

ISOQUINOLINE SYNTHESSES

By

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fulfillment of the requirements for the  
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1947

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"Beggar that I am, I am even poor in thanks, but I thank you."-- Shakespeare

The author wishes to express his gratitude and profound esteem to the following:

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## TABLE OF CONTENTS

	Page
INTRODUCTION.....	1
a. Pharmacology of the Isoquinoline Group.....	5
b. General Methods of Syntheses of the Isoquinoline Nucleus.....	6
c. Phytochemical Synthesis of the Isoquinoline Nucleus.....	10
d. Synthesis of Tetrahydroisoquinolines by the Method of Decker and Becker.....	14
e. Methods of Obtaining $\beta$ -Arethylamines.....	17
f. Research Aim.....	21
EXPERIMENTAL	
I. Synthesis of Substituted $\beta$ -Phenethylamines	
a. Mandelonitrile Benzoates.....	23
b. Substituted Mandelonitriles.....	26
c. $\omega$ -Nitrostyrenes.....	29
d. Aracetaldoximes.....	36
e. Hofmann Degradation of $\beta$ -Phenylpropionamides....	41
f. Rhodanine Method.....	43
g. Mandelonitrile Acetates.....	44
h. "Active" Catalyst.....	49
II. Attempts to Prepare Substituted Phenylacetaldehydes..	
51	
III. Ring Closure	
a. Phytochemical.....	53
b. The Method of Buck.....	56
c. Preparation of Dihydroisoquinolines.....	58
d. The Method of Decker and Becker.....	59
DISCUSSION OF RESULTS.....	66
SUMMARY.....	69
LITERATURE CITED.....	71

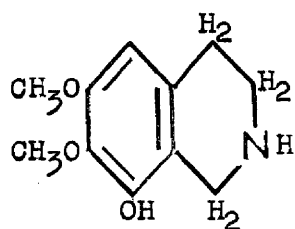
LIST OF TABLES

Table	Page
I. Phenyl-Substituted- $\omega$ -Nitrostyrenes.....	31
II. Schiff Bases.....	61
III. Tetrahydroisoquinoline Hydrochlorides.....	65

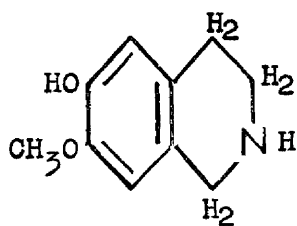
## INTRODUCTION

In the realm of alkaloidal chemistry the isoquinoline group, including various degrees of saturated and related compounds, occupies a significant position. Many of these alkaloids possess valuable physiological properties which have stimulated a great interest in the chemistry of isoquinoline compounds.

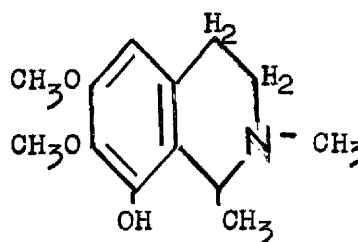
For convenience the isoquinoline alkaloids have been classified into several groups (1). The simplest group, isolated from cactus species, is represented by:



Anhalamine



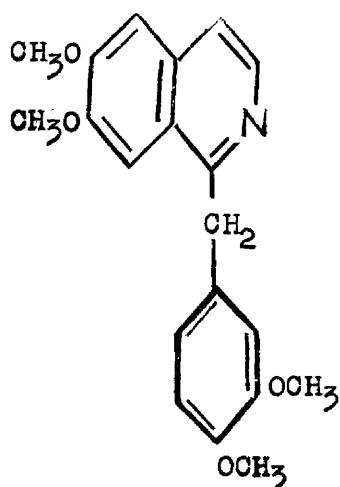
Salsoline



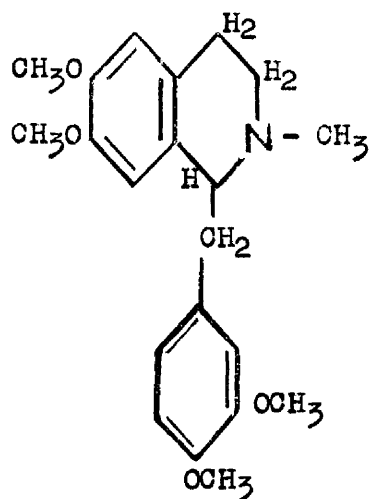
Pellotine

The tetrahydroisoquinoline, anhalamine, was synthesized by Späth and Beake (2). The anhalonium alkaloids are found in the flowering heads of several species of Anhalonium or Lophophoia cactus, known to the natives of Mexico as mescal buttons.

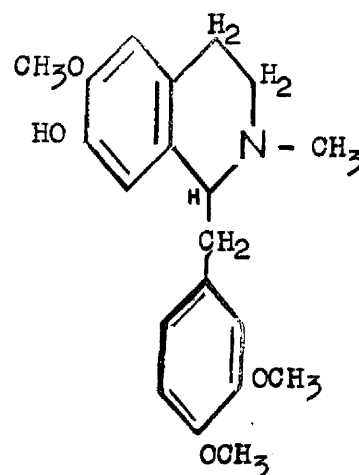
A second and large class comprises the benzyisoquinolines. These are of several types depending on the manner in which the benzyl radical is attached to the pyridinoid ring. The largest sources of the benzyisoquinoline alkaloids are those obtained from the Papaveraceae family:



Papaverine



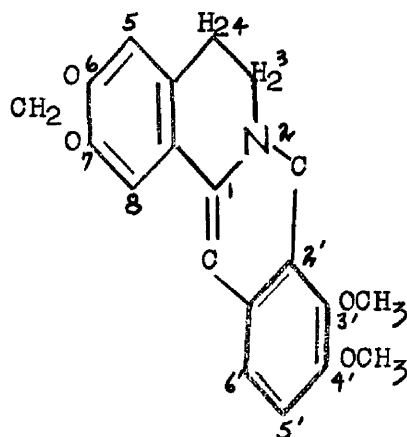
Laudanosine



Codamine

Papaverine is of special interest because it was the first case of the recognition of the natural occurrence of an isoquinoline derivative (3). It is an isoquinoline with the benzyl group in the 1-position. Pictet and Gams' preparation of papaverine (4) is a classical example of synthetic work in this field. Papaverine is found in all parts of the poppy and is present in opium to the extent of 0.5 to 1 per cent.

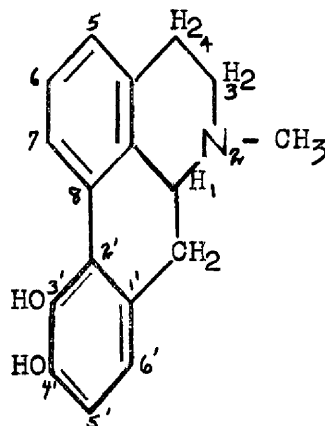
The second type of benzylisoquinoline alkaloid involves a ring closure with the nitrogen atom in the 2 position when the appropriate substituent is in the 2' position -- this gives the berberine type:



Berberine

Berberine has been synthesized by several investigators (5,6,7).

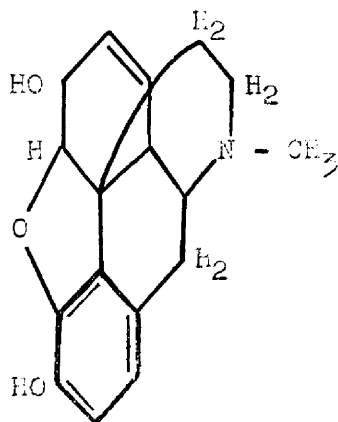
If the ring closure is between the 2' and 8 position a third type of structure is obtained. This is represented by apomorphine:



Apomorphine

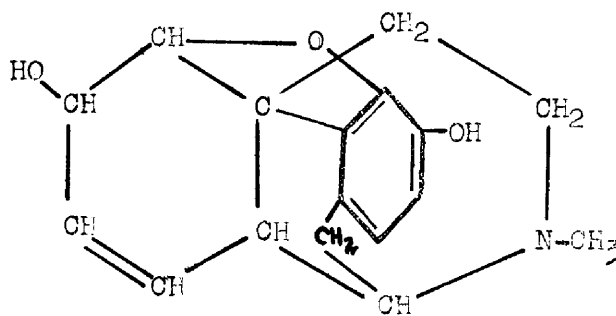
The dimethyl ether has been synthesized by Avenarius and Pschorr (8).

The benzylisoquinoline nucleus attains its greatest degree of complexity in the morphine type of alkaloids. Morphine itself has never been synthesized but its structure has been inferred from a study of its degradation products. The proposed structure of Gulland and Robinson (9) is supported by the experimental facts thus far found:





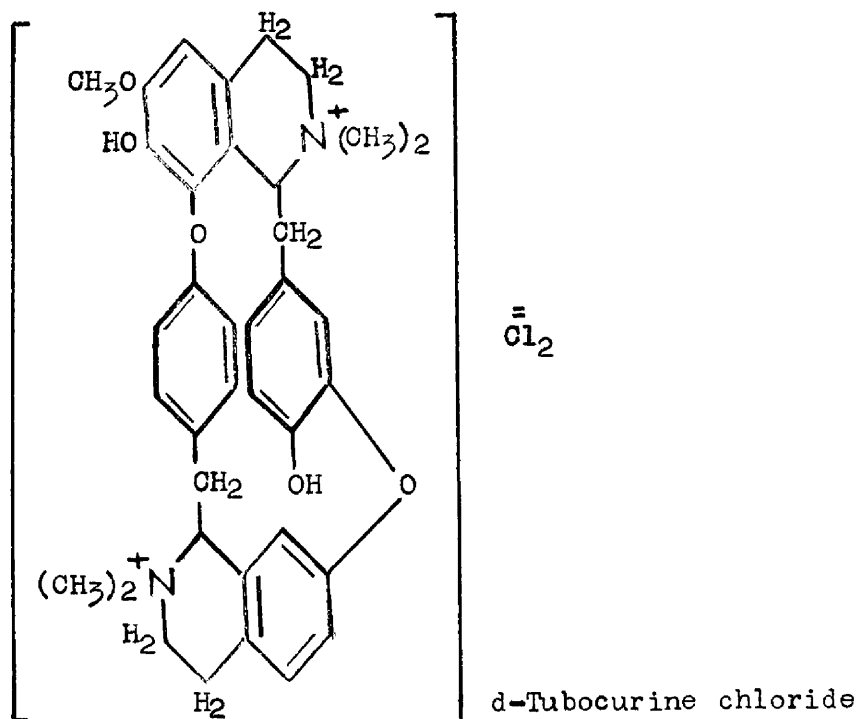
If Robinson's formula is projected in another way its benzyloisoquinoline structure is more readily appreciated:



The benzyloisoquinoline derivation is not easily shown by the planar formula; however, it can be seen that the 2' position of the benzyl portion of the molecule is attached to the quaternary carbon atom of the isoquinoline nucleus. Molecular models show this relationship clearly.

Other members of this group include codeine (monomethylated morphine), thebaine and heroin (diacetyl morphine). Morphine occurs to the extent of 10% in opium and was the first organic base to be isolated and characterized as such.

The third and last group are the bisbenzyloisoquinoline alkaloids. These are represented by the curare type alkaloids, whose structure was brilliantly elucidated by King (10), Wintersteiner, and Dutcher (11,12):



## THE PHARMACOLOGY OF THE ISOQUINOLINE GROUP

Analogous to the wide structural variations of the isoquinoline alkaloids is the great diversity of their pharmacological activity. It is beyond the scope of this dissertation to attempt an exhaustive survey of the manifold and diverse physiological actions of these compounds. Only the more salient facts will be stated here in order to emphasize the effect of structure on physiological activity.

Pharmacologically, the alkaloids of the anhalonium family (mescaline, anhaline, anhalamine) are characterized by their exhilarating effect and increased reflex excitability. The visual and auditory hallucinations probably are due to the action of mescaline (13). These effects are usually accompanied by bradycardia, mydriasis, loss of accurate time sense, nausea, faintness and headache.

The benzyloisoquinolines possess unusual pharmacological properties. The papaverine group (laudanoline, codeine) has only insignificant effects on the nervous system but exerts a definitely antispasmodic action on smooth muscle. Bruckner and Fodor (14) report that the presence of a methylene group between the heterocyclic and aromatic ring is not necessary. 1-Aryloisoquinolines compare favorably with the analogous benzyloisoquinolines in their neurospasmodic properties. In sharp contrast is the morphine group (codeine, thebaine) which acts chiefly on the central nervous system where a combination of depressant and stimulant effects is produced (15).

Apomorphine shows some of the morphine actions but the emphasis is much more on the excitant than on the depressant action. The medullary excitant action is most pronounced and is exercised mainly on the vomiting center, causing emesis with its concomitant symptoms of nausea, sweating, etc. Large doses cause convulsions (16).

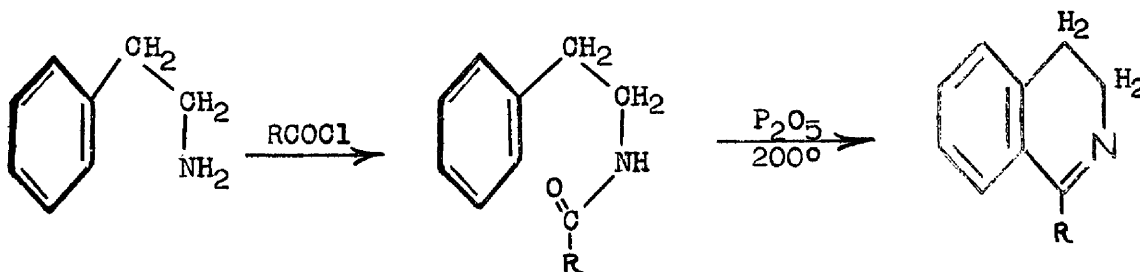
Curare, the South American Indian arrow poison, possesses the peculiar property of paralyzing motor nerve endings while leaving the sensory nerves intact. The alkaloid has been used clinically as an aid in shock therapy (17), for the treatment of spastic paralysis (18), and as an adjunct to anesthesia in surgery (19).

This short review of the physiological activity of the isoquinoline compounds does not do justice to this fascinating subject, but does suggest the importance of the isoquinoline nucleus in modern medicinal chemistry.

#### METHODS OF SYNTHESSES OF THE ISOQUINOLINE NUCLEUS

The synthesis of the isoquinoline nucleus has provided a fertile field for the imagination and skill of the organic chemist. There are many important methods of isoquinoline synthesis based on the closure of the pyridine ring. The most widely used and technically important methods start from  $\beta$ -arethylamines which may be condensed with acids, leading to dihydroisoquinolines, or with aldehydes to yield tetrahydroisoquinolines.

Method I: From acylated  $\beta$ -phenethylamines: The reaction of the acyl or aroyl derivatives of  $\beta$ -phenethylamines with dehydrating agents such as phosphorous pentoxide or zinc chloride at elevated temperatures to form the isoquinoline nucleus is known as the Bischler and Napieralski reaction (20).

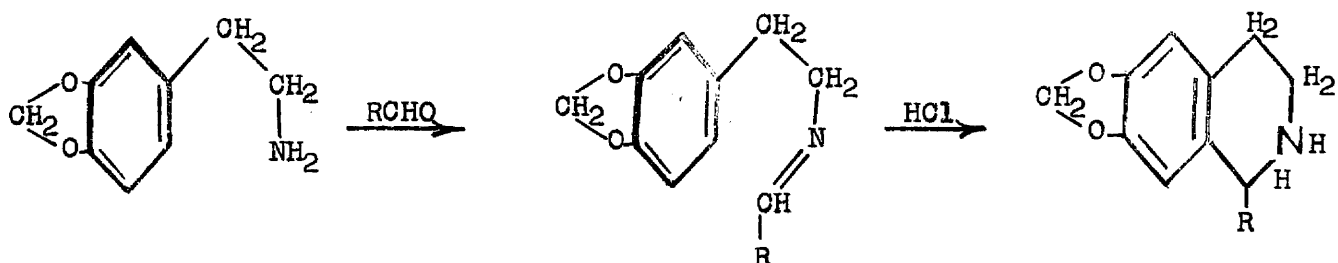


R may be aliphatic or aromatic

A detailed account of this reaction is given by Whaley (21) who is currently investigating this type of synthesis.

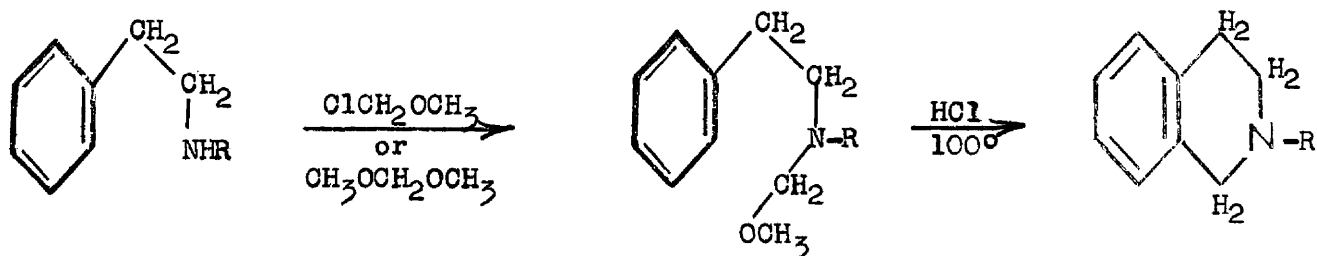
Method II: From  $\beta$ -arethylamines and aldehydes:  $\beta$ -arethylamines react readily with most aldehydes to give the alkylidene derivative (Schiff bases). These compounds then undergo ring closure when warmed with a variety of condensing agents such as hydrochloric acid, sulfuric acid, zinc chloride and thionyl chloride (22).

