

SYNTHESIS OF INDOLE COMPOUNDS

By

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...

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of the University of Maryland in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy

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My wife, Olive, through her patience and understanding under difficult circumstances, has been a prime mover in the completion of this thesis.

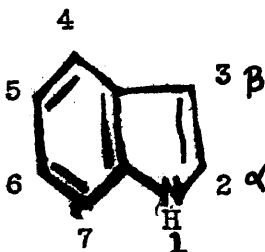
It is a pleasure to acknowledge the kindness of Miss Margaret Beatty in undertaking and completing so well the typing of this thesis.

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INTRODUCTION

Indole, which consists of a benzene ring fused to a pyrrole nucleus, also called 2,3-benzopyrrole, has the structure:



Indole itself occurs in jasmine (1), orange-flower oils (2), and it is found together with some homologues in the fraction of coal-tar which boils between 240 - 260° (3). It can be isolated from this fraction as its solid sodium or potassium derivative, just as pyrrole can be isolated from a lower-boiling fraction.

Indole is a white, crystalline solid, melting at 52°, and boils at 245° with decomposition. The odor of indole is characteristic and resembles that of naphthylamine, however, in dilute solution, and when pure, it has a flower-like odor which makes it a valuable ingredient of natural and synthetic perfumes. Solutions and vapors of indole produce the bright brick-red color characteristic of the pyrrole nucleus when pine shavings moistened with hydrochloric acid and alcohol are brought in contact with them (4).

One of the peculiarities of the chemistry of indole, which it shares with pyrrole, is its failure to exhibit strongly basic proper-

ties. In fact, both pyrrole and indole are weak bases. The explanation for this abnormal basicity lies in the fact that in the case of pyrrole, as well as indole, the free base is more greatly stabilized by resonance than is the positive ion in either case and thus there is a diminished tendency for the free base to unite with a proton (or to exhibit its basic properties) (5). As a matter of fact, it is one of the distinguishing characteristics of indole compounds that they are quickly resinified in the presence of strong acids. As in pyrrole, the imine hydrogen of indole can be replaced by sodium or potassium thus exhibiting the acidic properties of the pyrrole ring.

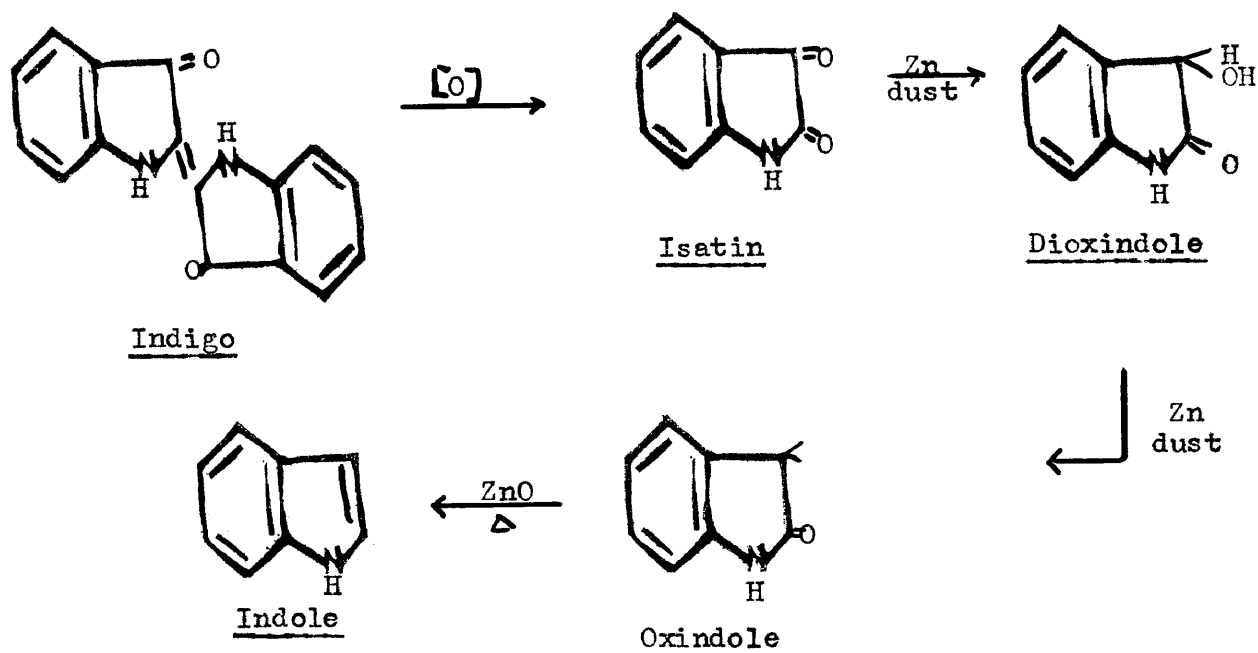
Indole is produced in many bacterial processes, in the feces of dogs and frequently in the feces of man (6). Herter (7) was able to isolate indole from the wood of Celtis reticulosa. Pus formation in the animal body usually produces some indole and undoubtedly this substance is partly responsible for the odor of such discharges (8). Putrefactive changes in milk (9) and vegetable protein (1) results in indole formation. The indole formed in these degradative changes is due to the decomposition of the amino acid typtophane present in the proteins.

During a study of the structure of indigo, Baeyer and Knop (10) reduced isatin and obtained two products $C_8H_7NO_2$ (dioxindole) and C_8H_7NO (oxindole) which they regarded as hydroxy derivatives of C_8H_7N . To this fundamental nucleus, C_8H_7N , of then unknown structure, they gave the name indole to emphasize its relationship to indigo. Baeyer and Esterling (11) continued the studies on indole and in 1869 proposed for it the currently accepted structure given above. This structure was a deduction mainly from the synthesis of indole by the fusion of o-nitrocinnamic acid with iron filings and sodium hydroxide.



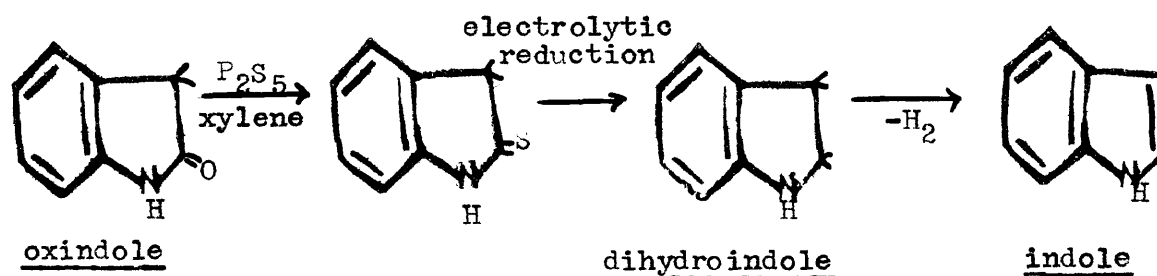
Indole Syntheses --

The resume of synthetic procedures for indole and its homologues presented below is by no means exhaustive, but is rather a comprehensive survey. The first synthesis of indole was reported by Baeyer (12) in which he oxidized indigo to isatin, reduced the isatin to dioxindole with zinc dust, the dioxindole was reduced by the zinc dust to oxindole, and the oxindole was reduced to indole by passing its vapors over hot zinc oxide.



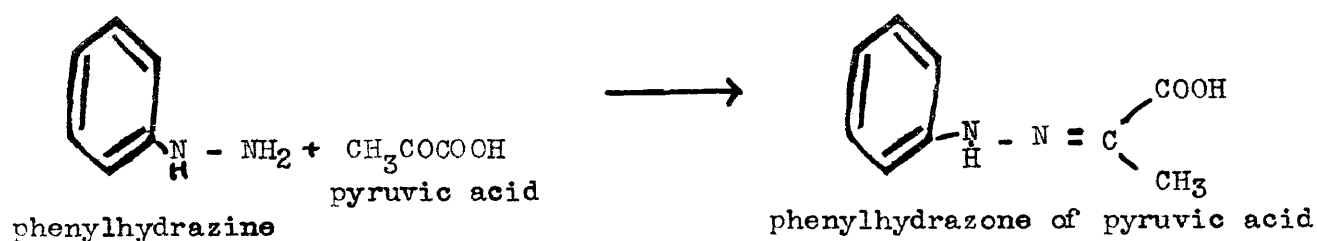
Vorländer and Apelt (13) were able to reduce indoxyl to indole using sodium amalgam or zinc dust and alkali and a United States patent was issued for the same reduction performed catalytically (14). It was also found possible to convert oxindole through its sulfur analog to

dihydroindole which could be dehydrogenated to indole (14).

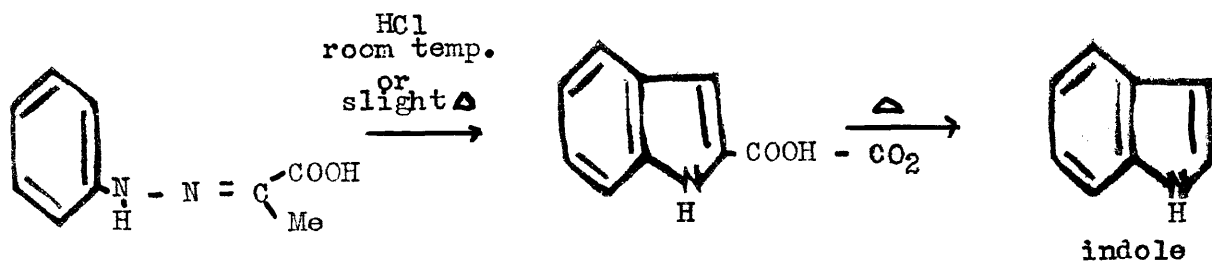


Small yields of indole have been reported in the synthetic preparation of indigo from phenylglycine (16, 17). The alkaline melt of indoxyllic acid when treated with sodium amalgam or zinc dust at 600 to 700 yielded indole (18).

The syntheses which have been considered above are chiefly of historical significance and are not general methods in the synthesis of indole compounds. In 1883, Fischer and Jourdan (19) made a study of the properties of the phenylhydrazones of pyruvic acid and discovered

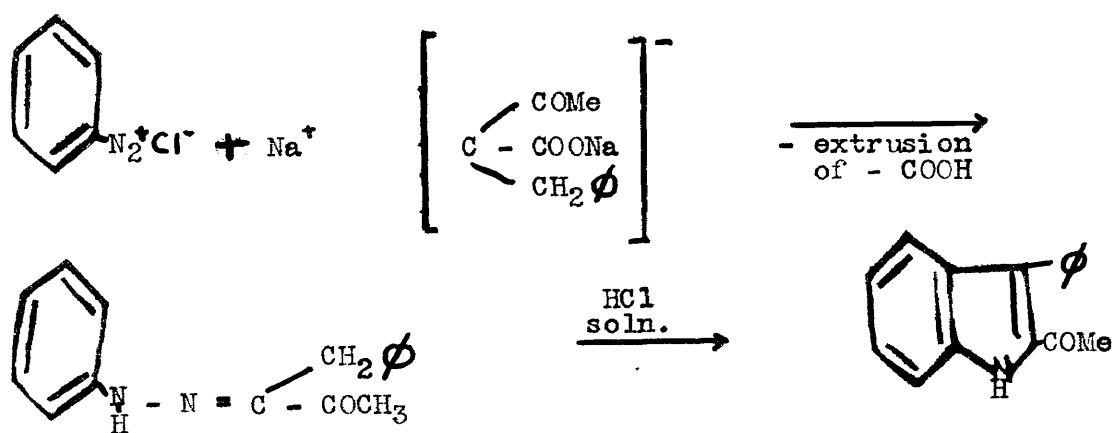


that with acids (alcoholic hydrochloric acid, sulfuric acid and zinc chloride) ammonia was eliminated, ring closure occurred, and 2-indole carboxylic acid resulted. This acid on decarboxylation yielded indole. In the years since its discovery this method has become one of the most

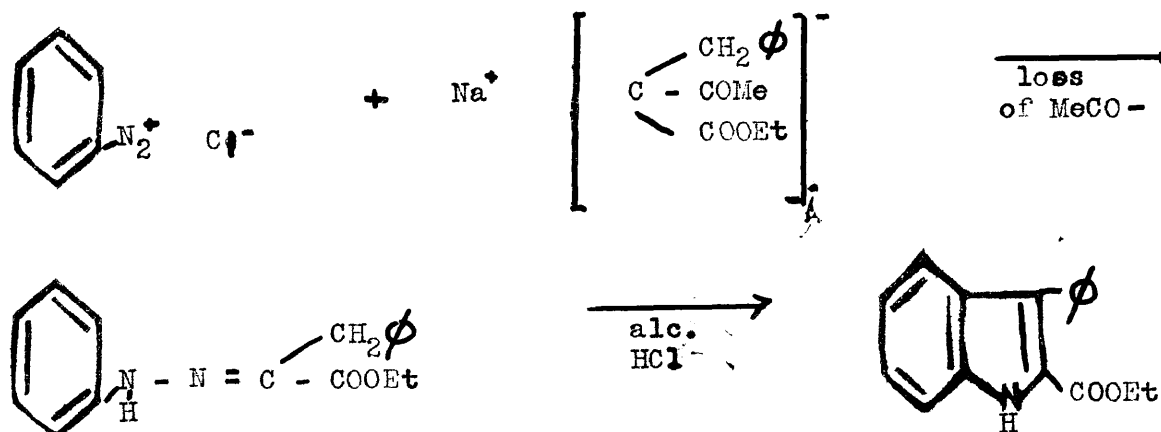


versatile for the preparation of indoles and, in honor of its discoverer, is called the Fischer Indole Synthesis.

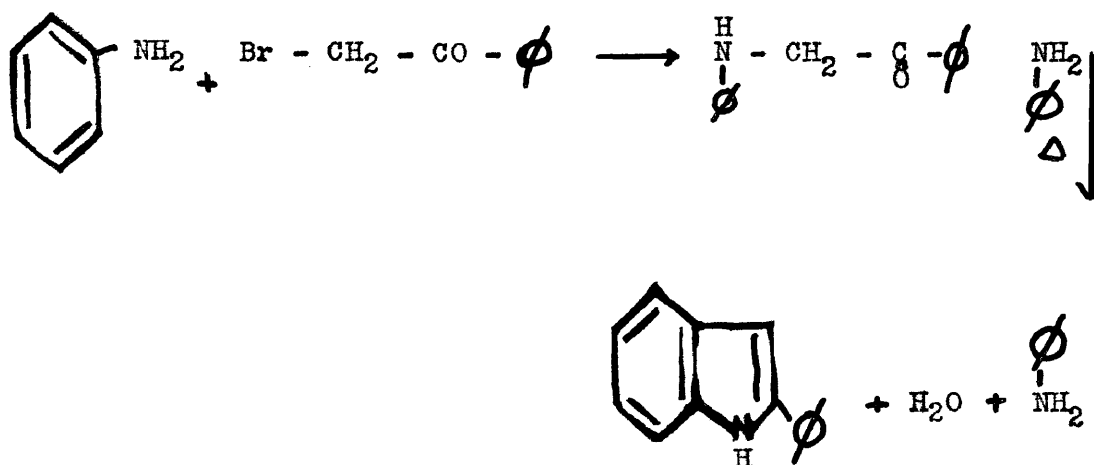
The Japp-Klingemann synthesis (19, 20) provides a means of preparing the hydrazone intermediates required in the Fischer synthesis and serves, in effect, to make the Fischer reaction even more general. This procedure makes it possible to obtain phenylhydrazones not otherwise attainable by the use of phenyldiazonium chloride and the sodium salt of a keto acid by extrusion of the carboxyl group. If the carboxyl group is protected by esterification the acetyl group is lost:



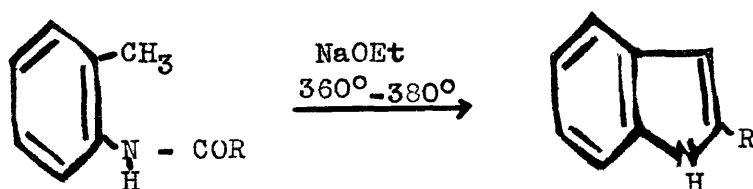
or carboxyl protected by esterification



Indoles may be synthesized by the reaction of arylamines with α -halogenated ketones (21, 22, 23). The first product of the reaction, which is usually not isolated, is a phenacyl aniline. The reaction is completed by a second molecule of the aniline. In place of the ketone, Berlinerblau (24, 25, 26) used α, β -dichloroethyl ether and similar compounds which dissociate in situ to chloroacetaldehyde.

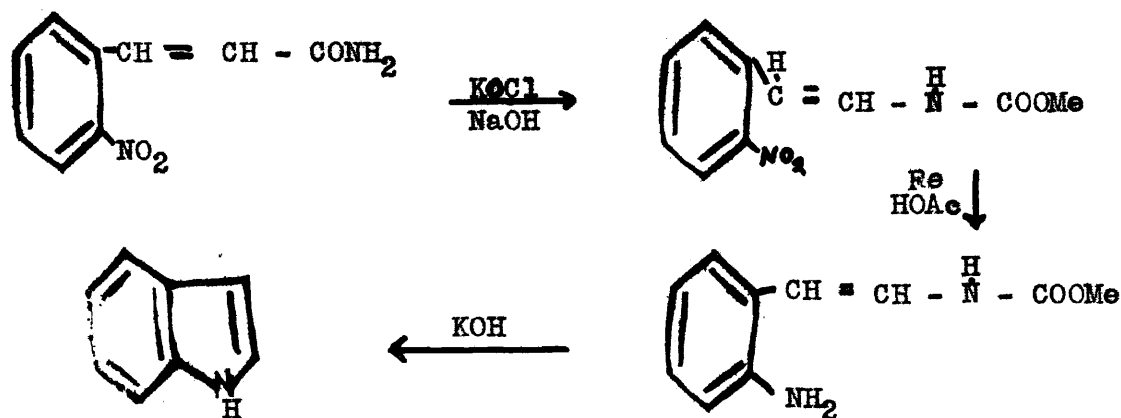


Madelung's synthesis (27, 28, 29) provides a useful general route to the indoles which consists of an intramolecular Claisen condensation of an acyl or aroyl derivative of an *o*-toluidine.

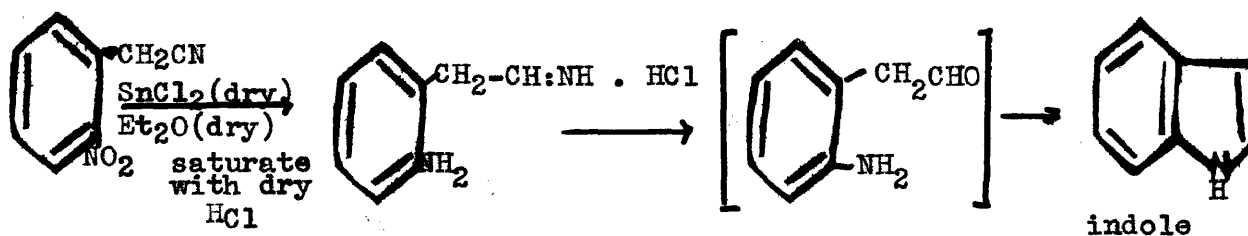


There are many other examples of indole formation by ring closure of an alkyl group ortho to a nitro group, an amino group, or a substituted amino group. To mention a few, Verley (28) treated *N*-aldehyde-*o*-toluidine with sodamide and obtained indole. Mauthner and Suida (30) obtained indole by distilling oxal-*o*-toluic acid with zinc dust or by dry distillation of its barium salt.

