REACTIONS OF METAL DERIVATIVES OF PYRROLE

WITH

PHENYL ISOCYANATE

BY

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submitted in partial fulfillment for the requirements

of the degree Master of Science

in the Chemistry Department of the

American University of Beirut

Beirut, Lebanon

June 1965

ABSTRACT

The reaction of pyrrylpotassium with phenyl isocyanate yields 1-pyrrolecarboxanilide in almost quantitative yield. This compound displays a rather low reactivity with regard to nucleophilic substitution reactions on the carbonyl carbon atom.

Upon heating with phenyl isocyanate, in the presence of triethylamine, 2-pyrrolecarboxanilide yields 2-phenylpyrrolo [1,2-c]-hydantoin in almost quantitative yield. The hydantoin ring in this compound is opened relatively easily by the action of nucleophiles.

The reaction of pyrrylmagnesium bromide with phenyl isocyanate yields a product composed of several compounds from which 2-(N-phenylcarbamyl)pyrrolecarboxanilide and 1,2-pyrroledicarbox-anilide have been isolated and characterized.

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INTRODUCTION

I. Reactions of Metal Derivatives of Pyrrole

A. Reactions of Pyrrylpotassium

Metallic potassium reacts readily with pyrrole to give pyrrylpotassium with evolution of hydrogen. This salt is the source of a large number of pyrrole derivatives, and on treatment with alkyl and acyl halides it gives the corresponding substituted pyrroles. As a rule substitution takes place predominantly at the nitrogen atom.[1,2,3] However, in a study of the reactions of pyrrylpotassium with allylic halides, it was observed that the position of alkylation depends considerably on the nature of the reaction medium. Thus, polar solvents, such as tetrahydrofuran, dioxane, etc., favor N-alkylation, whereas nonpolar solvents, such as benzene, toluene, etc., favor C-alkylation.[4]

B. Reactions of Pyrrylmagnesium Halides

Pyrrole reacts readily with Grignard reagents, and the pyrrylmagnesium halides formed are extremely valuable synthetic reagents since they interact readily with a large variety of compounds giving as a rule C-substituted pyrroles.[5,6]

There has been some controversy about whether the -MgX group in pyrrylmagnesium halides is attached to the N or to a C atom.[7,8,9] The formation of only one mole of methane by the reaction of pyrrole with methylmagnesium iodide, corresponding to the presence of only one

active hydrogen atom in the molecule of pyrrole, was interpreted by Gilman and Heck as indicating the attachment of the -MgX group to the nitrogen atom.[10]

In a systematic study of the reactions of pyrrylmagnesium bromide with alkyl halides, Skell and Bean observed that 2- and 3-substituted pyrroles were formed together with disubstituted pyrroles.[11] They further offered evidence that the -MgBr group is attached to the nitrogen atom in pyrrylmagnesium bromide, by observing the formation of only 1-D-pyrrole when pyrrylmagnesium bromide was treated with deuterium oxide, and also by the formation of deuteromethane when 1-D-pyrrole was treated with methylmagnesium bromide.

Recently, Reinecke and coworkers used nuclear magnetic resonance and infrared spectra to establish the constitution of the pyrryl-magnesium chloride.[12] They concluded that in ether as a solvent, the pyrrylmagnesium chloride has either of the following structures:
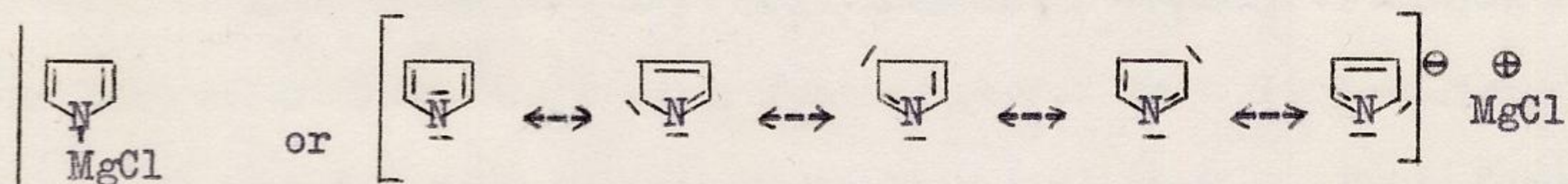

Very recently, Castro and coworkers presented evidence in the form of nuclear magnetic resonance and infrared spectra to support the structure
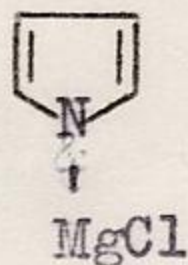
for the pyrrylmagnesium chloride in tetrahydrofuran as a solvent.[13]

C. The Pyrryl Ambident Anion

A review of the alkylation and acylation reactions of pyrryl-potassium and pyrrylmagnesium halides shows that the pyrryl anion, as is to be expected from its resonance structures,
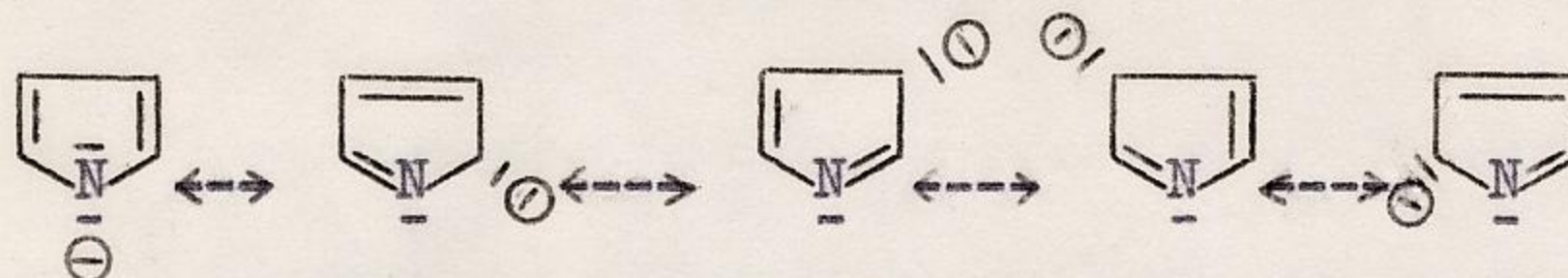
is an ambident anion and can undergo covalent bond formation at any one atom on the ring.

A study of the alkylation reactions of potassium, sodium and lithium salts of pyrrole with allyl bromide, crotyl bromide, and benzyl chloride, under a variety of conditions, led to the conclusion that factors favoring dissociation of the salt lead to predominant nitrogen-alkylation, whereas factors favoring association of the salt lead to predominant carbon-alkylation.[4]

To explain the fact that pyrrylmagnesium bromide is alkylated on carbon rather than on nitrogen, Bean suggested that the low dielectric constant of ether does not allow complete dissociation of the ion pairs of the Grignard reagent. Thus the nitrogen atom is blocked by the MgBr$^{\oplus}$ group and alkylation takes place on the carbon atom.[11]
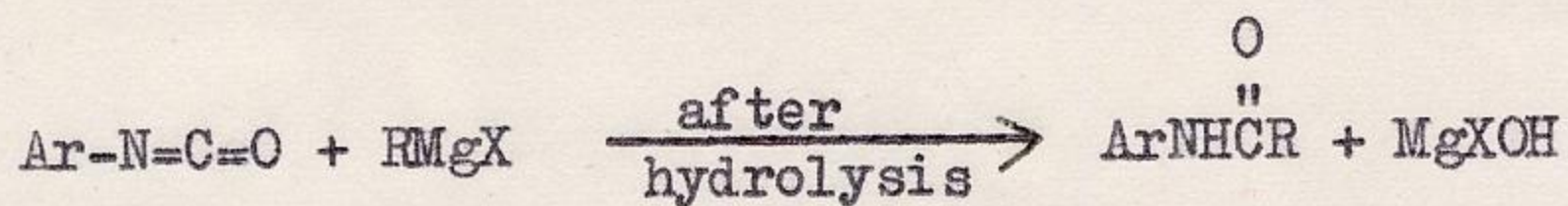
II. Reactions of Isocyanates

A. Reactions of Isocyanates with Carbanions

As early as 1901, it was reported by Blaise that phenyl isocyanate reacted with organomagnesium iodides to form products which, upon hydrolysis, yielded anilides.[14]

Gilman and Fury[15], and Schwartz and Johnson[16] reported that aryl

isocyanates reacted with Grignard reagents to form products which, upon hydrolysis, yielded substituted amides.

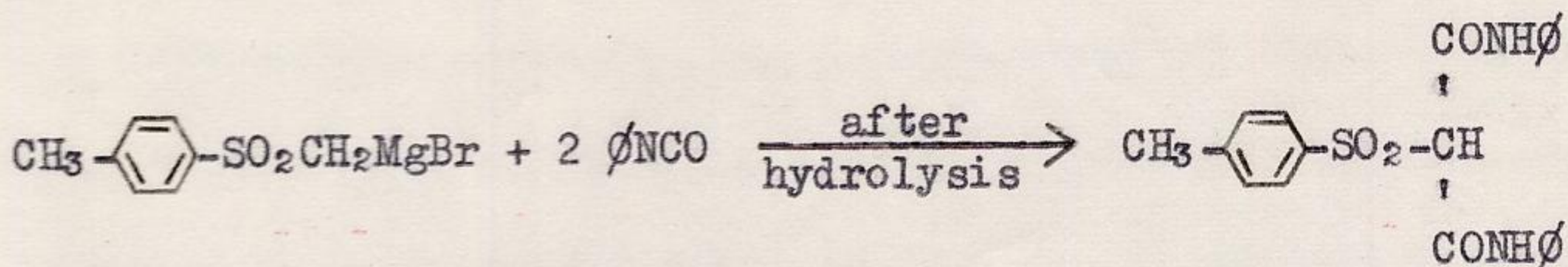$$Ar-N=C=O + RMgX \xrightarrow[\text{hydrolysis}]{\text{after}} ArNHCR + MgXOH$$

Since organomagnesium halides react smoothly with aryl iso-cyanates to produce substituted amides that are usually crystalline solids, this reaction has been recommended as a means of identification of Grignard reagents and of alkyl halides that can be converted into these.[15,16]

Isocyanates have two reactive groups: $-N=C=$ and $=C=O$ which can add the Grignard reagent. Little is known concerning the mechanism or the order of the reaction. However, the studies of Gilman and Kinney make it appear probable that the condensation of phenyl isocyanate with one molecule of the Grignard reagent is essentially an ionic addition to the terminal (C=O) double bond.[17]
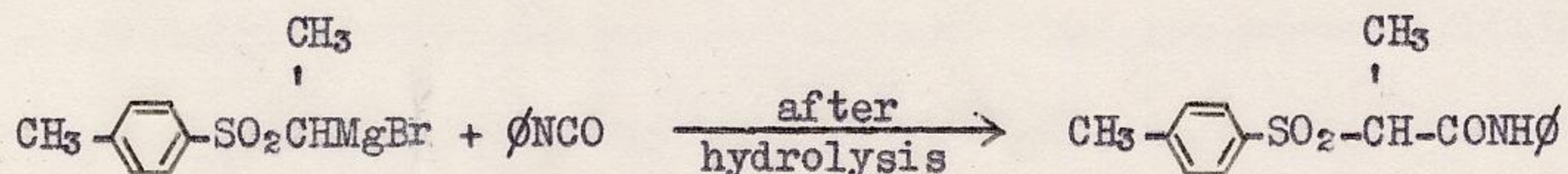
Shilov and Bogdanov reported that phenyl isocyanate trimer reacted with sodium phenoate to produce salicylanilide and diphenyl-urea.[18]

Field and coworkers observed that phenyl isocyanate reacted with p-tolylsulfonylmethylmagnesium bromide to yield after hydrolysis p-tolylsulfonylmalonanilide in 40% yield.[19]

$$CH_3 - \langle \rangle - SO_2CH_2MgBr + 2\ \emptyset NCO \xrightarrow[\text{hydrolysis}]{\text{after}} CH_3 - \langle \rangle - SO_2 - CH \begin{matrix} CONH\emptyset \\ | \\ | \\ CONH\emptyset \end{matrix}$$

No p-tolylsulfonylacetanilide was isolated. On the other hand, phenyl

isocyanate reacted with α-(p-tolylsulfonyl)ethylmagnesium bromide to

yield α-(p-tolylsulfonyl)propionanilide in 14% yield.

$$ CH_3 - \langle \rangle - SO_2CHMgBr + \emptyset NCO \quad \xrightarrow[\text{hydrolysis}]{\text{after}} \quad CH_3 - \langle \rangle - SO_2 - CH - CONH\emptyset $$

$$ \overset{CH_3}{|} \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \overset{CH_3}{|} $$

According to these investigators, the methyl group has an effect

on the reaction which favors the formation of the monoanilide rather

than the dianilide, but whether this effect is achieved via steric or

electronic means is not clear.

B. Reactions of Isocyanates with Benzene Derivatives

As early as 1885, it was observed that under Friedel-Crafts

conditions aryl and alkyl isocyanates reacted with benzene derivatives

to give N-substituted benzamides.[20]

Quite recently it was found that even the relatively unreactive

halobenzenes undergo the reaction.[21]

C. Reactions of Isocyanate with Heterocyclic Compounds

Fischer and coworkers observed that cryptopyrrole reacted with

phenyl isocyanate to yield an adduct which they assumed to be the

N-carboxanilide.[22]

Henry and Dehn reported the use of aryl isocyanates as reagents

for the identification of heterocyclic compounds containing one or

more imino groups in the ring.[23] Pyrrole and imidazole were among

the heterocycles studied. The authors observed that, in general, the

more basic the heterocyclic compound, the more rapid and complete its

reaction with the isocyanate. As an example, pyrrole reacts very

sluggishly with isocyanates, whereas the dihydro- and tetrahydropyrrole,

with the pronounced basic properties, react vigorously. The deri-
vatives from phenyl isocyanate were the most readily obtained and
recrystallized, but the reagent suffered from its susceptibility to
traces of water in the compounds identified and yielded the difficul-
ly separable diphenylurea. No attempt was made to determine the
structure of the obtained adducts which were assumed to be the N-
substituted heterocycles.

Treibs and Ott observed that pyrrole and its homologues react
readily at room temperature with phenyl isocyanate to give the
corresponding 2-pyrrolecarboxanilides.[24] These amides are stable and
well crystallized compounds, suitable for the identification of
pyrroles. The entering ØNHCO group occupies an α-position, unless
both of these positions are occupied by alkyl groups. In this case
the pyrrole reacts far more sluggishly and the addition takes place at
a β-position. Pyrrole itself reacts quite slowly at room temperature,
and three days are needed for completion of the reaction[*]. Alkyl sub-
stituted pyrroles, however react much faster, and with 2,4-dimethyl-
pyrrole the reaction is completed in a few minutes by mild heating.
It appears that the 1-position must be free for reaction to take place,
because 1-methylpyrrole does not react even on strong heating. These
pyrrolecarboxanilides are difficult to hydrolyze, e.g., 2,4-dimethyl-5-
pyrrolecarboxanilide resists hydrolysis even on prolonged boiling with

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* In the course of the present work, it was observed that actually the
  reaction is not complete even after several weeks.

concentrated hydrochloric acid, and concentrated aqueous or alcoholic sodium hydroxide. It is cleaved only by heating with concentrated sulfuric acid or by fusion with potassium hydroxide.

Staab reported that in the reaction of phenyl isocyanate with imidazole in tetrahydrofuran, the product was not 2-imidazolecarboxanilide but 1-imidazolecarboxanilide.[25] This product is interesting for its ability to dissociate into isocyanate and imidazole in chloroform solution even at room temperature
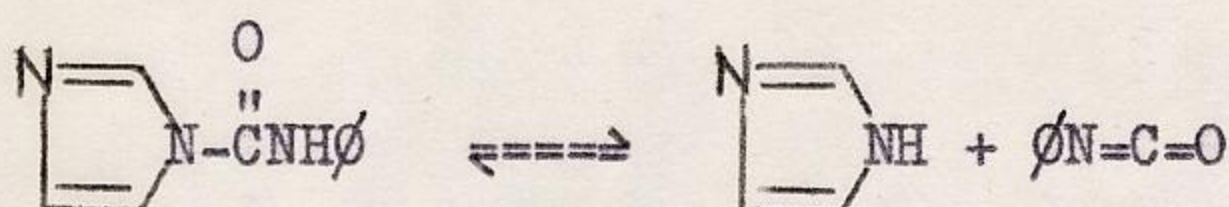
A similar behavior is shown by 1-benzimidazolecarboxanilide, whereas 1-(1,2,4-triazole)carboxanilide and 1-(1,2,3-benzotriazole)carboxanilide are stable in solution even on heating.[26] Because of their great tendency to dissociate, 1-imidazolecarboxanilides are at the head of the list of "masked isocyanates".[27] Whereas, as a rule, the dissociation of urethanes and trisubstituted ureas requires rather high temperature, 1-imidazolecarboxanilide solutions practically behave like isocyanate solutions even at room temperature. Prepared independently, they can be used for the synthesis of isocyanates. In the solid state, however, 1-imidazolecarboxanilides are crystalline, stable compounds, free of the toxic/side effects of isocyanates.

Staab studied also the nucleophilic substitution reactions of 1-imidazolecarboxanilide.[25] Treatment with aniline in tetrahydrofuran yielded N,N'-diphenylurea in 83% yield, and treatment with phenol gave phenyl N-phenylcarbamate in 86% yield. Similar results were obtained with 1-(1,2,4-triazole)carboxanilide.

In tetrahydrofuran solution, water decomposed 1-imidazolecarbox-anilide, as well as the corresponding derivative of 1,2,4-triazole, at room temperature, to carbon dioxide, aniline and imidazole or triazole.

According to Staab these nucleophilic substitution reactions do not follow a uniform mechanism.[27] Whereas 1-(1,2,4-triazole)car-boxanilide does not dissociate in solution even at 60^0, it reacts readily at room temperature with aniline to form N,N'-diphenylurea. In this, and the similar case of 1-(1,2,3-triazole)carboxanilide it appears that a nucleophilic attack occurs directly at the carbonyl group. On the other hand, in the case of 1-imidazolecarboxanilide and 1-benzimidazole-carboxanilide, with which a considerable dissociation to isocyanate is observed at room temperature, the reaction probably occurs through the liberated isocyanate. This view is supported by the fact that the N-methyl-1-imidazolecarboxanilide, for which dissociation to isocyanate is impossible, does not react with aniline.

