# REACTIONS OF METAL DERIVATIVES OF INDOLE WITH PHENYL ISOCYANATE AND PHENYL ISOTHIOCYANATE

BY

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Thesis Title

# REACTIONS OF METAL DERIVATIVES OF INDOLE WITH PHENYL ISOCYANATE AND PHENYL ISOTHIOCYANATE

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# ABSTRACT

Indolylpotassium and indolylmagnesium bromide react at room temperature with phenyl isocyanate and with phenyl isothiocyanate to give 1-indolecarboxanilide and 1-indolethiocarbanilide, respectively.

The direct reaction of indole with phenyl isothiocyanate at 80 - 90° yields 3-indole-thiocarbanilide.

In the presence of triethylamine, 2-indolecarboxanilide and ethyl 2-indolecarboxylate react with phenyl isocyanate to form 2-phenylindolo (1, 2-c) hydantoin, which is converted to the mono-thio and di-thiohydantoins by treatment with phosphorous pentasulfide. The hydantoin and thiohydantoin rings are opened relatively easily by the action of base.

Correlation of structures has been effected by oxidation of thiocarbanilides to carboxanilides, and thiohydantoins to hydantoins.

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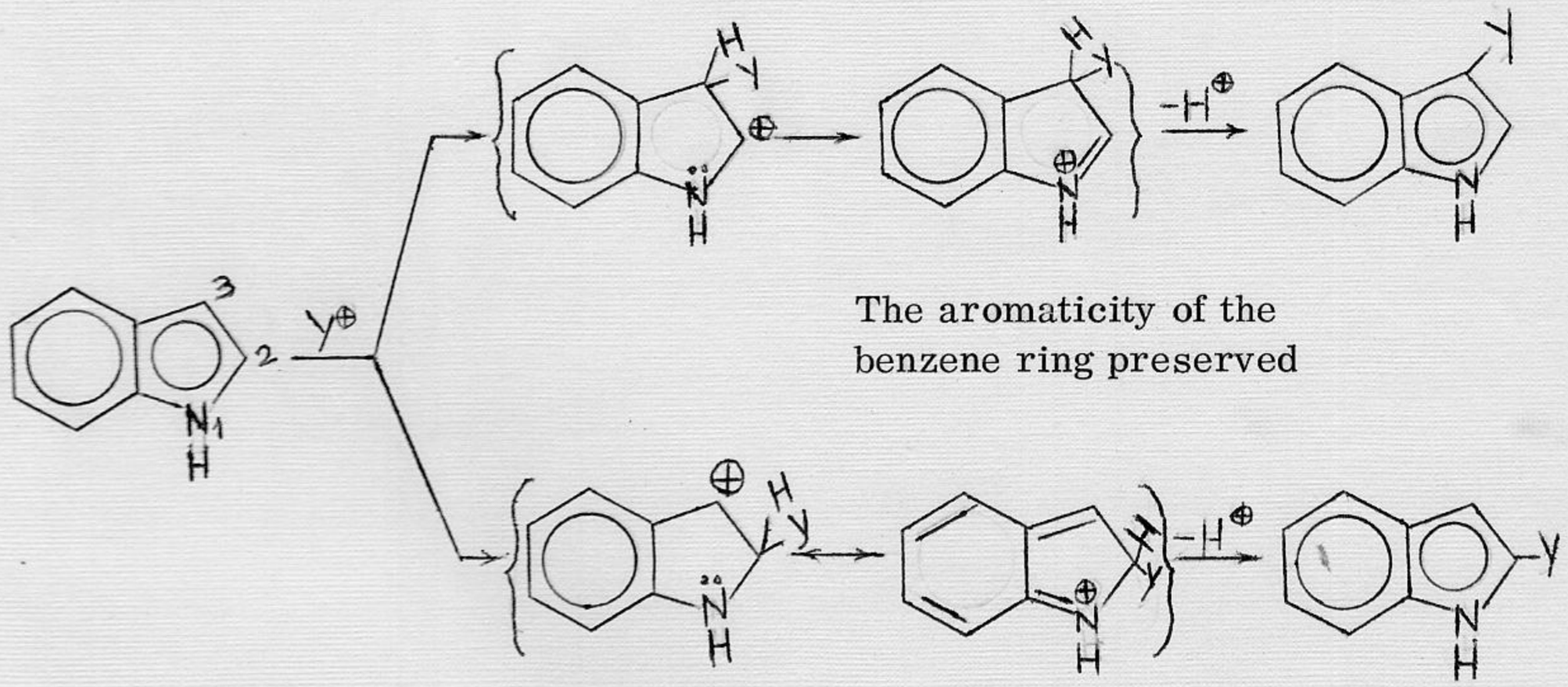
# INTRODUCTION

## Substitution Reactions of Indole and its Metal Derivatives.

### A. Electrophilic Substitution on Indole.

Electrophilic substitution on indole occurs generally at position 3. If this is blocked, position 2 is attacked. The benzene ring is only attacked when both positions 2 and 3 are already occupied and vigorous conditions are required.[1]

Fusing the benzene ring with the pyrrole ring alters the position of greater electron density of the latter from 2 to 3.[1] This greater reactivity of position 3, compared with position 2, is consistent with the expected greater stability of the intermediate formed by electrophilic attack at position 3, as shown below:




The substitution reactions of indole are complicated. The direct action of alkyl

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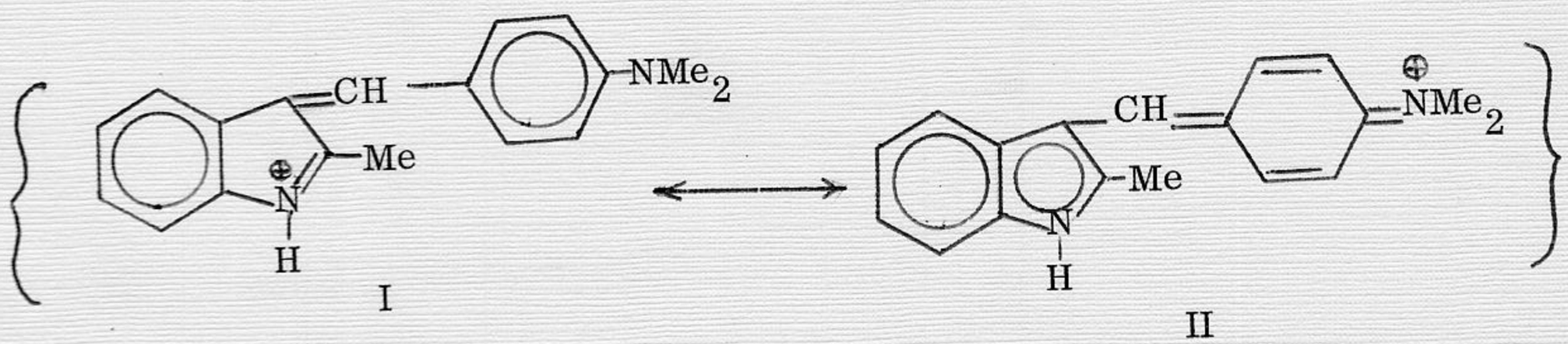
halides on indole occurs easily and yields the trialkyl derivative before it can be stopped.[2] Acetylation with hot acetic anhydride gives 1-acetyl indole along with the 1, 3-diacetyl derivative.[2] Halogenation with sulfuryl chloride, molecular bromine or iodine gives the 3-substituted compound.[3] The Gatterman and the Vilsmeier reactions lead to the 3-indole ketone and 3-indole carboxaldehyde, respectively. Acylation takes place at position 3 even in the presence of a strongly deactivating substituent at position 2. When position 3 is occupied by a strongly deactivating group substitution takes place in the benzene ring.[3] Indole reacts with p-N, N-dimethylaminobenzaldelyde, in the presence of hydrochloric acid, to give red to violet colors. This is known as Ehrlich's color test. 2- or 3-Mono substituted indoles also give a positive test. The test fails when both 2 and 3 positions are occupied. The color is associated with the fact that the positive charge can be delocalized and a quinonoid structure like II can be drawn:[1]




I II

B. Reactions of Indolylpotassium

The nitrogen atom of indole exhibits very weakly basic character, because the lone pair of electrons is not available to acids, as it is involved in maintaining the aromatic sextet of the pyrrole ring.[4] However, once a metal salt of indole is formed, the

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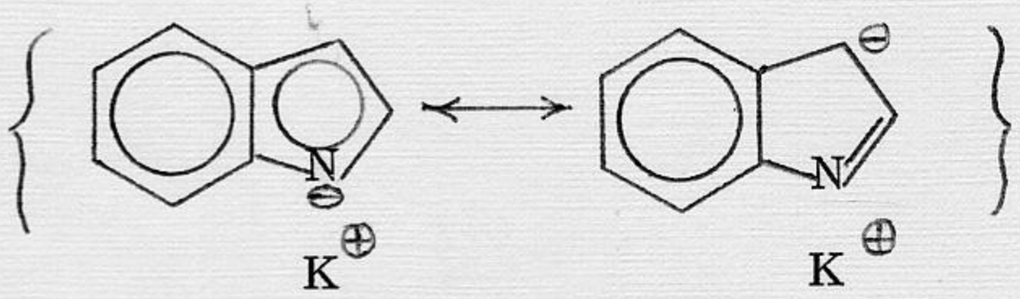
nitrogen atom becomes very effectively nucleophilic.

Indolylpotassium is prepared by the action of potassium on indole, or by the action of potassium hydroxide at elevated temperature.[2] Alkylation of the potassium salt of indole with methyl iodide gives N-methylindole as the major product along with small amounts of 2- and 3-methyl indoles.[1, 2] Studies of the alkylation of indolyl potassium with different alkyl halides, allyl halides and benzyl halides have been reported.[5, 6] In all instances the 1-substituted indole constitutes the prevailing product, with some 1, 3-disubstitution always taking place.[6]

The structure of the salt had been a matter of speculation for some time, until studies of the NMR spectrum of indolylpotassium showed absorption in the aromatic region only, which eliminates the presence of N-H and indicates ionic structure.[3]



## C. Reactions of Indolylmagnesium Halides

It was first reported in 1910 by Oddo that indolylmagnesium halides could be prepared readily from the interaction of indole with Grignard reagents.[2] They are valuable synthetic reagents since they interact readily with a large variety of compounds to give mainly C-substituted derivatives.[1, 2, 3, 4]

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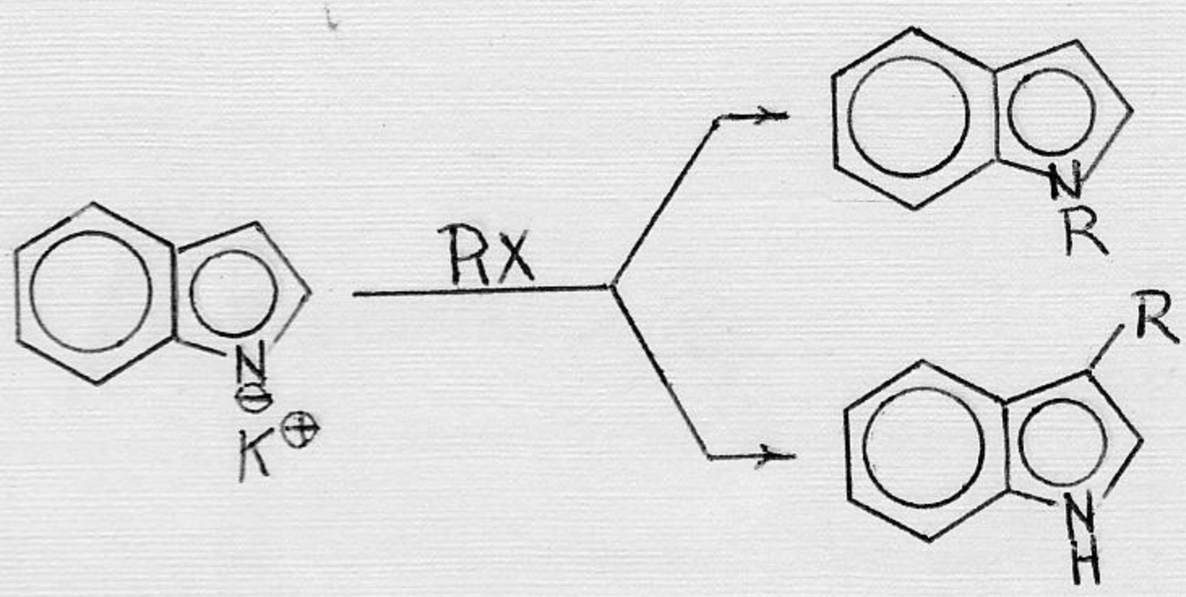
The indolylmagnesium halides are usually regarded as being N-MgX derivatives. In a recent investigation it was shown that the N-Mg bond has considerable covalent character in ether, while in THF it has increased ionic character.[7]

Indolylmagnesium iodide reacts readily with acid chlorides, alkyl halides, carbon dioxide and many other reagents to give the 3-substituted derivatives mainly, with small amounts of the 1-substituted indoles.[2] Indolylmagnesium halides react further with formaldehyde and ethylene oxide to give the expected 3-indole alcohol.[2]

The Indolyl Ambident Anion

The fact that, in their substitution reactions, the metal salts of indole give as a rule a mixture of the 1-and 3-substituted indoles suggests that the indolyl anion acts as an ambident system.




