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ALKYLATION OF METAL SALTS OF PYRROLE

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## ABSTRACT

This project is an investigation of the use of alkyl tosylates in studies of the factors which determine the position of alkylation of the ambident pyrrol anion.

It was observed in this study that the crucial factor which determines the position of alkylation of the ambident pyrrol anion seems to be the degree of dissociation of the pyrrol metal salt. Thus conditions that favor dissociation of the pyrrol metal salt, e.g., higher electropositive character and larger ionic radii of metal cations, more dissociating solvents, dilution, & higher temperatures, tend to favor N-alkylation whereas factors that depress the degree of dissociation, e.g. less electropositive and smaller metal cations, less dissociating media, & added common metal cation, favor C-alkylation.

TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION - HISTORICAL .....	1
II. DEFINITION OF THE PROBLEM .....	14
III. SUMMARY OF EXPERIMENTAL RESULTS .....	15
IV. DISCUSSION OF RESULTS .....	21
V. EXPERIMENTAL .....	25
VI. REFERENCES .....	44

## INTRODUCTION - HISTORIAL

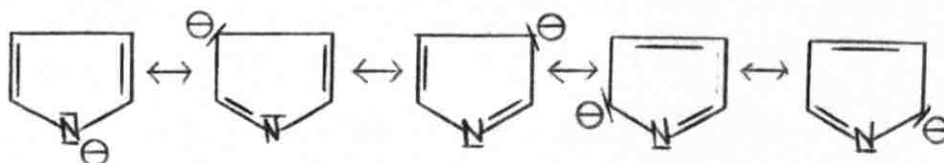
### I. Substitution Reactions of Ambident Ions

A. Definition: An ambident ion is one that possesses two or more nonequivalent positions, usually differing in electronegativity, at which it may undergo covalent bond formation. Examples of ambident ions are:

- a. all anions of tautomeric substances, e.g., the anion of sodium ethyl acetoacetate.



- b. the pyrryl anion.



- c. the cyanide, thiocyanate, phenoxide, naphthoxide and other anions.

Ambident ions provide a challenging problem to organic chemists and much work has been done to determine factors that would either limit substitution to only one position or favor such substitution.

### B. Factors that influence the positions of substitution of ambident ions.

The following factors were found to affect the position of substitution of ambident ions.

1. The nature of the ambident ion itself.<sup>2b,3,4,5,6,18,38,39</sup>

The same substituting agent attaches itself to different positions

when the nature of the ambident ion is changed. It is postulated that some ambident ions have a special preference to undergo substitution reactions at one of the two or more possible positions.<sup>38</sup>

Thus acetyl chloride forms the C-acylated product with the sodium salt of acetoacetic ester, a mixture of the O-acetyl and C-acetyl derivatives with sodium oxalacetic ester, and only the O-acetylated product with formylacetic ester.<sup>2b,18</sup> Also, whereas the phenoxide ion reacts with allylic halides in tetrahydrofuran to form exclusively the ethers, the  $\beta$ -naphthoxide ion yields a mixture of the O- and C-alkylated products.<sup>38,39</sup>

#### 2. The concentration of the ambident ion.

The more dilute the solution of the ambident ion, the more substitution at the more electronegative center is favored, and vice versa.

For example lower concentrations of phenol salts favor O-alkylation.<sup>7</sup> Also, in the reaction of pyrrol sodium with allyl bromide in tetrahydrofuran, the relative percentage of the N-alkylated product increases with increasing dilution of the solution.<sup>1</sup>

#### 3. The reactivity of the substituting agent.

The more reactive the substituting agent, the more favorable the attachment at the less electronegative center of the ambident ion and vice versa.<sup>1,7,8,9,10,17,19,38</sup>

Thus whereas allylic halides favor C-alkylation of the pyrrol<sup>1</sup> and  $\beta$ -naphthoxide<sup>38</sup> ions, the corresponding saturated halides favor N- and O-alkylation respectively.

#### 4. The nature of the leaving group of the substitution agent.

The position at which an ambident ion reacts depends on the nature

of the leaving group of the substituting agent.

The reaction of paranitrobenzyl halides, tosylate or trimethyl ammonium with the lithium salt of 2-nitropropane in dimethylformamide has given the results which are summarized in the following table.<sup>37</sup>

<u>Leaving Group</u>	<u>Temperature °C.</u>	<u>% C-alkylation</u>	<u>% O-alkylation</u>
+ NM <sub>3</sub>	25	93	0
Cl	-16	95	1
OTos	-16	40	32
Br	-16	17	9
I	-16	9	81

5. The homogeneity or heterogeneity of the reaction mixture.

According to Kornblum and coworkers the truly heterogeneous reaction, i.e., the reaction taking place on the surface of the crystalline salt, of sodium phenoxide with alkyl halides produces exclusively C-alkylation at the ortho position<sup>23,39</sup> while for the homogeneous reaction O-alkylation predominates.<sup>23</sup> However, the same investigators observed as much as 77% and 85% C-alkylation of the phenoxide and naphthoxide ions respectively under homogeneous conditions.<sup>24,39</sup> Besides, the homogeneous reaction of pyrrol lithium with allyl bromide in tetrahydrofuran produces a product only 1% of which is N-alkylated.<sup>1</sup>

6. The nature of the solvent.

a. Solvents which favor dissociation of salts lead to substitution at the more electronegative center of the ambident ion.

Whereas the methylation of the sodium salts of aldoximes gives rise



to exclusively N-methylated products in nonionizing solvents, the O-methylated products are predominant in ionizing solvents.<sup>3,4,5,6</sup> Also, for a given pyrryl metal salt in a series of media, the relative percentage of N-alkylation increases with increasing polarity of the medium.<sup>1,21a,22a</sup> Similar effects were observed in the alkylation of salts of phenols.<sup>8,9,10,20</sup> However, exactly the opposite trend was observed by Forsblād in the reaction of the lithium, sodium, potassium and bispiperidinium salts of the ethyl ester of  $\beta$ -hydroxycoumalinic acid with methyl iodide in methanol.<sup>41</sup> His data, as interpreted by Kornblum and coworkers<sup>38</sup>, seem to indicate that the dissociated salt produces more of the C-alkylated product than the associated salt.

b. Solvents which have hydrogen bonding capacities (protic solvents) tend to favor substitution at the less electronegative center of the ambident ion. Also, provided other factors are held constant, the greater the H-bonding capacity of the solvent the greater the magnitude of the observed effect.<sup>38,39</sup>

Thus salts of phenol and p-alkylphenols, dissolved in aprotic solvents such as dimethylformamide, dioxane, ethyleneglycol dimethyl ether, diethyl ether, tetrahydrofuran, or toluene, react with allylic halides to form exclusively the O-alkylated products. However, the corresponding reactions in protic solvents, such as water, phenol, and fluorinated alcohols, yield both the O- and C-alkylated products.<sup>39</sup> Also, in the two protic solvents, trifluoroethanol and ethanol, the reaction between  $\beta$ -naphthoxide and benzyl bromide produces 85% and 28% yields of the C-alkylated products respectively.<sup>38</sup>

Kornblum attributes this effect to "Intensive Solvation" of the phenoxide ion which results in the effective masking of the oxygen of the phenoxide ion by molecules of the solvent, so much so, that the availability of the oxygen for nucleophilic displacement is greatly diminished. Thus the carbon atoms, at the ortho and para positions, are able to compete for displacement reactions.

c. Effect of the dielectric constant of the medium.

Although no clear-cut correlation between the dielectric constant of the medium and the position of alkylation can be found in the reaction of metal salts of pyrrole with allylic halides<sup>1</sup>, it has been observed that in general solvents of high dielectric constant favor alkylation at the more electronegative center, and solvents of low dielectric constant, at the less electronegative center of the ambident ion.<sup>1,38</sup>

Thus whereas in dimethylformamide ( $\epsilon = 37$ ) the  $\beta$ -naphthoxide ion reacts with benzyl bromide at room temperature to produce the O-alkylated product exclusively, in tetrahydrofuran ( $\epsilon = 7$ ) 36% of the product is C-alkylated.

