STUDIES ON PYRIDINE I

THE DIPYRIDYLS

A Thesis submitted to the Chemistry Department of the American University of Beirut in partial fulfillment of the requirements for the Degree of Master of Arts in Chemistry,

by

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ACKNOWLEDGMENT

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INTRODUCTION

Reasons for interest in the six isomers of bipyridyl:

The six isomers of bipyridyl offer an interesting system for the study of the effect of directive influences on various properties of the molecule, especially as the only difference between the various isomers is the position at which the two rings are joined together.

This study is of particular interest due to the practically complete absence of any experimental treatment of the problem of pyridine free radicals. The only theoretical treatment (this will be considered later) by Wheland (8) is very qualitative and the calculations are almost fully based on "expected" behaviour of the pyridine nucleus.

Also, in view of the kinetic study of the thermal decomposition of pyridine by Dr. R.H. Linnell, it was necessary to find a micro qualitative-quantitative analytical method for the estimation of the various isomers in the thermal decomposition products. Naturally, the two studies are complementary and together could supply the answer to several properties of these compounds.

Properties of the Pyridine ring:

The properties of importance of Pyridine are:

1 - Its aromatic structure,

2 - The presence of nitrogen in the ring, an "electron sink",

3 - Tertiary amine properties.

The tertiary amine properties of pyridine are not of any special interest in this study. These were treated exhaustively by Bergstrom.(1).

The first two properties are so interrelated that they have to be treated together.

The presence of nitrogen, an "electron sink", diminishes the electron density throughout the ring and hence increases the resistance of the ring to attack by "electron seeking" groups - such as nitration and sulfonation. It is only under drastic conditions that there is any reaction. Vapor phase bromination of pyridine yields mainly 3-bromopyridine; as should be expected from an attack by an electron seeking free radical (Br.). Since the 3- position has the highest electron density, apart from the nitrogen.

Furthermore, the inequality of the electron density at the various positions makes the various C-H bonds unequal in strength:
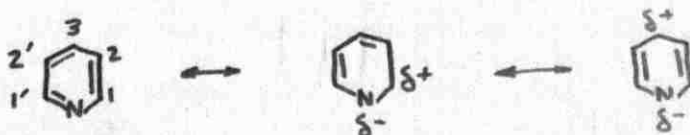
hence the nitrogen introduces an ortho-para directive influence with respect to low electron density and meta-directive influence with respect to high electron density. This is clearly similar to the effect of a nitro group in nitrobenzene. The gradation in bond strength $2 < 4 < 3$ or $4 < 2 < 3$ is strikingly demonstrated in two completely different reaction mechanisms.

These reaction mechanisms can be explained on the basis of free radical reactions. There is indirect evidence for such mechanisms in that the products are in complete agreement with those that should be expected and there is some direct evidence from studies on 1, I'diacetyl, tetrahydro 4,4' bipyridyl (discussed below).

The first reaction is that of sodium and pyridine, first studied by Anderson in 1870, (2a) and by C.R. Smith in 1924, (2b 3), and the acetic anhydride, zinc and pyridine reaction (4). Both reaction mechanisms are essentially the same.

1.
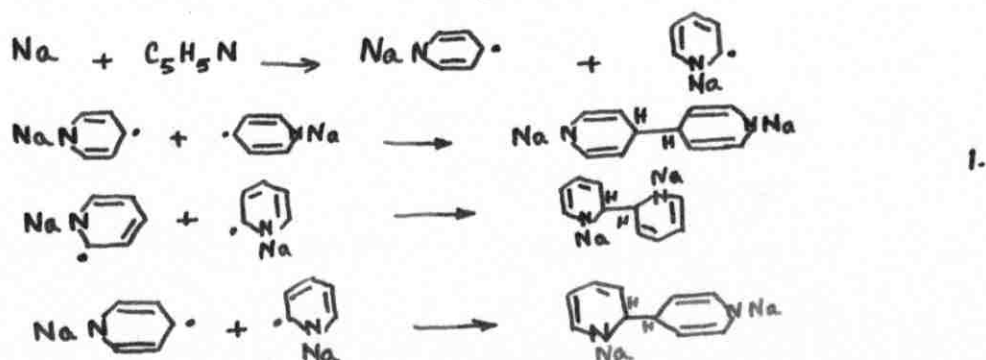
From the well known strongly electro positive nature of sodium one can safely assume that it donates almost completely its 3s electron to the ring nitrogen (in exactly the same way it is donated in sodium

amide) this will necessarily produce a general ring effect because
the ring electrons are no more held with the same strength as
before. The ortho position being nearest to the nitrogen still
has the lowest electron density, but, due to the resonating
structures available, there is a lone electron ready to be shared
by another group. The para position being furthest away from the
nitrogen is still more ready to share its lone electron with
another group. Obviously, the meta position does not enjoy such an
ability. Hence, from the above reasoning, we should expect the
4,4' bipyridyl to be the predominant product, then 2,4'- bipyridyl
and 2,2' bipyridyl. Traces of 2,3'- and 3,4'- could possibly be
produced by some secondary reactions such as a free radical attack
on the pyridine molecule: the 2 and 4 positions are favoured by
having weaker C-H bonds, while the 3- position is favoured by virtue
of its higher electron density which encourages a free radical
attack.
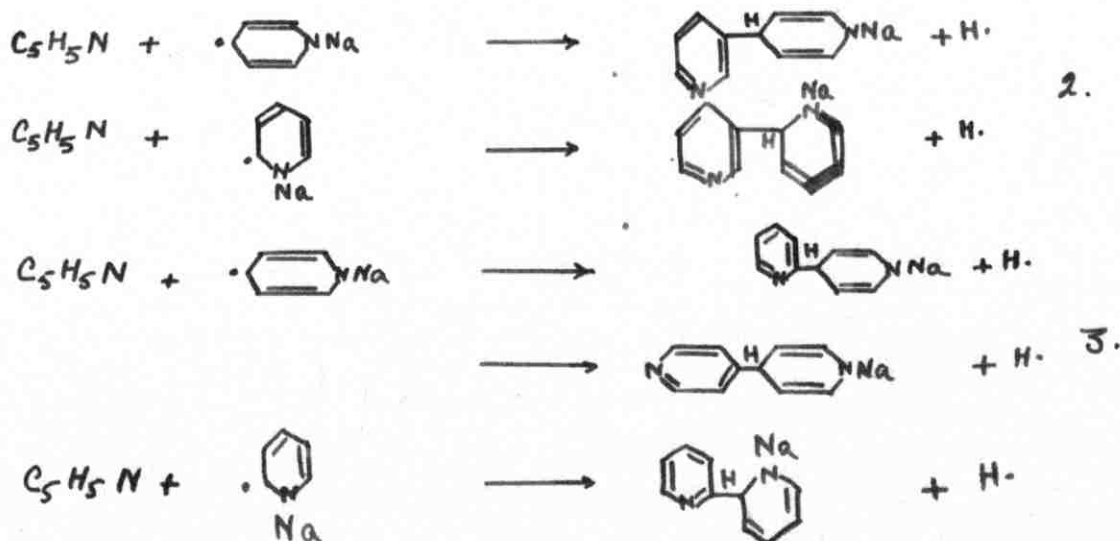
as will be discussed more fully in the experimental part, reactions of the type represented by (3) are the most important.

The (H) produced in (2,3) would account for the presence of reduced products such as neonicotine. No H_2 gas appears to be produced.

The relative proportion of the isomers is in agreement with such a mechanism. Other reactions take place to a large extent as shown by the presence of acridine and the low yield of isomers (about 25 - 30%).

The complete absence of heat reaction is somewhat surprising since the pyridine - a stable aromatic compound - changes to a non-aromatic free radical.

Direct evidence in favour of the free radical hypothesis is supplied by the almost identical reactions of acetic anhydride, pyridine and zinc:

$$(CH_3CO)_2O + Zn \longrightarrow ZnOOCCH_3 + CH_3CO-$$
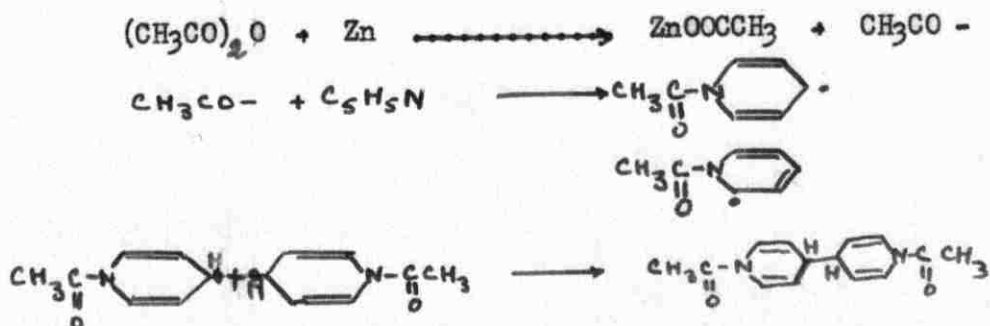
4

The final compound, N,N' diacetyl tetra hydro bipyridyl has been isolated by Dimroth, Heene, Roth, (4), and its free radical

properties demonstrated and studied by Frank, Pelletier and Starks in 1948 (5). Clearly, the acetyl group (CH$_3$CO-) is far less electropositive than sodium and nevertheless it is capable of freeing the para or ortho position and to stabilize the free radical.

The second reaction mechanism which shows a different gradation in bond strengths $(2 < 4 < 3)$ is the thermal decomposition of pyridine.

In the thermal decomposition we have:

$$C_5H_5N \ + \ Energy \ \longrightarrow \ \text{⬡} \cdot \ + \ H \cdot$$
$$\longrightarrow \ \text{⬡} \ + \ H \cdot$$

5.

Now the C-H bond is polarized so that:

$$\overset{\delta+}{C} - \overset{\delta-}{H}$$
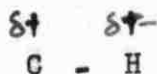
hence when H is removed the electron density in the ortho-para position will slightly decrease further and the unshared electron of the carbon is mainly distributed at the N.

Since the ortho position is nearest to the nitrogen, the free electron is shared most effectively and the free radical is stabilized; the para position lone electron is not shared so effectively and the free radical is less stable.

Hence we should expect more α-pyridyl radicals than γ-radicals

These free radicals can react together, so that:

$$\text{pyridyl} \cdot + \cdot \text{pyridyl} \longrightarrow 2,2 - \quad + \quad \text{Energy}$$

$$\text{pyridyl} \cdot + \text{pyridyl} \longrightarrow 2,4 - \quad + \quad \text{Energy}$$

$$\text{pyridyl} + \text{pyridyl} \longrightarrow 4,4 - \quad + \quad \text{Energy}$$

Because free radicals are molecules with an unshared electron, one can consider the problem from two points of view:

1.   Since there is an unshared electron, the free radical would seek a position with a low electron density which could share this lone electron; sodium is such a free radical.

2.   Also, the free radical could seek a position with a high electron density which could provide an electron to be shared by the free radical; Br. is such a free radical.

Since the pyridyl free radical has its charge distributed over the ring, we would expect it to be of the second type. Hence the pyridyl free radical would attack the 3-position so that:

$$C_5 H_5 N + \text{pyridyl} + \text{Energy} \longrightarrow 2,3' - \quad + H \cdot \qquad 7.$$

or:

$$\longrightarrow \text{pyridyl} \cdot + C_5 H_5 N$$

$$\text{pyridyl} \cdot + \text{pyridyl} \cdot \longrightarrow 2,3' - + \text{Energy}$$

These free radicals can react together, so that:

$$\text{(ring).} + \text{.(ring)} \longrightarrow 2,2- \quad + \quad \text{Energy}$$

$$\text{(ring).} + \text{(ring)} \longrightarrow 2,4- \quad + \quad \text{Energy}$$

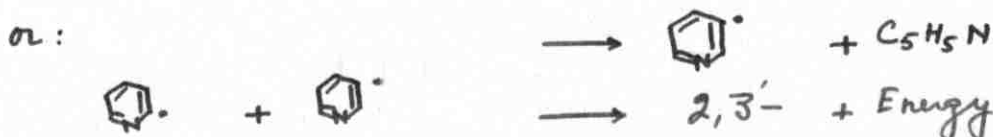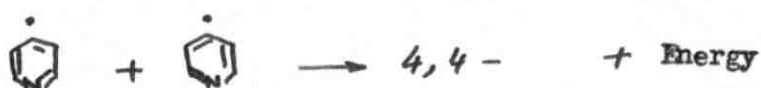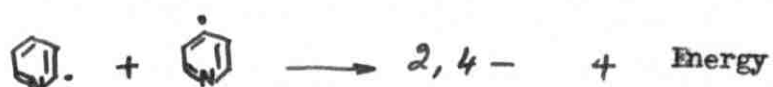$$\text{(ring)} + \text{(ring)} \longrightarrow 4,4- \quad + \quad \text{Energy}$$

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$$C_5H_5N + \text{(ring)} + \text{Energy} \longrightarrow 2,3'- \quad + \quad H. \qquad 7.$$

or:

$$\longrightarrow \text{(ring)} + C_5H_5N$$

$$\text{(ring).} + \text{(ring)} \longrightarrow 2,3'- + \text{Energy}$$

During the thermal decomposition the concentration of pyridine is predominant, since there is about 0.3% decomposition only in our studies (while other workers have used up to 30% decomposition), hence, there is a high probability that a free radical will collide with a pyridine molecule. There is an important factor that favors the reaction between a free radical and a molecule. From elementary kinetic theory we have for a reaction of the type:

$$A + B \longrightarrow C$$

$$\frac{d}{dt}\left[\text{conc. of C}\right] = K \left[A\right]\left[B\right]$$

where $K = V e^{-E/RT}$

V is the collision factor and E is the energy of activation for the reaction.

When we have two competing reactions both using a free radical the amount of the product for each depends on both V and E.

$$R\cdot + R\cdot \longrightarrow RR + Energy$$
$$R\cdot + MH \xrightarrow{E} RM + H\cdot$$
$$R\cdot + MH \xrightarrow{E} RH + M\cdot$$
$$R\cdot + M\cdot \longrightarrow MR + Energy$$
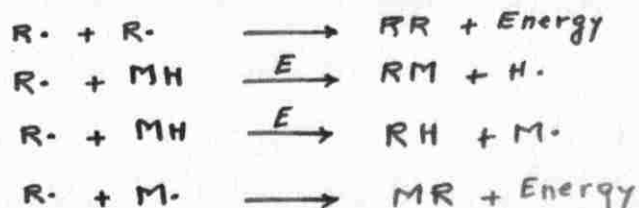
The usual assumption is made that free radical combination does not require any energy of activation. But, owing to the large amount of energy liberated, a third body should be present in order to take over the excess energy, otherwise the newly formed molecule possesses sufficient energy to dissociate in the time of one vibration.

Now, from elementary collision theory $\overset{V_3}{(3)}$, number of three body collisions per second is usually about $10^{-3}\ V_2$; where V_2 is number of two body collisions.

The requirements of a three body collisions for free radical combination favours the combination of the free radical with a **pyridine** molecule.

The second important consideration is that the reactions:

$$C_5 H_5 N + H\cdot + Energy \longrightarrow \bigcirc\cdot + H_2$$
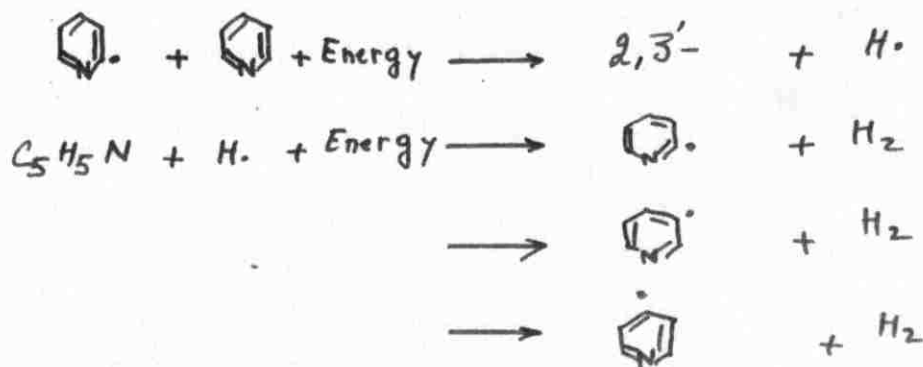
8.

all require a definite amount of energy of activation.

Hence, this factor would favour the combination of two free radicals rather than that of a free radical and a pyridine molecule.

Experimentally, it is reported by Krumholz that the yield of 2,3' is the same as that of 2,2'-.

On this basis, the main yields should be: -

2,2'-$\geqslant$2,3'-$>$2,4-$>$4,4- ; 3,4 ; 3,3'-
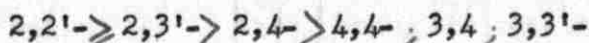
This is supported by the findings of several workers such as

Meyer and Hoffman-Meyer (6) and Krumholz (7).

Theoretical study of the directive influences of the ring nitrogen has been done by Wheland (8). In his paper he makes several assumptions as to the reaction mechanisms and the calculation of parameters. According to him, the order of bond strength is undoubtedly 2-, $<$ 4-, $<$ and 3-. Roberts and Szwarc (9) in their discussion of the results of the thermal decomposition of picolĭines (by a flow method, gas phase) where they obtained the values of the C-H bond energies in the methyl group as:

$$75.5 \text{ Kcal for } 2\text{-picoline}$$
$$76.5 \text{ " } \text{ " } 3\text{- "}$$
$$77.5 \text{ " } \text{ " } 4\text{- "}$$

give as support to this gradation the results of Haworth, Heilborn and Hey (10) who studied the reaction of phenyl and nitrophenyl radicals with pyridine (in the liquid phase). Obviously this is an unjustifiable extrapolation from a condensed phase and a free radical reaction where the free radical is not even a pyridine one.

Furthermore, the experimental results of Hey and his co-workers do not favour the meta to the para positions in pyridine, but favour the ortho position to any other position.

Preparation of the isomers:

Various methods for the preparation of the 2,2'- isomers have been ivestigated. In this work 2,2' has been obtained both from the sodium pyridine reaction and the thermal decomposition of pyridine. Several other methods are available. An excellent summary of these methods is given by Morgan and Burstall (II).

4,4'-bipyridyl has been prepared by the sodium pyridine (2,3') reaction and by the Zn acetic anhydride and pyridine reaction (4). The latter method is more time-consuming.

3,3'-bipyridyl was prepared from p-phenanthroline which was prepared by a Skraup synthesis according to Smith (12) and the isomer obtained by permanganate oxidation, and decarboxylation of the dibasic acid. The phenanthroline method can also be applied to the preparation of 2,2'-; 2,3'-bipyridyls. Small quantities of 3,3'- were also obtained from the sodium pyridine reaction.