A number of methods for the synthesis of indoles are based on the use of o-substituted cinnamic acids, styrenes, and stilbenes. Lipp (31) synthesized indole from o-aminochlorostyrene using sodium ethoxide as a condensing agent. o-Nitrocinnamamide was used by Weermann (32, 33, 34) for the synthesis of indole. The same author also produced



indole by the reduction of o-nitrophenylacetaldehyde (33). Reissert (35) and later Perkin (36) and Polyakov (37) reduced o-nitrophenylpyruvic acid to 2-indole carboxylic acid which was decarboxylated to indole. Although these reductions of o-nitrophenylpyruvic acid were performed chemically, Amin (38) was recently able to obtain the same cyclization to 2-indole carboxylic acid by catalytic reduction using palladinized charcoal. Stephen (39) was able to produce a ring closure to indole which is of particular interest to this thesis. He reduced o-nitrophenylacetonitrile through its imino-chloride into o-aminophenylacetaldehyde which cyclized to indole. The reducing agent is the stannous chloride-dry hydrogen chloride used by Stephen for converting nitriles to their corresponding aldehydes.

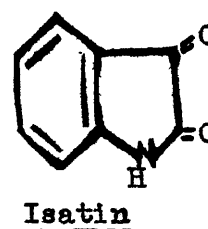
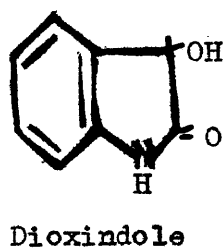
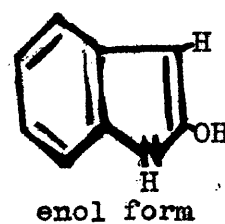
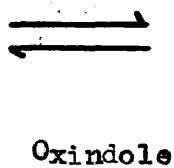
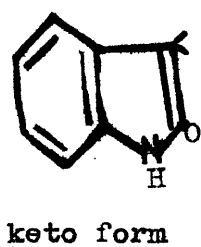
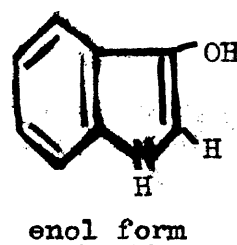
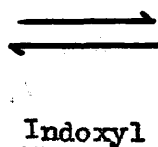
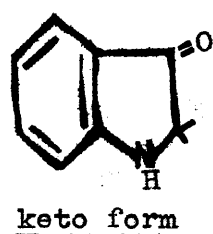


Pyrogenic methods have been employed for the preparation of indole, but, as might be expected, the drastic treatment necessary in these methods usually results in poor yields of indole. To mention a few such methods it is known that the fusion of albumin with potassium hydroxide produces indole (40, 41, 42) and also that acetylene and aniline yield indole when passed over metallic oxide catalysts (43).

Although the chemistry of indole and its derivatives has been the subject of many studies there have been no radically new methods developed for their synthesis. Even at present when it becomes essential to a research project to prepare indole derivatives one or another of the general methods given above is applied.

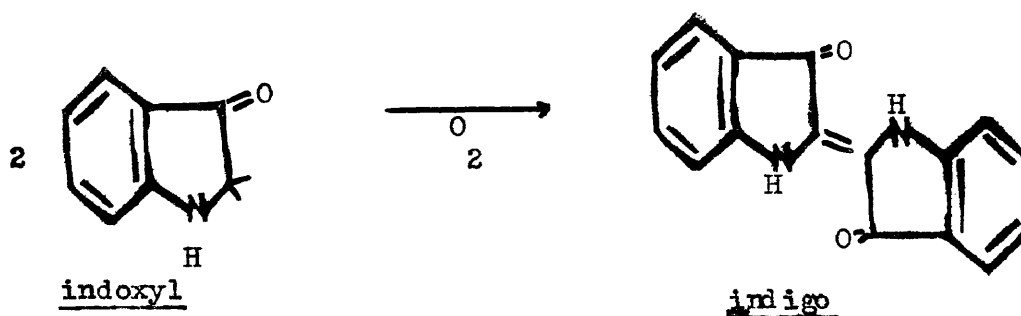
Indoxyl Syntheses --

Since the cyclizations to be studied in this project are those leading to substituted indoxyls, it might be well to survey the synthetic routes to indoxyl. Indoxyl is one of several oxygenated indoles the structures of which are given below:



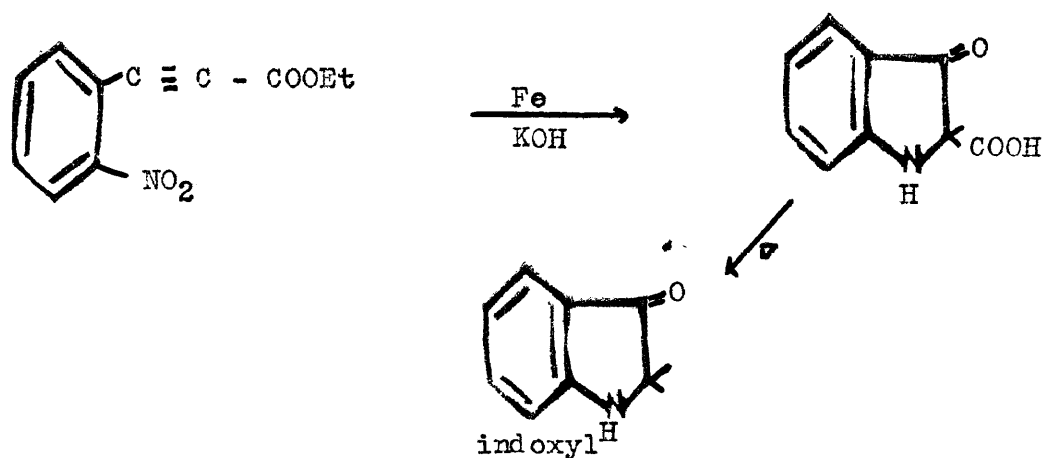
Indoxyl, 3-hydroxyindole, is a yellow solid with a fecal odor and melts at 85°. Solutions of indoxyl in water have a yellowish fluorescence. Indoxyl also possesses the instability characteristic of compounds with the indole nucleus as demonstrated by the ease with which it resinifies. It dissolves in concentrated hydrochloric acid with a red color. The fact that it is soluble in aqueous alkali and that it gives a red color with ferric chloride has been offered as evidence of its phenolic character (4, 44). Indoxyl occurs naturally in the indigo plant glucoside "indican" (45).

Indoxyl is an intermediate in the synthesis of indigo and consequently most methods for the synthesis of indigo are primarily procedures for the preparation of indoxyl. Thus two molecules of indoxyl can be condensed to indigo in the presence of an oxidizing agent such as hydrogen peroxide, ferric chloride, or air. This oxidation goes especially well in alkaline solution.

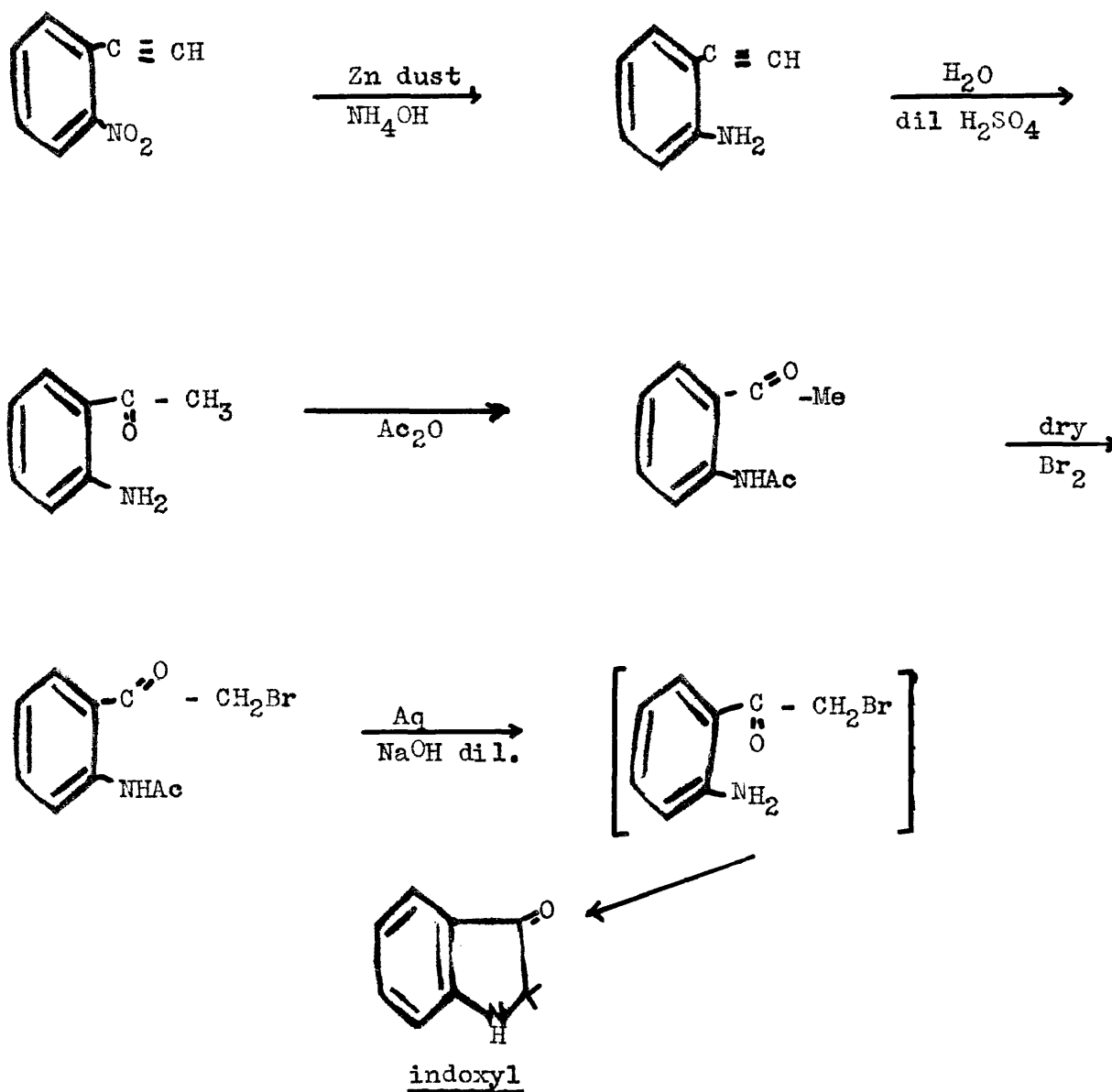


Coincident with its importance as an intermediate in the preparation of indigo has been the development of many methods for the synthesis of indoxyl and it would be well to consider here the more important ones. Baeyer in 1881 (46) used ethyl o-nitrophenylpropionate to prepare indoxyllic acid. He did not isolate the pure indoxyl, but rather he decarboxylated indoxyllic acid and reported a product which rapidly changed to indigo. The same synthesis was repeated by Vorländer and

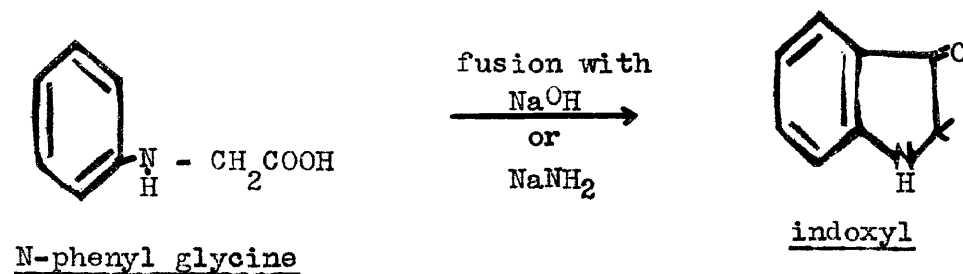
Drescher (47); however, they actually isolated and described the intermediate indoxyl. Baeyer was also responsible for another synthesis of



indoxyl involving the use of o-nitrophenylacetylene (48).

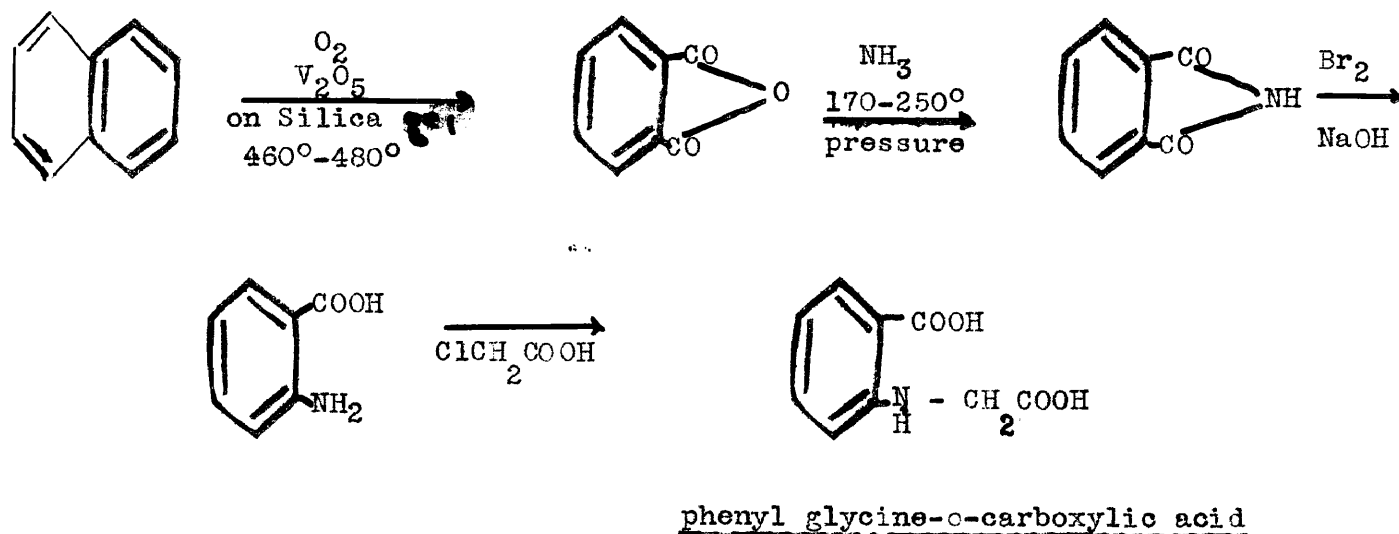


One of the more important commercial methods for the preparation of indoxyl is based on Heumann's discovery in 1890 that *N*-phenylglycine on fusion with alkali will cyclize to indoxyl (49). The glycine compound is heated with dry caustic alkali at 280-290° or, better at a



lower temperature with sodamide (50). The use of sodamide makes the reaction suitable for large-scale industrial operations. There have been a number of modifications of the fusion conditions all designed to temper the drastic conditions. The alkali has been mixed with calcium oxide and other alkaline earth oxides, with alkali cyanides, and also with calcium carbide. The fusion has also been carried out under reduced pressure or in a paraffin melt.

In the present day industrial preparation of indoxyl, phenylglycine-o-carboxylic acid is used (51). This method requires a cheap source of anthranilic acid which is now conveniently available from the catalytic oxidation of naphthalene.



Much less appears in the literature on substituted indoxyls than on the corresponding indoles and there appears to be only slight interest in their preparation. Most substituted indoxyls are prepared by introduction of the desired substituent into the preformed indoxyl or indole nucleus.

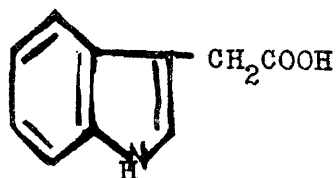
Indole compounds of industrial and medicinal interest --

It may appear that as industrial chemicals the indole compounds are of little importance. However, indigo, which has been called the most important organic dye, has an indole nucleus. Many substituted indigo dyes have been prepared and they constitute among the most important vat dyes. This class of dyes is still much in demand, in spite of their comparatively high price, due to their fastness to light, washing, alkali, and acid (52).

Indole compounds are also of widespread use in the perfume industry. Their dilute solutions are fragrant and many patents have been issued for their synthesis and incorporation into perfumes (53, 54).

From the standpoint of the medicinal chemist, the greatest interest in and importance of the compounds of indole lies, not so much in their industrial significance, but rather in their widespread occurrence in a diversified but highly important group of natural products. Without attempting to review completely the field it should prove interesting to survey the natural products with an indole nucleus.

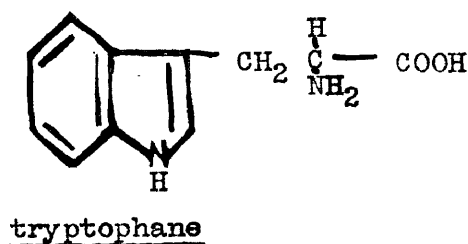
Among the carboxylic acids which contain the indole nucleus, 3-indole acetic acid is of special interest because of its role in the



3-indoleacetic acid

physiology of plants. The process of growth in the growing tip of a plant is regulated by the presence of certain compounds, the growth hormones (55). The unequal distribution in the plant of these hormones are the causes of phototropism and geotropism and differences of concentration of the compounds in the different parts of the shoot make the parts grow at different rates and thus determine the direction of growth.

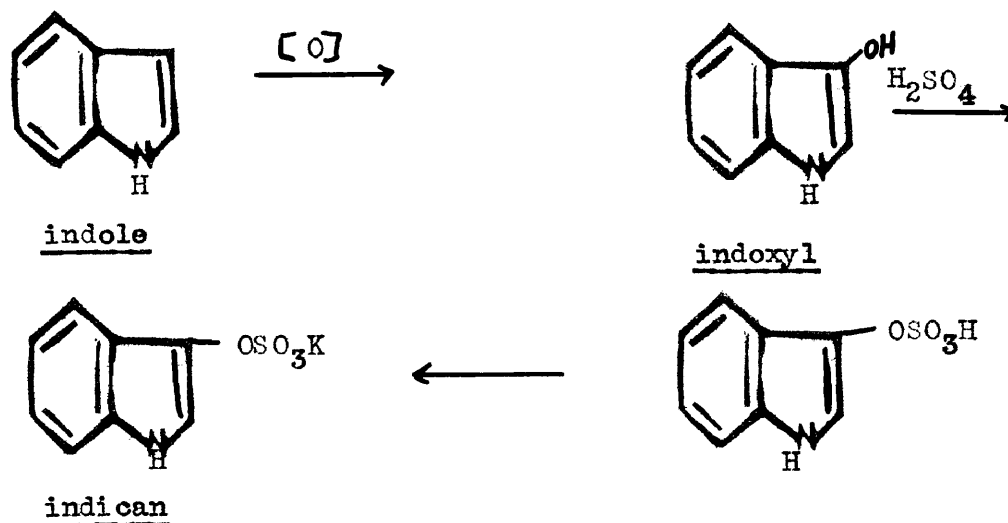
Tryptophane (α -amino- β -5 indole propionic acid) is indispensable and hence an essential amino acid. In experimental animals exclusion



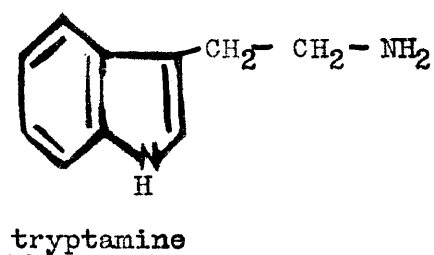
from the diet of any of the essential amino acids causes inhibition of growth and even loss of weight. This amino acid is a constituent of many naturally occurring proteins and serves as an important source of the indole nucleus in biological systems. It is also probable that tryptophane supplies pyrrole nuclei for the synthesis of cellular porphyrins, including the cytochromes and hematin. The exact function of tryptophane in intermediary metabolism is still not clear (56). There is, however, some evidence that tryptophane, at least in the rat, is an important precursor in the synthesis of nicotinic acid (57).

