REDUCTION STUDIES ON ARYLGLYOXYLOHYDROXAMYL CHLORIDES

AND AMIDES

By

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INTRODUCTION

In view of developments in the field of medicinal chemistry
since the turn of the century, the medicinal chemist is now more
than ever in a position to make definite correlations of physio-
logical activities with chemical structure of organic compounds.
This is especially true in the class of compounds which produce
a rise in blood pressure. Through the work of Barger and Dale (1)
it has been conclusively established that the phenethylamine nu-
cleus is the minimum structural requirement necessary for com-
pounds capable of producing a rise in blood pressure.

Hartung (2) in his review of β-Phenethylamine derivatives
gives an excellent discussion of possible modifications of the
phenethylamine nucleus and the pressor activity resulting from these
modifications. From this review it is apparent that compounds of the
following structure give optimum pressor activity:

$$Ar.\overset{|}{\underset{R}{C}H}.\overset{|}{\underset{NHR''}{C}HR'}$$
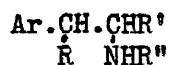
R may be hydrogen or hydroxyl. When R is hydroxyl, the activity of
the compound is increased and the toxicity is decreased. R' and R"
may be either hydrogen or methyl. It has been shown that when R' is
methyl, the compound is active when administered orally.

Through the general method of Hartung and his associates (3,4,
5,6), the arylpropanolamines have been made readily available for
pharmacological studies of the various members of this series. From

these studies it has been possible to draw general conclusions as to
the effect of chemical structure in this series on physiological act-
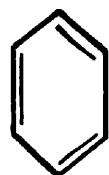ivity. Of this series propadrine, 1-phenyl-2-aminopropan-1-ol (I),
has been proved to posses a definite therapeutic value. A conclusive
comparison of the action of the arylpropanolamines to that of the a
arylethanolamines has not been accomplished because of the limited
number of derivatives of phenylethanolamine which are available for
study. The need, therefore, for a feasible method of synthesis of
the arylethanolamines is apparent.

In view of the success encountered in the study of the aryl-
propanolamines, a similar study of the arylethanolamines is indicat-
ed. With the availability of the various members of this series a
comprehensive study of the effect of structure on activity could be
made. For example, phenylethanolamine (II) itself has been shown to
have a pressor effect approximately equal to that of ephedrine (III)
with only one-third of the toxicity (7,8). However, this compound has
never fully acquired wide usage, the prime reason, probably, being
the lack of a good method of synthesis.

The most important of the arylethanolamines is 3,4-dihydroxy-
phenylethanolamine (IV) which is also known as nor-epinephrine, ar-
terenol, and nor-adrenalin. It has been shown that Cobefrine (V)
(norhomo-epinephrine) is less active and more toxic than epineph-
rine (VI). Epinephrine in turn is more toxic and less active than
nor-epinephrine. Barger and Dale (1), in their classic work postu-
lated that the hormone responsible for the sympathetic effect might
be a catechol with a primary amine side chain instead of epinephrine.

TYPICAL PRESSOR AMINES

CHOH–CH$_2$–CH$_3$
NH$_2$

PROPADRINE

(I)

CHOH–CH$_2$NH$_2$

PHENYLETHANOLAMINE

(II)

CHOH–CH–CH$_3$
NHCH$_3$

EPHEDRINE

(III)

OH
OH

CHOH–CH$_2$NH$_2$

NOR-EPINEPHRINE

(IV)

OH
OH

CHOH–CH–CH$_3$
NH$_2$

COBEFRINE

(V)

OH
OH

CHOH–CH$_2$–NHCH$_3$

EPINEPHRINE

(VI)
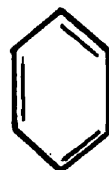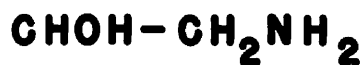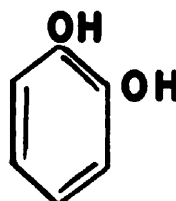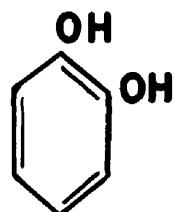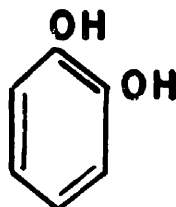
PLATE I

As yet the existence and identity of this substance has not been
proved; however, recent investigators (8,9,10) have suggested that
the elusive hormone (sympathin E) might be 3,4-dihydroxyphenylethan-
olamine, although the evidence supporting this theory is indirect.
v. Euler (12) recently reported evidence that the actions attribut-
ed to sympathin E are due to a substance shown to be present in ad-
rengeric nerves, having the properties of nor-epinephrine. In view
of this evidence and in view of the lack of evidence for the presence
of a sympathin E different from nor-epinephrine, v. Euler suggested
that the term sympathin E be dropped as inadequate in the strict
sense. 3,4-Dihydroxyphenylethanolamine Hydrochloride is listed as
Arterenolum Hydrochloricum in the Remedia-"Hoechst", a publication
of the Farbwerke vorm. Meister Lucius & Brüning. Its physical and
chemical properties were described, and it was recommended as a sub-
stitute for epinephrine in view of the fact that their physiological
properties are alike (13). The use of nor-epinephrine as a substitute
for epinephrine in local anesthetic combinations has been patented
by Winthrop Chemical Company (14).

The pressor activity of racemic nor-epinephrine in animals has
been reported to be 1.25-1.5 times that of racemic epinephrine (1,15).
A rather thorough study of the activity of this amine in animals has
been made by Tainter and his associates. These workers found that the
pressor activity of racemic nor-epinephrine 1.2 times that of l-epi-
nephrine and its toxicity to be only one-third that of l-epinephrine
(16). As a result of these studies, they pointed out that racemic
nor-epinephrine has a therapeutic index almost 3 times that of l-epi-

nephrine. Racemic nor-epinephrine has been found to be twice as active as l-epinephrine in the treatment of circulatory depression produced by experimental shock (17); in circulatory failure in cats due to phenol poisoning it was approximately 12 percent more active than l-epinephrine (18). Only recently has the resolution of nor-epinephrine been accomplished. In dogs under phenobarbital anesthesia the activity of (-)-nor-epinephrine has been found to be 164 $\pm$ 10 percent that of l-epinephrine. The ($\pm$)-nor-epinephrine has only 3 to 4 percent of the pressor activity of the levo. This ratio of activity is similar to that of the epinephrine isomers. In equivalent pressor doses, (-)-nor-epinephrine has a therapeutic index four times that of l-epinephrine (19).

In view of the favorable results thus far obtained in the studies of the physiological activity of the arylethanolamines, a general method for the synthesis of these compounds is definitely indicated. It is the purpose of this investigation to develop a satisfactory method for the synthesis of phenylethanolamine and its phenyl-substituted derivatives.

REVIEW OF PREVIOUS METHODS FOR THE SYNTHESIS
OF ARYLETHANOLAMINES

The synthesis of arylethanolamines must be based on intermed-
iates having the following minimum structural formula

$$\text{Ar.}\underset{\underset{O-}{|}}{C}\text{.C.N}\!\!<$$
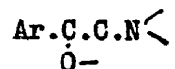
in which the oxygen is present as a potential hydroxyl group and the
nitrogen as a potential primary amine.

A review of the literature shows that (VII) arylnitroethanols,
(VIII) arylcyanohydrins, (IX) ω-aminoacetophenones, and (X) iso-
nitrosoacetophenones have been utilized in the synthesis of arylethan-
olamines:
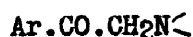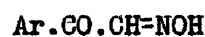
$\text{Ar.CHOH.CH}_2\text{NO}_2$	$\text{Ar.CHOH.C}\!\equiv\!\text{N}$
(VII)	(VIII)
$\text{Ar.CO.CH}_2\text{N}\!\!<$	Ar.CO.CH=NOH
(IX)	(X)

In addition one miscellaneous method has been reported. These
methods will be discussed according to the intermediates which were
employed in each. Since the miscellaneous method does not employ in-
termediates of the above classification it will be discussed separate-
ly.

Condensation of Aminoacetal with Phenols and Phenolic Derivatives.

An unusual method for the preparation of certain arylethanol-
amines has been devised by Hinsberg (20). He prepared nor-epineph-

rine by condensing catechol with aminoacetal as follows:

OH
OH
+ $NH_2.CH_2.CH(OC_2H_5)_2$ + HCl + HOH $\longrightarrow$

OH
OH
+ 2 C_2H_5OH
$CHOH.CH_2NH_2 \cdot HCl$
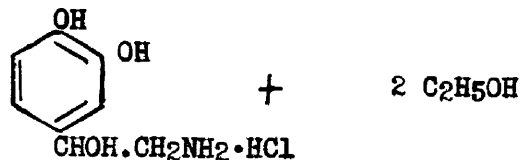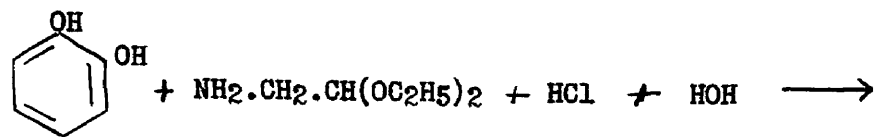
Hinsberg made no mention of the yield of nor-epinephrine obtained in this reaction. However, he reported that from 3 g. of pyrogallol he obtained a yield of 4.5 g. of the corresponding 3,4,5-trihydroxyphenylethanolamine hydrochloride. He also prepared the amino alcohols from the trimethyl ether of pyrogallol and gallic acid.

The difficulty experienced in the preparation of aminoacetal is the greatest disadvantage in the use of the Hinsberg method in the preparation of arylethanolamines. The method has a very limited application, since in the case of phenol, two molecules condense with one of aminoacetal to give 1,1-di-(p-hydroxyphenyl)-2-aminoethane instead of the desired p-hydroxyphenylethanolamine:

OH
2
+ $NH_2.CH_2.CH(OC_2H_5)_2$ $\longrightarrow$

OH

$HC.CH_2.NH_2$

OH
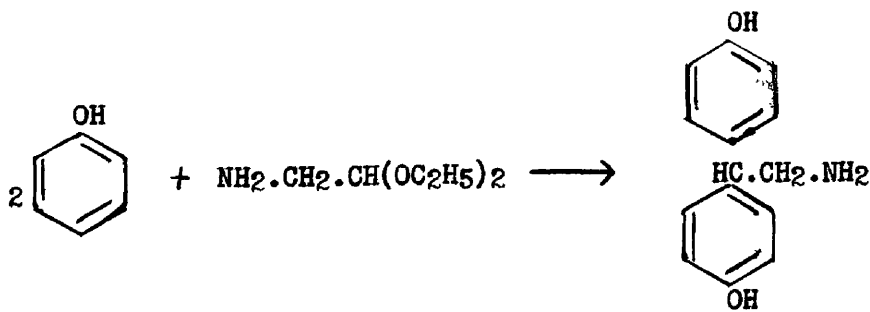
Phenetole also gives the corresponding diethyl ether. However, pyro-gallol, depending on the mole ratio of the reagents could yield either the corresponding arylethanolamine or the diarylethylamine. Thymol gives only the diarylethylamine derivative.

Although on the surface, the Hinsberg reaction as applied to the synthesis of arylethanolamines is very simple, it must be noted that the use or investigation of this method by other workers has never been reported.

A. Reduction of Arylnitroethanols.

The Rosenmund Synthesis. Rosenmund (21) reported a method for the synthesis of arylethanolamines based on the reduction of aryl-nitroethanols of the type, Ar.CHOH.CH2NO2. He prepared these inter-mediates by condensing the appropriate aromatic aldehyde with nitro-methane in the presence of sodium methoxide. Subsequent reduction with sodium amalgam in dilute alcohol containing some acetic acid yielded the corresponding amino alcohols. The scheme of reactions is as follows:

$$\text{Ar.CHO} \xrightarrow[\text{CH}_3\text{NO}_2]{\text{C}_2\text{H}_5\text{ONa}} \text{Ar.CHOH.CH:N} \underset{\text{ONa}}{\overset{\diagup\text{O}}{\diagdown}} \xrightarrow{\text{HOAc}} \text{Ar.CHOH.CH}_2\text{NO}_2 \xrightarrow[\text{HOAc}]{\text{Na}}$$

Ar.CHOH.CH2NH2
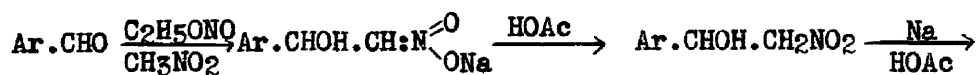
Rosenmund, by this procedure, prepared phenylethanolamine, p-methoxyphenylethanolamine, 3,4-dimethoxyphenylethanolamine and the dicarboethoxy derivative of 3,4-dihydroxyphenylethanolamine. Rosen-mund made no mention of the yields obtained.