2,3'-bipyridyl is prepared by the phenanthroline method (12, 13) also it is a by-product of the thermal decomposition of pyridine (6, 7). It could also be prepared by pyrolysis of anabasine, a naturally occuring alkaloid which is 3-(2-piperidine)pyridine, (14). C.R. Smith (2) states that 3,4'-bipyridyl has been prepared by the sodium method and that the compound when oxidised with permanganate yields the expected nicotinic and 4-picolinic acids.

$$3,4- \xrightarrow{[O]} \text{(pyridine)}-COOH + \text{(pyridine)}-COOH \qquad 9.$$

2,4 - bipyridyl:

Krumholz (15, 16) during his researches on the absorption spectra of bipyridyls and the thermal decomposition products of pyridine, noticed that the dissociation constants and the absorption spectra of this isomer were not in line with the expected properties of a 3,4'- substituted bipyridyl, but were those expected of the 2,4'-isomer.

Hence Krumholz oxidised the compound and was able to separate the picolinic and isonicotinic acids.

This should be expected because the proposed free radical mechanism discussed previously cannot account for a 3,4 bipyridyl with a yield coming next to 4,4- or 2,2- depending on the reaction.

Hence the 2,4-isomer is obtained in good yield from the thermal decomposition and sodium reaction of pyridine.

At present there are no suitable methods for the preparation of the 3,4-isomer. Krumholz obtained about 100 mg from the thermal decomposition of 1500 g of pyridine, (1500 g is the weight of the reacted pyridine). The separation method used by Krumholz might be wasteful and improved methods could cpossibly supply larger quantities.

A detailed discussion will be gone into later on the "synthetic absorption spectra" principle used by Krumholz as well as the dissociation constants.

All the six isomers have strong absorbing bands in the ultraviolet and none in the visible. As pointed out by Krumholz (15) the absorption of the various isomers is not very different from each other.

All 2-substituted rings have two absorbing peaks one at about 235 and the second at about 280 mu with an average extinction coefficient of about 12.10^3. In 3,3- the second peak is depressed while in 4,4- there is only one peak at 240 mu.

The most studied isomer is 2,2- whose iron complexes have been studied in great detail by several workers. 2,2- gives complexes with ferrous iron whose composition depends on the relative concentration of the reactants.

The most important one has the composition I Fe^{++} to 3(2,2-).

$$Fe + 3(2,2'-) \rightleftharpoons \left[Fe(2,2'-)_3\right]^{++} \qquad 10.$$

The colour of this complex is red. The second complex is made in the ratio $1Fe^{++}$ to $1(2,2'-)$
It also gives a complex with the ferric iron. The colour of this complex is blue. These complexes have been studied extensively (16).

The effect of various substituents on the complexing ability of 2,2'- has been studied extensively by Brstall and Morgan (11). Mellon (17a) states that the complexing ability resides in the system N - C - C - N.

2,2'- has one dissociation constant while all the remaining isomers have two. An interesting study of the crystal structure (17) revealed that the rings are placed in the trans position. Dipole measurements by Burstall (17b) also indicate that this is so in solution

It is interesting to note that the absence of a second dissociation constant and the dipole moment and crystallographic

studies necessarily mean that the effect of the first hydrogen ion
is transmitted to the second ring through the (2,2) bond and not
through any proximity effect, i.e. it is not due to the repulsive
force between two H on nearby N atoms as would be the case if the
rings were not in the trans position. When 2,2- takes I H the elec-
tron density at the N decreases further, hence the electron density
on the C atom in the 2 positions also decreases and hence increases
the electron density at the C at the end of the 2-2 bond.

Hence the C-C bond is polarised, very strongly, and the N in the se-
cond ring is unable to provide sufficient electron density for a
H to be held.

If the ring positions are not trans in water the steric
effect would be appreciable and it would contribute to the non-ability
of the 2nd N of acquiring any H. It appears from the above discussion
that most probably the relative positions of the two rings is trans.
It of course remains to be verified whether the rings in a medium of
such a high dielectric constant as water are still in their trans po-
sition. Hence a study of the relative positions of the rings in water
might throw light on whether the effect is transmitted through the
polarization of the 2-2 bond or not.

The investigation of the kinetics of formation of the
$(2,2-)_3$ ferrous complex by Philip and George (18) is very interesting
and it is mentioned in the article that there might be a close simila-
rity between this complex and hemoglobin; hence a study of this rela-
tively simple compound might throw light on a very complex and import-

ant compound.

A further interesting property of this complex has been ob-
served for the first time in the course of this research, namely a
reversible photolytic activity. Unfortunately, there was not enough
time to investigate the reaction in detail but a few experiments we-
re performed from which some general ideas could be obtained. The
photolytic reaction takes place in concentrated alcohol solutions and
it is qualitatively reversible unless the time of exposure in direct
sunlight is too long. For a diluted solution 15 minutes in direct sun-
light is sufficient to remove most of the colour and a yellow colour
remains. When the container is left in the dark for about 15 - 24 hours
the original colour is restored. This reaction should not be confused
with the decomposition of the complex through the oxidation of the
ferrous ion to ferric, because the reaction is reversible. Qualitati-
ve absorption spectra studies showed that the absorption of the exposed
solution is less than that of the original solution. When the solution
is exposed for a long period of time, the reaction is no more reversible.
The role of oxygen has not been determined. A detailed study of this
photoactivity is very interesting and might further relate the compound
to chlorophyll. Such a relation to both chlorophyll and hemoglobin,
might be instructive in the further study of photosynthesis processes
in general.

It has also been found that the 2,2' and 4,4' isomers undergo
photo-chemical decomposition when exposed to sunlight in water solution.
The 4,4' solutions gave a positive Nessler's test for ammonia. The mecha-
nism for the photodecomposition is probably similar to that of pyridine
(19).

Reduction of the isomers and polarographic work:

In contrast to the difficulty of reducing pyridine which requires sodium and alcohol, the isomers can be readily reduced with Zn plus HCl or with tin and HCl in the case of the 4- and 2- substituted rings. Smith (19) was able to separate the pyridyl piperidines on reduction of the isomers with S_n and HCl. The ease of reduction was given as 4,4- (easiest); 2,4- ; 2,2- ; 3,3- resisted reduction and the author in a later article on neonicotine (19) which is:

2-(3-pyridyl) piperidine

adds that 2,3- "probably" gives on reduction 3-(2-pyridyl) piperidine. From this statement arose the general belief as expressed by Elderfield (20) and Morton (21) that anabasine, 2-(3-pyridyl) piperidine, cannot be prepared by synthetic methods because the 3-ring is the one easiest to reduce.

Curiously, Elderfield gives the ease of reduction as 4,4- (easiest); 3,3-; 2,2- with the 2,2- resisting reduction. We were unable to find any reference to confirm this statement. Most probably this idea originated from the belief that the 3-ring in 2,3- is the easiest to reduce.

In this study a large amount of work was done to elucidate this problem and the reduction potentials of five of the six isomers have been studied at various pH and different concentrations. The relative ease of reduction has been finally established

to be: 4,4- (easiest); 2,4-; 2,2-; 2,3-; 3,3-; 3,4- was not studied because it is not yet available, but most probably will fall near 2,4- in the series.

The reduction of 4,4- is interesting because of an intenseley coloured intermediate which is very reactive and easily oxidised or reduced. The structure was studied by Dimroth and Frister in 1923 (22) who claim to have separated a dark green dyestuff composed of molecular proportions of 4,4- and I,I-dihydro -4,4-dipyridyl, isolated as the di-HCl salt $(C_{20}H_{20}N_4Cl_2)$.
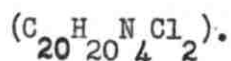
Clearly, this composition does not establish the suggested structure but it is in agreement with:

In this work this problem was investigated using absorption spectra, polarographic reduction and the results of chemical reduction.

Smith (23) in 1928 reduced five of the isomers using platinum oxide catalyst in acid medium and hydrogen. He found that the reduction is complete and no pyridyl piperidines could be separated whatever the conditions. He also reports that no reduction took place in neutral or basic medium.

The difficulties met with in the interpretation of the data

will be seen in detail in the polarographic study; some of the
difficulties are due to the surface active nature of the isomers.
This added greatly to the complications of the study because detail-
ed investigation had to be started on the electrocapillary curve of
mercury and the interpretation became more difficult than is usual-
ly the case.

SYNTHESIS OF BIPYRIDYLS

Synthesis of the Isomers of Bipyridyl: -

The Sodium Pyridine Method:

The reaction of sodium and pyridine seems to have been first investigated by Anderson in 1870 (2a) and later by C.R. Smith in 1924 (2b).

The reaction mechanism proposed in the introduction seems very plausible at first sight. Morton (24) as well as Elderfield (25) state that the reaction proceeds through the following mechanism:

$$2 Na + 2 C_5H_5N \longrightarrow Na\ N \overbrace{}^{H}_{H} \overbrace{} N\ Na \xrightarrow{O_2} 4,4-$$
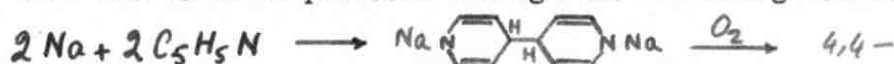
But Smith in his 1924 paper states that if the excess pyridine is removed by means of vacuum from a mixture of sodium and pyridine, a compound is left which has the composition one Na to two pyridine molecules. This would immediately suggest that the reaction between two sodium pyridyl free radicals is improbable and the main reaction is between a sodium pyridyl free radical and a pyridine molecule, that is:

$$Na + C_5H_5N \longrightarrow NaN \overbrace{} \cdot + C_5H_5N \longrightarrow Na\ N \overbrace{} \overbrace{} N + H.$$
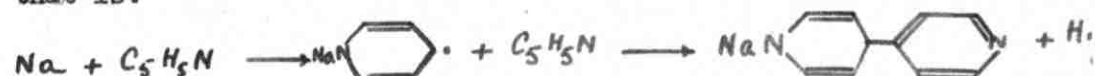
During this work several batches of Na plus pyridine were made and a record was kept of the amounts of pyridine used, the amount reacted and the sodium used. Unfortunately the Smith method was used initially for the separation of the products and as will be shown later, unless one is working with very large quantities, it is very difficult to obtain any of the isomers except 4,4- in any significant yield. Hence there is no record available at present of the variation of the yield in the various isomers while using different relative quantities of the reactants. When the results given in the following table are

T A B L E 1.

Batch No.	ml. of C$_5$H$_5$N used	ml. of C$_5$H$_5$N recovered	moles C$_5$H$_5$N reacted	gr. Na used	$\frac{\text{M. C}_5\text{H}_5\text{N}}{\text{M. Na}}$	$\frac{\text{M. react. C}_5\text{H}_5\text{N}}{\text{M. of Na}}$	$\frac{\text{M. Na}}{\text{M. C}_5\text{H}_5\text{N}}$
1	790	646[+] 1100	2.7	12 18	19 21	3.4	0.05
2	520	456[+]		6	25		
3	800	700	1.3	11	12.7	3.15	0.08
4	700	500	2.5	20	10	2.9	0.1

(M. stands for moles)
+ values calculated using fig. I

Note to table I : The values fiven for batches I and 2 are combined because the two batches were mixed together. The values of the amount of pyridine that should be recovered has been calculated from fig. I for batches I and 2. The agreement is clearly excellent.

Fig. 1.   Fig. 2.

y-axis (Fig. 1): $\dfrac{\text{moles of } C_5H_5N}{10 \text{ moles of } Na}$ values: 20, 10

y-axis (Fig. 2): $\dfrac{\text{moles of } C_5H_5N}{\text{mole of } Na}$ values: 0.10, 0.05

x-axis (Fig. 1): $\dfrac{\text{moles of reacted } C_5H_5N}{\text{mole of } Na}$ values: 3, 4

x-axis (Fig. 2): $\dfrac{\text{moles of reacted } C_5H_5N}{\text{mole of } Na}$ values: 3, 4

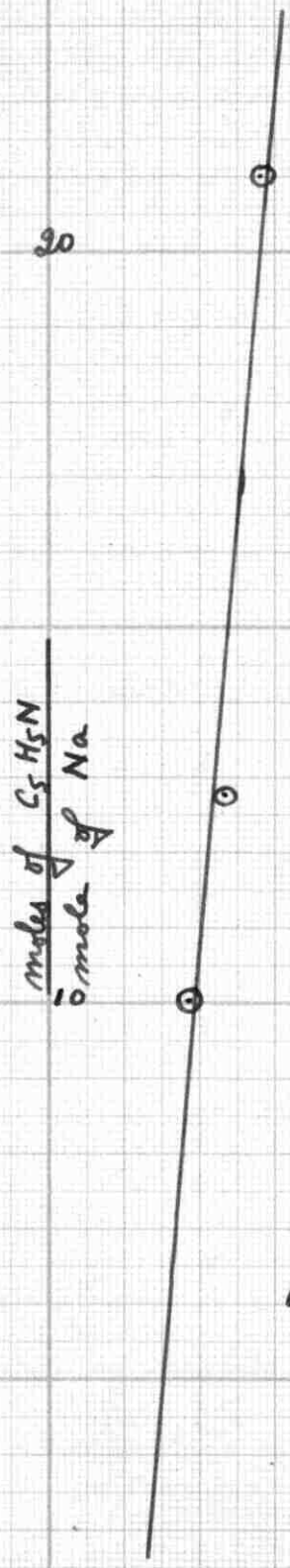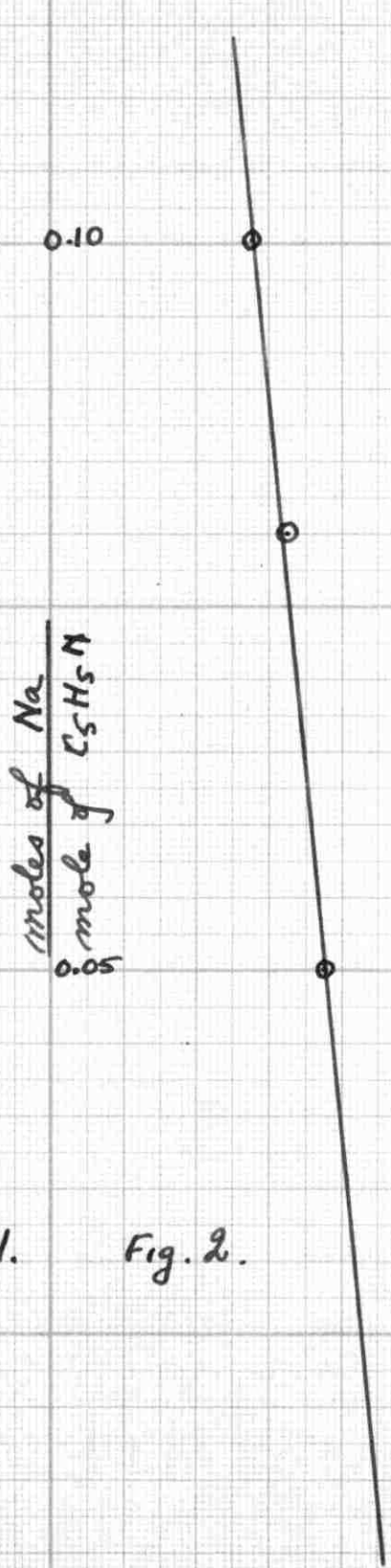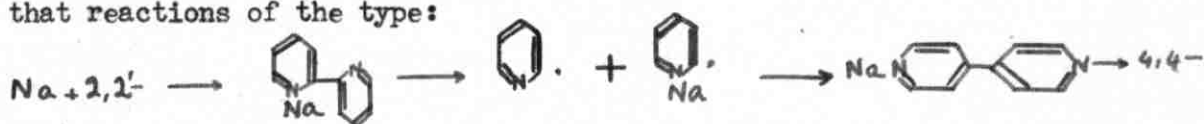Arc

plotted (fig. 1,2) two interesting graphs are obtained which show:

1 - That the yield in moles of reacted pyridine per mole of sodium is independent of the ratio of pyridine to sodium used,

2 - That other reactions of the sodium pyridine free radical are more probable than the reaction postulated for the reaction of sodium pyridine and pyridine. This second reaction is probably ring opening, because it is clear that for every mole of sodium used about 3 moles of pyridine react. Some polypyridyls may be formed. Experiments were performed using 4,4- and 2,3- with sodium to see whether any reaction takes place in order to determine whether the Na in the sodium dipyridine compound can loosen itself or not. It was clear that a reaction took place. When the benzene (which was used as a solvent) was tested for the presence of other isomers such as for the 2,2 in the 4,4- solution, no positive tests could be obtained: Initially it was thought that reactions of the type:

$$Na + 2,2'- \longrightarrow \quad \text{[ring-Na-ring]} \quad \longrightarrow \quad \text{[ring]}\cdot + \text{[ring]}\cdot \quad \longrightarrow \quad Na\,\text{[ring—ring]}\,N \longrightarrow 4,4-$$

are possible; obviously this is not supported by experiment. Since whenever sodium is tied up with two pyridine molecules it cannot react any more and since only about 25 to 30% of the products are bipyridyls it is clear that other reactions, probably ring opening, take part to a large extent.

Hence it is postulated that for every sodium atom that reacts with a pyridine to produce an isomer precursor, there is a sodium atom which produces a ring opening, which subsequently produces through a mechanism, which is not yet clear acridine, acids and polymers.

The acids are probably formed during air oxidation of the reactants.

Work is being carried on at present to identify the various compounds other than the isomers.

It is interesting to note that according to Smith (2b) when the reaction is conducted at room temperature and the mixture is not heated to 114 - 115 °C, before oxidation with dry air, the main yield is 4,4- bipyridyl.

This would indicate that the energy of activation for the reaction of the sodium pyridyl radical with the 2- position is greater than that for the reaction with the 4- position, secondly that the 4- free radical is more stable than the 2- free radical at low temperature and one has to reflux at elevated temperatures in order to get some of the molecules in a sufficient activated state to react to form the other isomers.

Experimental:-

As already mentioned, the relative amount of sodium and pyridine has not been studied with respect to the yield of the isomers. But it has been found that the reacted pyridine per mole of sodium is almost a constant. The subject should be pursued further.

Usually 700 - 800 ml of dry and pure pyridine, b.p. 115.3°C are treated with 10 - 15 gr. of Na. The reactants are kept in a closed flask at room temperature, there are no gases evolved or any heat reaction. The sodium mass turns quickly into a brown mass and then an almost uniform brown solution appears after 24 - 48 hours. The reactants are now refluxed at 114°C in an oil bath for 16 hours. This is followed by oxidation with dry air at 90°C until the disappearance of the blue or green colour (from a mixture of blue or brown) which change to reddish brown. At the end of the oxidation, the excess pyridine is distilled off and the remaining solids are treated with about 20 c.c. of water and extracted with ether. The ether extraction was tested and it was not found to be complete, even 2,2- and 4,4- which are almost insoluble in an alkaline medium fail to be easily extracted by about 2 liters of ether (about ten extractions of 200 c.c. each) per 200 grams of reacted pyridine.

The Smith method of separation and its defects:

Smith distilled the oil from the ether extraction at 270 - 310°C until "a slight decomposition and darkening of the distillate was apparent". When this method was used the whole lab was filled with suffocating fumes and it was apparent that such a procedure produced extensive decomposition of the products.