In the process of digestion the undigested protein undergoes putrefactive changes in the large intestine mainly through the action of bacteria. In this putrefaction, tryptophane is broken down to indole and skatole (β -methylindole) which are partly responsible for the odor of feces. Most of these putrefactive products are eliminated in

the feces; however, some are absorbed, partly oxidized, and combined with sulfuric acid to form indican which is eliminated in the urine.



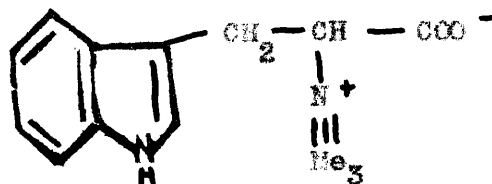
Tryptophane on decarboxylation forms tryptamine which bears the same relationship to the amino acid as does histamine to histidine.



Tryptamine produces only a slight rise in blood pressure and in cold-blooded animals causes vasodilatation. Although it does cause a definite slowing of the pulse rate and mydriasis, it has no effect on respiration (58). When given orally tryptamine is not too toxic, but large doses do cause vomiting. Injections of the amine produce more violent nausea, vomiting, and cramps.

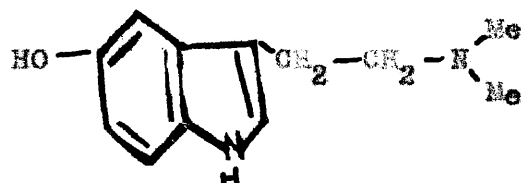
Among the alkaloids there are many which contain an indole nucleus. Hypaphorine is a betaine of tryptophane which occurs in the seeds of Erythrina hypaphorus (59). It is known to produce increased reflex

irritability followed by tetanic convulsions in the frog, but has little action on rats, pigeons, rabbits or guinea pigs (60).

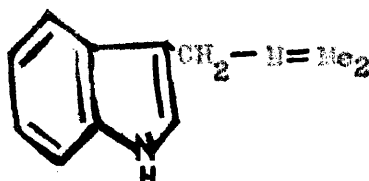


hypaphorine

Bufotenine, which is somewhat similar to hypaphorine in structure, is present in the venomous secretion of the European toad. It has been shown to contain an indole nucleus (61, 62).



Gramine was first detected in barley mutants by von Euler and Hellström (63).

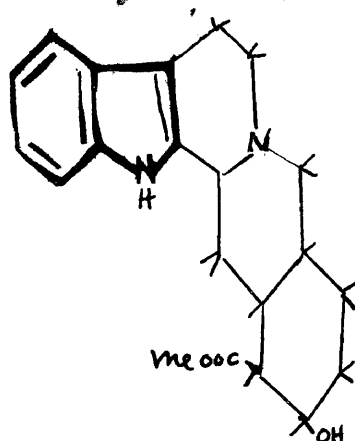


Gramine

In its pharmacological behavior gramine resembles ~~4~~-ephedrine. In small doses gramine raised the blood pressure in dogs, while larger doses cause a fall in blood pressure.

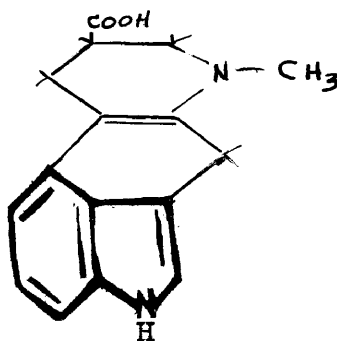
The alkaloids of Yohimbe bark, of which Yohimbine (Quebrachine) is probably the most interesting, are useful in veterinary medicine as

aphrodisiacs (64). The alkaloids contain an indole nucleus and recent studies by Barger and Scholz (65, 66, 67) have given a clearer picture of the constitution of yohimbine.



Yohimbine

Ergot is a parasitic fungus (Claviceps purpurea) which grows on rye and occasionally on other kinds of grain. The crude drug contains a mixture of several complex physiologically active alkaloids among which are ergotinine, ergotoxine, ergotamine, ergotaminine, ergonovine and ergometrinine. Lysergic acid, which is a hydrolytic product of all the ergot alkaloids, contains an indole nucleus and according to Craig and Jacobs has the following structure (68):

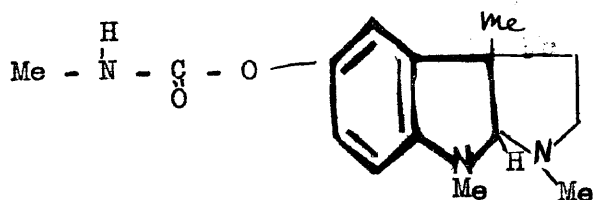


Lysergic acid

Although it has been used for a variety of medicinal purposes, ergot probably finds its greatest use in hastening postpartum expulsion

of the placenta and in the prevention of serious postpartum hemorrhage (69). Recently ergot has been used in the treatment of migraine and severe headaches of a periodic type.

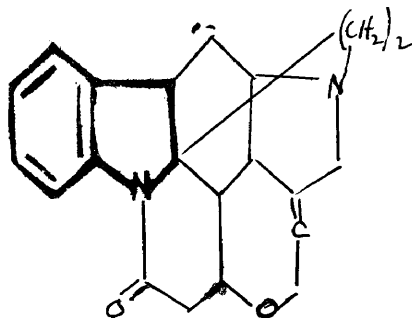
The calabar or ordeal bean contains several alkaloids, the most important being physostigmine or eserine. This alkaloid has been shown to contain an indole nucleus (70, 71).



Physostigmine

Eserine reduces intra-ocular pressure and for this reason it is used therapeutically in the treatment of glaucoma. The drug has also proved useful in reversing mydriasis and in the treatment of myasthenia gravis.

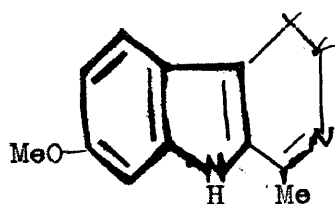
Another important group of alkaloids which contain an indole nucleus are those of Strychnos nux vomica. The two most important alkaloids in this group are strychnine and brucine. The alkaloids of strychnos nux vomica present a complex structural problem and, in spite of intensive and ingenious researches, even at present, it is not yet possible to write a structure for strychnine which is certain in every detail (72).



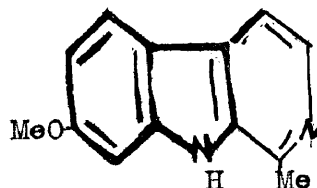
Strychnine

Strychnine is used therapeutically as a tonic and a respiratory stimulant (73) and because of its high toxicity is widely used as a pest exterminator.

The seeds and root of Peganum Harmala contain the harmala group of alkaloids among which are harmaline and harmine.



Harmaline



Harmine

The knowledge of the constitution of the alkaloids was due largely to work by Perkin and Robinson (74). The ring system present is a condensation of benzene, pyrrole, and pyridine nuclei, which Perkin and Robinson have designated as 4-carboline.

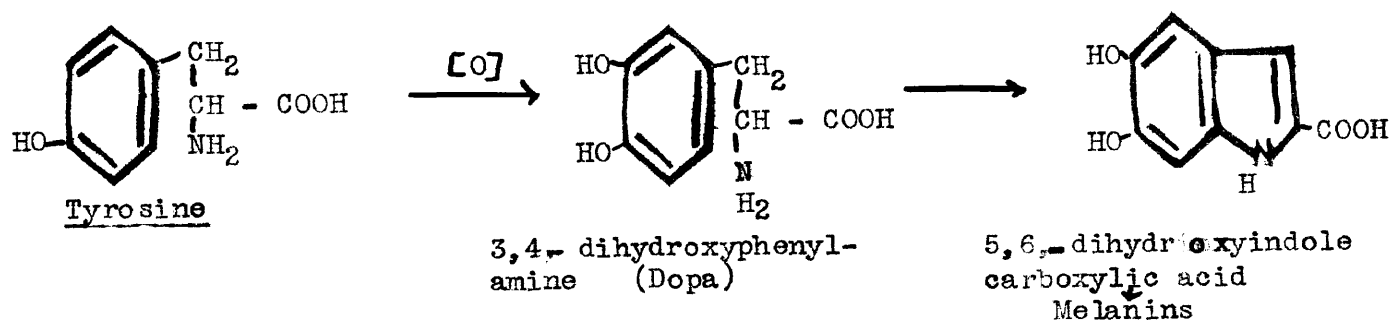
The harmala seeds have been used as anthelmintics and narcotics and Gunn and Marshall (75) claimed they were of value in the treatment of malaria. However, studies with avian malaria have not substantiated these claims (76). In large doses the alkaloids of this group cause tremors and clonic convulsions and poisonous doses eventually produce motor and respiratory paralysis and a lower body temperature (77).

Among pigments commonly occurring in the animal kingdom are the so-called indolic bichromes. These pigments are among the ultimate catabolic degradation products of the amino acids tyrosine, phenylalanine, and tryptophane or related phenolic compounds. In this class of bichromes are included the blue, red, or purple indigoids and the various more complex yellowish, ruddy, brown, or black melanins. Purple secretions

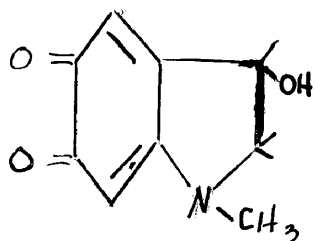
of certain gastropod molluscs, e.g., Nitro marex and purpurus have been known since ancient times, and the 6,6'-dibromoindigo, which constitutes the chief pigment, has been employed as a fabric dye. The red 5, 6 - quinone of 2, 3-dihydroxyindole-2-carboxylic acid constitutes an intermediate link in the formation of melanin and occurs also in the integument of the marine annelid worm, Halla parthenopoea costa, from whence it derives its name hallochrome. It is easily reducible and is considered by Friedheim to be an accessory respiratory catalyst in the oxygen consumption of mammalian erythrocytes.

The melanins are undoubtedly the most widely distributed of all animal pigments and give rise to various shades of black, gray, brown, ruddy, and tyndall blue. Among vertebrates, melanins are encountered not only in dermal and epidermal tissues but also in such integumentary products as hair, feathers, and scales (78).

Tyrosine is oxidized through the enzyme tyrosinase to melanin in the following manner (79):



There has been recent renewal of interest in the oxidation products of epinephrine, in particular, in adrenochrome which contains an indole nucleus. Adrenochrome possesses very interesting physiological activity and for this reason there have been attempts to devise a synthesis of the compound which would prove economically feasible for therapeutic purposes.

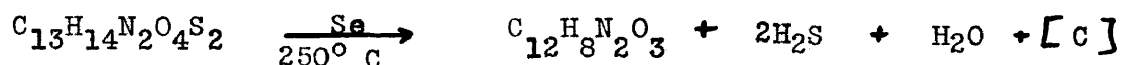


Adrenochrome

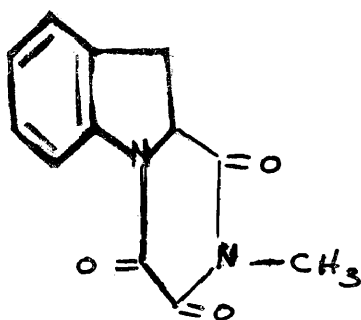
This bright-red crystalline substance when introduced into the body produces a decrease in blood sugar and a lowering of the blood pressure.

Adrenochrome administered along with insulin appears to be a useful adjuvant in the treatment of diabetes. This decrease in blood sugar on the administration of adrenochrome results from the fact that it serves as an oxidation catalyst in carbohydrate metabolism. As to its anti-pressor activity, adrenochrome, from what has been learned of it to date, appears to be the ideal anti-pressor since it neither possesses toxic properties nor does it give rise to secondary products with undesirable physiological activity, nor does it have any depressor effect. When, and if, sufficient adrenochrome is available for widespread experimental and clinical study it may be found to be valuable for use in the treatment of hypertension (80, 81, 82, 83, 84, 85, 86).

Among the antibiotics, gliotoxin which is excreted by Gliocladium fimbriatum has an indole nucleus. It has been studied for its chemical as well as biological properties and on treatment with selenium at 250° C. it underwent the following reaction:



the $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_3$ proved to have the structure:



Although gliotoxin is fungicidal, bacteriostatic, and bactericidal it is highly toxic to animals (87).

The formation of indole from tryptophane by certain microorganisms is the basis of a long used diagnostic test in systematic bacteriology. The presence of indole is indicated by the formation of a red color with acidified alcoholic solution of p-dimethylaminobenzaldehyde (Shrlich's reagent). Positive indole formation serves to differentiate the coli group from other enteric organisms (88).

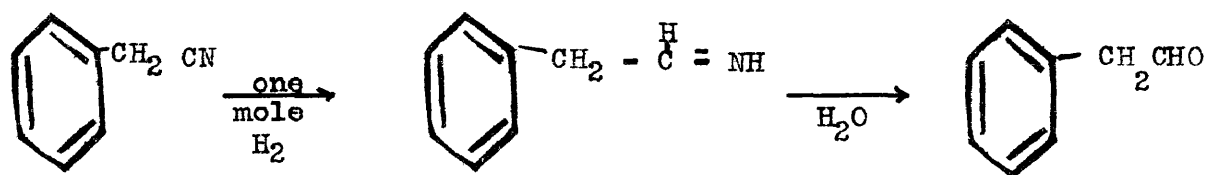
In 1921 Raistrick and Clark found that *Pseudomonas aeruginosa* (89) and other bacteria can decompose the indole ring, and since then their observation has been confirmed with other bacteria (90). Also, Fildes (91) observed that certain bacteria (*Eberthella typhosa* and *Corynebacterium diphtheriae*) which have been shown to require tryptophane for growth are capable of using indole in a concentration as low as 10^{-6} M. From this fact he deduced that tryptophane is synthesized by bacteria from ammonia in stages, one of which is indole.

Another example of the utilization of indole is found in the study by Gray (92). He discovered that, when various soil bacteria (*Pseudomonas indoloxidans* and *Mycobacterium globetrum*) are cultivated in broth or agar containing indole, the indole is oxidized to indigotin. These indole-oxidizing organisms are unable to produce indole from tryptophane, and indole does not serve as a source of energy for the growth.

RESEARCH AIM

Although substances with an indole nucleus are not too numerous, several such compounds are of biological importance, for example, tryptophane, indoleacetic acid, adrenochrome, etc. The instability of the indole nucleus, especially in the presence of acids, limits the usefulness of indole or its derivatives as starting materials. Therefore, it is the aim of this study to use readily available compounds from which the indole nucleus can be formed and which, when definitely accomplished, may point the way to the preparation of substances with probably desirable physiological properties.

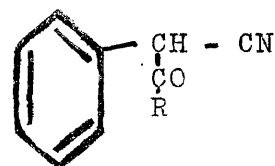
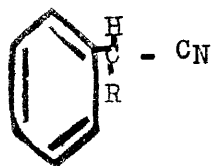
Heyman (93) recently observed that catalytic hydrogenation of benzyl cyanide could be stopped at the imine stage (as indicated by hydrogen uptake). The imine was then hydrolyzed to the corresponding aldehyde.



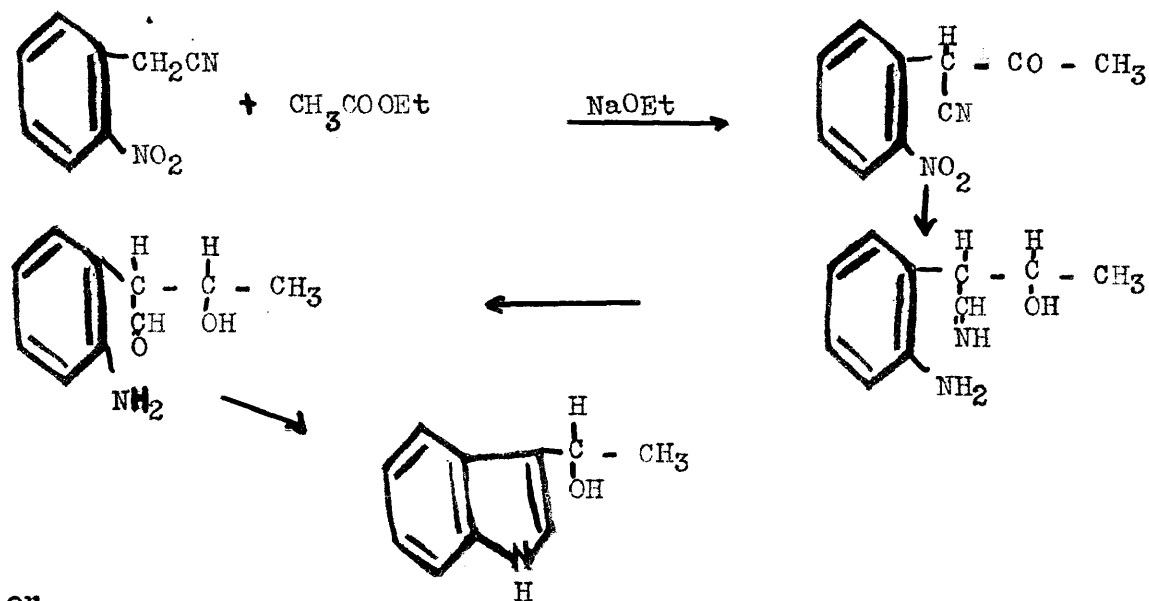
This reaction proved simple to perform and produced an easily isolable product in fair yield. The method was extended to the production, in 60% yields, of hydratropaldehyde from α -methyl phenylacetonitrile.

Stephen (39) was able to produce indole by a reductive cyclization, using $\text{SnCl}_2\text{-HCl}$, from o-nitrophenylacetonitrile. In an attempt to combine the fruits of Stephen's and Heyman's work, it was decided to attempt the preparation of β -substituted indoles from α -substituted o-nitrophenylacetonitriles.

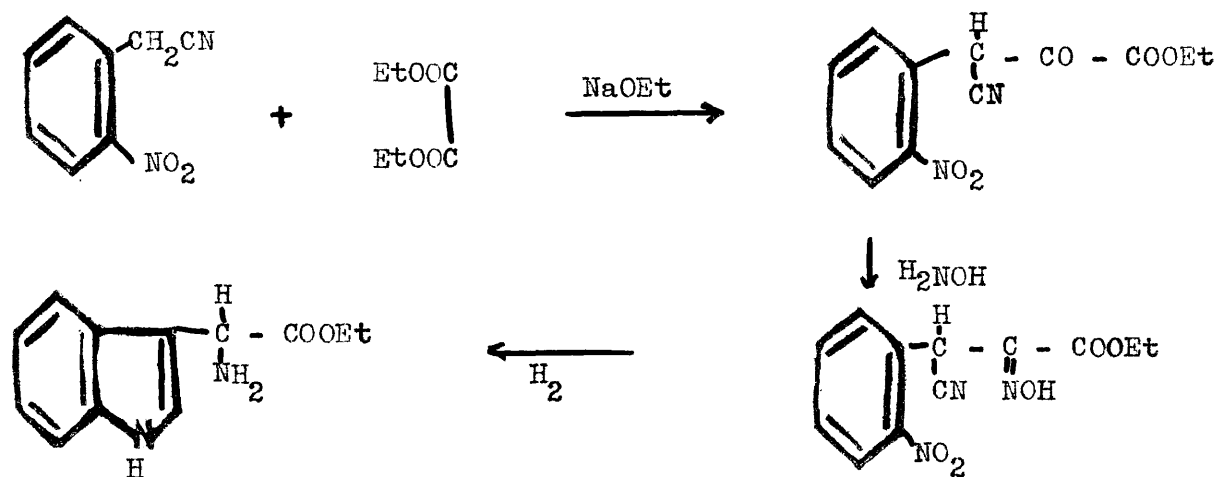
Since the hydrogen atoms on the α -carbon of phenylacetonitrile are reactive and can be replaced easily by alkyl or acyl groups to give compounds of the type (34),



it appeared reasonable to suppose that α -substituted *o*-nitrophenylacetonitriles could be prepared which would yield 3-substituted indoles.