Rosenmund's synthesis was applied to the preparation of phenyl-

ethanolamine by Kondo and Murayama (22). They obtained phenylnitro-
ethanol in yields of 80 percent from benzaldehyde and nitromethane.
The reduction was carried out using palladium hydrosol (1%) and a
little active carbon, however, the yield of the amino alcohol was not
mentioned. In the same manner, Kondo and Tanaka (23) prepared o-meth-
oxyphenylethanolamine. The reaction of 20 g. of o-methoxybenzalde-
hyde with nitromethane yielded 25 g. of the corresponding nitro-
ethanol; however, on reduction only 13 g. of the amino alcohol was
obtained.

Kanao (24), using the Rosenmund synthesis, prepared the di-
acetate of 3,4-dihydroxyphenylethanolamine. Excellent yields of the
nitroethanol were obtained by condensing the diacetate of proto-
catechuic aldehyde and nitromethane. Upon reduction, using zinc dust
and 30 percent acetic acid, 10 g. of the nitroethanol yielded only
5 g. of the amino alcohol.

Rosenmund's synthesis has been applied to phenylethanolamine by
Alles (7) and Alles and Knoefel (25), however, the experimental de-
tails or the yields of product obtained were not described.

Vinkler and Bruckner (26) have prepared N-benzoyl-3,4-dimethoxy-
phenylethanolamine using a nitroethanol intermediate:

$$\text{OCH}_3 \quad \text{OCH}_3 \qquad \xrightarrow{\text{(H)}} \qquad \text{OCH}_3 \quad \text{OCH}_3$$

$$\underset{\substack{| \\ \text{O} \\ | \\ \text{C:O} \\ | \\ \text{C}_6\text{H}_5}}{\text{CH.CH}_2.\text{NO}_2} \qquad\qquad \underset{\substack{| \\ \text{C:O} \\ | \\ \text{C}_6\text{H}_5}}{\text{CHOH.CH}_2\text{NH}}$$
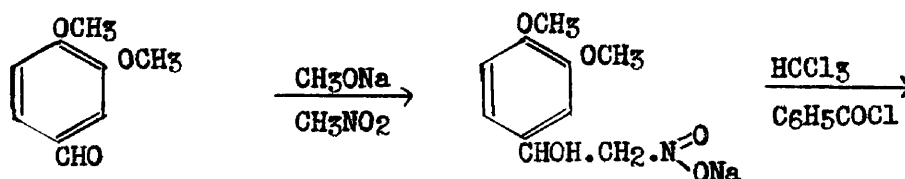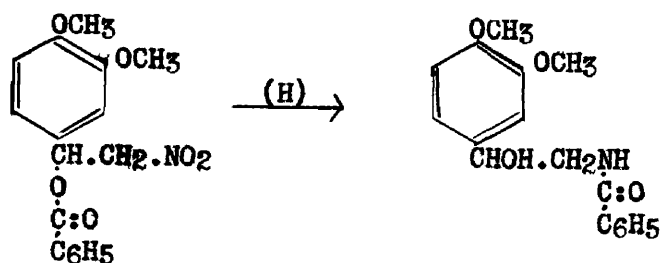
Unfortunately further information was not available.

The Rosenmund synthesis of arylethanolamines has been patented in spite of its objectionable features. Nor-epinephrine can be prepared by this method as follows:

$$\underset{\text{CHO}}{\text{OH} \quad \text{OH}} \xrightarrow{\text{ClCOOC}_2\text{H}_5} \underset{\text{CHO}}{\text{OCOOC}_2\text{H}_5 \quad \text{OCOOC}_2\text{H}_5} \xrightarrow[\text{CH}_3\text{NO}_2]{\text{CH}_3\text{ONO}} \underset{\text{CHOH.CH}_2\text{NO}_2}{\text{OCOOC}_2\text{H}_5 \quad \text{OCOOC}_2\text{H}_5}$$

$$\xrightarrow{\text{NaOH}} \xrightarrow{\text{HOAc}} \underset{\text{CHOH.CH}_2\text{NO}_2}{\text{OH} \quad \text{OH}} \xrightarrow{\text{(H)}} \underset{\text{CHOH.CH}_2\text{NH}_2}{\text{OH} \quad \text{OH}}$$
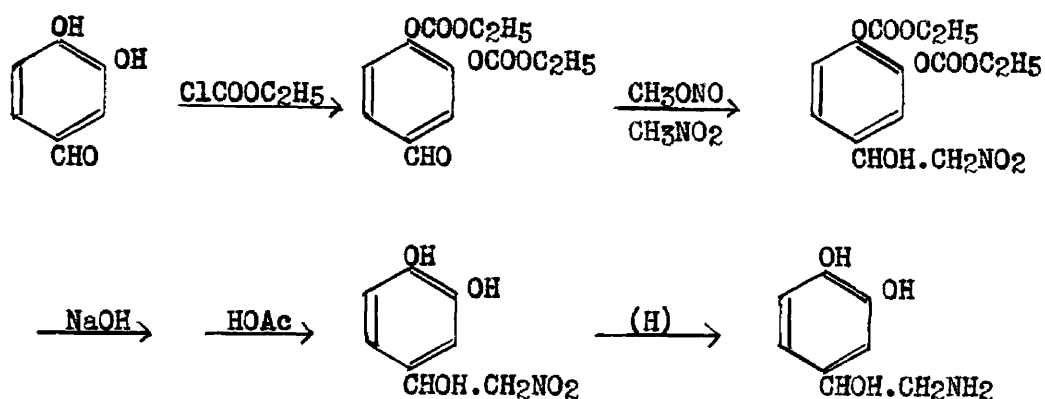
The compound obtained by this synthesis is of questionable purity. The yields were inconsistent and at best were only 5 percent (based on the aldehyde).

The greatest objection to this method is the difficulty encountered in obtaining the various substituted derivatives of benzaldehyde, especially 3,4-dihydroxybenzaldehyde, protocatechuic aldehyde, which would be necessary as an intermediate in the synthesis of nor-epinephrine. In addition, the intermediate nitroethanols also readily form ω-nitrostyrenes:

$$Ar.CHOH.CH_2NO_2 \longrightarrow Ar.CH:CHNO_2 + HOH$$
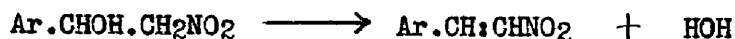
For this reason the yields of the nitroethanol may be lowered; side-reactions also occur and difficulty has been encountered in obtaining pure amino alcohols. Aromatic aldehydes bearing unprotected phenolic groupings can not be used as intermediates in the Rosenmund method, thus as in the case of nor-epinephrine two additional reactions are necessary.

ω-Nitrostyrene Method of Reichert and Koch. Reichert and Koch (27) have recently developed a method of synthesis of substituted phenylethanolamines utilizing ω-nitrostyrenes as intermediates.

$$Ar.CH:CHNO_2 \xrightarrow{\quad Br_2 \quad} Ar.CHBr.CHBrNO_2 \xrightarrow{\quad \frac{CH_3OH}{CH_3COOK} \quad}$$

$$Ar.CH:CBrNO_2 \xrightarrow{\quad \frac{CH_3OH}{KOH} \quad} Ar.C(OCH_3)_2.CH_2NO_2 \xrightarrow{\quad HCl \quad}$$

$$Ar.CO.CH_2NO_2 \xrightarrow{\quad (H) \quad} Ar.CHOH.CH_2NH_2$$
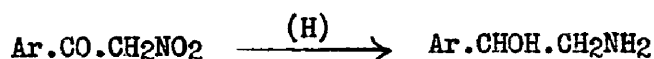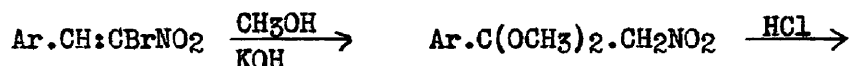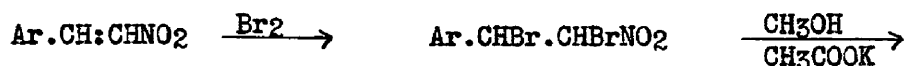
These workers reported that excellent yields of the dibromonitro-intermediate were obtained in the bromination, however, they made no mention of the yields obtained in the subsequent reactions. The reduction of the ω-nitroacetophenones, $Ar.CO.CH_2NO_2$ to the aryl-ethanolamines was carried out using platinum oxide catalyst. The yields in this reaction were reported to be 80 percent or better. Using this method 2-methoxy-, 4-methoxy-, 3,4-dimethoxy-, and 3,4-dimethylenedioxyphenylethanolamines were prepared.

It is apparent that the number of steps involved in this syn-

thesis is a distinct disadvantage. Furthermore, the reaction is not general; attempts to prepare 2,4-dimethoxyphenylethanolamine failed due to bromination of the ring.

B. Reduction of Arylcyanohydrins.

Method of Wolfheim. The use of arylcyanohydrins as intermediates in the synthesis of phenylethanolamines has been previously investigated by various workers. Wolfheim (28) was the first to obtain phenylethanolamine by the reduction of benzaldehyde cyanohydrin:

$$C_6H_5.CHOH.CN \xrightarrow{(H)} C_6H_5.CHOHCH_2NH_2$$
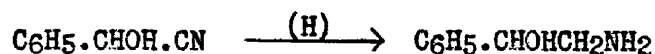
The reduction was accomplished by the use of 4 percent sodium amalgam in a solution composed of 33 percent alcohol and 50 percent acetic acid. The reduction was difficult and only 17.9 g. of crystalline phenylethanolamine was obtained from 50 g. of the cyanohydrin. The reduction of the cyanohydrins of benzaldehyde and protocatechuic aldehyde to the corresponding phenylethanolamines was covered in a German patent (29) prior to the publication of Wolfheim's work. The patent made no mention of the yields of the phenylethanolamines obtained.

Hess and Ulbrig (30) in attempting to repeat Wolfheim's work reported that they were able to obtain only 10 percent yields of phenylethanolamine in contrast to the 36 percent yields reported by that worker. In 1937, Bhatnagar, Narang, Chopra and Ray (31) reported that Wolfheim's method was unsatisfactory. By modifying the conditions of the reaction, these workers were able to obtain slightly better results, but at that, they were able to obtain only 20 percent yields

of phenylethanolamine from benzaldehyde cyanohydrin. They also reduced the cyanohydrin of piperonal and obtained 3,4-methylenedioxy-phenylethanolamine. In this case the yield was low, being less than 20 percent.

Hartung (32) found that catalytic reduction of benzaldehyde cyanohydrin gives, not phenylethanolamine, but rather phenylethyl-amine in 52 percent yields. The reduction is carried out in absolute alcoholic hydrogen chloride using a palladium-charcoal catalyst. In attempting to reduce the benzoate or acetate of the cyanohydrin he reports that phenylethylamine was obtained in both cases.

Using platinum oxide catalyst in alcoholic hydrogen chloride, Buck (33.) has reported that the reduction of arylcyanohydrins gives either the corresponding arylethanolamine or arylethylamine. When Ar- was 2-methoxyphenyl-, 2-chlorophenyl-, and 2,3-dimethoxyphenyl-, the corresponding arylethanolamines were obtained in 59, 41 and 23 percent yields, respectively. However, when Ar- was 4-chlorophenyl-, 3,4-dimethoxyphenyl-, 4-methoxyphenyl-, and 4-methylphenyl-, the reduction proceeded directly to the arylethylamines.

The use of arylcyanohydrins as intermediates in the synthesis of phenylethanolamines has not been satisfactorily established. Objections to this method are threefold; first, the necessary aldehydes are not readily available; second, the preparation of the cyano-hydrins is difficult and the yields are poor; third, the reduction procedure gives, at best, only fair yields of the desired amino alcohol and the formation of the arylethylamines is difficult to avoid.

Reduction of Aroyl Cyanides. Kindler and Peschke (34) have shown

that arylethanolamines can be preared by the reduction of aroyl cyanides. The aroyl cyanides were prepared by the oxidation of the corresponding arylcyanohydrins. The method of synthesis is as follows:

$$Ar.CHO \quad \xrightarrow{\frac{NaHSO_3}{KCN}} \quad Ar.CHOH.CN \quad \xrightarrow{(O)}$$

$$Ar.CO.CN \quad \xrightarrow{(H)} \quad Ar.CHOH.CH_2NH_2$$
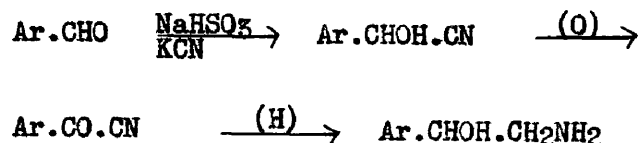
This method appears to be very satisfactory. The cyanohydrins were obtained in quantitative yields and were readily oxidized by chromic acid in glacial acetic acid to give 70 to 90 percent yields of the corresponding aroyl cyanides. Using palladium black catalyst, the reduction of these intermediates gave 70 to 80 percent yields of the arylethanolamines.

