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PHENANTHRIDINE DERIVATIVES  
PART I  
AND THE  
CATALYTIC ALKYLATION OF AMINES  
PART II

By  
GERSHON JOSEPH SHUGAR

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## FOREWORD

This dissertation deals with two problems. The first is concerned with the development of a new synthesis of phenanthridine derivatives and the reaction of these compounds with the Grignard Reagent.

The second problem involves the catalytic alkylation of amines with alcohols.

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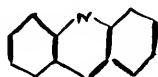
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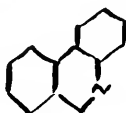
## INTRODUCTION TO PHENANTHRIDINE

The realization that quinine has certain toxicological effects on the human nervous system has stimulated the synthesis of anti-malarials with more desirable properties. As a result the literature contains the description of numerous compounds which have been synthesized as potential anti-malarials.

Of the ring systems employed as a basis for these compounds, probably none has been so widely used as the quinoline and isoquinoline nucleus. Atabrine, a benzoquinoline, has been one of the more effective recent discoveries and has met with a considerable medical use. Its basis is acridine, an isomer of phenanthridine.

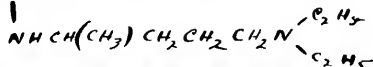
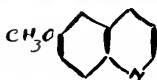


Acridine



Phenanthridine

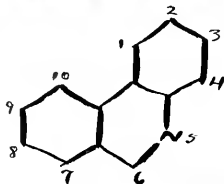
The synthesis in 1926 of plasmoquine, a promising anti-malarial,



has culminated in the preparation of a series of acridine derivatives which are quite potent anti-malarials. The therapeutic significance of each part of the Atabrine molecule cannot be gauged, but the close relationship between phenanthridine and acridine suggests that derivatives of this type in the phenanthridine series might possess valuable

properties.

Phenanthridine has been synthesized by a number of different methods. Its structure has been proven repeatedly by different methods of preparation. Unfortunately, the nomenclature used throughout the literature is not constant. The British use one system and the Americans, another. In order to eliminate confusion, the latest system of numbering the atoms employed by Chemical Abstracts will be used through this dissertation.



Phenanthridine

A review of the literature gives the following syntheses of phenanthridine and its derivatives.

1. Pictet and Ankersmit's (11) classical synthesis of phenanthridine involved the passing of the vapors of benzylidene aniline through a hot tube filled with pumice heated to redness.



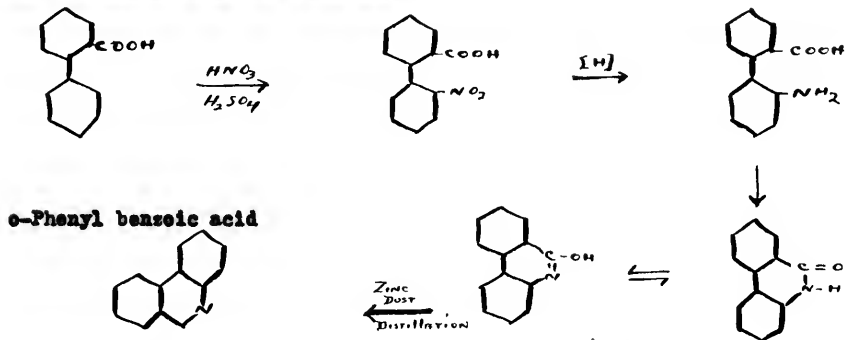
Benzylidene aniline

Phenanthridine

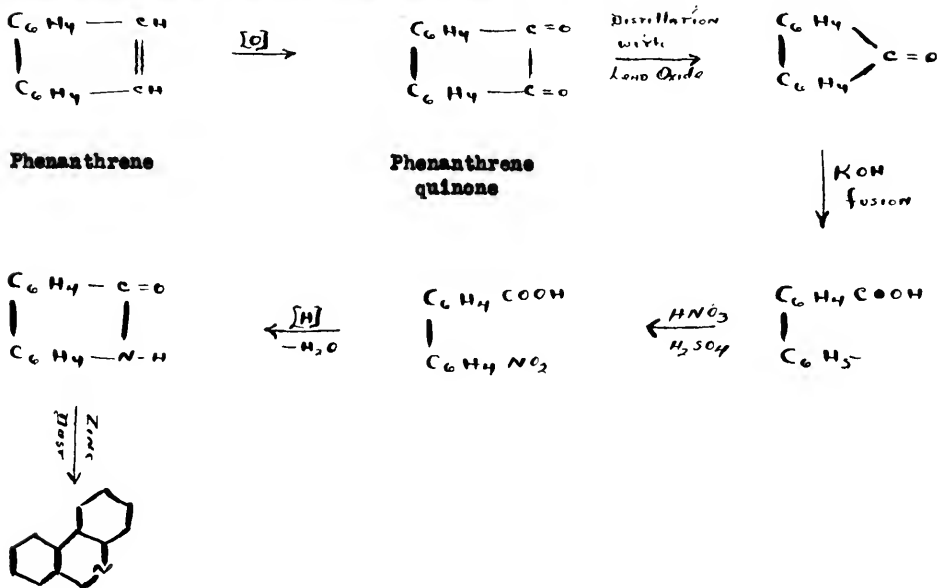
Hydrogen

2. Pictet and Ankersmit (12) prepared ortho-phenyl benzoic acid, nitrated and then reduced it. Thus they obtained by this method hy-

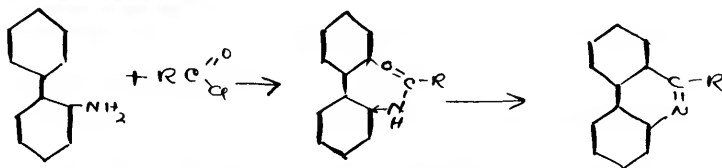
droxy phenanthridine as one of the isomers. On distillation with zinc dust phenanthridine was obtained.



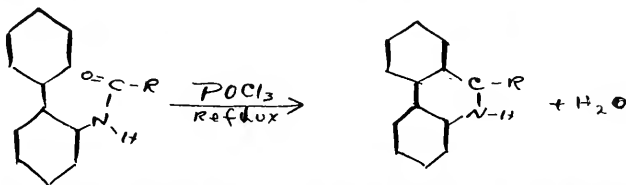
3. Starting with phenanthrene, Pictet and Ankersmit (14) obtained phenanthridine by the following reactions:



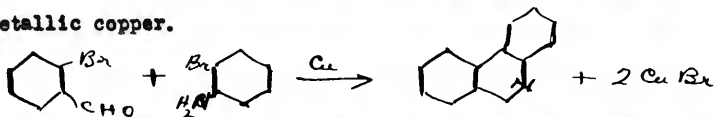
4. Pictet and Hubner (10) used *o*-amino biphenyl as their base, made the acyl derivative, and then condensed the anilide to give an alkyl phenanthridine.



5. Morgan and Walls (22) improved Pictet's method of dehydrating the acyl *o*-xenyl amine by refluxing the anilide with  $\text{POCl}_3$  instead of heating with zinc chloride. This reaction proceeds smoothly and has been used successfully in the preparation of alkyl, chloroalkyl, phenyl and nitrophenyl phenanthridines. The colorless acyl derivatives are converted to quaternary salts by Ulman's method, (7) using hot nitro-benzene as the solvent.

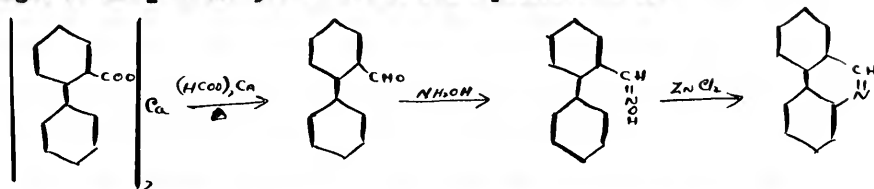


6. The ideal synthesis from separate benzene nuclei was developed by Kondo (7) who heated *o*-bromobenzaldehyde with *o*-bromoaniline in the presence of metallic copper.

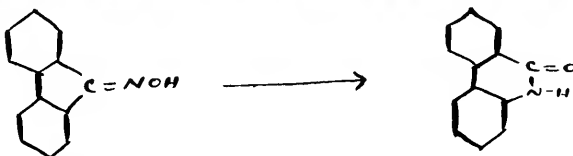


7. Pictet and Gosset (13) distilled equimolecular amounts of calcium formate and calcium *o*-phenyl benzoate and prepared *o*-phenyl benzaldehyde.

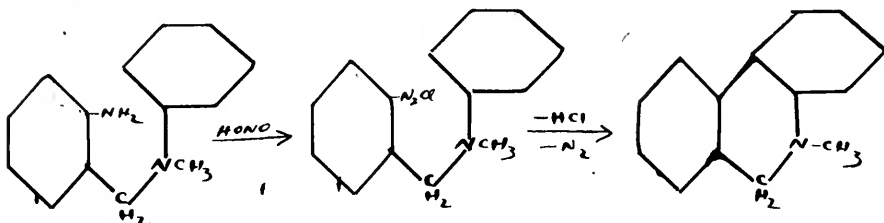
From this they obtained the oxime which was heated with 4-5 times its weight of  $ZnCl_2$  at  $280-300^\circ C$ . and obtained phenanthridine.



8. The Beckman rearrangement of fluorenone oxime by Pictet and Gosset (16) led to the formation of phenanthridone with a 30% yield.



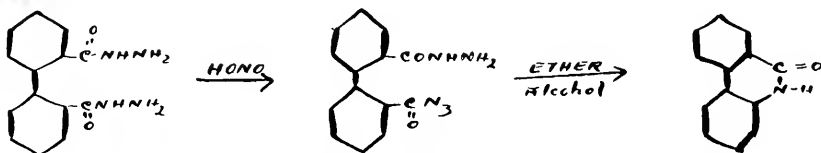
9. The diazotization of an aromatic amine with subsequent ring closure and the simultaneous evolution of nitrogen and hydrogen chloride was used by Pictet and Gosset (16) to obtain an N-methyl phenanthridine.



10. Pictet (15) by pyrolysis methods heated *N*-methyl carbazole and obtained phenanthridine in a 40% yield.



11. The Curtius degradation of diphenic acid hydrazides has been studied by Labriolu (9). He found that when diphenic acid dihydrazide was treated with one mole of nitrous acid, the azide-hydrazide was formed. This was unstable and reacted in alcohol-ether mixture to give phenanthridone.



12. Hey and Buchley (5) heated 2-amino biphenyl hydrochloride with methanol in an autoclave for 12 hours at 250-300°C. and obtained dimethyl phenanthridine.

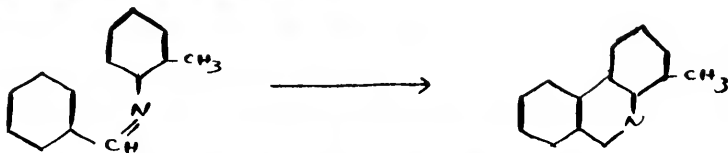
2-amino biphenyl hydrochloride -  $\frac{\text{CH}_3\text{OH}}{\text{Autoclave, 12 hours}}$  dimethyl phenanthridine

13. Phenanthridine has been found to be present in coal tar by Siebisch and Sandke (19), who isolated it and checked its constants with those reported in the literature. They were found to be identical.

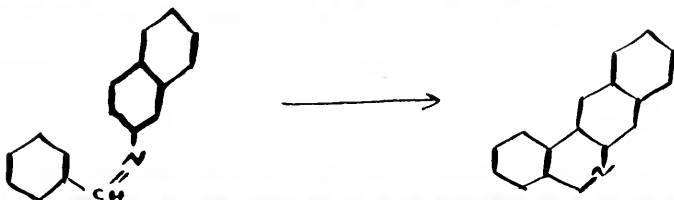
14. Employing the pyrogenous technique devised by Pictet and An-



kersnit, Etard (2) prepared a methyl phenanthridine by passing Benzal-o-Toluidine through a glowing tube.



15. Graebe (3) reported the unreliability of Pictet's synthesis by pyrogenous methods. He showed that the compounds produced from benzylidene alpha-naphthylamine and benzylidene beta-naphthylamine were in reality acridine derivatives. Pictet reported that benzylidene alpha-naphthylamine yielded a benzophenanthridine, viz:

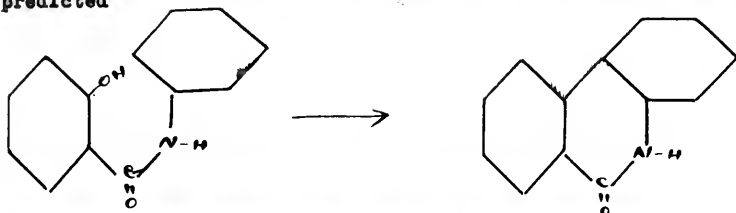


But, when Graebe synthesized this benzophenanthridine by an unambiguous method, he found that the two compounds were not identical. Hence, he showed that Pictet's compounds were acridine derivatives formed in the following manner.

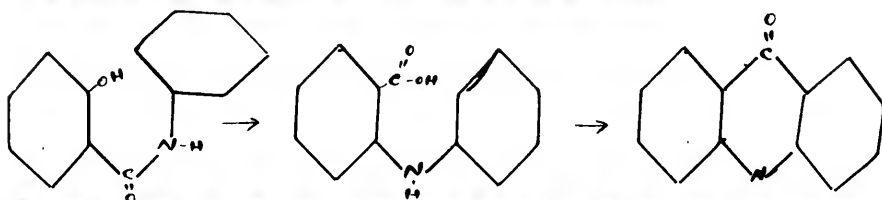


16. Pictet and Hubner (17) attempted the synthesis of Phenanthridine by dehydration reaction using salhydranilide as the starting material. It seemed that the reaction should proceed smoothly to give phenanthridone,

but actually, they obtained acridone. Instead of proceeding as they had predicted



a molecular rearrangement was involved giving acridone:

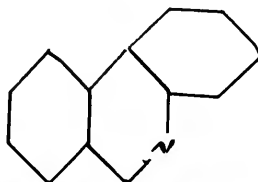
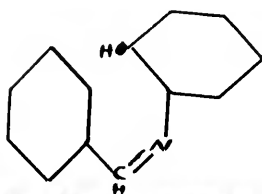


The salhydranilide was subjected to a dry distillation, and the residue extracted with alcohol. Analysis gave the formula to be  $C_{13}H_9NO$  corresponding to that of phenanthridone. Zinc dust distillation on the other hand yielded acridine, instead of the expected phenanthridine.

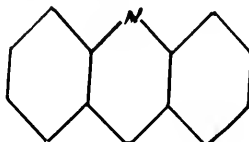
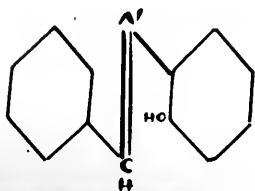
17. Kordo and Ulzco (8) obtained a weak base by the zinc dust distillation of lycorine, an alkaloid. The crystalline compound melted at  $104.5^{\circ}C.$ , and analysis showed it to be phenanthridine.

## THEORETICAL DISCUSSION

Pictet's and Ankersmit's paper (14) was of special interest to us, for they reported that all attempts to synthesize phenanthridine from benzylidene *o*-aminophenol were unsuccessful. They stated that when this compound, which is commonly known as an anil or Schiff's base, was heated with dehydrating agents such as  $P_2O_5$ ,  $ZnCl_2$  or sulfuric acid, no phenanthridine was obtained. However, they never isolated the reaction product except as the mercuric chloride double salt, whose melting point they reported was higher than that of phenanthridine's double salt. Therefore they concluded that acridine had been formed instead of phenanthridine. They also used the salicylidene aniline as their starting material, and again their results were negative. From a structural standpoint it seems very probable that the benzal-*o*-amino phenol should dehydrate and give phenanthridine.



