

were used to determine the pseudo-first-order specific rate constants. Duplicate experiments were carried out in each case.<sup>16</sup>

(16) The detailed kinetic data may be found in the Ph.D. thesis of G. R. Buell, University of Kansas, 1961.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS, LAWRENCE, KAN.]

## Factors Affecting the Position of Alkylation of Alkali Metal Salts of Pyrrole with Allylic Type Halides<sup>1</sup>

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The reaction of alkali-metal salts of pyrrole with allyl, crotyl and benzyl halides affords a mixture of the 1- and 2-substituted pyrroles, along with varying amounts of disubstituted pyrroles. It has been found that the product ratio of the two monosubstituted pyrrole isomers in each case is affected markedly by the nature of the medium and of the metal ion. In general, the percentage of alkylation at the nitrogen atom (1-position) increases with the solvating power of the medium and decreases with the coordinating ability of the metal ion. These effects are explained on the basis that dissociation of the pyrrol-metal ion pair favors nitrogen alkylation. It has been shown that disubstituted pyrroles arise only from 2-alkylated pyrroles by further alkylation.

### Introduction

The reaction of alkali metal salts of pyrrole with saturated alkyl halides, with few exceptions, has been reported to give nitrogen-substituted products.<sup>2-8</sup> Ciamician and Zanetti<sup>9</sup> reported that the reaction of pyrrolpotassium with an excess of refluxing methyl iodide gave only 1-methylpyrrole, but that increasing amounts of carbon-substituted product were formed when higher alkyl halides were used. For example, with an excess of refluxing amyl iodide, pyrrolpotassium afforded predominantly the carbon-substituted product,<sup>10</sup> a result which the authors attributed to the increase in reaction temperature brought about by substitution of amyl for methyl iodide. More recently, Cantor and VanderWerf<sup>11</sup> demonstrated that the reaction of pyrrolpotassium with allyl and with crotyl bromides in excess pyrrole-toluene gave preponderantly the corresponding 2-substituted pyrroles, a result more nearly to be expected for pyrrolmagnesium halides.<sup>4,12,13</sup> Treibs and Dietl<sup>14</sup> suggested that the position on the pyrrol anion resonance hybrid which makes the nucleophilic attack is determined by the ionic radius of the metal ion. Thus sodium and potassium salts (ionic radii of 0.98 for Na<sup>+</sup> and of 1.33 Å. for K<sup>+</sup>) of pyrrole form predominantly nitrogen-alkylated products, whereas lith-

ium and magnesium (each with an ionic radius of 0.78 Å.) salts give predominantly carbon-alkylated products. This suggestion is hardly adequate, however, to explain the varied behavior of pyrrol-metal salts in reaction with allylic halides.

Substitution reactions involving a number of other ambident ions have been rather thoroughly studied in recent years. Zagorevsky found that carbon substitution in metal  $\beta$ -naphtholates increased with increasing reactivity of the halide<sup>15</sup> and decreasing electropositive character of the metal<sup>16</sup> used. He observed that use of the tetramethylammonium salt strongly favored alkylation at the oxygen atom. Curtin, Crawford and Wilhelm<sup>17</sup> reported that in the reaction of alkali metal salts of phenols, carbon alkylation was increased, at the expense of oxygen alkylation, by use of the following: non-polar solvents, salts of less acidic phenols, higher salt concentrations, salts of less electropositive alkali metals and more reactive halides (allylic rather than saturated halides). These data were explained on the basis of an earlier suggestion of Ingold,<sup>18</sup> that factors which increase dissociation of the phenolic salt favor ether formation and factors which increase ion aggregate formation favor dienone formation.

Kornblum<sup>19</sup> has pointed out, however, that the position of alkylation of the phenolic salts may depend to a large extent upon the degree of homogeneity or heterogeneity of the reaction mixture, carbon substitution being favored by heterogeneous conditions and oxygen alkylation by homogeneous conditions. More recently, Kornblum's group<sup>20</sup> has demonstrated that in such strongly solvating solvents as water, phenol and fluorinated alcohols considerable carbon alkylation of phenolic salts

(1) This investigation was performed as a part of American Petroleum Institute Research Project 52 on "Nitrogen Constituents of Petroleum," which is conducted at the University of Kansas in Lawrence, Kan., and at the Bureau of Mines Experiment Stations in Laramie, Wyo., and Bartlesville, Okla.

(2) G. L. Ciamician and M. Dennstedt, *Ber.*, **15**, 2579 (1882).

(3) G. L. Ciamician and P. Silber, *ibid.*, **20**, 1368 (1887).

(4) K. Hess and F. Wissing, *ibid.*, **47**, 1416 (1914).

(5) B. Oddo, *ibid.*, **47**, 2427 (1914).

(6) P. Karrer and A. P. Smirnoff, *Helv. Chim. Acta*, **5**, 832 (1922).

(7) E. Ochiai, K. Tsuda and J. Yokoyama, *Ber.*, **68B**, 2291 (1935).

(8) N. D. Scott, U. S. Patent 2,488,336 (1949).

(9) G. L. Ciamician and C. M. Zanetti, *Ber.*, **22**, 659 (1889).

(10) C. M. Zanetti, *ibid.*, **22**, 2515 (1889).

(11) P. A. Cantor and C. A. VanderWerf, *J. Am. Chem. Soc.*, **80**, 970 (1958).

(12) K. Hess, *Ber.*, **46**, 3125 (1913).

(13) B. Oddo and R. Mameli, *Gazz. chim. ital.*, **43B**, 504 (1913).

(14) A. Treibs and A. Dietl, *Ann.*, **619**, 80 (1959).

(15) V. A. Zagorevsky, *J. Gen. Chem. (U.S.S.R.)*, **23**, 488 (1958).

(16) V. A. Zagorevsky, *ibid.*, **27**, 3055 (1957).

(17) D. Y. Curtin, R. J. Crawford and M. Wilhelm, *J. Am. Chem. Soc.*, **80**, 1391 (1958).

(18) C. K. Ingold, *Ann. Reports*, **23**, 142 (1926).

(19) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 705 (1959).

(20) N. Kornblum, P. J. Berrigan and W. J. le Noble, *ibid.*, **82**, 1257 (1960).

TABLE I  
REACTION OF PYRRYLMETAL SALTS WITH ALLYL AND CROTYL BROMIDES AND BENZYL CHLORIDE AT 65° UNDER HETEROGENEOUS CONDITIONS

Medium	Dielectric constant, D.	Cation	Halide	Yield, % 1- and 2-alkylpyrroles	Relative %, pyrrole 1-Alkyl- 2-Alkyl-
Tetrahydrofuran	7.4	K <sup>+</sup>	Allyl	75	81 19
Tetrahydrofuran	7.4	K <sup>+</sup>	Crotyl	43	79 21
Tetrahydrofuran	7.4	(CH <sub>3</sub> ) <sub>3</sub> NC <sub>6</sub> H <sub>5</sub> <sup>+</sup>	Allyl	4	96 4
Tetrahydrofuran	7.4	(CH <sub>3</sub> ) <sub>3</sub> NC <sub>6</sub> H <sub>5</sub> <sup>+</sup>	Benzyl	92	99.5 0.5
Dioxane	2.2	K <sup>+</sup>	Allyl	66	71 29
Dioxane	2.2	K <sup>+</sup>	Crotyl	48	68 32
Dioxane	2.2	K <sup>+</sup>	Benzyl	90	99.1 0.9
Benzene	2.2	K <sup>+</sup>	Allyl	60	15 85
Diisopropyl ether	3.9	K <sup>+</sup>	Allyl	55	21 79
Diisopropyl ether	3.9	K <sup>+</sup>	Crotyl	48	19 81
Diisopropyl ether	3.9	K <sup>+</sup>	Benzyl	40	65.0 35.0
Toluene	2.4	K <sup>+</sup>	Allyl	60	14 86
Toluene	2.4	K <sup>+</sup>	Crotyl	51	13 87
Toluene	2.4	Na <sup>+</sup>	Allyl	27	5 95
Toluene	2.4	Li <sup>+</sup>	Allyl	14	1 99
Toluene	2.4	(CH <sub>3</sub> ) <sub>3</sub> NC <sub>6</sub> H <sub>5</sub> <sup>+</sup>	Allyl	13	23 77
Toluene	2.4	K <sup>+</sup>	Benzyl	39	55.0 45.0
Toluene	2.4	(CH <sub>3</sub> ) <sub>3</sub> NC <sub>6</sub> H <sub>5</sub> <sup>+</sup>	Benzyl	44	92.0 8.0
Cyclohexane	2.0	K <sup>+</sup>	Allyl	54	13 87
Methylcyclohexane	..	K <sup>+</sup>	Allyl	53	13 87
n-Heptane	1.9	K <sup>+</sup>	Crotyl	51	14 86
Dimethoxyethane	..	K <sup>+</sup>	Allyl	67	81 19

occurs, apparently because the availability of the oxygen in phenoxide ion for nucleophilic displacement is greatly reduced by solvation.

