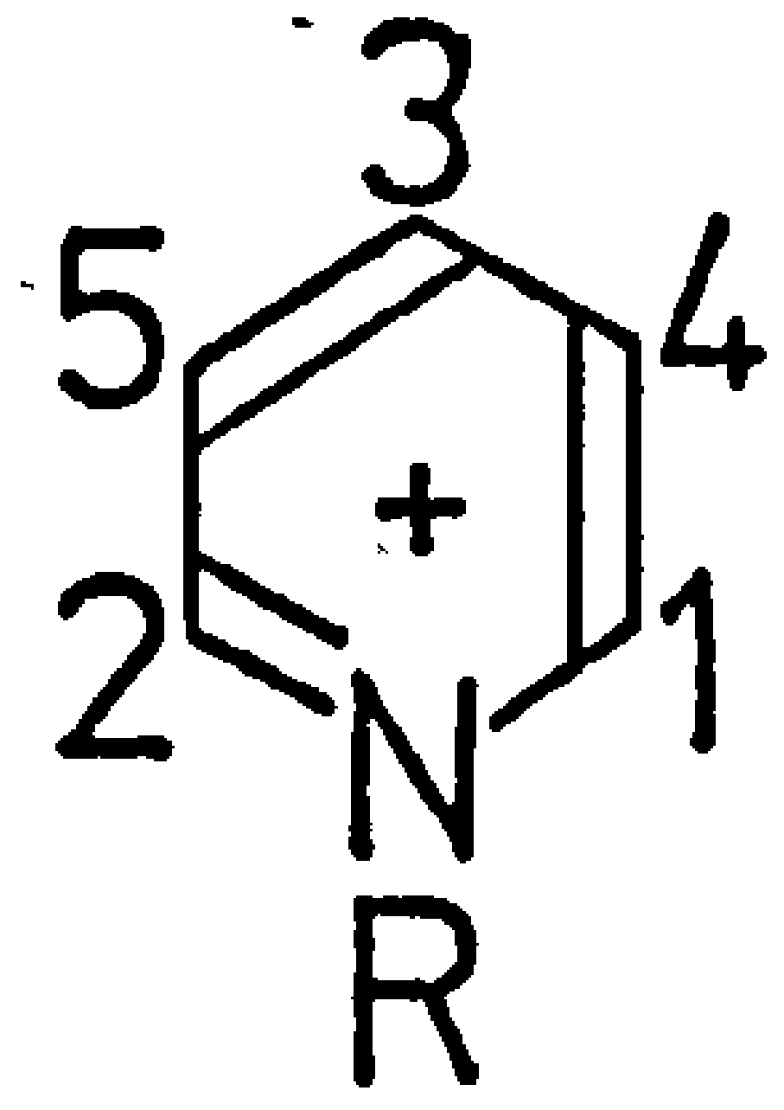
N = 6.4 Hz.
X = 3.0 Hz.
Y = 2.6 Hz.

And consequently, the same values resulted for the coupling constants :

$$J_{23} = 5.45 \text{ Hz.} \qquad J_{25} = 0.95 \text{ Hz.}$$
$$J_{35} = J_{26} = 0.90 \text{ Hz.}$$

The spectrum of the remaining, pyridinium ring was analysed as an AB_2X_2 type on a KDF 9 computer, using a normal five-spin programme. The data required for each computer calculation consisted of the chemical shifts of all five protons (obtained from the recorded spectrum) and values for all ten H/H coupling constants in the system. For the purposes of the calculations only, the protons were numbered in the same order as their chemical shifts (lowest field = H_1 ; etc.) and the coupling constants re-arranged to conform to this order. Input data was therefore presented in the following sequence :

$$\begin{array}{lllll}
\nu_1 \;; & \nu_2 \;; & \nu_3 \;; & \nu_4 \;; & \nu_5 \;; \\
J_{12} \;; & J_{13} \;; & J_{14} \;; & J_{15} \;; & \\
 & J_{23} \;; & J_{24} \;; & J_{25} \;; & \\
 & & J_{34} \;; & J_{35} \;; & \\
 & & & J_{45} \;; &
\end{array}$$



Having selected suitable coupling constants, the computer was programmed to calculate the spectrum using these values and the result compared with the observed spectrum. In the light of the computer calculations, the coupling constants were then re-assessed and the process repeated until the calculated and observed spectra corresponded exactly. When this situation was attained, the selected coupling constants were presumed to be the best possible approximations to the correct values. The results of only five calculations are reproduced here, including the best fit obtained (Run E). The relevant part of the observed spectrum is also added for comparison. It will be noted that this region of the spectrum is interrupted by the signal from the X protons of the other ring, which consequently obliterates part of the γ-proton resonance from the pyridinium ring. However, the peaks which are visible do compare extremely well with the final calculated spectrum, as is shown by the super-position of both (Fig. 1).

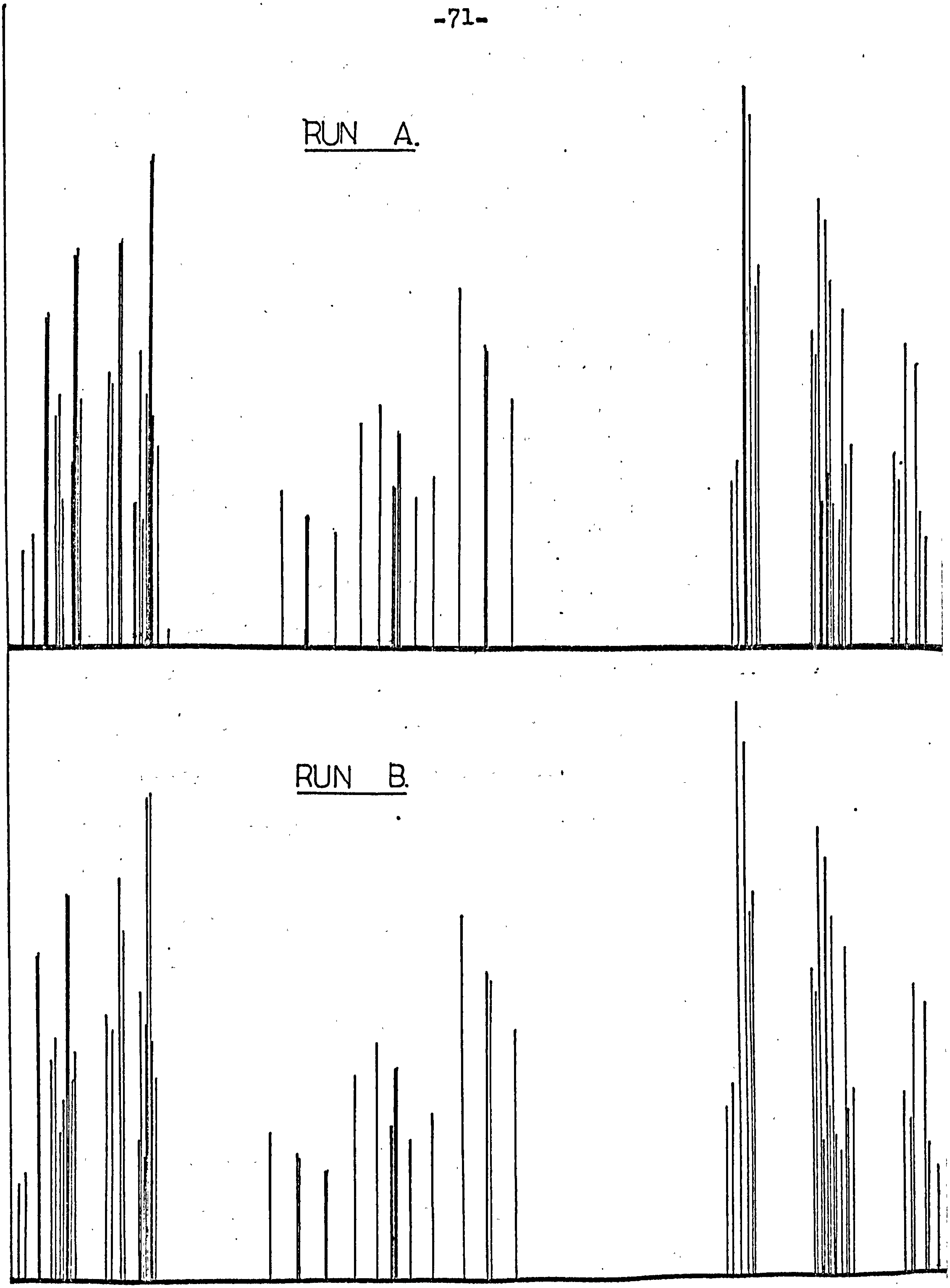
The parameters used in each calculation were as follows :

Run A

ν_1 = 43.2 Hz. ; ν_2 = 43.2 Hz. ; ν_3 = 65.4 Hz.
ν_5 = 96.0 Hz. ; ν_4 = 96.0 Hz.

J_{12} = 0.4 ; J_{13} = 1.9 ; J_{14} = 5.5 ; J_{15} = 0 Hz.
J_{23} = 1.9 ; J_{24} = 0 ; J_{25} = 5.5 Hz.
J_{34} = 6.5 ; J_{35} = 6.5 Hz.
J_{45} = 1.6 Hz.

By examining the spectrum calculated from these figures, it was clear that a wider separation of the two main components of the H_1/H_2 multiplet was required, achieved by increasing the magnitudes of both J_{14} and J_{25}. Similarly, the values of J_{34} and J_{35} needed increasing in order to produce a


RUN A.
RUN B.

greater separation of the three broad H_3/H_5 bands. These modifications were included in the following calculation :

Run B

Chemical shift values were as in Run A.

$J_{12} = 0.4$; $J_{13} = 1.9$; $J_{14} = 6.0$; $J_{15} = 0$ Hz.
$J_{23} = 1.9$; $J_{24} = 0$; $J_{25} = 6.0$ Hz.
$J_{34} = 7.0$; $J_{35} = 7.0$ Hz.
$J_{45} = 1.6$ Hz.

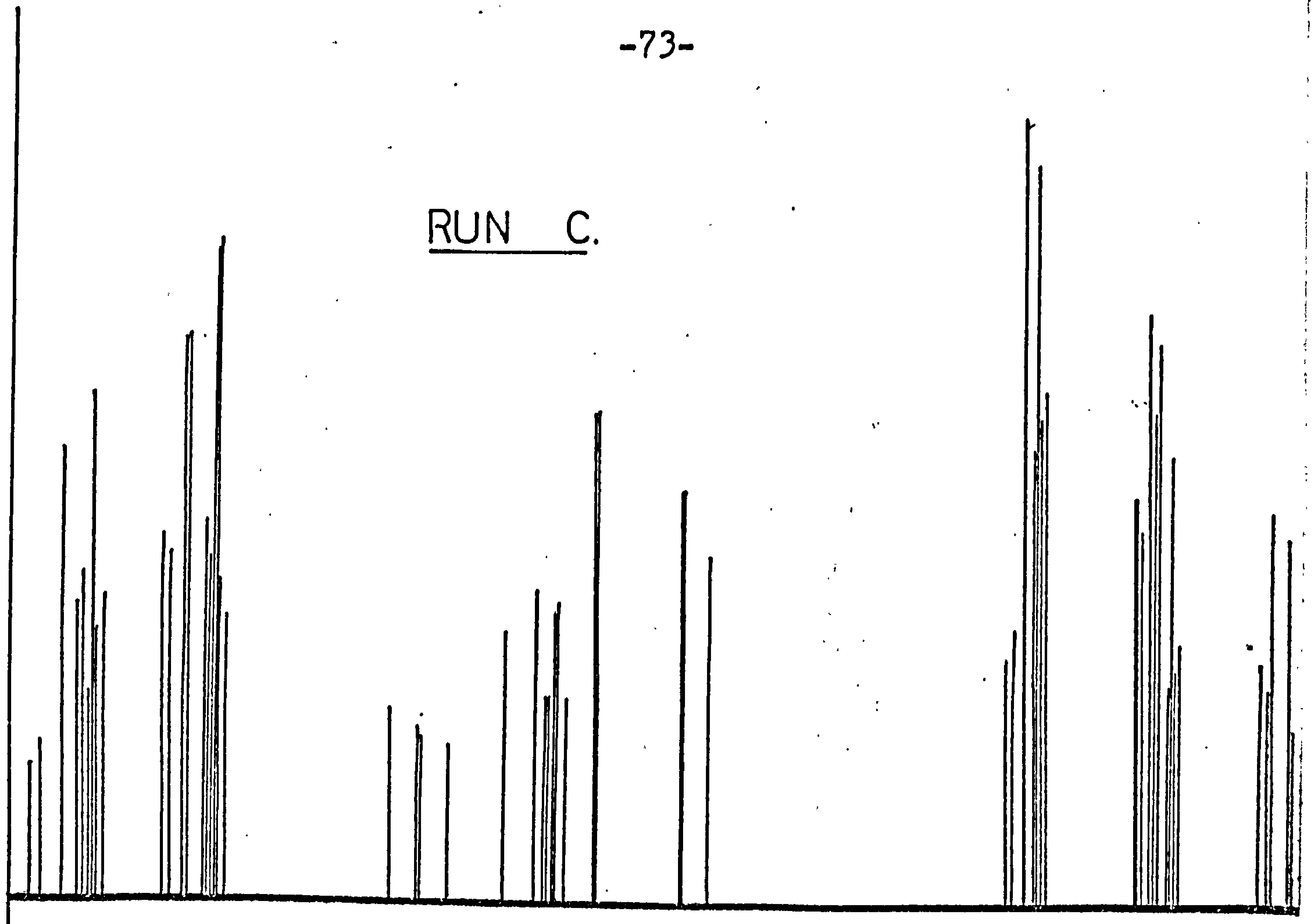
Again, by inspection, it was clear that the values of J_{14} and J_{25} were still not sufficiently large to produce the required splitting in the H_1/H_2 signal. The values of J_{34} and J_{35} now seemed to be correct since the calculated and observed separations in the H_4/H_5 resonance had become identical. A small reduction in the magnitude of J_{13} and J_{23} would have the effect of diminishing the minor doublet separation in the H_1/H_2 signal, which at this point is a little too great.

Run C

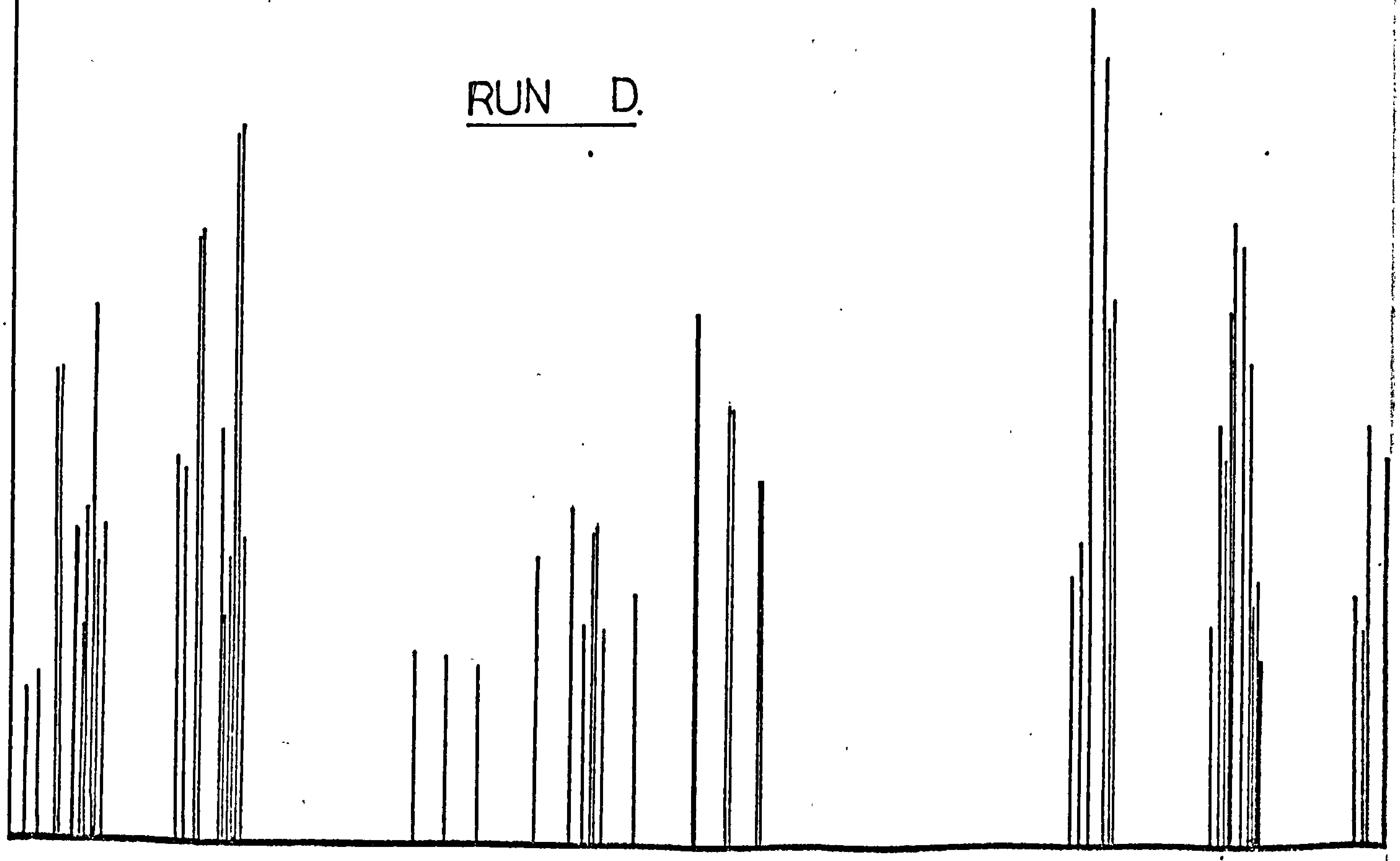
Chemical shift values were as in previous Runs.