If water is formed by the splitting out of the hydroxyl group in the ortho position of one ring and the hydrogen atom on the ortho position in the other ring, a sixmembered ring should be produced. They, however, stated that they had obtained acridine by the following method:



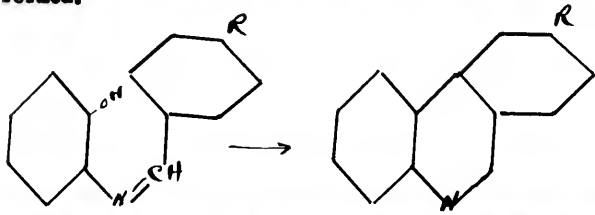
It seems that the reaction should proceed equally as smoothly to yield phenanthridine as acridine. A complete survey of the literature shows that in no case has phenanthridine been prepared by this method. Whenever a reference is made to the effect that this reaction does not go as predicted, the workers always refer to this original article. The work, as far as we have been able to find, has never been repeated.

Since these men never analyzed their product, which they believed to be acridine, we decided to repeat their work. Using an apparatus for working under reduced pressure, we heated benzal *o*-aminophenol with phosphorous pentoxide and obtained a base which melted at 104°C. Analysis showed it to have the molecular formula of phenanthridine, and no amount of purification by steam distillation, vacuum distillation, recrystallization, or decomposition of the hydrochloride would raise the melting point of the compound above 104°C. It, therefore, was assumed that the dehydration of this anil had yielded phenanthridine. Various amounts of phosphorous pentoxide were used with the anil and a range of temperatures were employed. In all cases the final compound melted at 104°C. The melting point of acridine is listed in the literature as from 107° to 112°C., while the majority of articles give the melting point of phenanthridine as 104°C.

As a result of this work we have shown that phenanthridine could be synthesized from benzal *o*-aminophenol by using phosphorous pentoxide as the dehydrating agent.

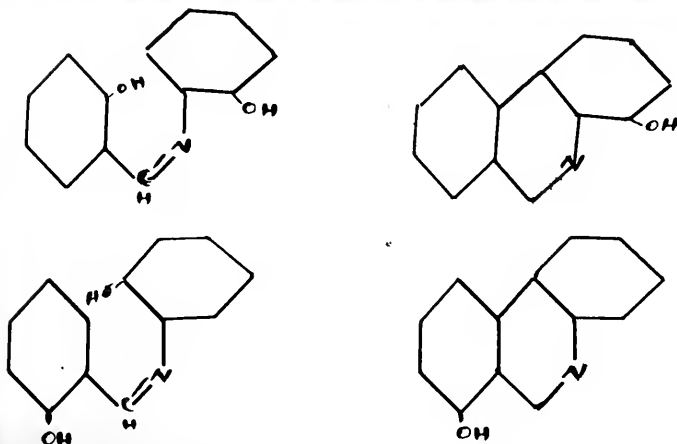
Having proved that synthesis by this method was feasible, a series of derivatives were prepared using the same general procedure. In all

cases the structure of the resulting phenanthridine was accepted on the basis of synthesis. For example, if the benzal portion of the molecule is substituted in the para position, there can be only one phenanthridine formed.



Since the substituted phenyl ring is attached to the carbon atom by a single bond, the phenyl ring is free to rotate. Hence it can be seen that the hydroxyl group has an equal opportunity to split off hydrogen from either of the two ortho positions of the other ring. Regardless of which hydrogen it reacts with, the resulting phenanthridine will be the same, since the substituted group is in the para position on that phenyl ring.

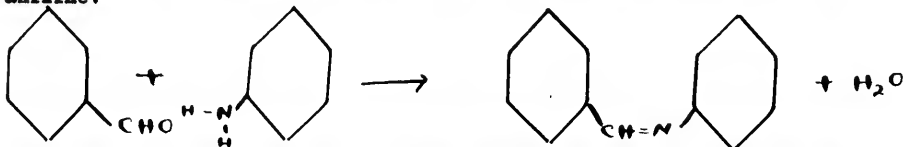
When two possible phenanthridines could be formed, the structure was proved by implication. That is, if salicylidene o-aminophenol were the starting anil, then two possible phenanthridines could be formed.



In this case one of the possibilities was eliminated by synthesizing the other phenanthridine and comparing the physical constants with those of the phenanthridine obtained by using salicylidene o-aminophenol as the starting material.

The presence of an ortho-hydrogen atom on one ring and an ortho-hydroxyl group on the other ring should lead to the formation of the same phenanthridine regardless of which ring the hydroxyl group is attached. A number of different anils were prepared in which every anil made had either one or more hydroxyl groups in the ortho position on the ring. All of these were treated under varying conditions of temperature, pressure, and concentration with regard to the dehydrating agent, phosphorous pentoxide, in order to determine whether or not they would yield the corresponding phenanthridine compound.

Every anil compound of o-aminophenol yielded a phenanthridine. However, those anils in which there was no hydroxyl group on the ortho position of the aniline portion of the molecule failed to cyclize. A series of anils was prepared by coupling 2-hydroxy-3-methoxy benzaldehyde and substituted anilines. The anils formed very easily, by adding the aldehyde and amine together in alcohol and warming. This reaction may be exemplified by the synthesis of benzal aniline from benzaldehyde and aniline:



These anils crystallized out in orange needles having the proper nitrogen

content. However, these anils, when heated with phosphorous pentoxide in the reaction vessel underwent a peculiar decomposition. At a definite temperature the intimate mixture of anil and anhydride started giving off brown fumes having a characteristic odor. The first sign of decomposition was the formation of a dark char on the surface of the mixture which spread rapidly and finally consumed the entire batch of material. During this time voluminous clouds of brown vapors were evolved which were not condensable at a temperature of  $-20^{\circ}\text{C}$ . Even when the source of heat was removed from the vessel, the decomposition proceeded in all cases. When the reaction was carried out in the dark, the flame of combustion was plainly visible. All of the anhydride was consumed by this reaction; the reaction mixture had practically doubled its size in the flask. There was no reaction of the final product with water, showing that all of the anhydride had been consumed. Extraction of the mass yielded a fluorescent solution, but in no case could definite products be identified.

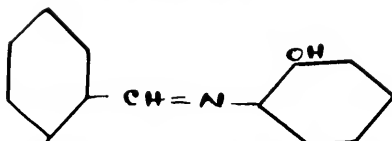
This charring did not take place when *o*-aminophenol was used in place of aniline or other substituted anilines. When the *ortho*-aminophenol was the aniline portion of the molecule, the two possibilities products were identified by synthesis, as in the case of the salicylidene-*o*-aminophenol. There has been no reference to such a reaction in the literature and personal inquiry provided no further information. It is supposed that certain phosphine or phosphine-like compounds were formed, but no attempts were made to identify the gases other than by their odor.

## THE SCHIFF'S BASES

The preparations of the anils or Schiff's Bases, which were used as intermediates in the synthesis of the phenanthridine derivatives, are described in the following pages. Seven new anils were prepared, and six previously reported anils were resynthesized.



## BENZAL-2-AMINOPHENOL

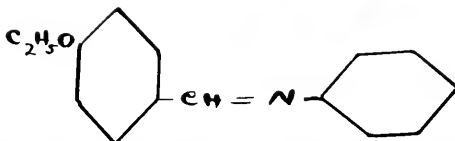


Equimolar quantities (0.2 mole) of benzaldehyde and 2-aminophenol were dissolved in boiling alcohol. On cooling brown crystals separated from the solution, and they were recrystallized several times from 95% ethanol and activated charcoal.

Empirical Formula	$C_{13}H_{11}NO$	
Molecular Weight	197	
Color	white	
Solubility		
water	insoluble	
alcohol	soluble in hot, fairly insoluble in cold	
Melting Point	89.5-90 experimental	
	89-90°C. reported (14)	
Analysis	found	calculated
nitrogen	7.0%	7.10%
Yield	75% theoretical	

## 4-ETHOXYBENZAL-2-AMINOPHENOL

(New Compound)



Equimolar quantities (0.1 mole) of 4-ethoxy benzaldehyde and 2-amino-phenol were dissolved in boiling alcohol and heated several minutes. Activated charcoal was added and the solution filtered. Water was added to the hot filtrate until turbidity began and the solution allowed to cool. Crystals were filtered off and recrystallized from 50% alcohol and water.

Empirical formula

C<sub>15</sub> H<sub>15</sub> O<sub>2</sub> N

Molecular weight

231 225

Color

light cream

Solubility

Alcohol

very soluble in hot alcohol

Melting Point

32.5-33°C.

Analysis

found                  calculated

nitrogen

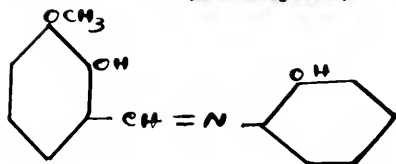
~~5.6%~~~~5.8%~~ 6.2

Yield

69% theoretical

## 2-HYDROXY-3-METHOXYBENZAL-2-AMINOPHENOL

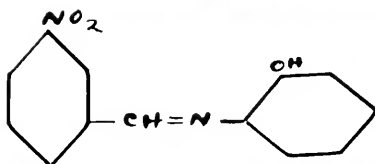
(New Compound)



The compound formed immediately when melted (0.2 mole of) 2-hydroxy-3-methoxybenzaldehyde was poured on 0.2 mole of 2-aminophenol. The anil was very insoluble in boiling 95% ethanol, but repeated leaching with boiling alcohol left the pure base as a residue.

Empirical Formula	$C_{14} H_{13} N O_3$	
Molecular weight	243	
Color	orange red	
Solubility		
water	insoluble	
ethanol	insoluble in boiling ethanol	
Melting Point	187-188°C.	
Analysis	found	calculated
nitrogen	5.7%	5.77%
Yield	63% theoretical	

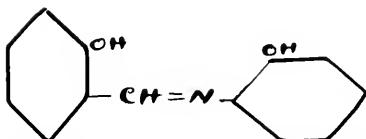
## 3-NITROBENZAL-2-AMINOPHENOL



Equimolar quantities (0.2 mole) of 3-nitro-benzaldehyde and 2-amino-phenol were added together in boiling alcohol. On cooling greenish needles separated out. It was recrystallized from 95% ethanol.

Empirical Formula	C <sub>13</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub>	
Molecular Weight	242	
Color	greenish	
Form	needles in clusters	
Solubility		
ethanol	soluble in hot ethanol	
water	insoluble in water	
Melting Point	133°C recorded in literature (21)	
Analysis	found	calculated
nitrogen	11.4%	11.56%
Yield	73% theoretical	

## 2-HYDROXYBENZAL-2-AMINOPHENOL

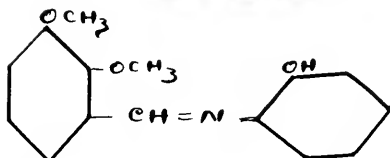


Equimolar quantities of (0.2 mole) salicylic aldehyde and 2-aminophenol were dissolved in boiling alcohol. On cooling blood-red crystals separated. Further recrystallizations from alcohol and activated charcoal yielded the pure anil.

Empirical Formula	$C_{13} H_{11} N O_2$	
Molecular weight	213	
Color	blood red	
Form	crystalline	
Solubility		
water	insoluble	
alcohol	soluble in hot alcohol	
Melting Point	186-7°C. experimental	
	186-7°C. recorded in literature (4-20)	
Analysis	found	calculated
nitrogen	6.5%	6.65%
Yield	70% theoretical	

## 2-3 DIMETHOXYBENZAL-2-AMINOPHENOL

(New Compound)

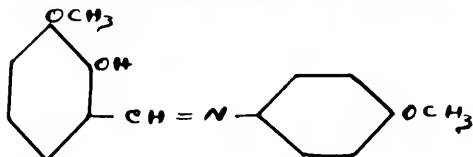


Equimolar quantities (0.2 mole) of 2-3 dimethoxy-benzaldehyde and 2-aminophenol were dissolved in boiling alcohol. On cooling crystals separated out. Recrystallization from 95% ethanol and activated charcoal yielded the pure base.

Empirical Formula	$C_{15} H_{15} N O_3$	
Molecular Weight	257	
Color	buff	
Solubility		
ethanol	soluble in hot ethanol	
water	insoluble in water	
Melting Point	92-93°C	
Analysis	found	calculated
nitrogen	5.2%	5.44%
Yield	56% theoretical	

## 2-HYDROXY-3-METHOXYBENZAL-4-METHOXYANILINE

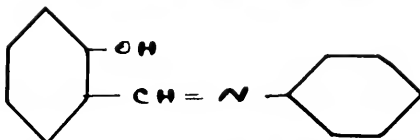
(New Compound)



Equimolar quantities (0.2 mole) of 2-hydroxy-3-methoxybenzaldehyde and 4-methoxyaniline were added together and the mixture heated gently for several minutes. The mass crystallized on cooling and was recrystallized from 95% ethanol and activated charcoal.

Empirical Formula	$C_{15} H_{15} N O_3$	
Molecular Weight	257	
Color	light orange	
Solubility		
ethanol	soluble in hot ethanol	
water	insoluble	
Melting Point	94-95°C.	
Analysis	found	calculated
nitrogen	5.3%	5.44%
Yield	72% theoretical	

## 2-HYDROXYBENZAL-ANILINE

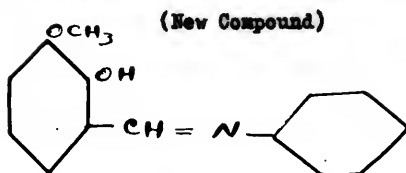


Equimolar quantities (0.2 mole) of salicylic aldehyde and aniline were heated together to boiling. When the solution cooled, alcohol was added and a precipitate formed. It was recrystallized from 95% ethanol and activated charcoal.

Empirical Formula	$C_{13}H_{11}NO$	
Molecular weight	197	
Color	yellow	
Form	crystalline	
Solubility		
alcohol	soluble in hot ethanol	
water	insoluble	
Melting Point	50-50.5°C. experimental	
	50-51°C. reported (14)	
Analysis	found	calculated
nitrogen	6.9%	7.10%
Yield	62% theoretical	



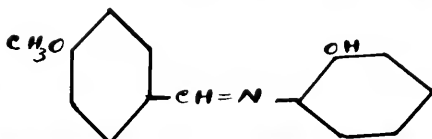
## 2-HYDROXY-3-METHOXYBENZAL ANILINE



Equimolar quantities (0.2 mole) of 2-hydroxy-3-methoxy benzaldehyde and aniline were heated in a beaker for several minutes, and 95% alcohol added. The solution became dark red in color, but would not crystallize on cooling. The solution was put under a pressure of about 1 mm. of mercury and the alcohol distilled off with gentle warming. Crystallization took place immediately, giving practically a quantitative yield. The crude material was recrystallized from alcohol, and a crude seed crystal used to induce crystallization. No amount of scratching of the beaker would induce the anil to crystallize without the seed.

Empirical Formula	$C_{14} H_{13} N O_2$	
Molecular weight	227	
Color	Orange-red	
Solubility		
alcohol	soluble	
Melting Point	82-83°C.	
Analysis	found	calculated
nitrogen	5.9%	6.16%
Yield	58%	

## 4-METHOXYBENZAL-2-AMINOPHENOL

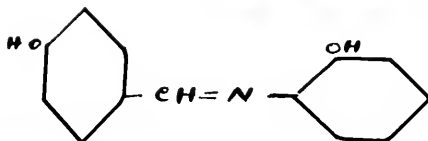


Equimolar quantities (0.2 mole) of 4-methoxy benzaldehyde and 2-aminophenol were dissolved in boiling alcohol. When the solution cooled, crystals separated out. These were recrystallized from 95% ethanol and activated charcoal.