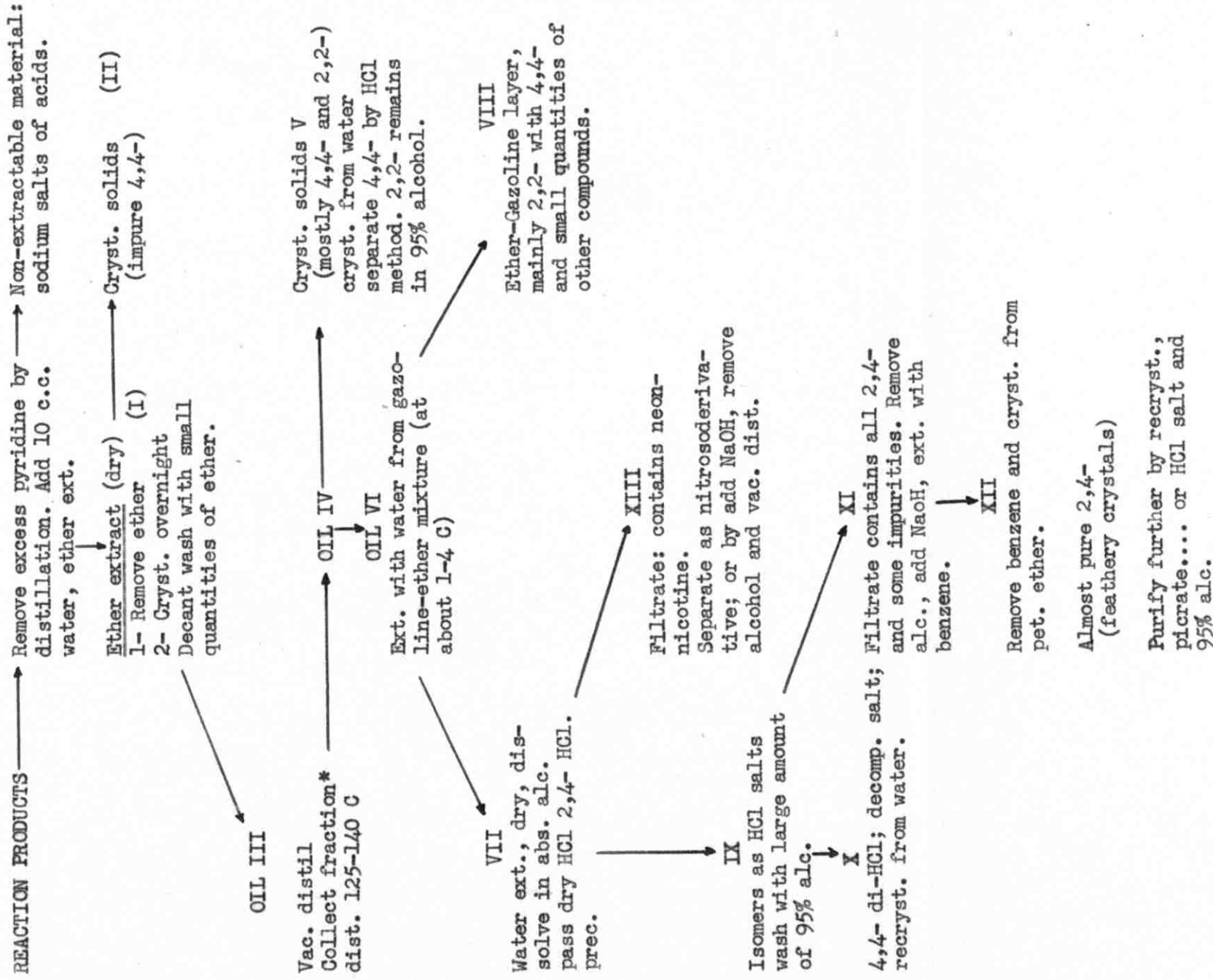Smith dissolves the distillate in conc. HCl and evaporates to

dryness, 95% alcohol is added to dissolve all isomers except 4,4-di HCl salt.

When this procedure was tested with 2,4- bipyridyl it was found (as expected from the known dissociation constants) that also 2,4- di HCl precipitates under the same conditions and as long as the quantity of absolute alcohol is small and limited the 2,4- is lost with the 4,4- . Hence such a method is not useful without certain necessary precautions.

After separation of the 4,4- di-HCl salt the remaining oil is salt decomposed and the oil obtained is again distilled and the oils distilling above 300°C are discarded. The oils from the distillate are extracted with water from ether gasoline and the 2,4- and 3,3- are dissolved in the water layer. The 2,2- remains in the ether gasoline layer. The 2,4- is separated from the 3,3- by extraction with benzene. Unfortunately, this method fails completely to give any pure compounds because of the finite solubilities of the isomers in these various solvents and also because of the change of solubility produced by the presence of other compounds. Since we were interested not only in the products but also in the reaction mechanism, it was necessary to review the whole separation scheme and to devise a method which yields the correct quantities.

Two methods are suggested for the determination and separation of the isomers. There is an important advantage in using two independent checks on the results. It is also planned to make determinations on the total vacuum distilled oils using methods to be developped for the thermal decomsposition study.

Method I for separation of the isomers of bipyridyl from the sodium
pyridine reaction products

REACTION PRODUCTS ⟶ Remove excess pyridine by ⟶ Non-extractable material:
distillation. Add 10 c.c.   sodium salts of acids.
water, ether ext.

Ether extract (dry)   (I)   Cryst. solids   (II)
1- Remove ether   (impure 4,4-)
2- Cryst. overnight
Decant wash with small
quantities of ether.

OIL III

Vac. distil
Collect fraction* ⟶ OIL IV
dist. 125-140 C

          OIL VI

Ext. with water from gazo-
line-ether mixture (at
about 1-4 C)

Cryst. solids V
(mostly 4,4- and 2,2-)
cryst. from water
separate 4,4- by HCl
method. 2,2- remains
in 95% alcohol.

VIII
Ether-Gazoline layer,
mainly 2,2- with 4,4-
and small quantities of
other compounds.

VII

Water ext., dry, dis-
solve in abs. alc.
pass dry HCl 2,4- HCl.
prec.

IX

Isomers as HCl salts
wash with large amount
of 95% alc.

X

4,4- di-HCl; decomp. salt;
recryst. from water.

XIII
Filtrate: contains neon-
nicotine.
Separate as nitrosoderiva-
tive; or by add NaOH, remove
alcohol and vac. dist.

XI

Filtrate contains all 2,4-
and some impurities. Remove
alc., add NaOH, ext. with
benzene.

XII

Remove benzene and cryst. from
pet. ether.

Almost pure 2,4-
(feathery crystals)

Purify further by recryst.,
picrate.... or HCl salt and
95% alc.

(‡)   The amount of water to be added depends on amount of resins etc...
      Water should be added until ether layer is clear.
(*)   Pressure is not known accurately, possibly 1-3 mm Hg.

Method II for the separation of the isomers of bipyridyl from the
sodium pyridine reaction products.

REACTION PRODUCTS ⟶ Remove excess pyridine by ⟶ Non-ext. material sodium
dist., add 10 c.c. water, sals of acids.
ether extract.

Ether ext. (dry)
1- Remove ether
2- Cryst. overnight ⟶ Cryst. solids V
Decant oil wash with (impure 4,4-)
small quantities of
ether.

OIL III
Vac. dist.
Collect fraction
dist. 125 - 140 C

OIL IV ⟶ V
Cryst. from pet Cryst. solids
ether for several 4,4- and 2,2- only.
days.

VI VII VIII
Crystals Pet. ether layer ⟶ Neonnicotine fraction
2,2-; 4,4-; 2,4- dissolve in benzene; and any 3,3- present
water ext.

VIA IX XII
Cryst. from Remove benzene ext. ⟶ Pet. ether contains
water. from water with pet. 2,2-; 4,4-
2,4- remains in ether. until 2,2-
water. 4,4- free.

VIB
Crystals XIII
2,2-; 4,4- Remove water, dry,
cryst. 2,4- from pet.
X ether, or purify
Ext. 2,4- with ppet. through HCl salt and
ether until 2,2-; 4,4- 95% alcohol.
free.

2,4- to be purified
further.

N.B. For convenience the various fractions containing 2,2- and 4,4- are combined
and the 4,4- separated from the 2,2- by the HCl 95% alc. method.
Furthermore, all the fractions containing the 2,4- are combined and purified
together recryst. or better by the HCl 95% alc. method.

These methods were tried and tested with various modifications in order to determine the optimum conditions hence the present results are of qualitative importance only and further work is necessary in order to get the exact yields. At present there is no doubt that the order of the products from Na method is 4,4- in greatest amount with 2,4- and 2,2- closely together and probably not more than 1/3 the yield of 4,4- . Inidcations are that the yield of 2,4- is somewhat larger than that of 2,2- . The yield of 3,3'- (if any) is extremely small. The yield of isomers is about 25% of the reacted pyridine, the remaining 75% is largely some pyridine substituted acids with smaller quantities of higher molecular weight compounds such as acridine and an ether soluble, water insoluble base. Work is being continued to determine the identity of all these compounds.
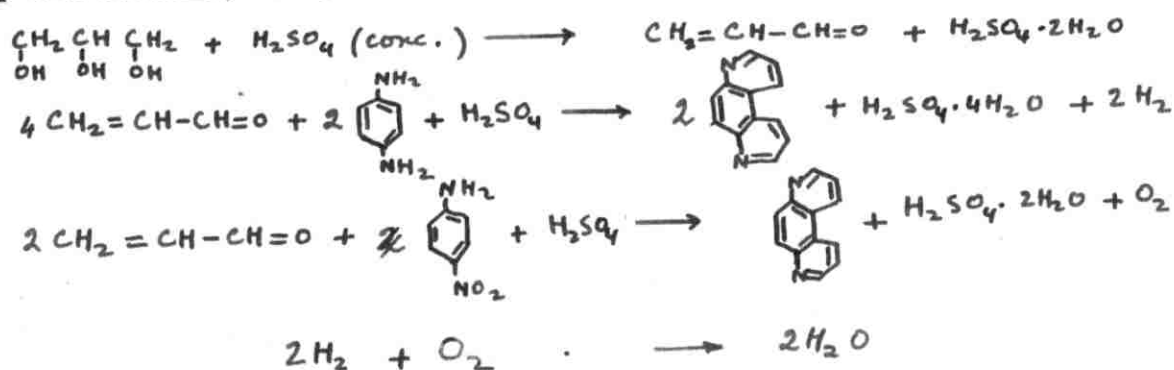
The presence of acridine was suspected when a fluoresence was noticed. The presence was established using colorimetric tests with metals such as yellow colour with zinc, green with cobalt, dark red with iron and the discharge of the fluoresence in the presence of the chromate ion. The tests were performed according to the directions given by Welcher (26). The quantity of acridine was very small, possibly because the tests were conducted on the materials remaining after either extraction from alkaline medium and the acridine may have thus been largely removed.

The preparation of 3,3- bipyridyl by the p-phenanthroline method:-

Because the properties of the 3-position discussed in detail in the introduction, it is very difficult to obtain any 3,3- by direct reactions of pyridine. As mentioned before only traces, if any, of 3,3- were found in the products from the sodium method and Krumholz (7) also mentions that only traces of 3,3- were obtained in his thermal decompostion studies with pyridine.

The only avaible method for the preparation of 3,3- is through the Skraup synthesis. An "improved" Russian method was tried first for the preparation of the p-phenathroline (27), using p-phenylenediamine, p-nitroaniline, conc. sulfuric acid and glycerine.

$$CH_2CH CH_2 \ (OH\ OH\ OH) + H_2SO_4 \ (conc.) \longrightarrow CH_2=CH-CH=O + H_2SO_4 \cdot 2H_2O$$

$$4 CH_2=CH-CH=O + 2 \ (NH_2 \bigcirc NH_2) + H_2SO_4 \longrightarrow 2 \ \bigcirc + H_2SO_4 \cdot 4H_2O + 2H_2$$

$$2 CH_2=CH-CH=O + 2 \ (NH_2 \bigcirc NO_2) + H_2SO_4 \longrightarrow \bigcirc + H_2SO_4 \cdot 2H_2O + O_2$$

$$2 H_2 + O_2 \ . \longrightarrow 2H_2O$$

According to the authors, the reaction is exothermic at temperatures above 146°C. It was very difficult to control the reaction and the temperature at which the reaction is exothermic was found to be 129 - 130°C because in an oil bath below 129°C the reaction mixture temperature did not go above that of the bath, while at temperature of 130°C or above, the temperature went up very fast specially in the inside of the flask. It is possible that the "moisture" conc. was higher than that used by the Russian workers.

The second method by Smith (12) was found to give satisfactory results and the reaction was easy to follow and to control.

Since the method was followed without significant alternation

it will not be given in detail. The reactants in this case are:
p-phenylenediame, arsenic acid, conc. sulfuric acid and glycerine.
A source of difficulty at first was the identification of the
p-phenathroline. A compound was obtained which had a melting point at
42°C and apparently sublimed at about 100°C; when these crystals are
heated further they were found to melt at 174°C, the melting point
of p-phenathroline. Hence the compound forms a stable hydrate which
steam distils at 100°C. It was also found that it sublimes fairly
easily. p-phenathroline as obtained from crystallization is in small
shining needle-like crystals, when it sublimes it forms crystals with
only a very slight yellowish colour.

The p-phenathroline was oxidised by the Smith method using alkaline
permangante with double the amount of KOH.
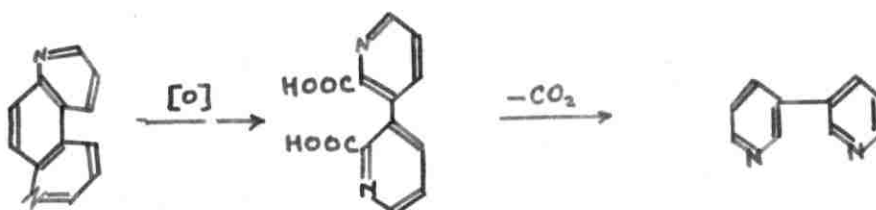
The dicarboxylic acid is decarboxylated by gentle heating in
glycerine and the 3,3- is extracted with ether.

Great care should be taken throughout this procedure so as to
keep to a minimum all possible impurities that might interfere later.
The purification as will be seen later is extremely difficult, because
the 3,3- does not form crystals, probably because of its pronounced
hygroscopic nature, it is difficult to separate the last traces of water.
Small quantities were purified by recrystallisation of the picrate and
by using a micro-vacuum distillation technique.

The Zinc pyridine and acetic anhydride reaction:

This method was investigated extensively by Dimroth, Heene and coworkers (4). The method was used to prepare N,Ndiacetyl, tetrahydro 4,4- bipyridyl an intermediate for the preparation of 4,4- and also to obtain other substituted compounds.

The method was used only once because the sodium pyridine reaction offered better possibilities for the preparation of the other isomers. The papers in the literature are complete and only a short discussion of the mechanism will be given so far as it is related to the sodium pyridine reaction.

In the introduction these two reactions were assumed to be identical but on further analysis of the experimental results it appeared that there are some important differences. The Na is far more electropositive than the CH_3CO- group and when it is attached to the N in the ring the free radical produced could be assumed to be more reactive than that of the $CH_3CO- C_5H_5N$ free radical because of the higher electron densities in the para and ortho positions. From the fact that N,N-diacetyltetrahydro bipyridyl was isolated it is evident that the reaction does not proceed by a mechanism of a free radical attack on the pyridine ring but by a direct combination of two free radicals. This is a significant difference between the two reaction mechanisms.

From the products isolated by workers in the field it is evident that ring opening reactions take place as in the sodium pyridine reaction.

Thermal decomposition studies:

There are several papers in the literature on the isolation of 2,2-; 2,3-; and 2,4- as the main products in the thermal decomposition of pyridine. The latest of these papers is by Krumholz (7). Under the conditions used by these workers a large amount of the pyridine was decomposed, about 30%. HCN and $(CN)_2$ were detected as well as H_2 (7a). During studies made by Dr. Linnell using low pressures (a few mm.) and the temperature range 750 - 850°C, H_2 seems to be the main gaseous decomposition product.

In this work the conditions were chosen so that the pyridine ring should not be disrupted. Of course this is an ideal case and the best that could be done was to use low pressures and the temperature about 825°C. This is based on the reasonable assumption that ring rupture is either a secondary reaction or a more difficult reaction, i.e. requires a higher heat of activation, than the splitting off of a hydrogen atom.

So far only a few studies were made and no conclusions can be made except those presented in the introduction.

One of the major problems is the development of a reliable technique for the micro-analysis of the thermal decomposition products. I believe that with the present available information on the polarographic reduction and absorption spectra of the isomers a method will be soon available.

Apparatus for thermal decomposition:

The following flow sheet (fig. 3) shows clearly the system used for the thermal studies.
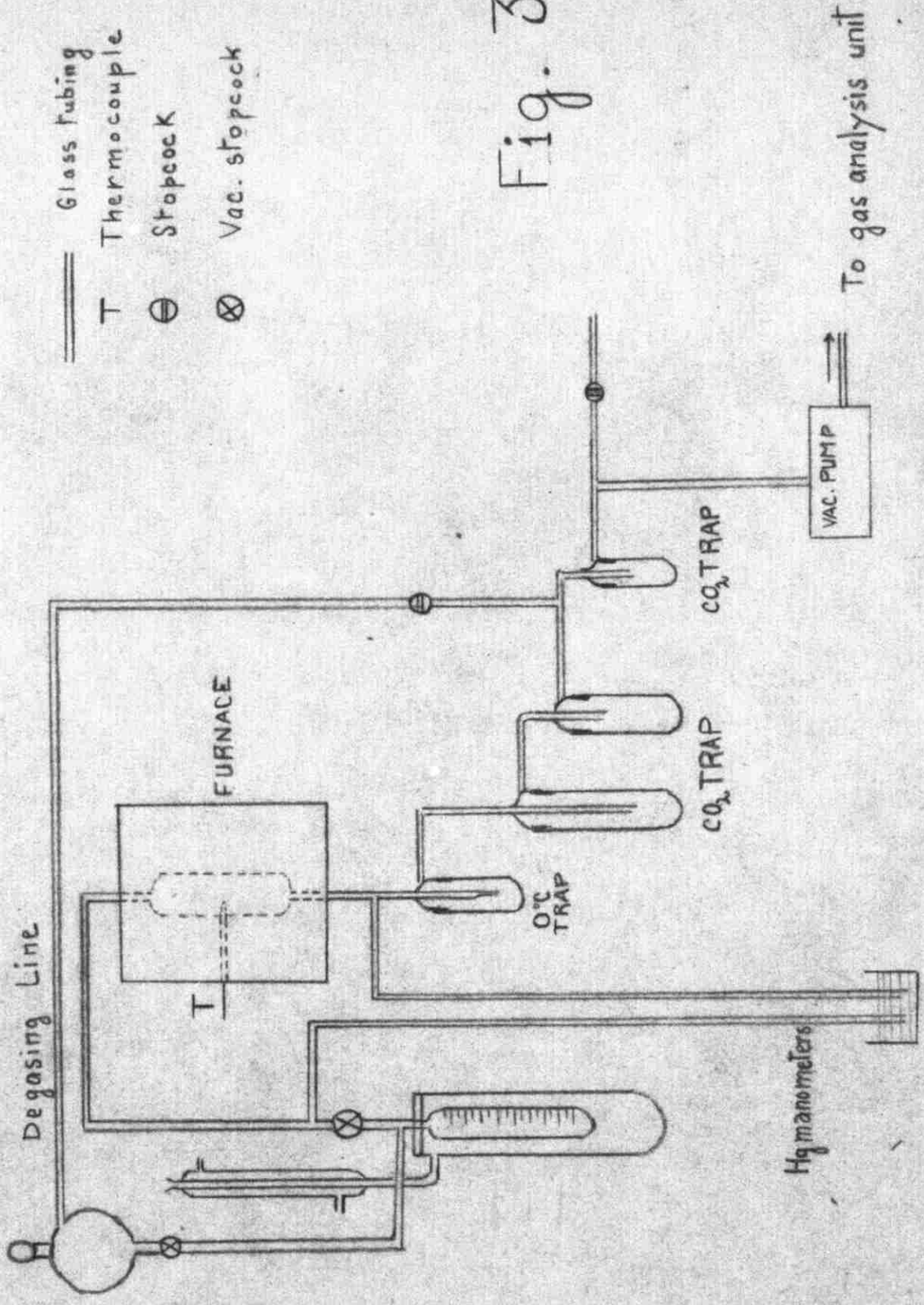
The furnace was designed (fig. 4) in order to supply enough heat for high flow rates and it was heavily insulated by packing with asbestos powder. The temperature was read using a calibrated platinum-platinum rhodium thermocouple and a high sensitivity galvanometer and potentiometer.