$J_{12} = 0.4$; $J_{13} = 1.5$; $J_{14} = 6.5$; $J_{15} = 0$ Hz.
$J_{23} = 1.5$; $J_{24} = 0$; $J_{25} = 6.5$ Hz.
$J_{34} = 7.0$; $J_{35} = 7.0$ Hz.
$J_{45} = 1.6$ Hz.

A further small increase in the values of J_{14} and J_{25} was still required in order to pull apart the main components of the H_1/H_2 multiplet to the separation measured in the



RUN C.



RUN D.

observed spectrum.

Run D

Chemical shift values were as in previous Runs.

$J_{12} = 0.4$; $J_{13} = 1.5$; $J_{14} = 7.0$; $J_{15} = 0$ Hz.
$J_{23} = 1.5$; $J_{24} = 0$; $J_{25} = 7.0$ Hz.
$J_{34} = 7.0$; $J_{35} = 7.0$ Hz.
$J_{45} = 1.6$ Hz.

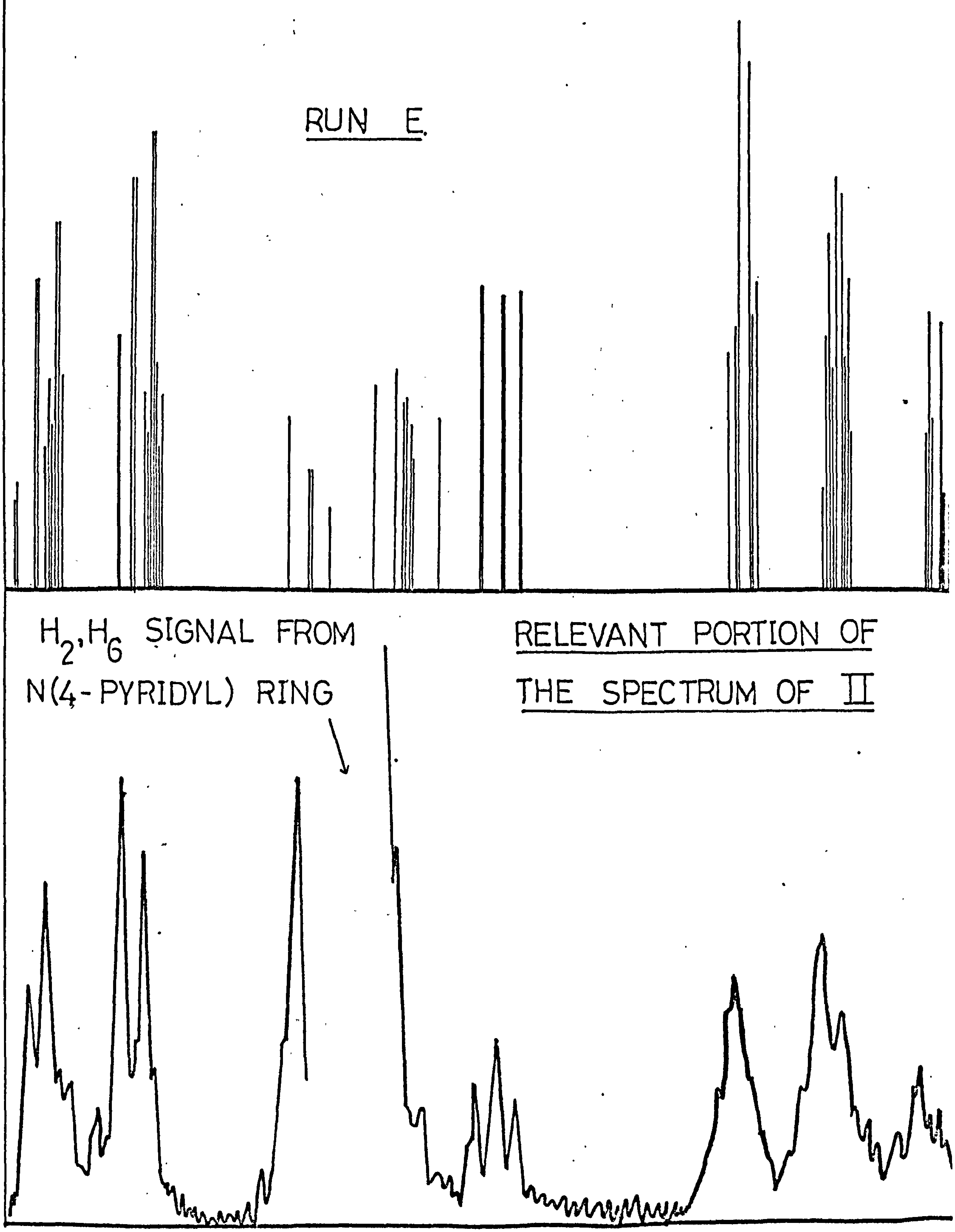
The effect of this small change in the values of J_{14} and J_{25} was to produce a much more ordered spectrum. A good deal of definition could now be seen in the H_3 signal and the main components of the H_1/H_2 multiplet were now at the correct separation. The secondary doublets were however a little too widely spaced and consequently, J_{13} and J_{23} required a further small reduction. In the light of work done on the ^{1}H n.m.r. of pyridine, by Castellano and co-workers (68), the sign of the coupling constant J_{12} was reversed and the spectrum then re-calculated.

Run E

Chemical shifts were as in previous Runs.

$J_{12} = -0.4$; $J_{13} = 1.4$; $J_{14} = 7.0$; $J_{15} = 0$ Hz.
$J_{23} = 1.4$; $J_{24} = 0$; $J_{25} = 7.0$ Hz.
$J_{34} = 7.0$; $J_{35} = 7.0$ Hz.
$J_{45} = 1.6$ Hz.

The spectrum obtained from this calculation was found to be virtually identical to that actually observed. This is demonstrated clearly by super-imposing the two spectra (Fig.2),


RUN E.
H_2,H_6 SIGNAL FROM N(4-PYRIDYL) RING
RELEVANT PORTION OF THE SPECTRUM OF II

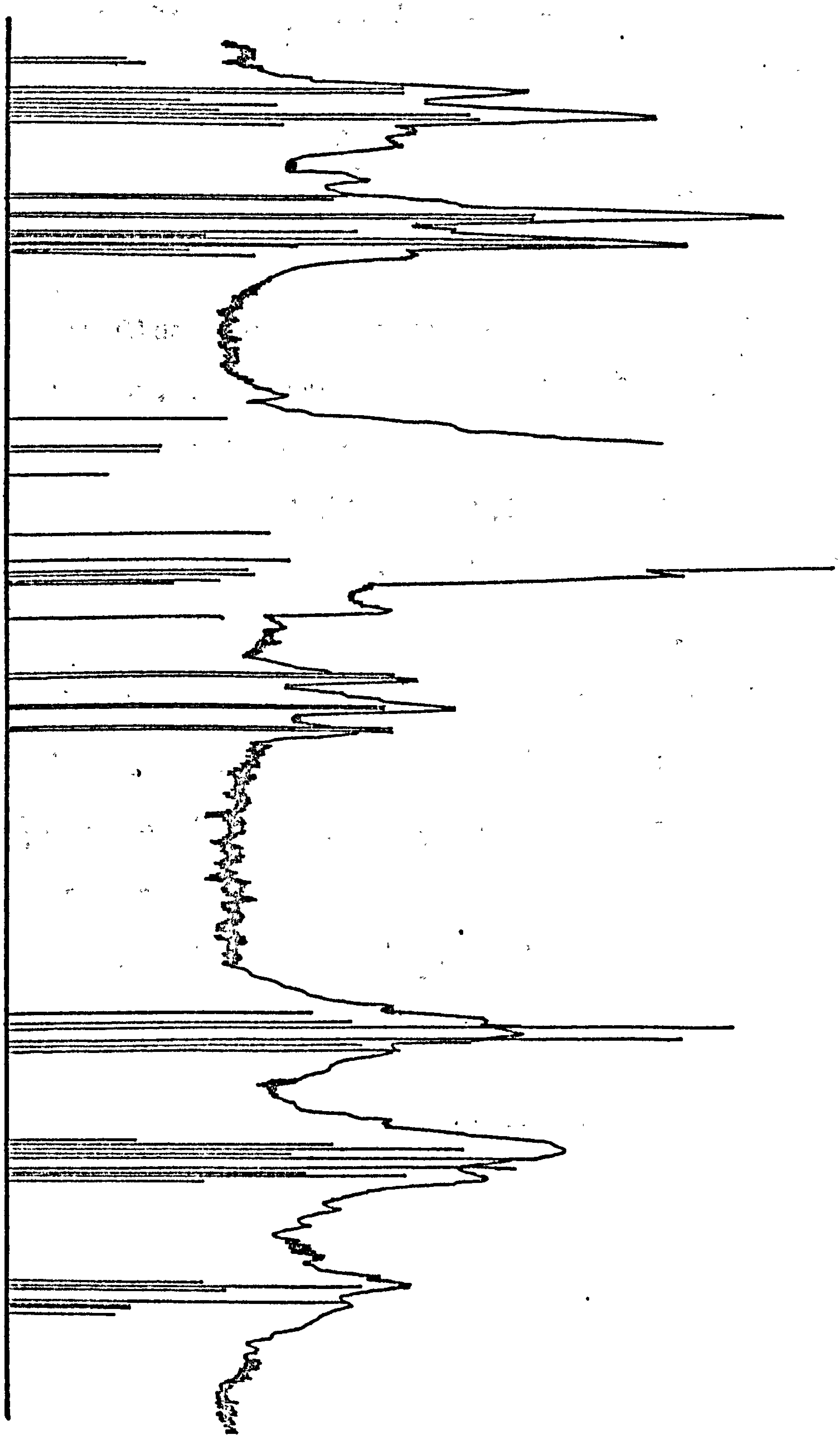


Fig.2

Subsequently, the signs of all meta coupling constants were changed (i.e. J_{12} , J_{13} , J_{23} and J_{45}). It was found that the form of the spectrum was relatively insensitive to all but that of J_{12}. It therefore seems likely that this parameter does in fact have a negative sign.

The complete ^{1}H n.m.r. spectrum of N(4-pyridyl) pyridinium chloride is reproduced in Fig. 3. The chemical shifts, relative to internal references of acetone and water, were as follows :

$$H_2/H_6 = 1.03\tau \; ; \quad H_3/H_5 = 2.03\tau.$$
$$H_7/H_{11} = 0.72\tau \; ; \quad H_8/H_{10} = 1.60\tau.$$
$$H_9 = 1.10\tau.$$

The calculated coupling constants (Hz.) were :

$J_{23} = 5.45$; $J_{25} = 0.95$; $J_{26} = J_{35} = 0.9$;

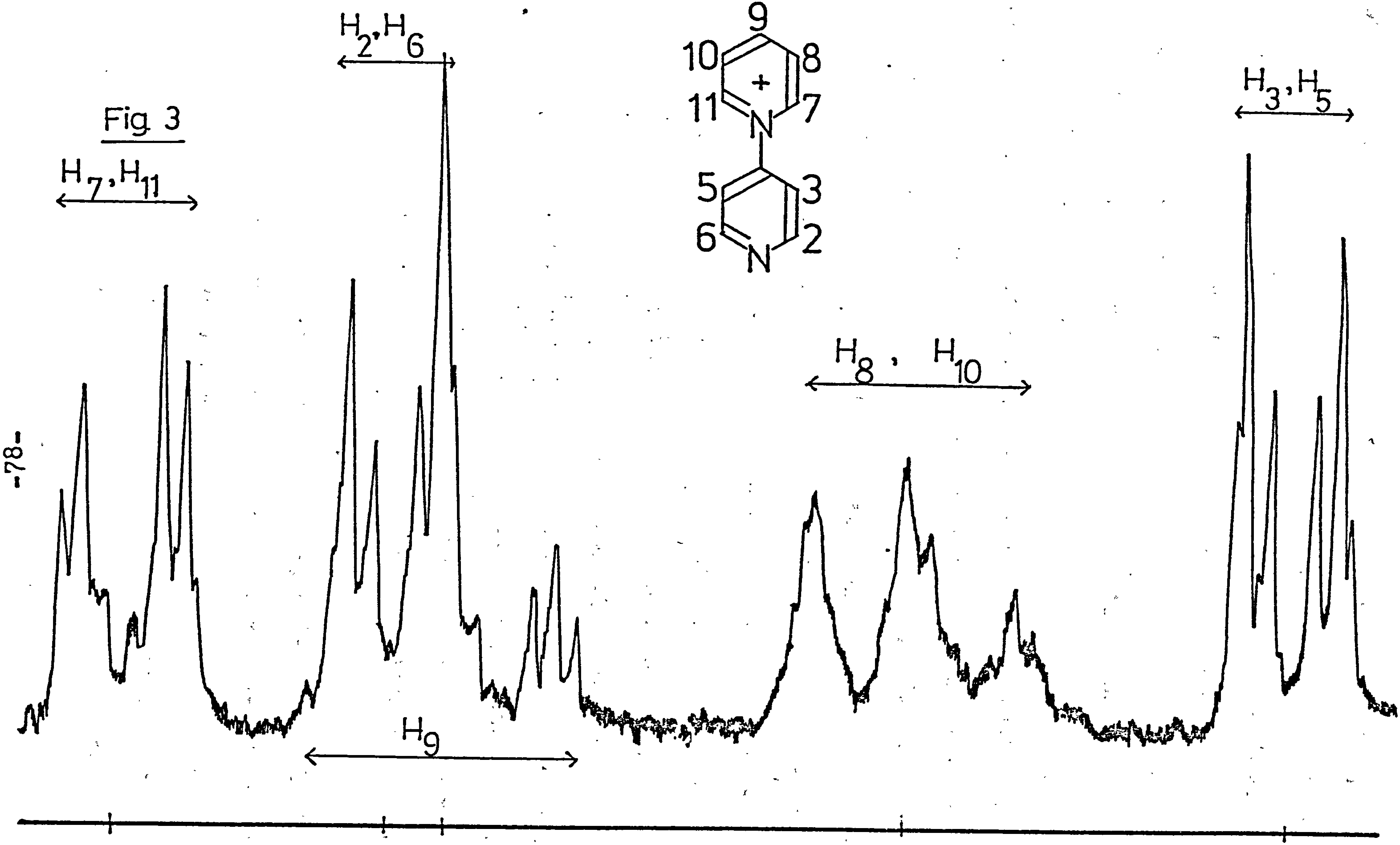
$J_{78} = 7.0$; $J_{79} = J_{9,11} = 1.4$;

$J_{7,10} = 0$; $J_{7,11} = -0.4$;

$J_{8,10} = 1.6$; $J_{8,11} = 0$;

$J_{89} = J_{9,10} = 7.0$;

Fig 3



In order to put the chemical shifts observed for N(4-pyridyl) pyridinium chloride into the correct perspective, a brief discussion of the factors influencing the proton resonances of pyridine and pyridinium ions is necessary. Probably the most striking features of these spectra are that :

(a) the H_γ resonance in pyridine is much closer to that of H_β than it is to the H_α signal.

(b) protonation of pyridine causes a low-field shift of all signals but that this effect is much less apparent in the H_α signal than it is for either H_β or H_γ.

It is now accepted that the position of the proton resonances in pyridine, and the small low-field shift of the H_α signal in the spectrum of the pyridinium ion, cannot be rationalised solely on the basis of π-electron density around the ring. Calculation has shown (69) that, due to its electronegativity, the nitrogen atom in pyridine removes π-electrons from both α and γ positions and in fact, may slightly increase the electron density at H_β. If the proton chemical shifts were determined only by the electron densities at each carbon atom, then we should expect that the γ resonance would lie at a median position between α and β signals. Consequently, there must be another effect operating, which will deshield the α protons by an additional 0.4 ppm. (See Table I).

It is equally unexpected that by protonating pyridine,

TABLE I

Sample		Chemical shifts (τ)			Reference
Pyridine :		α	β	γ	
(i)	Neat	1.41 ;	2.88 ;	2.49	(68)
(ii)	0.1M $CDCl_3$	1.56 ;	2.90 ;	2.50	(73)
(iii)	30% w/v D_2O	1.57 ;	2.75 ;	2.38	
Pyridine HCl					
(i)	20% w/v $CDCl_3$	0.89 ;	1.74 ;	1.29	(73)
(ii)	0.1M CH_3CN	1.16 ;	1.94 ;	1.44	(73)
(iii)	30% w/v D_2O	1.01 ;	1.81 ;	1.25	
Pyridine HBr					
(i)	20% w/v $CDCl_3$	0.80 ;	1.69 ;	1.22	(73)
(ii)	30% w/v D_2O	1.26 ;	2.01 ;	1.47	
_n_-propyl pyridinium iodide					
(i)	30% w/v D_2O	0.96 ;	1.79 ;	1.31	
N(4-pyridyl) pyridinium chloride					
(i)	30% w/v D_2O	0.72 ;	1.60 ;	1.10	

there is a preferential reduction of electron density at positions β and γ at the expense of H_a, but this would be the logical conclusion were the π-electron density the only factor responsible for the chemical shifts.

