REACTIONS OF SOME METAL DERIVATIVES OF PYRROLE

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REACTIONS OF SOME METAL DERIVATIVES OF PYRROLE

by

© Nam-Chiang Wang B.Sc., M.Sc.

A Thesis submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

Department of Chemistry
Memorial University of Newfoundland
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St.John's Newfoundland

ABSTRACT

Reaction of pyrrolylmagnesium bromide with iodomethane in diethyl ether gave only C-substituted pyrroles. When the reaction was carried out in the presence of more than two parts of hexamethylphosphoramide (HMPA) N-methylpyrrole was also obtained. The ratio of N-substituted pyrrole to C-substituted pyrroles increased with increasing amount of the HMPA added and if the HMPA was used as solvent, the product was almost exclusively N-methylpyrrole. It was believed that in the presence of an excess of this strongly basic complexing agent, the bond between the pyrrolyl group and the magnesyl group became dissociated. The reactions of pyrrolylmagnesium bromide with derivatives of carboxylic acids were believed to involve two types of Lewis acid and Lewis base reaction: (a) the reaction of the carbonyl carbon atom with the pyrrolyl group of the undissociated Grignard reagent; (b) the reaction of the carbonyl oxygen atom with the magnesyl group of the Grignard reagent. The carbonyl group of such compounds as acetyl chloride, acetic anhydride, phosgene and carbon dioxide where the electrophilicity of the carbonyl carbon atom was greatly enhanced by the electron-withdrawing group preferred the first type of Lewis acid and Lewis base reaction. The carbonyl group of such compounds as diethyl carbonate and

phenyl isocyanate where the nucleophilicity of the carbonyl oxygen atom was enhanced by electron-donating groups preferred the second type of Lewis acid and Lewis base reaction. The first type of reaction always gives C-substituted products while the second type of reaction always gives N-substituted products. The reaction of 2-methylpyrrolylmagnesium bromide with ethyl chloroformate gave only ethyl 2-methyl-5-pyrrolecarboxylate but the reaction of ethyl chloroformate with the Grignard reagent from ethyl 2-pyrrolecarboxylate gave only diethyl 1,2-pyrroledicarboxylate. The reaction of pyrrolyllithium with diethyl carbonate in 1,4-dioxane at room temperature gave almost exclusively ethyl 1-pyrrolecarboxylate. At the boiling temperature of 1,4-dioxane, the ethyl 1-pyrrolecarboxylate was converted slowly to the thermodynamically more stable products, ethyl 2-pyrrolecarboxylate and 1,2'-dipyrrolyl ketone.

ACKNOWLEDGEMENTS

The author wishes to express his sincere thanks to Dr. H. J. Anderson for his encouragement and valuable advice throughout the course of this work. Financial assistance from the National Research Council and a demonstratorship from the Department of Chemistry, Memorial University of Newfoundland are gratefully acknowledged.

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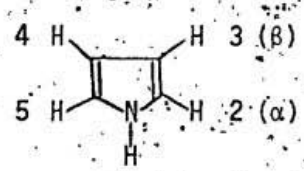
CHAPTER 1

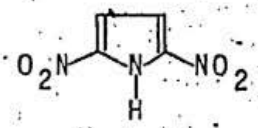
INTRODUCTION

In 1857 pyrrole was isolated as a pure compound from bone oil by Anderson (1) and in 1860 Schwanert (2) succeeded in synthesizing pyrrole by the dry distillation of ammonium mucate. The structural formula (I) was suggested for pyrrole by Baeyer (3).

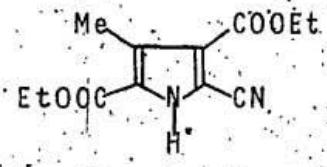
Pyrrole appears from its formula to be a secondary amine but its basic properties are very weak. It does not form quaternary salts with alkyl halides. Its weak basicity can be explained by its peculiar aromaticity. From colorimetric and spectroscopic studies, McEwen (4) derived the value pKa = 16.5 for pyrrole; but Yagil (5) reported that the pKa value was 17.5. The above two values are higher than that for methanol whose value is pKa = 16. Pyrroles containing electron attracting substituents are stronger acids than pyrrole. For example, 2,5-dinitropyrrole (II) is soluble in alkaline solution (6a) and the nitrile compound, diethyl 3-methyl-5-cyano-2,4-pyrroledicarboxylate (III) can even be titrated as a monobasic acid with phenolphthalein as indicator (6b). The acidity of the pyrrolyl NH also increases with an increasing number of electron attracting substituents and the acidity of the α-substituted pyrrole is greater than that of the corresponding β-substituted pyrrole (6c).



(I)



(II)



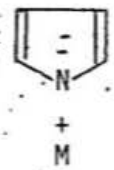
(III)

(A) Alkali Metal Salts

The imino hydrogen of pyrrole can be replaced by alkali metals to form alkali metal salts of pyrrole. Pyrrole will react with potassium in petroleum ether (7), benzene (8a), toluene (8b, c), xylene (8d) or liquid ammonia (8c, 9) to form pyrrolylpotassium (IVa) and liberate hydrogen gas. Sodium is much less reactive and lithium is unreactive under the same conditions except in liquid ammonia. Alkylpyrroles also react readily with potassium in boiling toluene to form the corresponding potassium salts (8c). Pyrrole reacts with sodium in liquid ammonia (9) or in tetrahydrofuran (10) to give pyrrolylsodium (IVb). The same compound can also be obtained by reaction of pyrrole with sodium hydride (11). Pyrrolyllithium (IVc) has been obtained by treating pyrrole with lithium in liquid ammonia (8c, 9). It has also been obtained by reaction of pyrrole with phenyllithium (12a) and n-butyl lithium (8c, 12b, c).

(a) K salts

Reaction of pyrrolylpotassium with ethyl chloroformate in absolute ether or toluene gives ethyl 1-pyrrolecarboxylate (8c, 13). With acyl halides at room temperature it was reported that the corresponding 1-substituted pyrroles were formed. For example, acetyl chloride reacts with pyrrolylpotassium in absolute ether to give 1-acetylpyrrole (14) and the reaction of benzoyl chloride with pyrrolylpotassium in toluene gives 1-benzoylpyrrole (15).



(IV)

(a) M = K

(b) M = Na

(c) M = Li

Reaction of pyrrolylpotassium with methyl iodide also produces the corresponding N-substituted alkylpyrrole (16). Treibs and Dietl reported that reaction of pyrrolylpotassium with dimethyl sulfate in liquid ammonia gave N-methylpyrrole (8c). In some cases reaction of pyrrolylpotassium with higher alkyl halides produces mixture of N-alkylpyrrole and C-alkylpyrrole. For example pehtyl iodide reacts with pyrrolylpotassium to give 1-pentylpyrrole and 2-pentylpyrrole (17).

(b) Na salts

Moon and coworkers reported that the reaction of 2,5-dimethylpyrrolylsodium with acetyl chloride gave N-substituted products (18a).

Reaction of pyrrolylsodium with methyl chloride in liquid ammonia also produces N-methylpyrrole (18b).

(c) Li salts

The reaction of pyrrolyllithium with ethyl chloroformate is reported to give ethyl 2-pyrrolecarboxylate with ethyl 1-pyrrolecarboxylate as side product (8c) but it is reported later that reaction of pyrrolyllithium with methyl chloroformate only produced methyl 1-pyrrolecarboxylate (12c).

It has been found that reaction of pyrrolyllithium with ethyl bromide in liquid ammonia gives only 1-ethylpyrrole. When the reaction was carried out in absolute ether the product

was a mixture of 1-ethylpyrrole, 2-ethylpyrrole, and 3-ethylpyrrole (19).

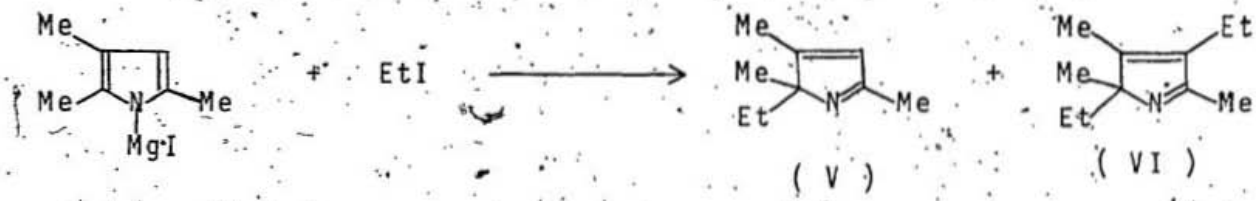
(B) Pyrrolyl Grignard Reagent

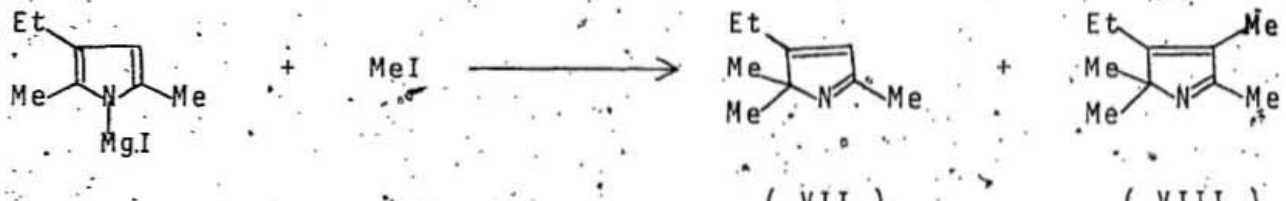
Oddo showed that pyrrolylmagnesium iodide can be obtained by cautiously dropping pyrrole into a solution of methylmagnesium iodide in absolute ether (20). He also claimed that pyrrolylmagnesium iodide can be prepared in a single operation by mixing the pyrrole, the methyl iodide and the magnesium in anhydrous ether (21). Pyrrolylmagnesium chloride and pyrrolylmagnesium bromide were prepared by the same method described by Oddo (22,23).

Reaction of pyrrolylmagnesium bromide with alkyl halides gives 2-, 3-, di-, and trialkylpyrrole and, when equivalent quantities of alkyl halides and pyrrolylmagnesium bromide are used, dialkylation and polyalkylation become important (19,24); but the dialkylpyrroles and polyalkylpyrrole have not been identified. In the reaction of pyrrolylmagnesium bromide and alkyl halides the reactivities of alkyl halides increase in the order : neopentyl < methyl < ethyl < s-butyl < isopropyl << allyl ≈ t-butyl ≈ t-amyl (19). Griffin and Obrycki (24) found that when a series of methylating reagents were used the methylation ability of the methylating reagents was : CH_3I < $(CH_3)_3PO_4$ < $(CH_3)_2SO_4$ ≈ CH_3OTs (methyl p-toluenesulfonate). They also pointed out that when $(CH_3)_2SO_4$ or CH_3OTs was used as methylating reagent, a small amount of 1-methylpyrrole was also obtained.

The alkylation of the Grignard reagent from a trialkylpyrrole has been examined by Booth (25). In the reaction of 2,3,5-trimethylpyrrolylmagnesium iodide with ethyl iodide a mixture of pyrrolenines (V) and (VI) was obtained. Similarly 3-ethyl-2,5-dimethylpyrrole gave compounds (VII) and (VIII) with methyl iodide. Methylation of 2,5-dimethylpyrrole or 2,3,4,5-tetramethylpyrrolyl Grignard reagent with methyl iodide gives compound (IX).

Reaction of pyrrolylmagnesium bromide with acetyl chloride gives 2-acetylpyrrole (X) and 3-acetylpyrrole (XI) with the former as the major product (26). Reaction of pyrrolylmagnesium bromide with acetic anhydride also gives 2-acetylpyrrole and 3-acetylpyrrole (26b). Carbon dioxide gives 2-carboxylic acids with Grignard reagents from pyrrole (20,27,28), but reaction of pyrrolyllithium with carbon dioxide only gives 1-carboxylic acid (12b). The reaction of phosgene with pyrrolylmagnesium bromide gives 2,2'-dipyrrolyl ketone (XII) (22a). Chelintzev (22a) also claimed that 2,2'-dipyrrolyl ketone could also be obtained by treatment of pyrrolylmagnesium halides with 2-pyrrolecarbonyl chloride obtained by the reaction of 2-pyrrolecarboxylic acid with phosphorus pentachloride. Potokhim (29) reported that reaction of pyrrolylmagnesium iodide with ethyl formate in benzene gave 2-formylpyrrole (XIII).


Me
Me
Me
N
Mg·I
+ EtI
Me
Me
Et
N
Me
(V)
+
Me
Et
Me
Et
N
Me
(VI)


Et
Me
Me
N
Mg·I
+ MeI
Et
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Me
N
Me
(VII)
+
Et
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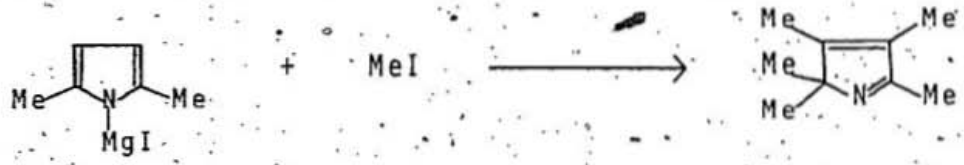
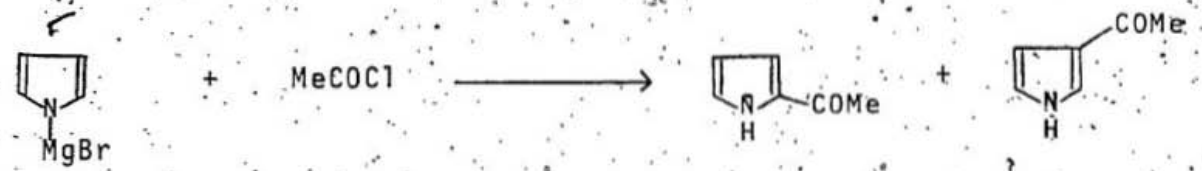
N
Me
(VIII)

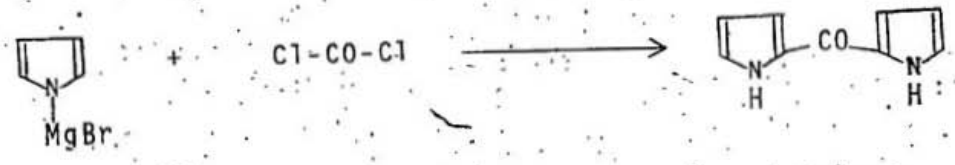


(IX)

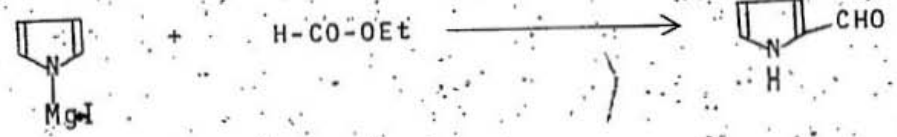


(X)

(XI)



(XII)

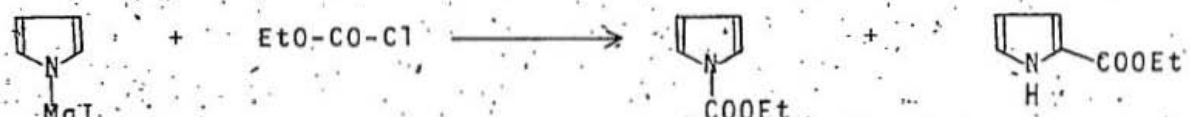


(XIII)

Sycheva et al. reported that the reaction of pyrrolylmagnesium bromide and methyl chloroformate gave methyl 2-pyrrolecarboxylate and methyl 3-pyrrolecarboxylate (30). They also reported that when excess of methyl chloroformate was used, dimethyl 1,3-pyrroledicarboxylate was also obtained. Oddo (20) reported that reaction of pyrrolylmagnesium iodide with ethyl chloroformate only produced ethyl 2-pyrrolecarboxylate (XV), but other workers claimed that besides ethyl 2-pyrrolecarboxylate, ethyl 1-pyrrolecarboxylate (XIV) and diethyl 1,2-pyrroledicarboxylate (XVI) were also obtained (31).

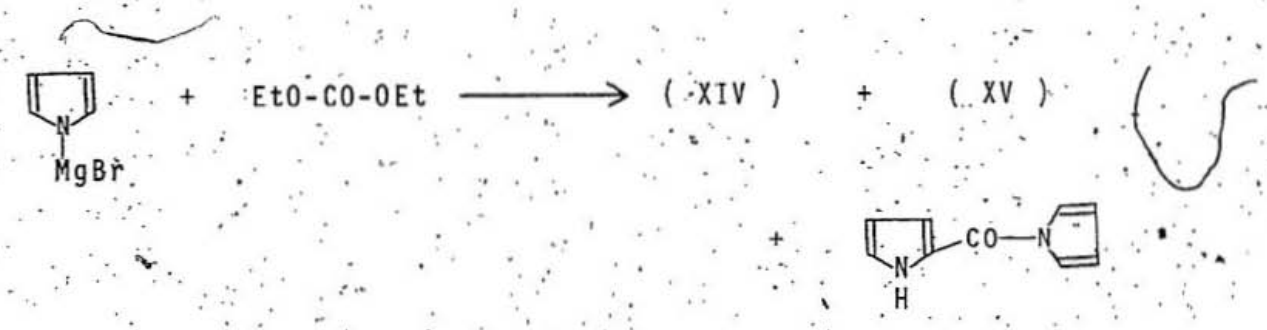
(C) N- vs. C-Substitution

Chelintzev and Karmanov reported that the chief product of the reaction of pyrrolylmagnesium bromide with diethyl carbonate was ethyl 1-pyrrolecarboxylate. Small amounts of ethyl 2-pyrrolecarboxylate and 1,2'-dipyrrolyl ketone (XVII) were also obtained (32). They explained that pyrrolylmagnesium halides were like the derivatives of pyrrolylpotassium, capable of giving according to conditions either N- or C-substituted pyrroles. With the pyrrolylpotassium the tendency is to form N-derivatives while the pyrrolylmagnesium halides tend to form C-derivatives. In comparing the behavior of pyrrolylmagnesium halides and pyrrolylpotassium, Oddo also reported that pyrrolylmagnesium halides yielded derivatives substituted in the C-position of the pyrrole nucleus, whereas



(XIV) (XV)

(XVI)



(XVII)

under the same experimental conditions, pyrrolylpotassium either did not react or yielded compounds substituted in the N-position of the pyrrole nucleus (33).

The effects upon the occurrence of N- and C-alkylation of varying the metal cation, temperature and the medium have been studied by Hobbs et al. (34). They found that 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. The following general conclusion were also drawn:

(i) For a given metal salt, both under heterogeneous conditions and in solution, the most polar solvents gave the highest percentage of 1-alkylation and the least polar solvents, the lowest percentage of 1-alkylation.

(ii) For a given medium, both under heterogeneous conditions and in solution, the relative percentage of 1-alkylation increases with decreasing coordinating ability of the cation in the order $Li^+ < Na^+ < K^+ < (CH_3)_3NC_6H_5^+$.

(iii) For pyrrolylpotassium, both under heterogeneous conditions and in solution, the relative percentage of 1-alkylation increases with increasing solubility of the salt in the medium.

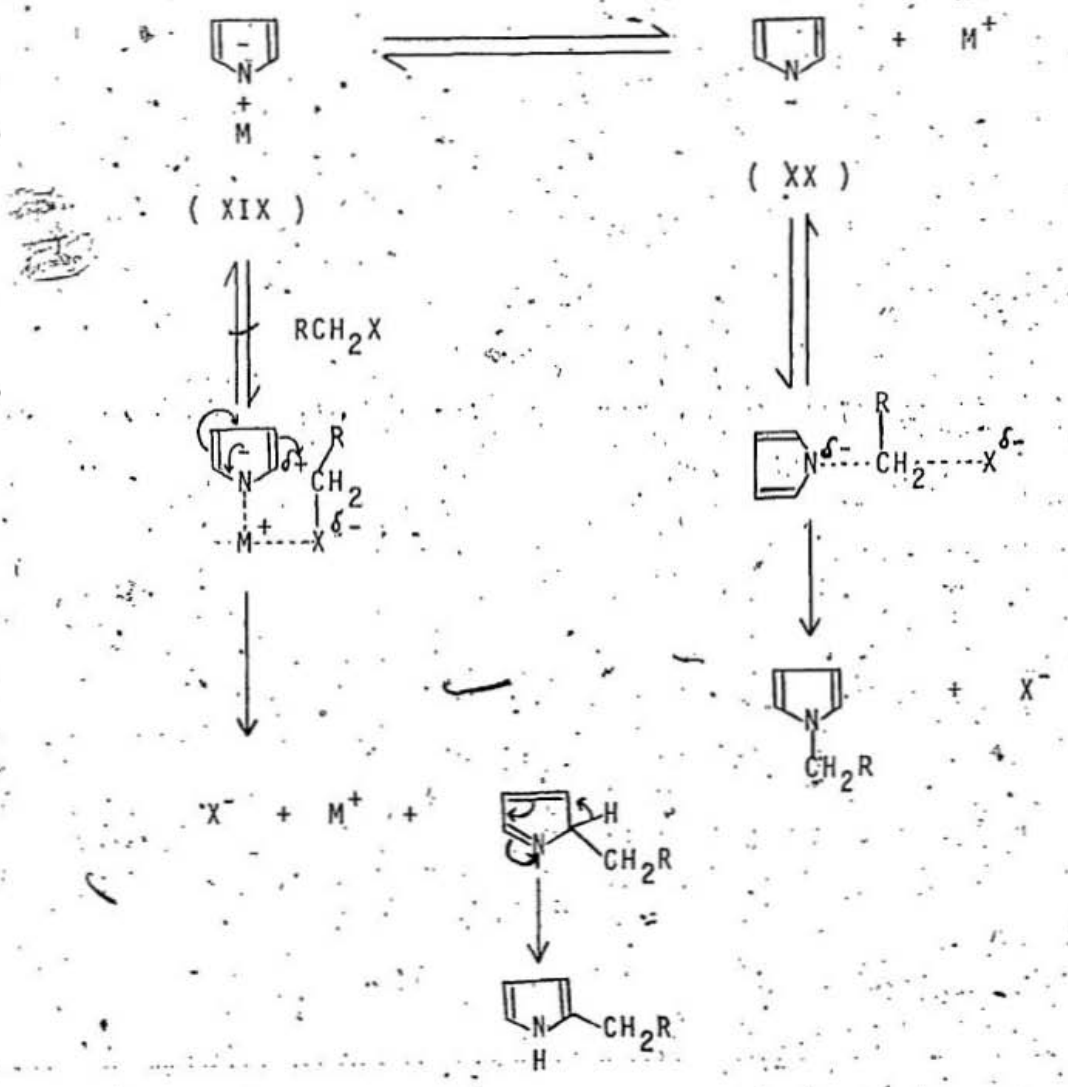
(iv) For a series of salts in a given medium, both under heterogeneous conditions and in solution, the relative percentage of 1-alkylation tends to increase with decreasing solubility of the salt in the medium or for homogeneous reactions with decreasing concentration of pyrrole salt in the reaction medium.

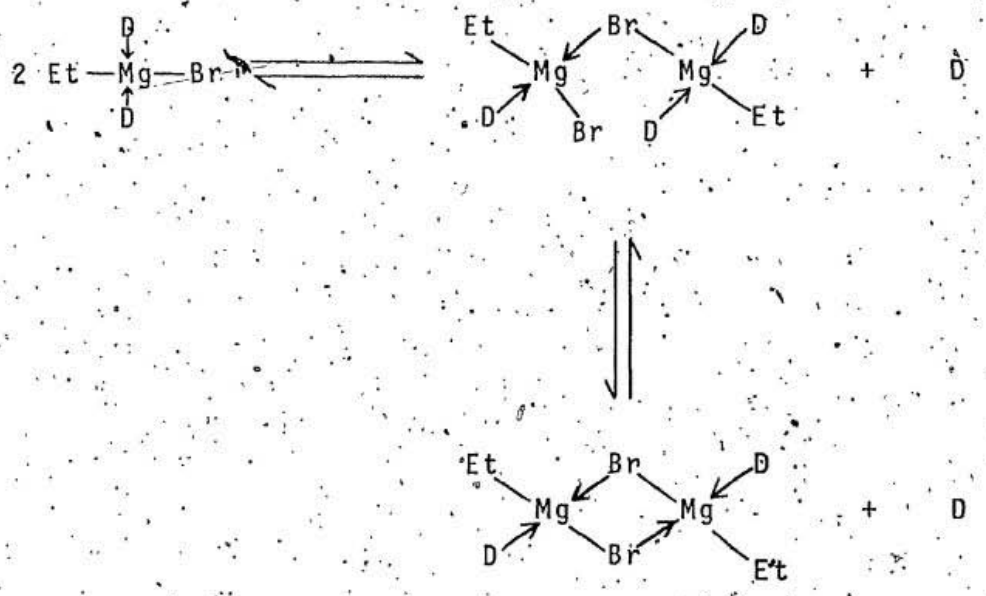
(v). Addition of tetrabutylammonium bromide to any reaction mixture increases the relative percentage of 1-alkylation.

To account for these observations, it was suggested that dissociation of the salt (XX) favors N-substitution and ionic association (XIX) favors C-substitution in homogeneous reaction.