The reaction vessel was a quartz tube with a well for the thermocouple to fit in. The whole apparatus was made of pyrex and a pyrex-quartz seal was used to connect the reaction tube to the rest of the system.

As shown in fig. 3 the first trap below the furnace is usually cooled with ice and salt mixture to condense most of the isomers produced as well as other high boiling products. The remaining traps are to condense pyridine using a dry-ice alcohol mixture as the cooling agent. The whole system and the pyridine are degased before every run to eliminate interference by oxygen and other gases.

The gas analysis apparatus is of the standard type. It has a mercury buretter to estimate the volume of the gas and several connected vessels that could be filled with KOH solution to remove HCN gas and $(CN)_2$; bromine water to remove acetylene and the remaining gas (which should be in this case H_2 plus N_2). Hence it is possible by this method to estimate the composition of the gas.

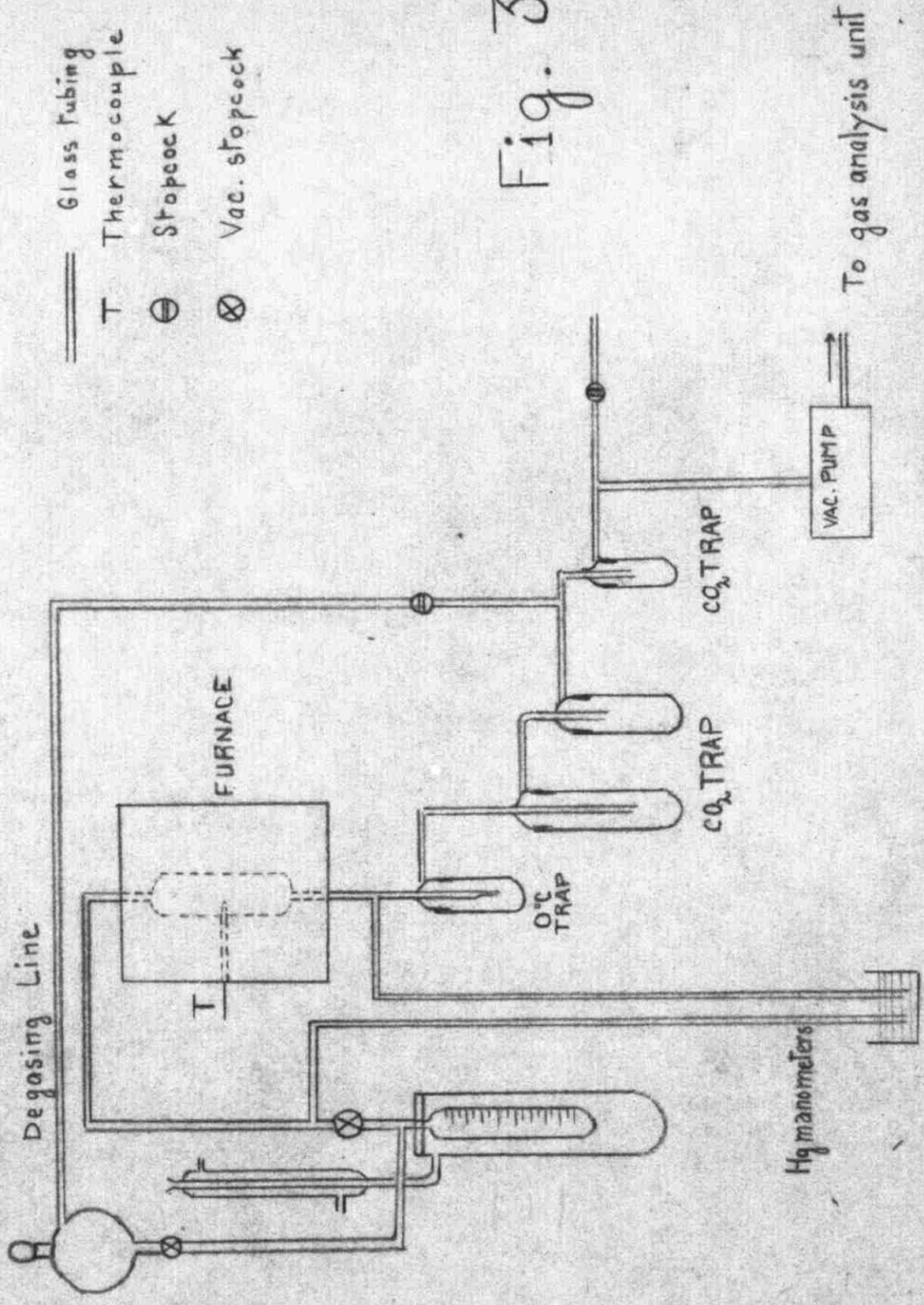I would like to express my thanks to Dr. Linnell for helping me to build the thermal decomposition system.

Glass tubing
T Thermocouple
⊕ Stopcock
⊗ Vac. stopcock

Degasing Line

FURNACE
T

0°C TRAP

CO₂ TRAP

CO₂ TRAP

VAC. PUMP

To gas analysis unit

Hg manometers

Fig. 3

THERMAL DECOMPOSITION SYSTEM

Legend:
- ═══ Glass Tubing
- T Thermocouple
- ⊕ Stopcock
- ⊗ Vac. stopcock

Fig. 3

THERMAL DECOMPOSITION SYSTEM
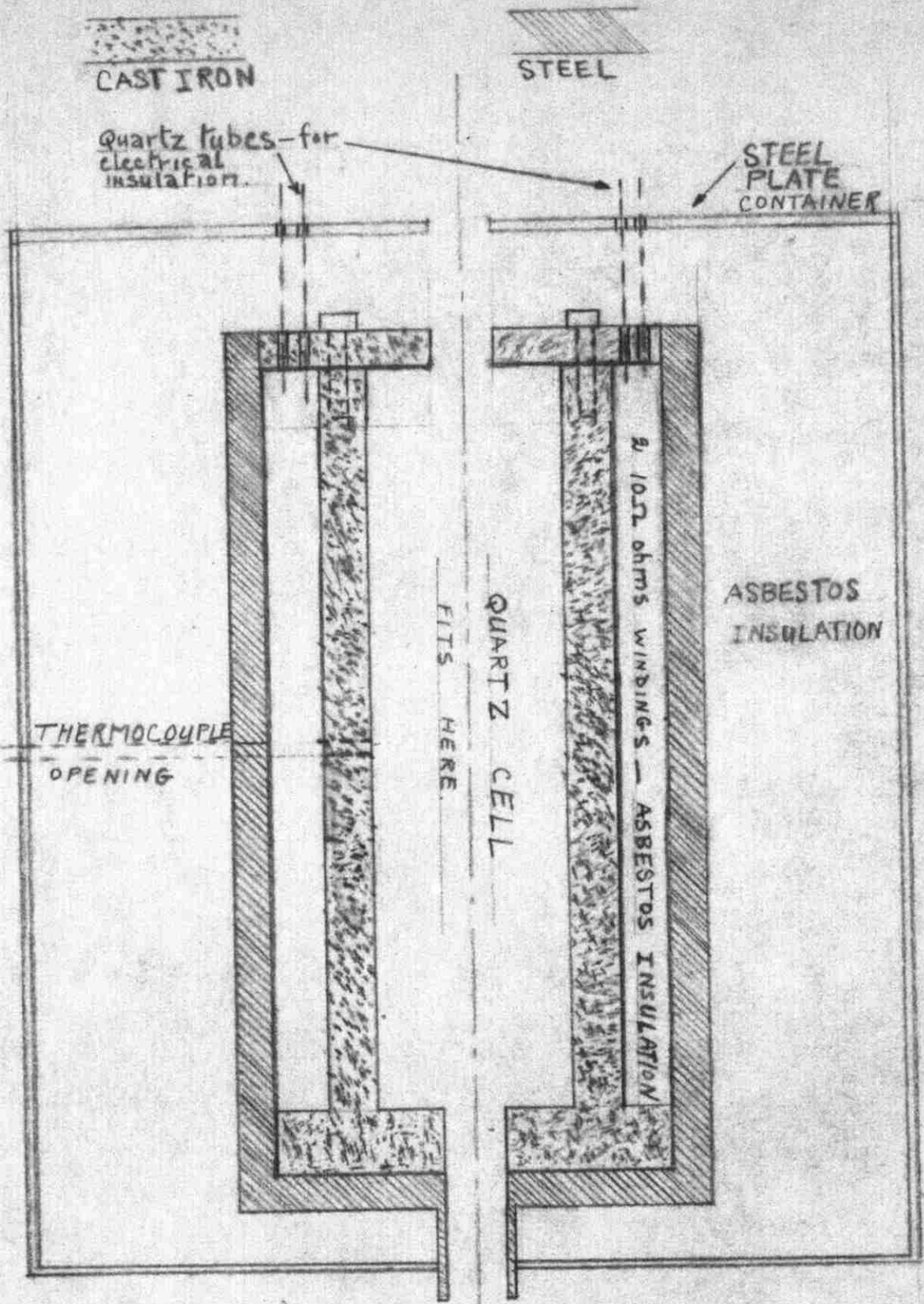
Labels within figure: Degasing Line, FURNACE, T, 0°C TRAP, CO₂ TRAP, CO₂ TRAP, Hg manometers, VAC. PUMP, To gas analysis unit

CAST IRON

STEEL

Quartz tubes—for electrical insulation.

STEEL PLATE CONTAINER

QUARTZ CELL

FITS HERE.

THERMOCOUPLE OPENING

2. 10 Ω ohms WINDINGS — ASBESTOS INSULATION

ASBESTOS INSULATION

FURNACE

FIG. 4.

CAST IRON

STEEL

Quartz tubes for electrical insulation.

STEEL PLATE CONTAINER

QUARTZ CELL

FITS HERE

2.10Ω ohms WINDINGS — ASBESTOS INSULATION

ASBESTOS INSULATION

THERMOCOUPLE OPENING

FURNACE

FIG. 4.

Purification:

The purification of the isomers varies a great deal depending
on the ease of crystallisation and the solubility in water. As will
be discussed later the solubility varies a great deal with tempera-
ture and with the compound.

2,2- and 4,4- can be easily purified by crystallisation from water
ethyl alcohol, petroleum ether or mixtures of these. For the products
obtained from the sodium reaction it is convenient to evaporate first
the isomer with conc. HCl and precipitate from 95% all the 4,4- as
the di-HCl salt. The 2,2- is soluble and can be washed with alcohol.
The remaining salt is now freed with KOH and the oil extracted and
crystallised from water to remove any traces of 2,4- .

A convenient and easy way to obtain pure 2,4- bipyridyl from crude
fractions has been developped as follows:- The 2,4- (crude) is evapora-
ted with conc. HCl and 95% alcohol added, the 2,4- di-HCl salt precipi-
tates and 2,2- is washed off. This precipitate is washed repeatedly
with 95% until the ferrous test for 2,2- and the zinc, acetic acid
test for 4,4- are negative. These two tests are very sensitive. The
alcohol is removed by decanting and vacuum. The salt is hygroscopic.

In all cases the criterion of purity was based on the absorption
spectra. The absorption spectra of the 2,4- isomer obtained in the
above manner was found to be different from that reported by Krumholz
by about 15% higher. The shape of the curve as well as the values
obtained were in better agreement with the "additivity principle"
applied by Krumholz. This will be further discussed in the absorption

section. Krumholz purified his 2,4- isomer by repeated recrystallisation from petroleum ether or n-hexane. Crystallisation of 2,4- was found to be difficult here in the lab. because of the high humidity, traces of moisture are enough to convert the crystals into an oil.

Although Smith mentions that he was able to crystallise 3,3- it seems he was unable to reproduce himself and at present all papers express the inability to crystallise the compound. Most probably this is due to traces of moisture which are very hard to remove. The compound was purified by means of the picrate and also by vacuum distilling small quantities in micro distillation tubes. The oil obtained from the vacuum distillation did not form any crystals.

The quantities of 2,3- obtained from the thermal decomposition are of the order of 30 to 50 mg and extensive purification could not be made. The oil was dissoved in benzene and was extracted repeatedly with a ferrous sulphate solution until 2,2- free. The remaining oil after complete removal of the benzene and water gave an absorption which agreed within 5 to 10% with Krumholz. The polarographic work reported in this work has been done on this "impure" compound. As soon as larger quantities will be available exhaustive purification will be made and the results checked.

So far, no 3,4- was obtained, the only available method is thermal decomposition and the yield is extremely small, hence some other method should be developped.

PHYSICAL PROPERTIES

Physical Constants:

Compound	M.P.C.	B.P.C	Picrate M.P.C.	Ref.
2,2-	70	272.5	155	(2b)
2,3-	oil	287.9	149.5	"
2,4-	62	297	215	"
3,3-	68	291.2	232	"
3,4-			199-201	(7)
4,4-	114	305	262	"
	73 (hydrate)			

NOTE: The picrates usually decompose before the melting point is reached. The only exception is 2,3- picrate.

Solubility of the Isomers

The solubility was determined by stirring a solution and excess of the compound under study between 7 and 20 hours in a water bath. A few ml of the saturated solution were sucked out and I ml was diluted to 1000 ml and the absorption spectra determined.

The case of 4,4- was slightly more complicated because the 4,4- crystals did not settle down but were carried over by the solution when it was sucked out. The technique used was to fit a small filter paper to the pipette and such in filtered solution. Furthermore the 4,4- crystallized out immediately from solution and the pipette had to be rinsed. 2,2- has a tendency to form supersaturated solutions and did not crystallise out quickly enough to give trouble. A few checks were carefully made to determine whether the errors introduced due to this method were appreciable. The results show that the error is probably less than 2%.

The results for both 2,2- and 4,4- are given in fig. 5. These results show that the solubility of 2,2- is greater at low temp. than that of 4,4- while at higher temp. 4,4- is very soluble and 2,2- gives two immiscible layers above its melting point.

No solubility study was required for 3,3- because it is extremely soluble (it is very hygroscopic) in water.