It has been suggested (70) that the H_a resonance in pyridine is influenced by a large paramagnetic contribution to the magnetic susceptibility due to the low-lying transition $n \rightarrow \pi^*$. Consequently, this signal appears at an abnormally low field value. On protonation, the above paramagnetic influence no longer exists (71) and hence the low field shift of the H_a resonance, due to the effects of the quaternary nitrogen, is artificially small when compared with the corresponding shifts of both β and γ protons.

The extent of ion-pair formation can also determine the relative chemical shifts of the ring hydrogens. In this respect it must be noted that the solvent has a considerable function, since the degree of ion-pairing is largely governed by the power of the solvating species. Thus, solvation of the anion or cation reduces the shielding or deshielding effect of one upon the other by increasing the inter-ionic distance. In the case of the pyridinium ion, the proximity of the counterion can be of critical importance due to its potential shielding influence, particularly on the a protons. The approach of the counter-ion is also restricted by the size of the substituent on nitrogen (72). Obviously, a large substituent has a high steric requirement and will not therefore permit the close approach of the counterion to the quaternary centre.

In this particular study, all spectra were recorded in D_2O and the relation of the observed data to some already published is summarised in Table I. It is clear that in such a solvent ion-pairing is substantially reduced, due to the ready solvation of the pyridinium ion. A comparison of the spectra of the hydrochloride and hydrobromide of pyridine shows that the separation of α, β and γ signals is almost identical in both cases. However, there is a general shift of all signals to higher field in the case of pyridine hydrobromide. This phenomenon can be understood as a result of the greater size of the bromide counterion. Since ion-pairing is greatly restricted in D_2O, the anion is relegated to some other position a little removed from the heterocyclic ring. Due to its greater radius, and therefore greater sphere of influence, the more polarisable bromide ion can exert a shielding effect on all proton resonances from a position some distance removed from the ring. At such a distance, however, the chloride ion is not capable of creating this reaction. Since the high-field shifts observed in the hydrobromide are all roughly equal, it is proposed that the anion occupies a position vertically above the centre of the ring, from where its effect on all protons is equivalent.

The chemical shifts recorded for N(4-pyridyl) pyridinium chloride can be rationalised in a similar manner. The rather low field values are a consequence of the quaternary nitrogen and the inductive effect of the 4-pyridyl substituent. However, the down-field shifts from the pyridine hydrochloride resonances are not equal for each proton, those of the β and γ protons being less than that of H_α. It is possible that, due to the inaccessibility of the quaternary centre, the chloride counterion is situated nearer to the electron deficient and less sterically hindered β and γ positions of the pyridinium ring (73). As a result, the low-field shifts of the β and γ protons are slightly smaller than that observed for H_α. This explanation may be applied to the spectrum of n-propyl pyridinium iodide also, where the disparity in the low-field shifts is much more marked.

Consequently, the solution form of N(4-pyridyl) pyridinium chloride can be regarded as comprising two distinct ions, the cation being solvated to some extent by D_2O and the anion being removed from the positive centre due to a high degree of steric crowding.

It is also possible to comment briefly on the relative orientation of the two rings. From the chemical shifts observed, it appears that the ring current generated in the N(4-pyridyl) substituent does not exert a deshielding influence on the α protons of the upper, pyridinium ring. This phenomenon was observed by Spotswood and Tanzer (74) in the ^{1}H n.m.r. spectrum of 2,2'bipyridyl, where the 3 and 3' protons were considerably deshielded by the neighbouring ring. From the extent of deshielding, they deduced an inter-planar angle of about 15°. In this present case, it seems apparent that the inter-planar angle is rather more, since no observable deshielding occurs. It also seems likely that this angle could be increased as a consequence of solvation at the quaternary centre (75).

EXPERIMENTAL

The salts used in this study were prepared by the method outlined in Chapter I and their spectra recorded on a Perkin-Elmer R. 10 instrument. Samples were measured , at 33°C, as 30% w/v solutions in deuterium oxide, against internal references of acetone and water, in spinning sample tubes of 5mm. outside diameter.

CHAPTER IV

(I) Thermal / Catalytic dehydrogenation of pyridine.

(II) Gas phase halogenation of pyridine.

  (a) Chlorination.

  (b) Bromination.

Thermal / Catalytic dehydrogenation of pyridine.

INTRODUCTION

When heated strongly, pyridine undergoes dehydrogenation forming bipyridyls. Pyrolysis of pyridine in quartz (76) resulted in the recovery of 15% decomposition products, based on the amount of pyridine used. 2,2'Bipyridyl was found to be the major component, but smaller amounts of 2,3', 3,3' and 4,4' bipyridyls were also detected. By-products identified included quinoline, terpyridyl, indole and other nitrogenous derivatives.

Perhaps the best known dehydrogenation reaction is that reported by Morgan and Burstall (77) in which, at temperatures in excess of 300°C, pyridine and ferric chloride were shown to generate bipyridyls. Although 2,2'bipyridyl again predominated, all other bipyridyl isomers, with the exception of 4,4', were detected in the product mixture, along with terpyridyl and alkyl pyridines. Wibaut (78) showed iodine to be an effective catalyst in the preparation of 2,2'bipyridyl, as he had already demonstrated for biphenyl (79). Raney nickel catalysts have been used to great effect in this field, again producing bi-aryls from pyridine, α-picoline, quinoline, 6-methyl-quinoline, nicotinic acid and acridine (78,80,81,82). Badger and Sasse (82) suggest that the process is not one of simple dehydrogenation. Since pyridine and similar hetero-aromatics are known to poison hydrogenation catalysts, it seems reason-

-able to propose that, as a preliminary step, the nitrogen lone-pair is involved in a covalent bond to the catalyst (83). The fact that the overall reaction is much slower when the approach to nitrogen is sterically hindered (81) would appear to endorse the idea of chemisorption. The next step would involve the addition of a hydrogen atom to nitrogen, resulting in the formation of an α or γ radical. Although the precise origin of this hydrogen atom is not clear, it is likely that it is derived from the dissociative adsorption of another pyridine molecule. When two such radical species are formed sufficiently close to each other, coupling would occur most readily at the α-positions due to the geometrical restrictions placed on other modes of dimerisation by the fact of chemisorption. Loss of hydrogen from the resulting tetrahydro-biaryls would occur smoothly, in view of their known instability, thereby affording the observed biaryls. The predominance of 2,2'bipyridyl in the product mixtures can clearly be rationalised on this basis. With heterocyclic compounds in which both α-positions are blocked, biaryl formation was not observed. Besides being an indication of the importance of the geometrical factors involved, this also lends further weight to the argument outlined above. The appearance of small amounts of other bipyridyls can be attributed to the non-selectivity of such radical processes.

RESULTS AND DISCUSSION

Metal oxide catalysts (notably of tungsten and molybdenum) were used in an attempt to dehydrogenate pyridine at elevated temperatures. Bipyridyl formation was fairly extensive, but by no means selective, and under optimum conditions, almost 18% overall conversion to bipyridyl was observed. At no time, however, did it appear that this approach could produce 4,4'bipyridyl in any significant yield. Indeed, this isomer was observed but once and even then in barely detectable amounts. 2,4'Bipyridyl was not detected at any time. The influence of a carrier gas on the course of the reaction was investigated and it was apparent that the use of air in this respect caused a marked reduction in the overall yield of bipyridyl. Incorporation of air also gave rise to an additional product whose g.l.c. retention time was not consistent with that of any bipyridyl.

Operating temperatures varied between 300 and 600°C and, under such conditions, 2,2'bipyridyl was generally the major product. On two occasions, however, it appeared that the formation of 2,3'bipyridyl was favoured at lower temperatures, an effect which diminished with rising temperature to the extent that, at 500°C, 2,2'bipyridyl again predominated.

At this point it should be noted that 2,4' and 4,4' coupling of pyridine appeared to be virtually impossible, whereas, 2,2', 2,3' and 3,3' isomers were formed in almost every case. These findings are consistent with a mechanism of adsorbed radical coupling. It is suggested that, after chemisorption of pyridine onto the catalyst surface, electron withdrawal by the catalyst results in the formation of adsorbed pyridyl radicals. Such radicals would be generated mainly at the α and γ positions of the ring, but it is not likely that they would be sufficiently long-lived to be detected or characterised. Coupling would then occur when two of these species are formed sufficiently close to each other to allow reaction. The resulting tetrahydro-biaryls, in view of their known instability (81), would readily undergo dehydrogenation thereby producing the free bipyridyls after desorption. From the reaction of pyridine with ferric chloride (22), amounts of molecular hydrogen have been detected, the explanation for which would appear to lie in such a mechanism.

Clearly, the main factor determining the nature of the bipyridyl is the relative orientation of the radicals about to undergo coupling and, due to the geometrical factors involved, one can construct an order of coupling ease :

$2,2' > 2,3' > 3,3' \gg 4,4' \simeq 2,4' \simeq 3,4'$.

The products detected did not contravene this order, since in every case, the first three isomers were always present, and in the predicted relative amounts, while the three latter modes were almost non-existent.

As has been noted above, the addition of air as a carrier gas caused a substantial decrease in the extent of coupling. One can understand this readily if the above mechanism operates. The reduction in the yields of bipyridyl is probably a consequence of a termination step involving the reaction of pyridyl radicals with molecular oxygen. If such be the case, then the unidentified product is probably an oxygenated pyridine. Indeed, its retention time (0.6 min) was found to be compatible with that of 2-pyridone. On the occasions when this product was formed, it appeared to be present in concentrations similar to those of 2,2'bipyridyl, although direct measurement of the yields was not possible. It is noteworthy that this compound was not positively characterised as 2-pyridone since only the retention times were compared. Preparative g.l.c. facilities were not available in order to achieve an unambiguous identification.

Nevertheless, in view of the above findings, it does seem likely that these catalysts couple pyridine by a mechanism of adsorbed radical dimerisation. The extent of coupling is rather poor by this method and, because of geometrical considerations, it is not a viable route to 4,4'bipyridyl.

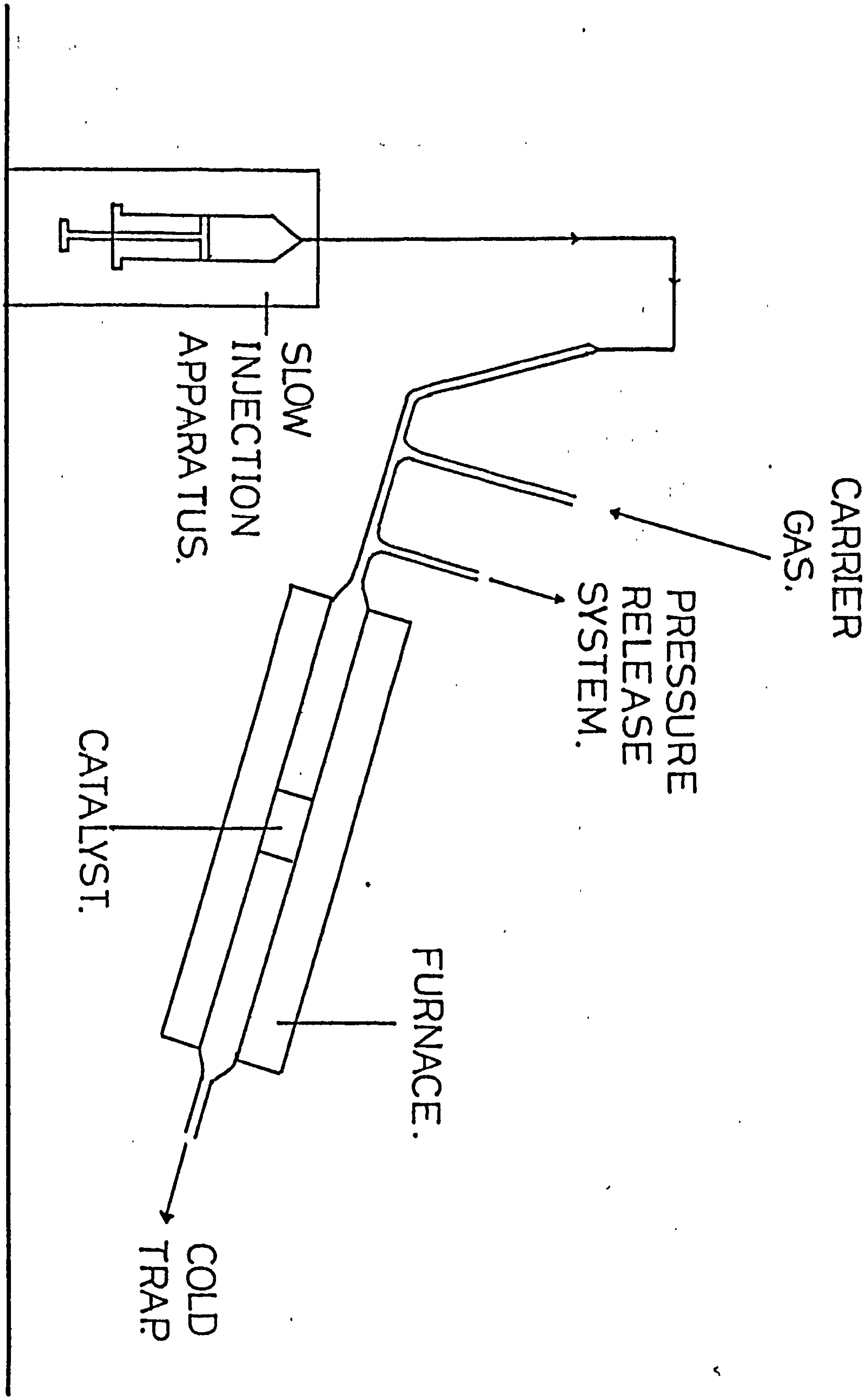
EXPERIMENTAL

Chemicals : Analar grade pyridine, stored over Linde molecular sieves, type 5A, and Analar grade bromine in carbon tetrachloride were introduced into the apparatus, wherever appropriate, by a slow injection pump. Carrier gases used were compressed air, propylene and dry nitrogen. All catalysts were supplied by I.C.I. (Mond Division). Analar grade solvents were used at all times. Input gases were carefully monitored on calibrated rotameters and the chlorine used was addionally regulated by a standard chlorine gauge.

Gas Chromatography : All solutions were analysed as 1 microlitre injections in carbon tetrachloride or pyridine. Separation of the bipyridyl products was achieved at 180°C on a glass column (1m. 4mm.) made for use with a Pye 104 Gas Chromatograph. The column packing consisted of 5% sodium dodecyl benzene sulphonate on 72 - 85 mesh Celite treated with 10% aqueous potassium hydroxide. Nitrogen was used as the carrier gas.

Apparatus : The apparatus used was as shown in Fig. 1. The method involved the slow injection of pyridine into the apparatus where it vapourised and was taken over the catalyst by the carrier gas to a cold trap where the products and unreacted pyridine condensed. The solution obtained was then concentrated and a sample analysed by gas chromatography. The reactor tube (silica glass) was 1 metre in length and 2.5 cm. in diameter. To prevent possible explosion hazards

Fig.1


SLOW INJECTION APPARATUS.
CARRIER GAS.
PRESSURE RELEASE SYSTEM.
CATALYST.
FURNACE.
COLD TRAP.

a pressure release device was incorporated in the apparatus; this consisted simply of two mercury bubblers connected in series.

(I) Blank run : Rate of injection was such that the flow of liquid pyridine was maintained at 20 mls / hour, for one hour. The liquid was allowed to vapourise, wi no carrier gas present, and simply passed down the heated silica tube. Prior to eac experiment, the system was thoroughly purged with nitrogen, thereby eliminating any oxygen. No catalyst was included.

Conditions	Retention Times (mins)	Bipyridyls	Yields (%)
20 mls pyr. at 300°C	1.1, 2.4, 3.2	2,2', 2,3', 3,3'	3; 1; 1
" " " " 400°C	1.1, 2.3, 3.2	" " "	3; 1; 1
" " " " 500°C	1.1, 2.4, 3.2	" " "	4; 2; 1
" " " " 600°C	1.1, 2.4, 3.0, 3.2	" " 4,4', 3,3'	5; 4; 1; 1

As expected, the yields of the bipyridyls rise with temperature. No 2,4' bipyridyl was detected at any time, but since its retention time is close to that of the 2,3' isomer, it may have escaped detection. Although charring was extensive at 600°C, 16 mls of liquid were recovered from the cold trap. . The absence of the 2,4' isomer was confirmed by reducing the nitrogen flow rate in the gas chromatograph, thereby increasing the difference inretention time between each isomer.

(II) Heated pyridine passed over the olefin dimerisation catalyst $WO_3/BO_3/SiO_2$. Again, pyridine injection was maintained at 20 mls / hour. No carrier gas was used.

Conditions	Retention Times (mins)	Bipyridyls	Yields (%)
20 mls pyr. at 300°C	1.1, 2.4, 3.2	2,2', 2,3', 3,3'	3; 1; 1
" " " " 400°C	1.1, 2.3, 3.15	" " "	3; 1; 1
" " " " 500°C	1.1, 2.4, 3.2	" " "	4; 1; 1
" " " " 600°C	1.1, 2.4, 3.2	" " "	5; 2; 1

Reaction yields were in no way increased by the use of this catalyst. In fact, no 4,4'bipyridyl was observed in any of the four experiments (cf. Blank run). Substantial blackening of the catalyst did occur at higher temperatures and was attributed to pyridine decomposition products. Regeneration of the catalyst was accomplished easily by heating to 550°C in a stream of oxygen for six hours.

(III) Heated pyridine passed over the olefin dimerisation catalyst $WO_3/BO_3/SiO_2$ at a rate of 20 mls liquid / hour, for one hour. Compressed air was used as a carrier.