Gompper and coworkers observed that a 2-imidazolecarboxanilide is formed in addition to the 1-imidazolecarboxanilide, when 4,5-diphenyl-imidazole is treated with phenyl isocyanate.[28] They maintained that the conditions of the reaction determine the position of addition in the imidazole ring. They studied the reaction of 4,5-diphenylimidazole (I) with phenyl isocyanate under three sets of conditions.

a) Refluxing of a mixture of I and phenyl isocyanate yielded the following products:

II   III   IV
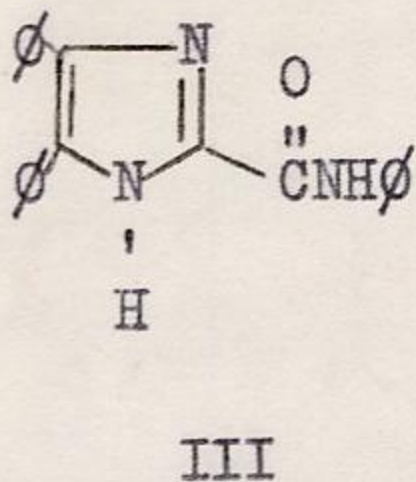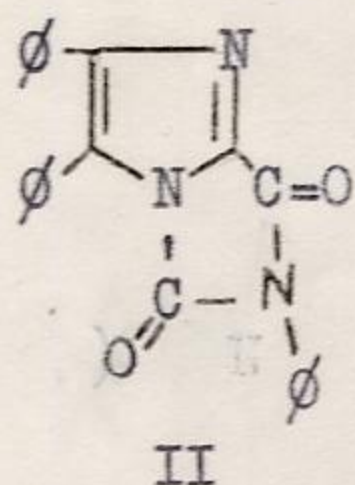
b) treatment of I with phenyl isocyanate in refluxing nitrobenzene gave the 2-substituted imidazole (III) as the only product. It is noteworthy that a similar reaction was observed with 1-alkylsubstituted imidazoles.

c) Treatment of I with phenyl isocyanate at room temperature resulted in the formation of the 1-substituted imidazole,
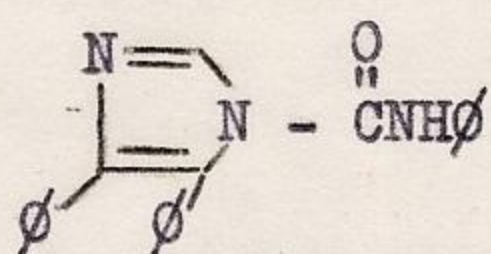
as the exclusive product.

On refluxing with aniline, the hydantoin II yielded a mixture of the 2-carboxanilide (III) and N,N'-diphenylurea (IV), whereas on hydrolysis with potassium hydroxide, it was converted into 4,5-diphenyl-2-imidazolecarboxylic acid.

The hydantoin structure for product II was further supported by the nature of the infrared spectrum of this compound with ν(C=O) at 1813, 1760, and 1709 cm^{-1}. In general, Gompper observed that the carbonyl stretching frequencies are above 1700 cm^{-1} for N-acylated imidazole derivatives, and below 1700 cm^{-1} for C-acylimidazole derivatives, e.g.

	ν(C=O)
1-imidazolecarboxanilide	1730
4,5-diphenyl-1-imidazolecarboxanilide	1739
2,5,6-triphenylimidazolo[1,2-c]hydantoin	1813, 1760, 1709
4,5-diphenyl-2-imidazolecarboxanilide	1668
2-benzimidazolecarboxanilide	1660

Similarly to the previous reactions, 2-methyl-4-phenyl-5-imidazolcarboxanilide (ν C=O 1644 cm^{-1}) resulted from the reaction of 2-methyl-4-phenylimidazole with phenyl isocyanate in refluxing nitrobenzene, and 3-phenyl-2-indolecarboxanilide (ν C=O 1673 cm^{-1}) from the reaction of 3-phenylindole with excess phenyl isocyanate under reflux. Further, benzimidazole reacted with phenyl isocyanate in boiling nitrobenzene to form 2-benzimidazolecarboxanilide, and theophylline reacted with excess phenyl isocyanate under reflux to yield 7(9)-theophyllinecarboxanilide.

Finally, refluxing of 2,4-diphenylpyrrole with excess phenyl isocyanate yielded a yellow crystalline substance to which Gompper assigned a hydantoin structure on the basis of its infrared spectrum (carbonyl stretching at 1762 and 1649 cm^{-1}), but whose elemental analysis did not correspond to any definite structure.

Seefelder reported that with more reactive isocyanates, e.g. p-toluenesulfonyl isocyanate, even N-substituted pyrroles undergo reaction.[29] It is noteworthy in such a case that pyrrole itself is reported to react at the 3-position, but no evidence is given by the authors regarding the position of substitution.

DISCUSSION OF RESULTS

A. 1-Pyrrolecarboxanilide

There is no reference in the literature concerning the reaction of phenyl isocyanate with metal derivatives of pyrrole. On the other hand, phenyl isocyanate has been reported to react with carbanions to yield, after hydrolysis, anilides.[14,15,16,18,19]

The investigation of the reaction of pyrryl potassium with phenyl isocyanate was originally undertaken with a view to studying the effect of the reaction medium on the position at which the pyrryl anion would react with the isocyanate. It was observed, however, that the product of the reaction of pyrrylpotassium with phenyl isocyanate was the same whether the reaction was run in a nonpolar solvent, such as toluene, or in a polar solvent, such as tetrahydrofuran.

The structure of 1-pyrrolecarboxanilide (I)

$$\underset{\text{(I)}}{\left[\text{N}-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{NH}-\phi\right.}$$
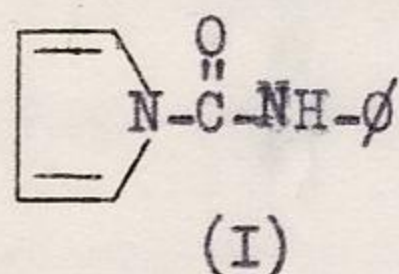
was assigned to the product of this reaction on the basis of the following evidence.

a) The composition found by analysis agreed with that calculated for $C_{11}H_{10}N_2O$.
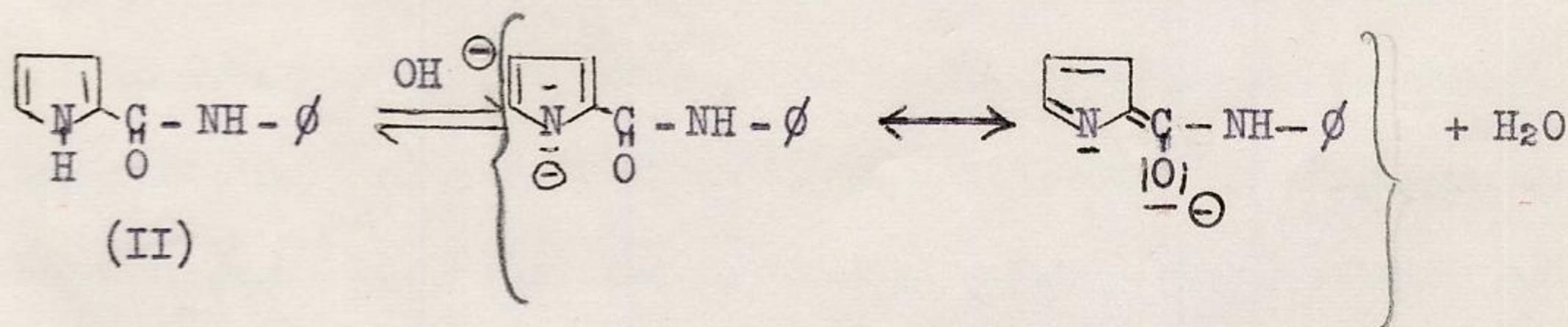
b) Active hydrogen determination showed the presence of one active hydrogen atom in the molecule.

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c) The infrared spectrum of this compound has a strong carbonyl absorption at 1720 cm^{-1} (Appendix I, II), whereas that of the known 2-pyrrolecarboxanilide has a strong carbonyl band at 1660 cm^{-1} (Appendix III, IV). This agrees with Gompper's observation that, in general, carbonyl stretching frequencies are above 1700 cm^{-1} for N-acylated imidazole derivatives, and below 1700 cm^{-1} for C-acyl-imidazole derivatives.[28] On the other hand there is no characteristic absorption in the region 3400 - 3500 cm^{-1}, where the pyrrole N-H stretching would be expected to appear[32], whereas the spectrum of 2-pyrrolecarboxanilide has a sharp band at 3450 cm^{-1}.

d) Hydrolysis gave equimolar quantities of pyrrole and aniline together with carbon dioxide.
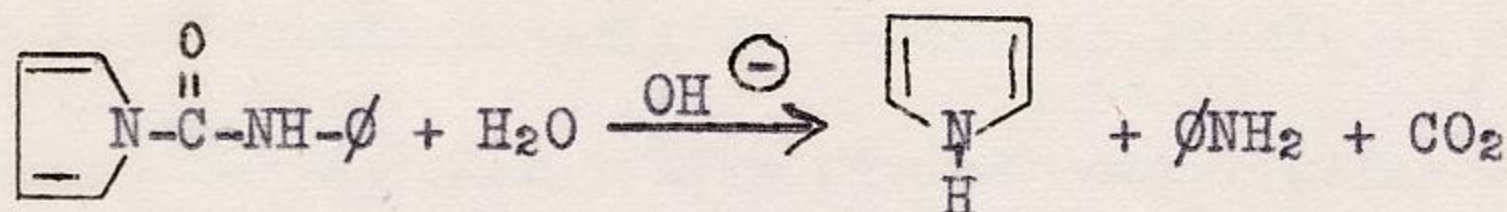
It is interesting to note that, in contrast to 1-pyrrolecarboxanilide, which is hydrolyzed readily, 2-pyrrolecarboxanilide (II) resists hydrolysis, e.g., it was recovered quantitatively after refluxing for 24 hours with alcoholic potassium hydroxide. This is in agreement with the observation that 3,5-dimethyl-2-pyrrolecarboxanilide[24] and 4,5-diphenyl-2-imidazolecarboxanilide[28] are not hydrolyzed even on prolonged treatment with boiling alkali. This resistence to hydro-lysis is probably due to the decreased electrophilic character of the carbonyl carbon atom in the anion formed in the alkaline medium:


(II)

In view of the nucleophilic substitution reactions which 1-imidazolecarboxanilide (III) readily undergoes[25], similar reactions were investigated with 1-pyrrolecarboxanilide. The results with aniline and piperidine as the nucleophiles showed that the pyrrole derivative is much less reactive in this respect.

In the case of 1-imidazolecarboxanilide, which to some extent dissociates in solution to imidazole and phenyl isocyanate, it appears that the reaction proceeds through the intermediate formation of the isocyanate[26]

(III)

With 1-pyrrolecarboxanilide, which is stable in solution, the reaction could be the result of a direct substitution on the carbonyl carbon atom (path 1), or it could proceed through the formation of the isocyanate as an intermediate (path 2)

Path 1:

Path 2:

The lower reactivity of 1-pyrrolecarboxanilide can be explained by the fact that the pyrryl anion is more difficult to displace because it is a stronger base than the imidazolyl anion. The available data

are not enough to allow a decision on the mechanism of the reaction.
In the presence of sodium hydride it is likely that at least part of
the reaction is forced to follow a path involving the intermediate
formation of phenyl isocyanate:
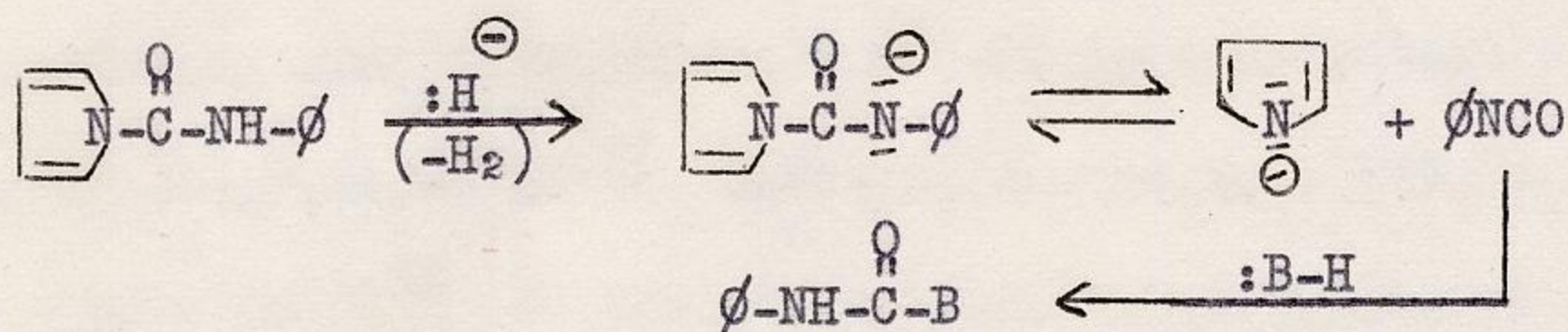
On the other hand, the fact that hydrolysis of 1-pyrrolecarbox-
anilide yields no N,N'-diphenylurea shows that, at least in this case,
there is direct nucleophilic substitution on the carbonyl carbon atom.
Given the stability of 1-pyrrolecarboxanilide in solution, and the
conclusions of Staab's work on imidazole- and triazolecarboxanilides,
it would appear that this mechanism (path 1) is generally the likelier
one.

B. 2-Phenylpyrrolo [1.2-c] hydantoin

The reaction of 2-pyrrolecarboxanilide with phenyl isocyanate, in
the presence of triethylamine, gave a crystalline product to which the
structure of 2-phenylpyrrolo [1.2-c] hydantoin (IV)

(IV)
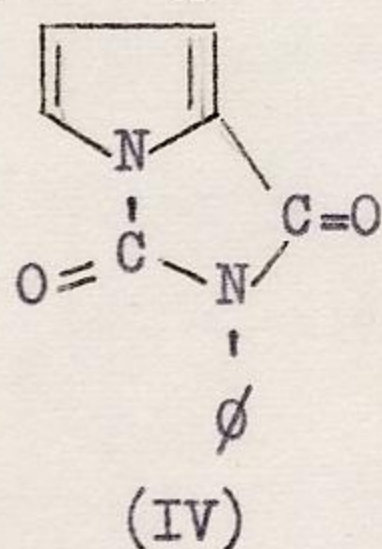
was assigned on the basis of the following evidence

a) The composition found by analysis agreed with that calculated
for $C_{12}H_8N_2O_2$.

b) Determination of molecular weight gave the value of 208 as compared to the calculated value of 212.

c) The infrared spectrum shows absorption at 1800 and 1750 cm^{-1}, (Appendix V, VI). It should be noted that according to Bellamy, compounds containing the group CO-NH-CO in a hydantoin structure show carbonyl absorptions as two bands in the regions 1790 - 1720 cm^{-1} and 1710 - 1670 cm^{-1}.[31] On the other hand, 2,5,6-triphenylimidazolo [1.2-c]-hydantoin (V) shows carbonyl absorption at 1813, 1760, 1709 cm^{-1}.[28]

d) Alkaline hydrolysis yielded 2-pyrrolecarboxanilide.

(IV)

It is noteworthy that the hydantoin V was converted, under similar conditions, to 4,5-diphenylimidazolecarboxylic acid.[28]

(V)

e) Reaction with aniline resulted in the formation of 2-pyrrole-carboxanilide and N,N'-diphenylurea.

(IV)

These results are again very similar to those obtained when the hydan-

toin V was heated with aniline.[28]

(V)
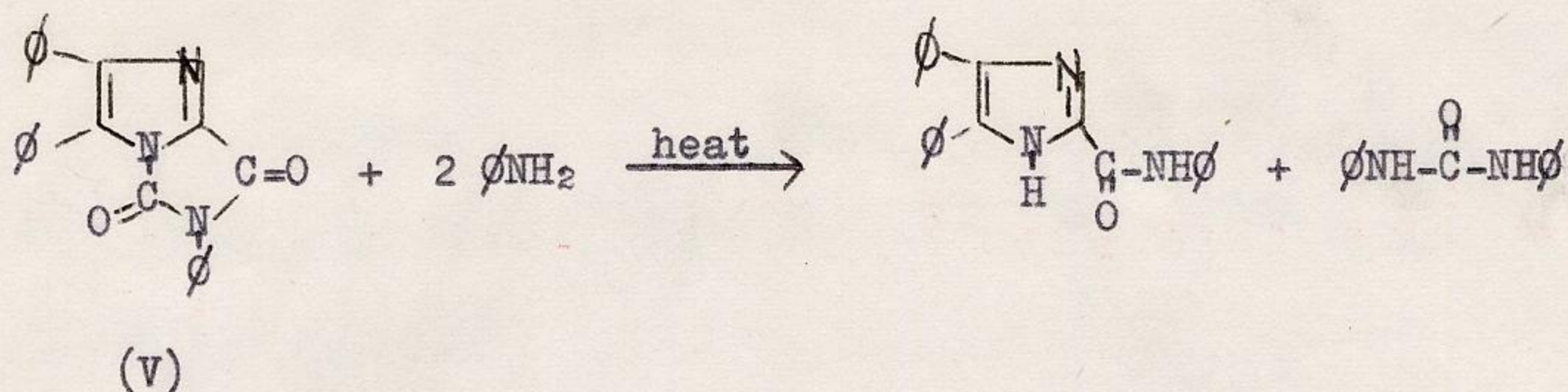
With regard to the mechanism of the reaction, there are three possible paths, of which path 1 is suggested by the clean decomposition of 2-(N-phenylcarbamyl)pyrrolecarboxanilide (VI) at its melting point (139 - 140°C) to 2-pyrrolecarboxanilide and phenyl isocyanate.