Recent studies show that the favored position of attack is determined by factors which tend to affect the ratio of association vs. dissociation of the indole metal salt.[5] In another investigation of the reactions of primary, secondary and tertiary alkyl halides, as well as, allyl and benzyl halides with indolylsodium it was found that there is a

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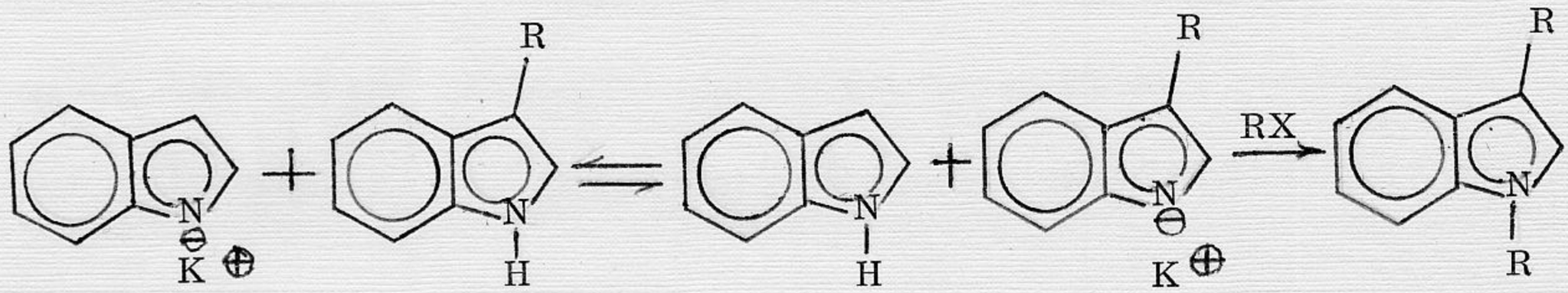
relationship between the structure of the alkyl halide and the site of attack.[6] The tendency of attack at position 3 increases with increasing electrophilic character of the alkyl halide, i.e. with increasing $S_N1$ character of the reaction. Further, solvents which solvate the cation strongly but the anion only to a negligible extent, favor attack at the more electronegative atom. On the other hand, the usually observed 1,3-disubstitution is explained by a fast proton transfer between the indole salt and the 3-substituted compound resulting in the formation of the anion of the 3-derivative as shown below:




## Reactions of Isocyanates and Isothiocyanates

### A. Reactions with Organometallic Compounds

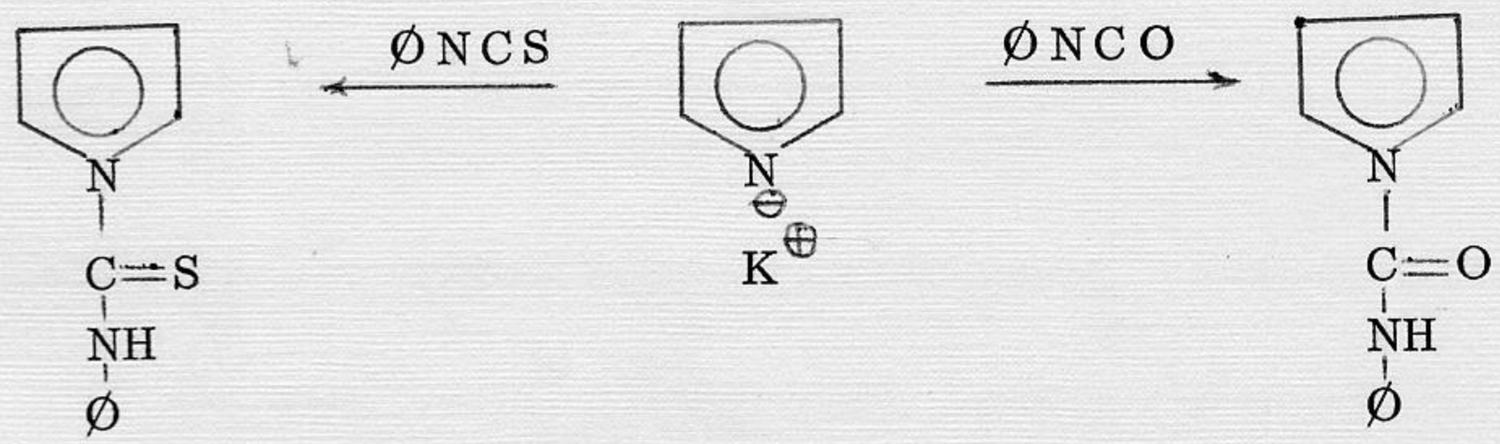
The reaction of phenyl isocyanate with organomagnesium halides was first investigated by Blaise in 1901.[8] The product obtained upon hydrolysis is the anilide. In 1903 Sachs and Loevy reported that phenyl isothiocyanate reacts similarly to form the thioanilide.[9]

In 1924 Gilman and co-workers studied the mechanism of the reaction and proved that addition takes place at the terminal part ( = C = O) of the isocyanate and the iso-

thiocyanate ( = C = S) group. Later on Schwartz and Johnson used this reaction for the characterization of alkyl halides and organomagnesium halides.[10,11] Phenyl isothiocyanate reacts with metal salts of acetylenes, amides and sulfonamides to form the corresponding thioanilides.[12,13]

Isocyanates react with 1, 3-dicarbonyl compounds, and aromatic compounds under Friedel-Crafts conditions to give the corresponding anilides.[14,15]

Pyrrolylpotassium reacts with phenyl isocyanate to form 1-pyrrole carboxanilide.[16] A similar outcome has been observed for the reaction with phenyl isothiocyanate.[17] Pyrrolylmagnesium bromide on the other hand yields mixtures of the 1- and 2-anilides or thioanilides.[17]

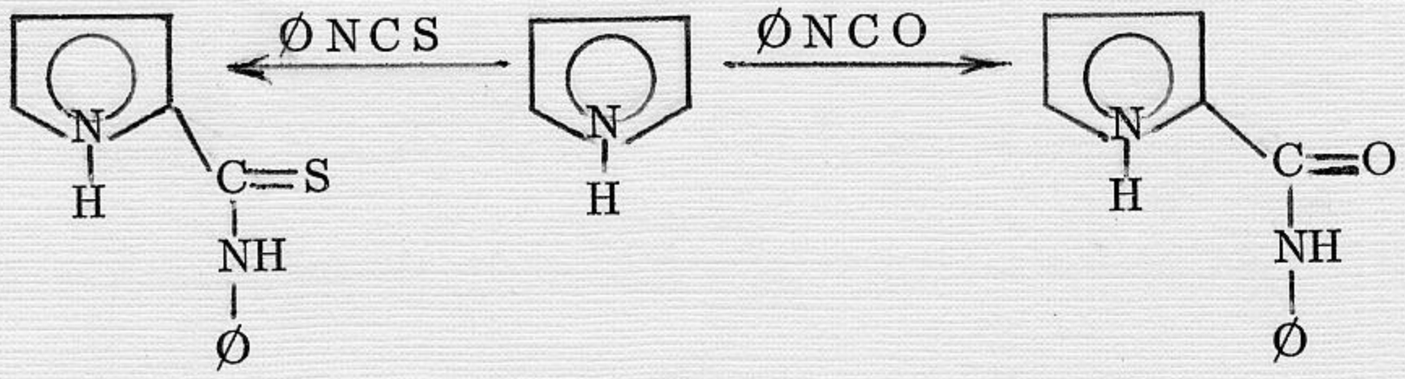



## B. Reactions of Isocyanates and Isothiocyanates with Heterocyclic Compounds

Reactions of isocyanates and isothiocyanates with heterocyclic compounds and subsequent cyclizations have been the object of considerable study in recent years.

Treibs and Ott observed that pyrrole and substituted pyrroles react readily with phenyl isocyanate to give the 2-substituted anilides.[18] When both ∝-positions

are occupied substitution takes place at the β-carbon, but the reaction proceeds sluggishly. Alkyl substituted pyrroles react much faster, while N-substituted pyrroles do not react even on strong heating.




Bullock and Abraham found that pyrroles react in a similar way with phenyl isothiocyanate to give the 2-pyrrolethioanilides.[19] The reaction is catalyzed by base and is sensitive to solvent changes. Quantitative yields of the thioanilide are obtained in N, N-dimenthylformamide after 12 hrs. at room temperature. A similar reaction in heptane does not yield any isolable product even after seven days.

Staab reported that phenyl isocyanate reacts with imidazole in tetrahydrofuran to give the 1-imidazole carboxanilide.[20] The product, however, dissociates into phenyl isocyanate and imidazole even at room temperature.

Imidazole further reacts with methyl isothiocyanate to give 1-(N-methylthiocarbamoyl)-imidazole.[21]

Gompper and co-workers investigated the reaction of 4, 5-diphenyl imidazole with phenyl isocyanate.[22] Heating of 4, 5-diphenyl imidazole with phenyl isocyanate at 80° for 12 hrs. yields 4, 5-diphenyl-1-imidazolecarboxanilide, whereas, refluxing of a solution of the two

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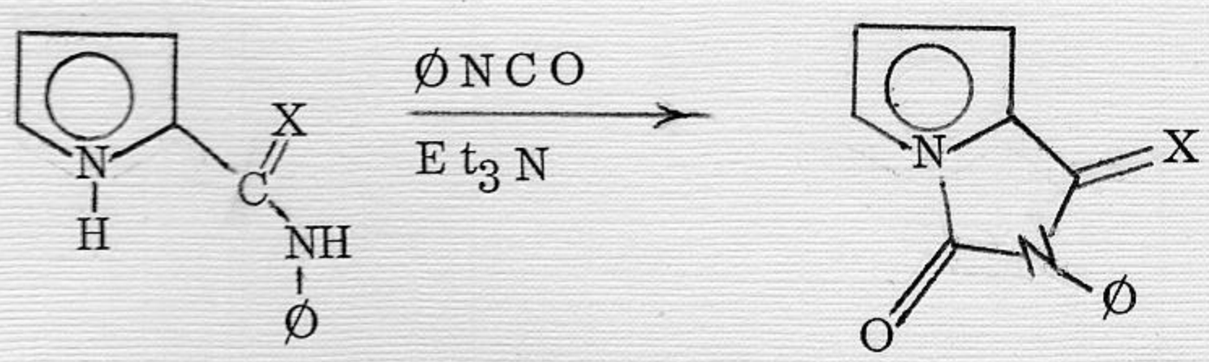
compounds in nitrobenzene yields 4, 5-diphenyl-2-imidazole-carboxanilide. When 4, 5-diphenylimidazole is refluxed with excess of phenyl isocyanate the product is composed of 4, 5-diphenyl-2-imidazolo (1, 2-c) hydantoin, the 2-carboxanilide and N, N' - diphenylurea.

2-Ethyl- $\triangle^2$ -oxazoline reacts, vigorously with phenyl isocyanate at room temperature to give 3-phenylcarbamoyl-oxazolidinyliden-(2)-ethylcarboxanilide. The reaction with phenyl isothiocyanate occurs under more forcing conditions to give the corresponding thioanilide.[23]

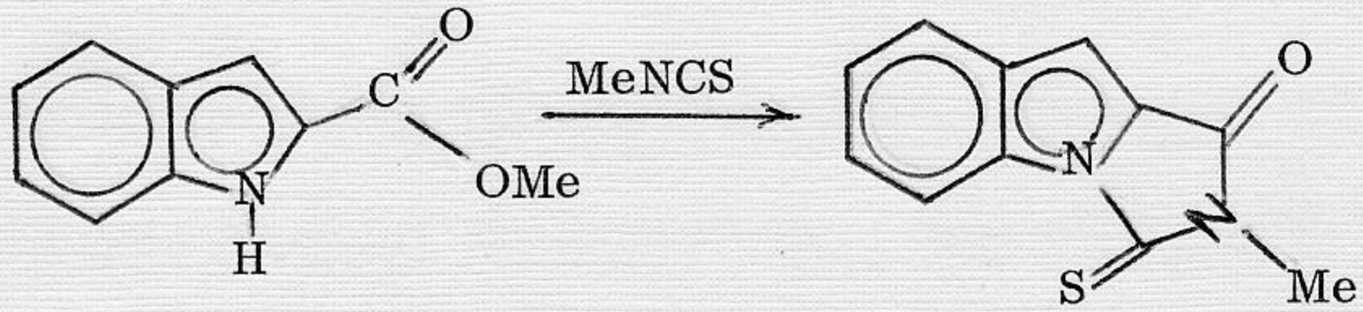
It was found that an equimolar mixture of 3-methylpyrazole and methyl isocyanate yields the condensation product 3-methyl-1-(N-methylcarbamoyl) pyrazole in high yield.[24]

Aziridine reacts with alkyl isocyanates to give the 1-aziridine carboxanilides, whereas, N-substituted aziridines yield 1, 3-disubstituted imidazolidinones.[25] Triethylamine catalyzes a cyclization reaction between 2-pyrrolecarboxanilide or 2-pyrrolethioanilide and phenyl isocyanate with formation of 2-phenylpyrrolo (1, 2-c) hydantoin or 2-phenyl-pyrrolo (1, 2-c)-1-thiohydantoin, respectively.[16, 17]




X = O, S

Methyl 2-indole carboxylate reacts with methyl isothiocyanate in a sealed tube at $180^{o}$ to give 2-methylindolo (1, 2-c)-2-thiohydantoin.[26]

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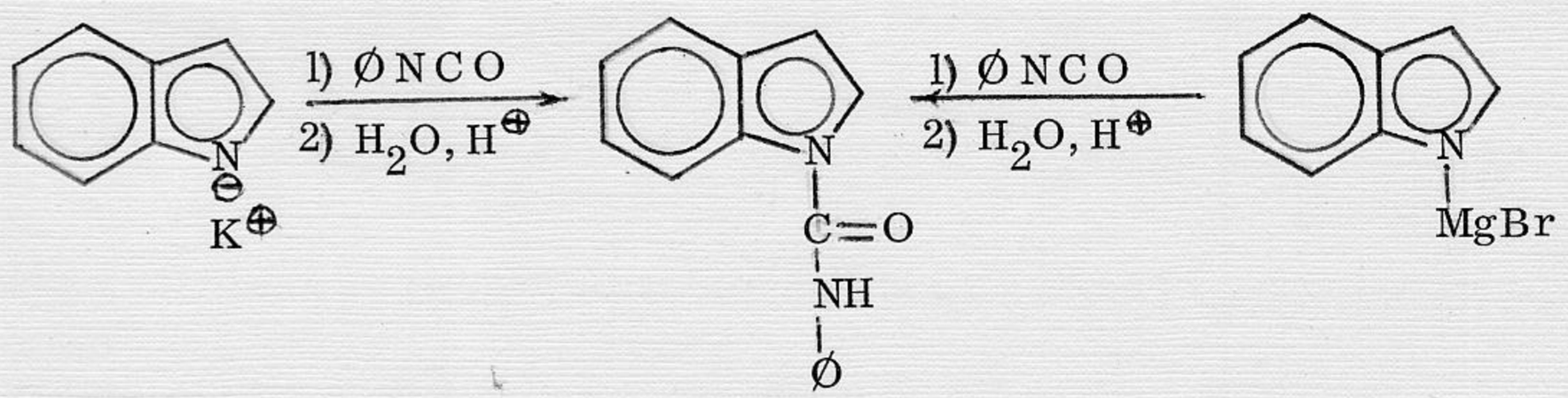
# DISCUSSION OF RESULTS

## A. Reactions of indolylpotassium and indolylmagnesium bromide with phenyl isocyanate and phenyl isothiocyanate.

Indolylpotassium reacts with phenyl isocyanate and phenyl isothiocyanate in exactly the same manner as pyrrolylpotassium. The reaction of indolylpotassium with phenyl isocyanate in tetrahydrofuran yields 1-indolecarboxanilide (I) as the only product.