Limitations of this method are as follows; first, the difficulty in obtaining nuclear-substituted derivatives of benzaldehyde; second, the method can not be applied to phenolic aldehydes in which the phenolic groups are unprotected; third, both the reduction and the use of aroyl cyanides as intermediates have not been studied in great enough detail.

C. Reduction of ω-Aminoacetophenones.

Condensation of Halogen Derivatives with Ammonia. German patents (35) describe the synthesis of nor-epinephrine by the condensation of 3,4-dihydroxy-ω-chloroacetophenone with ammonia to form 3,4-dihydroxy-ω-aminoacetophenone and subsequent reduction to the substituted phenyl ethanolamine. The reactions involved are as follows:
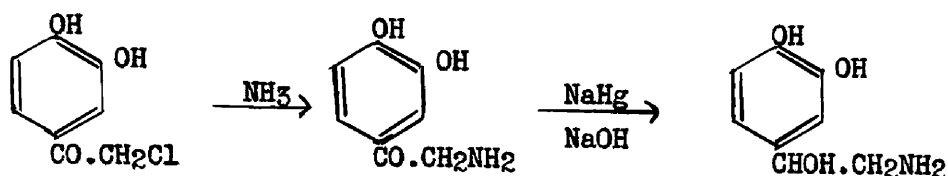
The above synthesis is of doubtful value in view of the fact that Tutin (36) and Boruttau (37) both failed to obtain p-hydroxy-ω-aminoacetophenone by the condensation of p-hydroxy-ω-chloroacetophenone with ammonia. In addition, Glynn and Linnell (38) were unable to condense 3,4-dichloro-ω-chloroacetophenone with ammonia in an attempt to prepare 3,4-dichloro-ω-amino acetophenone. In view of the results obtained by these workers this method can hardly be considered as a satisfactory method for preparing phenylethanolamine and its nuclear-substituted derivatives.

Application of the Hexamine Addition Products. Mannich and his associates (39,40) have shown that the addition product of an aryl-halogenomethylketone and hexamine can be hydrolyzed to an arylamino-methylketone. This ketone upon catalytic reduction gives the corresponding arylethanolamine. The reactions are as follows:

$$\text{Ar.CO.CH}_2\text{Cl} \quad + \quad (\text{CH}_2)_6\text{N}_4 \quad \longrightarrow \quad \text{Ar.CO.CH}_2\left[\text{N}_4(\text{CH}_2)_6\right]\text{Cl}$$

$$\text{Ar.CO.CH}_2\left[\text{N}_4(\text{CH}_2)_6\right]\text{Cl} \quad + \quad 12 \ \text{C}_2\text{H}_5\text{OH} \quad + \quad 3 \ \text{HCl} \quad \longrightarrow$$

$$\text{Ar.CO.CH}_2\text{NH}_2 \cdot \text{HCl} \quad + \quad 3 \ \text{NH}_4\text{Cl} \quad + \quad 6 \ \text{CH}_2(\text{OC}_2\text{H}_5)_2$$

$$\text{Ar.CO.CH}_2\text{NH}_2 \cdot \text{HCl} \quad + \quad 2 \ (\text{H}) \quad \longrightarrow \quad \text{Ar.CHOH.CH}_2\text{NH}_2 \cdot \text{HCl}$$
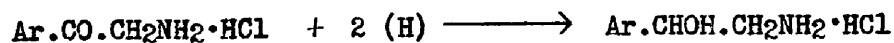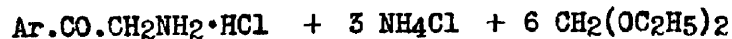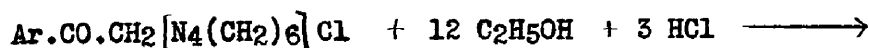
Mannich et al report yields of 70 percent or better for the formation of the addition product and subsequent hydrolysis. They also point

out that the bromides and iodides react more readily and give better yields than the corresponding chlorides. No mention was made of the yields obtained in the reduction, in which they employed a palladium-charcoal catalyst.

Slotta and Heller (41) prepared phenylethanolamine using the method of Mannich. These workers hydrolyzed the hexamine addition-product of phenacyl bromide to a mixture of the hydrochloride and hydrobromide salts of ω-aminoacetophenone. Upon reduction of 80 g. of this mixture, 23.8 g. of phenylethanolamine hydrochloride (crude product) was obtained.

Balzly and Buck (42) have utilized this method to prepare 2,5-dimethoxyphenylethanolamine. In the reduction they used a platinum oxide catalyst and reported that the method was capable of giving good yields.

The method of Mannich appears to be one of the best for the synthesis of arylethanolamines. The intermediates are easily obtained and the reduction procedure is fairly good. Disadvantages to the method are first, the phenolic substituted derivatives must be alkylated or acylated to prevent reaction with hexamine; and second, the hydrolysis reaction requires a period of approximately three days.

Phthalimide Method. Tutin, Caton and Hahn (36) have prepared p-hydroxyphenylethanolamine as follows:

$$CH_3O.C_6H_5 \xrightarrow[AlCl_3]{ClCH_2COCl} HO.C_6H_4.CO.CH_2Cl \xrightarrow{(AcO)_2O}$$

$$CH_3COO.C_6H_4.CO.CH_2Cl \xrightarrow{C_6H_4(CO)_2NK} CH_3COO.C_6H_4.CO.CH_2.N\underset{CO}{\overset{CO}{<}}C_6H_4$$

$$\xrightarrow[\text{HCl}]{\text{HOH}} \text{HO.C}_6\text{H}_4.\text{CO.CH}_2\text{NH}_2 \qquad \xrightarrow[\text{C}_2\text{H}_2\text{OH}]{\text{Na}} \text{HO.C}_6\text{H}_4.\text{CHOH.CH}_2\text{NH}_2$$
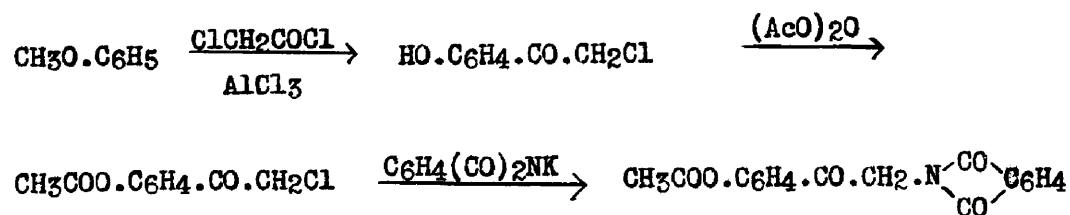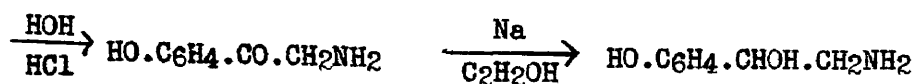
The authors report a yield of 42 percent in the condensation of the acetate of p-hydroxyphenacyl chloride with potassium phthalimide, but they give no indication of the overall efficiency of these reactions.

Subsequently Boruttau (37) used the same procedure for the preparation of p-hydroxyphenylethanolamine, 2,5-dihydroxyphenylethanolamine and 2,4-dihydroxyphenylethanolamine. He failed, however, to describe the reduction in detail and omitted the yields obtained.

Since there is a definite lack of experimental data, the phthalimide method of preparing phenylethanolamines was considered of minor importance.

Application of Azides. Baltzly and Buck (42) have prepared 2,5-dimethoxyphenylethanolamine in the following manner:

$$\text{Ar.CHO} \xrightarrow{\text{BrCH}_2\text{COOC}_2\text{H}_5} \text{Ar.CHOH.CH}_2.\text{COOC}_2\text{H}_5 \xrightarrow{\text{H}_2\text{NNH}_2}$$

$$\text{Ar.CHOH.CH}_2\text{CON}_2\text{H}_3 \xrightarrow{\text{HNO}_2} \text{Ar.CHOH.CH}_2\text{CON}_3 \xrightarrow{\hspace{2cm}}$$

Ar.CH————CH2
| | $\xrightarrow{\text{HCl}}$ Ar.CHOHCH2NH2
O.CO———NH
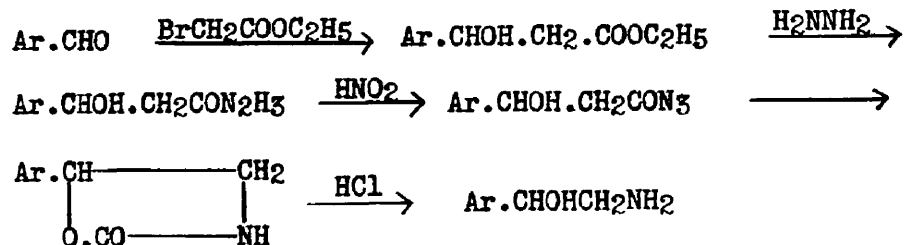
The yields obtained in this series are all upwards of 70 percent with the exception of the hydrolysis of the oxazolidone which gave poor yields of the phenylethanolamine.

Note: One wonders whether these oxazolidones might not
form good yields of the corresponding arylethyl-
amines if subjected to hydrogenolysis according
to the carbobenzyloxy method of Bergmann (cf.43)
as follows:

Ar.CH————CH2
| | $\xrightarrow{(H)}$ Ar.CH2.CH2NH2 + CO2
O.CO———NH
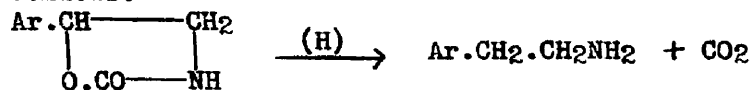
The application of azides as intermediates in the synthesis of phenylethanolamines is limited due to the lack of nuclear-substituted benzaldehydes.

Hydrogenolytic Debenzylation of Aracylamines. Simonoff and Hartung (43) showed that aracyl chlorides, of the type $Ar.CO.CH_2Cl$ could react with benzylamine or dibenzylamine to form the corresponding aracylbenzylamines. These intermediates were then subjected to hydrogenolytic debenzylation to give the corresponding aracylamines of the type $Ar.CO.CH_2NH_2$, which upon continued catalytic reduction yield the corresponding arylethanolamines. The reactions involved are as follows:

$$Ar.CO.CH_2Cl \underset{Ar.CO.CH_2.N(CH_2.C_6H_5)_2}{\overset{Ar.CO.CH_2NH.CH_2.C_6H_5}{<}} \longrightarrow Ar \rightarrow Ar.CHOH.CH_2NH_2$$
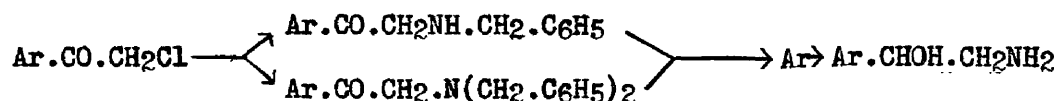
Through the use of this excellent method of synthesis, these workers were able to prepare, in good yields, the hydrochlorides of phenylethanolamine, p-hydroxyphenylethanolamine, and 3,4-dihydroxyphenylethanolamine.

The disadvantages of the method are twofold; first, the high cost of dibenzylamine which is converted into toluene in the reaction and second, the final step involves a loss of two-thirds, in the case of the dibenzylamino, of the molecular weight as a by-product.