(D.) Studies of the Grignard Reagent

The composition of the organomagnesium derivatives in solution is poorly understood and has only been studied in several special cases. Ashby and Smith reported that the degree of association for the bromides and iodides of organomagnesium increases uniformly with concentration, going from monomeric species at low concentrations ($\sim$ 0.05 mole) and approaching a dimeric species at the higher concentrations (0.5-1.0 mole)(35). Organomagnesium chlorides are essentially dimeric even at low concentrations. Evans and Khan were able to show the existence of the complex $C_6H_4FMgBr \cdot TMEDA$ (N,N,N',N'-tetramethylethylene-diamine) by n.m.r. studies (36). In a study of the rotatory power of the complex obtained by using an optically active solvent (XXI) Vink suggested a series of equilibria in the solution (37). In a study of the behavior of t-Bu_2Mg in tetrahydrofuran Coates and Heslop proposed that there was an equilibrium between t-$Bu_2Mg(THF)_2$ (XXII) and $(t\text{-}Bu_2Mg \cdot THF)_2$ (XXIII) but they were unable to distinguish between structures (XXIIIa) and (XXIIIb) (38). X-Ray studies have also been done


M+
(XIX)
(XX)
RCH2X
X-
M+

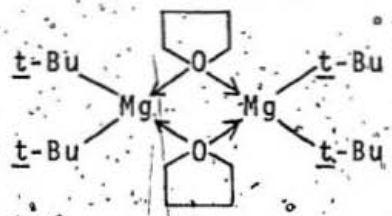


(XXI)

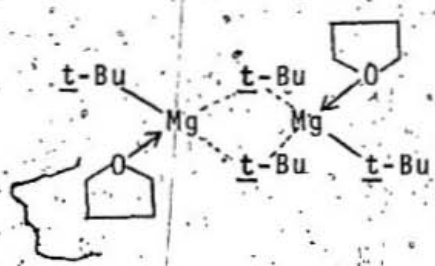
D = $CH_3-CH_2-O-CH_2-\underset{\underset{CH_3}{|}}{CH}-CH_2-CH_3$

$$2\ \underline{t}\text{-Bu}_2\text{Mg(THF)}_2 \rightleftharpoons (\underline{t}\text{-Bu}_2\text{Mg}\cdot\text{THF})_2 + 2\ \text{THF}$$

(XXII) (XXIII)

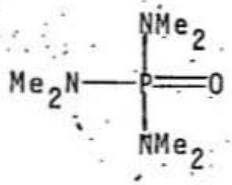


(XXIIIa)

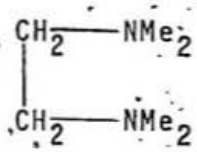


(XXIIIb)

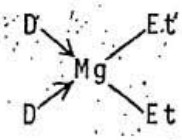
on solid samples and the composition of the organomagnesium halides below have been proposed: $C_6H_5MgBr \cdot 2Et_2O$ (39); $(C_2H_5)_2Mg \cdot 2Et_2O$ (39); $EtMgBr \cdot 2Et_2O$ (40); $(EtMgBr \cdot Et_3N)_2$ (41); $MeMgBr \cdot 3THF$ (42). The solvation abilities on dimethylmagnesium of give solvating agents in an inert solvent have been studied by an n.m.r. method (37, 43). They are HMPA (hexamethylphosphoramide) (XXIV); TMEDA (N,N,N',N'-tetramethylethylenediamine) (XXV); DME (dimethoxyethane); THF (tetrahydrofuran) and ethyl ether. In the cases of hexamethylphosphoramide and N,N,N',N'-tetramethylethylenediamine when the ratio of the solvating agent to the Grignard reagent is greater than two the reaction is complete and only disolvated monomer (XXVIa,b) is present in the inert solvent. On the contrary, for the other solvating agents, there is an equilibrium between the disolvated monomer (XXVII) and disolvated dimer (XXVIII) in the inert solvent. Ducom (43) also pointed out that the solvating ability of hexamethylphosphoramide was greater than that of N,N,N',N'-tetramethylethylenediamine. The behavior of solvating agents on alkyl- or arylmagnesium halides in ether has also been studied by the u.v. methods. When hexamethylphosphoramide is added to the Grignard reagents, the u.v. absorption of the Grignard reagents are shifted to longer wavelength until the ratio of the hexamethylphosphoramide to the Grignard is 2:1. Further addition of hexamethylphosphoramide does not then cause the shift of



(XXIV)

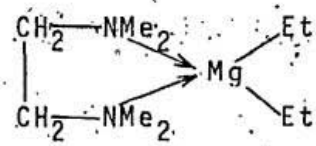


(XXV)

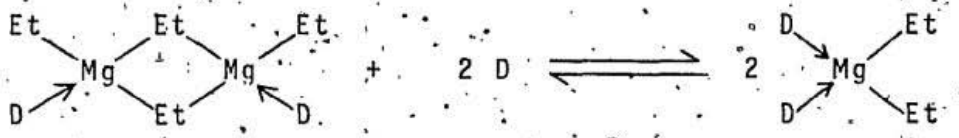


(XXVIa)

D = HMPA(XXIV)

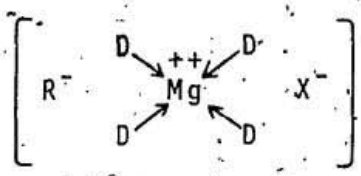


(XXVIb)



(XXVII) (XXVIII)

D = diethyl ether, tetrahydrofuran



(XXIX)

D = HMPA(XXIV)

the u.v. absorption of the Grignard to longer wavelength but there is an appearence of new absorption in the visible wavelength region which is said to be a characteristic absorption of a carbonium ion. The author suggested that the complex (XXIX) was present in the solution (44). Ducom and Denise measured the electrical conductivities of magnesium chloride and bromide, of diethylmagnesium as well as of ethylmagnesium chloride, ethylmagnesium bromide and of n-butylmagnesium bromide in hexamethylphosphoramide (45). In this strongly basic solvent the equivalent conductivity of Grignard compounds can be as high as $20\Omega^{-1}cm^{-2}mol^{-1}$. The authors proposed the following ionization equilibrium

$$R\text{-}Mg\text{-}X \rightleftharpoons R\text{-}Mg^{+} + X^{-}$$

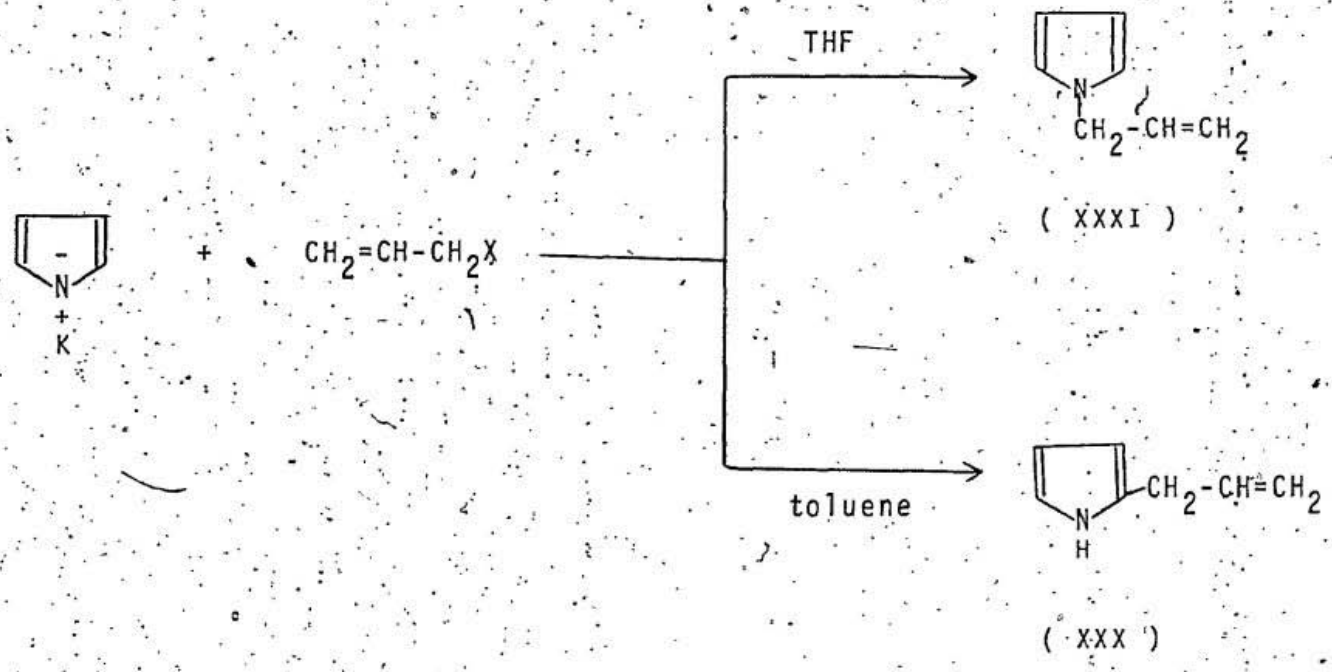
They reported that magnesium bromide was completely ionized and organomagnesium bromides were ionized to approximately 30%.

(E) Ambident Ion Studies

The term "ambident anions" has been used by Kornblum (46) for the anion systems containing two centers susceptible to electrophilic attack, but in which only one of these centers can take part in one transition state. Systematic studies of alkylation or acylation of ambident ions in the past few years have shown that the relative percentage of products resulting from the two possible reaction paths depends on factors such

as reaction medium, metal counter ion, structure of the alkylating or acylating agent, which lead to different product distribution (46,47).

Ingold (48) suggested that Claisen's C-alkylation reaction of phenol salts with allyl and benzyl halides in non-polar solvents such as benzene involved the reaction of the alkyl halide with associated sodium phenoxide, whereas the oxygen-alkylation in more polar solvents such as ethanol or acetone was attributed to reaction of the dissociated phenoxide ion. Kornblum and coworkers (46) reported that in reactions of alkyl halides with silver nitrite, the nitrite ester was the major product, while with potassium nitrite, the nitroparaffin was the major product. Hobbs and coworkers (34) demonstrated that the reaction of pyrrolylpotassium with allyl halides in toluene gave mainly the 2-substituted pyrrole (XXX); but the 1-substituted pyrrole (XXXI) was the major product when tetrahydrofuran was used as solvent. Curtin reported that in the reaction of metal salts of phenols, carbon alkylation was increased at the expense of oxygen alkylation by the salts of less electro-positive alkali metals (49). In a study of the alkylation of alkali metal salts of pyrrole, Treibs and Dietl suggested that the position on the pyrrolyl anion resonance hybrid which makes the nucleophilic attack was determined by the ionic radius of the metal ion. Thus pyrrolylpotassium and pyrrolylsodium formed

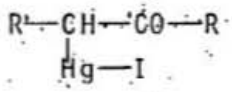


(XXXI)

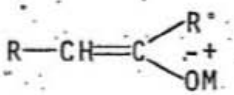
(XXX)

predominantly nitrogen-alkylated products, whereas pyrrolyllithium and pyrrolylmagnesium halides gave predominantly carbon-alkylated products (8c). Noble and Morris found that the use of hexamethylphosphoramide allowed not only better yields but also the highest O/C ratios for the reactions of alkali metal salts of acetoacetate with alkyl halides (50). The reason for the improved yield was not known. House and coworkers reported that mercury (II) salts were found to exist as α-C-metalated ketones (XXXII), but salts with lithium, sodium, zinc and magnesium exist as enolate structures in which either contact ion pairs (XXXIIIa) or solvent-separated ions (XXXIIIb) may be present (51). They also pointed out that the existence of metal enolates as solvent-separated ion pairs is favored (a) in a polar or a good solvating solvent such as 1,2-dimethoxyethane or N,N'-dimethylformamide rather than ether; (b) by the presence of a metal cation such as sodium, lithium or zinc rather than magnesium. In kinetically controlled reactions of metal enolates with acylating agents, O-acylation is the favored reaction with solvent-separated ion pairs and with α-metalated ketones. The contact ion pairs will increase the C-acylation. In a discussion of the dual reactivity of ambident anions Shevelev (47e) was able to use the principle of hard and soft acids and bases (47d,52) to explain the literature results.

From the examples we have given above, it is possible to make the following conclusions for pyrrole derivatives. All the

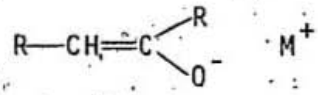


(XXXII)



(contact ion pair)

(XXXIIIa)



(solvent-separated ions)

(XXXIIIb)

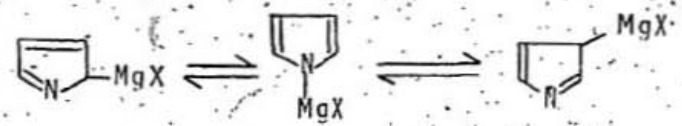
reactions of pyrrolylmagnesium halides with alkyl halides give only C-alkylated pyrroles. Alkylation of alkali salts of pyrrole in liquid ammonia only gives N-alkylated pyrroles. Acylations of pyrrolylmagnesium halides with some exceptions usually produce a mixture of C-substituted pyrroles and N-substituted pyrroles. Acylations of alkali metal salts of pyrrole always give N-substituted pyrroles. There has been no systematic study of the factors which determine the position of alkylation and acylation of the pyrrolylmagnesium halides. The constitution of pyrrolylmagnesium halides in the presence of strong complexing agent has not been studied. The ambident anion of pyrrole in solution is poorly understood and has only been studied in a few cases. We will discuss these topics in the following part of this thesis. The concept of hard and soft acids and bases is also used to explain our results.

CHAPTER II

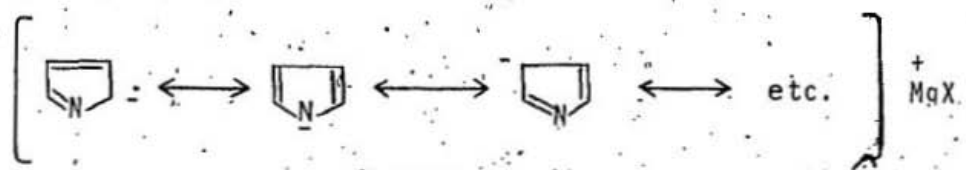
STRUCTURE AND COMPOSITION OF PYRROLYLMAGNESIUM HALIDES IN DIETHYL ETHER

After the preparation of the pyrrolylmagnesium halides (20-23), the structures of these pyrrolyl Grignard reagents have been studied extensively. Nenitzescu (53) suggested that the magnesyl groups of the pyrrolyl Grignard reagents were attached to carbon atom rather that to the nitrogen atom because they gave a violet color with Michler's ketone. The indolyl Grignard reagents gave a negative color test with Michler's ketone and it was thus believed that the magnesyl group was attached to the nitrogen atom. Gilman and Heck (54) pointed out that although pyrrolylmagnesium halides gave a positive color test with Michler's ketone it was not necessary that the magnesyl group be attached to the carbon atom because in the presence of acetic acid and iodine, which were used to develop the Michler's ketone test, pyrrole itself formed and gave a positive color test (54). They also showed that when pyrrole was treated with an excess of methylmagnesium iodide the number of active hydrogens was about 1.0, therefore they reached the conclusion that the magnesyl group of the pyrrolyl Grignard reagent was attached to the nitrogen atom in the pyrrole ring. If the magnesyl group was attached to the carbon atom, then pyrrole should show at least two active

hydrogen atoms. On the basis of the products of pyrrolylmagnesium halides in alkylation and acylation, Kharasch and Reinmuth (55) suggested that the reactions of pyrrolylmagnesium halides might be adequately accounted for by formulation as a mixture of the derivatives of the three hypothetical tautomeric forms (XXXIV), with the α-pyrrolenine derivative in marked preponderance or of considerably greater reactivity than the other forms. They also suggested that the pyrrolyl Grignard reagent might be formulated as an ionic, though not necessary highly dissociated, compound (XXXV) with a resonant anion in which the α-position was favored for electrophilic attack. The reaction of pyrrolylmagnesium bromide with heavy water showed that the magnesyl group was attached to the nitrogen atom because the pyrrole recovered from the hydrolysis by heavy water was N-d-pyrrole and contained no C-d-pyrrole at all (19). When N-d-pyrrole was treated with methylmagnesium bromide, the resulting gas was shown by its infrared spectrum to be CH_3D (19). This indicated that the imino hydrogen atom is more reactive than a hydrogen atom attached to a carbon atom and can be replaced by the magnesyl group of the alkyl Grignard reagent. N-Substituted pyrroles did not react with alkylmagnesium halides to produce the corresponding pyrrolyl Grignard reagents (56). This example



(XXXIV)



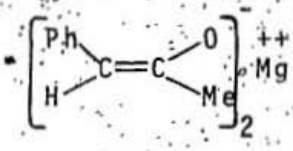
(XXXV)

(XXXVI)

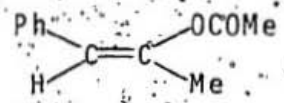
indicates that the magnesyl group of the alkyl Grignard reagent does not replace a hydrogen atom in the α- or β-position of the pyrrole ring to form the corresponding alkylpyrrolyl-magnesium halides.

Spectroscopic studies also indicated that the magnesyl group of the pyrrolyl Grignard reagent was attached to the nitrogen atom. It was found that the n.m.r. spectrum of a 10% ethereal solution of pyrrolylmagnesium chloride consisted of two triplets (2.90 and 3.63τ; J=2Hz) (11a) of equal area whose general appearence was very similar to those found in the n.m.r. spectrum of N-d-pyrrole (57) and pyrrolylsodium (3.16 and 3.74τ; J=2Hz) (11a). The triplet at the lower field was assigned to the protons in the α-position and the triplet at the higher field was assigned to the protons in the β-position. It was also found that no absorption which might be attributed to an N-H group could be detected in either the n.m.r. or infrared spectrum of the pyrrolylmagnesium chloride, although such peaks were observed for pyrrole itself. This evidence shows that the structure of pyrrolylmagnesium halides is best represented by formula (XXXVI) or the ionic, but not necessarily highly dissociated, resonance hybrid (XXXV). In the literature quite a large number of ambident anions also behave like the pyrrolyl group in the pyrrolylmagnesium halides (47).

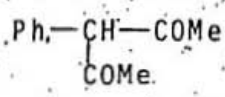
The n.m.r. spectrum of indolylmagnesium bromide shows that the magnesyl group is attached to the nitrogen atom (58a) and infrared spectroscopic studies also prove that the magnesyl group is associated with the nitrogen atom rather than the carbon atom in the 3-position (58b) of indolylmagnesium iodide; but reactions of the indolyl Grignard reagent with alkyl halides produce mainly the corresponding 3-substituted indole derivatives (58c). The n.m.r. spectrum of the magnesium enolate prepared from the reaction of one part of enol acetate of phenylacetone with one part of dimethylmagnesium showed that the magnesyl group is attached to the oxygen atom of the ambident anion (51), but acylation with acetic anhydride in diethyl ether gave 41% of O-acetyl derivative (XXXVIIa) and 43% of C-acetyl derivative (XXXVIIb). The acylation of the enolate anion (XXXVIIIa) derived from malonic ester, magnesium, a catalytic amount of carbon tetrachloride and ethanol, with ethyl chloroformate produced only the triethyl ester of methanetricarboxylic acid (XXXVIIIb) (59). Crotylmagnesium halides can be prepared by the reaction of crotyl halides or methylvinylcarbinyl halides with magnesium in absolute ether (60,61). The n.m.r. spectrum indicates that over 99% of the Grignard reagent is in the form of crotylmagnesium halide (XXXIXa) (61), but in reactions of crotylmagnesium



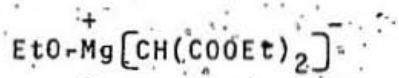
+ MeCO-O-COMe



(XXXVIIa)



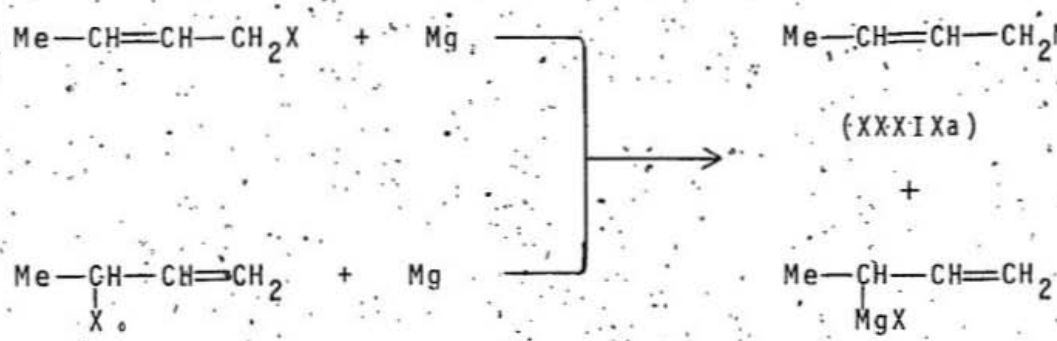
(XXXVIIb)



(XXXVIIIa)

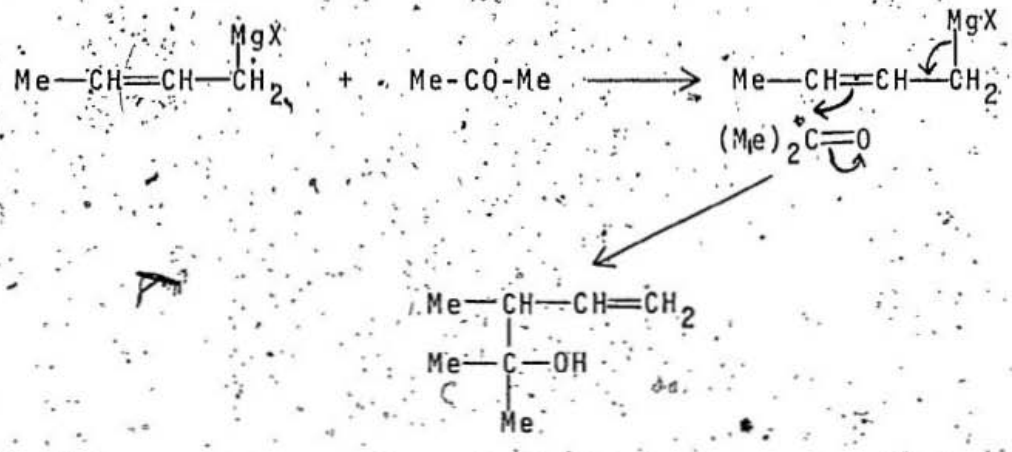
+ Cl-CO-OEt ⟶ $CH(COOEt)_3$

(XXXVLIIb)

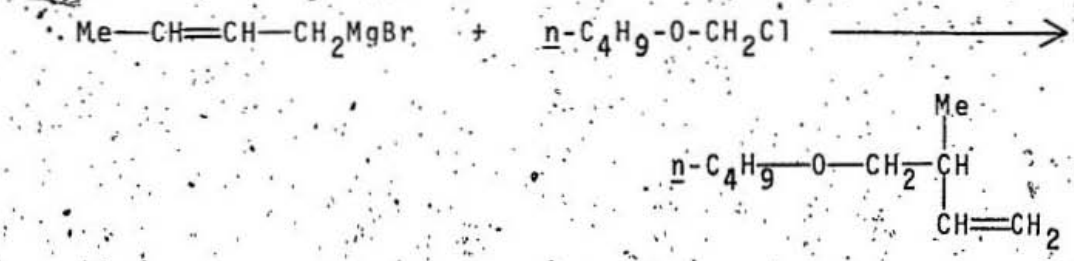


(XXXIXa)

(XXXIXb)



(XL)



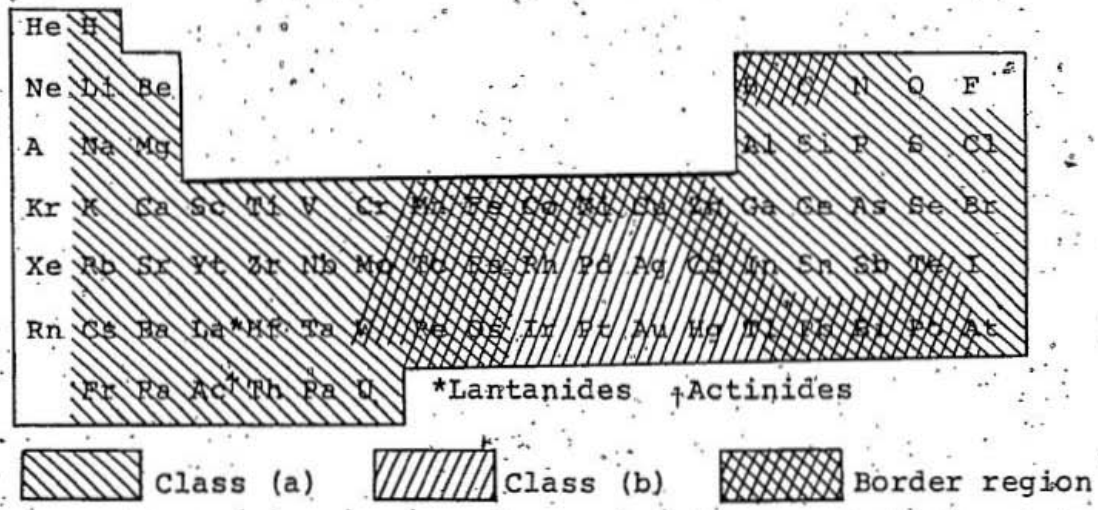
(XLI)

halides with relatively unhindered carbonyl compounds, the detectable products are the α-methallylcarbinols. In the case of acetone, the product is 2,3-dimethyl-4-penten-2-ol (XL) (62). It is suggested that the allylic Grignard reagent reacts with carbonyl compounds via a non-cyclic S_E2' rearrangement mechanism (63). Crotylmagnesium bromide couples with n-butyl chloromethyl ether to yield 2-methyl-3-butenyl n-butyl ether (XLI) (64). The examples, except the crotylmagnesium halides, given above show that the magnesyl group is tightly associated with the more electronegative atom in the ambident anion and hence prevents acylations and alkylations taking place at this atom. Most of the reactions of the pyrrolyl Grignard reagent in the literature were performed in ether, tetrahydrofuran or other less polar solvents with low basicity. We believe that in the solvents mentioned above the magnesyl group of the pyrrolylmagnesium halide not only attaches to the more electronegative nitrogen atom but also tightly associates with the nitrogen atom. This makes the alkylation and acylation at this nitrogen atom impossible unless in very strongly basic solvents as hexamethylphosphoramide or tetramethylethylenediamine.

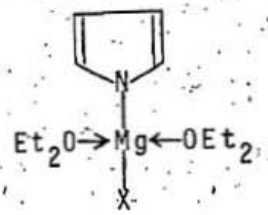
In a study of the relative affinities of ligand atoms for acceptor molecules and ions, Ahrland and coworkers (65) were able to classify the acceptors into two classes: (a) those

which form their most stable complexes with the first ligand atom of each periodic table group, i.e., with N, O, and F, and (b) those which form their most stable complexes with the second or a subsequent ligand atom. Some acceptors are in the border region as shown in Table I. Since magnesium is one of the class (a) acceptors, the magnesyl group of Grignard reagents in diethyl ether would form very stable complex with the oxygen atom of ether. Also, magnesium always shows preference for tetracoordination in diethyl ether therefore the monomer of the Grignard reagent in this solvent is likely to be disolvated (35,37,39,40,43,44,66,67). These are the common properties of Grignard reagents, therefore, we think that the disolvated monomeric species (XLIII) is the way the pyrrolyl Grignard reagent exists in the ethereal solution along with dimer or polymer and the magnesium is tetrahedrally coordinated.

TABLE I. Classification of acceptor atoms in their normal-valent states*



* From reference (65)



(XLIII)

CHAPTER III

REACTIONS OF THE PYRROLYL GROUP

(A) The Reaction of Pyrrolylmagnesium Bromide with Iodomethane

The reaction of pyrrolylmagnesium bromide with iodomethane (24,68a) and bromomethane (68b) has been examined by early workers. The same experiment was repeated under our own standard conditions for comparison.

After stirring for 17 hours at room temperature the reaction mixture from one part of pyrrolylmagnesium bromide and two parts of iodomethane was hydrolyzed with water. The yields of the products are recorded in Table III (p. 77) together with results which are discussed later in Chapter IV(B), and the methods of identification of products are described in the Experimental.