7. The nature of the cation.

It has long been noted that cations which have larger ionic radii, which are more polarizable, and which possess higher electropositive character favor substitution at the more electronegative center of ambident ions and vice versa.<sup>1,8,9,10,11,12,13,14,15,16,17</sup>

Thus the alkylation and acylation of the sodium salt of acetoacetic ester produces C-alkylated or acylated products while the corresponding

silver salt produces the O-alkylated product.<sup>11,12,13</sup> Also, for a series of pyrrol metal salts in a given medium, the relative percentage of the N-alkylated product increases with increasing electropositive character of the alkali metal cation.<sup>1</sup> In addition, it is observed that the lithium alcoholates of acetylenic alcohols undergo selective C-alkylation in liquid ammonia, while the corresponding potassium alcoholates are O-alkylated.<sup>16,17</sup>

Kornblum and coworkers have pointed out that the effect of the cation on the position of alkylation of an ambident ion should be discussed concurrently with the solvent because the properties of the ions in solution are modified and so are their effects on each other.<sup>38</sup> They reason that in aprotic solvents of low dielectric constant (e.g. tetrahydrofuran) the influence of the cation would be as mentioned above. However, in aprotic solvents of high dielectric constant (e.g. dimethylsulfoxide) that are effective in solvating cations but not anions, the salt would be dissociated and the anion would be free to react at the most electronegative center. In such cases the differences in the effects of the various cations would be minimized because the extent of solvation of the cation is a function of its size. Thus the smallest cation ( $\text{Li}^+$ ) would be most highly solvated while the largest cation ( $^+\text{NR}_3$ ) would be least solvated. The same investigators also observed that of two aprotic solvents of identical or nearly equal dielectric constants, the one that possesses the greater solvating ability towards sodium ions, gives rise to a greater percentage of the O-alkylated product in the reaction between benzylbromide and sodium naphthoxide.<sup>38</sup>

Finally, they postulate that in protic solvents the nature of the cation becomes unimportant as a factor that influences the position of substitution due to the intensive solvation described earlier (p. 5).

#### 8. The effect of pressure.

A study of the effect of pressure on the position of substitution was made by Le Noble<sup>40</sup> to support Kornblum's postulate that "Intensive Solvation" is responsible for the increased C-alkylation of phenolic salts in protic solvents. It is argued in this study that an increase in pressure would enhance solvation and should accordingly increase the percentage of C-alkylation. An increase in pressure should also increase the ratio:percentage para-alkylation to percentage ortho-alkylation because in an intensively solvated phenoxide ion the ortho position, due to its proximity to the solvation sphere, would become less favorable with respect to substitution than the para position.

It was observed that in the homogeneous alkylation of the phenoxide ion in water, an increase in pressure from 1 to 7000 atm. increases the ratio of C-alkylation to O-alkylation from 0.7 to 1.5 and the ratio of para-alkylation to ortho-alkylation from 1.2 to 2.3.

#### 9. The effect of temperature.

There are no consistent reports on the effect of temperature on the position of alkylation of ambident ions.

It has been found that whereas cupric acetoacetate reacts with benzoyl chloride in benzene at room temperature to produce mainly the C-benzoylated product at reflux temperature it produces mainly the

O-benzoylated product.<sup>2a</sup> An increase in temperature of the reaction of pyrrol potassium with crotylbromide and with benzylbromide in toluene<sup>21b</sup>,<sup>22b</sup> slightly increases C-alkylation but no definite temperature effect was observed in the reaction of pyrrol potassium with allyl bromide.<sup>1</sup> Further, no appreciable difference either in the yield or the proportion of C- to O-alkylation was noted for the reaction of the sodium salts of cyclic  $\beta$ -keto esters with ethyl chloroformate in benzene at room and reflux temperatures.<sup>42</sup>

#### 10. Steric effects.

Acylation of the sodium salts of five-, six-, and seven-membered cyclic  $\beta$ -keto esters in nonpolar solvents affords both C- and O-acylated products.<sup>42</sup> The greatest percentage of C-alkylation is observed with the seven membered ring compound. This fact is explained by the hindrance to axial attack on the carbocyclic ring which is a maximum in the six-membered ring (thus favoring O-alkylation) and a minimum in the seven-membered ring (thus increasing the percentage of C-alkylation).

#### C. Conclusion

Upon recapitulation of the above facts it seems that one cannot easily draw a comprehensive generalization that would account for all the observations. It is not surprising therefore that more than one generalization has been advanced to account for some of the observed effects. Two such generalizations are mentioned below.

a. Degree of dissociation of the salt.

According to this generalization, when the salt is dissociated the ambident anion is substituted at the more electronegative center whereas when the salt is associated substitution takes place at the less electronegative atom.

This is based on the experimental facts that more dissociating solvents (cf factor 6 a.), more electropositive cations (cf factor 7) and dilution (cf factor 2) tend to favor substitution at the more electronegative center of an ambident ion. Thus it is argued that in the dissociated salt the more electronegative center of the ambident ion would be 'free' and would therefore be the predominant position at which substitution is possible. Conversely, in the associated salt, access to the more electronegative center is impeded by the metal ion, and substitution at the less electronegative center is favored.

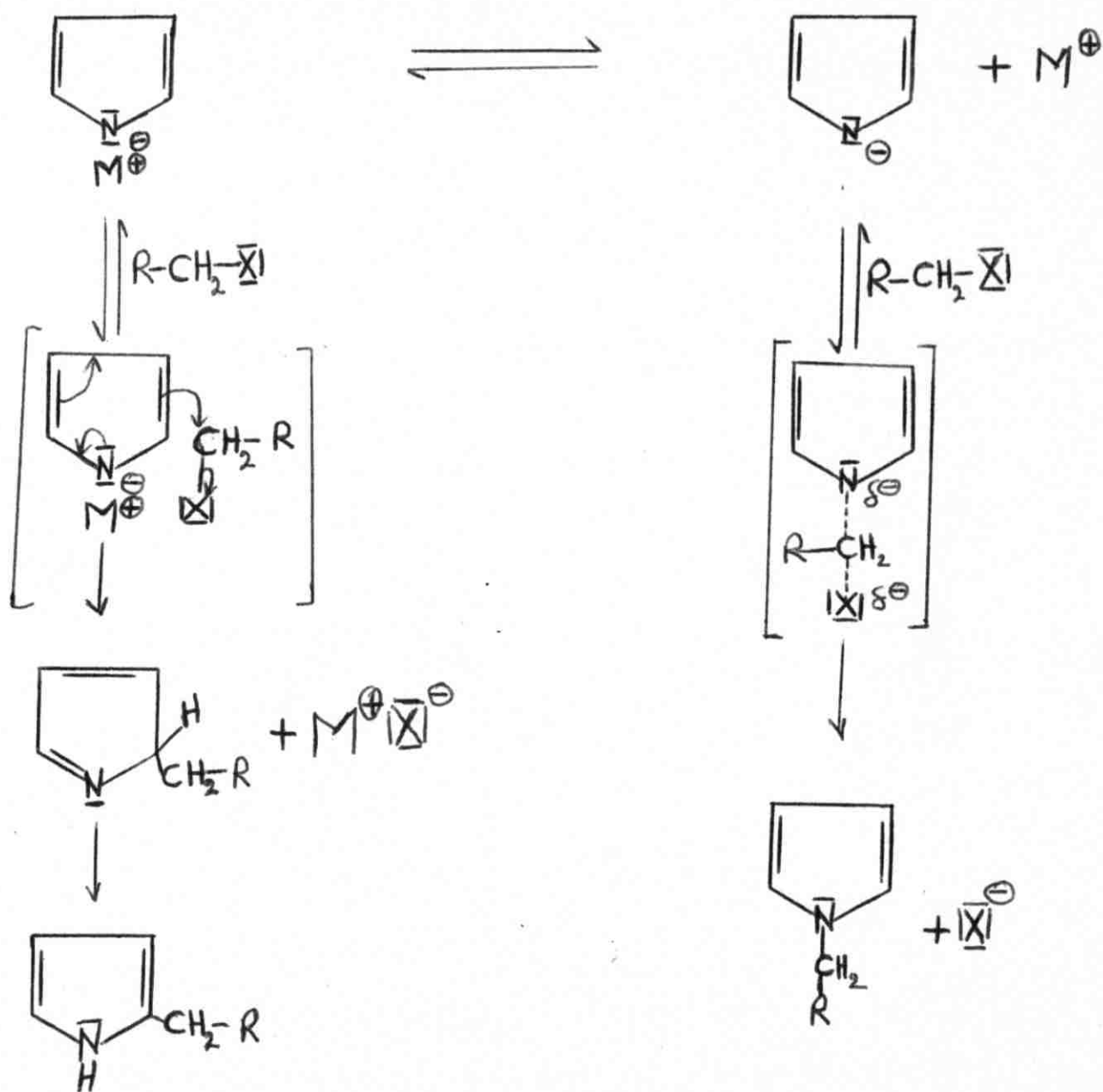
On the basis of this explanation the following alternative mechanisms for 1- and 2-alkylation of pyrrole salts are illustrated below. They were first proposed by Hobbs<sup>22c</sup> on the bases of mechanisms proposed earlier<sup>7,20</sup> for the alkylation of other ambident ions. They can be easily generalized so as to apply to any ambident ion in which the two competing positions are  $\lambda$ - to each other.