Empirical Formula	$C_{14} H_{13} N O_2$	
Molecular Weight	227	
Color	light-buff	
Solubility		
alcohol	Soluble in hot ethanol	
water	insoluble	
Melting Point	90-91°C. experimental	
	89°C. reported in literature (4)	
Analysis	found	calculated
nitrogen	5.9%	6.16%
Yield	74% theoretical	

## 4-HYDROXYBENZAL-2-AMINOPHENOL

(New Compound)

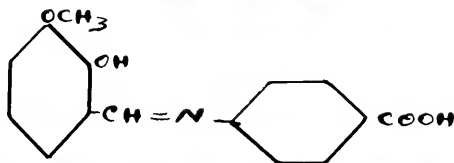


Equimolar quantities (0.2 mole) of 4-hydroxy benzaldehyde and 2-aminophenol were added to boiling alcohol. On cooling the viscous oil would not crystallize. The mass was frozen solid with ice plus HCl mixture and then vacuum distilled. The distillate was recrystallized from alcohol, to which water was added until the solution became turbid.

Empirical Formula	$C_{13} H_{11} N O_2$	
Molecular Weight	213	
Color	orange	
Form	crystals	
Solubility		
ethanol	soluble	
water	insoluble	
Melting Point	247.5-248.5°C.	
Analysis	found	calculated
nitrogen	6.4%	6.58%
Yield	52% theoretical	

## 2-HYDROXY-3-METHOXYBENZAL-4-AMINO BENZOIC ACID

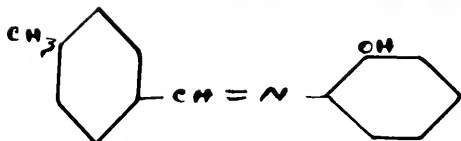
(New Compound)



Equimolar quantities of (0.2 mole) 2-hydroxy-3-methoxy benzaldehyde and 4-aminobenzoic acid were dissolved in boiling alcohol. On cooling crystals separated out. These were recrystallized from 95% ethanol and activated charcoal.

Empirical Formula	$C_{15} H_{13} N O_4$	
Molecular Weight	271	
Color	orange	
Form	flocculent	
Solubility		
ethanol	soluble in hot ethanol	
water	insoluble	
Melting Point	232-233°C	
Analysis	found	calculated
nitrogen	5.0%	5.2%
Yield	79% theoretical	

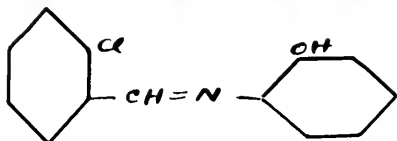
## 4-METHYLBENZAL-2-AMINOPHENOL



Equimolar quantities (0.2 mole) of 4-methyl benzaldehyde and 2-amino-phenol were dissolved in boiling alcohol. On cooling the solution and scratching the sides of the beaker, crystals separated out.

Empirical Formula	C <sub>14</sub> H <sub>13</sub> N O	
Molecular Weight	211	
Color	light buff	
Form	crystalline	
Solubility		
ethanol	very soluble	
water	insoluble	
Melting Point	108.5-109°C. experimental	
	108.5°C. reported in literature (21)	
Analysis	found	calculated
nitrogen	6.5%	6.63%
Yield	71% theoretical	

## 2-CHLOROBENZAL-2-AMINOPHENOL

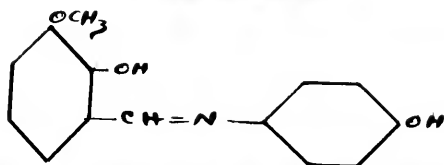


Equimolar quantities (0.2 mole) of 2-chlorobenzaldehyde and 2-aminophenol were dissolved in boiling alcohol. On cooling, the solution was agitated and the sides of the beaker scratched to induce crystallization. The anil precipitated and was recrystallized from 95% ethanol.

Empirical Formula	$C_{13} H_{10} N O Cl$	
Molecular Weight	231.5	
Color	yellow	
Form	crystals	
Solubility		
ethanol	soluble	
water	insoluble	
Melting Point	94°C. experimental	
	94°C. reported in literature (20)	
Analysis:	found	calculated
nitrogen	5.9%	6.04%
Yield	74% theoretical	

## 2-HYDROXY-3-METHOXYBENZAL-4-AMINOPHENOL

(New Compound)



Equimolar quantities (0.2 mole) of 2-hydroxy-3-methoxy benzaldehyde and 4-aminophenol were warmed together, and then a small volume of 95% ethanol added. The solution was heated to boiling and cooled. The dark red viscous oil would not crystallize by scratching the beaker. Water was added to the hot solution until turbidity set in and then the solution was mechanically stirred for 15 minutes. A flocculent precipitate formed which was recrystallized from ether and then dilute alcohol.

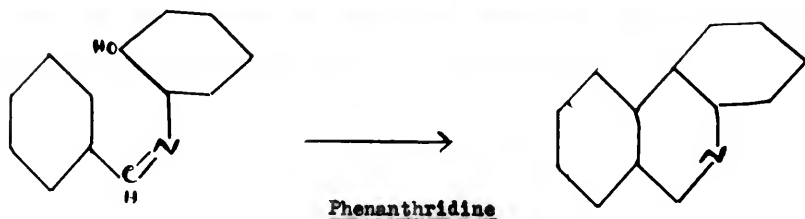
Empirical Formula	$C_{14}H_{13}NO_3$	
Molecular Weight	243	
Color	orange red	
Form	needles	
Solubility		
ether	soluble	
ethanol	soluble	
Melting Point	72.5-73-5°C.	
Analysis	found	calculated
nitrogen	5.4%	5.68%
Yield	50% theoretical	

### GENERAL PROCEDURE FOR SYNTHESIS OF THE PHENANTHRIDINES

A reaction vessel fitted with a ground glass joint was attached by means of a standard tapered stillhead to a distillation flask which served as a receiver. Connected to the side arm of the receiver was a vacuum pump fitted with a vapor trap and a manometer. The reaction vessel was heated by means of an oil bath in which a thermometer was immersed.

The anil was mixed intimately with an equal volume of phosphorous pentoxide and the pressure reduced to 5-20 mm. The reaction vessel was then lowered into the oil bath and a definite temperature was established for a certain time interval. After the required time interval the reaction vessel was disconnected from the set-up and allowed to cool. After cooling, the reaction mixture was treated by different procedures in order to isolate the resulting phenanthridine.

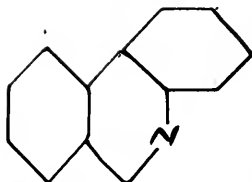
A Hanovia, quartz tube, ultraviolet-ray lamp was used to determine whether reaction had taken place. The anils do not fluoresce under the influence of the ultra-violet light. The phenanthridines fluoresce with colors varying from bright blues to brilliant greens and yellows, depending on the substituent groups in the molecule. The yields in all cases were low, never exceeding 10% of the theoretical.





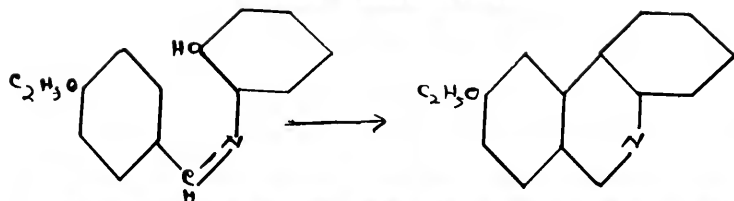
Benzal-2-aminophenol was mixed with an equal volume of phosphorous pentoxide and heated at a pressure of 5 mm. of mercury at 330°C. for 25 minutes. Crystals sublimed on the cool portion of the still-head. After the reaction mass was cooled, alcohol was added and a red solution resulted. The solution was poured into a large excess of water and a reddish precipitate separated. After chilling, the precipitate was filtered and mixed well with 25% NaOH solution. The unreacted anil formed the sodium salt. Ether extraction followed by evaporation of the ether and subsequent recrystallizations from dilute alcohol and activated charcoal yielded the phenanthridine. In order to get the last trace of color out of the batch for specimen purposes, a small amount of it was steam distilled, yielding white micaceous flakes melting at 104°C. This melting point checks with the values accepted in the literature (14-15-7-8-17-16-15-11). The vapors of the compound are irritating to the nose and eyes. The hydrochloride is decomposed by water. In alcoholic or ethereal solution it fluoresces blue in ultra-violet light. The per cent N found was 7.70 while the calculated value was 7.83% N.

## PERMANTERIDINE



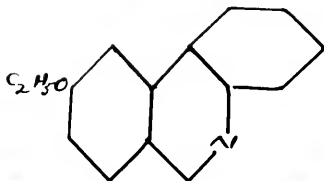
Empirical formula	$C_{13} H_9 N$	
Molecular Weight	179	
Crystalline Form	micaceous flakes	
Color	white	
Solubility		
alcohol	fairly soluble in cold	
water	insoluble	
dilute hydrochloric acid	soluble	
Melting Point	104° recorded in literature	
	104° experimental	
Analysis	found	calculated
nitrogen	7.7%	7.83%

## 9-ETHOXY PHENANTHERIDINE



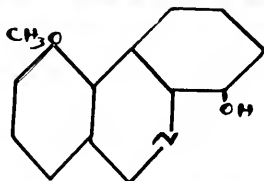
Four-ethoxybenzal-2-aminophenol was mixed intimately with phosphorous pentoxide and heated for two hours at 210°C. under a pressure of 8 mm. of mercury. Repeated ether extractions of the reaction mixture followed by evaporation of the ether yielded a residue. The residue was recrystallized from dilute alcohol and activated charcoal several times and yielded white micaceous flakes melting at 118-119°C. The percentage nitrogen calculated from the formula was 6.27%, that found was 6.1%. The compound fluoresces blue under the ultra-violet light.

## 9-ETHOXY PHENANTHRIDINE



Empirical formula	$C_{15} H_{13} N O$	
Molecular Weight	223	
Melting Point	118-119°C.	
Crystalline form	flakes	
Color	white	
Solubility		
water	insoluble	
alcohol	very soluble in hot	
ether	soluble in cold	
HCl (dilute, 1:1)	soluble in cold	
Analysis	found	calculated
nitrogen	6.1%	6.27%

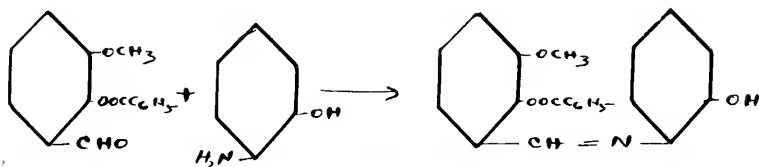
## 4-HYDROXY-10-METHOXY PHENANTHRIDINE



Two-hydroxy-3-methoxy benzal-2-aminophenol was mixed intimately with phosphorous pentoxide and heated under vacuum for 1/2 hour at 250°C. Vapors were given off which condensed on the upper portion of the still head. The reaction mixture was decomposed with alcohol, heated to boiling and filtered. The filtrate was treated with activated charcoal and filtered. Water was added dropwise to the filtered solution and an amorphous precipitate resulted. Ether extraction followed by subsequent recrystallization from dilute alcohol and activated charcoal yielded cream colored crystals melting 151-151.5°C. The compound fluoresced brilliant yellow under the ultra-violet light. The calculated percentage of nitrogen was 6.20%, that found was 6.0%.

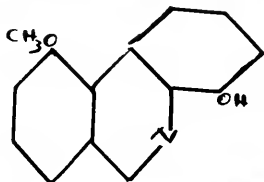
The structure of 4-hydroxy-10-methoxy phenanthridine is proved by the following considerations. Two-hydroxy-3-methoxy-benzaldehyde and benzoyl chloride in equivalent quantities were treated with a dilute solution of alkali as directed in Cummings et al. (27). The 2-benzoyloxy-3-methoxy benzaldehyde was isolated in the form of white flecks melting at 91-91.5°C. The benzoate was then heated in boiling alcohol with an equimolar quantity of 2-aminophenol, and a precipitate of 2-benzoyloxy-3-methoxy-benzal-2-aminophenol formed on cooling. Its melting point was 131-131.5°C. The calculated percentage of nitrogen was 5.66%, that found

was 5.5%. The reactions involved maybe shown as follows:



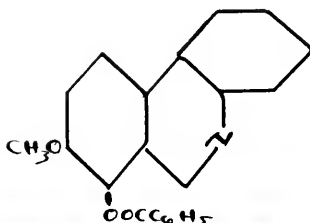
This new anil, 2-benzoyloxy-3-methoxybenzal-2-aminophenol was the basis for the synthesis of 7-benzoyloxy-8-methoxy-phenanthridine, which is discussed in the following pages.

## 4-HYDROXY-10-METHOXY PHENANTHERIDINE



Empirical Formula	$C_{14} H_{11} N O_2$	
Molecular Weight	225	
Melting Point	151-151.5°C.	
Color	cream	
Solubility		
water	insoluble	
alcohol	very soluble in hot	
ether	soluble in cold	
HCl (dil. 1:1)	soluble in cold	
Analysis	found	calculated
nitrogen	6.0%	6.20%

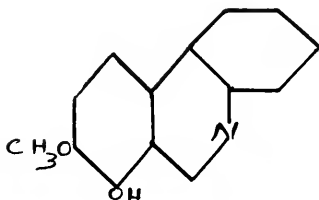
## 7-BENZOYLOXY-8-METHOXY PHENANTHRIDINE



The 2-benzoyloxy-3-methoxy-benzal-2-aminophenol was heated under reduced pressure for two hours at  $240^{\circ}\text{C}$ . The reaction mass was decomposed with alcohol, and water added. The resulting solution was extracted several times with ether, followed by evaporation of the combined ether extracts. The residue was recrystallized several times with alcohol which yielded white crystals and a gum. The crystals and gum were vacuum distilled, and the distillate on recrystallization from alcohol melted  $99.5-100.5^{\circ}\text{C}$ . The distillate had the smell of rotten cabbage. The compound fluoresces yellow under the ultra-violet light. The calculated percentage of nitrogen was 6.11%, that found 6.0%.



## 7-HYDROXY-5-METHOXY PHENANTHRIDINE

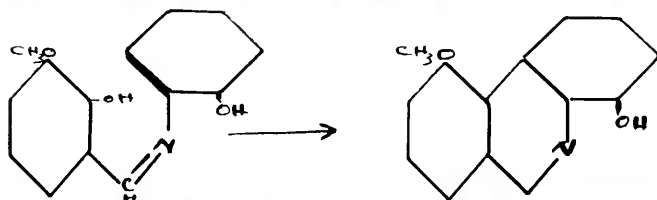


The 7-benzoyloxy-5-methoxy phenanthridine was dissolved in hot glycerine and solid KOH added. The solution was heated for a short time. The solution was extracted several times with ether, the ether extracts combined, and then evaporated to dryness. Recrystallization of the residue several times with dilute alcohol yielded a white mica-ccous compound, melting at 154-155°C. This compound has a slight greenish fluorescence under the ultra-violet light.

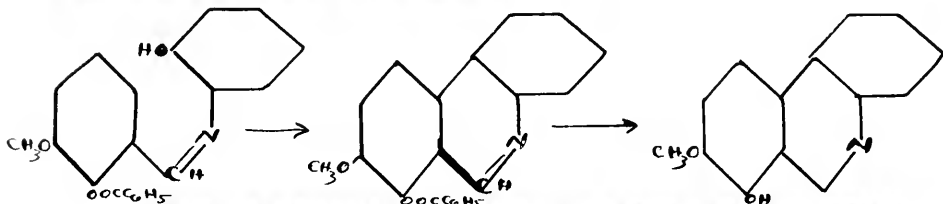
Empirical Formula	$C_{14} H_{11} N O_2$	
Molecular Weight	225	
Color	white	
Form	micaceous	
Solubility		
ether	soluble	
alcohol	soluble	
Analysis	found	calculated
nitrogen	5.9%	6.20%

## ESTABLISHMENT OF THE STRUCTURE OF 2-HYDROXY-10-METHOXY PHENANTHRIDINE

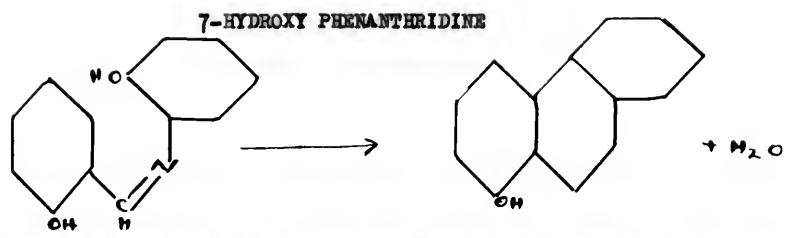
From an examination of the previous five pages it is evident that 2-hydroxy-10-methoxy phenanthridien was formed by the dehydration of the 2-hydroxy-3-methoxy-benzal-2-aminophenol by the following reaction:



for, the synthesis of the 7-hydroxy-8-methoxy phenanthridine carried out is unambiguous. One hydroxyl group was blocked, the reaction carried out, and then the hydroxyl group restored.