The products of this reaction were a mixture of 2-methyl-, 3-methyl-, 2,3-dimethyl-, 2,5-dimethyl-, and 2,3,5-trimethyl-pyrrole. No 1-methyl-, 3,4-dimethyl-, 2,4-dimethyl- or 2,3,4-trimethylpyrrole were detected. The reaction of pyrrolyl-magnesium bromide with (-)-2-bromobutane (68c) has been reported to follow a S_N2 type mechanism. The reaction of pyrrolylmagnesium bromide with iodomethane probably follows the same mechanism. It is likely that after the formation of the monosubstituted pyrroles they displaced the pyrrolyl group of another molecule

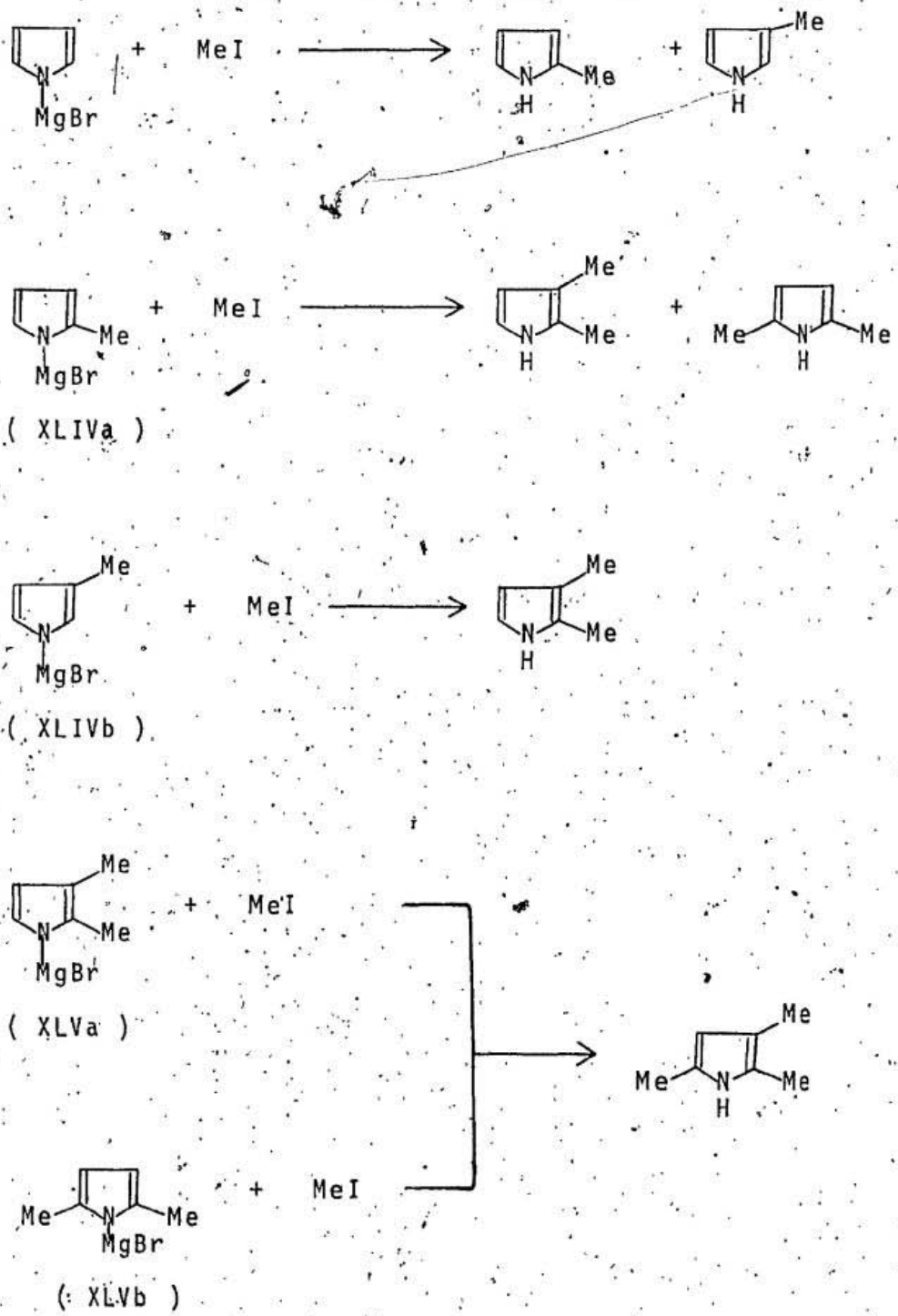
of Grignard reagent to form the corresponding monosubstituted pyrrolyl Grignard reagent. The reaction of 2-methylpyrrolylmagnesium bromide (XLIVa) with iodomethane gave a mixture of 2,3-dimethyl- and 2,5-dimethylpyrrole whereas 3-methylpyrrolylmagnesium bromide (XLIVb) only produced the former. After the formation of 2,3-dimethyl- and 2,5-dimethylpyrrole, they exchanged with the pyrrolyl group of the unreacted pyrrolylmagnesium bromide to form the corresponding dimethylpyrrolyl Grignard reagents which then reacted with another molecule of iodomethane to give 2,3,5-trimethylpyrrole. The above explanation is in agreement with our results.

(B) The Reaction of Pyrrolylmagnesium Bromide with Acetyl Chloride and Ethyl Acetate

The reactions of pyrrolyl Grignard reagent with acetyl chloride (26) and ethyl acetate (26b) have been reported.

Under our standard conditions, the reaction of pyrrolylmegnesium bromide and acetyl chloride gave a mixture of 1-acetylpyrrole (XLVIII), 2-acetylpyrrole (X) and 3-acetylpyrrole (XI). The ratio of substitution at nitrogen to total substitution at carbon (N/C ratio) is 3:97.

The reaction of pyrrolylmagnesium bromide with ethyl acetate produced a mixture of 1-acetyl- and 2-acetylpyrrole. These two compounds were identified by comparison of their infrared spectra and retention time with those of authentic

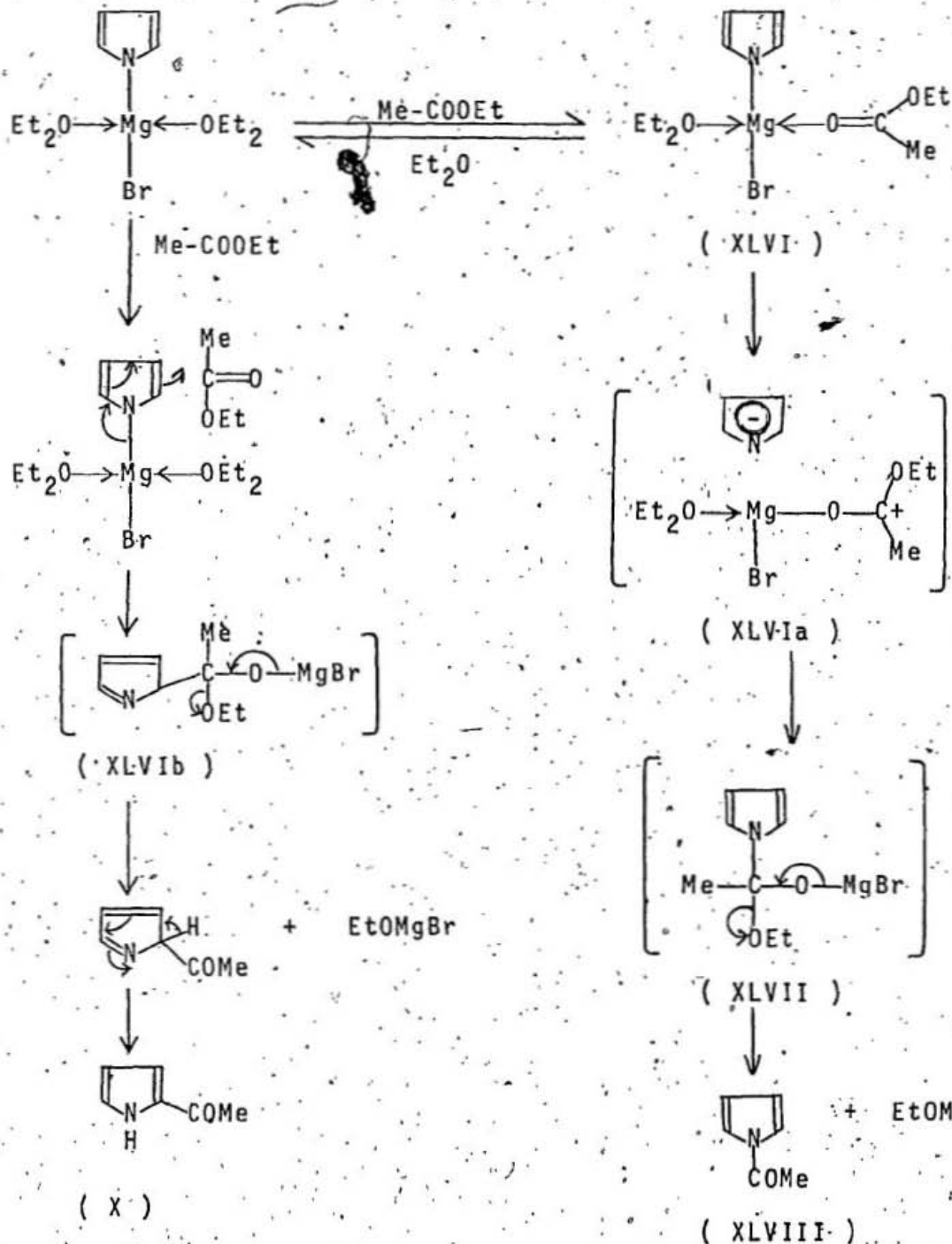


(The ether molecules attached to the magnesyl group are not shown in the above equations for the sake of simplicity.)

samples of 1-acetyl- and 2-acetylpyrrole. The ratio of N/C was 24:76. No 3-acetylpyrrole was detected.

The mechanism of reaction of Grignard reagent and ketones has been studied (35,64,67,69), but that of the reaction of Grignard reagent and esters has not yet been studied. These workers suggested that the first step of the reaction mechanism was the addition of the monomeric or dimeric Grignard reagent to the ketones to form a complex. But, this proposed mechanism cannot adequately explain our results: a mixture of N- and C-substituted pyrroles, in the acylation of pyrrolylmagnesium halide with ethyl acetate.

In the case of ethyl acetate it is reasonable to say that 1-acetylpyrrole and 2-acetylpyrrole are formed from different reaction pathways. If the ethyl acetate molecule reacts directly with the pyrrolyl group of the undissociated Grignard reagent, intermediate (XLVIb) would result. This intermediate can only produce 2-acetylpyrrole. It is known that ethyl acetate can coordinate with some Group II, Group III, and Group IV halides through its carbonyl oxygen atom to form addition compounds (70). Some of the acetate molecules might coordinate, through the carbonyl oxygen atom, to the magnesyl group of pyrrolyl Grignard reagent to form complex (XLVI) with the displacement of an ether molecule from the solvated Grignard reagent. Eventually a chemical bond (covalent or ionic) forms between the oxygen atom and the magnesyl group



(The ether molecules attached to the magnesyl group are not shown in (XLVIb) and (XLVII) for the sake of simplicity.)

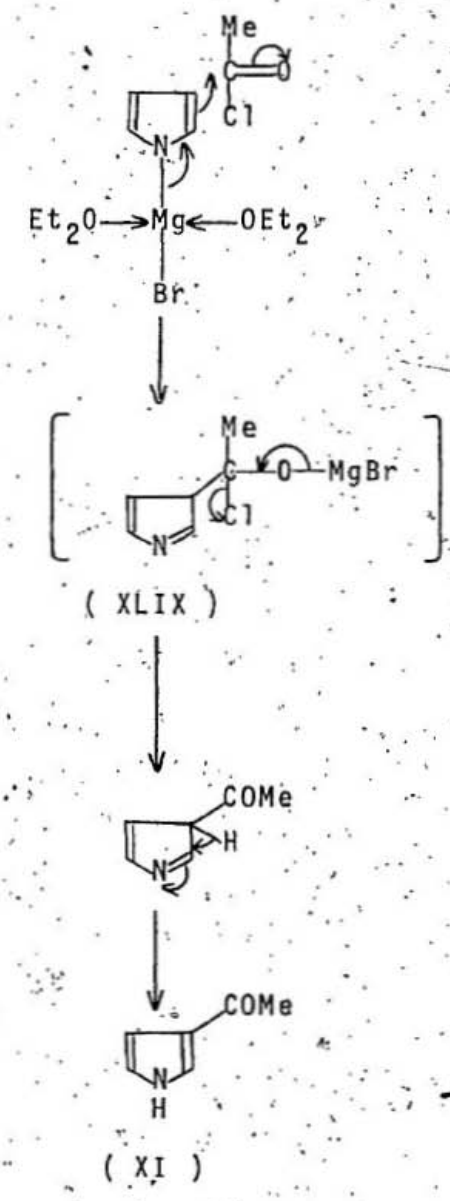
with the dissociation of a pyrrolyl group. The pyrrolyl group can either react with the positively charged carbon atom (hard Lewis acid) in (XLVIa) or the carbonyl carbon atom (hard Lewis acid) of another molecule of ethyl acetate through its nitrogen atom (hard Lewis base) to form intermediate (XLVII) which can then produce 1-acetylpyrrole. The principle of hard and soft acids and bases will be discussed in the later part of this thesis.

In the case of acetyl chloride, the pathway of formation of 1-acetyl and 2-acetylpyrrole should be the same as those described above. 3-Acetylpyrrole is probably produced from intermediate (XLIX) formed by the addition of one molecule of acetyl chloride to the 3-carbon atom of the pyrrolyl group of the undissociated Grignard reagent.

(C) The Reaction of Pyrrolylmagnesium Bromide with Ethyl Chloroformate and Diethyl Carbonate

Reactions of pyrrolylmagnesium halides with ethyl chloroformate (20,31) and diethyl carbonate (32) have been reported. We repeated these two reactions under our standard conditions described in the Experimental for comparison.

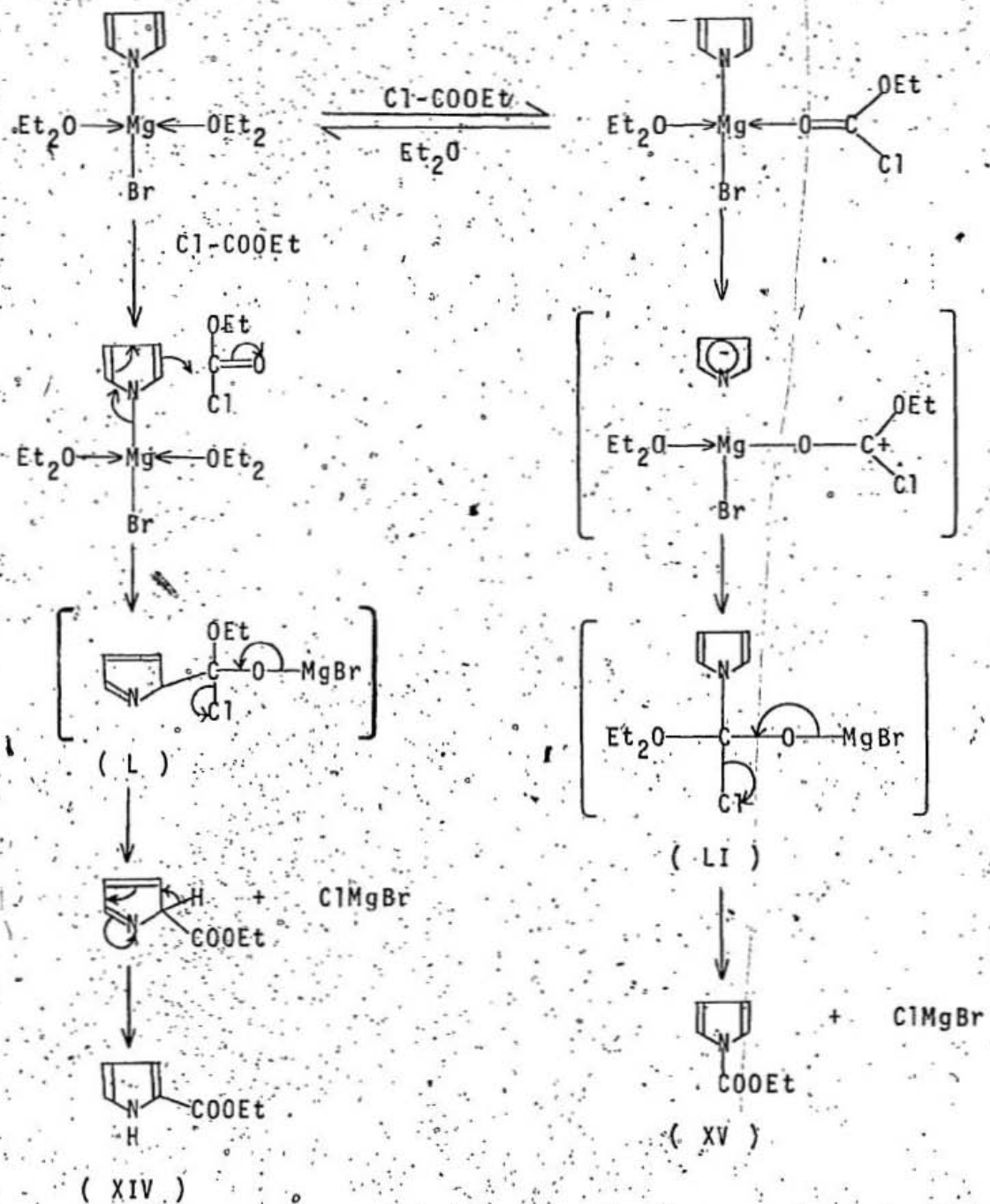
Ethyl chloroformate produced a mixture of ethyl 1-pyrrolecarboxylate (XV), ethyl 2-pyrrolecarboxylate (XIV) and diethyl 1,2-pyrroledicarboxylate (XVI). Compound (XIV) is probably produced by the intermediate (L) formed from the direct interaction of one molecule of ethyl chloroformate and a pyrrolyl group of the undissociated Grignard reagent. If the ethyl chloroformate molecule forms a complex through its carbonyl oxygen



(XLIX)

(XI)

(The ether molecules attached to the magnesyl group are not shown in (XLIX) for the sake of simplicity.)



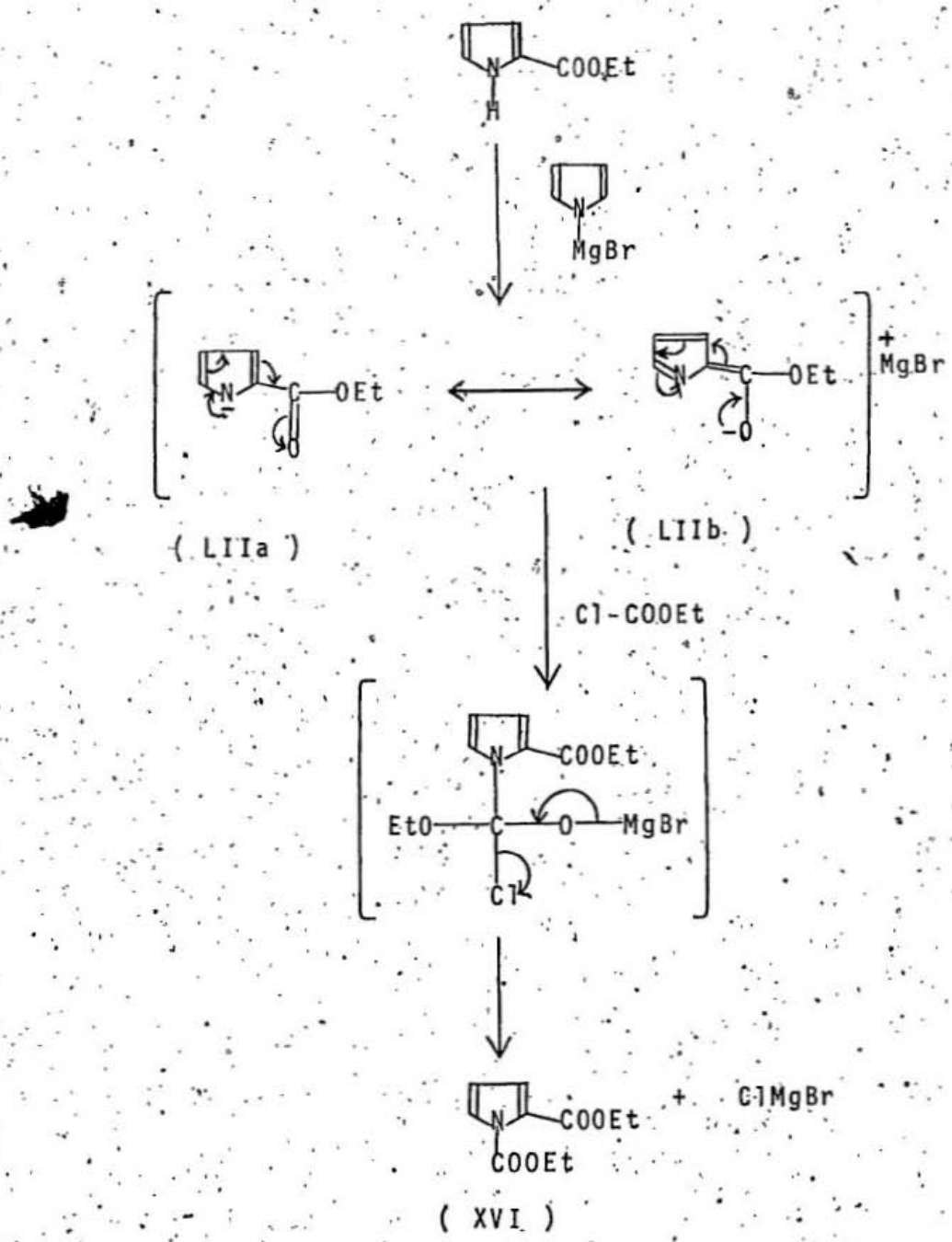
(The ether molecules attached to the magnesyl group are not shown in (L) and (LI) for the sake of simplicity.)

atom with the magnesyl group of the Grignard reagent the product is ethyl 1-pyrrolecarboxylate (XV) and the probable intermediate is (LI). After the formation of ethyl 2-pyrrolecarboxylate, some of this compound might react with the unreacted pyrrolylmagnesium bromide to form 2-carboxyethylpyrrolylmagnesium bromide (LII). The intermediate (LII) could then react slowly with another molecule of ethyl chloroformate to give the diethyl 1,2-pyrroledicarboxylate (XVI) which is discussed in Chapter IV(D).

Addition of ethyl chloroformate to the reaction mixture from ethylmagnesium bromide and ethyl 2-pyrrolecarboxylate also produced the same compound. In calculations of the ratio of N/C, ethyl 1,2-pyrroledicarboxylate was considered to be a C-substituted product. The ratio of N/C was 25:75.

A mixture of ethyl 1-pyrrolecarboxylate and ethyl 2-pyrrolecarboxylate was obtained when diethyl carbonate reacted with pyrrolyl Grignard reagent. The ratio of N/C was 97:3. The pathways of formation of these two compounds should be the same as that described above.

Diethyl carbonate easily reacts with magnesium halide with evolution of heat to form a molecular compound (71).



(The ether molecules attached to the magnesyl group are not shown for the sake of simplicity.)

(D) The Reaction of Pyrrolylmagnesium Bromide with Diethyl Oxalate

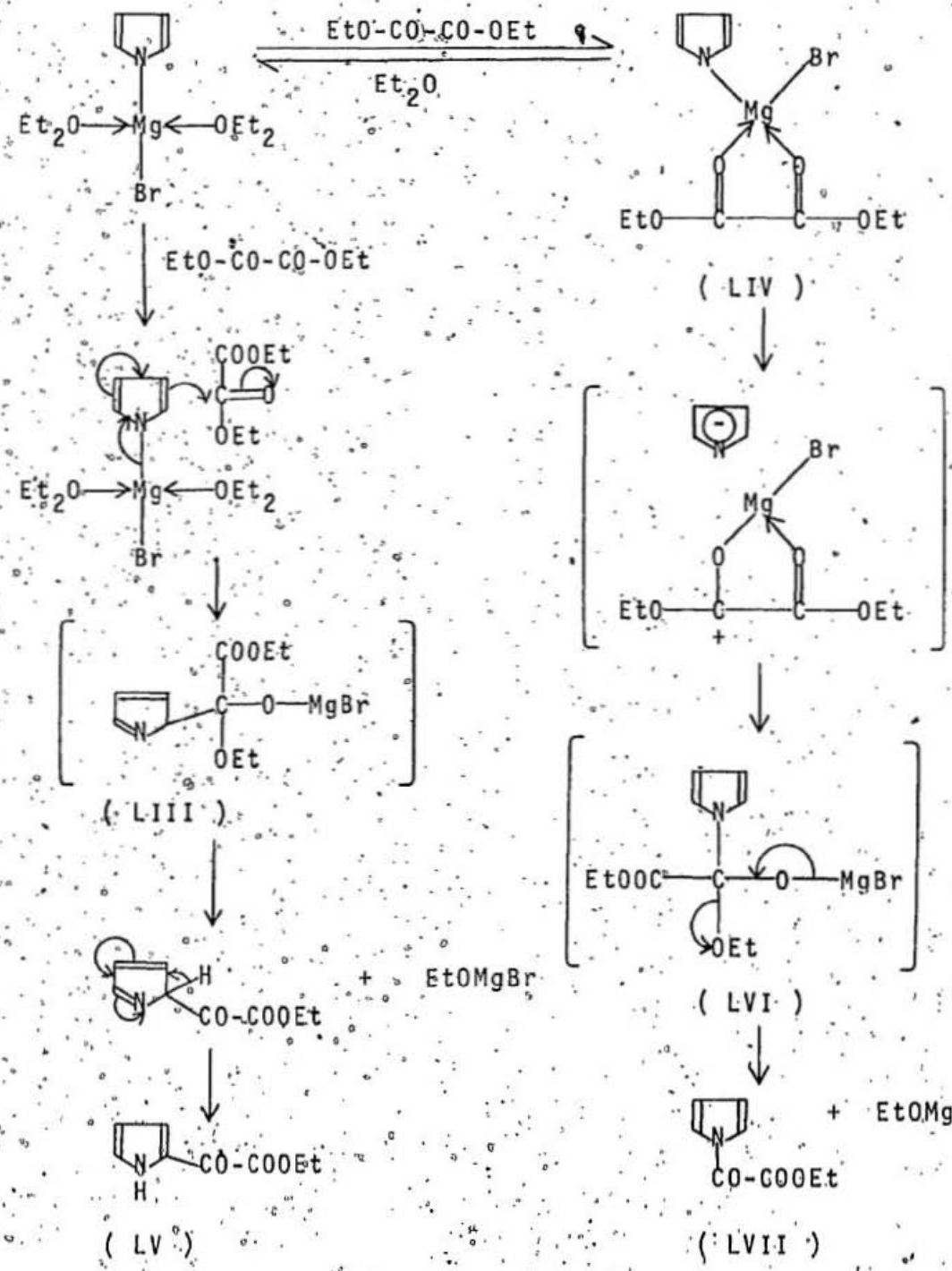
Reaction of the pyrrolyl Grignard reagent with ethyl oxalyl chloride was reported to give a 91% yield of ethyl 2-pyrrolylglyoxylate (LV) (72).

Reaction of pyrrolylmagnesium bromide with diethyl oxalate under our standard conditions also afforded a mixture of ethyl 1-pyrrolylglyoxylate (LVII) and ethyl 2-pyrrolylglyoxylate. Compound (LVII) was identified by microanalysis and spectroscopic properties. Here we also believe that the C-substituted pyrrole derivative was formed from the direct interaction of one molecule of diethyl oxalate and the pyrrolyl group of the undissociated Grignard reagent whereas the N-substituted pyrrole derivative was produced by the complex(LIV). The ratio of N/C was 46:54.

(E) The Reaction of Pyrrolylmagnesium Bromide with N,N'-Dicyclohexylcarbodiimide (DCC)

The reaction of N,N'-dialkylcarbodiimide with alkylmagnesium halide has been reported (73). It has been proposed that an addition product is formed by the addition of the magnesyl group to the nitrogen atom and the alkyl group to the carbon atom of the C=N bond of the carbodiimide (74).

The reaction of N,N'-dicyclohexylcarbodiimide with pyrrolylmagnesium bromide under our standard conditions



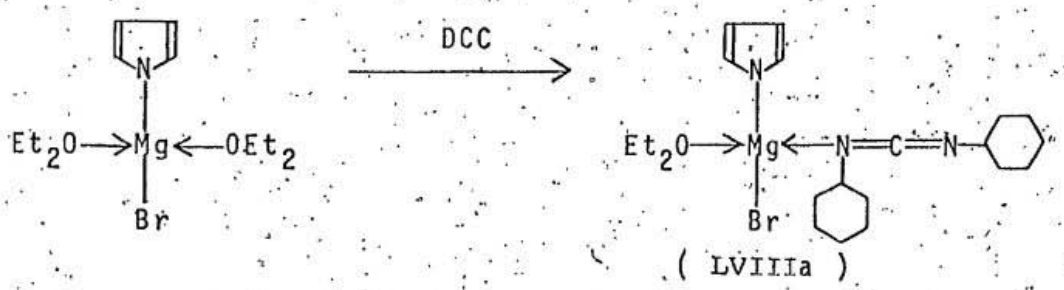
(The ether molecules attached to the magnesyl group are not shown in (LIII) and (LVI) for the sake of simplicity.)

afforded a 93% yield of N,N'-dicyclohexyl-1-pyrrolylcarbamidine (LIX). The structure of compound (LIX) is supported by micro-analysis and spectroscopic properties. Reduction of compound (LIX) with lithium aluminium hydride in diethyl ether gave N,N'-dicyclohexylformamidine (LX). The structure of compound (LX) is also supported by spectroscopic properties and its literature melting point (117). In 6M hydrochloric acid solution, compound (LIX) gave pale blue crystals. Free N,N'-dicyclohexyl-1-pyrrolylcarbamidine was regenerated on treating this solid with dilute sodium hydroxide solution. The solid is likely to be the hydrochloride of compound (LIX). No C-substituted pyrrole derivative was obtained.