Decker and Becker (23) condensed homopiperonylamine with a number of aldehydes and converted the resulting Schiff bases into tetrahydroisoquinolines by the action of concentrated hydrochloric acid:

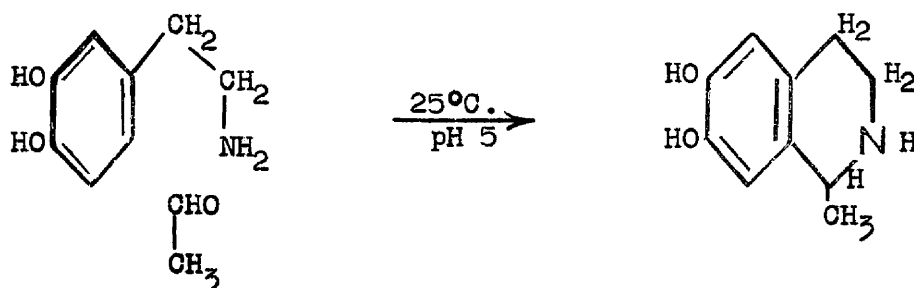


Alkaloids of the hydrastinine group have been synthesized by Decker (23) in this manner.

A special case of the above method is the synthesis of tetrahydroisoquinolines from methylal derivatives of  $\beta$ -arethylamines. The intermediate amino ether is isolated and used for the ring closure. The action of chloromethyl ether upon  $\beta$ -arethylamines also yields compounds of this type which may then be converted into isoquinolines (24).

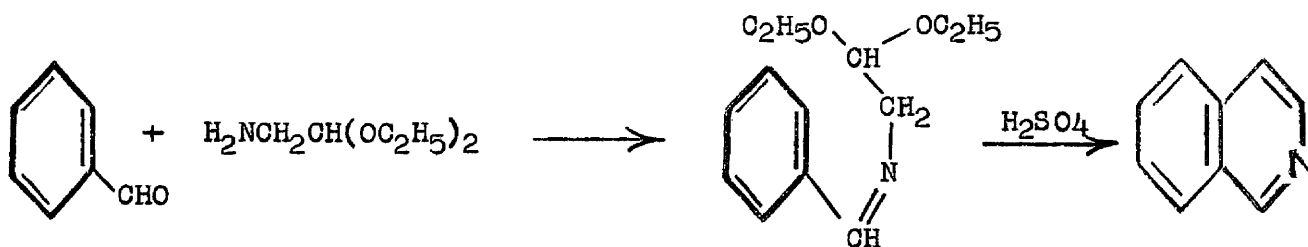


Method III: Biosynthesis of the isoquinoline nucleus: Following the inspiring researches of Robinson (25), whose "elegant" synthesis of tropanone from succindialdehyde, methylamine and acetone had intrigued many chemists with the possible phytochemical synthesis of alkaloids, Schöpf and Bayerle (26) synthesized 1-methyl-6-7-dihydroxy-tetrahydroisoquinoline without the aid of catalysts:



The reactants were in low concentration with temperature and pH within the range of cell-possible conditions.

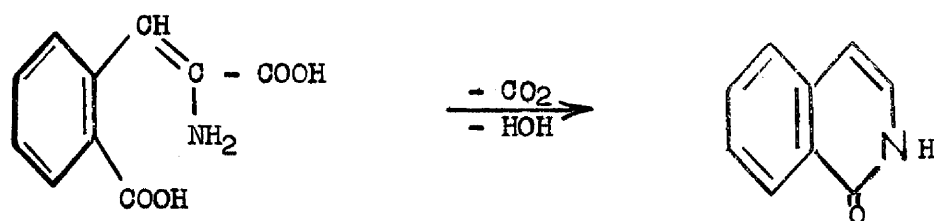
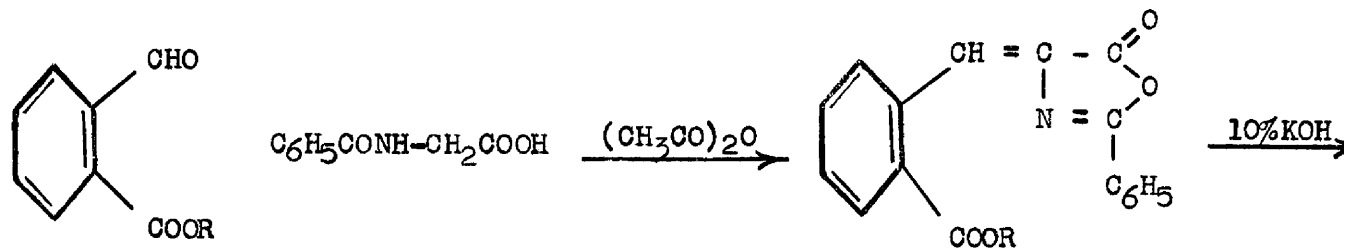
Method IV: From aromatic aldehydes and aminoacetals: Aminoacetals readily condense with aromatic aldehydes. The condensation products undergo ring closure with great facility when concentrated sulfuric acid or other dehydrating agents are used (27):



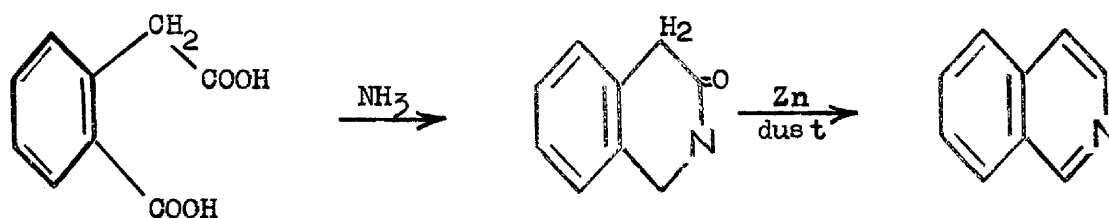
For this type of synthesis a system of conjugated double bonds, either real or potential,  $\phi - C = NCH=CHOR$ , is necessary (28).

Method V: From *o*-substituted benzoic acids or related compounds: The acids are easily converted to amides which can then undergo condensation with proper substituents in the ortho position (29):

a.



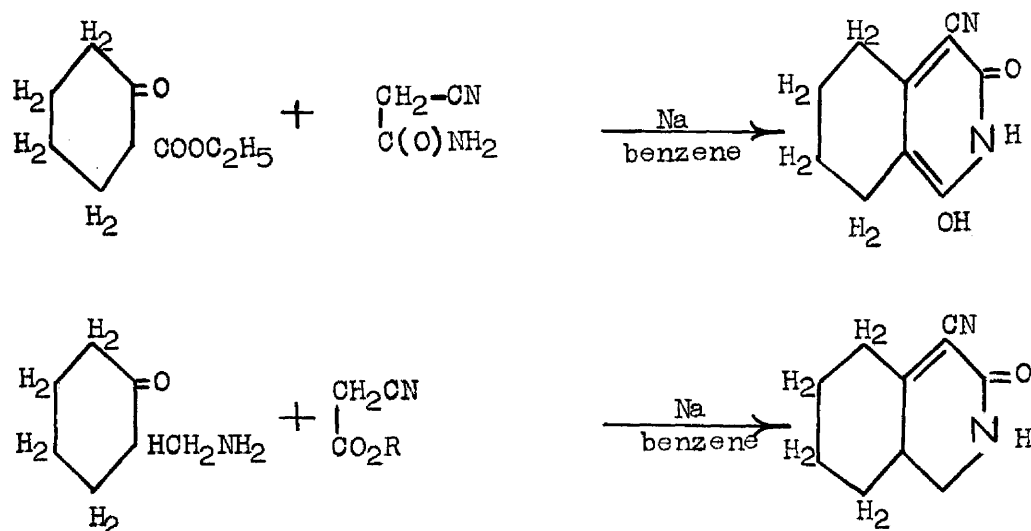
b.



This synthesis is important historically for it was by this method that isoquinoline was first prepared (30).

Method VI: From cyclohexanones: Ethyl cyclohexanone-*o*-carboxylate condenses with a cyanoacetamide; or an amine derived from the reduction product

of ethyl cyclohexanone-*o*-carboxylate, condenses with ethylcyanoacetate to yield the isoquinoline nucleus (31):

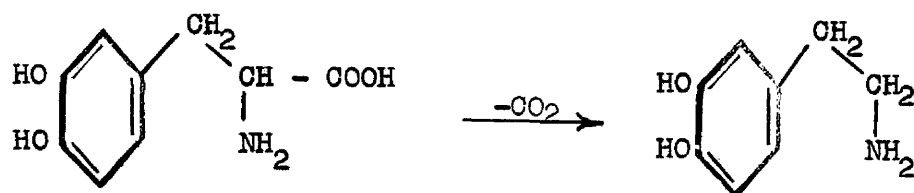


This brief survey shows the general methods which have been employed in synthesizing various isoquinolines and derivatives. Hollins (32), Morton (33) or Sidgwick (34) may be consulted for a more complete treatment of this subject.

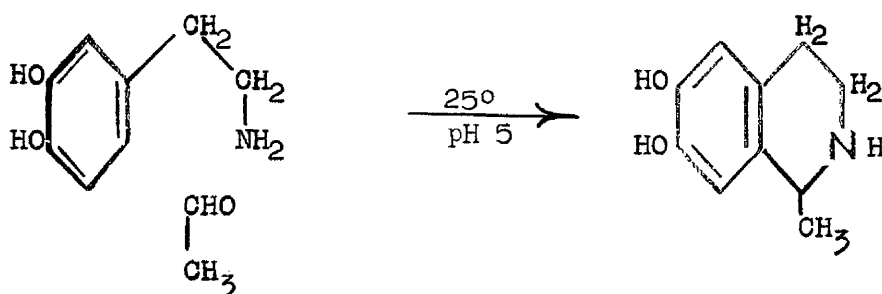
#### Phytochemical Synthesis of the Isoquinoline nucleus:

The manner in which plants produce alkaloids has always aroused interest. Winterstein and Trier (35) first suggested in 1910 that plants build series of closely related bases from a common parent substance, by reactions involving condensations, decarboxylation, methylation, oxidation and reduction, singly or in combination. It is generally accepted that in the heterocyclic portion of these alkaloids the nitrogen atom and the four carbon atoms come from an amino acid and the fifth carbon from an aldehyde. The substituted phenethylamines have long been thought of as the probable parent substances of the isoquinoline alkaloids. Many of these alkaloids have substituents in

the 1, 6 and 7 positions; these may be formed from the condensation of the appropriate aldehyde with 6,7-dihydroxyphenethylamine. The latter amine may arise from the degradation of dihydroxyphenylalanine.



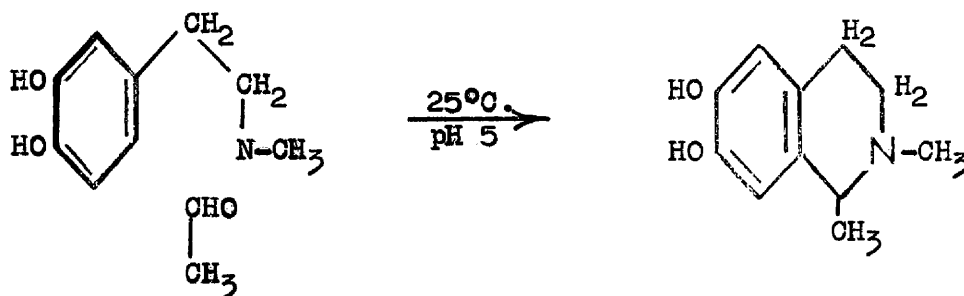
The pioneering work of Robinson (25) in establishing experimentally this theory of phytochemical synthesis by his production of tropanone served as an impetus to Schöpf and coworkers in applying this theory to isoquinoline syntheses. Schöpf and Bayerle (26) allowed a solution of M/25 3,4-dihydroxyphenethylamine and M/12.5 acetaldehyde to stand for 72 hours at 25°C. at pH 5; at the end of that time excellent yields of 1-methyl-6,7-dihydroxy-tetrahydroisoquinoline were obtained. The product is an O-desmethyl analog of salsoline (see p. 1).



The reaction is nonenzymatic and the nature of occurrence of salsoline as the racemic form suggests that the plant synthesized it in a similar way.



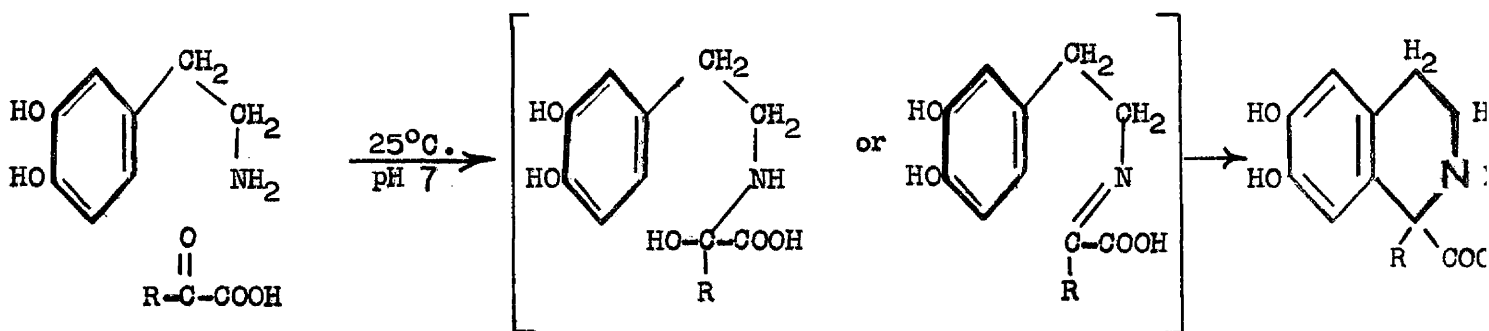
In an analogous manner Schöpf and Bayerle (26) condensed epinine [N-methyl-β-(3,4-dihydroxyphenyl)ethylamine] with acetaldehyde:



The N-methyl tetrahydroisoquinoline was isolated as the picrate.

The ring closure requires an activating substituent in the 3 position. Schöpf and coworkers concluded that the activating group must be a free hydroxyl.

In order to extend the scope of formation of tetrahydroisoquinolines under physiological conditions, Hahn et al and Schöpf et al used keto acids in place of aldehydes (36,37). As with aldehydes, the reaction proceeds through the Schiff base stage to the tetrahydroisoquinoline:



The optimum pH was found to be 7 but since atmospheric oxygen reacts with 3,4-dihydroxyphenethylamine, it was necessary to use an acid medium to obtain a pure product. Under some conditions spontaneous decarboxylation occurs (36).

The effect of pH on the rate of condensation has been studied by Schöpf (26,37). Thus, in the condensation of 3,4-dihydroxyphenethylamine

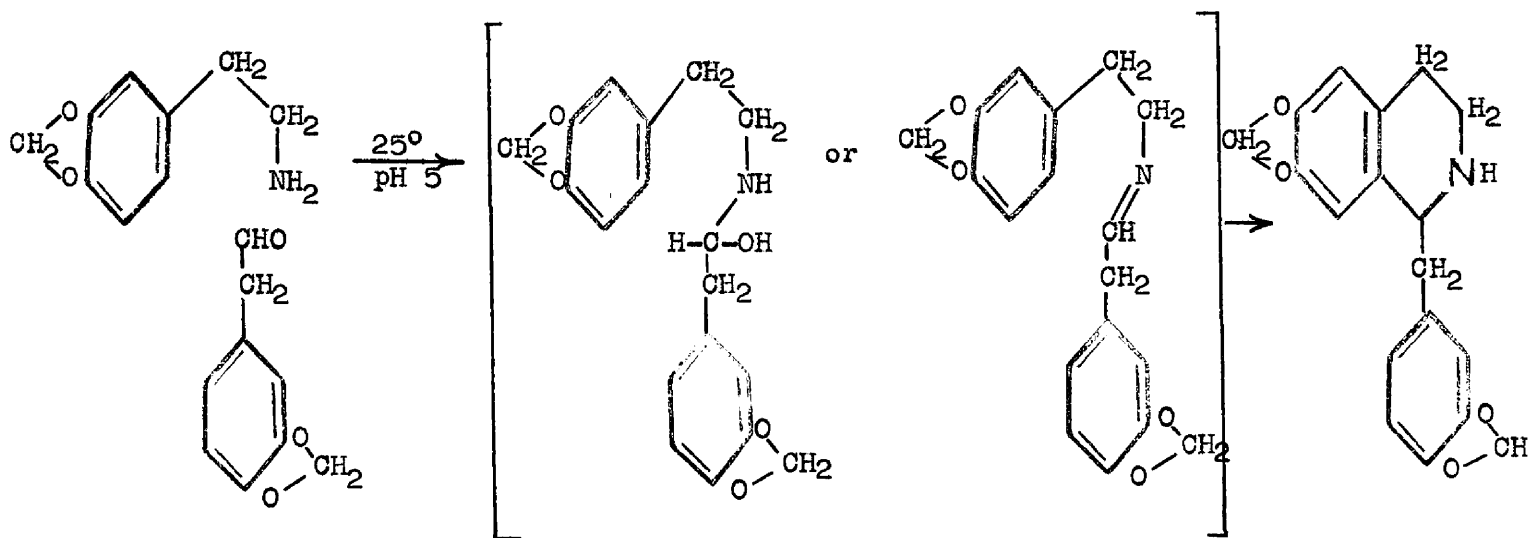
and homopiperonal the time required for formation of 30% of the tetrahydroisoquinoline was:

pH 3 --- 5 days  
 pH 4 --- 24 hours  
 pH 5 --- 4.5 hours  
 pH 6 --- 50 min.  
 pH 7 --- 13 min.