I

Structure (I) was assigned to the product of this reaction on the basis of the following evidence:

a) The composition found by analysis agrees with that calculated for $C_{15}H_{12}ON_2$.

b) The infrared spectrum shows a strong carbonyl absorption at 1710 $cm^{-1}$, which is in agreement with observations on the carbonyl absorption of 1-pyrrolecarboxanilide and 1-imidazolecarboxanilides.[16,22] In the 3400 - 3500 $cm^{-1}$ region, there is no peak which can be attributed to the indole N-H group. A weak absorption band at 3430 $cm^{-1}$ should be due to the amide N-H group.

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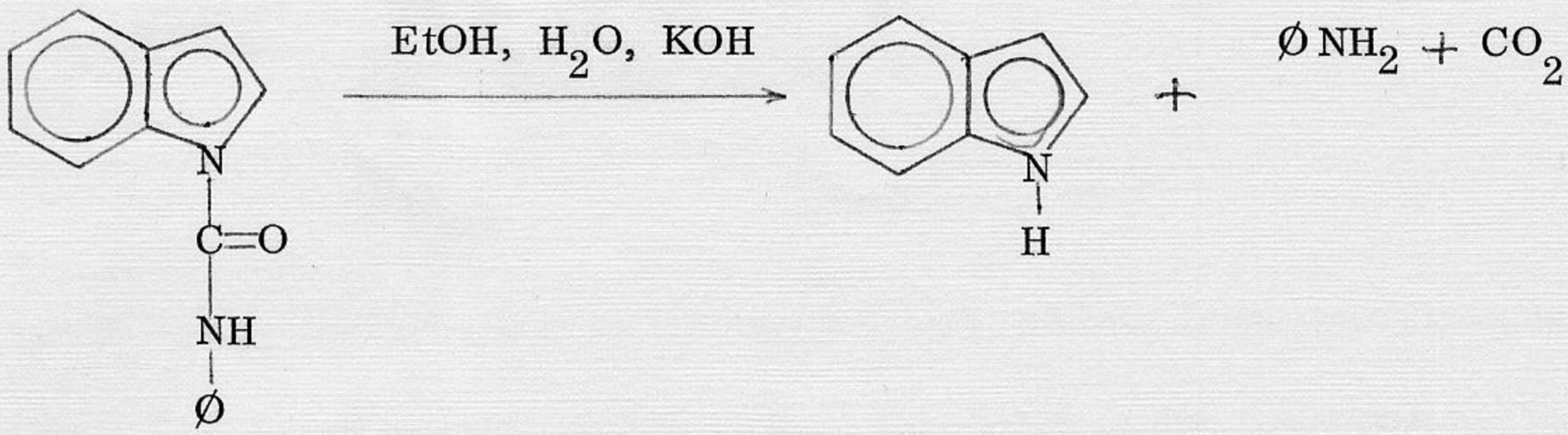
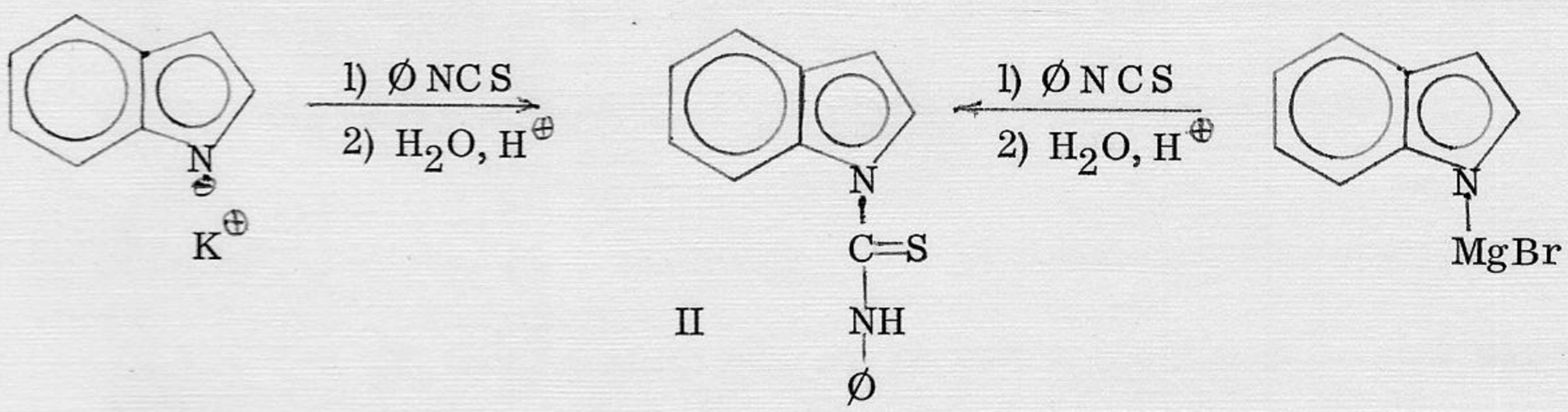
c) Alkaline hydrolysis of I yielded an equimolar mixture of indole and aniline:




The same compound, 1-indolecarboxanilide, is also obtained from the reaction in tetrahydrofuran of indolylmagnesium brom_ide with phenyl isocyanate, despite the known tendency of indolylmagnesium halides to yield predominantly 3-substituted indoles.[2]

In quite a similar way indolylpotassium reacts with phenyl isothiocyanate in tetrahydrofuran to give exclusively 1-indolethiocarbanilide (II).




The assignment of structure II to the product of this reaction is supported by the following facts:

a) Correct elemental analysis.

b) The infrared spectrum has an absorption band at 3375 $cm^{-1}$, which is at the right position for a thioamide, but too low for an indole N-H absorption.[27]

c) Oxidation with alkaline hydrogen peroxide (30%) converts II into 1-indolecarboxanilide.

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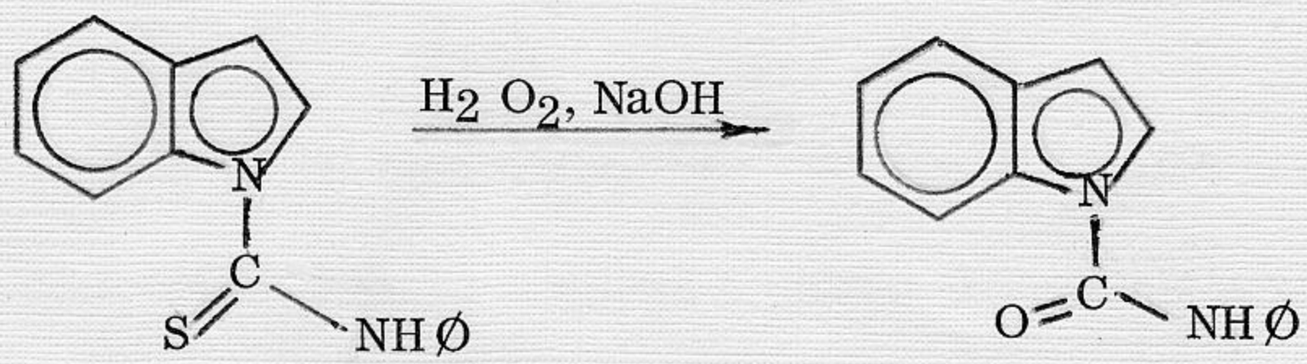
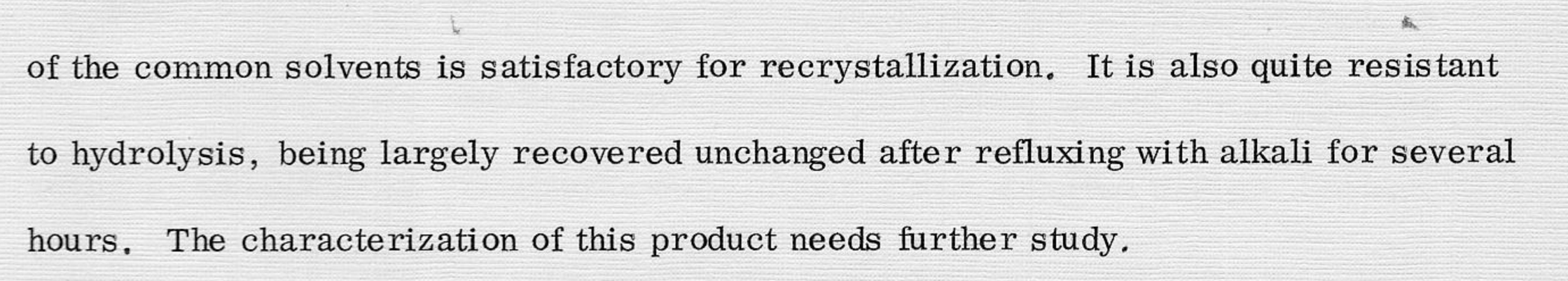



Again, 1-indolethiocarbanilide is the only product obtained from indolylmagnesium bromide and phenyl isothiocyanate, without formation of any 3-substituted isomer.

B. Reactions of indole with phenyl isocyanate and phenyl isothiocyanate

In contrast to the straight forward reaction of pyrrole with phenyl isocyanate to give 2-pyrrolecarboxanilide, the reaction of indole with phenyl isocyanate, which occurs readily at room temperature, does not yield any of the three indolecarboxanilides with the side chain at position 1, 2, or 3. The product is difficult to purify, because none of the common solvents is satisfactory for recrystallization. It is also quite resistant to hydrolysis, being largely recovered unchanged after refluxing with alkali for several hours. The characterization of this product needs further study.

Consistent with the lower reactivity of phenyl isothiocyanate, compared to phenyl isocyanate, the reaction of indole with the former reagent is quite slow and requires heating at 80 - 90° for 5 - 6 days.




V

The major component of the product of this reaction is 3-indolethiocarbanilide (V)

the structure of which is supported by the following evidence:

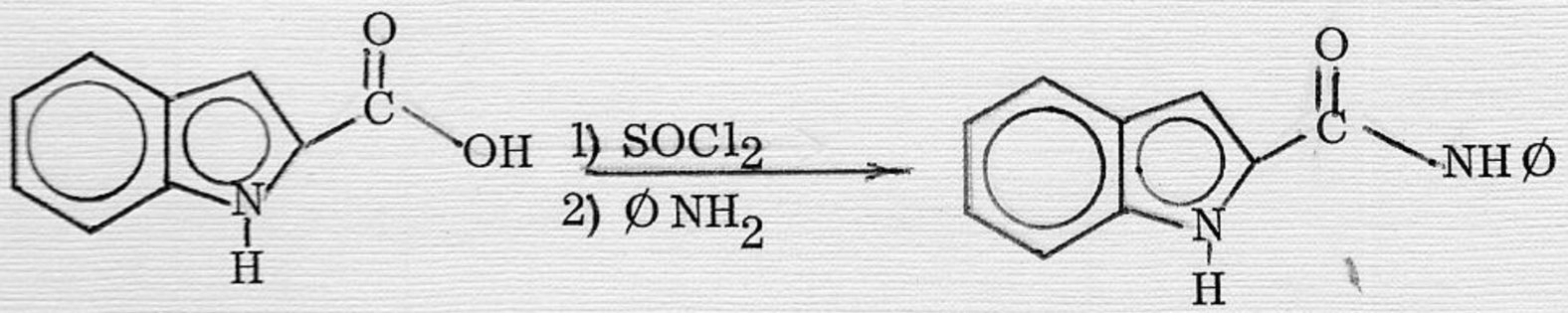
a) The elemental analysis agrees with the calculated composition.

b) Its infrared spectrum shows a strong absorption at 3460 $cm^{-1}$, corresponding to the indole N-H group, and a weaker band at 3380 $cm^{-1}$, arising from the thioamide N-H group.

c) Oxidation with alkaline hydrogen peroxide (30%) gives 3-indolecarboxanilide, identical in all respects with the compound prepared independently from 3-indolecarboxylic acid.

As a minor by-product, N,N'-diphenylthiourea was isolated from the reaction mixture.