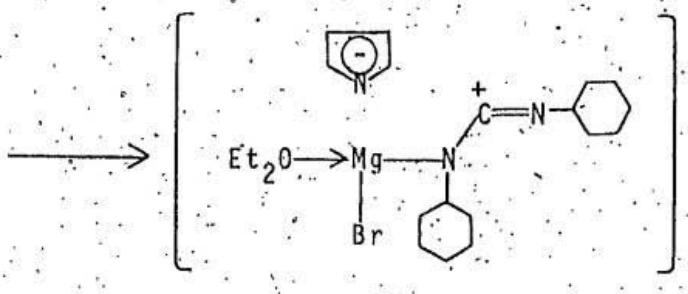
This reaction only produced N,N'-dicyclohexyl-1-pyrrolyl-carbamidine indicating that all of the N,N'-dicyclohexylcarbo-diimide molecule complexed with the magnesyl group of the pyrrolylmagnesium bromide with the displacement of an ether molecule to form the complex (LVIIIa) which then formed the intermediate (LVIIIb). Reaction of compound (LVIIIb) with water afforded N,N'-dicyclohexyl-1-pyrrolylcarbamidine.

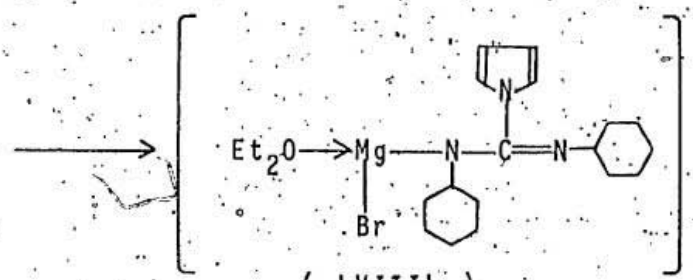
(F) The Reaction of Pyrrolylmagnesium Bromide with Dimethylcyanamide

Reactions between Grignard reagents and disubstituted cyanamides have been reported (75). For example, good yields of amidine hydrochlorides were reported by Adams and Beebe (76) as resulting from the treatment of dibenzylcyanamide with

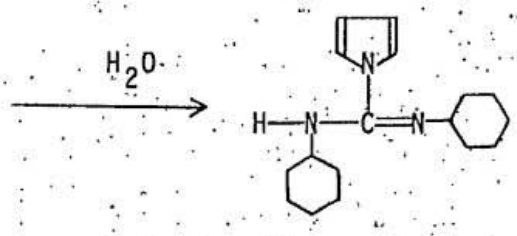


(LVIIIa)

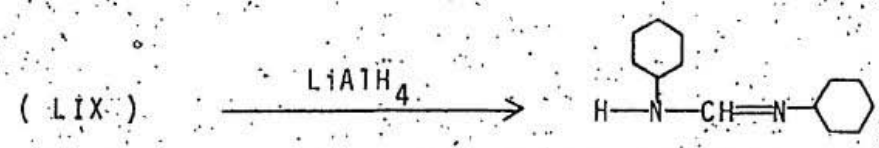




(LVIIIb)



(LIX)

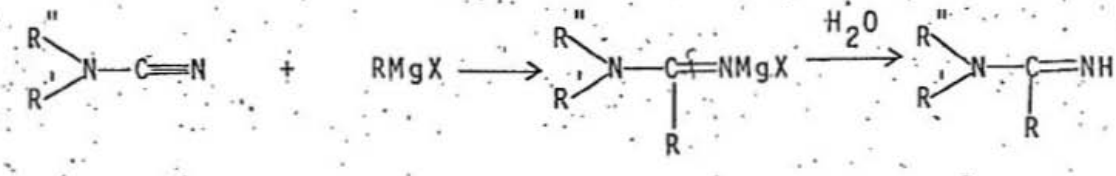


(LX)

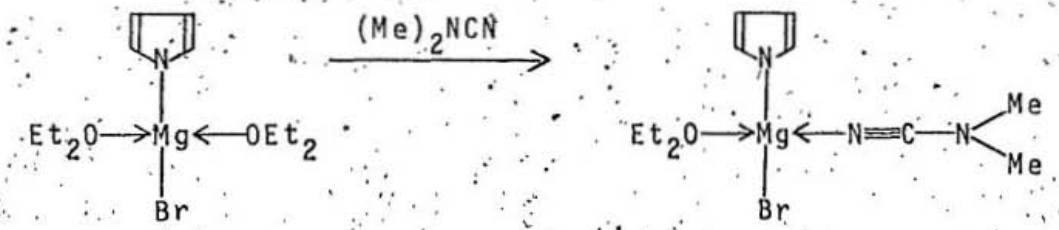
ethyl, phenyl, and p-tolylmagnesium halides. An amidine was also obtained from the reaction of dimethylcyanamide and phenylmagnesium bromide (77). It was thought that complexes of the general formula (LXIa) were formed by the addition of one mole of the Grignard reagent to one mole of the cyanamide. Reaction of (LXIa) with water then gave the corresponding amidines (LXIb). Coordination compounds of dimethylcyanamide and strong Lewis acids have also been isolated (78). The nitrile nitrogen atom here is a stronger donor than that of acetonitrile.

The reaction of pyrrolylmagnesium bromide with dimethylcyanamide in diethyl ether gave exclusively the N-substituted compound, N,N-dimethyl-1-pyrrolylcarbamidine (LXIII). As in the cases of diethyl carbonate and N,N'-dicyclohexylcarbodiimide, it is thought that all of the cyanamide molecule first complexed with the magnesyl group of the Grignard reagent to form complex (LXIIa) which then rearranged to intermediate (LXIIb). Reaction of intermediate (LXIIb) with water then gave N,N-dimethyl-1-pyrrolylcarbamidine.

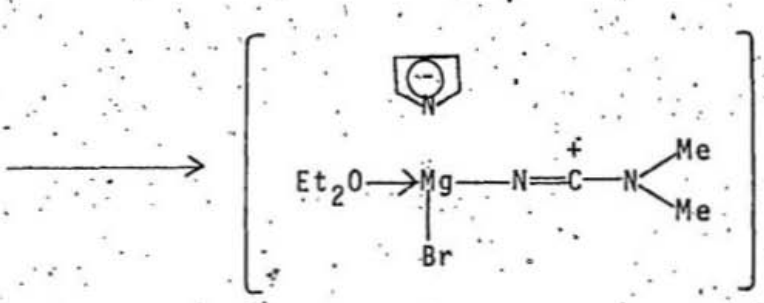
The reaction of dimethylcyanamide with pyrrolyllithium also gave the same product. In both cases, only 8-10% of product was obtained and most of the unreacted starting material, dimethylcyanamide, was recovered.

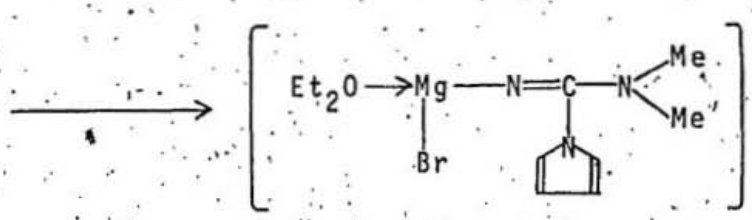


(LXIa) (LXIb)

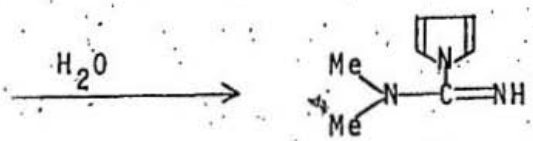


(LXIIa)





(LXIIb)



(LXIII)

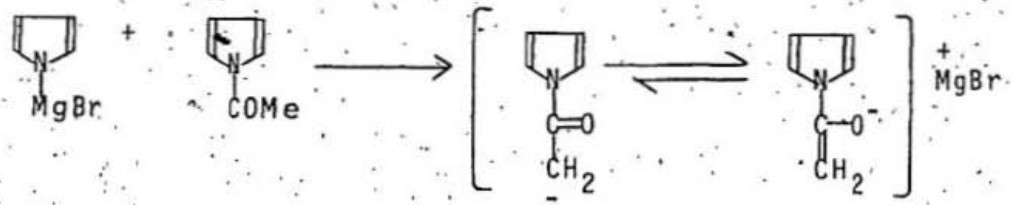
(G) The Reaction of 1-Acetylpyrrolylmagnesium Bromide with Ethyl Acetate

In the reaction of one part of pyrrolylmagnesium bromide with ethyl acetate in the presence of 1.5 parts of tetramethylethylenediamine (TMEDA), besides the 1-acetyl and 2-acetylpyrrole, a new compound, 1-acetoacetylpyrrole (LXV) was obtained. The reaction of ethyl acetate with 1-acetylpyrrolylmagnesium bromide (LXIVa) also produced the same product. It is likely that after the formation of the 1-acetylpyrrole, it reacted with another mole of unreacted pyrrolylmagnesium bromide to form a new organomagnesium reagent, 1-acetylpyrrolylmagnesium bromide. This organomagnesium reagent then reacted with another mole of ethyl acetate to give complex (LXIVb) which finally produced compound (LXV).

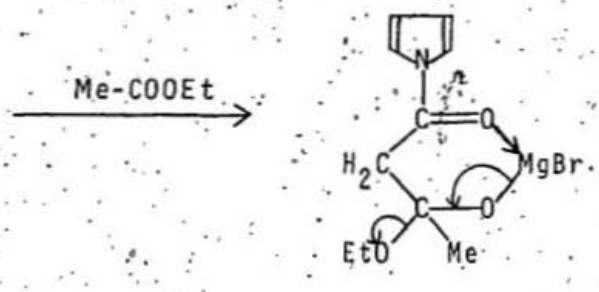
1-Acetoacetylpyrrole reacted with ferric chloride solution to give a pink-colored complex. The n.m.r. spectrum of 1-acetoacetylpyrrole in carbon tetrachloride indicated that there was a mixture of keto and enol forms in that solvent. In the more polar solvent, chloroform, the equilibrium was shifted to the right. At present we are not able to differentiate between the enol forms (LXVb) and (LXVc).

(H) The Reaction of Pyrrolylmagnesium Bromide with S-Ethyl Chlorothioformate

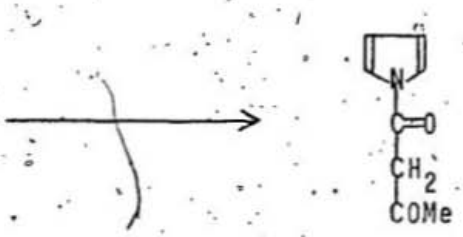
This reaction gave, in diethyl ether, mainly a mixture



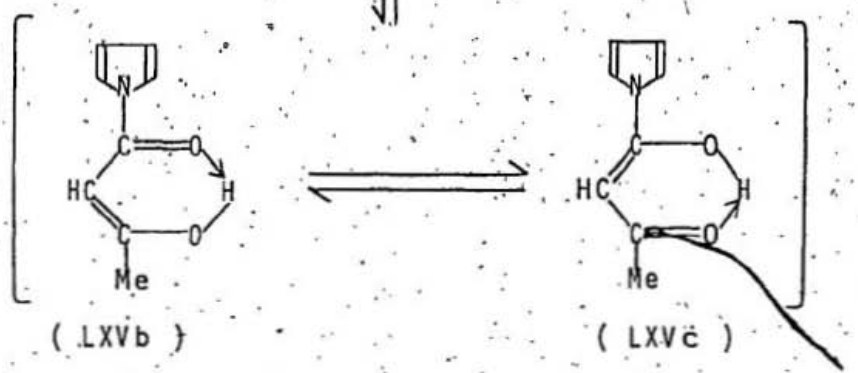
(LXIVa)



(LXIVb)



(LXVa)

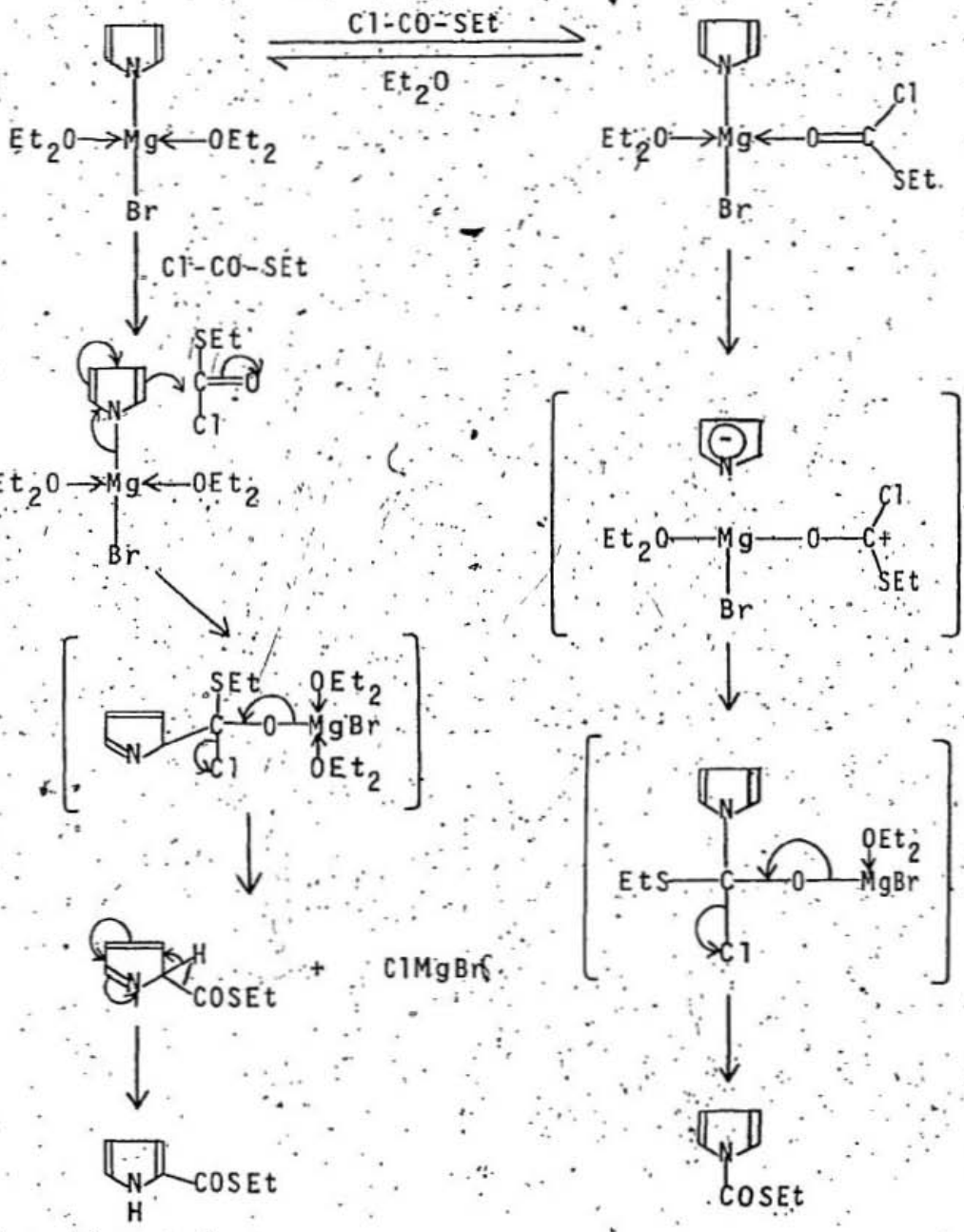


(LXVb) (LXVc)

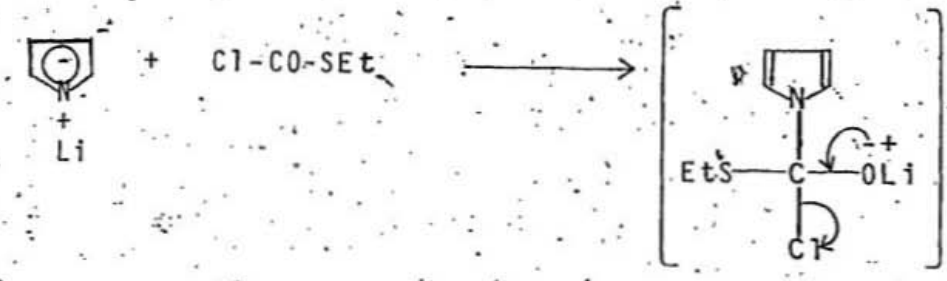
of S-ethyl 1-pyrrolethiocarboxylate (LXVI) and S-ethyl 2-pyrrolethiocarboxylate (LXVII). Traces of 1,2'-dipyrrolyl ketone and S,S'-diethyl dithiocarbonate were also detected. The pathways of formation of these two compounds will be discussed in a later part of this thesis. The ratio of N/C was 6:94. We believe that S-ethyl 2-pyrrolethiocarboxylate was formed by the direct interaction of the pyrrolyl group of the undissociated Grignard reagent and S-ethyl chlorothioformate whereas the S-ethyl 1-pyrrolethiocarboxylate was formed from the complex produced by the coordination of the carbonyl oxygen atom of S-ethyl chlorothioformate with the magnesyl group of the pyrrolyl Grignard reagent. The results of this reaction are recorded in Table IV (p. 78) together with results which are discussed later in Chapter IV(B).

(I) The Reaction of Pyrrolyllithium with S-Ethyl Chlorothioformate

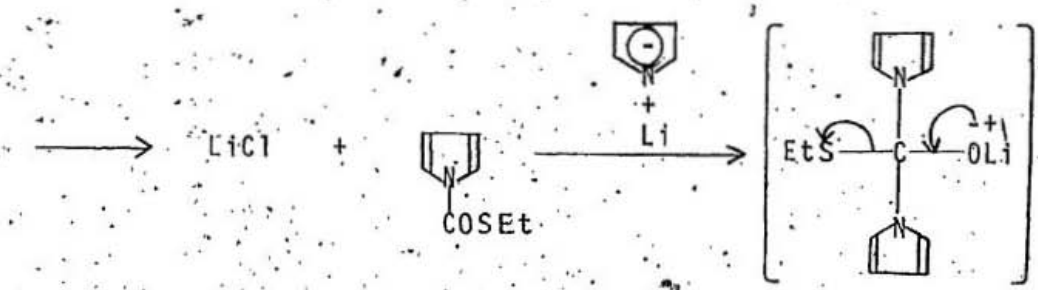
This reaction gave a mixture of S-ethyl 1-pyrrolethiocarboxylate and 1,1'-dipyrrolyl ketone (LXX). The S-ethyl 1-pyrrolethiocarboxylate was probably produced by the intermediate (LXVIII) formed from the reaction of the pyrrolyl group of the dissociated lithium salt with one molecule of S-ethyl chlorothioformate. This S-ethyl 1-pyrrolethiocarboxylate then reacted with another pyrrolyl group to give


Cl-CO-SEt
Et2O
Et2O→Mg←OEt2
Br
Cl-CO-SEt
SEt
Cl
Et2O→Mg←OEt2
Br
OEt2
MgBr
OEt2
COSEt
+ ClMgBr
COSEt
H
Et2O→Mg←O
Cl
SEt
Br
EtS
OEt2
MgBr
Cl
COSEt

(LXVII) (LXVI)

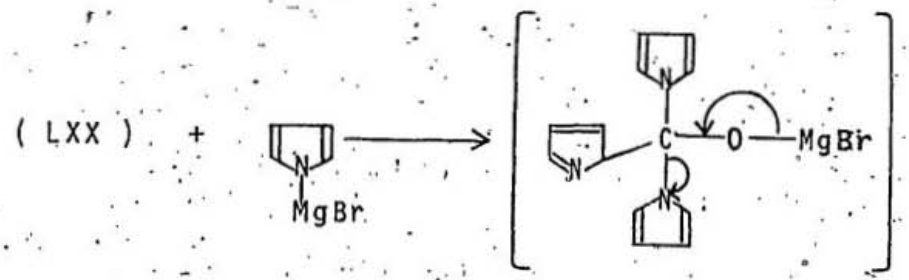


(LXVIII)

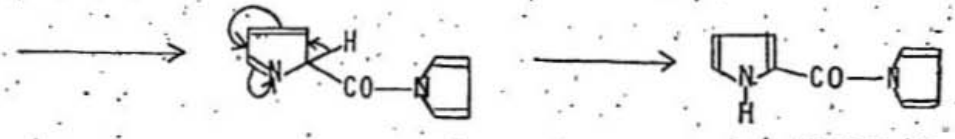


(LXIX)

(LXX)



(LXXI)



(LXXII)

intermediate (LXIX) which eliminated one molecule of LiSEt to give 1,1'-dipyrrolyl ketone.

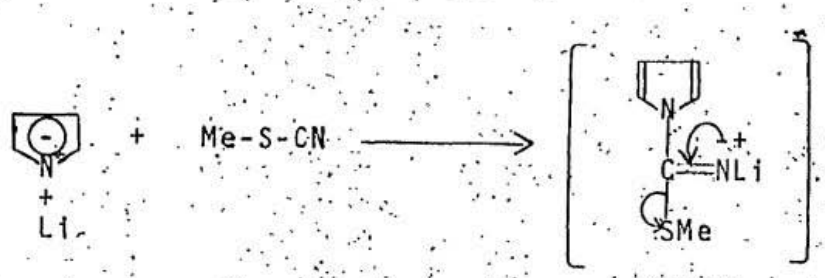
When this reaction was carried out in the presence of two parts of tetramethylethylenediamine, a mixture of the above two compounds was also obtained.

Reaction of 1,1'-dipyrrolyl ketone with pyrrolylmagnesium bromide in diethyl ether afforded 1,2'-dipyrrolyl ketone (LXXII). Complex (LXXI) is the probable intermediate.

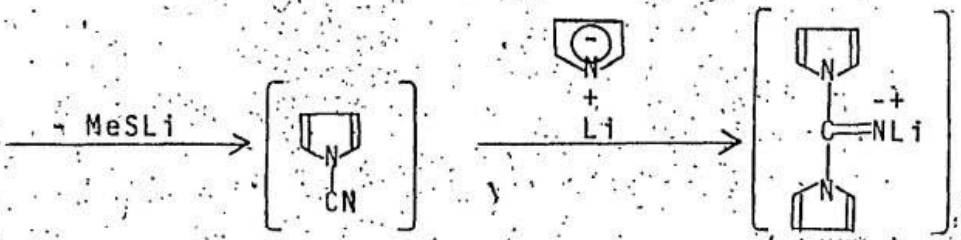
(J) The Reaction of Pyrrolyllithium with Methyl Thiocyanate

The reaction of pyrrolylmagnesium bromide with methyl thiocyanate has been reported (79). The sole product of this reaction was 2-pyrrolecarbonitrile.

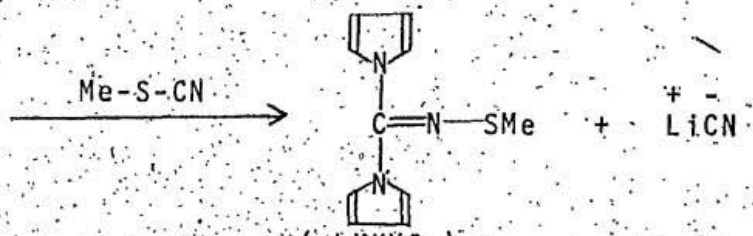
Reaction of the lithium salt of pyrrole with methyl thiocyanate did not give the expected 1-pyrrolecarbonitrile (LXXIV). Instead, a mixture of 1,1'-dipyrrolyl N-thiomethyl-ketimine (LXXVI) and 1,1'-dipyrrolyl ketimine (LXXVII) was obtained. These two compounds showed it is likely that 1-pyrrolecarbonitrile did occur in the reaction pathway. It was probably produced by the elimination of one molecule of MeSLi from intermediate (LXXIII). Under these conditions 1-pyrrolecarbonitrile reacted with another molecule of pyrrolyllithium to form the intermediate (LXXV) which then reacted with another molecule of methyl thiocyanate to form



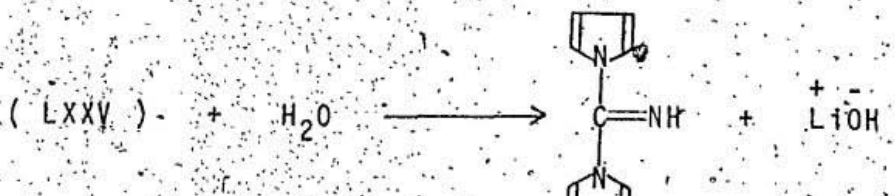
(LXXIII)



(LXXIV) (LXXV)



(LXXVI)



(LXXVII)

1,1'-dipyrrolyl N-thiomethylketimine with the elimination of one molecule of lithium cyanide.

Reaction of intermediate (LXXV) with water on working up gave 1,1'-dipyrrolyl ketimine.

CHAPTER IV

FACTORS WHICH AFFECT THE RATIO OF N/C SUBSTITUTION

(A) Effects of Substrates

(a) Acylation

The effects of substrates which determine the ratio of N/C in the acylation of pyrrolylmagnesium halide or alkali salts of pyrrole have not previously been studied. The same is true for the other ambident anions systems.

According to the literature, carboxylic acid derivatives were used as acylating agents in the Friedel-Crafts reaction, because they all could form stable complexes with such catalysts as AlX_3, ZnX_2, BX_3, MgX_2, SnX_4 etc. (80). These catalysts are strong Lewis acids. The carbonyl group of carboxylic acid derivatives itself consists of two reacting centers, the carbonyl carbon atom and oxygen atom. The carbonyl carbon atom is an electron acceptor (electrophile) or Lewis acid and the carbonyl oxygen atom is an electron donor (nucleophile) or Lewis base. Generally speaking, the nucleophilicity of the carbonyl oxygen atom depends upon the electron availability on that oxygen atom and the electrophilicity of the carbonyl carbon atom depends upon the

effective positive charge on that carbon atom (81). Strong electron-donating groups attached to the carbonyl group would increase the electron availability on the carbonyl oxygen atom (82) and strong electron-withdrawing groups attached to the carbonyl group would increase the effective positive charge on the carbonyl carbon atom (83).

The pyrrolylmagnesium halide can also be regarded as a Lewis acid and Lewis base complex. The magnesyl group is a Lewis acid or electron acceptor and the pyrrolyl group is a Lewis base or electron donor. When a carboxylic acid derivative is added to the pyrrolylmagnesium bromide, there occur two types of Lewis acid and Lewis base reactions. Each competes with the other. The first type of Lewis acid and Lewis base reaction is the direct reaction of the carbonyl carbon atom with the pyrrolyl group of the undissociated Grignard reagent. Since the nitrogen atom of the pyrrolyl group is tightly associated with the magnesyl group, the carbonyl carbon atom is forced to attack the 2- or 3-carbon atom of the pyrrole ring to form C-substituted pyrrole derivatives.

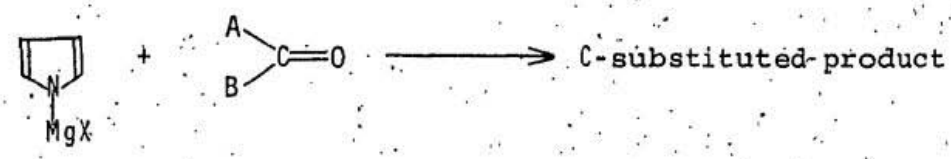
The second type of Lewis acid and Lewis base reaction is the coordination of the carbonyl oxygen atom of the substrate and the magnesyl group of the solvated pyrrolyl Grignard reagent with the displacement of one molecule of the coordinated diethyl ether. This kind of displacement

reaction occurs only when the nucleophilicity of the carbonyl oxygen atom is greater than that of the oxygen atom in diethyl ether. Eventually, a covalent (or ionic) bond forms between the oxygen atom and the magnesyl group with the dissociation of a pyrrolyl group. This dissociated pyrrolyl group then attacks the positively charged carbonyl carbon atom with its nitrogen atom to form an N-substituted pyrrole derivative. The first and second types of reaction are generalized in Schemes (I) and (II) respectively.

The carbonyl group of acetyl chloride and phosgene where the electrophilicity of the carbonyl carbon atoms are greatly enhanced by the electron-withdrawing chlorine atom, prefer the first type of reaction pathway (22a). Acetic anhydride (26b) and carbon dioxide (20,27,28) also prefer the first type of Lewis acid and Lewis base reaction when added to ethereal solution of pyrrolylmagnesium halide.