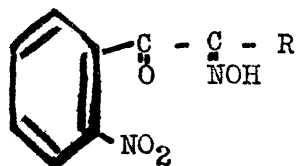


or

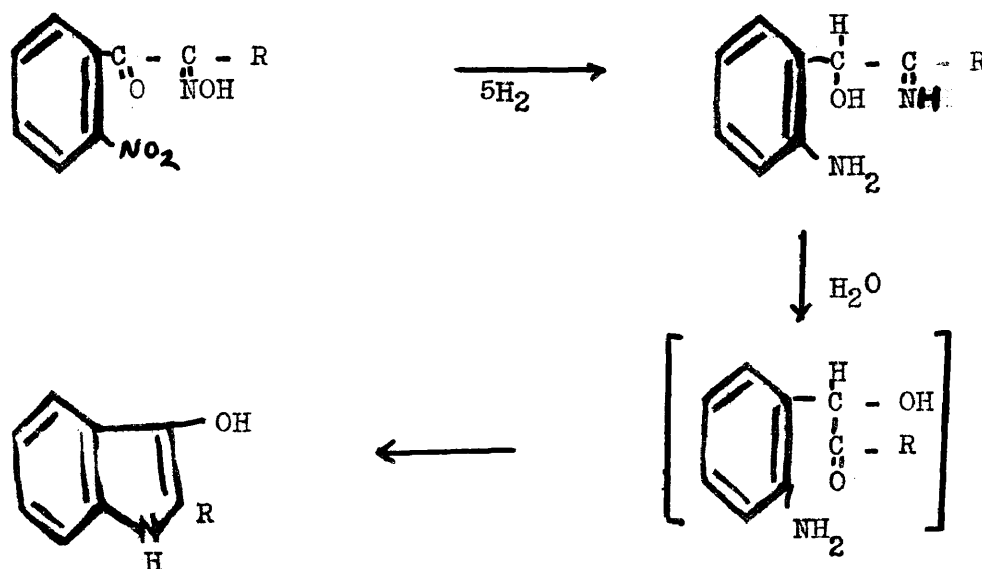


Furthermore, it was conceivable that, if these reactions are successful, suitable modifications may lead to the important amino acid tryptophane.

Another path which appeared interesting and worthy of investigation was the reduction of o-nitroisoxitrosoketones of the type:



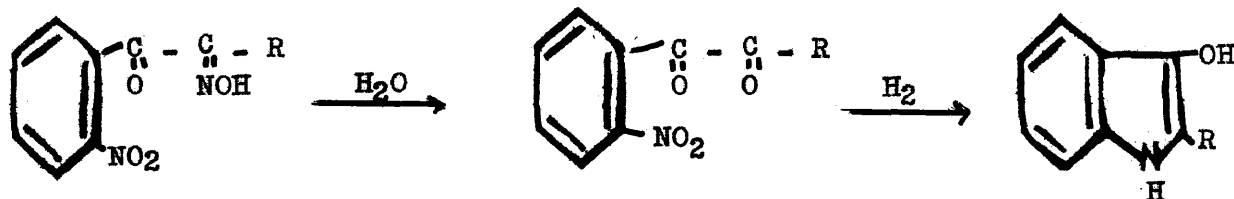
With these compounds it was hoped that hydrogenation would proceed as illustrated:



Although our present knowledge of the indoxyls resulting from reactions of this type do not point to their usefulness in themselves, their close relationship to adrenochrome suggest that they may serve as a convenient route to this interesting compound or its analogues. A synthesis of adrenochrome which proves economically feasible may provide this compound as an anti-pressor in the treatment of hypertension. Substances structurally related

to adrenochrome may also prove to possess similar valuable pharmacological properties.

It was considered worthy of a brief digression to attempt the hydrolysis of the o-nitroisonitrosoketones to their corresponding diketones which upon reduction may yield the same indoxyl nucleus.



Thus it was the ultimate objective of the work undertaken here to study reactions which might yield the secrets of a practicable route to physiologically active compounds with the indole nucleus.

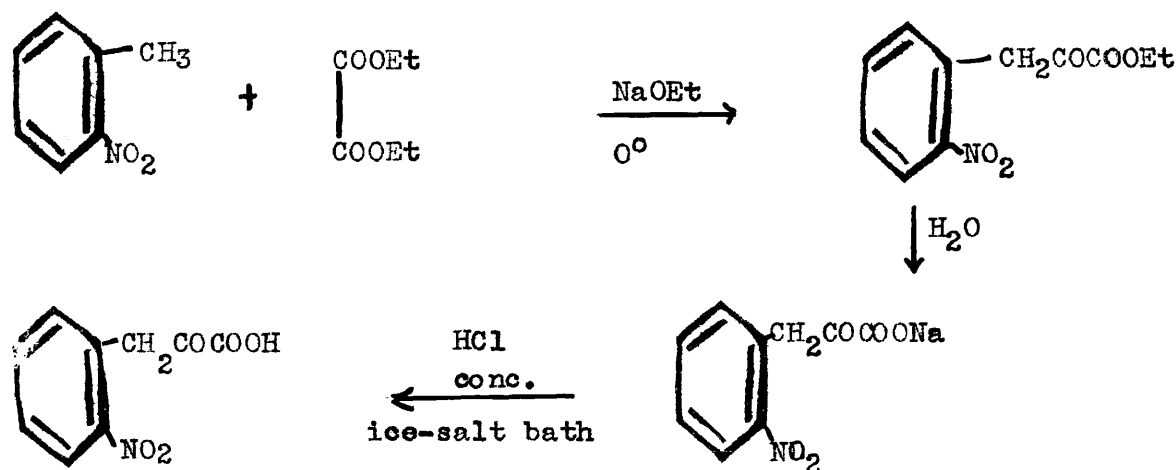
EXPERIMENTAL

General:

- 1) All melting points recorded are uncorrected and were observed on the Fisher-Johns melting point apparatus.
- 2) All boiling points given are uncorrected.
- 3) Volumes of hydrogen are uncorrected for either temperature, pressure, or the vapor pressure of H₂.

Preparation of Intermediates:

o-Nitrophenylpyruvic acid:



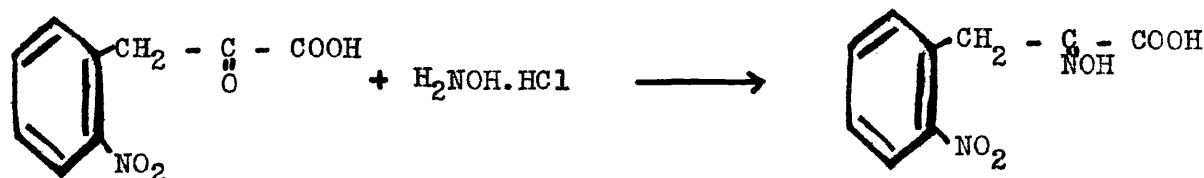
o-Nitrophenylpyruvic acid was first prepared by Mayer and Balle (95), but no mention was made of the yield. Elkes and his co-workers (96) in attempting to apply the method of Mayer and Balle found it time consuming and the yields resulting from the reaction were poor. DiCarlo (97) observed that the ethyl o-nitrophenylpyruvate formed in the initial reaction distills with steam and, if it was not hydrolyzed before the recovery of the unreacted o-nitrotoluene by steam distillation, a low yield of the acid was obtained.

Amin (38) applied a modification of the DiCarlo procedure and obtained 67% yields of o-nitrophenylpyruvic acid. The modified DiCarlo procedure, details of which follow, was used in this study to prepare the acid.

In a one-liter, three-neck flask, equipped with a mechanical stirrer, condenser, calcium chloride drying tube and dropping-funnel, was placed 160 ml. of absolute ethanol in which was dissolved 13.8 g. (0.6 atom) of sodium. The contents of the flask were cooled to 0-5° by means of an ice-salt bath and a mixture of 82.2 g. (0.6 mole) of o-nitrotoluene and 86.6 g. (0.6 mole) of ethyl oxalate was added with stirring over a period of thirty minutes. The reaction mixture was stirred at 0-5° for another three hours and was then allowed to stand at room temperature for fifteen hours. The reaction mixture was now refluxed on a water bath for thirty minutes after which 350 ml. of water was carefully added. The hydrolysis of the ester was completed by refluxing the water mixture for four hours and allowing it to stand overnight. In the meantime, a solid brown mass had separated at the bottom of the flask. The solution was distilled with steam and the unreacted o-nitrotoluene was recovered. Complete removal of the unreacted o-nitrotoluene seemed important in determining the purity of the product obtained. After complete removal of the o-nitrotoluene, the flask was stoppered and placed in an ice-salt bath. Concentrated hydrochloric acid was carefully added portionwise and with vigorous stirring to the cooled contents of the flask. As the acid was added, a yellow oil separated which solidified to light yellow particles on shaking. Efficient shaking of the reactants was necessary in the acidification and, where attempts were made to run the reaction in double quantities, a tarry mass was obtained unless the shaking secured efficient mixture of the reactants.

After complete acidification the flask was placed in the refrigerator overnight. The light yellow product, a fine-grained solid mixed with brown tarry masses, was filtered leaving behind as much of the brown tar as possible. It was washed with water and dried. The dried product was washed with hot toluene to remove the brown contaminant. The crude product which weighed 80 grams and melted from 114-117° was recrystallized from 40% ethanol (charcoal). The pure product which was pale yellow in color weighed 75 grams (60%) and melted at 120-121° (reported melting point is 119-121° (3)).

α -Oximino- β - (o-nitrophenyl)-pyruvic acid



In an attempt to find the best method, several different procedures were tried for the preparation of this compound.

Method No. 1: Used by Amin (38), this is a modification of the general method of Shemin and Herbst (98). In a 600 ml. beaker 16.7 g. (0.08 mole) of o-nitrophenylpyruvic acid was dissolved in 80 ml. of 50% alcohol. To this was added a solution of 17.0 g. (0.12 mole) of sodium acetate and 8.3 g. (0.12 mole) of hydroxylammonium chloride dissolved in 80 ml. of 50% ethanol. The mixture was warmed on the steam bath for ten minutes and was allowed to stand at room temperature for twenty hours. The reaction mixture, cooled to 0-5°, was made acid to Congo red with dilute hydrochloric acid. Water was added to precipitate the oxime and the beaker was placed in the refrigerator overnight. The product which had settled out was filtered and washed with water until the washings were

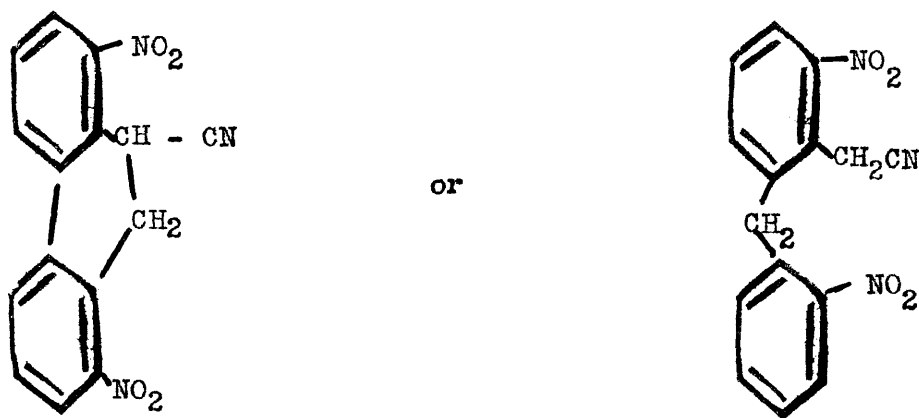
free of chloride. The product after recrystallization from 30% ethanol (charcoal) was almost white (slightly tan), weighed 11.7 g. (66%) and melted at 160-161° (this melting point agreed with that reported by Reissert (99)).

Method No. 2: The method was that described by Reissert (99). o-Nitrophenylpyruvic acid, 10.5 g. (0.048 mole) was dissolved in 50 g. of 10% sodium hydroxide and a concentrated solution of 3.5 g. of hydroxylammonium chloride in water was added. The mixture was allowed to stand overnight. When the red solution was acidified with concentrated hydrochloric acid the oxime precipitated as a brown flocculent mass. The product was filtered and washed thoroughly with water. The crude product was recrystallized by dissolving in dilute sodium carbonate solution and shaking the solution in the cold with charcoal. After several hours, the solution was filtered and the filtrate acidified carefully with dilute hydrochloric acid. The tan product after drying melted at 159-61° and weighed 8.0 g. (71%).

Method No. 3: This is a combination of features of methods No. 1 and No. 2 above. The procedure followed was exactly that of the Reissert technique (method No. 2) since it seemed to give better yields than method No. 1. However, since the recrystallization procedure of No. 1 gave a purer product, the product was recrystallized from 30% ethanol (charcoal). The yield was 76% of product melting 160-161°.

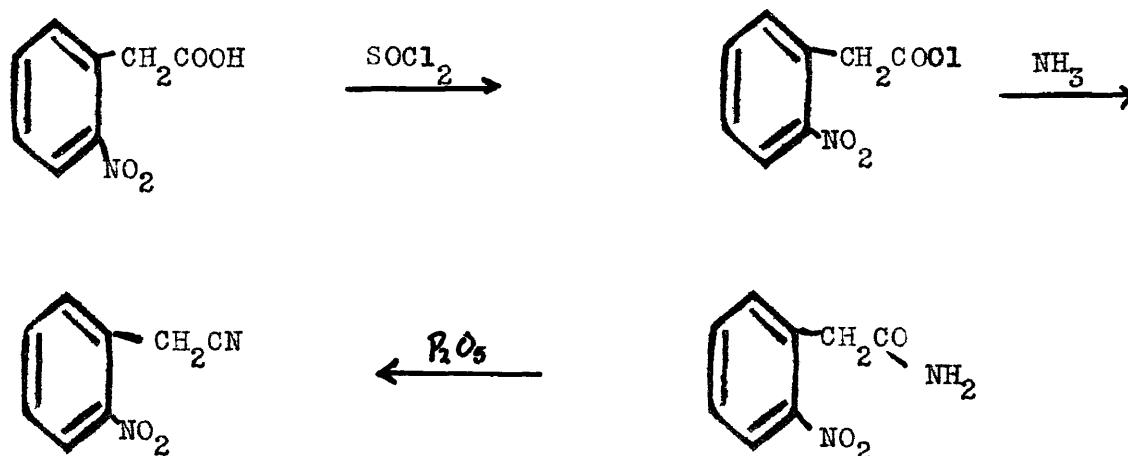
o-Nitrophenylacetonitrile:

Bamberger in 1886 (100) reported that when o-nitrobenzyl chloride was treated with potassium cyanide small yields of o-nitrobenzyl cyanide might be obtained; however, the main product of the reaction was a condensation product of either one of the structures shown below:

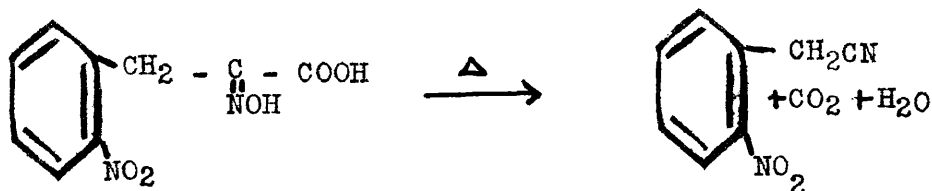


Heyman (95), in attempts to find some method for the preparation of *o*-nitrobenzyl cyanide, repeated the work of Bamberger. Her results confirmed the production of condensation products, but, unfortunately, no *o*-nitrobenzyl cyanide could be isolated. Heyman also tried unsuccessfully to obtain the nitrile by nitration of benzyl cyanide under various conditions. The reaction produced 60% yields of the para product, but none of the desired ortho product was isolated.

Pachorr and Hoppe (101) prepared the nitrile by the following sequence of reactions:



Reissert (99) also prepared *o*-nitrophenylacetonitrile by pyrolysis of α -oximino- β -(*o*-nitrophenyl)-propionic acid.



Since the intermediate oximino acid was available, it was decided to try the Reissert synthesis.

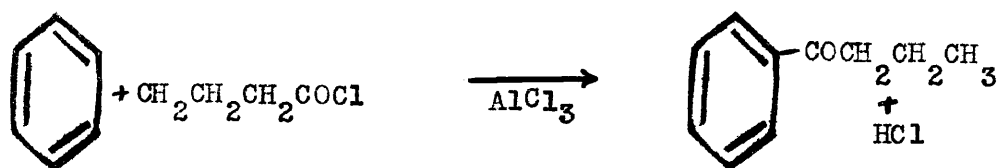
Five grams (0.0223 mole) of α -oximino- β -(o-nitrophenyl)-propionic acid was placed in a wide-mouthed Erlenmeyer flask which was heated in an oil bath. The temperature of the oxime was carefully maintained between 140-145° until all the solid had melted. At this stage the evolution of carbon dioxide was evident. More oxime was added while carefully controlling the temperature. When all the oxime had been added, the temperature suddenly rose to 160° at which time the flask was immediately removed from the oil bath. The black mass which had an odor of hydrogen cyanide was allowed to cool and the product soon crystallized. The largest batch of oxime thus converted to nitrile was 44 g. (0.20 mole). The crude mass was recrystallized several times from water (charcoal) producing 23 g. (71%) of white needles melting at 84° (melting point reported by Reissert 83-84°).

Recently, Redemann and co-workers (102) converted α -oximino acids to nitriles with acetic anhydride. A modification of their method, details of which follow, was tried for o-nitrophenylacetonitrile. Five grams (0.0223 mole) of α -oximino- β -(o-nitrophenyl)-propionic acid was suspended in 50 ml. of acetic anhydride and the mixture was heated to boiling. While boiling, carbon dioxide was visibly liberated and in five minutes the suspension became clear and red in color. The mixture was refluxed another thirty minutes after which the acetic anhydride was removed under reduced pressure. The residue was placed in the refrigerator overnight.

The brown needles which had precipitated were filtered and water was added to the filtrate, whereupon more solid precipitated. The filtration and addition of water to the filtrate was continued until solid no longer precipitated. The crude product was light brown and crystalline in nature. One recrystallization from water (charcoal) produced white needles melting at 84° and weighing 2.34 g. (65%).

Although time did not permit too extended a study of this reaction, it is felt that more experience would produce better yields than those of the pyrolytic process. Furthermore, when large amounts of oxime were pyrolyzed, the temperature had a tendency to rise too quickly to permit proper control and on several occasions the whole mass decomposed violently. In the anhydride procedure no such difficulty was experienced with larger amounts and the crude reaction product was much purer and more easily purified than in the pyrolytic process.

Butyrophenone:



Butyrophenone was prepared by the Friedel-Crafts reaction using the conditions as modified by Zenitz (103). The apparatus consisted of a 2 liter, three-necked, round bottom flask equipped with a mechanical stirrer, a reflux condenser joined to a gas absorption trap, and a dropping funnel. In the flask was placed 800 ml. of anhydrous benzene (excess benzene serving as a solvent) and 203 g. (2.2 moles) of anhydrous aluminum chloride. Over a period of forty-five minutes, 213 g. (2 moles) of butyryl chloride

was added to the mixture slowly while stirring. The evolution of hydrogen chloride was vigorous and the mixture in the flask refluxed. Meanwhile, the solution darkened to a red-brown color. After all the butyryl chloride had been added, refluxing was maintained by heating with a water-bath until the evolution of hydrogen chloride had practically ceased (about three hours). The gas absorption trap was removed and the condenser top was attached to a water pump. Suction was applied for an hour to remove the hydrogen chloride more completely, but care was taken that the suction did not cause the solvent to reflux too vigorously.