Zook and co-workers<sup>21</sup> have observed that for metallic enolates both the rate of alkylation and the percentage of alkylation at oxygen are greatly increased in solvents, such as monoglyme and diglyme, which solvate the metallic ions. Further, a marked increase in the rates of alkylation of butyrophenone anion was observed as the accompanying cation was varied from lithium to potassium.<sup>22</sup> Zaugg and co-workers<sup>23</sup> ascribe the striking increase in the rate of alkylation of sodiomalonic esters with alkyl halides brought about by the addition of small amounts of such polar additives as certain N,N-disubstituted amides and several coordinate covalent N-, P- and S-oxides to the specific ability of these additives to solvate sodium ion. In their new method for the synthesis of  $\gamma$ -keto acids by the displacement reaction between metallic salts of ketones and metallic salts of  $\alpha$ -halo acids, Puterbaugh and Readshaw<sup>24</sup> found that the reaction succeeded best when lithium was the cation, was much poorer with sodium and failed completely with potassium. They explain the superiority of lithium ion on the basis of its ready coordination with the ketone carbanion and with an oxygen of the halo acid to favor the ring mechanism which may facilitate the displacement.

Quite recently Scherf and Brown<sup>25</sup> have shown that in the solvents 1,2-dimethoxyethane (DME), 1,2-diethoxyethane (DEE), tetrahydrofuran (THF)

and dioxane, potassium reacts much more readily with fluorene than does sodium or lithium and that the order of the effectiveness of the ether is DME > DEE  $\approx$  THF > dioxane. The authors explain their results in terms of the electropositivities and sizes of the metals and the structures of the ethers.

Forsblad<sup>26</sup> has shown that the reaction between methyl iodide and the lithium-, sodium-, potassium- and bispiperidinium salts of  $\beta$ -hydroxycoumarilic acid ethyl ester is strictly second order. The varying reaction velocities obtained with different cations depend both on the relative degree of dissociation and on the different velocities of ion-pair reaction. Both increase as the radius of the cation increases, but the ion reaction is more significant in dilute solution, and the ion-pair reaction in concentrated solution.

Barnes and Schmid<sup>27</sup> found, as did Kornblum,<sup>20</sup> that highly polar hydroxylic solvents increase carbon alkylation in the reaction of sodium phenoxide with allyl bromide.

The present paper reports studies on the effect of the medium and of the nature of the cation upon the position of alkylation of pyrrol alkali metal salts in reaction with allyl bromide, crotyl bromide and benzyl chloride.

## Results

Alkali metal salts of pyrrole react with allyl, crotyl and benzyl halides to form a mixture of 1-alkylpyrrole and 2-alkylpyrrole, and varying amounts of dialkylated pyrroles. The allyl- and crotylpyrroles, as well as 1-benzylpyrrole, are known compounds. The structure of 2-benzylpyrrole, a new compound, was proved by comparison of its reduction product, 2-(cyclohexylmethyl)-pyrrolidine, with an authentic sample of 2-(cyclo-

(21) H. D. Zook and T. J. Russo, *J. Am. Chem. Soc.*, **82**, 1258 (1960).

(22) H. D. Zook and W. L. Gumby, *ibid.*, **82**, 1386 (1960).

(23) H. E. Zaugg, B. W. Horion and S. Borgwardt, *ibid.*, **82**, 2895 (1960).

(24) W. H. Puterbaugh and R. L. Readshaw, *ibid.*, **82**, 3635 (1960).

(25) G. W. H. Scherf and R. K. Brown, *Can. J. Chem.*, **38**, 2450 (1960).

(26) I. Forsblad, *Arkiv. Kemi*, **15**, 403 (1960).

(27) R. Barnes and H. Schmid, *Helv. Chim. Acta*, **43**, 1393 (1960).

hexylmethyl)-pyrrolidine prepared by reduction of the known 2-benzyl-1-pyrroline. Trace amounts of 3-alkylpyrroles were indicated in certain of the product mixtures which contained relatively large amounts of the 2-substituted isomers. The reactions with crotyl bromide gave the crotyl, rather than rearranged, products (see ref. 11).

A summary of the results of the reaction of pyrrolylmetal salts with allyl and crotyl bromides and with benzyl chloride in a variety of media under heterogeneous conditions is given in Table I.

The effect of the addition of an equivalent amount of tetrabutylammonium bromide to the reaction mixtures of pyrrolylpotassium with allyl bromide and crotyl bromide is shown in Table II.

TABLE II

EFFECT OF TETRABUTYLAMMONIUM BROMIDE (TBAB) OR TETRABUTYLAMMONIUM IODIDE (TBAI) ON REACTION OF PYRROLYLPOTASSIUM WITH ALLYL BROMIDE AND WITH CROTYL BROMIDE UNDER HETEROGENEOUS CONDITIONS

Medium	Bromide	Temp., °C.	Yield, % of 1- and 2-alkylpyrroles	Relative % 1-alkylpyrrole	Relative % 2-alkylpyrrole
Ethyl ether	Crotyl	37	25	28	72
Ethyl ether + TBAB	Crotyl	37	48	59	41
Ethyl ether	Allyl	37	53	17	83
Ethyl ether + TBAI	Allyl	37	50	67	33
Toluene	Allyl	65	60	14	86
Toluene + TBAI	Allyl	65	46	65	35

The solubilities in several solvents of some of the salts of pyrrole employed in this study are listed in Table III.

TABLE III

SOLUBILITIES OF SALTS OF PYRROLE IN TYPICAL SOLVENTS AT 65°

Salt	Solvent	Solubility, mg./100 ml. solvent
Pyrrolylpotassium	Toluene	29
Pyrrolylpotassium	Diisopropyl ether	43
Pyrrolylpotassium	Dioxane	60
Pyrrolylpotassium	Tetrahydrofuran	120
Pyrrolysodium	Toluene	30
Pyrrolylithium	Toluene	16
Pyrrolylithium	Tetrahydrofuran	4070
Pyrrolyltrimethylphenylammonium	Toluene	5

Results for the reaction of salts of pyrrole with allyl bromide and with benzyl chloride in a variety of solvents under completely homogeneous conditions are summarized in Table IV.

In all cases studied, an increase in reaction temperature brought about a slight increase in the relative percentage of 2-alkylation and favored further alkylation with the production of disubstituted pyrroles.