Associated salt

2-alkylation

Dissociated salt

1-alkylation



b. Nature of the ambident anion in solution.

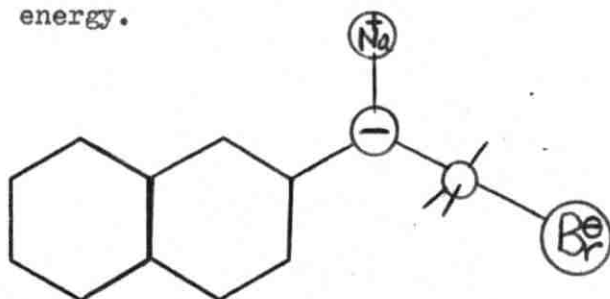
According to this generalization, due to Kornblum and coworkers, the mode of reaction of the ambident ion is determined by the state in which it exists in solution. This state is in turn determined by the nature of the solvent (cf factor 6).

It is postulated that, in the solutions of its salts, the ambident ion may exist as

- i. a free ion.
- ii. an intensively solvated ion.
- iii. an ion pair or higher aggregate.

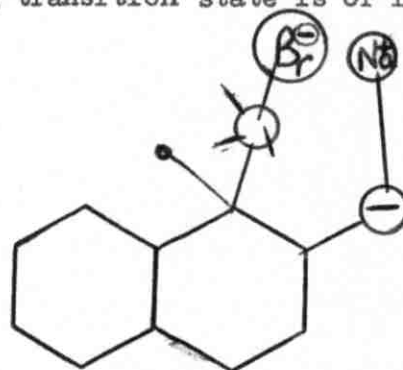
Free ambident ions are substituted at the more electronegative center.

Ion-pairs and ion-aggregates react preferentially at the less electronegative center, because the corresponding transition state is of lower energy.



I

Transition state leading  
to O-alkylation



II

Transition state leading  
to C-alkylation

Transition state (I) in which the leaving group is far removed from the sodium ion is of higher energy than transition state (II) in which the leaving group is close to the sodium ion. In the latter the



developing negative charge on the bromine is neutralized by the positive charge of the sodium ion.

In aprotic solvents of high dielectric constant (e.g. dimethylformamide or dimethylsulfoxide) the ambident ion is either free or in the form of ion-pairs. Since the energy of the transition state for O-alkylation is lowered considerably by the dielectric effect of the solvent it is not surprising that O-alkylation predominates or is observed exclusively.

In aprotic solvents of low dielectric constant (e.g. tetrahydrofuran) only ion-pairs or ion aggregates exist and C-alkylation is favored because the energy of the corresponding transition state is lower.

In H-bond forming solvents the ambident ion is intensely solvated at the more electronegative center and substitution takes place predominantly at the less electronegative atoms.

However, it should be born in mind that the data presented here have been accumulated from the study of different ambident ions (pyrryl, phenoxide, naphthoxide, etc..) and that each ion imposes its own intrinsic characteristics in any context and thus limits our ability to generalize safely.

## II. Use of Alkyl Sulfonates in Alkylation

### A. Alkylation of ambident ions.

Alkyl sulfonates have been widely used to effect alkylation of ambident anions. A survey of the literature<sup>25,26,27,28,29,30,31,32,33,34,35,36,37,49</sup> shows that, in their reactions with different alkyl sulfonates under varying conditions, ambident ions are generally substituted at their

most electronegative center. The following exceptions have been observed:

- a. The thiocyanate ion reacts with allyl tosylate in water to produce the N-alkylated product<sup>27</sup>, whereas with octadecyl tosylate in 90% ethanol it yields the C-alkylated product.<sup>34</sup>
- b. The 2-nitropropane anion reacts with paranitrobenzyl tosylate in dimethylformamide to produce a mixture of the C- and O-alkylated products.<sup>37</sup>

B. Reactions of alkyl sulfonates with Grignard reagents.

These reactions are complicated due to the simultaneous formation of many products.<sup>51</sup> In general, alkyl tosylates ( $R''-SO_2-O-R$ ) react with Grignard reagents ( $R'-MgX$ ) to produce the alkylated product ( $R'-R$ ) and the alkyl halide ( $R-X$ ).<sup>49,50,51,52,53,54</sup>

SUMMARY OF EXPERIMENTAL RESULTS

TABLE I

## REACTIONS OF PYRROL METAL SALTS WITH ALLYL TOSYLATE

Cation	Temp. °C	Solvent	% yield in mono-allylpyrroles	Relative Percent		
				1-Allylpyrrole	2-Allylpyrrole	3-Allylpyrrole
K <sup>+</sup>	65	DMSO	20	99	0.5	0.5
K <sup>+</sup>	65	THF	60	86	11	3.0
K <sup>+</sup>	65	C <sub>6</sub> H <sub>6</sub>	24	66	25	9.0
Na <sup>+</sup>	65	THF	33	29	53	18
Na <sup>+</sup>	65	THF	31	32	55	13
Na <sup>+</sup>	65	THF (inverse)	38	72	22	6.0
Na <sup>+</sup>	65	C <sub>6</sub> H <sub>6</sub>	22	42	44	14
Na <sup>+</sup>	65	C <sub>6</sub> H <sub>6</sub>	23	43	45	12
Li <sup>+</sup>	65	THF	21	24	59	17
Li <sup>+</sup>	65	C <sub>6</sub> H <sub>6</sub>	8.8	16	70	14

TABLE II

## REACTION OF PYRROL POTASSIUM WITH ALLYL TOSYLATE

## EFFECT OF TEMPERATURE

Solvent	Temp. °C.	% yield in mono- allylpyrroles	Relative Percent		
			1-Allylpyrrole	2-Allylpyrrole	3-Allylpyrrole
Dioxane	50	60	82	13	5.0
"	75	72	86	11	3.0
"	100	83	89	9.0	2.0
Toluene	50	36	46	37	17
"	50	30	47	37	16
"	75	39	54	32	14
"	75	33	51	35	14
"	100	38	62	25	13
"	100	40	62	25	13

TABLE III

REACTIONS OF PYRROL METAL SALTS WITH ALLYL TOSYLATE AT 65 °C.

EFFECT OF COMMON METAL ION

Cation	Solvent	Added salt	% yield in mono- allypyrroles	Relative Percent		
				1-Allylpyrrole	2-Allylpyrrole	3-Allylpyrrole
K <sup>+</sup>	THF	KBr	63	83	14	3.0
K <sup>+</sup>	THF	-	60	86	12	2.0
Na <sup>+</sup>	THF	NaBr	36	39	52	9.0
Na <sup>+</sup>	THF	NaBr	21	29	63	8.0
Na <sup>+</sup>	THF	NaBr	30	38	53	9.0
Na <sup>+</sup>	THF	-	33	29	53	18
Na <sup>+</sup>	THF	-	31	32	55	13
Li <sup>+</sup>	THF	LiBr	19	-	92	8.0
Li <sup>+</sup>	THF	-	21	24	59	17

TABLE IV

REACTIONS OF METAL SALTS OF PYRROLE WITH N-PROPYL TOSYLATE AT 65°C.