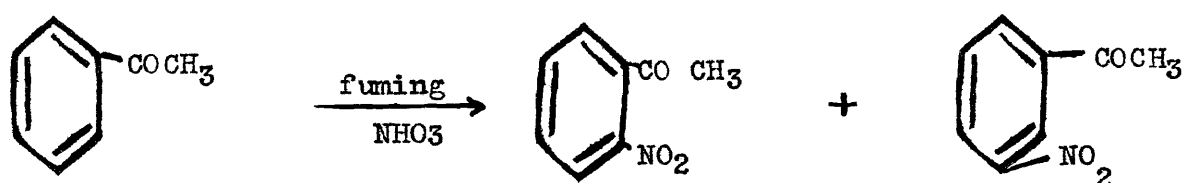
The reaction flask was surrounded by a cold water bath and the complex decomposed, in the presence of the solvent, by the dropwise addition of water from the separatory funnel. When the vigorous evolution of hydrogen chloride ceased, the decomposition was complete and the suspended aluminum compounds were dissolved by hydrochloric acid. The two layers were separated and the aqueous layer was extracted twice with benzene. The benzene extracts and benzene layer were combined and washed twice with water, with 10% sodium carbonate solution until the washings were alkaline, twice again with water, and then dried over calcium chloride. The excess benzene was removed by distillation and the residue was distilled to recover the ketone. The ketone obtained by distillation at atmospheric pressure boiled 227-229° (reported 227-231° (104)) and upon redistillation under reduced pressure the boiling point was 102-104°/7-9 mm. It was a sweet smelling, colorless liquid weighing 210 g. (74%).

Nitration of Ketones:

o and m-Nitroacetophenones:

Benitz (103) made a detailed study of the nitration of propiophenone under conditions which varied as to temperature and nitrating mixture. He

found that, the lower the temperature, the greater the yield of both ortho and meta nitro products. Although various nitrating mixtures, such as, sulfuric and concentrated nitric acids, sulfuric and fuming nitric acids, and glacial acetic and fuming nitric acids were tried, it was found that the use of fuming nitric acid alone gave the best results. Similar studies of the nitration of aralkyl ketones have been made by Morgan and Moss (105) and Wilson, Gibson and Johnson (106).



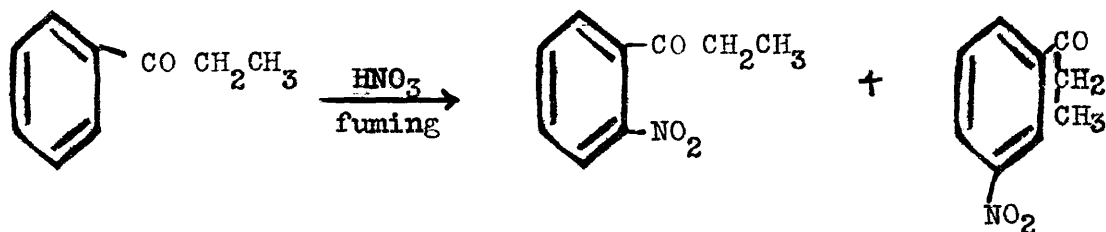
The nitration procedure used in this study is essentially that of Benitz. In a three-neck, liter, round bottom flask fitted with a mechanical stirrer, dropping funnel, and thermometer was placed 425 ml. of fuming nitric acid. The flask was surrounded by an ice-salt bath and stirring was started. When the temperature of the acid was between $0-2^\circ$, 60 g. (0.5 mole) of acetophenone was added in small portions from the dropping funnel. By adjusting the rate of addition, the temperature of the reaction was maintained between $0-5^\circ$. Stirring was continued for twenty to thirty minutes after the complete addition of the acetophenone.

The reaction mixture was poured upon 1000 g. of ice and the yellow oily crystals which separated were filtered with suction. The aqueous filtrate was extracted several times with 100 ml. portions of benzene, the benzene extracts were combined, warmed to 60° and used to dissolve the product on the filter. The benzene solution, after washing with three 40 ml. portions of water, with 10% sodium hydroxide until the washings were practically colorless, and finally three times more with 40 ml.

portions of water, was dried over calcium chloride and filtered. After removal of the benzene by distillation, a mixture of the ortho and meta isomers was obtained. The oily mixture was placed in a refrigerator overnight and the solid meta product was separated from the ortho product by filtration. The oily ortho isomer which still adhered to the solid meta product on the filter was removed by washing the mixture with cold 95% alcohol in which the meta isomer is insoluble. After removal of the alcohol by distillation, the ortho isomer was obtained as a brown oil and was placed in a refrigerator for several days to allow the separation of a small amount of the crystalline meta isomer which had been dissolved in it. The meta compound was filtered and combined with the product obtained earlier.

The crude o-nitroacetophenone was fractionated under reduced pressure and was obtained as a light yellow oil boiling at 164-166°/9-12 mm. which became tan on standing (reported boiling point 178-179°/32 mm. (106)). The yield of o-nitroacetophenone was 31.4 g. (33%). The meta nitroacetophenone was recrystallized from 95% alcohol yielding almost white crystals (slight yellow color) melting at 80-81° (reported m. pt. 81° (106)). The yield of the meta isomer was 37.0 g. (44.4%).

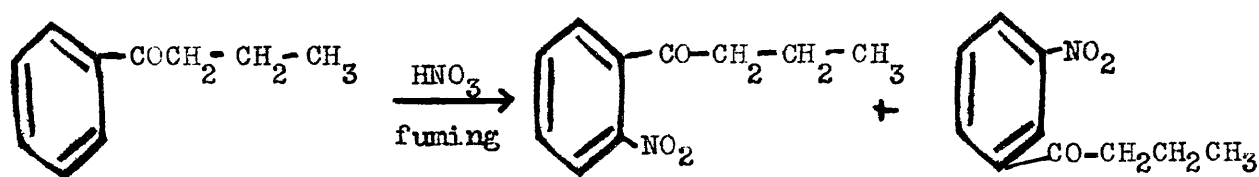
o and m-Nitropropiofenones:



By application of the procedure described for the nitration of acetophenone, 67 g. (0.5 mole) of propiophenone produced 26 g. (29.2%) of the light yellow oily ortho isomer boiling at 164-166°/4 mm. (reported

152-155°/2-3 mm. (103)). The meta isomer was obtained on recrystallization from 95% alcohol as a pale yellow crystalline solid weighing 32.5 g. (36.4%) and melting at 98-99° (reported 98.5-99° (103)).

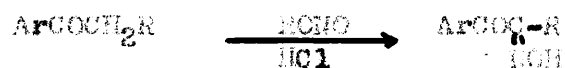
o and m-Nitrobutyrophenones:



The nitration of 74 g. (0.4 mole) of butyrophenone, by the procedure described for acetophenone, produced 49.4 g. (61.4%) of the ortho isomer which was a tan oil and darkened on standing. The constants for the ortho product were not obtained, for all attempts at distillation of the compound under reduced pressure resulted in an explosion and carbonization of the entire mass. Evidently, other workers have experienced the same difficulty in distilling o-nitrobutyrophenone, for a careful search of the literature does not reveal a boiling point for the compound although it is described in earlier papers. Possibly the compound could be distilled without decomposition, if the distillation were carried out under a sufficiently high vacuum. The meta nitro butyrophenone on recrystallization from 95% ethanol was obtained in pale yellow crystals melting at 62-63° (reported m. pt. 62-63° (106)). The yield was 35.2 g. (36.5%).

Nitrosation:

The general nitrosation reaction applied to ketones of the type ArCOCH_2R , where R is an alkyl group, producing oximinoketones according to the equation



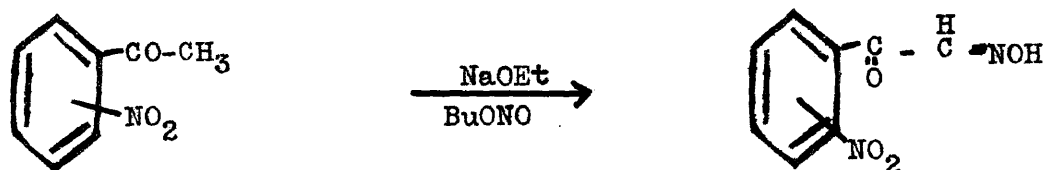
was first described by Claisen and Manasse (107). Later studies by Slater

(108) and by Hartung and his associates (109, 110, 111, 112) further showed that the oximinoketones could be prepared successfully in good yields by this scheme. Therefore, it was decided to try this procedure for the nitrosation of the ortho and meta nitro ketones prepared in this study. However, since Hartung and his group (111) reported that the nitrosation of acetophenone in the presence of hydrogen chloride is very unsatisfactory, it was considered best to use the method of Claisen (113) in nitrosating the acetophenones.

n-butyl nitrite:

The n-butyl nitrite used in these experiments was prepared by the method of Noyes (114).

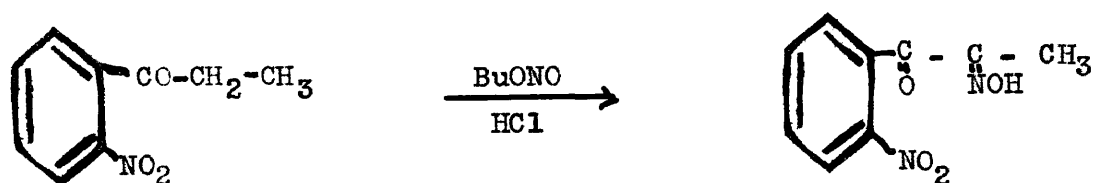
Attempted nitrosation of o- and m-nitroacetophenones:



A solution of 23 g. (1 atom) of sodium in 500 ml. of absolute alcohol was treated, while cooling, with 165 g. (1 mole) of either ortho or meta-nitroacetophenone and 103 g. (1 mole) of n-butyl nitrite. The nitrite and nitroacetophenone were added alternately, in small portions, with cooling after each addition. The red mixture was allowed to stand in the refrigerator for five days, after which 250 ml. of ether was added and the heavy, red sodium salt was filtered and sucked dry. The salt was dissolved in 285 ml. of water cooled to 5° and treated with 60 g. (1 mole) of glacial acetic acid. A brown oil resulted instead of the expected crystals. The oily liquid was extracted with ether and the extract was freed of ether by

the use of a stream of air. The residue separated into two layers, one of which was clear and seemed to be n-butyl alcohol. The two layers were separated and the brown oily layer was placed in the refrigerator for several weeks. Although the material had solidified in the refrigerator, it liquefied when kept at room temperature. The oily mass was extracted with ligroin and the ligroin was evaporated with a stream of air. On evaporation of the ligroin a light tan, low-melting solid was obtained which possessed a sweet odor. The compound would not crystallize, but on standing for several months in an evaporating dish small crystalline areas developed in the soft mass. If time had permitted, a modification of the procedure might have resulted in a crystalline product, but the sweet odor seems to indicate that the product was other than the isonitroso ketone expected.

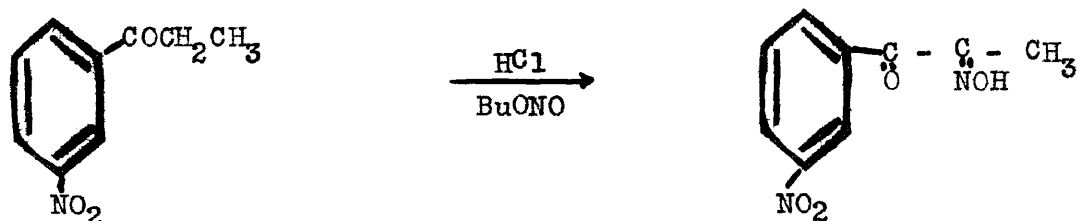
o-Nitrois onitrosopropiophenone:



The procedure for this nitrosation was essentially that used by Levin (115). In a one-liter, three-neck, round-bottom flask provided with a mercury-sealed mechanical stirrer, a reflux condenser connected to a gas absorption trap, a delivery tube for HCl, and a small dropping funnel was placed 140 g. (0.784 mole) of o-nitropropiophenone in 200 ml. of ether. The stirrer was set in motion and hydrogen chloride (generated by allowing concentrated sulfuric acid to fall on concentrated hydrochloric acid) was bubbled through the ether solution at the rate of about 2-4 bubbles per second; stirring and addition of hydrogen chloride being continued throughout the reaction. After the ether solution was saturated with hydrogen

chloride (five to ten minutes) 89 g. (0.861 mole) of freshly distilled n-butyl nitrite was added by means of the dropping funnel in 0.5 ml.-1.0 ml. portions. After addition of the first portions, the reaction mixture became orange-brown, and after several minutes, a pale yellow; these color changes occurred after the addition of each subsequent portion of the nitrite. When the last several portions of nitrite had been added, the orange-brown color remained. During the reaction the mixture gradually warmed up and the ether refluxed gently. Stirring and the addition of the hydrogen chloride were continued for another fifteen minutes after all of the nitrite had been added. Solid began to separate from the reaction mixture before all the nitrite was added. Air was blown through the flask to evaporate the ether and the orange crystals were filtered from the butyl alcohol remaining. The crude crystals weighing 106.0 g. were recrystallized from water (charcoal), yielding pale yellow needles melting 157-158° and weighing 90.0 g. (56.3%). Although this compound has not been described in the literature, Hartung (116) prepared it in his studies and reported a melting point of 156.5°.

m-Nitroisonitrosopropiophenone:

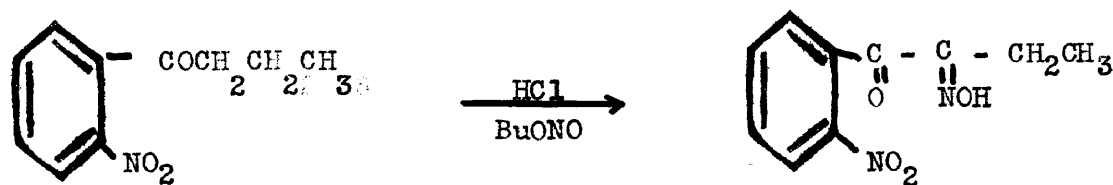


Using the procedure described above for the ortho isomer, 140 g. (0.784 mole) of m-nitropropiophenone was suspended in 500 ml. of ether and 89 g. (0.861 mole) of n-butyl nitrite was added in 0.5 ml. - 1.0 ml. portions. Contrary to the usual nitrosation procedure, the m-nitropropiophenone did not dissolve in the 500 ml. of ether and the usual change in

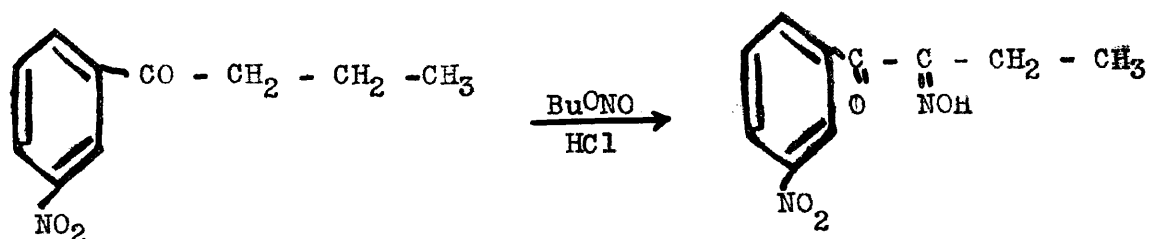
color, from orange to yellow, after the addition of the nitrite did not occur. However, when all the butyl nitrite was added, the refluxing suddenly became quite vigorous, all the solid went into solution, and the color became pale yellow. When the refluxing subsided solid began to precipitate and air was blown through the flask to remove the solvent. The crude product separated as a light tan crystalline mass weighing 157.0 g. After recrystallization from water (charcoal), white crystals resulted melting at 169-170° weighing 131 g. (80.5%).

The analytical data indicate that the nitrosation procedure did not yield a pure *m*-nitroisinitrosopropiophenone. This was not entirely unexpected after the odd manner in which the nitrosation took place. Since both *m*-nitropropiophenone and *m*-nitroisinitrosopropiophenone are solids and soluble in similar solvents, their separation presents a problem which was not successfully solved in this study. However, the analytical data indicate the product to be about 85% *m*-nitroisinitrosopropiophenone and 15% *m*-nitropropiophenone. The differences in melting point and the positive qualitative test for oximation discussed later all point to the validity of the conclusions drawn.

o-Nitroisinitrosobutyrophenone:



The procedure described above was tried with 143.5 g. (0.744 mole) of *o*-nitrobutyrophenone and 34.5 g. (0.32 mole) of *n*-butyl nitrite producing a tan solid. On recrystallization from water (charcoal), white needles were obtained melting 151-152° and weighing 91 g. (55%).

m-Nitroisonitrosobutyrophenone:

The nitrosation procedure described was applied to 143.5 g. (0.744 mole) of m-nitrobutyrophenone and 84.5 g. (0.82 mole) of n-butyl nitrite. After a few ml. of the nitrite had been added, all of the m-nitrobutyrophenone went into solution. At the end of the reaction, air was blown through the flask and the crude product thus obtained was recrystallized from water (charcoal). The white needles obtained on recrystallization weighed 108 g. (65%) and melted at 73-74°.

Qualitative Tests for Oximation:

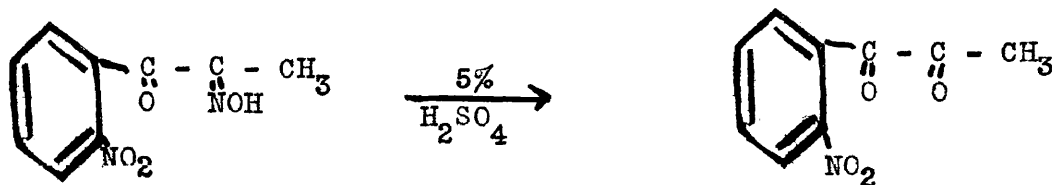
In order to obtain a qualitative indication of the success of the nitrosations, the glyoximes of the suspected isonitroso ketones were prepared and tested for by the formation of colored complexes with ammoniacal nickelous sulfate.

In the case of each nitrosation product, a solution of 0.5 g. of hydroxylammonium chloride in 3 ml. of water was added to a solution of 1 g. of the nitrosation product in alcohol. Sufficient alcohol was added, drop by drop, until a clear solution resulted. Several hours later, a few drops of ammoniacal nickel sulfate solution was added to 2 ml. of the solution prepared above. In each case strongly colored nickel chelate compounds formed.

<u>Isonitroso ketone</u>	<u>Chelate with NiSO₄(NH₂)</u>
o-nitroisonitrosopropiophenone -	deep orange precipitate
o-nitroisonitrosobutyrophenone -	deep red precipitate
m-nitroisonitrosopropiophenone -	deep blood-red precipitate
m-nitroisonitrosobutyrophenone -	orange precipitate

The qualitative tests indicated that the products tested were the isonitroso ketones desired.