In an attempt to trace the origin of the dialkylated products formed in variable amounts in all reactions which produced relatively large percentages of 2-alkylpyrrole, the reaction of 0.20 mole each of pyrrolylpotassium and allyl bromide in 300 ml. of toluene and the reaction of 0.40 mole

TABLE IV

REACTION OF SALTS OF PYRROLE WITH ALLYL BROMIDE AND BENZYL CHLORIDE AT 65° UNDER HOMOGENEOUS CONDITIONS

Cation	Halide	Yield of 1- and 2-alkylpyrroles, %	Relative % 1-alkylpyrrole	Relative % 2-alkylpyrrole
Solvent, dimethylsulfoxide				
K <sup>+</sup>	Allyl	47	92.2	7.8
Na <sup>+</sup>	Allyl	43	79.1	20.9
Li <sup>+</sup>	Allyl	47	56.3	43.7
K <sup>+</sup>	Benzyl	80	100	0
Na <sup>+</sup>	Benzyl	72	100	0
Li <sup>+</sup>	Benzyl	56	99.0	1.0
Solvent, dimethylformamide				
K <sup>+</sup>	Allyl	49	91.3	8.7
Na <sup>+</sup>	Allyl	43	66.6	33.4
Li <sup>+</sup>	Allyl	49	54.3	45.7
Li <sup>+</sup>	Benzyl	37	98.6	1.4
Solvent, tetrahydrofuran				
K <sup>+</sup>	Allyl	54	83.1	16.9
Na <sup>+</sup>	Allyl	50	19.9	80.1
Na <sup>+</sup> <sup>a</sup>	Allyl	56	38.7	61.3
K <sup>+</sup>	Benzyl	76	99.7	0.3
Na <sup>+</sup>	Benzyl	70	84.3	15.7
Na <sup>+</sup> <sup>a</sup>	Benzyl	73	91.5	8.5
Li <sup>+</sup>	Benzyl	35	19.2	80.8
Solvent, toluene				
K <sup>+</sup>	Allyl	44	84.0	16.0
Na <sup>+</sup>	Allyl	42	80.2	19.8
Li <sup>+</sup>	Allyl	40	62.3	37.7
(CH <sub>3</sub> ) <sub>3</sub> NC <sub>6</sub> H <sub>5</sub> <sup>+</sup>	Benzyl	46	99.1	0.9
K <sup>+</sup>	Benzyl	44	83.2	16.8
Na <sup>+</sup>	Benzyl	45	58.2	41.8
Li <sup>+</sup>	Benzyl	40	56.5	43.5

<sup>a</sup> Carried out under reverse addition, i.e., with very slow addition of a saturated solution of pyrrolysodium in THF to a solution of the halide in THF.

each of pyrrolylpotassium and benzyl chloride in 600 ml. of toluene, both at 85°, were studied. The choices of toluene as the medium and of the higher temperature were both calculated to favor the formation of relatively large amounts of disubstituted products. These reactions were carried out (1) in the absence of added alkylpyrrole (reference), (2) in the presence of 0.10 mole of 1-allylpyrrole or 0.082 mole of 1-benzylpyrrole and (3) in the presence of 0.10 mole of 2-allylpyrrole or 12.4 g. (0.079 mole) of 2-benzylpyrrole. Hypothetical compositions for the reactions run in the presence of the added monoalkylpyrroles were calculated from the data for the reference reactions, based on the assumption that the added monoalkylpyrroles were not further alkylated. The averaged experimental results, together with the hypothetical calculated values, are listed in Table V.

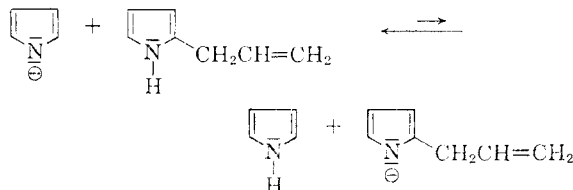
When 1-allyl- or 1-benzylpyrrole was added, the product compositions agreed with the calculated values within experimental error. When either 2-allylpyrrole or 2-benzylpyrrole was added, however, the product mixture in each case contained considerably less than the hypothetical calculated amount of 2-alkylpyrrole and more of the disubstituted pyrroles. This suggests that disubstituted

TABLE V  
EFFECT OF ADDED MONOALKYLPYRROLE ON PRODUCT RATIOS  
IN PYRROLE ALKYLATION

Halide	Reaction, compd. added	Composition of pyrrole product (mole %)		
		1-Alkyl-	2-Alkyl-	Di-alkyl-
Allyl bromide		10.1	65.1	24.8
Allyl bromide	1-Allylpyrrole (found)	57.7	31.0	11.3
Allyl bromide	(calcd.)	55.0	32.6	12.4
Allyl bromide	2-Allylpyrrole (found)	4.0	73.7	22.3
Allyl bromide	(calcd.)	5.0	82.6	12.4
Benzyl chloride		40.3	37.5	22.2
Benzyl chloride	1-Benzylpyrrole (found)	52.6	28.2	19.2
Benzyl chloride	(calcd.)	53.5	29.2	17.3
Benzyl chloride	2-Benzylpyrrole (found)	37.8	38.4	23.8
Benzyl chloride	(calcd.)	31.6	5.10	17.4

pyrroles arise only from 2-alkylpyrroles through further alkylation and, therefore, that, for the results reported in earlier tables, wherever high values for 2-alkylpyrrole percentages appear these values should actually be increased somewhat further to correct for the 2-alkylpyrrole lost through further alkylation to disubstituted products.

It was found, also, that no reaction took place when pyrrolpotassium was heated at 65° in toluene or dioxane with a known amount of 1-allylpyrrole. Under the same conditions, however, the pyrrol ion from pyrrolpotassium underwent partial proton exchange with 2-allylpyrrole to form a small amount of pyrrole, with an equivalent decrease in the amount of 2-allylpyrrole. The fact that this proton transfer was almost completely prevented by the addition of pyrrole to the reaction mixture suggests that the equilibrium point for the reversible protolysis lies far to the left. This con-



clusion is supported by the experimental fact that only traces of disubstituted products are formed when the reaction of pyrrolpotassium with allyl bromide is run in a large excess of pyrrole as the solvent, and would be predicted theoretically on the basis that the electron-releasing allyl group would serve to de-stabilize the 2-allylpyrrol ion relative to the unsubstituted pyrrol ion. Further, when the potassium salt of 2-allylpyrrole or 2-propylpyrrole was treated with an equimolar amount of pyrrole, 80 to 84% of the pyrrole was converted to the pyrrol ion, with the release of an equivalent amount of free 2-allylpyrrole or 2-propylpyrrole.

### Discussion

It is noteworthy that both in solution and under heterogeneous conditions, the nature both of the medium and of the cation exerts a profound influence on the relative amounts of 1- and 2-substituted products formed in the alkylation of alkali metal salts of pyrrole with allyl, crotyl and benzyl halides. From a study of the data in Tables I-V, these salient generalizations emerge: (1) For a given metal salt, both under heterogeneous

conditions (Table I) and in solution (Table IV), the most polar solvents give the highest percentage of 1-alkylation and the least polar solvents, the lowest percentage of 1-alkylation. The correspondence between dielectric constant of the medium and relative percentage of 1-alkylation is by no means exact, however.

(2) For a given medium, both under heterogeneous conditions (Table I) and in solution (Table IV), the relative percentage of 1-alkylation increases with decreasing coordinating ability of the cation in the order  $\text{Li}^+ < \text{Na}^+ < \text{K}^+ < (\text{CH}_3)_3\text{NC}_6\text{H}_5^+$ .

(3) For pyrrolpotassium (the only salt for which the study was made), at least, both under heterogeneous conditions (Table I) and in solution (Table IV), the relative percentage of 1-alkylation increases with increasing solubility of the salt in the medium (see Table III).

(4) For a series of salts in a given medium, both under heterogeneous conditions (Table I) and in solution (Table IV), the relative percentage of 1-alkylation tends to increase with decreasing solubility of the salt in the medium (see Table III), or, for homogeneous reactions, with decreasing concentration of the pyrrole salt in the reaction medium (see results in Table IV for reactions carried out under reverse addition).

(5) Addition of tetrabutylammonium bromide to any reaction mixture increases the relative percentage of 1-alkylation.

The fact that the nature of the medium exerts a profound influence on the position of alkylation of alkali metal salts of pyrrole with allyl, crotyl and benzyl halides both in heterogeneous reaction mixtures and in homogeneous solutions suggests that in every case the actual reaction is predominantly homogeneous. The fact that, for a given medium, the percentage of 1-alkylation increases with decreasing coordinating ability of the cation indicates, however, not only that the exact nature of the reacting species in solution is crucial in determining the position of alkylation, but also that dissociation of the alkali metal salt favors 1-alkylation and association, 2-alkylation.