Conditions	Retention Times (mins)	Bipyridyls	Yields (%)
20 mls pyr. at 350°C	(0.6), 1.1, 2.4	(?), 2,2', 2,3'	1; 1
" " " " 400°C	(0.6), 1.1, 2.4, 3.2	(?), 2,2', 2,3', 3,3'	1; 1
" " " " 500°C	(0.6), 1.1, 2.4, 3.2	(?), " " "	2; 1; 1

An obvious decrease in the yields of each bipyridyl resulted from the use of air as a carrier gas, to the extent that the 3,3' isomer was barely detectable even a 500°C. In addition to this, an unidentified product (retention time 0.6 mins) was observed. This did not correspond to any of the possible bipyridyls and is possibly a consequence of the carrier gas, air. At these concentrations it was not feasible to isolate this compound nor was it possible to measure its yield directly from the g.l.c. peak height as was the practice in the case of the bipyridyls.

At this point, further study of this system did not seem worthwhile. Instead, ammonium meta-tungstate, used as an olefin cracking catalyst, was investigated as a possible pyridine coupling agent. The catalyst was prepared by adding silica-gel to a 20% ammonium meta-tungstate solution in water and then removing the solvent under vacuum. The result is a deposit of the meta-tungstate on the silica-gel support. By baking this solid, ammonia is evolved leaving a deposit of WO_3 on silica-gel. This catalyst can be regenerated by simply heating in air at 550°C or in propylene at 450°C as recommended by the manufacturers.

(IV) Heated pyridine passed over 20% ammonium meta-tungstate on silica-gel at a rate of 20 mls liquid / hour, for one hour, in the absence of any carrier gas.

Conditions	Retention Times (mins)	Bipyridyls	Yields (%)
20 mls pyr. at 400°C	1.2, 2.3	2,2', 2,3'	1; 2
" " " " 500°C	1.2, 2.25	2,2', 2,3'	3; 3
" " " " 600°C	1.2, 2.3, 3.15	2,2', 2,3', 3,3'	9; 7; 1
Standard bipyridyls :	1.2, 2.3, 3.15	2,2', 2,3', 3,3'	

At lower temperatures, there seems to be a definite preference for the formation of the 2,3' isomer, but this effect falls off rapidly as temperature rises. It is also noteworthy that an increase in temperature from 500 to 600°C causes a three-fold increase in the yields of the bipyridyls.

(V) Heated pyridine passed over ammonium meta-tungstate on silica-gel at a rate of 20 mls liquid / hour, for one hour, using air as a carrier gas.

Conditions	Retention Times (mins)	Bipyridyls	Yields (%)
20 mls pyr. at 500°C	(0.6), 1.1, 2.4, 3.2	(?), 2,2', 2,3', 3,3'	2; 1; 1
" " " " 600°C	(0.6), 1.1, 2.4, 3.2	(?), 2,2', 2,3', 3,3'	3; 3; 1

As in Experiment III, the incorporation of air as a carrier gas caused a marked drop in the yield of each bipyridyl. In addition, the unidentified product (Retention time 0.6 mins) re-appeared in this Experiment in similar relative yields. This compound was previously observed in Experiment III.

(VI) After regeneration of the catalyst at 450°C in propylene, pyridine was passed over the heated catalyst, 20% ammonium meta-tungstate on silica-gel, at a rate of 20 mls liquid / hour, for one hour. Propylene was used as a carrier gas.

Conditions	Retention Times (mins)	Bipyridyls	Yields (%)
20 mls pyr. at 500°C	1.0, 2.2, 3.1	2,2', 2,3', 3,3'	3; 1; 1
" " " " 600°C	1.0, 2.2, 3.1	2,2', 2,3', 3,3'	5; 3; 1

There did not appear to be any advantage in the use of propylene as a carrier gas. The yields of each bipyridyl, although greater than those obtained when oxygen was used, were considerably less than those observed for Experiment IV, where no carrier gas was added.

(VII) Pyridine passed over heated cobalt molybdate pellets at a rate of 20 mls liquid / hour, for one hour. No carrier gas was used.

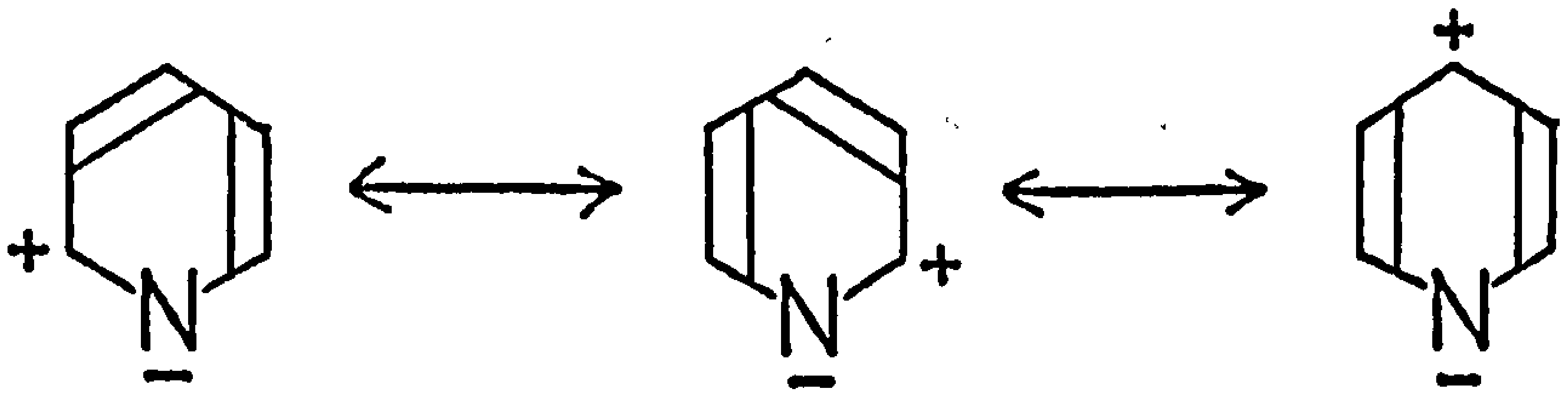
Conditions	Retention Times (mins)	Bipyridyls	Yields (%)
20 mls pyr. at 350°C	2.4	2,3'	1
" " " " 400°C	2.35	2,3'	2
" " " " 500°C	1:05, 2.30, 3.15	2,2', 2,3', 3,3'	2; 3; 1
" " " " 600°C	1.10, 2.30, 3.20	2,2', 2,3', 3,3'	3; 3; 1

There appears to be a definite preference for 2,3' formation at lower temperatures, an effect which falls off with rising tempreature. This could indicate a change in the mechanism of coupling.

Gas phase halogenation of pyridine.

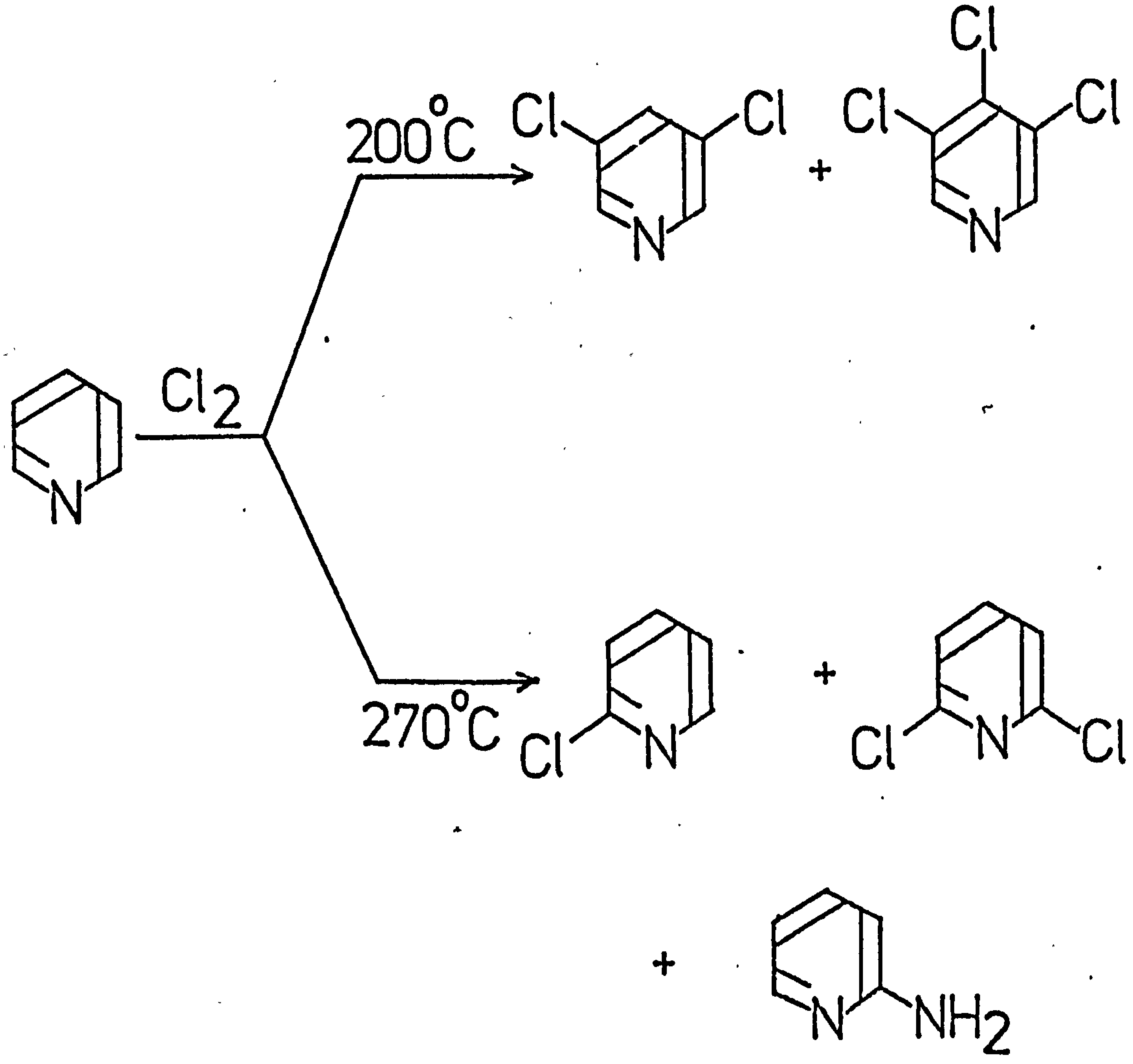
INTRODUCTION

Pyridine is less reactive than benzene in substitutions of this type, although the formation of molecular adducts of pyridine with the halogens makes direct comparisons rather difficult. The relative unreactivity of pyridine towards electrophilic agents such as the halogens may be explained by a consideration of the resonance hybrids contributing to the overall pyridine structure. The electron attracting properties of nitrogen lead to three deactivated species, an appropriate representation of which is :



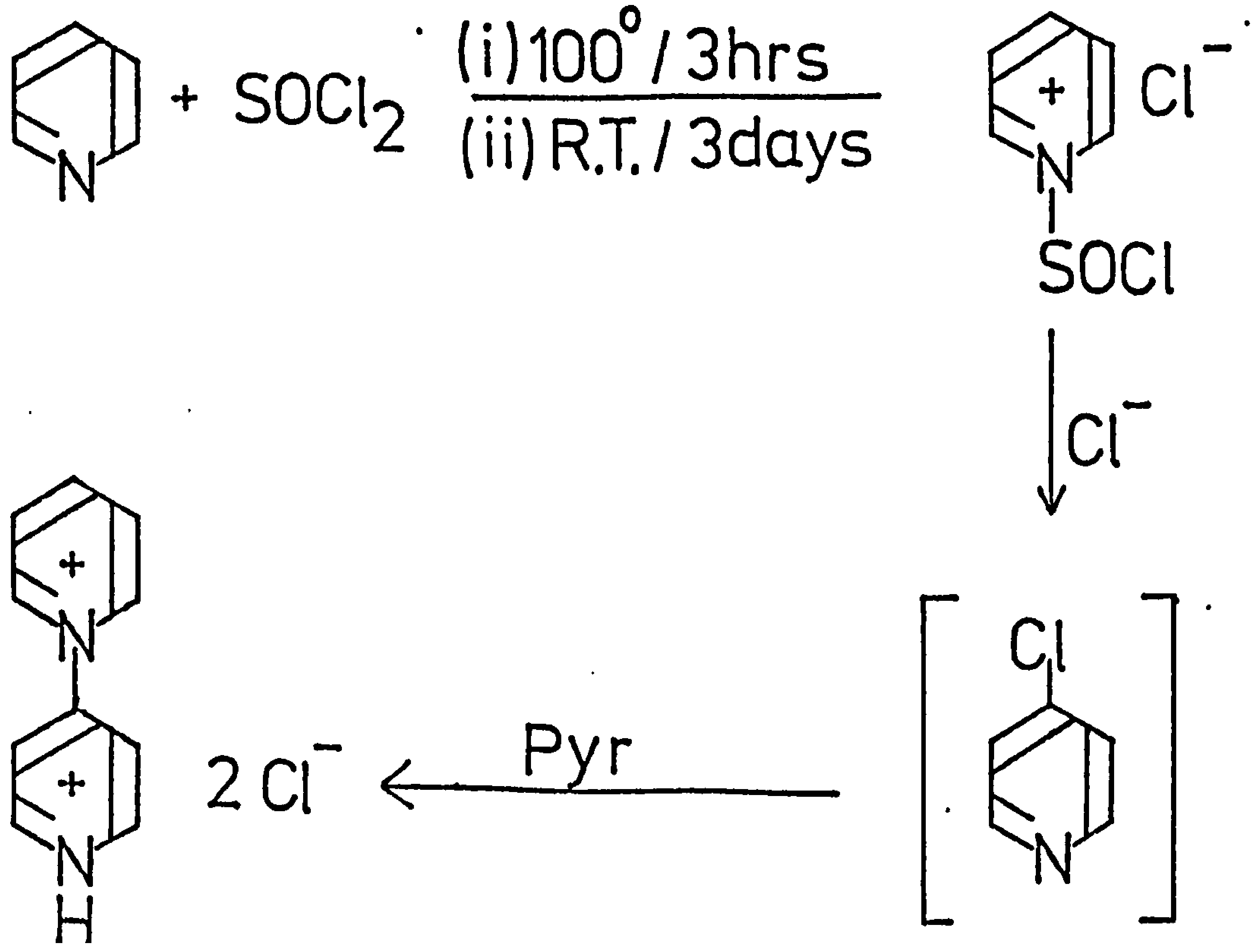
Although the two non-polarised forms are regarded as the major contributing species, the existence of the above states makes electrophilic substitution at positions 2 and 4 rather difficult. Consequently, if the course of halogenation is determined by an electrophilic mechanism, then the replacement of hydrogen occurs primarily at positions 3 and 5. This trend is even more marked in the case of pyridinium salts, where the quaternary nitrogen has a greater electron attracting ability than in the free base. Although the direct halogenation of pyridine is readily possible, each of the methods reported requires elevated temperatures to produce any reasonable yield of halopyridines. It has also been noted that the incorporation of a catalyst facilitates the substitution. These catalysts are generally no more sophisticated than contact surfaces such as pumice (84, 85).

Gas phase chlorination of pyridine has been studied extensively by Wibaut (84) who has shown that the pattern of chlorine substitution is heavily dependent on temperature, although this dependence is not quite so marked as in the case of bromine :

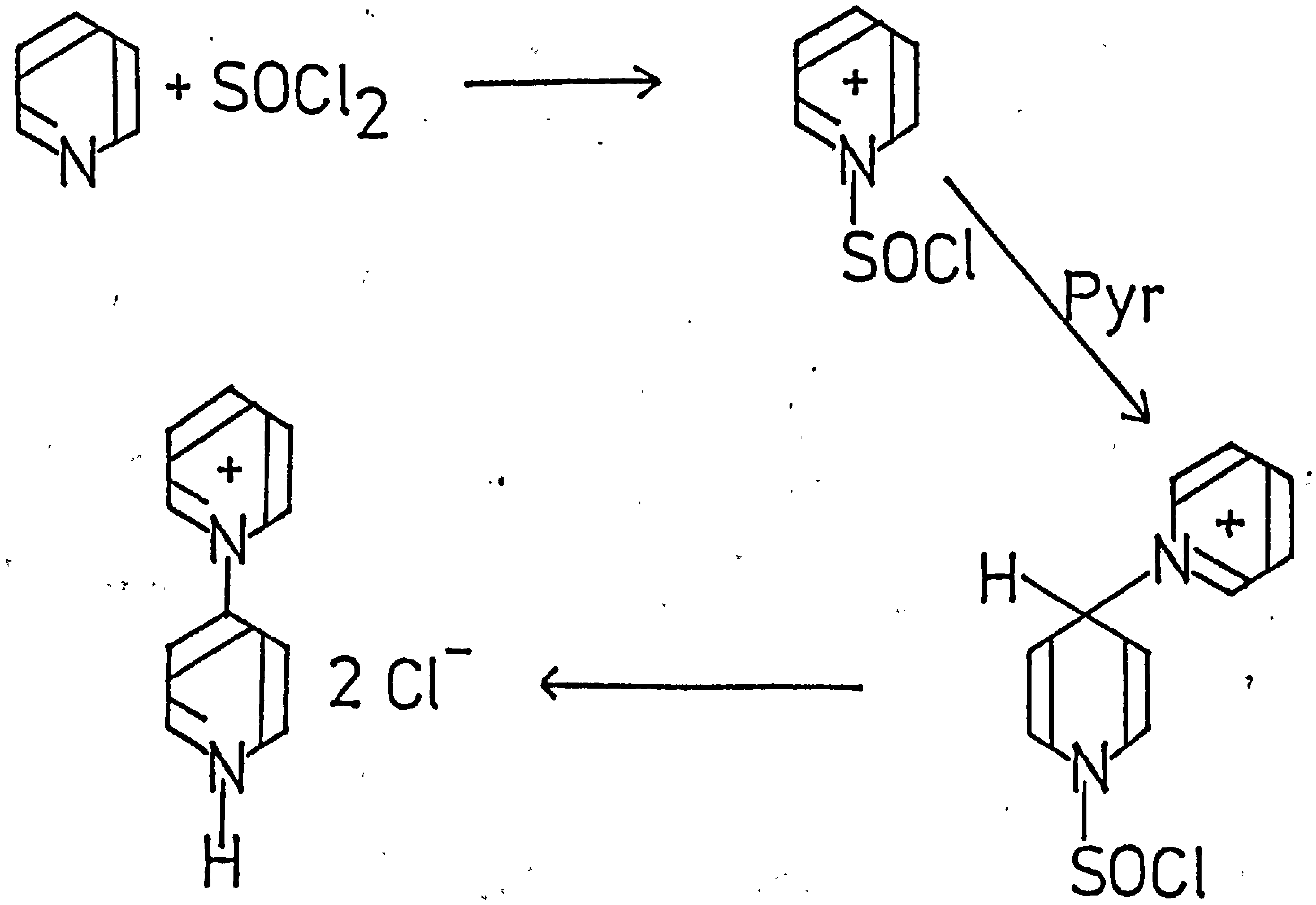


The variation in substitution pattern with temperature has been ascribed to a change in mechanism, from electrophilic at 200°C to radical at 270°C, but the relative thermodynamic stabilities of the products may influence the result. By hydrolysing the product mixture after the reaction at 270°C, Wibaut successfully isolated 2-aminopyridine. This has been taken to indicate the prior formation of N(2-pyridyl) pyridinium chloride from the reaction of 2-chloropyridine and free pyridine.