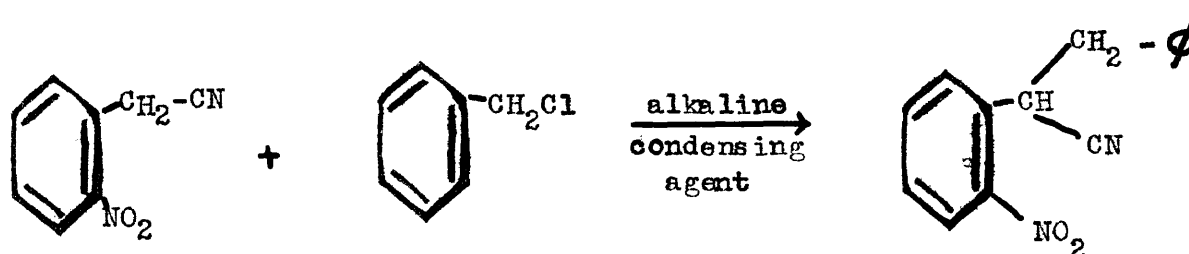
Attempted preparation of diketones:



Following the technique of Beecham and Müller (117) as modified by Ellin (118), 7 g. (0.034 mole) of o-nitroisonitrosopropiophenone was distilled for fourteen hours with 250 ml. of 5% sulfuric acid. Sulfuric acid and water were added to the distilling flask from time to time to replenish the hydrolysis mixture. A light yellow solid, which tended to clog the condenser, distilled over into the receiver. The solid was returned to the distilling flask and the distillation repeated several times. The solid product obtained from this reaction upon recrystallization checked in every respect with the original o-nitroisonitrosopropiophenone. The failure of the hydrolysis to the diketone may well have been a direct result of the insolubility of the o-nitroisonitrosopropiophenone in the dilute acid and the reaction may prove successful if some auxiliary agent is used to bring about solution of the oximino ketone in the acid. However, these studies were not pursued any further at this time.

Attempted condensations with o-nitrophenylacetonitrile:

Condensations with benzyl chloride - In o-nitrophenylacetonitrile, as in acetoacetic and malonic esters, the hydrogen of the $-\text{CH}_2$ group linked to the activating phenyl and $-\text{CN}$ groups is very readily replaced. Thus, sodium ethoxide gives monosodiobenzyl cyanide which reacts with alkyl halides to give alkyl-benzyl cyanides and with esters to give cyanoketones (94).



Experiment No. 1:

Using solid sodium hydroxide as a condensing agent as described by Janssen (119) for benzyl cyanide, 2 g. (0.012 mole) of o-nitrophenylacetonitrile, 20 ml. of dry ether, 0.495 g. (0.012 mole) of NaOH pellets, and 1.65 g. (0.013 mole) of benzyl chloride were refluxed together on a water-bath for two hours. While refluxing the solution became dark brown. When the mixture was cooled, the pellets of sodium hydroxide were intact, the odor of benzyl chloride was present, and the unreacted nitrile was recovered on evaporation of the ether. Apparently, sodium hydroxide pellets would not form the sodio-nitrile intermediate necessary for the condensation.

Experiment No. 2:

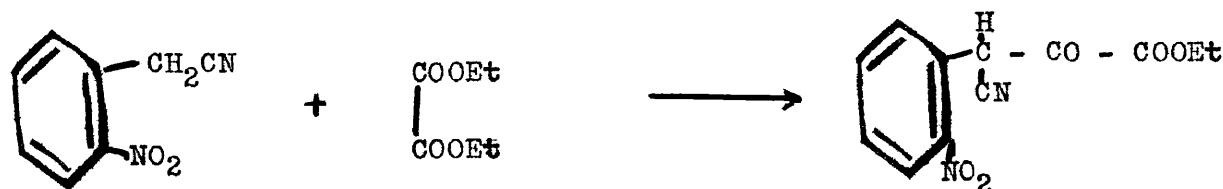
Sodium, 0.5 g. (0.022 atom), was dissolved in 15 ml. of absolute alcohol. To the alcoholic ethoxide solution was added 2 g. (0.012 mole) of o-nitrophenylacetonitrile, whereupon the solution became dark blue in color. After the addition of 1.65 g. (0.013 mole) of benzyl chloride, the mixture was refluxed on the water-bath for one hour and placed in the refrigerator overnight. The brown solid, which had precipitated, was filtered and tests proved it to be sodium chloride. The alcohol in the filtrate was evaporated and a viscous brown tar resulted. Attempts at working up this tar failed.

Experiment No. 3:

The procedure of experiment No. 2 was repeated, but the mixture was intermittently shaken in an ice bath for an hour, rather than refluxed, and

then placed in the refrigerator overnight. A precipitate of sodium chloride resulted from this experiment also and attempts to recover a product from the tarry residue failed.

Condensations with ethyl oxalate -



Experiment No. 1:

This reaction was attempted according to the procedure given in Organic Syntheses (120) for benzyl cyanide. To 3.56 ml. of absolute alcohol was added 0.285 g. of sodium (0.012 atom) and, when all the sodium was in solution, the mixture was placed in an ice-salt bath. To the sodium ethoxide was added 1.9 g. (0.013 mole) of ethyl oxalate and 2 g. (0.012 mole) of o-nitrophenylacetonitrile in 15 ml. of absolute alcohol. The mixture was shaken in the ice bath for one hour and placed in the refrigerator over-night. The blue color which appeared when the nitrile was added was still present. The contents of the flask were warmed to 35° and acidified to litmus with hydrochloric acid. The sodium chloride which precipitated was filtered. The alcohol was removed by distillation and the high boiling residue was allowed to cool. Although a yellow crystalline material precipitated, it proved, on recrystallization from water (charcoal), to be unchanged o-nitrophenylacetonitrile.

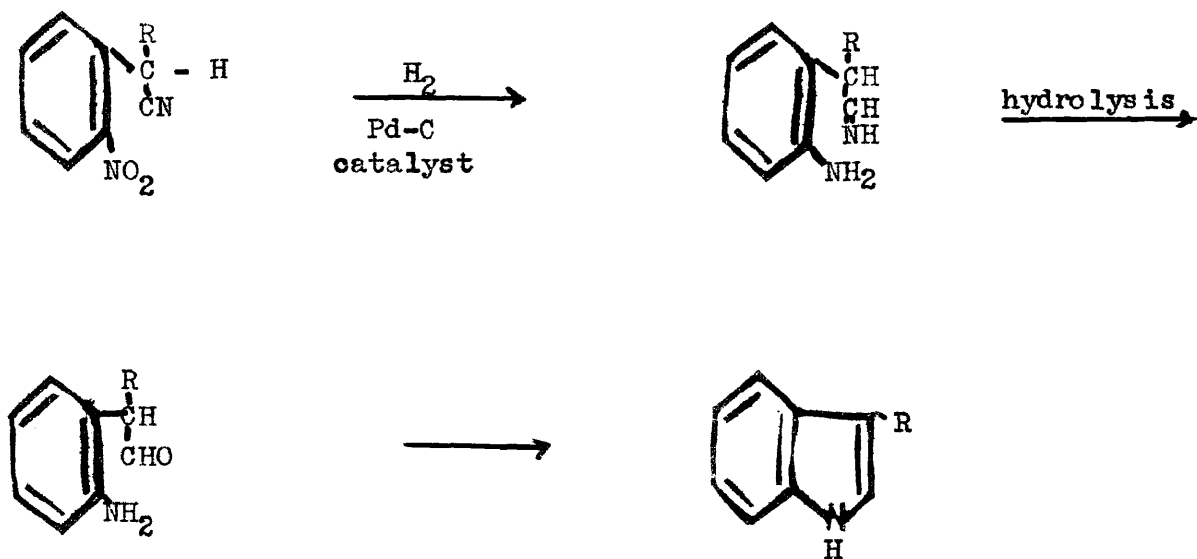
A preliminary study was made of similar condensations with o-nitrophenylacetonitrile and benzaldehyde in the presence of sodium ethoxide, but in every case no new material could be isolated. Because of the discouraging results with the condensations tried, it was decided not to pursue

these studies any further.

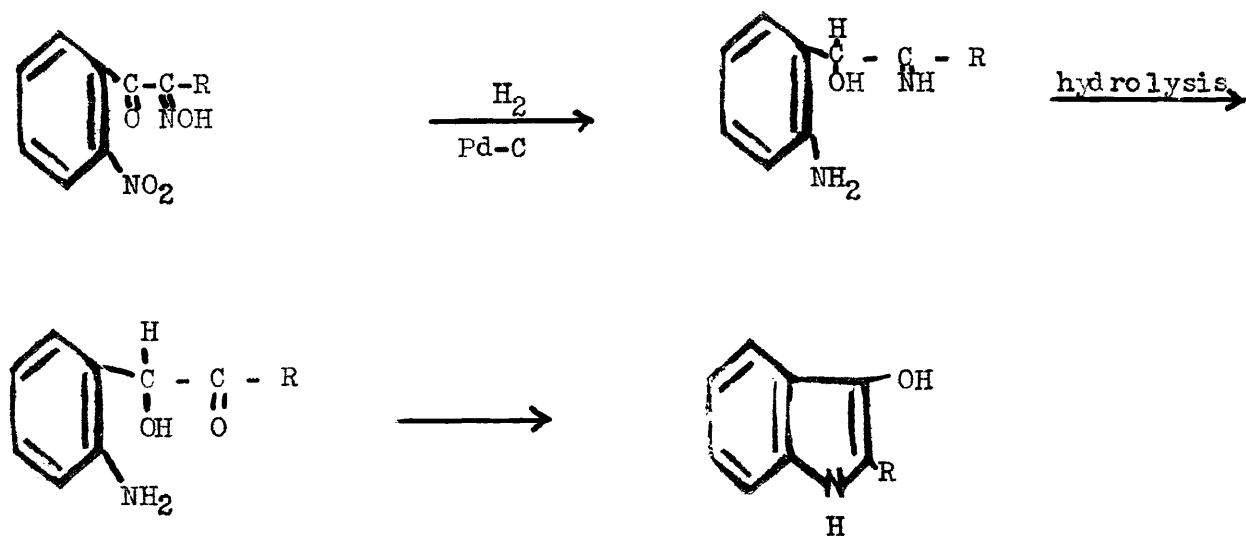
Reduction Studies:

The final phase of this problem may be conveniently divided into three main divisions:

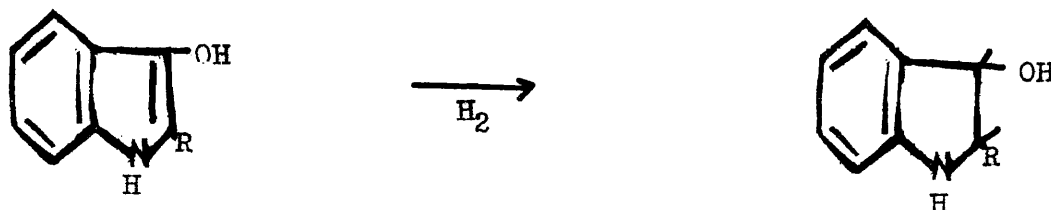
- a) Reduction of α -substituted o-nitrophenylacetonitriles to the corresponding 2-substituted indoles.



- b) Reduction of o-nitroisoxosketones to the corresponding indoxyls.



- c) Finally, it was of interest to try to reduce the double bond in the substituted indoxyls to the 2,3-dihydroindoxyl which would produce structures closely resembling that of adrenochrome.



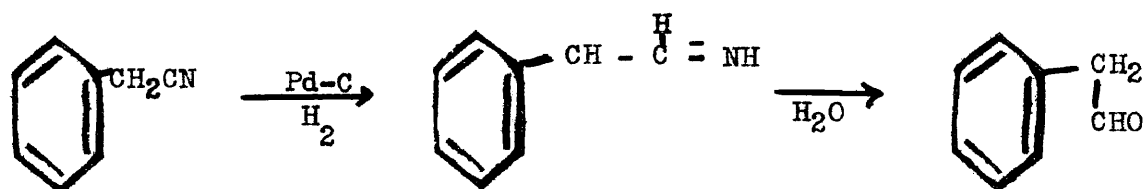
Attention was first given to the reduction of *o*-nitrophenylacetonitrile and its **analogs** . Unfortunately, it was impossible in this study to prepare the α -substituted *o*-nitrophenylacetonitriles and only the unsubstituted nitrile was available for reduction studies.

Ordinarily the reduction of the cyano group does not proceed uniformly at all either with nascent or catalytically excited hydrogen. The reason for this is the fact that the extremely reactive aldimines, formed by the addition of one mole of hydrogen, react faster in certain other ways than they can be reduced further to primary amines. The most important of these subsequent reactions is the formation of secondary amines.

The usual methods of hydrogenation by the Sabatier-Senderous (121) method or in alcoholic solution using palladium or platinum as catalysts (122) give considerable amounts of secondary amine as well as the normal product of reduction (123, 124, 125, 126, 127). Rosenmund and Frankuch (128) have described conditions for the catalytic reduction of some nitriles to primary amines using acetic acid as a solvent. According to Hartung (129), the yield of primary amine is increased at the expense of the side reactions by carrying out the hydrogenation in alcoholic solution containing one equivalent of hydrochloric acid. The addition of ammonia in the hydro-

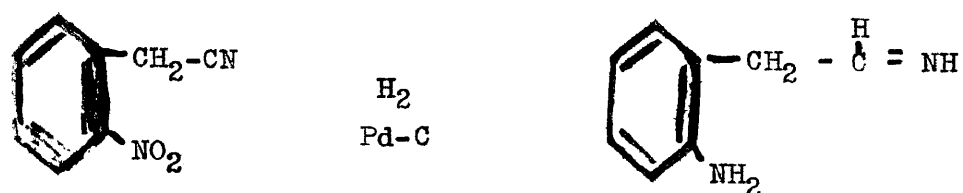
generation using Raney nickel also reduces the amount of secondary amine (130). Carothers and Jones (131) were able, by using PtO_2 and acetic anhydride as the solvent, to obtain good yields of the acetyl derivative of the primary amino.

Stephen (39) was able to convert nitriles into aldehydes by means of the intermediate imino-chloride by the use of stannous chloride saturated with hydrogen chloride in ether. Heyman (93) used palladium on charcoal, in the presence of two equivalents of hydrochloric acid, to hydrogenate catalytically phenylacetoneitrile to the intermediate imine, which could be hydrolyzed to phenylacetaldehyde. The object of this study was to



reduce o-nitrophenylacetoneitrile catalytically to indole by means of an intramolecular ring closure.

Since large amounts of o-nitrophenylacetoneitrile were not too easily available, it was decided to make the reduction studies on small samples (2 g. - 0.0124 mole). Furthermore, it was necessary, if cyclization to indole was to be accomplished, that the reduction be stopped at the imine stage; otherwise, it might continue to the primary amine and prevent inter-



nal ring closure. With all these factors in mind, it was considered

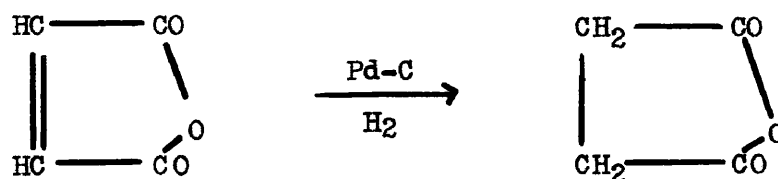
essential that the reduction be carried out using a measure of hydrogen uptake which was sufficiently sensitive to indicate small differences in hydrogen absorption. This was accomplished by using a straight tube mercury manometer which was attached to a meter stick so that heights in tenths of a centimeter could be read directly. The manometer was attached to the exhaust end of a Parr shaker type hydrogenator and the hydrogenation was started with both the exhaust valve (attached to the manometer) and the bottle inlet valve open. In this way, hydrogen uptake was immediately indicated by a fall in the height of the column of mercury in the manometer. It was possible in this manner to check hydrogen absorptions as small as 5-10 ml. The method was not without its disadvantages, for the manometer could only be used with those hydrogenations which would proceed at pressures of about 18 p. s. i. Higher pressures, of course, could not be recorded on this 100 cm. manometer.

Preparation of catalyst:

The catalyst was prepared by the usual procedure developed by Hartung (132). Into a Parr shaker bottle was placed 100 ml. of water, 3 g. of nuohar, 13.6 g. of sodium acetate ($\text{NaC}_2\text{H}_3\text{O}_2 \cdot 3\text{H}_2\text{O}$) and 3 ml. of a solution of palladium chloride (each ml. of this solution contained 0.1 g. of PdCl_2). This mixture was placed on the Parr hydrogenator and the bottle was alternately evacuated by water pump and then filled with hydrogen gas four times thus leaving an atmosphere of practically pure hydrogen in contact with the suspension. Agitation was begun and allowed to proceed until hydrogen was no longer absorbed. The catalyst was then filtered onto a Buchner funnel, washed several times with water, then ethanol, and finally ether. The catalyst was either used at once or stored in a desiccator until used.

Calibration of manometer:

It was necessary to calibrate the manometer before use. The reaction chosen for the calibration was the reduction of maleic anhydride to succinic anhydride.



The endpoint of the reaction was taken as that point at which hydrogen was no longer absorbed.

One-tenth of a mole (9.8000 g.) of pure, dry maleic anhydride was placed in a Parr hydrogenation bottle with 100 ml. of absolute alcohol and 3 g. of 10% Pd-charcoal catalyst prepared as described above. The gauge pressure at the start of the hydrogenation was 10 p. s. i. The manometer was attached to the apparatus and the column of mercury was allowed to come to equilibrium. When a thirty-minute period produced no visible drop in manometer reading, the hydrogenation was started. Since each mole of the maleic anhydride requires one mole of hydrogen for reduction of the double bond, complete hydrogenation of the mixture used would require:

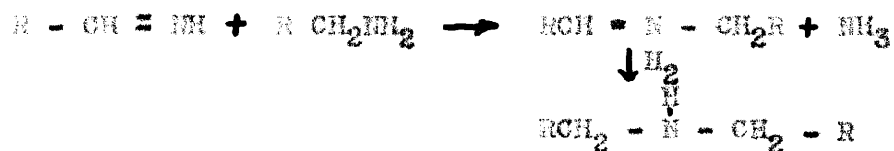
$$0.1 \times 22412 \text{ ml./mole} = 2241.2 \text{ ml. of hydrogen.}$$

<u>Time in minutes</u>	<u>Manometer readings in cm. of mercury</u>
0	83.6 cm
2	74.5
4	60.0
5	50.0
6	41.0
8	40.5
13	40.0
15	39.9
26	39.7
29	39.7
39	39.6
64	39.6
120	39.6 <u>stopped reduction</u>

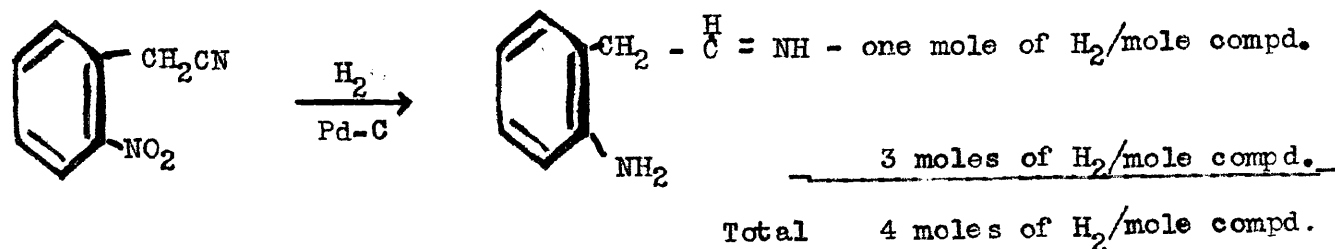
The reduction was assumed to be complete and quantitative and no attempt was made to isolate the product. Therefore, a drop of 44.0 cm. was equivalent to a hydrogen uptake of 2241.2 ml. Thus, each centimeter drop on the manometer is equivalent to 50.9 ml. of hydrogen.