It has been established<sup>28</sup> that even strong electrolytes are associated into ion pairs or higher aggregates in organic solvents such as benzene. Zook and Gumby<sup>22</sup> have emphasized the importance of coordination of reagent with alkali metal ion in its effect on the rate of alkylation of enolates. By analogy, it seems certain that in non-polar organic solvents the alkali metal salts of pyrrole are highly associated through coordination of the nitrogen in the pyrrol ion, the degree of association decreasing in the order  $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > (\text{CH}_3)_3\text{NC}_6\text{H}_5^+$ . Similarly, for a given alkali metal salt of pyrrole in a series of different solvents the degree of dissociation, and therefore the solubility of the salt, would increase with the specific ability of the medium to solvate the alkali metal ion, so that in such strongly solvating solvents as dimethyl sulfoxide and dimethylformamide, the salts are both highly dissociated and relatively soluble. On the other hand, for a given

(28) C. A. Kraus, *J. Phys. Chem.*, **60**, 129 (1956).

organic solvent, a change from a more to a less covalent salt would be expected to result in an increase in the degree of dissociation together with a decrease in solubility.

On this basis, we postulate that the homogeneous alkylation of the alkali metal salts of pyrrole with allyl, crotyl and benzyl halides can proceed by either of two mechanisms, as diagrammed in Fig. 1.

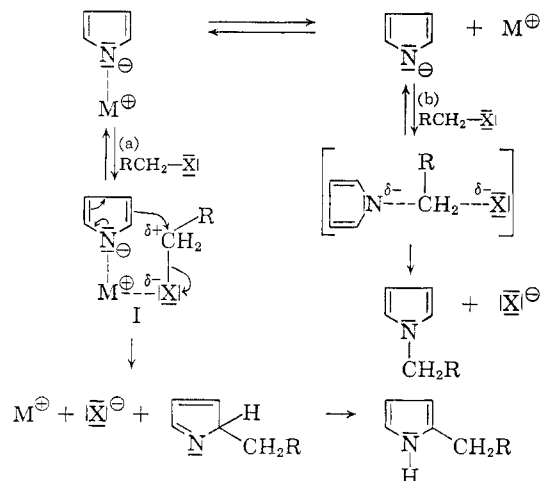


Fig. 1.—Alternative mechanisms for homogeneous alkylation of alkali metal salts of pyrrole with allylic type halides.

The first (a) of these mechanisms involves the reaction of the pyrrole ion-metal ion coordinated complex to produce the 2-alkylated product and the second (b) of the dissociated pyrrole ion to form the 1-alkylated product. Transition state I for 2-alkylation provides for mutual stabilization of the charges on the departing cation and halide ion, an important consideration in solvents of low solvating power.

This interpretation accounts for the increase, in any given medium, of 1-alkylation with a decrease in the coordinating ability of the metal ion. The effect of the addition of tetrabutylammonium bromide ion in increasing the percentage of 1-alkylation is explained simply by the assumption that there is a partial exchange of tetrabutylammonium ion for alkali metal ion in the pyrrole salt. Also, if it may be assumed that, for a given salt, the relative solubilities of the salt in a series of media parallel the specific solvating abilities of the various media toward the cation of the salt, this interpretation explains why, for a given salt in a series of media, the percentage of 1-alkylation increases with the solubility of the salt in the medium. We have observed, also, in a qualitative way that for any given salt both the relative rates of salt formation and the rates of the reaction of salt with allyl halides tend consistently to parallel the relative solubilities of the salts in the various media employed.

The fact that for a given reaction in a given medium the percentage of 1-alkylation is considerably less when the reaction mixture is heterogeneous rather than a homogeneous solution suggests that under the former condition appreciable heterogeneous reaction, which would be expected to result in 2-alkylation,<sup>19</sup> may occur. An alternative

explanation, however, is that dilution favors dissociation of the pyrrole salt, for under heterogeneous conditions the reacting solution is probably at all times essentially saturated with respect to pyrrole salt. If the reaction is carried out in solution, however, the actual concentration of pyrrole salt decreases steadily as the reaction proceeds. This explanation would also explain the fact that, for a given reaction, optimum percentages of 1-substituted product are observed when a solution of the pyrrole salt is added slowly to a solution of the alkyl halide (see results for the inverse addition reaction in Table IV), for under these conditions the concentration of pyrrole salt, and therefore the degree of association, is consistently at a minimum. This observation is important from the standpoint of synthetic organic chemistry in that it prescribes clearly the experimental condition which leads to the synthesis of 2-alkylpyrrole derivatives.

The fact that, for a series of salts in a given medium under heterogeneous conditions, the relative percentage of 1-alkylation tends to decrease with increasing solubility of the salt in the medium, *i.e.*, with increasing covalent character of the salt and with increasing concentration of the salt in the reaction solution, certainly suggests that it is the state of the pyrrole salt in solution, rather than just whether the reaction mixture is heterogeneous or homogeneous, that largely determines the preferred position of alkylation.

The relatively low solubility, compared with that of each of the other salts, of pyrrolithium in toluene, and the relatively high percentage of 1-alkylation of pyrrolithium in toluene, compared to that in other solvents, under homogeneous conditions is surprising and at the present time remains unexplained. The data suggest, however, that under heterogeneous conditions for the particular case of pyrrolithium in toluene, considerable heterogeneous alkylation may occur.

The proposed alternative mechanisms for pyrrole alkylation also offer a clue as to why pyrrole salts of alkali metals are alkylated extensively at the 2-position by allyl type halides, but not by saturated primary halides. Increased polarization of the carbon-halogen bond in allyl type halides over that in saturated alkyl halides would be expected to favor formation of transition state I for alkylation at the 2-position. The postulated transition state I also provides an obvious reason for the marked preponderance of 2- over 3-alkylation, although here the molecular orbital treatment<sup>29</sup> also provides a satisfactory explanation for the observed results.

It is known that benzyl chloride reacts with dimethyl sulfoxide<sup>30</sup> and also with dimethylformamide,<sup>31</sup> and presumably allyl and crotyl bromide react similarly. For this reason the yields of alkylpyrroles in these solvents were in most cases low, but the relative percentages of 1- and 2-alkylated products were nevertheless those expected for strongly solvating media.

(29) R. D. Brown and A. W. Collier, *Austral. J. Chem.*, **12**, 152 (1959).

(30) H. R. Nace and J. J. Monagle, *J. Org. Chem.*, **24**, 1792 (1959).

(31) G. M. Coppinger, *J. Am. Chem. Soc.*, **76**, 1372 (1954).

That 2-alkylation is favored over 1-alkylation by an increase in temperature is consistent with the postulation that ion aggregates react to form 2-substituted products, and relatively dissociated ions, to form 1-substituted products. A reaction involving relatively non-reactive ion aggregates<sup>32</sup> would possess a higher energy of activation than the corresponding reaction for free ionic species and hence would be favored by an increase in reaction temperature.

We propose that further alkylation of 2-substituted pyrroles is made possible by alkylation of the 2-alkylpyrryl ion



formed by partial proton exchange between 2-alkylpyrroles and simple pyrryl ion. Failure of 1-alkylpyrroles to undergo such proton exchange with pyrryl ion precludes the possibility of alkylation under the reaction conditions employed in these studies.

### Experimental

**Reagents.**—Pyrrole<sup>33</sup> was dried over sodium hydroxide pellets, purified by fractional distillation, b.p. 128.5–129.0° (740 mm.), and stored under nitrogen. Allyl bromide (Eastman Kodak Co. white label) was dried over magnesium sulfate, purified by fractional distillation, b.p. 68–70° (740 mm.), and stored over magnesium sulfate. Crotyl bromide was dried over a mixture of anhydrous magnesium sulfate and calcium carbonate and was purified by very careful fractional distillation through an all-glass Todd column; b.p. 103–105° (740 mm.),  $n_D^{20}$  1.4792.

Reagent grade benzyl chloride and benzyl bromide were dried over magnesium sulfate in the dark and were purified by fractional distillation, b.p. 71–72° (19 mm.) and 128° (80 mm.), respectively. Tetrahydrofuran was distilled from lithium aluminum hydride; b.p. 65° (740 mm.). Dioxane, diisopropyl ether, toluene, *n*-heptane, cyclohexane, methylcyclohexane and ethyl ether were dried over sodium wire and distilled. Dimethyl sulfoxide was distilled, b.p. 73–74° (10 mm.), immediately before use.