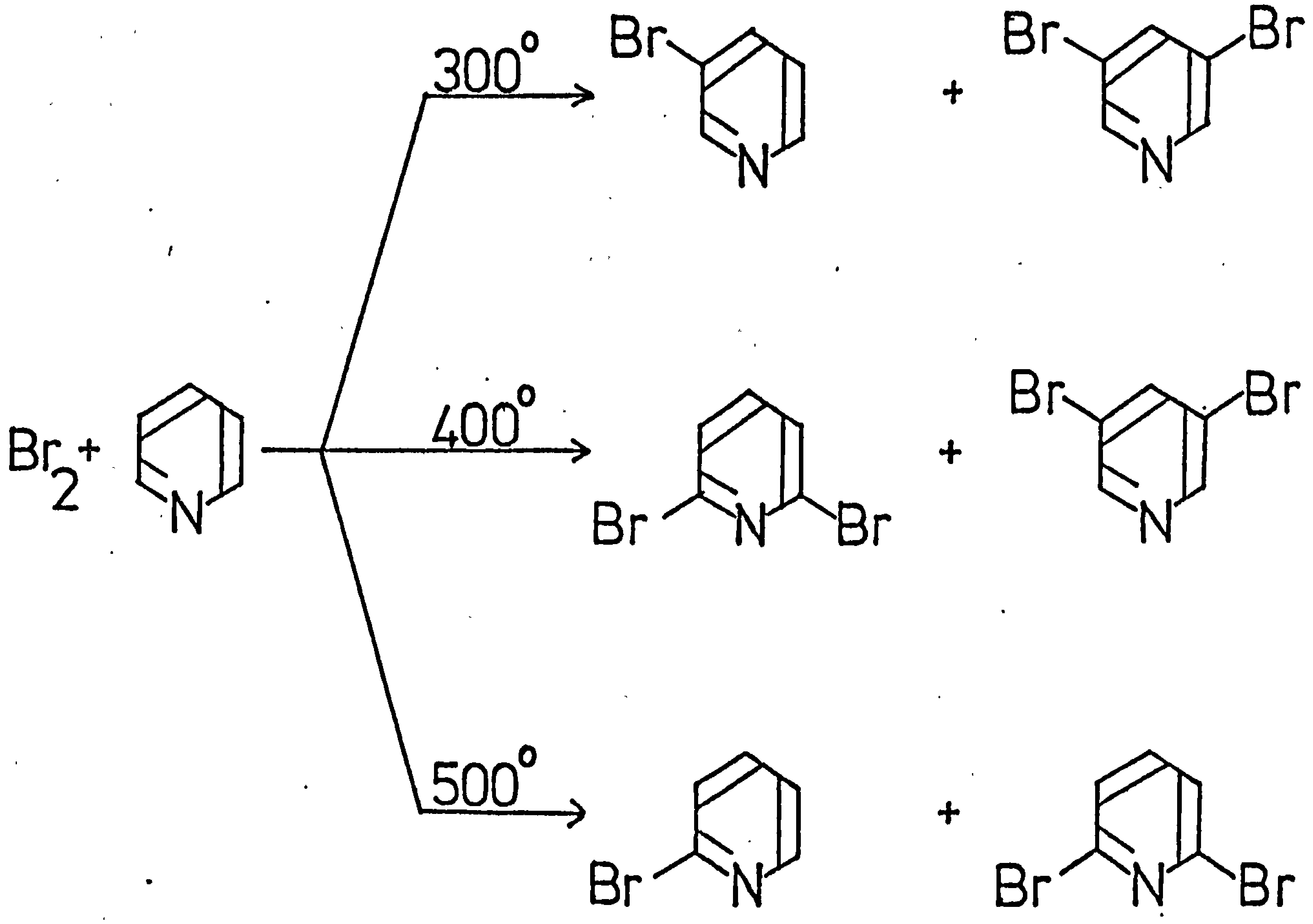
There is an obvious parallel to be drawn between this latter result and the findings of Koenigs and Greiner (86). By treating pyridine with thionyl chloride under different conditions, they were able to isolate N(4-pyridyl) pyridinium chloride hydrochloride :



It has been suggested that the above reaction sequence, involving the intermediate formation of 4-chloropyridine, explains the results satisfactorily. However, there does not seem to be any evidence which invalidates the alternative suggestion, that of nucleophilic attack of one pyridine on another which has been activated by thionyl chloride :



When pyridine is reacted with bromine at higher temperatures, nuclear bromination occurs. This was first reported by Hoffman (87, 88) who reacted pyridine hydrobromide with bromine in a sealed tube, thereby obtaining 3-bromo- and 3,5-dibromopyridines. More recently, the gas phase bromination of pyridine has been reported in greater depth by Wibaut and den Hertog (89, 90) :



A more extensive survey of this reaction, again by den Hertog (91), has shown that, although the above products predominate, others are formed due to the bromination of existing bromopyridines. It is of interest to note that no 4-bromopyridines were detected, possibly as a result of their instability. Once again, differences in product distribution have lead to a suggested electrophilic mechanism at 300°C and a radical mechanism at 500°C, with a combination of the two operating at intermediate temperatures (92).

Among the more interesting findings in this field are those reported by McElvain and Goese (85). By adding bromine directly to pyridine at temperatures below 25°C, they isolated the adduct $C_5H_5N.Br_2$. Subsequent pyrolysis of this compound yielded equal parts of a polymer and a volatile fraction. The latter has been shown to consist mainly of 3-bromo- and 3,4-dibromopyridines. In a manner similar to that proposed by Koenigs and Greiner (86), these will undergo auto-quaternisation, the nitrogen lone pair of 3-bromopyridine initiating a nucleophilic replacement of the γ-bromine in 3,4-dibromopyridine. The result is the salt N(3-bromo-4-pyridyl) 3-bromopyridinium bromide. It is thought that the polymer mentioned above has a polypyridylene structure, derived from the oxidative condensation of pyridine molecules by bromine.

Results of halogenation experiments.

(I) CHLORINATION :

$$C_5H_5N + Cl_2 \longrightarrow C_5H_5N.Cl_2$$

$$\begin{array}{l} C_5H_5N.Cl_2 \\ \quad \big\downarrow \Delta \end{array}$$

2,2'bipyridyl.

pyridine hydrochloride.

N(4-pyridyl) pyridinium chloride (trace).

2-chloropyridine.

2,4,6-trichloropyridine.

2,3,5,6-tetrachloropyridine.

(II) BROMINATION :

$$C_5H_5N + Br_2 \longrightarrow C_5H_5N.Br_2$$

$$\begin{array}{l} C_5H_5N.Br_2 \\ \quad \big\downarrow \Delta \end{array}$$

3-bromopyridine.

3,4-dibromopyridine.

a tribromopyridine.

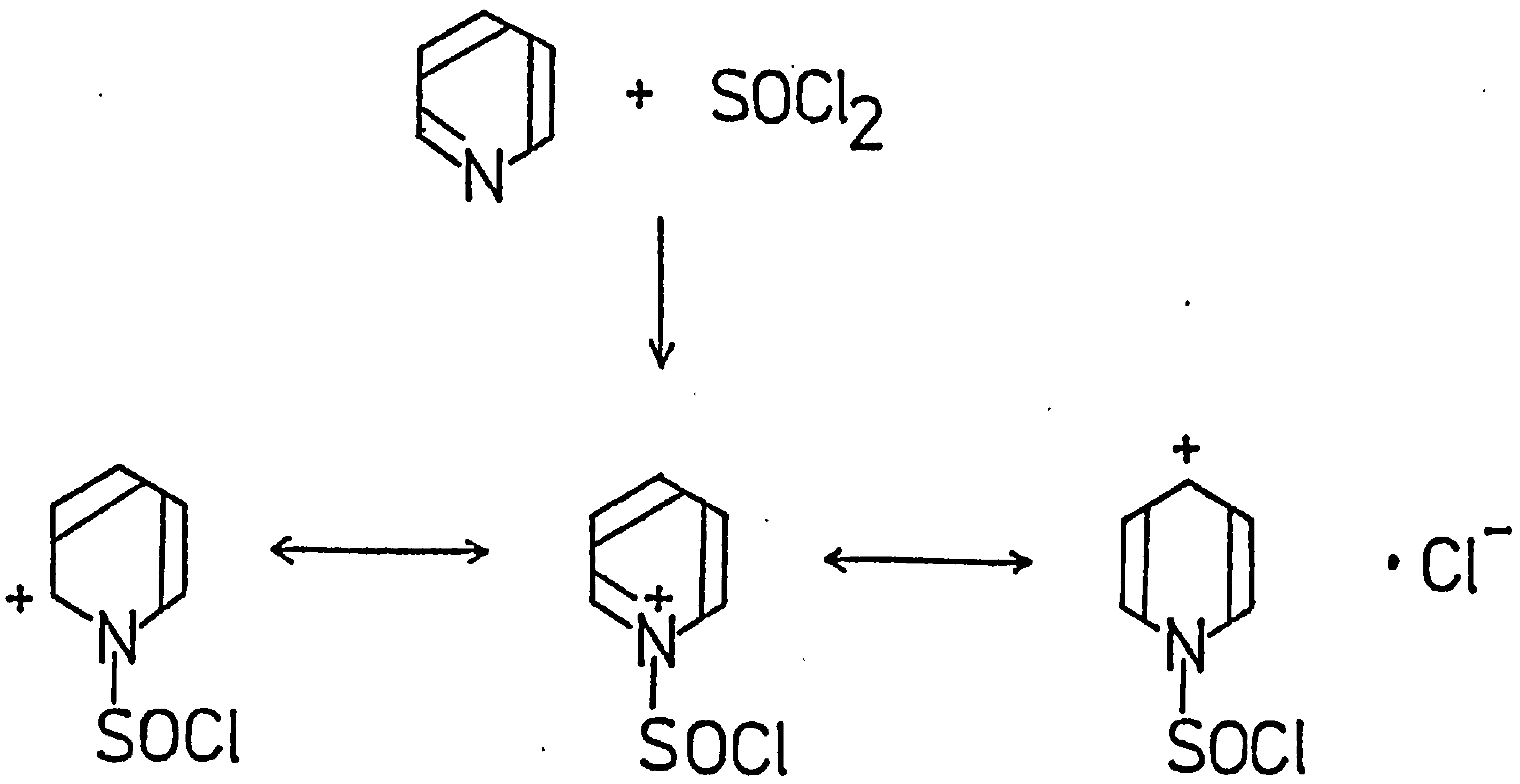
2-bromopyridine (trace).

DISCUSSION

(a) Gas phase chlorination of pyridine.

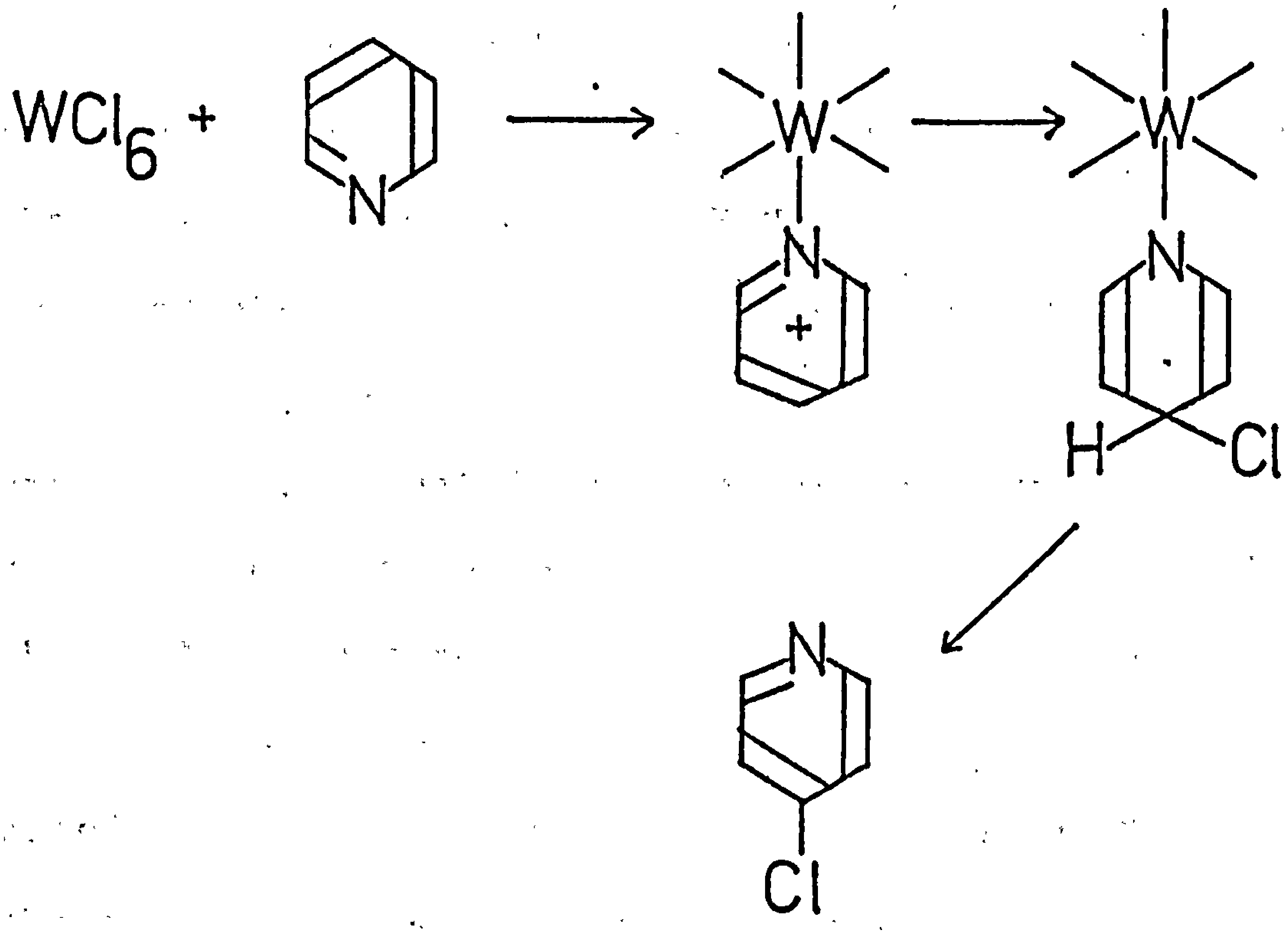
Direct chlorination of pyridine in the gas phase was attempted in the presence of potential catalysts of tungsten and molybdenum, at temperatures ranging between 120 and 250°C. Essentially, the aim was to generate 4-chloropyridine which, as was shown in Chapter II, will produce 4,4'bipyridyl under suitable conditions. A successful route to 4-chloropyridine was not found, although several other chloropyridines were identified as well as trace amounts of 2,2'bipyridyl. In all cases, pyridine hydrochloride was the predominant product.

In many ways, the proposed catalytic system was modelled on the reaction of pyridine with thionyl chloride.



If we consider that the catalyst activates pyridine in a manner similar to thionyl chloride (above), then there is an obvious case for nucleophilic chlorination at position 4. However, in the experiments conducted, evidence for γ-chlorination of pyridine was slight and consisted only of the identification of 2,4,6-trichloropyridine and trace amounts of N(4-pyridyl) pyridinium chloride.