Cation	Solvent	Relative Percent		
		1-n-Propylpyrrole	2-n-Propylpyrrole	3-n-Propylpyrrole
K <sup>+</sup>	THF	97	2.5	0.5
K <sup>+</sup>	C <sub>6</sub> H <sub>6</sub>	95	4.0	1.0
Na <sup>+</sup>	THF	67	31	2.0
Na <sup>+</sup>	THF	63	34	3.0
Na <sup>+</sup>	C <sub>6</sub> H <sub>6</sub>	74	22	4.0
Na <sup>+</sup>	C <sub>6</sub> H <sub>6</sub>	84	13	3.0
Li <sup>+</sup>	THF	25	70	5.0
Li <sup>+</sup>	C <sub>6</sub> H <sub>6</sub>	19	74	7.0

TABLE V

REACTIONS OF PYRROL MAGNESIUM BROMIDE WITH ALKYL TOSYLATES AT 0°C.

Tosylate	Medium	% yield in mono- alkylpyrroles	Relative Percent		
			1-Alkylpyrrole	2-Alkylpyrrole	3-Alkylpyrrole
Allyl	Ether	17	-	76	24
Allyl	THF	24	-	89	11
n-Propyl	Ether	-	5.0	77	18
n-Propyl	THF	-	14	69	17



## DISCUSSION OF RESULTS

The following generalizations, about the reactions of pyrrolylmetal salts with alkyl tosylates, may be drawn from Tables I to V.

1. For pyrrolylpotassium, the relative percentage of 1-alkylation increases with increasing polarity of the medium. The same is observed for pyrrolyllithium, but the trend seems to be reversed in the case of pyrrolysodium.

2. For a series of pyrrolylmetal salts, in a given medium, the relative percentage of 1-alkylation increases with increasing electropositive character of the cation.

3. For pyrrolysodium, the inverse addition reaction results in a marked increase in the relative percentage of 1-alkylation.

4. For pyrrolyllithium, 1-alkylation is essentially prevented when the reaction in tetrahydrofuran is run in the presence of an excess of lithium bromide. However, the presence of potassium bromide or sodium bromide in the corresponding reactions of pyrrolylpotassium and pyrrolysodium has no clear-cut effect.

5. For pyrrolylpotassium, the relative percentage of 1-alkylation increases with increasing temperature of the reaction. This increase is more noticeable for the reaction in toluene than for that in dioxane.

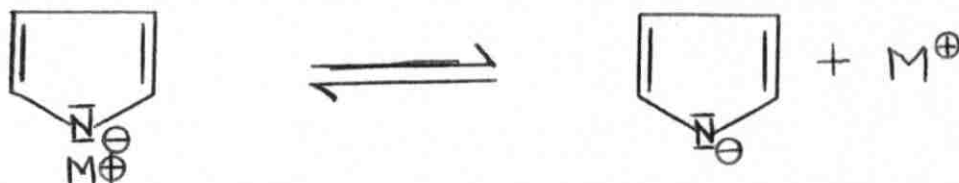
6. For the same pyrrolylmetal salt, in the same medium, the n-propyl tosylate produces more of the 1-alkylated product than the allyl tosylate.

7. Pyrrolylmagnesium bromide yields only C-alkylated products when treated with allyl tosylate. In its reaction with n-propyl tosylate,

however, some N-alkylated products are formed as well. The yield in monoallylpyrroles is quite lower than that obtained with allyl bromide.<sup>1</sup>

These experimental results are in general consistent with the view that the degree of dissociation of the salt plays an important role in determining the position of alkylation of an ambident anion.

In solutions of pyrrolylmetal salts the following equilibrium probably exists:



That is, ion pairs or higher aggregates are in equilibrium with the dissociated salt.

In reactions involving the free pyrrolyl ion, the nitrogen atom which has the greatest electron density would be expected to be the predominant reacting center. On the other hand, in reactions involving the associated salt the nitrogen atom is blocked and the reaction would be expected to be predominant on carbon (for mechanisms of N- and C-alkylation of the pyrrolyl ion, see p. 10). Any factor promoting dissociation of the salt would be expected to favor N-alkylation at the expense of C-alkylation and vice versa.

On the basis of this assumption the previously described experimental results of this investigation can be explained correspondingly as follows:

1. Polar media favor dissociation of the pyrrolyl metal salts and thus lead to a greater relative percentage of N-alkylation. No satisfactory

explanation can be offered for the lack of consistency in the case of pyrryl sodium.

2. Increased size and electropositive character of the cation decreases its coordinating ability and thus causes increased dissociation of the pyrrylmetal salt which favors N-alkylation.

3. The more dilute the solution of the pyrrylmetal salt the more dissociated it becomes. Under the conditions of the inverse addition reaction dilution is kept at a maximum and as a result N-alkylation is greatly favored.

4. The presence of the common metal ion depresses the degree of dissociation of the salt and thus favors C-alkylation. This effect is clearly observed in the case of the lithium salt but not with the potassium or sodium salts. A likely explanation for this difference could be the fact that lithium bromide is easily soluble in tetrahydrofuran whereas sodium bromide and potassium bromide are practically insoluble in it, since only <sup>a</sup> large concentration of the common metal ion would be expected to depress significantly the dissociation of the pyrrylmetal salt.

5. An increase in the reaction temperature is expected to increase the degree of dissociation of the pyrrylmetal salt and lead to a higher relative percentage of N-alkylation. This effect is better observed in a nonpolar solvent such as toluene where the dissociation is low to begin with.

6. The O-C bond in allyl tosylate is more polarized than in n-propyl tosylate. This causes the transition state for C-alkylation to be

of relatively lower energy in the case of the allyl ester and explains the higher percentage of C-alkylation generally observed in the reactions of allyl tosylate as compared to those of n-propyl tosylate.

It is worthwhile to mention that the results of this investigation are in satisfactory agreement with those obtained in analogous studies of alkylation reactions of pyrrometal salts with allyl, crotyl and benzyl halides.<sup>1,21,22</sup>

## EXPERIMENTAL

The apparatus used consisted of a 500 ml three-necked flask fitted with a water cooled bulb condenser, a sleeve type stirrer and a pressure equalizing dropping funnel. All reactions were carried out in an atmosphere of nitrogen which was continually passed through the system and whose rate of flow was controlled by means of a small, mercury containing, U-tube at the other end of which was fitted a small calcium chloride tube.

### I. Preparation of Starting Materials.

#### a. Preparation of allyl tosylate.<sup>43,44,46</sup>



A total of 175 ml of a 25% sodium hydroxide solution was slowly added to a vigorously stirred and thoroughly cooled (0° to -5°) mixture of 190 gms (1 mole) of tosyl chloride and 127.6 gms (2.2 mole) of allyl alcohol. The resulting mixture was stirred for a further four hours at 10 - 15°. It was then poured over 200 gms of ice and the resulting oily layer was extracted with ether. After a drying treatment over anhydrous potassium carbonate, the ether was removed by keeping the extract at 30 - 35° under 5 mm Hg. The remaining oily liquid was colored pale yellow and was used as such.

Attempts to distill the ester under reduced pressure resulted in an explosion as reported by Foldi.<sup>43</sup> However, Bomford and Stevens<sup>45</sup>, and Gilman and Beaber<sup>46</sup>, reported boiling points of 135 - 140°C/0.5 - 1.0 mm

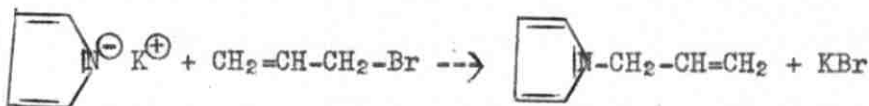
and 148 - 150°C/3 mm respectively. The ester as used was quite pure as was proved by Foldi.<sup>43</sup>

b. Preparation of n-propyl tosylate.



The procedure for the preparation of the allyl tosylate was followed. The oily residue remaining after removal of the solvent distilled as a colorless oil b.p. 140/2.3 mm. (Lit. 106-108°C/0.06 mm<sup>47</sup>; 182°/18 mm, 178°/13 mm, 150°/4 mm<sup>26</sup>).

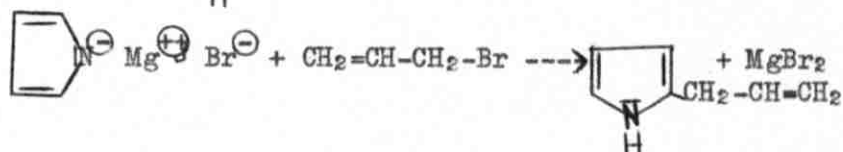
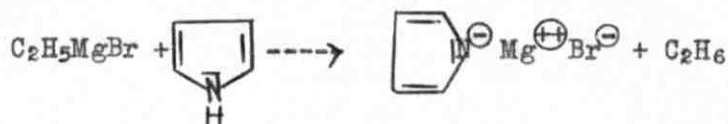
c. Preparation of 1-allylpyrrole<sup>1</sup>.