Path 1:

(VI)

Path 2:

(VII)

Path 3:

(VII)
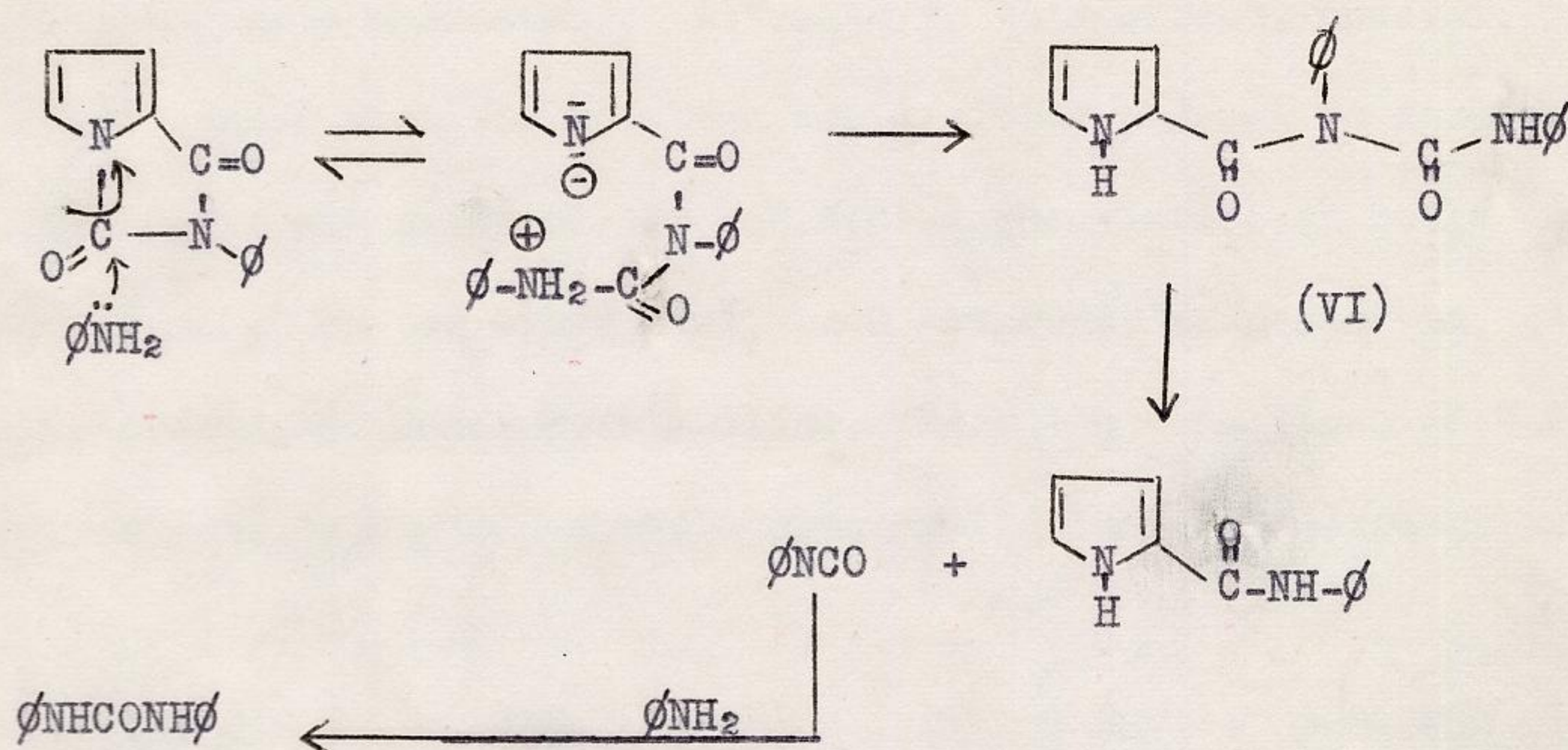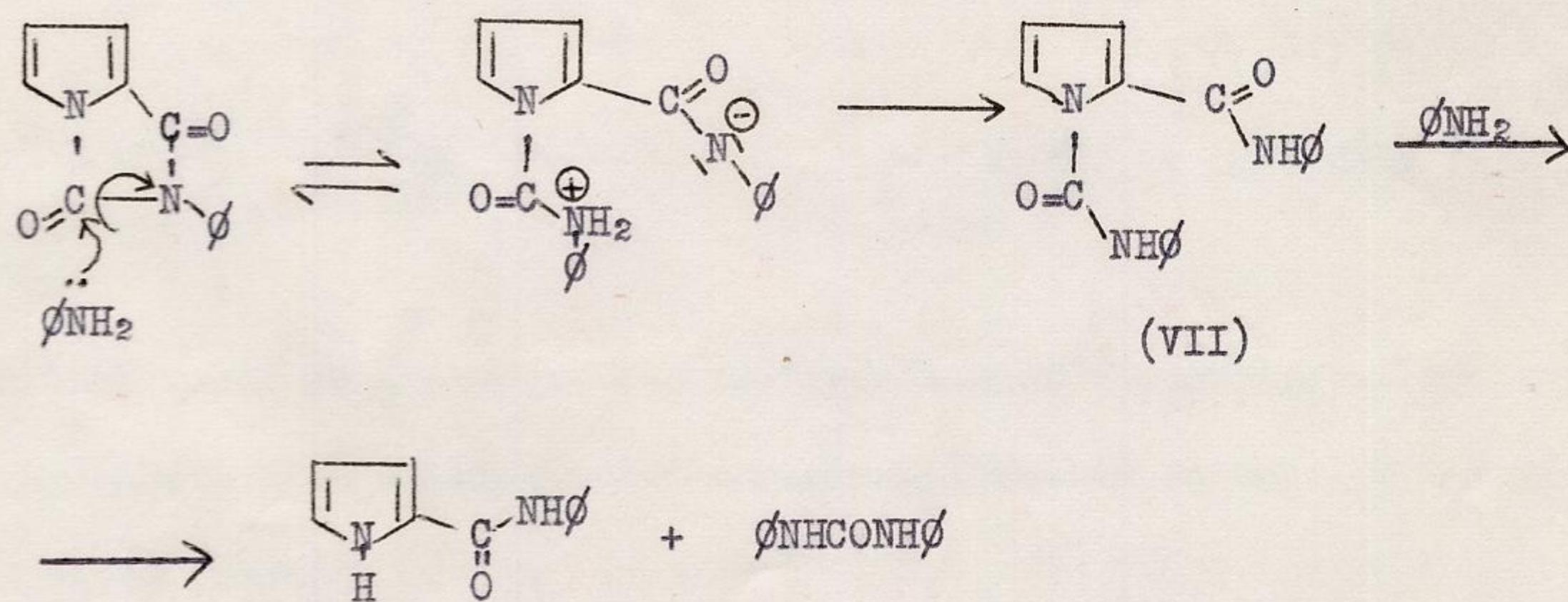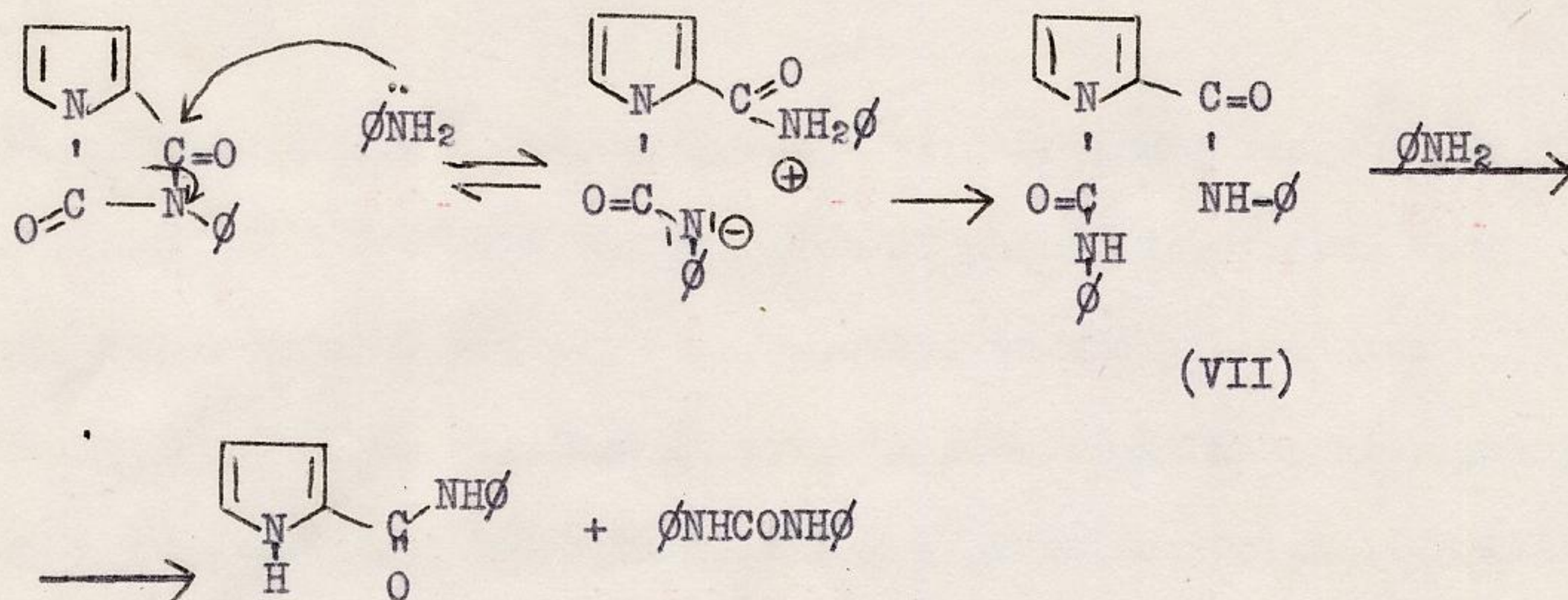
    The isolation of either 2-(N-phenylcarbamyl)pyrrolecarboxanilide (VI) or 1,2-pyrroledicarboxanilide (VII) from the reaction mixture would lend support to these mechanisms. Attempts to this effect, however, failed and it seemed that the reaction would either proceed to completion to form 2-pyrrolecarboxanilide and N,N'-diphenylurea, or would not take place at all. On the other hand, both compounds suspected as possible intermediates react with aniline, under the conditions of the previous reaction, to yield 2-pyrrolecarboxanilide and N,N'-diphenylurea:
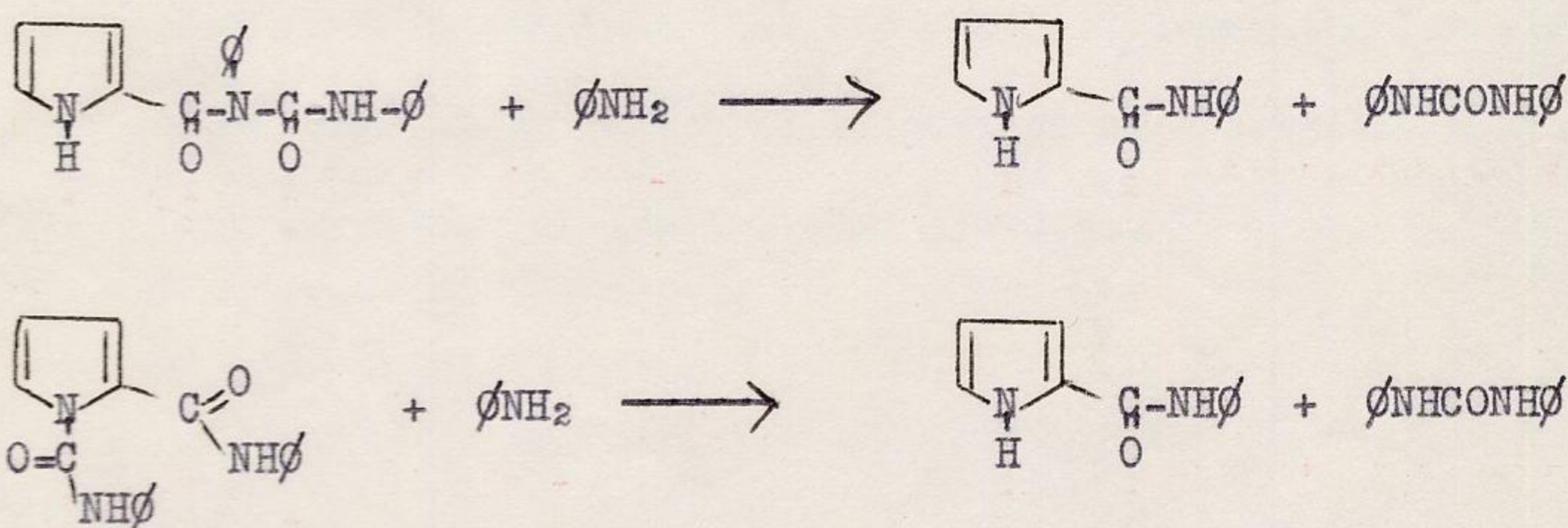
    On the basis of these results the reaction of 2-phenylpyrrolo-[1,2-c]hydantoin with aniline could conceivably follow either, or any of the suggested paths.

C. 2-(N-Phenylcarbamyl)pyrrolecarboxanilide and 1,2-Pyrroledicarbox-
anilide

Phenyl isocyanate is known to react with Grignard reagents to
form anilides[14,15,16,19] but the reaction of phenyl isocyanate with
pyrrylmagnesium halides has not been reported in the literature.

In this work, the reaction of pyrrylmagnesium bromide with phenyl
isocyanate in ether gave 2-(N-phenylcarbamyl)pyrrolecarboxanilide (VI),
as the major product, and 1,2-pyrroledicarboxanilide (VII), as the
minor product. The presence of 2-pyrrolecarboxanilide (II) in the
product was also detected, yet attempts to isolate it in pure form were
unsuccessful.

(VI)   (VII)   (II)

In general, the product of this reaction was a mixture of several
compounds difficult to separate from one another, hence the low yields
in the isolated compounds. Below is an outline of a possible mechanism
leading to the formation of the isolated products.

(II)

(VI)

(VII)

The structure of 2-(N-phenylcarbamyl)pyrrolcarboxanilide (VI) was assigned to the major isolated product of the Grignard reaction on the basis of the following evidence:

a) The composition found by elemental analysis agreed with that calculated for $C_{18}H_{15}N_3O_2$.

b) The infrared spectrum shows a sharp band at 3450 cm^{-1} where the pyrrole N-H stretching frequency would be expected to appear.[32] On the other hand, there is a strong carbonyl absorption at 1720 cm^{-1} (Appendix VII, VIII), in agreement with the observation that N,N-diacylanilines show a carbonyl stretching band in the 6 μ region which can be resolved into more than one band with higher resolution (e.g. 1724 (shoulder), 1709, 1701 (shoulder) cm^{-1}, for N,N-diacetylaniline).[33]

c) The N M R spectrum shows peaks at 11.6 ppm (1 proton), 9.5 (1 proton), and multiplets centered at 7.2 (11 protons), 5.7 (1 proton) and 4.5 (1 proton) (Appendix XI). On addition of trifluoroacetic acid the proton at 9.5 shifted downfield to 11.5 (Appendix XIII). This shift confirms the presence of a hydrogen atom attached to the nitrogen atom of the pyrrole ring.

d) The compound readily decomposes on melting to 2-pyrrolecarbox-anilide and phenyl isocyanate.
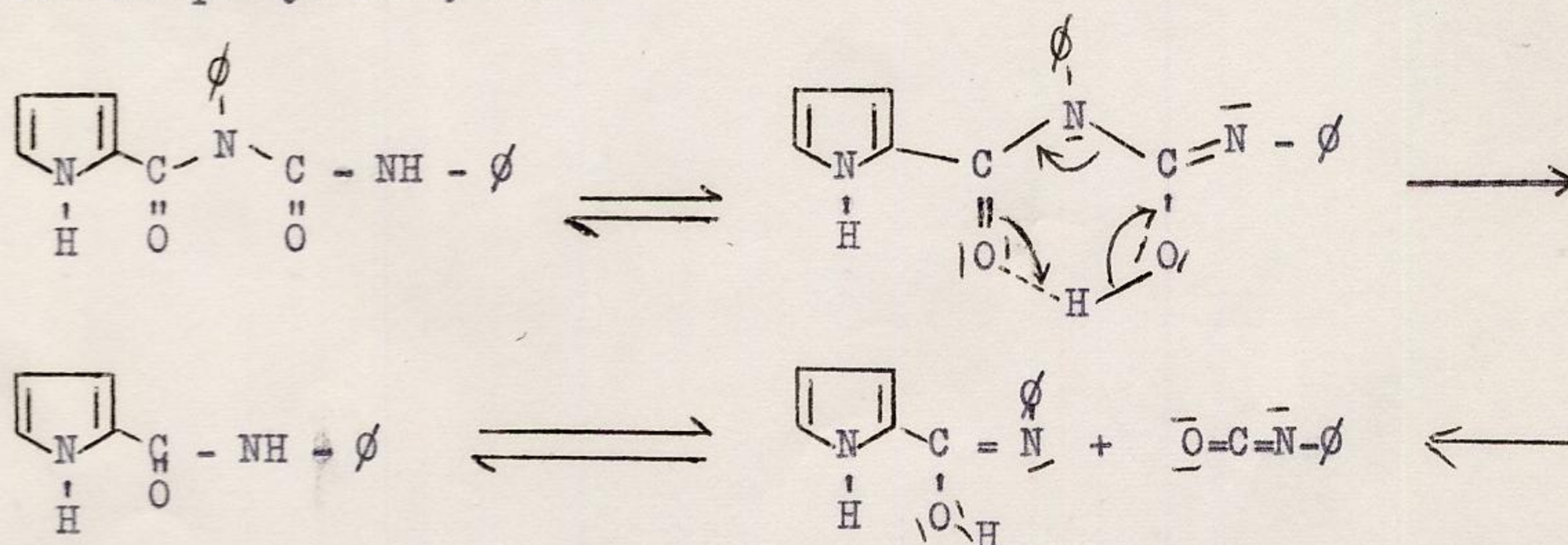
e) Alkaline hydrolysis yielded 2-pyrrolecarboxanilide and
N,N'-diphenylurea. The formation of the latter product can be inter-
preted by accepting intermediate formation of phenyl isocyanate as
shown below:
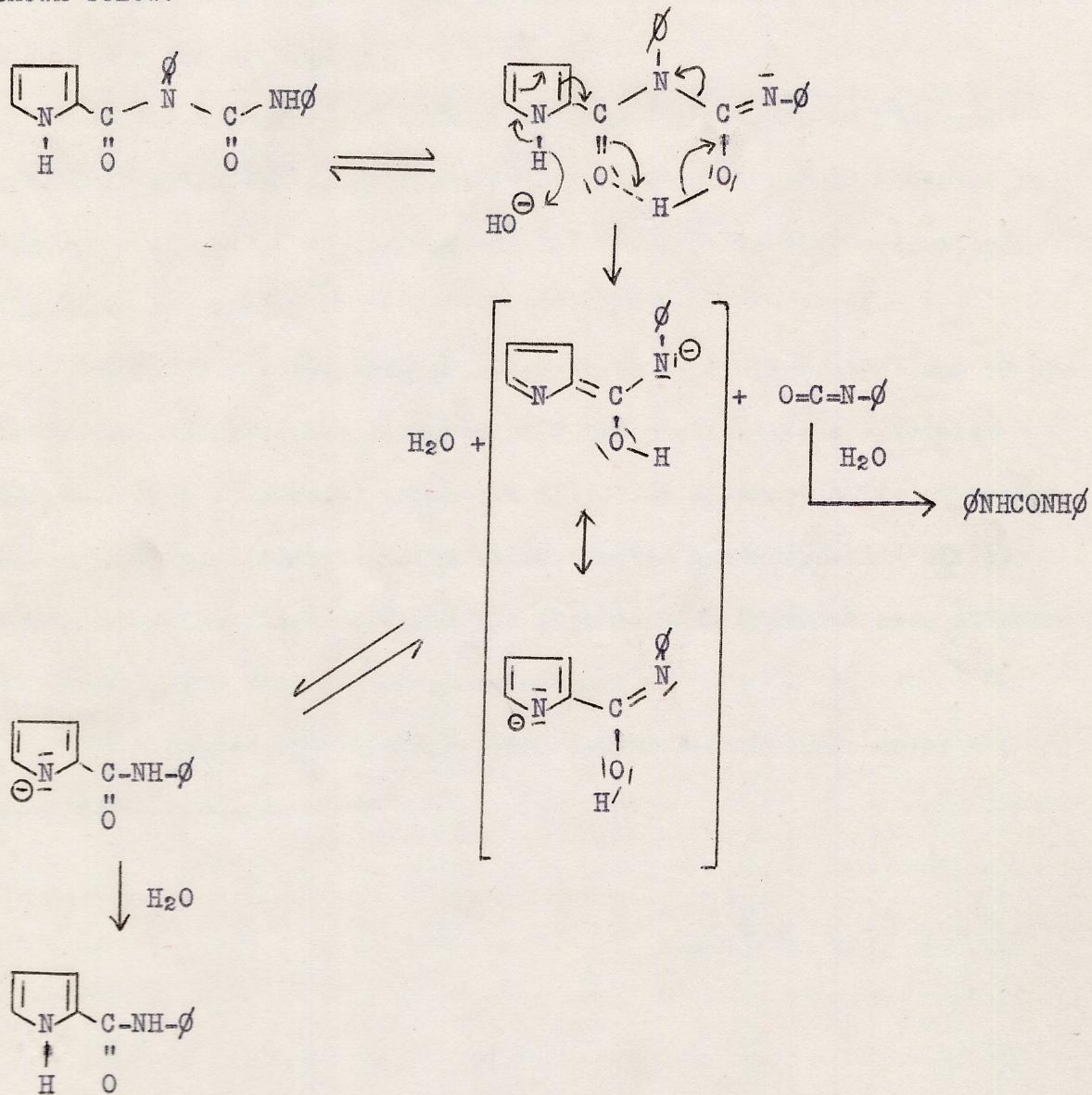
The structure of 1,2-pyrroledicarboxanilide (VII) was assigned
to the compound isolated as a minor product of the Grignard reaction
on the basis of the following evidence:

a) The composition found by elemental analysis agreed with that
calculated for $C_{18}H_{15}N_3O_2$.