In an analogous experiment 3,4-dihydroxyphenethylamine was condensed with piperonyl glyoxylic acid; the time required for 30% conversion was:

pH 5 --- 35-40 days  
 pH 6 --- 6 days  
 pH 7 --- 2.5 days

Hahn and Schales (38) did not accept the view of Schöpf and Bayerle that a free hydroxyl group in the 3 position is necessary for ring closure; it seemed improbable to them that the numerous methoxy and methylenedioxy analogs found in nature must be excluded as possible starting materials. They ran numerous experiments using alkoxy groups in the 3 position. The following is typical:



The reported yield of the 6,7,3',4'-bismethylenedioxybenzyl-1,2,3,4-tetrahydroisoquinoline was low and the reaction much slower (requiring 8 days) than when the hydroxyl group in the 3 position was unalkylated. The formation of the intermediate Schiff base was rapid as indicated by the disappearance of the reactants. The authors claim that the actual ring closure was much slower as shown by the formation of only 5% of the isoquinoline while apparently 90% of the intermediate was formed.

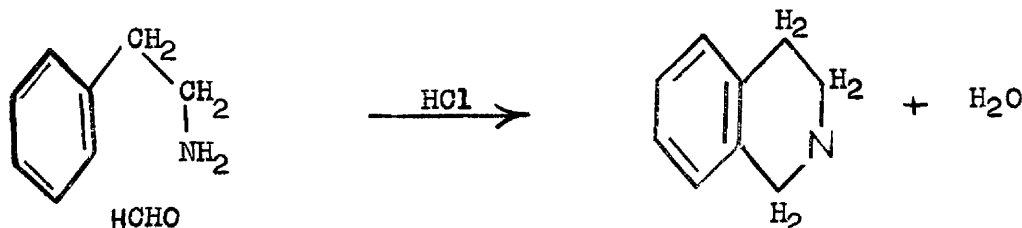
Späth, Kuffner and Keszler (39) could not duplicate the work of Hahn and Schales, but obtained the unchanged amine and Schiff base. The identity of the Schiff base was confirmed by comparison with a product previously prepared by the method of Decker and Becker (40).

The condensation of hydroxyphenethylamines with aldehydes under biological conditions to form tetrahydroisoquinolines depends too greatly on the nature of the amine and aldehyde to make the method capable of general application.

Synthesis of tetrahydroisoquinolines by the method of Decker and Becker:

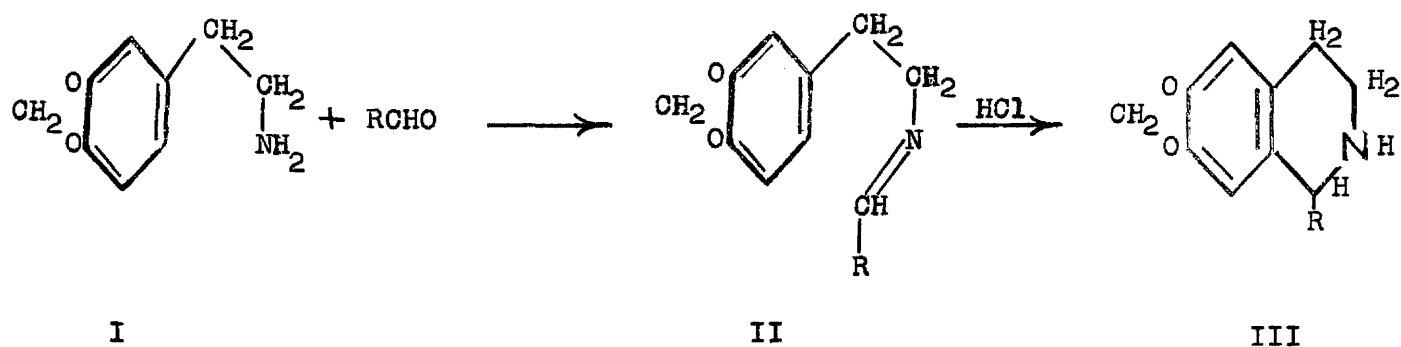
The synthesis of tetrahydroisoquinolines by condensing  $\beta$ -arethylamines with aldehydes in the presence of hydrochloric acid will be described in greater detail since it occupies the major aim of the present investigation.

Pictet and Spengler (41,42) prepared a series of tetrahydroisoquinolines by condensing substituted phenethylamine with formaldehyde (or methylal):



Concentrated hydrochloric acid was the condensing agent. The authors claim fair yields. In an analogous manner tyrosine and phenylalanine were converted to the corresponding isoquinolines.

This type of reaction was investigated extensively by Decker and Becker (23,43) who condensed substituted phenethylamines with a variety of aldehydes to form the Schiff bases (II). After isolation these were converted into the corresponding tetrahydroisoquinolines (III) by the action of concentrated hydrochloric acid. The mechanism of this cyclization is obscure.



Other condensing agents that have been used include anhydrous hydrogen chloride, phosphorous oxychloride, zinc chloride, thionyl chloride, and hydrogen bromide (43). In most cases the conversion went smoothly; however, in the reaction of formaldehyde and homopiperonylamine (L), five products were isolated:

1. Schiff base
2. Tetrahydroisoquinoline
3. N-methyltetrahydroisoquinoline
4. NN-dimethylhomopiperonylamine
5. High molecular base of unknown constitution

The Schiff base and tetrahydroisoquinoline are the expected products. The methylation of the nitrogen atom by formaldehyde during the ring closure should cause no surprise since it forms the basis of the Eschweiler reaction (44). The high molecular base of unknown constitution was thought at first to be a polymeric methylenhomopiperonylamine:



R = 3,4-methylenedioxyphenyl

However, the analysis did not agree with the expected product, but with a compound that contains three moles of the base and one of water.

Unfortunately, Decker and Becker are vague in their experimental details and give few quantitative relationships as to reactants or yields.

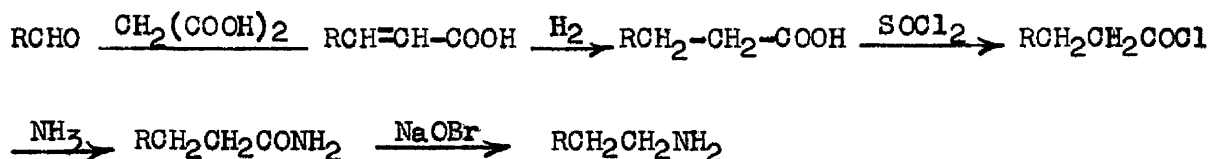
Buck (45) prepared a series of substituted tetrahydroisoquinoline hydrochlorides by a method very similar to that of Decker but reported no yields. The aldehyde used in every case was formaldehyde, the amine being varied. Buck noted some discrepancies between the properties of two methylenedioxytetrahydroisoquinolines found and those reported. A possible answer might be cyclization to give the 5,6 instead of the 6,7-methylenedioxy derivative as Buck suggests or a polymeric methylenhomopiperonylamine that Decker isolated.

In most condensations of this type a limited number of aldehydes was used. Formaldehyde seemed to be a favorite, perhaps because of its great versatility.

Decker (43) investigated the possibilities of some aldehydes other than formaldehyde; he condensed homopiperonylamine with benzaldehyde, cinnamylaldehyde, and piperonal. This reaction offers many interesting potentialities and merits further investigation.

METHODS OF OBTAINING  $\beta$ -ARETHYLAMINES

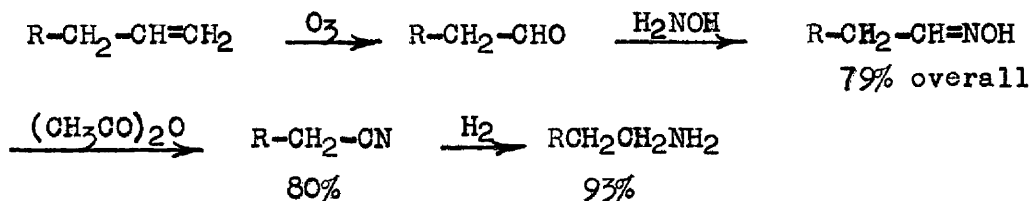
A review of the methods available for the preparation of the requisite  $\beta$ -arethylamines is given by Slotta and Heller (46) and by Morton (33). A favorite sequence with the early workers is:



R = substituted phenyl group

The 2,3-, 3,4-, and 3,5-dimethoxyphenethylamines (47,48,49,50) have been synthesized in this manner. This method is laborious and the overall yield is low.

Another method that found wide application is illustrated by Hahn and Schales' synthesis of homopiperonylamine (51):

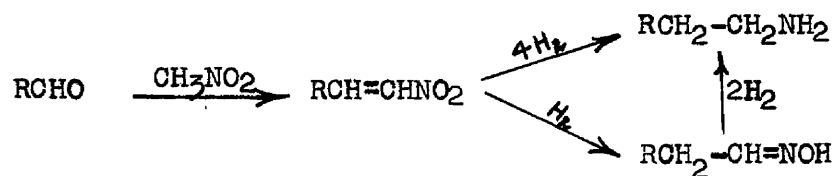


R = 3,4-methylenedioxyphenyl

For the reduction of the nitrile the method of Kindler and Peschke (52) was used. While the authors claim good yields for this sequence, the substituted phenylacetaldehydes are difficult to obtain.

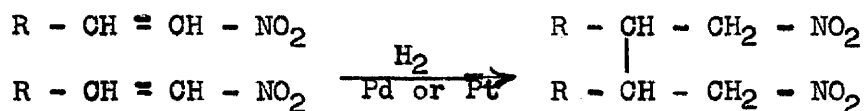
A synthesis of the  $\beta$ -arethylamines that has much appeal because of its simplicity and availability of starting materials employs  $\omega$ -nitrostyrenes. Nitromethane readily condenses with substituted benzaldehydes to yield the  $\omega$ -nitrostyrenes (53,54,55,56,57); these can be reduced, via

the oxime, (56) or directly to the corresponding  $\beta$ -arethylamines:



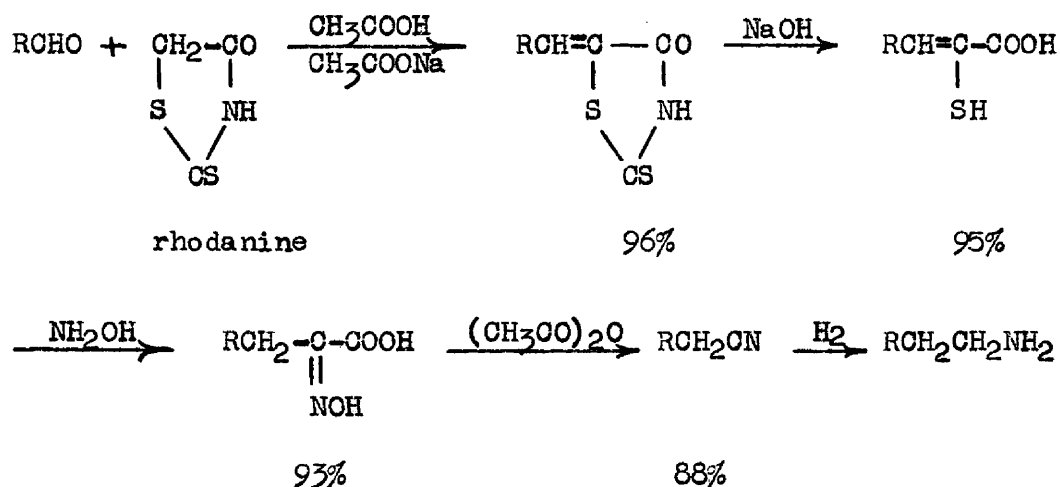
R = substituted phenyl

The catalytic reduction of the  $\omega$ -nitrostyrene is not as simple as expected, for Sonn and Schellenberg (54) have reported the formation of a diphenylbutane dimer.



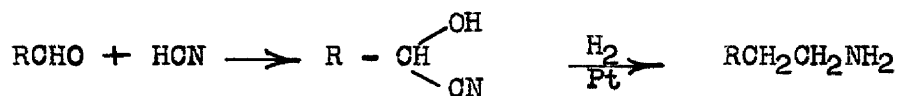
Skita and Keil (60) reduced catalytically the  $\omega$ -nitrostyrenes to the corresponding amines. Their work was improved later by Kindler, Brandt and Gehlhaar (61), who found that the reduction proceeded smoothly in the presence of sulfuric acid. The catalytic reduction of  $\omega$ -nitrostyrenes to the corresponding oximes was described by Reichert and Koch (58) who claim poor yields if direct reduction methods are used. These authors used pyridine as a solvent, thus binding the aci form of the nitro group and allowing the reduction to proceed to the oxime stage. The oxime was isolated and reduced either chemically or catalytically.  $\omega$ -Nitrostyrenes have also been reduced to the oxime stage by chemical means and thence to the amine (62,63). Electrolytic reduction has been employed with excellent results for the direct reduction of  $\omega$ -nitrostyrenes (64).

An unusual method for the preparation of homoarylamines, as given by Julian and Sturgis (65), involves the condensation of the appropriate aromatic aldehyde with rhodanine.



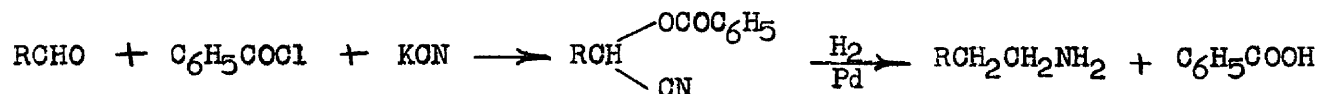
Although the series is long and laborious, excellent yields are reported.

Buck successfully employed the catalytic reduction of mandelonitriles to obtain  $\beta$ -arethylamines (66).



However, the mandelonitriles are sensitive compounds and must be highly purified prior to their reduction.

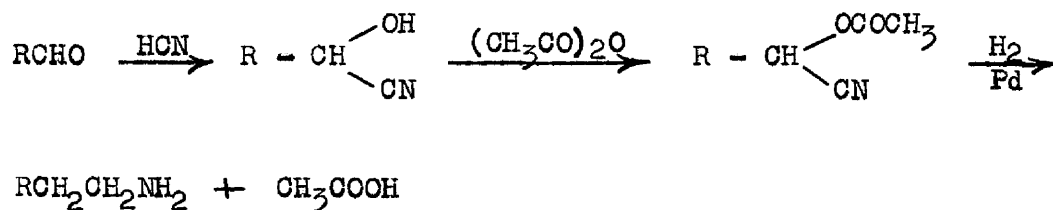
Benzoylated mandelonitriles can be conveniently prepared by several procedures (67,68,69). Hartung (70) reduced these to the corresponding  $\beta$ -arethylamines.



Hydrochloric acid was used to prevent formation of secondary amine.



An analogous method is that of Albert (71) who prepared mandelonitrile acetates; these were catalytically reduced to the corresponding  $\beta$ -arethylamines by Kindler and Peschke (52):



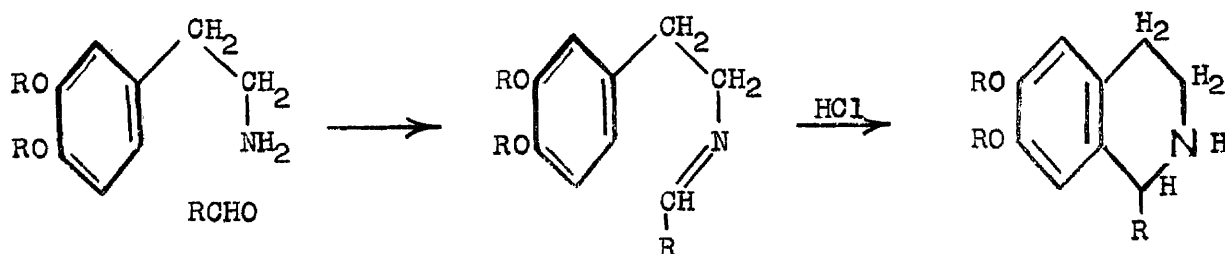
The intermediate mandelonitrile was not isolated, being converted directly to the acetate. The mandelonitrile acetates apparently reduce more readily than the corresponding mandelonitrile benzoates. The method is of general application and after modification was successfully used in the present investigation.

## RESEARCH AIM

The importance and natural occurrence of many isoquinoline derivatives and their varied pharmacodynamic properties suggests the hope that additional medicinally useful compounds may be found by further structural modifications in the parent isoquinoline nucleus. Two methods of synthesizing such compounds appeared attractive and were selected for further study in this investigation.