Since the product of the direct reaction of indole with phenyl isocyanate has not been identified, whereas use of indolylpotassium or indolylmagnesium bromide leads to the 1-substituted indole, the 2- and 3-indolecarboxanilides, needed for comparison purposes and for further reactions, were prepared by a different method. Commercial 2-indolecarboxylic acid was converted to the acid chloride by treatment with thionyl chloride. Subsequent reaction with aniline gave 2-indolecarboxanilide (III).

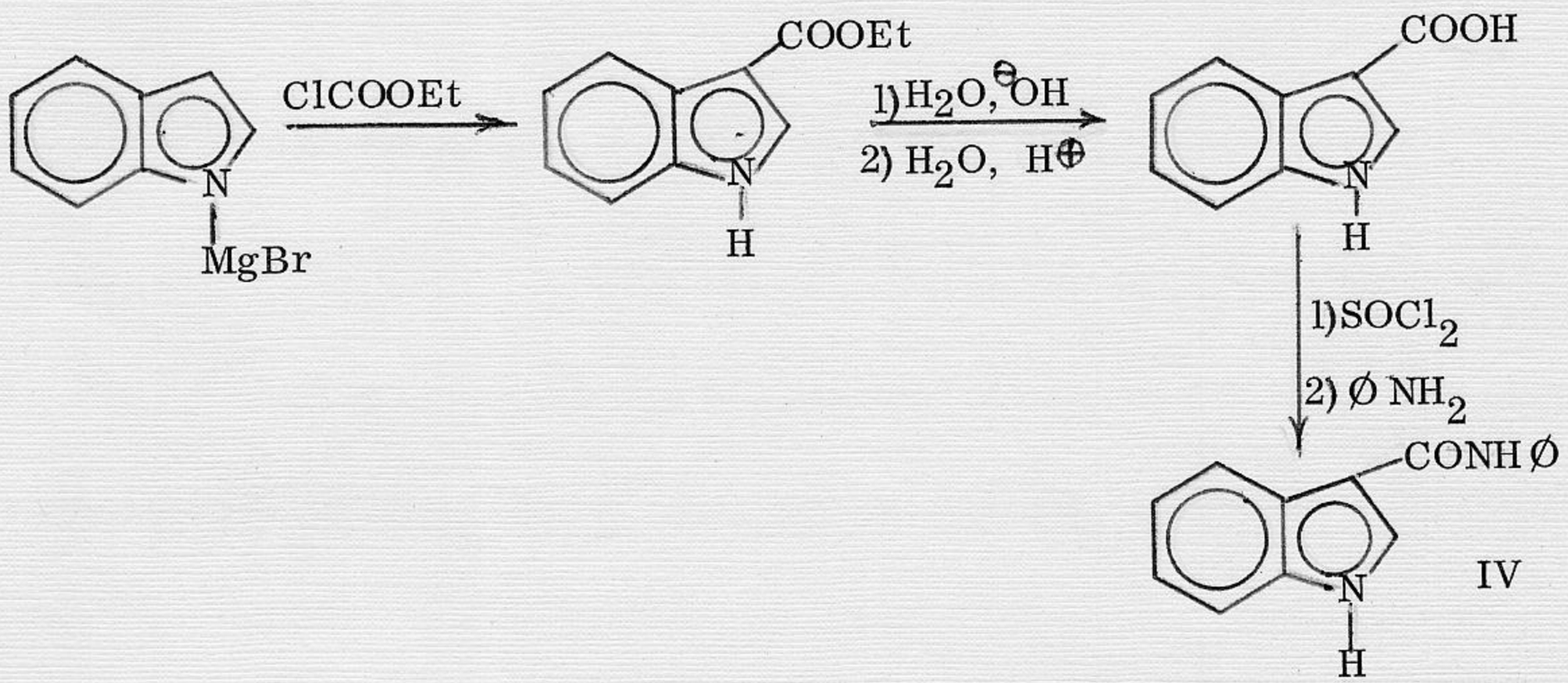



III

The infrared spectrum of this compound shows indole N-H absorption at 3440 $cm^{-1}$

and a carbonyl absorption at 1660 $cm^{-1}$. The latter is consistent with previous observations on the carbonyl absorption of C-substituted pyrrole- and imidazole-carboxanilides.[16, 22]

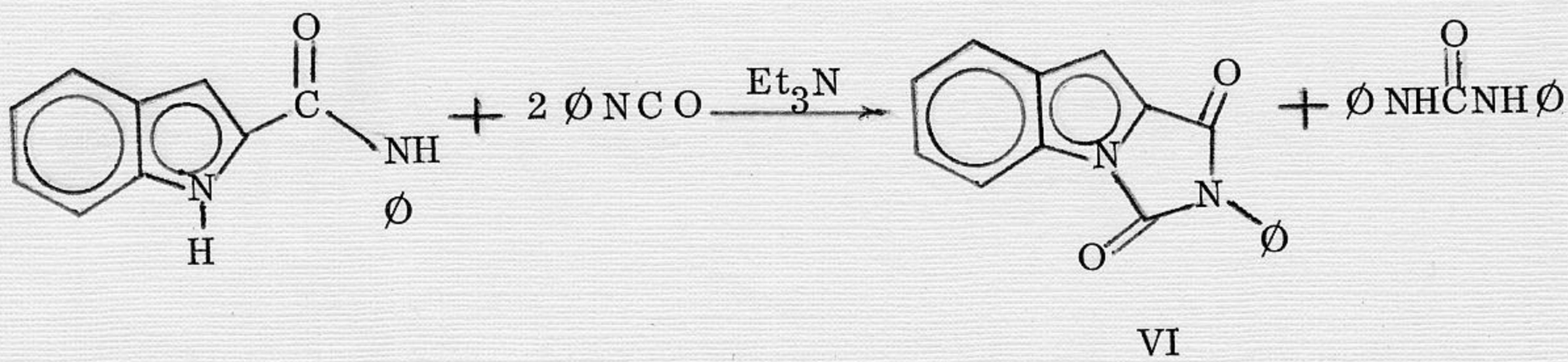
3-Indolecarboxanilide (IV) was prepared by the following sequence of reactions:




Indolylmagnesium bromide was made to react with ethyl chloroformate to form ethyl 3-indolecarboxylate. This ester was hydrolyzed to 3-indolecarboxylic acid, which was converted to the chloride by treatment with thionyl chloride. Finally, reaction of the acid chloride with aniline yielded 3-indolecarboxanilide. The infrared spectrum of this compound, which is identical with the product of oxidation of 3-indolethiocarbanilide, shows an indole N-H absorption at 3460 $cm^{-1}$ and a carbonyl absorption at 1655 $cm^{-1}$.

C. Formation of Indolohydantoins and Indolothiohydantoins

In complete analogy with the corresponding reaction of the pyrrole derivative, 2-indolecarboxanilide reacts with phenyl isocyanate in the presence of triethylamine to give 2-phenylindolo (1, 2-c)-hydantoin and N,N' -diphenylurea.



VI

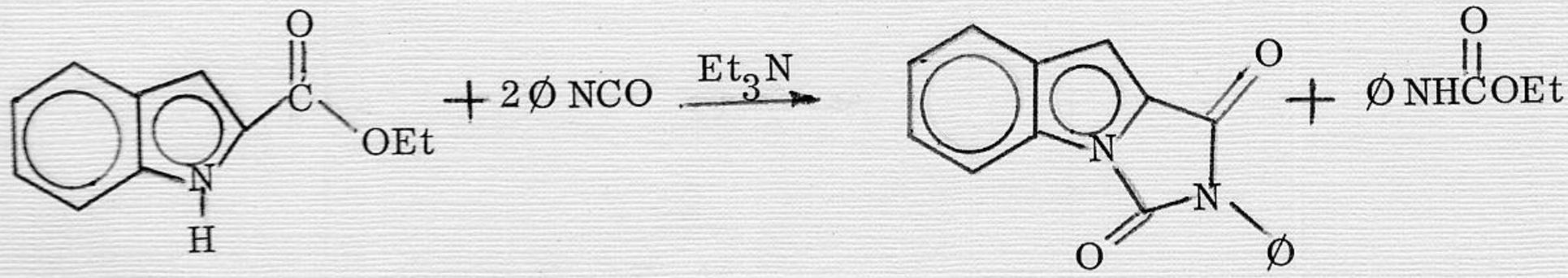
Structure VI was assigned to this compound on the basis of the following evidence:

a) The composition found by analysis agreed with that calculated for $C_{16}H_{10}O_2N_2$.

b) The infrared spectrum showed two carbonyl absorptions at relatively high fequencies, 1785 $cm^{-1}$ and at 1735 $cm^{-1}$, consistent with the strained five-membered ring hydantoin system.

c) Alkaline hydrolysis yielded 2-indolecarboxanilide.

Additional evidence was provided by the smooth formation of VI when ethyl 2-indolecarboxylate was heated with phenyl isocyanate in the presence of triethylamine.



The following mechanism can be postulated for the formation of the hydantoin system:

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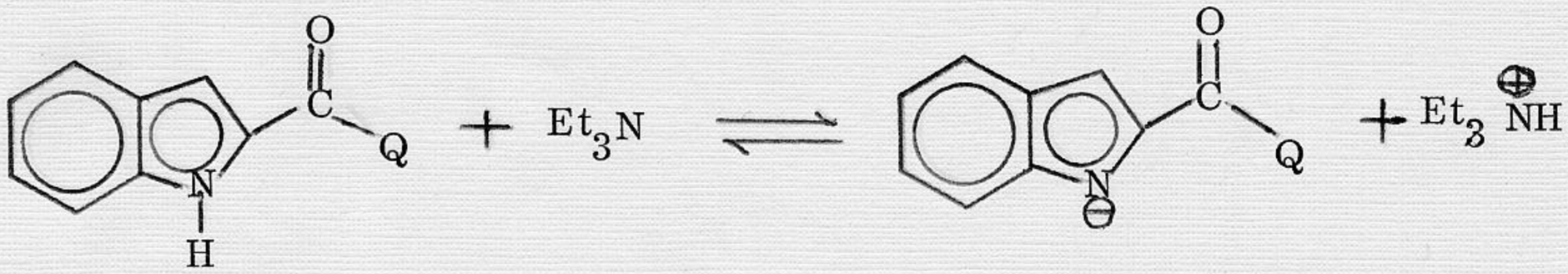
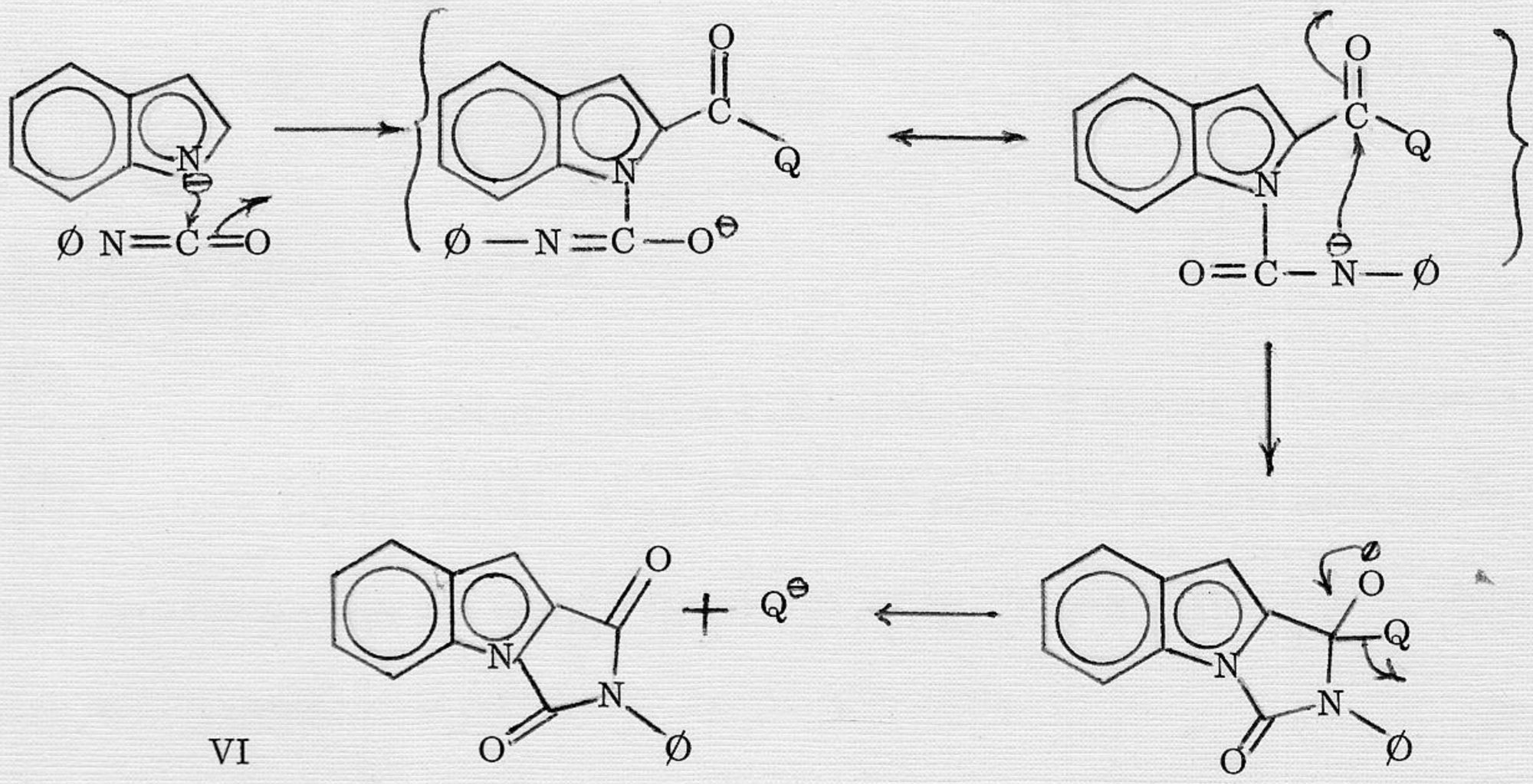
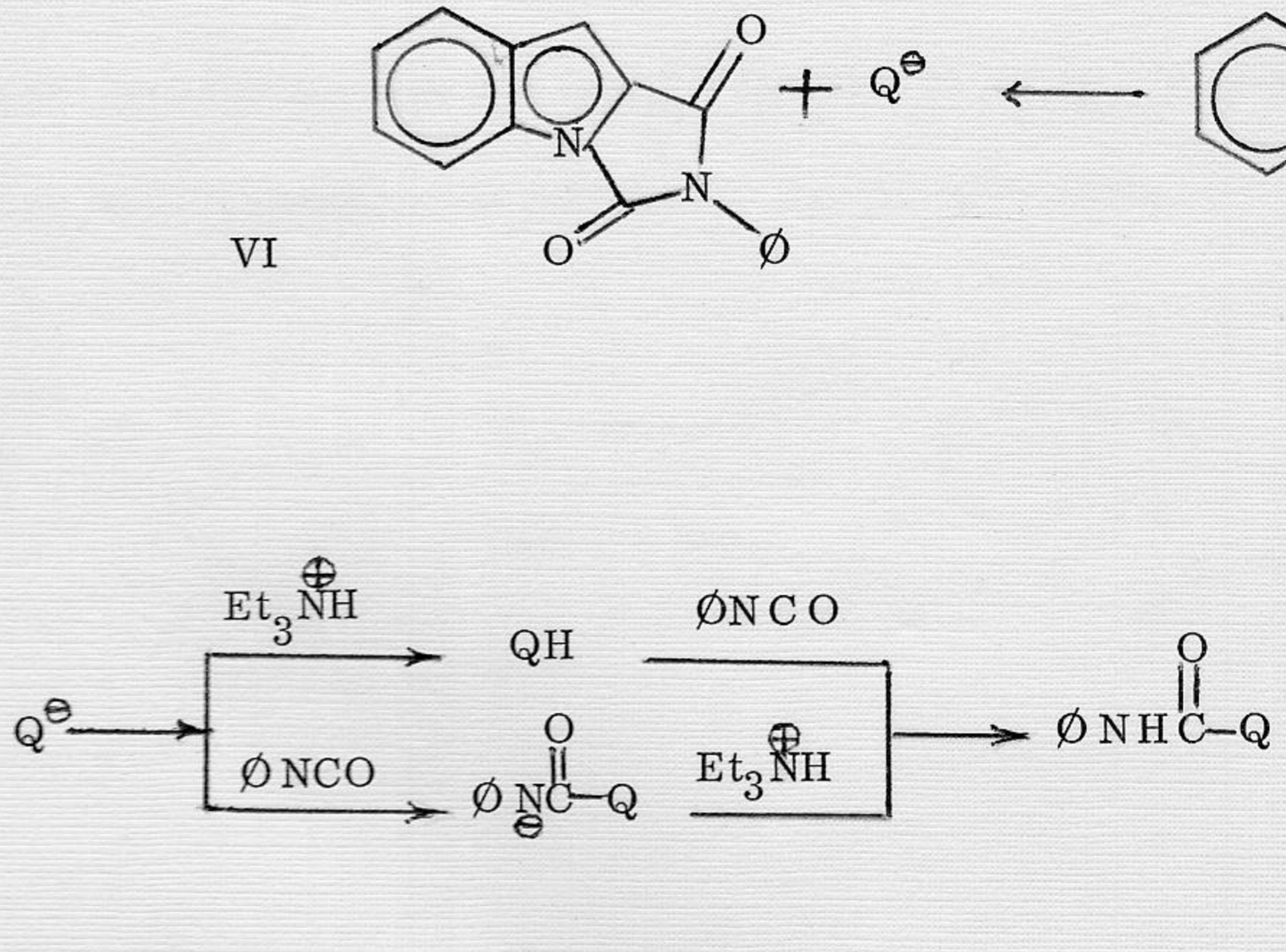