b) The infrared spectrum shows absorption bands at 1700 and
1640 cm^{-1} which can be attributed to the carbonyl groups attached to
the nitrogen and to the carbon atom of the pyrrole ring respectively
(Appendix IX, X).

c) The N M R spectrum shows singlets at 11 (1 proton) and 10 ppm
(1 proton), a multiplet centered at 7 (12 protons), and a triplet
centered at 6 (1 proton) (Appendix XII). No apparent shift of protons
was noticed upon addition of trifluoroacetic acid (Appendix XIII).
This last observation confirms the absence of a hydrogen atom attached
to the nitrogen atom of the pyrrole ring.

d) Alkaline hydrolysis yielded 2-pyrrolecarboxanilide as the
only solid product.
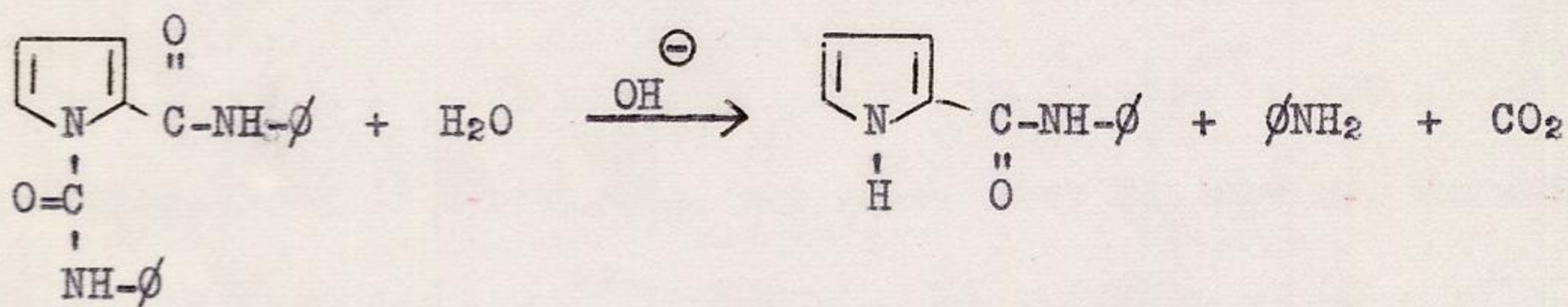
EXPERIMENTAL

1. Reaction of Pyrrylpotassium with Phenyl Isocyanate. Preparation of 1-Pyrrolecarboxanilide
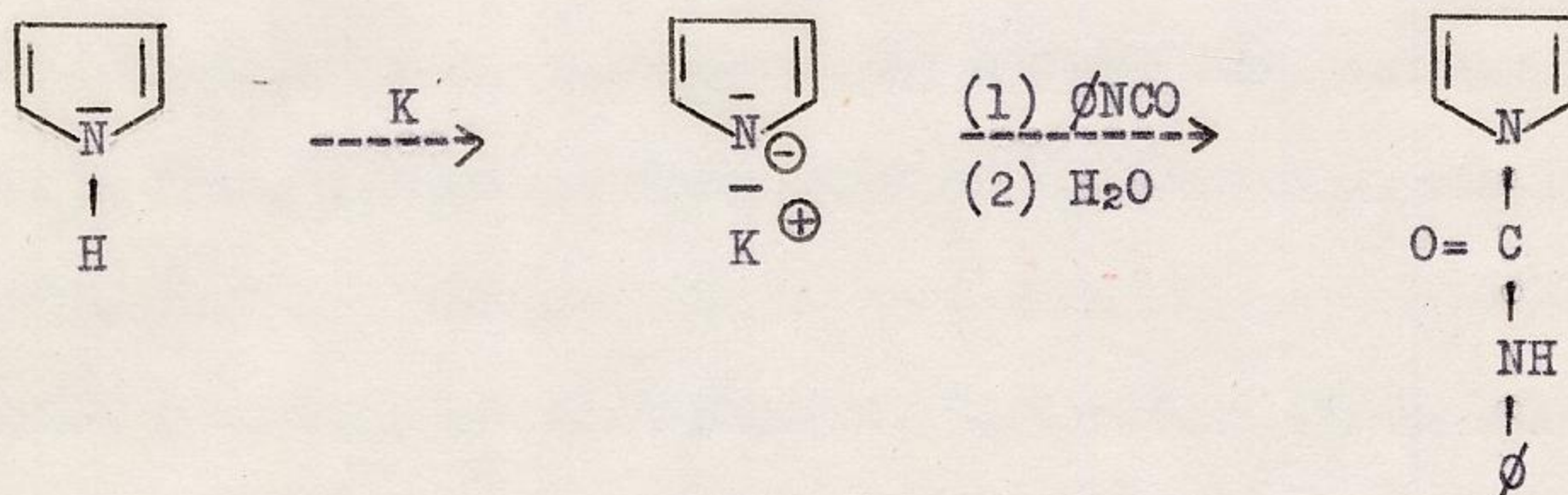
To a solution of 33.5 g (0.50 mole) of pyrrole in 200 ml of dry toluene was added a total of 15.6 g (0.40 mole) of potassium, freshly cut into small pieces under kerosine and rinsed with toluene. The mixture was stirred and heated at gentle reflux until all the potassium had reacted and the blue color of the slurry had disappeared. Heating was then interrupted and 200 ml of toluene was added followed by a solution of 38.1 g (0.32 mole) of phenyl isocyanate in 100 ml of toluene added dropwise over a period of one hour. The mixture was further stirred, without heating, for eight hours, and then at $60 - 70^0$ for another thirteen hours. At the end of this period, the product was cooled to room temperature, filtered by suction, and the solid material was washed three times with 50 ml portions of dry ether. The solid was then mixed thoroughly with water and left to stand for a few hours.

It was then filtered by suction and the solid material dried in the oven at 50 - 60°C. The yield was 56.0 g (94%) of essentially pure 1-pyrrolecarboxanilide as indicated by the infrared spectrum of the product.

The above reaction was run in the same way in tetrahydrofuran as solvent instead of toluene. The yield in 1-pyrrolecarboxanilide was 56.6 g (95.1%). After recrystallization from ethanol-water (75:25) white crystals melting at 157 - 158°C were obtained. On further recrystallization from ethyl alcohol the m.p. was 157.5 - 158.5°C.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04;

active hydrogen, 0.541.

Found: C, 70.74; H, 5.47; N, 14.98;

active hydrogen 0.561.

2. Hydrolysis of 1-Pyrrolcarboxanilide

A mixture of 14.0 g (0.075 mole) of 1-pyrrolecarboxanilide, 8.4 g of potassium hydroxide and 50 ml of ethyl alcohol was refluxed for four hours. At the end of this period, a sample of the alcoholic solution was analyzed by vapor phase chromatography and was found to contain roughly equimolar quantities of pyrrole and aniline. On evaporation at the aspirator, the mixture yielded a crystalline solid which reacted with hydrochloric acid with evolution of carbon dioxide.

3. Reaction of 1-Pyrrolecarboxanilide with Aniline in the Presence of Sodium Hydride
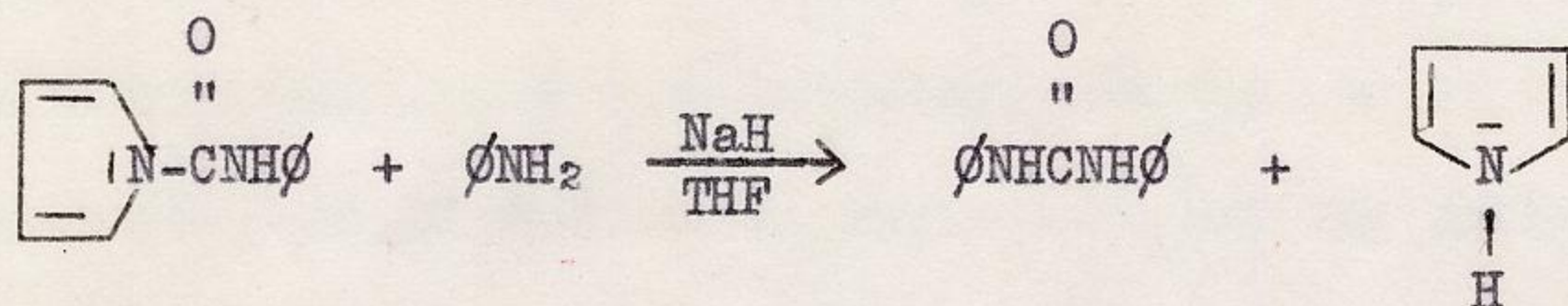
A mixture of 5.6 g (0.03 mole) of 1-pyrrolecarboxanilide, 5.6 g (0.06 mole) of aniline, and 0.72 g (0.03 mole) of sodium hydride in 50 ml of dry tetrahydrofuran was refluxed for six hours with stirring. At the end of this period, the solvent was evaporated at the aspirator, the residue was mixed thoroughly with water, and the mixture was filtered by suction. After drying, the solid was mixed with some chloroform, and the mixture was filtered to give 1.6 g (47%) of N,N'-diphenylurea. After recrystallization from ethanol white crystals melting at 239 - 240° C were obtained.

On evaporation of the chloroform solution to dryness 2.6 g of the starting material was recovered.

The above reaction was first attempted by refluxing a mixture of 5.6 g (0.03 mole) of 1-pyrrolecarboxanilide and 11.2 g (0.12 mole) of aniline in 50 ml of dry tetrahydrofuran for a period of twenty four hours. This time the yield in N,N'-diphenylurea was 0.28 g (26%), and 4.67 g of the starting material was recovered.

4. Reaction of 1-Pyrrolecarboxanilide with Piperidine in the Presence of Sodium Hydride
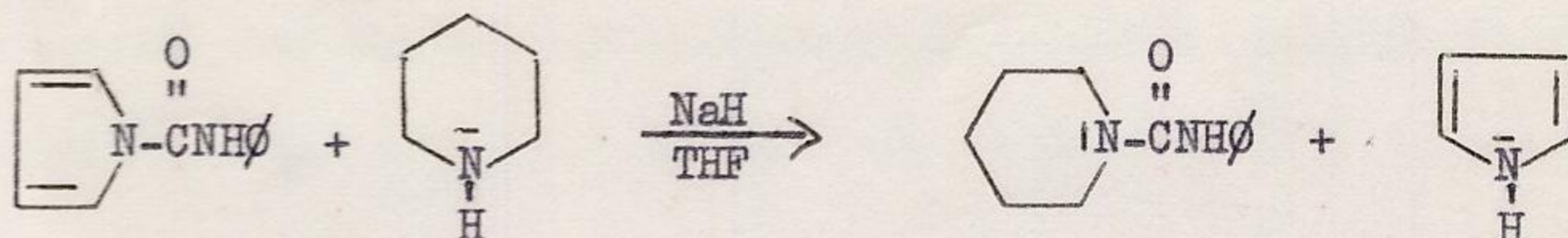
A mixture of 5.6g(0.03 mole) of 1-pyrrolecarboxanilide, 5.2 g
(0.06 mole) of piperidine (distilled over LiAlH$_4$), and 0.72 g (0.03
mole) of sodium hydride in 50 ml of dry tetrahydrofuran was refluxed
for twenty four hours with stirring. At the end of this period, the
solvent was evaporated at the aspirator, and the solid residue was
mixed with some water and filtered by suction. After drying, the
solid was identified as 1-piperidinecarboxanilide by comparison of
its infrared spectrum with that of an independently prepared sample
of this substance. The yield was 4.64 g (75.4%). After recrystalli-
zation from ethyl alcohol white crystal melting at 172 - 173^{0}C were
obtained. (Reported m.p. 168^0, 170 - 171^0, 171 - 172^0).[30]

The above reaction was also carried out in the absence of
sodium hydride. A mixture of 5.6 g (0.03 mole) of 1-pyrrolecarboxa-
nilide and 5.2 g (0.06 mole) of piperidine in 50 ml of dry tetra-
hydrofuran was refluxed for two days. The yield in 1-piperidine-
carboxanilide was only 8%.

5. Reaction of Pyrrole with Phenyl Isocyanate. Preparation of
2-Pyrrolecarboxanilide
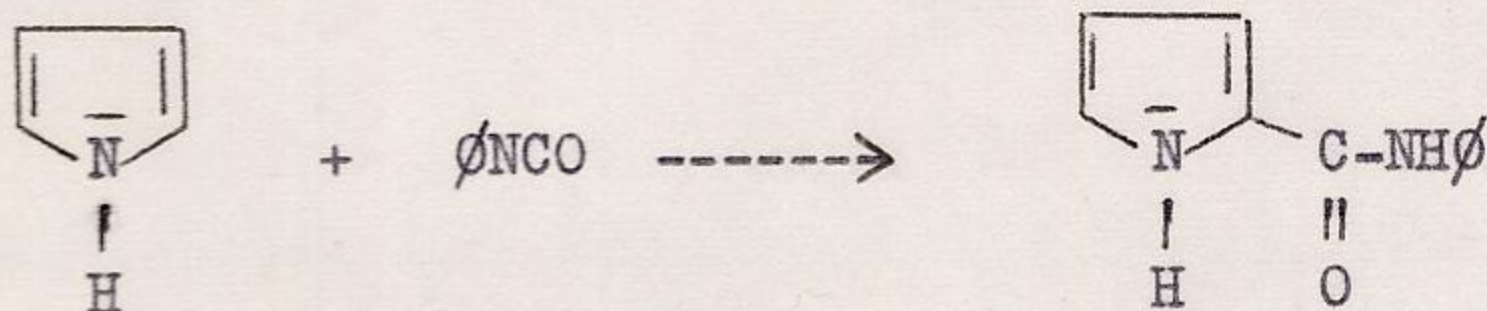
A mixture of 16.75 g (0.25 mole) of pyrrole and 29.75 g (0.25
mole) of phenyl isocyanate was placed in an Erlenmeyer flask attached
to a condenser the top of which was closed by a calcium chloride tube.
The mixture was heated in an oil bath at 80 - 90^0 for four days. By

the end of this period, the mixture had solidified completely to one compact cake, and it was necessary to break the flask to get the product. The solid cake was broken up and ground into a powder which was washed with some petroleum ether on a Buchner funnel. After recrystallization from benzene - methanol (85:15), including treatment with decolorizing charcoal, 23.9 g (51.2%) of 2-pyrrole-carboxanilide, m.p. 157 - 158°C., was obtained. On further recrystallization the m.p. was 158 - 158.5°C. (Literature, 153°C.).[24]

The same compound was also prepared by mixing equimolar quantities of pyrrole and phenyl isocyanate in an Erlenmeyer flask, closing it with a rubber stopper and leaving it inside a calcium chloride desiccator for several weeks, until most of the material had solidified.

6. Attempted Hydrolysis of 2-Pyrrolecarboxanilide

A mixture of 1.3 g (0.007 mole) of 2-pyrrolecarboxanilide, 1.4 g of potassium hydroxide and 40 ml of ethyl alcohol was refluxed for twenty four hours. At the end of this period, the ethyl alcohol was evaporated at the aspirator. On mixing the oily residue with water 1.3 g of a solid was obtained. The infrared spectrum of this compound was identical with that of the starting material, indicating that no hydrolysis took place.

7. Reaction of 2-Pyrrolecarboxanilide with Phenyl Isocyanate in the Presence of Triethylamine. Preparation of 2-Phenylpyrrolo [1.2-c]-hydantoin
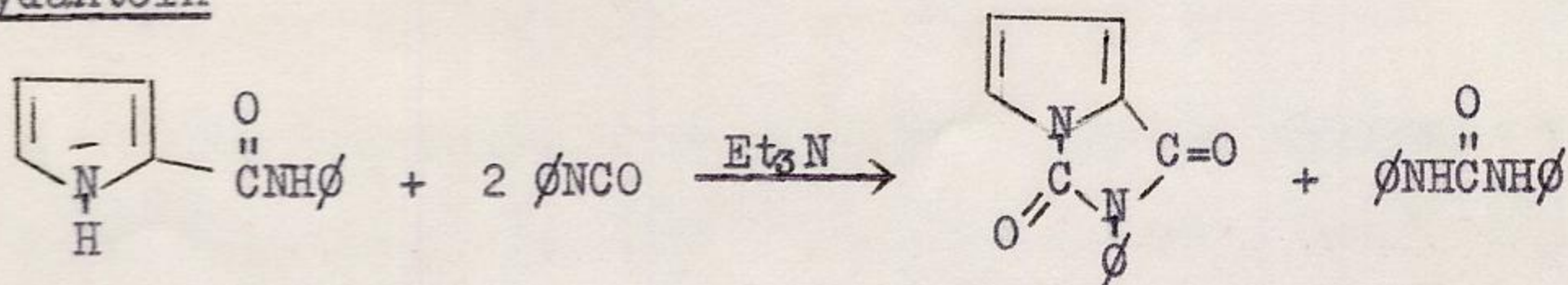
To 5.6 g (0.03 mole) of 2-pyrrolecarboxanilide placed in a 200 ml round-bottomed flask was added 1.53 g (0.015 mole) of triethylamine (distilled over lithium aluminum hydride just before use), and 7.14 g (0.06 mole) of phenyl isocyanate. The flask was fitted with a condenser the top of which was closed with a calcium chloride tube, and the mixture was heated in an oil bath at $60 - 70^0$ for twenty two hours. At the end of this period, the mixture had solidified and was free from the isocyanate smell and effect on the eyes. The solid product was broken up and ground into a powder which was shaken thoroughly with 800 ml of chloroform. The resulting mixture was filtered by suction, and the solid insoluble in chloroform was found to have an infrared spectrum identical with that of N,N'-diphenylurea. This material weighed 6.1 g corresponding to 95% of the theoretical yield.

The chloroform solution was evaporated at the aspirator. The solid residue was 5.9 g (94%) of 2-phenylpyrrolo [1,2-c] hydantoin as shown by its infrared spectrum. It was recrystallized from 95% ethanol to give white long needles melting at $232 - 232.5^0$C. After further purification by sublimation under low pressure it was sent for analysis:

Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20.

Found: C, 68.09; H, 3.89; N, 13.38.