The first is the formation of isoquinolines under so-called cell-possible conditions. Previous work (25,26,35,36,37,38,39) on these procedures has already been discussed. The aim was to adapt these methods to practical syntheses, not only of natural products or their hypothetical intermediates but also to compounds whose natural formation is not anticipated. Keagle's (72) success in preparing tropanone and its homologs encourages the belief that this is possible. In spite of the failure of other workers to duplicate the results of Hahn and Schales (38) it appeared desirable to try again the use of alkoxyphenethylamines as intermediates. Phenolic ethers are more tractable and readily obtainable, whereas the free phenols are more prone to undergo side reactions and are obtained with greater difficulty.

The second is the formation of tetrahydroisoquinolines by the methods of Decker and Becker (23,43) and Buck (45). This depends on the cyclization of Schiff bases according to the general equation:

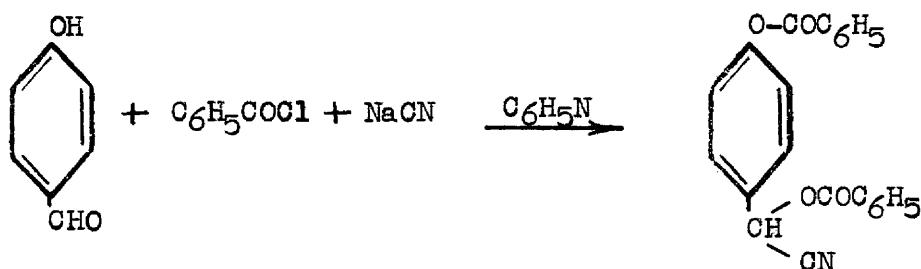


An extension of these earlier studies appeared attractive because of the availability of new intermediates. However, as the work progressed it developed that the methods are not so dependable or facile as indicated. Therefore, it became necessary to include a study of the experimental conditions which promote ring closure and give optimum yields.

## EXPERIMENTAL

SUBSTITUTED  $\beta$ -PHENETHYLAMINES:

For the preparation of the appropriate amines the method of Hamlin and Hartung (67) in preparing the substituted benzoylated mandelonitriles was first investigated; reduction of the nitrile to the corresponding amine was expected. In the light of Hartung's successful reduction of mandelonitrile benzoate to  $\beta$ -phenethylamine (70), it was felt that substituted mandelonitrile benzoates would undergo a similar reaction.

Preparation of p-hydroxymandelonitrile dibenzoate:

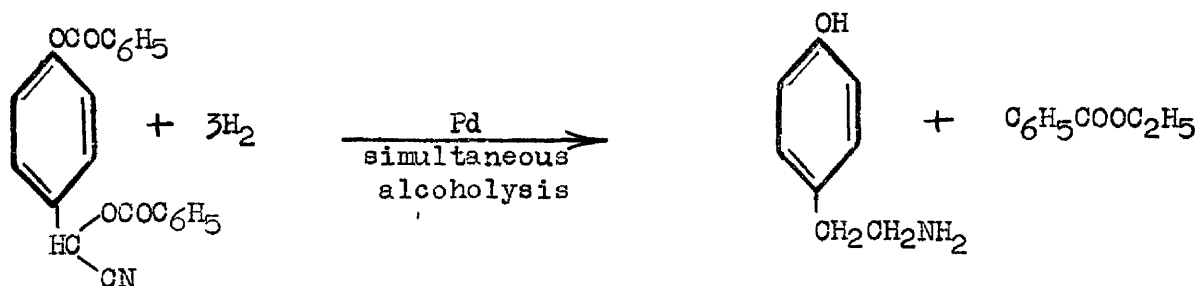
In a 250 cc. beaker was placed a solution of 12 gm. (0.1 mole) of p-hydroxybenzaldehyde in 16 gm. (0.2 mole) of pyridine; 14 gm. (0.1 mole) of benzoyl chloride was cautiously added. There was evolution of much heat. The mixture was now placed in an ice-water bath and kept cool during the remainder of the reaction. A saturated solution containing 5 gm. of sodium cyanide was slowly added. While vigorously shaking the beaker, 14 gm. (0.1 mole) of benzoyl chloride was carefully added. There was a brisk reaction accompanied by the evolution of heat. Dilute hydrochloric acid was poured into the reaction mixture. This caused an oil to separate which soon solidified. The solid was filtered by suction and recrystallized. After trying the usual organic solvents, a mixture of acetone-isopropyl ether was found to be suitable. The solid was dissolved in a minimum amount of boiling acetone, the solution filtered to remove any gross impurities, and after cooling, isopropyl ether added to produce a faint turbidity. After standing in the refrigerator

overnight, faintly yellow crystals separated. These were filtered and air-dried. Treatment with charcoal did not remove the yellow color. The product weighed 14 gm. (40% yield) and melted at 141°.

3-Methoxy-4-hydroxymandelonitrile dibenzoate was similarly prepared from vanillin in a yield of 44%. The compound melted at 149.5-150°.

The substituted mandelonitrile benzoates are difficult to isolate in a well defined crystalline state.

Reduction of p-hydroxymandelonitrile dibenzoate:



The palladium catalyst was prepared according to the general directions of Hartung (73). Three hundred mgm. of palladium chloride was dissolved in 100 cc. of a 1 molar solution of sodium acetate. This solution was added to 3 gm. of Norite and shaken in an atmosphere of hydrogen until saturated. The solution was filtered and the palladinized charcoal washed successively with several portions of distilled water, acetone, ethanol and ether. The catalyst was stored in a vacuum desiccator over sulfuric acid when not used.

Alcoholic hydrogen chloride was prepared by bubbling anhydrous hydrogen chloride into a weighed quantity of absolute ethanol.

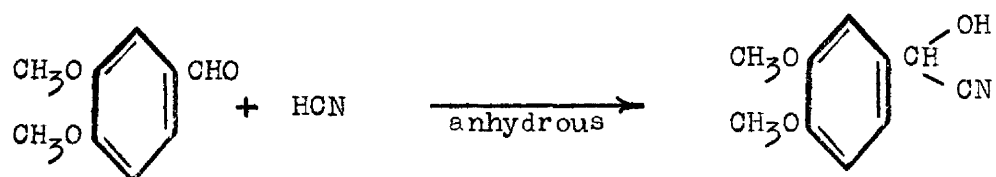
Eighteen gm. (.05 mole) of p-hydroxymandelonitrile dibenzoate was suspended in 120 cc. of absolute ethanol containing 2 equivalents (4 gm.) of hydrogen chloride. The previously prepared catalyst was added and the mixture shaken

in an atmosphere of hydrogen. After 4 hours of shaking, 20% of the theoretical amount of hydrogen was absorbed and reduction ceased. The catalyst was filtered off and occluded in it were some white crystals. The filtrate was saved for subsequent treatment. The catalyst was washed with hot acetone to remove the crystals. When a small portion of the acetone washings was diluted with water, a heavy white precipitate formed. The latter was filtered by suction and after air-drying melted at  $141^{\circ}$ . A mixed melting point with *p*-hydroxymandelonitrile showed no depression, confirming the identity of the material as unchanged nitrile. The original, alcoholic filtrate was distilled in vacuo to remove the solvent. The brown, oily residue was taken up in hot ethanol and ether added until a faint turbidity appeared; then placed in a refrigerator overnight. An amorphous, grey solid separated; this was filtered by suction and dried. The material melted above  $250^{\circ}$ . It is insoluble in water, dilute alkalis or dilute acids.

The reduction was repeated using a mixture of dioxane and absolute ethanol as the solvent for the nitrile but only unchanged nitrile could be recovered in pure state.

The reduction of 3-methoxy-4-hydroxymandelonitrile dibenzoate was attempted, using the pressure bomb of the American Instrument Company, at an initial pressure of 10 atmospheres. After shaking for 1 hour, only a small portion of the theoretical amount of hydrogen was taken up. Addition of approximately 0.1 gm. of palladium chloride directly to the reaction mixture failed to speed up the reduction. The expected hydrogenation did not take place and after several unsuccessful attempts was not further investigated.

In view of the difficulties encountered in reducing the benzoylated mandelonitriles and the apparent success of Buck (66) in reducing the cyanohydrins, it was decided to investigate this route for the preparation of substituted  $\beta$ -phenethylamines.

Preparation of substituted mandelonitriles:

Anhydrous hydrogen cyanide was prepared according to the directions given in "Organic Synthesis" (74). The liquified hydrogen cyanide was transferred to a burette and thence into previously drawn out test tubes, containing a few crystals of calcium chloride, in 2 cc. quantities (approximately .06 mole). The tubes were sealed with an oxygen-gas flame and stored in the refrigerator.

The method of preparing the cyanohydrins was the same in all cases; only the condensation catalyst was varied. The aldehyde was used in the dry state to obviate the effect of solvent. Ten gm. (.06 mole) of veratraldehyde was powdered finely in a mortar and transferred to a 125 cc. Erlenmeyer flask provided with a tightly-fitting rubber stopper. The reaction was carried out in a well-ventilated hood. One cc. of liquid catalyst was added and shaken with the aldehyde. The ampule containing the hydrogen cyanide (approximately 1.6 gm., .06 mole) was broken and its contents immediately poured into the flask, which was stoppered immediately. In some cases, heat was generated and evidence of immediate reaction was visible. In all cases, liquefaction occurred and coloring was more or less pronounced. The reaction mixture was allowed to stand overnight or for several days until solidification occurred.

With pyridine: There was slow liquefaction of the reaction mixture, it becoming yellow and very viscous. Two runs were made. The first run was allowed to stand overnight, then extracted with ether. The ether extract

was washed successively with 40% sodium bisulfite solution and 5% sodium hydroxide solution. The bulk of ether was removed by blowing a stream of air gently upon the mixture. Last traces of ether were removed by placing the evaporating dish into a vacuum desiccator, leaving a brown, amorphous residue with some crystalline material separating around the perimeter. The residue was pressed dry on a porous plate and a portion of it used to seed the second run. Within a few hours after seeding, the reaction mixture became entirely a cream colored solid. This was dissolved in ether, washed with bisulfite and dilute alkali and dried over anhydrous sodium sulfate. The excess ether was removed in vacuo and petroleum ether added to produce turbidity. After the mixture cooled in a refrigerator overnight, crystals separated. These were filtered by suction and dried in a desiccator. The product weighed 1.5 gm. (12%) and melted at 102-103°. (66)

Potassium cyanide as catalyst: There was evidence of immediate reaction. The reaction mixture became a dark red solid overnight.

Piperidine as catalyst: There was evidence of immediate reaction. The reaction mixture became a brownish-red solid upon standing for two days.

Calcium oxide as catalyst: One gm. of calcium oxide was mixed intimately with the powdered aldehyde in the mortar and transferred to an Erlenmeyer flask. The liquified hydrogen cyanide was poured upon the solid mass. The reaction mixture turned black where the bulk of the hydrogen cyanide soaked into the solid mass; the remainder of the reaction mixture solidified into a yellowish-red mass upon standing overnight.

Quinoline as catalyst: There was no evidence of immediate reaction. Upon standing two days and nights several clumps of white roseate crystal formations were visible in the yellow reaction mixture. Two other runs using



quinoline as catalyst were made. Run (I) used an equivalent amount of quinoline. Run (I) became quite warm and solidified after standing overnight, depositing deep red crystals from the heavy red liquor. Run (II) used only a few drops of quinoline. Run (II) solidified after standing several days to yield a light yellow mass. Quinoline looked most promising of all the catalysts used.

In spite of the poor yields obtained by these results, the possibility of using this reaction for the synthesis of substituted  $\beta$ -phenethylamines should not be ruled out.

Bucherer (75) has given a method for preparing aliphatic cyanohydrins in good yields. It was hoped that a modification of this method, generating the hydrogen cyanide, in situ, would yield the desired substituted mandelonitriles.

In a 1-liter, three-neck flask, fitted with a mechanical stirrer, dropping funnel and a special thermometer so constructed as to make low temperature readings easily visible above the side neck of the flask\*, was placed 13 gm. (0.2 mole) of potassium cyanide. A solution of 15 gm. (0.1 mole) of piperonal in 200 cc. of ether was poured into the flask, followed by 5 cc. of water. The flask was packed in an ice-salt mixture and with vigorous stirring 20 cc. of concentrated hydrochloric acid was added dropwise. During the addition of the acid (approximately one half hour), the temperature was kept below 5°. Upon removing the flask from the ice-salt bath, sufficient water was added to dissolve the precipitated potassium chloride and the ether-aqueous layers separated. The aqueous layer was extracted twice with a small quantity of ether. The combined ethereal layers were washed with 40% sodium

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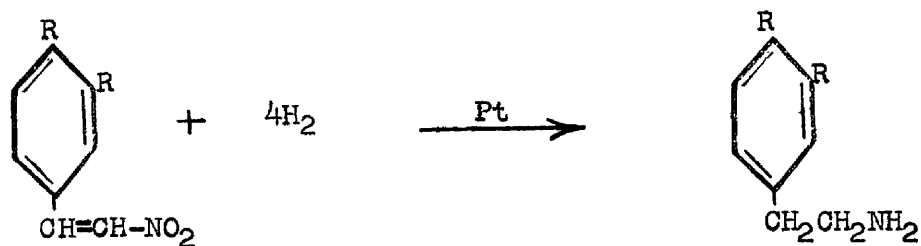
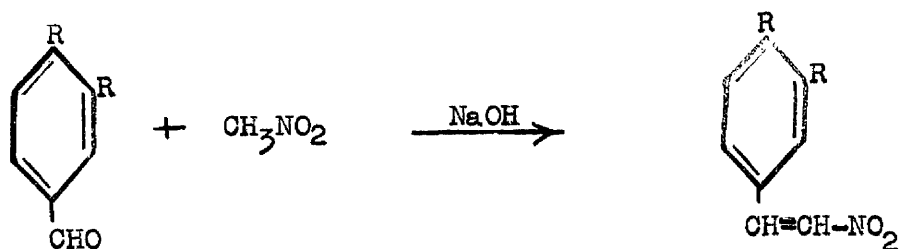
\*The thermometer was made by blowing a bulb on the end of a piece of large-bore capillary tubing, filling the bulb and a portion of the stem with 95% ethanol, colored red with p-rosaniline, and sealing. The thermometer can then be calibrated for -5°, 0°, 5° and 20°C. Cellulose tape affords a convenient means of marking the calibrations.

bisulfite solution to remove unchanged aldehyde. A heavy precipitate of the aldehyde-bisulfite addition product occurred. The ethereal layer was dried over anhydrous sodium sulfate and evaporated under diminished pressure to dryness. No residue was obtained.

Other runs were made with veratraldehyde and vanillin as starting materials. In the latter case, unchanged vanillin was recovered. The ratio of hydrogen cyanide to aldehyde was augmented and the length of reaction time increased but with equally poor results.

### *o*-Nitrostyrenes:

The preparation of the  $\beta$ -phenethylamines from the appropriate nitrostyrenes, as indicated below, appeared promising:



R = methoxy or methylenedioxy

The general method used to prepare the nitrostyrenes listed in Table I is illustrated by the preparation of 3,4-dimethoxy- $\omega$ -nitrostyrene.

In a 1 liter, three-neck flask, fitted with the afore-mentioned low temperature thermometer, mechanical stirrer and separatory funnel, was placed 27 gm. (0.16 mole) of veratraldehyde, 9.8 gm. (0.16 mole) of freshly distilled nitromethane and 200 cc. of methyl alcohol. During moderate stirring of the reaction mixture, a solution of sodium hydroxide [6.7 gm. (0.6 mole) of NaOH in 20 cc. of water and cooling] was added dropwise through the separatory funnel, maintaining the temperature below 10°. The stirring was continued until a sample of the reaction mixture gave a clear solution when diluted with water. At this stage 100 cc. of ice water was added to give a clear reaction mixture. A solution of hydrochloric acid (32 cc. of concentrated HCl diluted with 50 cc. of water) was placed in a 1 liter beaker and the reaction mixture slowly added to it during rapid stirring. A canary-yellow crystalline mass precipitated immediately as the alkaline solution came into contact with the acid. The solution was tested at this point to insure its still being acidic. The yellow mass was filtered off with the suction and washed thoroughly with distilled water until the washings were chloride free. The product was recrystallized from hot ethyl alcohol. The product weighed 18 gm. (54%) and melted sharply at 141°.

TABLE I

Phenyl-Substituted- $\omega$ -Nitrostyrenes

<u>Nitrostyrenes</u>	<u>Reference</u>	<u>m.p. in °C.</u>	<u>% yield of purified product</u>
Nitrostyrene	(53)	58°	80%
4-Methoxy- $\omega$ -nitrostyrene	(54)	87°	47%
3,4-Dimethoxy "	(55)	141°	54%
3,4-Methylenedioxy "	(56)	158°	43%

The phenyl-substituted- $\omega$ -nitrostyrenes are highly colored, definitely crystalline compounds of limited solubility in ethyl alcohol. The yield was reduced considerably by recrystallization. Reworking of the mother liquors proved futile. To determine whether the loss on crystallization of the crude product was caused by poor recovery, an accurately weighed amount of pure product was recrystallized from alcohol, dried and reweighed; it was recovered in 88% yield indicating that the crude product must contain many alcohol soluble impurities. During the preparation of the 3,4-methylene-dioxy- $\omega$ -nitrostyrene, it was necessary to add additional methyl alcohol to the reaction mixture to prevent solidification.