2,4- has a solubility behaviour similar to that of other nitrogen bases, such as the picolines, their salts and reduced
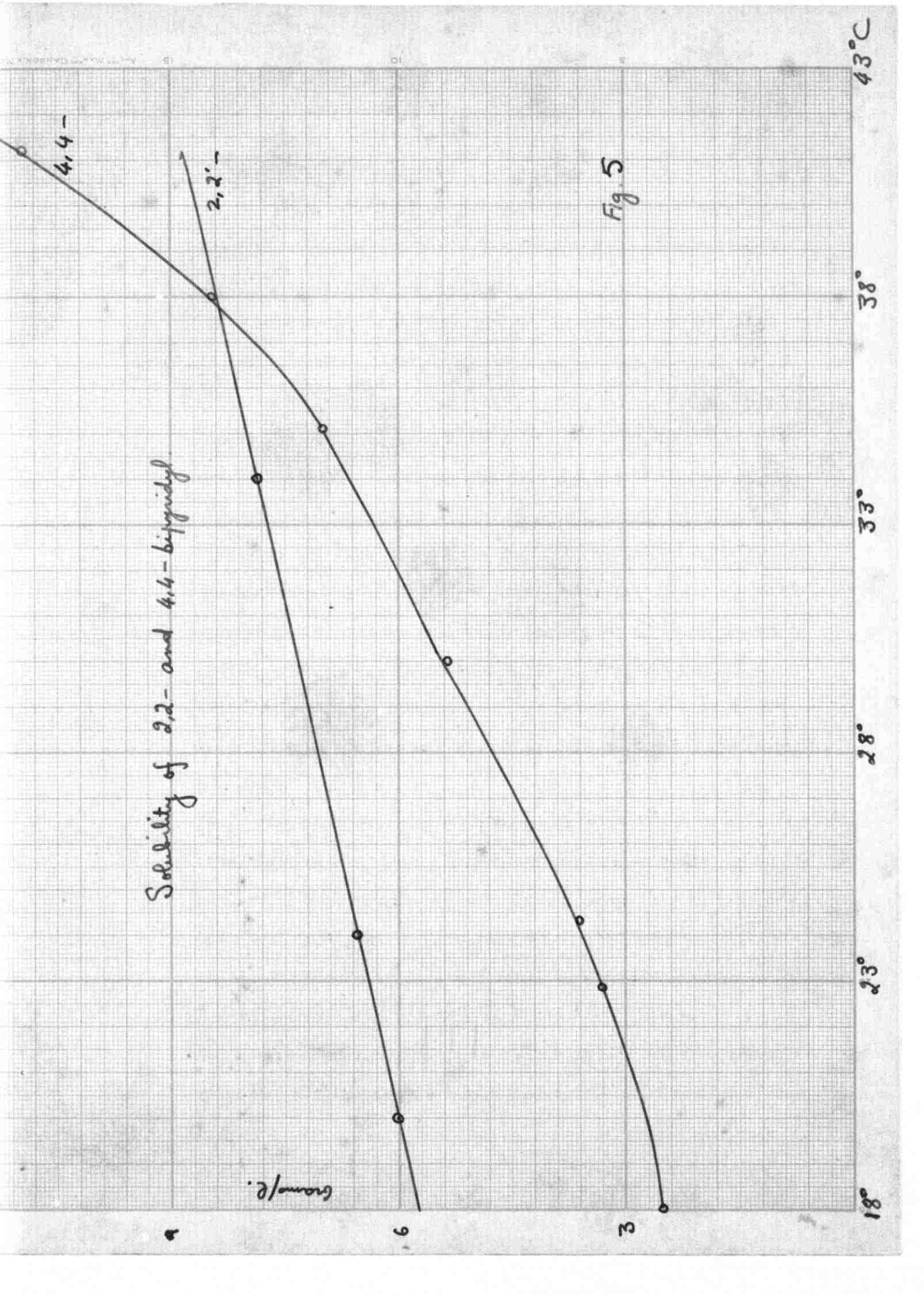
Solubility of 2,2'- and 4,4'-bipyridyl
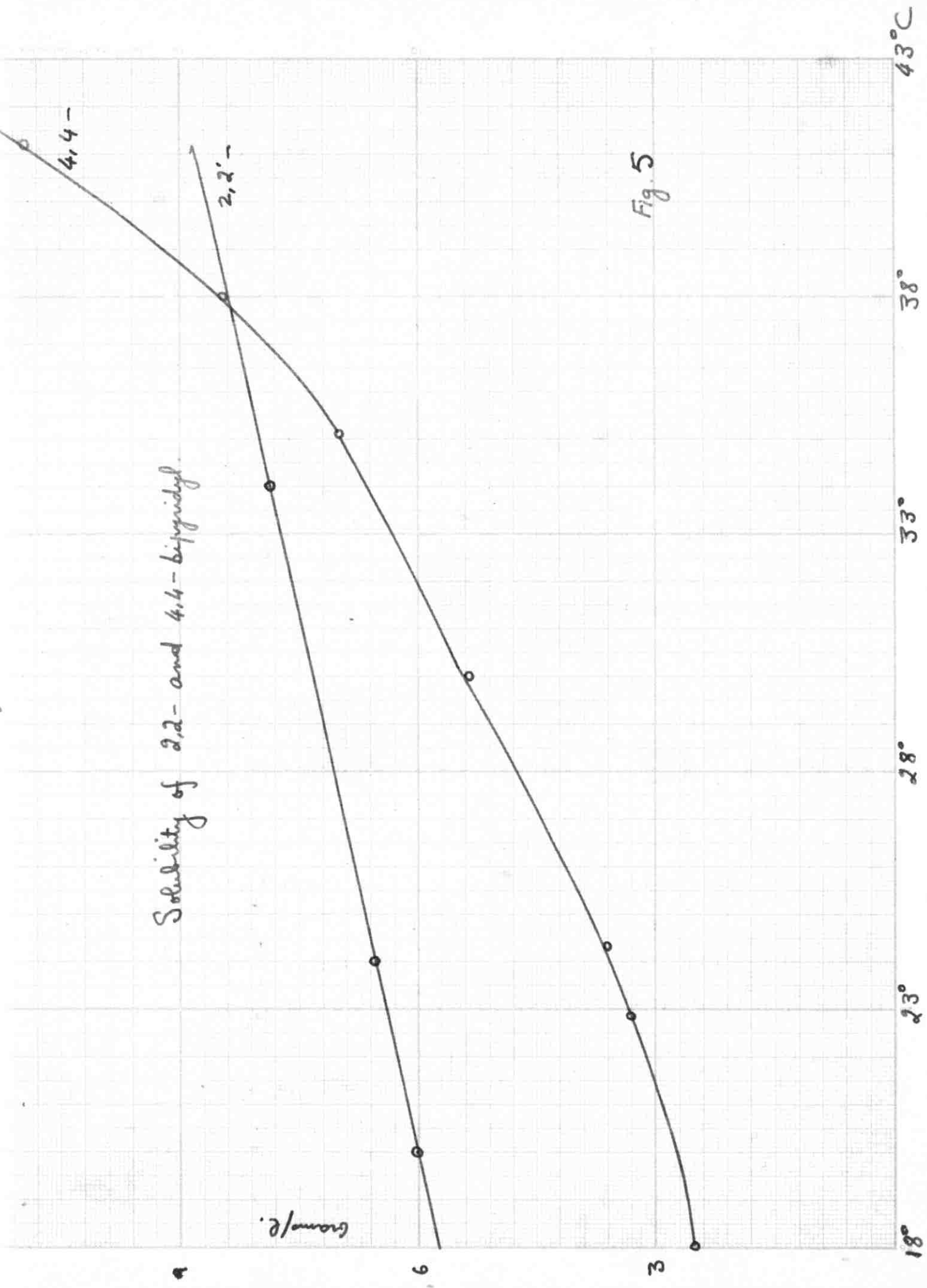
Fig 5

Solubility of 2,2'- and 4,4'-bipyridyl

Fig. 5

37.

products which were investigated by Flaschner (26) in 1909. The solubility of this isomer decreases with temp. and the compound is completely miscible with water in all proportions at low temp. (below 12.8° C) according to Smith (2b).

2,3- has a limited solubility in water, so far it was not determined but work will eventually be done to complete the study.

Discussion:

At present there are various attempts to correlate solubility to various properties of the molecule and the crystal structure. For example, Krebs and Speakman (27a) made studies on the determination of dissociation constants from solubility measurements in various buffers; while Bryson (28) states that the solubility is an inverse function of the lattice energy in the crystalline state. Bryson was interested in the solubility of substituted naphthalene compounds where highly polar structures are present due to the SO_3H and the NH_2 groups. These polar structures are due to the SO_3- and NH_3+.

Applying this reasoning to the three symmetrical isomers we can see that this is correct because the 3,3- is an intermediate structure between the 4,4- which forms a high melting point crystal (113° C) and also the 2,2- (70° C) and the 3,3- which forms a crystal with great difficulty, if at all. Hence the lattice energy should be in the order 4,4- (greatest); 2,2- and finally 3,3-. Hence the solubility should be in the order 3,3- (greatest); 2,2- and least 4,4-. This is the observed order at temp. below 35° C. Furthermore, this argument has a thermodynamic validity.

Dissociation Constants:

The correlation of dissociation constants to various properties of the molecule has been pursued intensively both theoretically and experimentally on a large number of aromatic and non-aromatic compounds. Comparison of the pK values has been restricted to the change in pK with various substituents considering a non-substituted compound as the reference compound.

Such a study has important limitations in that the introduction of a group produces some effects which it might be difficult to take into consideration quantitatively when the pK values are compared. Such effects are due to electrostatic forces in ortho substituted compounds, steric factors or chelation in some other compounds. Nevertheless these studies have made a permanent contribution to a better understanding of molecular structure as well as directive influence.

The following study in the bipyridyl series provides us with information relating to:

1- directive influence in one ring

2- variation of internuclear interaction with position of substituent.

In the following section on absorption spectra these properties will be correlated still further.

Krumholz (15) determined the dissociation of the six isomers. (Table 2 is from his paper).

TABLE 2

	$K_{1A}10^5$	$K_{2A}10^2$
Pyridine	.435	-
2,2-	3.6	-
2,3-	3.8	3
2,4-	1.7	6.5
3,3-	2.5	0.1
3,4-	1.4	0.1
4,4	1.5	.068

Krumholz assigns a probable error of 10% for K_{1A} and a larger error for K_{2A}. This must be remembered in the discussion later.

Comparison of these dissociation constants with the value for pyridine will show that the constant for pyridine is several times less, that is, its basic dissociation constant is several times greater. To make the idea clearer, the dissociation constants for the picolines are given in Table 3.

TABLE 3

		K_B x10^{-9}
In the picoline series all	2-picoline	9.1
the dissociation constants	3-picoline	8.0
are higher than that of pyridine.	4-picoline	11.0

This suggests that the pyridyl group as a whole is an electron sink; in whatever position it is substituted it tends to attract electrons to itself. In the picoline series the dissociation constant are higher because the methyl group is an electron donor, hence the electron density throughout the ring is increased rather

than decreased and so are the values of the basic dissociation constant.

In order to study the extent of interaction between the two rings I defined the quantity $T = K_1/K_2$ and called it the transmitivity across the two rings. It will be seen later in this section and also in the study of absorption spectra that T is an important function of internuclear interaction. Tabe 4 provides the values as calculated from the dissociation constants.

TABLE 4

	T	logT	10/logT
2,2-	(∞)		(0)
2,3-	770	2.9	3.44
2,4-	3720	3.58	2.78
3,3-	40	1.6	6.25
3,4-	72	1.85	5.4
4,4-	46	1.66	6.07

Two distinct types of interaction are brought out clearly by the variation of the value of T.

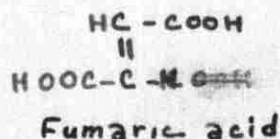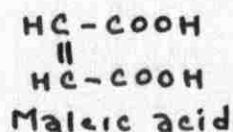1- σ- bond polarization

2- π- bond between two rings.

The values of T for 3- isomers are all of the order of magnitude expected when it is considered that the 3-ring cannot take part if any π-interaction. The value of T for 2,3- appears at first sight to be too high but it should be remembered that in this case we have maximum bond polarization, since the lowest and the highest (apart from the ring N) electron density positions are

connected together.

The value of T for 4,4- is surprisingly low. It indicates that π-interaction is not possible between the two rings.

When the values of log T or 10/logT are plotted against Fig 6 pK_{2B} a straight line is obtained on which all the experimental points fall except those values of pK_{2B} referring to a 3- ring; namely those for 3,4- and 3,3-. Such a deviation is expected on the ground that the meta position does not take part in the ionic resonance states of the ring. A Further confirmation that the transmission is through a σ-bond polarization is obtained from the following considerations.

To get an idea of the magnitude of the value of T for 3,3- when resonance does not make any contributions we go back to straight chain conjugated dicarboxylic acids and determine how much of the effect is transmitted across a chain. Unfortunately such data are not readily available and an alternative method for comparison had to be used. Data for the dissociation constants of saturated dicarboxylic acids and for maleic and fumaric acids were readily available in Feiser (29). Table 5 gives this data along with some calculated values for T and logT. At first sight it is surprising that maleic and fumaric acid should have such widely different dissociation constants. The following structures show why this is so.
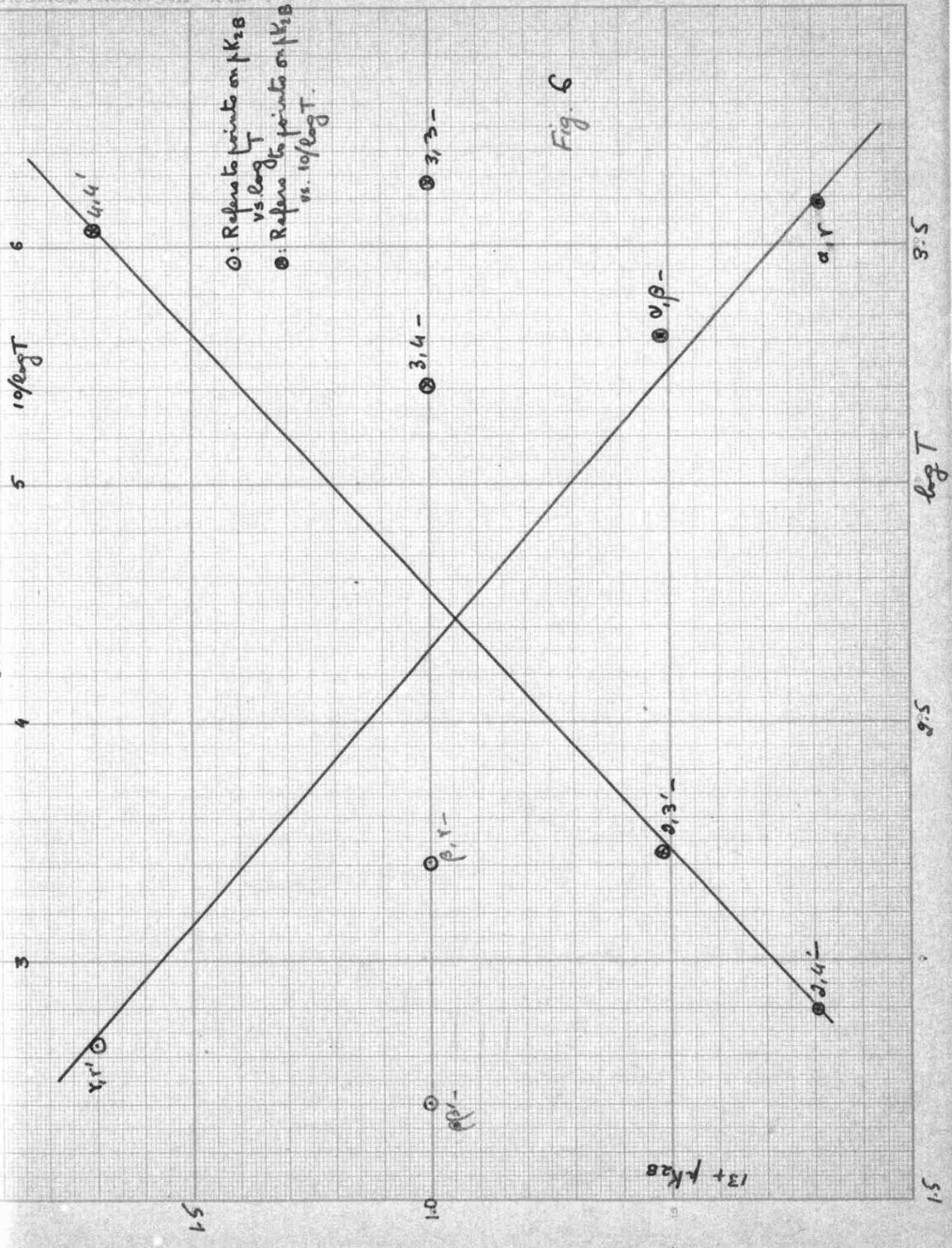
HC - COOH
‖
HC - COOH
Maleic acid

HC - COOH
‖
HOOC - C - H
Fumaric acid

Fig. 6

O : Refers to points on $\vert k_{2B}$ vs. log T

● : Refers to points on $\vert k_{2B}$ vs. $10/\log T$.

Fig. 6

○: Refers to points on $\log K_{2B}$ vs. $\log T$

⊗: Refers to points on $\log K_{2B}$ vs. $10/\log T$

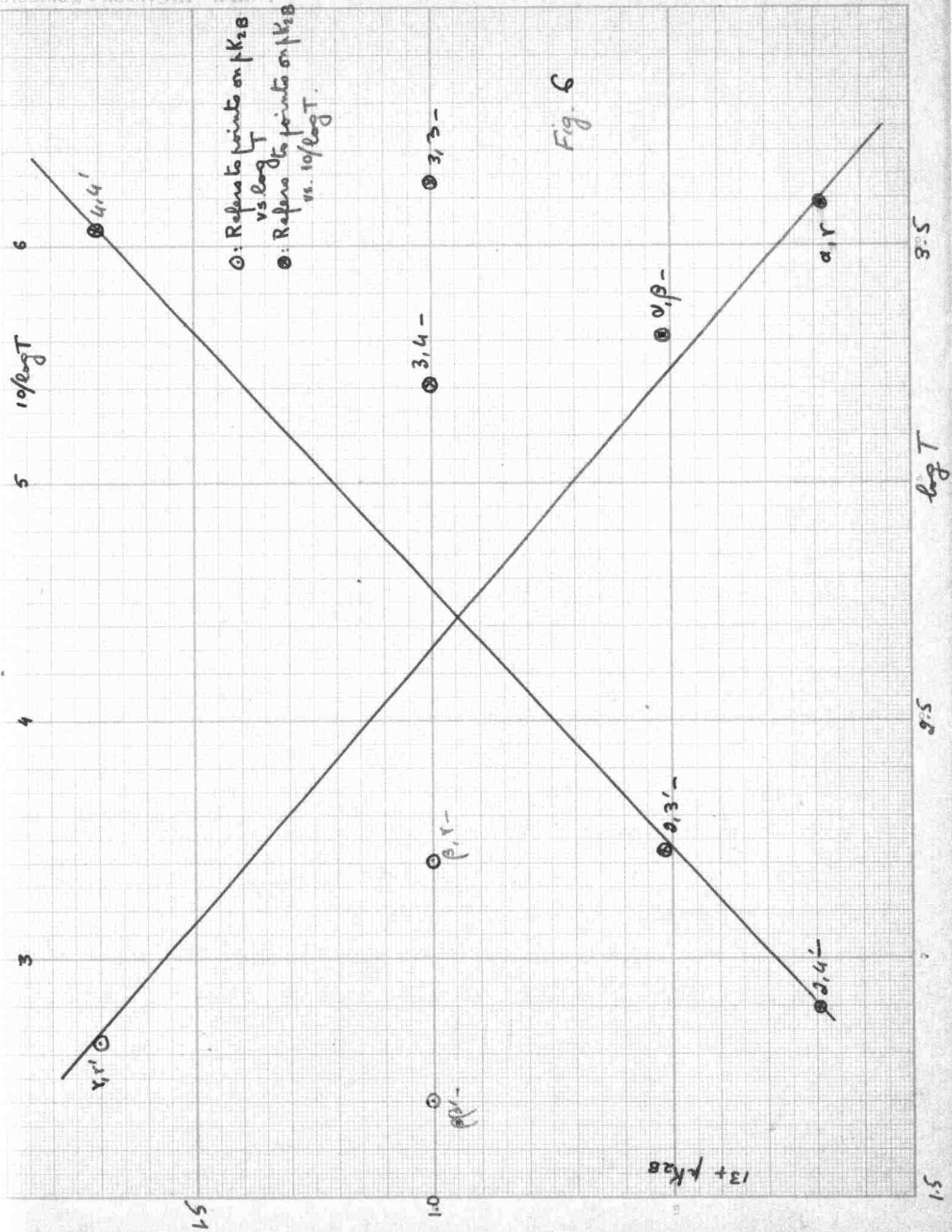$10/\log T$ (x-axis, values 3, 4, 5, 6)

$\log T$

$13 + \log K_{2B}$

$\log K_{2B}$

The electrostatic effect in the case of maleic acid accounts completely for this large difference. Since we will be dealing with longer chains where this effect is of little importance, we can consider directly fumaric acid. The value of T for fumaric acid is almost the same as for the corresponding saturated acid, succinic acid. For succinic T = 29.5 while for fumaric T = 33. Hence, as a first approximation, it can be safely assumed that transmission accross a conjugated system is the same as across a saturated system.

TABLE 5

Compound	No. of C atoms between the two COOH groups	$K_{1a} \times 10^5$	pK_{1a}	$K_{2a} \times 10^6$	pK_2	T	log T
Oxalic	0	3500	1.456	40	4.498		3.042
Malonic	1	160	2.796	1.4	5.854		3.058
Succinic	2	6.8	4.168	2.3	5.638	29.5	1.470
Glutaric	3	4.7	4.328	2.7	5.569	17.4	1.241
Adipic	4	3.7	4.432	3	5.477	12.3	1.045
Pimelic	5	3.4	4.469	3	5.477	11.3	1.055
Suberic	6	3	4.523	3	5.477	10	1.000
Azelaic	7	2.9	4.537	3	5.477	9.65	0.940
Sebacic	8	2.8	4.553	3	5.477	9.33	0.924
Fumaric	2	100		30		33	
Maleic	2	1200		0.3		40000	

The value of T as seen in table 5 decreases with increasing number of carbon atoms, for 6 carbon atoms and more the value is almost 10. This reasoning would indicate that if the effect is transmitted by a purely conjugated system the value of T for 3,3- should be the total sum of all transmissions across all the possible paths between the two nitrogen atoms. Clearly, there are four different ways we could follow. There are two paths with the same number of carbon atoms in between, this follows from symmetry and we cannot neglect any because the two are equally important. These four paths include 5,7,7,9 carbon atoms. T is almost 10 for this number of carbon atoms, hence the value of T should be 40. This is exactly the experimental value obtained for 3,3-.