8. Reaction of 2-Phenylpyrrolo [1,2-c] hydantoin with Aniline
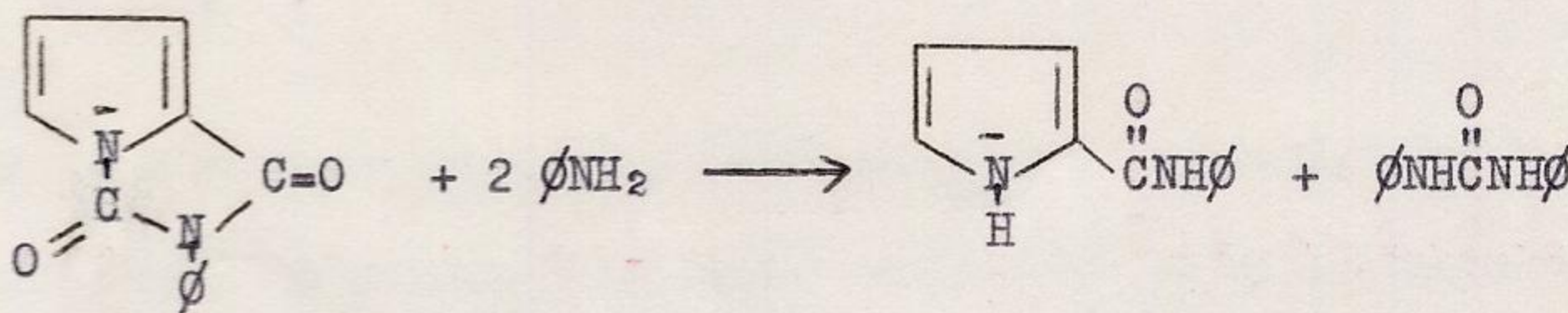
A mixture of 2.12 g (0.01 mole) of 2-phenylpyrrolo [1.2-c]-
hydantoin and 25 g of aniline was placed in a 200 ml round-bottomed
flask fitted with a condenser to the top of which was attached a
calcium chloride tube. The mixture was heated in an oil bath at 130 -
144°C for fifteen hours. At the end of this period, the product was
cooled in an ice-water mixture and the crystalline solid which separat-
ed out was filtered by suction. The infrared spectrum of this
compound was identical with that of N,N'-diphenylurea. The crude
product weighed 1.3 g (61%) of the theoretical yield.)

To the aniline filtrate was added about 50 ml of ether and the
resulting solution was washed with dilute hydrochloric acid. After
evaporation of the ether a solid residue was obtained which was
identified as the 2-pyrrolecarboxanilide on the basis of its infrared
spectrum. The yield was 1.4 g of crude product (74%).

When the same reaction was attempted at 110 - 120°C. for fifteen
hours, the starting material was recovered almost completely.

Finally this reaction was carried out at 120 - 130°C for a period
of fourty hours. The yield was 1.7 g of crude N,N'-diphenylurea (80%)
and 1.6 g of crude 2-pyrrolecarboxanilide (85%).

9. Hydrolysis of 2-Phenylpyrrolo [1.2-c] hydantoin
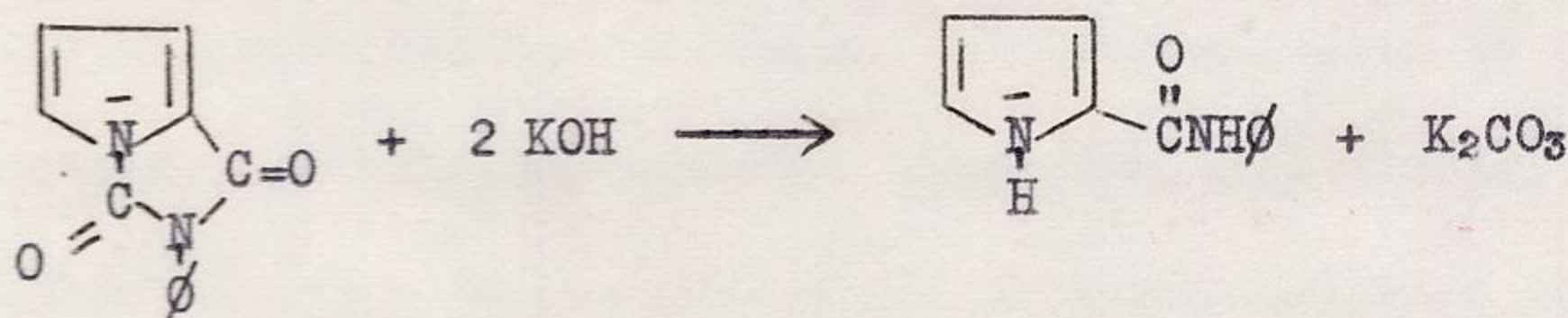
A mixture of 2.12 g (0.01 mole) of 2-phenylpyrrolo [1.2-c] hydantoin
and 5 g of potassium hydroxide pellets in 50 ml of water was refluxed for

four hours. At the end of this period, the solution was cooled and then filtered by suction. A solid was obtained which was identified as 2-pyrrolecarboxanilide on the basis of its infrared spectrum. The crude product weighed 0.90 g (49% yield).

10. <u>Reaction of the Potassium Salt of 2-Pyrrolecarboxanilide with</u>

   <u>Phenyl Isocyanate in Tetrahydrofuran</u>
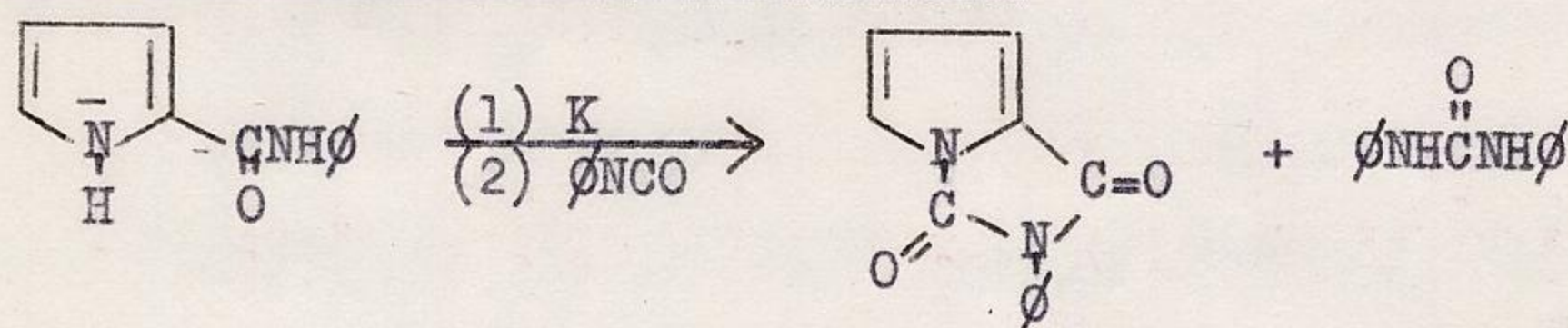
To 3.72 g (0.02 mole) of 2-pyrrolecarboxanilide in 45 ml of dry tetrahydrofuran was added 0.78 g (0.02 mole) of potassium, freshly cut into small pieces under kerosine and rinsed with tetrahydrofuran. The mixture was stirred at room temperature until all the potassium had reacted. A solution of 4.76 g (0.04 mole) of phenyl isocyanate in 15 ml dry tetrahydrofuran was then added dropwise over a period of 40 minutes. The mixture was stirred at 40 - 50°C for fifteen hours. At the end of this period, the solvent was removed by distillation at the aspirator. The residue was mixed with a small amount of benzene and then it was filtered by suction. The insoluble material was mixed thoroughly with ice-cold water and the resulting mixture was filtered by suction. The solid material was identified as N,N'-diphenylurea by its infrared spectrum. On recrystallization from 95% ethyl alcohol it gave crystals melting at 243 - 245°C. The yield in recrystallized product was 2.2 g (52%).

The benzene solution was evaporated almost to dryness to give a

crystalline yellow solid which was 2-phenylpyrrolo $[1.2-c]$ hydantoin as indicated by its infrared spectrum. After recrystallization from 95% ethyl alcohol the product melted at 230 - 231°C. The yield was 0.88 g (20.7% of the theoretical).

11. Reaction of Pyrrylmagnesium Bromide with Phenyl Isocyanate

$$C_2H_5Br + Mg \xrightarrow{ether} C_2H_5MgBr$$
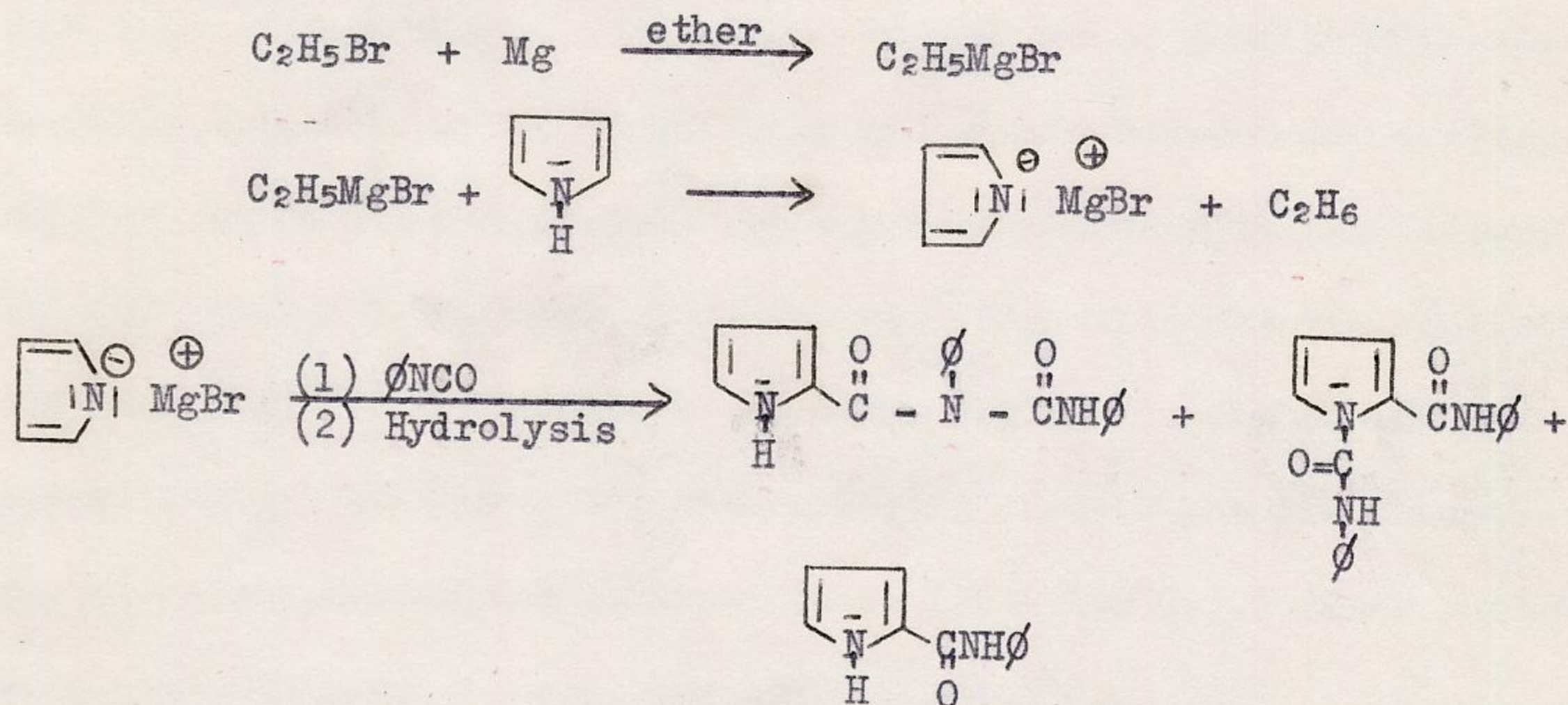
The apparatus used for this reaction consisted of a 1000 ml three-necked flask fitted with a water cooled bulb condenser, a sleeve type stirrer and a pressure equalizing dropping funnel. The reaction was carried in an atmosphere of nitrogen which was continually passed through the system and whose rate of flow was controlled by means of a small, mercury containing, U-tube at the other end of which was fitted a small calcium chloride tube.

A solution of 38.1 g (0.35 mole) of ethyl bromide in 80 ml of dry ether was added dropwise, with stirring, over a period of one hour, to 7.3 g (0.30 mole) of magnesium turnings covered with 80 ml of dry ether. The mixture was then refluxed for half an hour, by which time essentially all of the magnesium had reacted. A solution of 20.1 g

(0.30 mole) of pyrrole in 80 ml of dry ether was then added dropwise over a period of one hour, and the mixture was refluxed for a further half an hour. It was then cooled to room temperature and diluted with 80 ml of dry ether. This was followed by the addition of 29.8 g (0.25 mole) of phenyl isocyanate dissolved in 80 ml of dry ether dropwise over a period of one hour. The mixture was stirred at room temperature for about sixteen hours, after which a solution of 32.1 g (0.6 mole) of ammonium chloride in 300 ml of water was slowly added under cooling. The mixture was stirred vigorously for one hour and then it was filtered by suction through a sintered glass funnel. The solid material collected was washed with a little ether and after drying it weighed 16.2 g. On recrystallization from ethyl alcohol 9.7 g of 2-(N-phenylcarbamyl)-pyrrolecarboxanilide was obtained (m.p. 139 - 140°C.). After further recrystallizations the m.p. was 139.5 - 141.5°C.

Anal. Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.79; H, 4.95; N, 13.77

Found: C, 70.73; H, 4.94; N, 13.89

Evaporation of the mother liquor gave rise to a solid, obviously a mixture, which could not be separated into its components efficiently. From the infrared spectra of the various solid fractions isolated the presence of 2-pyrrolecarboxanilide was ascertained.

The filtrate (obtained after filtering the original reaction mixture) was placed in a separatory funnel, the organic layer was separated, and the water layer was extracted twice with ether. After the ether extracts had been combined with the original organic layer, the ether was removed at the aspirator and a dark oily residue was obtained. Crystallization was induced by the use of pentane, and after filtration and drying 19.5 g

of an impure solid was obtained. From this, after repeated recrystal-
lizations from ethyl alcohol, a further 3.2 g of 2-(N-phenylcarbamyl)-
pyrrolecarboxanilide was obtained (total yield 12.9 g, 16.9%), as well
as a small amount of 1,2-pyrroledicarboxanilide (0.5, 2.2, and 2.8 g,
in three different runs, 3.7% highest yield); m.p. 174 - 176°C.

Anal. Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.79; H, 4.95; N, 13.77

Found: C, 71.01; H, 4.98; N, 13.86

The rest of the material obtained by evaporation of the ether
solution was a mixture of several compounds, among which 2-pyrrole-
carboxanilide was again detected.

12. Reaction of 2-(N-Phenylcarbamyl)pyrrolecarboxanilide with Sodium Hydride
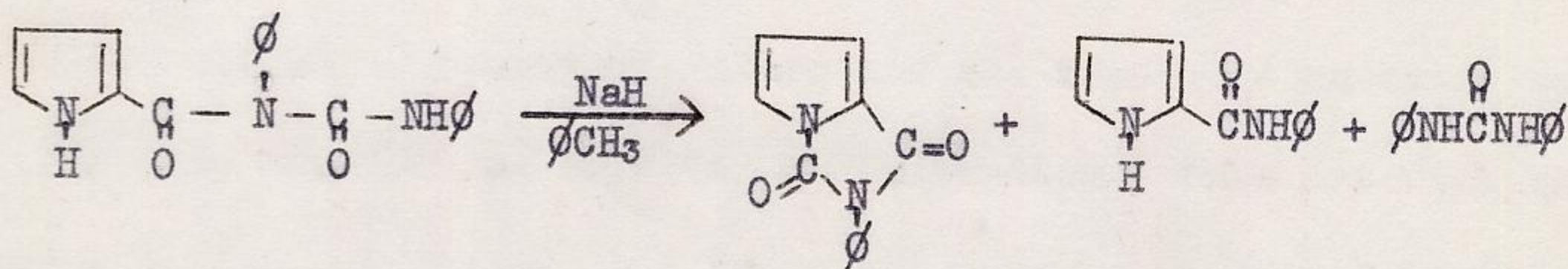
To a solution of 6.1 g (0.02 mole) of 2-(N-phenylcarbamyl)pyrrole-
carboxanilide in 70 ml of dry toluene heated at 70 - 80° was added 0.48 g
(0.02 mole) of sodium hydride. A vigorous reaction took place with
evolution of hydrogen. The mixture was then stirred at 70 - 80° for 20
minutes. At the end of this period, the reaction mixture was cooled to
room temperature, and the insoluble material was separated from the
toluene solution by filtration.

This material was treated with water and the mixture was filtered
by suction. The solid obtained was dried and was further treated with
chloroform and filtered. The material insoluble in chloroform was 1.7 g

(78%) of N,N'-diphenylurea. The chloroform solution gave, on evaporation to dryness, 1.2 g (71%) of 2-pyrrolecarboxanilide.

When the toluene solution was evaporated practically to dryness 1.0 g (47%) of 2-phenylpyrrole [1.2-c] hydantoin was isolated.

13. Reaction of 1,2-Pyrroledicarboxanilide with Sodium Hydride
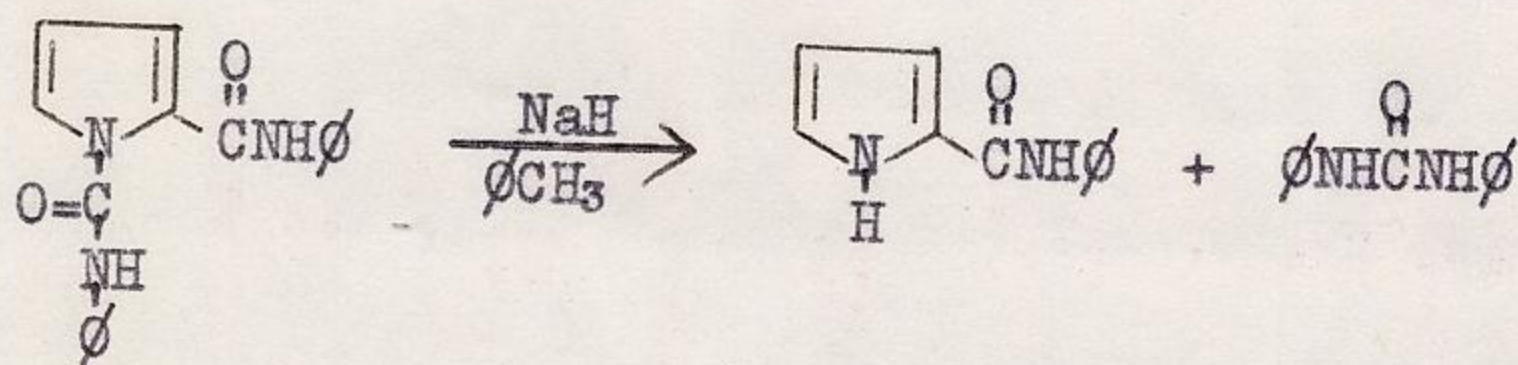
To a solution of 2.8 g (0.009 mole) of 1,2-pyrroledicarboxanilide in 80 ml of dry toluene heated to 100°C was added 0.24 g (0.01 mole) of sodium hydride whereupon an immediate reaction took place with evolution of hydrogen. The mixture was stirred at 70 - 80° for thirty minutes. then it was cooled to room temperature and the insoluble material was separated from the toluene solution by filtration. This material was treated with ice-cold water, and the solid material obtained in this way was separated by filtration, and it was then treated with some chloroform. The part which remained insoluble in chloroform was 0.8 g (41%) of N,N'-diphenylurea.

The chloroform solution gave, on evaporation, to dryness 0.52 g of 2-pyrrolecarboxanilide.

When the toluene solution was evaporated to dryness, a further 0.25 g of 2-pyrrolecarboxanilide was obtained (total yield: 0.77 g, 45%).