D. Reduction of Isonitrosoacetophenone and Derivatives.

Reduction of Isonitrosoketones. Isonitroso ketones, of the type, $Ar.CO.C(:NOH)H$, have been employed as intermediates in the preparation of phenylethanolamines. These compounds on catalytic reduction

yield the corresponding amino alcohol:

$$Ar.CO.C(:NOH)H \quad + \quad 3 \ H_2 \longrightarrow Ar.CHOH.CH_2NH_2 \quad + \quad HOH$$

The first synthesis of phenylethanolamine was accomplished through this scheme by Kolshorn (44) in 1904. He reduced isonitrosoaceto-phenone using 5 percent sodium amalgam in 50 percent alcohol. Since the yield was not mentioned, it must be assumed that it is low. It should be mentioned that prior to Kolshorn's work, Gabriel and Eschenbach (45) attempted the reduction of ω-aminoacetophenone using $2\frac{1}{2}$ percent sodium amalgam. Instead of obtaining phenylethanolamine the reduction proceeded as follows:

$$C_6H_5.CO.CH_2NH_2 \quad + \quad H_2 \longrightarrow C_6H_5.CO.CH_3 \quad + \quad NH_3$$

Pictet and Gams (46) successfully prepared N-acyl derivatives of phenylethanolamine from isonitrosoacetophenone:

$$C_6H_5.CO.C(:NOH)H \longrightarrow C_6H_5.CO.CH_2NH_2 \longrightarrow$$

$$C_6H_5.CO.CH_2NHCOR \longrightarrow C_6H_5.CHOH.CH_2NHCOR$$
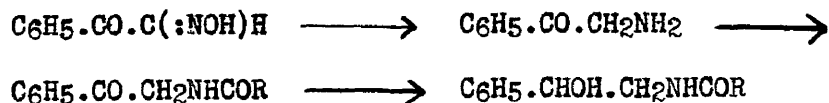
Isonitrosoacetophenone was reduced to ω-aminoacetophenone using stanous chloride in alcoholic hydrogen chloride; the N-acyl-ω-amino-acetophenones were reduced to the corresponding amino alcohols in 40 to 60 percent yields using sodium amalgam in alcohol.

Using 3,4-dichloroisonitrosoacetophenone as an intermediate, Glynn and Linnell (38) obtained 3,4-dichlorophenylethanolamine by the following reactions:

$$\underset{\text{CO.CH}_3}{\overset{\text{Cl}}{\overset{\text{Cl}}{\bigcirc}}} \xrightarrow[\text{C}_2\text{H}_5\text{ONa}]{\text{C}_5\text{H}_{11}\text{ONO}} \underset{\text{CO.C(:NOH)H}}{\overset{\text{Cl}}{\overset{\text{Cl}}{\bigcirc}}} \xrightarrow{\text{(H)}} \underset{\text{CO.CH}_2\text{NH}_2}{\overset{\text{Cl}}{\overset{\text{Cl}}{\bigcirc}}} \xrightarrow{\text{(H)}} \underset{\text{CHOH.CH}_2\text{NH}_2}{\overset{\text{Cl}}{\overset{\text{Cl}}{\bigcirc}}}$$
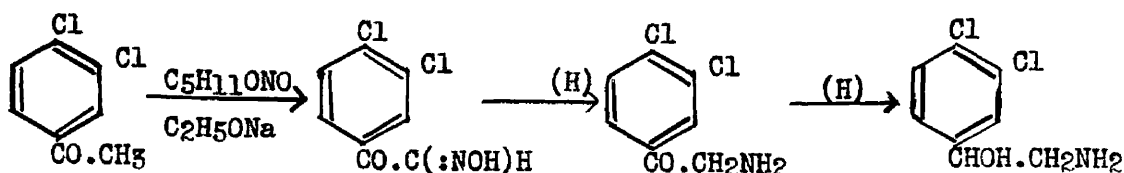
Utilizing the nitrosation method of Claisen (47,48), these workers obtained the isonitroso ketone in yields of 51 percent. The reduction of the isonitroso ketone to the amino alcohol failed when sodium amalgam in a mixture of absolute alcohol-glacial acetic acid was used as the reducing agent. The reduction, however, was accomplished in two steps; first, using stannous chloride and hydrogen chloride in absolute alcohol to reduce the isonitroso ketone to the amino ketone; second, reduction of the amino ketone to the amino alcohol by means of aluminum amalgam. The overall yield of the series is very poor, approximately 5 percent.

Hartung (3,4,5,6) in his reduction studies of oximino ketones using palladium-charcoal catalyst in alcoholic hydrogen chloride, obtained the corresponding amino alcohols in excellent yields:

$$\text{Ar.CO.CH(:NOH)} \xrightarrow{\text{(H)}} \text{Ar.CHOH.CHRNH}_2$$
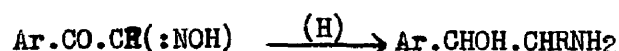
However, when this reaction was applied to isonitrosoacetophenone, the reduction did not proceed as readily. In only one instance was it possible to go directly from the oximino ketone to the phenylethanolamine. The procedure eventually adopted was to stop the reduction at the amino ketone stage; the product was isolated as the hydrochloride and then reduced in an aqueous solution by a fresh catalyst to the amino alcohol (4).

Edkins and Linnell (49) attempted a synthesis of phenylethanol-

amine and its chloro- and bromo- analogs as follows:

$$Ar.CO.CH_3 \xrightarrow[C_2H_5ONa]{RONO} Ar.CO.C(:NOH)H \xrightarrow{(H)}$$

$$Ar.CO.CH_2NH_2 \xrightarrow{(H)} Ar.CHOH.CH_2NH_2$$
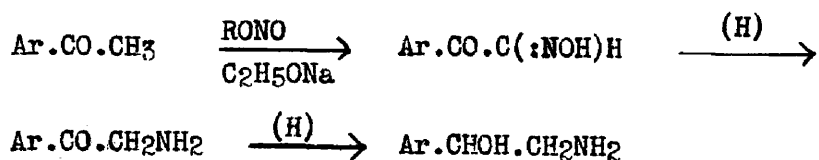
The first reaction in the series was accomplished with yields which varied from 37 to 75 percent. The reduction of the isonitroso ketones to the corresponding amino ketones was carried out using stannous chloride in hydrochloric acid. In the reduction of isonitrosoaceto-phenone the yield of ω-aminoacetophenone was 27 percent; no mention of the yields of the other amino ketones was made. The amino ketones were then reduced according to the method of Hartung (3). In the case of ω-aminoacetophenone, the yield of phenylethanolamine was 37.5 percent. With the halogen analogs of ω-aminoacetophenone, dehalo-genation occurred along with reduction and phenylethanolamine was obtained. Attempts to prevent loss of halogen failed.

Edkins and Linnell (49) also prepared p-hydroxyphenylethanol-amine in the following manner:
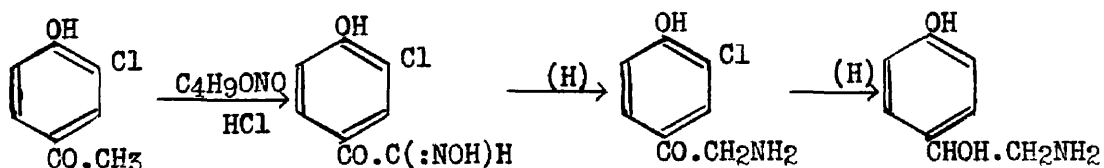
3-Chloro-4-hydroxyacetophenone was nitrosated using butyl nitrite and hydrogen chloride; the oximino ketone was not isolated but was reduced using the stannous chloride proceedure, no mention being made of the yields obtained. The amino ketone was then reduced by the method of Hartung (3) and only 0.097 g. of the amino alcohol was of-

tained from 4 g. of the amino ketone.

The chief objection to the use of isonitrosoketones in the synthesis of phenylethanolamines is the difficulty encountered in the preparation of these intermediates. The Claisen method of nitrosating methyl ketones of the type Ar.CO.CH₃ gives low or negligible yields (4,50). The yields are reported to be better when sodium ethoxide is used as catalyst in the nitrosation, however, they are variable and have not been confirmed. Most important, however, is the fact that this method of nitrosation can not be applied to acetophenones with unprotected phenolic groupings.

Reduction of Arylglyoxylohydroxamyl Chlorides. Levin (51) developed an excellent method of synthesis whereby he obtained, in good yields, compounds of the type Ar.CO.C(:NOH)X. The synthesis involved the nitrosation of halogenomethyl ketones and has been applied to phenacyl bromide, phenacyl chloride, and phenyl-substituted derivatives of phenacyl chloride. Catalytic reduction of the arylglyoxylohydroxamyl halides failed to give the desired arylethanolamine with the exception of one reduction in which a "very active" catalyst was used. The reactions involved in the synthesis are as follows:

$$\text{ArH} + \text{ClCH}_2\text{COCl} \xrightarrow{\text{Friedel-Craft}} \text{Ar.CO.CH}_2\text{Cl} \xrightarrow[\text{HCl}]{\text{RONO}}$$

$$\text{Ar.CO.C(:NOH)Cl} \xrightarrow{\text{(H)}} \text{Ar.CHOH.CH}_2\text{NH}_2$$
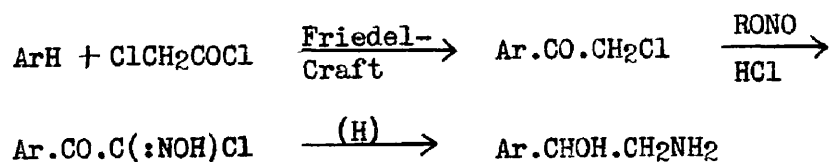
Levin reported very favorable yields in the preparation of the phenacyl halides. He obtained phenacyl chloride, p-chlorophenacyl chloride, p-methylphenacyl chloride, and p-phenylphenacyl chloride in

yields of 80 percent or better. Yields of the hydroxyphenacyl chlorides was in general lower, but 3,4-dihydroxyphenacyl chloride was obtained in yields of 60 percent. The yields obtained in the preparation of arylglyoxylohydroxamyl chlorides were excellent. Arylglyoxylohydroxamyl chlorides, Ar.CO.C(:NOH)Cl, in which Ar- was phenyl, p-methylphenyl-, p-xenyl-, p-chlorophenyl-, p-methoxyphenyl-, p-hydroxyphenyl-, and 3,4-dihydroxyphenyl-, were obtained in yields of 75 percent or better. The nitrosation failed only in the case of o-hydroxyphenacyl chloride.

Since the arylglyoxylohydroxamyl chlorides are so readily available in such good yields, they lend themselves as excellent intermediates for the synthesis of aryethanolamines. Levin pointed out that replacement of the chlorine atom with hydrogen, reduction of the oximino group to the amino group and the reduction of the carbonyl to hydroxyl would yield the desired arylethanolamines. In view of the .success, though limited, which Levin encountered in the reduction of arylglyoxylohydroxamyl chlorides, a more complete study of this reduction is definitely indicated.

F. Resolution. Arylethanolamines, of the general structural formula,

$$\text{Ar.}\underset{\overset{|}{\text{OH}}}{\overset{\overset{\text{H}}{|}}{\text{C*}}}\text{.CH}_2\text{NH}_2$$
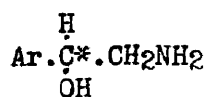
possess optical activity by virtue of an asymmetric carbon atom C*. Phenylethanolamine has been resolved by Alles and Knoefel (25).

Greer and his associates (52) reported that the resolution of nor-epinephrine was in progress, however, no report of success on their part has ever been published.

Tainter, Tullar, and Luduena (19) have recently announced the

successful resolution of nor-epinephrine, or arterenol as they choose

to call the compound. These workers were able to prepare (-)-artere-

nol by utilizing the fact that only the (-) isomer forms a hydrated

diastereoisomer with D-tartaric acid. The monohydrate of (-)-artere-

nol D-bitartrate was crystallized from an aqueous solution of equi-

molar amounts of racemic arterenol and D-tartaric acid. The crude (+)-

arterenol D-bitartrate obtained from the mother liquor was purified

by crystallization from 90 percent aqueous methanol. The optical iso-

mers of arterenol were then obtained from these salts by treatment

in aqueous solution with ammonium hydroxide.

RESEARCH AIM

The aim of this investigation was to study further the possible conversion of arylglyoxylohydroxamyl chlorides into the corresponding arylethanolamines. This study appeared desirable because of the need for a good general method for obtaining such amino alcohols, and because, as indicated, the arylglyoxylohydroxamyl halides are readily available and meet all the requirements for desirable intermediates, that is have the proper skelton bearing properly situated potential hydroxyl and amino groups in this skelton.

That these intermediates may, in fact, form the desired products is indicated by isolated but rare successful hydrogenations reported by Levin (51). Unfortunately such success was not consistent. Neither he or Simonoff (43), in numerous experiments, were able to account for the failures or explain the isolated successes.

Accordingly two approaches to the problem were envisioned:

i) Continued efforts to reduce the arylglyoxylohydroxamyl chlorides directly, and, if possible, to determine the conditions which will assure satisfactory results.

ii) Hydrogenation of derivatives of arylglyoxylohydroxamyl chlorides, such derivatives being readily obtainable and hypothetically capable of forming the desired arylethanolamines. Such derivatives appear in the arylglyoxylohydroxamamides.