Q = NHØ , -OEt



VI



The hydrolysis of the hydantoin must involve attack by the base on the carbonyl attached to the indole nitrogen, since the product is 2-indolecarboxanilide.

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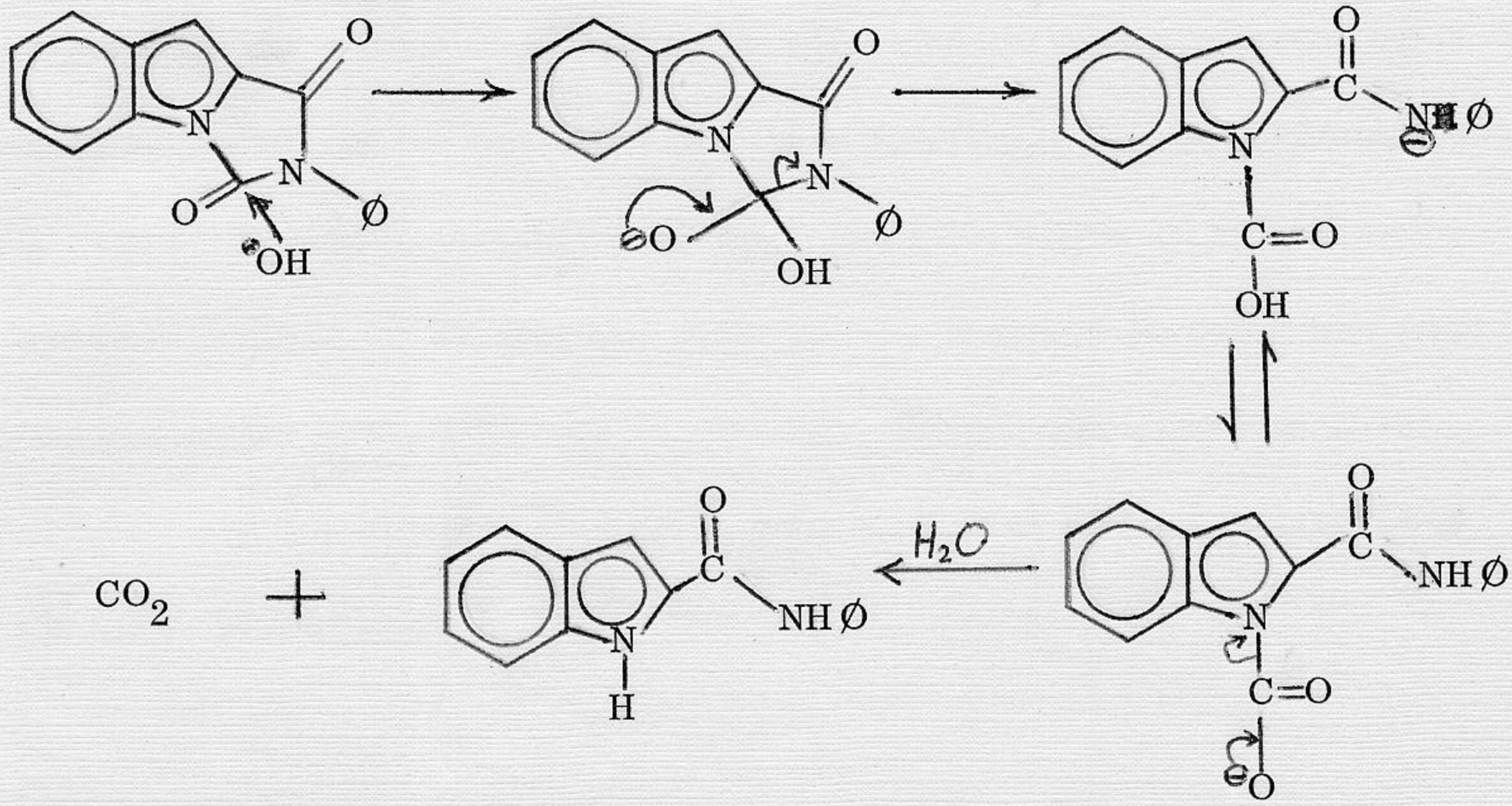
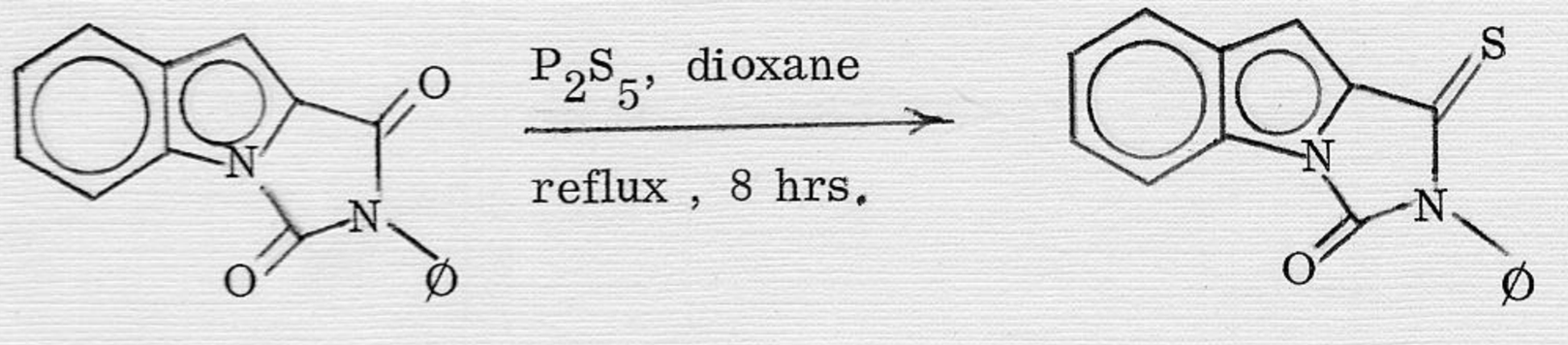
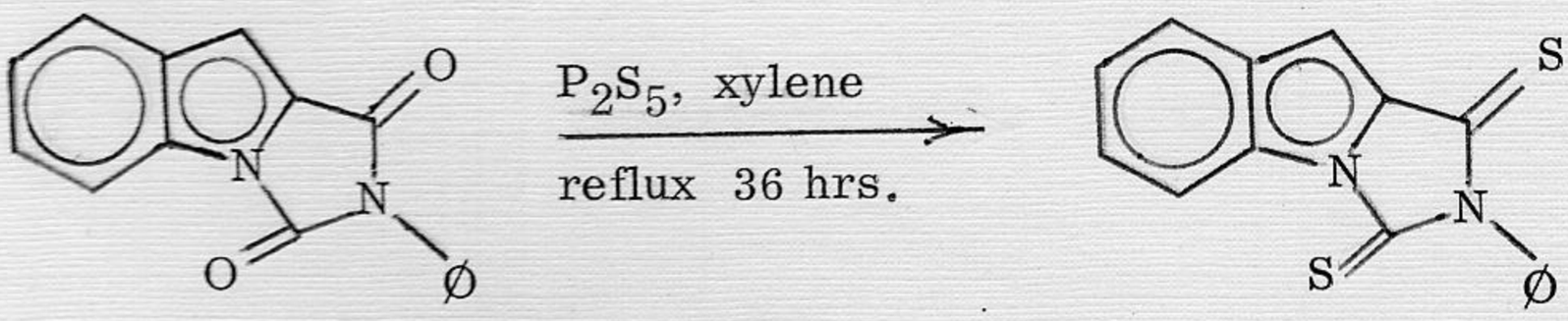


Treatment with phosphorous pentasulfide of the hydantoin VI results in the formation of a mono-and a dithiohydantoin. Exactly as in the case of the pyrrole derivatives, the carbonyl group attached to the 2-position of the indole ring is significantly more reactive than the carbonyl attached to the nitrogen atom.[16]



VII



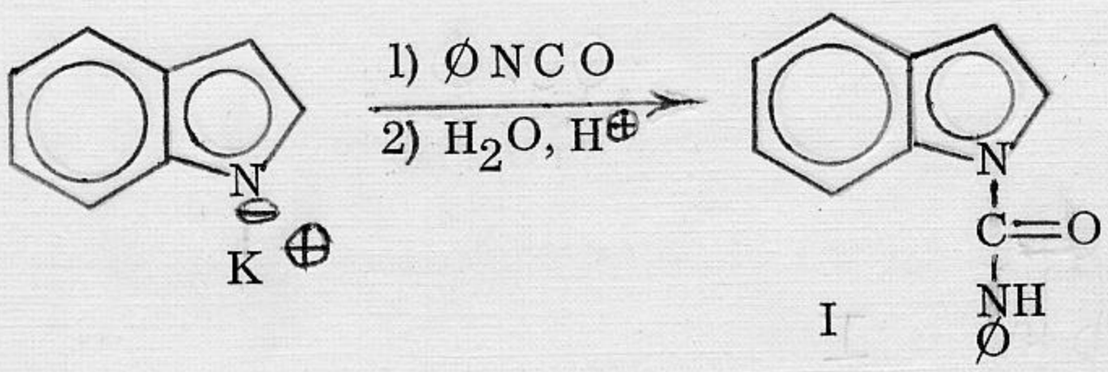
VIII

Thus, refluxing of the reactants in dioxane for a relatively short time converts VI into 2-phenylindolo (1, 2-c) -1-thiohydantoin (VII), whereas prolonged refluxing in xylene is necessary for the formation of 2-phenylindolo (1, 2-c) dithiohydantoin (VIII). The structures assigned to these compounds are supported by the results of elemental analysis and the fact that oxidation with hydrogen peroxide converted both thiohydantoins to the hydantoin VI. Further, the infrared spectrum of VII shows a carbonyl absorption at 1775 $cm^{-1}$, whereas that of VIII has no absorption band in the carbonyl region.