Reduction studies of o-nitrophenylacetonitrile:

As previously pointed out, it was hoped to find conditions which would permit the catalytic reduction of o-nitrophenylacetonitrile to the corresponding o-aminoimine. This imine could be hydrolyzed to o-aminophenylacetaldehyde which should cyclize to indole. It was anticipated that the reduction of the $-NO_2$ group (requiring 3 moles of hydrogen/mole of compound) would proceed first to be followed by the reduction of the $-CN$ group to $-C(=NH)NH_2$ (requiring one mole of hydrogen/mole of compound.) If, perchance, the reduction proceeded in such a way that a mixture of imine and primary amine were formed, very likely secondary amine would result as follows:



In order to suppress such secondary amine formation, use was made of the experience of Hartung (129) and Heyman (93) and the reduction was first attempted in the presence of hydrochloric acid. Into a Parr hydrogenation bottle was placed 2 g. (0.0124 mole) of o-nitrophenylacetonitrile, 3 g. of 10% Pd catalyst, 150 ml. of 70% alcohol, and 2 equivalents of hydro-



chloric acid (2.2 ml. conc. hydrochloric acid). The bottle was placed on the Parr hydrogenator and the air was removed by evacuating the apparatus,

filling it with hydrogen, and repeating the process at least four times. The manometer was attached to the exhaust valve and the apparatus was allowed to come to equilibrium before shaking was started. Since one mole of nitrile would require four moles of hydrogen to produce the desired aminoimine; therefore, 0.0124 mole would require 0.0494 mole of hydrogen.

$$0.0494 \times 22400 = 1106.6 \text{ ml. of hydrogen required}$$

$$\frac{1106.6}{50.9} = 21.8 \text{ cm. drop on manometer represents 1106.6 ml. of hydrogen.}$$

<u>Time in minutes</u>	<u>Manometer reading in cm. mercury</u>
0	69.6
5	58.0 69.6 - 21.8 = 47.8 cm.
7	52.6 theoretical stopping point.
8.5	← 51.9 <u>3 moles of hydrogen already absorbed</u>
11	51.2
13	50.5
15	50.0
17	49.8
18.5	49.5
29	49.4
35	49.4 - <u>Stopped reduction although 80 ml. hydrogen still to be absorbed.</u>

Apparently three mole equivalents of hydrogen were absorbed the first seven minutes and the remaining one mole equivalent required twenty-two minutes. This pointed to a rapid initial reduction of the $-\text{NO}_2$ group followed by a slower reduction of the $-\text{CN}$ to $-\text{C}(\text{H})=\text{NH}$. The bottle at the end of the reaction had an odor very suggestive of indole. The catalyst was filtered off and the filtrate possessed a definite indole-like odor. A little of the filtrate was made alkaline with sodium hydroxide solution and a few ml. of an alcoholic solution of picric acid was added resulting in an orange-red precipitate, which, in color, resembled the picrate of indole. The alcohol was removed from the remaining filtrate by distillation under reduced pressure. The residue was a milky solution with a strong indole-like odor from which a brown oil separated on cooling. While standing in

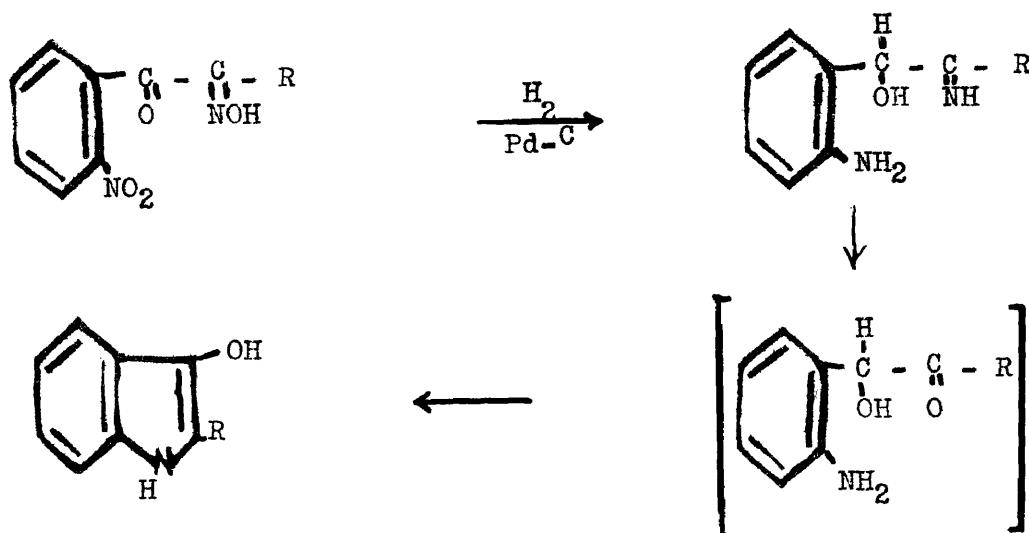
the refrigerator overnight, a crude crystalline product separated from the brown oil. The melting point of this crude product was higher than that of indole and attempts at recrystallization did not produce a compound which could be characterized. Evidently the acid which had been used in the reduction had caused a polymerization of the indole which easily polymerizes in the presence of acids. This experience forced the decision to try the reduction of the nitrile in the absence of hydrochloric acid.

Several reductions were tried without hydrochloric acid primarily to prove the formation of indole in the reaction. The quantities and conditions were the same as those given above, but the hydrochloric acid was omitted. Again all indications pointed to an initial rapid reduction of the $-NO_2$ group followed by reduction of the $-CN$. The reaction flask at completion of the reduction had a definite ammoniacal odor and moist red litmus held in the neck of the bottle turned blue. The filtrate after removal of the alcohol had a definite indole-like odor. Since attempts at obtaining crystals from this residue failed, it was extracted with petroleum ether. Evaporation of the petroleum ether produced white crystals which melted at $49-52^\circ$ (reported for indole 52.5° (133)). Qualitative tests for indole were positive with these crystals.

Another reduction without hydrochloric acid using the same quantities of nitrile and catalyst, but only using 100 ml. of 70% ethanol was run according to the procedure described above. The same reduction pattern was observed in this study as in those previously outlined. After the alcohol had been removed from the reaction liquor, white flaky crystals, which were slightly contaminated with a red oil, began to precipitate. The crystals possessed a definite indole odor and gave a positive test for indole with *p*-dimethylaminobenzaldehyde. The crude product was recrystallized from water (charcoal) yielding 0.796 g. (55%) of a white crystalline

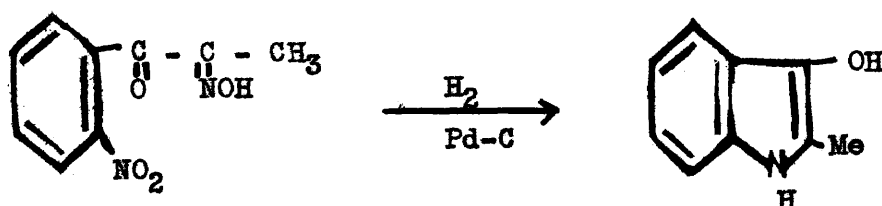
solid, with an odor suggestive of α -naphthylamine and melting at 52° . The pure white product became slightly pink on standing. An orange-red picrate prepared from this product melted at $173-177^\circ$ (reported $176-177^\circ$ (134)).

Attention was now focused on the reduction of the o-nitroisoximino-ketones to their corresponding indoxyls. The difficulties encountered in the reduction of oximes are essentially those discussed above for nitriles. Here again, the use of an acid reduction medium has made it possible catalytically to reduce oximes to the primary amines uncontaminated with the secondary product. Hartung and his students (134, 136, 137, 138, 139, 103) have extensively applied this method in the reduction of oximes to the corresponding amino compounds. Here, as in the case of the nitrile, the prime object was to secure reduction of $-\text{NO}_2$ to $-\text{NH}_2$ while simultaneously reducing the oximino group to the intermediate $-\overset{\text{H}}{\underset{\text{NH}}{\text{C}}}-$ which would upon hydrolysis produce an aminoketone which could cyclize to an indole-type nucleus. Since there was also a carbonyl group α to the oximino group in the original compound, which would on reduction become an α -hydroxyl, the final product would be a 2-alkyl substituted indoxyl.

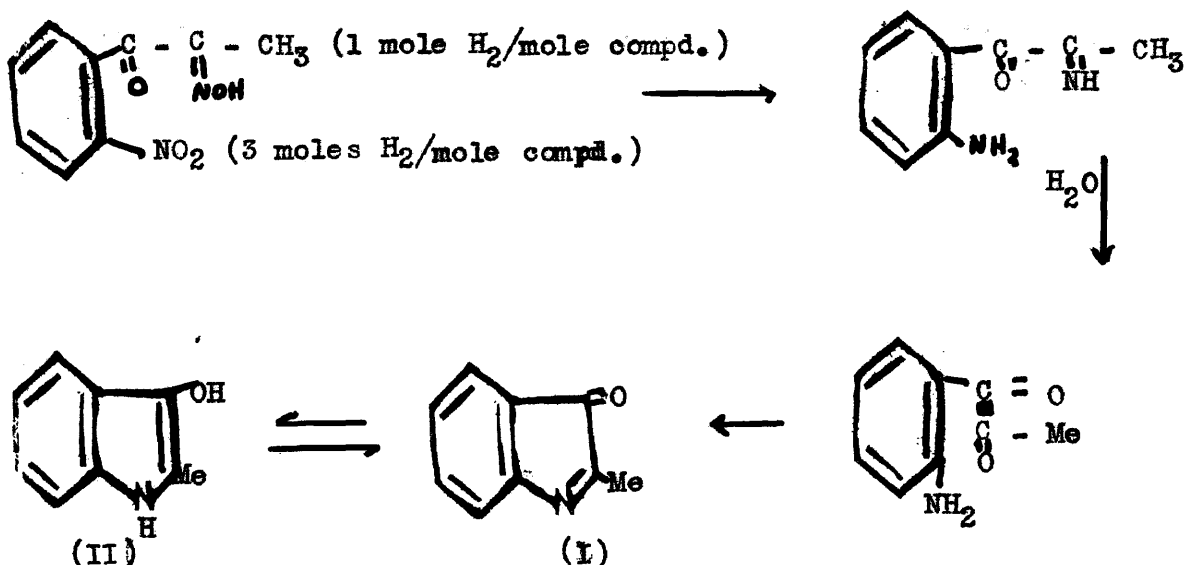


On the basis of experience gained in the reduction studies of o-nitrophenylacetonitrile and recognizing the deleterious effect of acids on the indole nucleus, it was decided to make all reductions in neutral medium. These reductions were also made on a small scale using the manometer to follow the course of hydrogenation.

Reduction studies of o-nitroisoxantropiophenone:

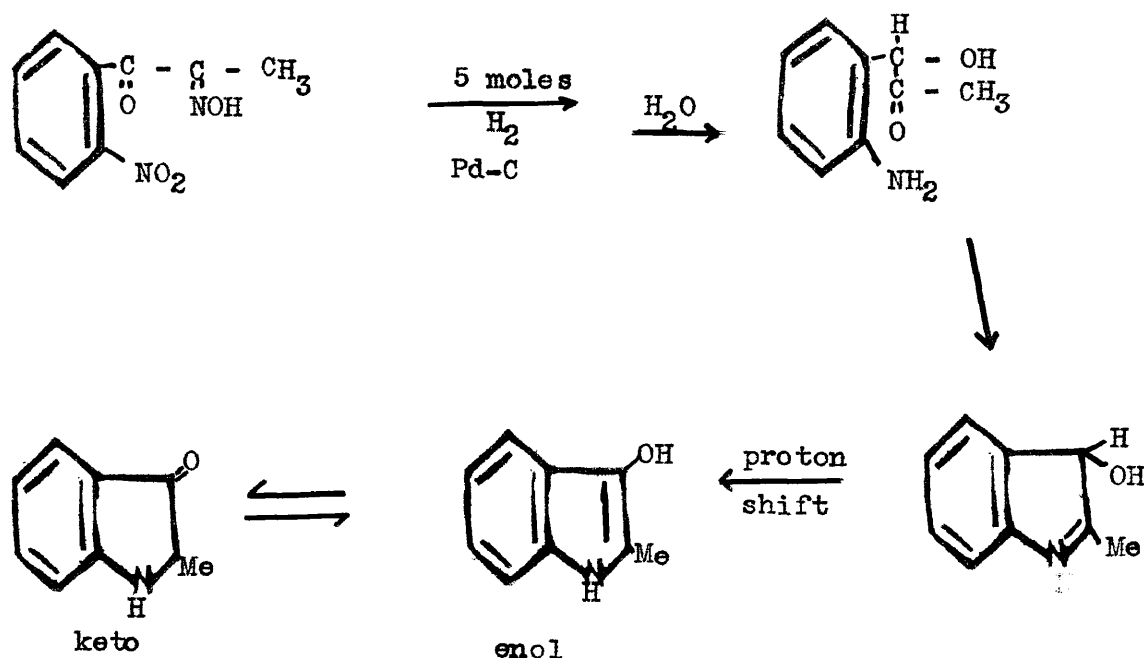


In a preliminary consideration of the hydrogenation of o-nitroisoxantropiophenone, it was erroneously calculated that absorption of four moles of hydrogen per mole of compound was capable of producing the keto form of 2-methyl indoxyl which could enolize to the hydroxy (enolic) form of the indoxyl. However, as can be seen by carefully studying product



(I) shown above, there is no H atom available for an enolization to product (II). Therefore, in order for the reduction to produce the desired product,

it was necessary for five moles of hydrogen to be absorbed per mole of o-nitroisonitrosoketone.



Unfortunately, several reductions were made before this error was realized.

In a typical reduction stopping at the four mole hydrogen absorption stage, 2 g. (0.0096 mole) of o-nitroisonitrosopropiophenone, 3 g. of 10% Pd-charcoal catalyst, and 100 ml. of 70% alcohol were all placed in a Parr hydrogenation bottle. The bottle was connected to the hydrogenation apparatus and the air was removed by evacuation, filling it with hydrogen and repeating the process at least four times. The manometer was joined to the apparatus as previously described and equilibrium was attained before hydrogenation was started. Since one mole of oximinoketone would require four moles of hydrogen, therefore, 0.0096 mole would require 0.0384 mole of hydrogen.

$$0.0384 \times 22400 = 860.2 \text{ ml. of hydrogen required}$$

$$\frac{860.2}{50.9} = 16.9 \text{ cm. drop on manometer represents 860.2 ml. of hydrogen.}$$

<u>Time in minutes</u>	<u>Manometer reading in cm. mercury</u>	
0	82.7 cm.	82.7-16.9=65.8 cm.
2	78.0	theoretical end point.
4	73.0	
5	70.0	← <u>3 moles of hydrogen already absorbed</u>
8	68.0	
13	65.8	<u>Stopped reduction</u>

Here, as in the case of the nitrile, three moles of hydrogen was absorbed in the first five minutes and the remaining one mole required eight minutes. This pointed to rapid reduction of the $-NO_2$ to $-NH_2$ at first, followed by a slower reduction of the $-C(=NOH)H$ to $-CH=NH$. The hydrogenation bottle at the end of the reaction had an ammoniacal odor and moist red litmus held in the mouth of the bottle turned blue. In spite of the presence of charcoal, the reaction mixture was seen to possess a definite greenish-yellow fluorescence. The catalyst was filtered from the reaction mixture and the filtrate was greenish-yellow with a definite fluorescence. The catalyst was washed several times, first with cold, then with hot absolute alcohol. The solvent was removed by distillation under reduced pressure and the residue placed in an evaporating dish. On cooling a yellow solid with an indole-like odor precipitated. The product was filtered and dried and on close examination seemed crystalline in nature. The crude product was recrystallized by dissolving in hot absolute alcohol (charcoal), filtering, and adding water to the filtrate to incipient crystallization. The pure product was an odorless, bright canary-yellow, amorphous solid weighing 0.4236 g. (30.2%) and melting at 133-134° (reported for 2-methyl indoxyl 40° (140)).

It was observed that the nature of the product was greatly affected by several factors. If the isonitrosoketone was not pure, the yield was poor and the product was resinous and oftentimes a black gummy tar. Also the lower the pressure under which the solvent was removed from the reaction

mixture the less resinous was the crude product.

According to Ingraffia (140) the following color reactions are characteristic for 2-methylindoxyl:

- 1) Cold concentrated hydrochloric acid - a pink color which darkens.
- 2) Hot and cold concentrated sulfuric acid - a violet color.
- 3) Cold glacial acetic acid - a yellow solution.

Hot glacial acetic acid - a red colored solution.

- 4) Cold acetic anhydride - a red color.

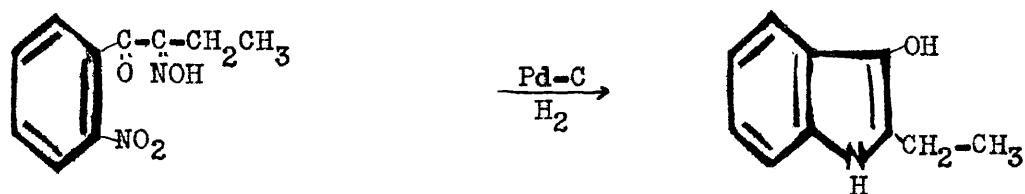
The product obtained gave these positive color tests with concentrated hydrochloric acid, concentrated sulfuric acid, glacial acetic acid, and acetic anhydride.

When it was realized that the desired product would require five moles of hydrogen per mole of isonitrosoketone, several reductions were tried allowing the absorption to proceed to the five mole stage. Following the technique described above and using the same quantities, a typical reduction proceeded as follows: 21.1 cm. drop on manometer required for five mole absorption which is equivalent to 1075.2 ml. of hydrogen.

<u>Time in minutes</u>	<u>Manometer reading in cm. mercury</u>	
0	84.9	84.9 - 21.1 = 63.8
2	78.0	theoretical endpoint
7	70.0	← 3 moles of hydrogen already
10	68.9	<u>absorbed</u>
13	68.2	
15	67.0	
20	66.6	
23	66.1	
35	65.7	
45	65.5	
52	65.0	
60	64.8	
85	64.6	
120	63.8	<u>stopped reduction</u>

Over three moles of hydrogen were absorbed in the first seven minutes of the reduction and the remaining two moles required one hundred and thirteen minutes. This provided more evidence that the $-\text{NO}_2$ group was reduced rapidly at first followed by a slower reduction of the keto and oximino groups. The nature of the reaction mixture and product was exactly as that for the four mole hydrogen absorption; however, the yield of the pure 2-methyl indoxyl was 0.7732 g. (84.5%) melting at $153-154^\circ$. All color tests were positive as above.

Reduction of o-nitroisoximobutyrophenone:



In a typical reduction 2 g. (0.00897 mole) of o-nitroisoximobutyrophenone, 3 g. of 10% Pd-charcoal catalyst, and 100 ml. of 70% alcohol were all placed in a Parr hydrogenation bottle. The bottle was connected to the Parr hydrogenation apparatus and was then evacuated and filled with hydrogen as in previous reductions. The manometer was then joined to the apparatus and the system was allowed to come to equilibrium before the reduction was begun. Since one mole of oximinoketone would require five moles of hydrogen to produce the desired aminohydroxyimine; therefore, 0.00897 mole would require 0.04485 mole of hydrogen.

$$\frac{0.04485 \times 22400}{50.9} = 19.7 \text{ cm. drop on manometer required for five mole hydrogen absorption.}$$

<u>Time in minutes</u>	<u>Manometer reading in cm. mercury</u>	
0	84.1	$84.1 - 19.7 = 64.4$ <u>theoretical</u>
2	79.3	<u>endpoint</u>
6	71.8	← <u>3 moles of hydrogen already</u>
10	69.0	<u>absorbed.</u>
18	68.0	
26	66.8	
32	66.1	
42	65.5	
52	64.8	
53	64.4	<u>stopped reduction</u>

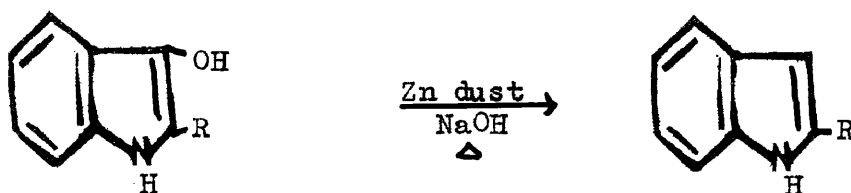
It is interesting that the absorption of three moles of hydrogen occurred in the first five minutes and the remaining two moles were absorbed in about fifty minutes. This is interpreted as substantiating the claim that the $-\text{NO}_2$ group is reduced first. The odor of the reaction bottle was ammoniacal and moist red litmus turned blue in the mouth of the bottle. After filtration of the catalyst mixture, the filtrate exhibited a greenish-yellow fluorescence. The catalyst was washed with cold and then hot absolute alcohol. The alcohol was removed by distillation under reduced pressure and the residue placed in an evaporating dish. On cooling a greenish-yellow solid precipitated. The solid, which had an indole-like odor, was filtered off and dried. The crude product was recrystallized by dissolving in hot absolute alcohol (charcoal), filtering, and adding water to the filtrate to incipient crystallization. The pure 2-ethyl indoxyl was an odorless, bright canary-yellow, amorphous solid weighing 0.7021 g. (48.6%) and melting at 166-167°.