The carbonyl group of diethyl carbonate where the nucleophilicity of the carbonyl oxygen atom is greatly enhanced by two electron-donating oxygen atoms, prefers the second type of Lewis acid and Lewis base reaction. Since a nitrogen atom is one of the strong electron-donating groups the nucleophilicities of the nitrile nitrogen atom of dimethylcyanamide and of the carbonyl oxygen atom of

(I) The first type of Lewis acid and Lewis base reaction:



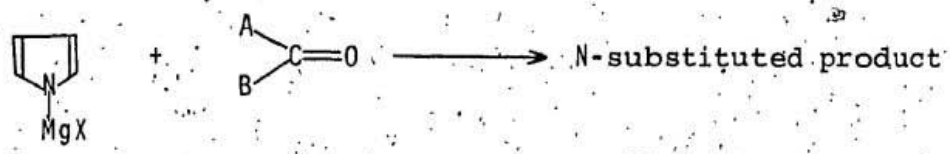
(a) A = R, B = Cl

(b) A = R, B = OCOMe

(c) A = B = Cl

(d) A, B = O

(II) The second type of Lewis acid and Lewis base reaction;



(e) A = B = OEt

(f) A, B = C_6H_5N

phenyl isocyanate are also greatly enhanced. Therefore phenyl isocyanate (84) gives mainly, and dimethylcyanamide gives exclusively, N-substituted products when they react with pyrrolylmagnesium bromide. Our results show that dicyclohexylcarbodiimide prefers the second type of Lewis acid and Lewis base reaction, because each nitrogen atom of this compound is also a strong Lewis base.

The results of the reactions of ethyl acetate, ethyl chloroformate and diethyl oxalate with pyrrolylmagnesium bromide show the existence of both types Lewis acid and Lewis base reactions in their behavior.

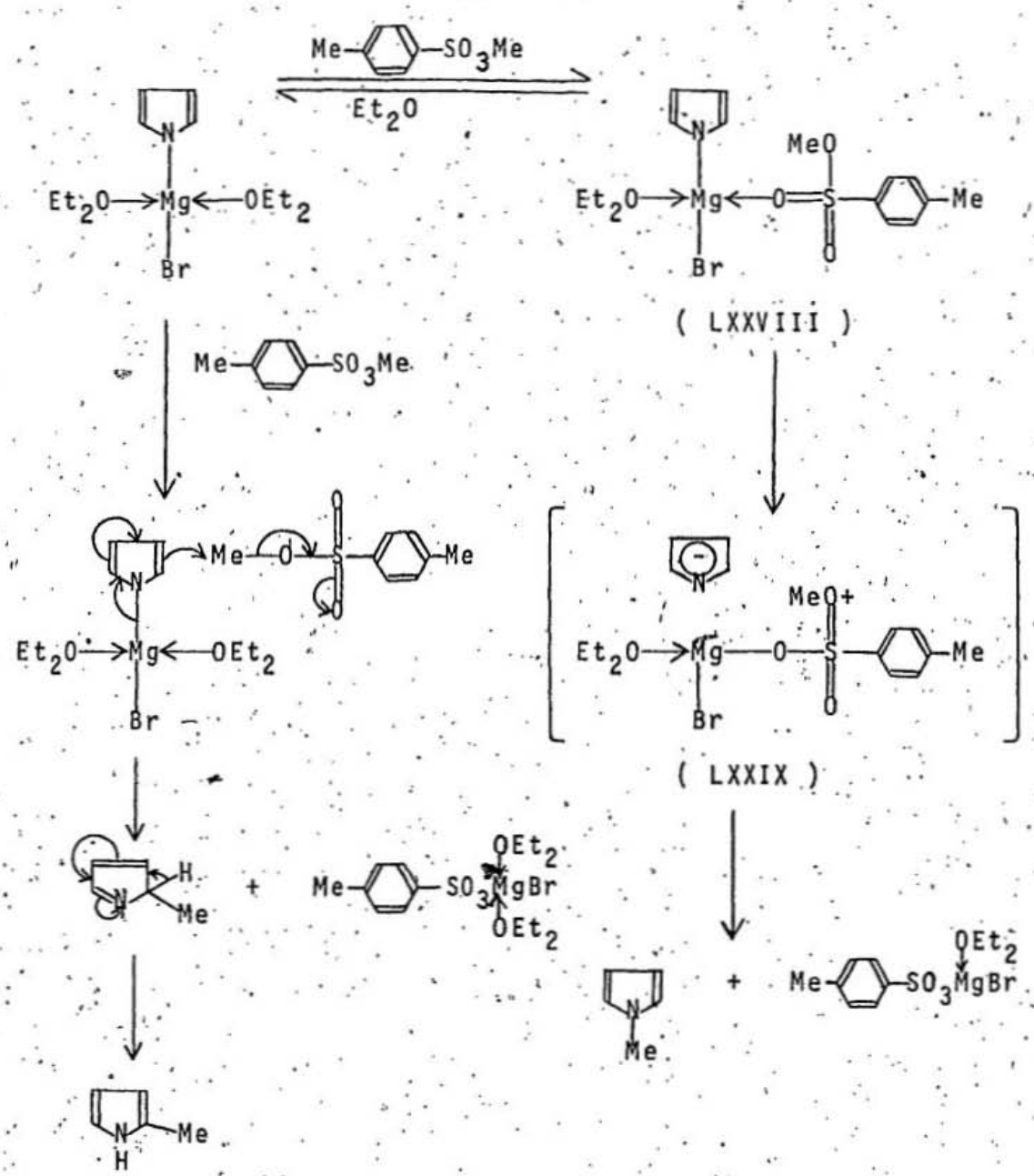
The sulfur atom is not a strong electron-donating group, therefore C-substituted pyrroles are the major products when S-ethyl chlorothioformate, S,S'-diethyl dithiocarbonate and ethyl thiocyanate react with the pyrrolyl Grignard reagent (79).

(b) Alkylation

Iodomethane is a weaker Lewis base than diethyl ether. In ethereal solution the alkyl halide molecule cannot coordinate to the magnesyl group of the solvated pyrrolyl Grignard reagent with the displacement of a diethyl ether molecule from this Grignard reagent. The formation of a

covalent (or ionic) bond between the halogen atom of the alkyl halide and the magnesyl group of the Grignard reagent with the dissociation of a pyrrolyl group, as in the second type of Lewis acid and Lewis base reaction previously described, is also impossible. The alkyl halide is forced to react directly with the pyrrolyl group, whose nitrogen atom is tightly associated with the magnesyl group of the Grignard reagent, on the 2- or 3-carbon atom to produce C-substituted products.

In the alkylation of pyrrolylmagnesium halide with methyl p-toluenesulfonate, dimethyl sulfate, and trimethyl phosphate besides the main product, 2- and 3-methylpyrrole, there is always a certain amount of 1-methylpyrrole(24). It is probably because the oxygen atom of the S=O group of the methyl p-toluenesulfonate molecule coordinates with the magnesyl group of the pyrrolyl Grignard reagent to form complex (LXXVIII). Eventually a covalent (or ionic) bond forms between the oxygen atom and the magnesyl group with the dissociation of a pyrrolyl group as shown in (LXXIX). This dissociated pyrrolyl group then reacts with the methyl group to form 1-methylpyrrole. The formation of 1-methylpyrrole from dimethyl sulfate and trimethyl phosphate can be explained in the similar way.


Me—SO3Me
Et2O
Et2O→Mg←OEt2
Br
MeO
O
S
Me
(LXXVIII)
(LXXIX)
MeO+
OEt2
MgBr
H
N
Me

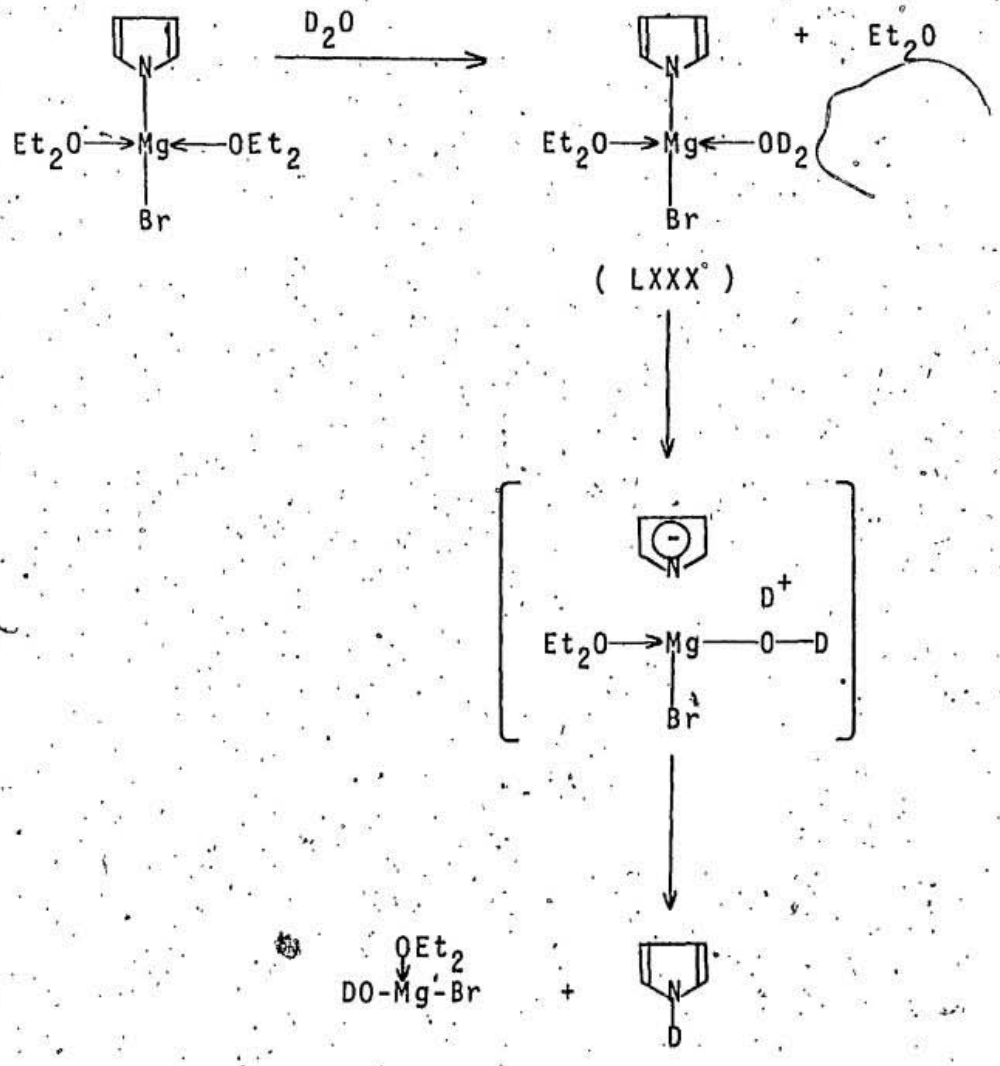
(c) Hydrolysis with D_2O

It has been reported that hydrolysis of pyrrolylmagnesium halide with heavy water, D_2O, gave only N-d-pyrrole (19).

Except for aluminium fluoride and boron trifluoride, aluminium halides (85) and boron trihalides (86) are readily hydrolyzed by water. Magnesium halides form very stable hydrates with water (87). These properties indicate that the oxygen atom of water molecule is a very strong Lewis base. When heavy water is added to the ethereal solution of pyrrolylmagnesium bromide it is likely that the oxygen atom of heavy water also coordinates to the magnesyl group of the pyrrolyl Grignard reagent to form a complex (LXXX). Finally a covalent (or ionic) bond forms between the oxygen atom and the magnesyl group with the dissociation of a pyrrolyl group and a deuteron. This pyrrolyl group then attacks the deuteron with its nitrogen atom to give N-d-pyrrole.

(B) Effects of Solvents

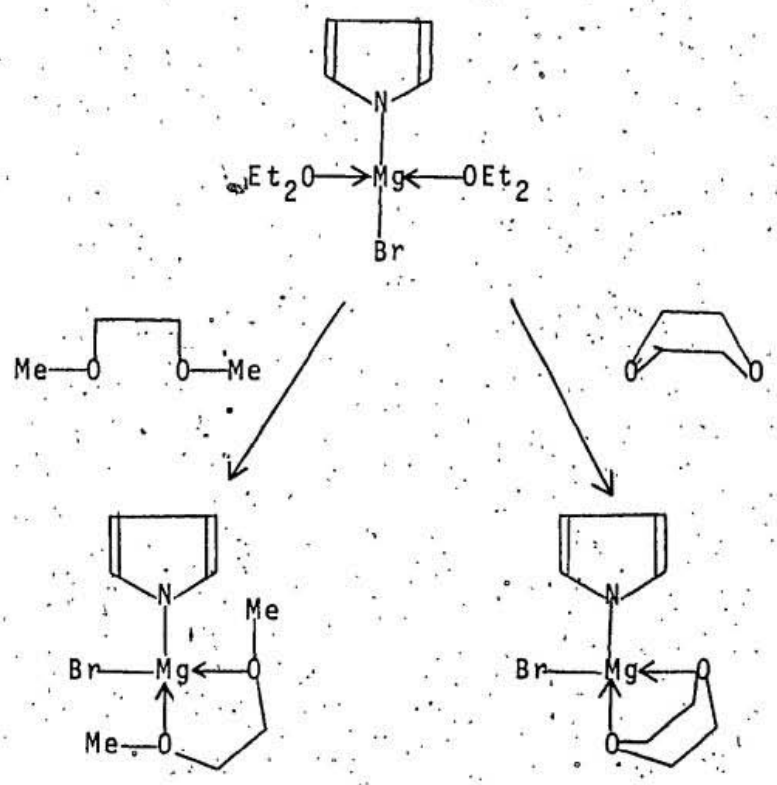
Judd reported that the reaction of pyrrolyllithium with ethyl iodide in diethyl ether gave a mixture of 1-ethyl-, 2-ethyl-, and 3-ethylpyrrole and the major products


D2O
Et2O
Et2O
Mg
OEt2
Br
+ Et2O
Et2O
Mg
OD2
Br
(LXXX°)
D+
Et2O
Mg
O
D
Br
OEt2
DO-Mg-Br
+
D

were from C-substitution (88). In liquid ammonia, pyrrolyllithium was alkylated only on the nitrogen atom. It has been reported that alkylation of pyrrolylmagnesium halide in diethyl ether, tetrahydrofuran, and dihexyl ether gave exclusively C-alkylated pyrroles (19). But the reaction of iodomethane and pyrrolylmagnesium bromide in hexamethylphosphoramide gave almost exclusively 1-methylpyrrole (89).

The ratio of N/C products obtained from the reaction of one part of pyrrolylmagnesium bromide and ethyl chloroformate in diethyl ether in the presence of 1.5 part of 1,2-dimethoxyethane or 1,4-dioxane was almost the same as that obtained from the same reaction in diethyl ether, although these two complexing agents might be expected to displace diethyl ether molecules from the solvated pyrrolyl Grignard reagent to form complexes (LXXXI) and (LXXXII) (43). When the same reaction was carried out in diethyl ether in the presence of 1.5 part of N,N,N',N'-tetramethylethylenediamine, ethyl 1-pyrrolecarboxylate was almost the exclusive product. The results and the ratios of N/C of the reactions mentioned above are recorded in Table II (p. 73).

The above examples indicate that only strongly basic solvents (or complexing agents) can change the courses of these reactions. The ways of changing the courses of reactions by strongly basic solvents (or complexing agents) are explained below.



(LXXXI) (LXXXII)

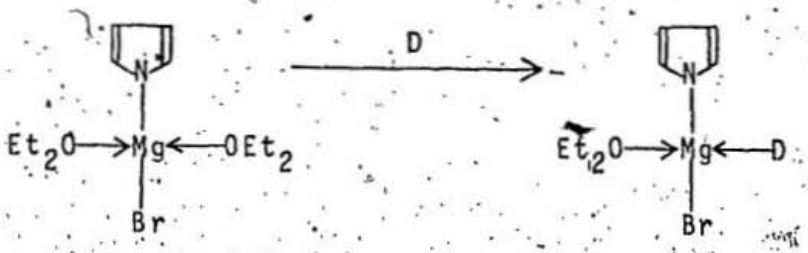
TABLE II. The reaction of one part of pyrrolylmagnesium bromide and ethyl chloroformate in the presence of 1.5 parts of complexing agent

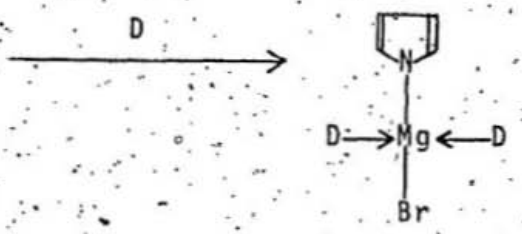
complexing agent	1-ester (XV) (%)	2-ester (XIV) (%)	1,2-di-ester (XVI) (%)	1,2'-ketone (LXXII) (%)	ratio of N/C	total yield (%)
(ether)	13	21	19	0	25 : 75	53
1,4-dioxane	6	7	22	0	17 : 83	35
dimethoxyethane	13	2	65	0	16 : 84	80
TMEDA*	76	1	0	1	98 : 2	78

* TMEDA = N,N,N',N'-tetramethylethylenediamine

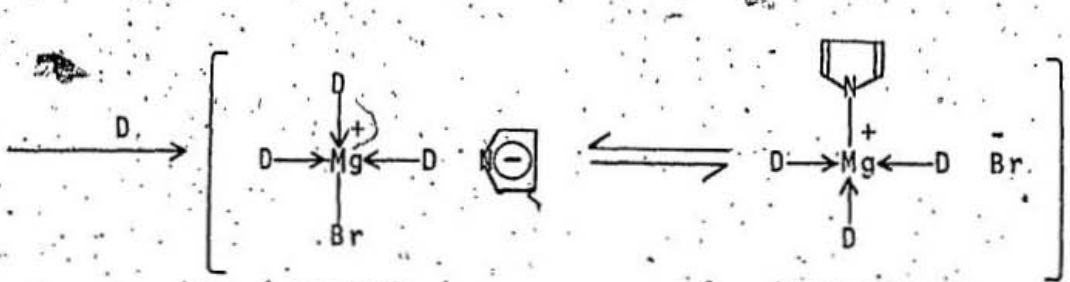
As we pointed out before, iodomethane is a weaker Lewis base than diethyl ether. It cannot displace a diethyl ether molecule from the pyrrolyl Grignard reagent to form a complex with the magnesyl group. Therefore the iodomethane molecule can only react directly with the undissociated pyrrolyl group to form C-substituted products.

When two parts of hexamethylphosphoramide were added to the ethereal solution of pyrrolylmagnesium bromide, heat was given off and white precipitate was also observed, but it did not cause the formation of any 1-methylpyrrole. Literature (44,90), and our results indicate that the two diethyl ether molecules in the disolvated pyrrolylmagnesium bromide are replaced, step by step, by two very strongly basic hexamethylphosphoramide molecules to form another disolvated Grignard reagent (LXXXIII). Complex (LXXXIII) can react with another molecule of hexamethylphosphoramide to form a mixture of trisolvated complexes (LXXXIVa) and (LXXXIVb) with the dissociation of a pyrrolyl group or a halide ion. The pyrrolyl group of dissociated complex (LXXXIVa) reacts with iodomethane to give 1-methylpyrrole but the pyrrolyl group of undissociated complex (LXXXIVb) can only give C-substituted pyrroles. This is demonstrated by the fact that 1-methylpyrrole was obtained only when the ratio

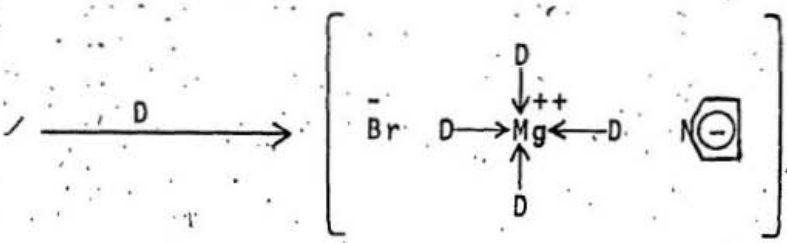




(LXXXIII)



(LXXXIVa) (LXXXIVb)



(LXXXV)

D = $(Me_2N-)_3P{=}O$ (HMPA)

of the added hexamethylphosphoramide to the pyrrolylmagnesium bromide was greater than two. The ratio of N/C increased with increasing ratio of the hexamethylphosphoramide to the pyrrolyl Grignard reagent. The results are recorded in Table III.

When still more hexamethylphosphoramide was added, both the complexes (LXXXIVa) and (LXXXIVb) were converted to the tetrasolvated complex (LXXXV). Reaction of the pyrrolyl group of the dissociated complex (LXXXV) with iodomethane only gave 1-methylpyrrole. This is confirmed by the results reported by Casnati and Pochini (89).

Solid crystals of $MgBr_2 \cdot 2HMPA$ and $MgBr_2 \cdot 4HMPA$ have been successfully isolated (91). That the organic radical is ionized in the presence of excess of hexamethylphosphoramide in ethereal solution has also been reported (44). These results support our above explanation.

The reaction of pyrrolylmagnesium bromide with S-ethyl chlorothioformate in diethyl ether produced a mixture of S-ethyl 1-pyrrolethiocarboxylate and S-ethyl 2-pyrrolethiocarboxylate. The ratio of N/C was 6:94. Only a trace of S,S'-diethyl dithiocarbonate (LXXXVII) was detected. If the reaction was carried out in the presence of more than two parts of N,N,N',N'-tetramethylethylenediamine, the ratio of N/C increased with the increasing amount of the complexing agent added. The results are recorded in Table IV. Quite a

TABLE III. The reaction of pyrrolylmagnesium bromide with iodomethane in absolute ether in the presence of different ratios of hexamethylphosphoramide (HMPA)

HMPA / MgBr	1-methyl (%)	2-methyl (%)	3-methyl (%)	2,3-dimethyl (%)	2,5-dimethyl (%)	2,3,5-trimethyl (%)	ratio of N/C
0 : 1	0.0	7.4	4.9	10.9	1.3	5.9	0 : 100
2 : 1	0.0	10.3	5.4	4.6	3.8	6.9	0 : 100
3 : 1	0.7	8.6	5.0	3.8	3.8	6.1	6 : 94
4 : 1	12.2	7.0	4.5	3.8	2.2	4.7	36 : 64
5 : 1	21.8	4.8	3.6	2.1	0.9	0.8	66 : 34

(30-40% of unchanged pyrrole was recovered from each reaction.)

TABLE IV. The reaction of pyrrolylmagnesium bromide with S-ethyl chlorothioformate in absolute ether in the presence of different ratios of N,N,N',N'-tetramethylethylenediamine (TMEDA)

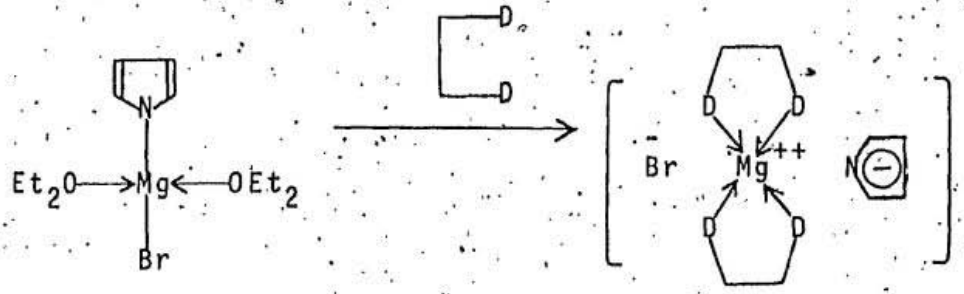
TMEDA / MgBr	1-thioester (LXVI) (%)	2-thioester (LXVII) (%)	1,1'-ketone (LXX) (%)	1,2'-ketone (LXXII) (%)	dithiocarbonate* (LXXXVII) (%)	ratio of N/C	total yield (%)
0 : 1	3	42	0	trace	2	6 : 94	45
1 : 1	3	31	0	trace	35	10 : 90	34
1.5 : 1	16	35	0	0	64	32 : 68	51
2 : 1	34	23	trace	trace	55	60 : 40	54
3 : 1	46	10	6	0	35	84 : 16	62
4 : 1	41	1	4	2	42	96 : 4	48
5 : 1	51	1	7	0	34	99 : 1	58

* Based on the quantity of the S-ethyl chlorothioformate used.

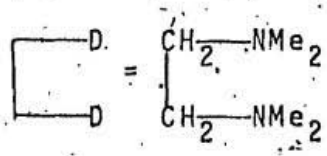
large quantity of S,S'-diethyl dithiocarbonate was also obtained. When five parts of N,N,N',N'-tetramethylethylenediamine was added, the product was almost exclusively N-substituted pyrrole. These results also indicated that the tetracoordinated pyrrolylmagnesium bromide (LXXXVI), which is very similar to complex (LXXXV), was also present in the reaction mixture.

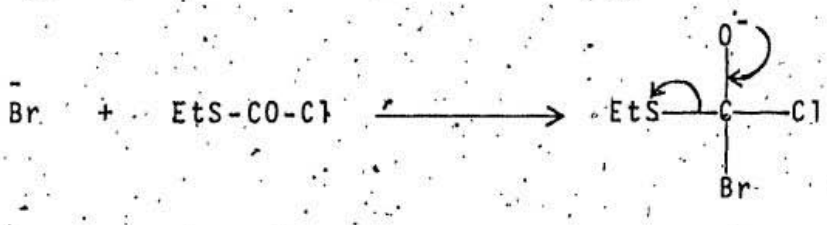
The presence of quite a large quantity of S,S'-diethyl dithiocarbonate may be explained as follows. After the addition of N,N,N',N'-tetramethylethylenediamine, some of the bromide ion of the pyrrolyl Grignard reagent dissociated. The bromide ion then reacted with one molecule of S-ethyl chlorothioformate to produce one molecule of ClCOBr and the ethanethiolate anion. The ethanethiolate anion then reacted with another molecule of S-ethyl chlorothioformate to give S,S'-diethyl dithiocarbonate (LXXXVII) as shown by the equations.

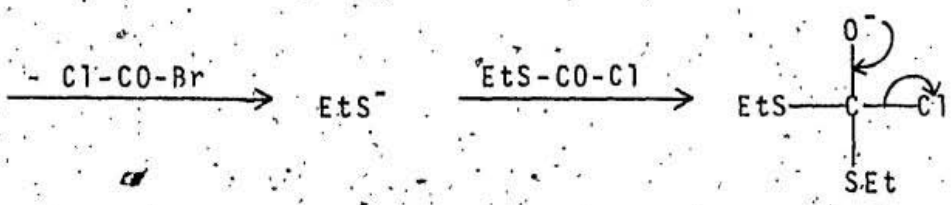
We also found that the compounds S-ethyl chlorothioformate, dimethyl sulfate, and methyl p-toluenesulfonate, which can form complexes with the magnesyl group of the pyrrolyl Grignard reagent and eventually produce N-substituted products, were very sensitive to hexamethylphosphoramide. The reaction of iodomethane with one part of pyrrolylmagnesium bromide in the presence of two parts of hexamethylphosphoramide did not produce N-methylpyrrole. Under the same conditions, S-ethyl chlorothioformate gave exclusively the N-substituted product, and dimethyl sulfate and methyl p-toluenesulfonate gave mainly N-substituted products. The results of the lattter are listed in Table V.

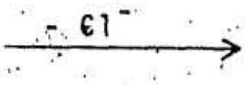


(LXXXVI)









(LXXXVII)

TABLE V. The reactions of one part of pyrrolylmagnesium bromide with iodomethane, dimethyl sulfate and methyl p-toluenesulfonate in absolute ether in the presence of two parts of hexamethylphosphoramide (HMPA)

reagent	1-methyl (%)	2-methyl (%)	3-methyl (%)	2;3-di-methyl (%)	2,5-di-methyl (%)	2,3,5-tri-methyl (%)	ratio of N/C
iodo-methane	0.0	10.3	5.4	4.6	3.8	6.8	0 : 100
dimethyl sulfate	16.5	6.1	5.0	2.1	0.6	0.0	56 : 44
methyl p-toluene-sulfonate	28.8	3.5	2.9	1.5	0.4	0.0	78 : 22

(C) Effects of Cations

Treibs and Dietl suggested that the position on the pyrrolyl group attacked by a nucleophile was determined by the ionic radius of the alkali metal ion (8c). Hobbs and coworkers also reported that the ratios of N/C decreased in the order K > Na > Li when alkali salts of pyrrole were treated with allyl bromide and benzyl chloride in the same solvent (34).