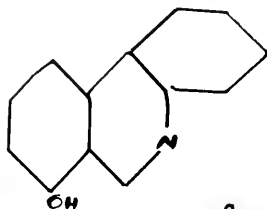


If the two compounds are identical, they should have the same melting point and should not give a depression when a mixture melting point is taken. A mixture melting point of the two compounds prepared above softens at 120°C. and finally melts at 137°C. On this basis it was concluded that the two compounds were not identical.



The 2-hydroxybenzal-2-aminophenol was mixed intimately with phosphorous pentoxide and was heated for  $\frac{1}{2}$  hour at 300°C. On cooling, the reaction mixture was decomposed with alcohol, and after boiling several minutes, water was added. Several recrystallizations from alcohol with activated charcoal yielded white micaceous crystals melting at 102-103°C. This compound fluoresces brilliantly under the ultra-violet light. The nitrogen percentage calculated from the formula was 7.15%, that found was 7.0%.

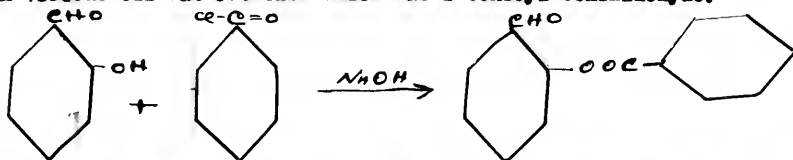
## 7-HYDROXY PHENANTHRIDINE



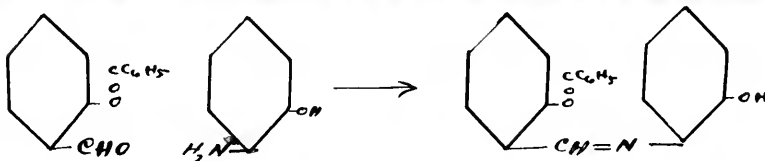
Empirical Formula	$C_{13} H_9 N O$	
Molecular Weight	195	
Melting Point	102-103°C.	
Color	white	
Crystalline Form	micaceous flakes	
Solubility		
water	insoluble	
alcohol	soluble in hot alcohol	
ether	soluble in cold ether	
Analysis	found	calculated
nitrogen	7.0%	7.18%

## ESTABLISHMENT OF THE STRUCTURE OF 7-HYDROXY PHENANTHRIDINE

Two hydroxy benzaldehyde was shaken with an equimolar quantity of benzoyl chloride in the presence of excess dilute sodium hydroxide. A viscous oil was obtained which was 2-benzoyl-benzaldehyde.

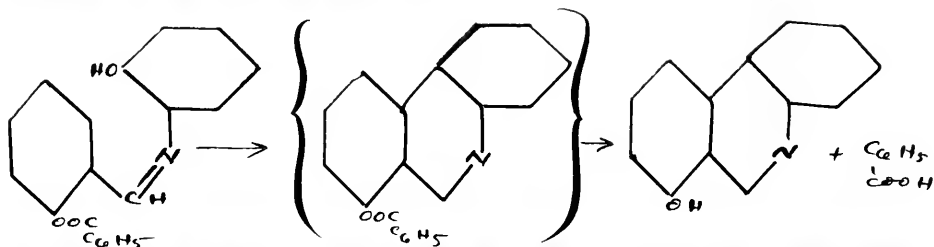


This oil was then mixed with an equimolar quantity of 2-aminophenol in boiling alcohol. When the solution was cooled, a quantity of crystals separated out, which melted at 143-44°C after recrystallization from dilute alcohol. This compound was 2-benzoyloxybenzal-2-aminophenol.

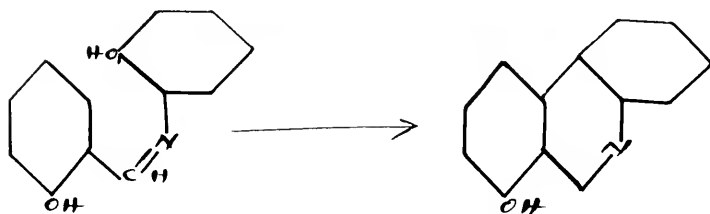


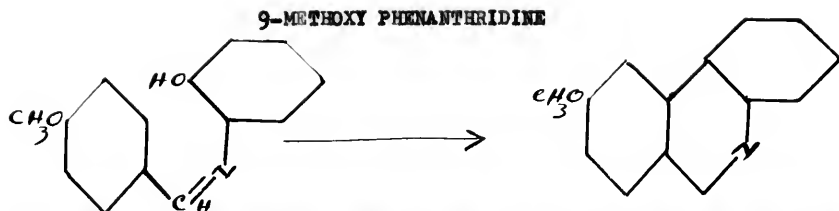
This anil was then heated with phosphorous pentoxide for two hours at 240°C. under reduced pressure. The reaction mixture was decomposed with alcohol and then poured into water. After standing overnight the tarry mass and brown powder were extracted with ether. Following the evaporation of the ether and recrystallization of the residue from alcohol, there were obtained white crystals. These crystals melted at 102-3°C. and gave no mixture melting point depression with the 7-hydroxy phenanthridien prepared by the other method. Obviously the benzoyloxy phenanthridine hydrolyses very easily to yield the 7-hydroxy phenanthridine as every attempt yielded the same compound melting at 102-3°C., The reaction may be ex-

pressed by the following equations:



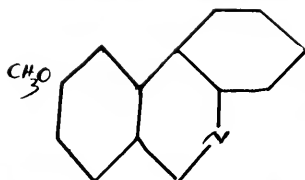
Therefore the phenanthridine synthesized from 2-hydroxybenzal-2-aminophenol has the formula shown by the following equation:





The 4-methoxy benzal-2-aminophenol was mixed intimately with an equal volume of phosphorous pentoxide and heated under reduced pressure at  $250^{\circ}\text{C}$ . for three hours. The reaction mass was decomposed with 95% ethanol and heated for a few moments. Water was added and then sodium hydroxide solution was added until the solution was basic to litmus. Ether extraction of the solution followed by evaporation of the ether yielded a residue. The residue, when recrystallized from dilute alcohol and activated charcoal, yielded clusters of white needles melting at  $99.5\text{--}100^{\circ}\text{C}$ . The compound fluoresced blue under the ultra-violet light. The analysis gave 6.5% nitrogen, the percentage calculated from the formula was 6.69%.

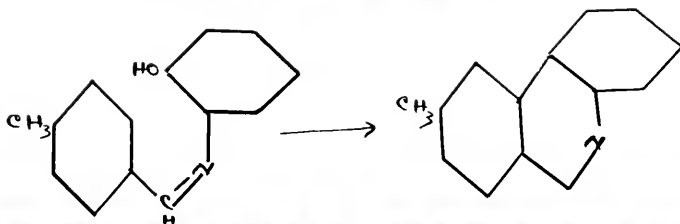
## 9-METHOXY PERMANTERIDINE



Empirical Formula	$C_{14}H_{11}NO$
Molecular Weight	209
Melting Point	99.5-100°C.
Crystalline Form	clusters of needles
Color	white
Solubility	
water	insoluble
alcohol	soluble in hot alcohol
ether	soluble in cold ether
Analysis	calculated      found
nitrogen	6.69%          6.5%

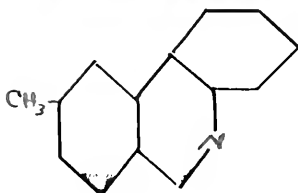


## 9-METHYL PERMANTERIDINE



The 4-methylbenzal-2-aminophenol was mixed intimately with an equal volume of phosphorous pentoxide and heated under reduced pressure at 250°C. for one and one-half hours. The reaction mixture was decomposed with 85% ethanol and poured into water. The resulting solution was steam distilled and clusters of needles melting at 111-112°C. were obtained when the distillate had cooled. The compound fluoresced blue under the ultra-violet light. The percentage of nitrogen calculated from the formula was 7.32%, the percentage found was 7.1%.

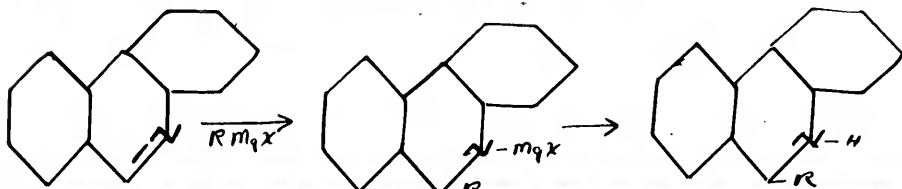
## 9-METHYL PHENANTHRIDINE



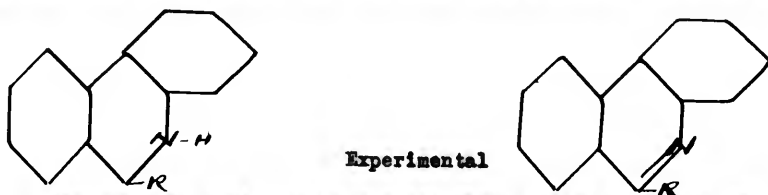
Empirical Formula	$C_{14}H_{11}N$	
Molecular Weight	193	
Melting Point	111-112°C.	
Crystalline Form	clusters of needles	
Solubility		
water	insoluble in cold water	
alcohol	soluble in hot alcohol	
ether	soluble in cold ether	
Analysis	found	calculated
nitrogen	7.1%	7.32%

## THE GRIGNARD REACTION

The possibility of attaching alkyl and substituted alkyl side chains on a phenanthridine nucleus was the next consideration. Phenanthridine can be considered an unsaturated six-membered heterocyclic ring: therefore, there was a possibility that the double bond attached to the nitrogen atom would react with a Grignard reagent:



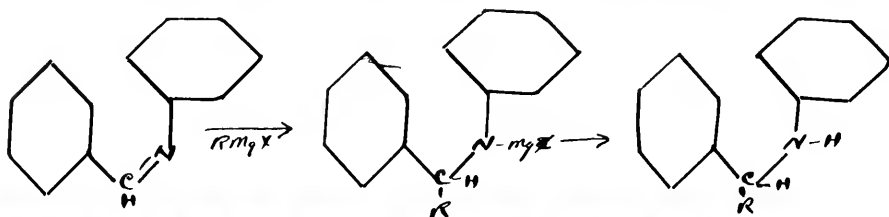
If such a reaction would take place, then a new series of dihydro-phenanthridines with various side chains could be prepared, and by simple oxidation with silver oxide, the alkylated phenanthridine could be synthesized.



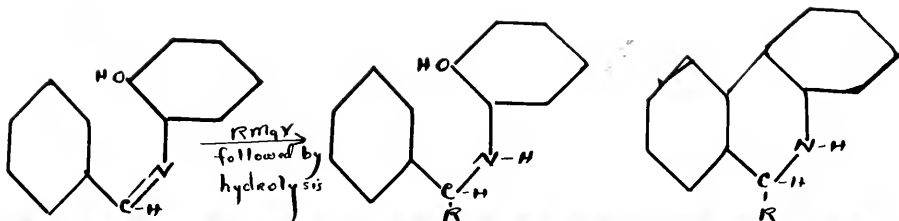
One-tenth mole of freshly cleaned magnesium turnings and 250 cc. of absolute ether were placed in a 500 cc. 3-necked flask fitted with a reflux condenser, mercury-sealed stirrer, and a dropping funnel. The stirrer was started and 0.1 mole of methyl iodide dissolved in 25 cc. of absolute ether was added dropwise. There was an evolution of heat and the solution in the flask turned gray in color. The reaction mixture began to reflux and, when addition of the methyl iodide was completed, the mixture was refluxed for ten minutes. Then 0.03 mole of phenanthri-

dine dissolved in absolute ether was put into the separatory funnel and added dropwise until addition was complete. After refluxing for 2 hours, the reflux condenser was replaced by a Liebig condenser and all of the ether distilled off. Then the residus was warmed with 200 cc. of water acidified with 20 cc. of concentrated sulfuric acid for one hour. The resulting solution was made basic, and extracted several times with ether. The combined ether extracts were evaporated to dryness and the residue taken up in alcohol. Recrystallization from dilute alcohol yielded white micaceous crystals melting at  $104^{\circ}\text{C}$ . A mixture melting point with phenanthridine showed no depression. From these results we concluded that no reaction had taken place.

The next method to be tried involved the addition of the Grignard reagent to the uncyclized anil. After addition the ring could be closed by the previous methods used for the synthesis of phenanthridine, It has been reported in the literature that the Grignard reagent will react with benzal-aniline in the following manner:



Therefore in an analogous manner, the Grignard reagent should react with benzal-o-aminophenol to give a secondary amine which could be cyclized giving a substituted phenanthridine:



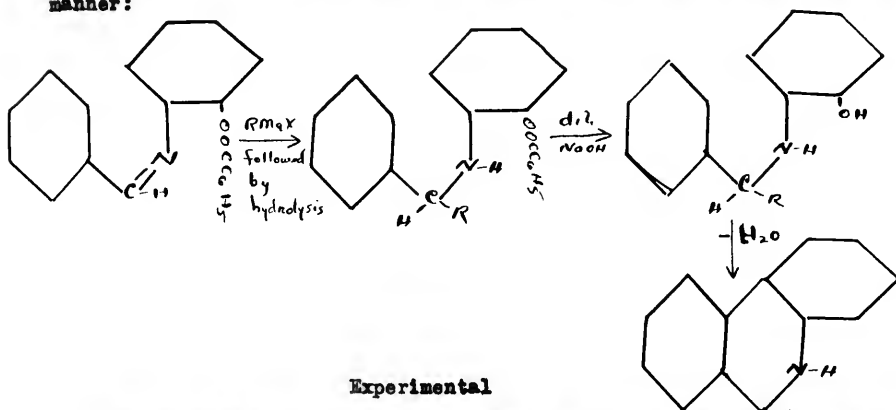
Once the reaction had been shown to work in a satisfactory manner, then different side chains would be substituted. First, however, the Grignard reagents used were methyl magnesium iodide, and ethyl magnesium bromide.

### Experimental

One-tenth mole of methyl magnesium iodide was prepared according to accepted methods with standard apparatus involving a 3-necked flask fitted with a reflux condenser, stirrer and a dropping funnel. After completion of the reaction, 0.1 mole of benzal-o-aminophenol dissolved in absolute ether was added dropwise to the Grignard reagent, a violent reaction took place, and the solution turned red. An orange-red compound precipitated out. After the addition of the anil was completed, the resulting reaction mixture was stirred for one hour under reflux. Then a solution of 200 cc. of water and 20 cc. of concentrated sulfuric acid was added, and the resulting solution stirred for one hour. The solution was made basic with excess sodium carbonate and ether extracted several times. The combined ether extracts were evaporated to dryness, the residue was recrystallized from alcohol. White micaceous crystals melting 89-90°C. were obtained. These gave no depression when a mixture melting

point with benzal-o-aminophenal was taken. The reaction which did occur was probably an addition which decomposed on acidification releasing the original compound.