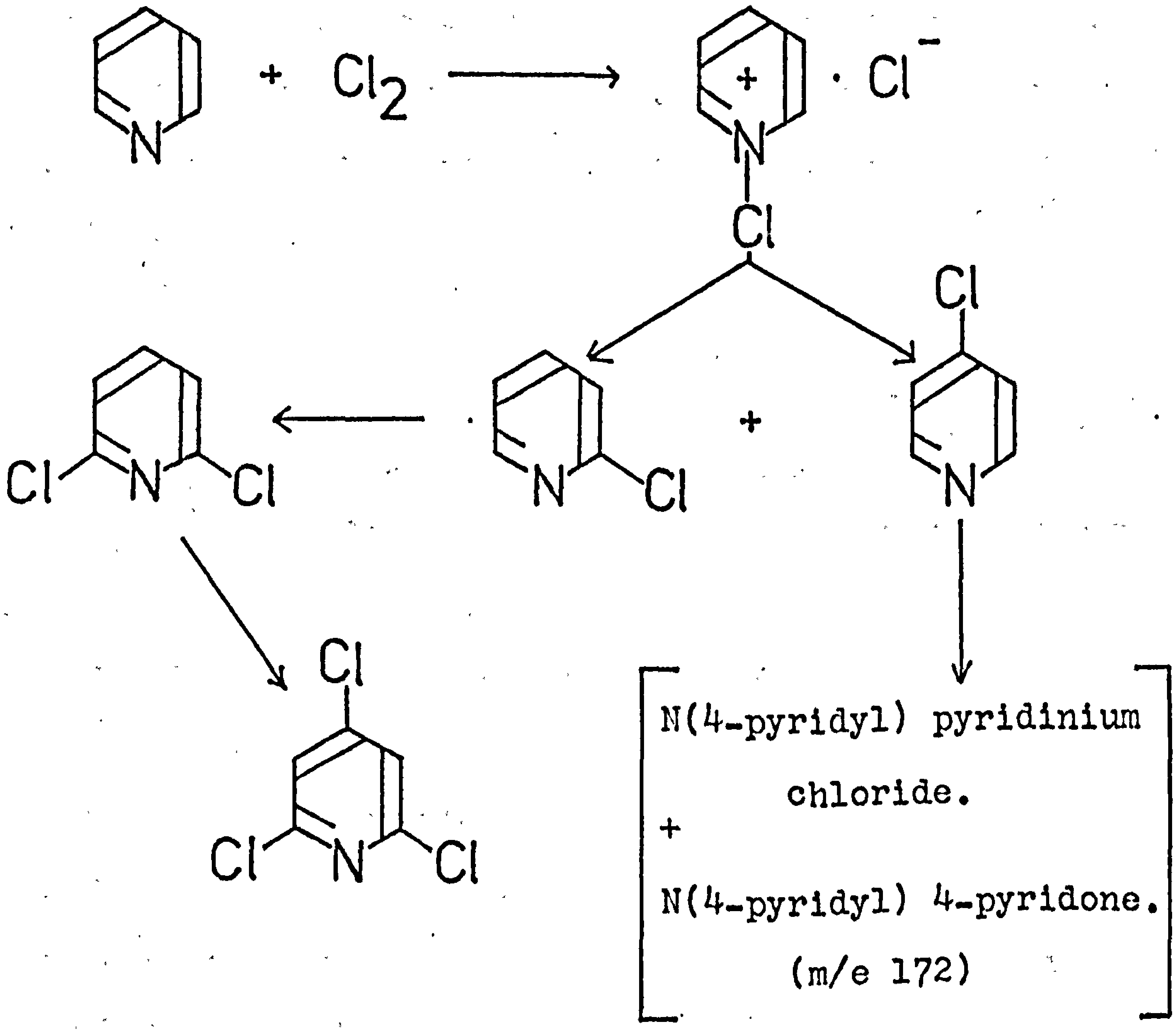
Tungsten hexachloride was screened as a possible catalyst. Experimental temperatures were restricted by the melting point of the halide, which is given as 275°C in literature. It was hoped that by using the hexachloride as a catalyst, coordination and hence activation of pyridine would be effected, thereby allowing chlorination to proceed by a nucleophilic mechanism :



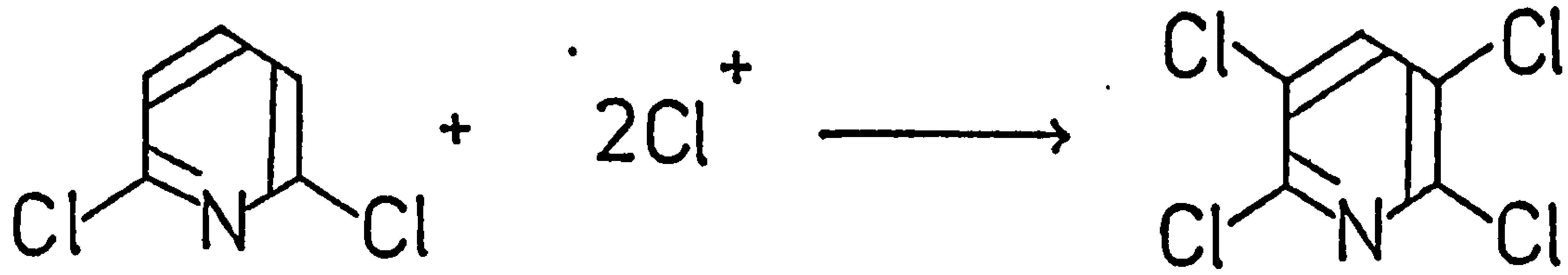
It is clear that such activation of pyridine would indeed be rather similar to that by thionyl chloride. It was further hoped that experimental temperatures would be sufficient to promote the high temperature reaction of pyridine with the 4-chloropyridine, thus forming 4,4' bipyridyl. It may be relevant to recall that, as was shown in Chapter II, the course of this reaction is very much dependent on temperature. In the vicinity of 80°C quaternisation occurs to form N(4-pyridyl) pyridinium salts, whereas by raising the temperature to 180°C, 4,4'bipyridyl results.

However, it appeared that under the conditions of chlorination, pyridine reacted preferentially with molecular chlorine rather than coordinating to tungsten hexachloride. Despite elaborate precautions to ensure that the gaseous reactants mixed only at the catalyst bed, thereby encouraging coordination of pyridine, it was found that the molecular adduct $C_5H_5N.Cl_2$ was formed in all cases. The products identified were then merely a consequence of the thermal decomposition of the adduct. In many of the experiments, adduct formation was monitored simply by the rise in temperature in the catalyst zone, attributable to the heat of this reaction. A mixed tungsten / molybdenum catalyst was also used in an attempt to effect pyridine coordination. Similar complications were encountered in the shape of immediate adduct formation. Reduction of the gas phase concentrations of pyridine and chlorine and an increase in the experimental temperature did not seem to influence the course of the reaction nor did they solve the problem of adduct formation. Carbon tetrachloride was used as a diluent but served only to cool down the reactor to the extent that, once formed, the adduct was deposited on the column and did not decompose further. By washing the column with portions of methanol, some evidence for the γ - chlorination of pyridine was found. N(4-pyridyl) pyridinium chloride was detected polarographically in 0.2% concentration. This was confirmed by the mass spectrum of the methanolic washings, which showed the presence of pyridine and a mono-chloropyridine, the pattern anticipated for the pyridyl pyridinium salt. In addition, a compound $C_{10}H_8N_2O$ (m/e 172) was detected. Bearing in mind Wibaut's work on autoquaternisation of 4-chloropyridine (95), it seems likely that this compound arises from that source. It is therefore probable that 4-chloropyridine has been formed at some stage, in small amounts, and has reacted with pyridine to form N(4-pyridyl) pyridinium chloride, while the autoquaternisation of 4-chloropyridine has occurred to a small degree giving rise to N(4-pyridyl) 4-pyridone, m/e 172. It is of course to be emphasised that the the amounts of these compounds were very small indeed and in no way inspire confidence in the ability of the catalytic system to generate 4-chloropyridine.

As has been indicated above, the main reaction occurring was the thermal degradation of the pyridine / chlorine adduct. The products can be rationalised if we allow that the initial step is the displacement of a chloride ion from a chlorine molecule by pyridine and subsequent nucleophilic attack by that chloride ion at positions 2 and 4. Since the pyridine ring has already been activated towards nucleophilic substitution by the Cl^+ cation (see below), this step is not so unlikely.



The products of such a reaction sequence are outlined above. By allowing a mechanism of radical coupling, one can envisage the formation of 2,2'bipyridyl from 2-chloropyridine. The intermediate formation of 4-chloropyridine has already been implied by the identification of small amounts of N(4-pyridyl) pyridinium chloride and the probable existence of N(4-pyridyl) 4-pyridone. The trichloropyridine was identified directly from its g.l.c. retention time. 2,2 Di-chloropyridine, although not detected, is postulated as an intermediate compound in the formation of the trichloropyridine by step-wise nucleophilic chlorination. It is further suggested that 2,3,5,6 tetra-chloropyridine results from the electrophilic chlorination of 2,6 di-chloropyridine.



The precise nature of the electrophile in this sequence is not clear, but the polarisation of a chlorine molecule by pyridine could provide a suitable species. The generation of large amounts of hydrogen chloride in the chlorination steps can readily account for the predominance of pyridine hydrochloride in the product mixtures.

It is possible that 2,4,6 tri-chloropyridine is derived from the progressive nucleophilic chlorination not of 2-chloro- but of 4-chloropyridine, but this process is thought to be less likely due to the extreme instability of 4-halopyridines, as reflected by the fact that 4-chloropyridine was inferred and not actually isolated.

(b) Gas phase bromination of pyridine.

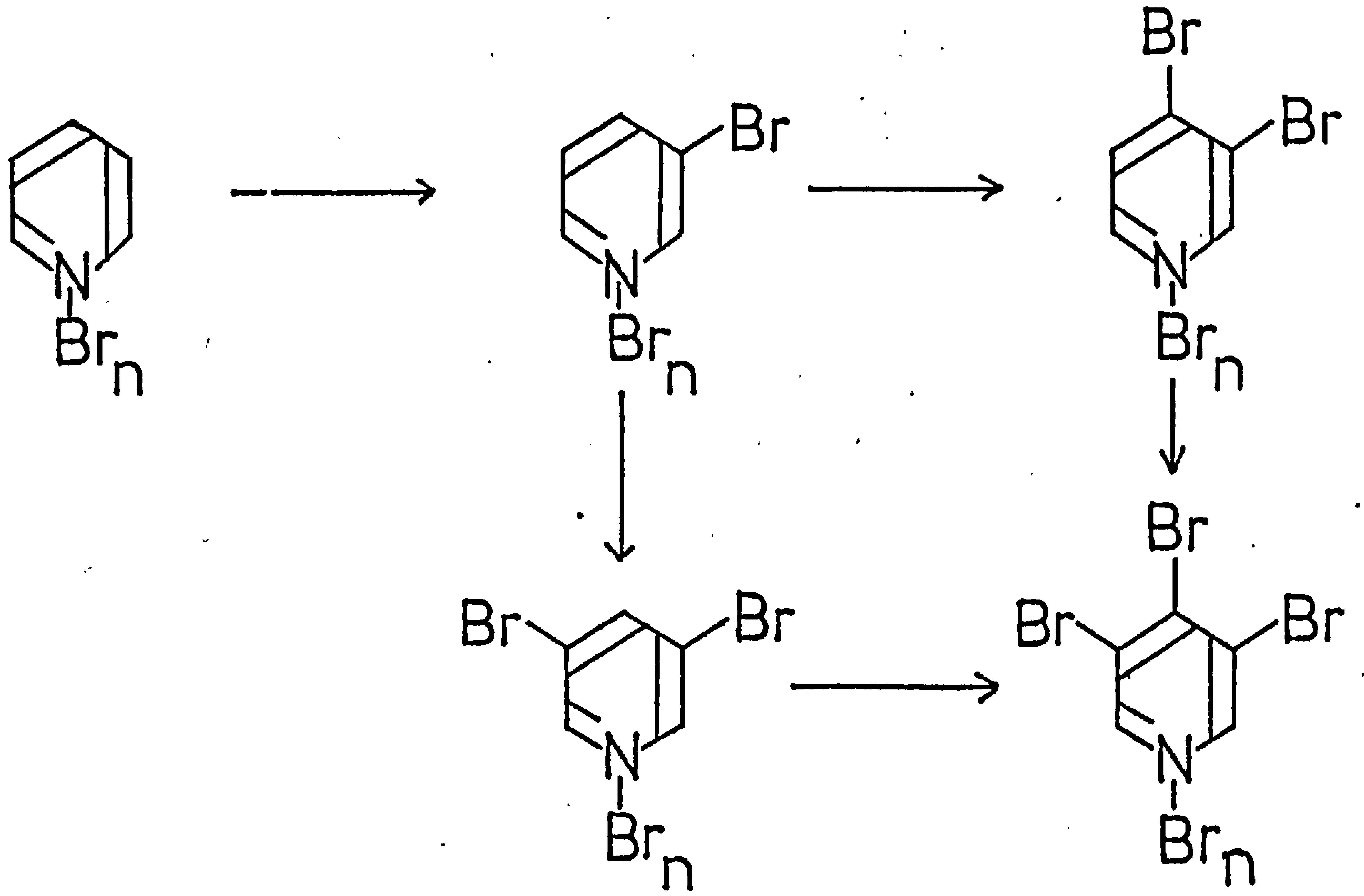
The direct bromination of pyridine in the vapour phase proved to be a particularly efficient flow system, although the products identified were not altogether those desired. In the experiments conducted, the same catalyst was used on all occasions, viz. W/Mo on TiO_2, and carbon tetrachloride was used as a solvent in the addition of bromine. Reaction temperatures ranged from 100 to 250°C but, as will be shown later, these values fluctuated greatly during the course of each experiment.

As in the case of chlorination, the aim of this particular section was to generate γ - brominated species and to couple them thermally to produce 4,4'bipyridyl. Bromination of pyridine appeared to proceed rather more readily than chlorination did and the mass spectrum of the crude product indicated the presence of a mono-bromopyridine, a di-bromopyridine and a tri-bromopyridine as well as pyridine hydrobromide and free bromine. No bipyridyl was detected at any time. As has been noted above, the bromination appeared to be a very practical flow system, the products running freely from the base of the reactor as a dark red oil. At no time was there any blockage of the column, nor were any of the products deposited within the reactor. This may have been due to the incorporation of fairly large amounts of carbon tetrachloride as a bromine carrier. However, the method was not without its disadvantages. It was readily apparent that the flow of carbon tetrachloride had a considerable cooling effect on the system and the temperature consequently fell appreciably during the course of each experiment. The extent of bromination did not diminish noticeably as temperature fell but the viscosity of the oil rose to the extent that clogging of the reactor became a real possibility. It may be worthwhile to note that the chlorination experiments did not suffer from the same effects, although similar amounts of carbon tetrachloride were used in the later runs. It is therefore possible that the initial reaction to form the molecular adduct is less exothermic in the case of bromine than in that of chlorine.

It is suggested that, in a manner similar to chlorination, the products are derived from the thermal decomposition of the adduct $C_5H_5N.Br_2$. There is, however, one obvious difference between chlorinated and brominated products. In the latter case, the extent of α-substitution is exceptionally small compared with that observed in chlorination. If one postulates that, during bromination reactions, the pyridine nitrogen atom has bromine associated with it, then one can readily understand that positions 2 and 6 are sterically blocked. This proposal could explain the appearance of molecular bromine in the mass spectrum of the crude product. Additionally. if one allows that such blocking occurs, then clearly, the occurrence of a γ-brominated pyridine, 3,4 di-bromopyridine, is easily under-

-stood. Again, this can be related to the low incidence of 4-chloropyridines, due to preferential 2-substitution which, in this case, is not inhibited by any such blocking by chlorine.

As has been suggested (93), the bromine / pyridine adduct will decompose on heating to form bromopyridines. The presence of a tri-bromopyridine molecular ion might be explained by the following reaction sequence :



The brominated products identified were 3-bromo- and 3,4-di-bromopyridines, but it is suggested that the tri-bromopyridine detected in the mass spectrum is the symmetrical 3,4,5-tri-bromopyridine. Since no 3,5-di-bromopyridine was detected, it is likely that the path of bromination does not lie through this compound but follows the alternative route. It must be emphasised that the amounts of the tri-bromopyridine detected were very small indeed and that the major products were 3-bromo- and 3,4-di-bromopyridines.