This study eventually will be developped to correlate the values of T with increase in the resonance energy for the two rings above that for pyridine. The "excess resonance energy" should be a function of internuclear interaction and such a study will correlate further the properties of the isomers.

In order to obtain further confirmation to the concept of transmittivity a large number of polybasic aromatic acids were compared and the results always indicate that the meta positions behave in a special manner.

T A B L E 6

Extinction Coefficients

mu	2,2- bipyridyl neutral	2,2- bipyridyl acidic	3,3- bipyridyl neutral	3,3- bipyridyl acidic
220	.627	.604		
225	.844	.565		
227	.932	.576		
228			.900	.732
230	1.032	.610	1.015	.710
1	1.043	.622	1.054	.716
3	1.032	.670	1.120	.778
5	.996	.682	1.060	.820
7	.951			
8		.687	1.139	.850
9	.852			
240		.680	1.120	.825
1			1.018×	.813
3	.692			.811
4		.658		
5	.577		1.04	.761
7	.490	.588		
8		.565		.715
9	.464	.544		
250		.522		.715
1		.485		
3	.511	.460	.922	.730
5		.432		.795
7	.627	.392	.782	.980
260	.728		.797	1.07
3	.815	.413	.855	1.170
5	.950	.453	.896	1.193
8				
270	1.049	.496	.878	1.178
3	1.210	.600	.830	1.10
5	1.282	.683		1.04
7	1.350	1775	.715	
8			.672	.790
280	1.382	.918	.570	.742
2	1.357	1.130		
3		1.062	.420	.460
4	1.105	1.105		
6	1.202	1.202	.295	.321
8	1.049	1.270		
290	.898	1.340	.178	.200
2	.757	1.390		
5	.543	1.420		
7	.388	1.430		
300	.215	1.420	.037	
3		1.328		
6		1.127		
310		1.02		
3		.920		
6		.672		.065
7		.596		
9		.454		

Extinction Coefficients

mu	4,4- bipyridyl		2,4- bipyridyl	
	Neutral	Acid	Basic	di-HCl
220	0.686	.407	0.576	0.496
5	.950		.758	.458
6		.605		
8			.890	.475
230	1.244	.816	.958	.496
2	1.348	.930	1.062	.515
4	1.422	1.058	1.091	.545
5		1.122		
6	1.484	1.180	1.138	.572
7	1.520			
8	1.502	1.290	1.138	.605
9	1.522	1.350		
240	1.522	1.398	1.123	.640
1		1.435		
2	1.480	1.481		
3		1.495		
4	1.437		1.042	.693
5	1.408	1.565		
6	1.373			
8	1.282	1.590	.892	.737
250	1.195	1.580		
1			.792	.760
3	1.075	1.520	.751	.780
5	.998	1.482	.740	.800
8		1.386	.757	.848
260	0.850	1.341	.798	.888
3		1.27	.871	.927
4	.744	1.223		.957
5			.970	
6				1.003
7		1.184		
270	.642	1.122	1.040	1.062
5	.519		1.080	1.163
280	.350	.755	.923	1.162
5	.188	.509	.70	1.080
290	.086	.288	.365	0.945
5			.164	0.750
300			.040	0.521

Studies in Absorption of Spectra:

The absorption of spectra in the ultraviolet of the isomers has been reported by Krumholz (15). In this work the results given by Krumholz were checked for four of the purified isomers; the absorption spectra of 2,4- was found to be 15% greater than that reported. It is difficult to compare my results with those of Krumholz because these are given in graphical form. The absorption spectra of 2,3- was determined on an impure sample (about 95% pure) because the quantities available so far from thermal decomposition are of the order of 50 mg. only. The 3,4- isomer has not been prepared and there does not seem to be any adequate method for its preparation. Krumholz obtained few mg. from the thermal decomposition of 1500 g. of pyridine.

Tables 6,7 give the extinction coefficients of 2,2-; 3,3-; 4,4-; 2,4- both in neutral and acidic medium. These results are plotted in figures 8,9,10 and 11. Fig. 12,13 give the absorption spectra as reported by Krumholz.

The absorption spectra of 2,2- and 4,4- were studied at various pH in order to calculate the dissociation constants spectrophotometrically; the results are not reported here.

The spectra of 2,2- and 4,4- shows that there is some ageing effect, most probably due to hydration. The 2,2- and 4,4- dissolve very slowly.
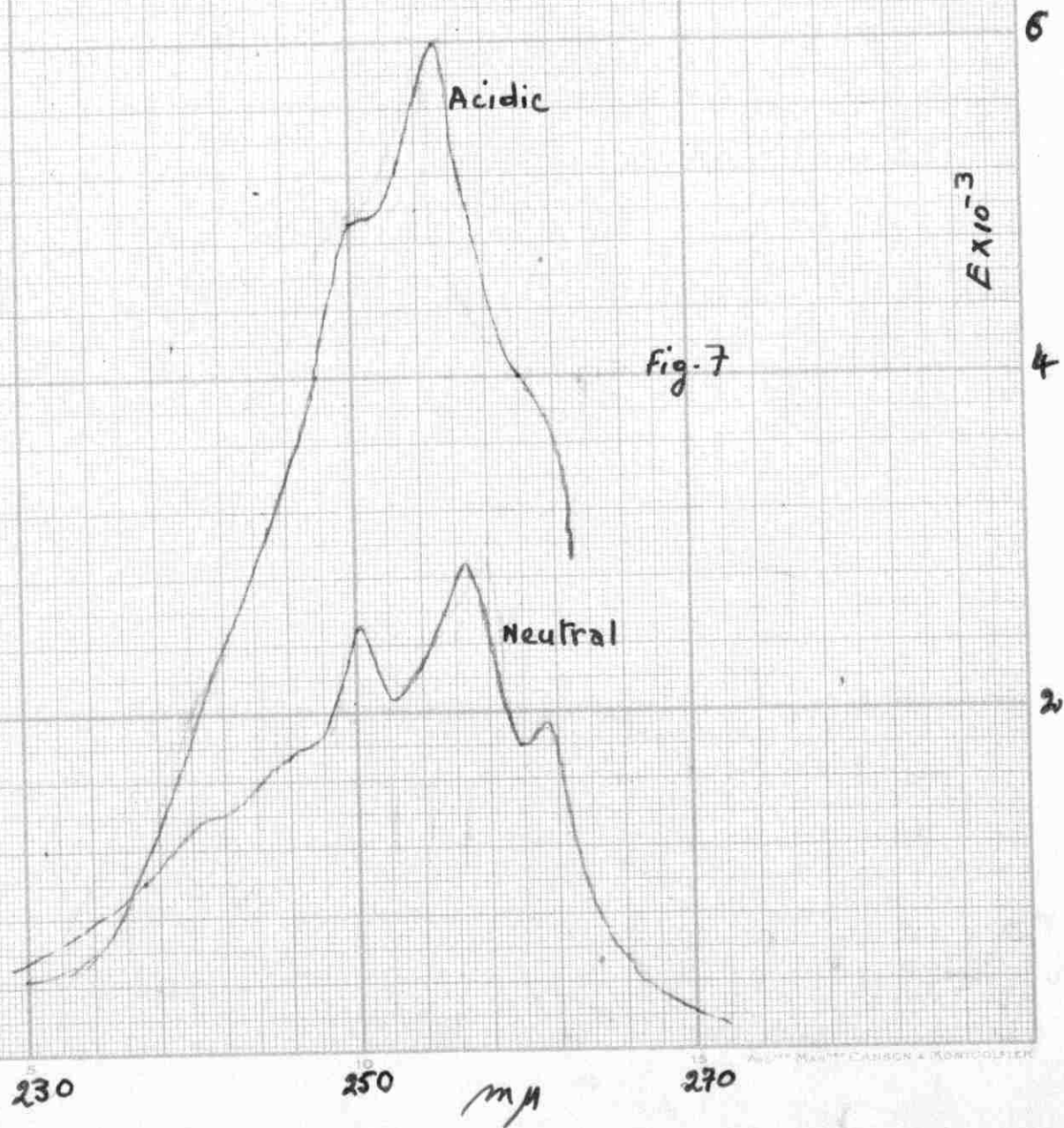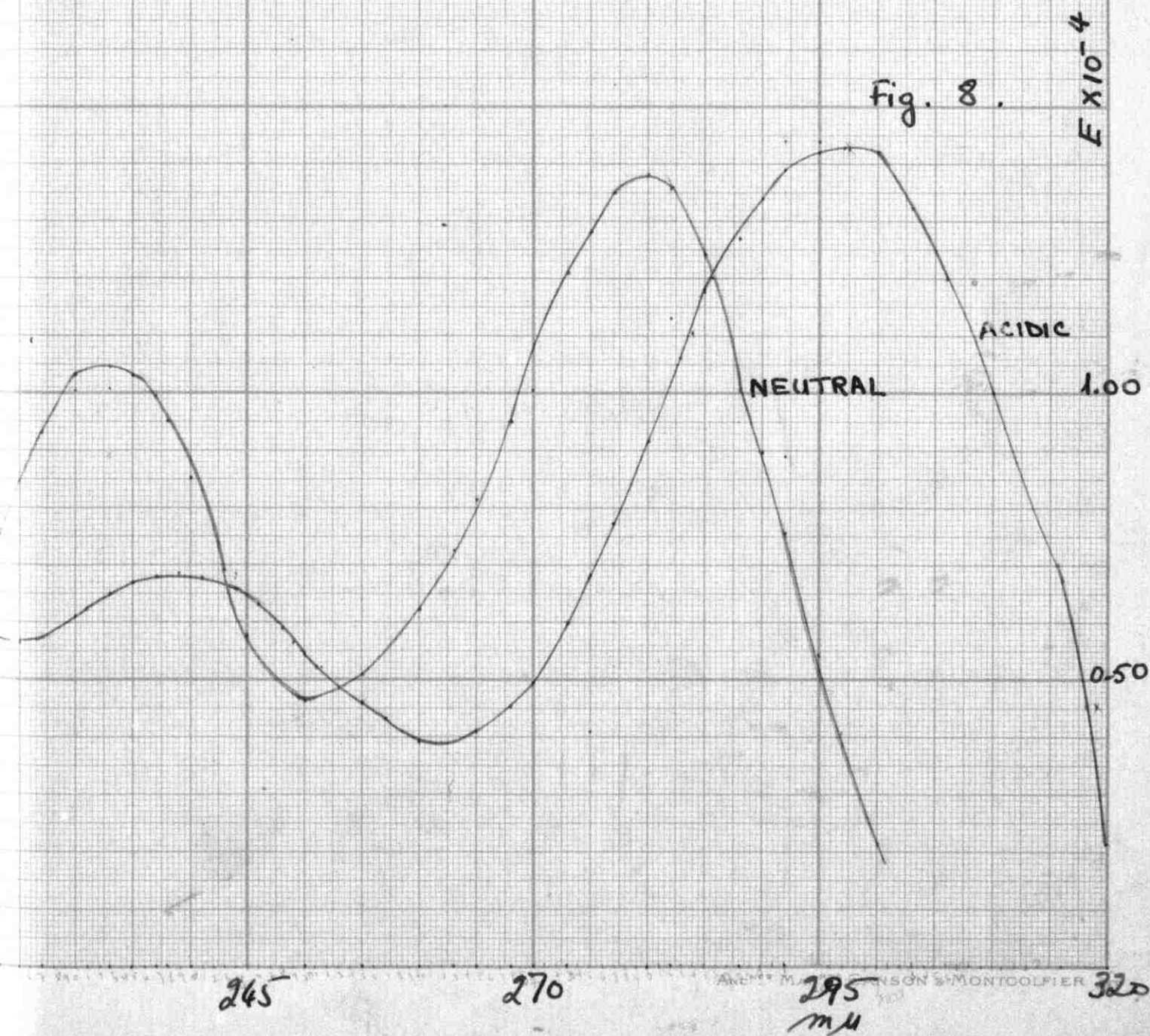
U-V Absorption Spectra of Pyridine

Acidic

Fig.7

Neutral

$E \times 10^{-3}$

6

4

2

230   250   270

$m\mu$

UV Absorption Spectra of 2,2-dipyridyl.

Fig. 8.

ACIDIC

NEUTRAL

$E \times 10^{-4}$

1.00

0.50

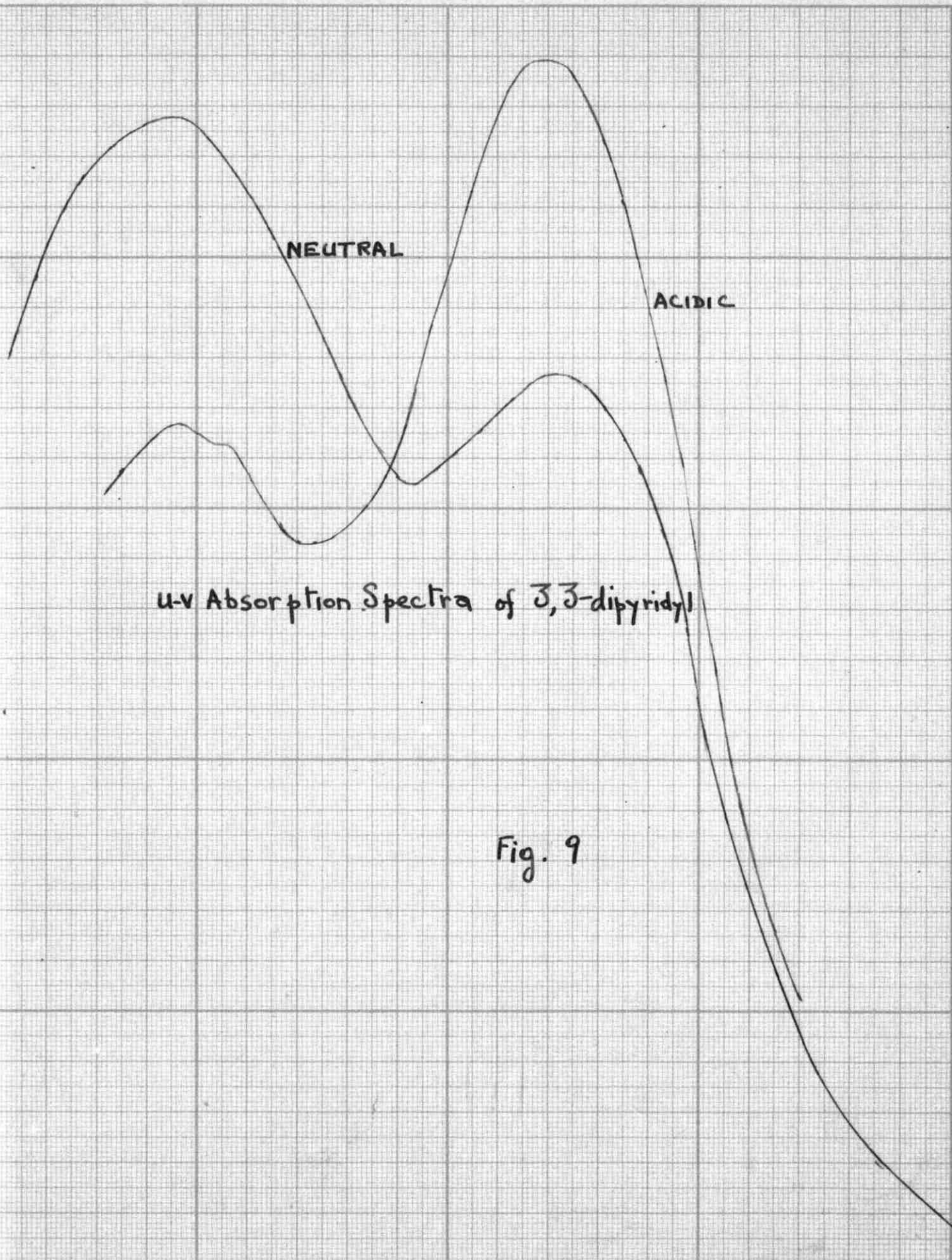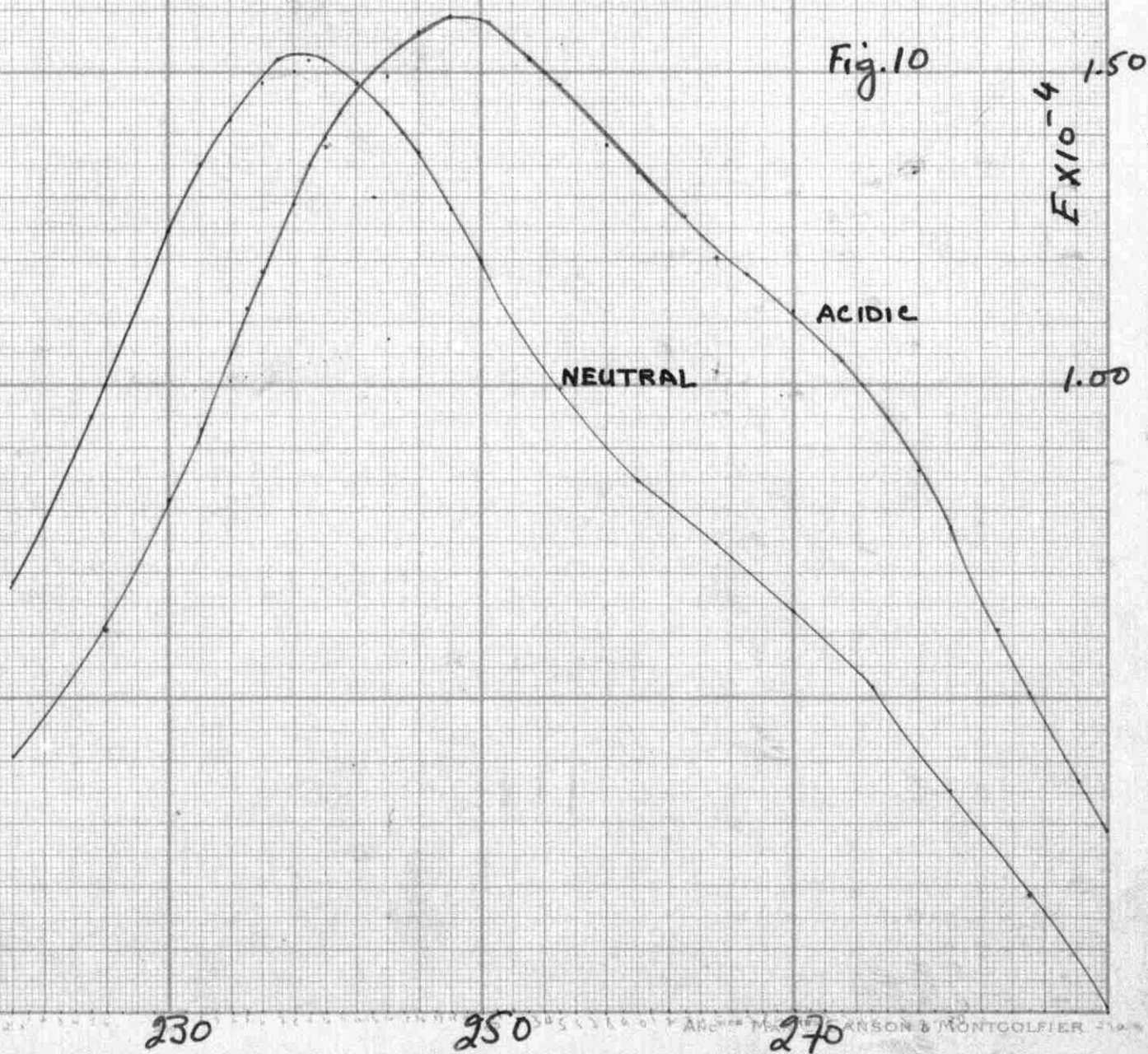245   270   295   320

$m\mu$

NEUTRAL

ACIDIC

U-V Absorption Spectra of 3,3-dipyridyl

Fig. 9

U-V Absorption Spectra of 4,4-dipyridyl

Fig.10

$E \times 10^{-4}$

1.50

ACIDIC

NEUTRAL

1.00

230   250   270

U-V Absorption Spectra of 2,4-dipyridyl.