Another attempt to make the Grignard reagent react with the anil was tried, but this time the benzoate of the anil was used instead of the free anil. Theoretically, the reaction should proceed in the following manner:

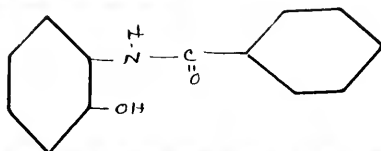


### Experimental

Methyl magnesium iodide was prepared according to the accepted procedure. The benzal-2-benzoyloxy aniline suspended in dry ether was added dropwise to the Grignard reagent with stirring. A violent reaction took place on mixing, causing the ether to reflux very rapidly. After all of the anil had been added, the reaction mixture was refluxed for one hour. Then 200 cc. of water containing 20 grams of concentrated sulfuric acid was added and the ether evaporated. A brown precipitate remained in the flask.

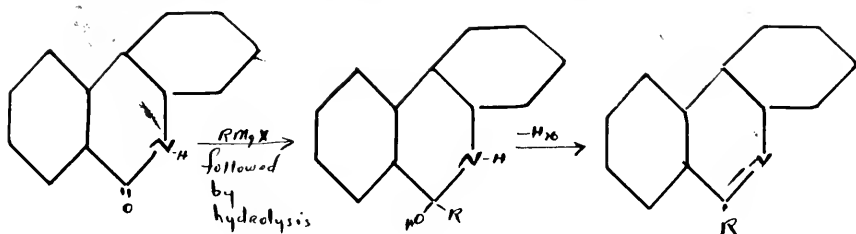
Concentrated sodium hydroxide solution was added to the flask until the reaction mixture was basic, to litmus then an excess was added.

After refluxing the contents for one hour, the reaction mixture was filtered to remove the tar. The filtrate was acidified with dilute sulfuric acid and filtered hot. The residue was recrystallized from alcohol and yielded white micaceous crystals melting at  $171-2^{\circ}\text{C}$ . A mixture melting point with 2-aminophenol gave a big depression. A mixture melting point with pure N-benzoyl-2-aminophenol showed to be N-benzoyl-2-aminophenol, as no depression was observed.



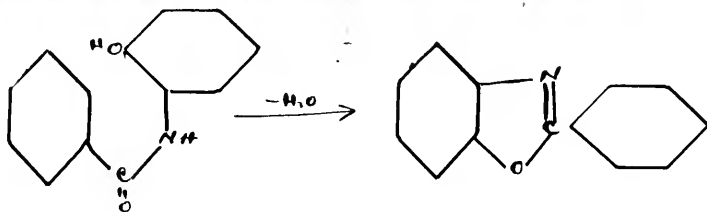
The filtrate obtained by filtering the hot acidified solution yielded benzoic acid on cooling.

Since, in no case were we successful in getting the Grignard reagent to react with the phenanthridine or the anil, we considered the following reactions. If it were possible to apply our synthesis of phenanthridine to phenanthridone, we could attempt to react the phenanthridone with the Grignard reagent. This, of course, would yield a tertiary alcohol which could be dehydrated to give the phenanthridine derivative.



### Experimental

N-benzoyl-2-aminophenol from the stock room was mixed intimately with phosphorous pentoxide in the reaction vessel and heat applied for one hour, the system being under 5 mm. of mercury. A white crystalline compound was distilled into the receiver, and when recrystallized gave a melting point of 102-3°C. Analysis showed that the compound was not phenanthridone, which melts at 293°C. (28), but 2-phenyl-benzoxazole (29). The reaction involved may be shown by the following method:



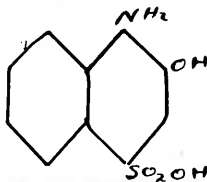
Regardless of the conditions used in the attempted formation of phenanthridone, only the 2-phenyl-benzoxazole was formed.



1-amino-2-naphthol-4-sulfonic acid

Attempts were made to apply our synthesis of phenanthridine to the benzophenanthridine sulfonic acids. In this way, by having one hydrophylic group attached to the molecule, the phenanthridines might possess desirable properties.

The 1-amino-2-naphthol-4-sulfonic acid should condense with benzaldehyde to give the corresponding Schiff base. A review of the literature showed that so far none of the anils had been prepared from the amino-naphthol-sulfonic acid:

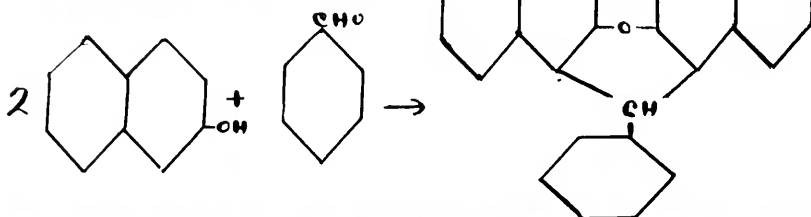


The following methods for condensing the aldehyde and amine were used, but no condensation products could be detected:

1. Refluxing the pure compound with benzaldehyde.
2. Heating the pure compound with benzaldehyde in an open flask.
3. Heating the hydrochloride of the base with benzaldehyde.
4. Shaking a suspension of the hydrochloride in a concentrated solution of sodium acetate with benzaldehyde.
5. Shaking the di-sodium salt of the base with benzaldehyde in a concentrated sodium acetate solution.

## SYNTHESIS OF THE PHENYL-DIBENZO-XANTHENS

When benzaldehyde was heated in absence of the solvent with beta-naphthol, a practically quantitative yield of 9-phenyl-1-2, 7-8 dibenzo-xanthen was formed.

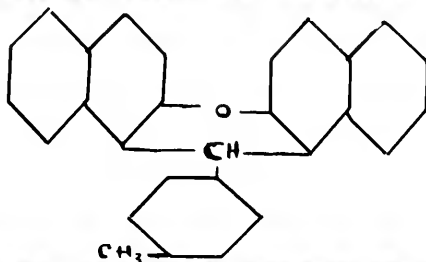


The crystalline compound was isolated and found to check with constants listed in Beilstein. It had previously been prepared by heating beta-naphthol with benzal chloride, by heating beta-naphthol with benzaldehyde in acetic acid solution in the presence of concentrated hydrochloric acid.

## Experimental

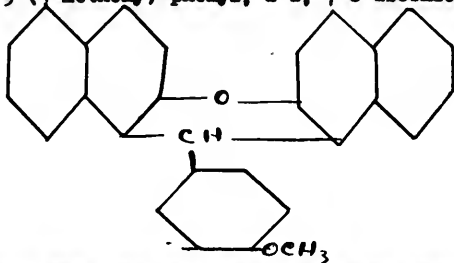
An excess of benzaldehyde was added to beta-naphthol and the resulting solution was boiled for ten minutes. After cooling alcohol was added to the solidified mass and crystals began to form. The compound was very insoluble even in boiling 95% alcohol, so leaching with hot alcohol removed the unreacted phenol and aldehyde. The 9-phenyl-1-2, 7-8 dibenzo-xanthen was extremely soluble in cold chloroform, and its melting point was 189-190°C.

## 9 (4-methyl)-phenyl, 1-2, 7-8 dibenzo-xanthen



The same procedure was employed as used for the synthesis of 9-phenyl, 1-2, 7-8 dibenzo-xanthen except that p-toluic aldehyde instead of benzaldehyde was used. It is a light gray compound melting 205-6°C., and is very soluble in chloroform, but insoluble in boiling alcohol.

## 9 (4-methoxy)-phenyl, 1-2, 7-8 dibenzo-xanthen



The same procedure was followed as used for the synthesis of 9-phenyl, 1-2, 7-8 dibenzo-xanthen, except that p-anisic aldehyde was used instead of benzaldehyde. The compound is light gray in color and melts 222-223°C. It is very soluble in chloroform, but is not soluble in boiling alcohol.

## SUMMARY PART I

1. The new synthesis of phenanthridine has been reported.
2. The following new phenanthridines have been synthesized.
  - a. 9-ethoxyphenanthridine
  - b. 4-hydroxy-10-methoxyphenanthridine
  - c. 7-hydroxy-8-methoxyphenanthridine
  - d. 7-hydroxy phenanthridine
  - e. 9-methoxyphenanthridine
  - f. 9-methylphenanthridine
  - g. 7-benzoyloxy-8-methoxyphenanthridine
3. The following new Schiff's Bases have been synthesized.
  - a. 4-ethoxybenzal-2-aminophenol
  - b. 2-hydroxy-3-methoxybenzal aniline
  - c. 2-hydroxy-3-methoxybenzal-2-aminophenol
  - d. 2-3dimethoxybenzal-2-aminophenol
  - e. 2-hydroxy-3-methoxybenzal-4-methoxyaniline
  - f. 2-hydroxy-3-methoxy-4-aminophenol
  - g. 4-hydroxybenzal-2-aminophenol
4. The failure of 1-amino-2-naphthol-4-sulfonic acid to condense with benzaldehyde under the conditions tried is noted.
5. The unreactivity of the benzal-2-aminophenol toward the Grignard reagent has been investigated.
6. Two new phenyl-dibenzo-xanthenes have been prepared.

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## Part II

## Catalytic Alkylation of Amines

Primary and secondary alcohols will react with primary and secondary amines under the influence of catalysts to yield secondary and tertiary amines respectively. The reaction may be expressed by the following equations:



However, since it has been shown (12) that tertiary alcohols do not show this type of reaction, the mechanism of the reaction may be assumed to be the dehydrogenation of the alcohol first to give the aldehyde or ketone, which would then react with an amine to give a product which is readily hydrogenated to give an amine (20).



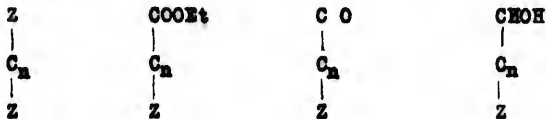
Maihe (13) found that thorium oxide or zirconium oxide acted as an efficient catalyst at 400-500°C. in the vapor phase reaction between aniline and methanol to give high yields of methyl aniline. He also found that aluminum oxide gave complete conversion of orthotoluidine into the secondary and tertiary amines with methanol at 350°C. by reprocessing (14).

T. B. Johnson (11) and A. J. Hill (5) used the hydrochlorides of the amines with the alcohol in autoclaves at a temperature of 175°C. with

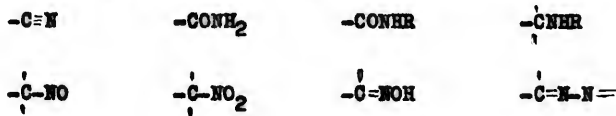
$\text{H}_2\text{Br}-\text{CuCl}_2-\text{CaCl}_2$  catalyst and obtained 87-91% of diethylaniline when anilinehydrochloride and ethanol were used, and A. E. Brown (2) used silicagel for the alkylation.

Raney nickel has been found to be a very efficient catalyst in reactions involving catalytic alkylation of amines and catalytic alkylation followed by hydrogenation. Adkins and Winans (21) reacted aniline and ethanol over Raney nickel in the presence of hydrogen. The nickel acted as a catalyst and this fact was confirmed as no reaction took place in the absence of nickel at  $200^\circ\text{C}$ . The temperature also plays a very important part as they found that at temperatures lower than  $185^\circ\text{C}$ , piperidine did not react with ethanol in the presence of nickel. Throughout their investigations they established the fact that the same yields were obtained whether hydrogen or nitrogen were used in the simple catalytic alkylation of amines.

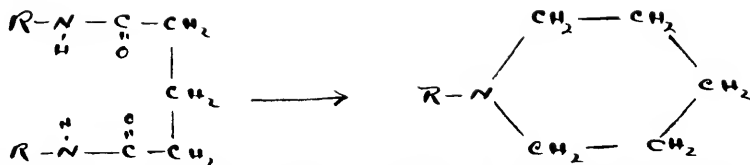
As a result of the work of Paden and Adkins (18), it has been shown that cyclic amines can be made by catalytic hydrogenation from the following type compounds:



where "n" may be 2, 3, or 4, and the functional radical "Z" may be:



For example:



The formation of secondary amines from primary amines during hydrogenation of cyanides over nickel may result from the following mechanisms:

1. The amine may react with the alcohol used as a solvent to give the alkylated amine and water.
2. Two molecules of the primary amine may react with themselves to give a secondary amine with the elimination of a molecule of ammonia.
3. The alkylidene imino compounds may react with themselves.

Kindler (12) showed that over palladium primary amines underwent the type #2 reaction given above to yield secondary amines. No tertiary amines were formed as is observed in the alkylation of amines with an alcohol.

Likely copper chromite catalyst has come into extensive use as a catalyst. Generally there is a trace of potassium fluoride, or barium chromite or other promoters mixed with the catalyst. Paden and Adkins (18) obtained good yields in their synthesis of pyrrolidones, piperidines, and hexa-hydroazepines by carrying out their reaction at 250-260°C. under 200-400 atmospheres of hydrogen and 700-800 cc. of dioxane per mole of diamine and glycol over copper chromite. In general Paden (17) found that glycols reacted with amines when the hydrogenation was carried out in

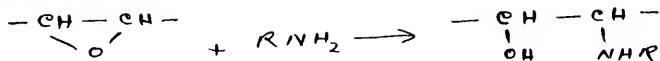


dioxane over copper chromite under 200-300 atmospheres of hydrogen.

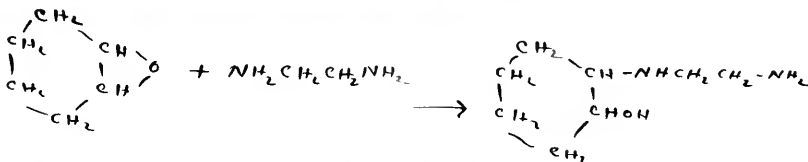
Solvents play an important part in the reaction. Above 165° alcohol cannot be used because it would react with the amine. Dioxane, ether, methylcyclohexane are all good solvents as they are inert and have boiling points that permit easy preparation of the reaction products (1).

### Summary of the Problem

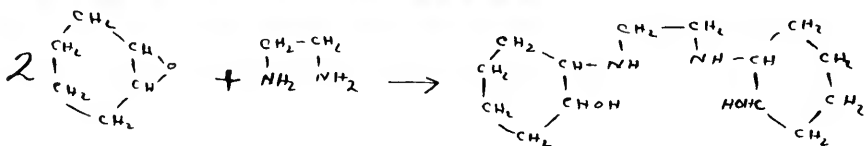
The reactions of epoxy compounds are almost always of the addition type. They usually react with compounds containing a labile hydrogen atom, such as alcohols, phenols, amines, etc. As illustrated by the following equation, the ethylene oxide ring opens up in such a way that the labile hydrogen atom attaches itself to the oxide linkage to form a hydroxyl group, while the rest of the radical migrates to the remaining portion of the oxide:



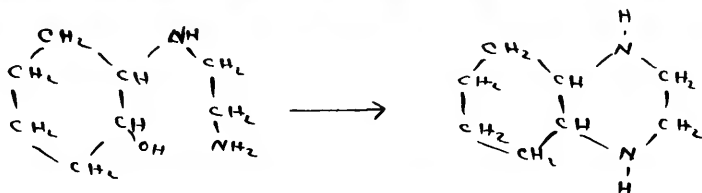
With this generalization in mind we decided to attempt to synthesize 2,3-benzopyrazine by the catalytic alkylation of amines. That is, we would prepare in the intermediate amino alcohol and then cyclize to the pyrazine derivative. Cyclohexene oxide reacts with ethylene diamine to yield N(ortho-hydroxy-cyclohexyl)-ethylenediamine:



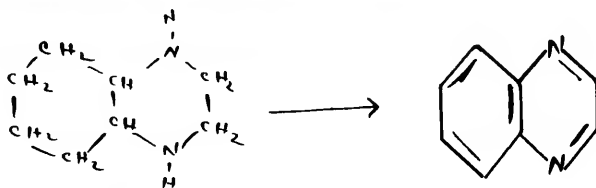
This reaction is complicated by the fact that the ethylene diamine has two functional groups and therefore may also yield the following compound, N, N' di(ortho-hydroxycyclohexyl) ethylene diamine:



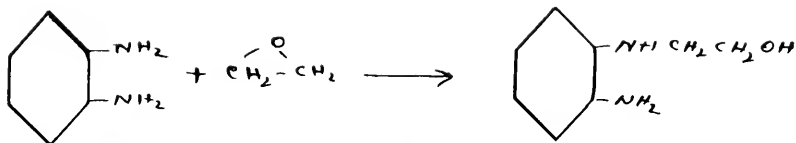
By catalytically internally alkylating the primary amine of the N-(ortho-hydroxycyclohexyl)-ethylene diamine a decahydrobenzopyrazine or decahydroquinoxaline would form as is illustrated by the following reaction:



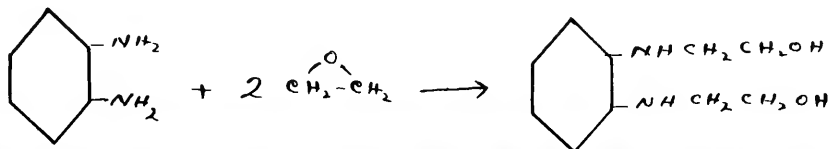
Then, by simply dehydrogenating the decahydroquinoxaline, we would have the 2-3-benzopyrazin or quinoxaline.