# EXPERIMENTAL

## 1-Indolecarboxanilide (I)

A. From Indolylpotassium:

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To a solution of 11.7 g. (0.1 mole) of indole in 50 ml. of dry tetrahydrofuran, 3.9 g. (0.1 g - atom) of potassium was added, and the mixture was refluxed with stirring until all the metal had reacted. Then 11.9 g. (0.1 mole) of phenyl isocyanate, dissolved in 50 ml. of dry tetrahydrofuran, was added dropwise and the mixture was stirred for 24 hrs. The solvent was removed by distillation under reduced pressure and the resulting thick residue was dissolved in 100 ml. of water. Acidification with dilute hydrochloric acid yielded a precipitate (25.8 g.) m.p. 110 - 115° C. One recrystallization from 95% ethanol and treatment with charcoal gave 12.5 g. (48%) of 1-indolecarboxanilide, m.p. 117 - 119° C. After several recrystallizations the m.p. was constant at 123 - 123.5° C.

Analysis: Calcd. for $C_{15}H_{12}N_2O$ :

C, 76.25; H, 5.12; N, 11.86;

Found: C, 76.38; H, 5.13; N, 11.96.

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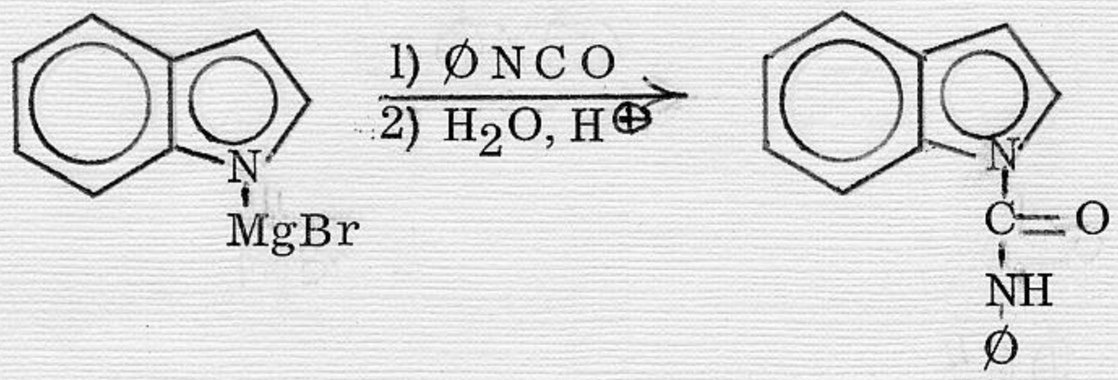
B. From Indolylmagnesium Bromide:




To a solution of ethylmagnesium bromide, prepared from 2.4 g. (0.1 g - atom) of magnesium and 13.1 (0.12 mole) of ethyl bromide in 100 ml. of dry tetrahydrofuran, was added dropwise 11.7 g. of indole dissolved in 50 ml. of tetrahydrofuran. This was followed by the gradual introduction of a solution of 10.8 g. (0.09 mole) of phenyl isocyanate in 50 ml. of tetrahydrofuran. After the resulting mixture had been stirred at room temperature for 17 hrs., it was hydrolyzed by the addition of a solution of 11 g. of ammonium chloride in 50 ml. of water. Separation of the layers, and combination of the organic layer with the ether extract of the aqueous layer, yielded a solution which was dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure. The solid residue (20.7 g.) was recrystallized from methanol to yield 9.1 g. of 1-indolecarboxanilide, m.p. 122.5 - 124.5° C. Dilution of the mother liquor with water yielded a second crop of product, 2.0 g. m.p. 121.5 - 122.5° C. Total yield:58%.

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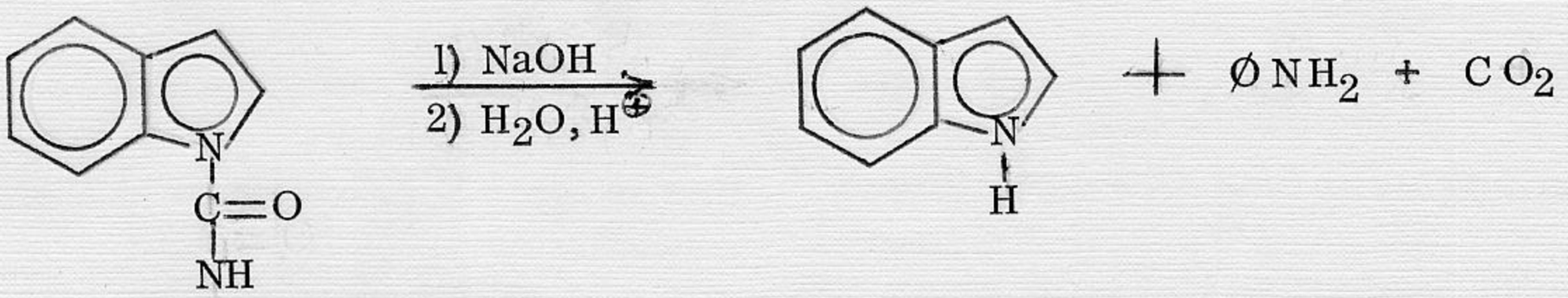
Hydrolysis of 1-Indolecarboxanilide




To a solution of 0.6 g. of (I) in 15 ml. of ethanol was added 1 pellet of potassium hydroxide and 2 ml. of water. The mixture was refluxed for 3 hrs. after which it was cooled and diluted with water. Extraction with ether and gas-liquid partition chromatography showed that the ether solution contained equimolar quantities of indole and aniline.

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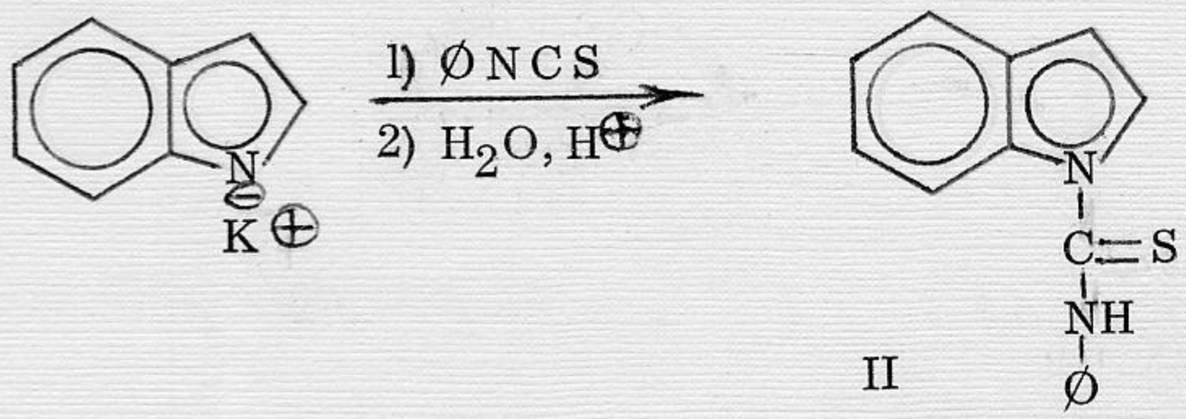
1-Indolethiocarbanilide (II)

A. From Indolylpotassium:




Into a 500 ml. three-necked, round bottomed flask, equipped with a stirrer, condenser and/dropping funnel, was placed a solution of 11.7 g. (0.1 mole) of indole in 50 ml. of tetrahydrofuran. To this solution 3.9 g. (0.1 g - atom) of potassium was added and the mixture was refluxed with stirring. When all the metal had reacted, the reaction mixture was diluted with 50 ml. of tetrahydrofuran, after which a solution of 13.5 g. (0.1 mole)

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of phenyl isothiocyanate in 50 ml. of dry tetrahydrofuran was added dropwise. The resulting mixture was stirred at room temperature for 20 hrs., after which the solvent was removed by distillation under reduced pressure, and the residual thick paste was dissolved in 100 ml. of water. Acidification with cold dilute hydrochloric acid caused the precipitation of a heavy oil, which solidified on cooling. The yield in crude product was 25.2 g., m.p. 115 - 117° C. Recrystallization from ligroin (b.p. 100 - 115°) and treatment with charcoal gave 15 g. of 1-indolethiocarbanilide, m.p. 123 - 126° C. After several recrystallizations the m.p. was constant at 125 - 126.5° C.

Analysis: Calcd. for $C_{15}H_{12}N_2S$:
C, 71.41; H, 4.80; N, 11.11; S, 12.69;

Found: C, 71.57; H, 4.70; N, 11.16; S, 12.73.

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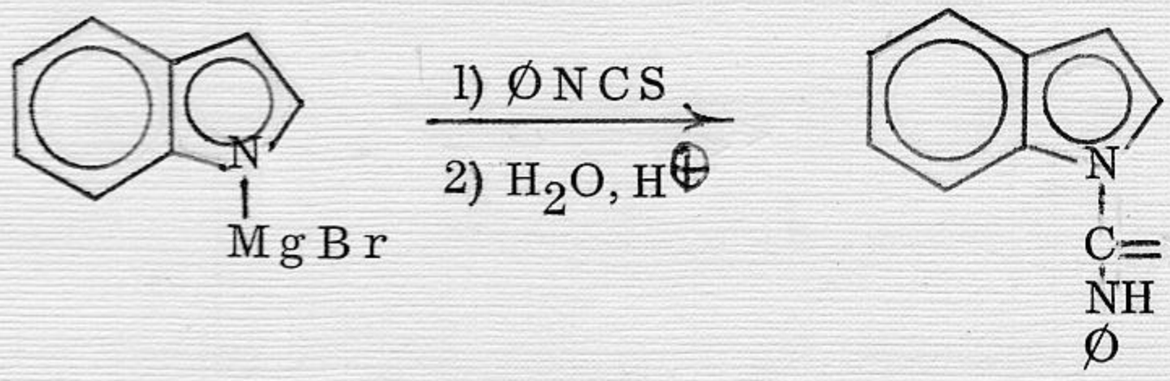
B. From Indolylmagnesium Bromide:




Indolylmagnesium bromide was prepared by the dropwise addition of 11.7 g. (0.1 mole) of indole dissolved in 50 ml. of tetrahydrofuran to a solution of ethylmagnesium bromide made from 13.6 g. (0.125 mole) of ethyl bromide and 2.4 g. (0.1g - atom) of magnesium

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in 150 ml. of tetrahydrofuran. Into the stirred reaction mixture a solution of 13.5 g. (0.1 mole) of phenyl isothiocyanate in 50 ml. of tetrahydrofuran was introduced dropwise over a period of 1 hr. The resulting solution was stirred at room temperature for 36 hrs., and it was hydrolyzed by the addition of 10.7 g. (0.2 mole) of ammonium chloride dissolved in 100 ml. of water. After separation of the layers and extraction of the aqueous layer with ether, the combined organic layers were treated with decolorizing charcoal and dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure to yield 23 g. of crude product. Recrystallization from ligroin (b.p. 100 - 115°) gave 13.5 g. (57%) of 1-indolethiocarbanilide, m.p. 125 - 126.5° C.

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Oxidation of 1-Indolethiocarbanilide (II) to 1-Indolecarboxanilide (I)

To a solution of 0.5 g. of II in 12 ml. of 95% ethanol were added four pellets of potassium hydroxide dissolved in 2 ml. of water. The resulting solution was cooled in an ice-bath, 1 ml. of hydrogen peroxide (30%) was introduced dropwise with swirling, and the mixture was left to stand in the ice-bath for one-half hour. Dilution with 100 ml. of water and acidification yielded 0.4 g. of a solid, m.p. 120-121, the infrared spectrum of which was identical with that of I. After recrystallization from 95% ethanol, the m.p. was 123 - 123.5°, undepressed on admixture with authentic 1-indolecarboxanilide.

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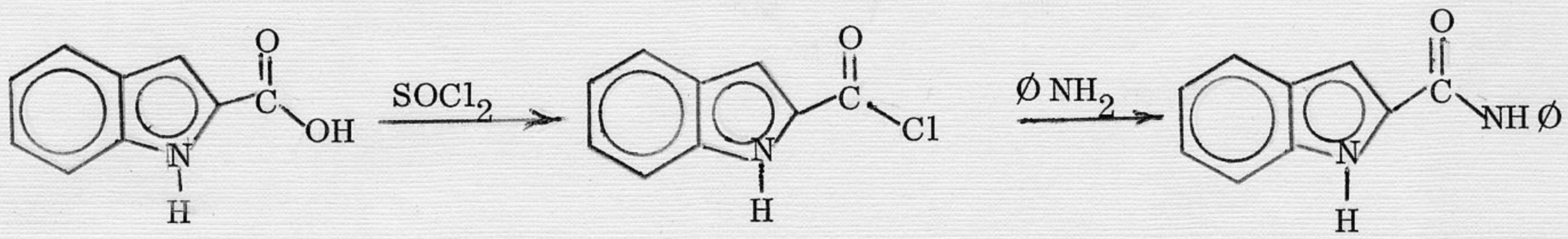
2-Indolecarboxanilide (III)




To 8 g. (0. 05 mole) of 2-indolecarboxylic acid was added 23. 8 g. (0. 2 mole) of thionyl chloride and the mixture was heated at 60 - 70° (bath temperature) for 3 hrs. The excess of thionyl chloride was then removed by distillation under reduced pressure, and the residue was mixed wi th 50 ml. of petroleum ether. Removal of the solvent by distillation under reduced pressure wa s followe d by a new addition of 50 ml. of petroleum ether and evaporation to dryness. The crude acid chloride wa s shaken wi th 200 ml. of dry ether and the resulting mixture wa s filtered into a solution of 9. 3 g. (0. 1 mole) of aniline in 200 ml. of dry ether. The ethereal solution was left to stand for 30 min. then it was filtered, and the precipitate was washed wi th dry ether. The combined ether filtrate and wa shings we re wa shed successively with three 50 ml. portions of dilute hydrochloric acid, two 50 ml. portions of water, 50 ml. of aqueous sodium bicarbonate and, again, 50 ml. of water. Followi ng a drying treatment over anhydrous sodium carbonate, the ether solution was evaporated to dryness. The residue was 7. 5 g. of crude product, m. p. 185 - 190°. Recrystallization from 95% ethanol yielded 4 g. of 2-indolecarboxanilide (III), m. p. 196 - 198°. An analytical sample melted at 198 - 199°.