Polarographic grade tetrabutylammonium bromide and Eastman Kodak Co. white label trimethylphenylammonium chloride were used without further purification. Hydrogenation catalysts used were Baker No. 310 5% rhodium—alumina and platinum oxide.

**2-Benzylpyrrole.**—Ethylmagnesium bromide was prepared from 20 g. (0.82 mole) of magnesium and 108 g. (0.99 mole) of ethyl bromide in 280 ml. of dry ether in a nitrogen atmosphere. The reaction mixture was cooled to 0° and a solution of 58 g. (0.87 mole) of pyrrole in 60 ml. of ether was added dropwise over a period of 1 hour. The reaction proceeded rapidly with the evolution of ethane. To this solution at 0°, 102.9 g. (0.60 mole) of benzyl bromide in 100 ml. of ether was added dropwise over a 75-minute period. Stirring was continued at 0° for another 5 hours, and then 250 ml. of a 5% aqueous solution of ammonium chloride was added over a 1-hour period. The mixture was separated, the aqueous layer was extracted with ether and the combined extracts were dried over magnesium sulfate. The solvent was removed by distillation at reduced pressure and the dark oily residue was distilled to give 29.6 g. (31%) of crude product, b.p. 90–105° (1.3–1.5 mm.). The material was redistilled to give pure 2-benzylpyrrole, b.p. 85–89° (0.12–15 mm.),  $n_D^{20}$  1.5822,  $n_D^{25}$  1.5806.

*Anal.* Calcd. for  $C_{11}H_{11}N$ : C, 84.0; H, 7.05; N, 8.9. Found: C, 83.7; H, 7.12; N, 9.2.

Repeated fractional distillation of the monobenzylpyrrole fraction from the reaction of pyrrylpotassium and benzyl

chloride in toluene gave a liquid, b.p. 77–83° (0.3 mm.),  $n_D^{25}$  1.5803, whose infrared spectrum was identical with that of the 2-benzylpyrrole obtained by the reaction of pyrrylmagnesium bromide with benzyl bromide.

A mixture of 10 g. (0.064 mole) of this material, 2 g. of rhodium—alumina catalyst and 50 ml. of glacial acetic acid was shaken in a Parr low-pressure hydrogenation apparatus at a hydrogen pressure of 60 p.s.i. A total of 0.32 mole of hydrogen was taken up in 17 hours. The product was filtered, treated with 50 ml. of concentrated hydrochloric acid and evaporated nearly to dryness. Then 150 ml. of water was added and the mixture made basic with concentrated potassium hydroxide solution. The dark oil which separated was taken up in ether and the aqueous phase extracted with ether. The ether extracts, after drying over magnesium sulfate, were stripped of solvent, and the residue distilled to give a basic material, b.p. 124–127° (16 mm.),  $n_D^{20}$  1.4831.

The reduction of the product obtained from the reaction of pyrrylmagnesium bromide and benzyl bromide gave the same material, b.p. 127–128° (19 mm.),  $n_D^{20}$  1.4836; 2,4-dinitrophenyl derivative, m.p. 137.1–138.2°. The infrared spectra of these two reduction products were identical with that of 2-(cyclohexylmethyl)-pyrrolidine, and mixed melting points of the 2,4-dinitrophenyl derivatives showed no depression.

**2-(Cyclohexylmethyl)-pyrrolidine.**—A mixture of 9.3 g. (0.06 mole) of 2-benzyl-1-pyrroline, prepared by the method of Starr, Bulbrook and Hixon,<sup>34</sup> 60 ml. of glacial acetic acid and 2 g. of rhodium—alumina catalyst was shaken in a Parr low-pressure hydrogenation apparatus. The theoretical amount of hydrogen (0.25 mole) was taken up in 10 hours. The product, after filtration to remove the catalyst, was treated with 50 ml. of concentrated hydrochloric acid and then evaporated nearly to dryness. The residue was taken up in 150 ml. of water and the mixture made alkaline with sodium hydroxide solution. The dark brown oil which separated was taken up in ether, and the water solution extracted with ether. The combined extracts, after drying over magnesium sulfate, were stripped of solvent, and the resulting residue was distilled under reduced pressure to give 2-(cyclohexylmethyl)-pyrrolidine, b.p. 127–130° (19 mm.),  $n_D^{20}$  1.4821; picrate, m.p. 104.3–105.2°.

The 2,4-dinitrophenyl derivative melted at 137.1–138.3°.

*Anal.* Calcd. for  $C_{17}H_{23}N_3O_4$ : C, 61.3; H, 6.96; N, 12.6. Found: C, 61.5; H, 6.96; N, 12.4.

**Pyrryltrimethylphenylammonium.**—One liter of ammonia and 32.3 g. (0.83 mole) of finely divided potassium metal were added to a 2-l., three-necked flask which had a sintered-glass disk and stopcock sealed in the bottom. Pyrrole (56.1 g., 0.84 mole) was added dropwise over a period of 1 hour, at the end of which time the initial dark blue color of the metallic solution had completely disappeared, leaving a clear, colorless solution. To this, 144 g. (0.84 mole) of dry trimethylphenylammonium chloride was added in small portions. After stirring at reflux temperature for 2 hours, the liquid ammonia solution was filtered through the sintered-glass disk and stopcock into a 1-l., three-necked flask (nitrogen atmosphere), the ammonia being allowed to evaporate. An additional 1500 ml. of liquid ammonia was added to the upper flask, was stirred with the solid residue for 2 hours and was then filtered into the lower flask. This process was repeated. When most of the ammonia had evaporated from the lower flask, the flask and its contents were quickly transferred to a large vacuum desiccator containing phosphoric anhydride and were allowed to stand at 0.25 mm. for 1 week. At the end of this time the pale yellow completely free flowing pyrryltrimethylphenylammonium was used without further purification.

Titration of an aqueous solution of the product with hydrochloric acid indicated a molecular weight of 205; calculated for  $C_{18}H_{18}N_2$ , 202.

**Reaction of Pyrrylpotassium with Allyl Bromide (Heterogeneous).**—A total of 7.82 g. (0.200 mole) of potassium, freshly cut into small pieces under *n*-heptane, was added to a solution of 16.8 g. (0.250 mole) of pyrrole in 100 ml. of the solvent under a dry nitrogen atmosphere. The apparatus consisted of a 1-liter 3-necked flask fitted with a water-cooled spiral condenser, a sleeve-type stirrer and a

(32) C. C. Evans and S. Sugden, *J. Chem. Soc.*, 270 (1949).

(33) Supplied through the kindness of the Electrochemicals Division of the E. I. du Pont de Nemours and Co.

(34) D. F. Starr, H. Bulbrook and R. M. Hixon, *J. Am. Chem. Soc.*, **54**, 3971 (1932).

pressure-equalizing addition funnel. The mixture was heated with stirring at gentle reflux until all of the potassium had reacted and any blue color in the slurry had disappeared. A further 100 ml. of solvent was then added, the temperature was adjusted to 65°, and a solution of 24.2 g. (0.200 mole) of allyl bromide in 100 ml. of solvent was added dropwise over a period of 1 hour. The reaction mixture was stirred at 65° for an additional 8 hours, then cooled to room temperature and filtered. The solid material was washed with ether and the washings were added to the filtrate. The washed solid material was then dissolved in a small amount of water, the resulting aqueous mixture was extracted with ether and the ether extracts, after a drying treatment over anhydrous magnesium sulfate, were added to the original filtrate. The bulk of the solvents was removed by flash distillation at the aspirator and the only residue was weighed and analyzed by gas chromatography.