A total of 15.6 gms (0.40 mole) of potassium, freshly cut into small pieces under kerosene and rinsed with tetrahydrofuran, was added to a solution of 33.5 gms (0.50 mole) of pyrrole in 200 ml. of tetrahydrofuran. The mixture was stirred at gentle reflux and, when all the potassium had reacted, an additional 300 ml of solvent was added and the temperature was adjusted to 65°. Then, 48.4 gms (0.40 mole) of allyl bromide dissolved in 100 ml of solvent was added dropwise over a period of one hour and the mixture was stirred at 65° for eight more hours. It was then filtered and the solid material was washed with dry ether. The filtrate and washings were then combined, the solvents removed by distillation at the aspirator, and the remaining oily liquid was distilled under reduced pressure. The experiment was repeated and the combined distillates were fractionated under reduced pressure first through a 3 ft. Todd Column packed with glass helices, and a second time through a 3ft. Todd Column

of the spiral type. The fraction b.p. 56 - 57<sup>0</sup>/25 mm contained pure 1-Allylpyrrole, (Lit. 56.5<sup>0</sup>/25 mm<sup>1</sup>), as was shown by gas chromatography.

d. Preparation of 2-allylpyrrole<sup>1</sup>.



To 12 gms (0.50 mole) of magnesium turnings covered with 100 ml of dry ether was slowly added 62.5 gms (0.58 mole) of ethyl bromide dissolved in 50 ml of dry ether. The mixture was stirred at room temperature and when all the magnesium had reacted, a solution of 33.5 gms (0.50 mole) of pyrrole in 50 ml of dry ether was added dropwise over a period of one hour and the resulting mixture was refluxed for one hour. Then, 250 ml of dry ether was added, the mixture was cooled in an ice-water bath, and a solution of 60.5 gms (0.50 mole) of allyl bromide in 50 ml of dry ether was added dropwise over a period of one hour. The reaction mixture was stirred for twelve hours under cooling in an ice-water bath. Then it was left to warm up to room temperature, and was stirred for a further ten hours. At the end of this time it was cooled again to 0<sup>0</sup>, and a solution of 53.5 gms (1 mole) of ammonium chloride in 300 ml of water was slowly added. The layers were separated and the aqueous layer was extracted with ether. The ether extracts were added to the organic layer and the resulting solution was dried over anhydrous magnesium

sulfate. The solvent was then removed by flash distillation at the aspirator and the remaining oily liquid was distilled under vacuum. This experiment was repeated using tetra hydrofuran as the solvent.

The combined products of the two experiments were fractionated under 25 mm Hg twice through a 3-ft Todd Column packed with glass helices and finally through a 3-ft Todd Column of the spiral type. The fraction b.p.  $79.5 - 80^{\circ}/25$  mm consisted of 2-Allylpyrrole, (Lit.  $83.5^{\circ}/23 - 24$  mm<sup>1</sup>), containing traces of 3-Allylpyrrole as was shown by gas chromatography.

## II. Reactions of Pyrrolymetal Salts with Alkyl Tosylates

### A. Reactions of Pyrrolypotassium.

#### 1. Reactions of pyrrolypotassium with alkyl tosylates.

To a solution of 16.8 gms (0.25 mole) of pyrrole in 100 ml of solvent was added a total of 7.82 gms (0.20 mole) of potassium, freshly cut into small pieces under kerosene and rinsed with the solvent used. The mixture was stirred and heated at gentle reflux until all the potassium had reacted and any blue color of the slurry disappeared.<sup>a) b)</sup> Then 100 ml of the solvent was added, the temperature was adjusted to  $65^{\circ}$ <sup>c)</sup>, and 0.20 mole of the corresponding tosylate dissolved in 100 ml of solvent was added dropwise over a period of one hour. The reaction mixture was stirred at  $65^{\circ}$  for 8 more hours after which time it was cooled to room temperature and filtered. After the solid material had been washed with ether, it was dissolved in water (about 100 ml) and the solution was extracted with ether.



The filtrate, ether washings and extracts were combined and dried over anhydrous magnesium sulfate. The bulk of the solvent was then removed by flash distillation at the aspirator and the remaining material was weighed and analyzed by gas chromatography. The results are summarized in Tables I, II, III, and IV.

- 
- a) The formation of pyrrylpotassium was completed in 3 - 4 hours in polar solvents such as tetrahydrofuran and dioxane but it needed more than 24 hours in nonpolar solvents such as benzene or toluene.
  - b) In cases where the effect of the common ion was studied one mole of potassium bromide was added at this stage.
  - c) Except in the cases where the effect of temperature was studied.

## 2. Reaction of Pyrrylpotassium with Allyl Tosylate in Dimethylsulfoxide.

Pyrryl potassium was prepared by the addition of 7.82 gms (0.20 mole) of potassium to 16.8 gms (0.25 mole) of pyrrole in 100 ml of tetrahydrofuran. After the reaction had been completed the flask was set for distillation and when all the tetrahydrofuran had been removed, the apparatus was reassembled, 200 ml of dimethylsulfoxide was added and the temperature adjusted to 65°. A solution of 42.4 gms (0.20 mole) of allyl tosylate in 100 ml of dimethylsulfoxide was slowly added over a period of one hour, and the reaction mixture was stirred at 65° for an

additional eight hours. Then it was cooled to room temperature and poured into a 2-liter beaker. The flask was rinsed with 100 ml of water and the washings together with a further 900 ml of water were added to the beaker. The resulting mixture was successively extracted with petroleum ether (50/70) and with ethyl ether. The ethyl ether extract was washed with a small amount of water to remove dissolved dimethylsulfoxide. The combined extracts were then dried over anhydrous magnesium sulfate. The bulk of the solvents was removed by flash distillation at the aspirator and the remaining material was weighed and analyzed by gas chromatography. It contained 4.3 gms of mono-allylpyrroles (20% yield) in the relative amounts 99% 1-Allylpyrrole, 0.5% 2-Allylpyrrole and 0.5% 3-Allylpyrrole.

## B. Reactions of Pyrrolysodium.

### 1. Reaction of Pyrrolysodium with Allyl Tosylate in Tetrahydrofuran.

To a slurry of 8.89 gms of a sodium hydride-oil emulsion containing 4.80 gms (0.20 mole) of sodium hydride in 50 ml of tetrahydrofuran, 16.8 gms (0.25 mole) of pyrrole in 50 ml of tetrahydrofuran was slowly added. The reaction proceeded vigorously with evolution of heat and hydrogen. After stirring the mixture at 50 - 60° for three hours it was diluted with 100 ml of tetrahydrofuran and the temperature was adjusted to 65°. Then 42.4 gms (0.20 mole) of allyl tosylate in 100 ml of tetrahydrofuran was added dropwise over a period of one hour and the resulting mixture was stirred at 65° for a further eight hours. Then

it was cooled to room temperature and was filtered. After washing the solid material with ether, it was dissolved in water and extracted with ether. Then the filtrate, washings, and extracts were combined and dried over anhydrous magnesium sulfate. The bulk of the solvents was then removed by flash distillation at the aspirator and the remaining material was weighed and analyzed by gas chromatography. It was found to contain:

- First run: 33% monoallylpyrroles in the relative amounts of 29% 1-allylpyrrole, 53% 2-allylpyrrole and 18% 3-allylpyrrole.
- Second run: 31% monoallylpyrroles in the relative amounts of 32% 1-allylpyrrole, 55% 2-allylpyrrole and 13% 3-allylpyrrole.

2. Reaction of Pyrrolysodium with n-Propyl Tosylate in Tetrahydrofuran.

The procedure was exactly as in (1). The product contained:

- First run: 67% 1-n-propylpyrrole, 31% 2-n-propylpyrrole and 2.0% 3-n-propylpyrrole.
- Second run: 63% 1-n-propylpyrrole, 34% 2-n-propylpyrrole and 3.0% 3-n-propylpyrrole.