Acylation of pyrrolylmagnesium bromide with ethyl chloroformate in diethyl ether produced a mixture of N-acylated and C-acylated pyrroles. The ratio of N/C was 25:75. But, acylation of the alkali salts of pyrrole with the same compound gave only N-acylated product. The results are recorded in Table VI. Similarly acylation of pyrrolylmagnesium bromide in diethyl ether with S-ethyl chlorothioformate gave a mixture of N-acylated and C-acylated pyrrole but acylation of pyrrolyllithium with the same compound gave only N-acylated pyrrole. These examples indicate that the ratio of N/C does not only depend upon the ionic radius of metal ion but also depends upon the charge on the metal ion. In the above examples, the ionic radii of both lithium and magnesium are 0.78Å but the formal charge on magnesium ion is twice as large as that on the lithium ion. The reason why the ratio of N/C from the pyrrolyl Grignard reagent is smaller

TABLE VI. The reaction of magnesium and alkali metal salts of pyrrole with ethyl chloroformate in absolute ether

cation	radius o (A)	1-ester (XV) (%)	2-ester (XIV) (%)	1,1-ketone (LXX) (%)	1,2-diester (XVI) (%)	ratio of N/C	total yield (%)
Mg^{++}	0.78	13	21	0	19	25 : 75	53
Li^{+}	0.78	39	0	16	0	100 : 0	55
Na^{+}	0.98	87	0	0	0	100 : 0	87
K^{+}	1.33	64	0	0	0	100 : 0	64

than that from pyrrolyllithium will be discussed in the later part of this thesis.

Pyrrolylmagnesium halide also gave a smaller ratio of N/C than did pyrrolyllithium in alkylation reactions (19,88).

(D) Effects of Substituents

Alkylation of the Grignard reagents from 2-methylpyrrole, 3-methylpyrrole, 2,3-dimethylpyrrole and 2,5-dimethylpyrrole with iodomethane all gave C-alkylated products. Acylation of the Grignard reagent from 2-methylpyrrole (92), 2-isopropylpyrrole (93), and 2,5-dimethylpyrrole (94) with methyl chlorothioformate or acetyl chloride also gave only C-acylated products. But, acylation of 2-carboxyethyl-pyrrolylmagnesium bromide (LII) with ethyl chloroformate gave only the N-acylated product, diethyl 1,2-pyrroledi-carboxylate (XVI). In the case of alkylpyrrolylmagnesium bromides, the alkyl groups on pyrrole ring inhibit dissociation of the bond between the nitrogen atom of the pyrrolyl group and the magnesyl group of the Grignard reagent, so the nitrogen is still tightly associated with the magnesyl group, therefore electrophilic attack at this nitrogen atom is inhibited. In the case of 2-carboxyethylpyrrolylmagnesium bromide, the strong electron-withdrawing ester group not only can dissociate the nitrogen atom from the magnesyl

group, the carbonyl oxygen atom of this ester group also can form a bond with the magnesyl group to give isomer (LIIb) (p. 47) as shown Chapter III (C). The nitrogen atom of isomer (LIIb) now is not blocked by the magnesyl group, and electrophilic attack at this position is made possible.

(E) Effects of Halide Ions

Reinecke and coworkers reported the reaction of indolylmagnesium halides with iodomethane in the presence of 2.8 parts of hexamethylphosphoramide, the chloride gave the highest ratio of N/C and iodide gave the lowest ratio of N/C (95). They explained that the increased electronegativity of the chlorine atom imparted more ionic character (polarity) to the bond between the nitrogen atom of the indolyl and the magnesyl groups of the Grignard reagent thereby leading to more extensive dissociation by the strongly complexing solvent.

The reaction of one part of each pyrrolylmagnesium halide with S-ethyl chlorothioformate in the presence of two parts of N,N,N',N'-tetramethylethylenediamine was studied. The chloride gave the highest ratio of N/C and iodide gave the lowest ratio of N/C. The results are recorded in Table VII.

TABLE VII. The reaction of pyrrolylmagnesium halides with S-ethyl chlorothioformate in the presence of N,N,N',N'-tetramethylethylenediamine in absolute ether*

 MgX	1-ester (XV) (%)	2-ester (XIV) (%)	1,1'-ketone (LXX) (%)	1,2'-ketone (LXXII) (%)	dithiocarbonate (LXXXVII) (%)	ratio of N/C	total yield (%)
Cl	52	6	0	0	38	89 : 11	58
Br	34	23	trace	trace	55	60 : 40	57
I	10	28	0	5	27	28 : 72	43

*. The ratio of N,N,N',N'-tetramethylethylenediamine to pyrrolylmagnesium halides was 2:1.

*. Based on the S-ethyl chlorothioformate used.

Magnesium bromide has been reported to behave as a stronger electrolyte than does magnesium chloride in hexamethylphosphoramide solution (45). This example shows that the chlorine atom is associated more tightly with the magnesyl group than is the bromine atom, therefore it is harder to dissociate the chloride ion from the magnesium chloride than the bromide ion from the magnesium bromide.

The trisolvated pyrrolylmagnesium halide (LXXXIV) (p. 75) probably is a mixture of isomers (LXXXIVa) and (LXXXIVb) as shown in Chapter IV (B). The chlorine atom which tends to associate tightly with the magnesyl group of the pyrrolyl Grignard reagent would shift the equilibrium to the left hand side of the equation and the iodine atom which does not associate with the magnesyl group as tightly as the chlorine atom, would shift the equilibrium to the right hand side of the equation. That is why chloride gave the highest ratio of N/C and iodide gave the lowest ratio of N/C.

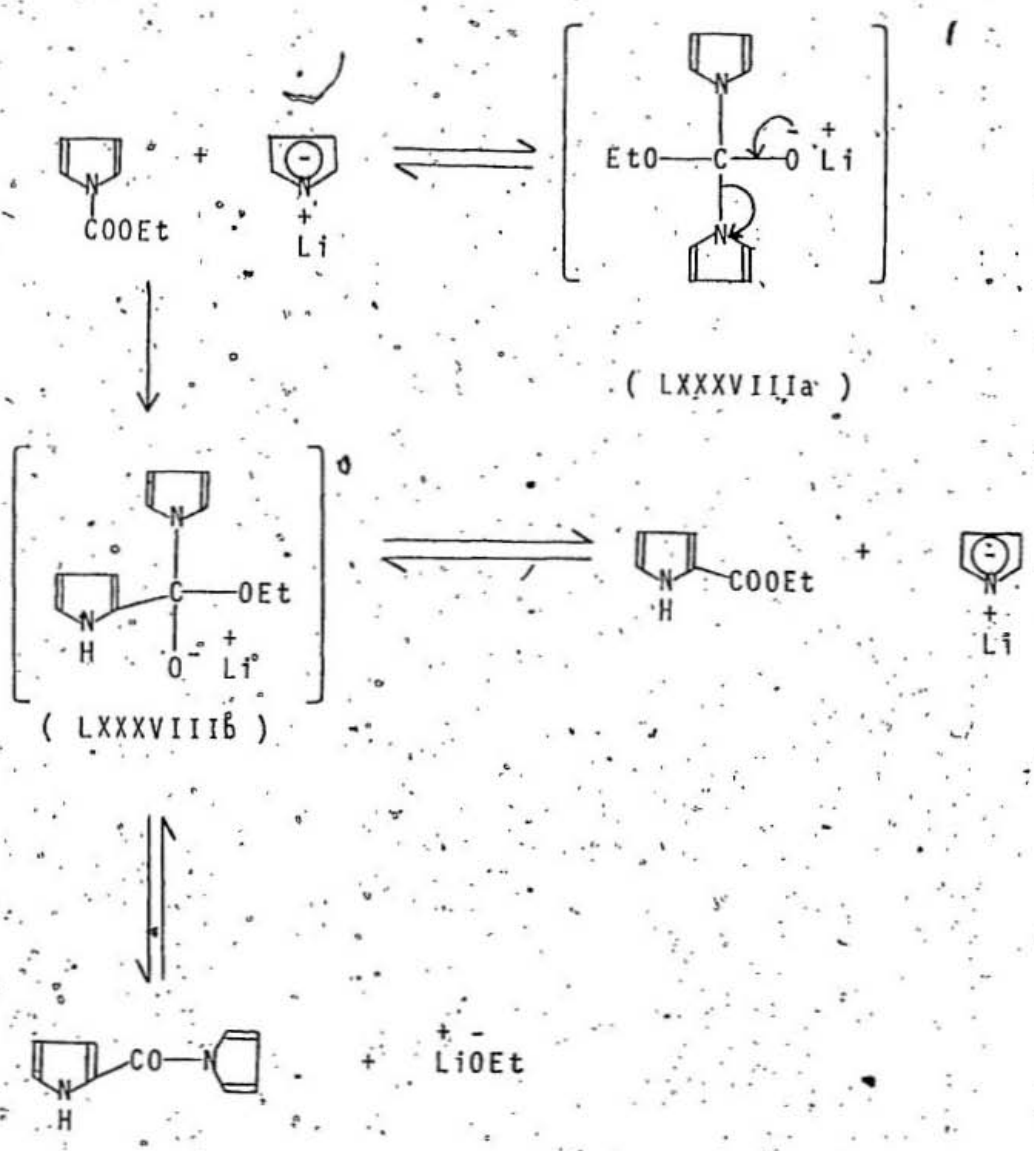
(F) Effects of Temperature

Alkylation and acylation of pyrrolylpotassium at low temperatures always produced N-substituted products, but the reaction of pyrrolylpotassium with carbon dioxide at 200° gave mainly the 2-carboxylic acid (96). With iodopentane

at 157°, no N-pentylpyrrole was obtained (97). This temperature is too low for the N-alkylpyrrole to rearrange to a C-alkylpyrrole directly (98). Papadopoulos and Tabello reported that in the treatment of pyrrolylpotassium with allyl p-toluenesulfonate in 1,4-dioxane an increase in the reaction temperature caused a small increase of the ratio of N/C (99).

The reaction of pyrrolyllithium with diethyl carbonate in 1,4-dioxane at room temperature gave almost exclusively ethyl 1-pyrrolecarboxylate, but the same reaction gave a mixture of ethyl 1-pyrrolecarboxylate, ethyl 2-pyrrolecarboxylate and 1,2'-dipyrrolyl ketone in boiling 1,4-dioxane (b.p. 101°). The ratio of N/C was 65:35. The following reactions in boiling 1,4-dioxane were also studied: (a) The reaction of pyrrolyllithium with ethyl 1-pyrrolecarboxylate produced a mixture of ethyl 2-pyrrolecarboxylate and 1,2'-dipyrrolyl ketone; (b) The reaction of pyrrolyllithium with ethyl 2-pyrrolecarboxylate produced only 1,2'-dipyrrolyl ketone; (c) The reaction of lithium ethoxide with 1,2'-dipyrrolyl ketone gave only ethyl 2-pyrrolecarboxylate.

Reaction (a) indicated that ethyl 1-pyrrolecarboxylate was probably the first product in the reaction mixture from pyrrolyllithium and diethyl carbonate. At this high temperature


COOEt
Li
EtO
C
O Li
(LXXXVIIIa)
OEt
H
O Li
(LXXXVIIIb)
COOEt
H
Li
CO
H
LiOEt

some of this compound reacted with another molecule of pyrrolyllithium to give intermediate (LXXXVIIIb). Elimination of lithium ethoxide from (LXXXVIIIb) yielded 1,2'-dipyrrolyl ketone and elimination of pyrrolyllithium gave ethyl 2-pyrrolecarboxylate. Reactions (b) and (c) showed that at boiling 1,4-dioxane temperature, the formation of intermediate (LXXXVIIIb) from one molecule of ethyl 1-pyrrolecarboxylate and one molecule of pyrrolyllithium was practically irreversible.

Reaction (a) is one of the examples in which the product of a kinetically controlled reaction, ethyl 1-pyrrolecarboxylate, is slowly converted to the thermodynamically more stable products, ethyl 2-pyrrolecarboxylate and 1,2'-dipyrrolyl ketone at high temperature (47a).

CHAPTER V

APPLICATION OF THE HARD AND SOFT ACIDS AND BASES PRINCIPLE

The concept of hard and soft acids and bases was first defined by Pearson (52).

Hard acids are Lewis acids with a high electronegativity and a low polarizability. These properties correspond to a high positive charge and a small size of the acceptor atom and the absence from it of an unshared electron pair.

Soft acids are Lewis acids with a low electronegativity and a high polarizability. These properties correspond to a low positive charge (or absence of charge), a large size of the acceptor atom, and the presence of an unshared electron pair (p or d electrons) at this atom.

Hard bases are Lewis bases with a high electronegativity, low polarizability, and resistant to oxidation, ie. hard bases firmly retain valence electrons.

Soft bases are Lewis bases with a low electronegativity, high polarizability, and readily oxidized, ie. they retain their valence electrons less firmly.

Pearson also generalized that hard acids prefer to bind to hard bases and soft acids prefer to bind to soft bases, or hard electrophilic centers (acids) react rapidly with

hard nucleophiles (bases), and soft electrophilic centers react rapidly with soft nucleophiles.

Using a reference hard acid, H^+ and a reference soft acid, CH_3Hg^+, three categories of bases were classified as shown in Table VIII. Using the bases in Table VIII, acids were also classified into three categories as shown in Table IX.

The pyrrolyl group contains three centers susceptible to electrophilic attack. They are the nitrogen atom, the α-carbon atom and the β-carbon atom. For simplicity here we just want to discuss the reaction on the nitrogen atom and the α-carbon atom. According to the definition of Pearson (52), the nitrogen atom is a hard Lewis base and the carbon atom is a soft Lewis base in the pyrrolyl group. Table IX shows that cations of alkali and alkaline earth metals are hard acids, therefore lithium, sodium, potassium (8c,11a) and magnesium (11a,100) prefer to attach to the hard Lewis base, nitrogen atom. The ionic radius of the alkali metal cation decreases in the order K(1.33 Å) > Na(0.98 Å) > Li(0.78 Å) but the hardness of these cations decreases in the reverse order. Under the same conditions the cation of potassium is less tightly associated with the nitrogen atom of pyrrolyl group than is the cation of lithium, therefore, pyrrolyl-potassium always gives a higher ratio of N/C than does

TABLE VIII. Classification of Lewis bases*

Hard	Soft	Borderline
H_2O, OH^-, F^-	R_2S, RSH, RS^-	$C_6H_5NH_2$,
$MeCO_2^-, PO_4^{3-}, SO_4^{2-}$	$I^-, SCN^-, S_2O_3^{2-}$	C_5H_5N, N_3^-,
$Cl^-, CO_3^{2-}, ClO_4^-, NO_3^-$	$R_3P, R_3As, (RO)_3P$	Br^-, NO_2^-, SO_3^{2-}
ROH†, RO^-, R_2O	CN^-, RNC, CO	N_2
NH_3, RNH_2, N_2H_4	C_2H_4, C_6H_6	
	H^-, R^-	

* From reference (52e).

† The symbol R stands for an alkyl group such as CH_3 or C_2H_5.

TABLE IX. Classification of Lewis acids*

Hard	Soft	Borderline
H^+, Li^+, Na^+, K^+	Cu^+, Ag^+, Au^+, Tl^+, Hg^+	Fe^{2+}, Co^{2+}, Ni^{2+},
Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Mn^{2+}	Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+}, Me_2Hg^+,	Cu^{2+}, Zn^{2+},
Al^{3+}, Sc^{3+}, Ga^{3+}, In^{3+}, La^{3+},	$Co(CN)_5^{2+}$, Pt^{4+}, Te^{4+}	Pb^{2+}, Sn^{2+},
N^{3+}, Cl^{3+}, Gd^{3+}, Lu^{3+}	Tl^{3+}, $TlMe_3$, BH_3, $GaMe_3$,	Sb^{3+}, Bi^{3+},
Cr^{3+}, Co^{3+}, Fe^{3+}, As^{3+}, $MeSn^{3+}$	$GaCl_3$, GaI_3, $InCl_3$	Rh^{3+}, Ir^{3+},
Si^{4+}, Ti^{4+}, Zr^{4+}, Th^{4+}, U^{4+}	RS^+, RSe^+, RTe^+	BMe_3, SO_2,
Pu^{4+}, Ce^{3+}, Hf^{4+}, WO^{4+}	I^+, Br^+, HO^+, RO^+	NO^+, Ru^{2+},
UO_2^{2+}, Me_2Sn^{2+}, VO^{2+}, MoO^{3+}	I_2, Br_2, ICN, etc.	Os^{2+}, R_3C^+,
$BeMe_2$, BF_3, $B(OR)_3$	Trinitrobenzene, etc.	$C_6H_5^+$, GaH_3
$AlMe_3$, $AlCl_3$, AlH_3	Chloranil, quinones, etc.	
RPO_2^+, $ROPO_2^+$	Tetracyanoethylene, etc.	
RSO_2^+, $ROSO_2^+$, SO_3	O, Cl, Br, I, N, RO·, RO_2·	
I^{7+}, I^{5+}, Cl^{7+}, Cr^{6+}	M^o (metal atoms)	
RCO^+, CO_2, NC^+	Bulk metals	
HX (hydrogen-bonding molecules)	CH_2, carbenes	

* From reference (52e).

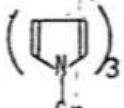
pyrrolyllithium in alkylation reactions (34). The ionic radius of magnesium is the same as that of lithium but the formal charge of the magnesium cation is greater than that of lithium cation, ie. it is harder than the latter. In alkylation reactions, the magnesyl group (a hard Lewis acid) of pyrrolyl Grignard reagent always tightly associated with the nitrogen atom (a hard Lewis base) of the pyrrolyl group and prevents the reaction from taking place at this position.

Hard Lewis acids like Cr^{3+}, Si^{4+}, B^{3+}, and RSO_2^+ always produce the corresponding N-substituted products (LXXXIX) (101), (XC) (102), (XCI) (103), (XCII) (104) and (XCIII) (105) respectively when they react with pyrrole, pyrrolylmagnesium halide or the alkali salts of pyrrole.

The carbonyl carbon atom is a hard Lewis acid, therefore it always reacts with the dissociated pyrrolyl group to give N-acylated compounds.

Cations like Zn^{2+} and Cu^{2+} give the corresponding N-substituted products (XCIV) (106) and (XCV) (107) respectively although their hardness is on the borderline. Carbonium carbon atoms also react with dissociated pyrrolyl groups to give N-alkylpyrroles.

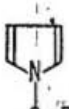
Mercury (II) is soft Lewis acid. The reaction of mercuric chloride (108) and mercuric acetate (109) with pyrrole gives only C-substituted products. In the later case the product



(LXXXIX)

(XC)

X = -Cl, -Me, -H, -N



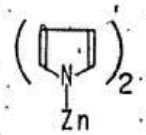
(XCI)

R = -Me, -n-Bu, -Ph

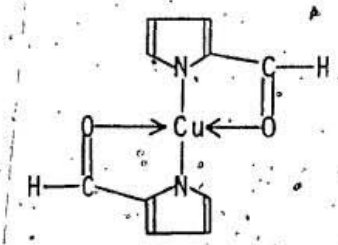
(XCII)

R = -H, -N

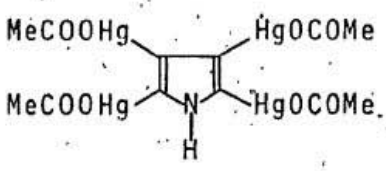
(XCIII)



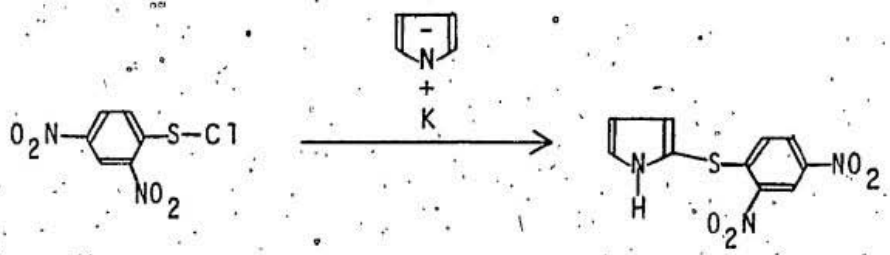
(XCIV)



(XCV)



(XCVI)



(XCVII)

is pyrrolyl-2,3,4,5-tetramercuric acetate (XCVI). The sulfur atom of the sulfenyl group, RS^+, is soft Lewis acid, therefore, reaction of 2,4-dinitrobenzenesulfenyl chloride with pyrrolylpotassium gives only C-substituted product, 2-(2,4-dinitrobenzenesulfenyl)pyrrole (XCVII) (110).

CHAPTER VI

EXPERIMENTAL

Part I

General

Melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus. Elemental analyses were determined by Alfred Bernhardt, West Germany. Analyses of the reaction mixtures were carried out on a Beckman GC-2A chromatograph equipped with a 13½ in. column packed with Apiezon L on firebrick and helium was used as the carrier gas.

The retention times of compounds, column temperatures and the pressures of carrier gas, were tabulated in Table X.

Isolation and identification of compounds are described in individual experimental Sections. The general method for identification and quantitative analysis of products on a gas chromatograph was as follows. After drying over anhydrous magnesium sulfate or sometimes anhydrous potassium carbonate, the volume of the reaction mixture was reduced to 50 ml or sometimes 100 ml, 1 ml of the solution was kept for analysis by gas chromatograph and the rest of the solution was used for isolation and identification of the compound being analyzed. Identification was done by comparison of the infrared spectrum with that of an authentic sample of the known compound. If it was a new compound, structure was assigned to it according to

Table X. The retention time of compounds from the acylation of pyrrolylmagnesium bromide at different temperatures and carrier gas pressure on Beckman GC-2A chromatograph equipped with a 13½ in column packed with Apiezon L on firebrick. Helium was used as the carrier gas.

Compound	Operating temp. (°C)	Operating pressure (psi)	Retention time (min)
Pyrrole	100	30	3.0
Ethyl 1-pyrrole-carboxylate	130	30	4.0
Ethyl 2-pyrrole-carboxylate	190	30	3.2
Diethyl 1,2-pyrrole-dicarboxylate	190	30	5.1
1-Acetylpyrrole	130	30	3.4
2-Acetylpyrrole	190	30	1.8
3-Acetylpyrrole	220	30	4.4
S-Ethyl 1-pyrrole-thiocarboxylate	160	30	5.8
S-Ethyl 2-pyrrole-thiocarboxylate	190	30	5.6
1-Acetoacetylpyrrole	190	30	3.4
1,1'-Dipyrrolyl ketone	190	30	3.3
1,2'-Dipyrrolyl ketone	220	50	3.4
2,2'-Dipyrrolyl ketone	220	55	9.8
1,1'-Dipyrrolyl ketimine	190	30	4.2
1,1'-Dipyrrolyl N-thiomethylketimine	220	45	2.5
N,N-Dimethyl-1-pyrrolyl-carbamidine	190	30	2.3
N,N'-Dicyclohexyl-1-pyrrolylcarbamidine	220	50	11.0

its spectroscopic properties, including infrared spectrum, n.m.r. spectrum, mass spectrum and results of elemental analysis. A standard solution of the sample being analyzed was prepared and it was used to select a suitable temperature at which a sharp chromatographic peak could be obtained. The reaction mixture was then analyzed under the same conditions. The paper under the two chromatographic peaks were cut out and weighed on an analytical balance. From the weights of the papers under the chromatographic peaks and the known concentration of the standard solution of the compound isolated from the reaction mixture, the concentration and hence the weight of the same compound in the reaction mixture could be calculated using the simple formula

$$\frac{A_1}{A_2} = \frac{C_1}{C_2}$$

where A_1 and A_2 were the weights of the paper under the chromatographic peaks obtained from the sample in the standard solution and in the reaction mixture respectively; C_1 and C_2 were the concentrations of the sample in the standard solution and in the reaction mixture respectively. The weight of the sample in the reaction mixture could be calculated using the formula below.

$$W_2 = C_2 \times V_2$$

where V_2 was the volume of the reaction mixture and W_2 was the total weight of the sample in the reaction mixture.

The percentage yield was calculated using the simple formula

$$\text{percentage yield} = \frac{\text{actual yield}}{\text{theoretical yield}} \times 100\%$$

The theoretical yield was always based on the quantity of the magnesium used in the reaction.

The percentage of N-acylation in total product was calculated by the formula below

$$\frac{\text{no. of moles of N-acylation}}{\text{no. of moles of N-acylation and C-acylation}} \times 100\%$$

and the percentage of C-acylation in the total product was calculated with the same formula

$$\frac{\text{no. of moles of C-acylation}}{\text{no. of moles of N-acylation and C-acylation}} \times 100\%$$

The ratio of N-acylation to C-acylation was also the ratio of the percentage of N-acylation and C-acylation in the total yield.

All the reactions were run under heterogeneous conditions.

(i) Preparation of Pyrrolylmagnesium Bromide

A solution of ethyl bromide (11.99 g, 0.110 mol) in absolute ether (40 ml) was added slowly to a mixture of magnesium (2.43 g, 0.100 mol) in absolute ether (20 ml) under nitrogen. The rate of addition was adjusted in a manner which maintained the solution at reflux. After the addition was completed, the solution was refluxed for another one hour. To the cold Grignard reagent, a solution of freshly distilled pyrrole (6.70 g, 0.100 mol) in absolute ether (30 ml) was added slowly. Bubbling of gas from the solution was observed. After the addition of pyrrole, the reaction mixture was refluxed for another one hour.

(ii) Reaction of Pyrrolylmagnesium Bromide with Ethyl Acetate

(a) The pyrrolylmagnesium bromide solution, prepared from ethyl bromide (0.110 mol), magnesium (0.100 mol) and pyrrole (0.100 mol), was cooled to -22° by using a mixture of Dry Ice and carbon tetrachloride. To this solution a solution of ethyl acetate (9.80 g, 0.100 mol) in absolute ether (90 ml) was added slowly in a period of about one and a half hours. The reaction mixture was stirred at -10° for another half an hour and then hydrolyzed with 1 M ammonium chloride solution (200 ml). Two layers were observed. The two layers were stirred until all the solid material disappeared. The organic layer was separated and the aqueous layer was extracted twice with an equal volume of ether. The combined ethereal solution

was washed twice with water (200 ml) and dried over anhydrous magnesium sulfate. The volume of the ethereal solution was reduced to 100 ml and 1 ml of the solution was saved for analysis on a Beckman GC-2A chromatograph.

The ether was removed by distillation and the residue was vacuum distilled. The liquid, which was identified as 1-acetylpyrrole (LXVIII), was collected at 80 - 81° at 13 mm pressure, literature b.p. 180 - 184° (111). The infrared spectrum of this compound was identical with that of an authentic sample of the compound obtained by the method described by Reddy (112).

The residue, after removal of 1-acetylpyrrole, was crystallized from cyclohexane. After recrystallization from the same solvent pure 2-acetylpyrrole (X) was obtained, m.p. 89 - 90°, literature m.p. 88 - 89° (113). Mixture m.p. undepressed on admixture with an authentic sample and the infrared spectra were identical. The yields of 1-acetyl and 2-acetylpyrrole were 0.69 g (6%) and 2.03 g (19%) respectively. The ratio of N-aclyation to C-acylation was 24:76, total yield 25%.

(b) The above experiment was repeated; but the reaction mixture of pyrrolylmagnesium bromide and theyl acetate was stirred at room temperature for 17 hours. The results of analysis showed that there was no significant change in ratio or yield of both 1-acetylpyrrole and 2-acetylpyrrole.