**Reaction of Pyrrolypotassium with Crotyl Bromide (Heterogeneous).**—A total of 7.8 g. (0.20 mole) of potassium metal, freshly cut into small pieces under *n*-heptane, was added to a solution of 16.8 g. (0.25 mole) of pyrrole in 100 ml. of solvent with stirring. The apparatus was flushed thoroughly with dry nitrogen for 1 hour before use and the reaction was conducted in a nitrogen atmosphere. The mixture was warmed until the potassium melted and then was stirred until all traces of potassium had disappeared. This required about 4 hours in dioxane and tetrahydrofuran and from 24 to 48 hours in the less polar solvents. Another 100 ml. of solvent was added to the slurry, the temperature was brought to 65° and a solution of 0.20 mole of the alkyl halide in 100 ml. of solvent was added dropwise over a period of 1 hour. The reaction mixture was stirred for an additional 8 hours at this temperature then cooled and filtered. The salt cake was washed with about 200 ml. of solvent and the combined filtrates were concentrated by removal of the solvent under reduced pressure. The crude product, dissolved in 100–150 ml. of *n*-heptane containing 0.2–0.3 g. of platinum oxide, was hydrogenated under a hydrogen pressure of 3 atmospheres in a Parr apparatus. The theoretical amount of hydrogen (0.20 mole) was absorbed in 30–60 minutes.

The crude reduction product was distilled in vacuum to give a mixture of monobutylpyrroles, b.p. 45–58° (10 mm.).

**Reaction of Pyrrolypotassium with Benzyl Chloride (Heterogeneous).**—Pyrrolypotassium, 0.40 mole, was prepared as previously described. To the slurry of pyrrolypotassium contained in 500 ml. of solvent and maintained at 65°, 50.6 g. (0.40 mole) of benzyl chloride dissolved in 100 ml. of solvent was added over a 1-hour period. The reaction mixture was stirred at 65° for an additional 8 hours, at the end of which time it was cooled, filtered and the salts washed with dry ether. The combined filtrates were stripped of solvent at the aspirator and the oily residue distilled in vacuum (nitrogen atmosphere) to give a mixture of monobenzylpyrroles, b.p. 80–93° (0.3 mm.). This monobenzylpyrrole fraction was subjected to quantitative infrared analysis without further treatment.

The residue, after the distillation of the monobenzylpyrroles from the product mixture of the reaction of pyrrolypotassium with benzyl chloride at 105° in toluene, was distilled to give a mixture of dibenzylpyrroles, b.p. 150–160° (0.35 mm.).

*Anal.* Calcd. for  $C_{12}H_{11}N$ : C, 87.4; H, 6.94; N, 5.7. Found: C, 87.4; H, 6.93; N, 5.4.

**Reaction of Pyrrolytrimethylphenylammonium with Benzyl Chloride in Toluene (Heterogeneous).**—A slurry of 9.99 g. (0.0480 mole) of pyrrolytrimethylphenylammonium in 60 ml. of toluene was stirred for 4 hours at 65°. To this mixture 6.13 g. (0.0480 mole) of benzyl chloride in 12 ml. of toluene was added over a period of 20 minutes. Stirring was continued at 65° for another 8 hours. The reaction mixture was then cooled to room temperature, filtered and the filtered salts washed with dry ether. The combined filtrates were stripped of solvent and the residue, placed in a small distilling flask, was maintained under a pressure of 0.4 mm. overnight. The residue, 2.8 g., was taken up in toluene and analyzed by vapor-phase chromatography.

**Reaction of Pyrrolylithium with Benzyl Chloride in Tetrahydrofuran (Heterogeneous).**—A mixture of 33.5 g. (0.50 mole) of pyrrole, 3.18 g. (0.40 mole) of lithium hydride and 100 ml. of tetrahydrofuran was heated to reflux with stirring until the evolution of hydrogen had ceased. An additional

400 ml. of solvent was added and the temperature was brought to 65°. Samples were withdrawn from this mixture for solubility determinations, leaving 0.39 mole of the salt in the reaction flask. To this mixture, maintained at 65°, a solution of 49.3 g. (0.39 mole) of benzyl chloride in 100 ml. of tetrahydrofuran was added over a period of 1 hour. The mixture was stirred at 65° for an additional 8 hours, then cooled and the solvent removed by distillation under reduced pressure. Water was added, the mixture was separated, and the aqueous layer extracted with ether. The dried ether solution was stripped of solvent and distilled at reduced pressure to afford the monobenzylpyrrole mixture, b.p. 60–95° (0.35 mm.), which was analyzed by quantitative infrared methods.

**Reaction of Pyrrolylithium with Benzyl Chloride in Tetrahydrofuran and Dimethylformamide (Homogeneous).**—Pyrrolylithium was prepared by gentle heating of a stirred mixture of 2.25 g. (0.281 mole) of lithium hydride, 23.5 g. (0.351 mole) of pyrrole and 150 ml. of solvent for 8 hours. An additional 400 ml. of solvent was added, and the temperature of the solution was brought to 65°. A solution of 35.6 g. (0.281 mole) of benzyl chloride in 46 ml. of solvent was added over a 1-hour period and the mixture was stirred for another 8 hours at 65°. The mixture was cooled and the bulk of the solvent removed at room temperature by evaporation under reduced pressure. Water was added and the layers were separated. The aqueous layer was extracted with ether and the combined organic phases, after drying over magnesium sulfate, were stripped of solvent. Distillation of the oily residue afforded a mixture of monobenzylpyrroles which was analyzed quantitatively by infrared methods.

**Reaction of Pyrrolysodium with Benzyl Chloride in Tetrahydrofuran (Homogeneous).** (a).—To a mixture of 4.6 g. (0.192 mole) of sodium hydride and 150 ml. of tetrahydrofuran, 16.1 g. (0.240 mole) of pyrrole was added slowly. The reaction was complete in 3 hours. An additional 228 ml. of tetrahydrofuran was added to this clear solution, the temperature brought to 65°, and 24.4 g. (0.192 mole) of benzyl chloride dissolved in 32 ml. of tetrahydrofuran was added dropwise over a period of 1 hour. The mixture was heated to 65° for another 8 hours, then cooled, filtered and the filtered salts washed with ether. The combined filtrates were stripped of solvent and the oily residue distilled to yield a mixture of monobenzylpyrroles, b.p. 62–83° (0.25–0.30 mm.).

(b).—A solution of 0.19 mole of pyrrolysodium in 150 ml. of tetrahydrofuran was prepared as described above. Then an additional 50 ml. of tetrahydrofuran was added, and the concentrated salt solution was filtered slowly through a fritted-glass funnel, closed to the atmosphere, into a solution of 24.4 g. (0.190 mole) of benzyl chloride in 260 ml. of tetrahydrofuran at 65°. The addition of the salt solution required 12 hours. The mixture was stirred at 65° for an additional 7 hours, then was cooled and filtered. The salt cake was washed with ether and the washings were combined with the original filtrate. The solvent was removed and the residue distilled under reduced pressure to afford a mixture of monobenzylpyrroles.

**Reaction of Pyrrolypotassium, Pyrrolysodium and Pyrrolylithium with Benzyl Chloride in Dimethyl Sulfoxide (Homogeneous).**—Pyrrolypotassium (0.192 mole) was prepared in 100 ml. of tetrahydrofuran as described for the heterogeneous reaction. When the preparation was complete, 240 ml. of dimethyl sulfoxide was added and the tetrahydrofuran was removed by distillation. To the resulting clear solution, maintained at 65°, 0.192 mole of benzyl chloride in 48 ml. of dimethyl sulfoxide was added over a 1-hour period. The reaction mixture was warmed at 65° for an additional 8 hours, then cooled and the bulk of the solvent removed by distillation at 40° (0.25–0.10 mm.). About 200 ml. of water was added, the organic layer was separated and the aqueous layer extracted with several 50-ml. portions of ether. The combined ether extracts and organic phase were stripped of solvent and the oily residue distilled to afford the monobenzylpyrrole mixtures, which were analyzed by quantitative infrared spectrophotometric methods.

The reactions of 0.192 mole of pyrrolysodium (from sodium hydride) in 378 ml. of dimethyl sulfoxide with 0.192 mole of benzyl chloride in 32 ml. of dimethyl sulfoxide, and of 0.281 mole of pyrrolylithium (from lithium hydride) in 550 ml. of dimethyl sulfoxide with 0.281 mole of benzyl chloride



in 46 ml. of dimethyl sulfoxide, were carried out in a similar manner.