An alternate method given by Raiford and Fox (55) for preparing 3,4-dimethoxy- $\omega$ -nitrostyrene was carried out: A mixture of 10 gm. (.06 mole) of veratraldehyde, 4 gm. (.05 mole) of ammonium acetate, 5.5 gm. (.09 mole) of nitromethane and 40 cc. of glacial acetic acid was gently refluxed for 4 hours. On cooling, a crystalline mass separated. This mass was recrystallized from 50% acetic acid. Beautiful golden flakes were deposited. The product weighed 6.5 gm. (52%) and melted at 140-140.5°. Raiford and Fox report a yield of 85%. Whether these investigators refer to the crude product or the recrystallized material is not indicated.

Reduction of 3,4-dimethoxy- $\omega$ -nitrostyrene (60):

5 gm. (.024 mole) of 3,4-dimethoxy- $\omega$ -nitrostyrene, 200 cc. of absolute alcohol, 30 cc. of glacial acetic acid and 0.4 gm. platonic oxide, prepared by the method of Adams (76), were placed in the glass liner of the pressure bomb of the American Instrument Company. The nitroolefin did not completely dissolve, but was suspended in the solvent. Hydrogenation was initiated under a pressure of 150 lbs. Fifteen minutes after hydrogenation was initiated, the calculated amount of hydrogen for reduction to the amine was taken up and the pressure drop ceased. Shaking was continued for fifteen minutes longer and the bomb opened. The reaction mixture had changed color from a golden yellow to a pale green. The catalyst was filtered with suction. Twenty cc. of dilute hydrochloric acid was added to the filtrate which was then evaporated to dryness in vacuo. The residue was taken up in a little water and extracted with ether. The aqueous solution was made alkaline with 10% sodium hydroxide solution and the precipitated base taken up in ether. The ethereal solution was dried over solid pellets of potassium hydroxide and evaporated under reduced pressure. A small quantity of a syrupy brown oil remained, to which was added dilute hydrochloric acid and a little alcohol. After standing for several hours in the refrigerator, small yellow crystals separated. The product was recrystallized from absolute alcohol and weighed 2 gm. (38%). The hydrochloride melted at 146°. The p-nitrobenzoyl derivative melted at 147° in agreement with the product described by Buck (66).

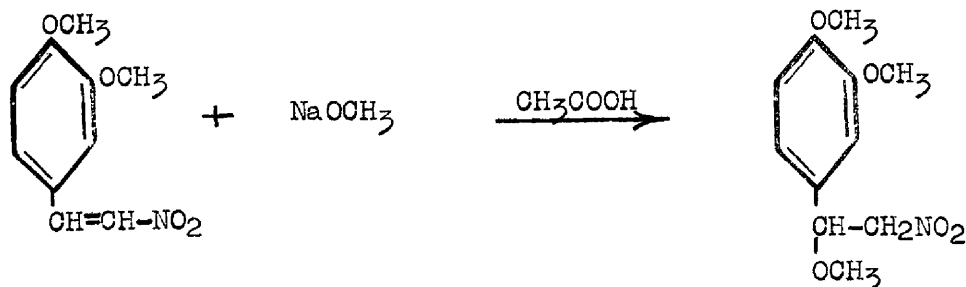
Several modifications of the above method were tried, in the hope of improving the yield but efforts were futile. One modification that seemed fruitful was to replace the above solvent with absolute ethanol containing 4 equivalents of anhydrous hydrogen chloride. In all cases the theoretical

amount of hydrogen was taken up but attempts to isolate the amine were unsuccessful. A possible explanation of this failure to isolate the product is that the reduction proceeds to the oxime or imine stage, these undergo hydrolysis to the aldehyde and the aldehyde undergoes reduction or polymerization during the isolation.

To validate this notion the following reduction was performed: Six gm. (.04 mole) of nitrostyrene was dissolved in 75 cc. of methanol. Ten cc. of phosphoric acid (85%) and 250 mgm. of platonic oxide was added to the solution and hydrogenation initiated under 4 atmospheres pressure. At the end of 40 minutes, reduction ceased although only one half of the theoretical amount of hydrogen was taken up. The catalyst was filtered off and the filtrate smelled very strongly of phenylacetaldehyde. An attempt was made to isolate this aldehyde by steam distillation of the filtrate. The distillate had the pleasant odor of phenylacetaldehyde and gave a positive fuchsin-aldehyde test but no oil separated, nor could any derivative be obtained.

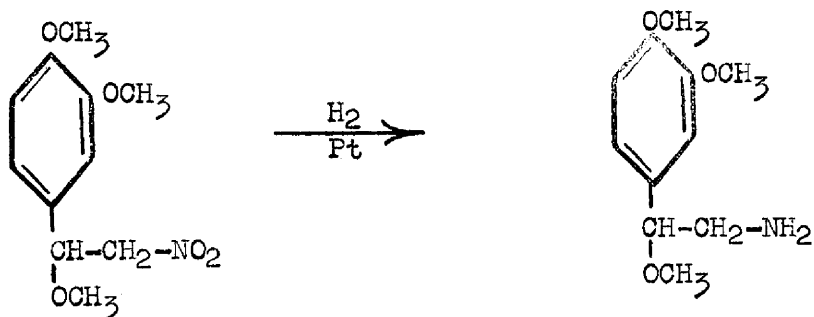
Since the phenyl-substituted  $\omega$ -nitrostyrenes can be easily converted into the ethers of  $\alpha$ -phenyl- $\beta$ -nitroethanols, these compounds were prepared in the hope of a smooth reduction to the corresponding amines since the vinylogy between the nitro group and the aromatic ring would then be broken.

Preparation of 1-methoxy-1-(3,4-dimethoxyphenyl)-2-nitroethane (77):



Five gm. (.024 mole) of finely powdered 3,4-dimethoxy- $\omega$ -nitrostyrene was suspended in 100 cc. of methanol and placed in a one liter flask. The flask was placed in an ice bath and fitted with a mechanical stirrer. Fifty cc. of a sodium methoxide solution (containing 4.5 gm. of sodium per 100 cc. of methanol) was added dropwise during vigorous stirring of the suspension. After approximately 4 minutes of stirring beyond the addition of the sodium methoxide solution, 6.5 cc. of glacial acetic acid was added. Stirring was continued for 10-15 minutes more and then the precipitated ether was filtered with suction. The filtrate was concentrated under reduced pressure to remove the methanol. An excess of water was then added and the precipitated product filtered with suction. The combined product was recrystallized from hot methanol. The yield of pure product melting at 107° was 4 gm. (70%).

Reduction of 1-methoxy-1-(3,4-dimethoxyphenyl)-2-nitroethane (78):



Three and two-tenths gm. (.014 mole) of the nitroethanol was partially dissolved in 200 cc. of absolute ethanol and 2.4 gm. (.019 mole) of oxalic acid added. Fifty mgm. of platonic oxide was suspended in the reaction mixture, which was shaken in hydrogen at atmospheric pressure. After two hours of agitation, only one third of the theoretical amount of hydrogen was taken up. The hydrogenation flask was heated by directing a stream of steam upon it and hydrogenation resumed. There was no appreciable increase in the hydrogen uptake. Three hours later hydrogenation was stopped, even

though only two-thirds of the theoretical amount of hydrogen had been taken up. Some white crystalline material had separated. In hope that these were the precipitated amine oxalate, the solvent was concentrated in vacuo. The solid residue was filtered with suction and dissolved, with difficulty, in boiling water. The aqueous solution was filtered to remove the catalyst and made alkaline. No turbidity resulted (as would have been expected if the free amine were liberated). The alkaline solution was extracted with ether, the ethereal solution dried with sodium hydroxide pellets and dry hydrogen chloride bubbled in. A slight turbidity occurred but no precipitated amine.

A second reduction of 1-methoxy-1-(3,4-dimethoxyphenyl)-2-nitroethane was carried out using high pressure hydrogenation. Double quantities of the previous run were used. Hydrogenation was initiated at 10 atmospheres. After three hours, hydrogenation ceased abruptly, and no further hydrogen was taken up, even after an hour of shaking. Upon working up the reaction mixture, unchanged 1-methoxy-1-(3,4-dimethoxyphenyl)-2-nitroethane was recovered.

Since the catalytic reduction of 1-methoxy-1-(3,4-dimethoxyphenyl)-2-nitroethane failed to yield the desired amine, a chemical reduction according to the method of Reichert (78) was carried out. The method consisted of treating an alcoholic solution of the nitro compound with amalgamated aluminum and glacial acetic acid. After the initial reaction subsided, the reaction mixture was gently refluxed for 12 hours. After removal of the inorganic salts by filtration, the filtrate was concentrated, made alkaline and extracted with ether. The combined ethereal extracts were fractionated and the distillate collected at 167°/25 mm. Only a very small quantity of a strongly smelling, deep red, viscous liquid was obtained. Attempts to prepare a hydrochloride from this liquid failed.



Chemical reduction of 3,4-dimethoxy- $\omega$ -nitrostyrene:

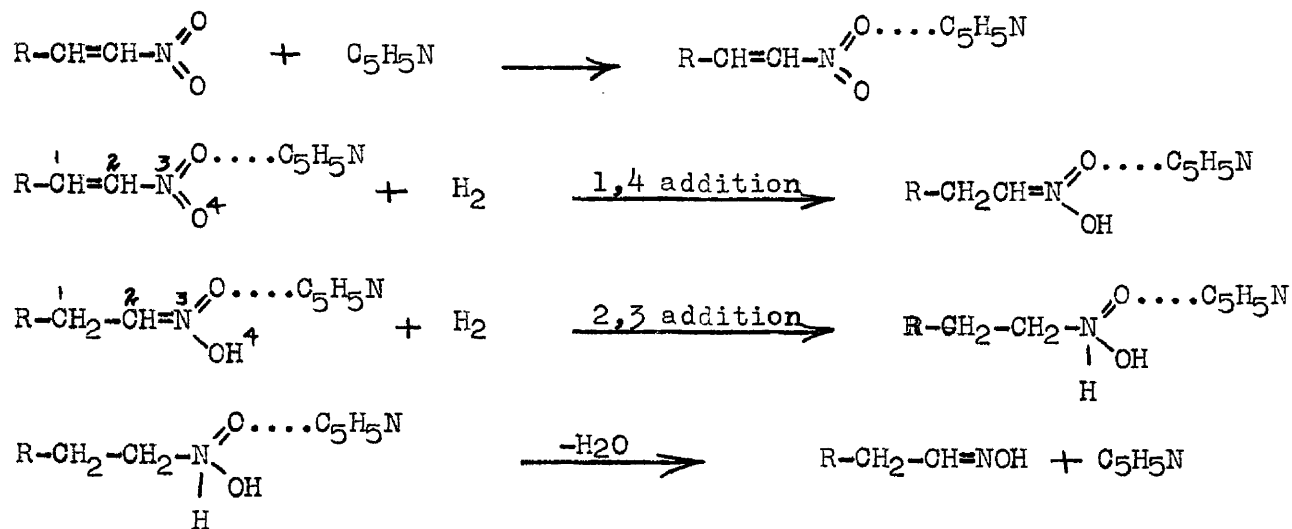
Since the direct reduction of the nitrostyrenes and the corresponding methyl ethers failed to yield the expected primary amines, it was decided to prepare the oximes by a chemical reduction similar to that used by Nightingale and Janes (79) and then reduce these oximes to the corresponding amines.

Twenty-five gm. (0.38 mole) of zinc dust was placed in a 1-liter, three-neck flask, fitted with a mechanical stirrer, dropping funnel and reflux condenser. A 200 cc. ethereal solution of 3,4-dimethoxy- $\omega$ -nitrostyrene was added and stirred vigorously while a 25% acetic acid solution was added over a two hour period at such a rate as to cause gentle refluxing of the ether. After all of the acid had been added, the reaction mixture was heated gently until it became colorless and bubbles of hydrogen ceased to form (approximately seven hours). The inorganic salts were separated by filtration and extracted with ether in a Soxhlet extractor to recover adsorbed product. The filtrate was concentrated and extracted with ether. The combined ethereal solutions were evaporated in vacuo. A dark red oil remained which resisted attempts at crystallization. The oxime of 3,4-dimethoxyphenylacetaldehyde has been described (58) as a colorless solid.

Reduction of 3,4-dimethoxy- $\omega$ -nitrostyrene to the oxime:

Reichert and Koch (58) claim that Skita and Keil's method of reducing substituted aryl nitrostyrenes (60) gives poor yields. Thus they reported that from 15 gm. of p-methoxy- $\omega$ -nitrostyrene only 2 gm. of the corresponding amine was obtained. Reichert and Koch stated that by using pyridine as the solvent the aci-form of the nitro compounds are bound allowing the reduction

to proceed smoothly to the oxime stage:



R = substituted phenyl

Unfortunately, Reichert and Koch are vague in their experimental information as to the temperature and amount of catalyst used during the reduction.

After many variations of the reduction procedure and isolation the following method was adopted: Ten and five-tenths gm. (.05 mole) of 3,4-methylenedioxy- $\omega$ -nitrostyrene was dissolved completely in 75 cc. of hot pyridine. During the solution, the color of pyridine deepened considerably (suggesting an addition product?). The catalyst was prepared as follows: Three-tenths gm. of palladium chloride was added to 100 cc. of distilled water. The salt did not completely dissolve. The mixture was heated to boiling and a few drops of concentrated hydrochloric acid added. A clear, wine-red solution resulted, which was added to 3 gm. of Norite. The mixture was shaken in an atmosphere of hydrogen and worked up in the usual manner (70). Six-tenths gm. of the prepared catalyst was added to the pyridine solution and hydrogenation initiated under a pressure of 10 atmospheres and 70°. After 20 minutes, reduction was complete. The catalyst was filtered by suction, washed with a little pyridine and saved for future runs. The filtrate was transferred to a 1 liter beaker placed in a water bath containing

water at room temperature. Dilute (10%) sulfuric acid was added dropwise until the reaction mixture was just acid (to Congo-red paper) when the oxime precipitated as a white, tinged-with-tan, crystalline mass. It was filtered by suction and air-dried. The crude product weighed 9 gm. Recrystallization from benzene yielded a snow-white product melting at  $110^{\circ}$  and weighing 4.5 gm. (50%). Nitrogen calculated for  $C_9H_9O_3N$ , 7.83%; Nitrogen found, 7.85% and 7.66%. The oxime was dehydrated to the cyanide; the cyanide hydrolyzed to the acid. The melting point of the homopiperonylic acid thus obtained was  $128^{\circ}$  in agreement with the literature (51).

4-Methoxyphenylacetaldoxime and 3,4-dimethoxyphenylacetaldoxime were prepared in an analogous manner. For detailed directions see Reichert and Koch (58).

Reduction of 3,4-methylenedioxyphenylacetaldoxime:

Hartung's method (70) was used. Four and five-tenths gm. (.025 mole) of the oxime was dissolved in 100 cc. of absolute ethanol containing 3 equivalents of anhydrous hydrogen chloride with the formation of a deep red color. Three gm. of the 10% palladium catalyst was added and the mixture hydrogenated under an initial pressure of 10 atmospheres. After shaking for 1 hour, the theoretical amount of hydrogen was taken up. After working up the product in the usual manner (70) a brown tarry mass was isolated which failed to give any definite crystalline product. It was not further characterized.

Complete reduction of  $\omega$ -nitrostyrene to the amine:

Kindler, Brandt and Gehlhaar (61) reported a method for the smooth reduction of  $\omega$ -nitrostyrene to the corresponding amine in the presence of concentrated sulfuric acid.

Four gm. (0.02 mole) of 3,4-methylenedioxy  $\omega$ -nitrostyrene was dissolved in 200 cc. of glacial acetic acid with the aid of gentle heat. After the addition of 12 cc. of concentrated sulfuric acid (during which the solution became wine-red) and 1 gm. of platinic oxide (Adams catalyst), reduction was initiated under 10 atmospheres. Hydrogenation was rapid; after 15 minutes the theoretical amount of hydrogen was taken up. After decanting the main portion of the solvent, the catalyst was removed by filtration and the filtrate treated with the calculated amount of 30% sodium hydroxide solution to neutralize the sulfuric acid. The precipitated sodium sulfate was filtered by suction and washed several times with glacial acetic acid. The acetic acid was removed under diminished pressure, the residue made alkaline and distilled with steam. The distillate was alkaline and had a pungent, ammoniacal odor suggesting deamination. The distillate was extracted with ether, dried over solid potassium hydroxide pellets and anhydrous hydrogen chloride bubbled into the dried ethereal solution. On cooling, a white solid separated which after drying melted at 196°. The reported melting point for homopiperonylamine hydrochloride is 208° (80). The yield was negligible. Attempts to make the picrate failed. Such modifications as decreasing the amount of sulfuric acid, cooling the filtrate during the neutralization of the sulfuric acid, and increasing the amount of catalyst were tried in hopes of improving the yield of the desired amine, but were unsuccessful.

It was thought that the steam distillation might have deaminated the amine, since compounds of the structure  $\text{R}-\overset{\text{H}}{\underset{\text{CH}_3}{\text{C}}}-\text{CH}_2-\text{NH}_2$  deaminate upon standing at room temperature (73). One modification which eliminated this possibility is as follows:

The procedure was identical with that given on the preceding page up to the isolation stage where the residue remaining after removal of the acetic acid in vacuo, was made alkaline. The alkaline solution was extracted with several portions of ether. The ethereal extractions were combined and dried over pellets of sodium hydroxide. The ethereal solution was filtered into a dry flask and anhydrous hydrogen chloride introduced. An immediate precipitate formed which soon darkened and became gummy. Attempts at recrystallization yielded a highly colored, impure product.