In order to further employ the use of epoxy compounds as starting materials and yet use the internal catalytic alkylation method of synthesis, we started with *o*-phenylene diamine and ethylene oxide. When one mole of the oxide reacts with the amine, the following compound is obtained:

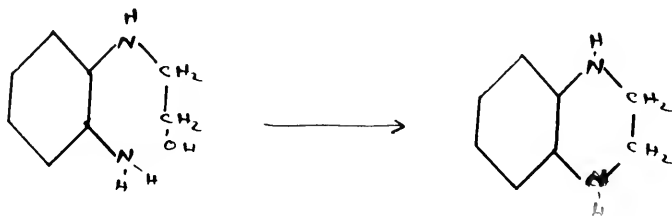


However, two molecules of the oxide may react with the diamine to give N-N'-di-(2-hydroxyethyl)-o-phenylene diamine:

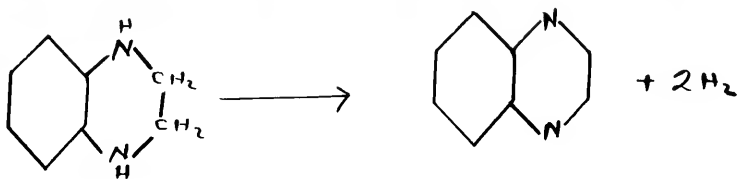


When the N-(2-hydroxyethyl)-o-phenylene diamine is desired, a larger molar excess of the diamine is used, so that the possibility of the N-N'-di-(2-hydroxyethyl)-o-phenylenediamine being formed will be diminished. It is understood that there will be some of the by product formed in a reaction.

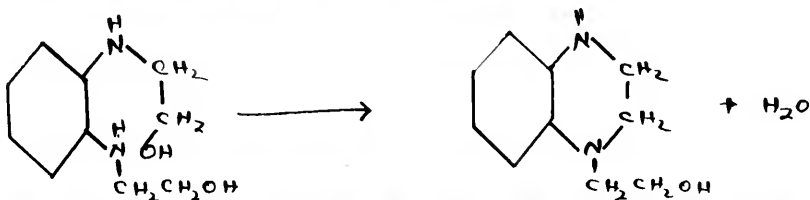
The N-(2-hydroxyethyl)-o-phenylenediamine can be internally catalytically alkylated as follows to yield 1-2-3-4 tetrahydropyrazine:



Then by dehydrogenating the tetrahydropyrazine, the 2-3-benzopyrazine is formed:

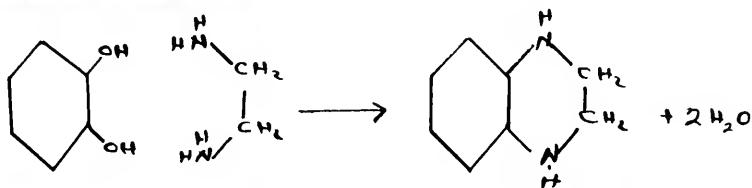


The N-N' di(beta-hydroxyethyl)o-phenylenediamine can be internally alkylated to give 1-(beta-hydroxyethyl)2-3-4 trihydroquinoxaline:

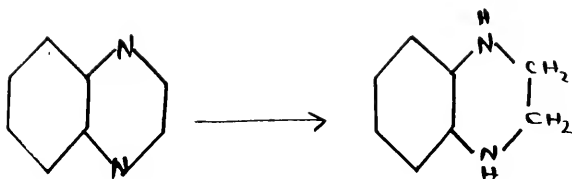


The 1-2-3-4 tetrahydropyrazine has been prepared by the following methods:

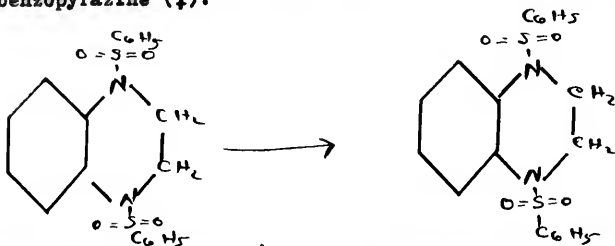
1. Heating catechol with ethylene diamine hydrate in a sealed tube for 15 hours (15):



2. Reduction of the 2-3 benzopyrazine (10) with sodium and alcohol:



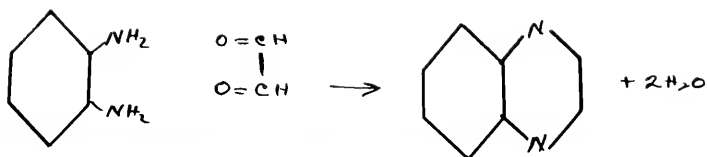
3. Hydrolysis of the 1-4-dibenzenesulfonyl, 1-2-3-4 tetrahydro-benzopyrazine (7):



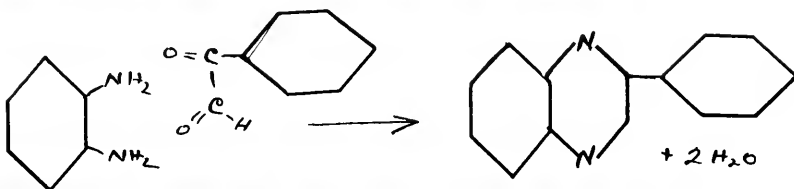
It is soluble in ether, alcohol, chloroform, benzene and hot water. An aqueous solution gives a blue stain with silver nitrate. It yields 2-3-benzopyrazine on oxidation with potassium ferricyanide (10). Ferric chloride solution gives a violet or blue color on being mixed with an aqueous solution which on addition of HCl turns green or light yellow and which further changes to brown or red on heating.

The 2-3 benzopyrazine or quinoxaline and its derivatives can be prepared by the following methods:

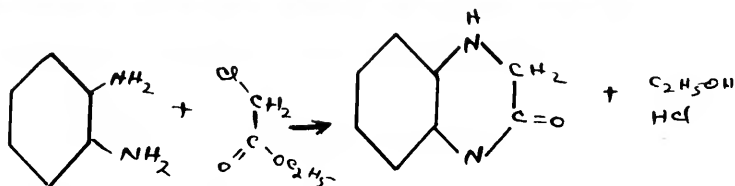
1. Reaction of *o*-phenylenediamine and glyoxal or its sodium sulfite addition product in an aqueous solution (6, 7):



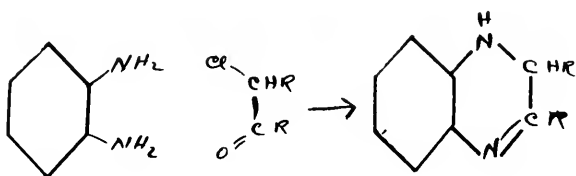
2. Reaction of *o*-phenylene diamine and a keto-aldehyde:

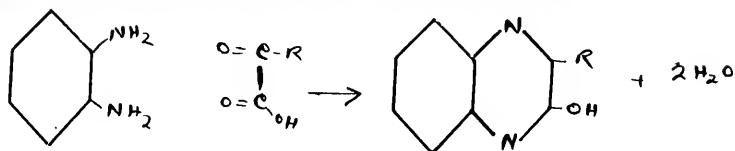
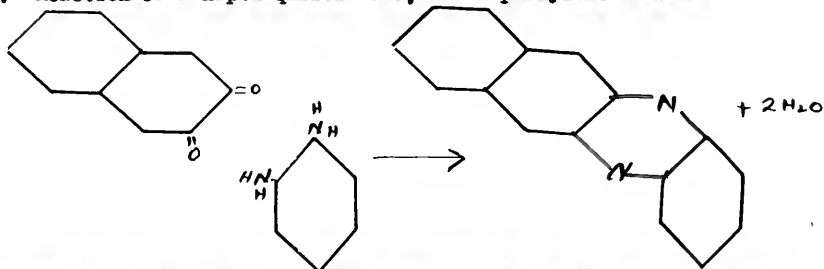


3. Reaction of *o*-phenylene diamine and an alpha-chloro-ester:

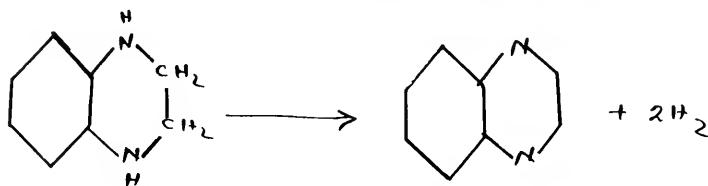


4. Reaction of *o*-phenylene diamine and an alpha-chloroketone:



5. Reaction of *o*-phenylene diamine and an alpha-keto-acid:6. Reaction of a naphthaquinone 1-2 $\gamma$  and *o*-phenylene diamine:

## 7. Oxidation of 1-2-3-4 tetrahydrobenzopyrazine to quinoxaline:

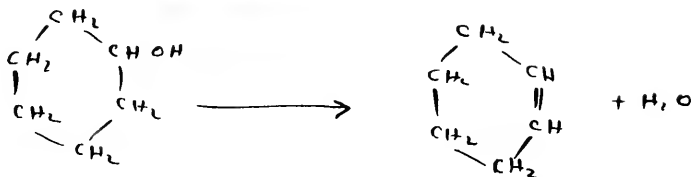


Quinoxaline is a crystalline compound melting at 27°C., boils at 220-223°C. 760 mm. mercury and has a quinoline-like odor in the cold and a piperidine-like odor on heating. It is soluble in all proportions in water, alcohol, ether, and benzene. It can be oxidized with potassium permanganate to pyrazine dicarboxylic acid (19). It forms salts with mineral acids, oxalic acid, and platinum chloride. A number of derivatives have been prepared (8-9-16). A solution of the free base in water gives a white pre-



precipitate with silver nitrate or mercuric chloride (8).

### Experimental



Cyclohexene was prepared according to the procedure outlined in "Organic Syntheses", collective volume, 1932 edition.

"In a 500 cc. modified Claisen flask were placed 400 grams (4 moles) of technical cyclohexanol and 12 cc. of concentrated sulfuric acid. The flask was connected to a condenser and a receiver immersed in ice bath. The flask was then placed in an oil bath and the temperature kept between 130 and 140°C. Ice water was circulated through the condenser by means of a small pump, in order to minimize the loss of cyclohexene due to evaporation. The distillation was continued until a small residue remained and the odor of sulfur dioxide was apparent. The distillation required 12 hours. (Reported in the original article as taking 5-6 hours).

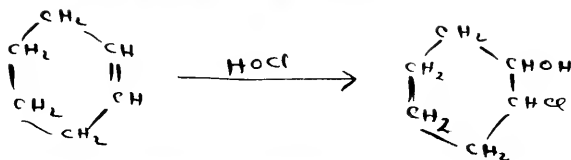
The distillate was saturated with salt and cyclohexene separated from the water layer. After drying over calcium chloride, the product was fractionated in an efficient column and the portion boiling 80-82°C. was collected."

When this work was repeated a yield of 80% of the theoretical yield was obtained.

2-Chloro-cyclohexanol

## Organic Syntheses

Collective Volume, 1932



"To a solution of 25 grams of mercuric chloride in 500 cc. water in a 5 liter flask 800 grams of cracked ice was added. A cold solution of 190 grams of NaOH in 500 cc. of water was added and a rapid stream of chlorine was passed into the mixture which was kept below 5°C. The addition of chlorine was continued until the yellow precipitate of HgO disappeared. Then 600 cc. of cold nitric acid (1.5 N) was added with stirring. The concentration of HOCl was determined by adding a measured volume to an excess of KI solution, acidified with HCl, and titrating with sodium thiosulfate. Usually the concentration runs between 3.5-4%. The amount necessary to react with 123 grams (1.5 moles) of cyclohexene was calculated.

In a 5 liter round bottom flask with a good mechanical stirrer was placed 123 grams of cyclohexene and to it was added 1/4 the calculated amount of HOCl solution. The mixture was kept below 15°C. and was stirred vigorously until 1 cc. test portion gave no yellow color when treated with KI solution and dilute HCl. When the first portion of HOCl has reacted a second portion is added and the process repeated. When all

of the HOCl has been added and the reaction is complete, the oily layer is on the bottom and a slight excess of HOCl is present. If these conditions are not fulfilled, 100 cc. portions of HOCl acid solution are added until the reaction is complete.

The solution was saturated with salt and steam distilled. About 2 liters of distillate were required before all of the 2-chloro-cyclohexanol passed over. The aqueous layer was extracted with 250 cc. of ether, and this was added to the main portion. After drying over  $\text{H}_2\text{SO}_4$  (anhydrous) the solution was distilled under reduced pressure, and after removing the ether by ordinary distillation. The fraction boiling 88-90°, 20 mm., or 104-106°, 45 mm. was collected."

When this work was repeated a yield of 43% of the theoretical yield was obtained.

## Cyclohexene Oxide

## Organic Syntheses

Collective Volume, 1932

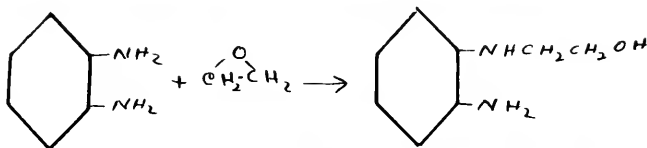
"In a 2 liter R. B. flask fitted with a mechanical stirrer was placed a solution of 70 grams of sodium hydroxide in 400 cc. water. To this solution was added 230 grams of 2-chloro-cyclohexanol. The mixture was stirred vigorously for 1 hour. The stirring was stopped and the upper layer separated in a separatory funnel. It was distilled through an efficient column, and the following fraction collected, 100-129; 129-134, 134-175. The first fraction is cyclohexene oxide and water which is separated with a separatory funnel before the second distillation. After the fraction boiling 100-129 was collected, the condenser was removed and dried thoroughly before collecting the second fraction. All of the fraction were refractionated and the portion boiling 129-134° was collected."

When this work was repeated 63% of the theoretical yield was obtained.