Levin (51) has shown that arylglyoxylohydroxamyl chlorides will react with aniline to form characteristic anilides as follows:

$$Ar.CO.C(:NOH)Cl + 2H_2NC_6H_5 \longrightarrow Ar.CO.C(:NOH)NHC_6H_5 + C_6H_5NH_2 \cdot HCl$$
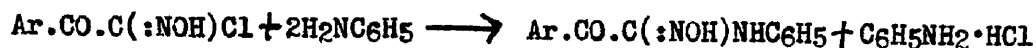
The reaction of arylglyoxylohydroxamyl chlorides with other amines should proceed similarly to form the corresponding arylglyoxylo-hydroxamamides. The reduction of the hydroxamamides should proceed in one or both of the following courses:

$$Ar.CO.C(:NOH)NHR \xrightarrow{4H_2} \begin{array}{l} Ar.CHOH.CH_2NH_2 \quad (A) \\ \\ Ar.CHOH.CH_2NHR \quad (B) \end{array}$$

$$Ar.CHOH.CH_2NHR \quad (B)$$
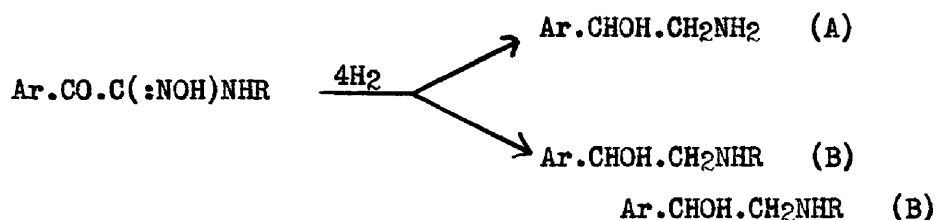
Should the reduction yield compound (A), then a conveinent method for the synthesis of arylethanolamines would be effected. If compound (B) were the reduction product, a method for preparing N-substituted aryl-ethanolamines would be the result; or, if R is hydrogen, the reaction could also be adapted to the preparation of primary arylethanolamines. If the reduction should only require three moles of hydrogen, then the following product is also possible:

$$Ar.CO.C(:NOH)NHR \xrightarrow{3H_2} Ar.CHOH.\underset{NH_2}{CHNHR}$$
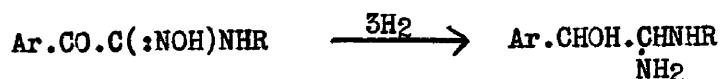
EXPERIMENTAL

A. SYNTHESIS OF INTERMEDIATES

Many of the intermediates used in this investigation were pur-
chased through ordinary commercial sources. The phenacyl chloride,
catechol, chloroacetyl chloride, aniline, butyl nitrite, methylamine
hydrochloride, 25 percent aqueous methylamine, ethylamine, and β-naph-
thylamine, all of "white label" purity, used in this investigation
were obtained from Eastman Kodak Company. The phosphorous oxychloride
was purchased from J. T. Baker Chemical Company. The morpholine and
ethanolamine were obtained from Carbide and Carbon Chemical Corpora-
tion. The isopropylamine, n-propylamine, di-n-butylamine and n-heptyl-
amine were purchased from Sharples Chemicals Inc.

3,4-Dihydroxyphenacyl Chloride. Levin (53) prepared this inter-
mediate by treating chloroacetic acid with phosphorous pentachloride
as follows:

$$ClCH_2COOH + PCl_5 \longrightarrow ClCH_2COCl + POCl_3 + HCl$$
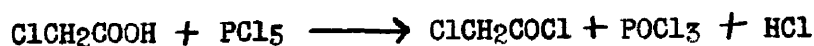
The mixture of products obtained was distilled and the distillate
boiling up to 115° was allowed to react with catechol to give 3,4-
dihydroxyphenacyl chloride:
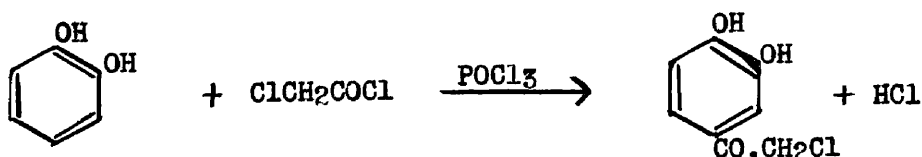
By this means Levin obtained a pure product in yields of 60 percent.

In this investigation the procedure used was a slight modification of the method of Levin. A mixture of 44.8 (0.4 mole) of chloroacetyl chloride and 60.8 g. (0.4 mole) of phosphorous oxychloride was added to a suspension of 44.0 (0.4 mole) of catechol in 200 ml. of benzene. The mixture was refluxed for fifteen hours after which, the solvent and some POCl₃ were removed by distillation under reduced pressure. A dark purple viscous residue was obtained which was dissolved in 400 ml. boiling water. The solution was then cooled while stirring rapidily and the crude product crystallized out. After standing overnight in the refrigerator, the precipitated material was filtered off and dried. The crude product was recrystallized from boiling water using 5 g. Nuchar as a decolorizing agent. In this manner 39 g. (59%) of colorless needles, decomposing at 173°, were obtained. The melting point of this compound as given in the literature (51) is 174° (dec.).

Phenylglyoxylohydroxamyl Chloride. The general procedure for the nitrosation of phenacyl chloride and its derivatives as developed by Levin (53) was employed in the preparation of this compound.

In a half-liter, three-neck, round bottom flask provided with a mechanical stirrer, a reflux condenser connected to a gas absorption trap, a delivery tube, extending beneath the surface of the liquid, for hydrogen chloride and a small dropping funnel, was placed 15.4 g. (0.1 mole) phenacyl chloride in 100 ml. anhydrous ether. The stirrer was set in motion, and after complete solution of the ketone, hydrogen chloride was introduced directly into the reaction mixture at the rate of 2 to 3 bubbles per second, stirring and the addition

of acid being continued throughout the reaction. The freshly distilled butyl nitrite (0.11 mole) was added through the dropping funnel in 0.5 to 1.0 ml. portions. After addition of the first portion, the reaction mixture became an orange-brown and after several minutes, light yellow in color. The mixture gradually warmed up and began to reflux gently. After all of the nitrite had been added (about 30 to 40 minutes), stirring and addition of hydrogen chloride were continued for an additional 15 minutes, after which the reaction mixture was allowed to stand for 1 or 2 hours, or preferably, overnight if convenient. The solvent was removed by distillation under reduced pressure. The residue was dried at 50° in a vacuum oven. The crude product was recrystallized from hot carbon tetrachloride and 18 g. (87%) of light tan crystals, melting at $129-131^{\circ}$, were obtained. A second recrystallization gave glistening needles melting at 133°. Levin reports the melting point of this compound as 133° (51).

3,4-Dihydroxyphenylglyoxylohydroxamyl Chloride. 3,4-Dihydroxyphenacyl chloride was nitrosated as a suspension in ether, using the same procedure as above. Complete solution occurred at mid-point in the nitrosation, and as the nitrosation proceeded, the reaction mixture gradually darkened. The solution obtained by the reaction of 18.7 g. (0.1 mole) 3,4-dihydroxyphenacyl chloride in 400 ml. ether (to which 3 ml. of water was added) with 12.6 ml. (0.11 mole) freshly distilled butyl nitrite was concentrated by distilling off one-half the volume of solvent. The addition of 200 ml. benzene precipitated 17.1 g. (82%) of 3,4-dihydroxyphenylglyoxylohydroxamyl chloride, m.p. $133-4^{\circ}$ (dec.). This agrees with the melting point reported

by Levin (51).

p-Methylphenylglyoxylohydroxamyl Chloride and p-Xenylglyoxylo-
hydroxamyl Chloride. These products were prepared by Levin (51).

B. PREPARATION OF ARYLGLYOXYLOHYDROXAMAMIDES

The arylglyoxylohydroxamamides were prepared according to the
following reaction:

$$Ar.CO.C(:NOH)Cl + 2H_2NR \longrightarrow Ar.CO.C(:NOH)NHR + RNH_2 \cdot HCl$$

Levin (51) pointed out that the formation of the anilide of the aryl-
glyoxylohydroxamyl chlorides proceeds smoothly and gives excellent
yields by simply mixing the amine and hydroxamyl chloride in an ether-
eal solution and allowing them to stand with occasional shaking for
a period of 12 hours. The amine hydrochloride precipitated out and
was then removed by filtration and the solution evaporated to dry-
ness. The crude residue so obtained was then recrystallized from an
appropriate solvent. However, when Levin attempted to obtain alipha-
tic amides in the same manner, he reported that the reaction took
place with violence.

After numerous attempts to carry out the reaction of arylglyoxylo-
hydroxamyl chlorides with aliphatic amines the following procedure
was adopted. Separate solutions of two moles of amine and one mole
of the hydroxamyl chloride in anhydrous ether were made. The solu-
tion of the amine was then added dropwise with vigorous stirring to
the solution of the chloride. Reaction occurred instantaneously as

noted by the precipitation of the amine hydrochloride. The isolation of the product was accomplished in the same manner as in the case of the anilides. It was found, however, that the phenylglyoxylohydroxamamides formed with aliphatic amines are semi-solid or oily in nature and all attempts to crystallize them failed.

The hydrochlorides of the phenylglyoxylohydroxamamides were prepared by spraying an ethereal solution of the hydroxamamide with hydrogen chloride. The hydrochlorides were found to be white powders having sharp melting points and were used to identify the respective hydroxamamides. These hydrochlorides were found to be fairly unstable and on treatment with water hydrolyzed readily to give the original hydroxamamide and hydrochloric acid.

N-Phenylphenylglyoxylohydroxamamide (Phenylglyoxylohydroxamanilide). This compound was prepared by the procedure of Levin (51). From 5 g. (0.027 mole) of the chloride and 5 g. (0.054 mole) aniline, 6.4 g. (99%) crude yellow crystals was obtained. The crude product was recrystallized from toluene and 4 g. (62%) yellow crystalline flakes, m.p. 142° (dec.), was obtained. This agrees with the melting point as given in the literature (51). Nitrogen: calculated for $C_{14}H_{12}O_2N_2$ 11.60%; found 11.69% and 11.57%.

N-Phenylphenylglyoxylohydroxamamide Hydrochloride. An ethereal solution of the hydroxamamide (anilide) was sprayed with hydrogen chloride and a white precipitate melting at 123-4° was obtained. The hydrochloride hydrolyzes readily when treated with water, giving the original hydroxamamide. Nitrogen: calculated for $C_{14}H_{12}O_2N_2 \cdot HCl$ 10.12%; found 10.12% and 10.11%.

N-β-Naphthylphenylglyoxylohydroxamamide. To a solution of 4.5

g. (0.025 mole) phenylglyoxylohydroxamyl chloride in 50 ml. of an-

hydrous ether was added an ethereal solution (25 ml.) of 7.2 g. (0.05

mole) of β-naphthylamine. The reaction was slow in starting and

was allowed to stand overnight. The naphthylamine hydrochloride was

removed by filtration and 3.6 g. (80%) was obtained. Identity of this

compound was proved by neutralizing an aqueous solution and obtaining

the free amine, m.p. 111-3°. Literature melting point of β-naphthyl-

amine is 111-2° (54). The ethereal filtrate was evaporated to dry-

ness and 7.8 g. (more than theoretical, probably due to partial solu-

tion in ether of some β-naphthylamine hydrochloride) of the crude

hydroxamamide was obtained. The crude product was washed with water

until free of amine hydrochloride and recrystallized from alcohol.

In this manner, 6.7 g. (93%) of yellow crystalline compound, which

sintered at 172° and decomposed at 178-9°, was obtained. Nitrogen:

calculated for $C_{18}H_{14}O_2N_2$ 9.65%; found 9.91% and 9.98%.

Phenylglyoxylohydroxamamide. A solution of 4.5 g. (0.025 mole)

of phenylglyoxylohydroxamyl chloride in 50 ml. anhydrous ether was

placed in a two-neck flask equipped with a $CaSO_4$ drying tube and a

delivery tube extending beneath the surface of the liquid. Ammonia

gas, generated by heating concentrated ammonium hydroxide, was pass-

ed through a sodium hydroxide drying column and bubbled into the

solution until the precipitation of NH_4Cl ceased. Near the end of the

reaction, the solution turned deep yellow in color. The NH_4Cl was

removed by filtration and the ethereal solution evaporated to dry-

ness. The yellow residue was decolorized with Nuchar and recrystal-

lized from dilute alcohol, yielding 2.2 g. (56%) pale yellow prisims, melting at 129-31°. Dilute alcohol is not the best solvent, for with it the recrystallization loses are high. The melting point of phenylglyoxylohydroxamamide as given in the literature is 133° (55). Nitrogen: calculated for $C_8H_8O_2N_2$ 17.08%; found 17.15% and 17.28%.