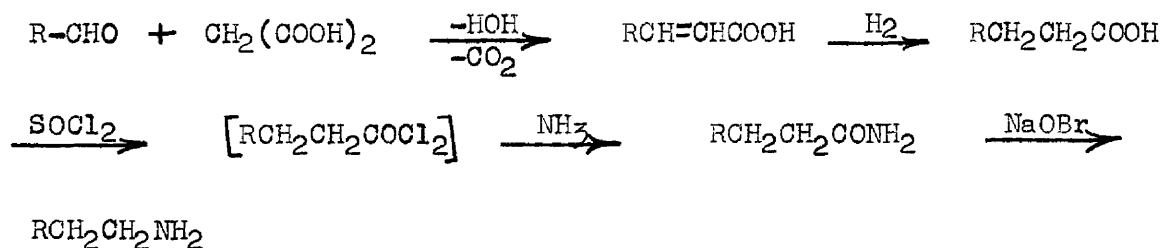
Another interesting modification was as follows:

Four gm. (0.02 mole) of 3,4-methylenedioxyrostyrene was suspended in 150 cc. of methanol. Ten cc. of syrupy phosphoric acid (85%) was added, accompanied by evolution of heat. Two hundred and fifty mgm. of platinum oxide (Adams catalyst) was added and the mixture hydrogenated under an initial pressure of 10 atmospheres. After shaking for 30 minutes, the theoretical amount of hydrogen was taken up. The catalyst was removed by filtration, washed with several portions of methanol and the pale green filtrate cooled in an ice bath and made alkaline with anhydrous ammonia (81). The precipitated ammonium phosphate was filtered by suction and washed with methanol. The combined washings and filtrate were evaporated under reduced pressure and the residue treated with excess 10% sodium hydroxide and well shaken during cooling. The emulsion was extracted with ether and dried over pellets of sodium hydroxide. The dried ethereal solution was cooled in an ice bath and anhydrous hydrogen chloride blown over the surface of the solution to prevent gumming. The precipitated material was kept in a refrigerator overnight and then filtered by suction. It darkened on drying and after being

recrystallized from dioxane it melted above 250°. The picrate was prepared and it too melted above 250°. The product was not soluble in water whereas homopiperonylamine is reported as being soluble (80). On heating an aqueous suspension of the product, some of it dissolved and some yellow material remained undissolved. The product was not soluble in dilute hydrochloric acid. It reacted with sodium hydroxide to form a product soluble in ether. Nitrogen calculated for  $C_9H_{11}O_2N \cdot HCl$ , 6.94%; Nitrogen found, 3.99% and 3.96%. The product was not further characterized, however, its properties and analysis substantiated the belief that it was dihomopiperonylamine (82).

#### Hofmann Degradation:

In view of the difficulties encountered thus far in the preparation of the substituted  $\beta$ -phenethylamines, the approach to these compounds via the Hofmann degradation of the amide was tried, according to the following equations:



R = 3,4-dimethoxyphenyl

#### Preparation of 3,4-dimethoxycinnamic acid (83):

One hundred gm. (0.6 mole) of veratraldehyde, 130 gm. (1.25 mole) of malonic acid and 5 cc. of piperidine were heated in 250 cc. of pyridine for 1½ hours on a steam bath, during which rapid evolution of carbon dioxide occurred. The reaction mixture was then heated on a hot plate under reflux for 10 minutes. By pouring the reaction mixture into an excess of dilute

hydrochloric acid a dense, white precipitate separated. The product was filtered by suction, and air-dried. The weight of acid melting at 178° was 105 gm. (85%).

$\beta$ -(3,4-Dimethoxyphenyl) propionic acid:

For the reduction of the substituted cinnamic acid to the dihydro derivative the method of Schwenk, Papa, et al (84) was used: Twenty gm. (0.1 mole) of 3,4-dimethoxycinnamic acid was dissolved in 600 cc. of a 10% sodium hydroxide solution. The solution was placed in a 2-liter, three-neck flask equipped with an air-stirrer, reflux condenser and thermometer. The flask was heated on a water bath to 90° and 60 gm. of Raney nickel-aluminum alloy added in very small portions during vigorous stirring. The evolution of hydrogen was allowed to subside before adding fresh Raney nickel. The hot solution was filtered and the residue washed thoroughly with water so that a layer of water was always covering the residue, which was pyrophoric if allowed to dry. The filtrate was cooled and acidified to Congo-red by adding it, with stirring, to concentrated hydrochloric acid. The precipitated inorganic salts were separated by centrifuging and extracted with ether in a Soxhlet extractor. The filtrate was extracted with ether (the dihydrocinnamic acid is soluble in water) and the ethereal extracts combined. The ether was removed by distillation at atmospheric pressure. White crystals were deposited as the last portion of ether was evaporated spontaneously. The weight of product melting at 96° (85) was 8 gm. (38%).

Preparation of  $\beta$ -(3,4-dimethoxyphenyl) propionamide (48):

Eight gm. (.038 mole) of the above acid was dissolved in 30 cc. of chloroform and 7 gm. (.058 mole) of thionyl chloride added. The reaction mixture was allowed to stand for 12 hours at room temperature and then

cautiously poured into a solution containing 120 cc. of concentrated ammonium hydroxide, 1 gm. of sodium hydroxide and 120 cc. of water. The chloroform was removed by heating on a water bath and the residual liquid treated with charcoal and filtered while hot. After cooling in a refrigerator, the amide separated in white needles. The yield was 1 gm. (12.5%). Because of the poor yields obtained and the laborious procedure this method was not considered practical for preparing the desired phenethylamines.

Rhodanine method:

A general method for the preparation of arethylamines and arylacetic acids is reported by Julian and Sturgis (65). The experimental procedure was followed exactly, substituting piperonal for veratraldehyde as given in their experimental directions.

Rhodanine: This compound was obtained in a yield of 87%. It crystallized from alcohol in almost colorless needles; melting at 165°.

Piperonylrhodanine: This product was obtained in a yield of 89% and melted at 256-258° with decomposition. Care was taken during the condensation not to overheat the reaction flask else charring would occur.

Cleavage of piperonylrhodanine with alkali: Forty gm. (0.15 mole) of piperonylrhodanine was used for the cleavage. No difficulty was experienced during the addition of acid, as Julian and Sturgis indicated. The yield of pale yellow acid melting at 208-210° was 89%.

$\alpha$ -Oximino- $\beta$ -3,4-methylenedioxyphenylpyruvic acid: The acid, upon recrystallization from water separated as beautiful white needles; and melted at 170-171°. The yield was 90%.



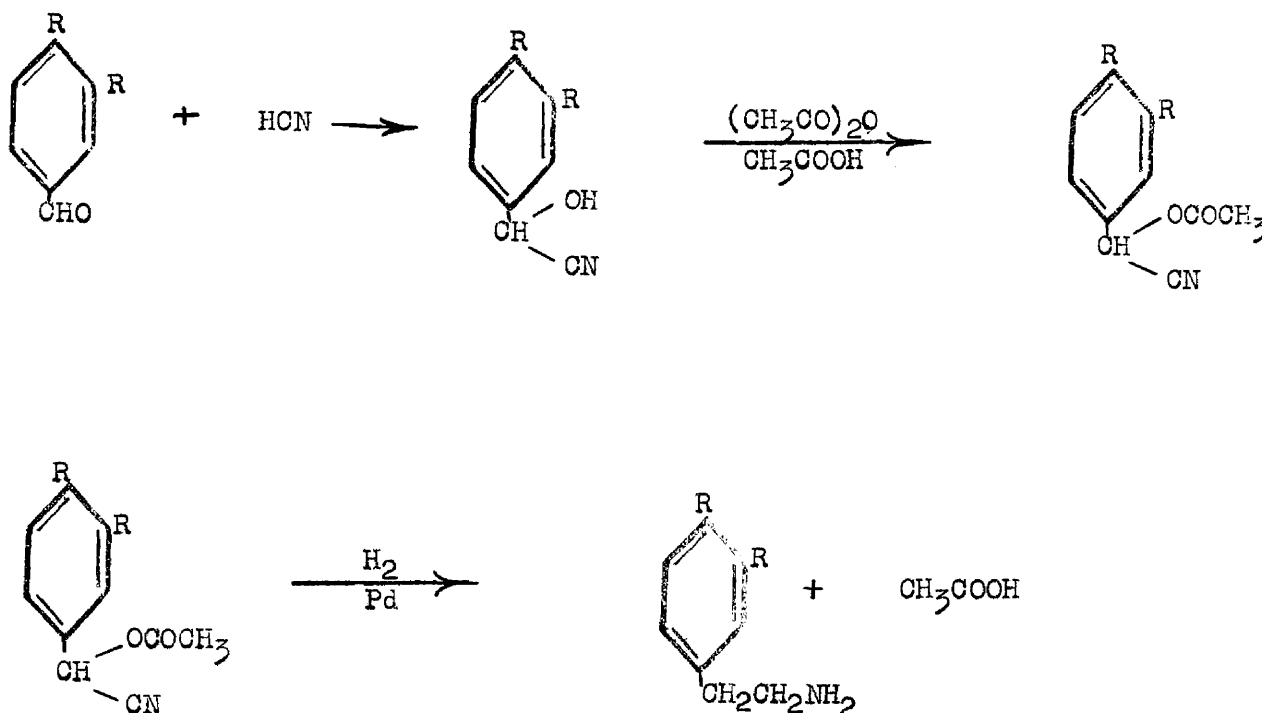
Decomposition of  $\alpha$ -oximino- $\beta$ -3,4-methylenedioxyphenylpyruvic acid: The recrystallized oximino acid was used for the decomposition. The ethereal layer was distilled under a pressure of 15 mm. The product distilling at 160-165° was collected. Upon cooling, yellow needles separated. The yield of 3,4-methylenedioxyphenylacetonitrile was 71%.

Reduction of 3,4-methylenedioxyphenylacetonitrile:

Eleven gm. (.07 mole) of the above nitrile was refluxed 15 minutes with 5 cc. of an alcoholic suspension of Raney nickel catalyst to remove any possible sulfur contamination. The Raney nickel was removed by filtration and the filtrate dissolved in 100 cc. of absolute ethanol containing 2 equivalents of hydrogen chloride. Three gm. of a 10% palladinized charcoal catalyst was added and reduction initiated at 4 atmospheres pressure. After shaking for 1 hour, no appreciable hydrogen was taken up; shaking was continued for an additional hour. A small amount of palladium chloride was added directly to the reduction mixture but this failed to augment the rate of hydrogen uptake. The catalyst was filtered off and 250 mg. of platonic oxide added to the filtrate which was then submitted to rehydrogenation at 4 atmospheres. Since hydrogenation did not proceed to any appreciable extent, the method was abandoned.

Mandelonitrile acetates:

The success of Kindler & Feschke (52) in catalytically reducing substituted mandelonitrile acetates to the corresponding  $\beta$ -arethylamines prompted an investigation of their procedure:



Preparation of 3,4-methylenedioxymandelonitrile acetate (71):

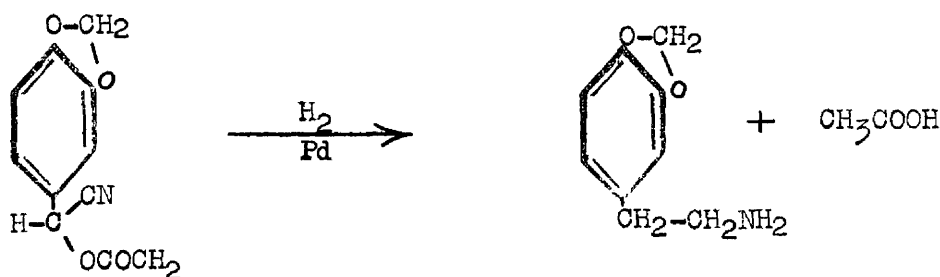
The reaction was carried out in a well-ventilated hood. Twenty gm. (0.31 mole) of potassium cyanide was intimately triturated with 30 gm. (0.2 mole) of piperonal in a glass mortar. To this mixture in a 500 cc., three-neck flask, equipped with a mechanical stirrer and dropping funnel, was added 40 cc. of water. The mixture was cooled in an ice-salt bath and while stirring vigorously, 30 cc. of concentrated hydrochloric acid was added dropwise over the course of one half hour. Stirring was continued 15 minutes after the last drop of acid was added. The cyanohydrin separated as a thick, orange oil. The reaction mixture was allowed to stand until complete separation of the cyanohydrin was accomplished. This was dissolved in 81.6 gm. (75 cc., 4 fold molar excess) of acetic anhydride, containing 7 gm. of anhydrous sodium acetate. The mixture was heated under reflux for 1 hour on a water bath. After standing overnight a solid mass usually separated. In either case, two methods of isolation were employed. The

acetylation mixture was extracted with ether, and the ethereal layer washed successively with 5% NaOH solution, H<sub>2</sub>O and 10% Na<sub>2</sub>CO<sub>3</sub> solution. The ethereal solution was concentrated by gently blowing off the ether in a stream of air. The crystals which separated were washed with several portions of ether. The washings were combined and treated as the original solution. An alternate and improved method of isolation was to place the acetylation mixture in a distilling flask and remove the excess acetic anhydride under reduced pressure. The residue was stirred with water, which leaves the cream-colored product behind. The crude product obtained by either method of isolation was recrystallized from commercial absolute alcohol. The alcoholic solution showed a great proclivity to supercool, but a slight scratching was all that was needed to initiate complete precipitation of the white product. The weight of the purified product melting at 71-71.5° was 37 gm. (70%). Repeated recrystallization did not raise the melting point.

In a similar manner, 3,4-dimethoxymandelonitrile acetate (melting at 75°) was prepared from veratraldehyde in a yield of 69%. The product was more difficult to crystallize than the corresponding methylenedioxy compound.

#### Homopiperonylamine:

Reduction of the methylenedioxymandelonitrile acetate to homopiperonylamine was accomplished after modifying the procedure given by Kindler and Peschke (52):



Five gm. (0.024 mole) of 3,4-methylenedioxymandelonitrile acetate was dissolved in 50 cc. of absolute ethanol containing 2 equivalents of hydrogen chloride and 3 gm. of 10% palladium-on-charcoal catalyst added. The mixture was subjected to hydrogenation at 4 atmospheres pressure in the Burgess-Farr apparatus at room temperature. The reduction proceeded extremely slowly. After shaking for 6 hours, only a small fraction of the calculated amount of hydrogen was taken up. Approximately 0.1 gm. of palladium chloride was added and shaking continued for 1 hour longer. The catalyst was removed by filtration and the filtrate concentrated by removing the alcohol in vacuo. The oily residue failed to yield a hydrochloride or a picrate.

The reduction was repeated, substituting Adams catalyst (platinum oxide) for the palladium catalyst. The reduction was equally as slow as in the previous runs.

Successful method of reduction: Five gm. (0.024 mole) of 3,4-methylenedioxymandelonitrile acetate was dissolved in 50 cc. of glacial acetic acid and 1 cc. of concentrated sulfuric acid added. A transient red color appeared as the sulfuric acid came in contact with acetic acid solution of the mandelonitrile acetate. Three gm. of previously prepared "active" catalyst\* was added and reduction initiated at 4 atmospheres pressure and at room temperature in the Burgess-Parr apparatus. The reduction was very rapid initially; after approximately two-thirds of the calculated amount of hydrogen was taken up, the rate of reduction slowed and the last third was rather refractory. The product was isolated by filtering off the catalyst (which was immediately washed successively with several portions of water, acetone, 95% ethanol and ether, and saved for future runs) and adding the calculated amount of sodium hydroxide (as a 20% solution) to neutralize the sulfuric acid. The turbid mixture was transferred to a Claisen distilling flask, and the acetic acid removed

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\*vide infra

under diminished pressure on a water bath. The residue was taken up in enough water to get complete solution (during some runs it was necessary to add a little dilute hydrochloric acid to prevent hydrolysis of the amine acetate) and extracted with ether to remove non-nitrogenous materials. The solution was then made distinctly alkaline and exhaustively extracted with ether. The combined ethereal extractions were dried over pellets of sodium hydroxide and filtered into a dry 500 cc., three-neck flask immersed in an ice-salt bath and fitted with a mechanical stirrer, calcium chloride tube, and a glass tube which came within 1 cm. of the surface of the ethereal solution. By means of this tube a stream of anhydrous hydrogen chloride was blown over the surface while stirring the cooled solution. The snow-white homopiperonylamine hydrochloride precipitated as a fluffy, amorphous mass. After standing overnight in a refrigerator, the product was filtered from the ethereal solution and dried in vacuo. The crude product melted at 190-195°. Recrystallization from absolute alcohol-absolute ether raised the melting point to 208-210°. The purified product weighed 4.1 gm. (85%). The hydrochloride was readily soluble in water. The following derivatives (86) were made by the usual methods: picrate mp. 173-4°; N-benzoate mp. 121°; chloroplatinate mp. 210°. The free amine was water-white and distilled at 90°/0.13 mm. It readily formed a carbonate (melting at 90°), abstracting CO<sub>2</sub> from the atmosphere.