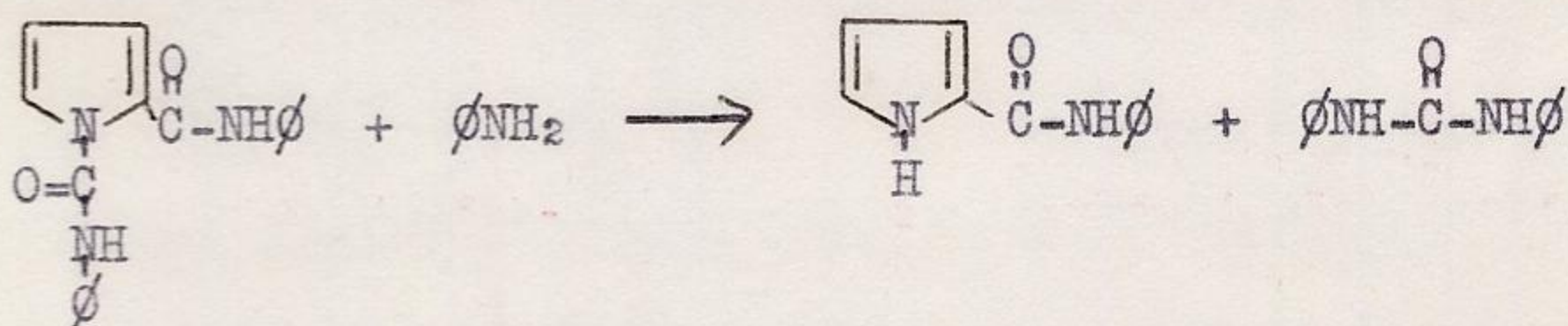## 14. Hydrolysis of 2-(N-Phenylcarbamyl)pyrrolecarboxanilide
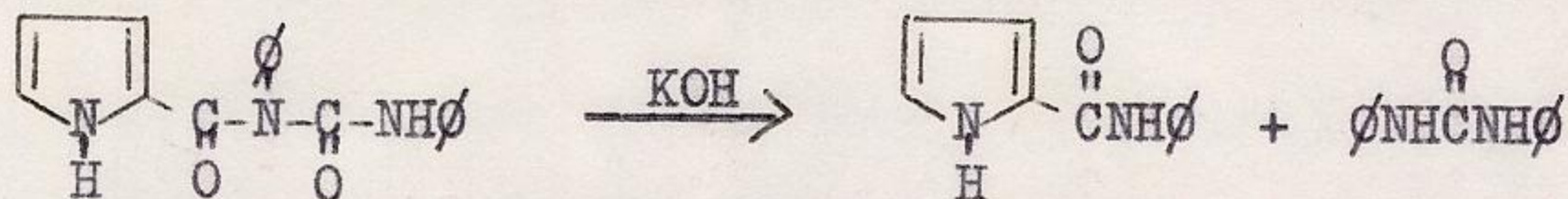
A mixture of 3.05 g (0.01 mole) of 2-(N-phenylcarbamyl)pyrrole-
carboxanilide amd 7.0 g of potassium hydroxide in 50 ml of water was
refluxed for two hours. At the end of this period, the mixture was
cooled, and the solid material was removed by filtration. On washing
with ether, part of this solid dissolved. The ether insoluble solid had
an infrared spectrum identical with that of N,N'-diphenylurea (1.1 g, 52%).

A crystalline white solid was obtained after evaporation of the
ether solution, the infrared spectrum of which was identical with that
of 2-pyrrolcarboxanilide (0.70 g, 38%).

15. Hydrolysis of 1,2-Pyrroldicarboxanilide
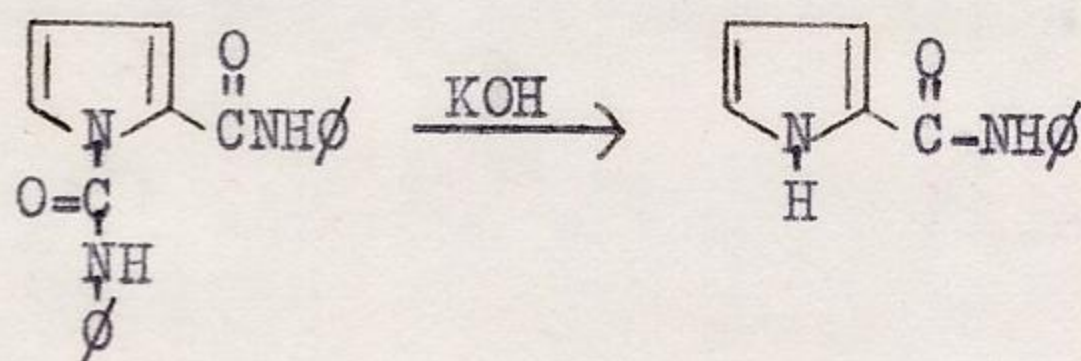
A mixture of 0.92 g (0.003 mole) of 1,2-pyrroledicarboxanilide
and 1.0 g of potassium hydroxide in 30 ml of water was refluxed for two
hours. At the end of this period the mixture was cooled to room
temperature. A crystalline solid formed which was filtered by suction.
Its infrared spectrum was identical with that of 2-pyrrolecarboxanilide
(0.54 g., 93%).

16. Reaction of 2-(N-Phenylcarbamyl)pyrrolecarboxanilide with aniline

$$\text{(pyrrole)}\overset{H}{N}\text{-}\underset{O}{\overset{\emptyset}{C}}\text{-}N\text{-}\underset{O}{C}\text{-}NH\emptyset + \emptyset NH_2 \longrightarrow \text{(pyrrole)}\overset{H}{N}\text{-}\underset{O}{C}\text{-}NH\emptyset + \emptyset NH\text{-}\underset{O}{C}\text{-}NH\emptyset$$
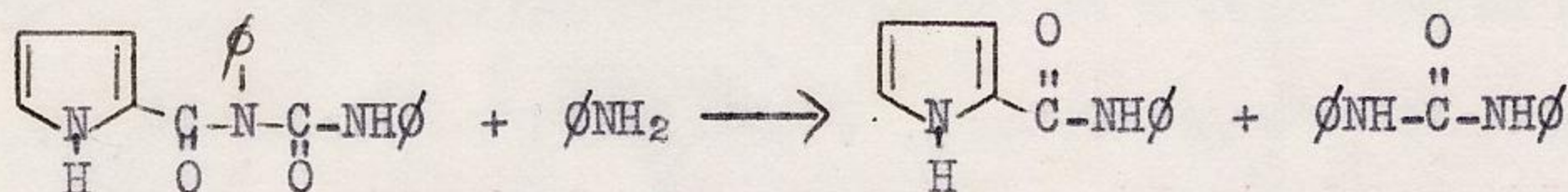
A mixture of 3.05 (0.01 mole) of 2-(N-phenylcarbamyl)pyrrole-
carboxanilide and 20 g of aniline was placed in a 200 ml round-bottomed
flask fitted with a condenser to the top of which was attached a calcium
chloride tube. The mixture was heated in an oil bath at 126°C for four
hours. At the end of this period, the mixture was cooled in an ice-
water bath and the white crystalline solid which precipitated was removed
by suction filtration. The infrared spectrum of this compound was identic-
al with that of N,N'-diphenylurea (1.8 g, 85%).

To the aniline filtrate was added 80 ml of ether and the resulting
solution was washed with dilute hydrochloric acid. After evaporation of
the ether a solid residue was obtained which was identified as the
2-pyrrolecarboxanilide on the basis of its infrared spectrum (1.5 g, 81.7%).

17. Reaction of 1,2-Pyrroledicarboxanilide with Aniline

$$\text{(pyrrole)} \underset{O=C}{N}\text{-}\underset{O}{C}\text{-}NH\emptyset + \emptyset NH_2 \longrightarrow \text{(pyrrole)}\overset{H}{N}\text{-}\underset{O}{C}\text{-}NH\emptyset + \emptyset NH\text{-}\underset{O}{C}\text{-}NH\emptyset$$

Exactly the same procedure as in (16) was employed, except that
2.35 g (0.0077 mole) of 1,2-pyrroledicarboxanilide was used, out of which
1.08 g was recovered unchanged. From the reaction mixture 0.42 g (55%)
of 2-pyrrolecarboxanilide, and 0.85 g (84%) of N,N'-diphenylurea were
isolated.

18. <u>Thermal Decomposition of 2-(N-Phenylcarbamyl)pyrrolcarboxanilide</u>

In a small distilling flask connected to a water cooled condenser was placed 4 g of 2-(N-phenylcarbamyl)pyrrolecarboxanilide. The receiver was connected to an aspirator and the flask was heated to about 140° in an oil bath. When the solid melted, a liquid distilled and was collected in the receiver, while the material in the flask resolidified. The distillate had the typical smell and lachrymatory effect of phenyl isocyanate, and its infrared spectrum was identical with that of the latter compound. Its weight was 1.25 g (theoretical for ∅NCO, 1.56 g). The solid material was powdered under light petroleum ether, and then it was filtered and dried. Its weight was 2.4 g (theoretical for 2-pyrrolecarboxanilide 2.42 g). Upon re-crystallization from benzene-methanol (85:15), 1.45 g of white crystals was obtained, the infrared spectrum of which was identical with that of 2-pyrrolecarboxanilide.

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32. C.N.R. Rao, "Chemical Application of Infrared Spectroscopy" Academic Press, New York, N.Y., 1963, p. 318.

33. R.A. Abramovitch, J. Chem. Soc., 1957, 1413.

FREQUENCY (CM⁻¹)

TRANSMITTANCE (%)

MICRONS

Appendix I

TRANSMITTANCE (%)

FREQUENCY (CM⁻¹)

MICRONS

Appendix III
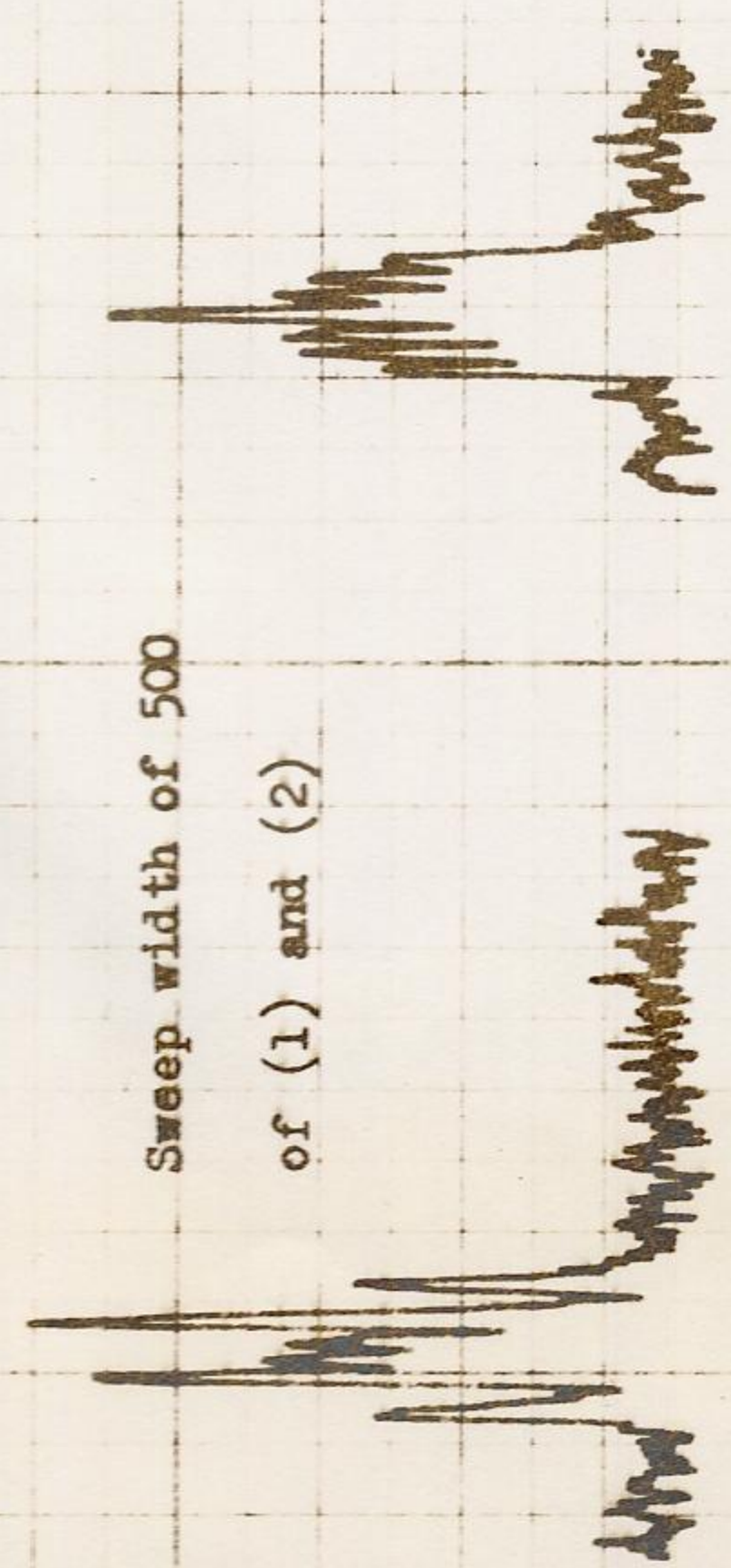
Appendix IV

Appendix VI

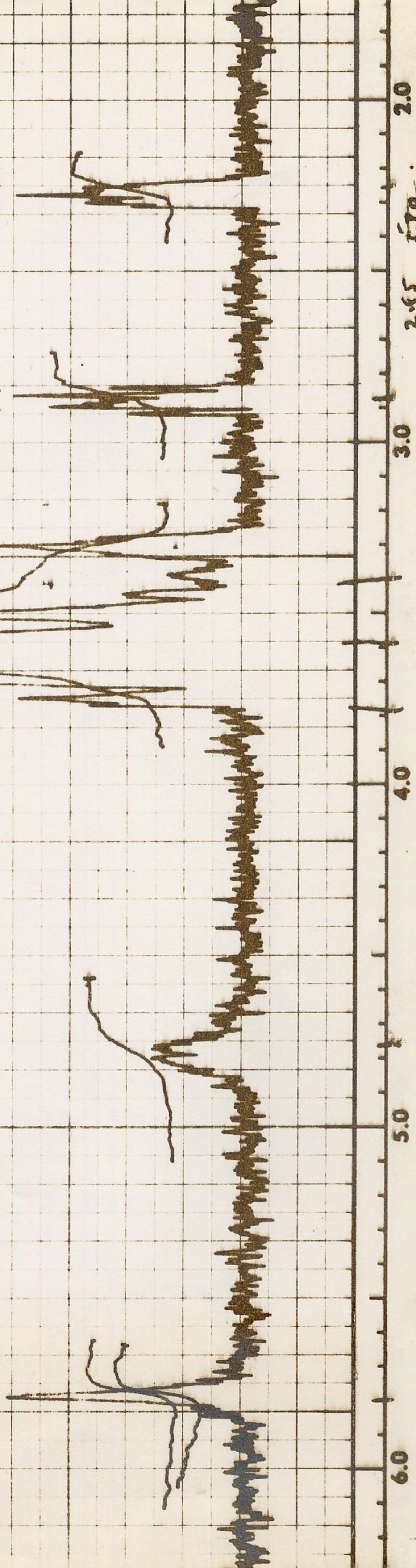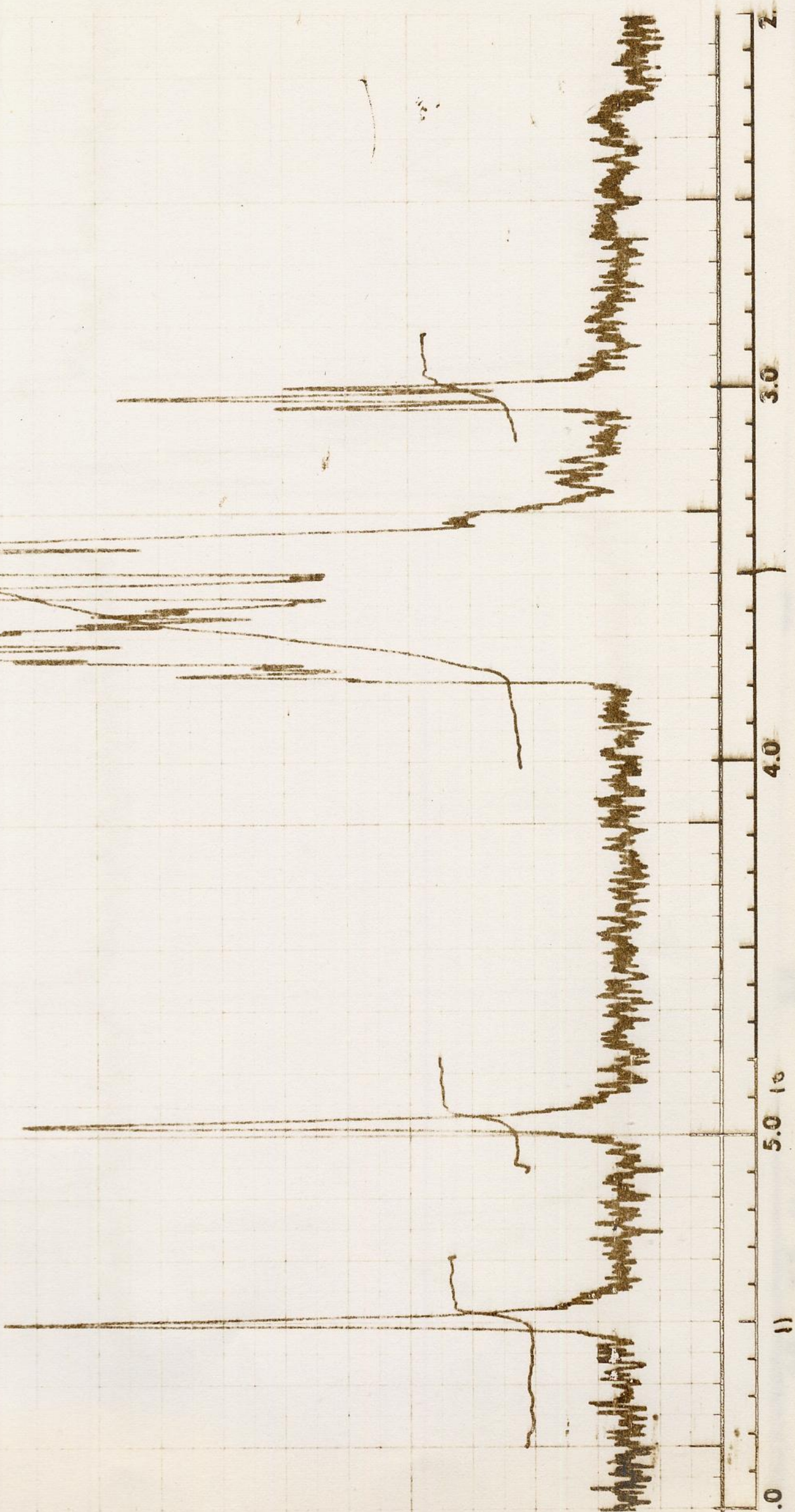FREQUENCY (CM⁻¹)