Fig. 11

ACIDIC 1.00

BASIC 0.750

.500

$E \times 10^{-4}$

225   250   275

$m\mu$.
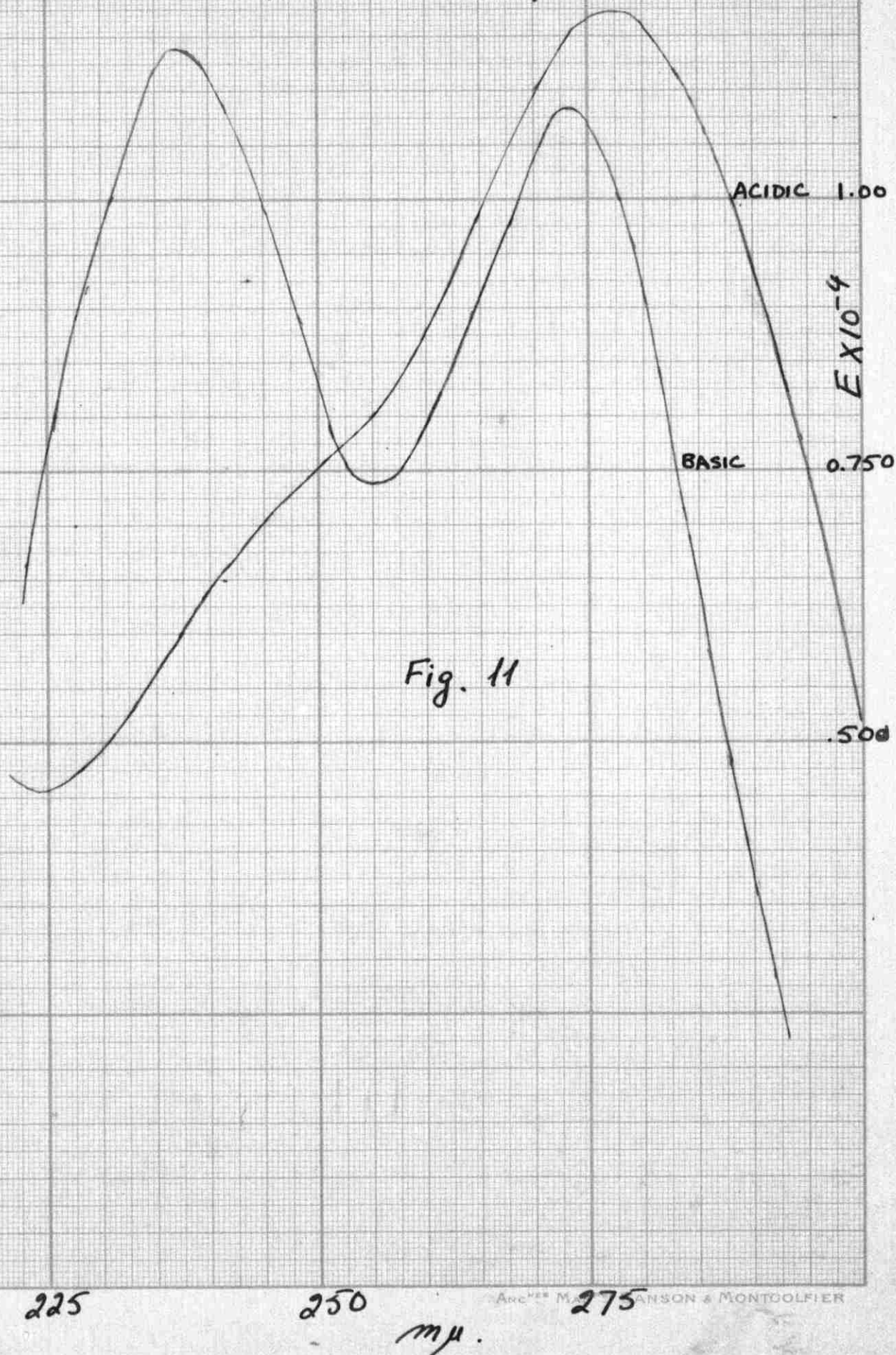
U.V Absorption Spectra
(same scale as given by Krumholz)

2,3-dipyridyl

Fig. 12

16 $Ex10^{-4}$

Acidic

Neutral

9.14

-4.57

237   275 290
mμ

3,4-dipyridyl

Fig 13

$Ex10^{-3}$

Neutral

13.71

9.14

4.57

Acidic

240   270 mμ
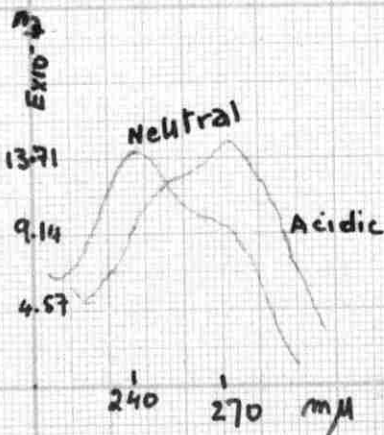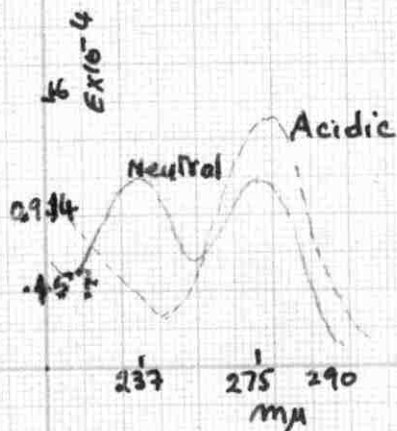
Test of Beer's Law for 4,4'-dipyridyl

x ——— $\lambda = 2390$ A, neutral sol.

⊙ ——— $\lambda = 2500$ A, acid sol.

Fig. 14

1.500

0.500

Optical Density

0.35   0.60   0.85

$\times 10^{-4}$

m/l
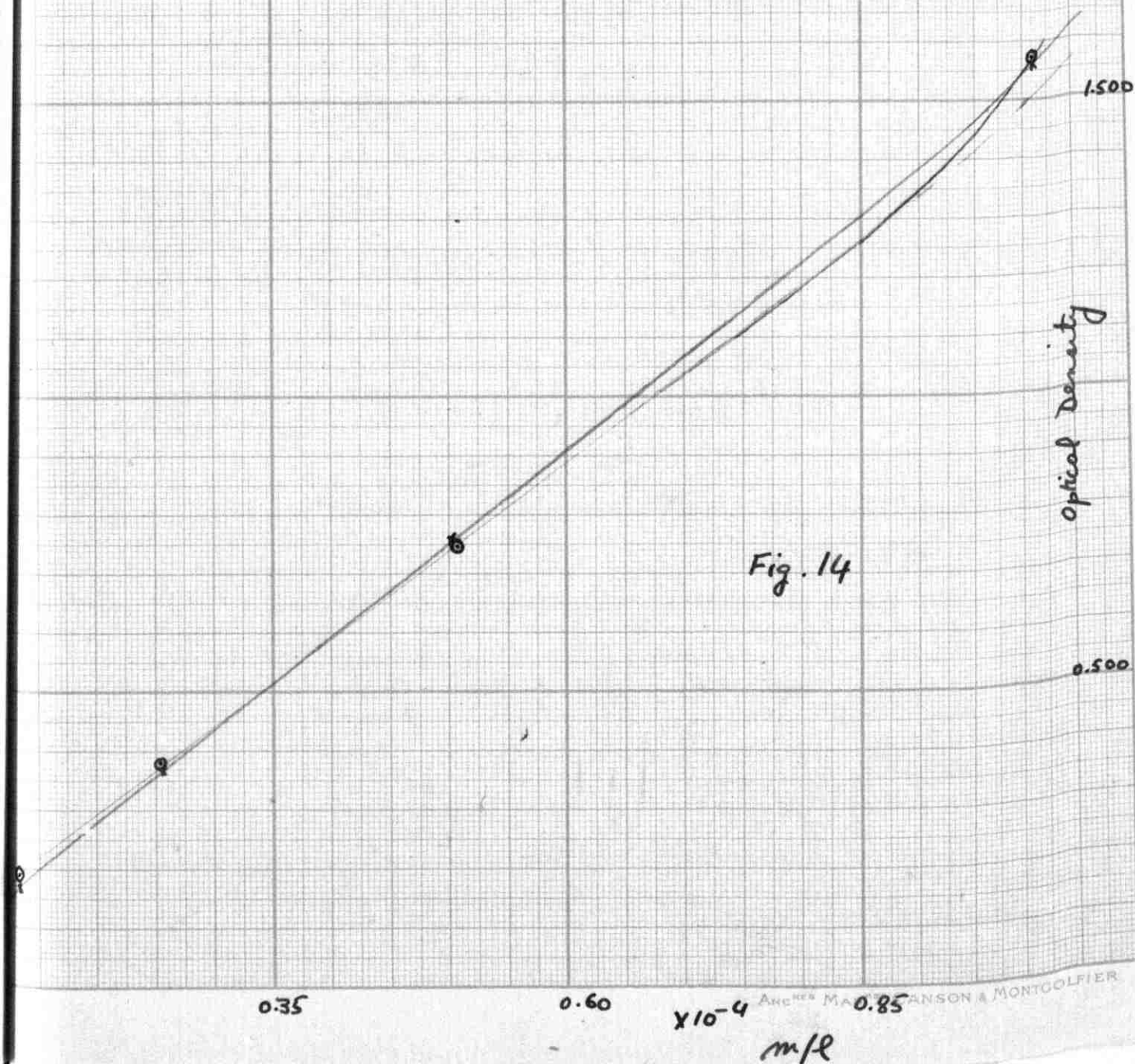
The effect of ionic strength on the absorption spectra
of 4,4- was also investigated because several compounds have been
reported to have an absorption dependent on the ionic strength.
No change in absorption was found in going from a solution of ionic
strength equal to zero to a solution of ionic strength equal to
one (IMKCI).

The applicability of Beer's law has been investigated. The
results are given in Fig. 14. It appears that there is a slight
deviation.

Discussion:

The absorption spectra has been reported by Krumholz in an
attempt to present a structural study of the isomers. His study
is very qualitative and no correlation is made between the absorption
spectra and other properties of the molecule.

The relation of absorption spectra to molecular structure has
been intensively followed by several workers both experimentally
and theoretically. But, owing to the several complicating factors,
the interpretation is always qualitative and usually restricted to
the study of the presence of some functional group, aromatic struc-
ture, coplanarity of rings and theeffect of substituents on this
coplanarity.

In this study I intend to correlate some properties such as
the dissociation constants to the absorption spectra. Such an
attempt is justifiable on theoretical grounds because the dissociation
constant of nitrogen bases is a measure of the "availability" of
the ring electrons at the nitrogen.

As a preliminary step, it is necessary to study the absorption spectra of these compounds more closely. It is noted that there are usually two bands: the first at about 235 mu (short wave band) and the second at about 270 mu (long wave band). These two bands are most distinct for the 2,2- isomer while for the case of the 4,4- isomer there is only a small hump in the curve at 260 mu. Hence there are two factors:

     1- The change in separation of the two bands

     2- The change in intensity of the bands

Since the following study is a correlation between some functions and the extinction coefficients it is essential to have a method for the estimation of the extent of overlapping of the two bands. For the various isomers this correction is not very large (possibly of the order of 10%) except for the 4,4- where the two bands merge into one.

It is postulated in this study that the first band is associated mostly with the pyridyl group as such and the second band is associated with internuclear interaction of the two pyridyl groups.

In order to justify this hypothesis, it is necessary to find two functions: One of these functions should be dependent on the pyridyl group while the second should be dependent on the internuclear interaction.

In the section of dissociation constants it was found desirable to introduce the concept of "transmittivity" across the two rings. It will be shown that this concept appears to have a sound physical basis.

The first dissociation constant of the isomer should be a function of the ring plus a contribution from the second pyridyl group. This should be so because as previously seen the first basic dissociation constant should vary with the position of the substituted pyridyl group and also the C-C bonding. It is necessary to correct for this transmission across the two rings.

In order to correct for this transmission effect I calculated a "corrected" basic dissociation constant "f" = $K_{1B} (1 + LogT)$. Table 8 gives the value of this function for the various isomers and the corresponding value of the extinction coefficients for the first band (short wave length, about 235 mu). Due to the overlapping of the two bands in the case of the 4,4- a corrected value for the extinction coefficient is necessary. There is no precise method to perform this calculation, but the second band can be roughly estimated and when this is done a value of 1.3×10^4 is obtained. Fig. 15 is a plot of this corrected dissociation constant against the extinction coefficient. The agreement is good. This not only justifies the "transmittivity" concept but also justifies the assignment of the first (short wave) band to the pyridyl group. Most probably a much better agreement could be obtained if all the extinction coefficients are corrected for overlapping.

Corrected pK_{IIB} ($=pf$) vs E (short wave band)

4,4 — ⊙?

3,4 —
⊙

2,3 —
⊙   ⊙ 3,3 —

$E \times 10^{-4}$

1.2

2,2 —
⊙

1.1

0.9   1.0   1.1   1.2   1.3

$(10 - \log f)$

Fig. 15

TABLE 8

Compound	$K_{1B}(1 - \log T)$	$10 - \log$	$E.10^{-4}$ (short wave length band)
2,2-			1.043
2,3-	1.03	1.01	1.16
2,4-	0.80	.91	1.14
3,3-	1.04	1.02	1.14
3,4-	2.05	1.31	1.25
4,4-	1.78	1.25	1.55 uncor. 1.3 cor.

TABLE 9

Compound	$10/\log T$	$E.10^{-4}$ (long wave length band)
2,2-	0	1.38
2,3-	3.44	1.1
2,4-	2.78	1.08
3,3-	6.25	0.9
3,4-	5.4	0.89
4,4-	6.07	0.8

Table 9 gives the values of the extinction coefficient at the second band (long waveband, about 270 mμ) and the value of a function of the transmittivity. From Fig. 16 it is very clear that there is an excellent correlation between 1/log T and E. As T increases 1/logT decreases and E increases. The values of E are not corrected for overlapping which is not large in this case.

A comparison of the absorption spectra of pyridine (Fig. 14) in acid and neutral solution to that of the isomers reveals an interesting and surprising difference between these compounds. An explanation can be worked out on the basis of the Mulliken (30) principle that the extinction coefficient increases with increase in the contribution of polar forms to the absorption spectra of the compound. On applying this principle to pyridine it is seen that the increase in absorption spectra is due to contribution from structures such as:

which have become more probable after the addition of H$^+$. For the case of the isomers, when H$^+$ is added to one group it transmits the effect to the second ring and the electron density in the second ring is diminished and hence contributions of this second ring to possible polar structures are suppressed. Hence the change in the value of the extinction coefficient should be a certain function of T. At present no effort is made to find a satisfactory function.
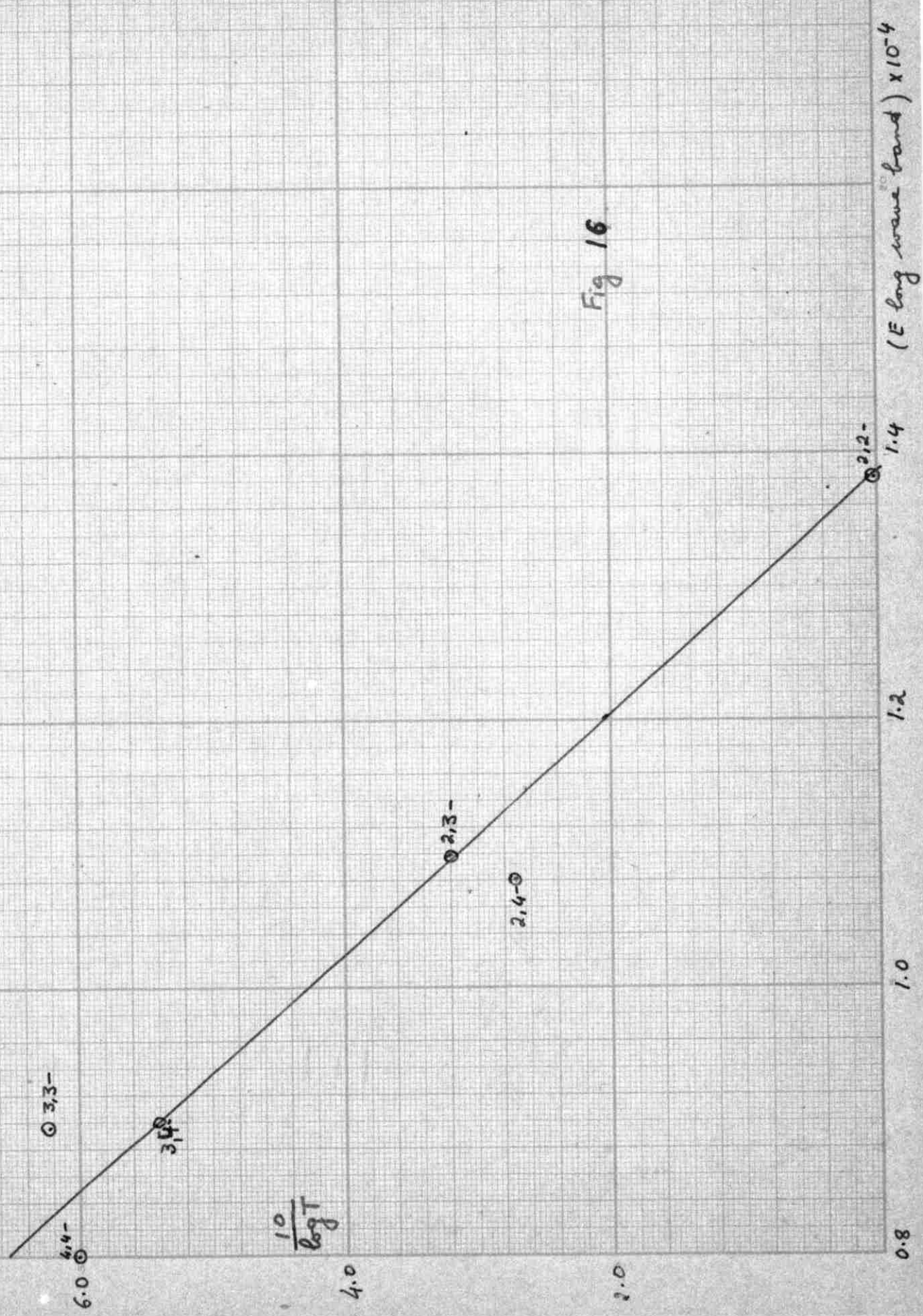
Fig 16

$\frac{10}{\log T}$

(E long wave band) $\times 10^{-4}$

Addivity Principle:

Krumholz found during his studies that the absorption of an unsymmetrical isomer could be computed from that of the corresponding symmetrical isomers. For example, the absorption of 2,4- is give by taking half the sum of the extinction coefficients of 2,2- and 4,4-. When the method was checked it gave qualitatively correct results. A slightly better agreement was found with the values obtained for 2,4- in this study.