### Preparation of the Copper-Chromite Catalyst

The method for the preparation of the catalyst was the same as used by Conner and Adkins (3). Nine hundred cubic centimeters of (50°C.) solution containing 261 grams of hydrated copper nitrate, 31.3 grams of barium nitrate was added to 900 cc. of a solution (25-30°C.), containing 151.2 grams of ammonium dichromate and 225 cc of 28% ammonium hydroxide. The precipitate was filtered and the cake pressed. After having sucked the cake as dry as possible with the suction flask, it was dried overnight at 75-80°. It was then pulverized and weighed 225 grams. It was decomposed in three portions in a casserole over a free flame. In carrying out the decomposition, the powder was stirred with a spatula from the beginning of the heating, and the flame was removed after decomposition was well started. After a little more stirring, there was a sudden evolution of gases and the entire mass became black. After stirring thoroughly, the powder was removed and allowed to cool. The combined products were leached with 600 cc. of 10% acetic acid solution for 30 minutes. The product was then filtered by suction and washed with 600 cc. of water in 6 portions. The cake was dried overnight at 125°C. and then pulverized.

## SYNTHESIS OF N-(BETAHYDROXYETHYL)-o-PHENYLENE DIAMINE



According to Gabel and Matzekevich (13) ethylene oxide reacts with *m*-phenylene diamine in a sealed tube in the presence of water to yield *N*-(beta-hydroxyethyl)*m*-phenylene diamine. However, work carried on at this institution utilizing this type reaction of epoxy compounds indicates that the use of the sealed tube is unnecessary. Consequently, we proceeded to carry out this reaction in cold methanol, since ethylene oxide and the *o*-phenylene diamine are soluble in that medium.

Exactly 108 grams of *o*-phenylene diamine were dissolved in warm methanol (c. 50°C.) in a 2-liter beaker, fitted with a mechanical stirrer and a gas inlet tube. The solution was then cooled slowly to room temperature. Thirty grams (2/3 mole) of ethylene oxide was poured into a 250 cc. suction flask connected to the gas inlet tube by means of a piece of rubber tubing. The flask was then closed with a rubber stopper. The stirrer was put into motion, and the ethylene oxide allowed to distill slowly into the methanol solution. (Note: ethylene oxide is poisonous, but it can be handled easily if kept in a cylinder under pressure.) After the ethylene oxide had distilled into the methanol solution, which had sucked back into the suction

flask as the last traces of ethylene oxide had volatilized, the solution in the flask was poured back into the beaker and then the methanol evaporated on a steam bath. As the solution became concentrated, it was transferred into a flask and the methanol distilled off. The residue was then fractionally distilled under reduced pressure and the following fractions obtained:

1st fraction: 145-155°C./20 mm. mercury

2nd fraction: 200°C/5 mm. of mercury

The first fraction was shown to be unreacted *o*-phenylene diamine and 65 grams were recovered. A mixture melting point with pure *o*-phenylene diamine melting at 104°C. gave no depression. The second fraction of 50 grams (81% theory) which had crystallized on cooling, was liquified by warming and then poured into 400 cc. of benzene. White micaeous crystals were separated out. After standing for several hours the crystals were filtered by suction in a Buchner funnel and dried in an oven at 65°C. The melting point of the crystals was 106.5-107.5°C. uncorrected. A mixture melting point with pure *o*-phenylene diamine gave a big depression, the mixture melted about 75-80°C. The pure compound was analyzed for nitrogen by the Kjeldahl method. Nitrogen calculated 18.4%, found 15.1%.

The compound is very soluble in methanol, ethanol, and dilute hydrochloric acid. It is best recrystallized from benzene, as it is slightly soluble in cold benzene and fairly soluble in hot. It is stable to atmospheric distillation, but turns brown on standing. A bottle which had been stoppered and stored several weeks gave off the odor of ammonia when opened.

Other runs were made in which 108 grams of the *o*-phenylene diamine were dissolved in the warm methanol solution and 44 grams of ethylene oxide (1 mole) were distilled slowly into the diamine solution. The methanol was distilled off at atmospheric pressure and the residue fractionated through a short column at atmospheric pressure. Two fractions were obtained:

1st fraction            bp 256/ 760 mm. mercury

2nd fraction            bp 338/ 760 mm. mercury

In this case 60 grams of the unreacted *o*-phenylene diamine were recovered as the first fraction. It distilled easily and solidified on cooling. The second fraction of 60 grams (86.5% theory) was recrystallized from benzene and gave no mixture melting point depression when taken with pure *N*-(betahydroxyethyl)*o*-phenylene diamine. A few grams of a high boiling red oil were obtained, which was shown to be *N-N'* di(betahydroxyethyl)-*o*-phenylene diamine by its boiling point.

The largest mole ratio of ethylene oxide to *o*-phenylene diamine used was 1 1/3 to 1. Under the same conditions as used previously, 60 grams (1 1/3 mole) of ethylene oxide was slowly distilled into 108 grams (1 mole) of *o*-phenylene diamine in 1200 cc. methanol and after first distilling off the methanol, the residue distilled at atmospheric pressure through a short column. Two fractions were obtained;

1st fraction            bp 256°C./760 mm. mercury

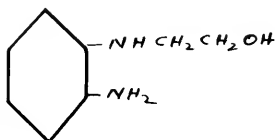
2nd fraction            bp 338°C./760 mm. mercury

Fifty grams of the unreacted *o*-phenylene diamine (fraction #1) were recovered. A total of 65 grams of the *N*-(betahydroxyethyl)-*o*-



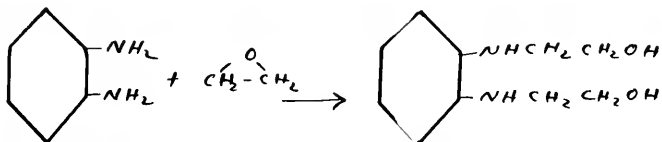
pheylene diamine were obtained, 83.5% theory. A total of ten different runs were made.

**N-(betahydroxyethyl)-o-phenylene diamine**



<b>Empirical formula</b>		$C_8 H_{12} O N_2$	
<b>Molecular Weight</b>		152	
<b>Melting Point</b>	6	106.5-107.5°C.	
<b>Color</b>		white	
<b>Solubility</b>			
benzene		fairly soluble in hot, slightly in cold	
methanol		very soluble	
ethanol		very soluble	
dilute HCl		very soluble	
<b>Analysis</b>		found	calculated
nitrogen		18.1%	18.4%

## SYNTHESIS OF THE N-N'-DI(BETAHYDROXYETHYL)-O-PHENYLENE DIAMINE



The same general procedure used for the preparation of the N-(beta-hydroxyethyl)-o-phenylene diamine was employed, except that the mole ratio of ethylene oxide to o-phenylene diamine was increased. Fifty-four grams of o-phenylene diamine (0.5 mole) were dissolved in 1200 cc. of methanol and 176 grams of ethylene oxide (4 moles) were slowly distilled into the methanol solution. A slight evolution of heat was noticed, so the beaker was immersed in an ice bath. The methanol was distilled off at atmospheric pressure and the residue fractionally distilled under reduced pressure through a short column. Two fractions were obtained:

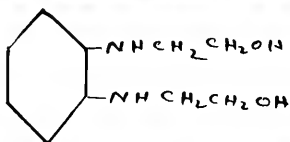
1st fraction      268°C./21 mm. mercury

2nd fraction      245-250°C./10 mm. mercury

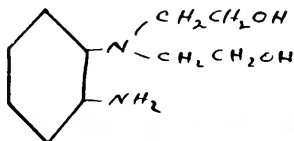
The first fraction crystallized on cooling. It was recrystallized from benzene and gave a melting point of 106-7°C. A mixture melting point with authentic N-beta-hydroxyethyl-o-phenylene diamine gave no depression. The second fraction came over as a light orange oil and solidified in 2 days. It was recrystallized from benzene which contained 2% ethanol and yielded pinkish violet crystals melting at 97-98°C. A mixture melting point with N-beta-hydroxyethyl-o-phenylene

diamine melted at  $75-80^{\circ}\text{C}$ . It was analyzed by both the boiling point rise and by the Kjeldahl methods. A boiling point rise of  $0.320^{\circ}\text{C}$ . was obtained when 2.3486 grams of the compound were dissolved in 40 grams of ethanol ( $K_b$  determined previously to be 1.05). This gave a molecular weight of 192. The calculated molecular weight was 196. Nitrogen by Kjeldahl: calculated 14.3%, found 14.0%. The compound darkened on standing. A total of 5 runs were made.

The following evidence was used to show that the formula of the N-N' di(beta-hydroxyethyl)-o-phenylene diamine was



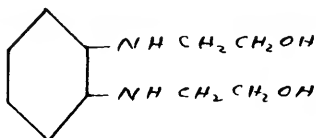
instead of the possible formula;



One tenth mole of the compound (19.6 grams) was dissolved in 300 cc. of water and 20 cc. of concentrated hydrochloric acid was added. Ice added until the solution temperature was below  $5^{\circ}\text{C}$ ., and then 30 cc. of concentrated hydrochloric acid poured in. The 10% sodium nitrite solution was added until the end point had been reached. Twelve and one-tenth grams of dimethyl aniline were added and the solution stirred. Then, caustic soda solution was added until the solution was basic. On filtering the reaction mixture, only a green scum was obtained, which led to the belief that only a nitroso compound might have been formed.

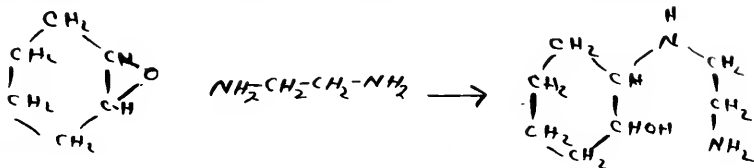
This indicated that there were no primary amino groups in the molecule.

**N-N' DI-(BETAHYDROXYETHYL)-O-PHENYLENE DIAMINE**



Empirical Formula	$\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_2$	
Molecular Weight	196	
Melting Point	97-98°C.	
Boiling Point	245-250°C./10 mm. mercury	
Color	pinkish violet	
Stability	darkens on standing	
Solubility		
alcohol	very soluble in cold	
benzene	insoluble in cold	
dilute HCl	soluble	
Analysis	calculated	found
nitrogen	14.3%	14.0%
molecular weight	196	192

## SYNTHESIS OF N-(ORTHOHYDROXYCYCLOHEXYL) ETHYLENE DIAMINE



Cyclohexene oxide

Ethylene diamine

Since the ethylene diamine has two functional amino groups, it is necessary to control the mole ratio of the cyclohexene oxide to the ethylene diamine so that the mono substituted derivative will be formed in preference to the di-substituted derivative. In order that there should always be an excess of diamine present, the cyclohexene oxide was added dropwise to the diamine.

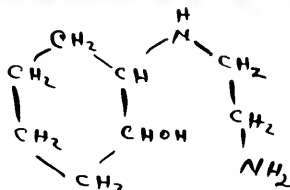
7 Two moles (120 grams) of freshly distilled ethylene diamine were dissolved in 500 cc. of cold methanol in a 1500 cc. beaker which was fitted with a mechanical stirrer. Forty-nine grams (0.5 mole) of cyclohexene oxide were placed in a dropping funnel and allowed to fall dropwise into the methanol solution of the ethylene diamine, and the stirrer was started. After the addition of the cyclohexene oxide was complete, the beaker was placed on a steam bath and the methanol evaporated. On cooling, a layer of white crystals settled out. These were filtered by suction, and then triturated with hot ethanol. The ethanol was filtered from the crystals by suction. The two filtrates were then mixed. The filtrates which had been combined were fractionally distilled under reduced pressure. Two fractions were obtained:

1st fraction        below 70°C./85 mm. mercury

2nd fraction        188-190°C./55 mm. mercury

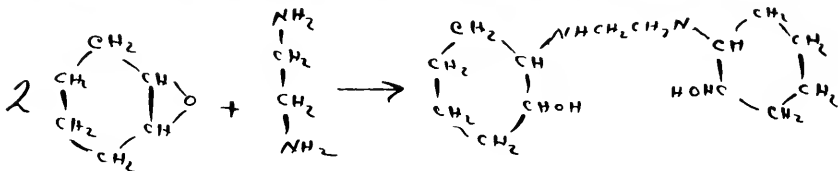
The first fraction was unused ethylene diamine, since it boiled at 116°C. under atmospheric pressure. The second fraction, a viscous oil with a peculiar odor crystallized to give a yellowish white mass. The melting point of the compound was determined in a transition point apparatus. The point of clear solution was 46°C. The compound was a mush-like solid at room temperature, and it retained that property regardless of the number of times that it was refractionated. A 70% yield of the compound was obtained. The compound was very soluble in ethanol, methanol, ether, tertiary butanol, and cold water. It was analyzed by means of a Kjeldahl determination. Nitrogen calculated 17.9%, found 17.7%. A total of four runs were made.



**N-(ORTHOHYDROXYCYCLOHEXYL)-ETHYLENE DIAMINE**

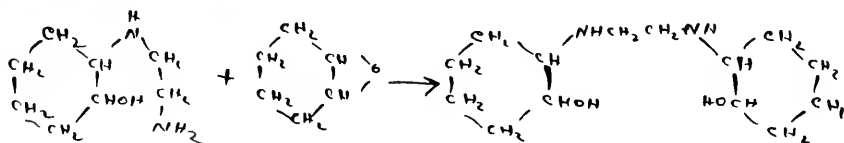
<b>Empirical Formula</b>	$C_8 H_{15} N_2 O$	
<b>Molecular Weight</b>	155	
<b>Melting Point</b>	46° (pt. of clear solution)	
<b>Form</b>	mush solid at room temperature	
<b>Color</b>	light yellow	
<b>Solubility</b>		
water	very soluble	
ethanol	very soluble	
ether	very soluble	
methanol	very soluble	
<b>Analysis</b>	calculated	found
nitrogen	17.9%	17.7%

**SYNTHESIS OF N-N' DI-(ORTHOHYDROXYCYCLOHEXYL)-ETHYLENE DIAMINE**

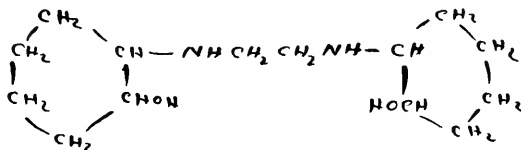


The white crystals which separated out from the reaction mixture during the synthesis of the N-(Orthohydroxycyclohexyl)-ethylenediamine were shown to be the N-N' di(orthohydroxycyclohexyl)-ethylenediamine. They melted at 205-206°C. and were insoluble in boiling ethanol. Nitrogen calculated 11.1%, found 11.0%. The structure was proved by synthesis.

Eight grams (0.05 mole) of N-orthohydroxycyclohexyl-ethylenediamine were dissolved in methanol and 5 grams of cyclohexene oxide (0.05 mole) were added. The solution was heated on a steam bath and the methanol driven off. White crystals were obtained on cooling. These melted at 205-6°C., and gave no depression when a mixture melting point was taken with the crystals obtained in the synthesis of the N-orthohydroxycyclohexyl-ethylenediamine. The reaction may be expressed as follows:

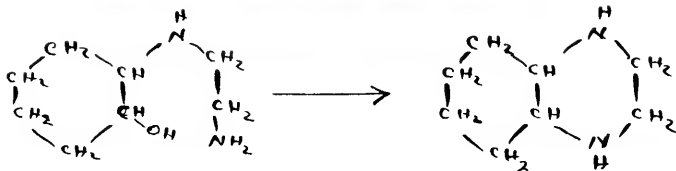


**N-N' DI-(ORTHOHYDROXYCYCLOHEXYL)-ETHYLENE DIAMINE**



<b>Empirical formula</b>	<b>C<sub>14</sub> H<sub>28</sub> N<sub>2</sub> O<sub>2</sub></b>	
<b>Molecular weight</b>	<b>256</b>	
<b>Melting Point</b>	<b>205-206°C.</b>	
<b>Color</b>	<b>white</b>	
<b>Solubility</b>		
<b>Water</b>	<b>insoluble</b>	
<b>Ethanol</b>	<b>insoluble in boiling ethanol</b>	
<b>Analysis</b>	<b>found</b>	<b>calculated</b>
<b>Nitrogen</b>	<b>11.0%</b>	<b>11.1%</b>

## SYNTHESIS OF DECAHYDROQUINOXALINE



Thirty grams of *N*-(orthohydroxycyclohexyl)-ethylenediamine, 400 cc. of purified dioxane, and 6 grams of copper chromite catalyst were placed in the bomb of an American Instrument Company "Bomb Shaker". The bomb was closed and the pressure on the reaction mixture raised to 100 pounds per square inch with hydrogen. Then the pressure was further increased to 800 pounds per square inch with nitrogen. The bomb was agitated for  $4\frac{1}{2}$  hours at  $250^{\circ}\text{C}$ . After cooling, the reaction mixture was poured out of the bomb and the catalyst, which had not turned a bright copper color was filtered off. The dioxane was distilled off through a short column, and then the residue was distilled at atmospheric pressure. One fraction was obtained, and it boiled at  $285-7^{\circ}$ . There had been no reaction.