(iii) Reaction of Pyrrolylmagnesium Bromide with Acetyl Chloride

The procedure and the quantities of chemicals used for this experiment were the same as those described in Section (ii)(a) except that acetyl chloride (7.85 g, 0.100 mol) was used instead of theyl acetate.

After removal of 1-acetylpyrrole and 2-acetylpyrrole by distillation under reduced pressure, the residue was dissolved in a minimum amount of a mixture of ether and carbon tetrachloride (1:1). The solution was boiled on a steam bath to remove the ether. Colorless crystals of 3-acetylpyrrole (XI) were obtained, m.p. 113 - 114°, literature m.p. 114 - 115° (114). The infrared spectrum of 3-acetylpyrrole from this experiment was the same as that of an authentic sample of the compound obtained by the method described by Loader and Anderson (114).

The yields of 1-acetylpyrrole, 2-acetylpyrrole and 3-acetylpyrrole were 0.10 g (1%), 4.08 g (37%) and 0.43 g (4%) respectively. The ratio of N-acylation to C-acylation was 3:97, total yield 42%.

(iv) Reaction of Pyrrolylmagnesium Bromide with Ethyl Chloroformate

(a) The procedure and the quantities of chemicals used in this experiment were the same as those described in Section (ii)(a).

The first product, which was identified as ethyl 1-pyrrolecarboxylate (XV), was collected at 78 - 81° at 14 mm pressure, literature b.p. 60 - 65° at 7 mm pressure (31),

yield 2.74 g (19%). The infrared spectrum of this compound was identical to that of an authentic sample of the compound obtained by the method described by Loader and Anderson (79). The second compound, which was identified as ethyl 2-pyrrolecarboxylate (XIV) was collected at 87 - 88° at 3 mm pressure, literature b.p. 100 - 110° at 7 mm pressure (31), yield 5.97 g (44%). The infrared spectrum of this compound and that of an authentic sample of ethyl 2-pyrrolecarboxylate (79) were superimposable. The third compound, diethyl 1,2-pyrroledicarboxylate (XVI) was distilled off at 86 - 87° at 1 mm pressure, literature b.p. 125 - 135° at 7 mm pressure (31), yield 0.55 g (5%). The n.m.r. and mass spectra of this product were not inconsistant with the proposed structure.

The ratio of N-acylation to C-acylation was 28 : 72, total yield 68%.

(b) The above experiment was repeated. The procedure was the same as that described in Section (ii)(b).

The yields of ethyl 1-pyrrolecarboxylate, ethyl 2-pyrrolecarboxylate and diethyl 1,2-pyrroledicarboxylate were 1.85 g (13%), 2.86 g (21%) and 1.99 g (19%) respectively.

The ratio of N-acylation to C-acylation was 25 : 75, total yield 53%).

(v) Reaction of 2-Carboxyethylpyrrolylmagnesium Bromide (LII) with Ethyl Chloroformate

A solution of ethyl 2-pyrrolecarboxylate (6.95 g, 0.050 mol) in absolute ether (30 ml) was added slowly to the Grignard reagent prepared from magnesium (1.22 g, 0.050 mol), ethyl bromide (5.45 g, 0.050 mol) and absolute ether (50 ml). During the addition of ethyl 2-pyrrolecarboxylate, large quantities of gas and heat were given off and a white precipitate was observed. The reaction mixture was refluxed for 30 minutes and then cooled in a mixture of Dry Ice and carbon tetrachloride. To this cold solution, a solution of ethyl chloroformate (5.35 g, 0.050 mol) in absolute ether (60 ml) was added slowly in a period of about 90 minutes. After stirring at room temperature for 17 hours, the reaction mixture was cooled and hydrolyzed with saturated ammonium chloride solution (100 ml). The aqueous layer was extracted twice with an equal volume of ether and the combined ethereal solution was washed twice with water and dried over anhydrous sodium carbonate. The only product, diethyl 1,2-pyrroledicarboxylate, was collected at 86 - 87° at 1 mm pressure, yield 8.80 g (83%). The infrared spectrum of this compound was identical with that of an authentic sample of the compound obtained by the method described in Section (iv) (a).

(vi) Reaction of Pyrrolylmagnesium Bromide with Ethyl Chloroformate in the Presence of N,N,N',N'-Tetramethyl-ethylenediamine.

(a) The solution of pyrrolylmagnesium bromide in absolute ether was prepared according to the method described in Section (i).

To this pyrrolylmagnesium bromide solution, a solution of N,N,N',N'-tetramethylethylenediamine (11.60 g, 0.100 mol) in absolute ether (20 ml) was added. During the addition of the complexing agent heat was given off and a white precipitate was observed and the colour of the solution turned from colourless to yellowish green. The reaction mixture was refluxed for 3 hours and then cooled in a mixture of Dry Ice and carbon tetrachloride. To this cold suspension a solution of ethyl chloroformate (10.85 g, 0.100 mol) in absolute ether (90 ml) was added slowly in a period of about 90 minutes. The reaction mixture was refluxed for 17 hours, and then cooled and hydrolyzed with 1 M ammonium chloride solution (200 ml). The two layers were separated and the aqueous layer was extracted twice with an equal volume of ether and the combined ethereal layer was washed twice with water and dried over anhydrous magnesium sulfate.

The yields of ethyl 1-pyrrolecarboxylate and ethyl 2-pyrrolecarboxylate were 7.09 g (51%) and 0.71 g (5%) respectively. The yield of a third compound, 1,2'-dipyrrolyl ketone, was 0.18 g (2%). After recrystallization from hexane the m.p. of 1,2'-dipyrrolyl ketone was 60 - 61°, literature

m.p. 58 - 60° (79). The infrared spectrum of this compound was identical to that of an authentic sample of the compound obtained by the method described by Loader and Anderson (79).

The ratio of N-acylation to C-acylation was 89 : 11, total yield 59%.

(b) When the ratio of pyrrolylmagnesium bromide to N,N,N',N'-tetramethylethylenediamine was 1 : 1.5 the yield of ethyl 1-pyrrolecarboxylate, ethyl 2-pyrrolecarboxylate and 1,2-dipyrrolyl ketone were 10.76 g (76%), 0.13 g (1%) and 0.10 g (1%) respectively.

The ratio of N-acylation to C-acylation was 98 : 2, total yield 78%.

(vii) Reaction of Pyrrolylmagnesium Bromide with Ethyl Chloroformate in the Presence of 1,2-Dimethoxyethane

The procedure and the quantities of chemicals used in this experiment were the same as those described in Section (vi) (b) except that 1,2-dimethoxyethane (13.00 g, 0.150 mol) was used instead of the N,N,N',N'-tetramethylethylenediamine, yield, ethyl 1-pyrrolecarboxylate 1.77 g (13%), ethyl 2-pyrrolecarboxylate 0.34 g (2%) and diethyl 1,2-pyrroledicarboxylate 6.90 g (65%).

The ratio of N-acylation to C-acylation was 16 : 84, total yield 80%.

(viii) Reaction of Pyrrolylmagnesium Bromide with Ethyl Chloroformate in the Presence of 1,4-Dioxane

The procedure and the quantities of chemicals used in this experiment were the same as those described in Section (vi)(b) except that 1,4-dioxane (13.20 g, 0.150 mol) was used instead of the N,N,N',N'-tetramethylethylenediamine. The yields of ethyl 1-pyrrolecarboxylate, ethyl 2-pyrrolecarboxylate and diethyl 1,2-pyrroledicarboxylate were 0.77 g (6%), 0.93 g (7%) and 2.33 g (22%) respectively.

The ratio of N-acylation to C-acylation was 17 : 83, total yield 35%.

(ix) Reaction of Pyrrolylmagnesium Bromide with Diethyl Carbonate

The procedure and the quantities of chemicals used in this experiment were the same as those described in Section (ii)(a). The yields of ethyl 1-pyrrolecarboxylate and ethyl 2-pyrrolecarboxylate were 13.76 g (70%) and 0.20 g (2%) respectively.

The ratio of N-acylation to C-acylation was 97 : 3, total yield 72%.

(x) Preparation of S-Ethyl 1-Pyrrolethiocarboxylate (LXVI)

The crude product of 1-pyrrolethiocarboxanilide was prepared by the method described by Papadopoulos (115).

To a mixture of 6 M sodium hydroxide solution (100 ml) and crude 1-pyrrolethiocarboxanilide (23.00 g, 0.120 mol) was

added ethyl iodide (24.96 g, 0.160 mol). After heating in a steam bath for one hour, the reaction mixture was cooled to room temperature and the organic layer was separated. The aqueous layer was extracted twice with an equal volume of ether. The combined organic layer was washed twice with water and dried over anhydrous magnesium sulfate. After removal of the ether, the crude product was mixed with 6 M sulfuric acid (100 ml) and heated in a steam bath for another one hour. The reaction mixture was cooled to room temperature and extracted twice with an equal volume of ether. The combined ethereal solution was washed with water, dilute sodium hydrogen carbonate, water and dried over anhydrous magnesium sulfate. After removal of the ether, the residue was vacuum distilled. The product, S-ethyl 1-pyrrolethiocarboxylate, was collected at 105 - 106° at 10 mm pressure, yield 6.25 g (34%). Analysis, calculated for C_7H_9NOS: C, 54.19; H, 5.85; N, 9.03; O, 10.32; S, 20.65; found: C, 54.32; H, 5.79; N, 9.13; S, 20.78. The mass and n.m.r. spectra of this product were not inconsistant with the proposed structure.

(xi) Reaction of Pyrrolyllithium with S-Ethyl Chlorothioformate in the Presence of N,N,N',N'-Tetramethylethylenediamine

Pyrrolyllithium was prepared according to the method described by Hodge and Rickards (12c)

To a solution of n-butyllithium (0.200 mol) in absolute ether (80 ml), stirred at 0° under nitrogen, was added dropwise

a solution of pyrrole (14.74 g, 0.220 mol) in absolute ether (80 ml) and the reaction mixture was stirred at room temperature for 30 minutes. To this white suspension was added a solution of N,N,N',N'-tetramethylethylenediamine (45.40 g, 0.400 mol) in dry ether (40 ml) at such a rate that it maintained the solution at reflux. After heating for another 30 minutes, the reaction mixture was cooled in ice bath and a solution of S-ethyl chlorothioformate (8.72 g, 0.070 mol) in dry ether (90 ml) was added dropwise. This reaction mixture was stirred in the ice bath for another 2.5 hours and then hydrolyzed with 1 M ammonium chloride solution (200 ml). The organic layer was separated and the aqueous layer was extracted twice with an equal volume of ether. The combined ethereal layer was washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was vacuum distilled. The first fraction, S-ethyl 1-pyrrolethiocarboxylate was collected at 105 - 106° at 10 mm pressure, yield 0.78 g (7%). The infrared spectrum of this compound was identical with that of an authentic sample of S-ethyl 1-pyrrolethiocarboxylate obtained by the method described in Section (x). The second compound which was identified as 1,1'-dipyrrolyl ketone (LXX) was collected at 78 - 81° at 1 mm pressure, yield 4.75 g (42%). Analysis, calculated for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49; O, 9.99; found : C, 67.62; H, 4.96; N, 17.44.

Only a trace of S-ethyl 2-pyrrolethiocarboxylate was detected. The retention time of the S-ethyl 2-pyrrolethio-

carboxylate was the same as that obtained by the method described by Loader and Anderson (79).

(xii) Reaction of Pyrrolyllithium with S-Ethyl Chlorothioformate

The procedure of this experiment was the same as those described in Section (xi) except for the quantities of the chemicals used below: n-buthyllithium (0.100 mol); pyrrole (8.04 g, 0.120 mol); S-ethyl chlorothioformate (12.45 g, 0.100 mol). The yields of S-ethyl 1-pyrrolethiocarboxylate and 1,1'-dipyrrolyl ketone were 4.85 g (31%) and 1.11 g (14%) respectively. Only a trace of S-ethyl 2-pyrrolethiocarboxylate was detected, total yield 45%.

The fourth compound, which was identified as S,S'-diethyl dithiocarbonate (LXXXVII), was also obtained, yield 1.48 g, b.p. 105 - 109° at 42 mm pressure, literature b.p. 85 - 87° at 19 mm pressure (116). The infrared spectrum of this compound was identical with that of an authentic sample of the compound obtained by the method described by Bulmer and Mann (116).

(xiii) Reaction of Pyrrolylmagnesium Bromide with S-Ethyl Chlorothioformate in the Presence of N,N,N',N'-Tetramethylethylenediamine

(a) The pyrrolylmagnesium bromide (0.040 mol) in absolute ether (60 ml) was prepared according to the method described in Section (i). To this Grignard reagent was introduced a solution of N,N,N',N'-tetramethylethylenediamine (9.28 g, 0.080 mol)

in absolute ether (10 ml). After refluxing for 3 hours the reaction mixture was cooled in a mixture of Dry Ice and carbon tetrachloride. To this cold pyrrolylmagnesium bromide was added a solution of S-ethyl chlorothioformate (7.47 g, 0.060 mol) in absolute ether (40 ml) in a period of about 60 minutes. After stirring at room temperature for 3 hours, the reaction mixture was cooled and hydrolyzed with 2 M ammonium chloride solution (100 ml). The two layers were separated and the aqueous layer was extracted twice with an equal volume of ether. The combined ethereal layer was washed with water and dried over anhydrous magnesium sulfate. Yield: S-ethyl 1-pyrrolethiocarboxylate, 2.07 g (34%); S-ethyl 2-pyrrolethiocarboxylate, 1.41 g (23%); S,S'-diethyl dithiocarbonate, 2.55 g. Only traces of 1,1'-dipyrrolyl ketone and 1,2'-dipyrrolyl ketone were detected.

The ratio of N-acylation to C-acylation was 60 : 40, total yield 56%.

(b) The same experiment was repeated several times using different ratios of N,N,N',N'-tetramethylethylenediamine and pyrrolylmagnesium bromide in absolute ether. The ratios were: (a) 0 : 1; (b) 1 : 1; (c) 1.5 : 1; (d) 3 : 1; (e) 4 : 1; (f) 5 : 1. The results of these experiments were tabulated in Table IV.

(xiv) Reaction of Pyrrolylmagnesium Bromide with 1,1'-Dipyrrolyl Ketone

The 1,1'-dipyrrolyl ketone was prepared according to the method described in Section (xi).

A solution of 1,1'-dipyrrolyl ketone (1.60 g, 0.010 mol) in dry ether (20 ml) was added slowly to the ethereal solution of pyrrolylmagnesium bromide prepared from magnesium (0.62 g, 0.025 mol), ethyl bromide (2.75 g, 0.025 mol) and pyrrole (1.68 g, 0.025 mol). After refluxing for 30 minutes, the reaction mixture was cooled and hydrolyzed with saturated ammonium chloride solution. The ethereal layer was separated and the aqueous layer was extracted twice with an equal volume of ether. The combined ethereal solution was washed with water and dried over anhydrous magnesium sulfate. After removal of the ether, the residue was vacuum distilled. The sole product, 1,2'-dipyrrolyl ketone (LXXII) was collected at 117 - 125° at 1 mm pressure, yield 1.13 g (70%). No 1,1'-dipyrrolyl ketone was recovered.

After recrystallization from hexane, the m.p. of the 1,2'-dipyrrolyl ketone was 57 - 59°, literature m.p. 58 - 60° (79). The infrared spectrum of this compound was identical with that of an authentic sample of the compound obtained by the method described by Loader and Anderson (79).

(xv) Reaction of Pyrrolylmagnesium Chloride with S-Ethyl Chlorothioformate in the Presence of N,N,N',N'-Tetramethylethylenediamine

The ethereal solution of n-butylmagnesium chloride was prepared by refluxing a mixture of magnesium (0.97 g, 0.040 mol) and n-butyl chloride (4.07 g, 0.044 mol) in absolute ether (30 ml) until all the metallic magnesium disappeared.

The pyrrolylmagnesium chloride was prepared according to the method described in Section (i) and then N,N,N',N'-tetramethylethylenediamine (9.28 g, 0.080 mol) in absolute ether (10 ml) was added. The reaction mixture was refluxed for 3 hours.

The procedure of the last part of this experiment was the same as that described in Section (xiii). The yields of S-ethyl 1-pyrrolecarboxylate, S-ethyl 2-pyrrolecarboxylate and S,S'-diethyl dithiocarbonate were listed in Table VII.

The ratio of N-acylation to C-acylation was 89 : 11, total yield 58%.

(xvi) Reaction of Pyrrolylmagnesium Iodide with S-Ethyl Chlorothioformate in the Presence of N,N,N',N'-Tetramethylethylenediamine

The pyrrolylmagnesium iodide was prepared by the method described in Section (i) and the procedure of the second part

of this experiment was exactly the same as that described in Section (xiii) (a).

The yields of S-ethyl 1-pyrrolethiocarboxylate, S-ethyl 2-pyrrolethiocarboxylate, 1,2'-dipyrrolyl ketone and S,S'-diethyl dithiocarbonate were listed in Table VII.

The ratio of N-acylation to C-acylation was 28 : 72, total yield 43%.

(xvii) Reaction of Pyrrolylmagnesium Bromide with Ethyl Acetate in the Presence of N,N,N',N'-Tetramethylethylenediamine

The reaction mixture of pyrrolylmagnesium bromide (0.300 mol) and N,N,N',N'-tetramethylethylenediamine (0.450 mol) in absolute ether (300 ml) was prepared according to the method described in Section (vi).

To the cold suspension was added a solution of ethyl acetate (17.60 g, 0.200 mol) in dry ether (90 ml). After stirring at room temperature for 17 hours, the reaction mixture was cooled in ice bath and hydrolyzed with 6 M hydrochloric acid (180 ml). Some solid material stayed at the interface of the ethereal and aqueous layers. After filtration of the solid material the two layers were separated. The aqueous layer was extracted twice with an equal volume of ether and the combined ethereal layer was washed with water and dried over anhydrous sodium sulfate.

The yields of 1-acetylpyrrole and 2-acetylpyrrole were 0.65 g (3%) and 0.33 g (1%) respectively. A third compound which was identified as 1-acetoacetylpyrrole (LXV) was distilled off at 83 - 84° at 1 mm pressure. This compound was purified by recrystallization from cyclohexane, m.p. 49 - 51°, yield 12.10 g (80%). Analysis, calculated for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27; O, 21.17; found : C, 63.67; H, 5.98; N, 9.25.

The solid material was treated with 6 M hydrochloric acid (50 ml) and extracted twice with an equal volume of chloroform. The combined chloroform extracts were washed with water and dried over anhydrous sodium carbonate. After removal of the solvent and recrystallization from cyclohexane another 1.56 g (10%) of 1-acetoacetylpyrrole was obtained. (A pink-coloured complex was formed when the 1-acetoacetylpyrrole was treated with dilute ferric chloride solution).

(xviii) Reaction of 1-Acetylpyrrolylmagnesium Bromide with Ethyl Acetate in the Presence of N,N,N',N'-Tetramethylethylenediamine

To a reaction mixture of ethylmagnesium bromide (0.050 mol) and N,N,N',N'-tetramethylethylenediamine (8.40 g, 0.750 mol in dry ether (40 ml) was added a solution of 1-acetylpyrrole (5.45 g, 0.050 mol) in absolute ether (20 ml). Large quantities of heat and gas were given off. After refluxing for one hour, the reaction mixture was cooled to room temperature and a

solution of ethyl acetate (4.84 g, 0.055 mol) in absolute ether (40 ml) was introduced in a period of 60 minutes. This reaction mixture was stirred at room temperature for 17 hours and then hydrolyzed with 6 M hydrochloric acid (90 ml). The organic layer was separated and the aqueous layer was extracted twice with an equal volume of ether. The combined ethereal layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed and the residue was distilled under reduced pressure. 1-Acetoacetylpyrrole was collected at 83 - 84° at 1 mm pressure, yield 2.55 g (60%). The infrared spectrum of this compound was identical with that of an authentic sample of the compound obtained by the method described in Section (xvii).

(xix) Reaction of Pyrrolylmagnesium Bromide with N,N'-Dicyclohexylcarbodiimide

(a) The procedure and quantities of chemicals used in this experiment were the same as those described in Section (ii) except that N,N'-dicyclohexylcarbodiimide (20.63 g, 0.100 mol) was used instead of ethyl acetate and that before hydrolysis with ammonium chloride solution, the reaction mixture was stirred at room temperature for 17 hours.

After removal of the solvent, the residue was vacuum distilled. The only product, which was identified as N,N'-dicyclohexyl-1-pyrrolylcarbamidine (LIX) was collected at 140 - 141° at 1 mm pressure, m.p. 42 - 44°, yield

25.50 g (93%). No N,N'-dicyclohexyl-2-pyrrolylcarbamidine was detected by either n.m.r. or i.r. Analysis, calculated for $C_{17}H_{27}N_3$: C, 74.68; H, 9.95; N, 15.37; found: C, 74.48; H, 10.11; N, 15.25.

(b) The hydrochloric acid salt of N,N'-dicyclohexyl-1-pyrrolylcarbamidine was prepared by treatment of the crude product of N,N'-dicyclohexyl-1-pyrrolylcarbamidine with 6 M hydrochloric acid. Pale blue crystals were obtained. The salt was purified by dissolving in absolute methanol and reprecipitating with ethyl acetate. This compound sintered at 208° and melted at 210 - 211°. After treatment with dilute sodium hydroxide solution, the free N,N'-dicyclohexyl-1-pyrrolylcarbamidine was regenerated.

(xx) Reduction of N,N'-Dicyclohexyl-1-pyrrolylcarbamidine by Lithium Aluminium Hydride

A mixture of N,N'-dicyclohexyl-1-pyrrolylcarbamidine (3.22 g, 0.012 mol), lithium aluminium hydride (0.88 g, 0.024 mol) and absolute ether (200 ml) was refluxed for 26 hours. After cooling in an ice bath the reaction mixture was hydrolyzed with water-saturated ether (200 ml). The organic solution was filtered, washed with water and dried over anhydrous magnesium sulfate. The solvent was removed and the residue was vacuum distilled. The product, N,N'-dicyclohexylformamidine, was collected at 120 - 121° at 1 mm pressure, yield 1.38 g (56%).

After recrystallization from ethyl acetate, colourless crystals were obtained, m.p. 102 - 104°, literature m.p. 106° (117). The Mass and n.m.r. spectra of this product were not inconsistant with the proposed structure.

(xxi) Reaction of Pyrrolylmagnesium Bromide with Dimethylcyanamide

The procedure of the first part of this experiment was the same as that described in Section (ii) except that dimethylcyanamide (7.00 g, 0.100 mol) was used instead of ethyl acetate.

After stirring at room temperature for 17 hours, a minimum amount of 2 M ammonium chloride solution was added slowly into the reaction mixture until all the solid substance in the reaction flask had just completely dissolved. The two layers were separated and the aqueous layer was extracted twice with an equal volume of ether. The combined ethereal solution was washed with water and dried over anhydrous magnesium sulfate. The sole product, N,N'-dimethyl-1-pyrrolylcarbamidine (LXIII), was distilled over at 109 - 110° at 15 mm pressure, yield 1.03 g (8%). Analysis, calculated for $C_7H_{11}N_3$: C, 61.29; H, 8.08; N, 30.63; found: C, 61.06; H, 8.04; N, 30.57.

The same experiment was repeated except for the steps below. A mixture of pyrrolyllithium (0.100 mol) and N,N,N',N'-tetramethylethylenediamine (23.00 g, 0.200 mol)

was used instead of pyrrolylmagnesium bromide and the final reaction mixture was hydrolyzed with water instead of ammonium chloride solution. The yield of N,N —dimethyl-1-pyrrolyl-carbamidine was 1.30 g (10%). Most of the unreacted dimethylcyanamide was recovered in both of the above experiments.

(xxii) Reaction of Pyrrolylmagnesium Bromide with Diethyl Oxalate

A pyrrolylmagnesium bromide solution (0.100 mol) was prepared according to the method described in Section (i). The Grignard reagent was cooled in a mixture of Dry Ice and methanol and a white precipitate was observed. A solution of diethyl oxalate (14.60 g, 0.100 mol) in absolute ether (50 ml) was added slowly in a period of 45 min. A yellow precipitate was observed. The reaction mixture was stirred at this temperature for 3 hours and then hydrolyzed with saturated ammonium chloride solution (100 ml). The aqueous layer was extracted twice with an equal volume of ether. The combined ethereal layer was washed with water and dried over anhydrous sodium carbonate. The solvent was removed and the residue was vacuum distilled. The first fraction which was identified as ethyl 1-pyrrolylglyoxylate (LVII) was collected at 70 - 71° at 1 mm pressure, yield 3.10 g (19%). Analysis, calculated for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38; O, 28.71; found: C, 57.57; H, 5.53; N, 8.45.

The second product, ethyl 2-pyrrolylgloxylate (LV) was distilled off at 105 - 109° at 1 mm pressure, yield

3.69 g (22%). After recrystallization from carbon tetrachloride the m.p. was 39 - 40°, literature m.p. 44.5° (72). The Mass and n.m.r. spectra of this product were not inconsistant with the proposed structure.

The ratio of N-acylation to C-acylation was 46 : 54 total yield 41%.

(xxiii) Reaction of Pyrrolyllithium with Methyl Thiocyanate in the Presence of N,N,N',N'-Tetramethylethylenediamine

The reaction product of pyrrolyllithium (0.100 mol) and N,N,N',N'-tetramethylenediamine (0.200 mol) in absolute ether was prepared according to the method described in Section (xi). The reaction mixture was cooled in a mixture of Dry Ice and methanol and a solution of methyl thiocyanate (7.30 g, 0.100 mol) was added slowly in a period of 30 minutes. After stirring at -22° for 60 minutes, the reaction mixture was hydrolyzed with 2 M ammonium chloride solution (100 ml). The organic layer was separated and the aqueous layer was extracted twice with an equal volume of ether. The combined ethereal layer was washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was vacuum distilled. The first product, 1,1'-dipyrrolyl ketimine (LXXVII), was collected at 84 - 88° at 1 mm pressure, yield 3.97 g (25%). After recrystallization from petroleum ether (30 - 50°) the m.p. was 47 - 48.5°. Analysis, calculated

for $C_9H_9N_3$: C, 67.91; H, 5.70; N, 26.40; found : C, 68.03; H, 5.79; N, 26.26.

The second product which was identified as 1,1'-dipyrrolyl N-thiomethylketimine (LXXVI) was collected at 105 - 110° at 1 mm pressure, yield 5.69 g (28%). After recrystallization from petroleum ether (30 - 50°), the m.p. was 41 - 42°. Analysis, calculated for $C_{10}H_{11}N_3S$: C, 58.53; H, 5.40; N, 20.84; S, 15.59; found : C, 58.50; H, 5.51; N, 20.38; S, 15.66.

(xxiv) Reaction of S-Ethyl Chlorothioformate with Magnesium Chloride in the Presence of N,N,N',N'-Tetramethylethylenediamine

A mixture of N,N,N',N'-tetramethylethylenediamine (6.96 g, 0.060 mol) and anhydrous magnesium chloride (2.91 g, 0.031 mol) in absoluted ether (60 ml) was refluxed under nitrogen for 2 hours and then it was cooled in a mixture of Dry Ice and carbon tetrachloride. To this cold reaction mixture was added dropwise a solution of S-ethyl chlorothioformate (7.47 g, 0.060 mol) in absolute ether (40 ml). After stirring at room temperature for 17 hours, the reaction mixture was cooled and hydrolyzed with 2 M ammonium chloride solution (100 ml). The organic layer was separated and the aqueous layer was extracted twice with an equal volume of ether. The combined ethereal solution was washed with water and dried over anhydrous magnesium sulfate. The yield of

S,S'-diethyl dithiocarbonate was 2.67 g (60%). The infrared spectrum of this compound was identical with that of an authentic sample of the compound obtained by the method described in Section (xii).

(xxv) Reaction of Pyrrolyllithium with Diethyl Carbonate in 1,4-Dioxane

The pyrrolyllithium in 1,4-dioxane was prepared by the method described in Section (xi) except that 1,4-dioxane was used instead of absolute ether.