In a similar manner, homoveratrylamine was prepared from 3,4-dimethoxy-mandelonitrile acetate in a yield of 82%. The hydrochloride is more difficult to purify than homopiperonylamine hydrochloride. The following derivatives (51) were prepared: hydrochloride mp. 154-155°; picrate mp. 162-3°; N-benzoate (87) mp. 97°. The free amine was a syrupy, water-white liquid distilling at 87°/0.13 mm. It, too, avidly formed a carbonate (melting at 93-94°), abstracting CO<sub>2</sub> from the atmosphere.

Preparation of "Active" Catalyst:

Since the reductions up to this point were not only erratic but generally disappointing, the catalyst was suspected. It had been observed that the palladous chloride (Coleman & Bell) showed aberrated properties and behaved differently from material previously used in these Laboratories. It has been noted occasionally, without adequate experimental foundation, that "recovered" palladium chloride frequently exhibited increased catalytic activity. A decision was made, therefore, to recover the metal from spent catalysts and investigate its catalytic properties. It should be added that the used catalyst generally was palladium-on-charcoal; and that, to it occasional platinum catalysts had been added. These were ashed with an oxygen-gas torch. The residue, containing globules of free metal was taken up in aqua regia. The material which did not dissolve was filtered off and the clear, wine-red filtrate was evaporated to dryness on a steam bath. The residue was heated with excess concentrated hydrochloric acid and again evaporated to dryness. Iridescent purplish-red plates were obtained. One gm. of these crystals was dissolved in 50 cc. of boiling water. It was necessary to add a few drops of concentrated hydrochloric acid to prevent hydrolysis; thus a deep red, clear solution was obtained. Fifty cc. of 1 molar sodium acetate solution was combined with the above solution and after the addition of 2 gm. of Norite, the mixture was shaken in an atmosphere of hydrogen until saturated. The "active" catalyst thus obtained was filtered, washed successively with four portions of water, acetone, 95% ethanol and ether. When not in use, it was stored in a screw-cap bottle. The catalyst showed no diminished activity upon repeated use.

The smooth reduction of the mandelonitrile acetates when employing the "active" catalyst prompted a reinvestigation of former reductions which failed.

Mandelonitrile benzoates:

p-Hydroxymandelonitrile dibenzoate was reduced using essentially the same procedure as given on page 24; substituting 3 gm. of the "active" catalyst for the one given there. Reduction was very slow and no definite product was isolated.

No mandelonitriles or substituted phenyl cyanides were available for trial with the "active" catalyst and time did not permit their reparation.

$\omega$ -Nitrostyrenes:

The reduction of 3,4-methylenedioxy- $\omega$ -nitrostyrene proved highly interesting. Four gm. (0.02 mole) of 3,4-methylenedioxy- $\omega$ -nitrostyrene was suspended in 100 cc. of glacial acetic acid to which was added 1 cc. of concentrated sulfuric acid (a transient red color appeared at the juncture of the two liquids). Three gm. of the "active" catalyst was added and the mixture hydrogenated at room temperature in the Burgess-Parr apparatus under an initial pressure of 4 atmospheres. The calculated amount of hydrogen was taken up in 5 minutes. The reaction bottle was quite warm after the reduction. The catalyst was filtered by suction, washed in the usual manner, and the filtrate treated with the calculated amount of 20% sodium hydroxide solution to neutralize the sulfuric acid. The mixture was transferred to a Claisen distilling flask and the solvent removed in vacuo. The residue was taken up in water and the turbid solution treated with a small amount of

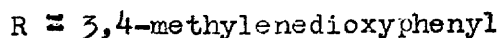
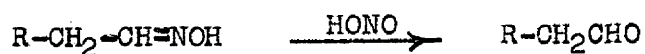
dilute hydrochloric acid to insure acidity and prevent hydrolysis of the amine acetate. Upon addition of the acid a grayish-white solid separated, which was filtered off and saved for later identification. The filtrate was worked up in the same manner as already described for the reduction of the mandelonitrile acetate with the "active" catalyst. Two gm. (50%) of purified homopiperonylamine hydrochloride, melting at 208-209° was obtained.

The grayish-white solid isolated above was treated with charcoal and recrystallized from glacial acetic acid. The weight of the purified product was 0.8 gm., melting at 249°. Its properties agreed with those reported by Sonn and Schellenberg (59) for 1,4-dinitro-2,3-bis(3,4-methylenedioxyphenyl) butane.

Unfortunately time did not permit following these investigations further. In view of the striking difference observed here between the two types of catalysts, it is suggested that a more detailed study of these phenomena will prove enlightening and profitable.

#### Attempts to Prepare Substituted Phenylacetaldehydes:

It was expected that Keagle's application (72) of Harries' method (88) for the hydrolysis of succindialdoxime, would yield the desired aldehyde from 3,4-methylenedioxyphenylacetaldoxime:



In the following experiments the oxime used was the same; i.e., 3,4-methylenedioxyphenylacetaldoxime.

Two and twenty-five hundredths gm. (.0125 mole) of the oxime (prepared as described on page 37) was ground with 13.5 cc. of 10% sulfuric acid in a



glass mortar. The mixture was transferred to a 50 cc. beaker, fitted with a mechanical stirrer, and immersed in an ice-salt bath. During moderate stirring, 1.75 gm. (0.024 mole) of sodium nitrite was added in small portions. The rate of addition was controlled by the avoidance of brown fumes and keeping the temperature at 0°. After the addition of the nitrite, the reaction mixture was allowed to come slowly to room temperature. A dark red plastic mass separated from the reaction mixture which failed to yield the aldehyde and was not further characterized.

The modification of Harries' method by Mannich and Budde (89) was tried with no success.

A third modification of the above method was to dissolve the oxime in dioxane, add a saturated solution of sodium nitrite to it and while stirring and cooling, dilute hydrochloric acid was added. The solvent was removed under diminished pressure and the residue extracted with ether. No aldehyde was isolated, although the fuchsin-aldehyde test was positive.

The method of Tiemann (90):

One gm. (0.0056 mole) of the oxime was mixed with 1 gm. (0.0067 mole) of phthalic anhydride and the dry mixture distilled with steam. The distillate (which gave a positive fuchsin-aldehyde test) was extracted with ether, dried over anhydrous magnesium sulfate and concentrated in vacuo. No aldehyde could be isolated although the concentrated ethereal solution possessed an aromatic odor (cf. phenylacetaldehyde).

The method of Hall, Hynes and Lapworth (91):

A modification of the method of these authors was used. One gm. (0.0056 mole) of the oxime was added to a mixture of 10 gm. of formalin

and 10 gm. of concentrated hydrochloric acid and the mixture was heated to boiling. The mixture, which darkened on heating, was cooled to room temperature and extracted with ether. No aldehyde was isolated.

Various other methods of hydrolysis, such as gentle reflux of the oxime with dilute sulfuric or hydrochloric acid were tried but with equally poor results. The difficulties in hydrolyzing these aldoximes parallel Waters's (92) inability to obtain  $\alpha$ -keto acids from the corresponding oximino acids without disrupting the expected product.

#### RING CLOSURE

Biological closure of the isoquinoline ring: Modifications of the methods of Hahn and Schales (38) and of Schöpf and Bayerle (26) were used for the ring closures.

#### Hahn and Schales (38):

To a solution of 1.6 gm. (0.008 mole) of homopiperonylamine hydrochloride in 150 cc. of water was added 1.91 gm. (0.018 mole) of benzaldehyde. The pH of the mixture was adjusted to 5 by means of a trisodium phosphate buffer and the final volume made up to 200 cc. The mixture was allowed to stand for 8 days at room temperature. During this period the mixture acquired a straw color. At the end of the period, the odor of benzaldehyde was still pronounced. The mixture was then evaporated to dryness under diminished pressure. The yellow residue was made alkaline and exhaustively extracted with ether. The ethereal solution was dried over pellets of sodium hydroxide and to it a cold, saturated, ethereal solution of hydrogen chloride added. The mixture was allowed to stand in a refrigerator overnight and the white precipitate collected by suction filtration and recrystallized from absolute alcohol-absolute ether. The recrystallized product weighed 1.3 gm.

and melted at 204-206°. A mixed melting point with homopiperonylamine hydrochloride showed no depression, confirming its identity as unchanged amine.

The above experiment was repeated with the exception that the time of standing was increased from 8 days to 16 days. The appearance of the mixture was the same as in the previous run and unchanged homopiperonylamine hydrochloride was recovered.

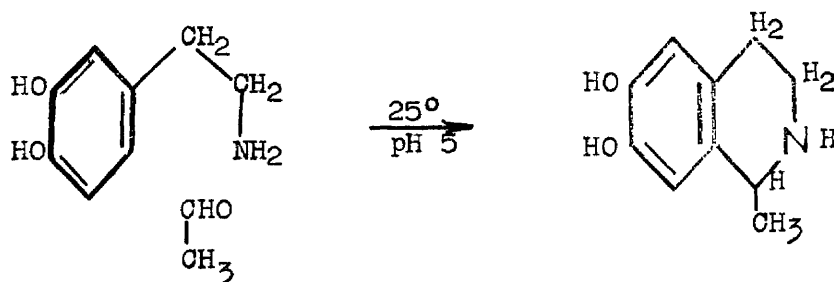
A third modification of the above experiment was to double the concentration of the reactants. Unchanged homopiperonylamine hydrochloride was recovered in almost quantitative yield.

A fourth modification was as follows: To a solution of 1.6 gm. of homopiperonylamine hydrochloride in 150 cc. of water was added 0.79 gm. (.018 mole) of acetaldehyde. The pH of the mixture was adjusted to 5 by means of a trisodium phosphate buffer and the final volume made up to 200 cc. The mixture was then divided into equal parts. Part (I) was allowed to stand for 8 days. Part (II) was allowed to stand for 16 days. Unchanged homopiperonylamine hydrochloride was recovered in both instances.

The failure of these experiments to duplicate the results of Hahn and Schales parallels the inability of Späth, Kuffner and Keszler (39) to repeat the former authors' work.

#### Schöpf and Bayerle (26):

The method of Schöpf and Bayerle in closing the isoquinoline ring under biological conditions requires a free hydroxyl group in the 3-position of the  $\beta$ -phenethylamines:



Attempts at demethylation of homopiperonylamine and homoveratrylamine were carried out as follows: Three 1 gm. quantities of homopiperonylamine were refluxed separately for 30 minutes with 20 cc. of constant boiling hydrobromic acid, hydroiodic acid and hydrochloric acid. The reaction mixture was concentrated, in vacuo, and the dark gummy residues allowed to stand in the refrigerator overnight. No crystalline product was isolated. Variations of this procedure, such as modifying the amount of acid used, altering the reflux time and method of isolation failed to yield the phenolic product.

A very elite method for the cleavage of the methylenedioxy ring reported by Mosettig and Burger (93), involves the use of aluminum bromide. However, by applying their procedure to the cleavage of homopiperonylamine, the phenolic compound was not obtained, but unchanged homopiperonylamine was recovered. This method merits further investigation.

Homoveratrylamine was treated with hydrobromic acid in the exact manner as given by Schöpf<sup>"</sup> and Bayerle (26) for its conversion to the catechol compound. No definite crystalline product could be isolated.

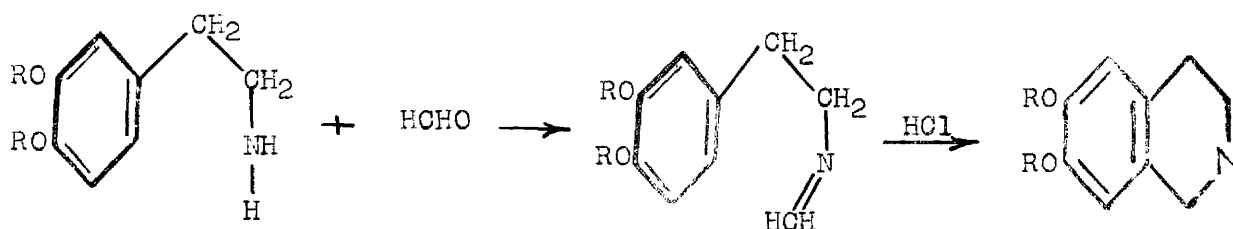
A variation of the above procedure is the following: Three and six-tenths gm. (0.02 mole) of homoveratrylamine was gently refluxed for 30 minutes with 60 cc. of constant boiling hydrobromic acid. The reaction mixture was cooled to room temperature and divided into equal portions. One portion was dissolved in 100 cc. of water and 0.79 gm. (0.018 mole) of acetaldehyde added. The pH was adjusted to 5 with trisodium phosphate and the final volume made up to 200 cc. with water. The brown, frothy mixture was allowed to stand for 3 days at room temperature. Some brown solid separated. The mixture was filtered and the golden yellow filtrate evaporated to dryness in vacuo, the dark residue made alkaline and extracted with ether. The

etheral extract was dried over pellets of sodium hydroxide. The dried, etheral solution was treated with cold etheral hydrogen chloride but no precipitation occurred.

The entire procedure, starting with the demethylation, was repeated substituting homopiperonylamine for the homoveratrylamine. The reaction mixtures behaved similarly to those of homoveratrylamine. Unchanged homopiperonylamine was recovered. Other variations such as increasing the reaction time up to 60 days, and increasing the concentrations were tried but none yielded the expected isoquinolines.

Ring Closure by the Method of Buck (45):

Aldehydes condense readily with amines to yield Schiff bases. These have been converted, without being isolated, into tetrahydroisoquinolines by Buck (45) who used hydrochloric acid as the condensing agent:



R = hydrogen, methyl or methylenedioxy

A number of tetrahydroisoquinoline hydrochlorides containing hydroxy, methoxy, methylenedioxy and N-methyl groups have been prepared by this method. The aldehyde used in every instance was formaldehyde (45). It seemed profitable to adopt this method for the preparation of 1-phenyl substituted tetrahydroisoquinolines.

Preparation of 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline hydrochloride:

This compound was prepared according to the procedure of Buck (45) in a yield of 60% and melted above 350°.

Preparation of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline:

This compound was prepared according to the procedure given by Buck (45) in a yield of 61% and melted at 253°.

Preparation of 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline:

Two and twelve-hundredths gm. (0.02 mole) of freshly distilled benzaldehyde was added to 3.6 gm. (0.02 mole) of freshly distilled homoveratrylamine in a 50 cc. beaker. A yellow color developed immediately and the mixture became quite warm. After manual stirring for several minutes, the turbid mixture was heated on a water bath for 30 minutes. The orange-red mixture was transferred to an evaporating dish, 25 cc. of 24% hydrochloric acid added, and the whole evaporated to near dryness. The cream colored solid which separated was recrystallized from absolute alcohol-absolute ether. The product weighed 4 gm. (56%) and melted at 253-254°.

Attempted preparation of 6,7-dimethoxy-1-phenyl-2'-ethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride: Three gm. (0.02 mole) of freshly distilled

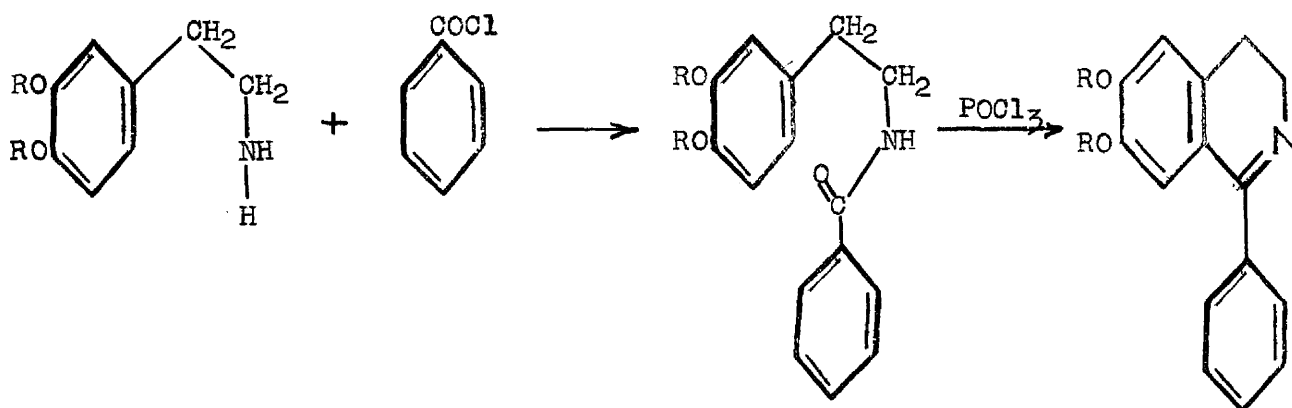
o-ethoxybenzaldehyde was added to 3.6 gm. (0.02 mole) of freshly distilled homoveratrylamine in a 50 cc. beaker. A yellow color developed immediately and the mixture became very warm. After manually stirring for a few minutes the mixture was heated on a water bath for 30 minutes. The oily mass was transferred to an evaporating dish and 25 cc. of 24% hydrochloric acid added. The whole was evaporated to "dryness". Attempts to recrystallize the gummy residue failed.

Attempted preparation of 6,7-methylenedioxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride: The procedure was identical with that given above, substituting homopiperonylamine for homoveratrylamine and benzaldehyde for *o*-ethoxybenzaldehyde. The behavior of the reaction mixture was similar to that above. No definite crystalline compound could be isolated.

Buck's procedure worked well for formaldehyde but was erratic for substituted benzaldehydes.

Preparation of dihydroisoquinolines:

The method used was the same in all cases and consisted essentially of Whaley's modification (21) of the original Bischler and Napieralski reaction (20).