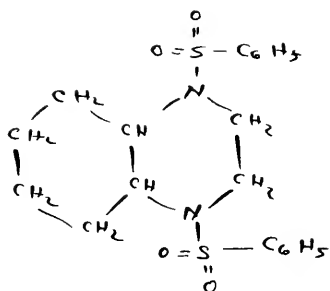
Since we know that temperature plays an important part in the catalytic alkylation of amines, we decided to raise the temperature to see if we could obtain an internal alkylation. Therefore, 30 grams of *N*-(orthohydroxycyclohexyl)-ethylenediamine, 400 cc. of purified dioxane, and 7 grams of copper-chromite catalyst were placed in the bomb. Pressure on the reaction mixture was raised to 100 pounds per square inch with hydrogen, and then further increased to 1000 pounds per square inch with nitrogen. The bomb was agitated for 5 hours at

a temperature range of 275-300°C. After the bomb had cooled overnight, it was opened. An ammoniacal odor was plainly detectable. The catalyst, which had turned a copper color was filtered off, and the dioxane distilled off through a short column. The residue was fractionated at atmospheric pressure and four fractions were obtained:

1st fraction	bp	116°C.
2nd fraction	bp	175-80°C.
3rd fraction	bp	228°C.
4th fraction	bp	285-87°C.

The first fraction, boiling at 116°C., had a strong ammoniacal odor and was soluble in water. Only about 1 cc. was obtained, which was ethylene diamine formed by thermal decomposition of the starting material. The second fraction, boiling at 175-80°C., came over as a light yellow oil. The third fraction, boiling around 228°C., also came over as a light yellow oil. The fourth fraction, boiling at 285-7°C., was the recovered N-(ortho-hydroxycyclohexyl)-ethylene diamine which had not reacted.

The second and third fractions were combined and refractionated. This time as the main product, a light yellow oil, boiling 220-222°C., was obtained. It was a mushy solid at room temperature. The benzene sulfonyl derivative was made according to standard procedure, and was insoluble in sodium hydroxide. This fact indicated that a secondary amine was present. The precipitate was filtered off and recrystallized from 95% ethanol and activated charcoal. On cooling, a white precipitate settled out melting at 188-9°C.



1-4 d. benzene sulfonyl-  
decahydroquinoxaline

In order to verify Adams and Winans observation (7) that the catalytic alkylation of amines proceeded equally as well with hydrogen as nitrogen, we made the following runs: Forty grams of N-(ortho-hydroxycyclohexyl)-ethylene diamine, 7 grams of copper chromite catalyst, and 400 cc. of purified dioxane were placed in the bomb. The bomb was closed and the pressure on the reaction mixture raised to 1000 pounds per square inch with nitrogen. The bomb was agitated to  $5\frac{1}{2}$  hours at  $280-310^{\circ}\text{C}$ ., and the pressure rose to 2500 pounds per square inch. After the bomb had cooled, it was opened. An ammoniacal odor was plainly detectable. The reacted copper-chromite catalyst was filtered off, and the dioxane was distilled off at atmospheric pressure. The residue was fractionated and two fractions were obtained:

1st fraction      b.p.  $218-220^{\circ}\text{C}$ .

2nd fraction      b.p.  $285-287^{\circ}\text{C}$ .

The first fraction, boiling at  $218-220^{\circ}\text{C}$ ., solidified to a mushy solid at room temperature. The benzene sulfonyl derivative was prepared and melted at  $188-9^{\circ}\text{C}$ . It did not give a melting point depression when mixed with the benzene sulfonyl derivative prepared from previous runs. Fifteen grams of the decahydroquinoxaline were obtained, 43%

of the theoretical yield. The second fraction was the unreacted N-(ortho-hydroxycyclohexyl)-ethylene diamine which boiled at 285-7°C.

Since we found that temperature plays an important part in the catalytic alkylation of this compound, we decided to see the effect of an increase in the amount of catalyst used during the reaction. Consequently, 60 grams of N-(ortho-hydroxycyclohexyl)-ethylene diamine, 400 cc. of purified dioxane, and 20 grams of copper chromite catalyst were placed in the bomb. The bomb was closed and the pressure raised to 1000 pounds per square inch with nitrogen. The bomb was agitated for five hours at 300°, and the pressure rose to 2500 pounds per square inch. The bomb was opened after it had cooled and the reacted catalyst was filtered off. The dioxane was then distilled off at atmospheric pressure. Fractionation at atmospheric pressure yielded two fractions:

1st fraction            b.p. 222-4°C./760 mm.

2nd fraction            b.p. 288°C./760 mm.

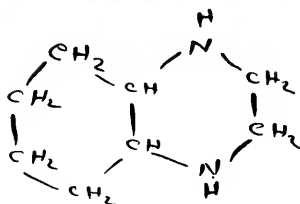
Thirty grams of the first fraction, decahydroquinoxaline, were obtained, which was 76.5% of the theoretical yield. The benzene sulfonyl derivative melted at 188.5-199.5°C. Ten grams of the reactant fraction, boiling at 288°C., were recovered. From these runs we have concluded that the increase in the amount of catalyst will increase the yield of the product. Six runs were made.

TABLE

Run	Grams of Reactant	Grams catalyst	Temperature	Per Cent Theoretical Yield
1	30	7	250°C.	0
2	30	7	275-300°C.	low (C. 20%)
3	40	7	280-310°C.	43%
4	40	7	290-300°C.	61.5%
5	30	20	290-300°C.	65%
6	60	20	300°C.	76.5%

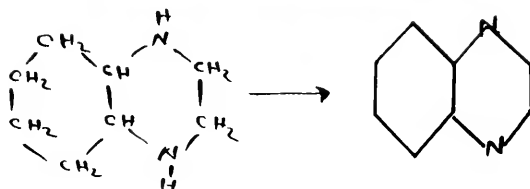


## DECAHYDROQUINOXALINE



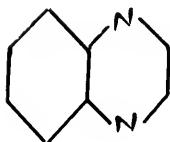
Empirical Formula	$C_8 H_{16} N_2$
Molecular Weight	140
Boiling Point	255°C./760 mm. mercury
Form	mush solid
Color	light yellow
Solubility	
water	insoluble in cold water
alcohol	soluble
dilute HCl	soluble
Yield	75.5% theory
Analysis	calculated      found
molecular weight	140              143

## SYNTHESIS OF QUINOXALINE

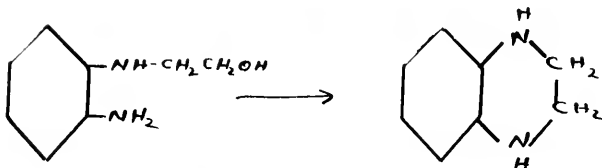


Twelve grams of decahydroquinoxaline, 10 grams of Raney nickel, and 400 cc. of dioxane were placed in the bomb. The bomb was closed and the pressure raised to 1000 pounds per square inch with nitrogen. The bomb was agitated for 4 hours at a temperature range of 250-300°C. (optimum conditions). After cooling, the bomb was opened and the black nickel catalyst filtered off. The dioxane was distilled off through a short column at atmospheric pressure. The residue was then fractionated through a short column and the fraction, boiling at 220-222°C. (reported value - 220-222 (7)) was collected. It was a light yellow oil, very fluid. It yielded no derivative with benzene-sulfonyl chloride. Five grams were collected, giving a yield of 45.5% theory. The quinoxaline was soluble in all proportions with water. Three runs were made, and the above procedure were the optimum conditions determined.

## QUINOXALINE

**Empirical Formula****C<sub>8</sub> H<sub>6</sub> N<sub>2</sub>****Molecular Weight****130****Boiling Point****220-222°C. Experimental****220-222°C. Literature****Color****light yellow****Solubility****water****miscible in cold****alcohol****soluble****dilute HCl****soluble****Analysis****calculated      found****nitrogen****21.5%****21.2%**

## SYNTHESIS OF 1-2-3-4-TETRAHYDROQUINOXALINE



Thirty and eight-tenths grams (0.2 mole) of *N*-(beta-hydroxyethyl)-*o*-phenylene diamine were dissolved in 400 cc. of purified dioxane and 4 grams of Raney nickel added. The mixture was placed in the bomb under 50 atmospheres of hydrogen and agitated for  $3\frac{1}{2}$  hours at 200°C. The Raney nickel was filtered off, and the dioxane was distilled off at atmospheric pressure. The residue was fractionated under reduced pressure, and one fraction, boiling 225°C. under 20 mm. of mercury was obtained. It solidified on cooling and was recrystallized from benzene. White micaceous crystals, melting at 102-3°C. were obtained, but they gave no melting point depression when a mixture melting point was taken out with *N*-(beta-hydroxyethyl)-*o*-phenylene diamine. No reaction had occurred.

In order to determine whether the copper-chromite catalyst would effect the alkylation, the following run was made. Thirty grams of the *N*-(beta-hydroxyethyl)-*o*-phenylene diamine was dissolved in 500 cc. of purified dioxane, and 4 grams of copper-chromite catalyst added. The pressure on the mixture was raised to 50 atmospheres with hydrogen and the bomb was agitated for  $4\frac{1}{2}$  hours at 210°C. The same procedure was followed as before. One fraction, boiling 215-225°C under

15 mm. of pressure was obtained. On cooling, it crystallized and recrystallization from benzene yielded buff colored crystals melting 103-4°C. There had been no reaction.

Having seen from the previous work that temperature played a very important part in the catalytic alkylation of amines, we decided to try Raney nickel again at a higher temperature. Forty grams of the *N*-(betahydroxyethyl)-*o*-phenylene diamine were dissolved in 400 cc. of dioxane and 10 grams of Raney Nickel added. The mixture was placed in the bomb, and the pressure was increased on the reaction mixture to 1000 pounds per square inch with nitrogen. The bomb was agitated for 4 hours at a temperature of 300°C. The catalyst was filtered off and the dioxane distilled off at atmospheric pressure. When the residue was fractionated, one fraction, boiling at 338°C., under atmospheric pressure was obtained. This was the boiling point of the *N*-(betahydroxyethyl)-*o*-phenylene diamine. There had been no reaction.

We did, however, obtain the desired product when we substituted the copper chromite catalyst for the Raney nickel. Twenty seven grams of *N*-(betahydroxyethyl)-*o*-phenylene diamine were dissolved in 600 cc. of purified dioxane, and 7 grams of the copper chromite catalyst added. The mixture was put under a pressure of 1000 pounds per square inch with nitrogen and agitated at 250-70°C. for 4½ hours. After the bomb had cooled, it was opened, and the reacted catalyst was filtered off. The dioxane was distilled off at atmospheric pressure and the residue fractionally distilled at atmospheric pressure. Two main fractions and a smaller one of a higher boiling compound were obtained:

1st fraction	254-6°C.
2nd fraction	278-88°C.
3rd fraction	higher than 330°C.

The first fraction turned out to be *o*-phenylene diamine formed by decomposition of the starting material. It was identified by its boiling point and melting point. Its mixture melting point with pure *o*-phenylene diamine gave no depression. The second fraction was refractionated and yielded a product boiling at 286-8°C. The reported value of this product is 288-9°C. It was recrystallized from petroleum ether and yielded buff colored crystals melting at 94-5°C. Further recrystallization from petroleum ether gave white micaceous flakes melting at 96-7°C. Reported value is 96-97°C.(10). It gave a melting point depression of twenty degrees when mixed with the pure *N*-(*β*-hydroxyethyl)-*o*-phenylene diamine. The following spot tests reported in the literature were obtained (10): An aqueous solution of the compound gave a blue stain with aqueous silver nitrate. On addition of ferric chloride to an aqueous solution of the compound, a violet color was obtained which turned yellow on addition of hydrochloric acid, and further turned brown when heated. A few drops of potassium ferricyanide poured into an aqueous solution of the compound gave a blue-violet color which turned red on addition of base.

An increase in the temperatures and the amount of catalyst will increase the yield of the desired product. A typical run is cited: 50 grams of the *N*-(*β*-hydroxyethyl)-*o*-phenylene diamine, 20 grams of copper chromite catalyst, 400 cc. of purified dioxane placed in bomb.

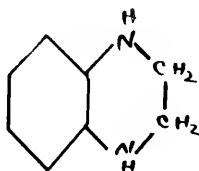
The bomb was put under a pressure of 1000 pounds per square inch, and agitated for 5 hours at 300°. Two fractions were obtained when the residue was fractionally distilled:

1st fraction            280-300°C.

2nd fraction            230-340°C.

When the first fraction was refractionated, 9 grams of product were obtained, boiling at 287-9°C., which was a yield of 20%. The compound when recrystallized several times from petroleum ether melted sharply at 96-97°C. It gave the specific spot tests listed previously.

## 1-2-3-4-TETRAHYDROQUINOXALINE



Empirical Formula	$C_8 H_{10} N_2$	
Molecular Weight	134	
Color	white	
Crystalline Form	micaceous flakes	
Boiling Point	286-8°C. reported in literature 286-8°C. experimental	
Melting Point	96-7°C. recorded in literature 96-7°C. experimental	
Solubility		
water	insoluble	
alcohol	soluble	
petroleum ether	insoluble in cold, soluble in hot	
Analysis	calculated	found
molecular weight	134	132



## SUMMARY "PART #2"

1. The reactivity of epoxy compounds toward diamines has been investigated.
2. Five new compounds have been reported:
  - (a) N-(ortho-hydroxycyclohexyl)-ethylene diamine
  - (b) N-N'-di(ortho-hydroxycyclohexyl)-ethylene diamine
  - (c) N-(beta-hydroxyethyl)-o-phenylene diamine
  - (d) N-N'-di(beta-hydroxyethyl)-o-phenylene diamine
  - (e) Decahydroquinoxaline
3. The fact that catalytic alkylation proceeds equally as well under nitrogen as hydrogen has been verified.
4. A new synthesis of 2-3 benzopyrazine has been reported.
5. A new synthesis of 1-2-3-4-tetrahydroquinoxaline has been reported.

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## BIOGRAPHICAL ITEMS

Gershon Joseph Shugar was born June 15, 1918, in Tarboro, North Carolina. He attended the public schools of Tarboro, North Carolina. In 1935 he entered The Citadel, Charleston, S. C., and transferred to the University of North Carolina, at Chapel Hill, N. C., in 1937. He was graduated from the University of North Carolina with degrees of Bachelor of Science in 1939 and Master of Arts in 1940. He has attended the University of Florida continuously from the fall of 1940 to the present.

While continuing his graduate work at the University of Florida, he held a graduate assistantship in Chemistry and a graduate scholarship.

Mr. Shugar is a member of the American Chemical Society, Gamma Sigma Epsilon Chemical Fraternity, and Delta Phi Alpha, honorary German language fraternity.

**Committee Report**

This dissertation has been prepared under the direction of the Chairman of the candidate's Supervisory Committee, and has been approved by all the members of the Committee. It was submitted to the Graduate Council and was approved as partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

Date Feb. 5, 1943

J. M. Simpson  
Dean

**Supervisory Committee:**

J. B. Seland  
Chairman

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