After a solution of diethyl carbonate (2.21 g, 0.019 mol) in absolute 1,4-dioxane (10 ml) was added to the solution of pyrrolyllithium (0.019 mol) in absolute 1,4-dioxane (50 ml), the reaction mixture was stirred at 36° for 13 hours. Most of the solvent was removed by distillation under reduced pressure and ether (150 ml) was added. The reaction mixture was hydrolyzed with an equal volume of cold water and the aqueous layer was extracted twice with an equal volume of ether. The combined ethereal solution was washed with water and dried over anhydrous magnesium sulfate. The yields of ethyl 1-pyrrolecarboxylate and ethyl 2-pyrrolecarboxylate were 1.06 g (41%) and 0.02 g (1%) respectively. The ratio of N-acylation to C-acylation was 98 : 2, total yield 41%.

If the reaction mixture was refluxed for 13 hours, the yields of ethyl 1-pyrrolecarboxylate, ethyl 2-pyrrolecarboxylate and 1,2'-dipyrrolyl ketone were 1.87 g (37%), 0.79 g (16%)

and 0.54 g (19%) respectively. The ratio of N-acylation to C-acylation was found to be 65 : 35, using the same procedure.

(xxvi) Reaction of Pyrrolylpotassium with Ethyl Chloroformate

Pyrrolylpotassium was prepared by a similar method to that described by Clemo and Ramage (8d).

To a mixture of metallic potassium (3.91 g, 0.100 mol) and dry ether (75 ml) was added a solution of pyrrole (10.40 g, 0.150 mol), absolute ethanol (two drops), and absolute ether (25 ml). The reaction mixture was refluxed until all the metallic potassium completely dissolved. To the suspension of pyrrolylpotassium a solution of ethyl chloroformate (10.85 g, 0.100 mol) in dry ether (20 ml) was added dropwise. After refluxing for 90 minutes, the reaction mixture was cooled with Dry Ice and hydrolyzed with an excess of water-saturated ether. The ethereal solution was filtered, washed with water and dried over anhydrous magnesium sulfate. The sole product, ethyl 1-pyrrolecarboxylate, was collected at 78 - 81° at 14 mm pressure, yield 8.86 g (64%). The infrared spectrum of this compound was identical with that of an authentic sample of the compound obtained by the method described in Section (iv).

(xxvii) Reaction of Pyrrolylsodium with Ethyl Chloroformate

Pyrrolylsodium was prepared by a similar method to that described by Hobbs et al (34).

A solution of pyrrole (8.41 g, 0.125 mol) in dry tetrahydrofuran (10 ml) was added slowly into a mixture of sodium hydride (1.39 g, 0.058 mol) and dry tetrahydrofuran (75 ml). After refluxing for 4 hours, the solvent was removed under reduced pressure and the residue was flushed with nitrogen for another 3 hours. After addition of dry ether (200 ml), the suspension was refluxed for another 30 minutes. To this reaction mixture, a solution of ethyl chloroformate (7.59 g, 0.070 mol) in dry ether (40 ml) was added slowly at room temperature. The final reaction mixture was stirred at room temperature for 17 hours.

The procedure of the second part of this experiment is the same as that described in Section (xxvi). The sole product, ethyl 1-pyrrolecarboxylate, was obtained in 7.10 g (87%) yield. The infrared spectrum of this compound was identical with that of an authentic sample of the compound obtained by the method described in Section (iv).

(xxviii) Reaction of Pyrrolyllithium with Ethyl Chloroformate

Pyrrolyllithium was prepared according to the method described in Section (xi).

The procedure of this experiment was the same as that described in Section (xxvii) except that pyrrolyllithium (0.100 mol) and ethyl chloroformate (10.85 g, 0.100 mol) were used. The first product, ethyl 1-pyrrolecarboxylate, was distilled off at 78 - 81° at 14 mm pressure, yield

5.45 g (39%). The second product, which was identified as 1,1'-dipyrrolyl ketone weighed 1.28 g (16%), total yield 55%. Neither ethyl 2-pyrrolecarboxylate nor 1,2'-dipyrrolyl ketone was detected. The infrared spectrum of 1,1'-dipyrrolyl ketone from this experiment was identical with that of an authentic sample of the compound obtained by the method described in Section (xi).

(xxix) Reaction of Pyrrolyllithium with Ethyl 1-Pyrrolecarboxylate in 1,4-Dioxane

A mixture of pyrrolyllithium (0.040 mol) and ethyl 1-pyrrolecarboxylate (5.98 g, 0.040 mol) was refluxed in 1,4-dioxane (200 ml) for 24 hours. The solvent was removed under reduced pressure and ether (200 ml) was added into the residue. The reaction mixture was hydrolyzed with water (100 ml) and the aqueous layer was extracted twice with an equal volume of ether. The combined ethereal solution was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed and the residue was vacuum distilled. The first product, ethyl 2-pyrrolecarboxylate, was collected at 86 - 87° at 1 mm pressure, yield 1.90 g (32%). The second product which was identified as 1,2'-dipyrrolyl ketone was obtained in 1.50 g (22%) yield. The infrared spectrum of this compound was identical with that of an authentic sample of the compound obtained by the method described in Section (vi).

(xxx) Reaction of Pyrrolyllithium with Ethyl 2-Pyrrolecarboxylate in 1,4-Dioxane

The procedure of this experiment was the same as that described in Section (xxix) except that pyrrolyllithium (0.050 mol) and ethyl 2-pyrrolecarboxylate (2.74 g, 0.020 mol) were used instead of pyrrolyllithium and ethyl 1-pyrrolecarboxylate. The product, 1,2'-dipyrrolyl ketone was obtained in 1.98 g (62%) yield. No ethyl 1-pyrrolecarboxylate was detected.

(xxxi) Reaction of Lithium Ethoxide with 1,2'-Dipyrrolyl Ketone in 1,4-Dioxane

A mixture of lithium ethoxide (0.020 mol) and 1,2'-dipyrrolyl ketone (1.60 g, 0.010 mol) was refluxed for 24 hours. The procedure of the second part of this experiment was the same as that described in Section (xxix). Ethyl 2-pyrrolecarboxylate was obtained in 0.47 g (34%) yield. No ethyl 1-pyrrolecarboxylate was detected.

(xxxii) Reaction of Pyrrolylmagnesium Bromide with S-Ethyl Chlorothioformate in the Presence of Hexamethylphosphoramide (HMPA)

A solution of hexamethylphosphoramide (14.34 g, 0.080 mol) in absolute ether (10 ml) was added slowly into a solution of pyrrolylmagnesium bromide (0.040 mol) in absolute ether (50 ml). Heat was given off and the color of the solution turned yellow. When the addition of hexamethylphosphoramide solution

was completed two layers were observed. The reaction mixture was refluxed for 30 minutes and then cooled in a mixture of carbon tetrachloride and Dry Ice. To this cold solution of pyrrolylmagnesium bromide a solution of S-ethyl chlorothioformate (7.47 g, 0.060 mol) in absolute ether (40 ml) was added in a period of about one hour. The cold bath was removed.

After stirring at room temperature for 3 hours, the reaction mixture was cooled in an ice bath and saturated solution of ammonium chloride (100 ml) was added. The reaction mixture was stirred until all the solid material in the flask completely dissolved. The ethereal layer was separated and the aqueous layer was extracted twice with an equal volume of ether. The combined ethereal layer was washed three times with an equal volume of water and dried over anhydrous magnesium sulfate. The volume of the ethereal solution was reduced to 50 ml and analyzed on g.l.c. The yields of S-ethyl 1-pyrrolethiocarboxylate and S,S'-diethyl dithiocarbonate were 4.33 g (70%) and 0.65 g respectively. No S-ethyl 2-pyrrolethiocarboxylate, 1,1'-dipyrrolyl ketone and 1,2'-dipyrrolyl ketone were detected by g.l.c.

Part II

General

Analyses of reaction mixtures were carried out on a Varian 1520B gas chromatograph equipped with a 12-foot column packed with 30% Carbowas 20M on Chromosorb W (80 - 100 mesh). Helium was used as carrier gas at a rate of 30 ml per minute. The column temperature was set at 120°. The retention time of pyrrole, mono-, di-, and tri-alkylpyrroles are tabulated in Table XI.

The methods of isolation and identification of compounds were described in the individual experiments. The quantitative analysis calculations were the same as those described in Part I of the Experimental Section.

The following compounds were prepared as authentic samples or starting materials for the experimental work. Given with the name of each compound is the number of the literature reference.

Compound	Literature
2-Formylpyrrole	118
S-Ethyl 4-formyl-2-pyrrolethiocarboxylate	114
2,5-Dimethylpyrrole	119
Ethyl 2-methyl-3-pyrrolecarboxylate	120
2,3-Dimethylpyrrole	121
2,5-Dimethyl-3-formylpyrrole	121

Table XI. The retention times of pyrrole, mono-alkylpyrroles, dialkylpyrroles and trialkylpyrrole on Varian 1520B chromatograph equipped with 12-foot long column packed with 30% Carbowax 20M on Chromosorb W (80 - 100 mesh). Helium was used as carrier gas at a rate of 30 ml/min. The column temperature was set at 120°.

Compound	Retention time (min)
1-methylpyrrole	23.0
pyrrole	140.0
2-methylpyrrole	169.5
3-methylpyrrole	183.0
2,5-dimethylpyrrole	213.5
2,3-dimethylpyrrole	242.5
2,3,5-trimethylpyrrole	296.0

(xxxiii) Reaction of Pyrrolylmagnesium Bromide with Methyl p-Toluenesulfonate in the Presence of Hexamethylphosphoramide (HMPA)

A mixture of pyrrolylmagnesium bromide (0.040 mol) and hexamethylphosphoramide (28.72 g, 0.160 mol) in absolute ether (60 ml) was prepared by the method described in Section (xxxii). This mixture was cooled in an ice bath and a solution of methyl p-toluenesulfonate (11.17 g, 0.060 mol) in absolute ether (40 ml) was added in a period of 30 minutes.

After stirring at room temperature for 17 hours cold water was added to the reaction mixture until most of the solid dissolved. The two layers were separated and the aqueous layer was extracted twice with an equal volume of ether. The combined ethereal layer was washed twice with water, flushed with nitrogen and dried over anhydrous potassium carbonate. The volume of the reaction mixture was reduced to 50 ml and analyzed by g.l.c. After removal of the solvent from the rest of the reaction mixture, a colorless liquid was collected by distillation at 113 - 114°. The i.r. and n.m.r. spectra of this compound were the same as that of an authentic sample of 1-methylpyrrole (122). A second fraction was collected at 130 - 131° and its i.r. was identical with that of an authentic sample of pyrrole. The yield of 1-methylpyrrole was 1.59 g (49%) and g.l.c. only showed a trace of 2-methylpyrrole and 3-methylpyrrole.

The same experiment was repeated but the ratio of hexamethylphosphoramide to pyrrolylmagnesium bromide was 2 : 1. The result of this experiment was included in Table V. The result of the reaction of dimethyl sulfate with pyrrolylmagnesium bromide under the same conditions was also included in Table V.

(xxxiv) Reaction of Pyrrolylmagnesium Bromide with Iodomethane

The pyrrolylmagnesium bromide (0.400 mol) in absolute ether (500 ml) was prepared by the standard method described in Section (i). The Grignard reagent was diluted with another 300 ml of absolute ether and cooled in an ice bath.

To the cold Grignard reagent a solution of iodomethane (113 g, 0.800 mol) in absolute ether (100 ml) was added slowly. After the addition was completed, the reaction mixture was stirred at room temperature for 17 hours. After cooling in an ice bath, cold water was added until most of the solid dissolved. The two layers were separated and the aqueous layer was extracted twice with an equal volume of ether. The combined ethereal layer was washed twice with water, flushed with nitrogen and dried over anhydrous potassium carbonate. The reaction mixture was reduced to 500 ml and analyzed on a Varian 1520B gas chromatograph. Identifications of the products in the reaction mixture were done by comparison of the retention times of authentic samples of 1-methylpyrrole, pyrrole, 2-methylpyrrole,

3-methylpyrrole, 2,5-dimethylpyrrole, 2,3-dimethylpyrrole and 2,3,5-trimethylpyrrole with those of the products in the reaction mixture.

The solvent was removed from the rest of the reaction mixture. The residue was distilled and then vacuum distilled. Fraction (a) was collected at 129 - 131° at atmospheric pressure. The infrared spectrum of this fraction showed that it was the unreacted pyrrole. Fraction (b) was collected at 147 - 149° at atmospheric pressure. The infrared spectrum and n.m.r. spectrum of this fraction showed that it was a mixture of 2-methylpyrrole and 3-methylpyrrole. Fraction (c) was collected at 65 - 67° at 10 mm pressure. Comparison of the n.m.r. spectrum of this fraction and those of authentic samples of 2,5-dimethylpyrrole and 2,3-dimethylpyrrole indicated that fraction (c) was a mixture of these two compounds. Fraction (d) was collected at 72 - 75° at 10 mm pressure. The n.m.r. spectrum of this fraction showed that it was a mixture of 2,5-dimethylpyrrole, 2,3-dimethylpyrrole and 2,3,5-trimethylpyrrole.

The yields of the compounds mentioned above were tabulated in Table III.

(xxxv) Reaction of Pyrrolylmagnesium Bromide with Iodomethane in the Presence of Hexamethylphosphoramide

The procedure of this experiment was the same as that described in Section (xxxiii) except that iodomethane (11.30 g, 0.080 mol) was used instead of methyl p-toluenesulfonate.

The same experiment was repeated with different ratios of hexamethylphosphoramide to pyrrolylmagnesium bromide and the results were tabulated in Table III.

(xxxvi) Reaction of 2-Methylpyrrolylmagnesium Bromide (XLIV) with Iodomethane

The Grignard reagent of 2-methylpyrrole (0.040 mol) in absolute ether (50 ml) was prepared according to the procedure described in Section (i) and the second part of this experiment was the same as that described in Section (xxxiv) except that the quantity of iodomethane and the volume of absolute ether were reduced to 11.30 g (0.040 mol) and 40 ml respectively. The reaction mixture was reduced to 50 ml and analyzed on the Varian 1520B chromatograph. The yields of 2,5-dimethylpyrrole, 2,3-dimethylpyrrole and 2,3,5-trimethylpyrrole were 0.55 g (17%), 0.43 g (11%) and 0.33 g (8%) respectively.

(xxxvii) Reaction of 3-Methylpyrrolylmagnesium Bromide (XLV) with Iodomethane

The Grignard reagent of 3-methylpyrrole (0.007 mol) in absolute ether (10 ml) was prepared according to the procedure described in Section (i).

The second part of this experiment was the same as that described in Section (xxxiv) except that the quantity of the iodomethane and the volume of the absolute ether were reduced to 2 g (0.014 mol) and 10 ml respectively. The reaction mixture was reduced to 10 ml and analyzed on chromatograph. The yields of 2,3-dimethylpyrrole and 2,3,5-trimethylpyrrole were 0.13 g (22%) and 0.17 g (24%) respectively.

(xxxviii) Reaction of 2,5-Dimethylpyrrolylmagnesium Bromide with Iodomethane

Grignard reagent of 2,5-dimethylpyrrole (0.95 g, 0.010 mol) in absolute ether (13 ml) was prepared according to procedure described in Section (i).

The second part of this experiment was the same as that described in Section (xxxiv) except that the quantity of the iodomethane and the volume of the absolute ether were reduced to 2 g (0.014 mol) and 10 ml respectively. The reaction mixture was reduced to 10 ml and analyzed on the gas-liquid chromatograph. The yield of 2,3,5-trimethylpyrrole was 0.22 g (20%).

(xxxix) Preparation of 2-Methylpyrrole

A mixture of diethylene glycol (50.0 ml), potassium hydroxide pellets (7.0 g), hydrazine hydrate (6.0 ml of 100%) and 2-formylpyrrole (4.8 g, 0.05 mol) was heated on a steam bath until most of the potassium hydroxide had dissolved and the solution was refluxed for one hour.

The solution was distilled at atmospheric pressure until the temperature reached 150°. Two layers were observed in the receiving flask. The two layers were separated and the aqueous layer was extracted twice with ether (20 ml). The organic layers were combined, flushed with nitrogen, and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was distilled under reduced pressure. The product, 2-methylpyrrole was collected at 87 - 88° at 67 mm pressure, literature b.p. 146 - 149° (121), yield 2.50 g (62%). The structure proposed for this compound was confirmed by consideration of its n.m.r. spectrum.

(xl) Preparation of 3-Methylpyrrole

A mixture of triethylene glycol (50 ml), potassium hydroxide (6.0 g), hydrazine hydrate (5.0 g of 80%) and S-ethyl 4-formyl-2-pyrrolethiocarboxylate (5.0 g, 0.027 mol) was heated at 125° for 90 minutes and then refluxed for 4 hours. The solution was distilled and the distillate collected until the temperature reached 180°. Two layers were observed in the receiving flask. The two layers were separated and the aqueous layer was extracted twice with ether (20 ml). The combined organic layer was flushed with nitrogen and dried over anhydrous magnesium sulfate. The product, 3-methylpyrrole was collected at 142 - 144°, literature b.p. 143 - 143.5° (121), yield 1.2 g (52%). The structure of this compound was confirmed by consideration of its n.m.r. spectrum.

(xli) Preparation of 2,3,5-Trimethylpyrrole

A mixture of triethylene glycol (50 ml), potassium hydroxide (7.0 g), hydrazine hydrate (8 ml of 80%) and 2,5-dimethyl-3-formylpyrrole (4.1 g, 0.030 mol) was heated on a steam bath until the potassium hydroxide had just dissolved. After refluxing for one hour the solution was distilled and the distillate was collected until the temperature reached 200°. Two layers were observed in the receiving flask. The two layers were separated and the aqueous layer was extracted twice with ether (20 ml). The combined organic layer was flushed with nitrogen and dried over anhydrous magnesium sulfate. The product, 2,3,5-trimethylpyrrole, was collected at 90 - 91° at 35 mm pressure, literature b.p. 78 - 80° at 16 mm pressure (121), yield 1.7 g (48%). The structure of this compound was confirmed by consideration of its n.m.r. spectrum.

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APPENDIX

Spectra

Infrared spectra were recorded on a Perkin-Elmer 273B grating spectrophotometer as potassium chloride discs (1 mg sample in 180 mg KCl). Ultraviolet spectra were recorded on a Perkin-Elmer 202 Ultraviolet spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 analytical spectrometer and a Varian HA-100 spectrometer and resonance positions were recorded on the τ scale, using tetramethylsilane as an internal reference. Mass spectra were recorded using a Hitachi-Perkin-Elmer RMU-6E mass spectrometer and the spectra were normalized. The value in the bracket following the mass number is the relative abundance of the ion compared with the base peak equal to 100%.

S-Ethyl 1-pyrrolethiocarboxylate (LXVI)

Ultraviolet spectrum (ethanol): λ_{max} 248 mμ (ε 12300).

Infrared spectrum*: ν_{max} 3125w(aromatic C-H), 3090w(aromatic C-H), 2950w, 2910w, 1755w, 1680s(C=O), 1575w, 1530w, 1460s, 1420w, 1380w, 1370w, 1330m, 1325m, 1275s, 1260s, 1090s, 1070m, 1050w, 975w, 865s, 740m(aromatic C-H) cm^{-1}.

N.M.R. spectrum ($CDCl_3$): τ 2.72 (2H, triplet, αH), 3.73 (2H, triplet, βH), 6.92 (2H, quartet, S-CH_2-), 8.63 (3H, triplet, -CH_3).

Mass spectrum: m/e 40(14), 41(19), 45(5), 53(5), 61(5), 66(21, M*-$COSC_2H_5$), 67(57, $C_4H_5N^+$), 68(6), 80(28), 89(25, M*-C_4H_4N),

94(14, M*-SC_2H_5), 98(5), 127(17), 155(100, M*), 156(12, M*+1), 157(6, M*+2).

1,1'-Dipyrrolyl ketone (LXX)

Ultraviolet spectrum (ethanol): λ_{max} 243mμ (ε 16700).

Infrared spectrum: ν_{max} 3055w(aromatic C-H), 3040w(aromatic C-H), 1725s(C=O), 1675m, 1600w, 1540w, 1475m, 1460m, 1420s, 1350s, 1295m, 1265m, 1250m, 1210m, 1080m, 1075m, 1040m, 980m, 935w, 860w, 840m, 745m, 735m(aromatic C-H), 700m cm^{-1}.

N.M.R. spectrum ($CDCl_3$): τ 2.70 (2H, triplet, αH), 3.65 (2H, triplet, βH).

Mass spectrum: m/e 40(11), 41(20), 44(7), 45(14), 51(5), 55(7), 56(7), 57(9), 66(100, M* - C_4H_4NCO), 67(14, $C_4H_5N^+$), 94(84, M* - C_4H_4N), 95(9), 104(11), 105(7), 118(7), 131(7), 141(7), 150(7), 159(27, M* - 1), 160(84, M*), 161(11, M* + 1).

1-Acetoacetylpyrrole (LXV)

Ultraviolet spectrum (ethanol): λ_{max} 350mμ (ε 30700).

Infrared spectrum: ν_{max} 3140w(aromatic C-H), 3100w(aromatic C-H), 1725m, 1710m(C=O), 1685m(C=O), 1625s(enol C=O), 1620s, 1540m, 1475s, 1460s, 1430s, 1385s, 1375s, 1325s, 1300s, 1200s, 1800s, 1160s, 1060s, 1030s, 1010m, 945m, 870m, 830m, 780s, 740m, 725s(aromatic C-H) cm^{-1}.

N.M.R. spectrum (CCl_4): τ 0.24 (0.6 x 1H, singlet, OH), 2.80 (2H, triplet, αH), 3.80 (2H, triplet, βH), 4.45 (0.6 x 1H, singlet, C=CH), 6.24 (0.4 x 2H, singlet, $-CH_2-$), 7.75 (0.4 x 3H, singlet, $-CH_3$), 7.95 (0.6 x 3H, singlet, $-CH_3$).

Mass spectrum: m/e 40(6), 41(12), 44(26), 67(100, $C_4H_5N^+$), 68(8), 85(8), 149(6) 151(15, M*).

N,N'-Dicyclohexyl-1-pyrrolylcarbamidine (LIX)

Ultraviolet spectrum (ethanol): λ_{max} 223mμ (ε 13400).

Infrared spectrum: ν_{max} 3290m(NH), 3100w(aromatic C-H), 3090w(aromatic C-H), 2920s, 2850s, 1640s(C=N), 1525m, 1515m, 1475s, 1460s, 1455m, 1445m, 1400w, 1370m, 1350m, 1330m, 1320s, 1285m, 1260m, 1250w, 1215w, 1190w, 1155w, 1115w, 1090m, 1075m, 1060w, 1040w, 1030w, 975w, 940m, 890w, 850w, 810w, 725s(aromatic C-H) cm^{-1}.

N.M.R. spectrum ($CDCl_3$): τ 3.25 (2H, triplet, αH), 3.86 (2H, triplet, βH), 6.00 (1H, singlet, NH), 6.78 (2H, singlet, broad, cyclohexyl N-CH), 8.54 (20H, overlapping multiplets, cyclohexyl $-CH_2-$).

Mass spectrum: m/e 41(23), 43(38), 55(43), 67(37, $C_4H_5N^+$), 68(8), 69(5), 81(15), 83(43), 93(10), 98(7), 110(8), 124(5), 125(100, M* - C_6H_{10}), 126(10), 191(8), 267(43, M* - C_4H_4N), 208(7), 273(52, M*), 274(13, M* + 1).

Ethyl 1-pyrrolylglyoxylate (LVII)

Ultraviolet spectrum (ethanol): λ_{max} 240mμ (sh, ε 450).

Infrared spectrum: ν_{max} 3130w(aromatic C-H), 3110w(aromatic C-H), 2970w, 2920w, 2890w, 1760s(C=O), 1725s(C=O), 1600w, 1560w, 1475s, 1450w, 1420m, 1390w, 1375m, 1360s, 1310m, 1250s, 1115s, 1080m, 1050w, 1020m, 920m, 865w, 825w, 750s(aromatic C-H) cm^{-1}.

N.M.R. spectrum ($CDCl_3$): τ 2.60 (2H, triplet, αH), 3.62 (2H, triplet, βH), 5.55 (2H, quartet, O-CH_2-), 8.59 (3H, triplet, -CH_3).

Mass spectrum: m/e 40(17), 41(25), 53(7), 66(49, M* - $COCO_2C_2H_5$), 67(100, $C_4H_5N^+$), 68(8), 80(53), 94(45, M* - $COOC_2H_5$), 95(6) 135(5), 167(78, M*), 168(9, M* + 1).

1,1'-Dipyrrolyl ketimine (LXXVII)

Ultraviolet spectrum (ethanol): λ_{max} 238mμ (ε 17800).

Infrared spectrum (Film): ν_{max} 3240m(NH), 3120m(aromatic C-H), 3100m(aromatic C-H), 2900w, 2850w, 1660s(C=N), 1625m, 1580w, 1540w, 1470s, 1420s, 1375s, 1360s, 1305m, 1260m, 1250s, 1200s, 1110s, 1090s, 1080s, 1050m, 975s, 945m, 925m, 890w, 870w, 810s, 730s(aromatic C-H), 710s cm^{-1}.

N.M.R. spectrum ($CDCl_3$): τ 2.34 (1H, singlet, broad, NH), 2.92 (2H, triplet, αH), 3.70 (2H, triplet, βH).

Mass spectrum: m/e 40(7), 41(14), 66(12), 67(100, $C_4H_5N^+$), 68(6), 92(6), 93(17, M* - C_4H_4N), 159(54, M*), 160(7, M* + 1).

1,1'-Dipyrrolyl N-thiomethylketimine (LXXVI)

Ultraviolet spectrum (ethanol): λ_{max} 239mμ (ε 9320), 296mμ (ε 11400).

Infrared spectrum: ν_{max} 3120w(aromatic C-H), 3090w(aromatic C-H), 2975, 2900w, 1720w, 1640s and 1625s(C=N), 1575w, 1530w, 1475m, 1465s, 1430w, 1410m, 1360s, 1320w, 1305w, 1260m, 1110s, 1090m, 1075m, 1055m, 990w, 950w, 860m, 775w, 730s(aromatic C-H), 675w cm^{-1}.

N.M.R. spectrum ($CDCl_3$): τ 3.80 (2H, triplet, αH), 3.71 (2H, triplet, βH), 7.32 (3H, singlet, SCH_3).

Mass spectrum: m/e 40(6), 41(8), 47(7), 65(6), 66(11), 67(42, $C_4H_5N^+$), 68(5), 92(59, (M* - C_4H_4N) - SCH_3), 93(21), 98(12), 112(7), 113(9), 124(13), 139(30, M* - C_4H_4N), 159(18), 205(100, M*), 206(15, M* + 1), 207(6, M* + 2).

N,N'-Dimethyl-1-pyrrolylcarbamidine (LXIII)

Ultraviolet spectrum (ethanol): λ_{max} 224mμ (ε 13000).

Infrared spectrum: ν_{max} 3300w(NH), 3120w(aromatic C-H), 3090w(aromatic C-H), 3000w, 2940w, 2900w, 2875w, 2790w, 1635s(C=N), 1480s, 1450m, 1405s, 1385s, 1280m, 1260w, 1240w, 1200w, 1150w, 1090s, 1070m, 1035m, 965m, 865w, 800w, 735s(aromatic C-H) cm^{-1}.

N.M.R. spectrum ($CDCl_3$): τ 3.15 (2H, triplet, αH), 3.83 (2H, triplet, βH), 3.90 (1H, singlet, broad, NH), 7.20 (6H, singlet, NCH_3).

Mass spectrum: m/e 41(7), 42(5), 44(6), 67(100, $C_4H_5N^+$), 68(6), 71(43, M* - C_4H_4N), 137(24, M*).

* s: the intensity is stronger than 2/3 of that of the strongest peak;
  m: the intensity is weaker than 2/3 but stronger than 1/3 of that of the strongest peak;
  w: the intensity is weaker than 1/3 of that of the strongest peak.

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