Krumholz was unable to justify this addivity. A physical basis could be found on the basis of the previous hypothesis. Since the first band is mostly characteristic of the pyridyl group it should add a constant contribution to the absorption spectra. Hence in the symmetrical isomers half of the absorption at the first band is due to every individual pyridyl group.

Now, the absorption at the second band is dependent upon the internuclear interaction. For the symmetrical isomers we can make the following assumption:

$$1/\log T\ (x,x) \quad = \quad 1/\log T\ (x-) \ + \ 1/\log T\ (x-)$$

Similarly for (y,y). When $1/\log T\ (x,y-)$ is calculated from the following equation:

$$1/\log T\ (x,y) \quad = \quad (1/2) \left[(1/\log T(x-) \ + \ 1/\log T(y-) \right]$$

we obtain values in reasonable agreement with the observed values of T. Table 10 shows the calculated and the observed values of $1/\log T$.

TABLE 10.

$IO/log T$

	This would indicate that the	Compound	Calc.	Obs.
2,3-	3.13	3.44
2,4-	3.03	2.78
3,4-	6.16	5.4

This would indicate that the
contribution of the pyridyl
group to the interaction is some-
what independent of the second
group. I am unable to justify this
on theoretical grounds. If this
could be justified, except by em-
pirical agreement, we have a
complete explanation of the addivity
principle.

PALAROGRAPHIC STUDIES

<u>Polarographic reduction of the isomers</u>:

The subject of polarography has been treated by Kolthof
and lingane (31) and by Muller (32).

The apparatus used in this study is a Sargent-Heyrovsky
Polarograph with automatic photographic recording.

The problems studied were:

1. The determination of the half wave potentials and
   the order of reduction of the isomers.

2. The variation of reduction potentials with pH.

3. The variation of the diffusion current with conc.
   This was done with a view to analytical applications.

4. Reduction mechanisms.

5. Correlation of results with other properties of the
   molecule.

The order of reduction of the isomers:

The following data in table 11 will settle the question of the relative ease of reduction of the various isomers.

All potentials are total applied voltages, the supporting electrolyte is 0.1M KCl, the buffer used for the measurements given in table 11 was 0.25 N NaAc and 0.4 N ØHAc plus 1% piperidine. The measured pH ≟ 4.2. The presence of piperidine was found to increase slightly the voltage range of the dropping mercury electrode; that is, it appears to increase slightly the hydrogen overvoltage. The presence of piperidine was later found to be unnecessary for reduction below 1.3 v.

Table 11.

Compound	2,2-	2,3-	2,4-	3,3-	4,4-
$E_{1/2}(I) =$	-I.I		-I.02	-I.55	-0.9
$E_{1/2}(2) =$	-I.25		- ?	-	-I.I

Note: Two distinct waves have been noted, denoted by (I) and (2). 2,4- at this pH does not have a well defined second wave. No values for 2,3- are given in this table because the 2,3- has been studied at pH ≟ 2.68 and compared with 2,2- at the same pH. The 2,3- appears to be reduced in two steps at -0.99 and -I.05 v.; while 2,2- has a wave at -0.98 and the second starting at -I.0I v. but does not have any plateau. This behaviour has been noticed for all the isomers at some low pH. This will be studied further. From this it follows that the two compounds are reduced at almost the same potentials.

Variation of reduction potentials with pH:

The reduction takes place at lower potentials the lower the pH. The variation with pH has been ivestigated most thoroughly for 4,4- and the remaining isomers have been studied at only 2 or 3 different pH; hence the discussion and the results will be confirmed to 4,4-.

Table 12 gives the two half wave potentials for 4,4- at various pH.

Table 12

pH =	2.68	4.2	4.5	6.4	(0.25M Na$_3$PO$_4$)
$-E_{\frac{1}{2}}(I)$ =	0.85	0.86	0.9	1.05	1.3
$-E_{\frac{1}{2}}(2)$ =	1.1	1.09	1.09	1.17	-

At low pH - 2.68, it was found that the two waves of 4,4- split into four different waves; the separation is not very good but this indicates that the lower the pH the clearer are the different steps in which the reduction proceeds. Hence it is intended to study the reduction in 80% sulfuric acid. The polarographic properties of this solvent have been recently investigated by James (33).

Studies to determine the reduction product of 4,4- using chemical reduction methods:

During the reduction of 4,4- at a conc. of 10^{-2} m/l (pH $=$ 4.2) it was observed that a blue colour appears on the surface of the mercury drops. This blue colour is identical with the colour obtained when 4,4- is reduced using Zn and acetic acid or HCl. Hence this shows that the reduction intermediates in the polarographic reduction are the same as those in the chemical reduction.

This observation suggested the idea of studying the absorption spectra of reduced 4,4- and to determine from the results the nature of the compound: whether a pyridyl-piperidine or a dipiperidine.

The extinction coefficient of pyridine is about 3000 while that of piperidine is about 500 at 255 mu. Hence the difference is large enough to indicate whether the compound has one ring or two rings reduced.

4,4- was reduced by a variety of methods using Al, Zn, Sn (refluxed for 24 hours) plus HCl or acetic acid (with Zn only). The absorption is of the order of 5.9 to 5×10^3 at 255 mu. basic medium and about 7.7×10^3 in acidic medium. There is also strong absorption in basic medium over a wide band 220-240 mu. Such a strong absorption cannot be due to a dipiperidine and is somewhat too high for a pyridyl-piperidine assuming that the absorption of the compound is that of the algebraical sum of the individual parts. This strong absorption cannot be due to the presence of unreduced dipyridyl, be-

cause when 2,2- is reduced under the same conditions there is no
absorption at 270 mu. which is a characteristic band for 2,2-.
Further evidence that this compound is a pyridyl-piperidine is
available from the fact that Smith reports to have been able to
separate from the Sn plus HCl reduction: pyridylpiperidine. Although
further work will be carried out to obtain conclusive evidence that
the reduction of 4,4- proceeds to a pyridyl-piperidine and not to a
dipiperidine this seems at present a good support of a hypothesis
that the reduction proceeds through uni-nuclear process. This will
be discussed further.

Variation of the diffusion current with concentration:

According to the Ilkovic equation (34) the diffusion current
is a linear function for the concentration for a reversible electro-
de reaction. This has been found to be correct for a large number of
organic compounds over a restricted range. Whenever this equation
does not hold calibration curves have to be constructed in order to
make use of the method for analytical purposes.

4,4- has been studied at different concentrations and it was
found to deviate a good deal from the Ilkovic equation. At high conc.
(10^{-2} m/l) and pH $=$ 4.5 the reduction wave has a maximum and the li-
miting current is lower than that calculated from that obtained at
conc. of 10^{-3}m/l.

In the course of this study it was observed that the isomers
are strongly surface active. Surface active compounds are usually used

to suppress max. while 4,4- appears to be surface active, to have

a max. and to self suppress itself.

In order to get a better idea of the electrode processes
the electrocapillary of mercury was investigated. Fig. 17 gives the
drop time for 10 drops. The curve is depressed a good deal below the
electrocapillary curve in the blank (not shown in figure) and further-
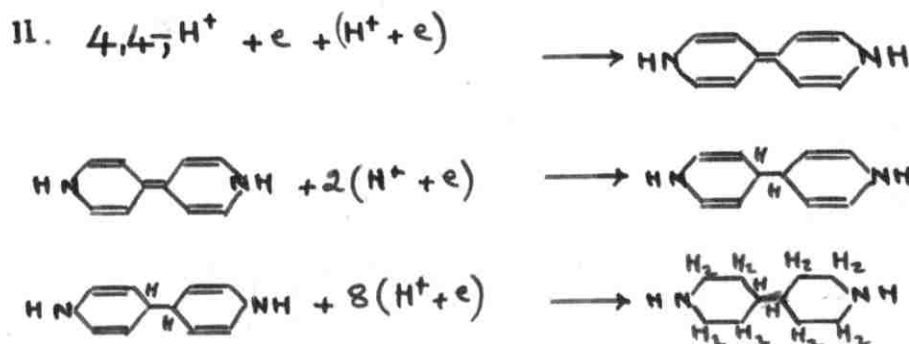more, the blank curve does not show the plateaus apparent in the
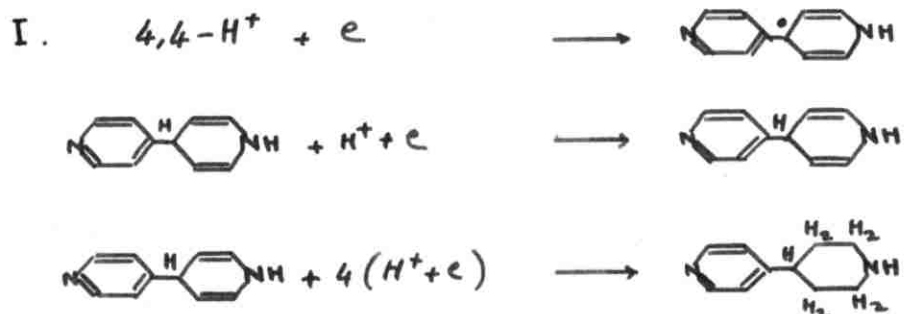4,4- curve.

The voltage current curve is plotted on the same figure in
order to show that the two max. on the electrocapillary curve are
associated with the reduction of 4,4- and that the max. produced at
-1.04 in the electrocapillary curve is associated with the minimum
in the 4,4- reduction. The half wave potential of 4,4- at this pH
is -0.9 v. but the blue compound could be seen at the surface of
the mercury drops slightly before -0.72 v. It is clear that the
shape of the curve is very unusual and no reference to such a curve
has been found. Work will be continued to obtain an explanation of
this phenomena.

Discussion:

Two ring versus one ring reduction hypothesis:

The available data as will be presently shown, supports strongly the hypothesis that the reduction of the dipyridyl proceeds to a pyridyl-piperidine and not to a dipiperidine; the study is not yet complete and the conclusions given here are therefore not final.

The following set of equations I and II show the different steps that should be followed if the reduction proceeds, I - to a pyridyl-piperidine; II - to a dipiperidine. The two processes are completely independent and there cannot be any overlapping between the two.
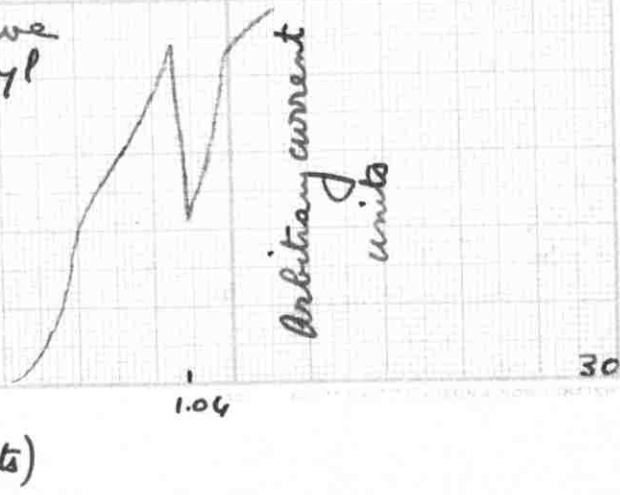
I.

$4,4 - H^+ + e \longrightarrow$

$+ H^+ + e \longrightarrow$

$+ 4(H^+ + e) \longrightarrow$

II.

$4,4 - H^+ + e + (H^+ + e) \longrightarrow$

$+ 2(H^+ + e) \longrightarrow$

$+ 8(H^+ + e) \longrightarrow$

Electrocapillary curve of Hg in

1.053 × 10⁻² m/l . 4,4- dipyridyl , 0.1 M KCl
0.25 N NaAc , 0.4 N H Ac
1% piperidine

Fig 17

0.728 V

1.04 V

Time for 10 drops in sec.

40 sec

35 sec

30
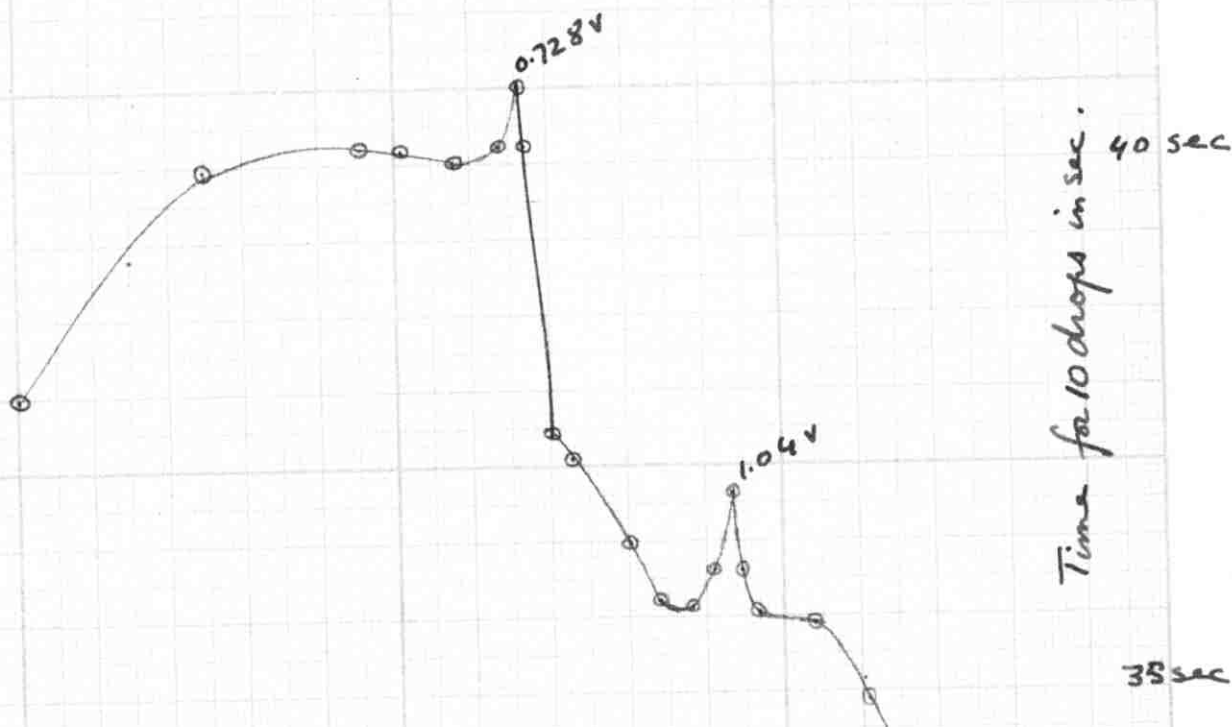
Voltage - Current curve
of 4,4- dipyridyl

Arbitrary current
units

0

.56

1.04

— (volts)

In I the first step is the production of a reactive free radical. The production of free radicals in electrolytic processes has been postulated by Waters (35) for some reduction processes such as the reduction of acridine. The reduction of this free radical will most probably take place at the same potential as the first step to a quinonoid form. This compound has the same empirical formula as the compound isolated by Dimroth and Frister (22) (see introduction p. 16 - 18). In the mechanism II the first reduction step is the quinonoid shown which also has the same composition as the compound isolated by Dimroth and Frister but this will eventually lead to a dipiperidine. It was seen in the discussion on the chemical reduction of the 4,4- that the compound obtained is most probably a pyridyl-piperidine and not a dipiperidine.

A second support is the order of reduction of the isomers. If the reduction proceeds through the reduction of one ring at a time it means that the order of the reduction of the unsymmetrical isomers should be the order of the 4-substituted (easiest), then 2-. The 3-ring will not be reduced first in the unsymmetrical isomers, because 3,3- is the hardest to reduce. This is exactly the order observed.

A final support is obtained from a combination of the transmittivity hypothesis and the order of reduction of the isomers. On the basis of the T values we have max. π -interaction for the 2,2- hence it should be the easiest to reduce because of the contributions of structures such as:
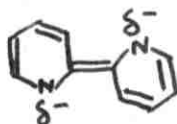
while 4,4- should be much harder to reduce because of the negligible T value. Since 4,4- is the easiest to reduce and 2,2- is reduced at a lower potential, it means that the mechanism II is improbable while I is the more probable.

Synthetic production of anabasine:

2,3- has been supposed by various workers (19, 20, 21) to reduce to 3-(2-pyridyl)piperidine. Since it was found that 2,3- reduces at almost the same potentials as 2,2- and more easily than 3,3-, this indicates that it is the 2-ring which is reduced most easily and not the 3-ring. Conclusive evidence has to be obtained from electrolytic reduction and isolation of the compound.

Anabasine has been shown to be 2-(3-pyridyl)piperidine (36). It therefore appears possible to synthesize anabasine from 2,3- dipyridyl.

S U M M A R Y

SUMMARY

Methods for the preparation of the isomers have been reviewed and free radical mechanisms have been suggested for the sodium pyridine reaction and for the thermal decomposition of pyridine. The relative yield of the isomers has been explained on the basis of variation of electron density in the pyridine nucleus. It was suggested that free radical attack on a molecule will be affected by the type of free radical and the electron densities throughout the ring. Two new methods for the separation of the isomers from the sodium pyridine reaction products have been suggested.

The solubility of 2,2- and 4,4- in water is reported and that of the other isomers discussed briefly.

A transmittivity hypothesis has been put forward which correlates well the absorption spectra and dissociation constants of the dipyridyls. This hypothesis was found of use in interpreting the interaction of two pyridyl groups in the various isomers.

The palarographic studies done on five of the isomers show conclusively that the order of reduction of the isomers is 4,4- (easiest); 2,4-; 2,2-; 2,3- and 3,3- (most difficult). The variation of electrode potential with pH is reported for 4,4- only. The electrocapillary curve of mercury in 4,4- solution has been determined. The results are discussed briefly.

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