Color tests on the 2-ethyl indoxyl gave the following results:

- 1) Cold concentrated sulfuric acid - blood red color.
- 2) Cold concentrated hydrochloric acid - pink color which darkened on standing.
- 3) Cold glacial acetic acid - yellow; on heating - orange color.
- 4) Cold acetic anhydride - yellow; on heating - orange color.

Zinc dust degradation studies on indoxyls:

Because the 2-methyl indoxyl produced in these studies differed considerably in melting point from that reported by Ingraffia (140), zinc dust distillations of both indoxyls were tried in order to reduce these compounds to their corresponding indoles. It was planned that the indoles be isolated and characterized, thus establishing the presence of the preformed

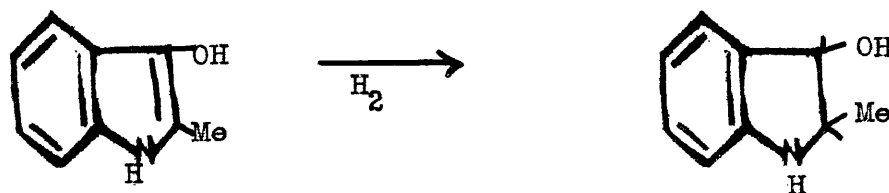


indole nucleus in the compounds under consideration.

The method of degradation was based on that of Vorländer and Apelt (13). About 100 mg. of either 2-methyl- or 2-ethylindoxyl was placed in a small Erlenmeyer flask with 50 ml. of 20% NaOH and to this was added 5 g. of zinc dust. The mixture was refluxed for one-half hour, during which the indoxyl went into solution, and then distilled with steam. The steam distillate possessed a definite fecal odor. Although small crystalline particles of solid could be seen in the steam distillate, no appreciable amounts of solid product could be obtained. On evaporation of the water from the steam distillate in a vacuum desiccator over P_2O_5 , a small amount of impure solid residue was obtained which was very low melting, but for which no melting point could be obtained. Addition of an ether solution of picric acid to this solid residue produced a bright orange precipitate so characteristic of the picrate of indole and its homologues. Unfortunately, insufficient picrate was produced to permit purification and determination of melting point. This failure at characterization of the products of degradation occurred with both the 2-methyl and 2-ethyl indoxyls.

As a substitute for the unsuccessful isolation of 2-methyl and 2-ethyl indoles, further degradations were run and the steam distillates were extracted with benzene. The benzene extracts were tested with Ehrlich's reagent (p-dimethylaminobenzaldehyde) and in each case a strong positive test for indoles (a bright red color) was obtained. Ehrlich's test on the original 2-methyl- and 2-ethylindoxyl was negative and the results of these experiments were taken as strong evidence in favor of a preformed indole nucleus in the compounds studied.

Reduction studies on 2-methyl indoxyl:



Experiment No. 1:

In a Parr reduction bottle was placed 0.8027 g. (0.0055 mole) of crude 2-methylindoxyl, 0.1 g. of PtO_2 , and 100 ml. of 70% alcohol. The details of hydrogenation were similar to previously considered cases. To reduce to the 2,3- dihydroindoxyl would require a 2.42 cm. drop on the manometer. After several hours shaking there was no apparent absorption of hydrogen and the reaction was stopped. Three grams of 10% Pd-charcoal catalyst was added to the mixture and the reduction was tried again. After four hours no drop was seen in the manometer and the shaking was interrupted at this point. Filtration of the reaction mixture and removal of the solvent only served to recover the original 2-methylindoxyl.

Experiment No. 2:

In this study, 2 g. (0.0096 mole) of o-nitroisonitrosopropiophenone, 100 ml. of 70% alcohol, and 0.1 g. PtO_2 were placed in the Aminco reaction

bomb for hydrogenation at 150 p. s. i. hydrogen pressure. After three hours the reduction had proceeded to the calculated 2,3-dihydroindoxyl stage and the reaction was stopped. Unfortunately, it was difficult, if not impossible, to obtain an accurate measure of the actual hydrogen uptake, for the Aminco bomb had a slight leak. At any rate, the reaction mixture yielded only the 2-methyl-indoxyl.

Experiment No. 3:

Fresh 10% Pd-charcoal catalyst was prepared in the usual manner, but 0.25 g. of H_2PtCl_6 was added to the mixture. This catalyst was placed in the Aminco reaction bomb with 2 g. (0.0090 mole) of o-nitroisonitrosobutyrophenone and 100 ml. of 70% ethanol at 150 p. s. i. hydrogen pressure. The reaction was allowed to proceed until no further uptake of hydrogen was observed (it was difficult to determine exactly this point because of the slight leak in the bomb.) Working up of the reaction mixture produced only 2-ethylindoxyl.

The further study of this reaction was not pursued further; however, it is felt that further detailed study of catalyst and conditions will produce the proper combination for the reduction of the double bond to the 2,3- dihydro compound.

Analytical Data:

<u>Name</u>	<u>Formula</u>	<u>Nitrogen %</u>	
		<u>Calc'd</u>	<u>Found</u>
o-nitroisonitrosopropiophenone	$\text{C}_9\text{H}_8\text{N}_2\text{O}_4$	13.46	13.42, 13.39
o-nitroisonitrosobutyrophenone	$\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_4$	12.61	12.42, 12.50
m-nitroisonitrosopropiophenone	$\text{C}_9\text{H}_8\text{N}_2\text{O}_4$	13.46	12.10, 12.18*
m-nitroisonitrosobutyrophenone	$\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_4$	12.61	12.46, 12.52
2-methylindoxyl	$\text{C}_9\text{H}_9\text{ON}$	9.52	9.51, 9.52
2-ethylindoxyl	$\text{C}_{10}\text{H}_{11}\text{ON}$	8.69	8.41, 8.42

*Not considered corroborative - discussion of these results page 40.

The analyses on the indoxyl compounds were run by the ordinary Kjeldahl procedure. Although acceptable analyses of the indoxyl compounds were obtained in this laboratory, it was considered worthwhile to have the results checked by a disinterested party. Verification of the analyses on the indoxyls was made through the courtesy of the laboratories of Sharp and Dohme, Inc. In the case of the o-nitroisonitrosoketones, it was necessary to resort to the use of a modified Kjeldahl to reduce the nitro group previous to digestion. This treatment was necessary, for the ordinary Kjeldahl procedure does not yield satisfactory results with $-\text{NO}_2$ compounds. The process that was given in the AOAC (141) using $\text{K}_2\text{S}_2\text{O}_3$ in place of K_2SO_4 in the digestion mixture. The m-nitroisonitrosoketones were analyzed by the Dumas procedure.

Pharmacological Studies:

Only preliminary blood pressure studies have been made on o-nitro-isonitrosobutyrophenone and 2-ethylindoxyl. These determinations were made on non-atropinized dogs anesthetized with nembutal administered intraperitoneally. Artificial respiration was not employed.

There was no change in blood pressure following intravenous injection in leg vein of 0.5 ml. of a solution of 10 mg./ml. concentration of o-nitroisonitrosobutyrophenone in 60% alcohol. 2-Ethylindoxyl was dissolved in 95% alcohol in a concentration of 0.5 mg./ml. One milliliter of this solution produced a rise in blood pressure from 155 mm. to 168 mm. of Hg. Because of the small amount of the compound which dissolved in alcohol, the compound was dissolved in propylene glycol, in which it is much more soluble, and, without weighing, a solution of about 10 mg./ml. was prepared. About 45 minutes after the injection of 2-ethylindoxyl in alcohol the blood pressure and respiration of the dog began to fail. At

this time one ml. of the propylene glycol solution of 10 mg./ml. was injected intravenously. Immediately the blood pressure level rose and respiration became more regular. The same sequence was repeated several times with the same effect after each injection of the compound.

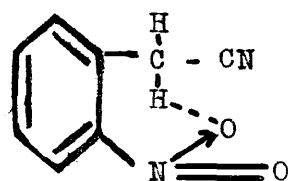
Because of the apparent effectiveness of 2-ethylindoxyl in propylene glycol when the animal appeared near death, it was decided to try the compound on another dog with accurately prepared solutions of known strength. An intravenous dose of 0.95 ml. of 2-ethylindoxyl of 10 mg./ml. concentration in propylene glycol produced no visible effect on the blood pressure or respiration of the animal. Similar results were obtained with doses as large as 4 ml.

The results were variable and inconclusive and it was not considered feasible at this time to continue the blood pressure studies of these compounds.

DISCUSSION OF RESULTS

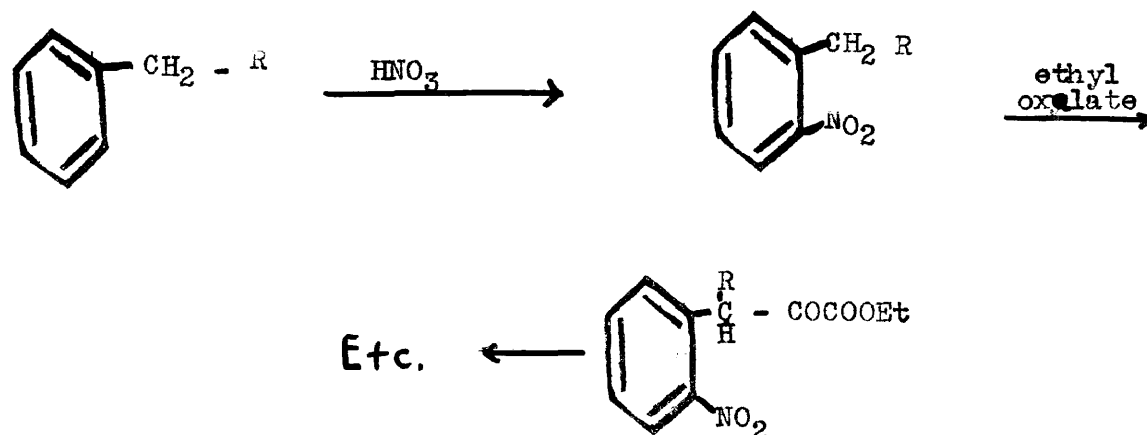
The much hoped for substitution of the α -hydrogen atoms in o-nitrophenylacetonitrile with subsequent reduction to the corresponding 3-substituted indoles did not succeed. The failure of these substitutions might, at first, seem strange since the α -hydrogen atoms of phenylacetonitrile itself are reactive and the -NO_2 group, especially in the ortho position, would be expected to activate the α -hydrogens even more strongly.

The explanation for this strange behavior probably lies in hydrogen bonding between the ortho nitro group and the α -hydrogens, thus, in effect, reducing the activity of the otherwise extremely reactive o-nitrophenylacetonitrile. By a similar line of reasoning, Dippy and Lewis (142, 143) explained certain abnormalities observed in the acid strengths of



o-nitrophenylacetic acids, as due to the chelation of the methylene and nitro groups.

It may be possible in some future study to prepare the desired 3-substituted indoles by introducing the substituent before nitration as follows:



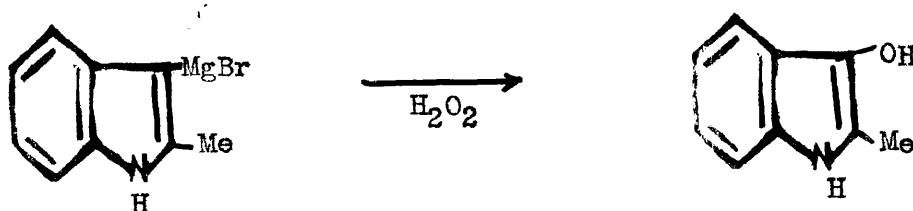
In the reduction of *o*-nitrophenylacetonitrile, it was possible to obtain a ring closure to indole in neutral medium. The yield matched that obtained by Stephen in his chemical reduction (39) and the indications are, that in larger scale operations, the yields would be improved. Furthermore, this method is much easier to perform than is Stephen's.

The course of the hydrogen uptake offers evidence that the $-\text{NO}_2$ group is reduced first to $-\text{NH}_2$ followed by reduction of the $-\text{CN}$ group to $-\overset{\text{H}}{\underset{\text{H}}{\text{C}}} = \text{NH}$. Evidently, in situ intramolecular cyclization, with the elimination of ammonia, occurs as soon as the nitrile is reduced to the imine and before intermolecular reaction to form secondary amine can take place to any extent.

Reduction studies of the *o*-nitroisocyanosketones to their corresponding indoxyls also took place in neutral medium. Here, as in the case of the *o*-nitrophenylacetonitrile, hydrogen uptake pointed to a rapid initial reduction of the $-\text{NO}_2$ group to $-\text{NH}_2$ followed by reduction of $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$ and $-\overset{\text{O}}{\underset{\text{NOH}}{\text{C}}}-$ to $-\overset{\text{H}}{\underset{\text{H}}{\text{C}}}\text{OH}$ and $-\overset{\text{H}}{\underset{\text{NH}}{\text{C}}}-$ respectively. Reductions which were terminated after four mole hydrogen uptake gave a product identical with that obtained from five mole hydrogen uptake, except that larger yields were obtained with five mole uptake. This is interpreted as proof that the first stage in the reduction consists of a reduction of the $-\text{NO}_2$ group of all the starting

material present to the $-NH_2$. Subsequent hydrogen uptake would convert the $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \\ \text{OH} \end{array} \rightarrow \begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \\ \text{OH} \end{array}$ and the $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \\ \text{HOH} \end{array} \rightarrow \begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \\ \text{NH} \end{array}$ at equal rates and immediate in situ cyclization, with the loss of ammonia, follows. Thus a four mole hydrogen uptake would merely carry less of the product beyond the aminoisonitrosoketone stage and would thus produce a smaller yield of the final product.

Ingraffia (140) reported the preparation of 2-methylindoxyl by the following reaction:



He reported no yields, but his compound was a yellow crystalline solid melting at 40° , not very stable, and in a short period became a black gummy mass. The product obtained in this study melts at $133-134^\circ$, is a bright yellow solid, is stable and gives positive results with all color tests cited by Ingraffia on his compound. It is very likely that Ingraffia's product was not very pure as evidenced by its rapid transformation into a black gummy mass. Thus, in this study it was observed that solutions of the indoxyls exposed to the air soon became highly colored (red-violet) resembling the behavior of indoxyl in going to indigo. Also, when impure isonitrosoketone was reduced, a resinous product was obtained which on standing became a black gummy mass. Furthermore, indoxyl melts at 85° and 2-methylindole melts at 59° and it seems unlikely that 2-methyl indoxyl would melt lower than either of these two.

Ingraffia's analysis for 2-methylindoxyl was high (calculated 5.62%N; found 5.75%N) and his product may have been contaminated with the low-melting 2-methylindole. Furthermore, his synthesis of 2-methylindoxyl

depends on an obscure application of the Grignard reaction and a search of the literature reveals that little is known of the method or its dependability. Rearrangements, which are not uncommon in Grignard reactions, may well play a part in this instance and produce an impure and low-melting product.

Evidence offered in support of the claim that the product of this study is 2-methylindoxyl follows:

- a) The analytical data on 2-methylindoxyl fits exactly that calculated for this compound.
- b) Water solutions of the compound are yellow-green and fluorescent - this property is a characteristic of indoxyl.
- c) Degradation with zinc dust and sodium hydroxide yields an indole which has either a free α - or β -position as indicated by a positive Ehrlich's test. The small quantities of the indoxyls available did not yield sufficient indole degradation product for further characterization.
- d) The compound produced a red color with ferric chloride solution - this property is also exhibited by indoxyl and is an indication of its phenolic character.

Similar evidence for the presence of an indoxyl nucleus was obtained from the reduction product of o-nitroisonitrosobutyrophenone.

It was impossible, in the short time available, to succeed in reducing the 2,3-double bond in the indoxyls to the corresponding 2,3-dihydro compounds to approximate more closely the adrenochrome structure. However, it is felt that further study of this phase of the problem will reveal proper conditions and catalysts for the preparation of the 2,3-dihydro-indoxyls.

S U M M A R Y

1) The Introduction provides a concise review of the important syntheses of the indole nucleus and indoxyl and a brief consideration of their role in industrial and medicinal chemistry.

2) The preparation of o-nitrophenylacetonitrile was possible by two routes (pyrolysis and reaction with acetic anhydride) both giving good yields (65-71%). The method using acetic anhydride possesses a number of advantages over pyrolysis and further study with this technique should improve the yields.

3) Limited attempts at preparing α -substituted o-nitrophenylacetonitriles were unsuccessful.

4) The catalytic reduction of o-nitrophenylacetonitrile in neutral medium produced indole in 55 % yields by a process much simpler to perform than the chemical method of Stephen (39). Undoubtedly, greater experience will permit this method to surpass the yields attained and thus give the method still greater advantage over the chemical reduction.

5) The following nitroketones were obtained by a process of nitration with fuming nitric acid:

o- and m-nitroacetophenones

o- and m-nitropropiophenones

o- and m-nitrobutyrophenones

6) The following nitroisonitrosoketones were prepared from the nitroketones by the usual nitrosation procedure:

o- and m-nitroisonitrosopropiophenones

o- and m-nitroisonitrosobutyrophenones

Qualitative indications of the success of the reaction were obtained by oximation and tests with ammoniacal nickel sulfate. Analytical results for the m-nitroisonitrosopropiophenone indicate the product was contaminated with some of the original ketone. Attempts at nitrosation of the o- and m-nitroacetophenones did not succeed.

7) Attempts at preparing o-nitro α,β -diketones from the corresponding nitroisonitrosoketones also failed.

8) Reduction studies of the o-nitroisonitrosoketones produced 2-alkyl substituted indoxyls in yields of 48-55%. Analyses, qualitative color test and zinc dust degradations offered supporting evidence of the nature of the products. Attempts to reduce the 2-alkylindoxyls to the corresponding 2,3-dihydroindoxyls met with no success in the preliminary study made.

9) Of the compounds prepared the following:

o-nitroisonitrosopropiophenone (a)

m-nitroisonitrosopropiophenone

o-nitroisonitrosobutyrophenone

m-nitroisonitrosobutyrophenone

2-methylindoxyl (b)

2-ethylindoxyl

are reported in the literature for the first time.

(a) Previously prepared by Hartung (116), but not reported in the literature.

(b) Reported by Ingraffia (140), but results here indicate his compound was impure and that the physical constants reported are incorrect.

10) Preliminary pharmacological studies of the pressor effects of o-nitroisonitrosobutyrophenone and 2-ethyl indoxyl were made. o-Nitro-isonitrosobutyrophenone was completely without effect. With 2-ethylindoxyl the results were variable and no definite conclusions could be drawn; however, the fragmentary results obtained do indicate that a further study of the indoxyls might prove them to have some effect on blood pressure.

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