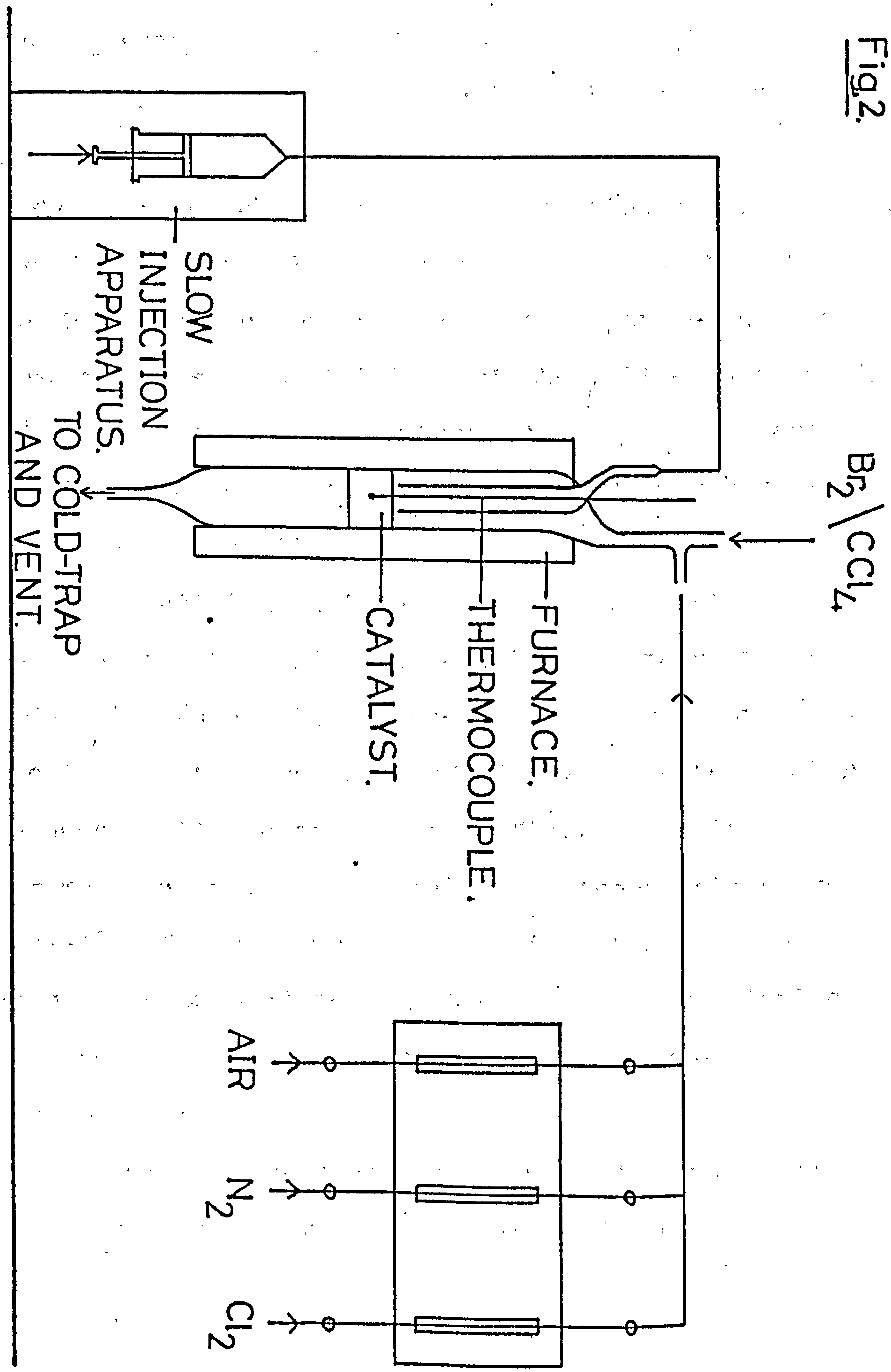
According to the work of McElvain and den Hertog (93, 94), these then react further on standing to form the salt N(3-bromo-4-pyridyl) 3-bromopyridinium bromide. Indeed the oily product became semi-crystalline very rapidly after the reaction and this would be consistent with the suggested quaternisation. The precise nature of the brominating species in each step is not clear, but at the operating temperatures, it seems likely that polarisation of a bromine molecule could give rise to the appropriate species.

EXPERIMENTAL

The apparatus used was as shown in Fig. 2. Once again, the method relied on the slow injection of pyridine on to a heated catalyst bed. Chlorine was added from a cylinder via a standard chlorine gauge and a calibrated rotameter and bromine added from a dropping funnel as a solution in carbon tetrachloride. It was hoped by this approach to simulate the conditions of Carius tube reactions where 4,4'bipyridyl had been successfully prepared. The temperature of the reactor zone was carefully monitored on a chrome-alumel thermocouple. Glass fragments of varying sizes were packed into the reactor to ensure that the gaseous reactants were thoroughly mixed before reaching the catalyst bed.

Pyridine, bromine and carbon tetrachloride were all Analar grade, the pyridine having been redistilled twice before use and dried over molecular sieves (Linde Type 5A).

Fig.2.


Br_2/CCl_4
SLOW INJECTION APPARATUS.
FURNACE.
THERMOCOUPLE.
CATALYST.
TO COLD-TRAP AND VENT.
AIR
N_2
Cl_2

(a) Chlorination

Tungsten hexachloride as a potential catalyst.

Earlier reactions of pyridine with high oxidation state metal halides suggested the existence of halopyridines as intermediate compounds in the formation of 4,4'bipyridyl. Among the more efficient coupling agents was tungsten hexachloride. In view of this, a reaction system was designed in order to test the viability of the halide as a catalyst in the gas phase coupling of pyridine. The powdered chloride was added to the to the reactor column under an atmosphere of dry nitrogen and the system flushed with nitrogen immediately before use. Gaseous chlorine was also added to the feed materials in an attempt to regenerate the depleted catalyst. Since the melting point of tungsten hexachloride is known to be 275°C, reaction temperatures were necessarily lower than this figure. Prior to any experimental work, the apparatus was thoroughly purged with N_2/Cl_2 for 24 hours. The effluent gases from the reactor were bubbled through two carbon tetrachloride traps and the solutions thus obtained analysed by gas chromatography.

Three runs were completed using tungsten hexachloride and the results are reproduced in detail below.

(I) Tungsten hexachloride catalyst at 120°C :

Input material :

12 mls liquid pyridine / hour;

50 mls Cl_2 / minute at 15°C ;

100 mls N_2 / minute at 15°C ;

These materials were then passed over a bed of coarse tungsten hexachloride (30 mls) at 120°C.

Gas flow rates at 120°C are :

4.78 litres of pyridine / hour ;

4.32 litres of chlorine / hour ;

8.65 litres of nitrogen / hour ;

Hence, total flow rate = 17.75 litres / hour ;

= 5 mls / second ;

Therefore contact time = 30/5

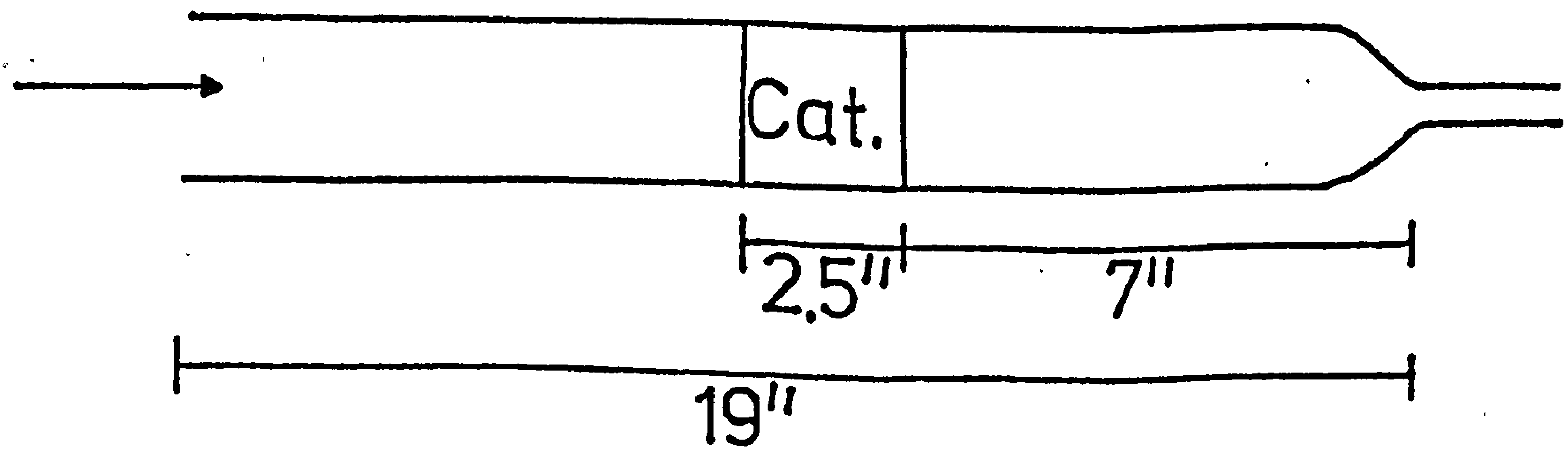
= 6 seconds.

Gas phase concentrations of the reactants were :

4.32/17.75 = 24.2% chlorine :

4.78/17.75 = 27.0% pyridine :

Gaseous chlorine and pyridine were allowed to mix freely at the top of the reactor column whose dimensions were :



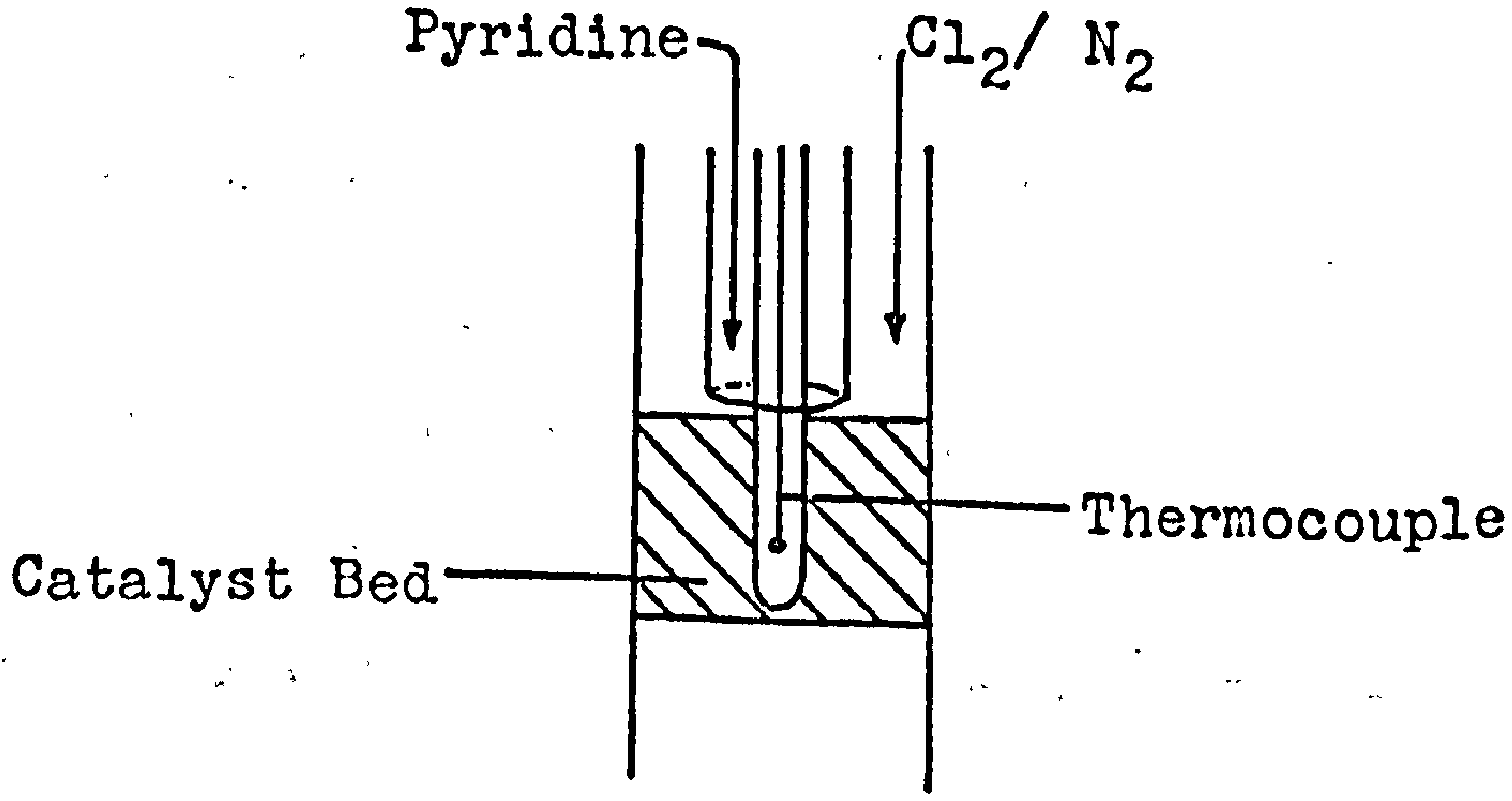
The temperatures of the furnace and the catalyst zone were monitored on chrome-alumel thermocouples and other data recorded was as shown :

Time.	Furnace Temp.		Reactor Temp.		Pyridine added.
(mins)	(mV.	°C)	(mV.	°C)	(mls)
0	6.0	147	5.0	122	0
10	5.2	127	5.3	129	2
20	6.0	147	5.3	129	4
30	5.5	134	5.9	144	6
40	5.1	124	5.6	137	8
50	6.0	147	5.1	124	10
60	5.5	134	5.3	129	12

No bipyridyls were detected in the CCl_4 traps nor were any halopyridines present. A considerable amount of a yellow flocculent solid was isolated from the traps and its melting point recorded. This was found to vary between 41 and 46°C, depending on the rate of heating. Although satisfactory analyses were not obtained, this compound was thought to be the adduct $C_5H_5N.Cl_2$.

(II) On this occasion, the reaction mixture was identical to that used in Experiment I. The reactor temperature, however, was raised to around 200°C in an attempt to initiate some chlorination of pyridine. This change caused the contact time to fall to five seconds. Neither column nor catalyst were changed from the previous experiment since it was thought that the reactor and catalyst were by that time thoroughly saturated. This proved to be a totally erroneous assumption since the gas flow ceased after only nine minutes, due to a blockage in the tube. On cooling, the solid deposit was washed clear with toluene (50 mls) and the reddish brown solution obtained shaken with dilute ammonium hydroxide (50 mls), brine (30 mls) and dried over magnesium sulphate. Analysis of this solution by gas chromatography showed the products to be 2,2'bipyridyl (in minute quantities) and slightly greater amounts of 2-chloro-, 2,4,6-tri-chloro- and 2,3,5,6-tetra-chloropyridines. However, by far the major product proved to be pyridine hydrochloride. These compounds appear to be the result of the thermal decomposition of the adduct $C_5H_5N.Cl_2$, which caused the original blockage.

(III) In an attempt to prevent further clogging from this source, the reactor column was re-designed such that pyridine and chlorine were allowed to mix only in the gas phase and in the vicinity of the catalyst bed :



A fresh batch of tungsten hexachloride was introduced into the reactor and the column flushed, as before, with a chlorine / nitrogen mixture. Reaction conditions were identical to those employed in Experiment I, as were the flow rates of input gases. Contact time of the reactants with the catalyst was therefore six seconds.

Time.	Furnace Temp.		Reactor Temp.		Pyridine added
(mins)	(mV.	°C)	(mV.	°C)	(mls)
0	5.3	129	5.3	129	0
10	6.1	149	5.2	127	2
20	5.8	142	5.8	142	4
30	5.5	134	5.7	139	6
40	5.4	132	5.7	139	8
50	6.1	149	5.3	129	10
60	5.8	142	5.3	129	12

Although the column remained clear throughout this experiment, a large amount of $C_5H_5N.Cl_2$ and its decomposition products were deposited at the base of the column. Furthermore, the tungsten hexachloride appeared to have melted, thus adding to the complexity of the product mixture. Analysis of the deposit in a manner similar to that reported for Experiment I showed it to consist of the same compounds identified previously. viz. 2,2'bipyridyl, 2-chloro-, 2,4,6-tri-chloro- and 2,3,5,6-tetra-chloropyridines, as well as a fairly substantial yield of pyridine hydrochloride.

20% 1:1 Tungsten / Molybdenum on TiO_2

This particular catalyst was used on all subsequent Experiments due to its stability to the reactants and to the ease of its regeneration, accomplished by heating to 450°C in air for twelve hours.

(IV) Tungsten / Molybdenum catalyst (30 mls) at 120°C.

Input material :

12 mls liquid pyridine / hour;
50 mls Cl_2 / minute at 15°C ;
100 mls N_2 / minute at 15°C ;

These materials were then passed over a bed of catalyst pellets (30 mls) at 120°C.

Gas flow rates at 120°C are :

4.78 litres of pyridine / hour ;
4.32 litres of chlorine / hour ;
8.65 litres of nitrogen / hour ;

Hence, total flow rate = 17.75 litres / hour ;
= 5 mls / second ;

Therefore contact time = 30/5
= 6 seconds.

Gas phase concentrations of the reactants were :

4.32/17.75 = 24.2% chlorine :
4.78/17.75 = 27.0% pyridine :

Other data recorded for this Experiment are reproduced below.

Time. (mins)	Furnace Temp. (mV.	°C)	Reactor Temp. (mV.	°C)	Pyridine added (mls)
0	5.6	137	5.5	134	0
10	5.7	139	5.6	137	2
20	5.6	137	6.3	154	4
30	5.5	134	6.2	152	6
40	5.3	127	6.0	147	8
50	5.7	139	6.2	152	10
60	5.5	134	6.2	152	12

Once again. a heavy deposit formed at the base of the reactor. This was removed by washing with methanol (60 mls) and, after reduction of the volume, a sample of this solution was analysed by g.l.c. The same mixture of chloropyridines was observed as in previous runs. As has been indicated, there was a substantial rise in the temperature of the reaction zone which was probably due to the heat evolved in the reaction of pyridine with chlorine to form the addition compound.

At this point, it seems that the main barrier to an efficient flow system is the ease of combination of pyridine and chlorine. In an attempt to solve this problem, the reaction temperature was once again raised and the pyridine flow rate increased to 27 mls/hour.

(V) 40 mls Tungsten / Molybdenum catalyst at 190°C.

Input material :

27 mls liquid pyridine / hour;
50 mls Cl_2 / minute at 15°C ;
100 mls N_2 / minute at 15°C ;

These materials were then passed over the catalyst bed at 190°C.

Gas flow rates at 190°C are :

27. litres of pyridine / hour ;
4.8 litres of chlorine / hour ;
9.7 litres of nitrogen / hour ;

Hence, total flow rate = 41.5 litres / hour ;
= 11.5 mls / second ;
Therefore contact time = 40/11.5
= 3.5 seconds.