MICRONS
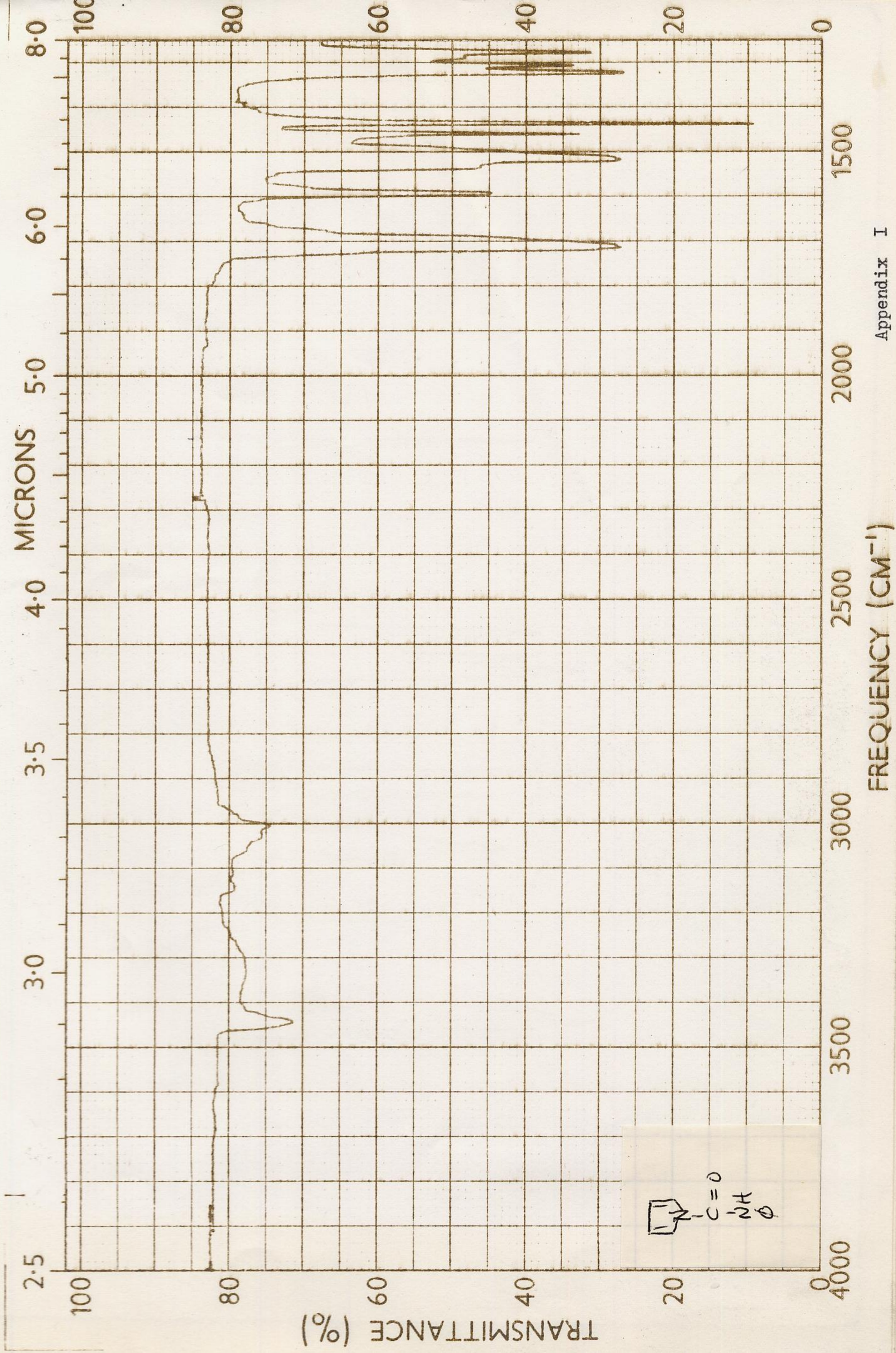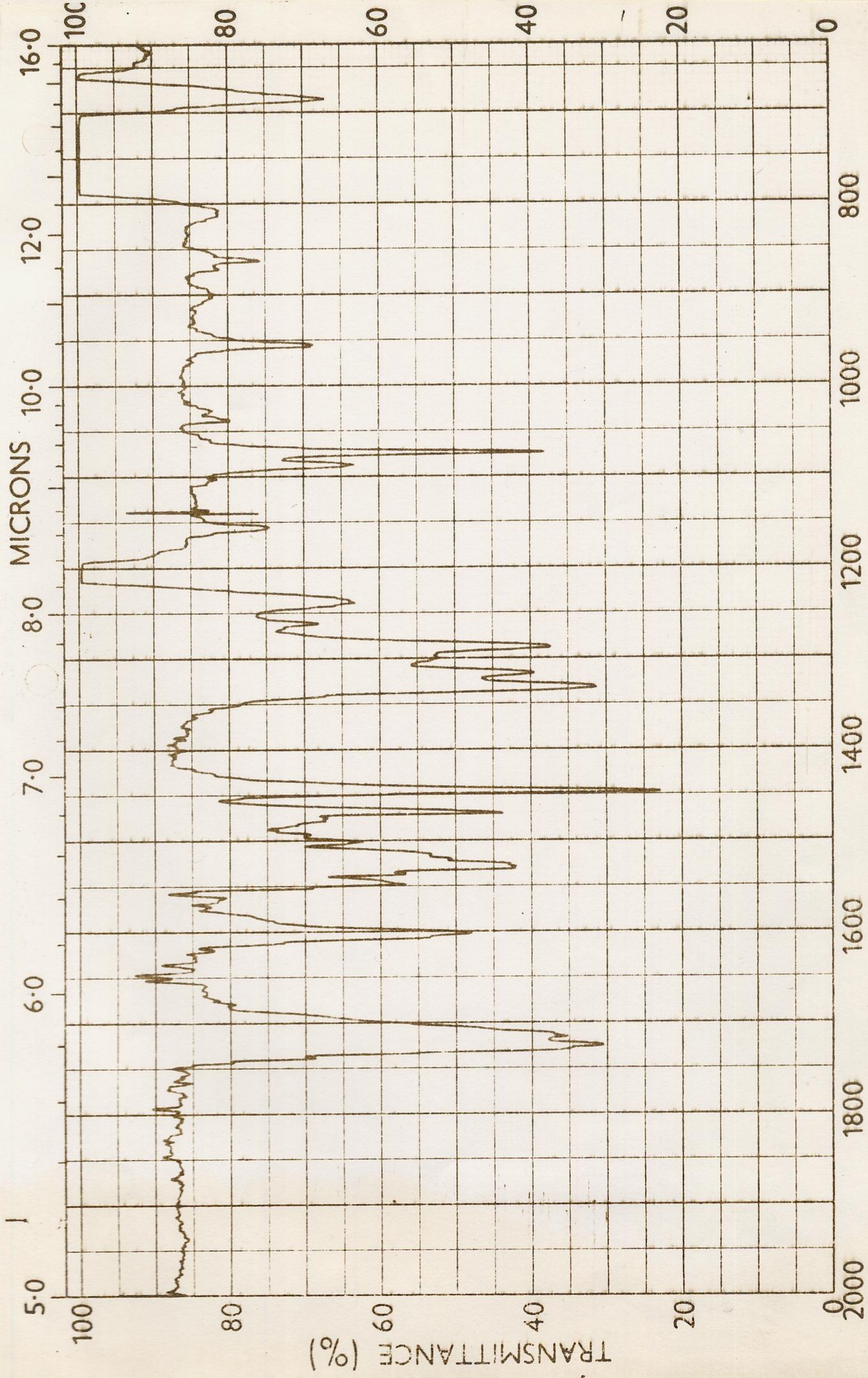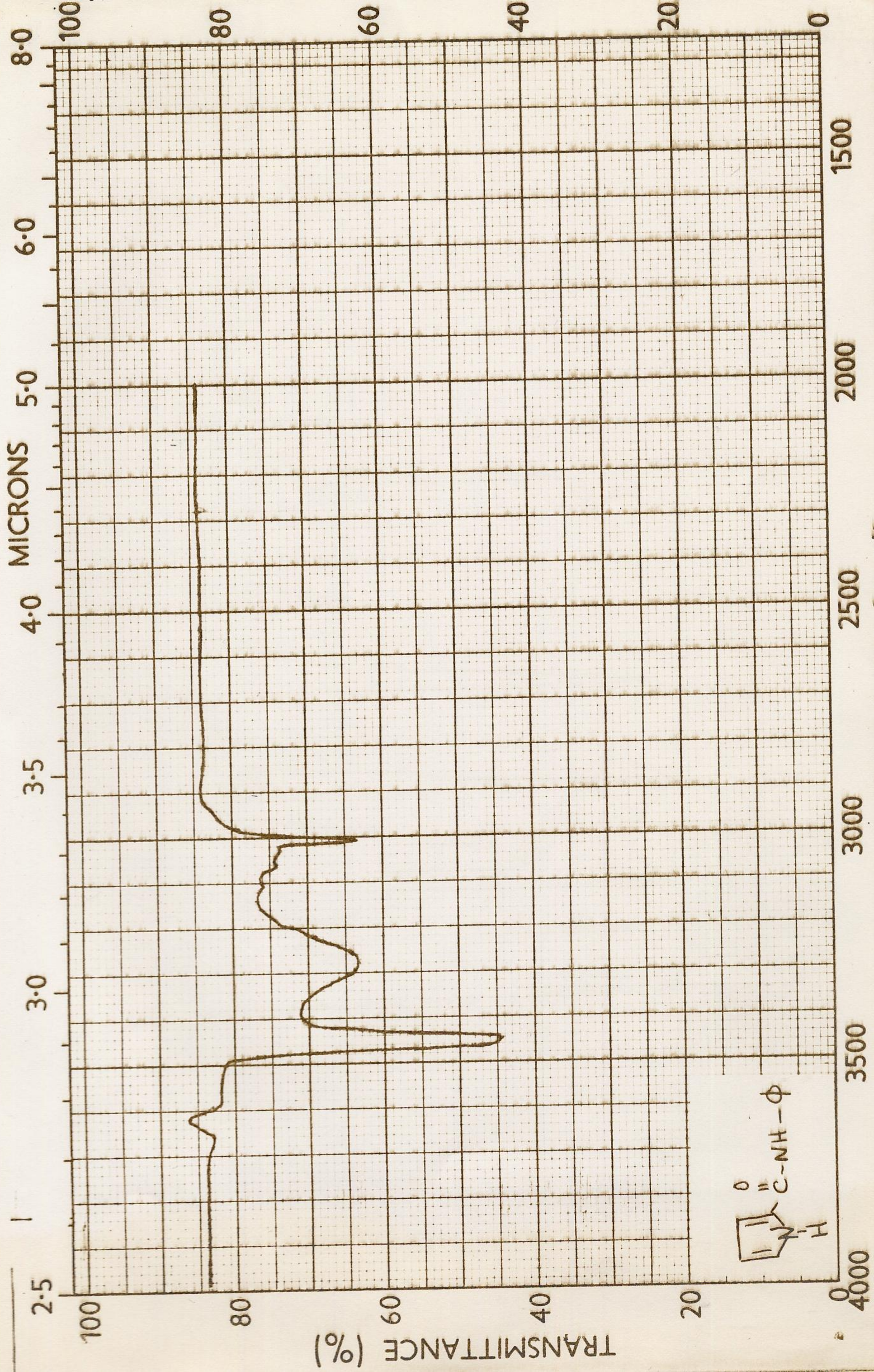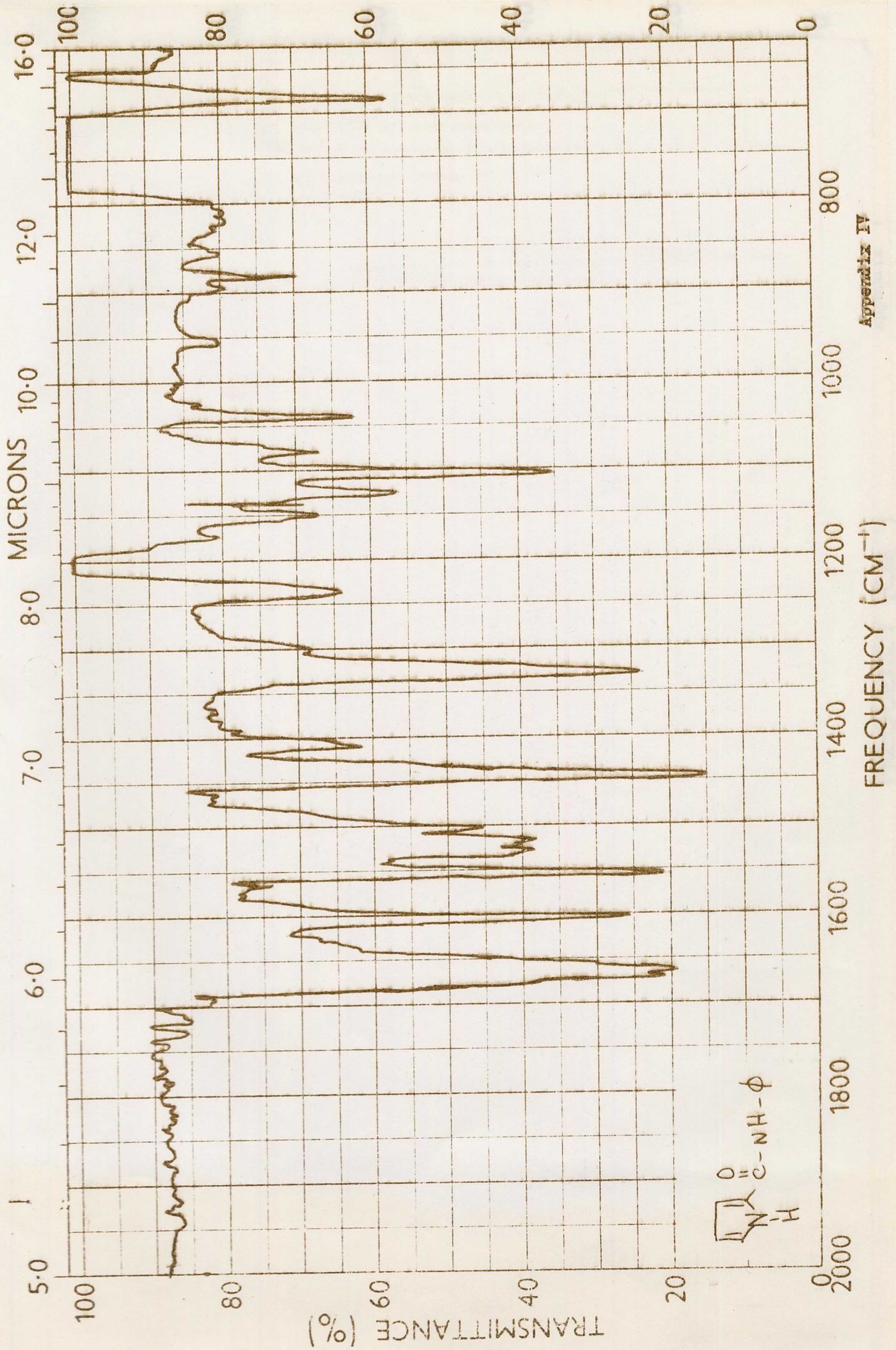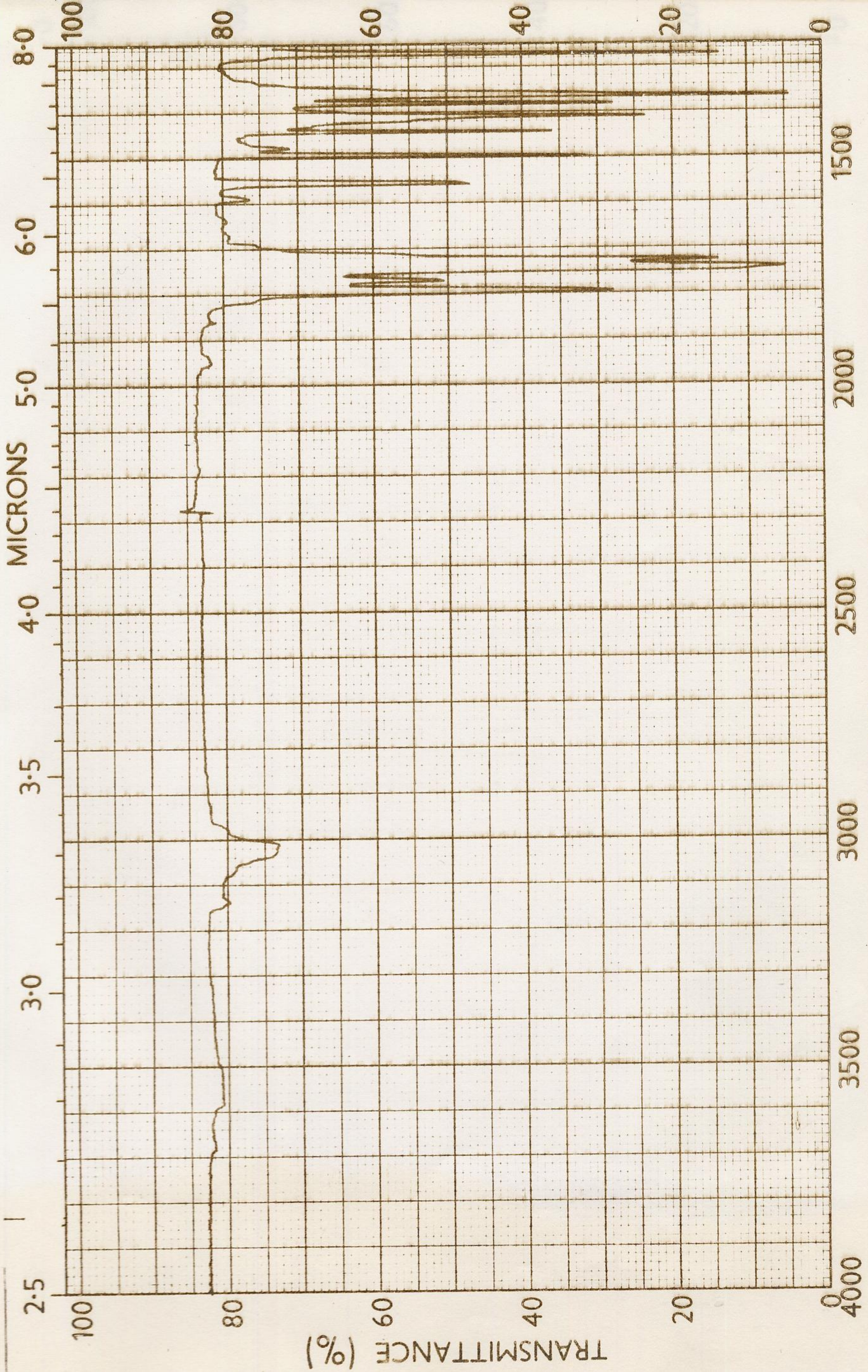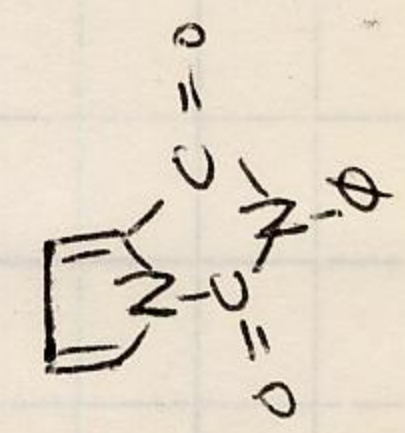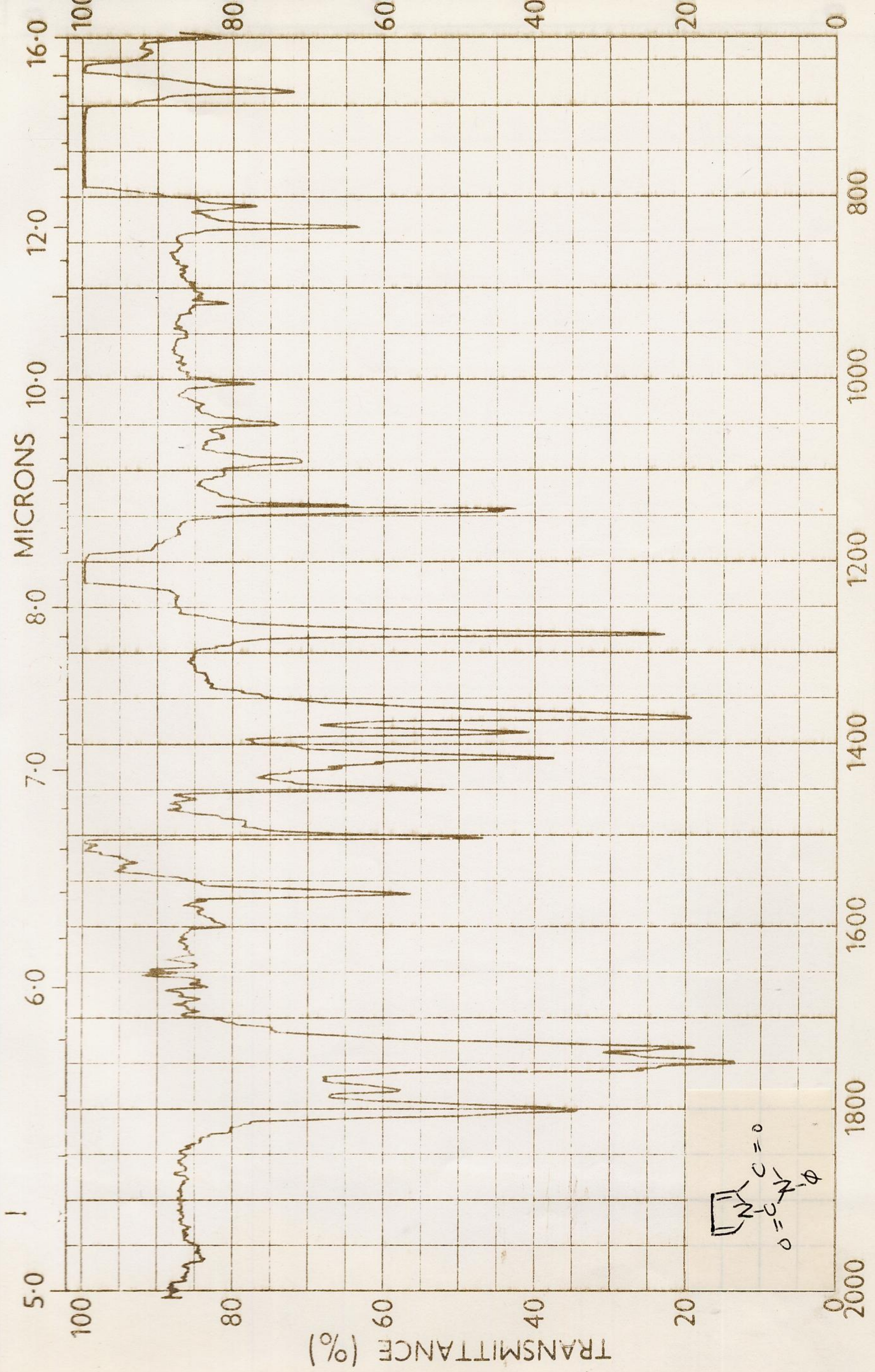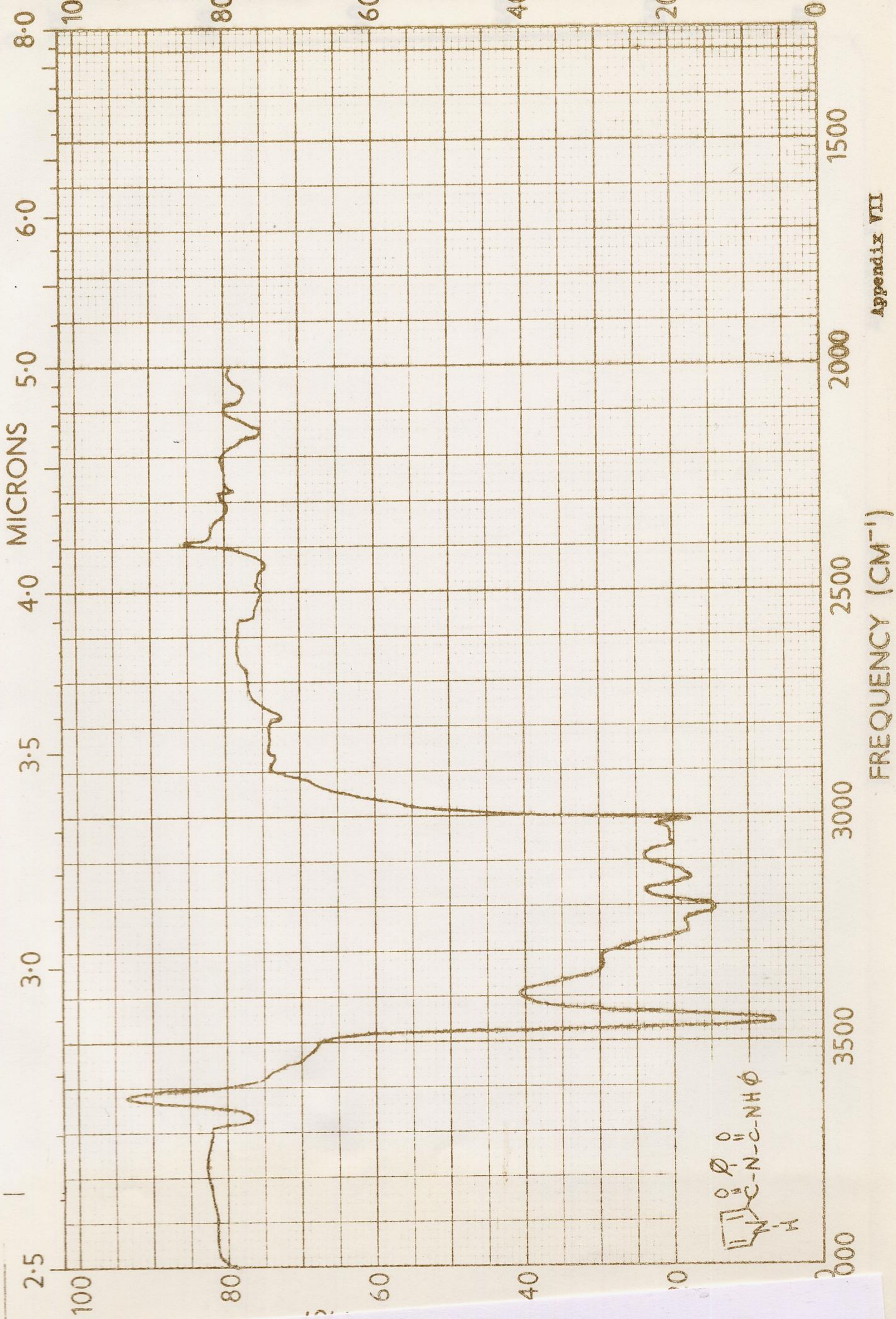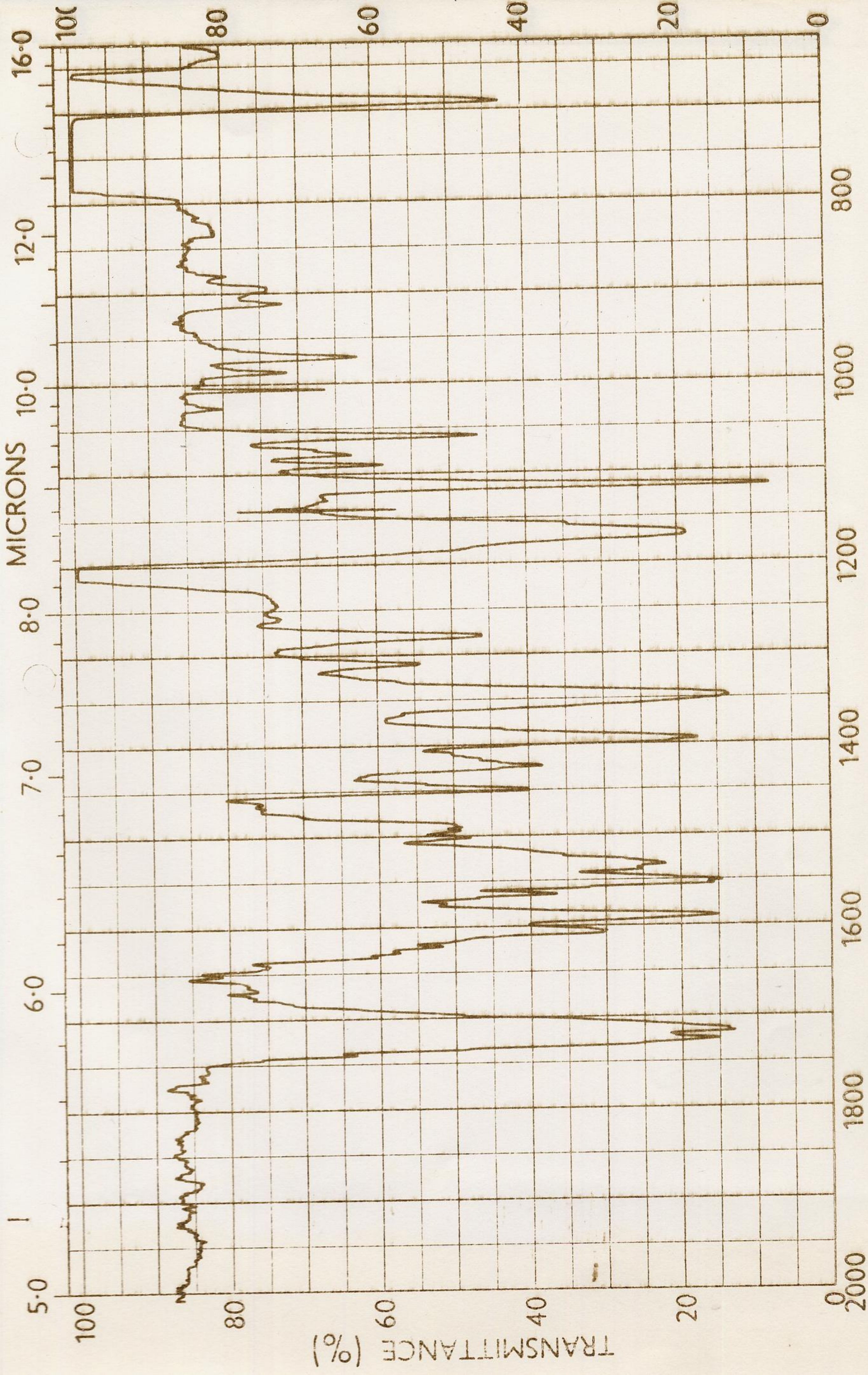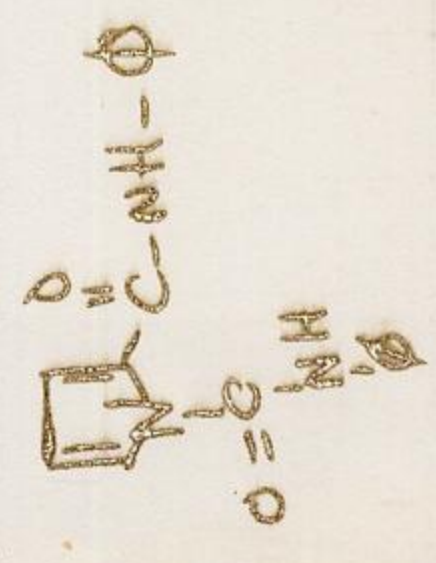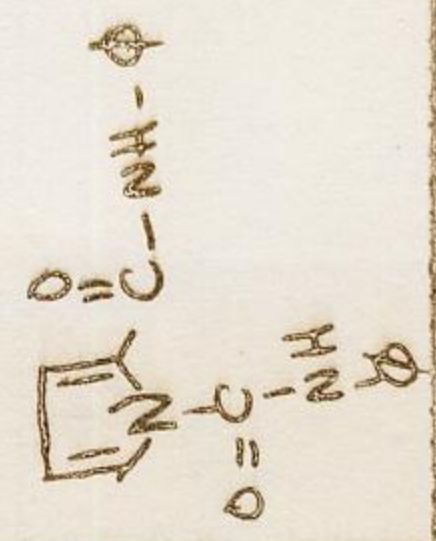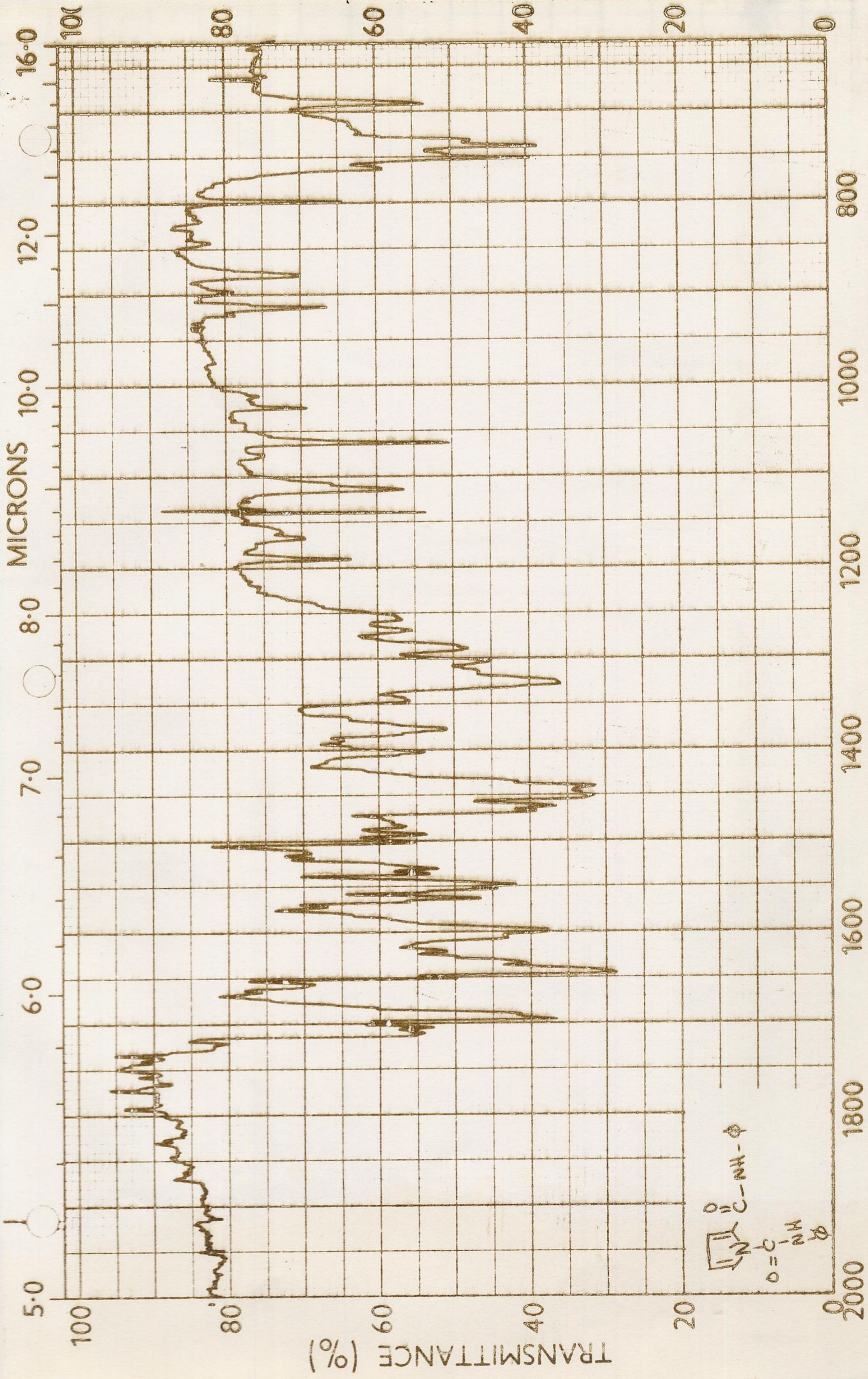
Appendix I