Analysis: Calcd. for $C_{15}H_{12}N_2O$:

C, 76. 25; H, 5. 12; N, 11. 86;

Found: C, 76. 14; H, 5. 04; N, 11. 91.

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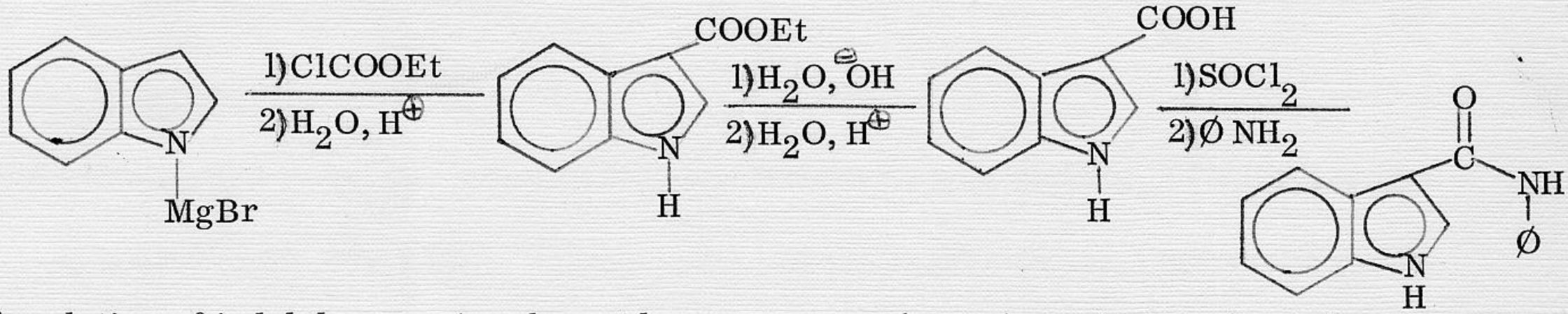
3-Indolecarboxanilide (IV)

a. Ethyl 3-indolecarboxylate[28]




A solution of indolylmagnesium bromide was prepared, as described earlier, from 2.4 g. (0.1 g - atom) of magnesium, 13.1 g. (0.12 mole) of ethyl bromide, and 11.7 g. (0.1 mole) of indole in a total of 200 ml. of ethyl ether. While cooling in a mixture of ice and salt, a solution of 9.8 g. (0.9 mole) of ethyl chloroformate in 50 ml. of ether was introduced dropwise over a period of 30 min. and the cooled reaction mixture was stirred vigorously for an additional hour. Then it was hydrolyzed by the addition of an ice-cold solution of 11 g. (0.2 mole) of ammonium chloride in 100 ml. of water and was worked-up as usual to yield an ether solution which was evaporated to dryness under reduced pressure. The residue was a thick liquid which solidified by treatment with petroleum ether (b.p. 30 - 70°) and cooling. Recrystallization from ligroin (b.p. 110 - 115°) yielded 8 g. of ethyl 3-indolecarboxylate, m.p. 122 - 124 (lit.[28] m.p. 118 - 119°).

b. 3-Indolecarboxylic acid

A mixture of 7 g. (0.04 mole) of ethyl 3-indolecarboxylate in 50 ml. of ethyl alcohol and 10 g. of sodium hydroxide in 30 ml. of water was refluxed for 4 hrs. Cooling and dilution with 100 ml. of water were followed by filtration and washing of the filtrate with ether. The chilled aqueous solution was acidified with glacial acetic acid and the precipitated 3-indolecarboxylic acid was collected by filtration, washed with water, and dried. The yield was 5 g. of essentially pure acid, m.p. 216 - 218° dec. (in a sealed

capillary). (lit.[28] m.p. 218 - 219°).

C. 3-Indolecarboxanilide

A mixture of 4 g. (0.025 mole) of 3-indolecarboxylic acid and 5 g. of thionyl chloride was heated at 80° for 4 hrs. After removal of the excess thionyl chloride at the aspirator, the reaction product was mixed twice with 50 ml. of petroleum ether (b.p. 30 - 70°) which was in each case evaporated to dryness under reduced pressure. The final residue was treated with 200 ml. of ether and the resulting mixture was filtered into a solution of 4.7 g. (0.05 mole) of aniline in 50 ml. of ether. The mixture was left to stand overnight and then it was filtered to yield a solution which was washed successively with dilute HCL, aqueous sodium bicarbonate and water and was evaporated to dryness under reduced pressure. The residue (1.5 g.) was recrystallized from 50% ethanol to give 1 g. of 3-indolecarboxanilide, m.p. 176.5 - 177.5°. Further recrystallization raised the m.p. to 178 - 179°. A mixture with the product of oxidation of 3-indolethiocarbanilide melted at 178.5 - 179.5°, and the infrared spectra of the two products were superimposable.

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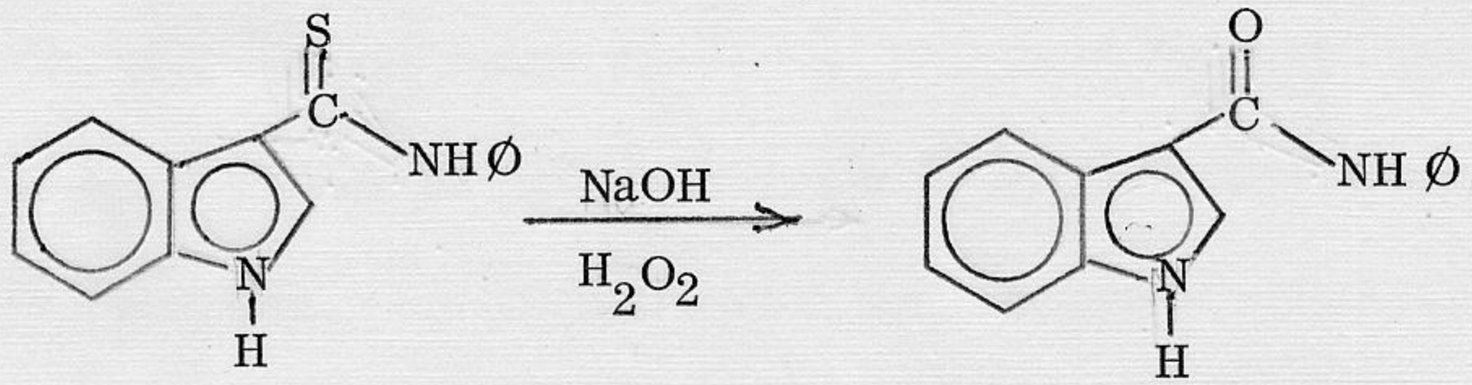
Oxidation of 3-Indolethiocarbanilide (V) to 3-Indolecarboxanilide (IV)




To a hot solution of 0.5 g. of 3-indolethiocarbanilide in 15 ml. of ethyl alcohol was added 7 ml. of hydrogen peroxide (30%) and 3 pellets of sodium hydroxide. After a few moments, a vigorous reaction took place with evolution of gas, probably oxygen. When the evolution of the gas had essentially stopped, the solution was poured into ice-cold water, and the precipitate formed was filtered and dried to yield 0.4 g. of 3-indolecarboxanilide, m.p. 176 - 178°. Recrystallization from 50% ethanol raised the m.p. to 177.5 - 178.5°.

Analysis: Calcd. for $C_{15}H_{12}N_2O$:

C, 76.25; H, 5.12; N, 11.86;

Found: C, 76.05; H, 5.12; N, 11.73

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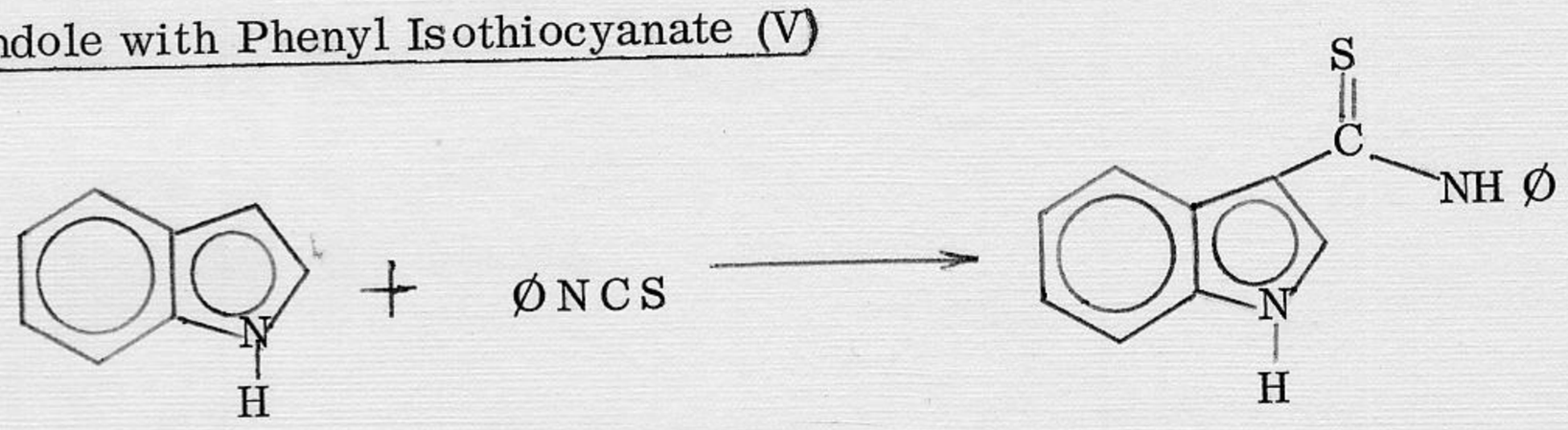
Reaction of Indole with Phenyl Isocyanate

A mixture of 11.7 g. (0.1 mole) of indole and 11.9 g. (0.1 mole) of phenyl isocyanate, protected from moisture with a calcium chloride tube, solidified when left to stand overnight. Washing of the product with petroleum ether yielded 17.7 g. of a solid, m.p. 223 - 226°. The purification of it presented difficulty, because a suitable solvent for recrystallization could not be found. Recrystallization from ethanol under reflux conditions gave a solid m.p. 226 - 231°. The results of the elemental analysis of two samples did not agree, neither did they correspond to any reasonable structure. The nature of this product needs further investigation.

Reaction of Indole with Phenyl Isothiocyanate (V)




A mixture of 11.7 g. (0.1 mole) of indole and 13.5 g. (0.1 mole) of phenyl isothiocyanate was placed into a 50 ml. round-bottomed flask, equipped with a calcium chloride drying tube, and was heated at 80 - 90° for 8 days. The resulting dark paste was refluxed with 100 ml. of ligroin (b.p. 100 - 115°). Filtration and evaporation of the hot solution yielded 0.5 g. of white crystals which, after recrystallization from 95% ethanol, showed a m.p. of 155 - 156°. This material was identified as N,N'-diphenyl-thiourea on the basis of its infrared spectrum and the mixture melting point with an

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authentic sample.

The solid residue was recrystallized from 95% ethanol to give 12.7 g. (50%) of brownish crystals, m.p. 180 - 185°, tentatively identified as 3-indolethiocarbanilide. An analytical sample melted at 188 - 189°C.

Analysis: Calcd. for $C_{15}H_{12}N_2S$:

C, 71.41; H, 4.80; N, 11.11; S, 12.69;

Found: C, 71.53; H, 4.85; N, 10.97; S, 12.83

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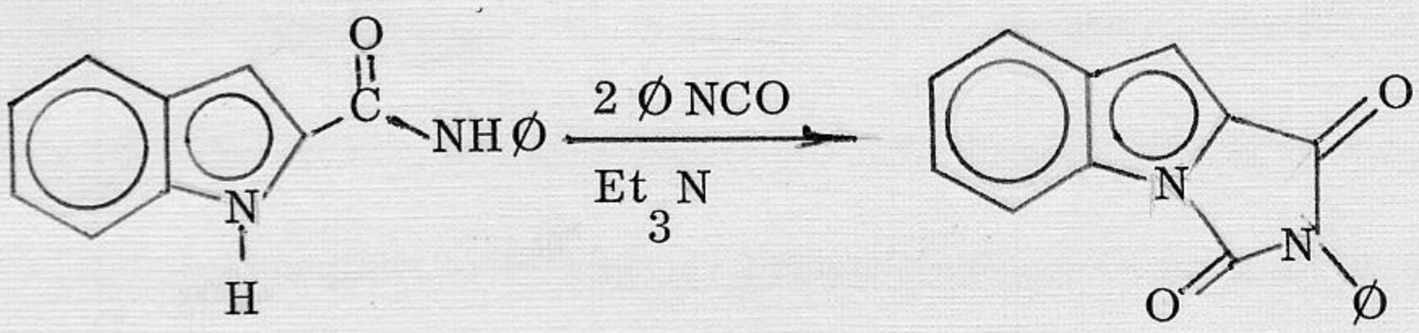
2-Phenylindolo (1,2-c) Hydantoin (VI)

A. From 2-indolecarboxanilide.




A mixture of 1 g. (0.0042 mole) of 2-indolecarboxanilide, 1 g. (0.0084 mole) of phenyl-isocyanate and 3 ml. of triethylamine was heated at 70 - 80° for 18 - 20 hrs. The resulting solid was washed with petroleum ether, and mixed with 100 ml. of chloroform. Filtration yielded a solid (0.4 g.) identified as N,N'-diphenylurea on the basis of its infrared spectrum and the mixture melting point with an authentic sample. Evaporation of the filtrate to dryness gave 0.8 g. of crude 2-phenylindolo (1, 2-c) hydantoin, m.p. 195 - 200°. After one recrystallization from 95% ethanol there was obtained 0.5 g. of the pure compound

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m.p. 212 - 213° C.