3. Inverse Addition Reaction.

After the pyrrolysodium had been formed as in (1), the solution was diluted with 100 ml of tetrahydrofuran and transferred to a dropping funnel equipped with a pad of glass wool to retain any unreacted residue from sodium hydride. It was then added dropwise over a period of four hours to a solution of 42.4 gms (0.20 mole) of allyltosylate in 100 ml of tetrahydrofuran kept at 65°. The reaction mixture was

further heated for six hours. It was then cooled to room temperature, filtered and the solid residue was washed with dry ether. The filtrate and washings were combined and the bulk of the solvents was removed by distillation at the aspirator. The remaining material was weighed, and analysis by gas chromatography showed the product to contain 9.20 gms of monoallylpyrroles (38% yield) in the relative amounts 72% 1-allylpyrrole, 22% 2-allylpyrrole and 6% 3-allylpyrrole.

4. Reaction of Pyrrolysodium with Allyl Tosylate in Tetrahydrofuran in the Presence of Sodium Bromide.

The procedure was the same as in (1) except that 1 mole of sodium bromide was added after the formation of the salt was complete. The product contained:

First run: 36% yield in monoallylpyrroles in the relative amounts of 39% 1-allylpyrrole, 52% 2-allylpyrrole and 9.0% 3-allylpyrrole.

Second run: 21% yield in monoallylpyrroles in the relative amounts of 29% 1-allylpyrrole, 63% 2-allylpyrrole and 8.0% 3-allylpyrrole.

Third run: 30% yield in monoallylpyrroles in the relative amounts of 38% 1-allylpyrrole, 53% 2-allylpyrrole and 9.0% 3-allylpyrrole.

5. Reaction of Pyrrolysodium with Allyl Tosylate in Benzene.

Pyrrolyl sodium was prepared by the slow addition of 16.8 gms (0.25 mole) of pyrrole in 50 ml of tetrahydrofuran to 8.89 gms of a sodium hydride-oil emulsion containing 4.80 gms of sodium hydride in 50 ml of

tetrahydrofuran and stirring the mixture at 50 - 60° for three hours. The flask (previously calibrated at 50 - 100 - 200 ml) was then set for distillation and when about 50 ml of tetrahydrofuran had been removed, 100 ml of benzene was added and the distillation was resumed until the volume was reduced to about 50 ml. This was repeated twice and the last time distillation was continued until the volume of benzene was reduced to 100 ml. Finally 100 ml of benzene was added, the temperature was adjusted to 65°, and 42.4 gms (0.20 mole) of allyl tosylate in 100 ml of benzene was added dropwise over a period of one hour. The reaction mixture was stirred at 65° for an additional eight hours and then it was treated as usual. Gas chromatography showed it to contain:

First run: 22% yield in monoallylpyrroles in the relative amounts of 42% 1-allylpyrrole, 44% 2-allylpyrrole, and 14% 3-allylpyrrole.

Second run: 23% yield in monoallylpyrroles in the relative amounts of 43% 1-allylpyrrole, 45% 2-allylpyrrole, and 12% 3-allylpyrrole.

6. Reaction of Pyrrylsodium with n-Propyl Tosylate in Benzene.

The same procedure as in (5) was followed. The product contained the following relative amounts of mono-n-propylpyrroles:

First run: 74% 1-n-propylpyrrole, 22% 2-n-propylpyrrole and 4.0% 3-n-propylpyrrole.

Second run: 84% 1-n-propylpyrrole, 13% 2-n-propylpyrrole and 3.0% 3-n-propylpyrrole.

### C. Reaction of Pyrryllithium.

#### 1. Reaction of Pyrryllithium with Allyl Tosylate in Tetrahydrofuran.

A mixture of 16.8 gms (0.25 mole) of pyrrole and 1.59 gm (0.20 mole) of lithiumhydride in 100 ml of tetrahydrofuran was stirred at 50 - 60° for six hours and then at 40 - 50° for an additional thirteen hours. The resulting mixture which looked dark green was diluted with 100 ml of tetrahydrofuran and the temperature was adjusted to 65°. A solution of 42.4 gms (0.20 mole) of allyl tosylate in 100 ml of tetrahydrofuran was then added dropwise over a period of one hour. The reaction mixture was heated for a further eight hours after which it was treated as usual. Gas chromatography showed the product to contain 4.6 gms of monoallylpyrroles in the relative amounts of 24% 1-allylpyrrole, 59% 2-allylpyrrole and 17% 3-allylpyrrole. Overall yield in monoallylpyrroles was 21%.

#### 2. Reaction of Pyrryllithium with Allyl Tosylate in Tetrahydrofuran in the Presence of Lithium Bromide.

The same procedure as in (1) was employed except that 0.10 molar quantities were used and 25 gms (0.29 mole) of anhydrous lithium bromide was added to the reaction mixture after formation of the salt. The product contained 2.1 gms of monoallylpyrroles (19% yield) in the relative amounts of 92% 2-allylpyrrole and 8.0% 3-allylpyrrole. Only traces of 1-allylpyrrole were detected.

#### 3. Reaction of Pyrryllithium with n-Propyl Tosylate in Tetrahydrofuran.

Exactly the same procedure as in (1) was followed. Analysis by gas

chromatography showed the product to contain the following relative amounts of mono-n-propylpyrroles, 25% 1-n-propylpyrrole, 70% 2-n-propylpyrrole and 5.0% 3-n-propylpyrrole.

4. Reaction of Pyrryllithium with Allyl Tosylate in Benzene.

A solution of pyrryllithium (0.20 mole) in 100 ml of tetrahydrofuran was prepared as in (1). The flask (previously calibrated at 50 - 100 - 200 ml) was set for distillation and when about 50 ml of tetrahydrofuran had been left, 100 ml of dry benzene was added and the distillation was resumed until the volume was reduced to 50 ml. A further 100 ml of dry benzene was added and the distillation was continued until the volume of the solvent in the flask was about 100 ml. Then the reaction mixture was diluted with enough dry benzene to make a total of 200 ml and the temperature was adjusted to 65<sup>o</sup>. A solution of 42.4 gms (0.20 mole) of allyl tosylate in 100 ml of dry benzene was added dropwise over a period of one hour and the reaction mixture was stirred at 65<sup>o</sup> for an additional eight hours. It was then cooled to room temperature and treated as usual. Analysis by gas chromatography showed that the product contained 8.8% yield in monoallylpyrroles in the relative amounts of 16% 1-allylpyrrole, 70% 2-allylpyrrole, and 14% 3-allylpyrrole.

5. Reaction of Pyrryllithium with n-Propyl Tosylate in Benzene.

Exactly the same procedure as in (4) was followed. The product was found to contain the following relative amounts of mono-n-propylpyrroles, 19% 1-n-propylpyrrole, 74% 2-n-propylpyrrole, and 7.0% 3-n-propylpyrrole.

D. Reactions of Pyrrolmagnesium Bromide with Alkyl Tosylates.

1. Reaction of Pyrrolmagnesium Bromide with Allyl Tosylate in Ether.

A solution of 26.5 gms of ethyl bromide (0.22 mole) in 25 ml of dry ether was slowly added to 4.8 gms of magnesium (0.20 mole) covered with 50 ml of ether. The mixture was stirred at room temperature until all of the magnesium had reacted. Then, 13.4 gms (0.20 mole) of pyrrole in 25 ml of dry ether was added dropwise over a period of one hour and the reaction mixture was stirred at gentle reflux for one hour. It was then cooled to room temperature and diluted with 100 ml of dry ether. The reaction mixture was then cooled in an ice-water bath and 42.4 gms (0.20 mole) of allyl tosylate in 100 ml of dry ether was added dropwise over a period of one hour. After it had been stirred for twelve hours in an ice-water bath, the reaction mixture was left to warm up to room temperature and was stirred for a further ten hours. Then it was cooled again to 0° and a solution of 22 gms (0.41 mole) of ammonium chloride in 120 ml of water was slowly added. The layers were separated and the aqueous layer was extracted with ether. The ether extracts were added to the organic layer and the total was dried over anhydrous magnesium sulfate. The bulk of the solvent was then removed by flash distillation at the aspirator and the remaining material upon analysis by gas chromatography was found to contain 3.7 gms of monoallylpyrroles (17% yield) in the relative amounts of 76% 2-allylpyrrole, and 24% 3-allylpyrrole.