**Reaction of Pyrrolpotassium, Pyrrolithium and Pyrrolsodium with Allyl Bromide in Dimethylformamide and Dimethyl Sulfoxide (Homogeneous).**—A mixture of 0.2 mole of the metal (7.8 g. of potassium) or the metal hydride (1.6 g. of lithium hydride, 4.8 g. of sodium hydride), 0.250 mole (16.8 g.) of pyrrole and 100 ml. of tetrahydrofuran was heated under dry nitrogen at 50–60° until completion of the reaction. Most of the tetrahydrofuran was then removed by distillation, 100 ml. of solvent (dimethylformamide or dimethyl sulfoxide) was added and the mixture was heated until all of the remaining tetrahydrofuran had distilled. More solvent was added (100 ml. of dimethylformamide in the case of potassium, 400 ml. of dimethylformamide in the cases of lithium and sodium, or 100 ml. of dimethyl sulfoxide in all cases), the temperature was brought to 65°, and 0.2 mole (24.2 g.) of allyl bromide dissolved in 100 ml. of solvent was added dropwise over a period of 1 hour at 65°. The mixture was stirred at 65° for 8 hours, then cooled to room temperature, filtered (in the cases of potassium and sodium in dimethylformamide and potassium in dimethyl sulfoxide), diluted with excess of water and extracted with a mixture of petroleum ether and diethyl ether. The extract was dried over magnesium sulfate, the solvent removed by distillation and the product distilled under reduced pressure.

**Reaction of Pyrrolithium and Pyrrolsodium with Allyl Bromide in Tetrahydrofuran (Homogeneous).** (a).—A mixture of 0.2 mole of the metal hydride (1.6 g. of lithium hydride, 4.8 g. of sodium hydride), 0.25 mole of pyrrole (16.8 g.) and 100 ml. of tetrahydrofuran was heated under dry nitrogen at 50–60° until completion of the reaction. The product was diluted with 400 ml. of tetrahydrofuran, the temperature brought to 65°, and 0.2 mole (24.2 g.) of allyl bromide dissolved in 100 ml. of tetrahydrofuran was added dropwise over a period of 1 hour at 65°. The mixture was stirred at 65° for 8 hours, then cooled to room temperature, filtered (in the case of the sodium salt), evaporated to a small volume, diluted with an excess of water and extracted with ether. After removal of the ether, the product was distilled under reduced pressure.

(b).—A solution of 0.2 mole of pyrrolsodium in 150 ml. of tetrahydrofuran was prepared as previously described and then added dropwise, over a 5-hour period, through a filtering layer of glass wool, into a solution of 24.2 g. (0.190 mole) of allyl bromide in 450 ml. of tetrahydrofuran at 65°. After the addition of the salt was complete, the mixture was stirred at 65° for an additional 6 hours, then was cooled and filtered. The solid was washed with ether and the washings added to the original filtrate. The solvents were then removed and the residue was distilled under reduced pressure.

**Reaction of Pyrrolsodium and Pyrrolithium with Allyl Bromide in Toluene (Homogeneous).**—Pyrrolsodium and pyrrolithium were prepared in a 2-l., three-necked flask equipped with a sintered-glass disk and a stopcock at the bottom, from 0.20 mole of the corresponding metal hydride and 0.25 mole of pyrrole in 100 ml. of tetrahydrofuran. After completion of the reaction, most of the tetrahydrofuran was removed by distillation, toluene was added, and the distillation was continued, with occasional addition of toluene, until the index of refraction of the distilling liquid was identical with that of toluene. Toluene (1500 ml.) was then added, the mixture was stirred at 65° overnight, and filtered through the sintered-glass disk into another 2-l., three-necked flask, with the help of slightly increased nitrogen pressure above the mixture being filtered or slight suction at the receiver. The temperature of the clear filtrate was brought to 65° and allyl bromide (0.3 g. in the case of sodium, 0.25 g. in the case of lithium—a considerable excess over the theoretical amount on the basis of the measured solubilities of the salts in toluene) dissolved in a small amount of toluene was added, and the mixture was stirred at 65° for 8 days. Toluene was then removed by distillation under reduced pressure. The residue was analyzed by vapor-phase chromatography.

**Reaction of Pyrrolsodium and Pyrrolithium with Benzyl Chloride in Toluene (Homogeneous).**—Pyrrolsodium was prepared by heating a mixture of 16.1 g. (0.240) of pyrrole, 4.60 g. (0.192 mole) of sodium hydride and 100 ml. of toluene at reflux temperature overnight. Pyrrolithium was prepared in a similar manner from 47.0 g. (0.700 mole)

of pyrrole and 4.50 g. (0.570 mole) of lithium hydride in 100 ml. of toluene. A 2-l., three-necked flask with a sintered-glass disk and stopcock sealed into the bottom was used for the preparation of the pyrrol salts. Each of the mixtures was filtered through the sintered-glass disk, and the filtrate was discarded. Toluene, 1500 ml., was then added to the flask and the mixture was stirred at 65° for 8 hours. The toluene was filtered into another 2-l., three-necked flask and the mixture stirred at 65° for about 8 hours. Benzyl chloride (0.64 g. in the case of the sodium salt, 0.42 g. in the case of the lithium salt) was added and the solution stirred at 65° for 7 days. The toluene was removed by distillation at reduced pressure and the residue transferred to a small distilling flask and maintained under vacuum (0.4 mm.) for about 10 hours to remove other volatile materials. The resulting oil was taken up in a minimum amount of toluene and analyzed by means of vapor-phase chromatography.

**Reaction of Pyrrolpotassium with Benzyl Chloride and with Allyl Bromide in Toluene (Homogeneous).**—Pyrrolpotassium was prepared in 0.192–0.200-mole quantities in 100 ml. of toluene as described for the heterogeneous reactions. When the reaction was complete, an additional 1400 ml. of toluene was added, the temperature was brought to 65° and the mixture stirred overnight. The mixture was filtered as before, and to the clear filtrate, maintained at 65°, was added either 1.0 g. of allyl bromide or 0.56 g. of benzyl chloride. The mixture was allowed to stir for 7 days, then was cooled and the toluene removed by distillation at reduced pressure. The product from the allyl bromide reaction was subjected to vapor-phase chromatographic analysis without further treatment. The product from the benzyl chloride reaction was placed in a small distilling flask and maintained under vacuum (0.4 mm.) overnight, then taken up in toluene and analyzed by vapor-phase chromatography.

**Reaction of Pyrrolpotassium with Benzyl Chloride and with Allyl Bromide in Tetrahydrofuran (Homogeneous).**—Pyrrolpotassium was prepared in 0.192–0.200-mole quantities in 100–150 ml. of tetrahydrofuran as described for the heterogeneous reaction. The volume of solvent was brought to 1500 ml. by the addition of tetrahydrofuran and the mixture heated overnight at 65°. By means of a sintered-glass disk and stopcock sealed into the bottom of the reaction flask, the mixture was filtered into an identically constructed flask. The filtrate was stirred at 65° overnight, and the resulting turbid mixture again filtered, this time through a sintered-glass funnel containing a mat of Filtercel. To this clear filtrate was added either 2.5 g. of allyl bromide or 2.2 g. of benzyl chloride, and the reaction was allowed to continue for either 8 or 6 days. In each case, the reaction mixture was worked up as described for the homogeneous reactions in toluene and the product analyzed by means of vapor-phase chromatography.

**Reaction of Pyrroltrimethylphenylammonium with Benzyl Chloride in Toluene (Homogeneous).**—A mixture of about 5 g. of pyrroltrimethylphenylammonium and 1500 ml. of toluene was stirred for 24 hours at 65°. The mixture then was filtered by means of a sintered-glass disk and stopcock sealed into the bottom of the flask, the filtrate heated to 65°, and 1.0 g. of benzyl chloride added. At the end of 1 week, the reaction mixture was cooled, freed of solvent and the residue placed in a small distilling flask under vacuum (0.4 mm.) for 12 hours. The resulting material was taken up in a small amount of toluene and analyzed by means of vapor-phase chromatography.