Analysis: Calcd. for $C_{16}H_{10}N_2O_2$:

C, 73.27; H, 3.84; N, 10.68;

Found: C, 73.46; H, 3.78; N, 10.71;

B. From Ethyl 2-Indolecarboxylate

A solution of 4 g. of 2-indolecarboxylic acid and 10 ml. of conc. sulfuric acid in 90 ml. of absolute ethanol was refluxed for 4 - 5 hrs. The reaction mixture was cooled, diluted with 100 ml. of water and filtered. The precipitate was washed with aqueous sodium bicarbonate, and dried to yield 4.3 g. of ethyl 2-indolecarboxylate, m.p. 122 - 124° (lit.[28] m.p. 125 - 126°C.).

To 1.9 g. (0.01 mole) of the ester was added 2.4 g. (0.02 mole) of phenyl isocyanate followed by 2 ml. of triethylamine, and the mixture was heated gently over a hot plate for about 20 min. During this period the solid first dissolved completely, and then a new precipitate was formed. The resulting mixture was cooled, diluted with petroleum ether (b.p. 30 - 75°), and filtered. Washing of the precipitate with petroleum ether and drying yielded 2.5 g. (90%) of crude 2-phenylindolo (1, 2-c)-hydantoin, m.p. 206-209°.

One recrystallization from 95% ethanol yielded the pure hydantoin m.p. 212 - 213°.

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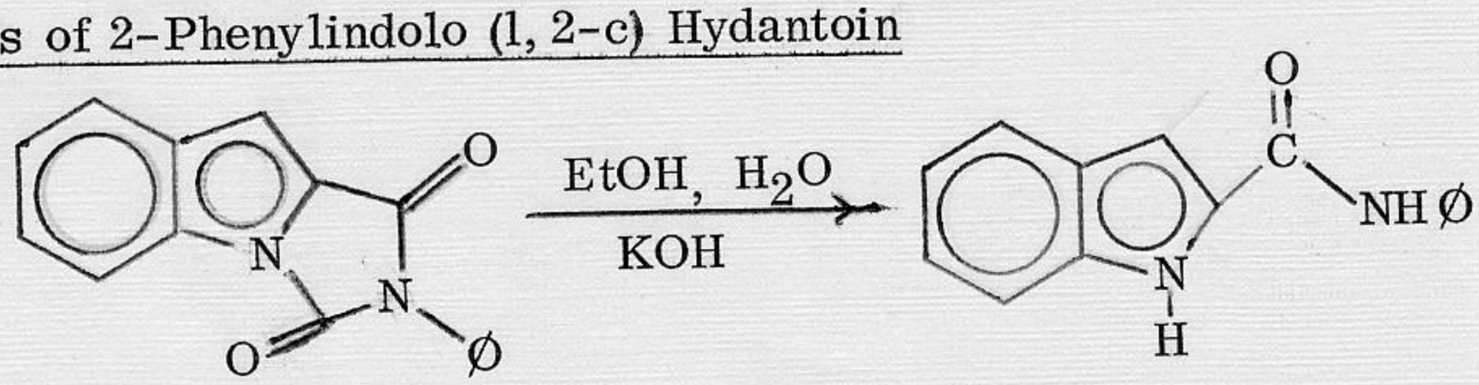
Hydrolysis of 2-Phenylindolo (1, 2-c) Hydantoin




A mixture of 0.2 g. of IV dissolved in 12 ml. of 95% ethanol and 2 pellets of potassium hydroxide dissolved in 1 ml. of water was warmed until a clear solution had been obtained. On cooling and dilution with 75 ml. of water a precipitate was formed which was collected and dried (0.1 g. m.p. 195 - 197°). Its infrared spectrum was identical with that of 2-indolecarboxanilide.

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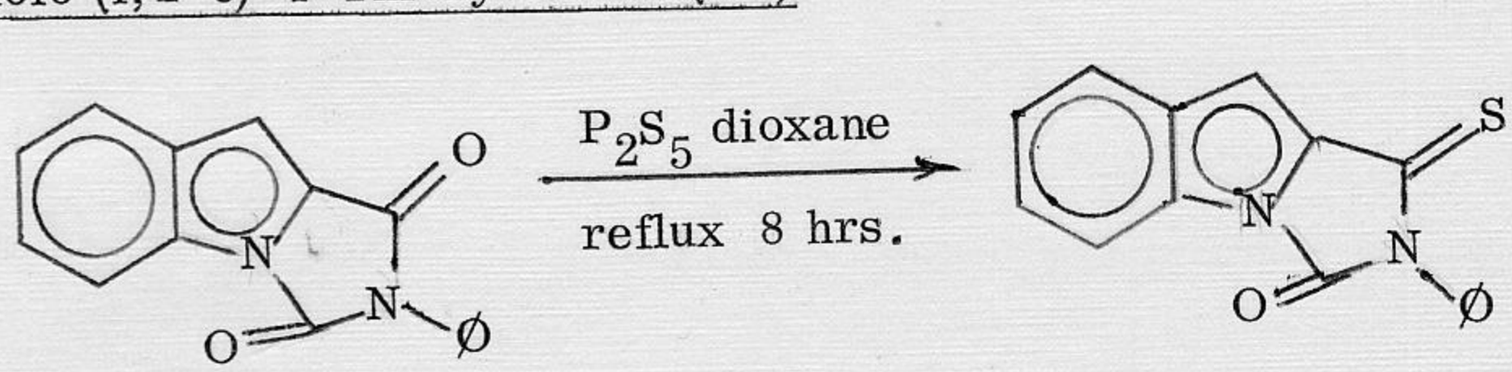
2-Phenylindolo (1, 2-c) -1-Thiohydantoin (VII)



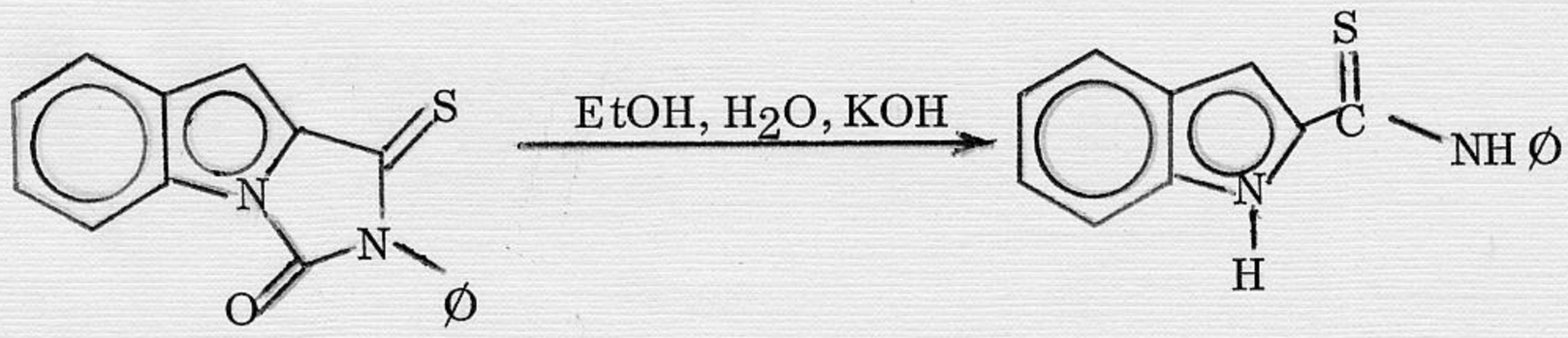

A mixture of 1 g. (0.004 mole) of IV, 30 ml. dioxane and 2 g. of phosphorous pentasulfide was refluxed for 4 hrs. Then a further 2 g. of phosphorous pentasulfide was added and the refluxing was continued for an additional 4 hrs. Filtration of the hot solution and removal of the dioxane by distillation under reduced pressure led to a dark residue. This was refluxed with ligroin (b.p. 100 - 115°) to yield a solution, evaporation of which gave 0.6 g. of crude 2-phenylindolo (1, 2-c)-1-thiohydantoin, m.p. 168-173°. Recrystallization from 95% ethanol raised the m.p. of the product (0.4 g.) to 178 - 180°. The melting point of an analytical sample was 182 - 183° C.

Analysis: Calcd. for $C_{16}H_{10}SN_2O$:

C, 69.06; H, 3.62; S, 11.50; N, 10.07;

Found: C, 69.20; H, 3.51; S, 11.48; N, 10.08

Hydrolysis of 2-Phenylindolo (1, 2-c)-1-Thiohydantoin (VII)




A mixture of 0.2 g. of V dissolved in 8 ml. of 95% ethanol and 2 pellets of potassium hydroxide dissolved in 1 ml. of water was warmed until a clear solution had been obtained. Cooling and dilution with 75 ml. of water, followed by acidification with dilute hydrochloric acid formed a precipitate which was collected and dried (0.1 g. m.p. 161 - 163°). After recrystallization from 95% ethanol the m.p. was constant at 162 - 163°. This compound is assumed to be the 2-indolethiocarbanilide, but its available amount was insufficient for analysis.

Oxidation of 2-Phenylindolo (1, 2-c)-1-Thiohydantoin (VII) to 2-Phenylindolo (1, 2-c) Hydantoin (VI).

A mixture of 0.3 g. of V, 3-4 ml. of acetic acid, 0.3 g. of sodium acetate trihydrate, and 2 ml. of hydrogen peroxide (30%) was stirred at room temperature for 24 hrs. Then a further 2 ml. of hydrogen peroxide was added and the stirring was continued for 24 hrs. more. Addition of another 2 ml. of hydrogen peroxide with further stirring for 24 hrs. changed the orange-red color of the mixture to very light yellow. Dilution with water and filtration yielded a precipitate which was washed with water and dried. The crude product was 0.12 g., m.p. 205 - 209°, and its infrared spectrum was identical with that of 2-phenylindolo (1, 2-c)-hydantoin.

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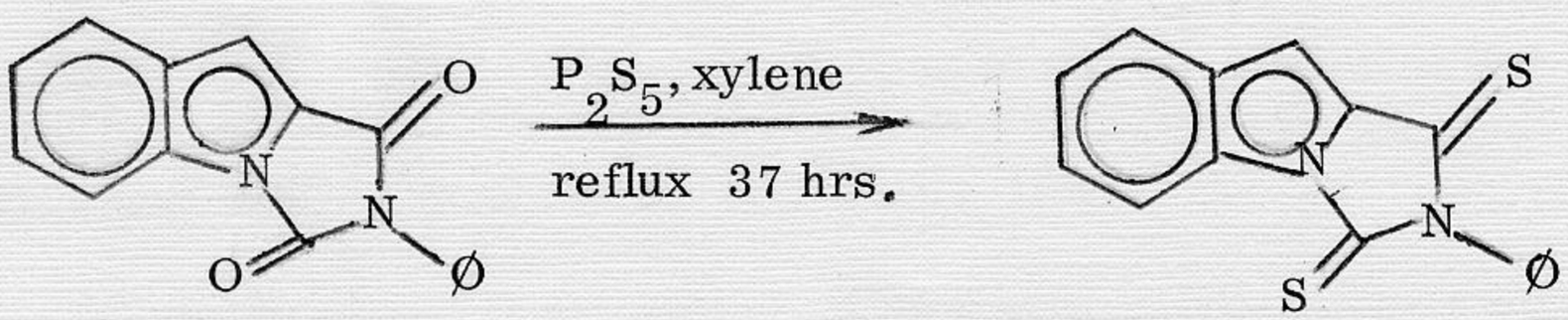
2-Phenylindolo (1, 2-c) Dithiohydantoin (VIII)




A mixture of 0.6 g. (0.002 mole) of IV, 2.4 g. of phosphorous pentasulfide, and 18 ml. of xylene was refluxed for 37 hrs. The solvent was removed by distillation under vacuum and the resulting residue was refluxed with ligroui (b.p. 100 - 115°) for 10 min. Evaporation of the extract yielded 0.57 g. of a solid m.p. 185 - 188°. One recrystallization from 95% ethanol yielded 0.2 g. of 2-phenylindolo (1, 2-c)dithiohydantoin, m.p. 191-195°. Subsequent recrystallization raised the m.p. to 195 - 196°.

Analysis: Calcd. for $C_{16}H_{10}S_2N_2$:

C, 65.30; H, 3.43; S, 21.75; N, 9.52;

Found: C, 65.36; H, 3.41; S, 21.61; N, 9.35

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Oxidation of 2-Phenylindolo (1, 2-c)dithiohydantoin (VIII) to 2-phenylindolo (1, 2-c) hydantoin (VI).

A mixture of 0.2 g. of VI, 2 ml. of acetic acid, 0.2 g. of sodium acetate trihydrate and 2 ml. of hydrogen peroxide (30%) was stirred for 24 hrs. A further 4 ml. of hydrogen peroxide (30%) was added in 2 ml. portions, at 24 hrs. intervals. The mixture was finally diluted with 100 ml. of water and filtered, and the collected precipitate dried to yield 0.1 g. of material, m.p. 208 - 210°, the infrared spectrum of which was identical with that of 2-phenylindolo (1, 2-c)hydantoin.

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