Gas phase concentrations of the reactants were:

4.8/41.5 = 11.5% chlorine :
27/41.5 = 65.0% pyridine :

Time.	Furnace Temp.		Reactor Temp.		Pyridine added
(mins)	(mV.	°C)	(mV.	°C)	(mls)
0	8.0	197	7.0	172	0
5	7.8	192	8.5	209	2.25
10	7.5	184	9.0	222	4.50
15	7.5	184	9.0	222	6.75
20	7.5	184	9.0	222	9.0
25	8.1	199	9.0	222	11.25
30	7.8	192	9.0	222	13.5

This course of action did not have the desired effect. The reactor was again blocked by a deposit of brownish crystalline material, and traces of the adduct $Py.Cl_2$ were found in the carbon tetra-chloride traps. The brown solid was separated from the catalyst by washing with methanol (30 mls). The methanolic solution was found to contain the same mixture of products as was detected previously by gas chromatography. viz. 2,2'bipyridyl, 2-chloro-, 2,4,6-tri-chloro- and 2,3,5,6-tetra-chloropyridines. Again, pyridine hydrochloride was found to be the major product and was isolated by sublimation and characterised by its mass spectrum.

In order to at least minimise the deposition of solid material on the column, the pyridine feed was diluted to 50% v/v with carbon tetrachloride and the mixture injected as before.

(VI) Pyridine/CCl_4 passed over Tungsten/Molybdenum catalyst at 160°C.

Input material :

50% v/v pyridine/CCl_4 at 45 mls / hour;
50 mls Cl_2 / minute at 15°C ;
50 mls N_2 / minute at 15°C ;

These materials were then passed over the catalyst bed at 160°C.

Gas phase concentrations of the reactants were :

16.7% chlorine, 36.2% pyridine.

Contact time = 4.8 seconds.

Time. (mins)	Furnace Temp. (mV.	°C)	Reactor Temp. (mV.	°C	Liquid added (mls)
0	6.5	159	6.5	159	0
10	7.2	177	7.9	194	7.5
20	7.0	172	9.0	222	15.0
30	7.0	172	9.0	222	22.5
40	6.7	164	8.5	209	30.0
50	6.5	159	8.2	202	37.5
60	6.5	159	7.6	185	45.0

No real blockage was observed in this case, and the g.l.c. analysis of the solutions in the traps showed the presence of all the chloropyridines previously mentioned. 2,2' Bipyridyl was, however, found to be absent. Nevertheless, it does seem clear that the product range is still determined by the initial reaction of pyridine with chlorine as shown by the considerable rise in the reactor temperature. To obviate this problem, the feed solution was reduced in concentration to 10% v/v pyridine in CCl_4 and the flow of chlorine was scaled down accordingly.

(VII) Input materials :

10% v/v pyridine/CCl_4 at 45 mls / hour;
15 mls Cl_2 / minute at 15°C ;
300 mls N_2 / minute at 15°C ;

These materials were then passed over the catalyst bed at 160°C.

Gas phase concentrations of the reactants were :

2.3% pyridine, 3.4% chlorine.

Contact time = 3.0 seconds.

Time.	Furnace Temp.		Reactor Temp.		Liquid added
(mins)	(mV.	°C)	(mV.	°C)	(mls)
0	7.0	172	6.0	147	0
10	6.2	152	6.6	162	7.5
20	6.5	159	6.6	162	15.0
30	6.5	159	6.5	159	22.5
40	7.0	172	6.5	159	30.0
50	6.0	147	6.4	157	37.5
60	6.5	159	6.5	159	45.0
70	6.4	157	6.3	154	52.5

At this point the reactor tube became blocked and a detailed analysis of the cause was undertaken. The column was washed with methanol (50 mls) and the resultant solution filtered. The solution was then analysed polarographically for N(4-pyridyl) pyridinium chloride, which was found to be present in 0.2% concentration. Gas chromatography showed the solution to contain a trace of 2,2'bipyridyl, small amounts of the chloropyridines already detected in the earlier Experiments and pyridine hydrochloride. After standing for several days, a pale buff precipitate formed in the solution and was removed by filtration. The mass spectrum of this solid showed it to consist of pyridine hydrochloride and a mono-chloropyridine. The filtrate, on standing for a further week, provided a second precipitate, this time rust in colour. This too was removed by filtration and its mass spectrum recorded. The following compounds were identified from the spectrum :

m/e 79 : pyridine.
m/e 113, 115 : a mono-chloropyridine.
m/e 172 : $C_{10}H_8N_2O$
m/e 156 : bipyridyl (very weak).

(VIII) 10% v/v pyridine/CCl_4 at 45 mls / hour ;
20 mls Cl_2 / minute at 15°C ;
180 mls N_2 / minute at 15°C ;

These materials were passed over the catalyst bed at 150°C. Gas phase concentrations of the reactants were :

3.25% pyridine, 5.5% chlorine.
Contact time = 4 seconds.

In this case, as can be seen from the Table below, the high volume of carbon tetrachloride, coupled with the slower overall flow rate serves only to cool down the reactor area to an impractically low temperature. The only product identified from this Experiment was the adduct $C_5H_5N.Cl_2$ and this was recovered both from the reactor and from the traps.

Time.	Furnace Temp.		Reactor Temp.		Liquid added
(mins)	(mV.	°C)	(mV.	°C)	(mls)
0	6.6	162	6.7	164	0
10	6.0	147	4.6	112	7.5
20	6.4	157	4.0	98	15.0
30	6.8	167	5.0	122	22.5
40	6.5	159	4.5	110	30.0
50	6.4	157	4.5	110	37.5
60	6.6	162	3.5	86	45.0

(b) Bromination.

Bromine and pyridine, both dissolved in carbon tetrachloride, were passed through the heated catalyst zone. Effluent gases were passed through three bubblers each containing carbon tetrachloride, thereby trapping any volatile products as well as excess bromine. Bromine was added to the apparatus in carbon tetrachloride solution and the rate of addition controlled manually.

(IX) 10% v/v bromine/CCl_4 (45 mls) added to the system over a one hour period. 7 mls pyridine in carbon tetrachloride (38 mls) added over the same time interval.

Reaction temperature was 200°C.

Flow rates at 200°C were :

1.94 litres of pyridine / hour ;
2.15 litres of bromine / hour ;
24.0 litres of nitrogen / hour ;
24.1 litres of CCl_4 / hour ;
Contact time = 2 seconds ;

Time. (mins)	Furnace Temp. (mV.	°C)	Reactor Temp. (mV.	°C)	Br_2/CCl_4 added (mls)
0	8.5	209	7.2	177	0
15	8.1	199	5.5	127	12.5
30	8.4	207	6.4	157	25.0
45	9.1	224	4.0	98	37.5
60	9.3	229	4.3	105	50.0

After only five minutes, a dark red oil, immiscible with carbon tetrachloride, ran freely from the base of the reactor. On cooling, this oil became semi-crystalline, and a sample was analysed by mass spectrometry. The molecular ions observed indicated the presence of pyridine, hydrogen bromide, bromine, a mono-bromopyridine, a di-bromopyridine and trace quantities of a tri-bromopyridine. During the course of the Experiment, the reactor temperature did fall quite appreciably, possibly due to the cooling effect of the high liquid feed rate.

(X) The conditions employed in the previous Experiment were used again in this case in order to check the reliability of the reactor thermocouple. Contact time was therefore 2 seconds at 200°C.

Time.	Furnace Temp.		Reactor Temp.		Br_2/CCl_4 added
(mins)	(mV.	°C)	(mV.	°C)	(mls)
0	8.5	209	8.1	199	0
10	8.3	205	8.2	202	8.3
20	8.5	209	7.0	172	16.6
30	8.5	209	5.5	135	25.0
40	9.6	236	6.2	152	33.3
50	10.4	257	5.7	139	41.6
60	10.4	257	6.0	147	50.0

Again, after only five minutes, a red viscous oil ran from the base of the reactor column. The temperature of the reactor dropped rapidly as the Experiment progressed, and , at time 30 minutes, the flow of input material was discontinued while the furnace was allowed to heat up to around 240°C. After restarting, the reactor temperature did fall slightly but seemed able to sustain itself around 150°C.

Once again, the red oil became semi-crystalline on cooling and showed the same pattern in its mass spectrum.

(XI) On this occasion, the feed materials were simply passed through a heated silica tube. No catalyst or glass fragments were present in the reactor, and all flow rates were the same as those used in the previous Experiment, thus maintaining an approximate contact time of 2 seconds at 200°C.

Time.	Furnace Temp.		Reactor Temp.		Br_2/CCl_4 added
(mins)	(mV.	°C)	(mV.	°C)	(mls)
0	8.4	207	8.0	200	0
10	8.3	204	4.5	110	8
20	8.3	204	4.6	112	17
30	8.5	209	4.5	110	25
40	8.5	209	4.8	116	34
50	8.2	203	4.5	110	42
60	8.4	207	4.3	105	50

As before, the red oil formed readily and was collected in the carbon tetrachloride traps. The oil was washed with ether (20 mls) and a sample analysed by mass spectrometry with the same results as before. The remainder of the product (8.2 gms) was then treated in a fashion similar to that already reported (56) in order to establish the precise composition of the mixture.

The oil was shaken thoroughly with 20% aqueous caustic soda (40 mls) and the resulting solution steam distilled until the volume of the distillate was about 50 mls. The distillate consisted of a heavy oil containing flecks of a white solid, and an aqueous layer. The latter was removed by decantation and extracted into ether. The remaining oil was also extracted into ether and the combined ethereal extracts distilled to yield the following fractions :

(i) 1.5 gms of pyridine, boiling at 113 - 115°C.
(ii) 3.0 gms of a fraction, boiling at 60 - 63°C at 15 mms.
(iii) 1.0 gms of a fraction, boiling at 65 - 75°C at 15 mms.
(iv) 0.6 gms of a fraction, boiling at 75 - 79°C at 15 mms.
(v) A black residue from which no recognisable compounds could be isolated.

This pattern is almost identical to that reported for the degradation of the pyridine / bromine molecular adduct (56), where the fractions are identified as :

(ii) Mixture of 3-bromopyridine and a small amount of 3,4-di-bromopyridine.
(iii) Mainly 3,4-di-bromopyridine.
(iv) Trace amount of 2-bromopyridine.

These compounds obviously fit the data derived from the mass spectrum of the crude product, although further explanation of the appearance of bromine is probably required.

REFERENCES

(1) Blau, Ber. 21. 1077, (1888)

(2) Clark, J. Chem. Soc. 1963. 1377.

(3) Bannick and Smith, Talanta 1. 153, (1958).

(4) Driver and Walker, Austral. J. Chem. 20. 1376, (1967)

(5) Emde and Horsters, Ger. Patent No. 358, (1920) ; via Chem. Abs. 17 2118^6, (1923).

(6) Wibaut and Dingemanse, Rec. Trav. Chim. 42. 240, (1923).

(7) Smith, J. Am. Chem. Soc. 46. 414, (1924).

(8) Frank and Reiner, J. Am. Chem. Soc. 72. 4182, (1950).

(9) Case and Kasper, J. Am. Chem. Soc. 78. 5842, (1956).

(10) Kuffner and Kaiser, Monatsh. 85. 896, (1954).

(11) Kuffner and Faderl, Monatsh. 87. 71, (1956).

(12) Arens and van Dorp, Rec. Trav. Chim. 66. 189, (1947).

(13) Arens and Wibaut, Rec. Trav. Chim. 61. 59, (1942).

(14) Dimroth and Heene, Ber. 54. 2394, (1921).

(15) Dimroth and Frister, Ber. 55. 3693, (1922).

(16) Case, J. Am. Chem. Soc. 68. 2574, (1946).

(17) Wibaut and Overhoff, Rec. Trav. Chim. 47. 761, (1928).

(18) Smith, J. Am. Chem. Soc. 53. 397, (1930).

(19) Lukes and Pliml, Chem. Listy. 49. 1836, (1955). via Chem. Abs. 50. 9402 h, (1956).

(20) Dubinin et al., J. Gen. Chem. USSR. 16. 105, (1946).

(21) Hein and Retter, Ber. 61. 1790, (1928).

(22) Morgan and Burstall, J. Chem. Soc. 1932. 20.

(23) Wibaut and Willink, Rec. Trav. Chim. 54. 275, (1935)

(24) See Ref. 21.

(25) See Ref. 22.

(26) Jubb, Brit. Patent No. 869,954.

(27) Mockel and Stark, Brit. Patent No. 870,700.

(28) Lang, Brit. Patent No. 1,014,076.

(29) Krumholtz, Selecta Chim. 8. 3, (1949).
via Chem. Abs. 44. 3992 i, (1950).

(30) See Ref. 26.

(31) Thomas, Compt. Rend. 126. 1211, (1898).

(32) Kovacic and Sparks, J. Am. Chem. Soc. 82. 5740, (1960).

(33) Kovacic and Sparks, J. Org. Chem. 28. 972, (1963).

(34) Olah, Friedel Crafts and Related Reactions.
Interscience, 1965, Vol. IV. p. 111.

(35) Sharp et al. J. Chem. Soc. A. 1966. 1031.

(36) Hieber and Bader, Ber. 61. 1720, (1928).

(37) Weinland et al. Z. fur Anorg. Chem. 120. 209, (1922).

(38) O'Donnell et al. Inorg Chem. 5. 1438, (1966).

(39) Novikov et al. Russ. J. Inorg. Chem. 6. 1019, (1961).

(40) McCarley and Brown, Inorg. Chem. 3. 1232, (1964).

(41) Clark and Williams, Inorg. Chem. 4. 350, (1965).

(42) Fowles and Hoodless, J. Chem. Soc. 1963. 33.

(43) Fowles and McGregor, J. Chem. Soc. 1958. 136.

(44) Fowles and Pleass, J. Chem. Soc. 1957. 1674.

(45) Wardlow and Webb, J. Chem. Soc. 1930. 2100.

(46) See Ref. 40.

(47) McCarley et al. Reactions of Coordinated Ligands and

/ OVER

(47) McCarley et al. Reactions of Coordinated Ligands and Homogeneous Catalysis. Advances in Chemistry Series, No.37. pp 243-255.

(48) See Ref. 37.

(49) Lloyd et al. J. Chem. Soc. 1928. 661.

(50) Forster, J. Chem. Soc. 1917. 812.

(51) Koenigs and Greiner, Ber. 64. 1049, (1931).

(52) Albert, J. Chem. Soc. 1951. 1376.

(53) Wibaut and Broekman, Rec. Trav. Chim. 58. 885, (1939).

(54) See Ref. 47.

(55) See Ref. 40.

(56) McElvain and Goese, J. Am. Chem. Soc. 65. 2227, (1943).

(57) See Ref. 53.

(58) Wibaut et al. Rec. Trav. Chim. 54. 807, (1935).

(59) Cotterell, The Strengths of Chemical Bonds. Butterworth's, London 1958, Table 11. 5. 1.

(60) Brugel, Z. fur Elektrochem. 66. 159, (1962).

(61) McConnell et al. J. Chem. Phys. 23. 1152, (1955).

(62) Pople et al. Can. J. Chem. 35. 1487, (1957).

(63) See Ref. 61.

(64) Bernstein et al. Can. J. Chem. 35. 1050, (1957).

(65) See Ref. 62.

(66) Pople, Bernstein and Schneider, High Resolution N.M.R. McGraw-Hill, 1959, Table 6. 18. p 141.

(67) See Ref. 62.

(68) Castellano et al. J. Chem. Phys. 46. 327, (1967).

(69) Brown and Heffernan, Austral. J. Chem. 12. 554, (1959).

(70) Baldeschwier and Randall, Proc. Chem. Soc. 1961. 303.

(71) Gil and Murrell, Trans. Faraday Soc. 60. 248, (1964).

(72) Farnum, J. Am. Chem. Soc. 86. 934, (1964).

(73) Okamoto and Shimakawa, J. Org. Chem. 35. 3752, (1970).

(74) Spotswood and Tanzer, Austral. J. Chem. 20. 1227 (1967).

(75) See Ref. 72.

(76) See Ref. 29.

(77) See Ref. 22.

(78) Wibaut and Willink, Rec. Trav. Chim. 54. 275, (1935).

(79) Wibaut and Willink, Rec. Trav. Chim. 53. 584, (1934).

(80) Wibaut and Willink, Rec. Trav. Chim. 50. 287, (1931).

(81) Wibaut and Willink, Rec. Trav. Chim. 54. 804, (1935).

(82) Badger and Sasse, J. Chem. Soc. 1956. 616.

(83) Maxted, Adv. Catalysis. 3. 129, (1951).

(84) Wibaut and Nicolai, Rec. Trav. Chim. 58. 709, (1939).

(85) See Ref. 55.

(86) See Ref. 51.

(87) Hoffman, Ber. 12. 984, (1879).

(88) Hoffman, Ber. 16. 586, (1883).

(89) Wibaut and den Hertog, Rec. Trav. Chim. 64. 55, (1945).

(90) Wibaut and den Hertog, Rec. Trav. Chim. 51. 381, (1932).

(91) den Hertog, Rec. Trav. Chim. 64. 85, (1945).

(92) Wheland, Resonance in Organic Chemistry.
Wiley, New York, 1965, p 485.

(93) See Ref. 56.

(94) See Ref. 91.

(95) Wibaut and Broekman, Rec. Trav. Chim. 58. 885, (1939).

PUBLICATION :

Sharp and O'Keane, The Manufacture of Pyridine Derivatives.
U.K. Patent Application No. 46829/69.