> Note: This procedure was repeated on three different
> occasions using anhydrous ammonia from a tank
> and in each instance a compound was obtained which
> was different from the one obtained above. In
> these cases a white powder, m.p. 80°, was obtain-
> ed. Repeated recrystallizations failed to raise
> the melting point. Nitrogen: found 10.07% and
> 10.26%. Regrettably time did not permit further
> characterization of this product.

N-Morpholinophenylglyoxylohydroxamamide. Using the same procedure as in the case of N-phenylphenylglyoxylohydroxamamide, morpholine was allowed to react with phenylglyoxylohydroxamyl chloride. Upon evaporation of the ethereal solution a yellow resin-like residue was obtained. The residue was rubbed with isopropyl ether and the compound crystallized, m.p. 98°. Recrystallization from isopropyl ether yielded 2.6 g. (2%) yellow crystalline flakes, m.p. 102°. Nitrogen: calculated for $C_{12}H_{14}O_3N_2$ 11.96%; found 12.20% and 12.08%.

N-β-Hydroxyethylphenylglyoxylohydroxamamide. By allowing ethanolamine to react with phenylglyoxylohydroxamyl chloride in the above manner 1 g. (1%) pale yellow solid dec. 85° was obtained.

N-Isopropylphenylglyoxylohydroxamamide. From the reaction of 5 g. (0.027 mole) phenylglyoxylohydroxamyl chloride and 3 g. (0.054 mole) isopropylamine, 2.16 g. (83%) of isopropylamine hydrochloride was obtained. The ethereal solution was allowed to stand overnight and no further precipitation was noted. Upon evaporation of the ether,

5.1 g. (90%) brown semi-solid mass was obtained. Attempts to crystallize this compound failed.

N-n-Propylphenylglyoxylohydroxamamide. From 5 g. (0.027 mole) of phenylglyoxylohydroxamyl chloride and 1.5 g. (0.054 mole) n-propylamine, 0.9 g. (74%) of n-propylamine hydrochloride was obtained. Evaporation of the ethereal solution gave 3.5 g. (68%) of a yellow semi-solid mass. Attempts to crystallize this product failed.

N,N-Di-n-butylphenylglyoxylohydroxamamide. From 4.5 g. (0.025 mole) phenylglyoxylohydroxamyl chloride and 6.5 g. (0.05 mole) di-n-butylamine, 4.9 g. (71%) yellowish waxy compound, melting at 70-80°, was obtained. The crude product was recrystallized from benzene-petroleum ether, and 2.5 g. (35%) of a white powder, m.p. 122-5°, was obtained. Nitrogen: calculated for $C_{16}H_{24}O_2N_2$ 10.13%; found 8.40% and 8.38%. No attempt was made to purify the product further.

N-n-Butylphenylglyoxylohydroxamamide. The n-butylamine used in this reaction was freshly distilled. From the reaction of 4.5 g. (0.025 mole) phenylglyoxylohydroxamyl chloride and 3.6 g. (0.05 mole) n-butylamine, 2.5 g. (92%) of n-butylamine hydrochloride was obtained. The melting point of the hydrochloride compares favorably with that given in the literature. Upon evaporation of the ethereal solution 4.6 g. (85%) of a yellow viscous oil was obtained.

N-n-Butylphenylglyoxylohydroxamamide Hydrochloride. The yellow oil from above, assumed to be N-n-butylphenylglyoxylohydroxamamide, was dissolved in anhydrous ether and sprayed with hydrogen chloride. A white powder was obtained, m.p. 120-5°. Nitrogen: calculated for $C_{12}H_{16}O_2N_2 \cdot HCl$ 10.99%; found 10.82% and 10.53%.

<u>N-Ethylphenylglyoxylohydroxamamide.</u> Anhydrous ethylamine was placed in a flask and heated. The gaseous amine was passed through a sodium hydroxide drying column into a solution of 4.5 g. (0.025 mole) phenylglyoxylohydroxamyl chloride. When precipitation of ethylamine hydrochloride ceased, the reaction was stopped and 1.0 g. (95%) of ethylamine hydrochloride was obtained. On evaporation of the reaction mixture, 3.8 g. (79%) of a yellow-brown viscous oil was obtained. A single attempt to isolate the hydrochloride of this product failed.

<u>N-Methylphenylglyoxylohydroxamamide.</u> Excess methylamine hydrochloride was dissolved in 300 ml. of 40 percent NaOH. The solution was heated and the gaseous amine was passed through a sodium hydroxide drying column into a solution of 4.5 g. (0.025 mole) phenylglyoxylohydroxamyl chloride. A quantitative yield of crude methylamine hydrochloride was obtained. From the reaction mixture, 3.5 g. (80%) of a yellow oil was obtained.

<u>N-Methylphenylglyoxylohydroxamamide Hydrochloride.</u> A solution of 2.5 g. of the hydroxamamide in anhydrous ether when sprayed with hydrogen chloride gave 1.2 g. (60%) of a yellow water-soluble solid, m.p. 132-3°. Nitrogen: calculated for $C_9H_{10}O_2N_2 \cdot HCl$ 13.05%; found 13.53% and 13.79%.

<u>N-n-Heptylphenylglyoxylohydroxamamide.</u> From 4.5 g. (0.025 mole) phenylglyoxylohydroxamyl chloride and 5.7 g. (0.05 mole) n-heptylamine, 2.6 g. (70%) n-heptylamine hydrochloride was obtained. Evaporation of the ethereal solution gave 4.6 g. (70%) of a yellow oil.

<u>N-n-Heptylphenylglyoxylohydroxamamide Hydrochloride.</u> An anhydr-

ous ethereal solution of 2.3 g. of the hydroxamamide when sprayed with hydrogen chloride gave 1.2 g. (40%) white crystalline compound, m.p. 123-5°. Nitrogen: calculated for $C_{15}H_{22}O_2N_2 \cdot HCl$ 9.39%; found 9.51% and 9.79%.

N-Benzylphenylglyoxylohydroxamamide. From 4.5 g. (0.025 mole) phenylglyoxylohydroxamyl chloride and 4.8 g. (0.05 mole) benzylamine, was obtained 5.1 g. (82%) of a semi-solid mass which failed to crystallize on standing in the refrigerator for two days. Attempts to obtain crystals were unsuccessful. The residue was then treated with anhydrous ether and a white solid compound insoluble in ether was obtained. The powder was recrystallized from dilute alcohol and decolorized with Nuchar and 1.8 g. white crystalline compound, m.p. 142-4°, was obtained. Nitrogen: found 9.86% and 9.46%.

N-Phenyl-p-methylphenylglyoxylohydroxamamide. From 5.6 g. (0.03 mole) of the chloride and 1.8 g. (0.06 mole) freshly distilled aniline, a quantitative yield of the crude hydroxamamide was obtained. Recrystallization of the crude product from isopropyl alcohol gave 7.0 g. (95%) colorless needles, dec. 163-4°. The melting point agrees with that given in the literature (51).

N-Methyl-p-methylphenylglyoxylohydroxamamide. To an ethereal solution of 10 g. (0.05 mole) p-methylglyoxylohydroxamyl chloride was added 10 ml. of 25 percent aqueous solution of methylamine. The mixture was shaken and allowed to stand for 30 minutes. The heat of reaction evaporated the ether and the crude product was recrystallized from isopropyl alcohol. 7.5 g. (75%) of white crystalline needles, m.p. 124°, were obtained. The compound was insoluble in hot and cold

water, dilute NaOH and dilute HCl; soluble in benzene, dioxane, hot ethyl alcohol, hot isopropyl alcohol and hot isopropyl ether.

N-n-Butyl-p-xenylglyoxylohydroxamamide. From 3.2 g. (0.0125 mole) p-xenylglyoxylohydroxamyl chloride and 1.8 g. (0.025 mole) n-butylamine, 2.5 g. (67%) of yellow semi-solid product was obtained. Upon recrystallization from dilute alcohol, 0.5 g. (13%) of a white powder was obtained, sinters 90°, dec. 145°. Nitrogen: calculated for $C_{18}H_{20}O_2N_2$ 9.45%; found 5.95% and 6.13%. No attempt was made to further purify this product.

Table I. Summary of Arylglyoxylohydroxamamides

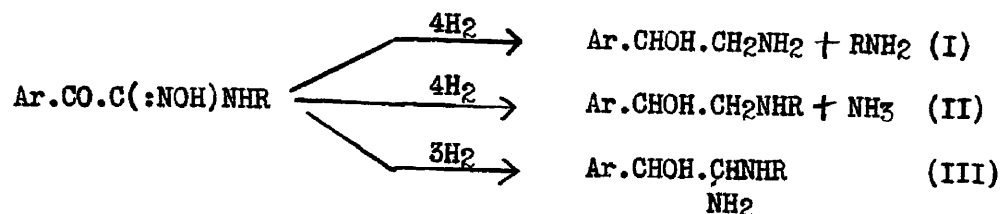| Ar.CO.C(:NOH)NHR		Melting Point	Melting Point of Hydrochloride	Characteristics	Yield	Nitrogen	
Ar-	R-					Calc'd	Found (A)
Phenyl	Phenyl	142°	123-4°	yellow flakes	62%	11.60%	11.69% 11.57%
Phenyl	β-Naphthyl	178-9°		yellow crystals	93%	9.65%	9.91% 9.98%
Phenyl	Hydrogen	129-31°		yellow prisims	56%	17.08%	17.28% 17.15%
Phenyl	Morpholino	98°		yellow flakes	2%	11.96%	12.20% 12.08%
Phenyl	β-Hydroxy ethyl	85°		yellow solid	1%		
Phenyl	Isopropyl			semi-solid	90%		
Phenyl	n-Propyl			Semi-solid	68%		
Phenyl	di-n-Butyl	122-5° (B)		white powder	35%	10.13%	8.40% 8.38%
Phenyl	n-Butyl		120-5°	viscous oil	85%	10.99% (C)	10.82% 10.53%
Phenyl	Ethyl			viscous oil	79%		
Phenyl	Methyl		132-3°	yellow oil	80%	13.05% (C)	13.53% 13.79%
Phenyl	Heptyl		123-5°	Yellow oil	70%	9.39% (C)	9.51% 9.79%
Phenyl	Benzyl			semi-solid	82%		
p-Methyl phenyl	Phenyl	163-4°		colorless needles	95%		
p-Methyl phenyl	Methyl	124°		colorless needles	75%		
4-Xenyl	n-Butyl	145° (B)		white powder	13%	9.45%	5.95% 6.13%

(A) Micro-analyses by Oakwold Laboratories, Alexandria, Va.

(B) Impure compound.

(C) Assayed as hydrochloride.

C. REDUCTION STUDIES OF ARYLGLYOXYLOHYDROXAMAMIDES

The catalytic reduction of arylglyoxylohydroxamamides should take one of the following courses:

$$Ar.CO.C(:NOH)NHR \xrightarrow{4H_2} Ar.CHOH.CH_2NH_2 + RNH_2 \quad (I)$$
$$\xrightarrow{4H_2} Ar.CHOH.CH_2NHR + NH_3 \quad (II)$$
$$\xrightarrow{3H_2} Ar.CHOH.\underset{NH_2}{CHNHR} \quad (III)$$

Compounds (I) and (II) are considered most likely, primarily from a negative view-point, that is, compounds of the type (III) are not widely known; they are structurally hemiacetals in the ammono system and should therefore be amenable to further reduction. However, compounds with two amino groups on a single carbon atom are known, for example, dianilinomalonic ester. By varying the conditions of the reaction it is conceivable that the reaction might be made to follow any of the three proposed courses.

The palladium chloride and platinic oxide used as catalysts in the following reductions were obtained from J. Bishop and Company.

Catalysts. The palladium-charcoal catalysts were prepared by essentially the same method as described by Hartung (3,32):

A suspension of palladium chloride and Nuchar in 1 N sodium acetate was shaken in an atmosphere of hydrogen until saturated. The palladinized-charcoal thus obtained was filtered off, washed with several portions of distilled water, followed by alcohol, and dried with suction. Drying required only about ten minutes. In some instances, highly active catalysts began to glow on drying and even ig-nited; the glow was immediately quenched with water and the catalyst

again washed with alcohol and finally used before all the alcohol had evaporated.

The following types of cataylsts were employed in the reduction of the arylglyoxylohydroxamamides:

Catalyst No. I:

10.0 g. Nuchar

1.0 g. Palladium Chloride

100 ml. 1 N Sodium Acetate

Catalyst No. II:

10.0 g. Nuchar

1.0 g. Palladium Chloride

0.150 g. Platinum Oxide

100 ml. 1 N Sodium Acetate

Reduction Apparatus. The reductions were carried out under 20 atmospheres of hydrogen. The apparatus used was a steel reaction bomb, fitted with a pressure gauge and automatic shaking attachment of the type manufactured by the American Instrument Company.