2. Reaction of Pyrrolylmagnesium Bromide with Allyl Tosylate in Tetrahydrofuran.

Exactly the same procedure as in (1) was followed. The product of this reaction contained 5.2 gms of monoallylpyrroles (24% yield) in the relative amounts of 89% 2-allylpyrrole and 11% 3-allylpyrrole.

3. Reaction of Pyrrolylmagnesium Bromide with n-Propyl Tosylate in Ether.

Exactly the same procedure as in (1) was followed. The product was found to contain the following relative percentages of mono-n-propylpyrroles, 5.0% 1-n-propylpyrrole, 77% 2-n-propylpyrrole, and 18% 3-n-propylpyrrole.

4. Reaction of Pyrrolylmagnesium Bromide with n-Propyl Tosylate in Tetrahydrofuran.

Exactly the same procedure as in (1) was followed. The product was analyzed by gas chromatography and was found to contain the following relative percentages of mono-n-propylpyrroles, 14% 1-n-propylpyrrole, 69% 2-n-propylpyrrole, and 17% 3-n-propylpyrrole.

III. Gas Chromatographic Analysis of the Products of the Reactions Studied.

A Perkin-Elmer Vapor Fractometer (Model 154) with a 275 cm column of copper tubing (internal diameter 0.4 cm), packed with Chromosorb W 60/80 containing 20% silicone and helium as the carrier gas was used throughout in this study. Conditions were as follows:

Temperature = 100°C., flow rate = 5.4 ml/sec. and Helium pressure = 25 psig.

Under these conditions the following retention times were observed.

<u>Compound</u>	<u>Time in minutes</u>
Pyrrole .....	5.5
1-Allylpyrrole .....	12
Bromobenzene .....	17
2-Allylpyrrole .....	20
3-Allylpyrrole .....	28

A 50-microliter Hamilton syringe was used to inject the samples and an Aristo type planimeter was used to measure the areas of the peaks in the gas chromatograms. Except for the reactions of n-propyl tosylate, the method of standard addition was employed to determine the composition of the reaction products. The internal standard used was bromobenzene because it satisfied most of the requirements of such a standard.<sup>48</sup> That is:

- a. It yielded a completely resolved peak (see chromatogram Fig. III).
- b. It was eluted close to the components to be determined (note retention times).
- c. It could be obtained in a high degree of purity (its chromatogram showed only one peak).

The method of standard addition involves<sup>48</sup>:

- a. Preparation of calibration curves for the components to be determined.
- b. Preparation of chromatograms of weighed samples of the reaction products containing a known percentage of the standard.

Calibration curves for the determination of 1-allylpyrrole and 2-allylpyrrole.

A series of 18 standard mixtures of known but varying composition of bromobenzene and the especially purified 1-allyl and 2-allylpyrroles were chromatographed. The ratio of the peak area of 1-allylpyrrole to the peak area of bromobenzene in the chromatograms of these mixtures was plotted against the corresponding ratio of the weight percent of 1-allylpyrrole to the weight percent of bromobenzene. A similar plot was made for 2-allylpyrrole (Table VI, Figs. I & II).

Determination of the percentages of 1-allylpyrrole and 2-allylpyrrole in the unknown samples.

The ratios of the peak areas of 1-allylpyrrole and 2-allylpyrrole to the peak area of the internal standard in the unknown samples were determined. From the peak area ratios and the calibration curves, (Figs. I & II), the ratios of the weight percent of 1-allylpyrrole and 2-allylpyrrole to the weight percent of the internal standard in the unknown samples were obtained. From these weight percent ratios and the known percentages of bromobenzene in the unknown samples, the percentages of 1-allyl and 2-allylpyrroles were determined. The percentage of 3-allylpyrrole was calculated from the calibration curve of 2-allylpyrrole by the same method. This introduced a slight error but could not be helped since 3-allylpyrrole could not be isolated pure.

In the case of the n-propylpyrroles, the samples were chromatographed and the peak areas of the 1-, 2-, and 3-n-propylpyrroles were added. Then the relative percentage of each was calculated.

TABLE VI

CALIBRATION CURVE DATA FOR 1-ALLYLPYRROLE AND 2-ALLYLPYRROLE

Standard sample	1-Allylpyrrole/standard		2-Allylpyrrole/standard	
	peak area ratio	weight percent ratio	peak area ratio	weight percent ratio
A	2.37	1.66	0.70	0.54
B	2.19	1.46	0.52	0.37
C	1.55	1.02	1.06	0.76
D	1.74	1.13	1.02	0.74
E	1.37	1.36	2.16	1.81
F	1.01	0.69	0.75	1.07
G	0.94	0.64	1.86	1.43
H	0.70	0.47	2.67	1.90
I	0.36	0.25	3.40	2.52
J	2.97	2.11	1.01	0.88
K	2.94	2.00	2.71	0.20
L	4.19	2.93	0.32	0.27
M	2.66	1.89	-----	-----
N	2.84	1.41	-----	-----
O	-----	-----	-----	-----
P	-----	-----	1.04	0.76
Q	1.30	0.88	1.73	1.28
R	1.58	1.06	3.75	3.05
			2.30	1.66