Appendix XI
Spectrum in CDCl₃
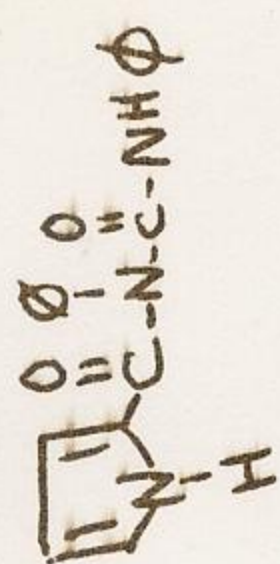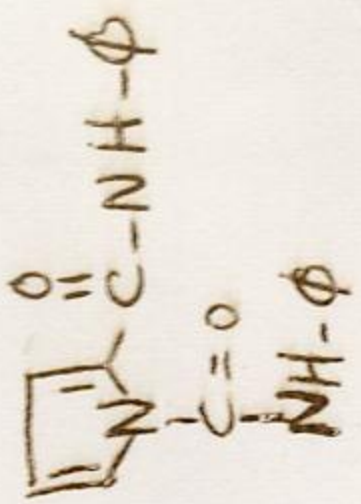
Sweep width of 500

of (1) and (2)

Sweep width of 1000 cps

(1)

(2)
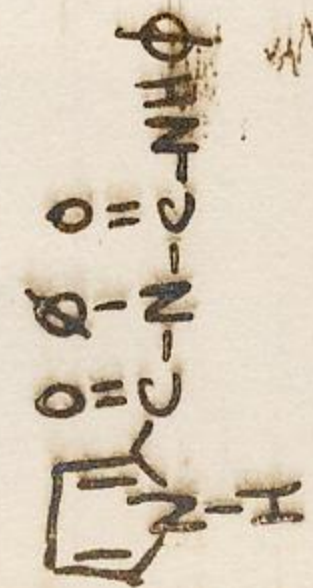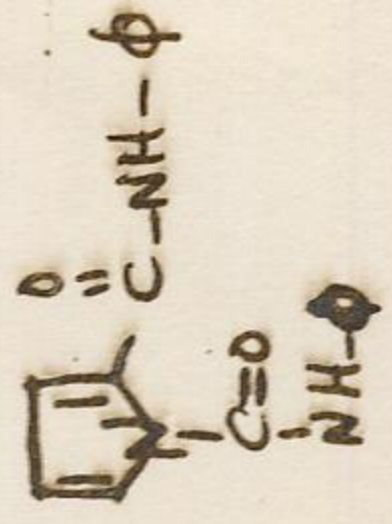
Appendix XII

Spectrum in DMSO

Appendix XIII

Spectra in DMSO + CF_3COOH