Reduction of N-Methyl-p-methylphenylglyoxylohydroxamamide. Five g. of N-methyl-p-methylphenylglyoxylohydroxamamide was dissolved in 100 ml. dioxane to which 5 ml. concentrated hydrochloric acid was added. Catalyst No. II was employed in the reduction. In the first two hours, the compound took up one and three-quarters moles of hydrogen. The reduction seemed to stop so it was fortified with 100 mg. of palladium chloride. In the next two hours approximately two moles of hydrogen were absorbed. The hydrogen uptake stopped, so the reduction

mixture was removed from the reaction bomb. The catalyst was filtered off and the reduction mixture was allowed to stand until all the dioxane evaporated. A brown solid separated out and was removed from the aqueous portion by filtration. The brown solid was dissolved in ether and the ethereal solution was allowed to e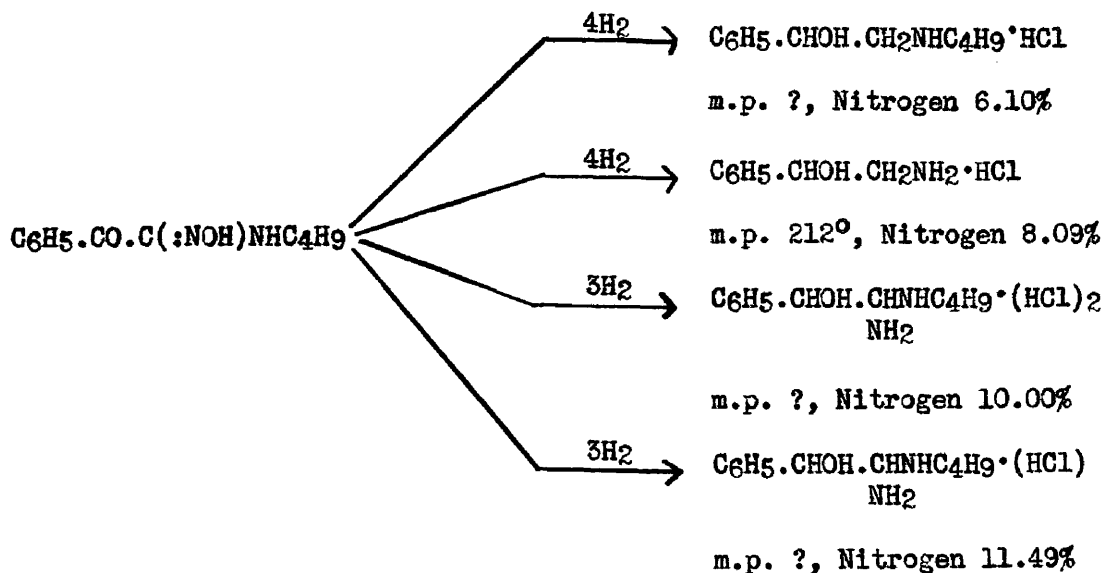vaporate spontaneously. A pale yellow compound was obtained and was recrystallized from isopropyl alcohol, dec. 176°. Nitrogen: found 9.04%. Attempts to identify this compound failed.

Reduction of N-Phenylphenylglyoxylohydroxamamide. 2.4 g. N-phenyl-phenylglyoxylohydroxamamide was dissolved in 95 ml. of 95 percent alcohol to which was added 5 ml. concentrated hydrochloric acid. The reduction procceeded readily using catalyst No. II and in two hours 3 moles of hydrogen was absorbed. The catalyst was filtered off and upon evaporation of the solvent, 2.2 g. of greenish crystals were obtained. The product was very hydroscopic and the highest melting point determined was 80-5°. Nitrogen found 9.29% and 9.12%. Possible products are as follows:

$C_6H_5.CO.C(:NOH)NHC_6H_5$

$\xrightarrow{5H_2}$ $C_6H_5.CH_2.CH_2NH_2 \cdot HCl$

m.p. 140°, Nitrogen 8.91%

$\xrightarrow{4H_2}$ $C_6H_5.CHOH.CH_2NH_2 \cdot HCl$

m.p. 212°, Nitrogen 8.09%

$\xrightarrow{4H_2}$ $C_6H_5.CHOH.CH_2NHC_6H_5$

m.p. ?, Nitrogen 5.61%

$\xrightarrow{3H_2}$ $C_6H_5.CHOH.CHNHC_6H_5 \cdot (HCl)_2$
$\qquad\qquad\qquad NH_2$

m.p. ?, Nitrogen 9.35%
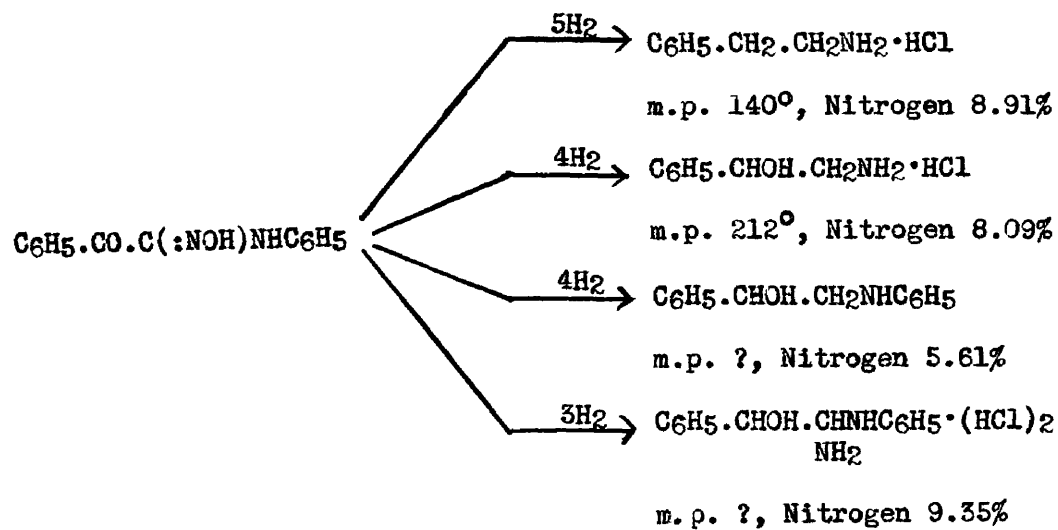
The reduction was repeated using the same conditions and catalyst. The product isolated was very hydroscopic, m.p. 80-5°. Nitrogen found 9.84% and 9.83%.

Reduction of N-Butylphenylglyoxylohydroxamamide. Four grams of N-butylphenylglyoxylohydroxamamide was reduced using the same conditions and catalyst as above. The compound took up approximately 3 moles of hydrogen. 2.1 g. of white hydroscopic crystals, m.p. 140-5°, were obtained. Nitrogen found 11.21% and 11.24%. Possible products are as follows:

$$C_6H_5.CO.C(:NOH)NHC_4H_9$$

$\xrightarrow{4H_2}$ $C_6H_5.CHOH.CH_2NHC_4H_9 \cdot HCl$

m.p. ?, Nitrogen 6.10%

$\xrightarrow{4H_2}$ $C_6H_5.CHOH.CH_2NH_2 \cdot HCl$

m.p. 212°, Nitrogen 8.09%

$\xrightarrow{3H_2}$ $C_6H_5.CHOH.CHNHC_4H_9 \cdot (HCl)_2$
NH_2

m.p. ?, Nitrogen 10.00%

$\xrightarrow{3H_2}$ $C_6H_5.CHOH.CHNHC_4H_9 \cdot (HCl)$
NH_2

m.p. ?, Nitrogen 11.49%

Reduction of Phenylglyoxylohydroxamamide. A solution of 3.3 g. of phenylglyoxylohydroxamamide in 95 ml. of 95% alcohol and 5 ml. of concentrated hydrochloric acid was reduced, using catalyst No. II. The reduction was complete in four hours; the compound took up 4 moles of hydrogen. The solvent was removed under reduced pressure and 4.4 g. of a brownish residue was obtained. The residue was recrystallized from absolute alcohol and anhydrous ether. A white crystalline solid, 1.1 g. m.p. 210-5° (dec.), was obtained. Melting point agrees with the melting point of phenylethanolamine hydrochloride.

D. REDUCTION STUDIES OF ARYLGLYOXYLOHYDROXAMYL CHLORIDES

The catalytic reduction of arylglyoxylohydroxamyl chlorides should proceed in the following manner:

$$Ar.CO.C(:NOH)Cl + 4H_2 \longrightarrow Ar.CHOH.CH_2NH_2 + HCl + HOH$$

one mole of hydrogen being required to reduce the carbonyl group to the hydroxyl group; two moles to reduce the oximino group to the primary amino group and one mole being necessary to replace the chlorine with hydrogen.

Catalysts. Catalysts numbers I and II as described under the reduction of arylglyoxylohydroxamamides were again used in this portion of the experimental work. In addition, the following catalyst was also employed:

Catalyst No. III:

0.150 g. Platinum Oxide

10.0 g. Nuchar

Reduction Apparatus. The apparatus used in these reductions was the same as that described under the reduction of arylglyoxylohydroxamamides.

In addition to catalytic reduction of arylglyoxylohydroxamyl chlorides, an attempt to dechlorinate the chloride with Raney nickel was made; a single chemical reduction of the chloride with lithium-aluminum hydride was also attempted.

Dechlorination of Phenylglyoxylohydroxamyl Chloride. An attempt to dechlorinate phenylglyoxylohydroxamyl chloride was made according

to the procedure of Mozingo (56). A suspension of 10 g. of Raney nickel, prepared according to Adkins (57), in 25 ml. of 95 percent alcohol was shaken for 20 minutes under two atmospheres of hydrogen. The catalyst was filtered off and added to a solution of 5 g. of the hydroxamyl chloride in 25 ml. of 95 percent alcohol. The mixture was refluxed for two hours and the catalyst was removed by filtration. the catalyst was extracted with boiling water and a yellow solution was obtained. The filtrate was evaporated to dryness and a semi-solid mass was obtained, which when recrystallized from dilute alcohol gave a reddish brown powder. This powder was not isonitrosoacetophenone and no attempt was made to identify it further.

Reduction of Phenylglyoxylohydroxamyl Chloride.

A. Lithium-aluminum Hydride. An attempt to reduce phenylglyoxylo-hydroxamyl chloride with lithium-aluminum hydride was made using the procedure of Nystrom and Brown (58). The lithium-aluminum hydride used was courteously furnished by Drs. Carhart and Krinitsky of the Naval Research Laboratories.

Four g. LiAlH4 was dissolved in 100 ml. of anhydrous ether and placed in a three-neck flask with a reflux condenser, mechanical stirrer and dropping funnel. The entire apparatus is protected from the atmosphere by the use of CaSO4 drying tubes. A solution of 4.0 g. of the hydroxamyl chloride in 50 ml. of anhydrous ether was added to the hydride dropwise. The reaction was vigorous and a gentle reflux was maintained by cooling the reaction flask with an ice bath. After the addition of the chloride was complete, the reaction was allowed to reflux for 3 hours, during which time a copious white precipitate

formed. The excess hydride was then decomposed by the careful addition of water. The reduction mixture was poured into 250 ml. of 10 percent sodium hydroxide solution and the ethereal solution was separated. The ethereal solution was evaporated to dryness and the residue was washed with anhydrous ether and a compound insoluble in anhydrous ether and soluble in water was obtained. The product melts at 85-90°. Nitrogen found 8.39% and 8.44%.

B. Raney Nickel. Two attempts to reduce phenylglyoxylohydroxamyl chloride with Raney nickel catalyst (57). In both instances the hydroxamyl chloride was dissolved in absolute alcohol (100 ml.) and the reduction was conducted under a carbon dioxide-hydrogen atmosphere. In the first, 25 atmospheres of carbon dioxide were led into the bomb followed by 25 atmospheres of hydrogen. In the second, 18 atmospheres of hydrogen were followed by 7 atmospheres of carbon dioxide. Two moles of hydrogen were absorbed in each instance; however, it was impossible to isolate a definite compound from either reduction mixture. Simonoff (43) also reported the failure to isolate and identify any products from an incomplete reduction of phenylglyoxylohydroxamyl chloride.

C. Noble Metal Catalysts.

In all of these reductions, the reaction solvent used was 95 ml. of 95 percent alcohol to which 5 ml. of concentrated hydrochloric acid had been added. The results of these reductions are summarized in Table II.