Fig. I

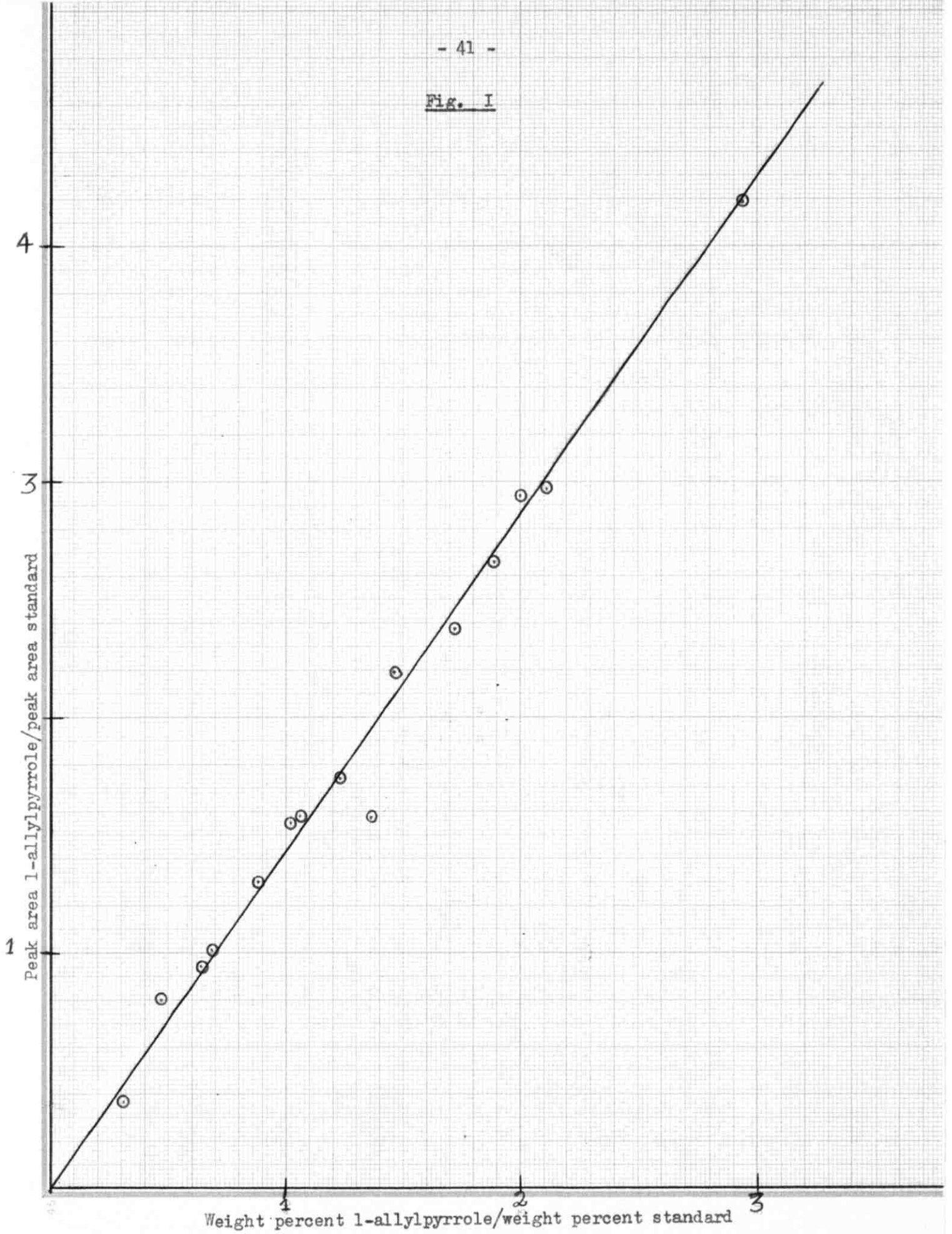
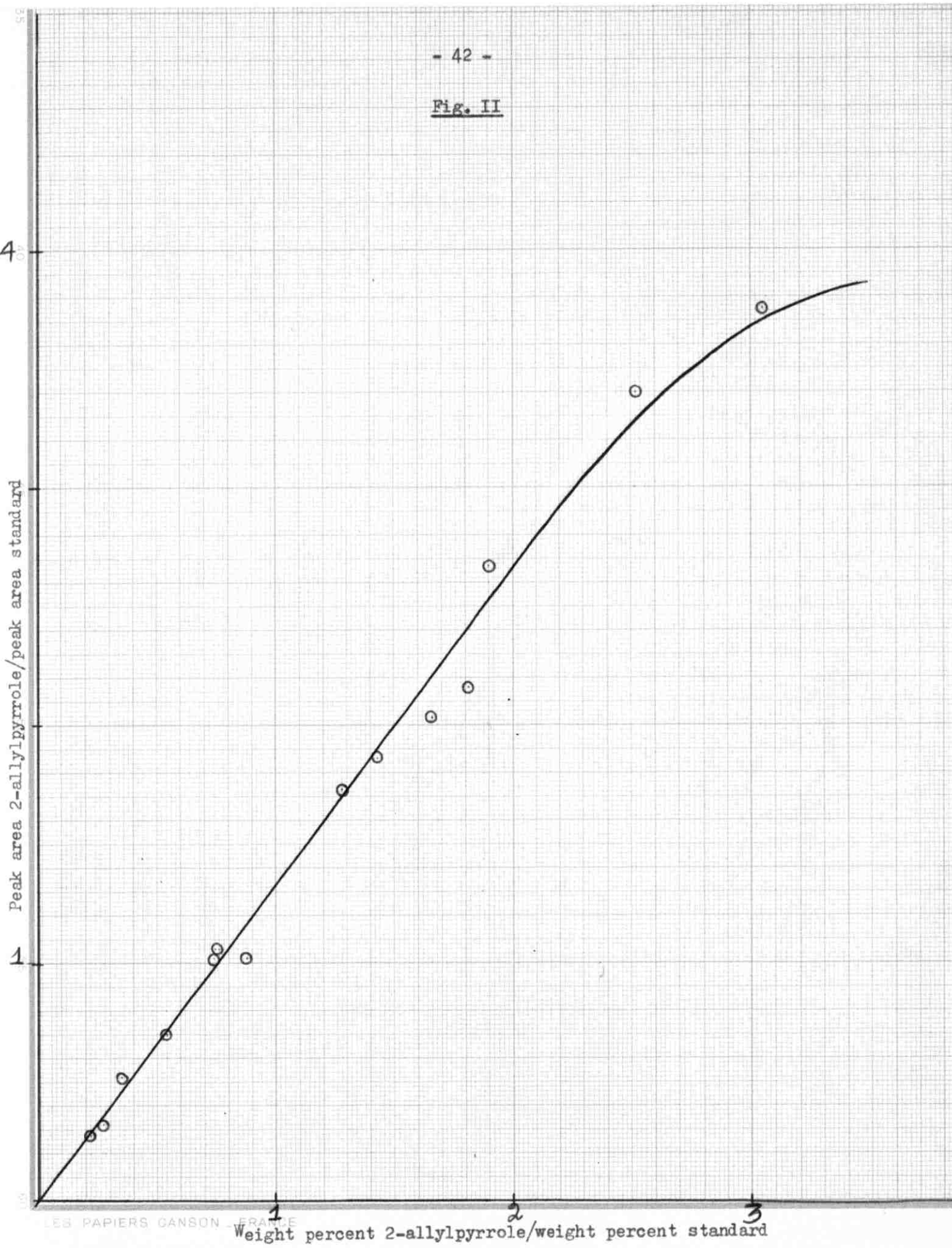


Fig. II





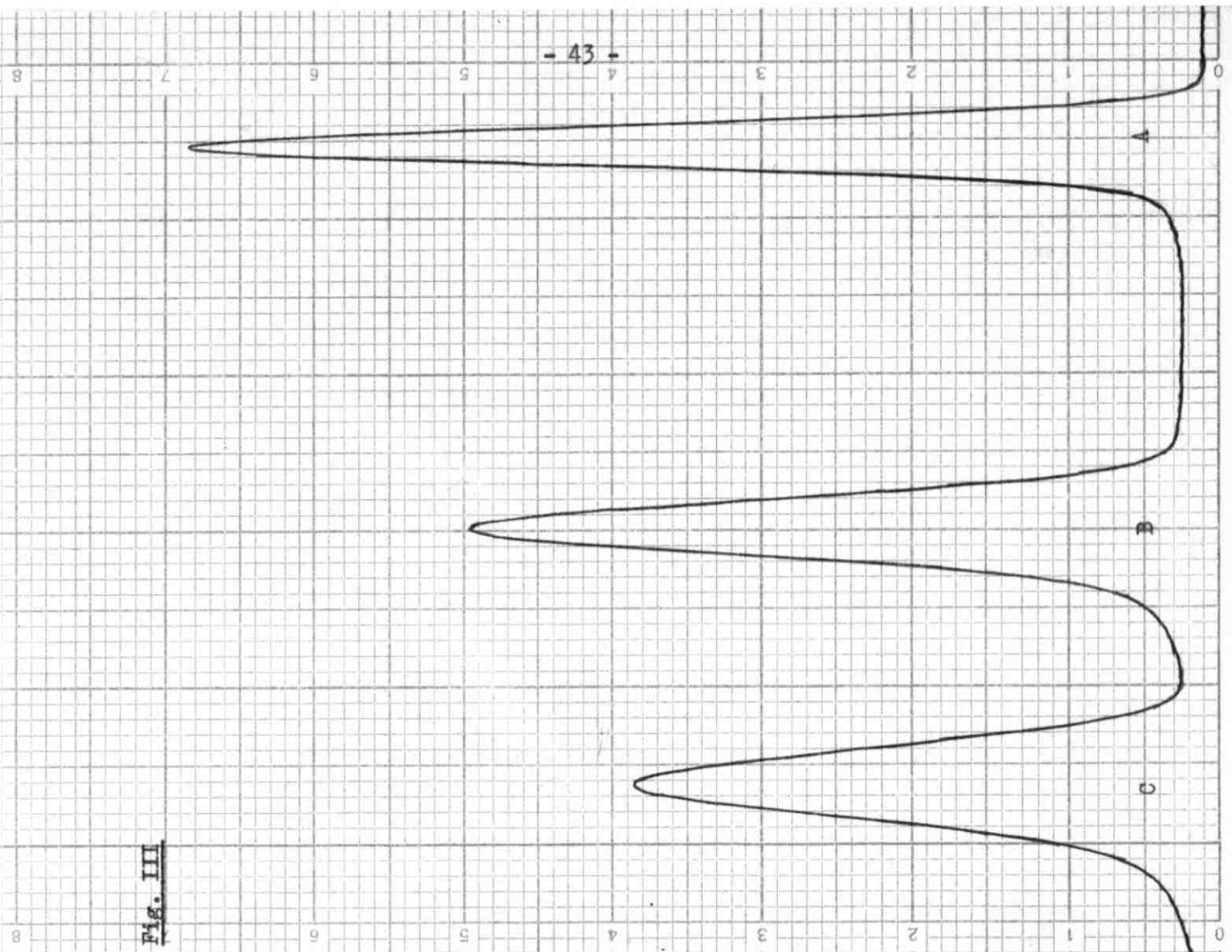


Fig. III

- A ..... 1-Allylpyrrole
- B ..... Bromobenzene
- C ..... 2-Allylpyrrole
- D ..... 3-Allylpyrrole

A

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