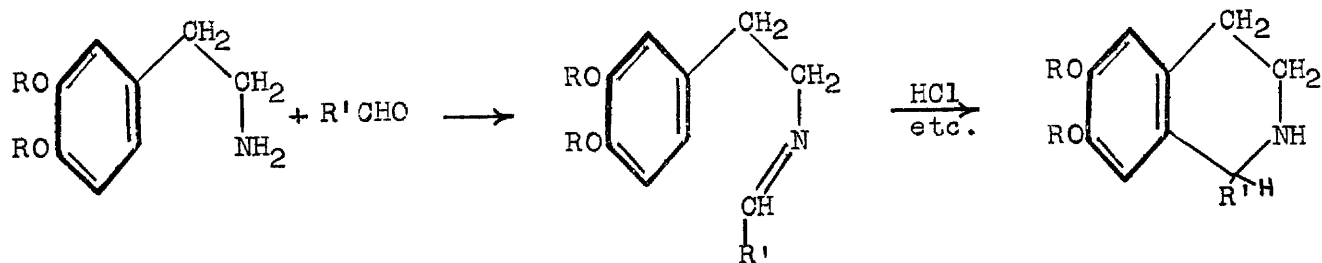
The general procedure is illustrated by the preparation of 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline: One gm. (0.005 mole) of homopiperonylamine was placed in a 200 cc., glass stoppered flask. Two cc. of 20% sodium hydroxide solution, 25 cc. of ether and 0.7 gm. (0.005 mole) of benzoyl chloride was added. The flask was shaken vigorously and the excess ether removed by gently blowing a stream of air in the flask. The benzamide formed was recrystallized from dilute alcohol. The weight of product melting at 117° was 1.3 gm. (quantitative).

Nine-tenths gm. (0.003 mole) of the above benz-( $\beta$ -3,4-methylene-dioxyphenethyl) amide was dissolved in 10 cc. of dry xylene and 3 gm. (0.019 mole) of phosphorous oxychloride added. The mixture was refluxed for 1 hour, cooled with ice chips and heated on a steam bath to obtain two clear layers. The xylene layer was discarded; the aqueous layer washed with ether and made strongly alkaline with 20% sodium hydroxide solution. The alkaline solution was extracted with ether and the ether evaporated in a stream of air. The crystalline residue was recrystallized from dilute alcohol. The product weighed 390 mgm. (32%) and melted at 136°.

In an analogous manner, 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline (m.p. 120-121°) was prepared from homoveratrylamine in a yield of 70%; 6,7,4'-trimethoxy-1-phenyl-3,4-dihydroisoquinoline (m.p. 120°) was prepared from homoveratrylamine and anisyl chloride in a yield of 65% (94).

Ring closure by the method of Decker and Becker (23):

This method of isoquinoline synthesis utilizes the ease in which Schiff bases are formed; these are isolated and cyclized by a variety of condensing agents--anhydrous hydrogen chloride, phosphorous oxychloride, zinc chloride, thionyl chloride and hydrogen bromide.



Decker and Becker condensed homopiperonylamine with a limited number of aldehydes.



Preliminary Notes:

During the course of this investigation, it was found necessary for optimum yields to distill freshly every liquid aldehyde and recrystallize every solid aldehyde prior to its use in the condensations. Likewise it is necessary to distill freshly the intermediate phenethylamines prior to their use; these amines were carefully protected from the atmosphere as they easily form carbonates.

The Schiff bases display a marked tendency to supercool during their recrystallization but only a slight shaking or scratching suffices to initiate complete crystallization.

Two general methods were developed for the preparation of the Schiff bases in excellent yields. The two methods take into account the physical state of the aldehyde.

Method I:

For liquid aldehydes: Three-hundredths of a mole of the aldehyde was added to 0.03 mole of the amine in a 100 cc. beaker. Heat was evolved and a yellow to orange color developed. The mixture was stirred manually until the mixture became viscous and finally set into a hard, dry mass, accompanied by the evolution of heat. Heating on a water bath was not necessary (with freshly distilled reactants) to complete the reaction. The products were recrystallized from dilute alcohol. After recrystallization the compounds were filtered with suction and air-dried. The yield was usually quantitative, allowing for normal manipulative losses.

Method II:

For solid aldehydes: Three-hundredths of a mole was dissolved in 30 cc. of commercial absolute alcohol (in some instances more alcohol and

a gentle warming was required for complete solution) in a 250 cc. Erlenmeyer flask. To this alcoholic solution 0.03 mole of the amine was added, accompanied by development of color. The reaction mixture was gently heated on a water bath to drive off most of the alcohol, then set aside to cool. On cooling, the entire mixture set to a druse of crystals. The product was recrystallized from dilute alcohol, filtered with suction and air-dried.

TABLE II

Schiff Bases of Homoveratrylamine

<u>Substituted Benzaldehydes</u>	<u>Appearance</u>	<u>M.P.°C</u>	<u>Yield of Purified Product</u>
3,4-Diethoxy	Colorless flakes	75-75.5°	Quantitative
4-Methoxy	Colorless plates	62°	82%
2-Hydroxy	Bright yellow needles	74-74.5°	90%
3-Methoxy-4-hydroxy*	Orange bulky plates	120°	88%
2-Chloro	Colorless plates	70-70.5°	86%
3-Nitro	Tiny felted white needles	98°	83%
4-Hydroxy	Light buff plates	161-161.5°	87%
2-Hydroxy-5-chloro	Scintillating yellow platelets	69°	Quantitative

Schiff Bases of Homopiperonylamine

3,4-Methylenedioxy(23)	Light green plates	92°	88%
3,4-Diethoxy	Lemon-yellow fluffy needles	71-72°	85%
Cinnamaldehyde(23)	Snow-white fluffy platelets	64-64.5°	86%

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\*Recrystallized from isopropanol

Cyclization of the Schiff bases:

Various methods of cyclization were tried before satisfactory methods were evolved.

Five gm. (0.025 mole) of homopiperonylamine was dissolved in 100 cc. of dry ether. Two and seven-tenths gm. of benzaldehyde was added and the mixture refluxed for 15 minutes. Ten cc. portions were used for the following condensations.

**Anhydrous hydrogen chloride as condensing agent:** Dry hydrogen chloride in the ethereal solution. There was an immediate reaction and a yellow solid mass separated. The reaction mixture was heated to dryness on the steam bath. The residue was recrystallized from 95% ethanol. The white crystalline product weighed 200 mgm. (34%) and melted at 262°. Decker and Becker (23) reported a melting point of 309-311° for this compound. The product did have the yellow-green fluorescence when heated with dilute nitric acid that these authors describe.

**Aqueous hydrochloric acid:** Ten cc. of the ethereal solution of the Schiff base was added with manual stirring to hot concentrated hydrochloric acid on the steam bath. The mixture was heated on the steam bath for 30 minutes, and enough alcohol added to obtain complete solution. After cooling, buff-colored crystals separated, which after drying weighed 200 mgm. (33%) and melted at 264°.

**Boron trifluoride as condensing agent:** There was an immediate reaction and a yellow solid separated. The mixture was heated to dryness on the steam bath. The residue after treatment with water, 20% sodium hydroxide solution and sodium acetate, was extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate and anhydrous hydrogen chloride introduced.

The precipitated product after recrystallization from 95% ethanol, melted at 262°. The yield was negligible.

Thionyl chloride as condensing agent: Upon the addition of thionyl chloride to the ethereal solution of the Schiff base a yellow solid separated. The mixture was evaporated to dryness on the steam bath. The red, oily residue was taken up in alcohol, warmed to effect solution and allowed to set in a refrigerator overnight. The buff-colored solid was collected and melted at 260-2°. The yield was negligible.

Three general methods for the cyclization were developed which yielded the desired isoquinolines in good yield. As a rule, the isoquinoline was obtainable in quantity by only one of the techniques which must be selected by trial:

Method I used anhydrous hydrogen chloride,

Method II used aqueous hydrogen chloride and

Method III utilized alcoholic hydrogen chloride.

Method I: In a 200 cc., three-neck flask, equipped with mechanical stirrer, calcium chloride tube and a glass tube which dipped below the surface of the reaction mixture, was placed a solution of 0.2 mole of the previously prepared Schiff base in 25 cc. anhydrous benzene. While vigorously stirring the solution, anhydrous hydrogen chloride was introduced through the glass tube. A yellow colored precipitate, indicative of the formation of the Schiff base hydrochloride, immediately separated. After the reaction flask was saturated with hydrogen chloride, the flow was stopped and gentle heat applied. If the condensation went well the yellow color of the Schiff base hydrochloride disappeared and the clear solution was allowed to cool in a refrigerator. The precipitated isoquinoline hydrochloride was removed by filtration and recrystallized from absolute alcohol-absolute ether.

In some instances the product isolated proved to be the unstable Schiff base hydrochloride. These compounds when dissolved in water split into their components. In attempting to make this method more widely applicable, several modifications were made in the general procedure. Modifications such as replacing the benzene with anhydrous xylene in order to obtain a higher boiling solvent, operating at lower temperatures and lengthening the reaction time did not give improved yields.

Method II: In a 200 cc., three-neck flask, fitted with a mechanical stirrer and reflux condenser was placed 0.3 mole of the previously prepared Schiff base and during vigorous stirring 40 cc. of 24% hydrochloric acid added. The Schiff base hydrochloride formed. The flask was heated on a water bath and stirring was continued for 40-60 minutes. The flask was cooled and if the product separated, it was filtered and recrystallized from absolute alcohol-absolute ether. Frequently the product did not separate upon cooling; if this occurred the reaction mixture was evaporated to dryness under reduced pressure (water aspirator) and the residue was dissolved in a minimum amount of hot absolute alcohol, cooled and absolute ether added to initiate precipitation of the isoquinoline hydrochloride.

Method III: In a 500 cc. Erlenmeyer flask was placed a solution of 0.2 mole of the Schiff base in 20 cc. of benzene and 20 cc. of 95% ethanol. To this was added 25 cc. of a saturated ethereal solution of hydrogen chloride and the whole concentrated to approximately one-eighth its volume on a water bath. The reaction mixture was cooled and absolute ether added to initiate precipitation. The isoquinoline was filtered by suction and recrystallized from absolute alcohol-absolute ether. Analytical samples were recrystallized until pure.

TABLE III

Isoquinoline	Prepn. Method	Appearance	M.P. <sup>o</sup> C.	Yield of purified product	Volhard Analysis	
					Cal'd Cl	Found Cl
6,7-Methylenedioxy-1-( $\beta$ -styryl) (23)	I	Light yellow needles	149-150 <sup>o</sup>	70%		
6,7-Dimethoxy-3',4'-diethoxy-1-phenyl	II <sup>a</sup>	Fluffy white needles	222-223 <sup>o</sup>	81%	9.02	9.03
6,7,4'-Trimethoxy-1-phenyl	I <sup>b</sup>	White, felted needles	151-152 <sup>o</sup>	75%	10.57	10.51
6,7-Dimethoxy-2'-hydroxy-1-phenyl	II <sup>c</sup>	White, tiny needles	242 <sup>o</sup>	78%	10.90	10.61
6,7-Dimethoxy-2'-hydroxy-5'-chloro-1-phenyl	II <sup>d</sup>	White platelets	258-260 <sup>o</sup>	68%	9.91	10.21
6,7-Diethoxy-2'-chloro-1-phenyl	II <sup>e</sup>	White plates	210-212 <sup>o</sup>	74%	10.43	10.24
6,7-Dimethoxy-4'-hydroxy-1-phenyl	III <sup>f</sup>	Druse of white needles	237 <sup>o</sup>	83%	11.01	10.89
6,7-Dimethoxy-3'-nitro-1-phenyl	II	White plates	253-254 <sup>o</sup>	80%	10.12	9.89

<sup>a</sup>Method I gave homoveratrylamine hydrochloride. Method III gave negligible yields of the isoquinoline. <sup>b</sup>Method II caused hydrolysis instead of cyclization. Method III gave 20% yield of the isoquinoline. <sup>c</sup>Method I yielded the Schiff base hydrochloride. Method III gave a 35% yield of the isoquinoline. <sup>d</sup>Method I gave a negligible yield and Method III gave a 34% yield of the isoquinoline. <sup>e</sup>Method I gave a gummy, unidentifiable product. Method III caused hydrolysis instead of cyclization. <sup>f</sup>Method II gave a 75% yield of the isoquinoline. Method I gave a gummy, unidentifiable product.

The compounds were, with the exception of the styryl compound, white and well crystallized. In general, they were soluble in water, moderately soluble in alcohol and sparingly soluble in ethyl acetate. They were insoluble in anhydrous ether.

## Discussion of Results

The prospect of employing arethylamines as intermediates for the preparation of dihydro- and tetrahydroisoquinolines necessitated first a study of their synthesis. The general methods examined are:

- a) Reduction of mandelonitriles
- b) Reduction of nitrostyrenes
- c) Reduction of oximes
- d) Reduction of benzyl cyanides

Unfortunately it was not appreciated early enough in these reduction studies that the catalyst was not functioning at its best, consequently the conclusions here stated are subject to later confirmation or modification.

Mandelonitriles were not prepared. Derivatives, however, were studied. It was found that mandelonitrile dibenzoates, obtained from phenolic benzaldehydes, do not yield, even with the "active" catalyst, the desired arethylamine. The acetate of 3,4-dimethoxy- and 3,4-methylenedioxy-mandelonitrile may be conveniently and satisfactorily employed for conversion into the corresponding arethylamines. Reduction proceeds only with "active" catalyst.

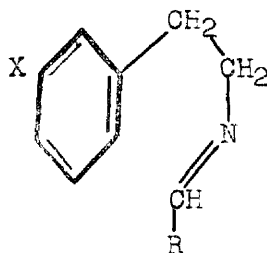
Nitrostyrenes were reduced, using palladium in the presence of pyridine, to good yields of aracetaldoximes. Hydrogenation with "active" catalyst gave 50% yields of the corresponding arethylamine; the product was accompanied by appreciable amounts of 1,4-dinitro-2,3-diarylbutane. This unusual reaction merits further study.

Aracetaldoximes proved refractory to the catalysts employed. The "active" catalyst was not tried.

The possibility of using substituted benzylcyanides was less extensively explored. However, in view of the promising possibility of their ready synthesis from the oximes of  $\alpha$ -keto acids (via the rhodanine route or the nitrosation of alkylmalonic acids), this approach deserves further investigation.

Schöpf<sup>11</sup> and his co-workers state that, in order to obtain ring closure under so-called biological conditions, the phenyl nucleus must contain a free hydroxyl group in the 3-position. Fahn and Schales report that an alkoxyl in the 3-position is also active in promoting cyclization. Results in the present investigation do not substantiate Fahn and Schales. The validity of Schöpf's<sup>11</sup> tenet was not examined here, since the experimental work was confined to the use of phenolic ethers.

The ring closure methods of Buck and Decker and Becker were studied. It develops that Buck's directions for ring closure are valid for Schiff bases of structure



X = activating group

if R is hydrogen or an unsubstituted phenyl; if R is o-substituted phenyl or m,p-dialkoxyphenyl, the cyclization is not as facile as indicated. Hydrolysis rather than cyclization of the intermediate has been observed. The Becker and Becker procedure also shows anomalous behavior, and the method is not always reliable. Modifications were developed, as described on page 63. These modifications are significant in that, depending on the intermediate Schiff base, the yield of cyclized product may vary from nothing to very good.



Data are as yet insufficient to permit prediction of the optimum method in each individual case.

One interesting observation was the color of the Schiff bases. An inspection of the table of Schiff bases will reveal that only those compounds having a hydroxyl group in the ortho or para-position in the aldehyde possess color. It has been suggested (95) that this was due to quinone formation.

## SUMMARY

1. Various methods of synthesizing  $\beta$ -arethylamines were investigated. The intermediates that were prepared but not successfully converted to the amines were:
  - a. mandelonitrile benzoates
  - b. substituted mandelonitriles
  - c. substituted phenylacetaldoximes
  - d.  $\alpha$ -phenyl- $\alpha$ -methoxy- $\beta$ -nitroethanes
  - e. substituted benzyl cyanides
  - f.  $\beta$ -phenylacetamides

The intermediates that were prepared and successfully converted to the requisite  $\beta$ -arethylamines were:

- a.  $\omega$ -nitrostyrenes
- b. mandelonitrile acetates

The mandelonitrile acetates were converted to the corresponding  $\beta$ -arethylamines in yields of 80%.

2. A catalyst of unusual high activity for catalytic hydrogenation was prepared.
3. Closure of the isoquinoline ring was investigated from three directions:
  - a. Phytochemical synthesis based on the work of Schöpf, Bayerle, Hahn and Schales.
  - b. Tetrahydroisoquinoline synthesis by formation of Schiff bases from  $\beta$ -arethylamines and aldehydes, and their subsequent cyclization based on the work of Buck.
  - c. Tetrahydroisoquinoline synthesis by formation and isolation of Schiff bases followed by their cyclization by one of three general methods based on the work of Decker and Becker.

4. Two general methods for the preparation of Schiff bases in excellent yield have been developed. A series of these compounds has been prepared.
5. A study of the necessary experimental conditions which promoted ring closure in optimum yields has been done from which three general methods have evolved. A series of these compounds has been prepared.
6. The possibility of these compounds having possible medicinal interest will be investigated later.

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