Table II. Reduction of Phenylglyoxylohydroxamyl Chloride

Exp. No.	Mole of Chloride	Cata-lyst	Moles of hydrogen consumed					
			1 mole	2 moles	3 moles	4 moles	5 moles	6 moles
1	0.02	II	2 min.	5 min.	20 min.	90 min.		
2	0.02	I	15 "	60 "				
3	0.02	II	2 "	10 "	15 "	90 "		
4	0.02	III	2 "	15 "	30 "	50 "	90 min.	270 min.
5	0.02	II	2 "	5 "	10 "	70 "		

In experiments 1, 3, and 5, four moles of hydrogen, or theoreti-cal amount for the reduction

$$\text{Ar.CO.C(:NOH)Cl} \xrightarrow{\;8\;(H)\;} \text{Ar.CHOH.CH}_2\text{NH}_2 \cdot \text{HCl}$$
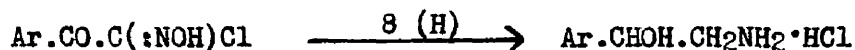
were adsorbed in approximately 90 minutes. The reduction pattern was almost identical in each instance. The reduction in each case con-sumed slightly more (0.003-0.005 mole) than the theoretical amount of hydrogen necessary for the complete reduction. After consumption of hydrogen ceased, the reaction mixture was removed from the bomb and the catalyst filtered off. The filtrate was evaporated to dry-ness in a vacuum desiccator over calcium chloride, soda lime, and concentrated H_2SO_4. The white residue so obtained was recrystallized from absolute alcohol and anhydrous ether. Colorless crystals, melt-ing at 209-10°, were obtained. This melting point agrees with that given in the literature for phenylethanolamine hydrochloride (40). The compound is water-soluble giving a positive chloride ion test with aqueous silver nitrate test solution. The picrate softens at

154°, melting at 158° (dec.). The melting point of the picrate of

phenylethanolamine is reported as 154° in the literature (40). The

yields obtained in experiments 1, 3, and 5 were 86, 91, and 85 per-

cent, respectively. Nitrogen: calculated for $C_8H_{11}ON \cdot HCl$ 8.07%; found

8.52% and 8.47%. Recrystallization raised the melting point of the

product to 210-11°, thereby indicating that the sample assayed con-

tained traces of impurity. Unfortunately time did not allow an assay

of the recrystallized product.

In experiment 2, an attempt to reduce phenylglyoxylohydroxamyl

chloride using catalyst No. I failed. The compound took up only two

moles of hydrogen and from the reduction, 0.7 g. of a white powder,

melting at 140°, was obtained. Nitrogen: found 18.38% and 18.02%.

No attempt to identify this compound was made, since the reduction

was incomplete and was in agreement with the results obtained by

Levin (51) and Simonoff (43).

In experiment 4, in which catalyst No. III was used, the reduc-

tion did not stop at the theoretical for reduction to the amino

alcohol, but proceeded until approximately 6 moles of hydrogen had

been consumed. Upon isolation in the usual manner, 2.5 g. of a white

crystalline product, melting at 195-205° was obtained. Nitrogen:

found 8.03% and 8.42%. Regrettably time did not allow further charac-

terization of this product.

Reduction of p-Xenylglyoxylohydroxamyl Chloride. Using catalyst

No. II, p-xenylglyoxylohydroxamyl chloride was successfully reduced

to p-xenylethanolamine (p-phenylphenylethanolamine) hydrochloride.

From the reduction of 5.2 g. (0.02 mole) of the chloride, in which

4 moles of hydrogen were adsorbed in 5 hours, 4.1 g. (84%) of a
white compound was obtained, m.p. 191-2°. The picrate of this pro-
duct melts at 114-5°. Nitrogen: calculated for $C_{14}H_{15}ON \cdot HCl$ 5.64%;
found 5.73% and 5.69%. Chlorine: calculated 14.06%; found 13.44% and
13.53%.

An aqueous solution of the hydrochloride was basified and ex-
tracted with ether. The ethereal solution was dried over anhydrous
$MgSO_4$ and evaporated to dryness in a desiccator under vacuum. A white
solid, m.p. 126-9°, was obtained.

Reduction of p-Methylphenylglyoxylohydroxamyl Chloride. In the
above manner, p-methylglyoxylohydroxamyl chloride was reduced to the
corresponding ethanolamine. Four moles of hydrogen were adsorbed in
two and one-half hours. The catalyst was filtered off and the fil-
trate evaporated to dryness. A white residue was obtained which was
recrystallized from hot absolute alcohol, giving colorless platlets.
An additional crop of crystals was obtained by concentrating the
mother liquor. From 3.9 g. (0.02 mole) of the chloride, 2 g. (54%)
of colorless platlets, m.p. 189-90°, were obtained. The picrate
melts at 155°. Nitrogen: calculated for $C_9H_{13}ON \cdot HCl$ 7.49%; found
7.82% and 7.98%.

Reduction of 3,4-Dihydroxyphenylglyoxylohydroxamyl Chloride. The
hydroxamyl chloride was reduced to nor-epinephrine using catalyst No.
II. The reduction was repeated five times and the results were identi-
cal in each instance. Using fresh catalyst, 4 moles of hydrogen were
taken up in three and one-half hours, when used catalyst was employ-
ed, the hydrogen uptake was somewhat slower. After filtration of the

reduction mixture to remove the catalyst, the filtrate was evaporated to dryness. A brown solid, very hydroscopic, was obtained. The residue was dried in a desiccator over P_2O_5 and 3.7 g. (88%) of a tan crystalline solid was obtained. The product is very hydroscopic, dissolving in water readily. An aqueous solution of the compound gives a white precipitate when treated with aqueous silver nitrate test solution. The product softens at 110° and melts at $135\text{-}9^\circ$ (dec.). This agrees with the melting point of 141° reported for nor-epinephrine hydrochloride (59). The product was dissolved in absolute alcohol and decolorized with Nuchar. Upon addition of anhydrous ether, a white precipitate was obtained, however, upon filtration the solid took up water and when dried over P_2O_5, gave tan crystals identical with the crude product.

DISCUSSION

The experimental data may be discussed under three headings:

A. Arylglyoxylohydroxamamides: Except for Levin's synthesis of aryl-
glyoxylohydroxamanilides (51) these compounds have received little
attention. In the course of this investigation the preparation of
these anilides was duplicated, and the synthesis of amides extended
to the reaction of arylglyoxylohydroxamyl chlorides with ammonia
and with aliphatic amines. The phenylglyoxylohydroxamamides, of the
type $C_6H_5.CO.C(:NOH)NHR$, in which R is phenyl-, β-naphthyl-, hydro-
gen, morpholino-, β-hydroxyethyl-, isopropyl-, n-propyl-, di-n-
butyl-, ethyl-, methyl-, n-heptyl-, and n-benzyl- have been prepared.
In addition N-phenyl-p-methylphenyl-, N-methyl-p-methylphenyl-, and
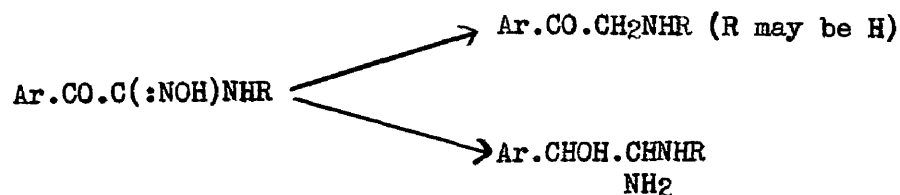N-n-butyl-p-xenylglyoxylohydroxamamides have been prepared.

The hydroxamamides formed with aromatic amines are well defined
solids. Those obtained from aliphatic amines are semi-solid, waxy,
and even oily in nature and are therefore less readily characterized.
It was possible, however, to force from an ether solution of several
of these amides by spraying with hydrogen chloride gas, crystalline
hydrochlorides, which possess characteristic melting points; these
are quite stable if kept dry, but hydrolyze readily in contact with
water. The hydrochlorides of N-phenyl-, N-n-butyl-, N-methyl-, and
N-n-heptylphenylglyoxylohydroxamamides were prepared and character-
ized.

B. Hydrogenation of Arylglyoxylohydroxamamides: These studies were
not completed, but such results as were obtained are interesting and

point to the desirability of carrying further this phase of the investigation. As already mentioned, for the conversion of these amides into a corresponding arylethanolamine four moles of hydrogen are required

$$Ar.CO.C(:NOH)NHR \xrightarrow{4H_2} Ar.CHOH.CH_2NHR \quad \text{or} \quad Ar.CHOH.CH_2NH_2$$
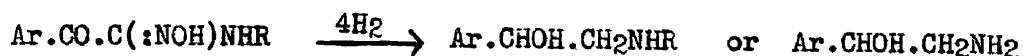
Only in the reduction of the simple amide, $C_6H_5.CO.C(:NOH)NH_2$, did this occur, in which instance the yield of the amino alcohol was 45 percent of theory. Under similar conditions the N-substituted amides, whether derived from aliphatic or aromatic amines, took up but three moles of hydrogen. At first glance this might suggest the formation of either of two types of compounds:

$$Ar.CO.C(:NOH)NHR \Big\langle \begin{array}{l} \longrightarrow Ar.CO.CH_2NHR \text{ (R may be H)} \\ \longrightarrow Ar.CHOH.CHNHR \\ \qquad\qquad NH_2 \end{array}$$

The properties and behavior of the products obtained did not agree with those which are characteristic for the postulated amino ketones. The other type of product, with two amino nitrogen atoms attached to a common carbon atom, is unusual and little known. As an ammono acetal its formation under these conditions would hardly be expected. Analyses of the products, as hydrochlorides, indicate the presence of more nitrogen than can be accounted for by one nitrogen atom per molecule. Analytical data for the product obtained from phenylglyoxylohydroxamanilide agree with the formula $C_6H_5.CHOH.CHNHC_6H_5 \cdot 2HCl$; and for the
NH_2

Product obtained from the corresponding N-butylamide, analysis suggests $C_6H_5.CHOH.CHNHC_4H_9 \cdot HCl$. These structures have not been estab-
$\quad\quad\quad\quad\quad\quad\quad\;NH_2$
lished, however, and no explanation is offered for the formation of a dihydrochloride from the anilide and a monohydrochloride from the aliphatic amide. Further studies are needed to determine whether compounds of the type indicated are really obtained. If they may be obtained, they should reveal interesting chemical properties, and they also merit pharmacological investigation.

C. Reduction of Arylglyoxylohydroxamyl Chlorides: Levin (51) and Simonoff (43) found it impossible to reduce consistently phenylglyoxylohydroxamyl chloride to phenylethanolamine with palladium-charcoal catalyst. In a further study of this problem it developed that palladium-platinum catalyst may be employed to reduce all aryl-glyoxylohydroxamyl chlorides consistently to the corresponding amino alcohols. After this fact had been established, it was learned privately from Dr. Sprague of Sharp and Dohme that the palladium catalyst they had been using for some years was in reality a mixed palladium-platinum catalyst. This information was all the more striking, for upon checking Levin's thesis (51) it was found that the one successful reduction of phenylglyoxylohydroxamyl chloride which he reported was performed using a "palladium" catalyst obtained from Sharp and Dohme. Levin attributed the successful reduction to a "very active" catalyst. It is now quite apparent, in view of the results obtained in this investigation and also in the light of Dr. Sprague's disclosures, that this isolated success was undoubtedly

due to the inadvertent use of a mixed palladium-platinum catalyst. Using this type of catalyst, phenyl-, p-methylphenyl-, p-xenyl-, and 3,4-dihydroxyphenylglyoxylohydroxamyl chlorides have been successfully and consistently reduced to the corresponding amino alcohols. The yields of amino alcohols are excellent and but for manipulative loses might be considered quantitative. Thus, the successful preparation of nor-epinephrine, the most active of the arylethanolamines, in good yields has been established.

SUMMARY AND CONCLUSIONS

1). A literature survey of the methods employed in the synthesis of arylethanolamines is presented.

2). The formation of arylglyoxylohydroxamamides from aliphatic and aromatic amines is described; the reaction has been applied to two aromatic amines, eleven aliphatic amines and to ammonia.

3). The hydrochlorides of various of these hydroxamamides have been prepared and utilized in characterizing the corresponding hydroxamamide.

4). Reduction studies of arylglyoxylohydroxamamides were undertaken. It has been found that the simple amide, $C_6H_5.CO.C(:NOH)NH_2$, takes up the calculated four moles of hydrogen to form the expected phenylethanolamine. The substituted amides take up but three moles and indications are that in the product both nitrogen atoms are still present.

5). Arylglyoxylohydroxamyl chlorides have been successfully reduced to the corresponding amino alcohols by using a mixed palladium-platinum catalyst.

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