**Reaction of Pyrrolpotassium with Benzyl Chloride in Toluene in the Presence of Added Monobenzylpyrroles.**—The reference reaction of pyrrolpotassium with benzyl chloride (each 0.40 mole in a total of 600 ml. of toluene) was conducted exactly as described for the heterogeneous reaction except that it was run at 85°. The reaction mixture was worked up as before and the distilled product analyzed quantitatively by means of infrared.

This reaction was repeated twice: (1) in the presence of 12.4 g. (0.790 mole) of 2-benzylpyrrole; b.p. 91–93° (0.25 mm.),  $n_D^{20}$  1.5825; and (2) in the presence of 12.8 g. (0.820 mole) of pure 1-benzylpyrrole; b.p. 67–69° (0.20–0.25 mm.),  $n_D^{20}$  1.5682. Results are summarized in Table V.

**Reaction of Pyrrolpotassium with Allyl Bromide in Toluene in the Presence of Added Monoallylpyrroles.**—For the reference reaction, 0.10 mole of pyrrolpotassium, prepared



from 0.11 mole of pyrrole and 0.10 mole of potassium in 50 ml. of toluene, was diluted with 150 ml. of toluene and stirred at 85° for 4 hours. Then, 0.10 mole of allyl bromide, dissolved in 50 ml. of toluene, was added dropwise over 30 minutes and the mixture stirred at 65° for 4 hours. After removal of the toluene, the product was distilled under reduced pressure. This procedure was repeated twice, first in the presence of 0.10 mole of added 1-allylpyrrole and then in the presence of 0.10 mole of added 2-allylpyrrole.

By means of a small pipet fitted with a sintered glass plug, samples were withdrawn for vapor-phase chromatographic analysis (after the mixture had been cooled in an ice-bath), at the following stages: (1) before the addition of the mono-substituted pyrrole, (2) immediately after its addition, (3) before the addition of the allyl bromide and (4) at the end of the reaction. The distilled product was similarly analyzed. Results are reported in Table V.

**Reaction of Pyrrole with 2-Allylpyrrolpotassium.**—A slight excess of 2-allylpyrrole (0.0916 mole) was heated with 0.0900 mole of potassium in 50 ml. of toluene for 24 hours. The product was diluted with 150 ml. of toluene, 0.0900 mole of pyrrole was added and the mixture was stirred at 65° for 4 hours. Samples were withdrawn at various stages (after the mixture had been cooled in an ice-bath) for analysis.

**Reaction of Pyrrole with 2-Propylpyrrolpotassium.**—Potassium, 0.100 mole, was added to a solution of 0.125 mole of 2-propylpyrrole in 50 ml. of toluene, and the mixture was heated for 24 hours. The product was diluted with 150 ml. of toluene, and 0.100 mole of pyrrole was added. The mixture was stirred at 65° for 4 hours. Samples were withdrawn at various stages (after the mixture had been cooled in an ice-bath) for analysis.

**Reaction of Pyrrolpotassium with Allyl Bromide in Pyrrole (Homogeneous).**—Pyrrolpotassium (0.20 mole) was prepared in pyrrole by vigorous stirring of a mixture of 7.8 g. (0.20 mole) of potassium and 285 ml. of pyrrole, first at room temperature and then at 65°, until a clear solution was obtained. Next, 24.2 g. (0.200 mole) of allyl bromide was added dropwise and the resulting mixture was stirred at 65° for 8 hours. The mixture was cooled and filtered, the solvent removed, and the residue fractionated through a packed column under reduced pressure.

**Analysis of Reaction Products by Vapor-phase Chromatography.** (a) **Butylpyrroles.**—A Perkin-Elmer model 154 B vapor fractometer was used for the analysis of mixtures of isomeric butylpyrroles obtained by reduction of crotylpyrroles. The column was constructed of  $\frac{1}{4} \times 0.030$ -inch Revere Dryseal copper tubing. Acid-washed firebrick, 30–60 mesh, containing 35 weight per cent. Dow Silicone Oil No. 550 (packing density 0.3 g./in.) was used in the first 1.5 meters of the column, followed by 3 meters of 60–80 mesh acid-treated Celite containing 35 weight per cent. Nias Triol L.H.T. -42<sup>35</sup> (packing density 2 g./in.).

Operation of the instrument at 225°, at a pressure differential of 25 p.s.i. and at a flow rate of 73 ml. of He/min. at 28°, gave the following retention time data: *n*-heptane (solvent, 2.1 min.; pyrrole, 4.2 min.; 1-*n*-butylpyrrole, 6.5 min.; 2-*n*-butylpyrrole, 10.9 min.).

The instrument was calibrated with known mixtures of 1-butylpyrrole and 2-butylpyrrole in *n*-heptane (internal standard and solvent). The peak-height method of analysis was used.

Very minor peaks at 5.7, 8.8 and 13.0 minutes were tentatively identified as 1-*sec*-butylpyrrole, 2-*sec*-butylpyrrole and 3-butylpyrrole, respectively.

(35) Union Carbide polypropylene glycol.

(b) **Propylpyrroles.**—The instrument and column used were the same as for the butylpyrroles. At a temperature of 220°, a pressure differential of 27 p.s.i. and a flow rate of 82–83 ml. He/min., the following retention times were observed: *n*-heptane, 1.9 min.; pyrrole, 3.8 min., 1-propylpyrrole, 4.7 min.; 2-propylpyrrole, 7.6 min.

Standard solutions of 1-propylpyrrole and 2-propylpyrrole in *n*-heptane were used to calibrate the instrument. The peak-height method of analysis was used throughout, with *n*-heptane as the internal standard.

(c) **Allylpyrroles.**—An 8-foot column containing 15% monohydroxyethyltriethoxypropylethylenediamine on 40–60 mesh solid support (made by heating Tide detergent at 180–190° for 24 hours, extracting the residue with petroleum ether and sieving it) was used with the Perkin-Elmer vapor fractometer at 150° and 20 p.s.i. Also, a Beckman 6-ft. silicone oil column was employed with the Beckman GC-2 vapor-phase chromatograph, at 163° and 25 p.s.i. The analyses were made on the basis of peak-area measurements, by means of the internal normalization method.

(d) **Benzylpyrroles.**—The Beckman GC-2 vapor phase chromatograph was used. The 2.5 meter column, constructed of  $\frac{1}{4} \times 0.030$ -inch Revere Dryseal copper tube, was filled with 35 weight per cent. of Nias Triol L.H.T.-42 on 60–80 mesh acid-treated Celite (packing density 0.3 g./in.). At 240° and 25 p.s.i., the retention times were: toluene (solvent), 1.5 min.; 1-benzylpyrrole, 10.0 min.; 2-benzylpyrrole, 18.0 min.

Quantitative determinations were made on the basis of peak-area measurements by means of the internal normalization method. Results obtained by this method were found to agree with those obtained by infrared methods within 3%.

**Analysis of Benzylpyrroles by Infrared Spectrophotometric Methods.**—Analyses were made with a Perkin-Elmer model 21 infrared spectrophotometer in 0.025-mm. sodium chloride cells. Samples were placed in the cell with solvent. An empty cell was used as the reference cell. A calibration curve was established with known mixtures of the pure isomers, 1-benzylpyrrole and 2-benzylpyrrole. The nitrogen-hydrogen stretching peak at 3340 cm.<sup>-1</sup> was used for the determinations.

**Solubility Determinations.**—The pyrrol salts were prepared as described previously, and the volume of solvent adjusted so that the solvent to salt ratio was 1500 ml. of solvent to one mole of salt. For pyrroltrimethylphenylammonium, a saturated solution of the salt was prepared by addition of 5 g. of the dry salt to 1500 ml. of solvent. The mixtures were then heated to 65° and stirred for 5–10 hours. A small pipet, capacity 5.296 ml. at 65°, closed at the bottom end by a sintered-glass plug, was inserted into the contents of the flask, allowed to warm to 65°, and a sample of saturated solution, free of undissolved salt, was withdrawn. The pipet was quickly emptied into a beaker and rinsed with solvent. The sample, diluted with about 10 ml. of water and 20 ml. of ethyl alcohol, was titrated potentiometrically with standard hydrochloric acid. The volume of acid added was measured by means of an Aminco-Koegel Menisco-matic buret.

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